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Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation

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Abstract

Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation

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Objectives: To assess the clinical effectiveness and cost-effectiveness of bevacizumab, combined with interferon (IFN), sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic renal cell carcinoma (RCC).
Data sources: Electronic databases, including MEDLINE, EMBASE and the Cochrane Library, were searched up to September/October 2007 (and again in February 2008).
Review methods: Systematic reviews and randomised clinical trials comparing any of the interventions with any of the comparators in participants with advanced and/or metastatic RCC were included, also phase II studies and conference abstracts if there was sufficient detail to adequately assess quality. Results were synthesised narratively and a decision-analytic Markov-type model was developed to simulate disease progression and estimate the cost-effectiveness of the interventions under consideration.
Results: A total of 888 titles and abstracts were retrieved in the clinical effectiveness review, including reports of eight clinical trials. Treatment with bevacizumab plus IFN or sunitinib had clinically relevant and statistically significant advantages over treatment with IFN alone, in terms of progression-free survival and tumour response, doubling median progression-free survival from approximately 5 months to 10 months. Temsirolimus had similar advantages over treatment with IFN in terms of progression-free and overall survival, increasing median overall survival from 7.3 to 10.9 months [hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.58 to 0.92)], as did sorafenib in comparison with best supportive care in terms of overall survival, progression-free survival and tumour response, with a doubling of progression-free survival (HR 0.51; 95% CI 0.43 to 0.60). However, the last was associated with an increased frequency of hypertension and hand–foot skin reaction compared with placebo. No fully published economic evaluations of any of the interventions could be located. However, estimates from the PenTAG model suggested that none of the interventions would be considered cost-effective at a willingness-to-pay threshold of £30,000 per quality-adjusted life-year (QALY). Estimates of cost per QALY ranged from £71,462 for sunitinib to £171,301 for bevacizumab plus IFN. Although there are many similarities in the methodology and structural assumptions employed by PenTAG and the manufacturers of the interventions, in all cases the cost-effectiveness estimates from the PenTAG model were higher than those presented in the manufacturers' submissions. Cost-effectiveness estimates were particularly sensitive to variations in the estimates of treatment effectiveness, drug pricing (including dose intensity data), and health-state utility input parameters.
Conclusions: Treatment with bevacizumab plus IFN and sunitinib has clinically relevant and statistically significant advantages over treatment with IFN alone in patients with metastatic RCC. In people with three of six risk factors for poor prognosis, temsirolimus had clinically relevant advantages over treatment with IFN, and sorafenib tosylate was superior to best supportive care as second-line therapy. The frequency of adverse events associated with bevacizumab plus IFN, sunitinib and temsirolimus was comparable with that seen with IFN, although the adverse event profile

is different. Treatment with sorafenib was associated with a significantly increased frequency of hypertension and hand–foot syndrome. Estimates from the PenTAG model suggested that none of the interventions would be considered cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

Contents

List of abbreviations

ADL	activities of daily living
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
BNF	*British National Formulary*
BSC	best supportive care
CALGB	Cancer and Leukemia Group B
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CT	computerised tomography
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
EAU	European Association of Urology
ECCO	European Cancer Organisation
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
EORTC	European Organisation of Research and Treatment of Cancer
EQ-5D	EuroQol 5 dimensions questionnaire
ERK	extracellular signal-regulated kinase
FACIT-fatigue	Functional Assessment of Chronic Illness Therapy – fatigue scale
FACT	Functional Assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy – General
FKSI	Functional Assessment of Cancer Therapy (FACT) – Kidney Symptom Index
FKSI-DRS	FKSI disease-related symptoms subscale
HIF-1	hypoxia-inducible factor-1
HR	hazard ratio
HRQoL	health-related quality of life
ICD-10	*International Classification of Diseases*, 10th edition
ICER	incremental cost-effectiveness ratio
IFN	interferon
IL-2	interleukin-2
ITT	intention to treat
KIT	stem cell factor receptor
LYG	life-year gained
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein kinase kinase
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Centre
mTOR	mammalian target of rapamycin
MU (or MIU)	million units
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute Common Terminology Criteria
NICE	National Institute for Health and Clinical Excellence
OS	overall survival
PD	progressive disease
PDGF	platelet-derived growth factor

continued

PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
PSA	probabilistic sensitivity analysis
PSS	personal social services
QALY	quality-adjusted life-year
Q-TWiST	Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment
RECIST	Response Evaluation Criteria in Solid Tumours
RCC	renal cell carcinoma
RCT	randomised controlled trial
RDT	randomised discontinuation trial
SD	standard deviation
SE	standard error
TARGET	Treatment Approaches in Renal Cancer Global Evaluation Trial
TNM	tumour-node-metastasis
TWiST	Time Without Symptoms of progression or Toxicity of treatment
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel–Lindau

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS) or it has been used only once or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of information that was deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence information removed and replaced by the statement 'commercial-in-confidence information removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences and parts of tables have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Executive summary

Background

Renal cell carcinoma (RCC) is a highly vascular type of kidney cancer arising in the epithelial elements of the nephrons. The most common histological subtype of RCC is clear cell carcinoma (approximately 75% of cases). RCC is often asymptomatic until it reaches a late stage. In England and Wales, kidney cancer is the eighth most common cancer in men and the fourteenth most common in women. Of those diagnosed with RCC in England and Wales, about 44% live for at least 5 years after initial diagnosis and about 40% for at least 10 years. However, prognosis following diagnosis of metastatic disease is poor, and only about 10% of people diagnosed with stage IV RCC live for at least 5 years after diagnosis.

Current NHS treatment options for metastatic RCC include radical nephrectomy and interferon (IFN). There is currently no standard NHS treatment for patients with metastatic RCC who do not respond to first-line immunotherapy or who are unsuitable for treatment with IFN. Recently developed therapeutic agents include: *bevacizumab*, licensed for use as first-line therapy in patients with advanced and/or metastatic RCC; *sorafenib tosylate*, licensed for first-line therapy in individuals who are not suitable for treatment with IFN and as second-line therapy in those in whom treatment with cytokine-based immunotherapy has failed; *sunitinib*, licensed for use in the first- and second-line treatment of advanced and/or metastatic RCC; and *temsirolimus*, licensed for first-line treatment of patients with advanced RCC who have at least three of six poor prognostic risk factors.

Objectives

To assess the clinical effectiveness and cost-effectiveness of bevacizumab combined with IFN, sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic RCC, specifically:

- to identify, appraise and synthesise the current evidence for the above in accordance with their marketing authorisations
- to determine what, if any, is the incremental cost-effectiveness of the interventions in comparison with current standard treatment.

The report addresses the following policy questions:

1. In those suitable for first-line treatment with immunotherapy: bevacizumab plus IFN versus IFN alone and sunitinib versus IFN alone, using IFN as a comparator.
2. In those not suitable for first-line treatment with immunotherapy: sorafenib and sunitinib, using best supportive care as a comparator.
3. In those with three or more of six poor prognostic factors: bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care, using IFN as a comparator.
4. In those in whom cytokine based immunotherapy has failed: second-line therapy with sorafenib and sunitinib, using best supportive care as a comparator.

Methods

Clinical effectiveness systematic review

Electronic databases, including MEDLINE, EMBASE and the Cochrane Library, were searched up to September/October 2007 (and again in February 2008). Systematic reviews and randomised clinical trials comparing any of the interventions with any of the comparators in participants with advanced and/or metastatic RCC were included. The use of data from phase II studies and non-randomised clinical trials was considered where there was insufficient evidence from good-quality randomised clinical trials. Conference abstracts were included if there was sufficient detail to adequately assess quality. Full papers for studies that appeared relevant were retrieved and screened in detail. All trials were fully data extracted and quality assessed. Results of the included trials were synthesised narratively. The validity of indirect comparison between interventions was considered, using the method proposed by Bucher and colleagues, where data from head-to-head randomised clinical trials were unavailable.

Review of economic evaluations, related literature and manufacturer submissions

Electronic databases were searched up to September/October 2007 (and again in March 2008). All titles and abstracts were assessed independently and all publications meeting the inclusion criteria were fully data extracted and discussed narratively. Searches were also performed to identify literature describing health-related quality of life of people with RCC, treatment costs and resource use associated with the treatment of RCC, and modelling methods used to model disease progression and cost-effectiveness in RCC. The cost-effectiveness analyses reported in the manufacturers' submissions were assessed against the NICE reference case and critically

appraised using the framework presented by Phillips and colleagues.

PenTAG cost–utility model

A decision-analytic Markov-type model was developed in EXCEL to simulate disease progression and estimate the cost-effectiveness of the drugs under consideration. The model has three health states – progression-free survival, progressive disease, and death – and uses estimates of effectiveness, costs and health-state utilities assigned to these states to model disease progression and cost-effectiveness over time. Future costs and benefits were discounted at 3.5% per annum. Weibull survival curves were fitted to the progression-free and overall survival Kaplan–Meier curves from clinical trials for the baseline comparator. Relative measures of treatment effectiveness (hazard ratios, HRs) were then used to estimate the expected disease progression compared with baseline. One-way, multi-way and probabilistic sensitivity analyses were used to explore structural and parameter uncertainty.

Results

Number and quality of effectiveness studies

A total of 888 titles and abstracts were retrieved. Thirteen publications describing eight clinical trials were included. Of these, seven were fully published randomised clinical trials and one was a protocol and conference abstract. Data contained within a further 19 conference abstracts relating to the included trials were also considered.

Three randomised clinical trials were identified that compared either bevacizumab plus IFN (two trials, one published in abstract form only) or sunitinib (one trial) with IFN alone as first-line therapy in those suitable for treatment with IFN. Preliminary results (abstract only) of one randomised clinical trial in which sorafenib tosylate was compared with best supportive care in people unsuitable for treatment with IFN, and one randomised clinical trial of temsirolimus versus IFN in people with three or more of six risk factors for poor prognosis were located. For second-line therapy, we found a randomised clinical trial and a randomised discontinuation trial of sorafenib versus best supportive care and two phase II single-arm trials of sunitinib.

We were unable to identify any data on clinical effectiveness in the following areas: sunitinib or best supportive care in patients unsuitable for treatment with immunotherapy; sorafenib in patients with poor prognosis; or sunitinib as second-line therapy.

All the fully published included studies were large, multicentre, good-quality trials. There was insufficient detail in the conference abstracts to fully appraise the quality of the trials.

Summary of benefits and risks

Bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy Treatment with both interventions had clinically relevant and statistically significant advantages over treatment with IFN alone, in terms of progression-free survival and tumour response, doubling median progression-free survival from approximately 5 months to 10 months. There was insufficient data on overall survival due to the early crossover of patients on control treatment following interim analyses; however, both interventions showed some benefits in terms of overall survival. An indirect comparison between sunitinib and bevacizumab plus IFN suggested that sunitinib may be more effective than bevacizumab plus IFN [HR 0.67; 95% confidence interval (CI) 0.50 to 0.89) in terms of progression-free survival. Sunitinib was associated with a lower frequency of adverse events than IFN, and bevacizumab plus IFN with slightly more than IFN alone.

Sorafenib tosylate and sunitinib compared with best supportive care as first-line therapy No trials met the inclusion criteria.

Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared with IFN as first-line therapy in people with poor prognosis Temsirolimus had clinically relevant and statistically significant advantages over treatment with IFN in terms of progression-free and overall survival, increasing median overall survival from 7.3 to 10.9 months (HR 0.73; 95% CI 0.58 to 0.92). There was also evidence to suggest that progression-free survival may be prolonged by treatment with the combination of bevacizumab plus IFN compared with IFN alone, though it is not clear whether this effect would be considered clinically and statistically significant. We were unable to find any data on sorafenib in this population. A significantly lower frequency of grade 3 and 4 adverse events was reported with temsirolimus than with IFN.

Sorafenib tosylate and sunitinib compared with best supportive care as second-line therapy Sorafenib had clinically relevant and statistically significant advantages over best supportive care in terms of overall survival, progression-free survival and tumour response, with progression-free survival doubling in the randomised clinical trial (HR 0.51; 95% CI 0.43 to 0.60). However, it was associated with an increased frequency of hypertension and hand–foot skin reaction compared with placebo. We were unable to locate any comparative trials of sunitinib as second-line therapy, but two single-arm phase II trials suggested that sunitinib may be efficacious in this population.

Summary of cost-effectiveness

We were unable to locate any fully published economic evaluations of any of the interventions. Although there are many similarities in the methodology and structural

assumptions employed by Peninsula Technology Assessment Group (PenTAG) and the manufacturers of the interventions, in all cases the cost-effectiveness estimates from the PenTAG economic evaluation were higher than those presented in the manufacturers' submissions.

Bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy The PenTAG model estimated that the cost per quality-adjusted life-year (QALY) for bevacizumab plus IFN versus IFN is £171,301. If the NHS is willing to pay £30,000 for an additional QALY, there is zero probability that this intervention would be considered cost-effective, and bevacizumab plus IFN is unlikely to be considered cost-effective at any reasonable willingness-to-pay threshold. For sunitinib versus IFN, the PenTAG model estimated a cost per QALY of £71,462. Sunitinib is likely to be considered cost-effective compared with both bevacizumab plus IFN and IFN alone only above a willingness-to-pay threshold of £75,000 per QALY.

Sorafenib tosylate and sunitinib compared with best supportive care as first-line therapy Insufficient clinical effectiveness data to perform a cost-effectiveness analysis.

Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared with IFN as first-line therapy in people with poor prognosis We were unable to locate appropriate overall and progression-free survival data with which to populate an economic model for the first three interventions or best supportive care. The base-case discounted incremental cost-effectiveness ratio (ICER) for temsirolimus versus IFN estimated from the PenTAG model was £81,687 per QALY. Temsirolimus is likely to be considered cost-effective compared with IFN only above a willingness-to-pay threshold of £82,000 per QALY. The cost–utility analyses performed in patient subgroups indicate cost per QALY estimates ranging from £64,680 to £132,778, although the clinical effectiveness data on which these analyses are based is uncertain.

Sorafenib tosylate and sunitinib compared with best supportive care as second-line therapy We were unable to locate any comparative trials of sunitinib as second-line therapy in this population. The PenTAG model estimated a cost per QALY for sorafenib versus best supportive care of £102,498. Compared with best supportive care, sorafenib is only likely to be considered cost-effective above a willingness-to-pay threshold of approximately £100,000 per QALY.

Sensitivity analyses

In all comparisons, the cost-effectiveness estimates were particularly sensitive to variations in the estimates of treatment effectiveness, drug pricing (including dose intensity data), and health-state utility input parameters. The ICERs were insensitive to a number of assumptions and data estimates, in particular discounting, time horizon, limiting IFN administration to 1 year, non-drug costs, inclusion of estimates associated with costs of death, and estimates of adverse event costs.

Discussion

The assessment was necessarily constrained by the marketing authorisations of the interventions under review, leading to difficulties in deriving research questions applicable to the population with RCC. We felt that it was important to use current standard treatment as the comparator wherever possible – considering IFN to be the comparator for first-line therapy in patients suitable for treatment with immunotherapy and best supportive care the comparator in all other situations. Suitability for treatment with immunotherapy was defined in terms of clinical contraindication to treatment (e.g. autoimmune disease or a history of depression). However, we acknowledge that a large proportion of people diagnosed with RCC in the UK will be deemed unsuitable for treatment with IFN as a result of clinical markers of prognosis. Informal extrapolation of available data suggests that if it is assumed that there is no difference in the relative effectiveness of best supportive care and IFN in this population, and that the cost of best supportive care would be less than the cost of treatment with IFN, it is possible that the new interventions would be less likely to be considered cost-effective at commonly used willingness-to-pay thresholds when compared with best supportive care.

Clinical trials suggested that all four interventions have clinically relevant and statistically significant advantages over current standard treatment (IFN or best supportive care) where data exists with which to make the comparison. The most robust clinical effectiveness data was for progression-free survival; treatment crossover following interim analyses was permitted in all but one (temsirolimus versus IFN) of the included trials resulting in confounding of overall survival data. There is therefore a large amount of uncertainty in the estimates used in the assessment of clinical effectiveness and cost-effectiveness.

The PenTAG model estimated that if the NHS is willing to pay £30,000 for an additional QALY, the probability that any of the interventions (in the undertaken comparisons) would be considered cost-effective is zero. Exploration of these results using one-way, multi-way and probabilistic sensitivity analyses indicated that the model is most sensitive to variations in the HRs for overall survival, drug pricing (including assumptions made about dose intensities and drug wastage) and health-state utility values. The sensitivity analyses for the HRs for progression-free survival have highlighted issues linked to the balancing of incremental costs and effects. In the PenTAG analysis, improvements in progression-free survival made the drugs less attractive in terms of value for money. This counterintuitive effect was seen across all of the analyses undertaken by PenTAG, was apparent for both cost per QALY and cost per life-year analyses and could be explained partly by the

relatively high incremental treatment costs (costs of the drug, drug administration and monitoring) associated with time spent in the progression-free disease health state. The cost-effectiveness estimates produced in the PenTAG economic evaluation were higher than the manufacturers' base-case estimates in all cases (although in two of the four analyses the results are similar). Although the manufacturers and PenTAG's analyses share some common aspects of methodology, there are also clear differences in the resulting cost-effectiveness estimates.

Strengths and limitations of the analyses

Strengths include comprehensive, explicit and systematic literature searches, including hand searching of conference proceedings, to locate evidence for the review of clinical effectiveness and inform the economic modelling study; work to fit the most appropriate survival curves to the empirical immature overall survival data; and extensive analyses of the uncertainty of the model using one-way, multi-way and probabilistic sensitivity analyses.

Limitations include the constraints on the assessment by the marketing authorisations of the interventions; the uncertainty of the overall survival and health-state utility data; the availability of clinical effectiveness data for all potential comparisons; issues around patient preference; consideration of the sequencing of treatments; some of the structural modelling assumptions used in the PenTAG model; and the scarcity of available information on resource use and costs.

Generalisability of the findings

All the trials included in the review of clinical effectiveness were conducted in patients with predominantly clear cell, metastatic RCC, the majority of whom had undergone previous nephrectomy and many of whom had favourable and intermediate prognosis and good performance status. None of the studies recruited patients with brain metastases (unless neurologically stable) and few patients with bone metastases were included (20% in the trial of bevacizumab plus IFN versus IFN and 30% in the trial of sunitinib versus IFN). Whether the results of this assessment can be extrapolated to other patient groups is unclear.

Conclusions

Evidence suggests that treatment with bevacizumab plus IFN and sunitinib has clinically relevant and statistically significant advantages over treatment with IFN alone in patients with metastatic RCC. Also, in people with three of six risk factors for poor prognosis, temsirolimus has clinically relevant advantages over treatment with IFN, and sorafenib tosylate is superior to best supportive care as second-line therapy. The frequency of adverse events associated with bevacizumab plus IFN, sunitinib and temsirolimus is comparable with that seen with IFN, although the adverse event profile is different. Treatment with sorafenib is associated with a significantly increased frequency of hypertension and hand–foot syndrome. The PenTAG cost-effectiveness analyses suggest that the probability that any of the interventions would be considered cost-effective at a willingness-to-pay threshold of £30,000 per QALY is zero.

Suggested future research questions and priorities

There are clear gaps in the evidence base needed to fully appraise the clinical effectiveness and cost-effectiveness of these four interventions in accordance with their marketing authorisations:

1. More randomised clinical trials in the following areas would be useful: in patients unsuitable for treatment with IFN because of contraindications or who have been defined as having intermediate and poor prognosis and therefore unlikely to benefit from IFN; studies of sorafenib tosylate, sunitinib, bevacizumab plus IFN and best supportive care; and comparative trials of sunitinib and sorafenib as second-line therapy.
2. Research to improve understanding of the impact of the interventions on health-related quality of life during progression-free survival and progressed disease would facilitate the decision-making process for clinicians and patients.
3. Research on current treatment pathways and practice (e.g. in the use of IFN) would reduce the level of uncertainty in future studies modelling the cost-effectiveness of drugs for treatment of renal cancer.
4. As more treatments are introduced, the issues of treatment sequencing become more important: more research is needed on the combination and order of treatments to provide maximum benefit in each patient population.
5. Modelling treatment of RCC presents methodological challenges when using summary data (survival analysis) from clinical trials: research on the impact of using aggregated versus individual patient-level data would be useful.

Chapter 1
Background

Description of underlying health problem

Definition and classification (staging)

Renal cell carcinoma (RCC) is a highly vascular type of kidney cancer arising in the epithelial elements of nephrons. In England and Wales, almost 90% of kidney cancers are RCCs.[1] The most common histological types of RCC are clear cell carcinoma (also known as conventional or non-papillary RCC) (approximately 75% of cases), type I papillary RCC, type II papillary RCC and chromophobe RCC.[2] There are differences in the characteristics of different RCC histologies, for example clear cell carcinoma produces vascular endothelial growth factor (VEGF), spreads early and may respond to treatment with immunotherapy. Papillary cancer is less well understood.[3] Although most (> 90%) cases of RCC occur sporadically, mutations in the von Hippel–Lindau (VHL) tumour suppressor gene appear to be responsible for about 60% of the cases of clear cell type[3] and gene silencing by methylation for most of the remainder. The sporadic form tends to be solitary and usually occurs in and beyond the fourth decade of life. The inherited form tends to be multifocal and bilateral and has an earlier onset.[3]

Staging of RCC uses the American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) system. Tumour stage is based on the combination of tumour size (T) and extent of spread from the kidneys (*Table 1*). TNM classifications are combined to produce stages II–V (*Table 2*) and describe a patients' overall disease stage.[4] This report is concerned with people diagnosed with RCC at stages III and IV.

Epidemiology of renal cell carcinoma

Incidence

In England and Wales, kidney cancer is the eighth most common cancer in men and the fourteenth most common in women. In 2004 there were 3567 registrations of newly diagnosed kidney cancer [*International Classification of Diseases* 10th edition (ICD-10) codes C64–66, C68] in men and 2178 in women.[5,6] Figures for England are shown in *Figure 1*; incidence begins to rise over the age of 40 years and is highest in those aged 65 years and above.

The worldwide incidence of kidney cancer has been rising steadily since the 1970s for both men and women.[7] Analysis of data from the USA suggests that part of the rise is due to an increase in incidental detection as a consequence of the increased use of imaging technology such as ultrasonography, computerised tomography (CT) and magnetic resonance imaging (MRI). Although the rise in the number of cases is greatest in small, localised tumours, there has also been a rise in advanced cases of RCC, which would suggest that increased detection of presymptomatic tumours cannot fully explain the rising incidence of RCC.[8]

In the UK, the incidence of kidney cancer in men has risen from 7.1 per 100,000 in 1975 to 12.8 per 100,000 in 2004. Over the same period, the incidence in women has increased from 3.2 to 6.5 per 100,000 (*Figure 2*). Increases have been greatest in men aged over 65 and women over 55 years of age.[9]

Aetiology

The main risk factors for kidney cancer include obesity,[10–13] hypertension,[8] smoking,[14] chronic and end-stage kidney disease and some genetic conditions, although none of these risk factors are particularly strong.[3] The risk of kidney cancer increases with age and is more common in men than in women. It has been estimated that approximately 25% of cases of kidney cancer diagnosed in Europe are attributable to obesity[12] and that 25% of cases in men are attributable to smoking.[14] A recent meta-analysis[15] of 24 studies of smoking as a risk factor for the development of RCC found that the relative risk for male smokers was 1.54 [95% confidence interval (CI) 1.42 to 1.68] and for female smokers was 1.22 (95% CI 1.09 to 1.36). For both men and women there was a strong dose-dependent increase in risk for ever-smokers and a reduction in relative risk for those who had quit smoking more than 10 years previously.

TABLE 1 *TNM system for staging of renal cell carcinoma*

Tumour size (T)		Regional lymph nodes (N)		Distant metastases (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	MX	Presence of distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M0	No distant metastasis
T1a	Tumour is 4 cm in diameter or smaller and is limited to the kidney	N1	No regional lymph node metastasis	M1	Distant metastasis present: includes metastasis to non-regional lymph nodes and/or other organs
T1b	Tumour is larger than 4 cm but smaller than 7 cm and is limited to the kidney				
T2	Tumour is larger than 7 cm but is still limited to the kidney	N2	Metastasis to more than one regional lymph node		
T3a	Tumour has spread into the adrenal gland or into fatty tissue around the kidney, but not beyond the Gerota's fascia (a fibrous tissue that surrounds the kidney and nearby fatty tissue)				
T3b	Tumour has spread into the large vein leading out of the kidney (renal vein) and/or into the part of the large vein leading into the heart (vena cava) that is within the abdomen				
T3c	Tumour has reached the part of the vena cava that is within the chest or invades the wall of the vena cava				
T4	Tumour has spread beyond the Gerota's fascia				

TABLE 2 *Staging renal cell carcinoma*

Stage	TNM classification	Description
Stage I	T1a–T1b, N0, M0	The tumour is 7 cm or smaller and limited to the kidney. There is no spread to lymph nodes or distant organs
Stage II	T2, N0, M0	The tumour is larger than 7 cm but is still limited to the kidney. There is no spread to lymph nodes or distant organs
Stage III	T1a–T3b, N1, M0 or T3a–T3c, N0, M0	There are several possible descriptions for stage III including any tumour that has spread to one nearby lymph node but not to more than one lymph node or other organs, and tumours that have not spread to lymph nodes or distant organs but have spread to the adrenal glands or to fatty tissue around the kidney and/or have grown into the vena cava
Stage IV	T4, N0–N1, M0 or any T, N2, M0 or any T, any N, M1	There are several possible descriptions for stage IV including any tumour that has spread directly through the fatty tissue and beyond the Gerota's fascia, and any tumour that has spread to more than one lymph node near the kidney or to any lymph node distant from the kidney or to any distant organs

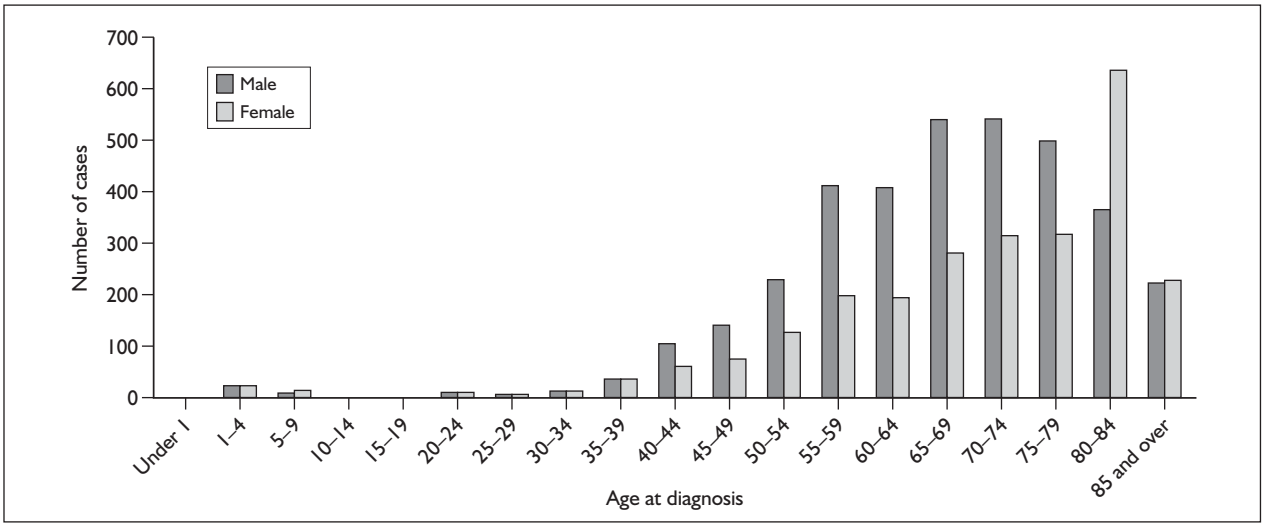

FIGURE 1 *Number of cases of diagnosed kidney cancer by age and sex registered in England in 2004. F, female; M, male. Source: Office for National Statistics.*[5]

Symptoms

Renal cancer is often asymptomatic until it reaches a late stage. A large number of patients with RCC are diagnosed as a result of clinical symptoms, although few cases now present with the classical triad of palpable abdominal mass, flank pain and haematuria. Paraneoplastic signs and symptoms include hypertension, cachexia, weight loss, pyrexia, neuromyopathy, amyloidosis, elevated erythrocyte sedimentation rate, anaemia, abnormal liver function and hypercalcaemia. Metastatic spread may involve the lymph nodes, bones, liver, brain and other organs.

In a retrospective analysis of 400 patients diagnosed with RCC in France between 1984 and 1999, Patard and colleagues[16] stratified tumours into three groups. In total, 41% of patients reported isolated local symptoms such as lumbar pain, palpable mass and haematuria; systemic symptoms [anorexia, asthenia, weight loss or symptoms associated with metastasis (bone pain, persistent cough)] were reported in 22% at presentation, and the remaining 37% of patients were asymptomatic at diagnosis.

The British Association of Urological Surgeons collects data on kidney cancer diagnoses in the UK. According to its figures,[17] of those diagnosed with kidney cancer in 2006 for whom staging information was available, just over one-third (40%) were diagnosed with stage I RCC, 18% had stage II

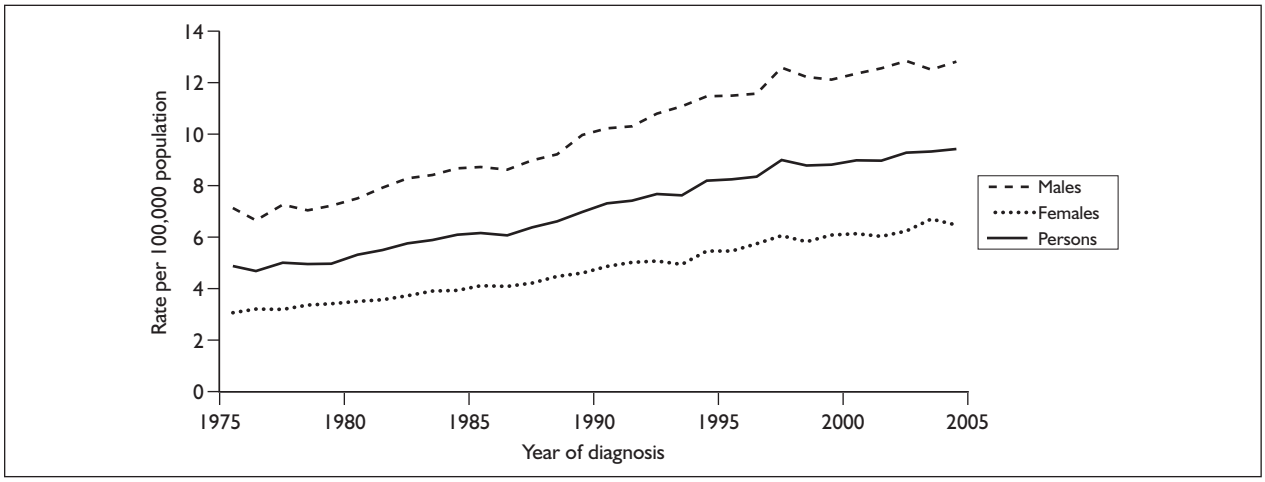

FIGURE 2 *Age-standardised (European) incidence rates of kidney cancer in the UK, 1975–2004. From* UK Kidney cancer statistics,[9] *with permission from Cancer Research UK (www.cancerresearchuk.org/cancerstats).*

RCC, 26% had stage III RCC and 17% had stage IV RCC. In just under one-quarter of those diagnosed with stage IV RCC the primary cancer had grown out of the kidney to involve other structures (stage IVa). In three-quarters of patients with stage IV disease the tumour had metastasised to distant sites (stage IVb).

The number of incidentally diagnosed tumours appears to be increasing. Early detection and treatment of RCC may be associated with an improved outcome.[18–20] However, mortality rates are also continuing to increase (see Mortality).

Prognosis

About 44% of people diagnosed with RCC in England and Wales live for at least 5 years after initial diagnosis and about 40% live for at least 10 years. However, the prognosis following the diagnosis of metastatic disease is poor and only approximately 10% of people diagnosed with stage IV RCC live for at least 5 years after initial diagnosis.

Anatomical, histological, clinical and molecular factors all influence prognosis in patients with RCC.

Anatomical factors include tumour size, venous invasion, renal capsule invasion, adrenal involvement and lymph node and distant metastasis. These factors are considered in the TNM staging classification system described earlier in this chapter. Histological factors include Fuhrman grade, histological subtype, presence of sarcomatoid features, microvascular invasion, tumour necrosis and collecting system invasion. Fuhrman nuclear grade is a four-tiered grading system based essentially on nuclear size and morphology and on the presence or absence of nucleoli. It is the most widely accepted histological grading system used in RCC. Although it is subject to intra- and interobserver discrepancies, it remains an independent prognostic factor.[21] Several studies have shown a trend towards a better prognosis for patients with resectable chromophobe and papillary RCC, with clear cell RCC having the worst prognosis.[22,23]

Clinical factors include patient performance status, localised symptoms, cachexia, anaemia and platelet count.[16] The Karnofsky scale[24] and ECOG-PS (Eastern Cooperative Oncology Group – Performance Status)[25] are convenient and commonly used scales that aim to take into account the overall impact of disease (*Tables 3* and *4* respectively). These measures are used to document clinical progress and also to assess eligibility for clinical trials. The Karnofsky scale assesses ability to perform activities of daily living (ADLs). There is evidence from several trials that ECOG-PS may be an independent prognostic factor of survival, with higher scores correlating with poorer survival.[16,26] There has been some work on the correlation between ECOG-PS and scores obtained on the Karnofsky scale. For example, in a study of patients with lung cancer,[27] ECOG-PS scores of 0 or 1 were equivalent to scores of 100, 90 and 80 on the Karnofsky scale; an ECOG-PS

TABLE 3 *Description of the Karnofsky scale*

Score (%)	Description of signs and symptoms
100	Normal, no complaints, no sign of disease
90	Capable of normal activity, few symptoms or signs of disease
80	Normal activity with some difficulty, some symptoms or signs
70	Caring for self, not capable of normal activity or work
60	Requiring some help, can take care of most personal requirements
50	Requires help often, requires frequent medical care
40	Disabled, requires special care and help
30	Severely disabled, hospital admission indicated but no risk of death
20	Very ill, urgently requiring admission, requires supportive measures or treatment
10	Moribund, rapidly progressive fatal disease processes
0	Death

Source: Yates *et al*.[24]

TABLE 4 *Description of the ECOG-PS score*

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of self-care but unable to carry out work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

Source: Oken *et al.*[25]

score of 2 to Karnofsky scores of 70 and 60; and an ECOG-PS score of 3 or 4 to Karnofsky scores of less than 60.

Several prognostic systems and nomograms that combine independent prognostic factors have been developed. There is some indication from studies[28–30] that these systems might be more accurate at predicting survival than individual characteristics (e.g. Fuhrman grade alone), although they may be less accurate in patients with metastatic disease because of the heterogeneous nature of the disease, the patients and available treatments.[31]

A system developed by Motzer and colleagues[32,33] at the Memorial Sloan-Kettering Cancer Centre (MSKCC) in the USA is commonly used in clinical trials of advanced RCC and is referred to as either the Motzer risk score or the MSKCC risk factor criteria. Five variables are used as risk factors for short survival: low Karnofsky performance status (< 80%), high lactate dehydrogenase (> 1.5 times the upper limit of normal), low serum haemoglobin, high corrected serum calcium (> 10 mg/dl) and time from initial RCC diagnosis to start of interferon-α (IFN-α) treatment of less than 1 year. Patients are then assigned to one of three risk groups according to the number of risk factors that they exhibit: those with zero risk factors are deemed to have favourable risk, those with one or two risk factors are categorised as having intermediate risk and those with three or more risk factors have poor risk. In a retrospective analysis of 463 patients with advanced RCC administered IFN as first-line therapy in six prospective clinical trials,[33] progression-free survival (PFS) was related to risk category with median time to death ranging from 30 months in the favourable group to 14 months in the intermediate group and 5 months in the group deemed to have poor risk.

Mortality

In 2006 there were 3099 deaths from kidney cancer in England and Wales. *Figure 3* shows the numbers of male and female deaths from kidney cancer (excluding cancer of the renal pelvis) in England and Wales in 2006.[5] Reflecting the incidence data there were more deaths in males than in females and the mortality rate was highest in those aged between 65 and 85 years.

As might be expected from the patterns of incidence of diagnosis of RCC (see Incidence) mortality rates have also been increasing. *Figure 4* shows the age-standardised (European) mortality rates for kidney cancer from 1971 to 2005. In 1971 the age-standardised mortality rate for kidney cancer in men was approximately 4.3 per 100,000 population; by 2005 this had risen to approximately 6 per 100,000 population.

Treatment

Medical treatment

Chemotherapy and hormone therapy

High levels of expression of the multiple drug resistance protein P-glycoprotein in RCC is one of the factors thought to explain the high level of resistance of RCC tumours to cytotoxic chemotherapy.[34,35]

The European Association of Urology (EAU) guidelines on RCC[21] recommend that

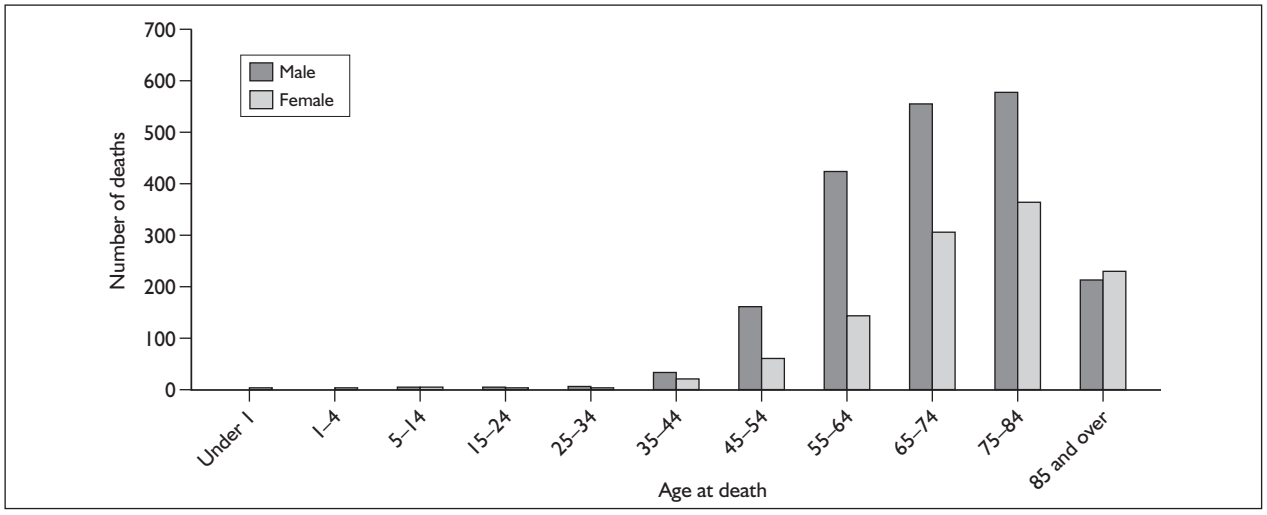

FIGURE 3 *Number of deaths from malignant neoplasm of the kidney excluding cancer of the renal pelvis (ICD-10 C64) by sex in England and Wales in 2006. Source: Office for National Statistics (www.statistics.gov.uk/downloads/theme-health/DR-2006/DR_06Mort-Stats.pdf).*

chemotherapy as monotherapy should not be considered as effective in patients with metastatic RCC.

A systematic review of systemic therapy for metastatic RCC,[36] published in 2000, identified 51 phase II trials in which 33 agents were studied in 1347 patients. The most extensively studied agents were floxuridine and fluorouracil, with response rates ranging from 0% to 20%. Vinblastine and hormonal agents such as medroxyprogesterone acetate have produced similarly disappointing results, as have combinations of chemotherapy and immunotherapy.[36]

Immunotherapy

Interferon-α is the immunotherapy agent most commonly used in England and Wales. The preferred option in the USA is high-dose interleukin-2 (IL-2). A recently updated Cochrane review[37] identified a total of 58 randomised clinical trials (total 6880 patients) in which immunotherapies had been used in the treatment of advanced RCC. Only one study had a placebo control arm although other therapies were used as controls, for example hormonal therapies, chemotherapy and nephrectomy. Four trials compared IFN-α with a non-immunotherapy control (vinblastine or medroxyprogesterone acetate) in patients with ECOG-PS from 0 to 2. The

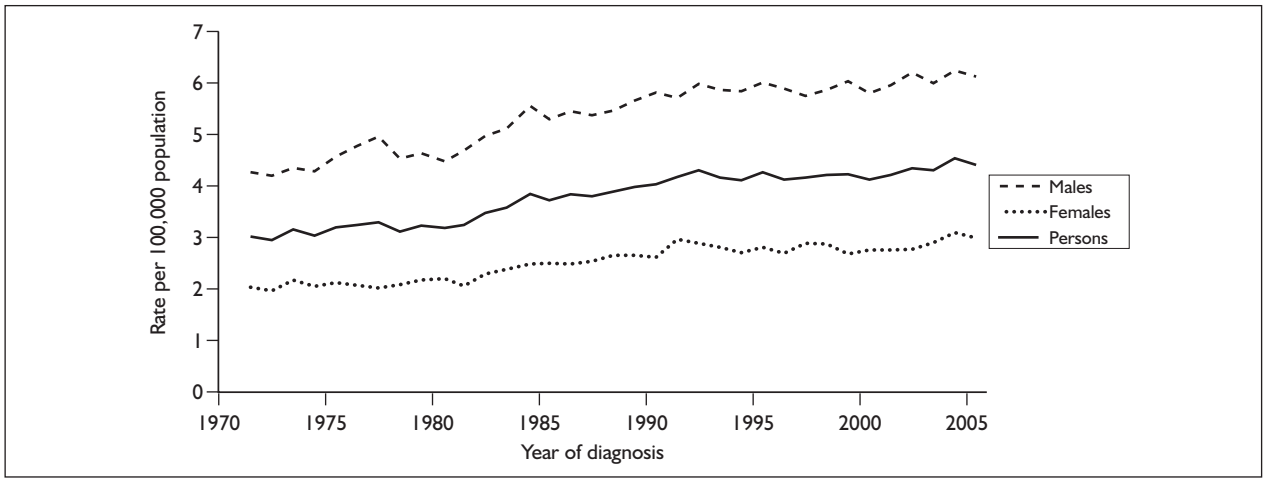

FIGURE 4 *Age-standardised (European) mortality rates for kidney cancer in the UK, 1971–2005. From* UK Kidney cancer statistics,[9] *with permission from Cancer Research UK (www.cancerresearchuk.org/cancerstats).*

pooled remission rate was 40/320 (12.5%) for IFN versus 5/324 (1.5%) for control treatments. The weighted average median survival was 3.8 months longer for IFN-α than for control treatments (11.4 versus 7.6 months).[37]

A phase III study[38] recently performed by the French Immunotherapy Intergroup (PERCY Quattro trial) in patients with intermediate prognosis (untreated patients with more than one metastatic site and a Karnofsky score of ≥ 80, and those with an intermediate prognosis for response to cytokine treatment) showed no improvement in median PFS or overall survival (OS) with use of cytokines alone or in combination when compared with a medroxyprogesterone acetate control. Survival was 14.9 months with medroxyprogesterone acetate, 15.2 months with IFN, 15.3 months with subcutaneous IL-2 and 16.8 months with IFN plus IL-2. Three-year survival in all groups was around 20%; 5-year survival was 10%. This confirms the findings of two case–control studies[39,40] that also demonstrated little benefit of cytokines in those who do not have good prognosis.

Response rates of between 7% and 27% have been demonstrated for IL-2.[41–43] Interestingly, a small subgroup (about 7%) of patients achieves long-term durable complete remissions with a high-dose IL-2 regimen.[44] Toxicity associated with IL-2 is substantially higher than that associated with IFN-α; high-dose IL-2 requires inpatient administration with intensive supportive care.[43] Commonly experienced adverse effects of both IFN-α and IL-2 include 'flu-like' symptoms, tiredness and depression.

Various combinations of cytokines have also been studied and, although there have been suggestions of improved response rates and PFS times, OS does not appear to be better than with monotherapy regimens.[45]

Surgical treatment

Surgical therapy is the principle potentially curative therapeutic approach for the treatment of RCC. The standard approach is radical nephrectomy, which includes removal of the entire kidney together with the Gerota's fascia. Removal of the ipsilateral adrenal gland and regional lymph nodes may also be necessary. Nephrectomy may also be performed in patients with metastatic disease. The combination of IFN-α and nephrectomy was shown to be superior to IFN-α alone in two studies in patients with metastatic RCC, one conducted in Europe[46] and the other in the USA.[47] Although there was no significant difference in remissions between groups in either study, OS was prolonged in both studies. When the results of both studies were combined, the weighted mean difference in median survival was 5.8 months (13.6 versus 7.8 months with or without initial nephrectomy respectively), with a lower risk of death in the first year for those having undergone initial nephrectomy.[48]

Recurrence and progression

As described earlier (see Prognosis) there are several scoring systems and algorithms that are used to stratify patients into groups of low, intermediate and high risk for developing tumour recurrence or metastases, and hence to predict prognosis and survival. EAU guidelines[21] recommend that, in patients classified as having intermediate and poor prognosis, intensive follow-up including CT scans at regular time intervals should be performed. A retrospective analysis of postoperative recurrence patterns,[49] published in 2005, reported that, amongst 194 patients with a diagnosis of RCC who had undergone complete surgical resection, recurrence occurred in 41 (21%). Mean time to recurrence was 17 months, with the tumour recurring within 2 years of surgery in 34 patients (83%). The lung was the most vulnerable site for recurrence.

Clinical trials frequently measure and report progression in terms of response to treatment as partial or complete remission according to standard criteria.[50–52] The RECIST (Response Evaluation Criteria in Solid Tumours) guidelines[51,52] were developed as a result of an international collaboration between the European Organisation of Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the USA and the National Cancer Institute of Canada Clinical Trials Group. The criteria provide a simplified, conservative method to compare imaging data and allow patients to be characterised within one of the following categories: complete response, partial response, progressive disease and stable disease (*Table 5*).

However, it should be noted that variability in the clinical course of metastatic RCC has been well documented and spontaneous remissions are known to occur.[53–55] In addition, the relationship between remission and OS is not clear,[37] and there is growing support for the use of PFS as a better marker of anticancer activity in this setting.

TABLE 5 *RECIST guidelines for categorising tumour response*

Category	Description
Complete response (CR)	Disappearance of all target lesions
Partial response (PR)	30% decrease in the sum of the longest diameters of target lesions
Progressive disease (PD)	20% increase in the sum of the longest diameters of target lesions or the appearance of new lesions
Stable disease (SD)	Small changes that do not meet the above criteria

Source: Therasse *et al*.[51]

Current service provision

The National Institute for Health and Clinical Excellence (NICE) manual on improving outcomes in urological cancers[56] recommends that all patients who are fit to undergo surgery (including those with metastatic disease) should be offered a radical nephrectomy (except those with small tumours). Patients with small tumours should be considered for nephron-sparing surgery. Surgery is often the only treatment needed for localised disease.

Treatment with immunotherapeutic agents (normally IFN-α in the UK) should be available for patients with metastatic disease. Thereafter, there is currently no standard NHS treatment for patients with metastatic RCC who do not respond to first-line immunotherapy, or those unsuitable for immunotherapy. The majority of patients diagnosed with RCC should be managed by local cancer teams. Referral to a specialist centre may be necessary for those whose tumours have or may have invaded the renal vein or vena cava, or whose tumours may involve the heart; those with limited metastatic disease that might be amenable to resection; those with bilateral disease or who require dialysis; and those with VHL disease or hereditary papillary tumours.[56]

Since the publication of these guidelines, results from several trials of immunotherapy for RCC have become available, which suggest that not all patients benefit equally from immunotherapy.[38–40] There is anecdotal evidence of variation in practice around the UK with some centres no longer treating patients considered to have a poor or intermediate prognosis with immunotherapy (expert advisory group, 2008, personal communication).

Quality of life

As there are currently no treatments that can reliably be expected to cure advanced RCC, relief of physical symptoms and maintenance of function are the primary objectives of medical interventions. There are several general quality of life instruments for people with cancer that can be used to assess quality of life both in clinical trials and in clinical practice, for example the Functional Assessment of Cancer Therapy (FACT) scale[57] and the EORTC QLQ-C30.[58] There are also several disease-specific instruments that have been used to evaluate symptoms of kidney cancer, for example the Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI)[59] and the FKSI disease-related symptoms (FKSI-DRS) subscale,[60] which was developed in an attempt to differentiate relief of disease-related symptoms from relief of symptoms experienced as a result of treatment. In a national cross-sectional study of adults with RCC in the USA,[61] the five most frequent symptoms among 31 patients with localised disease were irritability (79%), pain (71%), fatigue (71%), worry (71%) and sleep disturbance (64%). Approximately half of the patients in the survey had metastatic disease and reported fatigue (82%), weakness (65%), worry (65%), shortness of breath (53%) and irritability (53%) as the five most frequently experienced symptoms.

Despite the recognition that health-related quality of life (HRQoL) outcomes are important in this patient group, few clinical trials of new interventions have incorporated such measures (see Chapter 3).

Description of new interventions

Several new therapeutic agents have recently been developed for the treatment of advanced and/or metastatic RCC. The rationale for their development stems from the discovery that an early event in the development of an RCC tumour is inactivation of the VHL tumour suppressor gene. This can result in an increased concentration of hypoxia-inducible factor-1 (HIF-1), which in turn stimulates production of VEGF. VEGF [also known as vascular permeability factor (VPF)] is a dimeric glycoprotein and a member of the platelet-derived growth factor (PDGF) superfamily of growth factors, which are involved in the development of new vasculature from adjacent host blood vessels (angiogenesis) to allow for the transfer of oxygen and nutrition from the blood to the new cells that have formed. New blood vessels are essential for tumours to survive, grow and metastasise.[62] Preclinical models suggest that angiogenesis is necessary for tumour growth beyond one to two mm. Overexpression of VEGF, therefore, results in tumour growth and metastasis.[63–65]

The effects of VEGF are produced through activation of tyrosine kinase receptors on the cell surface, such as vascular endothelial growth factor receptors (VEGFR).[64]

Theoretically, therefore, inhibition of the VEGF and PDGF signalling pathways may reverse the pathological consequences of losing VHL protein function, disrupt the abnormal tumour blood vessels and consequently inhibit tumour progression or cause tumour cell death.[66]

The four new interventions considered in this assessment are summarised in *Table 6*.

Bevacizumab plus IFN-α

Pharmacology

Bevacizumab (Avastin®, Roche) is a humanised monoclonal antibody against all biologically active isoforms of VEGF. Once bound to VEGF, bevacizumab prevents VEGF from binding to its receptors on vascular endothelial and other cells, thus inhibiting angiogenesis, reducing tumour vascularisation and consequently inhibiting tumour growth and proliferation.[65,67,68]

Bevacizumab is administered as an intravenous infusion along with IFN treatment. The recommended dosage for advanced and/or metastatic RCC is 10 mg/kg of body weight given once every 2 weeks.

The antitumour activity of IFN-α is believed to result from stimulation of the immune response, direct antiproliferative effects, antiangiogenic effects and/or increased tumour antigen presentation.[68]

IFN-α is administered by subcutaneous injection three times per week, typically at a dose of 9–10 million units (MIU), and may be self-administered by patients.

Licensing

Bevacizumab received marketing authorisation for use as first-line therapy in combination with IFN-α in patients with advanced and/or metastatic RCC in December 2007.[69]

Adverse events

There are few published trials of bevacizumab in patients with advanced and/or metastatic RCC. However, it has also been studied in several other conditions, including colorectal cancer, breast cancer, non-small cell lung cancer and pancreatic

TABLE 6 *Summary of interventions*

Intervention	Licensed indication
Bevacizumab	First-line therapy in combination with interferon-α in patients with advanced and/or metastatic RCC
Sorafenib tosylate	First-line therapy in patients with advanced and/or metastatic RCC who are unsuitable for therapy with interferon-α or interleukin-2 and as second-line therapy in those with evidence of disease progression during cytokine-based treatment
Sunitinib	First- and second-line treatment of advanced and/or metastatic RCC
Temsirolimus	First-line treatment of patients with advanced RCC who have at least three of six poor prognostic risk factors

cancer. This wider application provides further insight into the toxicity of the agent.

Although reported adverse events suggest that bevacizumab has a generally acceptable risk–benefit profile in patients with advanced cancer, severe adverse effects have been reported. Potentially severe toxicities include hypertension, gastrointestinal perforation/wound healing complications, haemorrhage, thromboembolic events, proteinuria and congestive heart failure.[65]

Further discussion of adverse events associated with bevacizumab and IFN can be found in Chapter 2.

Cost

According to the *British National Formulary 55* (BNF55),[70] the cost of treatment with bevacizumab (10 mg/kg) plus IFN (9 MIU three times per week) for an 80-kg patient is £151.42 per day (exclusive of the costs of drug administration). Further discussion of the cost of bevacizumab plus IFN can be found in Chapter 3 (see Resource use/cost data inputs).

Sorafenib tosylate

Pharmacology

Sorafenib tosylate (Nexavar®, Bayer) is an orally administered bi-aryl urea that inhibits various tyrosine kinase receptors including VEGFR and platelet-derived growth factor receptors (PDGFR). Sorafenib may also inhibit Raf-1, a member of the mitogen-activated protein kinase (MAPK) intracellular signal transduction pathway [which comprises Raf, MAPK kinase (MEK) and extracellular signal-regulated kinase (ERK)], although whether appropriate concentrations are attained in patients is unclear. Sorafenib thus has two potential sites of action against tumour growth: by inhibiting VEGFR and PDGFR sorafenib is able to inhibit tumour progression and angiogenesis; and by interacting with Raf-1 kinase sorafenib may interrupt the Ras/Raf/MEK/ERK cascade pathway, which regulates cellular proliferation and survival.[71–75]

The recommended dose of sorafenib is 400 mg twice daily, taken either 1 hour before or 2 hours after food.

Licensing

Sorafenib tosylate has received marketing authorisation for use in patients with advanced and/or metastatic RCC as first-line therapy in those who are unsuitable for therapy with IFN-α or IL-2, and as second-line therapy in those with evidence of disease progression during cytokine-based treatment.

Adverse events

The most commonly reported adverse events associated with sorafenib treatment are dermatological effects including rash and hand–foot skin reactions. Further discussion of adverse events associated with sorafenib tosylate can be found in Chapter 2.

Cost

According to BNF55[70] the cost of sorafenib is £89.45 per day. Further discussion of the cost of sorafenib can be found in Chapter 3 (see Resource use/cost data inputs).

Sunitinib

Pharmacology

Sunitinib malate (Sutent®, Pfizer), formerly known as SU11248, is a novel, oral, multitargeted inhibitor of a group of closely related tyrosine kinase receptors [including VEGFR-1, -2 and -3, PDGFR-α and -β and stem cell factor receptor (KIT)] with antitumour and antiangiogenic activities.[66,76]

The recommended dose of sunitinib is one 50-mg dose orally taken daily for 4 consecutive weeks with a 2-week rest period, that is, a complete treatment cycle of 6 weeks. Dose modifications based on safety and tolerability may be applied but the total daily dose should not exceed 50 mg or decrease below 25 mg.[77] There is also some evidence from phase II trials that sunitinib may be effective at a continuous dose of 37.5 mg per day.[78]

Licensing

Sunitinib is licensed for use in the first- and second-line treatment of advanced and/or metastatic RCC.

Adverse events

The most commonly reported treatment-related adverse events (experienced by more than 20% of patients) in both treatment-naive and cytokine-refractory patients with metastatic RCC include fatigue, gastrointestinal disorders such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting, skin discolouration, dysgeusia (disruption of the sense of taste) and anorexia. Other adverse events include headache, hypertension, epistaxis,

hand–foot syndrome, dry skin, hair colour changes, pain in extremities, mucosal inflammation, thrombocytopenia, neutropenia and decline in left ventricular ejection fraction. Further discussion of the adverse events associated with sunitinib can be found in Chapter 2.

Cost

According to BNF55[70] the cost of sunitinib is £74.74 per day. Further discussion of the cost of sunitinib can be found in Chapter 3 (see Resource use/cost data inputs).

Temsirolimus

Pharmacology

Temsirolimus (Torisel®, Wyeth) is a selective inhibitor of the mammalian target of rapamycin (mTOR), a serine/threonine kinase which regulates a signalling cascade that controls growth factor-induced cell proliferation. Temsirolimus inhibits mTOR-dependent protein translation induced by growth factor stimulation of cells. Tumour growth may also be impaired indirectly as a result of inhibition of microenvironmental factors such as VEGF.[79–81]

Temsirolimus is administered intravenously. The recommended dose is 25 mg over a 30- to 60-minute period once weekly. Premedication with intravenous antihistamine is recommended to minimise the occurrence of allergic reactions.

Licensing

Temsirolimus was granted a marketing authorisation for the first-line treatment of patients with advanced RCC who have at least three of six poor prognostic risk factors.

Adverse events

The most commonly reported treatment-related adverse events of any grade associated with temsirolimus (experienced by more than 20% of patients) include asthenia, fever, abdominal pain, back pain, bleeding events such as epistaxis, gastrointestinal events including nausea, anorexia, diarrhoea and constipation, cardiovascular events including chest pain, anaemia, hyperlipidaemia, peripheral oedema, hyperglycaemia, hypercholesterolaemia, dyspnoea and increased cough and rashes.

Further discussion of the adverse events associated with temsirolimus can be found in Chapter 2.

Cost

The price of temsirolimus was not available at the time this report was prepared. Wyeth advised that the cost of a 30-mg vial was £515. Using this data the cost of temsirolimus was estimated as £73.57 per day (exclusive of drug administration costs). Further discussion of the cost of temsirolimus can be found in Chapter 3 (see Resource use/cost data inputs).

Current use of new interventions in the NHS

Anecdotal evidence suggests wide variations in the current uptake and availability of these interventions. In some areas of the UK the interventions are routinely available with all patients with metastatic RCC being offered sunitinib as first-line therapy; in other areas the interventions are not currently available to any patients.

Definition of the decision problem

The purpose of this report is to assess the clinical effectiveness and cost-effectiveness of bevacizumab combined with IFN, sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic RCC.

Interventions

The four interventions are considered in accordance with their marketing authorisations in two clinical settings:

- first-line therapy with bevacizumab plus IFN-α
- first-line therapy with sunitinib
- first-line therapy with sorafenib tosylate
- first-line therapy with temsirolimus
- second-line therapy with sorafenib tosylate
- second-line therapy with sunitinib.

Populations including subgroups

The relevant population for first-line therapy is people with untreated advanced and/or metastatic RCC. The relevant population for second-line therapy is people with advanced and/or metastatic RCC whose cancer has progressed during or after previous cytokine-based treatment. We also considered the following subgroups:

- patients who have/have not undergone surgical resection of the primary tumour
- patients diagnosed with clear cell and non-clear cell carcinoma.

The assessment is required to consider the interventions in relation to their marketing authorisations. Suitability for treatment with immunotherapy in this context is therefore defined in terms of contraindication to treatment, with patients defined as being 'unsuitable for treatment with immunotherapy' having clinical contraindications to therapy, for example autoimmune disease or a history of depression. We are aware that there is variation around the UK in the consideration of patients with intermediate and poor prognosis for treatment with IFN. In some centres such patients are offered treatment with IFN whereas in others they are considered to be 'unsuitable' for treatment with IFN and best supportive care (BSC) becomes their only treatment option. We have not considered that patients defined as having an intermediate or poor prognosis are 'unsuitable' for treatment with immunotherapy.

Relevant comparators

The interventions are compared with current standard treatments. This represents a deviation from the protocol (26 October 2007) in which we proposed to compare first-line therapies with BSC in patients who are suitable for treatment with immunotherapy. Following extensive appraisal of existing literature we re-evaluated the potential benefit of performing this analysis (which would have entailed a full analysis of the clinical effectiveness and cost-effectiveness of IFN compared with BSC) and concluded that to use current standard treatment as the relevant comparator in all cases was more appropriate. We had intended to consider both IFN-α and IL-2 as potential immunotherapy treatments. However, because of a lack of published evidence, and anecdotal evidence that IL-2 is not widely used in the UK, we have considered only IFN-α.

The relevant comparators are therefore as follows:

- first-line therapy:
  - in patients who are suitable for treatment with immunotherapy: immunotherapy (IFN-α) alone
  - in patients who are not suitable for treatment with immunotherapy: BSC
  - in patients with three or more of six poor prognostic factors: immunotherapy (IFN-α) alone
- second-line therapy:
  - BSC.

For all indications we have also considered the validity of indirect comparisons between interventions when appropriate.

Outcomes

Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus are assessed in terms of the following outcomes:

- overall survival
- progression-free survival
- tumour response rate
- adverse events/toxicity
- health-related quality of life
- cost-effectiveness and cost–utility.

Overall aims and objectives of the assessment

This project will review the evidence for the effectiveness and cost-effectiveness of bevacizumab plus IFN-α, sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic RCC according to their marketing authorisations. The assessment will look at first- and second-line use of the interventions (when appropriate) and will draw together the relevant evidence to try and determine what, if any, are the incremental cost-effective benefits of the interventions compared with current standard treatment.

More fully, the policy questions to be addressed are:

- First-line therapy:
  - In those who are suitable for treatment with immunotherapy, what is the clinical effectiveness and cost-effectiveness of bevacizumab plus IFN versus IFN alone and sunitinib versus IFN alone as first-line therapy?
  - In those who are not suitable for treatment with immunotherapy, what is the clinical effectiveness and cost-effectiveness of sorafenib tosylate and sunitinib as first-line therapy, using BSC as a comparator?
  - In those with three or more of six poor

prognostic factors, what is the clinical effectiveness and cost-effectiveness of bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and BSC as first-line therapy, using IFN as a comparator?

- Second-line therapy:
  - In those in whom treatment with cytokine-based immunotherapy has failed, what is the clinical effectiveness and cost-effectiveness of sorafenib tosylate and sunitinib as second-line therapy, using BSC as a comparator?

Confidential information

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 2

Assessment of clinical effectiveness

Methods for reviewing effectiveness

The clinical effectiveness of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus was assessed by a systematic review of published research evidence. The review was undertaken following the general principles published by the NHS Centre for Reviews and Dissemination (CRD).[82]

Identification of studies

The Cochrane Library (2007 Issue 3) [including Cochrane Database of Systematic Reviews (CDSR), CENTRAL and Health Technology Assessment (HTA) database], MEDLINE, EMBASE, Science Citation Index, ISI Proceedings and BIOSIS were searched for systematic reviews of randomised controlled trials (RCTs) and single RCTs in September/October 2007. No language restrictions were imposed. Bibliographies of included studies were searched for further relevant studies. Individual conference proceedings from 2006 and 2007 [American Society of Clinical Oncology (ASCO) and European Cancer Organisation (ECCO)] were searched using their online interface. All searches were rerun in February 2008. Full details of the search strategies are presented in Appendix 1. All references were managed using REFERENCE MANAGER (Professional Edition, version 11; Thomson ISI ResearchSoft) and Microsoft ACCESS 2003 software.

Relevant studies were identified in two stages. Two reviewers (JTC and ZL) independently examined all titles and abstracts. Full texts of any potentially relevant studies were obtained. The relevance of each paper was assessed (JTC and ZL) independently according to the inclusion and exclusion criteria and any discrepancies resolved by discussion. The level of agreement between reviewers on selection decisions was not formally assessed.

Inclusion and exclusion criteria

Randomised controlled trials (RCTs) were included if they compared any of the interventions with any of the comparators (see Chapter 1, Definition of the decision problem) in participants with advanced and/or metastatic RCC. Primary outcomes were OS and PFS. Secondary outcomes were tumour response rate, adverse events/toxicity and HRQoL. Only trials that reported at least one of the primary outcomes were included in the review. In trials in which patients were allowed to cross from comparator to active treatment following demonstration of efficacy in interim analyses we have only considered data collected before treatment crossover as this provides the least biased estimate of treatment effect size. The use of data from phase II studies and non-randomised studies was only considered when there was insufficient evidence from good quality RCTs. Conference abstracts were included if there was sufficient detail to assess quality or if they reported updated results of included trials.

Data extraction strategy

Data were extracted by one reviewer (ZL) using a standardised data extraction form in Microsoft ACCESS 2003 and checked independently by a second (JTC). Disagreements were resolved by discussion, with involvement of a third reviewer if necessary. Data extraction forms for each included study are included in Appendix 2.

Quality assessment strategy

The methodological quality of the studies was assessed according to criteria specified by the CRD.[82] Quality was assessed by one reviewer and judgements were checked by a second. Any disagreement was resolved by discussion, with involvement of a third reviewer as necessary. The level of agreement between reviewers on validity decisions was not formally assessed.

Methods of data synthesis

Details of the extracted data and quality assessment for each individual study are presented in structured tables and as a narrative description. Any possible effects of study quality on the effectiveness data are discussed. Survival data (OS and PFS) are presented as hazard ratios (HRs) when available.

When data on head-to-head comparisons between interventions were not available we considered the feasibility of performing adjusted indirect comparisons using an adaptation of the method described by Bucher and colleagues.[83] This method aims to overcome potential problems of simple direct comparison (i.e. comparison of simple arms of different trials) in which the benefit of randomisation is lost, leaving the data subject to the biases associated with observational studies. The method is only valid when the characteristics of patients are similar between the different studies being compared. Further details of the methods used can be found in Appendix 3.

Handling company submissions to NICE

All of the clinical effectiveness data included in the company submissions were assessed. When these met the inclusion criteria and had not already been identified from published sources they were included in the systematic review of clinical effectiveness.

Understanding the results from the clinical trials

Most of the clinical trials in which the efficacy of these interventions has been evaluated report results in terms of HRs, the ratio of hazard rates in two groups. The hazard rate describes the number of events per unit time per number of people exposed (i.e. the slope of the survival curve, or the instantaneous rate of events in the group). The treatment group hazard rate divided by the control group hazard rate is called the HR. A HR of one suggests that there is no difference between the two groups of patients. A HR of greater than one indicates that the event is happening faster in the treatment group than in the control group and a HR of less that one indicates that the event of interest is happening more slowly in the treatment group than in the control group.

Most trials report toxicities using the National Cancer Institute Common Terminology Criteria (NCI-CTC) (*Table* 7). For each adverse event, grades are assigned using a scale from 0 to 5. Grade 0 is defined as absence of adverse event or within normal limits for values. Grade 5 is defined as death associated with an adverse event.[84]

Results of clinical effectiveness

The results of the assessment of clinical effectiveness will be presented as follows:

- an overview of the quantity and quality of available evidence including a table summarising all included trials and a summary table of key quality indicators
- a critical review of the available evidence for each of the stated research questions, including:
  - the quantity and quality of available evidence
  - a summary table of the study characteristics
  - a summary table of the baseline population characteristics
  - comparison of the baseline populations in the included trials
  - study results presented in narrative and tabular form
  - comparison of the results in terms of effectiveness and safety.

TABLE 7 *National Cancer Institute Common Terminology Criteria (NCI-CTC) for adverse events*

Grade	Description
0	No adverse event or within normal limits
1	Mild adverse event
2	Moderate adverse event
3	Severe and undesirable adverse event
4	Life-threatening or disabling adverse event
5	Death related to an adverse event

Source: National Cancer Institute.[84]

Quantity and quality of research available

Number of studies identified

The electronic searches retrieved a total of 888 titles and abstracts. A total of 20 conference abstracts updating the results of included studies were located following hand searching of individual conference proceedings. No additional papers were found by searching the bibliographies of included studies. In total, 832 papers were excluded on title and abstract. Full text of the remaining 56 papers was requested for more in-depth screening. The updated searches retrieved an additional 166 titles and abstracts. No further full-text trials were identified; we found one paper updating the results of an included trial.[85] The process of study selection is shown in *Figure 5*.

Number of studies excluded

Papers were excluded for at least one of the following reasons: duplicate publications, narrative reviews, uncontrolled studies (when evidence from controlled trials was available for the research question) and publications (systematic reviews and individual studies) not considering relevant intervention, population, comparison or outcomes. The bibliographic details of studies retrieved as full papers and subsequently excluded, along with the reasons for their exclusion, are detailed in Appendix 4.

Number and description of included studies

Eight clinical trials reported in 13 publications met our inclusion criteria. A total of 20 conference abstracts[86–105] relating to the included trials were also located by hand searching and considered. All included citations are detailed in *Table 8*. A summary of the quality assessment of the studies is shown in *Table 9*.

We were unable to identify any suitable data on clinical effectiveness in the following areas:

- in patients unsuitable for treatment with immunotherapy we found no suitable data on sorafenib, sunitinib or BSC
- in patients with poor prognosis we found no data on sorafenib
- we were unable to locate any randomised clinical trials of sunitinib as second-line therapy
- we were unable to locate any randomised clinical trials of any of the interventions in comparison with IL-2.

Because of the lack of evidence on the use of IL-2 in these patients, and following consultation with our expert advisory group, who confirmed that IFN-α is the predominant immunotherapy treatment in use in the UK, we have assumed that treatment with immunotherapy will be with IFN-α.

Bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy

In this section we address research question 1: In those who are suitable for treatment with immunotherapy what is the clinical effectiveness of bevacizumab plus IFN and sunitinib as first-line therapy, using IFN as a comparator?

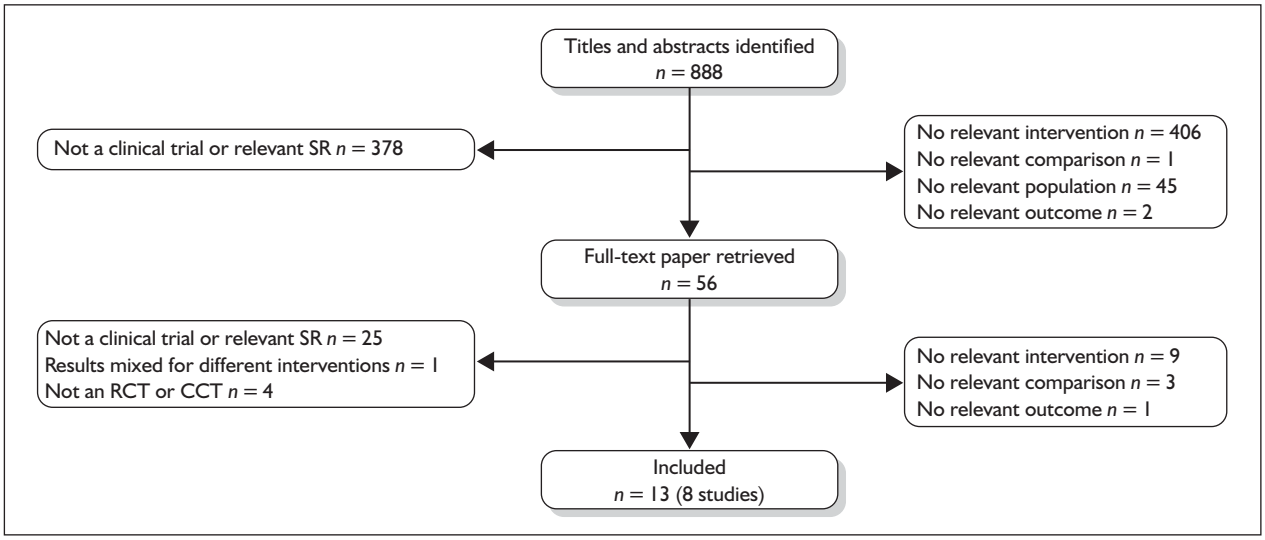

FIGURE 5 *Summary of study selection. CCT, controlled clinical trial; SR, systematic review.*

TABLE 8 *Summary information of all included studies by research question*

Study	Year published	Study type	*n*	Intervention	Comparator	Supplementary publications
Bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy						
Escudier *et al.*[106]	2007	R, DB, PC, phase III, international, multicentre	649	Bevacizumab + IFN-α-2a (IFN)	Placebo + IFN-α-2a	86, 107–110
Motzer *et al.*[107]	2007	R, BR, C, phase III, international, multicentre	750	Sunitinib	IFN-α-2a (IFN)	87, 88, 91–93, 104
Rini *et al.*[101]	2008	RCT, no further details available	732	Bevacizumab + IFN-α (IFN)	IFN-α	68
Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and BSC compared with IFN as first-line therapy in people with poor prognosis						
Hudes *et al.*[108]	2007	R, O, C, phase III, international, multicentre	626	Temsirolimus, temsirolimus + IFN-α-2a	IFN-α-2a	89, 94–97
Sorafenib and sunitinib compared with BSC as second-line therapy						
Escudier *et al.*[109]	2007	R, DB, PC, phase III, international, multicentre	903	Sorafenib	Placebo	98, 99, 102, 103, 114
Ratain *et al.*[110]	2006	RDT, retrospective BR, phase II, multicentre, international	202 (65 randomly assigned)	Sorafenib	Placebo	
Motzer *et al.*[111]	2006	O, single arm, phase II, multicentre, US	106	Sunitinib	N/A	85, 90, 100
Motzer *et al.*[112]	2006	O, single arm phase II, multicentre, US	63	Sunitinib	N/A	100

BR, independent (blind) central review of radiological images used to assess primary outcome; C, controlled; DB, double blind; N/A, not applicable; O, open; PC, placebo controlled; R, randomised; RDT, randomised discontinuation study.

Quantity, quality and characteristics of included studies

We identified three RCTs that are relevant to this question. A summary of the quality assessment of the studies is shown in *Table 9*; study characteristics are summarised in the following section and in *Table 55* in Appendix 5.

Study characteristics

Bevacizumab plus IFN versus IFN

Escudier and colleagues[106] report the results of the AVOREN study, an international (Australia, Belgium, Czech Republic, Finland, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, Singapore, Spain, Switzerland and Taiwan) and UK multicentre double-blind and placebo-controlled phase III RCT in which 649 patients with confirmed clear cell metastatic RCC were randomised to receive either bevacizumab and IFN or placebo and IFN. The trial has been reported in one full publication[106] and in five abstracts.[86,113–116] The aim of the study was to determine whether first-line bevacizumab plus IFN improves efficacy compared with IFN alone. Primary outcomes were OS and PFS. Overall response rate and safety were secondary outcomes. The study was designed to have 80% power for the log-rank test to detect an improvement in OS with an HR of 0.76, assuming an improvement in median survival from 13 months to 17 months, at a two-sided alpha level of 0.05. One interim analysis was planned, based on 250 deaths, after which the study was unblinded and patients in the IFN arm who had not progressed were offered bevacizumab plus IFN.

To be eligible for entry into the trial participants had to have a diagnosis of predominantly (> 50%) clear cell RCC based on routine assessment of

TABLE 9 *Summary of quality assessment – all included trials*

Study design	Escudier et al. 2007[106] RCT	Motzer et al. 2007[107] RCT	Rini et al. 2004[68,101] RCT	Hudes et al. 2007[108] RCT	Escudier et al. 2007[109] RCT	Ratain et al. 2006[110] RDT	Motzer et al. 2006[111] Single arm	Motzer et al. 2006[112] Single arm
Is a power calculation provided?	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes
Is the sample size adequate?	Yes	Yes	?	Yes	Yes	?	Yes	Yes
Was ethical approval obtained?	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes
Were the study eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the eligibility criteria appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were patients recruited prospectively?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was assignment to the treatment groups really random?	Yes	Yes	?	Yes	Yes	Yes	N/A	N/A
Was the treatment allocation concealed?	Yes	N/A	?	N/A	?	?	N/A	N/A
Were adequate baseline details presented?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Were the participants representative of the population in question?	Yes	Yes	?	Yes	Yes	Partial	Yes	Yes
Were the groups similar at baseline?	Yes	Yes	?	Yes	Yes	Yes	N/A	N/A
Were baseline differences adequately adjusted for in the analysis?	No	Yes	?	No	Yes	No	N/A	N/A
Were the outcome assessors blind?	Yes	Yes	?	Yes	Yes	Yes	N/A	N/A
Was the care provider blind?	Yes	No	?	No	Yes	Yes	N/A	N/A
Are the outcome measures relevant to the research question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is compliance with treatment adequate?	?	Yes	?	Yes	?	?	?	?
Are withdrawals/dropouts adequately described?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Are all patients accounted for?	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes
Is the number randomised reported?	Yes	Yes	No	Yes	Yes	Yes	N/A	N/A
Are protocol violations specified?	Yes	Yes	No	Yes	No	Yes	No	No
Are data analyses appropriate?	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes
Is analysis conducted on an ITT basis?	Partial	Partial	?	Partial	Yes	Partial[a]	Yes	Yes
Are missing data appropriately accounted for?	?	Partial	?	Partial	Partial	Partial	Yes	Yes
Were any subgroup analyses justified?	Yes	Yes	?	Yes	Yes	Yes	N/A	N/A
Are the conclusions supported by the results?	Yes	Yes	?	Yes	Yes	Yes	Partial	Partial

?, unclear or unknown; ITT, intention to treat; N/A, not applicable; RDT, randomised discontinuation study.
a For the randomly assigned patients.

tumour histopathology and were also required to have undergone nephrectomy or partial nephrectomy (if resection margins were clearly negative of disease), to have a Karnofsky performance score of 70% or more, to have normal hepatic, haematopoietic and renal function and to have received no previous systemic therapy for RCC.

Randomisation was performed centrally and patients were stratified according to country and MSKCC risk group. Patients were randomly assigned to receive bevacizumab (10 mg/kg body weight, delivered intravenously once every 2 weeks) ($n = 327$) or placebo ($n = 322$) plus IFN-α-2a (9 MIU, delivered subcutaneously three times per week for a maximum of 52 weeks). Treatment was continued until evidence of disease progression, the patient experienced unacceptable toxicity, or withdrawal of consent. No dose reduction of bevacizumab/placebo was allowed. A starting dose of IFN of less than 9 MIU was permitted as long as the full dose was reached within the first 2 weeks of treatment. Dose reduction to 6 MIU or 3 MIU was allowed to manage adverse events of grade 3 or higher that were attributable to IFN.

Median follow-up at data cut-off was 13.3 months (range 0–25.6 months) in the bevacizumab plus IFN group and 12.8 months (range 0–24.2 months) in the control group. Median duration of bevacizumab treatment was 9.7 months (range 0–24.4 months) in the bevacizumab plus IFN group, and median duration of placebo treatment was 5.1 months (range 0–24.0 months) in the control group. Median duration of IFN treatment was 7.8 months (range 0–13.9 months) in the bevacizumab plus IFN group and 4.6 months (range 0.2–12.6 months) in the control group.

Median bevacizumab/placebo dose intensity was 92% (range 24–112%; mean 88%) in the bevacizumab plus IFN arm and 96% (range 39–110%; mean 89%) in the IFN only arm.

No substantial additional clinical effectiveness data were located in the related conference abstracts on this study[86,113–116] or in the company submission for bevacizumab.[117]

Rini and colleagues[101] report the results of the Cancer and Leukaemia Group B (CALGB 90206) phase III, open-label trial of bevacizumab plus IFN versus IFN conducted in 732 patients with previously untreated metastatic clear cell RCC. Patients were randomised to receive either bevacizumab (10 mg/kg intravenously every 2 weeks) plus IFN (9 MIU subcutaneously three times weekly) or IFN alone. Randomisation was stratified by prior nephrectomy and MSKCC risk category. The primary end point was OS. Secondary end points were PFS, response rate (according to RECIST criteria) and safety. The trial was designed with 86% power to detect a difference in the HR of 30% assuming a two-sided significance level of 0.05. Preliminary results were reported at the ASCO Genitourinary Cancers Symposium in February 2008.[68,101]

We considered the validity of pooling the data from the two studies of bevacizumab plus IFN; however, as the study by Rini and colleagues is available only in abstract form, several key pieces of information were missing [e.g. the number of patients randomised to each group, the method for assessing progression, whether the analysis was carried out on an intention-to-treat (ITT) basis] and we were unable to fully assess the quality of the study. The authors were contacted to request additional data but were unwilling to comply. We were therefore unable to pool the data.

Sunitinib versus IFN

Motzer and colleagues[107] report the results of an international (Australia and USA), multicentre, phase III RCT in which 750 patients with metastatic RCC were randomised to receive either sunitinib or IFN. The trial has been reported in one full publication[107] and in five abstracts.[87,88,91–93]

The aim was to assess the efficacy of first-line treatment with sunitinib compared with IFN-α in the treatment of metastatic RCC. The primary outcome was PFS, defined as the time from randomisation to the first documentation of objective disease progression or to death from any cause, whichever came first. Secondary end points included the objective response rate, OS, quality of life outcomes and safety. The study was designed to have 90% power for the log-rank test to detect a clinically relevant increase in PFS from 4.7 to 6.2 months in patients treated with sunitinib, at a two-sided alpha level of 0.05.

To be eligible for entry into the trial participants had to have a diagnosis of metastatic RCC with a clear cell histological component confirmed by the participating centres. Patients also had to have measurable disease, an ECOG-PS of 0 or 1 and adequate haematological, hepatic, renal and cardiac function.

Patients were stratified according to baseline levels of lactate dehydrogenase, ECOG-PS and previous nephrectomy and randomly assigned to receive sunitinib (50 mg once daily, orally) in 6-week cycles (4 weeks on, 2 weeks off) or interferon-α-2a (Roferon-A®, Roche) (9 MIU three times per week, subcutaneously). Treatment was continued until evidence of disease progression, the patient experienced unacceptable toxicity, or withdrawal of consent. Dose reductions (sunitinib to 37.5 mg and then 25 mg per day and IFN to 6 MIU and then 3 MIU three times per week) were permitted to allow management of severe adverse events.

Three scheduled interim analyses were planned. The paper by Motzer and colleagues[107] published in 2007 provides the results of the second analysis, after which the study was unblinded. This paper states that, at this time point, patients in the IFN group with progressive disease (PD) were allowed to cross over into the sunitinib group. This analysis therefore provides the most complete results for the randomised population. It is not clear why patients with PD were offered further treatment as according to the protocol all treatment would be stopped on evidence of disease progression.

The median duration of treatment was 6 months (range 1–15 months) in the sunitinib group and 4 months (range 1–13 months) in the IFN group. Reasons for discontinuing treatment were PD (25% and 45% in the sunitinib and IFN groups respectively), adverse events (8% and 13% respectively), withdrawal of consent (1% and 8% respectively) and protocol violation (< 1% in each group). Dose intensity was not reported in the full-text paper. In the company submission, Pfizer report a relative dose intensity (total dose administered/total dose assigned multiplied by 100) of 86.40% for sunitinib and 83.10% for interferon, which is cited as originating from the trial of sunitinib versus IFN.[107] No further details are provided.

Assessment of study quality

Bevacizumab plus IFN versus IFN

The AVOREN trial reported by Escudier and colleagues[106] is a good quality, randomised, phase III trial. The evaluation of the trial in relation to study quality is shown in *Table 9*. Allocation concealment, details of randomisation methods and withdrawals were all adequately reported. The study is described as 'double blind', although it is unclear whether all members of the study team were blinded (e.g. patient, pharmacist, doctor and assessor).

The CALGB trial[101] has only been reported in abstract form and as such there are not sufficient details to adequately assess the quality of the data.

Sunitinib versus IFN

The study assessing sunitinib versus IFN is a large, good quality, international, multicentre, randomised, phase III study.[107] Although it was not possible to double blind the study because of the differences in route of administration, the assessments of the primary outcome measure and objective response rate were performed by a central and blinded review of radiological images. Further details of the quality assessment can be found in *Table 9*.

Population baseline characteristics

Bevacizumab plus IFN versus IFN

At baseline in the AVOREN study[106] the two treatment groups were well matched in terms of demographic characteristics and disease status (Karnofsky performance status, MSKCC risk group and the location of metastases) (*Table 10*).

As the trial by Rini and colleagues[101] has only been reported in abstract format, few details of the population characteristics at baseline are available. Overall, 85% of patients had undergone previous nephrectomy, and 26% were assessed as having favourable prognostic risk, 64% had intermediate risk and 10% had poor risk. No further details are provided.

Sunitinib versus IFN

At baseline in the study by Motzer and colleagues[107] the two treatment groups were well matched in terms of demographic characteristics and disease status (ECOG-PS, MSKCC risk factors, the number of patients with a previous nephrectomy and the number and sites of metastases) (*Table 10*).

Comparability of baseline population characteristics between trials

Participants in the two main trials[106,107] were similar in terms of age, gender distribution, RCC pathology (predominantly clear cell), the proportion that had previously undergone nephrectomy or partial nephrectomy (100% versus 90% for the bevacizumab plus IFN and sunitinib trials respectively), the number with metastatic RCC and the profile of prognosis according to MSKCC criteria (approximately 30% of patients have favourable prognosis, 60% intermediate and 10% poor). Although performance status was evaluated using different instruments, patients appear comparable, with the majority of patients

TABLE 10 *Population baseline characteristics: bevacizumab plus IFN and sunitinib versus IFN as first-line therapy*

	Escudier *et al.* 2007[106]		Motzer *et al.* 2007[107]	
Intervention	**Bevacizumab + IFN**	**IFN + placebo**	**Sunitinib**	**IFN**
Number randomised	327	322	375	375
Diagnosis	Predominantly (> 50%) clear cell RCC		Metastatic clear cell RCC	
Age (years), median (range)	61 (30–82)	60 (18–81)	62 (27–87)	59 (34–85)
Male, *n* (%)	222 (68)	234 (73)	267 (71)	267 (72)
ECOG-PS, n (%):				
0	Not reported	Not reported	231 (62)	229 (61)
1			144 (38)	146 (39)
Karnofsky performance status, n (%):				
100	144 (44)	124 (39)	Not reported	Not reported
90	105 (32)	126 (39)		
80	58 (18)	50 (16)		
70	20 (6)	22 (7)		
MSKCC risk factors, n (%):				
0 (favourable)	87 (27)	93 (29)	143 (38)	121 (32)
1–2 (intermediate)	183 (56)	180 (56)	209 (56)	212 (57)
≥ 3 (poor)	29 (9)	25 (8)	23 (6)	25 (7)
Not available	28 (9)	24 (7)	–	17 (5)
n (%) patients with a previous nephrectomy	327 (100)	322 (100)	340 (91)	355 (89)
n (%) patients with previous radiation therapy	Not reported	Not reported	53 (14)	54 (14)
n (%) patients with metastatic RCC	327 (100)	322 (100)	375 (100)	375 (100)
Number of metastases sites, n (%):				
1	Not reported	Not reported	55 (15)	72 (19)
2			106 (28)	112 (30)
≥ 3			214 (57)	191 (51)
Location of metastases, n (%):				
Bone	58 (18)[a]	65 (20)[a]	112 (30)	112 (30)
Liver	57 (18)[a]	56 (19)[a]	99 (26)	90 (24)
Lung	192 (62)[a]	179 (59)[a]	292 (78)	298 (79)
Lymph nodes	107 (34)[a]	107 (36)[a]	218 (58)	198 (53)

a Based on *n* = 312 in the bevacizumab + IFN group and *n* = 301 in the placebo + IFN group.

(61%) in the bevacizumab plus IFN trial being assessed as ECOG-PS 0, which equates to 'fully active, able to carry on all predisease performance without restriction', and 69% of patients in the sunitinib trial having a Karnofsky performance status of 100 ('normal, no complaints, no sign of disease') or 90 ('capable of normal activity, few symptoms or signs of disease').

Assessment of clinical effectiveness

Overall survival (*Table 11*)

Bevacizumab plus IFN versus IFN

Overall survival, defined as the time between the date of randomisation and death from any cause, was the primary end point in the AVOREN trial.[106] The analysis was performed on an ITT basis with patients without an event being censored on the

TABLE 11 *Summary of overall survival: bevacizumab plus IFN and sunitinib versus IFN as first-line therapy*

Study	Intervention	*n*	Median OS (months)	HR	95% CI for HR	*p*-value
Escudier *et al*. 2007[106]	Bevacizumab + IFN	327	Not reached	0.79[a]	0.62 to 1.02[a]	0.0670[a]
	Placebo + IFN	322	19.8			
Motzer *et al*. 2007[107]	Sunitinib	375	Not reached	0.65	0.45 to 0.94	0.02[b]
	IFN	375	Not reached			

a These results are for the unstratified analysis. A preplanned exploratory analysis stratified by MSKCC risk group and region produced a similar result.
b Did not reach the prespecified level of significance for the interim analysis.

day of the last follow-up assessment or the last day of study drug administration if no follow-up assessment was carried out. At the time of data cut-off, only 251 (56%) of the 445 deaths required for the final analysis of OS to be powered adequately had occurred. Median OS had not been reached in the bevacizumab plus IFN group and was 19.8 months in the IFN group, with a HR of 0.79 (95% CI 0.62 to 1.02; $p = 0.0670$). A preplanned exploratory analysis stratified by MSKCC risk group and region produced a similar result [HR 0.75 (95% CI 0.58 to 0.97; $p = 0.02670$)]. Analysis of OS stratified according to baseline MSKCC risk groups was similar to the unstratified analysis with HRs of 0.69 (95% CI 0.36 to 1.33), 0.74 (95% CI 0.53 to 1.02) and 0.87 (95% CI 0.48 to 1.56) for the favourable, intermediate and poor prognosis groups respectively.

Data on OS from the CALGB trial[101] are still pending.

Sunitinib versus IFN

At the time of analysis, median OS had not been reached in either group: 13% of patients in the sunitinib group and 17% in the IFN group had died. There was an improved OS with sunitinib, with a HR for death of 0.65 (95% CI 0.45 to 0.94; $p = 0.02$); the comparison did not meet the prespecified level of significance for the interim analysis.[107]

Progression-free survival (*Table 12*)

In all three studies PFS was defined as the time between randomisation and first documented disease progression or death due to any cause and was reported as median duration.

Bevacizumab plus IFN versus IFN

In the AVOREN study,[106] according to ITT analysis there was a statistically significant benefit in terms of median PFS observed for the bevacizumab plus IFN group (10.2 months) compared with the IFN and placebo group (5.4 months) [HR 0.63 (95% CI 0.52 to 0.75; $p = 0.0001$)]. An analysis stratified by MSKCC risk group and region confirmed these results [HR 0.61 (95% CI 0.51 to 0.73; $p < 0{\cdot}0001$)]. A test of interaction indicated that the treatment effect was consistent across the MSKCC risk groups ($p = 0.508$).

In the CALGB study[101] the method of assessing progression was not reported in the abstract. Median time to progression was 8.5 months in patients receiving bevacizumab plus IFN and 5.2 months in the group receiving IFN alone. The stratified estimate of the HR was 0.71 (95% CI 0.61 to 0.83; $p < 0.0001$). Further details of the analysis are not yet available.

Sunitinib versus IFN

Progression-free survival (primary end point) was assessed by blinded central review of imaging studies.[107] There was a statistically significant difference in PFS in patients receiving sunitinib (11 months; 95% CI 10 to 12 months) compared with those receiving IFN (5 months; 95% CI 4 to 6 months) corresponding to a HR of 0.42 (95% CI 0.32 to 0.54; $p < 0.001$). Similar results from the investigators' unblinded assessment of radiological images [11 months versus 4 months; HR 0.42 (95% CI 0.33 to 0.52; $p < 0.001$)] are also reported.

Tumour response (*Table 13*)

In all three studies tumour response was assessed according to RECIST criteria, based on patients with measurable disease at baseline. Responses were confirmed by a second assessment 4 weeks or more after the first response was recorded.

TABLE 12 *Summary of progression-free survival: bevacizumab plus IFN and sunitinib versus IFN as first-line therapy*

Study	Intervention	*n*	Median PFS (months)	HR	95% CI for HR	*p*-value
Escudier *et al*. 2007[106]	Bevacizumab + IFN	327	10.2	0.63	0.52 to 0.75	< 0.0001
	Placebo + IFN	322	5.4			
Rini *et al*. 2008[101]	Bevacizumab + IFN	NR	8.5[a]	0.71[a]	0.61 to 0.83[a]	< 0.0001[a]
	IFN	NR	5.2[a]			
Motzer *et al*. 2007[107]	Sunitinib	375	11[b]	0.42[b]	0.32 to 0.54[b]	< 0.001[b]
	IFN	375	5[a]			

NR, not reported.
a Preliminary results available in abstract form only; total number of patients in trial = 732.
b Results from independent central review of imaging studies.

Bevacizumab plus IFN versus IFN

In the AVOREN trial[106] tumour response was assessed by the investigators every 8 weeks up to 32 weeks and every 12 weeks thereafter until disease progression. At the time of analysis the overall number of patients in whom a tumour response was measured was significantly greater ($p = 0.0001$) in the bevacizumab plus IFN group ($n = 96$; 31%) than in the IFN group ($n = 37$; 13%). A small number of patients in both groups were assessed as having a complete response to treatment (four versus six in the bevacizumab plus IFN and IFN groups respectively), and 92 patients (30%) receiving bevacizumab plus IFN and 31 patients (11%) in the IFN group experienced a partial response to treatment (defined as a 30% decrease in the sum of the longest diameters of target lesions).

Few details are provided in the abstract describing the CALGB study.[101] The objective response rate was significantly ($p \leq 0.0001$) higher in patients receiving bevacizumab plus IFN [25.5% (95% CI 20.9% to 30.6%)] than in those receiving IFN [13.1% (95% CI 9.5% to 17.3%)].

Sunitinib versus IFN

Tumours were assessed both by independent central review and by the treating physicians at baseline, at day 28 of cycles 1–4 and every 2 weeks thereafter until the end of treatment. Assessments were also made if disease progression was suspected clinically. The objective response rate, assessed by blinded imaging studies, was significantly higher in the sunitinib group ($n = 103$; 31%) than in the IFN group ($n = 20$; 6%) ($p < 0.001$). No patients in either group were assessed as having a complete response. Results obtained from investigator review of images were similar [137 (37%) versus 33 (9%) patients in the sunitinib versus IFN groups, respectively; $p < 0.001$].

Health-related quality of life

Bevacizumab plus IFN versus IFN

Health-related quality of life was not reported in either of the trials of bevacizumab plus IFN versus IFN.[101,106]

Sunitinib versus IFN

Health-related quality of life was assessed using the Functional Assessment of Cancer Therapy – General (FACT-G) and FKSI questionnaires (see Chapter 1, Quality of life), which were administered before randomisation, on days 1 and 28 of each cycle and at the end of treatment. No data are available on the comparability of the groups at baseline on these measures. Using data from all postrandomisation assessments, least-square means were estimated for each treatment group. A higher score indicates a better outcome. Overall differences between the two groups were tested using repeated-measures mixed-effects models controlling for the assessment time, treatment by time interaction and the baseline score. *Table 14* shows that the overall results (total score and all subscales of the FACT-G and total score and the FKSI-DRS subscale) were all significantly better for patients in the sunitinib group than for those in the IFN group.

Indirect comparison of bevacizumab plus IFN and sunitinib

In order to perform an adjusted indirect comparison of the two competing interventions, the internal validity and similarity of the two main trials[106,107] were examined (*Table 15*). As already

TABLE 13 *Summary of tumour response rate: bevacizumab plus IFN and sunitinib versus IFN as first-line therapy*

Study	Intervention	*n*	Objective response rate, % (*n*)			*p*-value for overall response
			Overall	Complete	Partial	
[a]Escudier *et al.* 2007[106]	Bevacizumab + IFN	306	31 (96)	1 (4)	30 (92)	0.0001
	Placebo + IFN	289	13 (37)	2 (6)	11 (31)	
[b]Motzer *et al.* 2007[107]	Sunitinib	335	31 (103)	0	31 (103)	< 0.001
	IFN	335	6 (20)	0	6 (20)	

a Only patients with measurable disease at baseline are included in the analysis of response rate.
b Results from independent central review of radiological images.

described the baseline population characteristics of individuals in the trials were comparable in terms of demographics and disease status. IFN, the treatment common to both trials, was administered at the same dose (9 MIU) and according to the same schedule (subcutaneously, three times weekly) in both trials with dose reductions to 6 MIU and 3 MIU for management of adverse events allowed in both trials. The median treatment duration of IFN and the reported dose intensity were also similar. In addition, median PFS in patients treated with IFN was similar in both trials (5.4 months in the bevacizumab plus IFN trial and 5 months in the sunitinib trial). We therefore concluded that the two trials were suitably similar to indicate that an adjusted indirect comparison of bevacizumab plus IFN versus sunitinib was appropriate, although, as explained earlier (see Methods of data synthesis), results of indirect comparisons may not be as robust or as reliable as direct comparisons obtained from head-to-head randomised clinical trials and these results should therefore be treated with some caution.

The results (*Table 16*) suggest that in terms of PFS sunitinib may be superior to bevacizumab plus IFN [HR 0.67 (95% CI 0.50 to 0.89)]. A similar result was seen for OS [HR 0.82 (95% CI 0.53 to 1.28)], although the point estimate of effect is smaller and, as the CIs cross unity, the result is not statistically significant.

Adverse events

In the two main studies[106,107] data on adverse events and laboratory abnormalities were collected from the 'safety population'. That is, patients were

TABLE 14 *Summary of health-related quality of life results: sunitinib versus IFN as first-line therapy*

Intervention	Motzer *et al.* 2007[107]		
	Sunitinib	IFN	*p*-value
Number of patients	Not clear	Not clear	–
FACT-G			
FACT-G total score	82.34	76.76	–
Physical well-being subscale	21.28	19.87	< 0.001
Social/family well-being subscale	23.54	22.34	< 0.001
Emotional well-being subscale	18.32	17.54	< 0.001
Functional well-being subscale	18.98	17.00	< 0.001
FKSI			
FKSI total score	45.34	42.07	< 0.001
Disease-related symptoms subscale	29.36	27.37	< 0.001

FACT-G, Functional Assessment of Cancer Therapy – General scale; FKSI, FACT – Kidney Symptom Index.
A higher score indicates a better outcome.

TABLE 15 *Summary of study and population characteristics for indirect comparison: bevacizumab plus IFN versus sunitinib versus IFN as first-line therapy*

	Bevacizumab + IFN vs IFN	Sunitinib vs IFN
Study	**Escudier *et al*. 2007[106]**	**Motzer *et al*. 2007[107]**
n	649	750
Prognosis profile according to MSKCC criteria (favourable–intermediate–poor) (%)	27:56:9 (unavailable for 9% of patients)	38:56:6
Proportion of patients with clear cell carcinoma (%)	100	100
Proportion of patients having undergone previous nephrectomy (%)	100	90
Proportion of patients with metastases (%)	100	100
Dose of IFN (MIU)	9 (s.c. three times weekly)	9 (s.c. three times weekly)
Median (range) treatment duration for IFN (months)	4.6 (0.2–12.6)	5 (1–13)
Mean dose intensity of IFN (range)	89% (28–120%)[a]	83.1%[b]
Response to IFN (in terms of median PFS) (months)	5.4	5

s.c., subcutaneously.
a Dose intensity was calculated as the amount of drug administered vs the amount that should have been administered over the course of treatment.
b Reported in the company submission from Pfizer as relative dose intensity (total dose administered/total dose assigned multiplied by 100).

assigned to treatments in the analysis based on what they actually received, for example patients in the placebo arm receiving one or more doses of bevacizumab were assigned to the bevacizumab arm. Non-fatal adverse events reported up to 28 days after the last dose of study drug were included. Deaths were reported irrespective of when they occurred. Adverse events were measured according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. *Table 56* in Appendix 5 shows adverse events of any grade reported in the course of the two studies. Some additional information obtained from a conference abstract[107] of the AVOREN trial regarding the reasons for discontinuation of study drugs is shown in *Table 57* in Appendix 5. In *Table 17* only those adverse events classified as grade 3 or above are included.

Bevacizumab plus IFN versus IFN

In the AVOREN trial,[106] in both groups the most commonly reported 'any grade' adverse event was pyrexia (in 45% and 43% of patients treated with bevacizumab plus IFN and IFN alone respectively), followed by anorexia (36% and 30% of patients respectively), fatigue (33% and 27% respectively), asthenia (32% and 28% respectively) and influenza-like illness (24% and 25% respectively). There were 203 grade 3 or worse adverse events reported by patients who received one or more doses of bevacizumab compared with 137 reported by those who did not receive the drug. The frequency of grade 3 and 4 adverse events was low, being between < 1% and 12%, with most grade 3 or 4 adverse events occurring at a frequency of 3% or less. The mean number of grade 3 or worse adverse events per patient was 1.3 in the intervention

TABLE 16 *Indirect comparison: bevacizumab plus IFN versus sunitinib versus IFN as first-line therapy*

Study	Intervention	HR for OS	95% CI for OS HR	HR for PFS	95% CI for PFS HR
Escudier *et al*. 2007[106]	Bevacizumab + IFN vs IFN	0.79	0.62 to 1.02	0.63	0.52 to 0.75
Motzer *et al*. 2007[107]	Sunitinib vs IFN	0.65	0.45 to 0.94	0.42	0.33 to 0.52
Indirect comparison	Sunitinib vs bevacizumab + IFN	0.82	0.53 to 1.28	0.67	0.50 to 0.89

TABLE 17 *Adverse events grades 3 and 4: bevacizumab plus IFN and sunitinib versus IFN as first-line therapy*

	Escudier et *al*. 2007[106a]		**Motzer et *al*. 2007[107b]**	
Intervention	**Bevacizumab + IFN**	**IFN + placebo**	**Sunitinib**	**IFN**
n	337	304	375	375
	% of patients			
Diarrhoea	2	< 1	5	0[c]
Fatigue	12	8	7	12[c]
Asthenia	10	7	4	4
Nausea			3	1
Stomatitis			1	1
Vomiting			4	1[c]
Hypertension	3	< 1	8	1[c]
Hand–foot syndrome			5	0[c]
Mucosal inflammation			2	1
Rash			2	1
Dry skin			1	0
Epistaxis			1	0
Pain in a limb			1	0
Headache	2	1	1	0
Dry mouth			0	1
Decline in ejection fraction			2	1
Pyrexia	2	< 1	1	0
Chills			1	0
Myalgia			1	1
Influenza-like illness	3	2	0	1
Dyspnoea	< 1	2		
Bleeding	3	< 1		
Venous thromboembolic event	2	< 1		
Gastrointestinal perforation	1	0		
Arterial thromboembolic event	1	< 1		
Wound healing complications	< 1	0		
Congestive heart failure	< 1	0		
Anorexia	3	3		
Depression	3	1		
Leukopenia			5	2[c]
Neutropenia	4	2	12	7[c]
Anaemia	3	6	4	5
Increased creatinine			1	1
Thrombocytopenia	2	< 1	8	0[c]
Lymphopenia			12	22[c]
Increased lipase			16	6[c]
Increased aspartate aminotransferase			2	2

continued

TABLE 17 *Adverse events grades 3 and 4: bevacizumab plus IFN and sunitinib versus IFN as first-line therapy (continued)*

	Escudier *et al.* 2007[106a]		Motzer *et al.* 2007[107b]	
Intervention	**Bevacizumab + IFN**	**IFN + placebo**	**Sunitinib**	**IFN**
Increased alanine aminotransferase			3	2
Increased alkaline phosphatase			2	2
Increased uric acid			12	8
Hypophosphataemia			5	6
Increased amylase			5	3[c]
Increased total bilirubin			1	0
Proteinuria	7	0		

a Grade 3 or grade 4 adverse events that occurred with a frequency of 2%.
b Grade 3 or grade 4 adverse events and selected laboratory abnormalities that occurred in at least 10% of patients in the sunitinib group.
c Statistically significant difference between sunitinib and IFN ($p < 0.05$).

group and 0.9 in the control group. Details of statistical analyses are not provided. Adverse events that led to treatment discontinuation occurred more frequently in patients who received bevacizumab ($n = 95$; 28%) than in those who did not ($n = 37$; 12%). Proteinuria, hypertension and gastrointestinal perforation were the most common reasons for treatment discontinuation (*Table 56*, Appendix 5). Adverse event-related deaths were reported in eight (2%) patients who received bevacizumab and in seven (2%) patients who did not. Three of the deaths in patients who received bevacizumab (two bleeding events and one gastrointestinal perforation) were believed to be possibly related to bevacizumab.

The abstract of the CALGB study[101] states that overall toxicity in the bevacizumab plus IFN group was greater than that in the IFN only group, with significantly more patients reporting grade 3 hypertension (9% versus 0%), anorexia (17% versus 8%), fatigue (35% versus 28%) and proteinuria (13% versus 0%).

Sunitinib versus IFN

The most commonly reported 'any grade' adverse events and laboratory abnormalities in the sunitinib group were diarrhoea (53% of patients), fatigue (51% of patients), nausea (44% of patients), leukopenia, neutropenia, anaemia, increased creatinine, thrombocytopenia and lymphopenia (which all occurred in more than 50% of the patients treated with sunitinib). A similar adverse event profile was seen in the IFN group with fatigue (51%), pyrexia (34%), nausea (33%) and chills (29%) being the most frequently reported adverse events and anaemia, lymphopenia and leukopenia the most commonly reported laboratory abnormalities (all occurring in more than 50% of patients treated with IFN). There were statistically significant differences ($p < 0.05$) between groups in the frequency of reporting of the following adverse events at grade 3 and above: diarrhoea, fatigue, vomiting, hypertension, hand–foot syndrome, leukopenia, neutropenia, thrombocytopenia, lymphopenia, increased lipase and increased amylase, with all but fatigue, anaemia and lymphopenia occurring more often in the sunitinib group than in the IFN group. Approximately 12% of patients in the IFN group experienced grade 3 or 4 adverse events compared with 7% in the sunitinib group; this difference was statistically significant ($p < 0.05$). Treatment discontinuation as a result of unacceptable adverse events occurred more frequently in the IFN group than in the sunitinib group (13% versus 8%; $p = 0.05$); no further details are provided. A total of 38% of patients in the sunitinib group and 32% in the IFN group had a dose interruption because of adverse events and in a similar proportion dosage was reduced (32% and 21% in the sunitinib and IFN groups respectively).

It is not clear from the paper whether any deaths occurred during the trial that may have been attributable to the study medication.

Summary of safety data

From the adverse events reported in these trials the safety profile of both interventions appears to

be comparable to that of IFN, with some adverse events particularly associated with bevacizumab plus IFN (proteinuria, hypertension, bleeding events) and sunitinib (hypertension, hand–foot syndrome). However, randomised clinical trials are not designed to detect rare adverse events and we therefore briefly reviewed additional literature, obtained from the results of our initial and updated searches, to identify any further potential safety issues.

Sunitinib The most commonly reported treatment-related adverse events in an expanded access trial of sunitinib in 4000 patients in 36 countries were diarrhoea (39%), fatigue (35%) and nausea (33%).[118] A systematic review of toxicities associated with the administration of sorafenib, sunitinib and temsirolimus in phase I, II and III clinical trials found that all three interventions are associated with a large number of adverse events, although grade 3 or 4 events are less common (< 1% to 16% of patients experience grade 3 or 4 adverse events with sunitinib). The most commonly reported grade 3 and 4 adverse events associated with sunitinib across all trials were elevated lipase (16%), lymphopenia (12%), neutropenia (12%), hypertension (8%), fatigue (7%) and thrombocytopenia (8%).[119]

Postmarketing surveillance has resulted in several reports of cardiac failure associated with sunitinib, occurring at a frequency classed as uncommon (1/1000 to 1/100).[77]

In a paper describing a systematic review and meta-analysis of the risk and incidence of hypertension in patients treated with sorafenib,[120] the authors also discuss an unpublished meta-analysis of the risk of hypertension associated with sunitinib treatment. In this analysis sunitinib was associated with a 22.5% (95% CI 19.5% to 25.9%) incidence of hypertension with a relative risk of 3.89 (95% CI 2.6 to 5.9) compared with control treatments. No further details are provided.

We identified several conference abstracts in which reviews of the adverse events experienced by cohorts of patients treated with sunitinib were reported. These suggest that sunitinib treatment may also be associated with an increased incidence of macrocytosis[121] and thyroid dysfunction.[122] Further study is required to confirm these associations.

Bevacizumab In a systematic review and meta-analysis of the risk and incidence of proteinuria and hypertension associated with bevacizumab treatment a significantly increased risk of both proteinuria [relative risk 2.2 (95% 1.6 to 2.9)] and hypertension [relative risk 7.5 (95% CI 4.2 to 13.4)] were reported.[123] Patients in the included trials were all receiving treatment with bevacizumab for metastatic cancer (including lung, breast, colorectal and kidney) at doses of 10 or 15 mg/kg. In some trials patients were also receiving treatment with other chemotherapeutic agents such as fluorouracil, carboplatin and cisplatin.

Subgroup analyses

In the protocol we specified that, depending on the availability of data, we would consider the following subgroups of people with RCC: (1) people who had/had not undergone surgical resection of the primary tumour and (2) people diagnosed with clear cell and non-clear cell carcinoma. For the assessment of the clinical effectiveness of bevacizumab plus IFN and sunitinib as first-line therapy for the treatment of RCC the following subgroup data were available:

1. People who have undergone surgical resection of the primary tumour compared with those who have not. The AVOREN study[106] only included people who had undergone total or partial nephrectomy before entry to the study. This trial cannot therefore provide any information on the relative effectiveness of these treatments in people who have or have not undergone surgical resection of the primary tumour.
2. People with clear cell RCC compared with those with non-clear cell RCC. Only patients with predominantly clear cell pathology were eligible for entry to the studies. Neither study therefore provides any indication as to the relative effectiveness of the interventions amongst patients with clear cell RCC compared with those with non-clear cell RCC.

In the trial by Motzer and colleagues[107] a small proportion of people who had not had a previous nephrectomy were included [35 (9%) in the sunitinib group and 40 (11%) in the IFN group]. PFS for these subgroups using data from the independent central review of radiological images is reported (*Table 18*). The HR for patients who had undergone a previous nephrectomy ($n = 675$) is 0.38 (95% CI 0.30 to 0.53) and the HR for patients who had not undergone a previous nephrectomy ($n = 75$) is 0.58 (95% CI 0.24 to 1.03). These results may indicate that sunitinib is relatively more effective than IFN in patients who

TABLE 18 *Summary of progression-free survival for patients with and without previous nephrectomy: sunitinib versus IFN as first-line therapy*

	Motzer *et al.* 2007[107]		
	Sunitinib vs IFN		
	n	**HR for PFS**	**95% CI**
Previous nephrectomy	675	0.38	0.30 to 0.53
No previous nephrectomy	75	0.58	0.24 to 1.03
Total trial population	750	0.42	0.32 to 0.54

have undergone a previous nephrectomy than in those who have not. However, the 95% CIs for the latter comparison include no difference. This indicates that the interventions could be equally effective in these populations although the small number of patients involved in the comparison also makes a type II error possible. Interestingly, the 95% CI for patients who had undergone surgical removal of the primary tumour (0.30 to 0.53) is not distinct from that obtained for patients who had not undergone surgical removal of the primary tumour (0.24 to 1.03), which may suggest that, for this outcome, it is inappropriate to divide the population according to this characteristic. It is possible that this division of the population is confounded by other factors related to the reasons for some patients not having surgery, for example the position of the primary tumour and the performance status of the patient.

Overall conclusion: bevacizumab plus IFN and sunitinib versus IFN

From the limited clinical data available, treatment with both interventions (bevacizumab plus IFN and sunitinib) appears to have clinically relevant and statistically significant advantages over treatment with IFN alone in terms of PFS and tumour response. In two of the trials[106,107] median PFS was doubled from approximately 5 months to approximately 11 months with the interventions (HR for sunitinib 0.42, 95% CI 0.32 to 0.54; HR for bevacizumab plus IFN 0.63, 95% CI 0.52 to 0.75). Although promising, data on OS from these trials are not fully mature. Treatment crossover has now occurred in two of the trials[106,107] and further information from the randomised population will therefore not be available. It is not clear whether treatment crossover has occurred in the CALGB study yet and OS data are pending.[101]

Data on adverse events suggest that the interventions are not associated with a greater frequency of adverse events than IFN alone, although the adverse event profile is different and there is some emerging concern in the published literature relating to the frequency of cardiovascular events associated with sunitinib.

All three trials were conducted predominantly in patients with metastatic clear cell carcinoma, with MSKCC risk factors suggestive of a favourable or intermediate prognosis, who had undergone a previous nephrectomy. Whether these results can be extrapolated to other groups of patients with RCC (e.g. people diagnosed with non-clear cell RCC or defined as having a poor prognosis according to the MSKCC criteria) is unclear. As there is no head-to-head comparison data available for bevacizumab plus IFN versus sunitinib, we carried out an indirect comparison to consider which intervention might be the most clinically effective. The results suggest that, in terms of PFS, sunitinib may be superior to bevacizumab plus IFN (HR 0.82, 95% CI 0.55 to 0.89).

Sorafenib and sunitinib compared with best supportive care as first-line therapy

In this section we address research question 2: In those who are unsuitable for treatment with immunotherapy, what is the clinical effectiveness of sorafenib tosylate and sunitinib as first-line therapy, using BSC as a comparator?

Quantity and quality of included studies

We were unable to locate any fully published randomised clinical trials of these interventions in people with a diagnosis of advanced and/or metastatic RCC who are deemed unsuitable for treatment with immunotherapy.

Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared with IFN as first-line therapy in people with poor prognosis

In this section we address research question 3: In those with three or more of six poor prognostic factors, what is the clinical effectiveness of bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus, immunotherapy and BSC as first-line therapy, using IFN as a comparator?

Quantity, quality and characteristics of included studies

We identified one RCT relevant to this question, in which treatment with temsirolimus, temsirolimus plus IFN or IFN alone were compared in patients deemed to have poor prognosis.[108] A summary of the quality assessment of this study is shown in *Table 9*; study characteristics are summarised below and in *Table 58* in Appendix 5.

We were unable to locate any eligible studies of sorafenib, sunitinib or bevacizumab plus IFN in patients with poor prognosis, or any trials in comparison with BSC. However, approximately 10% of the people included in the studies described in the section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy were defined as having poor prognosis according to similar criteria. A summary of the study characteristics and quality assessment of these trials can be found in this section and in *Table 55* in Appendix 5.

Study characteristics

Temsirolimus versus IFN

Hudes and colleagues[108] report the results of the Global Advanced Renal Cell Carcinoma (ARCC) trial. An international (Argentina, Australia, Canada, Czech Republic, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Russia, Serbia and Montenegro, Slovakia, South Africa, Spain, Sweden, Taiwan and Turkey), multicentre, three-way parallel group, randomised phase III trial in which 626 people with previously untreated metastatic RCC, deemed to have poor prognosis according to criteria based on MSKCC risk score, received either temsirolimus, IFN or a combination of temsirolimus and IFN. The study has been published in one full paper[108] and in five abstracts.[89,94–97] The primary outcome was OS. PFS, objective response rate and the 'clinical benefit rate' (defined as the proportion of people with stable disease for at least 24 weeks or an objective response) were secondary outcomes. The study (with 200 patients per group) was designed to have 80% power to detect an improvement in OS of 40% for each comparison with the use of a two-sided stratified log-rank test at an overall 2.5% level of significance. Two interim analyses were planned after approximately 164 and 430 deaths and a final analysis, if necessary, after a total of 504 deaths had occurred; the paper by Hudes and colleagues[108] provides the results of the second analysis (after 446 patients had died).

Trial eligibility is defined in *Table 58* in Appendix 5. Participants were required to have a diagnosis of histologically confirmed RCC, a Karnofsky performance status of 60 or more and measurable disease according to RECIST criteria. All patients had to fulfil prespecified criteria for poor prognosis to be eligible. Although based on the MSKCC classification of prognosis, the criteria used in this trial were slightly different. The MSKCC classification includes *five* predictors of survival, of which a patient with poor prognosis needs to exhibit three. Participants in this trial were required to exhibit three of *six* features to be defined as having poor prognosis, the additional feature being 'metastases in multiple organs'.

Randomisation was performed centrally and patients were stratified according to the geographical location of the centre and whether they had undergone previous nephrectomy. Patients were randomly assigned to receive temsirolimus (25 mg, delivered intravenously, weekly) ($n = 209$), IFN (18 MIU, delivered subcutaneously three times per week) ($n = 207$) or a combination of both treatments ($n = 210$). Treatment was continued until evidence of disease progression, symptomatic deterioration or intolerable adverse events. IFN was started at a dose of 3 MIU for the first week, increased to 9 MIU for the second week and 18 MIU for the third week. Treatments were withheld if grade 3 or 4 adverse events occurred and restarted at a reduced dose after recovery to grade 2 or lower.

The results reported in the full publication[108] were obtained from the second interim analysis after 446 deaths. At the time of data analysis, median treatment duration for temsirolimus was 3.92 months (range 0.23–29.08 months) in the temsirolimus alone group and 3.46 months (range 0.23–31.85 months) in the group receiving combination treatment. For IFN the figures were 1.85 months (range 0.23–28.62 months) in the IFN group and 2.77 months (range 0.23–31.85 months) in the combination group.

The mean dose intensity of temsirolimus was 23.1 mg per week or 92% of the planned dose; corresponding figures for IFN are 30.2 MIU per week or 56% of the maximum planned dose in the first 8 weeks of treatment. No further details are provided.

Data from the final analysis were available from a conference abstract[89] and were presented in the company submission to NICE.[124] Median treatment duration at this analysis is not reported in either source.

Additional data relating to HRQoL, reported in a conference abstract[97] and the company submission, are also included (see section on assessment of clinical effectiveness).

Sunitinib versus IFN
See section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy.

Bevacizumab plus IFN versus IFN
See section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy.

Quality assessment

Temsirolimus versus IFN
This is a large, international, multicentre randomised clinical trial. Although, on the whole, methods are clearly reported, several aspects are not clear in the paper, making the assessment of quality somewhat difficult. Details of randomisation methods and withdrawals were adequately reported, but details of how the randomisation code was generated were omitted. Site investigators were not blind to treatment allocation, although radiological scans used for assessment of PFS and response rate were assessed both by site investigators and by central blinded review. Only the analysis of the primary end point (OS) was conducted on an ITT basis. Further details can be found in *Table 9*.

Sunitinib versus IFN
See section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy.

Bevacizumab versus IFN
See section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy.

Population baseline characteristics

Temsirolimus versus IFN
In this assessment we are interested in two of the three patient groups in this trial, temsirolimus alone and IFN alone as the combination of temsirolimus and IFN is not licensed for use in people with advanced and/or metastatic RCC. At baseline these two treatment groups were well matched in terms of demographic characteristics (age, gender, RCC histology) and disease status (Karnofsky performance status, MSKCC risk group and proportion of patients having undergone a previous nephrectomy) (*Table 19*). Most tumours had clear cell histology (approximately 80%) and most patients had Karnofsky performance scores of < 70 (approximately 80%) and had undergone a previous nephrectomy (approximately 65%). It is interesting to note that, according to MSKCC risk classification, approximately 30% of patients in both treatment groups would have been classified as having intermediate prognosis rather than poor prognosis, and about 5% of patients in both treatment groups did not meet the criteria for entry into the study (i.e. three or more of six factors suggestive of poor prognosis).

Sunitinib versus IFN
In the study by Motzer and colleagues,[107] 23 (6%) patients receiving sunitinib and 25 (7%) patients receiving IFN had three or more MSKCC risk factors and were therefore classified as having poor prognosis. As described above, this classification is slightly different from that used in the trial of temsirolimus. The baseline population characteristics of the entire trial population are described in the section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy.

Bevacizumab plus IFN versus IFN
In total, 9% ($n = 28$) of the patients who received bevacizumab plus IFN and 7% ($n = 24$) of the patients receiving IFN in the trial by Escudier and colleagues[106] had three or more MSKCC risk factors for poor prognosis. Again, the definition of poor prognosis differs from that used in the trial of temsirolimus. The baseline population characteristics of the entire population are described in the section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy.

Comparison of population baseline characteristics between trials
As population baseline characteristics are not presented separately for the poor prognosis subgroups in the trials of sunitinib and bevacizumab, comparison between the studies is problematic. However, assuming that the patients with poor prognosis were characteristic of the

TABLE 19 *Population baseline characteristics: temsirolimus versus IFN as first-line therapy in people with poor prognosis*

	Hudes *et al.* 2007[108]		
	Temsirolimus, *n* (%)	**IFN, *n* (%)**	**Temsirolimus + IFN, *n* (%)**
Randomised, *n*	209	207	210
Diagnosis	Advanced RCC (stage IV or recurrent)		
Age (years), median (range)	58 (32–81)	60 (23–86)	59 (32–82)
Male, *n* (%)	139 (66)	148 (71)	145 (69)
Karnofsky performance score, n (%):			
> 70	41 (20)	34 (16)	33 (16)
≤ 70	168 (80)	171 (83)	177 (84)
MSKCC risk factors, n (%):			
1–2 (intermediate)	64 (31)	50 (24)	50 (24)
≥ 3 (poor)	145 (69)	157 (76)	160 (76)
Patients with a previous nephrectomy, *n* (%)	139 (66)	139 (67)	141 (67)
Number of patients with clear cell histology, *n* (%)	169 (81)	170 (82)	163 (78)
Patients with poor prognostic features, n (%):			
≥ three of six	195 (93)	196 (95)	198 (94)
< three of six	14 (7)	11 (5)	12 (6)
Patients with protocol-defined poor prognostic features, n (%):			
Lactate dehydrogenase level > 1.5 times upper limit of normal	36 (17)	48 (23)	33 (16)
Haemoglobin level < lower limit of normal	172 (82)	168 (81)	178 (85)
Corrected serum calcium level > 10 mg/dl (2.5 mmol/l)	54 (26)	72 (35)	58 (28)
Time from initial diagnosis to randomisation < 1 year	174 (83)	164 (79)	179 (85)
Karnofsky performance score ≤ 70	168 (80)	171 (83)	177 (84)
≥ two sites of organ metastasis	166 (79)	165 (80)	168 (80)

Note: percentages may not total 100 because of rounding.

trial populations as a whole, the demographics (median age, gender mix) of patients included in all three studies appear similar. There are, however, differences between trials in terms of the proportion having undergone previous nephrectomy (100% versus 90% versus 65% in the trials of bevacizumab plus IFN, sunitinib and temsirolimus respectively) and the proportion of patients with clear cell carcinoma (100% versus 100% versus 80% in the trials of bevacizumab plus IFN versus sunitinib versus temsirolimus respectively).

Assessment of clinical effectiveness

Overall survival (*Table 20*)

Temsirolimus versus IFN

Overall survival was the primary outcome measure of the Hudes and colleagues trial[108] and was analysed on an ITT basis. At the time of the interim analysis, median OS was 7.3 months (95% CI 6.1 to 8.8 months) in the IFN group and 10.9 months (95% CI 8.6 to 12.7 months) in the temsirolimus group, producing a HR of 0.73 (95% CI 0.58 to 0.92; $p = 0.008$).

TABLE 20 *Summary of overall survival: temsirolimus versus IFN as first-line therapy in people with poor prognosis*

Study	Intervention	*n*	Median OS (months)	HR	95% CI for HR	*p*-value
Results of the second interim analysis						
Hudes *et al.* 2007[108]	Temsirolimus	209	10.9 (95% CI 8.6 to 12.7)	0.73	0.58 to 0.92	0.008
	IFN	207	7.3 (95% CI 6.1 to 8.8)			
Results of the final analysis						
DeSouza *et al.* 2008[89]	Temsirolimus	209	10.9 (95% CI 8.6 to 12.7)	0.78	0.63 to 0.97	0.0252
	IFN	207	7.3 (95% CI 6.1 to 8.8)			

In the final analysis, median OS in the IFN group was 7.3 months (95% CI 6.1 to 8.8 months) and in the temsirolimus group was 10.9 months (8.6 to 12.7 months), producing a slightly higher HR of 0.78 (95% CI 0.63 to 0.97; $p = 0.0252$) indicating that temsirolimus reduced the hazard of death by 22%.[89]

These results suggest that temsirolimus may be superior to IFN in this patient group. However, the 95% CIs surrounding the estimates are reasonably wide and approach unity at the upper limit (which would indicate no difference between treatments) highlighting the degree of imprecision of these results.

Bevacizumab plus IFN versus IFN and sunitinib versus IFN

Data on OS were not presented separately for the poor prognosis subgroups in these trials.

Progression-free survival

Bevacizumab plus IFN versus IFN

Median PFS (defined as time between randomisation and first documented disease progression or death due to any cause) for patients in the poor prognosis subgroup was 2.2 months for those receiving bevacizumab plus IFN and 2.1 months for those treated with IFN, producing a HR of 0.81 (95% CI 0.46 to 1.42) (*Table 21*). As the 95% CI crosses unity this result would not be considered statistically significant, but could be interpreted as indicating a possible benefit of treatment with bevacizumab plus IFN compared with IFN in this patient subgroup. The lack of statistical significance could be because bevacizumab plus IFN is not more effective than IFN in patients with a poor prognosis or it may reflect the small number of patients ($n = 52$) in this subgroup.

Sunitinib versus IFN

The study of sunitinib versus IFN includes results for PFS for subgroups according to baseline factors. For all subgroups the HR favours sunitinib. However, data for the group of patients with three or more MSKCC risk factors are not presented separately. This trial therefore does not provide any additional information about the effectiveness of sunitinib versus IFN in this particular population. A later analysis of the trial (following the decision to allow patients in the IFN group to receive sunitinib) is available as a conference abstract[91] and suggests that the benefit of sunitinib over IFN in terms of PFS (by investigator assessment) extends over all MSKCC risk groups.

Temsirolimus versus IFN

Progression-free survival (not formally defined in the paper[108]) was assessed both by the site investigators (who were not blind to treatment allocation) and by independent blinded evaluation of the radiological images (*Table 21*). In the interim analysis, as determined by the site investigators, median PFS was 1.9 months (95% CI 1.9 to 2.2 months) in the IFN group and 3.8 months in the temsirolimus group (95% CI 3.6 to 5.2 months).[108] Radiological images from 153 patients (74%) in the IFN group and 192 patients (92%) in the temsirolimus group were evaluated in the independent blinded review, the results of which suggest that median PFS was 3.1 months (95% CI 2.2 to 3.8 months) and 5.5 months (95% CI 3.9 to 7.0 months) for the IFN and temsirolimus groups respectively. The authors suggest that the reason for the discrepancy in these results is the inclusion in the evaluation by site investigators of patients with symptomatic deterioration that had begun before scheduled radiological measurements of the tumour. HRs are not provided in the paper, nor is there any indication of the results of statistical testing. However, the abstract of the paper states

TABLE 21 *Summary of progression-free survival: temsirolimus versus IFN as first-line therapy in people with poor prognosis*

Study	Intervention	*n*	Median PFS (months)	HR	95% CI for HR	*p*-value
Results of the second interim analysis[a]						
Hudes *et al.* 2007[108]	Temsirolimus	209	3.8 (95% CI 3.6 to 5.2)	NR	NR	NR
	IFN	207	1.9 (95% CI 1.9 to 2.2)			
Results of the final analysis[a]						
DeSouza *et al.* 2008[89]	Temsirolimus	209	5.6 (95% CI 3.9 to 7.2)	0.74	0.60 to 0.90	0.0028
	IFN	207	3.2 (95% CI 2.2 to 4.0)			
Escudier *et al.* 2007[106]	Bevacizumab + IFN	28	2.2	0.81	0.46 to 1.42	NR
	IFN	24	2.1			

NR, not reported.
a As assessed by site investigators – results from an independent review of images are also available for a reduced number of patients (see accompanying text).

that patients who received temsirolimus alone had longer PFS than did patients who received IFN alone ($p < 0.001$).

In the final analysis, median PFS by independent assessment was 5.6 months (95% CI 3.9 to 7.2 months) in the temsirolimus group and 3.2 months (95% CI 2.2 to 4.0 months) in the IFN group, with a HR of 0.74 (95% CI 0.60 to 0.91; $p = 0.0042$).[124] Again, the investigator evaluation resulted in slightly lower estimates of PFS (3.8 months versus 1.9 months for temsirolimus and IFN respectively). Interestingly, the HR was almost identical (0.74; 95% CI 0.60 to 0.90; $p = 0.0028$).[89]

Tumour response

Bevacizumab plus IFN versus IFN and sunitinib versus IFN

Tumour response results were not presented separately for the poor prognosis subgroup in these trials.[106,107]

Temsirolimus versus IFN

Before the start of treatment, the following imaging studies were performed: CT scans of the chest, abdomen and pelvis, a radionuclide bone scan and an MRI or CT scan of the brain. Scanning was repeated at 8-week intervals to evaluate tumour size. Response to treatment was assessed using the RECIST criteria. Objective response rates in the IFN and temsirolimus groups were 4.8% (95% CI 1.9% to 7.8%) and 8.6% (95% CI 4.8% to 12.4%), respectively, and did not differ significantly.

Health-related quality of life

Bevacizumab plus IFN versus IFN and sunitinib versus IFN

No additional information on the effect of these treatments on HRQoL in patients with poor prognosis was available from these trials.[106,107]

Temsirolimus versus IFN

No HRQoL outcomes were reported in the full-text paper.[108] In a subsequent conference abstract presented in 2007,[97] results for quality-adjusted survival (a predefined end point) are presented. Quality-adjusted survival and toxicity (Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment; Q-TWiST) were estimated by partitioning OS into three distinct health states: time with serious toxicity, time with progression and time without symptoms and toxicity (TWiST). Survival was value weighted when patients completed EuroQoL 5 dimensions (EQ-5D) questionnaires at weeks 12 and 32, when a grade 3 or 4 adverse event was reported, upon relapse or progression, or upon withdrawal from the trial. All 626 randomised patients in the trial were included in the computation of health state durations. This includes patients in all three treatment groups – temsirolimus alone, IFN alone and the combination of temsirolimus and IFN. EQ-5D questionnaires were obtained from 260 of 300 patients upon progression and from 230 of 570 patients after a grade 3 or 4 adverse event. Patients receiving temsirolimus had 38% greater TWiST than those receiving IFN (6.5 months versus 4.7 months for temsirolimus and IFN respectively;

TABLE 22 *Summary of health-related quality of life: temsirolimus versus IFN as first-line therapy in people with poor prognosis*

Study		*n*	Median EQ-5D
Parasuraman *et al*. 2007[97]	At baseline	601	0.689
	On progression	260	0.587
	During a grade 3 or 4 adverse event	230	0.585
	During stable disease (obtained at weeks 12 and 32 of treatment)	NR	0.689

NR, not reported.
Note: some data obtained from the slide presentation.

$p = 0.00048$) and 23% greater Q-TWiST than those receiving IFN (7.0 months versus 5.7 months for temsirolimus and IFN respectively; $p = 0.0015$). Median EQ-5D scores for the total trial population are shown in *Table 22*.

Indirect comparison of first-line therapy options in people with poor prognosis

No comparison with sorafenib is possible in this patient group as we were unable to locate any trials of sorafenib as first-line therapy.

To ascertain whether an indirect comparison of bevacizumab plus IFN, sunitinib and temsirolimus was valid we examined the internal validity and similarity of the three trials. Participants in all three trials were similar in age and gender distribution and were all undergoing first-line therapy for RCC. However, there were some important differences between the patient populations in terms of disease status, definitions of poor prognosis, dose of IFN used and dose intensity of IFN received, and the treatment duration and response to IFN in the comparator arms. These are detailed in *Table 23*.

TABLE 23 *Summary of study and population characteristics for indirect comparison: bevacizumab plus IFN, sunitinib, temsirolimus or IFN for first-line therapy in people with poor prognosis*

Study	Bevacizumab + IFN vs IFN Escudier *et al*. 2007[106]	Sunitinib vs IFN Motzer *et al*. 2007[107]	Temsirolimus vs IFN Hudes *et al*. 2007[108]
Proportion of patients with poor prognosis (%)	8.3	6.4	94
Definition of poor prognosis used	Three or more of five risk factors (MSKCC)	Three or more of five risk factors (MSKCC)	Three or more of six risk factors (five MSKCC plus evidence of multiple metastases)[a]
Proportion of patients with clear cell carcinoma (%)	100	81	100
Proportion of patients having undergone previous nephrectomy (%)	100	93[b]	67
Proportion of patients with metastases (%)	32[b]	100	100
Dose of IFN (MIU)	9	9	18
Response to IFN [in terms of median PFS (months)]	2.1	Not reported	3.1
Mean dose intensity of IFN (%)	89	Not reported	73
Median (range) treatment duration for IFN (months)	4.6 (0.2 to 12.6)	4 (1 to 13)	2.77 (0.23 to 31.85)

a 73% of patients in this trial were classified as 'poor prognosis' using the alternative definition.
b Proportion of patients in the entire trial with these characteristics; baseline characteristics for the subgroup with poor prognosis are not available.

We concluded that there were sufficient differences between the trials to render an indirect comparison between interventions inappropriate.

As many patients with poor prognosis will be managed with BSC rather than being considered for treatment with IFN, we also considered the validity of an indirect comparison between IFN and BSC in order to provide an estimate of the relative effectiveness of interventions compared with BSC. However, there are very few trials of IFN versus a control treatment,[37] and although some authors have considered treatments such as medroxyprogesterone and vinblastine to be equivalent to placebo or BSC we do not consider this a valid assumption. In addition, none of the available trials uses the MSKCC prognostic criteria to define prognosis. We therefore concluded that a formal indirect comparison between IFN and BSC should not be carried out.

Adverse events

Bevacizumab plus IFN versus IFN

See section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy. No additional data were provided for those in the poor prognosis subgroup.

Sunitinib versus IFN

See section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy. No additional data were provided for those in the poor prognosis subgroup.

Temsirolimus versus IFN

Adverse events were defined and graded according to the CTCAE, version 3.0. No further details were provided. *Table 59* in Appendix 5 details all adverse events of any grade reported by at least 20% of patients in any group. The tables include all adverse events, not only those considered to be drug related. Asthenia was the most commonly reported adverse event among patients in all treatment groups. Anaemia, nausea, anorexia, fever and chills were also commonly reported in all treatment groups. Patients treated with temsirolimus experienced more rashes, hyperlipidaemia, infection, peripheral oedema, hyperglycaemia, cough, hypercholesterolaemia and stomatitis than patients receiving IFN, although whether these differences were statistically significant is unclear.

Table 24 shows adverse events classified as grade 3 or 4 based on the adverse events that occurred in more than 20% of patients in any group (shown in *Table 59* in Appendix 5). For simplicity, only data for the temsirolimus and IFN groups are presented. More patients in the IFN group than in the temsirolimus group reported grade 3 or 4 adverse events (78% versus 67%; $p = 0.02$). The most commonly occurring grade 3 or 4 adverse event in the temsirolimus group was anaemia (in 20% of patients). Events that occurred more frequently in the temsirolimus group than in the IFN group include dyspnoea (in 9% and 6% of patients respectively) and rash (in 4% and 0% of patients respectively), although the number of patients affected is relatively small and whether these differences were considered statistically significant is unclear. Treatment was discontinued as a result of adverse events in twice as many people receiving IFN as temsirolimus, although the number of people involved was again small [29 (14%) and 15 (7%) in the IFN and temsirolimus groups respectively)]. The number of deaths as a result of adverse events was not reported.

Summary of safety data

Based on the data reported in these trials the frequency of treatment-related toxic events associated with bevacizumab plus IFN, sunitinib and temsirolimus appears to be comparable to or slightly better than the frequency of treatment-related toxic events associated with IFN. There are some particular adverse events associated with each of the three interventions: bevacizumab plus IFN – proteinuria, hypertension, bleeding events; sunitinib – hypertension, hand–foot syndrome; and temsirolimus – for example hyperglycaemia, hyperlipidaemia, hypercholesterolaemia, peripheral oedema, rash. However, randomised clinical trials are not designed to detect rare adverse events and we therefore briefly reviewed additional data sources to identify any further potential safety concerns. The results of this review are detailed on pp.28–29 for bevacizumab plus IFN and sunitinib. A systematic review of toxicities associated with the administration of sorafenib, sunitinib and temsirolimus in phase I, II and III clinical trials found that between 1% and 20% of patients experience grade 3 or 4 adverse events with temsirolimus treatment. The most commonly experienced grade 3 and 4 adverse events across all included trials of temsirolimus were anaemia (20%), fatigue/asthenia (11%), hyperglycaemia (11%) and dyspnoea (9%).[119]

Subgroup analyses

In the protocol we specified that, depending on the availability of data, we would consider the following subgroups of people with RCC: (1) people who

TABLE 24 *Proportion of patients (%) reporting adverse events (grade 3 or grade 4): temsirolimus versus IFN as first-line therapy in people with poor prognosis*

	Hudes *et al.* 2007[108]	
	Temsirolimus	**IFN**
Number of patients	208	200
Anaemia	20	22
Asthenia	11	26
Hyperglycaemia	11	2
Dyspnoea	9	6
Pain	5	2
Infection	5	4
Rash	4	0
Abdominal pain	4	2
Anorexia	3	4
Hyperlipidaemia	3	1
Back pain	3	4
Increased creatinine level	3	1
Neutropenia	3	7
Nausea	2	4
Peripheral oedema	2	0
Vomiting	2	2
Diarrhoea	1	2
Cough	1	0
Hypercholesterolaemia	1	0
Fever	1	4
Stomatitis	1	0
Weight loss	1	2
Headache	1	0
Thrombocytopenia	1	0
Chills	1	2
Increased aspartate aminotransferase level	1	4
Leukopenia	1	5
Constipation	0	1

Note: patients who underwent randomisation but received no treatment were not included: seven in the IFN group, one in the temsirolimus group and two in the combination-therapy group.

had/had not undergone surgical resection of the primary tumour and (2) people diagnosed with clear cell and non-clear cell carcinoma. For the assessment of the clinical effectiveness of bevacizumab plus IFN, sorafenib, sunitinib and temsirolimus as first-line therapy in people with poor prognosis, the following subgroup data were available:

1. People with clear cell RCC compared with those with non-clear cell RCC. Only patients with predominantly clear cell pathology were eligible for entry to the studies of bevacizumab plus IFN and sunitinib. Neither study, therefore, provides any indication as to the relative effectiveness of the interventions amongst patients with clear cell RCC compared with those with non-clear cell RCC. HRs for

overall and PFS for patients with and without clear cell RCC are presented for temsirolimus versus IFN in *Tables 25* and *26*, respectively; although the results suggest that temsirolimus may be more effective that IFN in people diagnosed with clear cell carcinoma and with non-clear cell carcinoma, there is a large amount of uncertainty in the estimates. It is not clear from the report whether the results were considered statistically significant.

2. People who have undergone surgical resection of the primary tumour compared with those who have not. The study[106] of the combination of bevacizumab and IFN compared with IFN alone only included people who had undergone total or partial nephrectomy before entry to the study. This trial therefore cannot provide any information on the relative effectiveness of these treatments in people who have or have not undergone surgical resection of the primary tumour. In the trial by Motzer and colleagues[107] a small proportion of people who had not had a previous nephrectomy were included [35 (9%) in the sunitinib group and 40 (11%) in the IFN group]. However, no additional information is provided on the MSKCC risk factor status of these patients. This trial is therefore not able to provide any further evidence as to the relative effectiveness of sunitinib and IFN in patients with poor prognosis who have or have not undergone previous nephrectomy. OS for people who have and have not undergone previous nephrectomy in the trial of temsirolimus versus IFN[108] is shown in *Table 27*. Patients in both subgroups appear to respond better to temsirolimus than to IFN, which is consistent with the overall result. Examination of the uncertainty around the results suggests that surgical removal of the primary tumour is not an important factor in predicting the likely response to these treatments, although a type II error

TABLE 25 *Summary of overall survival for patients with clear or non-clear cell RCC: temsirolimus versus IFN as first-line therapy in people with poor prognosis*

	Hudes *et al.* 2007[96,108]		
	Temsirolimus vs IFN		
	n	**HR for OS**	**95% CI**
Clear cell	339	0.85	0.64 to 1.06
Non-clear cell	73	0.55	0.33 to 0.90
Total trial population	412	0.73	0.58 to 0.92
Note: data missing for four patients.			

TABLE 26 *Summary of progression-free survival for patients with clear or non-clear cell RCC: temsirolimus versus IFN as first-line therapy in people with poor prognosis*

	Hudes *et al.* 2007[108a]		
	Temsirolimus vs IFN		
	n	**HR for PFS**	**95% CI**
Independent assessment			
Clear cell	339	0.84	0.67 to 1.05
Non-clear cell	73	0.36	0.22 to 0.59
Investigators' assessment			
Clear cell	339	0.82	0.66 to 1.02
Non-clear cell	73	0.40	0.25 to 0.65
a Data from Wyeth submission.[124]			

TABLE 27 *Summary of overall survival for patients with and without previous nephrectomy: temsirolimus versus IFN as first-line therapy in people with poor prognosis*

	Hudes *et al.* 2007[108]		
	Temsirolimus vs IFN		
	n	HR for OS	95% CI
Previous nephrectomy	278	0.84	0.63 to 1.11
No previous nephrectomy	138	0.61	0.41 to 0.91
Total trial population	416	0.73	0.58 to 0.92

remains possible. PFS data from the trial of temsirolimus versus IFN for people who have and have not undergone previous nephrectomy was not reported in the published paper,[108] but was reported in the Wyeth submission[124] (*Table 28*). HRs for PFS, assessed by either investigators or independent assessors, favoured poor prognostic patients who were treated with temsirolimus over those treated with IFN, irrespective of whether the patients had had a previous nephrectomy.

Overall conclusion: first-line therapy in people with poor prognosis

There is limited data available to draw clear conclusions about the most effective first-line therapy for people with RCC regarded as having poor prognosis.

We were unable to find any data on the use of sorafenib in this population, nor any head-to-head randomised trials of the new interventions, nor any comparisons with BSC.

Unfortunately, because of differences in study and baseline population characteristics we were unable to perform any indirect comparisons using the trials of the interventions versus IFN.

Bevacizumab plus IFN versus IFN

There is some evidence to suggest that, in the poor prognosis subgroup, the combination of bevacizumab plus IFN is more effective in terms of prolonging PFS than IFN alone (2.2 months versus 2.1 months; HR 0.81, 95% CI 0.46 to 1.42); this is consistent with the results obtained from the entire trial population. No additional safety data were available for this subgroup, but there is also nothing in the trial report to suggest that the

TABLE 28 *Summary of progression-free survival for patients with and without previous nephrectomy: temsirolimus versus IFN as first-line therapy in people with poor prognosis*

	Hudes *et al.* 2007[108,124]			
	Temsirolimus vs IFN			
	n	HR for PFS	95% CI	*p*-value[a]
Investigators' assessment				
Previous nephrectomy	278	0.74	0.58 to 0.95	0.4204
No previous nephrectomy	138	0.63	0.44 to 0.91	
Independent assessment				
Previous nephrectomy	278[b]	0.72	0.55 to 0.93	0.4735
No previous nephrectomy	138[b]	0.62	0.43 to 0.88	

a Interaction analysis.
b The number of patients for whom the results of independent assessment of radiological images were available is not reported in the industry submission; we assume that there were no missing data.

adverse event profile would be any different than that seen in the whole trial population.

Sunitinib versus IFN

Although some of the patients included in the trial of sunitinib versus IFN were characterised as having poor prognosis, the results of the trial were not reported according to prognosis and so this trial is also not able to offer any substantial evidence.

Temsirolimus versus IFN

From the limited clinical data available, treatment with temsirolimus appears to have clinically relevant and statistically significant advantages over treatment with IFN in people with poor prognosis, in terms of OS, PFS and tumour response. Median PFS was approximately doubled from 1.9 months with IFN to 3.8 months with temsirolimus (HR 0.74; 95% CI 0.60 to 0.90). Data on adverse events suggest that temsirolimus may be associated with a lower frequency of grade 3 or 4 adverse events than IFN, although the overall frequency of adverse events is still relatively high.

Data on patients with and without clear cell carcinoma and previous nephrectomy suggest that temsirolimus is more effective than IFN in all of these subgroups. Whether the results are sufficiently distinct from each other to suggest that people in these subgroups respond differently to temsirolimus is not clear.

Sorafenib and sunitinib compared with best supportive care as second-line therapy

In this section we address research question 4: In those who have failed treatment with cytokine-based immunotherapy, what is the clinical effectiveness of sorafenib tosylate, sunitinib and BSC as second-line therapy, using BSC as a comparator?

Quantity, quality and characteristics of included studies

We were unable to find any useful definitions of BSC in this population in the literature, or any trials that compare sorafenib or sunitinib with BSC. We identified two trials of sorafenib tosylate as second-line therapy, an RCT of sorafenib versus placebo[109] and a randomised discontinuation trial (RDT) of sorafenib versus placebo.[110] We have therefore assumed that treatment with placebo is equivalent to BSC.

We were unable to locate any RCTs of sunitinib as second-line therapy; however, we did identify two single-arm phase II trials.[85,111,112]

Study characteristics are summarised in the next section and in *Table 60* in Appendix 5. A summary of the quality assessment of these studies is shown in *Table 9*.

Study characteristics

Sorafenib versus best supportive care

Escudier and colleagues report the results of the TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) study, an international (Argentina, Australia, Belgium, Brazil, Canada, Chile, France, Germany, Hungary, Israel, Italy, Netherlands, Russia, South Africa, Ukraine, UK and USA), multicentre, double-blind and placebo-controlled phase III RCT in which 903 patients with histologically confirmed metastatic clear cell RCC were randomised to receive either sorafenib (400 mg orally twice daily; $n = 451$) or matched placebo ($n = 452$). Results of this trial have been reported in two full publications[109,114] and five abstracts.[98,99,102,103,125] The primary outcome was OS. PFS and overall response rate were amongst the secondary outcome measures. Data on safety and HRQoL were also collected. The study was designed to have 90% power to detect a 33.3% difference in survival between the two groups at a two-sided alpha level of 0.04 after 540 patients had died. Patients were stratified according to country and MSKCC prognostic score (low or intermediate).

Eligibility criteria included the presence of histologically confirmed metastatic clear cell RCC that had progressed after one systemic treatment within the previous 8 months, an ECOG-PS of 0 or 1, an intermediate or low risk according to the MSKCC prognostic score and a life expectancy of at least 12 weeks.

Treatment was continued until evidence of disease progression or withdrawal from the study because of adverse events occurred. Dose reductions (to 400 mg once daily and then to 400 mg every other day) were permitted to manage adverse events.

Enrolment of patients took place between 23 November 2003 and 3 March 2005. From November 2003 until April 2005 the sponsor and investigators were unaware of the study group assignments in the evaluation of data. In January 2005 a protocol-defined independent review of the status of 769 patients (384 in the sorafenib group

and 385 in the placebo group) was conducted. In April 2005 a decision was made by the independent data and safety monitoring committee that study group assignments should be revealed and that sorafenib should be offered to patients receiving placebo. The initial analysis of OS, which is presented in the main publication,[109] is based on data obtained before treatment crossover. A further analysis of OS was performed 6 months later.

The median duration of treatment (at the time of the interim analysis) was 23 weeks in the sorafenib group and 12 weeks in the placebo group. Dose intensity was not reported.

No supplementary additional data were identified in conference abstracts. (Commercial-in-confidence data have been removed.)[109]

In 2006, Ratain and colleagues[110] reported the results of an RDT of sorafenib versus placebo in a total of 202 patients with metastatic clear cell RCC. In an RDT (a study design that was developed in an attempt to assess the clinical activity of a drug whilst minimising exposure to placebo) all patients receive the study drug for an initial run-in period followed by random assignment of potential responders to either the active drug or placebo. The design creates a controlled trial without upfront randomisation and decreases the heterogeneity of randomised patients, resulting in increased statistical power with smaller patient numbers. The study initially permitted enrolment of patients ($n = 502$) with a variety of tumour types including metastatic RCC and metastatic colorectal cancer. Early indications of activity in patients with RCC caused a refocus on this patient population and resulted in 40% of patients in the overall trial having a diagnosis of metastatic RCC. The paper by Ratain and colleagues[110] describes only the RCC population. The primary outcome measure was the percentage of randomly assigned patients who remained progression free at 12 weeks following random assignment. Other end points included PFS after random assignment (randomised subset only), overall PFS (from start of treatment), tumour response rate and safety. The study was designed to have 81% power to detect a drug effect that corresponded to a reduction in the progression rate from 90% to 70% 12 weeks after randomisation.

Sorafenib (400 mg twice a day) was administered to all patients in a 12-week open-label run-in period after which disease status was assessed based on changes in bidimensional tumour measurements from baseline. Patients with ≥ 25% tumour shrinkage continued to receive sorafenib until disease progression or toxicity. Patients with PD (≥ 25% tumour growth or other evidence of progression) discontinued treatment. Patients who had a change in tumour size of < 25% were randomly assigned to either sorafenib (at the same dose) or matched placebo using centrally allocated allocation via a telephone randomisation system. Treatment was stopped on disease progression.

No additional supplementary data were identified either in abstract form or as part of the company submission for sorafenib.

Sunitinib

Motzer and colleagues report the results of two similar open-label, single-arm trials of sunitinib as second-line therapy in patients with metastatic clear cell RCC. In both trials, conducted in multiple centres in the USA and reported in 2006, patients received treatment with sunitinib [50 mg per day, self-administered orally, in repeated 6-week cycles (4 weeks on treatment followed by 2 weeks off)] until evidence of disease progression, unacceptable toxicity or withdrawal of consent.

In the earlier trial ($n = 63$),[112] eligible patients had a diagnosis of histologically confirmed metastatic RCC (of any subtype), evidence of failure of one cytokine-based therapy because of disease progression or unacceptable toxicity, and an ECOG-PS of 0 or 1. Entry criteria for the larger trial ($n = 105$)[111] were similar, but entry was restricted to patients with histologically confirmed clear cell typology who had undergone previous nephrectomy. The primary outcome measure in both trials was objective response rate according to the RECIST criteria.[111] A later publication providing OS data is also available.[85]

No additional supplementary data were identified within the relevant conference abstracts or the company submission for sunitinib.

Quality assessment

Sorafenib versus best supportive care

The quality assessment of these trials is summarised in *Table 9*. Both are well-conducted and well-reported large, multicentre trials. In the report of the RCT of sorafenib versus placebo[109] the authors state that the final planned analysis of OS (which was undertaken after treatment crossover) was conducted on an ITT basis. It is not clear whether the unplanned analysis of OS (before treatment crossover) was also performed under

these conditions. Methods for censoring in these analyses are also not provided.

The company submission to NICE from Bayer includes commercial-in-confidence subgroup analyses from this trial. (Commercial-in-confidence data have been removed.) For several reasons we have not considered the results of this analysis further. The clinical basis underlying an expected difference in response to treatment in these two groups of people is not immediately evident. (Commercial-in-confidence data have been removed.) To be considered eligible for the study, patients were required to have disease that had progressed after one systemic treatment within the previous 8 months; in 17% of patients the nature of this systemic therapy is not reported in the paper. (Commercial-in-confidence data have been removed.)

It appears from the details of the sample size calculation provided in the RDT that the investigators were aiming to recruit 50 randomly assigned patients to each group. In practice, a total of 65 patients was randomly assigned in the study.

Sunitinib

We have applied a similar list of quality assessment criteria to the two sunitinib trials as used in other critical appraisals in this assessment (*Table 9*), with obvious exceptions (e.g. methods of randomisation and concealment, etc.); they appear to be well designed and reported.

Population baseline characteristics

Sorafenib versus best supportive care

In the study by Escudier and colleagues,[109] population characteristics at baseline were well balanced between the groups in terms of demographic factors (age and gender distribution) and disease status (ECOG-PS and MSKCC prognostic risk score, the proportion of patients with multiple metastatic sites, the location of metastases, previous systemic therapy, the proportion of patients with previous nephrectomy and the median duration of disease) (*Table 29*). Approximately half of the people in the trial had an ECOG-PS of 0, most (83%) had had previous cytokine-based treatment and the majority (94%) had undergone previous nephrectomy. To be considered eligible for the study, patients were required to have disease that had progressed after one systemic treatment within the previous 8 months; in 17% of patients the nature of this systemic therapy is not reported in the paper.

A similar group of patients was entered into the RDT[110] and again the groups were well balanced at baseline. There were slightly more females in the placebo group, but this difference was not statistically significant.

Sunitinib

As already described the two trials of sunitinib[85,111,112] included patients with similar baseline characteristics, the main differences between trials being the proportion of patients with clear cell RCC and the proportion of patients with previous nephrectomy (*Table 29*).

Comparability of baseline population characteristics between trials

Participants in all four trials were similar in terms of age, gender distribution and disease status. Approximately 50% of people in all four trials had an ECOG-PS of 0 and a favourable prognostic score according to MSKCC criteria. Cytokine-based therapies had failed to halt disease progression in the majority of patients and most had undergone a previous nephrectomy. Almost all patients had two or more sites of metastatic disease with the lung being the most common site for metastases in all trials.

Assessment of clinical effectiveness

Overall survival (*Table 30*)

Sorafenib versus best supportive care

Overall survival (defined as the time between the date of randomisation until the date of death) was the primary end point in the RCT of sorafenib versus placebo.[109] In the analysis performed before treatment crossover, 220 of the 540 deaths required for the comparison to be adequately powered had occurred; 97 deaths in the sorafenib group and 123 deaths in the placebo group. Median actuarial OS had not been reached in the sorafenib group and was 14.7 months in the placebo group with a HR of 0.72 (95% CI 0.54 to 0.94; $p = 0.02$). This result was not considered statistically significant as it did not reach the O'Brien–Fleming threshold of 0.0005.

Overall survival was not an outcome measure in the RDT.[110]

Sunitinib

Overall survival was 23.9 months (95% CI 14.1 to 30.7 months) in the larger trial of 105 patients[85,111] and 16.4 months (95% CI 10.8 to not yet attained) in the smaller trial ($n = 63$).[112] Interpretation of these results is difficult because of the lack of a comparator group.

TABLE 29 *Baseline population characteristics: sorafenib and sunitinib versus BSC as second-line therapy*

	Escudier et *al.* 2007[109]		**Ratain et *al.* 2006[110a]**		**Motzer et *al.* 2006[85,111]**	**Motzer et *al.* 2006[112]**
	Sorafenib	**Placebo**	**Sorafenib**	**Placebo**	**Sunitinib**	**Sunitinib**
Number randomised	451	452	32	33	106	63
Diagnosis	Metastatic clear cell RCC		Metastatic RCC		Metastatic clear cell RCC	Metastatic RCC
Age (years), median (range)	58 (19–86)	59 (29–84)	58 (32–76)	60 (23–74)	56 (32–79)	60 (24–87)
Male, *n* (%)	315 (70)	340 (75)	21 (64)	26 (81)	67 (63)	43 (68)
Duration of disease (years), median (range)	2 (< 1–19)	2 (< 1–20)	3.3 (0–21.2)	2.8 (0–11.7)	NR	NR
ECOG-PS, n (%):						
0	219 (49)	210 (46)	18 (56)	18 (55)	58 (55)	34 (54)
1	223 (49)	236 (52)	14 (44)	15 (45)	48 (45)	29 (46)
2	7 (2)	4 (1)	0	0	0	0
Data missing	2 (< 1)	2 (< 1)	0	0	0	0
MSKCC risk factors, n (%):						
0 (favourable)	233 (52)	236 (52)	13 (41)	14 (42)	61 (57.5)	NR
1–2 (intermediate)	218 (48)	223 (49)	18 (56)	15 (45)	41 (38.7)[b]	
≥ 3 (poor)	0	0	0	3 (9)	4 (3.8)[c]	
Missing data	0	1 (< 1)	1 (3)	1 (3)	0	
Previous systemic therapy, n (%):						
Cytokine based	374 (83)	368 (81)	26 (81)	28 (85)	NR	NR
Interleukin-2	191 (42)	189 (42)	NR	NR	50 (47)	19 (30)
Interferon	307 (68)	314 (69)	NR	NR	47 (44)	35 (56)
Both interleukin-2 and interferon	124 (27)	135 (30)	NR	NR	9 (9)	9 (14)
Radiotherapy	124 (27)	108 (24)	9 (28)	11 (33)	20(19)	25 (40)
Number of patients with a previous nephrectomy	422 (94)	421 (93)	29 (91)	29 (88)	106 (100)	58 (92)

	Escudier et al. 2007[109]		Ratain et al. 2006[110a]		Motzer et al. 2006[85,111]	Motzer et al. 2006[112]
	Sorafenib	Placebo	Sorafenib	Placebo	Sunitinib	Sunitinib
Number of metastatic sites, n (%):						
1	62 (14)	63 (14)	8 (25)	4 (12)	13 (12)	8 (13)
2	131 (29)	129 (29)	7 (22)	15 (45)	38 (36)	NR
> 2	256 (57)	258 (57)	17 (53)	14 (42)	55 (52)	55 (87)
Missing data	2 (< 1)	2 (< 1)	0	0	0	0
Sites of metastases, n (%):						
Lung	348 (77)	348 (77)	28 (88)	23 (70)	86 (81)	52 (81)
Liver	116 (26)	117 (26)	5 (16)	10 (30)	29 (27)	10 (16)
Bone	NR	NR	NR	NR	27 (26)	32 (51)
Lymph nodes	NR	NR	14 (44)	16 (48)	62 (59)	NR
Kidney	NR	NR	12 (38)	15 (45)	NR	NR
Histology type, n (%):						
Clear cell	451 (100)[d]	452 (100)[d]	27 (84)	25 (76)	106 (100)	55 (87)
Papillary	0	0	0	3 (9)	0	4 (6)
Sarcomatoid variant	0	0	1 (3)	2 (6)	0	1 (2)
Missing data	0	0	4 (13)	3 (9)	0	3 (5)

NR, not reported.
a Data presented are from the randomisation period only.
b Number (%) of patients with MSKCC score = 1.
c Number (%) of patients with MSKCC score ≥ 2.
d Although it was a criteria for entry into this study that patients must have a diagnosis of clear cell RCC, the authors state in the paper that 99% of patients had clear cell RCC – no further details are provided.

TABLE 30 *Summary of overall survival: sorafenib and sunitinib versus BSC as second-line therapy*

Study	Intervention	*n*	Median OS (months)	HR	95% CI for HR	*p*-value
Escudier *et al.* 2007[109]	Sorafenib	451	Not reached	0.72	0.54 to 0.94	0.02
	Placebo	452	14.7			
Motzer *et al.* 2006[112]	Sunitinib	63	16.4 (95% CI 10.8 to not yet attained)	N/A	N/A	N/A
Motzer *et al.* 2006[85,111]	Sunitinib	105	23.9 (95% CI 14.1 to 30.7)			

N/A, not applicable.

Progression-free survival (*Table 31*)

Sorafenib versus best supportive care

Escudier and colleagues[109] determined disease progression on the basis of CT or MRI, clinical progression or death. Imaging studies were performed every 8 weeks and assessed according to the RECIST criteria. Investigators and independent radiologists who were unaware of treatment assignments assessed PFS. No information on the method of censoring of values is provided. Median PFS (defined as the time from the date of randomisation to the date of progression) based on 769 patients at the first preplanned interim analysis was 5.5 months in the sorafenib group and 2.8 months in the placebo group; it is unclear from the paper but we assume that this analysis was based on assessment by independent radiologists. Investigator-assessed PFS at the same time point was 5.9 months in the sorafenib group and 2.8 months in the placebo group, with a HR of 0.44 (95% CI 0.35 to 0.55; $p < 0.001$).

A similar result was obtained at treatment crossover when investigator-assessed PFS in 903 patients was found to be 5.5 months in the sorafenib group and 2.8 months in the placebo group (HR 0.51; 95% CI 0.43 to 0.60; $p < 0.001$). It is unclear why the authors have chosen to present results based on investigator assessment rather than on assessment by independent radiologists or if there were any differences in the results obtained by the two methods of assessment.

In the RDT of sorafenib versus placebo,[110] at 12 weeks post randomisation (24 weeks from study entry) there was a statistically significant ($p = 0.0077$) difference between groups in the

TABLE 31 *Summary of progression-free survival: sorafenib and sunitinib versus BSC as second-line therapy*

Study	Intervention	*n*	Median PFS (months)	HR	95% CI for HR	*p*-value
Escudier *et al.* 2007[109]	*Assessment by independent radiologists – first planned interim analysis:*					
	Sorafenib	384	5.5	0.44	0.35 to 0.55	< 0.001
	Placebo	385	2.8			
	Assessment by investigators – first planned interim analysis:					
	Sorafenib	384	5.9	NR	NR	< 0.001
	Placebo	385	2.8			
	Assessment by investigators – unplanned analysis before treatment crossover:					
	Sorafenib	451	5.5	0.51	0.43 to 0.60	< 0.001
	Placebo	452	2.8			
Motzer *et al.* 2006[112]	Sunitinib	63	8.7 (95% CI 5.5 to 10.7)	N/A	N/A	N/A
Motzer *et al.* 2006[85,111]	Sunitinib	105	8.8 (95% CI 7.8 to 13.5)	N/A	N/A	N/A

N/A, not applicable; NR, not reported.

proportion of patients in whom disease progression was evident (50% of patients treated with sorafenib versus 82% treated with placebo). Median PFS from the date of randomisation was also significantly longer in the sorafenib group than in the placebo group (24 weeks versus 6 weeks; $p = 0.0087$).

Sunitinib

The two trials of sunitinib produced similar results for PFS. In the smaller trial,[112] median PFS was 8.7 months (95% CI 5.5 to 10.7 months). Based on independent third-party assessment of response, median PFS in the larger trial[85,111] was 8.8 months (95% CI 7.8 to 13.5 months). Interpretation of these results is difficult because of the lack of a comparator group.

Tumour response (*Table 32*)

Sorafenib versus best supportive care

In the RCT of sorafenib and placebo,[109] at the initial planned interim analysis, tumour response was assessed (by independent reviewers according to RECIST criteria) in 672 patients, although data were missing for 87 (approximately 13%). Data were available for 297 patients in the sorafenib group and 288 in the placebo group. In the sorafenib group seven patients (2%) had a partial response, 261 (78%) patients had stable disease and 29 patients (9%) had PD. In the placebo group no patients were assessed as having a partial response, 186 (55%) had stable disease and 102 (30%) had PD. At the unplanned analysis before treatment crossover, according to blinded investigator assessment, one patient in the sorafenib group exhibited a complete response, 43 had a partial response and 333 had stable disease. In the placebo group the corresponding figures were none, eight and 239. Significantly ($p < 0.001$) more patients in the sorafenib group than the placebo group had a complete or partial response.

Tumour response was not an outcome measure in the RDT.[110]

Sunitinib

In the two trials of sunitinib objective tumour response, defined according to RECIST, was the primary end point. Assessments of tumour response were made using CT or MRI and bone scans (if bone metastases were present at baseline) at least after every two cycles (the assessment intervals were slightly different in the two trials) until the end of treatment. In the smaller trial ($n = 63$)[112] partial responses were achieved in 25 patients (40%; 95% CI 28% to 53%). Best response of stable disease for 3 or more months was observed in a further 17 patients (27%). The remaining patients ($n = 21$; 33%) had either progressive or stable disease of less than 3 months duration or were not assessable. In the larger trial[111] tumour response was assessed both by treating physicians and a third-party imaging laboratory (with two radiologists). According to third-party assessment of images, 33% of patients ($n = 35$) had a partial response and a further 30% of patients ($n = 31$) had stable disease for 3 or more months. The remainder ($n = 39$; 37%) were assessed as having PD or stable disease for less than 3 months. These results are difficult to interpret as there was no comparator group.

TABLE 32 *Summary of tumour response: sorafenib and sunitinib versus BSC as second-line therapy*

Study	Intervention	*n*	Complete response	Partial response	Stable disease	Progressive disease	Not assessed
Escudier *et al.* 2007[109a]	Sorafenib	451	1 (< 1)	43 (10)	333 (74)[b]	56 (12)	18 (4)
	Placebo	452	0	8 (2)	239 (53)[b]	167 (37)	38 (8)
Motzer *et al.* 2006[112]	Sunitinib	63	0	25 (40)	17 (27)[c]	21 (33) patients had progressive disease, stable disease for less than 3 months or were not assessable	
Motzer *et al.* 2006[85,111]	Sunitinib	105	0	35 (33)	31 (30)[c]	39 (37) patients had progressive disease, stable disease for less than 3 months or were not assessable	

Results presented as number (%) of patients.
a Results from blinded investigator assessment of images.
b Stable disease defined as stable disease for at least 28 days.
c Stable disease defined as stable disease for 3 months or more.

Health-related quality of life

Sorafenib versus best supportive care

In the RCT of sorafenib versus placebo,[109] the FACT-G and the FKSI were administered to assess the impact of treatment on HRQoL (see Chapter 1, Quality of life). Assessments were made every 6 weeks for the first 24 weeks and then every 8 weeks. Subjects completed the questionnaires before seeing the physician. No further assessments were made after withdrawal from treatment. There was no significant difference between the placebo and sorafenib groups in mean FACT-G physical well-being score nor any numerical or statistical difference in mean FKSI-10 total score between groups over the first 30 weeks of treatment ($p = 0.83$ and $p = 0.98$ respectively).

However, there were statistically significant changes in some of the individual items of the FKSI-15 in patients receiving sorafenib compared with those receiving placebo in the first 30 weeks of treatment. These included less coughing ($p < 0.0001$), fewer fevers ($p = 0.0015$), a greater ability to enjoy life ($p = 0.0119$) and less worry about their disease ($p = 0.0004$). Fewer patients in the placebo group reported being bothered by the side effects of treatment ($p < 0.0001$). There were no significant differences between groups in terms of patients' perceptions of fatigue, quality of sleep, pain, weight change or energy levels.

HRQoL was not assessed in the RDT.[110]

Sunitinib

The EQ-5D questionnaire and the Functional Assessment of Chronic Illness Therapy – fatigue scale (FACIT-fatigue) were used to assess HRQoL in the smaller trial of sunitinib.[112] EQ-5D questionnaires were administered on days 1 and 28 of each cycle, and the FACIT-fatigue questionnaire was completed on day 1 and then weekly for cycles 1–4. Compliance with questionnaires at baseline and subsequent visits was high (at or above 90% at each visit for each instrument).

Assessable baseline questionnaires for EQ-5D were received from 60 patients and compliance with subsequent assessments was high. Mean and median health state visual analogue scale scores indicated that the study population's quality of life before treatment was similar to that of an age-matched US general population. Mean and median health state visual analogue scale scores were similar to baseline scores throughout the 24 weeks of treatment.

Valid baseline questionnaires for the FACIT-fatigue scale were received from 62 patients. Mean and median baseline scores for the study population were similar to scores of a population with cancer (but no anaemia) but lower than those of a general US population. Median and mean fatigue scores were similar to baseline scores throughout 24 weeks of treatment, although the authors did notice a mild and reversible effect of treatment on fatigue levels.

These results are not easy to interpret or extrapolate as there was no comparator group.

Indirect comparison of sorafenib versus sunitinib versus best supportive care as second-line therapy

Although we were able to locate four trials relevant to this comparison, all of which included patients with similar baseline characteristics, because there was no common treatment arm we were unable to consider an indirect comparison of sorafenib, sunitinib and BSC.

Adverse events

In all trials adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0[110,112] or version 3.[109,111] *Table 61* in Appendix 5 shows adverse events of any grade reported during the course of all four studies. In *Table 33* only those adverse events classified as grades 3 or above are included. Criteria for reporting adverse events were slightly different in the four trials. The TARGET trial[109] reports all adverse events of any grade occurring in at least 10% of patients, with a breakdown of grade 2 events and all adverse events of grade 3 or 4 occurring in at least 2% of patients. In the RDT,[110] all adverse events occurring in at least 10% of patients in the total safety population are provided (no comparison with placebo). In the two phase II trials of sunitinib only adverse events that were considered to be treatment related occurring in 5%[112] and 20%[111] of patients were reported, together with selected laboratory abnormalities. The data available from the last two studies are therefore limited and reference should also be made to the section on bevacizumab plus IFN and sunitinib compared with IFN as first-line treatment where full details of the adverse events reported in the RCT of sunitinib as first-line treatment are discussed.

Sorafenib versus best supportive care

In the TARGET trial[109] the most common adverse events of any grade were fatigue (in 37% and 28%

of patients treated with sorafenib and placebo respectively), diarrhoea (43% and 13% of patients respectively), rash or desquamation (40% and 16% respectively), nausea (23% and 19% respectively), hand–foot skin reaction (30% and 7% respectively) and alopecia (27% and 3% respectively). There was a statistically significant difference between groups in the proportion of patients reporting grade 2 hypertension, weight loss, diarrhoea, hand–foot skin reaction, rash, alopecia and pruritus; these events were all more common in the sorafenib group. The difference remained significant for hypertension and hand–foot skin reaction when grade 3 and grade 4 adverse events were considered. Grade 3 or 4 bone pain was reported significantly more often by patients in the placebo group. In addition to the events described in *Table 33*, cardiac ischaemia or infarction occurred in 12 patients (3%) in the sorafenib group and two patients in the placebo group (1%); this difference was also statistically significant ($p = 0.01$). Of these events, 11 (including two deaths in the sorafenib group and one death in the placebo group) were considered to be serious adverse events associated with treatment. Serious adverse events leading to hospitalisation or death were reported in 154 patients (34%) in the sorafenib group (46 deaths;10%) and 110 patients (24%) in the placebo group (25 deaths; 6%) ($p < 0.01$). The most frequent drug-related serious adverse event was hypertension (in 1% and 0% of sorafenib and placebo patients respectively).

In the RDT of sorafenib versus placebo,[110] the most common treatment-emergent adverse events were fatigue (73% of patients), rash or desquamation (66%), hand–foot skin reaction (62%), pain (58%) and diarrhoea (58%). The most common grade 3 or 4 adverse event was hypertension, which was observed in 31% of patients. Nine patients discontinued drug treatment as a result of unacceptable toxicity. There were no adverse event-related deaths in the trial.

Sunitinib versus best supportive care

A similar adverse event profile is reported in both trials,[111,112] although these are described as 'selected treatment-related adverse events' and full information on all adverse events experienced within the trials is not available. The most commonly reported adverse events were fatigue (38%), diarrhoea (24%), nausea (19%), dyspepsia (19%) and stomatitis (16%) in one trial[112] and fatigue (28%), diarrhoea (20%), dyspepsia (16%), hypertension (16%) and hand–foot syndrome (15%) in the other.[111]

Decline in ejection fraction was also observed in both trials [eight patients (4.7%);[111] seven patients (11%)[112]], although it is unclear whether this represents incidental observation or the results of active monitoring. The decline was sufficient to warrant removal of four patients from the study.[112] One trial[111] reports a total of 31 deaths, 10 of these within 28 days of the last dose of sunitinib; one of these deaths (myocardial infarction) was considered to be possibly related to the study medication.

Summary of safety data

From the data reported in these trials, treatment with sorafenib appears to be associated with an increased frequency of hypertension, hand–foot skin reaction and some gastrointestinal events such as diarrhoea. Although some of the events were classed as grade 3 (severe and undesirable) and grade 4 (life-threatening or disabling), events of this severity occurred in a small proportion of patients (e.g. 4% and 6% for hypertension and hand–foot skin reaction, respectively, in the TARGET trial). Grade 3 hypertension is defined as needing more than one drug for treatment or more intensive treatment than used previously; hypertension with life-threatening consequences (e.g. hypertensive crisis) is the definition of grade 4 hypertension.

As randomised clinical trials are not designed to collect data on rare adverse events, we briefly reviewed additional literature obtained from the results of our initial and updated literature searches to identify any further safety concerns.

A systematic review of toxicities associated with sorafenib, sunitinib and temsirolimus in phase I, II and III clinical trials found that between 1% and 16% of patients experienced grade 3 or 4 adverse events. The most commonly reported grade 3 and grade 4 adverse events associated with sorafenib treatment across all trials were lymphopenia (13%), hypophosphataemia (13%), elevated lipase (12%), mucositis (6%) and hand–foot syndrome (6%).[119]

In an expanded access trial of sorafenib in the USA and Canada ($n = 2488$),[126] the following adverse events were experienced at a frequency of > 2% in patients receiving sorafenib as first-line treatment ($n = 1239$): hand–foot skin reaction (7.7%), fatigue (4.7%), hypertension (3.8%), rash or desquamation

TABLE 33 *Adverse events (grade 3 or 4): sorafenib and sunitinib versus BSC as second-line therapy*

	Escudier *et al.* 2007[109a]		Ratain *et al.* 2006[110b]	Motzer *et al.* 2006[111c]	Motzer *et al.* 2006[112d]
Intervention	**Sorafenib**	**Placebo**	**Sorafenib**	**Sunitinib**	**Sunitinib**
n	451	452	202	106	63
Blood/bone marrow			16 (8)		
Decreased haemoglobin	12 (3)	20 (4)	14 (7)	NR	NR
Cardiovascular general			71 (35)		
Hypertension	16 (4)	2 (< 1)[e]	62 (31)	6 (6)	1 (2)
Ejection fraction decline	NR	NR	NR	NR	1 (2)
Dermatology/skin			34 (17)		
Hand–foot skin reaction	25 (6)	0[f]	27 (13)	NR	NR
Rash/desquamation	4 (1)	1 (< 1)	5 (2)	NR	NR
Alopecia	1 (< 1)	0	NR	NR	NR
Dermatitis	NR	NR	NR	NR	1 (2)
Pruritus	1 (< 1)	0	NR	NR	NR
Constitutional symptoms			18 (9)		
Weight loss	3 (< 1)	0	5 (2)	NR	NR
Fatigue	22 (5)	16 (4)	13 (6)	12 (11)	7 (11)
Other symptoms	6 (1)	6 (1)	NR	NR	NR
Gastrointestinal			28 (14)		
Anorexia	3 (< 1)	5 (1)	6 (3)	1 (1)	0
Diarrhoea	11 (2)	3 (1)	8 (4)	3 (3)	2 (3)
Nausea	3 (< 1)	3 (1)	0	0	2 (3)
Vomiting	4 (1)	6 (1)	0	0	2 (3)
Dyspepsia	NR	NR	NR	1 (1)	0
Stomatitis	NR	NR	0	5 (5)	1 (2)
Mucosal inflammation	NR	NR	NR	1 (1)	NR
Constipation	3 (1)	3 (1)	0	NR	0

	Escudier et al. 2007[109a]		Ratain et al. 2006[110b]	Motzer et al. 2006[111c]	Motzer et al. 2006[112d]
Intervention	**Sorafenib**	**Placebo**	**Sorafenib**	**Sunitinib**	**Sunitinib**
Haemorrhage			8 (4)		
Hepatic			10 (5)		
Infection/febrile neutropenia			10 (5)		
Infection without neutropenia	NR	NR	10 (5)	NR	NR
Metabolic/laboratory			35 (17)		
Hyperglycaemia	NR	NR	6 (3)	NR	NR
Hypophosphataemia			14 (7)		
Neurology/sensory neuropathic	2 (< 1)	3 (1)	12 (6)		
Pain			25 (12)		
Extremity pain	0	0	NR	1 (1)	0
Abdominal pain	7 (2)	9 (2)	0	NR	NR
Headache	1 (< 1)	2 (< 1)	0	NR	NR
Joint pain	7 (2)	1 (< 1)	0	NR	NR
Bone pain	3 (1)	15 (3)	NR	NR	NR
Tumour pain	13 (3)	8 (2)	NR	NR	NR
Pulmonary			21 (10)		
Cough	1 (< 1)	1 (< 1)	0	NR	NR
Dyspnoea	16 (4)	11 (2)	18 (9)	NR	NR
Other pulmonary symptoms	NR	NR	7 (3)	NR	NR

NR, not reported.
Data presented as number (%) of patients. Figures indicate a statistically significant difference between groups.
a Grade 3 or 4 adverse events that occurred in at least 2% of patients.
b Grade 3 or 4 adverse events based on the incidence of adverse events of any grade occurring in 10% or more of patients in the total safety population.
c Grade 3 or 4 treatment-related adverse events that occurred in at least 20% of patients.
d Grade 3 or 4 selected treatment-related adverse events that occurred in at least 5% of patients.

(5.2%), dehydration (2.9%), diarrhoea (2.6%) and dyspnoea (2.6%). These data suggest an adverse event profile similar to that reported in the phase III trial.[126]

We identified a systematic review and meta-analysis of the incidence and risk of hypertension with sorafenib in patients with cancer conducted by Wu and colleagues[120] and published in February 2008 in *Lancet Oncology*. They identified nine studies in which 3567 patients with RCC or other solid tumours had received sorafenib, including the TARGET trial[109] and the RDT[110] described above. The overall incidence of all-grade hypertension amongst patients receiving sorafenib was 23.4% (95% CI 16.0% to 32.9%) with 5.7% (95% CI 2.5% to 12.6%) of patients experiencing grade 3 or 4 hypertension. The authors estimate the relative risk for all-grade hypertension in patients receiving sorafenib as 6.11 (95% CI 2.44 to 15.32; $p < 0.001$) using data from two RCTs ($n = 1089$). As with all meta-analyses this analysis is limited by the quality of the data in the contributing studies. The authors note possible areas of ambiguity in the grading of hypertension and the lack of data on baseline measurement of blood pressure, both of which may have influenced the results. Although a large proportion of the patients included in the analysis were from the expanded access programme where measurement of hypertension may not have been as precise as in laboratory conditions, the relative risk was calculated using only data allowing a comparison between events reported with and without sorafenib treatment.

A similar systematic review and meta-analysis of the incidence and risk of hand–foot skin reaction with sorafenib treatment, also published in 2008,[127] found a 33.8% (95% CI 24.5% to 44.7%) incidence of all-grade hand–foot skin reaction in patients treated with sorafenib. The relative risk of developing all-grade hand–foot skin reaction with sorafenib was 6.6 (95% CI 3.7 to 11.7; $p < 0.001$).

Comparison of the safety profile of sunitinib with that of BSC is not possible from the phase II trials. Sunitinib treatment was most frequently associated with fatigue, diarrhoea, nausea, hypertension and hand–foot skin reaction, although whether these events were as a result of the treatment or of the disease process is unclear. Further discussion of the adverse events associated with sunitinib is provided in the section on bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy.

Subgroup analyses

Neither of our protocol-defined subgroup analyses was possible for this comparison as none of the identified trials provides relevant data.

Overall conclusion: sorafenib and sunitinib compared with best supportive care as second-line therapy

From the limited clinical data available, second-line therapy with sorafenib appears to have clinically relevant and statistically significant advantages over treatment with placebo (BSC) in terms of OS, PFS and tumour response. Median PFS was approximately doubled from 2.8 months with BSC to 5.5 months with sorafenib (HR 0.44; 95% CI 0.35 to 0.55).

Data on adverse events suggest that treatment with sorafenib is associated with an increased risk of hypertension and hand–foot skin reaction.

Both trials of sorafenib were conducted in patients with metastatic clear cell RCC, the majority of whom had undergone previous nephrectomy and were classified as having a favourable or intermediate prognosis according to MSKCC criteria. However, whether these results can be extrapolated to patients with other baseline characteristics (e.g. non-clear cell RCC or features of poor prognosis) is not clear.

We were unable to identify any comparative data for sunitinib as second-line therapy. The results from the two single-arm phase II trials are difficult to interpret or extrapolate. Using the placebo arm of the sorafenib trial[109] as an informal comparator it would appear that sunitinib may be efficacious in this population. Although very limited, the safety data for patients treated with sunitinib as second-line therapy do not appear to differ from that obtained in first-line trials.

Formal indirect comparison of sorafenib and sunitinib was not possible in this assessment as there was no treatment arm common to all trials.

Chapter 3
Assessment of cost-effectiveness

Aim

The aim of this chapter is to assess the cost-effectiveness of sunitinib, sorafenib, bevacizumab plus IFN, and temsirolimus against relevant comparators for licensed indications. The assessment of cost-effectiveness comprises a systematic review of the literature on the cost-effectiveness of these drugs for RCC, a review of the manufacturer submissions on cost-effectiveness to NICE, and the presentation of Peninsula Technology Assessment Group (PenTAG) estimates of cost-effectiveness. An outline discussion is presented on the literature searching undertaken of the general literature on renal cancer, covering the costs associated with treatment for RCC, HRQoL (health-state values) in RCC, and the modelling of disease progression in RCC.

Cost-effectiveness: systematic review of economic evaluations

Methods

A systematic literature search was undertaken to identify economic evaluations of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus that met the inclusion criteria for the scope of the current report.

Appendix 1 reports details of the search strategy used and databases searched. Searches were limited to publications in the English language. Manufacturer submissions to NICE were reviewed to identify additional studies. Two reviewers (CG and MH) independently examined all titles and abstracts. Full texts of any potentially relevant studies were obtained. The relevance of each paper was assessed independently (CG and MH) according to the inclusion and exclusion criteria and any discrepancies resolved by discussion.

Results

The literature search did not identify any published economic evaluations meeting the inclusion criteria. The search identified six abstracts[104,128–132] meeting the inclusion criteria; three[104,128,129] reporting on sunitinib versus BSC and three[130–132] reporting on sorafenib versus BSC or IFN. There is insufficient detail in the abstracts identified to undertake a critical appraisal of the methods used. However, a summary of study characteristics (*Table 34*) and a short summary of the literature (abstracts) is reported below.

Summary: cost-effectiveness literature (abstracts)

The economic evaluations of sunitinib comprise two abstracts[128,129] reporting findings for second-line treatment only (versus BSC) and one study[104] reporting a model, with subsequent results, for both first-line treatment and second-line treatment. The three economic evaluations on sorafenib are for first-line treatment (versus BSC) and the abstracts report a common analytical approach applied in three different country settings (USA, Canada and Spain).

All identified cost-effectiveness abstracts report the use of decision-analytic models to estimate cost-effectiveness. All use a stated Markov modelling framework. Five of the abstracts state that models are structured around the three primary health states of PFS, PD and death. All models appear to use effectiveness data from clinical trials on the difference in PFS and OS between intervention and control arms. Information on the source of effectiveness data is not clear in three of the six abstracts.

Four studies[104,128,129,131] report estimates of cost per quality-adjusted life-year (QALY), but only one study[104] provides information on health-state utilities.

Cost-effectiveness: review of related literature

Health-related quality of life

We searched the literature to inform on the health-state values (utilities) for states associated with RCC and to identify studies informing on summary (preference) measures of HRQoL (see

TABLE 34 *Summary of abstracts reporting cost-effectiveness analysis*

Characteristics	Gao et *al.* 2006[132]	Maroto et *al.* 2006[131]	Jaszewski et *al.* 2007[130]	Aiello et *al.* 2007[129]	Contreras-Hernandez et *al.* 2007[128]	Remák et *al.* 2007[104]
Treatments	Sorafenib vs BSC	Sorafenib vs BSC	Sorafenib vs BSC	Sunitinib vs BSC, second-line	Sunitinib vs BSC, second-line	Sunitinib vs IFN-α, first- and second-line
Model type	Markov	Markov	Markov	Markov	Markov	Markov
Time horizon	Lifetime	Lifetime	Lifetime	Not stated	10 year	5 year and 10 year
Perspective	USA	Spain	Canada	Argentina	Mexico	USA
Effectiveness data (stated source)	Phase III RCT[109]	Unnamed clinical trial	Phase III RCT[109]	Unnamed clinical trial and US Medicare database	Unnamed clinical trials	Phase III study[107]
Results: ICER	US$75,354 per life-year gained	€37,667 per QALY	CDN$36,046 per life-year gained	Cost of 1 progression-free month, 1 life-year saved, 1 QALY AR$9596, AR$39,518, AR$53,445	US$35,238 per QALY	First-line: US$7769 and US$7782 per progression-free month over 5 and 10 years Second-line: US$67,215 per life-year gained, US$52,593 per QALY

search strategy in Appendix 1). No published studies were identified. Two conference abstracts were identified,[97,104] but these contained limited information on which to assess methods.

Remák and colleagues[104] report a cost-effectiveness analysis for sunitinib versus IFN (*Table 34*) and in material supporting their published abstract provide summary statistics for health states used in the analysis. However, there is no detail published to support the data used. Remák and colleagues refer to EQ-5D data collected in clinical trials, presumably with EQ-5D descriptions used to estimate health-state values from published tariffs, but the trials/studies cited to support health-state utilities used do not report EQ-5D data.

Remák and colleagues report the following health-state values: utility during sunitinib treatment 0.72, utility during 2-week rest period when on sunitinib treatment 0.76, utility during IFN treatment 0.71, utility on termination of first-line treatment 0.63, utility during second-line treatment 0.63, utility on termination of second-line treatment 0.55. These data have no published foundation (stated in one slide of conference presentation).

The abstract by Parasuraman and colleagues[97] reports health-state values derived as part of an RCT of temsirolimus, in patients with a poor prognosis. The abstract (supporting materials) presents baseline 'median' EQ-5D values by treatment group: temsirolimus 0.689, IFN 0.656, temsirolimus plus IFN 0.689. Health-state utility values are also reported for health-states defined by the trial: baseline 0.689, relapse 0.587, toxicity 0.585, health state without symptoms or toxicity 0.689. It is assumed here that these values are median values, but given that there is no supporting detail these data should be treated with some caution, as is the case for data in the study by Remák and colleagues.[104]

Treatment cost/resource use

To inform on the resource use and costs associated with treatment, medical management and BSC in RCC, a literature search was undertaken (see search strategy in Appendix 1). No studies were identified that reported on these issues. We note that in one of the manufacturer submissions to NICE a study[133] is used to inform on cost for BSC in RCC. However, this reference reports the cost of hospital and

hospice care in PD for women with stage IV breast cancer in the UK.

Modelling methods for renal cell carcinoma

To inform on the methods available to model disease progression and cost-effectiveness in RCC, a literature search was undertaken (see search strategy in Appendix 1). No studies were identified that reported methods for modelling treatment in RCC or that reported cost-effectiveness analysis (other than abstracts already noted in *Table 34*). A number of studies were identified that reported on the use of survival analysis to consider progression of disease in renal cancer (and RCC). However, these were predominantly related to consideration of disease progression before and after nephrectomy and were not relevant for the current research questions.

Cost-effectiveness: review of manufacturer submissions to NICE

Methods

The cost-effectiveness models reported in the manufacturer submissions were assessed against the NICE reference case[134] and critically appraised using the framework presented by Philips and colleagues,[135] who have synthesised the literature on the evaluation of decision-analytic models in a health technology assessment context to present guidelines for good practice. A summary of the reviews is presented below, with additional detail provided in Appendix 6.

Sunitinib (manufacturer analysis/model)

Summary of industry submission

In their submission[136] to the NICE technology appraisal process the manufacturer of sunitinib (Pfizer) presents cost-effectiveness analyses for sunitinib compared with IFN in first-line use and sunitinib versus BSC in second-line use in people with advanced RCC. The submission uses a model-based approach to estimate cost-effectiveness. The modelling framework is similar in each case but has different data inputs.

Pfizer also estimate the cost-effectiveness of bevacizumab plus IFN versus IFN alone (for first-line use) and sorafenib versus BSC (for second-line use). Pfizer use these estimates for comparative purposes and does not present head-to-head comparisons of these alternative treatments with sunitinib.

The cost-effectiveness model, written in Microsoft EXCEL®, comprises three health states: PFS, PD and death. The model uses a lifetime time horizon and a short model cycle [first-line 0.01 years (4 days) per cycle; second-line variable cycle lengths, 1–10 weeks). Patients start in PFS in both models. Modelling uses survival analysis, employing clinical effectiveness data from an RCT (first-line) and other sources (second-line) to model survival and disease progression over time. No subgroup analyses are presented in the submission.

In the cost-effectiveness analysis for first-line use, much of the data used are from the phase III RCT of sunitinib versus IFN.[107] The model uses a patient population defined as in this RCT and for baseline disease progression (IFN alone) uses Weibull survival curves, modelled from trial data.[107] To model differences between treatment (sunitinib) and control, the analysis applies relative measures of treatment effectiveness (HRs) from the RCT. In the sensitivity analysis the submission explores alternative methods for survival analysis and the estimation of treatment effects.

In the analysis for first-line use Pfizer assume that patients receive sunitinib or IFN until disease progression (PD state), and following progression patients receive BSC (second-line drugs are not part of the analysis). The analysis uses data on health-state utilities derived from EQ-5D data collected in the RCT reported by Motzer and colleagues[107] but not reported in the trial paper, with different utility values by treatment and health state (sunitinib/PFS 0.77; IFN/PFS 0.79; sunitinib/PD 0.72; IFN/PD 0.69). The resource use and cost data cover drug costs, drug administration costs, medical management, an allowance for the mean cost of differences in expected adverse events, and costs associated with ongoing BSC. Drug costs are adjusted according to RCT data on dose intensity (e.g. first-line drug cost for sunitinib weighted by 86.4%).

For second-line use of sunitinib (versus BSC) the model uses clinical data from multiple sources, applying data for sunitinib and BSC from separate sources. For sunitinib, data are from Pfizer trial RTKC-0511–014, a multicentre, phase II single-arm study[112] assessing the efficacy and safety of sunitinib in second-line treatment. For BSC the submission uses a pooled analysis of data from multiple sources. In the sunitinib treatment arm

patients take sunitinib until progression and then switch to BSC. In the BSC arm patients receive BSC whilst alive. Survival analysis is used to model disease progression, survival and treatment effect, with Weibull survival curves used to extrapolate from different (and independent) sources of data.

Health-state values for the second-line analysis were taken from data collected in the phase II trial,[112] using EQ-5D (details unpublished), and are applied in a treatment by health state manner (e.g. sunitinib/PFS 0.803; BSC/PFS 0.758; sunitinib/PD and BSC/PD 0.683).

For both sets of analyses (first- and second-line) summary findings are presented as cost per life-year gained (LYG) and cost per QALY. Cost-effectiveness analysis estimates are presented by treatment comparison, and the submission reports sensitivity analyses, using probabilistic sensitivity analysis (PSA) to address parameter uncertainty. In all analyses the Pfizer submission applies a manufacturer pricing strategy whereby the first cycle of sunitinib treatment is free of charge to the UK NHS.

Summary of cost-effectiveness analysis results

First-line use of sunitinib

The industry submission presents two levels of base-case analysis: (1) preplanned interim analysis data and (2) unplanned updated analysis data. We caution that the unplanned updated analysis data include patients who have crossed over from IFN to sunitinib, with potential for confounding in the estimates of treatment effect (HRs). Therefore, this summary refers to findings presented against the preplanned interim analysis. The base-case analysis presents a cost per LYG of £21,116, an estimate of £45,736 per progression-free year gained and an estimate of £28,546 per QALY gained, with results reported indicating that sunitinib increased OS by an additional 0.82 years, increased PFS by 0.38 years and resulted in an additional 0.60 QALYs compared with IFN.

One-way sensitivity analyses are reported against a range of scenarios. The most important factors affecting the incremental cost-effectiveness ratio (ICER) are the health-state utilities (values) assigned to the PFS and PD states, and the shapes of the OS and PFS curves (extrapolation method). The PSA reported that, at a willingness-to-pay threshold of £30,000 per QALY, sunitinib has a 54% probability of being cost-effective compared with IFN.

In the comparison of bevacizumab plus IFN versus IFN the manufacturer's (Pfizer) submission estimates a cost per LYG and a cost per QALY of £81,754 and £107,357 respectively.

Second-line use of sunitinib

For second-line use of sunitinib compared with BSC the submission estimates (base-case assumptions) a cost per LYG and a cost per QALY of £29,061 and £37,519, respectively, with results reported indicating sunitinib increased OS by 0.77 years and PFS by 0.54 years and resulted in an additional 0.60 QALYs compared with BSC.

Sensitivity analyses reported in the submission indicate that the most important factors affecting the ICER are the health-state utilities (values) assigned to the PFS and PD states, and the shapes of the OS and PFS curves (and data source). The PSA reported that at a willingness-to-pay threshold of £30,000 per QALY, sunitinib has a 36% probability of being cost-effective compared with BSC.

In the comparison of sorafenib versus BSC the manufacturer's (Pfizer) submission estimates a cost per LYG and a cost per QALY of £54,750 and £73,078 respectively.

Review of industry submission

Appendix 6 presents a summary review of the sunitinib manufacturer submissions against the main items in the NICE reference case requirements[134] and against criteria set out by Philips and colleagues.[135]

First-line use of sunitinib

Structure The submission uses a simple model of disease progression, considering PFS, PD and death. This seems appropriate given the decision problem and the data available. The time horizon and model cycle length employed are both appropriate. The model assumes that patients receive sunitinib or IFN until disease progression. Following progression, patients receive BSC. Patients cannot switch from sunitinib to IFN or visa versa, in line with the protocol of the phase III RCT.

The model uses survival analysis to consider disease progression and treatment effect, based on data from the RCT reported by Motzer and colleagues in 2007.[107] For baseline disease progression, Weibull curves were fitted separately to Kaplan–Meier data (from the RCT) for PFS and OS for IFN treatment. In the base case, treatment

effectiveness is modelled using the relative measures of treatment effectiveness (HRs for OS and PFS) from the RCT, to adjust the OS and PFS baseline progression. As data are available only for PFS and OS, the model calculates the proportion of patients in the PD health state over time as the proportion alive minus the proportion of patients in the PFS health state.

In sensitivity analyses, structural assumptions on modelling disease progression are tested, with OS and PFS curves for sunitinib fitted separately to trial data instead of using HRs to adjust baseline disease progression. Also in the sensitivity analysis, baseline disease progression (IFN) was estimated by fitting Weibull curves to OS data from three independent trials, with trial HRs used to model treatment effect, as in the base-case analysis.

We have some concerns with the model used to estimate the cost-effectiveness of sunitinib for first-line use. First, and a major concern, is that the Weibull curve fitted to trial data[107] on PFS for IFN is a poor fit to the empirical survival data. *Figure 6* shows that the Weibull curve fits the empirical data well up to about 0.5 years, but that thereafter the model predicts a much shorter tail (more rapid disease progression) than is shown by the actual PFS data. The manufacturer submission[135] acknowledges that the curve 'does not fit the latter proportion of the Kaplan–Meier data, and therefore the PFS benefit of IFN-α could be underestimated' (p. 58 of the industry submission). We suggest that the consequences of this poor fit are important and, in addition to the suggested underestimated benefit, the modelling creates an underestimate of the cost per QALY (because of incremental costs and effects associated with PFS).

We have noted that the Pfizer survival analysis for PFS is heavily influenced by the first few data points in the Kaplan–Meier trial data. The submission has the curve fitted to multiple data points each month [and the transformation of the Weibull survival function $S(t)$ for regression $\ln(-\ln(S(t))$ is very large and negative when $S(t)$ is just below 1, i.e. for small time t]. PenTAG suggests that the first few data points are outliers in the regression. When we fit a Weibull curve to fewer data points, in this case one data point per month, the fit to the actual data is much improved because there are then no outliers in the regression (*Figure 6*).

Using the PenTAG (improved) Weibull fit in the industry model submitted (all else equal), the base-case ICER increases greatly, from £28,500 to £48,100 per QALY. Furthermore, most of the ICERs in the sensitivity analyses increase substantially (*Table 35*). The ICERs increase mostly because time in the PFS health state increases and therefore the duration of treatment increases. Both IFN and sunitinib treatment costs increase but because of the much lower cost for IFN per cycle the mean incremental total cost for sunitinib (compared with IFN) increases and consequently the cost per QALY estimate is higher.

Our second concern is also about Pfizer's assumption for PFS with IFN but is related to sensitivity analysis undertaken using separate sources of data to predict baseline (IFN) disease progression (PFS data from the trial of sunitinib versus IFN by Motzer and colleagues[107] but OS data from the trial of bevacizumab plus IFN versus IFN by Escudier and colleagues[106]). The consideration of this sensitivity analysis is important because,

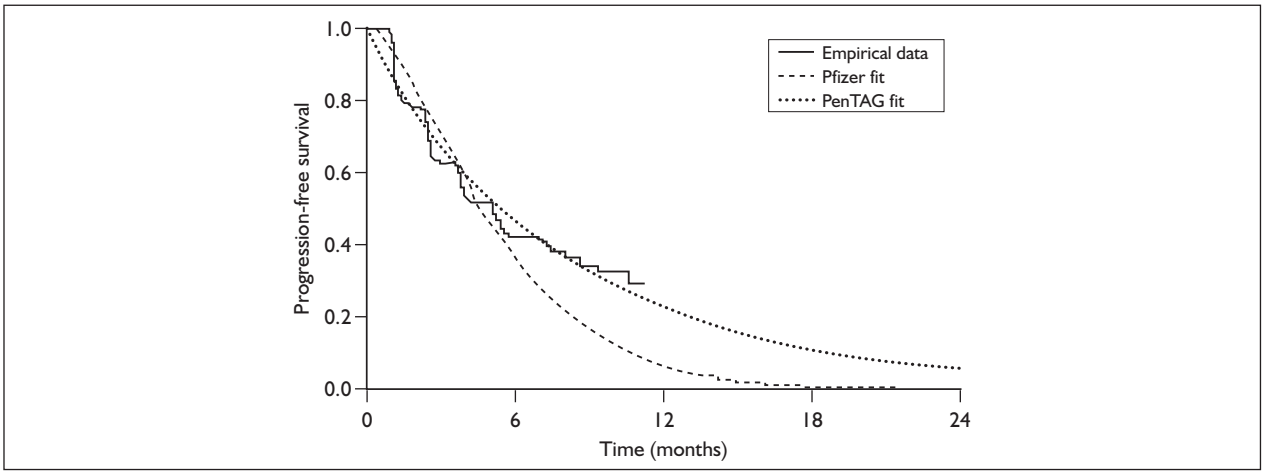

FIGURE 6 *Pfizer and PenTAG Weibull curve fits to empirical progression-free survival data for IFN. Source: Motzer* et al.*[107]*

TABLE 35 *Comparison of manufacturer cost-effectiveness analysis and PenTAG adjusted cost-effectiveness analysis (sensitivity analysis) for sunitinib versus IFN using the Pfizer model with PenTAG adjustment (modelled fit to progression-free survival data for IFN)*

Analysis	Base-case value	New value	Sunitinib vs IFN: ICER, Pfizer model	Sunitinib vs IFN: ICER, Pfizer model adjusted by PenTAG
Base-case results			£28,546	£48,052
Varying source of IFN-±, OS extrapolation	Trial data	Flanigan *et al.*[47]	£26,244	£43,334
		Mickisch *et al.*[137]	£27,709	£46,367
		Escudier *et al.*[106]	£30,965	£52,798
Extrapolation method	Weibull with hazard ratio	Independent Weibull	£40,536	£41,096
Restricting time horizon	Lifetime (10 years)	5 years	£34,223	£59,739
Alternative utility values	Varied by treatment and health state using EQ-5D	EQ-5D by treatment only	£29,766	£51,640
		EQ-VAS by treatment only	£25,908	£44,946
		EQ-VAS by treatment and health state	£29,207	£44,866
		EQ-5D values taken from sunitinib second-line trial	£30,828	£47,511
		Utility when progressed 0.5	£36,284	£48,689
		Utility when progressed 0.7	£31,207	£51,013
Discount rates	Costs and benefits discounted to 3.5%	No discounting	£27,508	£46,364
Relative dose intensity calculation	Includes dose interruptions and reductions: sunitinib 86.4%, IFN-α 83.08%	Includes dose interruptions only: sunitinib 97.20%, IFN-α 95.90%	£31,410	£53,936
	No dose reduction	All treatments 100%	£32,154	£55,484
IFN-α price	Price based upon Roferon (Roche)	Price based upon IntronA® (Schering-Plough) (£4.32 per MIU)	£29,145	£48,923

VAS, visual analogue scale.

as highlighted in the manufacturer submission, the most important source of uncertainty in the analysis is the extrapolation of OS data. The OS curves are immature; 65% of IFN patients and 67% of sunitinib patients are alive at the time of the interim analysis. This is the most complete unconfounded OS data available as patients were permitted to cross over to active treatment after this analysis. When Pfizer apply OS data from Escudier and colleagues,[106] the cost per QALY increases from the base case of £28,500 per QALY to £30,965 per QALY (£52,800 in PenTAG adjusted analysis). However, we feel that using different data sources for OS and PFS in the model has the consequence/potential to distort the modelled disease progression because of the fact that the number of people in the PD health state over time is calculated from (is a function of) related data on PFS and OS. We would suggest that when different OS data are used (because of possible limitations in the sunitinib trial data) baseline (IFN) disease progression for PFS should also come from that same data source, in this case the trial of bevacizumab plus IFN versus IFN reported by Escudier and colleagues in 2007.[106] This is the method used in the PenTAG analysis (see PenTAG cost-effectiveness analysis, Effectiveness data) and acknowledged by Pfizer as a valid approach (p. 67

of the manufacturer submission[136]). When Weibull curves are fitted (by PenTAG) to the manufacturer model using IFN PFS and OS curves from the RCT of bevacizumab plus IFN versus IFN,[106] the cost per QALY increases from £28,500 per QALY (Pfizer base case) to £56,000 per QALY. This increase is mostly due to the adjustment in the fit of PFS data for IFN.

In summary, we suggest that the manufacturer estimate of cost-effectiveness presents a cost per QALY that is underestimated. When we adjust the manufacturer model to address both highlighted structural concerns (albeit one is in sensitivity analysis), the base-case ICER increases from £28,500 per QALY to between £48,100 and £56,000 per QALY.

Data See Appendix 6 for more detailed comments on data inputs. In summary, the submission uses data from clinical trials to inform the patient population considered within the economic model of first-line treatment.[107] The above discussion considers the effectiveness data used from clinical sources to inform modelling of disease progression and treatment effect (and our main concerns). Drug costs are estimated using list prices, recommended dose data, and dose intensities from clinical sources. Pfizer assume that the first cycle of sunitinib is free to the NHS (this is not consistent with the NICE reference case requirements). Although the use of dose intensity data to adjust the drug costs in the model (i.e. in an ITT manner; sunitinib at 86.4%, IFN at 83.1%) is open to some debate, it seems reasonable to consider this when it is expected that some patients in the cohort will have periods 'off therapy'. The manufacturer model assumes that people receive sunitinib or IFN until disease progression. However, we believe, based on the views of the expert advisory group, that IFN will generally be prescribed for a maximum period of 12 months, as in the RCT of bevacizumab plus IFN versus IFN[106] Therefore, the model may overestimate the costs and effects associated with IFN treatment (i.e. underestimate the incremental cost for sunitinib).

When estimating drug administration costs the submission assumes that IFN is administered from a titrated pen syringe subcutaneously three times a week at home (by self, carer or district nurse). The submission estimates that 50% of patients self-inject and that the remainder have injections given by a district nurse at home, at a cost of £21 per visit. Although this assumption may be reasonable, we suggest that a higher proportion may self-administer; therefore, the submission probably slightly overestimates the cost of IFN. Furthermore, the submission assumes that patients receiving IFN make more frequent outpatient visits for clinical assessment of efficacy and toxicity than patients on sunitinib, a maximum of eight outpatients visits in the first 6 months. These issues are expected to have only a small impact on estimates of cost per QALY.

Health-state utilities/values are reported to be estimated from the results of the EQ-5D questionnaires administered in the phase III RCT of sunitinib versus IFN,[107] and values are derived from UK population data. Utility estimates were treatment and state specific: sunitinib/PFS 0.77 [standard deviation (SD) 0.22], sunitinib/PD 0.72 (SD 0.25), IFN/PFS 0.79 (SD 0.20), IFN/PD 0.69 (SD 0.29). We are concerned that these values are unpublished. There is one published abstract reporting utility data derived from the paper by Motzer and colleagues[138] and the RCT of sunitinib versus IFN,[107] and this abstract is not consistent with the data used in the manufacturer submission. However, we acknowledge that there are no other published data on health-state utilities for RCC.

The model assumes a monthly cost of £600 for hospital and hospice care following disease progression, based upon a study of stage IV breast cancer in the UK.[133] There is an absence of reported data (in the literature) to inform this model input and, although we suggest that the costs for BSC may be lower (on average) with care delivered from a primary care setting, the approach taken in the Pfizer model may be seen as reasonable.

Uncertainty/inconsistency In survival analysis we note that, for each fitted Weibull curve, the two parameters lambda and gamma were drawn from a multivariate normal distribution. However, these do not appear to have been used in the PSA and instead the PFS and OS HRs were assumed to follow independent univariate log-normal distributions. In the PSA the HRs for OS and PFS are not correlated for either sunitinib or bevacizumab plus IFN. In practice, these quantities are most probably correlated; however, if such correlations are not known the approach may be seen as reasonable.

The health-state utilities used in the model followed univariate normal distributions. Various cost data were varied stochastically. We suggest that

the approaches used in the PSA may underestimate the variability of the ICER.

In survival analysis, and modelling of effectiveness, the manufacturer submission quotes the appropriate standard errors (SEs) of the HRs for sunitinib and bevacizumab plus IFN compared with IFN for PFS and OS data. However, in the Pfizer model there is a potential mix-up as the SEs of the HRs for OS are used for PFS and vice versa (for both sunitinib versus IFN and bevacizumab plus IFN versus IFN). This confusion in the assignment of data will affect the results of the PSA. Specifically, the SE of the log-transformed HR between sunitinib and IFN for OS is assumed to be 0.10 but should be 0.19; the SE of the log-transformed HR between sunitinib and IFN for PFS is assumed to be 0.19 but should be 0.10; the SE of the log-transformed HR between bevacizumab plus IFN and IFN for OS is assumed to be 0.10 but should be 0.13; and the SE of the log-transformed HR between bevacizumab plus IFN and IFN for PFS is assumed to be 0.13, but should be 0.10.

In the sensitivity analysis Pfizer state that £259.20 represents the cost of 50 MIU of IntronA® (Schering-Plough; IFN-α), whereas this is the cost of 75 MIU (50 MIU/ml, 1.5 ml). Using the corrected value the ICER (sensitivity analysis in submission) changes slightly (from £29,145 per QALY to £29,880 per QALY).

We have highlighted that the submission includes an analysis based on the unplanned updated trial analysis data. We caution that these data include patients who have crossed over from IFN to sunitinib and thus this will confound the HR estimates to some extent. However, we assume that the manufacturer has analysed these data because they are more mature than the preplanned interim analysis data.

Bevacizumab plus IFN versus IFN

Pfizer do not perform an indirect comparison between sunitinib and bevacizumab plus IFN even though they state that the patient populations in the sunitinib versus IFN and bevacizumab plus IFN versus IFN RCTs are similar. Nonetheless, they do present a comparison of the cost-effectiveness of bevacizumab plus IFN versus IFN.

Second-line use of sunitinib

Structure The model structure has been outlined above. The cycle length and time horizon are appropriate. We have concerns about the effectiveness data used to model disease progression. The submission uses effectiveness data from trial RTKC-0511–014, a multicentre, phase II, single-arm study assessing the efficacy and safety of sunitinib in second-line treatment.[112] In the absence of a BSC arm in this trial, the submission modelled BSC survival based on pooled analysis[138] and an analysis of SEER-Medicare data. The pooled analysis is a review describing the survival of previously treated metastatic RCC patients who were candidates for clinical trial agents as second-line therapy. It pools survival analyses involving 251 patients with advanced RCC treated in 29 trials between 1975 and 2002. However, the population included in the review does not correspond to the trial population of RTKC-0511–014 in terms of previous first-line therapy received and response to previous therapy. Only 50% of patients received previous first-line cytokine immunotherapy in the review, compared with all patients in trial RTKC-0511–014.[112] In addition, the review considered clinical trials of second-line experimental treatment programs for metastatic RCC, which included cytokines. The submission does state that this could have had an impact on survival, suggesting that the use of these data alone to estimate survival in BSC patients could lead to an overestimation of survival.

One of our concerns with the submission's methods is the use of the SEER-Medicare data. We acknowledge that Pfizer caution that these data have important limitations. First, differences in patient characteristics and in underlying health status and projected course of RCC at baseline may call into question the comparability of the pooled analysis[138] and the SEER-Medicare populations. Second, the definition of cytokine failure used in the pooled analysis relies on clinical signs and symptoms, whereas the definition used in the SEER-Medicare analysis relies on observed health-care resource utilisation. Because of the gap between the time of clinical progression and the need for health-care services, the starting point for the survival analysis among the SEER-Medicare patients may be somewhat later than that for the patients in the pooled analysis. This lag is expected, everything being equal, to lead to shorter observed survival post diagnosis for the SEER-Medicare patients (lead-time bias). Moreover, close monitoring for cytokine failure is likely to be the norm once sunitinib or other effective second-line therapies become available, as there will be an incentive to detect cytokine failure.

We have serious concerns about the approach used to model sunitinib for second-line use. First,

and most importantly, the OS and PFS curves for sunitinib are taken from one trial[112] and the corresponding curves for BSC are taken from a different trial.[138] We believe that this approach is invalid as randomisation has been broken. Second, as the submission acknowledges, the two data sources for BSC survival have important limitations, as discussed above.

Finally, we highlight that the single-arm trial of sunitinib[112] was very small, with only 63 patients. Furthermore, OS for sunitinib from the single-arm trial is not mature. Approximately 40% of patients were still alive at data cut-off. Therefore, cost-effectiveness estimates are sensitive to extrapolation of OS beyond data cut-off. The submission does not state why the manufacturer did not model PFS and OS for sunitinib from the other single-arm trial of sunitinib, trial A6181006.[111]

Data The cost of sunitinib was estimated using list prices and the recommended dose. Pfizer estimated the dose intensity of sunitinib as 80.8% from the single-arm trial. The cost of sunitinib was reduced by this dose intensity.

Costs associated with BSC are the same in both arms of the model. BSC is defined as treatment to control, prevent and relieve complications and side effects and to improve comfort and quality of life. Within the BSC arm, costs for diagnostic tests, acquisition and administration are set to zero as they are included in the BSC costs. For the Pfizer comparison of sorafenib and BSC, resource use for sorafenib was assumed to be equal to that for sunitinib.

As in the first-line model, utility values were assigned by treatment and health state. The submission states that EQ-5D scores were derived from data taken from the single-arm trial[112] and are: sunitinib/PFS 0.803 (SD 0.25), sunitinib/PD 0.683 (SD 0.29). BSC patients in PFS were assigned the same utility as at baseline in the single-arm sunitinib trial (0.758, SD 0.227). BSC patients in PD were assigned the same utility as sunitinib patients in PD (0.683, SD 0.29). There is some weighting of utility values, based on values whilst on treatment or whilst in the rest period. However, in general we are concerned that these data are unpublished and there is insufficient detail to consider the methods used. We also note again that the number of people in the trial is low.[112]

Uncertainty/inconsistency In the PSA, parameter uncertainty was modelled in a similar fashion as in the first-line model. For each fitted Weibull curve the two parameters lambda and gamma were drawn from a multivariate normal distribution (see comment under first-line use). The utilities followed univariate normal distributions and various costs were modelled by gamma distributions.

Bevacizumab plus IFN (manufacturer analysis/model)

Summary of industry submission

In their submission to NICE[117] the manufacturer of bevacizumab (Roche) presents a cost-effectiveness analysis of bevacizumab plus IFN versus IFN alone as first-line therapy in patients with advanced RCC.

The submission uses a model-based approach to estimate cost-effectiveness. The cost-effectiveness model, written in Microsoft EXCEL, comprises three health states: PFS, PD and death. The model uses a lifetime time horizon and a model cycle of 1 month. The model uses survival analysis, employing clinical effectiveness data from the RCT reported by Escudier and colleagues,[106] to model survival and disease progression over time. As in the RCT, all patients in the cohort model start in PFS in the analysis. No subgroup analyses are presented.

The model uses a patient population defined as in the Escudier and colleagues RCT[106] and, for baseline disease progression (IFN alone), uses Weibull survival curves modelled from the same trial. To model differences between bevacizumab plus IFN and IFN the analysis considers PFS by applying a Weibull survival curve for bevacizumab plus IFN modelled from trial data.[106] For OS, modelling applies a relative measure of treatment effectiveness (HRs) from the RCT to the baseline survival analysis. The submission explores alternative mathematical survival curves in sensitivity analyses.

The modelling assumes that patients receive bevacizumab until disease progression and IFN until disease progression, although IFN use is limited to 1 year, consistent with the RCT.[106] Following disease progression (PD health state) patients receive BSC and are assumed to use second-line drugs. The health-state utilities used are taken from EQ-5D data collected in the sunitinib versus IFN RCT. The trial was reported by Motzer and colleagues in 2007,[107] but EQ-5D data are not reported in the trial paper. The Roche model uses a utility of 0.78 in PFS and 0.705 in PD, both applied independently of treatment (values

are derived by averaging over the treatment-specific data reported from the sunitinib versus IFN RCT[107]). The resource use data covers costs for drug acquisition, drug administration, medical management, adverse events and costs associated with BSC in PD. The costs of drug acquisition and administration are reduced according to the dose intensity data reported in the RCT.[106]

Summary findings are presented as cost per LYG and cost per QALY. Sensitivity analyses, using PSA to address parameter uncertainty, are presented. All cost-effectiveness analyses presented in the submission are based on a scenario in which a manufacturer pricing strategy is used to cap the cost of bevacizumab (this is not consistent with the NICE reference case requirements), whereby bevacizumab is free to the UK NHS once 10,000 mg has been purchased in an individual patient within a year of treatment initiation. (Roche describe this as a European-wide 'dose cap' scheme.)

Summary of cost-effectiveness analysis results

The submission reports a base-case cost per LYG of £58,712 and cost per QALY of £75,000; bevacizumab plus IFN increases OS by 0.34 years, increases PFS by 0.36 years and results in an additional 0.27 QALYs compared with IFN. The incremental costs for bevacizumab were around £20,000 (almost entirely made up of drug and drug administration costs). The PSA reported shows that, at a willingness-to-pay threshold of £30,000 per QALY, bevacizumab plus IFN has a 0% probability of being cost-effective compared with IFN.

Review of industry submission

Appendix 6 presents a summary review of the manufacturer submission against the main items in the NICE reference case requirements and against the criteria proposed by Philips and colleagues.[135]

Structure The model considers the cost-effectiveness of bevacizumab plus IFN versus IFN in first-line use, and the submission provides a rationale for not comparing bevacizumab plus IFN versus temsirolimus for poor prognosis patients.[117]

Although the model structure is simple, considering PFS, PD and death, this seems appropriate given the decision problem and the data available. The time horizon and model cycle length are appropriate. In the model, PFS is estimated separately for IFN and for bevacizumab plus IFN based on extrapolation of the Kaplan–Meier data from the RCT.[106] The OS data are modelled differently given that they are still immature for bevacizumab plus IFN (RCT-reported data). In the model, the RCT data on OS for IFN alone are used (as OS data in the IFN arm are more mature) to extrapolate and estimate the OS for IFN over time.[106] To model OS for bevacizumab plus IFN the baseline progression (IFN alone) is used in conjunction with the relative measure of effectiveness (HR) reported in the RCT.[106] The submission reports that several mathematical survival curves were fitted to the Kaplan–Meier data and that the Gompertz function is used in the model on the basis that it gave the best fit to both the PFS and OS data.

Data Drug costs are estimated using list prices and recommended dose data. Roche use the average body weight of 76.5 kg from the RCT by Escudier and colleagues[106] to estimate average dose and hence the cost of bevacizumab. Patients in the bevacizumab plus IFN arm received 10 mg/kg of bevacizumab every 2 weeks, and IFN three times per week at a dose of 9 MIU. As noted above, the analysis assumes a European-wide 'dose cap' scheme (in which costs for bevacizumab are much reduced, i.e. by a mean of £8900 in base-case analysis). Modelling assumes that IFN is administered by patients, with no additional resource use/cost. The model assumes one outpatient visit for every intravenous administration of bevacizumab (every 2 weeks), at a cost of £233 per visit.[139] For bevacizumab this administration cost is assumed to capture all other monitoring costs. In patients taking IFN alone, one outpatient appointment each month is assumed. The drug-related cost of bevacizumab administration (unit cost) was calculated as a weighted average of chemotherapy administration costs from NHS reference cost data.[139] Costs for adverse events are included in the analyses. The manufacturer analysis assumes that patients in the PD health state will be offered second-line drug treatments, such as sunitinib or sorafenib. They assume a cost of £405.50 per month in the bevacizumab plus IFN arm and £495.95 in the IFN arm. These figures are based on data from the RCT by Escudier and colleagues,[106] which details second-line treatments. A larger proportion of patients in the IFN arm received second-line treatment than in the bevacizumab plus IFN arm, with differences attributed to the relative lack of effectiveness of IFN. Specifically, the monthly costs of the second-line drug were estimated based on second-line drug use for 8.3 months, the duration of second-line PFS according to the second-line sunitinib trial for RCC patients.[111] The total expected drug cost in PD was

thus calculated and then the monthly cost in PD was estimated by spreading this total cost over the time spent in PD in the model (12.7 months). In addition, Roche assumes that all patients in PD had one outpatient appointment per month for monitoring.

As noted above, the health-state utilities (for PFS and PD health states) are taken from the sunitinib versus IFN RCT,[107] which used the EQ-5D measure. As noted in the PenTAG review of the sunitinib model (manufacturer submission) these utility data are not published and we are unable to consider them in much detail.

Uncertainty/inconsistency The submission presents findings from probabilistic modelling to address parameter uncertainty in cost per QALY estimates, but other sensitivity analyses are performed only on model structure, reporting against the choice of mathematical function of the survival curves (see below). PenTAG note that the absence of sensitivity analysis is a weakness in the reporting of the cost-effectiveness analysis and suggest that the submission could have performed/reported additional sensitivity analysis to help assess the uncertainty in results.

We have a number of concerns with the model and analysis presented in the Roche submission to NICE.

First, we highlight a concern over the assumptions and data used to estimate dose intensity, which is used to adjust drug and drug-related costs. The manufacturer analysis multiplies the costs of drug acquisition and drug administration using dose intensity data (unpublished data from the bevacizumab plus IFN RCT[106]). In the model, dose intensity data for bevacizumab is estimated using the average time taking the drug in the trial divided by the average time patients spend in PFS in the model. Similarly for IFN, the estimation is the average time actually taking the drug in the trial divided by the average time patients spend in PFS up to 1 year in the model. In this way the dose intensities are calculated as 62% for bevacizumab, 80% for IFN when used with bevacizumab and 63% for IFN alone (monotherapy). Although these data are not reported in the written submission they are used in the model. These data, applied to adjust costs, are different to those reported in the RCT[106] and different to the data quoted in the Roche submission[117] (Table 13 in the submission). Dose intensity data used in the model are generally much lower than the *mean* dose intensities reported in the RCT (88% for bevacizumab, 83% for IFN in bevacizumab plus IFN arm and 89% for IFN alone arm)[106] and lower than the *median* dose intensities quoted in the manufacturer submission.[117] When PenTAG have used the dose intensity data reported in the published RCT[106] in the manufacturer model the base-case ICER increases substantially, from £75,000 per QALY to £117,000 per QALY.

Second, we highlight a concern over the clinical effectiveness data (HRs) used in the manufacturer analysis for OS and PFS. The analysis uses the HR for OS from unpublished data on what is classed a 'safety population' (not the RCT data), using an OS HR of 0.709. This differs from the OS HR of 0.75 from the RCT reported by Escudier and colleagues.[106] When PenTAG have used the manufacturer model and applied the RCT HR for OS of 0.75 the ICER increases from £75,000 per QALY to £87,400 per QALY. It is not clear why the manufacturer analysis uses data from the safety population. Again, we note that the model uses a HR of 0.609 (95% CI 0.508 to 0.728) for PFS and that this is from a safety population (stratified by risk group) rather than from the data reported in the RCT. The RCT[106] reports a HR of 0.63 (95% CI 0.52 to 0.75) in unstratified analysis. However, in the model, a PFS HR is not explicitly applied, because PFS for both treatment arms is fitted to empirical trial data independently (we assume that this HR is implicit in the Kaplan–Meier data).

Also, in sensitivity analysis the submission reports findings in which cost-effectiveness has been assessed using a log-logistic model (instead of the Gompertz methods in the base-case analysis), and PenTAG would question the appropriateness and prominence of this sensitivity analysis. In this case the ICER falls greatly, from £75,000 per QALY to £40,000 per QALY, and, at a willingness-to-pay threshold of £30,000 per QALY, bevacizumab plus IFN has a 9% probability of being cost-effective compared with IFN. However, Roche acknowledge that this ICER may be unrealistic because the log-logistic model results in an expected lifetime that may be unrealistically long (*Figure 7*). We do not see the log-logistic method as a credible approach, that is, we agree with Roche that it is unreasonable to use the log-logistic distribution to model PFS and OS in the sensitivity analysis because the tail of the distribution is too long.

Temsirolimus (manufacturer analysis/model)

Summary of industry submission

In their submission to NICE,[124] the manufacturer of temsirolimus (Wyeth) presents a cost-effectiveness analysis of temsirolimus versus IFN in first-line use

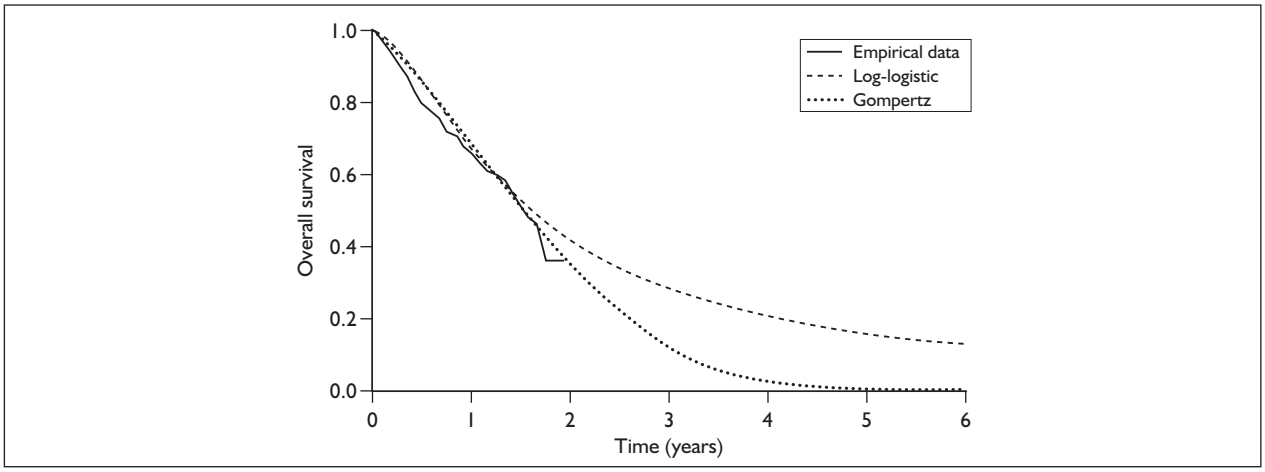

FIGURE 7 *Comparison of the fit to overall data for IFN, using Gompertz and log-logistic curves (as manufacturer sensitivity analysis). Source: Escudier* et al.*[106]*

in patients with poor prognosis. Wyeth also present an indirect comparison of temsirolimus versus BSC using data from an RCT of IFN versus BSC.

The submission uses a model-based approach to estimate cost-effectiveness. The cost-effectiveness model, written in Microsoft EXCEL, comprises three primary health states: PFS, post progression and death. However, the PFS health state is subdivided into three categories (substates) of complete and partial response and stable disease. The model uses a time horizon of 3 years and a model cycle of 1 month. The model uses survival analysis, employing clinical effectiveness data from a single RCT,[108] to model survival and disease progression over time. The approach uses Weibull regression models to calculate the time-dependent transition probabilities used to model disease progression and cost-effectiveness.

All patients start in PFS. Modelling assumes that patients receive temsirolimus and IFN until disease progression, consistent with the RCT.[108] In the post-progression health state patients receive BSC and second-line drugs. Health-state utilities were derived from the EQ-5D questionnaires collected during the RCT,[108] although these data are not reported in the trial publication. Resource use data cover costs for drug acquisition, drug administration, medical management, adverse events, and BSC and second-line drugs in the post-progression health state. The costs of temsirolimus and IFN and the cost of administration of temsirolimus are reduced according to dose intensity data from the temsirolimus RCT.[108] The administration of IFN is not adjusted by dose intensity data.

Summary findings are presented as cost per LYG and cost per QALY. Sensitivity analyses, using PSA to address parameter uncertainty, are presented. In addition to the base-case analysis, which uses data from all of the patients in the RCT, Wyeth present subgroup analyses for clear cell RCC, non-clear cell RCC, patients with previous nephrectomy and those with no previous nephrectomy.

Summary of cost-effectiveness analysis results

The base-case analysis estimates a cost per LYG of £35,577 and a cost per QALY of £55,814. The incremental LYG and QALYs were 0.21 and 0.13, respectively, and the incremental cost was £7493. The major components of the incremental cost were linked to additional drug costs for temsirolimus (£10,348) and a suggested cost saving (–£3347) in the cost for drug administration (temsirolimus compared with IFN). The results are given in more detail in Appendix 6. In manufacturer sensitivity analysis the cost-effectiveness was sensitive to changes in drug-related treatment costs/assumptions. PSA reports a 0% chance that temsirolimus is cost-effective compared with IFN at a willingness-to-pay threshold of £20,000 per QALY or £30,000 per QALY.

In subgroup analyses the ICER for the clear cell patient subgroup was £57,731 per QALY, for the non-clear cell subgroup was £51,159 per QALY, for patients with previous nephrectomy was £60,575 per QALY and for patients without previous nephrectomy was £49,690 per QALY. For the indirect comparison of temsirolimus versus BSC the ICER was £81,201 per QALY and the cost per LYG was £43,746 (see Appendix 6).

Review of industry submission

Appendix 6 presents a review of the manufacturer submission against the main items in the NICE reference case requirements and against the criteria set out by Philips and colleagues.[135] Summary detail is presented below.

Structure The model uses three primary health states (PFS, post progression, and death), which is similar to the other models presented for RCC. The model structure appears appropriate given the decision problem and data available. The time horizon is short at 3 years but appears to capture the main impacts of disease and treatment, although it has not been tested in sensitivity analysis. The cycle length is appropriate. The model is based on a set of time-dependent transit probabilities derived from individual patient-level data (not available to PenTAG) from the RCT by Hudes and colleagues.[108] We are unable to consider the derivation of these probabilities in any detail. Three Weibull functions are modelled: (1) PFS to post progression, (2) PFS to death and (3) post progression to death. These functions are used to derive the transition probabilities. For subgroup analysis, the PFS and OS Weibull curves are unique for each patient subgroup: clear cell, non-clear cell, nephrectomy, non-nephrectomy. A discussion on the effectiveness data available to model subgroups can be found in Chapter 2.

In the model, patients start in a PFS health state. The model assumes that patients starting in a PFS state are treated with IFN or temsirolimus and stop treatment when they enter a post-progression health state. After disease progression (post progression), patients take second-line drugs (sunitinib, sorafenib, bevacizumab) or receive BSC only.

We note/assume that when calculating disease progression (transition probabilities) the model uses effectiveness data from all patients in the RCT reported by Hudes and colleagues[108] It is important to remember that the definition of poor prognosis used in this trial differs from the MSKCC prognosis scale. Using this scale, only 75% of patients in this trial would be considered to have poor prognosis. The remaining 25% of patients had intermediate prognosis.

In the analysis undertaken (survival analysis/ transition probabilities), the shapes of the PFS and OS curves calculated (from transition probabilities) are noticeably different to the empirical Kaplan–Meier curves reported in the RCT[108] (*Figures 8* and *9* respectively). For PFS we believe that there are two reasons for this difference. First, the data presented in the RCT are empirical survival data, whereas the manufacturer has modelled PFS using transition probabilities calculated from individual patient data. Second, the manufacturer has used the independent assessment of PFS, whereas in the RCT reported by Hudes and colleagues[108] the published Kaplan–Meier curve for PFS was based on the site investigator assessment. In the PenTAG analysis, shown in *Figures 8* and *9*, PFS and OS are modelled based on the data available from the RCT reported by Hudes and colleagues[108] The differences apparent in the OS curves (*Figure 9*) would appear to be due to the use of individual patient-level data by Wyeth to calculate transition

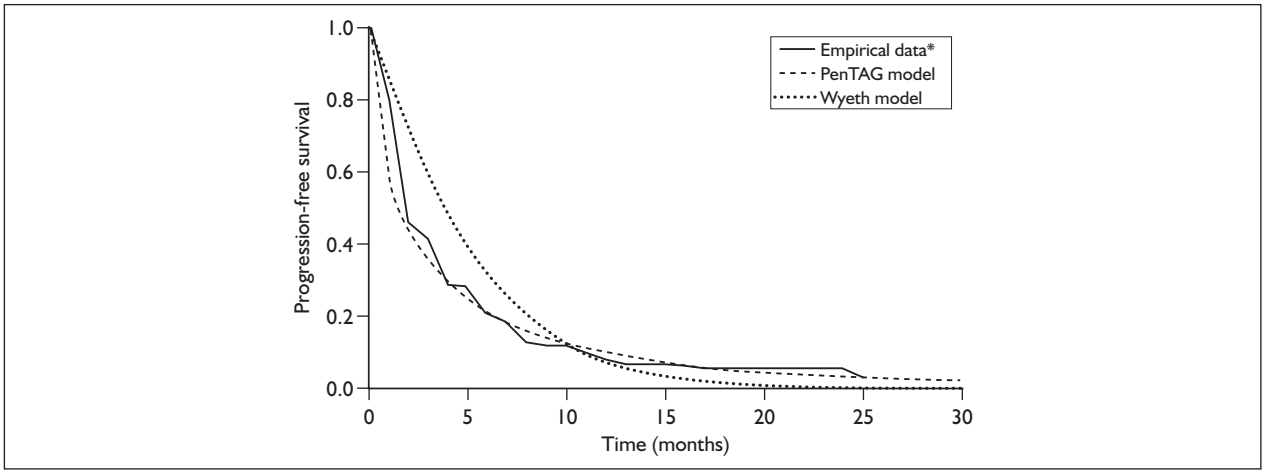

FIGURE 8 *Progression-free survival for IFN in Wyeth analysis and from RCT. *Source: Hudes* et al.*[108] (site investigator assessment of progression-free survival).*

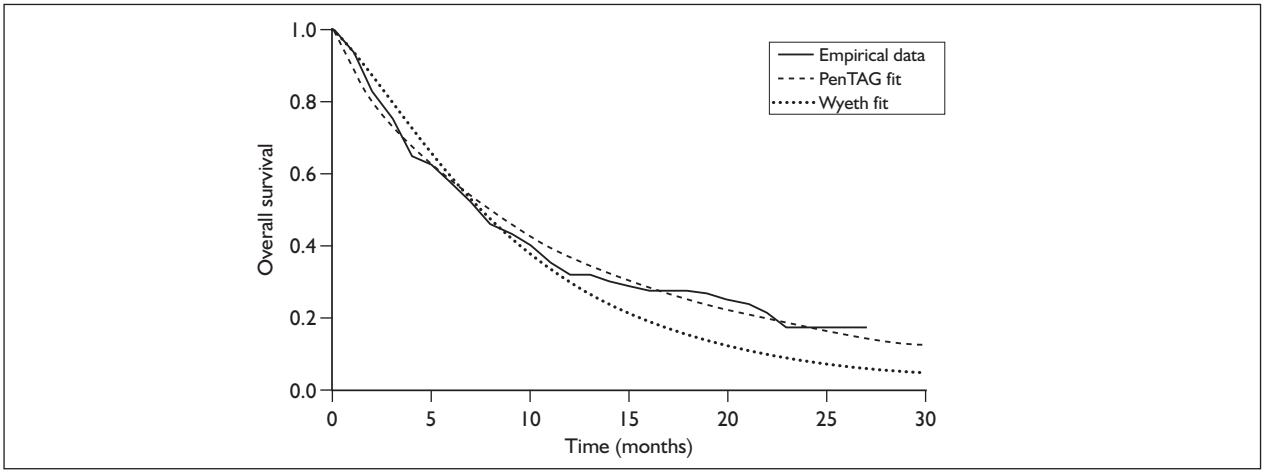

FIGURE 9 *Fit to empirical overall survival for IFN by Wyeth and PenTAG. Source: Hudes* et al.*[108]*

probabilities instead of the use of empirical data reported in the RCT.

Data We have some concerns over a number of the assumptions in the model over resource use and cost. We summarise our main concerns below, covering costs associated with administration of IFN and use of dose intensity data. See Appendix 6 for more detailed comments on data inputs.

The costs associated with the administration of IFN, and the cost differences between IFN administration and temsirolimus administration, are an important component in the cost-effectiveness estimates. The manufacturer model assumes that all IFN is administered in the hospital outpatient setting, costing £127.80 per visit. With IFN administered three times per week this leads to a high cost associated with IFN treatment. Based on information from the expert advisory group we do not believe that this is an accurate reflection of current practice. Based on the clinical opinions received we would expect that in most cases IFN injections would be administered in patients' homes, either by themselves or by friends, relatives or carers. It may be that in some cases a district nurse or community or practice nurse would give injections (in a patient's home). When we assume resource use based on the clinical opinion received (i.e. we assume that typically 25% of patients have IFN administered by a district nurse, at a cost of £25 per visit, and the remaining 75% self-inject, at no cost; see *Table 40*), the base-case ICER (using the manufacturer model) increases substantially from £55,814 per QALY to £102,000 per QALY. In subgroup analyses this pattern is also noted: the cost per QALY for the clear cell subgroup increases from £57,731 to £121,300, the cost per QALY for the non-clear cell subgroup increases from £51,159 to £63,100, the cost per QALY for patients with previous nephrectomy increases from £60,575 to £117,000 and the cost per QALY for patients without previous nephrectomy increases from £49,690 to £84,000.

A further concern is that the Wyeth submission assumes that the drug administration costs for temsirolimus should be adjusted using dose intensity data from the RCT,[108] that is, costs are reduced. However, Wyeth do not apply this same assumption to costs associated with IFN.

Drug costs are estimated using list prices (expected list prices) and recommended dose data. Patients receive IFN three times per week at a recommended dose of 18 MIU. In the Wyeth analysis the cost of temsirolimus is based on 25 mg per dose, one dose per week, at £20.60/mg, giving £515 per dose. The analysis acknowledges that because of vial size (30 mg each) there will be waste/overfill of 5 mg. There is some outline discussion on the potential for vial sharing schemes (and sensitivity analysis) but no detail is provided.

The temsirolimus model uses health-state utilities of 0.60 for the baseline entry health state of stable disease (analogous to PFS) and 0.446 for post progression. The model also includes an incremental gain in utility in patients in whom a response (positive) to initial treatment is reported, with a value of 0.658. The PD and response states (utility values) do not play a major part in the cost-effectiveness analyses and so we do not dwell on them here, focusing on the more generic states

of stable disease/PFS and post progression. The submission reports that utilities were modelled under the Q-TWiST structure, according to whether patients were in the TOX (toxicity) state (suffering grade 3 or 4 adverse events), PD or TWiST state. The submission states that utility values were derived from EQ-5D data collected during the temsirolimus RCT,[108] although limited details are available on this. We have some concerns over the lack of transparency in the data used to derive health-state utilities (see PenTAG cost-effectiveness analysis, Health state utilities).

Uncertainty/inconsistency The submission presents one-way sensitivity analyses. However, we are concerned that the manufacturer has performed no sensitivity analyses on the PFS and OS curves, especially as these are major drivers of the ICER. However, in the PSA the submission does incorporate some variation in these curves.

Indirect comparison: temsirolimus versus best supportive care For the comparison between temsirolimus and BSC the submission uses data from the Medical Research Council Renal Cancer Collaborators (MRCRCC) RCT[140] and we have concerns over the use of these data. The data are based on patients with a range of prognoses, not just those with poor prognosis. Therefore, we suggest that the results of the indirect comparison should be treated as suggestive only.

Sorafenib (manufacturer analysis/model)

Summary of industry submission

In their submission to NICE[141] the manufacturer of sorafenib (Bayer) presents a cost-effectiveness analysis of sorafenib versus BSC in patients with advanced RCC. Analysis is presented for the following patient groups: (1) patients on second-line therapy, (2) patients unsuitable for cytokines (IFN and IL-2) and (3) combined treatment group with both second-line therapy and patients unsuitable for treatment with cytokines. In addition, cost-effectiveness analyses are presented for further subgroups. The submission also estimates the cost-effectiveness of sorafenib versus sunitinib for second-line treatment.

The cost-effectiveness model of sorafenib versus BSC, written in Microsoft EXCEL, comprises three health states: PFS, PD and death. The model uses a 10-year time horizon and a 1-month model cycle. The model uses survival analysis, applying data from the RCT reported by Escudier and colleagues,[109] to model survival and disease progression over time. Data from the RCT are classed as mature for the PFS analysis but immature (short follow-up) for the OS analysis. Therefore, although trial data (Kaplan–Meier) were used for PFS for both sorafenib and BSC, for OS trial data were extrapolated (using an exponential function) over time. The analysis uses survival data (empirical or projected) for both sorafenib and BSC (to derive time-dependent transition probabilities), and the model does not use relative measures of treatment effect (HRs) to predict differences between treatment arms. In subgroup analyses, different methods were employed to model progression and treatment effect, adjusting baseline survival analysis using different data on median PFS and OS.

Modelling assumes that patients receive sorafenib until disease progression and that all patients start in the PFS state (consistent with RCT methods[109]). Following disease progression, patients receive BSC. The health-state utilities used are 0.737 for PFS and 0.548 for the PD health state, both being independent of treatment group. These data are taken from an unpublished survey of physicians. Resource use data cover costs of drug acquisition, medical management and adverse events, and BSC costs in the PD health state. There are no drug administration costs. Modelling assumes a dose intensity of 100% for sorafenib, that is, there is no reduction in the costs/price for sorafenib to reflect time off treatment.

Summary findings are presented as cost per LYG and cost per QALY. Sensitivity analyses, including PSA to address parameter uncertainty, are presented.

Summary of cost-effectiveness analysis results

(Commercial-in-confidence information has been removed.)

The submission acknowledges that there are no good data available for subgroup analysis, but a series of subgroup analyses are still reported. The submission considers the following subgroups: patients with previous nephrectomy, ECOG-PS 0, ECOG-PS 1, diagnosis of RCC greater than 18 months, no lung metastasis at treatment commencement and liver metastasis at treatment commencement.[141] See Appendix 6 for a summary.

Review of industry submission

Appendix 6 presents a summary review of the manufacturer submission against the main items in the NICE reference case requirements and against

the criteria by Philips and colleagues.[135] Here we present a short summary of the main issues.

Structure Although the model of disease progression is simple, considering PFS, PD and death, we regard this as appropriate given the decision problem and data available. The time horizon and model cycle length are also regarded as appropriate. As above, the model uses trial data to model disease progression, PFS and OS in the main analysis (combined patient groups). Using PFS and OS data, the time that patients spend in the PD state is calculated from estimated time alive minus time in PFS. As acknowledged by the manufacturer in the submission, data available to model subgroups are not of good quality, and the modelling is undertaken using an adjustment of the baseline disease progression against data on PFS and OS in the subgroups, with a ratio of median PFS in the subgroup to median PFS in all patients used for the adjustment. Although the method is clear there is some uncertainty over the data available on subgroups (PFS and OS), and these data are largely unpublished. Therefore, we are unable to comment further.

Data Drug costs are estimated using list prices and recommended dose data. In the model patients are on sorafenib treatment whilst in the PFS health state and were assumed to receive 400 mg sorafenib twice daily (costing £2721 per month). Although approximately 6% of patients receiving sorafenib in the RCT by Escudier and colleagues[109] had dose reductions, it was conservatively assumed that all patients would receive 400 mg sorafenib.

Resource use within the model was estimated via two internet-based surveys of six and 31 UK clinicians. Four clinicians with experience of sorafenib estimated resource use in the PFS state for sorafenib-treated patients, whereas clinicians who had not used sorafenib estimated resource use in patients receiving BSC in the PFS state. Resource use estimates were weighted by performance status (ECOG score), with an assumption of 35% ECOG-PS 0 and 65% ECOG-PS 1. There are no published data on resource use for RCC and there are limited alternatives to estimate resource use. Although we consider the estimates used to be high in some cases (i.e. higher than the estimated costs in the PenTAG analysis), for example the manufacturer estimate of £673 per month for patients treated with BSC in the PFS health state, it is acknowledged that this is an area where judgements may differ. We urge caution when using data from such surveys in small samples, and such caution also applies to the estimates used in the PenTAG analysis. See Appendix 6 for more detailed comments on cost data inputs.

Health-state utility data were collected from a survey of 31 UK clinicians working in the field of RCC using the EQ-5D questionnaire. EQ-5D values for patients on sorafenib were based on views elicited from only five physicians. We have significant concerns over the methods used here and note that physician valuations (descriptions) are not methodologically robust and are inconsistent with the NICE reference case requirements. Utilities were higher in PFS than in PD and higher for ECOG-PS 0 than for ECOG-PS 1: PFS ECOG-PS 0: 0.903 (95% CI 0.858 to 0.948); PFS ECOG-PS 1: 0.648 (95% CI 0.582 to 0.714); OS ECOG-PS 0: 0.692 (95% CI 0.606 to 0.778); OS ECOG-PS 1: 0.471 (95% CI 0.389 to 0.553). The analysis combining both ECOG values (all patient subgroups combined) used the average utility across both ECOG groups weighted by the proportion of patients in ECOG-PS 0 and ECOG-PS 1. These treatment-independent averages were 0.737 for PFS and 0.548 for PD for both sorafenib and BSC.

Uncertainty/inconsistency The submission presents one-way sensitivity analysis and PSA. There is no statement of model checking for consistency and/or accuracy, although there is a reference to an accurate prediction of median PFS in the TARGET trial.[109]

Further detail is provided in Appendix 6; we have no other major concerns with the modelling presented in this submission.

Summary

The above reviews on the four manufacturer submissions (cost-effectiveness analysis and modelling methods), although summary in nature, cover much ground. They are presented to introduce the reader to the submissions, research questions, methods used, data inputs and summary results and, importantly, to highlight our concerns. They are complemented by material presented in appendices, but we stress that the review of industry models has still been outline in nature and does not represent a thorough investigation of methods, data and model workings (i.e. not a 'cell by cell' audit of model implementation). In the next section we present the PenTAG cost-effectiveness analysis (methods, results, limitations, discussion). Unlike the individual manufacturer submissions, which have an emphasis on specific

products and data sources (i.e. trial/effectiveness data), the PenTAG analysis has attempted to apply common methods across the assessment of the cost-effectiveness of all drugs included in the scope for treatment of RCC.

In a later section (see Comparison of PenTAG and manufacturer cost-effectiveness analyses) we present a discussion and comparison of the cost-effectiveness analysis presented by PenTAG and the cost-effectiveness analyses presented in the manufacturer submissions to NICE, which presents more detail, in a comparative context, on the implications of many of the assumptions used by drug manufacturers in assessing cost-effectiveness.

PenTAG cost-effectiveness analysis

Statement of problem and perspective of cost-effectiveness analysis

The cost-effectiveness analysis presented here addresses the research questions set out in Chapter 1 (see Definition of the decision problem). The analysis takes the perspective of the NHS and personal social services (PSS) in the UK.

Strategies/comparators

The analysis estimates the cost-effectiveness of sunitinib, sorafenib, bevacizumab plus IFN and temsirolimus against relevant comparators for licensed indications (as detailed in Chapter 1, Description of new interventions), when data allows. The modelling of cost-effectiveness considers first-line treatment, second-line treatment and treatment of RCC patients with a poor prognosis (first-line) separately, using a similar model structure but employing different data to inform the model parameters.

Model structure/rationale

We developed a decision-analytic model to simulate disease progression in RCC and to estimate the cost-effectiveness of the drugs under consideration. The model uses survival analysis to consider progression of RCC in a cohort of patients over time. The model was written in Microsoft EXCEL. The structure was informed by a review of the available literature, clinical guidelines for treatment of RCC and expert opinion on the clinical progression of the disease.

The model uses three distinct health states: PFS, PD and death (*Figure 10*). The model uses estimates of effectiveness, costs and health-state values against these health states to model progression of disease and cost-effectiveness over time. The model uses a 10-year time horizon and a 6-week model cycle. This structure is regarded as appropriate for capturing the health effects and complexities of natural history/disease progression in RCC. Future costs and benefits are discounted at 3.5% per annum.[134]

In *Figure 10*, boxes represent health states and arrows represent transitions between states. At any moment a patient is assumed to be in one of the states. Patients move between states once during each cycle. This means that if a patient is in PFS, for example, then during the next cycle they can either die, move to PD or stay in PFS. The health states of a cohort of patients are modelled at each discrete model cycle. All patients enter the model in PFS, having been diagnosed with advanced/metastatic RCC. Patients remain in PFS until they die or the disease progresses. Once patients enter the PD state they remain there until death.

In the survival analysis used to structure the model, for each baseline strategy/treatment a Weibull curve is derived to describe the number of patients alive over time (OS data) and another Weibull curve describes the number of patients in PFS over time. Weibull survival curves were fitted separately, corresponding to a chosen baseline treatment (i.e. IFN or BSC), to the PFS and OS Kaplan–Meier curves from the RCT judged most appropriate. For each treatment being compared with the baseline disease progression (e.g. sunitinib versus IFN) the model uses relative measures of treatment effectiveness (HRs) to estimate the expected disease progression compared with baseline. For each treatment (baseline and comparator) the number of patients in the PD health state at any time is calculated as the number alive minus the number in the PFS health state at that time. This is analogous to the methods used in previous health technology assessments of treatment for metastatic colorectal cancer[142] and ovarian cancer[143] in which the mean duration that patients were in the progressive health state was calculated as the duration in the OS state minus the duration in PFS. Appendix 7 presents details of the methods used for the survival analysis used to structure the model.

The model uses the survival analysis approach to structure a Markov-type model, which estimates

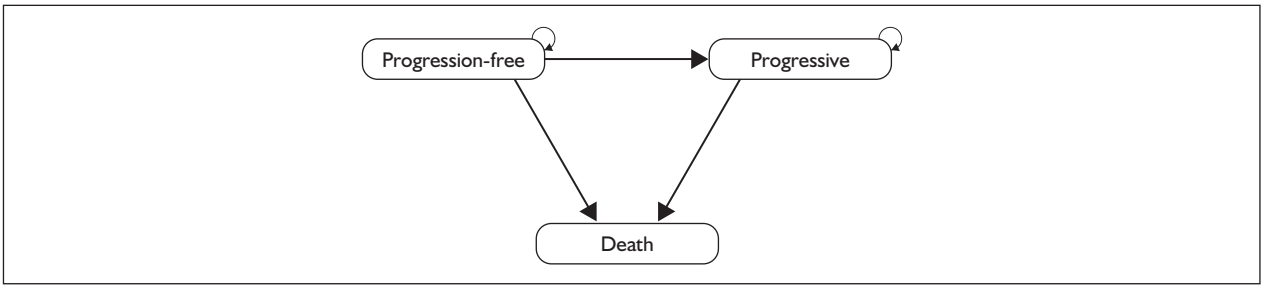

FIGURE 10 *Influence diagram for PenTAG RCC cost-effectiveness model.*

the costs and effects across a cohort of patients over time, estimating the costs and effects for each health state at each model cycle (to estimate a cost for each cohort at each cycle). A half-cycle correction is applied in the modelling.

In modelling cost-effectiveness, the approach includes additional costs associated with each of the treatment strategies (drugs), covering drug administration costs (where required) and medical management costs when in the PFS health state (outpatient monitoring, scans, tests, treatment of adverse events). The model makes assumptions over expected resource use to estimate the costs associated with BSC and the expected additional resources and costs associated with serious (grades 3 and 4) adverse events. When estimating drug costs, the modelling applies data on dose intensities (from RCTs) to adjust the costs of interventions. This complements ITT effectiveness data (with drug cost being a primary cost driver in analysis).

When manufacturers have advised of drug pricing strategies in submissions to NICE[117,136] these are *not* included in the modelling of the base-case cost-effectiveness of treatments, based on advice from NICE and the inconsistency of the pricing strategies with regard to the NICE reference case requirements. However, such pricing strategies have been included in sensitivity analyses.

Data

The modelling framework synthesises data from a number of different sources, including data for baseline disease progression, measures of clinical effectiveness from RCTs (see Chapter 2), health-state utilities (for PFS and PD health states), resource use and costs associated with drug treatment and non-drug-related resource use and costs. These are outlined below.

Patient cohort characteristics

All patients in the model were assumed to have advanced/metastatic RCC and all patients were assumed to start in PFS.

Model structure

In the approach employed (i.e. survival analysis), the baseline progression of disease is modelled in each cost-effectiveness analysis question using data from clinical trials, with treatment effect modelled using measures of relative treatment effect (as reported in relevant RCTs). These data are discussed in more detail below.

Effectiveness data

The details of the survival analysis for each of the cost-effectiveness (policy) questions are outlined below.

Question 1 – modelling survival data: In those who are suitable for treatment with immunotherapy, what is the cost effectiveness of (1) bevacizumab plus IFN and (2) sunitinib compared with IFN as first-line therapy?

To estimate baseline disease progression, that is, when patients are on IFN alone, data are taken from the RCT reported by Escudier and colleagues,[106] which compares bevacizumab plus IFN with IFN alone. For the IFN alone patient group, the OS and PFS data (Kaplan–Meier survival data) are used to model disease progression over time. PFS and OS data for IFN were read directly from the published Kaplan–Meier survival curves in the bevacizumab plus IFN RCT,[106] and Weibull curves were than fitted to the data for use in the PenTAG model. The fit of the

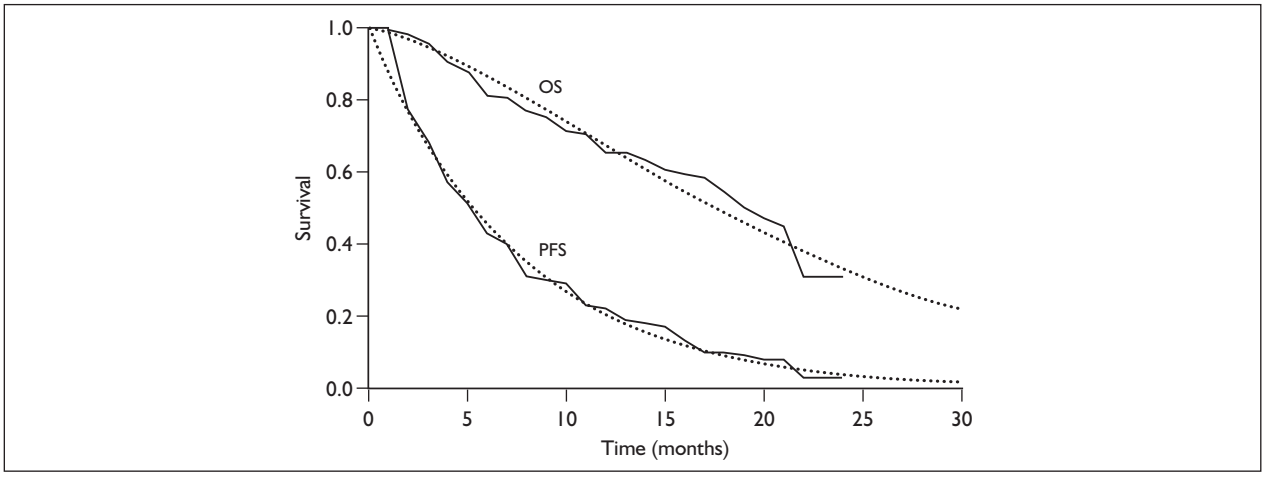

FIGURE 11 *Survival analysis for base case: Weibull curves fitted to IFN progression-free survival and overall survival Kaplan–Meier data. Source: Escudier* et al.*[106]*

Weibull curves to the empirical Kaplan–Meier data is shown in *Figure 11*. Appendix 7 reports further detail on the methods used to model survival data.

We chose data from the bevacizumab trial[106] to model baseline data based on our judgement that it is the most appropriate option from the two potential sources of data available. Alternatively, data from the trial of sunitinib versus IFN reported by Motzer and colleagues[107] could have been used. However, the Kaplan–Meier data for OS in this RCT have not been published and, second, the data are immature (*Figure 12*). Given the use of a multiple comparison approach for IFN, bevacizumab plus IFN and sunitinib, one baseline data source had to be chosen from the options available. However, this structural assumption is considered in the sensitivity analysis by using disease progression data from the RCT of sunitinib versus IFN.[107] PFS was taken from the published paper and OS from the Pfizer submission to NICE.[136] See *Figure 12* for the fit of the Weibull curves to the empirical survival data used in sensitivity analysis (note the shorter duration of empirical data).

Using the baseline (IFN alone) disease progression data, the disease progression for bevacizumab plus IFN and for sunitinib were estimated using the relative measures of treatment effect reported in Chapter 2 (see Bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy). For bevacizumab plus IFN the HRs for PFS and OS were 0.63 (95% CI 0.52 to 0.75) and 0.75 (95% CI

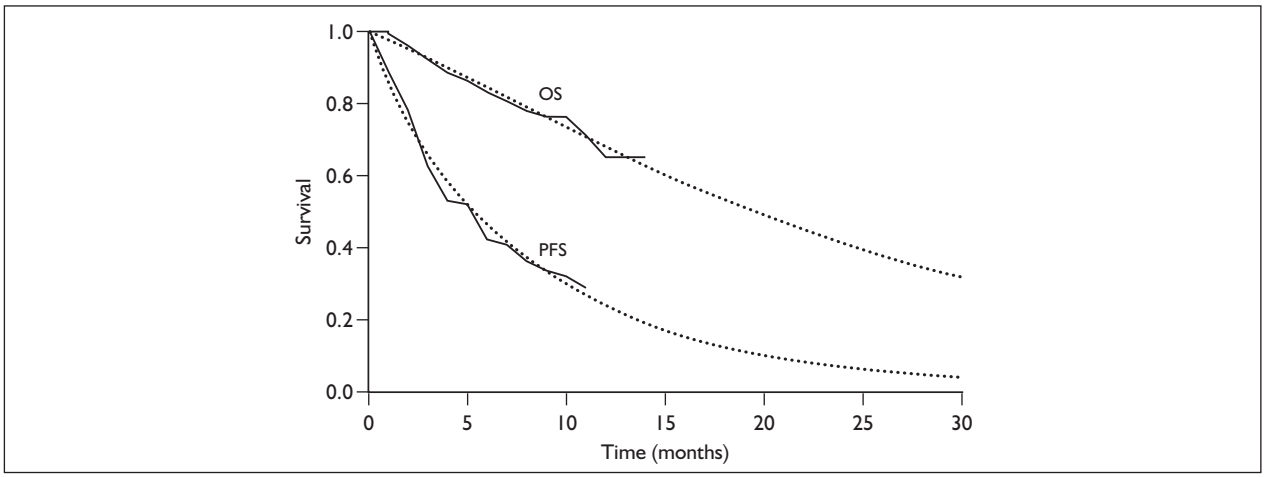

FIGURE 12 *Survival data for sensitivity analysis: Weibull curves fitted to IFN progression-free survival and overall survival Kaplan–Meier data. Sources: Motzer* et al.*[107] and Pfizer industry submission.[136]*

0.58 to 0.97) respectively. For sunitinib the HRs for PFS and OS were 0.42 (95% CI 0.33 to 0.52) and 0.65 (95% CI 0.45 to 0.94) respectively.

For this policy question we performed a multiple comparison of bevacizumab plus IFN, sunitinib and IFN alone. An indirect comparison of bevacizumab plus IFN versus sunitinib was possible because of the judged exchangeability of the RCTs reported. The patient characteristics (e.g. per cent nephrectomy, per cent clear cell, MSKCC severity scale, dose of IFN) are very similar in the RCTs of bevacizumab plus IFN versus interferon and sunitinib versus interferon (see Chapter 2, Bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy, Assessment of clinical effectiveness). However, the two RCTs differ in two ways that are relevant to the indirect comparison. First, in the RCT of sunitinib versus IFN patients took IFN whilst in the PFS category (with no constraint on time period), whereas in the RCT of bevacizumab plus IFN versus IFN (in both treatment arms) patients were able to stay on IFN up to a maximum of 1 year. In the base-case analysis undertaken we assumed the latter, that is, IFN is taken whilst in PFS up to a maximum of 1 year (this assumption was tested in sensitivity analysis). Second, the dose intensities (see discussion below) of IFN monotherapy differed slightly in the two RCTs: 83% in the sunitinib RCT[107] and 89% in the bevacizumab plus IFN RCT.[106] For the indirect comparison we chose the average of these values, that is, 86% for IFN monotherapy. All other dose intensities were set equal to the values from the relevant RCT.

Question 2 – modelling survival data: In those who are not suitable for treatment with immunotherapy, what is the cost-effectiveness of sorafenib and sunitinib compared with best supportive care?

There is an absence of clinical effectiveness data for this comparison and therefore no analysis has been undertaken.

Question 3 – modelling survival data: In those with three or more of six poor prognostic factors, what is the cost-effectiveness of bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared with IFN?

Against this question the only data identified to enable the modelling of the cost-effectiveness of treatment were for the comparison of temsirolimus with IFN (see Chapter 2, Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and BSC compared with IFN as first-line therapy in people with poor prognosis). Therefore, analyses for the other comparators were not undertaken. In particular, we report that we were unable to use data from the RCT of sorafenib[109] to help answer this question, as there were no poor prognosis patients in this trial (see Chapter 2, Sorafenib and sunitinib compared with BSC as second-line therapy). We have not modelled the cost-effectiveness of sunitinib for poor prognosis patients for two reasons. First, the clinical effectiveness data for OS in poor prognosis patients included in the RCT of sunitinib versus IFN[107] have not been reported. Second, only 48 patients in this RCT were reported as being of poor prognosis (see Chapter 2, Bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy). We have not modelled the cost-effectiveness of bevacizumab plus IFN for poor prognosis patients because there were only 52 poor prognosis patients in the RCT of bevacizumab plus IFN versus IFN.[106] More importantly, whilst noting the sparsity of data, we felt unable to consider any form of indirect comparison of bevacizumab plus IFN with temsirolimus for poor prognosis patients given that: (1) the definitions of poor prognosis in the bevacizumab plus IFN versus IFN and temsirolimus versus IFN RCTs differed and (2) the doses of IFN in these two RCTs differed: 9 MIU and 18 MIU respectively (see Chapter 2, Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and BSC compared with IFN as first-line therapy in people with poor prognosis).

To model temsirolimus versus IFN we used Kaplan–Meier survival data from the RCT reported by Hudes and colleagues.[108] In the base-case analysis we used data from the RCT for all patients in the trial, and Weibull curves were fitted to empirical Kaplan–Meier data on PFS and OS for the patient group on IFN (*Figure 13*). As the Kaplan–Meier curve for the independent assessment of PFS was not published, we used the published site investigator assessment of PFS. To model progression of disease in those treated with temsirolimus we applied relative measures of clinical effectiveness (HRs) for PFS (0.74; 95% CI 0.60 to 0.91) and OS (0.73; 95% CI 0.58 to 0.92) from Hudes and colleagues[108] (see Chapter 2, Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and BSC compared with IFN as first-line therapy in people with poor prognosis).

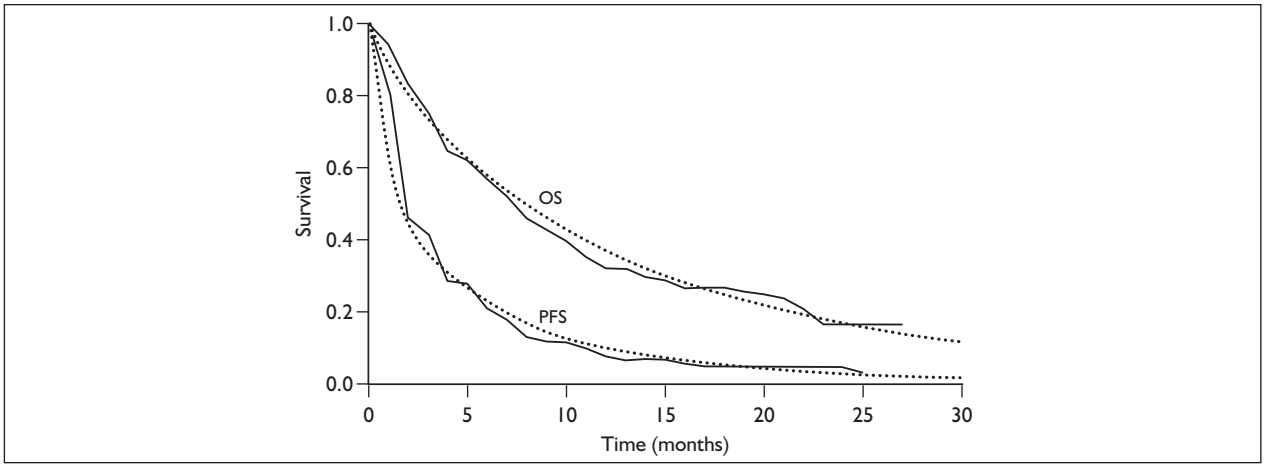

FIGURE 13 *Survival analysis for base case: Weibull curves fitted to IFN progression-free survival and overall survival Kaplan–Meier data.*

We note that, because of the definition of poor prognosis used in the RCT of temsirolimus versus IFN, only 75% of included patients were described as having poor prognosis according to the MSKCC prognostic score; the remainder had intermediate prognosis. Because of the absence of survival data (Kaplan–Meier curves) for only those patients with poor prognosis (MSKCC score) the 'all patients' data have been used in the base-case analysis.

In the comparison of temsirolimus with IFN we were able to consider subgroup analyses as data are available for five subgroups. However, the data available are on relative measures of clinical effectiveness (HRs for OS and PFS) (*Table 36*) and there are no data on baseline disease progression for the subgroups. In subgroup analysis for patients with an MSKCC poor prognosis score we adjusted the baseline IFN PFS and OS curves to model only the 75% of patients who have poor prognosis according to this scale. Specifically, we forced the modelled median PFS and OS times to equal the median PFS and OS times for the poor prognosis patients from the temsirolimus versus IFN RCT.[108] This was achieved by appropriately varying the parameter lambda of the Weibull distribution separately in the PFS and OS curves. For other subgroup analyses (clear cell, non-clear cell, previous nephrectomy, no previous nephrectomy) we assumed the same baseline IFN PFS and OS curves as for all patients from the temsirolimus versus IFN RCT,[108] using the reported HRs for these subgroups (*Table 36*).

Question 4 – modelling survival data: In those who have failed treatment with cytokine-based immunotherapy, what is the cost-effectiveness of sorafenib tosylate and sunitinib as second-line therapy compared with best supportive care?

For this question we identified data on sorafenib versus BSC only. Although data were identified on sunitinib versus BSC in second-line therapy these data come from two single-arm trials.[111,112] We did not use these data to model cost-effectiveness because of methodological concerns.[144]

We modelled disease progression and cost-effectiveness for sorafenib compared with BSC using data from the RCT reported by Escudier and colleagues.[109] We used data from this RCT for all patients in the trial, although we note that only 82% had been previously treated with immunotherapy. (Commercial-in-confidence information has been removed.)

Data from the BSC arm of the RCT[109] (Kaplan–Meier curves for PFS and OS) were used to model baseline disease progression. Weibull curves were fitted to the empirical data, detailed in Appendix 7. *Figure 14* reports the fit of the Weibull curves to the data. In modelling disease progression for people on sorafenib we used the HRs for PFS and OS reported by Escudier and colleagues; for PFS the (investigator-assessed) HR was 0.51 (95% CI 0.43 to 0.60) and for OS the HR was 0.72 (95% CI 0.54 to 0.94).[109]

TABLE 36 *Survival data: subgroup clinical effectiveness – hazard ratios of temsirolimus versus IFN*

Subgroup	Survival	Number of patients	Hazard ratio (95% CI)	Data source
All data[a]	PFS	416	0.74 (0.60 to 0.91)	Wyeth submission (p. 16) 2008[124]
	OS	416	0.73 (0.58 to 0.92)	Hudes *et al*. 2007[108]
Motzer poor prognosis[b]	PFS	301	0.69 (0.54 to 0.87)	Dutcher *et al*. 2007[94]
	OS	301	0.70 (0.55 to 0.89)	Dutcher *et al*. 2007[94]
Clear cell/ non-clear cell[a]	PFS	Clear cell 339, non-clear cell 73	Clear cell 0.84 (0.67 to 1.05), not-clear cell 0.36 (0.22 to 1.59)	Dutcher *et al*. 2007[94]
	OS	Clear cell 339, non-clear cell 73	Clear cell 0.85 (0.64 to 1.06), non-clear cell 0.55 (0.33 to 0.90)	Dutcher *et al*. 2007[94]
Previous nephrectomy (yes/no)[a]	PFS	Yes 278, no 138	Yes 0.74 (0.58 to 0.95), no 0.63 (0.44 to 0.91)[c]	Wyeth submission 2008[124] (p. 22)
	OS	Yes 278, no 138	Yes 0.84 (0.63 to 1.11), no 0.61 (0.41 to 0.91)	Wyeth submission 2008[124] (p. 22)

a Includes the 25% of patients with intermediate Motzer score.
b Baseline IFN PFS and OS curves adjusted (see text).
c Investigator assessment.

Health-state utilities

Table 37 presents the health-state values used in the PenTAG base-case analysis. We found no published data on health-state values for RCC across all of the patient groups and we are unable to draw on the published literature (see Cost-effectiveness: review of related literature) to inform the choice of health-state values in the PenTAG model. Manufacturer submissions to NICE did contain further information as model inputs (see Cost-effectiveness: review of manufacturer submissions to NICE), but uncertainties remain surrounding the collection and presentation of available data. We believe that all available sources of health-state value data for RCC have limitations, and some judgement is required to select parameters for the base-case scenarios in the PenTAG analysis.

In the base-case analysis we use the data presented in the sunitinib submission to NICE (Pfizer)[136] for health-state values for first- and second-line treatment. The health-state values in the submission are derived from trial data [stated source: RCT by Motzer and colleagues[107] (first-line) and Motzer and colleagues[112] (second-line)] and UK EQ-5D tariffs, although published reports of these trials do not include the EQ-5D data used to estimate health-state values. In the absence of supporting material for these reported health-state values, we are unable to comment further

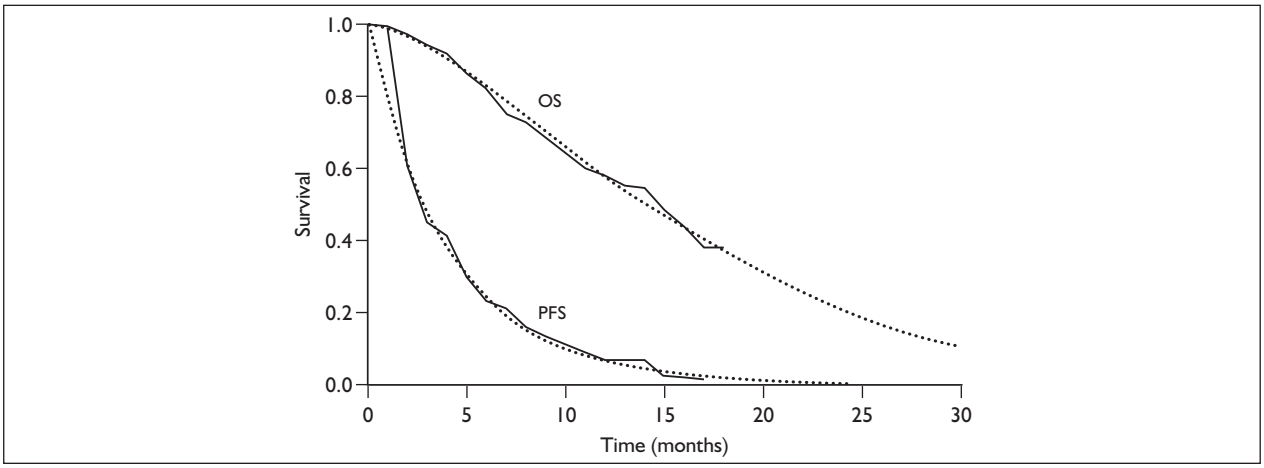

FIGURE 14 *Survival analysis for base case: Weibull curves fitted to BSC progression-free survival and overall survival Kaplan–Meier data.*

TABLE 37 *Health state utilities used in the PenTAG model*

Policy question	Treatments	Health state	Base case (SE)[a]	Source/justification
First-line (not poor prognosis)	IFN, sunitinib, bevacizumab + IFN	PFS	0.78 (0.01)	Pfizer submission 2008[136]
		PD	0.70 (0.02)	
First-line (poor prognosis)	IFN, temsirolimus	PFS	0.60 (0.06[b])	Wyeth submission 2008[124]
		PD	0.45 (0.04[b])	
Second-line and unsuitable IFN	Sorafenib, BSC	PFS	0.76 (0.03)	Pfizer submission 2008[136]
		PD	0.68 (0.04)	

a SEs derived from SDs and numbers of patients from RCTs, reported in industry submissions.
b SE estimated as 10% of mean.

on methods used. The manufacturer submission reports, and applies, treatment-specific health-state values; however, we do not support the use of treatment (drug)-specific health-state values. We assume at baseline in the trials that patients are similar and do not see support in the evidence for differential utilities by treatment.

In the PenTAG analysis we use the same estimates of health-state value for the health states of PFS and PD for both treatment and control arms in the model. For analysis of first-line treatment we use the health-state values presented 'by disease progression' in the manufacturer submission (Pfizer),[136] and for analysis of second-line treatment we apply the values reported against 'baseline' and 'progression', as per the same submission.

Data for health-state values in the poor prognosis treatment group are taken from the temsirolimus industry submission,[124] which are derived from EQ-5D data collected in the trial reported by Hudes and colleagues.[108] The EQ-5D data are not reported in the publication of the trial, although some brief detail is presented in a published abstract.[97] These values place PFS and PD for poor prognosis at a different point on the 0–1 health utility scale compared with the other indications, which may be legitimate given the poor prognosis for the patients in the temsirolimus RCT.[108] However, we feel that differences are significant and are potentially inconsistent with the data used for health-state values in analysis of first-line and second-line treatment. For patients with poor prognosis we note from data describing patient characteristics in clinical trials that these patients are reported at a worse/poorer level against measures of performance status. The majority of patients in the sunitinib RCT[107] had an ECOG-PS of 0 (approximately 60%), whereas 80% of patients in the temsirolimus RCT[108] had a Karnofsky performance score of 60 or 70,[108] which has been shown to be approximately equivalent to an ECOG-PS of 2 (where 2 is a worse status than 0 and 1).[4,27] However, we believe that the difference in utility values obtained from the two trials may not be adequately explained by differences in performance status, and by using data from different sources we may be introducing a lack of continuity in modelling the policy questions.

However, in the absence of other data, the estimates derived from the temsirolimus RCT[108] are used in the base case for the temsirolimus cost-effectiveness analysis, with further scenarios explored in sensitivity analyses. We do not use data from the manufacturer submission, which assumes an increment for the health state value (PFS) according to a measure of 'response' to treatment.

We note that when the multiple data sources are applied (as set out above) within a common modelling framework for first-line treatment, second-line treatment and poor prognosis patient groups there may be a lack of intuition over the disease pathway and perceived continuum of health-state values. Assumptions made give a utility difference between PFS and PD of 0.08 for first-line treatment, 0.075 for second-line treatment and 0.15 for poor prognosis. Patients starting in both first-line and second-line treatment have similar starting values, whereas patients with poor prognosis are assumed to have a much lower starting health-state value. We recognise that when patients fail first-line treatment (often against measurable criteria, e.g. tumour growth, rather than impact on HRQoL) they are then eligible for second-line treatment and start second-line treatment as PFS (with a similar health-state

value to that in first-line treatment because of a recognised new starting point for PFS/PD).

We acknowledge limitations in the utility data available to populate the model and we explore the impact of assumptions on health-state values in sensitivity analyses.

Resource use/cost data inputs

Resource use, and associated costs, are estimated from a range of sources and refer to the baseline costs of managing RCC and additional costs associated with different treatment options. The cost components include drug costs, related drug administration costs, costs for treatment of serious adverse events, costs associated with treatment-related monitoring when in the progresson-free survival health state and the costs associated with BSC when in the PD health state. As discussed earlier (see Cost-effectiveness: review of related literature, Treatment cost/resource use) there is an absence of published data to inform on the costs associated with treatment of RCC and assumptions have been made against a number of the cost components used in the modelling. Assumptions have been based on guidelines outlining current practice and the information provided by clinicians in the expert advisory group. BNF55 list prices are used for drug pricing and all other costs are inflated to 2007–08 values.[145]

Drug costs

Table 38 presents the drug prices used to inform the analysis and the estimated cost for each of the drugs for the 6-week cycle used in the model. Drug prices have been taken from BNF55[70] with the exception of the temsirolimus price, which was not listed at the time of writing. The pricing information for temsirolimus is based on advice to NICE by the manufacturer (Wyeth).

Where drug-pricing strategies have been presented by manufacturers, these have not been used in the current base-case cost-effectiveness analysis. The manufacturer of sunitinib (Pfizer) has advised that for the UK NHS the first cycle of sunitinib will be supplied free of charge.[136] The manufacturer of bevacizumab (Roche) has advised that for the UK NHS (also a European-wide scheme) there is a 'dose cap' pricing strategy in which there are no charges for bevacizumab once an individual has had 10,000 mg within 1 year of treatment

TABLE 38 *Drug costs in the PenTAG model*

Drug	Brand	Dose and frequency	Cost[a]	Cost per 6-week cycle
IFN-α (18 MIU)	Roferon-A	18 MIU[b] three times per week	£90.39 per 18 MIU[c]	£1265 first model cycle, £1627 future cycles
IFN-α (9 MIU)	Roferon-A	9 MIU[d] three times per week	£45.19 per 9 MIU[c]	£678 first model cycle, £813 future cycles
Bevacizumab	Avastin	10 mg/kg given once every 2 weeks	£924.40 per 400 mg	£5304[e]
Bevacizumab + IFN-α (9 MIU)	Avastin + Roferon-A	Combination of above		£5982 first model cycle, £6117 future cycles
Sorafenib	Nexavar	400 mg twice daily	£2504.60 per 200-mg 112-tablet pack	£357
Sunitinib	Sutent	50 mg daily for 4 weeks, followed by 2-week rest period	£3363 per 30-capsule 50-mg pack	£3139[f]
Temsirolimus	Torisel	25 mg once per week	£515 per dose[g]	£3090[g]

a All cost data taken from *British National Formulary* (BNF) No. 55[70] except that of temsirolimus, which was provided by Wyeth.[124]
b 3 MIU per dose in first week, 9 MIU per dose in second week, 18 MIU per dose thereafter.
c 3 MIU dose costs £15.07, 6 MIU dose costs £30.12, 9 MIU dose costs £45.19, 18 MIU dose costs £90.39.
d 3 MIU per dose in first week, 6 MIU per dose in second week, 9 MIU per dose thereafter.
e Assuming average weight of patients from the RCT of bevacizumab + IFN vs IFN[106] of 76.5 kg. Base-case figure assumes no wastage of bevacizumab. Allowing for wastage by assuming 800 mg taken per patient every 2 weeks increases cost per 6 weeks to £5546.
f In the sensitivity analysis we assume that the first 6-week treatment cycle is free to the NHS.
g £20.60 per mg (Wyeth). Assumes some wastage of temsirolimus given that all 30 mg in a vial is not used.

initiation.[117] When introducing these pricing strategies into sensitivity analysis we estimate that under the bevacizumab 'dose cap' scheme there will be no cost beyond 30 weeks of treatment (assuming a bevacizumab dose intensity of 88%, mean patient weight of 76.5 kg and a 765-mg dose every 2 weeks).

As noted in the footnotes in *Table 38* (footnote g), in the base-case cost-effectiveness analysis for temsirolimus we have assumed that there will be one 30-mg vial used per dose, which, given the licensed 25-mg dose, includes 5 mg waste in the cost-effectiveness analysis.

Drug cost: dose intensity

For all drugs in the cost-effectiveness analysis, with the exception of sorafenib, the clinical trials and/or the manufacturer submissions to NICE report data on dose intensity, that is, the mean dose of drug that is expected in a cohort of patients. The dose intensity of a drug is defined as the amount of drug administered in a clinical trial as a proportion of the amount that should have been administered if there had been no patient withdrawals or dose reductions. Reported dose intensities are presented in *Table 39*.

In the base-case cost-effectiveness analysis these dose intensity data are used in the modelling framework to adjust the cost of the drugs (*Figure 15*). This assumption is based on an acceptance that the clinical effectiveness data are from RCTs reporting ITT analysis, and the use of the reported dose intensity data makes some allowance in treatment cost (especially given the finding highlighted in the results section that drug cost is the major component of total cost) for an ITT analysis. This assumption is tested in sensitivity analyses.

Drug-related costs: administration of drugs

There is a drug-related administration cost for three of the drug treatment strategies: IFN, bevacizumab plus IFN, and temsirolimus. There is no administration cost for BSC, sunitinib (oral) or sorafenib (oral). Cost estimates are presented in *Table 40*.

IFN (monotherapy) is administered by injection three times per week. The assumption in the current analysis is that the administration of IFN is at home on all occasions, and by patients or carers in 75% of cases, with 25% of cases (injections) being administered by a district nurse. These assumptions are based on information on current practice provided by the clinical community (five members of our expert advisory group). The estimated cost per 6-week cycle for the administration of IFN is £112.

Both temsirolimus and bevacizumab are administered in a hospital setting, temsirolimus once per week and bevacizumab once every 2 weeks. We have assumed a cost per administration

TABLE 39 *Dose intensities applied to drug costs in the PenTAG model.*

Treatment	Drug dose intensity	Source
IFN (18 MIU), first-line	56%	RCT of temsirolimus vs IFN;[108] measured in first 8 weeks of treatment
Temsirolimus	92%	RCT of temsirolimus vs IFN;[108] measured in first 8 weeks of treatment
Sorafenib	100%[a]	Bayer submission[141]
Sunitinib	86%	Value quoted by Pfizer from RCT of sunitinib vs IFN,[107] but not published
Bevacizumab	88%	RCT of bevacizumab + IFN vs IFN[106]
IFN (9 MIU, with bevacizumab), first-line	83%	RCT of bevacizumab + IFN vs IFN[106]
IFN monotherapy (9 MIU), first-line	86%	Average of IFN monotherapy values from Motzer *et al.*[107] (value quoted by Pfizer of 83.1% from RCT of sunitinib vs IFN[107] but not published) and Escudier *et al.*[106] (89%)

a Approximately 6% of patients receiving sorafenib in the pivotal sorafenib RCT[109] had dose reductions.[141]

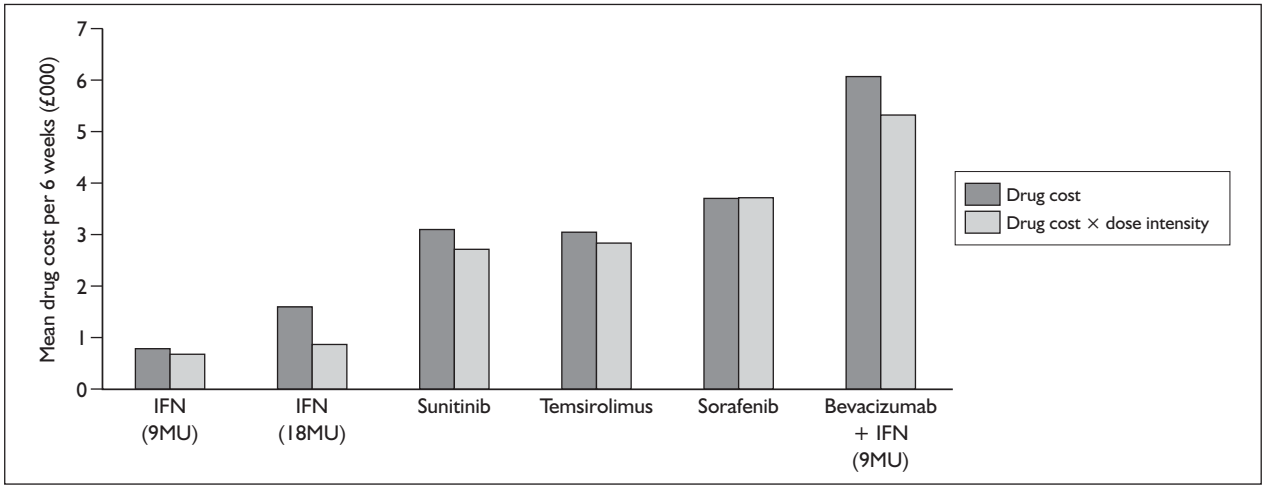

FIGURE 15 *Drug costs and mean drug costs adjusted for dose intensity.*

based on a Healthcare Resource Group (HRG) (SB15Z) from the NHS reference costs database, covering a 'chemotherapy outpatient' episode for delivery of chemotherapy. For each 6-week cycle we estimate drug administration costs of £590 for bevacizumab and £1179 for temsirolimus. These costs represent significant additional drug-related costs compared with IFN alone.

When estimating the costs associated with administration of drugs we do not adjust the cost for administration using the dose intensity data (reported above). This assumption is based on information from the clinical members of the expert advisory group who indicated that doses of IFN would be reduced rather than omitted/missed completely, suggesting that dose intensities should not be applied to reduce the cost of administration of IFN. We make this assumption (for consistency) across all three drugs with an administration cost. The assumption is tested in sensitivity analyses.

Medical management costs

When patients are in the health state of PFS and on drug treatment there is a resource use/cost associated with outpatient monitoring, scans and tests. We found no specific published literature to inform on such resource use and assumptions have been made on the resource use and subsequent costs associated with monitoring as part of the medical management of people with RCC.

Table 41 presents cost estimates per 6-week cycle for medical management. When patients are on drug treatment (in PFS) there is an assumption that they will all have one outpatient appointment every month, one CT scan every 3 months and standard blood tests once every month (with the outpatient appointment). When patients are not on active treatment with bevacizumab plus IFN, sunitinib, sorafenib, temsirolimus or IFN we assume that they will have a GP visit every month and a CT scan every 6 months.

TABLE 40 *Estimated costs for administration of IFN, bevacizumab and temsirolimus*

	IFN monotherapy	Bevacizumab	Temsirolimus
Dose frequency	Three per week	Once per 2 weeks	1 per week
Resource use	75% self-administered, 25% district nurse administered	Outpatient attendance (chemotherapy)	Outpatient attendance (chemotherapy)
Unit cost for resource use	£25 per district nurse administration[a]	£197 per administration[b]	£197 per administration[b]
Mean estimated 6-week cost for administration (SE)	£112 (£7)	£590 (£52)	£1179 (£105)

a Schema 9.1. Community nurse (includes district nursing sister, district nurse).[146]
b 'Chemotherapy outpatients.' HRG code SB15Z. 'Deliver subsequent elements of a chemotherapy cycle.'[145]

TABLE 41 *Cost parameters in the PenTAG cost-effectiveness model*

	PFS medical management		PD medical management
	BSC	**All drug treatments**	**All treatments (drugs and BSC)**
Consultations per month	One GP visit	One consultant outpatient visit	One GP visit, 1.5 community nurse visits
Tests	One CT scan per 6 months, blood tests monthly	One CT scan per 3 months, blood tests monthly	None
Other[a]	None	None	Pain medication (morphine sulphate) daily[b]
Cost per 6-week model cycle (SE)	£81 (£3)	£223 (£9)	£435 (£22)[c]

Unit costs (inflated to 2007–08): consultant, outpatient visit: £107 per visit,[145] £111 inflated to 2007–08 (Specialty code 370); GP visit: £34 per visit,[146] £35 inflated to 2007–08; community nurse visit: £83 per visit,[145] £86 inflated to 2007–08 (Band 2 – Palliative/Respite Care: Adult: Face-to-Face Total Contacts NHS); CT scan: £135 per scan,[139] £140 inflated to 2007–08 (Specialty code RBD1, 'Band D1 – CT'); haematology, blood tests (excluding anticoagulant services): £3 per test,[145] £3 inflated to 2007–08.

a In the base case we assumed no cost of death. As a sensitivity analysis we assumed a cost of £3923, taken from Coyle *et al.*,[147] averaged over hospital and hospice stays = £2701, revalued to 2007–08.

b Morphine sulphate, one dose per day (non-proprietary); 1 mg/ml, net price 50-ml vial prefilled syringe £5.00 per pack.[70]

c As a sensitivity analysis we assumed a cost of £937 per month for treatment in progressive disease for hospital and hospice care, based on a study of costs of managing women with stage IV breast cancer in the UK.[133] Mostly medication, scans, tests, hospitalisation, outpatient visits.

When patients are in the PD health state (both first- and second-line therapy) we assume that they will be managed in primary care (expert advisory group advice) and that they will have mean NHS resource use comprising one GP visit per month, 1.5 community nurse visits per month and pain medications throughout the month. This resource use over a 6-week cycle gives a mean cost estimate of £435 (*Table 41*). Sensitivity analysis tests the sensitivity of the cost-effectiveness analysis to this cost assumption, using an estimate from the literature on costs associated with BSC in breast cancer.[133]

The industry submissions to NICE include a cost associated with death. We have not included this item in our base-case cost-effectiveness analysis but carry out a sensitivity analysis in which a cost for death is included, based on an estimate from the literature.[133]

Costs associated with adverse events

The review of clinical effectiveness (see Chapter 2) reports adverse events for each of the treatment strategies. In the cost-effectiveness analysis the mean cost for treatment of adverse events is included. At a cohort level these costs are very small, given the relatively rare incidence of events regarded as serious and associated with NHS resource use. Only costs associated with grade 3 or 4 adverse events are included, as these are expected to be those that incur additional NHS costs. *Table 42* reports the basis for costing the adverse events included in the model.

For the comparison of sunitinib, bevacizumab plus IFN and IFN we considered only those adverse events with a meaningful difference in incidence between treatments, based on data from the two pivotal RCTs, those by Motzer and colleagues[107] and Escudier and colleagues.[106] In this multiple comparison it was not possible to use statistical significance as a guide and therefore there was an element of judgement, informed by clinical opinion. In the absence of data on statistically significant differences in adverse events, the same approach was taken for the comparison of temsirolimus versus IFN, using incidence of adverse events from the RCT of Hudes and colleagues.[108] For the comparison of sorafenib versus BSC we considered only those adverse events whose incidence differed with statistical significance between treatments according to the trial by Escudier and colleagues.[109]

The adverse events that required cost estimates were vomiting, diarrhoea and hypertension. In the absence of reported cost estimates for these events

TABLE 42 *Base-case mean cost estimates for adverse events (AEs) when on treatment for RCC*

Treatment	AEs modelled	Cost	AE incidence (% patients)	Base-case total cost per patient
IFN monotherapy (9 MIU)	Vomiting	£489 per event	0.5%	£3
	Hypertension	£367 per year	0.5%	
Bevacizumab + IFN	Diarrhoea	£489 per event	2%	£21
	Hypertension	£367 per year	3%	
Sunitinib	Diarrhoea	£489 per event	5%	£88
	Vomiting	£489 per event	4%	
	Hypertension	£367 per year	8%	
IFN monotherapy (18 MIU)	None			£0
Temsirolimus	None			£0
BSC	None			£0
Sorafenib	Hypertension	£367 per year	4%	£11

we made assumptions on NHS resource use. For vomiting and diarrhoea we assumed that these events would involve (on average) an inpatient stay of 2 days at a cost per event of £489 (£244.50 per day[146]). For ongoing hypertension treatment we assumed two GP visits per year (cost per visit £35[146]), two district nurse visits per year (cost per visit £25[146]) and medication for hypertension (cost per year £246[148]), with a total cost estimate of £367 per year. For the comparison of temsirolimus versus IFN we do not expect to see differential resource use/costs for adverse events (based on clinical effectiveness data and current practice). For the comparison between sorafenib and BSC we expect differential costs for adverse events to include only the ongoing treatment of hypertension (as cost estimate above) (*Table 42*).

When integrating costs for adverse events into the model we assumed that patients would have at most one episode of any adverse event during their treatment, except for hypertension, which we assumed would continue for the duration of PFS. The approach to costing adverse events in the model is a simple one and we acknowledge that it is a limitation. However, given the clinical profiles for adverse events, and the relatively small mean costs for treatment (and the fact that many adverse events have no treatment options or are reported as laboratory abnormalities with no/limited impact on HRQoL), we see the approach as parsimonious.

Summary data inputs

The estimates of resource use/cost identified above have been used to populate the PenTAG cost-effectiveness model. We acknowledge that data on costs and health-state utilities are sparse and that assumptions have been made over data inputs to the cost-effectiveness analyses. However, these assumptions have been tested in sensitivity analyses.

Presentation of results

Table 43 presents a summary of the research/policy questions that are the focus of the current assessment, highlighting the instances in which it has been possible to present cost-effectiveness analyses and those in which it has not (see also Chapter 2).

When cost-effectiveness estimates are presented, findings are presented against summary measures of cost-effectiveness (cost per LYG, cost per QALY), using ICERs, together with disaggregated data on mean incremental costs and benefits. All future costs and benefits are discounted (unless stated). When ICERs are presented (base case and sensitivity analysis) they are based on the use of deterministic modelling, applying mean parameter values for model inputs.

Assessment of uncertainty

Sensitivity analysis has been undertaken to address uncertainty in the cost-effectiveness analyses. Methodological and structural uncertainty have

TABLE 43 *Presentation of PenTAG cost-effectiveness estimates against research/policy questions*

Questions	Q1: First-line therapy vs immunotherapy	Q2: First-line therapy vs BSC	Q3: First-line therapy in poor prognosis vs IFN	Q4: Second-line therapy vs BSC
Sunitinib	✓	✗	✗	✗
Bevacizumab + IFN	✓	N/A	✗	N/A
Temsirolimus	N/A	N/A	✓	N/A
Sorafenib	N/A	✗	✗	✓

N/A, not applicable/not licensed indication; ✓, cost-effectiveness undertaken; ✗, cost-effectiveness not undertaken.
Note: see Chapter 1 (Definition of the decision problem) for detail on research/policy questions.

been considered in a number of cases in sensitivity analysis (e.g. time horizon, data for baseline disease progression, drug pricing strategies). Parameter uncertainty has been considered through one-way and multiway sensitivity analysis using deterministic modelling, and through PSA in which uncertainty across a range of parameter inputs is propagated in the model simultaneously. Probabilistic analyses were based on 1000 simulations of a cohort of patients (1000-patient cohort) with outputs presented as cost-effectiveness acceptability curves (CEACs). Appendix 8 and Appendix 10 also supplement the material presented in the main report, presenting cost-effectiveness planes from simulation analysis and the predicted profile (location) of the cohorts of patients over time.

A series of accuracy and consistency checks have been undertaken by PenTAG. The team members responsible for model development have undertaken checks to audit the model (for accuracy, structural wiring, data inputs). Model checking has also been undertaken by a PenTAG modeller not associated with this report/project/model. Further information is available from PenTAG.

PenTAG cost-effectiveness analysis results

Research/policy question 1 – Cost-effectiveness of bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy

Table 44 presents the mean estimates of costs and benefits for IFN, sunitinib, and bevacizumab plus IFN, and the incremental benefits associated with sunitinib and bevacizumab compared with IFN, in the patient group suitable for treatment with immunotherapy as first-line therapy.

The mean LYG varies between 1.63 years and 2.16 years, with sunitinib and bevacizumab having greater survival and greater mean QALY benefits than IFN alone. Compared with IFN alone, sunitinib and bevacizumab plus IFN are associated with increased total costs of £31,185 and £45,435 respectively. *Table 44* and *Figure 16* show the main components of the total cost estimates. For both sunitinib and bevacizumab plus IFN, drug costs are the main component of total cost, and for bevacizumab there is also a related drug cost for the administration of bevacizumab. Time on treatment (in the PFS health state) is greater for both sunitinib and bevacizumab plus IFN compared with IFN alone (IFN treatment was constrained in the model to 12 months maximum), with a treatment duration of 17.9 months for sunitinib and 12 months for bevacizumab.

Compared with IFN, sunitinib has an ICER of £58,647 per LYG and £71,462 per QALY gained. Compared with IFN alone, bevacizumab plus IFN has an ICER of £133,952 per LYG and £171,301 per QALY gained. In the comparison of sunitinib versus bevacizumab plus IFN, sunitinib presents with additional benefits at lower cost, dominating bevacizumab plus IFN.

Probabilistic sensitivity analysis

Figure 17 presents a measure of the uncertainty around the base-case estimates of cost-effectiveness (cost per QALY), using CEACs derived using the net-benefit statistic against a range of potential values representing the willingness of the NHS to pay for a QALY gained. See Appendix 9 for details on the probabilistic analysis undertaken. This figure shows that when the NHS are willing to pay £30,000 per QALY the probability that sunitinib is cost-effective compared with IFN is 0% and the probability that bevacizumab plus IFN is

TABLE 44 *PenTAG base-case cost-effectiveness analysis: mean costs and effects for bevacizumab plus IFN, sunitinib and IFN as first-line therapy*

	IFN monotherapy	Sunitinib	Bevacizumab + IFN	Sunitinib vs IFN	Bevacizumab + IFN vs IFN
LYG	1.63	2.16	1.96	0.53	0.34
QALYs	1.19	1.62	1.45	0.44	0.27
Time on treatment (months)	6.0	17.9	12.0	11.9	6.0
Drug cost	£2952	£34,012	£42,667	£31,060	£39,715
Drug administration	£491	£0	£5554	–£491	£5063
Medical management[a]	£1198	£2832	£1887	£1635	£689
BSC in PD	£3798	£2779	£3766	–£1019	–£31
Total costs	£8438	£39,623	£53,873	£31,185	£45,435
ICERs					
Cost/LYG				£58,647	£133,952
Cost/QALY				£71,462	£171,301

LYG, life-years gained.
a Refers to monitoring, blood tests, CT scans and adverse events combined.

cost-effective compared with IFN is also 0% (see cost-effectiveness planes presented in Appendix 8). Sunitinib is likely to be cost-effective compared with bevacizumab plus IFN and IFN only above a willingness to pay of approximately £75,000 per QALY. Bevacizumab plus IFN is not cost-effective compared with sunitinib and IFN for any reasonable willingness to pay.

Deterministic sensitivity analysis

One-way and multiway sensitivity analyses are reported in *Tables 45* and *46* and *Figures 18* and *19*. The cost-effectiveness results for sunitinib and bevacizumab plus IFN compared with IFN alone are particularly sensitive to variations in the estimates of treatment effectiveness, drug pricing (including dose intensity data) and health-state utility input parameters. The ICERs are insensitive to a number of assumptions and data estimates, in particular discounting, time horizon, limiting IFN administration to 1 year, non-drug costs, estimates associated with costs of death and estimates of adverse event costs.

The ICERs for both drugs are particularly sensitive to variations in the estimates of the HRs for OS from the clinical effectiveness review. This is a particularly uncertain parameter in the modelling

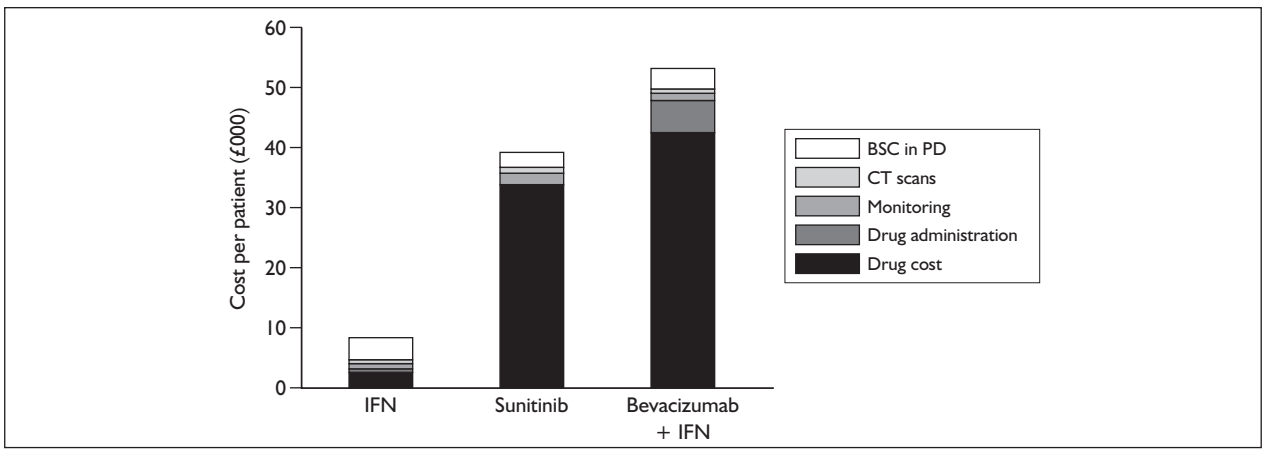

FIGURE 16 *Breakdown of the estimated mean total costs: bevacizumab plus IFN, sunitinib and IFN as first-line therapy.*

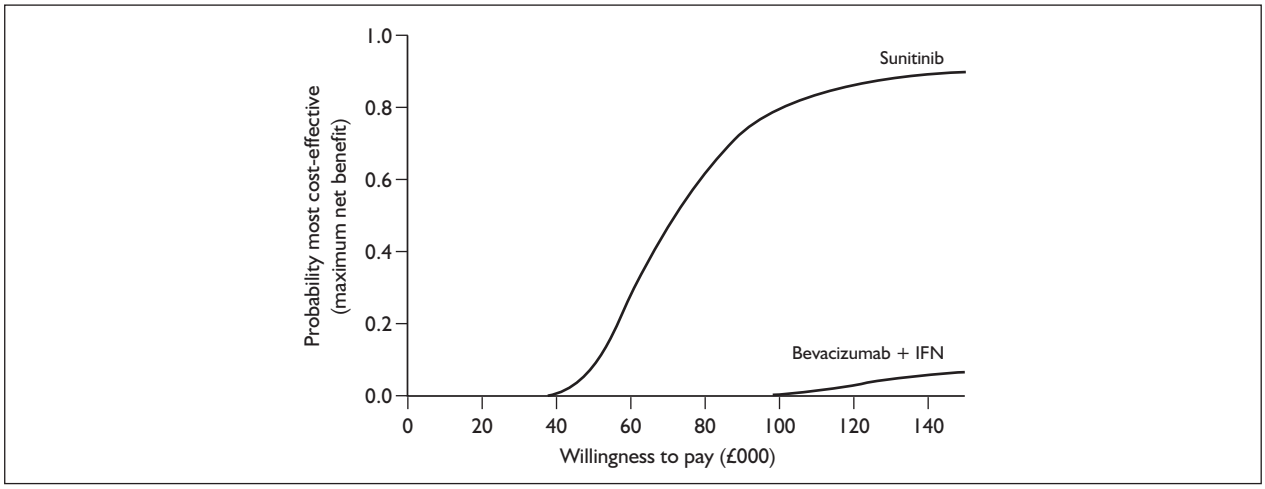

FIGURE 17 *Cost-effectiveness acceptability curves for sunitinib versus bevacizumab plus IFN versus IFN.*

of disease progression and cost-effectiveness, with wide CIs. The ICERs are less sensitive to changes in the estimates of clinical effectiveness against PFS, and are also seen to change in a counterintuitive manner. As would be reasonably expected, when the HR for OS is reduced (greater benefit), the ICER decreases. However, when the HR for PFS is reduced (greater benefit), the ICER *increases*. As shown in *Tables 45* and *46* and *Figures 18* and *19* this is the case for both sunitinib and bevacizumab plus IFN. This result is due to the fact that the change in effect size (HR) retains a greater proportion of patients in PFS, which has a relatively high incremental cost (drug and drug administration costs). The incremental costs in PFS outweigh the survival and QALY gains when in PFS. Sensitivity analysis against cost per LYG also shows the same finding when estimates of PFS effectiveness are varied, and the same effect can be seen in manufacturer models for sunitinib and sorafenib. We were unable to replicate the effect in the models of temsirolimus and bevacizumab plus IFN because off differences in methodology used.

The importance of the balance between costs and benefits in the PFS and PD states is also demonstrated when considering one-way sensitivity analysis of health-state utility inputs. Sensitivity analysis indicates that the ICER is much more sensitive to the difference in the health-state utility used for the PD health state than it is to differences in the incremental difference between health-state values for PFS and PD. This indicates, as above, that the effectiveness data for OS, and the difference between death (0) and the PD health-state utility (base case of 0.70), are the factors driving the ICER estimate (sensitivity of ICER). This is discussed further in Chapter 4 (see Uncertainties, Utilities).

The ICERs for sunitinib and bevacizumab plus IFN are also sensitive to the structural assumption in the model over the prediction of baseline disease progression for the IFN alone strategy. The base case uses data from the RCT reported by Escudier *et al.*,[106] with the rationale for this base-case assumption presented earlier in this section. However, when data from Motzer *et al.*[107] are used the ICER for sunitinib decreases by approximately £10,000 to £61,868 per QALY and the ICER for bevacizumab plus IFN decreases by approximately £33,000 to £138,745 per QALY.

Research/policy question 3 – Cost-effectiveness of temsirolimus compared with IFN as first-line therapy

Table 47 presents the mean estimates of costs and benefits for temsirolimus and IFN, and the incremental benefits associated with temsirolimus compared with IFN, in the patient group with three or more of six poor prognostic factors. For temsirolimus compared with IFN, the incremental LYG and QALYs gained are 0.45 and 0.24, respectively, and the incremental cost is £19,276. *Table 47* and *Figure 20* report the breakdown of the main components of the total cost estimates, with drug costs and the related costs for administration of temsirolimus reflecting the majority of the reported difference in costs. Time on treatment (in the PFS health state) is greater for temsirolimus, at 7.6 months, than for IFN, at 4.6 months.

TABLE 45 *Sensitivity analyses: sunitinib versus IFN as first-line therapy*

	Base case	Sensitivity analysis	ICER, sunitinib vs IFN
Base case	N/A	N/A	£71,462
General			
Time horizon	10 years	5 years	£75,766
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£68,627
Effectiveness			
Baseline progression data: RCT for fitting IFN OS and PFS	Bevacizumab[106]	Sunitinib[107]	£61,868
Effectiveness: HR PFS	0.42	0.33 (lower 95% CI)	£82,546
		0.52 (upper 95% CI)	£61,487
Effectiveness: HR OS	0.65	0.45 (lower 95% CI)	£39,759
		0.94 (upper 95% CI)	£263,363
Costs			
Drug pricing strategy: first-cycle sunitinib free?	No	Yes	£65,362
Cost associated with death	£0	£3923	£71,294
Cost estimate for BSC in PD health state (per 6 weeks)	£435	£1297[a]	£66,830
Cost IFN administration:			
(a) Assumption on cost (per 6 weeks) for administration	£112	£0	£72,587
		£224	£70,337
(b) Assumption on numbers treated (administration) at hospital	None	30% administration in hospital setting	£64,601
Cost monitoring, outpatient costs (per 6 weeks)	£154	£0	£69,008
		£308	£73,914
Cost CT scan (per 6 weeks)	£65	£0	£70,430
		£130	£72,500
Adverse event cost	£4 IFN, £88 sunitinib	£0 both treatments	£71,269
Dose intensity data	86% IFN monotherapy, 86% sunitinib	100% both treatments	£82,634
Duration IFN taken	PFS, max. 12 months	PFS, no limit	£69,633
Health-state utilities			
Utility estimates (by health state)	0.78 PFS, 0.70 PD	0.60 PFS, 0.45 PD[b]	£86,722
		PFS utility 0.76 (lower 95% CI)	£74,189
		PFS utility 0.80 (upper 95% CI)	£68,928
		PD utility 0.66 (lower 95% CI)	£69,734
		PD utility 0.74 (upper 95% CI)	£73,278
		0.70 PFS, 0.62 PD[c]	£79,181
Multiway			
First cycle sunitinib, HR PFS	Not free; HR 0.42	Free HR 0.33 (lower 95% CI)	£76,763
		Free; HR 0.52 (upper 95% CI)	£55,109
First cycle sunitinib, HR OS	Not free; HR 0.65	Free; HR 0.45 (lower 95% CI)	£36,587
		Free; HR 0.94 (upper 95% CI)	£238,849
First cycle sunitinib, utilities	Not free; utilities 0.78 PFS, 0.70 PD	Free; 0.60 PFS, 0.45 PD[b]	£79,320

a Based on Remák and Brazil.[133]
b Taken from Hudes *et al*.[108] RCT.
c PenTAG assumptions.

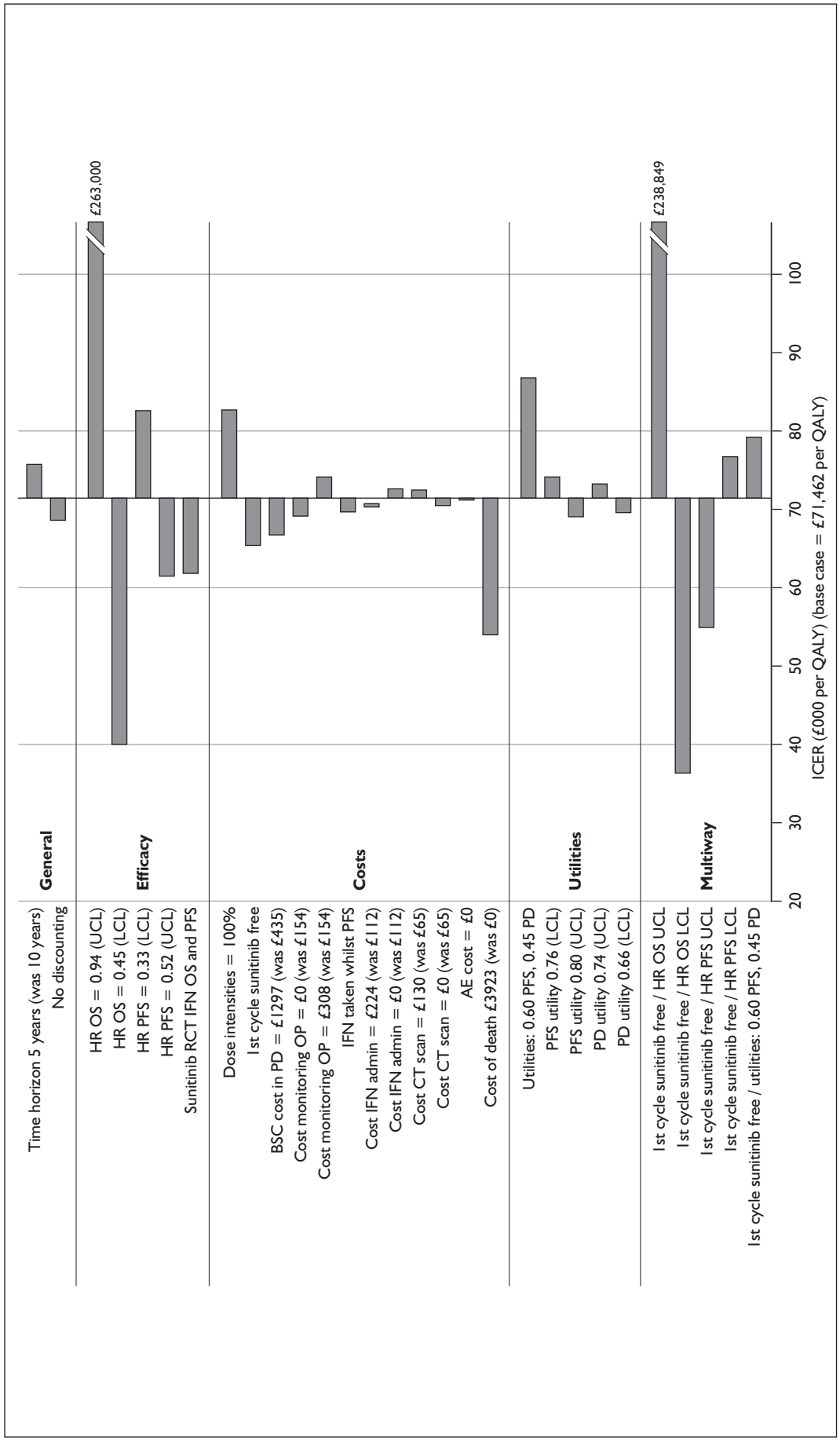

FIGURE 18 *Sensitivity analyses for sunitinib versus IFN. AE, adverse event; LCL, lower confidence limit; OP, outpatient; UCL, upper confidence limit.*

TABLE 46 *Sensitivity analyses: bevacizumab plus IFN versus IFN as first-line therapy*

	Base case	Sensitivity analysis	ICER, bevacizumab + IFN vs IFN
Base case	N/A	N/A	£171,301
General			
Time horizon	10 years	5 years	£182,490
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£161,955
Effectiveness			
Baseline progression data: RCT for fitting IFN OS and PFS	Bevacizumab[106]	Sunitinib[107]	£138,745
Effectiveness: HR PFS	0.63	0.52 (lower 95% CI)	£193,343
		0.75 (upper 95% CI)	£152,296
Effectiveness: HR OS	0.75	0.58 (lower 95% CI)	£90,693
		0.97 (upper 95% CI)	£868,881
Costs			
Drug pricing strategy: bevacizumab dose cap/manufacturer pricing strategy	No	Yes	£90,584
Cost associated with death	£0	£3923	£171,127
Cost estimate for BSC in PD health state (per 6 weeks)	£435	£1297[a]	£171,066
Cost IFN administration:			
(a) Assumption on cost (per 6 weeks) for administration	£112	£0	£170,810
		£224	£171,792
(b) Assumption on numbers treated (administration) at hospital	None	30% administration in hospital setting	£174,298
Cost bevacizumab administration (per 6 weeks)	£590	£0	£152,705
		£1180	£189,897
Cost monitoring, outpatient costs (per 6 weeks)	£154	£0	£169,551
		£308	£173,051
Cost CT scan (per 6 weeks)	£65	£0	£170,565
		£130	£172,037
Adverse event cost	£4 IFN, £21 bevacizumab + IFN	£0 both treatments	£171,237
Dose intensity	86% IFN monotherapy, 88% bevacizumab, 83% IFN (with bevacizumab)	100% all drugs	£192,369
Duration IFN taken	PFS, max. 12 months	PFS, no limit	£176,707
Bevacizumab wastage	No	Yes	£178,035
Health-state utilities			
Utilities	0.78 PFS, 0.70 PD	0.60 PFS, 0.45 PD[b]	£221,888
		PFS utility 0.76 (lower 95% CI)	£175,911
		PFS utility 0.80 (upper 95% CI)	£166,927

TABLE 46 *Sensitivity analyses: bevacizumab plus IFN versus IFN as first-line therapy (continued)*

	Base case	Sensitivity analysis	ICER, bevacizumab + IFN vs IFN
		PD utility 0.66 (lower 95% CI)	£171,086
		PD utility 0.74 (upper 95% CI)	£171,517
		0.70 PFS, 0.62 PD[c]	£190,824
Multiway			
Bevacizumab dose cap and assumptions over baseline data (RCT for fitting IFN OS and PFS)	Dose cap no; bevacizumab[106]	Dose cap yes; sunitinib[107]	£64,487
Bevacizumab dose cap and utilities	No; utilities 0.78 PFS, 0.70 PD	Yes; utilities 0.60 PFS, 0.45 PD[b]	£117,334
Bevacizumab dose cap and effectiveness estimate for HR PFS	No; HR 0.63	Yes; HR 0.52 (lower 95% CI)	£91,973
		Yes; HR 0.75 (upper 95% CI)	£88,308
Bevacizumab dose cap and effectiveness estimate for HR OS	No; HR 0.75	Yes; HR 0.58 (lower 95% CI)	£49,190
		Yes; HR 0.97 (upper 95% CI)	£448,811

a Based on Remák and Brazil.[133]
b Taken from Hudes *et al.*[108] RCT.
c PenTAG assumptions.

Compared with IFN temsirolimus has an ICER of £42,902 per LYG and £81,687 per QALY gained.

Probabilistic sensitivity analysis

Figure 21 explores the parameter of uncertainty around the base-case estimates of cost-effectiveness (cost per QALY) using a CEAC derived using the net-benefit statistic against a range of potential values representing the willingness of the NHS to pay for a QALY gained. See Appendix 9 for details on the probabilistic analysis undertaken. This figure shows that when the NHS is willing to pay £30,000 per QALY the probability that temsirolimus is cost-effective compared with IFN is 0%, this also being the case for all subgroup analyses (see cost-effectiveness plane presented in Appendix 8). Temsirolimus is likely to be cost-effective compared with IFN only above a willingness to pay of approximately £82,000 per QALY.

Subgroup cost-effectiveness analysis

Table 48 presents subgroup analysis for temsirolimus versus IFN by nephrectomy status, Motzer severity score and type of RCC (clear cell, non-clear cell). The estimated ICERs are higher than in the base case in those patients with a poor Motzer score (compared with the base case; similar benefits with higher costs), by type of RCC and in those patients with a previous nephrectomy. Note that these subgroup analyses are undertaken using the baseline disease progression applied in the base-case analysis (i.e. baseline disease progression on IFN from the RCT by Hudes *et al.*[108]). The ICER for the group with non-clear cell RCC is relatively close to the base-case cost per QALY, at £89,394 (with higher benefits but at greater cost). The ICER estimated for the subgroup with no previous nephrectomy is lower than that in the base case, at £64,680 per QALY. CEACs for subgroup cost-effectiveness analysis are presented in Appendix 11.

In the subgroup ICERs for the non-clear cell patients the incremental costs are very large, outweighing the increased effectiveness reported. The effect size for PFS in this subgroup is large, although not statistically significant (HR for PFS 0.36; 95% CI 0.22 to 1.59). Given that the HR used retains a large proportion of patients in the PFS state for a longer period of time (compared with IFN) there is a very high cost associated with a mean treatment duration of 22 months.

Deterministic sensitivity analysis

One-way sensitivity analysis is presented in *Table 49* and *Figure 22*. The cost-effectiveness of temsirolimus versus IFN is sensitive to variations in estimates of treatment effectiveness, the choice of health-state utility parameters and the costs

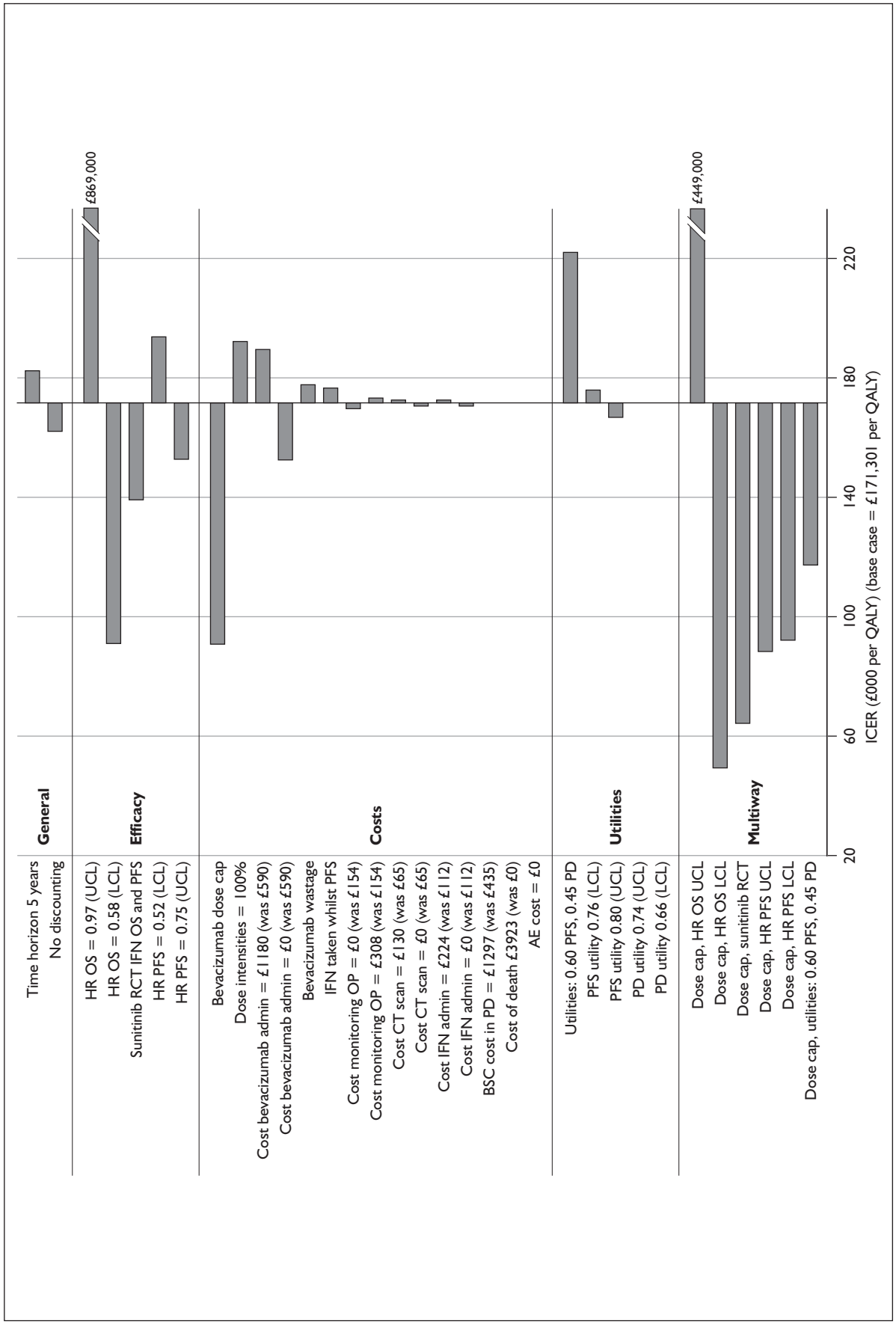

FIGURE 19 *Sensitivity analysis for bevacizumab plus IFN versus IFN. AE, adverse event; LCL, lower confidence limit; OP, outpatient; UCL, upper confidence limit.*

TABLE 47 *PenTAG base-case cost-effectiveness analysis: mean costs and effects for temsirolimus versus IFN as first-line therapy in patients with poor prognosis*

	IFN	Temsirolimus	Temsirolimus vs IFN
LYG	1.07	1.52	0.45
QALYs	0.53	0.77	0.24
Time on treatment (months)	4.6	7.6	3.0
Drug cost	£2823	£14,982	£12,159
Drug administration cost	£367	£6215	£5848
Medical management	£729	£1176	£447
BSC cost in PD	£2599	£3422	£822
Total costs	£6519	£25,794	£19,276
ICERs			
Cost/LYG			£42,902
Cost/QALY			£81,687

LYG, life-years gained.

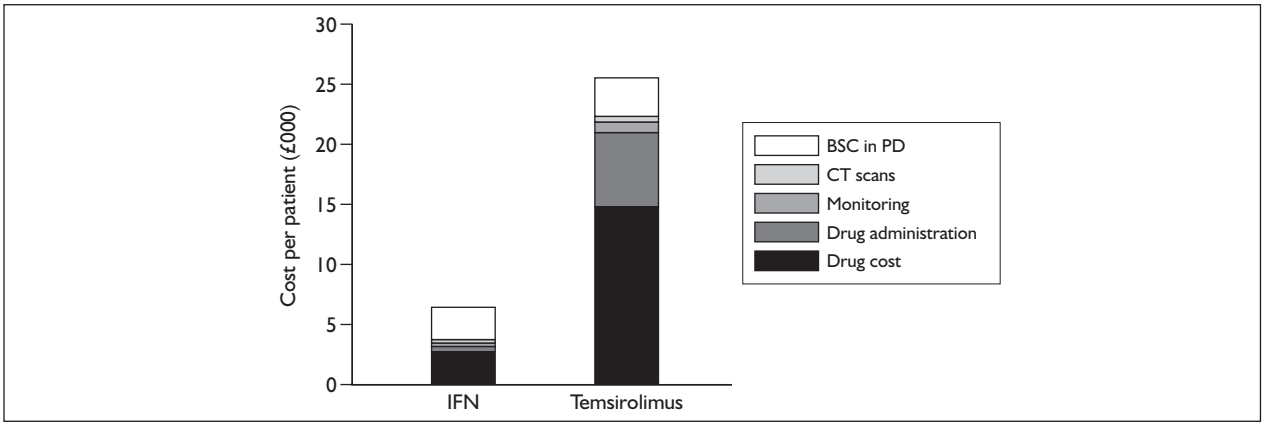

FIGURE 20 *Breakdown of the estimated mean total costs: temsirolimus versus IFN as first-line therapy in patients with poor prognosis.*

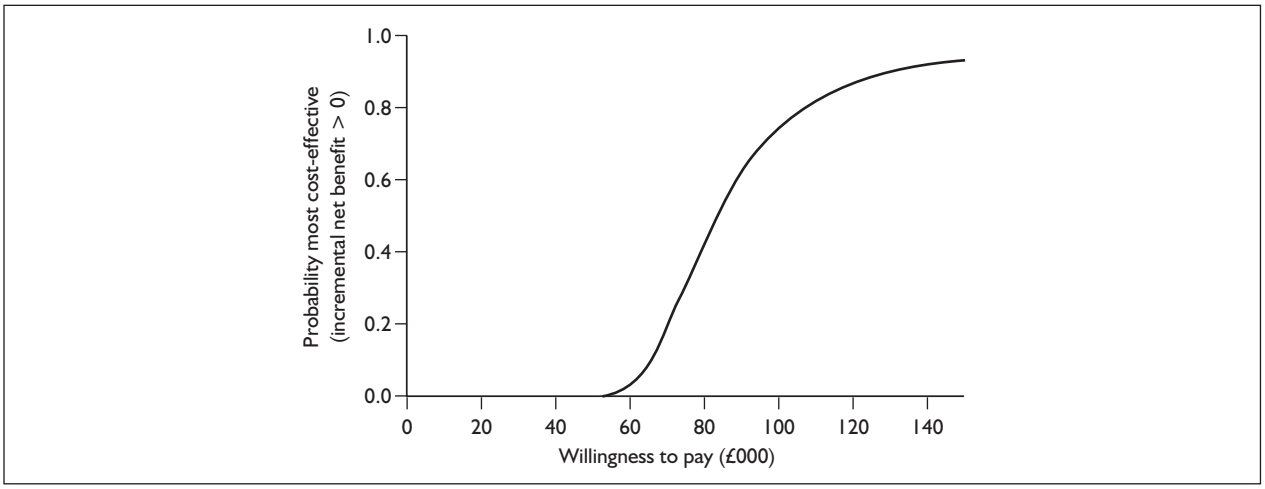

FIGURE 21 *Cost-effectiveness acceptability curve for all patients for temsirolimus versus IFN.*

TABLE 48 *PenTAG subgroup cost-effectiveness analysis: mean costs and effects for temsirolimus versus IFN as first-line therapy in patients with poor prognosis*

	Motzer poor			Clear cell		
	IFN	**Temsirolimus**	**Temsirolimus vs IFN**	**IFN**	**Temsirolimus**	**Temsirolimus vs IFN**
LYG	0.83	1.25	0.42	1.07	1.28	0.21
QALYs	0.46	0.70	0.25	0.53	0.65	0.11
Time on treatment (months)	6.8	12.0	5.2	4.6	6.2	1.6
Drug cost	£4132	£23,391	£19,259	£2823	£12,255	£9432
Drug administration	£529	£9704	£9175	£367	£5084	£4717
Medical management	£1051	£1836	£784	£729	£962	£233
BSC in PD	£1092	£1140	£48	£2599	£2955	£356
Total costs	£6804	£36,071	£29,267	£6519	£21,256	£14,737
ICERs						
Cost/LYG			£69,935			£68,599
Cost/QALY			£117,481			£128,872

LYG, life-years gained.

associated with the administration of temsirolimus. The ICER is only marginally influenced by the other parameters, including discounting, time horizon, dose intensity, non-drug costs and adverse event costs.

As discussed for sunitinib/bevacizumab plus IFN (sensitivity analysis) the ICER is particularly sensitive to the estimate of the HR for OS. From the clinical effectiveness review this is an uncertain parameter with a wide CI. The ICER is sensitive to the HR for PFS and, as discussed under sunitinib/bevacizumab, the effect of the PFS HR on the ICER is counterintuitive, with increased effectiveness (lower HR) resulting in a higher ICER and reduced effectiveness (higher HR) resulting in a lower ICER.

The ICER for temsirolimus is also sensitive to the choice of utilities and, as seen in sensitivity analysis for sunitinib/bevacizumab, when the increment in utility between the PFS and PD states is varied there is little impact on the ICER, but when the health-state value for the PD state is higher (with a greater difference between death, i.e. zero, and the PD health-state value) the ICER is reduced considerably (£57,887 per QALY), even though the difference in utility between the two health states is reduced by about 50%.

Research/policy question 4 – Cost-effectiveness of sorafenib tosylate compared with best supportive care as second-line therapy

Table 50 presents the mean estimates of costs and benefits for sorafenib and BSC, and the incremental benefits associated with sorafenib compared with BSC, in the patient group in whom treatment with cytokine-based immunotherapy has failed, that is, second-line therapy. For sorafenib compared with BSC the incremental LYG and QALYs gained are 0.30 and 0.23, respectively, and the incremental cost is £24,001. *Table 50* and *Figure 23* report the breakdown of the main components of the total cost estimates, with drug costs and the related medical management costs making up the difference in mean total costs. Time on treatment (in the PFS health state) for sorafenib is 8.7 months. Compared with BSC sorafenib has an ICER of £78,960 per LYG and £102,498 per QALY gained.

Probabilistic sensitivity analysis

Figure 24 incorporates parameter uncertainty in the base-case estimates of cost-effectiveness (cost per QALY) using a CEAC derived using the net-benefit statistic against a range of potential values representing the willingness of the NHS to pay for a QALY gained. See Appendix 9 for details on the

Non-clear cell			Nephrectomy			No nephrectomy		
IFN	Temsirolimus	Temsirolimus vs IFN	IFN	Temsirolimus	Temsirolimus vs IFN	IFN	Temsirolimus	Temsirolimus vs IFN
1.07	2.04	0.97	1.07	1.30	0.23	1.07	1.84	0.77
0.53	1.17	0.64	0.53	0.67	0.14	0.53	0.94	0.41
4.6	22	17.4	4.6	7.6	3.0	4.6	9.9	5.3
£2823	£41,574	£38,750	£2823	£14,982	£12,159	£2823	£19,265	£16,442
£367	£17,247	£16,880	£367	£6215	£5848	£367	£7992	£7625
£729	£3262	£2534	£729	£1176	£447	£729	£1512	£783
£2599	£1334	–£1265	£2599	£2602	£3	£2599	£3972	£1373
£6519	£63,418	£56,899	£6519	£24,975	£18,457	£6519	£32,741	£26,223
		£58,378			£79,596			£34,091
		£89,394			£132,778			£64,680

probabilistic analysis undertaken. This figure shows that when the NHS is willing to pay £30,000 per QALY the probability that sorafenib is cost-effective compared with BSC is 0% (see cost-effectiveness plane presented in Appendix 8). Sorafenib is likely to be cost-effective compared with BSC only above a willingness to pay of approximately £100,000 per QALY.

Deterministic sensitivity analysis

One-way sensitivity analysis is presented in *Table 51* and *Figure 25*. The cost-effectiveness of sorafenib versus BSC is sensitive to variations in estimates of treatment effectiveness, cost of sorafenib (dose intensity assumption) and to a lesser extent the health-state utilities used for the PFS and PD health states. The ICER is only marginally influenced by the other parameters, including discounting, time horizon and non-drug costs.

As discussed for sunitinib/bevacizumab plus IFN and temsirolimus (sensitivity analysis) the ICER is particularly sensitive to the estimate of the HR for OS; from the clinical effectiveness review this is an uncertain parameter with a wide CI. The ICER is sensitive to the HR for PFS; as discussed for sunitinib/bevacizumab and temsirolimus, the effect of the PFS HR on the ICER is counterintuitive, with increased effectiveness (lower HR) resulting in a higher ICER, and reduced effectiveness (higher HR) resulting in a lower ICER.

Although the available clinical effectiveness literature does not report on dose intensities for sorafenib (other than an assumption of 100%), when the dose intensity is reduced to 80% the ICER is reduced by £20,000 to £82,804.

The sensitivity analysis around the health-state utility parameters (PFS and PD utilities) reinforces the finding from the effectiveness analysis that the OS data is the prominent driver for cost-effectiveness, given the balancing of costs associated with the PFS health state when effectiveness dictates that patients remain in that state for a longer time (see Chapter 4). Sensitivity analysis is undertaken using alternative estimates from the data presented to NICE in the submission made by the manufacturer of sunitinib, and against the CIs in the data used in the base case. In the sensitivity analysis, when the difference in utilities between PFS and PD increases to 0.13 from 0.08 (using a PFS utility of 0.81, upper 95% CI limit for PFS health state) the ICER reduces by £7500 to £95,027; when the difference in utility values between the two health states reduces to 0.02 from 0.08 (using a PFS utility of 0.70, lower 95% CI limit for PFS health state) the ICER increases by £10,000; and when the utility difference between the two health states is zero (i.e. PD utility 0.76, using the upper limit of the 95% CI), but with the PD health-state value at a higher estimate (0.76 versus 0.68), the ICER increases by only £1700 to £104,214.

TABLE 49 *Sensitivity analysis: temsirolimus versus IFN as first-line therapy in patients with poor prognosis*

	Base case	Sensitivity analysis	ICER, temsirolimus vs IFN
Base case (cost/QALY)	N/A	N/A	£81,687
General			
Time horizon	10 years	5 years	£91,143
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£77,829
Effectiveness			
HR PFS	0.74	0.60 (lower 95% CI)	£99,321
		0.91 (upper 95% CI)	£65,104
HR OS	0.73	0.58 (lower 95% CI)	£49,359
		0.92 (upper 95% CI)	£217,243
Costs			
Costs associated with death	£0	£3923	£81,357
Cost for BSC in PD (per 6 weeks)	£435	£1297[a]	£88,601
Cost for IFN administration (per 6 weeks)	£112	£0	£83,242
		£224	£80,132
Cost for temsirolimus administration: (a) assumption on cost (per 6 weeks) for administration	£1179	£0	£55,348
		£2359	£108,026
Cost for IFN administration: (b) assumption on numbers treated (administration) at hospital	None	30% administration in hospital setting	£74,922
Cost monitoring, outpatient costs (per 6 weeks)	£154	£0	£80,379
		£308	£82,995
Cost CT scan (per 6 weeks)	£65	£0	£81,137
		£130	£82,237
Dose intensity	92% temsirolimus, 56% IFN	100% both treatments	£77,808
Health-state utilities			
Utilities	0.60 PFS, 0.45 PD	0.78 PFS, 0.70 PD[b]	£57,887
		PFS utility 0.48 (lower 95% CI)	£92,565
		PFS utility 0.72 (upper 95% CI)	£73,097
		PD utility 0.37 (lower 95% CI)	£87,862
		PD utility 0.52 (upper 95% CI)	£76,455
		0.65 PFS, 0.54 PD[c]	£71,915

a Based on Remák and Brazil.[133]
b Taken from Motzer *et al.*[107] RCT.
c PenTAG assumptions.

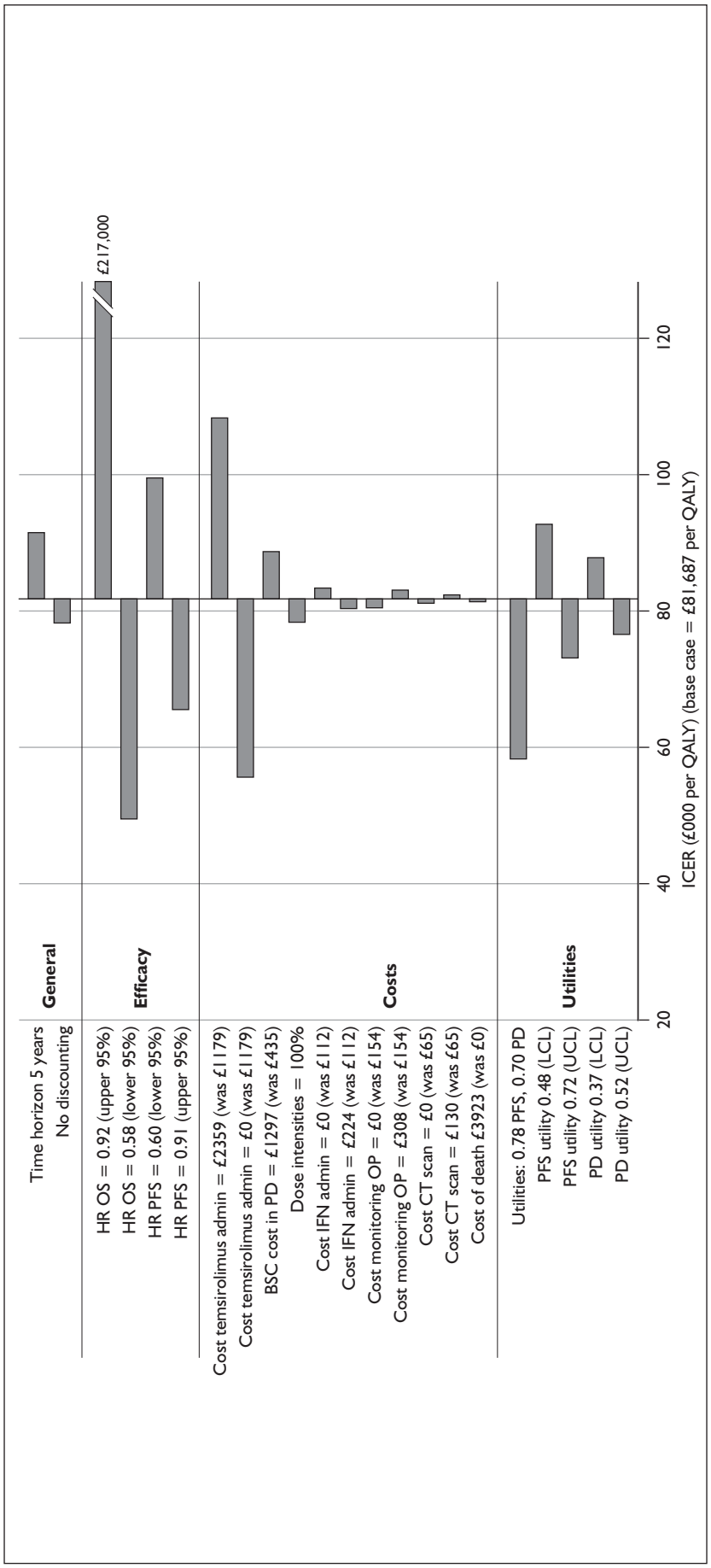

FIGURE 22 *Sensitivity analysis for temsirolimus versus IFN as first-line therapy in patients with poor prognosis. LCL, lower confidence limit; OP, outpatient; UCL, upper confidence limit.*

TABLE 50 *PenTAG base-case cost-effectiveness analysis: sorafenib versus BSC as second-line therapy*

	BSC	Sorafenib	Sorafenib vs BSC
LYG	1.30	1.60	0.30
QALYs	0.91	1.15	0.23
Time on treatment (months)	N/A	8.7	N/A
Drug cost	£0	£23,058	£23,058
Drug administration	£0	£0	£0
Medical management	£248	£1380	£1132
Cost for BSC in PD health state	£3549	£3360	–£189
Total costs	£3797	£27,797	£24,001
ICERs			
Cost/LYG			£78,960
Cost/QALY			£102,498

LYG, life-years gained.

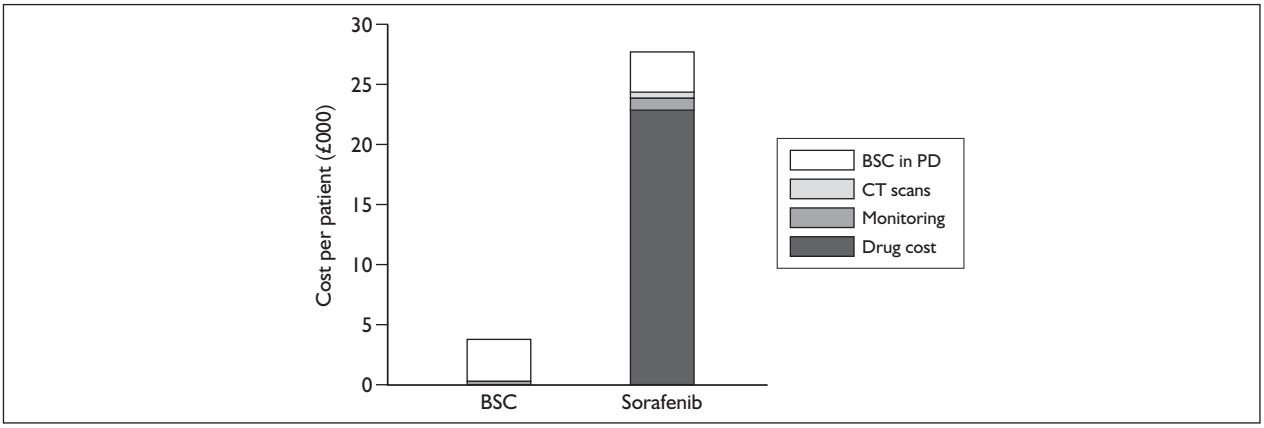

FIGURE 23 *Breakdown of estimated mean total costs: sorafenib versus BSC as second-line therapy.*

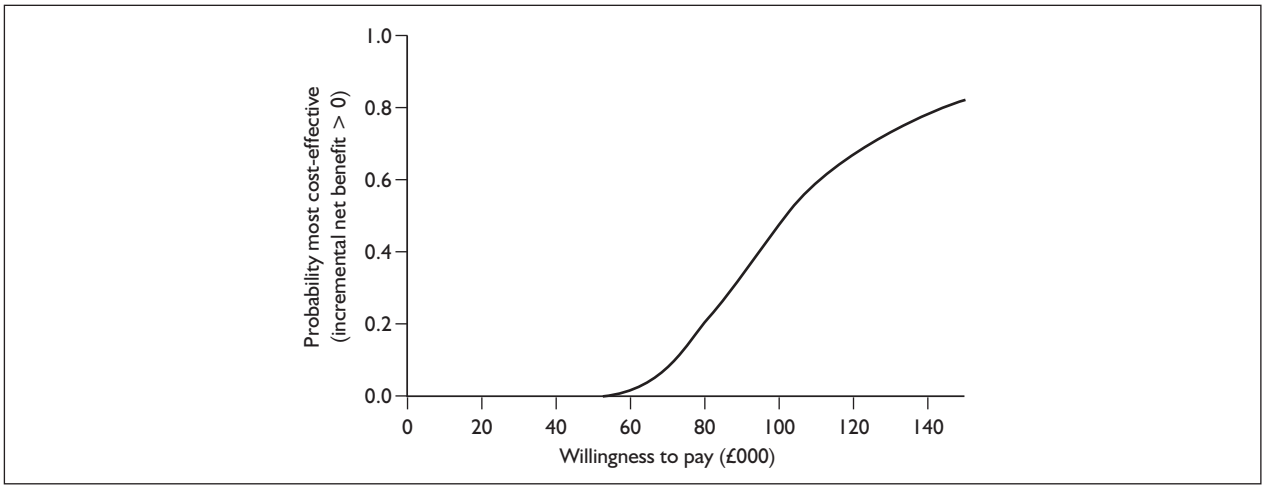

FIGURE 24 *Cost-effectiveness acceptability curve for sorafenib versus BSC.*

TABLE 51 *Sensitivity analysis: sorafenib versus BSC as second-line therapy*

	Base case	Sensitivity analysis	ICER, sorafenib vs BSC
Base case	N/A	N/A	£102,498
General			
Time horizon	10 years	5 years	£103,867
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£98,211
Effectiveness			
Effectiveness: HR PFS	0.51	0.43 (lower 95% CI)	£115,264
		0.60 (upper 95% CI)	£91,373
Effectiveness: HR OS	0.72	0.54 (lower 95% CI)	£55,585
		0.94 (upper 95% CI)	£368,830
Cost			
Cost associated with death	£0	£3923	£102,323
Cost for BSC in PD health state (per 6 weeks)	£435	£1297[a]	£100,900
Cost of monitoring, outpatient costs (per 6-week cycle)	£154 sorafenib	£0	£99,095
	£48 BSC	£308	£103,131
Cost CT scan (per 6-week cycle)	£65 sorafenib	£0	£101,224
	£32 BSC	£130	£102,928
Adverse event cost	£0 BSC	£0 both treatments	£102,453
	£11 sorafenib		
Dose intensity	100% sorafenib	80% sorafenib	£82,804
Health-state utilities			
Utilities	0.76 PFS, 0.68 PD	0.78 PFS, 0.70 PD[b]	£99,549
		PFS utility 0.70 (lower 95% CI)	£112,350
		PFS utility 0.81 (upper 95% CI)	£95,027
		PD utility 0.61 (lower 95% CI)	£100,923
		PD utility 0.76 (upper 95% CI)	£104,214
		0.62 PFS, 0.54 PD[c]	£124,704

a Based on Remák and Brazil.[133]
b Taken from Motzer *et al.*[107] RCT.
c PenTAG assumptions.

Comparison of PenTAG and manufacturer cost-effectiveness anlyses

The preceding sections have presented a summary of the cost-effectiveness analyses presented by the manufacturers of drugs in submissions to NICE, and detail on the cost-effectiveness analysis undertaken by PenTAG. Although there are some common aspects of methodology across manufacturer and PenTAG analyses, in both model structure and data inputs, there are clear differences in some of the baseline assumptions and in the resulting cost-effectiveness estimates. Although manufacturer submissions have been developed in isolation, PenTAG have sought to apply a common modelling approach across the

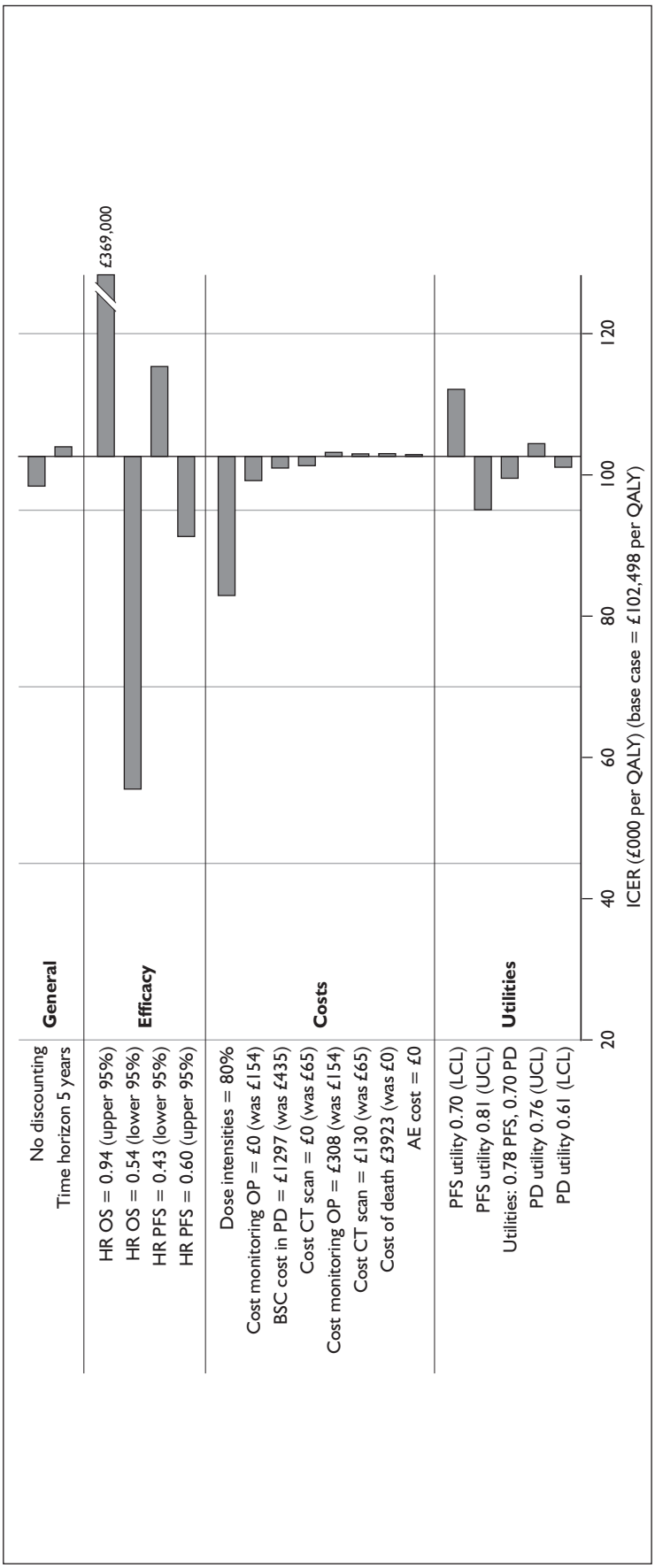

FIGURE 25 *Sensitivity analysis: sorafenib versus BSC as second-line therapy. AE, adverse event; LCL, lower confidence limit; OP, outpatient; UCL, upper confidence limit.*

policy questions. In all cases PenTAG presents base-case estimates of cost per QALY that are higher than those presented in manufacturer submissions to NICE. Manufacturer and PenTAG differences in base-case cost per QALY estimates are more marked in the assessment of cost-effectiveness for sunitinib versus IFN (first-line) and for temsirolimus versus IFN (poor prognosis patient group). Cost per QALY estimates for bevacizumab plus IFN and sorafenib are higher in the PenTAG analysis but not markedly so (when comparing bevacizumab analysis with 'dose cap' pricing scheme active in both models).

Table 52 presents summary cost per QALY estimates (base case) for the manufacturer submissions and the PenTAG cost-effectiveness analysis.

Sunitinib and bevacizumab (plus IFN) compared with IFN alone: cost-effectiveness analysis findings

When reviewing the cost-effectiveness analysis and model submitted by Pfizer for sunitinib compared with IFN, PenTAG has highlighted a number of differences in the structural assumptions and data inputs between the Pfizer and PenTAG analyses that can explain the differences seen in the cost per QALY estimates. One of the differences between the Pfizer and PenTAG models is due to the judgements made over the data used to model the baseline progression for IFN alone. PenTAG have chosen to use data on IFN progression from the RCT reported by Escudier and colleagues,[106] whereas the Pfizer base-case analysis uses data on IFN progression from the RCT reported by Motzer and colleagues,[107] which, although having a shorter follow-up for the OS data, is from a Pfizer study (which may explain their decision). PenTAG judge the data from Escudier and colleagues to be the most appropriate. However, when the PenTAG model is used with baseline progression modelled with data from Motzer and colleagues, as in the Pfizer model (but with a preferred/better fit, as discussed in the PenTAG cost-effectiveness analysis), the cost per QALY does decrease to £61,868. Therefore, we suggest that when the PenTAG model is used with the same baseline data as the Pfizer model (with adjusted fit for PFS data), and with the assumption that the first cycle of sunitinib is free of charge to the UK NHS, the estimates of cost per QALY (PenTAG £57,737 per QALY; Pfizer £48,052 per QALY) in the two models are similar (accepting small differences in a range of other data inputs, e.g. duration of treatment with IFN alone).

TABLE 52 *Summary comparison of base-case cost-effectiveness results from PenTAG and the manufacturers' economic analyses*

Comparison	Manufacturer base-case cost per QALY	PenTAG base-case cost per QALY
First-line treatment, suitable for immunotherapy		
Sunitinib vs IFN	£28,546	£71,462
	PenTAG adjustment: industry model using PenTAG fit of survival data for PFS: £48,052	PenTAG model with first cycle of sunitinib free of charge to the NHS (Pfizer strategy) and using data from Motzer *et al.*[107] (sunitinib RCT) for baseline progression: £57,737
Bevacizumab + IFN vs IFN	£74,978	£171,301 (base case)
	PenTAG adjustment: industry model without 'dose cap' pricing assumption: £108,329	£90,584 (with 'dose cap' pricing)
First-line treatment, poor prognosis		
Temsirolimus vs IFN	£55,814	£81,687
	PenTAG adjustment: applying PenTAG assumptions on cost of administration for IFN to Wyeth model: £102,000	
Second-line treatment		
Sorafenib vs BSC	(Commercial-in-confidence information has been removed)	£102,498

The PenTAG review of the cost-effectiveness analysis and model submitted to NICE by Roche for the comparison of bevacizumab plus IFN versus IFN alone has highlighted a number of differences in the structural assumptions and data inputs between the Roche and PenTAG analyses that can explain the differences seen in the cost per QALY estimates. The structure of the models (Roche and PenTAG) for disease progression are similar and assumptions over health-state utilities are the same in both models, so the estimates of LYG and QALYs gained are similar. However, assumptions over costs, especially drug-related costs, result in different cost-effectiveness estimates.

Importantly, the pricing strategy employed by Roche, the bevacizumab 'dose cap' scheme, which they suggest will mean that the UK NHS will not pay a product price beyond 10,000 mg for an individual patient (when 10,000 mg is exceeded in a 1-year period), influences base-case cost per QALY estimates in both analyses. Roche assume that the dose cap scheme is in place in the base-case analysis, whereas PenTAG (based on advice from NICE) have not assumed this for base-case estimates (giving a comparison of £75,000 per QALY versus £171,000 per QALY). When PenTAG assume the pricing strategy is 'in place/active' the base-case cost per QALY is £90,584. When PenTAG run the industry model, but without the pricing strategy, the cost per QALY from the industry model increases to £108,329.

Another important difference between the PenTAG and Roche models is the use of data on dose intensity. Dose intensity data are used to adjust the cost of bevacizumab and IFN. For bevacizumab, Roche use a dose intensity of 62%, whereas in the PenTAG model a value of 88% is used; for IFN in the bevacizumab plus IFN arm, Roche use a dose intensity of 80%, whereas in the PenTAG model a value of 83% is used; for IFN monotherapy, Roche use a dose intensity data of 63%, whereas in the PenTAG model a value of 86% is used. The Roche model uses dose intensity data that are different to those reported in the RCT of bevacizumab plus IFN compared with IFN.[106] When the RCT data are used (by PenTAG) in the Roche model (with RCT data almost identical to the data used in the PenTAG model), the cost per QALY from the Roche model increases from £75,000 to £117,000 (higher than that estimated by PenTAG, with the 'dose cap' pricing assumption).

There are a number of other differences between data inputs when comparing the models. For example, PenTAG's assumptions on the costs for drug administration and medical management are higher than those in the Roche model, and the data used by PenTAG for the modelling of PFS and OS in bevacizumab plus IFN (versus IFN) are different (PenTAG uses HRs of 0.63 and 0.75 respectively; Roche use HRs of 0.609 and 0.709 respectively). However, the main issues discussed above highlight that the two models are similar when different structural and data judgements are taken into consideration.

Temsirolimus compared with IFN alone (poor prognosis): cost-effectiveness analysis findings

For temsirolimus compared with IFN alone, in patients with poor prognosis, the report has reviewed the industry cost-effectiveness analysis and model (Wyeth) and has presented cost-effectiveness estimates using the PenTAG model. There are a number of key differences in the structures of the PenTAG and Wyeth models, and a number of different judgments have been made over data inputs to the model. Therefore, the PenTAG estimates of cost per QALY are somewhat different to those presented in the Wyeth submission to NICE (PenTAG base case £81,687 per QALY, Wyeth base case £55,814 per QALY).

Both the manufacturer model and the PenTAG model have used the same data on health-state utilities (for the primary health states), as well as effectiveness data from the same RCT source,[108] to model disease progression. However, the Wyeth model uses patient-level data from the trial to calculate time-dependent transition probabilities, for both temsirolimus treatment and IFN treatment. On the other hand, PenTAG uses summary published trial data on baseline progression for IFN alone and models treatment effectiveness using HRs reported in the RCT. The PenTAG model predicts larger mean survival and QALYs in each of the treatment groups and a higher incremental benefit from temsirolimus compared with IFN. Although model time horizons are different (Wyeth 3 years versus PenTAG 10 years) we do not believe that this is a major issue.

Whilst there are clear differences in the health outcomes predicted in the two models, with the PenTAG model estimating greater benefits, the PenTAG model also makes different assumptions on resource use and costs, resulting in a much higher mean incremental cost (£19,276) compared with the Wyeth model (£7493). The difference

between models in total costs and incremental costs can be largely explained by the different assumptions made over the cost associated with the administration of IFN. The cost for the administration of IFN is high in the Wyeth model compared with the assumptions made by PenTAG. As discussed in the section on the temsirolimus manufacturer analysis/model we disagree with the assumptions made in the manufacturer submission over the cost for administration of IFN (we do not agree with the assumption that it will be administered in a hospital setting three times per week). When we use the Wyeth model, but apply the PenTAG assumptions on cost for administration of IFN, the cost per QALY increases from £55,814 to £102,000.

When we have used the OS and PFS curves in the Wyeth submission (modelled using the transition probabilities in the manufacturer model) to predict disease progression in the PenTAG model, the cost per QALY estimates increase substantially, because of lower expected benefits. Although there are clear differences in the predicted disease progression and the incremental benefits, with the Wyeth model predicting a profile of disease progression that is worse (e.g. higher mortality) than that seen in the PenTAG model, the differences in assumptions on resource use/cost indicate the potential convergence of the cost per QALY estimates from each of the models.

Sorafenib compared with best supportive care (second-line treatment): cost-effectiveness analysis findings

In the PenTAG analysis a cost per QALY is estimated for sorafenib compared with BSC in second-line treatment for the patient group unsuitable for cytokine treatment. (Commercial-in-confidence information has been removed.) Here, we discuss only patients unsuitable for cytokines and second-line patients combined. The PenTAG base-case estimate is £102,498 per QALY, which is higher than that of Bayer, at (commercial-in-confidence information has been removed).

The PenTAG and Bayer models use the same data to predict disease progression (RCT reported by Escudier and colleagues[109]). However, Bayer and PenTAG have used different approaches to model disease progression. Bayer have modelled survival curves for sorafenib and BSC separately for OS and PFS (using time-dependent transition probabilities derived from Kaplan–Meier data). PenTAG have modelled baseline disease progression (BSC) using Kaplan–Meier data from the RCT and then modelled treatment effectiveness with sorafenib by applying the reported measures of clinical effectiveness (HRs) in the RCT. This difference in approach leads to slight differences in the modelled disease progression, as shown in *Figure*

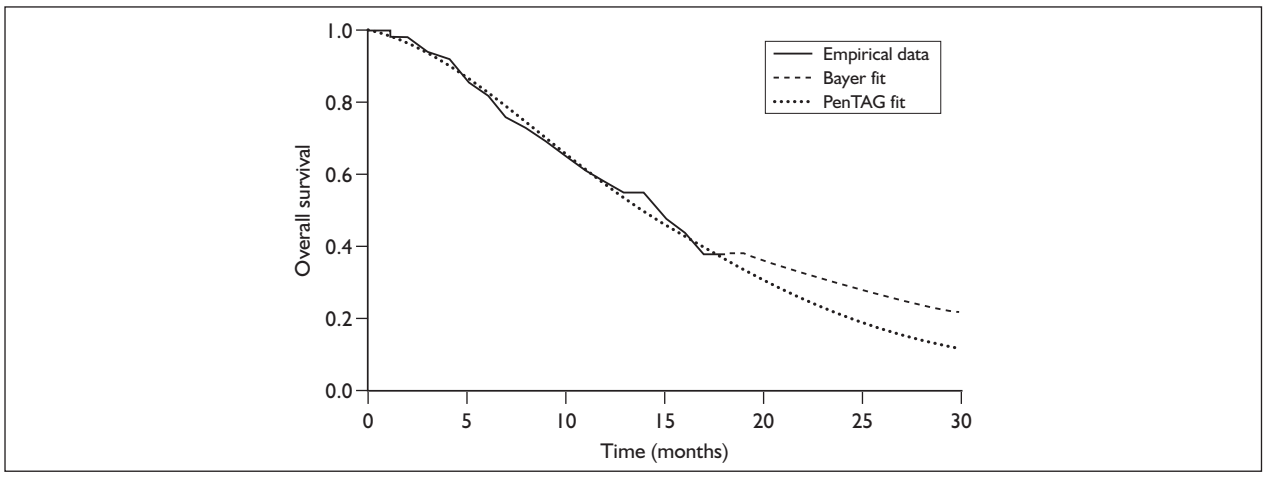

FIGURE 26 *Bayer and PenTAG fit to os for BSC. Source: Escudier* et al.*[109]*

TABLE 53 *Base-case cost-effectiveness analysis for sorafenib versus best supportive (second-line treatment, unsuitable for cytokines): comparison between PenTAG and manufacturer (Bayer) cost-effectiveness analyses.*

	BSC		Sorafenib		Sorafenib vs BSC	
	PenTAG	**Bayer**	**PenTAG**	**Bayer**	**PenTAG**	**Bayer**
LYG	1.30	(CiC)	1.60	(CiC)	0.30	(CiC)
QALYs	0.91	(CiC)	1.15	(CiC)	0.23	(CiC)
Drug cost	£0	(CiC)	£23,058	(CiC)	£23,058	(CiC)
Drug administration	£0	(CiC)	£0	(CiC)	£0	(CiC)
Medical management	£248	(CiC)	£1380	(CiC)	£1132	(CiC)
BSC in PD	£3549	(CiC)	£3360	(CiC)	–£189	(CiC)
Total costs	£3797	£13,230	£27,797	£37,079	£24,001	£23,849
Cost/LYG					£78,960	(CiC)
ICER					£102,498	(CiC)

Some CiC data were calculated by PenTAG using Bayer's model.
CiC, commercial-in-confidence information has been removed; LYG, life-years gained.

26, with the PenTAG model predicting a greater level of mortality over time (a shorter tail to the PenTAG OS curve). The PenTAG model predicts lower survival and lower incremental LYG (*Table 53*). The PFS profile is similar in the PenTAG and Bayer analyses. The incremental QALYs predicted by PenTAG are similar to those in the Bayer results, regardless of differences in mean LYG as a result of using different data on heath-state utilities. In the PenTAG model, although fewer people survive, there is a greater utility gain in those that do survive, because of the value of 0.683 in the PD health state compared with the Bayer input of 0.548 for PD. The PenTAG model uses a value of 0.758 for PFS, compared with 0.737 in the Bayer analysis. We note that when we use the Bayer model, but adjust the health-state values to reflect PenTAG assumptions, the cost per QALY falls from (commercial-in-confidence information has been removed), which widens the gap in the ICER between the PenTAG and Bayer results (with the disease progression noted above accounting for this).

The PenTAG and Bayer models both predict similar incremental total costs, although there are differences across the separate cost components (*Table 53*). The Bayer analysis reports higher costs for medical management than the PenTAG analysis. The Bayer analysis assumes higher monthly costs for medical management in the PFS health state when patients are in the BSC treatment arm; the Bayer analysis uses a cost of £673 per month, compared with the PenTAG estimate of £58 per month. For sorafenib, the Bayer analysis assumes a cost in PFS of £776 per month, compared with the PenTAG estimate of £158 per month. Bayer also applies higher costs for the PD health state than PenTAG: £672 per month compared with £314 per month. These assumptions on resource use for monitoring and medical management are uncertain because of an absence of data. PenTAG have used advice from clinical experts; Bayer have also used surveys of clinicians (internet-based surveys of six and 31 UK clinicians).

Chapter 4
Discussion and conclusions

This assessment has been necessarily constrained by the marketing authorisations of the interventions under review, which in turn dictated the scope of the assessment and the protocol and underlies our choice and derivation of appropriate research/policy questions on which to focus. We have wrestled with several important issues during this process, namely the definition of BSC, the definition of 'unsuitable' for treatment with IFN and the choice of comparators. We first discuss these issues and then for each of the four policy questions the discussion is structured as follows:

- We present a summary of the findings from the systematic review of clinical effectiveness followed by an overview of the results from the PenTAG economic evaluation.
- Key factors influencing the results are then explored and discussed to aid interpretation.
- The chief uncertainties in the economic evaluation are explored and discussed and we summarise the comparison of the PenTAG economic evaluations with those presented by the manufacturers.
- Strengths and limitations of the assessment and their potential impact on the results are then considered.
- Finally, we provide a summary of our conclusions and what we consider the most important current priorities for further research.

Definition of best supportive care

We were unable to find any consistent definitions of 'best supportive care' in this clinical context. We were also unable to locate any trials of BSC and understand the term to indicate that patients are receiving palliative care and monitoring. Several authors consider agents such as medroxyprogesterone and vinblastine to be 'placebo equivalent' in trials of IFN versus control. However, these agents are also considered as active treatments in some people. We have therefore estimated resource use and costs following consultation with our clinical expert advisory group, but recognise that this could be an area of wide variation both in clinical practice and patient need.

Definition of suitable for treatment with immunotherapy

We interpreted 'suitable for treatment with IFN' as meaning that a patient so defined would not possess any clinical contraindications to treatment, for example a history of depression or autoimmune disease. We did not consider people with intermediate or poor prognosis to be necessarily unsuitable for treatment with IFN.

However, it has become apparent since the publication of the PERCY Quattro trial of immunotherapy in patients with intermediate prognosis,[38] which has been interpreted as showing no benefit of IFN in this patient group, that there is some variation around the UK in the management of people deemed to have intermediate or poor prognosis. In some centres these people are offered treatment with IFN, whereas in others they are considered to be 'unsuitable' for treatment with IFN and BSC therefore becomes their only treatment option.

Extrapolation of the results of the PERCY Quattro study[38] to this assessment is complex as the definition of intermediate prognosis differs from that used in the included trials.[106,107,109–112] However, using the MSKCC definition approximately 30% of patients in the included trials of first-line therapy were considered to have favourable prognosis; approximately 50% of those in the second-line trials[109–112] had favourable prognosis. The remainder of all included patients in this assessment had either intermediate or poor prognosis and could be considered, using alternative definitions, to be unsuitable for treatment with IFN.

Choice of comparators

We believed that it was important as far as possible to use current standard treatment as the comparator for all research questions, considering IFN to be the comparator for first-line therapy in patients suitable for treatment with immunotherapy and BSC the comparator in all other situations. Our assessment does not take into account patient preference for treatment.

However, we recognise that a large proportion of people diagnosed with RCC in the UK will be deemed unsuitable for treatment with IFN as a result of clinical markers of prognosis and we therefore attempted to explore this issue further. We considered the validity of performing an indirect comparison between IFN and BSC to provide some estimate of the relative effectiveness and cost-effectiveness of the new interventions against BSC. However, there are very few trials of IFN versus BSC and those that have been performed do not provide results according to prognostic status.

Informal extrapolation of available data suggests that, if it is assumed that there is no difference in the relative effectiveness of BSC and IFN in this population, and that the cost of BSC would be less than the cost of treatment with IFN, it is possible that the new interventions would be less likely to be considered cost-effective at commonly used willingness-to-pay thresholds compared with BSC. That is, if IFN is considered as an expensive equivalent of BSC then the incremental costs of new drugs would all be greater when compared with BSC than when compared with IFN for no additional benefit.

Summary of main findings

Bevacizumab plus IFN and sunitinib compared with IFN as first-line therapy

In this section we summarise the findings relevant to research question 1: In those who are suitable for treatment with immunotherapy, what is the clinical and cost effectiveness of bevacizumab plus IFN and sunitinib as first-line therapy, using IFN as a comparator?

Clinical effectiveness

There is evidence from three good-quality randomised clinical trials that sunitinib and bevacizumab plus IFN have clinically relevant and statistically significant advantages over treatment with IFN alone in terms of PFS and tumour response (see *Tables 12* and *13*). Compared with IFN treatment, both interventions are associated with a two-fold increase in PFS (from around 5 months to 11 months).[106,107] Unfortunately, there are few empirical data available to inform the effect of these interventions on OS. Moreover, further analysis of these trials is unlikely to add significantly to this particular evidence base as treatment crossover has occurred following interim analyses.

We were unable to locate any head-to-head comparison data for bevacizumab plus IFN versus sunitinib. Results of an indirect comparison suggest that sunitinib may be more effective than bevacizumab plus IFN in terms of PFS (HR 0.67; 95% CI 0.50 to 0.89).

Data on adverse events suggest that sunitinib is not associated with a greater frequency of adverse events than IFN, although the adverse event profiles are different (see *Table 17*). There were more grade 3 and grade 4 adverse events reported with bevacizumab plus IFN than with IFN in the AVOREN trial (mean number per patient 1.3 versus 0.9 for the combination versus IFN monotherapy respectively). It is not clear whether this difference was statistically significant.

There have been no published full-text papers in which EQ-5D data (HRQoL data) collected during treatment with sunitinib, bevacizumab plus IFN or IFN alone are presented. The health-state utilities used in the PenTAG model of cost-effectiveness are further described in Chapter 3 (see PenTAG cost-effectiveness analysis) and are discussed later in this chapter (see Uncertainties, Utilities).

All three trials were conducted primarily in people with clear cell carcinoma with MSKCC risk factors suggestive of a favourable or intermediate prognosis, who had undergone previous nephrectomy. Whether the results can be extrapolated to other patient groups is unclear.

PenTAG economic evaluation (Table 44)

Compared with the current standard therapy of IFN, the PenTAG economic analysis predicts an incremental benefit to patients receiving bevacizumab plus IFN of approximately one-third of a life-year at an incremental cost of £45,435. When quality of life is taken into account the base-case cost per QALY for bevacizumab plus IFN compared with IFN monotherapy is £171,301.

People receiving sunitinib accrue a slightly greater incremental benefit (approximately half a life-year, giving 0.44 QALYs) at a lower incremental cost (£31,185) producing a base-case cost per QALY estimate for sunitinib versus IFN of £71,462.

Probabilistic sensitivity analysis estimates that when the NHS is willing to pay £30,000 per QALY the probability that either intervention is cost effective compared with IFN is zero. Bevacizumab plus IFN is not likely to be considered cost-effective compared with sunitinib or IFN at any reasonable willingness-to-pay threshold. Sunitinib is likely to be considered cost effective compared with bevacizumab plus IFN and IFN alone only above a willingness-to-pay threshold of approximately £75,000 per QALY.

In sensitivity analyses, when applying pricing strategies stated by manufacturers, the cost per QALY estimates are £90,584 for bevacizumab plus IFN versus IFN and £65,362 for sunitinib versus IFN.

Sorafenib and sunitinib compared with best supportive care as first-line therapy

In this section we address the findings relevant to research question 2: In those who are not suitable for treatment with immunotherapy, what is the clinical effectiveness and cost-effectiveness of sorafenib tosylate and sunitinib, using BSC as a comparator?

This assessment is required to consider the interventions in relation to their marketing authorisations. Suitability for treatment with immunotherapy in this context is therefore defined in terms of contraindication to treatment, with patients defined as being 'unsuitable for treatment with immunotherapy' having clinical contraindications to therapy, for example autoimmune disease or a history of depression. We have not considered that patients defined as having a poor prognosis are unsuitable for treatment with immunotherapy.

Unfortunately, we were unable to identify any studies of these interventions in people with a diagnosis of advanced and/or metastatic RCC deemed unsuitable for treatment with IFN that met the inclusion criteria of the review. We have therefore been unable to comment on the clinical effectiveness of these interventions or to populate the PenTAG economic model to estimate the cost-effectiveness of these interventions in this patient group.

The manufacturer of sorafenib (Bayer) presents a commercial-in-confidence analysis of the cost-effectiveness of sorafenib versus BSC in this patient population. A review and summary of this analysis can be found in Chapter 3 (see Cost-effectiveness: review of manufacturer submissions to NICE).

Bevacizumab plus IFN or sorafenib or sunitinib or temsirolimus or best supportive care versus IFN

In this section we summarise the findings relevant to research question 3: In those with three or more of six poor prognostic factors, what is the clinical effectiveness and cost-effectiveness of bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and BSC as first-line therapy, using IFN as a comparator?

Clinical effectiveness

Data from one large, good-quality randomised clinical trial[108] indicates that treatment with temsirolimus has clinically relevant and statistically significant advantages over treatment with IFN (18 MIU three times weekly) in people with poor prognosis in terms of progression-free and OS (see Chapter 2, Results of clinical effectiveness). This is the only comparison for which we have a robust estimate of OS. Compared with treatment with IFN, temsirolimus produces an increase in median OS from 7.3 to 10.9 months and a reduction in the risk of death of 22% (HR 0.73; 95% CI 0.58 to 0.92).

There is also some evidence to suggest that PFS may be prolonged by treatment with the combination of bevacizumab and IFN compared with IFN alone in this population, although the difference between treatments is minimal (median PFS was 2.2 and 2.1 months during treatment with bevacizumab plus IFN and IFN alone respectively) and may not be considered clinically significant. In addition, the 95% CI around the HR crosses unity and may not be considered statistically significant.

We were unable to find any data on the use of sorafenib tosylate in this population, nor any head-to-head randomised trials of the new interventions, nor any comparisons with BSC. Unfortunately, because of differences in study and baseline population characteristics, we were unable to perform any indirect comparisons between treatments.

Data on adverse events suggest that temsirolimus is associated with a significantly lower frequency of serious (grades 3 and 4) adverse events than IFN.[108] According to a recently published systematic review, between 1% and 20% of patients receiving temsirolimus reported grade 3 or grade 4 adverse events. The most commonly reported grade 3 and grade 4 adverse events were anaemia (20%), fatigue/asthenia (11%), hyperglycaemia (11%) and dyspnoea (9%); this includes both disease- and drug-related adverse events.[119]

There have been no published full-text papers in which EQ-5D data (HRQoL data) collected during treatment with temsirolimus or IFN are presented. However, the company submission suggests that EQ-5D data were collected during the trial of temsirolimus versus IFN.[108] The health-state utilities used in the PenTAG model of cost-effectiveness are further described in Chapter 3 (see PenTAG cost-effectiveness analysis) and are discussed later in this chapter (see Uncertainties, Utilities).

Results from this trial have also been presented according to tumour histology subtype and nephrectomy status.[108] There is a large amount of variation surrounding the estimates of effectiveness but nevertheless, the data suggest that temsirolimus may be more effective than IFN in all four subgroups (see Chapter 2, Results of clinical effectiveness).

PenTAG economic evaluation

As a consequence of the paucity of suitable data available in people with poor prognosis, the only comparison for which we have been able to provide an estimate of cost-effectiveness is temsirolimus versus IFN.

The PenTAG economic analysis predicts that people are in a period of PFS during which they receive treatment with temsirolimus for a mean of 7.6 months. In comparison, people receiving IFN do so for 4.6 months. The incremental benefit for temsirolimus is approximately half a life-year (giving 0.24 QALYs) at an incremental cost of £19,276. The incremental cost per QALY estimate for the comparison of temsirolimus versus IFN is £81,687.

The cost–utility analyses performed in patient subgroups estimate ICERs between £64,680 per QALY and £132,778 per QALY (*Table 48*). However, the effectiveness data on which these estimates are based is very uncertain with 95% CIs either approaching or crossing unity in most cases. These results should therefore be viewed with some caution. The validity of the subgroup analyses is discussed further later in this chapter.

The probabilistic sensitivity analyses suggest that, when the NHS is willing-to-pay £30,000 for an additional QALY, the probability that temsirolimus is cost-effective compared with IFN is zero. Temsirolimus is likely to be considered cost-effective compared with IFN only above a willingness-to-pay threshold of approximately £82,000 per QALY.

Second-line therapy: sorafenib or sunitinib versus best supportive care

In this section we summarise the findings relevant to research question 4: In those in whom cytokine-based immunotherapy has failed, what is the clinical effectiveness and cost-effectiveness of sorafenib tosylate and sunitinib, using BSC as a comparator?

Clinical effectiveness

Data from a large, good-quality RCT[109] and an RDT[149] in which sorafenib was compared with placebo suggest that sorafenib tosylate has clinically relevant and statistically significant advantages over BSC in terms of OS, PFS and tumour response. Data on median PFS are the most robust, and in the RCT[109] PFS was 5.5 months in the sorafenib group and 2.8 months in the placebo group (see Chapter 2, Results of clinical effectiveness).

We were unable to identify any comparative data for sunitinib in people in whom treatment with cytokine-based immunotherapy has failed. Two single-arm phase II trials suggest that sunitinib is efficacious in this patient group, but extrapolation from uncontrolled trials is difficult.[85,111,112] No indirect comparison between treatments was possible as there was no common treatment arm.

Treatment with sorafenib is associated with a significantly increased frequency of hypertension and hand–foot syndrome: 16% and 25% of people experienced these adverse events at grade 3 or grade 4, respectively, during treatment with sorafenib in the main trial.[109]

Safety data suggest that the frequency of adverse events during second-line therapy with sunitinib is no different from that reported during first-line therapy.

All of these trials were conducted in patients with metastatic clear cell RCC, the majority of whom had undergone previous nephrectomy and were classified as having favourable or intermediate prognosis according to the MSKCC risk score. Whether sorafenib or sunitinib have advantages over placebo in other patient groups is unclear.

PenTAG economic evaluation

As we were unable to locate any comparative trials of sunitinib as second-line therapy we were only able to examine the cost-effectiveness of sorafenib versus placebo (BSC) in this patient population.

The PenTAG model predicts an incremental benefit for sorafenib compared with placebo of approximately 0.3 life-years (giving 0.23 QALYs) at an incremental cost of approximately £24,001. The cost per QALY estimate for sorafenib versus placebo (BSC) is £102,498.

The probabilistic sensitivity analysis suggests that were the NHS willing to pay £30,000 for an additional QALY the probability that sorafenib would be considered cost-effective compared with BSC is zero. Compared with BSC sorafenib is only likely to be considered cost effective above a willingness-to-pay threshold of approximately £100,000 per QALY.

Uncertainties

In this section we discuss the key issues influencing the evaluation of clinical effectiveness and cost-effectiveness. We first consider issues that impact primarily on the assessment of clinical effectiveness, although their influence on the economic evaluation is also considered when appropriate. These include the paucity of available OS data and the potential effect of the ensuing extrapolation of trial data; the validity of the subgroup analyses described in the report; and the generalisability of our findings to a wider patient population.

Extrapolation of trial data

In the assessment of both clinical effectiveness and cost-effectiveness we have only considered data collected during the randomised period of treatment prior to any interim analyses and crossover of patients from control to active treatments. This means that the evidence for an effect on OS used in the economic evaluation is immature and consequently uncertain (see section on effectiveness data later in this chapter). However, because of the loss of randomisation, the risk of confounding and the use of other active agents following disease progression, data collected prior to treatment crossover are the best data available. There is evidence of confounding in at least one of the included trials; final analysis of OS in the TARGET trial[109] [after 48% ($n = 216$) of patients in the placebo group had crossed over to sorafenib treatment] produced a HR of 0.88, which was not statistically significant. Further analysis in which data from the crossed over patients were censored produced a HR of 0.78 ($p = 0.0287$).[98] Clearly the true effect of sorafenib in this trial lies somewhere between these two estimates. There is ongoing debate as to the validity of PFS as an end point with which to compare the effectiveness of interventions in oncology trials. On the one hand it is perhaps unrealistic to expect to collect mature OS data given the multiple options for active treatment now available after a failed first-line therapy. However, extension of PFS (during which a patient may receive an active agent and experience the associated adverse events) may have little clinical relevance if OS is not also suitably prolonged.

Use of data from pre-crossover only in the economic evaluation necessitates considerable extrapolation of trial data in order to populate the model for a time horizon of 10 years. For the same trial[109] the survival curves used in the model are based on empirical data for the first 15 months or so, henceforth the curves rely on extrapolation.

Validity of subgroup analyses

The scope of this assessment required that we considered two sets of subgroups when data were available; according to tumour histology subtype (clear cell and non-clear cell RCC) and nephrectomy status. Two of the included trials provided data on these subgroups and when appropriate we have described and analysed these data. However, although the subgroup analyses were preplanned and they provide some indication as to the effectiveness and cost-effectiveness of the interventions in different patient populations, we have reservations about the validity of these analyses. Primarily, the trials were not sufficiently powered to detect differences in effect in subgroups. For example, in the trial of sunitinib versus IFN[107] only 10% of patients ($n = 77$) in the trial had not undergone previous nephrectomy, and in the trial of temsirolimus versus IFN[108] 17% had non-clear cell RCC. Consequently, there is a

large amount of imprecision in the HRs; in most of the subgroup analyses the 95% CIs approach or cross unity indicating that the results would not be considered statistically significant.

In addition, whereas the division of patients according to tumour histology subtype does have a clinical basis, although a clear division can be made between patients in terms of nephrectomy status, the clinical relevance of this division is unclear. It is possible that division of the population according to nephrectomy status is confounded by other factors of disease status that underlie the reasons behind some people not undergoing surgery, such as the position of the primary tumour and the performance status of the patient.

Generalisability of results

All of the trials included in the review of clinical effectiveness were conducted in patients with predominantly clear cell, metastatic RCC, the majority of whom had undergone previous nephrectomy and many of whom were of favourable and intermediate prognosis and good performance status. None of the studies recruited patients with brain metastases (unless neurologically stable) and few patients with bone metastases were included (20% in the trial of bevacizumab plus IFN versus IFN[106] and 30% in the trial of sunitinib versus IFN[107]).

Whether the results of this assessment can be applied to other patient groups is unclear. Expanded access trials can provide some indication of the effectiveness of interventions in a wider patient population. Published results for sunitinib from an expanded access trial[118] in approximately 2000 patients suggest that overall effectiveness may be reduced in a less highly selected population (estimates of median PFS of 8.9 months from the expanded access trial compared with 11 months from the randomised clinical trial[107]), but also provide evidence that sunitinib may be effective in previously unstudied populations such as those with brain metastases, people over the age of 65 years and those with an ECOG-PS of 2 or more.

We now turn to the key issues that impact on the results of the economic evaluation, identified primarily in the deterministic sensitivity analysis. These include the estimates of treatment effectiveness, in particular OS, drug pricing (including variations in dose intensity and assumptions about wastage) and health values.

Effectiveness data

In the PenTAG economic evaluation, the effectiveness data used to model disease progression and cost-effectiveness includes data on progression-free and OS. Baseline disease progression, for IFN or BSC, has been modelled using Weibull survival analysis applied to empirical Kaplan–Meier data, with treatment effectiveness modelled using relative measures of treatment effectiveness, that is, HRs for progression-free and OS reported in the clinical trials.

Not surprisingly, in all comparisons the estimates of cost-effectiveness are most sensitive to variations in the HRs for OS. Because of the nature of the trials from which these data are derived, these data are also the most uncertain. For example, in the trial of sunitinib versus IFN,[107] the HR for OS is 0.65 with 95% CIs that range from 0.45 to 0.95. This level of precision equates to possible variations in the effect of the drug from having very little effect to more than halving the risk of death. As might be expected the consequential effects on the ICER of sunitinib versus IFN are also large. Compared with a base-case ICER of £71,462 per QALY, varying the HR for OS between the upper and lower limits of the 95% CIs produces results ranging from £39,759 per QALY (lower limit) to £263,363 per QALY (upper limit). For bevacizumab plus IFN (compared with IFN), temsirolimus (compared with IFN) and sorafenib (compared with BSC) there is a similar level of uncertainty around the estimate of the HR for OS, and similar marked swings in the cost per QALY estimates.

The sensitivity analyses for the HRs for PFS have highlighted issues linked to the balancing of incremental costs and effects. In the PenTAG analysis, an increase in the size of the treatment effect (a lower HR for PFS) results in a worsening cost-effectiveness profile. In other words, improvements in PFS make the drugs less attractive in terms of value for money. This counterintuitive effect is seen across all of the analyses undertaken by PenTAG, is apparent for both cost per QALY and cost per life-year analyses and can be explained partly by the relatively high incremental treatment costs (costs of the drug, drug administration and monitoring) associated with time spent in the progression-free disease health state. In our modelling, these costs are shown to outweigh (dominate) the incremental benefits (LYG, QALY gains) associated with spending a longer period of time in the progression-free disease health state. When people move from

progression-free disease to the PD health state they continue to benefit from treatment through the application of OS data. As the interventions have a significant treatment effect there is a difference in the predicted OS between groups. However, equal costs are incurred irrespective of treatment strategy (e.g. the cost incurred in the PD state for people in the sunitinib cohort is equal to the cost incurred in the PD state for people in the IFN cohort). Therefore, the balance of costs and effects associated with time in the progression-free disease health state favours the baseline scenario (either IFN or BSC). Consequentially, an improvement in PFS resulting in more time spent receiving treatment with a drug incurring a high incremental treatment cost leads to a higher estimate of cost-effectiveness.

None of the manufacturer submissions to NICE has explicitly presented sensitivity analyses using alternative assumptions for HRs for PFS. We have performed these sensitivity analyses using the manufacturer models for sunitinib (Pfizer) and sorafenib (Bayer) and observed the same counterintuitive effect.

Sensitivity analysis against the HRs for OS shows a more intuitive scenario. As expected, when the HR for OS is reduced (i.e. there is a greater treatment benefit), the cost per QALY decreases and the intervention would be more likely to be considered cost effective.

It is interesting to note that, although the effectiveness of treatments against outcomes for PFS has been used to emphasise the potential clinical benefits from treatment, it is the much less certain data on effectiveness against OS that are driving the estimates of incremental cost-effectiveness.

Drug pricing

There are several elements to the assumptions made about drug pricing within the PenTAG economic evaluation; the use of pricing strategies, assumptions about wastage and dose intensity and the costs associated with administration of drugs. Because of the relatively high costs of the new interventions, variations in the prices of the drugs for whatever reason have a relatively large impact on the estimates of cost-effectiveness.

Pricing strategies

Two of the manufacturers of interventions in this assessment [Pfizer (sunitinib) and Roche (bevacizumab plus IFN)] indicate that pricing strategies will be available for these agents in the UK. As expected, reductions in the total costs of the drugs have large implications for the resulting cost-effectiveness estimates, particularly in the comparison of bevacizumab plus IFN versus IFN in which the ICER is reduced from £171,301 per QALY to £90,584 (PenTAG analysis) with the incorporation of the manufacturers pricing strategy. Multiway sensitivity analyses in which the pricing strategy for bevacizumab is applied together with variation in the HRs for overall and PFS are shown in *Table 46*. Given the best estimates for the effectiveness of treatment (lower limits of 95% CIs for overall and PFS) and the presence of the dose-capping scheme the ICERs for the comparison of bevacizumab plus IFN versus IFN alone become £49,190 per QALY and £91,973 per QALY respectively.

The manufacturers pricing strategy for sunitinib has similar although less marked effects (*Table 45*).

Dose intensity

We have assumed in the model that people would be exposed to the same dose intensity of treatment as reported in the clinical trials from which the effectiveness data arise. As might be expected, increasing or decreasing the dose intensity of the intervention produces the expected increase or decrease in the ICER. We did not identify any data with which to clarify any possible relationship between dose intensity and the effectiveness of treatment, for example higher dose intensity leading to a better response to treatment, and it is unclear whether it would be realistic to expect higher dose intensities than those reported during trials because of the close monitoring provided within the context of a randomised clinical trial. Presumably, higher compliance with treatment would be associated with a greater incidence of adverse events as the primary reason for dose interruption or discontinuation in the trials was the incidence of unacceptable toxicity. However, as seen in the multiway sensitivity analyses in which increases in drug costs were varied together with an increase in the effectiveness of treatment (a decrease in the HR), if this could be achieved we might expect the estimates of incremental cost-effectiveness to decrease.

Wastage assumptions

Temsirolimus is produced in 30-mg vials, 25 mg of which is needed per patient per treatment; there is therefore the potential for vial sharing between patients. Following consultation with our clinical

experts, who advised that vial sharing was unlikely to occur on a regular basis because of the number of patients necessary, and because of the short shelf life of the product, the route of administration (intravenous infusion) and the need for previous treatment with antihistamine, we assumed that no vial sharing occurred in the base-case analysis.

Drug administration costs

In the comparison of temsirolimus versus IFN, variation in the cost of administration of both agents and the consequent incremental difference in costs has a large effect on the cost-effectiveness estimate. In the base case the difference in the administration costs for temsirolimus and IFN is £5848 (see *Table 47*) and forms a substantial component of the total cost difference. We have based our assumptions on the cost of administration of IFN on the opinions of our expert advisory group who reported that IFN is predominantly administered at home. If we assume that IFN is administered in the hospital setting (as in the evaluation performed by the manufacturer of temsirolimus) and is thus associated with higher administration costs, the incremental cost between treatments becomes smaller and the resulting cost-effectiveness estimates are also reduced.

Utilities

As described in Chapter 3 (see PenTAG cost-effectiveness analysis) we identified two sources of possible health-state utilities and were unsure as to the relationship, if any, between these data sets. We were not convinced that the difference in utility values obtained in the two trials[107,108] could be explained by differences in performance status and were concerned that we might be introducing a lack of continuity into the modelling of the policy questions by choosing to use health-state values from different sources in different questions. However, in the absence of other data, there was no persuasive alternative and we acknowledge the limitations in the data used.

The sensitivity of cost per QALY estimates to changes in health-state utilities is connected to the impact of effectiveness measures (HRs for progression-free and OS) on cost-effectiveness. As discussed earlier in this chapter, OS is a major driver in the cost-effectiveness analysis and has a greater impact than PFS (see Effectiveness data). In the same way, sensitivity analyses on health-state values demonstrate that variations in the health-state value for the PD health state have a bigger impact on cost per QALY estimates than variations in the utility interval between the PD and progression-free health states, because of the balancing of incremental costs and benefits. That is, when the difference in the utility interval between 'living' health-state values is varied in sensitivity analysis, this has a lesser impact on the cost-effectiveness estimate than changing the absolute value used for the PD state (i.e. the difference between alive in PD and dead).

Comparison of the PenTAG cost-effectiveness analysis with those produced by manufacturers

In this assessment we have reviewed the four economic evaluations submitted by the manufacturers of the interventions. We have not carried out an exhaustive audit of each of the models but have concentrated on reviewing the assumptions underlying the model structures and the data used to populate them, and provide a summary in Chapter 3 (see Cost-effectiveness: review of manufacturer submissions to NICE).

The cost-effectiveness estimates produced in the PenTAG economic evaluation are higher than the manufacturer base-case estimates in all cases (although in two of the four analyses the results are similar). Although there are some common aspects of methodology in both model structure and data inputs across the manufacturer and PenTAG analyses, there are also clear differences in the resulting cost-effectiveness estimates. These are reviewed and summarised in Chapter 3 (see Comparison of the PenTAG and manufacturer cost-effectiveness analyses). Where a potential area for divergence between models has been identified, exploration of both the PenTAG and manufacturer models, with incorporation of the alternative data, has indicated that it is possible to see similar results across models when the differences are taken into account.

Although the manufacturers have been able to present economic evaluations of their products in isolation, we have used a similar modelling framework across all research questions. However, there are several analyses included in the company submissions that we have not undertaken because of an absence of reliable effectiveness data, for example comparison of sunitinib versus BSC in second-line treatment and comparison of sorafenib versus BSC as first-line therapy in people unsuitable for treatment with IFN.

Strengths of the assessment

This is the first analysis of the effectiveness and cost-effectiveness of bevacizumab plus IFN, sorafenib tosylate, sunitinib and temsirolimus to inform policy in the UK NHS setting. We were unable to find any other fully published economic evaluations of these interventions.

Comprehensive, explicit and systematic literature searches, including hand searching of conference proceedings, were performed both to locate evidence for the review of clinical effectiveness and to inform the economic modelling study.

Overall survival data for these interventions are scarce and unlikely to become available with IFN as a comparator, as the agents are now readily available in Europe and the USA and used as first-line therapy for metastatic RCC. Careful consideration of the empirical survival data was therefore necessary, with attempts to fit the most appropriate survival curves to best extrapolate the available immature data.

Extensive analyses of the uncertainty of the model were performed with one-way, multiway and probabilistic sensitivity analyses.

Limitations of the assessment

Model-based cost-effectiveness analyses are an inevitable consequence of the need to integrate a range of information about a wide variety of factors to support policy-making decisions on new technologies. These relate to the natural history of disease, the efficacy and effectiveness of interventions, the treatment pathway and the resultant life expectancy and quality of life in different disease states and with different treatments.

We have already alluded to several limitations of this work including the constraint of the assessment by the marketing authorisations of the products leading to difficulties with the derivation of research questions and the subsequent applicability of these questions to the RCC population, and the uncertainty of the OS and health-state utility data. In this section we discuss some further issues that we believe may be limitations of the assessment. These include the availability of clinical effectiveness data for all potential comparisons, issues surrounding patient preference, consideration of the sequencing of treatments, some of the structural modelling assumptions used in the PenTAG model and the scarcity of available information on resource use and costs.

We were not able to identify data to inform on all of the potential interventions relevant to each policy question and despite attempts to perform indirect comparison when head-to-head data were not available from randomised clinical trials this was only possible for the comparison of bevacizumab plus IFN versus sunitinib as first-line therapy in patients suitable for treatment with IFN. As a result of this lack of primary clinical effectiveness data we have been unable to fully inform the policy questions.

As is common in health technology assessment we use summary data, not individual patient data, to model treatment effectiveness. We have estimated progression-free and OS for baseline treatment by fitting Weibull curves to Kaplan–Meier data. It is preferable to fit Weibull curves from individual patient data using the method of maximum likelihood[150] and this may have led to more precise estimates of cost-effectiveness. Individual patient data were used in one of the four company submissions (Wyeth[124]). As a result of the structural assumptions we have made in the PenTAG economic evaluation, modelling is driven by data on OS and PFS. This was a necessary consequence of the available clinical data but it does mean that time spent in PD has been indirectly calculated (the difference between OS and time spent in PFS). We have also been unable to identify any published data on time spent in PD during treatment with the interventions with which to calibrate the outputs from the model.

There is a scarcity of published data available to inform resource use and costs associated with treatment of RCC especially in terms of the provision of BSC and the monitoring and medical management of people with RCC, both during treatment (progression-free disease) and during PD. As is the case with most modelling studies, we have therefore adopted some simplifying assumptions. We acknowledge that this could be considered a limitation of the evaluation. However, we feel that the use of simplifying assumptions (which are adopted in a similar way across all interventions) has enabled us to examine the relationships between effectiveness, costs and utilities without additional uncertainty and complexity.

As more interventions become available for the treatment of metastatic RCC, the sequencing of treatment will become more important. We

chose to model first- and second-line treatment separately rather than produce an overall model of RCC as we felt that this was the most appropriate way to address the research questions in the context of the protocol without introducing additional unnecessary uncertainty. Currently, the only licensed treatment options for second-line therapy are sorafenib and BSC, although this is an area of much primary research activity (see Appendix 12). In our evaluation, people in PD receive BSC only. As clinical effectiveness data become available for the use of these interventions as second-line treatments, and subsequent treatment options emerge, the treatment pathway will inevitably become more complex, necessitating further evaluation.

As required by NICE, the assessment takes no account of individual patient preference for treatment. This may be particularly important when comparing an oral therapy taken at home with one that is administered as an intravenous infusion in hospital. It is possible that this type of information would be captured within utility values, but we do not believe that this is the case with the values that we have used. We might anticipate that patient preference would be for an oral tablet taken at home, but we found no published sources of data to inform on this or on patient preference for receiving IFN at home rather than in the hospital setting. Similarly, we have not considered the disutility of adverse events associated with treatment and have used disease-specific rather than treatment-specific utility values in the evaluation. We felt that this was most appropriate given the sparsity of available information on health-state values in RCC. Although the frequency of adverse events experienced during treatment is generally lower with the new interventions than with IFN, the adverse event profiles are different. We have no data to inform on the impact that this might have on utility values. Furthermore, we have taken no account of emerging concerns over long-term safety in the case of sunitinib.

Other relevant factors

All of the interventions in this assessment have been granted orphan drug status. However, when NICE have consulted on the methods for the assessment and appraisal of orphan drugs they have suggested no difference in the process or methodological guidance for the assessment of clinical effectiveness and cost-effectiveness.

Some additional data were made available to NICE by the manufacturer of sunitinib (Pfizer) after submission of the assessment report, but before the Appraisal Committee meeting. This included updated survival data for a maximum of 36 months of follow-up for the sunitinib versus IFN RCT originally reported by Motzer and colleagues.[111] A number of estimates were provided, including a final ITT analysis of the entire trial population, a final ITT analysis censored for those who crossed over from IFN to sunitinib on disease progression and an analysis of those who did not go on to receive any post-study treatment. Unfortunately, PenTAG were unable to formally appraise these data within the time frame necessary for inclusion within the monograph.

Conclusions

We conclude that there is evidence to suggest that treatment with bevacizumab plus IFN and sunitinib has clinically relevant and statistically significant advantages over treatment with IFN alone in patients with metastatic RCC. There is also evidence to suggest that, in people with three of six risk factors for poor prognosis, temsirolimus has clinically relevant advantages over treatment with IFN and sorafenib tosylate is superior to BSC as second-line therapy. The frequency of adverse events associated with bevacizumab plus IFN, sunitinib and temsirolimus is comparable with that seen during treatment with IFN, although the adverse event profiles are different. Treatment with sorafenib is associated with a significantly increased frequency of hypertension and hand–foot syndrome.

The PenTAG cost-effectiveness analysis suggests that the probability that any of the interventions would be considered cost-effective at a willingness-to-pay threshold of £30,000 per QALY approaches zero.

Suggested research priorities

There are clear gaps in the evidence base needed to fully appraise the clinical effectiveness and cost-effectiveness of these four interventions in accordance with their marketing authorisations:

- Further randomised clinical trials in the following areas would be useful:
  - trials of sorafenib, sunitinib, bevacizumab and BSC in patients unsuitable for

treatment with IFN either as a result of contraindications or because they have been defined as having intermediate and poor prognosis and may not benefit from IFN
  - comparative trials of sunitinib and sorafenib as second-line therapy.
- In the current evidence base there is a large amount of uncertainty surrounding the estimates of OS, primarily because of early crossover of people receiving control treatment following interim analyses. It is unrealistic and perhaps unethical to expect that further randomised clinical trials would be performed using IFN or BSC as a comparator for these interventions, which are now widely used in Europe and the USA. As the interventions provide little possibility of a cure, and in the absence of unconfounded estimates of OS from RCTs, further understanding of the impact of the interventions on HRQoL during PFS and PD would facilitate the decision-making process for clinicians and patients.
- Research on current treatment pathways and current practice (e.g. in the use of IFN) would reduce the level of uncertainty in future studies modelling the cost-effectiveness of drugs for treatment of renal cancer.
- As more agents are introduced for the treatment of metastatic RCC, the issues of treatment sequencing become more evident and raise many additional research questions surrounding the combination and order of treatments to provide maximum benefit in each patient population.
- When modelling treatment of RCC there are methodological challenges when using summary data (survival analysis) from clinical trials, and research to explore the impact of using aggregated data compared with individual patient-level data would be helpful.

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Expert advisory group

Penny Champion, Clinical Nurse Specialist in Renal and Testicular Cancer, Urology Centre, Guy's Hospital, London, UK; Dr Chris Coppin, Associate Professor, University of British Columbia and Division of Medical Oncology, BC Cancer Agency, Vancouver, Canada; Stephen Palmer, Senior Research Fellow, Centre for Health Economics, University of York, UK; Dr Rajaguru Srinivasan, Consultant Clinical Oncologist, Exeter Oncology Centre, UK. Four further UK clinical oncologists provided advice during the preparation of the report but later retracted their consent to be acknowledged by name in the report.

Competing interests of expert advisory group

Dr Chris Coppin was the lead author of a Cochrane Collaboration systematic review on the same topic.

Penny Champion, Stephen Palmer and Dr Rajaguru Srinivasan have no competing interests.

Four further UK clinical oncologists provided advice during the preparation of the report but later retracted their consent to be acknowledged here. These individuals declared the following competing interests: advisory boards; speaker bureau; research funding from Bayer, Pfizer, Roche and Wyeth; sponsorship from Bayer, Pfizer and Roche to attend meetings, honoraria for advisory board meetings and sponsored lectures from Bayer, Pfizer and Roche, and an honorarium for an advisory board from Wyeth; consultancy and speaking at company-sponsored events for Roche, Bayer, Pfizer and Wyeth and honoraria for these services; involvement in clinical studies of the agents under review; research support from Bayer and Pfizer; trustee of KCUK, which is a charity dedicated to the interests of people affected by kidney cancer; Chair of the Medical Advisory Committee of Cancerbackup; anti-angiogenic treatment of renal cancer as a primary academic and clinical interest; ad hoc adviser to Roche, Pfizer, Bayer and Chiron; consultant to Oxford Biomedica (unrelated vaccine being tested in renal cancer); and research funding from Pfizer for an unrelated project.

Contribution of authors

Colin Green (Senior Lecturer in Health Economics) contributed to the design of the assessment, led the cost-effectiveness aspects including the critique of submissions provided by industry, and contributed to writing and editing of the protocol and the report. Martin Hoyle (Research Fellow in Decision Analytic Modelling) contributed to the design and implemented the economic model, performed the critique of the industry submissions and contributed to the clinical effectiveness section and to writing and editing of the report. Zulian Liu (Research Assistant in Health Technology Assessment) assessed abstracts for inclusion and exclusion, performed the data extraction of the clinical effectiveness data, managed the reference database and contributed to the cost-effectiveness analysis and to writing and editing of the report. Tiffany Moxham (Information Scientist) carried out literature searches for the systematic reviews and identification of model parameters. Ken Stein (Professor of Public Health) contributed to the design of the assessment, the design and development of the cost-effectiveness analysis and the preparation and editing of the report. Jo Thompson Coon (Research Assisstant in Health Technology Assessment) provided overall project management, wrote the protocol, performed the systematic review of clinical effectiveness, contributed to writing and editing of the report and to the cost-effectiveness analysis. Karen Welch (Information Scientist) carried out

literature searches for the systematic reviews and identification of model parameters.

About PenTAG

The Peninsula Technology Assessment Group (PenTAG) is part of the Institute of Health Service Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers. The group is multidisciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme. Projects to date include:

Screening for hepatitis C among injecting drug users and in genitourinary medicine (GUM) clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. *Health Technol Assess* 2002;**6**(31).

The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review. *Health Technol Assess* 2002;**6**(33).

Systematic review of endoscopic sinus surgery for nasal polyps. *Health Technol Assess* 2003;**7**(17).

The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling. *Health Technol Assess* 2004;**8**(3).

Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. *Health Technol Assess* 2004;**8**(28).

Do the findings of case series studies vary significantly according to methodological characteristics? *Health Technol Assess* 2005;**9**(2).

The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema – a systematic review and economic evaluation. *Health Technol Assess* 2005;**9**(29).

The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation *Health Technol Assess* 2005;**9**(43).

Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. *Health Technol Assess* 2006;**10**(8).

The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(18).

The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(45).

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting $beta_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over. *Health Technol Assess* 2008;**12**(19).

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting $beta_2$ agonists for the treatment of chronic asthma in children under the age of 12 years. *Health Technol Assess* 2008;**12**(20).

The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technol Assess* 2009;**13**(44).

References

1. Office for National Statistics. *Cancer trends in England and Wales 1950–1999*. Studies on Medical and Population Subjects No. 66. London: Stationary Office; 2001.

2. Storkel S, Eble JN, Adlakha K, Amin M, Blute ML, Bostwick DG, *et al*. Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). *Cancer* 1997;**80**:987–9.

3. Linehan WM. Molecular genetics of kidney cancer: implications for the physician. *Proc (Bayl Univ Med Cent)* 2000;**13**:368–71.

4. Greene FL (ed.). *AJCC cancer staging manual*. 6th edn. Philadelphia, PA: Lippincott Raven; 2002.

5. Office for National Statistics. *Cancer statistics registrations*: *registrations of cancer diagnosed in 2004, England*. Series MB1 No. 35. London: National Statistics; 2006.

6. Welsh Cancer Intelligence and Surveillance Unit. *WCISU annual publication*: *cancer incidence in Wales 2000–2004*. Report No. SA6/01. Cardiff: Welsh Cancer Intelligence and Surveillance Unit; 2006.

7. McCredie M. Bladder and kidney cancers. *Cancer Surv* 1994;**19**–20:343–68.

8. Chow WH, Devesa SS, Warren JL, Fraumeni JF, Jr. Rising incidence of renal cell cancer in the United States. *JAMA* 1999;**281**:1628–31.

9. Cancer Research UK. *UK kidney cancer statistics*. URL: http://info.cancerresearchuk.org/cancerstats/types/kidney/. Cited 14 February 2008.

10. Chow WH, Gridley G, Fraumeni JF, Jr, Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* 2000;**343**:1305–11.

11. Pischon T, Lahmann PH, Boeing H, Tjonneland A, Halkjaer J, Overvad K, *et al*. Body size and risk of renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer* 2006;**118**:728–38.

12. Bergstrom A, Hsieh CC, Lindblad P, Lu CM, Cook NR, Wolk A. Obesity and renal cell cancer – a quantitative review. *Br J Cancer* 2001;**85**:984–90.

13. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. *Lancet Oncol* 2002;**3**:565–74.

14. Yuan JM, Castelao JE, Gago-Dominguez M, Ross RK, Yu MC. Hypertension, obesity and their medications in relation to renal cell carcinoma. *Br J Cancer* 1998;**77**:1508–13.

15. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. *Int J Cancer* 2005;**114**:101–8.

16. Patard JJ, Leray E, Rodriguez A, Rioux-Leclercq N, Guille F, Lobel B. Correlation between symptom graduation, tumor characteristics and survival in renal cell carcinoma. *Eur Urol* 2003;**44**:226–32.

17. British Association of Urological Surgeons. *BAUS cancer registry analyses of minimum data set for urological cancers January 1st to December 31st 2006*. Chart 81 Known Treatment Management – Kidney Tumours. London: BAUS; 2007.

18. Sasaki Y, Homma Y, Hosaka Y, Tajima A, Aso Y. Clinical and flow cytometric analyses of renal cell carcinomas with reference to incidental or non-incidental detection. *Jpn J Clin Oncol* 1994;**24**:32–6.

19. Pantuck AJ, Zisman A, Belldegrun A.S. The changing natural history of renal cell carcinoma. *J Urol* 2001;**166**:1611–23.

20. Fiala A, Urban M. Importance of early detection of renal carcinoma with regard to the prognosis. *Prakt Lék* 2001;**4**:197–8.

21. Ljungberg B, Hanbury DC, Kuczyk MA, Merseburger AS, Mulders PFA, Patard JJ, *et al*. Renal cell carcinoma guideline. *Eur Urol* 2007;**51**:1502–10.

22. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol* 2003;**27**:612–24.

23. Patard JJ, Leray E, Rioux-Leclercq N, Cindolo L, Ficarra V, Zisman A, *et al*. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol* 2005;**23**:2763–71.

24. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. *Cancer* 1980;**45**:2220–4.

25. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;**5**:649–55.

26. Kontak JA, Campbell SC. Prognostic factors in renal cell carcinoma. *Urol Clin North Am* 2003;**30**:467–80.

27. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer* 1996;**32**A:1135–41.

28. Zisman A, Pantuck AJ, Dorey F, Said JW, Shvarts O, Quintana D, *et al*. Improved prognostication of renal cell carcinoma using an integrated staging system. *J Clin Oncol* 2001;**19**:1649–57.

29. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol* 2002;**168**:2395–400.

30. Leibovich BC, Blute ML, Cheville JC, Lohse CM, Frank I, Kwon ED, *et al*. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer* 2003;**97**:1663–71.

31. Patard JJ, Leray E, Cindolo L, Ficarra V, Rodriguez A, De La Taille A, *et al*. Multi-institutional validation of a symptom based classification for renal cell carcinoma. *J Urol* 2004;**172**:858–62.

32. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999;**17**:2530–40.

33. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002;**20**:289–96.

34. Fojo AT, Ueda K, Slamont DJ, Poplackt DG, Gottesman MM, Pastan I. Expression of a multidrug-resistance gene in human tumors and tissues. *Proc Natl Acad Sci USA* 1987;**84**:265–9.

35. Mignogna C, Staibano S, Altieri V, De Rosa G, Pannone G, Santoro A, *et al*. Prognostic significance of multidrug-resistance protein (MDR-1) in renal clear cell carcinomas: a five year follow-up analysis. *BMC Cancer* 2006;**6**:293.

36. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. *J Urol* 2000;**163**:408–17.

37. Coppin C, Porzsolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer [update of *Cochrane Database Syst Rev* 2000;**3**:CD001425]. *Cochrane Database Syst Rev* 2005;**1**:CD001425.

38. Negrier S, Perol D, Ravaud A, Chevreau C, Bay JO, Delva R, *et al*. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer* 2007;**110**:2468–77.

39. Jones M, Philip T, Palmer P, von der Maase H, Vinke J, Elson P, *et al*. The impact of interleukin-2 on survival in renal cancer: A multivariate analysis. *Cancer Biother* 1993;**8**:275–88.

40. Fossa S, Jones M, Johnson P, Joffe J, Holdener E, Elson P, *et al*. Interferon-alpha and survival in renal cell cancer. *Br J Urol* 1995;**76**:286–90.

41. Rosenberg SA, Lotze MT, Yang JC, Topalian SL, Chang AE, Schwartzentruber DJ, *et al*. Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. *J Natl Cancer Inst* 1993;**85**:622–32.

42. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 1995;**13**:688–96.

43. McDermott DF, Regan MM, Clark JI, Flaherty LE, Weiss GR, Logan TF, *et al*. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2005;**23**:133–41.

44. Yang JC, Sherry RM, Steinberg SM, Topalian SL, Schwartzentruber DJ, Hwu P, *et al*. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol* 2003;**21**:3127–32.

45. Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, *et al*. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie. *N Engl J Med* 1998;**338**:1272–8.

46. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared

with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001;**358**:966–70.

47. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, *et al*. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;**345**:1655–9.

48. Flanigan RC, Mickisch G, Sylvester R, Tangen C, van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol* 2004;**171**: 1071–6.

49. Chae EJ, Kim JK, Kim SH, Bae SJ, Cho KS. Renal cell carcinoma: analysis of postoperative recurrence patterns. *Radiology* 2005;**234**:189–96.

50. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;**47**:207–14.

51. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer* 2006;**42**:1031–9.

52. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–16.

53. Oliver RT. Are cytokine responses in renal cell cancer the product of placebo effect of treatment or true biotherapy? What trials are needed now? *Br J Cancer* 1998;**77**:1318–20.

54. Gleave ME, Elhilali M, Fradet Y, Davis I, Venner P, Saad F, *et al*. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. *N Engl J Med* 1998;**338**:1265–71.

55. Vogelzang NJ, Priest ER, Borden L. Spontaneous regression of histologically proved pulmonary metastases from renal cell carcinoma: a case with 5-year followup. *J Urol* 1992;**148**:1247–8.

56. National Institute for Clinical Excellence. *Improving outcomes in urological cancers*. London: NICE; 2002.

57. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, *et al*. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;**11**:570–9.

58. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76.

59. Cella D, Yount S, Du H, Dhanda R, Gondek K, Langefeld K, *et al*. Development and validation of the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). *J Support Oncol* 2006;**4**:191–9.

60. Cella D, Yount S, Brucker PS, Du H, Bukowski R, Vogelzang N, *et al*. Development and validation of a scale to measure disease-related symptoms of kidney cancer. *Value Health* 2007;**10**:285–93.

61. Harding G, Cella D, Robinson D, Jr, Mahadevia PJ, Clark J, Revicki DA. Symptom burden among patients with renal cell carcinoma (RCC): content for a symptom index. *Health Qual Life Outcomes* 2007;**5**:34.

62. Schoffski P, Dumez H, Clement P, Hoeben A, Prenen H, Wolter P, *et al*. Emerging role of tyrosine kinase inhibitors in the treatment of advanced renal cell cancer: a review. *Ann Oncol* 2006;**17**:1185–96.

63. Board RE, Thistlethwaite FC, Hawkins RE. Anti-angiogenic therapy in the treatment of advanced renal cell cancer. *Cancer Treat Rev* 2007;**33**:1–8.

64. Rini BI. VEGF-targeted therapy in metastatic renal cell carcinoma. *Oncologist* 2005;**10**:191–7.

65. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clin Ther* 2006;**28**:1779–802.

66. Le Tourneau C, Raymond E, Faivre S. Sunitinib: a novel tyrosine kinase inhibitor. A brief review of its therapeutic potential in the treatment of renal carcinoma and gastrointestinal stromal tumors (GIST). *Ther Clin Risk Manag* 2007;**3**:341–8.

67. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Off-label uses of bevacizumab: renal cell carcinoma and other miscellaneous non-colorectal cancer indications. TEC Assessment Program. Vol. 21, No. 9, Executive Summary. Chicago, IL. BCBSA; October 2006. pp. 1–4.

68. Rini BI, Halabi S, Taylor J, Small EJ, Schilsky RL, Cancer and Leukemia Group. Cancer and Leukemia Group B 90206: a randomized phase III trial of interferon-alpha or interferon-alpha plus anti-vascular endothelial growth factor antibody (bevacizumab) in metastatic renal cell carcinoma. *Clin Cancer Res* 2004;**10**:2584–6.

69. European Medicines Agency. *EPARs for authorised medicinal products for human use*. *Avastin*: *European*

Public Assessment Report (Revision 9). URL: www.emea.europa.eu/humandocs/Humans/EPAR/avastin/avastin.htm. Cited 23 March 2008.

70. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary 55*. Online edition 2008. URL: www.bnf.org/bnf/extra/current/450035.htm. Cited 19 March 2008.

71. McKeage K, Wagstaff AJ. Sorafenib: in advanced renal cancer. *Drugs* 2007;**67**:475–83.

72. Hahn O, Stadler W. Sorafenib. *Curr Opin Oncol* 2006;**18**:615–21.

73. Hughes CL, Tan WW, Ferrone M. Sorafenib for the treatment of renal cell carcinoma. *J Pharm Technol* 2006;**22**:281–8.

74. Reddy GK, Bukowski RM. Sorafenib: recent update on activity as a single agent and in combination with interferon-alpha2 in patients with advanced-stage renal cell carcinoma. *Clin Genitourin Cancer* 2006;**4**:246–8.

75. Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, *et al*. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer [erratum appears in *Nat Rev Drug Discov* 2007;**6**:126]. *Nat Rev Drug Discov* 2006;**5**:835–44.

76. Motzer RJ, Hoosen S, Bello CL, Christensen JG. Sunitinib malate for the treatment of solid tumours: a review of current clinical data. *Exp Opin Invest Drugs* 2006;**15**:553–61.

77. European Medicines Agency. *Sutent European Public Assessment Report (EPAR).* URL: www.emea.europa.eu/humandocs/Humans/EPAR/sutent/sutent.htm. Cited 14 March 2008.

78. Srinivas S, Roigas J, Gillessen S, Harmenberg U, De Mulder PH, Fountzilas G, *et al*. Continuous daily administration of sunitinib in patients (pts) with cytokine-refractory metastatic renal cell carcinoma (mRCC): updated results. *J Clin Oncol* 2007;**25**(18S):5040.

79. Del Bufalo D, Ciuffreda L, Trisciuoglio D, Desideri M, Cognetti F, Zupi G, *et al*. Antiangiogenic potential of the mammalian target of rapamycin inhibitor temsirolimus. *Cancer Res* 2006;**66**:5549–54.

80. Patel PH, Chadalavada RS, Chaganti RS, Motzer RJ. Targeting von Hippel-Lindau pathway in renal cell carcinoma. *Clin Cancer Res* 2006;**12**:7215–20.

81. Hutson TE, Sonpavde G, Galsky MD. Targeting growth factor and antiangiogenic pathways in clear-cell renal cell carcinoma: rationale and ongoing trials. *Clin Genitourin Cancer* 2006;**5**(Suppl. 1):S31–9.

82. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness*. 2nd edn. York: NHS Centre for Reviews and Dissemination; 2001.

83. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;**50**:683–91.

84. National Cancer Institute. *Common terminology criteria for adverse events v.3.0 (CTCAE).* URL: http://ctep.cancer.gov/ProtocolDevelopment/electronic_applications/ctc.htm. Cited 14 March 2008.

85. Motzer RJ, Michaelson MD, Rosenberg J, Bukowski RM, Curti BD, George DJ, *et al*. Sunitinib efficacy against advanced renal cell carcinoma. *J Urol* 2007;**178**:1883–7.

86. Escudier BJ, Ravaud A, Bracarda S, Melichar B, Delva R, Sevin E, *et al*. Efficacy and safety of first-line bevacizumab (BEV) plus interferon-a2a (IFN) in subgroups of patients (pts) with metastatic renal cell carcinoma (mRCC). ASCO Genitourinary Cancers Symposium. Abstract 358; 2008.

87. Cella D, Li JZ, Bushmakin AG, Cappelleri JC, Kim ST, Chen I, *et al*. Health-related quality of life (HRQOL) and kidney cancer-related symptoms in patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib versus interferon (IFN)-alfa: results for European and US subsample analyses in a randomized, multinational phase III trial. *Eur J Cancer Suppl* 2007;**5**:114.

88. Motzer RJ, Michaelson MD, Hutson TE, Tomczak P, Bukowski RM, Rixe O, *et al*. Sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC): updated efficacy and safety results and further analysis of prognostic factors. *Eur J Cancer Suppl* 2007;**5**:301.

89. DeSouza P, Maart K, Laurell A, Hawkins RE, Berkenblit A, Galand L, *et al*. Results of a phase 3, randomized study of patients with advanced renal cell carcinoma (RCC) and poor prognostic features treated with temsirolimus, interferon[alpha] or the combination of temsirolimus + interferon[alpha]. *Eur J Cancer Suppl* 2007;**5**:282.

90. George DJ, Michaelson MD, Rosenberg JE, Redman BG, Hudes GR, Bukowski RM, *et al*. Sunitinib in patients with cytokine-refractory metastatic renal cell carcinoma (mRCC). *Eur J Cancer Suppl* 2007;**5**:303.

91. Motzer RJ, Figlin RA, Hutson TE, Tomczak P, Bukowski RM, Rixe O, *et al*. Sunitinib versus

interferon-alfa (IFN-α) as first-line treatment of metastatic renal cell carcinoma (mRCC): updated results and analysis of prognostic factors. *J Clin Oncol* 2007;**25**(Suppl. 18):5024.

92. Cella D, Li JZ, Cappelleri JC, Bushmakin A, Charbonneau C, Kim ST, *et al*. Quality of life (QOL) predicts for progression-free survival (PFS) in patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib compared to interferon-alpha (IFN-alpha). *J Clin Oncol* 2007;**25**(Suppl. 18):6594.

93. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, *et al*. Phase III randomized trial of sunitinib malate (SU11248) versus interferon-alfa (IFN-α) as first-line systemic therapy for patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2006;**24**(Suppl. 18).

94. Dutcher JP, Szczylik C, Tannir N, Benedetto P, Ruff P, Hsu A, *et al*. Correlation of survival with tumor histology, age, and prognostic risk group for previously untreated patients with advanced renal cell carcinoma (adv RCC) receiving temsirolimus (TEMSR) or interferon-alpha (IFN). *J Clin Oncol* 2007;**25**(Suppl. 18):5033.

95. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, *et al*. A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC). *J Clin Oncol* 2006;**24**(Suppl. 18).

96. Dutcher JP, de Souza P, Figlin R, Berkenblit A, Thiele A, Krygowski M, *et al*. Effect of temsirolimus versus interferon-α on survival of patients with advanced renal cell carcinoma of different tumor histologies. ASCO Genitourinary Cancers Symposium. 2008. Abstract no. 384

97. Parasuraman S, Hudes G, Levy D, Strahs A, Moore L, DeMarinis R, *et al*. Comparison of quality-adjusted survival in patients with advanced renal cell carcinoma receiving first-line treatment with temsirolimus (TEMSR) or interferon- (IFN) or the combination of IFN+TEMSR. *J Clin Oncol* 2007;**25**(Suppl. 18):5049.

98. Bukowski RM, Eisen T, Szczylik C, Stadler WM, Simantov R, Shan M, *et al*. Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: survival and biomarker analysis. *J Clin Oncol* 2007;**25**(Suppl. 18):5023.

99. Dhanda R, Gondek K, Song J, Cella D, Bukowski RM, Escudier B. A comparison of quality of life and symptoms in kidney cancer patients receiving sorafenib versus placebo. *J Clin Oncol* 2006;**24**(Suppl. 18):4534.

100. Rosenberg JE, Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Bukowski RM, *et al*. Sunitinib therapy for patients (pts) with metastatic renal cell carcinoma (mRCC): updated results of two phase II trials and prognostic factor analysis for survival. *J Clin Oncol* 2007;**25**(Suppl. 18):5095.

101. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena D, Ou S, *et al*. CALGB 90206: a phase III trial of bevacizumab plus interferon-alpha versus interferon-alpha monotherapy in metastatic renal cell carcinoma. ASCO Genitourinary Cancers Symposium. 2008. Abstract no. 350.

102. Eisen T, Bukowski RM, Staehler M, Szczylik C, Oudard S, Stadler WM, *et al*. Randomized phase III trial of sorafenib in advanced renal cell carcinoma (RCC): impact of crossover on survival. *J Clin Oncol* 2006;**24**(Suppl. 18):4524.

103. Procopio G, Verzoni E, Porta C, Escudier B, Martinetti A, Catena L, *et al*. A phase III randomized study with sorafenib in patients with advanced renal cell cancer. *Ann Oncol* 2006;**17**(Suppl. 11):xi3–4.

104. Remák E, Mullins CD, Akobundu E, Charbonneau C, Woodruff K. Economic evaluations of sunitinib versus interferon-alfa (IFN-α) in first-line metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2007;**25**(Suppl. 18):6607.

105. Maroto-Rey M, Bellmunt J, Trigo JM, López-Martín JA, Carles J, Antón-Torres A, *et al*. First-line phase II trial of sorafenib (BAY 43–9006) in patients with advanced renal cell carcinoma unsuitable for cytokine treatment. *J Clin Oncol* 2007;**25**(Suppl. 18):15640.

106. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, *et al*. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007;**370**:2103–11.

107. Motzer RJ, Hutson TE, Tomczak P, Michaelson D, Bukowski RM, Rixe O, *et al*. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;**356**:115–24.

108. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, *et al*. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;**356**:2271–81.

109. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, *et al*. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;**356**:125–34.

110. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, *et al*. Phase II placebo-controlled

randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;**24**:2505–12.

111. Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, *et al*. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006;**295**:2516–24.

112. Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, *et al*. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;**24**:16–24.

113. Escudier B, Koralewski P, Pluzanska A, Ravaud A, Bracarda S, Szczylik C, *et al*. A randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of bevacizumab in combination with interferon alfa-2a (Roferon) versus interferon alfa-2a and placebo as first-line treatment administered to nephrectomized patients with metastatic clear cell renal cell carcinoma. *J Clin Oncol* 2007;**25**(Suppl. 18):3.

114. Escudier B, Koralewski P, Pluzanska A, Ravaud A, Bracarda S, Szczylik C, *et al*. A randomized, controlled, double-blind phase III study (AVOREN) of bevacizumab/interferon-α2a vs placebo/interferon-α2a as first-line therapy in metastatic renal cell carcinoma. *J Clin Oncol* 2007;**25**(Suppl. 18):3.

115. Bracarda S, Koralewski P, Pluzanska A, Ravaud A, Szczylik C, Chevreau C, *et al*. Bevacizumab/interferon-a2a provides a progression-free survival benefit in all prespecified patient subgroups as first-line treatment of metastatic renal cell carcinoma (AVOREN). *Eur J Cancer Suppl* 2007;**5**:281.

116. Melichar B, Koralewski P, Pluzanska A, Ravaud A, Bracarda S, Szczylik C, *et al*. First-line bevacizumab improves progression-free survival with lower doses of interferon[alpha]2a in the treatment of patients with metastatic renal cell carcinoma (AVOREN). *Eur J Cancer Suppl* 2007;**5**:304.

117. Roche. An appraisal submission for the National Institute for Health and Clinical Excellence. *Achieving clinical excellence in renal carcinoma*: *Avastin (bevacizumab) renal cell carcinoma.* 16 January 2008.

118. Gore ME, Porta C, Oudard S, Bjarnason G, Castellano D, Szcaylik C, *et al*. Sunitinib in metastatic renal cell carcinoma (mRCC): preliminary assessment of toxicity in an expanded access trial with subpopulation analysis. *J Clin Oncol* 2007;**25**(Suppl. 18):5010.

119. Bhojani N, Jeldres C, Patard JJ, Perrotte P, Suardi N, Hutterer G, *et al*. Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma. *Eur Urol* 2008;**53**:917–30.

120. Wu S, Chen JJ, Kudelka A, Lu J, Zhu X. Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. *Lancet Oncol* 2008;**9**:117–23.

121. Price JA, Shaarbaf R, Wood LA. Sunitinib-related macrocytosis in patients with advanced renal cell cancer (RCC). *J Clin Oncol* 2007;**25**(Suppl. 18):15580.

122. Schoeffski P, Wolter P, Himpe U, Dychter SS, Baum CM, Prenen H, *et al*. Sunitinib-related thyroid dysfunction: a single-center retrospective and prospective evaluation. *J Clin Oncol* 2006;**24**(Suppl. 18):3092.

123. Zhu X, Wu S, Dahut Wl, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis* 2007;**49**:186–93.

124. Wyeth. An appraisal submission for the National Institute for Health and Clinical Excellence. *Appraisal of the clinical and cost-effectiveness of temsirolimus for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors*. 16 January 2008.

125. Bukowski R, Cella D, Gondek K, Escudier B, Sorafenib TARGETs Clinical Trial Group. Effects of sorafenib on symptoms and quality of life: results from a large randomized placebo-controlled study in renal cancer. *Am J Clin Oncol* 2007;**30**:220–7.

126. Ryan CW, Bukowshi RM, Figlin RA, Knox JJ, Hutson TE, Dutcher JP, *et al*. The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial: long-term outcomes in first-line patients (pts). *J Clin Oncol* 2007;**25**(Suppl. 18):5096.

127. Chu D, Lacouture ME, Fillos T, Wu S. Risk of hand-foot skin reaction with sorafenib: a systematic review and meta-analysis. *Acta Oncol* 2008;**47**:176–86.

128. Contreras-Hernandez I, Mould-Quevedo J, Salinas-Escudero G, Tapia-Valencia J, Davila-Loaiza G, Garduno-Espinosa J. A cost–utility analysis model for the second line treatment of metastatic renal cell carcinoma in Mexico. ISPOR 1st Latin America Conference. 2007.

129. Aiello EC, Muszbek N, Richardet E, Lingua A, Charbonneau C, Remák E. Cost-effectiveness of new targeted therapy sunitinib malate as second line treatment in metastatic renal cell carcinoma in Argentina. *Value Health* 2007;**10**:A127–8.

130. Jaszewski B, Gao X, Reddy P, Bhardwaj T, Bjarnason G, Finelli A, *et al*. Cost effectiveness of sorafenib versus best supportive care in advanced renal cell carcinoma in Canada. *J Clin Oncol* 2007;**25**(Suppl. 18):5111.

131. Maroto P, Villavicencio H, Pinol C, Urruticoechea L. Cost-effectiveness of sorafenib versus best supportive care in advanced renal cell carcinoma in Spain. *Value Health* 2006;**9**:A280.

132. Gao X, Reddy P, Dhanda R, Gondek K, Yeh YC, Stadler WM, *et al*. Cost-effectiveness of sorafenib versus best supportive care in advanced renal cell carcinoma. *J Clin Oncol* 2006;**24**:242S.

133. Remák E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. *Br J Cancer* 2004;**91**:77–83.

134. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. London: NICE; 2004.

135. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics* 2006;**24**:355–71.

136. Pfizer. Submission to the National Institute for Health and Clinical Excellence. *Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma*. 16 January 2008.

137. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R, European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001;**358**:966–70.

138. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, *et al*. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol* 2004;**22**:454–63.

139. Department of Health. *NHS reference costs 2005–06*. 2006. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_062884.

140. [No authors listed] Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Medical Research Council Renal Cancer Collaborators. *Lancet* 1999;**353**:14–7.

141. Bayer. *The clinical, cost-effectiveness and service impact of sorafenib (Nexavar) in the NHS of England and Wales for the treatment of patients with advanced renal cell carcinoma*. A submission by Bayer Schering Pharma to the National Institute for Health and Clinical Excellence. 16 January 2008.

142. Tappenden P, Chilcott J, Ward S, Eggington S, Hind D, Hummel S. Methodological issues in the economic analysis of cancer treatments. *Eur J Cancer* 2006;**42**:2867–75.

143. Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*. Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation. *Health Technol Assess* 2006;**10**(9):1–161.

144. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal: draft for consultation*. London: NICE; 2007.

145. Department of Health. *NHS reference costs 2006–07*. 2008. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_082571.

146. Curtis L. *Unit costs of health and social care 2007*. 2007. Canterbury: Personal Social Services Research Unit, University of Kent.

147. Coyle D, Small N, Ashworth A, Hennessy S, Jenkins-Clarke S, Mannion R, *et al*. Costs of palliative care in the community, in hospitals and in hospices in the UK. *Crit Rev Oncol Hematol* 1999;**32**:71–85.

148. National Institute for Health and Clinical Excellence. *NICE clinical guideline 34: national cost impact report to accompany 'Hypertension: the management of hypertension in adults in primary care (partial update)'*. London: NICE; 2006.

149. Ramsey SL, Aitchison M. Treatment for renal cancer: are we beyond the cytokine era? *Nature Clin Pract Urol* 2006;**3**:478–84.

150. Collett D. *Modelling survival data in medical research*. 2nd edn. Boca Raton, FL: Chapman & Hall/CRC; 2003.

151. Song F, Glenny AM, Altman DG. Indirect comparison in evaluating relative efficacy illustrated by antimicrobial prophylaxis in colorectal surgery. *Control Clin Trials* 2000;**21**:488–97.

152. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;**326**:472.

153. Amato RJ. Renal cell carcinoma: review of novel single-agent therapeutics and combination regimens. *Ann Oncol* 2005;**16**:7–15.

154. Atkins MB, Hidalgo M, Stadler WM, Logan TF, Dutcher JP, Hudes GR, *et al*. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004;**22**:909–18.

155. Choueiri TK, Garcia JA, Elson P, Khasawneh M, Usman S, Golshayan AR, *et al*. Clinical factors associated with outcome in patients with metastatic clear-cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *Cancer* 2007;**110**:543–50.

156. Chouhan JD, Zamarripa DE, Lai PH, Oramasionwu CU, Grabinski JL. Sunitinib (Sutent): a novel agent for the treatment of metastatic renal cell carcinoma. *J Oncol Pharm Pract* 2007;**13**:5–15.

157. Escudier B. New perspectives: an oral multikinase inhibitor in patients with advanced RCC. *Eur Urol Suppl* 2007;**6**:499–504.

158. Escudier B, Lassau N, Angevin E, Soria JC, Chami L, Lamuraglia M, *et al*. Phase I trial of sorafenib in combination with IFN alpha-2a in patients with unresectable and/or metastatic renal cell carcinoma or malignant melanoma. *Clin Cancer Res* 2007;**13**:1801–9.

159. George DJ. Phase 2 studies of sunitinib and AG013736 in patients with cytokine-refractory renal cell carcinoma. *Clin Cancer Res* 2007;**13**:753–7s.

160. Gore ME, Escudier B. Emerging efficacy endpoints for targeted therapies in advanced renal cell carcinoma. *Oncology* 2006;**20**(Suppl. 5):19–24.

161. Jain L, Venitz J, Figg WD. Randomized discontinuation trial of sorafenib (BAY 43–9006). *Cancer Biol Ther* 2006;**5**:1270–2.

162. Kane RC, Farrell AT, Saber H, Tang S, Williams G, Jee JM, *et al*. Sorafenib for the treatment of advanced renal cell carcinoma. *Clin Cancer Res* 2006;**12**:7271–8.

163. Lamuraglia M, Escudier B, Chami L, Schwartz B, Leclere J, Roche A, *et al*. To predict progression-free survival and overall survival in metastatic renal cancer treated with sorafenib: pilot study using dynamic contrast-enhanced Doppler ultrasound. *Eur J Cancer* 2006;**42**:2472–9.

164. Lara J, Quinn DI, Margolin K, Meyers FJ, Longmate J, Frankel P, *et al*. SU5416 plus interferon alpha in advanced renal cell carcinoma: a phase II California Cancer Consortium Study with biological and imaging correlates of angiogenesis inhibition. *Clin Cancer Res* 2003;**9**:4772–81.

165. Mancuso A, Sternberg CN. New treatment approaches in metastatic renal cell carcinoma. *Curr Opin Urol* 2006;**16**:337–41.

166. Margolin K, Atkins MB, Dutcher JP, Ernstoff MS, Smith II JW, Clark JI, *et al*. Phase I trial of BAY 50–4798, an interleukin-2-specific agonist in advanced melanoma and renal cancer. *Clin Cancer Res* 2007;**13**:3312–9.

167. Medioni J, Cojocarasu O, Belcaceres JL, Halimi P, Oudard S. Complete cerebral response with sunitinib for metastatic renal cell carcinoma. *Ann Oncol* 2007;**18**:1282–3.

168. Montorsi F. Kidney cancer: highlights from 2006. *Eur Urol Suppl* 2007;**6**:745–53.

169. Motzer RJ, Bukowski RM. Targeted therapy for metastatic renal cell carcinoma. *J Clin Oncol* 2006;**24**:5601–8.

170. Motzer RJ, Bolger GB, Boston B, Carducci MA, Fishman M, Hancock SL, *et al*. Kidney cancer clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2006;**4**:1072–81.

171. Patard JJ, Lechevallier E, Congregado RB, Montorsi F. New Research on kidney cancer: highlights from Urologic and Oncologic Congresses in 2006. *Eur Urol Suppl* 2007;**6**:396–403.

172. Patel PH, Schwartz LH, Baum MS, Motzer RJ. Superior efficacy of sunitinib compared with interferon as first-line therapy in patients with metastatic renal cell carcinoma. *Am J Hematol Oncol* 2007;**6**:260–4.

173. Peralba JM, DeGraffenried L, Friedrichs W, Fulcher L, Grunwald V, Weiss G, *et al*. Pharmacodynamic evaluation of CCI-779, an inhibitor of mTOR, in cancer patients. *Clin Cancer Res* 2003;**9**:2887–92.

174. Quan J. Akin to Nelson's band of brothers: activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *Am J Oncol Rev* 2006;**5**:297–9.

175. Raymond E, Alexandre J, Faivre S, Vera K, Materman E, Boni J, *et al*. Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer. *J Clin Oncol* 2004;**22**:2336–47.

176. Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. *J Clin Oncol* 2005;**23**:1028–43.

177. Rini BI, Weinberg V, Small EJ. Practice and progress in kidney cancer: methodology for novel drug development. *J Urol* 2004;**171**:2115–21.

178. Rini BI. SU11248 and AG013736: current data and future trials in renal cell carcinoma. *Clin Genitourinary Cancer* 2005;**4**:175–80.

179. Rini BI, Campbell SC. The evolving role of surgery for advanced renal cell carcinoma in the era of molecular targeted therapy. *J Urol* 2007;**177**:1978–84.

180. Rini BI, Jaeger E, Weinberg V, Sein N, Chew K, Fong K, *et al*. Clinical response to therapy targeted at vascular endothelial growth factor in metastatic renal cell carcinoma: impact of patient characteristics and Von Hippel–Lindau gene status. *BJU Int* 2006;**98**:756–62.

181. Rodriguez A, Sexton WJ. Management of locally advanced renal cell carcinoma. *Cancer Control* 2006;**13**:199–210.

182. Ryan CW, Goldman BH, Lara J, Mack PC, Beer TM, Tangen CM, *et al*. Sorafenib with interferon alfa-2b as first-line treatment of advanced renal carcinoma: a phase II study of the southwest oncology group. *J Clin Oncol* 2007;**25**:3296–301.

183. Schrader AJ, Varga Z, Hegele A, Pfoertner S, Olbert P, Hofmann R. Second-line strategies for metastatic renal cell carcinoma: classics and novel approaches. *J Cancer Res Clin Oncol* 2006;**132**:137–49.

184. Skolarikos A, Alivizatos G, Laguna P, de la Rosette J. A Review on follow-up strategies for renal cell carcinoma after nephrectomy. *Eur Urol* 2007;**51**:1490–501.

185. Strumberg D, Clark JW, Awada A, Moore MJ, Richly H, Hendlisz A, *et al*. Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. *Oncologist* 2007;**12**:426–37.

186. Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, *et al*. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;**349**:427–34.

187. Yang JC, Gordon M, Atkins M, Motzer R, Lipton A, Flanigan R, *et al*. Bevacizumab for patients with metastatic renal cancer: an update. *Clin Cancer Res* 2004;**10**:6367–70s.

188. The Chartered Institute for Public Finance and Accountancy. Online edition 2008 March. URL: www.cipfa.org.uk/. Cited March 2008.

189. Billingham LJ, Abrams KR, Jones DR. Methods for the analysis of quality-of-life and survival data in health technology assessment. *Health Technol Assess* 1999;**3**(10).

190. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation*. 1st edn. New York: Oxford University Press; 2006.

Appendix 1

Literature search strategies

Search strategy for clinical effectiveness

The MEDLINE search strategy was translated and run in:

- MEDLINE (Ovid) – 1950 to September Week 3 2007
- EMBASE (Ovid) – 1980 to 2007 Week 39
- Cochrane CENTRAL Register of Controlled Trials (CCTR) – 2007 Issue 3
- Cochrane Database of Systematic Reviews (CDSR) – 2007 Issue 3
- HTA database (in Cochrane Library) – 2007 Issue 3
- Science Citation Index (ISI Web of Science) – 1981 to 26 September 2007
- ISI Proceedings – 1980 to 1 October 2007
- BIOSIS – 1985 to 1 October 2007

MEDLINE (Ovid) 1950 to September Week 3 2007

Searched 26 September 2007

1. exp Carcinoma, Renal Cell/
2. (renal cell carcinoma$or cell renal carcinoma$or renal carcinoma$or kidney carcinoma$or kidney cell carcinoma$or renal adenocarcinoma$or kidney adenocarcinoma$or adenocarcinoma$renal or adenocarcinoma$kidney$).mp.
3. (hypernephroma$or nephroid carcinoma$or hypernephroid carcinoma$or kidney hypernephroma$or kidney pelvic carcinoma$or kidney pyelocarcinoma$or renal hypernephroma$or grawitz tumo?r$or renal cell neoplasm$or renal cell cancer$or renal tumo?r$or carcinoma chromophobe cell kidney$or chromophobe cell kidney carcinoma$).mp.
4. exp kidney neoplasms/
5. (cancer$adj2 kidney$1).ti,ab.
6. (neoplasm$1 adj2 kidney$1).ti,ab.
7. (neoplasm$1 adj2 renal).ti,ab.
8. (cancer$adj2 renal).ti,ab.
9. (tumo?r$1 adj2 kidney$1).ti,ab.
10. (tumo?r$1 adj2 renal).ti,ab.
11. or/1–10
12. (bevacizumab or avastin or sorafenib or nexavar or sunitinib or sutent or torisel or temsirolimus or "CCI-779").mp.
13. 11 and 12
14. limit 13 to humans
15. (editorial or letter).pt.
16. 14 not 15

Search strategy for cost-effectiveness

This search strategy was translated and run in:

- MEDLINE (Ovid) – 1950 to September Week 3 2007
- EMBASE (Ovid) – 1980 to 25 September 2007
- Cochrane CENTRAL Register of Controlled Trials (CCTR) – 2007 Issue 3
- Science Citation Index (ISI Web of Science) – 1981 to 24 October 2007
- BIOSIS – 1985 to 24 October 2007
- ISI Proceedings – 1980 to 24 October 2007
- NHS EED – 1995 to 24 October 2007
- NRR – 2000 to 24 October 2007
- Conferences searched on internet, including ECCO 14, ASCO, ISPOR and ISOP

MEDLINE (Ovid) 1950 to September week 3 2007

Searched 25 September 2007

Search one: for specific drug interventions linked to renal cell carcinoma

1. exp Cost-Benefit Analysis/or exp Economics, Pharmaceutical/or exp Drug Costs/or exp Models, Economic/
2. exp "Fees and Charges"/
3. (economic$or price or pricing or pharmacoeconomic$or pharmaeconomi$).tw.
4. (cost or costly or costing$or costed).tw.
5. (cost$adj2 (benefit$or utilit$or utilis$or minim$)).tw.
6. (expenditure$not energy).tw.
7. (value adj2 (money or monetary)).tw.
8. budget$.tw.
9. (economic adj2 burden$).tw.
10. "resource use".ti,ab.
11. exp economics/

12. exp economics hospital/
13. exp economics pharmaceutical/
14. exp economics nursing/
15. exp economics dental/
16. exp economics medical/
17. exp "costs and cost analysis"/
18. value of life/
19. exp models economic/
20. cost of illness/
21. or/1–20
22. letter.pt.
23. editorial.pt.
24. comment.pt.
25. or/22–24
26. 21 not 25
27. (bevacizumab or avastin or sorafenib or nexavar or sunitinib or sutent or torisel or temsirolimus or "CCI-779").mp.
28. CCI-779.rn.
29. 27 or 28
30. 26 and 29
31. exp carcinoma renal cell/
32. (renal cell carcinoma$or cell renal carcinoma$or renal carcinoma$or kidney carcinoma$or kidney cell carcinoma$or renal adenocarcinoma$or kidney adenocarcinoma$or adenocarcinoma$renal or adenocarcinoma$kidney$).ti,ab.
33. (kidney$1 adj2 cancer).ti,ab.
34. (hypernephroma$or nephroid carcinoma$or hypernephroid carcinoma$or kidney hypernephroma$or kidney pelvic carcinoma$or kidney pyelocarcinoma$or renal hypernephroma$or grawitz tumo?r$or renal cell cancer$or renal tumo?r$or carcinoma chromophobe cell kidney$or chromophobe cell kidney carcinoma$).ti,ab.
35. or/31–34
36. 30 and 35

Search two: for interferon interleukin plus cost filter plus renal cell carcinoma

1. exp Cost-Benefit Analysis/or exp Economics, Pharmaceutical/or exp Drug Costs/or exp Models, Economic/
2. exp "Fees and Charges"/
3. (economic$or price or pricing or pharmacoeconomic$or pharmaeconomi$).tw.
4. (cost or costly or costing$or costed).tw.
5. (cost$adj2 (benefit$or utilit$or utilis$or minim$)).tw.
6. (expenditure$not energy).tw.
7. (value adj2 (money or monetary)).tw.
8. budget$.tw.
9. (economic adj2 burden$).tw.
10. "resource use".ti,ab.
11. exp economics/
12. exp economics hospital/
13. exp economics pharmaceutical/
14. exp economics nursing/
15. exp economics dental/
16. exp economics medical/
17. exp "costs and cost analysis"/
18. value of life/
19. exp models economic/
20. cost of illness/
21. or/1–20
22. letter.pt.
23. editorial.pt.
24. comment.pt.
25. or/22–24
26. 21 not 25
27. exp carcinoma renal cell/
28. (renal or kidney$1).ti,ab.
29. (carcinoma$or cancer$or tumo?r$1 or adenocarcinoma$or pyelocarcinoma$).ti,ab.
30. 28 and 29
31. 26 and 27 and 30
32. limit 31 to (humans and english language)
33. exp Interleukin-2/
34. exp Interferon-alpha/
35. 32 and (33 or 34)
36. exp Interferon-alpha/ec [Economics]
37. exp Interferon Alfa-2b/ec [Economics]
38. exp Interleukin-2/ec [Economics]
39. or/36–38
40. 27 and 30 and 39
41. 35 or 40
42. limit 41 to (humans and english language)

Search three: for broad disease area search and cost filter

1. exp economics/
2. exp economics hospital/
3. exp economics pharmaceutical/
4. exp economics nursing/
5. exp economics dental/
6. exp economics medical/
7. exp "Costs and Cost Analysis"/
8. Cost Benefit Analysis/
9. value of life/
10. exp models economic/
11. exp fees/and charges/
12. exp budgets/
13. (economic$or price$or pricing or financ$or fee$or pharmacoeconomic$or pharma economic$).tw.
14. (cost$or costly or costing$or costed).tw.
15. (cost$adj2 (benefit$or utilit$or minim$or effective$)).tw.
16. (expenditure$not energy).tw.

17. (value adj2 (money or monetary)).tw.
18. budget$.tw.
19. (economic adj2 burden).tw.
20. "resource use".ti,ab.
21. or/1–20
22. (news or letter or editorial or comment).pt.
23. 21 not 22
24. exp Kidney Neoplasms/
25. exp carcinoma renal cell/
26. (renal or kidney$1).tw.
27. (neoplasm$or carcinoma$or cancer$or tumo?r$or adenocarcinoma$or pyelocarcinoma$).tw.
28. 26 and 27
29. or/24–25,28
30. 23 and 29
31. limit 30 to (humans and english language)
32. limit 31 to animals
33. 31 not 32
34. from 33 keep 1–833
35. (renal adj (neoplasm$or carcinoma$or cancer$or tumo?r$or adenocarcinoma$or pyelocarcinoma$)).tw.
36. (kidney$1 adj (neoplasm$or carcinoma$or cancer$or tumo?r$or adenocarcinoma$or pyelocarcinoma$)).tw.
37. 35 or 36
38. (renal adj2 (neoplasm$or carcinoma$or cancer$or tumo?r$or adenocarcinoma$or pyelocarcinoma$)).tw.
39. (kidney$1 adj2 (neoplasm$or carcinoma$or cancer$or tumo?r$or adenocarcinoma$or pyelocarcinoma$)).tw.
40. 38 or 39
41. or/24–25,37
42. or/24–25,40
43. 23 and 41
44. limit 43 to (humans and english language)
45. limit 44 to animals
46. 44 not 45
47. 23 and 42
48. limit 47 to (humans and english language)
49. limit 48 to animals
50. 48 not 49

Search strategy for quality of life

This search strategy was translated and run in:

- Ovid MEDLINE(R)
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
- EMBASE – 1980 to 2007 week 42
- PsycINFO including PsycARTICLES 2000 – Present

MEDLINE (Ovid) 1950 to October Week 2 2007

Searched 23 October 2007

1. (renal or kidney$).ti,ab.
2. (cancer$or neoplasm$or carcinoma$or tumo?r$1 or adenocarcinoma$or pyelocarcinoma$or hypernephroma$or nephroid carcinoma$).ti,ab.
3. 1 and 2
4. Carcinoma, Renal Cell/
5. (renal cell carcinoma or renal cancer$or RCC).ti,ab.
6. Kidney Neoplasms/
7. or/3–6
8. value of life/
9. quality adjusted life year/
10. quality adjusted life.ti,ab.
11. (qaly$or qald$or qale$or qtime$).ti,ab.
12. disability adjusted life.ti,ab.
13. daly$.ti,ab.
14. health status indicators/
15. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
16. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
17. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.
18. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
19. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.
20. (euroqol or euro qol or eq5d or eq 5d).ti,ab.
21. (hql or hqol or h qol or hrqol or hr qol).ti,ab.
22. (hye or hyes).ti,ab.
23. health$year$equivalent$.ti,ab.
24. ((health or cost$) adj3 utilit$).ti,ab.
25. (hui or hui1 or hui2 or hui3).ti,ab.
26. disutil$.ti,ab.
27. rosser.ti,ab.
28. quality of well being.ti,ab.
29. quality of wellbeing.ti,ab.
30. qwb.ti,ab.
31. willingness to pay.ti,ab.
32. standard gamble$.ti,ab.
33. time trade off.ti,ab.
34. time tradeoff.ti,ab.
35. tto.ti,ab.
36. (index adj2 well being).mp.

37. (quality adj2 well being).mp.
38. ((multiattribute$or multi attribute$) adj3 (health ind$or theor$or health state$or utilit$or analys$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39. quality adjusted life year$.mp.
40. (15D or 15 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41. (12D or 12 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
42. rating scale$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
43. linear scal$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
44. linear analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
45. visual analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
46. (categor$adj2 scal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
47. or/8–46 (100636)
48. (letter or editorial or comment).pt.
49. 47 not 48
50. 49 and 7
51. (Assessment of Quality of life at the End of Life or AQEL).ti,ab.
52. (Functional Assessment of Chronic Illness Therapy Measurement System or FACIT).ti,ab.
53. (Functional Living Index Emesis or FLIE).ti,ab.
54. (Functional Living Index Cancer or FLIC). ti,ab.
55. (Palliative Care Assessment or PACA).ti,ab.
56. (Palliative Care Outcome Scale or POS).ti,ab.
57. (Quality of Life Cancer Scale or QOL-CA). ti,ab.
58. Quality of Life Questionnaire Core 30 Items. ti,ab.
59. (Functional Assessment of Cancer Therapy or FACT-G).ti,ab.
60. (Fact Kidney Symptom Index or FKSI).ti,ab.
61. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62. 7 and 61
63. 50 or 62
64. limit 63 to (humans and english language)

Search strategy for model parameters

This search strategy was translated and run in:

- Ovid MEDLINE(R)
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
- EMBASE – 1980 to 2007 Week 42

MEDLINE (Ovid) 1950 to October Week 2 2007

Searched 24 October 2007

1. exp models, economic/
2. markov chains/
3. exp models, statistical/
4. monte carlo method/
5. "Proportional Hazards Models"/
6. ((Prognosis or natural history or disease progress$or disease course) adj5 (model$or simulat$)).ti,ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. ((renal or kidney$) adj2 (cancer$or neoplasm$or carcinoma$or tumo?r$1)).ti,ab.
9. (renal cell carcinoma or renal cancer$).ti,ab.
10. Carcinoma, Renal Cell/
11. *Kidney Neoplasms/
12. 8 or 9 or 10 or 11
13. 7 and 12
14. limit 13 to (humans and english language and yr="1990 – 2007")

Appendix 2

Data extraction forms

Escudier et al. (2007)

DESIGN

Study design:
RCT + crossover

Country (countries):
European countries (UK, France, Germany, Poland, etc) and USA

Number of centres:
-

Recruitment dates:
November 2003 to March 2005

Length of follow-up:
The median follow-up was 6.6 months for both groups

Source of funding:
Supported by Bayer Pharmaceuticals and Onyx Pharmaceuticals

ARM(S)

ARM 1:
Sorafenib 400mg bid
Intervention: Sorafenib

n=451. Oral sorafenib 400 mg bid.

Doses were delayed or reduced if patients had clinically significant hematologic or other adverse events that were considered to be related to sorafenib, as measured with the use of version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute. In such cases, doses were reduced to 400 mg once daily and then to 400 mg every other day. If further reductions were required, patients were withdrawn from the trial. If adverse events resolved to a grade of 1 or less, the dose could be escalated to the previous level at the investigator's discretion.

ARM 2:
Placebo
Intervention: Placebo

n=452

PARTICIPANTS

Number enrolled:
903

Attrition / dropout:
Sorafenib: n=36. Of the 36, eighteen had adverse events, 7 withdrew consent, and
11 had other reasons. Placebo: n=38. Of the 38, seventeen had adverse events, 11 withdrew consent, and 10 had other reasons.

Inclusion criteria:
Eligible patients were at least 18 years of age and had histologically confirmed metastatic clear cell renal-cell carcinoma, which had progressed after one systemic treatment within the previous 8 months. Additional eligibility criteria were a performance status of 0 or 1 on the basis of Eastern Cooperative Oncology Group criteria; an intermediate-risk or low-risk status, according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score; a life expectancy of at least 12 weeks; adequate bone marrow, liver, pancreatic, and renal function; and a prothrombin time or partial-thromboplastin time of less than 1.5 times the upper limit of the normal range.

Exclusion criteria:
Patients with brain metastases or previous exposure to VEGF pathway inhibitors were excluded.

ANALYSIS

Primary outcome measure:
Overall survival

Secondary outcome measure(s):
Progression-free survival;
Best overall response rate;
Kidney cancer symptoms;
HRQOL.

Method of assessing outcomes:
Progression of disease was determined on the basis of findings on computed tomography (CT) or magnetic resonance imaging (MRI), clinical progression, or death, with the use of the Response Evaluation Criteria in Solid Tumors (RECIST). Investigators and independent radiologists who were unaware of the study-group assignments assessed progression-
free survival. Another secondary end point was the best overall response rate (on the basis of
RECIST) within the last 10 days of each drug cycle. Assessments of responses required confirmatory findings on CT or MRI 4 or more weeks after the initial determination of a response. Evaluations of tumor responses were performed within the last 10 days of each cycle. Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events (CTCAE).

1st analysis: performed in May 2005 immediately before crossover was allowed (18 months after the trial started)
2nd analysis: performed in Novermber 2005, after 216 of 452 patients receiving placebo had switched to sorafenib and after 367 deaths had occurred (6 months after the crossover was allowed).

Overall response was assessed at the January 2005 cutoff (13 months after the trial started).

Kidney cancer symptoms and HRQOL were assessed by patient self-administration of the Functional Assessment of Cancer Therapy-Kindney Symptom Index (FKSI) and the Functional Assessment of Cancer Therapy-Grneral (FACT-G), respectively, before seeing the physician.The range of values for the FKSI-10 is from 0 to 40. A low FKSI score reflets being more symptomatic; a higher score represents being less symptomatic. The range of the FACT-G physical well-bing (FACT-G PWB) is 0 to 28 based on a Likert scale of 0 to 4. Low scores represent impaired HRQOL; higher scores reflect better HRQOL.

ADDITIONAL NOTES ON STUDY DESIGN

METHODS:
From November 2003 to March 2005, 903 patients with renalcell carcinoma that was resistant to standard therapy were randomly assigned to receive either continuous
treatment with oral sorafenib (at a dose of 400 mg twice daily) or placebo; 451 patients received sorafenib and 452 received placebo. The

B.Escudier (2007)

DESIGN

Study design:
RCT

Country (countries):
18 countries

Number of centres:
-

Recruitment dates:
Between June 2004 and October 2005

Length of follow-up:
see notes

Source of funding:
This study was funded by F. Hoffmann-La Roche Ltd, who also funded medical writing support by Gardiner-Caldwell Communications.

ARM(S)

ARM 1:

Bevacizumab (10mg/kg/2wks) + IFN-a2a (9MIU x 3/wk)

Intervention: Bevacizumab + IFN-a2a

n=327

IFN-a2a subcutaneously for a maximum of 1 year at the standard dose of 9MIU three times a week plus bevacizumab 10mg/kg once every 2 weeks, intravenously until disease progression, unacceptable toxicity, or withdrawal of consent.

The protocol specified that IFN-a2a could be initiated at a lower dose than 9MIU as long as the recommended dose was reached within the first 2 weeks of treatment. During treatment, IFN-a2a administration was withheld with the development of a grade 3 adverse event attributable to IFN-a2a. If the event necessitating IFN-a2a being withheld resolved within the first 28 days, IFN-a2a was to be restarted at a dose of 6MIU (three times a week). The dose of IFN-a2a was further reduced to 3MIU (three times a week) with the development of a subsequent grade 3 adverse event due to an IFN-a2a-attributable toxicity. Concurrent bevacizumab was maintained at the standard dose without reduction, even if IFN-a2a was discontinued.

ARM 2:

IFN-a2a + Placebo

Intervention: IFN-a2a + Placebo

n= 322.

IFN-a2a subcutaneously for a maximum of 1 year at the standard dose of 9MIU three times a week plus placebo once every 2 weeks, intravenously until disease progression, unacceptable toxicity, or withdrawal of consent.

The protocol specified that IFN-a2a could be initiated at a lower dose than 9MIU as long as the recommended dose was reached within the first 2 weeks of treatment. During treatment, IFN-a2a administration was withheld with the development of a grade 3 adverse event attributable to IFN-a2a. If the event necessitating IFN-a2a being withheld resolved within the first 28 days, IFN-a2a was to be restarted at a dose of 6MIU (three times a week). The dose of IFN-a2a was further reduced to 3MIU (three times a week) with the development of a subsequent grade 3 adverse event due to an IFN-a2a-attributable toxicity. Concurrent bevacizumab was maintained at the standard dose without reduction, even if IFN-a2a was discontinued.

PARTICIPANTS

Number enrolled:
649

Attrition / dropout:
Withdrawn prior to progression: in group 1: (n=105) 32%; in group 2: (n=50) 16%.

Inclusion criteria:
Patients ≥18 years;
Confirmed metastatic RCC with >50% clear cell histology;
After total or partial nephrectomy (if resection margins clearly negative of disease);
Karnofsky performance status of ≥70%;
Measurable or non-measurable disease (according to RECIST).

Exclusion criteria:
Prior systemic treatment for metastatic RCC disease;
Evidence of current central nervous system (CNS) metastases or spinal cord compression;
Evidence of bleeding diathesis or coagulopathy;
Full therapeutic doses of oral or parenteral anticoagulants;
Recent major surgical procedures;
Uncontrolled hypertension on medication;
Clinically significant cardiovascular disease or chronic corticosteroid treatment.

ANALYSIS

Primary outcome measure:
Overall survival

Secondary outcome measure(s):
PFS, overall response rate and safety.

Method of assessing outcomes:
Tumour assessments were performed every 8 weeks until week 32 and every 12 weeks thereafter.

Tumour response was assessed according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria.

The effects of baseline demographic and prognostic patient characteristics on PFS were analysed using a Cox proportional hazards model.

ADDITIONAL NOTES ON STUDY DESIGN

Hudes et al. (2007)

DESIGN

Study design:
Randomised controlled trial

Country (countries):
United States; Western Europe, Australia, and Canada; or Asia-Pacific, Eastern Europe, Africa, and South America

Number of centres:
-

Recruitment dates:
July 2003 to April 2005

Length of follow-up:
?

Source of funding:
Supported by Wyeth Research

ARM(S)

ARM 1:
IFN-α 3 MU sc x 3/wk
Intervention: IFN-α
n=207 (3 MU with an increase to 18 mU, sc x 3/wk)

ARM 2:
Temsirolimus (25 mg iv weekly)
Intervention: Temsirolimus
n=209

ARM 3:
Temsirolimus 15mg iv/wk + IFN-α 6 MUx3/wk
Intervention: Temsirolimus + IFN-α
n=210.

PARTICIPANTS

Number enrolled:
626

Attrition / dropout:
A total of 19 patients were lost to follow-up (10 in the interferon group, 4 in the temsirolimus group, and 5 in the combination-therapy group)

Inclusion criteria:
Eligibility criteria included histologically confirmed advanced renal-cell carcinoma (stage IV or recurrent disease) and a Karnofsky performance score of 60 or more (on a scale of 0 to 100, with higher scores indicating better performance), with no previous systemic therapy. Additional eligibility criteria were a tumor that was measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST), and adequate bone marrow, renal, and hepatic functions, which were defined as a neutrophil count of at least 1500 cells per cubic millimeter, a platelet count of at least 100,000 cells per cubic millimeter, and a hemoglobin count of at least 8 g per deciliter; a serum creatinine level of no more than 1.5 times the upper limit of the normal range; an aspartate aminotranferase level of no more than 3 times the upper limit of the normal range (≤5 times if liver metastases were present); and a total bilirubin level of no more than 1.5 times the upper limit of the normal range. A fasting level of total cholesterol of no more than 350 mg per deciliter (9.1 mmol per liter) and a triglyceride level of no more than 400 mg per deciliter (4.5 mmol per liter) were required. Patients with a history of brain metastases were eligible if their condition was neurologically stable and they did not require corticosteroids after surgical resection or radiotherapy.

Exclusion criteria:
-

ANALYSIS

Primary outcome measure:
Overall survival

Secondary outcome measure(s):
Progression-free survival;
Objective response rate;
Clinical benefit rate.

Method of assessing outcomes:
Response to treatment was assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST).

Progression-free survival was determined by the site investigators' assessment and a blinded assessment of imaging studies (performed by Bio-Imaging Technologies).

The objective response rate, and the clinical benefit rate, were defined as the proportion of patients with stable disease for at least 24 weeks or an objective response.

The primary end point was calculated on an intention-to-treat basis. All patients who received any treatment were included in the analysis of safety.

ADDITIONAL NOTES ON STUDY DESIGN

Patients were randomly assigned in equal proportions, with the use of permuted blocks of three, to one of three treatment groups.

Duration of interferon treatment: median 8 (range 1-124)wks; in combination with Temsirolimus: median 12 (range 1-138)wks.
Duration of temsirolimus treatment: median 17 (range 1-126)wks; in combination with interferion alfa: median 15 (range 1-138)wks.

Patients with ≥1 dose reduction:
Interferion alfa: 78 (39%); in combination with temsirolimus: 99 (48%)
Temsirolimus: 48 (23%); in combination with interferion alfa: 59 (30%)

Treatment Summary:

Patients with ≥1 dose delay:
Interferion alfa: 78 (39%); in combination with temsirolimus: 99 (48%)
Temsiroliomus: 137 (66%); in combination with interferion alfa: 163 (82%)

Mean dose intensity (the total exposure per week of treatment):
Temsirolimus: 23.1 mg/wk; in combination with interferion afla: 13.9 mg/wk.
Interferon: 30.2 million U/wk; in combination with Temsirolimus: 13.1 million U/wk.

Motzer et al. (2006)

DESIGN

Study design:
Phase II trial (open-label, single-arm, multicenter clinical trial)

Country (countries):
USA

Number of centres:
-

Recruitment dates:
Between February and November 2004,

Length of follow-up:
18 months

Source of funding:
Research support for this trial was provided by Pfizer Inc.

ARM(S)

ARM 1:
Sunitinib 50 mg qd
Intervention: sunitinib

Repeated 6-week cycles of sunitinib, 50 mg per day given orally for 4 consecutive weeks followed by 2 weeks off per treatment cycle.

PARTICIPANTS

Number enrolled:
106

Attrition / dropout:
One patient enrolled with a diagnosis of clear-cell RCC was withdrawn from the study because a repeat biopsy after treatment was initiated resulted in a diagnosis of cancer different than clear-cell RCC. This patient is included in the safety analysis but excluded from efficacy analyses.

Inclusion criteria:
Eligibility criteria included provision of written informed consent; participant age of 18 years or older; prior nephrectomy; histological confirmation of clear-cell RCC with metastases; measurable disease; failure of 1 cytokine therapy (IL-2, interferon-alfa, or combination) due to disease progression (radiographic confirmation); Eastern Cooperative Oncology
Group (ECOG) performance status of 0 or 1; and adequate organ function (based on tests of hematologic, hepatic, renal, and cardiac function). Eligibility required prior cytokine therapy to be discontinued for at least 4 weeks before study entry.

Exclusion criteria:
Patients were excluded if they had brain metastases or significant cardiac events within the 12 months prior to study drug administration.

ANALYSIS

Primary outcome measure:
Overall objective response rate (complete plus partial)

Secondary outcome measure(s):
Duration of response;
Progression-free survival;
Overall survival;
Safety.

Method of assessing outcomes:
Overall objective response rate was defined as the proportion of patients with confirmed complete or partial responses. Clinical response (complete response, partial response, stable disease, and progressive disease) was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) using CT/MRI scans and bone scans (if bone metastases were present at baseline) after each cycle for the first 4 cycles and every other cycle thereafter until the end of treatment. The responses were assessed by treating physicians (investigator assessment) and also by a third-party core imaging laboratory where the scan images of all patients were read by 2 radiologists for each time point (independent third-party assessment).

Duration of response is defined as the time from first documentation of objective response to progressive disease or death due to any cause during the on-study period, with patients being censored on the last day of the on-study period if no progression or death has occurred.

The on-study period is defined as the time of first study dose until the last on-treatment tumor assessment or 28 days after last study drug, whichever is greater.

Progressionfree survival is defined as the time from the start of treatment to progressive disease or death due to any cause during the on-study period (whichever comes first), with censored observations handled as described previously.

Overall survival is the time from start of treatment to death due to any cause, or to last follow-up for patients who did not die.

Adverse events: severity graded was assessed according to National Cancer Institute Common Terminology Criteria for AdverseEvents [CTCAE,Version3.0]; ECOG performance status; and hematology and clinical chemistry profiles. All blood samples weresent toacentral laboratory for analysis. Cardiac function was assessed by electrocardiogram on day 28 of cycle 1 and as clinically indicated, and by multigated acquisition scan on day 28 of every even cycle until the end of treatment. According to the CTCAE, adverse events are assessed by severity and denoted as grade 1, mild;

Motzer et al. (2006)

DESIGN

Study design:
Phase II clinical trial

Country (countries):
USA

Number of centres:
-

Recruitment dates:
Between January and July 2003

Length of follow-up:
24+ months

Source of funding:
Supported by Pfizer Inc, La Jolla, CA.

ARM(S)

ARM 1:
Sunitinib 50mg-75mg qd (dose may reduce)

Intervention: Sunitinib

The starting dose of SU11248 was 50 mg per day administered in repeated
6-week cycles of daily therapy for 4 weeks, followed by 2 weeks off. SU11248 was self-administered orally once daily without regard to meals.
Intrapatient dose escalation by 12.5 mg/d (up to 75 mg/d) was permitted in the
absence of treatment-related toxicity. Dose reduction for toxicity was allowed
to 37.5 mg/d and then to 25 mg/d, according to a nomogram for grade 3 to
4 severity.

PARTICIPANTS

Number enrolled:
63

Attrition / dropout:
0

Inclusion criteria:
Eligibility criteria included informed consent, histologic confirmation of RCC, measurable disease with evidence of metastases, failure of one cytokine (IFN-α, IL-2) -based therapy because of disease progression or unacceptable toxicity, Eastern Cooperative Oncology Group performance status of 0 or 1, normal serum amylase and lipase, a normal adrenocorticotropic hormone stimulation test, and adequate hematologic, hepatic, renal, and cardiac function. The latter was determined as a normal left ventricular ejection fraction by echocardiogram or multigated acquisition (MUGA) scan.

Exclusion criteria:
Patients were excluded for the presence of brain metastases or ongoing cardiac dysrhythmia, prolongation of QTc interval, or any significant cardiac event within the previous 12 months.

ANALYSIS

Primary outcome measure:
Overall response rate

Secondary outcome measure(s):
Time to progression;
Safety.

Method of assessing outcomes:
Objective clinical response rate (complete response or partial response) was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) using computed tomography or magnetic resonance imaging scan and bone scan (if bone metastases were present at baseline) after cycles 1, 2, and 4, and every two cycles thereafter until the end of treatment. CBC, cardiac enzymes, and biochemical profiles were obtained throughout the study. Cardiac function was assessed by ECG and echocardiogram or MUGA scan on day 28 of each treatment cycle. Quality of life was assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-Fatigue) and the EuroQoL EQ-5D instrument (EQ-5D). Patients completed the FACIT-Fatigue questionnaire before receiving SU11248 on day 1 (as the baseline assessment) and weekly for cycles 1 through 4 and the EQ-5D on days 1 and 28 of each cycle.

Response was assessed by investigators according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria and severity of adverse events according to the National Cancer Institute Common Toxicity Criteria version 2.0.

ADDITIONAL NOTES ON STUDY DESIGN

SU11248 treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Individual patients continued SU11248 treatment after progression if the investigator felt that the patient continued to derive clinical benefit. However, for purposes of analysis, the patient was considered to have met the study end point of disease progression.

CHARACTERISTICS OF PARTICIPANTS

	Sunitinib 50mg-75mg qd (dose may reduce)			
Characteristic	**N**	**k**	**Mean**	**SD**
Age (median, yrs)	63	-	6	-
ECOG performance status = 0	63	-	34	-
ECOG performance status = 1	63	-	29	-
Histology: clear cell	63	55	-	-
Histology: palillary	63	4	-	-
Histology: sarcomatoid varant (not otherwise specified)	63	1	-	-
Histology: unspecified	63	3	-	-
Male	63	43	-	-
Mean FACIT-Fatigue scale score	62	-	40.4	-
Mean health state visual analog scale scores	60	-	77.1	-
Median FACIT-Fatigue scale score	62	-	44	-
Median health state visual analog scale scores	60	-	8	-

Motzer (2007)

DESIGN

Study design:
Randomised controlled trial

Country (countries):
Australia, Brazil, Canada, Europe, and the United States

Number of centres:
-

Recruitment dates:
Between August 2004 and October 2005

Length of follow-up:
see notes

Source of funding:
Supported by Pfizer

ARM(S)

ARM 1:
sunitinib 50mg qd
Intervention: sunitinib

n=375 (sunitinib 50 mg orally once daily for 4 weeks, followed by 2 weeks
without treatment)

ARM 2:
IFN-α 9 MU sc x 3/week
Intervention: IFN-α

n=375 (IFN at 9 MU subcutaneously three times weekly)

PARTICIPANTS

Number enrolled:
750

Attrition / dropout:
-

Inclusion criteria:
1). ≥18 years of age;
2). Had metastatic renal-cell carcinoma with a clear-cell histologic component, confirmed by the participating centers;
3). Had not received previous treatment with systemic therapy for renal-cell carcinoma;
4). The presence of measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
5). Adequate hematologic, coagulation, hepatic, renal, and cardiac function.

Exclusion criteria:
Patients were ineligible if they had brain metastases, uncontrolled hypertension, or clinically significant cardiovascular events or disease during the preceding 12 months.

ANALYSIS

Primary outcome measure:
progression-free survival

Secondary outcome measure(s):
Objective response rate, overall survival, patient-reported outcomes, and safety.

Method of assessing outcomes:
Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), with the use of imaging studies at baseline, at day 28 of cycles 1 through 4, and every two cycles thereafter until the end of treatment. Such assessments were also used to confirm a response (at least 4 weeks after initial documentation) and whenever disease progression was suspected. The response was assessed by an independent third-party radiology group (independent central review), and by treating physicians (investigators' assessments). The third-party radiologists were unaware of assignments to study groups.

Median progression-free survival time was assessed by central review of imaging studies.

Safety was assessed at regular intervals by documentation of adverse events, physical examination, radiography, and multigated acquisition scanning.

Laboratory assessments (hematologic and serum chemical measurements) were performed throughout the study by a central laboratory.

Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0.

Health-related quality of life was assessed with the use of the Functional Assessment of Cancer Therapy — General (FACT-G) and FACT– Kidney Symptom Index (FKSI) questionnaires, which were administered before randomization, on days 1 and 28 of each cycle, and at the end of treatment.

ADDITIONAL NOTES ON STUDY DESIGN

METHODS:
Randomization was stratified according to baseline levels of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), ECOG performance status (0 vs. 1), and previous nephrectomy (yes vs. no). Patients were randomly assigned in a 1:1 ratio to receive either sunitinib or interferon alfa. Random permuted blocks of four
were used to attain balance within strata. It was estimated that 690 patients would be needed to enroll to observe 471 events.

FOLLOW-UP LENGTH:
At the time of analysis, the median duration of treatment was 6 months (range, 1 to 15) in the sunitinib group and 4 months (range, 1 to 13) in the interferon alfa group. Treatment was ongoing among 248 patients in the sunitinib group (66%) and 126 patients in the interferon alfa group (34%). Treatment in both groups was continued until the occurrence of disease progression, unacceptable adverse events, or withdrawal of consent. [Reasons for discontinuing treatment were progressive disease (in 25% of the patients in the sunitinib group and 45% in the interferon alfa group, P<0.001), adverse events (8% and 13%, respectively; P = 0.05), withdrawal of consent (1% and 8%, respectively; P<0.001), and protocol violation (<1% in each group).]

Ratain et al. (2006)

DESIGN

Study design:
Randomised discontinuation (or withdrawal) trial (RDT))

Country (countries):
USA and UK

Number of centres:
-

Recruitment dates:
September 25, 2002. (This report includes efficacy data up to December 31, 2004)
September 25, 2002

Length of follow-up:
12wks (run-in)+12wks (sorafenib or pb)

Source of funding:
Supported by Bayer Pharmaceuticals
Supported by Bayer Pharmaceuticals Corporation and Onyx Pharmaceuticals

ARM(S)

ARM 1:
Sorafenib 400mg bid (may reduce or delay)
Intervention: Sorafenib

n=32

Run-in: 400mg bid. Doses of sorafenib were delayed or reduced if clinically significant toxicities considered related to sorafenib occurred.

Patients who had a change in tumor size of less than25% and were randomly assigned to either sorafenib: at current dose.

After randomisation patients whose disease progressed while on sorafenib discontinued treatment.

ARM 2:
Placebo
Intervention: Placebo

n = 33. After randomisation patients whose disease progressed while on placebo were offered sorafenib.

Patients whose disease progressed while on placebo were offered sorafenib.

PARTICIPANTS

Number enrolled:
202

Attrition / dropout:
The 12-week run-in was completed by 187 patients (93%). Of the 15 patients who discontinued treatment before the 12-week assessment, the majority (12 patients) did so because of adverse events; one patient withdrew consent, one patient was lost to follow-up, and one patient died (as a result of pneumonia and metastatic disease, unrelated to the study drug).Of the 69 patients identified at 12 weeks were eligible for entry onto the randomized phase, two patients continued on open-label sorafenib (investigator protocol violation), and three patients withdrew (one patient each due to adverse events, to pursue other treatment options, and for clinical progression before random assignment). One patient who met the study criteria for progressive disease at week 12 was randomly assigned instead of discontinuing treatment. Therefore, a total of 65 patients were randomly assigned to receive sorafenib (32 patients) or placebo (33 patients). Seventy-three patients with tumor shrinkage of at least 25% at the 12-week assessment entered into the open-label part of the trial, plus six additional patientswhocontinued sorafenib, either at the discretion of the investigator or after being granted a waiver, despite having SD (n_3) or PD (n_2), or not receiving treatment for the entire run-in (n_1). Therefore, a total of 79 patients continued open-label sorafenib. Forty-three patients, who completed the 12-week run-in, discontinued treatment at a later time point; 40 patients because of PD, and three patients who had SD (and withdrew from the study).

Inclusion criteria:
Patients with histologically or cytologically confirmed metastatic refractory cancer;
Patient age of at least 18 years;
At least one measurable tumor;
Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
Life expectancy of at least 12 weeks;
Adequate bone marrow, liver, and renal function.

There was no limit on the extent of prior therapy, except for the exclusion of patients with previous exposure to a Ras pathway inhibitor.

Exclusion criteria:
Patients with other serious medical problems or CNS involvement were excluded.

ANALYSIS

Primary outcome measure:
patients remaining progression free
remaining progression free

Secondary outcome measure(s):
Progression-free survival (PFS) after random assignment (randomized subset only);

Overall PFS (from start of treatment);

Tumor response rate;

Safety.

Method of assessing outcomes:
The primary end point was the percentage of randomly assigned patients remaining progression free at 12 weeks following random assignment (24 weeks after study entry).

Secondary end points included progression-free survival (PFS) after random assignment (randomized subset only); overall PFS (from start of treatment); tumor response rate; and safety.

Tumor response was assessed at 12 weeks, and once every 6 weeks thereafter, in accordance with modified WHO guidelines for partial response (PR), stable disease (SD), and progressive disease (PD). Objective responses were confirmed at least 4 weeks after the original documentation. In order to verify investigator observations in an unbiased manner, independent assessment of radiologic scans was performed retrospectively for 152 (75%) of 202 patients. Some scans were not available for independent assessment, as a radiology charter specifying parameters for independent review was developed after the last patient was accrued. These independent radiographic assessments were performed by RadPharm (Princeton, NJ).

Safety was assessed for the entire treatment period (run-in plus randomization). All patients who received at least one dose of the study drug and who had post-treatment data available were assessable for safety. Safety assessments were performed every 3 weeks during the run-in and randomization phases, and once every 4 weeks thereafter. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0), and their relationship to the study drug was recorded.

ADDITIONAL NOTES ON STUDY DESIGN

Patients initially received oral sorafenib 400 mg twice daily during the initial run-in period for 12 weeks. Doses of sorafenib were delayed or reduced if clinically significant toxicities considered related to sorafenib occurred. Then:

1. Patients with≥ 25% tumor shrinkage continued open-label sorafenib, until disease progression or toxicity, in order to avoid concerns about

Rini et al. (2004)

DESIGN

Study design:
Randomised controlled trial

Country (countries):
Canada

Number of centres:
-

Recruitment dates:
NR

Length of follow-up:
NR

Source of funding:
supported by national cancer institutes

ARM(S)

ARM 1:
IFN: 9 MU tiw
Intervention: IFN-α
n=? (NR)

ARM 2:
IFN 9 MU tiw + bevacizumab 10mg/kg i.v./2 weeks
Intervention: IFN-α + bevacizumab
n=? (NR)

PARTICIPANTS

Number enrolled:
732

Attrition / dropout:
Not reported

Inclusion criteria:
Untreated metastatic/unresectable RCC with a clear cell component.

Exclusion criteria:
No prior systemic therapy of any kind is permitted. Patients with central nervous system metastases, vascular disease, blood pressure >160/90, or a history of thrombosis within 1 year or ongoing anticoagulation are excluded.

ANALYSIS

Primary outcome measure:
overall survival

Secondary outcome measure(s):
progression-free survival; objective response rate; toxicity.

Method of assessing outcomes:
NR

ADDITIONAL NOTES ON STUDY DESIGN

Patients are stratified by nephrectomy status and established prognostic factors to insure balanced randomization. The trial was designed with 86% power to detect a 30% decrease in hazard rate assuming a two-sided significance level of 0.05. The primary end point of the trial is overall survival, and the study is designed to detect an improvement in median survival from 13 months for IFN-α alone to 17 months for the combination, representing a hazard ratio of 1.3. Seven hundred patients will be enrolled over 3 years with a two-sided significance level of 0.05 and a power of 89%.

CHARACTERISTICS OF PARTICIPANTS

Data from the ASCO abatract: 85% of patietns had prior nephrectomy; 26% of patients had good risk, 64% intermediate risk and 10% poor risk disease.

RESULTS

	IFN: 9 MU tiw				IFN 9 MU tiw + bevacizumab 10mg/kg i.v./2 weeks				Comparison		
Outcome	**N**	**k**	**Mean**	**SD**	**N**	**k**	**Mean**	**SD**	**Est**	**SEM**	**P**
Median PFS (months)	-	-	5.2[c]	-	-	-	8.5[d]	-	0.71	-	< 0.0001[a]
Objective response rate	-	-	-	-	-	-	-	-	-	-	≤ 0.0001
Objective response rate	-	-	13.1[e]	-	-	-	25.5[b]	-	-	-	-
GRADE 3 ANOREXIA											
Overall toxicity	-	0	8	-	-	0	17	-	-	-	-
GRADE 3 HYPERTENSION											
Overall toxicity	-	-		-	-	-	9	-	-	-	-
GRADE 3 PROTEINURIA											
Overall toxicity	-	0		-	-	0	13	-	-	-	-
GTADE 3 FATIGUE											
Overall toxicity	-	0	28	-	-	0	35	-	-	-	-

Notes
[a] *95% CI: 0.61 to 0.83*
[b] *95% CI: 20.9 to 30.6*
[c] *95% CI: 3.1 to 5.6*
[d] *95% CI: 7.5 to 9.7*
[e] *95% CI: 9.5 to 17.3*

Outcome data were from the ASCO abstract.

Appendix 3

Method of indirect comparison

According to this method it is possible to simultaneously compare three treatments A, B and C when data are available from direct comparisons of treatments A and B (from trial X) and treatments A and C (from trial Y), providing the baseline population characteristics of the patients in the two trials are similar. Denoting *HRBAPFS* as the hazard ratio for PFS between treatments A and B from trial X, and *HRCAPFS* as the hazard ratio for PFS between treatments A and C from trial Y, the indirect comparison of hazard ratios for PFS between treatments B and C, *HRBCPFS*, is given as:

$$HR_{BC}^{PFS} = HR_{BA}^{PFS}/HR_{CA}^{PFS} \text{ or}$$
$$\ln(HR_{BC}^{PFS}) = \ln(HR_{BA}^{PFS}) - (HR_{CA}^{PFS})$$

A similar equation can be given for OS.

The SE of ln(*HR*) between treatments B and C for PFS is then given as:

$$SE[\ln(HR_{BC}^{PFS})] = \sqrt{\{SE[\ln(HR_{BA}^{PFS})]\}^2 + SE\{[\ln(HR_{CA}^{PFS})]\}^2}$$

A similar equation can be given for OS.

Although this method is able to partially account for baseline risk and other prognostic factors of participants in the individual trials the results may not be as robust or reliable as those obtained from a direct head-to-head comparison in a randomised clinical trial and should thus be interpreted with caution.[83,151,152]

Appendix 4

Table of excluded studies with rationale

TABLE 54 *Table of excluded studies with rationale*

Papers excluded	Reason for exclusion
Amato 2005[153]	Not a relevant intervention
BlueCross BlueShield Association 2006[67]	Not a relevant intervention
Atkins *et al*. 2004[154]	Not a relevant intervention
Choueiri *et al*. 2007[155]	Results mixed for different interventions
Chouhan *et al*. 2007[156]	Not a clinical trial or systematic review
Escudier 2007[157]	Not a clinical trial or systematic review
Escudier *et al*. 2007[158]	Not a relevant intervention
George 2007[159]	Not a clinical trial or systematic review
Gore and Escudier 2006[160]	Not a clinical trial or systematic review
Hughes *et al*. 2006[73]	No relevant comparison
Jain *et al*. 2006[161]	Not a clinical trial or systematic review
Kane *et al*. 2006[162]	Not a clinical trial or systematic review
Lamuraglia *et al*. 2006[163]	Not a clinical trial or systematic review
Lara *et al*. 2003[164]	Not a relevant intervention
Le Tourneau *et al*. 2007[66]	Not a clinical trial or systematic review
Mancuso and Sternberg 2006[165]	Not a clinical trial or systematic review
Margolin *et al*. 2007[166]	Not a clinical trial or systematic review
McKeage and Wagstaff 2007[71]	Not a clinical trial or systematic review
Medioni *et al*. 2007[167]	Not a clinical trial or systematic review
Montorsi 2007[168]	Not a clinical trial or systematic review
Motzer and Russo 2000[36]	Not a relevant intervention
Motzer and Bukowski 2006[169]	Not a clinical trial or systematic review
Motzer *et al*. 2006[170]	Not a clinical trial or systematic review
Motzer *et al*. 2006[111]	No relevant comparison
Motzer *et al*. 2006[112]	Not an RCT or controlled clinical trial
Patard *et al*. 2007[171]	Not a clinical trial or systematic review
Patel *et al*. 2007[172]	Not a clinical trial or systematic review
Peralba *et al*. 2003[173]	Not a clinical trial or systematic review
Quan 2006[174]	Not a clinical trial or systematic review
Raymond *et al*. 2004[175]	Not an RCT or controlled clinical trial
Rini and Small 2005[176]	Not a clinical trial or systematic review
Rini *et al*. 2004[177]	Not a clinical trial or systematic review
Rini 2005[178]	Not a clinical trial or systematic review
Rini 2005[64]	Not a clinical trial or systematic review

continued

TABLE 54 *Table of excluded studies with rationale (continued)*

Papers excluded	Reason for exclusion
Rini and Campbell 2007[179]	Not a relevant intervention
Rini *et al*. 2006[180]	Not an RCT or controlled clinical trial
Rodriguez and Sexton 2006[181]	Not an RCT or controlled clinical trial
Ryan *et al*. 2007[182]	Not an RCT or controlled clinical trial
Schoffski *et al*. 2006[62]	Not a clinical trial or systematic review
Schrader *et al*. 2006[183]	Not a clinical trial or systematic review
Shih and Lindley 2006[65]	No relevant comparison
Skolarikos *et al*. 2007[184]	No relevant outcomes
Strumberg *et al*. 2007[185]	No relevant comparison
Yang *et al*. 2003[186]	Not a relevant intervention
Yang *et al*. 2004[187]	Not a relevant intervention

Appendix 5

Review of clinical effectiveness – supplementary tables

TABLE 55 *Study characteristics: bevacizumab plus IFN versus sunitinib versus IFN as first-line therapy*

	Escudier *et al.* 2007[106]	**Motzer *et al.* 2007**[107]	**Rini *et al.* 2008**[101]
Participants	***Inclusion criteria:*** Age ≥ 18 years Confirmed RCC with > 50% clear cell histology Total or partial nephrectomy (if resection margins clearly negative of disease) Karnofsky performance status of ≥ 70% Measurable or non-measurable disease (according to RECIST criteria) Normal hepatic, haematopoietic and renal function ***Exclusion criteria:*** Previous systemic treatment for metastatic RCC disease Evidence of brain metastases Ongoing full dose oral or parenteral anticoagulant or antiplatelet aggregation treatment Recent major surgical procedures Uncontrolled hypertension on medication Clinically significant cardiovascular disease Chronic corticosteroid treatment	***Inclusion criteria:*** Age ≥ 18 years Metastatic RCC with a clear cell histological component, confirmed by the participating centres The presence of measurable disease An ECOG-PS of 0 or 1 Adequate haematological, coagulation, hepatic, renal and cardiac function ***Exclusion criteria:*** Previous systemic treatment for metastatic RCC disease Evidence of brain metastases Evidence of uncontrolled hypertension or clinically significant cardiovascular events or disease during the preceding 12 months	***Inclusion criteria:*** Metastatic clear cell RCC No further details available ***Exclusion criteria:*** Previous systemic treatment for metastatic RCC disease Evidence of central nervous system metastases Evidence of vascular disease, blood pressure above 160/90 mmHg or a history of thrombosis within 1 year Ongoing treatment with anticoagulant therapy
Interventions	**Bevacizumab or placebo:** bevacizumab 10 mg/kg body weight intravenously every 2 weeks **IFN:** IFN-α-2a 9 MIU subcutaneously three times per week for a maximum of 52 weeks No dose reductions of bevacizumab/placebo allowed IFN dose could be reduced to 6 MIU or 3 MIU to manage grade 3 and above adverse events if necessary All treatment stopped on evidence of disease progression, unacceptable toxicity or withdrawal of consent Other antineoplastic therapies were allowed subsequent to progression or toxicity	**Sunitinib:** 50 mg orally once daily for 4 weeks followed by 2 weeks without treatment **IFN:** 9 MIU subcutaneously three times per week. A reduced dose of 3 MIU was administered in the first week and 6 MIU in the second week, with the full dose of 9 MIU thereafter Dose reductions to 37.5 mg and then to 25 mg daily of sunitinib and to 6 MIU and then to 3 MIU three times per week of IFN were allowed for the management of severe adverse events All treatment stopped on evidence of disease progression, unacceptable adverse events or withdrawal of consent	**Bevacizumab:** bevacizumab 10 mg/kg body weight intravenously every 2 weeks **IFN:** IFN-α-2a 9 MIU subcutaneously three times per week

	Escudier *et al.* 2007[106]	**Motzer *et al.* 2007**[107]	**Rini *et al.* 2008**[101]
Study objectives	To determine whether first-line bevacizumab plus IFN improves efficacy compared with IFN alone	To evaluate the efficacy of sunitinib compared with IFN-α	To investigate the addition of bevacizumab to initial IFN therapy
Outcomes	**Primary:** OS **Secondary:** PFS, overall response rate (according to RECIST) and safety	**Primary:** PFS, defined as the time from randomisation to the first documentation of objective disease progression or to death from any cause, whichever occurred first **Secondary:** objective tumour response rate (according to RECIST), OS, patient-reported outcomes and safety	**Primary:** OS **Secondary:** PFS (defined from the date of randomisation to the date of progression according to RECIST criteria or death due to any cause), overall response and safety
Analysis	Efficacy was assessed by ITT analysis. For the safety analysis, patients were assigned to treatment groups on the basis of treatment received, with patients in the placebo arm receiving one or more doses of bevacizumab being assigned to the bevacizumab arm The study was designed to have 80% power for the log-rank test to detect an improvement in OS with an HR of 0.76, assuming an improvement in median survival from 13 months to 17 months, at a two-sided alpha level of 0.05 One interim analysis was planned based on 250 deaths after which the study was unblinded and patients in the IFN arm who had not progressed were offered bevacizumab plus IFN Results of the interim analysis are presented in this paper and represent an interim analysis of OS and a final analysis of PFS Patients without an event were censored on the day of the last follow-up assessment or on the last day of study drug administration if no follow-up assessment was carried out	Efficacy (primary end point) was assessed by ITT analysis. A blinded central review of radiological images was used to assess the primary end point and the objective response rate. Safety analyses were performed on the basis of the treatment actually received The study was designed to have 90% power for the log-rank test to detect a clinically relevant increase in PFS from 4.7 to 6.2 months in patients treated with sunitinib, at a two-sided alpha level of 0.05 Three scheduled interim analyses were planned; this paper provides the results of the second analysis, after which the study was unblinded and patients in the IFN group with PD were allowed to cross over into the sunitinib group	The study was designed with 86% power to detect a 30% decrease in hazard rate assuming a two-sided significance level of 0.05

TABLE 56 *Summary of adverse events (any grade): bevacizumab plus IFN versus sunitinib versus IFN as first-line therapy*

	Escudier et *al*. 2007[106a]		Motzer et *al*. 2007[107b]	
Intervention	**Bevacizumab + IFN**	**IFN + placebo**	**Sunitinib**	**IFN**
n	337	304	375	375
	% *of patients*			
Diarrhoea	20	15	53	12
Fatigue	33	27	51	51
Nausea			44	33
Stomatitis			25	2
Vomiting			24	10
Hypertension	26	9	24	1
Hand–foot syndrome			20	1
Mucosal inflammation			20	1
Rash			19	6
Asthenia	32	28	17	20
Dry skin			16	5
Skin discoloration			16	0
Changes in hair colour			14	1
Epistaxis			12	1
Pain in a limb			11	3
Headache	23	16	11	14
Dry mouth			11	6
Decline in ejection fraction			10	3
Pyrexia	45	43	7	34
Chills			6	29
Myalgia			5	16
Influenza-like illness	24	25	1	7
Dyspnoea	13	13		
Bleeding	33	9		
Anorexia	36	30		
Depression	12	10		
Leukopenia			78	56
Neutropenia	7	7	72	46
Anaemia	10	13	71	64
Increased creatinine			66	49
Thrombocytopenia	6	4	65	21
Lymphopenia			60	63
Increased lipase			52	42
Increased aspartate aminotransferase			52	34
Increased alanine aminotransferase			46	39

TABLE 56 *Summary of adverse events (any grade): bevacizumab plus IFN versus sunitinib versus IFN as first-line therapy (continued)*

	Escudier *et al.* 2007[106a]		Motzer *et al.* 2007[107b]	
Intervention	**Bevacizumab + IFN**	**IFN + placebo**	**Sunitinib**	**IFN**
Increased alkaline phosphatase			42	35
Increased uric acid			41	31
Hypophosphataemia			36	32
Increased amylase			32	28
Increased total bilirubin			19	2
Proteinuria	18	3		
Venous thromboembolic event	3	< 1		
Treatment discontinuation due to an adverse event	28	12	8	13
Deaths due to an adverse event	2	2		

a Adverse events and laboratory abnormalities that occurred with a frequency of 2% or more.
b Adverse events and selected laboratory abnormalities that occurred in at least 10% of patients in the sunitinib group.

TABLE 57 *Adverse events leading to discontinuation of study medication: bevacizumab plus IFN versus IFN as first-line therapy*

	Escudier *et al.* 2007[107]	
Intervention	**Bevacizumab + IFN**	**IFN + placebo**
n	337	304
	No. of patients (%)	**No of patients (%)**
General disorders	31 (9)	13 (4)
Renal and urinary disorders	16 (5)	3 (< 1)
Gastrointestinal disorders	13 (4)	4 (1)
Nervous system disorders	9 (3)	6 (2)
Infections	8 (2)	3 (< 1)
Psychiatric disorders	5 (1)	6 (2)
Blood and lymphatic system disorders	6 (2)	3 (< 1)
Metabolic and nutritional disorders	5 (1)	3 (< 1)
Vascular disorders	7 (2)	1 (< 1)

TABLE 58 *Study characteristics: temsirolimus versus IFN as first-line therapy in patients with poor prognosis*

	Hudes et *al*. 2007[108]
Participants	***Inclusion criteria:*** Histologically confirmed advanced RCC (stage IV or recurrent disease) A Karnofsky performance score of ≥ 60 At least three of the following six poor prognostic factors: a serum lactate dehydrogenase level of more than 1.5 times the upper limit of the normal range; a haemoglobin level below the lower limit of the normal range; a corrected calcium level of more than 10 mg/dl; a time from initial diagnosis of RCC to randomisation of less than 1 year; a Karnofsky score of 60 or 70; or metastases in multiple organs Measurable disease (according to RECIST criteria) Adequate bone marrow, renal and hepatic functions ***Exclusion criteria:*** Previous systemic therapy Evidence of brain metastases unless neurologically stable and not requiring corticosteroids after surgical resection or radiotherapy
Interventions	**Temsirolimus:** 25 mg intravenously weekly **IFN:** IFN- α-2a 18 MIU subcutaneously three times per week **Temsirolimus plus IFN:** Temsirolimus 15 mg intravenously weekly plus IFN- α-2a at a starting dose of 3 MIU subcutaneously three times per week rising to 6 MIU subcutaneously three times per week Dose reduction without treatment interruption was permitted at the discretion of the treating physician to manage grade 2 adverse events. Treatment was withheld for grade 3 or 4 adverse events and restarted at a reduced dose after recovery to grade 2 or lower. For the combination therapy group, one or both agents were withheld, depending on the adverse event Patients who received temsirolimus received premedication with 25–50 mg of intravenous diphenhydramine or a similar H1 blocker 30 minutes before each weekly infusion as prophylaxis against an allergic reaction Patients in the IFN group who were unable to tolerate 9 MIU or 18 MIU received the highest tolerable dose, which could be 3 MIU, 4.5 MIU or 6 MIU All treatment stopped on evidence of disease progression, symptomatic deterioration or intolerable adverse events
Study objectives	To compare temsirolimus and temsirolimus plus IFN with IFN alone in metastatic RCC
Outcomes	**Primary:** OS **Secondary:** PFS, objective response rate, clinical benefit rate and adverse events
Analysis	Efficacy (OS) was calculated on an ITT basis. No information is provided on the method of analysis of secondary end points All patients who received any treatment were included in the safety analysis The study (200 patients per group) was designed to have 80% power to detect an improvement in OS of 40% for each comparison with the use of a two-sided stratified log-rank test at an overall 2.5% level of significance Two interim analyses were planned after approximately 164 and 430 deaths and a final analysis, if necessary, after a total of 504 deaths had occurred; this paper provides the results of the second analysis (after 446 patients had died)

TABLE 59 *Proportion of patients (%) reporting adverse events (all grades): temsirolimus versus IFN as first-line therapy in patients with poor prognosis*

	Hudes *et al.* 2007[108]		
Intervention	**Temsirolimus**	**IFN**	**Temsirolimus + IFN**
n	208	200	208
Asthenia	51	64	62
Rash	47	6	21
Anaemia	45	42	61
Nausea	37	41	40
Anorexia	32	44	38
Pain	28	16	20
Dyspnoea	28	24	26
Hyperlipidaemia	27	14	38
Infection	27	14	34
Diarrhoea	27	20	27
Peripheral oedema	27	8	16
Hyperglycaemia	26	11	17
Cough	26	14	23
Hypercholesterolaemia	24	4	26
Fever	24	50	60
Abdominal pain	21	17	17
Stomatitis	20	4	21
Constipation	20	18	19
Back pain	20	14	15
Vomiting	19	28	30
Weight loss	19	25	32
Headache	15	15	22
Increased creatinine level	14	10	20
Thrombocytopenia	14	8	38
Chills	8	30	34
Increased aspartate aminotransferase level	8	14	21
Neutropenia	7	12	27
Leukopenia	6	17	31

Listed are all-grade adverse events occurring in at least 20% of patients. The analysis did not include patients who underwent randomisation but received no treatment: seven in the IFN group, one in the temsirolimus group and two in the combination therapy group.

TABLE 60 *Study characteristics: sorafenib versus sunitinib versus BSC as second-line therapy*

	Escudier et *al*. 2007[109]	**Ratain et *al*. 2006[110]**	**Motzer et *al*. 2006[111]**	**Motzer et *al*. 2006[112]**
Participants	***Inclusion criteria:*** Age ≥ 18 years Histologically confirmed metastatic clear cell RCC Evidence of progression after one systemic treatment within the previous 8 months An ECOG-PS of 0 or 1 MSKCC risk status of low or intermediate Life expectancy of at least 12 weeks Adequate bone marrow, liver, pancreatic and renal function ***Exclusion criteria:*** Evidence of brain metastases Previous exposure to VEGF pathway inhibitors	***Inclusion criteria:*** Age ≥ 18 years Histologically or cytologically confirmed metastatic refractory cancer At least one measurable tumour An ECOG-PS of 0 or 1 Life expectancy of at least 12 weeks Adequate bone marrow, liver and renal function ***Exclusion criteria:*** Evidence of central nervous system involvement Other serious medical problems Previous use of a Ras inhibitor	***Inclusion criteria:*** Age ≥ 18 years Histologically confirmed metastatic clear cell RCC Previous nephrectomy Measurable disease Failure of one previous cytokine-based therapy because of disease progression An ECOG-PS of 0 or 1 Adequate organ function ***Exclusion criteria:*** Evidence of brain metastases Evidence of significant cardiac events within the previous 12 months	***Inclusion criteria:*** Histologically confirmed metastatic RCC Measurable disease Failure of one cytokine-based therapy because of disease progression or unacceptable toxicity An ECOG-PS of 0 or 1 Normal serum amylase and lipase A normal adrenocorticotropic hormone stimulation test Adequate haematological, hepatic, renal and cardiac function ***Exclusion criteria:*** Evidence of brain metastases Evidence of cardiac dysrhythmia, prolongation of QTc interval or any significant cardiac event within the previous 12 months
Interventions	**Sorafenib:** 400 mg (or placebo) orally twice daily Dose reductions to 400 mg once daily and then 400 mg every other day were permitted to manage adverse events All treatment stopped on evidence of disease progression or withdrawal from the study as a result of adverse events or death	*Run in period:* **Sorafenib:** 400 mg orally twice daily Dose reductions/interruptions were permitted to manage adverse events *Randomisation period:* Patients with a reduction in tumour size of less than 25% were randomly assigned to either sorafenib at current dose or matching placebo Patients with a reduction in tumour size of more than 25% continued to receive sorafenib (current dose) Patients with disease progression discontinued treatment During the randomisation period patients whose disease progressed while on placebo were offered sorafenib	**Sunitinib:** 50 mg orally once a day in repeated 6-week cycles (4 consecutive weeks of treatment followed by 2 weeks off treatment) Dose reduction for toxicity was allowed (to 37.5 mg/day and then to 25 mg/day) to manage adverse events All treatment stopped on evidence of disease progression, unacceptable toxicity or withdrawal of consent	**Sunitinib:** 50 mg orally once a day in repeated 6-week cycles (4 consecutive weeks of treatment followed by 2 weeks off treatment) Dose escalation by 12.5 mg/day (up to 75 mg/day) was permitted in the absence of treatment-related toxicity Dose reduction was allowed (to 37.5 mg/day and then to 25 mg/day) to manage adverse events All treatment was stopped on evidence of disease progression, unacceptable toxicity or withdrawal of consent

	Escudier *et al*. 2007[109]	**Ratain *et al*. 2006**[110]	**Motzer *et al*. 2006**[111]	**Motzer *et al*. 2006**[112]
Study objectives	To determine the effects of sorafenib on PFS and OS in patients with advanced clear cell RCC in whom one previous systemic therapy had failed	To evaluate the effects of sorafenib on tumour growth in patients with metastatic RCC	To confirm the antitumour efficacy of sunitinib as second-line treatment in patients with metastatic clear cell RCC	To assess the clinical efficacy and safety of sunitinib in patients with cytokine-refractory metastatic RCC
Outcomes	**Primary:** OS Secondary: PFS, best overall response rate (according to RECIST criteria)	**Primary:** the percentage of randomly assigned patients remaining progression free at 12 weeks following randomisation **Secondary:** PFS after random assignment (randomised subset only), overall PFS (from start of treatment), tumour response rate and safety	**Primary:** overall objective response rate (assessed according to RECIST) **Secondary:** duration of response, PFS, OS and safety	**Primary:** objective tumour response rate (according to RECIST) **Secondary:** time to progression and safety
Analysis	Efficacy (OS) was assessed by ITT analysis No details on how patients were censored for analysis of OS are provided The study was designed to have 90% power to detect a 33.3% difference in survival between the two groups at a two-sided alpha level of 0.04 after 540 patients had died An interim analysis of PFS was planned after disease had progressed in approximately 363 patients. A further interim analysis of OS was performed prior to crossover	The primary end point was assessed by ITT analysis The study was designed to have 81% power to detect a drug effect that corresponded to a reduction in the progression rate from 90% to 70% 12 weeks after randomisation	This is an open-label, single-arm phase II clinical trial The study was designed to have 90% power to detect an objective response rate for sunitinib of 15% or more using an overall two-sided significance level of 0.05	This is an open-label, single-arm phase II clinical trial Sample size was determined using Simon's minimax two-stage design. The study was designed to have 85% power to evaluate the hypothesis that the objective response rate was greater than or equal to 15% at an alpha level of 5%

TABLE 61 *Summary of adverse events (any grade): sorafenib versus sunitinib versus BSC as second-line therapy*

	Escudier et *al*. 2007[109]		Ratain et *al*. 2006[110]	Motzer et *al*. 2006[111]	Motzer et *al*. 2006[112]
Intervention	**Sorafenib**	**Placebo**	**Sorafenib**	**Sunitinib**	**Sunitinib**
n	451	452	202	106	63
	% of patients				
Allergy/immunology			10		
Cardiovascular general			56		
Hypertension	17	2	43	16	5
Ejection fraction decline	NR	NR	NR	NR	11
Blood/bone marrow			31		
Decreased haemoglobin	8	7	27	NR	NR
Constitutional symptoms			90		
Fatigue	37	28	73	28	38
Weight loss	10	6	33	NR	NR
Other symptoms	10	6	22	NR	NR
Fever	NR	NR	12	NR	NR
Gastrointestinal			95		
Diarrhoea	43	13	58	20	24
Nausea	23	19	30	13	19
Anorexia	16	13	47	12	6
Vomiting	16	12	24	10	13
Constipation	15	11	32	NR	NR
Dysgeusia	NR	NR	NR	9	NR
Dyspepsia	NR	NR	NR	16	16
Stomatitis	NR	NR	NR	13	19
Mucosal inflammation	NR	NR	NR	12	NR
Other symptoms	NR	NR	29	NR	NR
Neurology/sensory neuropathy			68		
Abdominal pain	11	9	19	NR	NR
Headache	10	6	19	NR	NR
Joint pain	10	6	12	NR	NR
Bone pain	8	8	NR	NR	NR
Tumour pain	6	5	NR	NR	NR
Muscle pain	NR	NR	11	NR	NR
Pain, other	NR	NR	58	7	NR
Pulmonary			63		
Cough	13	14	28	NR	NR
Dyspnoea	14	12	38	NR	NR
Pulmonary, other	NR	NR	18	NR	NR
Dermatological			93		
Rash or desquamation	40	16	66	3	NR
Hand–foot skin reaction	30	7	62	15	NR
Alopecia	27	3	53	NR	NR

TABLE 61 *Summary of adverse events (any grade): sorafenib versus sunitinib versus BSC as second-line therapy (continued)*

	Escudier et *al.* 2007[109]		Ratain et *al.* 2006[110]	Motzer et *al.* 2006[111]	Motzer et *al.* 2006[112]
Intervention	**Sorafenib**	**Placebo**	**Sorafenib**	**Sunitinib**	**Sunitinib**
Dermatological					
Pruritis	19	6	NR	NR	NR
Dry skin	NR	NR	23	NR	NR
Flushing	NR	NR	16	NR	NR
Dermatitis	NR	NR	NR	NR	8
Dermatology, other			43		
Renal/genitourinary			25		
Creatinine	NR	NR	14	NR	14
Creatine kinase	NR	NR	NR	NR	15
Haemorrhage	NR	NR	22	NR	NR
Hepatic			29		
Alanine aminotransferase	NR	NR	11	NR	8
Aspartate aminotransferase	NR	NR	11	NR	NR
Infection/febrile neutropenia			37		
Infection without neutropenia	NR	NR	37	NR	NR
Musculoskeletal			14		
Metabolic/laboratory			42		
Neutropenia	NR	NR	NR	42	45
Lipase increased	NR	NR	NR	28	24
Anaemia	NR	NR	NR	26	37
Thrombocytopenia	NR	NR	NR	21	18
Lymphopenia	NR	NR	NR	NR	72
Hyperamylasaemia	NR	NR	NR	NR	10
Total bilirubin	NR	NR	NR	NR	5
Hyperglycaemia	NR	NR	17	NR	NR
Hyperuricaemia	NR	NR	13	NR	NR
Hypophosphataemia	NR	NR	15	NR	NR

NR, not reported.

Appendix 6

Critical appraisal of industry submissions

TABLE 62 *Comparison of manufacturer (Pfizer) submission cost-effectiveness analysis models of sunitinib versus IFN/BSC in first-line and second-line use with NICE reference case requirements*

NICE reference case requirement		**Reviewer comment first-line analysis/model**	**Reviewer comment second-line analysis/model**
Decision problem	As per the scope developed by NICE (especially technologies and patient group)	✓ Only two of four new drugs	✓ All second-line drugs and BSC considered
Comparator	Alternative therapies routinely used in the UK NHS	✓ IFN-α	✓ BSC
Perspective on costs	NHS and Personal Social Services	✓	✓
Perspective on outcomes	All health effects on individuals	✓	✓
Type of economic evaluation	Cost-effectiveness analysis	✓	✓
Synthesis of evidence on outcomes	Based on a systematic review	✓ Single RCT for comparison of sunitinib with IFN, single RCT for comparison of bevacizumab + IFN with IFN	✓ Single-arm trial for sunitinib, various trials for BSC
Measure of health benefits	QALYs	✓	✓
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	✓ EQ-5D from phase III RCT	✓ EQ-5D from single-arm sunitinib trial
Method of preference elicitation for health-state values	Choice-based method (e.g. time trade-off, standard gamble, not rating scale)	✓	✓
Source of preference data	Representative sample of the UK public	✓	✓
Discount rate	3.5% p.a. for costs and health effects	✓	✓

TABLE 63 *Critical appraisal checklist of the Pfizer economic evaluation for sunitinib versus IFN in first-line use*

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of first-line use of sunitinib vs IFN in a patient population with advanced RCC, low or intermediate prognosis. NICE is the primary decision-maker
S2	Statement of scope/ perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model
S3	Rationale for structure	✓	The model structure, based on the health states PFS, PD and death, has been described clearly and is consistent with the progression of RCC. Weibull models are common in survival analysis, allowing for time-dependent transition probabilities
S4	Structural assumptions	✓	Model assumptions are given. Weibull regression models were fitted to PFS and OS of the phase III RCT[107]
S5	Strategies/comparators	?	Sunitinib was compared with IFN, which is appropriate. Pfizer do not perform an indirect comparison between sunitinib and bevacizumab + IFN, although they do present a comparison of bevacizumab + IFN vs IFN
S6	Model type	✓	This type of model based on survival curves is frequently used in this type of decision problem
S7	Time horizon	✓	Treatment is administered whilst patients are in PFS and is well described. The model time horizon is lifetime, which is appropriate
S8	Disease states/pathways	✓	The disease states first-line PFS, PD and death reflect the underlying biological progress of the disease and are those generally accepted for this decision question
S9	Cycle length	✓	The cycle length of approximately 4 days is short enough to capture the complexities of the natural history of the disease
Data			
D1	Data identification	?/✓	Data identification methods are described. The data for the important parameters (transition probabilities and utilities) have been taken from the main phase III RCT. Data on utilities are not transparent
D2	Pre-model data analysis	?/✓	Data for calculating the costs of administration, routine follow-up, diagnostic tests, BSC, death and treating adverse events
D2a	Baseline data	✓	Pfizer have used the OS data from the phase III trial of sunitinib, which is reasonable, but we caution that given this data is immature the cost-effectiveness estimates are subject to a good deal of uncertainty. To address this uncertainty, Pfizer have used other sources of OS data for IFN. However, we believe that it is unwise to use OS data from one trial and PFS data from a different trial because of lack of consistency. Furthermore, Pfizer have used the HR of sunitinib vs IFN from the phase III trial of sunitinib, which is also subject to uncertainty because of the immaturity of the data; however, these are the only data available for this parameter The model patient population was defined to be the same as in the phase III trial of sunitinib, which is a reasonable assumption
D2b	Treatment effects	?	As stated in the previous point, Pfizer have used the OS HR between sunitinib and IFN, which is based on immature data and therefore subject to large uncertainty
D2c	Quality of life weights (utilities)	?/✓	Utilities were derived from EQ-5D data collected from approximately 600 patients during the Motzer *et al.* RCT.[107] However, data are unpublished and therefore assessment of detail/methods not possible

TABLE 63 *Critical appraisal checklist of the Pfizer economic evaluation for sunitinib versus IFN in first-line use (continued)*

Dimension of quality			Comments
D3	Data incorporation	?	Data incorporated in the model are referenced and generally well described. However, there are several references cited in the report for which full details are not given in the reference list. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified. However, we note that the description of the variables incorporated in the report does not match those actually used in the model
D4	Assessment of uncertainty	?/✓	All types of uncertainty have been addressed
D4a	Methodological	✗	Pfizer have used a single type of model
D4b	Structural	✓	Structural uncertainties, such as the use of alternative OS curves for IFN, have been modelled
D4c	Heterogeneity	✓	The Pfizer analysis does not model patient subgroups. However, given the data available, this is reasonable. For example, there are insufficient data to model the following patient subgroups: clear cell, non-clear cell, nephrectomy, no nephrectomy, good prognosis and intermediate prognosis
D4d	Parameter	?	Extensive univariate sensitivity analysis and PSA performed. However, the description of the variables incorporated in the PSA in the report does not match those actually used in the model
Consistency			
C1	Internal consistency	✗	No evidence has been presented to indicate that the mathematical logic of the model has been tested
C2	External consistency	?	The results of the model were not calibrated against independent data, although it is not clear that such independent data exist The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form

✓ indicates 'clear', × indicates 'concerns' and ? indicates 'uncertain/unknown'.
Checklist structure from Phillips and colleagues.[135]

TABLE 64 *Pfizer cost-effectiveness results per patient for bevacizumab plus IFN versus IFN*

	Bevacizumab + IFN-α	IFN-α	Incremental
Benefits			
Life-years gained	2.30	1.85	0.45
Progression-free years gained	0.84	0.61	0.23
Time in progressed state (years)	1.46	1.23	0.22
QALYs gained	1.65	1.31	0.34
Costs			
Drug acquisition	£40,002	£3667	£36,335
Administration costs	£1341	£0	£0
Follow-up	£0	£2296	–£2296
Diagnostic tests	£426	£296	£159
Adverse events	£5	£1	£4
Supportive care	£13,051	£11,670	£1380

continued

TABLE 64 *Pfizer cost-effectiveness results per patient for bevacizumab plus IFN versus IFN (continued)*

	Bevacizumab + IFN-α	**IFN-α**	**Incremental**
Total costs	£54,984	£18,001	£36,923
Cost-effectiveness	Bevacizumab + IFN-α vs IFN-α		
Incremental cost per life-year gained	£81,754		
Incremental cost per progression-free years gained	£162,110		
Incremental cost per QALY	£107,357		

TABLE 65 *Critical appraisal checklist of the Pfizer economic evaluation for sunitinib versus BSC in second-line use*

Dimension of quality			**Comments**
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of second-line use of sunitinib vs BSC in a patient population with advanced RCC. NICE is the primary decision-maker
S2	Statement of scope/ perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model
S3	Rationale for structure	✓	The model structure, based on the health states PFS, PD and death, has been described clearly and is consistent with the progression of RCC. Weibull models are common in survival analysis, allowing for time-dependent transition probabilities
S4	Structural assumptions	✗	Model assumptions are given. Weibull regression models were fitted to PFS and OS for sunitinib from a single-arm trial. Weibull models were fitted for BSC from several different trials; however, we believe that it is invalid to model sunitinib from one trial and BSC from different trials, because randomisation is broken
S5	Strategies/comparators	✓	Sunitinib was compared with BSC, which is appropriate. Pfizer do not perform an indirect comparison between sunitinib and sorafenib, although they do present a comparison of sorafenib vs BSC
S6	Model type	✓	This type of model based on survival curves is frequently used in this type of decision problem
S7	Time horizon	✓	Sunitinib is administered whilst patients are in PFS and is well described. The model time horizon is lifetime, which is appropriate
S8	Disease states/pathways	✓	The disease states PFS, PD and death reflect the underlying biological progress of the disease and are those generally accepted for this decision question
S9	Cycle length	✓	The cycle length of approximately 1–10 weeks is short enough to capture the complexities of the natural history of the disease
Data			
D1	Data identification	?	Data identification methods are described. The data for the important parameters (transition probabilities and utilities) for sunitinib have been taken from a single-arm trial, and for BSC from several different trials; however, we believe that it is not appropriate to use data from different trials for the two treatment arms
D2	Pre-model data analysis	✓	The methodology for calculating the costs of routine follow-up, diagnostic tests, BSC, death and treating adverse events are stated

TABLE 65 *Critical appraisal checklist of the Pfizer economic evaluation for sunitinib versus BSC in second-line use (continued)*

Dimension of quality			Comments
D2a	Baseline data	✗	Pfizer have used the sunitinib OS data from the single-arm trial of sunitinib. These data are not mature, hence the cost-effectiveness estimates are subject to a good deal of uncertainty. As Pfizer acknowledge, the two main sources of BSC survival data have important limitations. Furthermore, Pfizer do not state why PFS and OS for sunitinib were not modelled from the other single-arm trial of sunitinib, trial A6181006
			The model patient population was inconsistent between sunitinib and BSC
D2b	Treatment effects	✗	See above
D2c	Quality of life weights (utilities)	?/✓	Utilities were derived from EQ-5D data collected during the single-arm trial of sunitinib. However, data are unpublished and therefore assessment of detail/methods not possible. The PFS utility for BSC was assumed equal to the baseline utility of this trial, and the PD utility for BSC was assumed equal to that of sunitinib, which seems appropriate
D3	Data incorporation	✓	Data incorporated in the model are referenced and generally well described. However, there are several references cited in the report for which full details not given in the reference list. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified
D4	Assessment of uncertainty	✓	All types of uncertainty have been addressed
D4a	Methodological	✗	Pfizer have used a single type of model
D4b	Structural	✓	Structural uncertainties, such as the use of alternative OS curves for BSC, have been modelled
D4c	Heterogeneity	✓	Pfizer did not model patient subgroups; however, given the data available, this is reasonable
D4d	Parameter	✓	Extensive univariate sensitivity analysis and PSA performed
Consistency			
C1	Internal consistency	✗	No evidence has been presented to indicate that the mathematical logic of the model has been tested
C2	External consistency	?	The results of the model were not calibrated against independent data, although it is not clear that such independent data exist
			The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form

✓ indicates 'clear', ✗ indicates 'concerns' and ? indicates 'uncertain/unknown'.
Checklist structure from Phillips and colleagues.[135]

TABLE 66 *Pfizer base case per patient results of second-line sunitinib versus BSC*

	Sunitinib	BSC	Incremental
Benefits			
Life-years gained	1.52	0.75	0.77
Progression-free years gained	0.96	0.42	0.54
Time in progressed state (years)	0.56	0.33	0.23
QALYs gained	1.14	0.55	0.60
Costs			
Drug acquisition	£18,715	£0	£18,715
Follow-up	£1516	£0	£1516
Diagnostic tests	£699	£0	£699
Adverse events	£65	£0	£0
Supportive care	£6956	£5468	£1488
Total costs	£27,855	£5468	£22,387
Cost effectiveness	***Sunitinib vs BSC***		
Incremental cost per life-year gained	£29,061		
Incremental cost per progression-free years gained	£41,817		
Incremental cost per QALY	£37,519		

TABLE 67 *Pfizer per patient results of exploratory analysis of second-line sorafenib versus BSC*

	Sorafenib	BSC	Incremental
Benefits			
Life-years gained	1.66	1.31	0.35
Progression-free years gained	0.60	0.41	0.19.
Time in progressed state (years)	1.06	0.89	0.17
QALYs gained	1.18	0.91	0.27
Costs			
Drug acquisition	£16,971	£0	£16,971
Follow-up	£944	£0	£944
Diagnostic tests	£416	£0	£416
Adverse events	£0	£0	£0
Supportive care	£10,504	£9424	£1080
Total costs	£28,835	£9424	£19,411
Cost effectiveness	***Sorafenib vs BSC***		
Incremental cost per life-year gained	£54,750		
Incremental cost per progression-free years gained	£103,813		
Incremental cost per QALY	£73,078		

TABLE 68 *Comparison of Roche model of bevacizumab plus IFN versus IFN in first-line use with NICE reference case requirements*

NICE reference case requirement		Reviewer comment
Decision problem	As per the scope developed by NICE (especially technologies and patient group)	✓ Bevacizumab + IFN vs IFN in first-line use
Comparator	Alternative therapies routinely used in the UK NHS	✓ IFN
Perspective on costs	NHS and Personal Social Services	✓
Perspective on outcomes	All health effects on individuals	✓
Type of economic evaluation	Cost-effectiveness analysis	✓
Synthesis of evidence on outcomes	Based on a systematic review	✓ AVOREN RCT[106] for bevacizumab + IFN vs IFN
Measure of health benefits	QALYs	✓
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	✓ EQ-5D from Motzer *et al.*[107] RCT of sunitinib vs IFN
Method of preference elicitation for health state values	Choice-based method (e.g. time trade-off, standard gamble, not rating scale)	✓
Source of preference data	Representative sample of the UK public	✓
Discount rate	3.5% p.a. for costs and health effects	✓

TABLE 69 *Critical appraisal checklist of the Roche economic evaluation for bevacizumab plus IFN versus IFN in first-line use*

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of first-line use of bevacizumab plus IFN vs IFN in a patient population with advanced RCC. NICE is the primary decision-maker
S2	Statement of scope/ perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model
S3	Rationale for structure	?/✓	The model structure, based on the health states PFS, PD and death, has been described clearly and is consistent with the progression of RCC. Gompertz curves are common in survival analysis, allowing for time-dependent transition probabilities. However, we believe that log-logistic curves in sensitivity analysis are inappropriate because of their long tails
S4	Structural assumptions	✓	Model assumptions are given. Gompertz and log-logistic curves were fitted to PFS and OS data for bevacizumab plus IFN and IFN from the appropriate RCT. The HR for OS is used correctly
S5	Strategies/comparators	?	Bevacizumab plus IFN was compared with IFN, which is appropriate. However, although sunitinib is available for treating patients in first-line RCC, Roche do not perform an indirect comparison between bevacizumab plus IFN and sunitinib
S6	Model type	✓	This type of model based on survival curves is frequently used in this type of decision problem
S7	Time horizon	✓	The duration of treatment is well described. The model time horizon is lifetime, which is appropriate
S8	Disease states/pathways	✓	The disease states PFS, PD and death reflect the underlying biological progress of the disease and are those generally accepted for this decision question
S9	Cycle length	✓	The cycle length of 1 month is short enough to capture the complexities of the natural history of the disease

continued

TABLE 69 *Critical appraisal checklist of the Roche economic evaluation for bevacizumab plus IFN versus IFN in first-line use (continued)*

Dimension of quality			Comments
Data			
D1	Data identification	✓	Data identification methods are described. The data for the important parameters (survival probabilities and utilities) for bevacizumab plus IFN have been taken from appropriate RCTs
D2	Pre-model data analysis	?	Pre-model data analysis, e.g. cost of adverse events, is generally reasonable. However, we are sceptical of Roche's calculation of the dose intensities. The values estimated are lower than those published in the relevant RCT
D2a	Baseline data	?	Roche have used the PFS and OS data from the main RCT of bevacizumab plus IFN vs IFN. These data are not mature, hence the cost-effectiveness estimates are subject to a good deal of uncertainty because of extrapolation. As mentioned above, we do not believe that it is appropriate to model survival by the log-logistic curve because the tail is too long Half-cycle corrections have been used
D2b	Treatment effects	?	Treatment effects are taken from the main RCT. Roche use the PFS HR of 0.709 for the safety population instead of the value of 0.79 quoted in Escudier *et al.*[106] The value used is not quoted in Escudier *et al.*[106] and results in a lower ICER for bevacizumab plus IFN vs IFN. The treatment effects are assumed to continue after data cut-off in the main RCT, which is reasonable
D2c	Quality of life weights (utilities)	?/✓	Given that utilities are not available from the main RCT of bevacizumab plus IFN vs IFN, Roche have used utilities from EQ-5D data collected during the RCT of sunitinib vs IFN. Utilities were assumed independent of treatment, which is reasonable. Data used remain unpublished
D3	Data incorporation	✓	Data incorporated in the model are referenced and generally well described. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified
D4	Assessment of uncertainty	✓	All types of uncertainty have been addressed
D4a	Methodological	✗	Roche have used a single type of model
D4b	Structural	?	Roche have only assessed the structural uncertainty of using different mathematical functions for the survival curves
D4c	Heterogeneity	✓	Roche have not modelled patient subgroups; however, given the data available, this is reasonable
D4d	Parameter	✗	Roche have performed a PSA but not univariate sensitivity analysis on parameters
Consistency			
C1	Internal consistency	✗	Roche provide no evidence to indicate that the mathematical logic of the model has been tested
C2	External consistency	?	The results of the model were not calibrated against independent data, although it is not clear that such independent data exist The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form

✓ indicates 'clear', ✗ indicates 'concerns' and ? indicates 'unclear/unknown'.
Checklist structure from Phillips and colleagues.[135]

TABLE 70 *Comparison of Wyeth model with NICE reference case requirements*

NICE reference case requirement		Reviewer comment
Decision problem	As per the scope developed by NICE (especially technologies and patient group)	✓ Only one of four new drugs
Comparator	Alternative therapies routinely used in the UK NHS	✓ IFN and BSC
Perspective on costs	NHS and Personal Social Services	✓
Perspective on outcomes	All health effects on individuals	✓
Type of economic evaluation	Cost-effectiveness analysis	✓
Synthesis of evidence on outcomes	Based on a systematic review	✓ Single RCT for comparison with IFN, single RCT for comparison with BSC
Measure of health benefits	QALYs	✓
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	✓ EQ-5D from phase III RCT
Method of preference elicitation for health-state values	Choice-based method (e.g. time trade-off, standard gamble, not rating scale)	✓
Source of preference data	Representative sample of the UK public	✓
Discount rate	3.5% p.a. for costs and health effects	✓

TABLE 71 *Critical appraisal checklist of the Wyeth economic evaluation*

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of first-line use of temsirolimus vs IFN and BSC in a patient population with advanced RCC and poor prognosis. NICE is the primary decision-maker
S2	Statement of scope/ perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model
S3	Rationale for structure	✓	The model structure, based on the health states PFS, PD and death, has been described reasonably clearly and is consistent with the progression of RCC. Weibull models are common in survival analysis, allowing for time-dependent transition probabilities
S4	Structural assumptions	?	Model assumptions are given. Weibull regression models were fitted to PFS and post-progression survival outcomes of the phase III clinical trial (post-progression survival is defined as time from progression to death). However, without access to the underlying individual patient data we were unable to check the regression coefficients used to generate the Weibull curves
S5	Strategies/comparators	?	Temsirolimus was compared with IFN, which is appropriate. Temsirolimus is also compared with BSC, but we are unsure of the robustness of this comparison
S6	Model type	✓	This type of Markov state transition model is frequently used in this type of decision problem
S7	Time horizon	✓	The duration of treatment is well described. The model time horizon is 3 years, which is long enough to follow the great majority of patients to death
S8	Disease states/pathways	✓	The disease states first-line PFS, PD and death are those generally accepted for this decision question
S9	Cycle length	✓	The cycle length of 1 month is short enough to capture the complexities of the natural history of the disease

continued

TABLE 71 *Critical appraisal checklist of the Wyeth economic evaluation (continued)*

Dimension of quality			Comments
Data			
D1	Data identification	✓	Data identification methods are described. The data for the important parameters (transition probabilities and utilities) have been taken from the main phase III RCT, but some of these data are unpublished
D2	Pre-model data analysis	?/✓	The use of regression to derive the transition probabilities seems reasonable, but is not described in sufficient detail. The method for calculating the costs of treatment initiation, routine follow-up, disease progression, BSC, terminal care and treating adverse events seems reasonable
D2a	Baseline data	✓	The model patient population was defined to be the same as in the phase III trial of temsirolimus, which is a reasonable assumption
D2b	Treatment effects	✓	Wyeth assume that the Weibull function, extrapolated beyond the trial time period, accurately describes survival beyond the trial period, which is reasonable, especially as OS is almost completely (~80%) mature at data cut-off
D2c	Quality of life weights (utilities)	?/✓	Utilities were derived primarily from EQ-5D data collected from approximately 280 patients during the Hudes *et al.* RCT.[108] Utility data were used in the Q-TWiST framework. Data used not published
D3	Data incorporation	✓	Data incorporated in the model are referenced and generally well described. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified
D4	Assessment of uncertainty	?	Not all types of uncertainty have been addressed
D4a	Methodological	✗	Wyeth have used a single type of model
D4b	Structural	✗	Not assessed
D4c	Heterogeneity	✓	The model was applied to the following patient subgroups: clear cell, non-clear cell, nephrectomy, no nephrectomy
D4d	Parameter	✓	Extensive univariate sensitivity analysis and PSA performed
Consistency			
C1	Internal consistency	✗	No evidence has been presented to indicate that the mathematical logic of the model has been tested
C2	External consistency	✗	The results of the model were not calibrated against independent data. In the original submission, the model predictions of PFS and OS were not reconciled with the Kaplan–Meier curves reported in Hudes *et al.*[108] The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form

✓ indicates 'clear', ✗ indicates 'concerns' and ? indicates 'unclear/unknown'.
Checklist structure from Phillips and colleagues.[135]

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TABLE 72 *Wyeth clear cell and non-clear cell subgroup results*

Health outcomes, 36-month time horizon	Temsirolimus, clear cell	IFN, clear cell	Temsirolimus, non-clear cell	IFN, non-clear cell	Incremental, clear cell	Incremental, non-clear cell
Mean progression-free life-years – discounted	0.60	0.46	0.64	0.25	0.140	0.388
Mean life-years – discounted	1.01	0.85	1.12	0.66	0.161	0.458
Mean QALYs – discounted	0.50	0.39	0.55	0.29	0.109	0.260
Treatment costs (discounted)						
First-line drugs	£12,729	£2721	£13,621	£1163	£10,008	£12,458
First-line administration	£3176	£7333	£3399	£3284	–£4157	£115
Toxicities	£857	£982	£857	£982	–£124	–£124
Diagnosis/treatment initiation and routine follow-up	£2285	£1941	£2369	£1415	£345	£954
Progression	£510	£391	£404	£425	£119	–£21
Post progression (second-line + BSC)	£2881	£2743	£3424	£2899	£138	£524
Death	£10,991	£11,028	£10,527	£11,127	–£38	–£600
Total costs	£33,429	£27,139	£34,601	£21,296	£6291	£13,305
ICERs						
Total costs	£33,429	£27,139	£34,601	£21,296	£6291	£13,305
Total life-years	1.01	0.85	1.12	0.66	0.161	0.458
Total QALYs	0.50	0.39	0.55	0.29	0.109	0.260
Cost per life-year					£39,188	£29,035
Cost per QALY					£57,731	£51,159

TABLE 73 *Wyeth nephrectomy and no nephrectomy subgroup results*

Health outcomes, 36-month time horizon	Temsirolimus, nephrectomy	IFN, nephrectomy	Temsirolimus, no nephrectomy	IFN, no nephrectomy	Incremental, nephrectomy	Incremental, no nephrectomy
Mean progression-free life-years – discounted	0.58	0.42	0.64	0.41	0.161	0.225
Mean life-years – discounted	0.99	0.83	1.12	0.83	0.162	0.296
Mean QALYs – discounted	0.49	0.38	0.56	0.38	0.110	0.177
Treatment costs (discounted)						
First-line drugs	£12,274	£2432	£13,705	£2369	£9841	£11,337
First-line administration	£3062	£6589	£3420	£6425	–£3526	–£3005
Toxicities	£857	£982	£857	£982	–£124	–£124
Diagnosis/treatment initiation and routine follow-up	£2241	£1844	£2375	£1822	£397	£553
Progression	£510	£400	£454	£395	£110	£59
Post progression (second-line + BSC)	£2878	£2877	£3109	£2525	£1	£584
Death	£11,006	£11,015	£10,515	£11,115	–£9	–£600
Total costs	£32,828	£26,139	£34,436	£25,631	£6690	£8805
ICERs						
Total costs	£32,828	£26,139	£34,436	£25,631	£6690	£8805
Total life-years	0.99	0.83	1.12	0.83	0.162	0.296
Total QALYs	0.49	0.38	0.56	0.38	0.110	0.177
Cost per life-year					£41,188	£29,792
Cost per QALY					£60,575	£49,690

TABLE 74 *Temsirolimus versus BSC results from Wyeth model*

Health outcomes, 36-month time horizon	Temsirolimus	BSC	Incremental
Mean progression-free life-years – discounted	0.61	0.33	0.285
Mean life-years – discounted	1.02	0.64	0.381
Mean QALYs – discounted	0.51	0.30	0.205
Treatment costs (discounted)			
First-line drugs	£12,957	£458	£12,499
First-line administration	£3233	£0	£3233
Toxicities	£857	£0	£857
Diagnosis/treatment initiation and routine medical follow-up	£2310	£2612	–£302
Progression	£467	£369	£98
Post progression (second-line + BSC)	£2884	£2201	£683
Death	£10,903	£11,291	–£388
Total costs	£33,612	£16,932	£16,680
ICERS			
Total costs	£33,612	£16,932	£16,680
Total life-years	1.02	0.64	0.381
Total QALYs	0.51	0.30	0.205
Cost per life-year			£43,746
Cost per QALY			£81,201

TABLE 75 *Comparison of Bayer model of sorafenib versus BSC in second-line use and cytokine-unsuitable patients with NICE reference case requirements*

NICE reference case requirement		Reviewer comment
Decision problem	As per the scope developed by NICE (especially technologies and patient group)	✓ Sorafenib vs BSC in second-line and cytokine-unsuitable patients
Comparator	Alternative therapies routinely used in the UK NHS	✓ BSC
Perspective on costs	NHS and Personal Social Services	✓
Perspective on outcomes	All health effects on individuals	✓
Type of economic evaluation	Cost-effectiveness analysis	✓
Synthesis of evidence on outcomes	Based on a systematic review	✓ Escudier *et al.* RCT of sorafenib vs BSC[109]
Measure of health benefits	QALYs	✓
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	?/✓ EQ-5D survey of RCC clinicians
Method of preference elicitation for health-state values	Choice-based method (e.g. time trade-off, standard gamble, not rating scale)	✓
Source of preference data	Representative sample of the UK public	✓
Discount rate	3.5% p.a. for costs and health effects	✓

TABLE 76 *Main per patient results of Bayer cost-effectiveness analyses of sorafenib versus BSC and sunitinib versus sorafenib*

	Sorafenib vs BSC			
	Second-line and cytokine-unsuitable combined	**Second-line only**	**Cytokine-unsuitable only**	**Sunitinib vs sorafenib**
Increase in OS (years)	(CiC)	(CiC)	(CiC)	(CiC)
Increase in PFS (years)	(CiC)	(CiC)	(CiC)	(CiC)
Increase in QALYs	(CiC)	(CiC)	(CiC)	(CiC)
Cost per LYG	(CiC)	(CiC)	(CiC)	(CiC)
Cost per QALY	(CiC)	(CiC)	(CiC)	(CiC)
Prob. cost-effective WTP £30,000/QALY	(CiC)	(CiC)	(CiC)	(CiC)
Incremental costs				(CiC)
Total costs	(CiC)	(CiC)	(CiC)	
Drug cost[a]	(CiC)	(CiC)	(CiC)	
Drug administration[a]	(CiC)	(CiC)	(CiC)	
Adverse events[a]	(CiC)	(CiC)	(CiC)	
PFS excluding cost of sorafenib[a]	(CiC)	(CiC)	(CiC)	
PD[a]	(CiC)	(CiC)	(CiC)	

CiC, commercial-in-confidence data have been removed; LYG, life-year gained; WTP, willingness to pay.
a Calculated by PenTAG from Bayer model.

TABLE 77 *Bayer results for sorafenib versus BSC by subgroup. (a) Mean progression-free survival and overall survival*

		Mean PFS (months)			Mean OS (months)		
Subgroup	**Value**	**Placebo**	**Sorafenib**	**Difference**	**Placebo**	**Sorafenib**	**Difference**
Age	≥ 65 years	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Motzer score	Intermediate	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Nephrectomy	Yes	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Baseline ECOG-PS	0	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Baseline ECOG-PS	1	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Previous IL-2/IFN	No (unsuitable)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Previous IL-2/IFN	Yes (failed)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Metastasis in lung at BL	No	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Metastasis in liver at BL	Yes	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)
Diagnosis time at BL	≥ 1.5 years	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)	(CiC)

BL, baseline; CiC, commercial-in-confidence data have been removed.

TABLE 77 *Bayer results for sorafenib versus BSC by subgroup. (b) QALYs, life-years, costs and ICERs*

		QALYs		Life-years		Cost		ICER	
Subgroup	**Value**	**Placebo**	**Sorafenib**	**Placebo**	**Sorafenib**	**Placebo**	**Sorafenib**	**QALY**	**LYG**
Age	≥ 65 years	(CiC)	(CiC)	(CiC)	(CiC)	£10,484	£36,078	(CiC)	(CiC)
Motzer score	Intermediate	(CiC)	(CiC)	(CiC)	(CiC)	£10,450	£33,884	(CiC)	(CiC)
Nephrectomy	Yes	(CiC)	(CiC)	(CiC)	(CiC)	£11,686	£35,515	(CiC)	(CiC)
Baseline PS (average utility)	0	(CiC)	(CiC)	(CiC)	(CiC)	£13,043	£37,368	(CiC)	(CiC)
Baseline PS (PS 0 utility)	0	(CiC)	(CiC)	(CiC)	(CiC)	£13,043	£37,368	(CiC)	(CiC)
Baseline PS (average utility)	1	(CiC)	(CiC)	(CiC)	(CiC)	£10,554	£30,550	(CiC)	(CiC)
Baseline PS (PS 1 utility)	1	(CiC)	(CiC)	(CiC)	(CiC)	£10,554	£30,550	(CiC)	(CiC)
Previous IL-2/IFN	No (unsuitable)	(CiC)	(CiC)	(CiC)	(CiC)	£11,408	£38,583	(CiC)	(CiC)
Previous IL-2/IFN	Yes (failed)	(CiC)	(CiC)	(CiC)	(CiC)	£13,230	£36,263	(CiC)	(CiC)
Metastasis in lung at BL	No	(CiC)	(CiC)	(CiC)	(CiC)	£14,177	£40,471	(CiC)	(CiC)
Metastasis in liver at BL	Yes	(CiC)	(CiC)	(CiC)	(CiC)	£11,339	£36,154	(CiC)	(CiC)
Diagnosis time at BL	≥1.5 years	(CiC)	(CiC)	(CiC)	(CiC)	£14,177	£42,896	(CiC)	(CiC)

BL, baseline; CiC, commercial-in-confidence data have been removed; LYG, life-years gained; PS, performance status.

TABLE 78 *Critical appraisal checklist of the Bayer economic evaluation of sorafenib versus BSC in second-line use and for patients unsuitable for cytokine treatment*

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of sorafenib vs BSC in second-line use and for patients unsuitable for cytokine treatment in a patient population with advanced RCC. NICE is the primary decision-maker
S2	Statement of scope/ perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model
S3	Rationale for structure	✓	The model structure, based on the health states PFS, PD and death, has been described clearly and is consistent with the progression of RCC. Exponential curves are used to extrapolate OS for sorafenib and BSC, which is a valid method. However, it might have been useful to extrapolate with the Weibull distribution as this is more flexible than the exponential distribution
S4	Structural assumptions	?/✓	Model assumptions are given. The structural assumptions for utilities are described; however, use of data from a survey of clinicians is a weakness
S5	Strategies/comparators	✓	All feasible options have been evaluated
S6	Model type	✓	This type of model based on survival curves is frequently used in this type of decision problem
S7	Time horizon	✓	Treatment is given whilst in PFS and is well described. The model time horizon is 10 years, which is long enough to follow the great majority of patients to death
S8	Disease states/pathways	✓	The disease states PFS, PD and death reflect the underlying biological progress of the disease and are those generally accepted for this decision question
S9	Cycle length	✓	The cycle length of 1 month is short enough to capture the complexities of the natural history of the disease
Data			
D1	Data identification	?	Data identification methods are described. The data for the important parameters (PFS and OS curves and utilities) have been taken from the main RCT. However, the sources of the unit costs in PFS and PD and for adverse events given in the EXCEL model and in Appendix 3.2 of the report are not provided Costs were modelled at the following times: treatment initiation, routine monthly follow-up, disease progression, BSC and terminal care/death. At each of these times, costs were categorised as outpatient, inpatient, laboratory tests and radiological examinations. Unit costs were taken from standard UK sources.[70,139,188] We are concerned that resource use was obtained from a US perspective, although it was adjusted to a UK setting. Also, only five physicians were consulted
D2	Pre-model data analysis	✓	Pre-model data analysis, e.g. cost of adverse events, resource use in PFS and PD, is good
D2a	Baseline data	?	Bayer have correctly used the PFS and OS data from the main RCT of sorafenib vs BSC. Overall survival is not fully mature, hence Bayer have extrapolated using an exponential curve, which is valid. Half-cycle corrections have not been used
D2b	Treatment effects	✓	Treatment effects are taken from the main RCT. HRs are not used in the data for all patients combined. Instead, the sorafenib and BSC curves have been fitted separately, which is reasonable. The treatment effects are assumed to continue after data cut-off in the main RCT, which is reasonable
D2c	Quality of life weights (utilities)	?/✓	Given that utilities are not available from the main RCT of sorafenib vs BSC, Bayer have used utilities from EQ-5D data from a survey of clinicians. Utilities were assumed to be independent of treatment. Data used are unpublished. Small health valuation surveys of clinicians are not methodologically sound

TABLE 78 *Critical appraisal checklist of the Bayer economic evaluation of sorafenib versus BSC in second-line use and for patients unsuitable for cytokine treatment (continued)*

Dimension of quality			Comments
D3	Data incorporation	✓	Data incorporated in the model are referenced and generally well described. The exception is that the sources of the unit costs in PFS and PD and for adverse events given in the EXCEL model and in Appendix 3.2 of the report are not provided. For the PSA, the choice of distribution for each parameter has been described and justified
D4	Assessment of uncertainty	?	Not all types of uncertainty have been addressed
D4a	Methodological	✗	Bayer have used a single type of model
D4b	Structural	✗	Bayer have not investigated structural uncertainty
D4c	Heterogeneity	✓	Bayer modelled 10 patient subgroups
D4d	Parameter	✓	Bayer have performed a PSA and univariate sensitivity analysis on parameters
Consistency			
C1	Internal consistency	✗	Bayer provide no evidence to indicate that the mathematical logic of the model has been tested
C2	External consistency	?	The results of the model were not calibrated against independent data, although it is not clear that such independent data exist The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form

✓ indicates 'clear', ✗ indicates 'concerns' and ? indicates 'uncertain/unknown'.
Checklist structure from Phillips and colleagues.[135]

Appendix 7

Overall survival and progression-free survival model fitting

For a direct comparison between two treatments, Weibull curves were calculated as follows. First, Weibull curves were fitted separately to the PFS and OS Kaplan–Meier curves corresponding to a chosen baseline treatment from the appropriate RCT as follows. The Weibull survival function is:

$$S(t) = \exp(-\lambda t^{\gamma})$$

at time t, with scale parameter λ, shape parameter γ and hazard:

$$h(t) = \lambda\gamma t^{\gamma-1}$$

If $\gamma > 1$ the hazard increases with time, and if $0 < \gamma < 1$ it decreases with time. Parametric curves can be fitted to empirical Kaplan–Meier data using simple regression by transforming the survivor function to a linear function.[142,189] Accordingly, linearising:

$$\log(-\log(S(t))) = \log(\lambda) + \gamma \log(t)$$

from which parameters γ and λ are estimated. As a word of caution, outlier points are often found in this regression equation for values of $S(t)$ slightly less than 1, that is, for very small t. In this case, $-\log(S(t))$ is fractionally greater than 0, and hence $\log(-\log(S(t)))$ is very large and negative. In this case such outlier points were omitted from the regression. As a check, the fit of the estimated Weibull function to the Kaplan–Meier curve was inspected for reasonableness.

Second, a Weibull curve was assumed for the other treatment in the direct comparison between two treatments. This curve was obtained by application of the HR to the baseline survival curve for the first treatment.[142] In particular, γ for the second treatment was set equal to γ for the first treatment, and λ for the second treatment was calculated as λ for the baseline treatment multiplied by the HR between the two treatments. This method allows for uncertainty in the HRs for the PSA. Very occasionally using this method, at large time t, the number of patients in PFS is modelled to exceed the number of patients alive. Therefore, to avoid this we imposed the constraint that at any time t the number of patients in PFS was limited to the number of patients alive.

Now consider a simultaneous comparison between three treatments A, B and C, in particular a comparison between sunitinib, bevacizumab plus IFN and IFN. Suppose trial X compares treatments A and B, and trial Y compares treatments A and C. Weibull curves were calculated for PFS and OS for each of treatments A, B and C as follows. For the common treatment A, Weibull curves were fitted separately for OS and PFS from one of the two trials, as described above, to give parameters λ_A^{PFS}, λ_A^{OS}, γ_A^{PFS} and γ_A^{OS}. Overall survival and PFS Weibull curves for treatment B were obtained by application of the HRs HR_{BA}^{OS} and HR_{BA}^{PFS} from trial X, respectively, as described above, i.e. $\lambda_B^{PFS} = HR_{BA}^{PFS} \times \lambda_A^{PFS}$, $\gamma_B^{PFS} = \gamma_A^{PFS}$, $\lambda_B^{OS} = HR_{BA}^{OS} \times \lambda_A^{OS}$ and $\gamma_B^{OS} = \gamma_A^{OS}$. Similarly, OS and PFS Weibull curves for treatment C were obtained by application of the hazard ratios HR_{CA}^{OS} and HR_{CA}^{PFS} from trial Y respectively.

For each treatment we now have the number of patients in PFS and PD at each model cycle. The probabilities of transition between the three health states depend on time. However, it is neither possible nor necessary to calculate these probabilities. Transition probabilities should be calculated only to estimate the number of patients in the health states at any time. However, we calculate these as explained above. It is not possible to calculate the time-dependent transition probabilities indicated by the arrows in *Figure 10* because at each time there are three unknown transition probabilities but only two independent equations containing these three probabilities. Expressed differently, we do not know what proportion of the patients who die in each cycle come from PFS or PD. Transition probabilities can be calculated only if we know the health states of individual patients over time, as described in Billingham and colleagues.[189]

Appendix 8

Cost-effectiveness analysis results: cost-effectiveness planes to complement cost-effectiveness analysis presented in the report

Scatter plots (cost-effectiveness planes) are shown in *Figures 27–29*. In all cases notice that incremental total costs and benefits are highly correlated. This is because we assume that, for each treatment, the PFS HR and OS HR are correlated. Therefore, when the model samples a low PFS HR, thus incurring a higher incremental drug cost (as drugs are taken whilst in PFS), a low OS HR is sampled, thus incurring a higher incremental lifespan and hence incremental QALYs.

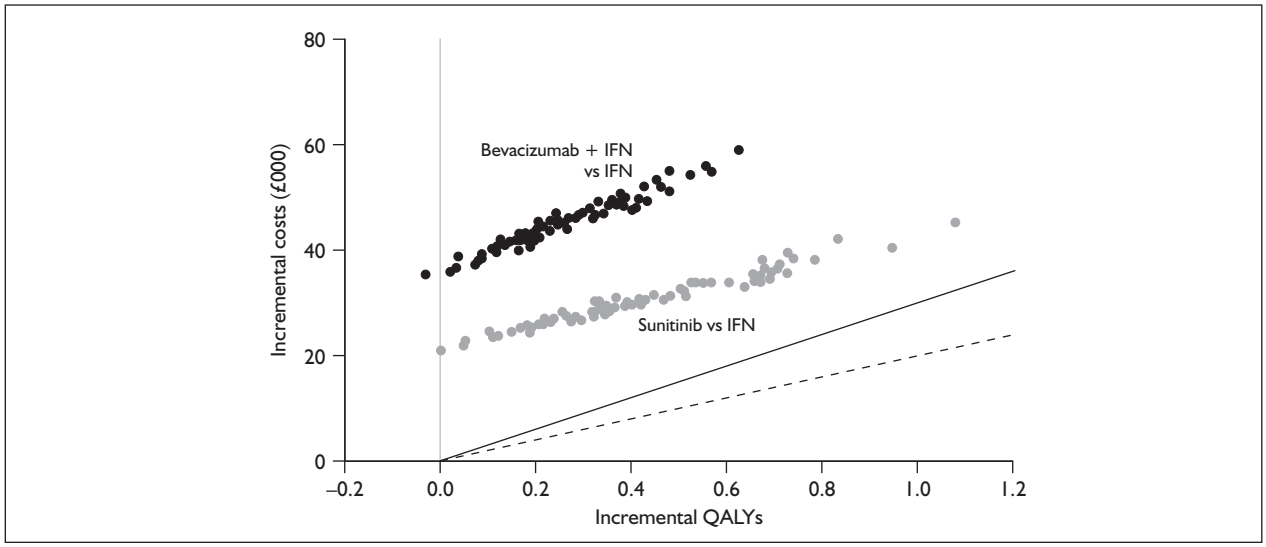

FIGURE 27 *Simulations of mean incremental total costs versus benefits for sunitinib versus IFN and bevacizumab plus IFN versus IFN. Willingness to pay of £20,000 per QALY and £30,000 per QALY are shown by the dotted and continuous lines respectively.*

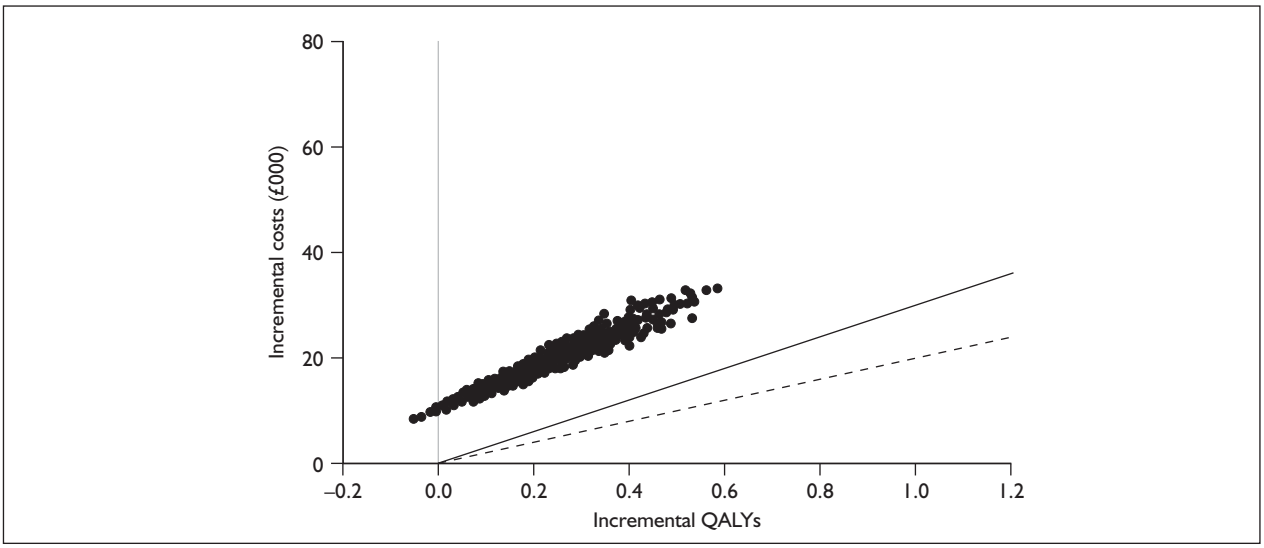

FIGURE 28 *Simulations of mean incremental total costs versus benefits for all patients for temsirolimus versus IFN. Willingness to pay of £20,000 per QALY and £30,000 per QALY are shown by the dotted and continuous lines respectively.*

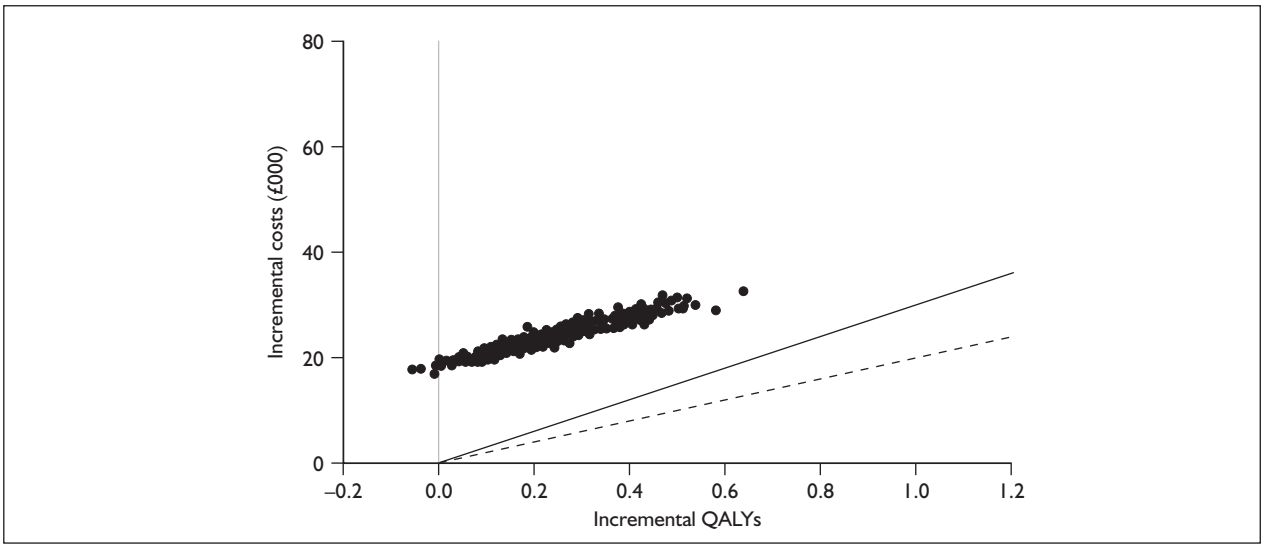

FIGURE 29 *Simulations of mean incremental total costs versus benefits for sorafenib versus BSC. Willingness to pay of £20,000 per QALY and £30,000 per QALY are shown by the dotted and continuous lines respectively.*

Appendix 9

Probabilistic sensitivity analysis

We performed Monte Carlo simulations to explore the impact of uncertainty in the model parameters on cost-effectiveness. Means, SEs and statistical distributions for these parameters are given in *Table 79*.

For each treatment we assumed that the OS and PFS HRs were perfectly correlated, which seems more realistic than completely uncorrelated. The two parameters of the Weibull distribution, $\ln(\lambda)$ and γ, for baseline PFS and separately for OS were drawn from bivariate normal distributions, using the method of Cholesky matrix decomposition. The variance–covariance matrices used in the matrix decomposition were estimated from linear regression of $\ln(-\ln S(t))$ against $\ln(t)$, described in Appendix 7, in which $S(t)$ is the survival function at time t.

For simplicity, adverse event costs were assumed deterministic because their impact on cost-effectiveness analysis is very small.

TABLE 79 *Stochastic parameters used in the PenTAG model*

Parameter type	Parameter	Mean cost per 6 weeks (SE)	Statistical distribution
Effectiveness	Weibull: λ, γ	See *Table 80*	Bivariate normal[a]
	Hazard ratios	See *Table 81*	Log-normal
Health-state utilities	All utilities	See *Table 82*	Beta[a]
Costs	Drug acquisition	Not stochastic	N/A
	Adverse events	Not stochastic	N/A
	Drug administration	IFN: £112 (£7); bevacizumab: £590 (£52); temsirolimus: £1179 (£105)[b]	Gamma[a]
	Medical management	PFS BSC: £81 (£3); PFS all drug treatments: £223 (£9); PD all treatments (drugs and BSC): £435 (£22)[b]	Gamma[a]

a Recommended by Briggs and colleagues.[190]
b SEs calculated from the interquartile ranges and number of data submissions given in references 145 and 139, except for the costs taken from reference 146, the cost of BSC in PD and the cost of administration of IFN, for which the SEs were estimated by assuming the average ratio of SE to mean (0.06) over all other costs.

TABLE 80 *Base-case parameters of the Weibull distribution used in the PenTAG model*

		PFS		OS	
Policy question	**Treatment**	λ	γ	λ	γ
First-line (not poor prognosis)	IFN	0.132	1.004	0.011	1.447
	Sunitinib	0.055	1.004	0.007	1.447
	Bevacizumab + IFN	0.083	1.004	0.008	1.447
First-line (poor prognosis)	IFN	0.542	0.582	0.127	0.829
	Temsirolimus	0.401	0.582	0.092	0.829
Second-line and unsuitable IFN	BSC	0.262	0.943	0.013	1.502
	Sorafenib	0.134	0.943	0.010	1.502

Note: time measured in months.

TABLE 81 *Hazard ratios used in the PenTAG model*

Policy question	**Treatment**	**PFS**	**OS**
First-line (not poor prognosis)	Sunitinib vs IFN	0.42 (0.33 to 0.52)	0.65 (0.45 to 0.94)
	Bevacizumab + IFN vs IFN	0.63 (0.52 to 0.75)	0.75 (0.58 to 0.97)
First-line (poor prognosis)	Temsirolimus vs IFN	0.74 (0.60 to 0.91)	0.73 (0.58 to 0.92)
Second-line and unsuitable IFN	Sorafenib vs BSC	0.51 (0.43 to 0.60)	0.72 (0.54 to 0.94)

Note: 95% confidence intervals given in parentheses.

TABLE 82 *Health-state utilities used in the PenTAG model*

Policy question	**Treatments**	**Health state**	**Base case (SE)[a]**	**Source/justification**
First-line (not poor prognosis)	IFN, sunitinib, bevacizumab + IFN	PFS	0.78 (0.01)	Pfizer submission[136]
		PD	0.70 (0.02)	
First-line (poor prognosis)	IFN, temsirolimus	PFS	0.60 (0.06[b])	Wyeth submission[124]
		PD	0.45 (0.04[b])	
Second-line and unsuitable IFN	Sorafenib, BSC	PFS	0.76 (0.03)	Pfizer submission[136]
		PD	0.68 (0.04)	

a SEs derived from SDs and numbers of patients from RCTs, reported in industry submissions.
b SE estimated as 10% of mean.

Appendix 10

Cohort composition

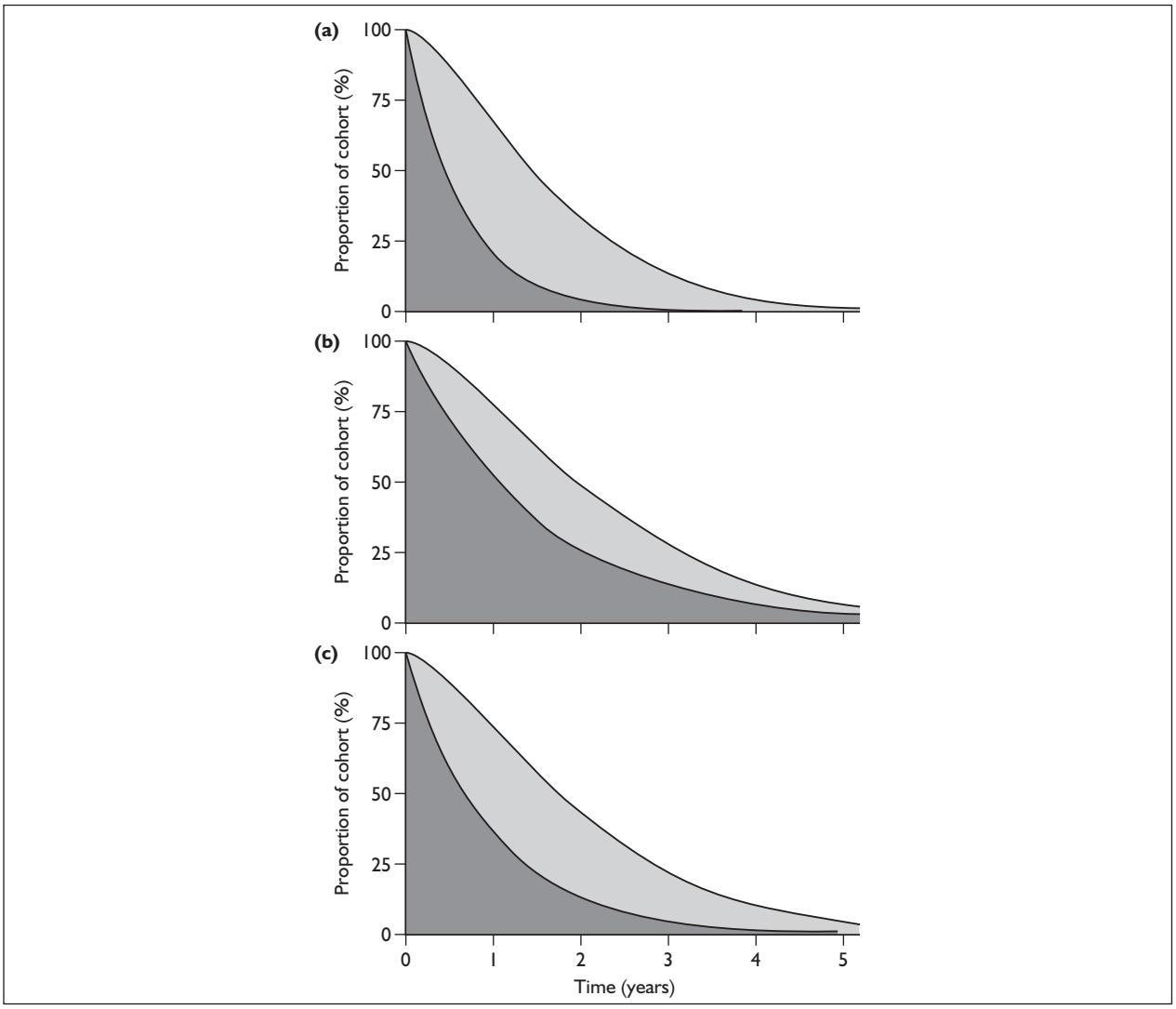

FIGURE 30 *Cohort compositions for policy question 1. (a) IFN; (b) sunitinib; (c) bevacizumab and IFN. Dark grey shading indicates progression-free survival, light grey shading indicates progressive disease and no shading indicates death.*

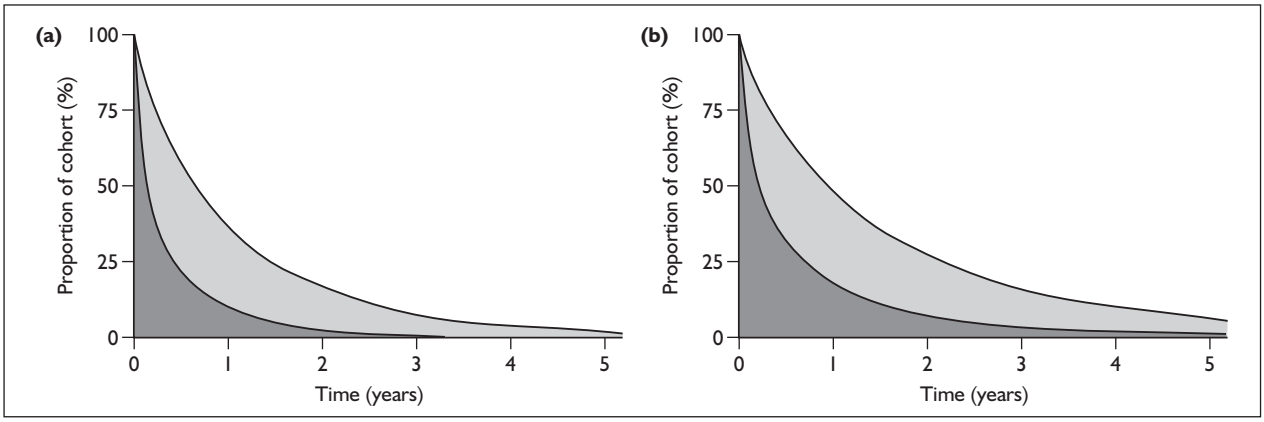

FIGURE 31 *Cohort compositions for policy question 2. (a) IFN; (b) temsirolimus. Dark grey shading indicates progression-free survival, light grey shading indicates progressive disease and no shading indicates death.*

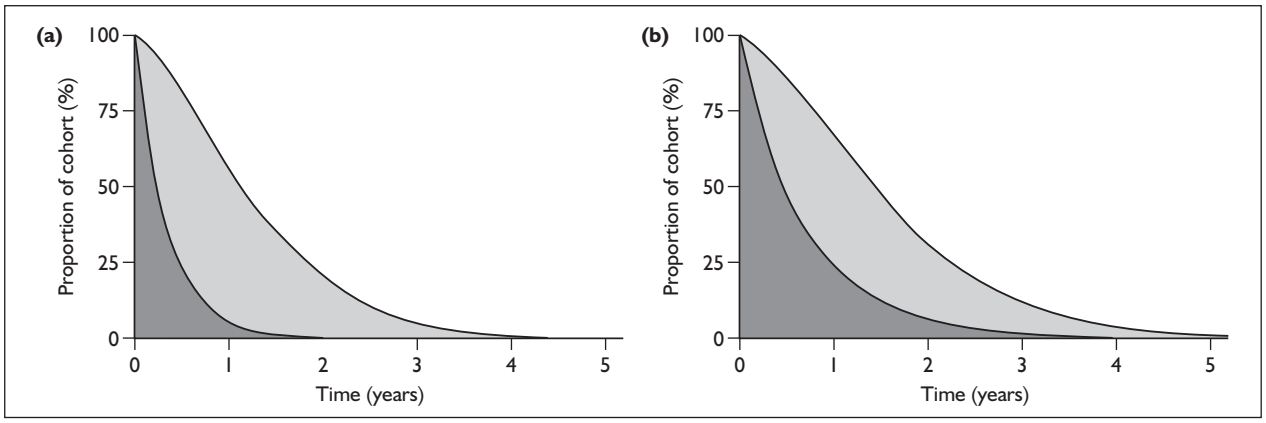

FIGURE 32 *Cohort compositions for policy question 3. (a) BSC; (b) sorafenib. Dark grey shading indicates progression-free survival, light grey shading indicates progressive disease and no shading indicates death.*

Appendix 11

Cost-effectiveness acceptability curves for patient subgroups for temsirolimus versus IFN

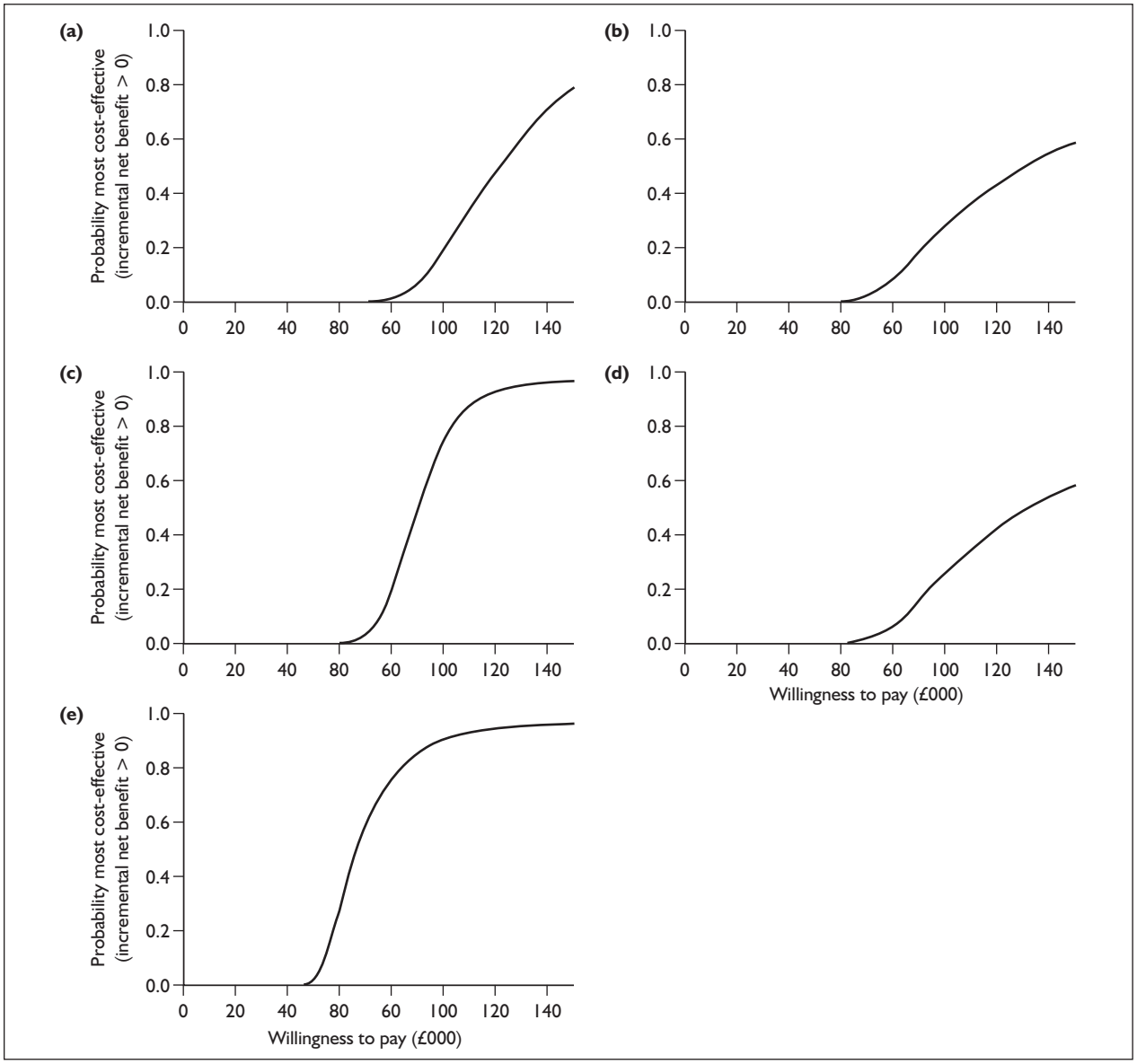

FIGURE 33 *Cost-effectiveness acceptability curves for patient subgroups for temsirolimus versus IFN. (a) Temsirolimus poor prognosis; (b) temsirolimus clear cell; (c) temsirolimus non-clear-cell; (d) temsirolimus previous nephrectomy; (e) temsirolimus no previous nephrectomy.*

Appendix 12

Ongoing/unpublished trials of bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma

Trial name	Register/ identifier number	Established/ anticipated sample size	Status
SORCE: a phase III randomised controlled study comparing sorafenib with placebo in patients with resected primary renal cell carcinoma at high or intermediate risk of relapse	NCT00492258	1656	Recruiting
Randomized phase IIb study of sorafenib dose escalation in patients with previously untreated metastatic renal cell carcinoma (RCC)	NCT00557830	170	Recruiting
Open label, non-comparative treatment protocol for the use of sorafenib in patients with advanced renal cell carcinoma	NCT00111020	2622	Active, not recruiting
A randomised, open-label, multi-centre phase II study of BAY 43–9006 (sorafenib) versus standard treatment with interferon alpha-2a in patients with unresectable and/or metastatic renal cell carcinoma	NCT00117637	Not reported	Active, not recruiting
A phase II study of BAY 43–9006 prior to and following nephrectomy in patients with metastatic renal cell carcinoma	NCT00110344	30	Terminated
A randomized phase II trial of sunitinib administered daily for 4 weeks, followed by 2-week rest vs 2-week on and 1-week off in metastatic renal cell carcinoma	NCT00570882	72	Recruiting
A randomized open label multicenter phase II study of first line therapy with sorafenib in association with IL-2 vs sorafenib alone in patients with unresectable and/or metastatic renal cell carcinoma	NCT00609401	90	Recruiting
A randomized trial of temsirolimus and sorafenib as second-line therapy in patients with advanced renal cell carcinoma who have failed first-line sunitinib therapy	NCT00474786	476	Recruiting
Pre-operative administration of sorafenib in patients with metastatic renal cell carcinoma undergoing cytoreductive nephrectomy	NCT00480389	30	Recruiting
Dynamic-contrast enhanced MRI pharmacodynamic study of BAY 43–9006 in metastatic renal cell carcinoma	NCT00606866	57	Active, not recruiting
A phase I/II study of sorafenib and RAD001 in patients with metastatic renal cell carcinoma	NCT00384969	73	Recruiting
A phase I/II study of sorafenib and palliative radiotherapy in patients with advanced renal cell carcinoma and symptomatic bony metastases	NCT00609934	36	Recruiting
A multicenter uncontrolled study of sorafenib in patients with unresectable and/or metastatic renal cell carcinoma	NCT00586105	40	Active, not recruiting
A phase II, multi-centre, open-label study to assess the efficacy, safety, tolerability and pharmacokinetics of intrapatient dose escalation of sorafenib as first line treatment for metastatic renal cell carcinoma	NCT00618982	80	Not yet recruiting
An open-label, non-comparative, treatment protocol for the use of BAY 43–9006 (sorafenib) in patients with advanced renal cell carcinoma	NCT00478114	15	Recruiting

continued

Trial name	Register/ identifier number	Established/ anticipated sample size	Status
Extension study for BAY 43–9006 in Japanese patients with renal cell carcinoma	NCT00586495	95	Active, not recruiting
An open label, non comparative, phase III study of the Raf kinase inhibitor BAY 43–9006 as a subsequent to first line therapy in patients with advanced renal cell carcinoma	NCT00492986	1164	Active, not recruiting
A randomized, double blinded, multi-center phase 2 study to estimate the efficacy and evaluate the safety and tolerability of sorafenib in combination with AMG 386 or placebo in subjects with metastatic clear cell carcinoma of the kidney	NCT00467025	150	Recruiting
A randomized discontinuation trial to determine the clinical benefit of continuation of sorafenib following disease progression in patients with advanced renal cell carcinoma	NCT00352859	260	Terminated
Phase II clinical trial, non-randomized, multicentre, on the combination of gemcitabine, capecitabine and sorafenib (Bay 43–9006) in treatment of patients with unresectable and/or metastatic renal cell carcinoma (RCC)	NCT00496301	40	Recruiting
A phase 1/2, open-label, dose escalation study to assess the safety and pharmacokinetics of recombinant interleukin 21 (rIL-21) administered concomitantly with sorafenib (Nexavar) in subjects with metastatic renal cell carcinoma	NCT00389285	48	Recruiting
A phase II study of sorafenib in patients with metastatic renal cell carcinoma	NCT00496756	23	Recruiting
A phase II study of sorafenib in patients with metastatic renal cell carcinoma	NCT00445042	44	Recruiting
The BeST trial: a randomized phase II study of VEGF, RAF kinase, and mTOR combination targeted therapy (CTT) with bevacizumab, sorafenib and temsirolimus in advanced renal cell carcinoma (BeST)	NCT00378703	360	Recruiting
Phase I/II trial of RAD001 plus Nexavar® for patients with metastatic renal cell carcinoma	NCT00448149	55	Recruiting
ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma	NCT00326898	1332	Recruiting
Mechanistic evaluations on sorafenib induced hypophosphatemia in patients with advanced renal cell carcinoma	NCT00622479	50	Not yet recruiting
A phase 2 study of sorafenib (BAY 43–9006) in metastatic renal cell cancer to the brain	NCT00301847	44	Active, not recruiting
Phase I/II trial of sorafenib (Nexavar) and RAD001 (everolimus) in the treatment of patients with advanced clear cell renal cell carcinoma	NCT00392821	81	Recruiting
A phase II neoadjuvant clinical trial to evaluate the efficacy of BAY 43–9006 (sorafenib) in metastatic renal cell carcinoma	NCT00126659	45	Active, not recruiting
A phase II clinical trial to evaluate the efficacy of BAY 43–9006 with or without low dose interferon in metastatic renal cell carcinoma	NCT00126594	80	Active, not recruiting
A phase I/II trial of BAY 43–9006 plus gemcitabine and capecitabine in the treatment of patients with advanced renal cell carcinoma	NCT00121251	35	Recruiting
A phase I/II trial of BAY 43–9006 in combination with bevacizumab in patients with advanced renal cell cancer	NCT00126503	58	Recruiting
A phase II study of the Raf-kinase inhibitor BAY 43–9006 (NSC0724772, IND 69,896) in combination with interferon-α2B in patients with advanced renal cancer	NCT00101114	Not reported	Completed

Sources: www.ukcrn.org.uk/index/clinical/portfolio_new/P_search.html, www.controlled-trials.com/mrct/, www.clinicaltrials.gov/, www.controlled-trials.com/ukctr/.

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We look forward to hearing from you.

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