Bevacizumab in combination with a taxane for the first-line treatment of HER2-negative metastatic breast cancer 📄

M Rodgers,[1]* M Soares,[2] D Epstein,[2] H Yang,[1] D Fox[1] and A Eastwood[1]

[1]Centre for Reviews and Dissemination, University of York, York, UK
[2]Centre for Health Economics, University of York, York, UK

*Corresponding author

Declared competing interests of authors: none

Abstract

This paper presents a summary of the evidence review group (ERG) report into the use of bevacizumab (Avastin®, Roche) in combination with a taxane for the treatment of untreated metastatic breast cancer (mBC). The main clinical effectiveness data were derived from a single, open-label randomised controlled trial (RCT) (E2100) that evaluated the addition of bevacizumab to weekly (q.w.) paclitaxel in patients with human epidermal growth factor receptor 2-negative mBC who had not previously received chemotherapy for advanced disease. This

trial reported statistically significant increases in median progression-free survival (PFS) for the addition of bevacizumab (5.8–11.3 months). Median overall survival was not significantly different between the two groups; whether this is a true null finding or due to crossover between treatment arms cannot be established, as relevant data were not collected. The manufacturer reported that the addition of bevacizumab to paclitaxel q.w. therapy was associated with a significant improvement in quality of life, as measured by FACT-B (functional assessment of cancer therapy for breast cancer) scores. However, the ERG noted that these results were based on extreme imputed values, the removal of which led to non-significant differences in quality of life. The manufacturer conducted an indirect comparison. However, owing to methodological limitations and concerns about the validity and exchangeability of the included trials, the ERG did not consider the findings to be reliable. One additional relevant RCT [AVADO (Avastin and Docetaxel); BO17708] evaluating the addition of bevacizumab to docetaxel was excluded from the manufacturer's submission. This was summarised by the ERG. In terms of response rate and PFS, AVADO reported a markedly smaller benefit of adding bevacizumab to docetaxel than that reported for adding bevacizumab to q.w. paclitaxel in E2100. AVADO also reported no statistically significant effect of combination therapy versus docetaxel in terms of overall survival. The manufacturer developed a de novo economic model that considered patients with the same baseline characteristics as women in the E2100 trial. The model assessed BEV + PAC – bevacizumab 10 mg/kg every 2 weeks in combination with paclitaxel 90 mg/m² weekly for 3 weeks followed by 1 week of rest; PAC q.w. – paclitaxel (monotherapy) 90 mg/m² weekly for 3 weeks followed by 1 week of rest; DOC – docetaxel (monotherapy) 75 mg/m² on day 1 every 21 days (considered current UK NHS clinical practice in the submission); and GEM + PAC – gemcitabine 1250 mg/m² on days 1 and 8 plus paclitaxel 175 mg/m² on day 1 every 21 days. Pairwise comparisons were made between BEV + PAC and PAC (using the E2100 trial), BEV + PAC and DOC, and BEV + PAC and GEM + PAC. Based on NHS list prices, the manufacturer's model estimated incremental cost-effectiveness ratios (ICERs) for BEV + PAC of £117,803, £115,059 and £105,777 per QALY gained, relative to PAC, DOC and GEM + PAC regimens, respectively. If the NHS Purchasing and Supply Agency prices for PAC with a 10-g cap on the cost per patient of BEV were used instead, the ICERs for BEV + PAC were estimated at £77,314, £57,753 and £60,101 per QALY, respectively. The submission suggested that the regimen of BEV + DOC is not cost-effective because it is considered less effective and more costly than BEV + PAC. Analysis by the ERG suggested that alternative assumptions can increase the ICERs further and, based on current prices, no plausible changes to the model assumptions will bring the ICERs for BEV + PAC lower.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS which is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor (in this instance, Roche). Typically, it is used for new pharmaceutical products that are close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Bevacizumab in combination with a taxane for the first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer*.

Description of the underlying health problem

Breast cancer is the most common cancer in the UK, with almost 45,700 women diagnosed with the disease in 2007.[1] The incidence rates of female breast cancer in the UK have increased by 5% in the last 10 years,[1] and around 260 men are also diagnosed each year.[2,3] In 2008, there were 12,116 deaths from breast cancer in the UK; 12,047 (99%) of these were women and 69 (1%) were men.[4] It is estimated that 16–20% of women diagnosed with breast cancer have advanced disease with metastases, and around 50% of those diagnosed with early (or localised) breast cancer will eventually develop metastatic cancer.[5]

Current UK treatment depends on patients' previous therapy, human epidermal growth factor receptor 2 (HER2) status and oestrogen receptor status. First-line therapy for metastatic breast cancer (mBC) is usually an anthracycline-based regimen; when an anthracycline is not considered appropriate, NICE clinical guideline 81 recommends docetaxel monotherapy as the first-line therapy.[6] Vinorelbine or capecitabine monotherapy is recommended for subsequent treatment.[6]

Scope of the evidence review group report

The decision problem specified by NICE was the use of bevacizumab (Avastin®, Roche), in combination with a taxane, for the treatment of untreated metastatic HER2-negative breast cancer in patients for whom anthracyclines are not appropriate. Bevacizumab is licensed for the first-line treatment of HER2-negative mBC. The decision problem specified that bevacizumab in combination with paclitaxel should be compared with bevacizumab in combination with docetaxel; other comparators specified were docetaxel monotherapy, paclitaxel monotherapy and paclitaxel in combination with gemcitabine.

The outcome measures considered were overall survival (OS), progression-free survival (PFS), response rates, adverse events, health-related quality of life and incremental cost per quality-adjusted life-year (QALY) gained.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's submission (MS) to NICE as part of the STA process.

The ERG appraised the literature searches and carried out a search for ongoing trials. The systematic review methodology was appraised and, owing to the limited quality assessment of included trials in the MS, the ERG performed additional quality assessment. The manufacturer's economic evaluation was appraised using a validated checklist[7] and a descriptive critical review, and the decision model was validated by running the model and conducting sensitivity analyses. The ERG also constructed a de novo decision model in EXCEL (Microsoft Corporation, Redwood, WA, USA) to explore sensitivity analyses and scenarios that were not fully addressed by the manufacturer's model.

Results

Summary of submitted clinical evidence

The clinical effectiveness data were primarily derived from a single, open-label randomised controlled trial (RCT) (E2100[8–16]) that evaluated the addition of bevacizumab to weekly (q.w.) paclitaxel in patients with HER2-negative mBC who had not previously received chemotherapy

for advanced disease. The trial reported statistically significant increases in median PFS from 5.8 to 11.3 months [hazard ratio (HR) 0.54, 95% confidence interval (CI) 0.44 to 0.67] for bevacizumab plus paclitaxel versus paclitaxel alone (*Table 1*). Median OS was not significantly different between the two groups (26.5 vs 24.8 months; HR 0.87, 95% CI 0.72 to 1.05). A post hoc analysis indicated that OS at 1 year was significantly higher with paclitaxel plus bevacizumab than with paclitaxel alone (81.4% vs 74.0%, *p* = 0.017). The addition of bevacizumab to paclitaxel therapy was associated with a significant improvement in quality of life as measured by the FACT-B (functional assessment of cancer therapy for breast cancer) trial outcome index (TOI-B) score at week 33 (*p* = 0.0042) and by the FACT-B total score (TOT-B) at week 17 (*p* = 0.0475) and week 33 (*p* = 0.0046) compared with paclitaxel alone.

The manufacturer conducted an indirect comparison based on the method described by Bucher *et al.*[27] This reported that bevacizumab plus q.w. paclitaxel was associated with a significant improvement in PFS when compared with 3-weekly (q3w) docetaxel (HR 0.56, 95% CI 0.39 to 0.78) and with gemcitabine plus q3w paclitaxel (HR 0.46, 95% CI 0.34 to 0.64). No significant difference was found for PFS between q.w. paclitaxel and q3w docetaxel (HR 1.15, 95% CI 0.89 to 1.48) or between q.w. paclitaxel and gemcitabine plus q3w paclitaxel (HR 0.96, 95% CI 0.76 to 1.21).

TABLE 1 Key characteristics and efficacy data from direct comparison bevacizumab RCTs (E2100 and AVADO)

	E2100[8–16]		AVADO[17–26]		
Participants	HER2-negative mBC not previously treated with chemotherapy (*n* = 722)		HER2-negative previously untreated locally recurrent or mBC (*n* = 736)		
Intervention	Bevacizumab 10 mg/kg + paclitaxel 90 mg/m², q.w.		Bevacizumab 7.5 mg/kg + docetaxel 100 mg/m², q3w Bevacizumab 15 mg/kg + docetaxel 100 mg/m², q3w		
Comparator	Paclitaxel 90 mg/m², q.w.		Placebo + docetaxel: docetaxel 100 mg/m², q3w		
Length of follow-up for the analysis	Patients were enrolled between December 2001 and May 2004		Patients were enrolled between March 2006 and April 2007		
	PFS and objective response		*PFS*		
	Data collected prior to 9 February 2005		Primary analysis: median follow-up 10.2 months Updated analysis: conducted at time of final OS analysis (additional 18 months of follow-up)		
	OS		*OS*		
	Data collected prior to 21 October 2006		Median follow-up 25 months		
	Paclitaxel (*n* = 354)	Bevacizumab + paclitaxel (*n* = 368)	Docetaxel + placebo (*n* = 241)	Bevacizumab 7.5 mg/kg + docetaxel (*n* = 248)	Bevacizumab 15 mg/kg + docetaxel (*n* = 247)
Median PFS (months)	5.8	11.3	8.0	8.7	8.8
			8.2ᵃ	9.0ᵃ	10.1ᵃ
PFS: HR (95% CI)	–	0.48 (0.39 to 0.61)	–	0.79 (0.63 to 0.98)	0.72 (0.57 to 0.90)
			–ᵃ	0.86 (0.72 to 1.04)ᵃ	0.77 (0.64 to 0.93)ᵃ
Response rate (%)	22.2	49.8	44.4	55.2	63.1
			46.4ᵃ	55.2ᵃ	64.1ᵃ
OS: HR (95% CI)	–	0.87 (0.72 to 1.05)	–	1.05 (0.81 to 1.36)	1.03 (0.79 to 1.33)

AVADO, Avastin and Docetaxel (BO17708); CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; q.w., weekly; q3w, 3-weekly.
a   Updated analysis applies for the AVADO trial only.

On the basis of the E2100 study and a large uncontrolled study [ATHENA (Avastin Therapy for Advanced Breast Cancer); MO19391],[28–34] the manufacturer concluded that bevacizumab is not associated with the commonly recognised side effects of cytotoxic anticancer therapies and that the most common adverse events associated with bevacizumab therapy are hypertension and proteinuria.

Summary of submitted cost-effectiveness evidence

The submission identified six cost-effectiveness analyses but stated that they were not relevant as they were all conducted outside the UK. The manufacturer, therefore, justified the development of a de novo economic model that considered patients with the same baseline characteristics as seen in women in the E2100 trial.[8–16] The model assessed:

- BEV + PAC bevacizumab 10 mg/kg (every 2 weeks) in combination with paclitaxel 90 mg/m^2 (weekly for 3 weeks followed by 1 week of rest)
- PAC q.w. paclitaxel (monotherapy) 90 mg/m² weekly for 3 weeks followed by 1 week of rest
- DOC docetaxel (monotherapy) 75 mg/m² on day 1 every 21 days (considered current UK NHS clinical practice in the submission)
- GEM + PAC gemcitabine 1250 mg/m² on days 1 and 8 plus paclitaxel 175 mg/m² on day 1 every 21 days.

Pairwise comparisons were made between BEV + PAC and PAC (using the E2100 trial[8–16]), BEV + PAC and DOC, and BEV + PAC and GEM + PAC.

The model was a Markov model with three states (progression free, progressed and dead) and used a 10-year time horizon. Parametric survival functions were used to model the rate of metastatic disease progression based on data from the E2100 trial.[8–16] Based on the results of the indirect comparison of treatment effects, it was assumed that the rate of disease progression was the same after PAC q.w. as after DOC and after GEM + PAC. It was assumed that the hazard of death after progression was constant over time and the same across all treatments, meaning that any difference in PFS between treatments is mirrored in terms of OS. The costs and disutility associated with treatment-related adverse events were included, based on the incidence of events in the E2100 trial.[8–16] Utility estimates were derived from a non-systematic literature review of studies of patients with breast cancer. A number of cost categories were considered: drug acquisition, drug administration, duration of treatment, supportive care, adverse event and end of life. Two alternative base-case analyses were presented for the acquisition costs of the drugs: product list prices (*British National Formulary*[35]) and PASA (Purchasing and Supply Agency, NHS) prices for paclitaxel along with a capping scheme for the cost to the NHS of bevacizumab.

Based on NHS list prices, the manufacturer's model estimated incremental cost-effectiveness ratios (ICERs) for BEV + PAC of £117,803, £115,059 and £105,777 per QALY gained, relative to PAC, DOC and GEM + PAC regimens, respectively. If PASA prices for PAC with a 10-g cap on the cost per patient of BEV are used instead, the ICERs for BEV + PAC are estimated at £77,314, £57,753 and £60,101 per QALY, respectively. The manufacturer stated that the regimen of BEV + DOC would not be cost-effective compared with BEV + PAC because it is considered less effective and more costly than BEV + PAC, but did not conduct an economic evaluation to compare these regimens. *Table 2* shows the results of the manufacturer's model for BEV + PAC versus PAC q.w.

Commentary on the robustness of submitted evidence
Strengths

The manufacturer's systematic review of the literature used appropriate search methods. The E2100[8–16] RCT was conducted in a relevant population and steps were taken to mitigate against

TABLE 2 Results of the main cost-effectiveness analyses undertaken by the manufacturer and the ERG

Scenario	Analyst	Intervention and comparator	Source of cost data	Source of effectiveness data	Incremental cost (£)	Incremental QALY	ICER (£)
1	MS	BEV + PAC vs PAC q.w.	List prices	E2100 PFS	30,469	0.259	117,803
2	MS	BEV + PAC vs PAC q.w.	PASA prices with cap on BEV	E2100 PFS	19,997	0.259	77,314
3	ERG	BEV + PAC vs PAC q.w.	PASA prices and no cap	E2100 PFS	28,573	0.259	110,475
4	ERG	BEV + DOC vs DOC q3w	List prices	AVADO PFS	34,712	0.136	254,530
5	ERG	BEV + PAC vs PAC q.w.	List prices	E2100 OS	29,675	0.114	259,267

AVADO, Avastin and Docetaxel (BO17708); BEV, bevacizumab; DOC, docetaxel; ERG, evidence review group analysis; ICER, incremental cost-effectiveness ratio; MS, manufacturer's submission; OS, overall survival – QALYs based on extrapolation from estimates of OS; PAC, paclitaxel; PASA, NHS Purchasing and Supply Agency (including discounts); PFS, progression-free survival – QALYs based on extrapolation from estimates of PFS; QALY, quality-adjusted life-year; q.w., weekly; q3w, 3-weekly.

methodological limitations (e.g. intention-to-treat analyses of independently reviewed outcomes were undertaken). The safety evaluation included the most comprehensive and robust study available to assess this outcome.

The MS largely conforms to the NICE reference case for cost-effectiveness analysis and was reasonably clearly presented.

Weaknesses

The manufacturer's search identified a second RCT (the AVADO trial[17–26]) that evaluates the addition of bevacizumab to q3w docetaxel. The manufacturer excluded this trial because they considered the docetaxel dose unrepresentative of UK clinical practice, but this conflicted with clinical advice given to the ERG.

The manufacturer identified an existing economic evaluation but stated that as it was populated with Swiss unit costs the results were not relevant to the NHS.[36] However, the effectiveness estimate used in this study was based on PFS and OS in the E2100 trial[8–16] and therefore has some relevance to this appraisal. This analysis found that the ICER for BEV + PAC versus PAC q.w. was €189,000 per QALY.

Limitations in the collection and analysis of data in E2100[8–16] affect the reliability of the trial's findings. Data were not collected on the treatment regimens received by patients after disease progression; therefore, the influence of postprogression treatment on OS in this trial is unknown. Also, the significant improvements in quality of life reported in E2100[8–16] were based on analyses using extreme imputed data for missing values; without these imputed data, differences between groups are statistically insignificant. These data were not further used in the cost-effectiveness model.

The ERG identified several methodological limitations relating to the indirect comparison. One inclusion criterion (< 60% of patients receiving second-line chemotherapy for mBC) may have been formulated to allow the inclusion of a specific trial. The AVADO trial[17–26] was excluded from the indirect comparison on the basis of docetaxel dose, but another trial that used the

same dose was included.[37] One included trial[38] had compromised internal validity owing to an imbalance in the proportion of patients receiving second-line treatment between the q.w. (16%) and q3w (41%) paclitaxel arms. There was also a lack of similarity in terms of the proportion of patients receiving second-line treatment between included trials (e.g. 55% in Jones *et al.*,[37] 0% in E2100[8–16] and Albain *et al.*[39]), highlighting the issue of exchangeability between treatment effects and different patient samples. Given these methodological limitations identified, the ERG did not consider the findings of the indirect comparison to be reliable.

The manufacturer's cost-effectiveness model did not consider all relevant comparators. Specifically, bevacizumab in combination with either docetaxel or q3w paclitaxel were not formally considered despite the latter being used in clinical practice in the UK. The manufacturer assumed that the rate of death after progression is constant over time and the same for all initial treatments, with the implication that differences in mean PFS between treatments are maintained in the mean OS estimates. However, the E2100 RCT did not find any statistically significant differences in OS, despite finding a statistically significant difference in PFS. The manufacturer stated that this might be because patients received different treatments after progression in each arm, including bevacizumab after failure of paclitaxel monotherapy. However, this may be a strong assumption and alternative model structures were not considered by the manufacturer. The manufacturer's model predicted a greater difference in OS for BEV + PAC versus PAC than in the result of the E2100 trial.[8–16]

The base-case model assumed that the regimens PAC, DOC and GEM + PAC are equally effective; no alternative scenarios were presented.

Despite the use of a disease-specific health-related quality of life instrument in the E2100 trial[8–16] (the FACT-B), no mapping algorithm was used to link this to a preference-based (utility) instrument, such as the European Quality of Life-5 Dimensions (EQ-5D). Instead, external utility estimates were used based on a literature search, which was not systematic. No attempt was made to collate or synthesise the alternative estimates, and the selection of utilities for the model appeared arbitrary.

In an alternative base case, the analysis assumed that the cost of bevacizumab would be capped at 10 g per patient. The ERG understands that the price cap assumed for bevacizumab has not been agreed with the Department of Health and should not, therefore, have been assumed in the model. The patent for docetaxel expired in November 2010, but the manufacturer did not explore the implications of a likely reduction in its acquisition cost. The analysis also ignored the possibility of dose reductions. The extent to which dose reductions occur may differ between alternative treatments, and the ERG expects this to affect the results. The manufacturer undertook no subgroup analysis. The model results were presented as a series of pairwise ICERs comparing BEV + PAC individually with the alternative regimens. This is inappropriate and a full incremental analysis should have been undertaken.

Areas of uncertainty

Efficacy outcomes for bevacizumab plus q.w. paclitaxel versus q.w. paclitaxel alone were based on an interim analysis of the E2100 trial.[8–16] PFS and response data were collected up to February 2005 and OS data were collected up to October 2006. Analysis of more complete follow-up data would be valuable, although the manufacturer stated that no such analyses are available.

The reason for the lack of OS benefit for combination therapy observed in the E2100 trial[8–16] cannot be established, as data on postprogression treatment were not collected.

Methodological limitations in the indirect comparison mean that the relative efficacy of bevacizumab plus q.w. paclitaxel versus comparators other than paclitaxel alone, outlined in the decision model, remains highly uncertain.

The methodological weaknesses in the model described above give rise to a number of uncertainties; the ERG undertook a series of analyses to explore their implications.

The use of the PASA discount (without the cap on the costs of BEV) made little difference to the incremental costs of BEV + PAC versus PAC, compared with using NHS list prices (see *Table 2*).

The ERG evaluated BEV+DOC versus DOC alone based on the results of the AVADO RCT.[17–26] This found that the ICER was more than £250,000 per QALY (see *Table 2*).

The ERG constructed an alternative model that was calibrated to the E2100[8–16] results for OS. The ICER of BEV + PAC versus PAC q.w. was > £250,000 per QALY in the revised model (see *Table 2*). This result should be considered a 'worst-case' scenario regarding the cost-effectiveness of BEV + PAC versus PAC q.w. because it is assumed that there is no difference in OS. The manufacturer's model might be considered a 'best-case' scenario as it assumes that the difference in PFS from the E2100 trial would be fully reflected in an equivalent difference in OS in clinical practice.

Conclusions

Despite some methodological limitations, the E2100 trial[8–16] provides direct evidence to suggest that the addition of bevacizumab to q.w. paclitaxel increases PFS and objective response in the first-line treatment of mBC. This trial fails to show a significant benefit in terms of OS. The ERG noted that the manufacturer inappropriately excluded the large relevant AVADO trial in which the docetaxel dosing regime was generally reflective of UK current practice. The ERG extracted the limited available published data from this trial,[17–26] which reported a markedly smaller benefit in terms of PFS and response rate of adding bevacizumab to docetaxel than was reported for adding bevacizumab to q.w. paclitaxel in E2100[8–16] (see *Table 1*). The AVADO trial also reported a non-significant benefit in combination therapy versus docetaxel monotherapy in terms of OS.[17–26]

Given the considerable limitations in the evidence selected and methods used for the indirect comparison, the manufacturer's reporting of a statistically significant benefit of bevacizumab plus q.w. paclitaxel over the currently recommended first-line treatment of docetaxel monotherapy cannot be considered reliable.

The cost-effectiveness analysis presented by the manufacturer included judgements and assumptions that are subject to uncertainty. The manufacturer's most optimistic analyses suggested an ICER for BEV + PAC versus PAC q.w. of £77,000 per QALY gained using PASA prices for PAC and a 10-g cap on BEV, and £118,000 using NHS list prices. Further analysis by the ERG suggested that more pessimistic assumptions about the relative impact of bevacizumab on OS can increase the ICERs yet further, and, based on current prices, no plausible changes to the model assumptions will bring the ICER for BEV + PAC versus PAC q.w. within the threshold currently considered cost-effective by NICE.

Summary of NICE guidance issued as a result of the STA

The guidance document issued by NICE in February 2011 states that bevacizumab in combination with a taxane is not recommended for first-line treatment of metastatic breast cancer. Following consultation on the appraisal consultation document, the manufacturer provided additional subgroup data; the ERG provided commentary and validity checks on the additional evidence submitted by the manufacturer, as requested by NICE.

During the course of this appraisal, the European Medicines Agency (EMA) conducted a review of the use of bevacizumab in combination with taxanes for the tretment of mBC. Following that review, the EMA's Committee for Medicinal Products for Human Use recommended that bevacizumab, when used to treat mBC, should be used only in combination with the taxane, paclitaxel.

Acknowledgements

Key references

1. Cancer Research UK. *CancerStats key facts on cancer*. URL: http://info.cancerresearchuk.org/cancerstats/keyfacts/index.htm (accessed 30 June 2010).

2. Welsh Cancer Intelligence and Surveillance Unit. *Cancer incidence in Wales 1992–2002*. 2002. URL: www.wales.nhs.uk/sites3/page.cfm?orgid=242&pid=2022 (accessed 30 June 2010).

3. Office for National Statistics. *Cancer statistics registrations: registrations of cancer diagnosed in 2005, England. Series MB1 number 36.* 2008. URL: www.statistics.gov.uk/statbase/Product.asp?vlnk=8843 (accessed 30 June 2010).

4. Cancer Research UK. *Cancer mortality – UK statistics*. URL: http://info.cancerresearchuk.org/cancerstats/mortality/index.htm (accessed 30 June 2010).

5. National Institute for Health and Clinical Excellence. *Technology Appraisal (TA) 34: The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer.* 2002. URL: http://guidance.nice.org.uk/TA34 (accessed 30 June 2010).

6. National Institute for Health and Clinical Excellence. *Clinical Guidelines CG81: Advanced breast cancer: diagnosis and treatment.* 2009. URL: http://guidance.nice.org.uk/CG81 (accessed 30 June 2010).

7. 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.

8. Cameron D. Bevacizumab in the first-line treatment of metastatic breast cancer. *Eur J Cancer* 2008;**6**(Suppl.):21–8.

9. Gray R, Bhattacharya S, Bowden C, Miller K, Comis RL. Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 2009;**27**:4966–72.

10. Klencke BJ, Bhattacharya S, Samant MK, Gralow JR, Dickler MN, Cobleigh MA, *et al.* Independent review of E2100 progression-free survival (PFS) with the addition of bevacizumab (B) to paclitaxel (P) as initial chemotherapy for metastatic breast cancer (MBC). *J Clin Oncol* 2008;**26**(Suppl.):abstract 1036.

11. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, *et al.* Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007;**357**:2666–76.

12. Miller K, Wang M, Gralow J, Dickler M, Cobleigh MA, Perez EA, *et al.* First-line bevacizumab and paclitaxel in patients with locally recurrent or metastatic breast cancer: a randomized, phase III trial coordinated by the Eastern Cooperative Oncology Group (E2100). *Eur J Cancer* 2005;**3**:77–8.

13. Miller KD. E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. *Clin Breast Cancer* 2003;**3**:421–2.

14. Miller KD, Wang W, Gralow J. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100) *Breast Cancer Res Treat* 2005;**94**(Suppl. 1):6, abstract 3.

15. Wagner L, Wang M, Miller K. Health-related quality of life among patients with metastatic breast cancer receiving paclitaxel versus paclitaxel plus bevacizumab: results from the eastern cooperative oncology group (ECOG) study E2100. *Breast Cancer Res Treat* 2006;**100**(Suppl. 1):239, abstract 5078.

16. Zon R, Miller KD, Wang M, Gralow J, Dickler M, Cobleigh M, *et al.* A randomized phase III trial of paclitaxel with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: Eastern Cooperative Oncology Group trial E2100. *Eur J Cancer* 2006;**4**(Suppl.):47.

17. Chan A, Vanlemmens L, Conte PF, Beith J, Samonigg H, Verma S, *et al.* Efficacy of bevacizumab (BV) plus docetaxel (D) does not correlate with hypertension (HTN), or G-CSF use in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) in the AVADO phase III study. *Cancer Res* 2009;**69**(Suppl.):abstract 1027.

18. Cortés J, Pivot X, Schneeweiss A, Wilcken N, Ellis P, Linderholm BK, *et al.* Safety of surgery in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) treated with docetaxel (D) plus bevacizumab (BV) or placebo (PL) in the AVADO phase III study. *Cancer Res* 2009;**69**(Suppl.):abstract 1030.

19. Dirix LY, Romieu G, Provencher L, Grimes D, de Souza Viana L, Paterson A, *et al.* Safety of bevacizumab (BV) plus docetaxel (D) in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) who developed brain metastases during the AVADO phase III study. *Cancer Res* 2009;**69**(Suppl.):abstract 4116.

20. Fumoleau P, Greil R, Rayson D, Müller V, Barni S, Aleknavicius E, *et al.* Maintenance therapy of bevacizumab (BV) results in superior PFS compared with placebo (PL) in the AVADO trial (BV + docetaxel [D] vs D + PL in first-line HER2-negative locally recurrent [LR] or metastatic breast cancer [mBC]). *Cancer Res* 2009;**69**(Suppl.):abstract 903.

21. Greil R, Im YH, Pienkowski T, Wardley A, Awada A, Ciruelos E, *et al.* Quality of life (QoL) in patients (pts) treated with bevacizumab (BV) and taxane therapy for locally recurrent (LR) or metastatic breast cancer (mBC). *Eur J Cancer Suppl* 2009;**7**:266.

22. Harbeck N, Chan A, ten Bokkel Huinink D, Chollet P, Gimenes D, Fabiani C, *et al.* No clinical evidence for increase in tumour aggressiveness or metastatic spread in patients with metastatic breast cancer (mBC) treated with bevacizumab (BV) and docetaxel (D) in the phase III AVADO study. *Cancer Res* 2009;**69**(Suppl.):abstract 6086.

23. Miles D, Chan A, Romieu G, Dirix L, Cortés J, Pivot X, *et al.* Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC). *Cancer Res* 2009;**69**(Suppl.):abstract 41.

24. Miles D, Chan A, Romieu G, Dirix LY, Cortes J, Pivot X, *et al.* Randomised, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol* 2008;**26**(Suppl.):abstract LBA1011.

25. Pivot X, Verma S, Thomssen C, Passos-Coelho JL, Latini L, Ciruelos E, *et al.* Clinical benefit of bevacizumab (BV) + first-line docetaxel (D) in elderly patients (pts) with locally-recurrent or metastatic breast cancer (mBC): AVADO study. *J Clin Oncol* 2009;**27**(Suppl.):abstract 1094.

26. Wardley A, Lohrisch C, Joy AA, Young S, Yi FF, Marme A, *et al.* Effect of anticoagulation therapy on bleeding and thromboembolic events (TEs) in the AVADO phase III study of bevacizumab (BV) plus docetaxel (D) in locally recurrent (LR) or metastatic breast cancer (mBC) *Cancer Res* 2009;**69**(Suppl.):abstract 1035.

27. 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.

28. Biganzoli L, Cortes-Funes H, Thomssen C, Pritchard KI, Pierga J, Kupp A, *et al.* Tolerability and efficacy of First-line bevacizumab (B) plus chemotherapy (CT) in elderly patients with advanced breast cancer (aBC): subpopulation analysis of the MO19391 study. *J Clin Oncol* 2009;**27**(Suppl.):abstract 1032.

29. Cortes-Funes H, Pritchard KI, Biganzoli L, Thomssen C, Pierga J, Koza I, *et al.* Multinational study (n=2041) of first-line bevacizumab (Bev) plus taxane-based chemotherapy (CT) for locally recurrent or metastatic breast cancer (LR/mBC): updated results of MO19391. *Eur J Cancer* 2009;**7**(Suppl.):265–6.

30. Pierga J, Pritchard KI, Cortes-Funes H, Biganzoli L, Thomssen C, Franke FA, *et al. MO*19391: an open-label safety study of bevacizumab plus taxane-based therapy as first-line treatment of patients with locally recurrent (LR) or metastatic breast cancer (MBC). *J Clin Oncol* 2008;**26**(Suppl.):abstract 1140.

31. Pierga J, Pritchard KI, Thomssen C, Cortes-Funes H, Biganzoli L, Padrik P, *et al.* Safety and efficacy of 1st-line bevacizumab (B) plus chemotherapy (CT) for locally recurrent or metastatic breast cancer (LR/mBC): analysis of MO19391 according to CT. *J Clin Oncol* 2009;**27**(Suppl.):abstract 1033.

32. Smith I, Biganzoli L, Cortes-Funes H, Franke F, Mostafa Kamel Y, Pierga JY, *et al. MO*19391: an open-label safety study of bevacizumab plus taxane monotherapy or in combination as first-line treatment of patients with locally recurrent or metastatic breast cancer (LR or MBC). *Eur J Cancer* 2007;**5**(Suppl.):221.

33. Smith I, Biganzoli L, Cortés-Funes H, Stroyakovskiy D, Franke FA, Chlistalla A, *et al.* Primary analysis of study MO19391, an open-label safety study of bevacizumab plus

taxane-based therapy as first-line treatment of patients with locally recurrent (LR) or metastatic breast cancer (mBC). *Cancer Res* 2009;**69**(Suppl.):abstract 4118.

34. Thomssen C, Pierga J, Pritchard K, Biganzoli L, Cortes-Funes H, Petrakova K, *et al.* First-line bevacizumab (Bev) combination therapy in triple-negative (TN) locally recurrent/metastatic breast cancer (LR/MBC): subpopulation analysis of study MO19391 in > 2000 patients (Pts). *Cancer Res* 2009;**69**(Suppl.):abstract 6093.

35. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary.* No. 58, September 2009. London: BMA and RPS; 2009.

36. Dedes KJ, Matter-Walstra K, Schwenkglenks M, Pestalozzi BC, Fink D, Brauchli P, *et al.* Bevacizumab in combination with paclitaxel for HER-2 negative metastatic breast cancer: an economic evaluation. *Eur J Cancer* 2009;**45**:1397–406.

37. Jones SE, Erban J, Overmoyer B, Budd GT, Hutchins L, Lower E, *et al.* Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 2005;**23**:5542–51.

38. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, *et al.* Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008;**26**:1642–9.

39. Albain KS, Nag SM, Calderillo-Ruiz G, Jordaan JP, Llombart AC, Pluzanska A, *et al.* Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol* 2008;**26**:3950–7.