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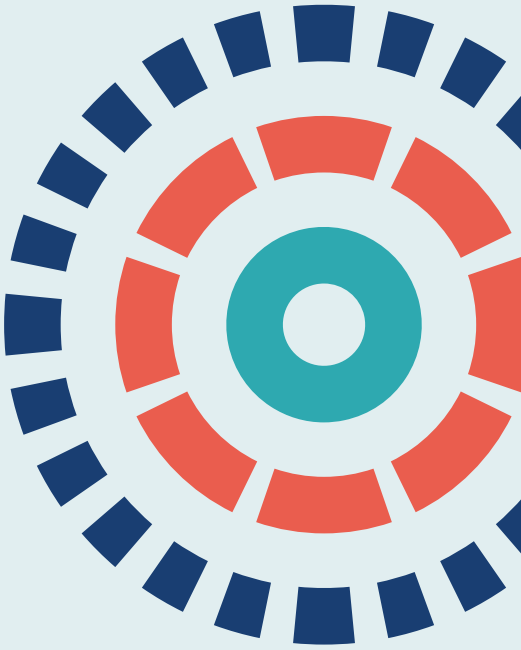

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Modelling approaches for histology-independent cancer drugs to inform NICE appraisals: a systematic review and decision-framework

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This report

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Abstract

Modelling approaches for histology-independent cancer drugs to inform NICE appraisals: a systematic review and decision-framework

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Background: The first histology-independent marketing authorisation in Europe was granted in 2019. This was the first time that a cancer treatment was approved based on a common biomarker rather than the location in the body at which the tumour originated. This research aims to explore the implications for National Institute for Health and Care Excellence appraisals.

Methods: Targeted reviews were undertaken to determine the type of evidence that is likely to be available at the point of marketing authorisation and the analyses required to support National Institute for Health and Care Excellence appraisals. Several challenges were identified concerning the design and conduct of trials for histology-independent products, the greater levels of heterogeneity within the licensed population and the use of surrogate end points. We identified approaches to address these challenges by reviewing key statistical literature that focuses on the design and analysis of histology-independent trials and by undertaking a systematic review to evaluate the use of response end points as surrogate outcomes for survival end points. We developed a decision framework to help to inform approval and research policies for histology-independent products. The framework explored the uncertainties and risks associated with different approval policies, including the role of further data collection, pricing schemes and stratified decision-making.

Results: We found that the potential for heterogeneity in treatment effects, across tumour types or other characteristics, is likely to be a central issue for National Institute for Health and Care Excellence appraisals. Bayesian hierarchical methods may serve as a useful vehicle to assess the level of heterogeneity across tumours and to estimate the pooled treatment effects for each tumour, which can inform whether or not the assumption of homogeneity is reasonable. Our review suggests that response end points may not be reliable surrogates for survival end points. However, a surrogate-based modelling approach, which captures all relevant uncertainty, may be preferable to the use of immature survival data. Several additional sources of heterogeneity were identified as presenting potential challenges to National Institute for Health and Care Excellence appraisal, including the cost of testing, baseline risk, quality of life and routine management costs. We concluded that a range of alternative approaches will be required to address different sources of heterogeneity to support National Institute for Health and Care Excellence appraisals. An exemplar case study was developed to illustrate the nature of the assessments that may be required.

Conclusions: Adequately designed and analysed basket studies that assess the homogeneity of outcomes and allow borrowing of information across baskets, where appropriate, are recommended. Where there is evidence of heterogeneity in treatment effects and estimates of cost-effectiveness, consideration should be given to optimised recommendations. Routine presentation of the scale of the consequences of heterogeneity and decision uncertainty may provide an important additional approach to the assessments specified in the current National Institute for Health and Care Excellence methods guide.

Further research: Further exploration of Bayesian hierarchical methods could help to inform decision-makers on whether or not there is sufficient evidence of homogeneity to support pooled analyses. Further research is also required to determine the appropriate basis for apportioning genomic testing costs where there are multiple targets and to address the challenges of uncontrolled Phase II studies, including the role and use of surrogate end points.

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List of abbreviations

ALK	anaplastic lymphoma kinase
BHM	Bayesian hierarchical model
BICR	blinded independent central radiologist
BRMA	bivariate random effects meta-analysis
BSES	Biomarker-Surrogate Evaluation Schema
CDF	Cancer Drugs Fund
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrI	credible interval
ctDNA	circulating tumour DNA
dMMR	deficient mismatch repair
DoR	duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ePAS	extended patient analysis set
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EVPPI	expected value of partial perfect information
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridisation
GI	gastrointestinal
GIST	gastrointestinal stromal tumour
GMI	growth modulation index
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IFS	infantile fibrosarcoma
IHC	immunohistochemistry
IPD	individual patient data
IQR	interquartile range
IQWiG	Institute for Quality and Efficiency in Health Care
IRC	Independent Review Committee
ITT	intention to treat
KRAS	Kirsten rat sarcoma
LYG	life-years gained
MAA	managed access agreement
MAIC	matching-adjusted indirect comparison
MASC	mammary analogue secretory carcinoma
MCC	Merkelcell carcinoma
MSI-H	microsatellite instability high
NE	not estimable
NET	neuroendocrine tumour
NGS	next-generation sequencing
NHB	net health benefit
NHL	non-Hodgkin's lymphoma
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
NNS	number needed to screen
NPV	negative predictive value
NSCLC	non-small cell lung cancer

NTRK	neurotrophic tyrosine receptor kinase
OR	odds ratio
ORR	overall response rate
OS	overall survival
PAS	primary analysis set
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PPS	post-progression survival
PPV	positive predictive value
PR	partial response
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
QALY	quality-adjusted life-year
RCP	Royal College of Pathologists
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	relative risk
RRcHL	relapsed or refractory classical Hodgkin's lymphoma
RT-PCR	reverse transcription polymerase chain reaction
SAG	Scientific Advisory Group
SAP	statistical analysis plan
SCLC	small cell lung cancer
SmPC	summary of product characteristics
SoC	standard of care
STC	Simulated Treatment Comparison
STE	surrogate threshold effect
TA	technology appraisal
TKI	tyrosine kinase inhibitor
TRK	tyrosine kinase
TSD	technical support document
TTE	time to event
TTP	time to progression
TTR	time to response
VGPR	very good partial response
VoH	value of heterogeneity
VOI	value of information
WGS	whole genome sequencing

Plain English summary

In May 2017, the US Food and Drug Administration granted the first approval for a cancer treatment based on a common biomarker rather than the location in the body at which the tumour originated (the tumour site); that is, a site-agnostic or 'histology-independent' indication was granted. Research from the National Institute for Health and Care Excellence suggests that there are approximately 20 technologies currently in development for histology-independent indications. The first marketing authorisation was granted in Europe in 2019.

Histology-independent treatments have the potential to have important effects in patient populations for whom there are currently limited or no available treatment options. However, it is also important to ensure that the use of these treatments in the NHS is supported by systematic and robust assessments of clinical evidence (i.e. how well the medicine or treatment works) and economic evidence (i.e. the medicine's value for money). These assessments are undertaken by the National Institute for Health and Care Excellence, usually for treatments targeting specific tumours sites. However, a histology-independent marketing authorisation would probably include many tumour sites and it is not possible for the National Institute for Health and Care Excellence to conduct a separate assessment for each tumour site for which the treatment could be beneficial. As a result, the National Institute for Health and Care Excellence needs to consider how these products can be appropriately assessed without creating unnecessary delays in patient access.

This research explores the extent to which the National Institute for Health and Care Excellence's existing approaches for assessing clinical and economic value can be applied to histology-independent indications, and any changes that might be required. We explore the nature and amount of evidence that is typically available at the point of initial marketing authorisation and develop recommendations to establish the evidence and analyses required to help inform the National Institute for Health and Care Excellence's decisions. We use case studies to highlight possible challenges and to explore ways that these challenges might be addressed. This research will help to inform future National Institute for Health and Care Excellence policy on how to appraise cancer drugs with histology-independent indications. It will also inform the development of guidance for those developing these treatments to help their understanding of the clinical effectiveness and cost-effectiveness assessments that will be required to inform the National Institute for Health and Care Excellence's appraisals.

Scientific summary

Background

In 2017, the US Food and Drug Administration (FDA) granted approval to pembrolizumab (Keytruda, Merck Group, Darmstadt, Germany) for the treatment of solid tumours with the microsatellite instability high (MSI-H) or the deficient mismatch repair (dMMR) biomarker. This was the first time that a cancer treatment was approved based on a common biomarker rather than the location in the body at which the tumour originated. It represented an important paradigm shift, which means that oncological diseases can now be classified by either tumour biomarker status or tumour histogenesis. The first histology-independent marketing authorisation was granted by the European Medicines Agency (EMA) in 2019.

A histology-independent marketing authorisation will include a large number of individual tumour sites. It is unlikely to be feasible or desirable for the National Institute for Health and Care Excellence (NICE) to conduct separate appraisals for each individual tumour site to inform whether or not approval of these products represents an efficient use of NHS resources. However, the scope of histology-independent indications and the nature of the evidence base will pose important challenges to the appropriate quantification of their value and the effective mitigation of any additional risks. NICE needs to consider how to develop a process that will allow a single, biomarker-driven appraisal for these drugs.

This research aims to inform future NICE policy on how to appraise cancer drugs with histology-independent indications.

Objectives

We sought to explore the implications of histology-independent products for the NICE technology appraisal (TA) process. The specific objectives were to:

1. identify the nature of the evidence likely to be available at initial marketing authorisation
2. determine the types of evidence and analyses required to support NICE appraisal
3. develop a case study to highlight methods and evidence challenges, and to explore alternative ways of addressing these challenges
4. develop a conceptual framework to establish the evidence and analyses required to guide NICE decision-making and potential Cancer Drugs Fund (CDF) data collection requirements
5. suggest any changes to the current NICE methods guide or additional requirements relating to histology-independent drugs
6. make recommendations for further research.

Methods

We undertook a series of targeted reviews to determine the type of evidence that is likely to be available at initial marketing authorisation and to consider the analyses required to support a NICE appraisal. These reviews included:

1. a review of FDA and EMA websites to identify relevant documents relating to regulatory issues and benefit–risk approaches for histology-independent indications
2. an overview of key statistical literature addressing the design and analysis of histology-independent trials
3. a systematic review to identify published meta-analyses evaluating the use of overall response rate (ORR) and duration of response (DoR) as surrogate end points for progression-free survival (PFS) and overall survival (OS).

These reviews were used to identify specific challenges for histology-independent appraisals and to identify approaches that might be used to investigate and account for different sources of uncertainty and heterogeneity.

We developed an exemplar model to illustrate the nature of the assessments that could be used to assess the cost-effectiveness of a new histology-independent treatment and to inform NICE decision-making. A framework to inform approval and research policies was also proposed to help determine the appropriateness of different policy recommendations and to identify key uncertainties that might inform and prioritise the value of further data collection.

Based on these findings, a series of recommendations were made concerning potential changes to the current NICE methods guide and priorities for further methodological research.

Results

Review of regulatory issues and benefit–risk approaches relevant for histology-independent indications

Our review found that histology-independent products are likely to be evaluated using more complex study designs that are intended to increase the efficiency of the drug development process, specifically basket trials with master protocols. Master protocols are used to evaluate multiple drugs and/or multiple cancer subpopulations in parallel, using a single protocol. Basket trials are used to evaluate a single investigational drug or drug combination in different populations (defined by disease stage, histology or treatment history), and are usually designed as single-arm activity-estimating trials with ORR as the primary end point.

Our review highlighted the importance placed by the regulators in the underlying biological rationale and strength of existing clinical evidence to support the assumption that a biomarker-defined population is sufficient to establish clinically relevant activity, independent of tumour histology. Importantly, neither the FDA nor the EMA concluded that the evidence for the existing histology-independent products was sufficient to support a routine approval decision. Although the treatment effect observed in the overall population was considered to be clinically important, the initial approvals were conditional on additional requirements for further evidence generation to increase the precision of the effect estimates and extend the length of follow-up. Hence, important new evidence will emerge over time.

Overview of key statistical literature addressing the design and analysis of trials

A critical consideration in the design of histology-independent trials is the potential for heterogeneity in prognosis across the different histologies; therefore, standardised response rates, reflecting tumour shrinkage, are typically used instead of survival outcomes. In addition, randomisation to a control arm is rare in basket trials owing to the differences in standard of care across the different tumour types. The reliance on surrogate outcomes and the lack of a concurrent, randomised, control arm remains a key limitation of these trial designs and for the interpretation of such trials for NICE appraisal.

Heterogeneity of effect across different baskets is a key consideration in the analysis of histology-independent trials. Once a decision has been made on whether or not heterogeneity is present, the analysis typically proceeds either as separate, independent studies for each basket or as a single aggregate study combining all of the baskets. Thus, either complete homogeneity or completely unrelated effects are assumed. A less restrictive assumption is that efficacy is similar (rather than equal or completely different) across baskets. Bayesian hierarchical models (BHMs) are particularly suited for this situation because they estimate the heterogeneity and allow borrowing of information on the

effects of the treatment across baskets. However, the BHM is advantageous only if it is considered reasonable to allow such borrowing. Alternatives to complete pooling or borrowing have been proposed, which extend the BHM to allow borrowing of information across similar baskets while avoiding overly optimistic borrowing for extreme baskets.

Although it is challenging to determine the correct level of borrowing of information, BHM approaches provide an explicit basis to allow the treatment effect in any basket to be informed by the effects in all other baskets, therefore maximising the information available.

A systematic review to identify published meta-analyses evaluating the use of response rates and duration of response as surrogate end points for progression-free and overall survival

In the context of histology-independent treatments, data on OS and potentially other time-to-event outcomes, such as PFS, are likely to be immature. Consequently, there may be a need to rely on surrogate outcomes, such as response rate, using data from external sources to estimate other more clinically meaningful final outcomes for NICE appraisal. We undertook a systematic review to assess the strength of the association between response outcomes and PFS, time to progression (TTP) or OS across different types of cancer (primarily advanced or metastatic), based on meta-analyses or meta-regression studies assessing the statistical relationship between these outcomes. Alternative sets of criteria were used to assess the strength of association between surrogate and final end points.

A total of 63 studies were included in the review, across 20 different cancer types. The most commonly analysed relationships were between ORR and either PFS or OS. The association between response outcomes and PFS/TTP/OS was found to vary widely between studies, and generally scored low to medium when assessed using existing criteria. No clear pattern for strength of association was identified by cancer type.

Our findings indicate that response end points may not be reliable surrogates for PFS or OS. However, despite the weak validity of response as a surrogate for PFS and OS, we concluded that it might still be preferable for NICE appraisals to adopt a surrogate-based modelling approach informed by predictions from meta-analyses that capture all relevant uncertainty, rather than ignoring surrogate relationships and extrapolating heavily censored PFS and OS data.

Exemplar case study

We also identified several additional potential challenges for NICE appraisals, including the need to account for heterogeneity in a number of areas, including the cost of testing, baseline risk, quality of life and routine management costs. A range of alternative analytical approaches are likely to be required to address these different areas.

The use of a single assessment of the incremental cost-effectiveness ratio (ICER) across multiple tumour sites with potentially different treatment effectiveness, comparators, costs and quality of life may be challenging for NICE to interpret. A single ICER may conceal significant variation in the tumour-specific ICERs, driven by a combination of factors, including observable variability in relative effectiveness between tumour types. Ignoring these differences could mean that a treatment that is not cost-effective for the total population may be cost-effective in specific subgroups. Conversely, a treatment that appears cost-effective for the total population may not be cost-effective in particular subgroups. Given the amount of heterogeneity associated with a histology-independent appraisal, estimating the average cost-effectiveness for the full patient population covered by the product's licence may not provide enough information to decision-makers about whether or not the drug is potentially cost-effective across all subgroups.

Given the importance of exploring the impact of heterogeneity on decision-making, explicit and transparent approaches are required that can accommodate different sources of heterogeneity within the overall population. These assessments should allow consideration of the average cost-effectiveness for the full patient population covered in the marketing authorisation, as well as facilitating an assessment of whether or not the drug is potentially cost-effective across relevant subgroups. The BHM framework provides an important approach that can more fully explore the potential heterogeneity in effects across tumours. The BHM approach allows assessments to be made for each tumour type, as well as a pooled assessment across all tumour types, accounting for the potential lack of uniformity of effect across tumours. An additional advantage of this type of model is the ability to predict the response probability that would be expected in a 'new' tumour type (i.e. a tumour that is not represented in the trial data), which will give a measure of the uncertainty in the response rates in tumour types in the target population but for which no data are available.

An exemplar case study was developed to illustrate the nature of the assessments that could be used to evaluate the cost-effectiveness of a new histology-independent treatment. The case study considered a hypothetical tyrosine kinase (TRK) inhibitor ('Drug X') for the treatment of solid tumours that harbour a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion compared with the current standard of care. The economic model used a landmark response-based structure incorporating separate PFS and OS distributions, conditioned on response status in the overall study population. Heterogeneity in response rates across individual tumour sites was reflected using a BHM approach. By linking the BHM estimates for response rates to conditional OS and PFS estimates, the case study model explores the implications for cost-effectiveness of heterogeneity in the overall population by considering individual histology-specific estimates of cost-effectiveness alongside estimates for the overall population.

In line with the NICE reference case, the model was based on a NHS and Personal Social Services perspective using a 3.5% discount rate. Results are presented over a lifetime (i.e. 30-year) time horizon.

The case study demonstrated the importance of understanding the frequency of histologies expected in the target population and the necessity of modelling histology-specific costs and health consequences. When the expected distribution of histologies is expected to differ between the trial and the target population, failure to account for this could result in a biased estimate of the pooled ICER. The magnitude of any bias will depend on the extent of heterogeneity in the relevant model inputs between tumour sites. Consideration will also be needed as to the potential effect in tumour histologies that are not represented in the trial data.

The case study also highlighted that even if homogeneity in all other model inputs is assumed between individual histologies (or other subgroups), the cost-effectiveness estimates will inevitably vary based on differences in the costs of identifying patients with the specific biomarker. The results demonstrate that even a low per-patient testing cost can result in significant variation in the ICER estimates driven by different biomarker prevalence rates across individual histologies.

The case study was used to illustrate how heterogeneity could be explored using pooled ICERs and individual histology ICERs to inform decision-making. However, ICERs have an important limitation: they do not give an indication of the scale of consequences for population health. Understanding the benefits and costs of treatment at a population level will help to interpret the consequences of decision-making in the presence of heterogeneity and uncertainty.

We developed a decision framework that could be used to inform approval and research policies for histology-independent products. The framework explored the uncertainties and risks associated with different approval policies. Alternative approaches to managing risk were identified, including the role of further data collection, the use of pricing schemes and stratified decision-making.

Conclusions

Our research found that the potential for heterogeneity in a range of model inputs, either across tumour histologies or other characteristics, is likely to be an important issue for NICE appraisals of histology-independent technologies. Consideration should be given to the appropriateness of the assumptions of homogeneity of treatment effects and NICE committees should expect to see an exploration of this assumption in company submissions. Where there is evidence of heterogeneity in treatment effects and estimates of cost-effectiveness, consideration should be given to optimised or 'stratified' recommendations. Routine presentation of the scale of the consequences of heterogeneity and decision uncertainty may provide an important additional approach to the assessments specified in the current NICE methods guide.

We identified several areas requiring further research. First, further exploration of BHM could help to determine whether or not there is sufficient evidence of homogeneity to support pooled analyses. Second, further research is required to determine the appropriate basis for apportioning genomic testing costs where there are multiple targets. Finally, further research is required concerning the challenges of uncontrolled Phase II studies and specifically the role and use of surrogate end points.

Funding

This project was funded by the National Institute for Health Research (NIHR) Evidence Synthesis programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 76. See the NIHR Journals Library website for further project information.

Chapter 1 Background

In May 2017, the US Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab (Keytruda, Merck Group, Darmstadt, Germany) for the treatment of solid tumours with the microsatellite instability high (MSI-H) or the deficient mismatch repair (dMMR) biomarker.[1] This was the first time that a cancer treatment was approved based on a common biomarker rather than the location in the body where the tumour originated (i.e. a histology-independent approval). It represented an important paradigm shift, meaning that oncological diseases can now be classified by either tumour biomarker status or tumour histogenesis. The first histology-independent marketing authorisation was also granted by the European Medicines Agency (EMA) in 2019.[2]

A histology-independent marketing authorisation would probably include a large number of tumour sites. For example, the main larotrectinib (Vitrakvi, Loxo Oncology Inc., Stamford, CT, USA, and Bayer, Leverkusen, Germany) study enrolled patients across 12 tumour types.[3] Given that it is unlikely to be feasible or desirable to conduct a separate appraisal for each tumour site contained within a histology-independent indication, the National Institute for Health and Care Excellence (NICE) will need to consider how to develop a process/approach that will allow a single, biomarker-driven appraisal for histology-independent cancer drugs.

This research aims to inform future NICE policy on how to appraise cancer drugs with histology-independent indications.

Aims and objectives

The main aim of the project was to explore the implications for the NICE technology appraisal (TA) process of assessing histology-independent products. The specific objectives were to:

1. determine the types of evidence and analyses required to support NICE appraisals of histology-independent products
2. identify the nature of the evidence likely to be available at the point of marketing authorisation
3. identify and implement a case study to highlight methods and evidence challenges and to explore alternative ways of addressing these
4. develop a conceptual framework to establish the evidence and analyses required to inform cost-effectiveness analyses and to guide NICE decision-making and potential Cancer Drugs Fund (CDF) data collection requirements
5. suggest any specific changes to the current NICE methods guide[4] for TAs or additional requirements relating to histology-independent drugs
6. make recommendations for further methodological research.

Objectives 1 and 2 are addressed in *Chapters 2–5*. We undertook a series of targeted reviews to determine the type of evidence that is likely to be available at the point of marketing authorisation and to consider the evidence and analyses likely to be required to support a NICE appraisal.

These reviews included:

- a review of FDA and EMA websites to identify relevant documents relating to regulatory issues and benefit–risk approaches relevant for histology-independent indications (see *Chapter 2*)
- an overview of key statistical literature addressing the design and analysis of histology-independent trials (see *Chapter 3*)

- a systematic review to identify published meta-analyses evaluating the use of overall response rate (ORR) and duration of response (DoR) as surrogate end points for progression-free survival (PFS) and overall survival (OS) (see *Chapter 4*)
- a targeted review of published NICE TAs where marketing authorisation was based on single-arm studies using ORR as a primary outcome (see *Chapter 5*).

Objectives 3 and 4 are addressed in *Chapters 6* and *7*. *Chapter 6* outlines a series of challenges for histology-independent appraisals and presents alternative approaches that might be used to investigate and account for different sources of uncertainty and heterogeneity. *Chapter 7* presents an exemplar economic model to illustrate the nature of the assessments that could be used to assess the cost-effectiveness of a new histology-independent treatment and to inform NICE decision-making. A framework to inform approval and research policies for histology-independent technologies is proposed to help determine the appropriateness of different policy recommendations and to identify key uncertainties that might be used to inform and prioritise the value of further data collection.

Objectives 5 and 6 are addressed in *Chapter 8*. Based on the findings of the research, a series of recommendations are provided concerning whether or not changes in the current NICE methods guide are required for the appraisal of histology-independent products. Finally, a series of recommendations are provided concerning priorities for further methodological research.

Chapter 2 A review of Food and Drug Administration and European Medicines Agency documents relating to regulatory issues and benefit–risk approaches relevant for histology-independent indications

A targeted search of the FDA and EMA websites was conducted to identify relevant documents outlining regulatory approaches to the evaluation of histology-independent indications. The FDA and EMA websites were searched using the following key terms: 'histology-independent', 'site-agnostic' and 'tissue-agnostic'. A narrative review of relevant documents was undertaken to summarise the regulatory requirements and guidance, including arrangements for post-licensing data collection. The objective was to provide insights into the current regulatory context for the benefit–risk evaluations performed by the FDA and EMA and to consider their relevance for economic modelling.

It is likely that histology-independent approvals will be granted via accelerated or conditional approval processes from the FDA and EMA. Hence, the narrative review was supplemented with relevant regulatory documents related to these processes. The list of identified regulatory sources considered is reported in *Appendix 1*.

The targeted searches were also used to identify any completed FDA/Oncologic Drugs Advisory Committee and EMA/Committee for Medicinal Products for Human Use (CHMP) reviews of existing histology-independent products to provide further insights into the nature of the evidence available at the time of approval, the key issues and uncertainties raised by FDA and EMA in assessing benefits and risks, and the nature of any mandated post-licensing data collection requirements.

Food and Drug Administration guidance for histology-independent products

The website searches yielded two preliminary guidance documents issued by the FDA in 2018, which addressed issues specific to histology-independent products: *Developing Targeted Therapies in Low-frequency Molecular Subsets of a Disease*[5] and *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics*.[6]

The FDA defines a therapy as 'targeted' if it is intended for subsets of patients within a clinically defined disease based on either a common molecular alteration or a grouping of different underlying molecular alterations that share a common functional effect. The FDA guidance on developing targeted therapies in low-frequency molecular subsets focuses on two main issues that appear relevant to histology-independent products: (1) recommendations on how to group patients with different molecular alterations for eligibility in clinical trials and (2) general approaches to evaluating the benefits and risks of targeted therapies, where some molecular alterations may occur at low frequencies.

The FDA guidance recognises that certain targeted therapies may be effective in multiple groups of patients who have different underlying molecular alterations because of similarities in the functional effect observed across different molecular alterations. Hence, the guidance allows grouping of patients with different molecular alterations where 'it is reasonable to expect that the grouped patients will have similar pharmacological responses based on a strong scientific rationale'.[5] Although this guidance is directed towards the grouping of molecular alterations, the same considerations might also apply to grouping different histologies based on a common molecular alteration. The FDA guidance notes that

evidence to support a grouping strategy can come from computational, experimental or clinical sources, with clinical sources being considered the strongest form of evidence, but that any submitted evidence must always support a strong scientific rationale.

The FDA guidance stipulates that evidence supporting the efficacy of the drug for each molecular subset should be transparently reported, including information on the number of patients with specific molecular alterations included in the trial and the outcomes of these patients. However, the guidance also acknowledges that, although targeted therapies may be effective in multiple molecular subsets, certain subsets may contain only a small number of patients (or even none) despite eligibility criteria that permit their inclusion. The FDA guidance document notes that the small numbers of patients in this situation would preclude meaningful empirical inferences about treatment benefits or risks in patients with those particular molecular alterations. However, the FDA posits that the grouping guidance should also permit the generalisation of evidence from other, better-populated patient subgroups within the same clinical trial. Consequently, provided that the company was able to support its case for molecular grouping, the FDA appears to be likely to approve the therapy for all patients who meet the inclusion criteria for the trial, irrespective of their actual enrolment. Although this issue is specifically directed towards different molecular subsets, it appears equally relevant to histology-independent products, for which specific histologies may include small patient numbers and some histologies may not be represented at all.

Importantly, the FDA guidance also highlights that the indication may need to be further refined after the initial approval. If substantive data emerge indicating a lack of efficacy in certain molecular subgroups for which the drug was initially indicated, the FDA will consider narrowing the intended population as appropriate. In addition, the FDA notes that additional post-marketing studies may be required to provide additional information regarding the risks and benefits of the drug in subsets of patients with limited or no enrolment in clinical trials. Such evidence may be requested based on real-world evidence, traditional controlled trials or data from other sources, including ongoing trials.

The FDA guidance also recognises the importance of using analytically validated assays when enrolling patients into clinical trials. The assay should be able to identify all possible molecular alterations typical of the patient groups that are expected to respond to the developed therapy. The FDA also recommends that, if a test is necessary for the safe and effective use of the drug, an approved assay should be already commercially available at the time of drug approval. An exception to this case might be granted for conditions with high unmet need (e.g. life-threatening diseases with no suitable treatment alternatives).

An additional characteristic of histology-independent drugs is the use of novel and more efficient trial designs using master protocols. Master protocols are used to evaluate multiple drugs and/or multiple cancer subpopulations in parallel, using a single protocol. The FDA guidance document notes that a range of different terms are used to refer to the specific design of trials within a master protocol (e.g. umbrella, basket or platform; see *Chapter 3* for further details on these designs).

The FDA guidance acknowledges the potential advantages of master protocols in terms of their flexibility and efficiency for drug development, but also raises concerns regarding difficulties in attributing efficacy and assessing safety, including overinterpretation of findings. In the context of histology-independent products, the most relevant aspects of the guidance relate to the use of basket trials to evaluate a single investigational drug or drug combination in different populations (defined by disease stage, histology or treatment history) and statistical considerations for non-randomised, activity-estimating designs. The guidance document highlights that basket trials undertaken using a master protocol are usually designed as single-arm activity-estimating trials with ORR as the primary end point. The guidance document notes that a strong response signal seen in a substudy may allow for subsequent expansion to generate data that could potentially support a marketing approval. The guidance document also emphasises the need for each substudy to include specific objectives, the scientific rationale for the inclusion of each population and a detailed statistical analysis plan (SAP) that includes justification for sample size and stopping rules for futility (i.e. the inability of the study to achieve statistically significant results).

The statistical guidance also makes recommendations for studies using non-randomised protocols, for which the primary end point is ORR, outlining that the planned sample size should be sufficient to rule out a clinically unimportant response rate based on the lower bound of the 95% confidence interval (CI) around the observed response rate. The guidance also recommends using designs, such as Simon's[7] two-stage design, that limit the exposure to an ineffective drug (see *Chapter 3*). Specific recommendations concerning the SAP include prespecification of the timing of the final analysis; ensuring adequate data collection and follow-up of all patients for efficacy and safety; and providing a description of the plan for independent review of confirmed ORR in solid tumours for each substudy.

Although the current guidance suggests that marketing approval requires subsequent expansion of a substudy or substudies, the guidance on statistical considerations also notes that if preliminary results suggest a major advance over available therapy, then the sponsor is encouraged to meet the FDA review division to discuss modifications to the protocol. Hence, it appears feasible for the results from master protocols using basket trials to be used to support marketing approval in specific circumstances and where the clinical protocol and SAP ensure that the data are of adequate quality.

Food and Drug Administration special approval processes

The initial histology-independent cancer drugs approved by the FDA represent novel products tackling severely limiting conditions with no alternative curative options. For this reason, they have not been considered within the standard FDA review process, but rather have been considered under processes that make provision for special approval to facilitate and expedite development and appraisal of new drugs treating serious or life-threatening conditions.[8] This has been the case for the three histology-independent approvals by the FDA for larotrectinib, pembrolizumab and entrectinib (Rozlytrek, Genentech Inc., South San Francisco, CA, USA).[1,9,10]

The accelerated approval pathway is intended for those drugs that provide evidence of an effect on a surrogate end point reasonably likely to predict benefit in terms of a meaningful advantage over existing therapies. Surrogate end points are defined as substitutes for clinical outcomes that directly measure the effectiveness of a drug on length and quality of life, feelings or functioning. In cases for which measuring direct clinical outcomes, such as OS, would be impractical or unethical, surrogate end points can be accepted. Importantly, the surrogate outcome is not a direct measurement of clinical benefit but must predict, and at a minimum correlate, with the clinical benefit of interest. The strength of the evidence supporting the surrogate relationship is, therefore, essential to justify the use of a specific surrogate outcome and to establish whether or not this can support a traditional approval route or accelerated approval.

To date, ORR has been the most commonly used surrogate end point supporting accelerated approvals by the FDA.[11] One important reason for this is that ORR can be directly attributable to drug effect and, hence, single-arm studies conducted in patients with refractory tumours for whom no available therapy exists are considered to provide an appropriate assessment of ORR. However, the FDA also acknowledges that the clinical benefits of interest may not always be predicted by, or correlate with, ORR. Hence, the use of measures, such as ORR, to support an accelerated approval or traditional approval end point ultimately depends on the disease context and the magnitude of the effect, among other factors.

Food and Drug Administration review of histology-independent products

Food and Drug Administration review of pembrolizumab

The FDA approved pembrolizumab on 23 May 2017 for the treatment of adult and paediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours. The approval is for patients who have

progressed following prior treatment and who have no satisfactory alternative treatment options, and for the treatment of unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin (Eloxatin, Sanofi-Aventis, Paris, France) and irinotecan (Campto, Pfizer, New York City, NY, USA).[1]

The efficacy of pembrolizumab in patients with MSI-H or dMMR solid tumours was derived from five uncontrolled, open-label, multicohort, multicentre, single-arm studies. Patients received either 200 mg of pembrolizumab every 3 weeks or 10 mg/kg of pembrolizumab every 2 weeks. Treatment continued until unacceptable toxicity or disease progression (up to a maximum of 24 months of treatment).

A total of 149 patients with MSI-H or dMMR cancers were included across the five clinical trials. The median age of patients was 55 years; 98% of patients had metastatic disease and 2% of patients had locally advanced, unresectable disease. In total, 90 (60%) out of the 149 patients had CRC, with the remainder diagnosed with other tumour types. The median number of prior therapies for metastatic or unresectable disease was two.

The identification of MSI-H or dMMR tumour status was prospectively established for the majority of patients ($n = 135/149$) using local laboratory-developed polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Tumours from the remaining 14 patients were retrospectively identified as MSI-H using a central laboratory-developed PCR test.

The primary end point used for the FDA review was ORR, as assessed by blinded independent central radiologists (BICRs) using the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (version 1.1). The ORR was 39.6% (95% CI 31.7% to 47.9%). DoR was considered as a key secondary end point. Although the median DoR was not reached, 78% of responding patients had a DoR of ≥ 6 months. Overall, the safety profile of pembrolizumab was considered acceptable relative to durable responses observed in patients with advanced MSI-H/dMMR cancers.

A total of 16 tumour types were included in the combined data set. Consistent responses were reported between subjects with gastrointestinal (GI) cancer (i.e. CRC, small bowel, gastro-oesophageal junction and pancreas) and subjects with non-GI MSI-H cancer, with ORRs of 36.8% (MSI-H GI, $n = 125$) and 41.7% (MSI-H non-GI, $n = 24$). However, the FDA noted that some of the tumours (e.g. breast, prostate, sarcoma and renal cell) were represented by only one or two patients and that there was uncertainty as to whether or not the results apply to all disease types with MSI-H/dMMR status.

The key question considered by the FDA within their review was whether or not the presence of MSI-H/dMMR represents a unique biomarker that predicts a consistent response to pembrolizumab and similar clinical benefit across different primary tumours. In addressing this question, the FDA highlighted specific features associated with MSI-H/dMMR that are common across primary cancers, including increased lymphocytic infiltration and an increased mutational tumour burden with non-synonymous mutations. These features were noted to have been previously identified as correlating with an increased response to checkpoint inhibitors, including pembrolizumab, in tumours that had not been assessed for MSI-H or dMMR. Based on these common histological features, the FDA concluded that there was a strong biologic rationale that MSI-H/dMMR cancer represents a specific subpopulation of patients with cancer who are likely to derive clinical benefit from pembrolizumab.

Pembrolizumab was approved by the FDA for this indication under accelerated approval based on ORR and DoR. Despite a common biology among MSI-H/dMMR tumours, the FDA review also highlighted other differences among patients with different types of cancer that could influence the response to therapy with pembrolizumab (e.g. the degree of immunosuppression related to previous cytotoxic chemotherapy). Given the uncertainties that remain concerning the generalisability of the results to all disease types with MSI-H/dMMR status, a condition of the approval requires the sponsor to submit results of further studies to better characterise the response rate and its duration. These studies

are required to include 124 patients with CRC and at least 300 patients with non-CRC, including a sufficient number of patients with prostate cancer, thyroid cancer, small cell lung cancer (SCLC) and ovarian cancer, as well as 25 children.

The FDA review noted that further randomised trials will be challenging to conduct in the histology-independent setting given concerns over equipoise. The FDA also questioned whether or not it would be scientifically appropriate to 'lump' all tumour types together into a single randomised trial given the different natural histories. The FDA also noted that, although response may not be entirely predictive of effects on clinical benefit, checkpoint inhibitor therapy, including pembrolizumab, has demonstrated beneficial effects on OS with similar response rates in other tumour types.

In the absence of a companion diagnostic test for the identification of MSI-H or dMMR tumour status, the FDA review noted the uncertainties regarding the use of laboratory-developed tests. These uncertainties concerned the rate of false positives in IHC tests for dMMR and false negatives in PCR tests for MSI-H, and whether or not performance characteristics may differ by the site of the primary tumour. Given these uncertainties, additional post-marketing studies were requested to assess and establish the performance characteristics of MSI-H and dMMR tests.

Food and Drug Administration review of larotrectinib

On 26 November 2018, the FDA granted accelerated approval to larotrectinib for adult and paediatric patients with solid tumours who have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation; who are metastatic or for whom surgical resection is likely to result in severe morbidity; who have no satisfactory alternative treatments; or whose cancer has progressed following treatment.[9]

As agreed with the FDA, the submission was supported by pooled safety and efficacy data from the first 55 patients who were enrolled in three multicentre, open-label single-arm studies. These studies enrolled subjects with solid tumours harbouring a *NTRK* fusion if they met the following criteria:

- documented *NTRK* fusion, as determined by local testing
- non-central nervous system (CNS) primary tumour with one or more measurable lesions at baseline, as assessed by RECIST 1.1
- received one or more doses of larotrectinib.

The ORR, which was determined by an Independent Review Committee (IRC), was used as the primary end point for efficacy. DoR was a secondary end point, which was defined as the number of months from the start date of partial response (PR) or complete response (CR) to the date of disease progression or death, whichever occurred earlier.

Assuming that the observed ORR was $\geq 50\%$, a sample size of 55 patients was selected to provide 80% power to achieve a lower boundary of the two-sided 95% exact binomial CI about the estimated ORR exceeding 30%. Ruling out a lower limit of 30% for ORR was considered clinically meaningful. All patients were required either to have progressed following previous systemic therapy for their disease or to have required surgery with significant morbidity for locally advanced disease. The data cut-off time point for the primary analysis was July 2017, approximately 6 months after enrolment of the 55th patient.

The pooled sample included 12 tumour sites, of which the most frequent were salivary gland tumours (22% of patients), soft tissue sarcoma (20%) and infantile fibrosarcoma (IFS) (13%). More common tumours, such as lung or colon cancer, were represented less ($n = 4$ patients; 7% each) because they tend to rarely express a *NTRK* fusion. The sample was also heterogeneous in terms of prior cancer therapy, with patients having undergone different types of therapy (i.e. surgery, radiotherapy, systemic therapy) and different numbers of previous lines of therapy (45% having undergone one to two lines, and 35% having undergone three or more lines).

At the time of data cut-off, the estimated ORR was 75% (95% CI 61% to 85%), including 22% of patients with a CR and 53% of patients with a PR. Although the median DoR had not been reached, 30 out of 41 (73%) responders had a DoR of at least 6 months and 16 out of 41 (39%) responders had a DoR of at least 12 months.

The clinical and statistical review included an exploratory subgroup analysis that was performed by study, demographics and tumour type. Based on these analyses, the effectiveness of larotrectinib was reported to be reasonably similar irrespective of age, sex and race; however, no definitive conclusions were made given the limited sample size. A numerical difference in ORR was reported among patients with different tumour types, *NTRK* gene fusions or status of radiotherapy. Across different tumour types, three tumour types had at least seven patients: salivary gland ($n = 12$), soft tissue ($n = 11$) and IFS ($n = 7$). The ORR in these tumour types was reported to be higher than 75%. Conversely, it was reported that the ORR in colon cancer appeared to be lower (one out of four patients). No response was reported in the two patients with primary CNS lymphoma.

The FDA review concluded that, although the results showed that treatment with larotrectinib results in durable overall responses in patients with a variety of tumour types, there was insufficient clinical experience to conclude that the response rates achieved with larotrectinib were consistent across all *NTRK* fusion cancers.

A key issue addressed in the review was the potential risk that larotrectinib could be ineffective in some tumour types, even in the presence of a *NTRK* fusion. The FDA concluded that the risk of ineffectiveness was low owing to the strong rationale presented by the company, which was supported by clinical and non-clinical data. The strength of the evidence was assessed against the following criteria: the ability of the biomarker to identify a population with common features, the similarity of response across tumour types and the ability to reliably identify the biomarker at the screening phase.

The FDA considered the totality of evidence presented by the sponsor to be sufficiently strong to consider pooling the results across trials and patients, supporting a histology-independent indication. The FDA also concluded that, although there was a risk that larotrectinib may be ineffective in some tumours, the level of risk was deemed to be low and was considered acceptable given that the product is approved only for the treatment of patients who have no satisfactory alternative treatment options or whose cancer has progressed following treatment. As a result, the FDA did not consider that patients would be forgoing effective therapies when treated with larotrectinib.

The primary risks of larotrectinib were identified as hepatotoxicity and neurotoxicity. However, these adverse reactions were considered largely manageable and reversible with dose modification or discontinuation. Overall, the toxicity profile of larotrectinib was considered acceptable when considered against the durable effects across different cancer types in patients with limited or no effective treatment options.

The ORR was considered to be a surrogate end point that was reasonably likely to predict benefit, in accordance with the requirements of the accelerated approval process. The clinical effect was deemed to be sufficiently large and the effect was durable, which provided a meaningful advantage over the available therapy for patients with *NTRK* fusion solid tumours. The population was also considered to have a high unmet medical need given the serious, life-threatening and rare nature of their cancers. However, the FDA specified that the ORR evidence was not sufficiently strong to support a regular approval, given the large number of histological subtypes and the small sample size. This led to a degree of uncertainty regarding the magnitude of the treatment effect of larotrectinib in any single histological subtype.

A key post-marketing requirement is that the company conduct further studies that provide additional data to verify and confirm the clinical benefit of larotrectinib through more precise estimation of ORR and DoR in several specific tumour types [CRC, non-small cell lung cancer (NSCLC), CNS tumours and melanoma]. These tumour types were not well represented in the existing efficacy population. A minimum of 40 patients with cancers other than CRC, NSCLC, CNS tumours, melanoma, soft tissue sarcoma, thyroid cancer, IFS and salivary cancers [e.g. breast cancer, gastrointestinal stromal tumours (GISTs), cholangiocarcinoma and biliary tract cancers] are also required to be studied. ORR and DoR are required as end points and all responding patients are required to be followed for at least 12 months from the onset of response. In addition, a final report is requested from the first 55 patients enrolled with *NTRK* fusion solid tumours to further characterise the DoR, including follow-up of at least 2 years from the onset of response for responding patients.

Importantly, the FDA concluded that it would not be feasible or appropriate to conduct a randomised trial to demonstrate that larotrectinib improves OS in patients with *NTRK* fusion. The reasons included the extreme rarity of *NTRK* fusion cancers, the lack of equipoise in settings without available therapies and the expectations for patient crossover. Consistent with their review of pembrolizumab, the FDA again queried whether or not it would even be scientifically appropriate to 'lump' these tumour types together into a single randomised trial, given differences in natural history between different tumour sites.

The identification of positive *NTRK* gene fusion status was determined in the clinical efficacy analysis set using next-generation sequencing (NGS) for 91% of patients and fluorescence in situ hybridisation (FISH) for the remaining 9% of patients. The company did not submit an application for an in vitro companion diagnostic device. Despite this, the clinical review team was supportive of approval, citing the availability of a reliable non-companion device and the efficacy of larotrectinib. However, the development and validation of a companion diagnostic test by the sponsor was agreed as part of a series of post-marketing commitments.

Food and Drug Administration review of entrectinib

On 15 August 2019, the FDA granted accelerated approval to entrectinib for adults and paediatric patients aged ≥ 12 years with solid tumours who have a *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or for whom surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy.[10]

This indication was approved by the FDA under accelerated approval based on ORR and DoR. The submission was supported by pooled efficacy and safety results from the first 54 adult patients with unresectable or metastatic solid tumours harbouring a *NTRK* fusion enrolled across three single-arm studies. All patients were required to have cancer that progressed following effective systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease.

The median age of the patients was 55 years. The most common tumours (≥ 5%) were lung cancer (56%), sarcoma (8%) and colon cancer (5%). In total, 96% of patients had metastatic disease and 4% had locally advanced, unresectable disease. All patients had received prior treatment for their cancer, including surgery, radiotherapy or systemic antineoplastic therapy.

The ORR and DoR, as assessed by BICR using RECIST v1.1, were the primary end points. PFS, as assessed by BICR and OS, was included as a secondary end point. The effectiveness of entrectinib in paediatric patients aged ≥ 12 years was established based on extrapolation of data in adult patients with solid tumours harbouring a *NTRK* gene fusion and pharmacokinetic data in adolescents enrolled in the STARTRK-NG study.[12]

In the first 54 patients, the ORR was 57% (95% CI 43% to 71%). This was clinically meaningful because the results excluded a lower bound of the 95% CI for ORR of 30%. At the data cut-off time point (i.e. 31 May 2018), the median DoR was not reached. Among the 31 responding patients, 55% had a DoR of $\geq$ 6 months and 39% had a DoR of $\geq$ 12 months.

Exploratory ORR results for subgroups defined by tumour type and by *NTRK* gene fusion partner were presented. Although there was no formal discussion of these results, a general disclaimer was provided that noted that the subgroup results should be treated with caution owing to the small sample sizes and the single-arm design.

Only limited details were reported for secondary end points. The estimated median PFS was reported to be 11.2 months (95% CI 8.0 to 14.9 months). Less than 30% of deaths were observed by the clinical cut-off date (31 May 2018), which was considered to be too immature to be considered in the clinical review.

The most serious adverse events reported with entrectinib were congestive heart failure (CHF), CNS adverse reactions, skeletal fractures, hyperuricemia, hepatotoxicity, QT prolongation and vision disorders. Although serious in nature, these events were also reported to be manageable and reversible with dose modification or discontinuation of entrectinib.

The FDA drew similar conclusions for entrectinib to their earlier review of larotrectinib (see *Food and Drug Administration review of larotrectinib*). Although acknowledging that there was uncertainty regarding the magnitude and durability of the treatment effect of entrectinib in any specific histological subtype of solid tumours, they concluded that the risk of treatment was low, using a similar rationale to that previously described for larotrectinib.

Similar post-marketing requirements were reported for entrectinib to those for larotrectinib. This requires the company to conduct additional single-arm studies to obtain data to verify and further characterise the clinical benefit of entrectinib in an adequate number of patients with common histological tumour types, including colon cancer and melanoma. Additional post-marketing requirements also include the conduct of additional studies to further characterise the risks of CHF and skeletal fractures with entrectinib.

European Medicines Agency guidance for histology-independent products

To date, the EMA has not published any guidance specific to the evaluation of histology-independent products. However, the proceedings of two workshops were identified in the searches: one specifically addressing histology-independent indications[13] and a second discussing the use of single-arm studies in oncology.[14]

A revision to the current *Guideline on the Evaluation of Anticancer Medicinal Products in Man*[15] is currently under consultation.[16] The concept paper underlying the revision explicitly states the need to address the use of biomarkers in oncology, which was not covered by the previous guideline. This development recognises the increasingly important role that biomarkers have in both defining disease and developing treatment strategies. Biomarker-based treatments also have the possibility to span across tumour sites and are likely to be assessed using innovative study designs, such as basket and umbrella trials. These study designs were not considered in the current guideline;[15] therefore, an update was recommended by the Oncology Working Party. The update will focus on better identifying the role of biomarkers in the development pathway, developing evidence standards in the context of rare cancers and outlining the main aspects and principles of innovative study design, including the use of basket trials.

European Medicines Agency special approval processes

Similar to the FDA, the EMA provides alternative marketing authorisation pathways to cover situations in which the nature or quality of the evidence would not be sufficient to support traditional approval. Conditional approval from the EMA is a form of conditional marketing authorisation for those medicines that target unmet medical needs for serious conditions with a positive benefit–risk balance, but that do not have comprehensive data available. To grant conditional approval, agreement is required on additional post-marketing studies to confirm the initial assessment of the benefit–risk balance. This marketing authorisation is valid for 1 year and can be renewed annually following a rolling review, provided that the benefit–risk assessment is still considered to be positive.

European Medicines Agency review of approved histology-independent indications

To date, only one histology-independent product has received marketing authorisation in the EU. Larotrectinib received conditional marketing authorisation on 19 September 2019.[2] The authorisation recommends larotrectinib as monotherapy for the treatment of adult and paediatric patients with solid tumours who display a *NTRK* gene fusion; who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity; and who have no satisfactory treatment options.

The EMA review was supported using several different analysis sets. The primary analysis set (PAS) was based on the same 55 patients who were considered in the earlier FDA review of larotrectinib. The analysis of the PAS was based on a pooled analysis of patients consecutively enrolled from three single-arm studies.

The EMA review identified several concerns regarding the PAS. First, the restriction to the first 55 patients was considered to have been arbitrarily chosen. Second, the exclusion of CNS tumours was considered to introduce a bias in the efficacy estimates. Finally, restricting the analysis to patients who received one or more doses was not considered to accord with the intention-to-treat (ITT) principle.

Following requests from the CHMP, further analysis sets [extended patient analysis set (ePAS) and ePAS2] were submitted, which included additional data from an extended follow-up and a larger pooled analysis population. The ePAS ($n = 73$) included all patients who met all PAS eligibility criteria, as of 19 February 2018, and had a central review of tumour response by the IRC. ePAS included an additional 18 patients compared with the PAS ($n = 55$). The ePAS2 ($n = 93$) included all patients who met all PAS eligibility criteria and had either discontinued the study or ≥ 6 months' follow-up by 30 July 2018. ePAS2 included an additional 38 patients compared with the PAS ($n = 55$). The ePAS2 was the main efficacy analysis set considered in the EMA review.

A further cohort that included paediatric and adult patients with primary CNS tumours ($n = 9$) was reported separately. This cohort represented a prespecified exclusion criterion from the original analysis of the PAS. This cohort was considered to have a potentially lower likelihood of response than the other cohorts given the results from earlier animal studies, which indicated low penetration of larotrectinib into CNS tissues. However, the review also acknowledged that CNS penetration in cancer patients taking larotrectinib may be more substantial than that suggested by prior evidence.

The primary end point considered was ORR by IRC assessment, which was defined as the proportion of patients with the best overall response of CR or PR. Secondary end points included time to response (TTR), DoR, PFS (including PFS rate at 6 and 12 months) and OS (including survival rate at 12 months).

In the ePAS2 analysis, the ORR by the IRC was 72% ($n = 67/93$) (95% CI 62% to 81%). The ORR results were considered by the EMA review to be outstanding. The median TTR was 1.8 months by the IRC [interquartile range (IQR) 1.71–1.94 months]. The median DoR was not estimable (NE). However, 72% of responding patients were reported to have had a DoR of ≥ 6 months and 42% had a DoR of ≥ 12 months. The review also noted that the percentage of patients with durable responses appeared to be larger in previously submitted data with shorter follow-up. Concerns were expressed that the difference in results between alternative follow-up times indicated that limited early data might overestimate the true treatment effect.

The EMA review noted that there was substantial heterogeneity across the three separate studies and that the primary end point was based on a crude proportion of responses. The review also highlighted that sensitivity analyses provided by the sponsor that utilised tumour type as a random factor provided slightly lower estimates than the crude proportions. Further re-analysis by the EMA involved investigating alternative selections of cohorts from the three studies. These analyses indicated that the crude ORR appeared in the upper end (the 90th percentile) of the distribution of possible estimates, suggesting a possible selection bias. However, the review also noted that a large majority of all possible ORR estimates were above 50%, indicating a true effect of a relevant magnitude.

The median PFS was 27.4 months [95% CI 13.8 to NE months] by the IRC. The PFS rate at 6 months was 77% and the PFS rate at 12 months was 64% (95% CI 51% to 76%). The median OS was not reached in the ePAS2 owing to the low event rate of 15% ($n = 14/93$ dead) at a median follow-up time of 16.7 months. The OS rate at 12 months was 88% (95% CI 81% to 95%). All nine patients in the CNS group were noted to still be alive at the final data cut-off time point.

The EMA review highlighted the immaturity of the OS and PFS data. In addition, although the PFS and OS data were considered important for contextualising the ORR and DoR results, the pooling of many different types of primary malignancies with inherently different prognoses led to a conclusion that the data should be interpreted with caution.

The subgroup analysis reported in the EMA review included an analysis of ORR by tumour type. The ORR was reported to be highly variable across the studied tumour types, ranging from 0% in individual patients with breast cancer, cholangiocarcinoma and pancreatic cancer to 100% in four patients with GIST. The review indicated that tumour types for which *NTRK* gene fusions are characteristic (or even considered pathognomonic) of the disease, such as IFS ($n = 13$), salivary gland/mammary analogue secretory carcinoma (MASC) ($n = 10$) and congenital mesoblastic nephroma ($n = 1$), tended to have higher ORRs (92%, 80% and 100%, respectively). However, the review also concluded that the tumour-specific estimates were not robust owing to the small sample sizes of the individual subgroups. Of the nine patients with primary CNS tumours, one had an objective response (PR) and the remaining eight had stable disease as the best response. Six patients were reported to be progression-free at last follow-up. The CHMP considered that there was no scientific rationale to exclude previously treated CNS patients with no satisfactory treatment options available and that the indication should cover these patients also.

A key question that was considered in the EMA review was whether or not the available data supported the assumption that *NTRK* gene mutations are oncogenic driver mutations and that the mechanism of action is independent of tumour histology. This assumption was considered necessary to conclude that larotrectinib would result in clinically relevant activity in tumours expressing *NTRK* fusion proteins, regardless of the tissue of tumour origin. Additional advice was sought to address this question from the Scientific Advisory Group (SAG) in Oncology and the EMA Biostatistics Working Party.

The consensus view of the SAG was that the available data did not support the hypothesis that *NTRK* gene fusions are universally oncogenic drivers, independent of tumour type/histology and other disease characteristics. The SAG also concluded that the mechanism of action may differ according to

histology and other characteristics, and that the existing data were insufficient to establish activity regardless of tumour type and other characteristics. However, the SAG also recognised that preclinical and clinical data supported *NTRK* as an oncogenic driver in some paediatric malignancies. In addition, fusion genes affecting *NTRK 1/2/3* were reported to be highly recurrent in certain rare malignancies. *ETV6–NTRK3* was noted to be present in > 95% of secretory carcinomas of the breast, MASC of the salivary glands, congenital fibrosarcoma and cellular mesoblastic nephromas. As reported in the EMA review, this led one expert to suggest the possibility of having a histology-independent approval for cancers with proven *NTRK* fusions as oncogenic 'drivers', provided that NGS could exclude other alterations being significant drivers for tumour progression. However, it was also noted that data do not currently exist to establish the efficacy of such a strategy.

The SAG acknowledged the strong rationale and the available clinical data for several specific tumour types (IFS, salivary gland/MASC and congenital mesoblastic nephroma) for which *NTRK* fusions have been established as oncogenic drivers independent of other characteristics. The SAG also noted that larotrectinib has shown important activity in GIST with *NTRK* after resistance/relapse with imatinib (Gleevec, Novartis, Basel, Switzerland) (ORR $n = 5/5$), reflecting a probable similar role for *NTRK* fusions. For these selected conditions, given the strong rationale and the available clinical data, the SAG concluded that efficacy has been established in the absence of available treatments of proven efficacy in terms of convincing clinical efficacy end points. However, for other conditions the review concluded that the role of *NTRK* fusions had not been properly studied and could not be appropriately established with existing data, given the lack of comprehensive sequencing of tumour tissue prior to treatment initiation. Concerns were also expressed from the SAG regarding the small sample sizes in different tumour types, the significant heterogeneity observed in terms of response rates and the very low ORR observed in different tumour types (ORR 0% to 33%). The low ORRs were also noted to be reported in common tumour types for which occurrence of *NTRK* gene fusion is rare (e.g. lung, colon and breast).

The SAG concluded that neither the available evidence nor the reasonable extrapolations supported the proposed indication to include all solid tumours independently of tumour type. The SAG considered that clinical decisions to use larotrectinib were justified for the rare conditions for which existing evidence more clearly supported the role of *NTRK* fusions as oncogenic drivers. For other conditions, the acceptable safety profile supported use in situations for which established alternatives are lacking or for which available alternatives are associated with high morbidity and mortality.

Further to the SAG comments, the CHMP highlighted that a certain degree of heterogeneity in response is unavoidable in the same way because there will be important effect modifiers within any indication. Thus, the critical issue considered by the CHMP was whether or not the studies were likely to be representative of the treated population once the product is authorised and whether or not the uncertainties are acceptable given the available data and the intended use as a last-line treatment in patients without satisfactory treatment options.

The clinical review concluded that, although the efficacy results were outstanding for a late-stage disease setting, significant uncertainties remained concerning the robustness and generalisability of these estimates. The review also acknowledged that the results may change in a negative direction as further evidence is generated. However, the magnitude of the current effect estimates was considered to be of sufficient size to support a probably large treatment benefit observed in practice. The review also noted that the interactions between treatment and tumour type required further exploration.

The available data were not considered comprehensive and a conditional approval was concluded to be appropriate by the EMA. The conditional approval was granted based on a positive benefit–risk balance and the requirement that the company provide additional comprehensive data. As part of this requirement, the company is required to submit a prospective cohort of 75 patients as part of the NAVIGATE study

(LOXO-TRK-15002),[3] for which at least 1 year of follow-up is available, and to perform an overall pooled analysis including the ePAS2/CNS cohort to give increased precision for the estimates of ORR and DoR. In addition, the company plans to enrol 200 additional patients in NAVIGATE (LOXO-TRK-15002)[3] and as part of the SCOUT study (LOXO-TRK-15003)[17] within a 36-month period post approval. It is planned for 80 patients to be recruited for four common tumour types (lung cancer, CRC, melanoma and non-secretory breast cancer) and 120 patients in other tumour types. At least nine (and up to 20) patients will be recruited in each of the four common tumour types, permitting a more precise estimate of efficacy in common cancers for which *NTRK* fusions are rare.

Overview of registered or completed trials for histology-independent products in development

Research from NICE suggests that there are approximately 20 technologies currently in development for histology-independent indications. We undertook searches of the clinicaltrials.gov website using the list of histology-independent products provided by NICE. Information was extracted for those trials that are more likely to be vehicles for regulatory approval, that is combined Phase Ib/II, Phase II and Phase III trials. The aim of this review was to clarify whether or not the level of evidence available during the FDA/EMA appraisals of the initial histology-independent products is likely to be representative of that of future products in other indications.

Appendix 2 provides a summary of the registered or completed Phase Ib/II, Phase II and Phase III trials identified using searches of the clinical trials.gov website. Of the 20 products considered, three products (pembrolizumab, larotrectinib and entrectinib) were excluded because more detailed evaluations of the regulatory submissions have been summarised in *Food and Drug Administration review of histology-independent products* and *European Medicines Agency review of approved histology-independent indications*. Of the remaining 17 products, only 13 products had registered trials that were considered potentially suitable for regulatory purposes. A total of 36 relevant trials were identified for these 13 products. In total, 13 of the trials were for one drug [olaparib (Lynparza, AstraZeneca, Cambridge, UK)]. The products that were identified included drugs already approved for specific indications (e.g. olaparib), for which there was an aim to expand their existing marketing authorisation, and novel products, for which initial approval in a histology-independent context may be sought (e.g. LOXO-295).

Over 90% ($n = 33$) of the 36 registered trials were single-arm studies. ORR was the most common primary end point ($n = 27$), although PFS was reported as a primary end point in four studies. DoR ($n = 18$), PFS ($n = 28$) and OS ($n = 24$) were commonly included as secondary end points.

Of the 36 trials, only three trials were formally referred to as basket trials. A total of 19 of the remaining 33 studies (58%) included separate treatment or population cohorts, suggesting that the analyses may explore differences between the separate cohorts. The remaining studies reported no details on specific cohorts or subgroups that might be considered.

Summary and implications

The study design and evidence considered by the FDA and EMA for the initial approvals of histology-independent products appear consistent with the type of evidence that may be expected for future approvals (e.g. single-arm studies with ORR as the primary end point). Although the FDA has now issued specific guidance concerning the conduct and reporting of basket trials to evaluate a single investigational drug or drug combination in different populations, the design of many ongoing or recently completed studies clearly pre-date this guidance. Only a small number of the trials were formally referred to as a basket trial and there was a lack of clarity in the design of many studies concerning whether or not separate cohorts would be formally considered. As a result, it appears

to be likely that the current case-by-case approach employed by the regulators in determining the appropriateness and quality of the underpinning evidence to support a histology-independent approval will continue for the foreseeable future.

The central question considered by both the FDA and the EMA concerns the biologic rationale and strength of existing clinical evidence to support the assumption that a biomarker-defined population (e.g. MSI-H/dMMR or *NTRK*) is sufficient to establish clinically relevant activity independent of tumour histology. Neither the FDA nor the EMA considered that the current evidence base for any of the three products was sufficiently robust to establish this. Indeed, both agencies raised important uncertainties regarding the generalisability of the results across all individual histology sites. However, the magnitude of the effect in the overall population was considered clinically important and the risk associated with approving the treatment in specific tumours was considered to be low owing to the strong biologic rationale and the intended approval as a last-line treatment in patients without satisfactory treatment options.

It is evident from the FDA and the EMA reviews for larotrectinib that the evidence base is rapidly developing over time, such that the later EMA review included an additional 38 patients ($n = 93$) compared with the FDA review ($n = 55$). It is also notable that the advice of the SAG to the EMA, based on this larger data set, appeared to differentiate the strength of the biological rationale and the available clinical evidence for several specific tumour types. For a few specific tumour types (IFS, salivary gland/MASC and congenital mesoblastic nephroma), the SAG concluded that *NTRK* fusions had been established as oncogenic drivers, independent of other characteristics. The SAG also concluded that evidence for GIST was sufficiently strong to support a similar role of *NTRK* fusions as an oncogenic driver. For these specific tumour types, the SAG concluded that efficacy has been established in the absence of available treatments of proven efficacy in terms of convincing clinical efficacy end points and that clinical decisions to use larotrectinib were justified. For other conditions, the acceptable safety profile supported use in situations for which established alternatives are lacking or for which available alternatives are associated with high morbidity and mortality.

Both the FDA and the EMA reviews ultimately concluded that the evidence for these existing products was not sufficient to support a routine approval for a histology-independent label. The further evidential requirements focus on three specific aspects: (1) increasing the precision for the estimates of ORR and DoR and extending the length of follow-up in the overall population; (2) the generation of new evidence to increase the precision of efficacy in more common cancers for which *NTRK* fusions are rare (e.g. lung, colorectal, melanoma and non-secretory) and for which current evidence is sparse; and (3) the development and validation of a companion diagnostic test. As a result, important new evidence will emerge over time to address some of the key uncertainties identified by the EMA and FDA.

The reviews also highlighted two important challenges that need further consideration. First, the design and conduct of trials to support histology-independent products are likely to differ from those of more conventional products. The use of novel and efficient basket trial designs using master protocols will present additional challenges to NICE in terms of Health Technology Assessment (HTA) assessment. Hence, the rationale and statistical basis for the design of these studies warrants further consideration. Second, the initial evidence supporting the basket trials is likely to be focused on surrogate end points, such as ORR and DoR. Our reviews show that, although data on more policy-relevant outcomes, such as PFS and OS, are being collected, there is likely to be a number of potential challenges regarding their interpretation in the absence of a comparator arm, possible bias owing to confounding (e.g. receipt of subsequent therapies) and the likely immaturity of these end points at the time of initial marketing authorisation.

It is notable that neither the FDA nor the EMA reviews considered that the evidence on PFS or OS was sufficiently robust to draw any meaningful conclusions in relation to these end points. Instead, both agencies relied on the magnitude of the ORR and DoR as providing evidence to support a

potentially meaningful difference in more policy-relevant intermediate (e.g. PFS) and final clinical outcomes (e.g. OS), drawing on existing surrogate relationships. Hence, the surrogate relationships between response-based outcomes (ORR and DoR) are likely to be central to HTA and economic modelling in helping to inform and/or validate longer-term extrapolations of PFS and OS owing to the probable immaturity of these end points.

The following chapters attempt to address these challenges by considering in more detail the nature and design of the trials (see *Chapter 3*) and the existing evidence evaluating the use of response-based outcomes as surrogate end points for PFS and OS (see *Chapter 4*).

Chapter 3 An overview of key statistical literature addressing the design and analysis of histology-independent trials

The literature on adaptive designs and complex innovative trial designs was reviewed, focusing on trial design and analysis methods proposed for oncology studies and, in particular, 'master protocol' designs proposed to assess histology-independent drugs. The review was based on known articles in the area (both methodological and applied) and following up of relevant reference lists.

Adaptive Phase II studies

The first step in evaluating a novel treatment is to conduct a Phase II study to determine whether or not the drug has a sufficient level of disease activity to warrant further investigation. To minimise the exposure of patients to ineffective drugs, adaptive two-stage designs have been proposed, in which the second stage of the study is not activated if the first stage shows that the treatment is not effective. The first such design was proposed by Gehan[18] in 1961, where the first stage enrols 14 patients and if no responses are observed the trial is terminated. If at least one response is observed in stage 1, the second stage of accrual is activated to obtain an estimate of the response probability with a prespecified standard error. Patients from both stages are used for the estimation of the response rate and an implicit 20% threshold for response rates is considered promising for further study. Fleming[19] also studied multistage designs, with acceptance (i.e. proceed with study) or rejection (i.e. stop the study) possible at each stage based on prespecified probabilities: p_0, the largest response probability that, if true, would imply that the drug is not sufficiently effective to warrant further investigation; and p_1, the smallest probability that would imply that the treatment has a therapeutic effect worthy of further investigation. The acceptable probabilities of making incorrect decisions (type I and type II errors) are also required. In Fleming's[19] design, early rejection occurs only when interim results are quite extreme, which permits the final analysis to be unaffected by interim monitoring; however, this is not always desirable for Phase II trials of agents that are likely to be inactive. Although these designs were popular for many years, they did not optimise sample size or allow for early termination when the drug has low tumour activity – a key ethics concern. This led to the development of Simon's two-stage design,[7] which minimises the expected sample size when the true response is less than some predetermined level. Similar to Fleming's approach,[19] investigators prespecify p_0, p_1 and the acceptable type I and type II error bounds. This is currently one of the most commonly used adaptive designs and, although it can be extended to multiple stages, in practice only two stages are usually used. Extensions of Simon's two-stage design[7] have been proposed to address the uncertainty in the expected response for p_1: if this is too optimistic, Simon's design[7] would reject a potentially promising treatment, whereas if it was too pessimistic, it would require more patients to be recruited than necessary.[20]

Bayesian approaches to adaptive Phase II trials have also been proposed.[21–24] These approaches terminate the trial early if the predictive probability that the treatment is not sufficiently effective at the maximum sample size is below a prespecified level; provide a posterior distribution for the true response probability; and allow the calculation that the true probability of response is above a certain value, or the calculation of an interval that has a 95% probability of containing the true response proportion (note that this is not provided by CIs obtained using a frequentist approach).

Master protocol designs

Typically, adaptive Phase II oncology studies are conducted separately for each patient subgroup, based on histology or biomarker activity. However, concerns have been raised about the ability of traditional

clinical trial designs to facilitate timely access to innovative technologies owing to the increasingly small populations being targeted in oncology trials. A traditional Phase III study would never be expected to recruit enough individuals to achieve statistical significance on the primary outcome. The use of complex innovative trial designs with 'master protocols' and basket trials has been proposed to accelerate the access to innovative targeted technologies and precision medicine. A consensus statement on their design, conduct and interpretation has recently been published.[25] Master protocol trials use a centralised screening platform to identify eligible patients and a common protocol for different substudies, which may each focus on patients with specific markers or histologies. The main advantages of master protocols are enhanced patient participation, given that more patients are eligible to enter the trial, and a simplification of the trial process, given that a single protocol is approved for use on multiple substudies. Basket trials typically include patients with diverse conditions who share a particular feature or biomarker that can be treated with a single therapy. The key underlying assumption of a basket trial is that the condition depends on the target pathway and that the proposed therapy inhibits this target.[26]

In oncology, basket trials use a master protocol to define patient eligibility by the presence of a particular biomarker or molecular alteration, regardless of histology. The substudies, or baskets, are then defined by a particular histology or other disease-specific characteristics, for example mutation type. Because individual patients are recruited independently of tumour location or subtype, they are more likely to be eligible for enrolment.[26–28] However, a critical consideration is the heterogeneity in prognosis across the different histologies; therefore, standardised response rates, reflecting tumour shrinkage, are typically used instead of survival outcomes, such as PFS or OS.[29] In addition, given that the majority of basket trials do not have a control arm, stable disease or survival outcomes would be difficult to interpret unless they were clearly better than what is expected under standard therapy for all tumours.[30] Therefore, a further crucial assumption in these designs is that response is a sufficient measure of clinical benefit.

Although designed to improve recruitment, basket trials can still fail to recruit sufficient patients to some or all baskets. For example, the CUSTOM trial[31] failed to recruit enough patients for some baskets covering rare mutations. In addition, because basket trials rely on the assumption that molecular profiling is a good predictor of response, they may fail in situations in which histological tumour type predicts response better than the biomarkers or mutations defining the baskets.[27,29,32]

Although advocated as ideal, randomisation to a control arm is rare in basket trials[33] owing to the differences in standard of care (SoC) across the different tumour types defining the baskets.[25,27,30] Adaptive designs for confirmatory basket trials with concurrent (non-randomised) control groups have been proposed, and their challenges and limitations discussed.[34] However, the lack of a concurrent, randomised, control arm remains a key limitation of these trial designs and, in particular, for the interpretation of such trials in HTA processes.[25]

Non-randomised basket trials are typically exploratory and use similar two-stage designs to traditional Phase II clinical trials, with each substudy (basket) analysed separately. Tumour types that are expected to have a sufficient frequency of the targeted genomic alteration are enrolled into their own basket, while others are enrolled into a combined basket. Typically, these studies are designed so that each basket will recruit a certain number of patients and if a certain prespecified proportion of these patients respond, the basket is considered 'promising' or successful, and either accrual is expanded or a separate confirmatory study is planned. If insufficient responses are observed, the basket is 'pruned' owing to low promise of efficacy and recruitment to that basket is stopped. Different designs can be used, with varying thresholds for response rates selected depending on the indication and prior expectations of efficacy, and with suitable corrections for false-positive rates.[29,35]

Heterogeneity of effect in basket trials

Heterogeneity of effect across different baskets is a key concern. One way to account for this is to analyse each basket separately as if it was an independent study. For example, a basket study

of vemurafenib (Zelboraf, Roche, Basel, Switzerland) in multiple non-melanoma cancers with *BRAF* V600 mutations used an adaptive Simon two-stage design[20] with stopping rules defined independently for each basket, and considered a response rate at week 8 of 15% to be low, a response rate of 45% to be high and a response rate of 35% to be low but still indicative of efficacy.[32] They found that not all tumour types responded homogeneously to treatment, with some tumour types not meeting the prespecified criteria for response. Similarly, the CUSTOM trial[31] used Simon's optimal two-stage design, defining $p_0 = 0.3$ and $p_1 = 0.6$ based on previous literature. The trial aimed to identify targets for molecular biomarkers in NSCLC, SCLC and thymic malignancies and to simultaneously evaluate five different targeted therapies in each of the three histologies, which resulted in a total of 15 study arms. A high response rate to erlotinib (Tarceva, Roche, Basel, Switzerland) was identified from only 15 NSCLC patients with an epidermal growth factor receptor (*EGFR*) mutation, but another therapy, selumetinib (Koselugo, AstraZeneca, Cambridge, UK), failed to achieve a promising response in patients with Kirsten rat sarcoma (*KRAS*) viral oncogene homologue mutations.[31]

However, a separate analysis of each basket does not allow for the possibility that some subgroups may react similarly to the drug, particularly if they share a common biomarker that the novel therapy is targeting. By analysing each basket separately, efficiency may be lost by not allowing information gathered from one basket to inform the next, thus increasing the required sample sizes in each basket. In practice, many standard Phase II designs will ignore potential heterogeneity and pool all patients for analysis, which, in effect, ignores the specific basket-defining tumour characteristics (e.g. histology) and assumes equal efficacy across all baskets.[35] If this approach is taken, trial planning and analysis are similar to a standard Phase II trial and, for example, Simon's two-stage design can be used. Although allowing analysis with a much smaller number of included patients, pooling all patients ignores the potential for heterogeneity across baskets and effectively assumes that it is zero, which can miss treatments that are active in only some baskets[36] and can lead to large biases in overall estimated effects. In addition, if the drug is truly active or inactive in all baskets, this will be an inefficient design.[37,38]

Frequentist adaptive designs for basket studies that try to acknowledge this potential for heterogeneity across baskets have been proposed. In the context of Phase II studies with heterogeneous populations, a design that tests global response across the whole population, while allowing a different response for each subgroup, was proposed by London and Chang.[39] Simon's two-stage design was extended to use a more flexible strategy that both tests each subgroup and tests the combined population, which allows the trial to stop if either a subgroup or the combined population show futility, that is the inability of the study to achieve statistically significant results, at prespecified thresholds (that are not necessarily the same).[40] Negative results in one subgroup would lead to stopping recruitment in that basket alone, unless the combined response for the whole population was below the acceptable threshold. This design leads to smaller sample sizes than separate analyses of each basket when the drug is inactive across all subgroups and to more power when there is activity in all subgroups. It also retains the individual tests for each subgroup, which allows the identification of promising baskets. This design requires prespecification of the expected response rates and prevalence in each subgroup to specify the expected response rate in the overall population. Although the average prevalence in the clinical population may be known, owing to the often small samples recruited, the observed prevalence as the trial enrols patients may be quite different. A design that allows the rejection values to be adjusted depending on the observed prevalence in the trial was proposed by Jung *et al.*[41]

Cunanan *et al.*[42] later proposed an efficient study design for the specific scenario of the typical basket trial in oncology, which assesses the homogeneity of the baskets' response rates at an interim analysis, aggregating the baskets in the second stage (i.e. full borrowing of information) if results suggest effectiveness in all or most baskets, or treating each basket separately (i.e. no borrowing) otherwise. Their basic premise is that the design can be made more efficient by aggregating information from separate baskets in which it can be assumed that the drug has similar efficacy, based on an interim analysis. Thus, the second stage of the design could have a much smaller sample size for the same power to

demonstrate clinical efficacy. The first stage of the design is based on the parallel, independent two-stage Simon's design. When each basket has recruited a small number of patients, the heterogeneity in response across baskets is evaluated. If the results support the assumption that the drug's effects are similar across baskets, either the trial is terminated for futility (if response is low) or a decision is made to continue to the second stage, at which all baskets will be pooled for analysis. If there is evidence of heterogeneity across the baskets, the trial will continue only for those baskets showing a promising level of response and these will be analysed separately at the end of the trial. This type of design answers the overall question of efficacy in the whole population more efficiently when there is evidence of homogeneity at an interim stage, while also shortening trial duration.[43] However, this is at the expense of loss of accuracy at assessing efficacy within each separate basket.[42] A different approach to testing has also been proposed, which replaces the question of whether or not there is response to therapy with the question of whether or not there are differences by tumour type (i.e. across baskets).[44]

Although acknowledging the potential for heterogeneity, once a decision has been made on whether or not heterogeneity is present, the analysis proceeds either as separate independent studies for each basket or as a single aggregate study combining all of the baskets. Thus, either complete homogeneity or completely unrelated effects are assumed. A less restrictive assumption is that efficacy is similar (rather than equal or completely different) across baskets, with the different histologies not determining a particular ordering of effectiveness a priori (i.e. the baskets are exchangeable). Bayesian hierarchical models (BHMs)[45,46] are particularly suited for this situation because they estimate the heterogeneity and allow information to be borrowed on the effects of the treatment across baskets, increasing precision of estimates compared with analysing all baskets separately, while reducing the chances of obtaining extreme estimates in baskets with few patients. Thall *et al.*[46] proposed a BHM that produces estimates of efficacy (e.g. probability of response) for each basket that are shrunken towards the mean efficacy (e.g. pooled probability of response) across all baskets. The model is an extension of a Bayesian Phase II design in which the trial is stopped if the posterior probability that the response rate is at least π^* falls below a prespecified cut-off point, and can be applied to both binary and time-to-event (TTE) data.[47] Each basket is assumed to have a different treatment effect (event probability or event rate), θ_j, and these are assumed exchangeable (i.e. similar) and correlated a priori. Specifically, it is assumed that the θ_j follows a BHM, while allowing a separate stopping rule for each basket. Thus, the model will identify subgroups in which results are not promising, which can be dropped at a subsequent stage. Because the effects are assumed to be correlated across baskets, data from each individual basket will provide information on the effects in all of the other baskets, so that, for example, a longer survival time for a patient in a given basket will increase the posterior distributions of all θ_j, on average. In other words, information is borrowed across baskets, which shrinks the observed effects towards the pooled mean effect. Outputs from the resulting analysis include the posterior distributions for the effect (e.g. response or event rate) in each basket, the posterior distributions for the pooled effect across all baskets and the posterior distribution for the heterogeneity across baskets. In addition, a predictive distribution for the effect in a new study sampling baskets from the same overall population can be calculated to reflect the full degree of uncertainty owing to both the sample size and the observed heterogeneity in effects across the observed baskets. A Phase II trial of imatinib in 10 histological subtypes of sarcoma used this design: accrual within a sarcoma subtype would stop if it was unlikely that its response rate was at least 30%.[36,46,48]

The BHM was shown to be a better design for a single-arm, non-randomised trial with a tumour response end point when there is a possibility of different effects in different subgroups of patients than Simon's optimal two-stage design and the Bayesian adaptive design with no borrowing.[49] However, the hierarchical borrowing can make it more difficult to find a single basket in which the treatment is promising, although it is more likely than the other designs to correctly conclude futility or efficacy.

Any borrowing and precision gains from a BHM are advantageous only if the exchangeability assumption is reasonable. An approach for assessing homogeneity at an interim analysis and proceeding with a BHM in the second stage only if efficacy is deemed reasonably homogeneous has been proposed.[50]

This approach avoids problems caused by implementing a complete pooling model at the second stage[42] or proceeding with a fully exchangeable BHM when there is evidence of outlying baskets.

Hierarchical designs have been criticised when there is insufficient information in the outcome data to determine whether or not borrowing across subgroups is appropriate.[36,51] In addition, unknown between-subgroup heterogeneity, which drives the amount of borrowing, poses a major problem when the number of baskets is small (less than 10, as a rule of thumb)[36] because it cannot be well inferred from the data and the results will be sensitive to model specification, in particular to the specification of the prior distribution for the borrowing parameter.[36,52] Alternatives to complete pooling or borrowing across all baskets have been proposed, which extend the BHM to allow borrowing of information across similar baskets while avoiding too optimistic borrowing for extreme baskets.[51,53–57]

A model that allows non-exchangeable prior distributions to be specified was proposed for the scenario in which it is not expected a priori that all subgroups will be exchangeable. For example, some tumour types may be associated with a better or worse prognosis and their response to treatment is expected to differ. Different models can be used to implement this assumption: we can accept that a particular tumour characteristic (e.g. prognosis) defines exchangeability so that different categories are formed and exchangeability is allowed only between tumours in the same category (e.g. poor, intermediate and good prognosis), or we can treat the appropriate grouping as a random quantity to be estimated from the data, indexed by a categorical covariate of interest (e.g. prognosis).[53] Thus, the estimation of the treatment effect for a particular subgroup borrows more strength from other subgroups that, according to the prior beliefs, are more likely to be exchangeable, but the models allow the data to correct any prior beliefs that are not supported by the available data. When there is no a priori information on which subgroups might be exchangeable or not, an exchangeable–non-exchangeable model[51] allows for selected special exchangeability patterns specified in the model to be determined by the treatment response data. This model extends the BHM to allow θ_j to be either exchangeable with some of the other subgroups or non-exchangeable with any of them, in which case the effect will be estimated independently of all other subgroups. Prior weights for the exchangeable probability of each subgroup are specified to reflect an a priori belief that a subgroup behaves systematically differently to the others. Essentially, the model determines whether some borrowing or no borrowing of information should be carried out across subgroups. Outputs include a global heterogeneity parameter across subgroups and mixture weights that describe the similarity of subgroups in the exchangeable component of the model, while also identifying subgroups that behave differently (i.e. show a low probability of being exchangeable). Although a pooled mean effect for the exchangeable component of the model can be obtained, the focus is on the effects for each individual subgroup, which incorporate different levels of borrowing according to the model. The prior distributions specified for the heterogeneity parameter and for the exchangeability weights can influence the results and need to be specified carefully. The use of this model for trial design requires careful consideration of the specification of the prior distributions and mixture weights, but has been found to perform well in various scenarios.[51] Extensions of these ideas to incorporate more information and, thus, improve performance of the trial design or simplify computation have been proposed. For example, the Bayesian latent subgroup trial design[54] defines different latent subgroups within which more borrowing is allowed by jointly modelling biomarker measurements and treatment responses. This allows grouping of different cancers according to biomarker measurements routinely collected during a trial, effectively using internal trial information to inform the adaptive borrowing, which determines the decision to proceed to the next stage. Fujikawa *et al.*[56] proposed a Bayesian basket design that borrows information across the subgroups that have the most similar posterior distributions based on a prespecified threshold of similarity, which is simple to compute. Decisions can be made at the interim stage to stop or continue with the trial and this design can also determine which subgroups show efficacy in the final analysis, based on predefined criteria. Unlike the fully exchangeable BHM, in these models obtaining and interpreting predictive distributions of effects is not meaningful given that we can no longer reasonably assume that a new tumour type (subgroup) would have been sampled from the same distributions as the observed subgroups (i.e. we cannot assume that all subgroups are exchangeable).

Owing to the increased number of parameters being estimated, the hierarchical approach may increase uncertainty unnecessarily if response to treatment is indeed homogeneous across all subgroups. Therefore, when there is a strong rationale for expecting a uniform level of response it may be preferable to use a simple pooling of information across subgroups.[36] However, a priori assumptions of homogeneity in trial design or analysis need to be carefully justified because, in most cases, basket trials include patients with very clinically heterogeneous tumour types. In addition, the available empirical evidence does not generally support the assumption of homogeneity of activity of drugs across different histologies.

Previous basket trials have shown heterogeneity in the effectiveness of agents across tumour types, which lends support to the a priori assumption that effects may be heterogeneous. A recent trial[32] of vemurafenib in 122 patients with *BRAF* V600–mutated cancers across multiple tumour types (including CRC, NSCLC, Erdheim–Chester disease and Langerhans'-cell histiocytosis, primary brain tumours, cholangiocarcinoma and anaplastic thyroid cancer) found evidence of response in some tumour types, including NSCLC and Erdheim–Chester disease and Langerhans cell histiocytosis, but not in CRC.[32] This heterogeneity in response was also observed in previous separate independent studies, which showed a positive response to vemurafenib in patients with *BRAF*-positive metastatic melanoma,[58] but not in *BRAF*-positive colon cancer patients.[59] A trial of imatinib,[60] a tyrosine kinase inhibitor (TKI), that included 196 patients across 40 different subtypes, found evidence of activity of imatinib in only five malignancies. Another basket trial of imatinib in 10 histological subtypes of advanced sarcoma concluded that, although rare dramatic responses were seen, imatinib was not an active agent in these subtypes, although it had previously shown effectiveness in another subtype of soft tissue sarcoma.[48] Similarly, trastuzumab (Herceptin, Roche, Basel, Switzerland), which is known to be effective in the treatment of women with HER2 (human epidermal growth factor receptor 2)-positive breast cancer,[61] was not shown to be effective in HER2-positive recurrent endometrial cancer[62] or HER2-positive NSCLC.[63] This evidence suggests that the treatment effects in different cancer types may not be exchangeable. Therefore, the design of basket trials should allow for the possibility of heterogeneity in treatment effects across tumour types, opting only for a design that assumes homogeneity in very special cases or where data from previous stages clearly support it.

Summary and implications

Complex innovative study designs are being used to address multiple clinical questions in an attempt to speed up regulatory approval and the access of drugs with new mechanisms of action to patients. Adaptive basket trials are particularly suited to assess efficacy of histology-independent drugs, although their reliance on surrogate outcomes, small sample sizes and mostly uncontrolled designs pose challenges for HTA.

A recent consensus statement has provided recommendations for the planning, design and statistical analysis of complex study designs, including considerations on ensuring their relevance for HTA.[25] These include encouraging comparative randomised studies; ensuring that the primary outcome, typically a surrogate of the clinical outcome of interest in HTA, is likely to adequately predict the clinical outcomes of interest; and using analysis methods that allow borrowing of information across baskets.[25]

Although it is challenging to determine the correct level of borrowing of information (exchangeability) across baskets,[25] the approaches described in *Heterogeneity of effect in basket trials* allow the treatment effect in any basket to be informed by the effects in all other baskets, therefore maximising the information available. Their interpretation and potential use in NICE TAs is described in *Chapters 6* and *7*.

Chapter 4 A systematic review to identify published meta-analyses evaluating the use of response rates and duration of response as surrogate end points for progression-free and overall survival

Introduction

It is generally accepted that decisions about the use of new and existing health technologies should ideally be informed by estimates of treatment effects derived from high-quality randomised controlled trials (RCTs) that measure patient-relevant end points over a clinically appropriate time frame. Such 'final' end points typically involve the measurement of health benefits and adverse events that reflect aspects of the disease and its treatment that are important to patients (and potentially also their carers) and that relate to 'how the patient feels, functions or survives'.[65] In the context of evaluating treatments for advanced/metastatic cancer, the key matter of concern is often whether or not the use of a given heath technology leads to improvements in OS (a final end point) compared with existing standard treatments. However, the estimation of treatment effects on OS may be subject to numerous problems, including potential confounding resulting from the use of post-progression treatments, insufficient study follow-up resulting in data immaturity or simply that data on OS have not been collected. In such instances, determining the impact of health technologies becomes more challenging and may rely on the use of other surrogate or intermediate end points to estimate treatment effects on final end points. These surrogate end points are intended to substitute for and predict a final patient-relevant clinical outcome.[66] In terms of advanced/metastatic cancer, potentially relevant surrogate end points may vary according to the tumour type and site, but commonly include PFS, time to progression (TTP) and response-based outcomes [such as ORR, CR, PR, very good partial response (VGPR) and DoR]. These surrogate end points are often considered attractive because they typically require smaller sample sizes, occur faster and are less expensive to collect in clinical trials than final outcomes, thereby reducing the costs associated with data collection and expediting the time required for bringing new technologies to market.

It has long been recognised that the reliance on surrogates may lead to invalid conclusions regarding the net health effects of technologies, which, in turn, have the potential to lead to patient harm.[67] Much of the published literature around the use of surrogate end points has focused on the development and application of frameworks for their validation.[68,69] In his seminal paper, Prentice[68] put forward stringent criteria for the validation of surrogate end points in Phase III trials. In general terms, these criteria require that the surrogate end point must be a correlate of the net effect of treatment on the final clinical outcome; in other words, there must be a single pathway from the treatment to the true end point that is mediated exclusively by the surrogate end point.[70] Applied surrogate validation studies commonly adopt a meta-analytic (meta-regression) approach based on multiple studies to assess whether or not the apparent relationship between the surrogate and the final end point remains

constant in the presence of various sources of heterogeneity, such as differences in patient population, study design and treatments received.[69]

Based on the National Institutes of Health Biomarkers Definition Working Group's preferred terms and definitions[71] and the 1999 JAMA Users' Guide,[72] Elston and Taylor[73] proposed a hierarchy of levels of surrogate validation. Level 3 of the hierarchy relates to biological plausibility; this is the weakest form of validation and is typically based on pathophysiological studies and/or an understanding of the disease process. Level 2 requires the presence of a consistent association between the surrogate outcome and the final end point; this may be assessed using observational studies or arm-based analyses of trials that have measured both the surrogate and the final outcome. This level of validation requires an assessment of the individual-level (absolute) association between end points and is usually undertaken using correlation analysis. Level 1 of the hierarchy represents the strongest level of surrogate validation; to achieve this level of validation, the treatment effects on the surrogate outcome must correspond to a commensurate treatment effect on the final outcome. Demonstrating this level of validity requires an analysis of correlation in terms of treatment effects between arms based on data from RCTs (sometimes referred to as trial-level association). Other validation frameworks have been proposed to assess the strength of association between surrogate and final end points. These include the criteria proposed by the German Institute for Quality and Efficiency in Health Care[74] (IQWiG) (based on the treatment effect association only) and the Biomarker-Surrogate Evaluation Schema (BSES2) criteria[75] (based on both absolute and treatment effect associations). These frameworks differ in terms of the types of analyses and the strength of the relationship required to determine the reliability of the surrogate.

The means by which health economic models use information on relationships between surrogate and final end points differ between appraisals, but may be broadly categorised into two general situations. First, data are available on both the surrogate and the final end points from one or more studies relating to the technology under consideration, and the relationship between the surrogate and the final end points is not informed by external data (and in some instances may not be quantified at all). Second, data are available on the impact of the technology on the surrogate end point, but information relating to the final end point from the same study is not available or is not used to inform the model. In this case, external data (e.g. meta-regressions and/or other forms of predictive model) may be required to quantify the relationship between the surrogate and the final end point. This review is more relevant to the second situation, whereby the degree of confidence that can be placed in the results of the model may be influenced by judgements about whether or not the surrogate can be considered valid.

In the context of histology-independent treatments, data on OS and potentially other TTE outcomes, such as PFS, are likely to be immature. Consequently, there may be a need to rely on surrogate outcomes, such as response rate, using data from external sources to estimate other more clinically meaningful final outcomes. This section presents a systematic review of response-based outcomes as surrogates for PFS, TTP and OS in advanced or metastatic cancer, across any tumour site. The review focuses on meta-analyses and meta-regressions. Analyses are presented both for absolute associations and for treatment-effect associations between response-based outcomes and PFS, TTP and/or OS. In addition, the IQWiG and BSES2 criteria are used to assess the strength of association between surrogate and final end points. Where data permit, the review also explores the surrogate threshold effect (STE) associated with response-based outcomes: this corresponds to the smallest treatment effect on the surrogate that predicts a non-zero treatment effect on the true end point.[76]

Where available, the results of published regression models are also reported; if the ORR was deemed to be valid in one or more tumour types, one option would be to use the coefficients from models to quantify the relationship between ORR and PFS/OS. Other approaches for incorporating surrogate outcomes in health economic models are discussed at the end of the chapter.

Methods

Review question

This systematic review sought to address the following research question: 'What is the strength of the association between response outcomes and PFS, TTP or OS across different types of cancer (primarily advanced or metastatic), based on meta-analyses or meta-regression studies assessing the statistical relationship between these outcomes?'.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the review are shown in *Table 1*. Inclusion was restricted to articles that reported meta-analyses and meta-regressions across multiple studies and that reported the strength of association between response outcomes (ORR, CR, PR, VGPR or DoR) and PFS, TTP or OS. The included meta-regressions could themselves include RCTs and/or single-arm studies. However, individual reports analysing single trials or single cohorts were excluded. Included meta-analyses could report absolute associations and/or treatment effect associations. These associations had to be reported as a correlation coefficient (e.g. Pearson r or Spearman's r_s) and/or a coefficient of determination (R^2) between relevant outcomes.

Studies of any cancer and any treatment were included. The review focused mainly on studies of advanced or metastatic cancers (and/or treatment with palliative intent) because these studies were more likely to report PFS and OS. However, studies reporting relevant outcomes were included even

TABLE 1 Inclusion and exclusion criteria

Field	Inclusion	Exclusion
Disease area	• Any cancer • Mainly advanced or metastatic cancer, and/or where treatment intent was palliative • Studies reporting relevant outcomes for which stage was not restricted to advanced/metastatic or for which this was unclear (particularly haematological cancers)	• Treatment with curative intent • Neo-adjuvant treatment • Adjuvant treatment
Surrogate end points	Response end points: • ORR = CR + PR • CR • PR • VGPR • DoR	• Other end points
Final end points	• PFS • TTP • OS	• Other end points
Study and data type	• Meta-analyses and meta-regressions across multiple studies • Included meta-analyses could include RCTs and/or single-arm studies • Included meta-analyses could use aggregate data (e.g. medians per study arm) and/or individual patient data	• Analyses of single trials or single cohorts
Type of analysis reported	• Studies must report absolute associations and/or treatment effect associations between relevant end points (see above) • Associations must be expressed as a correlation coefficient (e.g. Pearson's r or Spearman's r_s) and/or as a coefficient of determination (R^2)	• No correlation coefficient or regression R^2 reported
Language	• English language • Other language if sufficient detail in English abstract	• Non-English with insufficient detail

where the stage was not specifically restricted to advanced/metastatic disease for all patients or where this was unclear (this applied particularly to haematological cancers). Studies were excluded if they explicitly referred to adjuvant or neo-adjuvant treatment or treatments that are given with curative intent.

Search strategy

Five databases [MEDLINE, EMBASE™ (Elsevier, Amsterdam, the Netherlands), Web of Science™ (Clarivate Analytics, Philadelphia, PA, USA), the Cochrane Database of Systematic Reviews and Cumulative Index to Nursing and Allied Health Literature (CINAHL)] were searched from inception to March 2019. Search terms included cancer terms AND response terms AND terms for PFS, TTP and/or OS AND terms for regression, correlation, prediction, association or relationship AND terms for end point and/or surrogate. Search results were limited to the English language and to studies undertaken in humans. The MEDLINE search strategy is provided in *Appendix 3*.

In addition, a citation search was undertaken based on two existing meta-reviews[77,78] of surrogate relationships; this identified studies that have cited any of the 48 articles included in the review by Fischer *et al.*[77] and/or any of the 19 articles included in the review by Davis *et al.*[78] In addition, relevant existing meta-reviews, including Fischer *et al.*,[77] Davis *et al.*,[78] Savina *et al.*[79] and Haslam *et al.*,[80] and any further reviews identified during searching, were checked for relevant studies.

Study selection process

The titles and abstracts of the articles retrieved by the search were examined by one reviewer and a subset were checked by a second reviewer early in the process, followed by a discussion to ensure that there was consistency in the selection decisions. Full texts were examined by one reviewer and a subset were checked by a second reviewer, with any discrepancies resolved through discussion.

Data extraction

Data were extracted by one reviewer and all data were checked by a second reviewer. The following data were extracted:

- author and date
- cancer type and stage, number of patients, number of included studies and the design of included studies (RCT or single arm and publication dates)
- treatment type, treatment line and other subgroups, as reported
- data type [aggregate-level data or individual patient data (IPD)]
- surrogate and final end points analysed (e.g. ORR to OS)
- response criteria used, if reported (e.g. RECIST)
- measures of outcomes [e.g. hazard ratio (HR), odds ratio (OR), relative risk (RR) or difference between medians]
- statistical methods for correlation and regression, whether weighted, whether adjusted, coefficient reported [e.g. Pearson or Spearman correlation coefficient (r or r_s), regression coefficient of determination (R^2)]
- absolute association results (i.e. between absolute values of the surrogate and final end points based on data from individual arms of RCTs or single-arm studies) – correlation coefficient, regression R^2 and regression equation
- treatment effect association results (i.e. between treatment effects for surrogate and treatment effects for final end points, based on between-group differences from RCTs) – correlation coefficient, regression R^2 and regression equation
- data, as above, for subgroups
- STE,[76] that is the smallest treatment effect on the surrogate that predicts a non-zero treatment effect on the true end point.

Data synthesis

Data were tabulated and described in a narrative synthesis. Plots were constructed to illustrate the reported associations. Some of the included meta-regression studies reported multiple subgroup analyses with differing results. Therefore, for associations between absolute values of end points, the plots show the range of correlation coefficients per study, across all subgroup analyses. Where an included meta-regression study reported on more than one cancer type, these are shown separately on the plots. All types of correlation coefficient were included, for example Pearson's r and Spearman's r_s. If no correlation coefficient was reported, Pearson's r was calculated as the square root of R^2, if available.

For associations between treatment effects, the plots show the range of regression coefficients of determination (R^2) per study, across all subgroup analyses. The plots include both adjusted and unadjusted R^2 values, as well as values from weighted and unweighted regressions. For studies in which R^2 was not reported, this was calculated as the square of the Pearson's (r) correlation coefficient, if available. R^2 was not calculated from other correlation coefficients, such as Spearman's r, or where the method of correlation was unclear.

Scoring the strength of association

Two separate sets of criteria have been developed to assess the strength of association between end points. These include the criteria proposed by IQWiG[74] (based on the treatment effect association) and the BSES2 criteria[75] (based on both absolute and treatment effect associations). In this review, both the IQWiG and the BSES2 criteria were used to assess the strength of association between the surrogate and the final end points.

The IQWiG criteria[74] (*Table 2*) are based on the correlation coefficient (r) for the treatment effect association. Where r was not reported it was calculated as the square root of R^2, if available. Some slight modifications were made to the IQWiG scoring criteria because the medium score bracket was not clearly defined (see *Table 2*); these modifications were based on the approach used in the previous review by Savina *et al.*[79] The IQWiG score was generated based on the magnitude of r, irrespective of its sign (i.e. a negative correlation could generate a high score).

The BSES2 criteria[75] (*Table 3*) require R^2 values for both the individual and the treatment effect associations. Where R^2 was not reported, it was calculated as the square of r, if available. BSES2 criteria were used as an adaptation from the original BSES criteria, as described in Savina *et al.*[79] The original BSES criteria require R^2 for both individual-level and treatment effect associations and a value for the STE. Given that so few articles report STE, this review used BSES2, which does not require the STE.

TABLE 2 The IQWiG scoring criteria[74]

IQWiG score	Criteria (based on r for treatment–effect association)[a]
High	The lower CI of r is ≥ 0.85
Medium +[b]	$r \geq 0.85$ with no reported CI or $r \geq 0.85$ with wide CIs (lower limit < 0.85)
Medium	$0.85 > r \geq 0.7$ and the upper CI of r is ≥ 0.7 and the lower CI of r is < 0.85, or $0.85 > r \geq 0.7$ with no reported CI
Low	The upper CI of r is < 0.7 or $r < 0.7$ with no reported CI

a r is defined as any correlation parameter for the treatment–effect association, e.g. Pearson's, Spearman's or Kendall's tau. Where no correlation parameter was reported, if a univariate regression was performed and a R^2 value attained, then r (Pearson's correlation coefficient) was calculated as the square root of R^2. The reported r could be for any treatment effect estimate (e.g. HR and difference in medians); where more than one was reported, relative estimates (e.g. HR and OR) were used in preference to difference in medians.
b The Medium + category was based on the approach used in Savina *et al.*[79]
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TABLE 3 The BSES2 scoring criteria[75]

BSES2 score	Criteria (based on R^2 for both treatment effect and individual-level associations)[a]
Excellent	R^2 (treatment effect) ≥ 0.6 and R^2 (absolute) ≥ 0.6
Good	R^2 (treatment effect) ≥ 0.4 and R^2 (absolute) ≥ 0.4
Fair	R^2 (treatment effect) ≥ 0.2 and R^2 (absolute) ≥ 0.2
Poor	R^2 (treatment effect) < 0.2 and/or R^2 (absolute) < 0.2

a R^2 is the coefficient of determination for a regression analysis. Where R^2 was not reported, it was calculated as the square of the Pearson's correlation coefficient (r), if available. The reported R^2 could be for any treatment effect estimate (e.g. HR and difference in medians); where more than one was reported, relative estimates (e.g. HR and OR) were used in preference to difference in medians.

Results

Number of included studies

The literature search generated 2829 citations (*Figure 1*), of which 2630 were excluded during the review of titles and abstracts. In total, 64 references to 63 studies were included in the review.[81–144] The study characteristics for the 63 included studies are shown in *Appendix 4*. The detailed results of

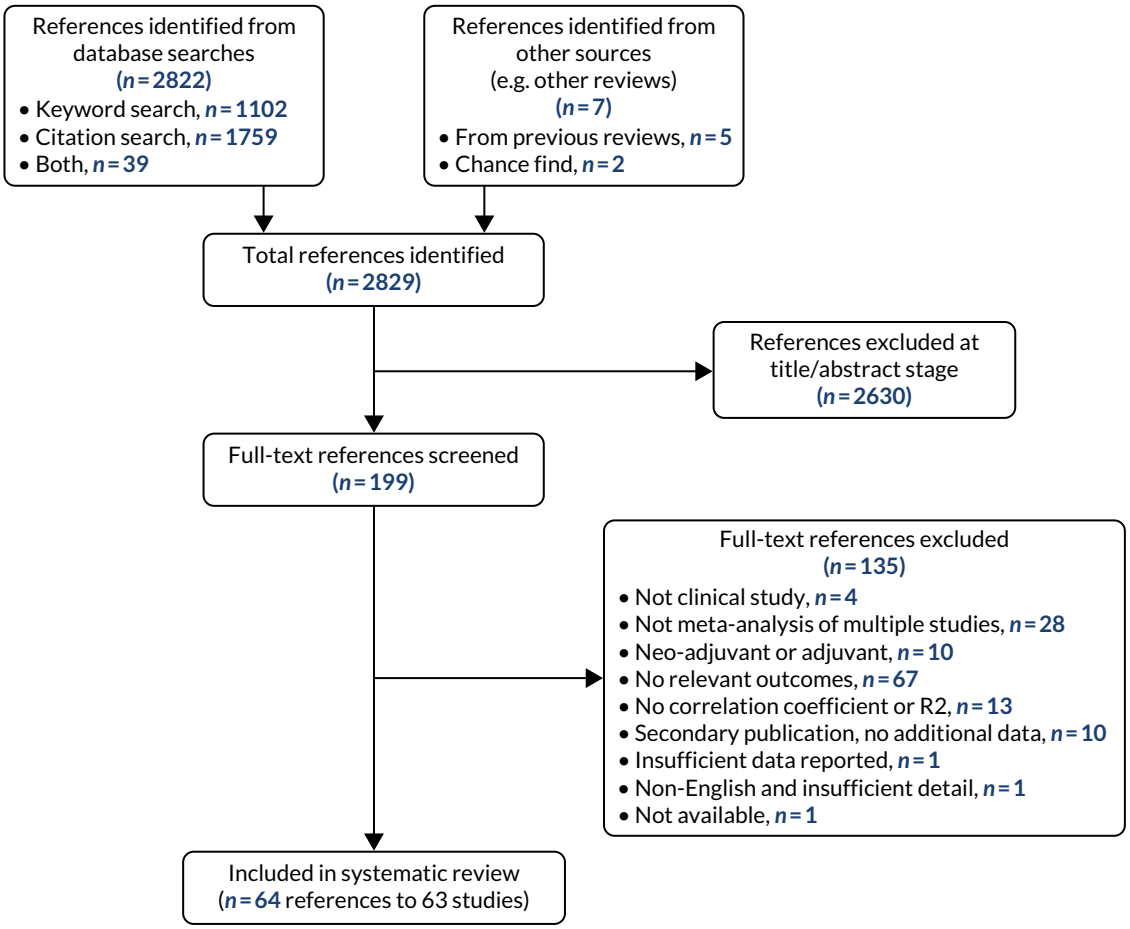

FIGURE 1 The PRISMA flow diagram for study inclusion. Reproduced with permission from Cooper *et al.*[64] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

the included studies are shown in *Appendices 5* and *6*. Studies excluded at the full-text stage, with reasons for exclusion, are listed in *Appendix 7*.

Characteristics of the included studies

Full details of the study characteristics for the 63 included studies are shown in *Appendix 4* (note that eight references[81,109,111,128,130,140,141,144] appear on more than one row because they report on more than one cancer type).

Surrogate relationships, cancer types and treatments

A summary of the surrogate relationships, cancer types and treatments is provided in *Table 4*. The most commonly reported surrogate relationships were ORR to OS ($n = 57$ studies), ORR to PFS ($n = 22$ studies), CR to OS ($n = 8$ studies) and CR to PFS ($n = 7$ studies). Other response outcomes (DoR, PR and VGPR/CR) were reported in only one to two studies each.

Twenty different cancer types were analysed (see *Table 4*), the most common being NSCLC ($n = 16$ studies), CRC ($n = 10$ studies), various solid tumours ($n = 8$ studies) and breast cancer ($n = 5$ studies).

TABLE 4 Study characteristics: surrogate relationships, cancer types and treatments

Surrogate relationship	Cancer type	Disease stage	Line of treatment	Treatment type
• ORR to OS ($n = 57$) • ORR to PFS ($n = 22$) • CR to OS ($n = 8$) • CR to PFS ($n = 7$) • DoR to OS ($n = 2$) • ORR to TTP ($n = 1$) • PR to PFS ($n = 1$) • PR to OS ($n = 1$) • VGPR/CR to PFS ($n = 1$) • DoR to PFS ($n = 1$)	• Lung (NSCLC) ($n = 16$) • Colorectal ($n = 10$) • Various solid ($n = 8$) • Breast ($n = 5$) • NHL ($n = 4$) • Lung (SCLC) ($n = 3$) • Ovarian ($n = 3$) • Pancreatic ($n = 3$) • Renal cell ($n = 3$) • Gastric ($n = 2$) • Neuroendocrine ($n = 2$) • Soft tissue sarcoma ($n = 2$) • Urothelial ($n = 2$) • AML ($n = 1$) • Biliary tract ($n = 1$) • Gastro-oesophageal ($n = 1$) • Glioblastoma ($n = 1$) • Multiple myeloma ($n = 1$) • Prostate ($n = 1$) • Unknown primary ($n = 1$)	• Advanced/ metastatic ($n = 43$) • Unclear ($n = 9$) • Advanced, locally advanced, unresectable or metastatic ($n = 2$) • Extensive disease ($n = 2$) • Limited or extensive disease ($n = 1$) • Advanced or recurrent ($n = 1$) • Advanced, locally advanced or recurrent ($n = 1$) • Relapsed/ refractory ($n = 1$) • Most stage III/ IV ($n = 1$) • Recurrent/ platinum-resistant ($n = 1$) • Various ($n = 1$)	• First ($n = 23$) • All/various ($n = 18$) • NR ($n = 8$) • First and second ($n = 5$) • Second ($n = 4$) • Second and subsequent ($n = 3$) • Second and third ($n = 2$)	• Chemotherapy ($n = 21$) • Immune checkpoint inhibitors ($n = 9$) • Targeted therapy ($n = 8$) • Various ($n = 7$) • Systemic ($n = 5$) • Chemotherapy or targeted therapy ($n = 3$) • Chemotherapy, immune checkpoint inhibitors or targeted therapy ($n = 2$) • NR ($n = 1$) • Chemotherapy and targeted therapy ($n = 1$) • Chemotherapy or immune checkpoint inhibitors ($n = 1$) • Chemotherapy, hormonal therapy and targeted therapy ($n = 1$) • Chemotherapy or biologic ($n = 1$) • Cytokine or targeted therapy ($n = 1$) • Gemcitabine (Gemzar, Eli Lilly, Indianapolis, IN, USA) and chemotherapy or targeted therapy ($n = 1$) • Bevacizumab (Avastin, Roche, Basel, Switzerland) and chemotherapy ($n = 1$)

AML, acute myeloid leukaemia; NHL, non-Hodgkin's lymphoma; NR, not reported.

Note

Totals may sum to more than the total number of studies ($n = 63$) because some studies reported more than one surrogate relationship or cancer type.

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The disease stage was advanced/metastatic in 43 studies and unclear in nine studies (see *Table 4*), while the remainder ($n = 11$ studies) gave other descriptions, mostly indicating advanced, extensive or recurrent disease. The treatment was first line in 23 studies, later lines or combinations of lines in 32 studies, and not reported in eight studies. The treatment type was chemotherapy in 21 studies, immune checkpoint inhibitors in nine studies, targeted therapy in eight studies and various other treatment combinations in the remainder of the studies.

Data types reported

Table 5 summarises the data types reported in the included meta-regressions. The various meta-regressions included between four and 191 primary studies and between 407 and 44,125 patients each. The majority of meta-regressions ($n = 44$) included only RCTs, while 17 included both RCTs and single-arm studies and two included single-arm studies only. Most of the meta-regressions ($n = 58$) analysed aggregate data (e.g. medians or another summary measure per study arm), while five analysed IPD. Across all meta-regressions, 32 reported absolute (individual-level) associations, 38 reported treatment effect (trial-level) associations and only four reported the STE.

Results of the included studies

Absolute (individual-level) correlation and regression

The range of the absolute (individual-level) correlation coefficients reported in each meta-regression is summarised in *Table 6* and illustrated in *Figures 2* (for the association between ORR and PFS) and *3* (for the association between ORR and OS). Each horizontal row in the plots illustrates the range of correlation coefficients across all subgroup analyses within a single meta-regression study. Where an included meta-regression reported on more than one cancer type, these are shown separately on the plots. It is worth noting that the meta-regressions varied both in terms of the number of included primary studies (shown as *N* on the plots) and in terms of the treatment type, line of treatment and precise clinical population; all of these details are provided in *Appendix 5*, together with correlation coefficients for all individual subgroup analyses.

Overall response rate and progression-free survival (or time to progression)

The reported correlation coefficients (Pearson's r or Spearman's r_s) between absolute ORR and PFS ranged from −0.72 to 0.96, based on multiple analyses within 12 studies across 10 cancer types (see *Figure 2* and *Table 6*; full details in *Appendix 5*).[107,108,115,117,118,122,125,126,128,129,135,141] Across those studies that report only a single analysis, the correlation coefficient was generally above 0.60; however, some estimates were lower. Confidence intervals around the correlation coefficients were rarely reported (not shown in *Figure 2*; see *Appendix 5*). Few separate meta-regressions reported on the same tumour site; therefore, it is difficult to assess whether or not the ORR may be a more reliable surrogate in certain cancer types than others. One study reported on the ORR and TTP (gastric cancer, correlation $r_s = 0.41$ to 0.56 across subgroup analyses, not shown on the plot).[105]

TABLE 5 Study characteristics: data types

Number of primary studies per meta-regression	Number of patients per meta-regression	Included study types per meta-regression	Data types	Absolute association reported	Treatment effect association reported	STE reported
$n = 4$–191	$n = 407$–44,125	• RCT only, $n = 44$ • RCT and SA, $n = 17$ • SA only, $n = 2$	• AD, $n = 58$ • IPD, $n = 5$	$n = 32$	$n = 38$	$n = 4$

AD, aggregate data; SA, single arm.

TABLE 6 Summary of the absolute (individual-level) correlations per study

Surrogate relationship	Number of studies	Cancer types and references	Range of r or r_s across studies and subgroup analyses	Further details
ORR to PFS	12	NSCLC,[108,128,141] ovarian,[129,135] RCC,[126] NHL,[117] SCLC,[122] MM,[118] CRC,[115] CUP,[125] NET[107] and various[141]	−0.72 to 0.96	See *Appendix 5* and *Figure 2*
ORR to TTP	1	Gastric[105]	0.41 to 0.56	See *Appendix 5*
ORR to OS	27	NSCLC,[108,112,113,128,131,134,141] CRC,[98,115,138] ovarian,[129,135] breast,[114,127] gastric,[105,133] various,[123,128,141] pancreatic,[100] RCC,[81,126] gastro-oesophageal,[124] urothelial,[81,82] AML,[83] SCLC,[122] glioblastoma,[101] CUP[125] and NET[106]	−0.40 to 1.00	See *Appendix 5* and *Figure 3*
CR to PFS	2	SCLC[122] and NHL[144]	0.22 to 0.83	See *Appendix 5*
CR to OS	3	NSCLC,[112] SCLC[122] and gastro-oesophageal[124]	−0.04 to 0.62	See *Appendix 5*
PR to PFS	1	SCLC[122]	0.35 to 0.70	See *Appendix 5*
PR to OS	1	SCLC[122]	0.29 to 0.66	See *Appendix 5*
VGPR/CR to PFS	0	–	[a]	See *Appendix 5*
DoR to PFS	0	–	–	–
DoR to OS	0	–	–	–

AML, acute myeloid leukaemia; CUP, cancer of unknown primary; MM, multiple myeloma; NET, neuroendocrine tumour; NHL, non-Hodgkin's lymphoma; RCC, renal cell carcinoma.

a One study[118] of MM reported VGPR/CR to PFS as adjusted $R^2 = 0.64$, but this could not be converted to r because it was adjusted.

Notes

Further detail on all studies and outcomes is shown in *Appendix 5*. The number of studies per outcome may vary from *Table 4* given that not all data are in the correct format.

Overall response rate and overall survival

The reported correlation coefficients between absolute ORR and OS ranged from −0.40 to 1.00, based on 27 studies across 15 cancer types (see *Figure 3* and *Table 6*; full details in *Appendix 5*).[81–83,98,100,101,105,106,108,112–115,122–129,131,133–135,138,141] The CIs around the correlation coefficients, where reported, were generally fairly wide (not shown in *Figure 3*). The majority of correlation coefficients were above 0.40; however, several estimates were lower. The correlation coefficients reported from multiple analyses within the same study, and those reported across separate studies, did not suggest a clear pattern by cancer type.

Complete response and progression-free survival or overall survival

The correlation coefficients between absolute CR and PFS in two studies of SCLC[122] and non-Hodgkin's lymphoma (NHL)[144] ranged from 0.22 to 0.83, while the correlation coefficients between absolute CR and OS ranged from −0.04 to 0.62, based on three studies of NSCLC,[112] SCLC[122] and gastro-oesophageal cancer[124] (see *Table 6*; full details in *Appendix 5*).

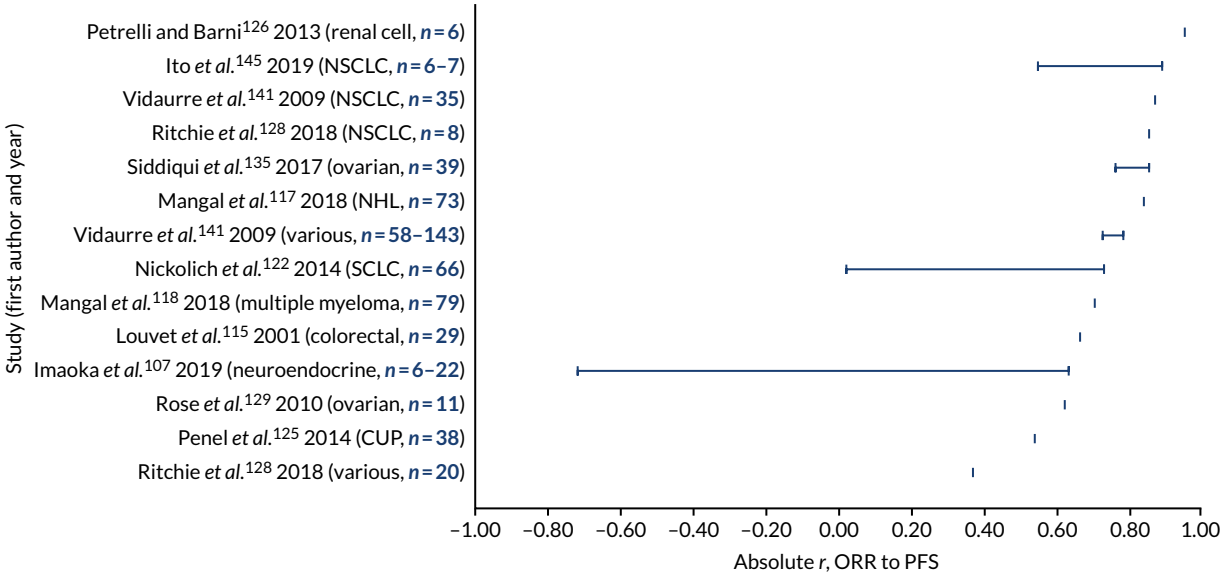

FIGURE 2 Correlation (r or r_s) between the absolute (individual-level) value of ORR and the absolute (individual-level) value of PFS. For each study, the plot illustrates the range of correlation coefficients across all subgroup analyses. *N* represents the number of studies included in each meta-regression. CUP, cancer of unknown primary. Reproduced with permission from Cooper *et al.*[64] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

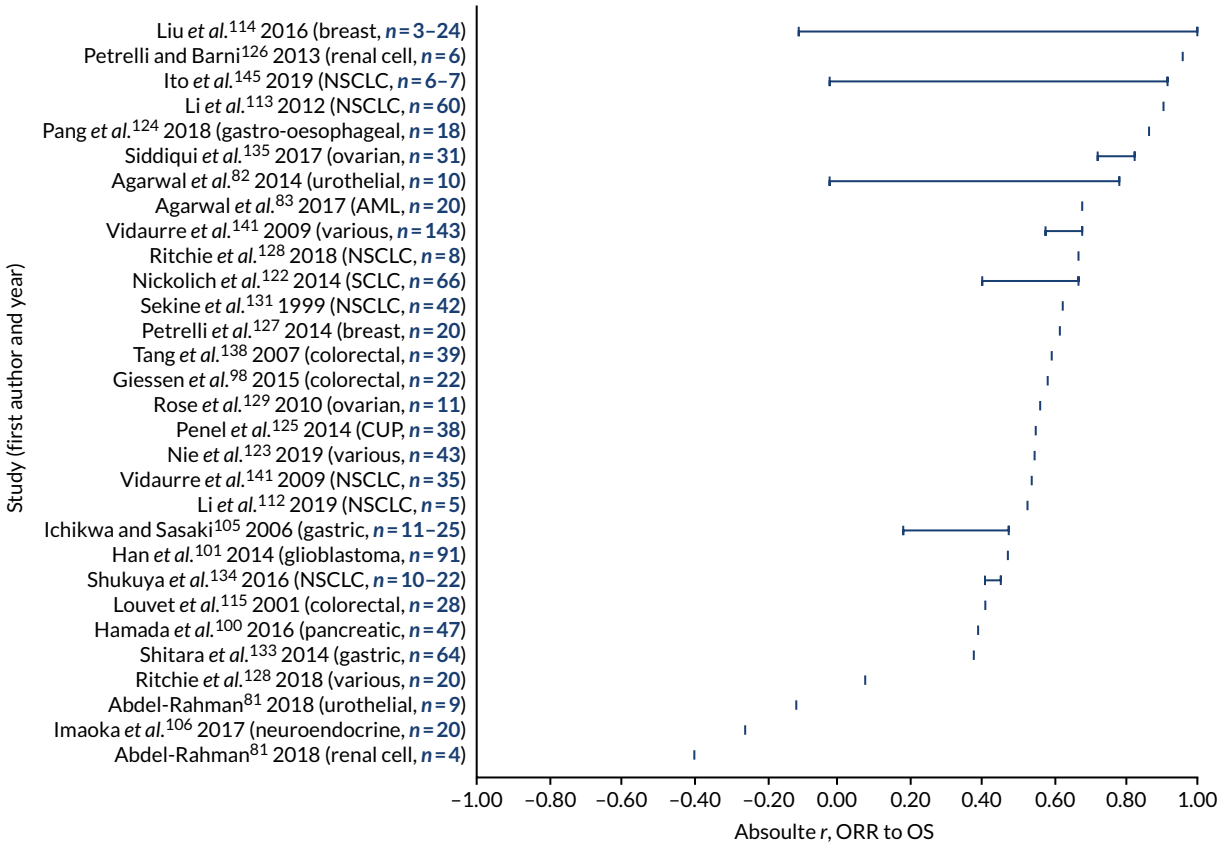

FIGURE 3 Correlation (r or r_s) between the absolute (individual-level) value of ORR and the absolute (individual-level) value of OS. For each study, the plot illustrates the range of correlation coefficients across all subgroup analyses. *N* represents the number of studies included in each meta-regression. AML, acute myeloid leukaemia; CUP, cancer of unknown primary. Reproduced with permission from Cooper *et al.*[64] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Partial response and progression-free survival or overall survival

The correlation coefficient between absolute PR and PFS ranged from 0.35 to 0.70 across subgroup analyses within one study of SCLC,[122] while the highest correlation coefficient between absolute PR and OS ranged from 0.29 to 0.66 in the same study[122] (see *Table 6*; full details in *Appendix 5*).

Duration of response and progression-free survival or overall survival

No studies reported on the absolute association between DoR and PFS or OS.

Treatment effect (trial-level) correlation and regression

The range of treatment effect (trial-level) R^2 values reported in each meta-regression is summarised in *Table 7* and illustrated in *Figures 4* (for the association between ORR and PFS) and *5* (for the association between ORR and OS). Each horizontal row in the plots illustrates the range of R^2 values across all subgroup analyses within a single meta-regression study. Where an included meta-regression reported on more than one cancer type, these are shown separately on the plots. It is worth noting that the meta-regressions varied both in terms of the number of included primary studies (shown as *n* on the plots) and in terms of the treatment type, line of treatment and precise clinical population; all of these details are provided in *Appendix 6*, together with R^2 values for all individual subgroup analyses.

Overall response rate and progression-free survival

The regression R^2 values for the treatment effect association between ORR and PFS ranged from 0.18 to 0.94, based on nine studies across four cancer types: NSCLC,[84,85,108,140] ovarian cancer,[90,135] CRC[89] and various solid tumours[130,142] (see *Figure 4* and *Table 7*; full details in *Appendix 6*). The majority of R^2 values were above 0.40. The R^2 values that were reported from multiple analyses within the same study and those that were reported across separate studies did not suggest a clear pattern by cancer type. Confidence intervals around the R^2 values, where reported, were generally fairly wide (not shown in *Figure 4*; see *Appendix 6*).

TABLE 7 Summary of the treatment effect (trial-level) R^2 per study

Surrogate relationship	Number of studies	Cancer types and references	Range of R^2 across studies and subgroup analyses	Further details
ORR to PFS	9	NSCLC,[84,85,108,140] ovarian,[90,135] various[130,142] and CRC[89]	0.18 to 0.94	See *Appendix 6* and *Figure 4*
ORR to TTP	0		–	–
ORR to OS	30	NSCLC,[84,85,103,108,109,121,140] CRC,[88,89,92,94,136] various,[110,120,123,130,142] pancreatic,[91,100,116] SCLC,[97,104] RCC,[95,126] breast,[86,99] ovarian,[90] prostate,[93] BTC[119] and soft tissue sarcoma[137]	–0.08 to 0.84	See *Appendix 6* and *Figure 5*
CR to PFS	1	NHL[132]	0.45 to 0.93	See *Appendix 6*
CR to OS	2	Breast[99] and SCLC[97]	0.05 to 0.48	See *Appendix 6*
PR to PFS	0		–	–
PR to OS	0		–	–
DoR to PFS	0		–	See *Appendix 6*
DoR to OS	0		[a]	See *Appendix 6*

BTC, biliary tract cancer; RCC, renal cell carcinoma.

a Two studies in CRC[92] and pancreatic cancer[91] reported Spearman's correlation coefficients between DoR and OS, ranging from 0.40 to 0.76.

Notes

Further detail on all studies and outcomes is shown in *Appendix 6*. The number of studies per outcome may vary from *Table 4* given that not all data are in the correct format.

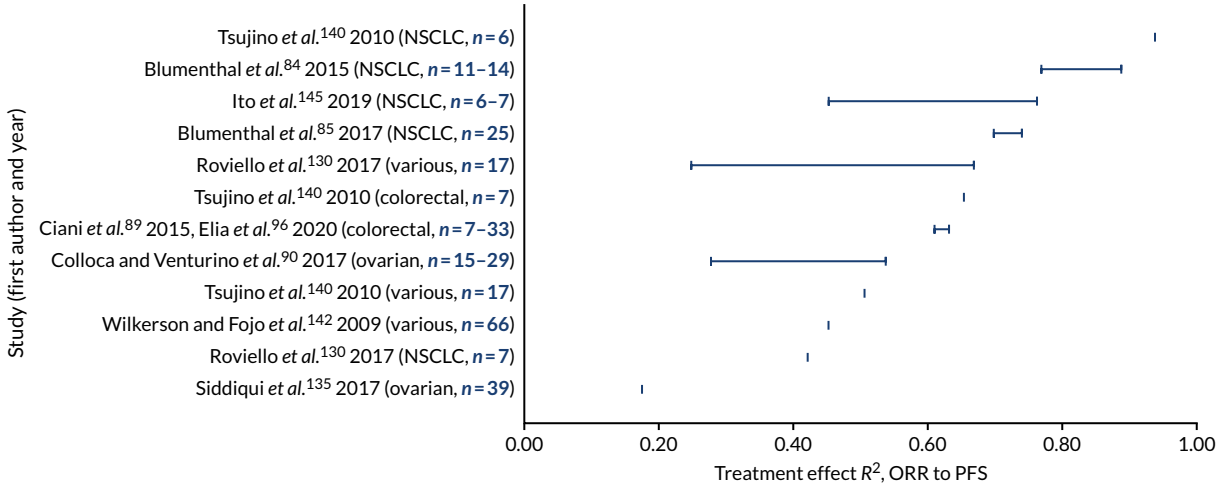

FIGURE 4 Regression R^2 between treatment effects (trial level) for ORR and PFS. For each study, the plot illustrates the range of correlation coefficients across all subgroup analyses. *N* represents the number of studies included in each meta-regression. Reproduced with permission from Cooper *et al.*[64] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

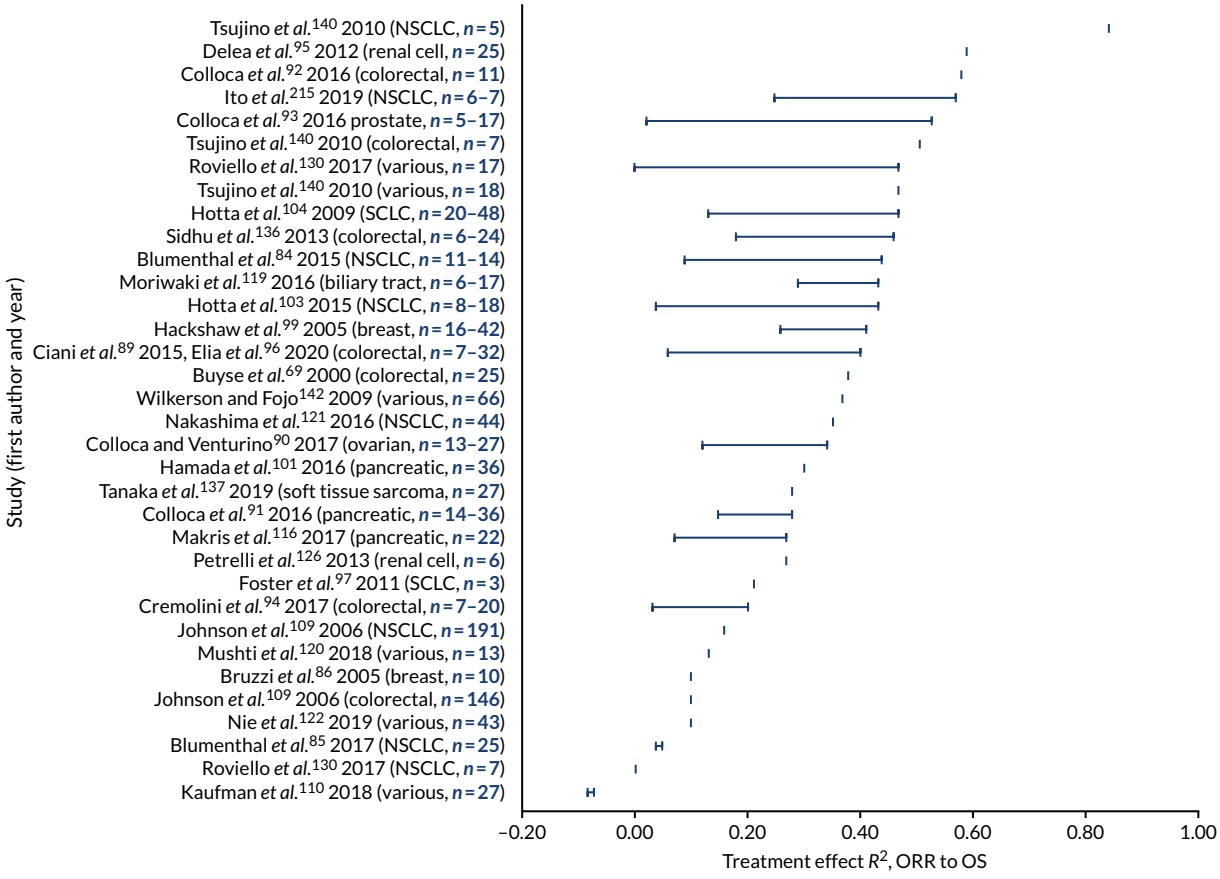

FIGURE 5 Regression R^2 between treatment effects (trial level) for ORR and OS. For each study, the plot illustrates the range of correlation coefficients across all subgroup analyses. *N* represents the number of studies included in each meta-regression. Reproduced with permission from Cooper *et al.*[64] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Overall response rate and overall survival

The regression R^2 values for the treatment effect association between ORR and OS ranged from −0.08 to 0.84, based on 30 studies across 11 cancer types (see *Figure 5* and *Table 7*; full details in *Appendix 6*).[84–86,88–95,97,99,100,103,104,108–110,116,119–121,123,126,130,136,137,140,142] With the exception of one analysis, all R^2 values were below 0.60. The R^2 values that were reported from multiple analyses within the same study and those that were reported across separate studies did not suggest a clear pattern by cancer type. Confidence intervals around the R^2 values, where reported, were generally wide (not shown in *Figure 5*).

Complete response and progression-free survival or overall survival

The regression R^2 for the treatment effect association between CR and PFS ranged from 0.45 to 0.93 in one study of NHL,[132] while the regression R^2 for the treatment effect association between CR and OS within two studies of breast cancer[99] and SCLC[97] ranged from 0.05 to 0.48 (see *Table 7*; full details in *Appendix 6*).

Partial response and progression-free survival or overall survival

No studies reported the treatment effect association between PR and PFS or OS.

Duration of response and progression-free survival or overall survival

No studies reported R^2 between DoR and OS or PFS. Two studies in CRC[92] and pancreatic cancer[91] reported Spearman's correlation coefficients between DoR and OS, ranging from 0.40 to 0.76 (see *Table 7*; full details in *Appendix 6*).

Regression equations

Regression equations for absolute (individual-level) relationships

Regression equations for absolute (individual-level) associations were reported in six studies[105,115,117,135,139,144] and are summarised in *Table 8*.

TABLE 8 Regression equations for absolute associations

Surrogate relationship	Cancer types and references	Surrogate	Final	Intercept	Slope
ORR to PFS	Colorectal[115]	ORR	Median PFS	3.20	0.10
	Lung (NSCLC)[139]	ORR	Median PFS	NR	0.07
	Ovarian[135]	ORR	Median PFS	2.59	0.12
	NHL[117]	Log-odds ORR	Log-median PFS	1.97	0.41
ORR to TTP	Gastric[105]	ORR	Median TTP	1.73	0.09
ORR to OS	Colorectal[115]	ORR	Median OS	10.45	0.09
	Lung (NSCLC)[139]	ORR	Median OS	NR	0.26
	Ovarian[135]	ORR	Median OS	9.48	0.28
	Gastric[105]	ORR	Median OS	5.89	0.08
CR to PFS	NHL[144]	CR	Median PFS	0.83	0.46
	NHL[117]	Log-odds CR	Log-median PFS	2.38	0.34

NR, not reported.

Overall response rate to progression-free survival/time to progression For the relationship between the ORR and the median PFS/TTP, five studies across five cancer types[105,115,117,135,139] reported regression equations (one study used log-odds ORR),[117] with intercepts ranging from 1.73 to 3.20 and slopes ranging from 0.07 to 0.41.

Overall response rate to overall survival For the relationship between the ORR and the median OS, four studies across four cancer types[105,115,135,139] reported regression equations, with intercepts ranging from 5.89 to 10.45 and slopes ranging from 0.08 to 0.28.

Complete response to progression-free survival For the relationship between the CR and the median PFS, two studies in NHL[117,144] reported regression equations (one study used log-odds CR),[117] with intercepts ranging from 0.83 to 2.38 and slopes ranging from 0.34 to 0.46.

Regression equations for treatment effect (trial-level) relationships

The regression equations for treatment effect (trial-level) associations were reported in 13 studies[87,89,94–96,99,104,109,119,121,130,132,140] and are summarised in *Table 9*. These are presented separately for regressions based on the difference in response and regressions based on the RR or OR for response. There was substantial variation in effect measures for both the surrogate and the final outcomes (e.g. difference in medians, HR and OR).

Overall response rate to progression-free survival For the relationship between ORR and PFS, one study of three cancer types[140] reported regression equations for the difference in ORR compared with the HR for PFS, with slopes ranging from −0.02 to −0.04 (intercepts were not reported). Three studies across three cancer types[87,89,96,130] reported regression equations for the log-OR for ORR compared with the log-HR for PFS, with intercepts ranging from −0.13 to 0.10 and slopes ranging from −0.32 to 0.50.

Overall response rate and overall survival For the relationship between ORR and OS, two studies in colorectal cancer[94,109] and NSCLC[109] reported regression equations for the difference in ORR compared with the difference in median OS, with intercepts ranging from −0.05 to 0.34 and slopes ranging from 0.07 to 0.14. One study of three cancer types[140] reported regression equations for the difference in ORR compared with the HR for OS, with slopes ranging from −0.01 to −0.03 (intercepts were not reported). Seven studies across six cancer types[89,94–96,99,119,121,130] reported regression equations for the ratio measures of ORR (OR or RR) compared with the ratio measures of OS (generally HR), with intercepts ranging from −0.13 to 0.12 and slopes ranging from −0.26 to 0.30. One study in SCLC[104] reported a regression equation for the RR of ORR compared with the difference in median OS, with an intercept of 0 and slopes ranging from 0.04 to 0.09.

Complete response to progression-free survival For the relationship between CR and PFS, one study in NHL[132] reported regression equations for log-OR CR compared with log-HR PFS, with intercepts ranging from −0.09 to 0.04 and slopes ranging from −0.73 to −0.64.

Complete response to overall survival For the relationship between CR and OS, one study in breast cancer[99] reported regression equations for log-OR CR compared with log-HR PFS, with an intercept of −0.01 (where reported) and slopes ranging from 0.09 to 0.16.

Surrogate threshold effect

The STE (the smallest treatment effect on the surrogate that predicts a non-zero treatment effect on the true end point)[76] was reported in only four studies (*Table 10*).[89,102,132,140] For the relationship between ORR and PFS, one study of various solid tumours[140] reported that a difference in ORR of 15% would be required to predict a non-zero treatment effect on the HR for PFS. For the relationship between ORR and OS, two studies in various solid tumours[140] and NSCLC[102] reported that a difference in ORR of 21% and 55%, respectively, would be required to predict a non-zero treatment effect on the HR for OS. In addition, one study[102] reported that a difference in ORR of 41% would be required to predict a non-zero treatment effect

TABLE 9 Regression equations for treatment effect (trial-level) associations

Surrogate relationship	Cancer types and references	Subgroup	Based on difference in response				Based on RR or OR for response			
			Surrogate	Final	Intercept	Slope	Surrogate	Final	Intercept	Slope
ORR to PFS	Lung (NSCLC)[140]		Difference in ORR	HR PFS	NR	−0.02				
	Colorectal[140]		Difference in ORR	HR PFS	NR	−0.04				
	Various[140]		Difference in ORR	HR PFS	NR	−0.02				
	Colorectal[89,96]						log-OR ORR	log-HR PFS	−0.05	−0.32
	Breast[87]						log-OR ORR	log-HR PFS	0.10	0.50
	Various (immuno)[130]						log-OR ORR	log-HR PFS	−0.13	−0.24
ORR to OS	Colorectal[94]	All	Difference in ORR	Difference in median OS	NR	0.07				
		Anti-angiogenic				0.13				
		Non-anti-angiogenic				0.14				
	Colorectal[109]		Difference in ORR	Difference in median OS	0.34	0.10				
	Lung (NSCLC)[109]		Difference in ORR	Difference in median OS	−0.05	0.09				
	Colorectal[140]		Difference in ORR	HR OS	NR	−0.03				
	Lung (NSCLC)[140]		Difference in ORR	HR OS	NR	−0.01				
	Various[140]		Difference in ORR	HR OS	NR	−0.02				
	Colorectal[89,96]	All					log-OR ORR	log-HR OS	−0.03	−0.05
		No crossover							−0.04	−0.10
	Breast[99]	All					log-OR ORR	log-HR OS	−0.01	0.28
		Recruited pre-1990							NR	0.28
		Recruited 1990 or after							NR	0.24

continued

TABLE 9 Regression equations for treatment effect (trial-level) associations (*continued*)

Surrogate relationship	Cancer types and references	Subgroup	Based on difference in response				Based on RR or OR for response			
			Surrogate	Final	Intercept	Slope	Surrogate	Final	Intercept	Slope
	Lung (NSCLC)[121]						ln-OR ORR	ln-HR OS	−0.02	−0.13
	Various (immuno)[130]						log-OR ORR	log-HR OS	−0.13	−0.26
	Colorectal[94]	All					RR of ORR	HR OS	NR	−0.03
		Anti-angiogenic								−0.11
		Non-anti-angiogenic								−0.06
	Renal cell[95]						ln-RR ORR	-ln-HR OS	−0.11	0.30
	Biliary tract[119]	Chemotherapy					Ratio of ORR	Log-ratio of median OS	0.01	0.28
		Gemcitabine							0.02	0.27
		Targeted therapy							0.12	0.16
	Lung (SCLC)[104]	All					RR of ORR	Difference in median OS	0.00	0.06
		Published 1990–96							0.00	0.04
		Published 1997–2008							0.00	0.09
CR to PFS	NHL[132]						log-OR CR at 30 months	log-HR PFS	−0.09	−0.64
	NHL[132]						log-OR CR at 24 months	log-HR PFS	0.04	−0.73
CR to OS	Breast[99]	All					log-OR CR	log-HR OS	−0.01	0.13
		Recruited pre-1990							NR	0.09
		Recruited 1990 or after							NR	0.16

NR, not reported.

TABLE 10 The STE

Surrogate relationship	Cancer types and references	Based on difference in response			Based on OR for response		
		Surrogate	Final	STE (%)	Surrogate	Final	STE
ORR to PFS	Various[140]	Difference in ORR	HR PFS	15			
ORR to OS	Colorectal[89]				OR ORR	OR OS	0.28
	NSCLC[102]	Difference in ORR	HR OS	55			
		Difference in ORR	Difference in median OS	41			
	Various[140]	Difference in ORR	HR OS	21			
CR to PFS	NHL[132]				OR CR at 30 months	HR PFS	1.56

on the difference in median OS, and a further study in CRC[89] reported that an OR of 0.28 for ORR would be required to predict a non-zero treatment effect on the OR for OS. Finally, for the relationship between CR and PFS, one study in NHL[132] reported that an OR of 1.56 for CR (at 30 months) would be required to predict a non-zero treatment effect on the HR for PFS.

Institute for Quality and Efficiency in Health Care and Biomarker-Surrogate Evaluation Schema-2 scores for the strength of association

This section reports the results from the IQWiG and BSES2 scoring for the strength of association between surrogate and final end points. As described in *Scoring the strength of association*, IQWiG scoring requires a correlation coefficient (r) for the treatment effect association, while BSES2 scoring requires R^2 values for both the individual-level and the treatment effect associations. IQWiG and BSES2 scores were calculated for all subgroup analyses with sufficient data; therefore, studies reporting more subgroups were more strongly represented in this analysis.

For the IQWiG scores (*Figure 6*), of 202 analyses (across 63 studies), zero (0%) scored high, 15 (7%) scored medium +, 26 (13%) scored medium, 76 (38%) scored low and 85 (42%) were not evaluable.

For the BSES2 scores (*Figure 7*), of 202 analyses (across 63 studies), zero (0%) scored excellent, three (1%) scored good, three (1%) scored fair, seven (3%) scored poor and 189 (94%) were not evaluable.

Discussion

Summary of the main findings

Types of analysis identified

This systematic review summarises correlation and regression analyses for the strength of the association between response outcomes and PFS, TTP or OS across different types of cancer (primarily advanced or metastatic), based on included meta-analyses and meta-regression studies. In total, the review included 63 studies across 20 cancer types, most commonly NSCLC, CRC and breast cancer and analyses of various solid tumours. The most commonly analysed relationships were between ORR and either PFS or OS, with other response outcomes (such as CR, DoR and PR) reported in fewer analyses. The majority of studies ($n = 44$) included only RCTs, while the remainder also included single-arm studies.

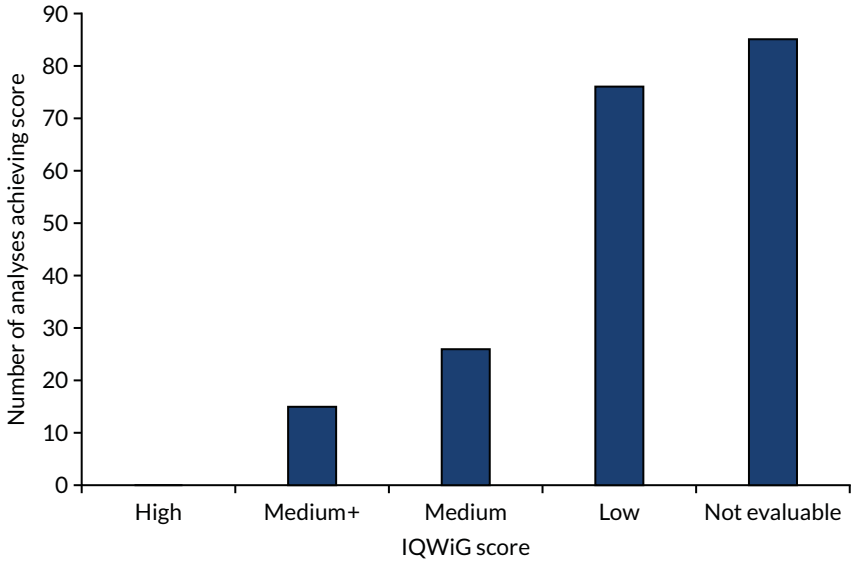

FIGURE 6 Summary of the IQWiG scores across all 202 analyses included in the review. Reproduced with permission from Cooper *et al.*[64] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

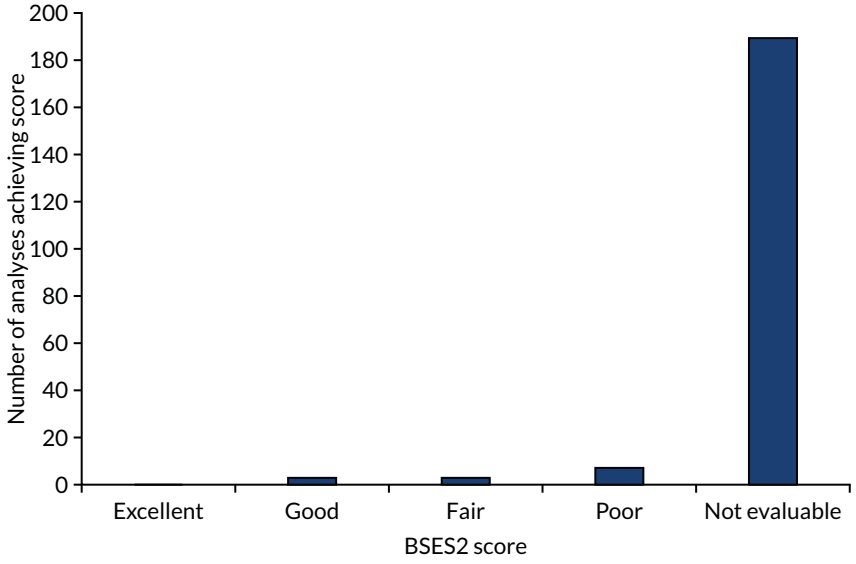

FIGURE 7 Summary of the BSES2 scores across all 202 analyses included in the review.

Absolute (individual-level) associations

For the absolute (individual-level) association, the reported correlation coefficients between ORR and PFS ranged from −0.72 to 0.96, based on multiple analyses within 12 studies across 10 cancer types, while correlations between ORR and OS ranged from −0.40 to 1.00, based on 27 studies across 15 cancer types. Confidence intervals were generally fairly wide and were often not reported. The correlation coefficients that were reported from multiple analyses within the same study, and those reported across separate studies, did not suggest a clear pattern by cancer type. For analyses of CR, the correlation coefficients between CR and PFS in two studies ranged from 0.22 to 0.83, while those between CR and OS ranged from −0.04 to 0.62, based on three studies.

Treatment effect (trial-level) associations

For the treatment effect (trial-level) association, the regression R^2 between ORR and PFS ranged from 0.18 to 0.94, based on nine studies across four cancer types, while the R^2 values between ORR and OS ranged from −0.08 to 0.84, based on 30 studies across 11 cancer types. Again, there was no clear pattern between cancer types. For analyses of CR, the highest R^2 between CR and PFS ranged from 0.45 to 0.93 in one study, while that between CR and OS ranged from 0.05 to 0.48 within two studies.

Regression equations and surrogate threshold effect

Regression equations were reported in 14 studies for the relationship between ORR and OS, and in eight studies for the relationship between ORR and PFS. There was substantial variation in effect measures for both the surrogate and the final outcomes (e.g. difference in medians, HR and OR). The STE, the smallest treatment effect on the surrogate that predicts a non-zero treatment effect on the true end point,[76] was reported in only four studies.

Strength of association between response and survival outcomes (Institute for Quality and Efficiency in Health Care and Biomarker-Surrogate Evaluation Schema-2 scoring)

The strength of association across all studies and all subgroup analyses was assessed using the IQWiG and BSES2 scoring systems. In general, scores were relatively low, which indicates poor association between response and survival outcomes overall. Of 202 analyses that used IQWiG scoring, 42% were not evaluable and 38% scored low, with 13% scoring medium, 7% medium + and 0% high. When using BSES2 scores, the majority of analyses (94%) were not evaluable because they did not report R^2 for both individual-level and treatment effect associations, with 3% scoring poor, 1% fair, 1% good and 0% excellent.

Strengths and limitations

In this review, a comprehensive search was undertaken to identify relevant studies. The reported data were highly heterogeneous in terms of the effect measure and method of analysis. Therefore, some simplifying assumptions had to be made to allow the data to be summarised. Correlation coefficients were summarised regardless of method (Pearson's, Spearman's or other). R^2 values were summarised irrespective of whether or not the regression was weighted and whether or not the R^2 was adjusted. For treatment effect associations, R^2 values were summarised regardless of effect measure (e.g. HR, OR and difference in medians).

Summary of findings

Based on this review, the association between response outcomes and PFS/TTP/OS varies widely between studies and generally scores low to medium on IQWiG and BSES2 scoring systems; however, a large number of analyses were not evaluable. There is no clear pattern for the strength of association by cancer type. Previous reviews assessing multiple surrogate end points have also concluded that response-based end points were poor surrogates for OS.[79,80]

Implications for the economic analysis of histology-independent therapies based on overall response rate as a surrogate for progression-free survival or overall survival

The review presented in this chapter provides information that could be used to inform judgements about whether or not response-based outcomes might be considered as a valid surrogate for PFS and OS. If the surrogate end point is considered valid, or potentially even if it is not, one may consider using that surrogate as the basis for estimating health gains within a health economic model. There are four main options relating to the use of response-based outcomes as a surrogate for OS or PFS within the economic analysis of histology-independent therapies.

1. Use meta-analyses to predict the relationship between the surrogate and the final outcome

As shown in *Tables 8* and *9*, 14 studies report regression equations for ORR to OS and eight studies report equations for ORR to PFS. These equations could be used together with the observed ORR in the studies of histology-independent therapies to estimate the absolute PFS/OS or the incremental gains in PFS/OS. However, the patient populations included in these studies may not correspond to the populations in the studies of histology-independent therapies in terms of tumour sites or types, and none specifically relate to patients with *NTRK* fusion-positive cancers (or other relevant biomarkers). From a practical point of view, a number of decisions would be required to apply these analyses within a model: (1) which regression equation to use in instances whereby multiple analyses exist for an individual histology site; (2) the form of regression analysis used to estimate the relationship (i.e. 'absolute' regressions that estimate final outcomes for an individual treatment group or 'trial-level' equations that predict the treatment effects between groups); and (3) how to model the surrogate relationship where no studies exist for an individual histology site. In addition, concerns regarding the strength of the relationship between ORR and PFS/OS within the tumour sites under consideration should be borne in mind.

It has been suggested that the stringent application of criteria for surrogate validation based on correlations may not be important and that predictions may still be made even where the association is weak, provided that they reflect all uncertainty surrounding the treatment effects.[146] In addition, NICE technical support document (TSD) 20[146] notes that the meta-regression approaches included in this review are limited because they ignore the uncertainty associated with the treatment effect on the surrogate end point (which is treated as a fixed covariate in the analysis), the consequence being that predictions based on these regression analyses will fail to fully reflect that uncertainty. Recently developed methods, such as the bivariate random-effects meta-analysis (BRMA) model and its extensions,[146,147] provide an approach for both the validation and the prediction of surrogate end points within a Bayesian framework. In principle, this approach could be used to generate predictions of treatment effects on final outcomes in a way that allows for borrowing of information across studies and that fully accounts for all uncertainty surrounding the surrogate relationship. In instances whereby the surrogate association is weak, this would manifest as a wider interval around the prediction and increased uncertainty surrounding modelled outcomes and costs. This approach is intuitively appealing; it would, however, render the published meta-regressions redundant because it would require re-analyses of the input data and the implementation of new meta-analyses for each histology site.

2. Land-marking analysis

This review included only meta-analytic studies and, by design, excluded individual studies that did not include multiple cohorts of patients. Some of the studies that were excluded from the review during the sifting stage adopted a land-marking approach (see *Chapter 7*, *Discussion*, for more details of this approach) within individual patient cohorts to explore the impact of response-based outcomes on OS, with differences between responders and non-responders reported in terms of a HR. Given an underlying baseline model of OS for non-responders, it may be possible to estimate the incremental impact on OS by combining the ORRs observed in the histology-independent studies with the HR derived from the land-marking analyses. However, the published land-marking studies generally related to a single tumour type and the study populations do not specifically relate to patients with *NTRK* fusion-positive tumours (or other relevant biomarkers).

3. Risk prediction models

During sifting, the review authors identified a small number of risk prediction studies. These studies reported multivariable statistical models to estimate the final outcome (OS/PFS) as a function of some response-based variable (e.g. ORR) together with other clinical parameters (e.g. age, sex and clinical characteristics). These studies may also provide a source of HRs for the impact of response on OS/PFS, but, again, these typically relate to a single tumour type and do not specifically relate to patients with *NTRK* fusion-positive tumours (or other relevant biomarkers).

4. Do not use response as a surrogate for progression-free survival/overall survival

The systematic review suggests that, taken generally, ORR may not be a reliable surrogate for PFS or OS based on current frameworks for surrogate validation. The review did not indicate any particular pattern whereby ORR performs better or worse according to tumour type or site. Even where a means of predicting PFS/OS on the basis of ORR for a given tumour site exists (e.g. using conventional meta-regressions or BRMA), in the absence of a strong relationship between the surrogate and the final end points the resulting estimates may be highly uncertain and difficult to interpret. It should be noted, however, that the alternative may involve extrapolating highly immature PFS and OS data, which are also subject to substantial uncertainty; hence, this may not represent a sufficiently robust solution either.

Conclusions

This systematic review suggests that response end points, such as ORR and CR, may not be reliable surrogates for PFS or OS. The strength of association varied widely between studies and subgroups and, in general, there was no clear pattern by cancer type.

Despite the potentially weak validity of response as a surrogate for PFS and OS, it may still be considered preferable to adopt a surrogate-based modelling approach informed by predictions from meta-analyses that capture all relevant uncertainty than to ignore potential surrogate relationships and extrapolate heavily censored PFS and OS data. The recently developed BRMA approach outlined in the Decision Support Unit (DSU) TSD 20[146] may serve an important role in ensuring that all uncertainty around the surrogate relationship is reflected in the predictions used in the model. Ultimately, the most appropriate modelling approach will depend on the characteristics of the evidence available from the histology-independent study.

Chapter 5 A targeted review of published National Institute for Health and Care Excellence technology appraisals for which initial marketing authorisation was based on response outcomes from single-arm studies

We undertook a targeted review of 10 published NICE TAs for which marketing authorisation was based on response rates from single-arm studies. The aim of the review was to highlight alternative analytic and structural approaches that have been proposed in previous appraisals to inform the extrapolation of surrogate end points based on ORR and DoR, and/or to handle uncertainties owing to immaturity in PFS and OS data. The case studies also served to identify a broader range of issues that are likely to be relevant for the appraisal of histology-independent products.

A thematic-based review is used to summarise key issues and uncertainties raised by the Evidence Review Groups (ERGs) and NICE committees. The review is presented in *Appendix 8*.

Summary and implications

The challenges of using a partitioned survival approach and relying on independent extrapolations of PFS and OS based on immature data are particularly evident in those appraisals for which median OS was not reached. In these specific appraisals, a range of alternative approaches were used, including conventional parametric extrapolation approaches, the use of expert judgement and the use of evidence from a proxy population with more mature evidence. In each of these appraisals, the committee highlighted significant concerns regarding the uncertainty and robustness of the incremental cost-effectiveness ratio (ICER) estimates, leading to recommendations within the CDF rather than routine NHS commissioning.

One important finding was that none of the 10 TAs explored the use of surrogate relationships to help to inform the PFS and OS extrapolations. This could be considered surprising, given that the primary end point in the underpinning studies is a surrogate end point for clinical benefit and given the concerns noted by EMA and FDA regarding the challenges of interpretation and potential bias in assessing TTE end points based on single arm studies using ORR as the primary end point. However, it might also reflect the concerns regarding the reliability of ORR and CR as surrogates for PFS or OS (see *Chapter 4*).

Owing to the nature of basket trials, significant heterogeneity may be present in the study populations enrolled in the trials (see *Chapter 3*). The potential importance of accounting for heterogeneity and exploring the cost-effectiveness in subgroups of the target population is acknowledged in the current NICE methods guide.[4] Differences in the cost-effectiveness and decision uncertainty across these separate subgroups may lead to an optimised recommendation that is more restrictive than the marketing authorisation.

The review also demonstrated that the heterogeneity within an overall target population is often a critical aspect of the appraisal. The committee acknowledged the importance of accounting for heterogeneity in a variety of sources in addition to relative effectiveness, including prognosis, health-related quality of life (HRQoL) and the cost of comparator therapies, which were likely to differ, impacting the cost-effectiveness estimates. The majority of TAs included only a small number of

subgroups, most commonly based on alternative positions of a new treatment in an existing pathway. It is notable that in most of these appraisals, either separate studies were available for different subgroups or it was more feasible to undertake subgroup analyses than in histology-independent appraisals, given the larger sample sizes. Although examples were identified that appeared more relevant to histology-independent appraisals, these were also limited to relatively small numbers of subgroups informed by separate studies or with sufficient numbers to present stratified results. However, it was evident from the appraisals of interventions with a broad marketing authorisation that the committee preferred to be explicit about the different sources of heterogeneity, leading to specific recommendations for subgroups within the broader population.

Committees have routinely considered the diagnostic accuracy of the available testing and the appropriateness of the proposed testing strategies. The feasibility of introducing new testing pathways was also the subject of committee discussions. The predictive validity of the target genetic mutations was well established, with company submissions providing an overview of the clinical basis for the predictive validity of the target mutation. The prognostic validity of target mutations was, in contrast, poorly understood in all three appraisals reviewed, which meant that only limited conclusions could be drawn regarding the prognosis of patients when receiving standard care.

Although the review of TAs identified several important themes that are likely to be relevant to histology-independent appraisals, there are also important differences owing to the nature of the study designs and the greater levels of heterogeneity within the target population. *Chapter 6* provides a more detailed consideration of some of the potential challenges that are envisaged and considers a range of alternative analytic approaches that might be required.

Chapter 6 Issues and challenges for exploring heterogeneity for histology-independent appraisals

The clinical effectiveness and cost-effectiveness of a treatment will often depend on the characteristics of patients and the circumstances under which they receive treatment. The fact that different patient groups have different characteristics and, therefore, will derive different benefit from treatments is called 'heterogeneity'.[149–151]

Heterogeneity matters for two main reasons. First, if benefits differ by patient characteristics, estimates of the treatment benefit must match the patient population that is expected to receive the treatment (the target population) in routine clinical practice. Second, there can be health benefits from making tailored decisions for particular groups of patients. This gain from recognising differences between subgroups of patients and potentially 'optimising' recommendations within a product's licence is called the value of heterogeneity (VoH).[150–152]

The exploration of sources of heterogeneity and the use of subgroup analysis is recommended within the NICE reference case analysis.[4] Ignoring these differences could mean that a treatment that is not cost-effective for the total population (combining all subgroups) may be cost-effective in specific subgroups. Making a 'one size fits all' recommendation would then result in a potentially cost-effective treatment being withheld from a subset of patients for whom the treatment would represent an appropriate use of NHS resources. Conversely, a treatment that appears cost-effective for the total population may not be cost-effective in particular subgroups. In this case a 'one size fits all' approach could result in the treatment being recommended in identifiable subgroups in which the value of providing the new treatment is lower than the opportunity cost. That is, the health gain for these specific subgroups is not sufficient to offset the potential health lost from a reduction in the provision of services elsewhere in the NHS that is necessary to fund the new treatment.

In the case of histology-independent treatments, heterogeneity is particularly important to consider. This is because an important source of heterogeneity is differences in tumour histology. Although a treatment may be clinically effective across a range of tumour sites, there are theoretical and empirical reasons to expect that cost and health consequences could vary significantly across tumour sites. This is in addition to the usual sources of heterogeneity (e.g. age and sex), which are present in conventional treatments.

There are a number of sources of heterogeneity that are relevant to histology-independent decision-making. The main focus of this chapter is heterogeneity between subgroups, as defined by histology. However, it must be stressed that heterogeneity owing to other characteristics is also relevant.

The following sections identify a number of particular challenges for histology-independent appraisals and present alternative approaches that might be used to investigate and account for different sources of heterogeneity. A formal framework is presented in *Chapter 7*.

Treatment effectiveness

The available evidence is likely to consist of response and immature PFS and OS data for patients with different tumours included in one or more single-arm studies with a basket design. Methods to test for heterogeneity in response by tumour type or other relevant characteristics (typically related to the target mutation) can be used during trial conduct and can inform stopping rules in an adaptive trial design framework (see *Chapter 3*). If heterogeneity is explored within the trial and it is concluded that a pooled analysis is justified (i.e. the treatment effect is sufficiently homogeneous across the tumour types), these results can be re-evaluated during the appraisal process and a decision can be made on whether or not it is appropriate to accept the company's proposal of a homogeneous treatment effect across the tumours. A decision made within the trial to discontinue recruitment to one or more baskets owing to an unsuitable response should caution against a completely histology-independent recommendation. In such cases, there will need to be a case made for which tumour types can be considered to have sufficient evidence of effect for a recommendation and which should be excluded, given the trial evidence of insufficient response.

Regardless of how the trial was originally designed and analysed, if outcomes are available for each tumour type, some of the frameworks described in *Chapter 3* can be useful to explore the potential for heterogeneity in effects across tumours. The adaptive phase can be ignored and the methods can be used to estimate mean outcomes for each histology, with appropriate uncertainty, as well as pooled posterior and predictive mean outcomes that account for the potential lack of uniformity of effect across tumours. The BHM[46] is simple to implement and is particularly suited to this framework given that it starts from the assumption that treatment effects are exchangeable (rather than identical) across tumours, a more reasonable assumption in the absence of evidence to the contrary, and produces estimates of the level of heterogeneity across tumours and of the pooled treatment effects for each tumour, which can be used to judge whether or not the assumption of homogeneity is reasonable. In addition, this model allows the prediction of the effect in unrepresented tumour types as long as they can also be assumed to have exchangeable effects (i.e. drawn from the same distribution of effects) as the included tumour types.

The BHM works by assuming that for each tumour type *j*, the measures of effect θ_j are exchangeable and follow a normal distribution:

$$\theta_j \sim \text{Normal}(\mu, \sigma^2), \tag{1}$$

where σ is the standard deviation quantifying the between-tumour heterogeneity and μ is the pooled mean effect across all tumour types. Prior distributions must be selected for μ and σ, and are likely to have some influence on the posterior estimates,[46,52] particularly when a small number of tumour types and patients per tumour are included. A Uniform(0,5) prior distribution was found to be robust in a simulation study.[52] The sensitivity of results to the prior distributions should be assessed. When the outcome is binary, for example response, θ_j represents the log-odds of response in tumour site, *j*, and the probability of response in each site, p_j, is recovered as:

$$p_j = \frac{\exp(\theta_j)}{1 + \exp(\theta_j)}. \tag{2}$$

The probabilities that the response rates for each tumour type are at least of a certain magnitude can also be calculated, and heterogeneity in these probabilities can guide conclusions on the plausibility of a homogeneous response. Typically, a value of 30% is used to define a meaningful response, but any other value can be used, depending on context.

In the case in which the tumour types included in the trial are not reflective of the entire licensed indication, the predictive distribution of effect (e.g. the probability response) in a new histology, θ_{NEW}, can be obtained as:

$$\theta_{NEW} \sim \text{Normal}(\mu, \sigma^2). \quad (3)$$

This will reflect the full degree of uncertainty owing to both the sample size and the observed heterogeneity in effects across the observed tumour sites. The resulting distribution represents the predictive probability of response in a 'new', that is, unrepresented tumour type.

Although in theory the BHM can be applied to dichotomous (e.g. tumour response) or TTE outcomes (e.g. PFS and OS),[46] the assumption of exchangeability of the effects of treatment on survival outcomes across tumour outcomes is harder to justify than the equivalent assumption made for the effects of treatment on response. As noted in *Chapter 3*, a critical consideration in designing basket trials is the heterogeneity in survival prognosis across the different histologies. This is the motivation for evaluating measures, such as standardised response rates, which reflect tumour shrinkage, rather than survival outcomes.[29,30] In addition, the nature of the survival data available, which tends to be immature and based on only a few patients per tumour type, will make estimation of a hierarchical model challenging, unless informative prior distributions are used on key parameters.

The model proposed by Leon-Novelo *et al.*[53] can be used in the scenario for which it is not expected that all subgroups will be a priori exchangeable (see *Chapter 3*) and there is a particular tumour characteristic (e.g. prognosis or type of *NTRK* fusion) that defines exchangeability, so that different categories can be predefined (e.g. poor, intermediate and good prognosis). If these a priori exchangeable categories can be predefined, the approach is similar to the BHM and a prediction for unrepresented tumour types in each category can be made. However, this would no longer generate a truly histology-independent recommendation because results might differ across tumours in different categories.

Hybrid exchangeable/non-exchangeable models,[51,53] in which exchangeability is determined by the data, are less relevant as exploratory models for HTA because their results would be harder to interpret. This is because exchangeability cannot be assumed to apply across all tumour types and predictive distributions of effects can no longer be assumed to represent the expected effect in unrepresented tumour types, given that these are not necessarily fully exchangeable with the included tumour types. In addition, in an exchangeable/non-exchangeable scenario, a histology-independent recommendation would be hard to justify because the assumption would be that effects differ across tumour types, which could affect clinical effectiveness and cost-effectiveness estimates.

Exploring heterogeneity in response: case study

To demonstrate the impact of allowing for heterogeneity in response and to explore the potential heterogeneity in effects across tumours, response data were analysed using a BHM framework.[46]

For the purpose of this analysis, the response data used were the published efficacy evidence available for the tyrosine kinase (TRK) inhibitor, larotrectinib.[3,153] The results, presented as a post hoc pooling of 55 patients covering 12 tumour types from three non-randomised single-arm Phase I/II basket studies, including the number of patients and responses by tumour type, are shown in *Table 11*.

We can consider each of the tumour types as a 'basket' or group and analyse the response data using a BHM framework to explore the potential heterogeneity in effects across tumours.

TABLE 11 The FDA results of ORR by tumour type

			ORR	
Tumour ID	Tumour type	Patients (*n*)	Responders (*n*)	Observed response (%)
1	Soft tissue sarcoma	11	10	91
2	Salivary gland	12	10	83
3	IFS	7	7	100
4	Thyroid	5	5	100
5	Lung	4	3	75
6	Melanoma	4	2	50
7	Colon	4	1	25
8	GIST	3	3	100
9	Cholangiocarcinoma	2	0	0
10	Appendix	1	0	0
11	Breast	1	0	0
12	Pancreas	1	0	0
Total		55	41	74.5

Methods

For the response outcome, data available for each of the tumour types in the published literature are the number of responders, x_j, out of the total number of patients, n_j for tumour type, j, which are assumed to follow a binomial likelihood:

$$x_j \sim \text{Binomial}(n_j, p_j), \tag{4}$$

where p_j is the probability of response for tumour type, j, with $j = 1, \ldots, G$, and G is the total number of tumour types. The log-odds of response in tumour type, j, θ_j, was modelled on the log-odds scale: $logit(\theta_j) = p_j$. The BHM assumes that for each of the G tumour types, the log-odds of response, θ_j, are exchangeable and follow a Normal distribution (see *Equation 1*).

We used a relatively conservative normal prior distribution for μ, centred around a probability of response of 0.3 (a log-odds of –0.8473), which is often considered as a promising response rate, with a variance of 10 across all tumour types. The sensitivity of the results to a more favourable prior distribution, for which the prior probability of response across all tumour types is centred around a mean of 0.5 (a log-odds of 0) with the same variance, was assessed.

The prior for the between-tumour heterogeneity standard deviation is specified as Uniform(0,5), which was found to be robust in a simulation study.[46,52] An inverse-gamma (2, 20) prior distribution for the between-tumour variance had previously been proposed,[46] meaning that the between-tumour precision has prior mean of 0.10 and variance of 0.005. Inverse-gamma prior distributions were found to lead to posterior distributions, which are highly sensitive to the chosen parameters and are, therefore, not recommended in most cases.[52] The sensitivity of the results to the inverse-gamma prior distribution, to the between-tumour heterogeneity variance and to using different half-normal prior distributions for the between-study standard deviation was assessed.[52] Half-normal prior distributions with precision from 0.01 to 0.1 and 1 were also assessed.

Given that the tumour types included in the analysis population are not reflective of the full licensed indication (i.e. a truly histology-independent marketing authorisation will encompass all tumour types, not just those represented in the trial), the predictive distribution for the response rate in a new tumour type is calculated to reflect the full degree of uncertainty owing to both the sample size and the observed heterogeneity in effects across the observed tumours. The resulting distribution is the probability of response in a 'new', that is, unrepresented, tumour type.

The model was adapted from Thall *et al.*[46] and was estimated using Markov chain Monte Carlo in OpenBUGS (OpenBUGS Foundation, MRC Biostatistics Unit, Cambridge, UK),[154] implemented in R (version 3.6.0) (The R Foundation for Statistical Computing, Vienna, Austria) using R2OpenBUGS[155] (version 3.2.3.2). The BUGS code used is presented in *Appendix 9*.

The model fit was assessed by plotting individual tumour contributions to the residual deviance (in a well-fitting model these are expected to be close to 1) and by comparing the total residual deviance with the number of tumour types, *G*. Convergence was assessed by visual inspection of the Brooks–Gelman–Rubin plots and assessment of the $\hat{R}$ statistic.[156,157]

Results

For all analyses, 55,000 iterations were run on two parallel chains and the first 5000 iterations were discarded as 'burn-in'. Model fit statistics are presented in *Appendix 10*.

The prior distributions used for the base-case analysis are:

$$\mu \sim \text{Normal}(-0.8473, 10) \sigma \sim \text{Uniform}(0.5) \quad (5)$$

The BHM estimates substantial between-group heterogeneity (posterior median of 2.86 on the log-odds scale), although there is considerable uncertainty [95% credible interval (CrI) of 0.92 to 4.83] (*Figure 8*). This suggests that there is considerable variability across tumour types.

The estimated mean response rate across all tumour types is 0.609 (95% CrI 0.160 to 0.918). This is lower than the mean response rate of 0.745 observed in the efficacy evaluable data set. The response probability predicted for an unrepresented tumour type is 0.569; however, the 95% CrI is wide, meaning that this probability could be as low as 0.2% or as high as 99.9% (*Table 12* and *Figure 9*).

The estimated probabilities of response for each tumour type are shown in *Table 13*. The effect of allowing information to be borrowed across the tumour types is to shrink the observed response

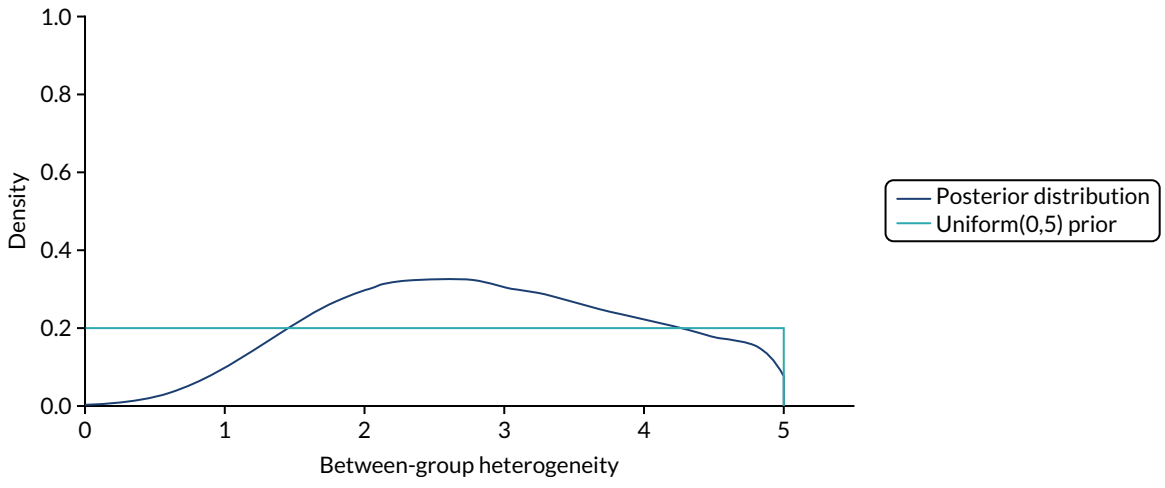

FIGURE 8 Prior and posterior distributions for the between-group heterogeneity standard deviations.

TABLE 12 Overall posterior and predictive probability of response

Probability	Mean	Median	95% CrI
Posterior	0.609	0.641	0.160 to 0.918
Predictive	0.569	0.649	0.002 to 0.999

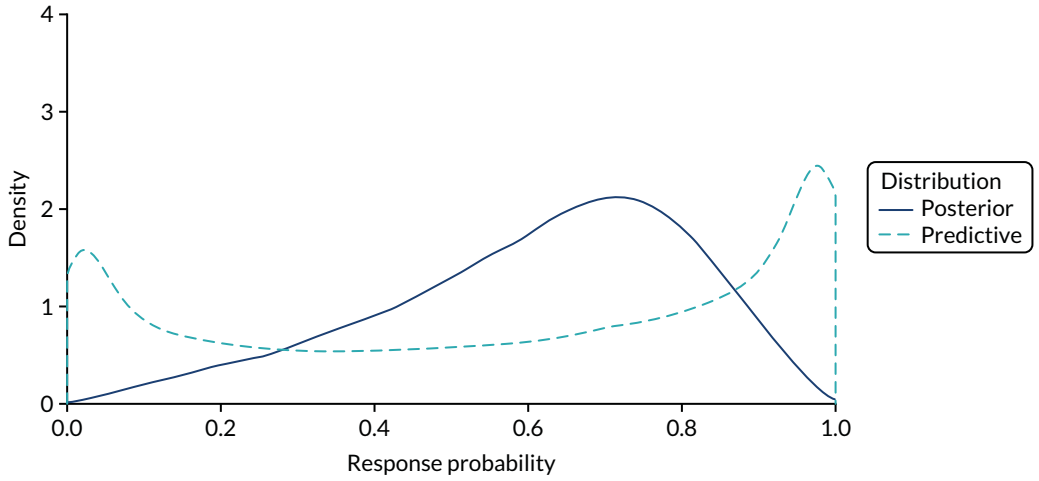

FIGURE 9 Posterior and predictive distributions of response probability.

TABLE 13 Probabilities of response for all tumour types

Tumour type	Observed response (%)	Estimated mean response based on BHM (%)	95% CrI (%)	Probability of response rate of ≥ 30%	Probability of response rate of ≥ 10%
Sarcoma	91	88	66 to 99	1.000	1.000
Salivary	83	82	58 to 97	1.000	1.000
IFS	100	93	70 to 100	1.000	1.000
Thyroid	100	92	63 to 100	1.000	1.000
Lung	75	73	30 to 98	0.976	0.999
Melanoma	50	52	12 to 89	0.835	0.984
Colon	25	32	3 to 75	0.484	0.854
GIST	100	88	49 to 100	0.996	1.000
Cholangiocarcinoma	0	21	0 to 76	0.281	0.555
Appendix	0	30	0 to 90	0.416	0.650
Breast	0	30	0 to 90	0.415	0.653
Pancreas	0	30	0 to 90	0.413	0.648

Prior distribution for log-odds of response centred on a probability of 0.3; uniform prior distribution for the between-tumour standard deviation.

probabilities towards the pooled mean response probability. Tumour types with a smaller number of patients borrow more information than tumour types with a larger number of patients and, therefore, have values closer to the pooled mean.

Figure 10 shows the posterior distributions of the probabilities of response for each of the 12 tumour types included in the efficacy evaluable data set. Although the observed response suggested that cholangiocarcinoma, appendix, breast and pancreas tumours did not respond to larotrectinib, the posterior distributions of these tumour types are wide and their 95% CrIs suggest that response rates of 76% are plausible.

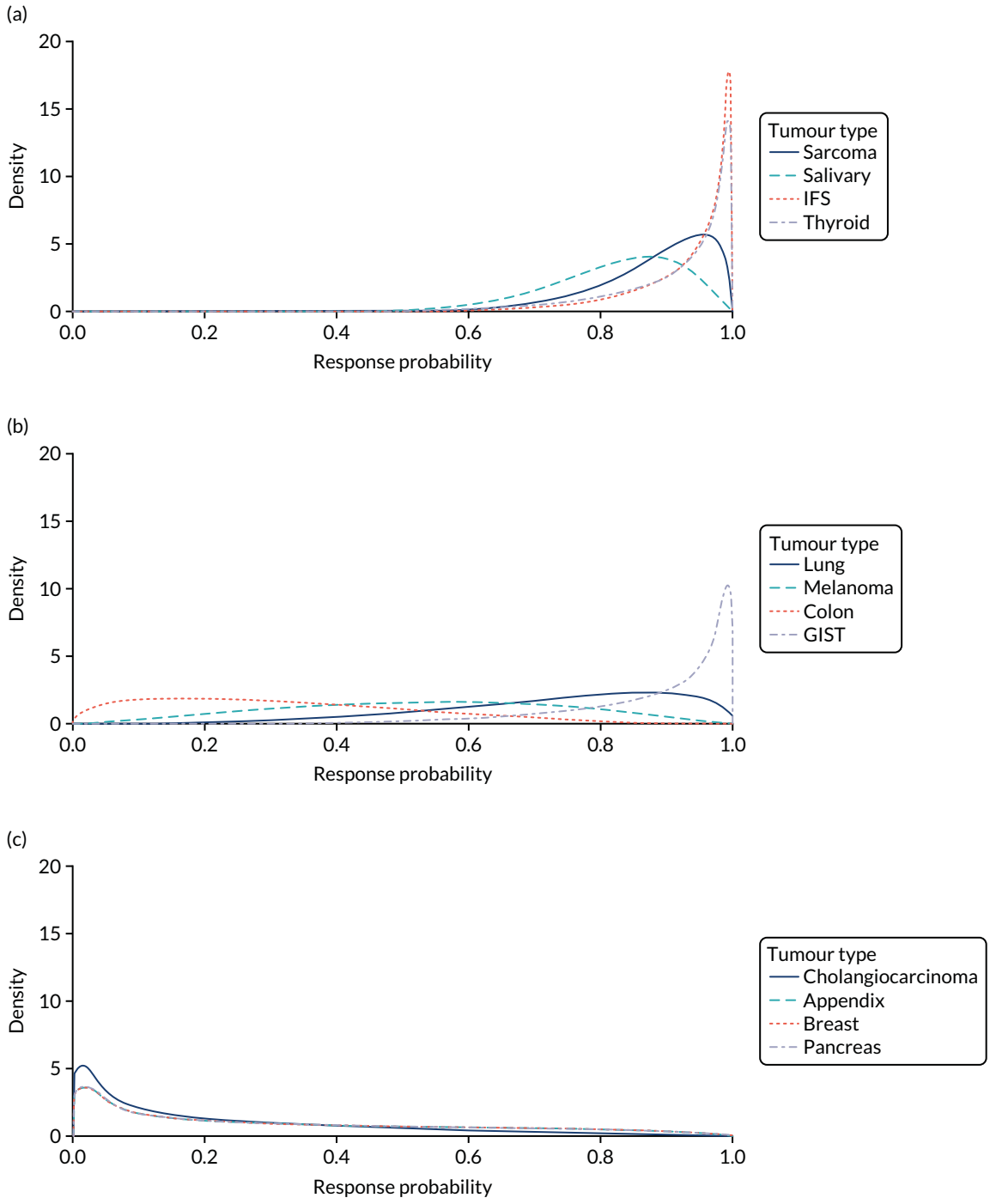

FIGURE 10 Posterior distribution for the probabilities of response by tumours type. (a) Sarcoma, salivary, IFS and thyroid; (b) lung, melanoma, colon and GIST; (c) cholangiocarcinoma, appendix, breast and pancreas.

The results were insensitive to the use of the inverse-gamma prior, the half-normal prior and the uniform prior centred on a log-odds of response of 0.5. The results were also insensitive to the use of a more favourable precision of the between-tumour heterogeneity standard deviation of 0.1 and 0.5. For full results of the sensitivity analysis, see *Appendix 11*.

Implications for the appraisal of histology-independent technologies

Heterogeneity in the treatment effects is likely to be an important issue in the appraisal of histology-independent technologies. As can be seen from the results of the worked example (see *Exploring heterogeneity in response: case study*), the BHM suggests that there is substantial heterogeneity in response across tumour types. This can be seen in the estimate of the between-group heterogeneity, with the BHM estimating a posterior median standard deviation for the heterogeneity of 2.86 on the log-odds scale, which is considered large. Heterogeneity can also be seen in the predictive distribution of response, appearing in *Figure 9* as a bimodal distribution with density concentrated around a probability of response of 0 and 1. This can be explained by the individual tumour response rates shown in *Figure 10*, which suggest that, even under the assumption of exchangeability of response, there are tumour types in which the data suggest that response is likely and tumour types in which it is not likely.

The results of this analysis challenge the strong assumption of homogeneity in response across such a variety of tumour types when treated with larotrectinib. The assumption of homogeneity may mask important information about empirical evidence of tumour response and the BHM provides a vehicle through which to account for the potential heterogeneity.

Counterfactual

The feasibility of conducting RCTs in histology-independent populations is likely to be challenging and it is expected that histology-independent technologies will often seek (and receive) EMA/FDA approval with limited or no data from randomised experiments (see *Food and Drug Administration review of larotrectinib* and *Food and Drug Administration review of entrectinib*. The lack of control data means that the evaluation of the cost-effectiveness of histology-independent technologies will require the generation of a comparator arm, for example by generating a control based on a historical control.

The interpretation of relative effect estimates from single-arm studies compared with historical controls is potentially subject to bias owing to differences between patients selected as historical controls and patients recruited to the single-arm studies. Differences between the patient populations can arise for a variety of reasons, including differences among accrual sites or differences in patient characteristics (e.g. age, performance status or other prognostic factors). For example, more recently diagnosed patients may have milder manifestations of a condition owing to improved (and, therefore, commonly increased) diagnostic sensitivity. Treatment effect differences may also be attributable to secular trends in clinical care (e.g. changes in diagnostic methods, classification criteria or outcome ascertainment) or other unknown confounders.

The challenges of generating an appropriate historical control are present in many appraisals wherever such comparisons are made. These challenges may be particularly acute when considering a histology-independent technology. In the context of a histology-independent appraisal, the generation of an appropriate historical control data set is complicated by the need to cover multiple tumour types/histologies, which not only creates challenges for generating an appropriate comparator data set, but also potentially exacerbates the potential for confounding bias.

The need to cover multiple tumour types/histologies means that it is unlikely that any single data set will provide sufficient coverage to represent the whole target population. It is, therefore, likely that multiple data sources will need to be identified, as was implemented in the ongoing NICE appraisal of larotrectinib.[158] The identification of historical control data would ideally be undertaken through an

appropriate systematic review; however, this creates practical challenges because the resource required to implement this across multiple tumour types/histologies is extensive. In the larotrectinib appraisal, the focus of company searches for historical control data was limited to previous NICE TAs covering the tumour types included in the company's single-arm study. Although this can be considered a reasonable pragmatic step, there is the potential for alternative, and plausibly more relevant, sources of historical data to be missed.

Other challenges that result from the need to generate a data set that covers such a broad variety of tumour types include the possibility that no relevant data exist for some relevant tumour types. For example, *NTRK* fusions are present in a number of rare tumour types that have not been subject to NICE guidance, and in the larotrectinib appraisal[158] the company submission was forced to make arbitrary assumptions regarding the outcomes of patients for whom relevant comparator data could not be identified.

The identification of appropriate historical data will also need to address uncertainties regarding the positioning of therapy and any discrepancy between the licensed indication and the trials. The line of therapy may be an important prognostic factor because patients in later lines of therapy will tend to have fewer treatment options and may have accrued chemotherapy-related toxicity, limiting their tolerability to further treatment. Attempting to match control patients' characteristics to the observed line of therapy in the intervention arm, however, creates challenges in relation to ensuring internal and external validity – namely, whether lines of therapy in the historical comparator data set should match those of the intervention arm or whether the historical control should attempt to reflect the eligible population and, therefore, maintain external validity, in which case the relative effect estimates may be biased. Indeed, this tension between internal and external validity may extend to other patient characteristics, particularly where the pool of patients in the intervention arm for a particular tumour is small, as recruited patients may not be fully representative of the eligible population. This tension, therefore, may typify a general issue of whether or not to match patient characteristics in the control arm to those in the intervention arm.

A further issue with using historical controls is that the target mutation may be prognostic in some or all tumours and it may be difficult to obtain relevant historical data limited to patients who harbour the target mutation, particularly where this mutation is rare. There is also the possibility that the prognostic value of the mutation may differ across tumour sites, which further complicates any attempt to adjust for the prognostic value of a mutation. In addition, in the context of a new target mutation, the prognostic value in different tumour types may not have been investigated sufficiently and is likely to be unknown for most, if not all, tumour types. For example, there is evidence to suggest an association between the presence of a *NTRK* fusion and unfavourable disease presentation[159,160] and better prognosis in patients with congenital mesoblastic nephroma who harbour a *NTRK* fusion than in those without the genetic abnormality.[161] The evidence across tumour types is limited but the prognosis of patients with *NTRK* fusions may vary between cancer types and between *NTRK* fusion types.[161] From the evidence available, it is also unclear if *NTRK* fusions are in themselves prognostic or if it is their association with other specific prognostic factors, such as age and Eastern Cooperative Oncology Group (ECOG) performance status, that drives the observed differences in prognosis.

Adjustment for confounding bias

A key factor in the reliability of estimates of effectiveness based on observational data is the statistical analysis used; a large number of studies have sought to develop and evaluate methods for adjusting and eliminating bias resulting from confounding. These include methods such as regression analysis, propensity scoring and population-adjusted indirect comparisons [matching-adjusted indirect comparison (MAIC) and Simulated Treatment Comparison (STC)].[162] These and other methods are frequently used in the literature and have been previously applied and accepted by NICE appraisal committees where no randomised evidence exists. In theory, these methods could be applied in the context of a histology-independent appraisal. Implementing such approaches could, however, be challenging because of the

large number of source data sets involved, which means that population characteristics may not be reported across all comparator data sources and would necessarily require strong assumptions about the prognostic value of population characteristics across tumour types. Furthermore, even if a suitable adjusted comparison could be generated, the small sample sizes typically seen in the Phase II trials would be able to account for only a small number of observed characteristics. This limits the potential for these methods to fully account for confounding biases and increases the likelihood of residual confounding bias. Despite these limitations, such methods would generally be considered to be preferable to a naive comparison, which takes no account of differences across groups.

Gaps in the reporting of baseline characteristics, variability in the prognostic value of characteristics across tumour types/histologies and difficulties of matching comparator data to the likely limited available Phase II trial for histology-independent technologies will also create additional challenges of interpretation and validation of comparisons with historical data, as it will be challenging to assess the comparability of patients in the historical control with those in the available single-arm trial data.

Alternative approaches to developing a comparator

Because of these significant concerns of confounding bias and the challenges of generating a truly comparable comparator data set, other approaches to generating a comparator data set should be considered and their limitations explored. For example, two alternative methods outlined in Hatswell *et al.*[163,164] could be used, in which patients in the single-arm trial are used to generate a control arm.

The first approach proposed by Hatswell *et al.*[163] uses effectiveness data on non-responders as a proxy for patients not receiving an active treatment. Comparator effectiveness estimates of PFS and OS under this approach would, therefore, be based on observed PFS and OS among non-responders in the integrated efficacy analysis. The advantage of this approach is that all patients in the non-responder subgroup met the same trial inclusion/exclusion criteria and received the same line of treatment. The rationale behind this approach is that patients in whom no response is observed represent those with a lack of treatment effect (because they have no response to treatment) and, therefore, are representative of a counterfactual for whom no effective therapy exists. The patient population is, therefore, likely to be better matched with the intervention arm because they are drawn from the same population.

This approach, however, also requires strong assumptions, namely that there are no differences other than response status between responders and non-responders that explain the survival outcomes and that non-responders derive equivalent benefit to that received on current SoC. The reasonableness of these assumptions is likely to be specific to a particular appraisal; however, as discussed in *Chapter 4*, the reliability of response as a surrogate is likely to be variable across tumour types. The assumption of no treatment benefit or harm may also not hold because some patients may receive some benefit from treatment, even if they do not have a PR or CR.

When considering the appropriateness of this approach, the relative advantages and disadvantages will need to be considered and it may be that this approach is considered reasonable only where there is substantive evidence of heterogeneity in treatment effects justifying the need to appropriately account for this heterogeneity in the economic analysis.

The second approach[164] uses data taken from the trial patients' previous line of treatment to derive OS and PFS curves. In this approach, the inverse of the ratio between the average TTP on their previous therapy and the mean extrapolated PFS with the active therapy [also called the growth modulation index (GMI) multiplier] is applied to all health outcomes (PFS and OS) for the active therapy. This crude adjustment assumes that the active therapy is more effective in terms of both PFS and OS than the comparator, by the same proportion as the GMI multiplier. Therefore, the resulting GMI-adjusted total mean life-years gained (LYG) and quality-adjusted life-years (QALYs) are assumed to correspond to comparator outcomes and are applied in the calculation of the ICER (based on LYG and QALYs).

The main advantage is that effect estimates are drawn from the same population as the intervention arm and, therefore, are better matched; however, there are also disadvantages. First, this can be implemented only for patients who have received a previous line of therapy. Second, it also assumes that the ratio of TTP across lines of therapy is indicative of the treatment effect and it is uncertain to what degree this is likely to hold true. Finally, because this method can estimate PFS only, it requires that assumptions are made about the impact of TTP gains on OS [namely that either OS increases proportionally with TTP or post-progression survival (PPS) is the same across therapies], which, similarly, may not hold true. Further research considering the reasonableness of these assumptions may be helpful. Consideration could also be given to the potential role of expert elicitation to inform these judgements.

Implications for the appraisal of histology-independent technologies

The broad marketing authorisation, heterogeneous populations and uncertainties regarding the position of histology-independent technologies creates a number of significant challenges to creating appropriate historical control data. The confidence in estimates of effect may increase by utilising methods of population adjustment, but the scope of such methods may be more limited in the context of histology-independent appraisals. The assessment of the scope for residual confounding bias is also likely to be made more complicated, further reducing the confidence in comparisons. It is unclear whether or not the use of non-randomised evidence and, in particular, single-arm studies will ever be considered adequate. Alternative methods of developing a comparator may, therefore, be of value to decision-makers and should be considered as alternatives.

Generalisability

The extent to which evidence is generalisable to the population of interest is a key consideration in the appraisal of histology-independent cancer technologies. There may be a number of uncertainties concerning the generalisability of the available evidence, including the different types and distribution of histologies in the clinical studies (and the extent to which these represent the specific types and distribution of histologies that would be expected in routine clinical practice); the potential impact of unrepresented histologies not represented in existing clinical studies; and the position in the treatment pathway. Each of these issues is discussed in turn in the following sections.

Distribution of tumour types

As outlined in *Chapter 2* (see *Food and Drug Administration review of histology-independent products* and *European Medicines Agency review of approved histology-independent indications*), the evidence likely to be available for decision-making will include a number of histologies or tumour types, with limited data on each. When integrating these clinical data into a cost-effectiveness analysis, one important issue is to consider the distribution of patients across the different tumour types.

One approach would be to utilise the distribution of tumour types present in the clinical evidence to generate an average cost-effectiveness estimate. Underlying this approach, however, is the assumption that the cost-effectiveness of a histology-independent technology does not vary across tumour types or that the proportions of histologies are representative of the proportions eligible to receive the intervention in the full licensed population. The former assumption is very unlikely to hold owing to the potential for differences in effectiveness across tumour types, prognosis, comparators, costs and HRQoL. Furthermore, as shown in the comparison of the distributions in *Table 14*, there is a mismatch between the distribution of certain histologies in the trial populations. For instance, breast cancer patients represent 11% of the entrectinib trial but only 1.8% of the larotrectinib trial. If we imagine that larotrectinib and entrectinib produce identical clinical results, the resulting average cost-effectiveness estimates of the two distributions will be different given that different tumour types have different testing costs (see *Genomic testing for histology-independent drugs*), different SoC costs and outcomes, and potentially different prognoses.

TABLE 14 Larotrectinib trial and entrectinib trial tumour distributions

Histology	Trial proportion (%)
Larotrectinib efficacy evaluable data set	
Soft tissue sarcoma	20.00
Salivary gland	21.80
Thyroid	9.10
Lung	7.30
Colon	7.30
Cholangiocarcinoma	3.60
Breast	1.80
Pancreas	1.80
IFS	12.70
Melanoma	7.30
GIST	5.50
Appendix	1.80
Entrectinib efficacy evaluable data set	
Sarcoma	24.00
Salivary gland (MASC)	13.00
Thyroid	9.00
NSCLC	18.00
Colorectal	7.00
Cholangiocarcinoma	2.00
Breast	11.00
Pancreatic	6.00
Neuroendocrine	6.00
Gynaecological	4.00

The significance of these differences for the overall assessment of cost-effectiveness will depend on the degree of heterogeneity across separate inputs relevant to economic modelling. If the trial distribution is not considered to represent the distribution expected to be seen in the population under a histology-independent license, any decision based on a single ICER estimate for the trial population will be subject to potential bias. The magnitude and direction of this bias will be difficult to determine without a more explicit assessment of heterogeneity in different sources relevant to the economic model.

Where differences between the trial population and the licensed population are considered significant, approaches should be explored that allow for the re-weighting of the clinical population so that the model population better reflects the treated population.

Unrepresented tumour types

A further issue to consider is whether or not the trial evidence encompasses all of the histologies covered by marketing authorisation. If histologies exist that are not represented in the trials but are covered under the marketing authorisation, decision-makers will have evidence on effectiveness from only the subset of the total population that is potentially eligible for the intervention.

For example, within the clinical evidence available for entrectinib (see *Table 11*), 12 histologies were included. However, it is known that upwards of a further 17 histologies have been shown to harbour *NTRK* fusions and will be covered by the anticipated marketing authorisation; hence, this total could be even larger.[165] Any decisions made on the evidence alone would, therefore, be implicitly assuming that the 12 included types are representative of the full population.

The impact of the unrepresented population is potentially significant and its importance will depend on the number of unrepresented histologies and the proportion of the eligible population in unrepresented histologies relative to the observed histologies. It is also important to consider unrepresented tumours for which there is significant uncertainty regarding the homogeneity of clinical benefits or significant heterogeneity in costs across tumour types. For example, where there is limited support for the assumption of homogeneous efficacy across histologies, it may be important to characterise the uncertainty in the efficacy within the unrepresented population. Equally, there is significant evidence of variability of testing costs across tumour types and, therefore, ignoring unrepresented tumour types may impact significantly on average testing costs.

Position in the treatment pathway

A further potential limitation regarding the generalisability of the available clinical evidence relates to the position in the pathway at which patients are treated. This is complicated in part because the position in the pathway may vary substantively across tumour types according to the availability of alternative treatments, but also because of the potential for a mismatch between the trial population and the eligible population, as dictated by the marketing authorisation. The latter may be a significant issue because the recruitment of patients to a histology-independent trial is necessarily more complicated and there are potential significant challenges to identifying patients owing to the relative rarity of target genetic mutations. Thus, as observed in the entrectinib and larotrectinib clinical data, patients were recruited across multiple lines of therapy, even within the same tumour type.

This heterogeneity generates a number of issues, not least with respect to the external validity of the trial. Line of therapy may be a significant prognostic factor and failure to adjust for this may impact significantly on estimates of relative effectiveness, particularly if the comparator population is not matched to the position that patients were treated in the treatment arm. This issue may also impact in other ways, including on the final distribution of patients eligible for treatment, because fewer patients will be eligible for treatment in second and subsequent lines of therapy. Furthermore, it may have implications for testing, affecting either the total costs of testing or the population that will be eligible for testing.

Example

The example considers the TRK inhibitor, larotrectinib, which is used for the treatment of solid tumours harbouring a *NTRK* gene fusion, and the proportion of tumour types presented in the clinical evidence, as outlined in *Exploring heterogeneity in response: case study*.

First, to quantify the size of the population that will benefit from TRK inhibitors, the total number of patients eligible each year was calculated. This was estimated using the tumour-specific *NTRK* fusion prevalence, cancer incidence and proportion of patients with advanced or metastatic disease:

$$\text{Annual eligible population} - \textit{NTRK}\ \text{prevalence} \times \text{cancer incidence} \times \frac{\text{advanced}}{\text{metastatic}}\ \text{disease}. \tag{6}$$

The full method for calculating the annual eligible population is described in *Appendix 12*.

Table 15 presents the calculations of the annual eligible population for TRK inhibitors based on the tumour types represented in the larotrectinib trial. The prevalence of *NTRK* fusion varies across tumour types, ranging from 92.2% (MASC) to 0.07% (breast cancer). Paediatric patients with infantile

TABLE 15 Calculation of the annual eligible population for TRK inhibitors

Tumour type	Prevalence of *NTRK* fusion (%)	Cancer incidence (England) (%)	Per cent with stage III/IV cancer at diagnosis	Annual TRK-inhibitor eligible population (*n*)
Soft tissue sarcoma	0.56	2740	32	5
Appendix	4.00	540	74	16
Breast	0.07	46,102	15	5
Cholangiocarcinoma	0.10	556	60	0
Colorectal	0.12	34,825	55	23
IFS	90.90	59	51	27
MASC	92.90	11	22	2
Melanoma	0.21	13,740	9	3
NSCLC	0.09	32,576	57	17
Pancreatic	0.26	8388	78	17
Thyroid	0.92	2195	31	6
GIST	1.28	734	40	4
Total				125

fibrosarcoma, a tumour type with a high *NTRK* fusion prevalence, make up the largest proportion of the eligible population ($n = 27$). Despite the low prevalence of *NTRK* fusion, patients with CRC contribute a substantial proportion of the eligible population ($n = 23$).

The resulting distribution of the eligible population (*Table 16*) shows that the proportions of tumour types in the eligible population differ substantially to the proportions in the larotrectinib trial (see *Table 16*). For example, soft tissue sarcoma represents 20% of the population in the larotrectinib trial yet represents only 4% of the population eligible to receive larotrectinib.

Unrepresented tumour types

In addition, *NTRK* fusions have been found in numerous tumour types that were not included in the larotrectinib trial. Following a histology-independent approval decision, patients with these tumour types will be eligible for treatment. In addition to the 12 tumour sites included in the larotrectinib trial, there is evidence of *NTRK* fusions in an additional 17 tumour types or anatomical sites.[165] The annual eligible population making up the unrepresented tumour types for larotrectinib was again estimated using *Equation 4*. The size of the unrepresented population was calculated to be 152 patients, 55% of the annual eligible population. The calculation of the size of the unrepresented population can be seen *Appendix 11*.

The eligible population, including the unrepresented population, is shown in *Table 16*. As can be seen from the comparison of the proportion of tumour types in the eligible population with and without the inclusion of the unrepresented tumour types, the proportions differ. Individuals with soft tissue sarcoma represented 4% of the tumours in the eligible population and 1.8% when the unrepresented population was included.

Position in the treatment pathway

If we assume that the TRK inhibitors will be given as a first-line therapy and that 100% of patients will receive it for every tumour type, the distribution of tumour types will be the real-world distribution. However, testing and position in the treatment pathway can impact this distribution.

TABLE 16 Alternative tumour distributions

Tumour Type	Trial population (*n*)	Distribution of tumour types in the trial (%)	Eligible population (*n*)	Distribution of tumour types in the eligible population (%)	Distribution of tumour types in the eligible population, including the unrepresented tumour types (%)	Assumed proportion treated based on line of therapy (%)	Treated population based on line of therapy	Eligible population including line of therapy (%)
Represented								
Soft tissue sarcoma	11	20	5	4.00	1.80	90	4.5	4.20
Appendix	1	2	16	12.80	5.80	30	4.8	4.40
Breast	1	2	5	4.00	1.80	30	1.5	1.40
Cholangiocarcinoma	2	4	0	0.00	0.00	30	0	0.00
Colorectal	4	7	23	18.40	8.30	30	6.9	6.40
GIST	3	5	4	3.20	1.40	30	1.2	1.10
IFS	7	13	27	21.60	9.80	90	24.3	22.40
MASC	12	22	2	1.60	0.70	60	1.2	1.10
Melanoma	4	7	3	2.40	1.10	30	0.9	0.80
Lung	4	7	17	13.60	6.20	60	10.2	9.40
Pancreatic	1	2	17	13.60	6.20	30	5.1	4.70
Thyroid	5	9	6	4.80	2.20	30	1.8	1.70
Unrepresented								
Congenital mesoblastic nephroma	–	–	0	–	0.10	30	0.07	0.10
Cervix	–	–	2	–	0.70	30	0.62	0.60
Gastro–oesophageal junction	–	–	4	–	1.40	30	1.16	1.10

continued

TABLE 16 Alternative tumour distributions (*continued*)

Tumour Type	Trial population (*n*)	Distribution of tumour types in the trial (%)	Eligible population (*n*)	Distribution of tumour types in the eligible population (%)	Distribution of tumour types in the eligible population, including the unrepresented tumour types (%)	Assumed proportion treated based on line of therapy (%)	Treated population based on line of therapy	Eligible population including line of therapy (%)
HNSCC	–	–	24	–	8.60	30	7.14	6.60
Neuroendocrine	–	–	7	–	2.50	30	2.08	1.90
Ovarian	–	–	4	–	1.40	30	1.13	1.00
Papillary thyroid tumour	–	–	44	–	15.80	30	13.07	12.10
Paediatric high-grade glioma	–	–	4	–	1.30	30	1.06	1.00
Paediatric melanoma	–	–	2	–	0.80	30	0.62	0.60
Prostate	–	–	44	–	16.00	30	13.29	12.30
Renal cell carcinoma	–	–	8	–	3.00	30	2.45	2.30
Salivary gland	–	–	6	–	2.00	30	1.68	1.60
Secretory breast carcinoma	–	–	1	–	0.20	60	0.35	0.30
Sinonasal adenocarcinoma	–	–	0	–	0.00	30	0	0.00
Uterine	–	–	1	–	0.50	30	0.43	0.40
High-grade glioma	–	–	1	–	0.50	60	0.8	0.70
Total	55	100	276	100	100	–	108	100

HNSCC, head and neck squamous cell carcinoma.

The position at which genomic testing is offered to identify *NTRK* fusions will alter the annual population eligible for larotrectinib and other TRK inhibitors. If testing was offered at the position in the treatment pathway that larotrectinib would be given, the annual eligible population will be smaller than the population identified by upfront screening because some individuals who were *NTRK* fusion positive could have responded to alternative therapies, not been fit enough or have died before becoming eligible for TRK inhibitor treatment (see *Genomic testing for histology-independent drugs*).

Given that the position of larotrectinib is likely to differ between tumours, owing to the availability of other 'satisfactory' therapies, the overall distribution of individuals across tumour types in the eligible population is likely to change relative to the distribution assuming that 100% of eligible patients receive the TRK inhibitor as a first-line therapy (see *Table 16*).

To demonstrate the impact that the position in the treatment pathway will have on the distribution of patients eligible for treatment with larotrectinib, an estimate of the likely position was obtained from the FDA review for larotrectinib.[9] For the tumour types for which there was no indication of where larotrectinib would be positioned, it was assumed that the drug would be offered as a third-line therapy. Based on clinical advice, it was assumed that, for the tumours for which larotrectinib was offered as first-line therapy, 90% of eligible patients would be fit enough for treatment. It was assumed that, in those who were offered larotrectinib as a second-line and third-line therapy, 60% and 30% of the eligible population would be treated with larotrectinib, respectively. As can be seen in *Table 16*, when the position in the treatment pathway is considered, the distribution of tumour types changes. For example, IFS increased from 9.8% to 22.4% of the population when accounting for the position in the treatment pathway.

By comparing the trial distribution in *Table 16* with the eligible population, including the unrepresented tumour types and allowing for the position in the treatment in the pathway, we can see the considerable difference in the proportions of tumour types. If the cost-effectiveness of a histology-independent technology is based on single estimates of costs and outcomes based on the average of tumour types present in the clinical evidence, the resulting uncertainty will be significant given that incremental costs and outcomes are likely to differ substantially across tumour types.

Implications for the appraisal of histology-independent technologies

In summary, the trial population may include only a subset of the total population potentially eligible for the intervention. Indeed, it is feasible that the majority of histologies potentially harbouring the biomarker will not be represented in the evidence. Furthermore, matching the line of therapy in the trial population to the eligible population is important given the likely prognostic effect of line of therapy. However, matching can be difficult if there is ambiguity in the treatment position specified within the relevant marketing authorisation.

Genomic testing for histology-independent drugs

Genomic testing is likely to be integral to identifying patients who are eligible for histology-independent therapy. The NICE approval of numerous targeted therapies has been coupled with significant investment in genomic testing services in the NHS.[153] Although genomic services are currently set up to identify oncogenic mutations in over 60 tumour types,[166] the provision of histology-independent testing poses new challenges that need to be considered before appraising the value of histology-independent technologies.

Overview of molecular testing in the UK

Substantial investment and changes to genomic testing services have been undertaken in the last 5 years after a demand to improve the access to genomic services in the NHS to inform the most

effective treatment pathway for a patient with cancer.[158] In 2018, the NHS launched the Genomic Medicine Service and a National Genomic Testing Strategy, which was based in seven genomic laboratory hubs across England.[153] Although this provides positive steps to improve the availability of genomic testing across the UK, the services are still being implemented, leading to limited capacity in some genomic laboratory hubs.

In March 2019, the genomic test directory listed 968 genomic tests available for 64 adult and paediatric tumour types.[166] Although this may seem an exhaustive number of tests for a large proportion of tumour types, it is far from inclusive. Patients with some common tumours, including prostate cancer (a population that contributes 15% of the annual incidence of solid tumours in England), are not eligible for any form of genomic testing because there are currently no effective targeted therapies licensed on the NHS. Although the absence of genomic testing until now may be because of limited evidence of known somatic or hereditary mutation that will be of prognostic or diagnostic value, the provision of a targeted histology-independent therapy would require screening of all cancers, regardless of current availability.

Types of genomic test

Tumourigenesis, the process of cancer growth and development, is driven by genetic alterations that result in sustained cell proliferation or the inhibition of cell division and death.[167] In fact, by the time that a cancer is diagnosed, there are likely to be millions of genetic mutations within a single malignancy.[168]

Many of these alterations occur during tumour development but do not contribute to tumour growth, commonly known as 'passenger mutations'; therefore, these play no functional role in cancer development. These mutations may occur in non-coding sequences of DNA that are removed during the transcription of DNA to RNA as part of gene expression. By contrast, the 'driver' mutations are involved in the neoplastic growth of the tumour, which directly result in the prolific growth of the cancer cells. Driver mutations can be differentiated further with respect to whether they solely influence the initial cancer development or whether oncogenic growth and proliferation are dependent on the mutation, regardless of its position in the disease pathway.[169]

Therefore, the role of genetic testing is two-fold: first, to detect the presence or absence of a specific mutation and, second, to determine whether the mutation is acting as an oncogenic driver or whether it is merely a passenger mutation in tumourigenesis.

There are a variety of tests that are available to identify the presence of a mutation in individuals. These include DNA- and RNA-based panel tests, whole-genome sequencing (WGS), IHC, FISH and reverse transcription polymerase chain reaction (RT-PCR). Each of these tests determines the presence or absence of a genetic mutation in different ways, from identifying a known driver mutation using targeted tests in DNA and RNA to sequencing the entire genome, or determining the level of expression of a particular protein. The suitability of the alternative types of test will probably depend on the target mutation and the test's diagnostic accuracy to correctly detect the respective alteration, the prevalence of the genetic mutation within each tumour type and the current testing provision. *Table 17* summarises the key characteristics of each test type, noting key advantages and limitations.

Tests may be combined as part of a testing strategy, where confirmatory testing is implemented to verify that a mutation is being expressed. This allows for diagnostic accuracy to be maintained, while reducing the use of more expensive and resource-intensive test types. For example, IHC may be used as a screening tool to detect protein expression, with a further confirmatory test implemented to verify that the protein expression is caused by the mutation of interest. The relevance of strategies based around IHC may, however, become more limited as panel testing using NGS is expanded within the NHS.

Because of the variable provision of testing in the NHS across tumour types, the most appropriate testing strategy will probably depend on the tumour type. For example, all paediatric patients with

TABLE 17 Summary of test features

Test	Methodology	Advantages	Disadvantages
DNA-based NGS	Analyses genomic DNA from a tumour sample and can be used to identify mutations in multiple genes concurrently. Targeted panels can be used to identify particular DNA rearrangement, known to have an oncogenic effect	• Negligible costs to add an extra mutation target to a panel • Simultaneous detection of more than one mutation • Routinely used in the NHS to detect a variety of structural variants across a range of cancer types[166]	• Limited coverage of non-coding (intronic) regions of DNA, potentially leading to false negatives • DNA-based NGS relies on targeted panels; this means that mutations that have not been previously identified and, hence, are not available on a target panel, cannot be detected[170]
WGS	Sequences the entire genome of DNA against a comparator to identify specific genetic alterations known to play a role in tumourigenesis	• The most comprehensive method to detect mutations, especially for novel mutations[170] • Currently available for paediatric patients and patients with soft tissue sarcoma[166]	• The depth of coverage is much smaller owing to the amount of DNA that needs to be sequenced[170] • Resource intensive as there are significant amounts of data produced[168]
RNA-based NGS	Analyses the transcriptome (the collection of all RNA sequences in a cell). RNA sequencing provides a more accurate test for determining whether or not genetic mutations are expressed as proteins	• RNA-based NGS provides a more accurate proxy to determine whether or not the DNA-level mutation has led to protein expression[168] • Simultaneous detection of more than one mutation • Can also be used to detect novel mutations, which are likely to be missed by targeted-panel DNA-based NGS	• Requires high-quality samples, which may make it unsuitable for high-throughput testing[170] • High failure rate, which means that samples will have to be re-tested • A relatively new test, so currently not routinely available on the NHS[166]
IHC	IHC detects the expression of a protein through the use of antibodies, which bind to a specific receptor (or antigen) on the protein of interest. A tag attached to the antibody will react if bound and produce a stain, which signals the expression of the protein	• Inexpensive and high throughput[171]	• Diagnostic accuracy can be highly variable depending on the target biomarker[172] • If a protein is naturally produced within a cell, IHC cannot differentiate this and the oncogenic, dysfunctional protein[171] • Assays are specific to each individual biomarker, so multiple tests would be required to identify multiple mutations
FISH	Uses a probe on a sequence of DNA that complements a particular genetic alteration.[173] Each probe is labelled with a fluorescent marker that, when illuminated, will indicate the presence of the mutation	• Inexpensive[171] • Relatively high sensitivity and specificity[171]	• Because the probes are often specific to each mutation, identifying novel mutations or multiple targets using conventional FISH is more challenging[171]
RT-PCR	Uses a probe on a sequence of RNA that complements a particular genetic alteration.[173] Each probe is labelled with a fluorescent marker that, when illuminated, will indicate the presence of the mutation	• Inexpensive[172] • Currently used to detect mutations including gene fusions[171]	• Knowledge of the mutation and target sequence is required[172] • High-quality RNA is required

advanced and metastatic cancer in the NHS will receive WGS at diagnosis by 2020[158] and, therefore, any testing strategy is likely to be built on this provision. The appropriateness of each testing strategy will also depend on the prevalence of the genetic alternations across tumour types. Diagnostic accuracy will vary depending on the prevalence of the genetic alteration within each tumour type even when the sensitivity and specificity are held constant (see *Appendix 12*).

Implications of testing for appraisal of histology-independent technologies

The need for companion diagnostic testing to implement histology-independent technologies has several consequences for cost-effectiveness. These considerations include resource implications associated with implementing testing and the impact of alternative testing strategies on the modelled population, as well as broader implications regarding the feasibility of expanding testing services. These issues are briefly discussed in the following sections, followed by a worked example considering the implementation of testing for *NTRK* fusions.

Costs

The costs associated with identifying patients will be driven by a range of factors, including the testing strategy adopted and current provision of testing in the NHS. Because these may vary across tumour types, incremental testing costs may also vary across tumour types. The variability in testing costs across tumour types will also be determined by variability in the frequency of a genetic mutation across specific tumour types, with increased rarity increasing the costs of identifying an eligible patient. As is illustrated in the worked example of *NTRK* fusions below, the variability in the frequency of target genetic alterations can be significant, ranging from $< 0.2\%$ to $> 90\%$. This has a significant impact on the number of patients who need to be screened [number needed to screen (NNS)] and, consequently, the variability in the tumour type-specific costs of identifying patients is similarly wide. Testing costs are a significant source of heterogeneity and, if all testing costs are attributable to a single histology-independent drug, are likely to render a technology cost-ineffective for some tumour types. In the context of *NTRK* fusions, which, on average, occur in $< 0.5\%$ of all advanced cancer patients, the average costs of testing are high and are likely to represent a significant proportion of the total incremental costs associated with the implementation of TRK inhibitors.

Attributing testing costs

The current NICE methods guide outlines that the costs of testing should be included if they are specifically associated with the provision of the technology being appraised.[4] The implementation of wide-scale genomic testing is, however, likely to represent a public good that may allow for the identification of other relevant genetic alterations (e.g. where wide-spread panel testing is implemented). This may be of particular relevance where there are multiple targeted therapies available or likely to become available in the near future. Accounting for such positive externalities may be important because testing costs may not justify the implementation of a specific single technology but may be justifiable when shared across multiple technologies. The estimation of the magnitude of any positive externalities resulting from testing is, however, non-trivial and methods of how to attribute testing costs across multiple technologies have not been established. How costs should be attributed across technologies is currently unclear; for example, costs could be split equally or by the size of the eligible population and would necessitate a co-ordinating role for either NHS England or NICE to potentially set a tariff on which attributable testing costs could be based.[9,10]

Feasibility

Although there is currently provision for genomic testing for several cancers within the NHS, there are significant uncertainties surrounding the practical feasibility of providing wide-scale histology-independent testing.

The feasibility of testing is also dependent on whether testing is offered at the point of diagnosis or at the position in the treatment pathway at which the drug would be given. Where testing is implemented on eligibility for treatment, the NNS will be indicative of the number of patients who will go on to

receive treatment because it is expected that all patients who test positive receive the therapy. Given that entrectinib and larotrectinib are offered when there is no 'acceptable' alternative therapy,[9,10] there may be significant disparity between the NNS and the final number of patients who go on to receive therapy. This is because there is significant attrition in the number of patients who go on to receive second or later lines of therapy, as a result of patients either dying or becoming unfit for treatment.

Given the potential variety of histology-independent drugs that could be available across a range of positions in treatment pathways in each tumour type, genomic testing at diagnosis of advanced or metastatic cancer is the most plausible, despite that the initial investment would be significant. Based on the annual incidence of cancer in the UK and the average proportion of individuals with advanced or metastatic cancer, 94,595 individuals would require genomic testing each year. This figure represents a significant increase in the number of molecular and genomic tests and, given the variability in the UK's capacity to implement wide-scale NGS testing, it is expected that it will take some time for the appropriate infrastructure to be put in place. A phased introduction of NGS panel testing is likely over the next few years, with NHS England anticipating that full implementation of pan-cancer testing will be in place by the end of 2022.[158]

Identifying patients eligible for TRK inhibitors based on the presence of a neurotrophic tyrosine receptor kinase fusion: a worked example

This section considers how testing for *NTRK* fusions might be implemented in the NHS and provides an illustrative example of how both NNS and testing costs might vary across tumour types.

A variety of testing strategies have been proposed for identifying patients with a *NTRK* fusion, pending the approval of two histology-independent TRK inhibitors.[172,174] The European Society for Medical Oncology (ESMO) proposes that the standard testing pathway should differ depending on the frequency of *NTRK* fusions in each tumour type and whether or not genomic sequencing is currently provided by the NHS.[166] In the tumour types for which there is a lower frequency of *NTRK* fusions and for which there is no genomic testing available, it is suggested that IHC is used for initial screening; *NTRK* gene rearrangements are then confirmed using RNA-based NGS. IHC is high throughput and inexpensive, making it a practical screening tool to use in a large population. Following this with more expensive and highly accurate RNA-based NGS is a plausible testing strategy for identifying tumours. Diagnostic accuracy is further taken into account by stratifying the tumour types into different testing strategies, depending on their *NTRK* fusion prevalence.

Conversely, it has also been suggested that front-line NGS should be offered to all individuals to detect a *NTRK* fusion.[174] Although this would require substantial investment, this testing strategy would 'future-proof' histology-independent testing because additional mutations could be added to pre-existing panels. This would mean that a single tumour sample could be screened to identify a number of genetic alterations. However, in the short term this testing strategy will require significant resources to implement nationally.

The most exhaustive approach to identify *NTRK* fusions utilises DNA-based NGS and RNA sequencing. Given that DNA-based NGS is currently available for some tumours, there will be reduced incremental investment in providing RNA sequencing, which would be used to confirm protein expression in the positive cases.

Although there is the potential for *NTRK* fusions to be observed in any tumour type, current evidence documents the occurrence of *NTRK* fusions in only around 30 different tumour types.[175–178] However, this list cannot be considered complete. It is plausible that *NTRK* fusions occur in common tumour types, but with such rarity that they are yet to be detected. There are also likely to be a number of rarer tumour types that express *NTRK* fusions but are not included in any current database.

To align with the available evidence on the prevalence of *NTRK* fusion, we distinguish between tumour types within a single anatomical site only when there is supporting evidence on the prevalence of *NTRK* fusions to do so.

Methods

For each tumour type for which there is evidence to support the prevalence of *NTRK* fusions, we estimated the following:

- the NNS, or number of individuals who would require genomic testing each year to identify one individual with a *NTRK* fusion
- the average cost of testing associated with identifying one *NTRK* fusion patient
- an illustration of the cost-effectiveness of *NTRK* testing for each tumour type.

This was implemented for three testing strategies that could be adopted to identify patients with *NTRK* fusions.

The first testing strategy was based on recent recommendations for the identification of *NTRK* fusions published by the ESMO.[174] IHC followed by confirmatory RNA-based NGS would be recommended for the tumour types in which *NTRK* fusions are rare. In the tumours where *NTRK* fusions are highly prevalent, first-line FISH should be utilised. For the tumour types for which WGS is currently available and reimbursed by the NHS, RNA-based NGS would be required to confirm the presence of an oncogenic *NTRK* fusion.

To complement the substantial investment in genomic testing services in the NHS, the second strategy was assumed to be based on using RNA-based NGS as a first-line test for all patients. For tumour types for which WGS is currently available, it was assumed that RNA-based NGS would be used to confirm the presence of an oncogenic *NTRK* fusion.

Finally, an alternative testing strategy was considered based on an exhaustive approach outlined by ESMO, which seeks to maximise current testing availability of DNA-based NGS in each tumour type. Under this approach, DNA-based NGS is used as a first-line screening tool, followed by confirmatory RNA-based NGS. This was suggested by ESMO to be the most exhaustive approach to identify *NTRK* fusions.[174]

Number needed to screen

The NNS to identify one patient eligible for TRK inhibitors is based on *NTRK* fusion prevalence and the diagnostic accuracy of the respective tests (see *Appendix 11* for details of the calculations). To our knowledge, there is no literature concerning the diagnostic accuracy of WGS in detecting *NTRK* fusions. As a result, the diagnostic accuracy of WGS for detecting *NTRK* fusions was based on sensitivity and specificity estimates of DNA-based NGS. *Table 18* presents the diagnostic accuracy for each test.

The NNS with a first-line (FL) test was estimated using the tumour type-specific prevalence of *NTRK* fusions and the corresponding first-line test sensitivity (Sn) using the following equation:

$$\mathrm{NNS}_{\mathrm{FL}} = \frac{1}{\mathrm{Sn} \times \textit{NTRK}\ \text{prevalence}}. \tag{7}$$

Confirmatory RNA testing is required for patients who require first-line IHC, WGS or DNA-based NGS. The NNS with a confirmatory (*C*) test was estimated using the sensitivity and specificity of the respective test and the tumour-specific *NTRK* fusion prevalence:

$$\mathrm{NNS}_{C} = \frac{1}{(\mathrm{Sn} \times \textit{NTRK}\ \text{prevalence}) + ((1 - \mathrm{sp}) \times (1 - \textit{NTRK}\ \text{prevalence}))}. \tag{8}$$

TABLE 18 Sensitivity and specificity of each genomic test for identifying *NTRK* fusions

Test	Sensitivity (%)	Specificity (%)
RNA sequencing[179]	100	100
WGS and DNA-based NGS[171]	81.10	99.86
Immunohistochemistry[180]	87.90	81.10
FISH (*ETV6–NTRK3*)[181]	80.00	100

The cost of testing to identify one eligible patient for TRK inhibitors

The incremental cost of testing to identify one eligible patient was estimated for each tumour. Genomic testing, in the form of DNA-based NGS, WGS and FISH, is currently reimbursed by the NHS for some tumours. The price for each test was acquired from a UK Genomic Centre: IHC and FISH were costed at £150, and DNA- and RNA-based NGS were priced at £250 and £350, respectively.[182] The cost of WGS was assumed to be £800.[182]

The incremental cost to identify one eligible patient in each tumour type was calculated by:

$$\text{Cost} = ((\text{NNS}_{\text{FL}} \times \text{Cost}_{\text{FL Test}}) + (\text{NNS}_{\text{c}} \times \text{Cost}_{\text{RNA NGS}})) - (\text{NNS}_{\text{FL}} \times \text{Cost}_{\text{Current Test}}). \quad (9)$$

An average of the tumour-specific testing costs was used to calculate the cost of identifying one individual with a *NTRK* fusion for each testing strategy. The average cost was weighted in accordance with the annual eligible population for TRK inhibitors for each tumour.

Value of implementing neurotrophic tyrosine receptor kinase testing

To illustrate how cost-effectiveness may vary across tumour types because of the variation in testing costs, a hypothetical scenario was considered in which ICERs were calculated for each tumour type. This analysis was based on the incremental costs of testing only and excludes other costs associated with the treatment (e.g. drug costs). The ICERs estimated the difference in testing costs between testing for *NTRK* and current testing provision relative to the benefits (quantified by QALYs). Incremental benefits were based on the Canadian Agency for Drugs and Technologies in Health[183] assessment of the cost-effectiveness of larotrectinib, which estimated that larotrectinib produced an additional 0.833 QALYs per patient compared with standard care.

Results

Tables 19–21 present the number of individuals who would need to be tested to identify one eligible patient for each testing strategy. The incremental cost associated with testing and hypothetical estimates of cost-effectiveness of testing are also presented.

Hierarchical approach: treating at diagnosis

For the tumour types represented in the trial, the tumour-specific costs to identify one eligible patient ranged from £0 (MASC) to £351,567 (breast cancer). Assuming that the eligible population is distributed in line with the trial distribution, the average incremental cost of testing is £64,198. Re-weighting the tumour-specific costs so that the tumour types included in the trial align with the expected prevalence of these tumours in the real world increases this to £107,030. However, this does not account for the testing costs associated with tumours that are not represented in the larotrectinib trial. When these are included and appropriately weighted in line with the prevalence of these tumour types, the average incremental cost to identify one individual eligible for treatment is £85,502. Based on this cost estimate and assuming that larotrectinib generates an additional 0.833 incremental QALYs, the ICER is estimated to be £102,644 per QALY gained, with tumour-specific ICERs ranging from less than £500 per QALY gained to over £500,000 per QALY gained.

TABLE 19 Summary of NNS and testing cost under a hierarchical testing approach

Tumour type	NNS		Incremental cost to identify one patient (£)	ICER (*NTRK* fusion testing vs. current testing provision) (£)
	First line	Confirmatory		
Tumours in the trial				
Appendix	30.83	6.16	6780	8139
Breast	1625.22	307.95	351,567	422,049
Cholangiocarcinoma	1137.66	215.80	246,179	295,533
Colorectal	948.05	179.97	205,195	246,333
GIST	88.88	17.58	19,486	23,393
IFS	1.36	1.00	350	420
MASC	1.35	0.00	0	0
Melanoma	541.74	103.17	117,372	140,903
NSCLC	1264.06	239.69	273,502	328,334
Pancreatic	437.56	83.48	94,853	113,870
Soft tissue sarcoma	220.19	1.31	457	549
Thyroid	123.66	24.16	27,003	32,417
Tumours not represented in the trial				
Cervix	344.74	65.94	74,791	89,785
Congenital Mesoblastic Nephroma	2.03	1.00	350	421
Gastro–oesophageal junction	1137.66	215.80	246,179	295,533
HNSCC	299.38	57.37	64,986	78,015
High-grade glioma	2275.31	430.82	492,084	590,737
Neuroendocrine	379.22	72.46	82,243	98,731
Ovarian	455.06	86.79	98,637	118,411
Papillary thyroid tumour	8.55	2.40	2124	2549
Paediatric high-grade glioma	23.27	1.03	361	433
Paediatric melanoma	11.10	1.01	355	426
Prostate	455.06	86.79	98,637	118,411
Renal cell carcinoma	455.06	86.79	98,637	118,411
Salivary gland	66.14	13.29	14,572	17,493
Secretory breast carcinoma	1.36	0.00	0	0
Sinonasal adenocarcinoma	455.06	86.79	98,637	118,411
Uterine	1137.66	215.80	246,179	295,533

First-line ribonucleic acid-based next-generation sequencing: treating at diagnosis

The incremental cost of testing to identify one individual eligible for TRK inhibitors using first-line RNA-based NGS is higher across tumour types than the cost of the hierarchical approach (with the exception of the tumours for which WGS is available). For the tumours included in the larotrectinib trial, the incremental testing costs range from £215 (MASC) to £500,000 (breast cancer). Based on the trial distribution, the average incremental cost to identify one eligible patient is £91,213.

TABLE 20 Summary of NNS and testing cost under first-line RNA-based NGS approach

Tumour type	NNS		Incremental cost to identify one patient (£)	ICER (£)
	First line	Confirmatory		
Tumours in the trial				
Appendix	30.83	0.00	10,789	12,952
Breast	1428.57	0.00	500,000	600,240
Cholangiocarcinoma	1000.00	0.00	350,000	420,168
Colorectal	833.33	0.00	291,667	350,140
GIST	78.13	0.00	27,344	32,826
IFS	1.36	1.00	350	420
MASC	1.08	1.00	215	258
Melanoma	476.19	0.00	166,667	200,080
NSCLC	1111.11	0.00	388,889	466,853
Pancreatic	384.62	0.00	134,615	161,603
Thyroid	220.19	1.31	457	549
Soft tissue sarcoma	108.70	0.00	38,043	45,670
Tumours not represented in the trial				
Cervix	303.03	0.00	106,061	127,324
Congenital mesoblastic nephroma	2.03	1.00	350	421
Gastro–oesophageal junction	1000.00	0.00	350,000	420,168
HNSCC	263.16	0.00	92,105	110,571
High-grade glioma	2000.00	0.00	700,000	840,336
Neuroendocrine	333.33	0.00	116,667	140,056
Ovarian	400.00	0.00	140,000	168,067
Papillary thyroid tumour	7.52	0.00	2632	3159
Paediatric high-grade glioma	23.27	1.03	361	433
Paediatric melanoma	11.10	1.01	355	426
Prostate	400.00	0.00	140,000	168,067
Renal cell carcinoma	400.00	0.00	140,000	168,067
Salivary gland	58.14	0.00	20,349	24,428
Secretory breast carcinoma	1.09	1.00	218	262
Sinonasal adenocarcinoma	400.00	0.00	140,000	168,067
Uterine	1000.00	0.00	350,000	420,168

Using the real-world distribution, this increases substantially to £151,967 per patient identified. When including the unrepresented tumour types, the average incremental costs fall slightly to £121,321 per patient identified. If larotrectinib were to provide an incremental clinical benefit of 0.833 QALYs, and assuming zero treatment costs, these testing costs would imply an ICER of £145,643 per QALY gained.

TABLE 21 Summary of NNS and testing cost under exhaustive testing strategy

Tumour type	NNS		Incremental cost to identify one patient (£)	ICER (£)
	First line	Confirmatory		
Tumours in the trial				
Appendix	30.83	1.04	8071	9689
Breast	1761.49	3.46	1213	1456
Cholangiocarcinoma	1233.05	2.72	309,215	371,206
Colorectal	1027.54	2.44	853	1024
GIST	96.33	1.13	24,480	29,387
IFS	1.36	1.00	350	420
MASC	1.33	1.00	483	580
Melanoma	587.16	1.82	637	765
NSCLC	1370.05	2.92	1021	1225
Pancreatic	474.25	1.66	119,144	143,030
Thyroid	220.19	1.31	457	549
Soft tissue sarcoma	134.03	1.19	415	498
Tumours not represented in the trial				
Cervix	373.65	1.52	93,945	112,779
Congenital mesoblastic nephroma	2.03	1.00	350	421
Gastro–oesophageal junction	1233.05	2.72	309,215	371,206
HNSCC	324.49	1.45	618,081	741,994
High-grade glioma	2466.09	4.45	81,630	97,995
Neuroendocrine	411.02	1.57	103,305	124,015
Ovarian	493.22	1.69	591	710
Papillary thyroid tumour	9.27	1.01	361	433
Paediatric high-grade glioma	23.27	1.03	355	426
Paediatric melanoma	11.10	1.01	354	425
Prostate	493.22	1.69	123,896	148,734
Renal cell carcinoma	493.22	1.69	123,896	148,734
Salivary gland	71.69	1.10	18,307	21,977
Secretory breast carcinoma	1.34	1.00	485	582
Sinonasal adenocarcinoma	493.22	1.69	123,896	148,734
Uterine	1233.05	2.72	309,215	371,206

Exhaustive approach: treating at diagnosis

Under the most exhaustive approach, in which DNA-based NGS is used as a first-line test followed by confirmatory NGS, the incremental costs of testing are lower than that for the other two strategies because a significant proportion of the costs for some tumour types are currently reimbursed.
The incremental cost associated with identifying an individual who is eligible for a TRK inhibitor is lowest in IFS (£350). Given that there is no genomic testing currently available for patients with cholangiocarcinoma, identifying one patient eligible for a TRK inhibitor is the most costly (£309,215)

within the trial population. Based on the distribution of tumour types within the trial, the average incremental testing cost associated with identifying one individual eligible for treatment is £15,252. Under the real-world distribution, this increases to £19,245 per patient identified. The average incremental cost to identify one individual eligible for treatment, including the tumour types unrepresented in the trial, is £53,480. The associated ICER was £64,202 per QALY gained.

Exhaustive approach: treating at line of therapy

Table 22 summarises the number of individuals who would need to be tested to identify one eligible patient using an exhaustive testing strategy carried out at diagnosis of advanced or metastatic cancer and treatment with larotrectinib provided in the appropriate position in the pathway. The incremental cost associated with testing and hypothetical estimates of cost-effectiveness of testing are also presented. The results show that the average incremental testing cost to identify one individual eligible for treatment is higher than when treatment is offered as first-line therapy. The annual population eligible for treatment is lower ($n = 109$); thus, the average incremental cost of testing to identify one individual eligible for treatment is estimated to be £113,424.

Implications for the cost-effectiveness of TRK inhibitors

The costs associated with additional testing for targets are likely to be substantial and will have a significant bearing on the cost-effectiveness of histology-independent technologies. Tumour-specific costs of identifying relevant fusions are also likely to represent a significant source of heterogeneity owing to the variable frequency of targets across tumour types. This heterogeneity in testing costs is likely to mean that for some tumour types for which *NTRK* fusions are rare, *NTRK* testing will not be cost-effective. Opportunities to share testing costs across multiple health-care technologies may reduce the cost burden of molecular testing on a specific health-care technology, potentially increasing the financial viability of testing. However, it is currently unclear what mechanism would be used to share testing costs across multiple technologies.

Model structure and extrapolation

Partitioned survival modelling (PSM) is the most common modelling approach used for NICE appraisals of interventions for advanced or metastatic cancers.[184] This approach uses survival analysis of observed TTE end points to derive state membership estimates. Given that estimates of mean survival times are required for cost-effectiveness analysis, parametric models are fitted to the observed TTE end points to extrapolate the observed survival data over an appropriate time horizon. The choice of appropriate parametric models to extrapolate the observed data is usually based on a series of assessments, including visual inspection of the Kaplan–Meier curves and log-cumulative hazard plots; visual fit of extrapolated models to observed data; statistical fit based on goodness-of-fit statistics; and clinical plausibility of the extrapolation.[185] In a PSM, PFS and OS are usually extrapolated independently and directly inform the state membership for the 'Progression-free' and 'Death' states over time, respectively. The difference between PFS and OS allows the proportion of patients in the progressed health state to be estimated.

The use of PSM presents several challenges for the assessment of histology-independent products. First, the more heterogeneous overall population may make it more challenging to fit a single conventional parametric curve. Second, the immaturity of the PFS and OS data will result in considerable uncertainty surrounding the extrapolated curves. This may lead to wide variation in the resulting predictions for survival models that have similar goodness of fit to the observed data. Each of these challenges is now considered in more detail.

Standard parametric models can include proportional hazard-based models (exponential, Weibull and Gompertz) and the accelerated failure time models (log-normal, log-logistic and generalised gamma). However, the additional heterogeneity arising from the inclusion of different tumour sites is likely to result in more complex hazard functions, which may not be appropriately captured using standard

TABLE 22 Summary of NNS and testing cost under exhaustive testing strategy when testing is carried out at diagnosis and treatment is provided at the appropriate line of therapy

Tumour type	Proportion eligible based on treating at line of therapy (%)	Incremental cost to identify *NTRK* fusion patient (£)	ICER
Tumours in the trial			
Appendix	30	26,903	32,297
Breast	30	4042	4852
Cholangiocarcinoma	30	1,030,717	1,237,355
Colorectal	30	2843	3413
GIST	30	81,598	97,957
IFS	90	389	467
MASC	60	805	966
Melanoma	30	2124	2549
NSCLC	60	1701	2042
Pancreatic	30	397,146	476,766
Soft tissue sarcoma	90	508	610
Thyroid	30	1384	1661
Tumours not represented in the trial			
Cervix	30	313,150	375,930
Congenital mesoblastic nephroma	30	1168	1402
Gastro–oesophageal junction	30	1,030,717	1,237,355
HNSCC	30	2,060,269	2,473,312
High-grade glioma	60	136,050	163,325
Neuroendocrine	30	344,349	413,384
Ovarian	30	1970	2365
Papillary thyroid tumour	30	1203	1444
Paediatric high-grade glioma	30	1183	1420
Paediatric melanoma	30	1180	1416
Prostate	30	412,985	495,781
Renal cell carcinoma	30	412,985	495,781
Salivary gland	30	61,022	73,256
Secretory breast carcinoma	60	808	969
Sinonasal adenocarcinoma	30	412,985	495,781
Uterine	30	1,030,717	1,237,355

parametric distributions. Consequently, the use of flexible parametric models, mixture models or response-based models may be required.[186]

Flexible parametric approaches directly model the effect of time on the hazard function using splines. The splines are used to form a series of polynomial distributions joined by 'knots'. Changes in the modelled hazard function at specific time points can be accommodated by using different polynomial distributions between each knot. The number of knots determines the number of parameters required

to model the hazard function. In a simple case with zero knots, these models are the same as conventional parametric distributions. These approaches provide greater flexibility than conventional parametric modelling. However, they also present potential challenges for histology-independent appraisals. First, the approach captures heterogeneity via the effect of time on the hazard function. This may not be appropriate for achieving accurate projections of PFS and OS where the main source of heterogeneity is the difference in the natural history between different tumour sites. Second, the flexible parametric approach extrapolates beyond the data using only the final segment of the curve. The small number of patients and the immaturity of the PFS and OS data may mean that survival projections are particularly unreliable in the final segment.

Although the impact of the inclusion of tumour sites that may have different natural histories on the hazard function might be accommodated by flexible parametric approaches, the inclusion of multiple subsets of patients may provide evidence of different survival distributions within the observed TTE data. Parametric mixture models can be used to capture heterogeneity within a population by using two (or more) distinct distributions. Although the use of a mixture model may provide a more appropriate approach to capture between-tumour heterogeneity, there may remain challenges in determining how many mixes are appropriate and whether or not the predicted long-term hazards are plausible from the resulting mixture. There also remain issues regarding the application of different HRQoL or cost estimates for individual tumour sites, as the different mixture distributions are not explicitly assigned to any individual tumour site or grouping. Hence, although mixture models provide an approach to account for heterogeneity within the TTE end points, they do not provide a basis for accounting for heterogeneity in other inputs, which may affect cost-effectiveness estimates.

Another approach that has been proposed to account for heterogeneity in TTE end points is the use of response-based landmark models. This approach models survival conditional on response status, identified at a predefined response evaluation landmark time based on a clinical definition of response. Survival is modelled from the landmark point to avoid the problem of 'immortal time' bias arising from the fact that responders have to survive to the point at which response is assessed. Separate survival curves are then fitted to the different response categories. Intuitively, this approach appears to be particularly aligned to the appraisal of histology-independent technologies where response measures are used as the primary end point. This approach allows for a distinction to be made between the HRQoL of responders and HRQoL of non-responders (and between individual tumour sites), as well as allowing for potential differences in the costs of care. However, there may be challenges in determining whether or not a single landmark time point is appropriate and how uncertainty around this should be dealt with. Although different response time points can be accommodated within the survival analysis using a time-varying covariate, inevitably this will increase the complexity of the economic model and may require individual patient simulation approaches. There also remain issues concerning the potentially small number of patients recruited in the underpinning studies and the immaturity of the PFS and OS data. Further subdividing patients into responder categories may result in more uncertain survival predictions. In addition, although separate survival curves may better account for heterogeneity within the survival data, the approach does not resolve the fundamental problem of immaturity in these end points.

Although several approaches exist to account for heterogeneity in survival end points, they all have several important limitations in the context of histology-independent appraisals. First, the use of single 'full population' ICERs, across multiple tumour sites with potentially different treatment effectiveness, comparators, costs and HRQoL, will be difficult to interpret. A single ICER may conceal significant variation in the tumour-specific ICERs, driven by a combination of factors, including the observable variability in the relative effectiveness between tumour types. Ignoring these differences could mean that a treatment that is not cost-effective for the total population (combining all subgroups) may be cost-effective in specific subgroups. Conversely, a treatment that appears cost-effective for the total population may not be cost-effective for particular subgroups. Given the amount of heterogeneity associated with a histology-independent appraisal, estimating the average cost-effectiveness for the

full patient population covered in the scope may not provide enough information to decision-makers about whether or not the drug is potentially cost-effective across all subgroups.

Second, the approaches rely on extrapolations of the observed survival data, which will potentially be immature at the time of initial appraisal such that the resulting predictions will be highly uncertain. Different survival models that appear to fit the observed data equally well may lead to significant variation in the longer-term survival predictions. Consequently, it is unlikely that a single survival distribution (or a single specification of a more flexible parametric, mixture model or response-based approach) will adequately characterise uncertainties over the longer-term extrapolation period. To more formally account for the uncertainty surrounding choice of survival distribution, a model averaging approach may be required.[187,188] This approach involves the parameterisation of uncertainty surrounding the choice of distribution, incorporating all plausible distributions as part of a weighted distribution. Uncertainty in the probabilistic analysis will then reflect both the parametric uncertainty associated within each distribution and the uncertainty surrounding the choice of preferred method. However, such an approach presents additional challenges in the context of histology-independent appraisals, for which the external validation of survival projections from a heterogeneous population including multiple tumour types will be difficult and expert elicitation may be required to determine the weights to be applied as part of any weighted distribution. Furthermore, this heterogeneity will also result in the 'at-risk' population changing over time. That is, tumour types with poorer prognosis will experience events earlier than patients with a more favourable prognosis. Hence, the composition of the population will probably change significantly over the extrapolation period. This limits the appropriateness of applying a single 'average' utility or cost to the population within the model.

The greater immaturity in PFS/OS for trials that are powered on response end points may present challenges to fitting reliable survival distributions. In these circumstances, surrogate relationships may be required to link response-based outcomes (e.g. ORR and DoR) to longer-term estimates of PFS and/or OS. Although *Chapter 4* highlighted a range of alternative approaches that could be used, the lack of any clear pattern by cancer type inevitably presents challenges for using a surrogate-based modelling approach to a model that includes a heterogeneous mix of patients.

Given the importance of exploring the impact of heterogeneity more explicitly for decision-making, approaches are required that can accommodate different sources of heterogeneity within the overall population, more appropriately estimate the average cost-effectiveness for the full patient population covered in the scope and facilitate assessment of whether or not the drug is potentially cost-effective across all subgroups. The BHM framework provides an important approach that can more fully explore the potential heterogeneity in effects across tumours. The BHM allows assessments to be made for each tumour type, as well as a pooled assessment across all tumour types, accounting for the potential lack of uniformity of effect across tumours. An additional advantage of this framework is the ability to predict the response probability that would be expected in a 'new' tumour type (i.e. a tumour that is not represented in the trial data), which will give a measure of the uncertainty in the response rates in tumour types in the target population but for which no data are available (see *Treatment effectiveness*).

Heterogeneity in TTE outcomes (PFS and OS) can be explored using the BHM in a similar way to that presented for response outcomes.[46] The model assumes a common parametric distribution for each tumour type, but with a different location parameter. Information on this parameter can be borrowed across the different tumours, according to an estimated heterogeneity parameter. The results from this model would be different distributions of PFS or OS for each tumour type, which could be incorporated in the economic model to further explore how heterogeneity in outcomes by tumour type influences the expected ICERs. Although the BHM can borrow information across tumour types and is designed to allow inferences with few events per tumour type, it is unclear whether or not this type of model would provide useful results given the immaturity of the survival data, the small number of

patients for most tumour types, the expected lack of exchangeability of the survival outcomes and the potential for requiring informative prior distribution.

To address concerns regarding the maturity of the TTE end points, BHM could be applied to specific landmark survival time points (e.g. 6 or 12 months) for which more robust data exist, with surrogate relationships employed to predict longer-term survival conditional on survival up to these specific time points. Alternatively, BHM could be applied to the response data, for which fewer observations are required on response outcomes to draw meaningful conclusions about differences between tumour types. These response assessments could then be applied to conditional PFS and OS distributions from the overall population or be linked to external surrogate relationships. However, as reported in *Chapter 4*, the use of external surrogate relationships would require the use of surrogate multivariable statistical models to estimate the final outcome (OS/PFS), which may not specifically relate to the different tumours or a specific biomarker population.

Although such an approach is less desirable than having robust TTE data for the overall population and each specific subgroup of interest, it may provide a basis for the initial explorations of the potential impact and importance of heterogeneity. This would appear more appropriate than ignoring this heterogeneity within initial assessments. Importantly, such assessments may also help to guide further data collection and prioritise specific subgroups for which existing evidence may be scarce and/or for which these exploratory analyses indicate potentially important impacts on the likely cost-effectiveness of a new treatment within the full population.

Summary and implications

The previous sections identified a number of particular challenges for histology-independent appraisals and have explored alternative approaches that might be used to investigate and account for different sources of heterogeneity and uncertainty. Although not comprehensive, we have focused on areas of evidence and analysis that are anticipated to be the most challenging for the appraisal of histology-independent products. Given the nature of these challenges, it is likely that a range of alternative approaches will be required to address different sources of heterogeneity. The implications for the assessments of cost-effectiveness and uncertainty will also need to be made explicit. Equally important is the need to ensure that these assessments present the results in a manner that can help to inform NICE decisions, both in determining the appropriateness of different recommendations and in identifying key uncertainties that might be used to inform and prioritise the value of further data collection.

Chapter 7 presents a potential framework that could be used to inform approval and research policies for histology-independent products, including NICE decision-making and CDF data collection arrangements.

Chapter 7 A decision framework to inform approval and research policies for histology-independent technologies

An exemplar case study was developed to illustrate the nature of the assessments that could be used to evaluate the cost-effectiveness of a new histology-independent treatment. Based on these assessments, a framework is proposed to help to inform approval and research policies for histology-independent technologies. A brief summary of the case study is presented in the following section. Further details are reported separately in *Appendix 12*.

Exemplar case study

The case study considers a hypothetical TRK inhibitor ('Drug X') compared with the current SoC for the treatment of solid tumours that harbour a *NTRK* gene fusion. Although the case study draws on clinical evidence from an existing TRK inhibitor, specifically the response outcomes and the BHM reported in *Chapter 6*, *Treatment effectiveness*, for larotrectinib, all other inputs are based on stylised assumptions. Importantly, the purpose of the case study is not to make any recommendations concerning the likely cost-effectiveness of any existing or new histology-independent treatment. Instead, the aim is to illustrate the nature and sequence of assessments that could potentially be used to help to inform NICE approval decisions and CDF data collection arrangements.

The economic model uses a landmark response-based structure (see *Chapter 6*, *Model structure and extrapolation*) that incorporates separate PFS and OS distributions, conditioned on response status in the overall study population. That is, the same conditional PFS and OS distributions that are assumed for responders and non-responders are applied to each individual histology. The use of conditional PFS and OS data, therefore, assumes a perfect surrogate relationship between response outcomes and PFS and OS end points, which is the same across all tumour types. Hence, heterogeneity in PFS and OS across individual histologies is assumed in the case study to be entirely mediated through different response rates.

The use of a response-based modelling approach necessitates additional assumptions compared with a situation in which robust TTE data are available for the overall population and each specific subgroup of interest. Equally, there may be a range of alternative modelling approaches that could be developed based on landmark survival times and/or alternative surrogate relationships. The purpose of the case study is not to make specific recommendations regarding the model structure and associated parameter assumptions, but to present a more general framework to demonstrate how heterogeneity within the overall population could potentially be explored within a cost-effectiveness analysis and how the results could be presented to inform alternative policy decisions more appropriately. However, it should be acknowledged that assessments of heterogeneity in survival outcomes at the point of initial marketing authorisation may be challenging unless these are linked to a surrogate outcome (e.g. response and DoR), for which more robust assessments of heterogeneity are likely to be feasible.

The model structure consists of three mutually exclusive health states: (1) progression-free disease, (2) progressed disease and (3) death. State occupancy in the model is derived using a dual-partitioned survival approach that uses PFS curves to partition OS into those patients who are progression-free and those who have progressed disease, based on response status at a specific landmark time point.

Survival for Drug X is calculated as a weighted average of the responder and non-responder survival curves based on the ORR assumed in the analysis. Survival in the SoC arm was modelled assuming a 0% response. The case study, therefore, also makes a strong assumption that effectiveness for SoC

management is the same across all tumour types and is equal to the conditional PFS and OS estimates derived from non-responders to Drug X.

In line with the NICE reference case, the model considers a NHS and Personal Social Services perspective in terms of capturing costs and QALYs, and discounts both using a 3.5% discount rate. Results are presented over a lifetime (30-year) time horizon.

The response rates used in the analysis were based on the BHM analysis of the larotrectinib FDA data (see *Table 13*). By linking the BHM estimates for response rates to the conditional OS and PFS estimates, the case study model explores the implications for cost-effectiveness of heterogeneity in the overall population by considering individual histology-specific estimates of cost-effectiveness alongside estimates for the overall population.

Stylised input parameters were used for all other economic model parameters and are summarised in *Table 23*. The acquisition cost for Drug X in the case study was assumed to be priced at a level such that the ICER in the overall population would be close to the upper limit of NICE's end-of-life

TABLE 23 Input parameters included in the economic model

Parameter	Value (95% CI)
Effectiveness (months)[a]	
Median PFS	
Responders	24 (21.6 to 26.4)
Non-responders	6 (5.4 to 6.6)
Median OS	
Responders	36 (32.4 to 39.6)
Non-responders	12 (10.8 to 13.2)
Utilities	
Progression-free	
Drug X	0.79 (0.71 to 0.87)
SoC	0.72 (0.65 to 0.79)
Post progression	
Drug X	0.64 (0.57 to 0.71)
SoC	0.64 (0.57 to 0.71)
Costs (£) (per month)	
Drug acquisition costs	
Drug X	1250 (–)
SoC	20 (–)
Health state costs[b]	
Progression free	350 (315 to 385)
Post progression	500 (450 to 550)
Terminal care cost	6878 (one-off cost) (–)

a It is assumed that the survival function of responders and non-responders follows an exponential distribution.
b Health state costs are assumed to be the cost of care excluding treatment costs per individual per month.

threshold range (circa £50,000 per QALY gained). Given that a number of separate scenarios are presented in the case study, the estimate of the acquisition cost was derived from the scenario that was considered to best represent a base-case scenario. This scenario included testing costs and estimates of the effectiveness in tumour sites that were not represented in the clinical evidence base. For a more detailed description of the underlying assumptions and justification for the parameters, see *Appendix 13*.

The model results are based on a probabilistic sensitivity analysis (PSA), which was implemented using 10,000 samples.

Histology-specific incremental cost-effective ratios and overall cost-effectiveness

The case study starts with an assessment of cost-effectiveness based on the trial population and excludes testing costs. Issues around the generalisability of the trial population and the impact of including testing costs are then explored.

Table 24 presents the mean total costs, QALYs and ICERs associated with the histology-independent technology (Drug X) and SoC for each histology included in the trial. Mean survival with SoC is < 2 years for all individual histologies and Drug X is expected to increase life expectancy by > 3 months. This suggests that the end-of-life criteria has been met and, therefore, the ICER for all histologies should be compared with a maximum threshold of £50,000 per additional QALY.[4]

The ICERs estimated for the individual histologies range from £27,213 to £37,930 per QALY gained. The large differences in response rates, ranging between 29.9% and 93.3%, appear to have only a moderate effect on the ICER estimates reported across individual histology sites. The reason for this is that the overall cost of Drug X is assumed to be closely related to the expected survival outcomes of treatment, specifically the duration of PFS. As the response rate increases (or decreases), the duration of treatment also increases (or decreases), such that the total cost of the treatment is closely related to the expected survival outcomes. For treatment regimens that are given for a fixed duration, as opposed to a treat-until-disease-progression (or unacceptable toxicity) strategy, the impact of heterogeneity in the response data would be expected to have a greater impact on the ICER estimates across individual histologies. Similarly, in situations in which heterogeneity in the surrogate relationship is also evident across tumour sites, a greater impact on the ICER estimates across individual histologies would be expected.

A 'histology-independent' recommendation is defined here as the approval of Drug X for use in any histology that exhibits the specific biomarker (e.g. *NTRK*). If a histology-independent approval is sought, it is necessary to consider the 'average' or 'pooled' ICER across all histologies. *Table 25* illustrates how a pooled ICER is calculated with the frequency of each histology based on the relative histology frequency observed in the trial (see *Table 14*).

This analysis illustrates that the pooled cost-effectiveness of Drug X depends on the frequency and distribution of the individual histologies. The frequency of histologies in the target population will ultimately be determined by the testing strategy implemented in clinical practice. Depending on the testing strategy and the expected distribution of histologies in the target population, the pooled ICER may alter. For example, evidence on the expected prevalence of *NTRK* fusions in specific histologies suggests that the distribution of histologies expected in clinical practice may differ significantly from that observed in the trial.

Table 26 shows the relative frequency of histologies expected in clinical practice, assuming routine screening of all histologies. The table also illustrates how the pooled ICER can change based on differences in the expected distribution of histologies in the target population compared with those observed within the trial.

TABLE 24 Histology-specific ICERs

	Per-patient level		
Subgroup	Cost (£)	QALYs	ICER (£)
Sarcoma			
Drug X	61,314	2.70	27,520
SoC	14,471	0.99	–
Salivary			
Drug X	58,697	2.58	27,969
SoC	14,471	0.99	–
IFS			
Drug X	63,332	2.79	27,213
SoC	14,471	0.99	–
Thyroid			
Drug X	62,615	2.76	27,318
SoC	14,471	0.99	–
Lung			
Drug X	55,032	2.41	28,721
SoC	14,471	0.99	–
Melanoma			
Drug X	46,963	2.03	31,267
SoC	14,471	0.99	–
Colon			
Drug X	38,667	1.65	36,857
SoC	14,471	0.99	–
GIST			
Drug X	61,234	2.69	27,535
SoC	14,471	0.99	–
Cholangiocarcinoma			
Drug X	34,261	1.45	43,658
SoC	14,471	0.99	–
Appendix			
Drug X	37,773	1.61	37,859
SoC	14,471	0.99	–
Breast			
Drug X	37,768	1.61	37,863
SoC	14,471	0.99	–
Pancreas			
Drug X	37,751	1.61	37,930
SoC	14,471	0.99	–

TABLE 25 Calculating a pooled ICER based on trial histology frequency

	Observed outcomes			Weighted consequences	
Subgroup	**ΔCost (£)**	**ΔQALYs**	**Frequency (%)**	**ΔCost (£)**	**ΔQALYs**
Sarcoma	46,844	1.70	20.00	9369	0.34
Salivary gland	44,227	1.58	21.82	9649	0.35
IFS	48,861	1.80	12.73	6219	0.23
Thyroid	48,144	1.76	9.09	4377	0.16
Lung	40,561	1.41	7.27	2950	0.10
Melanoma	32,492	1.04	7.27	2363	0.08
Colon	24,197	0.66	7.27	1760	0.05
GIST	46,763	1.70	5.45	2551	0.09
Cholangiocarcinoma	19,791	0.45	3.64	720	0.02
Appendix	23,302	0.62	1.82	424	0.01
Breast	23,297	0.62	1.82	424	0.01
Pancreas	23,280	0.61	1.82	423	0.01
Total				41,227	1.44
Pooled ICER					£28,573

The pooled ICER is simply a weighted average of the additional mean total costs of Drug X (ΔCost = £41,227) divided by a weighted average of the additional QALYs (ΔQALYs = 1.44), resulting in an ICER of approximately £28,573 per QALY.

TABLE 26 Calculating a pooled ICER based on histology frequency in the target population

	Observed outcomes			Weighted consequences	
Subgroup	**ΔCost (£)**	**ΔQALYs**	**Frequency (%)**	**ΔCost (£)**	**ΔQALYs**
Sarcoma	46,844	1.70	3.93	1840	0.07
Salivary gland	44,227	1.58	1.80	796	0.03
IFS	48,861	1.80	21.89	10,693	0.39
Thyroid	48,144	1.76	5.01	2412	0.09
Lung	40,561	1.41	13.37	5424	0.19
Melanoma	32,492	1.04	2.08	675	0.02
Colon	24,197	0.66	18.39	4450	0.12
GIST	46,763	1.70	3.01	1407	0.05
Cholangiocarcinoma	19,791	0.45	0.27	53	0.00
Appendix	23,302	0.62	12.78	2978	0.08
Breast	23,297	0.62	3.87	902	0.02
Pancreas	23,280	0.61	13.61	3169	0.08
Total				34,798	1.15
ICER					£30,364

The pooled ICER based on the distribution of histologies expected in clinical practice is £30,364 per QALY. This is marginally higher than the estimate based on the distribution of tumour sites reported in the trial data. The evidence indicates that more common tumour sites, such as colon and pancreas, that have low frequency of *NTRK* fusions may be under-represented in the trial population and, conversely, certain rarer tumour sites with high frequency of *NTRK* fusions are potentially over-represented (e.g. sarcoma and salivary gland).

This example illustrates the importance of understanding the frequency of histologies expected in the target population and the necessity of modelling histology-specific cost and health consequences. When the expected distribution of histologies is expected to differ between the trial and the target population, failure to account for this could result in a biased estimate of the pooled ICER. The magnitude of any bias will depend on the extent of heterogeneity in relevant model inputs between tumour sites.

Screening to identify eligible patients

The previous analyses did not include the costs of identifying the population of patients with the biomarker of interest. However, a variety of tests and testing strategies may be required to identify eligible patients. As a result, the cost of patient identification may vary significantly across histologies. Indeed, even if homogeneity in all other model inputs is assumed, the cost-effectiveness estimates will inevitably vary based on differences in the costs of identifying patients with the specific biomarker. Consequently, when evaluating the overall cost-effectiveness of a technology, it is necessary to consider the joint costs and benefits of the testing/treatment strategy.[189,190]

Table 27 updates the previous results by including an arbitrary per-patient testing cost of £50. The results clearly demonstrate that even a small per-patient testing cost can result in significant variation in the ICER estimates across the individual histologies.

Tumour-specific costs of identifying biomarker-positive patients are also likely to represent a significant source of heterogeneity owing to the variable frequency of targets across tumour types. This is evident in the individual ICER estimates, which now show much greater variation across different tumour sites than the previous analysis, which excluded per-patient testing costs.

The key variable driving the testing costs and the ICER estimates for the test/treat strategy is the NNS. For now, we assume that the test is perfect: it correctly classifies all individuals as having or not having the mutation (i.e. there are no false positives or false negatives). In this situation, the NNS is 1 divided by the expected frequency of the mutation in each histology. For histologies in which the mutation is very common ('high frequency histologies', for example salivary), there is a very small NNS because almost every person (92.9%) screened has the mutation. The opposite is the case for 'low frequency histologies' in which the mutation is rare. In pancreatic cancer, 1429 people (i.e. 1/0.07%) need to be screened to identify one individual with the mutation. A testing cost of £50 per test increases the overall costs of Drug X by £71,429, from £37,751 to £109,180 in pancreatic cancer. This increases the ICER from £37,930 to £154,304 in pancreatic cancer. The ICER for each histology has increased, but in the histologies with moderate to high frequency of mutation the increase in the ICER is more modest.

The above analysis assumes that the test (or testing strategy) is perfect; however, if this is not the case, this will result in patients being misclassified. Patients who do not have the mutation will be classified as having the mutation (false positives) and patients who have the mutation will be missed (false negatives). Such misclassifications may have important implications for costs and health.[149,190] The number of false positives and negatives will depend on the testing strategy, test characteristics (sensitively/specificity) and frequency of the mutation in each histology.[165,172,191] The possibility of misclassification presents two tasks: (1) calculating the correct ICER given a specific test or testing strategy, and (2) choosing the optimal test or testing strategy. Both of these tasks require estimates

TABLE 27 Including testing costs into histology-specific ICERs

Subgroup	Per-patient level		Frequency of mutation (%)	NNS (*n*)	Cost of testing (£50 per test) (£)	Cost (including testing) (%)	ICER (£)
	Cost (excluding testing) (£)	QALYs					
Sarcoma							
Drug X	61,314	2.70	0.56	178.57	8929	70,243	32,765
SoC	14,471	0.99		–	–	14,471	–
Salivary							
Drug X	58,697	2.58	92.90	1.08	54	58,751	28,003
SoC	14,471	0.99		–	–	14,471	–
IFS							
Drug X	63,332	2.79	90.90	1.10	55	63,387	27,244
SoC	14,471	0.99		–	–	14,471	–
Thyroid							
Drug X	62,615	2.76	0.92	108.70	5435	68,049	30,402
SoC	14,471	0.99		–	–	14,471	–
Lung							
Drug X	55,032	2.41	0.09	1111.11	55,556	110,588	68,060
SoC	14,471	0.99		–	–	14,471	–
Melanoma							
Drug X	46,963	2.03	0.21	476.19	23,810	70,773	54,178
SoC	14,471	0.99		–	–	14,471	–
Colon							
Drug X	38,667	1.65	0.12	833.33	41,667	80,334	100,326
SoC	14,471	0.99		–	–	14,471	–
GIST							
Drug X	61,234	2.69	1.28	78.13	3906	65,140	29,836
SoC	14,471	0.99		–	–	14,471	–
Cholangiocarcinoma							
Drug X	34,261	1.45	0.10	1000.00	50,000	84,261	153,956
SoC	14,471	0.99		–	–	14,471	–
Appendix							
Drug X	37,773	1.61	4.00	25.00	1250	39,023	39,889
SoC	14,471	0.99		–	–	14,471	–
Breast							
Drug X	37,768	1.61	0.07	1428.57	71,429	109,196	153,952
SoC	14,471	0.99		–	–	14,471	–
Pancreas							
Drug X	37,751	1.61	0.07	1428.57	71,429	109,180	154,304
SoC	14,471	0.99		–	–	14,471	–

of the costs and QALYs associated with false positives and false negatives, which will probably differ by histology. For costly new treatments and those with significant side effects, false positives may have substantial consequences. The scale of consequences associated with false negatives will depend on the additional benefits of treatment. This means that the consequences of missing a potential patient (false negative) will be larger in those histologies in which the treatment results in larger QALY benefits.

The value of heterogeneity and population health

The preceding sections show how heterogeneity in treatment effectiveness and testing costs can be explored using pooled ICERs and individual histology ICERs. However, ICERs have an important limitation: they do not give an indication of the scale of consequences for population health. Understanding the benefits and costs of treatment at a population level will help to understand the consequences of decision-making in the presence of heterogeneity and uncertainty.

To understand the implications of heterogeneity for population health requires that benefits and costs are expressed in health or monetary equivalents, using net health benefits (NHBs) or net monetary benefits (NMBs). The same information used to provide ICER estimates can also be expressed as the per-patient NHB (or NMBs), which includes benefits, harms and NHS/Personal Social Services costs.[192–194] The NHB is the difference between any health gained with the intervention and the health forgone elsewhere in the health-care system (i.e. owing to the need to displace existing treatments and services to fund a new and more costly treatment), all expressed in QALY terms. NMB is equivalent, but everything is expressed in monetary terms.

Table 28 illustrates how NHB and NMB are calculated given an assumed threshold of £50,000 per QALY. Testing costs are now included in this analysis.

For sarcoma, the additional per-patient cost of £55,772 can be represented as 1.12 QALYs (in NMB terms ≈ £55,572/£50,000) in health forgone elsewhere in the health system, based on a NICE threshold of £50,000 per QALY. This can then be compared with the additional benefits of 1.7 QALYs,

TABLE 28 Calculating per-person net health effects for Drug X

	Per-patient level		£50,000 per QALY threshold		
Subgroup	ΔCost (£)	ΔQALYs	Health forgone (ΔCost/£50,000)	NHB (ΔQALY – health forgone)	NMB (ΔQALYs × £50,000 – ΔCost) (£)
Sarcoma	55,772	1.70	1.12	0.59	29,337
Salivary gland	44,281	1.58	0.89	0.70	34,784
IFS	48,916	1.80	0.98	0.82	40,859
Thyroid	53,579	1.76	1.07	0.69	34,539
Lung	96,117	1.41	1.92	−0.51	−25,505
Melanoma	56,302	1.04	1.13	−0.09	−4342
Colon	65,863	0.66	1.32	−0.66	−33,039
GIST	50,670	1.70	1.01	0.68	34,245
Cholangiocarcinoma	69,791	0.45	1.40	−0.94	−47,125
Appendix	24,552	0.62	0.49	0.12	6223
Breast	94,725	0.62	1.89	−1.28	−63,961
Pancreas	94,709	0.61	1.89	−1.28	−64,020

resulting in an overall positive NHB of approximately 0.59 QALYs (≈ 1.7–1.12 QALYs) per person treated in this histology. Hence, for each sarcoma patient treated with Drug X, the overall gain to the health system is expected to be 0.59 QALYs per annum. However, for certain other histologies (e.g. colon), the additional health gained with Drug X is more than offset by health forgone elsewhere. This means that, for every colon cancer patient who receives Drug X, it is expected that 0.66 QALYs will be lost per annum elsewhere in the health system.

The advantage of NHBs and NMBs is that they can be used to help to understand the population-level consequences of alternative policy decisions. Understanding the scale of population consequences requires information on the number of patients who are expected to be treated by histology. This will depend on the incidence (number of new cases per year) and prevalence (number of current cases) of the mutation for each histology. It will also depend on the screening strategy used to identify cases and where in the treatment pathway Drug X is used. To simplify the case study, we assume only incident cases and a perfect screening strategy, which means that all patients who can potentially benefit are correctly identified. The expected population health consequences of approving Drug X are shown in *Table 29*.

The number of patients with sarcoma who express the biomarker is approximately five per year. This means that treating identified sarcoma patients with Drug X is expected to result in a gain of 2.88 QALYs per year to the health system when compared with SoC. This contrasts with treating biomarker-positive patients who have colon or pancreatic cancer. Using Drug X in these populations is expected to result in a loss of 15.19 and 21.78 QALYs, respectively, per year.

By totalling the yearly NHB across all histologies, *Table 29* shows that Drug X is expected to result in an overall loss of approximately 17 QALYs per year. This implies that a histology-independent approval for Drug X is not expected to be cost-effective. Although Drug X appears cost-effective in some individual histologies (e.g. sarcoma and IFS), the overall consequences of approving for all histologies would result in an overall annual loss of health to the health system. The analyses illustrate the importance of information on the relative frequency of histologies expected in the target population.

TABLE 29 Calculating population net health effects for Drug X

	Per patient level £50,000 per QALY threshold		Population level	
Subgroup	Health forgone (ΔCost/£50,000)	NHB (ΔQALY – health forgone)	Incidence	NHB, QALYs (NMB, £)
Sarcoma	1.12	0.59	5	2.88 (144,046)
Salivary gland	0.89	0.70	2	1.56 (78,201)
IFS	0.98	0.82	27	22.35 (1,117,570)
Thyroid	1.07	0.69	6	4.32 (216,219)
Lung	1.92	−0.51	17	−8.52 (−426,230)
Melanoma	1.13	−0.09	3	−0.23 (−11,276)
Colon	1.32	−0.66	23	−15.19 (−759,374)
GIST	1.01	0.68	4	2.57 (128,728)
Cholangiocarcinoma	1.40	−0.94	0.3	−0.31 (−15,727)
Appendix	0.49	0.12	16	1.99 (99,383)
Breast	1.89	−1.28	5	−6.19 (−309,616)
Pancreas	1.89	−1.28	17	−21.78 (−1,089,034)
Total			125	−17 (−827,110)

Histology-dependent recommendations and the value of heterogeneity

The assessments presented in *Table 29* can also be used to compare the population consequences of making different policy recommendations. Decision-makers, such as NICE, have the option of different approval policies:

1. no stratification – histology-independent approval
2. partial stratification – approval in a clinically defined set of histologies
3. full stratification – approval only in histologies in which cost-effective is demonstrated.

These policies will determine the type of recommendations that are feasible and the relevant health consequences that need to be considered. The following section deals only with approval policies based on expected values, without addressing the impact of uncertainty in decision-making. Uncertainty, the need for further evidence and alternative mechanisms to reduce the risk of decision-making are considered in subsequent sections.

No stratification: histology-independent approval

This represents an 'all or nothing' approval policy in which the intervention is approved for all histologies or for none. There is no stratification of decision-making by histology. In this case, the relevant metric is the pooled ICER (or pooled NHB/NMB equivalent) across all histologies. Based on the results shown in *Table 29*, Drug X would not be approved for use in any histology because the pooled NHB is negative (correspondingly, the pooled ICER would be higher than the £50,000 per QALY threshold). The health system is expected to lose approximately 17 QALYs per year if Drug X was granted a histology-independent approval.

However, a further consideration when making histology-independent decisions is that some histologies, which may harbour the mutation of interest, may not be directly observed in the evidence base at the time of decision-making, despite the inclusion/exclusion criteria of the trial permitting their inclusion. Given that these patients may be treated in clinical practice, consideration should be given to the potential impact of considering histologies that are not represented in the trial data. The larger the incidence of unrepresented *NTRK* fusion-positive histologies, the greater the influence this can have on decision-making. In this case study, it is estimated that there are 151 *NTRK* fusion-positive cases in the set of unrepresented histologies each year (see *Table 16*). This is a larger number than the 125 cases in the observed set of histologies represented in the trial and should be explicitly considered if a histology-independent approval is sought.

If, as in this case study, the economic model is developed around the probability or degree of response in each histology and a BHM has been used to analyse response, the predictive distribution could be used to estimate response in the unrepresented histologies. This assumes that the effects for the unrepresented histologies are exchangeable with the observed histologies. For Drug X, the predictive distribution for response in unrepresented histologies has a mean response probability of 57% and is highly uncertain, with a 95% CrI ranging from 1% to 100%. If estimates for the remaining parameters (e.g. quality of life and testing costs) can be sourced from the literature or generalised from the observed histologies, ICER and NHB estimates can also be estimated for unrepresented histologies.

The results shown in *Table 30* include the impact of including unrepresented histologies. To simplify the case study, we collapse all unpresented histologies into one 'unrepresented' histology category. The response probability comes from the predictive distribution from the BHM; costs and quality of life are assumed to be the same across all observed and unobserved histologies. The average testing costs for unrepresented histologies were estimated to be £14,322 per patient tested. This estimate was based on observational data on *NTRK* fusion prevalence (see *Appendix 12*).

TABLE 30 Incorporating unrepresented histologies into an estimate of population NHBs

	Per-patient level, £50,000 per QALY threshold		Population level	
Subgroup	Health forgone (ΔCost/£50,000)	NHB (ΔQALY – health forgone)	Incidence	NHB, QALYs (NMB, £)
Sarcoma	1.12	0.59	5	2.88 (144,046)
Salivary gland	0.89	0.70	2	1.56 (78,201)
IFS	0.98	0.82	27	22.35 (1,117,570)
Thyroid	1.07	0.69	6	4.32 (216,219)
Lung	1.92	−0.51	17	−8.52 (−426,230)
Melanoma	1.13	−0.09	3	−0.23 (−11,276)
Colon	1.32	−0.66	23	−15.19 (−759,374)
GIST	1.01	0.68	4	2.57 (128,728)
Cholangiocarcinoma	1.40	−0.94	0.3	−0.31 (−15,727)
Appendix	0.49	0.12	16	1.99 (99,383)
Breast	1.89	−1.28	5	−6.19 (−309,616)
Pancreas	1.89	−1.28	17	−21.78 (−1,089,034)
Unrepresented	0.97	0.15	151	22.33 (1,116,748)
Total			276	5.79 (289,638)

After taking account of the unrepresented histologies, Drug X is now estimated to be cost-effective in the overall population with positive NHBs. In this example, a histology-independent approval, including an assessment of the potential impact of unrepresented tumour sites, would result in an expected overall gain to the health system of approximately 5.79 QALYs (NMB ≈ £290,000) per year. Treating individuals with histologies that are unrepresented in the trial data is expected to result in positive NHB, given the assumptions made here. This is because of the relatively high mean response rate (57%) predicted by the BHM.

Although it may be challenging to identify data to inform benefits in unrepresented histologies, consideration to the magnitude and potential impact of these histologies should be explicitly considered.

Partial stratification: approval in a defined set of histologies

This is similar to the previous approval policy; however, in this case, the intervention is approved only for a clinically defined set of histologies, that is there is partial stratification of decision-making by histology. The relevant metric here is the pooled ICER (or pooled NHB equivalent) for the defined subset of histologies. The basis for selecting a subset of histologies can be based on theoretical and/or empirical grounds. For example, *Chapter 2*, *European Medicines Agency review of approved histology-independent indications*, highlighted comments from the SAG to the EMA about larotrectinib that appeared to differentiate the strength of the biological rationale and the available clinical evidence for several specific tumour types (e.g. IFS, salivary gland/MASC, congenital mesoblastic nephroma and GIST). For these specific tumour types, the SAG concluded that efficacy has been established in the absence of available treatments of proven efficacy in terms of convincing clinical efficacy end points and that clinical decisions to use larotrectinib were justified.

To illustrate the implications of a policy decision based on partial stratification, we assume that there is sufficient ground to consider restricting an approval decision for Drug X to only those patients with IFS, salivary gland and GISTs. Evidence for patients with congenital mesoblastic nephroma was not

available at the time of the FDA assessment; therefore, these patients are not included in the data used to inform the BHM.

As shown in *Table 31*, a decision to approve Drug X in only these three individual histologies is expected to result in an overall annual gain to the health system of 26.49 QALYs. Although partial stratification results in fewer patients receiving Drug X than in a full histology-independent approval (i.e. 33 patients annually vs. 276 patients), there would be an overall gain to the health system from a policy decision based on partial stratification. This gain is equivalent to approximately 20.7 QALYs per annum. In other words, a policy to fully approve a histology-independent product could result in an annual loss of 20.7 QALYs to the health system compared with an optimised approval decision based on a partial stratification approach.

The majority of the gains from partial stratification are achieved by avoiding the approval of Drug X in histologies with high testing costs and relatively high incidence (e.g. lung, colon, breast and pancreatic cancer), for which Drug X does not appear to be cost-effective based on current evidence. A further advantage of partial stratification over no stratification is that assumptions about unrepresented histologies can be avoided in decision-making. However, a disadvantage of partial stratification is a potential increase in monitoring costs required to prevent the use of Drug X outside its subset of approved histologies.[151]

Full stratification: approval only in histologies in which cost-effectiveness is demonstrated

This is a fully histology-dependent approval policy in which the technology is restricted for use only in those histologies in which it has been shown to be potentially cost-effective based on expected ICER/NHB estimates. Given the ICER/NHB estimates presented in *Table 29*, Drug X appears to be potentially cost-effective in the following histologies: sarcoma, salivary gland, IFS, thyroid, GIST and appendix. These are the histologies in which NHBs are greater than zero. Equivalently, they each have ICERs below £50,000 per QALY gained. Taking the sum of the NHB across each of these histologies results in an overall annual gain of 35.68 QALYs to the health system from a fully stratified approval decision for Drug X. The expected number of patients treated annually based on full stratification is estimated to be 60.

The additional value of distinguishing between different types of patients represents the VoH.[150–152] In this example, the VoH represents the difference between the NHB of a fully stratified recommendation and a histology-independent recommendation with no stratification. This difference is equivalent to 29.89 QALYs per year.

Exploring the VoH may help to inform NICE committees of the consequences of alternative policy options, in terms of both the expected number of patients who would be eligible to receive a specific new treatment and their overall consequences to the health system. Although a histology-independent

TABLE 31 Decision-making with partial stratification

	Per-patient level £50,000 per QALY threshold		Population level	
Subgroup	Health forgone (ΔCost/£50,000)	NHB, QALYs (NMB, £)	Incidence	NHB, QALYs (NMB, £)
Salivary gland	0.89	0.70 (34,800)	2	1.56 (78,200)
IFS	0.98	0.82 (40,850)	27	22.35 (1,117,600)
GIST	1.01	0.68 (34,250)	4	2.57 (128,700)
Total			33	26.49 (1,324,500)

approval might be considered appropriate on the basis that this results in an overall positive annual NHB compared with rejecting the technology, it is also important to consider the potential consequences of such an approval policy compared with a more restrictive or optimised recommendation. In this case study, there appear to be significant gains to the health system that could be achieved by an optimised recommendation. Importantly, an approval decision based on partial stratification using only three individual histologies appears to confer approximately 74% of the gains that are potentially achieved based on a full stratification policy.

Uncertainty and decision-making

Decisions about the approval of technologies were discussed in *Histology-specific incremental cost-effective ratios and overall cost-effectiveness*. However, decision-makers, such as NICE, also need to consider the risk associated with decision-making under uncertainty. Given the limitations in study design and sample size, there will always be uncertainties about the cost and health consequences associated with different treatment options. All ICERs and NHBs discussed previously will be associated with uncertainty. This means that, although the central estimate of the ICER/NHB indicates that a treatment is cost-effective, there is also a risk that the treatment is not cost-effective. For example, a treatment that meets the end-of-life criteria may have a central ICER estimate of £45,000 per QALY and, therefore, is expected to be cost-effective. However, owing to uncertainty, there may be a 40% chance that the true ICER is above £50,000 per QALY. The health losses associated with this eventuality are the risk of decision-making under uncertainty.

Uncertainties can be divided into two categories: those that arise from assumptions inherent in constructing models (structural uncertainties) and those that are a result of imprecision in parameter estimates owing to limited sample size (parameter uncertainties). Previous research has shown how uncertainties associated with imprecision can be addressed through further data collection or pricing schemes.[194,195] In this section, we will show how these approaches can be used to reduce risk in decision-making for histology-independent technologies. In addition, we show how stratified decision-making represents an additional approach to managing risk associated with uncertainty.

The consequences of uncertainty

This section introduces value of information (VOI) as a framework to quantify the health effects of uncertainty. VOI analyses can provide decision-makers with metrics to help to understand the drivers of decision uncertainty and assess alternative strategies that could be used to manage this risk. The uncertainty associated with a histology-independent decision ('no stratification') is illustrated below. The implications for partial and full stratification will be addressed in subsequent sections.

The NHB results previously reported in *Table 30* are illustrated graphically in *Figure 11*. In addition, uncertainty around the expected (mean) estimates of NHB are represented using a 95% CI. This is computed from the mean and 95% percentiles of the PSA for each histology. *Figure 11* also plots the patient-level pooled NHB. This is analogous to the pooled ICER reported in *Tables 25* and *26*. The pooled NHB is a weighted average of the NHB associated with different histologies. Weights come from the incidence of *NTRK*-positive histologies reported in *Table 30*, with a perfect screening strategy assumed.

Figure 11 shows that Drug X is expected to result in additional NHB in sarcoma, salivary, IFS, thyroid and GISTs, with the 95% CI not crossing the line of equivalence with SoC. It is also expected to be cost-effective in the appendix and in those histologies that are unrepresented in the trial, but this is uncertain. This uncertainty can be expressed in terms of the likelihood or probability that Drug X is not cost-effective compared with SoC (i.e. 47% and 39% in appendix and unrepresented cancers, respectively). For lung, melanoma, colon, cholangiocarcinoma, breast and pancreatic cancer, the model estimates that there is approximately 0% chance that Drug X is cost-effective.

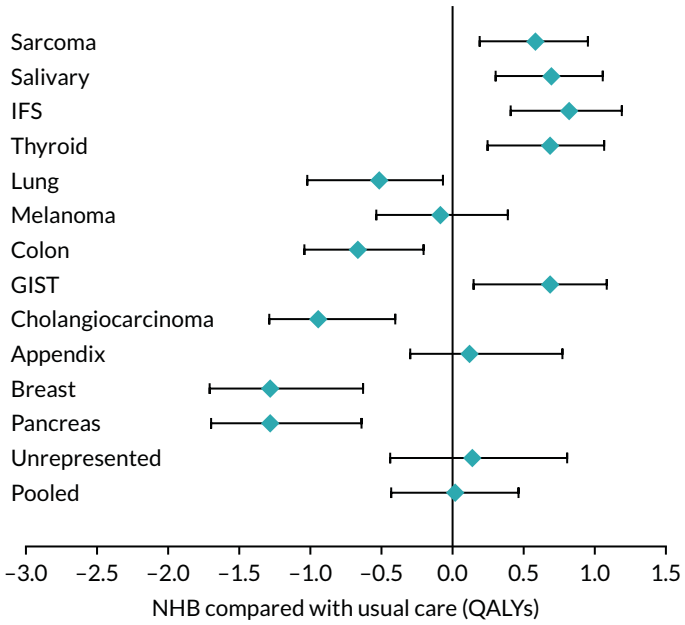

FIGURE 11 Net health benefits per person across histologies with uncertainty. Positive numbers favour the intervention (drug) compared with usual care alone.

As in the previous analysis, the pooled population represents the expected consequences of a histology-independent recommendation. Drug X is expected to result in 0.02 additional QALYs per person treated and there is a 52% chance that it is cost-effective compared with SoC. The pooled estimate relies on the relative incidence of histologies in the target population. Although uncertainty in histology incidence is not addressed quantitatively in this case study, this can be propagated through the PSA in the same manner as other uncertainties.

The health system consequences of decision-making can be better informed with reference to population health. *Figure 12* shows the population NHB for each histology and the pooled NHB. This is calculated by multiplying the per-person NHB for each group illustrated in *Figure 11* by the incidence for each group (see *Table 30*).

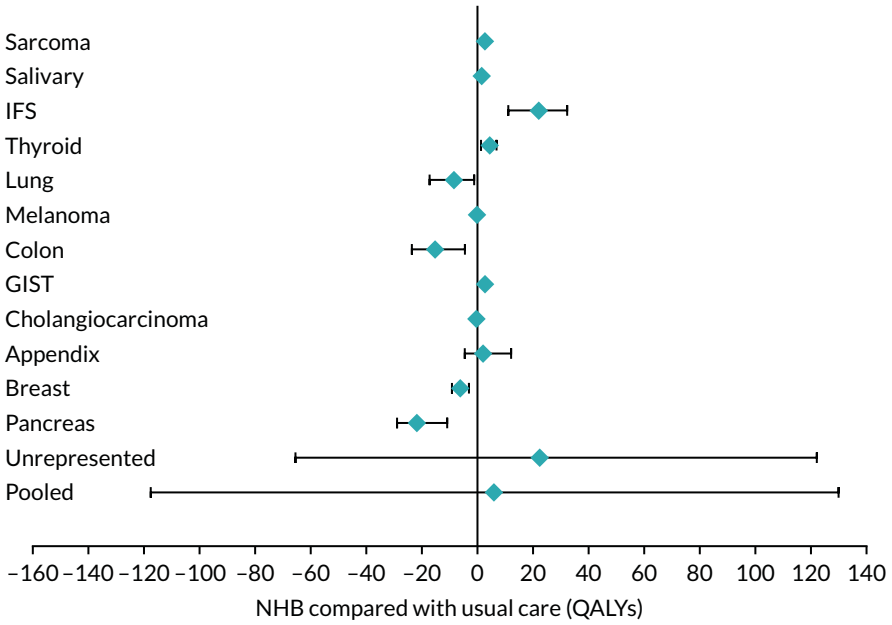

FIGURE 12 Population net health effects across histologies with uncertainty. Positive numbers favour the intervention (drug) compared with usual care alone.

Figure 12 shows that, although uncertainty in per-person NHB may be similar across histologies, the consequences of approval and uncertainty vary substantially when the size of populations are taken into account. The figure shows that for many histologies (e.g. sarcoma, salivary, melanoma and breast), the health consequences of approval and/or uncertainty are limited owing to their small population. By contrast, the health consequences associated with the unrepresented histologies are relatively large, as decisions in this group affect 151 individuals each year.

The pooled category represents the health consequences of the 'no stratification' approval policy (i.e. a histology-independent approval). A histology-independent approval is expected to result in a gain of 5.79 QALYs per year, on average (consistent with *Table 30*). However, the 95% CI indicates that this is highly uncertain, with approval potentially resulting in losses of up to 120 QALYs per year (illustrated in *Figure 12* by the lower CI, which extends to −120). The following section will describe how VOI methods can be used to quantify the health consequences of this uncertainty to help inform decision-making and approval policies.

Quantifying the health consequences of uncertainty

Histology-independent decision-making (no stratification) is concerned with making approval decisions based on pooled cost-effectiveness estimates. From *Figure 12*, Drug X is expected to provide an expected benefit of ($0.02 \times 276 \approx$) 5.79 QALYs per year at the pooled population level. However, there is uncertainty about this benefit. VOI methods can be used to quantify the health consequences of uncertainty, that is the risk associated with decision-making with current information.[193,196,197] Uncertainty matters because it means that there is a chance of making the wrong decision. Quantifying the expected health consequences of uncertainty is achieved by multiplying the chance of making a wrong decision by the health consequences of making the wrong decision. This is illustrated in *Figure 13*.

If Drug X is more cost-effective than SoC in the pooled population, there are zero health consequences of uncertainty. The tall left-hand bar in *Figure 13* shows that there is estimated to be a 52% chance that Drug X is cost-effective in the pooled population. This corresponds to a 52% chance of zero consequences of uncertainty.

Making an incorrect decision (e.g. approving Drug X when it is not cost-effective) will have health consequences. For the pooled population, there is a 48% chance that the decision to approve Drug X is

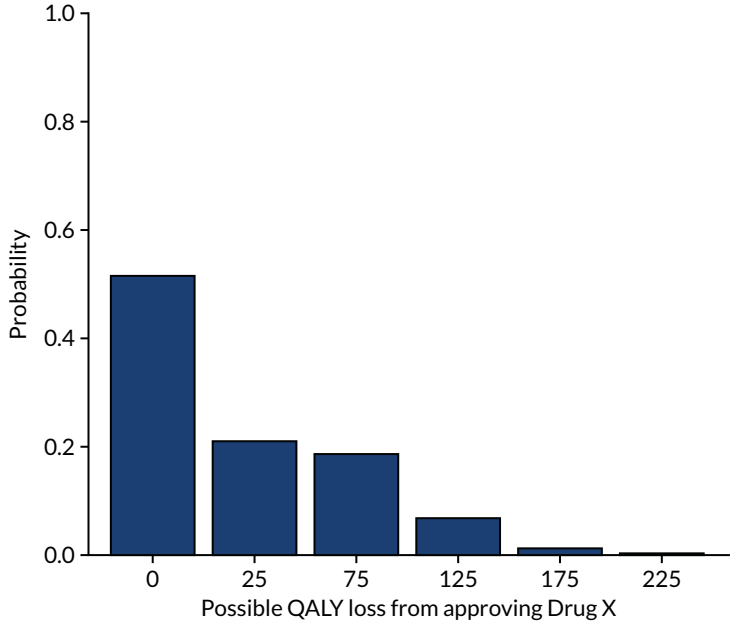

FIGURE 13 Estimating the health consequences of uncertainty.

incorrect. As shown in *Figure 13*, these health consequences are not uniform. There is a greater chance of more limited consequences than a smaller chance of greater consequences. *Figure 13* shows that there is a 21% chance of Drug X resulting in a loss of 25 QALYs per year (second bar from the left). There is a 19% chance of a loss of 75 QALYs per year (third bar from the left), and so on. The weighted average over this range of outcomes provides an estimate of the health consequences of uncertainty. This is estimated to be 29.52 QALYs per year, equivalent to approximately 0.108 QALYs per person.

This quantitative approach to the risks associated with uncertainty can be used to assess policy options that address this risk. In the following sections, we will illustrate three approaches to managing this risk: further data collection, pricing agreements and stratified decision-making.

Managing risk through further data collection

Further data collection is one approach to reduce risk associated with uncertainty. The imprecision in parameter estimates owing to limited sample size (e.g. OS) can be reduced by collecting data on these parameters.[198]

Decisions about further data collection are important because under current policy arrangements when NICE is unable to approve a technology for routine use owing to parameter uncertainties it may recommend it for inclusion into the CDF if it is eligible.[199] Topics that are eligible for the CDF are reimbursed for a time-limited duration following the development of a managed access agreement (MAA). The MAA consists of (1) a data collection agreement (DCA), which specifies the data that must be collected that could sufficiently resolve the parameter uncertainties identified by the appraisal committee, and (2) a commercial access agreement, which ensures that the technology is reimbursed at a cost-effective price during the period of the MAA. A technology remains in the CDF until the data collection agreed in the DCA is complete; it then proceeds to reappraisal and exits the fund.

The MAA covers the entire eligible population determined by the NICE guidance, which means that entry to the CDF is equivalent to an 'approval with research' decision, which is reassessed after the data collection period (usually 2 years).[199,200] The assessments required to inform the suitability of an 'approval with research' decision over 'only in research', approve and reject are covered in detail elsewhere.[197] Explicit consideration of these assessments could aid the transparency of CDF entry requirements. However, it is beyond the scope of this report to suggest reforms to CDF processes or to determine the appropriate size of the CDF budget. These issues have been commented on elsewhere and require further research.[200–202]

The aim here is to provide a framework to understand how the CDF, in its current form, can help to address the risk associated with histology-independent technologies. The intention is to demonstrate how a unified decision framework could enable CDF data collection arrangements to be considered alongside other risk reduction strategies (e.g. pricing schemes and stratified decision-making).

Decision uncertainty resolved by the Cancer Drugs Fund

Previously, the value of resolving all uncertainty was estimated to be 29.52 QALYs per year (NMB of ≈ £1.48M); therefore, this is an upper bound for the risk, which can be resolved through further research each year. However, there are many sources of uncertainty in any model, for example uncertainties in baseline risks, health-state costs and HRQoL. Different types of research will potentially be required to inform different model parameters. For example, observational survey research may be sufficient to address uncertainties about HRQoL in specific disease states, whereas randomised research may be required to resolve uncertainties in the relative effects of interventions.[198] Research on particular parameters will resolve more or less uncertainty depending on how central these parameters are to the decision between the treatment alternatives. This means that research on some parameters is more valuable than research on others.

The upper bound for the value of additional research on specific parameters (or set of parameters) can be calculated using an extension of VOI methods. These are called expected value of partial perfect information (EVPPI) methods.[197,203] To estimate the value of resolving uncertainty in a specific parameter, the EVPPI method estimates the payoff (in QALYs or GBP) from the clinical decision if the parameter of interest was known with certainty compared with the payoff if that parameter remained uncertain. The difference between these two scenarios is the EVPPI. This decomposes the overall upper bound for the value of research into the value of resolving uncertainty in specific parameters (or sets of parameters).

To illustrate the EVPPI analysis using the case study, consider the case in which only information on OS (for responders and non-responders) could be collected through CDF arrangements. This may be because of organisational or time constraints. Estimating EVPPI using the Gaussian process method suggested by Strong *et al.*,[203] the upper bound for the value of research on OS is 12.16 QALYs (NMB of ≈ £0.6M) per year. This can be compared with 29.52 QALYs per year (NMB of ≈ £1.48M), which is the value of resolving the uncertainty associated with all parameters in the model. EVPPI methods provide a more accurate assessment of the risk that can be resolved with particular data collection strategies. This same approach can be applied to any uncertainties that are parameterised in a decision model. As shown in *Tables 24* and *25*, the distribution of histologies in practice can influence the cost-effectiveness of Drug X when making histology-independent recommendations. If uncertainty about the distribution of histologies can be parameterised, EVPPI methods can be used to understand the value of research to resolve these uncertainties.

These methods can be used to help to prioritise data collection. Although the CDF financial resource constraint is softened by the expenditure control mechanism, the real resources required to co-ordinate and quality control data collection are limited.[199] In the case where high-quality data on certain parameters are challenging to collect through the CDF, EVPPI methods can be used to understand the risk that can be resolved by collecting data on these parameters. This can be used to determine (1) whether or not there is any value in collecting data on a specific parameter; (2) whether or not the benefits of the additional information are sufficient to justify the additional costs of collecting the data; and (3) whether or not other approaches, such as pricing schemes or stratification, would be more appropriate to resolve the decision risks.

The EVPPI methods are an important extension to VOI analysis in decision-making. However, EVPPI estimates are still upper bounds for the value of additional research on individual parameters. This is because EVPPI assumes that uncertainty in the parameter of interest is completely resolved, that is it is the value of research if an infinite sample size was collected. Expected value of sample information methods relax this assumption by assessing the value of commissioning research with finite sample sizes.[198,204,205]

Managing risk through pricing schemes

The NICE process allows for consideration of a variety of pricing schemes, including patient access schemes, commercial access agreements and flexible pricing.[206] These schemes can facilitate pricing arrangements, such as simple discounts or more complex 'pay-for-performance' arrangements. In this section, we illustrate the effect of a simple discount and a pay-for-performance scheme on uncertainty and the expected value of a technology.

Simple discounts have been identified in previous research as an effective approach for payers to reduce the risk of approving technologies that are not cost-effective.[194,195,200] Reducing the price of a technology that is expected to be cost-effective has two implications: (1) the value of implementing the technology will increase owing to the resources saved and (2) the risk of the technology not being cost-effective will decrease. Under the current price (£1250 per month), a histology-independent recommendation for Drug X is expected to result in 5.79 additional QALYs per year. However, owing to uncertainty in parameters, there is also a 48% chance that Drug X is not cost-effective. As shown previously, the expected health consequences of this uncertainty have been estimated to be 29.52 QALYs per year.

With a 10% simple discount (£1125 per month), the expected value of Drug X is estimated to increase to 21.4 QALYs per year. Furthermore, the risk of Drug X not being cost-effective is reduced to 42%. The potentially negative health consequences associated with the uncertainty are reduced to 23.91 QALYs per year (a reduction in risk of 5.61 QALYs). A 20% simple discount (£1000 per month) increases the expected value of Drug X to 30.04 QALYs per year and reduces the consequences of uncertainty to 21.3 QALYs per year (a reduction in risk of 8.22 QALYs).

To illustrate the use of more complex pricing schemes, we also implemented a pay-for-performance scheme. In this scenario, the undiscounted cost of Drug X (£1250 per month) is incurred only if a patient responds to treatment. This has two impacts on risk and cost-effectiveness. First, this acts in a similar manner to a price discount because the average response is expected to be approximately 60% according to the BHM (i.e. reducing the effective price by 40%). Second, the risk associated with Drug X not resulting in the expected outcomes is now shifted from the payer to the company.[194] These two impacts reduce the health consequences of uncertainty to the health system. With this pricing scheme, the expected value of Drug X increases to 51.95 QALYs per year and reduces the consequences of uncertainty (i.e. the expected risk) to 9.35 QALYs per year (a reduction in risk of 20.17 QALYs).

The examples here illustrate how alternative pricing approaches can be used to increase the expected value of a technology, as well as impacting the risk and consequences associated with uncertainty.

Managing risk through stratified decision-making

The previous discussion described how uncertainty can be addressed when making histology-independent decisions in which the technology is expected to be used across all histologies (no stratification). In this section, we discuss how to apply these same principles under partial and full stratification.

Partial stratification

The previous sections described how uncertainty and associated risk could be managed through further data collection and pricing schemes. Both assumed that the health technology would be approved for use in all histologies or none (i.e. histology-independent approval decisions). In this section, we discuss stratification as an additional approach to reducing risk in approval decisions for products with a histology-independent marketing authorisation.

In the case of partial stratification, the intervention is approved only for a clinically defined set of histologies. The relevant metric for decision-making is the pooled NHB for the subset of histologies of interest. Therefore, it is the uncertainty in this pooled NHB that is of relevance to decision-making. *Figure 14* illustrates the uncertainty in pooled NHB for the approval of Drug X in IFS, salivary gland and GISTs only.

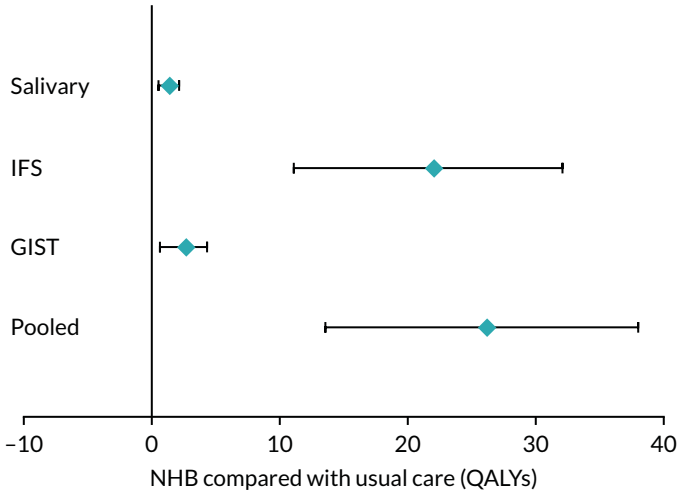

FIGURE 14 Population net health effects with uncertainty for partially stratified decision-making. Positive numbers favour the intervention (drug) compared with usual care alone.

Figure 14 shows that Drug X is expected to provide positive NHB in each of IFS, salivary gland and GISTs individually. Implementing Drug X in this subset is expected to result in approximately 26.5 additional QALYs per year over SoC (this corresponds to *Table 31*). *Figure 14* graphically represents the uncertainty in this estimate. The 95% CI for the pooled effect is far from the line of equivalence between Drug X and SoC, indicating that there is not much uncertainty in cost-effectiveness in this subset of histologies. Given the model assumptions, it is estimated that there is now a 0% risk that Drug X is not cost-effective. This means that the risk in approving Drug X has been eliminated, without the need to carry out additional research or wait for research to report. For this reason, a routine commissioning decision may be considered appropriate for this specific subset of tumour sites.

Full stratification

Under full stratification, there is the option to make different decisions for different histologies. This is a fully histology-dependent approval policy in which the technology is restricted for use only in those histologies that it has been shown to be cost-effective. *Figure 15* illustrates the population-level uncertainties in making fully stratified recommendations.

Approval in sarcoma, salivary gland, IFS, thyroid, GIST and appendix cancers is expected to provide a positive NHB for all. Approval of Drug X in the remaining histologies is expected to result in a loss of population health. *Figure 15* also shows that uncertainty about health benefits (or losses) differs across histologies. The 95% uncertainty bounds cross the line of equivalence for melanoma and appendix cancers only.

Because separate approval decisions can be made for each histology, the risk associated with decision-making should be estimated for each histology separately. The risk associated with uncertainty in each histology is reported in *Table 32*, along with the expected annual value of approving the treatment for each histology.

Table 32 shows that, of the histologies included, the largest risks are associated with decisions about appendix and melanoma histologies. This is because these two histologies have uncertainty bounds in *Figure 15* that cross the line of equivalence. Given that further research appears most valuable in these histologies, this may help to prioritise further data collection. EVPPI assessments can be applied to these histologies to understand the parameters that are driving uncertainty. For other histologies, it is clear that Drug X is cost-effective (e.g. IFS) or not cost-effective (e.g. pancreas) based on current evidence; therefore, there appears to be limited risk of making the wrong decision and little value in further research.

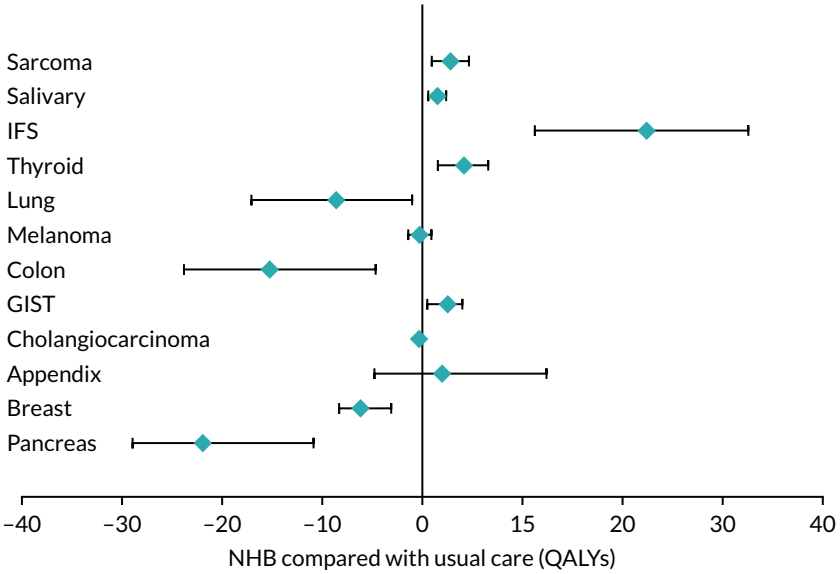

FIGURE 15 Population net health effects with uncertainty for fully stratified decision-making. Positive numbers favour the intervention (drug) compared with usual care alone.

TABLE 32 Benefits of approval and further research for fully stratified decision-making

	Population-level £50,000 per QALY threshold		
Subgroup	Incidence	Health impact of uncertainty per year, QALYs (NMB, £)	Health impact of approval per year, QALYs (NMB, £)
Sarcoma	5	0.02 (1216)	2.88 (144,046)
Salivary gland	2	0 (113)	1.56 (78,201)
IFS	27	0.01 (577)	22.35 (1,117,570)
Thyroid	6	0.01 (665)	4.32 (216,219)
Lung	17	0.03 (1398)	−8.52 (−426,230)
Melanoma	3	0.23 (9950)	−0.23 (−11,276)
Colon	23	0.02 (1045)	−15.19 (−759,374)
GIST	4	0.01 (407)	2.57 (128,728)
Cholangiocarcinoma	0	0 (2)	−0.31 (−15,727)
Appendix	16	1.1 (55,078)	1.99 (99,383)
Breast	5	0 (0)	−6.19 (−309,616)
Pancreas	17	0 (0)	−21.78 (1,089,034)
Total	125	1.41 (70,452)	

Table 32 also illustrates that the total risk associated with decision-making has reduced for stratified decision-making compared with no stratification. The expected health consequence of uncertainty was 29.52 QALYs per year for no stratification. This was zero for partial stratification and approximately 1.41 QALYs per year for full stratification (implying a reduction of 28.11 QALYs).

The change in uncertainty (as measured by VOI) from less stratification to more stratification has been called the 'dynamic value of heterogeneity' in the literature.[151] It should be noted that increasing stratification may increase or decrease the uncertainty in decision-making. When the characteristic that the treatment is being stratified by is important in explaining heterogeneity (such as histology in the case study), stratification will increase the value of implementing the treatment while reducing the risk of making an incorrect decision. This is because variability in outcomes is translated into heterogeneity. However, if a stratification characteristic contains little information to distinguish outcomes, uncertainty may increase with stratification owing to sample splitting.[151]

Comparing approaches to risk management in histology-independent technologies

When making a histology-independent approval decision, with current evidence and without any discount, Drug X appeared cost-effective based on expected values but the health consequences of uncertainty were estimated to be 29.52 QALYs per year. Three approaches to risk management were explored: further data collection, pricing schemes and stratified decision-making.

The upper bound for the value of further data collection on OS was expected to be 12.16 QALYs; this is compared with a reduction in risk of 5.61 QALYs from a 10% price discount, 8.22 QALYs from a 20% discount, 20.17 QALYs from a pay-for-performance scheme and a reduction of 28.11 QALYs from stratification.

The magnitude of uncertainty resolved through data collection will depend on which parameters can be informed by feasible research. Owing to institutional or ethics constraints, data collection may not be possible for some parameters and this places limits on this approach to risk management.

As discussed previously, the degree of uncertainty resolved through stratifying by histology will depend on the importance of histologies in explaining heterogeneity in cost-effectiveness. In cases in which cost-effectiveness does not vary significantly across histologies, the risk reduction from stratification will be lower. There may also be additional costs associated with (partially or fully) stratified recommendations, for example the costs of monitoring clinician behaviour to ensure that treatments are not being used in histologies for which they do not have approval.[150,151] In principle, this cost can be incorporated into the analysis of alternative policy options; however, reliable data to predict these costs may be difficult to find.[207]

When considering the impact of pricing schemes, the magnitude of risk reduction will depend on the pricing arrangement.[194] For simple discounts, the risk reduction will increase with the scale of the price reduction. Neither a 10% nor a 20% simple discount reduced the risk of approval as much as either further data collection or stratified decision-making in the case study. A pay-for-performance scheme reduced the risk more than further data collection, but not as much as stratified decision-making. It should be noted that, when comparing price reductions (or stratification) with data collection, it is important to take account of the fact that data collection takes time to report whereas the other risk management policies can theoretically begin immediately.

Pricing schemes and stratified decision-making can also increase the value of approving technologies in addition to addressing risk. A 10% and 20% discount increased the value of Drug X from 5.79 to 21.4 and 30.04 additional QALYs per year, respectively. Partial and full stratification increased this to 26.49 and 35.68 QALYs per year, respectively. The gain in value from stratification is a result of making more optimised decisions. This has been called the 'static value of heterogeneity' in the literature.[151] The pay-for-performance scheme increased the potential value of approval by the greatest extent. It resulted in an additional 51.95 QALYs per year from the approval of Drug X. This gain is mostly because of the substantial discount implied by the pay-for-performance scheme. Because these approaches to risk management (further data collection, pricing schemes and stratified decision-making) are not mutually exclusive, each one can be used in combination to address the risk of approving a technology that is not cost-effective.[195]

Discussion

We have illustrated a framework for decision-making that takes account of uncertainty and heterogeneity associated with histology-independent technologies. The aim was to outline assessments that can help to support NICE and CDF decision-making, both in making approval decisions and in managing risks associated with uncertainties.

It is evident that heterogeneity in the cost-effectiveness of histology-independent technologies can arise from a number of sources and that these should be explicitly considered when making decisions. Even if clinical outcomes were identical across individual histologies, differences in the costs of identification can lead to important cost-effectiveness differences between individual histologies. In situations in which the target population is expected to differ from the trial population (i.e. in terms of the distribution of histology types), explicit modelling of heterogeneity will be required to support NICE decision-making. If any histologies exist that are unrepresented in the trial population, consideration will be required to the potential costs and health consequences in unrepresented histologies along with their frequency in the target population to support a histology-independent approval.

The framework explored the health consequences associated with three different approval policies: no stratification (histology-independent approval), partial stratification and full stratification. This demonstrated the potential health gains from making stratified decisions. As discussed above, modelling the costs and health consequences associated with heterogeneity will often be required to make histology-independent decisions. This means that the assessments and assumptions required for

stratified decision-making will often be the same as those required for histology-independent decision-making. Furthermore, because partially and fully stratified decision-making allows for approval only in the subset of histologies for which there are observed data, these stratified approaches can be less dependent on strong assumptions. This is because they avoid the requirements to estimate ICERs/NHBs for unrepresented histologies.

The role of stratified decision-making was also illustrated as an approach to reducing the risk associated with uncertainty. This was compared with two other approaches to risk management: further data collection and pricing schemes.[195,196,204] This analysis showed that each approach can reduce the risk associated with uncertainty. Stratified decision-making was shown to be the most effective policy for risk reduction in the case study. The factors that determine the magnitude of uncertainty resolved by each approach were discussed and it was highlighted that these factors will differ across histology-independent technologies. The policy or combination of policies chosen in a specific scenario will depend on procedural feasibility and the characteristics of a given proposal.

Limitations of the analysis and directions for future research

A limitation of the analysis in this section is that 'unrepresented histologies' are included as a homogeneous group. In reality, there may be significant heterogeneity between different unrepresented histologies. The sections on stratified decision-making assumed that Drug X could be approved only in represented treatments. Theoretically, this need not be the case. If unrepresented histologies were not treated as a homogeneous group but were considered individually, it is likely that for some histologies Drug X would be expected to be cost-effective and for others it would not. The uncertainty surrounding each would also differ. If approval for individual unrepresented histologies was feasible, the decision uncertainty remaining after full stratification would be larger than reported in *Managing risk through stratified decision-making*. This is because the uncertainty reported for fully stratified decision-making (1.41 QALYs per year) considers uncertainty only in the represented histologies. Including uncertainty in unrepresented histologies would necessarily increase this.

For the sake of clearly illustrating the core principles of decision-making under uncertainty, other simplifying assumptions were made. Namely, one-off infrastructure costs, population prevalence and test uncertainty were not explicitly modelled; these assumptions should be relaxed in future research.[197]

One-off infrastructure costs are relevant to calculate per-person testing costs. In the case study, we have assumed a one-off testing cost of £50 per individual tested. However, testing approaches based on NGS may require large up-front investments in infrastructure. A recommended approach to incorporate capital costs, such as testing infrastructure, is to divide the one-off expenditure by the total population of patients who are expected to use the infrastructure.[197,208] For histology-independent technologies, this includes individuals across a range of histologies and over the expected lifetime for the infrastructure. This has several potential important implications for decision-making.

The first is that any stratification of approval by histology will necessarily mean that testing costs will be spread over a smaller number of patients. This will have the effect of increasing per-person testing costs when treatments are approved for subsets of histologies, reducing the expected health gains associated with stratification. Second, if reimbursement decisions are changed before the end of the assumed lifetime of the one-off infrastructure investment and some proportion of these costs are not recoverable, this has important implications for decision-making under uncertainty. The presence of significant irrecoverable costs increases the costs associated with initially implementing then subsequently removing a technology from general use. Taking account of these costs will tend to favour more conservative approaches to decision-making, which demand less uncertainty before a treatment is approved for widespread use.[197] This has implications for the CDF because MAAs stipulate approval of technologies for the entire eligible population as determined by the NICE guidance alongside research.[199] Explicit consideration of significant irrecoverable costs in this context will make the costs of inclusion into the CDF more transparent.

A third implication of investment costs is that testing infrastructure, such as NGS, may provide a basis for the use of other health technologies that use the same infrastructure. This means that the population of patients who are expected to use the infrastructure extends across all treatments and indications expected to use the infrastructure.

A further simplification of the case study was that it was assumed that the test that was used to identify eligible patients was perfect, that is it results in zero false positives and zero false negatives. The reality of testing will differ in two ways: (1) the accuracy of a test may not be perfect and will, therefore, misclassify a certain proportion of patients and (2) the false-positive and false-negative rate will be estimated with uncertainty, meaning that the rate of misclassification may not be known with certainty. For point (1), the consequences of misclassification and the analytical approaches to deal with this have been discussed in *Screening to identify eligible patients*. For point (2), if uncertainty in the false-positive and false-negative rate can be parameterised, the health consequences of this uncertainty can be managed using the same EVPPI methods as illustrated in the case study.

The case study was also built on a simplified surrogate relationship between response and survival. Survival was assumed to be determined by response, and, conditional on response or non-response, it was assumed to be homogeneous across histologies. The aim of this model was to link heterogeneity in response to heterogeneity in costs and health outcomes. However, as discussed in *Chapter 4*, the relationship between response and survival is highly uncertain, variable and may be very weak. Further research is required to better inform how surrogate outcomes, such as response, can be linked to costs and health outcomes.

Comparing approaches to risk management in histology-independent technologies compared data collection, pricing schemes and stratified decision-making as alternative approaches to manage risk and increase the health impact of decision-making. Considering the full range of options has important implications for price negotiations in histology-independent technologies. The health impacts of stratified decision-making could be used as a benchmark in negotiating discounts required for histology-independent approval. For example, to obtain a histology-independent approval, the reimbursement decision-maker could require a pricing scheme sufficient to reduce risk to the level that would exist under stratified decision-making. Any approval policy will create a specific set of incentives for research and pricing strategy.[209,210] Further research is required to understand the incentives provided by current arrangements and the potential benefits of changes to policy.

Finally, the case study focused on histology as the main source of heterogeneity. However, heterogeneity could be explored using a range of alternative characteristics and subgroups. To move from histology as the main source of heterogeneity to considering a wider range of characteristics requires an understanding of how different characteristics can be utilised and combined in different ways in decision-making.[151] How best to decide on which characteristics to utilise in decision-making and how they should interact is a complex question that requires further research. It is also important to note that the case study has focused on observable sources of heterogeneity. Inevitably, there will be unobservable sources of heterogeneity (e.g. unobserved differences between patients and/or studies) that cannot be explicitly addressed but will need to be taken into account by decision-makers when interpreting these findings.

Chapter 8 Recommendations for practice and further research

Drawing on the research findings, recommendations are provided relating to three distinct areas:

1. the types of analysis and evidence required to inform decisions regarding histology-independent drugs by NICE
2. potential changes to the NICE methods guide for TAs or additional requirements relating to histology-independent drugs
3. priorities for methodological research.

Types of analyses and evidence required to inform decisions regarding histology-independent products

Treatment effectiveness

Complex innovative study designs are increasingly used to improve the efficiency of the drug development process and to speed up regulatory approval and the access of drugs with new mechanisms of action. Adaptive basket trials are particularly suited to assess the efficacy of histology-independent drugs, although their reliance on surrogate outcomes, small sample sizes and mostly uncontrolled designs pose challenges for HTA. Adequately designed and analysed basket studies that assess the homogeneity of outcomes and allow borrowing of information across baskets, where appropriate, are recommended. In particular, the use of comparative and randomised designs and primary outcomes that can adequately predict the clinical outcomes of interest is recommended where feasible.

The potential for heterogeneity in treatment effects, either across tumour types or across other characteristics, is likely to be an important issue in the appraisal of histology-independent technologies. Careful consideration should be given to the appropriateness of the assumptions of homogeneity of treatment effects and NICE committees should expect to see an exploration of this assumption in company submissions. Bayesian hierarchical methods, which are frequently used in the analysis of basket trials, may provide a useful vehicle with which to explore any heterogeneity. Where there is evidence of heterogeneity in treatment effects and estimates of cost-effectiveness, consideration should be given to optimised recommendations.

Counterfactual

Generating a counterfactual is likely to be challenging in the context of histology-independent technologies and, in the absence of randomised evidence, it is likely that no single approach will be able to provide robust estimates of relative effectiveness. Companies developing histology-independent technologies, therefore, should be encouraged to consider several alternatives. Consideration should be given to the relative strengths and weaknesses of these alternatives when evaluating the most appropriate comparison. Evidence on the prognostic and predicative performance of the biomarkers should also be considered where possible, although it is recognised that such data may be limited at the time of submission.

Generalisability

The trial evidence available to support the approval of histology-independent technologies may differ substantially from the patients eligible for treatment in practice. Significant differences may, for example, be seen in the distribution of tumour types, positioning of the technology and subsequent treatments received. The potential for heterogeneity in treatment effects means that differences between the trial population and the eligible population may have an important impact on estimates of

cost-effectiveness. Where possible, it is important that such differences are properly accounted for. Consideration of the differences between the trial population and the eligible population should also be borne in mind when considering an appropriate counterfactual data set.

Trial evidence supporting histology-independent technologies may not offer complete coverage of the eligible population. For this reason, there may be no effectiveness evidence supporting a proportion of the eligible population. Appropriate consideration should be given to these unrepresented tumour types in the appraisal of histology-independent technologies. BHM may be able to provide an estimate of the distribution of treatment effects in this population. Data collection plans, where considered appropriate, should consider the potential for collecting evidence in unpresented tumours to better inform estimates of effect. Consideration should also be given to the fact that unrepresented tumours are not a single tumour type and may be heterogeneous. For this reason, blanket approval or collection of data in unrepresented tumours may not be appropriate.

Genomic testing

Genomic testing is likely to be integral to identify patients eligible for histology-independent therapy. Genomic testing costs may vary substantially across tumour types and, therefore, represent an important potential source of heterogeneity that should be appropriately considered. It is possible that some tumour types will not be cost-effective on the basis of genomic testing costs alone. Current NICE guidance provides that testing should be included where necessary to support a new health-care technology. Investment in universal provision of genomic testing, however, generates challenges to this model because some testing strategies may be used to identify multiple potential targets. In principle, it may, therefore, be appropriate to apportion testing costs over several technologies. It is currently unclear how this should be undertaken or who should make such judgments.

Model structure

Alternative sources of heterogeneity that may impact cost-effectiveness estimates (e.g. baseline risk, treatment effect, costs and HRQoL) should be explicitly acknowledged and appropriately reflected in any economic model. Where an economic analysis is developed using a partitioned survival analysis approach based on the direct extrapolation of TTE end points, appropriate exploration of the validity of pooling PFS and OS across prespecified subgroups and histologies (where data permit) should be undertaken (e.g. separate presentation of Kaplan–Meier curves and landmark PFS and OS rates). The process of internal and external validation should be clearly described.

The BHM approaches may be useful to support the validity of pooling PFS and OS data. Where there is substantive evidence of heterogeneity in treatment effects, consideration should be given to alternative model structures that are better able to reflect this heterogeneity, including the use of landmark response approaches. If such a model is used, evidence supporting the proposed surrogate final relationship should be presented and uncertainty surrounding the surrogate relationships included in the model should be fully characterised. Although concerns remain regarding the validity of response as a surrogate for PFS and OS, a surrogate-based modelling approach informed by predictions from meta-analyses that capture all relevant uncertainty may be preferable to the extrapolation of heavily censored and potentially confounded PFS and OS data. The BRMA approach outlined in DSU TSD 20[146] is recommended to ensure that all uncertainty around the surrogate relationship is reflected in the predictions used in the model.

Consideration of uncertainty

Uncertainty is inherent to all decisions made by NICE and other reimbursement agencies, but may be particularly acute when considering histology-independent technologies owing to the limitations of the underlying evidence base. When considering the implications of uncertainty, due consideration should be given to the scale and consequence of decisions because often populations may be small with limited consequences to the overall health system. Quantification of the consequences of uncertainty using NHB may provide an important framework to add to the assessments already routinely specified with the existing TA methods guide[4] to quantify decision uncertainty. Routine presentation of such metrics should be considered.

Potential changes to the National Institute for Health and Care Excellence methods guide for technology appraisals and/or additional requirements relating to histology-independent drugs

In practice, there may be barriers to NICE making partially or fully stratified decisions. This is because the NICE TA process has been developed primarily to make approval decisions for a technology in a defined population. However, stratified decision-making can be considered as a subgroup analysis in which histology is the relevant source of heterogeneity. The NICE methods guide recognises that costs and the capacity to benefit may differ across patients with differing characteristics and recommends that this should be explored as part of the reference case.[4] The assessments outlined in our report are consistent with and should be supplemented by the existing NICE guidance on subgroup analysis.

The quantity of subgroups that result from fully stratified decision-making could present a challenge to implementing this approach in practice. Partial stratification of approval decisions is one approach to address this. Partial stratification would reduce the number of approval decisions that must be made compared with full stratification. A transparent and accountable process for deciding which histologies should be grouped together would be required under this approach. The process for deciding which histologies should be grouped together could be usefully informed by the criteria for defining subgroups in the NICE methods guide. According to the current process, subgroups should be based on the expectation of 'differential clinical or cost-effectiveness, biologically plausible mechanisms, social characteristics or other clearly justified factors' (© NICE 2013. *Guide to the Methods of Technology Appraisal*. Available at: www.nice.org.uk/process/pmg9/chapter/foreword. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication).[4] The relevant subgroups should be defined at the scoping stage but with the possibility of subgroup identification later in the process. This same process may be appropriate to define which histologies should be grouped together to make partially stratified approval decisions.

A further issue for NICE methods and processes concerns the approval of a histology-independent treatment in histologies that are not included in the main clinical studies. This could be considered as a specific case of a more general problem concerning the approval of treatments in populations for which there is limited or no direct evidence. This problem is faced in different forms, two of which are outlined here to provide additional context for approval decisions covering unrepresented histologies. The first scenario pertains to making decisions about treatments using unrepresentative data. For example, approval is commonly granted for populations that are only imperfectly represented in trial data. This is the problem of external validity and is common with randomised trial data because clinical trials tend to be conducted populations that differ from the population of interest.[211] The second scenario is using a technology in new indications for which there are no data. For example, pembrolizumab has been submitted for approval in a range of indications, including squamous NSCLC, urothelial cancer, and head and neck cancer, among others.[212–214] In this case, approval may not be granted for a new indication unless there is direct evidence in the population of interest. The approval in unrepresented histologies for histology-independent technologies represents a space between these two scenarios. Approval decisions for treatments for use in unrepresented histologies will depend on context; in some cases it will be more similar to approving in a slightly different population and in others it will be more analogous to approving in a completely new indication.

Assessments of heterogeneity in survival outcomes at the point of initial marketing authorisation may be challenging owing to data immaturity and potential confounding, unless these are more explicitly linked to a surrogate outcome (e.g. response and DoR) for which more robust assessments of heterogeneity may be feasible. Although BHM approaches could in theory be explored in the context of TTE end points (PFS, OS), the small numbers, potential for greater heterogeneity, high censoring and potential confounding remain important obstacles. However, many of the challenges associated

with immaturity in TTE end points and the potential confounding in uncontrolled Phase II studies are not restricted to histology-independent appraisals. Our review of NICE TAs for products approved with ORR as the primary end point identified a potential disconnect between the regulators' acceptance of surrogate end points and the limited use of surrogate relationships in the corresponding NICE appraisals. Although this disconnect may reflect legitimate concerns regarding the reliability of ORR and CR as surrogates for PFS or OS, we recommend that exploration of the surrogate relationships between response-based outcomes (ORR and DoR) should be more routinely considered in economic modelling to help to inform and/or validate longer-term extrapolations of PFS and OS owing to the likely immaturity of these end points. NICE will need to consider whether or not their existing methods guide needs to be more explicit about the challenges of uncontrolled Phase II studies and whether or not more specific guidance is required concerning the role and use of surrogate end points in these circumstances.

The presentation of the scale of the consequences of heterogeneity and decision uncertainty using population NHB may provide an important additional approach to the assessments already routinely specified with the existing TA methods guide. Similar arguments have been made in the context of regenerative medicines and cell therapies.[194] As part of their ongoing methods review, NICE could consider whether or not the types of metrics presented in this report should be routinely requested within company submissions.

Priorities for future methodological research

Methods were suggested that allowed for potential sources of heterogeneity of effect across tumour type or other patient characteristics to be accounted for, while still allowing some degree of borrowing of strength when estimating treatment effectiveness. However, the estimation of the level of heterogeneity can be poor when evidence is sparse. Approaches for considering external evidence and expert opinion to construct an informative prior distribution for the heterogeneity parameter may be an area for further research.

Even if the heterogeneity parameter can be well estimated, it is unclear what degree of borrowing should be allowed when there is evidence of a high or very high level of heterogeneity. In particular, the implications of borrowing strength across treatment effects in the presence of very high heterogeneity and consequences for uncertainty in decision-making should be researched.

So far, methods, such as the BHM, that allow borrowing of information have mainly been applied to response end points. Their extension to TTE end points and potential for adjustment for known prognostic factors and other confounders would be an interesting area for further research. In addition, further research should also consider the application of BHM approaches to surrogate relationships to determine the validity of borrowing across different subgroups and drug classes.

Given the increasing use of uncontrolled Phase II studies to support initial regulatory approval based on surrogate end points, further methodological research is required to determine the basis for selecting between alternative surrogate end points for HTA assessments and, specifically, the appropriate basis for selecting specific landmark response and survival time points.

Given the importance of testing costs as a source of heterogeneity and the lack of a clear consensus on the appropriate basis for apportioning costs between current and future targets, further methodological research should more fully establish how these costs should be appropriately included in future NICE appraisals.

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Data-sharing statement

The report is based on an assessment of a hypothetical case study and, therefore, the data generated are not suitable for sharing beyond that contained within the report. Further information can be obtained from the corresponding author.

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Appendix 1 List of regulatory sources

- Workshop on site and histology-independent indications in oncology.[215]
- Workshop on single-arm studies in oncology.[216]
- Developing targeted therapies in low-frequency molecular subsets of a disease guidance for industry.[217]
- Master protocols: efficient clinical trial design strategies to expedite development of oncology drugs and biologics guidance for industry.[218]
- Guidance for industry-expedited programmes for serious conditions – drugs and biologics.[219]
- Table of surrogate end points that were the basis of drug approval or licensure.[220]
- Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.[221]
- Tissue agnostic therapies in oncology. Regulatory considerations for orphan drug designation.[222]
- Essential considerations for successful qualification of novel methodologies.[223]
- Scientific guidelines on biostatistics (e.g. investigation of subgroups in clinical trials, multiplicity issues in clinical trials, extrapolation of efficacy and safety in medicine development, methodological issues in confirmatory clinical trials planned with an adaptive design).[224]
- Predictive biomarker-based assay development in the context of drug development and lifecycle.[225]
- Guideline on the evaluation of anticancer medicinal products in man.[226]
- Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man.[227]

Appendix 2 Summary of trials

		Clinical evidence			
Product	**Indications**	**Study**	**Clinical outcomes**	**Study design**	**Patient population**
Merestinib (Eli Lilly, Indianapolis, IN, USA)	Solid tumours	NCT02920996	Primary: 1. ORR (up to 2 years) (*MET* cohort) Secondary: 1. OS rate (up to 2 years) (*MET* cohort) 2. PFS rate (2 years) (*MET* cohort) 3. DoR (up to 2 years) (*MET* cohort) 4. Safety (2 years) (all participants)	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 25$ • Allocation approach: non-randomised • Study start: 11 November 2016 • Estimated primary completion: October 2020 • Estimated study completion: March 2024	NSCLC with *MET* exon 14 mutation or solid tumours with a *NTRK* rearrangement
Avelumab (Bavencio, Merck Group, Darmstadt, Germany and Pfizer, New York City, NY, USA) plus talazoparib (Talzenna, Pfizer, New York City, NY, USA)	Locally advanced (primary or recurrent) or metastatic solid tumours	NCT03330405	Primary: 1. Safety (28 days) 2. Overall response (24 months) Secondary: 1. Pharmacokinetics (15 days) 2. Immunogenicity (15 days) 3. Overall response (24 months) 4. PSA or CA-125 tumour marker (24 months) 5. PD-L1 levels (24 months) 6. Time to tumour response (24 months) 7. DoR (24 months) 8. PFS (24 months) 9. OS (24 months) 10. PSA response (24 months)	• Design: Phase Ib/II (separate cohorts specified) • Estimated enrolment: $n = 242$ • Allocation approach: non-randomised • Study start: 19 October 2017 • Estimated primary completion: 28 March 2020 • Estimated study completion: 28 March 2020	Patients with locally advanced (primary or recurrent) or metastatic solid tumours, including NSCLC, triple negative breast cancer, hormone receptor positive (HR+) breast cancer, recurrent platinum sensitive ovarian cancer, urothelial cancer and castration resistant prostate cancer

Product	Indications	Clinical evidence			
		Study	Clinical outcomes	Study design	Patient population
	Locally advanced or metastatic *RAS*-mutant solid tumours	NCT03637491	Primary: 1. Safety (28 days) 2. Confirmed objective response (24 months) Secondary: 1. Pharmacokinetics (12 months) 2. Objective response (24 months) 3. Time to tumour response (24 months) 4. DoR (24 months) 5. OS (24 months) 6. PFS (24 months) 7. Pharmacokinetics (3 months) 8. Biomarker levels (PD-L1, tumour mutational burden and DNA damage repair)	• Design: Phase Ib/II • Estimated enrolment: $n = 127$ • Allocation approach: randomised • Study start: 15 August 2018 • Estimated primary completion: 1 May 2022 • Estimated study completion: 7 November 2022	Patients with locally advanced or metastatic *KRAS*- or *NRAS*-mutant NSCLC, pancreatic ductal adenocarcinoma or other *KRAS*- or *NRAS*-mutant solid tumours
	Solid tumours with a *BRCA* or *ATM* defect	NCT03565991	Primary: 1. Confirmed objective response (24 months) Secondary: 1. Confirmed objective response by the investigator (24 months) 2. Time to tumour response (24 months) 3. DoR (24 months) 4. PFS (24 months) 5. OS (24 months) 6. PSA and CA-125 response (24 months) 7. Circulating tumour cell level 8. Pharmacokinetics (up to 24 months) 9. Immunogenicity (up to 24 months)	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 200$ • Allocation approach: non-randomised • Study start: 18 June 2018 • Estimated primary completion: 8 March 2021 • Estimated study completion: 2 December 2022	Patients with locally advanced or metastatic solid tumours with a *BRCA* or *ATM* defect

		Clinical evidence			
Product	**Indications**	**Study**	**Clinical outcomes**	**Study design**	**Patient population**
LOXO-195 (Bayer, Leverkusen, Germany)	Solid tumours	NCT03215511	Primary: 1. MTD 2. Best overall response (up to 2 years) Secondary: 1. Safety (up to 24 months) 2. Overall response (24 months) 3. Pharmacokinetics (5 months) 4. DoR (up to 24 months) 5. PFS (up to 24 months) 6. OS (up to 24 months) 7. Clinical benefit rate (up to 24 months)	• Design: Phase I/II (separate cohorts specified) • Estimated enrolment: $n = 93$ • Allocation approach: non-randomised • Study start: 10 July 2017 • Estimated primary completion: August 2019 • Estimated study completion: 18 May 2026	Patients with unresectable or metastatic solid tumours and progressed or intolerant to prior TRK inhibitor
TPX-0005 (TP Therapeutics, Inc., San Diego, CA, USA)	Advanced solid tumours harbouring *ALK*, *ROS1*, or *NTRK1–3* rearrangements	NCT03093116	Primary: 1. Maximum tolerated dose (28 days of first dose) 2. Recommended Phase 2 dose (28 days of first dose) 3. ORR (2–3 months after treatment start) Secondary: 1. Effect of food on AUC (2–3 months after treatment start) 2. TTR (3 years) 3. DoR (3 years) 4. CBR (3 years) 5. PFS (3 years) 6. OS (3 years) 7. Intracranial ORR (3 years) 8. CNS PFS (3 years)	• Design: Phase I/II (separate cohorts specified) • Estimated enrolment: $n = 450$ • Allocation approach: non-randomised • Study start date: 27 February 2017 • Estimated primary completion date: January 2021 • Estimated study completion date: December 2021	Patients aged $\geq$ 18 years with histologically or cytologically confirmed locally advanced or metastatic solid tumour (including NHL) harbouring *ALK*, *ROS1*, *NTRK1–3* gene rearrangement

Product	Indications	Clinical evidence			
		Study	Clinical outcomes	Study design	Patient population
Sunitinib (Sutent, Pfizer, New York City, NY, USA)	Refractory solid tumours	NCT02691793	Primary: 1. PFS (24 months) Secondary: 1. ORR (24 months) 2. TTP (24 months) 3. OS (24 months) 4. Number of subjects with AE (24 months)	• Design: Phase IV • Estimated enrolment: $n = 25$ • Allocation approach: non-randomised • Study start date: 20 November 2017 • Estimated primary completion: December 2018 • Estimated study completion: December 2018	Patients aged $\geq$ 19 years with *RET* fusion positive or *FGFR2* fusion/other *FGFR* mutation refractory solid tumour and/or specific sensitivity to Sunitinib by Avatar scan that has progressed following standard therapy or that has not responded to standard therapy or for which there is no standard therapy
	Advanced rare tumours	NCT01396408	Primary: 1. OR (every 4 weeks) Secondary: 1. DoR/TTP/PFS/OS (48 months) 2. Translational research (48 months) 3. Safety (daily up to 4 weeks after treatment)	• Design: Phase II • Estimated enrolment: $n = 137$ • Allocation approach: non-randomised • Study start date: 14 July 2011 • Primary completion date: July 2015 • Study completion date: December 2019	Patients aged $\geq$ 16 years with histologically or cytologically confirmed advanced rare tumours: • vascular sarcomas • clear cell ovary carcinomas • thyroid carcinoma • neuro-endocrine tumours • adrenocorticocarcinoma • thymic carcinoma • hepatocellular carcinoma
Olaparib	Advanced (unresectable and/or metastatic) cancers	NCT03742895	Primary: 1. ORR (up to 53 months) Secondary: 1. DoR (up to 53 months) 2. OS (up to 53 months) 3. PFS (up to 53 months) 4. AEs (up to 53 months) 5. Time to earliest progression by cancer antigen-125 (up to 53 months)	• Design: Phase II • Estimated enrolment: $n = 370$ • Allocation approach: non-randomised • Study start date: 12 December 2018 • Primary completion date: 30 April 2023 • Study completion date: 30 April 2023	Patients aged $\geq$ 18 years with multiple types of advanced cancer (unresectable and/or metastatic) that (1) have progressed or been intolerant to SoC therapy, and (2) are positive for homologous recombination repair mutation or homologous recombination deficiency

Product	Indications	Clinical evidence			
		Study	Clinical outcomes	Study design	Patient population
	Advanced solid tumours, NHL or histiocytic disorders with defects in DNA damage repair genes	NCT03233204	Primary: 1. ORR (up to 4 years) Secondary: 1. PFS (up to 4 years) 2. Toxicity (up to 4 years) 3. PK (up to 4 years) Other: 1. Change in tumour genomic profile (up to 4 years)	• Design: Phase II • Estimated enrolment: $n = 49$ • Allocation approach: non-randomised • Study start date: 24 July 2017 • Estimated primary completion date: 30 September 2024 • Estimated study completion date: 30 September 2024	Patients aged 1–21 years with solid tumours, NHL or histiocytic disorders with defects in DNA damage repair genes that have spread to other places in the body and have come back or do not respond to treatment
	Glioma, cholangiocarcinoma or solid tumours with *IDH1* or *IDH2* mutations	NCT03212274	Primary: 1. ORR (up to completion of course eight) Secondary: 1. PFS (up to 1 year) 2. AE (up to 1 year)	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 145$ • Allocation approach: non-randomised • Study start date: 30 March 2018 • Primary completion date: 31 July 2019 • Study completion date: 31 July 2019	Patients aged $\geq$ 18 years diagnosed with a glioma, cholangiocarcinoma or other solid malignant tumour that has progressed despite standard therapy, or for which no effective standard therapy exists, with biopsy-confirmed evidence of an *IDH1* or *IDH2* mutation associated with neomorphic activity of the encoded proteins. Only specific mutations that lead to a neomorphic phenotype will be eligible for enrolment and include *IDH1* (R132V, R132G, R132S, R132L, R132C and R132H) and *IDH2* (R140W, R140L, R140Q, R172W, R172G, R172S, R172M and R172K)

Product	Indications	Clinical evidence			
		Study	**Clinical outcomes**	**Study design**	**Patient population**
	Advanced cancer with a confirmed *BRCA1* and/or *BRCA2* mutation	NCT01078662	Primary: 1. Tumour response rate (maximum up to 29 months) Secondary: 1. ORR (up to 29 months) 2. PFS (up to 29 months) 3. OS (up to 29 months) 4. OS (12 months) 5. DoR (up to 29 months) 6. Disease control rate at week 16	• Design: Phase II • Estimated enrolment: $n = 299$ • Allocation approach: non-randomised • Study start date: 21 February 2010 • Primary completion date: 31 July 2012 • Study completion date: 31 December 2019	Patients aged ≥ 18 years with malignant solid tumours for which no standard treatment exists and with confirmed documented deleterious or suspected deleterious *BRCA* mutation (ovarian, breast, prostate, pancreatic, advanced tumours)
	Patients with tumours harbouring damaging mutations in homologous DNA repair genes or mutations, such as *ATM*, *CHK2*, *MRN (MRE11/NBS1/RAD50)*, *CDKN2A/B* and *APOBEC*	NCT02576444	Primary: 1. ORR (change from baseline to 16 weeks)	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 64$ • Allocation approach: non-randomised • Study start date: November 2015 • Primary completion date: March 2020 • Study completion date: March 2020	Patients aged ≥ 18 years with histologically documented metastatic cancer (not hematologic malignancies)
	Relapsed or refractory tumour	NCT02813135	Primary: 1. ORR (56 days) 2. TTP (56 days)	• Phase I/II basket • Estimated enrolment: $n = 397$ • Allocation approach: non-randomised • Study start date: 3 August 2016 • Estimated primary completion: January 2022 • Estimated study completion: January 2022	Patients aged < 18 years with haematological or solid tumour malignancy that has progressed despite standard therapy, or for which no effective standard therapy exists

Product	Indications	Clinical evidence			
		Study	Clinical outcomes	Study design	Patient population
	Advanced cancer with a tumour that harbours a genomic variant known to be a drug target or to predict sensitivity to a drug	NCT02693535	Primary: 1. ORR (at 16 weeks of treatment) Secondary: 1. OS (up to 3 years)	• Phase II (separate cohorts specified) • Estimated enrolment: $n = 2980$ • Allocation approach: non-randomised • Study start date: March 2016 • Estimated primary completion: December 2021	Patients aged 12 years with histologically proven locally advanced or metastatic solid tumour, multiple myeloma or B-cell NHL who are no longer benefiting from standard anticancer treatment or for whom, in the opinion of the treating physician, no such treatment is available or indicated
	Relapsed or refractory advanced solid tumours, NHLs, or histiocytic disorders	NCT03155620	Primary: 1. ORR (up to 4 years) Secondary: 1. Safety (up to 4 years) 2. PFS (up to 4 years) 3. PK (up to 4 years) Other: 1. Genomics (up to 4 years)	Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 1000$ • Allocation approach: non-randomised • Study start date: 24 July 2017 • Estimated primary completion date: 30 September 2027 • Estimated study completion date: 30 September 2027	Paediatric patients with solid tumours, NHLs or histiocytic disorders that have progressed following at least one line of standard systemic therapy and/or for which no standard treatment exists that has been shown to prolong survival
	Cancers of unknown primary site	NCT03498521	Primary: 1. PFS (up to 48 months) Secondary: 1. OS (up to 48 months) 2. ORR 3. Duration of benefit (up to 48 months) 4. AE (up to 48 months)	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 790$ • Allocation approach: randomised • Study start date: 10 July 2018 • Estimated primary completion: 25 June 2021 • Estimated study completion: 25 June 2022	Patients aged $\geq$ 18 years with histologically confirmed cancer of unknown primary site (non-specific subset) in accordance with criteria from ESMO, version 1, who have achieved disease control after three cycles of first-line platinum doublet induction chemotherapy

Product	Indications	Clinical evidence			
		Study	Clinical outcomes	Study design	Patient population
	NHL, multiple myeloma and advanced solid tumours	NCT03297606	Primary: 1. ORR (4 years) Secondary: 1. AE (up to 4 years) 2. PFS (up to 4 years)	• Design: Phase II basket • Estimated enrolment: $n = 720$ • Allocation approach: non-randomised	Patients aged ≥ 18 years with a histologically proven incurable metastatic solid tumour (excluding primary brain tumours), multiple myeloma or B-cell NHL (excluding CLL, SLL and HCL), for whom there is no standard treatment known to prolong life or who have refused such treatment
	Refractory solid tumours	NCT03239015	Primary: 1. ORR (2 months) Secondary: 1. PFS (2 months) 2. OS (1 month) 3. AE (1 month)	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 60$ • Allocation approach: non-randomised • Study start date: 1 January 2017 • Estimated primary completion 30 June 2018 • Estimated study completion: 31 December 2019	Patients aged 18–75 years with malignant solid tumours diagnosed histologically. Common solid tumour patients that have no standard choice after multiple lines of therapy; rare solid tumour patients that did not have any standard recommended treatment
	Advanced solid tumours	NCT02029001	Primary: 1. Induction progression-free rate 2. PFS (up to 36 months) Secondary: 1. ORR (over induction period) 2. OS 3. QoL (QLQ-C30) 4. Safety Other: 1. DoR 2. Cost-effectiveness	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 560$ • Allocation approach: randomised • Study start date: March 2014 • Primary completion date: January 2020 • Study completion date: October 2022	Patients aged ≥ 18 years with histologically or cytologically confirmed diagnosis of metastatic or locally advanced and unresectable solid tumour of any type, not amenable to curative treatment. Concerning primitive tumours of the CNS, all histological types of malignant tumours (including parenchymal and meningeal tumours) are eligible

		Clinical evidence			
Product	**Indications**	**Study**	**Clinical outcomes**	**Study design**	**Patient population**
	Advanced solid tumour, multiple myeloma or NHL	NCT02925234	Primary: 1. Per cent of patients treated based on molecular profile (6 months after treatment initiation) 2. Objective tumour response (6 months) 3. Stable disease (6 months) 4. AE ≥ G3 (6 months) Secondary: 1. PFS (up to 1 year) 2. OS (up to 1 year) 3. Duration of treatment (6 months)	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 400$ • Allocation approach: non-randomised • Study start date: August 2016 • Estimated primary completion: August 2019 • Estimated study completion: December 2019	Patients aged ≥ 18 years with a histologically proven locally advanced or metastatic solid tumour, multiple myeloma or B-cell NHL who are no longer benefiting from standard anticancer treatment or for whom no such treatment is available or indicated
LOXO-292 (Bayer, Leverkusen, Germany)	Advanced solid tumours, *RET* fusion-positive solid tumours and medullary thyroid cancer	NCT03157128	Primary: 1. Dosage 2. ORR (up to 2 years) Secondary: 1. AE (2 years) 2. ORR (2 years) 3. ORR/DoR/CBR/PFS/OS (2 years) Other: 1. Genomics 2. HRQoL (QLQ-C30)	• Design: Phase I/II • Estimated enrolment: $n = 870$ • Allocation approach: non-randomised • Study start date: 9 May 2017 • Estimated primary completion date: August 2019 • Estimated study completion date: December 2019	Patients aged ≥ 12 years with advanced solid tumours, including *RET* fusion-positive solid tumours, medullary thyroid cancer and other tumours with *RET* activation

Product	Indications	Clinical evidence			
		Study	Clinical outcomes	Study design	Patient population
Epacadostat (Merck Group, Darmstadt, Germany and Incyte, Wilmington, DE, USA) with pembrolizumab	Advanced or metastatic solid tumours	NCT03085914	Primary: 1. Phase 1 – Safety and tolerability (up to 27 months) 2. Phase 2 – ORR (up to 24 months) Secondary: 1. Phase 1 – ORR (up to 24 months) 2. Phase 2 – safety and tolerability (up to 27 months) 3. DoR (up to 24 months) 4. PFS (up to 24 months)	• Design: Phase I/II (separate cohorts specified) • Estimated enrolment: $n = 70$ participants • Allocation approach: non-randomised • Study start date: 2 May 2017 • Estimated primary completion date: October 2019 • Estimated study completion date: January 2020	Patients aged ≥ 18 years with histologically or cytologically confirmed diagnosis of selected advanced or metastatic solid tumours
	Advanced or metastatic malignancies	NCT03277352	Primary: 1. Phase 1 – AE (up to 18 months) 2. Phase 2 – ORR/CRR (up to 18 months) Secondary: 1. Disease control rate (18 months) 2. DoR (18 months) 3. Duration of disease control (18 months) 4. PFS (18 months) 5. OS (at 1 and 2 years)	• Design: Phase I/II • Estimated enrolment: $n = 10$ participants • Allocation approach: non-randomised • Study start date: 21 November 2017 • Estimated primary completion date: March 2020 • Estimated study completion date: May 2020	Patients aged ≥ 18 years with locally advanced or metastatic disease; locally advanced disease must not be amenable to resection with curative intent
	Advanced solid tumours	NCT02959437	Primary: 1. Phase I – AE (up to 18 months) 2. Phase II – ORR (up to 18 months) Secondary: 1. Phase I ORR 2. Phase II AE 3. PFS (up to 18 months) 4. DoR (up to 18 months)	• Design: Phase I/II (separate cohorts specified) • Estimated enrolment: $n = 70$ • Allocation approach: non-randomised • Study start date: 26 January 2017 • Estimated primary completion date: 15 February 2019 • Estimated study completion date: 9 July 2020	Patients aged ≥ 18 years with histologically or cytologically confirmed advanced or metastatic solid tumours who have failed prior standard therapy (disease progression, subject refusal or intolerance is also allowable). Part 1 is a dose-escalation assessment to evaluate the safety and tolerability of the combination

		Clinical evidence			
Product	**Indications**	**Study**	**Clinical outcomes**	**Study design**	**Patient population**
					therapies. Once the recommended doses have been determined, subjects with previously treated NSCLC, microsatellite-stable CRC, head and neck squamous cell carcinoma, urothelial carcinoma, and melanoma will be enrolled into expansion cohorts in part 2
Durvalumab (Infinzi, AstraZeneca, Cambridge, UK) with tremelimumab	Advanced solid and haematological cancers	NCT03837899	Primary: 1. Recommended Phase II dose in patients receiving chemotherapy (15 months) 2. Safety and tolerability (up to 4 years) 3. ORR (up to 4 years) Secondary: 1. PK (15 months)	• Design: Phase I/II • Estimated enrolment: $n = 158$ participants • Allocation approach: non-randomised • Study start date: 7 March 2019 • Estimated primary completion date: 18 October 2021 • Estimated study completion date: 20 March 2023	Paediatric patients (up to 17 years) with solid tumours, which must have progressed or be refractory to standard therapies
	Advanced rare solid tumours	NCT02938793	Primary: 1. Antitumour activity (24 months) 2. AEs (24 months) Secondary: 1. Expression of PD-1	• Design: Phase II • Estimated enrolment: $n = 50$ • Allocation approach: non-randomised • Study start date: 1 December 2016 • Estimated primary completion date: 28 February 2020 • Estimated study completion date: 31 December 2021	Adult patients with a diagnosis of a rare advanced solid malignancy meeting EORTC criteria. Subjects must have failed or been ineligible for standard treatment options, if available

Product	Indications	Clinical evidence			
		Study	Clinical outcomes	Study design	Patient population
	Advanced malignancies	NCT02978482	Primary: 1. Plasma concentration 2. AEs 3. ORR (12 months after last patient is dosed or withdrawn, or study is discontinued) Secondary: 1. Anti-drug antibody 2. CR/PR/stable disease/progressive disease (6 months after last patient is dosed) 3. OS (12 months after last evaluable patient is first dosed)	• Phase I/II (separate cohorts specified) • Estimated enrolment: $n = 26$ • Allocation approach: non-randomised • Study start date: 1 December 2016 • Primary completion date: 28 July 2018 • Study completion date: 13 May 2019	Chinese adult patients with histologically or cytologically confirmed advanced and/or metastatic solid tumours other than HCC, refractory or intolerable to existing standard of treatment
	Advanced solid malignancies	NCT03084471	Primary: 1. Safety: AEs Secondary: 1. Safety: treatment-related adverse events and treatment discontinued/interrupted 2. OS (up to 5 years following date of first patient initiation)	• Phase I/II • Estimated enrolment: $n = 1200$ • Allocation approach: non-randomised • Study start date: 17 April 2017 • Estimated primary completion date: 26 March 2023 • Estimated study completion date: 26 March 2023	Adult patients with a life expectancy of $\geq$ 12 weeks and no prior exposure to anti-PD-1 or anti-PD-L-1
	Somatically hyper-mutated recurrent solid tumours	NCT03911557	Primary: 1. TTP ratio (2 years) Secondary: 1. PFS (2 years)	• Phase II basket • Estimated enrolment: $n = 48$ • Allocation approach: non-randomised • Estimated study start date: May 2019 • Estimated primary completion date: June 2023 • Estimated study completion date: June 2024	Adult patients with relapsed/refractory solid tumour patients (not previously treated with anti-PD-1/PD-L1 or anti-CTLA-4 immunotherapy), whose tumours expressed a high or moderate tumour mutational burden

		Clinical evidence			
Product	**Indications**	**Study**	**Clinical outcomes**	**Study design**	**Patient population**
	Advanced rare tumours	NCT02879162	Primary: 1. ORR (48 months) Secondary: 1. AEs 2. TTP (48 months) 3. PFS (38 months) 4. Response duration (48 months)	• Design: Phase II • Estimated enrolment: $n = 160$ • Allocation approach: non-randomised • Study start date: 19 October 2016 • Estimated primary completion date: August 2020 • Estimated study completion date: December 2020	Patients aged $\geq$ 16 years with histologically and/or cytologically confirmed cancer that is advanced/metastatic/ recurrent or unresectable and for which no curative therapy exists. The list includes salivary carcinoma; carcinoma of unknown primary site with tumour infiltrating lymphocytes and/or expressing PD-L1; mucosal melanoma; acral melanoma; osteosarcoma; undifferentiated pleomorphic sarcoma; clear cell carcinoma of the ovary; and squamous cell carcinoma of the anal canal
BLU-667 (Roche, Basel, Switzerland)	Solid tumours	NCT03037385 (EudraCT 2016–004390–41)	Primary: 1. Tolerability (12 months) 2. Safety (24 months) 3. ORR (up to 2 years) Secondary: 1. DoR, PFS and OS (up to 2 years) 2. *RET* gene status and correlation between *RET* gene status and ORR, DoR and DCR (up to 2 years) 3. Pharmacokinetics (4 months) 4. Pharmacodynamics (12 months)	• Design: Phase I/II (separate cohorts specified) • Estimated enrolment: $n = 360$ • Allocation approach: non-randomised • Study start: 15 December 2015 • Estimated primary completion: 28 August 2023 • Estimated study completion: 28 August 2023	Enrolling patients with medullary thyroid cancer, *RET*-altered NSCLC and other *RET*-altered solid tumours

Product	Indications	Clinical evidence			
		Study	Clinical outcomes	Study design	Patient population
Atezolizumab (Tecentriq, Roche, Basel, Switzerland)	Solid tumours	NCT02458638	Primary: 1. NPR (18 weeks) Secondary: 1. NPR (24 weeks) 2. ORR (24 weeks) 3. BOR (24 weeks) 4. DoR (24 weeks) 5. PFS (24 weeks) 6. TTP (24 weeks) 7. OS (24 weeks) 8. Safety (24 weeks)	• Design: Phase II • Estimated enrolment: $n = 477$ • Allocation approach: non-randomised • Study start: 15 December 2015 • Estimated primary completion: 14 April 2018 • Estimated study completion: 13 December 2019	Enrolling adults patients with advanced solid tumours who have received at least one line of prior systemic therapy or for whom no alternative therapy to prolong survival exists
Cobimetinib (Cotellic, Roche, Basel, Switzerland)	Solid tumours	NCT02639546	Primary: 1. Safety (1 month) 2. Dosing (1 month) 3. Pharmacokinetics (12 months) 4. Percentage of patients with OR (6.75 years) 5. PFS (6.75 years) Secondary: 1. DoR (up to 6.75 years) 2. OS (up to 6.75 years)	• Design: Phase I/II • Estimated enrolment: $n = 50$ • Allocation approach: non-randomised • Study start: 20 May 2016 • Estimated primary completion: 21 February 2023 • Estimated study completion: 21 February 2023	Enrolling paediatric and young adult participants with solid tumours with known or potential kinase pathway activation (RAS/RAF/MEK/ERK pathway involvement) for whom standard therapy has proven to be ineffective or intolerable or for whom no curative standard-of-care treatment options exist

		Clinical evidence			
Product	**Indications**	**Study**	**Clinical outcomes**	**Study design**	**Patient population**
Crizotinib (Xalkori, Pfizer, New York City, NY, USA)	Solid and liquid tumours	NCT01524926 (CREATE)	Primary: 1. Antitumour activity Secondary: 1. Safety 2. PFS 3. DCR 4. OS 5. DoR	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 582$ • Allocation approach: non-randomised • Study start: September 2012 • Estimated primary completion: December 2017 • Estimated study completion: December 2018	Enrolling patients with advanced tumours induced by causal alterations of *ALK* and/or *MET*
	Solid tumours	NCT02034981	Primary: 1. ORR (8 weeks) Secondary: 1. Safety (up to 2.5 years) 2. DCR (4 months) 3. DoR 4. PFS 5. OS	• Design: Phase II (separate cohorts specified) • Estimated enrolment: $n = 246$ • Allocation approach: non-randomised • Study start: August 2013 • Estimated primary completion: June 2018 • Estimated study completion: July 2022	Enrolling patients harbouring an alteration on *ALK*, *MET* or *ROS1*

ALK, anaplastic lymphoma kinase; BOR, best overall response; DCR, disease control rate; NPR, non-progression rate; PD, pharmacodynamics; PK, pharmacokinetics.

Appendix 3 The MEDLINE search strategy

Date range searched: inception to March 2019.

Date searched: March 2019.

Search strategy

1. *Neoplasms/
2. (cancer$ or neoplasm$ or tumour$ or tumour$ or malignan$ or oncology or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or carcinoma$).tw.
3. 1 or 2
4. tumour response$.tw.
5. tumour response$.tw.
6. objective response$.tw.
7. ORR.tw.
8. “duration of response$”.tw.
9. dor.tw.
10. response rate$.tw.
11. complete response$.tw
12. overall response$.tw
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 3 and 13
15. Regression analysis/
16. regression.tw.
17. relationship.tw.
18. correlation.tw.
19. prediction.tw.
20. association.tw.
21. 15 or 16 or 17 or 18 or 19 or 20
22. 14 and 21
23. endpoint$.tw.
24. end point$.tw.
25. (surrogate or surrogacy).tw.
26. 23 or 24 or 25
27. 22 and 26
28. progression-free survival/
29. “progression free survival”.tw.
30. “overall survival”.tw.
31. (pfs or os).tw.
32. “time to progression”.tw.
33. ttp.tw.
34. 28 or 29 or 30 or 31 or 32 or 33
35. 27 and 34
36. limit 35 to (english language and humans)

Appendix 4 Table of study characteristics (ordered by cancer type, then author)

Study (first author and year)	Cancer	Surrogate outcome	Final outcome	Stage	Line	Treatment	Studies (*n*)	Patients (*n*)	Study types	Publication/ search years	Data type	Response criteria	Absolute association	Treatment effect association	STE reported
Agarwal 2017[83]	Acute myeloid leukaemia	ORR and CR	OS	Various	First	Systemic	20[a]	NR	RCT and SA	2004–16	AD	NR	Yes		
Moriwaki 2016[119]	Biliary tract	ORR	OS	Advanced	First	Chemotherapy	17[a]	2040	RCT	Up to 2015	AD	NR		Yes	
Bruzzi 2005[86]	Breast	ORR	OS	Metastatic	All	Chemotherapy	10	2126	RCT	1991–2001	IPD	WHO ($n = 8$), ECOG ($n = 1$), NR ($n = 1$)		Yes	
Burzykowski 2008[87]	Breast	ORR	PFS and OS	Metastatic	First	Chemotherapy	11	3953	RCT	1999–2008	IPD	WHO		Yes	
Hackshaw 2005[99]	Breast	ORR and CR	OS	Metastatic	First	Chemotherapy	42[b]	9163	RCT	1966–2005	AD	NR		Yes	
Liu 2016[114]	Breast	ORR[b]	OS	Metastatic	Second and third	Chemotherapy	24	8617	RCT	1999–2014	AD	NR	Yes		
Petrelli 2014[127]	Breast	ORR	OS	Metastatic or advanced	First	Targeted therapy and chemotherapy	20[a]	10,138[a]	RCT	2000–12	AD	NR	Yes		
Buyse 2000[88]	Colorectal	ORR	OS	Advanced	First	Chemotherapy	25	3791	RCT	Collected 1990–6	IPD	WHO		Yes	
Ciani 2015[89] Elia 2020[96]	Colorectal	ORR	PFS and OS	Advanced or metastatic	All	Systemic	33	NR	RCT	2003–13	AD	RECIST or WHO		Yes	Yes
Colloca 2016[92]	Colorectal	ORR and DoR	OS	Metastatic	First	Bevacizumab and chemotherapy	11	NR	RCT	2000–14	AD	RECIST		Yes	
Giessen 2015[98]	Colorectal	ORR	OS	Metastatic	Second	Chemotherapy	22	10,509	RCT	2000–13	AD	RECIST ($n = 17$), WHO ($n = 5$)	Yes		
Cremolini 2017[94]	Colorectal	ORR	OS	Metastatic	Second	Targeted therapy	20[b]	7571	RCT	Up to 2015	AD	NR		Yes	
Johnson 2006[109]	Colorectal	ORR	OS	Metastatic	First	Chemotherapy	146[a]	35,337[a]	RCT	Up to 2005	AD	NR (very few RECIST)		Yes	
Louvet 2001[115]	Colorectal	ORR	PFS and OS	Metastatic	First	Various	29	13,498	RCT	1990–2000	AD	NR	Yes		
Sidhu 2013[136]	Colorectal	ORR	OS	Metastatic	First (most)	Chemotherapy ± targeted therapy	24[a]	20,438[a]	RCT	2000–11	AD	NR		Yes	
Tang 2007[138]	Colorectal	ORR	OS	Metastatic	First	Chemotherapy	39	18,668	RCT	1990–2005	AD	NR	Yes	Yes	
Tsujino 2010[140]	Colorectal	ORR	PFS and OS	Advanced	NR	Targeted therapy	7	NR	RCT	Up to 2009	AD	NR		Yes	
Ichikawa 2006[105]	Gastric	ORR	TTP and OS	Advanced	First	Chemotherapy	25	4593	RCT	NR	AD	WHO, SWOG, RECIST, Japan	Yes		
Shitara 2014[133]	Gastric	ORR[b]	OS	Advanced	Second and third	Chemotherapy	64	4286	RCT and SA	2002 to 2012–13	AD	NR	Yes		

Study (first author and year)	Cancer	Surrogate outcome	Final outcome	Stage	Line	Treatment	Studies (*n*)	Patients (*n*)	Study types	Publication/ search years	Data type	Response criteria	Absolute association	Treatment effect association	STE reported
Pang 2018[124]	Gastro-oesophageal	ORR[b] and CR	OS	Advanced	First and second	Targeted therapy	18	7892	RCT	Up to 2018	AD	RECIST	Yes		
Han 2014[101]	Glioblastoma	ORR	OS	Unclear	Various	Various	91[a]	7125[a]	RCT and SA	1991–2012	AD	NR ('standard criteria')	Yes		
Blumenthal 2017[85]	Lung (NSCLC)	ORR	PFS and OS	Metastatic	Various	Chemotherapy, immune checkpoint inhibitors or targeted therapy	25	20,013[a]	RCT	2003–16	AD	RECIST or WHO		Yes	
Blumenthal 2015[84]	Lung (NSCLC)	ORR	PFS and OS	Metastatic	Various	Chemotherapy or targeted therapy	14	12,567[a]	RCT	2003–13	AD	RECIST ($n = 11$) or WHO ($n = 3$)		Yes	
Hashim 2018[102]	Lung (NSCLC)	ORR	OS	Advanced	Second and subsequent	Various	140	41,725	RCT	Up to 2016	AD	NR		Yes	Yes
Hotta 2015[103]	Lung (NSCLC)	ORR	OS	Advanced	Various	Targeted therapy	18	7633[a]	RCT	2003–14	AD	NR		Yes	
Ito 2019[145]	Lung (NSCLC)	ORR	PFS and OS	Advanced	Various	Immune checkpoint inhibitors [PD-(L)1]	7	3752[a]	RCT	NR	AD	NR	Yes	Yes	
Johnson 2006[109]	Lung (NSCLC)	ORR	OS	Advanced	First	Chemotherapy	191[a]	44,125[a]	RCT	Up to 2005	AD	NR (very few RECIST)		Yes	
Li 2019[112]	Lung (NSCLC)	ORR[b] and CR	OS	Advanced	First and second	Immune checkpoint inhibitors	5[a]	4803[a]	RCT	Up to 2018	AD	RECIST	Yes		
Li 2012[113]	Lung (NSCLC)	ORR	OS	Advanced	First and second	Targeted therapy	60	9903	RCT and SA	Up to 2011	AD	RECIST ($n = 52$), WHO ($n = 10$)	Yes		
Nakashima 2016[121]	Lung (NSCLC)	ORR	OS	Advanced, locally advanced and recurrent	First	Chemotherapy	44	22,709	RCT	2005–15	AD	RECIST		Yes	
Ritchie 2018[128]	Lung (NSCLC)	ORR[b]	PFS and OS	Advanced	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	8	NR	RCT	2000–17	AD	NR	Yes	Yes	
Roviello 2017[130]	Lung (NSCLC)	ORR	PFS and OS	Unclear	Various	Immune checkpoint inhibitors	7[b]	3369[b]	RCT	Up to 2017	AD	RECIST or mWHO		Yes	
Sekine 1999[131]	Lung (NSCLC)	ORR	OS	Unclear	Various	Chemotherapy	42	1935	SA and one RCT	1988–97	AD	WHO	Yes		
Shukuya 2016[134]	Lung (NSCLC)	ORR	OS	Advanced	All	(a) Immune checkpoint inhibitors (PD-(L)1)	(a) 10[a]	NR	RCT and SA	2012–16	AD	RECIST (most)	Yes		
						(b) Chemotherapy [docetaxel (Taxotere, Sanofi-Aventis, Paris, France)]	(b) 22[a]								

Study (first author and year)	Cancer	Surrogate outcome	Final outcome	Stage	Line	Treatment	Studies (*n*)	Patients (*n*)	Study types	Publication/ search years	Data type	Response criteria	Absolute association	Treatment effect association	STE reported
Tsujino 2010[140]	Lung (NSCLC)	ORR	PFS and OS	Advanced	NR	Targeted therapy	6	NR	RCT	Up to 2009	AD	NR		Yes	
Tsujino 2009[139]	Lung (NSCLC)	ORR	PFS and OS	Advanced	NR	Targeted therapy	28	6171	RCT and SA	Up to 2007	AD	RECIST ($n = 21$), WHO ($n = 9$)	Yes		
Vidaurre 2009[141]	Lung (NSCLC)	ORR[b]	PFS and OS	Advanced, locally advanced, unresectable or metastatic	NR	Chemotherapy or targeted therapy	35	NR	RCT and SA	2006–8	AD	NR	Yes		
Foster 2011[97]	Lung (SCLC)	ORR and CR	OS	Extensive stage	First	Chemotherapy	Three RCTs (32 centres)	596[a]	RCT	Trials initiated 1987–99	AD	NR (CR = disappearance; PR ≥ 50% reduction)		Yes	
Hotta 2009[104]	Lung (SCLC)	ORR	OS	Extensive disease	First	Chemotherapy	48	8779	RCT	1990–2008	AD	WHO ($n = 23$), ECOG ($n = 2$), RECIST ($n = 1$), Japan ($n = 1$) or NR		Yes	
Nickolich 2014[122]	Lung (SCLC)	ORR, CR and PR	PFS and OS	Limited or extensive disease	First and second and maintenance	Various	66[a]	8471[a]	RCT and SA	1983–2010	AD	NR	Yes		
Mangal 2018[118]	Multiple myeloma	ORR,[b] CR, VGPR or CR	PFS	Relapsed/ refractory	Second and subsequent	Various	79[a]	13,322[a]	RCT and SA	1999–2016	AD	IMWG	Yes		
Imaoka 2019[107]	Neuroendocrine	ORR	PFS	Advanced	Various	Systemic	22	1310	RCT and SA	1996–2016	AD	RECIST ($n = 20$) and WHO ($n = 2$)	Yes		
Imaoka 2017[106]	Neuroendocrine	ORR	OS	Advanced	Various	Systemic	20	2530	RCT and SA	1996–2016	AD	NR	Yes		
Lee 2011[111]	NHL (aggressive)	CR	PFS and OS	Unclear	First	Chemotherapy	36[a]	16,103[a]	RCT	1990–2009	AD	NR		Yes	
Lee 2011[111]	NHL (indolent)	CR	PFS and OS	Unclear	First	Chemotherapy	15[a]	5128[a]	RCT	1990–2009	AD	NR		Yes	
Mangal 2018[117]	NHL	ORR[b] and CR	PFS	Stage III/IV > 75% in most cohorts	Various	Various	73	6071	RCT and SA	1996–2015	AD	NR	Yes		
Shi 2017[132]	NHL (indolent; follicular)	CR 30 months and CR 24 months	PFS	Unclear	First	Chemotherapy or immunotherapy (induction or maintenance)	13	3837	RCT	1990–2011	IPD	NR (CR = disappearance)		Yes	Yes
Zhu 2017[144]	NHL (indolent; follicular)	CR	PFS	Unclear	NR	Chemotherapy, immunotherapy or targeted therapy	13	NR	RCT and SA	1993–2013	AD	NR	Yes		

Study (first author and year)	Cancer	Surrogate outcome	Final outcome	Stage	Line	Treatment	Studies (*n*)	Patients (*n*)	Study types	Publication/ search years	Data type	Response criteria	Absolute association	Treatment effect association	STE reported
Zhu 2017[144]	NHL (mantle cell)	CR	PFS	Unclear	NR	Chemotherapy, immunotherapy or targeted therapy	NR	NR	RCT and SA	1993–2013	AD	NR	Yes		
Colloca 2017[90]	Ovarian	ORR and CR	PFS and OS	Advanced	First	Chemotherapy	29	NR	RCT	1990–2016	AD	WHO ($n = 24$), RECIST ($n = 8$)		Yes	
Rose 2010[129]	Ovarian	ORR[b]	PFS and OS	Recurrent/ platinum-resistant	Second	Various	11	407	SA	1994–2004	IPD	WHO ($n = 10$) and RECIST ($n = 1$)	Yes		
Siddiqui 2017[135]	Ovarian	ORR[b]	PFS and OS	Advanced, recurrent	Second and subsequent	Chemotherapy	39[a]	9223[a]	RCT	2000–15	AD	NR	Yes	Yes	
Colloca 2016[91]	Pancreatic	ORR and DoR	PFS and OS	Advanced or metastatic	First	Gemcitabine and chemotherapy or targeted therapy	36[b]	NR	RCT	1997–2014	AD	RECIST		Yes	
Hamada 2016[100]	Pancreatic	ORR	OS	Advanced	First	Chemotherapy	47	15,906[a]	RCT	1995–2015	AD	NR	Yes	Yes	
Makris 2017[116]	Pancreatic (adenocarcinoma)	ORR	OS	Locally advanced, unresectable or metastatic	First	Chemotherapy (gemcitabine)	22[b]	10,379[b]	RCT	2000–15	AD	NR (RR = shrinkage or disappearance)		Yes	
Colloca 2016[93]	Prostate	ORR	OS	Metastatic (castration resistant)	First and second	Chemotherapy, hormonal and targeted therapy	17	NR	RCT	1995–2014	AD	NR (CR = disappearance; PR = ≥ 30% reduction)		Yes	
Abdel-Rahman 2018[81]	Renal cell	ORR	OS	Advanced	Various	Immune checkpoint inhibitors [PD-(L)1]	4	1093	RCT and SA	Up to 2017	AD	RECIST	Yes		
Delea 2012[95]	Renal cell	ORR	OS	Metastatic	NR	Cytokine or targeted	25[b]	10,943[a]	RCT	1997–2010	AD	NR		Yes	
Petrelli 2013[126]	Renal cell	ORR	PFS and OS	Metastatic	First	Targeted	6[a]	3188[a]	RCT	Up to 2011	AD	NR	Yes	Yes	
Tanaka 2019[137]	Soft tissue sarcoma	ORR	OS	Advanced	First	Chemotherapy	27[a]	6156[a]	RCT	1974–2017	AD	NR		Yes	
Zer 2016[143]	Soft tissue sarcoma	ORR	OS	Advanced or metastatic	All	Systemic	52[a]	9762[a]	RCT	1974–2014	AD	NR		Yes	
Penel 2014[125]	Unknown primary	ORR[b]	PFS and OS	Unclear	NR	NR	38[a]	NR	SA	1997–2011	AD	RECIST or WHO	Yes		
Abdel-Rahman 2018[81]	Urothelial	ORR	OS	Advanced	Various	Immune checkpoint inhibitors [PD-(L)1]	9	1699	RCT and SA	Up to 2017	AD	RECIST	Yes		
Agarwal 2014[82]	Urothelial	ORR	OS	Advanced (operable or metastatic)	Second	Chemotherapy or biologic	10	560	RCT and SA	NR	AD	RECIST	Yes		

Study (first author and year)	Cancer	Surrogate outcome	Final outcome	Stage	Line	Treatment	Studies (*n*)	Patients (*n*)	Study types	Publication/ search years	Data type	Response criteria	Absolute association	Treatment effect association	STE reported
Kaufman 2018[110]	Various solid tumours	ORR	OS	Unclear	Various	Immune checkpoint inhibitors ± chemotherapy	27[a]	10,300[a]	RCT	2005–17	AD	RECIST or mWHO		Yes	
Mushti 2018[120]	Various solid tumours	ORR[b]	OS	Unclear	NR	Immune checkpoint inhibitors [PD-(L)1]	13	6722	RCT	2014–16	AD	RECIST		Yes	
Nie 2019[123]	Various solid tumours	ORR[b]	OS	Advanced or recurrent	Various	Immune checkpoint inhibitors [PD-(L)1]	43[a]	15,088[a]	RCT and SA	Up to 2018	AD	RECIST	Yes	Yes	
Ritchie 2018[128]	Various solid tumours	ORR[b]	PFS and OS	Advanced	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	20[a]	10,828[a]	RCT	2000–17	AD	NR	Yes	Yes	
Roviello 2017[130]	Various solid tumours	ORR	PFS and OS	Unclear	Various	Immune checkpoint inhibitors	17[a]	8994[a]	RCT	Up to 2017	AD	RECIST or mWHO		Yes	
Tsujino 2010[140]	Various solid tumours	ORR	PFS and OS	Advanced	NR	Targeted	18	NR	RCT	Up to 2009	AD	NR		Yes	Yes
Vidaurre 2009[141]	Various	ORR[b]	PFS and OS	Advanced, locally advanced, unresectable or metastatic	NR	Chemotherapy or targeted	143[a]	6974[a]	RCT and SA	2006–08	AD	NR	Yes		
Wilkerson 2009[142]	Various solid tumours	ORR	PFS and OS	Metastatic	NR	NR	66[a]	NR	RCT	NR	AD	NR		Yes	

AD, aggregate data; IMWG, International Myeloma Working Group (criteria); mWHO, modified World Health Organization (criteria); NR, not reported; SA, single arm; WHO, World Health Organization (criteria).
a Unclear for individual subgroups.
b Calculated from reported data.

Note
Of the 63 included studies (64 refs), eight references[81,109,111,128,130,140,141,144] appear on two to three rows as they report on two to three different cancer types.

Appendix 5 Absolute correlation and regression results (ordered by outcome type, then cancer type, then author)

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Absolute correlation methods	Correlation coefficient	Absolute regression methods	Regression R^2 (95% CI); *p*-value	Linear regression equation
ORR vs. PFS (or TTP)												
Louvet 2001[115]	ORR	PFS	Colorectal	First	Various	29	13,498	Spearman (ORR vs. median PFS)	$r_s = 0.66$; $p < 0.0001$	LR (ORR vs. median PFS)		PFS = 3.2 + 0.1 × ORR
Ichikawa 2006[105]	ORR	TTP	Gastric	First	Chemotherapy (any)	12[a]	2144	Spearman weighted (ORR vs. median TTP)	$r_s = 0.49$; $p < 0.0001$	WLR (ORR vs. median TTP)		TTP = 1.73 + 0.09 × ORR
Ichikawa 2006[105]	ORR	TTP	Gastric	First	Chemotherapy (novel)	8[a]	1077	Spearman weighted (ORR vs. median TTP)	$r_s = 0.41$; $p = 0.018$			
Ichikawa 2006[105]	ORR	TTP	Gastric	First	Chemotherapy (non-novel)	7[a]	1067	Spearman weighted (ORR vs. median TTP)	$r_s = 0.56$; $p = 0.0053$			
Ito 2019[145]	ORR	PFS	Lung (NSCLC)	Various	Immune checkpoint inhibitors [PD-(L)1]	6	3752[b]	(a) Pearson weighted	(a) $r = 0.55$; $p < 0.0001$	WLR R^2 (ORR vs. median PFS)	$R^2 = 0.30$; $p = 0.206$	
								(b) Spearman weighted (ORR vs. median PFS)	(b) $r_s = 0.33$; $p < 0.0001$			
Ito 2019[145]	ORR	PFS	Lung (NSCLC)	Various: high PD-L1 expression	Immune checkpoint inhibitors [PD-(L)1]	7	1381	(a) Pearson weighted	(a) $r = 0.90$; $p < 0.0001$	WLR R^2 (ORR vs. median PFS)	$R^2 = 0.81$; $p = 0.006$	
								(b) Spearman weighted (ORR vs. median PFS)	(b) $r_s = 0.48$; $p < 0.0001$			
Ritchie 2018[128]	ORR	PFS	Lung (NSCLC)	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	8	NR	Correlation (NR) (ORR vs. 6-month PFS)	$r = 0.85$ (95% CI 0.63 to 1.06); p = NR			
Tsujino 2009[139]	ORR	PFS	Lung (NSCLC)	NR	Targeted therapy	18[a]	3790[a]			LR (ORR vs. median PFS)	R^2 = NR; $p = 0.001$	Slope: 0.072
Vidaurre 2009[141]	ORR	PFS	Lung (NSCLC)	NR	Chemotherapy or targeted therapy	35	NR			Regression (NR) (ORR vs. median PFS)	$R^2 = 0.75$; $p < 0.0001$	
Nickolich 2014[122]	ORR	PFS	Lung (SCLC)	First and second and maintenance: limited or extensive	Various	66[b]	8471[b]	Pearson (ORR vs. median PFS)	$r = 0.73$; $p < 0.0001$			
Nickolich 2014[122]	ORR	PFS	Lung (SCLC)	First and second and maintenance: limited disease	Various	66[b]	8471[b]	Pearson (ORR vs. median PFS)	$r = 0.02$; $p = 0.978$			
Nickolich 2014[122]	ORR	PFS	Lung (SCLC)	First and second and maintenance: extensive disease	Various	66[b]	8471[b]	Pearson (ORR vs. median PFS)	$r = 0.51$; $p = 0.013$			

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Absolute correlation methods	Correlation coefficient	Absolute regression methods	Regression R^2 (95% CI); *p*-value	Linear regression equation
Mangal 2018[118]	ORR	PFS	Multiple myeloma	Second and subsequent	Various	79[b]	13,322[b]			WLR adjusted R^2 (logit ORR vs. log-median PFS)	Adjusted $R^2 = 0.50$; $p =$ NR	
Imaoka 2019[107]	ORR	PFS	Neuroendocrine	Various	Systemic	22	1310	Pearson (ORR vs. median PFS)	$r = 0.37$ (95% CI −0.05 to 0.80); $p = 0.085$			
Imaoka 2019[107]	ORR	PFS	Neuroendocrine	Various: published 1996–2010	Systemic	6[a]	NR	Pearson (ORR vs. median PFS)	$r = -0.08$ (95% CI −0.76 to 0.60); $p = 0.824$			
Imaoka 2019[107]	ORR	PFS	Neuroendocrine	Various: published 2011–16	Systemic	16[a]	NR	Pearson (ORR vs. median PFS)	$r = 0.43$ (95% CI −0.07 to 0.93); $p = 0.095$			
Imaoka 2019[107]	ORR	PFS	Neuroendocrine	Various	Cytotoxic	Nine arms	NR	Pearson (ORR vs. median PFS)	$r = 0.63$ (95% CI 0.03 to 1.22); $p = 0.041$			
Imaoka 2019[107]	ORR	PFS	Neuroendocrine	Various	Non-cytotoxic	18 arms	NR	Pearson (ORR vs. median PFS)	$r = 0.18$ (95% CI −0.27 to 0.62); $p = 0.432$			
Imaoka 2019[107]	ORR	PFS	Neuroendocrine	Various	Targeted	19 arms	NR	Pearson (ORR vs. median PFS)	$r = 0.42$ (95% CI −0.06 to 0.90); $p = 0.086$			
Imaoka 2019[107]	ORR	PFS	Neuroendocrine	Various	Non-targeted	Eight arms	NR	Pearson (ORR vs. median PFS)	$r = -0.72$ (95% CI −1.09 to −0.35); $p < 0.001$			
Mangal 2018[117]	ORR	PFS	NHL	Various	Various	73	6071			LR adjusted R^2 (logit ORR vs. log-median PFS)	Adjusted $R^2 = 0.70$; $p =$ NR	log-(median PFS) = 1.97 + 0.414 × logit (ORR)
Rose 2010[129]	ORR	PFS	Ovarian	Second	Various	11	407	(a) Pearson	(a) $r = 0.62$; $p = 0.044$			
								(b) Kendall Tau-b (ORR vs. median PFS)	(b) $r = 0.48$; $p = 0.042$			
Siddiqui 2017[135]	ORR	PFS	Ovarian	Second and subsequent	Chemotherapy	39[b]	9223[b]	(a) Pearson weighted (ORR vs. median PFS)	(a) $r = 0.85$; $p < 0.001$	(a) WLR R^2 (ORR vs. median PFS): unadjusted;	(a) $R^2 = 0.72$; $p =$ NR	Median PFS = 2.59 + 0.12 × ORR
								(b) Pearson unweighted (ORR vs. median PFS)	(b) $r = 0.76$; $p < 0.001$	(b) WLR R^2 (ORR vs. median PFS): adjusted	(b) Adjusted $R^2 = 0.72$; $p =$ NR	
Petrelli 2013[126]	ORR	PFS	Renal cell	First	Targeted	6[b]	3188[b]	Spearman weighted (ORR vs. median PFS)	$r_s = 0.96$; $p < 0.0001$			

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Absolute correlation methods	Correlation coefficient	Absolute regression methods	Regression R^2 (95% CI); *p*-value	Linear regression equation
Penel 2014[125]	ORR	PFS	Unknown primary	NR	NR	38[b]	NR	Pearson via WLR (ORR vs. median PFS)	$r = 0.54$; $p < 0.0001$			
Ritchie 2018[128]	ORR	PFS	Various solid tumours	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	20[b]	10,828[b]	Correlation (NR) (ORR vs. 6-month PFS)	$r = 0.37$ (95% CI 0.06 to 0.95); p = NR			
Vidaurre 2009[141]	ORR	PFS	Various	NR	Chemotherapy	85	3982[a]			Regression (NR) (ORR vs. median PFS)	$R^2 = 0.53$; $p < 0.0001$	
Vidaurre 2009[141]	ORR	PFS	Various	NR	Targeted	58	2992[a]			Regression (NR) (ORR vs. median PFS)	$R^2 = 0.61$; $p < 0.0001$	
Vidaurre 2009[141]	ORR	PFS	Various	NR	Chemotherapy or targeted therapy	143[b]	6974[b]			Regression (NR) (ORR vs. median PFS)	$R^2 = 0.56$; $p < 0.0001$	
ORR vs. OS												
Agarwal 2017[83]	ORR	OS	Acute myeloid leukaemia	First	Systemic	20[b]	NR			WLR adjusted R^2 (logit ORR vs. log-median OS)	Adjusted $R^2 = 0.45$; p = NR	
Liu 2016[114]	ORR	OS	Breast	Second and third	Chemotherapy	24	8617	Spearman (ORR vs. median OS)	$r_s = 0.54$ (95% CI 0.29 to 0.72); $p < 0.0001$			
Liu 2016[114]	ORR	OS	Breast	Second and third: previous anthracycline/ taxanes	Chemotherapy	15[a]	NR	Spearman (ORR vs. median OS)	$r_s = 0.62$ (95% CI 0.32 to 0.84); p = NR			
Liu 2016[114]	ORR	OS	Breast	Second and third: previous trastuzumab/ bevacizumab	Chemotherapy	5[a]	NR	Spearman (ORR vs. median OS)	$r_s = 0.78$ (95% CI 0.19 to 1.0); p = NR			
Liu 2016[114]	ORR	OS	Breast	Second and third	Chemotherapy (taxanes)	21[a]	NR	Spearman (ORR vs. median OS)	$r_s = 0.49$ (95% CI −0.19 to 0.92); p = NR			
Liu 2016[114]	ORR	OS	Breast	Second and third	Chemotherapy (antimetabolites)	22[a]	NR	Spearman (ORR vs. med OS)	$r_s = -0.10$; p = NR			
Liu 2016[114]	ORR	OS	Breast	Second and third: HER2 positive	Chemotherapy	5[a]	NR	Spearman (ORR vs. median OS)	$r_s = 0.96$ (95% CI 0.80 to 1.00); p = NR			
Liu 2016[114]	ORR	OS	Breast	Second and third: HER2 negative	Chemotherapy	3[a]	NR	Spearman (ORR vs. median OS)	$r_s = 1.00$; p = NR			

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Absolute correlation methods	Correlation coefficient	Absolute regression methods	Regression R^2 (95% CI); *p*-value	Linear regression equation
Petrelli 2014[127]	ORR	OS	Breast	First	Targeted therapy and chemotherapy	20[b]	10,138[b]	Spearman weighted (ORR vs. median OS)	$r_s = 0.61$ (95% CI 0.59 to 0.63); p = NR			
Giessen 2015[98]	ORR	OS	Colorectal	Second	Chemotherapy	22	10,509	Pearson weighted (log-odds ORR vs. log-median OS)	$r = 0.58$ (95% CI 0.38 to 0.72); $p = 0.003$			
Louvet 2001[115]	ORR	OS	Colorectal	First	Various	28[a]	13,284[a]	Spearman (ORR vs. median OS)	$r_s = 0.41$; $p = 0.0009$	LR (ORR vs. median OS)		OS = 10.45 + 0.088 × ORR
Tang 2007[138]	ORR	OS	Colorectal	First	Chemotherapy	39	18,668	Spearman (ORR vs. median OS)	$r_s = 0.59$ (95% CI 0.42 to 0.72); $p < 0.000001$			
Ichikawa 2006[105]	ORR	OS	Gastric	First	Chemotherapy (any)	25	4593	Spearman weighted (ORR vs. median OS)	$r_s = 0.45$; $p < 0.0001$	WLR (ORR vs. median OS)		OS = 5.89 + 0.08 × ORR
Ichikawa 2006[105]	ORR	OS	Gastric	First	Chemotherapy (novel)	11[a]	1170	Spearman weighted (ORR vs. median OS)	$r_s = 0.18$; $p = 0.12$			
Ichikawa 2006[105]	ORR	OS	Gastric	First	Chemotherapy (non-novel)	20[a]	3423	Spearman weighted (ORR vs. median OS)	rs = 0.47; $p < 0.0001$			
Shitara 2014[133]	ORR	OS	Gastric	Second and third	Chemotherapy	64	4286	Spearman (ORR vs. median OS)	$r_s = 0.38$ (95% CI 0.16 to 0.6); p = NR			
Pang 2018[124]	ORR	OS	Gastro-oesophageal	First and second	Targeted	18	7892	Correlation (NR) (ORR vs. median OS)	$r = 0.86$; $p < 0.0001$			
Han 2014[101]	ORR	OS	Glioblastoma	Various	Various	91[b]	7125[b]			WLR R^2 (ORR vs. median OS)	$R^2 = 0.22$ (95% CI 0.04 to 0.42); p = NR	
Ito 2019[145]	ORR	OS	Lung (NSCLC)	Various	Immune checkpoint inhibitors (PD-(L)1)	6	3752[b]	(a) Pearson weighted	(a) $r = -0.02$; $p = 0.4564$			
								(b) Spearman weighted (ORR vs. median OS)	(b) $r_s = -0.14$; $p < 0.0001$			
Ito 2019[145]	ORR	OS	Lung (NSCLC)	Various: high PD-L1 expression	Immune checkpoint inhibitors [PD-(L)1]	7	1381	(a) Pearson weighted	(a) $r = 0.92$; $p < 0.0001$;	WLR R^2 (ORR vs. median OS)	$R^2 = 0.84$; $p = 0.004$	
								(b) Spearman weighted (ORR vs. median OS)	(b) $r_s = 0.77$; $p < 0.0001$			
Li 2019[112]	ORR	OS	Lung (NSCLC)	First and second	Immune checkpoint inhibitors	5[b]	4803[b]	Pearson (ORR vs. median OS)	$r = 0.52$; $p = 0.28$	LR (ORR vs. median OS)	$R^2 = 0.27$; p = NR	

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Absolute correlation methods	Correlation coefficient	Absolute regression methods	Regression R^2 (95% CI); *p*-value	Linear regression equation
Li 2012[113]	ORR	OS	Lung (NSCLC)	First and second	Targeted therapy	60	9903			WLSR R^2 (ORR vs. median OS)	$R^2 = 0.83$; $p < 0.000001$	
Ritchie 2018[128]	ORR	OS	Lung (NSCLC)	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	8	NR	Correlation (NR) (ORR vs. 12-month OS)	$r = 0.66$ (95% CI 0.17 to 1.08); $p =$ NR			
Sekine 1999[131]	ORR	OS	Lung (NSCLC)	Various	Chemotherapy	42	1935	Pearson (ORR vs. median OS)	$r = 0.62$; $p < 0.001$			
Shukuya 2016[134]	ORR	OS	Lung (NSCLC)	All	Immune checkpoint inhibitors [PD-(L)1]	10[b]	NR	Spearman weighted (ORR vs. median OS)	$r_s = 0.45$; $p = 0.141$			
Shukuya 2016[134]	ORR	OS	Lung (NSCLC)	All	Chemotherapy (docetaxel)	22[b]	NR	Spearman weighted (ORR vs. median OS)	$r_s = 0.41$; $p = 0.053$			
Tsujino 2009[139]	ORR	OS	Lung (NSCLC)	NR	Targeted therapy	28	6171			LR (ORR vs. median OS)	$R^2 =$ NR; $p < 0.0001$	Slope: 0.258
Vidaurre 2009[141]	ORR	OS	Lung (NSCLC)	NR	Chemotherapy or targeted therapy	35	NR			Regression (NR) (ORR vs. median OS)	$R^2 = 0.28$; $p = 0.0024$	
Nickolich 2014[122]	ORR	OS	Lung (SCLC)	First and second and maintenance: limited or extensive	Various	66[b]	8471[b]	Pearson (ORR vs. median OS)	$r = 0.66$; $p < 0.0001$			
Nickolich 2014[122]	ORR	OS	Lung (SCLC)	First and second and maintenance: limited disease	Various	66[b]	8471[b]	Pearson (ORR vs. median OS)	$r = 0.40$; $p = 0.193$			
Nickolich 2014[122]	ORR	OS	Lung (SCLC)	First and second and maintenance: extensive disease	Various	66[b]	8471[b]	Pearson (ORR vs. median OS)	$r = 0.44$; $p = 0.012$			
Imaoka 2017[106]	ORR	OS	Neuroendocrine	Various	Systemic	20	2530	Spearman (ORR vs. median OS)	$r_s = -0.26$ (95% CI −0.64 to 0.11); $p = 0.164$			
Rose 2010[129]	ORR	OS	Ovarian	Second	Various	11	407	(a) Pearson	(a) $r = 0.56$; $p = 0.071$			
								(b) Kendall Tau-b (ORR vs. median OS)	(b) $r = 0.40$; $p = 0.086$			
Siddiqui 2017[135]	ORR	OS	Ovarian	Second and subsequent	Chemotherapy	31[b]	9223[b]	(a) Pearson weighted (ORR vs. median OS)	(a) $r = 0.82$; $p < 0.001$	(a) WLR R^2 (ORR vs. median OS): unadjusted	(a) $R^2 = 0.67$; $p =$ NR	Median OS = 9.48 + 0.28 × ORR
								(b) Pearson unweighted (ORR vs. median OS)	(b) 0.71; $p < 0.001$	(b) WLR R^2 (ORR vs. median OS): adjusted	(b) Adjusted $R^2 = 0.66$; $p =$ NR	

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Absolute correlation methods	Correlation coefficient	Absolute regression methods	Regression R^2 (95% CI); *p*-value	Linear regression equation
Hamada 2016[100]	ORR	OS	Pancreatic	First	Chemotherapy	47	15,906[b]	Spearman (ORR vs. median OS)	$r_s = 0.39$ (95% CI 0.20 to 0.55); $p < 0.001$			
Abdel-Rahman 2018[81]	ORR	OS	Renal cell	Various	Immune checkpoint inhibitors [PD-(L)1]	4	1093	Pearson (ORR vs. median OS)	$r = -0.40$; $p = 0.436$			
Petrelli 2013[126]	ORR	OS	Renal cell	First	Targeted	6[b]	3188[b]	Spearman weighted (ORR vs. median OS)	$r_s = 0.96$; $p < 0.0001$			
Penel 2014[125]	ORR	OS	Unknown primary	NR	NR	38[b]	NR	Pearson via WLR (ORR vs. median OS)	$r = 0.54$; $p < 0.0001$			
Abdel-Rahman 2018[81]	ORR	OS	Urothelial	Various	Immune checkpoint inhibitors [PD-(L)1]	9	1699	Pearson (ORR vs. median OS)	$r = -0.12$; $p = 0.758$			
Agarwal 2014[82]	ORR	OS	Urothelial	Second	Chemotherapy or biologic	10	560	Pearson (ORR vs. 12-month OS)	$r = 0.37$; $p = 0.30$	(a) WLR R^2 (ORR vs. 12-month OS): unadjusted	(a) $R^2 = 0.26$; p = NR	
										(b) WLR R^2 (ORR vs. 12-month OS): adjusted (RE)	(b) Adjusted $R^2 = 0.16$; $p = 0.1359$	
Agarwal 2014[82]	ORR	OS	Urothelial	Second: operable	Chemotherapy	NR	214[b]	Pearson (ORR vs. 12-month OS)	$r = 0.78$; p = NR	WLR adjusted R^2 (ORR vs. 12-month OS)	Adjusted $R^2 = 0.54$; p = NR	
Agarwal 2014[82]	ORR	OS	Urothelial	Second: metastatic	Chemotherapy	NR	391[b]	Pearson (ORR vs. 12-month OS)	$r = -0.018$; p = NR	WLR adjusted R^2 (ORR vs. 12-month OS)	Adjusted $R^2 = -0.13$; p = NR	
Nie 2019[123]	ORR	OS	Various solid tumours	Various	Immune checkpoint inhibitors [PD-(L)1]	43[b]	15,088[b]			Squared Spearman (ORR vs. median OS)	$R^2_s = 0.29$; $p < 0.001$	
Ritchie 2018[128]	ORR	OS	Various solid tumours	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	20[b]	10,828[b]	Correlation (NR) (ORR vs. 12-month OS)	$r = 0.08$ (95% CI −0.17 to 0.70); p = NR			
Vidaurre 2009[141]	ORR	OS	Various	NR	Chemotherapy	85	3982[a]			Regression (NR) (ORR vs. median OS)	$R^2 = 0.35$; $p < 0.0001$	
Vidaurre 2009[141]	ORR	OS	Various	NR	Targeted therapy	58	2992[a]			Regression (NR) (ORR vs. median OS)	$R^2 = 0.45$; $p < 0.0001$	
Vidaurre 2009[141]	ORR	OS	Various	NR	Chemotherapy or targeted therapy	143[b]	6794[b]			Regression (NR) (ORR vs. median OS)	$R^2 = 0.33$; $p < 0.0001$	

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Absolute correlation methods	Correlation coefficient	Absolute regression methods	Regression R^2 (95% CI); *p*-value	Linear regression equation
CR vs. PFS												
Nickolich 2014[122]	CR	PFS	Lung (SCLC)	First and second and maintenance: limited or extensive	Various	66[b]	8471[b]	Pearson (CR vs. median PFS)	$r = 0.71$; $p < 0.0001$			
Nickolich 2014[122]	CR	PFS	Lung (SCLC)	First and second and maintenance: limited disease	Various	66[b]	8471[b]	Pearson (CR vs. median PFS)	$r = 0.22$; $p = 0.491$			
Nickolich 2014[122]	CR	PFS	Lung (SCLC)	First and second and maintenance: extensive disease	Various	66[b]	8471[b]	Pearson (CR vs. median PFS)	$r = 0.35$; $p = 0.116$			
Mangal 2018[118]	CR	PFS	Multiple myeloma	Second and subsequent	Various	79[b]	13,322[b]			WLR adjusted R^2 (logit CR vs. log-median PFS)	Adjusted $R^2 = 0.47$; $p =$ NR	
Mangal 2018[117]	CR	PFS	NHL	Various	Various	73	6071			LR adjusted R^2 (logit CR vs. log-median PFS)	Adjusted $R^2 = 0.57$; $p =$ NR	log-(median PFS) = 2.38 + 0.340 × logit (CR)
Zhu 2017[144]	CR	PFS	NHL (indolent; follicular)	NR	Chemotherapy, immunotherapy or targeted therapy	13	NR			(a) WLR R^2: CR vs. median PFS	(a) $R^2 = 0.69$ (95% CI 0.22 to 0.89); $p =$ NR	Median PFS = 0.83 + 0.46 × CR
										(b)) WLR R^2: CR vs. 3-year PFS	(b) $R^2 = 0.44$; $p =$ NR	
Zhu 2017[144]	CR	PFS	NHL (mantle cell)	NR	Chemotherapy, immunotherapy or targeted therapy	NR	NR			WLR R^2 (CR vs. median PFS)	$R^2 = 0.39$; $p =$ NR	
CR vs. OS												
Agarwal 2017[83]	CR	OS	Acute myeloid leukaemia	First	Systemic	20[b]	NR			WLR adjusted R^2 (logit CR vs. log-median OS)	Adjusted $R^2 = 0.48$; $p =$ NR	
Pang 2018[124]	CR	OS	Gastro-oesophageal	First and second	Targeted	18	7892	Correlation (NR) (CR vs. median OS)	$r = 0.43$; $p = 0.18$			
Li 2019[112]	CR	OS	Lung (NSCLC)	First and second	Immune checkpoint inhibitors	5[a]	4103[a]	Pearson (CR vs. median OS)	$r = 0.19$; $p = 0.75$	LR (CR vs. median OS)	$R^2 = 0.04$; $p =$ NR	
Nickolich 2014[122]	CR	OS	Lung (SCLC)	First and second and maintenance: limited or extensive	Various	66[b]	8471[b]	Pearson (CR vs. median OS)	$r = 0.62$; $p < 0.0001$			
Nickolich 2014[122]	CR	OS	Lung (SCLC)	First and second and maintenance: limited disease	Various	66[b]	8471[b]	Pearson (CR vs. median OS)	$r = -0.04$; $p = 0.863$			
Nickolich 2014[122]	CR	OS	Lung (SCLC)	First and second and maintenance: extensive disease	Various	66[b]	8471[b]	Pearson (CR vs. median OS)	$r = 0.19$; $p = 0.295$			

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Absolute correlation methods	Correlation coefficient	Absolute regression methods	Regression R^2 (95% CI); *p*-value	Linear regression equation
PR (or VGPR or CR) vs. PFS												
Nickolich 2014[122]	PR	PFS	Lung (SCLC)	First and second and maintenance: limited or extensive	Various	66[b]	8471[b]	Pearson (PR vs. median PFS)	$r = 0.35$; $p = 0.019$			
Nickolich 2014[122]	PR	PFS	Lung (SCLC)	First and second and maintenance: limited disease	Various	66[b]	8471[b]	Pearson (PR vs. median PFS)	$r = 0.70$; $p = 0.011$			
Nickolich 2014[122]	PR	PFS	Lung (SCLC)	First and second and maintenance: extensive disease	Various	66[b]	8471[b]	Pearson (PR vs. median PFS)	$r = 0.49$; $p = 0.035$			
Mangal 2018[118]	VGPR or CR	PFS	Multiple myeloma	Second and subsequent	Various	79[b]	13,322[b]			WLR adjusted R^2 (VGPR or CR vs. median PFS)	Adjusted $R^2 = 0.64$; $p =$ NR	
PR vs. OS												
Nickolich 2014[122]	PR	OS	Lung (SCLC)	First and second and maintenance: limited or extensive	Various	66[b]	8471[b]	Pearson (PR vs. median OS)	$r = 0.29$; $p = 0.018$			
Nickolich 2014[122]	PR	OS	Lung (SCLC)	First and second and maintenance: limited disease	Various	66[b]	8471[b]	Pearson (PR vs. median OS)	$r = 0.60$; $p = 0.009$			
Nickolich 2014[122]	PR	OS	Lung (SCLC)	First and second and maintenance: extensive disease	Various	66[b]	8471[b]	Pearson (PR vs. median OS)	$r = 0.66$; $p = 0.0002$			

LR, linear regression; NR, not reported; *r*, Pearson correlation; R^2, regression coefficient of determination; R^2_s, squared Spearman rank correlation; r_s, Spearman rank correlation; WLR, weighted linear regression; WLSR, weighted least squares regression.

a Calculated from reported data.

b Unclear for individual subgroups.

Appendix 6 Treatment effect correlation and regression results (ordered by outcome type, then cancer type, then author)

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
ORR vs. PFS															
Burzykowski 2008[87]	ORR	PFS	Breast	First	Chemotherapy	11	3953	Spearman via LR with Plackett copula (log-OR ORR vs. log-HR PFS)	$r_s = 0.96$ (95% CI 0.73 to 1.19); $p =$ NR	LR		log-HR PFS = 0.10 + 0.50 × log-OR ORR	NR	Medium +	NE
Ciani 2015[89] Elia 2020[96]	ORR	PFS	Colorectal	All	Systemic	33	NR			LR: adjusted R^2 (log-OR ORR vs. log-HR PFS)	Adjusted $R^2 = 0.61$ (95% CI 0.27 to 0.87); $p =$ NR	log-HR PFS = −0.05 − 0.32 × log-OR ORR	NR	Medium	NE
Ciani 2015[89] Elia 2020[96]	ORR	PFS	Colorectal	All: no crossover	Systemic	7	NR			LR: adjusted R^2 (log-OR ORR vs. log-HR PFS)	Adjusted $R^2 = 0.63$ (95% CI 0.03 to 0.99); $p =$ NR	log-HR PFS = −0.05 − 0.31 × log-OR ORR	NR	Medium	NE
Tsujino 2010[140]	ORR	PFS	Colorectal	NR	Targeted	7	NR			LR (unweighted) R^2 (difference in ORR vs. HR PFS)	$R^2 = 0.65$; $p = 0.029$	Slope: −0.037	NR	Medium	NE
Blumenthal 2017[85]	ORR	PFS	Lung (NSCLC)	Various	Chemotherapy, immune checkpoint inhibitors or targeted therapy	25	20,013[b]			(a) WLR R^2: OR ORR vs. HR PFS	(a) $R^2 = 0.74$ (95% CI 0.55 to 0.88); $p =$ NR		NR	Medium +	NE
										(b) WLR R^2: 6-month ratio ORR vs. HR PFS	(b) $R^2 = 0.70$ (95% CI 0.50 to 0.84); $p =$ NR				
Blumenthal 2015[84]	ORR	PFS	Lung (NSCLC)	Various	Chemotherapy or targeted therapy	14	12,567[b]			WLR R^2 (log-OR ORR vs. log-HR PFS)	$R^2 = 0.89$ (95% CI 0.80 to 0.98); $p =$ NR		NR	Medium +	NE
Blumenthal 2015[84]	ORR	PFS	Lung (NSCLC)	Various	Chemotherapy	11	11,701[b]			WLR R^2 (log-OR ORR vs. log-HR PFS)	$R^2 = 0.77$ (95% CI 0.58 to 0.96); $p =$ NR		NR	Medium +	NE
Ito 2019[145]	ORR	PFS	Lung (NSCLC)	Various	Immune [PD-(L)1]	6	3752[b]	(a) Pearson weighted	(a) $r = -0.87$; $p < 0.0001$	WLR R^2 (OR ORR vs. HR PFS)	$R^2 = 0.76$; $p = 0.011$		NR	Medium +	Fair
								(b) Spearman weighted (OR ORR vs. HR PFS)	(b) $r_s = -0.97$; $p < 0.0001$						
Ito 2019[145]	ORR	PFS	Lung (NSCLC)	Various: high PD-L1 expression	Immune checkpoint inhibitors [PD-(L)1]	7	1381	(a) Pearson weighted	(a) $r = 0.67$; $p < 0.0001$	WLR R^2 (OR ORR vs. HR PFS)	$R^2 = 0.45$; $p = 0.101$		NR	Low	Good
								(b) Spearman weighted (OR ORR vs. HR PFS)	(b) $r_s = 0.56$; $p < 0.0001$						

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Ritchie 2018[128]	ORR	PFS	Lung (NSCLC)	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	8	NR	Correlation (NR), weighted (OR ORR vs. HR PFS)	$r = 0.74$ (95% CI 0.38 to 1.08); $p =$ NR				NR	Medium	Good
Roviello 2017[130]	ORR	PFS	Lung (NSCLC)	Various	Immune checkpoint inhibitors	7[a]	3369[a]			WLR R^2 (log-OR ORR vs. log-HR PFS)	$R^2 = 0.42$ (95% CI 0.003 to 0.85); $p = 0.06$		NR	Low	NE
Tsujino 2010[140]	ORR	PFS	Lung (NSCLC)	NR	Targeted	6	NR			LR (unweighted) R^2 (difference in ORR vs. HR PFS)	$R^2 = 0.94$; $p = 0.002$	Slope: −0.015	NR	Medium +	NE
Colloca 2017[90]	ORR	PFS	Ovarian	First	Chemotherapy	29	NR	Spearman (difference in ORR vs. difference in median PFS)	$r_s = 0.64$; $p < 0.001$	LR R^2 (log-RR ORR vs. log-HR PFS)	$R^2 = 0.28$; $p = 0.005$		NR	Low	NE
Colloca 2017[90]	ORR	PFS	Ovarian	First: published 1990–2002	Chemotherapy	15	NR	Spearman (difference in ORR vs. difference in median PFS)	$r_s = 0.64$; $p = 0.018$	LR R^2 (log-RR ORR vs. log-HR PFS)	$R^2 = 0.32$; $p = 0.046$		NR	Low	NE
Colloca 2017[90]	ORR	PFS	Ovarian	First: published 2003–16	Chemotherapy	16	NR	Spearman (difference in ORR vs. difference in median PFS)	$r_s = 0.58$; $p = 0.019$	LR R^2 (log-RR ORR vs. log-HR PFS)	$R^2 = 0.53$; $p = 0.003$		NR	Medium	NE
Siddiqui 2017[135]	ORR	PFS	Ovarian	Second and subsequent	Chemotherapy	39[b]	9223[b]	Pearson weighted (OR ORR vs. HR PFS)	$r = 0.42$; $p =$ NR				NR	Low	Poor
Colloca 2016[91]	ORR	PFS	Pancreatic	First	Gemcitabine and chemotherapy or targeted therapy	33[a]	NR	Spearman (difference in ORR vs. difference in median PFS)	$r_s = 0.34$; $p =$ NR				NR	Low	NE
Colloca 2016[91]	ORR	PFS	Pancreatic	First	Gemcitabine and targeted therapy	14[a]	NR	Spearman (difference in ORR vs. difference median PFS)	$r_s = 0.25$; $p =$ NR				NR	Low	NE
Ritchie 2018[128]	ORR	PFS	Various solid tumours	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	20[b]	10,828[b]	Correlation (NR), weighted (OR ORR vs. HR PFS)	$r = 0.63$ (95% CI 0.35 to 0.89); $p =$ NR				NR	Medium	Poor

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Roviello 2017[130]	ORR	PFS	Various solid tumours	Various	Immune checkpoint inhibitors	17[b]	8994[b]			WLR R^2 (log-OR ORR vs. log-HR PFS)	$R^2 = 0.32$ (95% CI 0.02 to 0.76); $p = 0.01$	log-HR PFS = –0.1281 – 0.2384 × log-OR ORR	NR	Low	NE
Roviello 2017[130]	ORR	PFS	Various solid tumours	Various	Immune checkpoint inhibitors (CTLA-4)	17[b]	8994[b]			WLR R^2 (log-OR ORR vs. log-HR PFS)	$R^2 = 0.67$ (95% CI 0.02 to 1.00); $p = 0.05$		NR	Medium	NE
Roviello 2017[130]	ORR	PFS	Various solid tumours	Various	Immune checkpoint inhibitors [PD-(L)1]	17[b]	8994[b]			WLR R^2 (log-OR ORR vs. log-HR PFS)	$R^2 = 0.25$ (95% CI 0.02 to 1.00); $p = 0.08$		NR	Low	NE
Tsujino 2010[140]	ORR	PFS	Various solid tumours	NR	Targeted	17	NR			LR (unweighted) R^2 (difference in ORR vs. HR PFS)	$R^2 = 0.50$; $p = 0.001$	Slope: –0.022	15%	Medium	NE
Wilkerson 2009[142]	ORR	PFS	Various solid tumours	NR	NR	66[b]	NR			(a) LR (unweighted R^2): difference in ORR vs. HR PFS	(a) $R^2 = 0.45$; $p < 0.0001$		NR	Medium	NE
										(b) LR (unweighted R^2): difference in ORR vs. difference in median PFS	(b) $R^2 = 0.62$; $p < 0.0001$				
ORR vs. OS															
Moriwaki 2016[119]	ORR	OS	Biliary tract	First	Chemotherapy	17[b]	2040			WLR R^2 (ratio ORR vs. log-ratio median OS)	$R^2 = 0.29$ (95% CI 0.01 to 0.65); $p = 0.021$	log-ratio median OS = 0.013 + 0.282 × ratio ORR	NR	Low	NE
Moriwaki 2016[119]	ORR	OS	Biliary tract	First	Chemotherapy (gemcitabine)	14[b]	1880			WLR R^2 (ratio ORR vs. log-ratio median OS)	$R^2 = 0.39$ (95% CI 0.02 to 0.75); $p = 0.013$	log-ratio median OS = 0.020 + 0.268 × ratio ORR	NR	Low	NE
Moriwaki 2016[119]	ORR	OS	Biliary tract	First	Targeted	6[b]	953			WLR R^2 (ratio ORR vs. log-ratio median OS)	$R^2 = 0.43$ (95% CI 0.03 to 0.89); $p = 0.090$	log-ratio median OS = 0.119 + 0.155 × ratio ORR	NR	Low	NE

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Bruzzi 2005[86]	ORR	OS	Breast	All	Chemotherapy	10	2126			(a) WLR R^2: log-OR ORR vs. log-HR OS	(a) $R^2 = 0.10$ (95% CI 0.00 to 0.43); p = NR		NR	Low	NE
										(b) WLR R^2: difference in ORR vs. difference in median OS	(b) $R^2 = 0.20$ (95% CI 0 to 0.65); p = NR				
Burzykowski 2008[87]	ORR	OS	Breast	First	Chemotherapy	11	3953	Spearman via LR with Plackett copula (log-OR ORR vs. log-HR OS)	$r_s = 0.57$ (95% CI −0.31 to 1.44); p = NR				NR	Medium	NE
Hackshaw 2005[99]	ORR	OS	Breast	First	Chemotherapy	42[a]	9163			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.34$; $p < 0.0001$	log-HR OS = −0.0081 + 0.28 × log-OR ORR	NR	Low	NE
												Slope: 0.28			
Hackshaw 2005[99]	ORR	OS	Breast	First: recruited pre-1990	Chemotherapy	26[a]	5244[a]			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.26$; $p = 0.004$	Slope: 0.28	NR	Low	NE
Hackshaw 2005[99]	ORR	OS	Breast	First: recruited 1990 or after	Chemotherapy	16[a]	3919[a]			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.41$; $p = 0.005$	Slope: 0.24	NR	Low	NE
Buyse 2000[88]	ORR	OS	Colorectal	First	Chemotherapy	25	3791			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.38$ (95% CI 0.09 to 0.68); p = NR		NR	Low	NE
Ciani 2015[89] Elia 2020[96]	ORR	OS	Colorectal	All	Systemic	32	NR	Spearman (log-OR ORR vs. log-OR OS)	$r_s = 0.53$; $p < 0.01$	(a) WLSR R^2 (log-OR ORR vs. log-OR OS) (time point NR)	(a) $R^2 = 0.06$ (95% CI 0.01 to 0.29); p = NR	log-HR OS = −0.03 − 0.05 × log-OR ORR	0.28	Low	NE
										(b) Adjusted R^2 (log-OR ORR vs. log-HR OS)	(b) Adjusted $R^2 = 0.33$ (95% CI 0.00 to 0.91); p = NR				
Ciani 2015[89] Elia 2020[96]	ORR	OS	Colorectal	All: no crossover	Systemic	7	NR			LR: adjusted R^2 (log-OR ORR vs. log-HR OS)	Adjusted $R^2 = 0.40$ (95% CI 0.00 to 0.96); p = NR	log-HR OS = −0.04 − 0.10 × log-OR ORR	NR	Low	NE
Colloca 2016[92]	ORR	OS	Colorectal	First	Bevacizumab and chemotherapy	11	NR	Spearman (difference in ORR vs. difference in median OS)	$r_s = 0.82$; $p < 0.001$	LR R^2 (difference in ORR vs. difference in median OS)	$R^2 = 0.58$; $p = 0.002$		NR	Medium	NE

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Cremolini 2017[94]	ORR	OS	Colorectal	Second	Targeted	20[a]	7571	(a) Pearson (via WLR): rr ORR vs. HR OS	(a) $r = 0.17$; $p = 0.476$	(a) WLR R^2: rr ORR vs. HR OS	(a) $R^2 = 0.03$; $p = 0.476$	(a) Slope: 0.029	NR	Low	NE
								(b) Pearson (via WLR): difference in ORR vs. difference in median OS	(b) $r = 0.35$; $p = 0.092$	(b) WLR R^2: difference in ORR vs. difference in median OS	(b) $R^2 = 0.12$; $p = 0.092$	(b) Slope: 0.071			
Cremolini 2017[94]	ORR	OS	Colorectal	Second	Targeted, anti-angiogenic	13[a]	NR	(a) Pearson (via WLR): rr ORR vs. HR OS	(a) $r = 0.36$; $p = 0.249$	(a) WLR R^2: rr ORR vs. HR OS	(b) $R^2 = 0.13$; $p = 0.249$	(a) Slope: −0.113	NR	Low	NE
								(b) Pearson (via WLR): difference in ORR vs. difference in median OS	(b) $r = 0.52$; $p = 0.038$	(b) WLR R^2: difference in ORR vs. difference in median OS	(b) $R^2 = 0.27$; $p = 0.038$	(b) Slope: 0.133			
Cremolini 2017[94]	ORR	OS	Colorectal	Second	Targeted, not anti-angiogenic	7[a]	NR	(a) Pearson (via WLR): rr ORR vs. HR OS	(a) $r = 0.44$; $p = 0.274$	(a) WLR R^2: rr ORR vs. HR OS	(b) $R^2 = 0.20$; $p = 0.274$	(a) Slope: −0.064	NR	Low	NE
								(b) Pearson (via WLR): difference in ORR vs. difference in median OS	(b) $r = 0.63$; $p = 0.068$	(b) WLR R^2: difference in ORR vs. difference in median OS	(b) $R^2 = 0.40$; $p = 0.068$	(b) Slope: 0.143			
Johnson 2006[109]	ORR	OS	Colorectal	First	Chemotherapy	146[b]	35,337[b]			WLSR R^2 (difference in ORR vs. difference om median OS)	$R^2 = 0.10$; $p < 0.0001$	Difference in median OS = 0.340 + 0.096 × difference in ORR	NR	Low	NE
Sidhu 2013[136]	ORR	OS	Colorectal	First (most)	Chemotherapy ± targeted	24[b]	20,438[b]	(a) Correlation (NR): OR ORR vs. HR OS	(a) $r = 0.62$ (95% CI 0.37 to 0.79); p = NR	(a) LR (unweighted) R^2: OR ORR vs. HR OS	(a) $R^2 = 0.39$ (95% CI 0.13 to 0.62); p = NR		NR	Medium	NE
								(b) Correlation (NR): difference in ORR vs. HR OS	(b) $r = 0.64$ (95% CI 0.39 to 0.79); p = NR	(b) LR (unweighted) R^2: difference in ORR vs. HR OS	(b) $R^2 = 0.41$ (95% CI 0.15 to 0.63); p = NR				
								(c) Correlation (NR): ratio ORR vs. HR OS	(c) $r = 0.52$ (95% CI 0.23 to 0.72); p = NR	(c) LR (unweighted) R^2: ratio ORR vs. HR OS	(c) $R^2 = 0.27$ (95% CI 0.05 to 0.52); p = NR				

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Sidhu 2013[136]	ORR	OS	Colorectal	First (most)	Targeted and chemotherapy	13	12,060[a]	(a) Correlation (NR): OR ORR vs. HR OS	(a) $r = 0.50$ (95% CI 0.05 to 0.75); $p =$ NR	(a) LR (unweighted) R^2: OR ORR vs. HR OS	(a) $R^2 = 0.25$ (95% CI 0.00 to 0.57); $p =$ NR		NR	Medium	NE
								(b) Correlation (NR): difference in ORR vs. HR OS	(b) $r = 0.58$ (95% CI 0.19 to 0.80); $p =$ NR	(b) LR (unweighted) R^2: difference in ORR vs. HR OS	(b) $R^2 = 0.33$ (95% CI 0.04 to 0.64); $p =$ NR				
								(c) Correlation (NR): ratio ORR vs. HR OS	(c) $r = 0.42$ (95% CI 0.00 to 0.71); $p =$ NR	(c) LR (unweighted) R^2: ratio ORR vs. HR OS	(c) $R^2 = 0.18$ (95% CI 0.00 to 0.51); $p =$ NR				
Sidhu 2013[136]	ORR	OS	Colorectal	First (most)	Targeted (anti-*EGFR*)	9	7792[a]	(a) Correlation (NR): OR ORR vs. HR OS	(a) $r = 0.67$ (95% CI 0.27 to 0.86); $p =$ NR	(a) LR (unweighted) R^2: OR ORR vs. HR OS	(a) $R^2 = 0.45$ (95% CI 0.07 to 0.74), $p =$ NR		NR	Medium	NE
								(b) Correlation (NR): difference in ORR vs. HR OS	(b) $r = 0.72$ (95% CI 0.35 to 0.88); $p =$ NR	(b) LR (unweighted) R^2: difference in ORR vs. HR OS	(b) $R^2 = 0.52$ (95% CI 0.12 to 0.78); $p =$ NR				
								(c) Correlation (NR): ratio ORR vs. HR OS	(c) $r = 0.52$ (95% CI 0.00 to 0.79); $p =$ NR	(c) LR (unweighted) R^2: ratio ORR vs. HR OS	(c) $R^2 = 0.27$ (95% CI 0.00 to 0.62); $p =$ NR				
Sidhu 2013[136]	ORR	OS	Colorectal	First (most)	Targeted (anti-*EGFR*), *KRAS* non-mutant	6[a]	4916[a]	(a) Correlation (NR): OR ORR vs. HR OS	(a) $r = 0.68$ (95% CI 0.07 to 0.89); $p =$ NR	(a) LR (unweighted) R^2: OR ORR vs. HR OS	(a) $R^2 = 0.46$ (95% CI 0.01 to 0.80); $p =$ NR		NR	Medium	NE
								(b) Correlation (NR): difference in ORR vs. HR OS	(b) $r = 0.81$ (95% CI 0.38 to 0.94); $p =$ NR	(b) LR (unweighted) R^2: difference in ORR vs. HR OS	(b) $R^2 = 0.65$ (95% CI 0.15 to 0.88); $p =$ NR				
								(c) Correlation (NR): ratio ORR vs. HR OS	(c) $r = 0.48$ (95% CI 0.00 to 0.82); $p =$ NR	(c) LR (unweighted) R^2: ratio ORR vs. HR OS	(c) $R^2 = 0.23$ (95% CI 0.00 to 0.67); $p =$ NR				
Tang 2007[138]	ORR	OS	Colorectal	First	Chemotherapy	39	18,668	Spearman (difference in ORR vs. difference in median OS)	$r_s = 0.39$ (95% CI 0.08 to 0.63); $p = 0.015$				NR	Low	Poor

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Tsujino 2010[140]	ORR	OS	Colorectal	NR	Targeted therapy	7	NR			LR (unweighted) R^2 (difference in ORR vs. HR OS)	$R^2 = 0.51$; $p = 0.072$	Slope: 0.029	NR	Medium	NE
Blumenthal 2017[85]	ORR	OS	Lung (NSCLC)	Various	Chemotherapy, immune checkpoint inhibitors or targeted therapy	25	20,013[b]			(a) WLR R^2: OR ORR vs. HR OS	(a) $R^2 = 0.04$ (95% CI 0.0002 to 0.28); p = NR		NR	Low	NE
										(b) WLR R^2: 6-month ratio ORR vs. HR OS	(b) $R^2 = 0.05$ (95% CI 0.0001 to 0.31); p = NR				
Blumenthal 2015[84]	ORR	OS	Lung (NSCLC)	Various	Chemotherapy or targeted therapy	14	12,567[b]			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.09$ (95% CI 0 to 0.33); p = NR		NR	Low	NE
Blumenthal 2015[84]	ORR	OS	Lung (NSCLC)	Various	Chemotherapy	11	11,701[b]			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.44$ (95% CI 0.08 to 0.80); p = NR		NR	Low	NE
Hashim 2018[102]	ORR	OS	Lung (NSCLC)	Second and subsequent	Various	140	41,725	(a) Correlation (NR) via WLR: difference in ORR vs. log-HR OS	(a) $r = 0.17$ (95% CI 0.00 to 0.38); p = NR				NA	Low	NE
								(b) Correlation (NR) via WLR: difference in ORR vs. difference in median OS	(b) $r = 0.18$ (95% CI 0.02 to 0.34); $p = 0.032$						
Hashim 2018[102]	ORR	OS	Lung (NSCLC)	Second and Phase III	Various	59	32,348	(a) Correlation (NR) via WLR: difference in ORR vs. log-HR OS	(a) $r = 0.37$ (95% CI 0.09 to 0.60); p = NR				NA	Low	NE
								(b) Correlation (NR) via WLR: difference in ORR vs. difference in median OS	(b) $r = 0.13$ (95% CI 0.00 to 0.38); $p = 0.32$						

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Hashim 2018[102]	ORR	OS	Lung (NSCLC)	Second and Phase III, excluding per–protocol crossover	Various	54	30,654	(a) Correlation (NR) via WLR: difference in ORR vs. log-HR OS	(a) $r = 0.40$ (95% CI 0.10 to 0.63); $p =$ NR				NA	Low	NE
								(b) Correlation (NR) via WLR: difference in ORR vs. difference in median OS	(b) $r = 0.36$ (95% CI 0.10 to 0.57); $p = 0.0074$						
Hashim 2018[102]	ORR	OS	Lung (NSCLC)	Second and Phase III, excluding per–protocol crossover	Various	38	22,574	(a) Correlation (NR) via WLR: difference in ORR vs. log-HR OS	(a) $r = 0.52$ (95% CI 0.18 to 0.75); $p =$ NR				(a) 55%	Medium	NE
								(b) Correlation (NR) via WLR: difference in ORR vs. difference in median OS	(b) $r = 0.45$ (95% CI 0.15 to 0.67); $p = 0.0051$				(b) NA		
Hashim 2018[102]	ORR	OS	Lung (NSCLC)	Second and Phase III, excluding crossover or unbalanced post-progression treatments	Various	18	13,349	(a) Correlation (NR) via WLR: difference in ORR vs. log-HR OS	(a) $r = 0.16$ (95% CI 0.00 to 0.60); $p =$ NR				(a) NA	Low	NE
								(b) Correlation (NR) via WLR: difference in ORR vs. difference in median OS	(b) $r = 0.53$ (95% CI 0.08 to 0.80); $p = 0.024$				(b) 41%		
Hotta 2015[103]	ORR	OS	Lung (NSCLC)	Various	Targeted therapy	18	7633[b]			WLR R^2 (OR ORR vs. HR OS)	$R^2 = 0.10$; $p =$ NR		NR	Low	NE
Hotta 2015[103]	ORR	OS	Lung (NSCLC)	Various and molecularly selected	Targeted therapy	8	NR			WLR R^2 (OR ORR vs. HR OS)	$R^2 = 0.04$; $p =$ NR		NR	Low	NE
Hotta 2015[103]	ORR	OS	Lung (NSCLC)	Various: non-molecularly selected	Targeted therapy	10	NR			WLR R^2 (OR ORR vs. HR OS)	$R^2 = 0.43$; $p =$ NR		NR	Low	NE

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Ito 2019[145]	ORR	OS	Lung (NSCLC)	Various	Immune checkpoint inhibitors [PD-(L)1]	6	3752[b]	(a) Pearson weighted	(a) $r = -0.75$; $p < 0.0001$	WLR R^2 (OR ORR vs. HR OS)	$R^2 = 0.57$; $p = 0.051$		NR	Medium	Poor
								(b) Spearman weighted (OR ORR vs. HR OS)	(b) $r_s = -0.96$; $p < 0.0001$						
Ito 2019[145]	ORR	OS	Lung (NSCLC)	Various: high PD-L1 expression	Immune checkpoint inhibitors [PD-(L)1]	7	1381	(a) Pearson weighted	(a) $r = -0.50$; $p < 0.0001$	WLR R^2 (OR ORR vs. HR OS)	$R^2 = 0.25$; $p = 0.253$		NR	Low	Fair
								(b) Spearman weighted (OR ORR vs. HR OS)	(b) $r_s = -0.21$; $p < 0.0001$						
Johnson 2006[109]	ORR	OS	Lung (NSCLC)	First	Chemotherapy	191[b]	44,125[b]			WLSR R^2 (difference in ORR vs. difference in median OS)	$R^2 = 0.16$; $p < 0.0001$	Difference in median OS = −0.048 + 0.090 × difference in ORR	NR	Low	NE
Nakashima 2016[121]	ORR	OS	Lung (NSCLC)	First	Chemotherapy	44	22,709	Spearman, weighted (ln-OR ORR vs. HR OS)	$r_s = 0.57$; $p =$ NR	WLSR adjusted R^2 (ln-OR ORR vs. ln-HR OS)	Adjusted $R^2 = 0.35$; $p =$ NR	ln-HR OS = −0.023 − 0.133 × ln-OR ORR	NR	Low	NE
Ritchie 2018[128]	ORR	OS	Lung (NSCLC)	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	8	NR	Correlation (NR) weighted (OR ORR vs. HR OS)	$r = 0.68$ (95% CI 0.08 to 1.10); $p =$ NR				NR	Low	Good
Roviello 2017[130]	ORR	OS	Lung (NSCLC)	Various	Immune checkpoint inhibitors	7[a]	3369[a]			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.0007$ (95% CI 0.09 to 0.91); $p = 0.94$		NR	Low	NE
Tsujino 2010[140]	ORR	OS	Lung (NSCLC)	NR	Targeted therapy	5	NR			LR (unweighted) R^2 (difference in ORR vs. HR OS)	$R^2 = 0.84$; $p = 0.030$	Slope: −0.011	NR	Medium +	NE
Foster 2011[97]	ORR	OS	Lung (SCLC)	First	Chemotherapy	3 (32 centres)	596[b]	Spearman (log-OR ORR vs. log-HR OS)	$r_s = 0.52$; $p =$ NR	WLSR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.21$; $p =$ NR		NR	Low	NE
Hotta 2009[104]	ORR	OS	Lung (SCLC)	First	Chemotherapy	48	8779			WLR R^2 (rr ORR vs. difference in median OS)	$R^2 = 0.33$; $p =$ NR	Difference in median OS = 0.00 + 0.06 × rr ORR	NR	Low	NE
Hotta 2009[104]	ORR	OS	Lung (SCLC)	First: clear criteria	Chemotherapy	43 comparisons	NR			WLR R^2 (rr ORR vs. difference in median OS)	$R^2 = 0.19$; $p =$ NR		NR	Low	NE
Hotta 2009[104]	ORR	OS	Lung (SCLC)	First: WHO criteria	Chemotherapy	23 comparisons	NR			WLR R^2 (rr ORR vs. difference in median OS)	$R^2 = 0.13$; $p =$ NR		NR	Low	NE

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Hotta 2009[104]	ORR	OS	Lung (SCLC)	First: non-WHO criteria	Chemotherapy	20 comp	NR			WLR R^2 (rr ORR vs. difference in median OS)	$R^2 = 0.28$; $p =$ NR		NR	Low	NE
Hotta 2009[104]	ORR	OS	Lung (SCLC)	First: published 1990–6	Chemotherapy	26 comp	NR			WLR R^2 (rr ORR vs. difference in median OS)	$R^2 = 0.23$; $p =$ NR	Difference in median OS = 0.00 + 0.04 × rr ORR	NR	Low	NE
Hotta 2009[104]	ORR	OS	Lung (SCLC)	First: published 1997–2008	Chemotherapy	26 comp	NR			WLR R^2 (rr ORR vs. difference in median OS)	$R^2 = 0.47$; $p =$ NR	Difference in median OS = 0.00 + 0.09 × rr ORR	NR	Low	NE
Colloca 2017[90]	ORR	OS	Ovarian	First	Chemotherapy	27	NR	Spearman (difference in ORR vs. difference in median OS)	$r_s = 0.41$; $p = 0.035$	LR R^2 (log-RR ORR vs. log-HR OS)	$R^2 = 0.12$; $p = 0.073$		NR	Low	NE
Colloca 2017[90]	ORR	OS	Ovarian	First: published 1990–2002	Chemotherapy	13	NR	Spearman (difference in ORR vs. difference in median OS)	$r_s = 0.65$; $p = 0.016$	LR R^2 (log-RR ORR vs. log-HR OS)	$R^2 = 0.15$; $p = 0.199$		NR	Low	NE
Colloca 2017[90]	ORR	OS	Ovarian	First: published 2003–16	Chemotherapy	14	NR	Spearman (difference in ORR vs. difference in median OS)	$r_s = -0.02$; $p = 0.940$	LR R^2 (log-RR ORR vs. log-HR OS)	$R^2 = 0.34$; $p = 0.027$		NR	Low	NE
Siddiqui 2017[135]	ORR	OS	Ovarian	Second and subsequent	Chemotherapy	31[b]	9223[b]						NR	NE	NE
Colloca 2016[91]	ORR	OS	Pancreatic	First	Gemcitabine and chemotherapy or targeted therapy	36[a]	NR	Spearman (difference in ORR vs. difference in median OS)	$r_s = 0.29$; $p = 0.067$				NR	Low	NE
Colloca 2016[91]	ORR	OS	Pancreatic	First	Gemcitabine and chemotherapy	22[a]	NR	Spearman (difference in ORR vs. difference in median OS)	$r_s = 0.23$; $p = 0.250$	LR R^2 (log-RR ORR vs. log-HR OS)	$R^2 = 0.15$; $p =$ NR		NR	Low	NE
Colloca 2016[91]	ORR	OS	Pancreatic	First	Gemcitabine and targeted therapy	14[a]	NR	Spearman (difference in ORR vs. difference in median OS)	$r_s = 0.55$; $p = 0.035$	LR R^2 (log-RR ORR vs. log-HR OS)	$R^2 = 0.28$; $p =$ NR		NR	Low	NE

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Hamada 2016[100]	ORR	OS	Pancreatic	First	Chemotherapy	36	15,906[b]	Spearman via WLSR (log-OR ORR vs. log-HR OS)	$r_s = -0.16$ (95% CI −0.27 to −0.05); $p = 0.007$	WLSR adjusted R^2 (log-OR ORR vs. log-HR OS)	Adjusted $R^2 = 0.30$; $p = 0.007$		NR	Low	Poor
Makris 2017[116]	ORR	OS	Pancreatic (adenocarcinoma)	First	Chemotherapy (gemcitabine)	22[a]	10,379[a]	(a) Pearson (log-HR OS vs. log-OR ORR): weighted by sample size	(a) $r = 0.27$ (95% CI −0.14 to 0.60); $p = 0.20$				NR	Low	NE
								(b) Pearson (log-HR OS vs. log-OR ORR): fixed effect	(b) $r = 0.52$ (95% CI 0.16 to 0.76); $p = 0.007$						
								(c) Pearson (log-HR OS vs. log-OR ORR): random effects	(c) $r = 0.45$ (95% CI 0.07 to 0.72); $p = 0.02$						
Colloca 2016[93]	ORR	OS	Prostate	First and second	Chemotherapy, hormonal and targeted therapy	17	NR	Pearson (difference in ORR vs. difference in median OS)	$r = 0.38$; $p = 0.132$	LR R^2 (log-RR ORR vs. log-HR OS)	$R^2 = 0.007$; $p = 0.789$		NR	Low	NE
Colloca 2016[93]	ORR	OS	Prostate	First and second: published 1995–2004	Chemotherapy, hormonal and targeted therapy	5	NR	Pearson (difference in ORR vs. difference in median OS)	$r = 0.35$; $p = 0.560$	LR R^2 (log-RR ORR vs. log-HR OS)	$R^2 = 0.53$; $p = 0.275$		NR	Medium	NE
Colloca 2016[93]	ORR	OS	Prostate	First and second: published 2005–14	Chemotherapy, hormonal and targeted therapy	12	NR	Pearson (difference in ORR vs. difference in median OS)	$r = 0.41$; $p = 0.185$	LR R^2 (log-RR ORR vs. log-HR OS)	$R^2 = 0.02$; $p = 0.690$		NR	Low	NE
Delea 2012[95]	ORR	OS	Renal cell	NR	Cytokine or targeted therapy	25[a]	10,943[b]	Pearson weighted (ln-rr ORR vs. −ln-HR OS)	$r = 0.78$; $p < 0.0001$	WLSR adjusted R^2 (ln-rr ORR vs. −ln-HR OS)	Adjusted $R^2 = 0.59$; $p < 0.0001$	−ln-HR OS = −0.11 + 0.30 × ln-rr ORR	NR	Medium	NE
Petrelli 2013[126]	ORR	OS	Renal cell	First	Targeted therapy	6[b]	3188[b]	(a) Pearson weighted	(a) $r = 0.52$; $p < 0.0001$	LR	$R^2 = 0.27$; $p =$ NR		NR	Low	Fair
								(b) Spearman weighted (difference in median OS vs. difference in ORR)	(b) rs = 0.49; $p < 0.0001$						

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Tanaka 2019[137]	ORR	OS	Soft tissue sarcoma	First	Chemotherapy	27[b]	6156[b]	Kendall's Tau (log-OR ORR vs. log-HR OS)	$\tau = 0.41$; $p =$ NR	Regression (NR) R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.28$ (95% CI 0.02 to 0.54); $p =$ NR		NR	Low	NE
Zer 2016[143]	ORR	OS	Soft tissue sarcoma	All	Systemic	52[b]	9762[b]	Correlation (NR) via WLR (OR ORR vs. HR OS)	$r = 0.51$; $p =$ NR				NR	Low	NE
Kaufman 2018[110]	ORR	OS	Various solid tumours	Various	Immune checkpoint inhibitors and chemotherapy	27[b]	10,300[b]			WLR adjusted R^2 (OR ORR vs. HR OS)	Adjusted $R^2 = -0.07$; $p = 0.866$		NR	NE	NE
Kaufman 2018[110]	ORR	OS	Various solid tumours	Various	Immune checkpoint inhibitors alone	NR	NR			WLR adjusted R^2 (OR ORR vs. HR OS)	Adjusted $R^2 = -0.08$; $p = 0.799$		NR	NE	NE
Mushti 2018[120]	ORR	OS	Various solid tumours	NR	Immune checkpoint inhibitors [PD-(L)1]	13	6722			WLR R^2 (OR ORR vs. HR OS)	$R^2 = 0.13$; $p =$ NR		NR	Low	NE
Nie 2019[123]	ORR	OS	Various solid tumours	Various	Immune checkpoint inhibitors [PD-(L)1]	43[b]	15,088[b]			WLR R^2 (ln-OR ORR vs. ln-HR OS)	$R^2 = 0.10$; $p = 0.053$		NR	Low	Poor
Ritchie 2018[128]	ORR	OS	Various solid tumours	All	Immune checkpoint inhibitors [PD-(L)1 or CTLA4]	20[b]	10,828[b]	Correlation (NR), weighted (OR ORR vs. HR OS)	$r = 0.57$ (95% CI 0.23 to 0.89); $p =$ NR				NR	Low	Poor
Roviello 2017[130]	ORR	OS	Various solid tumours	Various	Immune checkpoint inhibitors	17[b]	8994[b]			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.47$ (95% CI 0.03 to 0.77); $p = 0.001$	log-HR OS = −0.1329 − 0.2575 × log-OR ORR	NR	Low	NE
Roviello 2017[130]	ORR	OS	Various solid tumours	Various	Immune checkpoint inhibitors (CTLA-4)	17[b]	8994[b]			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.00$ (95% CI 0.00 to 0.97); $p = 0.96$		NR	Low	NE
Roviello 2017[130]	ORR	OS	Various solid tumours	Various	Immune checkpoint inhibitors [PD-(L)1]	17[b]	8994[b]			WLR R^2 (log-OR ORR vs. log-HR OS)	$R^2 = 0.18$ (95% CI 0.00 to 0.97); $p = 0.17$		NR	Low	NE
Tsujino 2010[140]	ORR	OS	Various solid tumours	NR	Targeted therapy	18	NR			LR (unweighted) R^2 (difference in ORR vs. HR OS)	$R^2 = 0.47$; $p = 0.002$	Slope: −0.016	21%	Low	NE
Wilkerson 2009[142]	ORR	OS	Various solid tumours	NR	NR	66[b]	NR			(a) LR (unweighted R^2): difference in ORR vs. HR OS	(a) $R^2 = 0.37$; $p < 0.0001$		NR	Low	NE
										b) LR (unweighted R^2): difference in ORR vs. difference in median OS	(b) $R^2 = 0.34$; $p < 0.0001$				

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
CR vs. PFS															
Lee 2011[111]	CR	PFS	NHL (aggressive)	First	Chemotherapy	12[b]	NR	Spearman (difference in CR vs. difference in 3-year PFS)	$r_s = 0.63$ (95% CI 0.21 to 0.84); $p = 0.005$				NR	Medium	NE
Lee 2011[111]	CR	PFS	NHL (indolent)	First	Chemotherapy	6[b]	NR	Spearman (difference in CR vs. difference in 3-year PFS)	$r_s = 0.41$ (95% CI −0.52 to 0.88); $p = 0.35$				NR	Medium	NE
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First	Chemotherapy or immunotherapy (induction or maintenance)	13	3837			(a) WLSR R^2	(a) R^2 WLS = 0.88 (95% CI 0.77 to 0.96); p = NR	log-HR PFS = −0.093 − 0.636 × log-OR CR 30 months	1.56	Medium +	NE
										(b) Bivariate Plackett copula model (log-OR CR 30 months vs. log-HR PFS)	(b) R^2 Copula = 0.86 (95% CO 0.72 to 1.00); p = NR				
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First	Rituximab-based (induction or maintenance)	9	2851			(a) WLSR R^2	(a) R^2 WLS = 0.85 (95% CI 0.62 to 0.97); p = NR		NR	Medium +	NE
										(b) Bivariate Plackett copula model (log-OR CR 30 months vs. log-HR PFS)	(b) R^2 Copula = 0.80 (95% CI 0.56 to 1.00); p = NR				
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First	Non-rituximab-based (induction or maintenance)	4	986			(a) WLSR R^2	(a) R^2 WLS = 0.91 (95% CI 0.05 to 1.00); p = NR		NR	Medium +	NE
										(b) Bivariate Plackett copula model (log-OR CR 30 months vs. log-HR PFS)	(b) R^2 Copula = 0.96 (95% CI 0.90 to 1.00); p = NR				
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First	Induction	8	2207			(a) WLSR R^2	(a) R^2 WLS = 0.89 (95% CI 0.75 to 0.98); p = NR		NR	Medium +	NE
										(b) Bivariate Plackett copula model (log-OR CR 30 months vs. log-HR PFS)	(b) R^2 Copula = 0.89 (95% CI 0.74 to 1.00); p = NR				

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First	Maintenance	5	1630			(a) WLS (reported as R^2 WLS)	(a) R^2 WLS = 0.93 (95% CI 0.84 to 1.00); p = NR		NR	Medium +	NE
										(b) Bivariate Plackett copula model (reported as R^2 copula), CR 30 months vs. PFS	(b) R^2 Copula = 0.89 (95% CI 0.71 to 1.00); p = NR				
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First: high FLIPI score	Chemotherapy or immunotherapy (induction or maintenance)	9	1415			(a) WLSR R^2	(a) R^2 WLS = 0.87 (95% CI 0.68 to 0.98); p = NR		NR	Medium +	NE
										(b) Bivariate Plackett copula model (log-OR CR 30 months vs. log-HR PFS)	(b) R^2 Copula = 0.73 (95% CI 0.42 to 1.00); p = NR				
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First: low to intermediate FLIPI score	Chemotherapy or immunotherapy (induction or maintenance)	10	1882			(a) WLSR R^2	(a) R^2 WLS = 0.45 (95% CI 0.02 to 0.93); p = NR		NR	Low	NE
										(b) Bivariate Plackett copula model (log-OR CR 30 months vs. log-HR PFS)	(b) R^2 Copula = 0.57 (0.17 to 0.97), p = NR				
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First	Chemotherapy or immunotherapy (induction or maintenance)	11	2728			(a) WLSR R^2	(a) R^2 WLS = 0.84 (95% CI 0.63 to 0.95); p = NR	log-HR PFS = 0.043 – 0.726 × log-OR CR 24 months	NR	Medium +	NE
										(b) Bivariate Plackett copula model (log-OR CR 24 months vs. log-HR PFS)	(b) R^2 Copula = 0.67 (95% CI 0.35 to 0.99); p = NR				
Shi 2017[132]	CR	PFS	NHL (indolent; follicular)	First: stage IV	Chemotherapy or immunotherapy (induction or maintenance)	NR	2585			(a) WLSR R^2	(a) R^2 WLS = 0.92 (95% CI 0.85 to 0.97); p = NR		NR	Medium +	NE
										(b) Bivariate Plackett copula model (log-OR CR 30 months vs. log-HR PFS)	(b) R^2 Copula = 0.94 (95% CI 0.87 to 1.00); p = NR				
Colloca 2017[90]	CR	PFS	Ovarian	First	Chemotherapy	12	NR	Spearman (difference in RR vs. difference in median PFS)	$r_s = 0.19$; $p = 0.555$				NR	Low	NE

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
CR vs. OS															
Hackshaw 2005[99]	CR	OS	Breast	First	Chemotherapy	41[a]	9163[b]			WLR R^2 (log-OR CR vs. log-HR OS)	$R^2 = 0.12$; $p = 0.02$	log-HR OS = −0.0097 + 0.13 × log-OR CR Slope: 0.13	NR	Low	NE
Hackshaw 2005[99]	CR	OS	Breast	First: recruited pre-1990	Chemotherapy	26[a]	5244[b]			WLR R^2 (log-OR CR vs. log-HR OS)	$R^2 = 0.05$; $p = 0.24$	Slope: 0.09	NR	Low	NE
Hackshaw 2005[99]	CR	OS	Breast	First: recruited 1990 or after	Chemotherapy	15[a]	3919[b]			WLR R^2 (log-OR CR vs. log-HR OS)	$R^2 = 0.36$; $p = 0.01$	Slope: 0.16	NR	Low	NE
Foster 2011[97]	CR	OS	Lung (SCLC)	First	Chemotherapy	Three (32 centres)	596[b]	Spearman (log-OR CR vs. log-HR OS)	$r_s = 0.50$; $p =$ NR	WLSR R^2 (log-OR CR vs. log-HR OS)	$R^2 = 0.48$; $p =$ NR		NR	Low	NE
Lee 2011[111]	CR	OS	NHL (aggressive)	First	Chemotherapy	36[b]	16,103[b]	(a) Spearman: difference in CR vs. difference in 3-year OS	(a) $r_s = 0.58$ (95% CI 0.29 to 0.77); $p = 0.004$				NR	Medium	NE
								(b) Spearman: difference in CR vs. difference in 5-year OS	(b) $r_s = 0.50$ (95% CI 0.23 to 0.74); $p = 0.01$						
Lee 2011[111]	CR	OS	NHL (indolent)	First	Chemotherapy	15[b]	5128[b]	(a) Spearman: difference in CR vs. difference in 3-year OS	(a) $r_s = 0.41$ (95% CI −0.10 to 0.74); $p = 0.098$				NR	Medium	NE
								(b) Spearman: difference in CR vs. difference in 5-year OS	(b) $r_s = 0.21$ (95% CI −0.34 to 0.50); $p = 0.44$						
Colloca 2017[90]	CR	OS	Ovarian	First	Chemotherapy	12	NR	Spearman (difference in pCR vs. difference in median OS)	$r_s = 0.42$; $p = 0.180$				NR	Low	NE

Study (first author and year)	Surrogate outcome	Final outcome	Cancer	Line subgroups	Treatment	Studies (*n*)	Patients (*n*)	Treatment effect correlation methods	Correlation coefficient	Treatment effect regression methods	Regression R^2	Linear regression equation	STE	IQWiG	BSES2
DoR vs. OS															
Colloca 2016[92]	DoR	OS	Colorectal	First	Bevacizumab and chemotherapy	5	NR	Spearman (difference in median DoR vs. difference in median OS)	$r_s = 0.70$; $p = 0.188$				NR	Medium	NE
Colloca 2016[91]	DoR	OS	Pancreatic	First	Gemcitabine and chemotherapy or targeted therapy	7[b]	NR	Spearman (difference in median DoR vs. difference in median OS)	$r_s = 0.76$; $p = 0.049$				NR	Medium	NE
Colloca 2016[91]	DoR	OS	Pancreatic	First	Gemcitabine and chemotherapy	3[b]	NR	Spearman (difference in median DoR vs. difference in median OS)	$r_s = 0.50$; $p = 0.667$				NR	Low	NE
Colloca 2016[91]	DoR	OS	Pancreatic	First	Gemcitabine and targeted	4[b]	NR	Spearman (difference in median DoR vs. difference in median OS)	$r_s = 0.40$; $p = 0.600$				NR	Low	NE

ln, natural logarithm; log, logarithm; NR, not reported; pCR, pathologic complete response; *r*, Pearson correlation; R^2, regression coefficient of determination; r_s, Spearman rank correlation; WLR, weighted linear regression; WLSR, weighted least squares regression.

a Calculated from reported data.

b Unclear for individual subgroups.

Appendix 7 Studies excluded at full-text screening (n = 135)

Not a clinical study (n = 4)

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Appendix 8 A targeted review of published National Institute for Health and Care Excellence technology appraisals for which initial marketing authorisation was based on response outcomes from single-arm studies

For each TA, a summary of the main clinical studies supporting the intervention being assessed along with the number of patients, the study location, the magnitude of the ORR and whether or not PFS and OS data were available were extracted. Full results can be seen in *Table 33*.

Issue 1: overall response rate as a primary end point and possible surrogate relationship assumed for progression-free survival/overall survival

Given the different maturity in PFS and OS data evident in *Table 33*, the review further subdivides the TAs based on whether both median PFS and OS were reached or median PFS only was reached. This allowed the consideration of whether or not the approaches to dealing with different levels of maturity in these end points differed.

All 10 TAs used a model structure based on a PSM or area under the curve analysis comprising three mutually exclusive health states: (1) PFS (progression free), (2) progressive disease (PD; progression) and (3) death. Importantly, despite ORR being the primary end point supporting marketing authorisation, none of the TAs made use of the ORR or DoR data. Instead, the proposed approaches relied on extrapolations of the available PFS and OS data or used external evidence and/or assumptions.

Median progression-free survival and overall survival reached

The seven TAs for which the median PFS and OS had been reached are:

- TA395[228] – ceritinib (Zykadia, Novartis, Basel, Switzerland) for anaplastic lymphoma kinase (*ALK*) and NSCLC
- TA492[244] – atezolizumab for PD-L1 and urothelial cancer
- TA510[248] – daratumumab (Darzalex, Janssen-Cilag Ltd, Beerse, Belgium) for relapsed and refractory multiple myeloma
- TA462[235] – nivolumab (Opdivo, Bristol-Myers Squibb, New York City, NY, USA) for relapsed or refractory classical Hodgkin lymphoma (RRcHL)
- TA540[258] – pembrolizumab for RRcHL
- TA487[238] – venetoclax (Venclyxto, Abbvie, Lake Bluff, IL, USA) for chronic lymphocytic leukaemia
- TA571[260] – brigatinib (Alunbrig, Takeda, Tokyo, Japan) for *ALK*-positive NSCLC.

The observed survival data in each TA were extrapolated over a lifetime horizon using conventional parametric survival modelling. In accordance with the NICE DSU *Technical Support Document 14*,[185] each company approached the data limitation by fitting various candidate distributions to the observed data, assessing statistical goodness of fit and clinical plausibility. Although median PFS and OS were reached in the clinical studies, the ERGs consistently highlighted concerns with the immaturity of the OS data relative to the long extrapolation periods applied within the economic models.

TABLE 33 Summary of clinical studies supporting the NICE TAs

Intervention	NICE TA	Clinical study	Sample size (*n*)	Number of countries	ORR outcomes, response rate (%) (95% CI)	PFS outcomes, median (months) (95% CI)	OS outcomes, median (months) (95% CI)
Ceritinib	TA395[228]	ASCEND-1[229]	163	Multiple	56.4 (48.5 to 64.2)	6.9 (5.6 to 8.7)	16.7 (14.78 to NE)
		ASCEND-2[230]	140	Multiple	38.6 (30.5 to 47.2)	5.7 (5.4 to 7.6)	14.9 (13.5 to NE)
Osimertinib (Tagrisso, AstraZeneca, Cambridge, UK)	TA416[231]	AURA ext[232]	201	Multiple	61.3 (54.2 to 68.1)	NC (8.1 to NC)	NC
		AURA2[233]	210	Multiple	70.9 (64.0 to 77.1)	8.6 (8.3 to 9.7)	NC
		Pooled[234]	411	Multiple	66.1 (61.2 to 70.7)	9.7 (8.3 to NC)	NC
Nivolumab	TA462[235]	CheckMate 205 cohort B[236]	80	Multiple	67.5 (57.2 to 77.8)	14.78 (11.33 to NA)	NRe
		CheckMate 205 cohort C[236]	98	Multiple	73.0 (64.3 to 81.7)	11.17 (8.51 to NA)	NRe
		CA209–039[237]	15	Multiple	60 (NRe)	12.65 (5.91 to NA)	NRe
Venetoclax	TA487[238]	M12–175[239]	67	Multiple	82.1 (70.8 to 90.4)	41.4 (17.7 to 41.5)	NA
		M13–982[240,241]	158	Multiple	77.2 (66.9 to 83.5)	27.2 (21.9 to NA)	NRe
		M14–032 (cohort A)[242,243]	43	Single	67.4 (51.5 to 80.9)	NRe	NRe
		M14–032 (cohort B)[242]	21	Single	57.1 (34.0 to 78.2)	NRe	NRe
Atezolizumab	TA492[244]	IMvigor 210 Cohort 1[245,246]	119	Multiple	19.3 (12.66 to 27.58)	2.7 (2.1 to 4.2)	15.9 (10.4 to NE)
		IMvigor 210 Cohort 2[247]	310	Multiple	15.1 (11.3 to 19.6)	2.1 (2.1 to 2.1)	7.9 (6.7 to 9.3)
Daratumumab	TA510[248]	MMY2002[249]	106	Multiple	29.2 (20.8 to 38.9)	3.7 (2.8 to 4.6)	18.6 (13.7 to NRe)
		GEN501[250]	42	Multiple	35.7 (21.6 to 52.0)	6.2 (4.2 to 11.6)	NRe (18.7 to NRe)
		Pooled[251]	148	Multiple	31.1 (23.7 to 39.2)	4.0 (2.8 to 5.6)	20.1 (16.6 to NRe)
Avelumab	TA517[252]	JAVELIN Part A[253]	88	Multiple	33.0 (23.3 to 43.8)	2.7 (0.03 to 28.9)	12.9 (7.5 to NE)[d]
		JAVELIN Part B[254]	39	Multiple	62.1 (42.3 to 79.3)[b]	9.1 (1.9 to NRe)	NRe (9.1 to NRe)[c]

Intervention	NICE TA	Clinical study	Sample size (*n*)	Number of countries	ORR outcomes, response rate (%) (95% CI)	PFS outcomes, median (months) (95% CI)	OS outcomes, median (months) (95% CI)
Crizotininb	TA529[255]	PROFILE 1001[256,257]	53	Multiple	69.8 (55.7 to 81.7)	19.3 (14.8 to NRe)	NRe
Pembrolizumab	TA540[258]	KEYNOTE-087 cohort 1[259]	69	Multiple	75.4 (63.5 to 84.9)	16.7 (11.2 to NRe)	NA
		KEYNOTE-087 cohort 2[259]	81	Multiple	66.7 (55.3 to 76.8)	11.1 (7.6 to 13.7)	NA
Brigatinib	TA571[260]	ALTA (arm B)[261]	110	Multiple	56.4 (45.2 to 67.0)[a]	15.6 (11.1 to 21.0)	34.1 (27.7, NRe)
		ALTA (arm A)[261,262]	112	Multiple	45.5 (34.8 to 56.5)[a]	9.2 (7.4 to 11.1)	29.5 (18.2, NRe)
		Study 101	25	Multiple	76 (54.9 to 90.6)[a]	16.3 (9.2 to NE); range 0.5–27.8)	NRe (1.4 to 24.3)

NA, not available; NC, not calculable; NRe, not reached.
a 97.5% CI for ALTA ORR (investigator).
b 3-month follow-up, $n = 29$.
c Full analysis, $n = 39$.
d 18-month follow-up not reported.

Note
No IQR was provided except where specified.

There appeared to be no obvious trend in terms of the committee's final decision based solely on median OS having been reached. Atezolizumab and daratumumab both received recommendations for use in the CDF owing to uncertainty in their respective ICER estimates attributed to survival data immaturity.[244,248] Venetoclax also received a recommendation for use in the CDF. However, the uncertainty raised by the committee for this TA centred on the trial population and whether or not their disease severity reflected those in the NHS and not specifically uncertainty in the survival data.[238] Nivolumab and brigatinib both received recommendations for routine use in the NHS, despite immaturity of the survival data being highlighted by the committee and the ERGs.[235,260]

Median progression-free survival reached and median overall survival not reached

The TAs based on studies that had not reached median OS were:

- TA416 – osimertinib for *EGFR* T790M mutation-positive NSCLC[231]
- TA517 – avelumab for Merkel cell carcinoma (MCC)[252]
- TA529 – crizotinib for *ROS1*-positive NSCLC.[255]

For these appraisals, there was a clearer trend in the final NICE decision, given the greater uncertainty surrounding the OS data. Recommendations for all three products were restricted to use in the CDF. There was also greater variation in the modelling approaches used to extrapolate OS data.

The TA of osimertinib[231] included data from two studies, neither of which reached median OS at the time of the NICE appraisal. Despite the immaturity of the OS evidence, the extrapolation of OS was still undertaken using conventional parametric survival modelling. The committee concluded that these extrapolations were highly uncertain based on the very immature OS data, making it difficult to determine a robust cost-effectiveness estimate. Osimertinib was subsequently approved for use within the CDF despite the lack of robustness of the ICER estimates. The most critical factor appeared to be the committee's view that there was plausible potential in the ICER estimates and that the uncertainties in OS would be addressed by an ongoing Phase III RCT.

For the TA of avelumab,[252] the evidence base was derived from two cohorts: (1) treatment-experienced (second-line and further) metastatic patients (JAVELIN part A) and (2) treatment-naive (first-line) metastatic patients (JAVELIN part B). Each cohort was considered separately, reflecting a potentially different position of avelumab in the pathway. However, important differences in data maturity were evident in the second-line and further (median PFS and OS reached) and first-line (mean PFS but not OS reached) positions. Recruitment of first-line patients was also reported to be ongoing, such that more mature survival data were expected over time.

For the first-line and further populations, the company considered that the data were too immature to be extrapolated. As an alternative to extrapolating based on the immature evidence, the company proposed to estimate the relative improvement with avelumab that might be seen in treatment-naive patients compared with those in the treatment-experienced group. The company elicited a hypothetical HR for PFS and OS from clinical experts. The elicited HRs were then applied to the treatment-experienced avelumab PFS and OS curves (based on more mature evidence) to estimate equivalent estimates for treatment-naive patients receiving avelumab.

The ERG expressed significant concerns regarding the approach employed to adjust treatment effectiveness between treatment lines. Despite the immaturity in the survival data, the ERG expressed a preference to use independent survival functions fitted to the available PFS and OS data rather than using elicited HRs. However, the ERG also noted that using the observed survival data did not solve the fundamental issue of data immaturity in the treatment-naive population.

For first-line treatment of MCC, NICE recommended that avelumab was used in the CDF. This reflected the committee's concerns regarding the immaturity of the PFS and OS data and the proposed

use of clinical assumptions rather than direct evidence. The committee acknowledged that ongoing data collection in JAVELIN part B would reduce the uncertainty about the progression-free and overall survival benefit and that there was plausible potential for first-line use of avelumab to be cost-effective, if further trial data proved favourable.

Crizotinib for treating *ROS1*-positive advanced NSCLC was the only TA in which the evidence of clinical benefit was based on a single clinical study. The clinical-effectiveness evidence was based on a single-arm study ($n = 53$), with a median follow-up of 25.4 months. Median OS had not been reached at the time of the appraisal. Owing to the small study and immature survival data from this study, the company proposed the use of more mature PFS and OS data from previous RCTs of crizotinib for *ALK*-positive NSCLC as a proxy for *ROS1*-positive patients.

The committee considered the use of proxy data for *ROS1*-positive patients from a RCT to be more robust than using the available immature *ROS1*-positive PFS and OS curves from a single-arm study. However, using data from a proxy population was concluded to be far from ideal, making the assessment of clinical effectiveness and cost-effectiveness highly uncertain. Although the committee agreed to explore the proxy data in its decision-making, the committee also stated that the approach was very unusual and should not set a precedent for such an approach in future appraisals.

Given these uncertainties, crizotinib was not recommended for routine use in the NHS for patients. However, crizotinib was recommended for use in the CDF. The committee considered that further data on the use of crizotinib within the CDF would help to address uncertainties in existing survival data estimates, particularly the comparability of *ROS1*-positive and *ALK*-positive advanced NSCLC.

Issue 2: challenges of heterogeneous populations

Owing to the nature of basket trials, significant heterogeneity may be present in the study populations enrolled in the trials. The potential importance of accounting for heterogeneity and exploring the cost-effectiveness in subgroups of the target population is acknowledged in the current NICE methods guide.[4] Differences in the cost-effectiveness and decision uncertainty across these separate subgroups may lead to an optimised recommendation that is more restrictive than the marketing authorisation.

Although the review of the 10 TAs provided examples of appraisals in which heterogeneity had been accounted for within an overall target population, the evidence for the separate subgroups was commonly derived from separate studies relevant to specific subgroups or from studies in which there were relatively large numbers of patients to undertake meaningful subgroup analysis. These appraisals also typically considered only a small number of subgroups, most commonly based on alternative positions of a new treatment in an existing pathway (i.e. first or second line). Although these findings are helpful in demonstrating the potential importance of accounting for heterogeneity within a target population, important differences are also expected for histology-independent appraisals, given the potential for a much larger number of potential subsets and smaller sample sizes. The review was subsequently broadened to consider select additional TAs for which issues related to heterogeneity were considered more like those expected for histology-independent appraisals.

The NICE appraisals for neuroendocrine tumours (NETs), considered in TA449 [everolimus (Afinitor®; Novartis, Basel, Switzerland) and sunitinib] and TA539 (lutetium), appear to be particularly relevant. NETs affect different organs, namely the pancreas, GI tissue and lungs. The broad population covered by the marketing authorisation was acknowledged in the NICE scoping documents, which stated that the relevant population was people with progressed unresectable or metastatic neuroendocrine tumours according to the specific locations covered by the existing and anticipated marketing authorisations. However, heterogeneity with the licensed population was recognised and the NICE scopes also stated that the location of the tumour should be considered as a basis for identifying possible subgroups.

In both TAs, the NICE committee considered each organ separately and issued optimised recommendations based on tumour site. For example, everolimus and sunitinib were both recommended for pancreatic NET, while everolimus was recommended only for GI and lung NETs. The optimised recommendations were possible because the companies either submitted separate evidence for the different sites or provided subgroup analysis related to specific organs. In these appraisals, the committee acknowledged the importance of considering each organ separately, noting that prognosis, quality of life and cost of comparator therapies were likely to differ, which would affect the cost-effectiveness estimates.

A similar example is found in the appraisal of denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (TA265). The scope of this appraisal covered a broad population characterised by a wide range of histologies, given that almost any form of solid tumour can metastasise to the bone. Again, the NICE scope acknowledged that there was possible heterogeneity within the licensed population and suggested that the appraisal should also consider patient subgroups based on location or type of primary cancer.

Separate studies were available for TA265 for different tumour types, thus allowing for separate clinical effectiveness and cost-effectiveness analyses to be performed. For example, the company submitted a model assessing the cost-effectiveness of denosumab in the three different patient groups: breast, prostate and other solid tumours. Different risks, such as skeletal-related adverse events and mortality, and utility values were assigned to reflect differences between cancer types. The separate analyses led, again, to separate recommendations. Denosumab was approved for routine use for adults with bone metastases from breast cancer and other solid tumours, but not from prostate cancer.

Issue 3: challenges of developing a counterfactual

Company submissions supporting histology indications will frequently, if not always, present data collected as part of single-arm studies. The lack of a direct comparator creates challenges because estimates of comparative effectiveness are essential to perform robust cost-effectiveness assessments. A previous review comparing the results from single-arm studies with those from randomised designs led the authors to conclude that single-arm studies can be considered to provide reliable indicators of treatment benefit only when the disease natural history is very well known, the patient population is homogeneous and the control (standard care) treatment has little affect on outcomes.[194] Current guidance on the selection of a counterfactual and methods to deal with possible biases has also been reported to be limited.[263]

Hatswell *et al.*[263] previously performed a review and developed a taxonomy of approaches used in economic modelling for drugs, which were previously licensed by the FDA or EMA without RCT data. The most commonly identified approach used a historical control, although there was variation in the sources of comparison data (i.e. single trial, meta-analysis of multiple trials, registry data or expert opinion). Importantly, the review highlighted that most submissions did not try to control for differences between trials, thus performing a 'naive' comparison.

Naive comparisons are prone to bias in the presence of systematic differences between patients across clinical studies. Several approaches have been proposed to control for observable (and unobservable) differences between non-randomised comparisons by balancing baseline covariates or matching patients. These methods are outlined in a series of NICE DSU TSDs[162,264] and a related report.[265] TSD17[264] provides practical guidance on methods used to analyse treatment effect data from non-randomised studies, including an algorithm for method selection. The methods reviewed are separated according to the assumption of selection on observables (such as regression adjustment and propensity score matching) or selection on unobservables (instrumental variable and panel data methods). Natural experiment designs are also considered, utilising difference in differences and regression discontinuity approaches.

A subsequent DSU report builds on TSD17 by assessing current guidance by NICE on the use of real-world data,[265] another situation in which the analyses are particularly prone to selection bias. Finally, TSD18[162] (namely in its sub-sections 'Matching-adjusted Indirect Comparisons" and "Simulated Treatment Comparisons') considers the use of novel methodologies for improving indirect comparisons, while controlling for imbalances in baseline characteristics across different studies.

The approach used to estimate the counterfactual in the 10 NICE TAs included in the review was classified according to the taxonomy developed by Hatswell *et al.*[263] This taxonomy distinguishes between the approach taken to developing a comparison group and the source of these data (*Table 34*). One appraisal was excluded (TA529)[255] because the submission was based on proxy data from a randomised trial.

All nine TAs generated a counterfactual by using a historic control. However, there was variation in the source of comparison data.

Single clinical trial

The four TAs generating a counterfactual using data from a single external trial arm were TA395 (ceritinib for *ALK* and NSCLC),[228] TA416 (osimertinib for *EGFR* T790M and NSCLC),[231] TA487 (venetoclax for chronic lymphocytic leukaemia)[238] and TA571[260] (brigatinib for *ALK* and NSCLC). Each of these TAs considered only a single source of external evidence or, when multiple sources were available, did not make an attempt to pool the data, and instead conducted indirect comparisons using one source at a time.

In these appraisals, the committee expressed concerns that the single-arm design of the trials made it difficult to assess the efficacy of the new treatment owing to the lack of a comparator arm. The committee also expressed concerns that these difficulties were compounded by the small numbers of patients in the trials. Although the use of a historic control from a single external trial was generally accepted as an approach to inform the counterfactual, the committees clearly closely scrutinised the source of external data and the adjustment approaches applied. This was particularly evident when only naive comparisons were presented, as was the case for the appraisals of ceritinib and venetoclax.

The evidence used in the ceritinib submission was critiqued by the committee owing to the lack of an appropriate match between patient characteristics and the limited information about the treatments received by the historical control. This led the committee to conclude that the naive approach presented by the company was inappropriate. However, in the absence of any suitable alternative estimates or approaches, the committee concluded that the results presented by the company represented the best evidence available for their decision-making even though they were highly uncertain.

TABLE 34 Classification of approaches taken to construct a counterfactual

		Classification	
Intervention	**NICE TA**	**Approach taken**	**Source of comparison data**
Ceritinib	TA395[228]	Historical control	Clinical trial
Osimertinib	TA416[231]	Historical control	Clinical trial
Nivolumab	TA462[235]	Historical control	Case series
Venetoclax	TA487[238]	Historical control	Clinical trial
Atezolizumab	TA492[244]	Historical control	Meta-analysis
Daratumumab	TA510[248]	Historical control	Mixed sources
Avelumab	TA517[252]	Historical control	Mixed sources
Pembrolizumab	TA540[258]	Historical control	Case series
Brigatinib	TA571[260]	Historical control	Clinical trial

Similarly, in the venetoclax appraisal the committee highlighted the lack of any attempt to match for difference in baseline characteristics and considered the approach to be biased in favour of venetoclax. Again, in the absence of any alternative approaches, the naive approach was concluded to provide an acceptable basis for decision-making, but the results were highly uncertain.

Both the osimertinib and the brigatinib appraisals used adjusted comparisons. The osimertinib appraisal used a subgroup of patients with *EGFR* T790M+ in the control arm of an external prospective, randomised Phase III study and undertook comparative analyses using propensity score matching. Although the committee and the ERG acknowledged the company's approach to adjusting for possible confounding, concerns remained regarding the immaturity of OS data and the small number of patients.

In the brigatinib appraisal, data for the comparator, ceritinib, came from two separate trials that were assessed separately. The company performed both a naive comparison and an unanchored MAIC. The committee acknowledged the consistency of the results across both the naive and the adjusted analysis. Despite limitations identified relating to the assumptions of the MAIC, the consistency across the different sets of results appeared to provide reassurance to the committee, who considered that the comparator evidence was acceptable.

Case series

The TAs supporting the submission with the use of case series data were TA462 (nivolumab for classical Hodgkin's lymphoma)[235] and TA540 (pembrolizumab for classical Hodgkin lymphoma).[258] Both submissions compared their respective product with SoC data collected from a US database of patients who had been treated with brentuximab vedotin between 2007 and 2015. In both submissions, naive indirect comparisons and MAICs were carried out. The main issue raised by the committee was related to the relevance of the US database to UK practice. For both TAs, the committee acknowledged that the US database might not fully represent UK practice. However, the committee also deemed it to be the best available evidence, while acknowledging that the comparative effectiveness results were highly uncertain.

Meta-analysis

TA492 (atezolizumab for PD-L1 and urothelial cancer)[244] derived comparator data from historical trial sources using a range of approaches, including a STC, MAIC and network meta-analysis.

The initial company submission presented a STC. A STC is a statistical model that describes the outcomes in terms of the covariates fitted to the IPD for the treatment of interest. This model is used to predict the outcomes that would have been observed in a population with the same characteristics as the historical comparator data source(s). The company then performed a network meta-analysis by linking the outcomes of the various STCs for separate comparators. The ERG highlighted several concerns, particularly the limited number of covariates used in the STC prediction model and the lack of justification for the covariate selection. In response to consultation, the company also provided results from a MAIC to validate the results from the STC.

The committee acknowledged the ERG's concerns and concluded that the STC analysis was not robust. The committee agreed that the MAIC provided useful validation, but that did not alter its view that the adjustment approaches were not robust. Although the committee acknowledged that atezolizumab was likely to be clinically effective, they had concerns about the magnitude of the effect size given the lack of robust adjustment. Atezolizumab was subsequently approved for use within the CDF based on the committee's view that there was plausible potential the treatment was cost-effective and that the key uncertainties surrounding comparative efficacy would be addressed by an ongoing RCT.

Mixed sources

Two TAs, TA510 (daratumumab for multiple myeloma)[248] and TA517 (avelumab for MCC),[252] considered different approaches and sources. The main submission for daratumumab was based on a MAIC

between the daratumumab trials and other comparator trials. However, the ERG and committee expressed concerns about the unreliability of the estimates because of the number of variables that could be controlled for. The company subsequently performed an additional regression analysis of IPD from the pooled daratumumab cohort and the International Myeloma Foundation registry. The ERG considered that multivariate regression and MAIC were very different methods and, therefore, it was inappropriate to use the multivariate regression to validate the results of the MAIC. Accordingly, the committee concluded that it was not possible to establish the relative effectiveness of daratumumab owing to the high level of uncertainty in the relative effectiveness estimates, issues with the number of variables controlled for in the MAIC and the lack of cross-validation of the MAIC with other estimates. Despite these concerns, the committee approved daratumumab for use in the CDF. This was justified by the committee based on the plausible potential that daratumumab could be cost-effective and the view that additional data being collected within the early access programme would provide more robust evidence on the clinical effectiveness of daratumumab.

In the avelumab appraisal, the company performed a naive comparison with a retrospective observational study of patients with metastatic MCC. The company supplemented this with regression analysis, but the ERG had concerns owing to data immaturity and small numbers of patients. Again, problems were mostly around identification of subgroups and variables that might influence the final estimates and lack of suitable head-to-head data.

Issue 4: validation of a new test and biomarker

Three TAs were selected for the case studies in this section; these were of targeted technologies that were 'first in class' or positioned at a new point in the treatment pathway at which diagnostic testing was not presently commonplace for the relevant genomic alteration. These appraisals contained a discussion of the specific issue of identifying patients with the genomic alteration for which the technology was licensed. We explored how evidence related to the diagnostic accuracy of the test and the predictive and/or prognostic performance of the biomarker was considered.

Diagnostic accuracy

To ensure that individuals are able to access targeted treatments, diagnostic tests are required to identify eligible patients. These tests are not specifically appraised during the STA process; however, it is important to consider the diagnostic accuracy of available testing and the appropriateness of proposed testing strategies because these have implications on the population that is identified and the costs incurred. Implementation of diagnostic strategies with a low sensitivity (high rates of false negative patients) would mean that a proportion of patients are likely to be missed, while strategies with low specificity (high rates of false-positive patients) may result in additional resources allocated to unnecessary procedures.

Crizotinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer (TA406)

To identify an *ALK*-positive patient, it was assumed that the implemented testing strategy would consist of patients first tested with IHC, with positive cases confirmed by FISH. Little detail was provided into the diagnostic accuracy of these types of test to identify *ALK* mutations; however, it was stated that studies have indicated that IHC is sensitive and specific for determining *ALK* status and is a viable alternative to FISH. Although the validation of a companion diagnostic test is not required in the context of a NICE submission, the company's IHC test for detecting *ALK* status did have FDA approval as a companion diagnostic for crizotinib and also received CE marketing for use in Europe.

To calculate the cost per *ALK*-positive patient of testing for *ALK* status, the company submission described the expected distribution of NSCLC patients according to IHC and FISH tests using data pooled from two sources to estimate the total testing costs. These used assumptions regarding the positivity rate of the

IHC test using a specific antibody for *ALK* testing to estimate the number of confirmatory FISH tests that would be required. The company noted that two antibodies were available for use in *ALK* testing; however, only the antibody that was considered to be more accurate was used in the analysis.

The ERG provided further detail on the accuracy of the IHC test compared with the FISH test. It was acknowledged that there was a possibility that some patients would be incorrectly treated with crizotinib if this testing strategy is adopted, but the exact number was unknown. The ERG considered that the proposed test strategy of IHC followed by confirmatory FISH to be reasonable in the context of their diagnostic accuracy.

Osimertinib for T790M non-small cell lung cancer (TA416)

The testing strategy in the analysis of osimertinib consisted of either tissue biopsy or circulating tumour DNA (ctDNA) followed by biopsy in those who were negative for the T790M mutation.

The clinical effectiveness of osimertinib was evaluated in the AURA clinical trial programme. Patients were screened using a tissue biopsy and were centrally assessed. The tissue biopsy was shown to have a high accuracy rate, with the large majority of patients who were screened as eligible for osimertinib being confirmed as T790M positive (three patients were later found to not have the T790M mutation and one was of unknown status with insufficient tissue to carry out the test).

The sensitivity and specificity of the tissue biopsy and ctDNA were described within the context of estimating the expected testing costs to identify a patient with the T790M mutation. The sensitivity and specificity of tissue biopsy were obtained from a single study and from unpublished results for ctDNA. The company estimated the overall positive detection rate of 60.1% (i.e. for every 1.66 patients tested, one patient is identified as T790M-mutation positive and is eligible for osimertinib treatment). Owing to limitations of data, the company made assumptions regarding the diagnostic accuracy, assuming that it would be equal in patients who would be eligible for osimertinib as a second-line and as a third-line treatment. The affect of varying the diagnostic accuracy of these tests on the cost-effectiveness of osimertinib was not explored.

Crizotinib for ROS1*-positive non-small cell lung cancer (TA529)*

The primary testing strategy for the identification of patients with the *ROS1* oncogene was expected to consist of IHC screening followed by confirmatory FISH. However, in the pivotal clinical trial for crizotinib in *ROS1*-positive NSCLC, the majority of patients were identified at the screening stage through either central or local testing using FISH and a small number were identified using PCR. Retrospective testing using NGS showed that two patients in the trial were actually *ROS1* negative.

The cost of identifying *ROS1*-positive patients in the economic analysis consisted of IHC followed by confirmatory FISH. The number of confirmatory FISH tests required was based on the expected sensitivity and specificity of IHC. The company cited an 83% specificity and 100% sensitivity for IHC, as suggested by a validation study for the use of *ROS1* IHC staining in screening for *ROS1* translocations in lung cancer. FISH was assumed to have a sensitivity and specificity of 100%, given that FISH was the reference test in the diagnostic accuracy study that provided the specificity of IHC in *ROS1* testing.

Predictive validity

Predictive biomarkers provide an estimate of the expected response to treatment and are often targets for treatment. If a biomarker is not predictive, the targeted treatment will not work for patients without the biomarker present. It is important to understand the predictive nature of the biomarker: it will be difficult, without evidence to support this, to estimate and adjust for the degree of error in estimates of relative effectiveness.

Crizotinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer (TA406)

Anaplastic lymphoma kinase was identified as a key oncogenic driver in a number of cancers, including NSCLC. The role of the *ALK* oncogene in cancer development and the clinical basis for the underlying mechanism of crizotinib in relation to the *ALK* oncogene is described in the company submission. Crizotinib is an inhibitor of *ALK* and is alleged to block the activity of the abnormal *ALK* protein, which slows the growth and spread of the cancer in *ALK*-positive NSCLC and may cause the cancer to shrink.

Given that there was no evidence presented for the impact of crizotinib in *ALK*-negative patients, it was not possible to compare outcomes with those who are *ALK* positive; therefore, for this reason, the predictive validity of the *ALK* oncogene cannot be commented on in this respect.

Osimertinib for T790M non-small cell lung cancer (TA416)

The submission provided a description for the clinical basis of the predictive validity of the T790M mutation. Osimertinib was positioned as a second-line option for those who did not respond to an *EGFR* TKI for NSCLC. *EGFR* mutation status had been established as a key predictive biomarker in NSCLC, correlating with sensitivity to an *EGFR* TKI. However, patients subsequently develop resistance to therapy, which can be because of either secondary mutations or activation of bypass signalling pathways. The T790M mutations account for 50–60% of all cases of acquired resistance, and secondary T790M mutations were believed to provide resistance to *EGFR* TKIs by two potential mechanisms.

As with crizotinib for *ALK*-positive NSCLC, no mutation-negative patients received treatment with osimertinib; therefore, it was not possible to compare outcomes with those who are mutation positive and, subsequently, evaluate empirical evidence of the predictive validity of the T790M mutation.

Crizotinib for ROS1*-positive non-small cell lung cancer (TA529)*

Given that there was no comparative evidence for patients in a *ROS1*-positive population, the company assumed equivalent efficacy of crizotinib as was observed in *ALK*-positive patients. The similarities between these two groups of patients were recognised by the EMA, who considered the generalisability of data from *ALK*-positive patients to the *ROS1*-positive patients to be sufficient in their approval of crizotinib. The rationale for the similarities was described in terms of both their biological basis and the similarities in observed clinical behaviour, such as response to crizotinib, patient characteristics (e.g. age and smoking status) and histology.

The appraisal committee considered that relative effectiveness remained uncertain but agreed to explore the proxy data in its decision-making. However, the committee regarded this approach as very unusual and stated that this should not set a precedent for the use of data from proxy populations in future appraisals. The lack of knowledge on the implications of the *ROS1* oncogene was a factor in the decision to recommend crizotinib through the CDF to collect data about its use in *ROS1*-positive advanced NSCLC. The committee concluded that collecting data on disease progression in people with *ROS1*-positive NSCLC treated with crizotinib would help to address the uncertainties around the survival benefit and the comparability of *ROS1*-positive and *ALK*-positive NSCLC populations.

Retrospective testing using NGS showed that two patients enrolled in the pivotal trial crizotinib were actually *ROS1* negative. Although the *ROS1*-negative patients were included in the ITT analysis of the trial data, the company presented a scenario in which these patients were excluded from the analyses. These two patients were described as having a worse response than or comparable response to most other *ROS1*-positive patients, which suggests a predictive impact associated with the *ROS1* oncogene.

Prognostic validity

Prognostic biomarkers indicate the likelihood that a patient will have a particular disease course or natural history independent of treatment, such as the risk of disease progression or the mean survival time. Those with the biomarker present might be expected to experience a different course of disease to someone without the biomarker. The prognostic implications of the target mutation are important when considering the outcomes of patients receiving standard care. This is especially the case given that trials of new targeted therapies often do not contain a control arm. In many cases in which the relevance of the biomarker is a new discovery, evidence for the natural history of patients with the target mutation will be limited. When only the clinical outcomes of the targeted therapy are known, estimating the relative clinical effectiveness, and subsequently the cost-effectiveness, will be challenging.

Crizotinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer (TA406)

The evidence on the prognosis of *ALK*-positive patients receiving standard chemotherapy was limited at the time of the appraisal, with research into *ALK*-positive patients having been studied only in the context of investigations of crizotinib.

The life expectancy for patients with *ALK*-positive NSCLC receiving standard care could not be established with any certainty. Four estimates of the median OS for chemotherapy were presented, but the applicability of these trials to the decision problem was limited. Two trials were identified that enrolled a population that was not specifically *ALK* positive, that is it is possible that both *ALK*-positive and *ALK*-negative patients were enrolled, and a further trial was identified of *ALK*-positive patients, of whom the majority were not a first-line population, having received previous treatments for advanced disease.

The prognosis of *ALK*-positive patients was compared to that of general NSCLC patients, but it was considered that differences in survival could be a result of differences in the patient populations. It was established that *ALK*-positive patients tended to be younger, with a median age in the early 50s for *ALK*-positive patients as opposed to mid- to late 60s for *ALK*-negative NSCLC, and are more likely to be non-smokers.

However, no information was presented regarding the disease burden of *ALK*-positive patients relative to *ALK*-negative NSCLC patients and, therefore, it was not possible to draw any conclusions as to the impact of *ALK* status to the prognosis of these patients.

Osimertinib for T790M non-small cell lung cancer (TA416)

The role of the T790M mutation in patient prognosis was not understood at the time of this appraisal, and the discussion regarding a plausible biological basis for any differences between groups of patients was not presented. However, the company presented a number of analyses comparing outcomes for T790M mutation-positive and T790M mutation-negative patients to demonstrate empirically the extent to which this biomarker may influence prognosis.

The company presented the results of a subgroup analysis by the presence of T790M status for patients receiving chemotherapy. However, it was acknowledged that the trial used in the example was not designed to explore differences between T790M mutation-positive and T790M mutation-negative patients, and the patients were identified retrospectively as having the *EGFR* T790M mutation; therefore, the conclusions that could be drawn from this analysis were limited.

The median TTP for patients on untargeted chemotherapy was demonstrated as being similar between T790M mutation-positive and T790M mutation-negative patients; however, there was some limited evidence to show that there may be some long-term differences, with a Kaplan–Meier plot for OS illustrating some divergence between the two groups after 12 months (the T790M mutation-positive group having marginally poorer survival).

Clinical advice given to the ERG, however, contradicted this evidence of poorer prognosis and suggested that patients with *EGFR* mutation-positive NSCLC have a better prognosis than patients in an unselected advanced NSCLC population. This is because they tend to be younger and have fewer co-morbidities. This difference in opinion demonstrates that the role of T790M mutations in the prognosis of NSCLC was yet to be established.

Crizotinib for ROS1*-positive non-small cell lung cancer (TA529)*

The *ROS1* oncogene was a relatively new discovery at the time of the appraisal and *ROS1*-positive advanced NSCLC is an ultra-orphan indication. For this reason, little was known about the natural history, patient characteristics and clinical effectiveness of untargeted chemotherapy for tumours that are *ROS1* positive.

For this reason, the majority of the discussion regarding the prognostic validity of the *ROS1* mutation was limited to its biological basis, with very limited clinical evidence yet available to demonstrate any differences between *ROS1*-positive and *ROS1*-negative groups empirically.

At the time of the appraisal, differences between the characteristics of *ROS1*-positive patients and the characteristics of patients with unselected NSCLC had been established to only a limited degree, with *ROS1* positivity showing some associations with non-smoker status and a younger age at diagnosis, both of which are established prognostic factors. NSCLC associated with an underlying *ROS1* gene rearrangement is fundamentally different from unselected NSCLC, as disease progression in *ROS1*-positive NSCLC patients is dependent on the activated *ROS1* receptor tyrosine kinase protein.

A systematic review conducted by the company found that the limited studies that reported long-term outcomes for *ROS1* patients on chemotherapy were based on very small patient numbers and were not considered to provide reliable estimates of OS. As a result, the prognosis of *ROS1* patients on chemotherapy was assumed to be equivalent to that of *ALK*-positive patients, and data from patients with *ALK*-positive NSCLC were used as a proxy for the life expectancy of *ROS1*-positive NSCLC patients treated with current SoC. The similarities between *ROS1*-positive and *ALK*-positive NSCLC allowed for the use of the better-quality data available in the latter indication. Evidence in the *ALK*-positive population was more established, with a large Phase III trial of previously treated patients and two previous NICE appraisals in this indication, and there was greater clinician experience. Clinical experts predicted that *ROS1*-positive advanced NSCLC patients will be comparable with overall *ALK*-positive patients owing to the similar patient characteristics and homology (see *Chapter 6*, *Types of genomic test*). Similar to *ALK*-positive NSCLC, *ROS1*-positive NSCLC was not considered to be a favourable prognostic factor.

As a result of the uncertainty regarding the comparability of the *ROS1* and *ALK* populations, the most plausible ICERs were considered highly uncertain and crizotinib was recommended for use in the CDF for this indication. This enabled evidence to be collected on patient characteristics and natural history, to further understand the *ROS1* population and similarities to the *ALK*-positive population.

Issue 5: implementation challenges of incorporating a new diagnostic approach/pathway

To ensure that individuals can access targeted treatments, such as those that are histology independent, the infrastructure to identify such patients is required. The introduction or alteration of such infrastructure is associated with several challenges. Capacity constraints have been identified as a key barrier to the introduction of precision medicines into the NHS.[266] An increase in service provision may result in an investment in NHS genomics services to increase staffing capacity and laboratory infrastructure and a need for education and training to ensure that clinicians are aware of where

targeted medicines could fit within the treatment pathway. Not only will the requirement of diagnostic tests for patient identification result in additional costs to the NHS, the way that patients are identified could also have implications on the type of patients who receive treatment and how similar they are to the patients enrolled in the trials. There may be a variety of testing strategies that could be used in clinical practice, including the diagnostic tests that are used and in which sequence they are used. The time at which patients are identified, whether tested at diagnosis or after treatment failure, may influence the relevant comparator treatment, which differs by treatment line. In this section, we discuss the extent to which these issues are explored in a number of TAs of targeted therapies.

Crizotinib for anaplastic lymphoma kinase-positive non-small cell lung cancer (TA406)

Crizotinib for the treatment of *ALK*-positive NSCLC was evaluated initially as a second-line therapy (TA296), with a first-line indication evaluated subsequently in this appraisal. At the time of the appraisal, infrastructure was already in place for the service provision and management of molecular testing to confirm *ALK* status, with several providers set up with this testing facility. Several issues regarding the implementation of *ALK* testing were discussed, including the testing strategy, the timing of testing, the unit costs of testing and the impact of testing to the number of eligible patients who receive treatment.

Testing strategy

The company provided details of a two-tiered testing approach to identify *ALK*-positive patients in clinical practice. This was a strategy that was endorsed by two professional bodies [ESMO and the Royal College of Pathologists (RCP)] and was also implemented in the economic analysis. No specific tests are detailed in the summary of product characteristics (SmPC) for crizotinib and, therefore, the company provided a description of the specific IHC and FISH assays that are endorsed and validated by other clinical bodies, such as ESMO, RCP and FDA. This approach to diagnosis appears to differ to the strategy that was used in the pivotal trial of crizotinib, for which the identification of *ALK* patients was based only on a FISH test. However, limited discussion was given as to the implications of the differing testing strategies regarding the patient population identified, although the ERG noted the potential for a two-tiered approach resulting in delays to treatment and patients having a reduced capacity to benefit from treatment if the disease is allowed to progress.

The clinical effectiveness and cost-effectiveness implications of testing strategies using alternative diagnostic tests, such as NGS or RT-PCR, were not explored by the company in this appraisal. The company justified their approach by stating that IHC and FISH represent the significant majority of tests used in the NHS and provided supporting information on the number of IHC tests used in practice. However, the ERG noted that the possibility of using NGS would make the cost of *ALK* testing less predictable in the near future.

Timing of testing

In this appraisal, crizotinib was evaluated as a first-line treatment for NSCLC. At the time, first-line treatments for NSCLC existed that targeted the *EGFR* mutation. The company assumed that testing would be carried out upfront at diagnosis, alongside *EGFR* testing, based on feedback from an advisory board. Upfront testing alongside *EGFR* tests means that there is no significant increase in the number of tests required and no potential capacity issues. Sequential testing of *ALK* status (i.e. after *EGFR* testing) was not acknowledged as an option.

Unit costs of testing

At the time of the appraisal, there was some uncertainty regarding the unit costs of testing because it was unclear whether or not laboratory and overhead costs were included in the cost supplied by the company. The impact to the cost-effectiveness of crizotinib by using alternative unit costs of treatment that were estimated by other sources was explored, with a higher cost of testing being associated with a modest increase to the ICER. However, the committee considered that the true cost remained uncertain and that it was likely to lie between the ranges identified.

Impact on the number of patients identified

The challenges of a new diagnostic process were described as having an impact on the number of patients expected to be eligible for crizotinib treatment, noting that the number of patients who received the treatment while it was available on the CDF for a later line of treatment was smaller than the expected number of eligible patients, given that not all *ALK*-positive patients were being identified in practice.

Osimertinib

Osimertinib, appraised for NSCLC patients with a T790M mutation (TA416),[231] was positioned as a second-line treatment option following treatment with an *EGFR* TKI, given the low prevalence of T790M mutations at diagnosis. The challenges in the diagnostic pathway with a second-line therapy were discussed, including the increase in service provision and the testing strategy required.

Increase in service provision

The identification of patients eligible for osimertinib was discussed as the main additional resource use to the NHS. The appraisal discusses how not all centres routinely test for the *EGFR* T790M mutation either at diagnosis or after treatment failure with a first-line *EGFR* TKI, and its introduction will, therefore, necessitate a change in service provision.

The expansion of testing was not considered to be problematic because the pathway for acquisition, handling and testing of tissue, in addition to mechanisms for reporting of results, was described as being well-established; therefore, no additional costs were associated with the assessment of tumour specimens beyond the increase in testing volumes. Details of the laboratories enrolled to conduct *EGFR* testing and their current ability to detect T790M mutations using existing platforms were provided to support this assumption.

However, tissue biopsy at disease progression following resistance to *EGFR* TKI therapy is not routine, and the company provided a detailed description of how the change of pathway to acquire tumour specimens would be implemented. There were a number of challenges highlighted, including the optimal selection of lesions for biopsy owing to tumour heterogeneity and reduced willingness to undergo tissue biopsy. Feasibility studies to validate the pre-analytical steps of the plasma processing pathway were expected to commence shortly after the appraisal.

Testing strategies

Four possible testing strategies to detect T790M mutations were described: (1) tissue biopsy, (2) ctDNA (plasma) test followed by tissue biopsy in patients identified as T790M negative by ctDNA, (3) ctDNA alone and (4) tissue biopsy followed by ctDNA. The company considered that only the first two testing strategies were relevant and in line with the SmPC for osimertinib and included a weighted average of these strategies in their base-case analysis based on the proportion expected to be identified in each way. A number of clinical benefits with the use of ctDNA were described, with it being a less expensive alternative and offering more rapid results, and mitigating the complications associated with the acquisition of lung tissue samples, which may be of particular concern for later-stage disease.

Crizotinib for ROS1*-ve non-small cell lung cancer*

The appraisal of crizotinib for treating *ROS1*-positive advanced NSCLC (TA529)[255] also highlighted some uncertainty with the introduction of diagnosis into the patient pathway. Diagnostic testing was not routinely carried out in England and Wales to identify *ROS1*-positive patients at the time of the appraisal; however, there were pre-existing targeted treatments available for NSCLC for which patients were tested for the associated biomarker for *EGFR* and *ALK* at diagnosis of NSCLC. The discussions around the challenges of identifying *ROS1*-positive patients focused on the point in the pathway that *ROS1* would be detected and the implications of testing to the time of crizotinib treatment.

Timing of testing

The company presented different scenarios to illustrate the impact of introducing testing at different points in the treatment pathway: one scenario where testing could be carried out upfront on diagnosis alongside testing for other targets associated with treatment for NSCLC (*EGFR* and *ALK*) or a scenario where testing would be carried out sequentially after confirmed *EGFR* negativity and *ALK* negativity. Upfront testing minimises tissue wastage and avoids delays in the access to therapy by waiting for the patient to complete testing for the targets with existing therapies.

Other parties, including NHS England and the NICE technology appraisal committee (TAC), also considered that upfront testing was more appropriate than sequential testing. The ERG also considered the affect of the timing of testing on the cost that it incurs. For example, there may be a discount available for upfront testing when testing for more than one mutation at the same time. In addition, patients treated in the subsequent line would already have been tested for *ALK* and/or other mutations, so the cost of testing these (*ALK*-positive) patients need not be taken into account.

Implications of testing to the timing of treatment

The issue was also raised of the positioning of crizotinib in the pathway. Although the economic analysis considered crizotinib against a comparator that is commonly used as first-line treatment in NSCLC, it was expected that patients treated by crizotinib in clinical practice may be either treatment naive or treatment experienced. If access to diagnostic testing causes delays in the diagnosis of *ROS1* positivity, or *ROS1* testing had not been carried out prior to initiating first-line therapy, patients would be treatment experienced on starting crizotinib; however, over time it was expected for patients to become predominantly treatment naive as testing becomes more established and diagnosis occurs at an earlier stage in the treatment pathway.

Appendix 9 OpenBUGS code

Bayesian Hierarchical Model: Uniform(0,5) prior distribution for the between-tumour standard deviation

```
# CODE ADAPTED FROM: Thall et al (2003)
# Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes.
# Statist. Med., 22: 763-780. doi:10.1002/sim.1399
#
# Uniform prior distribution for between-group SD, as recommended by Cunanan et al. (Clinical
Trials, 2019)
#
model{
for (i in 1:numGroups){  # numGroups is k, the number of different probabilities
  x[i] ~ dbin(p[i],n[i]) # In each group, x is the number of responses and n is the number of
patients
  # set up deviance code with correction for zero cells
  x1[i] <- max(x[i],0.1) # zero cell correction
  xhat[i] <- p[i] * n[i] # expected value of the numerators
  xhat1[i] <- max(xhat[i], 0.1) # zero cell correction
  # Deviance contribution with zero cell correction
  dev1[i] <- 2 * (x1[i] * (log(x1[i])-log(xhat1[i]))
            +  (n[i]-x1[i]) * (log(n[i]-x1[i]) - log(n[i]-xhat1[i])))
  # deviance contribution for for zero cells
  dev0[i] <- 2 * n[i] * log(n[i]/(n[i]-xhat[i]))
  # deviance contribution
  dev[i] <- dev1[i] * (1-equals(x[i],0)) + dev0[i] * equals(x[i],0)
  # logit model for p
  logit(p[i]) <- rho[i]
  rho[i] ~ dnorm(mu,tau) # RE for log-odds
  # Probability that the response rate for each group is > than targetResp (given as data)
  pg[i] <- step(p[i] - targetResp)
  pg2[i] <- step(p[i] - targetResp2)
 }
totresdev <- sum(dev[])            # total residual deviance
# Priors
mu ~ dnorm(mean.Mu, perc.Mu)       # pooled mean of log-odds
#tau ~ dgamma(tau.alpha, tau.beta) # used in Thall (2003)
#sd <- 1/sqrt(tau)                 # between-group sd (log-odds scale)
sd ~ dunif(0,5)                    # recommended by Cunanan (2019)
tau <- pow(sd,-2)
# predictive distribution
rho.new ~ dnorm(mu,tau)            # log-odds response across groups
# convert to probabilities
logit(p.pooled) <- mu    # mean probability of response across groups
logit(p.new) <- rho.new  # probability response across groups
# predictive probabilities of response rates > targetResp (given as data)
pg.new <- step(p.new - targetResp)
pg2.new <- step(p.new - targetResp2)
}
```

Data

list(x=c(2,2,9,2,6,5,1,6,0,0,0,0), n=c(11,12,7,5,4,4,4,3,2,1,1,1), numGroups=13, mean.Mu=-0.847298, perc.Mu=0.1, targetResp=0.3, targetResp2=0.1)

Appendix 10 Model fit statistics and residual deviance base case

For all analyses, 55,000 iterations were run on two parallel chains and the first 5000 iterations were discarded as 'burn-in'. Convergence was assessed by visual inspection of the Brooks–Gelman–Rubin plots and assessment of the $\hat{R}$ statistic.[156,157]

The model fit statistics for the base-case and the sensitivity analyses are shown in *Table 35*. The results show that all models fit the data well. The inspection of box plots of individual groups' contributions to the residual deviance support this.

TABLE 35 Model fit statistics for the base-case and sensitivity analyses

Prior distribution	Posterior mean of the residual deviance[a]	DIC
Base case: uniform (0, 5), 0.3 mean response probability	11.6	30.7
Uniform (0, 5), 0.5 mean response probability	11.9	30.9
Inverse gamma (2, 20)	10.4	28.9
Half-normal (0,0.01)T(0,)	10.9	30.5
Half-normal (0,0.1)T(0,)	12.1	31.4
Half-normal (0,0.5)T(0,)	14.8	33.1

a Compare with 12 groups.

Appendix 11 Bayesian hierarchical model sensitivity analyses

The sensitivity of the BHM results to the prior distribution were assessed. The results showed that the BHM estimated substantial heterogeneity between tumour types irrespective of the prior distribution or the response probability. This can be seen in the estimates of the posterior distributions for the between-group heterogeneity standard deviations in *Table 36*. The 95% CrIs around all of the results are wide, which indicates considerable uncertainty in these estimates.

TABLE 36 Sensitivity analyses of the BHM to alternative prior distributions

Prior distribution	Posterior distributions for the between-group heterogeneity standard deviations (95% CrI)
Base-case: uniform (0,5), 0.3 mean response probability	2.863 (0.922 to 4.826)
Uniform (0, 5), 0.5 mean response probability	2.828 (0.865 to 4.828)
Inverse gamma (2, 20)	3.273 (1.879 to 5.901)
Half-normal (0,0.01)T(0,)	3.738 (0.970 to 9.544)
Half-normal (0,0.1)T(0,)	2.740 (0.812 to 5.814)
Half-normal (0,0.5)T(0,)	1.820 (0.455 to 3.466)

Appendix 12 Estimating the annual eligible population

Diagnostic accuracy illustration

The diagnostic accuracy of a test will vary depending on the prevalence of the genetic alteration within each tumour type, even when the sensitivity and specificity are held constant. This can be expressed by looking at the positive predictive value (PPV) and the negative predictive value (NPV) of a test. The PPV is defined as the likelihood that an individual with a positive test truly has the condition. Alternatively, the NPV is the likelihood that the individual with a negative test truly does not have the condition. The predictive value of a test will differ depending on the prevalence of a genetic alteration.

For example, the sensitivity and specificity of an IHC test for detecting *NTRK* fusions is 88% and 81%, respectively. If IHC was used to detect *NTRK* fusions in 2000 patients, 1000 with GIST (*NTRK* fusion prevalence 0.1%) and 1000 with papillary thyroid tumour (*NTRK* fusion prevalence 13.30%), the PPV and NPV of a test will differ. *Table 37* demonstrates how the prevalence of *NTRK* fusion changes the PPV and NPV of a test.

Estimation of the eligible population

Table 38 details the sources used to estimate the annual eligible population.

The prevalence of *NTRK* fusions for each tumour type was determined from a pragmatic review of the literature. For the majority of tumour types, the prevalence of *NTRK* fusions was acquired from Foundation Medicine (Cambridge, MA, USA) data in the FDA review for larotrectinib, which assessed 34,476 tumour samples.[177] The frequencies of *NTRK* fusions for the remaining tumour types were taken from published evidence.[175,176,178] Despite *NTRK* fusions having been identified in renal cell carcinoma,[307] ovarian cancer[307] and prostate cancer,[308] the exact frequencies are not recorded. Therefore, it was assumed that the *NTRK* fusion frequency in these tumours was the same as the average frequency of *NTRK* fusions across all tumours, which is estimated to be 0.26%.[180]

TABLE 37 Illustrative example of how the diagnostic accuracy of IHC (sensitivity 88%, specificity 81%) is different for two tumour types with differing *NTRK* fusion prevalence

Parameter	Papillary thyroid cancer	Gastrointestinal stromal tumour
NTRK fusion prevalence	13%	1%
Total population with *NTRK* fusion	130	10
True positives (test positive, *NTRK* positive)	114	9
False positives (test positive, *NTRK* negative)	165	1
True negatives (test negative, *NTRK* negative)	705	871
False negatives (test negative, *NTRK* positive)	165	119
Positive predictive value	88%	99%
Negative predictive value	7%	98.9%

TABLE 38 Literature sources (first author and year) of *NTRK* fusion prevalence, annual cancer incidence and the proportion of patients diagnosed with stage III/IV cancer in the tumour known to harbour a *NTRK* fusion

Tumour type	*NTRK* fusion prevalence	Annual cancer incidence (England)	Proportion stage III/IV at diagnosis
Represented tumour types			
Appendix cancer	Amatu 2016[178]	Based on an incidence of 0.97/100,000[267] and the population in England in 2017[268]	Marmor 2015[267]
Breast cancer (NOS)	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Cancer Registration Statistics*[269]	Cancer Research UK. *Breast Cancer Incidence by Stage at Diagnosis*[270]
Cholangiocarcinoma	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Rare and Less Common Cancers*[271]	Tsuchiya 2015[272] (assumed to be the same as hepatocellular carcinoma)
Colorectal cancer	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Cancer Registration Statistics*[269] and Thrumurthy 2016[273]	Cancer Research UK. *Bowel Cancer Incidence by Stage at Diagnosis*[274]
GIST	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	Starczewska Amelio 2014[275]	PDQ Adult Treatment Editorial[276]
IFS	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	Based on an incidence of 0.5/100,000[177] and the population in England in 2017[268]	Orbach 2009[277]
MASC	Skálová 2010[278]	*Cancer Registration Statistics*[269] and Luk 2015[279]	Sethi 2014[280]
Melanoma	Okamura *et al.* 2018[176]	*Cancer Registration Statistics*[269]	Cancer Research UK. *Melanoma Skin Cancer Incidence by Stage at Diagnosis*[281]
NSCLC (NOS)	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*National Lung Cancer Audit*[282]	*National Lung Cancer Audit*[282]
Pancreatic cancer	Okamura *et al.* 2018[176]	*Cancer Registration Statistics*[269] and Pancreatic Cancer UK 2018[283]	Cancer Research UK. *Pancreatic Cancer Incidence by Stage at Diagnosis*[284]
Soft tissue sarcoma	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	Cancer Research UK. *Soft Tissue Sarcoma Incidence Statistics*[285]	American Cancer Society 2017[286]
Thyroid	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Cancer Registration Statistics*[269]	Deen 2016[287]
Unrepresented tumour types			
Cervical cancer	Okamura *et al.* 2018[176]	*Cancer Registration Statistics*[269]	Cancer Reasearch UK. *Cervical Cancer Incidence by Stage at Diagnosis*[288]
Congenital mesoblastic nephroma	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Rare and Less Common Cancers*[271] and Gooskens 2017[289]	Gooskens 2017[289]
Gastro–oesophageal junction adenocarcinoma	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	NICE[290]	Cancer Research UK. *Oesophageal Cancer Incidence by Stage at Diagnosis*[291]
Head and neck squamous cell carcinoma (NOS)	Okamura *et al.* 2018[176]	*Cancer Registration Statistics*[269]	Cancer Research UK. *Head and Neck Cancer Statistics*[292]

TABLE 38 Literature sources (first author and year) of *NTRK* fusion prevalence, annual cancer incidence and the proportion of patients diagnosed with stage III/IV cancer in the tumour known to harbour a *NTRK* fusion (*continued*)

Tumour type	*NTRK* fusion prevalence	Annual cancer incidence (England)	Proportion stage III/IV at diagnosis
High-grade glioma	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	Public Health England[293]	All high-grade glioma cancers are advanced or metastatic[294]
NET	Sigal 2018[175]	UK and Ireland Neuroendocrine Tumour Society[295]	UK and Ireland Neuroendocrine Tumour Society[295]
Ovarian cancer (NOS)	Assumption based on average prevalence (Solomon 2019[180])	*Cancer Registration Statistics*[269]	Cancer Research UK. *Ovarian Cancer Incidence by Stage at Diagnosis*[296]
Paediatric high-grade glioma	Okamura *et al.* 2018[176]	Farrimond 2010[297]	Wang 2013[294]
Paediatric melanoma	Okamura *et al.* 2018[176]	Cancer Research UK. *Children's Cancer Incidence Statistics*[298]	Austin 2013[299]
Papillary thyroid tumour[a]	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Cancer Registration Statistics*[269] and Brzeziańska 2006[300]	Deen 2016[287]
Prostate cancer (NOS)	Assumption based on average prevalence (Solomon 2020[180])	*Cancer Registration Statistics*[269]	Cancer Research UK. *Prostate Cancer Incidence by Stage at Diagnosis*[301]
Renal cell carcinoma	Assumption based on average prevalence (Solomon 2020[180])	*Cancer Registration Statistics*[269] and Cancer Research UK. *Kidney Cancer: Stages, Types and Grades*[302]	Cancer Research UK. *Kidney Cancer: Stages, Types and Grades*[302]
Salivary gland (non MASC)	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Cancer Registration Statistics*[269]	Assumed to be the same as head and neck squamous cell carcinoma[292]
Secretory breast carcinoma	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Cancer Registration Statistics*[269] and Horowitz 2012[303]	Jacob 2016[304]
Sinonasal adenocarcinoma	Assumption based on average prevalence (Solomon 2020[180])	*Cancer Registration Statistics*[269] and Rushton 2010[305]	Assumed to be the same as head and neck squamous cell carcinoma[292]
Uterine carcinoma	*NDA Multidisciplinary Review and Evaluation: Larotrectinib*[177]	*Cancer Registration Statistics*[269]	Cancer Research UK. *Uterine cancer incidence by stage at diagnosis*[306]

a Prevalence of *NTRK* fusions in the papillary thyroid tumour is based on the average of two estimates provided in the NDA multidisciplinary review.

In England, the annual incidences of tumours in anatomical sites (e.g. pancreatic cancer) were obtained from the *Cancer Registration Statistics*[269] and *Rare and Less Common Cancers: Incidence and Mortality in England*[271] databases. Where the *NTRK* fusion has been reported in a specific tumour type (e.g. pancreatic adenocarcinoma) rather than an anatomical site, we used an estimate of the proportion of patients with that cancer type, based on published evidence. The incidence estimates for NSCLC, NETs and soft tissue sarcoma were not available and were obtained from other published sources.[282,295,309] Given that there was no crude incidence available for appendiceal adenocarcinoma, the annual incidence was estimated using an incidence per 100,000 and the annual population within the UK in 2017.[267,268]

The proportion of individuals diagnosed with stage III/IV cancer was used as a proxy measure for the proportion of the patients with locally advanced or metastatic cancer. Values for this were primarily obtained from Cancer Research UK. For the tumour types for which data were not available, values were taken from published sources.[267,272,277,280,282,287,289,299,307] For the tumour types for which a known proportion of the patient population had an unknown stage at diagnosis, the unidentified proportion of stage III/IV cancer at diagnosis was assumed to follow the same distribution as the known proportion.

Table 39 presents the calculations of the annual eligible population for each testing strategy.

Modelled testing strategies

Tables 40–42 present the testing strategies that would be used to identify *NTRK* fusions for each tumour type across the three testing strategies. The appropriate test is dependent on *NTRK* fusion frequency and current testing availability.

TABLE 39 Calculations of the annual eligible population for three testing strategies based on the prevalence of *NTRK* fusion, the annual incidence of cancer in England and the proportion of patients with advanced or metastatic cancer at diagnosis

Tumour type	Prevalence of *NTRK* fusion (%)	Cancer incidence (England)	Percentage with stage III/IV cancer	Annual TRK-inhibitor eligible population		
				Hierarchical	RNA-based NGS	Exhaustive
Tumours represented in the trial						
Appendix	4.00	540	74	14.04	15.97	12.95
Breast	0.07	46,102	15	4.25	4.84	3.93
Cholangiocarcinoma	0.10	556	60	0.29	0.33	0.27
Colorectal	0.12	34,825	55	20.20	22.98	18.64
GIST	1.28	734	40	3.30	3.76	3.05
IFS	90.90	59	51	24.04	27.35	22.18
MASC	92.90	11	22	1.80	2.25	1.82
Melanoma	0.21	13,740	10	2.28	2.60	2.11
NSCLC	0.09	32,576	57	14.69	16.71	13.55
Pancreatic	0.26	8388	78	14.95	17.01	13.80
Soft tissue sarcoma	0.56	2740	32	4.32	4.91	3.98
Thyroid	0.92	2195	31	5.50	6.26	5.08
Tumours not represented in the trial						
Cervix	0.33	2591	24	1.80	2.05	1.66
Congenital mesoblastic nephroma	60.70	2	17	0.20	0.23	0.18
Gastro–oesophageal junction	0.10	7569	73	3.40	3.87	3.14
High-grade glioma	0.05	2781	100	1.18	1.34	1.09
HNSCC	0.38	9946	63	20.93	23.81	19.31

TABLE 39 Calculations of the annual eligible population for three testing strategies based on the prevalence of *NTRK* fusion, the annual incidence of cancer in England and the proportion of patients with advanced or metastatic cancer at diagnosis (*continued*)

Tumour type	Prevalence of *NTRK* fusion (%)	Cancer incidence (England)	Percentage with stage III/IV cancer	Annual TRK-inhibitor eligible population		
				Hierarchical	RNA-based NGS	Exhaustive
Neuroendocrine	0.30	4363	53	6.10	6.94	5.63
Ovarian	0.25	2724	55	3.29	3.75	3.04
Paediatric high-grade Glioma	5.30	67	100	3.11	3.54	2.87
Paediatric melanoma	11.11	56	34	1.83	2.08	1.68
Papillary thyroid tumour	13.30	1057	31	38.30	43.57	35.34
Prostate	0.25	41,201	43	38.93	44.29	35.92
Renal cell carcinoma	0.25	7438	43	7.19	8.18	6.64
Salivary gland	1.72	517	63	4.92	5.60	4.54
Secretory breast carcinoma	91.70	7	9	0.46	0.58	0.47
Sinonasal adenocarcinoma	0.25	5	63	0.01	0.01	0.01
Uterine	0.10	7862	18	1.24	1.42	1.15

TABLE 40 Testing strategy for each tumour type under the hierarchical approach

Testing strategy	Costs	Tumour type	
FISH	No incremental costs	• MASC	• Secretory breast carcinoma
WGS and confirmatory RNA-based NGS	Cost of confirmatory RNA-based NGS only	• Congenital mesoblastic nephroma • IFS	• Paediatric high-grade glioma • Paediatric melanoma • Soft tissue sarcoma
IHC and RNA-based NGS	Total cost of IHC and RNA-based NGS	• Appendiceal adenocarcinoma • Breast cancer (NOS) • Cervical cancer (NOS) • Cholangiocarcinoma • Colorectal adenocarcinoma • GIST • GEJ adenocarcinoma • HNSCC (NOS) • High-grade glioma • Melanoma (NOS)	• Neuroendocrine (NOS) • NSCLC (adenocarcinoma) • Ovarian cancer (NOS) • Pancreatic adenocarcinoma • Papillary thyroid tumour • Prostate cancer (NOS) • Renal cell carcinoma • Salivary gland carcinoma • Sinonasal adenocarcinoma • Thyroid tumour (NOS) • Cancer of unknown primary • Uterine carcinoma

TABLE 41 Testing strategy for each tumour type under the first-line RNA-based NGS approach

Testing strategy	Costs	Tumour type	
First-line RNA-based NGS	Incremental costs of displacing FISH	• MASC	• Secretory breast carcinoma
WGS and confirmatory RNA-based NGS	Cost of confirmatory RNA-based NGS only	• Congenital mesoblastic nephroma • IFS	• Paediatric high-grade glioma • Paediatric melanoma • Soft tissue sarcoma
First-line RNA-based NGS	Total cost of RNA-based NGS	• Appendiceal adenocarcinoma • Breast cancer (NOS) • Cervical cancer (NOS) • Cholangiocarcinoma • Colorectal adenocarcinoma • GIST • GEJ adenocarcinoma • HNSCC (NOS) • High-grade glioma • Melanoma (NOS)	• Neuroendocrine (NOS) • NSCLC (adenocarcinoma) • Ovarian cancer (NOS) • Pancreatic adenocarcinoma • Papillary thyroid tumour • Prostate cancer (NOS) • Renal cell carcinoma • Salivary gland carcinoma • Sinonasal adenocarcinoma • Thyroid tumour (NOS) • Cancer of unknown primary • Uterine carcinoma

TABLE 42 Testing strategy for each tumour type under the exhaustive approach

Testing strategy	Costs	Tumour type	
DNA-based NGS and confirmatory RNA-based NGS	Incremental costs of displacing FISH	• MASC	• Secretory breast carcinoma
WGS and confirmatory RNA-based NGS	Cost of confirmatory RNA-based NGS only	• Congenital mesoblastic nephroma • IFS	• Paediatric high-grade glioma • Paediatric melanoma • Soft tissue sarcoma
DNA-based NGS and confirmatory RNA-based NGS	Total cost of DNA-based NGS and RNA-based NGS	• Appendiceal adenocarcinoma • Cervical cancer • Cholangiocarcinoma • GIST • GEJ adenocarcinoma • HNSCC (NOS) • High-grade glioma	• NET • Pancreatic adenocarcinoma • Prostate cancer (NOS) • Renal cell carcinoma • Salivary gland carcinoma • Sinonasal adenocarcinoma • Cancer of unknown primary • Uterine carcinoma
DNA-based NGS and confirmatory RNA-based NGS	Cost of confirmatory RNA-based NGS only	• Breast cancer (NOS) • Colorectal adenocarcinoma • Melanoma (NOS) • NSCLC	• Ovarian cancer (NOS) • Papillary thyroid tumour • Thyroid tumour (NOS)

Appendix 13 Case study: economic model

Survival

The distribution of patients in each health state is determined using observed PFS and OS. Traditionally, the observed TTE data for PFS and OS are utilised for both treatment arms and, depending on the maturity of the data, direct extrapolation is required. However, TTE data for PFS and OS were not available in the literature for either of the approved TRK inhibitors (larotrectinib and entrectinib).

The literature did report the median PFS and OS for both larotrectinib and entrectinib; however, there were significant differences between the median survival estimates of larotrectinib and entrectinib. The median PFS and OS was 28.3 months and 44.4 months, respectively, for patients in the larotrectinib study, and 11.2 months and 20.9 months, respectively, for patients in the entrectinib study.[310,311] Furthermore, the reported OS and PFS data were deemed highly uncertain owing to the significant data immaturity and uncertainty about the extent to which OS is driven by the efficacy of subsequent therapies.

Owing to these uncertainties, hypothetical estimates of PFS and OS were used in the economic model and can be seen in *Table 43*. Standard errors were assumed to be 10% of the mean.

It is assumed that the survival function of responders and non-responders follows an exponential distribution. Exponential parametric survival curves were, therefore, generated based on median OS and PFS values.

The resulting OS and PFS curves for responders and non-responders can be seen in *Figure 16*.

Utilities

Stylised health state utilities were used in the economic model and can be seen in *Table 44*. The utility values used for progression-free disease for Drug X and progressed disease were based on the mean values reported in the NICE TA of brigatinib for the treatment of patients with *ALK*-positive advanced NSCLC previously treated with crizotinib.[74,105,260] Given the cytotoxic nature of chemotherapy and the targeted nature of Drug X, the utility value of SoC was assumed to be lower than that of Drug X. As a result, a utility value of 0.72 was used for SoC. This value was based on the utility reported in the NICE TA of crizotinib for treating *ROS1*-positive advanced NSCLC.[255] The progressed disease health state utilities for Drug X and SoC were assumed to be equivalent because active treatment was assumed to be discontinued on disease progression.

It was assumed that the health state utilities were unchanged across tumour types. To reflect uncertainty in the utilities, standard errors were assumed to be 10% of the mean.

TABLE 43 Survival estimates

Parameter	Median PFS (months) (95% CI)	Median OS (months) (95% CI)
Responders	24 (21.6 to 26.4)	36 (32.4 to 39.6)
Non-responders	6 (5.4 to 6.6)	12 (10.8 to 13.2)

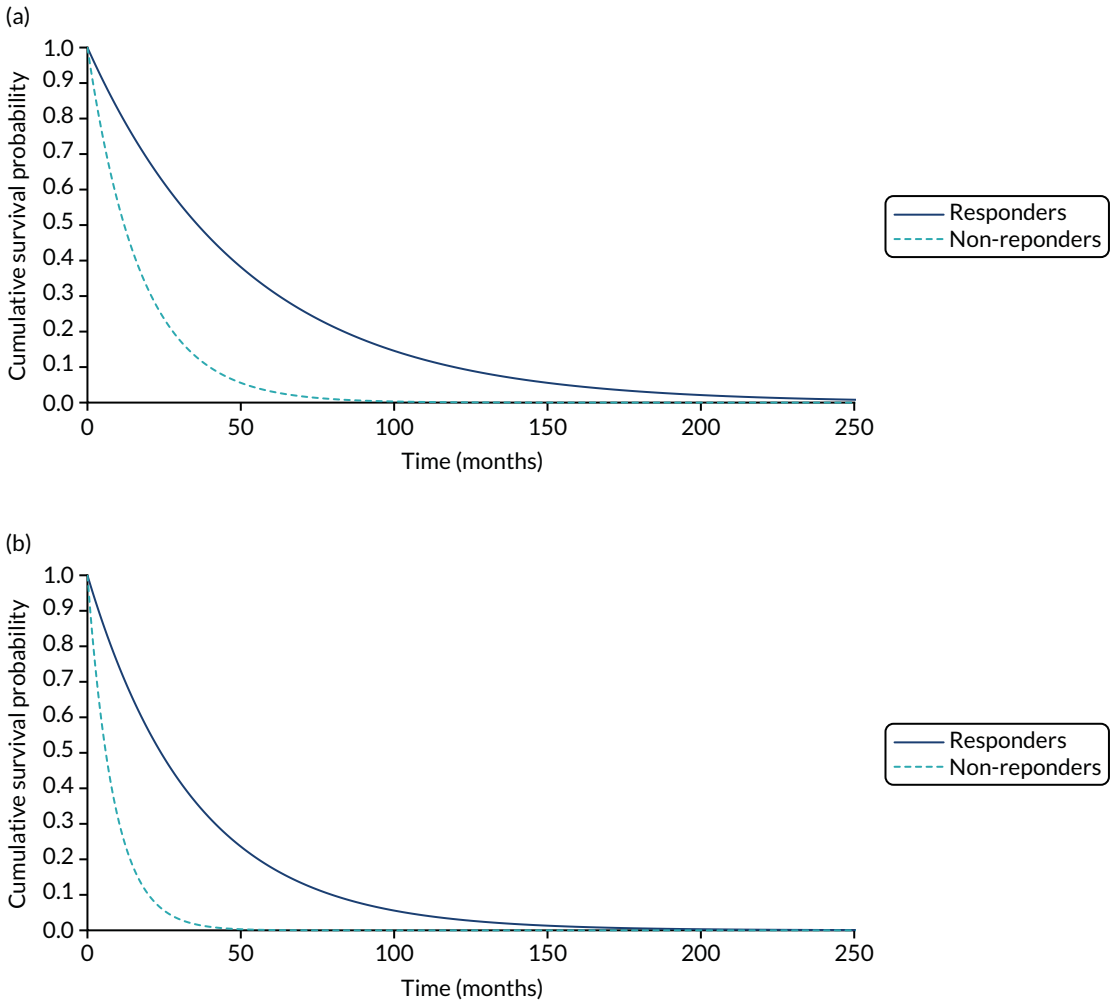

FIGURE 16 Plots showing the stylised (a) progression-free survival and (b) the OS curves for responders and non-responders.

TABLE 44 Health state utilities

Parameter	Drug X (95% CI)	SoC (95% CI)
Progression-free disease	0.79 (0.71 to 0.87)	0.72 (0.65 to 0.79)
Progressed disease	0.64 (0.57 to 0.71)	0.64 (0.57 to 0.71)

Resource use and costs

In the absence of the acquisition cost of any currently available TRK inhibitors inclusive of pricing discounts for the NHS, it is assumed that the manufacturer of Drug X would employ a value-based approach to pricing. This assumes that the drug acquisition cost would be set at a level that results in a histology-independent ICER (inclusive of testing costs and weighted according to the eligible population) at approximately NICE's decision threshold. For the purpose of the case study, Drug X is assumed to meet NICE's end-of-life criteria, allowing a maximum willingness-to-pay threshold of £50,000 per QALY.

To ensure generalisability of the results, the preferred approach to generate a weighted average is to use the eligible population rather than the trial population. This should also include the unrepresented tumour types. The threshold analysis used to generate the value-based price of Drug X is conducted

using the eligible population, including the unrepresented tumour types. The acquisition cost of SoC is assumed to be £20 per month.

For simplicity, it is assumed that there are no costs associated with administering Drug X or SoC and that there are no adverse event costs. It is also assumed that patients discontinue Drug X and SoC on disease progression.

Health state costs were assumed to be £350 per month per patient in the progression-free disease state and £500 per month per patient in the progressed disease health state. These values were informed by the health state costs reported in the NICE TAs of brigatinib and crizotinib.[255,260]

To reflect uncertainty in the health state costs, standard errors were assumed to be 10% of the mean.

A one-off terminal care cost of £6878 is applied on transition from the progressed disease state to the death state. The terminal care cost was obtained from Georghiou and Bardsley.[312]

The cost parameters used in the economic model can be seen in *Table 45*.

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a PSA was undertaken using 10,000 samples. All results reported are the mean averages of the 10,000 iterations.

Testing costs for unrepresented tumours

Table 46 provides a summary of the NNS, the annual eligible population and the testing costs for the tumours unrepresented in the trial. This illustrative example assumes that the testing costs equal £50 with a 100% sensitivity and specificity. The average cost to identify one individual eligible for treatment is estimated to be £14,322.

TABLE 45 Drug acquisition costs and health state costs

Parameter	Costs (£) (95% CI)
Drug acquisition costs	
Drug X	1250
SoC	20
Health state costs	
PFS	350 (315 to 385)
PPS	500 (450 to 550)
End of life	6878

TABLE 46 Summary of the NNS, the annual eligible population and the testing costs for the tumours unrepresented in the trial

Tumour type	Annual eligible population	NNS	Cost to identify one patient eligible for *NTRK* treatment (£)
Cervix	2	303.0	15,152
Congenital mesoblastic nephroma	0	2.0	102
Gastro–oesophageal junction	4	1000.0	50,000
Head and neck squamous cell carcinoma	24	263.2	13,158
High-grade glioma	1	2000.0	100,000
Neuroendocrine	7	333.3	16,667
Ovarian	4	400.0	20,000
Papillary thyroid tumour	3	23.3	1163
Paediatric high-grade glioma	2	9.0	450
Paediatric melanoma	44	461.4	23,070
Prostate cancer (NOS)	8	400.0	20,000
Renal cell carcinoma	6	58.1	2907
Salivary gland	1	1.1	55
Secretory breast carcinoma	0	400.0	20,000
Sinonasal adenocarcinoma	44	7.5	376
Uterine	1	1000.0	50,000
Total	151		

EME
HS&DR
HTA
PGfAR
PHR

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