ORIGINAL RESEARCH

Short running header: Post-progression survival in oncology

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The impact of increased post-progression survival on the cost-effectiveness of interventions in oncology

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Abstract:

Purpose: Cost-effectiveness analyses (CEA) of new technologies typically include 'background' costs (those associated with supportive care, such as monitoring, concomitant medications and staff time) as well as drug costs. In oncology, these are often expensive. The cost-effectiveness ratio associated with marginal survival ('CER_{MS}') calculates the ratio of background costs to QALYs during post-progression. With high background costs, the incremental cost-effectiveness ratio (ICER) can become less favourable as survival increases and the ICER moves closer to the CER_{MS}, making cost-effectiveness prohibitive.

This study assessed different methods to determine whether high ICERs are caused by high drug costs, high 'background costs' or a combination of both and how different approaches can alter the impact of background costs on the ICER where the CER_{MS} is close to, or above, the cost-effectiveness threshold.

Methods: NICE oncology technology appraisals published or updated between October 2012 and October 2017 were reviewed. An 'exemplar' case study was selected, and the CEA was replicated. Three modelling approaches were tested on the case study model.

Results: Applying one-off 'transition' costs during post-progression reduced the ongoing 'incremental' costs of survival, which meant that the CER_{MS} was substantially reduced and problems associated with additional survival were less likely to impact the ICER. Similarly, the use of two methods of additional utility weighting for end-of-life cases meant that the CER_{MS} was reduced proportionally, again lessening the impact of increased survival.

Conclusion: High ICERs can be caused by factors other than the cost of the drug being assessed. Appropriate measurement of costs and benefits of post-progression can avoid, or reduce, some of the challenges associated with the costs of increased survival. Further research is needed to assess how alternative approaches to the measurement and application of

background costs and benefits may provide an accurate assessment of the incremental benefits of life-extending oncology drugs.

Keywords: cancer, cost, economics, overall survival, quality of life, modelling

Introduction

Modelling in National Institute for Health and Care Excellence Oncology Technology Appraisals

In England and Wales, oncology drugs are assessed for recommendation for use in the NHS by the National Institute for Health and Care Excellence (NICE) via the technology appraisal (TA) programme. TAs review the clinical and economic evidence associated with a new technology, with economic evaluation of cost-effectiveness being a key factor in the recommendation made by NICE. If the incremental cost-effectiveness ratio (ICER) is £20,000 or less per quality-adjusted life year (QALY) gained, a technology is usually judged to be cost-effective [1], although if the technology meets end of life criteria the threshold may be increased [2].

Oncology technologies are commonly modelled using partitioned survival models with three health states [3]. On entry into the model, patients enter the 'pre-progressed' health state, typically reflecting the time in which patients are receiving the active treatment which may delay further disease progression. This period is known as 'progression free survival' (PFS). Patients then proceed to the 'post-progressed' health state (PPS), which reflects the point at which the disease has developed beyond the stage where active treatment is beneficial. Patients remain in this state until death, the final health state. The rate at which individuals move between the health states in each treatment arm is estimated by means of parametric equations derived from clinical trial data, with some form of extrapolation function. Costs and QALYs associated with being in each health state are applied to the cohort over a set number of cycles, and aggregated to estimate the overall cohort costs and QALYs in each treatment arm.

NICE Technology Appraisal Requirements

In line with the published NICE manual for the development of NICE guidelines, economic evaluations include not only treatment-related costs, but all costs relevant to the disease [4]. This

includes the ‘background’ or ‘supportive care’ healthcare costs, such as monitoring, concomitant medications, staff time, and follow-on treatments (both pharmaceutical and surgical), which may change as a result of an intervention, thus being relevant to the economic analysis [1,5]. In oncology, these background costs can be considerable, and may include expensive treatments such as radiotherapy and surgery [6,7]. Background costs are typically applied in economic models at a constant rate each cycle.

Background costs of disease management are often particularly high in the post-progression stage of the disease, when service provision shifts from active treatment using outpatient services, to an increased requirement for acute inpatient support. For example, a US study found that in the 6 months before death, cancer-related acute inpatient care increased from $1,785 per patient at 6 months before death, to $20,559 1 month before death [6]. Subsequently, extending survival and increasing a patient’s time in the post-progressed stage can be costly. In addition, in the later stages of disease, health-related quality of life (HRQoL) may be relatively low. Therefore, with extended patient survival following the intervention, the higher healthcare costs may outweigh the benefits accrued through that survival gain and ultimately, this can decrease an intervention’s likelihood of being cost-effective.

The Paradox of the CER$_{MS}$

A NICE Decision Support Unit (DSU) paper [8] describes four scenarios, supported by examples of TAs, in which clinically effective new technologies may not be considered cost-effective even if it were possible to acquire and administer them at zero price. Three of these scenarios describe situations in which costs relating to the disease of interest from additional life years gained outweigh the QALY benefits accrued in that period, generating a negative net benefit impact. The increased incremental cost may be accrued through one, or a combination, of the following: (i) survival gain for patients requiring continued resource use to treat ongoing health-care needs, (ii) survival gain in the post-progressed health state where costs are high for palliative care and HRQoL is low; or

(iii) survival gain in the pre-progressed health state, in which active treatment costs remain high. The fourth scenario describes a situation in which the survival gain increases the risk for an unrelated high-cost event that would not be experienced by patients in the comparator arm. Again, the associated costs outweigh the QALY gain from the increased survival. No TA was identified that demonstrated this scenario.

In oncology treatments that extend overall survival (OS), it is common for much of the survival gain to be accrued in the post-progressed health state. We report the cost-effectiveness ratio of marginal survival (CER_{MS}), which calculates the ratio of background costs during post-progression to background QALYs obtained during the same period. Assuming that the intervention is only used to treat patients prior to disease progression (although this assumption may not always hold in clinical practice, it is common in economic evaluation), as OS increases, the overall ICER will be influenced to a greater extent by the background costs and QALYs associated with the post-progressed health state, and the ICER value will tend towards the CER_{MS}. If the CER_{MS} exceeds the NICE cost-effectiveness threshold, which may happen in cases where PPS background costs are high or PPS utility is low, it becomes very difficult or, in some cases impossible, for the technology to achieve an ICER below the threshold, and the problem becomes greater, the longer that the intervention increases survival. Whilst this might be a legitimate cause of high ICERs, it is often conflated with discussions around drug costs (e.g. patient access schemes).

Study objectives

This study aimed to disentangle the effects of drug costs and 'background' costs on the ICER, and to understand how the effect of 'CER_{MS}' can vary, under a range of different scenarios, and whether these can help to address the issues outlined in the NICE Decision Support Unit document.

Methods

Review

All oncology technology appraisals published or updated by NICE between October 2012 and October 2017 were screened for inclusion in the review. Any that reported a conventional late-stage oncology partitioned survival model were included for data extraction.

From each included TA, the details of the appraisal, the technology and the model included in the company submission were extracted. While we understand that NICE decisions are commonly made on the basis of the adjusted model presented by the Evidence Review Group (ERG), ERG reports typically did not contain adequate granularity for data extraction of model input parameters.

Where possible, the CER_{MS} was calculated for each TA by dividing the monthly cost of post-progression survival by the monthly QALY gained by being in that state. Where multiple inputs were used in models (eg different utility values for different comparators), an average of all relevant values was applied. Where transition costs, or PPS background costs for different stages of PPS, were used in models (eg greater costs close to death), the cyclical PPS costs (not one-off transition costs) for the first stage of PPS were applied only.

Case Study

Following data extraction a case study was selected to explore whether alternative approaches may be useful in avoiding some of the problems outlined in the DSU report. To select an exemplar appraisal, the following criteria were used: (i) well-reported data available in the submission, (ii) a CER_{MS} close to, or above, £20,000, (iii) a technology that was 'not recommended' by NICE, (iv) a simple three-state partitioned survival model, and (v) a combination therapy (ie associated with higher therapy costs).

Following selection of a case study, the model was replicated as closely as possible by matching inputs to those reported (see Supplement B for full commentary on the model replication).

The case study model was then used to test a variety of scenarios. This paper presents 3 'test' scenarios that illustrate instances where conventional modelling approaches may miss important aspects of how the costs and benefits associated with marginal survival are implemented. It evaluates whether alternative approaches, that may better reflect the true distribution of costs and benefits, alleviate the problems associated with background costs. These scenarios (described in detail below), were as follows:

Test Scenario 1: Separation of post-progression background costs into ongoing and one-off costs.

Test Scenario 2: Adopting end-of-life criteria using the arbitrary QALY weighting approach.

Test Scenario 3: Adopting end-of-life criteria using the 'population norm' weighting approach.

The impact of these modelling approaches on the ICER was assessed with reference to the case study model as the base case, as well as two different disease scenarios in which the proportion of time spent in pre- and post- progression was varied from the base case relative to OS, but absolute gains between the treatment and comparator arms were kept stable. These scenarios represent the impact that these modelling approaches might have on drugs with comparative treatment benefits, but differing disease trajectories. In Disease Scenario 1, OS was shorter than in the base case, with the survival gain equating to approximately 50% of treatment OS, while Disease Scenario 2 had longer OS compared with the base case, with survival gain equating to approximately 15% of treatment OS.

Test Scenario 1: separation of post-progression background costs

In oncology models, background costs are typically applied on a monthly (or cyclical) basis, using a constant rate for each period. This does not necessarily reflect the true distribution of service use, whereby some costs are likely to be incurred as one-offs. The impact of adjusting the way these are applied was investigated by splitting the total PPS background costs into a combination of one-off costs and smaller monthly costs as follows:

Timing of costs 1: All PPS costs applied at a constant monthly rate.

Timing of costs 2: 80% of the total PPS cost applied as a one-off cost on transition from pre-progression to progression, with the remaining costs spread at a constant monthly rate.

Timing of costs 3: 80% of the total PPS cost applied as a one-off cost on transition from PPS to death, with the remaining costs spread at a constant monthly rate.

Timing of costs 4: 40% of the total PPS cost applied as a one-off cost on transition from pre-progression to progression, 40% of the total PPS cost applied as a one-off cost on transition from PPS to death, with the remaining costs spread at a constant monthly rate.

Test Scenario 2: adopting 'end-of-life' criteria - arbitrary QALY weighting

To reflect the added value of interventions that extend survival in conditions with a shorter life expectancy, NICE allows some modification of the utility gain for those patients. This can be approached in different ways. The first method is to weight all QALYs throughout the model so that the survival benefit has a greater impact on the ICER. There is little guidance about the extent to

which the QALYs can be weighted, however the maximum QALY weighting that may be considered 'reasonable' under certain circumstances, according to NICE DSU guidance, is 2.5 [9].

Test Scenario 3: adopting 'end-of-life' criteria – population norm QALY weighting

The second approach to weighting the QALY, is to apply population norm utilities to the QALY gains achieved during the period of extended survival (as outlined in the NICE Methods Guide). Within test scenario 3, this was calculated by multiplying the difference between the utility applied during post-progression and the population norm utility, by the mean survival gain in years, to generate additional QALYs for the treatment arm. These were discounted at 3.5%, before this additional QALY gain was added to the total treatment QALYs.

Analysis

The above scenarios were compared in order to determine whether or not each approach would be likely to avoid the problems outlined in the NICE DSU paper. Specifically, for each scenario, we estimated the CER_{MS} to determine the likely effect of each additional month of survival (ie testing whether an additional month of survival, at no extra drug cost, would reduce or increase the ICER).

Results

Review

Following screening of 40 technology appraisals, 29 were included for data extraction (Table 1; see Supplement A for details of exclusions).

<<insert Table 1>>

Case Study

TA403 was selected as an exemplar case study as the model that best fit our selection criteria (see *Methods*). The model could not be replicated exactly due to insufficient detail included in the submission for precise replication of the survival curves. Model results reported in the company submission and those estimated by our replication are reported in full in Supplement B. While total and incremental costs were closely replicated, total and incremental QALYs were higher in our replication, particularly in the pre-progressed state, reducing the overall ICER. In recognition of this, we explored the impact of artificially deflating the utilities to produce a closer model match. The pattern of results following the subsequent application of modelling approaches was the same, thus this paper reports only the results for the replication in which the original model inputs reported by the company submission were used. In addition, the ERG noted that an error in the company submission resulted in the application of an effective discount rate of 10.9%. In our analyses, the discount rate was corrected to 3.5% in line with the NICE reference case [5]. Table 2 shows the results of the model replication used in the current study as a base case, and to which different modelling approaches were applied.

<<insert Table 2>>

The CER_{MS} for this model was £12,721 (with the corrected discount rate). All else being equal, in order for the case study treatment to come below the NICE cost-effectiveness threshold of £20,000 per QALY, a drug cost discount of over 90% would be required. It should be noted that, even in a biologically implausible scenario where OS remained at 100% in the treatment arm for the whole duration of the model (ie reflecting no deaths across the 15 year time horizon), the ICER remained above the £20,000 threshold, at £21,833 per QALY, due to a combination of the drug cost and the high 'background' cost of living with the disease.

Test Scenario 1: separation of post-progression background costs

In the base case (case study) model, total PPS background costs were £11,059 in the treatment arm, and £9,706 in the comparator arm. On average, patients in the treatment arm spent approximately 14 months in post-progression, while those in the comparator arm spent 12 months in post-progression.

In Disease Scenario 1 (where OS was shorter than the base case), total PPS background costs were £3,017 in the treatment arm, and £1,826 in the comparator arm. On average, patients in the treatment arm spent approximately 4 months in post-progression, while those in the comparator arm spent around 2 months in post-progression.

In Disease Scenario 2 (where OS was longer than in the base case), total PPS background costs were £10,015 in the treatment arm, and £8,781 in the comparator arm. On average, patients in the treatment arm spent approximately 13 months in post-progression, while those in the comparator arm spent around 11 months in post-progression.

Accordingly, where substantial one-off costs were applied (as opposed to spreading the costs evenly across all months), monthly background costs were £162, £160 and £157 in the base case, disease scenario 1 and disease scenario 2 respectively.

<<insert Table 3>>

Regardless of the timing of the one-off cost, separation of the PPS costs resulted in a 3 to 4% reduction in the ICER across all disease scenarios (Table 3). The CER_{MS} was reduced by almost 75%, from £12,721 to around £3,200 across all disease scenarios.

All else being equal (ie assuming the base case survival inputs), in order for the case study treatment to fall below the NICE cost-effectiveness threshold of £20,000 per QALY, a drug cost

discount of around 90% would still be required despite these changes. However, in contrast to applying the PPS background costs evenly across all months, should OS remain at 100% in the treatment arm (ie reflecting no deaths across the 15 year time horizon), the ICER would be below the threshold, at between £7,000 and £8,000 per QALY (depending on scenario). In fact, by manipulating the hazard ratio between the treatment and comparator OS curves, a HR of 0.4 applied to all disease scenarios would bring the ICER below £20,000. Again, whilst such a HR may be biologically implausible, it is now mathematically possible to achieve a sub-threshold ICER, which was not possible in the base case.

Test Scenario 2: adopting 'end-of-life' criteria - arbitrary QALY weighting

The maximum QALY weighting recommended according to NICE guidance is 2.5. Even with this weighting, a drug price discount of 70% would be required to produce an ICER below £20,000. In cases where the ICER is closer to the threshold, this adjustment may have a greater bearing on the NICE appraisal outcome.

Although applying QALY weightings had a greater impact on the ICERs than scenario 1, the CER_{MS} was reduced to a lower degree (Table 4), with a maximum reduction of 60% applying extensive weightings of 2.5. For the biologically implausible scenario where OS remained at 100% in the treatment arm for the whole duration of the model (ie reflecting no deaths across the 15 year time horizon), the ICER was below £20,000 with even minimal QALY weightings of 1.1.

<<insert Table 4>>

Test Scenario 3: adopting 'end-of-life' criteria – population norm QALY weighting

Regardless of the disease scenario, this modelling approach resulted in an ICER reduction of 25% to 26% (Table 5). This is to be expected, since the QALY gains have simply been inflated in a proportional manner. It is important to note, however, that the CER_{MS} reduced in all scenarios. Specifically, the CER_{MS} dropped from £12,721 in the base case to £9,525 whenever the population norm utility was applied. In the 100% survival in the treatment arm scenario, this adjustment would bring the base case model ICER below the £20,000 threshold, to £17,328 per QALY, with a hazard ratio of 0.25 required to remain subthreshold.

<<insert Table 5>>

Combining modelling approaches

In addition to the scenarios above being tested individually, combinations of scenarios were also tested. This involved only the changes that made the biggest impact on the ICER and CER_{MS} (ie the impact of applying an 80% one-off cost on transition to death in combination with QALY weightings).

<<insert Table 6>>

The impact on the ICER of combining the two approaches were slightly greater than with adopting the QALY weighting approach alone (Table 6). However, the impact on the CER_{MS} was the largest observed, with an 88% reduction even with minimal QALY weightings. As with the QALY weighting approach alone, 100% survival in the treatment arm would bring the ICER under £20,000 for all weightings.

Discussion

Findings and implications

This study used an exemplar technology appraisal to explore the impact of a number of different modelling scenarios upon the incremental costs and QALYs associated with increased survival in oncology. Although our case study used a partitioned survival model approach, the issues raised in this paper would apply to any modelling approach where increased survival is likely to accrue substantial additional costs. The analysis suggested that (in the example used), some of the problems highlighted by a previous NICE DSU report could be avoided, or at least reduced, by appropriately measuring the true costs and benefits of incremental survival. Specifically, the test scenarios showed that, when 'post progression' costs are broken down into one-off 'transition' and variable incremental components, then increased survival tended to be more favorable in terms of cost-effectiveness. Likewise, when the QALYs associated with additional survival were given increased weighting, there was less evidence of the problems outlined in the NICE DSU report.

Therefore, many interesting questions are raised regarding the valuation and quantification of quality of life and costs in the stages around the end of a patient's life. NICE recommends additional weighting for QALYs that are gained in cases where death is imminent, but there is little research undertaken to demonstrate society's true preferences for such weightings. Similarly, whilst aggregated costs are often presented for periods spanning several months, there is little research linking the costs with the prognosis of the patient, such that accurate costing predictions could be made based on changes in prognosis.

Given that background care costs are not at the control of the companies developing new technologies, one could argue that the current approach (including all such costs) is unfair in situations where they prevent the technology from being considered cost-effective even at zero price. For some submissions, companies may wish to explore the plausibility of options for presenting scenario analyses in which the background costs associated with the marginal increases in post-progression survival are excluded, in order to better illustrate this issue. In any

case, there is a need for greater understanding of this issue by HTA agencies, as if HTA modelling requirements prevent effective new treatments from coming to market, the ultimate loser is the patient and wider society.

Limitations

Many of the models reported in the TAs reviewed were complex or poorly reported, limiting our ability to calculate the CER_{MS} in many cases. The scenarios tested in this study were applied to a case study, and as such may be case study specific; other models may find that the same changes have a different impact on the ICER. In addition, it was not possible to replicate the case study model exactly. It was deemed, however, that use of the case study model with alternative disease scenarios provided a useful illustrative example of the impact of different scenarios.

A final limitation of the study was that the first scenario tested, in which the total background costs associated with the progressed health state were split into one-off and ongoing costs, was not evidence-based. The proportion of the total background costs applied as a one-off cost in this study was arbitrary, and in our recommendations below we describe the need for further research to ensure that the costs and benefits associated with late-stage disease are accurately reflected in the model.

Recommendations for future research and decision-making

In order to better represent the costs and benefits associated with progressed disease in a way that is fair, more research is required. One aspect of this would be to investigate the plausibility of the traditional approach of applying all background costs in a cyclical fashion, the impact of which was explored using arbitrary splits in Scenario 1. It may be that in some oncology indications a greater amount of resources are used soon after progression, while in others, the bulk of the cost may be accumulated closer to death. In such cases, it may be more appropriate to include some background costs, such as pain relief, as ongoing cyclical costs, and others, such as CT scans, as

'one-offs'. Applying these costs in a way that reflects their true timing may then mean that the impact of the one-off costs affects the treatment and comparator arms equally, with the cost implications of treatment-related survival gain including only those costs that can be truly described as 'ongoing'.

There are also considerations on the other side of the ICER equation; the measurement of HRQoL. Typically single separate utility values are applied to the entire period of pre- and post-progression. Disutilities may also be included to measure the impact of adverse events associated with the treatment or comparator. However, in practice, HRQoL is unlikely to remain static throughout the pre- or post-progressed health state, and the timing of utility measurement for each may impact the model. If collected soon after progression, the post-progressed utility value may overestimate true utility if the patients' condition has not deteriorated fully, or underestimate it in situations where HRQoL is still negatively affected by ongoing treatment toxicity or anxiety and depression following the prognosis. Similar problems may affect the measurement of the true treatment benefits associated with pre-progression, particularly in models where adverse event disutilities are applied. If utility is measured in a trial population, the impact of adverse events may already be captured in the utility value, thus resulting in double-counting HRQoL decrements and ultimately undervaluing the benefits of maintaining progression-free survival. Some models submitted to TAs have recognized the issue of changing utility by applying different utilities within a particular health state; they have been applied on a 'time-from-death' basis (TA428 [10]), or with different utilities applied to different stages of supportive treatment (TA406 [11]). This is far from common practice, and it would be interesting to know the impact of such approaches on the CER_{MS} and the ICER.

Conclusion

This study demonstrates that high ICERs can be caused by factors other than the cost of the drug being assessed. Furthermore, some of the issues outlined in the NICE DSU paper can be avoided, or at least reduced, by appropriately measuring the costs and benefits associated with

the late stages of a person's life. However, in some cases, the cost-effectiveness of treatments may still be prohibited because of excessive 'background' costs associated with increased survival. Further research is needed to assess how alternative approaches to the measurement and application of background costs and benefits may provide an accurate assessment of the incremental benefits of life-extending oncology drugs.

Author contributions

MT, MJ and CK initiated the study. JR, HD and MJ contributed to the review, the case study and the modelling approaches. JR drafted the initial manuscript. All authors contributed to the interpretation of the findings and the editing and revision of the manuscript.

Disclosure

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Table 1 Details of TAs and CER^{MS}

TA	Broad indication	Drug name	Annual PPS background costs	PPS utility	CER_{MS}	ICER	NICE Decision
458	Breast (stage III or IV)	Trastuzumab emtansine	£2,072	0.53	£3,910	£98,525 to £131,473	R
423	Breast (stage III or IV)	Eribulin	£2,799	0.679	£4,122	£35,624 to £36,244	CR
263	Breast (stage IV)	Bevacizumab (with capecitabine)	£9,648	0.496	£19,452	£77,318	NR
463	RCC (advanced)	Cabozantinib	£2,017	0.777	£2,596	-	R
417	RCC (advanced)	Nivolumab	£3,676	0.663*	£5,549	£42,417 to £83,829	R
333	RCC (advanced)	Axitinib	£4,147	0.61	£6,798	-	R
405	Bowel (metastatic)	Trifluridine (with tipiracil hydrochloride)	£2,319	0.64	£3,623	£44,032	R
377	Prostate (metastatic)	Enzalutamide	£37,024*	0.612*	£60,497	£27,076 to £95,685	R
428	Lung (stage III or IV)	Pembrolizumab	£1,853	0.763	£2,429	£23,424 to £49,048	CR
447	Lung (stage IV)	Pembrolizumab	£6,545	0.668	£9,798	£44,896	CR
416	Lung	Osimertinib	£7,255	0.678	£10,701	-	CR

	(stage III or IV)						
406	Lung (stage III)	Crizotinib	£2,327*	0.565*	£4,119	-	R
411	Lung (stage III or IV)	Necitumumab	£4,016	0.55	£7,302	£60,133 to £119,912	NR
403	Lung (stage III or IV)	Ramucirumab (with docetaxel)	£11,007	0.599	£18,375	£84,985 to £1,106,497	NR
395	Lung (stage III)	Ceritinib	£3,764	0.46	£8,183	£62,456	R
374	Lung (stage III)	Erlotinib and Gefitinib	£9,949	0.4734	£21,016	£15,359 to £61,132	CR Erlotinib; Gefitinib NR
347	Lung (recurrent or metastatic)	Nintedanib	£4,380*	0.638	£6,866	£27,008 to £50,776	R
310	Lung (recurrent or metastatic)	Afatinib	£18,744*	0.52*	£36,046	-	CR
421	Breast (stage III)	Everolimus	-	-	Incalculable	£61,046	R
432	RCC (metastatic)	Everolimus	-	-	Incalculable	£52,261 to £58,316	R
378	Bowel (advanced)	Ramucirumab (with paclitaxel)	-	0.587	Incalculable	£53,830 to £188,640	NR
307	Bowel (metastatic)	Aflibercept (with irinotecan	-	-	Incalculable	£30,474 to £36,294	NR

		and fluorouracil)					
473	Head & neck (recurrent or metastatic)	Cetuximab (with platinum-based therapy)	-	0.52	Incalculable	-	CR
422	Lung (stage III)	Crizotinib	-	0.61	Incalculable	-	R
402	Lung (stage III or IV)	Pemetrexed	-	-	Incalculable	£70,538	CR
412	Prostate (metastatic)	Radium-223 dichloride	-	0.47 and 0.56	Incalculable	£25,963	CR
391	Prostate (metastatic)	Cabazitaxel (with prednisone)	-	0.6266	Incalculable	£49,327	CR
259	Prostate (metastatic)	Abiraterone acetate (with prednisolone)	-	0.5	Incalculable	£52,851 to £170,550	CR
316	Prostate (metastatic)	Enzalutamide	£1,941	-	Incalculable	£14,795 to £102,751	R

Notes: * indicates instances where multiple inputs were used in models. The CER_{MS} was calculated by averaging all relevant utility inputs and applying only ongoing background PPS costs (not one-off costs).

Abbreviations: TA, technology appraisal; PPS, post-progression survival; ICER, incremental cost-effectiveness ratio; CER_{MS}, cost-effectiveness ratio(s) of marginal survival; R, recommended; CR, conditional recommendation; NR, not recommended.

Table 2 Replicated TA403 model results with corrected discount rate

	Treatment	Comparator	Incremental
Costs			
Tx cost - pre-progression	£24,412	£1,134	£23,278
Background: pre-progression	£1,689	£1,195	£494
Background: post-progression	£11,059	£9,706	£1,353
Cost of death	£0	£0	£0
AEs	£807	£656	£152
Total cost	**£37,968**	**£12,691**	**£25,276**
QALYs			
Pre-progression QALYs	0.423	0.299	0.124
Post-progression QALYs	0.602	0.528	0.074
AEs	-0.003	-0.003	0.000
Total QALYs	**1.022**	**0.825**	**0.197**
ICER			**£128,233**

Abbreviations: Tx, treatment; AE, adverse event; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

Table 3 Results of Scenario 1 (separation of post-progression background costs)

Scenario	Cost timings	PPS monthly Cost	Total treatment costs	Total comparator costs	Incremental costs	ICER	CER_{MS}
Base case	Original	£635	£37,968	£12,691	£25,276	£128,233	£12,721
	80% at death	£162	£37,417	£13,267	£24,150	£122,521	£3,245
	80% at progression	£162	£37,851	£13,632	£24,219	£122,868	
	40% at death and 40% at progression	£162	£37,634	£13,450	£24,185	£122,695	
Disease Scenario 1: Shorter OS	Original	£635	£29,059	£4,006	£25,053	£144,878	£12,721
	80% at death	£160	£28,044	£3,810	£24,234	£140,143	£3,205
	80% at progression	£160	£28,700	£4,548	£24,152	£139,668	
	40% at death and 40% at progression	£160	£28,371	£4,179	£24,193	£139,906	
Disease Scenario 2: Longer OS	Original	£635	£39,050	£13,900	£25,150	£133,296	£12,721
	80% at death	£157	£38,392	£14,272	£24,120	£127,839	£3,145
	80% at progression	£157	£38,674	£14,498	£24,176	£128,137	

	40% at death and 40% at progression	£157	£38,533	£14,385	£24,148	£127,988	

Abbreviations: OS, overall survival; PPS, post-progression survival; ICER, incremental cost-effectiveness ratio; CER_{MS}, cost-effectiveness ratio(s) of marginal survival.

Table 4 Results of Scenario 2 (adopting end-of-life criteria using arbitrary QALY weightings)

	QALY weighting								
	1.00	**1.10**	**1.30**	**1.50**	**1.70**	**1.90**	**2.10**	**2.30**	**2.50**
CER_{MS} for all disease scenarios	£12,721	£11,565	£9,786	£8,481	£7,483	£6,695	£6,058	£5,531	£5,088

Notes: As survival gain in pre- and post-progression was equal across all disease scenarios and monthly costs were the same, the impact of QALY weighting on the CER_{MS} was the same across all scenarios.

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; $CER_{MS,}$ cost-effectiveness ratio(s) of marginal survival.

Table 5 Results of Scenario 3 (adopting end-of-life criteria using population norm QALY weightings)

Scenario	**Change**	**PPS utility**	**"Population norm" utility**	**Mean survival gain**	**Additional discounted QALYs**	**CER_{MS}**	**ICER**
Base case	**Original**	0.599	-	4.4 months	-	£12,721	£128,233
	Adjusted	0.599	0.800	4.4 months	0.067	£9,525	£95,848

Disease Scenario 1	**Original**	0.599	-	3.74 months	-	£12,721	£144,878
	Adjusted	0.599	0.800	3.74 months	0.061	£9,525	£106,978
Disease Scenario 2	**Original**	0.599	**-**	4.03 months	-	£12,721	£133,178
	Adjusted	0.599	**0.800**	4.03 months	0.062	£9,525	£100,190

Abbreviations: PPS, post-progression survival; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CER_{MS}, cost-effectiveness ratio(s) of marginal survival.

Table 5 CER_{MS}s by QALY weighting with applied transition costs

	Base case	**Applied transition costs (ie reduced monthly cost of survival) *and* QALY weighting**								
		1.00	**1.10**	**1.30**	**1.50**	**1.70**	**1.90**	**2.10**	**2.30**	**2.50**
Base case	£12,721	£3,245	£2,950	£2,496	£2,164	£1,909	£1,708	£1,545	£1,411	£1,298
Disease Scenario 1	£12,721	£3,205	£2,914	£2,466	£2,137	£1,885	£1,687	£1,526	£1,394	£1,282
Disease Scenario 2	£12,721	£3,145	£2,859	£2,419	£2,097	£1,850	£1,655	£1,498	£1,367	£1,258

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CER_{MS}, cost-effectiveness ratio(s) of marginal survival.