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Assessment of Overall Survival, Quality of Life, and Safety Benefits Associated With New Cancer Medicines

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IMPORTANCE There is a dearth of evidence examining the impact of newly licensed cancer medicines on therapy. This information could otherwise support clinical practice, and promote value-based decision-making in the cancer drug market.

OBJECTIVE To evaluate the comparative therapeutic value of all new cancer medicines approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) between 2003 and 2013.

DESIGN, SETTING, AND PARTICIPANTS We used a narrative synthesis approach to systematically synthesize and analyze English, French, and Australian health technology assessments (HTAs) of all new cancer medicines licensed in the United States and Europe between 2003 and 2013.

INTERVENTIONS Sixty-two new molecular entities with a primary oncology indication.

MAIN OUTCOMES AND MEASURES Overall survival (OS), quality of life (QoL), and safety.

RESULTS Of the 62 new active cancer molecules approved by the FDA and EMA between 2003 and 2013, 53 were appraised by English, French, or Australian HTA agencies through May 2015. Of these 53 drugs, 23 (43%) increased OS by 3 months or longer, 6 (11%) by less than 3 months, and 8 (15%) by an unknown magnitude; there was no evidence to suggest that the remaining 16 (30%) increased OS over best alternative treatments. Where overall survival gains could be quantified, all new cancer drugs were associated with a mean (SE) total increase in OS of 3.43 (0.63) months over the treatments that were available in 2003. Drug-related improvements in OS were, however, widely distributed across therapeutic targets—ranging between 0 (thyroid, ascites) and 8.48 months (breast cancers)—and were sometimes based on modeled data, indirect or nonactive comparisons, or nonvalidated evidence. Although 22 (42%) of 53 new medicines were associated with an increase in QoL, 24 (45%) were also associated with reduced patient safety. Of the 53 new cancer drugs, 42 (79%) were associated with at least some improvement in OS, QoL, or safety.

CONCLUSIONS AND RELEVANCE Although innovation in the oncology drug market has contributed to improvements in therapy, the magnitude and dimension of clinical benefits vary widely, and there may be reasons to doubt that claims of efficacy reflect real-world effectiveness exactly. These findings raise important questions for clinical decision-making and value-based policy.

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Supplemental content

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There are growing questions about the value gained from spending on what seem to be ever more expensive cancer medicines. Rising expenditures may make it difficult for patients to access or remain compliant with life-extending therapies.[1,2] Yet, some have argued that high prices may be justified if new and innovative treatments offer significant benefits to patients.[2,3] Even as studies point to gains in overall survival (OS) from innovative cancer medicines,[4] efforts to examine the value from spending on new cancer drugs remain stymied by a dearth of systematic evidence on their clinical risks and benefits. This lack of evidence makes it difficult for the public to demand more from innovation,[5] and, where costs factor into the decision-making process, for clinicians and patients to balance preferences for the expected impact of treatment against rising drug expenditures.

One difficulty in characterizing the clinical impact of new cancer drugs is the multiplicity of outcome measures. Overall survival has traditionally been taken as the gold standard among oncology efficacy endpoints.[6,7] The United States Food and Drug Administration (FDA), for its part, designates OS as the only "universally accepted" and the "most reliable" direct measure of benefit in oncology drug trials.[8] The European Medicines Agency (EMA) similarly states that convincing favorable effects on OS are, from a clinical and methodological perspective, the "most persuasive outcome" of oncology trials.[9] As policymakers adopt new regulations to expedite access to medicines for serious conditions,[10,11] interest has grown in measuring effectiveness through surrogate markers.[12] These, however, are not yet systematically measured by regulators[8,13] and still have inconsistent or uncertain predictive clinical value.[14,15] Despite its potential limitations, the American Society for Clinical Oncology's (ASCO) recently published[16] Value Framework in fact recommends that efficacy benefits be measured through progression-free survival or response rates only if OS is not reported.[17] In addition to efficacy measures, quality of life (QoL) and safety are also used by regulators and clinicians to fully consider the impact on how patients feel and function owing to treatment.[17-19]

To shed light on the clinical risks and benefits from new cancer drugs, this study took a narrative synthesis approach to review regulatory assessments of the impact on OS, QoL, and safety from all cancer medicines newly licensed in the US and Europe over the past decade. Since US licensing decisions do not require proof of comparative efficacy and may not consider OS benefits under accelerated licensing procedures,[20,21] we extracted and reviewed summary conclusions of drug-related OS, QoL, and safety benefits from English (The National Institute for Health and Care Excellence, NICE), French (Haute Autorité de Santé, HAS), and Australian (Pharmaceutical Benefits Advisory Committee, PBAC) health technology assessment (HTA) agencies. We find that OS benefits vary widely, improvements in OS and QoL often come at the cost of safety, and there are reasons to doubt whether clinical efficacy has been matched by effectiveness in the real world. This study provides additional clarity on the potential risks and benefits of new cancer medicines. It also raises questions about how clinical impact is measured by regulators, how the scientific evidence is used to inform clinical practice, and how much value is generated from cancer drug spending.

Key Points

Question What are the overall survival, quality of life, and safety benefits of recently licensed cancer medicines?

Findings An analysis of health technology assessment reports found that new cancer drugs were associated with increased overall survival by an average of 3.43 months between 2003 and 2013, with 43% increasing overall survival by 3 months or longer, 11% by less than 3 months and 30% were not associated with an increase in overall survival. Most new cancer drugs improved quality of life, and were associated with reduced patient safety.

Meaning The added benefits of new cancer medicines vary widely across and within therapeutic indications and may be based on modeled data, indirect or nonactive comparisons, or nonvalidated evidence.

Methods

Inclusion and Exclusion Criteria

All new molecular entities (NMEs) approved by the FDA and EMA between 2003 and 2013 with a primary indication for oncology were eligible for inclusion. This study focused exclusively on primary indications, which are likely to reflect main intended use. Drug inclusion criteria were adapted from a previous study by Roberts et al.[22] Because this study did not use or access patient-level data the London School of Economics and Political Science determined that ethical approval was not required.

Drug Appraisals

Evaluations of the clinical impact of new cancer drugs were obtained from English, French, and Australian agency HTAs published through May 2015. These agencies regularly publish HTAs in the English language, and are required to evaluate the clinical impact of new medicines in relation to existing standards of treatment that would most likely be replaced by the new intervention.[23-25] Health technology assessments were selected for review if they pertained to the same target condition as the first FDA-approved indication. If multiple reports evaluated the same target condition, we selected the latest report that most closely matched the first FDA-approved indication with respect to any treatment restrictions (eg, cancer staging). In ambiguous cases, determinations were made in consultation with a medical expert. Initial EMA-approved indications were used if the drug had not been approved by US regulators through May 2015.

Data Extraction and Synthesis

Two reviewers (S.S.V. and R.L.) adapted the patient, intervention, comparator, outcomes framework[26] to independently review assessments of the clinical impact of new cancer medicines. Information on recommended patient populations, novel interventions, and therapeutic comparators were extracted

from each drug appraisal, as were evaluations of the impact on OS, QoL, and safety of drug treatment. The **Table** lists the classes of evidence that were typically evaluated and reported by English, French, and Australian authorities to assess OS, QoL, and safety. This approach captured key outcome measures that are regularly considered during formal drug reviews,[8,18,19] and reflected ASCO's recently published conceptual framework for measuring the value of cancer treatment options.[17]

A rules-based process was undertaken to evaluate evidence reported by HTA agencies. For this, we considered overall judgments of the available evidence on OS, QoL, and safety from HTA summary sections, their acknowledgement of the significance of clinical trial results, or referral to prior evaluations of the primary evidence. If these were absent, or if an HTA agency concluded that clinical benefits could not be assessed, corresponding extraction parameters were marked as missing. Disagreements on how to interpret HTA agency summaries about the clinical impact of treatment were resolved through consensus. Overall survival benefits were categorized as 3 months or longer, less than 3 months, increase but of unknown magnitude, and no demonstrated increase. A recent ASCO working group has suggested that improvements in median OS of at least 20% may demonstrate a clinically meaningful improvement in survival. However, our approach was designed to reflect the system that is currently used in England to identify OS improvements that are large enough to justify additional expense in end-of-life care,[27] and used at times by Australian authorities to assess new health technologies.[28] Quality of life and safety benefits were categorized as improvement, reduction, mixed evidence, or no difference relative to the standards of care existing at time of evaluation. A hierarchical process was followed to generate a composite measure of the drug-related effect on OS, QoL, and safety. In instances where assessments were available from multiple HTA agencies, this involved identifying the most positive drug-related survival benefit to represent what may be possible from treatment. For QoL and safety, if 1 HTA agency indicated that the new medicine was associated with an overall improvement in therapy, but another found no change, we classified the drug as producing a net positive gain. If opposing evidence existed, we classified the drug as being associated with mixed evidence. Please see the eMethods section in the Supplement for additional information. Defining features of each drug appraisal were also recorded, and a physician classified all eligible drugs into therapeutic target groups according to their FDA-approved primary indication. A summary of drug-related effects on OS, QoL, and safety is provided in eTable 1 in the Supplement, and an overview of the regulatory evidence used in our analysis is provided in eTable 2 in the Supplement.

Descriptive statistics were used to summarize composite measures of the impact on OS, QoL, and safety of all medicines included in this analysis. Krippendorff's α coefficient was used to measure the level of agreement among HTA agency assessments of the clinical benefits of treatment, and to inform our interpretation of results.[29] Because reliability standards should relate to local requirements,[30] our interpretation of this statistic focuses on the difference between coefficients. For convenience, however, we take an α level of .67 or greater to

Table. Evidence Generally Reported by HTA Agencies to Evaluate Drug-Related Effects on Key Outcome Measures

Outcome Measure	Evidence
OS	Median OS[a,b,c]
	Mean OS[a,c]
	Survival probability (%)[b,c]
	OS (mean/median, NOS)[b,c]
	Expectations of impact on mortality (NOS)[b]
QoL	Symptom improvement[a,b]
	Time to change (deterioration/improvement) in functioning or symptoms[a,b,c]
	QoL instruments[a,b,c,d]
	Impact on utility[a]
	Expectations of impact on QoL (NOS)[a,b,c,e]
	Patient representative/clinical expert inputs[a,b,f]
Safety	Incidence of AE[a,b,c,g]
	Incidence of severe or serious AE[a,b,c,h]
	Time to first AE (≥grade 3)[a]
	Treatment discontinuation or dose reduction[a,b,c]
	Overall tolerance and safety profile (NOS)[a,b,c,i]
	Treatment-related deaths[a,b,c,j]
	Patient representative/clinical expert inputs[a,b,c,k]

Abbreviations: AE, adverse events; HTA, health technology appraisal; NOS, not otherwise specified; OS, overall survival; QoL, quality of life.

[a] The National Institute for Health and Care Excellence.

[b] Haute Autorité de Santé.

[c] Pharmaceutical Benefits Advisory Committee.

[d] For example, Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire, Time Without Symptoms and Toxicity (TwiST) and Quality-Adjusted Survival and Toxicity (Q-TwiST); Short Form Health Survey-Version 2.0 (SF12 v2), EQ-5D and EuroQol-5 Dimensions-Visual Analogue Scale (EQ-5D-VAS); Functional Assessment of Cancer Therapy-General (FACT-G); Brief Pain Inventory-Short Form (BPI-SF); Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym); Functional Assessment for Cancer Therapy–Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS); Functional Assessment for Cancer Therapy–Kidney Symptom Index-15-Item (FKSI-15); Functional Assessment of Cancer Therapy-Prostate (FACT-P); EORTC Core Quality of Life Questionnaire (QLQ-C30); EORTC Multiple Myeloma Module (QLQ-MY20); Cancer Treatment Satisfaction Questionnaire (CTSQ); Karnofsky performance status; Eastern Cooperative Oncology Group (ECOG) performance status; Lung Cancer Symptom Scale (LCSS).

[e] Internal HTA agency opinion or expectation regarding aspects of clinical impact, not directly informed by the available evidence.

[f] May include inputs on preference for oral or intravenous administration, amount of time in hospital, number of hospitalizations, meaningfulness of improvements in symptoms (eg, fatigue, pain), and ability to perform daily activities.

[g] Described as adverse events (NOS), treatment-emergent adverse events (TEAEs) without specification of serious grade, grades 1/2 adverse events, adverse events of mild to moderate intensity

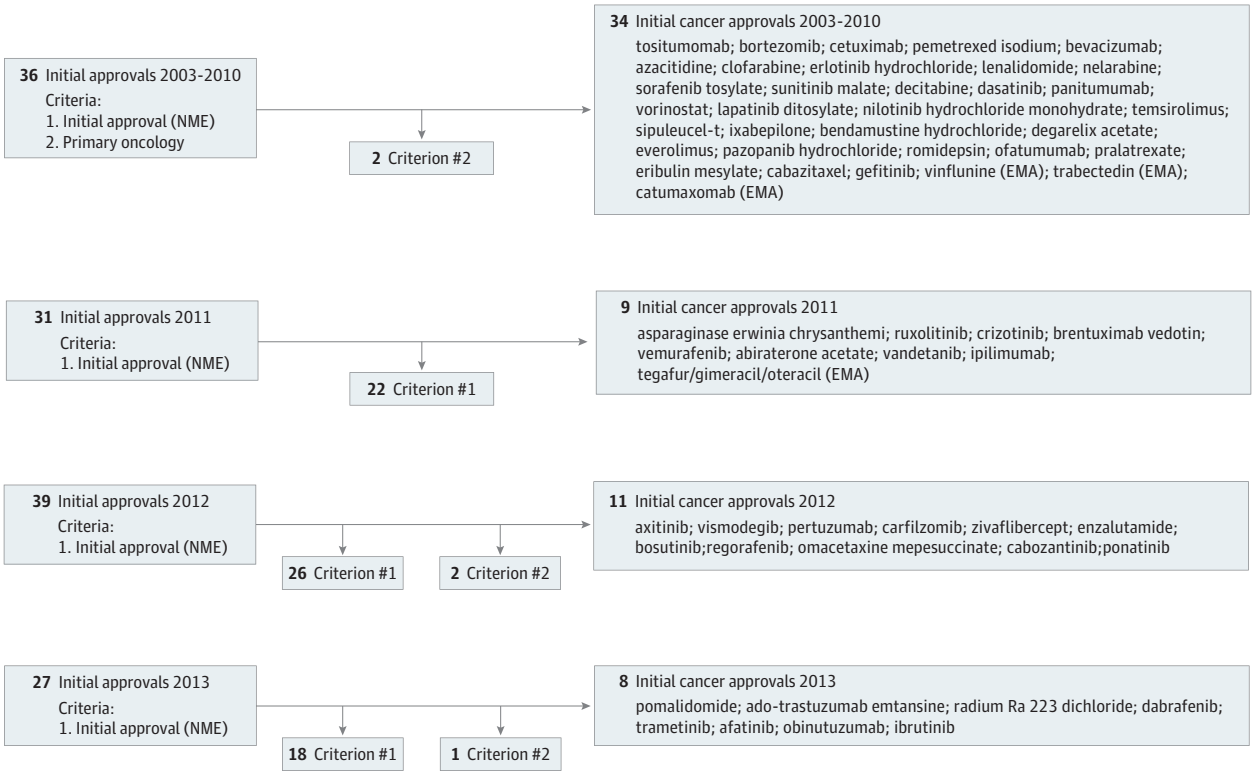
[h] Described as serious adverse events (SAEs), grades 3/4 adverse events, treatment-related syndromes (eg, systemic inflammatory response syndrome)

[i] For example, discussion of overall tolerance and safety profile without reporting of primary evidence in assessment.

[j] Including grade 5 adverse events.

[k] Examples of inputs from patients, patient representatives, or clinical experts included comments on patient willingness to accept adverse effects given the benefits of treatment, and comparability of adverse reaction profiles.

Figure 1. **Flow Diagram of Review Process**



Flow diagram depicting the process used to systematically identify all initial US Food and Drug Administration approvals occurring between 2003 and 2013 for molecules with an active primary indication for cancer. Exclusion criterion #1 identifies all molecules that are neither used in oncology, nor indicated as an active treatment for cancer. Exclusion criterion #2 identifies all molecules that are used in oncology, but are not indicated as an active treatment for cancer. Food and Drug Administration initial approvals identified through Roberts et al[22] and Drugs@FDA registry.[31] European Medicines Agency initial approvals identified through the European Medicines Agency's European public assessment reports search engine.[32]

indicate a high level of agreement.[30] Finally, to attempt to externally validate our results, we sought informal feedback on our analysis from 2 medical experts from the FDA. After providing their informed consent to participate anonymously, both experts were given a written description of our methods and a copy of all results. They were asked to review all materials and provide feedback as to whether our synthesis was consistent with their own perception of the impact from new cancer medicines on clinical therapy in the United States. Please see the eMethods section in the Supplement for further details on our methodology as well as a discussion of potential limitations.

Results

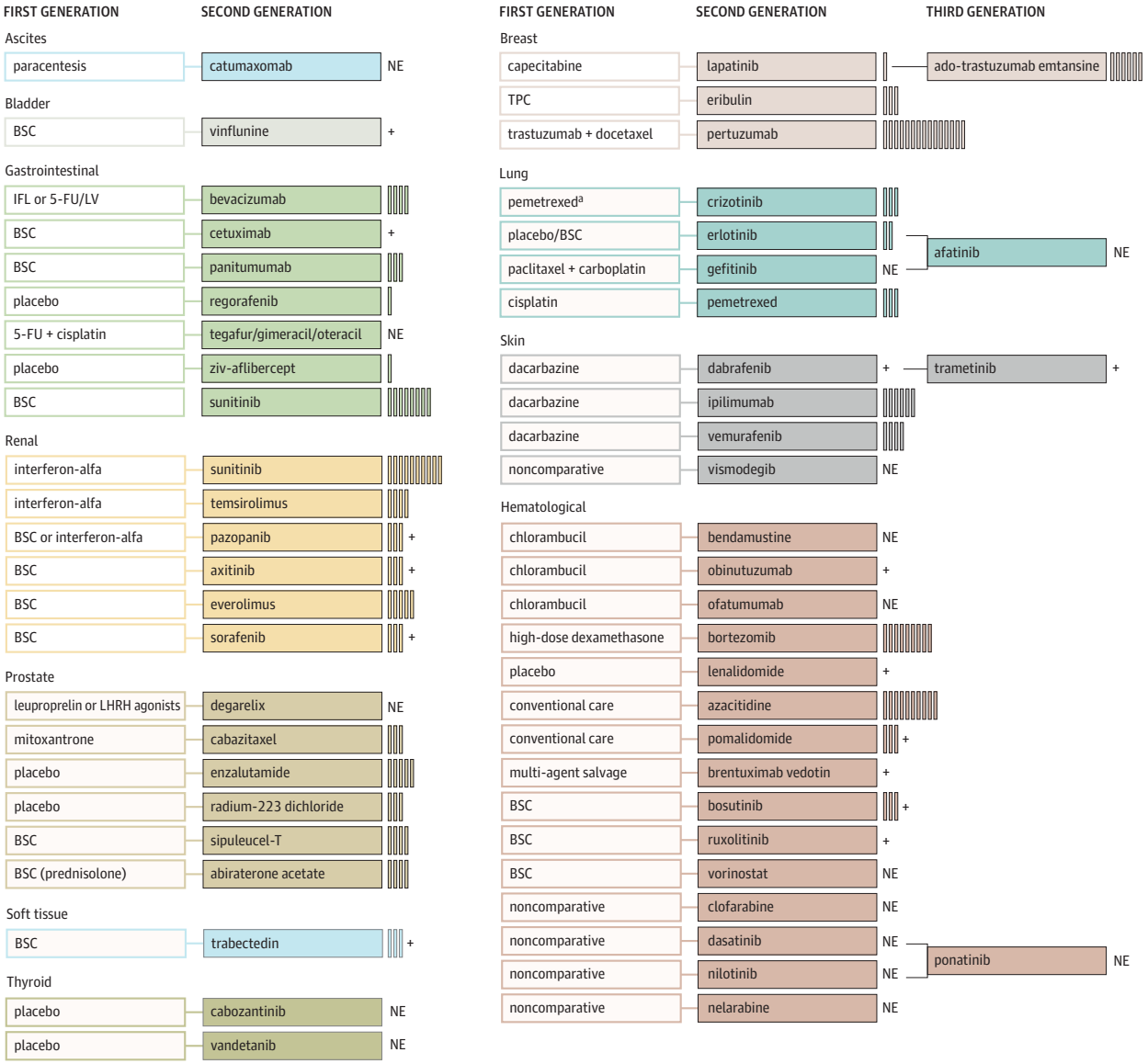
A total of 62 new active cancer molecules were eligible for this study (**Figure 1**), 4 of which were approved by the EMA but not the FDA through May, 2015. Molecule descriptors are provided in eTable 2 in the Supplement. Of those 62 drugs, 53 (85%) were assessed for OS by at least 1 of the 3 international HTA agencies considered through May, 2015. The remaining 9 molecules may have been evaluated after our study end-date, not have been reviewed by HTA agencies if considered low-priority,[33] or may have been rejected by European (EMA) or national licensing authorities. Of the 53 drugs that were included in this study, 35 drugs were assessed by all 3 agencies, 7 were assessed by 2, and 11 were assessed by 1 agency. In most cases, HTA agency assessments were based on the same set of comparators (eTable 2 in the Supplement).

Overall Survival

Of the 53 drugs that were evaluated, 23 (43%) were confirmed by at least 1 HTA agency to increase OS by at least 3 months, though an exact magnitude of increase could not be estimated by HTA agencies for 6 of these 23 medicines. Six (11%) of the 53 drugs increased OS by less than 3 months, and 8 (15%) produced an increase in OS of unknown magnitude. The remaining 16 (30%) cancer drugs did not demonstrate an increase in OS over alternative treatments, either because no difference was found or because a determination was not or could not be made by HTA agencies on the basis of the available evidence (eTable 1 in the Supplement).

We examined total gains in OS made over the last decade by mapping new interventions against the treatment comparators that would be replaced, as identified in HTAs (**Figure 2**). In all cases where OS gains could be quantified, new cancer drugs produced a total mean (SE) improvement in OS

Figure 2. Analysis of Improvements in Overall Survival



Development of new cancer medicines (2003-2013), mapped according to therapeutic comparator used by health technology appraisal agencies in appraisal documents to assess therapeutic value. "First generation" drugs are the set of comparators not approved between 2003 and 2013, whereas "third generation" drugs are those that were evaluated against medications that were newly licensed in the study period ("second generation"). Pemetrexed[a] represents use for a nonprimary indication—it is therefore considered independently of the pemetrexed indication that is evaluated in this study. Survival benefits associated with parallel treatment pathways (afatinib-erlotinib/gefitinib; ponatinib-nilotinib/dasatinib) are considered independently of each other, as are those associated with multiple primary indications (sunitinib). The gain in overall survival (OS) relative to initial standards of care, for all drugs where marginal increases in OS could be quantified, is provided with the use of bars that represent the number of months gained (rounded to nearest integer). If a range of values corresponding to OS benefits were available across health technology appraisal agencies, an average was taken. Uncertain increase in OS is represented with a "+"; NE indicates no established increase in OS.

of 3.43 (0.63) months (or 0.29 [0.05] years) relative to the treatments that were available in 2003. These benefits, however, varied across and within different classes of therapeutics. For instance, drugs indicated for thyroid cancers produced an average (SE) increment of 0 (0) months in OS; ascites, 0 (0) months; lung cancers, 2.09 (0.75) months; hematological cancers, 2.61 (1.69) months; gastrointestinal cancers, 2.90 (1.12) months; prostate cancers, 3.17 (0.69) months; skin cancers, 4.65 (1.05) months; renal cancers, 6.27 (1.92) months; and breast cancers, 8.48 (3.84) months.

For drugs that were assessed by all 3 agencies, English authorities were most likely to attribute significant OS improvements to new medicines, while Australian authorities were least likely to do so (eFigure 1 in the Supplement). Across the entire sample, Krippendorff's α was 0.38, suggesting a low to moderate level of agreement in assessments of OS benefits

among all 3 HTA agencies (eTable 3 in the Supplement). Interagency agreement was, however, higher when English evaluations were excluded and for the set of drugs that produced marginal to no improvement in OS (eTable 3 in the Supplement). This may suggest that regulators become increasingly uncertain about claims of drug-related survival benefits as the magnitude of those claims increases.

Indeed, HTA agency conclusions for 10 of the 23 drugs that were deemed to increase OS by 3 months or more (axitinib, bosutinib, crizotinib, everolimus, panitumumab, pazopanib, pomalidomide, sorafenib, sunitinib, and trabectedin) were based on modeled data, indirect comparisons, or agency opinions. For 5 of the 23 drugs (axitinib, crizotinib, enzalutamide, panitumumab, and pazopanib), significant OS benefits were also found relative to 1 treatment comparator, but were not established in relation to other possible comparators.

Quality of Life

Of the 53 drugs that were evaluated by at least 1 HTA agency, 22 (42%) improved QoL, 2 (4%) reduced QoL, 1 (2%) was associated with mixed evidence, and 28 (53%) did not demonstrate a difference in QoL relative to best alternative treatments (eTable 1 in the Supplement).

As for OS, England's HTA agency was most likely to find that new cancer drugs improved QoL (eFigure 1 in the Supplement). Across the entire sample, there was a moderate to high level of agreement among HTA agencies in the assessed level of QoL benefit from new cancer drugs (α, 0.61) (eTable 3 in the Supplement). This suggests that HTA agencies tend to similarly interpret the QoL evidence—more so than that of OS—and lends confidence to the notion that new cancer drugs are providing QoL benefits to patients.

Still, not all regulatory opinions were based on robust evidence. Of the 22 drugs that were deemed to improve QoL, evaluations for 17 were based on a review of empirical evidence, including data from validated QoL instruments. The QoL benefits associated with the remaining 5 drugs (pertuzumab, trametinib, ziv-aflibercept, sipuleucel-T, and vemurafenib) were based exclusively on testimony from patient representatives and clinical experts.

Safety

Eight (15%) of the 53 drugs that were evaluated by HTA agencies were found to improve safety. A far larger share (24, or 45%), however, reduced patient safety. Ten (19%) were associated with mixed evidence and 11 (21%) did not demonstrate any difference in safety compared with alternative treatments (eTable 1 in the Supplement).

Mirroring earlier trends for OS, English and Australian authorities were least and most likely to determine that new cancer drugs reduced patient safety, respectively (eFigure 1 in the Supplement). Across the entire sample, there was a low level of agreement between HTA agencies on the impact on safety from new cancer medicines. This was however driven by a lack of consensus with Australia's HTA agency: interagency agreement was moderate to high when limited to English and French assessments (eTable 3 in the Supplement).

Clinical Benefits of Treatment

Of the 23 drugs that significantly increased OS by at least 3 months, 15 (65%) were also found to improve QoL, while the remaining 8 (35%) produced no measurable change. In contrast, of the 23 drugs that significantly extended OS, 5 (22%) improved safety, 11 (48%) reduced safety, 5 (22%) were associated with mixed evidence, and 2 (9%) produced no difference in safety relative to existing standards of care. Most new cancer medicines that significantly extend life therefore also improve QoL, but reduce patient safety (eTable 1 in the Supplement).

There was a noticeably smaller improvement in QoL in the drugs that produced marginal to no improvement in OS. Of the 30 evaluated drugs that did not increase OS by at least 3 months, 7 (23%) were found to improve QoL, 2 (7%) worsened QoL, 1 (3%) had a mixed effect, and 20 (67%) were not associated with any effect on QoL. Safety nevertheless remained a concern. Of the 30 drugs that did not increase OS by at least 3 months, 3 (10%) were classified as improving safety, 13 (43%) reduced patient safety, 5 (17%) were associated with mixed evidence; the remaining 9 (30%) did not demonstrate any difference in safety over alternative treatments.

Across the entire sample, 42 of the 53 new cancer medicines (79%) licensed in the United States and the European Union between 2003 and 2013, and evaluated by English, French, and Australian HTA agencies, demonstrated at least some evidence of an OS, QoL, or safety benefit. These results were supported by the feedback that we received from 2 medical experts from the FDA, both of whom generally agreed with the results that were obtained. One—an oncologist—stated that the results summarized in eTable 1 in the Supplement were "in line with [his personal] perceptions" of the added clinical benefits of the new cancer medicines.

Discussion

All new cancer drugs licensed between 2003 and 2013 by the FDA and EMA extended OS by an mean (SE) of 3.43 (0.63) months (0.29 [0.05] years) over the treatments that were available in 2003. This figure is based on regulatory assessments and is consistent with those reported by similar studies.[34]

While perhaps modest, this OS benefit represents an important step forward for patients and society, as even minor improvements in survival can have an effect on reducing mortality at the population level. It is encouraging to therefore find that most new cancer drugs were associated with some known (55%) or at least unknown (70%) OS benefit, with the largest share (43%) extending life by an amount that English and Australian regulators consider to be clinically meaningful (≥3 months).

To our knowledge, this analysis is the first to take a systematic approach to evaluate the OS, QoL, and safety benefits associated with new cancer drugs. Our findings indicate that most newly approved cancer medicines (79%)

increased OS by some known or unknown magnitude, or demonstrated at least some evidence of improved QoL or safety over alternative treatments. In general, innovation in the oncology drug market therefore appears to be bringing real value to patients and society.

There was evidence to suggest that these benefits are also concentrated in particular classes of therapeutics. Ten immunologic drugs were present in our sample, most of which function by antigenic targeting of cancer cells. Ipilimumab was the only drug of a novel class of immunomodulating agents, the immune checkpoint modulators. With the exception of bevacizumab—which elicits an antiangiogenic response—immunologic drugs were, on average, better at extending OS compared to nonimmunologic drugs (5.02 vs 2.30 months). However, this was not true of all immunologic drugs. Perhaps owing to a limited sample size, statistical testing also showed that this group difference was nonsignificant, and that there was no greater effect on quality of life or safety (data not shown). Ipilimumab was itself associated with a marginally larger OS benefit (5.7 months). Future studies may adapt our methodology to examine the efficacy of the newer immune checkpoint modulators, such as nivolumab and pembrolizumab.

Though perhaps promising, findings from this study should be interpreted with caution. To validly draw inference on the impact from new immunologic drugs and other cancer therapeutics, this analysis should be repeated as the number of available molecules grows. Across the entire sample, regulatory evidence is sometimes based on modeled data, nonvalidated inputs, or comparisons against nontargeted or older active treatments (eg, BSC, chlorambucil), though this may reflect the state of clinical practice. Even if these issues are ignored, interagency agreement on drug-related OS benefits decreases as the level of benefit increases, indicating that there may be greater uncertainty about the value from new cancer drugs that claim to bring the greatest health benefit. And, as shown with frequently contrasting English and Australian assessments, the regulatory milieu seems to shape the interpretation of evidence on the clinical impact from new cancer medicines. These findings raise important questions about how clinical benefits are measured and used to inform evidence-based policy, and they give reason to adapt treatment guidelines to the unique circumstances and preferences of the patient.

Regulators nevertheless often have the authority to require submission of all applicable clinical data that is "necessary to address the remit and scope of the technology appraisal."[35] To estimate the clinical value of new medicines in the absence of real-world observational data, the approach used in this study may therefore be preferable to secondary reviews of the published scientific literature.

Still, technological assessments may not always accurately reflect the full extent of clinical risks and benefits that are observed in practice. For instance, as is the case for *KRAS* expression in colon cancer, particular genomic profiles are now known to predict OS benefits. In part for this reason, gene expression profiling is increasingly recommended as a tool to guide chemotherapy decisions.[36,37] Since many new anticancer drugs target proteins that are downstream of genes with driver somatic mutations,[36] any misapprehension about the genetic mediators of disease may prevent regulators from fully appreciating their clinical value. Validated biomarkers in fact often do not exist to guide the selection of patients in clinical trials who would most likely benefit from treatment.[5] Clinical practice may instead incorporate new evidence on the genetic predictors of response as and when it develops,[36] enabling personalized and cost-efficient care that optimizes patient outcomes. To better reveal the real-world benefits from new cancer medicines, future studies should therefore periodically repeat this analysis with postmarketing,[38] observational or pragmatic clinical trial evidence. The National Cancer Institute's upcoming National Cancer Knowledge System may provide crucial insights in this regard.

As it stands, 1 in 3 (30%) of all newly approved cancer medicines are not associated with any OS benefit, while 1 in 5 (20%) neither extend life nor improve QoL or safety. While perhaps reflective of nonactive comparisons, the approval of new medicines for orphan indications with no alternative treatment, or the growing use of surrogate efficacy endpoints during regulatory evaluations,[12] these findings suggest that expenditures for up to 1 out of every 5 new cancer drugs may be spent without any OS, QoL, or safety benefit to the patient.

In the short term, these findings help to inform clinical decision-making by patients and clinicians who, in personalizing treatment, may have to consider the economic implications of drug prescriptions alongside individual preferences for treatment-related risks and benefits. This may be true for US cancer patients, who typically shoulder high amounts of cost-sharing, but also if public health systems (eg, England's NHS) do not publicly reimburse for new cancer medicines. Over the longer term, efforts should be made to develop evidence on mechanisms to weight clinical outcome measures according to their value to patients, and to align these initiatives with the regulatory review process.

These findings raise a number of important questions about value-for-money in oncology. We find that there is in fact a wide distribution in the therapeutic benefits associated with recent cancer drug innovations, suggesting a similarly wide variation in the value that they bring to society. Some medications (eg, pertuzumab) have significantly extended life, perhaps giving reason for large and growing expenditures. Others, however, appear to bring little to no tangible benefit to health, raising questions about the justification for additional expense over alternative treatments. Though further research is needed, our analysis may indicate that spending on new cancer drugs is not always commensurate with their clinical benefits. This may be reason for patients and clinicians to take pause when considering new treatments, particularly if related expenditures are of concern.

Conclusions

Cancer drug innovation over the past decade is, on the whole, expected to have contributed to improvements in patient OS and QoL. These gains, however, are unevenly distributed across all newly licensed medicines, often come at the cost of safety,

and may not always translate to real-world practice. As calls for value-based health care grow, this analysis raises questions about how clinical benefits are measured by regulators, how regulatory guidance is used to inform clinical decision-making, and how much value is generated from spending in the oncology drug market.

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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Online-Only Supplement

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eTable 1. Therapeutic profile of all cancer medicines approved by the FDA between 2003-2013 (Summary of eTable 2)

Active ingredient	FDA- or EMA-approved indication	Appraisal dates	Comparator(s)	OS effect[a] (in months)	QoL effect	Safety effect
Ascites						
catumaxomab	Ascites (EMA)	Dec 09	paracentesis	NE	NE	NE
Bladder						
vinflunine	Carcinoma of the urothelial tract (EMA)	Dec 09–Jan 13	BSC	Exact magnitude uncertain	NE	Reduction
Breast						
ado-trastuzumab emtansine	Breast cancer	Mar 14–Nov 14	lapatinib + capecitabine	≥ 3 (5.8)	Improvement	Mixed evidence
eribulin	Breast cancer	Jul 11–Nov 13	TPC	< 3 (2.5–2.7)	NE	Reduction
ixabepilone	Breast cancer	n/a	n/a	n/a	n/a	n/a
lapatinib	Breast cancer	Nov 07–May 10	capecitabine monotherapy	< 3 (0.3–2.4)	NE	Reduction
pertuzumab	Breast cancer	Jul 13–Mar 14	trastuzumab + docetaxel	≥ 3 (15.7)	Improvement	Reduction
Gastro-intestinal						
bevacizumab	Colorectal carcinoma	Jun 05–Jul 08	IFL/5-FU/LV	≥ 3 (3.0–4.7)	NE	Reduction
cetuximab	Colorectal carcinoma	Mar 05–Mar 09	BSC	Exact magnitude uncertain	NE	Reduction
panitumumab	Colorectal carcinoma	Apr 08–Nov 13	BSC/cetuximab (safety)	≥ 3 (2.7–3.2)	NE	NE
regorafenib	Colorectal cancer	May 14–Jul 14	placebo	< 3 (1.4)	NE	Reduction
tegafur/gimeracil/oteracil	Gastric cancer (EMA)	Oct 12–Mar 13	5-FU/cisplatin	NE	NE	NE
ziv-aflibercept	Colorectal cancer	Jul 13–Mar 14	placebo	< 3 (1.4)	Improvement	Reduction
Gastro-intestinal/Renal						
sunitinib	Gastrointestinal stromal tumor / Renal cell carcinoma	Sep 06–Sep 09 / May 07–Mar 09	BSC/interferon-alfa	≥ 3 (7.8) / ≥ 3 (10.0)	Improvement	Reduction
Hematological						
asparaginase E. chrysanthemi	Acute lymphoblastic leukemia	n/a	n/a	n/a	n/a	n/a
azacitidine	Myelodysplastic syndromes	Jul 09–Mar 11	conventional care	≥ 3 (9.4–9.6)	Improvement	Reduction
bendamustine	Lymphocytic leukemia	Oct 10–Feb 11	chlorambucil	NE	Reduction	Reduction
bortezomib	Multiple myeloma	Oct 04–Oct 07	high-dose dexamethasone	≥ 3 (6.1–11.5)	Improvement	Mixed evidence
bosutinib	Chronic myelogenous leukemia	Nov 13–Feb 14	BSC	≥ 3 (exact gain uncertain)	NE	Improvement
brentuximab vedotin	Hodgkin lymphoma / Systemic	Mar 13–Mar 14	multi-agent salvage	Exact	NE	Mixed

	lymphoma		chemotherapy	magnitude uncertain		evidence
carfilzomib	Multiple myeloma	n/a	n/a	n/a	n/a	n/a
clofarabine	Acute lymphoblastic leukemia	Dec 06	non-comparative	NE	NE	NE
dasatinib	Chronic myeloid leukemia // Acute lymphoblastic leukemia	Mar 07–Jan 12	non-comparative	NE	NE	Mixed evidence
decitabine	Myelodysplastic syndromes	n/a	n/a	n/a	n/a	n/a
ibrutinib	Mantle cell lymphoma	n/a	n/a	n/a	n/a	n/a
lenalidomide	Transfusion-dependent anemia due to myelodysplastic syndromes	Mar 13–Nov 14	placebo	Exact magnitude uncertain	Improvement	Reduction
nelarabine	Acute lymphoblastic leukemia / Lymphoblastic lymphoma	Dec 07	non-comparative	NE	NE	NE
nilotinib	Chronic myelogenous leukemia	Feb 08–Jan 12	non-comparative	NE	NE	Improvement
obinutuzumab	Chronic lymphocytic leukemia	Jul 14–Mar 15	chlorambucil	Exact magnitude uncertain	Mixed evidence	Mixed evidence
ofatumumab	Chronic lymphocytic leukemia	Oct 10–Nov 14	chlorambucil	NE	NE	NE
omacetaxine mepesuccinate	Chronic myeloid leukemia	n/a	n/a	n/a	n/a	n/a
pomalidomide	Multiple myeloma	Jan 14–Mar 15	standard care / high-dose dexamethasone (safety)	≥ 3 (exact gain uncertain)	Improvement	Reduction
ponatinib	Chronic myeloid leukemia / Acute lymphoblastic leukemia	Nov 14–Jan 15	dasatinib/nilotinib	NE	NE	Reduction
pralatrexate	Peripherallymphoma	n/a	n/a	n/a	n/a	n/a
romidepsin	Cutaneous lymphoma	n/a	n/a	n/a	n/a	n/a
ruxolitinib	Myelofibrosis	Jan 13–Jul 13	BSC	Exact magnitude uncertain	Improvement	Reduction
tositumomab	Non-Hodgkin's lymphoma	n/a	n/a	n/a	n/a	n/a
vorinostat	Cutaneous lymphoma	Mar 11	BSC	NE	NE	Mixed evidence
Lung						
afatinib	Non-small cell lung cancer	Jul 13–Apr 14	erlotinib/gefitinib	NE	Improvement	Reduction
crizotinib	Non-small cell lung cancer	Sep 13–Nov 14	pemetrexed	≥ 3 (3.1–3.5)	Improvement	NE
erlotinib	Non-small cell lung cancer	Mar 06–Nov 08	placebo/BSC	< 3 (2.0)	Improvement	Mixed evidence
gefitinib	Non-small cell lung cancer	Nov 09–Jul 13	paclitaxel + carboplatin	NE	Improvement	Improvement
pemetrexed	Pleural mesothelioma	Mar 05–Jan 08	cisplatin	≥ 3 (2.8–3.3)	Improvement	Reduction
Prostate						
abiraterone acetate	Prostate cancer	Feb 12–Jul 12	BSC (prednisolone)	≥ 3 (3.9–4.6)	Improvement	Improvement
cabazitaxel	Prostate cancer	Nov 11–Oct 12	mitoxantrone	≥ 3 (2.4–4.2)	NE	Reduction
degarelix	Prostate cancer	Sep 09–Apr 14	leuproprelin + LHRH agonists	NE	NE	Reduction

enzalutamide	Prostate cancer	Nov 13–Jul 14	placebo	≥ 3 (4.5–4.8)	Improvement	Mixed evidence
radium-223 dichloride	Prostate cancer	Apr 14	placebo	< 3 (2.8)	NE	NE
sipuleucel-T	Prostate cancer	Feb 15	BSC	≥ 3 (4.0)	Improvement	Improvement
Renal						
axitinib	Renal cell carcinoma	Jan 13–Feb 15	BSC	≥ 3 (exact gain uncertain)	NE	Mixed evidence
everolimus	Renal cell carcinoma	Nov 09–Apr 11	BSC	≥ 3 (5.2)	Improvement	Reduction
pazopanib	Advanced renal cell carcinoma	Feb 11–Jun 13	BSC/interferon-alfa	≥ 3 (exact gain uncertain)	NE	Mixed evidence
sorafenib	Renal cell carcinoma	Sep 06–Aug 09	BSC	≥ 3 (exact gain uncertain)	Improvement	Reduction
temsirolimus	Renal cell carcinoma	Feb 08–Aug 09	interferon-alfa	≥ 3 (3.6)	Improvement	Improvement
Skin						
dabrafenib	Melanoma	Oct 14	dacarbazine/vemurafenib (safety)	Exact magnitude uncertain	Reduction	Improvement
ipilimumab	Melanoma	Nov 12–Nov 14	dacarbazine	≥ 3 (5.7)	NE	Reduction
trametinib	Melanoma	Nov-14	dabrafenib	Exact magnitude uncertain	Improvement	NE
vemurafenib	Melanoma	Oct 12–Mar 13	dacarbazine	≥ 3 (3.3–3.9)	Improvement	Reduction
vismodegib	Basal cell carcinoma	Dec 13	non-comparative	NE	NE	NE
Soft tissue						
trabectedin	Soft tissue sarcoma (EMA)	Apr 08–Feb 10	BSC	≥ 3 (exact gain uncertain)	NE	Improvement
Thyroid						
cabozantinib	Medullary thyroid cancer	Dec14	placebo	NE	NE	Reduction
vandetanib	Medullary thyroid cancer	Jun 12	placebo	NE	NE	NE

Source: Authors' analysis of data from sources identified in the "Methods" section.

Notes:
Drug and therapeutic features associated with all new cancer medicines approved by the FDA between 2003-2013, and appraised by NICE, HAS, or PBAC through May 2015. Change in overall survival (OS), quality of life (QoL) and safety is given as composite magnitude of therapeutic improvement for each drug relative to existing standards of care across all three HTA agencies (see Methods).

n/a = no appraisal available through May 2015.

NE = none established.

[a] OS benefits are classified as a categorical variable (months). A range (in parentheses) was also developed to reflect the maximum OS benefit acknowledged by the HTA agencies that were able to quantify the magnitude of gain.

eTable 2. Regulatory evidence in support of classification of drug clinical benefits

abiraterone acetate	FDA primary indication		
ATC code: L02BX03 Orphan Status: – Licensure: FDA/EMA Target: Prostate	A CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.		
Agency	NICE	HAS	PBAC
Appraisal date	Jun-12	Feb-12	Jul-12
Comparator	BSC (prednisolone)	BSC (prednisolone)	BSC (prednisolone)
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: 4.6-month increase in median OS compared to prednisolone; estimated mean overall survival gain was greater than 3 months, though exact value was "commercial in confidence" **QoL**: Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home, and is associated with few adverse reactions. The benefit related to being an oral drug was not captured in the analysis because the model applied the same utility benefit to abiraterone as to mitoxantrone. Committee therefore acknowledged that abiraterone provides HRQoL benefits other than those captured in the QALY calculation for patients currently receiving mitoxantrone **Safety**: The Committee also noted that abiraterone is not associated with the more severe adverse reactions that can	**OS**: 3.9-month increase in median OS compared to placebo (prednisone or prednisolone) **QoL**: The patients' quality of life deteriorates less under treatment than with placebo **Safety**: No judgment given on comparative differences in safety	**OS**: 3.9-month increase in median OS compared to BSC (prednisone/ prednisolone plus other care); OS increase compared to mitoxantrone (based on indirect comparison), though magnitude of increase not given; no significant increase compared to cabazitaxel (based on indirect comparison) **QoL**: Statistically significant differences in functional assessment of cancer therapy – prostate (FACT-P) scores between the abiraterone and placebo arms of Trial 301 were demonstrated. However, the magnitude of changes in FACT-P Total Scores between trial arms were small and changes in subscale FACT-P scores were similar in both groups **Safety**: Whilst PBAC considered there were uncertainties inherent from indirect comparisons, it accepted the

		occur with cytotoxic drugs such as mitoxantrone. The Committee heard from the clinical specialists that abiraterone is a well-tolerated oral medication		submission's clinical claims: (1) abiraterone + prednisone/ prednisolone is equivalent in terms of comparative safety over BSC (prednisone/prednisolone alone); (2) abiraterone + prednisone/ prednisolone is superior in terms of comparative safety over mitozantrone plus prednisone/prednisolone alone; (3) abiraterone + prednisone/ prednisolone is superior in terms of comparative safety over cabazitaxel plus prednisone/prednisolone alone
Effects	Merged data			
OS increase	3.9–4.6 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	+	+	+	+
Safety change	+	+	NA	No difference (BSC); + (mitoxantrone); + (cabazitaxel) = +

ado-trastuzumab emtansine	FDA primary indication		
ATC code: L01XC14	HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: (a) Received prior therapy for metastatic disease, or (b) Developed disease recurrence during or within six months of completing adjuvant therapy.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: Breast			
Agency	NICE	HAS	PBAC
Appraisal date	Aug-14	Mar-14	Nov-14
Comparator	lapatinib + capecitabine	lapatinib + capecitabine	lapatinib + capecitabine
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: 5.8-month increase in median OS compared to lapatinib + capecitabine **QoL**: The Committee was aware that EMILIA was an open- label trial, which may have introduced bias in the	**OS**: 5.8-month increase in median OS compared to lapatinib + capecitabine **QoL**: In view of the available results from clinical trials, especially the EMILIA study, ado-trastuzumab is	**OS**: 5.8-month increase in median OS compared to lapatinib + capecitabine **QoL**: The PBAC noted strong support for the listing of T-DM1 received through the consumer comments facility

		outcomes reported by patients, but concluded that a marginally higher utility value for trastuzumab emtansine in the progression-free state could be accepted in this appraisal **Safety**: The Committee understood that fewer patients stopped treatment because of an adverse event in the trastuzumab emtansine group than in the lapatinib + capecitabine group	expected to have a moderate impact in terms of morbidity, mortality and QoL **Safety**: A smaller proportion of AEs of grade 3 or worse and serious AEs (SAE) of grade 3 or worse was reported in the trastuzumab emtansine group compared to the control group	expressing a range of benefits from treatment including improved QoL **Safety**: T-DM1 second-line: the previous resubmission described T-DM1 as superior in terms of comparative safety over lapatinib plus capecitabine. In March 2014, the PBAC accepted this clinical claim, although noted that some of the toxicity profile of T-DM1 was less favourable than that of its comparator
Effects	Merged data			
OS increase	5.8 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	+	+	+	+
Safety change	+/-	+	+	+/-

afatinib	FDA primary indication		
ATC code: L01XE13 Orphan Status: – Licensure: FDA/EMA Target: Lung	A kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.		
Agency	NICE	HAS	PBAC
Appraisal date	Apr-14	Feb-14	Jul-13
Comparator	erlotinib, gefitinib	cisplatin-based chemotherapy	erlotinib, gefitinib
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: Committee concluded that on balance afatinib is likely to have similar clinical efficacy to erlotinib and gefitinib. Because of the immaturity of the OS data available, there was uncertainty about whether treatment with afatinib resulted in OS benefit compared with chemotherapy, therefore no increase	**OS**: In view of the available clinical data and in comparison with cisplatin-based chemotherapy, it should be noted that there is no improvement in terms of OS **QoL**: In view of the available clinical data and in comparison with cisplatin-based chemotherapy, a moderate	**OS**: PBAC noted that there was no significant survival advantage reported for afatinib or the other two TKIs in trials considered. Comparing afatinib with chemotherapy, there was no observed benefit in OS **QoL**: PBAC considered that the benefit

		was established **QoL**: The Committee did not draw any specific conclusions about the HRQoL benefits and utility values **Safety**: The Committee concluded that although afatinib has a different adverse reaction profile from erlotinib and gefitinib, overall the toxicity of the tyrosine kinase inhibitors was similar	additional impact QoL is expected in patients treated with first-line afatinib. In the absence of any clinical data comparing afatinib with other tyrosine kinase inhibitors, the medicinal product afatinib is not expected to have any additional impact on QoL in the current treatment strategy for these patients **Safety**: While HAS makes a few claims on AE rates, the agency gives no assessment of comparative differences in safety	of afatinib was due only to a prolongation of PFS which is associated with some improvement in QoL **Safety**: PBAC considered that many serious adverse events including grade 3 or higher appeared more often in the afatinib arm compared to the cisplatin/pemetrexed arm. They noted that there were relatively high rates of adverse events (AEs) associated with afatinib relative to doublet platinum chemotherapy, including more Grade 3 or higher AEs, in the LUX Lung 3 trial. There was a higher proportion of dose reductions during treatment with afatinib compared to treatment with either gefitinib or erlotinib, although there were limitations for those indirect comparison
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	+	NA	+(cisplatin);No difference(TKIs)=+	+
Safety change	-	No difference	NA	-

asparaginase E. chrysanthemi	FDA primary indication		
ATC code: L01XX02	An asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli-derived asparaginase.		
Orphan Status: EU			
Licensure: FDA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	NA	NA	NA
Comparator	NA	NA	NA
Modelled/indirect comparison	NA	NA	NA

Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

axitinib	FDA primary indication		
ATC code: L01XE17	A kinase inhibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.		
Orphan Status: EU (w)			
Licensure: FDA/EMA			
Target: Renal			
Agency	NICE	HAS	PBAC
Appraisal date	Feb-15	Jan-13	Nov-14
Comparator	BSC	sorafenib	everolimus
Modelled/indirect comparison	Yes	No	Yes
Basis for classification	**OS**: More than 3-month increase compared to BSC was "likely" (based on indirect and simulated treatment comparisons), though exact magnitude of increase was uncertain as the comparison results were "improbable"; Committee concluded that axitinib "was likely to have clinical effectiveness comparable to pazopanib and sunitinib" **QoL**: NICE was satisfied with the HRQoL data collected and found no significant difference versus sorafenib in FKSI-15. QoL was maintined while patients remained in both treatment groups. For EQ-5D, the overall between-treatment comparison for axitinib compared with sorafenib was	**OS**: An increase compared to sorafenib was not established in the overall population or patient subgroups as no statistically significant difference was observed; Committee considered that the indirect comparison to everolius was "exploratory in nature from [which] no conclusions can be drawn with a sufficient level of evidence" **QoL**: In view of the clinical study results showing no gain in terms of overall survival or quality of life, the expected impact of axitinib in terms of morbidity, mortality and quality of life can only be small **Safety**: The frequency of serious adverse events was of the same order	**OS**: An increase compared to everolimus was not established given "the limitations of the comparative evidence and the methodological limitations of the simulated treatment comparison and matching-adjusted indirect comparison", though Committee accepted claim of non-inferiority **QoL**: NA **Safety**: PBAC accepted the clinical claim that axitinib is non-inferior to everolimus in terms of comparative effectiveness and safety

		not statistically significant (no p value given); however, QoL was maintained while patients remained on treatment and declined when patients stopped trial medication **Safety**: The Committee noted that diarrhoea occurred with similar frequency in the axitinib and sorafenib groups. It was aware that hypertension, dysphonia, nausea and hypothyroidism occurred more frequently in the axitinib group, although hand–foot syndrome, rash and alopecia occurred more frequently in the sorafenib group. The Committee concluded that axitinib has a manageable adverse event profile compared with other treatments	between axitinib and sorafenib	
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain uncertain)	None established	None established
QoL change	None established	No difference	No difference	NA
Safety change	+/-	+/-	No difference	No difference

azacitidine	FDA primary indication		
ATC code: L01BC07	Indicated for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.		
Orphan Status: US/EU			
Licensure: FDA/EMA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	Mar-11	Apr-09	Jul-09
Comparator	conventional care	conventional care	conventional care
Modelled/indirect comparison	No	No	No

Basis for classification		**OS**: 9.6-month increase in median OS compared to conventional care regimens (i.e. BSC, low-dose chemotherapy, and standard-dose chemotherapy); OS increase significant compared to BSC and low-dose chemotherapy, but not significant compared to standard-dose chemotherapy though the Committee "was aware that the small patient numbers limited the precision and certainty of the outcome estimates in these groups" **QoL**: Committee heard from the patient experts that compared with other treatment options, azacitidine was associated with relief from fatigue, fewer infection-related hospitalisations, a decreased need for blood and platelet transfusion, and increased ability to perform day-to-day activities. No QoL data were collected in AZA-001, although EORTC data collected in CALGB 9221 suggested improvements in overall health with azacitidine. **Safety**: No comparative assessment made on AEs and safety	**OS**: 9.4-month increase in median OS compared to conventional care regimens (i.e. no active treatment, low-dose cytarabine, and standard chemotherapy) **QoL**: In view of the available clinical data and current therapeutic strategies, azacitidine is expected to have a significant impact on morbidity, mortality and QoL **Safety**: No explicit judgment provided discussing the comparative evidence on drug-related changes in AEs and safety	**OS**: 9.4-month increase in median OS compared to conventional care regimens (i.e. BSC, low-dose cytarabine, and standard-dose chemotherapy) in patients with high risk MDS **QoL**: No explicit discussion on HRQoL data, though there is a brief discussion of the "paucity of available utility data" and the "uncertainty" in the values used in submitted health economic evaluations **Safety**: PBAC agreed that BSC (which included low dose cytarabine and standard chemotherapy) was the appropriate comparator and that the clinical trial data supported the claim that azacitidine was significantly more effective than conventional care but was associated with more toxicity when used for the treatment of INT-2/high risk MDS patients
Effects	Merged data			
OS increase	9.4–9.6 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	+	+	+	NA
Safety change	-	NA	NA	-

bendamustine	FDA primary indication
ATC code: L01AA09	An alkylating drug indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line

Orphan Status: US	therapies other than chlorambucil has not been established.		
Licensure: FDA/EMA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	Feb-11	Oct-10	NA
Comparator	chlorambucil	chlorambucil	NA
Modelled/indirect comparison	No	No	NA
emBasis for classification	**OS**: No statistically significant difference in median OS between bendamustine and chlorambucil **QoL**: During the treatment period, patients' QoL was assessed using the EORTC questionnaires. Patients' overall QoL was modestly improved in both groups during treatment, with no significant differences between the groups. The manufacturer explained in its submission that the QOL data collected during the trial showed that patients receiving the more effective therapy (bendamustine) experienced a greater number of adverse events during the treatment period, leading to a QoL detriment in some health dimensions **Safety**: The only available treatment for these patients is chlorambucil. The Committee heard that although bendamustine is slightly more toxic and is associated with more AEs, the clinical specialists considered bendamustine to be the more effective treatment. The Committee also noted the views of the patient groups in their submissions to NICE that because of its improved efficacy compared with chlorambucil,	**OS**: Insignificant difference in terms of median OS compared to the benchmark (65.4 months in the chlorambucil group and not achieved in the bendamustine group) **QoL**: There is a lack of HRQoL data **Safety**: HAS noted that grade 3–4 adverse events were more common in the bendamustine group than in the chlorambucil group, especially haematological adverse events and infections	NA

		people with the condition would be willing to accept the side effects		
Effects	Merged data			
OS increase	None established	None established	None established	NA
QoL change	-	-	NA	NA
Safety change	-	-	-	NA

bevacizumab	FDA primary indication		
ATC code: L01XC07	In combination with intravenous 5-fluorouracil–based chemotherapy is indicated for first- line treatment of patients with metastatic carcinoma of the colon or rectum.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: GI			
Agency	NICE	HAS	PBAC
Appraisal date	Jan-07	Jun-05	Jul-08
Comparator	IFL	IFL	IFL or 5-FU/LV
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: 4.7-month increase in median OS compared to IFL (irinotecan, bolus 5-FU and leucovorin); no significant difference compared to 5-FU/LV (two studies); Committee noted that the comparators "cannot be considered current standard practice in NHS," though was "persuaded that the results seen in the studies could be considered generalizable to NHS practice" **QoL**: Committee recommends studies to investigate the impact of bevacizumab and cetuximab treatment on HRQoL **Safety**: In all the studies there was a	**OS**: 4.7-month increase in median OS compared to IFL (first-line); no significant difference in median OS was observed compared to FUFOL (5-FU plus folinic acid) **QoL**: Time to deterioration in QoL were similar in both groups **Safety**: In the pivotal study, grade 3-4 toxicity was higher in the IFL + Avastin group than in the IFL alone group	**OS**: 3- to 4-month increase in OS compared to first-line chemotherapy (i.e. IFL or 5-FU/LV), although the differences were not statistically significant in two of the three trials; Committee also noted that IFL was "no longer accepted as best practice in Australia or the USA" **QoL**: No HRQoL data presented **Safety**: Overall, the risk of several AEs, particularly hypertension, proteinuria and arterial thromboembolic events, was found to be elevated following the addition of bevacizumab to chemotherapy

		higher incidence of grade 3 and 4 adverse events in the groups receiving bevacizumab compared with the control groups		
Effects	Merged data			
OS increase	3.0–4.7 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	None established	NA	No Difference	NA
Safety change	-	-	-	-

bortezomib	FDA primary indication		
ATC code: L01XX32	bortezomib for injection is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. The effectiveness of VELCADE is based on response rates (see CLINICAL STUDIES section). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.		
Orphan Status: US			
Licensure: FDA/EMA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	Oct-07	Oct-04	Mar-06
Comparator	high-dose dexamethasone	Not given	high-dose dexamethasone
Modelled/indirect comparison	No	Yes	No
Basis for classification	**OS**: 6.1-month increase in median OS compared to high-dose dexamethasone **QoL**: No HRQoL information provided. Further research into the effectiveness of bortezomib for the treatment of relapsed multiple myeloma is needed. Such studies should include: measurement of quality of life in patients with relapsed multiple myeloma, including the effect of treatment and adverse events **Safety**: Committee understood from the	**OS**: 8.5- to 11.5-month improvement in median survival based on comparison of OS data from single-arm bortezomib study and OS data from literature for similar patient population **QoL**: Regarding QoL treatment, improved items including the overall score of QoL, the physical score and social score were observed in 2 of the three scales used (QLQ-C30 scale EORTC-QLQ Module MY24). Variation of the scores of the FACIT-Fatigue scale score was not statistically	**OS**: Committee "acknowledged that bortezomib has significant advantages in the short term over the comparator HDD in terms of…increasing the proportion of individuals alive at one year" but noted that "a number of uncertainties arose over the interpretation of the...trial results," including wide 95% confidence intervals, significant patient crossover, and "doubts about the acceptability of HDD as being representative for the main comparator"

		clinical specialists that there was a greater frequency of peripheral neuropathy and gastrointestinal adverse effects in the bortezomib arm, but that bortezomib was associated with less bone destruction and fewer infections than HDD	significant **Safety**: No comparative data	**QoL**: NA **Safety**: Overall incidence of AEs were similar in both groups, with 100% of bortezomib patients and 98% of HDD patients experiencing one AE. Overall pattern of AE differed. Incidence of Grade 3 and those leading to discontinuation was higher in the bortezomib group
Effects	Merged data			
OS increase	6.1–11.5 months	≥ 3 months	≥ 3 months	Uncertain
QoL change	+	NA	+	NA
Safety change	+/-	+/-	NA	-

bosutinib	FDA primary indication		
ATC code: L01XE14	A kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.		
Orphan Status: US/EU			
Licensure: FDA/EMA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	Nov-13	Feb-14	NA
Comparator	BSC	NA	NA
Modelled/indirect comparison	Yes	No	NA
Basis for classification	**OS**: At least 3-month extension compared to BSC, though exact magnitude of increase uncertain (based on modeled data) **QoL**: NA **Safety**: The Committee heard from a patient expert that, in their own	**OS**: An increase was not established given the lack of comparative data presented to the Committee **QoL**: The proprietary medicinal product bosutinib is not expected to have any impact on morbidity, mortality or QoL in comparison with cited treatments	NA

		experience, previous tyrosine kinase inhibitors had resulted in them being unable to work and needing cardiac and surgical interventions. However, bosutinib had been tolerated	**Safety**: No comparative data available	
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain uncertain)	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	+	+	NA	NA

brentuximab vedotin	FDA primary indication		
ATC code: L01XC12 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological	A CD30-directed antibody-drug conjugate indicated for: (a) Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates; and (b) Systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. These indications are based on response rate.		
Agency	NICE	HAS	PBAC
Appraisal date	NA	Mar-13	Mar-14
Comparator	NA	non-comparative	multi-agent salvage chemotherapy
Modelled/indirect comparison	NA	No	No
Basis for classification	NA	**OS**: Median OS was not achieved during the primary analysis and does not enable conclusions to be drawn regarding this endpoint; available data are not sufficient (absence of comparative data in particular) to enable an evaluation of the expected impact of brentuximab vedotin on the morbidity, mortality and quality of life of patients treated	**OS**: The PBAC accepted the claim that BV is associated with significant additional OS and patient relevant efficacy in the first line salvage setting for patients that have had no prior SCT **QoL**: NA **Safety**: PBAC considered that the submission's claim of less toxicity relative to multi-agent salvage chemotherapy was reasonable with

			QoL: NA **Safety**: No comparative data available	respect to most acute toxicity, but that severe peripheral neuropathy was an important toxicity more likely in BV treated patients
Effects	Merged data			
OS increase	Exact magnitude uncertain	NA	None established	Uncertain
QoL change	None established	NA	NA	NA
Safety change	+/-	NA	NA	+/-

cabazitaxel	FDA primary indication		
ATC code: L01CD04	A microtubule inhibitor indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: Prostate			
Agency	NICE	HAS	PBAC
Appraisal date	May-12	Oct-12	Nov-11
Comparator	mitoxantrone	mitoxantrone	mitoxantrone
Modelled/indirect comparison	Yes	No	No
Basis for classification	**OS**: More than 3-month increase compared to mitoxantrone (4.2 months based on modeled mean OS gain); 2.4-month increase in median OS was observed in the trial **QoL**: No statistically significant difference in pain response between the treatment arms. No significant difference in time to pain progression between the treatment arms **Safety**: The Committee was initially	**OS**: 4.1-month increase in median OS compared to mitoxantrone in subgroup of patients who had stopped treatment due to disease progression and had a histologically poorly differentiated tumor; 2.4-month increase in median OS compared to mitoxantrone in the whole trial population **QoL**: In the absence of data, the impact on the QoL of treated patients is not quantifiable. Nevertheless, a negative impact (safety issues) on QoL	**OS**: 2.4-month increase in median OS compared to mitoxantrone; Committee stated that the modeled mean OS gain of 4.26 months appeared to be an overestimate and was uncertain **QoL**: A regulatory judgment of the submitted HRQoL (Q-TWIST) evidence is not given **Safety**: The PBAC agreed that the clinical claim that cabazitaxel is superior in terms of comparative effectiveness and inferior in terms of comparative

		concerned that in TROPIC more participants in the cabazitaxel arm died from cardiac and renal complications than in the mitoxantrone arm. The Committee concluded that there is no evidence of additional risk other than that included in the SPC and that the health economic model adequately reflected the disutility associated with adverse reactions. The Committee further heard that patient experts are aware that cabazitaxel is associated with serious ARs and that it would not be suitable for some patients who are not fit for chemotherapy	cannot be ruled out **Safety**: Safety was not as good in the cabazitaxel group as in the mitoxantrone group	safety over mitozantrone is reasonable
Effects	Merged data			
OS increase	2.4–4.2 months	≥ 3 months	≥ 3 months	< 3 months
QoL change	None established	No difference	NA	NA
Safety change	-	-	-	-

cabozantinib	FDA primary indication		
ATC code: L01XE26	A kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).		
Orphan Status: US			
Licensure: FDA/EMA			
Target: Thyroid			
Agency	NICE	HAS	PBAC
Appraisal date	NA	Dec-14	NA
Comparator	NA	placebo	NA
Modelled/indirect comparison	NA	No	NA
Basis for classification	NA	**OS**: The available data showed no benefit, and given current therapeutic strategies, low impact in terms of	NA

			morbidity and mortality is expected **QoL**: The available clinical data (including a Phase III placebo-controlled trial) showed a gain of 7 months progression-free survival with better response rates, but no benefit on overall survival or profit (or worsening) of QoL **Safety**: Treatment discontinuations due to adverse events were higher for patients in the cabozantinib group versus placebo patients	
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	-	NA	-	NA

carfilzomib		FDA primary indication		
ATC code: L01XX45 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological		A proteasome inhibitor indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA

QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

catumaxomab		FDA primary indication		
ATC code: L01XC09		indicated for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.		
Orphan Status: US/EU				
Licensure: EMA				
Target: Ascites				
Agency		NICE	HAS	PBAC
Appraisal date		NA	Dec-09	NA
Comparator		NA	paracentesis	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: Median OS did not differ between the two groups: 72 days in the REMOVAB group compared with 68 days in the control group **QoL**: In view of the methodology of the study (open-label), QoL data are difficult to interpret. The need for 11 days of hospitalisation for the treatment while no evidence is available of an improvement in QoL **Safety**: No comparative evidence presented	NA
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	None established	NA	NA	NA

cetuximab	FDA primary indication		
ATC code: L01XC06 Orphan Status: – Licensure: FDA/EMA Target: GI	Used in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. cetuximab administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.		
Agency	NICE	HAS	PBAC
Appraisal date	Jan-07	Mar-05	Mar-09
Comparator	cetuximab monotherapy	cetuximab monotherapy	BSC
Modelled/indirect comparison	No	No	Yes
Basis for classification	**OS:** No statistically significant difference in median OS between cetuximab-irinotecan combination therapy and cetuximab monotherapy. Relative effectiveness against current standard care remains uncertain **QoL:** The Committee recommends studies to investigate the impact of bevacizumab and cetuximab treatment on health-related quality of life **Safety:** In the RCT the incidence of some AEs was higher in patients receiving cetuximab plus irinotecan compared with those receiving cetuximab alone: grade 3 and 4 adverse events; diarrhoea; neutropenia; grade 3 or 4 acne-like rash.	**OS:** No gain in OS has been demonstrated between cetuximab-irinotecan and cetuximab monotherapy **QoL:** Available data do not allow to quantify the contribution of cetuximab in terms of quality of life vis-à-vis existing therapies **Safety:** 71% of patients in the combination group experienced at least one Grade 3–4 events against 53% monotherapy group	**OS:** PBAC noted 3.6-month survival gain over BSC arm in modeled data. However, submission estimate likely overestimated the OS. PBAC considered that the extent of OS benefit over BSC in the KRAS subgroup remained uncertain **QoL:** For key results, see Nov 2008 PSD. No information indicating drug-induced change **Safety:** For key results, see Nov 2008 PSD. Cetuximab in combination with irinotecan tended to have more serious AEs and Grade 3/4 AEs compared to cetuximab monotherapy. These AEs were expected to be less in the BSC group. Cetuximab monotherapy had a greater incidence of any adverse event of grade 3 or higher compared to the BSC group ($p<0.001$). Patients in the cetuximab monotherapy group had a higher incidence of rash, infection without neutropenia, confusion and other pain as well as hypomagnesemia and infusion reactions

Effects	Merged data			
OS increase	Exact magnitude uncertain	None established	None established	Uncertain
QoL change	None established	NA	NA	NA
Safety change	-	-	NA	-

clofarabine	FDA primary indication		
ATC code: L01BB06 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.		
Agency	NICE	HAS	PBAC
Appraisal date	NA	Dec-06	NA
Comparator	NA	non-comparative	NA
Modelled/indirect comparison	NA	Yes	NA
Basis for classification	NA	**OS**: Expected to have an impact in terms of morbi-mortality by facilitating access to an allograft. However, in the absence of a formalized comparison with historic data, the impact can only be small. Moreover, because of the uncertainty about drug tolerance, extrapolation of the test results to real life is itself uncertain. **QoL**: No comparative data presented to evaluate HRQoL **Safety**: Tolerance data are limited at present. No comparative evaluation of drug-related safety as comparator arm unavailable. Additional absence of "formalized comparisons with historical	NA

			data on relapsed or refractory patients having had at least two previous treatments"	
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	NA	NA
Safety change	None established	NA	NA	NA

crizotinib	FDA primary indication		
ATC code: L01XE16	A kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate.		
Orphan Status: -			
Licensure: FDA/EMA			
Target: Lung			
Agency	NICE	HAS	PBAC
Appraisal date	Sep-13	Apr-13	Nov-14
Comparator	docetaxel	pemetrexed or docetaxel	pemetrexed
Modelled/indirect comparison	Yes	No	Yes
Basis for classification	**OS**: Committee "accepted that treatment would result in gain compared with docetaxel but the exact magnitude was uncertain; Committee "considered that the IPTCW2 method, which resulted in an OS benefit of 7.1 months, may be a reasonable assumption given the lack of robust data" but that "an exact value could not be reliably established" **QoL**: Committee heard from the clinical specialists that patients with progressed disease continued to experience some additional health-related QoL benefit for	**OS**: An increase compared to chemotherapy (i.e. docetaxel or pemetrexed) not established as no statistically significant difference was observed **QoL**: In view of the available clinical data, crizotinib showed a significant improvement in QoL versus docetaxel or pemetrexed **Safety**: No judgment given on comparative differences in drug-related safety profile	**OS**: Committee considered the "likely incremental gain "is between 3.1 to 3.5 months compared to pemetrexed (based on modeled data); Committee concluded that "given both the limitations of the randomized trial (small sample size, immature follow-up and post-progression cross-over to crizotinib in the pemetrexed arm) and also the usual concerns with attempting comparative treatment effect inferences by comparing across results for different groups of patients, no completely compelling conclusions could be drawn

		some time after treatment was withdrawn compared with those on chemotherapy, but that this would deteriorate over time. It accepted that some utility benefit might be expected from crizotinib discontinued at disease progression, though there are no data to suggest how great a benefit this might be or for how long it would persist. The Committee was also aware that there might be a benefit to utility of continuing crizotinib, but there were no data to show whether such continued treatment benefits patients or for how long **Safety**: The Committee concluded that crizotinib is associated with some ADRs but these would be tolerable for most patients and generally easily managed.		about the extent of incremental overall survival gain for crizotinib over pemetrexed" **QoL**: Consumer comments described a range of benefits, including the ability to return to work **Safety**: The PBAC accepted the claims for crizotinib having superior effectiveness and non-inferior safety compared to pemetrexed
Effects	Merged data			
OS increase	3.1–3.5 months	Uncertain	None established	≥ 3 months
QoL change	+	+	+	+
Safety change	None established	NA	NA	No difference

dabrafenib	FDA primary indication		
ATC code: L01XE23	A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: Skin			
Agency	NICE	HAS	PBAC
Appraisal date	Oct-14	May-14	Mar-13
Comparator	dacarbazine	dacarbazine	DTIC

Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: The Committee concluded that compared with dacarbazine, dabrafenib probably improved OS, but it was unable to draw firm conclusions about the magnitude of the benefit **QoL**: The mean change in EQ-5D utility index score from baseline to week 15 was lower in the dabrafenib group than in the dacarbazine group **Safety**: The Committee concluded that the current evidence suggests that ADRs from dabrafenib treatment were not a major concern when compared with those from alternative treatments	**OS**: In view of the available data, which shows no increase, the impact of dabrafenib on morbidity and mortality is considered low. On this date, there was no difference between the two therapeutic groups, dabrafenib vs dacarbazine (at six months) **QoL**: evaluatation using EORTC QLQ-C30 and EuroQoL EQ-5D questionnaires did not show any difference between the two treatment groups **Safety**: Treatment discontinuations due to adverse events were similar in both groups	**OS**: Dabrafenib, unlike vemurafenib, has not demonstrated an unequivocal advantage over DTIC. There was no statistically significant difference both treatment groups. However, OS data at time of cut-off was not mature, therefore no conclusions could be drawn **QoL**: NA **Safety**: Dabrafenib and DTIC have different toxicity profiles, with dabrafenib being associated with manageable toxicity versus DTIC. PBAC noted that dabrafenib has a preferable toxicity profile vs vemurafenib as evidenced by fewer and less extensive dose intensity reductions and by favourable differences in rates for AEs such as photosensitivity, cutaneous squamous cell carcinoma – but not pyrexia
Effects	Merged data			
OS increase	Exact magnitude uncertain	Uncertain	None established	None established
QoL change	-	-	No difference	NA
Safety change	+	No difference	No difference	NA (dacarbazine); + (vemurafenib) = +

dasatinib	FDA primary indication		
ATC code: L01XE06 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological	Indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. Also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.		
Agency	NICE	HAS	PBAC

Appraisal date		Jan-12	Mar-07	Jul-07
Comparator		non-comparative	non-comparative	non-comparative
Modelled/indirect comparison		Yes	Yes	Yes
Basis for classification		**OS**: Clinical trials were non-comparative, of short duration and had used surrogate outcomes to predict OS. The Committee noted the poor quality of the evidence base **QoL**: No regulatory judgment made on comparative differences in HRQoL **Safety**: Committee concluded that dasatinib and nilotinib are better tolerated than imatinib, and that older treatments, particularly interferon alfa, can be poorly tolerated	**OS**: Available clinical studies do not evaluate OS benefits directly **QoL**: No comparative data presented with which to evaluate comparative differences in HRQoL **Safety**: While safety of dasatinib evaluated, no comparison against other treatments is made	**OS**: Clinical benefits as determined by number of patients achieving complete cytogenic response. Outstanding areas of concern for the Committee were whether cytogenetic response outcomes later in the course of the chronic phase of CML result in survival gain and, if so, what is the magnitude of the gain **QoL**: NA **Safety**: Evaluation indicated that dasatinib has significant advantages in effectiveness over imatinib but has more toxicity
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	None established	NA	NA	NA
Safety change	+/-	+	NA	-

decitabine	FDA primary indication		
ATC code: L01BC08	Indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.		
Orphan Status: US/EU			
Licensure: FDA/EMA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	NA	NA	NA
Comparator	NA	NA	NA

Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

degarelix	FDA primary indication		
ATC code: L02BX02 Orphan Status: – Licensure: FDA/EMA Target: Prostate	A GnRH receptor antagonist indicated for treatment of patients with advanced prostate cancer.		
Agency	NICE	HAS	PBAC
Appraisal date	Apr-14	Sep-09	Jul-10
Comparator	LHRH agonists	leuproprelin	leuproprelin
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: Committee noted that duration of trials was short and were not sufficiently powered to detect differences between treatment groups. Mixed treatment comparison also did not show statistically significant differences. Lack of evidence to support OS benefit compared with LHRH agonists **QoL**: Patient experts noted that subcutaneous injections of degarelix are administered monthly and this dosing schedule may be inconvenient for some patients compared with subcutaneous administration of the LHRH agonists every 3 months. The manufacturer presented data for	**OS**: Not expected to have impact on morbidity and mortality. No clinical data demonstrating the benefits of this product in the treatment of prostate cancer **QoL**: Degarelix has not been shown to provide any improvement in treated patients **Safety**: The safety profiles of the two treatments were similar, apart from the emergence of anti- degarelix antibodies. There was no observed correlation between emergence of these antibodies and the efficacy and safety of degarelix after one year of treatment	**OS**: Submission provided no evidence to demonstrate whether outcomes observed in the first month of possible long-term treatment with degarelix would have significant effects on overall survival compared with leuproprelin **QoL**: NA **Safety**: The PBAC noted that there are more injection site reactions compared with leuprorelin and therefore degarelix may not be non-inferior with regards to safety. The majority of treatment-emergent ADRs were general disorders and administration site conditions including injection-site reactions which

		HRQoL, which was assessed using different measures and questionnaires. All the SF12 v2 scores were comparable across treatment groups and study days. **Safety**: The Committee heard from the patient experts that the safety profile is comparable to that of the LHRH agonists and the potential benefits of outweigh the adverse effects associated with it		occurred in 73 patients in the degarelix 240/80 mg group compared with 1 patient in the leuprorelin arm
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	None established	No difference	No difference	NA
Safety change	-	No difference	No difference	-

enzalutamide	FDA primary indication		
ATC code: L02BB04	An androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.		
Orphan Status: -			
Licensure: FDA/EMA			
Target: Prostate			
Agency	NICE	HAS	PBAC
Appraisal date	Jul-14	Nov-13	Jul-14
Comparator	placebo	placebo	abiraterone
Modelled/indirect comparison	No	No	Yes
Basis for classification	**OS**: 4.5-month increase in median OS compared to placebo; no statistically significant difference compared to abiraterone (based on indirect comparison)	**OS**: 4.8-month increase in median OS compared to placebo; Committee noted that there was no comparison to active comparators **QoL**: The fragmented QoL data cannot	**OS**: An increase compared to abiraterone was not established given limitations associated with the indirect comparison, though Committee accepted claim of non-inferiority

		QoL: There was a statistically significant difference in QoL for patients receiving enzalutamide compared with placebo, as measured using Functional Assessment of Cancer Therapy-Prostate (FACT-P) **Safety**: NICE noted that ADRs were generally manageable and reversible. However, the Committee was aware of the increased risk of seizures with enzalutamide treatment, and noted that the summary of product characteristics advises caution when treating people with a history of seizures or other predisposing factors for seizures	quantify the impact of enzalutamide on the QoL of the patients treated **Safety**: Although the Committee refers to differences in the safety profile of enzalutamide versus placebo, the Committee judges neither the strength nor direction of difference	**QoL**: The comments describe a range of benefits from treatment with enzalutamide, including improvement in survival and QoL **Safety**: PBAC considered that the claim of non-inferior comparative safety was reasonable
Effects	Merged data			
OS increase	4.5-4.8 months	≥ 3 months	≥ 3 months	None established
QoL change	+	+	NA	+
Safety change	+/-	+/-	NA	No difference

eribulin	FDA primary indication		
ATC code: L01XX41 Orphan Status: – Licensure: FDA/EMA Target: Breast	A microtubule inhibitor indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.		
Agency	NICE	HAS	PBAC
Appraisal date	Nov-13	Jul-11	Nov-13
Comparator	TPC	TPC	TPC
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: 2.7-month increase in median OS compared with TPC in the overall ITT population. The Committee considered	**OS**: 2.5-month increase in median OS (primary endpoint) in the eribulin mesylate group versus TPC group	**OS**: 2.7-month increase in median OS compared with TPC. The PBAC acknowledged that eribulin was an

		that it had not seen sufficient evidence to indicate that eribulin offers an extension to life of at least 3 months **QoL**: The Committee noted that no HRQoL data were collected during the EMBRACE trial and that data were presented from two phase II trials in which there was no comparator arm **Safety**: It was also aware of the importance of the side effects of hair loss, grade 3 and 4 peripheral neuropathy and febrile neutropenia, all of which occurred more frequently with eribulin than with TPC. The Committee concluded that eribulin was associated with a greater overall survival benefit compared with TPC but with a less favourable toxicity profile	**QoL**: The impact of the treatment on the QoL is not documented; no QoL data available **Safety**: The incidence of grade 3-4 adverse events was higher in the eribulin mesylate group than those treated with TPC	effective drug that offered a modest survival benefit at the end of life **QoL**: NA **Safety**: The PBAC noted that eribulin appeared to cause higher rates of adverse events than potential comparators. Overall, the PBAC considered that the safety profile of eribulin is different to vinorelbine with higher rates of peripheral neuropathy, and worse than best supportive care and some other potential comparators
Effects	Merged data			
OS increase	2.5–2.7 months	< 3 months	< 3 months	< 3 months
QoL change	None established	NA	NA	NA
Safety change	-	-	-	-

erlotinib	FDA primary indication		
ATC code: L01XE03	Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: Lung			
Agency	NICE	HAS	PBAC
Appraisal date	Nov-08	Mar-06	Nov-07

Comparator		No treatment	placebo	BSC
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: 2.0-month increase in median OS compared to no treatment. Difference in benefit with docetaxel is uncertain in the absence of direct comparisons **QoL**: Committee noted that patients may prefer erlotinib treatment to docetaxel because it is orally administered and they would therefore need to spend less time in hospital receiving treatment **Safety**: Clinical specialists and patient experts emphasised erlotinib's favourable toxicity profile, with fewer serious AEs reported during treatment with erlotinib than with docetaxel	**OS**: 2.0-month increase in median OS (primary endpoint) compared to placebo. No survival benefit in patients treated whose tumor EGFR expression was negative **QoL**: Time to deterioration of the three symptoms (cough, dyspnoea and pain) was significantly increased in patients treated with erlotinib: cough 2.9 months, dyspnoea 2 months and pain approximately 1 month **Safety**: The most commonly reported undesirable effects in the comparative study were diarrhoea and a skin rash. The dose was reduced because of undesirable effects in 19% of patients in the erlotinib group compared with 2% in the placebo group. Treatment was withdrawn from 5% of patients in the erlotinib group. Although AE rates and incidence is given, overall assessment of drug-related change in safety is not given by HAS	**OS**: Statistically significant differences versus BSC regarding all event rates, including overall survival. Statistically significant differences versus BSC regarding all event rates, including overall survival. Although exact gain in OS is not given, the label refers to various, placebo-controlled trials in the NEJM (referred to as BSC in a PBAC label published in 2006) which indicate that gain in OS associated with treatment is 2.0 months. **QoL**: NA **Safety**: Study BR.21 showed that erlotinib was associated with significantly more rash and diarrhoea compared to placebo, although they were mild to moderate intensity. There was no relevant haematological toxicity reported. For PBAC's comments on these results, see Recommendation and Reasons
Effects	Merged data			
OS increase	2.0 months	< 3 months	< 3 months	< 3 months
QoL change	+	+	+	NA
Safety change	+/-	+	NA	-

everolimus	FDA primary indication
ATC code: L01XE10	A kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.
Orphan Status: EU (w)	
Licensure: FDA/EMA	

Target: Renal				
Agency		NICE	HAS	PBAC
Appraisal date		Apr-11	Jan-10	Nov-09
Comparator		BSC	placebo	BSC
Modelled/indirect comparison		Yes	No	No
Basis for classification		**OS**: More than 3-month increase compared to BSC (exact magnitude of was uncertain given that it was "based on modelled data as opposed to data directly observed in the trial"); Committee considered a modelled 5.2-month increase compared to BSC "more plausible" than the 8.2-month increase derived by the manufacturer **QoL**: Time to deterioration in functioning/symptoms was delayed with everolimus + BSC by 3.5 months compared with placebo + BSC. The median time to deterioration according to FKSI–DRS score was 7.4 months for everolimus + BSC and 3.9 months for placebo + BSC. Difference was statistically significant **Safety**: The Committee noted the increased frequency of AEs (including serious) associated with everolimus treatment. There was a greater incidence of AEs (including serious) reported in the everolimus + BSC arm (40.1%) than the placebo + BSC arm (22.6%)	**OS**: An increase compared to placebo (optimum symptomatic treatments) not established as no improvement was observed; Committee acknowledged that an assessment was difficult "given the premature termination of the pivotal study and the fact that patients whose disease had demonstrably progressed were allowed to transfer" **QoL**: No improvement was demonstrated in the pivotal study (QLQ-C30) **Safety**: More patients in the everolimus group stopped treatment as a result of adverse effects than in the placebo group	**OS**: No statistically significant difference was observed compared to BSC **QoL**: PBAC considered that the results for Karnofsky performance status, physical function, and QoL scores showed no statistically significant differences and performance status between everolimus and placebo treated patients. However, these results are difficult to interpret because of the substantial crossover of placebo patients to everolimus treatment **Safety**: Everolimus has significant on-treatment toxicity compared to placebo, including increased risk of serious infection, non-infectious pneumonitis, dyspnea, stomatitis, hyperglycaemia, anaemia, lymphopenia as well as neurotoxicity
Effects	Merged data			
OS increase	5.2 months	≥ 3 months	None established	None established
QoL change	+	+	No difference	No difference
Safety change	-	-	-	-

gefitinib	FDA primary indication		
ATC code: L01XE02 Orphan Status: – Licensure: FDA/EMA Target: Lung	Indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.		
Agency	NICE	HAS	PBAC
Appraisal date	Jul-2010	Nov-2009	Jul-2013
Comparator	paclitaxel + carboplatin	paclitaxel + carboplatin	paclitaxel + carboplatin
Modelled/indirect comparison	No	No	No
Basis for classification	**OS:** Committee was aware that the analysis of OS was an interim analysis of immature data. The Committee noted that a longer progression-free survival may correlate with improved overall survival in NSCLC, but there was uncertainty around this **QoL:** Committee agreed that treatment … offers an advantage because it can be taken at home. Committee accepted the ERG's view that EGFR-TK mutation-positive patients who were randomised to receive gefitinib had a clinically relevant improvement in health-related quality of life and disease symptoms compared with patients randomised to receive paclitaxel and carboplatin **Safety:** The Committee concluded that gefitinib was associated with an improved adverse effects profile compared with platinum-based chemotherapy. Clinical specialists confirms that gefitinib had been shown	**OS:** Median overall survival did not differ between the two groups (18.6 months in the IRESSA group and 17.3 months in the comparator group). The overall survival results are not mature (number of events not reached) **QoL:** quality of life analysis results showed an improvement in the IRESSA group in two of the three scales used (FACT-L and TOI) **Safety:** No comparative data presented	**OS:** The data were updated for trials NEJ002 and WJTOG3405, but were still immature for the WJTOG3405 trial. As seen in the IPASS (paclitaxel + carboplatin) and First-SIGNAL (cisplatin + gemcitabine) trials, there was no significant difference between the two treatment arms in terms of OS (NEJ002 HR=0.89; 95% CI: 0.63, 1.24; WJTOG3405: HR=1.19; 95% CI: 0.77, 1.83) **QoL: T**he PBAC accepted that the clinical benefit of listing gefitinib in patients with EGFR M+ NSCLC as first-line treatment in addition to the current listing for second-line treatment is an improvement in quality of life **Safety:** Overall, safety profiles varied across the treatment arms, but gefitinib appeared to have less serious toxicity than platinum-based therapy … the PBAC accepted that gefitinib appears to have less serious toxicity than platinum-based doublet chemotherapy

		to be well tolerated in clinical practice		
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	+	+	+	+
Safety change	+	+	NA	+

ibrutinib		FDA primary indication		
ATC code: L01XE27		A kinase inhibitor indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

ipilimumab		FDA primary indication		
ATC code: L01XC11		A human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for the treatment of unresectable or metastatic melanoma.		
Orphan Status: –				
Licensure: FDA/EMA				
Target: Skin				
Agency		NICE	HAS	PBAC

Appraisal date		Jul-14	Nov-14	Nov-12
Comparator		dacarbazine	dacarbazine / temozolomide / vemurafenib	Dacarbazine
Modelled/indirect comparison		No	Yes	Yes
Basis for classification		**OS**: 5.7-month increase in mean OS compared to dacarbazine when given as first-line (2.1-month increase in median OS); mean OS was available because of the long duration of the trial and lack of crossover **QoL**: First- and second-line, no HRQoL data reported **Safety**: Severe, serious, drug-related and AEs leading to discontinuation were all more frequent in the ipilimumab 10 mg/kg + dacarbazine group than in dacarbazine alone group. In second-line treatment, the Committee concluded that the ADRs and mortality associated with ipilimumab seen in the MDX010-20 trial were considerable	**OS**: Committee noted that the results of an indirect comparison with several comparators (dacarbazine, temozolomide, and vemurafenib) suggested that OS improved with ipilimumab, but did not allow for a formal conclusion **QoL**: A negative impact on quality of life cannot be ruled out mainly because of significant side effects experienced. No explicit judgment on comparative differences in HRQoL given **Safety**: The safety data provided in this new indication are comparable to the safety profile seen to date for this specialty	**OS**: Committee considered that the "magnitude of the incremental benefit of ipilimumab remained uncertain" compared to dacarbazine as the submission was "reliant on extrapolation of trial results to a ten-year time horizon" **QoL**: NA **Safety**: Ipilimumab has a different safety profile than BSC (DTIC/fotemustine), with irAEs (immune-related adverse events) which are manageable and controllable. Even though the PBAC considers this claim reasonable, it does not indicate whether it believes differences to be clinically meaningful and does not give a value judgment
Effects	Merged data			
OS increase	5.7 months	≥ 3 months	Uncertain	Uncertain
QoL change	None established	NA	NA	NA
Safety change	-	-	No difference	NA

ixabepilone	FDA primary indication		
ATC code: L01DC04 Orphan Status: – Licensure: FDA Target: Breast	A microtubule inhibitor, in combination with capecitabine is indicated for treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane. Also indicated as monotherapy for treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine.		
Agency	NICE	HAS	PBAC

Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

lapatinib	FDA primary indication		
ATC code: L01XE07 Orphan Status: – Licensure: FDA/EMA Target: Breast	A kinase inhibitor, indicated in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.		
Agency	NICE	HAS	PBAC
Appraisal date	May-10	Jul-08	Nov-07
Comparator	capecitabine monotherapy	capecitabine monotherapy	capecitabine monotherapy
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: 2.4-month increase in overall median survival; certainly not enough evidence that the extension of life provided was 3 months or greater **QoL**: No HRQoL information presented in report **Safety**: The lapatinib + capecitabine group had a marginally higher incidence of diarrhoea and palmar-plantar erythrodysaesthesia than the capecitabine monotherapy group	**OS**: At the cut-off point for the first interim analysis, no difference was observed between the two treatment arms. In view of the premature termination of the study, the benefit of lapatinib + capecitabine compared with capecitabine alone in terms of overall survival cannot be evaluated **QoL**: The available data are insufficient to estimate the impact of lapatinib + capecitabine in reducing the morbidity and mortality associated with metastatic breast cancer and in	**OS**: 1.1-week increase in median overall survival. However, study was terminated early by independent monitoring board, and patient crossover. Early termination reduces the likelihood of detecting a significant difference in overall survival. There is some evidence improves survival compared to capecitabine alone, but full extent of survival benefit is not known and is not statistically different from comparator treatment alone **QoL**: NA

			improving QoL, compared with the current form of management **Safety**: Main AEs were often raised in the lapatinib + capecitabine arm compared with the capecitabine arm, including for: diarrhoea, palmar-plantar erythrodysaesthesia, nausea, rash, and vomiting. However, the HAS does not make a judgment as to the statistical or clinical significance of these findings	**Safety**: The overall safety profile of lapatinib + capecitabine, in terms of the incidence, types and intensities of adverse events, appears similar to that reported in the published studies for different trastuzumab-containing chemotherapies for patients with metastatic breast cancer
Effects	Merged data			
OS increase	0.3–2.4 months	< 3 months	None established	Uncertain
QoL change	None established	NA	NA	NA
Safety change	-	-	NA	No difference

lenalidomide	FDA primary indication		
ATC code: L04AX04	Indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.		
Orphan Status: US/EU			
Licensure: FDA/EMA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	Sep-14	Nov-14	Mar-13
Comparator	placebo	placebo	placebo (BSC)
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: No statistically significant difference. Placebo arm could cross over to lenalidomide treatment, therefore benefit of lenalidomide may be underestimated. Lenalidomide could indirectly improve OS by improving transfusion independence, but this was	**OS**: Available clinical data shows better cytogenic response but without benefit in OS **QoL**: Given current therapeutic strategies, the available clinical data indicates a moderate impact in terms of	**OS**: While results did not show statistically significant change in OS, possibly owing to patient cross-over, the PBAC considered that there was a trend favoring lenalidomide **QoL**: For key results, see Mar 2011

		uncertain **QoL**: Committee considered the results of the MDS-004 study: the rates of transfusion independence (at 26 weeks, lenalidomide 10 mg: 56.1%, placebo: 5.9%) and improvements in the FACT-An questionnaire (mean change, lenalidomide 10 mg: 5.8, placebo: -2.5) were significantly better in people treated with lenalidomide compared with placebo **Safety**: Committee was aware that lenalidomide may be associated with higher rates of venous thrombo-embolism than placebo. A higher proportion of people in the lenalidomide 10 mg (95.7%) and 5 mg groups (98.6%) had at least 1 drug-related AE compared with the placebo group (49.3%). However, it heard from the clinical specialist and patient experts that AEs associated with lenalidomide treatment are managed with dose interruptions and are generally well tolerated. The Committee concluded that, although lenalidomide is associated with some AEs, these can be managed by dose interruptions	morbidity and mortality and quality of life should be expected from lenalidomide. The "transferability of test results to the practice can be regarded as assured" **Safety**: The safety profile observed in the lenalidomide MDS patients of low risk associated with a deletion 5q was comparable to that already experienced in patients with myeloma. Regarding the first 16 weeks of the double-blind phase, at least one adverse event was observed in all patients of lenalidomide group (69 patients in the 5 mg group and 69 patients in the 10 mg group) and in 96% of 67 patients in the placebo group	PSD. PBAC noted clinical meaningful change in patients HRQoL after 24 weeks of treatment with lenalidomide and a worsening in placebo patients. However, the results were confounded due to loss to follow up **Safety**: PBAC considered that treatment with lenalidomide was associated with more toxicity than best supportive care and that dose reduction would be required to manage side effects in a number of patients
Effects	Merged data			
OS increase	Exact magnitude uncertain	Uncertain	None established	Uncertain
QoL change	+	+	+	NA
Safety change	-	-	No difference	-

nelarabine	FDA primary indication

ATC code: L01BB07		Indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	Dec-07	NA
Comparator		NA	non-comparative	NA
Modelled/indirect comparison		NA	Yes	NA
Basis for classification		NA	**OS**: Facilitates the use of allografts, therefore expected to have an impact on morbidity and mortality, which can only be low. Because of the uncertainty about the tolerability of this drug, extrapolation of the trial results to real life is uncertain **QoL**: NA **Safety**: There are "currently few safety data". Safety-related data drawn from non-comparative adult and child studies	NA
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	NA	NA
Safety change	None established	NA	NA	NA

nilotinib	FDA primary indication
ATC code: L01XE08	A kinase inhibitor indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included imatinib.
Orphan Status: US/EU	
Licensure: FDA/EMA	

Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		Jan-12	Feb-08	Mar-08
Comparator		non-comparative	non-comparative	non-comparative
Modelled/indirect comparison		Yes	No	Yes
Basis for classification		**OS**: Clinical trials were non-comparative, of short duration and had used surrogate outcomes to predict OS. The Committee noted the poor quality of the evidence base **QoL**: No regulatory judgment made on comparative differences in HRQoL **Safety**: Committee concluded that dasatinib and nilotinib are better tolerated than imatinib, and that older treatments, particularly interferon alfa, can be poorly tolerated	**OS**: No comparative evaluation of OS relative to available treatments **QoL**: No comparative data presented **Safety**: There are currently few safety data. No comparative data presented	**OS**: Committee does not present any conclusion regarding OS benefits. Evidence for nilotinib after imatinib and dasatinib treatment is from single arm open-label nilotinib study for CML-CP and CML-AP **QoL**: NA **Safety**: PBAC noted that whilst nilotinib has a different safety profile to both high dose imatinib and dasatinib, there is considerable uncertainty around the claims that nilotinib has significant activity after failure of both imatinib and dasatinib and that nilotinib has a superior safety profile to dasatinib
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	None established	NA	NA	NA
Safety change	+	+	NA	NA

obinutuzumab	FDA primary indication
ATC code: L01XC15	A CD20-directed cytolytic antibody and is indicated, in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia.
Orphan Status: US/EU	
Licensure: FDA/EMA	
Target: Hematological	

Agency		NICE	HAS	PBAC
Appraisal date		Mar-15	Feb-15	Jul-14
Comparator		chlorambucil	rituximab / chlorambucil	chlorambucil
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: Obinutuzumab + chlorambucil was associated with statistically significantly greater OS compared with chlorambucil monotherapy. However, the Committee acknowledged that the OS data were immature **QoL**: The clinical expert and patient expert acknowledged that some people may prefer oral treatment with chlorambucil instead of having to attend a day unit for intravenous treatment with obinutuzumab or bendamustine **Safety**: Some people may prefer to have obinutuzumab instead of bendamustine, because obinutuzumab is associated with fewer AEs. The Committee took into consideration the summary of product characteristics and concluded that obinutuzumab had an acceptable adverse event profile	**OS**: Impact compared to the comparator (R-Clb) is not quantifiable **QoL**: The impact compared to the comparator (R-Clb) is not quantifiable **Safety**: Compared to rituximab, the incidence of AEs ≥ grade 3 was higher in the G-Clb group than in the R-Clb group	**OS**: PBAC accepted the claim that obinutuzumab + chlorambucil is superior in terms of comparative effectiveness and inferior in terms of comparative safety over chlorambucil alone. While hazard ratio for OS was not statistically significant, the trend was in favor of obinutuzumab + chlorambucil and the more recent data is approaching statistical significance **QoL**: Consumer comments captured the notion that obinutuzumab provides a treatment option for older, less fit patients with CLL and prolongs remission during which time patients can live a "normal life" **Safety**: PBAC accepted the submission's claim that obinutuzumab + chlorambucil is inferior in terms of comparative safety over chlorambucil alone
Effects	Merged data			
OS increase	Exact magnitude uncertain	Uncertain	None established	Uncertain
QoL change	+/−	-	NA	+
Safety change	+/−	+	-	-

ofatumumab	FDA primary indication
ATC code: L01XC10	A CD20-directed cytolytic monoclonal antibody indicated for the treatment of patients with chronic lymphocytic leukemia

Orphan Status: US/EU		(CLL) refractory to fludarabine and alemtuzumab. The effectiveness of ofatumumab is based on the demonstration of durable objective responses.		
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		Oct-10	Oct-10	Nov-14
Comparator		non-comparative	non-comparative	chlorambucil
Modelled/indirect comparison		Yes	Yes	No
Basis for classification		**OS**: No data on median OS available for patients responding to treatment because data were immature. Although it was likely that ofatumumab is effective based on the observed ORRs, and partly based on manufacturer's model regarding extensions to life (">5 months relative to BSC"), it was not possible to estimate the size of the effect with certainty because of the absence of robust and comparative evidence and the immaturity of the data **QoL**: No HRQoL information presented in report. HRQoL had not been collected in the pivotal study **Safety**: The Committee concluded that ofatumumab may be associated with AEs, but the extent and impact of these was uncertain owing to a lack of robust evidence and the lack of a group of patients who did not receive ofatumumab in the trial	**OS**: The quality of the data available is not sufficient to allow an evaluation of the impact in terms of mortality of the medicinal product. Comparison of ofatumumab with historical data does not allows unbiased evaluation to be made of the size of effect, therefore it is not considered by the Committee **QoL**: NA **Safety:** The efficacy and tolerance data are limited, as they are drawn from a non-comparative phase II study	**OS**: No difference was observed in direct comparison with chlorambucil, which may be due to the limited follow-up of the trial for patients with indolent CLL. Overall, incomplete and less than rigorous comparison of ofatumumab with rituximab (modelled evaluation) **QoL**: NA Safety: PBAC noted no important overall differences in adverse events
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	None established	NA	NA	NA

Safety change	None established	NA	NA	No difference

omacetaxine mepesuccinate		FDA primary indication		
ATC code: L01XX40		Adult patients (injection) with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI). This indication is based upon response rate.		
Orphan Status: US				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

panitumumab	FDA primary indication		
ATC code: **L01XC08**	Indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.		
Orphan Status: -			
Licensure: FDA/EMA			
Target: GI			
Agency	NICE	HAS	PBAC
Appraisal date	Jan-12	Apr-08	Nov-13
Comparator	BSC	palliative care	cetuximab
Modelled/indirect comparison	Yes	No	No
Basis for classification	**OS**: Approximately 3-month extension	**OS**: An increase compared palliative	**OS**: No statistically significant difference

		to life compared to BSC (mean life extension estimated to be 2.7 to 3.2 months after adjusting for patient crossover in the trial); no statistically significant difference in overall survival was observed in the trial **QoL**: No HRQoL data presented in report **Safety**: Committee did not discuss specific issues around the AEs to the technologies appraised but it was aware of the special warnings and precautions for use outlined in the SPC	care not established as no statistically significant difference was observed **QoL**: In light of the available data (just one post hoc analysis on subgroups of the pivotal study), the impact of panitumumab on morbidity, mortality and quality of life cannot be quantified **Safety**: Safety data are currently limited. There is no judgment of comparative differences in toxicity	was observed compared to cetuximab (third-line) **QoL**: NA **Safety**: The PBAC considered the claim that panitumumab is non-inferior in terms of safety to cetuximab to be reasonable in the third-line setting where both drugs were used as monotherapy
Effects	Merged data			
OS increase	2.7–3.2 months	≥ 3 months	None established	None established
QoL change	None established	NA	NA	NA
Safety change	None established	NA	NA	No difference

pazopanib	FDA primary indication		
ATC code: L01XE11	A kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma.		
Orphan Status: EU (w)			
Licensure: FDA/EMA			
Target: Renal			
Agency	NICE	HAS	PBAC
Appraisal date	Feb-11	Jun-13	Mar-12
Comparator	BSC/interferon-alfa	placebo/sunitinib	BSC/sunitinib
Modelled/indirect comparison	Yes	No	Yes
Basis for classification	**OS**: More than 3-month increase	**OS**: An increase compared to sunitinib	**OS**: No statistically significant difference

		compared to BSC (based on RPSFT model) and interferon-alfa (based on indirect comparison), though exact magnitude of increase uncertain; no significant difference compared to sunitinib based on results from head-to-head trial the Committee noted would be available in 2012 **QoL**: For the VEG105192 trial, there were no statistically significant differences between pazopanib and placebo for any of the instruments used (European Organisation for Research and Treatment of Cancer [EORTC] QoL questionnaire – Core 30, EQ-5D, EQ-5D-VAS) **Safety**: Committee heard from the clinical specialists that the evidence presented by the manufacturer suggested that pazopanib has a more favourable toxicity profile than sunitinib, especially in relation to hand-foot syndrome. The clinical specialists and patient experts were of the opinion that pazopanib is a useful option because it has a more favourable toxicity profile than sunitinib	not established (first-line) as no statistically significant difference was observed; Committee noted that non-inferiority compared to sunitinib was "the subject of serious doubt"; increase compared to placebo not established as no statistically significant difference was observed **QoL**: No reliable conclusions could be drawn from evaluation scores as to any difference between the two treatments. In fact, results varied depending on the scale used: there was no difference on one scale (FACIT-F), although there were differences on the FKSI-19 and CTSQ scales but with values below the threshold for clinical relevance **Safety**: For 1st RCC, the safety profile differed between the two groups, with notably a higher incidence of abnormal liver function tests in the pazopanib group and a higher incidence of hand-foot syndrome in the sunitinib group. For 2nd RCC, treatment discontinuation due to AEs was twice as common in the pazopanib group as in the placebo group	was observed compared to BSC (even after adjusting for patient crossover with IPCW and RPSFT models); no statistically significant difference was observed compared to sunitinib (based on indirect comparison) **QoL**: NA **Safety**: PBAC concluded that pazopanib has a different side-effect profile to sunitinib. Patients taking sunitinib tend to experience events such as diarrhoea, fatigue, hypertension, mucositis, hand-foot syndrome, and myelosuppression; patients taking pazopanib tend to experience diarrhoea, hypertension and liver dysfunction. These differences are insufficient to change an overall conclusion that pazopanib is non-inferior to sunitinib in terms of safety.
Effects	Merged data			
OS increase	Exact gain over 3 months uncertain	≥ 3 months (Exact gain over 3 months uncertain)	None established	None established
QoL change	None established	No difference	No difference	NA
Safety change	+/−	+	+/− (1st RCC); − (2nd RCC) = +/−	No difference

pemetrexed	FDA primary indication		
ATC code: L01BA04	In combination with cisplatin for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.		
Orphan Status: US/EU (w)			
Licensure: FDA/EMA			
Target: Lung			
Agency	NICE	HAS	PBAC
Appraisal date	Jan-08	Mar-05	Nov-07
Comparator	cisplatin	cisplatin	cisplatin
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: 2.8-month increase in median OS compared to cisplatin **QoL**: Committee noted that there was some evidence showing that pemetrexed plus cisplatin was associated with significant symptomatic improvements compared with cisplatin alone. Committee agreed that the economic analyses may have underestimated the overall quality of life benefits of pemetrexed in people with MPM. Combination treatment appears to demonstrate advantages in QoL **Safety**: Severe to life-threatening or disabling adverse events were statistically significantly more frequent in patients receiving pemetrexed plus cisplatin than in those receiving cisplatin alone	**OS**: 3.3-month increase in median OS compared to cisplatin in subgroup of patients fully supplemented with vitamins; 2.8-month increase in median OS compared to cisplatin in the intention-to-treat population **QoL**: It was also observed a reduction of certain clinical symptoms (dyspnea, pain) related to the disease and improving lung function **Safety**: No comparative data presented	**OS**: 2.8-month increase in median OS **QoL**: data from the pivotal trial using the Patient Lung Cancer Symptom Scale (LCSS) were presented. There were significant improvements in fatigue, dyspnea, pain, symptom distress, activity level, and overall LCSS, except for hemoptysis, in the pemetrexed+ cisplatin treatment arm. Although the global QoL scale did not show significant changes, the total LCSS as an average of all nine items reached a statistically significant difference in favor of pemetrexed **Safety**: Serious AEs occurred more frequently in the PMT+cisplatin arm than the cisplatin alone arm. Overall, frequency of Grade 3/4 laboratory toxicity was higher in the PMT+cisplatin arm than in the cisplatin alone arm. Severe toxicity was uncommon in the cisplatin arm, compared to the PMT+cisplatin arm where Grade 3⁄4 neutropenia were the most common haematologic toxicities

Effects	Merged data			
OS increase	2.8–3.3 months	< 3 months	≥ 3 months	< 3 months
QoL change	+	+	+	+
Safety change	-	-	NA	-

pertuzumab	FDA primary indication		
ATC code: L01XC13 Orphan Status: – Licensure: FDA/EMA Target: Breast	A HER2/neu receptor antagonist indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.		
Agency	NICE	HAS	PBAC
Appraisal date	NA	Jul-13	Mar-14
Comparator	NA	trastuzumab + docetaxel	trastuzumab + docetaxel
Modelled/indirect comparison	NA	No	No
Basis for classification	NA	**OS**: An increase compared to trastuzumab + docetaxel was observed (by a second interim analysis not scheduled in the protocol), but the size of the increase was uncertain given that median OS had not yet been achieved **QoL**: The treatment is not expected to have any impact on patients' quality of life evaluated using the FACT-B questionnaire specific to the disease **Safety**: In addition to similar drop-out rates from AEs, no difference was seen between the two groups (pertuzumab vs placebo) as regards the incidence of grade 3-4 events	**OS**: 15.7-month increase in median OS compared to trastuzumab + docetaxel **QoL**: PBAC noted strong support for pertuzumab received through the consumer comments facility expressing a range of benefits from treatment including improving QoL **Safety**: PBAC considered the claim that pertuzumab, when used in combination with trastuzumab + docetaxel, to be "slightly worse" in terms of comparative safety. PBAC considered the trial results indicated that adding pertuzumab to trastuzumab + docetaxel results in statistically significant increased toxicity in trastuzumab naïve (sensitive) compared to trastuzumab + docetaxel

Effects	Merged data			
OS increase	15.7 months	NA	Uncertain	≥ 3 months
QoL change	+	NA	No difference	+
Safety change	-	NA	No difference	-

pomalidomide	FDA primary indication		
ATC code: L04AX06 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological	A thalidomide analogue indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.		
Agency	NICE	HAS	PBAC
Appraisal date	Mar-15	Jan-14	Jul-14
Comparator	standard care	high-dose dexamethasone	high-dose dexamethasone
Modelled/indirect comparison	Yes	No	No
Basis for classification	**OS**: At least 3-month extension compared to standard NHS care (e.g. bendamustine) (based on modeled data); Committee was "not able to judge with any confidence how much more effective pomalidomide was compared with the current treatment options based on the available evidence"; nevertheless, the Committee was "persuaded that pomalidomide extends life for at least 3 months on average when compared with standard NHS care" based on data modeled data that was "not considered robust" **QoL**: HRQoL was measured using the EORTC questionnaire for patients with cancer (QLQ-C30), the EORTC multiple myeloma module (QLQ-MY20) and the EuroQol-5 dimensions survey (EQ-5D).	**OS**: An increase compared palliative care not established; median OS was not reached in pomalidomide treatment arm; Committee noted that 29% of patients in the high-dose dexamethasone group had received pomalidomide because of disease progression **QoL**: In light of the available clinical trial data, no impact in terms of morbidity and mortality and QoL is expected for the proprietary medicinal product pomalidomide in combination with dexamethasone **Safety**: The most commonly observed serious AEs had a comparable incidence in the two groups, in particular pneumonia and deterioration	**OS**: Committee considered that OS increased compared to high-dose dexamethasone, but the magnitude of the increase was redacted **QoL**: The PBAC also noted that the EQ-5D showed a trend towards improved QoL with pomalidomide + LDD compared with HDD, noting however that the differences in the EQ-5D utility index score between treatment arms were generally not statistically significant **Safety**: The PBAC considered that pomalidomide has inferior, but manageable, safety compared with HDD

		Most results presented by the company suggest favourable trends with pomalidomide compared with dexamethasone **Safety**: The Committee noted that the proportion of patients with adverse reactions were similar between those taking pomalidomide and high-dose dexamethasone	in general health	
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain uncertain)	None established	Uncertain
QoL change	+	+	No difference	+
Safety change	-	No difference	No difference	-

ponatinib	FDA primary indication		
ATC code: L01XE24 Orphan Status: EU Licensure: FDA/EMA Target: Hematological	A kinase inhibitor indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. This indication is based upon response rate.		
Agency	NICE	HAS	PBAC
Appraisal date	NA	Jan-15	Nov-14
Comparator	NA	non-comparative	dasatinib / nilotinib
Modelled/indirect comparison	NA	Yes	Yes
Basis for classification	NA	**OS**: No expected impact in terms of morbidity and mortality compared with current therapeutic management **QoL**: There is no expected impact in terms of morbidity and mortality and QoL for the specialty ponatinib compared with current management	**OS**: There is no direct evidence available for the comparative efficacy of ponatinib vs dasatinib or nilotinib. Based on single-arm comparative evidence, it is not clear whether ponatinib is better or worse than dasatinib or nilotinib in the treatment of chronic phase CML

			Safety: No comparative data available	**QoL**: NA **Safety**: The PBAC considered that ponatinib had an inferior toxicity profile to imatinib, dasatinib, and nilotinib, especially with regard to serious vascular occlusive event
Effects	Merged data			
OS increase	None established	NA	None established	None established
QoL change	None established	NA	No difference	NA
Safety change	-	NA	NA	-

pralatrexate		FDA primary indication		
ATC code: L01BA05 Orphan Status: EU Licensure: FDA/EMA Target: Hematological		A folate analogue metabolic inhibitor indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

radium Ra 223 dichloride	FDA primary indication

ATC code: V10XX03 Orphan Status: – Licensure: FDA/EMA Target: Prostate		An alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	Apr-14	NA
Comparator		NA	Placebo	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: 2.8-month increase vs placebo demonstrated in available studies **QoL**: The expected impact on preserving QoL remains difficult to assess, improved time observed to degradation of FACT-P score and the EQ-5D utility score are not considered clinically relevant and the absence of pain assessment. In the absence of comparative data versus currently used treatments, the expected impact of radium-223 dichloride in terms of improving QoL compared to those treatments currently used cannot be quantified **Safety**: Although HAS discusses several adverse events that were observed more frequently in the radium-223 dichloride group than in the placebo group, the agency does not provide an overall assessment of drug-related changes in safety	NA
Effects	Merged data			
OS increase	2.8 months	NA	< 3 months	NA
QoL change	None established	NA	NA	NA

Safety change	None established	NA	NA	NA

regorafenib		FDA primary indication		
ATC code: L01XE21		A kinase inhibitor indicated for the treatment of metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.		
Orphan Status: -				
Licensure: FDA/EMA				
Target: GI				
Agency		NICE	HAS	PBAC
Appraisal date		NA	May-14	Jul-14
Comparator		NA	placebo	placebo
Modelled/indirect comparison		NA	No	No
Basis for classification		NA	**OS**: 1.4-month increase in median OS in regorafenib group relative to placebo (primary analysis) **QoL**: It is not expected that this and a proprietary medicinal product will provide any additional impact in terms of morbidity and mortality or quality of life **Safety**: The overall incidence of serious adverse events considered as being treatment-related was higher in the regorafenib group	**OS**: 1.4-month increase in median OS. PBAC considered that clinical evidence from the CORRECT clinical trial was mature, there was not cross-over and subsequent therapy was relatively balanced between treatment groups. CORRECT unlikely to have underestimated the effectiveness of regorafenib compared to BSC. However OS benefit not considered to be clinically significant **QoL**: PBAC noted that no patients in the trial had a complete response and that EQ-5D data showed no improvement compared to BSC **Safety**: PBAC agreed that regorafenib was inferior in comparative safety to BSC and noted severe AEs associated with the drug, particularly hepatotoxicity and hand-foot skin reactions
Effects	Merged data			

OS increase	1.4 months	NA	< 3 months	< 3 months
QoL change	None established	NA	No difference	No difference
Safety change	-	NA	-	-

romidepsin		FDA primary indication		
ATC code: L01XX39		A histone deacetylase (HDAC) inhibitor indicated for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

ruxolitinib	FDA primary indication		
ATC code: L01XE18	A kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.		
Orphan Status: US / EU (w)			
Licensure: FDA/EMA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	Jun-13	Jan-13	Jul-13
Comparator	BSC	placebo	BSC (hydroxyurea and placebo)
Modelled/indirect comparison	Yes	No	Yes

Basis for classification		**OS**: The Committee concluded that it was plausible that ruxolitinib could offer a survival benefit. However, the reason for this benefit remained unclear **QoL**: The Committee noted that in COMFORT-I significantly more patients treated had a 50% or more reduction in total symptom score than those on placebo, and that there was a significantly greater reduction in mean change from baseline total symptom score with ruxolitinib than placebo. **Safety**: The Committee concluded that ruxolitinib did have a negative impact on haematological outcomes in the short term, but agreed that these were manageable	**OS**: The impact of the treatment on OS and leukaemic transformation cannot be evaluated at present because of the small number of events reported **QoL**: Ruxolitinib is expected to have a low impact on the morbidity of patients treated. However, the impact of treatment on quality of life is difficult to evaluate (several reasons given) **Safety**: The overall incidence of serious adverse effects was similar in the treatment groups in the two pivotal studies at around 30%.	**OS**: PBAC accepted the clinical claim of superior efficacy likely in OS, although the magnitude of the survival benefit is uncertain due to high number of cross-over and confounding factors **QoL**: PBAC accepted the claim of superior efficacy demonstrated in spleen response and QoL measures **Safety**: PBAC did not accept the claim for equivalence in comparative safety. Patients experienced significantly more drug-related AEs than patients treated with either BAT (in COMFORT-II) or placebo (in COMFORT-I). There were also significantly more cases of thrombocytopenia and anaemia in ruxolitinib treated patients compared to BAT treated patients in COMFORT-II
Effects	Merged data			
OS increase	Exact magnitude uncertain	Uncertain	None established	Uncertain
QoL change	+	+	NA	+
Safety change	-	-	No difference	-

sipuleucel-T	FDA primary indication		
ATC code: L03AX17	An autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: Prostate			
Agency	NICE	HAS	PBAC
Appraisal date	Feb-15	NA	NA
Comparator	BSC	NA	NA

Modelled/indirect comparison		No	NA	NA
Basis for classification		**OS**: 4.0-month median extension compared to BSC (based on meta-analysis of three trials) in subgroup of patients who had not previously received chemotherapy; two of the three trials showed that sipuleucel-T extended life, including the pivotal trial with a 4.1-month increase in median OS; Committee concluded that "it would be reasonable to assume that sipuleucel-T and abiraterone had similar effectiveness in prolonging overall survival" (based on indirect comparison). **QoL**: Patient organisations expected sipuleucel-T to reduce pain, improve mental and physical health, and offer an additional treatment option at an early stage of disease. The Committee concluded that patients would like to have the option of having treatment with sipuleucel-T within the NHS. **Safety**: The Committee noted that the European public assessment report stated that sipuleucel-T is considered less toxic than other therapies (such as abiraterone, enzalutamide, docetaxel and cabazitaxel) that are currently used for treating metastatic hormone-resistant prostate cancer	NA	NA
Effects	Merged data			
OS increase	4.0 months	≥ 3 months	NA	NA
QoL change	+	+	NA	NA
Safety change	+	+	NA	NA

sorafenib	FDA primary indication		
ATC code: L01XE05 Orphan Status: US/EU Licensure: FDA/EMA Target: Renal	Indicated for the treatment of patients with advanced renal cell carcinoma.		
Agency	NICE	HAS	PBAC
Appraisal date	Aug-09	Sep-06	Mar-08
Comparator	BSC	placebo	BSC
Modelled/indirect comparison	Yes	No	No
Basis for classification	**OS**: More than 3-month increase compared to BSC was "likely" for people in whom immunotherapy has failed (second-line), though exact magnitude was uncertain; trial was "terminated early, on ethical grounds, after an independent review decided that sorafenib should be offered to participants who were receiving placebo" **QoL**: No HRQoL difference between placebo and sorafenib groups in mean FACT-G physical well-being score, nor any significant difference in mean FKSI−10 total score over the first 32 weeks of treatment. However, median time to health status deterioration, as defined by a four-point or more drop in FKSI-10 total score, was significantly greater than placebo. Those who had received sorafenib scored significantly better on the following items of the FKSI-15 index: coughing; fever; worry about their disease; ability to enjoy life. **Safety**: associated with more AEs than	**OS**: An increase compared to placebo not established (second-line); median OS was not reached in the sorafenib group before patients receiving placebo were allowed to switch to sorafenib on the basis of "encouraging" progression-free survival results **QoL**: After 24 weeks of treatment, an improvement was observed: in the FKSI-10 score (44% in sorafenib versus 22% in placebo); in the FACT-G score (47% in sorafenib versus 21% in placebo). According to the results of clinical trials sorafenib is expected, in theory, to have a moderate effect on morbidity, mortality and quality of life. **Safety**: No Committee evaluation provided to describe comparative differences in safety	**OS**: No statistically significant difference was observed compared to BSC, though Committee noted the influence that patient crossover had on the ability of the submission to demonstrate efficacy in terms of OS; Committee agreed that trial data suggested increase in progression-free survival as second-line treatment but "considered that the clinical importance of this gain had not been demonstrated…as a surrogate to predict future survival gain" **QoL**: NA **Safety**: PBAC noted that sorafenib is associated with a variety of AEs including dermatologic and gastrointestinal events, hypertension, sensory neuropathy, and neutropenia. Additionally, a six-fold increase in cardiac ischaemia/infarction was found in Trial 11213 for sorafenib treated patients compared to placebo. Diarrhoea, rash, fatigue, hand-foot syndrome, alopecia and nausea were reported in >20% patients

		BSC, particularly hand–foot skin reactions and hypertension. A significantly greater number of people reported 'bothersome side effects of treatment' than those receiving placebo. Skin rashes, hypertension, diarrhoea and hand–foot syndrome were more common in the sorafenib arm.		
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain uncertain)	None established	None established
QoL change	+	+	+	NA
Safety change	-	-	NA	-

sunitinib	FDA primary indication		
ATC code: L01XE04	Indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. Aso indicated for the treatment of advanced renal cell carcinoma. Approval for advanced renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of sunitinib demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.		
Orphan Status: EU			
Licensure: FDA/EMA			
Target: Renal			
Agency	NICE	HAS	PBAC
Appraisal date	Sept-09 (GIST) Mar-09 (RCC)	Sept-06 (GIST) May-07 (RCC)	Jul-09 (GIST) Jul-08 (RCC)
Comparator	BSC (GIST) / interferon-alfa (RCC)	BSC (GIST) / interferon-alfa (RCC)	BSC
Modelled/indirect comparison	Yes	No	Yes
Basis for classification	**OS**: More than 3-month increase compared to BSC as GIST treatment (7.8 months based on RPSFT model); more than 3-month increase compared to interferon-alfa as first-line RCC treatment (10 months according to model based on "Committee's preferred assumptions")	**OS**: An increase compared to placebo not established in GIST treatment given that median OS was not reached in both treatment arms; increase not established compared to interferon-alfa in first-line RCC treatment as median OS was not reached in either treatment arm before patients receiving	**OS**: Committee considered that the magnitude of increase compared to BSC for treatment of GIST was "uncertain", noting that the 7.8-month survival benefit estimated by the RPSFT model "may be an overestimate"; no statistically significant difference was observed compared to interferon-alfa for

		QoL: More than 75% of people completed the EQ-5D questionnaire at each time point and there were no statistically significant differences reported. For RCC, overall results for HRQoL (total score and all subscales) were significantly better in the sunitinib arm compared with the IFN-α arm. **Safety**: For GIST, treatment-related AEs and serious AEs were more common in the sunitinib arm (83%) than in the placebo arm (59%). For RCC, the frequency of adverse events associated with sunitinib is comparable to that associated with IFN-α monotherapy. A total of 8% of participants receiving sunitinib discontinued treatment because of adverse events compared with 13% in the IFN-α arm.	interferon-alfa were allowed to cross over to sunitinib based on progression-free survival results **QoL**: For GIST, NA. For RCC, a moderate theoretical impact may be expected of sunitinib in terms of reducing morbidity and improving quality of life in comparison to interferon alpha, as a first-line treatment. Statistically and clinically significant improvement in QoL, analysed through 3 FACT-G, FKSI and EQ-5D questionnaires, was observed in the sunitinib group compared to the interferon alpha group **Safety**: For GIST, no regulatory judgment is given on the comparative differences in safety across groups. For RCC, Grade III AEs were more frequent in the sunitinib group compared to IFN-α arm	treatment of RCC was observed, though Committee "acknowledged that because patients that progressed were allowed to cross-over this would bias later overall survival analyses towards the null, thereby underestimating the likely true difference between the therapies" **QoL**: NA **Safety**: For GIST, sunitinib is described as inferior in terms of comparative safety over placebo. For RCC, the PBAC noted the increase in AEs with sunitinib over BSC/placebo. Of particular concern to the PBAC was more recent evidence of cardiac side effects of ischemia and heart failure
Effects	Merged data			
OS increase	7.8 months (GIST); 10 months (RCC)	≥ 3 months	None established	Uncertain
QoL change	+	No Difference (GIST); + (RCC) = +	NA (GIST); + (RCC) = +	NA (GIST); NA (RCC) = NA
Safety change	-	– (GIST); No Difference (RCC) = −	NA (GIST); − (RCC) = −	− (GIST); − (RCC) = −

tegafur/gimeracil/oteracil	FDA primary indication		
ATC code: L01BC53	Indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.		
Orphan Status: EU (w)			
Licensure: EMA			
Target: GI			
Agency	NICE	HAS	PBAC

Appraisal date		NA	Oct-12	NA
Comparator		NA	fluorouracil (5-FU) / cisplatin	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: There was very little difference in median OS (primary endpoint) between the two groups: 8.6 months in the TEYSUNO group vs 7.9 months in the 5-FU group (HR = 0.92, 95% CI: [0.80; 1.05]). The median overall survival (primary endpoint) was similar across the two groups. As this was a superiority study, the primary objective was not achieved **QoL**: the overall FACT-Ga score, which evaluates quality of life, was also similar between the two groups. Available data do not show ... the improvement in quality of life **Safety**: Similar overall incidence of AEs of any grade across both groups. Treatment stopped due to AE in 10.7% of treated patients vs 14.4% of comparator patients. Incidence profile for AEs were different between groups, with treatment producing greater number of AEs in some cases, and comparator producing greater number of AEs in other cases. However, the primary superiority objective was not achieved (OS) … the results for the secondary endpoints, including safety, were of an exploratory nature and did not allow any conclusions to be drawn”	NA
Effects	Merged data			
OS increase	None established	NA	None established	NA

QoL change	None established	NA	No difference	NA
Safety change	None established	NA	No difference	NA

temsirolimus	FDA primary indication		
ATC code: L01XE09	A kinase inhibitor indicated for the treatment of advanced renal cell carcinoma.		
Orphan Status: US/EU			
Licensure: FDA/EMA			
Target: Renal			
Agency	NICE	HAS	PBAC
Appraisal date	Aug-09	Feb-08	Jul-08
Comparator	interferon-alfa	interferon-alfa	BSC
Modelled/indirect comparison	No	No	Yes
Basis for classification	**OS**: 3.6-month increase in median OS **QoL**: Participants receiving temsirolimus had a significantly longer time in both TWiST and Q-TWiST health states compared with participants receiving IFN-α alone **Safety**: The frequency of treatment-related toxic events associated with bevacizumab plus IFN-α, sunitinib and temsirolimus appears to be comparable or slightly better than IFN-α, based on the data reported in these trials	**OS**: 3.6-month increase in median OS **QoL**: The available data are too limited for an evaluation of the product's impact on quality of life **Safety**: Grades 3–4 adverse effects were more common in the interferon alpha arm	**OS**: Committee considered "there was uncertainty about the magnitude of the treatment effect of temsirolimus compared with BSC" (based on indirect comparison); Committee was aware of the 3.6-month increase in median OS compared to IFN-α but did not consider IFN-α to be an appropriate comparator **QoL**: PBAC considered that there was uncertainty regarding the effect of temsirolimus on QoL, as the two trials in the submission used different QoL instruments **Safety**: PBAC noted that AEs occurred at a significantly greater frequency in temsirolimus-treated patients compared to IFN-α patients and concluded that the profile of side effects for was different to I IFN-α, rather than that temsirolimus

				was better tolerated than IFN-α. However, PBAC considered that the submission did not consider the relative harms in comparison with BSC, including their impact on incremental QALYs and cost-effectiveness
Effects	Merged data			
OS increase	3.6 months	≥ 3 months	≥ 3 months	Uncertain
QoL change	+	+	NA	NA
Safety change	+	+	+	NA

tositumomab		FDA primary indication		
ATC code: V10XA53		Tositumomab and Iodine-131. Tositumomab is indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.		
Orphan Status: US/EU (w)				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA

trabectedin	EMA primary indication
ATC code: L01CX01	Indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.
Orphan Status: –	

Licensure: EMA			
Target: Soft Tissue			
Agency	NICE	HAS	PBAC
Appraisal date	Feb-2010	Apr-2008	
Comparator	BSC	non-comparative	NA
Modelled/indirect comparison	Yes	No	NA
Basis for classification	**OS**: Median OS was 13.9 months (95% CI 12.5 to 18.6). The Committee concluded that the use of historical controls (BSC) was appropriate. The manufacturer reported increased median OS over historical control patients treated with ifosfamide 6.6 months (95% CI 5.0 to 9.0), dacarbazine 6.6 months (95% CI 4.3 to 8.4) and etoposide 6.3 months (95% CI 4.4 to 8.9). Although the Committee "considered the clinical effectiveness data presented by the manufacturer, and noted the median OS for patients randomised to the licensed dosage of trabectedin exceeded that for patients receiving BSC", it does not indicate specify the exact gain in OS **QoL**: No comparative HRQoL data presented **Safety**: The Committee heard from the clinical specialist and patient experts that there were fewer, less severe and less frequent AEs than with the other agents. It understood that the AEs associated with trabectedin were manageable, but nevertheless important, as with other chemotherapy agents used to treat soft tissue sarcoma.	**OS**: There was no difference between the two groups with regard to median overall survival time: 13.9 months in the group receiving treatment once every three weeks versus 10.8 months in the group receiving treatment every week **QoL**: No comparative evidence provided **Safety**: No comparative evidence provided	NA

Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain over uncertain)	None established	NA
QoL change	No difference	No difference	NA	NA
Safety change	+	+	NA	NA

trametinib	FDA primary indication		
ATC code: L01XE25	A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: Skin			
Agency	NICE	HAS	PBAC
Appraisal date	NA	NA	Nov-14
Comparator	NA	NA	dabrafenib
Modelled/indirect comparison	NA	NA	No
Basis for classification	NA	NA	**OS**: PBAC was satisfied that trametinib + dabrafenib, is more effective than dabrafenib alone, however the size of the incremental treatment effect is still uncertain, particularly for OS **QoL**: Report recalls consumer comments remarking on some benefits, including ability to return to work **Safety**: PBAC considered that the revised claim of different, but no worse comparative safety of trametinib + dabrafenib to dabrafenib monotherapy was reasonable, noting a decrease in rate of cutaneous hyperproliferative events and photosensitivity, but increase in rate of pyrexia and ejection fraction decrease

Effects	Merged data			
OS increase	Exact magnitude uncertain	NA	NA	Uncertain
QoL change	+	NA	NA	+
Safety change	None established	NA	NA	No difference

vandetanib	FDA primary indication		
ATC code: L01XE12	A kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.		
Orphan Status: US / EU (w)			
Licensure: FDA / EMA			
Target: Thyroid			
Agency	NICE	HAS	PBAC
Appraisal date	NA	Jun-12	NA
Comparator	NA	Placebo	NA
Modelled/indirect comparison	NA	No	NA
Basis for classification	NA	**OS**: Did not differ between the two groups during the analysis of the progression-free survival **QoL**: Impact is not measurable **Safety**: The Committee indicated that during the double-blind treatment period, treatment was stopped due to adverse events for 12% of patients in the vandetanib arm and 3% of patients in the placebo arm. Grades ≥ 3 events involved 55% of patients in the vandetanib group and 24% of patients in the placebo group. However, the Committee did not provide an overall assessment of comparative changes in drug-related safety	NA

Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	NA	NA
Safety change	None established	NA	NA	NA

vemurafenib	FDA primary indication		
ATC code: L01XE15 Orphan Status: – Licensure: FDA/EMA Target: Skin	A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.		
Agency	NICE	HAS	PBAC
Appraisal date	Dec-12	Oct-12	Mar-13
Comparator	dacarbazine	dacarbazine	dacarbazine
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: 3.3-month increase in median OS; Committee "agreed it that it was appropriate to adjust the OS results…to control for switching using statistical modelling or other techniques" but "agreed that any estimate obtained using these techniques would be subject to uncertainty" **QoL**: The Committee agreed with the manufacturer's assumption of a higher utility value for progression-free survival, given its improved clinical profile, including oral administration compared with intravenous administration for dacarbazine **Safety**: Treatment-related AEs were	**OS**: 3.6-month increase in median OS compared to dacarbazine (based on follow-up OS analysis not scheduled in protocol); 1.5-month increase in median OS compared to dacarbazine (based on OS analysis scheduled in protocol) **QoL**: Although HAS indicates that a negative impact on quality of life cannot be ruled out, particularly in view of the safety problems encountered, there is no indication that it believes that worsened QoL is most likely outcome. The statement that worsened QoL can occur does not provide definitive proof one way or the other	**OS**: 3.3-month increase in median OS compared to dacarbazine (without censoring at crossover); 3.9-month increase in median OS compared to dacarbazine (with censoring at crossover); Committee considered “the true estimate" of OS gain would lie between those two points **QoL**: NA **Safety**: The PBAC concluded that vemurafenib and DTIC have different toxicity profiles, with vemurafenib being associated with manageable toxicity. PBAC also noted that dabrafenib has a preferable toxicity profile as evidenced by fewer and less extensive dose

		recorded for more people who received vemurafenib, may be explained by the fact that they stayed on treatment longer than those on dacarbazine	**Safety**: Safety data is limited due to the short follow-up period, especially in the pivotal study	intensity reductions and by favourable differences in rates for AEs such as photosensitivity, cutaneous squamous cell carcinoma – but not pyrex
Effects	Merged data			
OS increase	3.3–3.9 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	+	+	NA	NA
Safety change	-	-	NA	NA (dacarbazine); − (dabrafenib) = −

vinflunine	EMA primary indication		
ATC code: L01CA05	Indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.		
Orphan Status: –			
Licensure: EMA			
Target: Bladder			
Agency	NICE	HAS	PBAC
Appraisal date	Jan-2013	Dec-2009	Nov-2011
Comparator	BSC	BSC	BSC
Modelled/indirect comparison	No	No	No
Basis for classification	**OS:** The Committee noted that the difference between the study arms was not statistically significant for the ITT population, but was significant for the eligible ITT population ... It considered that the results from the ITT population were the most appropriate basis for its deliberations because randomisation had not been broken. It concluded that the extent of clinical effectiveness of vinflunine compared with BSC had not been conclusively demonstrated because of the uncertainty of the overall survival results	**OS**: The study objective was not reached in the ITT population: median overall survival was 6.9 months (95% CI [5.7 – 8.0 months]) in the JAVLOR arm versus 4.6 months (95% CI [4.1 – 7.0 months]) in the comparator arm (RR= 0.88; 95% CI [0.69 – 1.12], NS). Two other types of analyses (multivariate, eligible ITT) discussed, but focus given on describing results for ITT population **QoL**: There was no difference in the quality of life assessment and clinical benefit between the two [study] arms.	**OS:** The PBAC noted that the increment is uncertain and, at best, is between 2.3 (ITT) and 2.6 months (eligible ITT) … the selection of the eligible ITT population was considered highly uncertain … The PBAC agreed that the ITT population should be used in considering the effectiveness of vinflunine. The PBAC accepted that vinflunine may be superior in terms of comparative efficacy over BSC although the magnitude of the overall survival gain is uncertain (less than 3 months) **QoL:** No comparative data presented

		QoL: There were no statistically significant differences in overall EORTC QLQ-C30 global health status score between the two arms (p=0.658). [The Committee] noted that there were no significant differences in HRQoL between patients receiving vinflunine and those receiving BSC alone **Safety**: Grade 3 or 4 toxicities relating to neutropenia, anaemia and constipation occurred in 50%, 19% and 16% respectively of patients in the vinflunine arm of study 302, compared with 1%, 8% and 1% of patients respectively in the best supportive care arm. Febrile neutropenia occurred in 6% of patients receiving vinflunine (none in the best supportive care arm). The Committee concluded that there were concerns about the tolerability of vinflunine	**Safety**: Treatment discontinuations more likely in the vinflunine arm compared with BSC alone arm. Grade 3-4 neutropenia and anaemia was higher in treatment arm. Higher incidence of non-haematological AEs reported in treatment arm.	**Safety:** AEs significantly more frequent in treatment arm included abdominal pain, constipation, diarrhea, nausea, stomatitis, vomiting, among others. Grade III/IV AEs experienced more frequently included abdominal pain, constipation, nausea, vomiting, fatigue, among others. One death directly related to vinflunine, though 6% in vinflunine and 1% in BSC died within 30 days of final dose. PBAC noted that rates of AEs were higher in the treatment arm than in the BSC alone arm, and that the pattern of AE and serious AEs suggested very high levels of toxicity.
Effects	Merged data			
OS increase	Exact magnitude uncertain	None established	None established	Uncertain
QoL change	None established	No difference	No difference	NA
Safety change	-	-	-	-

vismodegib	FDA primary indication		
ATC code: L01XX43	A hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: Skin			
Agency	NICE	HAS	PBAC
Appraisal date	NA	Dec-13	NA

Comparator		NA	non-comparative	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: In light of the available clinical trial data in a non-comparative phase II study, an impact in terms of morbidity is not expected. In the efficacy trial (ERIVANCE), median OS was deemed not evaluable in the mBCC or laBCC cohorts **QoL**: In light of the available clinical trial data, an impact in terms of morbidity or QoL is not expected **Safety**: No comparative data presented	NA
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	None established	NA	NA	NA

vorinostat	FDA primary indication		
ATC code: L01XX38	A histone deacetylase (HDAC) inhibitor indicated for: treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.		
Orphan Status: US			
Licensure: FDA/EMA			
Target: Hematological			
Agency	NICE	HAS	PBAC
Appraisal date	NA	NA	Mar-11
Comparator	NA	NA	BSC
Modelled/indirect comparison	NA	NA	No
Basis for classification	NA	NA	**OS**: No survival data are available from

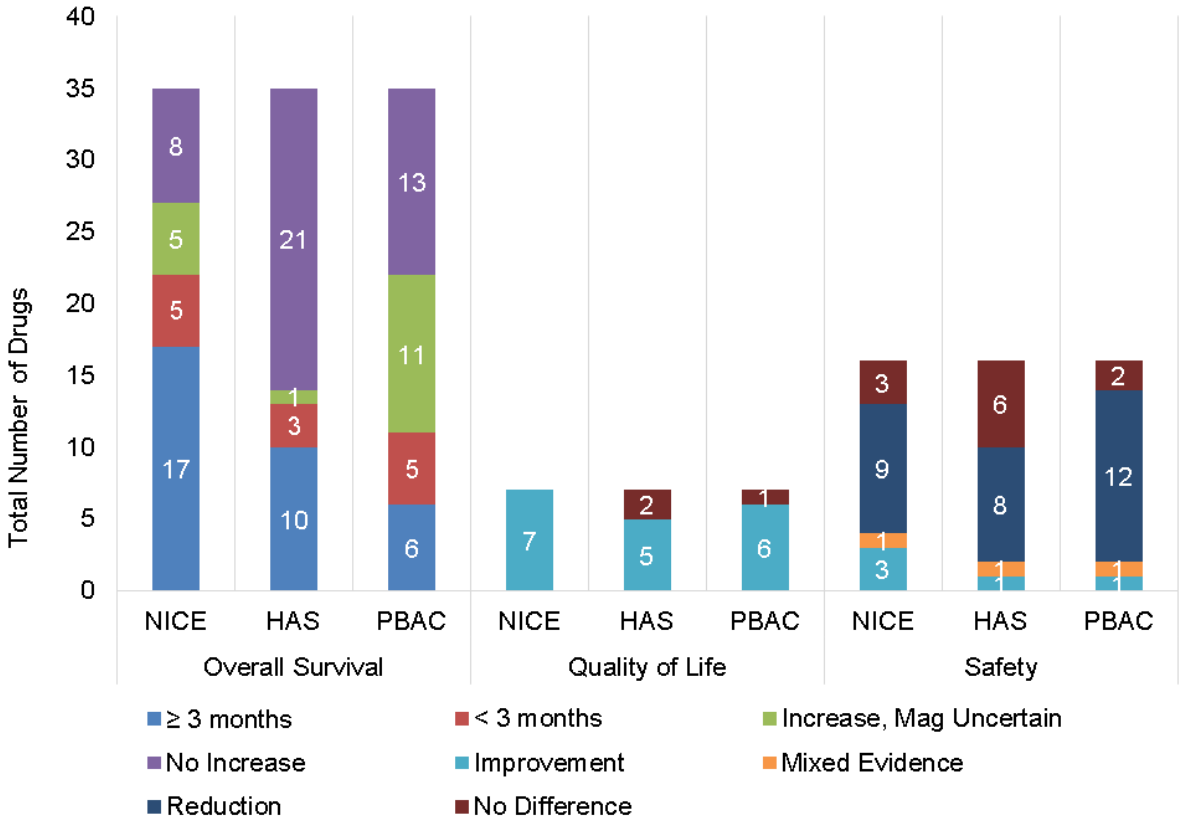
				study P001 or from the non-comparative chemotherapy studies. Quality of data is extremely limited. Vorinostat has superior efficacy to palliative care, however, no conclusion can be reach with respect to other available therapies **QoL**: NA **Safety**: The PBAC agreed that vorinostat has significant toxicities, and is inferior in safety to palliative care. However, expert testimony suggests it is less toxic than cytotoxic chemotherapies
Effects	Merged data			
OS increase	None established	NA	NA	None established
QoL change	None established	NA	NA	NA
Safety change	+/-	NA	NA	– (placebo); + (chemotherapy) = +/−

ziv-aflibercept	FDA primary indication		
ATC code: L01XX44 Orphan Status: – Licensure: FDA/EMA Target: GI	In combination with 5-fluorouracil, leucovorin, irinotecan- (FOLFIRI) indicated for metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.		
Agency	NICE	HAS	PBAC
Appraisal date	Mar-14	Jul-13	Jul-13
Comparator	placebo	placebo	placebo
Modelled/indirect comparison	Yes	No	No
Basis for classification	**OS**: 1.4-month increase in median OS. The Committee was not satisfied that estimates produced by the model were sufficiently robust to accept that the 3-	**OS**: 1.4-month increase in median OS **QoL**: The expected additional impact of this medicinal product in terms of	**OS**: 1.4-month increase in median OS compared to placebo for the K-RAS mutant patient population. The PBAC considered this survival gain to be

		month life extension criterion is fulfilled **QoL**: Although the Committee, echoing comments from a patient expert, would have liked the manufacturer to have collected trial data on HRQoL, the Committee noted that patients consider therapies such as ziv-aflibercept to improve QoL compared with chemotherapy **Safety**: The Committee concluded that treatment with aflibercept + ziv-aflibercept was associated with a considerable burden of AEs, but that, being a new treatment, less is known about its AE profile than for other available treatments.	morbidity and mortality and QoL can only be very small **Safety**: Comparing ziv-aflibercept arm to placebo arm, frequency of treatment discontinuations due to AEs was greater	modest and the clinical relevance and importance to be doubtful **QoL**: NA **Safety**: PBAC considered the claim that ziv-aflibercept is non-inferior in terms of comparative safety over cetuximab to not be a reasonable assumption, considering treatment to be potentially worse in comparative harms
Effects	Merged data			
OS increase	1.4 months	< 3 months	< 3 months	< 3 months
QoL change	+	+	No difference	NA
Safety change	-	-	-	-

Source: Authors' analysis of data from sources identified in the "Methods" section
Notes: '+' denotes improvement; '−' denotes reduction; '+/−' denotes mixed evidence. Orphan drug status obtained from Orphanet for the US and EU, with withdrawn, (w).

eFigure 1. Number of cancer drugs that were evaluated by all three HTA agencies, sorted by magnitude of clinical benefits



Source: Authors' analysis of data from sources identified in the "Methods" section

Notes: Number of cancer drugs assigned to each level of clinical benefit by each HTA agency. To compare regulatory practices across each clinical benefit, the cancer drug sample was restricted to those drugs that were evaluated for that clinical benefit by all three HTA agencies. For the purposes of comparison, drugs deemed to increase OS by some unquantifiable increase of greater than or equal to 3 months were here grouped with drugs that were associated with a quantifiable increase of greater than or equal to 3 months.

eTable 3. Interagency agreement – Krippendorff's alpha coefficients

Rater	Overall Survival		Quality of Life		Safety	
	Entire sample	! = ≥3 months	Entire sample	! = Improvement	Entire sample	! = Improvement
Ordinal						
NICE + HAS + PBAC	0.380235	0.632742	0.608365	0	0.230789	-0.143208
NICE + HAS	0.316244	0.525054	0.608365	0	0.592507	0.127778
NICE + PBAC	0.233290	0.775789	-0.055263	–	-0.033927	-0.439335
HAS + PBAC	0.618591	0.560272	0.547619	1	-0.046384	0.081633
Nominal						
NICE + HAS + PBAC	0.354930	0.475309	0.535817	0	0.285894	0.126514
NICE + HAS	0.319274	0.412811	0.549839	0	0.508850	0.396648
NICE + PBAC	0.343593	0.618462	-0.027027	–	0.205556	0.080808
HAS + PBAC	0.403390	0.354115	0.547619	1	0.174041	0.080808
Units	*186*	*117*	*186*	*117*	*186*	*147*

Source: Authors' analysis of data from sources identified in the "Methods" section

Notes: Krippendorff's alpha coefficients were used to measure interagency agreement on the level of clinical benefit assessed by each agency. Krippendorff's alpha coefficients were measured for different agency pairings (left) and for either the entire sample ("Entire Sample") or for drugs that were not associated with an increase in overall survival of greater than or equal to 3 months ("!= ≥ 3 months") or with an improvement in quality of life or safety ("!= Improvement"). Given the inherent order in the clinical benefit classifications used (OS: ≥3 months, <3 months, increase but magnitude uncertain, no increase; QoL, safety: improvement, mixed evidence, reduction, no difference), base case Krippendorff's alpha coefficient were calculated by modeling clinical benefit data as an ordinal variable (top). To test for robustness, sensitivity analyses modelled the data as a nominal variable (bottom). For the purposes of comparison, drugs deemed to increase OS by some unquantifiable increase of greater than or equal to 3 months were here grouped with drugs that were associated with a quantifiable increase of greater than or equal to 3 months.

eMethods

Drug inclusion/exclusion criteria

Drugs that did not directly treat cancer, or which were intended to manage symptoms, pain, or the side effects of active treatment, were excluded. Oncology drugs approved by the US Food and Drug Administration (FDA) between 2003-2010 were obtained the FDA's Drugs@FDA registry[1] and from Roberts and colleagues,[2] with two exclusions: plerixafor, on the grounds it does not directly treat cancer and palifermin, on the grounds that it is primarily intended to manage side effects. Drugs approved between 2011-2013 were obtained by reviewing all novel FDA drug approvals for 2011,[3] 2012,[4] and 2013,[5] and applying inclusion/exclusion criteria. FDA recommended indications were obtained through the Drugs@FDA registry. Initial approvals for medicines with a primary oncology indication were also obtained from the European Medicines Agency's (EMA) European public assessment reports search engine.[6] The above criteria were used to identify new cancer medicines that were authorized by the EMA between 2003-2013.

Drug appraisals

Several issues made it difficult to systematically evaluate the comparative clinical benefits of new cancer medicines on the basis of FDA drug reviews (available within the Drugs@FDA registry). First, the FDA's mandate is limited to examining whether new drugs are able to demonstrate efficacy and safety—it is not required to evaluate comparative therapeutic benefits, though it may do so under certain circumstances.[7] Second, the FDA's medical and statistical reviews are also inconsistently structured, and are often disseminated with non-rendered text, making it difficult to systematically extract agency conclusions regarding the clinical benefits from drug treatment. Finally, early phase clinical trials often seek to "evaluate safety and identify evidence of biological drug activity, such as tumor shrinkage", while later phase, confirmatory efficacy studies instead seek to "evaluate whether a drug provides a clinical benefit such as prolongation of survival or an improvement in symptoms."[8] Particularly in the case of medicines that are indicated of treatment of severe conditions with high medical need, such as cancer, FDA statistical and medical reviews may therefore only inconsistently contain an evaluation of drug-related clinical benefits that is based on late phase clinical trial evidence. At the same time, high failure rates of Phase III clinical trials in oncology may indicate that Phase II clinical trials alone—often used in

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[1] US Food and Drug Administration. "Drugs@FDA: FDA Approved Drug Products." 2015. Available from: https://www.accessdata.fda.gov/scripts/cder/drugsatfda/

[2] Roberts SA, Allen JD, Sigal E V. "Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe." Health Aff. 2011 Jul;30(7):1375–81.

[3] US Food and Drug Administration. "Drug Innovation - Novel Drug Approvals for 2011." 2011. Center for Drug Evaluation and Research. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm285554.htm

[4] US Food and Drug Administration. "Drug Innovation - Novel Drug Approvals for 2012." 2012. Center for Drug Evaluation and Research. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm336115.htm

[5] US Food and Drug Administration. "Drug Innovation - Novel Drug Approvals for 2013." 2013. Center for Drug Evaluation and Research. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm381263.htm

[6] European Medicines Agency. "European public assessment reports." Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=

[7] Temple R. "A regulator's view of comparative effectiveness research." Clin Trials. 2012;9(1):56-65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21975523

[8] Food and Drug Administration. "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics." 2007. Rockville, MD. Available from: http://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

accelerated approvals—may be insufficiently informative on the effectiveness of new medicines in real-world settings.[9]

In the absence of publicly available observational data, this analysis attempted to overcome these challenges by analyzing evaluations of clinical impact from cancer drug treatment from three health technology appraisal (HTA) agencies in England (National Institute for Health and Care Excellence, NICE), France (*Haute Autorité de Santé*, HAS) and Australia (Pharmaceutical Benefits Advisory Committee, PBAC), published through May 2015. These organizations are required to synthesize the scientific evidence to evaluate the clinical benefits of new medicines in relation to existing clinical standards that are used for the same indication,[10,11,12] and this information is often used to then help regulate drug coverage, pricing, and reimbursement. Since new drug molecules are often first approved in the United States,[2] confirmatory clinical trials are more likely to be incorporated into the reviews on clinical effectiveness from HTA agencies. Furthermore, these agencies operate within countries that are similar to the United States in terms of social and economic development, and they regularly publish comprehensive, and consistently structured, HTA reports in English. Though limited, the comparative evidence that exists appears to suggest that clinical practice guidelines for cancer treatment often coincide across developed healthcare settings.[13,14,15] And though cancer drug molecules typically become available for use in the US first, they also often gain licensure in other settings.[16] Where a HAS appraisal could not be found using the agency website's native search engine, an additional search was performed for HAS reports using a general online search engine (Google) that included the drug's active ingredient and "HAS Santé" (e.g. "Bortezomib HAS Santé"). In the few cases where French technological appraisals were not available in English, the documents were translated into English. Discussions of drug costs were not considered. Orphan drug status in the US and EU was obtained for each FDA-approved cancer drug indication from www.orpha.net. If the FDA or EMA approved two indications in its first evaluation of a new cancer drug (e.g. sunitinib), appraisals for both primary indications were extracted.

To examine the clinical benefits from recently licensed cancer medicines, two researchers independently used the patient, intervention, comparator, outcomes framework to review technological appraisals that assessed their comparative clinical efficacy. This framework is often used in medical and health services

[9] Sharma MR, Stadler WM, Ratain MJ. "Randomized phase II trials: a long-term investment with promising returns." J Natl Cancer Inst. 2011;103(14):1093–100. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3139588&tool=pmcentrez&rendertype=abstract

[10] National Institute for Health and Care Excellence. "NICE technology appraisal guidance." 2016. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance

[11] Haute Autorité de Santé. "Medical device assessment in France: Guidebook." 2009. Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/guide_dm_gb_050310.pdf

[12] Pharmaceutical Benefits Advisory Committee. "About the Guidelines." 2014. Available from: https://pbac.pbs.gov.au/information/about-the-guidelines.html

[13] Fong ZV, Tanabe KK. "The clinical management of hepatocellular carcinoma in the United States, Europe, and Asia: a comprehensive and evidence-based comparison and review." Cancer. 2004;120(18):2824–38. http://doi.org/10.1002/cncr.28730

[14] Hogeveen SE, Han D, Trudeau-Tavara S, Buck J, Brezden-Masley CB, Quan ML, Simmons CE. "Comparison of international breast cancer guidelines: are we globally consistent? cancer guideline AGREEment." Current Oncology. 2012;19(3):e184–90. http://doi.org/10.3747/co.19.930

[15] Wolters R, Regierer AC, Schwentner L, Geyer V, Possinger K, Kreienberg R, … Wöckel A. (2012). "A comparison of international breast cancer guidelines - do the national guidelines differ in treatment recommendations?" European Journal of Cancer. 2012;48(1):1–11. http://doi.org/10.1016/j.ejca.2011.06.020

[16] Roberts SA, Allen JD, Sigal EV. (2011). "Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the United States than in Europe." Health Affairs (Project Hope). 2011;30(7):1375–81. http://doi.org/10.1377/hlthaff.2011.0231

research as a structured approach to evaluate the clinical benefits from new interventions.[17] Information on recommended patient populations (treatment indications, usage restrictions), novel interventions [anatomical therapeutic chemical (ATC) code, orphan status, therapeutic target] and therapeutic comparators were obtained from each drug appraisal. HTA agency conclusions pertaining to the overall survival (OS), quality of life (QoL), and safety benefits from treatment were also extracted. Methodological details pertaining to specific outcomes are discussed below. The data that was extracted is summarized in eTable 1.

Overall survival

Both reviewers identified and extracted median or mean overall survival estimates for the first approved indication of each newly licensed cancer drug. These were typically obtained from appraisal summary or conclusion sections, and were characterized by explicit value judgments of the supporting evidence, acknowledgement of the significance of clinical trial results, or referral to prior evaluations of the primary evidence. OS benefits that were given as a continuous variable were also coded as a categorical variable. For this, HTA documents, particularly those from NICE, frequently distinguish between OS gains of ≥ or <3 months over best alternative treatments.[18] This rating system can be used to measure the likelihood of benefit from treatment: England's HTA agency may take survival benefits of at least three months as "sufficient evidence to indicate that the treatment offers an extension to life."[19] England also uses this threshold to identify OS improvements that are large enough to justify additional expense in end-of-life care,[20] and Australian authorities may use it to assess new health technologies.[21] Besides a known drug-related increase in OS of greater or less than 3 months, HTA agencies may conclude that drugs are associated with an unquantifiable increase in overall survival, or they may be unable to make any conclusion on drug-related survival benefits due to a lack or insufficiency of evidence.

Drugs were classified as producing an overall survival gain of ≥3 months if HTA agencies concluded that the drug was associated with a OS gain of ≥3 months (continuous variable), or if one-sided directional or range estimates fell within this space. Other possible categories of overall survival benefits included: known gains in OS of <3 months; an increase in survival, but of unknown magnitude; and no demonstrated increase in overall survival. After independent analysis, both researchers compared results and sought consensus if there was any disagreement in the extracted parameters. Inputs from a third researcher were sought where consensus could not be reached. Krippendorff's alpha coefficient (α) were used to assess interagency agreement in this categorical variable reflecting HTA agency conclusions of overall survival benefits. This statistic should be interpreted as the percentage of the data that are coded to a degree better than chance.[22] Krippendorff's alpha coefficients were calculated by modelling OS benefits as an ordinal variable. To check for robustness, sensitivity analyses also modelled OS benefits

[17] National Institute for Health and Care Excellence. "Developing review questions and planning the systematic review." In: The guidelines manual. Process and methods [PMG6]; 2012. Available from: https://www.nice.org.uk/article/pmg6/chapter/4-Developing-review-questions-and-planning-the-systematic-review

[18] National Institute for Health and Care Excellence. "Value based assessment of health technologies." 2014. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/VBA-TA-Methods-Guide-for-Consultation.pdf

[19] National Institute for Health and Care Excellence. "Guide to the methods of technology appraisal 2013." 2013. Available from: https://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf.

[20] National Institute for Health and Care Excellence. "Appraising life-extending, end of life treatments." 2009. Available from: https://www.nice.org.uk/guidance/gid-tag387/resources/appraising-life-extending-end-of-life-treatments-paper2

[21] Pharmaceutical Benefits Advisory Committee. Vinflunine, Solution Concentration for I.V. Infusion, 50 Mg in 2 mL and 250 Mg in 10 mL (as Ditartrate), Javlor®.; 2011.

[22] Krippendorff K. Content Analysis: An Introduction to Its Methodology. 2004. Second Edit. SAGE Publications; p. 242.

as a nominal variable. Krippendorff's alpha coefficients were calculated using the krippalpha package in Stata 13 (College Station, TX: StataCorp LP).[23]

A composite classification of overall survival benefits was developed for each drug by combining HTA agency appraisals. To do this, a hierarchical process was followed: if only one HTA agency evaluated a given drug, its assessment of gains in overall survival was taken. If drug appraisals were available from multiple HTA agencies, the most positive estimate of drug-related survival benefit was taken to identify the clinical benefits that may be possible from treatment. If no difference in overall survival could be established by any of the three agencies, then we classified the drug as producing no measurable change in overall survival. This methodology was used even if HTA agencies evaluated new medicines against a different set of comparators: since English, French, and Australian HTA agencies are required to evaluate the clinical impact of new medicines in relation to existing standards of treatment that would most likely be replaced by the new intervention,[10,11,12] all comparator treatments were assumed to reflect possible courses of therapy for the given indication.

Treatment standards can also change over time, giving rise to multiple comparators that should be used to evaluate the comparative clinical effectiveness of new medicines. To calculate the total average increase in overall survival between 2003-2013, the following approach was taken: if cancer drugs were associated with a range of values for their overall survival benefit—representing a range in the maximum overall survival benefit that was accepted by English, French, and Australian HTA agencies—an average was taken. Investigators mapped new cancer drugs against the treatment comparators that they would replace, as identified by HTA appraisals (Figure 2). For this, it was necessary for primary treatment indications to be consistent across the new intervention and the mapped comparator. Drug-specific gains in OS were then summed across mapped comparators to calculate the total mean gain in OS over the past 10 years. The following are two examples of how this process was carried out: subsequent to its approval by the FDA in 2004 for the treatment of malignant pleural mesothelioma, pemetrexed was used by French and Australian HTA agencies to evaluate the clinical effectiveness of crizotinib (approved by the FDA in 2011 for locally advanced or metastatic non-small cell lung cancer, NSCLC). While these two drugs were compared against each other, the first FDA-approved indication for each of these medicines was not identical—the FDA eventually granted pemetrexed a licensing extension in 2006 so that it could be used for the same indication as crizotinib, but we did not consider non-primary indications in this study. Since pemetrexed and crizotinib therefore did not have an equivalent primary indication for use, their overall survival benefits were considered independently of each other. In contrast, erlotinib was approved by the FDA in 2004 for patients with locally advanced or metastatic non-small cell lung cancer and evaluated against placebo and BSC. Afatinib was approved by the FDA in 2013 for the same clinical indication, and its clinical efficacy was compared against that of erlotinib and gefitinib by HTA agencies. Since both afatinib and erlotinib/gefitinib were indicated for the same purpose, we compared the overall survival benefits associated with each medicine. Survival benefits associated with parallel treatment pathways (afatinib-erlotinib/gefitinib; ponatinib-nilotinib/dasatinib) were also considered independently of each other, as were those associated with drugs that had multiple primary indications for different populations (e.g. sunitinib). This exercise allowed us to map the gradual change of clinical standards over time, even as new drugs entered the market, and to estimate the total gain overall survival between 2003-2013 within and across treatment indications. Finally, gains in OS were averaged across all available treatments, and further stratified by therapeutic target groups (hematologicals, lung, GI, renal, breast, prostate, thyroid, skin, bladder, ascites, soft connective tissue).

Quality of life

Drug-related changes in QoL and toxicity were, generally, not quantified, but were instead evaluated qualitatively by HTA agencies. Preliminary analysis revealed that, where discussed, HTA agency conclusions regarding QoL could be classified into four categories: an overall improvement or reduction in QoL, mixed evidence, or no established difference relative to best alternative treatments. A detailed

[23] Staudt A, Krewel M. "krippalpha: Stata module to compute Krippendorff's alpha intercoder reliability coefficient." Available from: http://ideas.repec.org/c/boc/bocode/s457750.html

description of the QoL-related evidence that was generally considered by each HTA agency is given in the main text.

To classify the effect on QoL from each drug, two researchers independently highlighted and analyzed all relevant text within appraisal summary sections. If one evaluation found there to be an improvement in quality of life, but a second found no change, we marked the drug as producing a net improvement in patient quality of life. If there were two opposing conclusions—e.g. if quality of life improved for one primary indication, but worsened in another—then we marked the drug as producing mixed evidence. Given the potential implications for clinical practice, this approach allowed us to capture the full range of clinical benefits to patients that may be possible from use of new cancer drugs. After independent analysis, both researchers compared results and sought consensus where disagreement existed. Inputs from a third researcher were sought where consensus could not be reached. Krippendorff's alpha coefficient was used to assess interagency agreement in the magnitude of QoL benefits from new cancer drugs. For this, base case analyses took QoL benefits as an ordinal variable. Sensitivity analyses also modelled QoL benefits as a nominal variable.

As for overall survival, we developed a composite QoL score from all available HTA agency assessments to provide an unbiased, summary measure of the expected clinical benefits from treatment. To do this, a procedure similar to that described above for overall survival was followed: if one HTA agency indicated that it believed that treatment with the new medicine improved QoL, but another found no change, we classified the drug as producing a net positive gain in QoL. If opposing conclusions existed—e.g. if one agency indicated that the drug was associated with an improvement in QoL, but another concluded that the drug worsened QoL—we classified the drug as producing mixed evidence. If no difference in QoL was established in any of the three agencies due to a lack or insufficiency of evidence, then we classified the drug as associated with no established change in QoL.

Safety

Summaries of the overall effect on safety from drug treatment were also extracted from HTA appraisals and analyzed to identify HTA agency conclusions regarding drug-related safety benefits. We did not consider discussion of treatment effects on the incidence of individual types of adverse events, unless the HTA agency explicitly stated that these were of major interest to them. Instead, our evaluations were based on HTA agency summary conclusions on: treatment effect on incidence of all AEs, incidence of serious AEs, adverse drug reactions, treatment-related AEs, treatment discontinuations or required dose reductions due to AEs (Table 1). Both researchers compared results after independent analysis and sought consensus if there was disagreement. Inputs from a third researcher were sought where consensus could not be reached. Krippendorff's alpha coefficient was used to assess interagency agreement in the magnitude of safety benefits from cancer drug treatment. As before, base case analyses calculated Krippendorff's alpha by taking safety benefits as an ordinal variable. Sensitivity analyses also modelled these as a nominal variable.

A composite safety score was also developed to summarize drug therapeutic potential using the same procedure as that used to develop composite QoL scores.

Overall therapeutic benefits

To assess the overall clinical value to patients from newly developed cancer drugs, simple descriptive statistics were used to examine concomitant effects on OS, QoL, and safety from each drug in our sample. To calculate the percentage of all new cancer drugs that were associated with at least some evidence of overall survival, quality of life, or safety benefits, we considered the drugs that were associated with any evidence of improved OS (composite classification: ≥3 months, <3 months, or unquantifiable increase), QoL (composite classification: improvement, or mixed evidence), or safety (composite classification: improvement, or mixed evidence).

Limitations

Surrogate measures of efficacy were not considered in this analysis, as they are not regularly measured in drug appraisals[8] and their value to health remains unclear.[24] This approach reflects the FDA's position that surrogate efficacy markers are "thought to predict clinical benefit, but [are] not [themselves] a measure of clinical benefit".[25] Nevertheless, surrogate efficacy markers can inform clinical practice. Since they are not considered, this study has no bearing on the use of surrogate end points in clinical or regulatory practice. Improvements in efficacy were instead measured through overall survival, which is universally taken to indicate clinical benefit in oncology trials.[26,27,28] However, if surrogate markers do in fact represent unique dimensions to the benefit that is derived from treatment, then their absence would mean that our analysis is incomplete. *Surrogacy*, however, implies that their value to patient health is at least in part captured by the three outcome measures—overall survival, quality of life, and safety—that are considered.

To our knowledge, there is no large-scale patient-level registry on treatment and outcomes occurring prior to and following entry of new cancer drugs. In its absence, this study undertook a systematic process to review regulatory assessments and to examine the impact on therapy that would be expected from recent cancer drug innovations. Results from clinical trials may go unpublished, and primary clinical trial data is often not available for secondary analysis. HTA agencies, in contrast, may have the authority to require submission of all applicable clinical data,[29] in theory minimizing the level of bias in their assessment. By drawing on these, and in the absence of observational, patient-level data, our synthesis reflects what is arguably the best informed analysis of the clinical impact from new drug treatments, at least at time of drug evaluation. Still, trial-based regulatory assessments of clinical impact may not translate to the real-world. To more precisely measure the clinical risks and benefits from treatment, future studies should extend this analysis by also incorporating post-marketing studies,[30] or using observational data or pragmatic clinical trial evidence, as it becomes available. Future academic initiatives may be able to leverage data from the National Cancer Institute's upcoming National Cancer Knowledge System—a component of the US Precision Medicine Initiative® that will integrate genomic information with clinical response data and outcomes information—to assess the real-world clinical impact from newly developed cancer drugs and to inform value-based supply- and demand-side decisions.

[24] Davis S, Tappenden P, Cantrell A. "A review of studies examining the relationship between progression-free survival and overall survival in advanced or metastatic cancer." Available from: http://www.nicedsu.org.uk/PFSOS%20Report.FINAL.06.08.12.pdf

[25] US Food and Drug Administration. "Information for Healthcare Professionals (Drugs) - Accelerated Approval Program." Center for Drug Evaluation and Research; 2016. Available from: http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm313768.htm

[26] McCain JA. "The Ongoing Evolution of Endpoints in Oncology." Manag Care. 2010;19(5):Supplement 1.

[27] Han K, Ren M, Wick W, Abrey L, Das A, Jin J, et al. "Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials." Neuro Oncol. 2014 May;16(5):696–706.

[28] Beauchemin C, Johnston JB, Lapierre MÈ, Aissa F, Lachaine J. "Relationship between progression-free survival and overall survival in chronic lymphocytic leukemia: a literature-based analysis." Curr Oncol. 2015 Jun;22(3):e148–56.

[29] National Institute for Health and Care Excellence. "Guide to the processes of technology appraisal." 2014. Process and Methods PMG19. Available from: https://www.nice.org.uk/article/pmg19/chapter/3-the-appraisal-process

[30] Kim C, Prasad V. "Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals." JAMA Intern Med. 2015 Dec;175(12):1992–4.