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REVIEW

Do patient access schemes for high-cost cancer drugs deliver value to society?—lessons from the NHS Cancer Drugs Fund

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Background: The NHS Cancer Drugs Fund (CDF) was established in 2010 to reduce delays and improve access to cancer drugs, including those that had been previously appraised but not approved by NICE (National Institute for Health and Care Excellence). After 1.3 billion GBP expenditure, a UK parliamentary review in 2016 rationalized the CDF back into NICE.

Methods: This paper analyses the potential value delivered by the CDF according to six value criteria. This includes validated clinical benefits scales, cost-effectiveness criteria as defined by NICE and an assessment of real-world data. The analysis focuses on 29 cancer drugs approved for 47 indications that could be prescribed through the CDF in January 2015.

Results: Of the 47 CDF approved indications, only 18 (38%) reported a statistically significant OS benefit, with an overall median survival of 3.1 months (1.4–15.7 months). When assessed according to clinical benefit scales, only 23 (48%) and 9 (18%) of the 47 drug indications met ASCO and ESMO criteria, respectively. NICE had previously rejected 26 (55%) of the CDF approved indications because they did not meet cost-effectiveness thresholds. Four drugs—bevacizumab, cetuximab, everolimus and lapatinib—represented the bulk of CDF applications and were approved for a total of 18 separate indications. Thirteen of these indications were subsequently delisted by the CDF in January 2015 due to insufficient evidence for clinical benefit—data which were unchanged since their initial approval.

Conclusions: We conclude the CDF has not delivered meaningful value to patients or society. There is no empirical evidence to support a 'drug only' ring fenced cancer fund relative to concomitant investments in other cancer domains such as surgery and radiotherapy, or other noncancer medicines. Reimbursement decisions for all drugs and interventions within cancer care should be made through appropriate health technology appraisal processes.

Key words: cancer economics, health policy, clinical benefit scales, patient access schemes, health technology assessment

Introduction

The Cancer Drugs Fund (CDF) was established in 2010 by the UK government to provide patients with access to cancer drugs not available through the NHS, because the drugs had not been appraised, were in the process of being appraised, or had been appraised but not recommended by the National Institute of Health and Care Excellence (NICE). As well as reducing delays and improving access to cancer drugs within the NHS it also

offered an opportunity to provide funding for orphan indications or rare conditions that NICE would ordinarily not appraise [1].

The CDF had an initial budget of £50 million per annum with the plan to move towards a value-based pricing scheme by 2014. However, the costs of maintaining the fund rapidly increased, with the budget set at £200 million in 2013/2014, £280 million in 2014/2015, and £340 million in 2015/2016. At the time of its unification with NICE (see Figure 1), the CDF had cost of UK

- Following a three-month consultation between November 2015 and February 2016 the Cancer Drugs Fund (CDF) moved to a new operating procedure that resulted in it becoming closely aligned with NICE.
- Drugs available through the CDF that had been previously appraised by NICE and rejected, were no longer to be funded unless the manufacturers were able to provide new evidence or to change the terms of reimbursement to support its routine commissioning. As an example abiraterone, cabazitaxel and enzalutamide were all approved for the treatment of advanced prostate cancer from Feb 2016.
- In July 2016 the CDF became a managed access fund providing access to new cancer drugs for a time limited period (expected to be no more than 2 years) in circumstances where the clinical and cost effectiveness of the drug is deemed uncertain by NICE.
- The NICE appraisal process will now also start much earlier, publishing draft guidance prior to a drug receiving its marketing authorisation and then final guidance within 90 days of marketing authorisation. <https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf>

Figure 1. Current status of the CDF Nov 2016.

taxpayer a total of £1.27 billion [2], the equivalent of 1 year's total spend on all cancer drugs in the NHS [3].

Despite an extensive public consultation, fundamental issues about whether the CDF was a beneficial and fair public policy decision that actually delivered value have been absent from the discourse. Such analysis is essential to inform pharmaceutical policy in other countries contemplating such patient access pathways for high-cost cancer drugs.

Methods

In this policy analysis, we review the utility of such patient access funds for pharmaceutical agents by assessing the value delivered to both individuals and society by the CDF. Six value criteria have been used in our analysis. This includes an assessment of:

1. The index trial data that provided the evidence for the drugs' efficacy
2. Observational studies assessing the effectiveness of selected CDF approved drugs in 'real world' populations
3. The value of approved drugs according to validated clinical benefit scales developed by The American Society of Clinical Oncology (ASCO) and The European Society for Medical Oncology (ESMO)
4. Whether the drugs would meet cost-effectiveness thresholds set by NICE

5. The CDF committee's own review (in January and November 2015) of drugs they had approved
6. The value delivered by CDF-approved drugs to NHS patients based on utilization patterns

These criteria were chosen as they provide a multi-dimensional approach to assessing value in the absence of clinical data on outcomes for patients receiving drugs through the CDF. The first measures clinical efficacy based on the index clinical trial data, and the second, the translation of trial efficacy to a real world population in light of the socio-demographic make-up of trial participants. The third criteria goes beyond a simple evaluation of absolute study end-points to assess meaningful benefit according to value scales developed by two professional bodies, ASCO and ESMO.

The fourth looks at the issue of distributive justice by assessing cost-effectiveness according to health technology assessment frameworks, in this case NICE. The fifth criteria, represents an evaluation of the CDF committee's own audit of each of the approved drugs and indications using their own value framework undertaken in January and November 2015. The sixth and final criteria collates the evidence for value based on patterns of use of CDF drugs (dose, volume) where data is available and the likely benefits that have been derived when considering the index trial data.

We focus on the systemic therapies that were made available and could be prescribed through the CDF prior to the January 2015 update when the fund was first rationalized [4]. Up to this point, 29 drugs had been approved for 47 indications, three of which—bevacizumab (9), cetuximab (4), and everolimus (3)—had been approved for more than two indications.

Results

Did sufficient clinical evidence exist to suggest patients would benefit from CDF approved drugs?

On review of the index trial data for the 47 drug indications approved by the CDF [5–53], only 18 (38%) reported a statistically significant overall survival (OS) benefit (Table 1) [5–7, 9, 13, 14, 18, 20, 23, 26, 27, 38, 41, 44, 45, 47, 50, 51]. The median OS benefit was 3.2 months, ranging from 1.4 months (hazard ratio 0.82) for aflibercept in metastatic bowel cancer [6] to 15.7 months (HR 0.68) for pertuzumab in first line metastatic Her-2 positive breast cancer [44].

Of the remaining 29 indications in the CDF, 17 were approved despite no statistically significant OS benefit being observed in the index trials. These included axitinib [8] bevacizumab (five indications) [10–12, 16, 17], cabozantinib [19], cetuximab (two indications) [21, 22], everolimus (four indications) [29–32], lapatinib [35], panitumumab [36], pazopanib [39], and pemetrexed [42]. The primary end-point of 14 of these studies was PFS, of which five allowed cross-over of the control population at progression to the intervention arm [30–32, 35, 36] and one had significant post-study utilization (49.6%) of the intervention drug among the control arm [22].

12 further indications had been approved without OS data being available. The primary end-point in the index trial for eight

of these indications was PFS [15, 24, 25, 33, 36, 46, 48, 49, 52] of which five allowed cross-over of the control population at progression [24, 25, 46, 48, 52]. The other four indications were not able to report any PFS or OS benefit as they were based on noncomparator studies [40, 43, 53].

Given that over half of the drug indications ($n = 29$) approved by the CDF lacked any OS benefit, it is valid to ask whether a gain in PFS is a meaningful surrogate endpoint for OS. While we acknowledge this is a subject of much debate as there are differences of opinion as to what constitutes benefit, there is unanimity that prolongation of OS is an unequivocal benefit and desired [54–57]. From a patient's perspective, a gain in PFS may not equate to a clinical benefit given the serious toxicities that arise from many of these therapies, including those classified as 'targeted' and the fact that progression often occurs without any symptoms such that delaying progression is not delaying symptoms [58].

Furthermore, the extent to which benefits claimed in clinical trials are true can be debated. For end-points such as OS and PFS, it is expected that all patients randomized at the start of the study are followed up until either the end point is reached or the study is completed (intention-to-treat analysis). If a patient is censored prior to the end point being reached, their outcome is estimated based on other patients in the same arm who have not reached the end point, but have been under longer follow-up. This will result in an over-estimation of benefit if their reason for being censored is linked to their prognosis, i.e. toxicity, low participation in follow-up, or the initiation of an alternative therapy [59]. This type of censoring is more common in the assessment of PFS compared with OS where censoring predominantly occurs as a result of a death [60].

In PFS analyses, censoring is often driven by drug toxicity and the extent of censoring as regards PFS has been increasing in many trials (disproportionately so in the experimental arm) rendering the results questionable as to the true benefit observed [61, 62]. Several of the indications for drug funding on the CDF were based on trials in which excessive censoring was a feature [19, 28, 30]. For everolimus plus exemestane in breast cancer, the 4.4 months difference in OS was not significant although the PFS difference of 4.6 months was highly significant albeit in the setting of excessive censoring in the everolimus arm due to toxicity [28, 62].

Could the reported clinical trial benefits be realized in the 'real world'?

Randomized control trials (RCTs), have strong internal validity through randomization, pre-specified end points and blinding, however their external validity is limited [63]. This is because patients similar to those frequently encountered in a clinical practice are often excluded, raising questions as to the generalizability of clinical trial results to populations, settings or conditions not reflected in the trial [64, 65].

For example, the median age of study participants in the index trials of CDF approved drugs was 60 (Table 1). Over 90% of the study populations had an Eastern cooperative oncology group (ECOG) performance status score of 0 or 1 (or equivalent) in the majority of the trials. The under-representation of men and women

over 65 in RCTs is a long-standing issue [66, 67]. As a result, decision-makers are expressing interest in 'real world data' [68].

In metastatic renal cell carcinoma (mRCC), data from the 'real world' provide a sobering assessment of outcomes. The International Metastatic Renal Cell Carcinoma Database consortium study found that the 35% of patients that did not meet trial eligibility criteria had a disappointing 12.3 months survival compared with 28.4 months survival in those that would have been deemed trial-eligible [69]. A recent study that analysed the SEER 18 (Surveillance, Epidemiology and End Results) registry database to calculate the relative survival rates for advanced RCC patients during 2001–2005, 2006–2007 and 2008–2009 concluded there was no significant improvement in relative survival rates among patients with mRCC in the era of targeted agents [70].

Increased rates of toxicity are also observed in real world populations. A US SEER database study evaluated the effectiveness of adding bevacizumab to first-line combination chemotherapy for Medicare patients (aged 65 years and over) with metastatic colorectal cancer (mCRC) [71]. The data showed unequivocally there was no benefit to adding bevacizumab to FOLFOX-based regimens in this Medicare population, but importantly the addition of bevacizumab increased the risk of stroke (4.9% versus 2.5%, respectively; $P < 0.01$) and GI perforation (2.3% versus 1.0%, respectively; $P < 0.01$).

From a clinical standpoint would oncologists consider the predicted benefits of the CDF approved drugs to be clinically meaningful?

In many cases, the answer appears to be no. In 2014, The American Society of Clinical Oncology (ASCO) published what it considered meaningful clinical benefit in the hopes the design of future clinical trials would produce results that would be valuable for patients, i.e. meaningful improvements in survival, quality of life or both [72]. The ASCO Cancer Research Committee (CRC) that developed the criteria deliberately chose modest threshold to ensure their relevance and attainability. OS was chosen as the primary clinical end-point of interest and minimum gains in survival and HR thresholds were defined for each tumour type, virtually all in the metastatic setting. Secondary end-points included PFS, and thresholds for OS and PFS were adjusted depending on the toxicity profile of the drug.

An analysis of drugs approved by the FDA between 2002 and 2014 for the treatment of solid tumours found that only 42% of the 71 approved drugs met the ASCO or comparable standards [73]. Similarly, only 23 (48%) of the 47 CDF approved drug indications met the very modest ASCO criteria with uncertainty regarding six drug indications (see Table 1).

In 2015, The European Society for Medical Oncology (ESMO), produced further guidelines (following consultation with over 250 of its expert membership) to stipulate the boundaries for meaningful clinical benefit [74]. The scoring scheme was based on:

- Treatment intent (curative versus noncurative)
- Expected duration of PFS and OS in the control arm
- PFS or OS benefit including the hazard ratios
- Evidence of improved or worsening toxicity profiles
- Evidence for improvement in quality of life

Table 1. Details of the cancer drugs available through the NHS Cancer Drugs Fund prior to the first update in January 2015

Drug	Site	Indication	Author of index trial [REF]	Primary endpoint (s)	Median PS 0/1 (%)	PFS (HR)	OS (HR)	Approval on ASCO score criteria	ESMO score	NICE status Jan 2015	CDF status Jan 2015	CDF status Nov 2015
Abiraterone	Prostate	1st line CRPC (pre chemo)	Ryan 2014 [5]	PFS/OS	100	8.3 (0.53)	4.3 (0.80)	Yes	3	Not approved	Approved	Approved
	Bowel	2nd line metastatic CRC with irinotecan/5FU	Van Cutsem 2012 [6]	OS	98	2.2 (0.76)	1.4 (0.82)	No	1	Not approved	Removed	Removed
Albunin bound paclitaxel	Pancreas	1st line metastatic pancreatic cancer with gemcitabine	Von Hoff 2013 [7]	OS	KS > 80 = 92%	1.8 (0.69)	1.8 (0.72)	No	3	Not approved	Approved	Removed
	Renal	2nd line advanced RCC	Motzer 2013 [8]	PFS	99	2.6 (0.66)	NS	No	3	Awaiting appraisal	Approved	Approved by NICE therefore removed
Bevacizumab	Cervix	1st line Metastatic cervical ca	Tewari 2014 [9]	OS/Toxicity	46	2.3 (0.67)	3.7 (0.71)	Yes	3	Awaiting appraisal	Approved	Approved
Bevacizumab	Breast	Metastatic triple negative breast cancer	Miller 2007 [10]	PFS	56	5.9 (0.6)	NS	No	2	Not approved	Approved	Removed
Bevacizumab	Bowel	1st line advanced CRC with 5FU	Cunningham 2013 [11]	PFS	76	4 (0.53)	NS	No	2	Not appraised	Removed	Removed
Bevacizumab	Bowel	1st line metastatic CRC with oxaliplatin based regimen	Saltz 2008 [12]	PFS	60	1.4 (0.83)	NS	No	1	Not approved	Removed	Removed
Bevacizumab	Bowel	1st line metastatic CRC with irinotecan based regimen	Hurwitz 2004 [13]	OS	59	4.4 (0.54)	4.7 (0.66)	Yes	3	Not approved	Removed	Removed
Bevacizumab	Bowel	2nd line/3rd line metastatic CRC with oxaliplatin based chemo	Giantonio 2007 [14]	OS	61	2.6 (0.61)	2.1 (0.75)	No	2	Not approved	Approved	Removed
Bevacizumab	Bowel	3rd line in low grade gliomas of childhood with irinotecan	Gururangan 2013 [15]	PFS	8.4	KS > 50 = 100% PFS 85% at 6 months, 48% at 2 yrs	NR	Uncertain	2	Not appraised	Approved	Approved
Bevacizumab	Ovarian	1st line advanced ovarian, peritoneal or fallopian cancer	Burger 2011 [16]	PFS	60	3.8 (0.72)	NS	No	3	Not approved	Approved	Approved
Bevacizumab	Ovarian	2nd line advanced ovarian, fallopian or primary peritoneal cancers (platinum sensitive)	Aghajanian 2012 [17]	PFS	61	4 (0.48)	NS	No	3	Not approved	Removed	Removed
Cabazitaxel	Prostate	Metastatic CRPC previously treated with docetaxel	De bono 2010 [18]	OS	67	1.4 (0.7)	2.4 (0.7)	No	2	Not approved	Removed	Reinstated
Cabozantinib	Thyroid	1st line advanced medullary thyroid cancer	Elisei 2013 [19]	PFS	55	56% PS=0	NS	Yes	2	Awaiting appraisal	Approved	Approved
Cetuximab	Head and Neck cancer	Advanced Head and Neck Cancer	Vermoken 2008 [20]	OS	57	KS > 80 = 80%	2.7 (0.8)	No	3	Not approved	Approved	Approved
Cetuximab	Bowel	1st line metastatic CRC (K ras wild type) with oxaliplatin or irinotecan based regimens	Tejpar 2012 [21]	Pooled subgroup analysis	60	1.4 (0.47)	NS	Yes	3	Not approved for all indications	Approved	Approved
Cetuximab	Bowel	2nd or 3rd line treatment of metastatic CRC (K ras wild type) with irinotecan	Sobrero 2008 [22]	OS	61	2.4 (0.69)	NS	No	1	Not approved	Removed	Removed

Continued

Table 1. Continued

Drug	Site	Indication	Author of index trial [REF]	Primary endpoint (s)	Median PS 0/1 (%)	PFS (HR)	OS (HR)	Approval on ASCO criteria	ESMO score	NICE status Jan 2015	CDF status Jan 2015	CDF status Nov 2015
Cetuximab	Bowel	3rd or 4th line metastatic CRC (Kras wild type) as single agent	Karapetis 2008 [23]	OS	80	1.8 (0.40)	4.7 (0.55)	Yes	4	Not approved	Approved	Removed
Crizotinib	Lung	2nd line ALK +ve advanced/metastatic NSCLC	Shaw 2013 [24]	PFS	92	4.7 (0.49)	NR	Yes	4	Not approved	Approved	Approved
Dabrafenib	Melanoma	Unresectable or metastatic melanoma with a BRAF V600 mutation and intolerance to vemurafenib	Hauschild 2014 [25]	PFS	66% PS=0	2.4 (0.3)	NR	Yes	4	Appraisal ongoing	Approved	Approved by NICE therefore removed
Enzalutamide	Prostate	1st line CRPC (pre-chemo)	Beer 2014 [26]	PFS/OS	72	>12 months (0.19)	2.2 (0.71)	Uncertain	3	Awaiting appraisal	Approved	Approved
Eribulin	Breast	3rd line metastatic breast cancer	Cortes 2011 [27]	OS	92	1.5 (0.87)	2.5 (0.81)	No	2	Not approved	Removed	Reinstated
Everolimus	Breast	Metastatic breast cancer in combination with exemestane	Baselga 2012 [28]/Piccart 2014 [29]	PFS	62	4.6 (0.43)	NS	No	2	Not approved	Removed	Reinstated
Everolimus	PNET	1st or 2nd line moderately differentiated PNET	Yao 2011/2014 [30/31]	PFS	58	6.4 (0.27)	NS	No	2	Awaiting appraisal	Approved	Removed
Everolimus	PNET	Well differentiated PNET	Yao 2011/2014 [30/31]	PFS	58	6.4 (0.27)	NS	No	2	Awaiting appraisal	Removed	Removed
Everolimus	Renal	Metastatic RCC	Motzer 2010 [32]	PFS	61	KS > 80 = 91%	NS	No	3	Not approved	Removed	Reinstated
Imatinib	Sarcoma (GIST)	Adjuvant therapy for completely resected GIST at high relapse risk	Dematteo 2009 [33]	RFS	99	RFS gain 13%	NR	Yes	A	Awaiting appraisal	Approved	Approved by NICE therefore removed
Lapatinib	Breast	Advanced breast cancer, Her 2 +ve	Geyer 2006 [34]/cameron 2008 [35]	PFS	54	4 (0.47)	NS	No	3	Not approved	Removed	Removed
Panitumumab	Bowel	3rd or 4th line metastatic CRC (Kras wild type) as single agent	Van Cutsem 2007 [36]	PFS	62	1.1 (0.54)	NS	No	2	Not approved	Approved	Removed
Panitumumab	Bowel	1st line metastatic CRC with FOLFOLX or irinotecan (Kras wild type)	Douillard 2010 [37]/Douillard 2014 [38]	PFS	62	1.4 (0.80)	4.4 (0.88)	Yes	3	Awaiting appraisal	Approved	Approved
Pazopanib	Sarcoma	Advanced non-adipocytic soft tissue carcinoma	van der Graaf 2012 [39]	PFS	56	3 (0.31)	NS	No	2	Not appraised	Removed	Removed
Pegylated liposomal doxorubicin	Sarcoma	1st or 2nd line for angiosarcoma	Judson 2001 [40]	Toxicity/RR	52	NA	NA	Uncertain	Uncertain	Not appraised	Removed	Removed
Pegylated liposomal doxorubicin	Sarcoma	For patients with sarcoma with cardiac impairment or contraindication to doxorubicin	Judson 2001 [40]	Toxicity/RR	52	NA	NA	Uncertain	4	Not appraised	Approved	Approved
Pemetrexed	Lung	Maintenance post 4 cycles cisplatin/pemetrexed for NSCLC	Ciuleanu 2009 [41]	PFS	60	1.7 (0.5)	2.8 (0.79)	Yes	2	Not approved	Removed	Reinstated

Continued

Table 1. Continued

Drug	Site	Indication	Author of index trial [REF]	Primary endpoint (s)	Median age	PS 0/1 (%)	PFS (HR)	OS (HR)	Approval on ASCO criteria	ESMO score	NICE status Jan 2015	CDF status Jan 2015	CDF status Nov 2015
Pemetrexed	Lung	2nd line NSCLC	Hanna 2004 [42]	OS	59	88	NS	NS	No	1	Not approved	Removed	Removed
Lutetium Octreotate/Yttrium Octreotide	NETs	For inoperable well-differentiated neuroendocrine tumours (NETs) with progressive disease	Kam 2012 [43]	Symptoms/tumour regression	NR	NR	NA	NA	No	1	Not appraised	Approved	Removed
Pertuzumab	Breast	1st line locally advanced Her2 +ve breast cancer	Swain 2013 [44]	PFS	54	99	6.3 (0.69)	15.7 (0.68)	Yes	4	Not approved	Approved	Approved
Radium 223	Prostate	CRPC and bone mets, no visceral mets	Parker 2013 [45]	OS	71	87	NR	3.6 (0.7)	Yes	5	Awaiting appraisal	Approved	Approved by NICE there-fore removed
Regorafenib	Sarcoma (GIST)	Imatinib and sunitinib resistant GIST	Demetri 2013 [46]	PFS	60	100	3.9 (0.27)	NR	No	3	Not appraised	Removed	Reinstated
Sorafenib	Liver	1st line HCC	Llovet 2008 [47]	OS/Time to symptom progression	65	92	2.7 (0.58)	2.8 (0.69)	Yes	3	Not approved	Approved	Approved
Sorafenib	Thyroid	Metastatic/inoperable thyroid cancer refractory to radioiodine	Brose 2014 [48]	PFS	63	97	5 (0.8)	NR	Yes	2	Not appraised	Approved	Approved
Sunitinib	PNET	well differentiated PNET	Raymond 2011 [49]	PFS	56	100	5.9 (0.42)	Trial stopped early	Uncertain	2	Not appraised	Approved	Approved
Temsirolimus	Renal	Advanced RCC	Hudes 2007 [50]	OS	59	KS > 70 = 17%	2.4	3.6 (0.73)	Yes	4	Not approved	Approved	Approved
Trastuzumab emtansine (Kadcyla)	Breast	Relapsed Her2 +ve breast cancer	Verma 2012 [51]	PFS/OS and safety	53	99	3.2 (0.65)	5.8 (0.68)	Yes	5	Not approved	Approved	Approved
Vandetanib	Thyroid	Medullary thyroid ca	Wells 2012 [52]	PFS	51	96	11.2 (0.46)	NR	Yes	2	Not appraised	Approved	Approved
Vismodegib	Skin	Metastatic basal cell cancer	Sekulic 2012 [53]	Objective response rate	62	NR	NA	NA	Uncertain	2	Not appraised	Approved	Approved

OS, overall survival (months); PFS, progression free survival (months); HR, median hazard ratio; TTP, Time to progression; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; PS, Eastern cooperative oncology group performance score; KS, Karnofsky score; NR, not reported; NS, not statistically significant; NA, endpoint not assessed; CRC, colorectal cancer; RCC, renal cell cancer; CRPC, castrate resistant prostate cancer; PNET, pancreatic neuroendocrine tumour; HCC, hepatocellular carcinoma; GIS, gastrointestinal stromal tumour; NSCLC, non small cell lung cancer.

Cancer drugs indicated in the noncurative setting are scored 1 (lowest) to 5 (highest), and those in the curative setting are graded A (highest) or B (lowest). Drugs scoring 4, 5 or A are considered to provide a high level of proven clinical benefit according to the criteria. Our analysis of the 47 drug indications on the CDF found that only 9 (18%) indications achieved scores of 4, 5 or A, (see Table 1) while 23 (50%) of drug indications scored 2 or less on the ESMO scale, i.e. they were based on study data which had demonstrated limited evidence of clinical benefit. The nine indications that met ESMO criteria for meaningful clinical benefit included, cetuximab for colorectal cancer [23], crizotinib for lung cancer [24], dabrafenib for metastatic melanoma [25], imatinib as adjuvant therapy for GIST [33], pertuzumab and trastuzumab emtansine for breast cancer [44, 51], temsirolimus for renal cell cancer [50], radium 223 for prostate cancer [45] and pegylated doxorubicin for sarcoma [40].

Would an HTA body, in this instance NICE, consider the benefits of drugs on CDF of sufficient value to be reimbursed?

In the UK, NICE is responsible for ensuring rational and fair decisions are made on resource allocations by performing cost effectiveness analyses for new health interventions. The advantage of the cost per QALY is its universality when making decisions regarding the entire spectrum of health care interventions across all specialities [75]. NICE focus on both short and long-term outcomes of treatment and direct patient benefits [76].

We found that 26 (55%) CDF approved drugs had previously been rejected by NICE on the grounds of not meeting cost effectiveness criteria. Three (dabrafenib, imatinib and radium 223) were due to receive approval in early 2015 (Table 1). Seven were awaiting appraisal but draft consultation advice had been issued. Eleven indications had not been appraised and no plans for their assessment were evident. In some cases, this was due to the rarity of the disease (e.g. regorafenib, in soft tissue sarcoma) or their off-label use (bevacizumab third line in paediatric low-grade glioma).

What the CDF committee considered the value of CDF approved drugs to be?

The CDF committee undertook detailed assessment of each of the drugs listed in its access scheme in January and November 2015 using a bespoke framework to assess its value. This included, but was not limited to, PFS, OS, quality of life, toxicity, unmet need and cost [77]. In total, 24 indications (51% of all indications) for 14 drugs were removed from the CDF list following this appraisal, of which six were later reinstated.

Table 2 summarizes details about four drugs whose value to the NHS can be debated: *bevacizumab*, *lapatinib*, *cetuximab*, and *everolimus*. These four drugs were approved by the CDF for 18 separate indications—bevacizumab (9), cetuximab (4), everolimus (4) and lapatinib (1). Following the initial review of the CDF in January 2015, nine of these indications were delisted. A further four indications were delisted in November 2015, following a subsequent review. The value delivered by bevacizumab in particular is debatable given that six of the nine indications were delisted. Only one of these indications would have met ASCO

criteria and none would have achieved the ESMO meaningful clinical benefit criteria, or NICE cost-effective thresholds.

In this respect, the criteria and value judgements initially used by the CDF has been criticized for its lack of rigour and relevance for prioritizing drugs for reimbursement through the fund [78]. The tabulation also underscores the fluid nature of the CDF and raises questions as to whether approvals were occurring too quickly or are being driven by factors other than academic/scientific considerations.

Is there any evidence that the CDF has been of value to NHS cancer patients?

At the time of commencement in 2010, it was expected that basic outcome data would be collected from April 2012 including the date of treatment cessation, side effects observed, 30-day mortality and date of death/next relapse. However, even after audit data collection became mandatory in 2014, 93% of outcome data was incomplete for 2014–2015 [79].

We therefore have no evidence as to whether recipients of drugs from the CDF derived any meaningful benefit in terms of survival, improved quality of life or decreased episodes of toxicity. As a proxy, we have attempted to define the value achieved by NHS cancer patients receiving cancer drugs through the CDF by assessing actual patterns of drug utilization, in conjunction with their anticipated benefits according to the original trial data.

Stephens and Thomson in 2012 [80] using IMS health dispensing data demonstrated that between April and December 2011, 59% of CDF applications were for five drugs: bevacizumab, lapatinib, sorafenib, cetuximab, and everolimus; a prescribing pattern confirmed by Chamberlain et al. in a subsequent analysis examining the period from October 2007 to October 2012 [81]. No data on the volume of drugs utilized has since been made available, nor information on patient weight or number of cycles completed by each patient.

The study reported that following the introduction of the CDF there were statistically significant increases in utilization of bevacizumab (2-fold), and lapatinib (3-fold), and these together with sorafenib, cetuximab, and sunitinib constituted a significant proportion of drug prescriptions. The exact indication for which these drugs were prescribed remains unknown. Analysis of the volume data found that the growth in drug utilization was lower than expected when compared with the doses and duration of treatment received by patients enrolled in the original RCTs. This is therefore likely to reflect earlier disease progression, or the occurrence of intolerable adverse events, suggesting their clinical effectiveness and tolerability do not match results in the RCTs [82]. In addition, there was evidence of inequitable access to the fund across English regions (2010–2013) and according to age and sex [79, 83].

This then raises concerns that the 'real benefits' in fact are not benefits at all since they would never have achieved statistical validity in a RCT or if they did, may not have been of sufficient magnitude to warrant the added toxicity that invariably occurs. Keeping in mind the median OS benefit of CDF-approved indications was 3.1 months can we be sure that 1 month less than this would be statistically better or better enough to favourably tip the risks to benefits scale?

Table 2. Details of four drugs—bevacizumab, cetuximab, everolimus and lapatinib—which were approved by the CDF for 18 separate indications prior to January 2015

Drug	Site	Indication	Author of index trial (REF)	PFS (HR)	OS (HR)	Approval on ASCO criteria	ESMO score	NICE status Jan 2015	CDF status Jan 2015	CDF status Nov 2015
Bevacizumab	Cervix	1st line metastatic cervical ca	Tewari 2014 [9]	2.3 (0.67)	3.7 (0.71)	Yes	3	Awaiting appraisal	Approved	Approved
Bevacizumab	Breast	Metastatic triple negative breast cancer	Miller 2007 [10]	5.9 (0.6)	NS	No	2	Not approved	Approved	Removed
Bevacizumab	Bowel	1st line advanced CRC with 5FU	Cunningham 2013 [11]	4 (0.53)	NS	No	2	Not appraised	Removed	Removed
Bevacizumab	Bowel	1st line metastatic CRC with oxaliplatin-based regimen	Saltz 2008 [12]	1.4 (0.83)	NS	No	1	Not approved	Removed	Removed
Bevacizumab	Bowel	1st line metastatic CRC with irinotecan-based regimen	Hurwitz 2004 [13]	4.4 (0.54)	4.7 (0.66)	Yes	3	Not approved	Removed	Removed
Bevacizumab	Bowel	2nd line/3rd line metastatic CRC with oxaliplatin-based chemo	Giantonio 2007 [14]	2.6 (0.61)	2.1 (0.75)	No	2	Not approved	Approved	Removed
Bevacizumab	Bowel	3rd line in low-grade gliomas of childhood with irinotecan	Gururangan 2013 [15]	PFS 85% at 6 months, 48% at 2 yrs	NR	Uncertain	2	Not appraised	Approved	Approved
Bevacizumab	Ovarian	1st line advanced ovarian, peritoneal or fallopian cancer	Burger 2011 [16]	3.8 (0.72)	NS	No	3	Not approved	Approved	Approved
Bevacizumab	Ovarian	2nd line advanced ovarian, fallopian or primary peritoneal cancers (platinum sensitive)	Aghajanian 2012 [17]	4 (0.48)	NS	No	3	Not approved	Removed	Removed
Cetuximab	Head and Neck cancer	Advanced head and neck cancer	Vermoken 2008 [20]	2.3 (0.54)	2.7 (0.8)	No	3	Not approved	Approved	Approved
Cetuximab	Bowel	1st line metastatic CRC (K ras wild-type) with oxaliplatin or irinotecan-based regimens	Tejpar 2012 [21]	1.4 (0.47)	NS	Yes	3	Approved for specific indications	Approved	Approved
Cetuximab	Bowel	2nd or 3rd line treatment of metastatic CRC (K ras wild-type) with irinotecan	Sobrero 2008 [22]	2.4 (0.69)	NS	No	1	Not approved	Removed	Removed
Cetuximab	Bowel	3rd or 4th line metastatic CRC (K ras wild-type) as single agent	Karapetis 2008 [23]	1.8 (0.40)	4.7 (0.55)	Yes	4	Not approved	Approved	Removed
Everolimus	Breast	Metastatic breast cancer in combination with exemestane	Baselga 2012 [28]/Piccart 2014 [29]	4.6 (0.43)	NS	No	2	Not approved	Removed	Reinstated
Everolimus	PNET	1st or 2nd line moderately differentiated PNET	Yao 2011/2014 [30, 31]	6.4 (0.27)	NS	No	2	Awaiting appraisal	Approved	Removed
Everolimus	PNET	Well differentiated PNET	Yao 2011/2014 [30, 31]	6.4 (0.27)	NS	No	2	Awaiting appraisal	Removed	Removed
Everolimus	Renal	Metastatic RCC	Motzer 2010 [32]	3 (0.33)	NS	No	3	Not approved	Removed	Reinstated
Lapatinib	Breast	Advanced breast cancer, Her 2 +ve	Geyer 2006 [34]/Cameron 2008 [35]	4 (0.47)	NS	No	3	Not approved	Removed	Removed

OS, overall survival (months); PFS, progression free survival (months); HR, median hazard ratio; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; NR, not reported; NS, not statistically significant; NA, endpoint not assessed; CRC, colorectal cancer; RCC, renal cell cancer; PNET, pancreatic neuroendocrine tumour.

Discussion and policy recommendations

Because some argued that UK lagged behind other Western countries in delivering therapies to cancer patients and this could lead to disparity in outcomes, the CDF was established to ensure access to drugs available in other countries [84]. In this respect, the CDF has delivered its intended aims. However, we would argue from this analysis that the CDF has not provided meaningful value to cancer patients and wider society because the supporting data has been wanting.

The majority of CDF-approved indications have been based on studies that reported minimal to no benefit in survival. Other endorsements have relied on surrogate endpoints such as PFS that remain controversial given inherent flaws in trial design and the increasing abuse of censoring. The thresholds for meaningful clinical benefit proposed by ASCO or ESMO support our argument since the majority of CDF-approved indications were unable to meet these modest levels of efficacy (Table 1).

Patients would find many of the approved indications wanting as regards actual benefit, even before considering the burden of the associated toxicities [85]. Current evidence suggests the majority of cancer patients with a life expectancy ≤ 4 months prefer treatment that relieves pain and discomfort rather than extending life [86] and that they expect a minimum survival benefit of 3 months in this setting and potentially longer if the therapy is associated with more severe side effects [87, 88].

We must also consider the welfare loss to society from the CDF after expenditure of over one billion pounds [79]. An impact equality assessment of the CDF has been undertaken for patients receiving cancer drugs through the CDF in 2013/2014 ($n = 19\,560$) [79]. It reported that the potential benefit of the CDF to cancer patients, estimated at 3500 QALYS, has resulted in overall net harm to population health when one considers the health opportunity costs, with nearly 18 000 QALYS being displaced from patients elsewhere in the NHS [89, 90]. It is important therefore, to tread with caution when arguments are forwarded that all cancer drugs offering meaningful clinical benefit should be funded irrespective of price, without considering issues of value, distributive justice, and fairness. In the NHS, waiting times for diagnostic interventions and elective procedures continue to rise, many of which are directly affecting cancer patients [91].

At its inception, critics argued that the introduction of the CDF would reduce the negotiating power of the NHS, specifically the ability to negotiate fair prices of cancer drugs with pharmaceutical companies [81]. This is no more evident than when one considers the reversals of six indications delisted in January 2015 (see Table 3). None of the reinstated indications meet the criteria for clinical benefit according to the ESMO scale. However, negotiations were prompted by the threat of the drug being delisted, suggesting that the creation of a ring fenced access fund for cancer drugs provides a negative incentive for drug price negotiation. This is especially pertinent given recent evidence that the price of drugs is based on what the market will bear as opposed to the level of its clinical benefit [92]. Cabazitaxel, eribulin, and everolimus (for breast cancer) have all since been approved by NICE as a result of discounts being applied by pharmaceutical companies through the patient access scheme [93–95].

Table 3. Details of the six de-listed drugs, which were re-approved by the CDF following a second review in November 2015

Drug	Site	Indication	Author of index trial [REF]	PFS (HR)	OS (HR)	Approval on ASCO criteria	ESMO score	NICE status Jan 2015	CDF status Jan 2015	CDF status Nov 2015
Cabazitaxel	Prostate	Metastatic CRPC previously treated with docetaxel	De bono 2010 [18]	1.4 (0.7)	2.4 (0.7)	No	2	Not approved	Removed	Reinstated
Eribulin	Breast	3rd line metastatic breast cancer	Cortes 2011 [27]	1.5 (0.87)	2.5 (0.81)	No	2	Not approved	Removed	Reinstated
Everolimus	Breast	Metastatic breast cancer in combination with exemestane	Baselga 2012 [28]/Piccart 2014 [29]	4.6 (0.43)	NS	No	2	Not approved	Removed	Reinstated
Everolimus	Renal	Metastatic RCC	Motzer 2010 [32]	3 (0.33)	NS	No	3	Not approved	Removed	Reinstated
Pemtrexed	Lung	Maintenance post 4 cycles cisplatin/pemetrexed for NSCLC	Ciuleanu 2009 [41]	1.7 (0.5)	2.8 (0.79)	Yes	2	Not approved	Removed	Reinstated
Regorafenib	Sarcoma (GIST)	Imatinib and sunitinib resistant GIST	Demetri 2013 [46]	3.9 (0.27)	NR	No	3	Not appraised	Removed	Reinstated

OS, overall survival (months); PFS, progression free survival (months); HR, median hazard ratio; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; NR, not reported; NS, not statistically significant; NA, endpoint not assessed; CRC, colorectal cancer; RCC, renal cell cancer; CRPC, castrate resistant prostate cancer; GIST, gastrointestinal stromal tumour; NSCLC, non small cell lung cancer.

Given the evidence set forth, decisions regarding access appear politically motivated. The CDF was created following intense public and political pressure to provide access no matter what the cost or the evidence for their benefit. There was no stated estimation of the ‘number of lives that could be saved’, nor, more realistically, of the number of lives that may be extended. This was a debate played out in the media, limiting the role of NICE as the final arbiter for deciding what constitutes optimal value for society [82]. However, 6 years later, and after considerable expenditure we are now reverting to a pre-existing format, namely an independent health technology appraisal service (i.e. NICE) providing recommendations for NHS commissioning (see Figure 1).

Indeed, the evidence used by the CDF committee to re-appraise the value of drugs in January 2015 was in most cases available prior to the approval process, especially in circumstances where NICE had already undertaken an HTA appraisal. Of the 17 indications delisted in January 2015, 13 were for indications that were previously deemed not cost-effective by NICE (Table 1). A further seven indications were delisted in November 2015 of which five had been rejected following NICE appraisal. While these reversals may seem innocent, if a drug approved for an indication is subsequently deemed of insufficient value as data become available and its benefit is questioned we must acknowledge that it has then been given to patients who may have endured toxicity without any benefit.

Finally, while the stated goal of the CDF was to ‘empower clinicians, and to enable them to use the cancer drugs that they and their patients agree are needed to extend or improve life’, it is reasonable to ask why so many clearly ineffective drugs were prescribed in the first place. The issues are complex and cannot be answered without in-depth qualitative research. However, two factors may be important. The first is the so-called ‘moral hazard’. When patients and providers are shielded from the costs associated with an intervention (through insurance *per se*), they will be more willing to accept/deliver health care interventions even if the benefits are marginal [96]. Second, decision-making in the context of illness has been shown to be prone to biases resulting in an over-estimation of the level of risk of disease or potential benefits of treatment [97, 98].

Future options

One lesson from this costly saga is the need to strengthen regulatory and reimbursement processes and ensure they remain free from political interference. The use of clinically meaningful benefit thresholds such as that proposed by ASCO and ESMO seems enormously prudent. The ASCO metric in effect calls for minimum OS gains of 2.5–4.5 months or 25–50% gain over existing time scales and the ESMO threshold essentially prioritizes gains in survival (> 3 months with hazard ratios < 0.65), quality of life and reduction in toxicity compared with current standards of care.

We would suggest other countries considering a patient access scheme for drugs awaiting formal health technology appraisal use value frameworks that determine the likely benefit from reimbursement as part of the appraisal process. If drugs are made available pending an appraisal process, this should be accompanied by rigorous collection of outcome data through coverage with evidence development schemes. However, they should not replace assessment of the overall cost-effectiveness, which seeks

to ascertain the societal benefit gained from drug reimbursements relative to other health technologies across the disease spectrum.

Improvements on the current system could also be achieved through new payment systems based on the attainment of pre-determined outcomes [99–101] or the introduction of value-based co-payments [102]. Another option would be to link HTA appraisal of the benefits and costs of new drugs with national rebate agreements [89]. The rebate would cover the difference between the manufacturers intended price of the drug and how much the NHS can afford to pay for its intended benefits. This would highlight to pharmaceutical companies of the price the NHS is willing to pay for the benefits offered by a new drug. Companies charging high prices for drugs with limited efficacy, would be expected to pay higher rebates. This would encourage research funders to support cancer clinical trials whose design and end points genuinely look for therapeutic advances that deliver meaningful clinical benefit rather than a low bar for response.

Conclusions

Despite significant expenditure, there remains no evidence that the CDF has delivered meaningful value to NHS cancer patients. We have analysed the value of CDF approved drugs according to six criteria including validated clinical benefit scales, and health technology appraisal from organizations such as NICE. From this, it is clear that the decision-making tools used by the CDF for prioritization of new drugs have failed given that a number of drugs were approved and subsequently delisted based on evidence that previously existed.

We recommend the avoidance of similar ‘ring-fenced’ drug access funds in other countries. The lack of empirical evidence that prioritizing drug expenditure (the greatest cancer care costs after inpatient care) will improve outcomes for cancer patients over and above greater investment in the whole cancer management pathway (screening, diagnostics, radiotherapy, surgery) and reducing access barriers (e.g. co-payments) argue against its widespread adoption. Ultimately, what is most important is that reimbursement decisions for all drugs, procedures and interventions within cancer care are made through appropriate health technology appraisal processes, which use the best available evidence to ensure decisions maximize value for cancer patients and society as a whole.

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References

1. Davies JE, Neidle S, Taylor DG. Developing and paying for medicines for orphan indications in oncology: utilitarian regulation vs equitable care[quest]. *Br J Cancer* 2012; 106: 14–17.

2. House of Commons Committee of Public Accounts. Cancer Drugs Fund—20th Report. House of Commons, 2016.
3. NHS England Clinical Effectiveness Team. NHS England Consultation: Proposals for a Sustainable Cancer Drug Fund. NHS England, 2014.
4. NHS England. National Cancer Drugs Fund List. 2015.
5. Ryan C, Smith M, Fizazi K et al. 7530 final overall survival (OS) analysis of COU-AA-302, a randomized phase 3 study of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (MCRPC) patients (PTS) without prior chemotherapy. *Ann Oncol* 2014; 25: iv255–iv255.
6. Van Cutsem E, Tabernero J, Lakomy R et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012; 30: 3499–3506.
7. Von Hoff DD, Ervin TJ, Arena FP et al. Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). *J Clin Oncol* (Meeting Abstracts) 2013; 31(suppl 4): LBA148.
8. Motzer RJ, Escudier B, Tomczak P et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 552–562.
9. Tewari KS, Sill MW, Long HJ III et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014; 370: 734–743.
10. Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; 357: 2666–2676.
11. Cunningham D, Lang I, Marcuello E et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14: 1077–1085.
12. Saltz LB, Clarke S, Díaz-Rubio E et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; 26: 2013–2019.
13. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335–2342.
14. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; 25: 1539–1544.
15. Gururangan S, Fangusaro J, Poussaint TY et al. Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas—a Pediatric Brain Tumor Consortium study. *Neuro-Oncology* 2013; 16(2): 310–317.
16. Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011; 365: 2473–2483.
17. Aghajanian C, Blank SV, Goff BA et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012; 30: 2039–2045.
18. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; 376: 1147–1154.
19. Elisei R, Schlumberger MJ, Müller SP et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013; 31: 3639–3646.
20. Vermorken JB, Mesia R, Rivera F et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; 359: 1116–1127.
21. Tejpar S, Celik I, Schlichting M et al. Association of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab. *J Clin Oncol* 2012; 30: 3570–3577.
22. Sobrero AF, Maurel J, Fehrenbacher L et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 2311–2319.
23. Karapetis CS, Khambata-Ford S, Jonker DJ et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; 359: 1757–1765.
24. Shaw AT, Kim D-W, Nakagawa K et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013; 368: 2385–2394.
25. Hauschild A, Grob J-J, Demidov LV et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012; 380: 358–365.
26. Beer TM, Armstrong AJ, Sternberg CN et al. Enzalutamide in men with chemotherapy-naïve metastatic prostate cancer (mCRPC): results of phase III PREVAIL study. *J Clin Oncol* 2014; 32(suppl 4): LBA1.
27. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011; 377: 914–923.
28. Baselga J, Campone M, Piccart M et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; 366: 520–529.
29. Piccart M, Hortobagyi GN, Campone M et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. *Ann Oncol* 2014; 25(12): 2357–2362.
30. Yao JC, Shah MH, Ito T et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364: 514–523.
31. Yao JC, Pavel M, Lombard-Bohas C et al. Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 study. *J Clin Oncol* 2016; 34: 3906–3913.
32. Motzer RJ, Escudier B, Oudard S et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma. *Cancer* 2010; 116: 4256–4265.
33. Dematteo RP, Ballman KV, Antonescu CR et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 373: 1097–1104.
34. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; 355: 2733–2743.
35. Cameron D, Casey M, Press M et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat* 2008; 112: 533–543.
36. Van Cutsem E, Peeters M, Siena S et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007; 25: 1658–1664.
37. Douillard J-Y, Siena S, Cassidy J et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; 28(31): 4697–4705.
38. Douillard J, Siena S, Cassidy J et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol* 2014; 25: 1346–1355.
39. van der Graaf WTA, Blay J-Y, Chawla SP et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012; 379: 1879–1886.
40. Judson I, Radford JA, Harris M et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by

- the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2001; 37: 870–877.
41. Ciuleanu T, Brodowicz T, Zielinski C et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009; 374: 1432–1440.
 42. Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; 22: 1589–1597.
 43. Kam B, Teunissen J, Krenning E et al. Lutetium-labelled peptides for therapy of neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2012; 39: 103–112.
 44. Swain SM, Kim S-B, Cortés J et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2013; 14: 461–471.
 45. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369: 213–223.
 46. Demetri GD, Reichardt P, Kang Y-K et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; 381: 295–302.
 47. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378–390.
 48. Brose M, Nutting C, Jarzab B et al. On behalf of the DECISION investigators: sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014; 384: 319–328.
 49. Raymond E, Dahan L, Raoul J-L et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364: 501–513.
 50. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; 356: 2271–2281.
 51. Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783–1791.
 52. Wells SA, Robinson BG, Gagel RF et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012; 30: 134–141.
 53. Sekulic A, Migden MR, Oro AE et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med* 2012; 366: 2171–2179.
 54. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? *J Clin Oncol* 2012; 30: 1030–1033.
 55. Fiteni F, Westeel V, Pivot X et al. Endpoints in cancer clinical trials. *J Visc Surg* 2014; 151: 17–22.
 56. Liu LY, Yu H, Bai JL et al. Verification of the correlation between progression-free survival and overall survival considering magnitudes of survival post-progression in the treatment of four types of cancer. *Asian Pac J Cancer Prev* 2015; 16: 1001–1006.
 57. Gill S, Sargent D. End points for adjuvant therapy trials: has the time come to accept disease-free survival as a surrogate end point for overall survival? *Oncologist* 2006; 11: 624–629.
 58. Prasad V, Massey PR, Fojo T. Oral anticancer drugs: how limited dosing options and dose reductions may affect outcomes in comparative trials and efficacy in patients. *J Clin Oncol* 2014; 32: 1620–1629.
 59. Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when evaluating oncology products. *J Clin Oncol* 2009; 27: 2874–2880.
 60. Prasad V, Bilal U. The role of censoring on progression free survival: oncologist discretion advised. *Eur J Cancer* 2015; 51: 2269–2271.
 61. Burotto M, Prasad V, Fojo T. Non-inferiority trials: why oncologists must remain wary. *Lancet Oncol* 16: 364–366.
 62. Templeton AJ, Ace O, Amir E et al. Influence of censoring on conclusions of trials for women with metastatic breast cancer. *Eur J Cancer* 2015; 51: 721–724.
 63. Baltussen R, Ament A, Leidl R. Making cost assessments based on RCTs more useful to decision-makers. *Health Policy* 1996; 37: 163–183.
 64. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; 23: 3112–3124.
 65. Mullins CD, Montgomery R, Tunis S. Uncertainty in assessing value of oncology treatments. *Oncologist* 2010; 15: 58–64.
 66. Hutchins LF, Unger JM, Crowley JJ et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; 341: 2061–2067.
 67. Lewis JH, Kilgore ML, Goldman DP et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003; 21: 1383–1389.
 68. Garrison LP, Jr, Neumann PJ, Erickson P et al. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health* 2007; 10: 326–335.
 69. Heng D, Choueiri T, Rini B et al. Outcomes of patients with metastatic renal cell carcinoma that do not meet eligibility criteria for clinical trials. *Ann Oncol* 2014; 25: 149–154.
 70. Shah BK, Ghimire KB. Survival trends among patients with advanced renal cell carcinoma in the United States. *Urol Int* 2015; 94: 133–136.
 71. Meyerhardt JA, Li L, Sanoff HK et al. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. *J Clin Oncol* 2012; 30(6): 608–615.
 72. Ellis LM, Bernstein DS, Voest EE et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014; 32: 1277–1280.
 73. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. *JAMA Otolaryngol Head Neck Surg* 2014; 140: 1225–1236.
 74. Cherny NI, Sullivan R, Dafni U et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 2015; 26: 1547–1573.
 75. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. *BMJ* 2004; 329: 224–227.
 76. Huttin C. Drug price divergence in Europe: regulatory aspects. *Health Aff (Millwood)* 1999; 18: 245–249.
 77. NHS England. Cancer Drugs Fund decision summaries. 2017.
 78. Dixon P, Chamberlain C, Hollingworth W. Did it matter that the cancer drugs fund was not NICE? A retrospective review. *Value in Health* 2016; 19(6): 879–884.
 79. National Audit Office. Investigation into the Cancer Drugs Fund. Department of Health and NHS England (ed). 2015.
 80. Stephens P, Thomson D. The Cancer Drug Fund 1 year on—success or failure? *Lancet Oncol* 2012; 13: 754–757.
 81. Chamberlain C, Collin SM, Stephens P et al. Does the cancer drugs fund lead to faster uptake of cost-effective drugs? A time-trend analysis comparing England and Wales. *Br J Cancer* 2014; 111: 1693–1702.
 82. Aggarwal A, Ginsburg O, Fojo T. Cancer economics, policy and politics: what informs the debate? Perspectives from the EU, Canada and US. *J Cancer Policy* 2014; 2: 1–11.
 83. Chamberlain C, Collin SM, Hounsome L et al. Equity of access to treatment on the Cancer Drugs Fund: a missed opportunity for cancer research? *J Cancer Policy* 2015; 5: 25–30.
 84. Richards M. Extent and causes of international variations in drug usage. London: The Central Office of Information, 2010.
 85. Davis C. Drugs, cancer and end-of-life care: a case study of pharmaceuticalization? *Soc Sci Med* 2015; 131: 207–214.
 86. Mack JW, Weeks JC, Wright AA et al. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol* 2010; 28: 1203–1208.
 87. Slevin ML, Stubbs L, Plant HJ et al. Attitudes to chemotherapy: comparing views of patients with cancer with those of doctors, nurses, and general public. *BMJ* 1990; 300: 1458–1460.

88. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. *BMJ* 1998; 317: 771–775.
89. Claxton KP. Pharmaceutical pricing: early access. The Cancer Drugs Fund and the Role of NICE. Centre for Health Economics, University of York, 2016.
90. Claxton K, Martin S, Soares M et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess* 2015; 19: 1–503, v–vi.
91. Triggle N, Most areas ‘struggling’ on cancer care. BBC News Website, 2016.
92. Vogler S, Vitry A, Babar Z-U-D. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. *Lancet Oncol* 17: 39–47.
93. NICE. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel. National Institute for Health and Care Excellence, 2016.
94. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens—Technology appraisal guidance (TA423). National Institute for Health and Care Excellence, 2016.
95. NICE. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy—Technology appraisal guidance (TA421). National Institute for Health and Care Excellence, 2016.
96. Tierney WM, Miller ME, McDonald CJ. The effect on test ordering of informing physicians of the charges for outpatient diagnostic tests. *N Engl J Med* 1990; 322: 1499–1504.
97. Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. In: *Wendt D, Vlek CA (eds), Utility, Probability, and Human Decision Making*. Dordrecht-Holland: D. Reidel Publishing Company, Springer 1975; 141–162.
98. Redelmeier DA, Rozin P, Kahneman D. Understanding patients’ decisions: cognitive and emotional perspectives. *JAMA* 1993; 270: 72–76.
99. Siddiqui M, Rajkumar SV. The high cost of cancer drugs and what we can do about it. In *Mayo Clinic Proceedings*. Elsevier 2012; 935–943.
100. Goldstein DA, Stemmer SM, Gordon N. The cost and value of cancer drugs—are new innovations outpacing our ability to pay? *Isr J Health Policy Res* 2016; 5: 40.
101. Hwang TJ, LaMattina JL. Measuring the value of new medications and implications for medicare’s proposed part B drug payment model. *JAMA Oncol* 2016; 2: 1125–1126.
102. Aggarwal A, Sullivan R. Affordability of cancer care in the United Kingdom—Is it time to introduce user charges? *J Cancer Policy* 2014; 2: 31–39.