Global spending on end-of-life treatments is rising and high prices for cancer drugs are growing to be a concern to both payers and patients (Danzon et al, 2010). According to the American Cancer Society, approximately 580,350 patients are expected to die of cancer this year in the USA—almost 1600 people every day (American Cancer Society, 2013). In the UK, around 325,000 people were diagnosed with cancer in 2010, which amounts to 890 people per day (Cancer Research UK, 2012a).

The cost of cancer in the USA is staggering; the National Institutes of Health estimates that the overall costs of cancer in 2008 were $201.5 billion (American Cancer Society, 2013). In the UK, the costs are equally astounding, with the National Cancer Research Institute estimating the total annual cost of all cancers at £15.8 billion (Cancer Research UK, 2012b).

Against this backdrop, health spending overall continues to increase and there is a divergence between GDP and national health spending in the US (Figure 1). This trend is being observed in many nations across the globe with the so called ‘scissors of doom’ (Figure 2) appropriately defining the situation in the UK.

Overview of current global developments in oncology

Despite the economic crisis, pharmaceutical developments in oncology are moving at a considerable pace, with use of biomarkers to identify patients who will benefit from targeted therapeutics. Oncology treatment is changing; and as targeted agents gain adoption and use in the clinic, demand is increasing for products with high (and durable) efficacy and low toxicity (Laing et al., 2012).

Combining targeted treatments has clear scientific rationale, as most tumours are driven...
by multiple driver mutations and molecular abnormalities. Therefore, it makes sense to target more than one pathway and combining therapies offers the opportunity to overcome resistance and obtain maximum response.

Combining oncology therapies has the potential to deliver impressive efficacy results and the recently approved breast cancer drug pertuzumab (Perjeta, Roche) when combined with trastuzumab (Herceptin, Roche) and docetaxel demonstrated an increase of 6.1 months progression-free survival (hazard ratio for progression or death 0.62; 95% confidence interval, 0.51 to 0.75; \( P < 0.001 \)) (Baselga et al, 2012). Although combining oncology therapies may lead to a significant increase in efficacy, there remains the danger of increased toxicity (Fralick et al, 2012). Clinicians do remain cautious regarding the ‘hype’ of oncology combinations and it is not currently day-to-day practice to use this approach.

The main concern regarding combination therapy, however, is the potential cost and budget impact of this approach given most countries in the EU, and also the USA, are currently in the midst of austerity drives.
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assessment through the establishment of the National Institute for Health and Care Excellence (NICE) in 1999, the market has traditionally allowed companies to price medicines freely. VBP in theory marks a shift away from the ability of companies to determine price and NICE is expected to take a central role in the new system. Remarkably, six months from implementation, details around the new system remain scarce, which has led to criticism from industry, patient groups and even the Health Select Committee in Parliament (Health Select Committee, 2013).

In the UK, all new cancer medications are currently required to go through NICE’s single technology appraisal (STA) process. NICE has received a lot of negative press for rejecting cancer medications (Borland, 2012); although it claims that 64% of all recommendations in line with a product’s market authorisation are ‘recommended’, or in specific circumstances, ‘optimised’ (NICE, 2013).

For most oncology drugs going through NICE, to achieve the acceptable cost-effectiveness level, a patient access scheme (PAS) is required. A PAS is initiated by the manufacturer either upfront or in response to a draft rejection by NICE. NICE also currently offers a rapid review facility to enable manufacturers to come back to the table following a final negative decision, which allows the rejected product a fast-track route onto NICE’s work programme. Please see Table 3 for

Comparison of approach in funding cancer medications

United Kingdom

In the UK, we have a universal healthcare system which is free at the point of delivery. The NHS remains in the middle of the so called ‘Nicholson Challenge’, which requires the system to deliver £20 billion of efficiency savings by 2015. Cancer care in the UK is generally seen as good (Gray, 2011), however, there is much to do in the UK in terms of providing a personalised approach to end of life care (Duffy, 2011).

Policy makers are seeking to switch the current system of profit control with the Pharmaceutical Price Regulation Scheme (PPRS), to a system based on value and cost-effectiveness. Value-based pricing (VBP) of drugs has been academically debated and politically courted for a number of years in the UK. The NHS currently spends approximately £11 billion annually on drugs, of which £8 billion is on branded drugs—representing about 13% (total) and 10% (branded) respectively of the available budget (Claxton et al, 2008).

Although the UK has had a central focus on cost-effectiveness via health technology (PM Live, 2012). As budget holders struggle to deal with the price of current oncology therapies, the notion of using two potentially expensive agents is likely to cause alarm.

Table 1. Selected Combination Programs on-going in Oncology

<table>
<thead>
<tr>
<th>Companies</th>
<th>Combination regimen</th>
<th>Mode of action</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</td>
<td>Dabrafenib, Trametinib</td>
<td>BRAF, MEK 1/2</td>
<td>Melanoma, other solid tumours</td>
</tr>
<tr>
<td>Novartis</td>
<td>BEZ235, MEK 162</td>
<td>PI3K-m TOR, MEK1/2</td>
<td>Solid tumours</td>
</tr>
<tr>
<td>Merck and Sanofi</td>
<td>MSC 1936369, SAR245-409</td>
<td>MEK 1/2, PI3K-m TOR</td>
<td>Solid tumours</td>
</tr>
<tr>
<td></td>
<td>MSC 1936369, SAR245-408</td>
<td>MEK 1/2, PI3K</td>
<td>Solid tumours</td>
</tr>
<tr>
<td>AstraZeneca and Merck</td>
<td>Selumetinib, MK-2206</td>
<td>MEK 1/2 , Akt</td>
<td>NSCLC, CRC, melanoma</td>
</tr>
</tbody>
</table>

Laing et al, 2012
Table 2. Breakdown of decisions in published technology appraisals for anti-cancer agents

<table>
<thead>
<tr>
<th>Recommendations for cancer appraisals</th>
<th>1 March 2000 to 31 January 2013</th>
<th>1 to 31 January 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STA</td>
<td>MTA</td>
</tr>
<tr>
<td>Yes</td>
<td>27 (52%)</td>
<td>54 (65%)</td>
</tr>
<tr>
<td>Optimised</td>
<td>4 (8%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Only in research</td>
<td>2 (4%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>No</td>
<td>19 (36%)</td>
<td>22 (26%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>52 (100%)</td>
<td>84 (100%)</td>
</tr>
</tbody>
</table>

STA = single technology appraisal; MTA = multiple technology appraisal. Source: NICE website

a list of cancer drugs recommended by NICE with a PAS. It is interesting to note the increasing frequency and that the schemes have become mainly simple discounts over time.

For drugs rejected by NICE, patients have the opportunity to apply for drugs via the Cancer Drugs Fund (CDF). The CDF was announced by the Department of Health in October 2010 with the aim of providing £200 million a year in funding for cancer drugs from April 2011 to April 2014 (Department of Health, 2010). On 1 April 2013, NHS England took on responsibility for the operational management of the CDF. There is now a single, national list of drugs and indications that the CDF will routinely fund and standard operating procedures for administration of the fund.

USA
Healthcare in the USA is provided and funded via a combination of private and public organisations. In the US, the system is highly fragmented (IMS Health, 2012); even healthcare schemes agreed at the federal level, vary from state to state and offer different benefits depending on the cover the patient requires.

There are a number of privately available plans in the USA and often patients have access to healthcare insurance via their employers. However, employers are currently feeling the effects of the financial squeeze and are experiencing significant rises in their premiums (Kaiser Foundation, 2012).

From a public sector perspective, Medicare, which provides publicly-funded healthcare coverage to citizens over the age of 65 is particularly important with regards to oncology as by 2030, 20% of the USA population is likely to be over 65 (National Palliative Care Research Center, 2013). According to the USA Census Bureau, the programme covered 44.3 million people in 2010, accounting for around 14.5% of the total population (IMS Health, 2013).

The Affordable Care Act (ACA) was signed into law on 23 March 2012 with the aim of putting in place comprehensive health insurance reforms to enhance the quality of care for all Americans. From an oncology perspective, the ACA will ensure that patients with cancer will not be denied coverage from cancer due to pre-existing conditions or charged more for their coverage due to their health status. Also, the ACA means that patients will no longer face annual or lifetime coverage limits that cause a sudden termination of care. Annual dollar limits will be firmly restricted for most plans and eliminated by 2014.

The ACAs main impact will be increasing the number of patients who gain coverage which will see an increase in costs (American Cancer Society, 2013). Although there is likely to be downward pressure on pharmaceutical companies’ drug prices, the likelihood is that it will be employers who are likely to bear the cost of increased usage (Kaiser Foundation, 2012). Pockets of resistance to high drug prices
in oncology has already begun in the USA, with three doctors at the Memorial Sloan-Kettering Cancer Center in New York writing an open letter in the New York Times explaining that the Center would not be funding the advanced colorectal cancer drug ziv-aflibercept (Zaltrap, Sanofi) on the basis of cost (Bach et al, 2012). Interestingly, the response from the manufacturer was to immediately offer a business discount to hospitals and oncologists, which was slightly different from the triumphant headline ‘Sanofi halves price of cancer drug’ made by The New York Times (Pollack, 2012).

The reality in the USA is that if a drug is approved by the Food and Drug Administration (FDA) and listed in the National Comprehensive Cancer Network (NCCN) oncology guidelines, plans will cover it. How sustainable this reality is in the long-term remains to be seen.

Palliative care is a key aspect of the healthcare debate in the USA, particularly in oncology, as the cost of anti-cancer medication is expensive (Temel et al, 2010). There is evidence that providers are investing heavily in palliative care in an attempt to get patients into hospices and away from medication in end-of-life scenarios; faced with a high co-pay for an expensive new therapy that may only extend life a few weeks, patients with low life expectancy and poor quality of life may prefer the option of good palliative care, not to invest in drug therapy due to affordability.
Global payer challenges in oncology

The challenges facing payers in oncology is knowing which treatments to fund to obtain best value for money. In such a sensitive environment, these decisions transcend purely balancing the books and payers are making decisions against patient, public and political pressure. However, even in the USA, funding the latest treatments is clearly not problem-free and on both sides of the Atlantic the situation is not sustainable in the long-term. Payers are likely to use a number of traditional options to restrict access in the near future. In the USA, it is likely that payers will continue to use the NCCN guidelines as a way of restricting new product usage. In the UK, it is likely that NICE will continue to use PAS as a way of negotiating rebates with manufacturers.

There are currently four areas which are particularly challenging for payers in oncology.

1. The media

Oncology being a high-profile therapy area in the media spotlight is actually a double-edged sword—on the one hand it can make restricting drugs very difficult for payers, however, as we have seen with the Zaltrap example in the USA, public pressure can portray pharmaceutical pricing in a negative light and put pressure on the company to reduce pricing. In the UK, both NICE and patient groups often call for a company to submit a PAS in response to an initial negative decision. The media is thus a powerful tool on both sides of the fence.

2. Evidence requirements

Payers will continue to want to see an improvement in overall survival (OS), and despite an acknowledgement that progression-free survival (PFS) is acceptable in cancers with a longer life expectancy and initially at product launch, the pressure is on pharmaceutical companies to demonstrate benefit for new molecules and combinations. Payers have an initial expectation of benefit they want to see from new oncology drugs, and particularly with combinations, an improvement over standard of care (SoC) is vital to achieving reimbursement. At the time of writing, the breast cancer medicine Perjeta has just been turned down by NICE’s Appraisal Committee at draft stage (NICE, 2013)
and the comments from NICE Chief Executive Sir Andrew Dillon, illustrate the requirements of payers:-

‘The Appraisal Committee couldn’t be sure of the benefits of pertuzumab. The main clinical trial did not reflect current medical practice in the UK and despite the research data suggesting the treatment could help delay the growth and spread of the disease, the evidence was not robust enough to confirm for how long pertuzumab may actually extend people’s lives.’

Patient-reported outcomes (PROs) can be combined with survival to determine quality of survival (Gotay, 2008); however, payers are still cautious in interpreting their results. Payers generally view PROs as better than reporting surrogate markers to demonstrate clinical effectiveness, however, for the purpose of economic modelling, payers still prefer to see traditional approaches using OS and PFS to drive cost-effectiveness.

3. Disease knowledge
‘Oncology’ is a difficult subject for payers to be experts in purely due to the number of tumour types available and the subtleties and specialism required to assess value in each. Cancer Research UK estimates there are more than 200 types of cancer and that there are 60 organs in the body where a cancer can develop (Cancer Research UK, 2013). It is therefore unrealistic to expect payers to have the same level of knowledge as the top key opinion leaders (KOLs) in each field.

In the UK, NICE rely on the input of clinical experts as its Appraisal Committee are not specialists in reviewing oncology drugs due to being formed of a cross-section of the NHS, patient and carer organisations, academia and the pharmaceutical and medical devices industries. In the USA, payers are working side-by-side with KOLs to devise treatment pathways, starting with the largest tumour types and restricting drug use to those approved on the pathway.

4. Balancing oncology against other therapy areas
While oncology remains an area that has been traditionally associated with high-cost medicines, payers are also facing challenges from other therapy areas for vital funding, which have high-price medications and strong levels of political and public support. Disease areas such as cystic fibrosis and lysosomal storage diseases have seen high-cost innovations from the pharmaceutical industry, and combined with political sensitivity, make it an equal if not more pressing challenge for payers compared to oncology drugs. Finding space for innovation across therapy areas makes the space available for new oncology drugs smaller; and as a result, ensures payers are more sceptical around the evidence base and value of new oncology treatments.

Conclusions
It is clear that innovations in oncology are moving at a very fast pace and that great strides are being made towards making cancer a long-term condition rather than a death sentence. Patients quite rightly have great expectations, as do the companies in terms of getting a reward for their investment, and as always, it is the role of the payer to manage these. If in a market as big as the USA, the underlying psyche of the healthcare system is moving towards cost-effectiveness, then this signals the changing winds of what is affordable on a global scale.
The UK has long had a system of HTA and a solid focus on cost-effectiveness and VBP merely signifies a shift from profit control to a greater focus on value for money. The media is likely to have a considerable influence in not only putting pressure on payers to make new products available, but also on companies to consider rebates and pricing arrangements to make new medicines available. The expectations in oncology continue to rise; it remains to be seen as to whether healthcare systems—on both sides of the Atlantic—have the capacity available to make them a reality.

Reference