Potential approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and the implications

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Introduction: There are growing concerns among European health authorities regarding increasing prices for new cancer medicines, prices not necessarily linked to health gain and the implications for the sustainability of their healthcare systems. **Areas covered**: Narrative discussion principally among payers

and their advisers regarding potential approaches to the pricing of new cancer medicines. **Expert commentary**: A number of potential pricing approaches are discussed including minimum effectiveness levels for new cancer medicines, managed entry agreements, multicriteria decision analyses (MCDAs), differential/ tiered pricing, fair pricing models, amortization models as well as de-linkage models. We are likely to see a growth in alternative pricing deliberations in view of ongoing challenges including the considerable number of new cancer medicines in development including new gene therapies and being launched with uncertainty regarding their value, continued high prices coupled with the extent of confidential discounts for reimbursement; however, balanced against the need for new cancer medicines. This will lead to greater scrutiny over the prices of patent oncology medicines as more standard medicines lose their patent, calls for greater transparency as well as new models including amortization models. We will be monitoring these developments.

Key points:

- There is continued growth in medicine expenditure driven by increasing expenditure on speciality and complex treatments including those for cancer, which will soon account for 50% of total expenditure
- Concurrent with this, we are seeing new cancer medicines being launched at high prices with often considerable uncertainty regarding their future role. These concerns are leading to the development of different pricing approaches including establishing minimum effectiveness levels for new oncology medicines to be seen as an advantage, managed entry agreements, multicriteria decision analyses and fair pricing models to potentially reduce disparities in their availability and funding across Europe
- The value of existing patented oncology medicines will increasingly be re-evaluated as more standard treatments becoming available as low cost generics or biosimilars
- However, ongoing initiatives must be balanced against the need to still continuing to stimulate research into new oncology medicines including new gene therapies

Introduction

By 2023, it is estimated that global spending on medicines will reach US$1.5 trillion, growing at an annual compounded growth rate of 3–6% [1]. Approximately 50% of total expenditure will be on specialty medicines, including those for chronic, complex, or rare diseases incorporating oncology medicines [1]. As a result, oncology will continue to dominate spending on medicines especially in high income countries [2,3]. The cost of cancer care also now accounts for up to 30% of total hospital expenditure across Europe [4]. World-wide sales of oncology medicines are expected to grow to $237 billion by 2024 [2], with this growth likely to continue with over 500 companies actively pursuing development of new oncology medicines in over 600 indications [5], and envisaged high price expectations [6].

We have seen the median annual cost for new oncology medicines exceed US$150,000 per person per year in 2017 compared with US$79,000 in 2013, with prices continuing to rise [3]. The price per life year gained for new oncology medicines has also risen in recent years, rising four-fold during the past twenty years after adjusting for inflation [7]. However, there are concerns with reimbursed prices for new oncology medicines among especially higher-income countries and the actual level of health gain seen [8,9]. However, Molto et al (2020) found that 40% of new oncology medicines recently received a breakthrough therapy designation, and were more likely than non-breakthrough therapies to provide a meaningful clinical benefit [10]. In addition, Lauenroth *et al.* (2020) found that the reforms in Germany led to reimbursed prices for new oncology medicines falling following evaluation; subsequently, more in line with the clinical benefit seen [11].

High requested prices for new oncology medicines though are resulting in appreciable disparity in their availability across Europe [9,12,13], mirroring the situation with biological medicines for arthritis and inflammatory bowel disease [14]. Alongside this, increasing concern with the sustainability of universal healthcare systems across countries [15]. The launch of new advanced therapy medicinal products (ATMPs), including new high-priced gene therapies, will put further pressure on countries' abilities to continue providing universal healthcare [16,17]. The current situation has already resulted in requests for price moderation for new oncology medicines in countries with high patient co-payment levels [18,19], and this will continue. We are already aware that current prices for new oncology medicines means they will be beyond the reach of the majority of low- and middle- income countries (LMICs) who struggle even to fund trastuzumab [20,21]. This is a concern that needs addressing as

LMICs currently witness the fastest growth in mortality from cancer [22,23]. The growing availability of low cost biosimilars should help here [24].

Payers and their advisers are increasingly aware of the low production costs of a number of oncology medicines including those deemed cost ineffective by national authorities in Western Europe [25]. This is illustrated by price reductions up to 97.8% for oral cancer medicines once multiple sourced products become available [26], an 83% reduction in total expenditure on adalimumab in Denmark once biosimilars became available [27], and AbbVie in the Netherlands reducing the price of Humira® by 89% just before biosimilars became available [28]. However, there are concerns that cost-based pricing approaches can be difficult to implement especially with challenges in transparency and could result in disincentives to address areas of unmet need [29]. This is a concern given the level of unmet need with currently 9.6 million deaths annually from cancer globally and growing [22,30].

Payers and their advisers are also aware of an increasing number of medicines with small patient volumes such as targeted oncology medicines and those for orphan diseases are reaching global sales of over €1billion (US$1.2bn) per year under the current system, with the number of medicines in this category continuing to rise [31]. In addition, up to the end of 2017 there were 33 oncology medicines with average annual sales exceeding US$1billion per year, with high sales often persisting after patent loss [9]. Alongside this, there is increasing uncertainty with the value of new oncology medicines at launch. For instance, 50% of the new oncology drugs approved by the US Food and Drug Administration (FDA) in 2017 were solely based on data from a phase II trial with 21% based on phase I/II trials [3], and in 2018 the FDA granted accelerated approval for larotrectinib for adults and children with certain targeted tumours based on findings from only 55 patients across 12 cancers [32]. The majority of accelerated approvals (79%) are now for oncology medicines [33], and it is often left to European health authorities to fund these approved treatments under early access schemes until more data becomes available with limited opportunities to re-coup the monies spent if there are subsequent concerns with their effectiveness in practice [34,35]. In addition, fast-track oncology medicines are often associated with increased risk of safety-related issues [33].

Consequently, there is a recognised need among especially European health authorities to re-evaluate pricing approaches towards new oncology medicines given these multiple challenges. They are also aware that expenditures on new oncology medicines in the US for those approved just in 2018 could be as high as US$39.5 billion if they were prescribed in all eligible patients that year [36]. This figure does not include expenditure on oncology medicines either side of this [36]. Such expenditures would pose a threat to the principals of equity and solidarity even among high income European countries. However, there are concerns that any potentially new proposed pricing approach may not always incorporate key issues for new valued oncology medicines including issues such as their impact on productivity and/ or current disabilities, reducing carer support, improving adherence rates where these are an issue as well as considering the impact of new knowledge gained on improving future treatments and the value of hope [37-39].

Current proposals to address concerns include establishing meaningful minimum effectiveness levels for new oncology medicines to be funded at higher prices than current standards, first proposed in the United Kingdom in 2000 [40,41], defining what is meant by innovation [42], and implementing fair and transparent approaches towards the pricing of new oncology medicines proposed by European payers, the World Health Organization (WHO) and others although there are concerns with issues including fully costing R. & D. [43-45]. Potential proposals also include re-looking at managed entry agreements (MEAs) with countries concerned they may not always be getting optimal discounts in practice with rebates continuing to be confidential [46,47]; however, balanced against increased opportunities of reimbursement with such schemes combined with the potential to gain valuable evidence of the performance new oncology medicines in routine clinical care [46,48]. This is important given concerns with the lack of subsequent studies confirming effectiveness aspiration using clinical outcomes contained in the initial approval of novel new medicines following their launch [49].

Other proposals include the development of new multicriteria decision analyses (MCDAs) models [50,51] as well as potentially de-linkage models combining academic consortia with separate manufacturers to make new oncology medicines available at low prices [52]. Alongside this, we are already seeing countries and regions in Europe and wider become appreciably more pro-active in their approaches to funding new medicines in designated populations starting up to three years pre-launch and continuing post-launch to assess their role and value in routine clinical care [53,54]. Some

authors are also arguing for differential pricing to enhance access to new oncology medicines in LMICs as well as further stimulate innovation, which could be based on economic indicators . Alongside this, argue for differential pricing by indication to broaden reimbursed indications [55-57]. However, there are reservations with the practicalities of these approaches.

Consequently, the principal aim of this perspective paper is to summarise, frame and debate potential approaches to the pricing and reimbursement of oncology medicines given current concerns. As such, help lay a foundation for the future.

2. Body of the paper

2.1 General considerations

The views expressed and debated will principally be from a European payer's perspective as they are key personnel involved in funding and reimbursement decisions for new oncology medicines across Europe. We have chosen to concentrate principally on Europe in view of continuing debates about possible ways of valuing new medicines including those for cancer and orphan diseases, ongoing initiatives to improve the managed entry of new medicines, current controversies surrounding adaptive pathways and MEAs as well as a plethora of demand-side measures to enhance the prescribing of multiple source products and biosimilars when available [26,35,55,58]. We are aware this contrasts with the USA with its absence of single-payer health care systems where patients or families who can afford it often demand expensive oncology therapies despite marginal survival expectations, although there are concerns among some with potentially high expenditures on new oncology medicines [36]. However, we believe our deliberations will be of interest to all countries, and especially LMICs, given continual pressure on healthcare resources exacerbated by the COVID-19 pandemic.

We will principally use the knowledge and experience of the senior level co-authors from across Europe typically working for health authorities or health insurance companies or advisers to them to debate potential pricing approaches and their ease of administration.

2.2 Defining innovation

The Expert Panel on effective ways of investing in Health (EXPH) suggested "value-based healthcare (VBHC)" should be built on four pillars namely (i) appropriate care to achieve patients' personal goals - personal value, (ii) technical value incorporating the achievement of best possible outcomes with available resources, (iii) allocative value including the equitable resource distribution across all patient groups which is seen as very important in Europe with its universal healthcare and opportunity costs a key consideration and (iv) societal value including the societal contribution of any healthcare intervention to social participation and connectedness [59]. This mirrors some of the considerations of Garrison et al. [38,60]. Opportunity costs is a key consideration for cancer care as discussed by Barrett et al. (2006) when Herceptin® first became available in the United Kingdom [61]. However, it is recognised that additional considerations should be given to reimburse and fund new premium priced treatments that address unmet need in patients with severe diseases such as cancer to stimulate innovation [51,62].

We are also aware that Berdud et al. (2020) have recently suggested implementing variable cost/ QALY limits for new medicines for orphan diseases, which could include new oncology medicines for targeted populations, depending on the size of the patient population [63]. These build on existing approaches in countries including Sweden and the UK [62,64]. However, there are concerns that such approaches could be abused as seen in the Netherlands where there was considerable pressure for the Government to fund new medicines for Pompe's disease up to €15 million/ QALY as well as concerns with their moral justification [64,65].

2.3 Minimum effectiveness criteria

Ferguson *et al.* in the UK in 2000 suggested that a minimum of 3 to 6 months of additional survival compared with current standards should be the threshold level for hospitals and health authorities to consider authorising and funding any new oncology medicine at a higher price than current standards [40]. Others have suggested similar considerations although there are concerns that an additional three months may be considered a marginal benefit by clinical experts whilst expressing concerns with the value of surrogate markers in decision making [9,41,66-68].

Lower thresholds have been suggested [69]. However, this is a concern with Kantarjian *et al*. (2013) noting that of the twelve oncology medicines approved by the US FDA in 2012 only three actually prolonged survival and in only one was this by more than two months. However, among the twelve, nine were priced at more than US$10,000 per patient per month [70]. Davis *et al* (2017) in their analysis also found that 57% of new oncology medicines approved by the EMA between 2009 and 2013 had no evidence of quality of life or a survival benefit at the time of approval, or if present, these were not clinically meaningful in most cases with many new cancer medicines approved on the basis of only surrogate markers [71]. Cohen in an accompanying editorial in the BMJ highlighted that despite often limited health gain, these medicines were often associated with high prices [8], and warned against potential overestimation of the clinical benefits of new oncology medicines when approval is granted in the context of early access policies. Having said this, Salas-Vega in their analysis found that 43% of new oncology medicines approved either by the FDA or the European Medicines Agency (EMA) between 2003 and 2013, and subsequently reviewed by health technology agencies, did improve overall survival by 3 months or longer [72]. In addition, as mentioned, Molto et al. (2020) found that 40% of new treatments recently received a breakthrough therapy designation, and were more likely than non-breakthrough therapies to provide a high clinical benefit [10]. Consequently, minimum thresholds of three to six months are likely to remain.

However, payers are aware they need to look more critically at important factors for patients including issues of toxicity and quality of life along with caution when appraising requested prices if only surrogate endpoint data is available during negotiations and the data is still immature [33,34,41]. Health authorities and patients can play a key role in future funding decisions especially across Europe by agreeing what is meant by meaningful clinical benefit to establish baselines for granting higher prices for new cancer medicines versus current standards building on current examples [41,59].

2.3 Managed Entry Agreements (MEAs)

There has been an increase in the number of MEAs in recent years especially for new oncology medicines given pharmaceutical company requests for high prices coupled with concerns with affordability [48,73].

MEAs can generally be divided into financial-based schemes, which typically involve confidential rebates, discounts, or price volume agreements, and performance or outcomes-based schemes, which typically include outcome guarantee schemes or agreed prices based on agreed outcomes [47]. Financial-based schemes are increasingly seen in practice as they are viewed as easier to administer and are more suited to manage uncertainty regarding overall budgets [46,47].

In its recent report addressing the challenges in access to oncology medicines, the OECD (2020) suggests that the design of outcome- or performance-based MEAs should be improved to better support the generation of real-life clinical data to reduce the uncertainty regarding the effectiveness and safety of new oncology medicines in routine clinical care [74]. This is because financial based agreements typically only help control the economic impact of new medicines and do not address clinical uncertainty. This is a concern with, as mentioned, new cancer medicines increasingly launched with immature data and the high failure rates of translating promising Phase II into positive findings in Phase III and beyond [75,76]. Alongside this, only a relatively limited number of European countries and regions have good patient level data infrastructures to routinely capture outcome data in practice without the need to design specific schemes for each new oncology medicine. Concerns with the latter have resulted in the plethora of MEAs in Italy failing to collect any meaningful clinical data, alongside disputes with manufacturers regarding any payback, with current MEA arrangements principally demonstrating that healthcare professionals followed prescribing guidance [77]. Consequently, key stakeholder groups including payers and patient groups will need to decide in advance if the value of information retrieved through MEAs will be clinically meaningful and

compensate for the cost of any subsequent data collection [78]. Agreements between payers and pharmaceutical companies will also need to be strengthened given concerns with continued reimbursement despite at times issues with their value as more evidence becomes available [79].

Potential ways forward especially in Europe include the harmonisation of the clinical data that can routinely be collected in busy oncology clinics for any future outcome-based MEA. This builds on approaches such as the Cancer Medicines Outcome Project (CMOP) programme in Scotland starting with prostate cancer [80,81], as well as the Data the Systemic Anti-Cancer Therapy (SACT) dataset project in England [82]. This also builds on recent initiatives in the United Kingdom that pharmaceutical companies need to start collecting outcome data for any new oncology medicines targeted for consideration for funding within the UK Cancer Drug Fund, with such situations likely to grow [83]. However, this must be balanced against the considerable costs that can occur with increased monitoring of patients especially where there is uncertainty regarding the role and value of new treatments [84]; however, costs can be reduced with initiatives such as CMOP and SACT.

Potential advantages and disadvantages of MEAs have recently been summarised by Zampirolli Diaz *et al.* (2020) with payers and their advisers from a number of countries and continents involved in such activities (Table 1), building on deliberations by Antonanzas et al., Carlson et al., Hampson et al., Toumi et al. and others [46,48,85-87].

Table 1 – Summary of advantages and disadvantages of MEAs [adapted from Al-Omar et al, Antonanzas et al., Carlson et al., Hampson et al, Toumi et al. and Zampirolli Diaz et al [46,48,86-89]].

Advantages	
General	• Provide access to new medicines where affordability is an issue and/ or where there are concerns with the uncertainty of the effectiveness or cost-effectiveness of the new oncology medicine when introduced into routine use. • Potentially improve prescribing in a more predictable, transparent and rational way to a defined patient population enhanced by subsequent monitoring of prescribing against agreed guidance, e.g. Italy and Sweden, and that agreed outcomes are being reached in practice [77,90-92] • Offers flexibility in terms of the potential budget impact and value when considering new oncology medicines characterised by appreciable levels of uncertainty especially as more biological medicines are losing their patents, with the potential for payback mechanisms if outcomes and subsequent value are less than expected [48,86]
Financial-based schemes	• Easier to implement than outcome-based schemes, helping to contain costs and keep expenditure within agreed limits. • Potential for cross product agreements among Pharmaceutical Companies and health authorities to help keep annual expenditures within agreed limits • Potential to improve the cost-effectiveness of new oncology medicines through lowering the incremental cost-effectiveness ratio (ICER)
Outcome-based schemes	• Potentially provides new oncology medicines to patients including those most likely to benefit, e.g. CAR-T cell therapies among EU countries including future re-assessment of prices and/ or rebates based on agreed outcomes in France, Germany and the UK, with re-assessments of staged payments in Italy and Spain [93] • Potentially incentivize R&D activities more than reimbursement and funding policies based on cost effectiveness criteria • Provide additional 'real-world' evidence – especially important when new medicines are approved with limited Phase I and II data • Can help consolidate the development of a set of meaningful data that can be routinely collected in busy oncology clinics to improve

	future decision making such as the CMOP programme in Scotland [80] • Potentially provide evidence about a new oncology medicine in different patient populations • Can in time help to update guidelines within a country on appropriate medicine use as more data becomes available. • Potential to prolong the time for capturing meaningful data on the effectiveness, safety and cost-effectiveness of a new oncology medicine in a more restricted environment with clinicians adhering to agreed protocols and no off-label use. As a result, more rapidly enhance the evidence base. This is increasingly important in the case of oncology medicines if initial data sets are based on surrogate markers such as progression free survival rather than overall survival and impact on quality of life
Disadvantages	
General	• Whether countries are getting the optimal discount in reality and concerns with good governance [9] • Volume agreements do not necessarily ensure the most appropriate patients receive the new medicine – the concomitant instigation of demand-side measures including prescribing against agreed protocols can help here • In pertinent countries, patient co-pays will be higher in ambulatory care if co-payments are based on list rather than actual prices - balanced though against wholesalers, distributors and retail pharmacists typically paid on list rather than actual prices across countries • Potentially higher administrative and transaction costs including the length of time for negotiations especially for outcome-based schemes, lack of expertise and potentially a lack of regulations. • In multiple-payer healthcare systems, data tracking is challenging when members move from one plan/ insurance company to another. • Early approval and funding via MEAs for new oncology medicines could potentially be considered by physicians and patients as improvements compared to current standards without necessarily being the case [34]
Financial-based schemes	• Companies potentially asking for higher prices initially especially if they believe discounts are inevitable. • The confidential nature of discounts and rebates could mean companies seek a high list price in a reference priced country, especially in a country with considerable economic power to negotiate good discounts, to the detriment of other countries with less economic power
Outcome-based schemes	• Information collected in outcome-based schemes may not necessarily enhance the evidence base especially where there are concerns with trial design • Patient accessibility may be compromised if the new oncology medicine is only available in a limited number of centres, and the temporary nature of certain agreements may make companies cautious about progressing with them. • The confidential nature of data captured/ privacy issues adds to the difficulties with transparency when analysing the findings with typically strict criteria within health authorities to accessing patient level data under governance issues • Issues of transparency are also important in discussions with patients about the temporary nature of any funding for new medicines under outcome based MEAs. • Concerns with the length of time of some outcome-based schemes - especially important in rapidly changing disease areas

	or where generics/ biosimilars will become available by the time the outcome-based scheme is finished. • Who pays for the cost of the oncology medicine during the evaluation period – seen as a particular issue with olaratumab [34] • Health authorities may not always be fully compensated in payback schemes when the new oncology medicine is not as effective or cost-effective in routine clinical care as expected • Possible difficulties at the time of finishing agreements to lower prices if pertinent to reflect the actual observed effectiveness in clinical practice if there is a reluctance among companies to reduce the prices of their patented medicines (especially in reference priced countries) alongside pressure from clinicians who have already incorporated the new medicine into their clinical protocols

It is likely there will be a growth in MEAs in the coming years given the likely increase in the number of new high cost oncology medicines being launched including personalized medicine approaches such as CAR-T therapies, with MEAs seen as a viable means of addressing concerns with immature data at launch alongside high requested prices, increasing pressure on available resources exacerbated by the COVID-19 pandemic, and the absence of other approaches to enhance the affordability of new oncology medicines in Europe and wider. In addition, re-assess potential rebates under value-based pricing schemes when the initial standards used in reimbursement and funding negotiations become available as either low cost generics or biosimilars as a pragmatic way forward [9].

Greater knowledge about the outcome of current schemes would be beneficial going forward to aid all key stakeholder groups. However, timelines for any schemes have to be reasonable for all key stakeholder groups. There are also considerations for the introduction of independent platforms for outcome-based contracting which aligns the interests of all key stakeholders and promotes inclusivity and transparency. We will be looking to explore this feasibility in Europe going forward [94].

The formation of purchasing consortia especially in Europe (progressing) and South America via PAHO (as seen with new medicines for Hepatitis C) may help to address the current lack of transparency with prices, discounts, and rebates fulfilling recent WHO recommendations for increasing pricing transparency for medicines across countries [45,59,95]. Alongside this, enhance the concomitant instigation of demand-side measures across countries, including prescribing against agreed protocols, to optimise the use of new oncology medicines as part of any agreement [9].

It is also likely we will see more outcome-based schemes as IT-infrastructures become more sophisticated across countries. Lastly, there is growing recognition that the appraisal of the value of new oncology medicines is more a continuum than a ‘one-off’ evaluation; however, mindful of the concerns (Table 1) [46,54]. The continuum will be helped by an increasing number of centres collaborating together including research agendas from basic science to the collection of outcome data [96].

2.4 Multicriteria decision analyses (MCDA)

In formulating recommendations for reimbursements, appraisal committees typically interpret the results of an assessment in a broader perspective to inform decision-makers making use of MCDAs. This is an intrinsically complex and a value-laden task that requires careful judgement. It is likely we will see a growth in MCDAs including for new oncology medicines in view of concerns with current approaches including transparency [97]. These models may well build on suggested models for new medicines for orphan diseases [55,98,99], as well as the deliberations of Lakdawalla *et al*. who discuss additional considerations for valuing new medicines including the value of hope and the real option value. The “real option value” is generated whereby the prescribing of a new medicine that extends life potentially creates opportunities for patients to benefit from future advances, improves equity, and may result in scientific spill overs from one new medicine to another [37].

We are aware that several public agencies and health insurers are already using, or proposing, MCDA approaches in healthcare decision making including an MCDA introduced by the

reimbursement authorities in Italy to help define the level of innovation of new medicines, and this is likely to grow including LMICs [100-102].

Hsu et al (2019) recently developed a MCDA for targeted therapies for colorectal cancer centring on clinical, economic and social values (Table 2) [50].

Table 2 – Multicriteria for assessing the value of targeted therapies for colorectal cancer [adapted from Hsu et al [50]]

Dimension	Criteria
Clinical	• Comparative efficacy – overall survival and progression free survival (months) • Overall safety, e.g. incidence of adverse events including severe adverse events and potential for drug: drug interactions • Convenience (including length of treatment) and impact on health-related quality-of-life
Economic	• Cost-effectiveness - incremental cost-effectiveness ratio (ICER) • Number of patients – number of patients by indication who could potentially be treated • Expenditure – overall expenditure (budget impact)
Society values	• Degree of innovation – including likely approval times by the authorities • Societal concerns and patient needs – including the extent of alternatives • Experience/ funding – Extent funded within other countries

Angelis *et al.* (2020) also recent developed an advanced value framework for new medicines for prostate cancer [103]. Their key criteria are presented in Table 3. Perhaps not surprisingly, the level of therapeutic benefit consistently ranked first in relative importance among the studied countries (Belgium, Poland, Spain, Sweden). Whilst there were some differences in value preferences between respondents (assessors and experts) in the given countries, drug rankings in terms of the relative value of the different medicines for prostate cancer including abiraterone, cabazitaxel, and enzalutamide, remained the same across the studied countries [103].

Table 3 – Criteria for assessing the value of therapies for prostate cancer [adapted from Angelis et al [103]]

Dimension	Key criteria
Clinical (outcome)	• Overall survival (months) • Health related quality-of-life (stable and progressive disease) – utility scores (EQ5D)
Clinical (surrogate)	• Radiological progression free survival (months) • PSA response (%)
Clinical (side-effects, etc.)	• Treatment discontinuation (%) • Contra-indication (type)
Other clinical/ value considerations	• ATC level (mechanism of action) • Experience – number of patients enrolled into Phase II and III trials for given indications • Delivery posology
Economic	Medical costs/ budget impact

Ezeife et al (2020) used a multi-stakeholder approach using 2 patients,2 public members 2 patient advocacy group leaders, 2 pharmacists, 1 industry representative, 6 oncologists, 1 ethicist, 3 health economists. 3 members of an appraisal committee (pCODR), 2 cancer agency members, and a Ministry of Health government representative. They identified the criteria through published literature, and let the stakeholders assign weights equalling 100 [104]. The highest weights assigned included quality of life (weight of 19), overall survival (weight of 15), and unmet clinical need (weight of 15), with the lowest weights being for disease severity (weight of 5) and caregiver well-being (weight of 4) [104].

However, there are concerns that quantitative MCDA approaches may not be that transparent in reality and may not necessarily lead to good quality recommendations [105]. This has resulted in more structured deliberative approaches including those used by the pan-Canadian Oncology Drug Review (pCODR) in Canada [106], and ongoing initiatives in the Netherlands and the UK [107]. This means that appraisal committees make judgments on the overall value of a technology using some rules. These rules subsequently guide trade-offs between explicitly defined criteria such as disease severity and cost per quality adjusted life years (QALYs) [108]. We will continue to monitor such activities to provide future direction, similar to ongoing activities regarding MEAs.

2.5 Differential/ tiered pricing including multi-indication pricing

We also see growing debates regarding indication-based prescribing, i.e. differential pricing by indication especially if there are appreciable differences in the value of a new medicine by indication [57,109-111]. However, there are a number of concerns with this approach.

These include the fact that at maximum prices per indication, this favours pharmaceutical companies over health authorities [112]. This approach could potentially lead to higher prices for patients who benefit the most, which is an issue where there are already high patient co-payments [56,113]. In addition, monitoring against manipulated diagnoses ("up-coding") is challenging, as experiences from introducing hospital payment schemes based on diagnosis-related groups (DRGs) have shown. There are also concerns among companies that if the low value indication is launched first, the cost of developing the high value indication may be prohibitive [57].

However, improved planning and proactivity within countries as well as robust IT systems that collect data on indications alongside utilisation data can help address some of these concerns. Alternatively, through requirements to collect data through registries [57,109,114]. However, different European countries are at different stages with their IT systems especially regarding linking medicines dispensed with an indication [115]. Consequently, it may be that a review of existing discounts and rebates is a practical approach in the short term since R & D costs have already been accounted for during pricing negotiations for the first indication [112]. Subsequently, re-visit the situation as health authorities further develop their IT system.

Mestre-Ferrandiz *et al.* (2018) recently identified six key issues when key stakeholders consider multi-indication pricing (Table 4) [114]. A review of potential discounts for new medicines where companies are seeking additional indications would appear to be the most prevalent and possible approach to date to address indication-based pricing (IBP) as this takes into consideration issues of higher profitability with new indications as R & D costs have already been accounted for [112]. This is also consistent with a recent systematic review by Campillo-Artero *et al.* (2020) who found no application of indication-based pricing (IBP) systems in practice and their practical consequences [112]. The authors concluded that MEAs most closely resemble the IBP approach; however, such arrangements are generally confidential [112], which is a continual concern.

Table 4 – Key considerations when considering multi-indication pricing (adapted from Mestre-Ferrandiz *et al.* [114])

Key consideration	Implication
Incentives	Incentives need to be designed to encourage the collection and use of reliable data including indication data, e.g. in Italy it is in the hospitals' interest to collect utilisation data by indication as part of MEAs for new medicines [116,117]
Registries	Registries need to be improved and allow for the incorporation of real world evidence into reimbursement and funding decisions
Co-ordination	• Co-ordination needs to be enhanced at all levels for effective systems. This includes the national level, but may also include the regional level data if there are already different prices for medicines across regions in a country • There also needs to be co-ordination at the hospital level to monitor usage by patient and indication if this is linked to managed entry and other schemes
Transparency	There needs to be greater transparency regarding who actually benefits from such approaches as part of any future situation
Contractual pricing arrangements	Any contractual pricing arrangements need to be flexible in order to take account of any new evidence surrounding existing and new indications as well as changes in the prices of medicines being used to treat that tumour and stage. This is especially important if pertinent medicines become available as low cost multiple sourced medicines or biosimilars
Modelling the impact of differential pricing approaches	• There is also a recognised need for further research to help model the potential budget impact of differential pricing especially if this leads to lower overall expenditure • If subsequently greater expenditure – how can this be equitably and transparently shared between payers and pharmaceutical companies with companies seeking to maximise prices for each indication [109]

2.6 Fair and Transparent Pricing Models

There are ongoing discussions across Europe and within other countries concerning what is considered a fair price for a new medicine, including a new oncology medicine, depending on the perspective of the stakeholder [43,118,119].

This includes concepts surrounding fair pricing incorporating proposed models from payer groups such as the International Association of Mutual Benefit Societies (AIM) and others [43,44,119,120]. Moon *et al.* (2020) believe the price of a new medicine should allow for the societal need for that medicine; however, government interventions are usually needed to ensure a fair and equitable price to benefit all key stakeholder groups [119]. Typically, this means greater transparency around key issues including R & D, production costs and pricing approaches [118]. The aim is to stimulate and reward the development of new medicines in areas of unmet need including new innovative oncology medicines whilst limiting funding for new oncology medicines where high prices are sought for limited health gain. The WHO (2020) in their recent guidelines on country pharmaceutical policies also ask for increased price transparency as well as potentially a cost-plus approach to pricing if the lack of transparency in price setting continues [45].

Whilst Moon and colleagues discussed in general terms what they mean by fair pricing, there currently appears no standard definition of what actually constitutes a fair price for new oncology medicines [119]. Having said thus, the European Cancer Leagues recently defined a fair price for a new oncology medicine as '*A fair price is transparent, understandable, affordable, proportionate and based on objective factors such as R & D investment, delivery, marketing and sales costs, and a clearly defined profit margin connected to the proven therapeutic value (if available compared with other treatments). They believed a fair price was profitable enough to steer innovation in the long term, but would not pose a threat to the long term sustainability of healthcare systems'* [121]. Overall, they believed proposed prices should combine economic aspects such as the cost-effectiveness and budget impact of any new oncology medicine as well as likely estimates of the costs associated with

R & D [121]. However, there is currently an absence of reliable published data on development costs which is a concern although most commonly accepted estimates lie between US$200million and US$2.9billion [9]. In their model, Moon *et al.* (2020) proposed the concept of a 'fair pricing zone' that lies between a price floor and a price ceiling. The price floor for a new medicine, including a new oncology medicine, should be the lowest sustainable price at which suppliers, typically pharmaceutical companies, can sell a medicine and still incentivise innovation. This includes R & D costs, manufacturing, and distribution costs as well as a fair profit [119]. The price ceiling is the maximum price that a buyer, e.g. a European health authority, can afford [119]. Moon *et al.* identified seven key information and analysis requirements that are needed in order to apply their fair pricing framework (Table 5) [119].

Table 5 - Key information and analysis requirements needed in order to apply a fair pricing framework [adapted from Moon et al [119]]

Factors to consider	Information and analysis requirements
Sellers (including those conducting R & D as well as the manufacturers/ companies)	
Cost of R&D	Typically this information is not disclosed and is contentious to estimate as seen by appreciable differences in published sources for bringing new medicines to the market ranging from US$200million and US$2.9billion [9]
Cost of manufacturing and distribution	Generally this information is not disclosed although it is seen as feasible to estimate and usually disclosed in competitive markets as seen by some of the low costs for generics and biosimilars and other estimates of production costs [26,28,122,123]
Fair profit	• Typically aggregate profits are disclosed by companies but these are typically not product specific • Such activities will typically entail a judgement as there have been concerns among health authority personnel that companies typically set prices for new medicines for cancer and orphan diseases based on previous benchmarks and what they feel are attainable prices irrespective of the health gain involved [8,124-127]
Other costs including registration, administration and pharmacovigilance	Again, usually such information is typically not disclosed by companies but is feasible to estimate based on previous benchmarks
Buyers (including health authorities and patients)	
Affordability of new medicines	Additional analytical work will generally be required to identify concrete affordability ceilings for health authorities and patients given concerns with ever increasing prices for new cancer medicines and those for orphan diseases [7,126,128]
Value to health systems across continents	• HTA can contribute to such analyses [129]. However, different methods may be needed to fully incorporate the benefits and value of new medicines for cancer into future pricing considerations given affordability constraints that exist within countries, especially LMICs. • Willingness-to-pay studies have been conducted among the public in Brazil to help establish possible prices for new vaccines serving as potential benchmarks [130,131]

Supply security	Information on potential volumes and producers (for multi-sourced products) are needed to maintain competition and supply for specific products, which such data seen as feasible to collect. This is because supply shortages are becoming a key issue across countries [132]

The International Association of Mutual Benefit Societies (AIM) were more specific in their recent approach [43] (Table 6) believing their suggested model ensures fairness to pharmaceutical companies in view of the unmet need that still exists for example for new oncology medicines whilst considering fairness towards European healthcare systems struggling to cope with competing demands including the consequences of increased prevalence rates for cancer [43].

Table 6 - Potential parameters proposed by the International Association of Mutual Benefit Societies (AIM) for pricing considerations for new medicines [43] as well as by Uyl-de Groot *et al.* for new oncology medicines [44]

Potential parameters AIM Model	**Potential considerations model of Uyl-de Groot *et al.***
1. R & D costs – a lump sum of €250million for each new medicine. Higher amounts if these can be justified using a specific approved methodology (incorporating issues such as expenses incurred minus sponsor/ government money, costs of failure and buyouts) up to a total amount of €2.5billion 2. Amount of R & D allocated to Europe (which represents 42% of the population of the main markets for new innovative medicines) 3. Target population, i.e. whether ultra rare, rare, or for a chronic disease treatment rate, market share and likely duration of treatment 4. Whether a new indication or the 2nd or 3rd indication 5. Alternatives for the same indication, i.e. are there already alternative medicines on the market or will this new medicine be a first in the class 6. Production and overhead costs 7. Sales and marketing costs – 20% of R & D costs will be allowed and gradually reduced 8. Basic profit of 8% based on the upper range of returns in risky industries 9. Innovation bonus ranging from 5 to 40% depending on the expected added therapeutic value of the new medicine versus current standards 10. Differential price depending on issues such as GDP per country	• R&D costs incorporating medicines that have been abandoned during their development (attrition rate) • Costs including manufacturing, sales and marketing and overheads • A profit margin linked to the level of clinical benefit versus current treatments to stimulate innovation based on for instance ASCO and ESMO criteria which are linked to the length of additional survival and other key parameters, e.g. 20% to 40% margins • The envisaged number of patients likely to be treated with the new medicines • The length of patent (years) after registration

However, there are concerns that such approaches disincentivize R & D efficiency, do not factor in failures, may not sufficiently encourage innovation and may be highly disruptive [29,51,134]. In view of this, the AIM approach (Table 6) may be more applicable; however, this remains to be seen. In addition, the instigation of cross-border purchasing consortia among European countries such as the Beneluxa, Nordic and the Valetta consortia, may lead to greater transparency in pricing approaches; however, there are concerns whether such collaboration will fully work in practice [9,135,136].

2.7 Other approaches

Suleman et al (2020) have recently proposed new business models for R & D to help achieve fair pricing building on previous publications [55,120,137]. These include 'push' models that typically provide grants for research projects in advance; 'pull' mechanisms that provide rewards for agreed research accomplishments at various stages of the drug development process, and pooling mechanisms which facilitate access to knowledge to help advance scientific knowledge and hence shorten development timelines and costs [120]. Pooling mechanisms include collaborative initiatives

that share R & D as well as open source initiatives that apply open source, open access, open data, or open knowledge principles, to progress R & D in key areas [137]. Interest in pull mechanisms, or combining push and pull mechanisms, has risen in recent years with a number of schemes now in operation [120,137]. These include initiatives to develop new antimicrobials including those for HIV and tuberculosis, new vaccines as well as new medicines for orphan diseases and cancer [137].

Other pricing approaches include amortisation or leasing scheme approaches for new high priced medicines as well as seeking to de-link the costs of R&D from a medicine's price [134]. De-linkage models have been proposed for new cancer medicines to help lower their costs given increasing recognition that most basic research for new cancer medicines is now predominantly undertaken in universities or funded by public sources [52,138]. However, there is concern that such approaches my disincentivise companies in the future.

Concerns with requested prices for new Advanced Therapy Medicinal Products (ATMPs), as well as regenerative medicines, coupled the envisaged number in development and the uncertainty surrounding their performance, is also leading to suggestions for performance based annuity payments [139]. However, such models need to take into account the current legal and other frameworks within a country as emphasized recently in Belgium when appraising potential options for funding new ATMPs [140,141]. They also need to take into account concerns among payers about potential rebates if 'one-off' treatments such as gene therapies fail to achieve their desired effect. However, greater evidence generation alongside appropriate MEAs may help here [142].

Two-part pricing approaches have also been proposed to help spread the costs of new premium-priced but valued medicines [134]. Under this system, manufacturers and payers agree an entry fee for a population or sub-population and for every treatment, with the manufacturer receiving a 'user fee' for every patient treated. However for such schemes to work, there has to be a degree of certainty surrounding the outcome with new treatments such as schemes proposed for hepatitis C [134,143]. Consequently, such schemes may be difficult to implement for new oncology medicines, especially those for solid tumours where only surrogate data is available at launch, given the considerable uncertainty that exists regarding their future effectiveness at launch [3]. However, greater knowledge with the help of a growing number of oncology databases should help here.

Finally, Chalkidou and colleagues (2020) recently proposed the development of an Innovation Uptake Institute (IUI) to address key issues including affordability of medicines for LMICs as well as stimulating research to address unmet need in neglected or de-prioritised disease areas [144]. This includes focusing more on demand-side strengthening, and includes new HTA mechanisms as well as investing in IT systems to collect real world evidence alongside the development of cost conscious clinical guidelines [144]. The authors envisage that IUI would be financed via a mixed funding model [144]. However, methodologies for obtaining valid "real world evidence" are still in their infancy, and more input is needed before such developments can become realities

3. Conclusion

We are likely to see a growth in alternative pricing models given concerns with the current system, the level of unmet need, and the desire to maintain the sustainability of healthcare systems especially among European countries. This will include re-evaluating prices or rebates of existing patented oncology medicines as more standard oral and biological medicines become available as generics or biosimilars.

Likely additional activities among payers will include a greater focus on MCDAs for new oncology medicines building on recent developments including those in Italy, Netherlands and the UK, as well as MEAs especially with the development of IT systems and a potential consensus regarding pragmatic patient level data to collect during routine oncology clinics. In addition, health authorities and insurers are likely to more critical when negotiating rebates and discounts for MEAs building on growing knowledge of the low cost of goods of many oncology medicines and biologicals once patents have been lost. However, this must not be at the detriment of incentivising innovation given the level of unmet need that still exists for new cancer medicines.

Ongoing activities especially among health authorities and their advisers are also likely to include continual re-evaluation of proposed models for fair pricing including those from AIM building on recent

proposals by the WHO and others. Multi-indication pricing is also a potential consideration going forward as patient level database systems grow across Europe,

We will continue to monitor and debate the situation to provide future guidance to all key stakeholder groups.

4. Expert Opinion

There is likely to be an increasing scrutiny over the value of new oncology medicines among health authority personnel in the future especially with likely continued requests for higher prices as new oncology therapies become available and are likely to be more targeted and more complex. This will be coupled with greater knowledge of the effectiveness and safety of oncology medicines in routine clinical care with developments in health services databases, data collection methods, and electronic health records. We are already seeing health service records and databases being adapted to collect more clinical data to aid decision making and this will grow building on current systems and proposals such as the ongoing SACT programme in England and the CMOP programme in Scotland. Greater scrutiny will also be driven by the increasing number of oncology medicines currently used as first and second line treatments becoming available as either low-cost generics or biosimilars, with originator companies also increasingly likely to lower their prices once biosimilars become available to help maintain market share as seen with AbbVie in the Netherlands. This is likely to lead to greater scrutiny regarding rebates offered by Companies of still patented oncology medicines for continued reimbursement under existing MEAs and value-based pricing approaches once the medicines they used for price justifications during negotiations become available as multiple sourced medicines or biosimilars. In addition, greater consideration for fair pricing models.

Increasing scrutiny over potential prices for new oncology medicines is also likely to lead to greater discussions over potential clinical threshold levels for reimbursement and funding of new premium priced cancer medicines at various stages of the disease, coupled with restrictions of use and/ or greater discounts where there are initial concerns until more data becomes available. In addition, there is likely to be increasing discussions regarding fair pricing for new oncology medicines as more models are proposed building on suggestions of AIM and others along with greater evaluation of new MCDAs especially those for new oncology medicines. Concurrent with this, accelerated discussions regarding the potential for spreading the cost of new high-priced medicines over a number of years to enhance their affordability across Europe including new ATMPs

We are already seeing new cancer medicines being given conditional approval based on a limited number of patients in Phase II trials, and this trend is likely to grow to accelerate access to potentially new innovative therapies. Consequently, payers will need to become increasingly vigilant over such developments and potentially reflect this in their pricing negotiations and deliberations during any conditional approval or MEA; however, mindful of existing unmet need.

Overall, we are likely to see greater transparency in all aspects of pricing of new oncology medicines with the development of new pricing models and purchasing consortia especially with new proposals from the WHO, and in time potential convergence in prices across Europe. It is also likely that there will be an increase in the re-evaluation of the value, prices and rebates of existing patented medicines once the comparator medicines used for negotiations lose their patent. However, such deliberations have to be balanced against sufficient incentives in the system to develop new oncology medicines to address areas of unmet need.

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