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Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology

D. Dankó [a,*], J-Y. Blay [b], L.P. Garrison [c]

[a] Ideas & Solutions, Kelenhegyi út 16B, 1118 Budapest, Hungary
[b] Centre Léon Bérard, Lyon, France
[c] University of Washington, Department of Pharmacy, Seattle (WA), United States

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ABSTRACT

Background: The use of targeted combination therapy (TCT) is becoming the standard of care in oncology as cancers are attacked through multiple inhibition mechanisms. TCTs pose a budget challenge to health systems and an economic return challenge for companies developing them.
Methods: We conducted a systematic literature review to identify challenges specific to TCTs and reviewed publicly available reports by health technology assessment and pricing and reimbursement bodies. We synthesized our findings into a problem map.
Results and discussion: Challenges and policy solutions linked to TCTs remain almost fully unexplored; we identified few resources that explicitly addressed TCTs. Contributors to the budget challenge are found at different layers; they and include static willingness-to-pay (WTP) for TCTs and inefficiencies in managing prices of backbone therapies. Economic return challenges are related to payer-imposed restrictions, peculiarities of TCT development, and conflicting incentives of pharmaceutical companies that own constituent therapies. Consequences are delayed or restricted patient access to TCTs, disincentives for research and development, and fewer life years gained.
Conclusions: Multiple issues will lead to the unsustainability of funding systems and possible conflict between stakeholders around access to TCTs. To manage these, new value assessment and attribution methodologies, modified trial designs and differentiated WTP thresholds can be considered in ways that are customized to the characteristics of different health systems.

1. Introduction

Targeted combination therapy (TCT) refers to the combined use of targeted anti-cancer medicines to enable parallel inhibition mechanisms in several molecular pathways, or multiple levels of blockade of the same pathway [1–5]. As cancers often arise through the accumulation of multiple genetic events or genomic alterations it is unlikely that, for most cancer types, a single agent will be sufficient to block cancer cell growth significantly and durably. Strong driver mutations (e.g. in chronic myelogenous leukaemia [CML], gastrointestinal stromal tumour [GIST], or cancers with driver translocation involving neurotropic tropomyosin receptor kinase [NTRK]) are the exception, with most cancers arising through the combined biological consequences of activating multiple weak oncogenic drivers. Considering this, the combined use of targeted inhibitors is imperative in most cancers [6].

Terminology regarding TCTs is evolving. We will refer to their components as *constituent therapies*. Of these, the *backbone therapy* is usually registered first (commonly as monotherapy or in combination with chemotherapies). Later, *add-on therapies* are studied in combination with the backbone therapy and their labels reference this. As new medicines are registered, add-on therapies may themselves become the backbone of new regimens.

TCTs are authorised in precisely specified, labelled clinical indications. Nevertheless, their use may be relevant in other indications harbouring the same molecular alterations (e.g. BRAF mutation). Specific national research programmes, such as the AcSé (*Accès Sécurisé à des thérapies ciblées innovantes*, Safe Access to Innovative Targeted Therapies) research protocols in France, explore treatments outside their initial label rigorously and safely at a national level [7].

The recent wave of marketing authorizations and the number of ongoing trials project an explosion of TCTs [8]. Payers are reacting to this by scrutinizing their added clinical benefit and cost-effectiveness [9], by challenging their prices, and by imposing access restrictions. Interestingly, while the financial implications of

* Corresponding author.
E-mail address: david.danko@i-s.hu (D. Dankó).

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immuno-oncology and orphan oncology are being relatively widely discussed [10], to date this has not been true for TCTs. Some important unanswered questions include:

- Are value assessment methods currently applied by health systems appropriate for capturing the value of TCTs?
- How can the clinical and economic benefit of a TCT be attributed to the constituent therapies? If constituent therapies belong to different intellectual property right (IPR) owners, should assessment of the add-on therapy have implications for the backbone therapy?
- In a broader perspective, do clinical development programmes and registration requirements match the underlying science of TCTs?

In this article, we will discuss these challenges with the aim of contributing to the intensifying policy dialogue around improvements to the value assessment, pricing, and funding of TCTs.

2. Methods

We used a three-step methodology (Appendix 1). First, we conducted a systematic literature review in PubMed to identify payer challenges in the value assessment, pricing, and funding of TCTs (Appendix 2). We also conducted internet research to identify conference presentations, 'white papers' by consultancy organizations, and online articles.

The second step was the analysis of reports and recommendations for TCTs by health technology assessment (HTA) agencies and pricing and reimbursement (P&R) bodies in seven geographies where such information is publicly available: Australia, Canada, England, France, Germany, Scotland, and Sweden. TCTs were identified in the European Medicines Agency (EMA) authorised medicines database.

In the third step, results were synthesised into a *problem map,* and were complemented with considerations transferred from comparable combined technologies, especially the use of companion diagnostics to empower personalised medicinal treatments [11]. The problem map dissects complex challenges into causes and consequences and helps to define cancer policies specific to TCTs. Policy effort should be focused on problems that lead to several consequences.

3. Results

3.1. Literature review and analysis of HTA and P&R reports

Financial challenges and policy solutions linked to TCTs remain almost fully unexplored. We could identify only one recent publication which explicitly addressed TCTs [12] and internet research identified only few conference presentations, white papers, and online articles [8,13–16]. Statements found in these online sources most relevant to the challenges around TCTs are presented in Table 1. These statements can be subdivided broadly into potential causes, possible consequences, and suggested solutions to these challenges.

Our screening identified 16 TCTs in the EMA authorised medicines database (Table 2).

The analysis of HTA and P&R reports showed that:

- No HTA agency or P&R body uses differentiated criteria for assessing and recommending TCTs. Progression-free survival (PFS), overall survival (OS, or the lack of OS data), and budget impact are major concerns for agencies
- No specific mechanisms exist for attributing added clinical benefit to the constituent therapies
- In health systems applying cost-effectiveness assessment (Canada, England, Scotland, Sweden), add-on therapies are usually not cost-effective (in some cases even at zero cost) due to the incremental direct costs of constituent therapies
- Positive funding decisions are contingent on discounts and managed entry agreements (MEAs), especially in the UK. Some countries (Canada, Sweden) implemented volume controls (e.g. restrictions on patient populations)
- Where HTA is focused on added clinical benefit (France, Germany), most concerns are not specific to TCTs. Clinical study design, tolerability, lack of proven benefit, and the adequate efficacy of monotherapy have been major objections
- Payers seem unable to manage the conflicting incentives of different IPR owners. Current MEA frameworks are applicable to constituent therapies with the same IPR owner only

Table 1
Statements relevant to challenges related to TCTs, as described in online sources.

Causes	• Impact of changing treatment duration on total treatment cost [8] • Challenges in clinical trial design [8] • Limitations in applying cost- and risk-sharing schemes [15] • Disproportionate workload on treatment sites to cope with payer requirements [15] • Pricing ambiguity due to lack of head-to-head studies and low competition [16]
Consequences	• Limited patient access due to limitations on treatment sites [15] • Short-term funding agreements with different payer organizations [15]
Solutions	• Further development of cost- and risk-sharing models [8] • Need for novel pricing models [13] • Need for real-world data and tracking systems [13] • Value-based pricing approaches [13]

3.2. Problem map

The problem map dissected challenges into interlinked causes and consequences and grouped these into six domains: pricing and funding; value assessment and willingness-to-pay (WTP); legal context; economic incentives; clinical development; and health system losses (Fig. 1).

4. Discussion

Each field within the problem map is numbered and referenced accordingly in the discussion.

4.1. The budget challenge and its causes

TCTs pose a budget challenge (#1) to payers. This stems from three sources: the high research and development (R&D) costs of novel oncology medicines *in general* (#11); specific inefficiencies in managing backbone therapy prices (#3); and the observation that oncology budgets do not seem to keep up with the increasing range of targeted therapeutic strategies (#2), a significant number of which have been associated with prolonged survival [17]. Current budget constraints (#2) are most directly related to the fact that payers, with some notable and sometimes controversial exceptions (e.g. the UK's Cancer Drug Fund [CDF, 18] or Highly Specialised Technologies [HST]), have shown no increased WTP for targeted cancer drugs in general and TCTs in particular (#4), compared with conventional cancer therapies. They may therefore not invest addi-

Table 2
Combination therapies with EMA marketing authorization (February 2019).

Active substance (brand)	Combination indication
carfilzomib (Kyprolis)	in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
binimetinib (Mektovi)	in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
cobimetinib (Cotelic)	in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
dabrafenib (Tafinlar)	in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation
daratumumab (Darzalex)	in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
elotuzumab (Empliciti)	in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy
encorafenib (Braftovi)	in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
idelalisib (Zydelig)	in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): who have received at least one prior therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies
ixazomib (Ninlaro)	in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
lapatinib (Tyverb)	in combination with trastuzumab for patients with hormone-receptor-negative metastatic disease that has progressed on prior trastuzumab therapy or therapies in combination with chemotherapy
lenvatinib (Kisplyx)	in combination with everolimus for the treatment of unresectable advanced or metastatic renal cell carcinoma
nivolumab (Opdivo)	as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults
panobinostat (Farydak)	in combination with bortezomib and dexamethasone for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent
pertuzumab (Perjeta)	in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease // in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence
ramucirumab (Cyramza)	in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy
trametinib (Mekinist)	as monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation

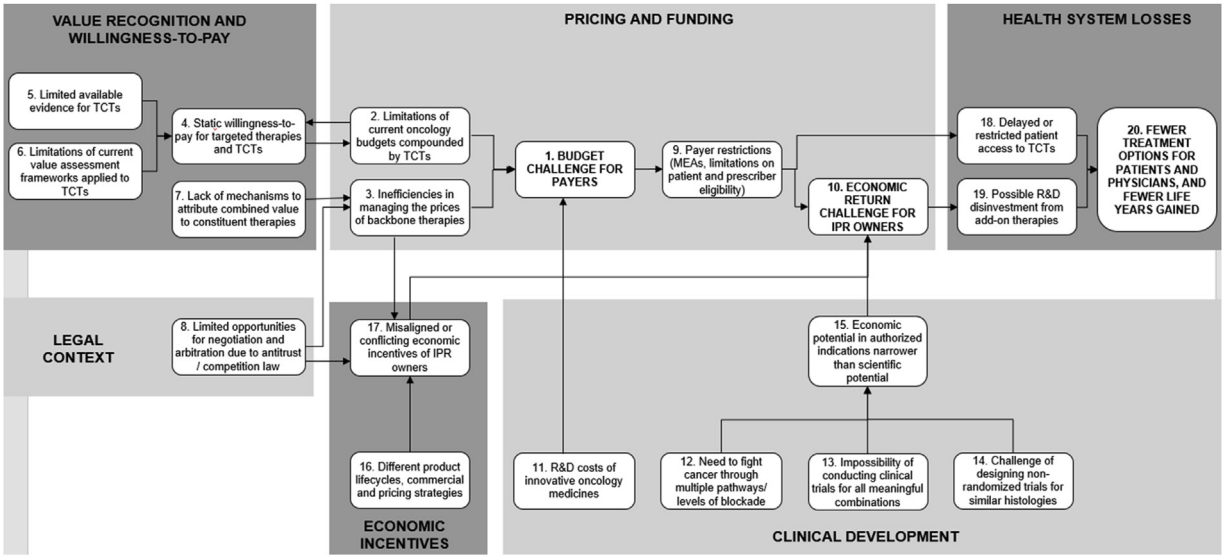

Fig. 1. Problem map for targeted combination therapies.

tional resources into cancer drugs, which leads to a high number of high-cost medicines vying for flat (or marginally increasing) budgets. Obviously, such budgetary tensions are being exacerbated as TCTs are becoming the standard of care.

Static WTP seems to originate in the superimposition of limited available evidence (#5) (and hence significant uncertainty for payers) and the application of such value assessment frameworks to TCTs (#6) that are prone to lead to their limited value recognition. Limited available evidence (#5), and especially the common lack of OS data, are major concerns for payers, and the 'evidence gap' seems to be widening as TCTs are registered based on partial evidence, such as Phase 2 data and/or intermediate endpoints [19]. In addition, current budgets may not fully reflect societal priorities to invest into cancer treatments. Regarding value assessment

frameworks (#6), the methodologies used in different health systems to assess value differ considerably [20] but are instrumental to what payers in each health system will consider 'value-added' technologies: methodologies define choices [21,22], and it is debatable whether value assessment frameworks currently applied in practice are fully appropriate for TCTs. In health systems where value assessment is focused on *added clinical benefit* (e.g. France, Germany, Italy), the magnitude of improvement offered by TCTs is not always captured appropriately. Analyses of median PFS and OS may fail to recognise prolonged 'plateaus of survival' or 'cure fractions', or to differentiate between 'transient' treatments and those that transform certain cancers into chronic diseases. Moreover, without head-to-head evidence comparing the TCT to the backbone therapy, the TCT will be assessed against a third comparator even if this is not meaningful based on actual treatment patterns.

In systems using *cost-effectiveness analysis* (CEA, e.g. UK, Sweden, Poland), TCTs are also affected by the inability of current frameworks to capture sources of product value such as value extension, insurance value, real option value, value of hope, and other spill-over effects. (For a definition of these value elements see [23,24]) Value assessment frameworks rarely capture societal value judgments (for both conceptual and methodological reasons [25]), therefore assessment reports and budget allocation decisions may or may not reflect actual societal priorities related to oncology. Methods focused on health gains and cost offsets have also led to situations where add-on therapies are found not to be cost-effective even at zero cost, due to the increased therapy duration and hence the additional direct costs of using the backbone therapy for longer [12,26]. This has led to discussions in the UK around pertuzumab added to trastuzumab and chemotherapy, and the National Institute for Health and Care Excellence (NICE) reaching out to its Decision Support Unit for specific advice [27]. Similar cases have been reported for cinacalcet and vinflunine [26]. From another perspective, these observations highlight issues with including survival-related indirect costs in CEAs [28,29]. On the other hand, it could be argued that when TCTs are assessed as single technologies and are found not to be cost-effective, this is simply due to the cumulative price of the backbone and the add-on therapy not being proportional to the cumulative health gain. This is related to inefficiencies in managing the prices of backbone therapies (#3), in particular the inherent lack of price adjustments of these therapies when used in specific combinations (e.g. through indication-based pricing).

Such inefficiencies are linked partly to the lack of value attribution mechanisms (#7) [30,31] and partly to the impact of antitrust/competition law (#8), which prevents IPR owners from agreeing on a value-based price for TCTs and/or dividing it between constituent therapies. Currently, the value appraisal of a TCT does not affect the standalone HTA appraisal of the backbone therapy: its cost-effectiveness and price will not be revisited. Typically, the TCT will be assessed at the price corresponding to the sum of its constituent therapies, whereby the IPR owner of the add-on therapy has no influence over the pricing of the backbone therapy. Thus, the combination price will likely exceed WTP [11], and the add-on therapy may be denied funding [12] or be subject to discounts or restrictions. This means the added value of the TCT *is not properly attributed to constituent therapies*: most of the combination value tends to be absorbed by the backbone therapy whereas the add-on therapy is funded on a 'residual' principle or is not funded at all. MEAs help resolve such problems at net price levels only if all constituent therapies belong to the same IPR owner [31]. In all other cases, multilateral arbitration/negotiation between payers and IPR owners could theoretically be used, but its application is currently restricted by antitrust/competition law (#8; a thorough description in the US context is given in a recent white paper [32]). If market structure or pricing are affected, antitrust/competition law does not permit any direct or indirect negotiation/arbitration to take place between IPR owners, even though these are intended to respond to the real payer need of attributing value and decreasing total treatment costs. Thus, only bilateral negotiations are lawful between the payer and each IPR owner, and only through these can the payer attempt to carry out value attribution and re-negotiate prices.

4.2. Payer reactions to the budget challenge

Payers usually react to the budget impact challenge by applying restrictions (#9). Many health systems outside the US use conventional rebates and budget caps with a short time horizon. These will not solve the mid-/long-term financial challenge as the number of available TCTs will increase, patient numbers will grow, and treatment will be prolonged due to increased survival. Nevertheless, the focus on conventional MEAs is likely to persist until evidence on the long-term therapeutic benefits of TCTs becomes widely available, and systemic budget management solutions are developed including indication-based pricing [12], fees per treatment period, or performance-linked payment models. The practical benefits of such methods are currently unexploited, but the limits on their potential are also unknown. As well as rebates and budget caps, restrictions on patient or prescriber eligibility commonly seem to be enforced by payers. These limit the use of TCTs to certain subgroups or to second (and subsequent) therapy lines. Use may also be restricted to selected treatment sites to 'ration' access to TCTs.

4.3. Economic return challenge and its causes

While payers are struggling with the budget challenge, IPR owners (pharmaceutical companies developing TCTs) are weighing the clinical and societal benefits of these therapies against uncertainties in their economic return (#10). This economic return challenge is related to the financial restrictions applied by payers (#9), the peculiarities of clinical development (#12–15), and misaligned incentives (#17).

Financial restrictions (#9) have been explained. Within clinical development, multiple factors contribute to the economic return challenge. A combination of different substances from different classes of medicines that target different signalling pathways or biological mechanisms contributing to disease progression (e.g. targeted oncogene therapy and immunotherapy) are required to treat cancer (#12). However, for economic reasons, and because patient numbers are small in most cancer indications, the conduct of clinical trials evaluating all meaningful combinations of targeted medicines is not feasible (#13). Therefore, trials lead to the registration of selected 'promising' combinations of active substances only, instead of all potential therapy-relevant combinations [33,34]. In another layer of complexity, similar associated genomic events (e.g. amplification of HER1, PI3K or Ras mutation) are observed in a variety of different cancers, but only in a small proportion of each of these cancers. This implies that the challenge of conducting clinical trials for homogenous histologies with small patient populations could theoretically be overcome by combining different histologies with similar genomic alterations into a larger, non-randomised trial. However, the usefulness of this approach would be challenged by the limited knowledge produced on the biological significance of a given mutation in different disease types, and such trials would hardly meet registration purposes in the current regulatory paradigm (#14). For all these reasons the 'authorised' economic potential of TCTs is narrower than their 'scientific/clinical' potential (#15).

With respect to economic incentives, as mentioned earlier, constituent therapies often belong to different companies, and this trend will increase based on ongoing clinical trials. In such cases,

product life cycles and commercial and pricing strategies may diverge substantially (#16). When an add-on therapy is launched, the owner of the backbone therapy will likely defend its economic potential through price maximization, benefiting from the system-level inefficiencies related to managing backbone prices (#3), and is to some degree 'protected' by antitrust/competition law (#8). The backbone therapy will thus appropriate a large chunk of the combination value through the price already set for the monotherapy, and the economic return for the add-on therapy will be contingent on this price. This implies that, in general, add-on therapies may not be able to reap the economic reward proportional to their clinical benefit. Hence, economic incentives are often misaligned or directly conflicting among different IPR owners (#17).

As treatment standards move towards combination therapy, the backbone therapy will also experience some dependence on the add-on therapy. Thus, the economic potential of each constituent therapy will be contingent on *1)* the strategic and tactical behaviour of the IPR owner of the other therapy, *2)* developments in the clinical data set of the other therapy, and *3)* the nature and impact of payer interventions targeting the other therapy. This interdependence is likely to persist until the backbone therapy loses marketing exclusivity, when a different layer of complexity appears with generic/biosimilar products [26], and changes in prices and market shares.

4.4. Health system losses

All the discussion above leads to real health system losses: payer restrictions on patient and prescriber eligibility (#9) lead to delayed or restricted patient access to TCTs (#18). The economic return challenge for IPR owners may lead companies to disinvest from add-on therapies by redeploying resources into monotherapy development (#19) [26]. Since discontinued developmental add-on therapies could later have become backbone therapies, the R&D disinvestment may be associated with a negative multiplicative effect.

These negative consequences project that fewer treatment options will be available for physicians and future patients. At a technical level, this will likely result in sustained physician requests for off-label use, conserving and possibly increasing the bureaucratic burden on health systems. Ultimately, fewer treatment options will translate into fewer life years gained (#20).

4.5. Recommended interventions

Some causes of the challenges associated with TCTs are external circumstances which, by their nature, are difficult to change, including increasing R&D costs of innovative oncology medicines (#11), the need to fight cancer through multiple pathways or multiple levels of blockade (#12), and the impossibility of conducting clinical trials for all meaningful combinations (#13). Others, however, depend on regulation, policy and applied methodology, and are modifiable, albeit over different timeframes. Current value assessment frameworks applied to TCTs (#6) can be improved, mechanisms can be developed to attribute combined value to constituent therapies (#7), and opportunities for negotiation and arbitration can be established within the context of antitrust/competition law (#8). Similarly, alternative clinical trial designs may be better exploited for TCTs (#14) and, although widely debated, there may be arguments for differentiated WTP thresholds for TCTs.

1 *Refinement of value assessment frameworks applied to TCTs as single technologies.* Methodology issues related to the cost-effectiveness assessment of TCTs in health systems applying CEA have been described in the Discussion. In view of these difficulties, broader value concepts could be explored that include wider economic analyses for TCTs based on direct and indirect costs and benefits. For example, valuation methods used in financial markets may be investigated for a more precise approximation of derived value components, and for linking the added value of the add-on therapy to the 'underlying asset' [35], i.e. the backbone therapy. This would help account for currently unrecognised value components of TCTs. Part of these methods may require the increased use of horizon scanning information. In health systems where value assessment is focused on added clinical benefit, it would be beneficial if harmonised procedures and guidelines could be adopted regarding appropriate comparators (including the revisiting of how 'standard of care [SoC]' is defined where there is no one obvious SoC) and acceptable sources of evidence [36]. Sooner rather than later, it will be imperative to define which key primary endpoints can be accepted and used consistently by major regulatory and value assessment agencies [37]. In close relation with this, HTA agencies should formulate clear guidance on the acceptability and assessment of non-conventional designs (e.g. multi-arm, multi-drug trials [38,39]). Also, if survival gains beyond a certain magnitude were recognised by HTA agencies and payers as clinically meaningful for TCTs, accelerated access could eventually be granted to combinations meeting this requirement, supported by adequate programmes of further evidence generation.

2 *Answers to unresolved issues of value attribution.* It seems imperative to ameliorate disincentives and enable the legitimate and efficient price revisions of backbone therapies. To drive this, health systems may consider building value attribution into the general HTA process by appointing an official body to perform it (e.g. the HTA agency, the P&R body, or a specially designated committee). Alternatively, competition/antitrust law permitting, negotiation-based systems may be considered. In these, value attribution is a result of negotiation or arbitration processes whose results will be binding for all stakeholders.

   There are some prerequisites for any value attribution framework. Firstly, as most TCTs will be used in multiple indications, and their added value will differ across these, flexible pricing and payment models will be needed that enable indication-based or combination pricing [12]. Secondly, data collection systems will be required to make indication-based pricing feasible. These systems, already within reach in countries with developed patient registries, will collect data at least by clinical indication, therapy line, and type of combination. They will also keep track of dosing, treatment durations, and real-world effectiveness endpoints at a patient level. Thirdly, in decentralised systems where assessment and pricing take place at different levels (e.g. Canada, Italy), it must be decided whether value attribution is a centralised or decentralised competence.

3 *Safe harbour clauses for price re-negotiation.* In conjunction with the development of value attribution methodologies, 'safe harbour' clauses will be necessary in antitrust/competition law to ensure that multilateral discussions or arbitration are permitted when the purpose is to couple the eventual re-assessment and price revision of the backbone therapy to the value assessment of the add-on therapy [32].

4 *Design of registration trials.* TCTs are guided by genomic alterations, and this is leading R&D towards TCTs used across different tumours. In the long term, classical randomised controlled trials will be inadequate to deal with the resulting complexity, and this may lead to a paradigm change in the acceptance of non-randomised registration trials. In the short term, however, only incremental adjustments seem realistic as is seen already in the use of non-conventional trial designs.

5 *Differentiated WTP thresholds.* Although certainly a subject of debate, differentiated WTP thresholds for TCTs may be imple-

mented, or at least explored, in public policy analysis in cases where a societal preference to invest more health resources in oncology by treating tumours more aggressively with TCTs is assumed. Within the current paradigm of measuring direct benefits against direct costs, differentiated thresholds may be counter-intuitive for payers as they can lead to higher reimbursement outflow. However, considering a broader scope of costs and benefits, higher WTP thresholds could be rational if indirect and/or long-term costs can be reduced or benefits can be increased; or if spill-over effects from funding a medicine can be expected to lead to further, potentially more valuable, innovation; or simply if it is accepted that it is a necessity of fighting cancer through multiple pathways, or multiple levels of blockade.

5. Conclusions

Our analysis suggests that multiple unresolved issues around the clinical development, value recognition, pricing and funding of TCTs will lead to the unsustainability of funding (reimbursement) systems and possible conflicts between stakeholders around access to TCTs. Due to the high number of TCTs entering Phase 3 clinical trials and registration processes, persistent issues with financial sustainability will not be limited to already budget-constrained environments, rather these compound challenges will also affect affluent health systems across the world. In the case of TCTs these issues are compounded by R&D sustainability challenges that have an impact on all companies that develop TCTs, and on those developing add-on therapies in particular. Our overview demonstrates that the first signs of this are already visible. If the challenges described in our analysis are addressed TCTs will be able to fulfil their increasing role as SoC; if not, their accessibility will continue to be restricted, with associated spill-over effects, such as widespread off-label use.

The urgent need to identify working, implementable policy solutions is clear. As health systems are different, each system will need to define its policies and tools which best fit its legal context, value assessment traditions, clinical practice, and culture of conflict resolution. This requires dialogue between policymakers, payers, HTA experts, patients, specialists and pharmaceutical companies so that viable solutions are identified before the number of TCTs has multiplied. In a next step, international collaboration platforms can share these experiences between countries.

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Appendix A. Supplementary data

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