



# Feature

## Targeted combination therapies in oncology: Challenging regulatory frameworks designed for monotherapies in Europe

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The pharmaceutical value chain, including clinical trials, pricing, access, and reimbursement, is designed for classical monotherapies. Although there has been a paradigm shift that increases the relevance of targeted combination therapies (TCTs), regulation and common practice have been slow to adapt. We explored access to 23 TCTs for advanced melanoma and lung cancer as reported by 19 specialists from 17 leading cancer institutions in nine European countries. We find heterogeneous patient access to TCTs between countries, differences in country-specific regulations, and differences in the clinical practice of melanoma and lung cancer. Regulation that is better tailored to the context of combinational therapies can increase equity in access across Europe and promote an evidence-based and authorized use of combinations.

**Keywords:** targeted combination therapy; access; Europe; melanoma; lung cancer; pricing and reimbursement; research and development

### Introduction

Understanding the molecular profile of a tumor enables personalized treatments that can yield substantial survival benefits.<sup>1</sup> Over the past decade, technological advances, including next-generation sequencing, have drastically shifted our view of melanoma and nonsmall cell lung cancer (NSCLC) from histopathological descriptions to molecular disease mechanisms.<sup>2,3</sup> By disputing specific cell molecules necessary for tumor development

and carcinogenesis, targeted therapies have proven to be an effective therapeutic strategy for melanoma and NSCLC. To exploit complementary mechanisms of action and overcome treatment resistance, targeted therapies are also increasingly combined.<sup>1,4</sup> A targeted combination therapy (TCT) is defined as the deliberate use of two therapies in combination in which at least one of the therapeutic agents is specifically targeted biological processes within cancer cells. Currently, they are

used for several tumor types, including immunotherapy and tyrosine kinase inhibitors in melanoma (BRAF/MEK) and NSCLC (EGFR and ALK-TKIs).<sup>5</sup> The clinical importance of targeted and combination therapies is also reflected in recent high-profile publications of *Drug Discovery Today*.<sup>6–13</sup> In addition to important scientific and patient-related considerations, combining therapies raises several challenges in the pharmaceutical value chain of drug development, because the research

and development (R&D) and the pricing and reimbursement (P&R) processes are designed for monotherapies.<sup>14,15</sup>

In this feature, we review the regulatory challenges TCTs are facing during R&D and P&R, a survey of access to TCTs for lung cancer and melanoma, and recommendations to close regulatory gaps in R&D and P&R processes to improve patient access.

### Regulatory challenges of TCTs

One of the main challenges in the R&D of TCTs is conducting high-quality trials to generate sufficient and robust evidence. The R&D phase of TCTs is not only expensive, but the appropriate study design can also be demanding. Performing high-quality trials with the preferred long-term outcomes is difficult because TCTs often require complex, multi-armed studies with specific patient populations<sup>15</sup>. When TCTs are developed by different manufacturers, additional challenges, such as misaligned incentives, competition concerns, and data constraints, can impede clinical development.<sup>16</sup> This reinforces a trend in precision oncology, where an increasing proportion of European Medicines Agency (EMA) product approvals are based on Phase II studies and surrogate endpoints.<sup>17</sup> As a consequence, the reliance on less mature data increases uncertainty in the clinical and economic evaluation of TCTs during the P&R processes, which can lead to heterogeneity in the acceptance and use of TCTs.<sup>18</sup>

Another challenge in the P&R process relates to the pricing of TCTs, because one of the therapies is usually registered first, and is considered the 'backbone therapy', and 'add-on therapies' are those that are subsequently registered as treatments to be given in combination.<sup>19</sup> This presents a challenge for budgetary negotiations, especially when the combinations do not involve a common manufacturer. P&R issues arise when the price of the add-on therapy is added to the price of the backbone therapy without moderating the price of the latter. When the TCT is developed by a common manufacturer, it is possible to renegotiate agreements regarding its price and use with the payer. However, when different manufacturers are involved, the add-on therapy might not be capable of generating a price proportional to its incremental benefit and,

consequently, it might not be commercially viable.<sup>19</sup> The adaptability of the price of the backbone therapy can also depend on its remaining patent life. If the therapy is expected to be under patent protection for many years and holds a sufficiently large market share, its manufacturer is probably not incentivized to moderate its pricing.<sup>20</sup> Furthermore, concerns about legal challenges regarding competition law complicate the process of price negotiations.<sup>21</sup>

As a consequence of the regulatory challenges in the P&R and R&D, increasing evidence shows that access to TCTs might be restricted.<sup>22</sup> Specialists from renowned cancer institutions in Europe are left with their own practices and experience. Our study exemplifies how the lack of unified guidelines can lead to heterogeneous use of combination therapies across nine countries in Europe.

### Access to TCTs for advanced melanoma and lung cancer in the EU

To obtain an overview of current patient access to TCTs, a questionnaire was composed for European melanoma and lung cancer specialists. This analysis has deliberately selected two contrasting examples of TCT indications: melanoma and lung cancer. TCTs for the treatment of melanoma are relatively well established in clinical practice in several countries, whereas their use for treating lung cancer is emerging. Combinations of interests were selected through expert input of European oncologists and included at least one product registered as targeted therapy. The survey for melanoma focused on the combination of encorafenib and/or cetuximab and/or binimetinib. For lung cancer, the survey focused on the use of osimertinib in combination with other TKIs. All TCTs that were available at that time through reimbursed coverage, clinical studies, or early access programs (EAPs) were included in the list. Particular consideration was given to the use of combination therapies in their hospital, context of access (regular coverage, early access program, or off-label use) and constraints in prescription of TCTs. Oncologists were invited to participate through the Organisation of European Cancer Institutes' network of European Comprehensive Cancer Centers. To complete the overview, information was added about the manufac-

turer(s), the magnitude of clinical benefit (ESMO-MCBS score) and the status of published results of clinical trials specifically for melanoma or lung cancer.

An overview of access to TCTs for advanced melanoma, revealing variation in use and coverage between countries (Table 1). Standard combinations, such as 'nivolumab + ipilimumab' or 'encorafenib + binimetinib', were accessible and covered in seven countries. The more novel, and triple combinations, such as 'encorafenib + binimetinib + cetuximab' and 'dabrafenib + trametinib + pembrolizumab', are in clinical development for melanoma and, therefore, were reported as not covered. 'Encorafenib + cetuximab' was accessible and reported covered to patients in only three countries (Belgium, Czech Republic, and The Netherlands). However, this TCT has no published evidence from clinical trials specifically for melanoma. Five of ten physicians (Czech Republic, Norway, UK, and Finland) also reported constraints in prescribing TCTs related to national cost-and/or guideline-based restrictions.

In the overview of access to TCTs for lung cancer (Table 1), considerable variation was observed in TCT access between countries. EAPs were more common in Belgium and The Netherlands compared with other countries. This also resulted in differences in access within countries (e.g., osimertinib + dabrafenib in The Netherlands and Belgium). The TCT 'atezolizumab + bevacizumab' with Phase III evidence was covered in Norway and The Netherlands and accessible through an EAP in Belgium. The TCTs 'ramucirumab + erlotinib' and 'osimertinib + chemotherapy' with Phase III evidence were only covered in Belgium. Only four TCTs had published evidence to support their use in lung cancer. With no published trial evidence supporting their use in lung cancer, some TCTs were still accessible through EAPs (e.g., osimertinib + trametinib and osimertinib + alectinib). Six of nine specialists (Belgium, Czech Republic, Hungary, The Netherlands, and Spain) experienced prescription constraints related to reimbursement status (unapproved combination and no EAP) and toxicity concerns.

These results show that the routine practice of melanoma and lung cancer specialists differs across Europe. Differences in

TABLE 1

Summarizes experiences of TCT coverage and use in melanoma and lung cancer by 19 specialists from 17 leading cancer institutions in nine European countries.

	Same MAH	ESMO-MCBS	BE	BE	CZ	NL	NL	NO	NO	UK	FI	DK	ES	HU
<b>A. Melanoma</b>														
<b>Type of access:</b>														
Nivolumab + ipilimumab*	x	4												
Encorafenib + binimetinib*	x	4												
Dabrafenib + trametinib*	x	4/5												
Vemurafenib + cobimetinib*	x	4												
Encorafenib + cetuximab		NA												
Dabrafenib + trametinib + anti-pd1*	x	NA												
Encorafenib + binimetinib + cetuximab		NA												
Dabrafenib + trametinib + pembrolizumab		NA												
<b>Constraints in prescribing</b>					x			x	x	x	x			
<b>B. Lung cancer</b>														
<b>Type of access:</b>														
Atezolizumab + bevacizumab*	x	3												
Osimertinib + chemotherapy*	NA	NA												
Ramucirumab + erlotinib*		3												
Erlotinib + bevacizumab*	x	NA												
Osimertinib + savotinib		NA												
Osimertinib + selpercatinib		NA												
Osimertinib + tepotinib		NA												
Osimertinib + trametinib		NA												
Osimertinib + dabrafenib		NA												
Osimertinib + erlotinib		NA												
Brigatinib + cetuximab		NA												
Osimertinib + carboplatin + necitumumab		NA												
Osimertinib + necitumumab		NA												
Osimertinib + alectinib		NA												
Osimertinib + trastuzumab emtansine		NA												
<b>Constraints in prescribing</b>			x		x	x	x						x	x

Regular coverage	Early access program	Clinical trial	No access	Not available	No data
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Experiences of TCT coverage and use in melanoma and lung cancer.

\*TCT has a clinical trial with published results specifically for Melanoma/Lung cancer; ESMO-MCBS: European Society of Medical Oncology-Magnitude of Clinical Benefit Scale; MAH: Market Authorisation Holder; BE: Belgium; CZ: Czech Republic; NL: The Netherlands; NO: Norway; UK: United Kingdom; DK: Denmark; ES: Spain; HU: Hungary.

coverage were reported not only between countries, but also between physicians. A possible explanation could be that the use of the TCT was allowed for other tumor indications and/or the medicines were already separately covered as monotherapies. Reimbursed access appeared generally more prevalent for TCTs supported by clinical trials. In the absence of such, more variety in access was observed through either EAPs or trials. This could also explain observed differ-

ences in access between melanoma and lung cancer because the selected TCTs for melanoma included EU-approved standard first-line combinations, whereas the selected TCTs for lung cancer included mostly unapproved second-line combinations. We also observed that, in general, TCTs provided by a common manufacturer were reported as more accessible compared with TCTs with different manufacturers. For example, only the TCTs from a common manufacturer had published

clinical trial results specifically for melanoma. For TCTs without a common manufacturer, evidence generation was largely still in progress, often with trials additionally funded by hospitals and research foundations rather than by the manufacturers themselves.

#### Discussion and recommendations

As observed in the survey, generating high-quality evidence and appropriate clinical and economic evaluation methods

appear key challenges to improve the R&D and P&R processes, to increase equal access to TCTs in European countries. We make various recommendations based on our findings.

First, trials for TCTs should be considered and start as early as possible after Phase I rather than following the market authorization of one of its components, because potential benefits can be at least partly anticipated through a combination of clinical knowledge and molecular diagnostics.<sup>13</sup> Adaptive trial designs could be used to identify the most effective TCTs in patients.<sup>16</sup> For example, by testing multiple immune checkpoint blockade combinations in parallel (TONIC trial) or by using imaging and molecular analysis to predict responsiveness (I-SPY 2). When using adaptive trial designs during later stages of clinical development of TCTs (e.g., seamless Phase II/III trials), negotiations with regulatory agencies are recommended to align evidence requirements because adaptive designs have more limitations compared with classic designs. It is important that their use in a particular application is clearly justified and results are interpreted correctly.<sup>23</sup>

Second, the current pharmaceutical environment fails to sufficiently incentivize the development of TCTs, especially if the combinations do not have a common manufacturer.<sup>21</sup> Increased funding for nonprofit public or academic studies could stimulate necessary evidence generation for TCTs. Academic or publicly funded (investigator-initiated) trials can combine targeted therapies from different manufacturers and develop innovative treatment options that might be less commercially attractive to industry.<sup>24</sup> For example, the National Cancer Institute supports trials that focus especially on the development of TCTs (e.g., tRCC) and launched a platform trial (NCI-ComboMATCH). From our sample, a Phase I/II trial with 'dabrafenib + trametinib + anti-pd1' was sponsored by a Belgian hospital. The use of existing public contributions to the R&D process of TCTs could be used as leverage to limit excessive pricing for TCTs.<sup>25</sup> However, the present patent system indirectly impedes public clinical development of TCTs. If both therapies are still on patent and, therefore, at full price, performing public trials is likely to either be expensive or require conces-

sions on price to be agreed between the manufacturers involved. Moreover, the present system fails to reward innovative or unexpected combinations but rather enforces evergreening of monotherapies.<sup>26</sup> To stimulate public or academically funded trials, the value of (secondary) patents for TCTs could be reassessed, and innovative reimbursement schemes, intellectual property arrangements, and R&D incentives should be considered.<sup>25</sup>

Third, more acceptance of real-world evidence in the application for EMA authorization as well as in the national P&R processes could ease the regulatory path of TCTs. By being more inclusive regarding specific patient populations, real-world data complete the results of clinical trials.<sup>27</sup> TCTs for indications with profound medical need that face difficulties collecting data through traditional routes (e.g., small patient populations) can obtain authorization through the EMA's adaptive pathway approach.<sup>28</sup> Real-world data are also collected in some countries through EAPs to support national Health Technology Assessments (HTAs), pricing, and real-life effectiveness during the P&R processes (e.g., Dutch DRUG Access Protocol initiative & UK's Cancer Drug Fund).<sup>21</sup> Greater harmonization and transparency regarding EAPs recommended by Committee for Medicinal Products for Human Use could enhance access to TCTs for profound medical needs while generating structured real-world data collection. Note that there are still methodological advances necessary to increase acceptable evidence from real-world data that can inform the P&R processes.

Lastly, there have been suggestions of separate pricing mechanisms for expensive TCTs to meet cost-effectiveness thresholds.<sup>29</sup> However, we believe that TCTs should be clinically and economically assessed in combination, using the same willingness-to-pay for the combination as for single therapies. Consequently, cost-effectiveness will only be possible with indication-specific pricing for TCTs that allows for readjusted prices of the backbone and add-on treatments when administered in combination.<sup>30</sup> However, indication-specific pricing is a controversial topic and needs to be approached with care. Although some, including pharmaceutical manufacturers, suggest that differ-

ential prices per indication offer an opportunity to better align payment with value,<sup>31</sup> others, including academics, argue that indication-specific pricing will lead to higher prices and public expenditure.<sup>32</sup> To tailor existing P&R processes to TCTs, an innovative value assessment framework could be implemented within current HTA processes. The framework should be based on the estimated benefit that each therapy adds to the overall benefit of the TCT and take imperfect information (e.g., add-on was never assessed as monotherapy) and unbalanced market power (different manufacturers) into consideration.<sup>19</sup> This requires further research to adjust for challenges in methodology and competition law.

Putting the above recommendations into practice will require significant commitment and collaboration from various stakeholders across Europe. Although regulators, in principle, might be best placed as independent actors to advance overall socially optimal solutions, coordinating a common approach across multiple member states when reimbursement is a national competence remains challenging.<sup>33</sup> Moving forward, there is a need for further research to advance pricing models and a health economic appraisal methodology that guide and provide evidence on the reimbursement and use of TCTs across indications in Europe. This must include novel intellectual property arrangements and the proposed novel value assessment frameworks that are tailored to TCTs. Furthermore, there is a need to advance the methodology around adaptive and pragmatic clinical trials, which make use of a structured real-world data collection in the pricing of TCTs. Although we see the need for methodology advancements by academics as a first step, a coordinated approach to the implementation across Member States, potentially under the umbrella of the EUnetHTA initiative,<sup>34</sup> is necessary. Irrespective of who leads reforms to TCT pricing frameworks, the cooperation of industry will be essential in making them workable.

### Concluding remarks

In view of the growth and different patterns of access to TCTs, early anticipation in the pharmaceutical value chain and (publically funded) clinical trials with adaptive study designs are advised. Fur-

thermore, we urge for the optimized use of real-world evidence to obtain EU authorization and EU collaborations related to data-generating EAPs. Lastly, reassessment of the (secondary) patent system and indication-specific pricing for TCTs are needed. Otherwise, the present challenges surrounding TCT accessibility and unauthorized use of combinations across Europe will become a more pressing issue.

### Data availability

Data will be made available on request.

### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'The authors have nothing to disclose for the work under consideration for publication. Prof. van Harten reported non restricted grants from Novartis, Intuitive Surgical and Agendia all ending over three years ago, Prof. Retèl reported non restricted grants from Intuitive and Agendia outside the submitted work. Dr. Burgers reported funding of an investigator initiated study by MSD and consultancy for Roche (payments to his institution). The other authors have nothing to declare.'

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### References

- Ge F et al. Deubiquitinating enzymes: promising targets for drug resistance. *Drug Discov Today*. 2022;27:2603–2613.
- Chen Z, Fillmore CM, Hammerman PS, Kim CF, Wong KK. Non-small-cell lung cancers: a heterogeneous set of diseases. *Nat Rev Cancer*. 2014;14:535–546.
- Luke JJ, Flaherty KT, Ribas A, Long GV. Targeted agents and immunotherapies: optimizing outcomes in melanoma. *Nature Rev Clin Oncol*. 2017;14:463–482.
- Joo WD, Visintin I, Mor G. Targeted cancer therapy—are the days of systemic chemotherapy numbered?. *Maturitas*. 2013;76:308–314.
- Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell*. 2015;161:205–214.
- Jain R, Dubey SK, Singhvi G. The Hedgehog pathway and its inhibitors: emerging therapeutic approaches for basal cell carcinoma. *Drug Discov Today*. 2022;27:1176–1183.
- Pontes O, Oliveira-Pinto S, Baltazar F, Costa M. Renal cell carcinoma therapy: current and new drug candidates. *Drug Discov Today*. 2022;27:304–314.
- Sang M et al. A graph model of combination therapies. *Drug Discov Today*. 2022;27:1210–1217.
- Wang B, Warden AR, Ding X. The optimization of combinatorial drug therapies: strategies and laboratory platforms. *Drug Discov Today*. 2021;26:2646–2659.
- Du S, Yu Y, Xu C, Xiong H, Yang S, Yao J. LMWH and its derivatives represent new rational for cancer therapy: construction strategies and combination therapy. *Drug Discov Today*. 2019;24:2096–2104.
- Arranz-Romera A, Esteban-Pérez S, Garcia-Herranz D, Aragón-Navas A, Bravo-Osuna I, Herrero-Vanrell R. Combination therapy and co-delivery strategies to optimize treatment of posterior segment neurodegenerative diseases. *Drug Discov Today*. 2019;24:1644–1653.
- Singh G, Schulthess D, Hughes N, Vannieuwenhuysse D, Kalra D. Real world big data for clinical research and drug development. *Drug Discov Today*. 2018;23:652–660.
- Settleman J, Neto JMF, Bernards R. Thinking differently about cancer treatment regimens. *Cancer Discov*. 2021;11:1016–1023.
- Fountzilias E, Tsimberidou AM, Vo HH, Kurzrock R. Clinical trial design in the era of precision medicine. *Genome Med*. 2022;14:101.
- Flaum N, Hall P, McCabe C. Balancing the economics and ethics of personalised oncology. *Trends Cancer*. 2018;4:608–615.
- Jin H, Wang L, Bernards R. Rational combinations of targeted cancer therapies: background, advances and challenges. *Nature Rev Drug Discovery*. 2022.
- Del Paggio JC, Berry JS, Hopman WM, Eisenhauer EA, Prasad V, Gyawali B. Evolution of the randomized clinical trial in the era of precision oncology. *JAMA Oncol*. 2021;7:728–734.
- Zeveerijn LJ et al. Harmonising patient-access programmes: the Dutch DRUG Access Protocol platform. *Lancet Oncol*. 2022;23:198–201.
- Dankó D, Blay JY, Garrison LP. Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology. *Health Policy*. 2019;123:1230–1236.
- Briggs AH et al. *An Attribution of Value Framework for Combination Therapies*. Tokyo: Takeda; 2021.
- Latimer NR et al. Challenges in valuing and paying for combination regimens in oncology: reporting the perspectives of a multi-stakeholder, international workshop. *BMC Health Serv Res*. 2021;21:412.
- Mihajlović J, Dolk C, Tolley K, Simoens S, Postma MJ. Reimbursement of targeted cancer therapies within 3 different European health care systems. *Clin Ther*. 2015;37:474–480.
- Buyse M. Limitations of Adaptive Clinical Trials. *Am Soc Clin Oncol Edu Book*. 2012;32:133–137.
- Dogan S, Yamamoto-Ibusuki M, Andre F. Funding sources of practice-changing trials. *Ann Oncol*. 2018;29:1063–1065.
- Franzen N, Retèl VP, Schats W, van Harten WH. Evidence underlying policy proposals for sustainable anticancer drug prices: a systematic review. *JAMA Oncol*. 2020;6:909–916.
- Strohbehm GW, Kacew AJ, Goldstein DA, Feldman MJ, Ratain MJ. Combination therapy patents: a new front in evergreening. *Nat Biotechnol*. 2021;39:1504–1510.
- Makady A et al. Policies for use of real-world data in Health Technology Assessment (HTA): a comparative study of six HTA agencies. *Value in Health*. 2017;20:520–532.
- EMA. *Adaptive Pathways Workshop*. Amsterdam: EMA; 2016.
- Persson U, Norlin JM. Multi-indication and combination pricing and reimbursement of pharmaceuticals: opportunities for improved health care through faster uptake of new innovations. *Appl Health Econ Health Policy*. 2018;16:157–165.
- Latimer NR, Towse A, Henshall C. Not cost-effective at zero price: valuing and paying for combination therapies in cancer. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21:331–333.
- Pauwels K, Huys I, Casteels M, Simoens S. Industry perspectives on market access of innovative drugs: the relevance for oncology drugs. *Front Pharmacol*. 2016;7:144.
- Chandra A, Garthwaite C. The economics of indication-based drug pricing. *N England J Med*. 2017;377:103–106.
- Allen N, Liberti L, Walker SR, Salek S. A comparison of reimbursement recommendations by European HTA agencies: is there opportunity for further alignment?. *Front Pharmacol*. 2017;8:384.
- EunetHTA. <https://www.eunetha.eu/> [Accessed 11 May 2023].

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