ACCESS TO ONCOLOGY COMBINATION THERAPIES IN EUROPE: MOVING FORWARD

2023 Executive Summary

March 2024

EFPIA Oncology Platform's (EOP) Journey to Improving Patient Access to Novel Combination Therapies: Executive Summary 2023

Introduction

Ensuring access to novel oncology combination therapies in Europe has been complex and challenges continue to vary between countries. Given the substantial medical benefits that novel oncology combination therapies offer to cancer patients, there is an increased urgency to address these challenges and enhance patient access. In 2022, the EOP aimed to better identify the key barriers, assess their variability between countries, and identify solutions under discussion. The current access landscape for novel oncology combination therapies was analysed across several European countries. Multi-stakeholder discussions were also held with various organisations, including a roundtable with the Irish Pharmaceutical Healthcare Association (IPHA) and other stakeholders, and contribution to the first edition of the Belgium Combination Therapies Forum, organised by pharma.be, amongst others. A European-level workshop with 16 national trade associations (NTAs), organised by the EOP, also fostered collaboration and facilitated knowledge-sharing across countries. Additionally, the EOP developed a situation paper titled, "Access to Oncology Combination Therapies in Europe: Today's Challenges and Solutions", which summarised the current challenges for patient access to novel oncology combination therapies in Europe, potential solutions, and specific recommendations. These initiatives were disseminated during ISPOR Europe 2022 and ESMO 2022 congresses. Collectively, these efforts underlined EFPIA's strong commitment to improving patient access to novel oncology combination therapies in Europe.

The EOP's efforts in improving patient access to novel oncology combination therapies have continued throughout 2023 and were based on three key objectives:

- Highlight the medical benefits of novel oncology combination therapies
- Quantitatively analyse the impact of access challenges on novel oncology combination therapy availability, and time to access across European countries
- Maximise learning by sharing updates on current initiatives and best practices between National Trade Associations (NTAs).

Methodology

Firstly, the EOP began developing a medical rationale consensus document to define the mechanistic advantages and medical benefits of oncology combination therapies. A literature review identified such patient-relevant benefits of combination therapies. These benefits were then reviewed and validated by medical experts from member companies of the EOP's combination therapies working group, before conducting interviews with leading non-industry experts (e.g., medical oncologists, policymakers, health economists and patient advocacy group representatives) to gain additional insights and finalise the report.

Secondly, quantitative analyses were performed to assess the availability of, and time-to-access for, novel oncology combination therapies across 13 European countries. Data were extracted from multiple datasets, collated, and evaluated to draw conclusions on patient access to novel oncology combination therapies, before being disseminated at an ISPOR Europe 2023 podium presentation.

Finally, a second edition of the European-level NTA workshop was held with representatives from 14 European countries to share learnings from the development of combination therapy solutions and best practices.

Mechanistic Advantages and Medical Benefits of Novel Oncology Combination Therapies

Novel oncology combination therapies exhibit a multitude of mechanistic advantages over monotherapies. They employ a 'multi-pronged,' synergistic approach to combat cancer by simultaneously targeting multiple signalling pathways, enhancing the anti-cancer effects of each medicine.[1,2] Additionally, such therapies can reduce the probability of the tumour developing drug resistance as the cancer cells cannot adapt rapidly enough to evade the anti-cancer effects.[1,2] These distinct mechanistic benefits of novel oncology combination therapies translate to significant medical benefits for cancer patients, such as delivering value to patients which can be greater than the values of each constituent.[1] Improved clinical efficacy compared to monotherapies and an increased likelihood of the patients overcoming drug resistance may also be provided, extending the duration of the anti-cancer effects. Specifically, studies have demonstrated novel oncology combinations to provide significant improvements in overall survival (OS), progression-free survival (PFS), and overall response rate (ORR), versus monotherapies.[3,4]

The Impact of Challenges on Combination Therapies Availability and Access Timelines

The EOP quantified the impact of access challenges on both the availability and the time required for patient access to novel oncology combination therapies. Although such challenges have previously been described in the literature, the impact on patient access has not previously been quantified.

The EFPIA Oncology Platform's analysis **(Figure 1)** showed that compared to the other countries, Germany had the greatest availability of novel oncology combinations approved between 2015 and 2021. However, these combination therapies entered the market before the new mandatory 20% combinations discount was implemented; if/how this new law may impact the availability of combination therapies is unknown. France had the second-greatest availability of novel oncology combination therapies, followed by Italy; whereas Bulgaria and Poland had the lowest number of novel oncology combinations reimbursed, mainly due to several combinations not being assessed. As can be seen from this analysis, significant discrepancies in the availability of novel oncology combination therapies exist across European countries, emphasising the ongoing access challenges for patient treatment equality.

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1 Zimmermann GR, Lehar J, Keith CT. Multi-target therapeutics: when the whole is greater than the sum of the parts. Drug Discov Today. 2007;12:34-42

2 National Cancer Institute (2016) Why Do Cancer Treatments Stop Working? Overcoming Treatment Resistance.

3 Jardim DL, et al., Efficacy and safety of anticancer drug combinations: a meta-analysis of randomized trials with a focus on immunotherapeutics and gene-targeted compounds. Oncoimmunology. 2020 Jan 1;9(1):1710052.

4 Wolchok JD, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40(2):127-137

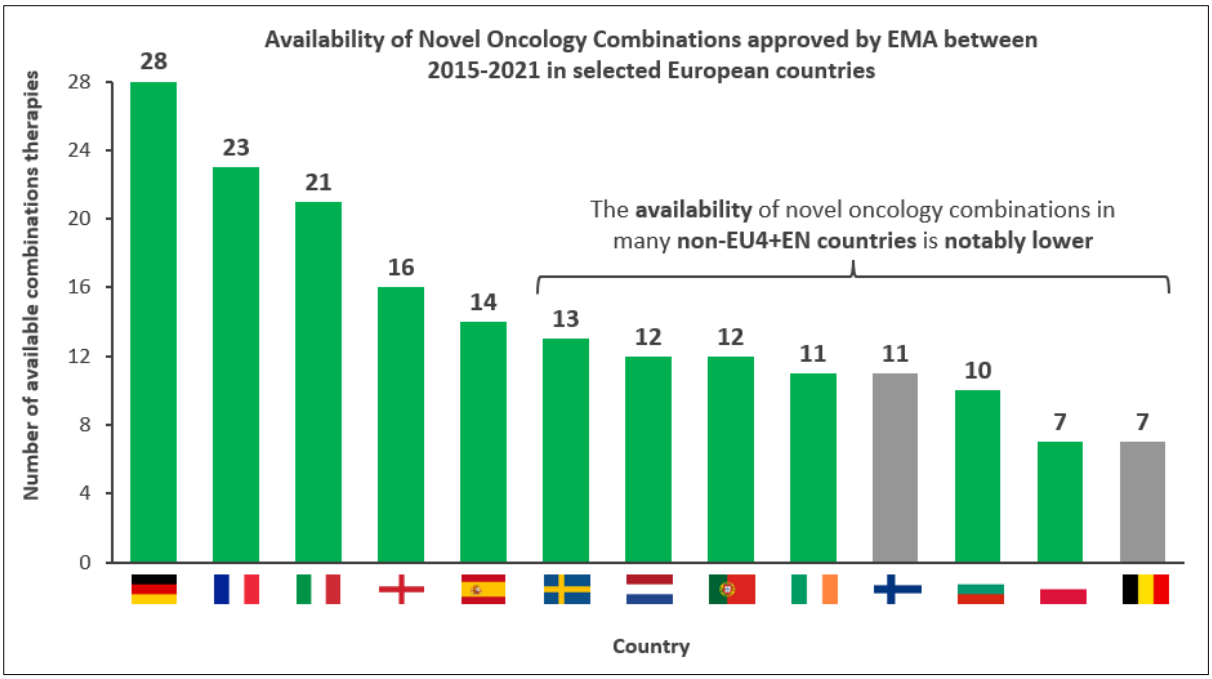

Figure 1 - Availability of Novel Oncology Combination Therapies approved by the EMA between 2015-2021 in selected European Countries. *Sources: CRA analysis of NAVLIN data, input from EOP member companies, & EFPIA W.A.I.T. indicator data from 2015-2023. Available = combination therapy is reimbursed and available to patients, either in full (in line with the EMA-indicated label), or via conditional recommendations (possibly restricted to later treatment lines and/or patient sub-populations). Data displayed in grey bars for FL and BE may not be fully representative as HTA/reimbursement information is not readily available; however, some data from EOP companies was provided to support the analysis.*

In terms of proportional availability, defined as the percentage of EMA-approved products reimbursed and available to patients, this was on average 17 percentage points lower for novel oncology combination therapies compared to all oncology products approved over the same period, across the selected European countries **(Figure 2)**. For combination therapies entering the German market before the new mandatory 20% combinations discount was implemented, there was a negligible difference between the proportion of novel combinations vs oncology products reimbursed. Conversely, the Netherlands and England had the largest percentage point differences in proportional availability of novel oncology combinations vs all oncology products, 31 and 22 percentage points respectively, with England having greater disparity in proportional availability than France, Germany, Italy, and Spain. In England, 9 appraisals were terminated due to manufacturers not submitting additional data, and a discrepancy of 21 percentage points was seen in Sweden, highlighting the challenges that combination therapies often face in cost-effectiveness-focused countries.

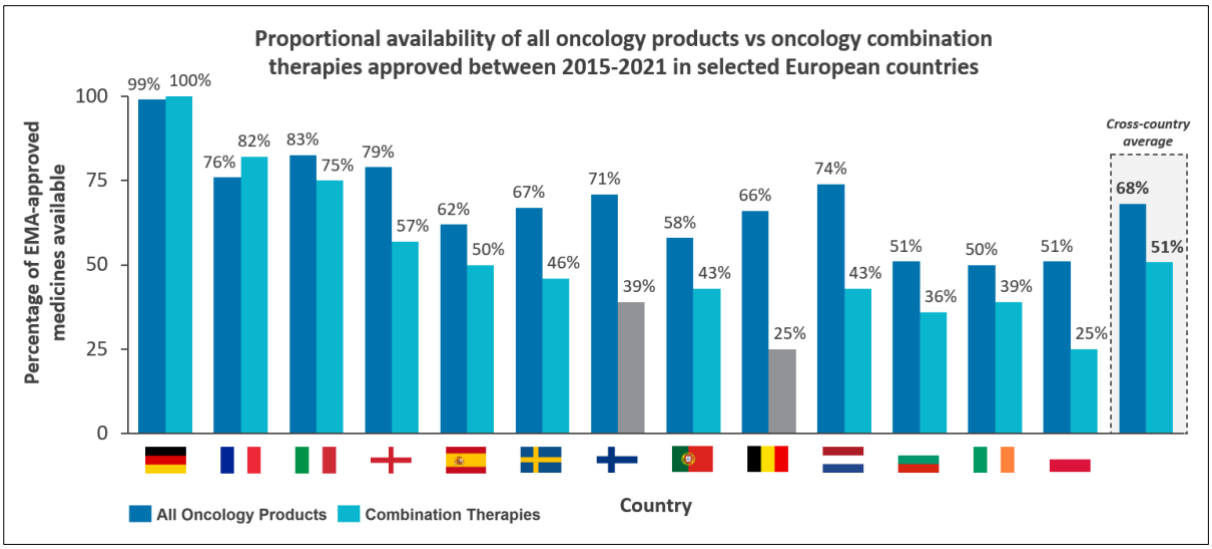

Figure 2 - Proportional availability of all oncology products vs oncology combination therapies approved between 2015 and 2021 in selected European countries. *Sources: CRA analysis of NAVLIN data, input from EOP member companies, & EFPIA W.A.I.T. indicator data from 2015-2023. Available = combination therapy is reimbursed and available to patients, either in full (in line with the EMA-indicated label), or via conditional recommendations (possibly restricted to later treatment lines and/or patient sub-populations). Data displayed in grey bars for FL and BE may not be fully representative as HTA/reimbursement information is not readily available; however, some data from EOP companies was provided to support the analysis.*

Not only have significant disparities been observed in the proportional availability of novel combination therapies versus all oncology products, but such combinations also took on average 193 days longer to become available for patients, compared to all oncology products **(Figure 3)**.

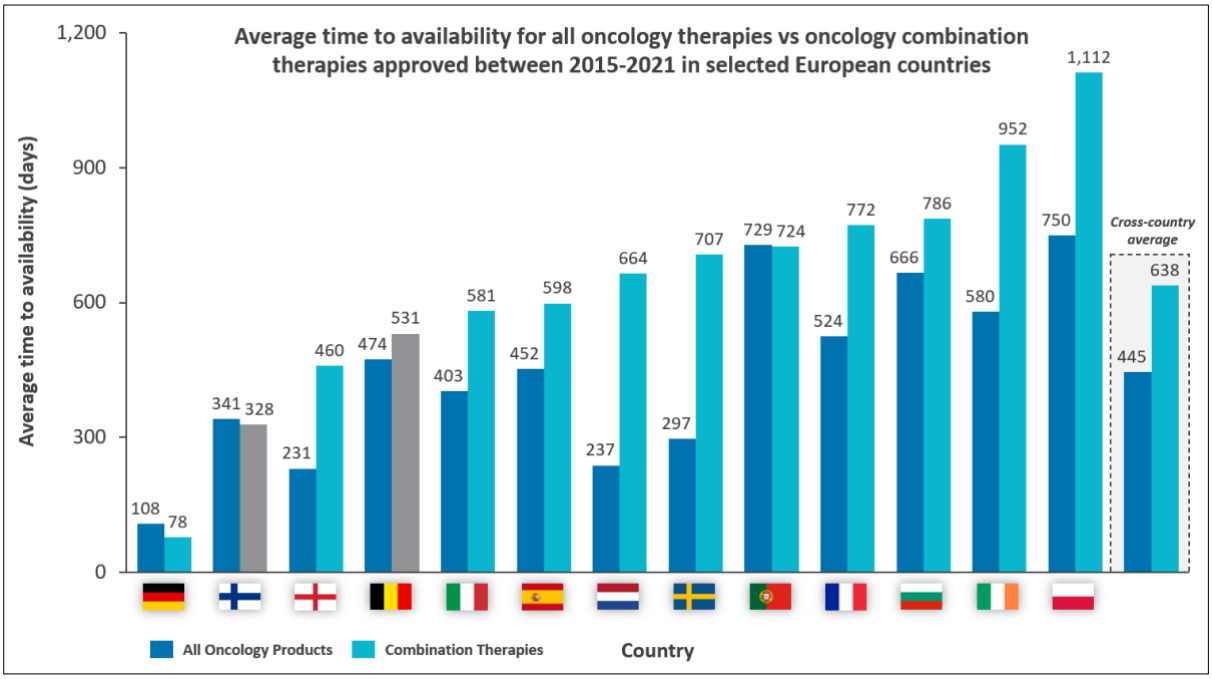

Figure 3 – Average time to availability for all oncology products vs oncology combination therapies approved between 2015 and 2021 in selected European countries. *Sources: CRA analysis of NAVLIN data, input from EOP member companies, & EFPIA W.A.I.T. indicator data from 2015-2023. Available = combination therapy is reimbursed and available to patients, either in full (in line with the EMA-indicated label), or via conditional recommendations (possibly restricted to later treatment lines and/or patient sub-populations). Data displayed in grey bars for FL and BE may not be fully representative as HTA/reimbursement information is not readily available; however, some data from EOP companies was provided to support the analysis.*

Out of EU4+England countries, England had the largest time-to-availability difference between all oncology products and combinations, taking approximately double the time for combination therapies to receive reimbursement, compared to all oncology products. Additionally, the Netherlands, Sweden and Ireland had the largest percentage difference between time to reimbursement of combinations and all oncology products, whilst Germany had the shortest. Overall, this research confirms that patient access is being negatively affected by the challenges of assessing combination therapies, leading to inequitable access to novel oncology combination therapies between European markets.

Reasons for Sub-Optimal Reimbursement of Novel Oncology Combination Therapies

The EFPIA Oncology Platform also explored the underlying reasons for sub-optimal reimbursement (i.e., not fully reimbursed in line with the EMA-approved label; restricted/denied) of such treatments. As is reflected in the analysis in countries like England, Sweden, and Ireland, one of the most common reasons for sub-optimal reimbursement is that negotiations are terminated due to an inability to comply with cost-effectiveness thresholds. Additionally, payer uncertainties over the clinical data availability, negative spillovers for value considerations in other indications (resulting in no submission from the company), and restricted reimbursement to patient sub-population(s) were also significant reasons for sub-optimal access. Overall, this multitude of reasons for sub-optimal reimbursement of combination therapies further highlights the ongoing reimbursement challenges, resulting in delayed or denied patient access.

Moreover, the number of novel oncology combination therapies receiving EMA approval is expected to increase over the next 5 years, compared to the number of approvals since 2015: approximately 55 novel oncology combination therapies are expected to launch in Europe,[5] with many of these containing products from two (or more) manufacturers. Therefore, challenges for patient access to combination therapies will likely continue unless suitable solutions are proposed.

Current NTA Initiatives Aiming to the Access Challenges for Combination Therapies

During 2023, several European NTAs continued their efforts in developing potential solutions that aim to address the access challenges for combination therapies, and therefore provide such highly effective treatments to patients faster. NTAs that have been working on such initiatives include the Association of the British Pharmaceutical Industry (ABPI), Läkemedelsindustriföreningen (LIF) Sweden, pharma.be (Belgium), and the Irish Pharmaceutical Healthcare Association (IPHA).

The ABPI's 'Commercial Transaction Approach' & UK Competition and Markets Authority Opinion

In the UK, the ABPI has been exploring a solution to ensure patient access to combination therapies that may struggle to be cost-effective. This framework seeks to address a potential market failure in scenarios where: (1) two or more branded medicines have been developed for use in combination; (2) the clinical benefits of using the medicines in combination are greater than the individual treatment options and the price of the component medicines together is too high for the combination therapy to be considered cost-effective by NICE; (3) the (add-on) company responsible for the NICE submission cannot price their medicine accordingly for the combination therapy to

5 CRA analysis of ClinicalTrials.org and Evaluate-Pharma. Launch years were estimated based on the following assumptions: for combinations in phase 4, the launch year is the trial completion year + 1 yr, capped at 2022; for phase 3 combinations, the completion year +2 yrs capped at 2024; for phase 2 combinations, completion year +5 yrs capped at 2026; for phase 1 combinations, completion year +7 capped at 2028. Products were then filtered based on the number of manufacturers involved in the clinical trial. Between 2023-2027, the assumed attrition rate is 20% (therefore giving an assumed successful launch rate of 80% from Ph3 trials)

remain cost-effective; and (4) without such a "commercial transaction" between the companies who hold the licences for the medicines used in the combination, reimbursement will not be agreed upon in the UK and patients will not access the treatment.

In November 2023, the UK Competition and Markets Authority (CMA) released a statement providing clarity over how it would view pricing discussions between manufacturers entering into a combination therapy. The CMA stated that it "will not prioritise investigations under the Competition Act 1998 (the 'CA98') into specific forms of engagement between medicine manufacturers which are carried out in good faith and aimed at making a combination therapy available to NHS patients in the UK, where certain market features are present and particular conditions are met". This statement is a first of its kind from any competition authority and provides hope in supporting UK National Health System (NHS) patient access to effective combination therapies.

LIF Sweden's Joint Report on Refinements to Economic Evaluations of Combination Therapies

In June 2023, a novel approach to the pricing of novel combination therapies in Sweden was proposed in a joint report by representatives of the regions, the New Therapies (NT) Council, and LIF. The report proposes that various stakeholders, including manufacturers, could voluntarily participate in the negotiations leading to a national recommendation from the NT Council. Via the NT Council, Swedish regions could develop a process for the recommendation of branded hospital medicines used in combination. It was proposed that TLV be responsible for managing the confidentiality linked to access to necessary medical information between companies. According to the report, assumptions about a medicine's future use (e.g., in a monotherapy vs combination therapy indication) could better inform the economic evaluation. Different prices per usage (combination vs monotherapy) could be weighted to produce a price that can be defined in an agreement, as determined by the NT Council at the national level.

The authors of the report proposed a pilot project for suitable candidates found via horizon scanning, and a meeting with the Swedish Competition Authority is recommended to receive comments on compliance with competition and antitrust laws. The proposed approach would likely be reserved for a limited number of combination therapies that are challenging to price using conventional methods, but this further highlights the strong support manufacturers are receiving from NTAs to improve patient access to combination therapies.

pharma.be's Proposed 'Mirroring Reimbursement Procedure'

Given the current inability to assess the constituents of combination therapy in parallel in Belgium, leading to patient access delays for such treatments, pharma.be is proposing a 'Mirroring Reimbursement Procedure' that allows both constituents to be evaluated simultaneously. In this proposed solution, the National Institute for Health and Disability Insurance (NIHDI) would retain its important role in HTA and decision-making by processing the information coming from two (or more) manufacturers, instead of one. According to pharma.be such moderation via the NIHDI could lead to better-informed discussions regarding the value assessment and estimations of patient numbers and budget impact (due to the input from both companies).

In this process, all components of the combination therapy would be involved in the assessment process, and the specificities of each component can be discussed regarding the use within the combination therapy's indication. pharma.be has noted that this "clear and predictable" proposed solution aims to make simultaneous assessments possible, but not mandatory.

IPHA and Bird & Bird's Competition Law Advisory Policies for Combination Therapy Manufacturers

Throughout 2023, the IPHA has been working closely with a legal firm, Bird & Bird, to develop advisory policies for manufacturers entering pricing discussions with each other for combination therapies. Bird & Bird were asked to provide high-level advice on; competition law issues that arise from the formation of combination product pricing in Ireland, types of solutions that might help to mitigate competition law risks when competitors collaborate (including a review and advice in respect of potential pathway solutions to combination pricing), and a recommendation on the most appropriate collaboration model for combination product pricing from a legal perspective.

Concluding Remarks

Throughout 2023, initiatives led by the EFPIA Oncology Platform have further highlighted the ongoing access challenges for novel combination therapies across Europe. As mentioned, the average availability rates of novel oncology combination therapies approved between 2015 and 2021 were lower than that of all oncology products, and times to availability for novel oncology combination therapies are continuing to lag behind oncology products in general. As a substantial number of combination therapies are expected to launch in Europe over the next five years, leveraging upcoming HTA reforms will be crucial to ensuring timely patient access across all European countries. Alongside prioritising the consideration of new policies and potential solutions, collaborative efforts among various stakeholders are essential to ensure that patients living with cancer have access to these innovative and effective treatments.