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ACCESS TO ONCOLOGY COMBINATION THERAPIES IN EUROPE: TODAY'S CHALLENGES AND SOLUTIONS

Summary of the EOP Combination Therapies Subgroup 2022 Situation Report

April 2023

Background

Over the past 20 years, there have been significant advances in the cancer treatment landscape, leading to improvements in prognosis and overall patient survival. Combination therapies (therapies made up of two or more "constituents") have contributed significantly to such advances and, in many cases, are more effective and offer prolonged overall and/or progression-free survival compared to monotherapies. Despite these benefits, ensuring patient access to combination therapies in Europe has proved difficult. In particular, free-dose combinations of on-patent therapies, especially when constituents are marketed by different manufacturers and have multiple indications, face unique access challenges within the oncology space.

Although multiple stakeholder groups have debated the problem and the potential solutions, there is still limited awareness about the situation and progress in addressing this problem has been slow. Consequently, access to on-patent oncology combinations has lagged behind access to oncology medicines in general. If no further action is taken, the limitations on treatment availability and consequences for patients are expected to worsen especially as an increasing number of oncology combination therapies are due to launch over the next five years. This is a significant issue with approximately one in five oncology medicine expected to be a combination therapy (compared to approximately one in ten over the past five years). If this challenge persists, manufacturers may be disincentivised to invest in the development of combination therapies, limiting the potential of future research.

This analysis aims to describe the challenges affecting patient access to oncology combination therapies across various European markets (Belgium, England, France, Germany, Ireland, Poland, Spain, and Sweden), with a specific focus on the value assessment, pricing negotiation and reimbursement conditions. Progress on the most prominent solutions is discussed, along with considerations regarding their implementation.

Methodology

A three-step approach was followed (i) a literature review, (ii) interviews with representatives from national trade associations of the countries in scope and member companies of the EOP combination therapies working group, and (iii) multi-stakeholder discussions in Belgium and Ireland. Additional discussions were also held with member pharmaceutical companies of Farmaindustria and Läkemedelsindustriföreningen (LIF), in Spain and Sweden respectively.

Challenges affecting access to oncology combination therapies and solutions under debate

Across European countries, the value assessment and pricing and reimbursement (P&R) processes for medicines are generally designed for the assessment and pricing of monotherapies. These have been applied to combination therapies where only one constituent is on-patent without additional concerns but have not been adapted for the assessment and pricing of novel combination therapies. Consequently, free-dose oncology combination therapies involving multiple on-patent constituents are currently facing challenges that might delay or even prevent patient access to the combination. Such challenges are exacerbated when the constituents within the combination are marketed for multiple indications and/or are owned by different manufacturers, as is increasingly common.

Due to the complexity and multifaceted nature of these challenges, multiple solutions have been debated and are under consideration, such as those listed below.

Key Issue 1:

Current value assessment frameworks have not been specifically adapted for combination therapies and in some cases (especially in HTA systems using cost-effectiveness methodologies) may represent a significant barrier to accessing new oncology combinations even when the second therapy in the combination is priced at zero.

Potential solutions:

In situations where the assessment process is a critical barrier and the value of one or more constituents cannot be fairly recognised, assessment methodologies/frameworks could be considered to ensure that the constituents are rewarded with prices representative of their clinical benefit, such as:

- A 'Voluntary Arbitration Framework', including a phased approach to multi-party pricing negotiations, whereby the proportional value of the constituents is mathematically determined and is expressed as proportions of incremental benefit
- An 'Outcomes-Based Value Attribution Framework', including a price-adjustment mechanism for the first constituent (e.g., combination use-specific pricing), whereby there is the adoption of a mathematical approach to attribute value between the constituents of combination therapies that is representative of their incremental clinical benefit over the standard of care.

It is worth noting that approaches to the value attribution problem will not in themselves fully resolve the broader policy challenge to access novel oncology combinations and would require other tools to be effective, such as the adoption of a combination-specific pricing approach and a dedicated pricing negotiation process.

Key Issue 2:

If the constituents of the combination are produced by different manufacturers, the companies may not be able to coordinate directly with each other due to concerns of infringing anti-trust regulations designed to prevent price collusion, even though a mutually beneficial, and societally positive, agreement is possible that improves patient access to combination therapies.

Potential solutions:

Several mechanisms have already been tested, or are currently being tested, to mitigate such legal concerns in the pricing and reimbursement process, including:

- New frameworks for direct multi-manufacturer negotiations (e.g., in England, the ABPI is proposing a process which does not require the exchange of any pricing/market share information and aims to support companies in coming to a solution when combination therapies are not considered cost-effective by NICE)
- Introduction of third parties to facilitate pricing negotiations (e.g., the industry association could facilitate negotiations between the payers and respective manufacturers of the constituents)
- The use of independent digital trading platforms to remove the need for manufacturers to meet without involving a third party to act as a 'guarantor' (e.g., a platform was trialled in Sweden in 2019, but it was determined that further testing would be required to overcome technical challenges and to ensure the outcome allows for a better alignment between price and value)
- Obtaining 'safe harbour' arrangements (which do not require the participation of a third party) from competition authorities to enable manufacturers to engage in direct price discussion without the risk of infringing competition laws.

Key Issue 3:

For the price of the combination therapy to align with the combination's value from the payer's perspective, a price reduction for the first constituent may be required. The manufacturer of the first constituent is unlikely to offer a price reduction if the first constituent is already marketed in other indications and as this would negatively impact the price of other indications, where prices reflect the value they deliver.

Potential solutions:

- Combination-specific pricing to allow net prices to change depending on whether the constituent is being used as a monotherapy or in a combination therapy
    a. This mechanism would allow manufacturers to reduce the price of the first constituent when used in combination without affecting its price in other indications, increasing the headroom in the cost-effectiveness threshold to pay for the second constituent to the benefit of both manufacturers and patients
- Alternatively, a 'blended price' mechanism could be adopted where the price is based on the estimated number of patients using a product in combination vs monotherapy
    a. This may allow for better linkage between the cost to the payer and the value delivered
- Innovative contracting mechanisms, such as payments by results linked to the use as combination therapy, could be used to provide different rebates for the use as a monotherapy (such innovative pricing agreements having been recommended for oncology combinations in Poland).

What is the way forward?

Over the next five years, approximately 68 oncology combination therapies are expected to launch, and the proportion of all oncology launches that are combination therapies is also expected to increase. Without action, some of these may not be launched in certain European countries. There is a clear societal need for the development of frameworks for assessing and pricing combination therapies to ensure patients receive timely access to such treatments. A fair and efficient system for assessing the value and appropriately rewarding combination therapies should:

- Ensure that innovative and valuable combinations are made available to patients and should incentivise research and development
- Learn from the experience of existing solutions. There are solutions which will soon be operative, particularly when key stakeholders (other than the pharmaceutical industry) are collaborating on addressing the problem or have worked well until recently (such as the blended approach to pricing in Germany).

All of these solutions require the collaboration of multiple stakeholders and the willingness to adopt a combination-based approach.