Oncology Combination Market Access Conundrum in Europe

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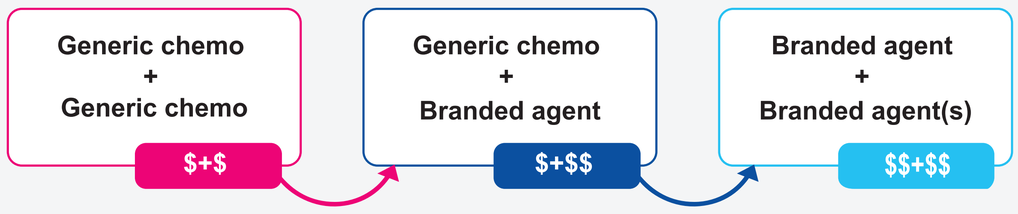
Objective

Examine current market access trends for branded combination oncology therapies in France, Germany, Italy, and the UK

Background:

The number of combination oncology therapies is on the rise with significant budget impact implications

Oncology combination therapies have evolved from inexpensive generic chemotherapies used adjunctively to a combination of ≥2 on-patent medicines



This trend is clearly noted with immunotherapies, which are used across most solid tumors..

- Many PD-1/L1 inhibitors are being used as combination therapies with other molecules as they are becoming backbone treatments
- >5,500 clinical trials are ongoing investigating PD-1/L1 inhibitors; 80% of these trials are as combination therapies

7 PD-1/L 1
pathway checkpoint inhibitors approved by FDA to date

300 targets
in total being investigated in PD-1/L 1 combination trials

5,761 trials
testing PD-1/L 1 inhibitors worldwide in 2021

Combination therapies pose a challenge for sustainability, funding and access.

Methods

- We reviewed pricing, reimbursement, and market access when two branded oncology agents are approved for combination use
- Because of the extensive use of PD-1s across multiple cancers, we focused on branded combinations with either pembrolizumab or nivolumab
- Four branded product combinations were analyzed
  1. Keytruda (pembrolizumab) and Inlyta (axitinib) for RCC
  2. Opdivo (nivolumab) and Cabometyx (cabozantinib) for RCC
  3. Keytruda (pembrolizumab) and Kisplyx (lenvatinib) for RCC
  4. Opdivo (nivolumab) and Yervoy (ipilimumab) for melanoma
- Several characteristics were considered in the analysis including
  - Date of approval of combination therapy in Europe
  - Backbone therapy (manufacturer)
  - Add-on therapy (manufacturer)
  - Nature of collaboration between manufacturers if any
  - HTA/PRMA filing responsibility for the combination therapy
- Data gathered from European Medicines Agency (EMA), national Health Technology Assessment (HTA) agencies, and Pricing and Reimbursement (P&R) bodies

Results

Opdivo (nivolumab) and Yervoy (ipilimumab) was the only combination therapy from the same manufacturer, all other combinations analyzed included constituent therapies from different manufacturers (Table 1).

Table 1: Characteristics of combination therapies analyzed

Characteristics	Keytruda (pembrolizumab) and Inlyta (axitinib) [Advanced RCC- 1L]	Opdivo (nivolumab) and Cabometyx (cabozantinib) [Advanced RCC- 1L]	Keytruda (pembrolizumab) and Kisplyx (lenvatinib) [Advanced RCC- 1L]	Opdivo (nivolumab) and Yervoy (ipilimumab) [Advanced unresectable melanoma]
Date of approval of combination therapy in Europe	04-Sep-2019	14-Apr-2021	29-Nov-2021	11-May-2016
Backbone therapy (mfg)	Axitinib (Pfizer)	Nivolumab (BMS)	Pembrolizumab (Merck)	Nivolumab (BMS)
Add-on therapy (mfg)	Pembrolizumab (Merck)	Cabozantinib (Ipsen)	Lenvatinib (Eisai)	Ipilimumab (BMS)
Nature of collaboration between manufacturers if any	No collaboration (Merck initiative)	Clinical development collaboration	Clinical development and commercialization joint collaboration	Same manufacturer
HTA submission/market access responsibility for the combination therapy	Merck	Ipsen	Eisai	BMS

- Health system approaches to pricing and reimbursement negotiations of combination therapies differ especially with regard to the manufacturer responsible for the burden of proof and P&R negotiations (Figure 1)

Figure 1: Health system approaches to P&R of combination therapies

FRANCE

- Because the extension of use as a combination is deemed as a **change in terms of "conditions of use" of the backbone, it triggers a re-negotiation for manufacturers of both constituent therapies**
- Prices at list or net level likely to be re-negotiated for both constituents of the combination (including price-volume agreements)
- Payers could re-negotiate the list price of the incumbent or the rebates influencing the net price to make room for the combination

GERMANY

- No price cuts negotiated on any incumbent background therapies
- **Onus for price negotiations completely on the manufacturer initiating the new filing/submission**
- As per recent reform (SHI Finance Stabilization Act- 2022) 20% discount applies for combination therapies, except if
  - Backbone therapy is generic/biosimilar
  - Combination is assigned a considerable/major additional benefit (discount can be waived)

ITALY

- Confidential discounts and/or budget caps likely **re-negotiated for both constituent molecules** given increasing budget impact
  - Clear separation of impact of combos difficult, since price renegotiations addressed multiple changes in the regulatory status of products (e.g., new combo regimen renegotiated along with one/additional new indications)

UK

- **The manufacturer initiating the new filing/submission is usually responsible for demonstrating cost- effectiveness**
- **NICE can review the combination via the MTA pathway (Multiple Technology Assessment) as a potential way forward when manufacturers of constituent therapies do not have a collaborative approach**
- Cost-effectiveness threshold, is the same for combination therapies and monotherapies
  - ~1/3rd of combination oncology therapies submitted to NICE are either not recommended or have their appraisal terminated due to the inability to prove cost-effectiveness

- Outcomes of negotiations are substantially impacted by the nature of collaboration between manufacturers of constituent therapies (i.e., joint or independent development and commercialization)
- Analysis of specific combination therapies resulted in key observations below (Figure 2) based on limited publicly available information
- Because of differences in health system approaches, confidential discounts, and/or budget caps, price-volume agreements are likely to be re-negotiated
- Furthermore, surpassing sales thresholds with approval of multiple indications could shape negotiations along with the nature of the collaboration between manufacturers of constituent therapies (i.e., no collaboration/clinical only/clinical and commercial collaboration)

Figure 2: Pricing and reimbursement outcomes of combination therapies analyzed

Pembrolizumab and axitinib [Advanced RCC- 1L]	Nivolumab and cabozantinib [Advanced RCC- 1L]	Pembrolizumab and lenvatinib [Advanced RCC- 1L]	Nivolumab and ipilimumab [Advanced unresectable melanoma]
• **No visible price cuts** noted for either therapy in the countries assessed • However confidential discounts and/or budget caps likely re-negotiated in France, Italy • **Not recommended for reimbursement in England by (NICE) because of uncertainty in cost-effectiveness**	• **A slight visible price reduction** was observed only in **Germany for cabozantinib** (although other indication could also have contributed) • Confidential discounts and/or budget caps potentially re-negotiated in France, Italy • **Terminated appraisal in England (NICE) because BMS withdrew the submission**	• **A slight visible price reduction** was observed only in **Germany for lenvatinib** (although other indication could also have contributed) • Confidential discounts and/or budget caps potentially re-negotiated in France, Italy • **Reimbursed as part of multiple technology assessment (MTA) in England (NICE)**	• **Visible price cuts were observed in France and Germany on nivolumab likely due to multiple indications** • **A slight visible price cut also noted in Germany for ipilimumab** • Confidential discounts and/or budget caps potentially re-negotiated in France, Italy • **Recommended for use based on managed access agreement in England (NICE)**

Conclusions

- Branded oncology combination therapies are a particular pain point for payers who often question if the additive cost of the combination is proportionate to the incremental value being offered to patients
  - This problem is exacerbated when not just two, but several branded agents (3 to 5) are recommended for use in combination (e.g., multiple myeloma)
- While payers have struggled with managing the rising costs for a number of years, there is an evolution toward a slightly more structured approach that is intended to target runaway costs in this area
  - Country-specific approaches differ with varying responsibilities of the manufacturers of the constituent therapies
- It is crucial to understand these differences and monitor the changing environment in order to navigate and find solutions tailored to individual health systems for more favorable outcomes
- Furthermore, with several branded oncology combinations in development, new frameworks for valuing and paying for them to maintain incentives for investment on the one hand while creating a sustainable ecosystem on the other require a delicate balance
- Loss of exclusivity for PD-1s anticipated in the coming years is likely to impact the landscape and potentially make some combination therapies with PD-1 biosimilars as backbone more affordable and accessible
  - Uptake of these biosimilars across countries and the headroom they create from a funding perspective will need to be monitored in the coming years
  - Additionally, patent protection on combination therapies is likely to impact this scenario

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