Importance of the Re-Challenge Assumption in the Assessment of Immune-Oncology Agents in Early Cancer

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INTRODUCTION

- While immuno-oncology (IO) treatments are now established as the standard of care in different advanced oncologic indications, their recent expansion to earlier stages raises questions about implications on IO re-challenge in later stages.[1,2]
- The question of IO re-challenge introduces numerous uncertainties due to the limited scientific evidence available. Previous HTA submissions have often relied on subjective factors, such as clinical expert opinion, to guide the determination of re-challenge strategies.[2,3]
- Different re-challenge assumptions may affect the cost-effectiveness result and implicate the economic evaluation and reimbursement

OBJECTIVES

This study aimed to review existing modelling approaches and explores scenarios to assess the significance of IO re-challenge assumptions in health technology assessments (HTAs).

METHODS

This study consisted of two steps: a targeted literature review (TLR) of eligible HTA submissions, and exploratory cost-effectiveness analyses (CEAs) to test the IO rechallenge scenarios identified from TLR (Fig. 1).

Figure 1. Approach

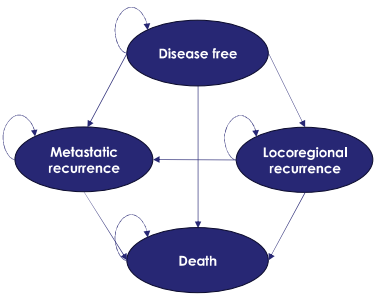
Targeted Literature Review

- A comprehensive search for all HTA submissions of IO treatments in early-stage cancer was performed in March 2024 in three HTA databases: NICE, HAS, and CDA (Canadian's Drug Agency), without date or language restriction.
- Information including cost-effectiveness model (CEM) type, assumptions about IO re-challenge, modelling approaches for cost and efficacy in the re-challenge phase, scenarios tested and criticism by the HTA agencies, were extracted.

Cost-Effectiveness Model (CEM)

- An exploratory state transition CEM with four health states (Fig. 2) was developed reflecting a common approach identified as part of the TLR. The key modelling parameters were programmed to reflect the approach reported in NICE TA851[4], which assessed pembrolizumab in early or locally advanced breast cancer. As key data was restricted due to confidentiality, assumptions were informed by available literature.

Figure 2. CEM structure



- The identified IO re-challenge scenarios from the TLR were tested, including: (S1) no IO re-challenge allowed (used for reference), (S2) no restriction on IO re-treatment (S3) no IO re-challenge with the same IO but other IO options allowed, and (S4) re-challenge allowed with time restriction of 24 months. Given the indication, all scenarios were applied to the metastatic health state where IOs are approved and often considered SoC.
- Additional scenarios were tested in which IOs were hypothetically considered available in the locoregional setting. The scenario was purely hypothetical and assumed that pembrolizumab's efficacy would be comparable to that reported for patients with Stage II melanoma..[7]
- To understand the impact of the results in other indications with higher frequency of recurrence (such as pancreatic, gallbladder cancer, and hepatocellular carcinoma) a simple hazard ratio (HR) was applied to the recurrence-free and post-progression survival curves to test the IO re-challenge scenarios in high-recurrence population.

RESULTS

Targeted Literature Review

- A total of 23 HTAs of IOs were identified, 15 of which assessed immune checkpoint inhibitors (ICIs) in adjuvant breast and lung cancer, urothelial carcinoma, renal cell carcinoma and melanoma.
- The assumption of IO re-challenge was accepted by most agencies and included in 67% of base case analyses and explored in 27% of scenario analyses.
- While all HTAs considering IO re-challenge evaluated costs, explicit modelling of increased survival due to IO use in metastatic settings was included in 73% of the models, mostly using mean/median OS data weighted by treatment distribution.
- IO re-challenge assumptions were always supported by clinical expert opinion and often raised criticism, mainly due to limited evidence.
- The impact on the result varied across TAs with two examples where the IO re-challenge assumption had a major impact:
  - NICE TA876: the extension of IO re-challenge restriction from 6 to 12 months decreased the ICER by 42% while the restriction removal increased the ICER by 72%.[4]
  - NICE TA837: prohibiting pembrolizumab rechallenge in the metastatic stage increased the ICER by 40%.[5]

Figure 3. IO re-challenge by setting

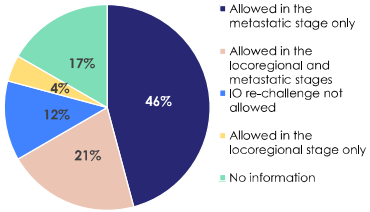


Figure 4. HTA criticism

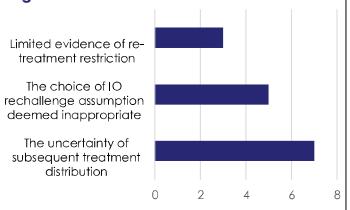


Figure 5. Approach to modelling efficacy in the metastatic stage

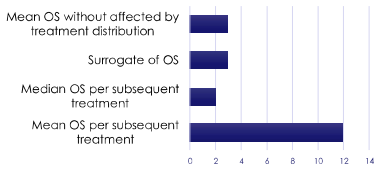
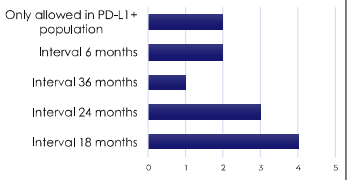


Figure 6. IO re-challenge restrictions



Cost-Effectiveness Model Results

- The results of the CEM highlighted the large difference between scenarios, which were prominent when simulating an indication with IO treatment available in the locoregional setting and for indications with high-risk of recurrence.

Table 1. CEM results – Change in incremental cost-effectiveness ratio (ICER) versus Full IO re-challenge restriction scenario (S1)

	IO allowed with no restriction (S2)	Different IO Allowed (S3)	Any IO re-treatment allowed after 24m (S4)
Low-risk indication with IOs re-challenge in the metastatic setting	2.6%	3.6%	2.4%
Low-risk patients + IOs re-challenge in the locoregional and metastatic settings	166.3%	82.7%	122.3%
High-risk indication with IOs re-challenge in the metastatic setting	23.6%	26.4%	15.4%

CONCLUSIONS

- IO re-challenge approaches significantly impact the ICER, particularly in locoregional settings or multiple post-progression states, where IOs are considered.
- Enhanced clinical evidence is crucial for refining IO re-challenge modelling given the current data gap across all indications.

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DISCLOSURES

NTA, ME, AR, and AG are employees of Amaris Consulting and have conducted this work without additional funding.