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# A multi-stakeholder perspective on the challenges in demonstrating the long-term clinical benefit of cancer immunotherapy

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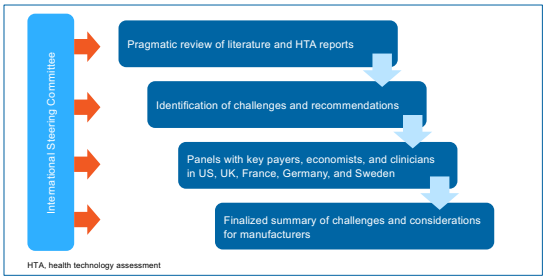
## Background

- Immuno-oncology drugs (IOs) differ from conventional chemotherapies in that they target the patient's immune system rather than directly attacking the tumor.
- This immune activation can lead to durable responses and improved long-term overall survival (OS) in some patients.
- Assessing the value of a new oncology drug is a key goal of health technology assessment (HTA) and pricing and reimbursement negotiations, and the gold-standard efficacy criterion in oncology for most HTA agencies is OS.
- However, providing robust evidence on OS would require large sample sizes and many years of trial follow-up.
- Manufacturers are, therefore, faced with the challenge of demonstrating the long-term benefit of their IOs with short-term survival data.
- The aim of this research was to identify and characterize a summary of challenges specific to IOs in demonstrating their long-term benefits at HTA submission.

## Methods

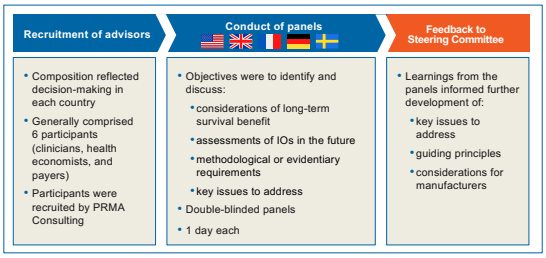
- Primary research was undertaken between July 2017 and February 2018; the methods are outlined in Figure 1.
- To complement and update the understanding of the challenges, and to ensure no important issues were missed, a pragmatic review of published literature was conducted prior to the primary research.
  - The IOs considered in this review were ipilimumab, nivolumab, and pembrolizumab; a total of 27 papers and 86 HTA reports from agencies in Australia, Canada, Germany, Sweden, and the UK were reviewed.

**Figure 1. Overview of research methodology**




- An international, multi-stakeholder steering committee (SC) comprising nine payers, economists, and clinicians from the US, UK, France, Italy, and Sweden was engaged to develop a summary of the challenges at HTA submission that are specific to IOs.
- The summary was refined via five double-blind multi-stakeholder expert panels, who made recommendations on how manufacturers may overcome these challenges in future submissions (Figure 2).
- The SC finalized the summary of challenges and a corresponding list of questions for manufacturers to consider at HTA submission.

**Figure 2. Panels were convened in the US, UK, France, Germany, and Sweden to identify the key issues and how to address them**




## Results

- The challenges for evaluating and communicating the long-term benefits of IOs to HTA agencies are summarized in Table 1.
- Overall, the SC and country-level panels observed that basing HTAs on standard parametric survival models to estimate long-term OS is likely to underestimate the impact of IO treatment on survival outcomes if IO treatment generates a plateau in the survival curve.
- Three key areas identified for IOs when demonstrating survival benefit were: (1) lack of a model structure that fully captures how IO therapy affects the course of disease; (2) immature data available at the time of the HTA submission; and (3) survival analysis and extrapolation.

**Table 1. Summary of key challenges in presenting the value of IOs in HTA submissions**

| Challenge | Considerations for manufacturers |
|---|---|
| **Mechanism of action** | |
| Representation of the underlying biological model | • Has the underlying biological model and how it links with any survival analysis/statistical modeling been clearly explained? |
| Possibility of cure underlying the long-term survival | • Have published external data or additional clinical trial data been presented as supportive evidence of long-term survivorship? |
| Addressing pseudo-progression | • Has pseudo-progression been raised as an issue?<br>• If so, were outcome measures used in the trials that take this phenomenon into account? |
| **Limited clinical trial evidence at HTA submission** | |
| Duration of follow-up and maturity of OS and PFS | • Have the trial endpoints been presented within the context of completeness (e.g., censoring, numbers at risk)? |
| Availability and use of intermediate and/or surrogate endpoints (TFI, DFS, response) | • Have the surrogate endpoints been presented, and their relationship to long-term OS demonstrated? |
| **Model structure and survival extrapolation methodology** | |
| Use of non-standard model structure to capture immunotherapy effect | • Has the use of non-standard models been justified, including their use in previous IO economic evaluations? |
| Capturing heterogeneity in treatment effect and outcomes | • Has heterogeneity in treatment effect been explored and were any subgroup analyses based on mechanism of action and clinical plausibility? |
| Availability and use of early response biomarkers to predict long-term survival | • Have any biomarker data been presented as the predicate for considering heterogeneity? |
| Shape of the survival curve/plateau and smoothing estimators of the hazard function | • Has the survival analysis/statistical modeling been presented and justified both in terms of statistical performance and how it reflects the underlying biological model? |
| Clinical plausibility and validation of the survival extrapolation using real-world evidence or other data | • Have real-world data been included to support estimates of long-term OS? |
| **HTA submission** | |
| Linking central points with payer, clinician, and patient perspectives on immunotherapy | |

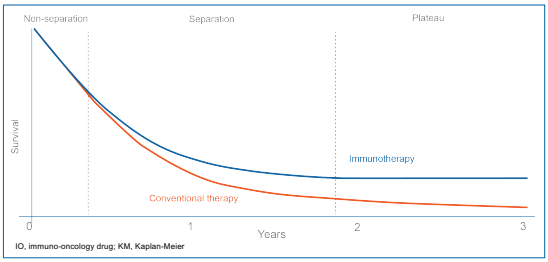
DFS, disease-free survival; HTA, health-technology assessment; IO, immuno-oncology drug; OS, overall survival; PFS, progression-free survival; TFI, treatment-free interval.

## Results (continued)

### Mechanism of action

- The underlying mechanism of action of IOs and resulting tumor response kinetics underpin the challenges in demonstrating the potential long-term OS benefit of these drugs.
- Response patterns can differ significantly from traditional anticancer drugs and can roughly be divided into three stages (Figure 3):
  - non-separation of Kaplan-Meier (KM) survival curves for IO and standard chemotherapy during the initial months of treatment
  - separation of the KM curves as the IO mechanism of action leads to a clinically measurable effect
  - plateauing or flattening of the tail of the IO KM curve many months after the first administration and continuing long after treatment has ceased.[1,2]

**Figure 3. Typical KM survival curve observed with IOs**




IO, immuno-oncology drug; KM, Kaplan-Meier

- Some patients may be 'statistically cured', meaning their expected mortality is comparable to that of the general population matched for age and sex.
- Durable responses to IOs cannot currently be predicted with accuracy at the initiation of treatment although numerous biomarkers have been investigated, including programmed death-ligand (PD-L1),[1] tumor mutational burden,[3,4] gene expression profiling of the tumor microenvironment,[5] microsatellite instability in tumors,[6] microbiome status,[7] analysis of immune system and cancer interactions,[8] and a holistic 'immune scoring' approach.[9]

### Estimating long-term outcomes

- In common with chemotherapy, long-term OS benefit for IOs is currently estimated for HTA submission from available trial and external data.
- Several studies have explored the methods of survival analysis and extrapolation within the context of IOs and questioned their performance.[10,11]
- Innovative modeling techniques are needed to handle data immaturity and the response patterns of IOs.

### Within-trial analysis of survival

- Standard median survival and hazard ratios that are commonly used to assess survival in HTAs may fail to capture the magnitude of survival benefit for IOs, as shown in Figure 3.[12,13]
- Alternative metrics, such as landmark survival analysis[14] and restricted mean survival time,[15] may better capture the long-term benefit of IOs.

### Estimating long-term OS by extrapolating from clinical trial data

- Standard methods of survival extrapolation, such as parametric modeling, are better suited to conventional chemotherapy.[12]
- The mechanism of action for IOs exacerbates multiple methodological challenges: assessing non-proportional hazards, the plateau effect, loss of statistical power in the tail of the survival curves, and unobserved heterogeneity in the patient population that morphs over time.
- More flexible approaches are needed to capture the characteristic IO pattern of delayed treatment effects and, for a subset of patients, the plateau of long-term OS. These include piecewise models, cubic splines, response-based models, cure fraction modeling, and mixture cure modeling.

### Data limitations at the time of HTA submission

- Given the challenges in accurately estimating the long-term OS for IOs, supplemental evidence have been put forth, including surrogate endpoints and real-world evidence.
- Despite some surrogate endpoints being accepted by regulators, there is conflicting evidence on their reliability in predicting meaningful survival benefit for IOs.[16,17]
- Real-world evidence has two potential applications: to provide data that will help generalize the clinical trial to real-world clinical practice,[18,19] and to validate externally both the clinical trial data and any predictive modeling of long-term OS.[20]
- Real-world evidence is still considered to be of lower quality and less reliable than data from randomized controlled trials.[21]

## Conclusions

- Despite almost a decade of use, manufacturers face multiple challenges in demonstrating the long-term OS benefit with IOs at HTA submission.
- Many of these challenges are well known and have been discussed in published literature, but currently remain largely unresolved.
- We have recommended steps that manufacturers should take in order to develop and submit evidence to HTA agencies in a structured and consistent way, and to lead wider education across all stakeholders – manufacturers, payers, and clinicians – in considering the long-term OS benefit with IOs.
- Manufacturers should continue to analyze survival data using methods that are appropriate to the IO mechanism of action and continue to communicate its impact on long-term response, survival benefit, and methods of analysis.
- Manufacturers should use biomarkers, surrogate endpoints, and real-world evidence in economic and predictive modeling when available.
- HTA agencies should recommend modeling approaches for IOs and improve communication with manufacturers prior to submission, to align on appropriate methods of analysis.

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## Declarations

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