# Modeling the Path to Cure: How (Neo)adjuvant Drug Therapies Are Evaluated in Health Technology Assessment (HTA)

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## Background and Objectives

- There is a growing interest in (neo)adjuvant drug therapies for solid tumors that have shown substantial clinical benefit. However, challenges arise in evaluating these treatments' cost-effectiveness due to the reliance on assumptions and estimates of cure and long-term survival[1]
- Response to immunotherapy (IO) treatment in (neo)adjuvant settings has shown an increase in the proportion of patients who achieve long-term survival, in comparison with conventional therapies[2]
- This highlights the need to understand how to determine when a patient who achieves long-term survival following treatment in (neo)adjuvant settings can be considered cured. The term "cure" is important in health technology assessments (HTA), as payers assess the value of a therapy over a lifetime, while trial data have limited follow-up to assess clinical outcomes, often a few years
- The aim of this study is to compare approaches among HTA agencies concerning estimating cure and incorporating assumptions into cost-effectiveness models

## Methodology

- A targeted review of HTAs dated from 2018 to 2023 was carried out, focusing on markets in Australia, Canada, France, Germany, Ireland, and the UK (**Table 1**)
  - While Germany was involved in the HTA review, G-BA submissions were excluded from this poster, as they were not relevant to its purpose
- The review focused on reports published in the adjuvant and neoadjuvant settings in lung cancer, melanoma, and breast cancer
- The selected HTA reports were further categorized into 3 different categories:
  - HTA reports that do not mention "cure"
  - HTA reports where "cure" is mentioned a few times (≤3 times)
  - HTA reports where "cure" is mentioned several times (>3 times)
- Alternative scenarios were developed to group the identified indications together, with the respective reports following specific rules that are based on EMA authorization dates and the frequency of "cure" mentioned in the reports
- One scenario was selected for the final selection of 28 reports. The indications that include HTA reports that mention "cure" were prioritized
- However, reports where "cure" was not mentioned were also included in the HTA review if the indication was being selected to understand the differences between HTA bodies' views on "cure" within the same products' respective assessments (**Table 2**)
- The final selection included a total of 4 treatments across specific indications: atezolizumab for non-small cell lung cancer, dabrafenib combined with trametinib for melanoma, and olaparib and pembrolizumab for breast cancer

**Table 1. Targeted review on HTA assessments – search strategy**

| # | Criteria |
|---|---|
| 1 | The HTAs of the proposed scope countries focused on and identify lung cancer, melanoma, breast cancer. The identification was based on EMA approval for drugs in adjuvant, neoadjuvant, and peri-adjuvant settings in the selected cancers. HTA websites will be searched for those specific drug assessments. |
| 2 | The HTA reports referring to the adjuvant, neoadjuvant, and peri-adjuvant settings only will be selected. |
| 3 | The selected HTA reports will be further categorized into 3 different categories:<br>HTA reports that do not mention "cure"<br>HTA reports where "cure" is mentioned a few times (≤3 times)<br>HTA reports where "cure" is mentioned several times (>3 times)<br>For HAS in France, which publishes HTA reports in French, the words "guerison" and "guer*" will be looked for in the French version when the English version is not available. |
| 4 | Scenarios were developed to group the identified indications together, with the respective reports following specific rules that are based on EMA authorization dates and the frequency of "cure" mentioned in the reports.<br>A final selection of one scenario to be included in the HTA review was made, which included at least 20 HTA reports from selected indications. |

**Table 2. HTA data extraction form/grid**

| Section | Data item |
|---|---|
| Publication information | HTA agency and submission number<br>Year<br>Title<br>Reimbursement decision (Y/N)<br>Link |
| Disease and drug information | Indication full (EMA, MHRA, Health Canada, TGA)<br>Drug (generic and brand names) |
| Intervention | Setting of treatment (eg, neoadjuvant, adjuvant) |
| Population/ indication | Disease/indication<br>Mean age (SD)<br>Performance status<br>Histology<br>Staging |
| Trial outcomes | Patient-relevant trial outcomes (eg, EFS, DFS, RFS, OS)<br>Duration of follow-up (median, maximum)<br>HTA commentary on survival endpoints linked to the concept of cure |
| Economic model structure | Model type<br>Model figure/approach<br>Time horizon<br>Extrapolation approaches for long-term outcomes |
| Cure assumptions in economic model | Timing of cure[a] and cure fraction (if relevant)<br>Assumptions around waning of treatment effect<br>Modeling efficacy/utility/cost beyond cure point (including approach to modeling [eg, MCM, NMCM] and use of additional health states)<br>Company's rationale and evidence for using the "cure" approach<br>Validation and generalizability of cure assumptions |
| HTA response | HTA and clinical experts' feedback on cure assumptions:<br>• Level of acceptance of cure assumptions (accepted/criticized)[a]<br>• Cure time point[a]<br>• Estimating "cure" proportions<br>• Mortality/recurrence beyond cure point (critique on chosen survival endpoints)<br>• Acceptance of survival extrapolation critiques<br>• HTA commentary on external sources used |

**Abbreviations:** DFS, disease-free survival; EFS, event-free survival; EMA, European Medicines Agency; MCM, mixture cure model; MHRA, Medicines and Healthcare products Regulatory Agency; NMCM, non-mixture cure model; N, No; OS, overall survival; RFS, recurrence-free survival; SD, standard deviation; Therapeutic Goods Administration; Y, Yes.
[a]Note: May include information on other endpoints, such as recurrence, used as a concept of cure.

## Results

Twenty-four HTAs were reviewed, with the majority resulting in a positive recommendation.[3-27]

**Table 3. HTA recommendation per indication across agencies[a]**

| Drug (Indication) | PBAC | CDA | HAS | NCPE | NICE | SMC | Recommendation |
|---|---|---|---|---|---|---|---|
| Atezolizumab (adjuvant) | Jul-22[3] | Sept-22[4] | Jan-23[5] | Jul-23[6] | Sept-22[7] | Aug-22[8] | Recommended |
| Dabrafenib + trametinib (adjuvant) | Mar-19[9], Jul-19[10] | May-19[11] | Jun-19[12] | Aug-20[13] | Oct-18[14] | Feb-19[15] | Recommended with restrictions |
| Olaparib (adjuvant) | Nov-23[16] | Mar-23[17] | Feb-23[18] | Ongoing[19] | May-23[20] | Oct-23[21] | Not recommended |
| Pembrolizumab (neoadjuvant and adjuvant) | Mar-23[22] | Sept-22[23] | Dec-22[24] | Dec-23[25] | Nov-22[26] | Jun-23[27] | Ongoing |

[a]Research conducted in April 2024.
**Abbreviations:** CDA, Canadian Drug Agency; HAS, Haute Autorité de Santé (French National Authority for Health); NCPE, National Centre for Pharmacoeconomics; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium.

- Survival estimates used in economic models were generally based on piecewise models built from observed trial data linked to parametric distributions applied to observed trial data incorporating cure modeling or in-built cure assumptions. Dabrafenib plus trametinib submissions were the only ones including manufacturer cure models.

**Table 4. Cases where HTA agencies questioned the cure assumptions of the submitted model**

| Indication | Cure models | HTA critiques |
|---|---|---|
| Atezolizumab[3-8] | All models were Markov, with some variations in the number of health states.<br>Piecewise survival curves were the basis of all manufacturer models, with extrapolations adjusted for assumption of "cure" at a fixed time point. | PBAC: While the manufacturer's rationale for the adjustment for sustained DFS appeared reasonable, the time point when the patients achieved sustained DFS and the magnitude of the change in the proportion of patients with sustained DFS over time were not well justified by the submission.[3] |
| Dabrafenib + trametinib[9-15] | The majority of models were Markov, with similar 3-5 health states (depending on how granularity post-recurrence was described) using RFS data.<br>Different approaches to survival modeling, mostly reliant on mixture cure models (CDA, HAS, NICE, and NCPE explicitly specified that submitted models were cure models). | PBAC, CDA, and NCPE did not accept cure assumption due to OS data immaturity and considered delaying recurrence as more plausible.[9,11,14] |
| Olaparib[16-21] | All semi-Markov models with the same set of health states.<br>Piecewise survival curves were the basis of all manufacturer models, with extrapolations adjusted for assumption of "cure" at a fixed time point. | PBAC: Questioned the cure assumption: Delayed recurrence more plausible than assumption of cure.[16] |
| Pembrolizumab[22-27] | All Markov models with the same set of health states.<br>Observed EFS data combined with long-term extrapolation of EFS using independent parametric functions (supported by lack of PH). | No agency questioned the cure assumption. |

**Abbreviations:** CDA, Canadian Drug Agency; DFS, disease-free survival; EFS, event-free survival; HAS, Haute Autorité de Santé (French National Authority for Health); NCPE, National Centre for Pharmacoeconomics; NICE, National Institute for Health and Care Excellence; OS, overall survival; PH, public health; RFS, recurrence-free survival.

- Agencies were generally open to the idea of cure at a conceptual level but had questions around how assumptions were made and implemented in models. The HTA commentary on cure assumptions across the four indications reveals varying levels of scrutiny, with a shared focus on ensuring that cure assumptions were well justified by clinical evidence and expert opinion across different indications.

**Table 5. Cases where HTA agencies questioned the cure assumptions of the submitted model**

| Themes | Common considerations |
|---|---|
| Immature OS data | None of the submissions reported mature OS data (ie, where median OS was established). While no agency questioned the choice of primary endpoint in the trial, all agencies – except for the SMC – expressed concerns about relying on assumptions and estimates of cure and long-term survival due to immature OS data.[3-27] |
| Proportional hazard assumptions | PBAC, CDA, HAS, and NICE expressed uncertainty about proportional hazards assumptions, noting treatment effect variation over time, particularly in the dabrafenib submission.[9,11,12,14] |
| Selection of parametric forms and trial subgroup differences | HTA agencies scrutinized the selection of the parametric approaches for survival endpoint extrapolation.<br>• In the NICE atezolizumab submission, the model was revised from independent log-logistic curves to log-normal extrapolation with cure adjustments[7]<br>• In the HAS pembrolizumab submission, fractional polynomial method should have been favored[24]<br>In the olaparib submissions, concerns arose about trial subgroup differences by PBAC, CDA, HAS, and NICE (ie, related to breast cancer subtypes) affecting parametric form choices and cure time point assumptions, which were anticipated to differ across groups (ie, TNBC and HR+/HER2-).[16-18,20] |
| Expert opinion and RWE | Assumptions based on external sources were often challenged by the agencies due to the nature of the data.<br>• In the atezolizumab and olaparib submissions, PBAC did not accept RWE, as the sources were not considered relevant to clinical practice.[3,16] This was also expressed by NICE in the atezolizumab submission[7]<br>Local expert clinicians informed many of the differences between agencies, leading to model adaptations or modifications of cure assumptions or model structures.<br>• In the olaparib submission, HAS/NICE accepted clinical experts' opinion for an amendment in the risk of recurrence[18,20]<br>• In the dabrafenib and pembrolizumab submissions, NICE accepted clinical experts' opinion to validate clinical plausibility of selected curves and EFS extrapolation, respectively[14,26] |

**Abbreviations:** CDA, Canadian Drug Agency; EFS, event-free survival; HAS, Haute Autorité de Santé (French National Authority for Health); HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; RWE, real-world evidence; SMC, Scottish Medicines Consortium; TNBC, triple-negative breast cancer.

### Recommendations for overcoming the market access challenges associated with modeling the path to cure

- The primary (non-OS) endpoint will need to be formally validated as a surrogate/patient-relevant endpoint to support the assumption of lifelong treatment benefit/cure
- Time-varying treatment effects should be explored in parallel with proportional hazard testing. Any assumptions of proportional hazards, if assumed, need to be justified clinically and statistically
- The optimal strategy for modeling would be to choose a flexible approach (eg, piecewise modeling with in-built cure assumptions), to allow for accurate representation of time-varying hazards and treatment effects. If a cure model is to be submitted, it will be subject to extensive scrutiny around the functional form and assumptions required
- Parametric approaches to survival extrapolation should be selected based on goodness-of-fit statistics and graphical inspection as well as clinical plausibility (aligned with the NICE Decision Support Unit (DSU) algorithm). Validation from clinical experts may be required, especially when the selected approach differs from the guidance in the NICE DSU algorithm
- External evidence will need to be robust, reflecting local clinical practice and the proposed indication (eg, geographic scope, disease stage)

## Conclusions

- A variety of cure modeling approaches have been employed, with mixed receptivity. Thoughtful, integrated approaches across agencies would be beneficial to address key challenges such as variability in time point and cure assumptions within subgroups

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