A conceptual framework for the approach to the evaluation of oncology survival benefit in health technology assessment

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Introduction

Health technology assessment (HTA) methods for evaluating oncology survival benefit were introduced when the predominant drug treatments were cytotoxic regimens for advanced disease, delivering moderate survival benefit in most indications. The development of immunotherapies and the increased use of both cytotoxic and immunotherapy treatments as adjuvant therapy have presented new challenges for HTA agencies, with much greater diversity in overall survival profiles. HTA methods have evolved and a complex range of metrics and tools are applied to evaluate oncology survival benefit, depending on the specific challenges presented by each technology.

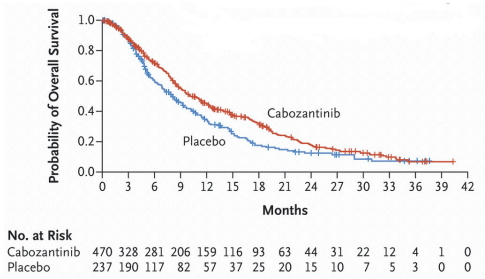
We propose a conceptual framework to categorize therapies in a way that conforms to the key challenges for evaluating survival benefit from pivotal clinical trials and identifies the most relevant metrics and methods to be applied. The framework accommodates both clinical benefit and cost-effectiveness perspectives in HTA.

We propose using durable response rates to categorize therapies as follows:

- Palliative: 0 to 10% durable response
- Mixed: 10% to 50% durable response
- Curative: >50% durable response

Palliative therapies

Figure 1: Palliative - Cabozantinib in hepatocellular carcinoma



Abou-Alfa et al.[1]

Palliative therapies provide moderate survival gains across the treated population, without the prospect of durable response for a significant proportion of patients. Palliative therapies become relevant after curative options have failed or when they are not feasible due to diagnosis at an advanced stage. Palliative therapies may be introduced last line or earlier.

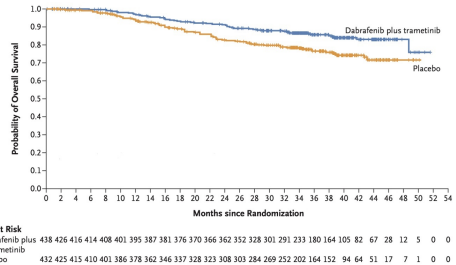
Median survival and hazard ratio (HR) are appropriate metrics for decision-making in comparative effectiveness HTA, while proportional hazards (PH) methods are usually appropriate for estimating mean overall survival (OS) for cost-effectiveness HTA. OS data are usually sufficiently mature for decision-making, particularly when PH is considered a reasonable assumption.

Assessment of health-related quality of life (HRQL) focuses on the period of treatment or progression-free survival (PFS) to understand any detriment to HRQL or utility from toxicities that needs to be balanced against the benefit of potentially prolonged survival.

A frequent problem in evaluating survival benefit from pivotal trials is potential confounding from crossover. In these circumstances, assessment may need to rely on PFS or statistical adjustment of OS for crossover. Subsequent therapy confounding and OS maturity may also be an issue in indications where survival prognosis remains long at the advanced stage.

Curative therapies

Figure 2: Curative - Adjuvant dabrafenib plus trametinib in melanoma



Long et al.[2]

Curative therapies can produce transformative outcomes and do so for most patients. Curative drug therapies include adjuvant therapies in solid tumors, some highly efficacious therapies in hematological indications (e.g. imatinib in chronic myeloid leukemia) and immunotherapies that deliver especially high rates of response.

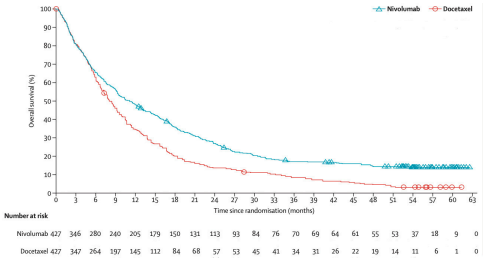
Because of the high efficacy of treatments, OS data will be insufficiently mature and surrogate endpoints are required to assess survival benefit. Landmark analysis of PFS, event-free survival (EFS) or disease-free survival (DFS) endpoints may be used but will still require clinical trials with very long follow-up. Consequently, regulatory approval may be sought based on response endpoints, such as complete response (CR), minimal residual disease (MRD), molecular CR (mCR), pathological CR (pCR), etc.

Surrogate endpoint validation becomes a key step for clinical benefit assessment in HTA. Validation should demonstrate that an improvement in the (observed) surrogate outcome is a sufficiently reliable predictor of improvement in (unobserved) OS. This may include assessment of clinical and biological plausibility, strength of association and the transferability of the evidence to the specific indication and population in the HTA[3,4]. Cost-effectiveness HTA involves additional complexity, with surrogate modelling needed to estimate mean OS from surrogate endpoint data. This requires not only validation of surrogacy, but also quantification of the relationship within acceptable bounds of uncertainty.

Quality of long-term survival becomes an important consideration for curative therapies, with a focus on understanding potential long-term adverse events and the extent of the recovery of patient general health and functioning following aggressive cancer therapies.

Mixed therapies

Figure 3: Mixed - Nivolumab in non-small-cell lung cancer



Antonia et al.[5]

Mixed therapies can provide transformative benefit but do so for a minority of patients, with the majority receiving either moderate or no survival benefit. Mixed therapies include immunotherapies in solid tumor indications, CAR-T therapies and cytotoxic therapies used as a bridge to curative stem-cell therapy in hematological indications.

The presence of non-PH makes HR and median difference in OS inappropriate for quantifying survival benefit across the patient population[6]. Landmark survival and restricted mean survival time may be used instead, but potentially the most important metric of value is cure fraction. In the absence of mature OS, analysis of response, PFS or proportions of patients progressing to curative therapy may be used to inform estimates of the likely cure fraction.

Estimating mean survival for cost-effectiveness HTA becomes particularly complex. More flexible models are required to capture the survival distribution of patients both with and without durable response. For therapies where the cure fraction is assumed to be relatively low, accelerated failure time models may be sufficient, or piecewise extrapolation may be used. Flexible parametric models, mixture-cure models, or response-based landmark models may be necessary where the cure fraction is larger[7,8].

Assessment of HRQL becomes most complex, requiring both short- and long-term evaluation, reflecting the different prognosis for survival and risk-benefit balance for patients with and without durable response.

Summary

Table 1: Conceptual framework

	Palliative 0% to 10% DR	Mixed 10% to 50% DR	Curative > 50% DR
Endpoint	OS PFS (when crossover)	OS PFS/EFS, CR	CR, mCR, MRD, etc. PFS/EFS/DFS
Comparative effectiveness	HR, median difference	Landmark survival, RMST, cure fraction	Response rates Landmark survival
Mean survival modeling	Conventional parametric curve fitting	Piecewise modeling Mixture-cure models Response models	Surrogate modeling
Distributions	PH distributions	AFT distributions Cubic splines	Variable
Toxicity & HRQL	Short-term AEs HRQL on treatment	Short-term and long-term AEs	Long-term AEs
Challenges	Crossover	Immature data Identifying cure fraction	Surrogate validation Surrogate valuation

Abbreviations: AE = adverse event; AFT = accelerated failure time; CR = complete response; DFS = disease-free survival; DR = durable response; EFS = event-free survival; HR = hazard ratio; HRQL = health-related quality of life; mCR = molecular complete response; MRD = minimal residual disease; OS = overall survival; PFS = progression-free survival; PH = proportional hazards; RMST = restricted mean survival time

Recommendations

This conceptual framework can help HTA agencies and developers to focus on the most appropriate metrics and methods and target the most important issues in the assessment of oncology therapies. HTA methodologists may wish to consider the framework to guide the development of new tools and methods, focused on mixed and curative therapies in particular. We recommend further development of the framework, including the criteria and method for categorizing therapies based on pivotal trial data, to help maintain quality and consistency in HTA decision-making in an increasingly diverse and complex oncology treatment landscape.

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