Challenges associated with surrogate endpoints for healthcare decision-making in oncology

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Background and objectives

- The emergence of advanced technologies necessitates faster market access to enable treatment of serious conditions in disease areas with high unmet medical needs, such as in oncology.
- Increasing drug development costs and intense competition have increased the pressure on manufacturers to bring products to market more quickly.
- The use of surrogate primary endpoints is often essential to enable earlier regulatory approval; as a result, health technology assessment (HTA) agencies often have to base their decisions on smaller samples, shorter follow-up, and higher uncertainty in the clinical evidence.[1-3]
- No recent studies have analyzed how surrogate endpoints in oncology affect product development. This research aims to identify challenges from a payer perspective and provide recommendations for optimal HTA submissions.

Methods

- We conducted a targeted literature review to identify HTA guidance on surrogate endpoints and their impact on patient access.
- We compared opinions across HTA agencies in England (National Institute for Health and Care Excellence, NICE), France (French National Authority for Health [Haute Autorité de santé], HAS), Germany (Federal Joint Committee [Gemeinsamer Bundesausschuss], G-BA), Australia (Pharmaceutical Benefits Advisory Committee, PBAC), and Canada (Canadian Agency for Drugs and Technologies in Health, CADTH) on the use of progression-free survival (PFS) and invasive disease-free survival (iDFS) in breast cancer (BC).

Results

Surrogate endpoints in HTA decision-making

- Payers, clinicians, and patients assign varying importance to non-OS benefits, necessitating diverse evidence.
- Payers emphasize efficient resource allocation and reducing uncertainty, placing greater weight on long-term outcomes than regulators.
- In oncology, commonly used endpoints (eg, PFS) and emerging surrogate markers (eg, iDFS) are prevalent, with differences in accuracy, credibility, and costs, requiring thorough consideration in HTA.
- Surrogate endpoints facilitate quicker drug market entry but require a valid clinical relationship to patient-relevant outcomes to ensure surrogate outcomes are predictive of the true outcome and reduce uncertainty in payer decisions.

Key challenges associated with surrogate endpoints from a payer's perspective

- Demonstrating the correlation between the surrogate and the patient-relevant endpoint does not guarantee the surrogacy association.
- Validation also depends on the clinical, epidemiological, and biological plausibility, as well as the association between treatment effects on early and late outcomes.
- Both PFS and iDFS are intermediate endpoints, and not classical surrogate endpoints, despite being used as surrogate endpoints in oncology. Therefore, while PFS/iDFS provides an indication of disease control and stabilization, the relationship between PFS/iDFS and OS is not always validated.
- The validity of surrogate endpoints may vary across patient groups, diseases, and drug classes, especially in precision medicine.
- Tumor subtypes, gene expression patterns, and treatment mechanisms can all affect the relationship between surrogate and patient-relevant endpoints.[4]
- The emergence of diverse drug classes makes it harder to measure the surrogate effect on patient outcomes, as the attributes of the treatment may result in a different pathway between the surrogate and the patient-relevant endpoint.
- Emerging biomarkers, such as circulating tumor DNA, can influence surrogate endpoints in trials, especially when introducing a new biomarker. Understanding whether the biomarker is prognostic or merely predictive of treatment effects is crucial for assessing its impact.
- Other issues such as censoring rules, different definitions of disease progression, switching treatments, and post-progression treatments can influence the credibility and acceptance of surrogate endpoints in HTA.[5,6]

Considering all the above, surrogacy needs to be validated for each treatment/class, setting, and patient group of interest.[7]

Payers' perspectives on the use of PFS/iDFS as surrogate endpoints

- Olaparib, abemaciclib, and talazoparib were identified as examples of oncology treatments for which HTA submissions included PFS/iDFS data as surrogate endpoints.
- The magnitude of PFS/iDFS gains and the associated uncertainty, particularly in predicting final OS outcomes, were considered by all stakeholders, but decision-making processes varied.
- The acceptance of iDFS/PFS as surrogate endpoints varied across countries. For example, the G-BA typically does not accept them and requires data on OS, health-related quality of life, and safety.
- Acceptance of iDFS and PFS appears to be influenced by the stage of the disease: iDFS for early stages and PFS for advanced/metastatic disease.

Recommendations for overcoming the market access challenges associated with surrogate endpoints

Surrogate endpoints and trial design optimization

- Manufacturers should carefully weigh up the trade-offs between trials designed to achieve earliest regulatory approval and designs aimed at providing robust evidence for payer decision-making.
- Where feasible, OS should be used as a co-primary or key secondary endpoint; trial endpoints that have been accepted by payers should be used in preference.

Evidence that supports the relationship between the surrogate endpoint and the outcome

- Validation of surrogate endpoints, traditionally reliant on randomized controlled trials (RCTs), faces challenges with the emergence of precision medicine.[4, 24]
- Manufacturers need to consider treatment-specific biological mechanims and biomarker prevalence.
- Payers' willingness to accept surrogate endpoints depends on the market and decision context; for example, flexibility in evidence requirements may be more likely in areas with high unmet medical needs, provided treatment costs are reasonable.

Evidence generation that is aligned with payers' expectations

- Given the lack of trial evidence supporting the relationships between surrogate and final endpoints, manufacturers need to generate the required level of evidence to reduce the uncertainty in the use of surrogate endpoints.
- A robust evidence generation strategy should consider how to demonstrate a novel surrogate endpoint's prognostic value for long-term clinical outcomes at the early stages of trial design.
- The use of real-world evidence (RWE) in addition to RCT data can enhance the validation of surrogate endpoints.[25, 26]
- Developing endpoint strategies and registry data specifically deisgned to capture the link between surrogate and long-term endpoint could provide evidence to support the surrogacy relationship.

Table 1: Key oncology treatments granted HTA approval with iDFS/PFS as the primary endpoints

Treatment/ indication	NICE (England)	HAS (France)	G-BA (Germany)	PBAC (Australia)	CADTH (Canada)
iDFS					
Olaparib High-risk early BC with gBRCAm, HER2- previously treated with neoadjuvant/ adjuvant chemotherapy	**HTA decision**				
	Recommended as per marketing authorization (May 2023[8]).	Early access authorization (March 2022[9]). Recommended as per marketing authorization, except in patients receiving pembrolizumab. SMR: substantial, ASMR: III (January 2023[10]).	Recommended as per marketing authorization. Hint of minor additional benefit (February 2023[11]).	Not recommended (March 2023[12]).	Recommended with conditions (March 2023)[13].
	Impact of surrogate endpoint on HTA decision				
	Final decision based on statistically significant improvement in both iDFS and OS.	Granted ASMR rating based on statistically significant improvements in both iDFS and OS.	iDFS not considered a suitable surrogate for decision-making. Mortality assessed solely based on OS.	iDFS not considered a suitable surrogate for decision-making.	Final decision based on statistically significant improvement in both iDFS and OS
Abemaciclib in combination with endocrine therapy Early BC at high-risk of recurrence (HR+, HER2- node+) as adjuvant treatment	**HTA decision**				
	Recommended as per marketing authorization (July 2022[14]).	Not recommended (September 2022[15]).	Recommended as per marketing authorization. Premenopausal women: hint of minor additional benefit. Postmenopausal women: additional benefit not proven (November 2022[16]).	Not recommended (March 2022[17]).	Recommended with conditions: (October 2022[18]).
	Impact of surrogate endpoint on HTA decision				
	iDFS considered a suitable surrogate for decision-making, but not a predictor of OS benefit.	iDFS not considered a suitable surrogate for decision-making at the current state of knowledge.	iDFS not considered a suitable surrogate for decision-making. Mortality assessed solely based on the OS.	Use of iDFS as a surrogate for OS was considered generally plausible. However, relationship between iDFS and OS was considered uncertain.	iDFS considered a suitable surrogate for decision-making, but not a predictor of OS benefit.
PFS					
Talazoparib Locally advanced or metastatic BC with gBRCAm, HER2- as monotherapy after previous therapy with an anthracycline and/ or a taxane in the (neo)adjuvant or metastatic setting, or unsuitable for these treatments	**HTA decision**				
	(Draft guidance). Not recommended (ID1342[19]).	Recommended as per marketing authorization. SMR: substantial, ASMR: V (December 2019[20]).	Recommended as per marketing authorization. Hint of considerable added benefit. Patients with HR+BC should have received prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy (November 2020[21]).	Not recommended (November 2019[22]).	Unable to recommend reimbursement as a submission was not filed by the manufacturer (January 2021[23]).
	Impact of surrogate endpoint on HTA decision				
	Treatment with talazoparib improved PFS. Problematic interpretation of OS results was among the key issues arising from technical engagement.	Modest improvement in PFS and absence of OS data were taken into account.	PFS not considered a suitable surrogate for decision-making. Mortality assessed solely based on OS.	Talazoparib provided a moderate improvement in PFS. Unclear given immature OS data whether talazoparib would provide any gain in OS.	NA

Recommended | Recommended with restrictions | Not recommended | Not assessed

ASMR, clinical added value (amélioration du service médical rendu); gBRCAm, germline BRCA1 and/or BRCA2 mutation; HER2-, human epidermal growth factor receptor-2 negative; HR+, hormone receptor positive; HRQL, health-related quality of life; ITC, indirect treatment comparison; SMR, clinical benefit (service médical rendu)

Conclusions

- To reduce uncertainty in HTA submissions, a comprehensive surrogate endpoint strategy is vital in the fast-paced word of drug development.
- Innovative evidence generation strategies to support the acceptability of surrogate endpoints, including RWE, should be explored.
- Effective strategies require early engagement with stakeholders such as key opinion leaders and patient groups to gain acceptance of surrogate endpoints and supporting methods. This engagement could include discussions with regulators and HTA agencies.
- Cross-functional collaboration is essential for succesful market access when incorporating surrogate endpoints.

References

1. Weir IR *et al*. (2022) Pharmaceutical Statistics, 21(1), 163-175.
2. Grigore B *et al*. (2020) Pharmacoeconomics, 38(10), 1055-1070.
3. Ciani O *et al*. (2017) Value in Health, 20(3), 487-495.
4. Burstein HJ (2022) The Breast, 62, S67-S69.
5. Papanikos T *et al*. (2020) Statistics in Medicine, 39(8), 1103-1124.
6. Beauchemin C *et al*. (2014) OncoTargets and Therapy, 1101-1110.
7. Lux MP *et al*. (2021) Cancer Management and Research, 8457-8471.
8. NICE (2023) Olaparib.
9. HAS (2022) Olaparib.
10. HAS (2023) Olaparib.
11. G-BA (2023) Olaparib.
12. PBAC (2023) Olaparib.
13. CADTH (2023) Olaparib.

Further references available on request