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Research Article

Beyond Overall Survival: The Value of Oncology-Relevant Endpoints in HTA Body / Payer Decision-Making

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Abstract

Introduction: HTA bodies/payers have focused on overall survival (OS) to evaluate oncology medicine's efficacy during decision-making. While OS remains important, reliance on it poses three challenges: potential delayed patient access to medicines due to extended time to measure OS in some indications and settings, poor ability to capture impact on quality of survival, and vulnerability to confounding. Better value recognition of oncology-relevant endpoints (OREs), which includes all endpoints used in oncology clinical trials, including patient-reported outcomes, may address these challenges. This work explores the value of OREs and their role in HTA body/payer decision-making.

Methods: This work is based on a literature review, interviews and three roundtables with 13 stakeholder group representatives (physicians, patient, former HTA bodies/payers) in US and Europe.

Results: OREs beyond OS can be standalone efficacy measures through capturing outcomes beyond survival that are important to patients and clinicians. They can also act as surrogates by providing earlier measure of a medicine's efficacy and are less influenced by confounding than OS. Value recognition of OREs beyond OS varies across stakeholders and should be considered per cancer type and stage.

Conclusions: Clinicians, patients and regulators recognize the value of OREs beyond OS but HTA bodies/payers can be skeptical, driven by concerns about how ORE value translates to meaningful outcomes for patients and healthcare systems. Stakeholders should build a portfolio of fit-for-purpose OREs by cancer type and stage based on shared understanding of their value to improve their acceptance in decision-making and advance patient access to novel therapies.

Keywords: Oncology-relevant endpoints; HTA body; Payer; Decision-making; Value

Introduction

Uncertainty is a key driver of why different decisions are taken in different settings and contexts. In the context of pricing and reimbursement decisions of therapies, uncertainty stems from many factors including which outcomes are most important, how they are selected and by whom [1-3]. In the area of oncology, overall survival (OS) is a reliable measure of therapeutic efficacy as it quantifies the direct clinical benefit of a medicine through extended patient survival [4]. Its objectivity and suitability for comparing treatment regimens make it the preferred clinical efficacy measure in regulatory and Health Technology Assessment (HTA) body / payer decision-making. However, reliance on OS in regulatory and HTA body / payer decision-making for novel cancer medicines presents three key limitations. Firstly, while extending OS is important, OS data does not show how a treatment affects survival quality. On the one side, advances in scientific understanding on physiopathology and more sophisticated oncology medicines have improved outcomes and prognoses for patients. On the other side, studies show that patients value outcomes beyond survival as much as OS [1,2]. Secondly, in cancers with improved prognoses or treated at an early stage, time to measure mature OS data can now reach over a decade [1,2,5]. Despite this, HTA bodies / payers continue to state a preference for mature OS data, in some cases denying, delaying, or restricting reimbursement for patients in its absence [1,2]. Thirdly, the vulnerability of OS to confounding (i.e., the distortion of outcomes caused by factors not related to the medicine being investigated, or by switching between the control and investigation arm in the clinical trial) means that OS benefits may in some cases go undetected, particularly for treatments used in early disease. Together, these challenges limit HTA bodies' / payers' ability to accurately evaluate new treatments and potentially deny patients' access to potentially effective medicines. Oncology-relevant endpoints (OREs), which refer to OS and all endpoints used in oncology clinical trials to measure outcomes beyond survival, including patient-reported outcomes, (e.g. progression-free survival (PFS), disease-free survival (DFS) and response rate (RR)) may address these challenges. However, use of OREs beyond OS in decision-making can be limited, driven by disparities between medicine assessment criteria used by regulators versus HTA bodies / payers across Europe. This may lead to situations where the therapeutic benefit of potentially innovative therapy is not fully recognized in HTA body / payer decision-making [6].

Methods

This research was based on one-on-one interviews with 13 stakeholders (physicians, patient advocates, and former HTA bodies / payers). Physicians were screened for good technical understanding of oncology endpoints and direct involvement in patient care, patient advocate groups with a focus on oncology were identified, and former HTA body representatives / payers were prioritized to gather perspectives across Europe. Interviewees were asked a series of questions on the following topics: current limitations of OS, value of OREs beyond OS and barriers to greater acceptance and potential stakeholder actions. A structured literature review was conducted by searching on PubMed over 2016 – 2023 using key words, such as "HTA", "payer", "reimbursement", "OS", "non-OS", Patient Reported Outcomes ("PROs"), "oncology", as well as national HTA body / payer websites for the latest guidelines. At three round-table discussions with clinicians, patient advocates, and former HTA bodies / payers, experts discussed the benefits and drawbacks of OS, the value of OREs beyond OS, and ways to improve their value recognition by HTA bodies / payers.

Results

The value of OREs beyond OS

The range of outcomes relevant to multiple stakeholders is broad and there, while OREs are relevant across all oncology treatment indications and settings, their value (i.e., selection and interpretation) may differ between them (e.g., by disease stage or by hematologic versus solid tumor type). Oncology-relevant endpoints can be classified into time-to-event (e.g., progression-free survival), response rate (e.g., overall response rate), and patient-reported (e.g., quality of life measures).

OREs beyond OS have value as they are measures of efficacy in their own right by capturing clinically important outcomes, act as surrogates for OS or other target outcomes, and theoretically are less influenced by confounding than OS, helping to inform the reimbursement and pricing of novel therapies. The value of OREs beyond OS may differ to patients, clinicians and other stakeholders including healthcare systems and carer's depending on the cancer type and stage, reflecting the different values that these stakeholders have and their influence in their perception of value [7]. For example, the value of PRO data might differ between early-stage cancers, where disease may be asymptomatic, and the metastatic stage.

"The natural history of a disease needs to be considered at each stage and this must directly influence the endpoints that are used. For example, in early prostate cancer, patients want to prolong time to metastasis due to the impact of metastatic pain on their Health Related Quality of Life (HRQoL), meaning that medicines that can prolong the time to this event will be highly clinically relevant."

Europa UOMO – Voice of Men with Prostate Cancer, Vice President

OREs beyond OS as surrogates

ORE use as OS surrogates allows earlier assessment of medicine efficacy [8]. This may accelerate regulatory approval and patient access to effective treatments. Faster access to potentially efficacious innovative medicines may reduce disease-/symptom-related healthcare costs and encourage further innovation [9,10]. However, there is a lack of consensus among stakeholders on the evidence requirements for using OREs beyond OS as OS surrogates, and uncertainty about their ability to predict survival [3]. In instances where the endpoint is a poor predictor of survival, patients may be exposed to potential harm with no additional benefit. For example, bevacizumab in combination with paclitaxel for metastatic HER-2 negative breast cancer was approved on the basis of improvement to progression-free survival, but subsequent studies found no benefit in OS and an increased toxicity, and market authorization (MA) was later withdrawn [8,11].

Primary research has suggested general agreement amongst academics, regulators, and payers that the most robust method to determine whether an endpoint will predict survival is to perform a meta-analysis across multiple Randomized Controlled Trials (RCTs) to quantify the correlation between the treatment improvement to the endpoint and improvement to OS [8]. However, there remains a lack of guidance by regulators and payers on what the acceptable threshold of correlation should be, the number of RCTs that must be analyzed, and the required specificity of the analysis to line of therapy, tumour type, and class of drug [8,12,13].

"*Using endpoints such as progression-free survival (PFS) has massive implications as it removes the need to wait for OS. This is an opportunity for medicine developers to accelerate approval and would enable patients to gain access to potentially life-prolonging medicines sooner."*

International Myeloma Foundation, Chief Medical Officer

Lower likelihood of confounding

OREs beyond OS are theoretically less likely to be confounded than OS in well-managed cancers and early lines of therapy [14]. This is because OREs beyond OS such as PFS are typically measured up to a disease-related event within one line of therapy, reducing the impact of subsequent treatments on outcomes of interest [14].

Standalone value of OREs beyond OS

OREs capture important patient-relevant outcomes beyond survival as they are assessing a treatment's ability to improve disease- and symptom-related burden by prolonging time to progression and disease-free periods. This can identify medicines that initially improve patient functioning, HRQoL, and, indirectly, healthcare resource use associated with disease and symptom management [15]. The structured literature review identified a recent systematic review of treatment outcome preferences across 4,374 patients found that HRQoL was most frequently prioritised over OS, demonstrating the standalone value to patients of endpoints that measure outcomes beyond survival [16]. The value of PROs data is already being recognized in reimbursement decisions, as demonstrated by a study in oncology HTA submissions between 2011-2016 in Germany, France and the UK. This study found that improvements in HRQoL led to higher benefit ratings by the G-BA and HAS and supported clinical benefit assigned by SMC and NICE despite a lack of OS data in some cases [17].

"*For patients, OS is important, but it is also important that medicines have been evaluated for their impact on HRQoL and the level of treatment burden associated with them."*

Lung Cancer Europe, President

"A PCa novel endpoint which has standalone value is Androgen Deprivation Therapy-Free Survival (ADTFS) or time to ADT. This captures the Quality of Life (QoL) threat by castration, including the metabolic syndrome, including loss of libido and impotence, fatigue and hot flushes, muscular loss, increased fat deposition, depression, osteoporosis, type II diabetes and cardiovascular morbidity."

European Association of Urology, Chairman

Figure 1: case studies of the value of OREs beyond OS

Case studies were identified by asking roundtable participants to identify examples where the value of oncology-relevant endpoints have been demonstrated in certain cancer types and stages. Findings from the case studies were also supported by evidence from the structured literature review.

Case study example 1: the value of OREs beyond OS in multiple myeloma
Context:
The treatment paradigm for multiple myeloma has changed significantly over the last decade, leading to improved patient prognoses and extending the median time to overall survival (OS) to over a decade for some patient groups [18]. Multiple myeloma patients also typically cycle through multiple lines of therapy, making OS data highly susceptible to confounding [19].
OREs beyond OS with potential for use in HTA body / payer decision-making:
Progression-free survival (PFS), minimal residual disease (MRD)
Detail:
PFS is considered an appropriate surrogate for OS in myeloma patients [20–23]; however, with treatment advances, it can now take 5 years to demonstrate PFS.24 MRD status can detect patient response to a medicine with greater sensitivity than radiological measures of response and holds promise as a surrogate for PFS and OS, enabling faster identification of treatment benefits [25]. However, acceptance by HTA bodies / payers is limited by a lack of standardization in measurement techniques, including inconsistent timing of assessments, different thresholds for MRD negativity and varying degrees of sensitivity in tools.

Case study example 2: the value of OREs beyond OS in breast cancer
Context:
In early breast cancer, the time to demonstrate OS is increasing, and it can now take over a decade to generate median OS data [1].
OREs beyond OS with potential for use in HTA body / payer decision-making:
Disease-free survival (DFS), pathological complete response (pCR), circulating tumour DNA (ctDNA)
Detail:
There is evidence supporting DFS as an early predictor of OS [26–29]. For patients who have undergone first-line neo adjuvant therapies, extending DFS also has standalone value due to the recurrence of disease with the associated symptoms, psychological impact, and need for additional treatment [2,30 29].

Barriers to acceptance of OREs beyond OS

Uncertainties on OREs' surrogacy to OS and their ability to identify outcomes relating to disease- or symptom burden

Uncertainty around the correlation of OREs beyond OS with OS is a key barrier to their use in HTA body / payer decision-making [31]. HTA body / payer methodological guidelines typically express a preference for OS data or limit the use of surrogates to those where there is strong evidence for validation [12,13,31].

"*The challenge with OREs stems from the uncertainty of their surrogacy to OS and their ability to identify outcomes related to disease- or symptom burden."*

Huntsman Cancer Institute, Physician

Despite the potential value of OREs beyond OS in capturing outcomes beyond survival, there is concern amongst stakeholders, particularly HTA bodies / payers, over their ability to quantify the value of OREs beyond OS to patients and healthcare systems accurately [32-34].

"*Using OREs that haven't been validated for their surrogacy or evaluated for their standalone value increases the risk of additional treatment cost and of exposing patients to treatment burden without additional benefit*."

European Hematology Association, Physician

Misalignment within and between stakeholder groups on the value of OREs beyond OS

Regulators recognize the need to facilitate patient access to novel therapies and have approved oncology drugs based on OREs beyond OS. For example, the literature review identified a study of 108 adult oncology drugs approved by the Food and Drug Administration (FDA) from 2006 – 2017, which stated that the majority (73%) were approved based on surrogate endpoints, 38% being response rate (RR), and 35% being PFS / Relapse-Free Survival (RFS) [35]. Furthermore, in a study analysing 125 market authorizations for oncological medicines that were

first-time approved by the European Medicines Agency (EMA) between 2009 – 2017, PFS, OS and Overall Response Rate (ORR) constituted primary endpoints in 49%, 34% and 22% of market authorizations respectively [36]. However, HTA bodies / payers continue to prioritize OS [1]. EUnetHTA21 guidelines consider final outcomes, such as OS, as the initial standard [37]. This stance is not aligned with the perceptions of the patients and clinicians interviewed for this paper, who state that they value OREs beyond OS equally if not above OS in some treatment settings [1,38].

"*Currently, there are cases where clinical decision-making is guided by outcomes other than OS, such as PRO data. One example of this is the use of ruxolitinib in myelofibrosis, to treat splenomegaly and fatigue rather than prolong OS. There is a need for HTA bodies / payers to also recognise the importance of these HRQoL outcomes in their decision-making*."

European Haematology Association, Physician

In regulatory versus HTA body / payer decision-making, regulators are more amenable to valuing OREs than HTA bodies / payers [39,40]. While regulators accept and may grant approval based on OREs beyond survival, HTA bodies / payers are less accepting of these endpoints and, in cases where they are accepted, may limit access until OS evidence is generated [36,39,41]. This discrepancy may be driven in part by the different remits of these two stakeholder groups; with regulators focusing on the risk: benefit of novel medications, whereas HTA bodies / payers assess their added value against existing treatments and standards of care. Furthermore, interviews with HTA bodies / payers as part of this research indicate a misalignment within the HTA body / payer stakeholder group. As an example, some HTA body / payer agencies (e.g., NICE in the UK, HAS in France, AIFA in Italy) are open to the use of PFS, while IQWIG in Germany does not recognise it [42].

"*In the EU there is a disconnect between the EMA and the HTA agencies on which endpoints they use and consider as important; there is also variation between countries in terms of the relative weighting of different endpoints in HTA body / payer decision-making. This needs to be addressed*."

The Cancer Medicine Development Forum, Director

Inconsistencies in data collection and reporting of OREs

Data collection and reporting challenges may hinder HTA body / payer acceptance of OREs beyond OS. Firstly, tools used for PROs collection may be considered too generic and may not capture outcomes that are specific to the disease, staging or treatment characteristics [43-46]. Secondly, selection of PROs data as well as data collection methodologies and reporting might vary within an indication, limiting comparability across studies and thus impacting the general acceptability of these OREs. This has prompted the development of new methodologies that promote early consideration of why certain outcomes have been selected per treatment stage and setting, and how the value of these outcomes vary according to different stakeholder perspectives [7]. This shows a need for scoping and including normative inquiry when selecting and analysing the value of the different selected outcomes.

For emerging biomarker-based endpoints such as Minimal Residual Disease (MRD) and Circulating Tumor DNA (ctDNA), uncertainties around the methodologies used to collect data also need to be addressed [47-49]. For example, MRD sample analysis techniques, assessment timing and negativity thresholds have yet to be standardised. Detection of ctDNA is less developed than MRD; as such, the best methods for ctDNA extraction, sample volumes, and detection methods are still debated [50,51].

"*PROs data have the most potential for improvement, particularly through more structured methods and tools for collecting these data points. Currently, variability in methodologies prevents comparison across trials and is a barrier to wider adoption*."

European Haematology Association, Physician

Conclusions

OREs are relevant across all oncology treatment indications and settings, but their selection and interpretation may differ between them. OS continues to inform regulatory, reimbursement, and clinical decisions through providing a robust and comparable measure of a cancer medicine's clinical benefit. However, there are some treatment indications and settings, for example in early-stage cancers, where endpoints beyond OS are required to ensure timely access to potentially life-changing medicines.

Actions can be taken within and across stakeholder groups to address key HTA body / payer concerns preventing greater use of OREs beyond OS in HTA body / payer decision-making in oncology. Adopting a multifaceted and cross-stakeholder approach (including the values) will ensure that future HTA body / payer assessments result in the best outcomes for patients. As a first step, stakeholders, including patients, clinicians, regulators, HTA bodies / payers and industry, should align on the outcomes which are most important per cancer type / stage and identify appropriate OREs to capture those. Moreover, it is worth analysing where the differences reside among the diverse stakeholders and which are the reasons that justify those differences in order to disentangle the current approaches to outcomes definitions, normative or empirical. Once identified, collection of these OREs should use standardised methodologies, and evidence generated to address uncertainties around their translation into patient-relevant and clinically relevant outcomes [3]. This will help to build a portfolio of fit-for-purpose OREs per cancer type and stage, which could be agreed across stakeholder groups. The frontiers in the different

cancer types differ and this should be reflected in what is asked to innovators and by whom.

Each individual stakeholder group will have a role to play. Patients are key in determining the most important outcomes for each cancer type and stage. Clinicians should drive the selection of OREs that measure important outcomes based on their scientific and clinical understanding to ensure effective delivery and application of a new therapy within their setting. Regulators and HTA bodies / payers need to provide guidance on acceptable core outcome set requirements and appropriate methodologies to measure these and harmonised their petitions on designs and outcomes to improve efficiency in evidence generation. Furthermore, regulators and HTA bodies / payers should work with clinicians to align on specific evidence requirements for OREs per cancer type and stage and which correlations between OREs and OS could make sense. Industry should consider these OREs and methodologies when designing clinical studies, whilst driving evidence generation activities to validate additional OREs that better capture novel medicine value.

Increased adoption of OREs beyond OS, when this makes sense, across different settings may support HTA body / payer decision-making, which will improve patients' outcomes, and optimise the cost to healthcare systems. Continued progress in incorporating OREs beyond OS depends on the collaboration of all stakeholders to reduce uncertainty, overcome barriers and to ensure that HTA body / payer decision-making can result in the best outcomes for patients.

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