Beyond Overall Survival: Advancing the Understanding and Use of Surrogate Endpoints in Oncology

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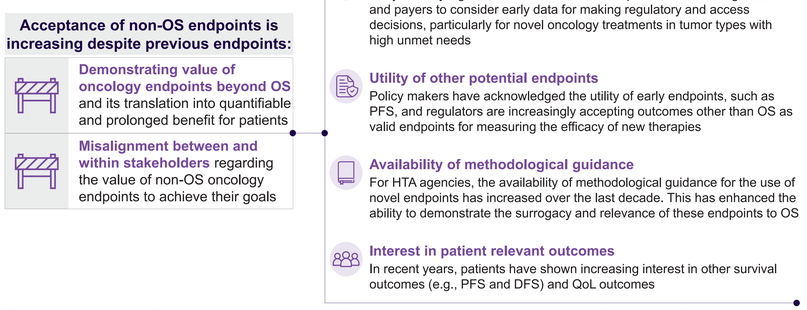
Background

- Although overall survival (OS) is considered to be a robust and clinically relevant outcome in oncology, it presents significant measurement challenges, such as lengthy follow-up periods, that can potentially delay access to new medicines.[1,2]
- OS measurements are often confounded by all-cause mortality data and the influence of subsequent therapies.[2]
- Additionally, the impact of new treatment on health-related quality of life (HRQoL), which patients consistently identify as a crucial aspect in their treatment journey is not accounted for in a unidimensional measure, such as OS.[2]
- Regulatory bodies (European Medicines Agency [EMA] and Food and Drug Administration [FDA]) accept non-OS endpoints, such as progression-free survival (PFS), response rate, and more recently minimal residual disease (MRD), for approvals, but health technology assessment (HTA) agencies remain cautious regarding the acceptance of non-OS endpoints in access discussions[1] (**Figure 1**).
- A key objection is the uncertainty regarding how non-OS endpoints translate into meaningful patient benefits, including OS.

Figure 1. Barriers to acceptance of non-OS surrogate endpoints[3-6]



DFS, disease-free survival; HTA, health technology assessment; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

Objectives

- **To summarize existing and emerging non-OS endpoints and to understand the clinical rationale behind their use and their relevance for patients (objective 1).**
- **To assess the potential of these endpoints to become commonly accepted outcomes across different stakeholders (objective 2).**

Methods

Search strategy and study selection

- A targeted literature review was conducted using Embase (Jan 2019 to Feb 2024), and a hand search of conference records (2022 and 2023) and grey literature was conducted to identify relevant studies evaluating non-OS endpoints, based on the PICOS criteria outlined in **Table 1**.
- Relevant abstracts and subsequent full texts were thoroughly screened by a single reviewer, and a second reviewer screened ~15% of references to assess quality.

Table 1. Eligibility criteria for inclusion of relevant studies

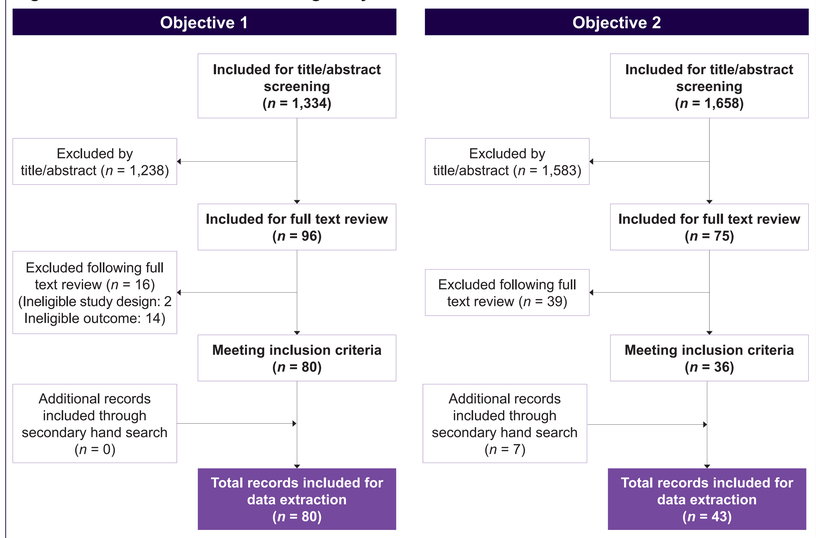
PICOS	Included	Excluded
Population	Solid tumors or hematological malignancies	Studies on other diseases
Intervention	Any	None
Comparator	Any	None
Outcomes	**Future non-OS endpoints** DCR, EFS, FSC, MFS, MRD, option-value, pCR, PFS, PR, PROs, QTwiST, RR, TFI, TR, TTF, TTCP, TTNT, TTR, TTRP **Any clinical endpoints that have resonated with patients** ADLs, patient experience, patient preference, QoL, quality of survival	Studies not discussing non-OS endpoints
Study design	Literature reviews, expert consensus statements, patient survey/interviews, position papers, or patient preference studies	Clinical trials, case reports, case series, comments, editorials, letters, and news

Search was not restricted to specific endpoints.
ADLs, activities of daily living; CNS, central nervous system; DCR, disease control rate; EFS, event-free survival; FSC, flattening of survival curve; MFS, metastatic-free survival; MRD, minimal residual disease; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; PR, partial response; PROs, patient-reported outcomes; QoL, quality of life; QTwiST; Quality-adjusted time without symptoms or toxicity; RR, relapse rate; TFI, treatment-free interval; TR, treatment response; TTF, time to treatment failure; TTCP, time to CNS progression; TTNT, time to next treatment; TTR, time to response; TTRP, time to radiographic progression.

Results

- For objective 1, the initial search identified 1,334 records, of which 80 studies reporting non-OS outcomes were included. For objective 2, forty-three studies reporting the relevance of non-OS endpoints from patients' perspectives were identified (**Figure 2**).

Figure 2. PRISMA flowchart illustrating study selection

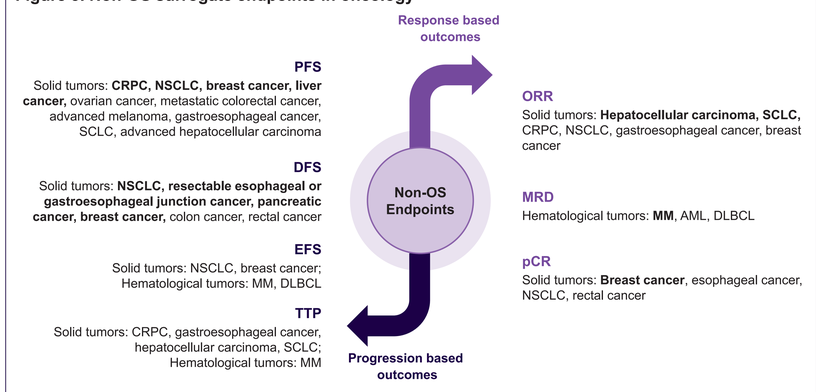


n, number of records; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Non-OS endpoints

- **Figure 3** presents commonly reported non-OS endpoints for solid and hematological tumors. The strength of correlation between these endpoints and OS varies depending on the tumor type, disease stage, and treatment modality.

Figure 3. Non-OS surrogate endpoints in oncology



Tumour types shown in **bold** indicate high strength of evidence
AML, acute myeloid leukemia; CRPC, castration-resistant prostate cancer; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; MM, multiple myeloma; MRD, minimal residual disease; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pCR, pathologic complete response; SCLC, small cell lung cancer; TTP, time to progression.

- These endpoints were primarily included as additional measures of efficacy in trials; they have demonstrated their relevance in clinical practice. However, from a reimbursement standpoint, the requirements are robust, necessitating validation studies that establish a clear link to OS (**Table 2**). Although certain HTA bodies acknowledge the clinical value of these endpoints, they often exclude them from reimbursement criteria due to insufficient validation.[2,7]
- Establishing robust surrogacy requires patient-level and trial-level data to establish relevance and relationship with OS. Validation should be conducted specifically for each tumor type, taking into account the clinical context; tumor location, stage, and indication; and treatment modality. For instance, this approach was applied to MRD, as illustrated in **Table 2**.

Table 2. Established evidence and open questions regarding key surrogate endpoints

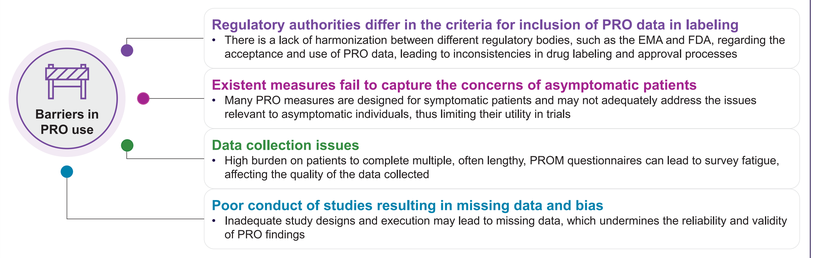
Endpoint	Pros	Cons
MRD[8]	• In 2024, the FDA ODAC supported the use of MRD for accelerated approval of MM treatment based on a meta-analysis that used patient-level data to establish MRD as an early endpoint in patients with MM[9]	• Translation into clinical practice and reimbursement decisions remain uncertain
PFS[10]	• Provides early results; less influenced by competing causes of death; and not affected by subsequent treatments • Evidence is strong in: - First-line advanced/metastatic TNBC; weaker in HR+/HER2+ metastatic BC - Immune checkpoint inhibitors in advanced HCC	• Heterogeneity in results across different studies (patient-level meta-analyses vs. other quantitative approaches yield varying results) • Clear recommendations required for its use as a surrogate endpoint
DFS[11,12]	• Earlier efficacy assessment; frequent events (smaller sample size); not confounded by subsequent treatments • Evidence is strong in: - BC (HER2+) - Pancreatic cancer - Neoadjuvant/perioperative settings: Valid surrogate endpoint for OS in EC/GEJC cancers	• Association between DFS and OS may vary
pCR[13]	• Studies are evaluating pCR as a surrogate endpoint for various BC subtypes • Achieving pCR after neoadjuvant chemotherapy was significantly associated with improved BCSS in TNBC patients • Significant association between pCR and improved OS in TNBC and HER2+ HR- BC patients who received trastuzumab	• Minimal association between pCR and OS • Single-institution retrospective analysis with small sample size; and the nonavailability of tumor grade

BC, breast cancer; BCSS, breast cancer-specific survival; DFS, disease-free survival; EC, esophageal cancer; FDA, food and drug administration; GEJC, gastroesophageal junction cancer; HCC, hepatocellular carcinoma; HER2+, human epidermal growth factor receptor 2 Positive; HR-, hormone receptor negative; HR+, hormone receptor positive; MM, multiple myeloma; MRD, minimal residual disease; ODAC, oncologic drugs advisory committee; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; TNBC, triple-negative breast cancer.

Importance of patient perspective

- Patient preferences are important/crucial as the meaning and values of patient-reported outcomes (PROs) can differ between physicians and patients. For example, patients with acute myeloid leukemia prioritize QoL post hematopoietic stem cell transplantation, while physicians prioritize 2-year relapse-free survival.[14]
- Use of PRO data has been limited in regulatory approvals as well as HTA assessments.
- Also, patients indicate that PRO data may not comprehensively capture all their concerns, especially those of asymptomatic patients. **Figure 4** illustrates the various barriers in adopting PROs.

Figure 4. Barriers in PRO adoption by regulatory bodies[15]



EMA, European Medicines Agency; FDA, Food and Drug Administration; PROs, patient-reported outcomes; PROM, patient-reported outcome measures.

Conclusions

- **While OS is considered a gold standard in oncology, it presents measurement challenges that can delay access to new treatment.**
- **Non-OS oncology endpoints are valuable efficacy measurements and are important surrogates of OS.**
- **Robust validation of surrogate endpoints using patient-level data as well as trial-level data is needed for standardized assessment across datasets.**
- **Meta-analysis of individual patient data represents the gold standard for surrogate validation, enabling standardized assessment across datasets. Validation of MRD endpoint for MM in collaboration with the FDA provided a good process roadmap of a validation process.**
- **Patients with cancer are increasingly prioritizing HRQoL/QoL as important endpoints, along with survival. A patient-centered approach is essential, involving the validation and standardization of QoL assessment tools to highlight the role of PROs in clinical trials.**
- **Broader acceptance of non-OS endpoints by regulators and payers requires coordinated action across the healthcare continuum. This includes establishing patient relevance (through patient-value outcomes such as QoL and daily functioning), translating clinical trial results into real-world settings, robust validation using patient-level data, defining clear reimbursement parameters, and stakeholder commitment to ensure timely access to innovative therapies.**

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CONFLICTS OF INTEREST
MS and CF are employees of Sanofi and may hold stocks and/or stock options in the company. KP and IB were employees of Sanofi at the time this study was conducted.

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