Evaluation of the Use of Surrogate Endpoints in Oncology Clinical Trials

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Introduction

- Overall survival (OS) is considered the gold standard efficacy measure in oncology clinical trials. Over the last decade endpoints such as progression-free survival (PFS) and objective response rate (ORR), have been recognized by the FDA as efficacy surrogate
- The Biomarkers Definition Working Group defines a surrogate endpoint as "a biomarker" intended for substituting a clinical endpoint and expected to predict clinical benefit, harm or lack of these" (BDWG 2001).
- · The use of surrogate endpoints may not be generalizable or appropriate across all cancer types. A recent systematic literature review that identified 47 studies that concluded that PFS was good surrogate for OS, however for 15 of these (32%), there was no quantitative argument made for surrogacy (Berlin 2020). Of 194 drug authorizations based on surrogate endpoints, 33% were used for the first time for a specific cancer type and the rest were subsequent use of surrogate endpoints (Chen 2020).
- While use of surrogate endpoints for authorizations has increased, there are conflicting opinions among regulatory bodies and payers regarding the use of surrogate outcomes in drug trials. Only 5 HTA agencies have developed more detailed prescriptive criteria for the favorable reception of surrogate endpoints (UK National Institute for Care and Excellence; the German Institute for Medical Documentation and Information and Institute for Quality and Efficiency in Health Care; the Australian Pharmaceutical Benefits Advisory Committee; and the Canadian Agency for Drugs and Technologies in Health) (Grigore 2020). Further, a recent analysis found inconsistent consideration of the level of evidence and statistical validation associated with surrogate endpoints across HTA agencies (Ciani
- The purpose of this study was to identify and quantify the frequency and trends of surrogate endpoints utilized across oncology clinical trials

Methods

- A search was conducted on 02 November 2021 in ClinicalTrials.gov to retrieve Phase 2/3 or Phase 3 interventional trials in adults with solid tumors or blood cancer indications. between 1 January 2017 – 31 October 2021.
- · Trials were excluded if they were studying benign cancer or diseases other than cancer, prophylactic treatments, diagnostic tests, preventive treatment, safety or PK-PD endpoints.
- · For the purposes of this review, surrogate endpoints were defined as any primary endpoint other than the OS. Among the surrogate endpoints, PFS followed by ORR were considered as widely accepted and validated surrogate endpoints while the remaining endpoints were termed as 'evolving'.

Search Approach

- . The following information was extracted from the included trials:
- Cancer type: leukemia, lymphoma, myelodysplastic syndrome, myeloma, carcinoma, melanoma, sarcoma or mixed
- . Line of therapy: first-line (1L), second-line (2L), later-line (2L+) or mixed
- Setting: advanced/metastatic stage or early/intermediate stage (including adjuvant/neoadjuvant) and other

Endpoints: primary and secondary efficacy endpoint(s)

· Frequency of OS versus surrogate endpoints as primary endpoints was assessed

according to cancer type, line of therapy, and disease setting. · This is a descriptive study; no formal statistical analysis was conducted to quantify the differences between the endpoints

Study Selection

- Out of total 5.507 records retrieved from ClinicalTrials.gov searches, 879 Phase 2/3 or 3 interventional trials reporting solid tumor or blood cancer efficacy endpoints were included, of which 80% were in solid tumors (Figure 1).
- · OS was listed as a primary endpoint in 32% of included trials, of which approximately half (15% of trials) had OS listed with a surrogate primary endpoint (Figure 2).
- The majority of trials (68%) listed surrogates alone as the primary endpoint (Figure 2).
- · When stratified according to the cancer type, a greater proportion of blood cancer trials listed a surrogate endpoint alone as primary endpoint (82%) compared to solid tumors (64%) (Figure 2).

Figure 1: Trial Study Selection Flow Chart

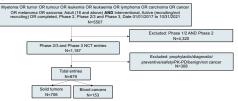


Figure 2: Percentage of Trials Reporting Primary Endpoints According to Cancer

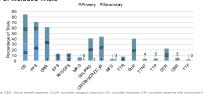


Primary and Secondary Endpoints Reported in Included Trials

- . Other than OS, PES and ORR, commonly reported primary endpoints included eventfree survival (EFS), relapse-free survival (RFS), and response (Figure 3).
- · Other less frequently reported "evolving" primary endpoints (reported in <3% of included
 - minimal residual disease (MRD) negativity, major pathological response (MPR), major molecular response (MMR) rate, treatment failure-free survival (TFFS), very good partial response (VGPR). complete tumor ablation, composite endpoints, complete metabolic response (CMR), major cytogen response (MCyR), duration of disease control and other disease-specific endpoints.
- . Approximately 40% of trials included QoL/PROs as secondary endpoints (Figure 3).

Results

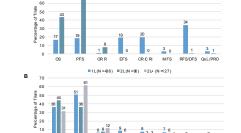
Figure 3: Percentage of Primary and Secondary Endpoints by Type Reported in ≥3% of Included Trials



Primary Endpoints by Disease Setting and Line of Therapy

- PFS was the most frequently used surrogate endpoint in trials in advanced/metastatic setting while evolving surrogate endpoints such as EFS, CR/CRi, MFS, RFS/DFS and QoL/PROs were more frequently used in the early/intermediate setting (Figure 4A).
- OS was used in similar proportions of trials in 1L and 2L+ lines of therapy, PFS and ORR were listed as a primary endpoint more frequently in 2L+ lines of therapy compared to first or second lines (Figure 4B). These results should be interpreted with caution, given the inconsistencies in reporting of information on the line of therapy, across the trials.
- · Relatively fewer evolving surrogate endpoints appeared in the later line setting as compared to the 1L setting (Figure 4B)

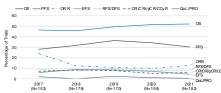
Figure 4: Percentage of Primary Endpoints by A) Disease Setting and B) Line of Therapy ■ Fartyl dermedateStage (N = 167) ■ Advanced / Metastatic Stage (N= 1449)



Primary Endpoint Time Trend

 Since 2019 the use of OS as a primary endpoint has declined, and the use of PFS and ORR has increased.

Figure 5: Percentage of Primary Endpoints Reported by Trial Start Date



Limitations

- · Records were screened by a single reviewer with a quality check carried out on 50% of
- · Records from ClinicalTrials.gov database could be incomplete, as sometimes individual studies may be missing from the database, or the study information may be missing from

Conclusions

- Compared to OS, surrogate primary efficacy endpoints are frequently used in Phase 2/3 or 3 oncology clinical trials with blood cancer trials using surrogate primary endpoints alone (without OS) more frequently than solid tumor trials (82% vs 68%)
- · Evolving surrogate endpoints are more often used in early/intermediate disease settings than in advanced/metastatic settings and were more frequently listed as primary endpoints in early lines of therapy compared to the later lines of therapy.

References

Biomarkers Definitions Working Group (2001) Clinical Pharmacy and Therapeutics 69:89-95 Berlin (2020) British Journal of Cancer 122:1707–1714 Chen (2020) JAMA Internal Medicine 180(6):912-914

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