

Post Progression Endpoints in Oncology trials: Current Clinical and Reimbursement Perspectives

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INTRODUCTION

Access to approved cancer treatments based on progression-free survival (PFS) may face reimbursement challenges when cancers have prolonged post-progression survival and overall survival (OS) outcomes are immature. Post-progression endpoints (PPEs) may offer clinically meaningful and patient-relevant data for regulatory and reimbursement decision-making.

OBJECTIVES

Clinical trials with PPEs identified from 01/2008 to 04/2019 were evaluated for their influence on regulatory and health technology assessment (HTA) reviews.

METHODS

Clinical trials listed in clinicaltrials.gov, EU Clinical Trials Register, and TrialTrove were reviewed for inclusion of PPEs. Analyses were limited to studies in cancer identified by 'Trial status' (planned, open, closed, completed), 'Trial phase' (phase 2, 2/3, and 3), 'Sponsor type' (industry only), and for patients with metastatic or early stage solid tumors or hematologic malignancies.

Table 1: Identified Post-progression Endpoints

Endpoints	Definition
PFS2	Time from randomization to objective tumor progression on next-line treatment or death from any cause
PPS	Randomization to the time a patient's tumour starts to grow or spread again, or he/she dies, while the patient is on 2 nd /3 rd /4 th line treatment
TFST	The time from randomization in a trial to the time a patient starts his/her second line of treatment
TSST	The time from randomization to the time a patient starts his/her third line of treatment
PRO	Patient relevant outcomes including measures related to physical, mental, emotional, and social functioning

RESULTS

In >8,000 studies of patients with cancer, 235 were identified with PPEs as either primary (7%), secondary (70%), exploratory (2%), or other endpoints (21%). PPEs were most frequently identified in ovarian (17%), multiple myeloma (15%), NSCLC (13%), colorectal (10%), prostate (10%) and breast (8.5%) cancer studies. Among these indications, PFS2, TSFT, and TSST were reported as endpoints in 80%, 27%, and 18% of studies, respectively. Recent trends also suggest increasing use of PPE with 171 trials using post progression endpoints (2014 to 2018) vs. only 49 trials previous to 2013.

14 studies served as the basis for marketing authorization reviews by the FDA or EMA and 9 studies were reviewed by EU HTA/reimbursement agencies. The utility of PPEs in regulatory and reimbursement reviews were supplemental to traditional endpoints in these assessments.

Table 2: Details of trials which included PPEs assessed as part of HTA submissions

Cancer	Product name	Trial name	Phase	FDA approved	EMA approved	Primary Endpoints/ Results	PPEs included	EU5 HTA assessment
Ovarian Cancer	LYNPARZA (olaparib)	SOLO 1 (NCT01844986)	P3	✓ 1L, maintenance, BRCA-mut	✗ NA	PFS (olaparib vs. placebo): not reached vs. 13.8 months	PFS 2, TFST, TSST	Not completed
		SOLO 2 (NCT01874353)	P3	✓ 2L+, maintenance, BRCA-mut	✓ 2L+, maintenance, BRCA-mut	PFS (olaparib vs. placebo): 19.1 months vs. 5.5 months	PFS 2, TFST	Completed
	ZEJULA (niraparib)	NOVA (NCT01847274)	P3	✓ 3L, BRCA-mut Platinum-sensitive	✓ 3L, BRCA-mut Platinum-sensitive	PFS, gBRCAmut Cohort (niraparib vs placebo): 21 months vs. 5.5 months; PFS, non gBRCAmut Cohort (Niraparib vs placebo): 9.3 months vs. 3.9 months	PFS2, TFST	Completed
	RUBRACA (rucaparib)	ARIEL3* (NCT01968213)	P3	✓ 3L, BRCA-mut Platinum-sensitive	✓ 3L, BRCA-mut Platinum-sensitive	PFS (rucaparib vs placebo): 10.8 months vs. 5.4 months	PFS2 (Exploratory endpoint)	Not completed
NSCLC	TAGRISSO (osimertinib)	AURA3 (NCT02151981)	P3	✓ 2L, EGFR+, T790m	✓ 2L, EGFR+, T790m	PFS (osimertinib vs chemotherapy): 10.1 months vs. 4.4 months	PFS2 (Exploratory endpoint)	Completed
		FLAURA (NCT02296125)	P3	✓ 1L, EGFR+	✓ 1L, EGFR+	PFS (osimertinib vs placebo): 18.9 months vs. 10.2 months	PFS2 (Exploratory endpoint)	Completed
	IMFINZI (durvalumab)	PACIFIC (NCT02125461)	P3	✓ Unresectable Stage III	✓ Unresectable Stage III	PFS (durvalumab vs. placebo): 16.8 months vs. 5.6 months	Time to chemotherapy	Completed
Prostate Cancer	ZYTIGA (abiraterone)	COU-AA-302 (NCT00887198)	P3	✓ 1L mCRPC	✓ 1L mCRPC	rPFS (*abiraterone combo vs. prednisone-alone): 16.5 months vs. 8.3 months	Time to chemotherapy	Completed
		LATITUDE (NCT03635788)	P3	✓ 1L, mHSPC	✓ 1L, mHSPC	PFS (*abiraterone combo vs. **placebo combo) 33 months vs. 14.8 months	TFST, time to chemotherapy	Completed
	XTANDI (enzalutamide)	PREVAIL (NCT01212991)	P3	✓ 2L, mCRPC	✓ 2L, mCRPC	rPFS (enzalutamide vs. placebo): not reached vs. 3.9 months	Time to chemotherapy	Completed
	ERLEADA (apalutamide)	SPARTAN* (NCT1946204)	P3	✓ nmCRPC	✓ nmCRPC	PFS (apalutamide vs placebo): 40.5 months vs. 14.7 months	Time to chemotherapy	Completed
Breast Cancer	LYNPARZA (olaparib)	OlympiAD* (NCT02000622)	P3	✓ BRAC-mut	✓ BRAC-mut	PFS (olaparib vs. placebo): 7.0 months vs. 4.2 months	PFS 2	Not completed
Multiple Myeloma	DARZALEX (daratumumab)	POLLUX* (NCT02076009)	P3	✓ Relapsed/ refractory	✓ Relapsed/ refractory	PFS (daratumumab vs. placebo): not reached vs. 18.4 months	PFS2	Completed
Melanoma	TAFINLAR (dabrafenib)	BREAK-3* (NCT01227889)	P3	✓ 1L, BRAF+	✓ 1L, BRAF+	PFS (dabrafenib vs Dacarbazine): 5.1 months vs. 2.7 months	PFS2	Completed

CONCLUSIONS

Use of PPEs in clinical trials in cancer is increasing and are supplementing traditional efficacy endpoints. Their utility in regulatory and reimbursement decision-making are still in an emergent stage, and based on this review, agencies are likely to acknowledge their supportive value, but are not ready to make assessments solely or largely based on PPEs. PPEs may provide additional value for oncology product efficacy such as characterizing data for treatment sequencing (e.g., time to subsequent therapy). Such PPE data may also further inform economic models in cost-effectiveness markets such as the UK, Canada and Australia.

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Figure 1: Filtering approach to shortlist trials using Post Progression end points

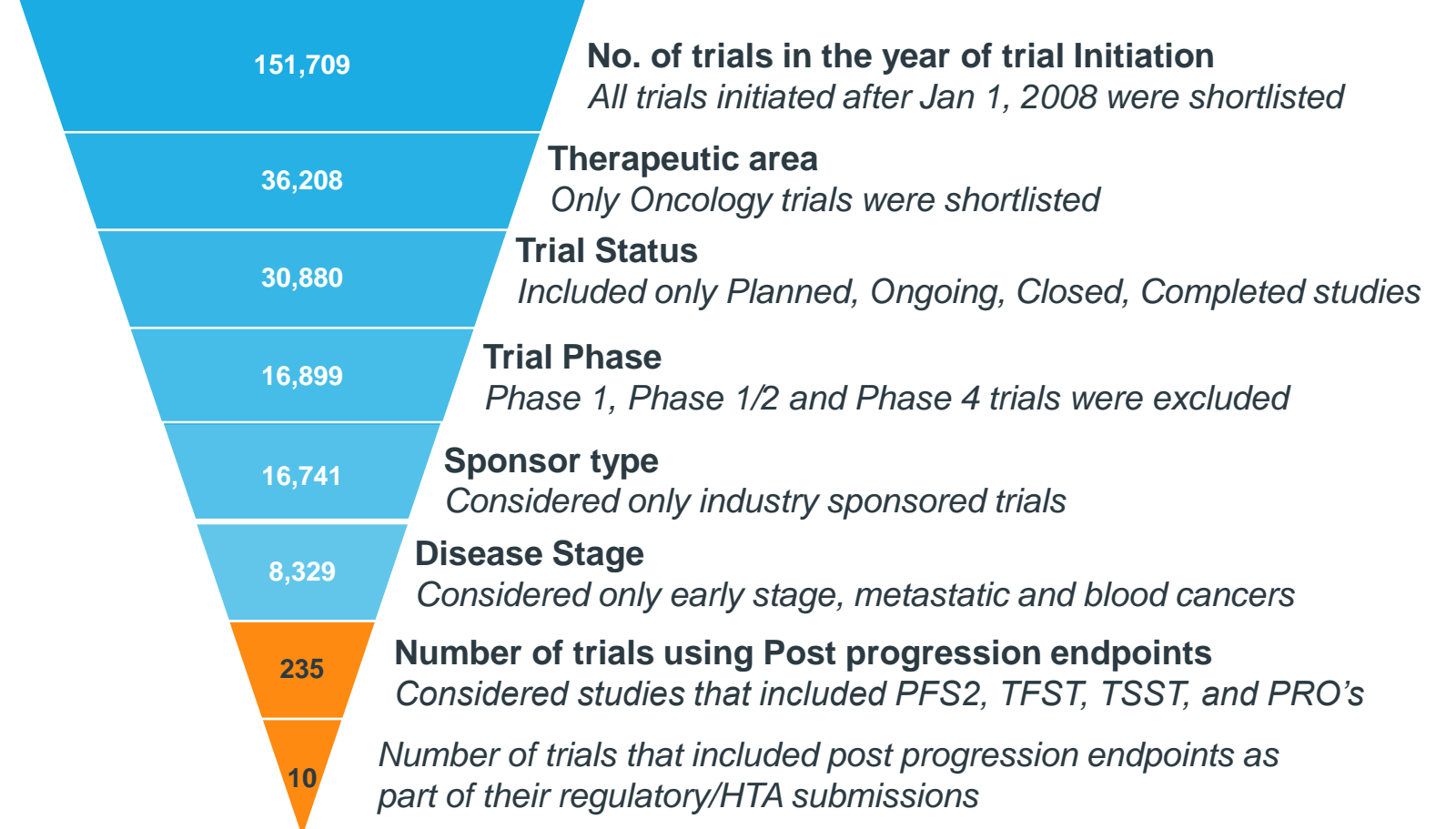


Figure 2: Trials using PPEs by Phase, Indication and Drug type

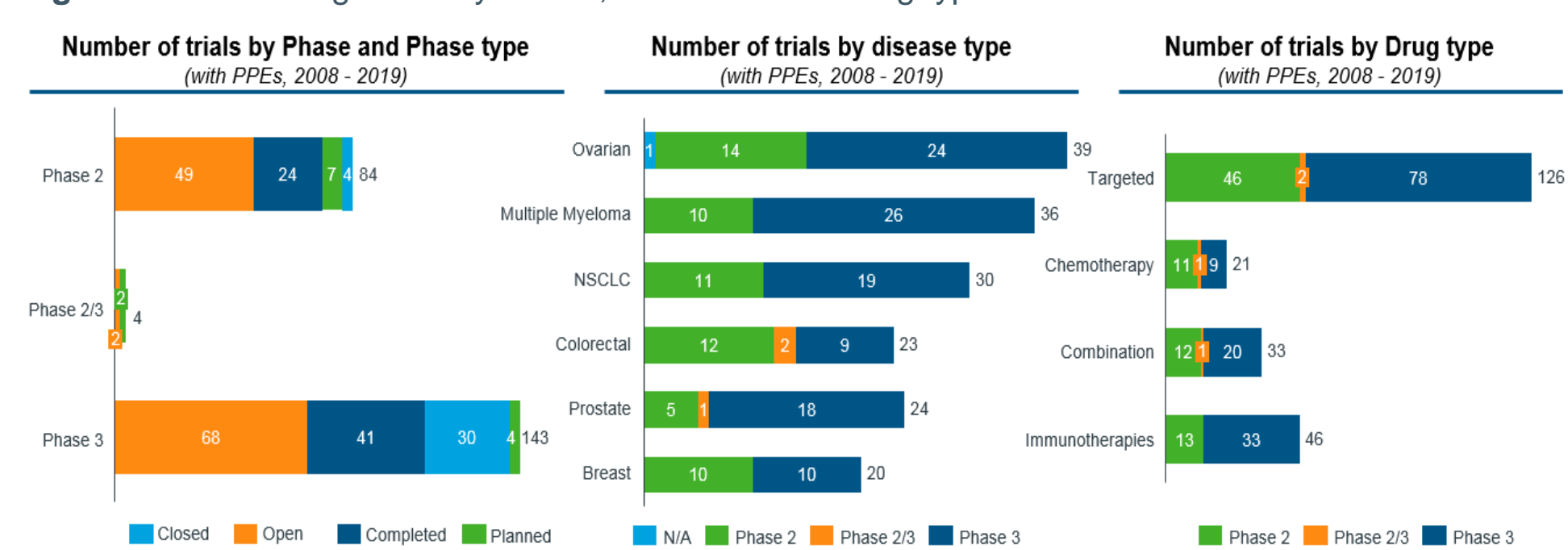


Figure 3: Trials using PPEs by molecule, sponsor type and indication

