CO198

Avalere Health™

Exploring progression-free survival 2 endpoint trends and uptake in the US healthcare landscape

Peter Okorozo, Ian Daniel, Jennifer Sander; Avalere Health, USA

Introduction

Overall survival (OS) is often considered the gold standard primary endpoint for demonstrating clinical efficacy in oncology trials and is universally accepted by regulatory agencies. However, there are challenges to presenting mature OS data.[1] There is growing interest in alternative endpoints such as progression-free survival 2 (PFS2), which is defined as the time from randomization to objective tumor progression on the first subsequent therapy (next-line therapy) or death from any cause.[1] By incorporating PFS2 as an endpoint, investigators can elucidate the long-term benefits and potential challenges associated with new therapeutics.[1] The European Medicines Agency (EMA) has suggested the use of PFS2 as an alternative when OS is not feasible since 2017, which means PFS2 is considered by many stakeholders as an acceptable endpoint for efficacy in clinical trials, especially in Europe.[2] In the USA, the use of PFS2 in oncology trials has also gained some traction due to its ability to capture the full spectrum of disease progression and treatment effects; however, the use and acceptability of PFS2 in regulatory assessments is less clear.[1,3]

Objectives

Through an analysis of recent trials and regulatory guidance, this study aimed to assesses the relevance of PFS2 in the US and its acceptance by the US Food and Drug Administration (FDA), providing insights into the evolving landscape of oncology research and the role of PFS2 in shaping future clinical trial interpretation.

Methods

FDA guidance for oncology trials was reviewed to determine regulatory requirements for clinical endpoints. A US landscape assessment was conducted using secondary research to examine trends in the use of PFS2 within the US healthcare system, including its application in clinical trials. The ClinicalTrials.gov database was searched to identify studies that included PFS2 within the past five years.

Results

Our review of FDA guidance showed that PFS2 is not officially listed as an acceptable primary, secondary, or surrogate endpoint. There are, however, many ongoing trials that incorporate PFS2 in their analyses. The search of ClinicalTrials.gov identified nearly 170 trials using PFS2 as a clinical endpoint that were either recruiting (118 trials) or active but not recruiting (56 trials).[4] The number of trials that included PFS2 appeared to increase the most from 2019 to 2020: from 23 trials to 36 trials per year. The number of trials has remained steady since, ranging from 31 to 37 per year. The most common disease areas in trials were multiple myeloma (37 trials), lung cancer (32 trials), breast cancer (19 trials), ovarian cancer (16 trials), and prostate cancer (10 trials). AstraZeneca is the sponsor for highest number of trials (33) that are using PFS2 as an endpoint, followed by Janssen Research & Development, LLC (12), with the remaining trials distributed among other sponsors. Most of these trials are currently in Phase 3 (96), followed by Phase 2 (35).

Table 1: Number of trials using PFS2, by year

Year	Number of trials
2019	23
2020	36
2021	31
2022	35
2023	37
2024	7

Table 2: Number of trials using PFS2, by cancer type

Cancer type	Number of trials
Breast	19
Cervical	1
Colon	1
Colorectal	6
Endometrial	6
Gastric	3
Head and neck	2
Leukemia	2
Liver	2
Lung	32
Lymphoma	3
Melanoma	3
Mesothelioma	1
Multiple myeloma	37
Nasopharyngeal	1
Neoplasms	5
Ovarian	16
Pancreatic	4
Prostate	10
Renal	3
Soft tissue	1
Solid tumor	5
Thyroid	1
Uterine	1
Not listed	4

Table 3: Number of trials using PFS2, by phase

Phase	Number of trials
1	4
1/2	6
2	35
2/3	4
3	96
4	4
Blank or NA	20

Conclusions

The use of PFS2 as an endpoint in oncology clinical trials in the US represents a key advance in the assessment of treatment efficacy and patient outcomes. Efforts to standardize trial methodologies, address regulatory considerations, and enhance data collection and analysis techniques will also be essential to maximize the utility of PFS2 in oncology research. Integration of PFS2 as an endpoint in US oncology trials likely represents a crucial step toward improving our understanding of cancer treatment outcomes and advancing new medicines. Our findings show that PFS2 is currently being used in nearly 170 ongoing trials across many cancer types. However, the FDA still has not fully recognized PFS2 as an acceptable endpoint, and it remains unclear when or if it will include PFS2 in its official guidance. Considering many of the ongoing trials that have incorporated PFS2 as an endpoint are in Phase 3, there may be an opportunity in the future to reassess and better understand the FDA's position, once the agency has completed its review of Phase 3 trial outcomes. Continued research and collaboration in this area will be vital to furthering the field of oncology and ultimately improving patient outcomes. In future studies, it would be helpful to understand clinician perspectives and adoption of PFS2 in clinical practice, in the absence of mature OS data. Such findings will prove important in areas like oncology and hematology, where the timescales for OS data to mature are longer than in some other disease areas.

References

1. Woodford RG, et al. The validity of progression-free survival 2 as a surrogate trial end point for overall survival. Cancer. 2022 Apr 1;128(7):1449-1457. doi: 10.1002/cncr.34085. Epub 2022
2. Committee for Medicinal Products for Human Use. Guideline on the Evaluation of Anticancer Medicinal Products in Man. European Medicines Agency. Published December 22, 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf (Accessed January 9, 2024)
3. MARIPOSA trial. https://www.prnewswire.com/news-releases/landmark-phase-3-mariposa-study-meets-primary-endpoint-resulting-in-statistically-significant-and-clinically-meaningful-improvement-in-progression-free-survival-for-rybrevant-amivantamab-vmjw-plus-lazertinib-versus-osimertinib--301941646.html (Accessed January 9, 2024)
4. ClinicalTrials.gov

Poster presented at ISPOR US, May 5–8, 2024, Atlanta, GA, USA