PharmaSUG 2024 - Paper DS- 271

Programming Considerations in Deriving Progression-Free Survival on Next-Line Therapy (PFS2)

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ABSTRACT

Historically, oncology clinical trials have relied on Overall Survival (OS) and Progression Free Survival (PFS) as primary efficacy endpoints. While OS is often the most desired estimate, it requires many years of follow-up to derive an unbiased estimate from the study. Additionally, even with follow-up, OS estimates are subject to confounding due to subsequent therapies which are commonplace in the treatment of cancer. As a proxy for OS, the European Medicines Agency (EMA) has recommended the evaluation of Progression Free Survival after next line of treatment - also known as Progression Free Survival 2 (PFS2). According to the EMA, “PFS2 is defined as the time from randomization (or registration, in non-randomized trials) to second objective disease progression, or death from any cause, whichever first.” Despite this definition, PFS2 requires complex data collection and derivation. Within our oncology team at Bristol-Myers Squibb (BMS), different studies approach the derivation in unique ways. In this paper, we will share how our team at BMS collects the relevant data to derive the PFS2 endpoint with a consistent approach in both the advanced and early settings. Furthermore, we will explain how we structure our ADAM datasets to assist in our derivation of the endpoint.

1. INTRODUCTION

Historically, oncology clinical trials have relied on Overall Survival (OS) and Progression Free Survival (PFS) as primary efficacy endpoints. While OS is often the most desired estimate, it requires many years of follow-up to derive an unbiased estimate from the study. Additionally, even with follow-up, OS estimates are subject to confounding due to subsequent therapies which are commonplace in the treatment of cancer.

While PFS is often viewed as the next best estimate for OS, it is also possible that even if a treatment has advantageous outcomes in terms of PFS, it may still be associated with poorer OS. This much was said in the “CHMP Appendix 1 to Guideline on Evaluation of Anticancer Products in Man 2012” by the European Medicines Agency (EMA). To address these concerns, the EMA proposed Progression-Free Survival after next line of treatment, also known as Progression-Free Survival 2 (PFS2), as a surrogate for OS, particularly for trials evaluating maintenance therapy.

According to the EMA, “PFS2 is defined as the time from randomization (or registration, in non-randomized trials) to second objective disease progression, or death from any cause, whichever first.” Despite having a definition and general understanding of the PFS2 endpoint, at Bristol-Myers Squibb (BMS), we identified inconsistencies and gaps in some of our studies regarding PFS2 derivation.

This work is to standardize the PFS2 definitions across indications and different settings of the protocols - metastatic and adjuvant. Section 2 will provide the censoring and event scheme used for PFS2 as well as describe CRF considerations needed for ADAM specification creation. Section 3 will describe how the censoring and event scheme and CRF structure come together programmatically. Section 4 will provide a summary of the ADAM datasets needed for PFS2 derivation and conclude with a hypothetical example to illustrate the dataset’s structure.

2. PROGRESSION-FREE SURVIVAL 2 PROPOSAL

As defined by the EMA, PFS2 is the time from randomization to second objective disease progression. For the purposes of this paper, we will discuss PFS2 using terminology from the metastatic setting. However, this standard works well in the adjuvant setting. The primary difference is that the PFS2 event is second recurrence in the early setting while the PFS2 event in the metastatic setting is progression. Additionally, subsequent systemic therapy (SST) after first progression is referred to as next

line therapy in the metastatic setting. Table 1 below describes the censoring and event scheme for PFS2, while the start date of PFS2 would be the date of randomization for all subjects.

Table 1. PFS2 Censoring and Event Scheme

Step	Scenario	Outcome	Event or Censor Date
1	Second progression following SST after first progression	Event	Date of second progression
2	New primary non-study cancer before second progression or death	Censored	Date of new primary cancer
3	Death	Event	Date of death
4	No new primary non-study cancer and no first progression / death	Censored	Last Known Alive Date

2.1 CRF CONSIDERATIONS

There are separate CRFs to collect the date of disease progression, the date of new primary non-study cancers, and date of death for a patient. Last known alive date is derived based on the known dates from multiple domains that date information is collected for a patient.

Progression dates after a patient starts SST are collected on the subsequent therapy CRF page along with other data relevant to that subsequent therapy such as SST start and end dates, the best response to the SST and the primary reason the SST is discontinued.

3. IMPLEMENTATION

Date of first progression, date of death, and date of new primary non-study cancers can be derived directly from the data collected on the corresponding CRF with standard imputation applied when partial dates are reported.

Not all SSTs reported on the subsequent therapy CRF page will be considered as a next line therapy since subsequent therapies can be initiated or discontinued due to reasons other than a previous progression such as study drug toxicity, regimen completed, etc.

To define the second disease progression, we must subset the SSTs to only those therapies which were started after the first disease progression occurred. The earliest start date of these SST marks the start date of eligibility for a second progression. This date is also referred to as the start of next line therapy in the metastatic setting. Disease progressions after these therapies will be considered as the second progression except in the case when a primary non-study cancer is reported prior to the first progression. When a primary non-study cancer is reported, the subject will be censored at the date of the primary non-study cancer. The other event for PFS2 is death. Considering this definition, we must derive four separate dates to derive PFS2.

The first date to derive is the earliest progression date. For the purposes of this paper, the first progression date considers any progression. The next date is the earliest primary non-study cancer date - if there was a new primary non-study cancer. The third date to derive is the start date of SST after first progression. And, lastly, the date of second progression must be derived. With these four dates, PFS2 can be derived.

4. ADAM DATASETS FOR PFS2 DERIVATION

4.1 ADAM DATASETS OVERVIEW

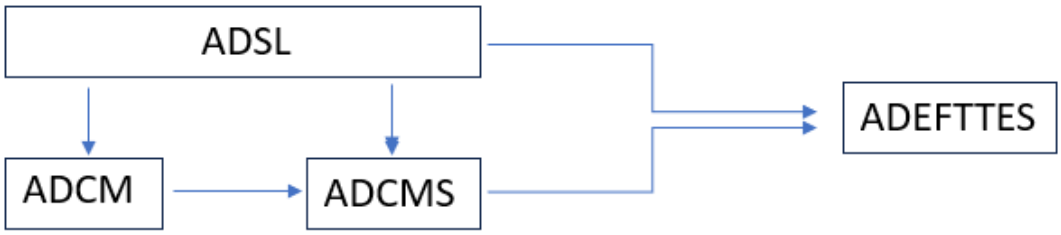
In BMS's ADaM model using implementation guide 1.3, PFS2 is derived in the time to event analysis dataset, ADEFTTES. This dataset is based on three other ADAM datasets - ADSL, ADCM, and ADCMS. Figure 1 below illustrates the order of dataset generation to complete the PFS2 derivation.

- **ADSL:** Subject-level dataset containing baseline demographic and disposition data. It also includes important dates of events the subject has experienced. For example, progression date, new primary

non-study cancer date, death date, and last known alive date.

- **ADCM:** Occurrence data structure containing records of non-study medications, including concomitant medication as well as subsequent anti-cancer therapies.
- **ADCMS:** The non-study medication summary analysis dataset includes data for prior and subsequent cancer treatment of randomized subjects. The ADCMS dataset is a basic data structure (BDS).
- **ADEFTTES:** The efficacy time-to-event analysis dataset includes endpoints for time to event analysis including overall survival, progression free survival, progression free survival 2, etc. ADEFFTES is a BDS class of dataset.

Figure 1. Order of Dataset Derivation for PFS2 Endpoint



4.2 Dataset Structure with Example

This section will utilize hypothetical data to demonstrate the data structures for PFS2 derivation. Subject -123 is a patient who has a qualified PFS2 event due to a second progression - not death. The second subject, patient -456 is a patient who has a second progression following the development of a new primary non-study cancer.

Table 2 shows the data required from the ADSL dataset - primarily, the randomization date (RANDDT), the treatment start date (TRTSDT), the last known alive date (LSTALVDT), patient death date (DTHDT), the investigator progression date (INVPRODT), as well as the date of a new primary non-study cancer (NEWPRCDT). Last known alive date is required for censoring values. The investigator progression date is used to identify the first progression and compare to new therapy dates to determine the start date of next line therapies. For the purposes of this illustration, both subjects have been randomized, treated, and experienced their first progression on the same dates.

Table 2. ADSL

USUBJID	RANDDT	TRTSDT	NEWPRCDT	LSTALVDT	DTHDT	INVPRODT
XXX-123	2021-01-01	2021-01-02		2023-01-01	.	2022-02-21
XXX-456	2021-01-01	2021-01-02	2023-04-01	2023-06-01	.	2022-02-21

Table 3 displays an example of the ADCM dataset. The ADCM dataset provides all relevant data on subsequent therapies - the start date, end date, and regimen number of each subsequent therapy (CMGRPID). Additionally, ADCM provides the reason for ending the associated regimen (RNOFTY), and the progression date of any progression that occurred on the associated regimen (PGDT). This data is required for deriving all variables associated with next line therapy as well as potential second, next line therapies. Subject -123 started their subsequent therapy, Regimen 2 and then progressed. Whereas subject -456 completed a subsequent therapy, Regimen 2, and then had a progression while on Regimen 3.

Table 3. ADCM

USUBJID	CMGRPID	ASTDT	AENDT	BESTRSP	RNOFTY	PGDT
XXX-123	REGIMEN 2	2022-03-01	2023-05-08	PD	PROGRESSION/ RECURRENCE	2023-05-01
XXX-123	REGIMEN 3	2023-05-10	2023-07-10	PD	PROGRESSION/ RECURRENCE	2023-07-01
XXX-456	REGIMEN 2	2022-03-01	2023-05-08	SD	TREATMENT COMPLETION	
XXX-456	REGIMEN 3	2022-05-10	2023-06-08	PD	PROGRESSION/ RECURRENCE	2023-06-01

Table 4 provides an example of the structure of the ADCMS dataset. The ADCMS dataset contains all important dates associated with SST after first progression (or next line therapies), date of second progression, and dates used to impute the date of progression when progression is indicated. Specifically with regards to imputation, there are three parameters in support of the PFS2 derivation- "Discontinuation of next line therapy" (NLTHERPD), "Start of Second Next Line Therapy" (SNLTHER), and "Progression on Next Line Therapy with Imputation" (NLTHERPS). These parameters assist in imputation in the case that there is critical missing information regarding the second progression date.

This dataset along with the ADSL dataset are the two datasets required to derive PFS2. Subject -123 has a straightforward profile in this dataset having a second progression on their next line therapy, called Regimen 2 in this example. Subject -456 started and finished their first subsequent therapy, Regimen 2, in response to their first investigator progression. They then progressed while on Regimen 3.

Table 4. ADCMS

USUBJID	PARAMCD	PARAM	ADT	AVALC	AVAL
XXX-123	NLTHER	START OF NEXT-LINE THERAPY	2022-03-01	REGIMEN 2	2
XXX-123	NLTHERP	PROGRESSION ON NEXT-LINE THERAPY	2023-05-01	REGIMEN 2	2
XXX-123	NLTHERPD	DISCONTINUATION OF NEXT-LINE THERAPY	2023-05-08	PROGRESSION	
XXX-123	SNLTHER	START OF SECOND NEXT-LINE THERAPY	2023-05-10		
XXX-123	NLTHERPS	PROGRESSION ON NEXT-LINE THERAPY OR SURROGATE	2023-05-01		
XXX-456	NLTHER	START OF NEXT-LINE THERAPY	2022-03-01	REGIMEN 2	2
XXX-456	NLTHERP	PROGRESSION ON NEXT-LINE THERAPY	2023-06-01	REGIMEN 3	3
XXX-456	NLTHERPD	DISCONTINUATION OF NEXT-LINE THERAPY	2023-05-08	OTHER	
XXX-456	SNLTHER	START OF SECOND NEXT-LINE THERAPY	2022-05-10		
XXX-456	NLTHERPS	PROGRESSION ON NEXT-LINE THERAPY WITH IMPUTATION	2023-06-01		

Table 5 shows the final dataset that contains all PFS2 data for the study. Using ADCMS and ADSL, the date of PFS2 can be derived as well as the event description indicating whether the subject was censored or not and for what reasons. As shown, per our definition, subject -123 has a PFS2 event

on 2023-05-01. Subject -456 is censored on 2023-04-01 - the date a new primary non-study cancer occurred. While subject -456 had a second progression on a next line therapy, this occurred after the new primary non-study cancer.

Table 5. ADEFTTES

USUBJID	PARAMCD	ADT	CNSR	EVNTDESC
XXX-123	PFS2INV	2023-05-01	0	PROGRESSION ON NEXT LINE THERAPY
XXX-456	PFS2INV	2023-04-01	1	NEXT LINE THERAPY AND NEW PRIMARY NON-STUDY CANCER

CONCLUSION

The ADaM dataset structures described in this paper allow programming standardization of the complex PFS2 endpoint derivation across the oncology therapeutic area at BMS. This thorough departmental standard for PFS2 derivation enables more efficient and consistent programming within BMS oncology. The standards laid out work across indications within oncology and can handle different protocol settings and designs. Having an established standard allows for future macro development to further enhance programming efficiencies.

REFERENCES

European Medicines Agency. “Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man.” Accessed January 8, 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/appendix-1-guideline-evaluation-anticancer-medicinal-products-man-methodological-consideration-using-progression-free-survival-or-disease-free-survival-confirmatory-trials_en.pdf

ACKNOWLEDGMENTS

The authors would like to thank the BMS oncology clinical team, in particular Jenny Zhang and Sarah Keidel, for lending their expertise to this standard development. Additionally, the authors would like to thank Stephanie Meadows-Shropshire for her knowledge and perspective from the oncology statistics group.

RECOMMENDED READING

- *CDISC ADAM Implementation Guide V1.3 or higher*

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