PharmaSUG 2019 - Paper SS-027

Progression-Free Survival (PFS) Analysis in Solid Tumor Clinical Studies

Na Li, Na Li Clinical Programming Services

ABSTRACT

Progression-free survival (PFS) is commonly used as a primary endpoint in Phase III of solid tumor oncology clinical studies. PFS is defined as the time from randomization or start of study treatment until objective tumor progression or death depending on study protocol. This paper describes the PFS concept and its analysis methods following ADaM standard to generate ADDATES and ADTTE analysis data sets. This paper also discusses some of the challenges encountered to define progression disease (PD) and censoring events. In addition, this paper explains some statistical methods that are commonly used to estimate the distribution of duration of PFS. Such methods include PROC LIFETEST procedure to provide Kaplan-Meier estimates and PROC PHREG to provide Hazard Ratio estimate.

INTRODUCTION

Clinical studies evaluating cancer treatment effect in solid tumors commonly use Response Evaluation Criteria in Solid Tumors (RECIST) for objective response on tumor assessment. Endpoints (e.g. Progression Free Survival (PFS), Objective Response Rate (ORR)) categorized by RECIST have been used as either primary or supportive endpoints for regulatory approval of new therapeutics by both FDA and EMEA.

ABOUT RECIST

RECIST was first published in 2000. In 2009, a newer version 1.1 was released to incorporate major changes. RECIST provides a standardized set of rules to evaluate response based upon changes in tumor size of target lesions with measurable disease, non-target lesions, and post baseline new lesions. The evaluation is in the categories of Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progression Disease (PD) or Not Evaluable (NE).

Along with RECIST, there are other standards for solid tumor response assessment depending on therapeutic area. Gynecological Cancer Intergroup (GCIG) criteria on the basis of CA-125 changes are used for ovarian cancer therapy; Prostate Cancer Working Group 3 (PCWG3) progression criteria are used for prostate cancer therapy; Immunotherapy RECIST (iRECIST) criteria are developed for immunotherapy.

PFS ANALYSIS – RECIST IMPLEMENTATION

There are two types of analysis for tumor response evaluation following RECIST. One is categorical analysis, including ORR, Clinical Benefit Rate (CBR), Disease Control Rate (DCR), etc. The other is time-to-event analysis, including PFS, Time to Progression (TTP), Duration of Response (DOR), etc. The time-to-event analysis portrays patients' response not only on whether an event occurred but also on when it occurred. PFS is in the time-to-event analysis category. PFS is defined as the time from randomization/treatment start date until objective tumor progression (PD) or death. This statistical endpoint is normally used as primary endpoint evaluation and it is the focus of this article.

TUMOR RESPONSE DATA COLLECTION

In order to conduct PFS analysis, the data from patient's overall tumor response is acquired in CRF or through data set transfer. The tumor response assessment is conducted either by the investigator (INV) or by the Independent Review Committee (IRC). The tumor assessment from IRC is usually used for primary endpoint to minimize bias in radiographic interpretation especially in open label studies. The assessment from INV can be used for sensitivity analysis depending on protocol and statistical analysis plan (SAP).

Below is an example of tumor response data collection in a CRF:

Was the Overall Response Performed?	Yes ☐ No ☐	1
Date of Assessment (dd/mmm/yyyy)	__ __ / __ __ __ / __ __ __ __	2
Target Lesion Response	CR ☐ PR ☐ PD ☐ SD ☐ Not Done ☐	3
Non-Target Lesion Response	CR ☐ Non CR/Non PD ☐ PD ☐ Not Done ☐	4
Did the subject have new lesions since the last tumor assessment? (Auto-populated)		5
Overall Response	CR ☐ PR ☐ PD ☐ SD ☐ Not Evaluable ☐ Not Done ☐	6

In this CRF example at a scheduled visit defined in clinical study protocol, there are 4 sections of tumor response evaluations. This CRF includes assessments of target lesion response with measurable disease, non-target lesion response, and new lesion response. The Overall Response evaluation section following RECIST 1.1 chart for patient with target (measurable) disease is in Table 1.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 1. RECIST 1.1 Chart for Patient with Target Disease

PFS CONCEPT AND CALCULATION CONSIDERATION

PFS analysis is conducted by using tumor response data from CRF as the example above shows. The tumor response data is then mapped into standard SDTM data set RS domain. Besides RS domain, TR/TU domains recording tumor result and tumor identification respectively are also a part of tumor evaluation SDTM domains. This article focuses on the usage of RS domain.

PFS value is based on a duration period between two time points for a patient considering all of tumor response assessment related factors or death. The duration calculation formula is (event/censoring date – start timepoint +1). In order to calculate PFS duration, two elements for the analysis are critical to understand. First is how to define event versus censoring (censor), second is how to define the event/censor date in order to calculate the duration from a start timepoint (randomization or start of study treatment).

EVENT VERSUS CENSORING

PFS analysis evaluates a duration period of each patient. One important element is if a patient experienced a protocol defined event or not.

When the patient has protocol defined non-censoring PD event based on RECIST overall tumor response, the patient is then considered as having a PD event (depending on protocol, some studies need to have PD confirmed); if the patient didn't have PD event but the patient died, the patient is also considered as having an event.

If a patient doesn't experience PD or death until end of study or data cutoff date, the patient is considered as a censored patient without event. If a patient terminated study prior to the scheduled tumor response evaluation visit (no post baseline tumor response assessment), the patient is also considered as a censored patient without any contribution to an event. If an interruption event occurs such as other anti-tumor treatments are introduced or patient skipped 2 scheduled tumor response visits, the tumor response assessments that follows interruption are not considered as valid anymore and hence the patient is considered as a censored patient.

ACQUIRING EVENT/CENSORING DATE

For the patient who has PD event, the event date is the date of the first occurrence of tumor response as PD. For the patient who has death event, the death date is the event date. For the censored patient who doesn't have post baseline tumor response assessment, the censoring date is the same date as the start timepoint (i.e. randomization date/first treatment date depending on study protocol). For the censored patient who has interventional tumor treatment, the censoring date is the date of the tumor response assessment prior to the date of interventional treatment. For the patient who does not experience PD nor death, nor interruption treatment/censoring event occurred, the censoring date is the last tumor assessment date until end of study or until data cutoff date.

PFS CALCULATION DEMONSTRATION

Patient with PD event

Patient 102-01101 has PD events. Data below shows tumor response evaluation of new lesion, target lesion, non-target lesion, and overall response at visit=WEEK 8 and visit=WEEK 16 in RS domain.

USUBJID	RSSEQ	RSTESTCD	RSTEST	RSSTRESC	RSDTC	VISIT
STDY101-102-01101	1	NEWLPROG	New Lesion Progression	N	2018-04-10	WEEK 8
STDY101-102-01101	2	NTRGRESP	Non-target Response	PD	2018-04-10	WEEK 8
STDY101-102-01101	3	TRGRESP	Target Response	SD	2018-04-10	WEEK 8
STDY101-102-01101	4	**OVRLRESP**	Overall Response	**PD**	2018-04-10	WEEK 8

STDY101-102-01101	5	NEWLPROG	New Lesion Progression	Y	2018-06-06	WEEK 16
STDY101-102-01101	6	NTRGRESP	Non-target Response	PD	2018-06-06	WEEK 16
STDY101-102-01101	7	TRGRESP	Target Response	SD	2018-06-06	WEEK 16
STDY101-102-01101	8	**OVRLRESP**	Overall Response	**PD**	2018-06-06	WEEK 16

Table 2. Patient 102-01101 RS Domain Data with PD Event

The RSTESTCD=OVRLRESP is for the Overall Response assessment. On RSDTC=2018-04-10 at VISIT=WEEK 8, this patient's target lesion response (RSTESTCD=TRGRESP with RSSTRESC) is SD and non-target lesion response (RSTESTCD=NTRGRESP with RSSTERC) is PD without new lesion (RSTESTCD=NEWLPROG with RSSTRESC=N). Therefore, the overall response (RSTESTCD=OVRLRESP with RSSTRESC) is PD following RECIST 1.1 standard chart with Table 1. Similarly, on RSDTC=2018-06-06 at VISIT=WEEK 16, this patient has new lesion (RSTESTCD=NEWLPROG with RSSTRESC=Y), so the overall response is PD.

In summary, as the above data shows, this patient has progression disease (PD) on RSDTC=2018-04-10. This PD is confirmed at the following scheduled visit at week 16 on 2018-06-06.

Let's say this patient is randomized on ADSL.RANDDTC=2018-02-10. The PFS value with 60 days is from randomization date to the first identified PD event date at visit=WEEK 8 on 2018-04-10 (RSDTC-RANDDT+1).

Patient with Death Event

Patient 102-01102 was randomized on 2018-02-10 and the patient had no PD events in Overall Response (RSTESTCD=OVRLRESP with RSSTRESC='SD') at visit=WEEK 8 and visit=WEEK 16 as shown below:

USUBJID	RSSEQ	RSTESTCD	RSTEST	RSSTRESC	RSDTC	VISIT
STDY101-102-01102	4	OVRLRESP	Overall Response	SD	2018-04-10	WEEK 8
STDY101-102-01102	8	OVRLRESP	Overall Response	SD	2018-06-06	WEEK 16

Table 3. Patient 102-01102 RS Domain Data without PD Event

This patient died on 2018-07-02. The PFS value is calculated as 143 days. The calculation is from randomization date to death event date on 2018-07-02 +1 (i.e. ADSL.DTHDT-ADSL.RANDDTC+1).

Patient without PD/Death Event

Patient 102-01103 was also randomized on 2018-02-10 and didn't have PD event or death, so this patient is a censored patient. This patient censoring date is on 2018-06-06 at visit=WEEK 16 since this date is the last tumor response evaluation date. The PFS value is calculated as 117 days (RSDTC – RANDDT+1).

USUBJID	RSSEQ	RSTESTCD	RSTEST	RSSTRESC	RSDTC	VISIT
STDY101-102-01103	4	OVRLRESP	Overall Response	SD	2018-04-10	WEEK 8
STDY101-102-01103	8	OVRLRESP	Overall Response	SD	2018-06-06	WEEK 16

Table 4. Patient 102-01103 RS Domain Data without PD Event

Patient with No Post Baseline Tumor Response Assessment

When a patient doesn't have any post baseline tumor response assessment, the patient is a censored patient. Let's say patient 102-01104 is randomized on 2018-02-10 and has no tumor response assessment, this patient PFS value is 1 day (ADSL.RANDDT – ADSL.RANDDT+1) with censoring date the same as randomization date since no tumor response date can be acquired.

Patient with Interruption Treatment While on Study Treatment

Patient 102-01105 was randomized on 2018-02-10 and the patient had PD event in Overall Response (RSTESTCD=OVRLRESP with RSSTRESC=PD) at visit= WEEK 24 as shown below:

USUBJID	RSSEQ	RSTESTCD	RSTEST	RSSTRESC	RSDTC	VISIT
STDY101-102-01105	4	OVRLRESP	Overall Response	SD	2018-04-10	WEEK 8
STDY101-102-01105	8	OVRLRESP	Overall Response	**SD**	2018-06-06	WEEK 16
STDY101-102-01105	12	OVRLRESP	Overall Response	**PD**	2018-08-02	WEEK 24

Table 5. Patient 102-01105 RS Domain Data with PD Event

Prior to visit=WEEK 24 visit, this patient was given a non-study anti-cancer intervention treatment on 2018-07-05. Because the intervention occurred prior to tumor response with PD, its response is no longer valid due to this unplanned treatment intervention. Therefore, this patient is a censored patient. The censoring date is the tumor assessment date (2018-06-06) at visit=WEEK 16, which is prior to the initiation of this intervention treatment date of 2018-07-05. The PFS value is 117 days (RSDTC – RANDDT+1).

TUMOR RESPONSE ADAM DATA SETS FOR PFS ANALYSIS

ADAM DATA SET ADTTE

Since PFS analysis is in the category of time-to-event analysis, it is conducted in ADaM data set ADTTE (Time-to-Event analysis data set). This ADaM data set is with Basic Data Structure (BDS). Essential variables usually are USUBJID, TRTP, STARTDT, ADT, PARAMCD, PARAM, AVAL, CNSR, EVNTDESC, and CNSDTDSC. These variables' metadata and their utilization notes are shown in the chart below.

Variable Name	*Variable Label*	*Type*	*Length*	*CDISC note*
USUBJID	Unique Subject Identifier	text	20	
TRTP	Planned Treatment	text	100	
STARTDT	Time to Event Origin Date for Subject	integer		The original date of risk for the time-to-event analysis. This is generally the time at which a subject is first at risk for the event of interest evaluation (as defined in the Protocol or Statistical Analysis Plan). For example, this may be the randomization date or the date of first study therapy exposure.
ADT	Analysis Date	Integer		Analysis date of event or censoring associated with AVAL in numeric format.
PARAMCD	Parameter Code	text	8	
PARAM	Parameter	Text	100	
AVAL	Analysis Value	integer		AVAL is the elapsed time to the event of interest from the origin. For example, if AVAL is measured

				in days, AVAL would be ADT – STARTDT or ADT – STARTDT + 1.
CNSR	Censor	integer		CNSR is a required variable for a time-to-event analysis data set, though it is a conditionally required variable with respect to the ADaM BDS. For example, CNSR = 0 for event and CNSR > 0 for censored records.
EVNTDESC	Event or Censoring Description	text	100	Describes the event of interest or an event that warrants censoring. Values for EVNTDESC will be defined in the metadata as sponsor-defined controlled terminology.
CNSDTDSC	Censor Date Description	text	100	Describes the circumstance represented by the censoring date if different from the event date that warrants censoring.

Table 6. ADTTE Metadata

Following ADTTE ADaM standard data structure, the PFS analysis results in the above example scenarios are derived in this snapshot below:

USUBJID	**PARAMCD**	**PARAM**	**CNSR**	**STARTDT**	**ADT**	**AVAL**	**EVNTDESC**	**CNSDTDSC**
STDY101-102-01101	PFS	Progression Free Survival (Days)	0	2018-02-10	2018-04-10	60	DOCUMENTED PROGRESSION	
STDY101-102-01102	PFS	Progression Free Survival (Days)	0	2018-02-10	2018-07-02	143	DEATH	
STDY101-102-01103	PFS	Progression Free Survival (Days)	**1**	2018-02-10	2018-06-06	117	COMPLETED STUDY	LAST RADIOLOGIC ASSESSMENT SHOWING NO PROGRESSION
STDY101-102-01104	PFS	Progression Free Survival (Days)	**1**	2018-02-10	2018-02-10	1	NO BASELINE ASSESSMENT	RANDOMIZATION
STDY101-102-01105	PFS	Progression Free Survival (Days)	**1**	2018-02-10	2018-06-06	117	NEW ANTI-CANCER THERAPY	LAST RADIOLOGIC ASSESSMENT PRIOR TO NEW ANTI-CANCER THERAPY

Table 7. ADTTE Sample Data Set

INTERMEDIATE DATA SET ADDATES FOR PROSTATE CANCER THERAPY

The ADTTE data set carries PFS values for each patient. The values are derived from the information in ADSL, RS domain across visits, or other ADaM data sets. The traceability gets lost in the process of only creating ADTTE data set. The values cannot provide the information on how the censoring/event date is derived unless the reviewer follows define.xml file and goes to numerous data sets to figure it out.

Using patient 102-01105 as an example, this patient is censored due to an occurrence of anti-tumor treatment, the treatment date is kept in ADCM data set; patient 102-01102 has death event, the death date is kept in ADSL data set; for all patients, the tumor response date at each visit is kept in RS domain. In order to understand where ADT=2018-06-06 is derived, the reviewer needs to look at all of RSDTC across all visits in RS domain and also needs to find the definition on how anti-tumor treatment is derived in ADCM data set. This process is tedious and confusing.

In order to fulfill the traceability's requirement and simplify ADTTE data set generation, an intermediate data set ADDATES for prostate cancer therapy was introduced in 2017 through Therapeutic Area User Guide for Prostate Cancer (TAUG-PrCa) v1.0. Similarly, for breast cancer, ADEVENT was also introduced as intermediate data set from TAUG-BrCa. This article focuses on ADDATES data structure demonstration.

ADDATES is created based on other ADaM data sets (e.g. ADSL) and SDTM domains. It contains all candidate date information in variable ADT, which supports the time-to-event analysis in ADTTE. In order to trace back to the whereabouts of the source data, variables SRCDOM, SRCVAR, SRCSEQ fulfill this purpose. In addition, variables ADTDESC and ADTDESCD provide descriptions of these dates' information. The ADDATES metadata with these variables is shown below:

Variable Name	***Variable Label***	***Type***	***Length***	***Derivation comment***
ADT	Analysis Date	integer		This is the date that the event occurred.
ADTDESC	Description of Analysis Date	text	40	This is a text description of the event of interest that occurred on ADT and at study day. This variable is restricted to $40 characters so that the value can be used as a label if the data set was transposed.
ADTDESCD	Description of Analysis Date Code	text	8	This is an 8-character code for the date. Restricting this variable to 8 characters will allow this value to be used as a variable name if the data set was transposed.
SRCDOM	Source Domain	text	8	This is the source SDTM domain or ADaM data set to which the record being used for the analysis value can be traced.
SRCVAR	Source Variable	text	8	This is the variable in the source SDTM domain or ADaM data set to which the analysis value can be traced.
SRCSEQ	Source Sequence	Integer		This is the sequence number -- SEQ or ASEQ of the row in the domain identified in the SRCDOM that relates to the analysis value being derived.

Table 8. ADDATES Metadata

Following the metadata structure from TAUG PrCa, the example patient 102-01102 and 102-01105 ADDATES data are presented below:

USUBJID	ADTDESC	ADTDESCD	ADT	RSVISIT	SRCDOM	SRCVAR	SRCSEQ	PDFL
STDY101-102-01102	Overall Response Date	OVRLDT	2018-04-10	WEEK 8	RS	RSDTC	4	
STDY101-102-01102	Overall Response Date	OVRLDT	2018-06-06	WEEK 16	RS	RSDTC	8	
STDY101-102-01102	Date of Death	DTHDT	2018-07-02		ADSL	DTHDTC	1	
STDY101-102-01105	Overall Response Date	OVRLDT	2018-04-10	WEEK 8				
STDY101-102-01105	Overall Response Date	OVRLDT	2018-06-06	WEEK 16				
STDY101-102-01105	Overall Response Date	OVRLDT	2018-08-02	WEEK 24				Y
STDY101-102-01105	Any Antineoplastic Therapy Start Date	ANTXSDT	2018-07-05		ADCM	CMSTDTC	15	

Table 9. ADDATES Sample Data Set

As the above data shows, ADDATES data set builds a bridge between ADTTE data set and data sources. The reviewer using this data set alone can pinpoint the record that is used for the analysis in ADTTE for the patient. The SRCxxx related variables help to link the record with its source data.

To help to understand the relationship among source data sets, ADDATES data set, and ADTTE data set, TAUG PrCa v 1.0 documentation provides a data structure hierarchy example.

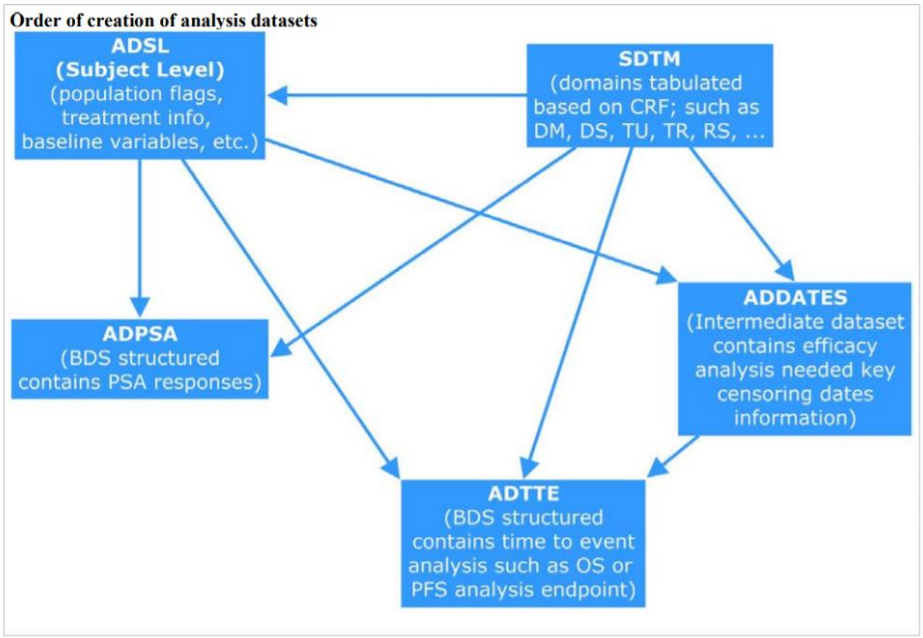

Figure 1. ADaM Data Sets Hierarchy Structure

PFS ANALYSIS CHALLENGES

Although the concept of PFS analysis is not difficult to understand, it can be a challenge when drilling down to the nitty-gritty of defining event/censoring and the event/censoring date. Various factors could affect clinical conduct and tumor assessment. Patients may be lost to follow-up, skip scheduled visits, have intervention, or have unscheduled visits. These factors affect PFS analysis components, especially when unexpected situations occur causing imbalance in treatment groups. In such cases, the result may be biased. In order to show robustness of primary PFS analysis with key assumptions, sensitivity analyses are explored. In such cases, the scope of primary and sensitivity analyses shall be clearly specified in SAP and PFS primary endpoint and sensitivity endpoints shall have its own PARAMCD/PARAM in ADTTE ADaM data set.

TAUG-PrCa document provides a list of commonly used censoring consideration items:

- Subjects who started new anti-cancer therapy prior to documented PD or death will be censored at the last radiological assessment prior to initiation of new anti-cancer therapy.
- Subjects who did not have PD or death will be censored at the date of last radiological assessment.
- Subjects who had PD or death after missing two or more consecutive scheduled radiological assessments will be censored at the last prior adequate radiological assessment.
- Subjects who had no baseline or post-baseline radiological assessment will be censored on Day 1 (either randomization date or first dose date for nonrandomized study).

Here are some scenarios in the studies that I have encountered:

MISSING SCHEDULED VISITS OR HAVING PD AT UNSCHEDULED VISITS

One of the scenarios is that the patient has a long period of time without tumor assessment due to skipping two or more scheduled visits consecutively. The patient is evaluated with PD after this gap of a long period of time. In this case, it is difficult to determine when PD has occurred due to the skipping of visits before the PD assessment. The PD event date cannot be determined, with the argument that the PD could have happened earlier if the patient hadn't missed the scheduled visit. In this scenario, the patient is censored at the last tumor assessment prior to the skipped visit which is prior to the PD event. This patient is considered as a censored patient rather than having a PD event when no death event occurred either.

Another scenario is that the patient has PD assessment at an unscheduled visit. Since the PD assessment does not occur at the protocol defined scheduled visit, whether such unscheduled PD shall be considered as an event needs to be evaluated. One approach is to move the PD date to the next scheduled visit date to follow protocol defined scheduled visit.

METHODOLOGY CHANGE IN TUMOR ASSESSMENT

CT or MRI imaging are commonly used for solid tumor assessment. The tumor response assessment depends on a consistency of imaging evaluation method. When the imaging method is changed, it causes a variation among these assessments so the results among visits are inaccurate. In such cases, the assessment after the method change of imaging would need to be censored at the last date of tumor assessment prior to such method change.

INTERVENTION

When a patient has unexpected anti-cancer treatment/procedure introduced prior to PD event, the PD event following the treatment/procedure would need to be censored. The censoring date is the date of tumor assessment prior to the intervention. Sensitivity analysis can be conducted by bypassing such intervention and still considering the PD as an event.

CLINICAL PD ASSESSMENT

Some clinical studies collect the end of treatment information with PD evaluation as a treatment termination reason in a CRF. Such PD is called clinical assessed PD because it is not a protocol-defined

evidence of radiographic progression following protocol defined tumor assessment visits. This type of PD is also considered as a PD event in a sensitivity analysis and the event date is the end of treatment date.

INV ASSESSMENT

If a clinical study has tumor response assessment from both IRC and INV, when IRC data is used as primary endpoint, the INV data is used in sensitivity analysis.

In summary, depending on protocol and clinical study conduct, SAP shall state what is the primary analysis and what are the sensitivity analyses along with censoring rules and event definition. ADTTE analysis data set spec in define.xml document shall state the rules in detail covering special cases and scenarios.

STATISTICAL METHOD FOR PFS ANALYSIS

Based on values from variable AVAL along with its PARAMCD in ADTTE ADaM data set, PFS summary table is produced. The table provides summary of PFS events, censoring reasons, and most importantly the estimate of the distribution of duration of PFS.

An example of such a reporting table is shown below. The summary includes 25%, 50% (median), and 75% percentile estimates. 95% Confidence Interval (CI) around median for each treatment group is based on Kaplan-Meier estimates using PROC LIFETEST. P-value of the two treatments comparison is based on log-rank test of PROC LIFEEST procedure. Hazard ratio with its 95% CI is based on Cox model using PROC PHREG procedure.

Progression-Free Survival - Primary Efficacy Analysis
Based on Independent Central Review Assessment
(ITT Population)

	TRT1 (N=933)	TRT2 (N=468)	Treatment Comparison (TRT1 vs. TRT2)
Status of PFS			
Events[1]	219 (23.5%)	228 (48.7%)	
Progression by IRC	187 (20.0%)	224 (47.9%)	
Death Without Documented Radiographic Progression	32 (3.4%)	4 (0.9%)	
Censored[2]	714 (76.5%)	240 (51.3%)	
No Postbaseline Assessments	37 (4.0%)	22 (4.7%)	
Missed 2 Consecutive Scans before PD	43 (4.6%)	21 (4.5%)	
New therapy prior to progression	35 (3.8%)	30 (6.4%)	
No Progresson Disease at datacut date	599 (64.2%)	167 (35.7%)	
PFS [3] (in Months)			
n	933	468	
25th Percentile	21.6	7.2	
Median (95% CI)	36.6 (37.1 , NR)	14.7 (14.2 , 15.0)	
75th Percentile	NR	33.0	
p-value [4]			<0.0001
Hazard Ratio (95% CI) [4]			0.292 (0.251 , 0.372)

NR=Not Reached.
[1]: Based on the earliest contributing event (radiographic progression or death due to any cause within 75 days after treatment discontinuation).
[2]: Patients who were not known to have had an PFS event at the time of analysis data cutoff are censored at date of last assessment showing no objective evidence of radiographic progression prior to initiation of anti-tumor treatment or two or more consecutive missed tumor assessments. [3]: Based on Kaplan-Meier estimates.
[4]: P-value is based on a log-rank test. Hazard ratio is based on a Cox regression model (with treatment as the only covariate) and is relative to TRT2 with < 1 favoring TRT1.

Table 10. PFS Report Sample

KAPLAN-MEIER CURVE AND STATISTICAL ESTIMATE WITH PROC LIFETEST

In PFS analysis, the Kaplan-Meier curve estimate is commonly used to provide estimate of treatment effect. The Kaplan-Meier curve uses PROC LIFETEST procedure. It provides a survival curve along with its estimate. The example curve for two treatments is shown below:

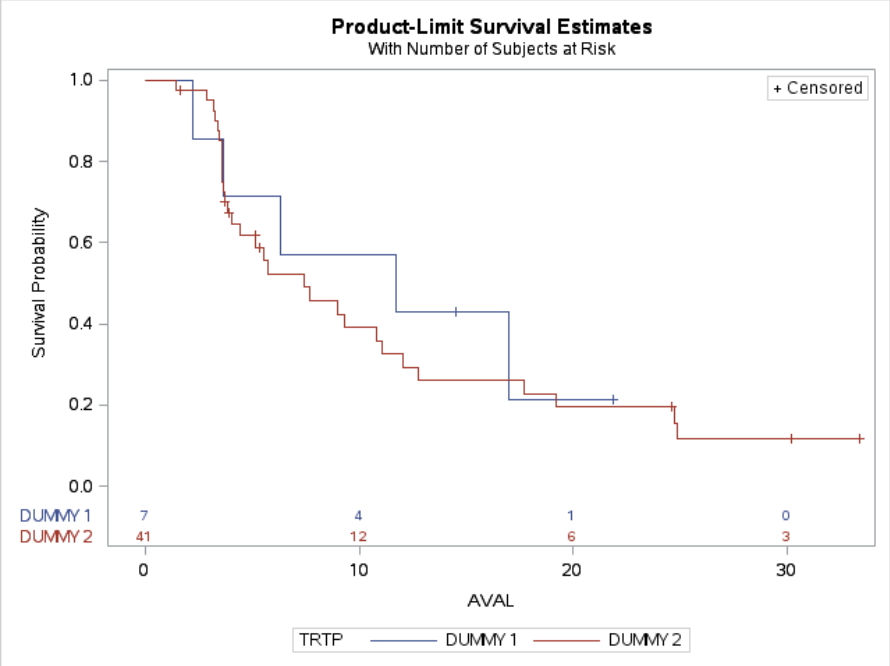

Figure 2. Kaplan-Meier Curve with Two Treatment Groups

PROC LIFETEST basic sample code using Statistical Analysis Software (SAS®)

```
ods output quartiles=qd;
proc lifetest data=adtte
plots=survival (atrisk=0 to 30 by 10);
     time aval*cnsr(1);
     strata trtp;
run;
```

The SAS output example for the estimates with 25%, 50% (median), 75% estimate along with their 95% CI is shown below for 'Dummy 1' treatment group. The median represents the time at which half of the patients have experienced the event of interest. The 25% and 75% represent when ¼ and ¾ of patients have experienced the event of interest. The output also shows 2-sided 95% confidence interval for its estimate with transform=LOGLOG.

Quartile Estimates				
	Point	95% Confidence Interval		
Percent	Estimate	Transform	[Lower	Upper]
75		LOGLOG	9.9534	
50	10.6119	LOGLOG	5.5524	
25	8.6735	LOGLOG	5.2567	10.6119

Output 1. Kaplan-Meier Estimates with Confidence Interval

P-value with Long-rank test comparing treatments sample code:

```
ods output HomTests=pval(where=(test='Log-Rank'));
proc lifetest data=adtte notable;
      time aval*cnsr(1);
      strata trtp;
run;
ods output close;
```

The SAS output is shown below with P-value as 0.6397. This P-value is stratified with TRTP estimate with log-rank test.

The LIFETEST Procedure

Testing Homogeneity of Survival Curves for AVAL over Strata

Rank Statistics	
TRTP	Log-Rank
DUMMY 1	-1.0277
DUMMY 2	1.0277

Covariance Matrix for the Log-Rank Statistics		
TRTP	DUMMY 1	DUMMY 2
DUMMY 1	4.81828	-4.81828
DUMMY 2	-4.81828	4.81828

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.2192	1	0.6397

Output 2. KAPLAN-MEIER Estimates with P-value Log Rank Test

HAZARD RATIO ESTIMATE USING PHREG WITH COX MODEL

The hazard function is a useful way to describe the distribution of PFS duration. The hazard ratio is the ratio of the hazard functions between two treatment groups. A hazard ratio of <1 indicates that the PFS is prolonged for patients randomized to group A compared with patients randomized to group B. The null and alternative hypotheses, respectively, can be written as follows:

$$H_0: \frac{\lambda_{ArmA}}{\lambda_{ArmB}} = 1 \qquad H_A: \frac{\lambda_{ArmA}}{\lambda_{ArmB}} \neq 1$$

The hazard ratio, $\lambda_{ArmA} / \lambda_{ArmB}$, is estimated using Cox regression model with SAS PHREG procedure.

PROC PHREG with 95% CI sample code:

```
Ods output parameterestimates=hzdata;
proc phreg data=adtte;
 class trtp;
 model aval*cnsr(1)=trtp/cl ties=discrete risklimit;
 hazardratio trtp;
run;
```

Ties= is an option, can also be efron, etc.

The SAS output example shows the hazard ratio=0.795 in favor of Group A prolonged PFS with 95%CI range from 0.304 to 2.079.

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
TRTP	DUMMY 1	1	-0.22890	0.49012	0.2181	0.6405	0.795	0.304	2.079	TRTP DUMMY 1

Hazard Ratios for TRTP

Description	Point Estimate	95% Wald Confidence Limits	
TRTP DUMMY 1 vs DUMMY 2	0.795	0.304	2.079

Page Break

Output 3. Proc Phreg for Hazard Ratio Estimate

CONCLUSION

There have been some PharmaSUG papers covering the topic of PFS analysis on solid tumor response. Most of them focus on statistical analysis which is used for PFS endpoint. A few papers focus on ADTTE data set. Although these papers help readers to understand the critical components of PFS analysis, they still lack understanding of the whole picture from clinical data collection to reporting. This article shows a framework of PFS analysis with a streamline from tumor response data collection to summary report presentation. It shares some considerations in order to define event/censoring rules as well as sensitivity analysis.

Most importantly, Clinical Data Interchange Standards Consortium (CDISC) requires data traceability from source data sets to derived results (e.g. ADTTE). Due to the complexity of PFS derivation rules, it becomes a challenge to satisfy such traceability requirements. This article explains the intermediate process by using ADDATES as an example to show how derived variables in ADTTE data set can be traced back to the source data sets.

REFERENCES

The ADaM Basic Data Structure for Time-to-Event Analyses Prepared by the CDISC Analysis Data Model (ADaM) Team, Version 1.0, available at http://www.cdisc.org

Therapeutic Area User Guide for Prostate Cancer Version 1.0 (Provisional), available at http://www.cdisc.org

Oncology Disease-specific Therapeutic Area Supplement to the Study Data Tabulation Model Implementation Guide Prepared by the CDISC Submission Data Standards Oncology Sub-Team,

available at http://www.cdisc.org

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, FDA, 2018, available at https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

“Progression Free Survival (PFS)”, available at https://www.phusewiki.org/wiki/index.php?title=Progression_Free_Survival_(PFS)

ACKNOWLEDGMENTS

I am grateful to PharmaSUG Section Chair Carey Smoak and my daughter Patricia Jia for their review comments and feedback of this paper.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Name: Na Li
Enterprise: Na Li Clinical Programming Services
E-mail: naliconsulting@gmail.com