Statistical Programming Analysis Considerations for Oncology Study：
A Phase III Trial of PD-1 on NSCLC Patients

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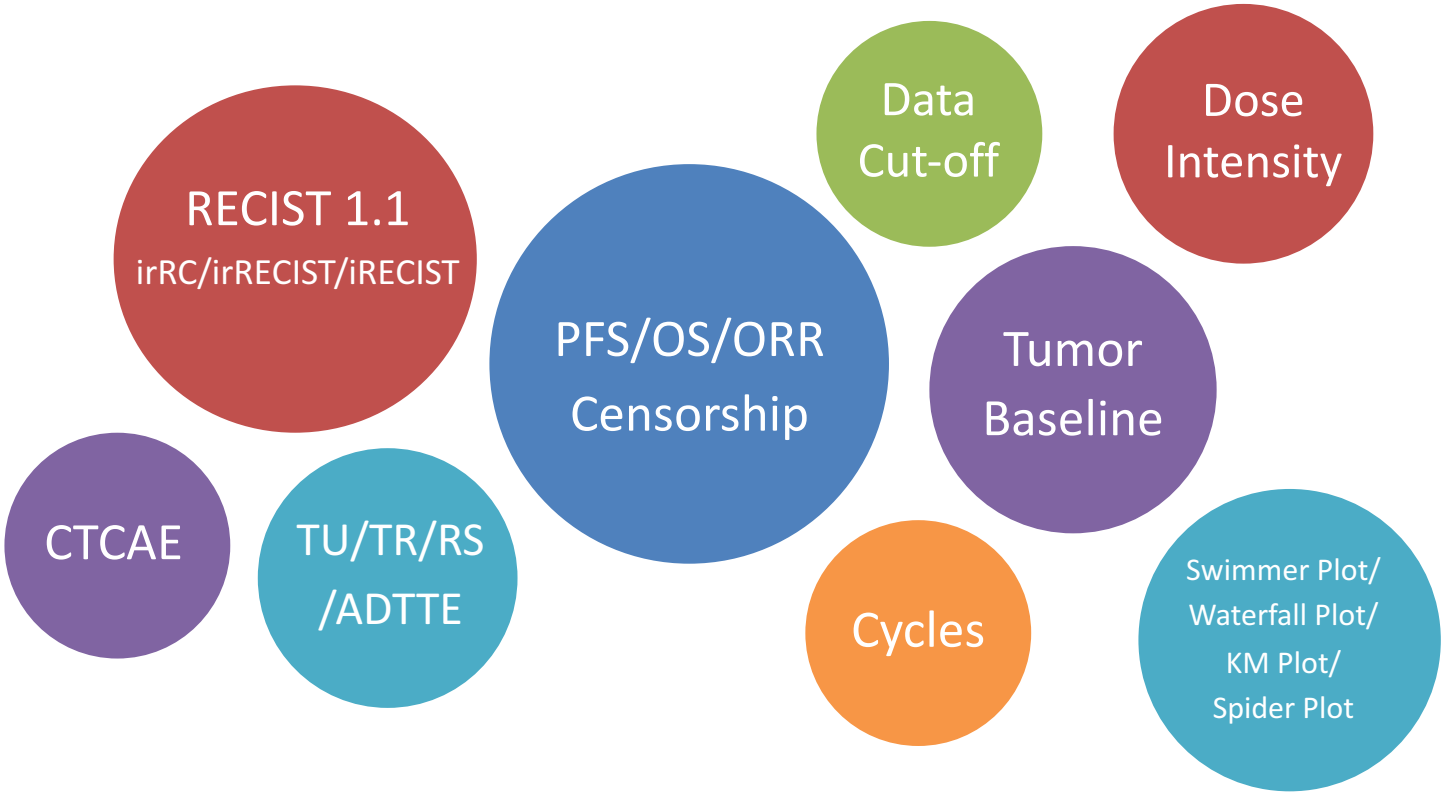
Considerations for Oncology Study



Contents

01

Calculation of Cycles

- ✓ Cycle Begin Date
- ✓ Cycle End Date
- ✓ Cycle Length and Cycle Numbers

Calculation of Cycles

- Cycle
  - A cycle is defined as the time from Cycle Day 1 to the day before the next Cycle Day 1.

- Planned Cycle Length
  - Based on schedule of activities

    (XX days for each cycle)

Calculation of Cycles

➢ Cycle Begin Date and Cycle End Date

Cycle Number	Cycle Name	Cycle Begin Date	Cycle End Date
-1	Pre-Treatment	Birthday	The first cycle (or lead-in period) start date - 1
0	Lead-In	First dose date in the lead-in period	Cycle 1 start date -1
n	Cycle n	First dose date in the cycle	Next cycle day 1 - 1
Last Cycle	Cycle n	First dose date in the cycle	**Ongoing subjects**: Last cycle start date + planned cycle length - 1
			Completed or discontinued subjects: Min (Last cycle start date + planned cycle length – 1, first new anti-cancer treatment after last dose date)
999	Follow Up	Last cycle end date + 1	Start date + Length of follow up period defined in protocol

02

Dose Intensity

- ✓ Intended Dose Intensity
- ✓ Actual Dose Intensity
- ✓ Relative Dose Intensity

Intended Dose Intensity

- Intended Dose Intensity =

  Intended Cumulative Dose Per Cycle/ Planned cycle length

Actual Dose Intensity

- By Cycle Actual Dose Intensity =
  Cumulative dose in the cycle / Actual number of *time units* in the cycle

- Overall Actual Dose Intensity =
  Overall cumulative dose / Intended treatment duration in *time unit*

Relative Dose Intensity

- By Cycle Relative Dose Intensity (%) =
  100 * By cycle actual dose intensity / Intended dose intensity

- Overall Relative Dose Intensity (%) =
  100 * Overall actual dose intensity / Intended dose intensity

03

Analysis of AE

- ✓ Time to Onset of AE
- ✓ Duration of AE
- ✓ Other Analysis: Prevalence of AE, Exposure-Time Adjusted Incidence

Time to Onset of AE

- Definition
  - Time to first onset = (AE start date - first dose date + 1).

- Analysis Method (By Preferred Terms)
  - Descriptive summaries
  - Kaplan-Meier Analysis
    - Subjects without the AE will be censored to the last cycle end date.
    - Median time to AE onset and 25% and 75% quartiles will be derived

Duration of AE

- Definition
  - Duration = (AE end date - AE start date + 1) per episode.

- Analysis Method (By Preferred Terms)
  - Descriptive summaries
  - Kaplan-Meier Analysis
    - If the AE resolved at the time of analysis, then the duration of AE is an event.
    - If a subject has an AE that was ongoing at the time of analysis, the time is censored at the last available on study visit date.
    - Median time to AE onset and 25% and 75% quartiles will be derived

04

Primary Efficacy Endpoints

- ✓ Understandings of Definitions of A Few Endpoints
- ✓ Considerations on Selection of Primary Efficacy Endpoints (PFS/OS/ORR)

Understandings of Definitions of A Few Endpoints

➢ PFS/OS/TTP

Endpoint	Definition	Event
PFS (Progression Free Survival)	It's the time from start date to date of first documentation of PD or death due to any cause, whichever occurs first.	PD or Death
OS (Overall Survival)	It's the time from start date to date of death due to any cause.	Only Death
TTP (Time to Progression)	It's the time from start date to date of first documentation of PD .	Only PD

➢ BOR/CBR/ORR/DCR

Endpoint	Definition	Considerations
BOR (Best Overall Response)	It's the best response recorded from start date until disease progression or start of new anti-cancer therapy.	CR, PR, SD, non-CR/non-PD, PD, NE
CBR (Clinical Benefit Response)	A patient with a BOR of CR or PR at any time, or non-CR/non-PD or SD for at least T weeks from start date is defined as having **Clinical Benefit Response**.	CR, PR, SD, non-CR/non-PD
ORR (Objective Response Rate)	It's the Percentage of patients with complete response (CR) or partial response (PR) for best overall response according to RECIST (1.1)	CR, PR
DCR (Disease Control Rate)	**DC rate at T weeks** could be calculated based on the percentage of patients with a BOR of CR at T weeks, PR at T weeks, non-CR/non-PD for at least T weeks or SD for at least T weeks.	CR, PR, SD, non-CR/non-PD

Considerations on Selection of Primary Efficacy Endpoints (PFS/OS/ORR)

Endpoint	Advantage	Disadvantage	Regulatory Evidence
PFS	1. Smaller sample size and shorter follow-up necessary compared with survival studies 2. Measurement of stable disease included 3. Not affected by crossover or subsequent therapies 4. Generally based on objective and quantitative assessment	1. Not statistically validated as surrogate for survival in all settings 2. Not precisely measured; subject to assessment bias particularly in open-label studies 3. Definitions vary among studies 4. Frequent radiological or other assessments 5. Involves balanced timing of assessments among treatment arms	Surrogate for accelerated approval or regular approval
OS	1. Universally accepted direct measure of benefit 2. Easily measured 3. Precisely measured	1. May involve larger studies 2. May be affected by crossover therapy and sequential therapy 3. Includes non-cancer deaths	Clinical benefit for regular approval
ORR	1. Can be assessed in single-arm studies Assessed earlier and in smaller studies compared with survival studies 2. Effect attributable to drug, not natural history	1. Not a direct measure of benefit 2. Not a comprehensive measure of drug activity 3. Only a subset of patients who benefit	Surrogate for accelerated approval or regular approval

05

Questionnaires

- ✓ EORTC QLQ-C30
- ✓ EORTC QLQ-LC13
- ✓ EQ-5D

EORTC QLQ-C30

➢ Definition

- A Core Quality of Life Questionnaire
- The EORTC QLQ-C30 Consists of 30 Questions

We are interested in some things about you and your health. Please answer all of the questions yourself by checking (x) the box that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or suitcase?	☐	☐	☐	☐
2. Do you have any trouble taking a long walk?	☐	☐	☐	☐
3. Do you have trouble taking a short walk outside of the house?	☐	☐	☐	☐
4. Do you need to stay in bed or a chair during the day?	☐	☐	☐	☐
5. Do you need help with eating, dressing, washing yourself or using the toilet?	☐	☐	☐	☐

EORTC QLQ-LC13

➢ Definition

- A 13-item Lung Cancer-specific Questionnaire

EORTC QLQ - LC13 (LUNG CANCER):

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week . Please answer by checking (x) the box that best applies you.

During the past week:	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
31. How much did you cough?	☐	☐	☐	☐
32. Did you cough up blood?	☐	☐	☐	☐
33. Were you short of breath when you rested?	☐	☐	☐	☐
34. Were you short of breath when you walked?	☐	☐	☐	☐
35. Were you short of breath when you climbed stairs?	☐	☐	☐	☐

EQ-5D

➢ Definition

- A validated and reliable self-report preference-based measure to assess health-related quality of life

By placing a check mark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Statistical Analysis

Questionnaire	Derived Endpoint	Analysis Method
All the Three Questionnaires	The scores of all items	Descriptive analysis
	The number and proportion of patients who improved, worsened, or remained stable for all items	Categorical analysis
EORTC QLQ-C30 and QLQ-LC13	TTD (time to deterioration) of pain, dyspnea or cough symptoms	Kaplan-Meier analysis
	Rates of improvement in pre-specified symptoms (pain in chest, dyspnea, and cough)	Categorical analysis
EQ-5D	Proportions of patients reported having “no”, “some”, or “extreme”	Categorical analysis

06

Censor Criteria

- ✓ Rules for PFS Censoring
- ✓ Rules for OS/AE Censoring

Rules for PFS Censoring

- Event
  - Objective progression
  - Death without objective progression
- Censor

Situations for Censorship	Censor Date
No adequate baseline assessments	Start date
No on-study disease assessments unless death occurred prior to the first planned assessment (in which case the death is an event)	
Given new anti-cancer treatment prior to tumor progression	Date of last objective disease assessment documenting no progression prior to the new treatment
Withdrew consent for follow-up	Date of the last objective disease assessment that verified lack of disease progression
Lost to follow-up	
In follow-up for progression	
Unacceptable gap between PD or Death to the most recent prior adequate assessment	Date of the last objective disease assessment that verified lack of disease progression

Rules for OS Censoring

- Event
  - Death due to any cause

- Censor
  - Patients last known to be alive/contact are censored at date of last alive/contact.

Rules for AE Censoring

- Time to Onset of AE
  - Event: Occurrence of AE
  - Censor: Subjects without the AE will be censored to the last cycle end date.

- Duration of AE
  - Event: AE is resolved
  - Censor: If a subject has an AE that was ongoing at the time of analysis, the time is censored at the last available on study visit date.

07

Immune-Related Response Criteria

- ✓ irRC, irRECIST, Irecist Comparison
- ✓ Data Structure

Immune-related Response Criteria

- RECIST1.1 Remains the Gold Standard in Solid Tumors
  - However, new lesions or flare equals progression disease under RECIST1.1 guidelines
  - Inaccurate interpretation of response can result in premature termination of therapy and patient removal from a trial
- Need New Response Criteria
  - Immune-related response criteria (irRC), 2009
    - Based on WHO criteria
  - Immune-related RECIST (irRECIST), 2013
    - Combines elements of irRC and RECIST
  - Immune RECISIT (iRECIST), 2017
    - Standardizes and validates immune response criteria
  - All account for novel response patterns seen with immunotherapies

irRC, irRECIST, iRECIST Comparison

- All Account for Delayed Response and Flare Effect by Repeat Imaging up to 12 Weeks after Treatment
- All Allow for the Presence of Lesions

irRC

- ✓ Bidimensional measurements (Longest diameter X the longest perpendicular diameter)
- ✓ **Rarely used today**

irRECIST

- ✓ Unidimensional measurements (longest diameter) have been shown to have less variability
- ✓ PD thresholds for irRECIST and RECIST are aligned, allowing for comparisons to be made between trials and to historical data
- ✓ **Most trials today evaluate response using irRECIST and RECIST 1.1**

irRECIST

- ✓ Unidimensional measurements (longest diameter)
- ✓ PD thresholds for iRECIST and RECIST are aligned
- ✓ Progression confirmation rules are defined
- ✓ Resetting the bar if PD is followed at the next TP by tumor shrinkage (iUPD must occur again)
- ✓ **Will be most used going forward**

Data Structure

- SDTM Dataset of RS in CDISC Standards
- Adam Dataset of ADRS in CDISC Standards
- Different Data from Different Response Criteria Can be Set Together Using Variable RSCAT to Differentiate

08

Practice

- ✓ CDISC Standards: TU, TR, RS / ADTTE
- ✓ Examples

CDISC Standards: TU, TR, RS / ADTTE

- TU - Data that Uniquely Identifies Tumors
- TR - Tumor Measurements
- RS - Response Evaluations Determined from the Data in TR
  - Data from Other Sources (in Other SDTM domains) Might also Be Used in An Assessment of Response.
- ADTTE - Time to Event Endpoints
  - It Could Contain:
    PFS/OS/TTF/TTP/TTD/RFS/Time to onset of AE/
    Duration of response/Duration of AE, etc

Example for TU

TULNKID	TUTESTCD	TUTEST	TUORRES	TUSTRESC	TULOC	TULAT	TUMETHOD
TO3	TUMIDENT	肿瘤识别	TARGET	TARGET	胸壁	右侧胸壁软组织	螺旋CT增强
NTO1	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	骨	骨（左髂骨及右第8肋骨）	螺旋CT增强
NTO2	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	肝	肝脏	螺旋CT增强
TO3	TUMIDENT	肿瘤识别	TARGET	TARGET	胸壁	右侧胸壁软组织	螺旋CT增强
NTO1	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	肺	双肺	螺旋CT增强
TO1	TUMIDENT	肿瘤识别	TARGET	TARGET	肺	左肺	螺旋CT增强
NTO2	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	淋巴结	多发淋巴结	螺旋CT增强
TO2	TUMIDENT	肿瘤识别	TARGET	TARGET	肺	左肺	螺旋CT增强
NTO1	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	肺	双肺	螺旋CT增强
TO1	TUMIDENT	肿瘤识别	TARGET	TARGET	肺	左肺	螺旋CT增强
NTO2	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	淋巴结	多发淋巴结	螺旋CT增强
TO2	TUMIDENT	肿瘤识别	TARGET	TARGET	肺	左肺	螺旋CT增强
NTO1	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	肺	双肺	螺旋CT增强
TO1	TUMIDENT	肿瘤识别	TARGET	TARGET	肺	左肺	螺旋CT增强
NTO2	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	肝	肝脏	螺旋CT增强
TO2	TUMIDENT	肿瘤识别	TARGET	TARGET	肺	右肺	螺旋CT增强
NTO3	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	淋巴结	多发淋巴结	螺旋CT增强
TO3	TUMIDENT	肿瘤识别	TARGET	TARGET	肝	左肝	螺旋CT增强
NTO4	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	腹水	腹水	螺旋CT增强
TO4	TUMIDENT	肿瘤识别	TARGET	TARGET	肝	右肝	螺旋CT增强
NTO5	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	骨	多发	螺旋CT增强
NTO6	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	胸水	右侧胸水	螺旋CT增强
NEWO1	TUMIDENT	肿瘤识别	NEW	NEW	肝	肝脏	螺旋CT平扫
NTO1	TUMIDENT	肿瘤识别	NON-TARGET	NON-TARGET	肺	双肺	螺旋CT平扫
TO1	TUMIDENT	肿瘤识别	TARGET	TARGET	肺	左肺	螺旋CT平扫

Example for TR

TRGRPID	TRLNKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	TRSTRESC	TRSTRESN	TRSTRES	TRMETHOD
TARGET	R1-TO1	DIAMETER	直径	80	mm	80	80	mm	螺旋CT增强
TARGET	R1-TO1	DIAMETER	直径	110	mm	110	110	mm	螺旋CT增强
TARGET		SUMDIAM	直径总和	72.0	mm	72.0	72	mm	
TARGET		SUMDIAM	直径总和	110.0	mm	110.0	110	mm	
NON-TARGET	R1-NTO1	TUMSTATE	肿瘤状况	存在		存在	.		螺旋CT增强
NEW	R1-NEWO1	TUMSTATE	肿瘤状况	明确的		明确的	.		螺旋CT增强
NEW	R1-NEWO2	TUMSTATE	肿瘤状况	明确的		明确的	.		螺旋CT增强
NEW	R1-NEWO3	TUMSTATE	肿瘤状况	明确的		明确的	.		螺旋CT增强
NON-TARGET	R1-NTO1	TUMSTATE	肿瘤状况	存在		存在	.		螺旋CT增强
TARGET	R1-TO1	DIAMETER	直径	19	mm	19	19	mm	螺旋CT增强
TARGET	R1-TO2	DIAMETER	直径	16	mm	16	16	mm	腹部增强CT
TARGET	R1-TO3	DIAMETER	直径	10	mm	10	10	mm	胸部增强CT
TARGET	R1-TO1	DIAMETER	直径	24	mm	24	24	mm	螺旋CT增强
TARGET	R1-TO2	DIAMETER	直径	20	mm	20	20	mm	螺旋CT增强
TARGET	R1-TO3	DIAMETER	直径	12	mm	12	12	mm	螺旋CT增强
TARGET		SUMDIAM	直径总和	45.0	mm	45.0	45	mm	
NON-TARGET	R1-NTO1	TUMSTATE	肿瘤状况	存在		存在	.		螺旋CT增强
NON-TARGET	R1-NTO2	TUMSTATE	肿瘤状况	存在		存在	.		螺旋CT增强
TARGET	R1-TO1	DIAMETER	直径	12	mm	12	12	mm	螺旋CT增强
TARGET	R1-TO2	DIAMETER	直径	28	mm	28	28	mm	螺旋CT增强
TARGET	R1-TO1	DIAMETER	直径	54	mm	54	54	mm	螺旋CT增强
TARGET	R1-TO2	DIAMETER	直径	35	mm	35	35	mm	螺旋CT增强
TARGET		SUMDIAM	直径总和	40.0	mm	40.0	40	mm	
TARGET		SUMDIAM	直径总和	89.0	mm	89.0	89	mm	
NON-TARGET	R1-NTO1	TUMSTATE	肿瘤状况	存在		存在	.		螺旋CT增强
NON-TARGET	R1-NTO2	TUMSTATE	肿瘤状况	存在		存在	.		螺旋CT增强
NEW	R1-NEWO1	TUMSTATE	肿瘤状况	明确的		明确的	.		螺旋CT增强

Example for RS

RSLNKGRP	RSTESTCD	RSTEST	RSCAT	RSORRES	RSSTRESC	RSSTAT	RSREASND
A04	NEWLPROG	新病灶发生	临床评估	明确的	明确的		
A02	NTRGRESP	非靶病灶评估	临床评估	非CR/非PD	非CR/非PD		
A03	NTRGRESP	非靶病灶评估	临床评估	非CR/非PD	非CR/非PD		
A02	OVRLRESP	疗效总评估	临床评估	SD	SD		
A03	OVRLRESP	疗效总评估	临床评估	SD	SD		
A02	TRGRESP	靶病灶评估	临床评估	SD	SD		
A03	TRGRESP	靶病灶评估	临床评估	SD	SD		
A04	TRGRESP	靶病灶评估	临床评估	SD	SD		
A02	NTRGRESP	非靶病灶评估	临床评估	非CR/非PD	非CR/非PD		
A03	NTRGRESP	非靶病灶评估	临床评估	非CR/非PD	非CR/非PD		
A04	NTRGRESP	非靶病灶评估	临床评估	非CR/非PD	非CR/非PD		
A05	NTRGRESP	非靶病灶评估	临床评估	非CR/非PD	非CR/非PD		
A06	NTRGRESP	非靶病灶评估	临床评估	非CR/非PD	非CR/非PD		
A02	OVRLRESP	疗效总评估	临床评估	PR	PR		
A03	OVRLRESP	疗效总评估	临床评估	PR	PR		
A04	OVRLRESP	疗效总评估	临床评估	PR	PR		
A05	OVRLRESP	疗效总评估	临床评估	PR	PR		
A06	OVRLRESP	疗效总评估	临床评估	PR	PR		
A02	TRGRESP	靶病灶评估	临床评估	PR	PR		
A03	TRGRESP	靶病灶评估	临床评估	PR	PR		
A04	TRGRESP	靶病灶评估	临床评估	PR	PR		
A05	TRGRESP	靶病灶评估	临床评估	PR	PR		
A06	TRGRESP	靶病灶评估	临床评估	PR	PR		
A02	NEWLPROG	新病灶发生	临床评估	明确的	明确的		
A02	NEWLPROG	新病灶发生	临床评估	明确的	明确的		
A02	TRGRESP	靶病灶评估	临床评估	SD	SD		
A02	NEWLPROG	新病灶发生	临床评估	明确的	明确的		
A02	NTRGRESP	非靶病灶评估	临床评估	不能评估	不能评估	ND	患者突然出现病情变化，无法评估
A02	TRGRESP	靶病灶评估	临床评估	未知	未知	ND	患者突然出现病情变化，无法评估
A02	NTRGRESP	非靶病灶评估	临床评估	不能评估	不能评估	ND	没有非靶病灶
A03	NTRGRESP	非靶病灶评估	临床评估	不能评估	不能评估	ND	没有非靶病灶

Example for ADTTE

PARAM	PARAMCD	AVAL	ADT	STARTDT	CNSR	EVNTDESC	CNSDTDSC
Progression Free Survival (months)	PFS	4.8	2017-04-14	2016-11-21	0	DOCUMENTED PROGRESSION	
Time to Death (months)	TTD	10.8	2017-10-16	2016-11-21	1	STILL ALIVE	LAST KNOWN ALIVE DATE
Time to Progression (months)	TTP	4.8	2017-04-14	2016-11-21	0	DOCUMENTED PROGRESSION	
Duration of Response (weeks)	DOR	25.6	2017-07-20	2017-01-23	1	NO RELAPSE RECORDED	LAST ASSESSMENT SHOWING NO PROGRESSION
Progression Free Survival (months)	PFS	7.9	2017-07-20	2016-11-23	1	NO DOCUMENTED PROGRESSION	LAST ASSESSMENT SHOWING NO PD
Time to Death (months)	TTD	11.1	2017-10-27	2016-11-23	1	STILL ALIVE	LAST KNOWN ALIVE DATE
Time to Progression (months)	TTP	7.9	2017-07-20	2016-11-23	1	NO DOCUMENTED PROGRESSION	LAST ASSESSMENT DATE SHOWING NO PD
Duration of Response (weeks)	DOR	.	.	.	.	NO POSITIVE RESPONSE DURING THE STUDY and NO POST BASELINE TUMOR ASSESSMENT	
Progression Free Survival (months)	PFS	0	2016-12-02	2016-12-02	1	NO POST BASELINE TUMOR ASSESSMENT	RANDOMIZATION DATE
Time to Death (months)	TTD	9.4	2017-09-13	2016-12-02	1	WITHDRAWAL BY SUBJECT	WITHDRAWAL DATE
Time to Progression (months)	TTP	0	2016-12-02	2016-12-02	1	NO POST BASELINE TUMOR ASSESSMENT	RANDOMIZATION DATE
Duration of Response (weeks)	DOR	.	.	.	.	NO POSITIVE RESPONSE DURING THE STUDY	
Progression Free Survival (months)	PFS	0.6	2016-12-23	2016-12-07	0	DOCUMENTED PROGRESSION	
Time to Death (months)	TTD	0.9	2017-01-01	2016-12-07	0	DEATH	
Time to Progression (months)	TTP	0.6	2016-12-23	2016-12-07	0	DOCUMENTED PROGRESSION	

THANKS