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Two different use cases to obtain best responses using RECIST 1.1: SDTM and ADaM

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ABSTRACT

Each therapeutic area has its own unique data collection and analysis. Especially, Oncology has a unique way to collect and analyze the data and one of unique data points in oncology study is best response. The paper will be based on Solid Tumor and RECIST 1.1, and it will show use cases on how best response will be collected in SDTM domains and derived in ADaM datasets using RECIST 1.1 in solid tumor oncology study.

The paper will provide the brief introduction of RECIST 1.1 such as legions type (i.e., target, non-target and new) and their selection criteria(e.g., size and number). The paper will provide the practical application on how tumor measurements for target and non-target lesions are collected in TR domain, how those measurement are assessed according to RECIST 1.1, and eventually how responses are represented in RS domain based on the assessment from tumor measurements.

We will also put in prospective a pictorial road map on which way we choose to derive responses to give a prospective to the user and the process to get from beginning to end objective. This paper will also discuss a use case where the visit level response are been derived programmatically in ADaM and perform a sensitive analysis in comparison to investigator provides visit level response to SDTM RS domain. This case study will help user identify the differences between both the methodologies and help answer any anomalies from investigator inference prospective vs analytical calculations by the programmer.

INTRODUCTION OF ONCOLOGY CLINICAL TRIAL STUDIES

There are three types of oncology clinical trial studies: Solid Tumor, Lymphoma and Leukemia Response.
The solid tumor studies usually follow RECIST 1.0 or 1.1 on tumor response evaluation criteria, Lymphoma studies usually follow Cheson 1997 or 2007, and Leukemia studies follow the study-specific criteria.

RECIST 1.1

INTRODUCTION OF RECIST

RECIST is Response Evaluation Criteria in Solid Tumor and there are two versions- 1.0 and 1.1. Most recent studies follow the recent version, RECIST 1.1, released on October 2008. The paper will follow RECIST 1.1.

LESION

A lesion is any abnormality in the tissue of an organism and can be described as a cut, an injury, an infected area or a tumor. In oncology study, lesions are tumors. They are divided into three types for the purpose of their measurements.

- Target lesions
- Non-target lesions
- New lesions

In clinical trials, lesions are categorized as measurable or non-measurable at baseline. A lesion is considered measurable if its length of longest diameter is longer than 10 mm by CT scan, 10 mm caliper measurement by clinical exam or 20 mm by Chest X-ray. A lesion is considered non-measurable if its length is less than 10 mm by CT scan or truly non-measurable. The measurement of lesions helps to determine whether lesions are target or non-target at baseline in oncology studies.

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TARGET LESIONS

In clinical trials following RECITS 1.1, target lesions selection at baseline follows as

- Measurable
- 5 lesions total
- Maximum of 2 lesions per organ
- Representing all involved organs
- Quantitative measurements
    - Longest diameter of lesions
    - Short axis of Lymph nodes
    - Sum of diameters (both lesions and lymph nodes)

NON TARGET LESIONS
Non-target lesions selection at baseline follows as

- All other lesions beside target lesions
- Qualitative measurements – present, absent or unequivocal progression.

NEW LESIONS
New lesions at post-baseline follows as

- any lesions that are newly found at post-baseline.
- Either quantitative or qualitative measurements

RESPONSE CRITERIA
There are six types of responses of tumor lesions to treatments

- CR – Complete Response
- PR – Partial Response
- SD – Stable Disease
- PD – Progression Disease
- NE – Not Evaluable
- NonCR/NonPD - Non Complete Response/Non Progressive Disease

And, overall response criteria are determined by the responses of target lesions, non-target lesions and new lesions.

RESPONSE CRITERIA OF TARGET LESIONS

- Complete Response (CR) – Disappearance of all target lesions
- Partial Response (PR) – 30 % decrease in the sum of diameters from baseline
- Stable Disease (SD)
- Progression Disease (PD) – 20 % increase from nadir, the smallest sum of diameter (at least more than 5 mm)
- Not Evaluable (NE)

RESPONSE CRITERIA OF NON TARGET LESIONS

- Complete Response (CR) – Disappearance of all non-target lesions
- Non Complete Response/Non Progressive Disease (NonCR/NonPD)
- Progression Disease (PD) - Unequivocal progression (an overall level of substantial worsening in non-target diseases)
- Not Evaluable (NE)

OVERALL RESPONSE AT GIVEN TIME POINTS
According to response criteria of target lesions, non-target lesions and new lesions, overall responses at given time point can be derived.

Table 1 - Time point response: patients with target (+/-non-target) disease in RECIST 1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	NonCR/NonPD	No	PR
CR	NE	No	PR
PR	NonCR/NonPD or NE	No	PR
SD	NonCR/NonPD or NE	No	SD
NE	NonCR/NonPD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

BEST OVERALL RESPONSE
Best Overall Response for each subject can be derived in two different ways.

CR or PR confirmation is not required
The best one will be selected from all the overall responses.

CR or PR confirmation is required
Usually, the confirmation is required for non-randomized trials where response is the primary endpoint so that the responses are not measurement errors. The repeat assessment will be performed after the criteria for response are first met. The interval should be longer than 4 weeks, but it could depend on study.

Table 2 – Best overall response when confirmation of CR and PR required in RECIST 1.1

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR
CR	SD	SD provided minimum criteria for SD duration met, PD
CR	PD	SD provided minimum criteria for SD duration met, PD
CR	NE	SD provided minimum criteria for SD duration met, PD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, PD
PR	NE	SD provided minimum criteria for SD duration met, NE
NE	NE	NE

Stable Disease duration is usually from the start of the treatment (in randomization trials, from date of randomization) to the progression disease.

ENDPOINS IN SOLID TUMOR

The most common efficacy end points in Solid Tumor studies are

- OS (Overall Survival)
  - Time from randomization until death.
  - The most common and reliable cancer endpoint.
- ORR (Objective Response Rate)
  - Rate of partial and complete responses to non-responses.
  - until 1970s, FDA usually approved cancer drugs based on ORR.
- DFS (Disease Free Survival)
  - Time from randomization until death or recurrence of tumor.
- PFS (Progression Free Survival)
  - Time from randomization until objective tumor progression or death
  - Death is NOT censored.
- TTP (Time to Progression)
  - Time from randomization until objective tumor progression
  - Death is censored.

ORR, DFS, PFS and TTP are based on tumor assessments.

CIDSC TUMOR DOMAIN

CDISC recently developed Oncology-related domains both in SDTM and ADaM.

SDTM

- TU : Tumor Identification
- TR : Tumor Results
- RS : Response

ADaM

- ADTTE : Time to Event ADaM datasets

AN EXAMPLE USING RECIST 1.1 AND NEW TUMOR CDISC DOMAIN

Below examples are the randomized and open label Phase II study. It measures the solid tumor using RECIST 1.1 and has 5 cycles. The primary efficacy is objective response rate. At screening, there are 3 target and 3 non-target lesions

- Table 3 will introduce SDTM tumor domains (TU, TR, RS) and how SDTM domains are used to collect tumor results and responses.
- Table 4 will show how ADaM datasets are used to determine tumor results for response criteria.
- Table 5 will show how ADaM datasets are used to determine responses from tumor results ADaM datasets.
- Table 6 will show how objective response parameter is derived using ADaM datasets for Objective Response Rate (ORR)

Table 3.1 - SDTM TU (Tumor identification) dataset

USUBJID	TULINKID	TUTESTCD	TUTEST	TUORRES	TULOC	TUMETHOD
001-01-001	T01	TUMIDENT	Tumor Identification	TARGET	ABODOMEN	CT SCAN
001-01-001	T02	TUMIDENT	Tumor Identification	TARGET	ABODOMEN	CT SCAN
001-01-001	T03	TUMIDENT	Tumor Identification	TARGET	THYROID	CT SCAN
001-01-001	NT01	TUMIDENT	Tumor Identification	NON-TARGET	LIVER	CT SCAN
001-01-001	NT02	TUMIDENT	Tumor Identification	NON-TARGET	KIDNEY	CT SCAN
001-01-001	NT03	TUMIDENT	Tumor Identification	NON-TARGET	SPLEEN	CT SCAN

Key points to note in the example are:

- Subject 001 has 3 target and 3 non-target lesions throughout the studies.

Table 3.2 - SDTM RELREC (Related Records) dataset

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
001	TU		TULINKID		ONE	
001	TR		TRLINKID		MANY	

Key points to note in the example are:

- TU.TULINKID is connected to TR.TRLINKID

Table 3.3 - SDTM TR (Tumor Results) dataset

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT	TRDTC	TRBLFL
001-01-001	Target	T01	LDIAM	Longest Diameter	Measurement	23	mm	Screening	2011-01-01	Y
001-01-001	Target	T02	LDIAM	Longest Diameter	Measurement	22	mm	Screening	2011-01-01	Y
001-01-001	Target	T03	LDIAM	Longest Diameter	Measurement	25	mm	Screening	2011-01-01	Y
001-01-001	Target		SUMDIAM	Sum of Diameter	Measurement	70	mm	Screening	2011-01-01	Y

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT	TRDTC	TRBLFL
001-01-001	Non-Target	NT01	TUMSTATE	Tumor State	Qualitative	PRESENT		Screening	2011-01-01	Y
001-01-001	Non-Target	NT02	TUMSTATE	Tumor State	Qualitative	PRESENT		Screening	2011-01-01	Y
001-01-001	Non-Target	NT03	TUMSTATE	Tumor State	Qualitative	PRESENT		Screening	2011-01-01	Y
001-01-001	Target	T01	LDIAM	Longest Diameter	Measurement	10	mm	Cycle 1	2011-03-01	
001-01-001	Target	T02	LDIAM	Longest Diameter	Measurement	10	mm	Cycle 1	2011-03-01	
001-01-001	Target	T03	LDIAM	Longest Diameter	Measurement	15	mm	Cycle 1	2011-03-01	
001-01-001	Target		SUMDIAM	Sum of Diameter	Measurement	35	mm	Cycle 1	2011-03-01	
001-01-001	Non-Target	NT01	TUMSTATE	Tumor State	Qualitative	PRESENT		Cycle 1	2011-03-01	
001-01-001	Non-Target	NT02	TUMSTATE	Tumor State	Qualitative	PRESENT		Cycle 1	2011-03-01	
001-01-001	Non-Target	NT03	TUMSTATE	Tumor State	Qualitative	PRESENT		Cycle 1	2011-03-01	

Key points to note in the example are:

- Target lesions were measured quantitatively and non-target lesions qualitatively.
- Row 1 to 3 : There are three target lesions at Baseline.
- Row 5 to 7 : There are three non-target lesions at Baseline.
- Row 8 to 10 : There are still three target lesions at Cycle 1.
- Row 12 to 14 : There are still three non-target lesions at Cycle 1.
- Row 4 and 10 : Sum of Diameter was collected, not derived.
- Row 11 : Sum of Diameter in target lesions changed from 70 mm at Screening to 35 mm at Cycle 1.
- Row 12 to 14 : No changes in non-target lesions.
- No new lesions were found at Cycle 1.

Table 3.4 - SDTM RS (Response) dataset

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSDTC	RSSEQ
001-01-001	TRGRESP	Target Response	RECIST 1.1	PR	Cycle 1	2011-03-01	1
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 1	2011-03-01	2
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PR	Cycle 1	2011-03-01	3
001-01-001	TRGRESP	Target Response	RECIST 1.1	SD	Cycle 2	2011-06-01	4
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 2	2011-06-01	5
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	SD	Cycle 2	2011-06-01	6

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSDTC	RSSEQ
001-01-001	TRGRESP	Target Response	RECIST 1.1	SD	Cycle 3	2011-09-01	7
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 3	2011-09-01	8
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	SD	Cycle 3	2011-09-01	9
001-01-001	TRGRESP	Target Response	RECIST 1.1	PR	Cycle 4	2011-12-01	10
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 4	2011-12-01	11
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PR	Cycle 4	2011-12-01	12
001-01-001	TRGRESP	Target Response	RECIST 1.1	PD	Cycle 5	2012-03-01	13
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 5	2012-03-01	14
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PD	Cycle 5	2012-03-01	15

Key points to note in the example are:

- Row 1 : The sum of diameter of target lesions changed from 70 mm to 35 mm, 50 % decrease in sum of diameter at Cycle 1 from baseline. So, it is PR for target lesions.
- Row 2 : At baseline, 3 non-target lesions exist and at Cycle 1, 3 non-target lesions still exist, so it is NonCR/NonPD at Cycle 1.
- Row 3 : According to table 1, if target lesion is PR, non-target lesion is NonPD/NonCR and no new lesions, then overall response is PR at Cycle 1.
- Row 6, 9, 12 and 15 also follow the same patterns. Overall responses are derived according to table 1.

Table 3.5 - SDTM RS (Response) dataset when the confirmation is not needed.

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSDTC	RSSEQ
001-01-001	BESTRESP	Best Overall Response	RECIST 1.1	PR	End of Study	2011-06-01	16

Key point to note in the example is that the investigator selects the best response from all the responses(PR, SD, SD, PR, PD) from Cycle 1 to Cycle 5.

Table 3.6 - SDTM RS (Response) dataset when the confirmation is needed.

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSDTC	RSSEQ
001-01-001	BESTRESP	Best Overall Response	RECIST 1.1	SD	End of Study	2011-06-01	16

Key point to note in the example is that the investigator selects the best response using table 2.

- PR at Cycle 1 and SD at Cycle 2, so SD at Cycle 1
- SD at Cycle 2 and SD at Cycle 3, so SD at Cycle 2
- SD at Cycle 3 and PR at Cycle 4, so SD at Cycle 3
- PR at Cycle 4 and PD at Cycle 5, so SD at Cycle 4
- PD at Cycle 5, so PD at Cycle 5
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ADaM DATASETS FOR TUMOR RESULTS AND OVERALL RESPONSE

All the data in SDTM RS (Response) are collected in eCRF, but sometime the programmers should derive response data or the programmers should check response data that are determined by the investigator. The following table 4.1 to 4.4 will show how the programmers can derive tumor results data using ADaM dataset and the table 5.1 to 5.3 will show how the programmers determine the overall response using ADaM dataset.

ADTR (Tumor Results Analysis Dataset)

ADTR dataset uses CRIT1 to CRIT6 to indicate the responses.

Table 4.1 - Analysis Dataset Metadata for ADTR

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADTR	Tumor Results Analysis Data	adtr.xpt	one record per subject per parameter per analysis visit	USUBJID, PARAMCD, AVISITN	BDS	c-adtr.txt

Table 4.2 - Analysis Variable Metadata including Analysis Parameter Value-Level Metadata for ADTR

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
ADTR	*ALL*	USUBJID	Unique Subject Identifier	text	$20		ADSL.USUBJID
ADTR	*ALL*	SITEID	Site ID	text	$20		ADSL.SITEID
ADTR	*ALL*	SEX	Sex	text	$20	M, F	ADSL.SEX
ADTR	*ALL*	FASFL	Full Analysis Set Population Flag	text	$1	Y, N	ADSL.FASFL
ADTR	*ALL*	TRTPN	Planned Treatment (N)	integer	1.0	1 = Control, 2 = Study Drug	ADSL.TRTPN
ADTR	*ALL*	TRTP	Planned Treatment	text	$20	Control, Study Drug	ADSL.TRTP
ADTR	LDIAM1, LDIAM2, LDIAM3, SUMDIA,SDFRSM	PARCAT1	Parameter Category 1	text	$50	TARGET LESIONS	
ADTR	TUMSTAT1, TUMSTAT2, TUMSTAT3, NUMNTG	PARCAT1	Parameter Category 1	text	$50	NON-TARGET LESIONS	
ADTR	NEWLES	PARCAT1	Parameter Category 1	text	$50	NEW LESIONS	

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
ADTR	PARAMCD	PARAMCD	Parameter Code	text	$8	LDIAM1, LDIAM2, LDIAM3, SUMDIA, SDFRSM, TUMSTAT1, TUMSTAT2, TUMSTAT3, NUMNTG, NEWLES	
ADTR	*ALL*	PARAM	Parameter	text	$50	Longest Diameter of Target 1 (mm), Longest Diameter of Target 2 (mm), Longest Diameter of Target 3 (mm), Sum of Diameter (mm), Sum of Diameter from smallest Sum of Diameter (mm), Tumor State of Non-Target 1, Tumor State of Non-Target 2, Tumor State of Non-Target 3, Number of Present Non-Target Lesion, New Lesion	
ADTR	SDFRSM, NUMNTG, NEWLES	PARAMTYP	Parameter Type	text	$20	DERIVED	
ADTR	*ALL*	AVISITN	Analysis Visit (N)	integer	3.0	1 = Baseline, 2 = Cycle 1, 3=Cycle 2, 4=Cycle 3, 5=Cycle 4, 6=Cycle 5	TR.VISITNUM
ADTR	*ALL*	AVISIT	Analysis Visit	text	$20	Baseline, Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5	TR.VISIT
ADTR	*ALL*	ABLFL	Baseline Record Flag	text	$1	Y	TR.TRBLFL
ADTR	LDIAM1, LDIAM2, LDIAM3, SUMDIA	AVAL	Analysis Value	float	8.2		TR.TRSTRESN
ADTR	SDFRSM	AVAL	Analysis Value	float	8.2		TR.TRSTRESN at TRTESTCD='SUMDIA'

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
ADTR	TUMSTAT1, TUMSTAT2, TUMSTAT3	AVALC	Analysis Value (C)	text	$20		TR.TRSTRESC
ADTR	NUMNTG	AVAL	Analysis Value	float	8.2		Count(AVALC='PRESENT') for non-target lesion
ADTR	NEWLES	AVALC	Analysis Value (C)	text	$1	Y, N	'Y' if any TR.TRGRPID='NEW' 'N' if no TR.TRGRPID = 'NEW'
ADTR	SUMDIA	BASE	Baseline Value	float	8.2		AVAL at ABLFL='Y'
ADTR	SDFRSM	BASE	Baseline Value	float	8.2		Previous smallest AVAL at PARAMCD='SUMDIA'
ADTR	SUMDIA, SDRFSM	CHG	Change from Baseline	float	8.2		BASE - AVAL
ADTR	SUMDIA, SDFRSM	PCHG	Percent Change from Baseline	float	8.2		(BASE – AVAL)/BASE
ADTR	SUMDIA	CRIT1	Analysis Criteria 1	text	$50	AVAL = 0	
ADTR	SUMDIA	CRIT2	Analysis Criteria 2	text	$50	PCHG < -30	
ADTR	SDFRSM	CRIT3	Analysis Criteria 3	text	$50	PCHG > 120 and CHG > 5	
ADTR	NUMNTG	CRIT4	Analysis Criteria 4	text	$50	AVAL = 0	
ADTR	TUMSTAT1, TUMSTAT2, TUMSTAT3	CRIT5	Analysis Criteria 5	text	$50	AVALC = 'UNEQUIVOCAL'	
ADTR	NEWLES	CRIT6	Analysis Criteria 6	text	$50	AVALC = 'Y'	
ADTR	SUMDIA	CRIT1FL	Criteria 1 Evaluation Result Flag	text	$1	Y or Null	'Y' if CRIT1 is satisfied.
ADTR	SUMDIA	CRIT2FL	Criteria 2 Evaluation Result Flag	text	$1	Y or Null	'Y' if CRIT2 is satisfied.
ADTR	SDFRSM	CRIT3FL	Criteria 3 Evaluation Result Flag	text	$1	Y or Null	'Y' if CRIT3 is satisfied.
ADTR	TUMSTAT1, TUMSTAT2, TUMSTAT3	CRIT4FL	Criteria 4 Evaluation Result Flag	text	$1	Y or Null	'Y' if CRIT4 is satisfied.

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
ADTR	NUMNTG	CRIT5FL	Criteria 5 Evaluation Result Flag	text	$1	Y or Null	'Y' if CRIT5 is satisfied.
ADTR	NEWLES	CRIT6FL	Criteria 6 Evaluation Result Flag	text	$1	Y or Null	'Y' if CRIT6 is satisfied.
ADTR	*ALL*	TRSEQ	Sequence Number	float	8.2		TR.TRSEQ

Key points to note in the example are:

- Target Lesions
  - SUMDIA (Sum of Diameter)
    - if CRIT1FL = 'Y', overall response on target lesions is CR.
    - if CRIT2FL = 'Y', overall response on target lesions is PR.
  - SDFRSM (Sum of Diameter from Nadir) : if CRIT3FL = 'Y', overall response on target lesions is PD.
  - If CRIT1FL, CRIT2FL, and CRIT3FL are all null, overall response on target lesions is SD.
- Non Target Lesions
  - NUMNTG : if CRIT4FL = 'Y', overall response on non-target lesions is CR.
  - TUMSTAT1, TUMSTAT2, and TUMSTAT3 : if CRIT5FL='Y', overall response on non-target lesions is PD.
  - if CRIT4FL and CRIT5FL are all null, overall response on non-target lesions is NonCR/NonPD.
- New Lesions
  - NEWLES : if CRIT6FL = 'Y', overall response on new lesions is Y ; if not, overall response on new lesions is N.

Table 4.3 – ADTR dataset at Cycle 1

USUBJID	TRTP	PARCAT 1	PARAM	PARAMTYP	AVISIT	AVAL	BASE	CHG	PCHG	AVALC	BASEC	CRIT 1FL	CRIT 2FL	CRIT 3FL	CRIT 4FL	CRIT 5FL	CRIT 6FL
001-01-001	Study Drug	TARGET LESIONS	Longest Diameter of Target 1 (mm)		Cycle 1	10	23										
001-01-001	Study Drug	TARGET LESIONS	Longest Diameter of Target 2 (mm)		Cycle 1	10	22										
001-01-001	Study Drug	TARGET LESIONS	Longest Diameter of Target 3 (mm)		Cycle 1	15	25										
001-01-001	Study Drug	TARGET LESIONS	Sum of Diameter (mm)		Cycle 1	35	70	-35	-50				Y				
001-01-001	Study Drug	TARGET LESIONS	Sum of Diameter from smallest Sum of Diameter (mm)	DERIVED	Cycle 1	35	70	-35	-50								

USUBJID	TRTP	PARCAT1	PARAM	PARAMTYP	AVISIT	AVAL	BASE	CHG	PCHG	AVALC	BASEC	CRIT1FL	CRIT2FL	CRIT3FL	CRIT4FL	CRIT5FL	CRIT6FL
001-01-001	Study Drug	NON-TARGET LESIONS	Tumor State of Non-Target 1		Cycle 1					PRESENT	PRESENT						
001-01-001	Study Drug	NON-TARGET LESIONS	Tumor State of Non-Target 2		Cycle 1					PRESENT	PRESENT						
001-01-001	Study Drug	NON-TARGET LESIONS	Tumor State of Non-Target 3		Cycle 1					PRESENT	PRESENT						
001-01-001	Study Drug	NON-TARGET LESIONS	Number of Non-Target Lesion	DERIVED	Cycle 1	3											
001-01-001	Study Drug	NEW LESIONS	New Lesion	DERIVED	Cycle 1					N							

Key points to note in the example are:

- Row 4 : CRIT2FL = 'Y' since PCHG < -30, so this will lead to PR for target lesion at Cycle 1.

ADRS (Tumor Response Analysis Dataset)

Table 5.1 - Analysis Dataset Metadata for ADRS

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADRS	Response Analysis Data	adrs.xpt	one record per subject per parameter per analysis visit	USUBJID, PARAMCD, AVISITN	BDS	c-adrs.txt

Table 5.2 - Analysis Variable Metadata including Analysis Parameter Value-Level Metadata for ADRS

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
ADRS	*ALL*	USUBJID	Unique Subject Identifier	text	$20		ADSL.USUBJID
ADRS	*ALL*	SITEID	Site ID	text	$20		ADSL.SITEID
ADRS	*ALL*	SEX	Sex	text	$20	M, F	ADSL.SEX
ADRS	*ALL*	FASFL	Full Analysis Set Population Flag	text	$1	Y, N	ADSL.FASFL

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
ADRS	*ALL*	TRTPN	Planned Treatment (N)	integer	1.0	1 = Control, 2 = Study Drug	ADSL.TRTPN
ADRS	*ALL*	TRTP	Planned Treatment	text	$20	Control, Study Drug	ADSL.TRTP
ADRS	PARAMCD	PARAMCD	Parameter Code	text	$8	TRGRESP, NTRGRESP, NEWRESP, OVRLRESP	
ADRS	*ALL*	PARAM	Parameter	text	$50	Target Response, Non-target Response, New Lesion Progression, Overall Response	
ADRS	TRGRESP, NTRGRESP, NEWLPROG, OVRLRESP	PARAMTYP	Parameter Type	text	$20	DERIVED	
ADRS	*ALL*	AVISITN	Analysis Visit (N)	integer	3.0	1 = Screening, 2 = Cycle 1, 3=Cycle 2, 4=Cycle 3, 5=Cycle 4, 6=Cycle 5	ADTR.VISITNUM
ADRS	*ALL*	AVISIT	Analysis Visit	text	$20	Screening, Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5	ADTR.VISIT
ADRS	TRGRESP	AVALC	Analysis Value (C)	text	$20	CR, PR, PD, SD, NE	CR if ADTR.CRIT1FL='Y', PR if ADTR.CRIT2FL='Y', PD if ADTR.CRIT3FL='Y', SD if CRIT1FL, CRIT2FL and CRIT3FL are null
ADRS	NTRGRESP	AVALC	Analysis Value (C)	text	$20	CR, NonCR/NonPD, PD, NE	CR if ADTR.CRIT4FL='Y', PD if ADTR.CRIT5FL='Y', NonCR/NonPD if CRIT4FL and CRIT5FL are all null
ADRS	NEWLPROG	AVALC	Analysis Value (C)	text	$1	Y, N	Y if ADTR.CRIT6FL='Y', Otherwise N
ADRS	OVRLRESP	AVALC	Analysis Value (C)	text	$20	CR, PR, NonCR/NonPD, PD, SD, NE	See overall response table 1 and 2 in RECIST 1.1

Key points to note in the example are:

- ADTR should be derived before ADRS since ADRS is using ADTR.

Table 5.3 – ADRS dataset

USUBJID	TRTP	PARAM	PARAMTYP	AVISIT	AVALC
001-01-001	Study Drug	Target Response	DERIVED	Cycle 1	PR
001-01-001	Study Drug	Non-target Response	DERIVED	Cycle 1	NonCR/NonPD
001-01-001	Study Drug	New Lesion Progression	DERIVED	Cycle 1	N
001-01-001	Study Drug	Overall Response	DERIVED	Cycle 1	PR

Key points to note in the example are:

- Row 1 : Since ADTR.CRIT2FL = 'Y', Target Response is PR (Partial Response).
- Row 2 : Since ADTR.CRIT4FL and ADTR.CRIT5FL are null, Non-Target Response is NonCR/NonPD (Non Complete Response/Non Progressive Disease)
- Row 3 : since ADTR.CRIT6FL is null, New Lesion Progression is N.
- Row 4 : Using RECIST 1.1 Overall Response table, overall response at Cycle 1 is PR (Partial Response).

BEST OVERALL RESPONSE FOR ORR (OBJECTIVE RESPONSE RATE)

For ORR (Objective Response Rate) analysis as a primary endpoint, objective response should be derived. Usually, the FDA defines PR (Partial Response) or CR (Complete Response) as objective response to the treatment. Best overall response will be used to derive objective response. Best overall response can be selected as the best response among all responses. The best overall response does not worsen over time – if a subject achieves CR at cycle 3 and PD at cycle 5, the best overall response is still CR.

ADORS (Objective Response Analysis Dataset)

ADORS will be derived from SDTM RS domain, not from ADRS.

Table 6.1 - Analysis Dataset Metadata for ADORS

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADORS	Objective Response Analysis Data	adors.xpt	one record per subject per parameter per analysis visit	USUBJID, PARAMCD, AVISITN	BDS	c-adors.txt

Table 6.2 - Analysis Variable Metadata including Analysis Parameter Value-Level Metadata for ADORS

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
ADORS	*ALL*	USUBJID	Unique Subject Identifier	text	$20		ADSL.USUBJID
ADORS	*ALL*	SITEID	Site ID	text	$20		ADSL.SITEID
ADORS	*ALL*	SEX	Sex	text	$20	M, F	ADSL.SEX
ADORS	*ALL*	FASFL	Full Analysis Set Population Flag	text	$1	Y, N	ADSL.FASFL

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
ADORS	*ALL*	TRTPN	Planned Treatment (N)	integer	1.0	1 = Control, 2 = Study Drug	ADSL.TRTPN
ADORS	*ALL*	TRTP	Planned Treatment	text	$20	Control, Study Drug	ADSL.TRTP
ADORS	PARAMCD	PARAMCD	Parameter Code	text	$8	OVRLRESP, BESTRESP, OBJRESP	
ADORS	*ALL*	PARAM	Parameter	text	$50	Overall Response, Best Overall Response, Objective Response	
ADORS	BESTRESP, OBJRESP	PARAMTYP	Parameter Type	text	$20	DERIVED	
ADORS	*ALL*	AVISITN	Analysis Visit (N)	integer	3.0	1 = Screening, 2 = Cycle 1, 3=Cycle 2, 4=Cycle 3, 5=Cycle 4, 6=Cycle 5	
ADORS	*ALL*	AVISIT	Analysis Visit	text	$20	Screening, Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5	
ADORS	OVRLRESP	AVALC	Analysis Value (C)	text	$20		RS.RSORRES when RSTESTCD='OVRLRESP'
ADORS	BESTRESP	AVALC	Analysis Value (C)	text	$20		Best of AVALC at PARAMCD='OVRLRESP'
ADORS	OBJRESP	AVALC	Analysis Value (C)	text	$20		'Y' if AVALC at PARAM='Best Overall Response' is 'CR' or 'PR' 'N' otherwise
ADORS	*ALL*	RSSEQ	Sequence Number	float	8.2		RS.RSSEQ

Table 6.3 – ADORS dataset when the confirmation is not needed.

USUBJID	TRTP	PARAM	PARAMTYP	AVISIT	AVALC	RSSEQ
001-01-001	Study Drug	Overall Response		Cycle 1	PR	3
001-01-001	Study Drug	Overall Response		Cycle 2	SD	6
001-01-001	Study Drug	Overall Response		Cycle 3	SD	9
001-01-001	Study Drug	Overall Response		Cycle 4	PR	12
001-01-001	Study Drug	Overall Response		Cycle 5	PD	15

USUBJID	TRTP	PARAM	PARAMTYP	AVISIT	AVALC	RSSEQ
001-01-001	Study Drug	Best Overall Response	DERIVED	End of Study	PR	

Key points to note in the example are:

- Row 6 : At Cycle 1 and 4, the subject have PR, but at cycle 5, he has PD. But since it is best overall response, best overall response for the subject will be PR.

Table 6.4 – ADORS dataset when the confirmation of CR and PR is needed.

USUBJID	TRTP	PARAM	PARAMTYP	AVISIT	ADT	AVALC	RSSEQ	_NAVALC	_DUR	_COR
001-01-001	Study Drug	Overall Response		Cycle 1	2011-03-01	PR	3	SD	91	SD
001-01-001	Study Drug	Overall Response		Cycle 2	2011-06-01	SD	6	SD	91	SD
001-01-001	Study Drug	Overall Response		Cycle 3	2011-09-01	SD	9	PR	91	SD
001-01-001	Study Drug	Overall Response		Cycle 4	2011-12-01	PR	12	PD	91	SD
001-01-001	Study Drug	Overall Response		Cycle 5	2012-03-01	PD	15			PD
001-01-001	Study Drug	Best Overall Response	DERIVED	End of Study		SD				
001-01-001	Study Drug	Objective Response	DERIVED	End of Study		N				

Key points to note in the example are:

- Temporary ADaM plus variables
  - _NAVALC : Subsequent Analysis Value
  - _DUR : Duration (Days) from first time point to subsequent time point
  - _COR : Confirmed Overall Response
- Row 1 : According to table 2, since PR at the first time point (AVALC = 'PR'), SD at the subsequent time point (_NAVALC='SD') and duration is bigger than 4 weeks (_DUR=61), the best overall response at cycle 1 is SD (_COR='SD')
- Row 2 : According to table 2, since SD at the first time point (AVALC = 'SD'), PD at the subsequent time point (_NAVALC='SD') and duration is bigger than 4 weeks (_DUR=61), the best overall response at cycle 2 is SD (_COR='SD')
- Row 3 : According to table 2, since SD at the first time point (AVALC = 'SD'), PD at the subsequent time point (_NAVALC='PR') and duration is bigger than 4 weeks (_DUR=61), the best overall response at cycle 3 is SD (_COR='PR')
- Row 4 : According to table 2, since PR at the first time point (AVALC = 'PR'), PD at the subsequent time point (_NAVALC='PD') and duration is bigger than 4 weeks (_DUR=61), the best overall response at cycle 4 is SD (_COR='SD')
- Row 6 : Best overall response is SD at cycle 1, 2 and 3. So, the best overall response for subject 001 is SD.

Table 6.5 – Final ADORS dataset with Objective Response parameter

USUBJID	TRTP	PARAM	PARAMTYP	AVISIT	ADT	AVALC	RSSEQ
001-01-001	Study Drug	Overall Response		Cycle 1	2011-03-01	PR	3
001-01-001	Study Drug	Overall Response		Cycle 2	2011-06-01	SD	6

USUBJID	TRTP	PARAM	PARAMTYP	AVISIT	ADT	AVALC	RSSEQ
001-01-001	Study Drug	Overall Response		Cycle 3	2011-09-01	SD	9
001-01-001	Study Drug	Overall Response		Cycle 4	2011-12-01	PR	12
001-01-001	Study Drug	Overall Response		Cycle 5	2012-03-01	PD	15
001-01-001	Study Drug	Best Overall Response	DERIVED	End of Study		SD	
001-01-001	Study Drug	Objective Response	DERIVED	End of Study		N	

Key points to note in the example are:

- Temporary ADaM plus variables (_NAVALC, _DUR and _COR) are dropped.
- Row 7 : Objective Response parameter is derived.

CONCLUSION

Oncology studies need to collect and measure tumor results of the patients. The responses to treatments are provided by clinicians or investigators and also collected. But, can the responses to the treatments be derived using tumor results? Yes, they can be derived in Solid Tumor using RECIST 1.1. For Solid Tumor studies, RECIST 1.1 provides the programmers and statisticians with the standardized methodology to derive the responses to the treatment. RECIST 1.1 has the systematic methodologies to derive the best response to treatment for each patient. So, the programmers will be able to derive the best responses in ADaM using tumor results in SDTM TR domain. Then, the programmers compare the best responses in ADaM and in RS domains that investigators or clinicians has provided. So, the responses to treatments can be programmatically checked and confirmed.

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