CDISC Italian User Network 2020

Milan, Italy | 7 October 2020

Efficacy ADaM datasets applicable to all solid Tumour studies

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Agenda

1. Introduction
2. Definitions
3. Types of output
4. ADaM datasets

Introduction

Primary efficacy endpoints

Primary efficacy endpoints in solid Tumour

Tumour Response:

- Best Overall Response Rate (ORR)
- Overall response (OR)
- Disease control rate (DCR)
- Clinical Benefit Response Rate

Time to event endpoints:

- Progression Free Survival (PFS)
- Overall Survival (OS)
- Disease Free Survival (DFS)
- Duration of Response

The ADaM Basic Data Structure for Time-to-Event Analyses

What the statistician need to know...

- How «*Tumour Response*» is defined
- What kind of data the physicians need
- How to create efficient ADaM

Definitions

How «*Tumour Response*» is defined

RECIST v 1.1

Definition of Tumour Response: RECIST guideline[1]

RECIST (Response Evaluation Criteria in Solid Tumour) is a guideline that describes the standard approach to solid tumour measurement and the definitions for objective assessment of change in tumour size.

TARGET LESION

- Max 5 lesion total
- Maximum of 2 lesions per organ
- Representing all involved organs
- Quantitative measurements (measurable)

NON-TARGET LESION

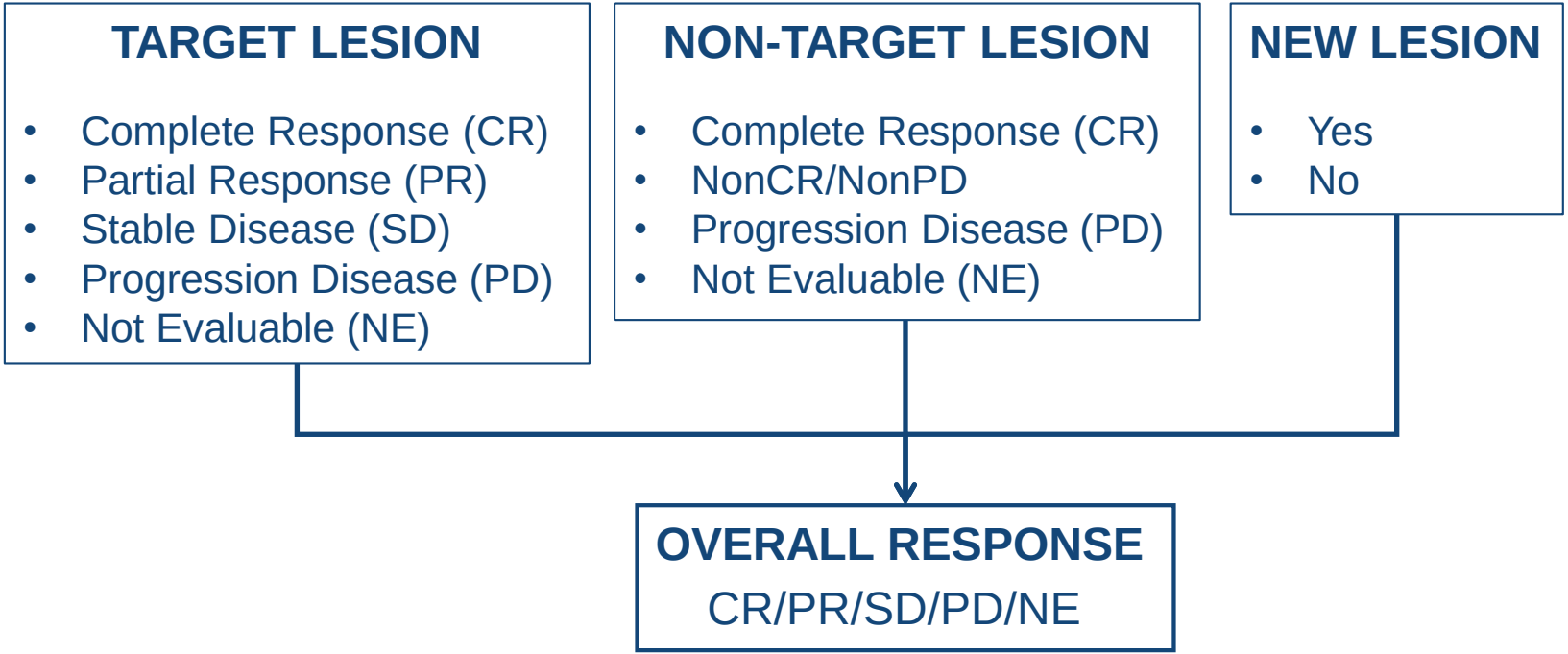
- All other lesions beside target lesions
- Qualitative measurement

NEW LESION

- Any lesion that are newly found at post baseline
- Either quantitative or qualitative measurements

[1]Source: Eisenhauera E.A., Therasseb P., Bogaertsc J., et al. «New Response Evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)» - EUR. J. CANCER, 2009 Jan; 45(2):228-47

RECIST guideline: Response Criteria[1]



[1]Source: -Eisenhauera E.A. , Therasseb P. , Bogaertsc J., et al. «New Response Evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)» - EUR. J. CANCER, 2009 Jan; 45(2):228-47

Types of output

What kind of data the physicians need

Tables & Figures

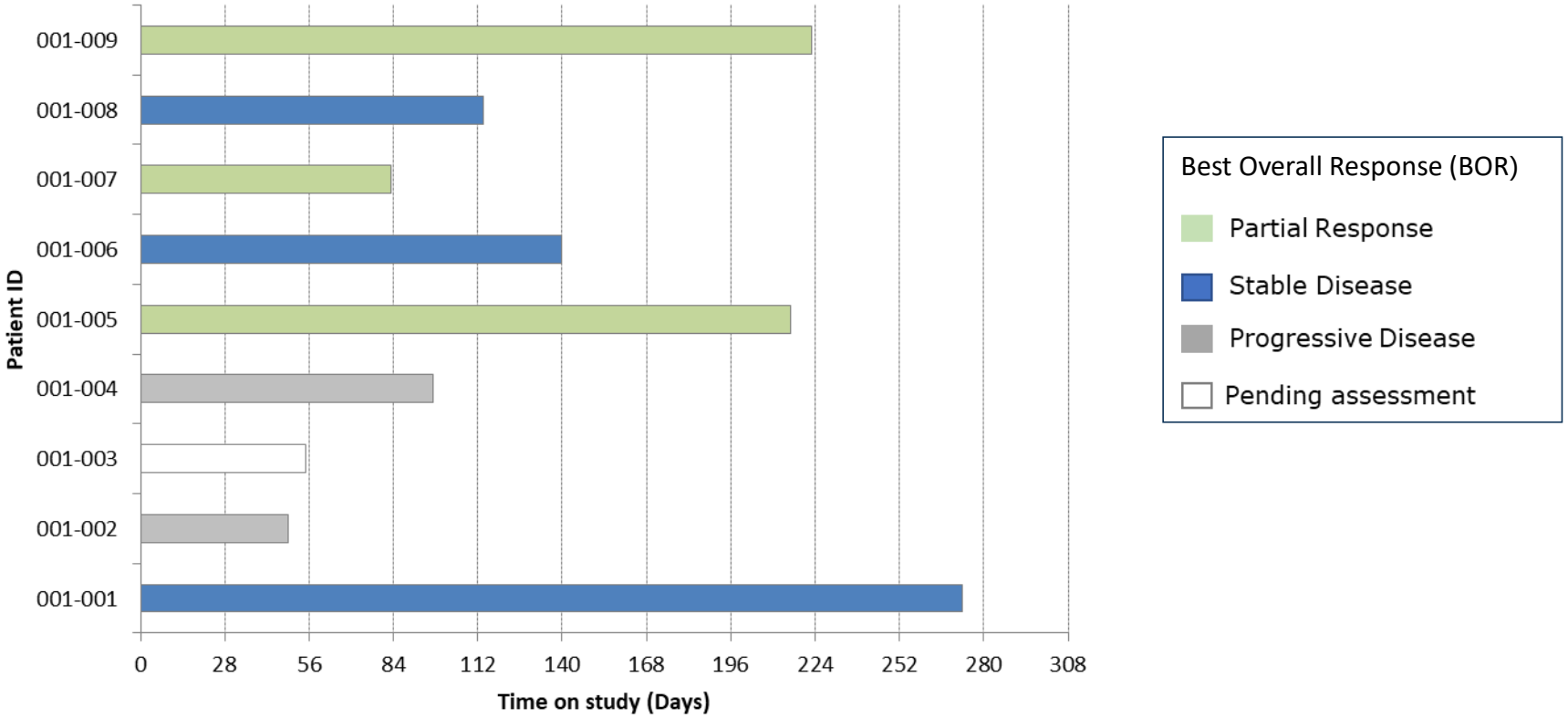
Output Definitions

Best Overall Response (BOR) is defined according to the type of trial:

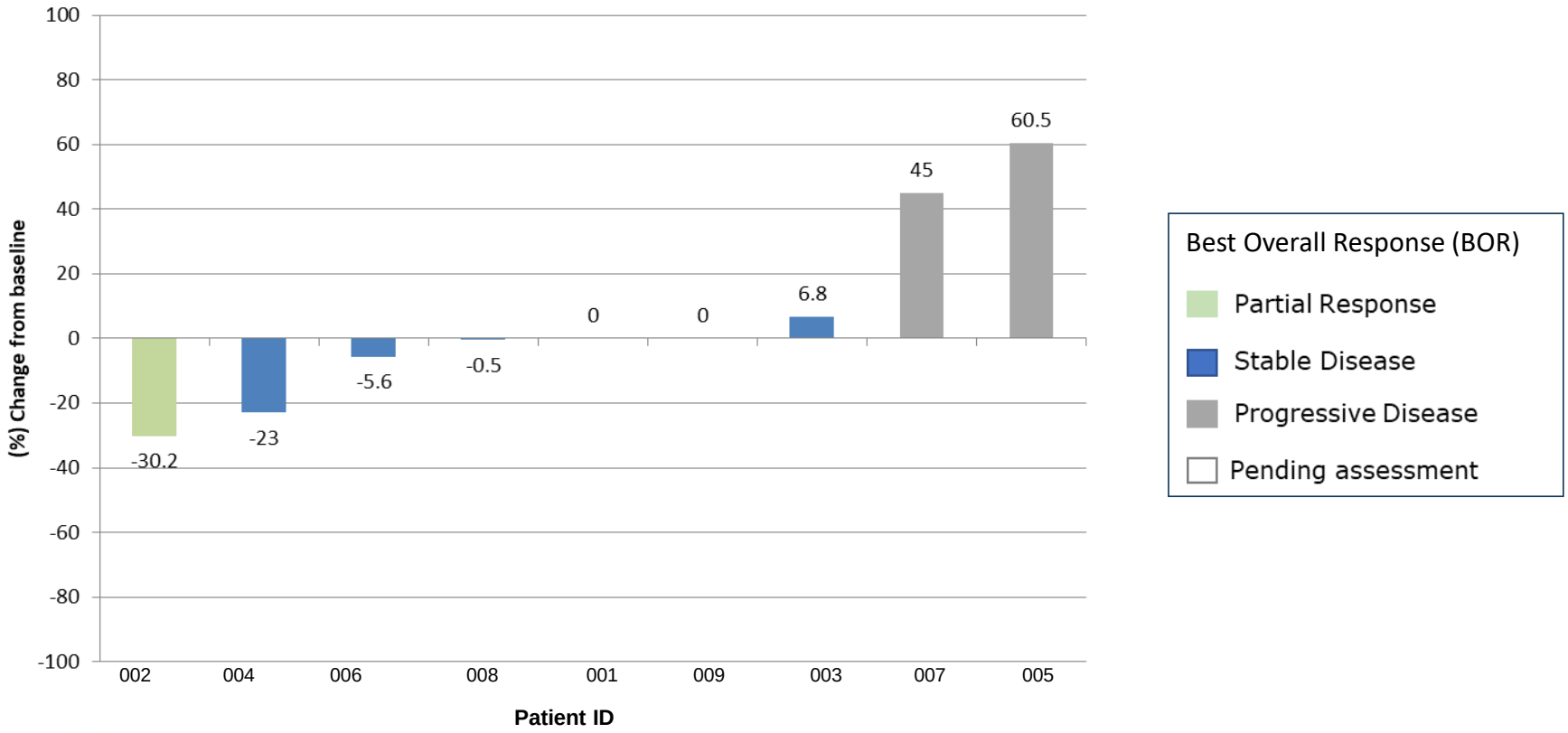
1. **Confirmation of CR/PR IS NOT** required: BOR is defined as the best response across all time points. When SD is believed to be best response, it must also meet the **protocol specified minimum time** from baseline.
2. **Confirmation of CR/PR IS** required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point **as specified in the protocol** (generally 4 weeks later).

Best Tumour Shrinkage (objective response) is the maximum percentage of reduction in tumour measurement from baseline.

Graphic of Best Overall Tumour Response



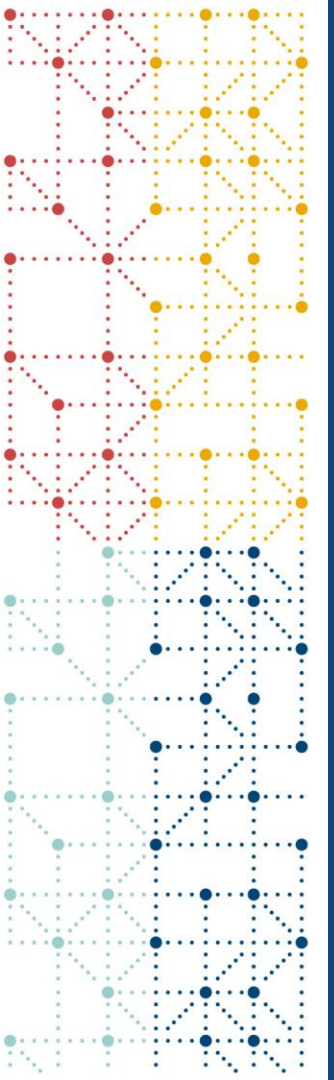
Graphic of Best Tumour Shrinkage



Summary of Tumour Response

		Treatment (N=XX)	Control (N=XX)
Best Overall Response			
	Complete Response (CR)	XX (XX.X)	XX (XX.X)
	Partial Response (PR)	XX (XX.X)	XX (XX.X)
	Stable Disease (SD)	XX (XX.X)	XX (XX.X)
	Progression Disease (PD)	XX (XX.X)	XX (XX.X)
	Not Evaluable (NE)	XX (XX.X)	XX (XX.X)
Overall Response (CR+PR)	(%)	XX (XX.X)	XX (XX.X)
	95% CI	[X.XX , X.XX]	[X.XX , X.XX]
Disease Control Rate (CR+PR+SD)	N(%)	XX (XX.X)	XX (XX.X)
	95% CI	[X.XX , X.XX]	[X.XX , X.XX]
Clinical Benefit Response Rate (CR+PR+Durable* SD)	N(%)	XX (XX.X)	XX (XX.X)
	95% CI	[X.XX , X.XX]	[X.XX , X.XX]

*Note: Durable SD defined according to the study protocol.
Note2: SD as Best Overall Response is defined according to the study protocol.



ADaM datasets

How to create efficient ADaM

Data Flow

eCRF

- Folders/Forms created according to RECIST

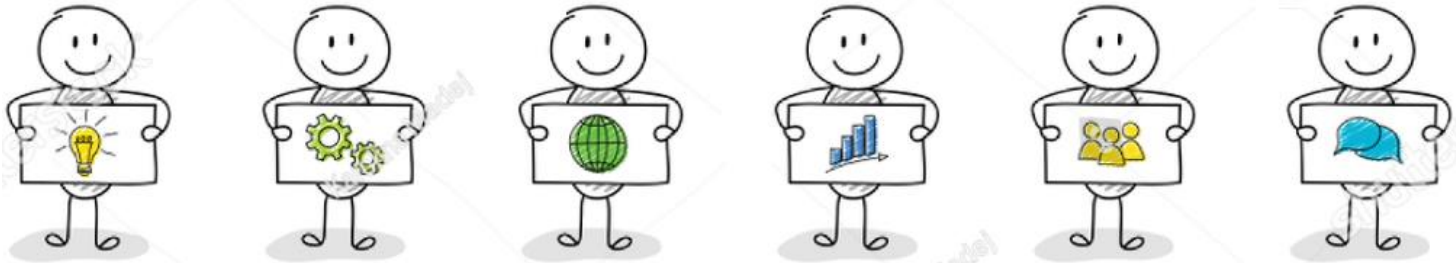
(i.e. Tumour assessment)

SDTM

- Tumour Identification (TU)
- Tumour Results (TR)
- Response (RS)

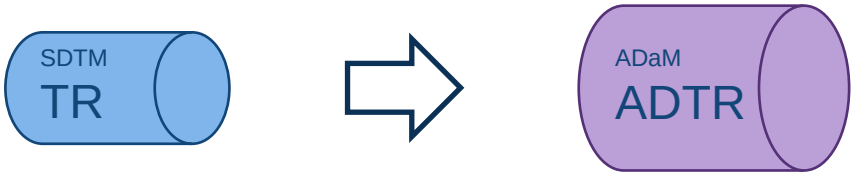
ADaM

- Tumour Results (ADTR)
- Tumour Response (ADRS)
- Objective Response (ADORS)



ADaM
Tumour Results (ADTR): Analysis dataset Metadata

Dataset Name	Dataset Description	Dataset Structure	Key Variable of dataset	Class of Dataset
ADTR	Tumour Results	One record per subject per parameter per analysis visit	USUBJID, PARAMCD, AVISITN	BDS



ADaM
Tumour Results (ADTR): Analysis variable Metadata

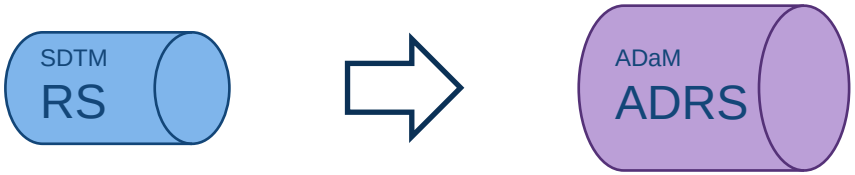
Dataset Name	Variable Name	Variable Label	Variable Type	Code list/ Controlled Terms	Source/Derivation
ADTR	PARCATx	Parameter Category x	Char	TARGET LESIONS NON-TARGET LESIONS	
ADTR	PARAMCD	Parameter Code	Char	TDIAMx SUMDIAM TUMSTATEy NUMNTG	TR. TRTESTCD
ADTR	PARAM	Parameter	Char	Diameter of Target x (mm) Sum of Diameter (mm) Tumour State of Non-Target y Number of Present Non-Target Lesion	
ADTR	AVAL	Analysis Value	Num		TR.TRSTRESN
ADTR	AVALC	Analysis Value (c)	Char		TR.TRSTRESC
ADTR	BASE	Baseline Value	Num		Equal to AVAL at ABLFL='Y'
ADTR	ABLFL	Baseline Flag	Char	Y	
ADTR	CHG	Change from Baseline	Num		AVAL-BASE
ADTR	PCHG	Percent Change from Baseline	Num		((AVAL-BASE)/BASE)*100
ADTR	ANL01FL	Analysis Flag 01	Char	Y	MIN(PCHG) by USUBJID Identify the «Best Tumour Shrinkage»

ADaM
Tumour Results (ADTR): Dataset

STUDYID	USUBJID	PARCAT1	PARAMCD	PARAM	AVAL	AVALC	BASE	ABLFL	CHG	PCHG	ANL01FL	AVISIT	AVISITN	EPOCH	ADT
TEST01	001-001	TARGET LESION	TDIAM1	Diameter of Target 1 (mm)	10		10	Y	.	.		Visit 1-Cycle 1	1	Cycle 1	10JAN2019
TEST01	001-001	TARGET LESION	TDIAM2	Diameter of Target 2 (mm)	15		15	Y	.	.		Visit 1-Cycle 1	1	Cycle 1	10JAN2019
TEST01	001-001	TARGET LESION	SUMDIAM	Sum of Diameter (mm)	25		25	Y	.	.		Visit 1-Cycle 1	1	Cycle 1	10JAN2019
TEST01	001-001	NON-TARGET LESION	TUMSTATE1	Tumor State of Non-Target 1		Present		Y	.	.		Visit 1-Cycle 1	1	Cycle 1	10JAN2019
TEST01	001-001	TARGET LESION	TDIAM1	Diameter of Target 1 (mm)	8.5		10		-1.5	-15	Y	Visit 1-Cycle 3	5	Cycle 3	21FEB2019
TEST01	001-001	TARGET LESION	TDIAM2	Diameter of Target 2 (mm)	12		15		-3	-20	Y	Visit 1-Cycle 3	5	Cycle 3	21FEB2019
TEST01	001-001	TARGET LESION	SUMDIAM	Sum of Diameter (mm)	20.5		25		-4.5	-18	Y	Visit 1-Cycle 3	5	Cycle 3	21FEB2019
TEST01	001-001	NON-TARGET LESION	TUMSTATE1	Tumor State of Non-Target 1		Non-CR/Non-PD			.	.	Y	Visit 1-Cycle 3	5	Cycle 3	21FEB2019
TEST01	001-001	TARGET LESION	TDIAM1	Diameter of Target 1 (mm)	9.2		10		-0.8	-8		End of Study	99	End of Study	11MAR2019
TEST01	001-001	TARGET LESION	TDIAM2	Diameter of Target 2 (mm)	14		15		-1	-6.7		End of Study	99	End of Study	11MAR2019
TEST01	001-001	TARGET LESION	SUMDIAM	Sum of Diameter (mm)	23.2		25		-1.8	-7.2		End of Study	99	End of Study	11MAR2019
TEST01	001-001	NON-TARGET LESION	TUMSTATE1	Tumor State of Non-Target 1		PD			.	.		End of Study	99	End of Study	11MAR2019

ADaM
Tumour Response Analysis (ADRS): Analysis dataset Metadata

Dataset Name	Dataset Description	Dataset Structure	Key Variable of dataset	Class of Dataset
ADRS	Tumour Response Analysis Dataset	One record per subject per parameter per analysis visit	USUBJID, PARAMCD, AVISITN	BDS



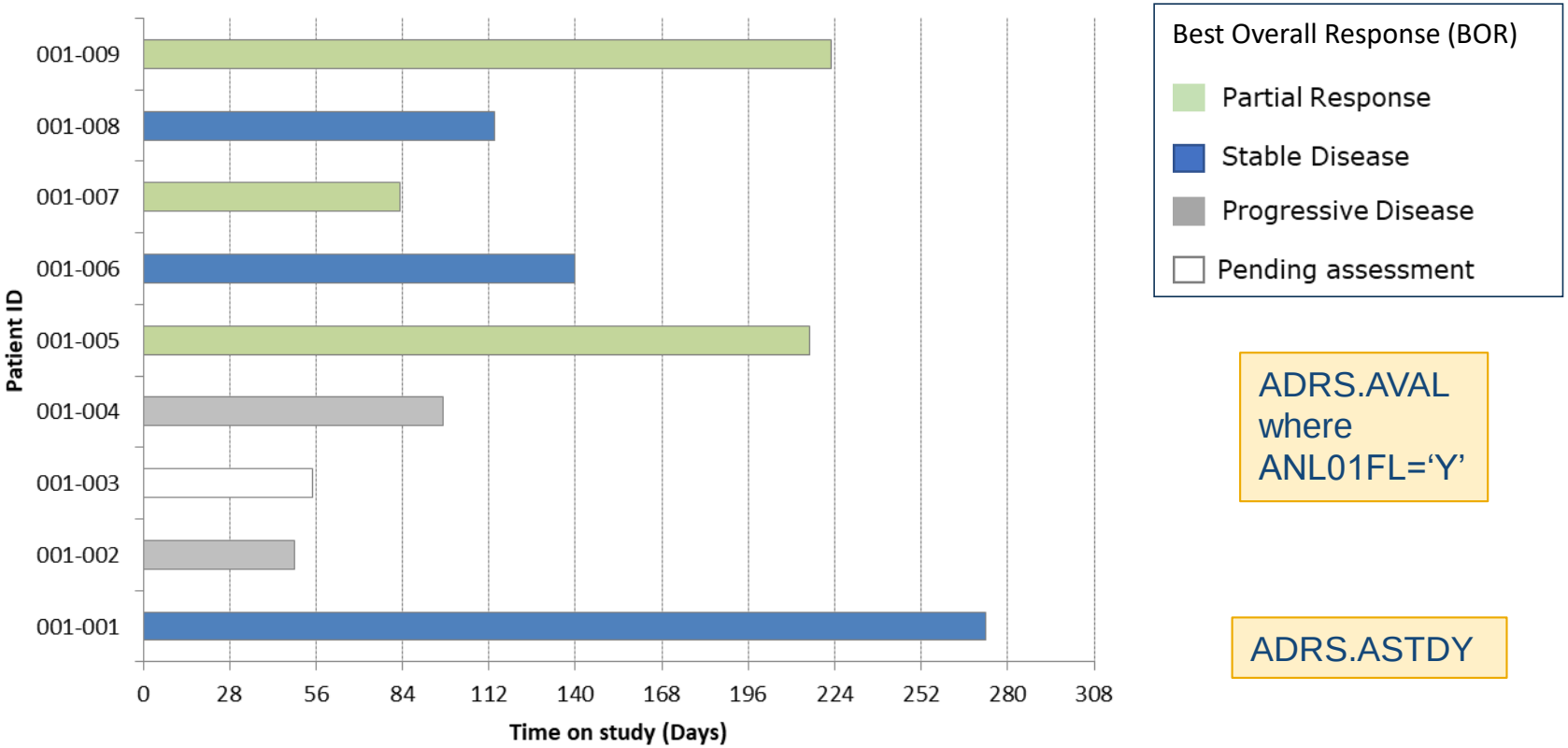
ADaM
Tumour Response Analysis (ADRS): Analysis variable Metadata

Dataset Name	Variable Name	Variable Label	Variable Type	Code list/ Controlled Terms	Source/Derivation
ADRS	PARAMCD	Parameter Code	Char	TRGRESP NTRGRESP NEWLIND OVRLRESP	RS. RSTESTCD
ADRS	PARAM	Parameter	Char	Target Response Non-Target Response New Lesion Indicator Overall Response	RS. RSTEST
ADRS	ABLFL	Baseline Record Flag	Char	Y	
ADRS	AVAL	Analysis Value	Num	Where PARAMCD in ('TRGRESP',' OVRLRESP') 1=CR 2=PR 3=SD 4=PD 5=NE Where PARAMCD='NTRGRESP' 1=CR 2=NonCR/NonPD 3=PD 4=NE Where PARAMCD='NEWLIND' 1=Y 0=N	Numeric code assigned to AVALC
ADRS	AVALC	Analysis Value (c)	Char	CR PR PD SD NE NonCR/NonPD Y N	RS.RSSTRESC
ADRS	ADT	Analysis Date	Num		Date associated with AVAL/AVALC in numeric format
ADRS	ASTDY	Analysis Start Relative Day	Num		Number of days from enrolled to the date of the reported event
ADRS	ANL01FL	Analysis Flag 01	Char	Y	='Y' for the best Overall Response assessment

ADaM
Tumour Response Analysis (ADRS): Dataset

STUDYID	USUBJID	PARAMCD	PARAM	AVAL	AVALC	ADT	ASTDY	ANL01FL	AVISIT	AVISITN	EPOCH
TEST01	001-001	TRGRESP	Target Response	4	PD	10JAN2019	0		Visit 1-Cycle 1	1	Cycle 1
TEST01	001-001	NTRGRESP	Non-Target Response	3	PD	10JAN2019	0		Visit 1-Cycle 1	1	Cycle 1
TEST01	001-001	OVRLRESP	Overall Response	4	PD	10JAN2019	0		Visit 1-Cycle 1	1	Cycle 1
TEST01	001-001	TRGRESP	Target Response	3	SD	21FEB2019	56	Y	Visit 1-Cycle 3	5	Cycle 3
TEST01	001-001	NTRGRESP	Non-Target Response	2	NonCR/NonPD	21FEB2019	56	Y	Visit 1-Cycle 3	5	Cycle 3
TEST01	001-001	NEWLIND	New Lesion Indicator	0	No	21FEB2019	56	Y	Visit 1-Cycle 3	5	Cycle 3
TEST01	001-001	OVRLRESP	Overall Response	3	SD	21FEB2019	56	Y	Visit 1-Cycle 3	5	Cycle 3
TEST01	001-001	TRGRESP	Target Response	4	PD	11MAR2019	74		End of Study	99	End of Study
TEST01	001-001	NTRGRESP	Non-Target Response	2	PD	11MAR2019	74		End of Study	99	End of Study
TEST01	001-001	NEWLIND	New Lesion Indicator	1	Yes	11MAR2019	74		End of Study	99	End of Study
TEST01	001-001	OVRLRESP	Overall Response	4	PD	11MAR2019	74		End of Study	99	End of Study

Graphic of Best Overall Tumour Response Annotated

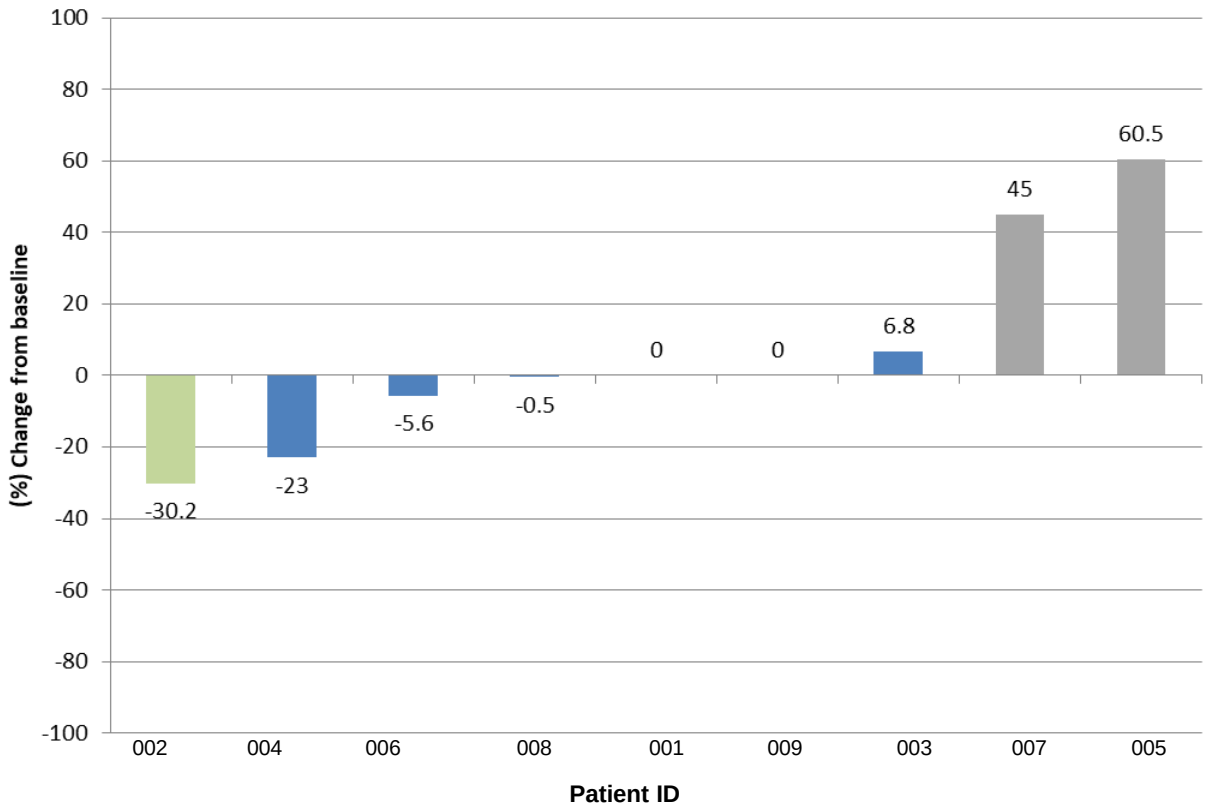


ADRS.USUBJID

ADRS.AVAL where ANL01FL='Y'

ADRS.ASTDY

Best Tumour Shrinkage Annotated



Best Overall Response (BOR)

- Partial Response
- Stable Disease
- Progressive Disease
- Pending assessment

ADTR.USUBJID

ADTR.PCHG where BESTFL='Y'

ADRS.AVAL Where PARAMCD= 'OVRLRESP' and AVISIT='End of Study'

ADaM
Objective Res. Analysis (ADORS): Analysis dataset Metadata

Dataset Name	Dataset Description	Dataset Structure	Key Variable of dataset	Class of Dataset
ADORS	Objective Response Analysis Data	One record per subject per parameter per analysis visit	USUBJID, PARAMCD, AVISITN	BDS

ADaM
Objective Res. Analysis (ADORS): Analysis variable Metadata

Dataset Name	Variable Name	Variable Label	Variable Type	Code list/ Controlled Terms	Source/Derivation
ADORS	PARAMCD	Parameter Code	Char	BOR BORRR BORDCR BORCBR	
ADORS	PARAM	Parameter	Char	Best Overall Response Overall Response (CR+PR) Disease Control Rate (CR+PR+SD) Clinical Benefit Response Rate (CR+PR+Durable SD)	
ADORS	AVAL	Analysis Value		Where PARAMCD='BOR' 1=CR 2=PR 3=SD 4=PD 5=NE Where PARAMCD in ('BORRR','BORDCR','BORCBR') 1=Y 0=N	PARAMCD='BOR' AVAL=ADRS.AVAL where ANL01FL='Y PARAMCD='BORRR' AVAL=1 if AVAL in (1,2) and PARAMCD='BOR' PARAMCD='BORDCR' AVAL=1 if AVAL in (1,2,3) and PARAMCD='BOR' PARAMCD='BORCBR' AVAL=1 where PARAMCD='BOR' AVAL in (1,2) or AVAL=3 and ADRS.ASTDY>XX
ADORS	AVALC	Analysis Value (c)	Char	Complete Response (CR) Partial Response (PR) Progression Disease (PD) Stable Disease (SD) Not Evaluable (NE) NonCR/NonPD Yes No	

ADaM
Objective Res. Analysis (ADORS): Dataset

STUDYID	USUBJID	PARAMCD	PARAM	AVAL	AVALC	AVISIT	AVISITN	EPOCH
TEST01	001-001	BOR	Best Overall Response	3	Stable Disease (SD)	Visit 1-Cycle 3	5	Cycle 3
TEST01	001-001	BORRR	Overall Response (CR+PR)	0	No	Visit 1-Cycle 3	5	Cycle 3
TEST01	001-001	BORDCR	Disease Control Rate (CR+PR+SD)	1	Yes	Visit 1-Cycle 3	5	Cycle 3
TEST01	001-001	BORCBR	Clinical Benefit Response Rate (CR+PR+Durable SD)	1	Yes	Visit 1-Cycle 3	5	Cycle 3

Summary of Best Overall Tumour Response
Annotated

ADORS.AVALC where PARAMCD='BOR'

		Treatment (N=XX)	Control (N=XX)
Best Overall Response			
	Complete Response (CR)	XX (XX.X)	XX (XX.X)
	Partial Response (PR)	XX (XX.X)	XX (XX.X)
	Stable Disease (SD)	XX (XX.X)	XX (XX.X)
	Progression Disease (PD)	XX (XX.X)	XX (XX.X)
	Not Evaluable (NE)		
Overall Response (CR+PR)	(%)	XX (XX.X)	XX (XX.X)
	95% CI	[X.XX , X.XX]	[X.XX , X.XX]
Disease Control Rate (CR+PR+SD)	N(%)		
	95% CI	[X.XX , X.XX]	[X.XX , X.XX]
Clinical Benefit Response Rate (CR+PR+Durable SD)	N(%)	XX (XX.X)	XX (XX.X)
	95% CI	[X.XX , X.XX]	[X.XX , X.XX]

ADORS.AVAL where PARAMCD='BORRR'

ADORS.AVAL where PARAMCD='BORDCR'

ADORS.AVAL where PARAMCD='BORCBR'

Conclusions

- ADTR, ADRS and ADORS are all based on RECIST guidelines
- These 3 ADaMs are suitable for all solid tumour trial (datasets are totally **independent from the type of tumour**)
- In a single ADaM (ADORS) we have **all the variables** necessary for the assessment of the efficacy endpoints on tumour response *(time-to-event endpoints are part of other ADaM datasets)*
- Direct correspondence betwen SDTM and ADaM
  - (TR → ADTR)
  - (RS → ADRS)

Reference

- Eisenhauera E.A., Therasseb P., Bogaertsc J., et al. «New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)» - EUR. J. CANCER, 2009 Jan; 45(2):228-47
- Lee K., Jain V. «Two different use cases to obtain best responses using RECIST 1.1: SDTM and ADaM» - PharmaSUG 2015, Paper IB06
- Almond S. «Deconstructing ADRS: Tumour Response Analysis Data Set » - PharmaSUG 2016 - Paper DS08
- CDISC Japan User Group (CJUG) ADaM Team «ADaM & Analysis Specific to Oncology»
- Lee K. «CDISC Journey in Solid Tumour using RECIST 1.1»
- https://www.phusewiki.org/wiki/index.php?title=Best_Overall_Tumour_Response_for_Solid_Tumours


THANK
YOU