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Efficacy ADaMs in Oncology – Step by Step (Dataset by Dataset)

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Why Oncology is different?

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry (December 2018).

Some of most common efficacy endpoints:

- Overall Survival (OS)
- Time to Progression (TTP)
- Progression Free Survival (PFS)
- Objective Response Rate (ORR)
- Clinical Benefit Rate (CBR)
- Duration of Response (DOR)
- Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir (presented in Waterfall graphics)

2 types of endpoints: “with” or “without” censoring => 2 types of ADaM sets for efficacy subject-level derived parameters (endpoints)

Data Source

ADSL

Date of randomization, Dates of first / last dose of study treatment, Last known alive date, Date of death, First date of new anti-cancer treatment, ...

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SDTM domain TU (Tumor Identification)

Data that uniquely identifies tumors, that were tracked during the study

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SDTM domain TU (Tumor Identification)

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SDTM domain TR (Tumor Results)

Time-point Diameters of target lesions, Result of time-point assessment of non-target lesions, Time-point summation of diameters of target lesions

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Date of randomization, Dates of first / last dose of study treatment, Last known alive date, Date of death, First date of new anti-cancer treatment, ...

SDTM domain TU (Tumor Identification)

Data that uniquely identifies tumors, that were tracked during the study

SDTM domain TR (Tumor Results)

Time-point Diameters of target lesions, Result of time-point assessment of non-target lesions, Time-point summation of diameters of target lesions

SDTM domain RS (Disease Response)

Results of responses of time-point evaluations

Analysis Data Set ADTR (Tumor Results)

Resembles SDTM TR domain (without sum of target lesion diameters)

One observation per subject per timepoint per tumor per response assessment criteria per evaluator

In case of new lesions, 2 records are suggested for each new lesion: for initial appearance and for unequivocal assessment (may have different dates and time-points)

Suggested parameters:

- 'Longest Diameter (mm)'
- 'Short Axis Diameter (mm)'
- 'Tumor State - Non-Target Lesion'
- 'Tumor State - New Lesion - Initial Appearance'
- 'Tumor State - New Lesion - Unequivocal Assessment'

Analysis Data Set ADTR - Example

USUBJID (Unique Subject Identifier)	ATPT (Analysis Timepoint)	TRLNKID (Link ID)	PARAM (Parameter)	ADT (Analysis Date)	AVAL (Analysis Value)	AVALC (Analysis Value (C))	EVAL (Evaluator)	EVALID (Evaluator Specified)	ACPTFL (Accepted Record Flag)
1111	SCREENING	TNL1	Longest Diameter (mm)	2017-01-01	20		INDEP. ASSESSOR	READER1	Y
1111	SCREENING	TL1	Short Axis Diameter (mm)	2017-01-02	15		INDEP. ASSESSOR	READER1	Y
1111	SCREENING	NT1	Tumor State - Non-Target Lesion	2017-01-01		Present	INDEP. ASSESSOR	READER1	Y
1111	WEEK 6	TNL1	Longest Diameter (mm)	2017-02-15	18		INDEP. ASSESSOR	READER1	Y
1111	WEEK 6	TL1	Short Axis Diameter (mm)	2017-02-15	13		INDEP. ASSESSOR	READER1	Y
1111	WEEK 6	NT1	Tumor State - Non-Target Lesion	2017-02-16		Present	INDEP. ASSESSOR	READER1	Y
1111	WEEK 6	NEW1	Tumor State - New Lesion - Initial Appearance	2017-02-16		Yes	INDEP. ASSESSOR	READER1	Y
1111	WEEK 12	TNL1	Longest Diameter (mm)	2017-04-01	0		INDEP. ASSESSOR	READER1	Y
1111	WEEK 12	TL1	Short Axis Diameter (mm)	2017-04-01	17		INDEP. ASSESSOR	READER1	Y
1111	WEEK 12	NT1	Tumor State - Non-Target Lesion	2017-03-31		Absent	INDEP. ASSESSOR	READER1	Y
1111	WEEK 12	NEW1	Tumor State - New Lesion - Unequivocal Assessment	2017-03-31		Present	INDEP. ASSESSOR	READER1	Y
1111	SCREENING	TNL1	Longest Diameter (mm)	2017-01-01	21		INDEP. ASSESSOR	READER2	
1111	SCREENING	TL1	Short Axis Diameter (mm)	2017-01-02	16		INDEP. ASSESSOR	READER2	
1111	SCREENING	NT1	Tumor State - Non-Target Lesion	2017-01-01		Present	INDEP. ASSESSOR	READER2	
1111	WEEK 6	TNL1	Longest Diameter (mm)	2017-02-15	20		INDEP. ASSESSOR	READER2	
1111	WEEK 6	TL1	Short Axis Diameter (mm)	2017-02-15	15		INDEP. ASSESSOR	READER2	
1111	WEEK 6	NT1	Tumor State - Non-Target Lesion	2017-02-16		Present	INDEP. ASSESSOR	READER2	
1111	WEEK 12	TNL1	Longest Diameter (mm)	2017-04-01	0		INDEP. ASSESSOR	READER2	
1111	WEEK 12	TL1	Short Axis Diameter (mm)	2017-04-01	10		INDEP. ASSESSOR	READER2	
1111	WEEK 12	NT1	Tumor State - Non-Target Lesion	2017-03-31		Absent	INDEP. ASSESSOR	READER2	

Analysis Data Set ADTRS (Time-point Responses)

Contains time-point level results

One observation per subject per timepoint per parameter per response assessment criteria per evaluator

Set of Analysis Flags (ANLzzFL) indicate observations, that fulfill requirements for different analyses (example: per SAP / Sensitivity Analysis to include time-point evaluations occurred after more than one missing assessment)

Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters (Example: 'Timepoint Overall Response by Independent Reviewer').

Possible Parameters:

- 'Timepoint Sum of Target Lesion Diameters: Lymph Nodes (mm) by Investigator'
- 'Timepoint Sum of Target Lesion Diameters: Non-Lymph Nodes (mm) by Investigator '
- 'Timepoint Sum of all Target Lesion Diameters (mm) by Investigator '
- 'Timepoint Target Lesions Response by Investigator '
- 'Timepoint Non-Target Lesions Response by Investigator '
- 'Initial Appearance of New Lesions by Investigator '
- 'Timepoint Overall Response by Investigator '

Analysis Data Set ADTRS - Example

RECIST 1.1 criteria is applied without confirmation of response

Sensitivity analysis to include time-point evaluations after more than 1 missing assessment

USUBJID (Unique Subject Identifier)	ATPT (Analysis Timepoint)	PARAM (Parameter)	ADT (Analysis Date)	AVAL (Analysis Value)	AVALC (Analysis Value (C))	PCHG (Percent Change from Baseline)	ANL01FL (Analysis Flag 01)	ANL51FL (1st Occur of Response Flag)	ANL02FL (Analysis Flag 02)	ANL52FL (1st Occur of Response – Sensitivity FI)
2222	SCREENING	Timepoint Sum of all Target Lesion Diameters (mm) by Investigator	2017-04-01	50			Y		Y	
2222	WEEK 6	Timepoint Sum of all Target Lesion Diameters (mm) by Investigator	2017-05-15	40		-20.0	Y		Y	
2222	WEEK 6	Timepoint Target Lesions Response by Investigator	2017-05-15		SD		Y		Y	
2222	WEEK 6	Timepoint Non-Target Lesions Response by Investigator	2017-05-15		Non-CR / Non-PD		Y		Y	
2222	WEEK 6	Initial Appearance of New Lesions by Investigator	2017-05-15		No		Y		Y	
2222	WEEK 6	Timepoint Overall Response by Investigator	2017-05-15		SD		Y		Y	
2222	WEEK 24	Timepoint Sum of all Target Lesion Diameters (mm) by Investigator	2017-09-20	30		-40.0			Y	
2222	WEEK 24	Timepoint Target Lesions Response by Investigator	2017-09-20		PR				Y	
2222	WEEK 24	Timepoint Non-Target Lesions Response by Investigator	2017-09-20		Non-CR / Non-PD				Y	
2222	WEEK 24	Initial Appearance of New Lesions by Investigator	2017-09-20		No				Y	
2222	WEEK 24	Timepoint Overall Response by Investigator	2017-09-20		PR				Y	Y

Analysis Data Set ADEF

- Should contain subject-level derived efficacy parameters when the censoring is irrelevant
- One observation per subject per subject-level parameter per response assessment criteria per evaluator
- Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters (Example: Best Overall Response by Independent Reviewer).
- Based on ADTRS and using Analysis Flags
- Most common parameters:
 - Best Overall Response – for all subjects from Full Analysis Set
 - Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir (will be needed for waterfall graphic) – only for subjects having baseline and at least one post-baseline measurements of sum of target lesion diameters
- Contains variables for:
 - BOR description (provide the rationale behind assigning BOR) – important when BOR is assigned as 'NE'
 - Objective Response Flag (when BOR in ('CR', 'PR'))
 - Disease Control Flag (when BOR in ('CR', 'PR', 'SD'))

Analysis Data Set ADEF - Example

USUBJID (Unique Subject Identifier)	PARAM (Parameter)	AVAL (Analysis Value)	AVALC (Analysis Value (C))	BORDESC (Best Overall Response Description)	EFORFL (Objective Response Flag)	EFDCFL (Disease Control Flag)
2222	Best Overall Response by Investigator		SD	Observed SD		Y
2222	Best Overall Response – Sensitivity Analysis by Investigator		PR	Observed PR	Y	Y
2222	Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir by Investigator	-20.0				
2222	Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir - Sensitivity Analysis by Investigator	-40.0				

Analysis Data Set ADTTE

- Should contain subject-level derived efficacy parameters requiring censoring
- One observation per subject per subject-level parameter per response assessment criteria per evaluator
- Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters (Example: Progression Free Survival Time (months) by Independent Reviewer).
- Based on ADTRS (and using Analysis Flags) and ADEF
- Follows CDISC Guidance “ADaM Basic Data Structure for Time-to-Event Analysis. Version 1.0”
- Most common parameters:
 - Overall Survival (months) – for all subjects from Full Analysis Set
 - Progression Free Survival (months) – for all subjects from Full Analysis Set
 - Duration of Response (months) – for all subjects, marked as responders in ADEF
- Contains variables for:
 - Durable Stable Disease Flag (when DEF.BOR = ‘SD’ and PFS $\geq$ xx weeks)
 - Clinical Benefit Flag (when BOR in (‘CR’, ‘PR’), or Durable Stable Disease Flag = ‘Y’)

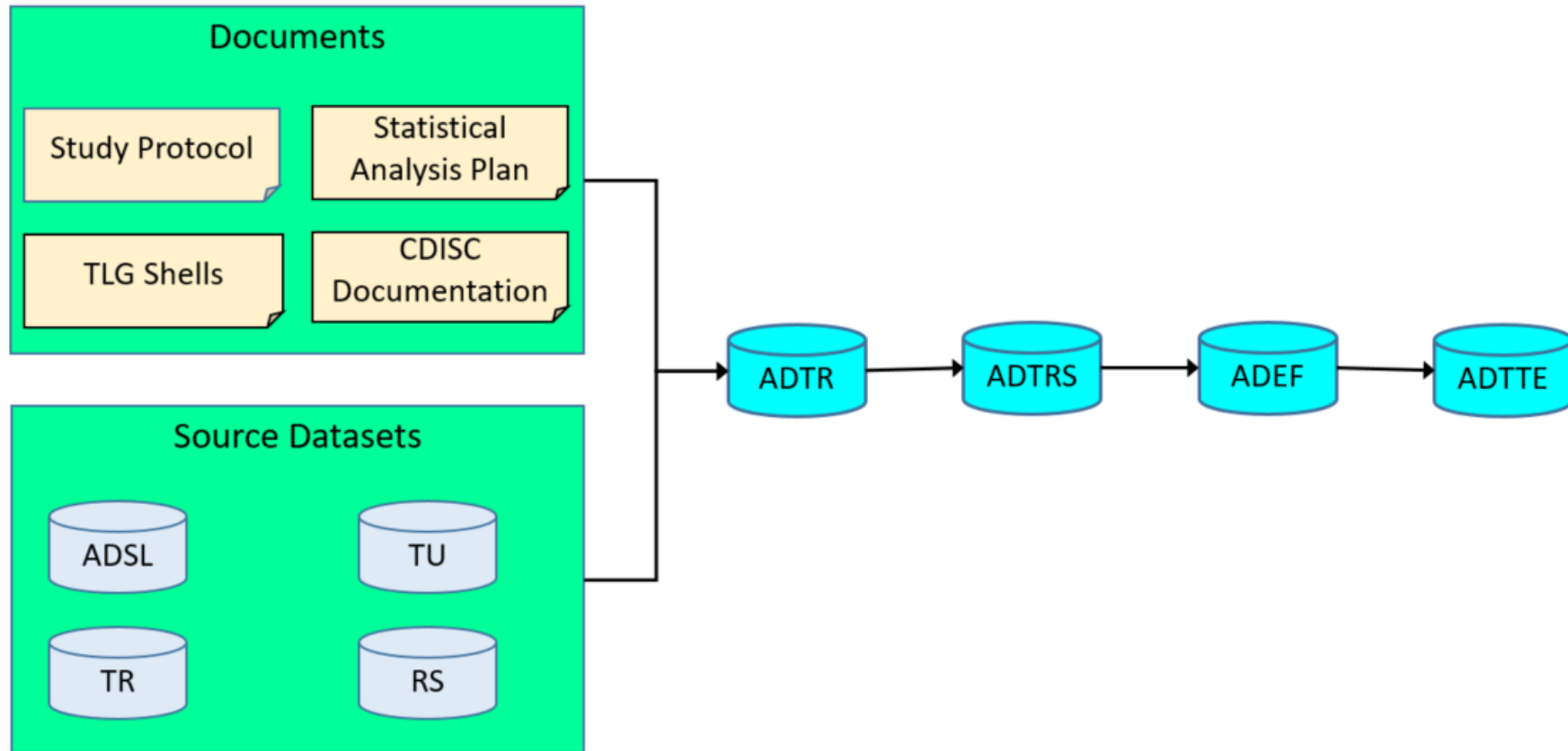
Analysis Data Set ADTTE - Example

- Date of Randomization: 2017-04-04 (CORE var.)
- Start Date of Response – only for Sensitivity Analysis: 2017-09-20 (source ADTRS)
- Last Known Alive Date: 2018-10-10 (CORE var.); Death is not recorded
- Protocol / SAP requires duration of Stable Disease ≥ 23 weeks to qualify for Durable Stable Disease

USUBJID (Unique Subject Identifier)	PARAM (Parameter)	AVAL (Analysis Value)	CNSR (Censor)	STARTDT (Time to Event Origin Date for Subject)	ADT (Analysis Date)	EVNTDESC (Event or Censoring Description)	CNSDTDSC (Censor Date Description)	EFDUSDFL (Durable SD Flag)	EFCBFL (Clinical Benefit Flag)
2222	Overall Survival (months)	18.23	1	2017-04-04	2018-10-10	No Death at Time of Data Cut-off	Last Known Alive Date		
2222	Progression Free Survival (months) by Investigator	1.38	1	2017-04-04	2017-05-15	More than one missing adequate assessment'	Date of the Last Adequate Overall Tumor Assessment by SAP		
2222	Progression Free Survival – Sensitivity Analysis (months) by Investigator	5.59	1	2017-04-04	2017-09-20	No Death or PD at Time of Data Cut-off	Date of the Last Adequate Overall Tumor Assessment by requirements of Sensitivity Analysis		Y
2222	Duration of Response – Sensitivity Analysis (months) by Investigator	0.03	1	2017-09-20	2017-09-20	No Death or PD at Time of Data Cut-off	Date of the Last Adequate Overall Tumor Assessment by requirements of Sensitivity Analysis		

Conclusion

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Questions



Thank You!

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