CDISC Journey in Solid Tumor using RECIST 1.1

Kevin Lee
Statistician/CDISC Consultant/Programmer

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Question

1. What is the role of ADaM?
   - Analysis
2. What is the analysis in Solid Tumor?
   - Overall Survival
   - Objective Response Rate
   - Time to Progression
   - Progression Free Survival
3. What are the endpoints in Solid Tumor?
   - Overall Survival (Death)
   - Objective Response Rate (Response)
   - Time to Progression (Response)
   - Progression Free Survival (Response)

Question (2)

4. What are Responses in Solid Tumor?
   - CR, PR, SD, PD
5. How can we define the responses? What determines CR, PR, SD or PD?
   - Changes in tumor measurements
6. What rule or algorithm can we measure the tumor lesions by?
   - RECIST (Response Evaluation Criteria in Solid Tumor)

Cancer Facts

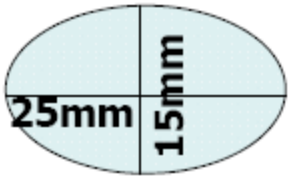
- In 2008, there were estimated 12,665,500 new cases of cancel worldwide.
- One in eight deaths in the world are due to cancer.
- Cancer is the leading cause of death in developed countries.
- NIH reported that the cost of cancer in 2007 in the U.S. was 226.8 billion overall.
- There are 28 million cancer survivors worldwide.
- Men who have never married are up to 35% more likely to die from cancer than those who are married.

Oncology Study

- Types of Oncology Studies
  - Solid Tumor – RECIST 1.1
  - Lymphoma – Cheson 2007
  - Leukemia – Study-specific

RECIST

- RECIST (Response Evaluation Criteria in Solid Tumor)
  - Version 1.0 and 1.1 (released on October 2008)
- Lesions
  - Measurable and Non-Measurable
    - 10 mm by CT scan
    - 20 mm by chest X-ray
  - Target and Non-Target
- One-dimensional measurement (longest diameter).



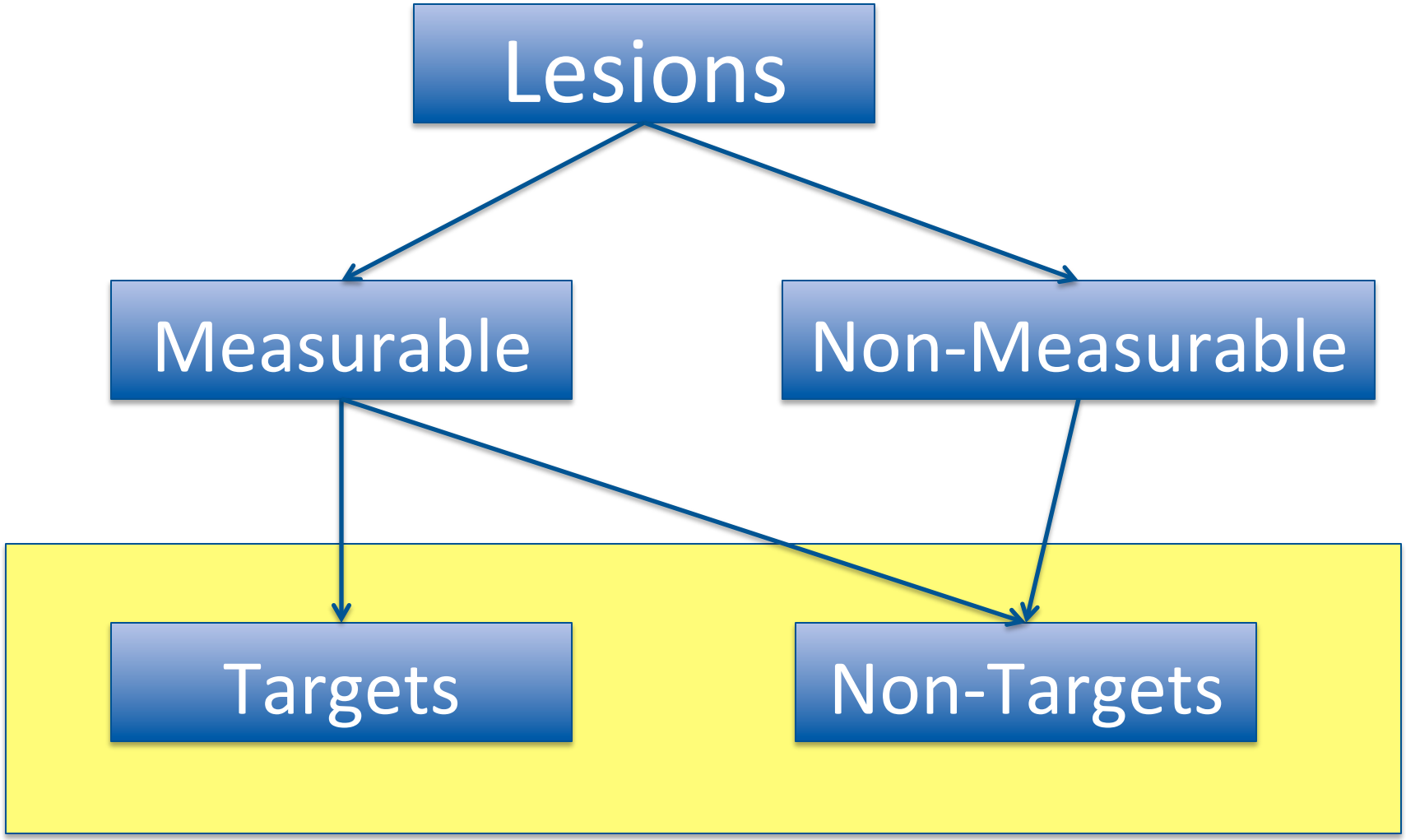
Target Lesions according to RECIST 1.1

- Measurable
- Up to 5 lesions
- Maximum of 2 lesions per organ
- Measurement
  - Lesion with longest diameter
  - Lymph nodes with a short axis
  - Sum of diameters

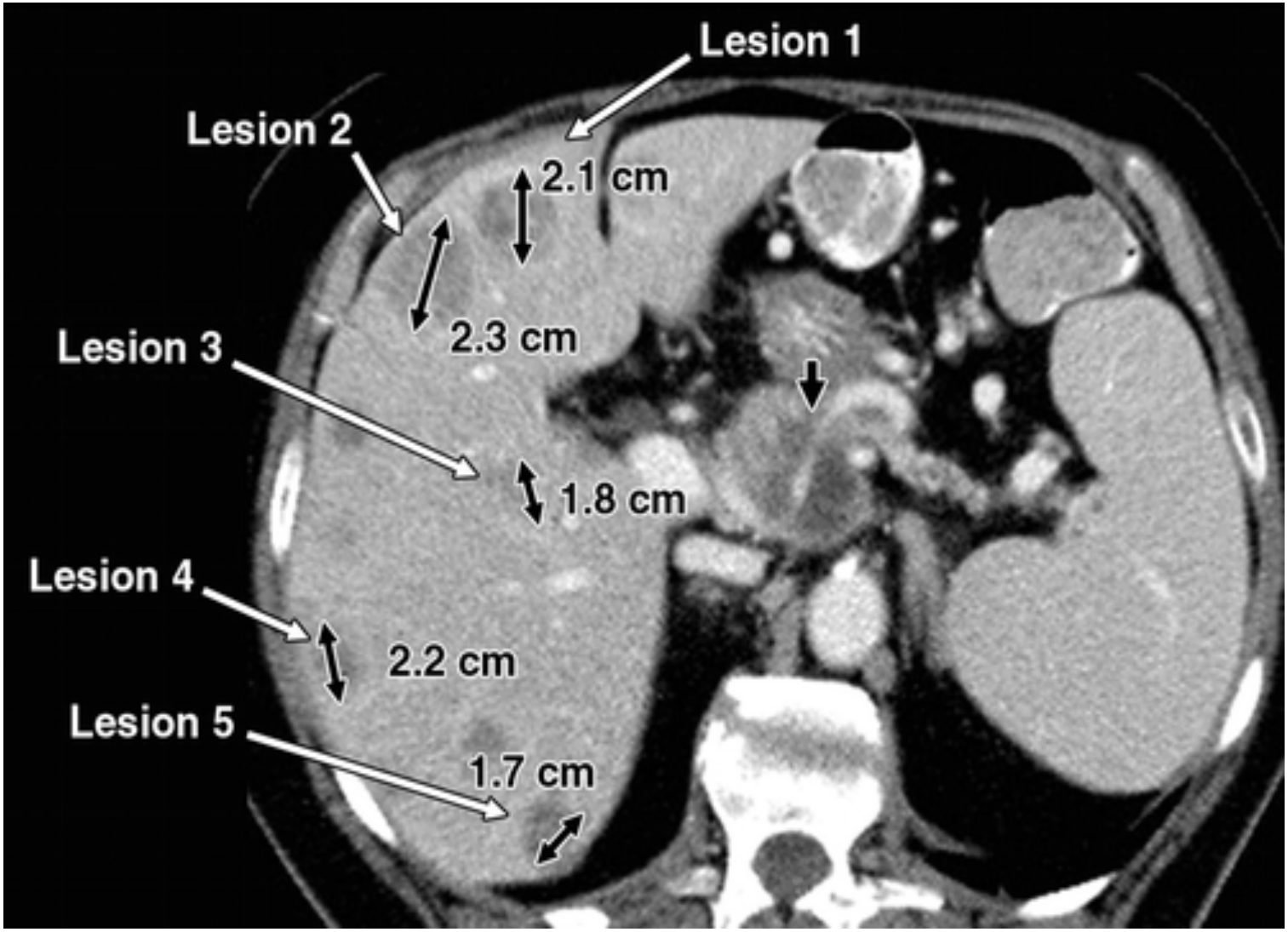
Non-Target Lesions according to RECIST 1.1

- All other lesions
- Measurement
  - Present, absent, unequivocal progression.

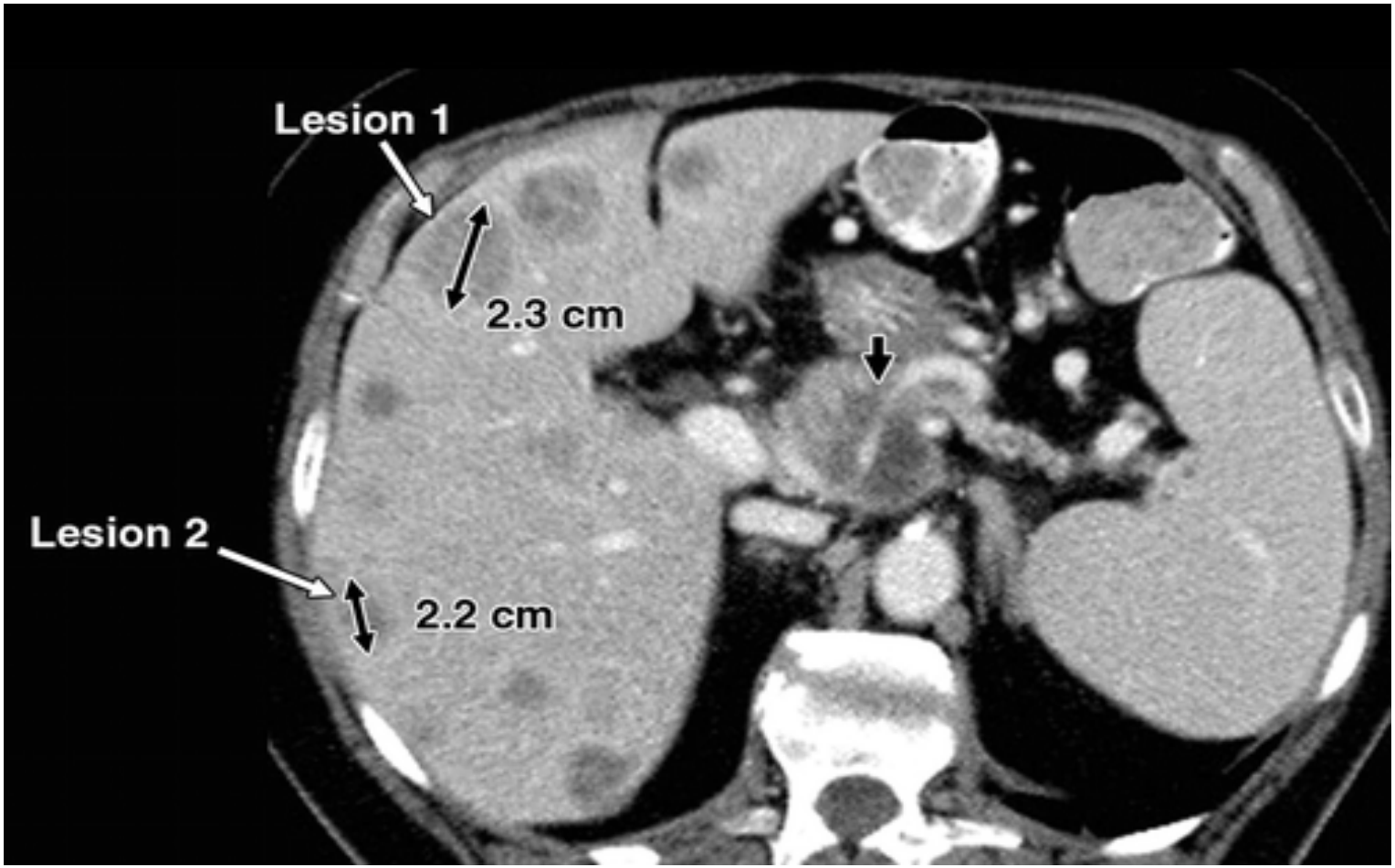
Lesions



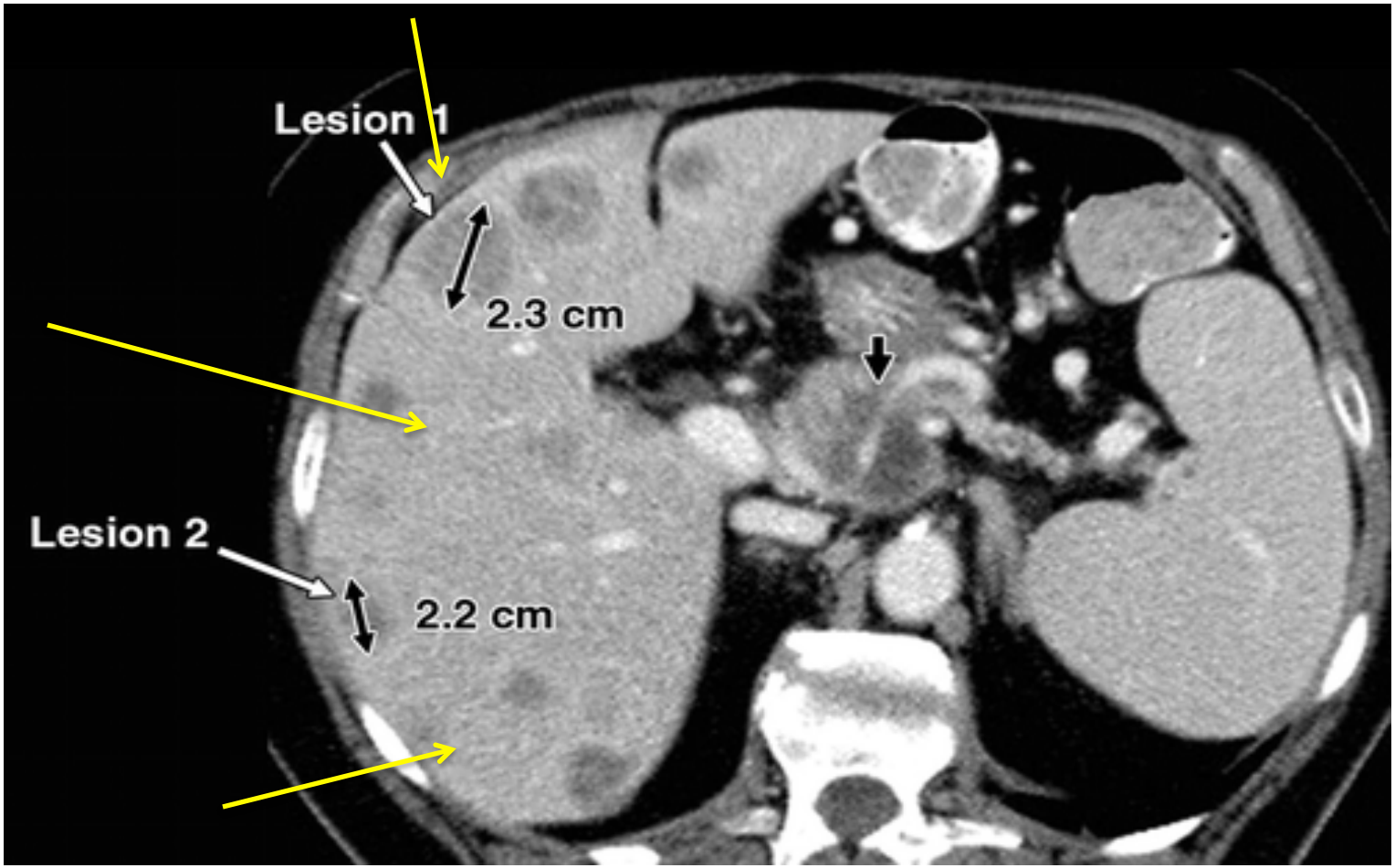
Measurable Lesion



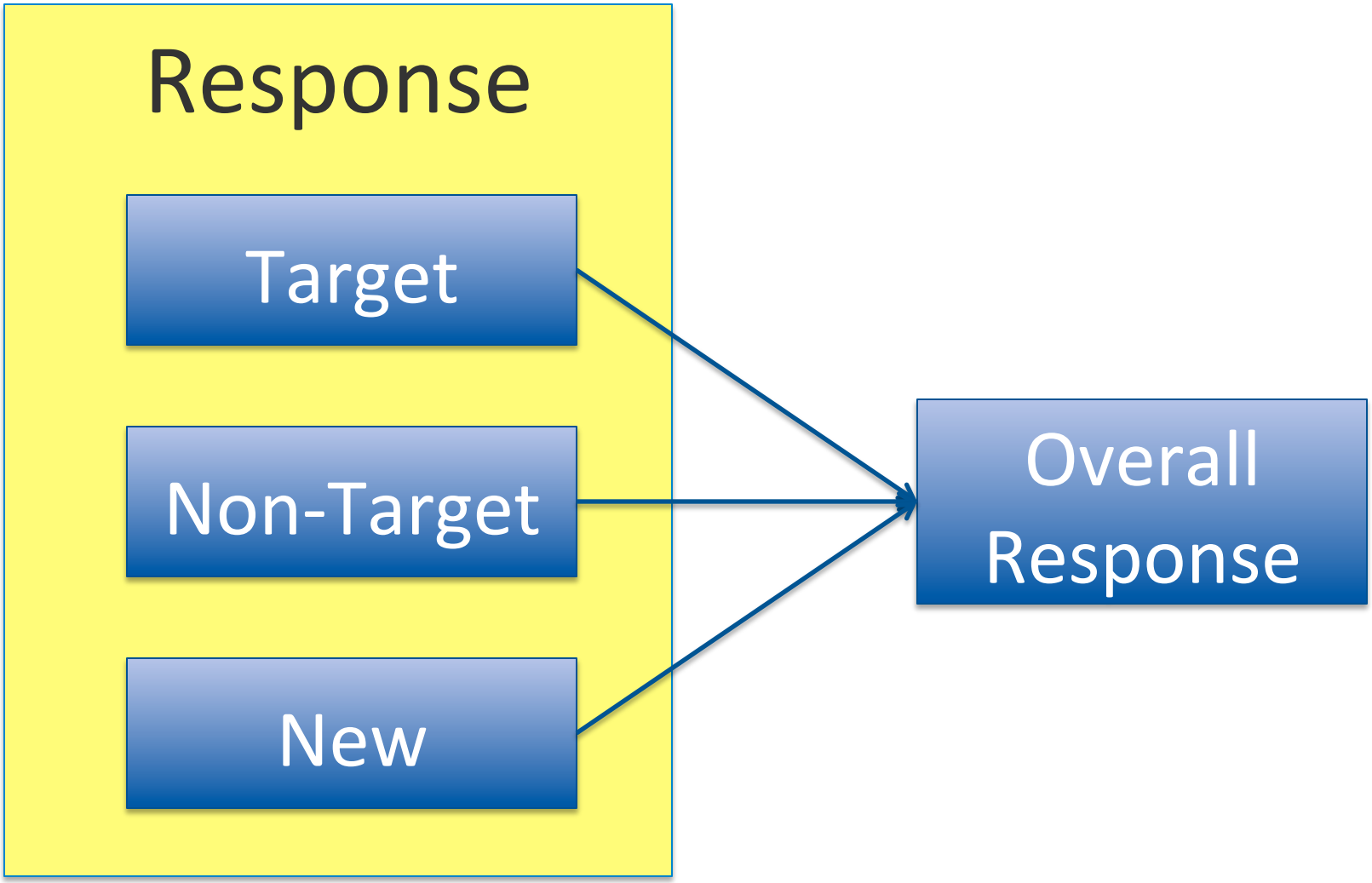
Target Lesions according to RECIST 1.1



Non Target Lesions



Evaluation of Changes in Tumor Results Measurements for Responses



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
- Progressive Diseases (PD) : 20 % increase from the smallest (at least more than 5 mm)
- Stable Disease (SD) :
- In-evaluable (NE)

Response Criteria of Non-Target lesions

- Complete Response (CR) : Disappearance of all non-target lesions
- Non-CR/Non-PD
- Progressive Diseases (PD) : unequivocal progression (an overall level of substantial worsening in non-target diseases)
- In-evaluable (NE)

Overall Response at given time point

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

Example

- Randomized and open label Phase II Study
- Solid Tumor following RECIST 1.1
- 5 cycles
- 3 target and 3 non-target lesions at screening
- Primary Efficacy – Objective Response Rate
- Secondary – Time-to-Progression and Progression Free Survival

CDISC Tumor Domain

- SDTM
  - TU : Tumor Identification
  - TR : Tumor Results
  - RS : Response
- ADaM (Time to Event ADaM datasets)
  - ADTR : Tumor Results Analysis Dataset
  - ADRS : Response Analysis Dataset
  - ADTTP : Time to Progression Analysis Dataset
  - ADPSF : Progression Free Survival Analysis Dataset

SDTM TU (Tumor Identification)

USUBJID	TULINKID	TUTESTCD	TUTEST	TUORRES	TULOC	TUMETHOD
001-01-001	T01	TUMIDENT	Tumor Identification	TARGET	ABDOMEN	CT SCAN
001-01-001	T02	TUMIDENT	Tumor Identification	TARGET	ABDOMEN	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

- Subject 001 has 3 target and 3 non-targets
- TU.TULINKID is connected TR.TRLINKID

SDTM TR at Screening

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT	TRDTC
001-01-001	Target	T01	LDIAM	Longest Diameter	Measurement	23	mm	Screening	2011-01-01
001-01-001	Target	T02	LDIAM	Longest Diameter	Measurement	22	mm	Screening	2011-01-01
001-01-001	Target	T03	LDIAM	Longest Diameter	Measurement	25	mm	Screening	2011-01-01
001-01-001	Target		SUMDIAM	Sum of Diameter	Measurement	70	mm	Screening	2011-01-01
001-01-001	Non-Target	NT01	TUMSTATE	Tumor State	Qualitative	PRESENT		Screening	2011-01-01
001-01-001	Non-Target	NT02	TUMSTATE	Tumor State	Qualitative	PRESENT		Screening	2011-01-01
001-01-001	Non-Target	NT03	TUMSTATE	Tumor State	Qualitative	PRESENT		Screening	2011-01-01

Key points

- Sum of Diameter was collected
- Target lesions were measured quantitatively and non-target qualitatively

SDTM TR at Cycle 1

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT	TRDTC
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

- Sum of Diameter changed from 70 mm to 35 mm
- No changes in non-target.

SDTM RS (Response)

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
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							14
001							15

Target Lesion	Non-target Lesions	New Lesions	Overall Response
PR	Non-PD or NE	No	PR

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

Analysis Variable Metadata including Analysis Parameter value level Metadata for ADTR (1)

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / 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 = Placebo, 2 = Study Drug	ADSL.TRTPN
ADTR	*ALL*	TRTP	Planned Treatment	text	$20	Placebo, Study Drug	ADSL.TRTP
ADTR	*ALL*	AVISITN	Analysis Visit (N)	integer	3.0		TR.VISITNUM
ADTR	*ALL*	AVISIT	Analysis Visit	text	$20		TR.VISIT

Analysis Variable Metadata including Analysis Parameter value level Metadata for ADTR (2)

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / 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,	

Analysis Variable Metadata including Analysis Parameter value level Metadata for ADTR (3)

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADTR	SDFRSM, NUMNTG, NEWLES	PARAMTYP	Parameter Type	text	$20	DERIVED	
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'
ADTR	TUMSTAT1, TUMSTAT2, TUMSTAT3	AVALC	Analysis Value (C)	text	$30		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'

Analysis Variable Metadata including Analysis Parameter value level Metadata for ADTR (5)

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
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 1	text	$50	PCHG > 120 and CHG > 5	

Key points (Target Lesions) :

- SUMDIA
  - if CRIT1FL = 'Y', CR
  - if CRIT2FL = 'Y', PR
- SDFRSM : if CRIT3FL = 'Y', PD
- no CRIT1, CRIT2 and CRIT3, SD

Analysis Variable Metadata including Analysis Parameter value level Metadata for ADTR (4)

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADTR	TUMSTAT1, TUMSTAT2, TUMSTAT3	CRIT4	Analysis Criteria 1	text	$50	AVALC = 'UNEQUIVOCAL'	
ADTR	NUMNTG	CRIT5	Analysis Criteria 1	text	$50	AVAL = 0	
ADTR	NEWLES	CRIT6	Analysis Criteria 1	text	$50	AVALC= 'Y'	

Key points

- Non-Target Lesions
  - TUMSTAT1, TUMSTAT2, TUMSTAT3 : if CRIT4FL = 'Y', PD
  - NUMNTG : if CRIT5FL = 'Y', CR
  - no CRIT4 and CRIT5, NonCR/NonPD
- New Lesions
  - NEWLES : if CRIT6FL = 'Y', 'Yes'; if not, 'No'

ADTR (Tumor Results Analysis Dataset) for Target Lesion at Cycle 1

USUBJID	PARAM	PARAMTYP	AVISIT	AVAL	AVALC	BASE	CHG	PCHG	CRIT2FL
001-01-001	Longest Diameter of Target 1 (mm)		Cycle 1	10		23			
001-01-001	Longest Diameter of Target 2 (mm)		Cycle 1	10		22			
001-01-001	Longest Diameter of Target 3 (mm)		Cycle 1	15		25			
001-01-001	Sum of Diameter (mm)		Cycle 1	35		70	-35	-50	Y
001-01-001	Sum of Diameter from smallest Sum of Diameter (mm),	DERIVED	Cycle 1	35		70	-35	-50	

Key points

- No CRIT1(aval=0) and CRIT3(pchg>120 and chg>5)
- CRIT2FL(CHG < -30) = 'Y', so PR
- Row 5: BASE(70) is the smallest Sum of Diameter

ADTR (Tumor Results Analysis Dataset) for non-target and new at Cycle 1

USUBJID	PARAM	PARAMTYP	AVISIT	AVAL	AVALC	BASE
001-01-001	Tumor State of Non-Target 1		Cycle 1		PRESENT	PRESENT
001-01-001	Tumor State of Non-Target 2		Cycle 1		PRESENT	PRESENT
001-01-001	Tumor State of Non-Target 3		Cycle 1		PRESENT	PRESENT
001-01-001	Number of Non-Target Lesion	DERIVED	Cycle 1	3		
001-01-001	New Lesion	DERIVED	Cycle 1		N	

Key points

- Non-Targets
  - No CRIT4(avalc='UNEQUIVOCAL') and CRIT5(aval=0), NonCR/NonPD
- New
  - No CRIT6(avalc='Y'), No

Responses Evaluation in Solid Tumor

- Efficacy Analysis
  - Objective Response Rate (ORR)
  - Time to Progression (TTP)
  - Progression Free Survival (PFS)
- Phase 1
  - Usually the secondary endpoints.
- Phase 2
  - Can be the primary endpoints.
  - All eligible patients (treated) patients
- Phase 3
  - Almost always a secondary endpoint

Best Overall Response for ORR

- Select the best overall response for a subject
- The best overall response does not worsen over time. - if a subject achieve CR at cycle 3 and PD at cycle 5, the best overall response is still CR

Confirmation of Response

- Needed for the trials where response is the primary end point.
- The confirmation of CR and PR
  - In Randomized trials, not needed.
  - In non-randomized trials or unblinded studies, the confirmation is needed at the subsequent visits (usually 4 weeks)
- The confirmation of SD – usually 6 to 8 weeks.

ADRS : Best Overall Response 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
001-01-001	Study Drug	Best Overall Response	DERIVED	End of Study	PR	
….						

Best Overall Response table when confirmation of CR and PR required

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, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE

ADRS : Best Overall Response when the confirmation of PR and CR IS needed (1)

USUBJID	TRTP	PARAM	AVISIT	AVALC	ADT	RSSEQ	_NAVALC	_DUR	_FOR
001-01-001	Study Drug	Overall Response	Cycle 1	PR	2011-03-01	3	SD	61	SD

Overall Response First Time point	Overall Response Subsequent time point	Best Overall Response
PR	SD	SD

USUBJID	TRTP	PARAM	AVISIT	AVALC	ADT	RSSEQ	_NAVALC	_DUR	_FOR
001-01-001	Study Drug	Overall Response	Cycle 4	PR	2011-12-01	12	PD	61	SD

Overall Response First Time point	Overall Response Subsequent time point	Best Overall Response
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Key points

- _NAVALC, _DUR, and _FOR are temporary ADaM plus variables
- AVALC for Best Overall Response will be collected from _FOR

ADRS : Best Overall Response when the confirmation IS needed (2)

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

Key point

- _NAVALC, _DUR, and _FOR are removed.

Final ADRS : Best Overall Response parameter for ORR analysis

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADRS	PARAMCD	PARAMCD	Parameter Code	text	$8	OBJRESP	
ADRS	OBJRESP	AVALC	Analysis Value (C)	text	$1	Y, N	'Y' If AVAL at "Best Overall Response" is 'CR' or 'PR'. 'N' otherwise.

USUBJID	TRTP	PARAMCD	PARAM	AVISIT	AVALC
001-01-001	Study Drug	BESTRESP	Best Overall Response	End of Study	PD
001-01-001	Study Drug	OBJRESP	Objective Response	End of Study	N
001-01-002	Control	BESTRESP	Best Overall Response	End of Study	SD
001-01-002	Control	OBJRESP	Objective Response	End of Study	N
001-01-003	Control	BESTRESP	Best Overall Response	End of Study	SD
001-01-003	Control	OBJRESP	Objective Response	End of Study	N
001-01-004	Study Drug	BESTRESP	Best Overall Response	End of Study	PR
001-01-004	Study Drug	OBJRESP	Objective Response	End of Study	Y
001-01-005	Study Drug	BESTRESP	Best Overall Response	End of Study	PD
001-01-005	Study Drug	OBJRESP	Objective Response	End of Study	N

Time to Progression (TTP)

USUBJID	TRTP	PARAM	AVAL	STARTDT	ADT	CNSR	EVNTDESC
001-01-001	Study Drug 1	Time to Progression (Days)	452	2011-01-01	2012-03-01	0	PROGRESSION DISEASE
001-01-002	Control	Time to Progression (Days)	338	2011-02-01	2012-01-05	1	LOST TO FOLLOW-UP
001-01-003	Control	Time to Progression (Days)	212	2011-02-05	2011-09-05	1	DEATH
001-01-004	Study Drug 1	Time to Progression (Days)	463	2011-03-20	2012-06-25	1	COMPLETED STUDY
001-01-005	Study Drug 1	Time to Progression (Days)	67	2011-03-26	2011-06-01	0	PROGRESSION DISEASE

Key point

- In TTP, DEATH is censored.

Progression Free Survival (PFS)

USUBJID	TRTP	PARAM	AVAL	STARTDT	ADT	CNSR	EVNTDESC
001-01-001	Study Drug 1	Progression Free Survival (Days)	452	2011-01-01	2012-03-01	0	PROGRESSION DISEASE
001-01-002	Control	Progression Free Survival (Days)	338	2011-02-01	2012-01-05	1	LOST TO FOLLOW-UP
001-01-003	Control	Progression Free Survival (Days)	212	2011-02-05	2011-09-05	0	DEATH
001-01-004	Study Drug 1	Progression Free Survival (Days)	463	2011-03-20	2012-06-25	1	COMPLETED STUDY
001-01-005	Study Drug 1	Progression Free Survival (Days)	67	2011-03-26	2011-06-01	0	PROGRESSION DISEASE

Key point

- In PFS, DEATH is NOT censored.

Conclusion

- ADaM
  - Science – RECIST 1.1 in sold tumor and ADaM IG
  - Art – telling a story about analysis
- ADaM is a story about analysis
  - Where it comes from
  - How it is built for analysis
  - How it will be used for analysis
- Very important to know about therapeutic characteristics and method for the study

Questions?