

CDISC Journey in Solid Tumor using RECIST 1.1

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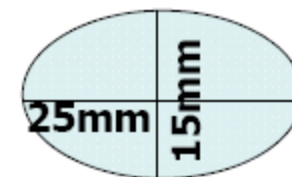
1. Introduction of Oncology
2. Introduction of RECIST
3. CDISC SDTM
4. CDISC ADaM
5. Conclusion
6. Questions

- In 2008, there were estimated 12,665,500 new cases of cancer worldwide.
- NIH reported that the cost of cancer in 2007 in the U.S. was 226.8 billion overall.
- One in eight deaths in the world are due to cancer.
- Cancer is the leading cause of death in developed countries.
- 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.

- How are the oncology studies different from other studies?
 - Tumor measurements and their response to drug
- How do we measure tumor and response?
 - Solid Tumor – RECIST 1.1
 - Lymphoma – Cheson 2007 or IWCLL 2008
 - Leukemia – Study specific

$$\mathcal{L}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

- RECIST(Response Evaluation Criteria in Solid Tumor)
 - Version 1.0 and 1.1 (released on October 2008)
- Lesions
 - Any abnormalities in the tissue of an organism - tumors
 - Measurable and Non-Measurable
 - 10 mm by CT scan
 - 10 mm caliper measurement by clinical exam
 - 20 mm by Chest X-ray
 - Target, Non-Target and New
- One-dimensional measurement (longest diameter).



- 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

$$\mathcal{L}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

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

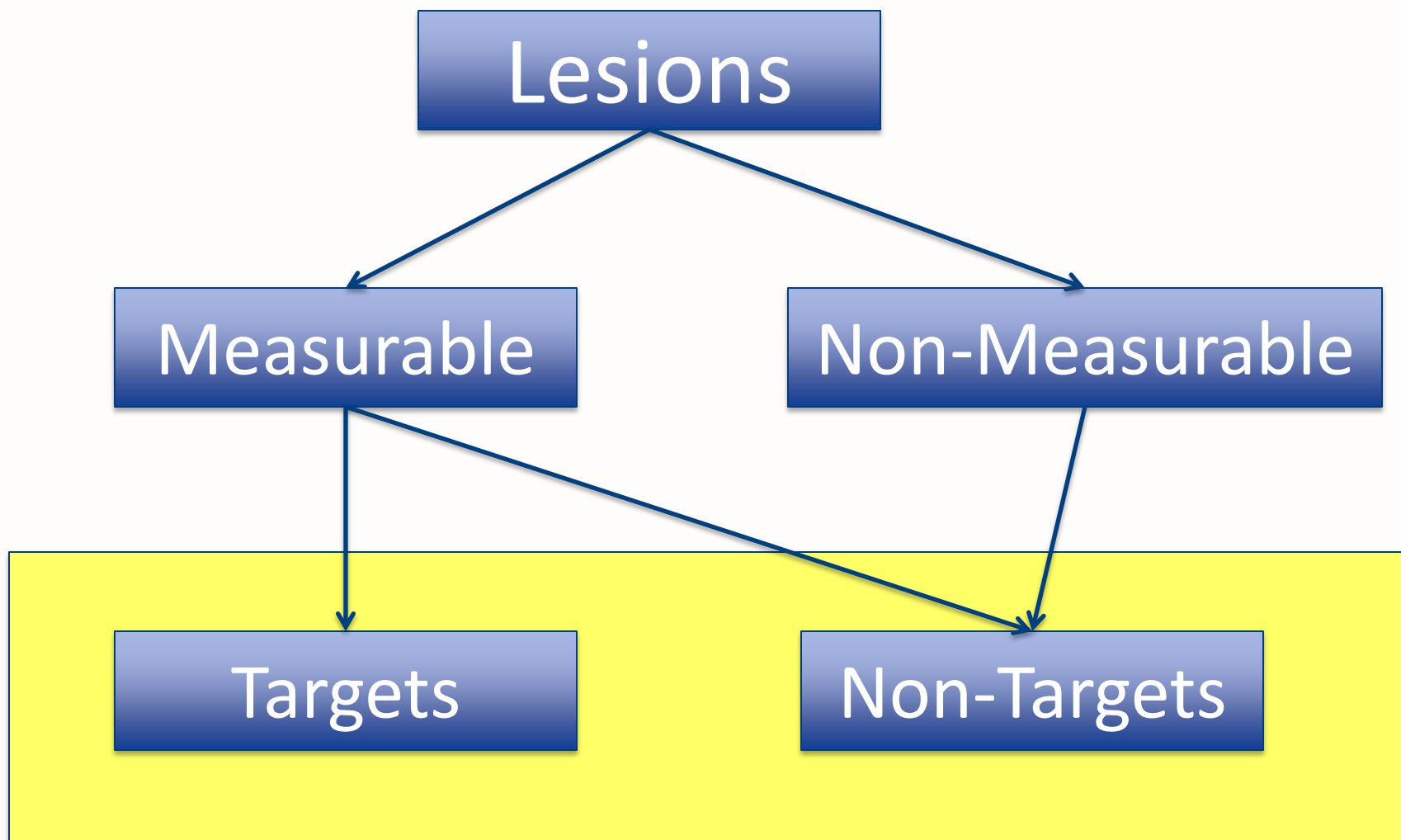
New Lesions according to RECIST 1.1

$$\mathcal{L}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

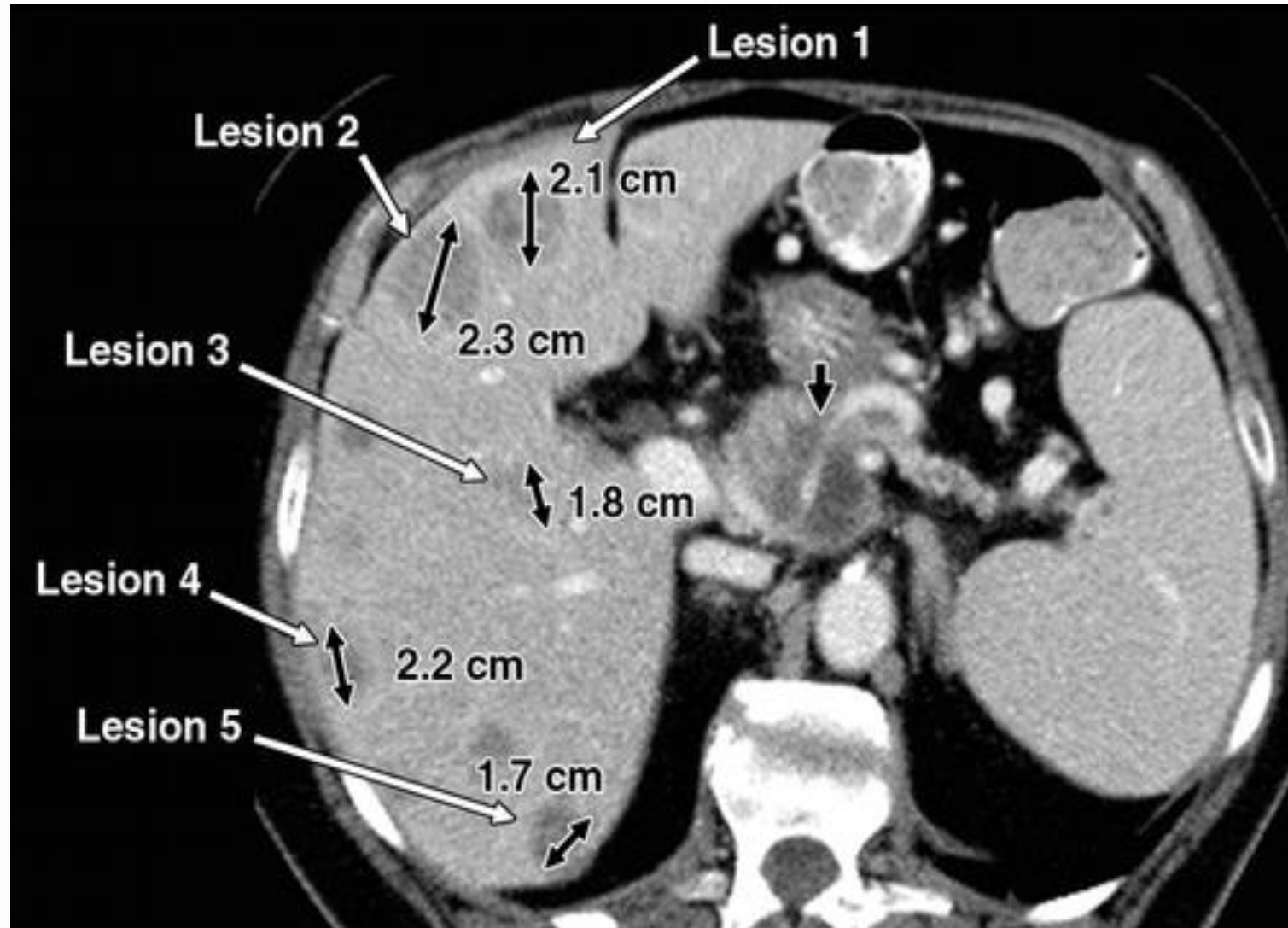
- Any lesions that are newly found at post-baseline
- Either quantitative or qualitative measurements

Lesions at baseline

$$\mathcal{P}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$



Measurable Lesions at baseline

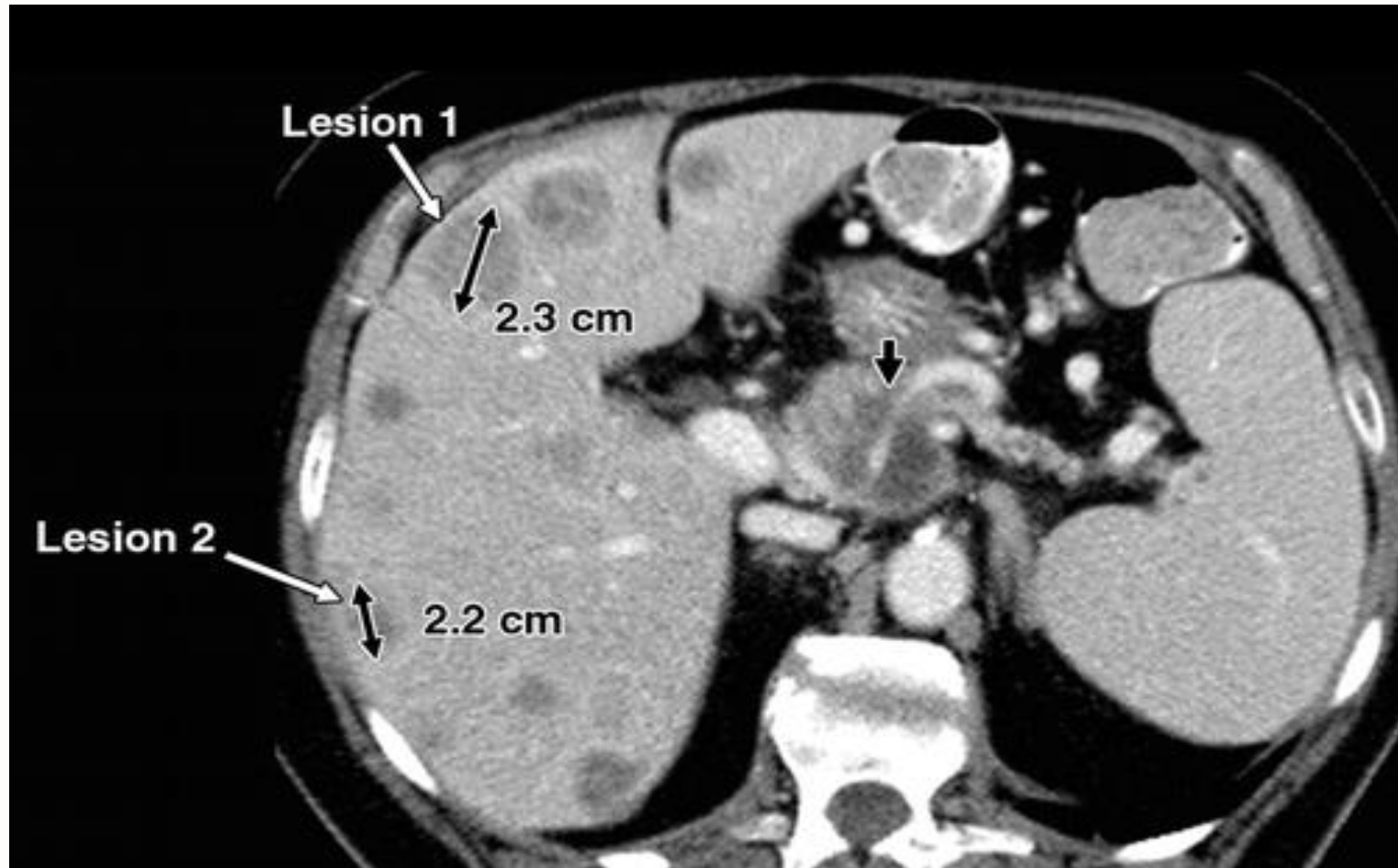


$$\mathcal{L}_U(z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

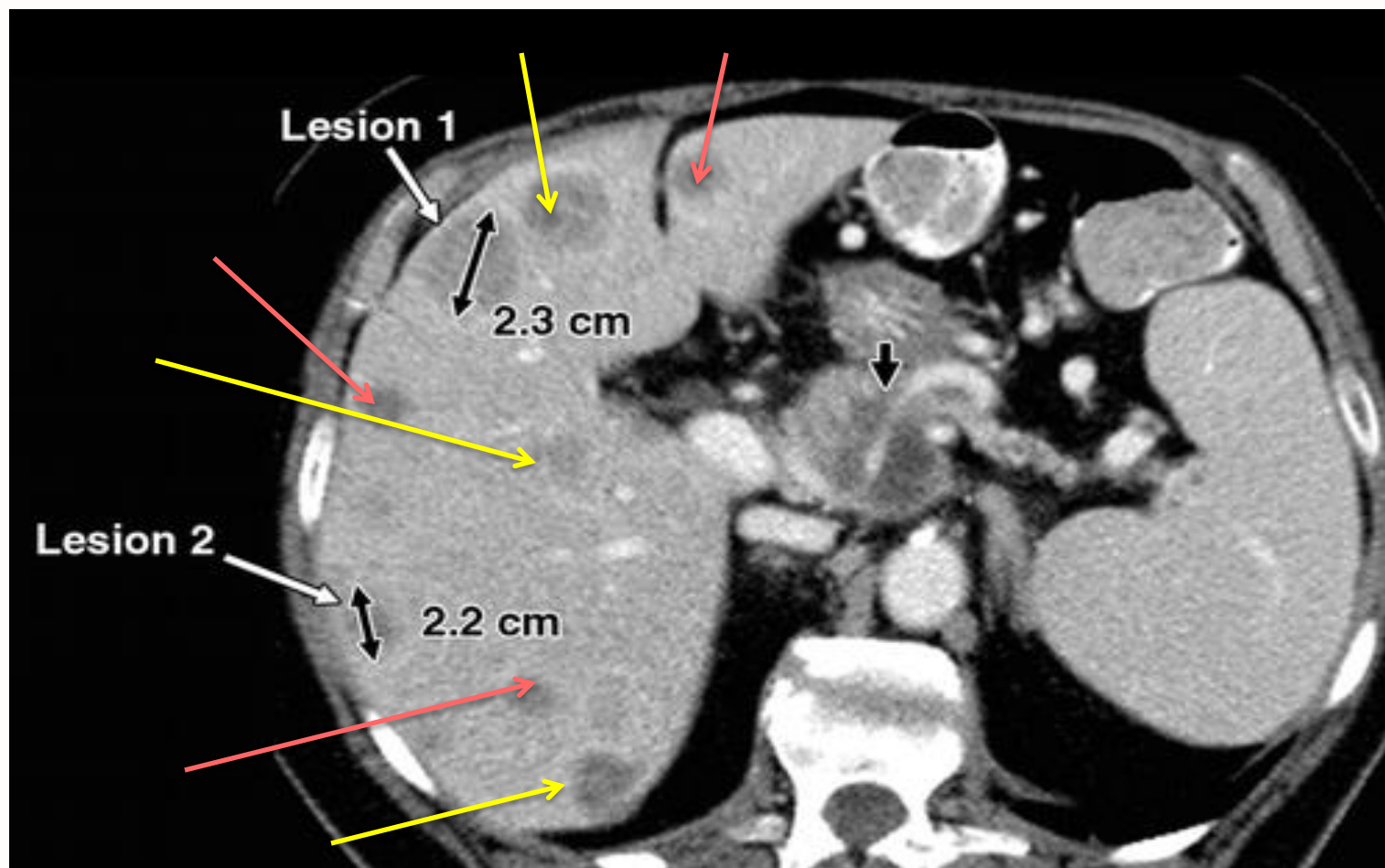
Target Lesions at baseline according to RECIST 1.1

Cytel

$$\mathcal{L}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

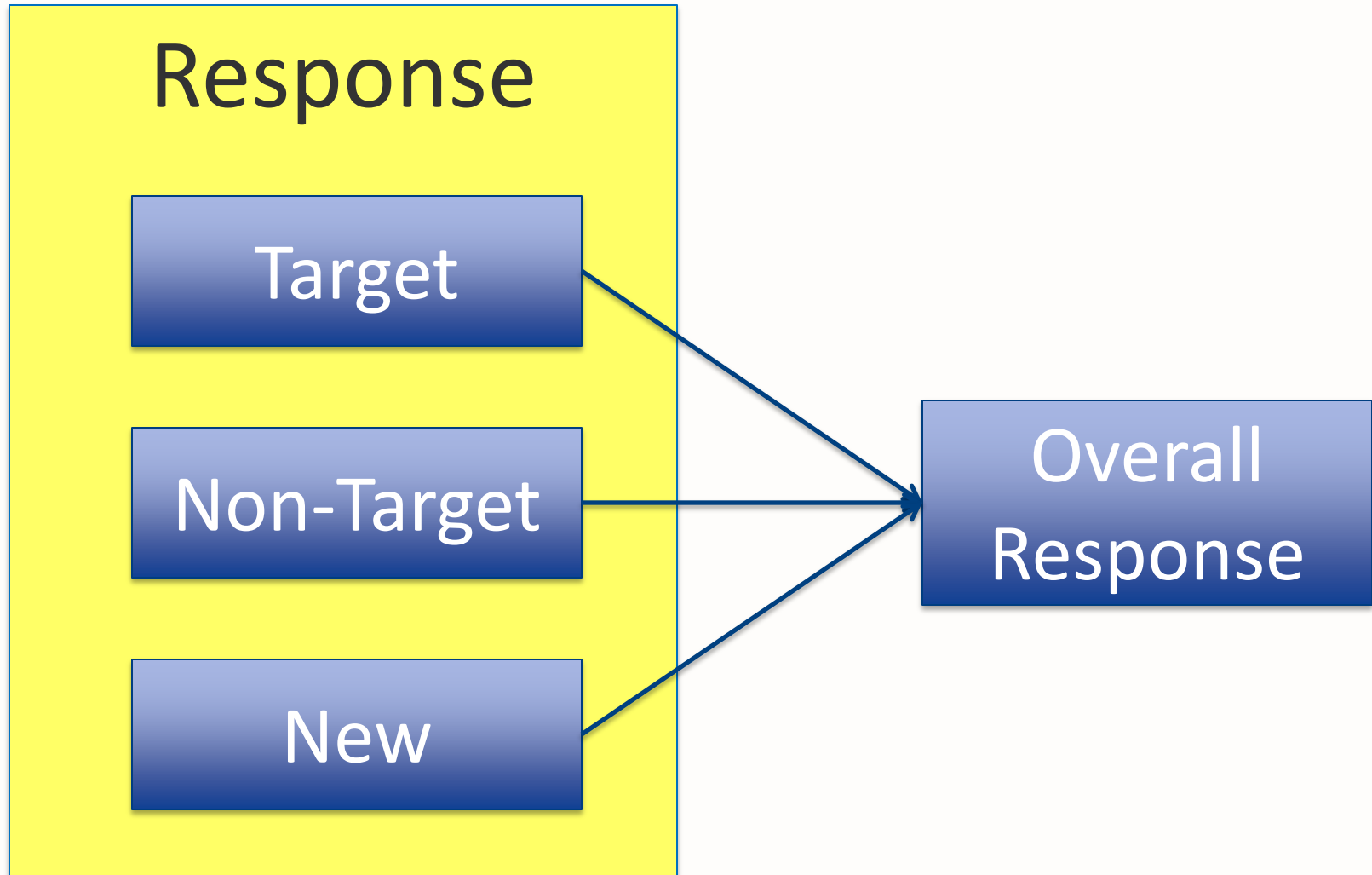


Non Target Lesions at baseline



Evaluation of Changes in Tumor Results Measurements for Responses

$$\mathcal{P}_u(z_1) = \Pr(Z_2 > b_2 \mid Z_1 = z_1, \delta = 0)$$



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

- 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)
- Not Evaluable (NE)

$$\mathcal{L}_U(Z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

Overall Response at given time point

$$\mathcal{L}_U(Z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

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

$$\mathcal{L}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

- 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

$$\mathcal{L}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

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

SDMT 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 to note:

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

SDMT TR at Screening

USUBJID	TRGRID	TRLINKID	TRTEST CD	TRTEST	TRCAT	TORRES	TORRESU	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 to note:

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

SDMT TR at Cycle 1

USUBJID	TRGRID	TRLINKID	TRTEST CD	TRTEST	TRCAT	TRORRES	TRORESU	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 to note:

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

SDMT RS (Response)

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSBTC	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	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 1	2011-03-01	3
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PR	Cycle 1	2011-03-01	4
001-01-001	TRGRESP	Target Response	RECIST 1.1	SD	Cycle 2	2011-06-01	5
001-01-001	Target Lesion		Non-target Lesions		New Lesions		6
001-01-001							7
001-01-001							8
001-01-001	PR		Non-PD or NE		No		9
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 3	2011-09-01	10
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 3	2011-03-01	11
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PR	Cycle 3	2011-09-01	12
001-01-001	TRGRESP	Target Response	RECIST 1.1	PR	Cycle 4	2011-12-01	13
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 4	2011-12-01	14
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	Y	Cycle 4	2011-03-01	15
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PD	Cycle 4	2011-12-01	16

Responses Efficacy Evaluation in Solid Tumor

$$\mathcal{L}_U(Z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

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

Best Overall Response for ORR

$$\mathcal{L}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

- 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

$$\mathcal{L}_U(Z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

- 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.

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 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	PR	9
001-01-001	Study Drug	Overall Response		Cycle 4	PD	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	
....						

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

USUBJID	TRTP	PARAM	AVISIT	AVALC	ADT	RSSEQ	_NAVALC	_DUR	_CBOR
001-01-001	Study Drug	Overall Response	Cycle 1	PR	2011-03-01	3	SD	61	SD
001-01-001	Study Drug	Overall Response	Cycle 2	SD	2011-03-01	6	SD	62	SD
Overall Response First Time point		Overall Response Subsequent time point			Best Overall Response				
PR		SD			SD				
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		PD			SD provided minimum criteria for SD duration met, otherwise, PD				
Drug		Response		Study					

Key points to note:

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

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	PD	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 points to note:

- _NAVALC, _DUR, and _CBOR are removed.

Final ADRS : Objective 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 points to note:

- 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 points to note:

- In PFS, DEATH is NOT censored.

$$\mathcal{L}_U(z_1) = \Pr(Z_2 > b_2 | Z_1 = z_1, \delta = 0)$$

- Standard
 - RECIST 1.1 : Tumor Measurements and Responses
 - CDISC – SDTM : data collection
 - CDISC – ADaM : analysis
- Very important to know about therapeutic specific characteristics and method.

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Questions?

