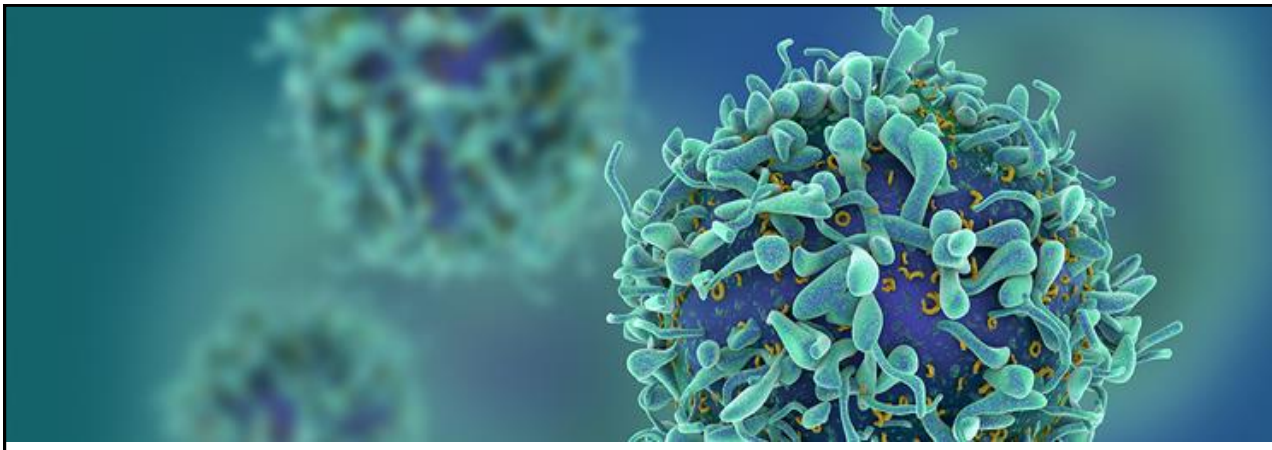


Oncology Study Seminar

Kevin Lee, AVP at Genpact

1

Rules for Today

- Participate. Get engaged.
- Make mistakes.
- Learn from mistakes. Learn from each other.
- Raise your hands.
- Ask questions. There are no dumb questions.
- Bring your own questions.
- If you need a break, please take a break.
- Bring notepad so you can do exercise.
- Discuss.
- Laugh. Have a fun.

2

Agenda

- Introduction of Oncology
- Oncology Subtypes – Solid Tumor, Lymphoma, Leukemia
- Response Criteria – RECIST, irRC, Cheson, IWCLL
- Solid Tumor - RECIST 1.1 and data collections
- Oncology-specific CDISC Standards (SDTM, ADaM, CT)
- Immunotherapy – irRC, data collection and CDISC
- Lymphoma – Cheson, data collections and CDISC
- Leukemia – IWCLL, data collections and CDISC
- Oncology-specific Analysis (ORR, OS, PFS, Kaplan Meier Curve)
- End to End Standards-driven Oncology Studies
- Conclusion

3

Cancer Facts

- The word 'cancer' is related to the Greek word "crab" because its finger-like projections were similar to the shape of the crab
- The economic cost of the disease worldwide is estimated at $1.16 trillion.
- One in eight deaths in the world are due to cancer.
- Cancer is the second leading cause of death in the world.
- There were new cancer cases of 1.9 million in 2021 in US and about 600k people died of the cancer.
- 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. In terms of surviving cancer, women also benefited from being married, but to a lesser extent.

4

FDA CDER NMEs and BLAs Approval

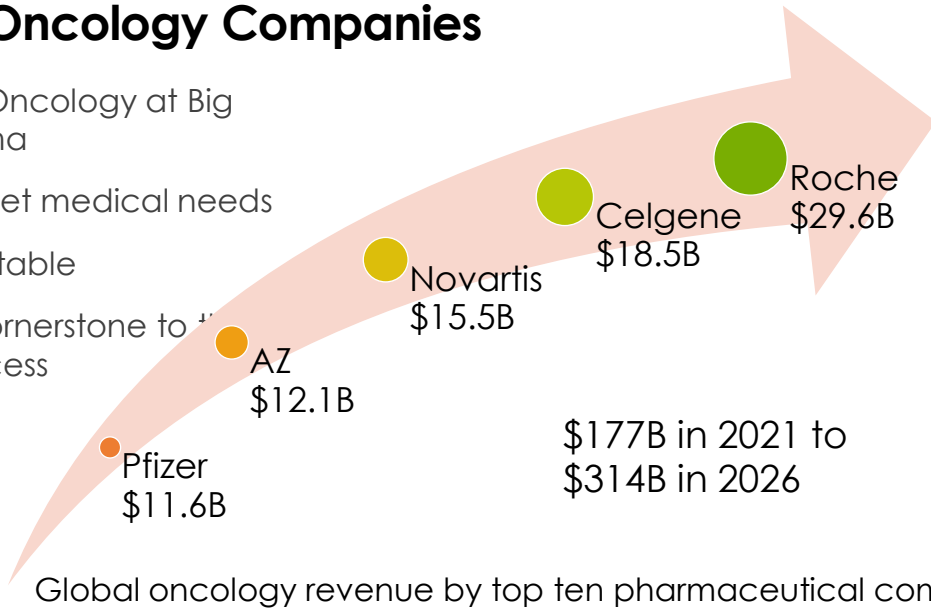
- 2012 - 39 Approval, 13 Oncology (33 %)
- 2013 - 27 Approval, 8 Oncology (30 %)
- 2014 - 41 Approval, 9 Oncology (22%)
- 2015 - 45 Approval, 13 Oncology (29%)
- 2016 - 22 Approval, 6 Oncology (27%)
- 2017 - 46 Approval, 12 Oncology (26%)
- 2018 - 59 Approval, 14 Oncology (24%)
- 2019 - 48 Approval, 9 Oncology (19%)
- 2020 - 53 Approval, 18 Oncology (34%)
- 2021 - 50 Approval, 16 Oncology (32%)
- Note: based on the reports of **NMEs and BLAs approved by CDER**

5

Top Oncology Companies

Why Oncology at Big Pharma

- Unmet medical needs
- Profitable
- A cornerstone to t
  success



Global oncology revenue by top ten pharmaceutical companies 2017

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Difference in Oncology Studies

- Many different study types
- Tumor measurements and their response to drug
- Oncology-specific measurements for response criteria (e.g., Liver and Spleen Enlargement, Bone Marrow Infiltrate and Blood Counts)
- Oncology-diagnosis measurements (e.g., immunophenotype, performance status on ECOG, staging)
- Drug Exposure
- Toxicity (Lab and AE)
- Time to Event Analysis (e.g., OS, PFS, TTP and ORR)
- CDISC – SDTM, ADaM, CT
- Unique Study Design

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Oncology Subtypes

- Solid Tumor
  - An abnormal mass of tissue that is not cysts or liquid
  - Most common
  - Type – breast, prostate, lung, liver and pancreatic cancer and melanoma
- Lymphoma
  - Cancer that starts in Lymph Node
  - Tumor type: Enlarged Lymph Node, Nodal Mases, Extra Nodal Masses
- Leukemia
  - Cancer that usually begins in the bone marrow and result in high number of WBC
  - Types:
    - Chronic Lymphocytic Leukemia(CLL)
    - Chronic Myeloid Leukemia(CML)
    - Acute Lymphoblastic Leukemia (ALL)
    - Acute Myeloid Leukemia (AML)

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Oncology Specific Standards

Response Criteria Guideline

- What to collect
- How to measure
- How to determine responses from measurements

CDISC

- How to store information/data

Analysis

- ORR
- Time to Event Analysis (e.g., OS, PFS, KM curves)

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Response Criteria

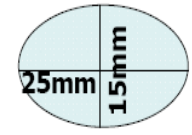
10

Response Criteria Guidelines

Solid Tumor	Lymphoma	Leukemia
• RECIST (Response Evaluation Criteria in Solid Tumor) 1.1 • irRECIST(Immune-related RECIST) 2013 • iRECIST (Immune RECIST) 2017	• Cheson 2007 • Cheson 2014 (2014 Lugano classification)	• IWCLL 2008 • IWAML 2003 • NCCN Guideline 2012 on ALL • CML ESMO Guidelines

RECIST

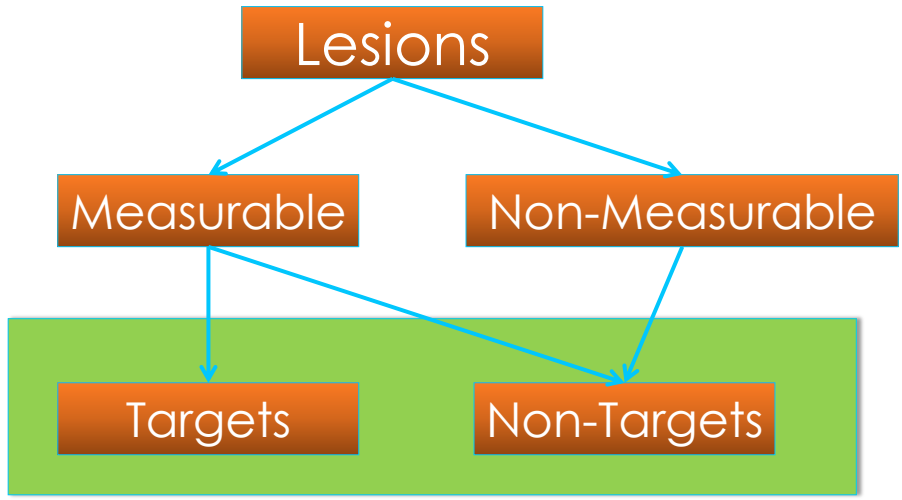
- Response Criteria for Solid Tumor
- RECIST(Response Evaluation Criteria in Solid Tumor)
  - Version 1.0 and 1.1 (released on October 2008)
- Lesions
  - Any abnormalities in the tissue of an organism - tumors
  - Measurable and Non-Measurable
    - 10 mm by CT scan
    - 10 mm caliper measurement by clinical exam
    - 20 mm by Chest X-ray
  - Target, Non-Target and New
- One-dimensional measurement (longest diameter) – 25 or 15?



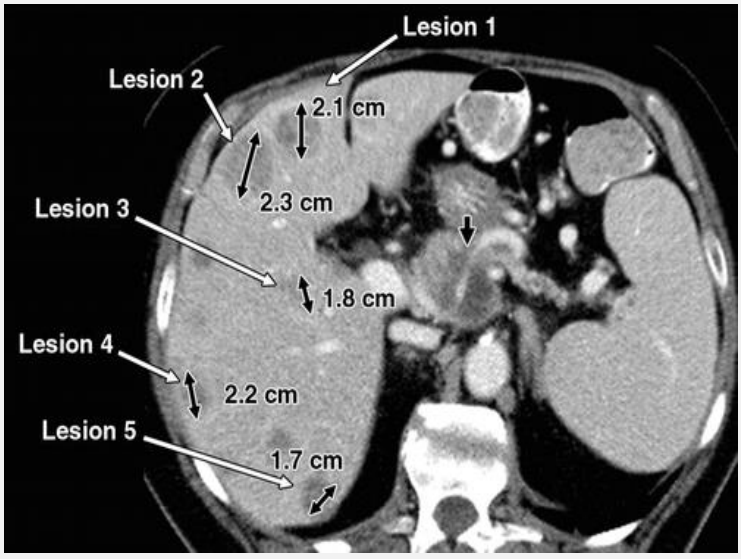
Target/Non-Target Lesions according to RECIST 1.1

- Target Lesions
  - 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 (SUM = Lesion 1 + Lesion 2 + Lesion 3)
- Non-Target Lesions
  - All other lesions beside Target lesions
  - Measurement - Present, Absent, Unequivocal progression.
- New Lesions
  - Any lesions that are newly found at post-baseline
  - Either quantitative or qualitative (Equivocal / Unequivocal) measurements

Lesions at Baseline



Measurable Lesions Found at Baseline



Questions

- Any measurable lesions?
- Any non-measurable lesions?
- Which ones are target?
- Which ones are non-target?

5 Measurable Lesions on this organ

15

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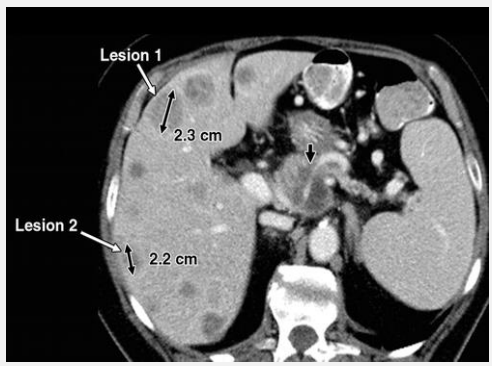
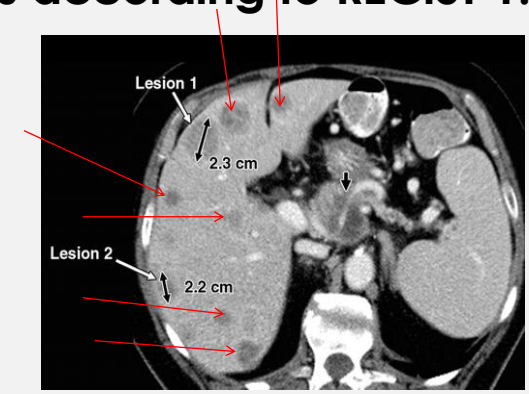
Target & Non-Target Lesions according to RECIST 1.1



Target Lesions

- Target Lesion 1 : 23 mm
- Target Lesion 2 : 22 mm



Non-Target Lesions

- Non-Target Lesion 1
- Non-Target Lesion 2
- Non-Target Lesion 3
- Non-Target Lesion 4
- Non-Target Lesion 5
- Non-Target Lesion 6

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Response Criteria of Target & Non-Target Lesions

- Target Lesions
  - 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)

- 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)
  - Not Evaluable (NE)

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Exercise : Response of Target & Non-Target Lesions

- Target Lesions
  - If Baseline (50 mm) & Visit 1 (0 mm), response at Visit 1?
  - If Baseline (50 mm) & Visit 1 (30 mm), response at Visit 1?
  - If Baseline (50 mm) & Visit 1 (20 mm) & Visit 2 (25 mm) , response at Visit 1 and Visit 2?
  - If Baseline (50 mm) & Visit 1 (40 mm), response at Visit 1?
- Non-Target Lesions
  - If Baseline (3 non-target lesions) & Visit 1 (none), response at Visit 1?
  - If Baseline (3 non-target lesions) & Visit 1 (2 non-target lesions), response at Visit 1?
  - If Baseline (3 non-target lesions) & Visit 1 (2 non-target lesions & one non-target is unequivocal progression), response at Visit 1?

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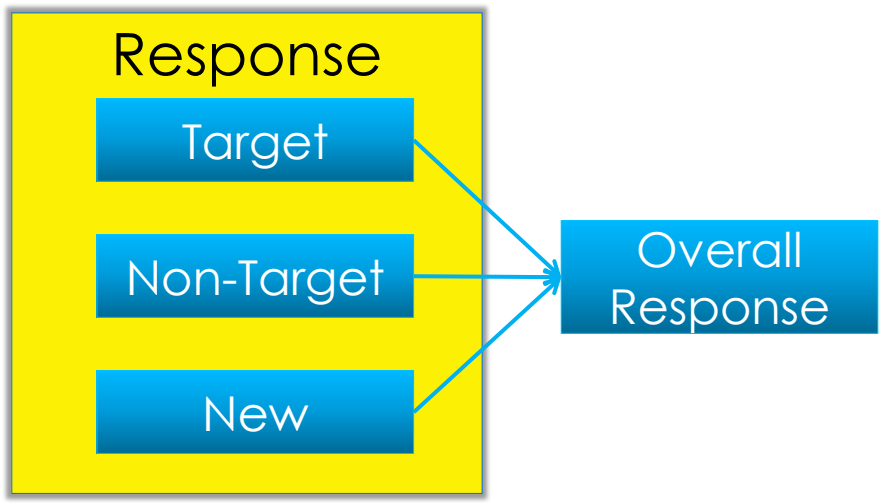
Exercise : Response of Target & Non-Target Lesions

- Target Lesions
  - If Baseline (50 mm) & Visit 1 (0 mm), response at Visit 1? CR
  - If Baseline (50 mm) & Visit 1 (30 mm), response at Visit 1? PR (-20/50 = -40%)
  - If Baseline (50 mm) & Visit 1 (20 mm) & Visit 2 (25 mm) , response at Visit 1 and Visit 2? PR (-30/50 = -60%) at Visit 1 & PD (5/25 = 20%) at Visit 2
  - If Baseline (50 mm) & Visit 1 (40 mm), response at Visit 1? SD (-10/50 = 20%)
- Non-Target Lesions
  - If Baseline (3 non-target lesions) & Visit 1 (none), response at Visit 1? CR
  - If Baseline (3 non-target lesions) & Visit 1 (2 non-target lesions), response at Visit 1? NON-CR/NON-PD
  - If Baseline (3 non-target lesions) & Visit 1 (2 non-target lesions & one non-target is unequivocal progression), response at Visit 1? PD

Evaluation of Changes in Tumor Results Measurements for Responses at given visit



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

Questions: Overall Response?

RSTEST	RSORRES	VISIT
Target Response	PR	Cycle 1
Non-target Response	NON-CR/NON-PD	Cycle 1
New Lesion Progression	N (EQUIVOCAL)	Cycle 1
Overall Response	PR	Cycle 1
Target Response	SD	Cycle 2
Non-target Response	PD	Cycle 2
New Lesion Progression	N (EQUIVOCAL)	Cycle 2
Overall Response	PD	Cycle 2
Target Response	CR	Cycle 3
Non-target Response	NON-CR/NON-PD	Cycle 3
New Lesion Progression	N (EQUIVOCAL)	Cycle 3
Overall Response	PR	Cycle 3
Target Response	PR	Cycle 4
Non-target Response	NON-CR/NON-PD	Cycle 4
New Lesion Progression	Y (UNEQUIVOCAL)	Cycle 4
Overall Response	PD	Cycle 4

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Confirmation of Response

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

Note : Duration is defined in study protocol.

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Best Overall Response table when confirmation of CR and PR required

Overall Response First Time point (Cycle 1)	Overall Response Subsequent time point (Cycle 2)	Best Overall Response (Cycle 1)
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

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Confirmation of Response

USUBJID	PARAM	AVISIT	AVALC
001-01-001	Overall Response	Cycle 1	CR
001-01-001	Overall Response	Cycle 2	CR
001-01-001	Overall Response	Cycle 3	PR
001-01-001	Overall Response	Cycle 4	PD
001-01-001	Overall Response	Cycle 5	SD
001-01-001	Confirmed Overall Response	Cycle 1	CR
001-01-001	Confirmed Overall Response	Cycle 2	PR
001-01-001	Confirmed Overall Response	Cycle 3	SD
001-01-001	Confirmed Overall Response	Cycle 4	PD
001-01-001	Confirmed Overall Response	Cycle 5	

1. Cycle 1 : CR (current cycle) & CR (next cycle) then CR
2. Cycle 2: CR (current cycle) & PR (next cycle) then PR
3. Cycle 3: PR (current cycle) & PD (next cycle) then SD if more than 60 days

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Exercise : Review on RECIST 1.1

Tumor Lesions	Measurement	location
01	23	Lung
02	15	Lung
03	16	Lung
04	Non-measurable	Lung
05	16	Liver
06	11	Liver
07	Non-measurable	Liver
08	Non-measurable	Liver
09	15	Prostate
10	14	Prostate
11	11	Prostate
12	Non-measurable	Prostate

Q: Patient has 12 tumor lesions at baseline.

- What are target lesions?
- What are not target lesions?
- Sum of diameter?

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Exercise : Review on RECIST 1.1

Tumor Lesions	Measurement	location
01	23	Lung
02	15	Lung
03	16	Lung
04	Non-measurable	Lung
05	16	Liver
06	11	Liver
07	Non-measurable	Liver
08	Non-measurable	Liver
09	15	Prostate
10	14	Prostate
11	11	Prostate
12	Non-measurable	Prostate

Q: Patient has 12 tumor lesions at baseline.

- What are target lesions?
  - 01,03, 05, 09,10
- What are not target lesions?
  - All other
- Sum of diameter?
  - 23 + 16 + 16 + 15 + 14 = 84

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Oncology specific CDISC Standards

CDISC Oncology Specific Standards

- SDTM / CDASH
  - TU : Tumor/Lesion Identification
  - TR : Tumor/Lesion Results
  - RS : Disease Response
- ADaM
  - -TTE : Time to Event Analysis Datasets
- CT
  - Response Criteria :
    - CR(Complete Response)
    - PR(Partial Response)
    - PD(Progressive Disease)
    - SD(Stable Disease)
    - NE (Not Evaluable)
    - irCR, irPR, irPD, irSD / iCR, iPR, iPD, iSD

CDISC Oncology Specific Standards

- CT
  - Tumor Measurements :
    - DIAM(Diameter)
    - SUMDIA(Sum of Diameter)
    - LDIAM(Longest Diameter)
    - LPERP(Longest Perpendicular)
    - AREA(Area)
    - SUMAREA(Sum of Area; Sum of Products of Perpendicular Diameters)
    - TUMSTATE(Tumor State)
  - Response :
    - TRGRESP(Target Response)
    - NTRGRESP (Non-Target Response)
    - NEWLPROG(New Lesion Progression)
    - OVRLRESP(Overall Response)
    - BESTRESP(Best Response)

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CDASH TU (Tumor Identification)

CDASHIG Variable	Question Text	SDTMIG Target	Permissible Values
TUYN	Were any [target/non-target/new/sponsor-defined) [tumors/lesions] identified?		Yes/No
TUDAT	What was the date of the [examination/procedure] used for [tumor/lesion identification]?	TUDTC	
TUEVAL	Who provided the information?; Who was the evaluator?	TUEVAL	
TUEVALID	What was the identifier of the evaluator?	TUEVALID	
TULNKID	What was the [tumor/lesion] (link) identifier?	TULNKID	T01;T02;NT01;NT01;N01;N02
TUMETHOD	What was the method used to [evaluate/identify] the [tumor/lesion]?	TUMETHOD	
TUREFID	What was the procedure [reference identifier/accession number]?	TUREFID	
TUTEST	What was the [tumor/lesion] Identification test name?	TUTEST; TUTESTCD	Tumor Identification ; Tumor Split ; Tumor Merged
TUORRES	What is the [type/classification] of [tumor/lesion] as defined by the criteria being employed?	TUORRES	TARGET ; NON-TARGET ; NEW
TUCHANGE	Indicate what type of change to the tumor was indentified	TUORRES	Tumor Split ; Tumor Merged
TULOC	What was the anatomical location of the [tumor/lesion] (identified)?	TULOC	
TULAT	What was the laterality of the anatomical location?	TULAT	
TUDIR	What was the directionality of the anatomical location?	TUDIR	
TULOCDTL	If applicable, what is the additional detail about the tuor location?	QVAL	

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SDTM TU (Tumor Identification)

- SDTM domain that identifies the tumor.
- Main variables in TU
  - TULINKID (Link ID) – link with TR.TRLINKID
  - TUTESTCD (Tumor Identification Short Name)
  - TUTEST (Tumor Identification Test Name)
    - TUMIDENT – Tumor Identification
    - TUSPLIT – Tumor Split
    - TUMERGE – Tumor Merged
  - TUORRES (Tumor Identification Result) – TARGET, NON-TARGET, NEW
  - TULOC (Location of the Tumor)
  - TUMETHOD (Method of Identification)
  - TUEVAL (Evaluator)
  - VISITNUM
  - TUDTC

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SDTM TU (Tumor Identification)

- Permissible variables in TU
  - TUGRPID (Group ID) – used to link together a block of related records within a subject
  - TUREFID (Reference ID) – internal or external identifier. Ex. Medical image ID number
  - TUSPID (Sponsor ID) – sponsor-defined identifier
  - TUSTRESC (Tumor Identification Result Std. Format)
  - TUCAT (Category for Tumor Identification)
  - TUSCAT (Sub-category for Tumor Identification)
  - TUNAM (Vendor Name)
  - TULAT (Laterality) – Ex. LEFT, RIGHT, BILATERAL
  - TUDIR (Directionality) – Ex. UPPER, INTERIOR
  - TUPORTOT (Portion or Totality) – Ex. ENTIRE, SINGLE, SEGMENT, MULTIPLIE
  - TUEVALID (Evaluator Identifier)
  - TUACPTFL (Accepted Record Flag) – for accepted assessment.

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SDTM TU Example

TULINKID	TUTESTCD	TUTEST	TUORRES	VISIT
T01	TUMIDENT	Tumor Identification	TARGET	Screening
T02	TUMIDENT	Tumor Identification	TARGET	Screening
T03	TUMIDENT	Tumor Identification	TARGET	Screening
T04	TUMIDENT	Tumor Identification	TARGET	Screening
NT01	TUMIDENT	Tumor Identification	NON-TARGET	Screening
NT02	TUMIDENT	Tumor Identification	NON-TARGET	Screening
NT03	TUMIDENT	Tumor Identification	NON-TARGET	Screening
T04.01	TUSPLIT	Tumor Split	TARGET	Cycle 1
T04.02	TUSPLIT	Tumor Split	TARGET	Cycle 1
….				
T02/T03	TUMERGE	Tumor Merged	TARGET	Cycle 2
NEW01	TUMIDENT	Tumor Identification	NEW	Cycle 2

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CDASH TR (Tumor Results)

CDASHIG Variable	Question Text	SDTMIG Target	Permissible Values
TRLNKGRP	What was the [tumor/lesion] [link group] identifier?	TRLNKGRP	C1; C2; C3
TRSTAT	Indicate if the [tumor/lesion] evaluation was not done.	TRSTAT	NOT DONE
TRREASND	What was the reason that the [tumor/lesion] was not [evaluated/assessed]?	TRREASND	
TREVAL	Who provided the information?; Who was the evaluator?	TREVAL	
TREVALID	What was the identifier of the evaluator?	TREVALID	
TRDAT	What was the date of the procedure used for [tumor/lesion] assessment?	TRDTC	
TRLNKID	What was the [tumor/lesion] Identifier?	TRLNKID	T01;T02;NT01;NT01;N01; N02
TRTEST	What was the [tumor/ lesion] (assessment) test name?	TRTEST; TRTESTCD	Diameter; Sum of Diameter ; Tumor Sate
TRORRES	What is the result for the [tumor/lesion assessment]?	TRORRES; TRTESTCD;	
TRORRESU	What was the unit of the [result/measurement]?	TRORRESU	mm
TRNAM	What was the name of the vendor used?	TRNAM	

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SDTM TR (Tumor Results)

- SDTM domain that collects quantitative measurements and qualitative assessments of the tumor identified in TU domains.
- Main variables in TR
  - TRLINKID (Link ID) – link with TU.TULINKID
  - TRTESTCD (Tumor Assessment Short Name)
  - TRTEST (Tumor Assessment Test Name)
    - LDIAM – Longest Diameter
    - SUMDIAM – Sum of Diameter
    - TUMSTATE – Tumor State (PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION)
    - AREA – Area
    - SUMAREA – Sum of Area
  - TRORRES / TRORRESU / TRSTRESN / TRSTRESC (Tumor Result)
  - TULOC (Location of the Tumor)
  - TRMETHOD (Method of Identification)
  - TREVAL (Evaluator)
  - VISITNUM
  - TRDTC

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SDTM TR (Tumor Result)

- Permissible variables in TR
  - TRGRPID (Group ID)
  - TRREFID (Reference ID)
  - TRSPID (Sponsor ID)
  - TRSTAT (Completion Status)
  - TRREASND (Reason Tumor Measurement Not Performed)
  - TRNAM (Vendor Name)
  - TREVALID (Evaluator Identifier)
  - TRACPTFL (Accepted Record Flag) – for accepted assessment.

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SDTM TR Example

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	VISIT
001-02-001	Target	T01	LDIAM	Longest Diameter	23	mm	Screening
001-02-001	Target	T02	LDIAM	Longest Diameter	22	mm	Screening
001-02-001	Target	T03	LDIAM	Longest Diameter	25	mm	Screening
001-02-001	Target		SUMDIAM	Sum of Diameter	70	mm	Screening
001-02-001	Non-Target	NT01	TUMSTATE	Tumor State	PRESENT		Screening
001-02-001	Non-Target	NT02	TUMSTATE	Tumor State	PRESENT		Screening
001-02-001	Target	T01	LDIAM	Longest Diameter	22		Cycle 1
001-02-001	Target	T02	LDIAM	Longest Diameter	25		Cycle 1
001-02-001	Target	T03	LDIAM	Longest Diameter			Cycle 1
001-02-001	Target	T03.01	LDIAM	Longest Diameter	15	mm	Cycle 1
001-02-001	Target	T03.02	LDIAM	Longest Diameter	17	mm	Cycle 1
001-02-001	Target		SUMDIAM	Sum of Diameter	79	mm	Cycle 1
001-02-001	New	NEW01	TUMSTATE	Tumor State	PRESENT		Cycle 1
001-02-001	Non-Target	NT01	TUMSTATE	Tumor State	PRESENT		Cycle 1
001-02-001	Non-Target	NT02	TUMSTATE	Tumor State	ABSENT		Cycle 1

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CDASH RS (Disease Response)

CDASHIG Variable	Question Text	SDTMIG Target	Permissible Values
RSPERF	Was the [(disease) response/clinical classification] assessment performed?	RSSTAT	Yes/No
RSREASND	Why was the [disease response/clinical classification] assessment not performed?	RSREASND	
RSDAT	What was the date the response or clinical classification was performed?	RSDTC	
RSEVAL	What was the role of the person performing the [disease response/clinical classification] assessment?	RSEVAL	
RSEVALID	What is the evaluator identifier?	RSEVALID	
RSLNKGRP	What was the [Disease Response or Clinical Classification] Link Group Identifier?	RSLNKGRP	
NEWLIND_RSORRES	Was a new lession detected at this assessment?	RSTEST ; RSORRES	RSTEST = 'New Lesion Progression" ; RSORRES = 'Y'
TRGRESP_RSORRES	What was the Target Response?	RSTEST ; RSORRES	RSTEST = "Target Response" ; RSORRES = 'CR'/'PR'/'SD'/'PD'/'NE'
NTRGRESP_RSORRES	What was the Non-Target Response?	RSTEST ; RSORRES	RSTEST = "Non-target Response" ; RSORRES = 'CR'/'PR'/'NON-CR/NON-PD'/'PD'/'NE'
OVRLRESP_RSORRES	What was the Overall Response?	RSTEST ; RSORRES	RSTEST = "Overall Response" ; RSORRES ='CR'/'PR'/'SD'/'PD'/'NE'

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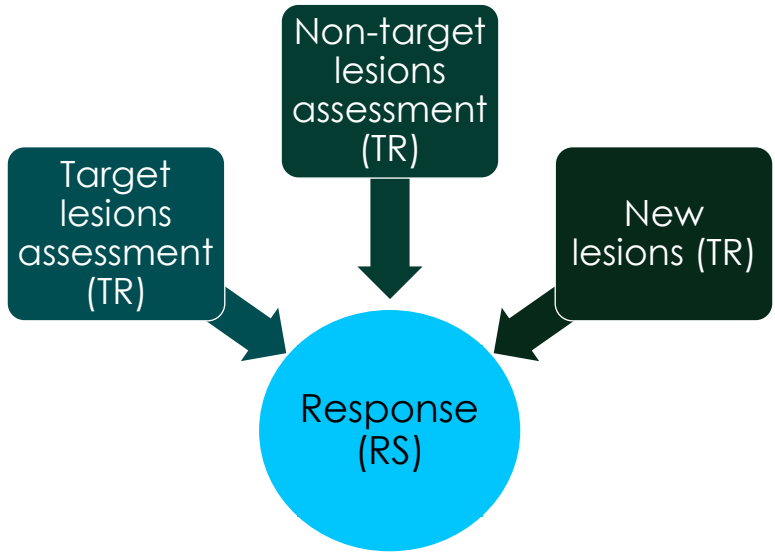
SDTM RS (Disease Response)

- SDTM domain that indicates the response evaluation determined from data in TR domain.
- Main variables in RS
  - RSTESTCD (Assessment Short Name)
  - RSTEST (Response Assessment Test Name)
    - TRGRESP – Target Response
    - NTRGRESP – Non-target Response
    - NEWLPROG – New Lesion Progression
    - OVRLRESP – Overall Response
  - RSORRES (Response Assessment)
    - CR (Complete Response)
    - PR (Partial Response)
    - SD (Stable Disease)
    - PD (Progressive Disease)
  - RSEVAL (Evaluator)
  - VISITNUM
  - RSDTC

SDTM RS (Disease Response)

- Permissible variables in RS
  - RSGRPID (Group ID)
  - RSREFID (Reference ID)
  - RSSPID (Sponsor ID)
  - RSCAT (Category for Response Assessment)
  - RSSTAT (Completion Status)
  - RSREASND (Reason Tumor Measurement Not Performed)
  - RSNAM (Vendor Name)
  - RSEVALID (Evaluator Identifier)
  - RSACPTFL (Accepted Record Flag) – for accepted assessment.

Data Collection and its SDTM in Solid Tumor using RECIST



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SDTM RS Example

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT
001-01-001	TRGRESP	Target Response	RECIST 1.1	PR	Cycle 1
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 1
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 1
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PR	Cycle 1
001-01-001	TRGRESP	Target Response	RECIST 1.1	SD	Cycle 2
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 2
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	Y	Cycle 2
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PD	Cycle 2
001-01-001	TRGRESP	Target Response	RECIST 1.1	PD	Cycle 3
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 3
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 3
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PD	Cycle 3
001-01-001	TRGRESP	Target Response	RECIST 1.1	CR	Cycle 4
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	CR	Cycle 4
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 4
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	CR	Cycle 4

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Ex. SDTM TU at Screening

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

Key points to note:

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

Ex. SDTM TR at Screening

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

Key points to note:

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

Ex. SDTM TU at Cycle 1

USUBJID	TULINKID	TUTESTCD	TUTEST	TUORRES	TULOC	TUMETHOD	VISIT
001-01-001	T01	TUMIDENT	Tumor Identification	TARGET	ABDOMEN	CT SCAN	Cycle 1
001-01-001	T02	TUMIDENT	Tumor Identification	TARGET	ABDOMEN	CT SCAN	Cycle 1
001-01-001	T03	TUMIDENT	Tumor Identification	TARGET	THYROID	CT SCAN	Cycle 1
001-01-001	NT01	TUMIDENT	Tumor Identification	NON-TARGET	LIVER	CT SCAN	Cycle 1
001-01-001	NT02	TUMIDENT	Tumor Identification	NON-TARGET	KIDNEY	CT SCAN	Cycle 1
001-01-001	NT03	TUMIDENT	Tumor Identification	NON-TARGET	SPLEEN	CT SCAN	Cycle 1

Key points to note:

- Subject 001 has 3 targets and 3 non-targets at Cycle 1
- TU.TULINKID is connected TR.TRLINKID using RELREC.
- Q: Any changes from screening?

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Ex. SDTM TR at Cycle 1

USUBJID	TRGRID	TRLNKID	TRLNKGRP	TRTESTCD	TRTEST	TRORRES	TRORRESU	VISIT
001-01-001	Target	T01	C1	LDIAM	Longest Diameter	10	mm	Cycle 1
001-01-001	Target	T02	C1	LDIAM	Longest Diameter	10	mm	Cycle 1
001-01-001	Target	T03	C1	LDIAM	Longest Diameter	15	mm	Cycle 1
001-01-001	Target		C1	SUMDIAM	Sum of Diameter	35	mm	Cycle 1
001-01-001	Non-Target	NT01	C1	TUMSTATE	Tumor State	PRESENT		Cycle 1
001-01-001	Non-Target	NT02	C1	TUMSTATE	Tumor State	PRESENT		Cycle 1
001-01-001	Non-Target	NT03	C1	TUMSTATE	Tumor State	PRESENT		Cycle 1

Key points to note:

- Sum of Diameter changed from 70 mm to 35 mm
- No changes in non-target.
- No new lesions
- Q: what is the response at Cycle 1?

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Ex. SDTM RS at Cycle 1

USUBJID	RSLNKGRP	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSSEQ
001-01-001		TRGRESP	Target Response	RECIST 1.1	PR	Cycle 1	1
001-01-001		NTRGRESP	Non-target Response	RECIST 1.1	NON-CR /NON-PD	Cycle 1	2
001-01-001		NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 1	3
001-01-001	C1	OVRLRESP	Overall Response	RECIST 1.1	PR	Cycle 1	4

Key points to note:

- TR.TRLNKGRP is connected to RS.RSLNKGRP by RELREC.
- Overall Response at Cycle 1 is derived from responses of
  - Target Response – PR (-50%)
  - Non-target Response – NON-CR/NON-PD (No Change)
  - New Lesion Progression – No new lesion found

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EX. SDTM TU at Cycle 2

USUBJID	TULINKID	TUTESTCD	TUTEST	TUORRES	TULOC	TUMETHOD	VISIT
001-01-001	T01	TUMIDENT	Tumor Identification	TARGET	ABDOMEN	CT SCAN	Cycle 2
001-01-001	T02	TUMIDENT	Tumor Identification	TARGET	ABDOMEN	CT SCAN	Cycle 2
001-01-001	T03	TUMIDENT	Tumor Identification	TARGET	THYROID	CT SCAN	Cycle 2
001-01-001	NT01	TUMIDENT	Tumor Identification	NON-TARGET	LIVER	CT SCAN	Cycle 2
001-01-001	NT02	TUMIDENT	Tumor Identification	NON-TARGET	KIDNEY	CT SCAN	Cycle 2
001-01-001	NT03	TUMIDENT	Tumor Identification	NON-TARGET	SPLEEN	CT SCAN	Cycle 2
001-01-001	T03.1	TUSPLIT	Tumor Split	TARGET	THYROID	CT SCAN	Cycle 2
001-01-001	T03.2	TUSPLIT	Tumor Split	TARGET	THYROID	CT SCAN	Cycle 2
001-01-001	T01/T02	TUMERGE	Tumor Merged	TARGET	ABDOMEN	CT SCAN	Cycle 2

Split / Merging at Cycle 2

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Ex. SDTM TR at Cycle 2

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	TRSTAT	VISIT
001-01-001	Target	T01	LDIAM	Longest Diameter			NOT DONE	Cycle 2
001-01-001	Target	T02	LDIAM	Longest Diameter			NOT DONE	Cycle 2
001-01-001	Target	T03	LDIAM	Longest Diameter			NOT DONE	Cycle 2
001-01-001	Target	T01/T02	LDIAM	Longest Diameter	25	mm		Cycle 2
001-01-001	Target	T03.1	LDIAM	Longest Diameter	11	mm		Cycle 2
001-01-001	Target	T03.2	LDIAM	Longest Diameter	12	mm		Cycle 2
001-01-001	Target		SUMDIAM	Sum of Diameter	48	mm		Cycle 2
001-01-001	Non-Target	NT01	TUMSTATE	Tumor State	PRESENT			Cycle 2
001-01-001	Non-Target	NT02	TUMSTATE	Tumor State	PRESENT			Cycle 2
001-01-001	Non-Target	NT03	TUMSTATE	Tumor State	PRESENT			Cycle 2

Ex. SDTM RS at Cycle 2

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSSEQ
001-01-001	TRGRESP	Target Response	RECIST 1.1	PD	Cycle 2	1
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NON-CR/NON-PD	Cycle 2	2
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 2	3
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PD	Cycle 2	4

Key points to note:

- Overall Response at Cycle 2 is derived from responses of
  - Target Response – PD (+37%)
  - Non-target Response – NON-CR/NON-PD (No Change)
  - New Lesion Progression – No new lesion found

Answer: SDTM RS

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSSEQ
001-01-001	TRGRESP	Target Response	RECIST 1.1	PR	Cycle 1	1
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NON-CR/NON-PD	Cycle 1	2
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 1	3
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PR	Cycle 1	4
001-01-001	TRGRESP	Target Response	RECIST 1.1	PD	Cycle 2	5
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NON-CR/NON-PD	Cycle 2	6
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 2	7
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PD	Cycle 2	8

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

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Q: How to add "New" lesion in TU and TR at Cycle 3

USUBJID	TULINKID	TUTESTCD	TUTEST	TUORRES	TULOC	TUMETHOD	VISIT
001-01-002	N01	TUMIDENT	Tumor Identification	NEW	ABDOMEN	CT SCAN	Cycle 3

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	VISIT
001-01-002	NEW	N01	LDIAM	Longest Diameter	10	mm	Cycle 3
or							
001-01-002	NEW	N01	TUMSTATE	Tumor State	PRESENT		Cycle 3

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT
001-01-002	TRGRESP	Target Response	RECIST 1.1	Any	Cycle 3
001-01-002	NTRGRESP	Non-target Response	RECIST 1.1	Any	Cycle 3
001-01-002	NEWLPROG	New Lesion Progression	RECIST 1.1	Y	Cycle 3
001-01-002	OVRLRESP	Overall Response	RECIST 1.1	PD	Cycle 3

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Considerations on SDTM Tumor domains

- RELREC domains for TU & TR domains

RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
TU		TULINKID		ONE	TUTR-1
TR		TRLINKID		MANY	TUTR-1

- Data Collection consideration in CRF
  - Pages – Target, Non-Target & New lesions
  - Tumor lesion number to follow up
  - Merged & Split information
- Response in CRF might not include "New" lesion information. It could only contain overall response information.

Immunotherapy Study: Data Collections & CDISC

Response Criteria for Immunotherapy

- Background
  - Immunotherapy involves agents which harness the body's own immune system to fight cancer.
  - Immunotherapy usually takes longer for patients to respond to drugs.
  - Immunotherapy can also increase tumor burden and new lesions before a response was obtained.
- Type
  - irRC (Immune-related Response Criteria) in 2009
  - irRECIST (Immune-related RECIST) in 2013
  - iRECIST (Immune RECIST) in 2017
  - imRECIST (Immune-modified RECIST) in 2018
- Its usage
  - Mainly for data collection and exploratory analysis
  - Mostly used in early phases

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irRECIST (Immune-related RECIST)

- The response criteria for immunotherapy studies
- irRECIST (immune-related RECIST) – released in 2013
- Use Tumor Burden rather than index lesions (measurable, target lesions at baseline)
- Different response for new lesions

	RECIST	irRECIST
New, measurable lesions	PD	Incorporate into tumor burden
New, non-measurable lesions	PD	Not always PD, but not irCR

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Tumor Burden Example between RECIST1.1 & irRECIST

New Lesion in RECIST

TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT
Target	T01	LDIAM	Longest Diameter	Measurement	20	mm	Cycle 1
Target	T02	LDIAM	Longest Diameter	Measurement	15	mm	Cycle 1
Target	T03	LDIAM	Longest Diameter	Measurement	15	mm	Cycle 1
Target		SUMDIAM	Sum of Diameter	Measurement	50	mm	Cycle 1
New	N01	LDIAM	Longest Diameter	Measurement	10	mm	Cycle 1

New Lesion in irRECIST using Tumor Burden

TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT
Target	T01	LDIAM	Longest Diameter	Measurement	20	mm	Cycle 1
Target	T02	LDIAM	Longest Diameter	Measurement	15	mm	Cycle 1
Target	T03	LDIAM	Longest Diameter	Measurement	15	mm	Cycle 1
New Target	N01	LDIAM	Longest Diameter	Measurement	10	mm	Cycle 1
Target		SUMDIAM	Sum of Diameter	Measurement	60	mm	Cycle 1

Assuming T01, T02 and T03 have not changed from baseline, response in RECIST is PD, but SD in irRECIST.

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irRECIST Response

Tumor burden – baseline target(index lesions) + measurable new lesions

- irCR (immune-related Complete Response) – Disappearance of all lesions in two consecutive observations not less than 4 weeks
- irPR (immune-related Partial Response) - >= 30% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart
- irSD (immune-related Stable Disease) - < 30% decrease and < 20% increase in tumor burden
- irPD (immune-related Progressive Disease) - at least 20% increase in tumor burden compared with nadir (at any single time point) in two consecutive observation at least 4 week part

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irRECIST Response at given time point

Measurable response		Non-measurable response		Overall Response
Tumor Burden(Target at baseline + New)		**Non-index lesions (Non-Target at baseline)**	**New, non-measurable lesions**	**Using irRECIST**
↓ 100	irCR	Absent	Absent	irCR
↓ 100	irCR	Stable	Any	irPR
↓ 100	irCR	Unequivocal progression	Any	irPD
↓≥ 30	irPR	Absent/Stable	Any	irPR
↓≥ 30	irPR	Unequivocal progression	Any	irPD
↓< 30 to ↑< 20	irSD	Absent/Stable	Any	irSD
↓< 30 to ↑< 20	irSD	Unequivocal progression	Any	irPD
↑< 20	irPD	Any	Any	irPD
Any	Any	Any	Unequivocal progression	irPD

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Exercise

- Baseline
  - Target : target 1(10), target 2(20) & target 3(20) and SUMDIAM = 50 mm
  - Non-target : 3 present
- Cycle 1
  - Target SUMDIAM stays in 50 mm
  - Non-target : 3 present
  - New measurable lesion – 10 mm
- What is Response at Cycle 1 based on RECIST
  - Target ( ) Non-target ( ) New lesion ( )
  - Overall –
- What is Response at Cycle 1 based on irRC
  - Tumor burden ( ) Non-target ( ) New lesion ( )
  - Overall -

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Exercise

- Baseline
  - Target : target 1(10), target 2(20) & target 3(20) and SUMDIAM = 50 mm
  - Non-target : 3 present
- Cycle 1
  - Target SUMDIAM stays in 50 mm
  - Non-target : 3 present
  - New measurable lesion – 9 mm
- What is Response at Cycle 1 based on RECIST
  - Target (SD) Non-target (NON-CR/NON-PD) New lesion (Y)
  - Overall – PD
- What is Response at Cycle 1 based on irRC
  - Tumor burden (irSD) Non-target (irSD) New lesion (Y)
  - Overall - irSD

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iRECIST (Immune RECIST)

- The response criteria for immunotherapy studies
- iRECIST (immune RECIST) – released in 2017
- Use Tumor Burden rather than index lesions (measurable, target lesions at baseline)
- Confirmation is needed for PD : iUPD and at next cycle, iCPD from the previous cycle iUPD.

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irRECIST Response

- iCR (immune Complete Response) – Disappearance of all lesions & No new lesion
- iPR (immune Partial Response) - >= 30% decrease in tumor burden
- iSD (immune Stable Disease) - < 30% decrease and < 20% increase in tumor burden
- iUPD (immune Unconfirmed Progressive Disease) - at least 20% increase in tumor burden or presence of new lesion
- iCPD (immune Confirmed Progressive Disease) - confirmation of iUPD with >= 5 mm increase or an increase of new lesion

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iRECIST Overall Response at given time point

Target Lesion	Non-Target Lesions	New Lesions	Overall Response (no prior iUPD)	Overall Response (prior iUPD)
iCR	iCR	No	iCR	
iCR	iSD	No	iPR	
iPR	iSD	No	iPR	
iSD	iSD	No	iSD	
iCR, iPR, iSD	iUPD	No	iUPD	iCPD if any increase in NT lesions iUPD Otherwise
iUPD	iSD / iCR	No	iUPD	iCPD if SOM increased by >= 5 mm iUPD Otherwise
iUPD	iUPD	No	iUPD	iCPD if SOM of T lesion increased by >= 5 mm if any increase in NT lesions iUPD Otherwise
iUPD	iUPD	Yes	iUPD	iCPD if SOM of T lesion increased by >= 5 mm if any increase in NT lesions if New lesions increase in size or number iUPD Otherwise
iCR, iPR, iSD	iCR, iPR, iSD	Yes	iUPD	iCPD if New lesions increase in size or number iUPD Otherwise

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iRECIST Overall Response Example

Response	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
T lesions	100	125 (PD)	65 (PR)	65 (PR)	60 (PR)	90 (PD)
NT lesions	2 Present	2 Present (SD)	2 Present (SD)	2 Present (SD)	2 Present (SD)	2 Present (SD)
New lesions		Yes (PD)	No (SD)	No (SD)	Yes (PD)	No (SD)
RECIST1.1 Overall Response		PD	PD	PD	PD	PD
iRECIST Overall Response		iUPD	iPR	iPR	iUPD	iCPD

For Progression Analysis

- RECIST 1.1 starts at Cycle 1
- iRECIST starts at Cycle 4 since iUPD of Cycle 4 is confirmed at the subsequent Cycle. Just note that iUPD at Cycle 1 is not confirmed at the subsequent cycle.

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Comparison Between RECIST and irRECIST

	RECIST 1.1	IrRC	irRECIST	iRECIST	imRECIST
Release Date	2008	2009	2013	2017	2018
Measuring Dimension	One	Two	One	One	One
PD of Target lesions	20% increase from the nadir	25% increase from the nadir	20% increase from the nadir	20% increase from the nadir	20% increase from the nadir
New lesions present	PD always	Measurement of new lesions are included in sum of diameter	Measurement of new lesions are included in sum of diameter	Initially in iUPD At the subsequent cycle, iCPD if additional NL or PD of T & NT lesion.	Measurement of new lesions are included in sum of diameter

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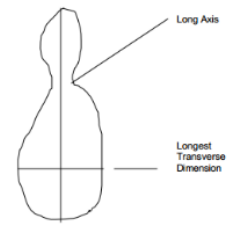
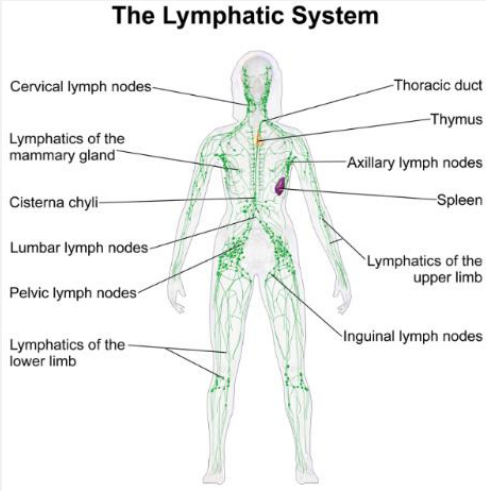
Lymphoma Study: Data Collections & CDISC

Cheson

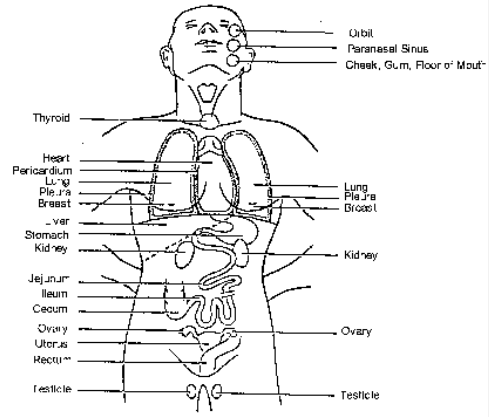
- Response Criteria for Lymphoma studies, which cancer starts in Lymph node.
- History
  - IWG (International Working Group) 1999 and Cheson 2007, Cheson 2014 (Lugano Classification)
- Lesions (tumors)
  - Type :
    - Enlarged Lymph Nodes (long axis > 15 mm or its greatest perpendicular axis > 10 mm by CT scan)
    - Nodal Masses
    - Extra Nodal Masses (> 10 mm)
- Two-dimensional measurement - product of longest diameter and its greatest perpendicular axis (e.g., 40 mm * 15 mm = 600 mm^2)



Lymphatic System vs Extra Nodal Site



A Nodal Mass is the conglomerate of several enlarged nodes touching one another which are not distinguished from individual nodes anymore.



Extra nodal – a lymphoma that is detected outside of lymphatic system.

What is to measure in Lymphoma according to Cheson

- Tumor measurements in CT / MRI
  - Lymph Node, Nodal Masses and Extra Nodal Masses
- PET scan on lesions (to distinguish viable tumor from fibrosis)
- Bone Marrow Assessment
- Spleen and Liver Enlargement Assessment

Tumor Lesions According to Cheson

- Target Lesions
  - Normally 6 lesions
    - lymph nodes or nodal masses
    - Two perpendicular diameters should be clearly measurable
  - Quantitative measurements
    - Longest diameter and its greatest transverse perpendicular diameter
    - Products of the diameters
    - Sum of the products of the diameters (SPD) up to 6 target lesions
- Non-Target Lesions
  - All other lesions beside target lesions
  - Extra nodal (i.e., Liver, Spleen)
  - Quantitative measurements
    - Longest diameter and its greatest transverse perpendicular diameter
    - Products of the diameters
  - Qualitative measurements – present, absent, increased or decreased.
- New Lesions
  - Any lesions that are newly found at post-baseline
  - Either quantitative or qualitative measurements

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SDTM TU (Tumor Identification)

USUBJID	TULINKID	TUTESTCD	TUTEST	TUORRES	TULOC	TUMETHOD
001-01-001	T01	TUMIDENT	Tumor Identification	TARGET NODAL	PELVIC LYMPH NODE	CT SCAN
001-01-001	T02	TUMIDENT	Tumor Identification	TARGET NODAL	AXILARY LYMPH NODE	CT SCAN
001-01-001	T03	TUMIDENT	Tumor Identification	TARGET NODAL	CERVICAL LYMPH NODE	CT SCAN
001-01-001	NT01	TUMIDENT	Tumor Identification	NON-TARGET EXTRA NODAL	LIVER	CT SCAN
001-01-001	NT02	TUMIDENT	Tumor Identification	NON-TARGET EXTRA NODAL	SPLEEN	CT SCAN
001-01-001	T01	TUMIDENT	Tumor Identification	TARGET NODAL	PELVIC LYMPH NODE	FDGPET
001-01-001	T02	TUMIDENT	Tumor Identification	TARGET NODAL	AXILARY LYMPH NODE	FDGPET
001-01-001	T03	TUMIDENT	Tumor Identification	TARGET NODAL	CERVICAL LYMPH NODE	FDGPET

Key points to note:

- Subject 001 has 3 target and 2 non-targets
- TU.TULINKID is connected TR.TRLINKID using RELREC.
- Two tumor measurement method – CT SCAN & FDGPET

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SDTM TR at Screening

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT	TRMETHOD
001-01-001	Target	T01	LDIAM	Longest Diameter	Measurement	20	mm	Screening	CT SCAN
001-01-001	Target	T01	LPERP	Longest Perpendicular	Measurement	25	mm	Screening	CT SCAN
001-01-001	Target	T01	AREA	Area	Measurement	500	mm^2	Screening	CT SCAN
001-01-001	Target	T02	AREA	Area	Measurement	600	mm^2	Screening	CT SCAN
001-01-001	Target	T03	AREA	Area	Measurement	400	mm^2	Screening	CT SCAN
001-01-001	Target		SUMAREA	Sum of Area	Measurement	1500	mm^2	Screening	
001-01-001	Non-Target	NT01	TUMSTATE	Tumor State	Qualitative	PRESENT		Screening	CT SCAN
001-01-001	Non-Target	NT02	TUMSTATE	Tumor State	Qualitative	PRESENT		Screening	CT SCAN

Key points to note:

- Area and Sum of Area were collected
- Area of target 01 is 20 * 25 = 500
- SPD at screening for 001 is 1,500 mm^2

SDTM TR at Cycle 1

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT	TRMETHOD
001-01-001	Target	T01	LDIAM	Longest Diameter	Measurement	12	mm	Cycle 1	CT SCAN
001-01-001	Target	T01	LPERP	Longest Perpendicular	Measurement	10	mm	Cycle 1	CT SCAN
001-01-001	Target	T01	AREA	Area	Measurement	120	mm	Cycle 1	CT SCAN
001-01-001	Target	T02	AREA	Area	Measurement	300	mm	Cycle 1	CT SCAN
001-01-001	Target	T03	AREA	Area	Measurement	200	mm	Cycle 1	CT SCAN
001-01-001	Target		SUMAREA	Sum of Area	Qualitative	620	mm	Cycle 1	
001-01-001	Non-Target	NT01	TUMSTATE	Tumor State	Qualitative	PRESENT		Cycle 1	CT SCAN
001-01-001	Non-Target	NT02	TUMSTATE	Tumor State	Qualitative	PRESENT		Cycle 1	CT SCAN

Key points to note:

- Sum of Area at visit 1 for 001 is 620, more than 50 % decrease

Bone Marrow - SDTM LB and FA

USUBJID	LBCAT	LBSPEC	LBSPID	LBTEST	LBORRES	LBORRESU	VISIT
001-01-001	HEMATOLOGY	BONE MARROW	BR01	Bone Marrow Infiltrate	35	%	Screening
001-01-001	HEMATOLOGY	BONE MARROW	BR01	Bone Marrow Infiltrate	9	%	Cycle 1

USUBJID	FACAT	FASPID	FATEST	FAORRES	VISIT
001-01-001	BONE MARROW BIOPSY	BR01	Bone Marrow Biopsy Results	POSITIVE	Screening
001-01-001	BONE MARROW BIOPSY	BR01	Bone Marrow Biopsy Results	NEGATIVE	Cycle 1

Key points to note:

- LB.LBSPID is connected to FA.FASPID
- We can also use BR (Biopsy) domain following SDTM terminology
- Row 1: Bone Marrow Infiltration (i.e., 35%) and its result (i.e., POSITIVE) are collected, so the example has infiltration number in LB and results in FA.

Liver and Spleen Palpable Assessment - SDTM PE

USUBJID	PECAT	PEMETHOD	PETESTCD	PETEST	PEORRES	VISIT
001-01-001	PHYSICAL EXAMINATION	PALPATION	SPLEENEN	Spleen Enlargement	YES	Screening
001-01-001	PHYSICAL EXAMINATION	PALPATION	SPLEENEN	Spleen Enlargement	NO	Cycle 1
001-01-001	PHYSICAL EXAMINATION	PALPATION	LIVEREN	Liver Enlargement	YES	Screening
001-01-001	PHYSICAL EXAMINATION	PALPATION	LIVEREN	Liver Enlargement	NO	Cycle 1

Key points to note:

- Subject 001 was palpable at Screening, but not palpable at Visit 1

Complete Response (CR)

- Nodal Masses
  - Target- all the lymph nodes/nodal masses regress to normal size (<= 15 mm in their greatest transverse diameter or < 10 mm in short axis if their greatest transverse diameter is between 10 and 15)
  - Non-target – Regress to normal
- Spleen and Liver – Not palpable, nodules disappeared
- Bone Marrow – Infiltrate cleared; if indeterminate by morphology, immunohistochemistry should be negative

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Partial Response (PR)

- Nodal Masses
  - A 50% decrease in the sum of the product of diameters (SPD) of six target lesions
  - No increase in any lesions
  - Typically FDG-avid lymphoma - if PET is positive in screening, PET is positive at least one lesion.
  - Variably FDG-avid lymphoma - all the lymph nodes/nodal masses regress.
- Spleen and Liver – Not palpable, nodules regressed by 50 % in SPD.
- Bone Marrow – Irrelevant

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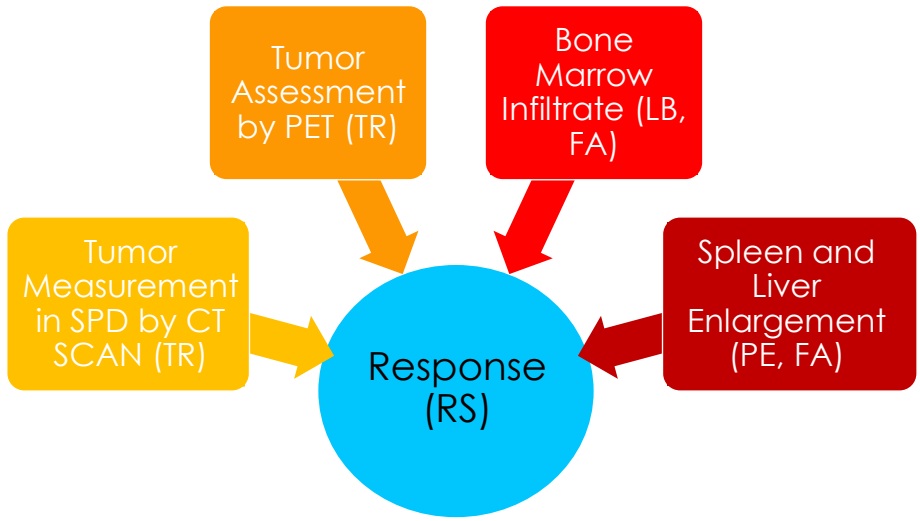
Progressive Disease (PD)

- Nodal Masses
  - Any new lesions (more than 15 mm in any axis)
  - An increase by 50% in SPD from nadir of any involved lesions
  - An increase by 50% in the longest diameter from nadir of any involved lesions
  - Positive PET.
  - Unequivocal progression in non-target nodal masses
- Spleen and Liver – nodules increase by 50 % in SPD.
- Bone Marrow – New or recurrent involvement

Data Collection and its SDTM in Lymphoma using Cheson



SDTM RS (Response)

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSDTC	RSSEQ
001-01-001	OVRLRESP	Overall Response	CHESON 2007	PR	Cycle 1	2011-03-01	1
001-01-001	OVRLRESP	Overall Response	CHESON 2007	SD	Cycle 2	2011-06-01	2
001-01-001	OVRLRESP	Overall Response	CHESON 2007	PR	Cycle 3	2011-09-01	3
001-01-001	OVRLRESP	Overall Response	CHESON 2007	PD	Cycle 4	2011-12-01	4
001-01-001	OVRLRESP	Overall Response	CHESON 2007	PD	Cycle 5	2012-03-01	5

Key points to note:

- Overall Response for each visit was collected.

Leukemia Study : Data Collections & CDISC

What is Leukemia

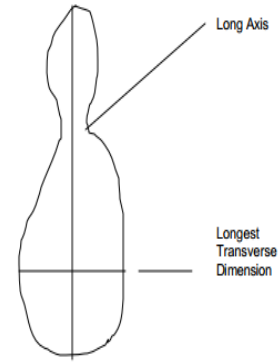
- Cancer that usually begin in the bone marrow and result in high numbers of abnormal white blood cells(lymphocytes).
- Type of Leukemia & its response criteria
  - Acute Lymphoblastic Leukemia(ALL) - a rapid increase in the number of immature white blood cells. NCCN(National Comprehensive Cancer Network) Guideline 2012
  - Acute Myeloid Leukemia (AML) - a rapid increase in the number of abnormal white blood cells in bone marrow that interfere with the production of normal blood cells. IWAML 2003
  - Chronic Lymphocytic Leukemia (CLL) - excessive buildup of relatively mature, but still abnormal, white blood cells. IWCLL 2008
  - Chronic Myeloid Leukemia (CML) - the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood. CML ESMO Guideline

Introduction of Chronic Lymphocytic Leukemia (CLL)

- Lymphocytic – if the cancerous change takes place in marrow that forms lymphocytes (white blood cells)
- Myelogenous – if the cell change takes place in marrow that forms red blood cells.
- Process of CLL Diseases
  1. Mutation of stem cells in Bone Marrow
  2. Abnormal WBC (CLL cells) are formed
  3. CLL cells increase in bone marrow
  4. CLL cells increase in blood

Introduction of IWCLL (International Workshop on Chronic Lymphocytic Leukemia)

- History
  - IWCLL 1996, 2008, and 2018
- Diagnosis of CLL
  - Blood : > 5 * 10^9 B lymphocytes/L (5000 / uL) in blood.
  - Immunophenotype (flow cytometry) of Lymphocytes:
    - A presence of T-cell antigen CD5
    - A presence of B-cell surface CD19, CD20, CD23
    - Low surface immunoglobin CD20, CD79b
- Tumor Measurement
  - Enlarged Lymph Nodes (long axis > 15 mm)
  - Two-dimensional measurement - product of longest diameter and its greatest perpendicular axis (e.g., 40 mm * 15 mm = 600 mm^2) - up to 5



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What are to measure for response criteria according to IWCLL 2008

- Tumor measurements in CT / MRI
  - Lymph Node
- Lymphocytes Assessment
- Spleen and Liver Enlargement Assessment
- Bone Marrow Assessment
- Blood Count Assessment – Neutrophils, Platelets, and Hemoglobin.
- Immunophenotype (flow Cytometry) Assessment
- Performance Status by ECOG(Eastern Cooperative Oncology Group)
- Staging – assessment of disease progress for treatment plan
  - Rai : 0 (Low risk), 1&2 (Intermediate risk), 3 (High risk)
  - Binet : A, B, C

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SDTM TU (Tumor Identification)

USUBJID	TULINKID	TUTESTCD	TUTEST	TUORRES	TULOC	TUMETHOD
001-01-001	T01	TUMIDENT	Tumor Identification	TARGET NODAL	PARAAORTIC LYMPH NODE	CT SCAN
001-01-001	T02	TUMIDENT	Tumor Identification	TARGET NODAL	AXILARY LYMPH NODE	CT SCAN
001-01-001	T03	TUMIDENT	Tumor Identification	TARGET NODAL	ILLIAC LYMPH NODE	CT SCAN
	…..					

Key points to note:

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

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SDTM TR at Screening

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT	TRMETHOD
001-01-001	Target	T01	LDIAM	Longest Diameter	Measurement	20	mm	Screening	CT SCAN
001-01-001	Target	T01	LPERP	Longest Perpendicular	Measurement	15	mm	Screening	CT SCAN
001-01-001	Target	T01	AREA	Area	Measurement	300	mm^2	Screening	CT SCAN
001-01-001	Target	T02	LDIAM	Longest Diameter	Measurement	25	mm	Screening	CT SCAN
001-01-001	Target	T02	LPERP	Longest Perpendicular	Measurement	20	mm	Screening	CT SCAN
001-01-001	Target	T02	AREA	Area	Measurement	500	mm^2	Screening	CT SCAN
	….								
001-01-001	Target		SUMAREA	Sum of Area	Measurement	2560	mm^2	Screening	

Key points to note:

- Area and Sum of Area were collected
- SUMAREA at screening for 001 is 2,560 mm^2

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SDTM TR at Cycle 1

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRCAT	TRORRES	TRORRESU	VISIT	TRMETHOD
001-01-001	Target	T01	LDIAM	Longest Diameter	Measurement	15	mm	Cycle 1	CT SCAN
001-01-001	Target	T01	LPERP	Longest Perpendicular	Measurement	10	mm	Cycle 1	CT SCAN
001-01-001	Target	T01	AREA	Area	Measurement	150	mm^2	Cycle 1	CT SCAN
001-01-001	Target	T02	LDIAM	Longest Diameter	Measurement	15	mm	Cycle 1	CT SCAN
001-01-001	Target	T02	LPERP	Longest Perpendicular	Measurement	10	mm	Cycle 1	CT SCAN
001-01-001	Target	T02	AREA	Area	Measurement	300	mm^2	Cycle 1	CT SCAN
001-01-001	Target		SUMAREA	Sum of Products of Perpendicular Diameters	Measurement	1200	mm^2	Cycle 1	

Key points to note:

- SUMAREA at visit 1 for 001 is 1,200, more than 50 % decrease.

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Bone Marrow - SDTM LB and FA

USUBJID	LBCAT	LBSPEC	LBSPID	LBTEST	LBORRES	LBORRESU	VISIT
001-01-001	HEMATOLOGY	BONE MARROW	BR01	Percentage of Cellularity	75	%	Screening
001-01-001	HEMATOLOGY	BONE MARROW	BR01	Percentage of Cellularity	50	%	Cycle 1

USUBJID	FACAT	FASPID	FATEST	FAORRES	VISIT
001-01-001	BONE MARROW BIOPSY	BR01	Bone Marrow Cellularity	HYPERCELLULAR	Screening
001-01-001	BONE MARROW BIOPSY	BR01	Bone Marrow Cellularity	NORMOCELLULAR	Cycle 1
001-01-001	BONE MARROW BIOPSY	BR01	B-Lymphoid Nodule	PRESENT	Screening
001-01-001	BONE MARROW BIOPSY	BR01	B-Lymphoid Nodule	ABSENT	Cycle 1

Key points to note:

- Bone Marrow Cellularity – hyper (> 70%), normal (30 – 70%), hypo (< 30%)
- If nodules are present in Bone Marrow, they are also collected in TR and TU.
- CLL Lymphocytes count in Bone Marrow could be collected in LB.

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Liver Palpable Assessment - SDTM PE and FA at Screening & Cycle 1

USUBJID	PECAT	PESPID	PEMETHOD	PETESTCD	PETEST	PEORRES	VISIT
001-01-001	PHYSICAL EXAMINATION	LP01	PALPATION	LIVEREN	Liver Enlargement	YES	Screening
001-01-001	PHYSICAL EXAMINATION	LP01	PALPATION	LIVEREN	Liver Enlargement	NO	Cycle 1

USUBJID	FACAT	FASPID	FATEST	FAORRES	FAORRESU	VISIT
001-01-001	SPLEEN AND LIVER MEASUREMENT	LP01	Measurement of Liver Enlargement	16	cm	Screening
001-01-001	SPLEEN AND LIVER MEASUREMENT	LP01	Measurement of Liver Enlargement	10	cm	Cycle 1

Key points to note:

- PE.PESPID and FA.FASPID are linked thru RELREC
- The liver of Subject 001 was palpable at Screening, but not palpable at Cycle 1. Its size decreased from 16 to 10 cm.

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Spleen Palpable Assessment - SDTM PE and FA at Screening & Cycle 1

USUBJID	PECAT	PESPID	PEMETHOD	PETESTCD	PETEST	PEORRES	VISIT
001-01-001	PHYSICAL EXAMINATION	SP01	PALPATION	SPLEENEN	Spleen Enlargement	YES	Screening
001-01-001	PHYSICAL EXAMINATION	SP01	PALPATION	SPLEENEN	Spleen Enlargement	YES	Cycle 1

USUBJID	FACAT	FASPID	FATEST	FAORRES	FAORRESU	VISIT
001-01-001	SPLEEN AND LIVER MEASUREMENT	SP01	Measurement of Spleen Enlargement	15	cm	Screening
001-01-001	SPLEEN AND LIVER MEASUREMENT	SP01	Measurement of Spleen Enlargement	14	cm	Cycle 1

Key points to note:

- PE.PESPID and FA.FASPID are linked thru RELREC
- The spleen of Subject 001 was palpable at Screening and Cycle 1. Its size decreased from 15 to 14 cm.

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SDTM LB for Leukemia Blood counts

USUBJID	LBCAT	LBTESTCD	LBTEST	LBORRES	LBORRESU	VISIT
001-01-001	HEMATOLOGY	NEUT	Neutrophils	1,400	/uL	Screening
001-01-001	HEMATOLOGY	PLAT	Platelets	90,000	g/dL	Screening
001-01-001	HEMATOLOGY	HGB	Hemoglobin	13	/uL	Screening
….						
001-01-001	HEMATOLOGY	NEUT	Neutrophils	1,600	/uL	Cycle 1
001-01-001	HEMATOLOGY	PLAT	Platelets	100,500	g/dL	Cycle 1
001-01-001	HEMATOLOGY	HGB	Hemoglobin	13	/uL	Cycle 1

Key points to note:

- Leutrophils counts increased from 1,400 to 1,600 /uL
- Platelets counts increased from 90,000 to 100,500 /uL
- Hemoglobin counts did not change
- Lab blood counts improved to PR (red-circled) according to response criteria

SDTM CP for Lymphocytes and CLL Lymphocytes

USUBJID	CPTESTCD	CPTEST	CPORRES	CPORRESU	CPSPEC	VISIT
001-01-001	BLYCE	B-Lymphocytes	6,000	/uL	BLOOD	Screening
001-01-001	CLLLYM	CLL Lymphocytes	1,400	/uL	BONE MARROW	Screening
….						
001-01-001	BLYCE	B-Lymphocytes	4,500	/uL	BLOOD	Cycle 1
001-01-001	CLLLYM	CLL Lymphocytes	1,400	/uL	BONE MARROW	Cycle 1

Key points to note:

- B-Lymphocytes and CLL Lymphocytes counts could be collected at CP (Cell Phenotype) domains.

Complete Response (CR)

- Group A
  - Lymph Nodes – all <= 15 mm in longest diameter
  - Blood Lymphocytes < 4.0 * 10^9 /L (4,000 /uL)
  - Spleen – Not palpable
  - Liver – Not palpable

- Group B - Blood Counts
  - Neutrophils > 1.5 * 10^9 /L (1,500 /uL)
  - Platelets > 100 * 10^9 /L (100,000 /uL)
  - Hemoglobin > 11.0 g/dL
  - Bone Marrow
    - Normocellular for age
    - No CLL cells
    - No B-Lymphoid nodules
- Note : All of the criteria has to be met.

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Partial Response (PR)

- Group A
  - Lymph Nodes : Sum of Area decreases >= 50%, no increase in any lymph node and no new enlarged lymph nodes
  - Blood Lymphocytes : Decrease >= 50% from baseline
  - Spleen : Decrease >= 50%
  - Liver : Decrease >= 50%

- Group B - Blood Counts
  - Platelets > 100 * 10^9 /L (100,000 /uL)or increase >= 50% from baseline
  - Hemoglobin > 11.0 g/dL or increase >= 50% from baseline
  - Bone Marrow (either one of them)
    - Presence of CLL cells
    - Presence of B-Lymphoid nodules
    - Not done
- At least Two of Group A and one of Group B should be met

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Progressive Disease (PD)

- Group A
  - Lymph Nodes : Sum of Area increase>= 50% or new enlarged lymph nodes
  - Blood Lymphocytes : Increase >= 50% with at least $5*10^9$
  - Spleen : Increase >= 50%
  - Liver : Increase >= 50%
- Group B - Blood Counts
  - Platelets : Decrease >= 50% or $< 100* 10^9$ /L
  - Hemoglobin : Decrease of > 2 g/dL or < 10 g/dL
  - Bone Marrow (either one of them)
    - Increase of CLL cells >=50%
- At least one from Group A or Group B

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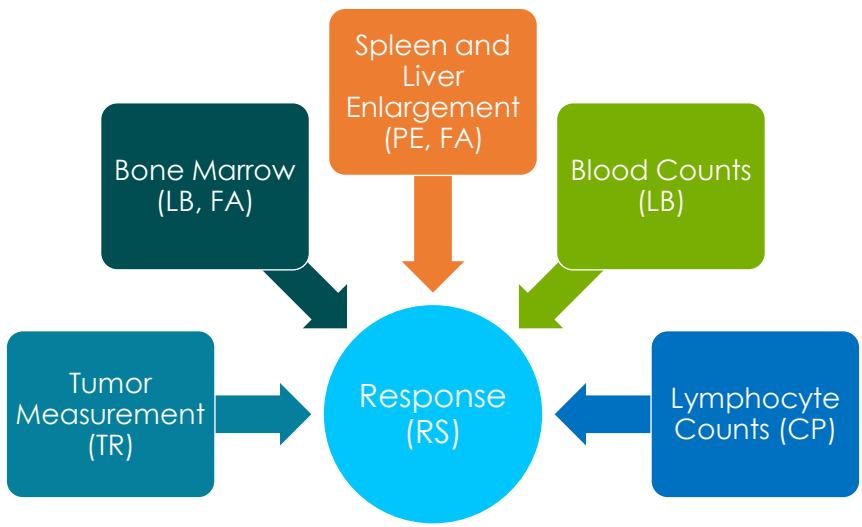
Data Collection and its SDTM on Leukemia Study



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SDTM RS (Response) – Overall Response at Each Visit

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT	RSDTC	RSSEQ
001-01-001	OVRLRESP	Overall Response	IWCLL 2018	PR	Cycle 1	2011-03-01	1
001-01-001	OVRLRESP	Overall Response	IWCLL 2018	SD	Cycle 2	2011-06-01	2
001-01-001	OVRLRESP	Overall Response	IWCLL 2018	PR	Cycle 3	2011-09-01	3
001-01-001	OVRLRESP	Overall Response	IWCLL 2018	PD	Cycle 4	2011-12-01	4
001-01-001	OVRLRESP	Overall Response	IWCLL 2018	PD	Cycle 5	2012-03-01	5

Key points to note:

- Using Tumor measurement, Bone Marrow Checkup, Spleen/Live assessment and Blood counts, overall Response for each visit was measured and collected.
- Usually, Responses were measured and collected by investigator, not programmatically.

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Other Oncology-specific data collections, CDISC & Analysis

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Oncology exposure – EC and EX

Some oncology drugs should be admitted per patient's weight. In this study, DRUG A should be admitted in 4 mg per patient's weight in Kg.
If 1 mL of injection contains 100 mg of DRUG A, USUBJID = 001-01-001 at 75 kg weight requires 3 mL. USUBJID=002 at 100 kg requires 4 mL. USUBJID=003 at 80 kg requires 3.2 mL.

EC – Exposure as collected

USUBJID	ECTRT	ECDOSE	ECDOSU	ECPSTRG	ECPSTRGU	VISIT
001-01-001	DRUG A	3	mL	100	gm/mL	Cycle 1
001-01-002	DRUG A	4	mL	100	gm/mL	Cycle 1
001-01-003	DRUG A	3.2	mL	100	gm/mL	Cycle 1

EX- Exposure

USUBJID	EXTRT	EXDOSE	EXDOSU	VISIT
001-01-001	DRUG A	4	mg/kg	Cycle 1
001-01-002	DRUG A	4	mg/kg	Cycle 1
001-01-003	DRUG A	4	mg/kg	Cycle 1

VS

USUBJID	VSTESTCD	VSSTRESN	VISIT
001-01-001	WEIGHT	75	Cycle 1
001-01-002	WEIGHT	100	Cycle 1
001-01-003	WEIGHT	80	Cycle 1

Additional Cancer Related Data Collections

1. Immunophenotype (flow Cytometry) Assessment
2. Performance Status by ECOG(Eastern Cooperative Oncology Group)
3. Staging – assessment of disease progress for treatment plan
    1. Rai : 0 (Low risk), 1&2 (Intermediate risk), 3 (High risk)
    2. Binet : A, B, C
4. Cytogenetics – chromosome abnormalities in cancer patients (especially in CLL)
5. Disease Stage – Stage 1 to 4

- Questions : What SDTM domains should we collect this data? - TR, TU or Custom Domains?

Oncology-specific Efficacy Analysis

- Main Oncology-specific Efficacy Analysis
  - Objective Response Rate (ORR)
  - Overall Survival (OS)
  - Progression Free Survival (PFS)
  - In 1970s, FDA usually approved drugs based on ORR. But, FDA determined that cancer drug approval should be based on more direct evidence of clinical benefits such as OS and PFS.
- Main Efficacy Reports
  - Log-Rank Test
  - Cox Regression Model
  - Kaplan Meier Curves

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Objective Response Rate (ORR)

- Objective Response Rate (ORR)
  - The proportion of patients with tumor size reduction, usually CR and PR
  - Direct measurement of anti-tumor activity
  - Can be done in single arm study
  - Usually secondary endpoint, but could be the primary endpoint, especially for accelerated approvals
- ORR preparation process
  1. Collect Overall Responses at each visit for each patient
  2. Find the Best Overall Response for each patient
  3. Derive Objective Response for each patient
  4. Calculate Objective Response Rate

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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 2 and PD at cycle 5, the best overall response is still CR

USUBJID	TRTP	PARAM	DTYPE	AVISIT	AVALC
001-01-001	Study Drug	Overall Response		Cycle 1	PR
001-01-001	Study Drug	Overall Response		Cycle 2	SD
001-01-001	Study Drug	Overall Response		Cycle 3	SD
001-01-001	Study Drug	Overall Response		Cycle 4	SD
001-01-001	Study Drug	Overall Response		Cycle 5	PD
001-01-001	Study Drug	Best Overall Response	BEST	End of Study	?
001-01-002	Control	Overall Response		Cycle 1	SD
001-01-002	Control	Overall Response		Cycle 2	PR
001-01-002	Control	Overall Response		Cycle 3	PR
001-01-002	Control	Overall Response		Cycle 4	CR
001-01-002	Control	Overall Response		Cycle 5	PD
001-01-002	Control	Best Overall Response	BEST	End of Study	?

Final ADORR : Objective Response parameter for ORR analysis

Variable Name	Where	Variable Type	Display Format	Codelist / Controlled Terms	Origin	Derivation / Comment
AVALC	PARAMCD = 'OBJRESP'	text		Y, N	Derived	'Y' if "Best Overall Response" is 'CR' or 'PR'. 'N' otherwise.

```
PROC FREQ DATA=ADORR;
  WHERE PARAM="Objective Response";
  TABLE TRTP*AVALC / CHISQ;
RUN;
```

USUBJID	TRTP	PARAMCD	PARAM	AVISIT	AVALC
001-01-001	Study Drug	BESTRESP	Best Overall Response	End of Study	PR
001-01-001	Study Drug	OBJRESP	Objective Response	End of Study	Y
001-01-002	Control	BESTRESP	Best Overall Response	End of Study	CR
001-01-002	Control	OBJRESP	Objective Response	End of Study	Y
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

Oncology-specific Analysis – Time to Event

- Overall Survival (OS)
  - Time from randomization until death
  - The most reliable cancer endpoint
  - Primary endpoint
  - Preferred endpoint
  - Randomized controlled studies.

- Progression Free Survival (PFS)
  - Time from randomization until progressive disease or death
  - Primary or secondary endpoint
  - Randomized controlled studies.

Time to Event ADaM Model

- Main Dataset model for Time to Event Analysis such as OS
- Key information – Events and Censor
- Time to Event Variables
  - STARTDT – Time to Event Origin Date for Subject
  - CNSR - Censor
  - EVNTDESC – Event or Censoring Description
  - CNSDTSC – Censor Date Description

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADTTE	Time to Event Analysis Data	adtte.xpt	One record per subject per parameter	USUBJID, PARAMCD	BDS	c-adtte.txt

Time to Event ADaM - Metadata

Variable Name	Variable Label	Variable Type	Display Format	Code list / Controlled Terms	Source / Derivation
USUBJID	Unique Subject Identifier	text	$20		ADSL.USUBJID
SEX	Sex	text	$20	M, F	ADSL.SEX
TRTP	Planned Treatment	text	$20	Control, Study Drug	ADSL.TRP
PARAMCD	Parameter Code	text	$20	OS, PFS	
PARAM	Parameter	text	$50	Overall Survival (Days), Progression Free Survival (Days)	
STARTDT	Time to Event Origin Date for Subject	integer	YYYY-MM-DD		ADSL.RANDDT
ADT	Analysis Date	integer	YYYY-MM-DD		Numeric date of DS.DSSTDTC
AVAL	Analysis Value	integer	8.		ADT – STARTDT + 1
CNSR	Censor	integer	1.	0,1	0 if EVNTDESC = 'PROGRESSIVE DISEASE' or 'DEATH' 1 if otherwise
EVNTDESC	Event or Censoring Description	text	$50		DS.DSDECOD

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TTE ADaM Dataset for Overall Survival

USUBJID	SEX	TRTP	PARAM	AVAL	STARTDT	ADT	CNSR	EVNTDESC
001-01-001	M	Study Drug 1	Overall Survival (Days)	157	2011-01-04	2011-06-10	1	COMPLETED THE STUDY
001-01-002	M	Study Drug 2	Overall Survival (Days)	116	2011-02-01	2011-05-28	1	LOST TO FOLLOW-UP
001-01-003	F	Study Drug 2	Overall Survival (Days)	88	2011-02-05	2011-05-04	0	DEATH
001-01-004	F	Study Drug 1	Overall Survival (Days)	102	2011-03-20	2011-06-30	1	PROGRESSIVE DISEASE
001-01-005	M	Study Drug 1	Overall Survival (Days)	101	2011-03-26	2011-07-05	1	ONGOING

Key points to note:

- Among all the events, death is not censored.
- If PARAM = PFS, how will CNSR change?

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TTE ADaM Dataset for PFS

USUBJID	SEX	TRTP	PARAM	AVAL	STARTDT	ADT	CNSR	EVNTDESC
001-01-001	M	Study Drug 1	Progression Free Survival (Days)	157	2011-01-04	2011-06-10		COMPLETED THE STUDY
001-01-002	M	Study Drug 2	Progression Free Survival (Days)	116	2011-02-01	2011-05-28		LOST TO FOLLOW-UP
001-01-003	F	Study Drug 2	Progression Free Survival (Days)	88	2011-02-05	2011-05-04		DEATH
001-01-004	F	Study Drug 1	Progression Free Survival (Days)	102	2011-03-20	2011-06-30		PROGRESSIVE DISEASE
001-01-005	M	Study Drug 1	Progression Free Survival (Days)	101	2011-03-26	2011-07-05		ONGOING

Key point to note:

- Among all the events, death and progressive disease events are not censored.

Log-Rank Test & Cox SAS Codes Using Time to Event ADaM Dataset

- Log-Rank Test

```
PROC LIFETEST DATA=ADTTE;
        WHERE PARAM="Overall Survival (Days)";
        TIME AVAL*CNSR(1);
        STRATA TRTP;
RUN;
```

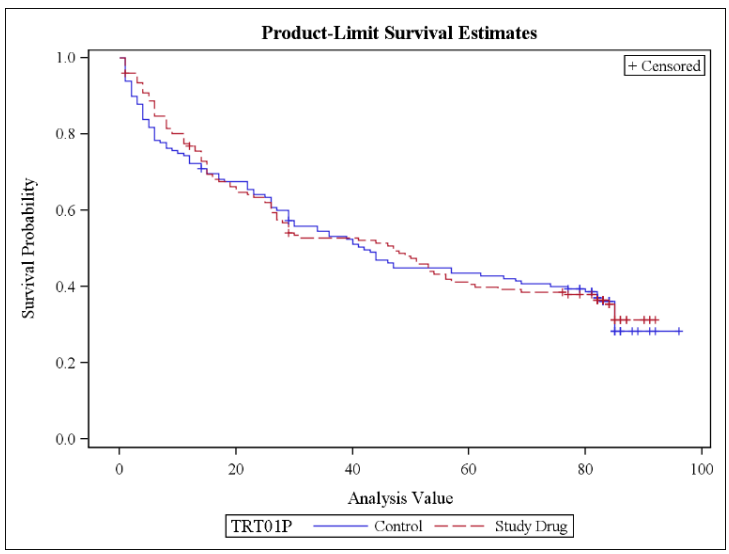
- Cox Regression Model

```
PROC PHREG DATA=ADTTE;
        WHERE PARAM ="Overall Survival (Days)";
        MODEL  AVAL*CNSR(1) = TRTP SEX;
RUN;
```

Simple KM Curve SAS Codes Using TTE ADaM Dataset

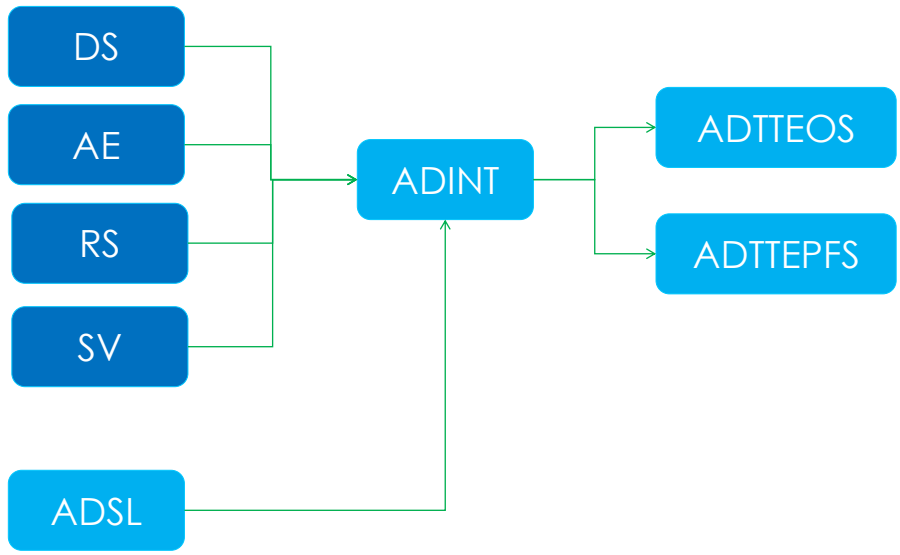
```
ods trace on;  ods listing close;  ods path sashelp.tmplmst(read);
ods graphics on ;
ods rtf file="C:\Survival Graph.rtf" bodytitle ;
ods noptitle;
ods select survivalplot;

**** Graph;
proc lifetest data=ADTTE ;
      where param = 'Overall Survival (Days)';
      time aval*cnsr(1);
      strata trtp;
      **** Title & footnote;
      title1 "Survival Plot";
run;
**** Closing ODS;
options orientation=landscape ;  ods path sashelp.tmplmst(read);
ods rtf close; ods graphics off; ods listing; ods trace off;
```


Kaplan-Meier Curve Using Simple SAS Template Codes



- Y axis – probability of survival
- X axis – time of observation
- Each drop – uncensored event
- Key point - Median survival probability

Intermediate ADaM Efficacy datasets



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Sample ADINT (intermediate ADaM dataset for OS)

USUBJID	ASEQ	PARAM	PARMACD	AVALC	ADT	SRCDOM	SRCVAR
001-01-001	1	Randomization Date	RANDDT	2011-01-04	2011-01-04	DM	RANDTC
001-01-001	2	First Treatment Date	TRTSDT	2011-01-16	2011-01-16	ADSL	TRTSDT
001-01-001	3	Last Treatment Date	TRTEDT	2014-03-20	2014-03-20	ADSL	TRTEDT
001-01-001	4	Last AE Start Date	LAESTDT	2014-02-26	2014-02-26	AE	AESTDTC
001-01-001	5	Last Visit Date	LVDT	2014-03-27	2014-03-27	SV	SVDTC
001-01-001	6	Study Completion Date	COMPDT	2014-03-27	2014-03-27	DS	DSDTC
001-01-001	7	Date of Death	DDDT			DD	DDDTC

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Clinical Trial Design in Oncology

- Randomized controlled Trials (Superiority)
  - Most reliable method to show statistically significant improvement in clinically meaningful endpoints.
- Single Arm Studies
  - No available therapy
  - End Points : ORR & Response Duration
- Master Protocol
  - Single trial design that can simultaneously evaluate multiple drugs in multiple sub-studies/ sub-populations to expedite drug development.
- Adaptive Design
  - Trial Design that could adopt to the different population based on interim analysis.

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End to End Standards driven oncology studies

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Challenges on Biometric Department

How to scale infrastructures for more oncology studies

How to conduct complex oncology studies

Complex problem for 6th grader

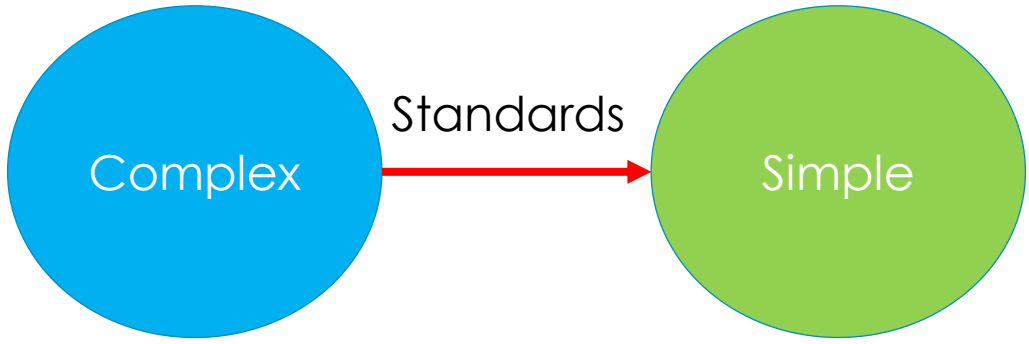
If (x + 2) = 1000,

what is $x^2 - 4 = ?$

$x = 1000 - 2 = 988$

$988^2 - 4 =$

How can we solve the complex problem?



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Oncology-specific Standards

- Oncology Study Types - Solid Tumor, Lymphoma, Leukemia
- Response Criteria Guidelines - RECIST 1.1, Cheson 2007, IWCLL 2008
- Collection
  - Tumor Measurement
  - Bone Marrow Assessment
  - Spleen and Liver Enlargement Assessment
  - Blood Counts
  - Response Assessment
- CDISC – CDASH(TU, TR, RS), SDTM (TU, TR, RS), ADaM (--TTE), CT
- Analysis - OS, PFS,TTP, ORR, DFS
- Programming
  - Reporting – TFL
  - SAS Macros
  - R / Python packages
  - Algorithm / derivation (company specific, industry)
- Documents – Links, Traceability, Instruction, Working Guidelines, SOP

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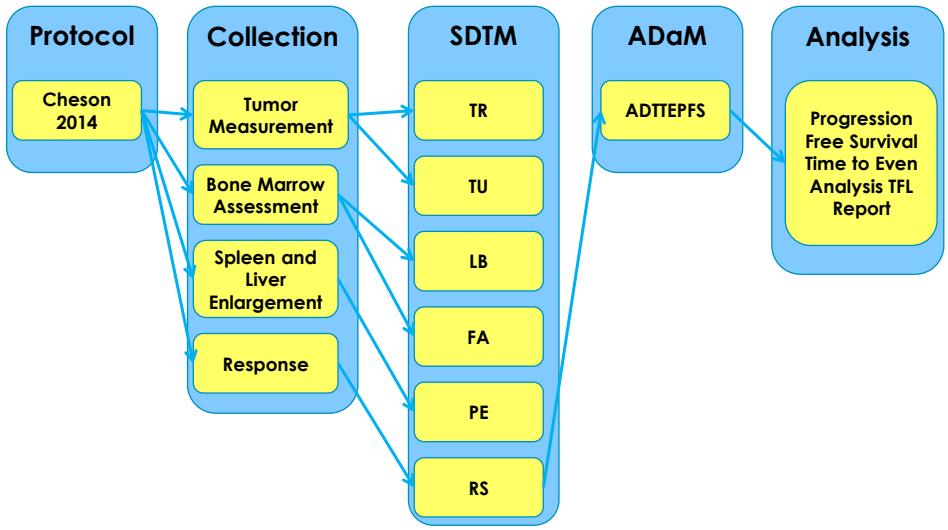
E2E Standards-driven Oncology Studies



Standardized way to solve the complex problem

If (x + 2) = 1000,

What is $x^2 - 4$ =?

(x + 2) (x - 2) = 1000* 996 = 996,000

Final Thoughts

- Why should we know about oncology?
  - To become more effective programmer/statistician
  - To bring oncology drugs faster
  - To help patients.
  - For our career
- What should we know about oncology?
  - Oncology subtypes and its response criteria
  - Collection – tumor measurements & oncology-specific measurements
  - CDASH/SDTM – TU, TR, RS
  - ADaM - TTE
  - Analysis – Time to Event, Censor, Hazard Ratio and Kaplan Meier plots
- E2E Standards driven oncology
  - Standards (metadata / data) driven oncology study development

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