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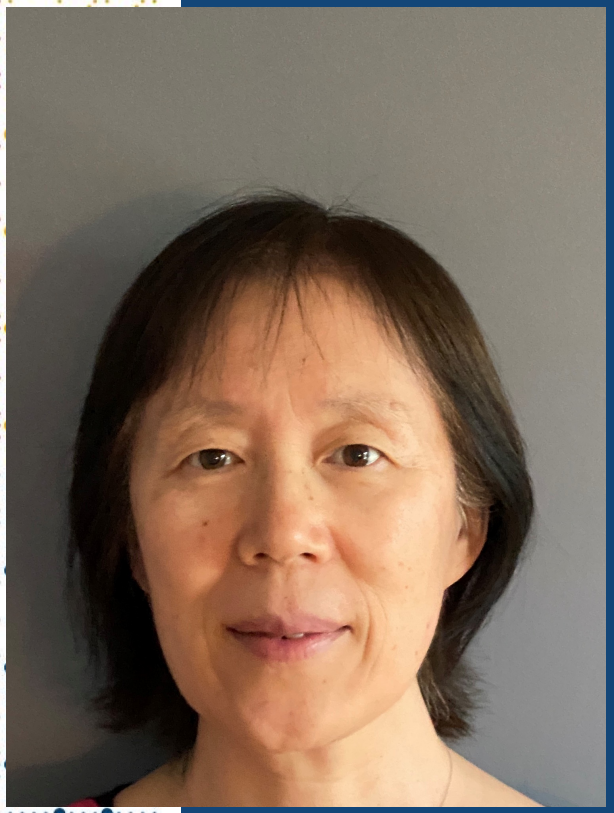
2022
US
INTERCHANGE
26-27 OCTOBER | AUSTIN

Standardize ADRS ADTTE per Lugano Criteria for Hematology Efficacy Analysis

Presented by Song Liu, BeiGene Inc



Meet the Speaker

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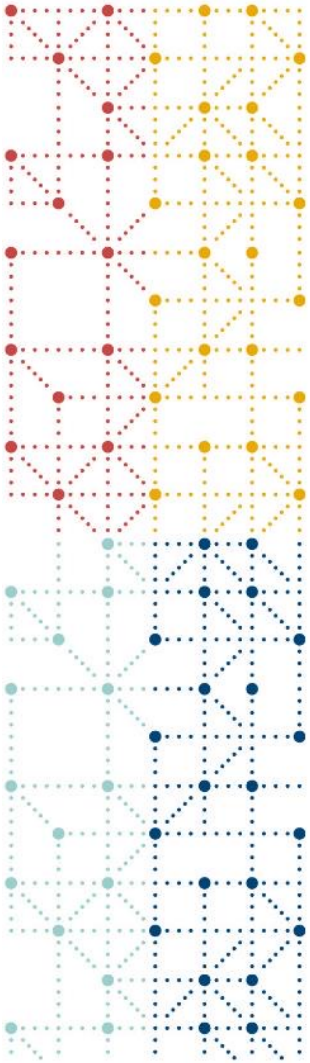


Agenda

1. Introduction of Lymphoma
2. Lugano Classification and Efficacy Endpoints
3. Roadmap of Developing ADRS and ADTTE
4. Role of Intermediate data ADEFPRE (BDS Structure)
5. ADRS Derivation and Sample Data
6. ADTTE Drivation and Censoring Rules
7. Q&A

Introduction of Lymphoma

Two Major Types:

- Hodgkin's lymphoma (HL): presence of a specific type of abnormal cell called a Reed-Sternberg cell under a microscope.
- Non-Hodgkin's lymphoma (NHL): none CLL/SLL or does not involve Reed-Sternberg cells. It generally develops in the lymph nodes and lymphatic tissue in other areas of the body (extranodal) and involves bone marrow and blood.

What is Lugano classification

It is Lymphoma staging and evaluation system for non-Hodgkin and Hodgkin lymphoma:

- FDG-PET for FDG-avid lymphoma
- CT for non-FDG-avid lymphoma

PET-CT	CT
Standard for FDG-avid lymphomas	Indicated for non-avid histology ➢ Histology with low or variable FDG avidity ➢ Regions of the world where PET-CT is unavailable.
▪ **Use Five-Point Scale (5-PS) to assess treatment response** • **Not recommended to change treatment based soly on PET-CT response assessment** • **CR and PD must be confirmed by PET scan for FDG-avid subjects in this study**	➢ Lesion measurements on longest diameter (LDi), shortest diameter (SDi) and Sum of products of diameters (SPD) In absence of PET, mass that has decreased in size but persists is a PR ➢ Need biopsy documenting absence of lymphoma to upgrade to CR

NOTE: CRu (complete remission unconfirmed) is a response category per Cheson et al 1999 but not for Lugano Classification.

Efficacy Endpoint: Response (ADRS)

- ORR (Overall Response Rate):
  Proportion of patients achieving a best overall response of either partial response (PR) or complete response (CR).
  The IRC assessment is the primary endpoint

- BOR (Best Overall Response):
  Best response recorded from randomization until data cut or the start of new anticancer treatment. Take the first response value in this order (CR/CRu, PR, stable disease [SD], and PD) as the best response.

- DCR (Disease Control Rate):
  Percentage of patients with response status CR, PR or SD before the cutoff date.

Efficacy Endpoint: Time to Event (ADTTE)

- PFS (Progression-free survival):
  Time (months) from the date of randomization to the date of the first objectively documented tumor progression, or death, whichever occurs first.

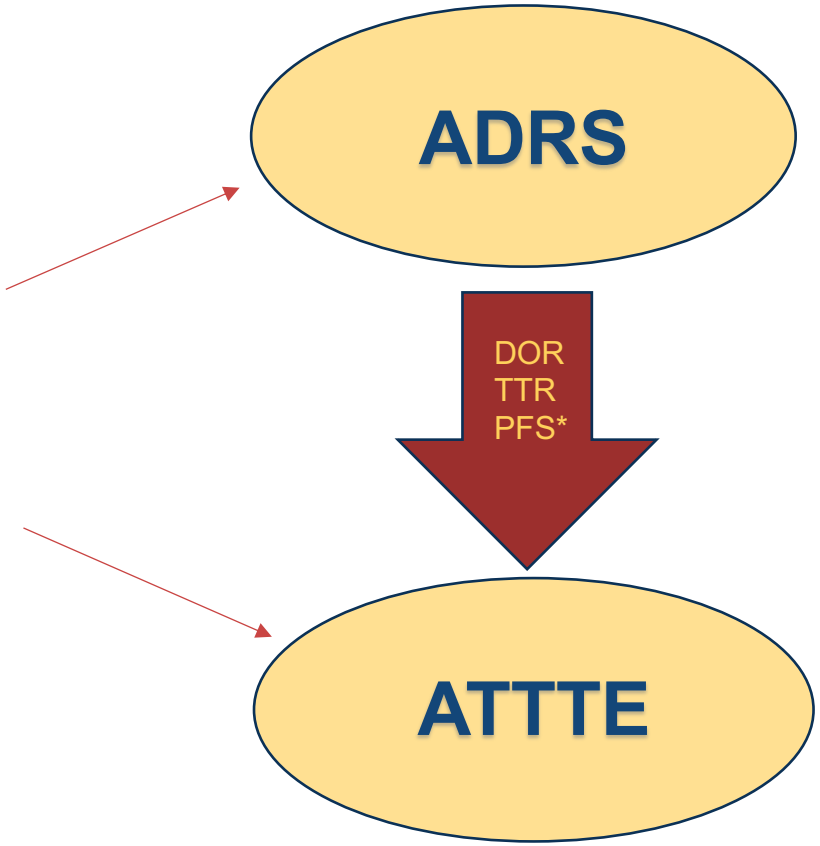
- DOR (Duration of Objective Response):
  Time (months) from the first determination of an objective response date to the first documentation of progression or death, whichever occurs first

- TTR (Time to Response):
  Time (months) from randomization to the date of the earliest qualifying response (PR or better).

Roadmap of Developing ADRS and ADTTE

Intermediate ADaM BDS data ADEFPRE: dates derived from SDTM CM PR TR TU and RS:

AVAL for most of the PARAM serves ADT in ADTTE



Role of Intermediate data ADEFPRE (BDS Structure)

PARAMs in ADEFPRE support ADRS and ADTTE efficacy endpoints:

- AVAL for PARAMCD FPDDT will be the ADTTE.ADT for PFS
- It create ADRS PARAMs such as disease control duration, which doesn't require censoring and should not be in ADTTE.

PARAMCD	PARAM	AVAL	Specification
FPDDT	First PD Date Before Anti-Can Trt	26-Oct-22	First RS.RSDTC where RS.RSSTRESC= 'PD' when RS.RSTESTCD='OVRLRESP' and RSEVAL = 'INVESTIGATOR' prior to New Anti-Cancer Treatment Start Date
POD24	PD Within 24 Months	Y	Set to 'Y' when disease control duration ≤ 24 months from the anchor date to PD, and BOR is 'CR', 'PR', 'SD' or 'NON PD'.

Response Data Collection by IRC

Imaging	Response Criteria	Level of Assessment
PET-CT	Lugano (primary)	**Oncology (Combined Clinical Information)**
PET	Lugano	**Oncology (Combined Clinical Information)**
PET	Lugano	Radiologist1, Radiologist2
CT	Lugano	**Oncology (Combined Clinical Information)**
CT	Lugano	Radiologist1, Radiologist2
CT	Cheson (exploratory)	**Oncology (Combined Clinical Information)**
CT	Cheson	Radiologist1, Radiologist2

To report IRC oncologist assessment, how many sets of response variables in ADRS?

SDTM RS Sample Data

USUBJID	RSSPID	RSTESTCD	RSTEST	RSSCAT	RSORRES	RSSTRESC	RSEVAL	RSEVALID	Visit
001-002	FDG-AVID	OVRLRESP	Overall Response	CT AND CLINICAL CHESON ASSESSMENT	PR	PR	INDEPENDENT ASSESSOR	ONCOLOGIST	CYCLE 06
001-002	FDG-AVID	OVRLRESP	Overall Response	CT AND CLINICAL LUGANO ASSESSMENT	PR	PR	INDEPENDENT ASSESSOR	ONCOLOGIST	CYCLE 06
001-002	FDG-AVID	OVRLRESP	Overall Response	MODIFIED PET-CT/CT ASSESSMENT	NON-PD	NON-PD	INDEPENDENT ASSESSOR	ONCOLOGIST	CYCLE 06
001-002	FDG-AVID	OVRLRESP	Overall Response	PET AND CLINICAL LUGANO ASSESSMENT	NE	NE	INDEPENDENT ASSESSOR	ONCOLOGIST	CYCLE 06
001-002	FDG-AVID	NEWLSN	New Lesions Impact	CT CHESON ASSESSMENT	N	N	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	NTRGRESP	Non-target Response	CT CHESON ASSESSMENT	CR	CR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	OVRLRESP	Overall Response	CT CHESON ASSESSMENT	PR	PR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	TRGRESP	Target Response	CT CHESON ASSESSMENT	CR	CR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	NEWLSN	New Lesions Impact	CT LUGANO ASSESSMENT	N	N	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	OVRLRESP	Overall Response	CT LUGANO ASSESSMENT	PR	PR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	TRGRESP	Target Response	CT LUGANO ASSESSMENT	CR	CR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	LIVRC	Liver Cheson Assessment	LIVER ASSESSMENT	NORMAL	NORMAL	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	OVRLRESP	Overall Response	PET LUGANO ASSESSMENT	NE	NE	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	FDG-AVID	SPLNRESP	Spleen Response	SPLEEN ASSESSMENT	PR	PR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06

Investigator response is all by Laguna combined clinical information

Applying PARQUAL as PARAM Qualifier

FDA OOD v1.3 introduced in ADEXSUM

Imaging	Response Criteria	PARQUAL	Level of Assessment
PET-CT	Lugano (primary)	IRC_PETCT_LUGANO_CLIN	**Oncology (Combined Clinical Information)**
PET	Lugano	IRC_CT_LUGANO_CLIN	**Oncology (Combined Clinical Information)**
PET	Lugano	IRC_PET_LUGANO	Radiologist1, Radiologist2
CT	Lugano	IRC_CT_LUGANO_CLIN	**Oncology (Combined Clinical Information)**
CT	Lugano	IRC_CT_LUGANO	Radiologist1, Radiologist2
CT	Cheson (exploratory)	IRC_CT_CHESON_CLIN	**Oncology (Combined Clinical Information)**
CT	Cheson	IRC_CT_CHESON	Radiologist1, Radiologist2

Sample ADRS Data: Visit Level

USUBJID	PARAMCD	PARAM	PARQUAL	AVALC	RSEVAL	RSEVALID	AVISIT
001-002	LIVRC	Liver Cheson Assessment	IRC	NORMAL	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	NEWLSN	New Lesions Impact	IRC_CHESON	N	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	NEWLSN	New Lesions Impact	IRC_CT_LUGANO	N	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	NTRGRESP	Non-target Response	IRC_CHESON	CR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	OVRLRESP	Overall Response	IRC_CHESON_CLIN	PR	INDEPENDENT ASSESSOR	ONCOLOGIST	CYCLE 06
001-002	OVRLRESP	Overall Response	IRC_CT_CHESON	PR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	OVRLRESP	Overall Response	IRC_CT_LUGANO	PR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	OVRLRESP	Overall Response	IRC_LUGANO_CLIN	PR	INDEPENDENT ASSESSOR	ONCOLOGIST	CYCLE 06
001-002	OVRLRESP	Overall Response	IRC_PET_LUGANO	NE	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	OVRLRESP	Overall Response	IRC_PET_LUGANO_CLIN	NE	INDEPENDENT ASSESSOR	ONCOLOGIST	CYCLE 06
001-002	OVRLRESP	Overall Response	INV_LUGANO	PR	INVESTIGATOR	INVESTIGATOR	CYCLE 06
001-002	OVRLRESP	Overall Response	IRC_PETCT_LUGANO_CLIN	NON-PD	INDEPENDENT ASSESSOR	ONCOLOGIST	CYCLE 06
001-002	SPLNRESP	Spleen Response	IRC	PR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	TRGRESP	Target Response	IRC_CT_CHESON	CR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06
001-002	TRGRESP	Target Response	IRC_CT_LUGANO	CR	INDEPENDENT ASSESSOR	RADIOLOGIST 1	CYCLE 06

Sample ADRS Data: Overall

USUBJID	ADT	AVISIT	PARAMCD	PARAM	PARQUAL	AVALC	AVAL
001-002			ORR	Objective Response Rate	IRC_PETCT_LUGANO_CLIN	Y	
001-002			ORR	Objective Response Rate	INV_LUGANO	Y	
001-002			DCDUR	Disease Control Duration (mon)	IRC_PETCT_LUGANO_CLIN		x.x
001-002			DCDUR	Disease Control Duration (mon)	INV_LUGANO		y.y
001-002	01/27/20	CYCLE 03	BOR	Best Overall Response	IRC_PETCT_LUGANO_CLIN	PR	
001-002	01/27/20	CYCLE 03	BOR	Best Overall Response	INV_LUGANO	PR	
001-002	01/27/20	CYCLE 03	OVRLRESP	Objective Response Rate	IRC_PETCT_LUGANO_CLIN	PR	
001-002	03/30/20	CYCLE 06	OVRLRESP	Objective Response Rate	IRC_PETCT_LUGANO_CLIN	Non-PD	
001-002	07/13/20	CYCLE 09	OVRLRESP	Objective Response Rate	IRC_PETCT_LUGANO_CLIN	Non-PD	
001-002	10/05/20	CYCLE 12	OVRLRESP	Objective Response Rate	IRC_PETCT_LUGANO_CLIN	Non-PD	
001-002	03/22/21	CYCLE 18	OVRLRESP	Objective Response Rate	IRC_PETCT_LUGANO_CLIN	PR	
001-002	10/04/21	CYCLE 24	OVRLRESP	Objective Response Rate	IRC_PETCT_LUGANO_CLIN	Non-PD	
001-002	02/14/22	CYCLE 30	OVRLRESP	Objective Response Rate	IRC_PETCT_LUGANO_CLIN	Non-PD	
001-002	01/27/20	CYCLE 03	OVRLRESP	Objective Response Rate	INV_LUGANO	PR	
001-002	03/30/20	CYCLE 06	OVRLRESP	Objective Response Rate	INV_LUGANO	PR	
001-002	07/13/20	CYCLE 09	OVRLRESP	Objective Response Rate	INV_LUGANO	PR	
001-002	10/05/20	CYCLE 12	OVRLRESP	Objective Response Rate	INV_LUGANO	PR	
001-002	03/22/21	CYCLE 18	OVRLRESP	Objective Response Rate	INV_LUGANO	PR	
001-002	10/04/21	CYCLE 24	OVRLRESP	Objective Response Rate	INV_LUGANO	PR	
001-002	02/14/22	CYCLE 30	OVRLRESP	Objective Response Rate	INV_LUGANO	PR	

ADTTE Derivation and Censoring Rules

PARAMCD	PARAM	Variable	Comment
PFS	Progression-Free Survival	ADT	See details in the Table 5 below
PFS	Progression-Free Survival	AVAL	(ADT-ANCHDT +1)/7
PFS	Progression-Free Survival	CNSR	See details in the table 5 below
DOR	Duration of Response	ADT	Same as PFS (only for subjects with ADRS.AVALC='Y' and PARAMCD='ORR')
DOR	Duration of Response	AVAL	ADT- ORRDT +1
DOR	Duration of Response	CNSR	Same as PFS
DOR	Duration of Response	STARTDT	ADEFPRE.ADT when PARAMCD='ORRDT'
TTR	Time to Response	ADT	Set to ADEFPRE.ADT when PARAMCD='ORRDT and not missing; else set to ADEFPRE.LEVLDTA (last evaluable response date before taking new anti-cancer therapy)
TTR	Time to Response	AVAL	(ADT-ANCHDT +1)/7
TTR	Time to Response	CNSR	Set to 0 when ADEFPRE.PARAMCD='ORRDT and ADEFPRE.ADT not missing; else set to 1

ADTTE Derivation and Censoring Rules (1)

Situation	Date of Progression Event or Censoring	Outcome
1. Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Event
2. Death before first PD assessment or between adequate assessment	Date of death	Event
3. No baseline and/or post-baseline disease assessments	Reference start date	Censored
4. New anticancer treatment started before PD or death	Date of last disease assessment without PD prior to start of a new anticancer treatment	Censored
5. Death or PD immediately after more than *xx* after last disease assessment	Date of last disease assessment that is before death or PD	Censored
6. Alive and without PD	Date of last disease assessment visit	Censored

xx defined as two times protocol specified interval between tumor assessments plus the protocol allowed window

ADTTE Derivation and Censoring Rules (2)

Table 6: ADTTE Variables for PFS

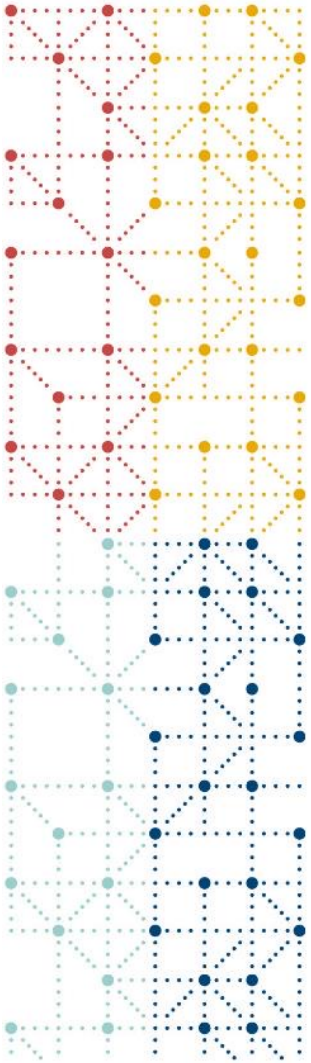
Seq.	Condition	Date of Event/Censor (ADT)	Censor (CNSR)	Event Description (EVNTDESC)	Censor Date Description (CNSDTDSC)
1	Death or PD between planned disease assessments	Minimum (PD date and Death Date)	0	PD/Death	
2.	Death before first PD assessment or between adequate assessment	Death	0	Death	
3	No baseline or post baseline response assessment	Anchor Date	1	No baseline/post-baseline assessment	Randomization or TRTSDT
4	New anticancer treatment started before PD or death	Last evaluable disease assessment w/o PD before New anti-cancer therapy	2	New Anti-Cancer Therapy	
5	No evaluable post-baseline assessment (up to new anti-cancer therapy if it exists), with early death and without new anti-cancer therapy prior to death	Death Date	0	Death	
6	Disease progression or death right after more than one missed scheduled disease assessment at the time of data cutoff	Anchor Date	3	Progressive disease/death after >1 missed assessment	Randomization or TRTSDT

ADTTE Derivation and Censoring Rules (3)

Seq.	Condition	Date of Event/Censor (ADT)	Censor (CNSR)	Event Description (EVNTDESC)	Censor Date Description (CNSDTDSC)
7	2 or more consecutive missing TAs prior to PD or Death after at least 1 evaluable response assessment without taking new anti-cancer therapy prior to relapse or PD/death	Last evaluable assessment date prior to the missing assessment	4	Missed >= 2 Assessments	Last Assessment Showing No Progression
8	No relapse or PD, no Death, no new anti-cancer therapy; at least 1 evaluable assessment, EOS status is ongoing	Last evaluable assessment date	5	Ongoing Without Event	Last Assessment Showing No Progression

Summary

- Tedious and prone to error to create unique PARAM/PARAMCD with PARCATn to designate different response assessments
- Create ADEFPRE, an intermediate date variables in BDS structure and apply PARQUAL to indicate PARAM in ADRS and ADTTE provide better traceability



Q & A

Thank You!

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