



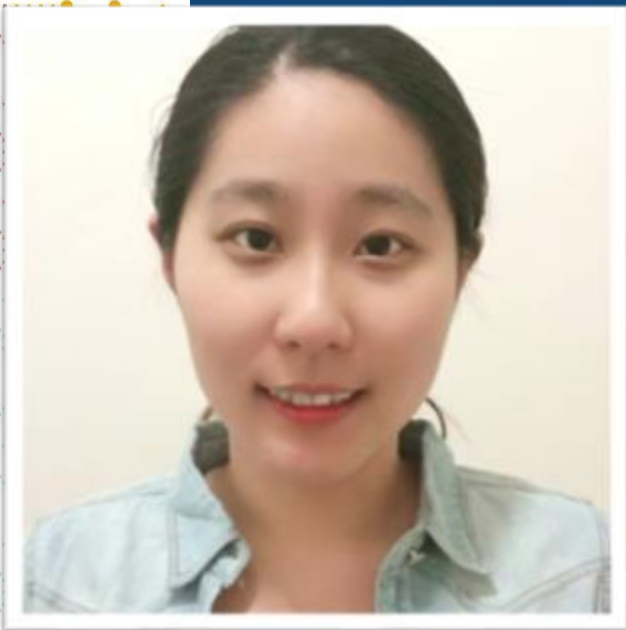
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CHINA
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29-30 JULY | VIRTUAL EVENT

RANO-BM Criteria and CDISC application

Presented by Yawen Ouyang, Statistical Programmer
Statistics Department, Xuanzhu Biopharm
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Meet the Speaker

Yawen Ouyang

Title: Statistical Programmer

Organization: Xuanzhu Biopharm

Yawen Ouyang, Master, a Statistical Programmer from Xuanzhu Biopharm with 3-year clinical industry experience and 7-year SAS experience. Participated in Phase I, II, III of oncology studies and bioequivalence studies with intimate knowledge of CDISC standard.

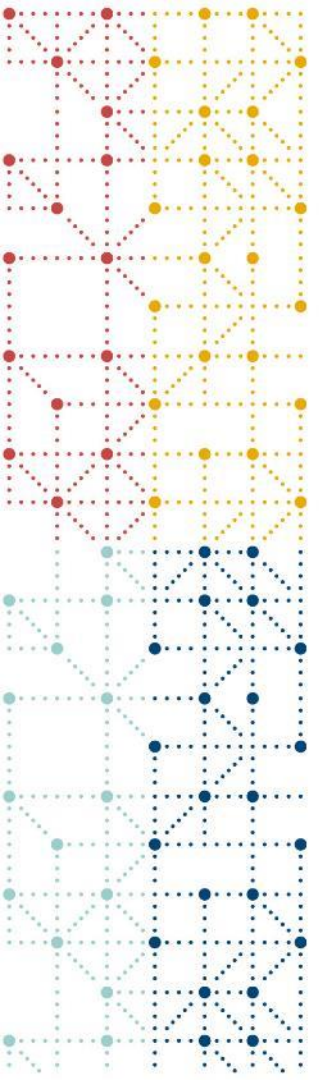
Disclaimer and Disclosures

- *Despite the growing inclusion of Blood Brain Barrier (BBB) penetrant and improving radiographic quality, assessment of Brain Metastases (CNS Metastases) remains challenging. RECIST 1.1 mainly referred as assessment criteria in oncology clinical trials, present apparent drawbacks addressed by RANO-BM proposed in 2015. The fundamental of RANO-BM is the separately identified target, non-target, and post-baseline new lesions from intracranial and extracranial lesions. With the RANO-BM applied in more and more clinical trials, this presentation intends to propose an integrated approach that marries the RANO-BM and CDISC standard.*
- *The author(s) have no real or apparent conflicts of interest to report.*



Agenda

1. Intro of RANO-BM Criteria
2. Relevant CDISC standard datasets
3. Statistical Output Sample



Intro of RANO-BM

Background and Criteria Content Introduction



Background

Any Type of cancer can spread to the brain, followings are the types with higher possibility:

- 50% of patients with CNS Metastases have **lung cancer**
- 20% of patients with CNS Metastases have **breast cancer**
- 50% of patients with **Melanoma** have CNS Metastases

Survival after diagnosis of CNS Metastases is usually short

Reference: Brain metastases: the role of clinical imaging by SOPHIE H. A. E. DERKS, MD, ASTRID A. M. VAN DER VELDT, MD, PhD and MARION SMITS, MD, PhD posted on 20210904



Background

Development of R&D and Radiographic Tech:

Blood-Brain Barrier (BBB) penetrant

- Lack of BBB penetrant causes under-exposure on CNS Metastases

Image Quality

- Present golden standard – Enhanced MRI is more sensitive on smaller lesions

CNS Metastases are pressing and more and more patients with CNS Metastases are included in clinical trials. Accurate and uniform assessment criteria is required.



Background

Limitations of RECIST1.1

Only Image features are considered

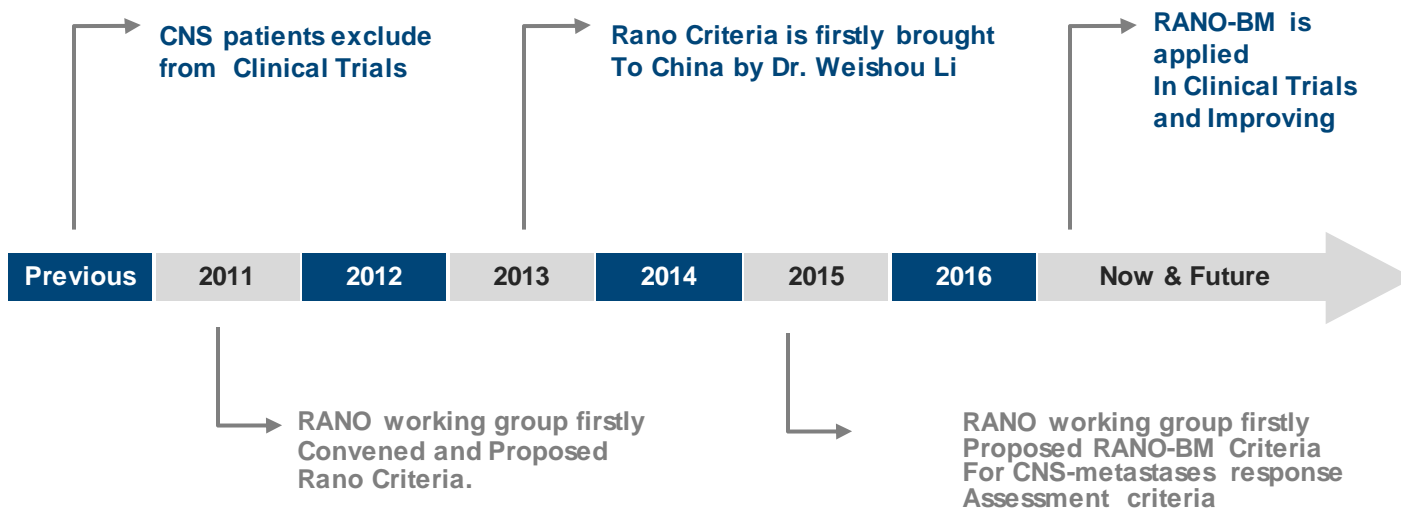
- Deteriorated clinical performance sometimes not radiographic progression disease

CNS and extra-CNS lesions are treated equivalently

- CNS lesions and extra-CNS lesions might reflect different efficacy results.

Background

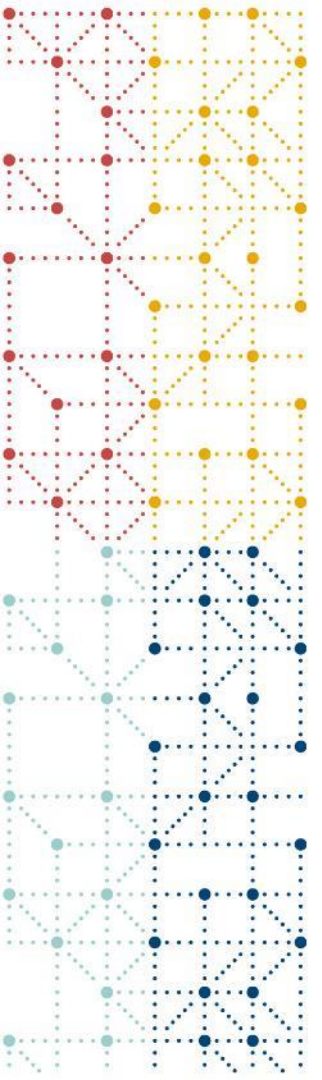
Timeline of RANO-BM



RANO-BM Criteria

Standard of Assessment

	CR	PR	SD	PD
Target Lesions	None	$\geq 30\%$ ↓ of sum(baseline)	$< 30\%$ ↓ & $< 20\%$ ↑ of sum(baseline)	$\geq 20\%$ ↑ of sum(nadir) & $\geq 5\text{mm}$ ↑ of sum
Non-Target Lesions	None	Stable or improved	Stable or improved	Unequivocal PD
New Lesions	None	None	None	Present
Corticosteroids	None	Stable or decreased	Stable or decreased	NA
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Worse



CDISC Standard Datasets

Relevant SDTM and ADaM datasets



SDTM - TU

TU domain – unique identification of tumors or lesions

Lesions are identified as intracranial target, non-target, new lesions or extracranial target, non-target, new lesions since intracranial lesions are assessed under RANO-BM and extracranial lesions are assessed under RECIST 1.1

- Target: Measurement with minimum 10mm diameters (usually longest)
- Non-Target: lesions which are not considered as target lesions
- New: Unequivocal not due to technical or slice variation

SDTM - TU

USUBJID	TULNKID	TUTESTCD	TUORRES
A00001	T01	TUMIDENT	TARGET
A00001	NT01	TUMIDENT	NON-TARGET
A00001	N01	TUMIDENT	NEW
A00001	T02.1	TUSPLIT	TARGET
A00001	T02.2	TUSPLIT	TARGET
A00001	T03/T04	TUMERGE	TARGET
A00001	CNS-T01	TUMIDENT	TARGET
A00001	CNS-NT01	TUMIDENT	NON-TARGET
A00001	CNS-T02/CNS-T03	TUMERGE	TARGET
A00001	CNS-T04.1	TUSPLIT	TARGET
A00001	CNS-T04.2	TUSPLIT	TARGET
A00001	CNS-N01	TUMIDENT	NEW



SDTM - TR

TR domain – Measurement of lesions

Lesions are independently measured under RANO-BM and RECIST 1.1:

- Diameters of target lesions
- Status of non-target lesions
- Indicator of new lesions
- Sum of Diameters

SDTM - TR

USUBJID	TRLNKID	TRLNKGRP	TRTESTCD	TRORES	VISIT
A00001	T01	A1	DIAMETER	15	SCREENING
A00001	T02	A1	DIAMETER	30	SCREENING
A00001		A1	SUMDIAM	45	SCREENING
A00001	NT01	A5	TUMSTAT	Absent	C3D1
A00001	N01	A7	TUMSTAT	Present	C5D1
A00001	CNS-T01	B1	DIAMETER	10	SCREENING
A00001	CNS-T02	B1	DIAMETER	12	SCREENING
A00001		B1	SUMDIAM	22	SCREENING
A00001	CNS-T01	B5	DIAMETER	Too Small to Measure	C3D1
A00001	CNS-T02	B5	DIAMETER	8	C3D1
A00001		B5	SUMDIAM	13	C3D1
A00001	CNS-NT01	B5	TUMSTAT	Absent	C3D1



SDTM - RS

RS domain – Assessment of Disease Response, or Clinical Classification

Assessment under RANO-BM and RECIST 1.1 are independent:

- Except for Target, Non-Target response and new lesion indicator, overall response is included
- Usage of Corticosteroids and Clinical Status are included under RANO-BM

SDTM - RS

USUBJID	RSLNKGRP	RSCAT	RSTESTCD	RSORRES	VISIT	RSDTC
A00001		RECIST 1.1	TRGRESP	PD	C3D1	2020-10-10
A00001		RECIST 1.1	NTRGRESP	NON-CR/NON-PD	C3D1	2020-10-10
A00001		RECIST 1.1	NEWLIND	Y	C3D1	2020-10-10
A00001	A5	RECIST 1.1	OVRLRESP	PD	C3D1	2020-10-10
A00001		RANO-BM	TRGRESP	PR	C3D1	2020-10-11
A00001		RANO-BM	NTRGRESP	NON-CR/NON-PD	C3D1	2020-10-11
A00001		RANO-BM	CORTRESP	Decreased	C3D1	2020-10-11
A00001		RANO-BM	CPRFSTAT	Improved	C3D1	2020-10-12
A00001	B5	RANO-BM	OVRLRESP	PR	C3D1	2020-10-12



ADaM – ADTR

ADTR resembles SDTM.TR

Data Structure follows ADaM standard and usually add variables of baseline flag, base and change from baseline

- Diameters of target lesions
- Status of non-target lesions
- Indicator of new lesions
- Sum of Diameters (Target Lesions)

ADaM - ADTR

USUBJID	TRLNKID	PARAMCD	AVAL	AVALC	ABLFL	BASE	CHANGE	AVISIT
A00001	T01	DIAMETER	15					SCREENING
A00001	T02	DIAMETER	30					SCREENING
A00001		SUMDIAM	45		Y			SCREENING
A00001	T01	DIAMETER	20					C3D1
A00001	T02	DIAMETER	35					C3D1
A00001		SUMDIAM	55			45	10	C3D1
A00001	CNS-T01	DIAMETER	12					SCREENING
A00001		SUMDIAM	12		Y			SCREENING
A00001	CNS-T01	DIAMETER	15					C3D1
A00001		SUMDIAM	15			12	3	C3D1
A00001	NT01	TUMSTAT		NON-CR/NON-PD				C3D1
A00001	N01	TUMSTAT		Present				C3D1



ADaM – ADRS

ADRS contains disease response

- CR/PR Confirmation is conditionally required (non-randomized and response is the primary endpoint)
- Best Overall Responses under RANO-BM and RECIST 1.1 are separately derived
- Analysis Date is depending on scanning date and rules which are specified in SAP

ADaM - ADRS

USUBJID	PARAMCD	AVALC	AVISIT	PARCAT1	RSEVAL	ADTC
A00001	TRGRESP	PR	C3D1	RECIST 1.1	Investigator	2020-05-01
A00001	NTRGRESP	NON-CR/NON-PD	C3D1	RECIST 1.1	Investigator	2020-05-03
A00001	OVRLRESP	PR	C3D1	RECIST 1.1	Investigator	2020-05-03
A00001	TRGRESP	SD	C5D1	RECIST 1.1	Investigator	2020-07-05
A00001	NTRGRESP	PR	C5D1	RECIST 1.1	Investigator	2020-07-06
A00001	OVRLRESP	PR	C5D1	RECIST 1.1	Investigator	2020-07-06
A00001	BESTRESP	PR		RECIST 1.1	Investigator	2020-05-03
A00001	TRGRESP	SD	C3D1	RANO-BM	Investigator	2020-05-03
A00001	NTRGRESP	PD	C3D1	RANO-BM	Investigator	2020-05-02
A00001	CPRFSTAT	Stable	C3D1	RANO-BM	Investigator	2020-05-10
A00001	CORTRESP	Worse	C3D1	RANO-BM	Investigator	2020-05-09
A00001	OVRLRESP	PD	C3D1	RANO-BM	Investigator	2020-05-02
A00001	BESTRESP	PD		RANO-BM	Investigator	2020-05-02

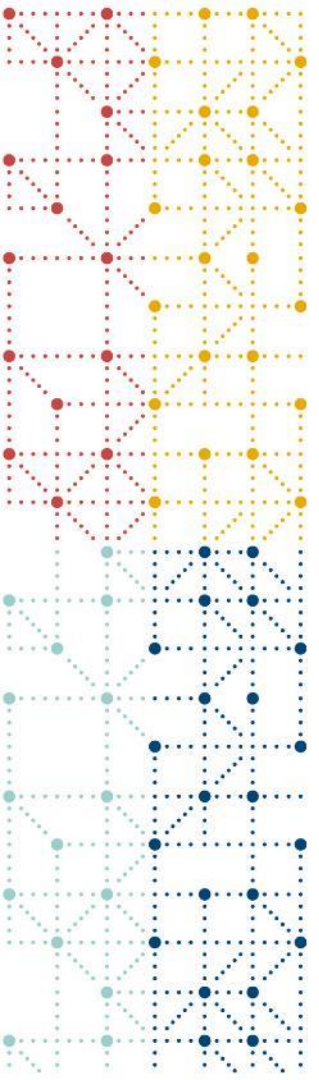
ADaM – ADTTE

ADTTE present a data structure for Time-To-Event analysis

- There is either event or censoring for each subject
- End point is selected upon purpose of study

ADaM - ADTTE

USUBJID	PARAM	AVAL	STARTDT	ADT	CNSR	EVNTDESC	CNSDTDSC	RSCAT	RSEVAL
A00001	Overall Survival (months)	18.35	2017-04-04	2018-10-10	1	No Death at Time of Cut-off	Last Known Alive Date		
A00001	Progression Free Survival (months)	16.03	2017-04-04	2018-08-01	1	No Death or PD at Time of Data Cut-off	Date of Last Adequate Overall Tumor Assessment	RECIST 1.1	Investigator
A00001	Progression Free Survival (months)	14.18	2017-04-04	2018-06-06	0	PD		RANO-BM	Investigator
A00001	Progression Free Survival (months)	16.03	2017-04-04	2018-08-01	1	No Death or PD at Time of Data Cut-off	Date of Last Adequate Overall Tumor Assessment	RECIST 1.1	Independent Assessor
A00001	Progression Free Survival (months)	14.18	2017-04-04	2018-06-06	0	PD		RANO-BM	Independent Assessor



Statistical Output Sample

Sample output delivery

Sample Output

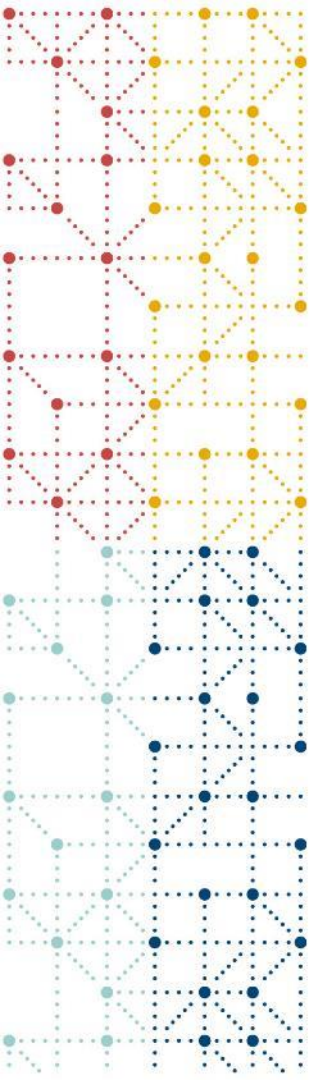
Efficacy Table under RANO-BM (population)

	Group A N=N
CNS Metastases	XX
Event	xx(xx.x)
Death	xx(xx.x)
PD	xx(xx.x)
Censoring	xx(xx.x)
Median PFS Time and 95% CI	XX.X [xx.xx,xx.xx]



Reference

- CDISC SDTM Controlled Terminology, 2021-12-17
- SDTM Implementation Guide, V3.3
- ADaM Implementation Guide, V1.2
- *Brain metastases: the role of clinical imaging* by SOPHIE H. A. E. DERKS, MD, ASTRID A. M. VAN DER VELDT, MD, PhD and MARION SMITS, MD, PhD posted on 20210904
- *Efficacy ADaMs in Oncology – Step by Step (Dataset by Dataset)* by Ilya Krivelevich, Eisai Inc., Woodcliff Lake, USA, Ran Xie, Eisai Inc., Woodcliff Lake, USA, Simon Lin, Eisai Inc., Woodcliff Lake, USA posted on US 2020 The Clinical Data Science Conference



Thank You!

cdisc