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Jumping out of Solid Tumor - Exploring Lugano 2014 in Hematologic Neoplasms Studies

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ABSTRACT

In oncology studies, response criteria are critical to our efficacy endpoints. In recent years, we have been very familiar with the criteria in solid tumor, for example, RECIST 1.1, now when came to hematologic neoplasms studies, there are more criteria we can learn like Lugano 2014, 2017 ELN, iwCLL 201, etc. These criteria are more complex and medical-driven than RECIST 1.1, programmers need to explore the background and application in data manipulation and derivation.

This paper will use Lugano 2014 as an example to illustrate the similarities and differences with RECIST 1.1, and the considerations we should pay in generating SDTM and ADaM: 1) How to better map response component to SDTM efficacy domain (TU, TR, and RS); 2) How these component affect RSDTC; 3) Cut-off rule application in TU, TR, and RS; 4) Confirmation in BOR (ADRS).

INTRODUCTION

Standardized response criteria provide uniform endpoints for clinical trials, allowing for comparisons amongst studies, facilitating the identification of more effective therapies, and aiding the approval process for new agents by regulatory agencies. Before 1999, response criteria for malignant lymphomas varied widely among study groups and cancer centers with respect to the size of a normal lymph node, the frequency of assessment and the time point the response assessment was made, the methods used to assess response, whether response was assessed prospectively or retrospectively, the percentage increase required for disease progression, and many other factors.[1] Even relatively minor differences in the definition of normal size of a lymph node can have a major influence on response rates.[2]

In 1999, an international working group (IWG) of clinicians, radiologists, and pathologists with expertise in the evaluation and management of patients with non-Hodgkin's lymphoma (NHL) published guidelines for response assessment and outcomes measurement.[1] These recommendations were adopted rapidly and widely by clinicians and regulatory agencies, and were used in the approval process for a number of new agents. However, they were subject to considerable inter- and intraobserver variation and recommended technologies, such as gallium scans, are no longer considered state-of-the-art. Several points were subject to misinterpretation, notably the application of the complete remission/unconfirmed (CRu), and the recommendations did not include assessment of extranodal disease. The widespread use of positron emission tomography (PET) scans and immunohistochemistry warranted a reassessment of the prior response criteria.[3]

Since the Hodgkin's lymphoma study groups had adopted these IWG criteria, any new recommendations needed to account for those patients as well. As a result, in 2007, an International Harmonization Project was initiated by the German Competence Network Malignant Lymphoma to develop recommendations that were consistent across study groups. PET with the glucose analog FDG as a tracer has been used in the evaluation.[3]

In 2014, the most recent revised criteria were published.[3] The evolution of this revised criteria was based on the need to define tumor FDG-avidity with greater objectivity and reproducibility. These new criteria were the direct outgrowth of integrating the previously defined Deauville criteria with the input of investigators at follow-up International Workshop Conferences in 2011 and 2013.[4]

LUGANO 2014 CRITERIA FOR RESPONSE ASSESSMENT

PET-CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity. A complete metabolic response even with a persistent mass is considered a complete remission.

A PR requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to six representative nodes or extranodal lesions. Progressive disease by CT criteria only requires an increase in the PPDs of a single node by 50%. Surveillance scans after remission are discouraged, especially for DLBCL and HL, although a repeat study may be considered after an equivocal finding after treatment. Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.[3]

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Figure 1. Criteria for Response Assessment[3]

Lugano 2014 vs Recist 1.1

The RECIST 1.1 criteria provide a standardized and quantifiable set of rules to evaluate tumor response based on changes in the size of target lesions, non-target lesions, and the appearance of new lesions post baseline.

The Lugano system assigns response based on the modified Deauville five-point scale. (PET-CT is recommended to be used for response assessments in FDG-avid histologies, and CT for low or variable FDG avidity.) The SUV_{max} of the most metabolically active lesion is determined and based on where that value falls in the Lugano 5PS, the response is assigned as Complete (Metabolic) Response, Partial (Metabolic) Response, Stable Disease or No Metabolic Response, and Progressive (Metabolic) Disease.[5]

Criteria	Lugano 2014	Recist 1.1
Used for	Lymphoma	Solid tumor
Target lesions	no more than 6	no more than 5, no more than 2 per organ
Overall response	Evaluate the response based on: 1. PET-CT in FDG-avid histologies 2. CT or low or variable FDG avidity (Target lesions, Non-target lesions, New lesions, Liver and Spleen) 3. Bone marrow aspirate/biopsy 4. Pathological biopsy	Evaluate the response based on: 1. Target lesions 2. Non-target lesions 3. New lesions
BOR	Confirm not required	Confirm required

Table 1. The key difference of Lugano 2014 and RECIST 1.1

RAW DATA TO SDTM

The primary purpose of this section is how programmers generate SDTM (TU, TR, RS) bases for submission purposes from EDC data in the efficacy section. The CRF forms used for efficacy assessment were target lesions, non-target lesions, new lesions, liver and spleen assessment, PET-CT, bone marrow biopsy/bone marrow aspiration, pathological biopsy, and B symptoms. SDTM IG v3.3, TR (**Tumor/Lesion Results**), A findings domain that represents quantitative measurements and/or qualitative assessments of the tumors or lesions identified in the tumor/lesion identification (TU) domain[6]. RS (**Disease Response**

and Clin Classification), A findings domain for the assessment of disease response to therapy, or clinical classification based on published criteria[6]. In general, TR was used for efficacy-related measurements or assessments, and RS was used for disease response to treatment. Combined with the above two points, we can map the CRF form as follows:

CRF Form	SDTM
Target lesions 1. Measurement 2. Target response	 1. TU, TR 2. RS
Non-target lesions 1. Results of Assessment 2. Non-target response	 1. TU, TR 2. RS
New lesions 1. Were there any unequivocal new lesions	 1. TU, TR
Spleen and liver 1. Was the spleen enlarged as assessed by imaging? 2. Long diameter of spleen	 1. TU, TR 2. RS
FDG-PET-CT (5PS, SUV, Bone marrow, new lesions)	TR
Bone marrow aspirate/biopsy	TR
Pathological biopsy	TR
B Symptoms	TR
Overall response CT response PET-CT response Overall response	 RS

Table 2 CRF form mapping

RSDTC MAPPING

The investigator or IRC tends to perform the overall assessment later than the PET-CT or CT scan date, and in order to make the PFS more accurate and the analysis more rigorous, we will re-map the RSDTC without using the assessment date collected in the CRF. Other sponsors generally update dates in ADAM level. But for ongoing projects, we need cut SDTM. Some complex rules should be considered when cut, for example, the overall response is RS, but RSDTC > CUTOFF date. We need to check if the latest scan date for this visit in TR data > CUTOFF date. If date > CUTOFF date, record for that visit is not kept in RS, otherwise keep it. Then in ADaM, we need consider the complex rules again. So we can take the action in SDTM level and it is convenient for cut.

This action is the most complex step in our generation of RS datasets. Lugano 2014 's response is divided into three categories: PET-CT Based Evaluation, CT Based Evaluation, and Overall Evaluation.

PET-CT based evaluation of the date is directly from the FDG-PET-CT form. For CT based evaluation and overall evaluation, there are many sources of dates. CT based evaluation is derived from target lesions, non-target lesions, new lesions, liver and spleen assessment dates, so RSDTC needs to be grasped from these forms. If response is PD, chose the minimum date from Target lesions, Non-target lesions, New lesions, and Liver/Spleen by Imaging that triggered PD as RSDTC. If the response was not PD, chose the latest examination date of Target lesions, Non-target lesions, New lesions, and Liver/Spleen by Imaging as RSDTC.

For the overall evaluation, both CT examination time and PET-CT examination time need to be considered. See the table below for details:

Response	RSDTC
PET-CT Based response	PET-CT assessment date
CT Based response	**Non-PD response**: The latest examination date of Target lesions, Non-target lesions, New lesions and Liver/Spleen by Imaging. **PD response**: The minimum date from Target lesions, Non-target lesions, New lesions and Liver/Spleen by Imaging that triggered PD.
Overall response	**Non-PD response**: The maximum date of CT assessment (Target lesions, Non-target lesions, New lesions and Liver/Spleen), PET-CT assessment, Bone marrow aspirate/biopsy and B Symptoms **PD response**: The minimum date of CT assessment (Target lesions, Non-target lesions, New lesions and Liver/Spleen), PET-CT assessment, Bone marrow aspirate/biopsy and Pathological biopsy that triggered PD.

Table 3. Mapping Rule for RSDTC

Since the difference in VISIT between oncology data and clinical data. We can't merge the two kinds of data by VISIT directly. We should convert the visit of clinical data to oncology visit as below.

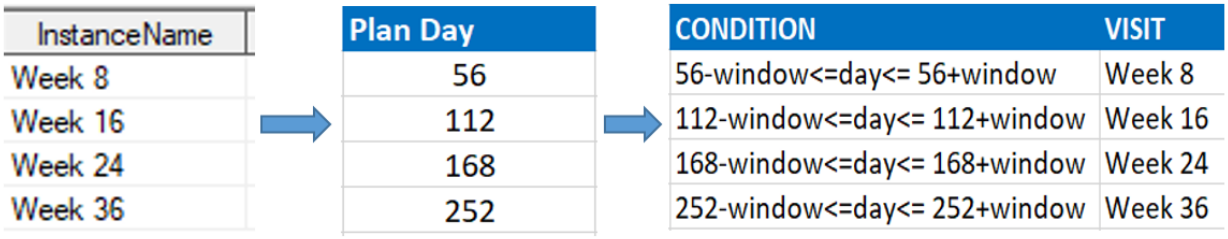

Figure 2. Map the visit of clinical data to oncology visit

As shown in Figure 3, subject 001 is PD at week 8 Target response, CT response and PET-CT based response, and RSDTC was the remapped to actual assessment date.
CT response was PD, of which trigger PD was:

1. target lesion TRLNKID = T-01 enlargement (marker 1), TRDTC = 2023-02-26

2. new lesion (marker 2), TRDTC = 2023-02-26;

3. spleen long diameter growth > 50% of the original long diameter increase (marker 3), TRDTC = 2023-02-27;

Therefore, the earliest of the three RSDTCs corresponding to CT response is 2023-02-26.

Similarly, overall response was PD, of which trigger PD was:

1. target lesion TRLNKID = T-01 enlargement (marker 1), TRDTC = 2023-02-26

2. new lesion (marker 2), TRDTC = 2023-02-26;

3. spleen long diameter increase > 50% of the original long diameter increase (marker 3), TRDTC = 2023-02-27;

4. 5PS score of 4 with uptake increase from baseline, TRDTC = 2023-02-28;

Therefore the RSDTC of overall response is 2023-02-26.

STUDYID	DOMAIN	USUBJID	RSSEQ	RSLNKGRP	RSTESTCD	RSTEST	RSORRES	VISITNUM	VISIT	RSDTC	RSDY
XYZ	RS	XYZ	1		TRGRESP	Target Response	PD	9999.08	Week 8	2023-02-26	56
XYZ	RS	XYZ	2		NTRGRESP	Non-target Response	Non-CR/Non-PD	9999.08	Week 8	2023-02-26	56
XYZ	RS	XYZ	3		CTRESP	CT Response	PD	9999.08	Week 8	2023-02-26	56
XYZ	RS	XYZ	4		PETRESP	PET-CT Response	PD	9999.08	Week 8	2023-02-28	58
XYZ	RS	XYZ	5	A2	OVRLRESP	Overall Response	PD	9999.08	Week 8	2023-02-26	56

Figure 3. Example Data Records from RS

STUDYID	DOMAIN	USUBJID	TRSEQ	TRGRPID	TRLNKGRP	TRLNKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	TRMETHC	VISITNUM	VISIT	TRDTC	TRDY
XYZ	TR	XYZ-001	1	TARGET NODAL	A1	T-01	LDI	Longest Diameter	19.08	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	2	TARGET NODAL	A1	T-01	SDI	Shortest Diameter	19.08	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	3	TARGET NODAL	A1	T-01	PPD	Product Perpendicular Diameters	364.05	mm2	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	4	TARGET NODAL	A1	T-02	LDI	Longest Diameter	21.23	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	5	TARGET NODAL	A1	T-02	SDI	Shortest Diameter	21.23	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	6	TARGET NODAL	A1	T-02	PPD	Product Perpendicular Diameters	450.71	mm2	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	7	TARGET EXTRA NODAL	A1	T-03	LDI	Longest Diameter	17.55	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	8	TARGET EXTRA NODAL	A1	T-03	SDI	Shortest Diameter	17.55	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	9	TARGET EXTRA NODAL	A1	T-03	PPD	Product Perpendicular Diameters	308.0	mm2	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	10	TARGET	A1		SPD	Sum Product Perpendicular Diam	1122.76	mm2	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	11	NON-TARGET NODAL	A1	NT-01	TUMSTATE	Tumor State	PRESENT		CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	12	NON-TARGET EXTRA NODAL	A1	NT-02	TUMSTATE	Tumor State	PRESENT		CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	13	TARGET SPLEEN	A1	TS-01	LSRES	Spleen Long Diameter	12	cm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	14	FDG-PET	A1		SUVM	SUVmax	12.6		PET-CT	9999.00	Screening	2023-01-01	-1
XYZ	TR	XYZ-001	15	FDG-PET	A1		FDPL5PS	FDG PET Lymphoma 5PS Score			PET-CT	9999.00	Screening	2023-01-01	-1
XYZ	TR	XYZ-001	16	FDG-PET	A1		FDGABM	FDG-Avid Disease in Bone Marrow	No		PET-CT	9999.00	Screening	2023-01-01	-1
XYZ	TR	XYZ-001	17		A1		BONEMAR	Bone Marrow	Positive			9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	18		A1		LNORTPAS	Lymph Node or Tissue Pathology	Negative			9999.00	Screening	2023-12-30	-3
XYZ	TR	XYZ-001	19		A1		BSYMPTOM	B Symptoms	PRESENT			9999.00	Screening	2023-12-30	-3
XYZ	TR	XYZ-001	1	TARGET NODAL	A2	T-01	LDI	Longest Diameter	26	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	2	TARGET NODAL	A2	T-01	SDI	Shortest Diameter	26	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	3	TARGET NODAL	A2	T-01	PPD	Product Perpendicular Diameters	676	mm2		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	4	TARGET NODAL	A2	T-02	LDI	Longest Diameter	21.23	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	5	TARGET NODAL	A2	T-02	SDI	Shortest Diameter	21.23	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	6	TARGET NODAL	A2	T-02	PPD	Product Perpendicular Diameters	450.71	mm2		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	7	TARGET EXTRA NODAL	A2	T-03	LDI	Longest Diameter	17.55	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	8	TARGET EXTRA NODAL	A2	T-03	SDI	Shortest Diameter	17.55	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	9	TARGET EXTRA NODAL	A2	T-03	PPD	Product Perpendicular Diameters	308.0	mm2		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	10	TARGET	A2		SPD	Sum Product Perpendicular Diam	1122.76	mm2		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	11	NON-TARGET NODAL	A2	NT-01	TUMSTATE	Tumor State	PRESENT			9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	12	NON-TARGET EXTRA NODAL	A2	NT-02	TUMSTATE	Tumor State	PRESENT			9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	13	NEW	A2	NEW-01	TUMSTATE	Tumor State	PRESENT			9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	14	TARGET SPLEEN	A2	TS-01	LSRES	Spleen Long Diameter	15	cm		9999.08	Week 8	2023-02-27	57
XYZ	TR	XYZ-001	15	FDG-PET	A2		SUVM	SUVmax	22.5			9999.08	Week 8	2023-02-28	58
XYZ	TR	XYZ-001	16	FDG-PET	A2		FDPL5PS	FDG PET Lymphoma 5PS Score	4			9999.08	Week 8	2023-02-28	58
XYZ	TR	XYZ-001	17	FDG-PET	A2		FDGABM	FDG-Avid Disease in Bone Marrow	No			9999.08	Week 8	2023-02-28	58
XYZ	TR	XYZ-001	18		A2		BONEMAR	Bone Marrow	Negative			9999.08	Week 8	2023-02-27	57
XYZ	TR	XYZ-001	19		A2		LNORTPAS	Lymph Node or Tissue Pathology	Negative			9999.08	Week 8	2023-02-27	57
XYZ	TR	XYZ-001	20		A2		BSYMPTOM	B Symptoms	PRESENT			9999.08	Week 8	2023-02-27	57

Figure 4. Example Data Records from TR

STUDYID	DOMAIN	USUBJID	RSSEQ	RSLNKGRP	RSTESTCD	RSTEST	RSORRES	VISITNUM	VISIT	RSDTC	RSDY
XYZ	RS	XYZ	1		TRGRESP	Target Response	SD	9999.08	Week 8	2023-02-26	56
XYZ	RS	XYZ	2		NTRGRESP	Non-target Response	Non-CR/Non-PD	9999.08	Week 8	2023-02-26	56
XYZ	RS	XYZ	3		CTRESP	CT Response	SD	9999.08	Week 8	2023-02-26	56
XYZ	RS	XYZ	4		PETRESP	PET-CT Response	SD	9999.08	Week 8	2023-02-28	58
XYZ	RS	XYZ	5	A2	OVRLRESP	Overall Response	SD	9999.08	Week 8	2023-02-28	56

Figure 5. Example Data Records from RS

As shown in Figure 5, subject 001 is SD at week 8 Target response, CT response and PET-CT based response, and RSDTC was the remapped to actual assessment date. The RSDTC is the latest date for each response.

STUDYID	DOMAIN	USUBJID	TRSEQ	TRGRPID	TRLNKGRP	TRLNKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	TRMETHC	VISITNUM	VISIT	TRDTC	TRDY
XYZ	TR	XYZ-001	1	TARGET NODAL	A1	T-01	LDI	Longest Diameter	19.08	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	2	TARGET NODAL	A1	T-01	SDI	Shortest Diameter	19.08	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	3	TARGET NODAL	A1	T-01	PPD	Product Perpendicular Diameters	364.05	mm2	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	4	TARGET NODAL	A1	T-02	LDI	Longest Diameter	21.23	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	5	TARGET NODAL	A1	T-02	SDI	Shortest Diameter	21.23	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	6	TARGET NODAL	A1	T-02	PPD	Product Perpendicular Diameters	450.71	mm2	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	7	TARGET EXTRA NODAL	A1	T-03	LDI	Longest Diameter	17.55	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	8	TARGET EXTRA NODAL	A1	T-03	SDI	Shortest Diameter	17.55	mm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	9	TARGET EXTRA NODAL	A1	T-03	PPD	Product Perpendicular Diameters	308.0	mm2	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	10	TARGET	A1		SPD	Sum Product Perpendicular Diam	1122.76	mm2	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	11	NON-TARGET NODAL	A1	NT-01	TUMSTATE	Tumor State	PRESENT		CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	12	NON-TARGET EXTRA NODAL	A1	NT-02	TUMSTATE	Tumor State	PRESENT		CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	13	TARGET SPLEEN	A1	TS-01	LSRES	Spleen Long Diameter	12	cm	CT	9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	14	FDG-PET	A1		SUVM	SUVmax	12.6		PET-CT	9999.00	Screening	2023-01-01	-1
XYZ	TR	XYZ-001	15	FDG-PET	A1		FDPL5PS	FDG PET Lymphoma 5PS Score			PET-CT	9999.00	Screening	2023-01-01	-1
XYZ	TR	XYZ-001	16	FDG-PET	A1		FDGABM	FDG-Avid Disease in Bone Marrow	No		PET-CT	9999.00	Screening	2023-01-01	-1
XYZ	TR	XYZ-001	17		A1		BONEMAR	Bone Marrow	Positive			9999.00	Screening	2022-12-31	-2
XYZ	TR	XYZ-001	18		A1		LNORTPAS	Lymph Node or Tissue Pathology	Negative			9999.00	Screening	2023-12-30	-3
XYZ	TR	XYZ-001	19		A1		BSYMPTOM	B Symptoms	PRESENT			9999.00	Screening	2023-12-30	-3
XYZ	TR	XYZ-001	1	TARGET NODAL	A2	T-01	LDI	Longest Diameter	19.08	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	2	TARGET NODAL	A2	T-01	SDI	Shortest Diameter	19.08	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	3	TARGET NODAL	A2	T-01	PPD	Product Perpendicular Diameters	364.05	mm2		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	4	TARGET NODAL	A2	T-02	LDI	Longest Diameter	21.23	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	5	TARGET NODAL	A2	T-02	SDI	Shortest Diameter	21.23	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	6	TARGET NODAL	A2	T-02	PPD	Product Perpendicular Diameters	450.71	mm2		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	7	TARGET EXTRA NODAL	A2	T-03	LDI	Longest Diameter	17.55	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	8	TARGET EXTRA NODAL	A2	T-03	SDI	Shortest Diameter	17.55	mm		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	9	TARGET EXTRA NODAL	A2	T-03	PPD	Product Perpendicular Diameters	308.0	mm2		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	10	TARGET	A2		SPD	Sum Product Perpendicular Diam	1122.76	mm2		9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	11	NON-TARGET NODAL	A2	NT-01	TUMSTATE	Tumor State	PRESENT			9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	12	NON-TARGET EXTRA NODAL	A2	NT-02	TUMSTATE	Tumor State	PRESENT			9999.08	Week 8	2023-02-26	56
XYZ	TR	XYZ-001	14	TARGET SPLEEN	A2	TS-01	LSRES	Spleen Long Diameter	12	cm		9999.08	Week 8	2023-02-27	57
XYZ	TR	XYZ-001	15	FDG-PET	A2		SUVM	SUVmax	12.6			9999.08	Week 8	2023-02-28	58
XYZ	TR	XYZ-001	16	FDG-PET	A2		FDPL5PS	FDG PET Lymphoma 5PS Score	4			9999.08	Week 8	2023-02-28	58
XYZ	TR	XYZ-001	17	FDG-PET	A2		FDGABM	FDG-Avid Disease in Bone Marrow	No			9999.08	Week 8	2023-02-28	58
XYZ	TR	XYZ-001	18		A2		BONEMAR	Bone Marrow	Negative			9999.08	Week 8	2023-02-27	57
XYZ	TR	XYZ-001	19		A2		LNORTPAS	Lymph Node or Tissue Pathology	Negative			9999.08	Week 8	2023-02-27	57
XYZ	TR	XYZ-001	20		A2		BSYMPTOM	B Symptoms	PRESENT			9999.08	Week 8	2023-02-27	57

Figure 6. Example Data Records from TR

SDTM DATA CUT

For ongoing studies, SDTM needs to be cut. TU dataset only keeps the records before Cutoff date, TR keeps the records before Cutoff date, but if the overall assessment of a visit is PD, keep all records of that visit, even if TRDTC > Cutoff date.

Domain	Cutoff Rule
TU	Include if less than or equal to Cutoff Date
TR	Include if less than or equal to Cutoff Date; Note: If the **overall** response of one visit is PD and the date is before Cutoff date, then keep all record of this visit even if TRDTC > Cutoff date
RS	Include if less than or equal to Cutoff Date; Note: If the **overall** response of one visit is PD and the date is before Cutoff date, then keep all record of this visit even if RSDTC > Cutoff date

Table 4. Cutoff rules for SDTM

If the cutoff date is 2023-02-26, and since the response of week 8 is PD, all the records of week 8 in TR and RS are kept.

BOR CONFIRMED

A confirmed response is not required in lymphoma, which is not likely to RECIST when calculating ORR.

CONCLUSION

This paper is aimed to introduce a mapping approach to efficacy partial data in lymphoma studies, as well as data cut rule. Since CDISC hasn't public the related TA Guidance, mapping rule is not clear. If there is a better method afterward, we can still update the corresponding mapping rules. Examples presented in

this paper are hypothetical and for illustrative purpose only, and this paper puts forward a special view of the Cutoff rule and SDTM mapping rule. Further detailed analysis process could depend on the study protocol and statistical analysis plan (SAP), CDISC ADaM Guidance.

REFERENCES

1. Cheson BD, Horning SJ, Coiffier B, et al: Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244-1253, 1999
2. Grillo-Lo´ pez AJ, Cheson BD, Horning SJ, et al: Response criteria for NHL: Importance of "normal" lymph node size and correlations with response rates. Ann Oncol 11:399-408, 2000
3. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014.
4. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the first international workshop on interim-PET-scan in lymphoma. Leuk Lymphoma. 2009;50(8):1257–1260.
5. Kuldeep Sen, Sumida Urval, Yang Wang. CDISC Compliant Implementation of iRECIST and LYRIC for Immunomodulatory Therapy Trials. PharmaSUG 2020 - Paper DS-117.
6. Study Data Tabulation Model Implementation Guide: Human Clinical Trials Version 3.3 from CDISC: https://www.cdisc.org/system/files/members/standard/foundational/SDTMIG_v3.3_FINAL.pdf

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