A Novel Methodology for Assessing Response to Lymphoma Treatment in Real-World Studies – Real-World Lugano (rwLugano)

MSR101

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BACKGROUND

- In lymphoma clinical trials, blinded independent central review (BICR) using the Lugano 2014 criteria is the standard for assessing treatment response.
- Real-world evidence (RWE) can support United States Food and Drug Administration (US FDA) review of cancer drugs.
  - As BICR is less available (due to feasibility, challenges, and costs of conducting BICR) in the real-world settings, novel methods are needed to standardize assessment of treatment response.
- Physician-charted response is the standard method used for treatment outcome assessment using real-world data (RWD).
  - To address these limitations, we developed real-world Lugano (rwLugano), an objective, novel RWD-based methodology for assessing lymphoma treatment response.

OBJECTIVE

- To evaluate performance of assessing lymphoma treatment response classified via rwLugano-derived and physician-charted compared to BICR-assessed response.

METHODS

Study design and participants

- A multicenter, retrospective chart review study conducted at 6 sites within the Cardinal Health Oncology Practice Research Network (PRN), a consortium of US-based community oncologists and hematologists.
- The study included patients ≥18 years old with histologically confirmed, diffuse large B-cell lymphoma (DLBCL) treated with chemoimmunotherapy as first-line (1L) therapy.
- Each participating PRN site selected consecutive patients, starting with the earliest eligible, at each practice.
  - — Deidentified data, captured via an electronic case report form (eCRF).
  - — Digital PET-CT scans were deidentified upon upload to a secure platform.
- All study materials were reviewed by a central Institutional Review Board.

Figure 1. Study endpoints

- Response Assessment Methods:
  - **Physician-charted** initial response to 1L therapy as charted in the patient medical record.
  - **rwLugano-derived** calculated response based on Lugano classification (**Table 1**) components available on pretreatment (baseline) scans compared to scans on-treatment, with at least 1 on-treatment scan performed at initial response.
  - **BICR-assessed** response assigned by 2 independent radiologists by comparing pretreatment (baseline) scan to scans on-treatment with at least 1 on-treatment (1L) scan performed at initial response (**Table 1**).

Inclusion criteria

- Adults with a diagnosis of DLBCL (with histologic confirmation) between 2015 and 2022.
- Treated with an anthracycline-containing chemoimmunotherapy regimen that includes an anti-CD20 monoclonal antibody.
- PET-CT images available at baseline (within 8 weeks prior to 1L therapy initiation) and initial response assessment scan (within 8-24 weeks of initiating 1L therapy).
- At least 6 months follow-up from 1L therapy initiation, including eligible patients who died within this period.

Exclusion criteria

- Central nervous system (CNS) involvement at the time of DLBCL diagnosis.
- Treated for other malignancies during 1L therapy.
- Enrolled in a clinical trial during 1L therapy.

Treatment response assessment methods

- The Lugano classification, which uses a 5-point scale (i.e., Deauville score) and is based on the standardized uptake value (SUV) of the most metabolically active lesion, assesses treatment response using PET-CT imaging (**Table 1**).
- rwLugano was derived from Lugano 2014 criteria by using the abstracted EMR data associated with imaging reports and scans.
- The other 2 response assessment methods are BICR-reported and physician-charted response.

Table 1. Lugano Classification of Response (Simplified)

Modified Lugano 5PS (Deauville Score)	Change from baseline	New lesions	Bone marrow	Lugano response
1, 2, or 3	Reduced	No	No	CR
4 or 5	Reduced	No	Reduced	PR
4 or 5	No charge	No	No change	NR
4 or 5	Increased	No	Yes	PD
Any	Any	Yes	Yes	PD

5PS, 5-point scale based on SUV of most metabolically active lesion: 1) no uptake above background; 2) uptake ≤ mediastinum; 3) uptake > mediastinum but ≤ liver; 4) uptake moderately increased compared to liver; 5) markedly increased uptake above liver at any site and/or new lesions. NR, no response.

Outcome

- The primary end point was agreement of physician-charted- and rwLugano-derived CR, each compared to BICR-assessed CR (using Lugano 2014 criteria).
- Secondary endpoints included PR, SD, PD, and ORR and were evaluated via agreement across the 3 assessment methods.

Statistical analysis

- Lymphoma treatment responses classified as CR were compared using the 3 methods based on percent agreement and concordance (Cohen's kappa [κ]).
- A generalized linear mixed model (GLMM) with a logit link estimated the odds ratio (OR) of CR comparing rwLugano and physician-charted response to BICR, adjusting baseline characteristics such as provider ID, disease characteristics, stage at diagnosis, anemia, and heart disease.

RESULTS

- 178 patients with DLBCL were eligible for study inclusion (**Table 2**).
- Median (P25-75) follow-up from 1L therapy initiation was 25.6 (16.8-43.8) months.
- Assignment of CR at initial response assessment was proportionately lower for physician-charted (63.5%) compared with rwLugano-derived (81.5%) and BICR-reported (83.1%) response (**Tables 3 and 4**).
- The overall percent agreement between physician-charted versus BICR-assessed assignment of initial responses was 71.3%, whereas rwLugano-derived versus BICR-assessed was 83.7% (**Tables 3 and 4**).
- Overall and CR agreement with BICR (**Table 5**) was numerically higher for rwLugano-derived (overall: 83.7%, κ=0.50; CR: 87.9%, κ=0.52) than physician-charted response (overall: 71.3%, κ=0.43; CR: 77.0%, κ=0.40).
- GLMM analyses found a statistically significant difference between physician-charted and BICR-assessed CR (**Table 6**).
  - Compared to BICR, physician-charted responses had lower CR estimation (OR=0.23; 95%CI:0.12-0.43).
  - Compared to BICR, rwLugano-derived CR was not statistically different (OR=1.19; 95%CI:0.61-2.33).
  - Other variables significantly associated with treatment response were the physicians, bulky disease, disease stage, anemia, and heart disease (**Table 6**).

Table 2. Baseline patient demographic and clinical characteristics

Participant characteristics	N=178
Age at diagnosis (years), mean (SD)	66.4 (12.8)
Sex, n (%)	
Male	105 (59.0)
Female	73 (41.0)
Race, n (%)	
American Indian or Alaska Native	0 (0)
Asian	5 (2.8)
Black or African American	18 (10.1)
Native Hawaiian or Other Pacific Islander	0 (0)
White	137 (77.0)
Unknown	18 (10.1)
Ethnicity, n (%)	
Hispanic or Latino	13 (7.3)
Not Hispanic or Latino	143 (80.3)
Unknown	22 (12.4)
Duration of follow-up from 1L therapy initiation (months), median (P25-P75)	25.6 (16.8-43.8)
Ann Arbor stage at 1L therapy initiation among patients with known stage, n (%)	154 (86.5)
Stage I	24 (15.6)
Stage II	42 (27.3)
Stage III	38 (24.7)
Stage IV	50 (32.5)
Bulky disease (≥7 cm), n (%)	35 (19.7)
Comorbidities prior to 1L therapy initiation, n (%)	
Anemia	49 (27.5)
Heart disease	38 (21.3)

Table 3. Physician-charted vs BICR-assessed initial response assessment

Agreement between physician-charted and BICR-assessed initial response	BICR-assessed			
Physician-charted	**CR**	**PR**	**SD/NR**	**PD**
CR	107	5	0	1
PR	37	17	1	1
SD/NR	1	2	1	1
PD	0	1	1	2

Table 4. rwLugano-derived vs BICR-assessed initial response assessment

Agreement between BICR-reported and rwLugano-derived initial response	BICR-assessed			
rwLugano-derived	**CR**	**PR**	**SD/NR**	**PD**
CR	134	10	0	1
PR	10	12	1	2
SD/NR	2	0	0	1
PD	2	0	0	3

RESULTS

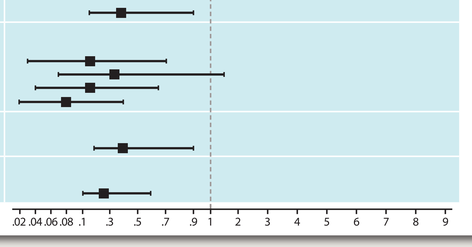
Table 5. Concordance among the 3 methods for initial response assessment (N=178)

	Reference = BICR
	Kappa/Weighted Kappa (95% CI)
Physician-charted	
CR	0.40 (0.27-0.54)
PR	0.28 (0.14-0.42)
SD/NR	0.23 (-0.17-0.63)
PD	0.43 (0.02-0.84)
ORR	0.57 (0.28-0.86)
All response categories	0.43 (0.30-0.57)
CR agreement, %	77.0
Overall agreement, %	71.3
rwLugano-derived	
CR	0.52 (0.35-0.68)
PR	0.44 (0.24-0.63)
SD/NR	-0.01 (-0.02-0.00)
PD	0.48 (0.13-0.84)
ORR	0.48 (0.17-0.79)
All response categories	0.50 (0.34-0.67)
CR agreement, %	87.9
Overall agreement, %	83.7

ORR is sum of patients with CR or PR divided by number of total patients.

Table 6. Multivariable analysis to identify predictors of treatment response (within 6 months from initiation of treatment) using GLMM

Covariates	OR (95% CI)
Method	
BICR-reported	Reference
Physician-assessed	0.23 (0.12, 0.43)
rwLugano-derived	1.19 (0.61, 2.34)
Site	
02	Reference
03	2.31 (0.63, 8.40)
04	2.31 (0.76, 7.04)
06	1.68 (0.44, 6.49)
07	0.12 (0.03, 0.52)
08	2.35 (0.77, 7.19)
Bulky disease	
No	Reference
Yes	0.37 (0.15, 0.90)
Stage at diagnosis	
Stage I	Reference
Stage II	0.16 (0.03, 0.71)
Stage III	0.33 (0.07, 1.57)
Stage IV	0.16 (0.04, 0.67)
Not available	0.08 (0.02, 0.40)
Anemia	
No	Reference
Yes	0.39 (0.17, 0.90)
Heart disease	
No	Reference
Yes	0.25 (0.11, 0.59)



CONCLUSIONS

- rwLugano classification performed similarly to BICR for classifying initial treatment response to 1L DLBCL therapy.
- Physician-charted response, for lymphoma treatment response assessment, resulted in proportionally fewer estimates of an inital response of CR compared with BICR.
- rwLugano is a novel methodology that may be a relevant measure of outcome classification in real-world lymphoma research.
- Further study is needed to validate these findings.
- Implications of our findings:
  - Though resource intensive, BICR can be a viable method for outcome assessment in using RWD when imaging data are available.
  - When BICR is not feasible in observational research due to lacking capability or resource restraints, rwLugano may offer an alternative, less resource intense approach while maintaining construct validity.

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