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Programming LYRIC Response in Immunomodulatory Therapy Trials

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ABSTRACT

The **LY**mphoma **R**esponse to **I**mmunomodulatory therapy **C**riteria (LYRIC) is a newly proposed tumor response criteria for immunomodulatory therapies such as immune checkpoint inhibitors. The current Lugano criteria work well for traditional chemotherapeutic regimens and chemoimmunotherapeutic regimens. It includes complete remission (CR), partial remission (PR), complete remission unconfirmed (CRu), stable disease (SD), relapsed disease (RD) and progressive disease (PD). However, Lymphoma therapy with immune mechanisms may cause tumor flares. These tumor flares can be associated with clinical and imaging findings suggesting progressive disease (PD). Since tumor flares generally occur during the first two or three weeks of treatment, without a more flexible interpretation, it is possible that some patients can be prematurely removed from a potentially beneficial treatment, thus leading to underestimation of the magnitude of the clinical benefit of the testing agent.

LYRIC criteria introduces a new term “Indeterminate Response (IR)”. Adding this new term allows distinguishing of flare/pseudo-progression and true PD by biopsy or subsequent imaging. This paper explains how this IR term data is collected and derived. It also discusses the data collection and programming challenges.

INTRODUCTION

While WHO criteria, RECIST and PERCIST are used for solid tumors, over the years, a number of criteria have been proposed for hematological malignancies including Hodgkin lymphoma (HL) and Non- Hodgkin lymphoma (NHL). In 1998, the International Working Criteria (IWC) used clinical or radiological CT exam to classify patient response to complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), as well a new classification of “unconfirmed complete response” (CRu) . In 2005, PET was integrated into the IWC criteria. In 2007, Cheson et al addressed the false-positive PET findings following chemotherapy, recommending PET acquisition 3-8 weeks after chemotherapy and 8-12 weeks after radiation therapy. After addressing the possibility of false-positive PET findings, CRu was eliminated and the classification includes CR, PR, SD, and PD. In 2009, the Deauville five point scoring system (D5PS) assessed treatment response qualitatively. At the 12th ICML, convened in Lugano, Switzerland in 2013, the consensus revision of both the criteria for staging and the 2007 IWG response criteria led to the development of Lugano classification. In the Lugano classification, separate sets of response criteria were proposed for PET and CT imaging, The PET-based criteria built on the 5-point categorical scale established by the D5PS by adding considerations for new or recurring involvement of lymph nodes and bone marrow as well as organomegaly. CT alone based criteria is also proposed.

In 2016, Cheson etc. proposed LYRIC response criteria. Because many new immunotherapy other than traditional cytotoxic chemotherapy have been studied on many clinical trials and their response assessment may be complicated by the development of a flare reaction, also called pseudo-progression. There are three patterns being observed: an increase in the size of lesions, the development of new lesions despite regression of the initial lesions, or increased F-fluorodeoxyglucose (FDG)-avidity despite no change in lesion size. Unless this phenomenon is recognized, patients may be taken off a drug that is actually effective. Thus, a new response Indeterminate Response (IR) is introduced, which is assigned to patients until a subsequent scan distinguishes response from progressive disease.

INTERMEDIATE RESPONSE (IR)

Under immunodulatory therapy, a delayed response and an immune-mediated flare can occur in early treatment period. It is difficult to distinguish them from true disease progression. However, by introducing this new term IR, we can allow patients to continue treatment. A mandatory subsequent evaluation within 12 weeks is required to confirm or refute true progressive disease. IR is defined as one or more of the following:

- IR1: an increase in overall tumor burden of ≥50% of up to six measurable lesions in the first 12 weeks of therapy, without clinical deterioration
- IR2: appearance of new lesions or growth of one or more existing lesions ≥50% at any time during treatment occurring in the context of lack of overall progression of overall tumor burden
- IR3: an increase in FDG uptake of one or more lesions without a concomitant increase in lesion size or number

At one time point, a patient could fulfill criteria for both IR1 or IR2 and IR3. If patients are categorized as IR, a mandatory repeat imaging is required after 12 weeks (or earlier if clinically indicated) and response should be re-evaluated with the following considerations:

- The comparison should be between the first IR and the current overall tumor burden, with an increase of ≥10% constituting progressive disease. An increase of ≥5 mm of at least one lesion for lesions ≤2 cm and 10 mm for lesions >2 cm should also be considered.
- The new or growing lesions should be added to the target lesions, up to a total of more than six lesions.
- Since inflammatory response may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have progressive disease unless there is evidence of progressive disease by an increase in lesion size or the development of a new lesion.

If a patient is assessed as having IR and then “true” PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR. We recognize that these lesions may remain stable during the time of observation, but, even if this is the case, the initial designation of IR should be changed to PD.

IR CRF IMPLEMENTATION

To add IR information in the response CRF, two additional fields can be used to trigger IR specific information collection. 1) Did the patient meet criteria for an indeterminate response (IR) per LYRIC? 2) if Yes, please select the response subcategory. This is shown in Figure 1.

Then two additional CRFs can be used to collect IR2 lesions and SPD assessments as shown in Figure 2 and Figure 3.

Investigator assessment of **OVERALL RESPONSE per Lugano 2014** at this timepoint RSALL (char, 40)	*List displayed dependent on response to "How was the response assessed?"* *If 'CT only…' or 'Clinical only':* **[CT-1]** Complete Response **[CT-2]** Partial Response **[CT-3]** Stable Disease **[CT-4]** Progressive Disease **[CT-5]** Not Evaluable *If 'PET or PET/CT…':* **[PET-1]** Complete Metabolic Response **[PET-2]** Partial Metabolic Response **[PET-3]** No Metabolic Response **[PET-4]** Progressive Metabolic Disease **[PET-5]** Not Evaluable
Did the patient meet criteria for an indeterminate response (IR) per LYRIC? LYRICIR (num, 8)	Pulldown: **<ynnevbl>** **[1]** Yes **[0]** No **[95]** Not Evaluable
If ***Yes***, please select the response subcategory: LYRICSUB (num, 8)	Pulldown: **<ir_TR3>** **[1]** IR1 **[2]** IR2 **[3]** IR3

Figure 1:IR information collection. If a patient meets criteria for an IR2 per LYRIC, selecting 'Yes' in the 2nd question and 'IR2' in the 3rd question trigger a set of IR2 specific CRFs. IR1 and IR3 response do not need additional CRFs.

LYRIC IR2 Lesions [LYRICIR2]

<This form will be created manually by DM >

Complete one unique form for every lesion that meets the criteria for an IR2 response.

Specify which form the lesion was reported on prior to becoming IR2: IR2FORM (num, 8)	Pulldown: <ir2form> [1] Imaging (Lugano 2014) – New Lesions [2] Imaging (Lugano 2014) – Non-Target Lesions (Baseline) [3] Imaging (Lugano 2014) – Target Lesions (Baseline)
Specify which log line the IR2 Lesion is reported on, from the form reported above: IR2LINE (num, 8)	
• For **New Lesions**, report lesion data from all visits prior to the visit where the new lesion was first reported. • For **Non-Target** lesions (Baseline), report lesion data from Baseline through PD (PD per LYRIC after an IR2) or End of Study, whichever comes first • For **Target** lesions (Baseline), do not report any data below	

#	Visit VISIT (num, 8) *Drop down dynamic list with all visits previously entered*	Lesion Status by Visit *(Report for New Lesions Only)* TUSTATVS (num, 8) Pulldown: <stat1> [1] Target [2] Non-Target [3] Present, not Target or Non-Target [4] Absent	Exam Type *(Report for New Lesions Only)* TRMETHOD (num, 8) Pulldown: <radmeth2_TR2> [1] CT Neck [2] CT Chest [3] CT Abdomen [4] CT Pelvis [5] PET [6] Other	Measurement #1 TRORRES1 (dec,5.2)	Measurement #2 TRORRES 2 (dec,5.2)	Not Assessed by CT TRSTAT (num, 8)	SUV_{max} Activity *(Report for New Lesions Only)* PETSUV (dec, 7.3)	SUV_{max} Activity Not Assessed *(Report for New Lesions Only)* SUVSTAT (num, 8)
1						▫[1]		▫[1]
2						▫[1]		▫[1]

Log lines to be added by the site

Figure 2: IR2 lesions CRF. IR2 includes new lesions or growth of one or more existing lesions. The top two questions identify the history of this particular IR lesion: Was it a New lesion, Non-target lesion or Target lesion. The bottom part of the figure documents the measurements for new lesions or the new target lesion, whose prior time point was a non-target lesion. The log lines document all the prior visit information for this lesion.

LYRIC IR2 SPD ASSESSMENT [LYRICSPD]

<This form will be created manually by DM >

Specify the visit where this instance of IR2 is reported in the Response Assessment form IR2VISIT (num, 8)	*Drop down dynamic list with all visits previously entered*

For all visits, calculate the SPD that includes Baseline Target lesions and lesions that later became Target per IR2.

#	Visit VISIT (num, 8) *Drop down dynamic list with all visits entered*	SPD per LYRIC (cm^2) LYRICSPD (dec, 6.2)	Nadir Visit Pre-IR2 NADIR (num, 8) *Choose the one visit that was used as nadir SPD prior to this instance of IR2*
1			▫[1]
2			▫[1]
Log lines to be added by the site			

Figure 3: IR2 SPD Assessment CRF. If an IR2 is identified, all the SPD values prior to this visit are calculated and entered into the log lines in this CRF. The "Nadir Visit Pre-IR2" is the visit with the lowest SPD per LYRIC value.

The Baseline set of Target and Non-Target lesions are identified at Baseline, and the Baseline status cannot be changed once identified except to add additional measurements to Baseline Non-Target Lesions that become Target Lesions per IR2 at a subsequent visit. New lesions identified post-Baseline should be added to the Baseline CRF with the Baseline status of the lesion. Target and Non-Target Lesions Identified at Baseline will be assessed for the duration of the response assessments for the study.

For post baseline visit, in addition to the SPD for the set of Target Lesions identified at Baseline, the SPD for the set of IR2 Target lesions must be assessed and recorded. In addition, the Nadir for that set of IR2 Target Lesions must also be determined and recorded.

STDM DATASET IMPLEMENTATION

Although LYRIC criteria and IR information is quite recent in the oncology industry it will be interesting to learn how IR information can be mapped to TR/TU/RS domains with all the other tumor measurement information. If a PD response is confirmed after an IR response, the IR should be imputed to PD. This imputation at the programming level should be documented in SAP at the beginning of the trial. It is also possible to create a separate custom IR domain to store the IR data.

CONCLUSION AND DISCUSSION

LYRIC criteria is proposed by Dr. Cheson etc. in 2016 and it is still in a provisional version. We are excited about the improvement and have started to design CRFs. But we have not yet had a chance to implement it in real trials. The CRF designs are only examples to show the concept, how trial data is collected is system dependent and can be very different from trial to trial. Some studies took the intermediate response into consideration without implementing the whole LYRIC assessment, for example, variables can be added to CRF to prevent patient being taken off the study at flare or false PD at Cycle 2.

REFERENCES

Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano classification response criteria for lymphoma in the era of Immunomodulatory therapy: The LYmphoma response to Immunomodulatory therapy criteria (LYRIC). Blood. 2016 August 29.

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