WHITE PAPER

THE 2014 LUGANO CLASSIFICATION[1]

Using the New "Cheson" Criteria in Lymphoma Clinical Trials

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1 Cheson B, Fisher R, Barrington S, Cavalli F, Schwartz L, et al: Recommendations for Initial Evaluation, Staging, and Response Assessent of Hodgkin and non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 32:3059-3067, 2014.

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LYMPHOMA ASSESSMENT GUIDELINES

The Lugano Classification, published in August 2014, is the 2nd revision to the first universally accepted guidelines on assessing Lymphoma therapeutic response/progression in clinical trials.

The 2014 Lugano Classification modernizes recommendations for the assessment of lymphoma by removing ambiguity in the application of the criteria in forthcoming lymphoma clinical trials. This will facilitate the comparison of patients and results by providing a standardized guidance on how data should be analyzed for response to therapy.

Implementation of the Lugano Classification for your specific therapeutic, patient population and indication should be prospectively defined in protocol. This includes interpretation of CT, imaging schedules for CT and PET scans, PET scoring implications, rules for handling missing lesions/anatomy, and rules around challenging scenarios for the given therapeutic under investigation.

Additionally, given that the scans have such an important role in response outcome, robust imaging guidelines are essential to a successful clinical trial in lymphoma.

Lastly, there is no better way to communicate how criteria are applied in a protocol /trial than to use example cases that are made available to both the Principal Investigators and the central readers.

PAREXEL in conjunction with Dr. Bruce Cheson is pleased to present here our recommendations on using the 2014 Lugano Classification in Lymphoma Clinical Trials.

The Lugano Classification is not drastically different from the previous guideline (IWG-NHL 2007) but there are important clarifications and modifications provided including the following key aspects:

FDG-PET Interpretation in Lymphomas

- Standardized staging for FDG-avid lymphomas
- Response assessment in FDG-avid histologies is made according to the 5-Point Scale (5PS)[2]
- Bone marrow biopsy no longer indicated for the routine staging of HL and most DLBC. FDG-PET imaging should be used instead for the assessment.

CT Interpretation in Lymphomas

- Progressive disease evaluation is determined by the Products of the Perpendicular Diameters (PPD) progression of single site.
- Progressive disease evaluation no longer includes Sum of the Products (SPD).
- Routine surveillance scans are discouraged to minimize unnecessary scans to patients.
- Splenic involvement is quantified with > 13 cm considered enlarged on CT by cranial to caudal length

2 Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32:3048-3058, 2014.

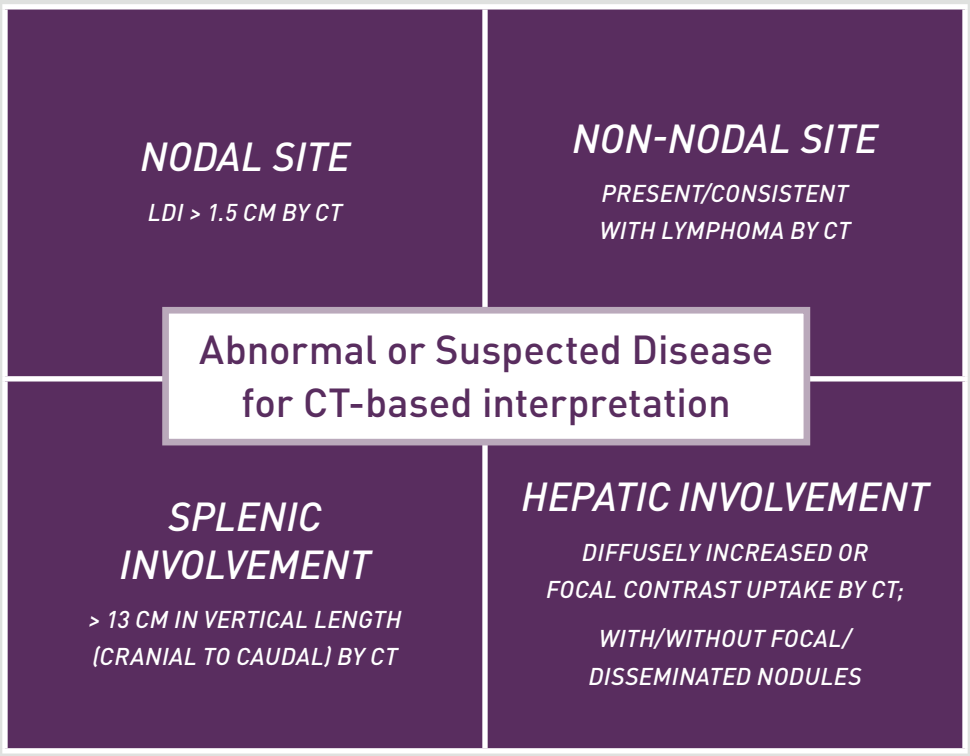


Figure 1. Abnormal or suspected disease according to the Lugano Classification

The Lugano Classification Workflow

TARGET NODAL LDI > 1.5 CM

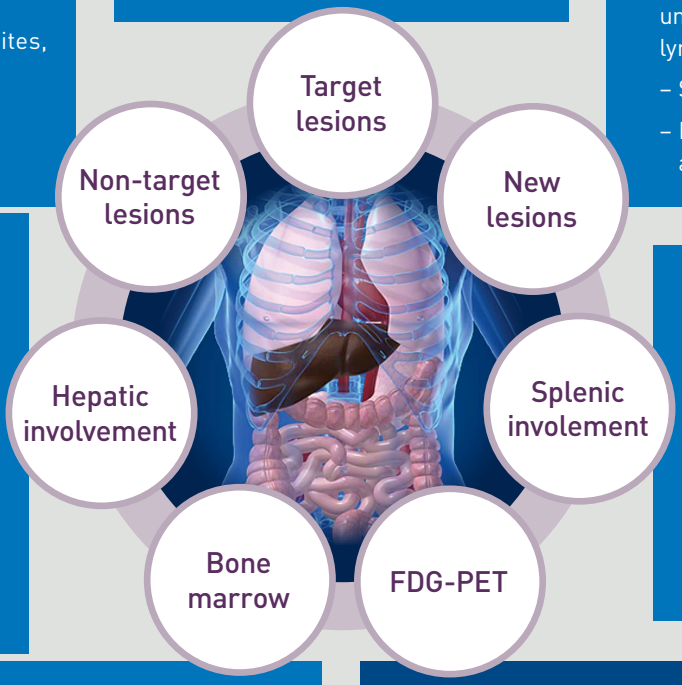
TARGET EXTRANODAL LDI > 1.0 CM

- Up to 6 of the largest nodes, nodal masses or other lymphomatous lesions including extranodal disease measurable in two diameters (LDi and SDi)
- Represent overall disease burden / Include mediastinal and retroperitoneal disease, if involved

- All other disease not selected as target lesions consistent with lymphoma
- Abnormal nodes, extranodal sites, assessable sites*

(*Cutaneous, gastrointestinal, bone lesions, pleural or pericardial effusions, ascites)

- Regrowth of resolved lesions
- New node > 1.5 cm in any axis
- New extranodal site > 1.0 cm in any axis
- New extranodal sites that must be unequivocal and attributable to lymphoma include:
  - Sites < 1.0 cm in any axis, or
  - Non-measurable truly assessable site of disease



- Assess involvement qualitatively by CT
- Pre-existing persistent liver involvement with lymphoma prevents CR unless no longer avid
- New uptake in liver → PD
- For clinical trials, follow hepatic nodules as target, non-target and new extranodal lesions

- Assess splenic size for involvement by vertical (cranial to caudal) length
- > 13 cm is considered involved
- For clinical trials, follow splenic nodules as target, non-target and new extranodal lesions

Involved bone marrow at baseline (If required for subtype):

- Must be normal for CR (when all other sites are CR by CT)

- No evidence of Focal FDG-avid disease in marrow for CMR

- FDG-avid lymphoma subtypes
- Assess by 5PS
- Qualitative assessments should be based on SUV maps*
- Integrate with the CT based response

* FDG-PET images need to be converted from images representing signal intensity to images of standardized uptake values.

This table represents the changes in the evaluation of the spleen compared to the IWG-NHL 2007 criteria:

PROGRESSION OF PRE-EXISTING SPLENOMEGALY	*NEW SPLENOMEGALY*	*RECURRENT SPLENOMEGALY*
Splenic length must increase by > 50% in enlarged portion from baseline.	If no prior splenomegaly, splenic length must increase > 2 cm from baseline and be currently enlarged (> 13 cm).	Spleen enlarged at baseline, normalizes, and subsequently becomes enlarged again.
Example:	**Example:**	**Example:**
• At baseline the spleen was 15 cm (Enlarged portion is 2 cm). • Thus a 1 cm increase to a spleen that is > 16 cm at follow-up is progression.	• At baseline the spleen was 10 cm. • A 14 cm spleen at follow-up is consistent with progression. • A 12 cm spleen at follow-up is NOT consistent with progression.	• At baseline the spleen was 14 cm. • At follow-up it normalizes to a size of 12 cm then subsequently grows to 14 cm. • Progression is met when the spleen reaches 14 cm.

INCORPORATING FDG-PET

PET-CT which has been part of the lymphoma response guidelines since its incorporation in the IWG-NHL 2007, is already widely used as part of clinical trials and to evaluate patients outside of clinical trials. In a typical clinical trial with an FDG-avid lymphoma, CT scans occur more frequently than PET scans. The integration of PET into the more frequently acquired CT evaluation does present a challenge to the way patient data is assessed in a clinical trial. As clinical trials evaluate patients by 'visit', response assessments are tracked over time based on these individual captures of data. Thus the approach to integrating a PET scan result into a patient's data set must be clearly defined. Specific care should be taken with respect to the anticipated schedule and frequency of CT and PET imaging and the required data so that a response status can be derived incrementally as the patient's scans are acquired and other clinical data, if required by protocol, is captured.

PET scans should be performed at pre-specified times for example before treatment and at well defined times during and/or after the end of treatment. They may also be acquired to confirm a result on CT, for instance a CR /PR on CT scan. Dependent on the outcome, further scans may be acquired.

Thus it may be appropriate to capture the three components of the assessment at a given response assessment visit:

- CT based timepoint response assessment
- PET score and PET-CT based timepoint response assessment
- An integration of PET-CT based assessment and CT based assessment

GUIDING PRINCIPLE 1	GUIDING PRINCIPLE 2
FOR TIMEPOINTS WHEN FDG-PET IS AVAILABLE, THE FDG-PET ASSESSMENT TRUMPS THE CT RESPONSE	***FOR TIMEPOINTS WHEN ONLY CT IS AVAILABLE, FOLLOWING A PRIOR FDG-PET ASSESSMENT, CT ASSESSMENTS MAY BE AFFECTED BY THE PRIOR PET/CT ASSESSMENT***

Example:	PET assessment is consistent with CR and CT scan assessment is consistent with PR. A scan at subsequent timepoint CT still demonstrates PR. Thus the overall assessment, even in the absence of PET, is CR, until another PET assessment demonstrates otherwise or the CT scan worsens.

5 (5PS) – POINT SCALE

PET images, prior to the recent update, were most commonly assessed either truly qualitatively or by SUV analysis with insufficient agreement across the industry. The 5PS is a semi-quantiative analysis that is a pragmatic yet robust predictor of patient outcome.

The following table is from the Lugano Classification and outlines how PET can change CT radiology response.

Score 1	*No uptake above background*
Score 2	*Uptake ≤ mediastinum*
Score 3	*Uptake > mediastinum, but ≤ liver*
Score 4	*Uptake moderately > liver**
Score 5	*Uptake markedly higher than liver and/or new lesions**
X	*(New) areas of uptake unlikely to be related to lymphoma*[3]

*The Barrington paper suggests the following: "The terms moderately and markedly were not defined initially, because there were insufficient data to define scores quantitatively. Meanwhile, it is suggested according to published data that score 4 be applied to uptake greater than the maximum SUV in a large region of normal liver and score 5 to uptake 2X to 3X greater than the maximum SUV in the liver."

3 Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32:3048-3058, 2014.

The tables below present a condensed view of how assessments are derived for PET-CT based response versus CT based response. Please note, for FDG-avid lymphomas, PET-CT based responses should be determined as the key descriptor of patient status.

CMR/CR	*PET-CT BASED RESPONSE*	*CT BASED RESPONSE*
	Complete Metabolic Response (CMR)	**Complete Radiologic Response (CR) (ALL of the following)**
Target Nodal Extranodal	**Score of 1, 2, or 3*** with or without a residual mass on 5PS Residual masses allowed - if not FDG-avid	**Nodal Disease:** < 1.5 cm in LDi **Extranodal Disease:** Absent
Non-target		
Spleen		Regress to normal
New lesions		None
Bone marrow	No evidence of FDG-avid focal disease in marrow	Normal by morphology; if indeterminate, IHC negative

PMR/PR	*PET-CT BASED RESPONSE*	*CT BASED RESPONSE*
	Partial Metabolic Response (PMR)	**Partial Radiologic Response (PR) (ALL of the following)**
Target Nodal Extranodal	**Score of 3*, 4 or 5** with reduced uptake compared to baseline with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. It is expected that there will be residual mass(es) present.	>= 50% decrease from baseline in SPD of all target lesions
Non-target		No increase
Spleen		> 50% decrease from baseline in enlarged portion of spleen (value > 13 cm)
New lesions		None
Bone marrow	• Residual uptake higher than uptake in normal marrow but reduced compared with baseline • Persistent focal changes in the marrow with nodal response, • Further evaluation with MRI or biopsy, or an interval scan may be advisable	Not applicable

* The protocol will need to define the significance of a score 3.
Depends on the disease under study (risk: benefit analysis), patient characteristics and goal of therapy
Score 3: PET negative- Low risk disease and no further treatment necessary (e.g.Follicular Lymphoma)
Score 3: PET positive- High risk disease that is curable and aggressive (e.g. HL, DLBC)

NMR/SD	*PET-CT-BASED RESPONSE*	*CT-BASED RESPONSE*
	No Metabolic Response (NMR)	**Stable Disease (SD)**
Target Nodal Extranodal	**Score of 3*, 4 or 5** with no significant change in FDG uptake from baseline	• < 50% decrease from baseline in SPD of all target lesions • No criteria for PD are met
Non-target		No progression
Spleen		No progression
New lesions		None
Bone marrow	No change from baseline	Not applicable

PMD/PD	*PET-CT-BASED RESPONSE*	*CT-BASED RESPONSE*
	Progressive Metabolic Response (PMR)	**Progressive Disease (PD) (One of the following)**
Target Nodal Extranodal	**Score of 3*, 4 or 5** with increased uptake compared to the visually determined nadir with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. and/or • New FDG-avid foci consistent with lymphoma • Consider biopsy or interval scan if etiology of new lesions uncertain	**PPD Progression:** 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
Non-target		Unequivocal Progression
Spleen		• Progression of existing splenomegaly • New or Recurrent splenomegaly
New lesions		• Regrowth of previously resolved lesions • New node > 1.5 cm in any axis • New extranodal site > 1.0 cm in any axis • New extranodal site < 1.0 cm in any axis or unequivocal/attributable to lymphoma. • Any size assessable disease unequivocal/ attributable to lymphoma
Bone marrow	New/recurrent FDG-avid foci	New/recurrent involvement

Let's look at some examples:

In scenario A, the PR at Week 12 is based on CT without accompanying PET scan. At Week 24, the subsequent PET image supports CMR based on the change in score from 3 (assumed positive at baseline in this example) to a score of 1.

SCENARIO A	*CT ASSESSMENT*	*PET-CT ASSESSMENT*	*COMBINED OVERALL TIMEPOINT ASSESSMENT*
Baseline CT and PET	Select disease on CT	Score = 3	Not applicable
CT TP2 – Week 12	PR	No PET	PR
CT TP3 and PET – Week 24	CR	Score = 1	CMR/CR

In scenario B, the PET is considered positive at baseline with a score of 3, 4 or 5. While PR is met on CT, the PET score of 2 at Week 12 is consistent with a CMR. The subsequent PR on CT at Week 24 , does not preclude an overall CMR even in the absence of PET, provided there is no worsening on CT between Week 12 and Week 24.

SCENARIO B	*CT ASSESSMENT*	*PET-CT ASSESSMENT*	*COMBINED OVERALL TIMEPOINT ASSESSMENT*
Baseline CT and PET	Select disease on CT	Score = 3, 4 or 5	Not applicable
CT TP2 and PET – Week 12	PR (Residual extranodal disease present)	Score = 2	CMR/CR
CT TP3 – Week 24	PR (Residual extranodal disease present)	No PET	CMR/CR

In scenario C, the PET is positive at baseline with a score of 4. In this scenario, it is assumed that the protocol does not require scheduled PET until Week 24. At Week 24, a CT demonstrates PR but a PET score of 3 (changing from score of 4 at baseline) this may be consistent with PMR or CMR; If a score of 3 is considered positive by PET per protocol this remains PMR even if the subsequent CT suggest a CR. A subsequent PET is recommended to clarify the subject's response status. If a score of 3 is considered negative by PET per protocol, a subsequent PET is not necessary.

SCENARIO C	*CT ASSESSMENT*	*PET-CT ASSESSMENT*	*OVERALL TIMEPOINT ASSESSMENT*
Baseline CT and PET	Select Disease on CT	Score = 4	Not applicable
CT TP2 – Week 12	SD	No PET	SD
CT TP3 and PET – Week 24	PR	Score = 3	PMR/PR or CMR/CR
CT TP4 – Week 36	CR	No PET	PMR/PR or CMR/CR

In scenario D, the PET is positive at baseline with a score of 4. At Week 12, a CT demonstrates PR but a PET score of 3 (changing from score of 4 at baseline) may be consistent with PMR or CMR as in scenario C. At Week 24, the CT demonstrates progression but no PET is acquired to verify the progression on CT. If the PD on CT scan is equivocal (single new lesion for example while other disease is responding) – verification with additional imaging is recommended; If the PD on CT is unequivocal (multiple new lesions, progression of target lesions) – PET verification is not required to report PD for the subject at Week 24.

SCENARIO D	*CT ASSESSMENT*	*PET-CT ASSESSMENT*	*OVERALL TIMEPOINT ASSESSMENT*
Baseline CT and PET	Select Disease on CT	Score = 4	Not applicable
CT TP2 and PET – Week 12	PR	Score = 3	PMR/PR or CMR/CR
CT TP3 – Week 24	PD	No PET	PD

IMAGING RECOMMENDATIONS

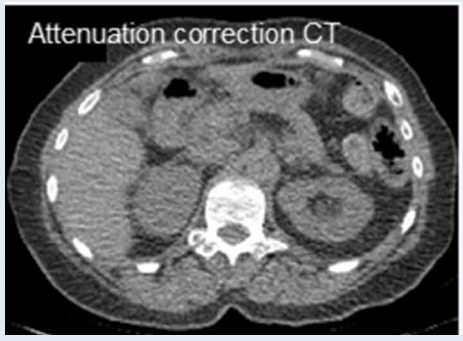
While there will always be challenges in the assessment of disease on imaging and the acquisition of scans, there are ways to minimize image quality concerns in the evaluation of lymphoma. With regard to CT/MRI, consistent imaging of the neck and lower pelvis is challenging with the neck often not performed by site even when required. Thus it is critical to enforce strict Imaging Guidelines, it is equally important to prospectively define how missing regions will be handled during an evaluation. These should be clearly defined in the study protocol.

With PET-CT, clinical sites very often need clear communication from the sponsor on imaging requirements and training on the imaging guidelines for the trial. Often sites need some further assistance on what needs to be collected, submitted or archived specifically around attenuation corrected PET imaging versus non-attenuation corrected PET imaging, clinical data to provide with the PET, reminders on diagnostic CT requirements, fused imaging, and anatomical coverage. Most importantly however, the imaging schedule and how scans will be evaluated for response outcomes must be prospectively defined in the protocol and clear to those performing and interpreting scans outcomes.

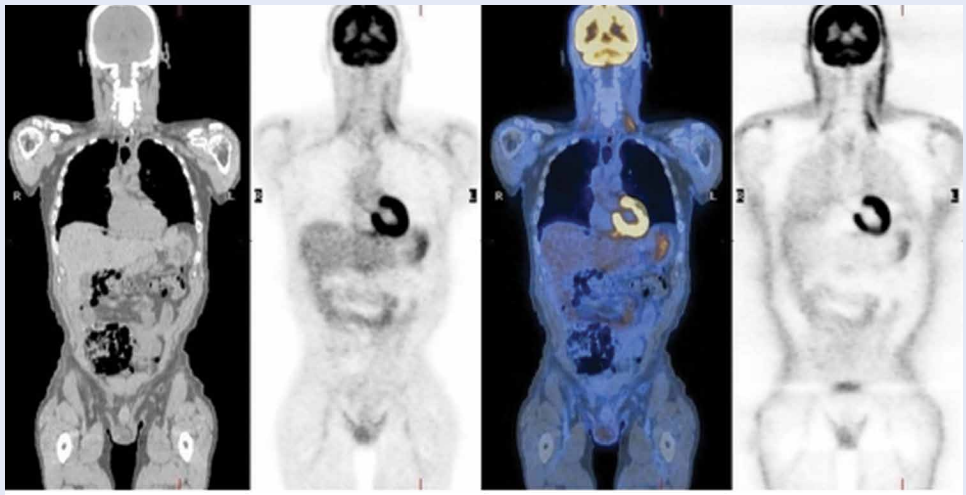
CT-MRI SCANNING RECOMMENDATIONS	Anatomical Scan Coverage: **neck, chest, abdomen and pelvis** From skull base through lesser trochanters ensuring complete coverage of the pelvis and inguinal areas
FDG-PET SCANNING RECOMMENDATIONS	Anatomical Scan Coverage: **whole body images, from base of skull to mid-thigh (eyes to thighs)** • Examinations should be consistent across all timepoints including amount of tracer, location of injection, arm location, and scan delay. • The following information should also be collected per sites, standard procedures: height, weight, gender, administered dose, time between dose administration and imaging, and glucose level. - The PET images should be converted to SUV maps to support comparison across timepoints and to standardize viewing conditions.

PET-CT SCANNING RECOMMENDATIONS

- Hybrid PET-CT scanners may be used to acquire the required CT images only if CT produced by the scanner is of diagnostic quality, adheres to specified scan parameters, and includes intravenous contrast (unless medically contraindicated).
- Non-diagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only CT scan for the timepoint. Diagnostic CT images with contrast (unless medically contraindicated) with a standalone CT scanner must be acquired if PET-CT is unable to acquire diagnostic CT images.



- If the diagnostic CT and PET are acquired on the same day, it is strongly recommended that the PET is performed prior to the CT with IV contrast as to not compromise PET results.



CT Transmission Scan | **Attenuation Corrected PET Emission Scan** | **PET-CT Fusion Scan** | **Non-Attenuation Corrected (NAC) Emission Scan**

FREQUENTLY ASKED QUESTIONS

You will find below a Q&A of the most frequently asked questions and concerns about implementation of the Lugano Classification.

FDG-PET ASSESSMENT IN THE LUGANO CLASSIFICATION	
Question: In the context of clinical trial PET-CT imaging for the Lugano criteria, is a CT with contrast needed?	Yes, having diagnostic quality CT (including the contrast) will be necessary for an adequate assessment of the CT imaging and will be important in the interpretation of the PET. This is also the institutional standard at many sites provided contrast is not contraindicated for the particular patient.
Question: How can FDG-PET criteria be standardized across centers and monitored in a clinical trial?	The consensus coming out of the Deauville and Lugano meetings has been that while we still see variability in the acquisition (specifically wait times and serum glucose levels) across subjects and from timepoint to timepoint per subject, the usage of FDG-PET in FDG-avid patient populations is sufficiently standard and has been meaningful in predicting patient outcome for certain lymphoma subtypes. The qualitative assessments are more subjective but appear to be more robust to physiological variations and operational constraints at the sites than quantitative approaches. Relating the avidity to a within subject reference tissues (liver and mediastinum) is critical to this robustness. For clinical trials, PAREXEL recommends the use of standardized Imaging Acquisition Guidelines and clear details on imaging in the protocol. The following should be collected at a minimum to support interpretation and the conversion of signal intensity images to SUVmaps: • height • weight • injected amount • wait time (scan delay) and • serum glucose levels In addition PAREXEL recommends the use of specifically trained (smaller groups) of readers.

Question: Is the 5PS a qualitative or quantitative assessment?	The scoring is in essence semi-quantitative. For the implementation of the Lugano PET-CT based responses the appreciation of overall change of avidity from baseline to follow-up drives the metabolic response determination. PAREXEL recommends that images are normalized to SUVmaps for standardization purposes and to facilitate a more direct comparison across timepoints. This is also in alignment with the Lugano Classification companion paper by Barrington et al (2014).
Question: For patients missing a baseline PET scan, would a PET based response still be applicable, based on an interim PET or no prior PET at all?	For the appropriate application of the Lugano classification FDG-PET imaging is required for FDG-avid lymphomas at baseline and follow-up. In theory, a FDG-PET scan on follow-up without a prior baseline scan can still inform on persistent disease or potential new findings, however adequate determination of change from baseline is not possible.
Question: Which part of the mediastinum and liver are used for comparison?	Most nuclear medicine physicians like to apply a "gestalt" approach to the overall mediastinal blood pool (ignoring the variable uptake within the heart) and healthy liver activity, especially in the context of qualitative assessments. For the mediastinum this will typically be the more uniform portions of the mediastinal blood pool consisting of the aorta, vena cava, and pulmonary vessels; for the comparison to liver one will typically refer to presumed healthy tissue of the most uniform section of the liver, well away from the edge of the organ.
Question: Is there a maximum number of FDG-avid lesions to follow with the 5PS?	No, the 5PS takes the overall FDG-avid disease into account; however the score will be driven by the hottest area of the avid lesion and/or new avid lesions.
Question: If you do not have a change in the FDG-PET 5PS (e.g. 4 is still 4) how do you gauge "PR" intensity?	In many instances a response will be accompanied by a change in score, however one can imagine a case where there is extensive disease that demonstrates an uptake greater than than the maximum of SUV of normal liver at baseline. At follow-up a significant amount of disease displays a lower uptake or no uptake above background, however there remains, for example, one region that still has this uptake greater than than liver and there are no new foci noted. This could qualify for partial response. PAREXEL recommends the conversion of the FDG-PET signal intensity images to SUVmaps for standardization and to facilitate this interpretation of potential change on follow-up.
Question: How can a score of 5 be consistent with No Metablolic Response (NMR)?	To determine whether a patient's status is improving, deteriorating or in essence not changing, the score of the current timepoint must be compared to the prior timepoint. As an example, a patient where one or more of the observed FDG-avid lesions demonstrates an uptake higher than the liver at baseline would be scored a 5. If there is no significant change in FDG-uptake for this patient on the follow-up, this patient would be assessed as NMR.

Question: Is there additional information to assist in the determination of whether a patient is a score of 4 or a score of 5?	Barrington et al (2014) state the following: "The terms moderately and markedly were not defined initially, because there were insufficient data to define scores quantitatively. Meanwhile, it is suggested according to published data that score 4 be applied to uptake greater than the maximum SUV in a large region of normal liver and score 5 to uptake 2X to 3X greater than the maximum SUV in the liver. It is acknowledged that mean liver SUV may be less influenced by image noise than maximum SUV, but reproducibility is more dependent on standardizing the location and size of the region of interest. Work is ongoing to assess optimal tumor and liver metrics."
IMAGING SCHEDULE	
Question: After CR has been established at the end of therapy, are PET scans required during long term follow-up to maintain CR status?	Surveillance FDG-PET scans are not recommended. Specifically, the Cheson et al 2014 JCO Lugano Classification[1] states: "Published studies fail to support routine surveillance scans, and they are discouraged. The false-positive rate with PET scans is greater than 20%, leading to unnecessary investigations, radiation exposure, biopsies, expense, and patient anxiety. Follow-up scans should be prompted by clinical indications."
Question: How often should a CT be performed when the primary endpoint is objective response rate?	If partial responses are an important part of your endpoint, the CT based, quantified assessments should also be performed. The timing and schedule of the CT imaging will need to be carefully considered to allow for the detection of potential treatment effect while balancing radiation exposure for patients. Key aspects are: • Particular patient population (how likely are they to respond? Risk/benefit of radiation burden) • The anticipated treatment effect (when would the CR be expected) should be data driven usually from earlier phase experience • Anticipated difference between treatment arms PAREXEL considers every 12 weeks after treatment completion reasonable for PFS surveillance but this schedule and the question for how long patients should be followed will need to be adjusted according to the above bullets. We have heard of instances where the FDA suggested earlier or more frequent imaging, while KOLs may suggest a downscaling of the image frequency over time. PAREXEL recommends the discussion of the imaging schedule with the FDA whenever possible. Once a response has been achieved, subsequent scans may not, in theory, be needed until the patient's status clinically suggests otherwise (suspected worsening). However, additional secondary endpoints may drive the need for subsequent scheduled imaging.

Question: How should I plan my FDG-PET schedule?	It depends on the lymphoma subtype and scope of the trial. • For FDG avid lymphoma, FDG-PET is needed at screening and after completion of treatment for re-staging. On treatment FDG-PET can be added for diseases like Hodgkin's Lymphoma • For a study with overall response rate as an endpoint, FDG-PET is needed at screening. Optional during treatment as interim and again required 6-8 weeks after completion of treatment • For a study with PFS as an endpoint, FDG-PET is needed at screening and 6-8 weeks after completion of treatment • For PFS surveillance CT is sufficient and would typically be acquired every 12 weeks following completion of treatment. FDG-PET is not required in this context

TIMING FOR IMPLEMENTING THE LUGANO CLASSIFICATION

Question: For ongoing programs with IWG-NHL 2007 underway in a protocol or program, do you recommend new studies keep with the 2007 criteria or move to using Lugano.	This will depend on the sponsors comfort and the program flexibility in using criteria that have not been road-tested. PAREXEL still see trials using 1999 criteria. With respect to the CT-based interpretation, we find that there is more clarification in Lugano than modification, and these are helpful even if using 2007 criteria for a trial. In general, if other Phase III trials in a program or a comparator trial are using IWG-NHL 2007, it may not be practical to change midstream. However, one could potentially add some clarifications that were made in Lugano, especially around spleen and liver assessments and the grouping and total number of target lesions. Similarly, as the Lugano removes the requirement to have no B symptoms for CR, one might consider adding this modification. This can be helpful as B symptoms are one of the most frequently missing pieces of clinical data and because there is now documented clinical evidence that the presence of B symptoms does not preclude long term response. Progression by CT-based criteria also underwent further clarification in Lugano 2014. The criteria now explicitly defines single lesion progression (by PPD) with minimum lesion size and absolute changes required. Long and short axis single lesion progression was removed. It may be appropriate to include the 5PS by a central review as an exploratory endpoint in trials where the combined CT and FDG-PET-CT based Lugano Classification will not be used. According to our experience the integration of the PET score with subsequent CT and or PET-CT timepoints may lack standardized approach across sites. This has certainly been challenging with the 2007 guidelines. PAREXEL strongly recommends careful training with specific examples on how the PET assessment is to be applied and how the assessment will affect downstream CT assessments in the absence of PET.

HOW TO HANDLE NON-MEASURABLE / NON-TARGET DISEASE	
Question: What is the significance of the non-measurable/non-target lesion assessment?	PAREXEL recommends that the entire disease burden be followed. At baseline, all target lesions should be identified and any remaining disease should be considered non-target disease and organ enlargement. There are specific aspects to consider in the handling of non-target lesions. For example, if non-target disease is present but has not progressed (with or without decrease in the non-measurable disease), PR would still be an appropriate response provided target disease and any splenic involvement meets criteria for PR. Non-target disease alone can drive progression. Non target disease would have to completely resolve for CR.
Question: What is the difference between measurable and assessable disease?	Assessable disease refers to disease such as pleural effusions, ascites, or other sites consistent with lymphoma that are generally not suitable for measurement. Target lesions by definition should be measured, while non-target and assessable disease is followed qualitatively. Non-target disease may include lesions that would qualify as targets but are in addition to the maximum number of target lesions allowed. They may also include disease not suitable for measurements that do not meet the minimum target lesions size requirements. However, if a node is to be considered as a non-target lesion, it should be abnormal at baseline and the size should be taken into account when assessing 'normal/abnormal' at follow-up.
LIVER EVALUATION	
Question: Should liver enlargement be considered either by clinical assessment or by CT scan? How is this evaluated for disease?	Providing a general guidance on liver involvement is challenging as numerous factors contribute to the variability in absolute size. There is no ubiquitously accepted size threshold defining enlargement. It is not uncommon to see lesions in the liver in lymphoma but it is rare that the liver is considered as 'enlarged and related to lymphoma'. The Lugano Classification also does not specifically speak to liver assessment in table 3 of the article. • If the liver is considered 'enlarged' it has to normalize for a CR. • If the liver was normal and becomes unequivocally enlarged, the liver may be considered consistent with progression. • Otherwise, the liver has no definitive impact on the assessment.

SPLEEN EVALUATION	
Question: Is spleen considered nodal or extranodal disease? Should a splenic nodule be considered extranodal?	The spleen is usually considered as lymphatic in terms of character. In terms of assessing splenic involvement the organ is treated separately and spleen size should be followed as a distinct category, separate from nodal disease. Malignant nodules in the spleen should be followed as extranodal lesions. For example, if a subject had nodal involvement, splenic nodule involvement, and an enlarged spleen, the splenic nodules would be followed as extranodal and sub categorized as targets or non-targets. The size of the actual spleen would be followed separately under an organ enlargement. Nodes would be followed in a third category, abnormal nodes. This distinction is important, as splenic nodules may disappear while the spleen may still be enlarged (and considered abnormal).

OUR REGIONAL LEADS ARE ALWAYS AVAILABLE FOR A CONVERSATION.

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