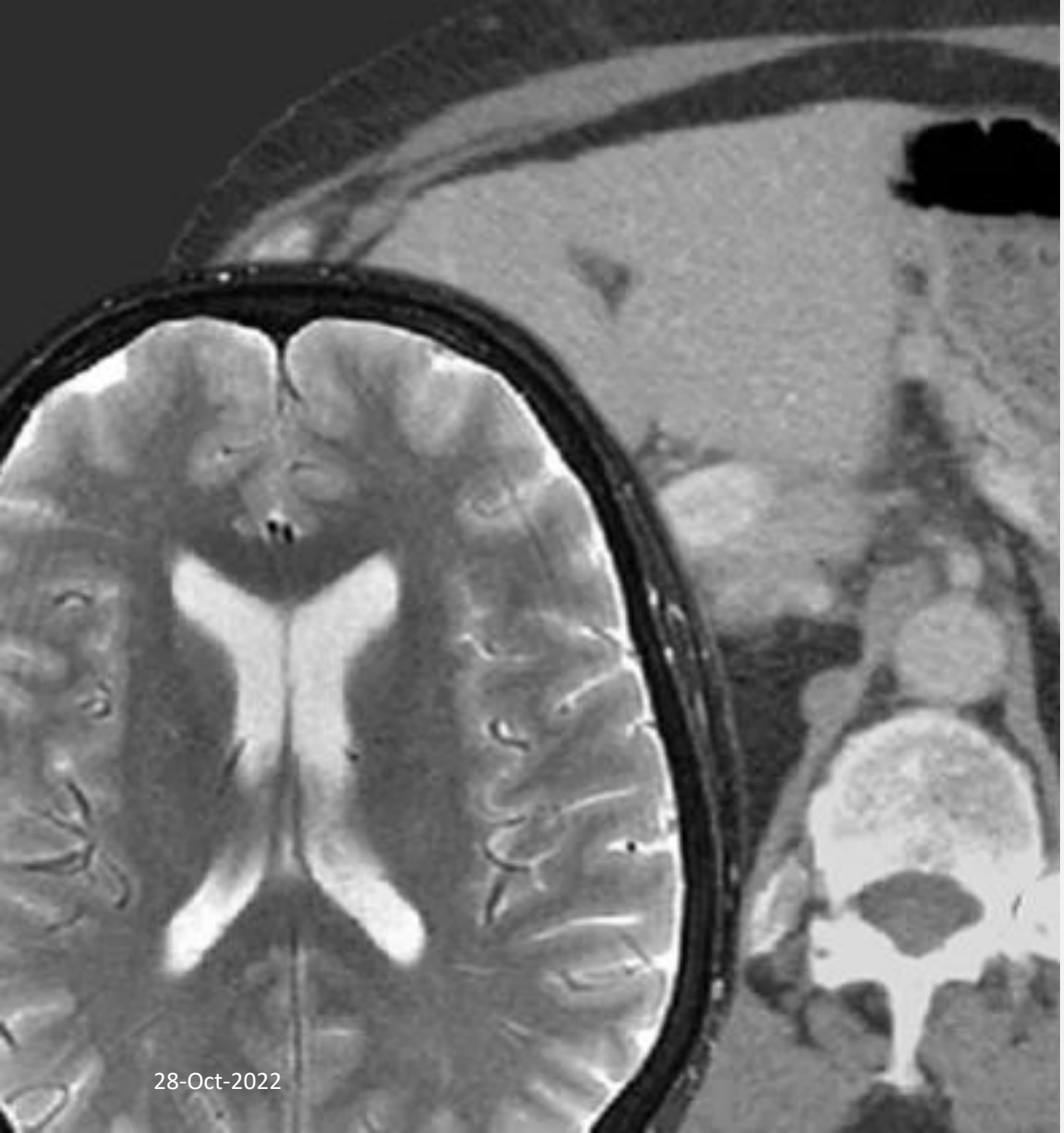

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PINTaD Response Criteria in Lymphoma Working Group

PRoLoG

28-Oct-2022

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PRoLoG Aims and Committee Members

PRoLoG Committee Members: Annette Schmid, Ron Korn, Fabien Ricard, Bruce Cheson, Sally Barrington, Judith Trotman, Gilles Salles, Guenther Brueggenwerth, Larry Schwartz, Greg Goldmacher, Rudresh Jarecha, Jayant Narang, Florence Broussais, Paul Galette, Min Liu, Surabhi Bajpai, Eric Perlman , Julie Gillis, Ira Smalberg, Pierre Terve, Gudrun Zahlmann

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APPLICATION OF THE LUGANO CLASSIFICATION FOR INITIAL EVALUATION, STAGING, AND RESPONSE ASSESSMENT OF HODGKIN AND NON-HODGKIN LYMPHOMA: THE PROLOG CONSENSUS INITIATIVE (PART 1- CLINICAL)

Fabien Ricard, Bruce Cheson, Sally Barrington, Judith Trotman, Annette Schmid, Guenther Brueggenwerth, Gilles Salles, Larry Schwartz, Greg Goldmacher, Rudresh Jarecha, Florence Broussais, Jayant Narang, Paul Galette, Min Liu, Surabhi Bajpai, Eric Perlman, Julie Gillis, Ira Smalberg, Pierre Terve, Gudrun Zahlmann and Ron Korn

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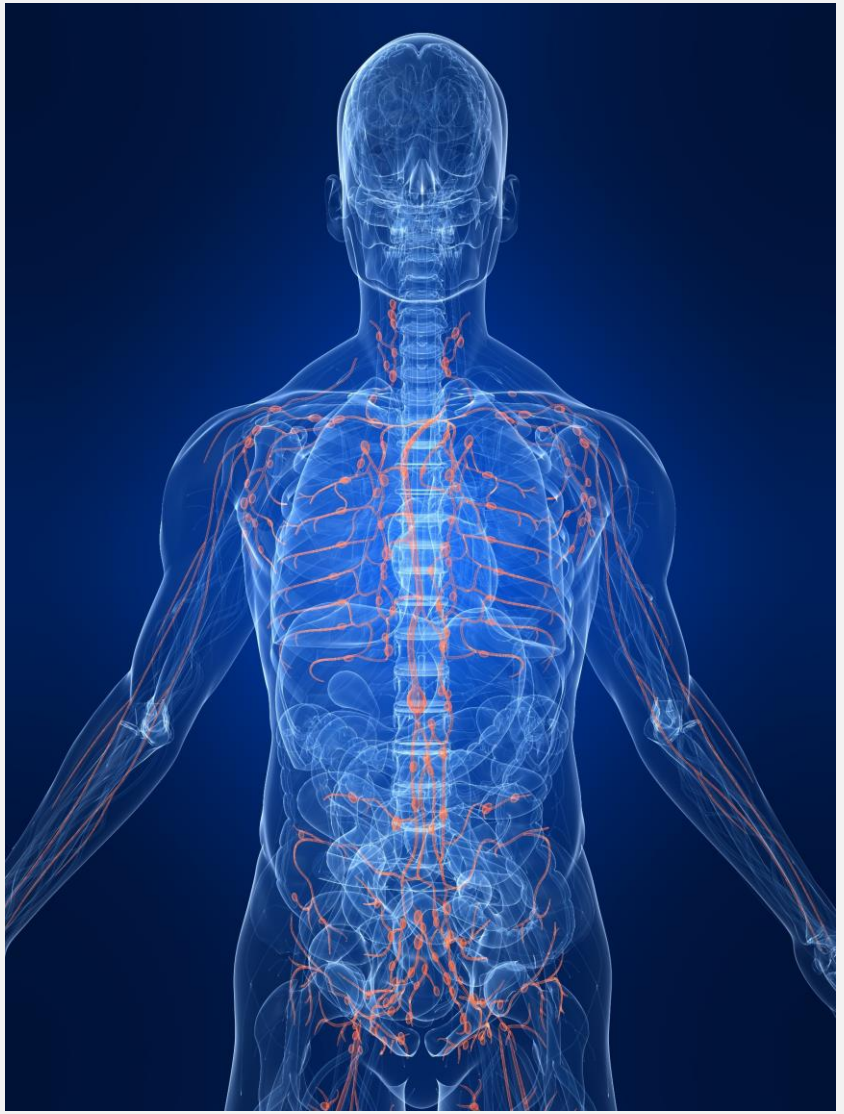
Agenda

- Intro: background, methodology/consensus process, key takeaways and lessons learned: Ron and Annette
- Image acquisition and FDG avidity: Fabien
- Lesion classification, scoring and response assessment: Jayant
- Incorporation of clinical data and evaluation of spleen, liver, nodes: Surabhi
- Panel Discussion



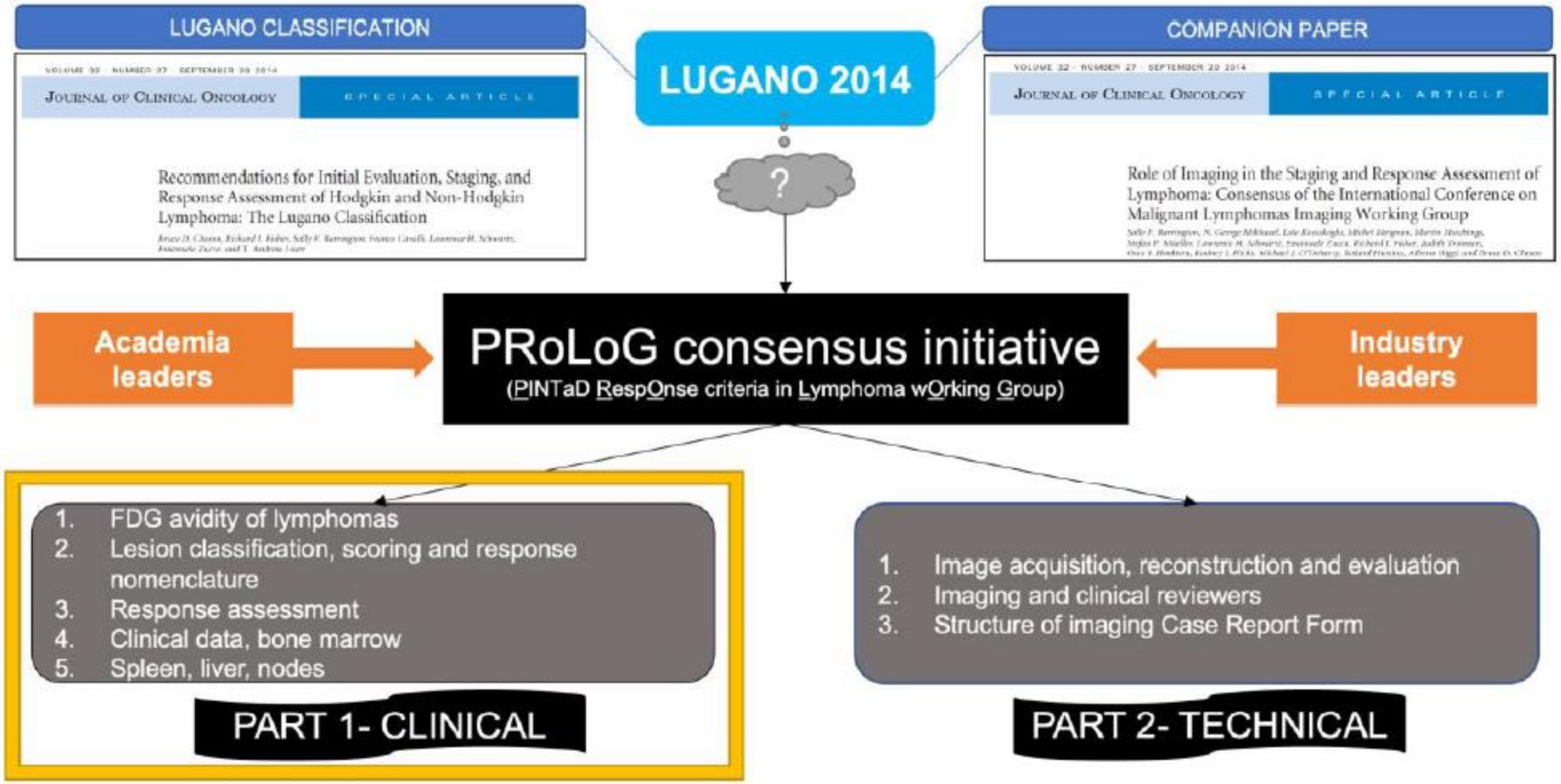
Introduction: PINTaD Response Criteria In Lymphoma Working Group Consensus Initiative

- Insight that the implementation of the lymphoma criteria was insufficiently harmonized and certain aspects could benefit from clarification and advice
- An opportunity for PINTaD to make a difference
  - Given the membership, experience and wide expertise of the network
  - The vision and mission of PINTaD
    - "To provide a forum to evaluate, discuss and recommend methods and strategies for imaging in clinical trials to all stakeholders"*
    - "a voice for the various stakeholders in imaging clinical trials to effectively influence and advance the field and to further the acceptance by the industry and regulatory bodies"*
- Established a PINTaD subgroup **P**INTAD **R**esp**o**nse Criteria in **L**ymphoma W**o**rking **G**roup "PRoLoG"

  2019/2020 to explore and address these challenges

* PINTaD mission statement and purpose

PRoLoG Consensus Initiative



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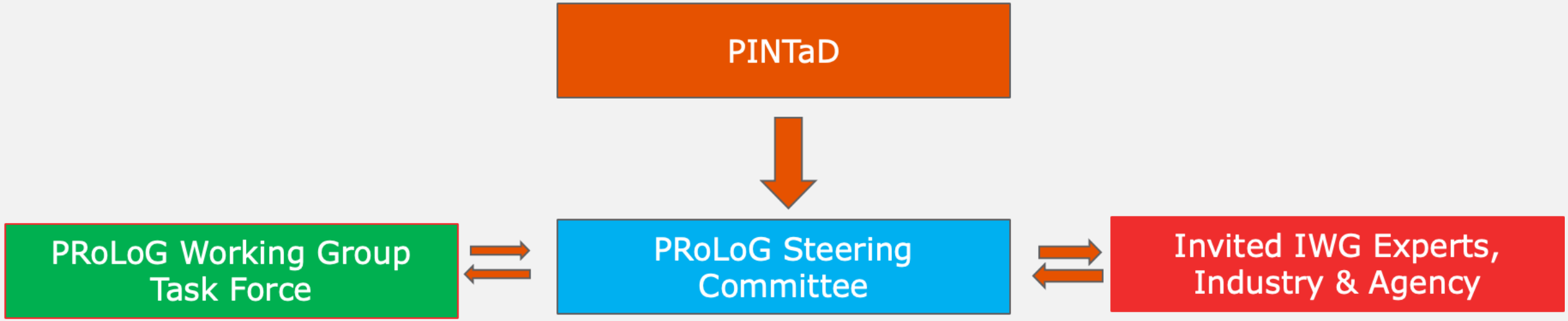
PRoLoG Task Force Methodology

- Goal to share best practices for harmonized and consistent application of the Lugano Classification
- Determined key aspects that needed clarification and standardization
- Created taskforce of stakeholder experts to develop recommendation
- Recommendations were based upon the following:
    - Data and publications as available
    - Best practice recommendation
    - Taskforce Consensus

PRoLoG Working Group Structure



- Evaluates current criteria language, areas of uncertainties, best practices, etc.
- Provides recommendations
- Engages with key parties to address findings and feedback

- Identify topics that require PRoLog focus in Lugano 2014
- Prioritizes topics/issues needed for investigation
- Establishes working group Task Forces as need
- Collects and summarizes recommendations (White Paper) for review
- Facilitates/ coordinates dialogue with the criteria authors
- Engages key parties in dialogue to address findings and recommendations
- Communicates with PINTAD members
- Maintains frequent meetings and manages progress of deliverables

- Provide guidance and feedback regarding recommendations
- Suggest modifications and alternate recommendations
- Supports publication and distribution of recommendations

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Key Takeaways and Lessons Learned

- PRoLoG structure allowed us to reach our goals and objectives
- TF members were both charitable with their time and generous with their input
- Keeping it non-competitive and real-world
- IWG members were very supportive of our initiative and collaborative in finding best solutions
- Members of the FDA were part of the initial discussions

Consensus Recommendations- Imaging Acquisition Considerations

- The use and frequency of acquisition of PET-CT and/or a diagnostic CT depends upon the clinical question, lymphoma histology and stage, FDG-avidity, and efficacy endpoints
- In FDG-avid lymphomas, a diagnostic CT scan may not be required at each scheduled tumor assessment where PET-CT is scheduled
- Similarly, PET-CT may not be required at each time point, e.g. 18F-FDG PET-CT is usually discouraged for surveillance
- While the role of surveillance imaging is not established in clinical practice, a diagnostic CT may still be required in follow-up of clinical trials using time-dependent endpoints (e.g. PFS)
- the terminology PET-CT-based versus CT-based response criteria in Lugano refers to
  - PET-CT as PET corrected for attenuation by CT (metabolic assessment and localization of lesions)
  - CT as diagnostic quality CT for morphologic assessment

Consensus Recommendations- FDG avidity of Lymphoma Entities

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- Routinely FDG-avid lymphoma (e.g., HL, DLBCL, FL, MCL, nodal peripheral T-cell lymphoma, lymphoblastic and Burkitt lymphoma)
  - To be assessed by 18F-FDG PET-CT and, when anatomic assessment is required, by diagnostic CT.
- Generally, not FDG-avid lymphomas (e.g., SLL, CLL)
  - To be assessed with diagnostic CT and not with PET-CT, unless for suspected or documented transformation.
- Other lymphomas (e.g., some marginal-zone lymphoma , some T-cell notably cutaneous T-cell lymphomas)
  - No formal recommendation for which type of imaging to be performed
  - Should be based on the lymphoma entity and can be aligned with Health Authorities
  - In general, baseline may include PET-CT and diagnostic CT
    - No FDG-avid lesions at baseline: follow with diagnostic CT
    - FDG-avid lesions at baseline: PET-CT may be used for response assessment

Consensus Recommendations: Lesion Classification

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AREAS OF INCONSISTENCY AND AMBIGUITY:

- Nomenclature (Index vs Target, Use of CMR/CR in CT versus PET assessments)
- Use of PET (Visual vs quantitative)
- Integration of anatomic, metabolic and Clinical responses
- Missing assessments and carrying forward responses

CT Based Assessments	PET Based Assessments
Target Lesions (TL), assessed quantitatively Non-Target Lesions (NTL, assessed qualitatively) Nodal and extranodal lesions to be documented separately • Aligns with RECIST approach for lesion labeling • Keeps compliant with CDISC standards • Different treatment regimens may affect nodal vs extranodal disease differently	5-point scale (5-PS) is based on the single most metabolically active lesion (with visual or semi-quantitative assessment) Most hypermetabolic lesion can vary at each timepoint SUV max can be captured Other measurements (SUV peak, SUV mean, TMTV, radiomics) are being explored

Consensus Recommendations: Response Assessment Nomenclature

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RESPONSE assessment Nomenclature:

- CT Based : CAR, PAR, SAD, PAD
- PET Based: CMR, PMR, NMR (preferred or SMD), PMD
- Combined imaging response : CR, PR, SD, PD

Type of Response*	Metabolic	Anatomic	Overall†
Complete response	CMR	CAR	CR
Partial response	PMR	PAR	PR
Stable disease/No response	NMR (preferred term, otherwise SMD)	SAD	SD
Progressive disease	PMD	PAD	PD

**this table is for terminology purpose only and does not describe how to combine metabolic and anatomic responses (see section "Response Assessment")*

†*overall response (used for determining endpoints) integrates imaging response (metabolic, anatomic, or combination of both, when available) and clinical data, when available*

Consensus Recommendations: Lesion scoring

- TL selected on CT at baseline should be FDG avid in FDG avid lymphomas
  - Higher uptake than liver (5-PS > 3)
- Eligibility for FDG avid lymphoma should include to have at least one FDG avid lesion
- Score 4 of the 5-PS = lesion uptake greater than uptake in a large region of normal liver
  - Removes the "moderately" greater condition from original classification
- Score 5 of the 5-PS = lesion uptake markedly greater than liver or NL or both
  - Document the reason for score 5
  - Semi-quantitative = at least 2 times SUVmax in the normal liver (no recommendation on 2 or 3 times as threshold)
- In metabolic response assessment the overall metabolic uptake (i.e., intensity and extent) should be considered.
  - With reduced intensity and no increase in extent, it is PMR
  - With increased intensity and/or extent, it is PMD
  - With stable intensity and no increase in extent, it is NMR (preferred or SMD)
- X category = unlikely to be related to lymphoma
  - Always assign a 5-PS score in addition to X

Consensus Recommendations: Combined Imaging Responses and Discordant Responses 1/2

- For FDG AVID lymphomas – metabolic response should take precedence over the anatomic response
    - Overall timepoint response can be overridden during clinical review (clinical data, biopsy, follow-up etc)
- In cases of PAD but no PMD, consensus recommendation is to NOT downgrade PET response in FDG avid lymphomas
    - If response is downgraded (not recommended), it may be reassigned an overall response based on clinical review after biopsy or follow-up imaging
- Biopsy of growing/new lesion and/or follow-up is strongly encouraged (if clinically indicated) as well as search for alternative causes
    - If progression is confirmed (positive biopsy, follow-up), PD will be backdated to the first appearance of the growing/new lesion

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Consensus Recommendations: Combined Imaging Responses and Discordant Responses 2/2

- Any new lesion not considered to be lymphoma, whether metabolically active or not, does not represent PD
  - This clarifies the requirement from the original classification to have no new lesion in CMR, PMR and NMR
- In non-FDG-avid lymphomas, CT results should supersede PET for the imaging time point response assessments
  - If CT is missing and PET-CT was done, reviewer will judge if CT portion of the PET-CT is of diagnostic quality

Consensus Recommendations: Assessment of Response When PET-CT or diagnostic CT Imaging Visits Are Missing

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- When PET-CT is not available, but a diagnostic CT is, the PET-CT response can be carried forward from the prior visit to provide an imaging response assessment
    - As long as the diagnostic CT scan does not suggest disease deterioration (nor clinical status)
- When diagnostic CT is not available, but there has been no substantial change on PET-CT, the results of the prior CT can be carried forward.
    - CT portion of PET (CTAC) can be used to assess the CT disease burden if considered of suitable diagnostic quality.

Consensus Recommendations: Incorporation of Clinical Data

- Consensus recommendation: Clinical review combining imaging assessment with clinical data
- No requirement for integrating clinical information per Lugano guidance, except for bone marrow (BM) biopsy (BMB) and aspiration for lymphoma histologies where PET-CT may not be a substitute for this information.
- Clinical data
  - Defined in study documents, e.g.
    - BMB data
    - lesion biopsy/fluid evaluation,
    - concomitant therapy
    - infection/inflammation etc
  - No need for Physical exam data except which cannot be covered on imaging.
  - Prior radiation information for selection of lesions at baseline (for imaging reviewer)

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Consensus Recommendation: Assessment of Bone Marrow involvement

- Historical BMB may be used for baseline (typically if dated no longer than 3 months and unless clinical changes suggest otherwise)
  - To be discussed and prespecified in study documents
- FDG avid lymphoma:
  - BMB- at baseline: assign CR if CMR is reached without repeating BMB
  - HL/DLBCL: PET-CT may substitute for BM evaluation
  - FL: PET-CT does not uniformly substitute for BM evaluation
  - BMB+ at EOT prevents CR even in case of CMR (downgrade CR to PR)
- Non or variably FDG avid lymphoma:
  - BM- at baseline: assign CR if CAR (and CMR if PET-CT is done)
  - BM not obtained at EOT: prevents CR even in case of CAR (downgrade CR to PR)

Note: in case of indeterminate BM evaluation, it is reasonable to downgrade CR to PR where PET cannot substitute for BM evaluation

Consensus Recommendation: Evaluation Of Spleen, Liver And Nodal Involvement

AREAS OF INCONSISTENCY AND AMBIGUITY:

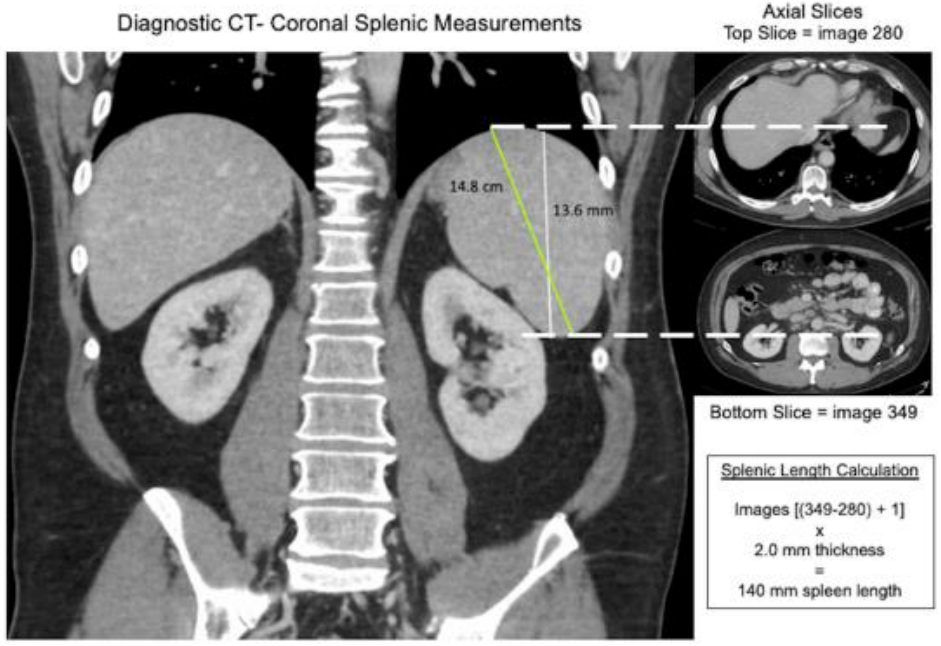
- Spleen and Liver size
- Method of assessment for determining length
- Nadir versus baseline for progression

CONSENSUS RECOMMENDATIONS

- Expert Clinical judgement of the reviewer should be used in instances where the size measurement is inconsistent with the rest of the tumor burden.
  - Expert reviewer should determine the status of the spleen when measurement is close to 13cm
- Liver size should no longer be considered as part of the assessment.
- Nodules/masses in the spleen and liver should be recorded as part of the anatomic tumor lesion assessment (TL/NTL).

Consensus Recommendations: Spleen Measurement Methodology

- Use a diagnostic CT and measure the vertical length
- If a diagnostic CT is not available, use CTAC if considered to be of acceptable quality by reviewer
- Measurements on PET are discouraged
- Clinical palpation is not considered adequate for measuring the spleen



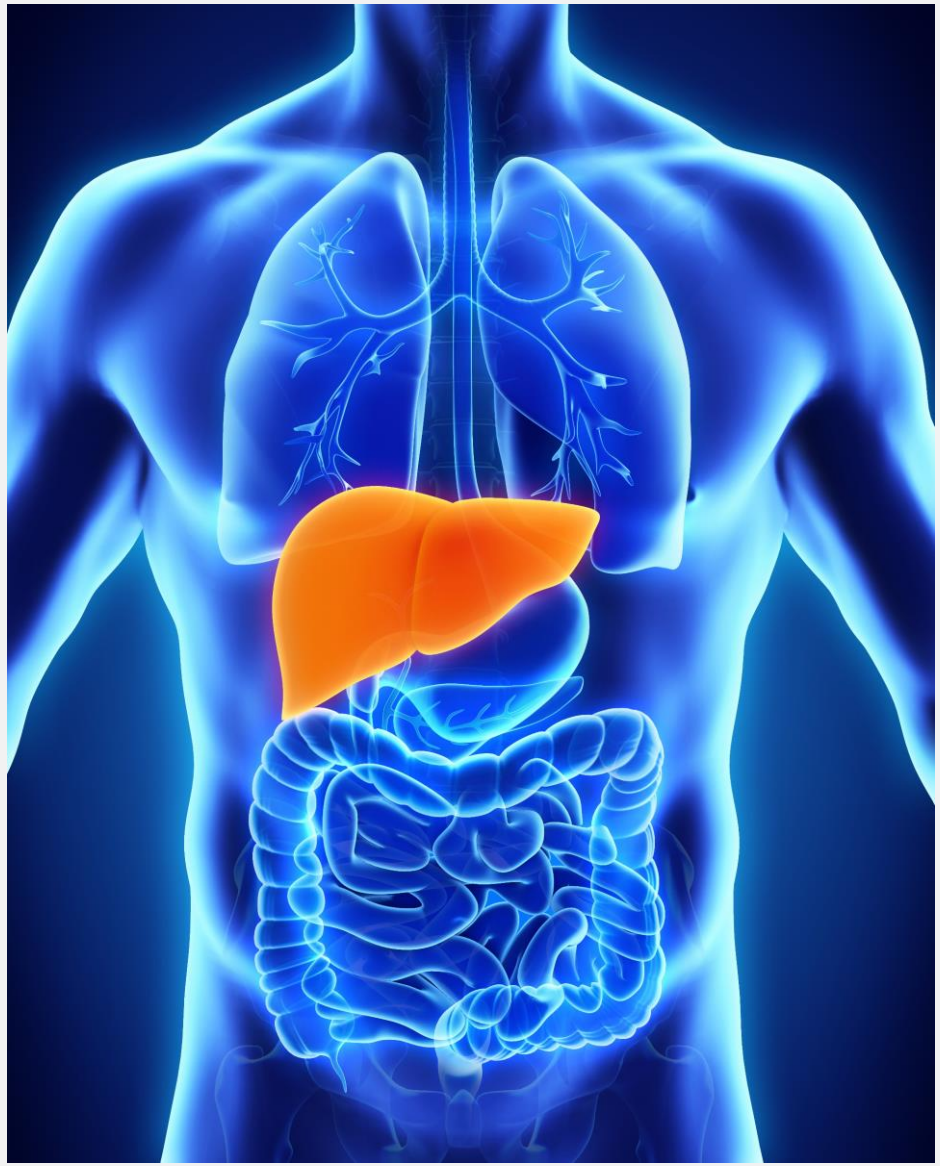
Coronal and Axial methods to measure spleen size on CT. If the coronal length of the spleen is used to measure the spleen size, it should be measured from the most cranio-caudal portions of the spleen (13.6cm). Oblique coronal length measurement should be avoided (14.8cm). Courtesy of Imaging Endpoints Core Lab, USA.

Consensus Recommendations: Spleen Responses

- Progression is assessed compared to nadir (which can be baseline) and response is assessed compared to baseline
- New and recurrent splenomegaly
  - Increase of at least 2.0cm (and be over 13cm) should be applied to both new and recurrent splenomegaly
- Splenectomy
  - Prior to trial: proceed without spleen category
  - During the trial: censor response at the time of splenectomy unless spleen was free of lymphoma

Consensus Recommendations: Liver

- Liver as reference for 5PS: avoid the liver margins and any focal hepatic involvement
- Diffuse hepatic involvement, use expert judgement (no recommendation on alternative reference tissue provided)
- Uptake higher than liver in areas with high physiological uptake may not always preclude the assessment of a CMR.



Consensus Recommendations: Nodal lesions

- New/Recurrent nodal lesion
  - Apply a 5mm absolute increase threshold in addition to the >15mm rule
    - To avoid overcalling progression due to small size variation
- Discordance between nodal and splenic responses
  - Nodal response with unequivocal new/recurrent splenomegaly due to lymphoma = PD
  - CMR in nodes and remaining splenomegaly without FDG uptake higher than liver can be called CMR
  - Always consider other conditions that may cause diffuse increase in organ FDG uptake (e.g., treatments to support blood counts)

Conclusion and Key POINTS

- Question: How can the Lugano classification be consistently applied among clinical end users?
- Pertinent Findings: These consensus recommendations should be used as a companion to the Lugano Classification with regards to FDG-avidity of different lymphoma entities, response nomenclature and lesion classification and scoring. Response assessment, usage of clinical data and spleen, liver and nodal evaluation are clarified.
- Implications for patient care: This guidance will enhance usage of the Lugano Classification, facilitating clinical trial conduct and regulatory review, ultimately leading to improved lymphoma patient outcome.

Panel Discussion

- Practical application of these guidelines and possible challenges
  - Is it another set of guidelines?
  - Are these new terminologies acceptable and CDISC compliant?

- Is there data backing up these guidelines ?

- Why is use of CTAC (CT portion of PET) recommended? When would you recommend a separate contrast enhanced diagnostic CT?

THANK YOU!