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PERSPECTIVE

Working towards harmonization of clinical trial reporting in Hodgkin lymphoma

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The *13th International Symposium on Hodgkin Lymphoma (ISHL13)* hosted a workshop titled "Working towards harmonization of clinical trial reporting in Hodgkin lymphoma" in Cologne, Germany. Attended by 46 international experts, the workshop focused on standardizing imaging and biomarker data collection in HL clinical trials. Participants included hematologists, nuclear medicine physicians, oncologists, radiologists, and statisticians from across Europe and North America. The purpose was to discuss the clinical trial reporting and sample collection of biomarker material that is performed in current academic and pharmaceutical trials. Workshop discussions, presentations, and open voting shaped the consensus summarized in this report.

Imaging is critical for staging, response assessment, and treatment decisions in Hodgkin lymphoma (HL). However, imaging data collected across clinical trials remain heterogeneous. Unnecessary or redundant details—such as extensive anatomical measurements—are frequently reported, while key parameters such as total metabolic tumor volume (MTV) are often missing.[1,2] These practices increase the complexity of data collection without clearly advancing scientific objectives. Another concern is the persistence of outdated imaging practices. Some trial protocols still include chest x-rays for mediastinal mass monitoring, despite more accurate methods like computed tomography (CT) or positron emission tomography (PET)/CT. Similarly, contrast-enhanced CTs are often mandated during follow-up in patients with complete remission (CR), although the likelihood of useful findings is minimal. These unnecessary procedures increase patient risk and trial costs.

Recent studies highlight serum TARC (sTARC) and circulating tumor DNA (ctDNA) as promising biomarkers in HL. sTARC levels correlate with disease activity and response,[3–5] whereas ctDNA offers noninvasive monitoring of genetic alterations and tumor burden.[6,7] However, wide variability in collection and analysis protocols limits their integration into clinical practice. Standardization is urgently needed to harness their potential in disease monitoring and personalized treatment.

STATUS QUO

Case records forms (CRFs) were collected from different study groups from large HL trials to capture current standard practice. Imaging information that was gathered in the CRFs of these trials is summarized in Tables S1 and S2.

There was heterogeneity in the parameters collected across the four first-line trials (HD21 [NCT02661503], AVENuE [NCT03617666], AHL2011 [NCT01358747], and REALYSA [NCT03869619] and S1826 [NCT03907488]) and three second-line trials (AERN [NCT03480334], ANIMATE [NCT03337919], and REVOLUMHOD [NCT04621604]), reflecting variations in trial design, priorities, and the extent of data collected. This lack of standardization can complicate cross-trial comparisons and limit the generalizability of findings.

Collected information ranged from "information heavy" (e.g., individual lesion Deauville scores, product of perpendicular diameters) to

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"information light" (e.g., overall stage, Lugano response). Optional parameters included MTV, standardized uptake values (SUVs), and immune-related imaging effects. Biomarker data were generally absent from these CRFs due to their novelty and lack of routine measurement.

WORKSHOP RECOMMENDATIONS

The workshop resulted in practical recommendations to improve consistency and efficiency in HL clinical trials. These focus on imaging and biomarker protocols while acknowledging that current response criteria (e.g., Lugano classification) remain the standard.[8]

Imaging

The workshop consensus distinguished between minimum required and optimal imaging parameters at baseline and for response assessment (see Table 1). Measurement of MTV was considered the most efficient way to integrate most PET parameters currently requested in CRFs since these are routinely included when scans are segmented to measure MTV (e.g., tumoral SUVmax, nodal and extranodal locations). The recommended method is MTV4, which includes lesions with an SUV ≥ 4.0 and volumes ≥ 3 mL, with manual inclusion of smaller lesions, if it is considered it will affect prognosis. This method is simple[9] and reproducible among readers and can be performed using commercial software.[10] An international benchmark dataset is available (https://zenodo.org/records/11409717).

The Deauville score, developed for treatment response assessment, should not be applied at baseline. It was also recommended to omit individual lesional Deauville scores, and CT size measurements when FDG PET is the primary response tool. However, CT-based sum of product of perpendicular diameter (SPD) measurements may be useful in specific contexts (e.g., single-agent immunotherapy[11]) to differentiate between disease progression and ambiguous response, though MTV may ultimately prove more reliable.

Central imaging data collection remains essential for future radiomics and additional analyses. Centralized repositories help ensure standardized data acquisition, annotation, and assessment.

TABLE 1 Recommended items to be captured in imaging case report forms.

Recommended items		Description/categories/units
Baseline		
Required	Imaging stage	I–IV
	Mediastinal bulk—using CTR on CT component of PET-CT	Y/N
	MTD	*X* cm
	Location of MTD	Prespecified list to be agreed
	Assessable disease that is FDG-avid	Y/N
	Nodal site with largest MTD (Stages I–III)	Tick box; prespecified list to be agreed
	Nodal sites (only if needed for prognostic risk scores, i.e., Stages I–II); extranodal sites (Stage IV)	Tick box; prespecified list to be agreed
Optimal	MTV*	*X* mL; ideally with sites labeled by location
	SUVmax tumor	x.x
	Location of SUVmax	
	Nodal sites and location	Prespecified list to be agreed
	Extranodal sites and location *particularly bone lesions*	Prespecified list to be agreed
(Interim-) response assessment		
Required	Deauville score	1–5, measured on hottest lesion only
	New lesions due to lymphoma	Y/N
	SUVmax tumor	x.x
	Location of SUVmax	Prespecified list to be agreed
	SUVmax MBP	x.x
	SUVmax liver	x.x
	Lugano response	CMR, PMR, NMR or SMD, PMD
	PPD of up to 6 lesions to calculate SPD (as per Lugano/LyRIC)	Only consider if PMD to determine if IR or PD in patients on single-agent PD1/PDL1 inhibitors or in combination with other immunotherapeutic agents
Optimal	MTV for cases with D4 or D5 only	*X* mL
	SUVpeak for hottest lesion	
	Location of SUVpeak	
	SUVmean MBP and SUVmean liver	

Abbreviations: CT, computed tomography; CTR, cardiothoracic ratio greater than a third of the transthoracic diameter; D4 or D5: Deauville score 4 or 5; FDG, ^{18}F fluorodeoxyglucose; LyRIC, lymphoma response to immunomodulatory therapy criteria; MBP, mediastinal blood pool; MTD, maximum tumor diameter; MTV, metabolic tumor volume; PET, positron emission tomography; PPD, product of perpendicular diameter; SPD, sum of product of perpendicular diameter; SUV, standardized uptake value.

TABLE 2 Recommended material to be collected for biomarker analysis.

Recommendations		Notes
Required		
Material	20 mL of blood in cfDNA collection tubes for ctDNA measurement	Plasma and serum should be separated and stored in 1–2 mL aliquots. For plasma separation, the validated workflow of the used cfDNA collection tube should be followed, which is usually available from the manufacturer. The cell pellet from the plasma tube should be stored as well for germline DNA analysis, which is needed for many ctDNA analysis workflows
	10 mL of blood in serum tubes for TARC measurement	
Timepoints	Pretreatment	
	Decision timepoints	As determined by the study design, usually at the same timepoint as interim PET/CT-imaging
	End of treatment	
	Follow-up	At study-designated intervals
Optimal		
Analyses	Quantification of ctDNA load and MRD at follow-up timepoints	Performed using a technically and clinically validated assay
	Quantification of sTARC levels	A commercially available ELISA kit (R&D Systems) with precoated plates is recommended to reduce variability

Abbreviations: cfDNA, cell-free DNA; CT, computed tomography; ctDNA, circulating tumor DNA; MRD, minimal residual disease; PET, positron emission tomography; sTARC, serum TARC.

Biomarkers

Strong interest in ctDNA and sTARC was evident, although standardization and access remain barriers. The group agreed that these biomarkers should be integrated into trials where possible although not as minimal required data. At a minimum, appropriate sample collection should allow for future testing (see Table 2).

For sTARC, serum is preferred over plasma because of higher sensitivity due to platelet-mediated uptake. A validated commercially available ELISA kit (R&D Systems) with precoated plates is recommended to reduce variability. The authors have obtained most experience and consistent results with Human CCL17/TARC ELISA Kit-Quantikine (R&D Systems, Catalog #DDN00), although other validated assays may also be applied. Because of the significant elevation at baseline, pretreatment samples are generally diluted 10, 50, and 100 times. Baseline levels above 1000 pg/mL are typically considered elevated, and this cutoff was recently validated for optimal detection of relapse during follow-up.[12–14] sTARC should optimally be tested together with imaging and has high potential to identify a significant proportion of PET-positive patients with favorable outcome and can be studied in clinical trials to guide treatment.[5] Also, sTARC might be applied for disease monitoring during follow-up.

For ctDNA, validated assays capable of accurate load and minimal residual disease (MRD) quantification are essential. Validation should include contrived samples for reproducibility, sensitivity, and correlation with imaging.[15] Assays must comply with local regulatory standards (e.g., CLIA, IVDR). Although optimal cutoffs and timing are undefined, studies suggest rapid ctDNA clearance in HL, which may signal effective treatment.[6,7] ctDNA testing should be incorporated into HL trials where feasible, either as part of ctDNA-guided treatment protocols or as ancillary research. Optimally, both sTARC and ctDNA should be tested together. Data from these trials will help determine the best practices for incorporating both sTARC and ctDNA into routine monitoring and treatment planning.

The *2024 International Symposium on Hodgkin Lymphoma* workshop highlighted critical challenges and opportunities in the harmonization of clinical trial reporting for HL.

Our recommendations aim to enhance the quality, comparability, and efficiency of future trials while reducing the unnecessary burden of data collection and radiation exposure for patients. The adoption of clearly defined imaging parameters and consistent blood biomarker collection protocols, particularly for ctDNA and sTARC, will pave the way for more effective trial designs and ultimately support the advancement of personalized treatment strategies in HL.

AUTHOR CONTRIBUTIONS

Carsten Kobe: Writing—original draft; writing—review and editing; project administration. **Philippe Armand**: Writing—original draft; writing—review and editing. **Sven Borchmann**: Writing—original draft; writing—review and editing. **Graham P. Collins**: Writing—original draft; writing—review and editing. **Anne-Segolene Cottereau**: Writing—original draft; writing—review and editing. **Justin Ferdinandus**: Writing—original draft; writing—review and editing; project administration. **Alex F. Herrera**: Writing—original draft; writing—review and editing. **Davide Rossi**: Writing—original draft; writing—review and editing. **Wouter J. Plattel**: Writing—original draft; writing—review and editing. **Sally F. Barrington**: Writing—original draft; writing—review and editing; supervision. **Martin Hutchings**: Supervision; writing—original draft; writing—review and editing.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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