Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

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Supplementary Table S1 : The Ann Arbor Staging [1,2]

Stage	Description
I	Involvement of a single lymph node region (eg. cervical, axillary, inguinal, mediastinal) or lymphoid structure such as spleen, thymus, and Waldeyer's Ring
II	Involvement of two or more lymph node regions or lymph node structures on the same side of the diaphragm
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
IV	Additional noncontiguous extranodal involvement
Additional note	
"E" designates limited direct extension to an extranodal site for stage I to III	
"X" designates presence of bulky disease	

Of note, the definition of bulky disease "X" has been variable over time and studies, with sizes ranging from 6 cm to 10 cm. Recent recommendation (Cheson, B et al. J Clin Oncol 2014; 32:3059-68) suggests omitting the use of this term and recording the largest size of the tumor.

The presence or absence of systemic symptoms (B-symptoms) has been used to complete this staging classification as "A" (absence) or "B" (presence). However, given the lack of independent prognostic significance, it has been recently suggested that recording of B-symptoms is no longer mandatory for patients with non-Hodgkin lymphoma (Cheson, B et al. J Clin Oncol 2014; 32:3059-68) and can be reserved for patients with Hodgkin lymphoma.

B-Symptoms include the presence of one or more of the following:
- Unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation
- Unexplained persistent or recurrent fever with temperatures above 38 C during the previous month
- Recurrent drenching night sweats during the previous month

Supplementary Table S2: Lugano Classification Response Criteria [2,3]

Response assessment	PET – CT		CT based
Complete		**Complete metabolic response**	**Complete radiologic response**
	Tumor lesions	Score 1,2 or probably 3 on the Deauville scale	All target lesions regress to ≤1.5 cm in their longest transverse diameter
	Bone marrow	Lack of FDG uptake	Absence of pathological involvement of the biopsy by morphology and immunohistochemistry
Partial		**Partial metabolic response**	**Partial radiologic response**
	Tumor lesions	Score 4 or 5 with reduced uptake compared to baseline	Reduction by ≥50% of the size (SPD) of the lesions (consider the SPD of up to 6 target lesions)
	Bone marrow	Residual uptake reduced from baseline	Not applicable
Stable disease		**No metabolic response**	**Stable disease**
	Tumor lesions	Score 4 or 5 without significant change from baseline	Reduction by <50% or increase by <50% of the size (SPD) of the lesions (consider the SPD of up to 6 target lesions)
	Bone marrow	No change from baseline	Not applicable
Progressive disease		**Progressive metabolic disease**	**Progressive disease**
	Tumor lesions	Score 4 or 5 with increase in intensity from baseline and/or new FDG-avid lesion	Increase of nodal or extrandal lesions by ≥50% of the product of the longest transverse diameter and its perpendicular diameters from nadir[¶], or appearance of new nodal lesions >1.5 cm (1 cm for unequivocal extranodal lesion)
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: SPD=sum of the product of the perpendicular diameters of the lesion

* In clinical trials, interpretation of a score of 3 observed at interim PET depends on the treatment plan.

[¶] the increase of nodal or extrandal lesions by ≥50% of the product of the longest transverse diameter and its perpendicular diameters should be accompagnied by an increase from nadir of the longest diameter by at least 0.5 cm for lesions ≤ 2 cm and 1 cm for lesions > 2 cm

Supplementary Table S3: The Deauville Five-Point Scale [3]

Deauville Score	18-FDG PET findings
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

The use of this scale is recommended for reporting response assessment by PET-CT at the end of treatment. The Deauville five-point scale scores the area of most intense 18-fluorodeoxyglucose (18-FDG) uptake in a site of initial disease, if present, as follows. Scores 1 and 2 represent complete metabolic response (CMR); score 3 also likely represents CMR in patients receiving standard treatment. Scores 4 and 5 with reduced 18-FDG uptake from baseline likely represents partial metabolic response, but at the end of treatment, corresponds to residual metabolic disease. A score of 5 with no change in 18-FDG uptake, increased 18-FDG uptake, or new sites of 18-FDG uptake in keeping with lymphoma represents treatment failure and/or progression.Treatment-related inflammation, intercurrent infection or underlying concomitant inflammatory disease may result in non-specific 18-FDG uptake. PET-CT results should be interpreted in the overall clinical context, including anticipated prognosis and other markers of response.

Supplementary Table S4: Select Recent Trials in Untreated Diffuse Large B-Cell Lymphoma

Treatment Regimen	Phase	Eligibility	N	Outcome	p-value	Reference
Advanced-Stage						
R-ACVBP *vs* R-CHOP	3	Age 18-59 y; aaIPI=1	380	3-y PFS 87% *vs* 73% 3-y OS 92% *vs* 84%	0.002 0.007	Recher et al.[4]
R-CHOP-14 *vs* R-CHOP-21	3	Age ≥18 y; stage IA bulky (>10cm)/IB -IV	1080	2-y PFS 75% *vs* 75% 2-y OS 83% *vs* 81%	NS NS	Cunningham et al.[5]
R-CHOP-14 *vs* R-CHOP-21	3	Age 60-80 y; aaIPI≥1	602	3-y EFS 56% *vs* 60% 3-y OS 69% *vs* 72%	NS NS	Delarue et al.[6]
R-megaCHOEP vs R-CHOEP-14	3	Age 18-60 y; aaIPI=2-3	275	3-y EFS 61% *vs* 70% 3-y OS 77% *vs* 85%	NS NS	Schmitz et al.[7]
R-CHOP + ASCT *vs* R-CHOP	3	Age 15-65 y; aaIPI=2-3	370	2-y PFS 69% *vs* 55% 2-y OS 74% *vs* 71%	0.005 NS	Stiff et al.[8]
R-HDS + ASCT *vs* R-CHOP-14	3	Age 18-65 y; stage II bulky (>10cm)-IV; aaIPI=2-3 or IPI 3-5	246	3-y EFS 65% *vs* 62% 3-y OS 77% *vs* 74%	NS NS	Cortelazzo et al.[9]
DA-EPOCH-R *vs* R-CHOP	3	Age ≥18 y; stage II-IV	491	2-y PFS 79% *vs* 76% 2-y OS 87% *vs* 86%	NS NS	Bartlett et al.[10]
Obinutuzumab-CHOP *vs* R-CHOP	3	Age ≥18 y; aaIPI≥2, or IPI=1 and age ≤60y, or IPI=0 and bulky (≥7.5 cm)	1418	3-y PFS 70% *vs* 67% 3-y OS 81% *vs* 81%	NS NS	Vitolo et al.[11] (GOYA trial)
Bortezomib-R-CHOP *vs* R-CHOP	2	Age ≥18 y; non-GCB subtype by Hans IHC algorithm	206	2-y PFS 82% *vs* 78% 2-y OS 93% *vs* 88%	NS NS	Leonard et al.[12] (Pyramid trial)
Bortezomib-R-CHOP *vs* R-CHOP	3	Age ≥18 y; stage I bulky (>10cm)-IV; sufficient diagnostic material for GEP	918	30-m PFS 74% *vs* 70% 30-m OS 83% *vs* 82%	NS NS	Davies et al.[13] (REMoDL-B trial)
Ibrutinib-R-CHOP *vs* R-CHOP	3	Age ≥18 y; non-GCB subtype by Hans IHC algorithm; stage II-IV; R-IPI≥1	838	3-y EFS 70% *vs* 67% 3-y OS 83% *vs* 81%	NS NS	Younes et al.[14] (PHOENIX trial)
Lenalidomide-R-CHOP *vs* R-CHOP	2	Age ≥18 y; stage II bulky (>10cm)-IV; IPI≥2	349	3-y PFS 73% *vs* 61% 3-y OS 83% *vs* 75%	0.03 0.05	Nowakowski et al.[15]
Lenalidomide-R-CHOP *vs* R-CHOP	3	Age ≥18 y; stage II-IV; IPI≥2; ABC subtype by GEP NanoString	570	2-y PFS 67% *vs* 64% 2-y OS 79% *vs* 80%	NS NS	Nowakowski et al.[16] (ROBUST trial)

Limited-Stage						
R-CHOPx3 + XRT	2	Stage I-nonbulky stage 2 (<10cm); Sm-IPI≥1	60	4-y PFS 88% 4-y OS 92%	-	Persky et al.[17]
R-CHOPx4 + 2R *vs* R-CHOPx6	3	Age 18-60 y; stage I-II; nonbulky (<7.5cm); aaIPI=0	588	3-y PFS 96% *vs* 94% 3-y OS 99% *vs* 98%	NS NS	Poeschel et al.[18] (FLYER trial)
PET-guided: R-CHOPx4-6 + XRT *vs* R-CHOPx4-6	3	Age 18-75 y; stage I-II; nonbulky (<7.0cm)	334	 5-y EFS 92% *vs* 89% 3-y OS 96% *vs* 92%	 NS NS	Lamy et al.[19]
PET-guided: PET^+: R-CHOPx3 + XRT + RIT PET^-: R-CHOPx4	2	Stage I-II nonbulky (<10cm)	132	 5-y PFS 86%; OS 85% 5-y PFS 89%; OS 91%	-	Persky et al.[20]
PET-guided: PET^+: R-CHOPx3 + XRT PET^-: R-CHOPx4	N/A*	Stage I-II nonbulky (<10cm); no B-symptoms	319	 5-y TTP 80%; OS 77% 5-y TTP 92%; OS 89%	-	Sehn et al.[21]

Legend to Supplementary Table 4: Results from select recent clinical trials in patients with untreated advanced-stage and limited-stage DLBCL, including novel immunochemotherapy combinations, the addition of novel agents to standard R-CHOP, and the use of PET-guided approaches. *population-based analysis

Abbreviations: n, number; aaIPI, age-adjusted International Prognostic Index; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone, methotrexate consolidation; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; PFS, progression-free survival; OS, overall survival; R-CHOP14, R-CHOP administered every 14 days; R-CHOP21, standard dose R-CHOP administered every 21 days; EFS, event-free survival; R-CHOEP-14; R-CHOP-14 + etoposide; R-MegaCHOEP, dose-escalated sequential high dose therapy +ASCT, autologous stem cell transplant; R-HDS, rituximab with high dose sequential chemotherapy; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; IHC, immunohistochemistry; GEP, gene-expression profiling; R-IPI, revised-International Prognostic Index; Sm-IPI, stage-modified International Prognostic Index; XRT, radiation therapy; RIT, radioimmunotherapy (ibritumomab); PET^+, PET-positive; PET^-, PET-negative; TTP, time-to-progression**.**

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