Clinical benefit of tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma: real-world data from the EarlyMIND study

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Supplementary data

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Methods

Study outcomes

Primary endpoint

The primary endpoint was best objective response (bOR) (complete response [CR] or partial response [PR]), assessed locally, according to the 2007 International Working Group response criteria for malignant lymphoma.[1]

Secondary endpoints

Secondary endpoints included the following:

- **bOR in the second line of treatment,** defined as the best response (CR or PR) obtained with the combination of tafasitamab with lenalidomide administered in the second line of treatment (2L cohort).
- **bOR in the third or fourth line of treatment,** defined as the best response (CR or PR) obtained with the combination of tafasitamab with lenalidomide administered in the third or fourth of treatment (3L + 4L cohort).
- **Duration of response (DOR),** defined as the time from initial response (CR or PR) until documented disease progression or death or date of censoring (whatever comes first).
- **Overall survival (OS),** defined as the time from the index date until death from any cause (documented by the date of death) or date of censoring (whatever comes first).
- **Disease control rate (DCR),** defined as the proportion of patients with CR, PR, or stable disease (SD; DCR = bOR + SD) during the follow-up period.
- **Time to next treatment (TTNT),** defined as the time from index date to initiation of the next line of therapy.
- **Event-free survival (EFS),** defined as the time between index date until one of the following events occurs, whichever comes first: (1) Disease progression during therapy (progressive disease [PD]); (2) institution of any additional unplanned anti-tumor treatment; (3) relapse after achievement of CR or PR; (4) death due to any cause.
- **Progression-free survival (PFS),** defined as the time between index date until disease progression during therapy or death.
- Number and type of treatment received prior to and post tafasitamab treatment.
- Use of treatment regimens by lines of therapy prior to and after tafasitamab treatment.
- Duration of tafasitamab treatment (regardless of concomitant treatment with lenalidomide).
- Duration of lenalidomide treatment (i.e. doses, dates of administration, date of dose change, if any).
- Details of first and last dose of tafasitamab administered.
- Modifications of dose and treatment schedule of lenalidomide**.**

Statistical analyses

Populations

Efficacy outcomes were analyzed among patients who had received tafasitamab-lenalidomide. All analyses were based on the assessments of clinical efficacy by the investigator/treating physician. The primary and secondary endpoints were analyzed on the per protocol (PP) set and full analysis set (FAS).

The FAS was defined as all patients who agreed to participate and who took the study treatment as second-, third-, or fourth-line therapy.

The PP analysis set included FAS patients who fulfilled all eligibility criteria and had at least one evaluation of efficacy, with a minimum of 6 months of follow-up. This rule was used to minimize bias that may have occurred if:

- A patient responded (CR or PR) or progressed or died within 6 months from index date (from study day 1 to 183);

OR

- A patient had at least one disease response assessment with SD as “indeterminate,” “not evaluable,” or “other” within 6 months from index date (from study day 1 to 183), with at least one assessment or death at 6 months or later (on or after study day 184);

OR

- A patient had at least one disease response assessment with SD as “indeterminate,” “not evaluable,” or “other” within 6 months from index date (from study day 1 to 183), with at least one assessment or death at 6 months or later (on or after study day 184).

Patients did not fulfill the minimum of 6 months of follow-up time if they were non-responding (e.g. SD or PD as best response), with a first tumor response assessment beyond 6 months.

Primary analysis of primary endpoint

The primary endpoint was the best objective response (bOR) rate (i.e. PR or CR) after the combination of tafasitamab with lenalidomide administered in the second line of treatment (2L cohort) and in the third or fourth line (3L + 4L cohort). Response assessments after next line of treatment initiation were considered “not evaluable.”

Numerator: Number of patients with objective response (CR or PR) between the initiation of treatment and death, next anti-lymphoma treatment (NALT), or end of observation period, whatever comes first.

Denominator: All patients in the FAS and PP populations.

Patients with unknown response to therapy (e.g. no response assessment before lost to follow-up or death) were considered non-responders. bOR, CR, and PR rates were presented, along with their 95% confidence interval (CI) limits, using Clopper-Pearson exact methods. Censoring reasons were reported.

Sensitivity analysis of primary endpoints

The bOR rate was defined as above, with one change:

- **Numerator:** Number of patients with objective response (CR or PR) between the initiation of treatment and death, NALT, or end of observation period, whatever comes first.
- **Denominator:** All patients in the FAS and PP populations. Patients with unknown response to therapy were excluded from the numerator and denominator.

Secondary analysis for secondary endpoints

All endpoints were descriptively analyzed. Kaplan-Meier methodology was used to evaluate median survival, 95% CIs, and presenting survival curves for DCR, DOR, OS, EFS, and PFS.

- **bOR rate** in the second line of treatment was calculated in the 2L cohort.
- **bOR rate** in the third or fourth line of treatment was calculated in the 3L + 4L cohort.
- **DOR** was defined as the time from initial response (CR or PR) until documented disease progression or death or date of censoring (whatever comes first).
- **OS** was defined as the time from the initiation of tafasitamab date until death from any cause (documented by the date of death) or date of censoring (whatever comes first).
- **DCR** was defined as the proportion of patients with CR, PR, or SD (DCR = bOR + SD) during the follow-up period.
- **TTNT** was defined as the time from the index date to initiation of the next line of therapy.
- **EFS** was defined as the time between the index date until one of the following events occurs, whichever comes first: (1) disease progression during therapy (PD); (2) institution of any additional unplanned anti-tumor treatment; (3) relapse after achievement of CR or PR; (4) death due to any cause.
- **PFS** was defined as the time between the index date until disease progression during therapy (PD) or death.

Numerator: Number of patients with objective response (CR or PR) between index date (start of treatment) and death, NALT, or end of observation period, whatever comes first.

Denominator: All patients in the FAS and PP populations. Patients with unknown response to therapy (e.g. no response assessment before lost to follow-up or death) were considered as non-responders. All efficacy outcome measures were descriptively analyzed. bOR, DCR, CR, PR, and SD rates were presented, along with their 95% CI limits, using Clopper-Pearson exact methods. The median and associated CI were calculated using the Kaplan-Meier method for DOR, OS, TTNT, EFS, and PFS endpoints. Censoring reasons were reported.

Sensitivity analysis for secondary endpoints
Secondary endpoints were defined as above, with one change:

- **Numerator:** Number of patients with objective response (CR or PR) between start of treatment and death, NALT, or end of observation period, whatever comes first.
- **Denominator:** All patients in the FAS and PP populations. Patients with unknown response to therapy were excluded from numerator and denominator. No sensitivity analysis was planned for DOR, OS, TTNT, EFS, and PFS endpoints.

Exploratory subgroup analyses
Analyses were performed in the overall population and per cohort.

Efficacy outcomes (bOR, DCR, PFS, OS, DOR, EFS, and TNTT) were evaluated in patients' subgroups:

- Primary refractory/non–primary refractory disease;
- Eastern Cooperative Oncology Group performance status (<2 *vs*. ≥2);
- International Prognostic Index score at baseline (<3 *vs*. ≥3);
- Germinal center B-cell–like subtype (GC) and non-GC patients;
- Type of response: CR, PR, no response.

DOR, OS, and PFS was also analyzed according to the best response experienced during the study (CR or PR).

Calculation of the duration of follow-up
Duration of follow-up was defined as death or last contact – date of treatment initiation (months).

Tables

Online Supplementary Table S1. Participating sites.

Type of site	Sites	Investigator					Total number of patients enrolled
		Title	Last name	First name	Department	Town	
Clinic	Clinique Sainte Anne	Dr	Maloisel	Frédéric	Oncology	Strasbourg	11
CLCC	ICANS Strasbourg	Pr	Fornecker	Luc-Matthieu	Haematology	Strasbourg	11
CHU	AP-HP Hopital Avicenne	Pr	Braun	Thorsten	Clinical Haematology	Bobigny	8
CHU	Hopital Robert Debre	Dr	Durot	Eric	Haematology	Reims	9
CHU	CHU Brest Hopital Morvan	Dr	Tempescul	Adrian	Haematology	Brest	8
CH	CH Bretagne Atlantique	Dr	Cherel	Brieuc	Haematology	Vannes	7
CH	CH Laval	Dr	Agape	Philippe	Haematology	Laval	5
CHU	CHU Caen	Dr	Delapierre	Baptiste	Haematology	Caen	6
CH	CH Des Pays de Morlaix	Dr	Nicol	Christophe	Haematology	Morlaix	4
CH	CH Michel Mazeas	Dr	Le Bris	Anne-Sophie	Medicine 2	Douarnenez	3
CH	CH Saint Nazaire	Dr	Lestang	Elsa	Haematology	Saint Nazaire	5
CHU	CHU Lille	Dr	Escurre	Guillaume	Haematology	Lille	5
CLCC	Institut Paoli Calmettes	Dr	Brisou	Gabriel	Haematology	Marseille	26
CHU	AP-HM Hopital la Conception	Dr	Ivanov	Vadim	Haematology	Marseille	8
CLCC	Centre Leon Berard	Dr	Lebras	Laure	Haematology	Lyon	6
CLCC	Centre Antoine Lacassagne	Dr	Gastaud	Lauris	Oncology Haematology	Nice	10
CH	CH Perpignan	Dr	Serrier	Caroline	Haematology	Perpignan	7
CHU	CHU Clermont Ferrand	Pr	Tournilhac	Olivier	Cellular therapy & Clinical Haematology	Clermont-Ferrand	6
Clinic	Clinique du Parc Castelnau	Dr	Delage	Jeremy	Haematology	Castelnau Le Lez	7
CHU	Institut Lucien Neuwirth	Dr	Fouillet	Ludovic	Haematology	Saint Priest En Jarez	4
Clinic	Clinique Saint Georges	Dr	Cassuto	Ophelie	Oncology	Nice	2
CH	CH Vichy	Dr	Levy	Anthony	Haematology	Vichy	3

Type of site	Sites	Investigator					Total number of patients enrolled
		Title	Last name	First name	Department	Town	
CH	CH Cote Basque	Dr	Bernard	Sophie	Haematology	Bayonne	11
CH	CH Blois	Dr	El Yamani	Abderrazak	Clinical Haematology	Blois	6
CH	CH Brive	Dr	Villesuzanne	Camille	Oncology Haematology	Brive La Gaillarde	5
CH	CH Niort	Dr	Olivier	Gaëlle	Haematology	Niort	4
CHU	CHU Montpellier	Pr	Herbaux	Charles	Haematology	Montpellier	8
CHU	CHU Angers	Dr	Paillassa	Jerome	Haematology	Angers	6

CH: hospital center; CHU: university hospital center; CLCC: Centre de Lutte Contre le Cancer (Cancer Research Centers).

Online Supplementary Table S2. Treatment outcomes for the 13 patients who received CAR-T cell therapy before tafasitamab-lenalidomide combination (PP set)

Endpoints		N	% (95% CI)
bOR		**9**	30.8 (9.09-61.43)
	CR	2	15.4 (1.92-45.45)
	PR	2	15.4 (1.92-45.45)
	SD	0	NA
	PD	5	38.5 (13.86-68.42)
DOR		**4**	**%**
Censored reasons	Death after PR (event)	1	25.0
	PD after PR (event)	2	50.0
	Alive after CR (censored)	1	25.0
OS		**13**	**%**
	Death (event)	10	76.9
PFS		**13**	**%**
	Death (event)	5	38.5
	PD (event)	7	53.8
	Alive (censored)	1	7.7

bOR: best objective response; CAR-T: chimeric antigen receptor T-cell therapy; CI: confidence interval; CR: complete response; NA, not applicable; OS: overall survival; PD: progressive disease; PP: per protocol; PFS: progression-free survival; PR: partial response; SD: stable disease.

Online Supplementary Table S3a. Patients having received treatments post tafasitamab-lenalidomide (PP set, N=186).

Treatments post tafasitamab-lenalidomide		**N (%)**
Did the patient receive a treatment line after tafasitamab-lenalidomide?	No	119 (64)
	Yes	67 (36)
Number of treatment lines	1	45 (67.2)
	2	19 (28.4)
	3	3 (4.5)
Bridge	No	65 (97)
	Yes	2 (3)

PP: per protocol.

Online Supplementary Table S3b. Details of the treatments post tafasitamab-lenalidomide. A total of 67 patients received post tafasitamab-lenalidomide treatments. Forty-five patients received 1 line post tafasitamab-lenalidomide, 19 patients received 2 lines post tafasitamab-lenalidomide, and 3 patients received 3 lines post tafasitamab-lenalidomide. The details of the post tafasitamab-lenalidomide received are provided for each group of patients (based on the total number of lines received post tafasitamab-lenalidomide) and in sequential order. The 3rd line of treatment category includes patients of the 2L cohort who received a post tafasitamab-lenalidomide treatment. These patients may have received 1 to 3 lines post tafasitamab-lenalidomide.

Post tafasitamab-lenalidomide treatments according to the line		**1L (N=45)**	**2L (N=19)**	**3L (N=3)**	**Total (N=67)**
3L	**N**	**22**	**13**	**2**	**37**
	Bispecific ± chemotherapy	2 (9.1%)	0 (0.0%)	0 (0.0%)	2 (5.4%)
	CAR-T–like regimen	3 (13.6%)	1 (7.7%)	0 (0.0%)	4 (10.8%)
	Platinum-based regimen	2 (9.1%)	1 (7.7%)	0 (0.0%)	3 (8.1%)
	R and/or non-curative chemo	14 (63.6%)	10 (76.9%)	2 (100%)	26 (70.3%)
	R-mini-CHOP–like regimen	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (2.7%)
	Other	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Duration* (months)	Mean ± SD	3.94 ± 3.45	3.89 ± 2.25	4.40 ± 2.26	3.95 ± 2.97
	Median	2.60	3.40	4.40	3.20
	Q1, Q3	2.00, 5.00	2.80, 4.40	2.80, 6.00	2.20, 5.00
	Min, Max	0.2, 16.2	1, 10	2.8, 6	0.2, 16.2
4L	**N**	**17**	**17**	**3**	**37**
	Bispecific ± chemotherapy	4 (23.5%)	1 (5.9%)	0 (0.0%)	5 (13.5%)
	CAR-T–like regimen	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (2.7%)
	Platinum-based regimen	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (5.4%)
	R and/or non-curative chemo	8 (47.1%)	12 (70.6%)	3 (100.0%)	23 (62.2%)
	Other	3 (17.6%)	3 (17.6%)	0 (0.0%)	6 (16.2%)
Duration** (months)	Median	1.60	4.00	2.60	2.40
	Mean ± SD	2.08 ± 1.95	4.02 ± 2.54	2.47 ± 0.61	3.01 ± 2.34
	Q1, Q3	0.60, 3.20	2.00, 5.60	1.80, 3.00	1.40, 4.40
	Min, Max	0, 6.8	0.4, 9.2	1.8, 3	0, 9.2
5L	**N**	**6**	**6**	**3**	**15**
	Bispecific ± chemotherapy	2 (33.3%)	4 (66.7%)	0 (0.0%)	6 (40%)
	CAR-T–like regimen	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
	Platinum-based regimen	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (6.7%)
	R and/or non-curative chemo	1 (16.7%)	1 (16.7%)	1 (33.3%)	3 (20%)
	Other	2 (33.3%)	1 (16.7%)	1 (33.3%)	4 (26.7%)
Duration*** (months)	Median	5.60	2.10	1.80	2.20
	Mean ± SD	6.00 ± 4.35	3.77 ± 4.93	1.67 ± 0.42	4.24 ± 4.28
	Q1, Q3	2.40, 8.60	1.20, 3.40	1.20, 2.00	1.20, 7.60
	Min, Max	1.2, 12.6	0.2, 13.6	1.2, 2	0.2, 13.6
6L	**N**	**-**	**2**	**1**	**3**
	Anthracyclin-like regimen	-	0 (0.0%)	1 (100.0%)	1 (33.3%)
	R and/or non-curative chemo	-	1 (50.0%)	0 (0.0%)	1 (33.3%)
	Other	-	1 (50.0%)	0 (0.0%)	1 (33.3%)
Duration† (months)	Median	-	0.20	0.00	0.00

*Death or last news or period between 4th line initiation - 3rd line initiation. **Death or last news or period between 5th line initiation – 4th line initiation. ***Death or last news or period between 6th line initiation – 5th line initiation. †Death or last news – 6th-line initiation. CAR-T: chimeric antigen receptor T-cell therapy; Chemo: chemotherapy; L: line; Max: maximum; Min: minimum; Q: interquartile; R: rituximab; R-mini-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; SD: standard deviation.

Online Supplementary Table S4. Demographic and baseline clinical and disease characteristics of patients with CR as bOR (N=54) (PP set).

Characteristic	2L cohort (N=32)	3L + 4L cohort (N=22)	Total (N=54)
Sex, n (%)			
Female	12 (37.5)	11 (50.0)	23 (42.6)
Age at tafasitamab initiation (years)			
Median	81.0	74.0	79.0
Min ; max	56 ; 89	32 ; 87	32 ; 89
>70 years, n (%)	30 (93.8)	16 (72.7)	46 (85.2)
Number of cycles to achieve best response	4.0	4.0	4.0
Time to achieve CR as best response (weeks)	15.1	15.4	15.3
ECOG PS, n (%)			
<2	26 (81.3)	19 (86.4)	45 (83.3)
≥2	6 (18.8)	3 (13.6)	9 (16.7)
IPI, n (%)			
<3	11 (34.4)	9 (40.9)	20 (37.0)
≥3	21 (65.6)	13 (59.1)	34 (63.0)
Histology, n (%)			
DLBCL NOS	19 (59.4)	11 (50.0)	30 (55.6)
GCB-DLBCL	9 (56.3)	3 (33.3)	12 (48.0)
Non–GCB-DLBCL	7 (43.8)	6 (66.7)	13 (52.0)
Missing	3 (15.8)	2 (18.2)	5 (16.7)
Transformed indolent DLBCL	8 (25.0)	2 (9.1)	10 (18.5)
THRLBCL	1 (3.1)	3 (13.6)	4 (7.4)
HGBCL	4 (12.5)	6 (27.3)	10 (18.5)
Double/triple hit, n (%)			
Yes	3 (16.6)	1 (7.1)	4 (12.5)
No	15 (83.3)	13 (92.9)	28 (87.5)
Missing	14 (43.8)	8 (36.4)	22 (40.7)
Refractory/relapsed, n (%)			
Primary refractory disease + early relapse	21 (65.6)	15 (68.2)	36 (66.7)
Primary refractory* (<6 months)	16 (76.2)	14 (93.3)	30 (83.3)
Early relapse (6-12 months)	5 (23.8)	1 (6.7)	6 (16.7)
Late relapse (≥12 months)	11 (34.4)	7 (31.8)	18 (33.3)
Refractory to last therapy	19 (59.4)	16 (72.7)	35 (64.8)
Prior CAR-T, n (%)	0	2 (9.1)	2 (3.7)
Prior systemic therapy, n (%)			
Anthracycline-containing regimen	14 (43.8)	16 (72.7)	30 (55.6)
R-mini-CHOP–like regimen	14 (43.8)	3 (13.6)	17 (31.5)
R and/or non-curative chemotherapy	2 (6.3)	1 (4.5)	3 (5.6)
Platinum-based regimen	2 (6.3)	2 (9.1)	4 (7.4)
Other	0	0	0

2L: second line; 3L: third line; 4L: fourth line; bOR: best objective response; CAR-T: chimeric antigen receptor T-cell therapy; CR: complete response; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; GCB: germinal center B-cell; HGBCL: high-grade B-cell lymphoma; IPI: International Prognostic Index; max: maximum; min: minimum; NOS: not otherwise specified; PP: per protocol; Anthracycline-containing regimen: R-CHOP/R-CHOP–like; R: rituximab; R-mini-CHOP: attenuated immunochemotherapy regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; THRLBCL: T-cell/histiocyte-rich large B-cell lymphoma.

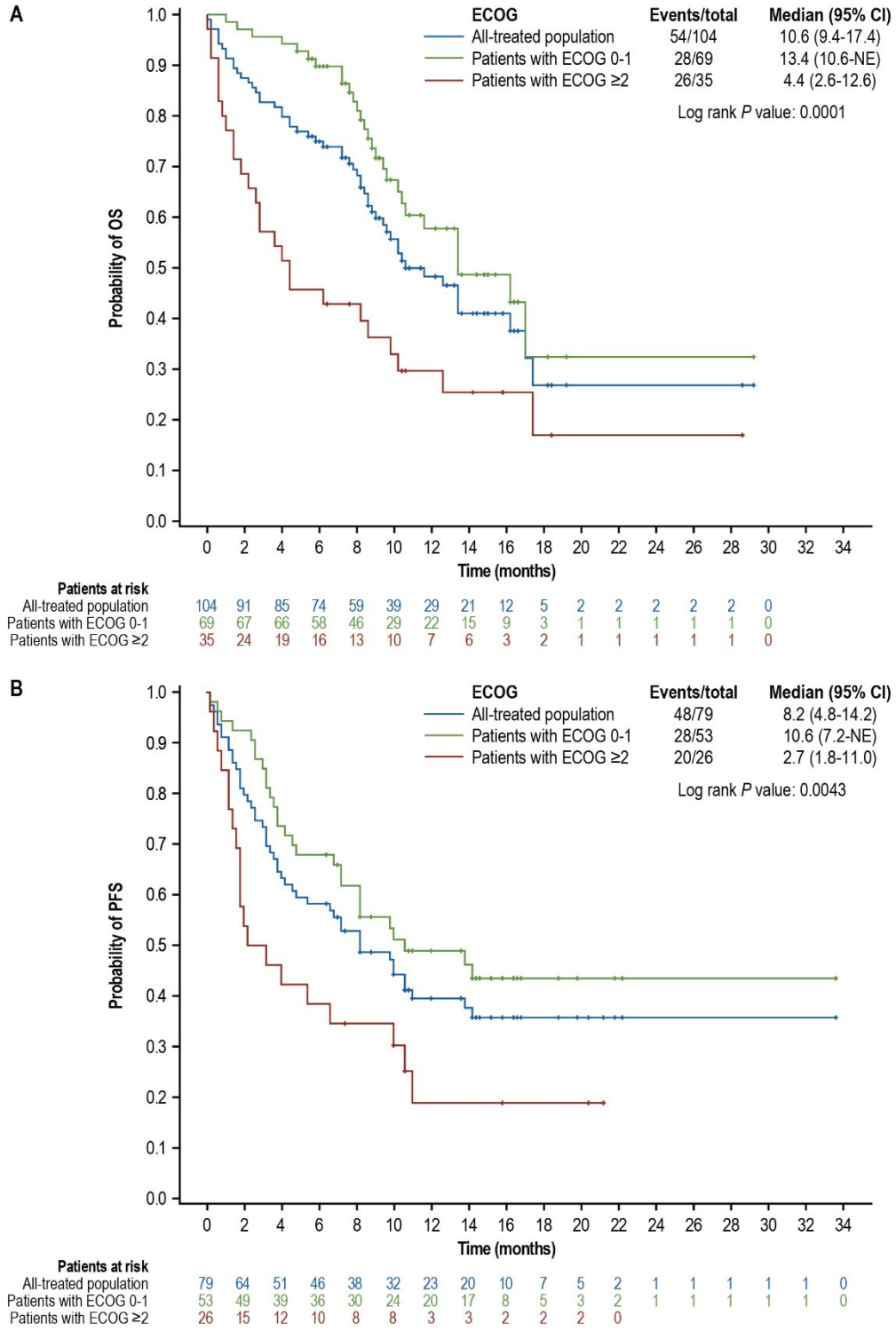
Online Supplementary Table S5. Reasons for EarlyMIND patients ineligibility to L-MIND (n=160)

Reasons for L-MIND ineligibility	**N (%)**
Primary refractory DLBCL according to the definition of the L-MIND protocol*	114 (71.25)
Yes	112
Missing	2
History of DHL/THL	39 (24.37)
DHL	5
THL	2
Unknown	32
ECOG	29 (18.12)
>2	26
Missing	3

*Defined as a disease progressing in the course of the 1st line treatment as per International Working Group response criteria (Cheson et al., 2007), and/or, showing a response of less than a PR to 1st line treatment or disease recurrence/progression within <6 months from the completion of first-line therapy. DHL: double hit lymphoma; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; PR: partial response; THL: triple hit lymphoma.

Figures

Online Supplementary Figure S1. Kaplan-Meier curves illustrating overall survival observed for patients in the (A) 2L cohort (N=104) and (B) 3L + 4L cohort (N=79), and their respective subsets, based on ECOG PS score. Tick marks indicate censored patients. Log-rank P-values represent ECOG 0-1 compared to ECOG ≥2. 2L: second line; 3L: third line; 4L: fourth line; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; NE: not evaluable; PFS, progression-free survival; OS, overall survival.



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