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► To cite this version:

Gilles Salles, Johannes Duell, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, et al.. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncology*, 2020, 21 (7), pp.978-988. 10.1016/S1470-2045(20)30225-4 . hal-02935846

HAL Id: hal-02935846

<https://hal.science/hal-02935846>

Submitted on 22 Aug 2022

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A prospective phase II multicentre study of tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma

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1 **Summary**

2 **Background**

3 Patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) ineligible for
4 autologous stem-cell transplantation (ASCT) have poor outcomes and limited treatment options.
5 Tafasitamab (MOR208) is an Fc-enhanced humanised anti-CD19 monoclonal antibody that
6 showed preclinical and single-agent activity in patients with relapsed or refractory B-cell
7 malignancies. Preclinical data suggested that tafasitamab may act synergistically with
8 lenalidomide. This study aimed to assess the antitumour activity and safety of tafasitamab plus
9 lenalidomide in patients with relapsed or refractory DLBCL ineligible for ASCT.

10 **Methods**

11 In this open-label, single-arm, multicentre, phase 2 study (L-MIND; NCT02399085), patients
12 (>18 years) with histologically confirmed DLBCL, who relapsed or were refractory after 1–3
13 systemic regimens (with at least one anti-CD20 therapy), and not candidates for high-dose
14 chemotherapy and subsequent ASCT, Eastern Cooperative Oncology Group performance
15 status of 0–2, and had measurable disease at baseline were recruited from 35 centres in 10
16 countries. Patients received co-administered tafasitamab (12 mg/kg) and lenalidomide (25
17 mg/day) intravenously for up to 12 cycles (28 days each), followed by tafasitamab monotherapy
18 (in patients with stable disease or better) until disease progression. The primary endpoint was
19 objective response rate (centrally assessed). Efficacy analyses are based on all patients who
20 received at least one dose of both tafasitamab and lenalidomide; safety analyses were based
21 on those who received at least one dose of either study medication. Recruitment is complete,
22 and the trial is in follow-up.

23 **Findings**

24 Between January 18, 2016 and November 15, 2017, 156 patients were screened; 81 were
25 enrolled and received at least one dose of either study medication, and 80 received at least one
26 dose of both tafasitamab and lenalidomide. Median follow-up was 13.2 months (IQR, 7.3–20.4)
27 as of data cut-off November 30, 2018. The objective response rate was 60% (95% confidence
28 interval [CI], 48–71); 34/80 (43%; 95% CI, 32–54) had a complete response and 14/80 (18%;
29 95% CI, 10–28) had a partial response. The most common treatment-emergent adverse event
30 grade 3 or higher were neutropenia (39/81 [48%]), thrombocytopenia (14/81 [17%]), febrile
31 neutropenia (10/81 [12%]). Adverse events reduced in frequency and severity during the
32 tafasitamab monotherapy phase compared with the lenalidomide combination phase. Serious
33 adverse events (SAEs) occurred in 41/81 (51%) patients. The most frequently reported SAEs (in
34 ≥ 2 patients) were pneumonia (five [6%]), febrile neutropenia (five [6%]), pulmonary embolism
35 (three [4%]), bronchitis (two [3%]), atrial fibrillation (two [3%]), and congestive cardiac failure
36 (two [3%]).

37 **Interpretation**

38 Tafasitamab in combination with lenalidomide was well tolerated and resulted in high complete
39 response rates in patients with relapsed or refractory DLBCL ineligible for ASCT, and may
40 represent a new therapeutic option in this setting.

41 **Funding**

42 Funded by MorphoSys AG; L-MIND ClinicalTrials.gov number NCT02399085

43 **Word count: 436/300**

44

45 **Research in context**

46 **Evidence before this study**

47 With the aim of gaining a greater understanding of the current treatment landscape for diffuse
48 large B-cell lymphoma (DLBCL), we searched PubMed for reports published in English from Jan
49 1, 2017, to Dec 31, 2019, using the terms “treatment guidelines” AND (“recurrent” OR “relapsed”
50 OR “previously treated”) AND (“diffuse large B-cell lymphoma” OR “diffuse large B cell
51 lymphoma” or “DLBCL”). Current treatment options for patients with relapsed or refractory
52 diffuse large B-cell lymphoma (DLBCL) are usually some form of platinum-based salvage
53 chemotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation
54 (ASCT), which many patients are ineligible for due to comorbid conditions and/or age. Such
55 therapies are associated with significant toxicities. There is no standard of care for patients with
56 relapsed or refractory DLBCL who are ineligible for high-dose chemotherapy and ASCT,
57 representing an unmet medical need. Novel therapeutic approaches are being developed to
58 address this.

59 We also searched PubMed for reports published in English from Jan 1, 2017, to Dec 31, 2019,
60 using the terms “antibody” AND (“recurrent” OR “relapsed” OR “previously treated”) AND (“B
61 cell” OR “B-cell”) AND “lymphoma”. We did similar searches in PubMed, adding the terms,
62 (“CD19” OR “CD-19”) OR (“anti-CD19” OR “anti CD-19”) OR (“diffuse large B-cell lymphoma”
63 OR “diffuse large B cell lymphoma” or “DLBCL”). The CD19 antigen, which is expressed broadly
64 across the B-cell lineage and in virtually all types of DLBCL, is as an important therapeutic
65 target of interest as evidenced by the recent emergence and regulatory approval of CD19-
66 directed chimeric antigen receptor (CAR)-T therapies. Prior approaches with CD19-directed
67 antibodies (either naked antibody or antibody–drug conjugate) were not successful due to
68 insufficient activity and associated toxicities.^{1–4}

69 Tafasitamab (MOR208), an Fc-enhanced (increased affinity for Fc gamma receptors through
70 the introduction of two amino acid modifications within the Fc region), humanised anti-CD19
71 monoclonal antibody in combination with the immunomodulatory agent lenalidomide led to

72 increased antitumour effects, both in vitro and in vivo. The combination has potential for a
73 synergistic activity in the treatment of DLBCL.

74 **Added value of this study**

75 In a patient population with high median age, eventually carrying multiple comorbidities and
76 ineligible for high-dose chemotherapy or ASCT, tafasitamab in combination with lenalidomide
77 followed by tafasitamab until progression, was well tolerated and demonstrated promising
78 clinical activity. Durable responses with prolonged overall survival were observed in a significant
79 proportion of patients, including those who were refractory to their prior therapies, such as
80 CD20-directed immunochemotherapy.

81 **Implications of the available evidence**

82 The CD19 CAR-T therapies were recently approved in patients who have failed two or more
83 prior systemic therapies. However, they have important limitations preventing a broad
84 application: those are associated with manufacturing challenges, high cost of delivery,
85 significant toxicities, and need for patient referral to specialised treatment centres. Polatuzumab
86 in combination with bendamustine and rituximab represents another recently approved option
87 providing an encouraging progression-free survival, but associated with several hematological
88 toxicities.

89 Tafasitamab in combination with lenalidomide is a novel approach that may offer a potentially
90 effective, well-tolerated, immunomodulatory treatment option for patients with relapsed or
91 refractory DLBCL ineligible for salvage chemotherapy followed by HDC and ASCT.

92

93

94 INTRODUCTION

95 Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's
96 lymphoma.⁵ Since the introduction of the anti-CD20 antibody rituximab, approximately 50–70%
97 of patients may achieve cure with initial standard-of-care immunochemotherapy.⁶ For patients
98 who are refractory to or relapse after frontline therapy, prognosis is poor.⁷ Salvage
99 chemotherapy followed by high-dose chemotherapy (HDC) and autologous stem-cell
100 transplantation (ASCT) has limited benefit in this setting and is associated with significant
101 toxicities.⁸ Moreover, most patients are ineligible for this approach and have even fewer
102 treatment options.⁷ Recent therapeutic advances, such as chimeric antigen receptor (CAR) T-
103 cell therapy and the antibody–drug conjugate polatuzumab vedotin, have the potential to
104 improve patient outcomes.^{9–11} Despite these advances, there remains a significant need to
105 provide effective and tolerable treatment options for patients with relapsed or refractory DLBCL,
106 in particular those ineligible for ASCT.¹²

107 CD19 is broadly and homogeneously expressed across B-cell malignancies, and enhances B-
108 cell receptor signaling and tumour cell proliferation.^{13,14} Tafasitamab (MOR208, previously
109 XmAb5574) is an Fc-enhanced (increased affinity for Fc gamma receptors through the
110 introduction of two amino acid modifications within the Fc region),¹⁵ humanised anti-CD19
111 monoclonal antibody, which mediates antibody-dependent cellular cytotoxicity and antibody-
112 dependent cellular phagocytosis, and exerts direct cytotoxicity.^{15,16} Preclinical studies have
113 shown potent in vitro and in vivo activity of tafasitamab in lymphoma and leukemia models.^{15,16}
114 Single-agent tafasitamab was well tolerated and demonstrated encouraging activity in patients
115 with relapsed or refractory B-cell malignancies, with several patients achieving durable
116 responses.¹⁷ Lenalidomide has direct anti-neoplastic activity, and stimulates natural killer (NK)-
117 cell proliferation and activation.¹⁸ In addition, lenalidomide enhances NK cell-mediated,
118 antibody-dependent cellular cytotoxicity with tafasitamab in vitro.¹⁶ When considering the

119 outcomes of single-agent lenalidomide and tafasitamab in patients with relapsed or refractory
120 DLBCL, we hypothesize that the combination of these two drugs has synergistic potential.^{17,19,20}

121 Here, we report the results of the primary analysis of the phase 2 L-MIND study of tafasitamab
122 in combination with lenalidomide in patients with relapsed or refractory DLBCL ineligible for
123 ASCT.

124 **METHODS**

125 **STUDY DESIGN AND PARTICIPANTS**

126 This study was approved by study sites' institutional review boards and conducted in
127 accordance with the International Conference on Harmonisation Good Clinical Practice
128 guidelines and the Declaration of Helsinki. All patients provided written informed consent.

129 Employees of MorphoSys AG designed this study. All authors interpreted the results and agree
130 on accountability for all study aspects, including accuracy, integrity, and protocol adherence. All
131 authors contributed to study design or conduct, data analyses, or manuscript writing.

132 This open-label, single-arm, multicentre, phase 2 study enrolled patients from 35 sites
133 (appendix page 2) in ten countries. Follow-up to assess safety, duration of response, and
134 survival is ongoing.

135 Patients (>18 years) with histologically confirmed DLBCL (including transformed indolent
136 lymphoma with a subsequent DLBCL relapse); who relapsed after or were refractory to at least
137 one, but no more than three systemic regimens (with at least one anti-CD20 therapy); and who
138 were not candidates for high-dose chemotherapy and subsequent ASCT were eligible.

139 Relapsed disease was defined as the appearance of any new lesions or increase by $\geq 50\%$ of
140 previously involved sites from nadir, according to the International Working Group response
141 criteria, after the most recent systemic therapy. Refractory disease was defined as progression,

142 as per International Working Group response criteria, and/or, showing a response of less than a
143 partial response (PR) or disease recurrence/progression within <6 months from the completion
144 of first-line therapy, or less than a PR to the most recently administered systemic therapy.
145 Those considered ineligible for high-dose chemotherapy and subsequent ASCT included:
146 patients of high age (>70 years), patients with organ dysfunction or comorbidities precluding the
147 use of high-dose chemotherapy/ASCT on the basis of unacceptable risk of treatment, patients
148 who had failed prior ASCT, patients who did not respond to salvage therapy, patients who
149 refused ASCT, or patients who were unable to receive ASCT due to an inability to successfully
150 collect peripheral blood stem-cells. Additional inclusion criteria were adequate organ function,
151 Eastern Cooperative Oncology Group performance status of 0–2, and measurable disease at
152 baseline. Patients must also have had: an absolute neutrophil count $\geq 1.5 \times 10^9/L$ (unless
153 secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow
154 aspiration and bone marrow biopsy); a platelet count of $\geq 90 \times 10^9/L$ (unless secondary to bone
155 marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone
156 marrow biopsy); a total serum bilirubin $\leq 2.5 \times$ upper limit of normal (ULN) unless secondary to
157 Gilbert's syndrome or documented liver involvement by lymphoma (patients with Gilbert's
158 syndrome or documented liver involvement by lymphoma may be included if their total bilirubin
159 was $\leq 5 \times$ ULN); an alanine transaminase, aspartate aminotransferase and alkaline phosphatase
160 $\leq 3 \times$ ULN or $< 5 \times$ ULN in cases of documented liver involvement; a serum creatinine clearance
161 of ≥ 60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula.
162 Exclusion criteria included any other histological type of lymphoma; a history of 'double/triple-hit'
163 DLBCL if already known; prior treatment with anti-CD19 therapy or immunomodulatory drugs
164 such as thalidomide or lenalidomide; or primary refractory DLBCL, defined as no response to, or
165 progression during or within 6 months of frontline therapy; prior history of malignancies other
166 than DLBCL, unless disease-free for ≥ 5 years; seropositivity for hepatitis B and/or C, and
167 seropositivity for or history of HIV; central nervous system (CNS) lymphoma involvement;

168 history or evidence of clinically significant cardiovascular, CNS and/or other systemic disease
169 that would preclude or compromise study participation. Prior to a protocol amendment
170 (introduced in June 2016), only patients who relapsed within 3 months of a prior anti-CD20-
171 containing regimen were defined as primary refractory and excluded.²¹ Thus, patients having
172 relapsed or progressed between 3 and 6 months of frontline therapy were recruited before the
173 protocol amendment, and considered as primary-refractory patients as per B-cell lymphoma
174 National Comprehensive Cancer Network guidelines.²² Central pathology review
175 (immunohistochemistry [Hans' algorithm] and gene expression profiling [NanoString]) were
176 performed retrospectively.

177 **PROCEDURES**

178 Treatment comprised co-administration of tafasitamab and lenalidomide for up to 12 cycles (28
179 days each), followed by tafasitamab monotherapy (in patients with stable disease or better) until
180 disease progression. Tafasitamab was administered intravenously at a dose of 12 mg/kg, over
181 approximately 2 hours. For cycles 1–3, tafasitamab was administered weekly on days 1, 8, 15,
182 and 22; an additional loading dose was administered on day 4 of cycle 1. From cycle 4,
183 tafasitamab was administered every 14 days,¹⁷ on days 1 and 15 of each cycle. Premedication
184 (as prophylaxis for infusion-related reactions for tafasitamab) comprised of antipyretics,
185 histamine (H1 and H2) blockers, glucocorticoids and meperidine. Tafasitamab was interrupted
186 for any grade 2–4 infusion-related reactions or other protocol-defined toxicities. Patients
187 discontinued if they experienced a grade 4 infusion-related reaction. Patients self-administered
188 lenalidomide orally, starting with 25 mg daily on days 1–21 of each 28-day cycle. A stepwise
189 dose reduction (decrease by 5 mg/day in each step, only once per cycle, without re-escalation)
190 of lenalidomide was performed in cases of protocol-defined toxicities. Central laboratory
191 assessments were performed on day 1 (± 2 days) of all cycles up until cycle 24. Tumour
192 assessment was based on computerised tomography (CT) scans conducted after cycle 2, 4, 6,

193 9 and positron emission tomography (PET) which was mandatory at baseline and after cycle 12.
194 Patients could be withdrawn from the study due to adverse events, abnormal laboratory values,
195 abnormal test procedure results, protocol violation, patient withdrawal of consent, loss to follow-
196 up, administrative problems, radiologically confirmed disease progression, and withdrawal of a
197 patient at the specific request of the sponsor. All adverse events were recorded at each visit.

198 **OUTCOMES**

199 The primary endpoint was objective response rate, defined as complete response plus partial
200 response, as assessed by an independent review committee, according to the 2007
201 International Working Group response criteria for malignant lymphoma.²³ Secondary endpoints
202 included disease control rate (complete plus partial response plus stable disease), duration of
203 response (the time between the initial time point of complete or partial response and the first
204 date of recurrence of progressive disease), time to next treatment (the time from first dosing to
205 the institution of next therapy for any reason), progression-free survival (the time between first
206 dosing and lymphoma progression or death from any cause), overall survival (the time from first
207 dosing until the date of death from any cause), time to progression (the time from the day of
208 enrolment until documented lymphoma progression or death as a result of lymphoma), and
209 incidence and severity of adverse events, as well as immunogenicity (presence of anti-
210 tafasitamab antibodies), pharmacokinetics, B-, T-, and NK-cell measurements over time, and
211 exploratory and diagnostic biomarker analyses (including gene expression profiling for cell of
212 origin subtyping; CD19, CD20, BCL-2, and BCL-6 expression; CD16 expression on NK cells;
213 antibody-dependent cellular cytotoxicity capacity; and evaluation of adverse events and
214 objective response rate stratified by FcγRIIIa and FcγRIIIa polymorphism).

215 **STATISTICAL ANALYSIS**

216 Analysis of the primary endpoint occurred when all patients had completed a minimum of 12
217 months of follow-up. Efficacy analyses are based on the full analysis set comprising all patients
218 who received at least one dose of both tafasitamab and lenalidomide; safety analyses were
219 based on those who received at least one dose of either study medication. Patients without
220 adequate post-baseline assessment were considered as non-evaluable in the overall response
221 analysis. Earlier studies of tafasitamab and lenalidomide were used to calculate assumptions on
222 response rates for the purpose of sample size calculation.^{20,24} Sample size was determined
223 assuming that combination treatment could improve the objective response rate from 20%
224 (monotherapy) to 35% (combination therapy). Applying an exact binomial test with a two-sided
225 significance level of 5% and a power of 85%, the estimated sample size was 73 patients.
226 Assuming a drop-out rate of 10%, a total sample size of 80 patients was estimated. There was
227 no interim analysis. For both primary and secondary outcomes, descriptive statistics were used
228 to summarise response rates and safety. Progression-free survival, overall survival and duration
229 of response were analysed using the Kaplan-Meier method, and 95% CIs for the median
230 calculated accordingly. The median follow-up time for PFS and OS was calculated using the
231 reverse Kaplan-Meier method. Statistical analysis was performed using SAS® Software
232 version 9.4 or above (SAS Institute, Cary, NC). This study is registered with ClinicalTrials.gov,
233 number NCT02399085.

234 **ROLE OF THE FUNDING SOURCE**

235 The study sponsor participated in the study design, data collection, analysis, interpretation, and
236 writing of the report. All authors had full access to all study data and the corresponding author
237 had final responsibility for the decision to submit for publication.

238 RESULTS

239 The data cut-off for primary analysis was November 30, 2018. The median observed follow-up
240 was 13.2 months (interquartile range [IQR], 7.3–20.4) and minimum follow-up was 0.5 months.
241 Between January 18, 2016 and November 15, 2017, a total of 156 patients were screened; 81
242 were enrolled and received at least one dose of either study medication (and evaluated for
243 safety), and 80 received at least one dose of both tafasitamab and lenalidomide (evaluated for
244 efficacy; one patient who received tafasitamab only was excluded from the efficacy analysis;
245 figure 1). The most common reasons for screen failure (figure 1) were: 31/156 patients (20%)
246 failed to meet laboratory criteria; 13/156 (8%) did not have protocol-defined relapsed and/or
247 refractory disease or had an absence of measurable disease; and ten/156 (6%) had other
248 histological types of lymphoma, primary refractory DLBCL inconsistent with the protocol, or a
249 history of ‘double/triple-hit’ DLBCL. The median age of enrolled patients was 72 years (range,
250 41–86) and all patients received R-CHOP or equivalent anthracycline-containing
251 immunochemotherapy prior to study entry (table 1). Of note, 40/81 (49%) of patients had
252 received only one prior line of therapy, 15/81 (19%) had progressed during or within 6 months
253 after completion of their first line of therapy (thus classified as primary refractory) and 36/81
254 (44%) other patients were refractory to their last line of therapy (defined as lack of response or
255 progression within 6 months of the last treatment cycle for latter lines of therapy). Cell of origin
256 information was missing for 22/81 (27%) patients by Hans’ algorithm and was missing / not
257 evaluable for 49/81 patients (60%) by the NanoString method, due to insufficient tumour tissue.
258 Based on immunohistochemistry (Hans’ algorithm), 38/81 (47%) patients were categorised as
259 germinal centre B-cell-like (GCB), and 21/81 (26%) patients as non-GCB. By gene expression
260 profiling (NanoString method), 7/81 (9%) patients had GCB-DLBCL, 19/81 (24%) had ABC-
261 DLBCL and 6/81 (7%) had unclassified cell of origin.

262 In total, 30 (37%) patients successfully completed 12 cycles of tafasitamab and lenalidomide
263 therapy and 28 (35%) were receiving tafasitamab monotherapy at data cut-off. Lenalidomide
264 dose reductions are described in the supplementary appendix (appendix page 16).

265 The independent review committee-assessed objective response rate was 60% (95% CI, 48–
266 71), with 34/80 (43%; 95% CI, 32–54) patients achieving a complete response and 14/80 (18%;
267 95% CI, 10–28) patients achieving a partial response (table 2). The overall concordance
268 between centrally and investigator-assessed (appendix page 17) objective response rate was
269 88%. PET scans were performed in 30 of the 34 patients with a CT-assessed complete
270 response and confirmed those results in all 30 cases. For the remaining four cases with CT-
271 assessed complete response, a confirmatory PET scan was not available. A disease control
272 rate of 74% (95% CI, 63–83) was achieved in 59/80 patients. The median time to response
273 (partial or complete response) was 2 months (range 1·7–16·8).

274 Analysis of objective response rate by patient baseline characteristics indicated high and
275 consistent response rates across most subgroups (appendix page 9), including patients with
276 one prior line of therapy and patients with a history of 2 or more prior therapies (28/40, 70%
277 [95% CI, 54–83]; 20/40, 50% [34–66], respectively). Patients that were refractory to their last
278 therapy achieved approximately equivalent objective response rates when compared with
279 patients without refractoriness to their last therapy (21/35, 60% [42–76]; 27/45, 60% [44–74],
280 respectively). Additionally, patients with a history of primary refractory DLBCL achieved similar
281 objective response rates when compared with patients without non-primary refractory DLBCL
282 (9/15, 60% [32–84]; 39/65, 60% [47–72] respectively). Patients with a germinal center B-cell
283 (GCB) phenotype DLBCL achieved slightly lower objective response rates (18/37, 49% [32–66])
284 when compared with patients with a non-GCB phenotype DLBCL (15/21, 71% [48–89]).
285 Objective response rates by reasons for ASCT ineligibility are shown in the supplementary
286 appendix (appendix page 18). In addition, seven patients had DLBCL arising from a prior

287 indolent lymphoma. All of these patients responded to the tafasitamab + lenalidomide treatment
288 (two/81 patients [2%] had a complete response and five/81 had a partial response [6%]), and
289 the two patients who had a complete response as best response were still in remission at data
290 cut-off.

291 Of the 48/80 patients (60%) achieving a response, the median duration of response was 21·7
292 months (95% CI, 21·7 – not reached [NR]; event rate, 13/48 [27%]) and the 12-month duration
293 of response rate was 71·6% (95% CI, 55·1–82·9; figure 2A). Among patients achieving a
294 complete response (34/80 [42%]), the median duration of response was not reached (event
295 rate, 3/34 [9%]; figure 2B); the 12-month and 18-month duration of response rate was 93·2%
296 (95% CI, 75·4–98·3). For those patients achieving a partial response (14/80 [18%]), the median
297 duration of response was 4·4 months (95% CI, 2·0–9·1; event rate, 10/14 [71%]; figure 2B). A
298 subgroup analysis of the 12-month duration of response rate for important patient subgroups is
299 shown in the supplementary appendix (appendix page 10). Thirty-nine of 80 patients (49%)
300 experienced a PFS event (disease progression or death). Median progression-free survival was
301 12·1 months (95% CI, 5·7–NR; figure 2C). Median follow-up for PFS was 17·3 months (95% CI,
302 11·5–21·2). Patients free from progression at 12 months (50·2% [95% CI, 37·9–61·2]) are
303 estimated to remain progression-free at 18 months (45·8% [95% CI, 33·4–57·4]). Median
304 progression-free survival after discontinuation of lenalidomide was 12·7 months (95% CI, 2·3–
305 NR). Median time-to-progression was 16·2 months (95% CI, 7·4–NR; event rate, 35/80 [44%]).
306 Median time-to-next-treatment was 15·4 months (95% CI, 7·6–NR; event rate, 43/80 [54%]).
307 Twenty-nine of 80 patients (36%) died; median overall survival was not yet reached (median
308 follow-up was 19·6 months [95% CI, 15·3–21·9].; figure 2D); 73·7% (95% CI, 62·2–82·2) of
309 patients were alive at 12 months and 63·6% (95% CI, 50·9–73·7) of patients were alive at 18
310 months. Two patients from this study subsequently received consolidation with stem cell
311 transplant, one patient each with ASCT and allogeneic stem-cell transplantation, respectively.

312 One additional patient subsequently received CD19 CAR-T therapy after disease progression in
313 this study, achieved a complete response and was in remission at the time of this report.

314 Seven patients had a *c-MYC* translocation that was identified during central pathology review:
315 three achieved a complete response and one a partial response. Of these patients, one
316 presented with 'double-hit' and another with 'triple hit' translocations, achieving a partial
317 response (lasting 5·8 months) and a complete response (ongoing at 20·1 months), respectively.

318 The median duration of exposure to study treatment was 9·3 months (range 0·2–32·1); median
319 duration of exposure to combination treatment or lenalidomide was 6·2 months (range 0·1–
320 12·5) and to tafasitamab monotherapy (following discontinuation of lenalidomide) was 4·1
321 months (range 0·1–20·8). Ten/81 (12%) patients discontinued the study (during the combination
322 therapy) due to adverse events (figure 1).

323 Treatment-emergent adverse events of any grade occurred in 81 (100%) patients. The most
324 common adverse event (all grades) and the most common grade 3 or higher adverse event was
325 neutropaenia, occurring in 40/81 (49%) and 39/81 (48%) patients, respectively (table 3).

326 Neutropaenia was managed by granulocyte colony-stimulating factor in 36/81 (44%) patients,
327 and the majority (81% with grade 3/4 neutropaenia) recovered to baseline levels within 1 week.

328 The next most common grade 3 or higher events were thrombocytopenia (14/81 [17%]
329 patients), febrile neutropaenia (ten/81 [12%]), leukopenia (seven/81 [9%]), anaemia (six/81
330 [7%]), and pneumonia (five/81 [6%]; table 3; appendix page 19–21). The majority of non-
331 haematologic adverse events were grades 1 and 2; diarrhea was the most common, occurring
332 in 27/51 (33%) patients (nine/81 [11%] with grade 2 and one/81 [1%] with grade 3), and with a
333 median duration of 8 days. Twenty-nine/81 (36%) patients experienced different types of rash,
334 most of which were grade 2 or lower (appendix page 21): seven/81 (9%) patients experienced a
335 (non-serious) rash of grade 3, in three patients classified as allergic dermatitis, and in one

336 patient each as maculopapular rash, erythematous rash, pruritus, and psoriasis (appendix page
337 21). All of these patients with grade 3 rash recovered between 2 and 40 days after event onset,
338 but one patient with allergic dermatitis recovered with sequelae 45 days after event onset (both
339 study drugs were discontinued). In one patient with psoriasis, lenalidomide was discontinued
340 due to the event, and in two patients with allergic dermatitis, lenalidomide was temporarily
341 interrupted due to the event. Infusion-related reactions (all grade 1) were observed in five/81
342 (6%) patients. All occurred once during the first infusion and no discontinuation of infusion was
343 required.

344 Serious adverse events (SAEs) occurred in 41/81 (51%) patients. The most frequently reported
345 SAEs (in ≥ 2 patients) were pneumonia (five/81 [6%]), febrile neutropaenia (five/81 [6%]),
346 pulmonary embolism (three/81 [4%]), bronchitis (two/81 [3%]), atrial fibrillation (two/81 [3%]),
347 and congestive cardiac failure (two/81 [3%]). SAEs suspected to be treatment-related by the
348 investigators occurred in 15/81 (19%) patients; these were primarily infections (eight/81 [10%];
349 including bronchitis, pneumonia, cytomegalovirus infection, lower respiratory tract infection,
350 sepsis, respiratory syncytial virus infection, and urinary tract infection) or febrile neutropaenia
351 (four/81 [5%]). In addition, treatment-related SAEs included pulmonary embolism (two/81 [3%]),
352 and agranulocytosis, chronic obstructive pulmonary disease, fatigue, pyrexia, atrial fibrillation,
353 and tumour flare (one event each, 1/81 [1%]).

354 In total, 20/81 (25%) patients discontinued treatment with one or both study drugs due to
355 adverse events during the study (appendix page 22). Seven (9%) patients experienced an
356 adverse event of special interest (defined by the protocol): three with tumour flares (one each at
357 grades 1–3), one with grade 2 basal cell carcinoma, and three with grade 3 allergic dermatitis.

358 Thirty/81 (37%) deaths were recorded; eight occurred during study treatment and 22 post-
359 treatment. Twenty-three deaths were related to lymphoma progression and seven were

360 unrelated to disease progression. Treatment-emergent adverse events leading to death
361 occurred in four of 30 patients: sudden death, respiratory failure, cerebrovascular accident, and
362 worsening of progressive multifocal leukoencephalopathy (appendix page 8). The latter patient
363 had neurological symptoms prior to initiation of protocol treatment, and died 68 days after the
364 end of treatment. The investigators did not consider any of these four treatment-emergent
365 adverse events to be related to study treatment. Three of the 30 deaths, unrelated to disease
366 progression, occurred during the post-treatment period and were reported as intracerebral
367 haemorrhage, lung oedema due to cardiac failure, and pneumonia.

368 Upon discontinuation of lenalidomide (either cycle 13 onwards as per protocol or earlier in case
369 of toxicities), the incidence and severity of treatment-emergent adverse events decreased under
370 tafasitamab monotherapy; grade 3 or 4 neutropenia occurred in only 3/51 (6%) patients after
371 lenalidomide discontinuation during this phase (appendix page 11). In total, adverse events of
372 grade 3 or 4 were reported in 56/80 (70%) patients before lenalidomide discontinuation,
373 compared with 15/51 (29%) patients after lenalidomide discontinuation.

374 Levels of circulating B, T and NK cells were analysed from baseline until cycle 8, day 15
375 (appendix page 12–14): B cell numbers decreased rapidly at day 8 of cycle 1, T cell numbers
376 showed transient changes, and the numbers of NK cells were found to be higher in patients at
377 day 15 of cycle 8. In 32 patients with samples available both at baseline and cycle 8, day 15,
378 there was a slight increase in peripheral NK cell numbers, from 168 cells/ μ L (IQR, 59–237) at
379 baseline to 203 cells at cycle 8, day 15 (range, 121–547; appendix page 15).

380 In this study, tafasitamab demonstrated a pharmacokinetic profile consistent with earlier studies
381 (data not shown). No clinically relevant treatment-emergent immunogenicity was observed. Due
382 to limited sample availability, full assessment of exploratory and diagnostic biomarkers (CD19,
383 CD20, BCL-2, and BCL-6 expression, CD16 expression on NK cells, antibody-dependent

384 cellular cytotoxicity capacity) and evaluation of adverse events and objective response rate
385 stratified by FcγRIIIa and FcγRIIa polymorphism were incomplete and are not reported.

386 **DISCUSSION**

387 In this population of patients with relapsed or refractory DLBCL ineligible for stem-cell
388 transplantation, combination treatment with tafasitamab and lenalidomide elicited an overall
389 objective response in 60% of patients and a complete response in 43%. Furthermore, the
390 responses were durable, with a median duration of response of 21·7 months. Among patients
391 with a complete response, the 18-month duration of response rate was 93·2%. A high overall
392 response rate was observed in the subgroup of patients with one prior therapy. With a median
393 follow-up of 19·6 months, median overall survival had not yet been reached. In particular, 30/80
394 patients remain in remission at data cut-off for this report.

395 The population in this study was notable for being considered ineligible for ASCT and its older
396 age (median 72 years). This study also included a substantial proportion of patients belonging to
397 subgroups known for poor prognosis, in particular those refractory to prior therapies;
398 tafasitamab and lenalidomide had similar activity in patients with or without refractory disease,
399 whether refractory to their last prior therapy or to rituximab, or having a history of primary
400 refractory DLBCL. Encouraging responses were reported in patients with GCB DLBCL. Given
401 that single-agent lenalidomide is historically less active in the GCB subgroup,^{19,20,25} these results
402 suggest a greater activity and synergy of the tafasitamab-plus-lenalidomide combination,
403 irrespective of the cell of origin. However, a more complete interpretation is limited as cell of
404 origin was unknown for 27% of patients and gene expression profiling results were not
405 evaluable for 60% of patients, due to insufficient tumour tissue.

406 Based on their single-agent safety profiles, no new safety signals were identified for either agent
407 or the combination during this study.^{15,16,19,20,25–28} The study treatments were generally well

408 tolerated in this elderly and pretreated population. The majority of events were manageable;
409 neutropenia was common, although short in duration and responsive to supportive treatment.

410 Prior studies in similar patient populations have reported objective response rates of 25% for
411 ibrutinib monotherapy,²⁹ 28% for lenalidomide monotherapy,¹⁹ and 33% for lenalidomide plus
412 rituximab.²⁴ More recently, novel therapeutic options in patients with relapsed or refractory
413 DLBCL have been approved. Trials with CAR T therapies have reported objective response
414 rates of 52 to 82% but 89 to 95% of the patients experienced grade ≥ 3 adverse events.^{9,10} The
415 most common adverse event of any grade was cytokine release syndrome (58–93%). Access
416 and eligibility to CAR-T cell therapy remains a constraint for some patients.^{9,10} Polatuzumab
417 vedotin combined with bendamustine and rituximab demonstrated an objective response rate
418 (at end of treatment) of 45%, a complete response rate of 40%, and a median progression-free
419 survival of 9.5 months in 40 patients.¹¹ Median overall survival was reached at 12.4 months
420 (95% CI, 9.0–not evaluable) and only 7/40 patients (including one having received allogenic
421 stem-cell transplantation) remained disease-free at ~20 months.¹¹ In the polatuzumab
422 combination treatment arm, 33% of patients discontinued all treatment due to adverse events,
423 most commonly due to thrombocytopenia and neutropenia.¹¹

424 One of the limitations of this study is its open-label, single-arm phase 2 design, precluding
425 comparison of outcome measures with other existing therapeutic approaches or to single-agent
426 lenalidomide. Due to the small proportion of primary refractory (19%) and double/triple hit
427 lymphoma (3%) patients that were enrolled in this study, the results for these subgroups cannot
428 be extrapolated wider to these patient populations who usually experience a poor outcome to
429 routinely administered therapies. Also, approximately half of the patients received only one prior
430 therapy line and were considered by investigators as transplant ineligible; however, they may
431 have potentially been considered for ASCT, despite their older ages and underlying
432 comorbidities. Finally, response rates favouring the patient subgroup with low or low-

433 intermediate risk International Prognostic Index (IPI) score (0–2) indicates that the benefit of this
434 combination in patients with intermediate-high or high-risk IPI score (3–5) needs to be further
435 confirmed.

436 The L-MIND study indicates the benefit provided by the addition of tafasitamab to lenalidomide,
437 given that single-agent lenalidomide has demonstrated objective response rates ranging from
438 28% to 35% in patients with relapsed or refractory aggressive non-Hodgkin's lymphoma
439 (including DLBCL),^{19,20,26} and single-agent tafasitamab has demonstrated an objective response
440 rate of 26% in relapsed or refractory DLBCL.¹⁷ The greater activity in L-MIND is most likely
441 based on the complementary mechanism of action of both agents and lenalidomide-mediated
442 decreased activation threshold³⁰. The observed increase in NK-cell numbers during treatment
443 may also be a contributing factor behind this synergy. CD19 appears to be a useful alternative
444 target in patients who were not cured with prior anti-CD20-based immunochemotherapy, and a
445 randomised phase 2/3 study is ongoing to explore the combination of tafasitamab with
446 chemotherapy in patients previously exposed to rituximab (NCT02763319).

447 These trial data support the use of tafasitamab plus lenalidomide as an effective, well-tolerated,
448 immunomodulatory treatment option for treatment of patients with relapsed or refractory DLBCL
449 ineligible for ASCT.

450 CONTRIBUTORS

451 GS, JD, JW, MD-H, SA, and GF-R all contributed to data analysis and interpretation. All authors
452 contributed to data acquisition, manuscript development, and approval.

453 DECLARATION OF INTERESTS

454 This study was sponsored by MorphoSys AG. EGB reports receiving personal fees for
455 consultancy from Janssen, Gilead, Sandoz, Celltrion, Keona and Celgene, and honoraria from
456 Roche, Janssen, AbbVie and Takeda. GG reports receiving personal fees for advisory board
457 participation from AbbVie, Janssen, AstraZeneca and Sunesys, and for participation in a
458 speaker bureau from Janssen. GS reports receiving personal fees for consultancy from
459 Epizyme; advisory board participation from Amgen; advisory board participation or symposia
460 from MorphoSys, Amgen, Acerta, Autolus, BMS, Merck, AbbVie, Janssen, Novartis, Gilead/Kite,
461 Servier, Celgene, Roche, Pfizer and Takeda outside the submitted work; and has patent issued
462 (WO2012010561A1: characterisation of another anti-CD19 monoclonal antibody, having ADCC
463 function, and developed in collaboration with IDD-biotech; this antibody and the company has
464 no relationship with the anti-CD19 antibody described in the current paper (tafasitamab) and
465 has not been licensed to any third party. KM reports receiving personal fees for advisory board
466 participation from MorphoSys during the conduct of the study, and from Pharmacyclics, Teva,
467 AstraZeneca, Celgene and Seattle Genetics outside the submitted work. MD reports receiving
468 an institutional research grant from Celgene; personal fees for advisory board participation from
469 Celgene and MorphoSys and speaker fees from Celgene, all outside the submitted work. NK
470 reports receiving research funding from Celgene, outside the submitted work. OT reports
471 receiving personal fees from Roche, Gilead, AbbVie, Celgene, Janssen, Sandoz and Iquone,
472 and travel grants from Roche, Gilead, AbbVie, Celgene and Janssen outside the submitted
473 work. WJ reports receiving research funding from MorphoSys during the conduct of the study,

474 and Roche, Sandoz and Celltrion, outside the submitted work. JW, MDH, SA and GFR are
475 employees of MorphoSys AG, Planegg, Germany. All other authors declare no competing
476 interests. Disclosure forms provided by the authors are available with the full text of this article
477 at thelancet.com.

478 **DATA SHARING**

479 Additional documents and data sharing will be considered only for non-commercial use on a
480 case-by-case basis (to be approved by Morphosys AG;
481 Sumeet.Ambarkhane@morphosys.com), starting 12 months from acceptance of the manuscript
482 and until 36 months.

483

484 **ACKNOWLEDGMENTS**

485 We thank the patients and their families, clinical researchers, and their teams and hospitals that
486 have participated in this study. This study was sponsored by MorphoSys AG. Medical writing
487 assistance was provided by Ori Bowen, PhD of Syneos Health and funded by MorphoSys AG.

488

489

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577 **TABLES AND FIGURES**578 **Table 1.** Baseline characteristics

	Safety set (N=81)
Median age, years (range)	72 (41–86)
Sex, n (%)	
Male	44 (54)
Female	37 (46)
Race, n (%)	
Asian	2 (3)
White	72 (89)
Other	1 (1)
Missing	6 (7)
Median time since first DLBCL diagnosis, months (range)	26·9 (9–190)
Prior lines of systemic therapy, n (%)	
Median (range)	2 (1–4)
1	40 (50)
2	35 (43)
3	5 (6)
4	1 (1)
Prior anti-CD20 therapy	
Yes	81 (100)
No	0 (0)
Prior anthracycline	
Yes	81 (100)
No	0 (0)
Primary refractory, n (%)	
Yes	15 (19)
No	66 (81)
Rituximab refractory, n (%)	
Yes	34 (42)
No	46 (57)
Unknown	1 (1)
Refractory to last prior therapy, n (%)	
Yes	36 (44)
No	45 (56)
Prior ASCT, n (%)	
Yes	9 (11)
No	72 (89)

Ann Arbor stage at screening, n (%)	
I/II	20 (25)
III/IV	61 (75)
ECOG performance status, n (%)	
0	29 (36)
1	45 (56)
2	7 (9)
IPI score at screening, n (%)	
0–2 (low and low–intermediate risk)	40 (49)
3–5 (intermediate–high and high risk)	41 (51)
Bulky disease, [‡] n (%)	
Present	15 (19)
Absent	65 (80)
Missing	1 (1)
LDH levels at screening, n (%)	
Elevated	45 (56)
Within reference range	36 (44)
Cell of origin (by IHC), n (%)	
GCB	38 (47)
Non-GCB	21 (26)
Unknown	22 (27)
Patients with DLBCL arising from a prior indolent lymphoma, n (%)	7 (9)
Reasons ASCT ineligibility	
High age	37 (46)
Chemorefractory [§]	19 (23)
Refusal	13 (16)
Comorbidities	11 (14)
Other [¶]	1 (1)

579 [‡]Bulky disease is defined as having a longest lesion diameter of ≥ 7.5 cm (by central radiological
580 assessment). [§]Patients with failure to achieve a partial or complete response with salvage therapy or who
581 underwent ASCT before enrollment. ^{||}All patients who are not chemorefractory and who have
582 comorbidities (comorbidities are listed in appendix page 23). [¶]All patients not included in one of the two
583 previous categories. Other reasons include ‘Subject refusal of high-dose therapy/ASCT’ and ‘Other’
584 (inability to successfully collect stem cells).
585 ASCT=autologous stem-cell transplantation; DLBCL=diffuse large B-cell lymphoma; ECOG=Eastern
586 Cooperative Oncology Group; GCB=germinal center B cell; IHC=immunohistochemistry; IPI=International
587 Prognostic Index; LDH=lactate dehydrogenase; R-CHOP=rituximab, cyclophosphamide, doxorubicin
588 hydrochloride, vincristine, prednisone.

589 **Table 2.** Best objective response (per independent radiology/clinical review committee)

	Tafasitamab plus lenalidomide (N=80)[†]
Best objective response, n (%)	
CR	34 (43)
PR	14 (17)
SD	11 (14)
PD	13 (16)
NE*	8 (10)
PET-confirmed CR, n (%)	30/34 (88)
ORR (CR + PR), n (%) [95% CI]	48 (60%) [48–71]
DCR (CR + PR + SD), n (%) [95% CI]	59 (74%) [63–83]

590 *NE patients had no valid post-baseline response assessments. [†]One patient received tafasitamab only.

591 CI=confidence interval; CR=complete response; DCR=disease control rate; NE=not evaluable;

592 ORR=objective response rate; PD=progressive disease; PET=positron emission tomography; PR=partial
593 response; SD=stable disease.

594

595

596 **Table 3.** Treatment-emergent adverse events occurring in $\geq 10\%$ of patients or any grade 3/4/5
 597 treatment-emergent adverse event reported

Event (preferred term)	Grade 1/2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Hematologic events				
Neutropenia	1 (1)	22 (27)	17 (21)	0
Anemia	22 (27)	6 (7)	0	0
Thrombocytopenia	11 (14)	10 (12)	4 (5)	0
Leukopenia	5 (6)	6 (7)	1 (1)	0
Febrile neutropenia	0	8 (10)	2 (2)	0
Lymphopenia	2 (2)	2 (2)	1 (1)	0
Agranulocytosis	0	0	1 (1)	0
Non-hematologic events				
All rash*	22 (27)	7 (9)	0	0
Diarrhea	26 (32)	1 (1)	0	0
Asthenia	17 (21)	2 (2)	0	0
Cough	17 (21)	1 (1)	0	0
Peripheral edema	18 (22)	0	0	0
Pyrexia	16 (20)	1 (1)	0	0
Decreased appetite	16 (20)	0	0	0
Hypokalaemia	10 (12)	4 (5)	1 (1)	0
Back pain [†]	11 (14)	2 (2)	0	0
Fatigue	12 (15)	2 (2)	0	0
All urinary tract infection*	9 (11)	3 (4)	1 (1)	0
Constipation	13 (16)	0	0	0
Muscle spasms	12 (15)	0	0	0
Nausea	12 (15)	0	0	0
Bronchitis	10 (12)	0	1 (1)	0
Vomiting	11 (14)	0	0	0
Dyspnea	9 (11)	1 (1)	0	0
Abdominal pain	7 (9)	1 (1)	0	0
Upper respiratory tract infection	6 (7)	2 (2)	0	0
Hypertension	4 (5)	3 (4)	0	0
Increased blood creatinine [†]	5 (6)	1 (1)	0	0
Mucosal inflammation	5 (6)	1 (1)	0	0
Pneumonia	1 (1)	5 (6)	0	0
Hypocalcaemia	4 (5)	1 (1)	0	0
Hypogammaglobulinaemia	4 (5)	1 (1)	0	0
Increased gamma-	4 (5)	1 (1)	0	0

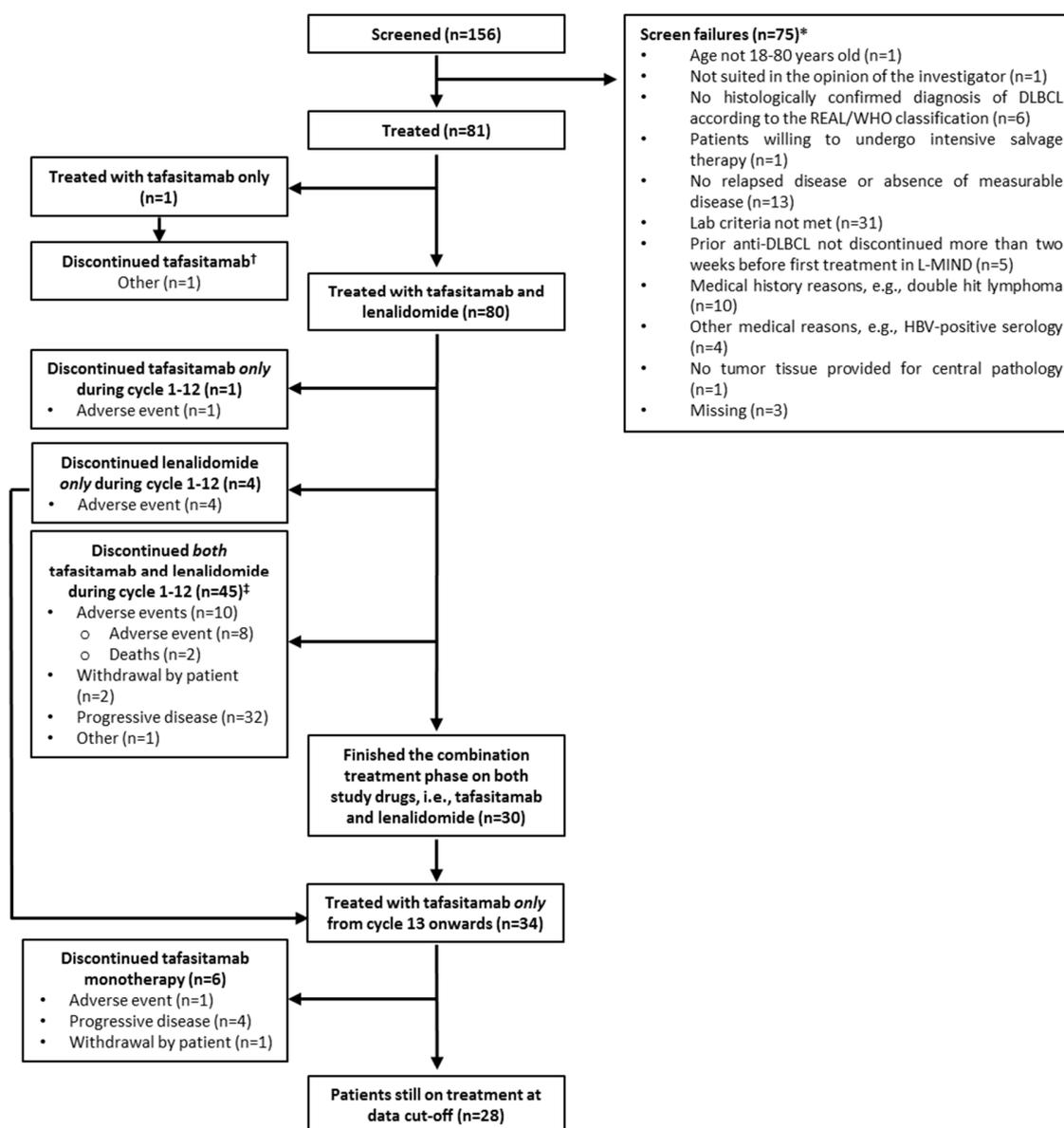
glutamyltransferase				
Atrial fibrillation	1 (1)	2 (2)	1 (1)	0
Pulmonary embolism	0	2 (2)	2 (2)	0
Sinusitis	3 (4)	1 (1)	0	0
Deep vein thrombosis	2 (2)	0	1 (1)	0
Hyperbilirubinaemia	2 (2)	1 (1)	0	0
Increased blood bilirubin	2 (2)	1 (1)	0	0
Increased transaminases	1 (1)	2 (2)	0	0
Lower respiratory tract infection	2 (2)	1 (1)	0	0
Renal failure	1 (1)	2 (2)	0	0
Syncope	2 (2)	1 (1)	0	0
Tumour flare	2 (2)	1 (1)	0	0
Cataract	1 (1)	1 (1)	0	0
Congestive cardiac failure	0	2 (2)	0	0
Muscular weakness	1 (1)	1 (1)	0	0
Urinary incontinence	1 (1)	1 (1)	0	0
Arthritis	0	1 (1)	0	0
Atrial flutter	0	1 (1)	0	0
Biliary colic	0	1 (1)	0	0
Bronchopulmonary aspergillosis	0	0	1 (1)	0
Cardiac failure	0	0	1 (1)	0
Cerebrovascular accident	0	0	0	1 (1)
Cervicobrachial syndrome	0	1 (1)	0	0
Cranial nerve infection	0	1 (1)	0	0
Cytomegalovirus infection	0	1 (1)	0	0
Device related thrombosis	0	1 (1)	0	0
Enterobacter bacteraemia	0	1 (1)	0	0
Febrile infection	0	0	1 (1)	0
Femur fracture	0	1 (1)	0	0
Haematuria	0	1 (1)	0	0
Hyperkalaemia	0	1 (1)	0	0
Hypersensitivity	0	1 (1)	0	0
Hyponatraemia	0	1 (1)	0	0
Infected bite	0	1 (1)	0	0
Klebsiella sepsis	0	1 (1)	0	0
Lower limb fracture	0	1 (1)	0	0
Lung infection	0	1 (1)	0	0
Myocardial ischaemia	0	0	1 (1)	0
Myositis	0	1 (1)	0	0
Nephrolithiasis	0	1 (1)	0	0
Neutropenic sepsis	0	1 (1)	0	0

Osteonecrosis	0	1 (1)	0	0
Peripheral sensorimotor neuropathy	0	1 (1)	0	0
Progressive multifocal leukoencephalopathy	0	0	0	1 (1)
Recurrent marginal zone lymphoma	0	1 (1)	0	0
Respiratory failure	0	0	0	1 (1)
Respiratory syncytial Virus infection	0	1 (1)	0	0
Sepsis	0	0	1 (1)	0
Soft tissue infection	0	1 (1)	0	0
Streptococcal sepsis	0	0	1 (1)	0
Sudden death	0	0	0	1 (1)
Varicella zoster virus infection	0	0	1 (1)	0
Wound complication	0	0	1 (1)	0

598 *Defined by customized Medical Dictionary for Regulatory Activities query. †One report of back
599 pain and one report of increased blood creatinine lacked toxicity grading.

600

601

602 **Figure 1.** L-MIND CONSORT diagram

603

604 *A single patient can be counted under more than one reason for screen failure.

605 †Discontinuation due to physician decision. ‡Two scenarios are covered in this instance: (1)

606 discontinuation of both drugs at the same time and (2) sequential discontinuation (only the

607 reason for the 'later' discontinuation is reported). Regarding the number of deaths, two patients

608 discontinued treatment with both study drugs due to a non-PD-related death (sudden death;

609 respiratory failure); a further 6 deaths were reported, however, these were classified as
610 discontinued both drugs due to PD (5 patients; PD-related death) or discontinued both drugs
611 due to AE (one patient; discontinued due to pulmonary embolism but died due to a
612 cerebrovascular accident and thereby considered to have died “on treatment” as within 30 days
613 post-treatment discontinuation).

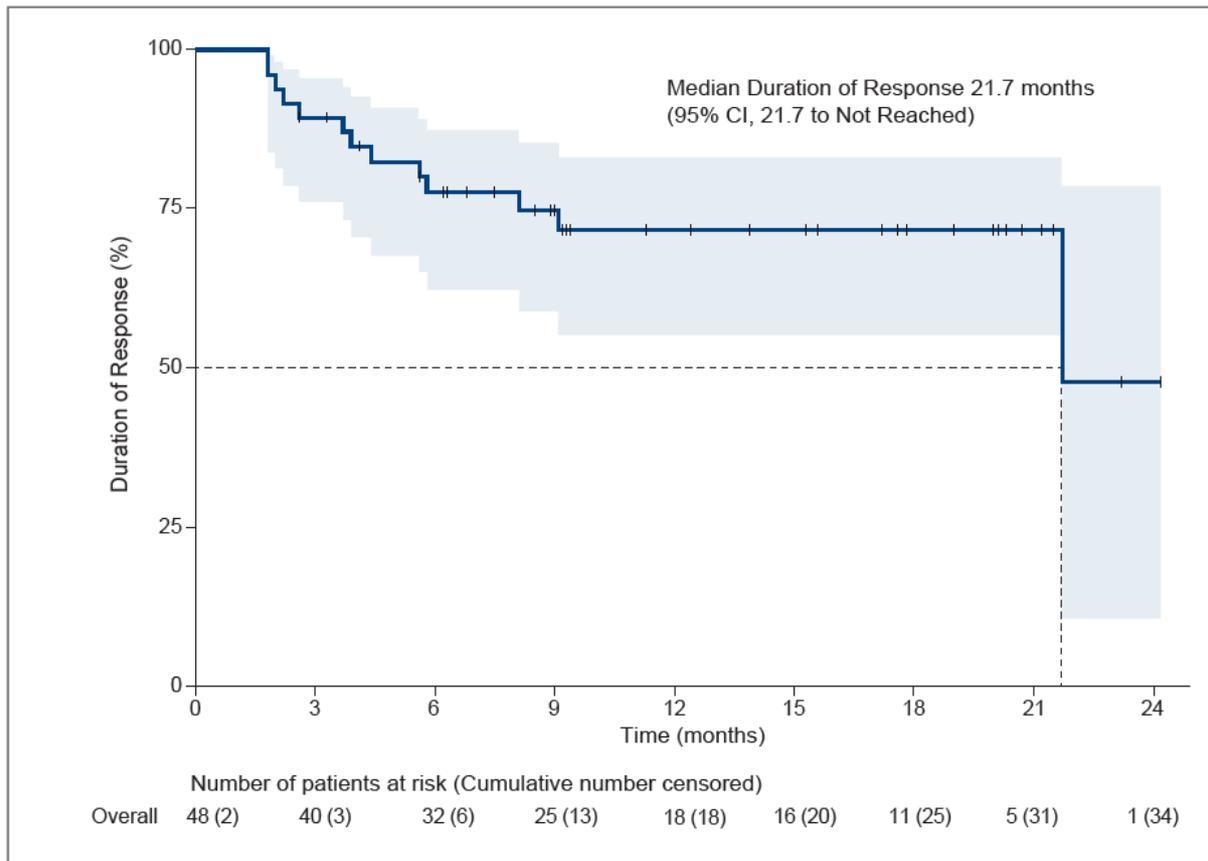
614 DLBCL=diffuse large B-cell lymphoma. HBV=hepatitis B virus. REAL=Revised European
615 American Lymphoma. WHO=World Health Organization.

616

617

618 **Figure 2.** Patient outcomes (median 13.2 months of follow-up): A. Duration of response (full
 619 analysis set); B. Duration of response by best achieved response; C. Progression-free survival
 620 (full analysis set); D. Overall survival (full analysis set)

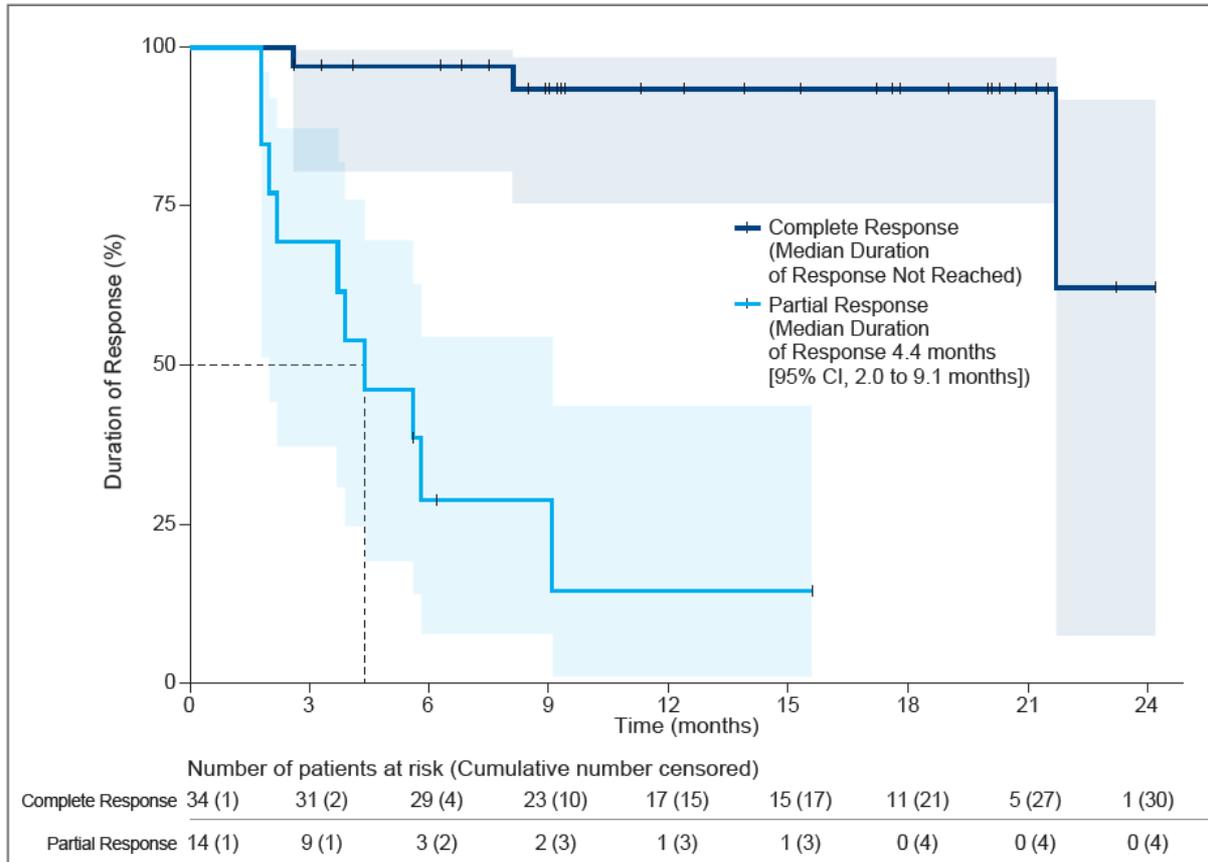
621 **A**



622

623

624 **B.**



625

626

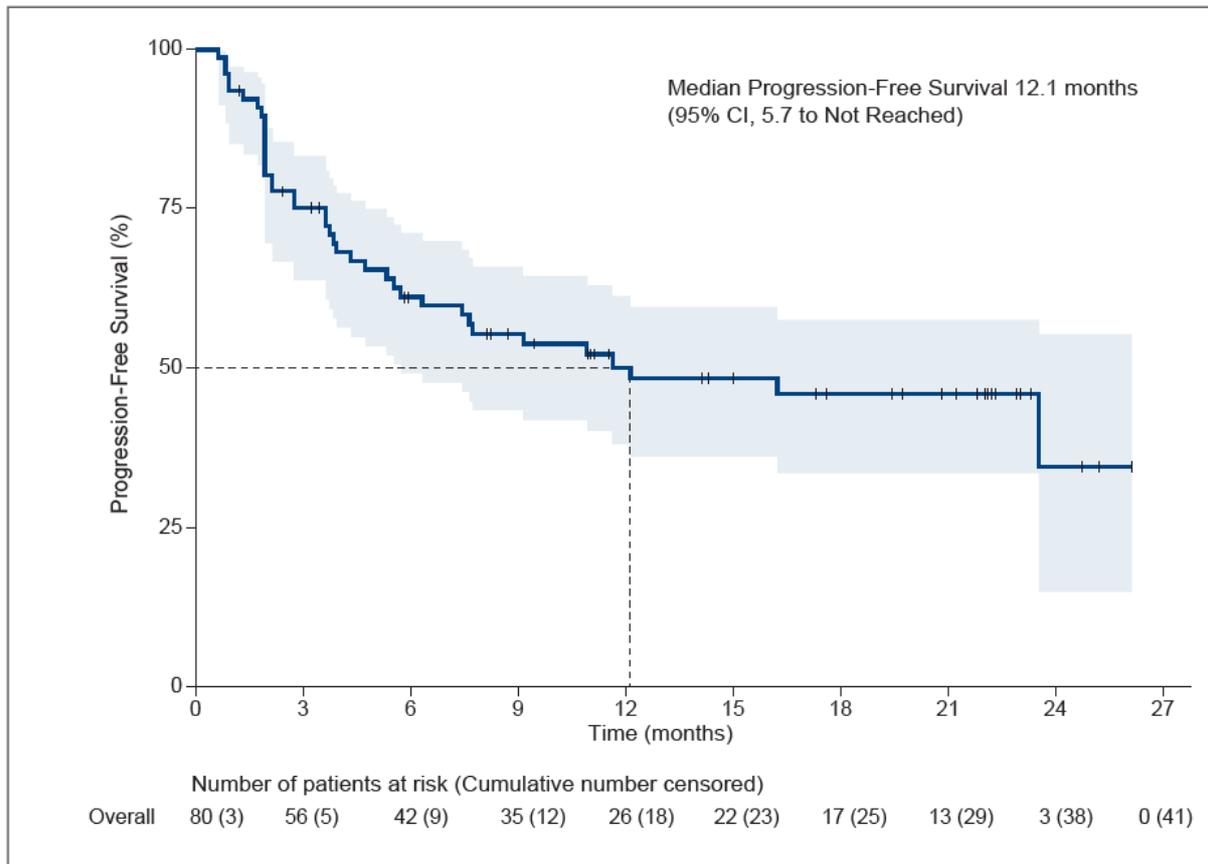
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630

631 **C.**

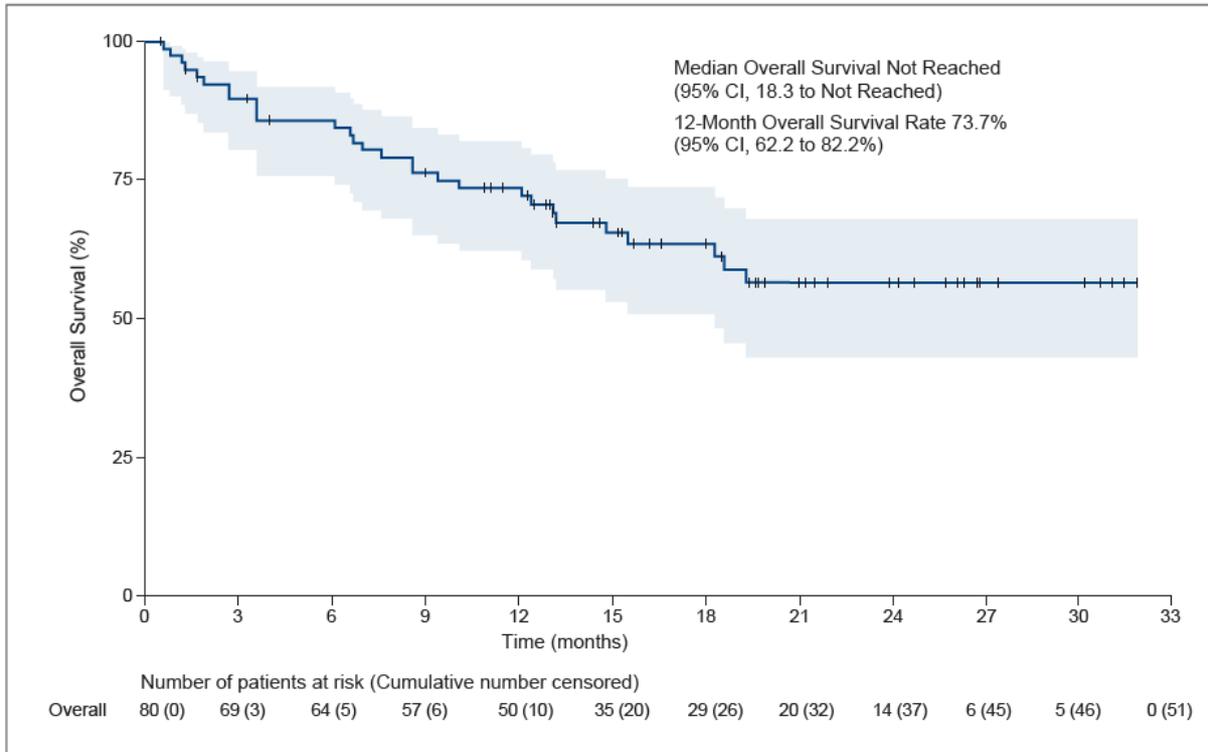


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633

634

635 **D.**



636

637 CI=confidence interval.

638

639