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Outcomes of ibrutinib plus lenalidomide combination in patients with large B-cell lymphoma refractory to or relapsing after CAR-T-cell therapy and who failed or were ineligible for bispecific antibodies: a multicenter real-world REALI-T study

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Abbreviations: BCR, B-cell receptor; BsAbs, bispecific antibodies; BTK, Bruton's tyrosine kinase; COO, cell of origin; CMR, complete metabolic response; DOR, duration of response; Ibru-Len, ibrutinib–lenalidomide combination; GCB, germinal center B-cell–like; HGBL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; mAbs, monoclonal antibodies; OMRR, overall metabolic response rate; OS, overall survival; PFS, progression-free survival; PMR, partial metabolic response; R/R LBCL, relapsed/refractory large B-cell lymphoma

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Authorship

CJR and PS designed the study. CJR, PS, LMF, BG, LF, ACh, ACa, FXG, GB, HM, VC, SG, FC, and DB collected the data. MI performed the statistical analyses. CJR and PS analyzed the data. CJR and PS analyzed and interpreted the results. CJR and PS wrote the manuscript. LMF, BG, LF, ACh, ACa, FXG, GB, HM, VC, SG, FC, DB, CG, VS, EF, EB, and HG revised the manuscript. All the authors significantly contributed to the study and reviewed the final version of the manuscript.

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honoraria from AbbVie, AstraZeneca, Bristol Myers Squibb, Ideogen, Janssen (Johnson & Johnson), Kite/Gilead, Lilly, Novartis, Secura Bio, Sanofi, Roche and Takeda. VS reports consultancy and/or honoraria from Kite Gilead, Johnson and Johnson, Beigene, Lilly, Janssen. EF reports consultancy and/or honoraria from Abbvie, Kite Gilead, Johnson and Johnson, BeOne, Lilly, Astra Zeneca. EB reports consultancy and/or honoraria from Kite/Gilead, ADC Therapeutics, Roche, Novartis, Takeda, Janssen, Bristol Myers Squibb, Incyte, AbbVie, and Amgen, and research funding from Bristol Myers Squibb and Amgen. HG reports consultancy and/or honoraria from Roche, BMS, Takeda, Gilead, Abbvie. PS has received honoraria from AbbVie, BMS, Chugai, Janssen, Kite/ Gilead, Novartis and Roche. All remaining authors have declared no conflicts of interest.

The treatment landscape of relapsed/refractory large B-cell lymphoma (R/R LBCL) has been significantly transformed by the advent of anti-CD19 CAR-T-cell therapies and CD20×CD3 bispecific antibodies (BsAbs), resulting in high response rates in heavily pretreated patients(1–4). However, the prognosis of patients who relapse after these T-cell engager therapies remains extremely poor, with no standard of care established in this setting(5). Thus, therapeutic strategies aiming to simultaneously target tumor-intrinsic survival pathways and the immune microenvironment may offer renewed clinical benefit to circumvent relapse. Ibrutinib, a Bruton’s tyrosine kinase (BTK) inhibitor, has shown modest single-agent activity in ABC-subtype LBCL and is known to modulate tumor–immune interactions(6). On the other hand, Lenalidomide, an immunomodulatory drug, has demonstrated efficacy in R/R LBCL and synergistic activity when combined with BTK inhibitors in preclinical models(7). Previous studies have reported promising results of the ibrutinib–lenalidomide combination (Ibru-Len) in R/R LBCL, but most of the patients were not exposed to CAR-T cells or BsAbs(8–10), which is now the standard 2nd- and/or 3rd-line therapies(11). On the basis of this rationale, we conducted a retrospective multicenter observational study across ten academic hematology centers in France, to evaluate the efficacy and safety of Ibru-Len in a cohort of consecutive patients with R/R LBCL previously exposed to CAR-T-cell therapy and who failed or were ineligible for BsAbs.

Patients were systematically identified through interrogation of the DESCAR-T and REALYSA databases, plus queries to disease experts at each participating center, and were included if they received Ibru-Len for R/R LBCL between January 2022 and December 2024. Eligible patients were required to have received prior anti-CD19-directed CAR-T-cell therapy and to either (i) have been subsequently treated with BsAbs or (ii) have been deemed ineligible for BsAbs. Ineligibility was defined as the absence of CD20 expression (<5% of tumor cells by immunohistochemistry), a lack of clinical access to bispecific agents at the time of relapse, and/or central nervous system involvement. We applied no further exclusion criteria.

Patients who received additional therapy alongside Ibru-Len (such as oral targeted therapies and monoclonal antibodies, mAbs) were eligible for inclusion; these regimens are referred to as “Ibru-Len-based” throughout to reflect this heterogeneity. Data were extracted manually from source medical records using a harmonized variable list. Formal centralized monitoring was not performed; however, data quality was ensured through internal consistency reviews and cross-checks against DESCAR-T and REALYSA databases. The study was conducted in

accordance with French regulatory requirements for retrospective analyses, with the approval of the local Data Protection Officer of the Hospices Civils de Lyon and the institutional study board. Non-opposition statement was obtained after ad hoc information was given to all patients/relatives. Responses were evaluated by local investigators, all LYSARC experts, as per Lugano 2014 criteria through ^{18}F -FDG PET imaging. Toxicities were graded according to the latest version of the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The primary outcome was the best overall metabolic response rate (OMRR). The secondary outcomes were the complete metabolic response (CMR) rate, overall survival (OS), progression-free survival (PFS), duration of response (DOR) and safety. For time-to-event endpoints, patients without an event were censored at the last follow-up. Patients who underwent autologous or allogeneic transplantation were not censored at transplant and remained under follow-up for both PFS and OS; post-transplant progression and deaths were included. No imputation was performed; analyses used available data for each variable. PFS, OS and DOR were estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Swimmer plots were constructed to illustrate individual treatment durations and response dynamics. All the statistical analyses were performed using R software (v4.3.0).

The baseline characteristics are shown in Table 1. A total of 27 consecutive patients were included in the study. Among them, 6/21 (29%) had high-grade B-cell lymphoma (HGBL), and according to the commonly used Hans algorithm, 14/27 (52%) were classified as having germinal center B-cell–like (GCB) LBCL, while 11/27 (41%) were classified as non-GCB LBCL. Molecular profiling of LBCL was available for 8/27 (30%) patients. Almost all patients (25/27, [93%]) were considered as refractory or early relapsers, defined as a lack of response or relapse within 1 year of first-line therapy. At the time of Ibru–Len initiation, the median age was 62 years (range: 23–83), and the majority of patients were male (16/27, [59%]). Most patients presented with advanced disease (Ann Arbor stage IV, 22/26 [85%]; elevated LDH, 17/24 [71%]), with a median of 4 (range: 2–7) prior therapies. All had previously failed CAR-T-cell therapy, including 23/27 (85%) who were treated with axicabtagene ciloleucel (axi-cel), and 15/27 (56%) who had received salvage therapy with BsAbs. Ineligibility to BsAbs after CAR-T-cells was due to (i) negative CD20 expression (n=4), (ii) exclusion criteria for clinical

trials providing early access (n=5), or (iii) central nervous system involvement (n=3). Median time from CAR-T-cell therapy to Ibru-Len regimen was 6.4 months (range, 2.1 – 35.2).

Ibrutinib was used continuously and was initiated at 560 mg daily in 24/27 (89%) of the patients. Lenalidomide was used for 3 out of 4 weeks and was started at 20 mg daily in 11/27 (41%) of the patients. Ibru-Len was combined with ≥ 1 additional therapy in 14/27 (52%) of cases, including 12/27 (44%) anti-CD20 mAbs and 6/27 (22%) other targeted therapies (Figure 1). After two patients achieved complete remission with Ibru-Len, they received consolidative stem cell transplantation, including one autologous and one allogeneic transplant.

Among the 27 patients treated with Ibru-Len, the OMRR was 52% (14/27), including 37% (10/27) who achieved CMR and 15% (4/27) who achieved partial metabolic response (PMR) (Figure 2A). Stratified by the cell of origin (COO), the OMRR was 82% (9/11) in the non-GCB group and 29% (4/14) in the GCB group ($p=0.01$) (Figures 2B and C). With a median follow-up period of 8.8 months (range, 1.18–32.8), the median PFS was 5.9 months (95% CI, 2.6–14.5) and the median OS was 18 months (95% CI, 7.5–NR) (Figure 2D). Some responses were durable with a median DOR of 11.6 months (95% CI, 6.9 – NA) (Supplementary Figure 1A and supplementary Figure 2). In the non-GCB group, the median PFS was 9.2 months (95% CI, 5.93–NA) and the median OS was not reached. In the GCB group, the median PFS was 2.4 months (95% CI, 1.97–NA) and the median OS was 7.5 months (95% CI, 3.02–NA). Although the differences were not statistically significant, PFS and OS tended to be longer in the non-GCB group ($p=0.13$ and 0.081 , respectively) (Figures 2E and F). Exploratory subgroup outcomes (exposition to additional therapy, lenalidomide dose, prior bispecific exposure, HGBL subtype) are shown in supplementary Table 1. After relapse on Ibru-Len 11/20 patients (55%) received further therapy (Supplementary Figure 1B).

Regarding the safety profile of the Ibru-Len regimen, 76% of the patients (19/25) experienced at least one grade ≥ 3 adverse event (AE), including neutropenia in 52% (13/25), infections in 40% (10/25), thrombocytopenia in 20% (5/25), and nausea or asthenia in 12% (3/25) (Supplementary Figure 3). No treatment-related deaths were reported. Toxicities, as attributed by treating clinicians, led to dose reductions in 1 patient for ibrutinib (hematologic toxicity) and in 6 patients for lenalidomide (hematologic toxicity and/or diarrhea, $n = 5$; infections, $n = 1$). Ibrutinib was discontinued in 2 patients because of grade 4 thrombocytopenia ($n = 1$) and grade 3 infection ($n = 1$), whereas lenalidomide was

discontinued in 2 patients because of grade 4 neutropenia and thrombocytopenia (n = 1) and grade 2 rash (n = 1). Given the cumulative toxicity from prior therapies and the overlapping toxicity profiles of the two agents, this attribution reflects real-world clinical judgment rather than a formal causality assessment.

The results of the DESCAR-T analysis showed the dismal prognosis of patients with R/R LBCL after anti-CD19 CAR-T-cell therapy, and underscored the urgent need for effective salvage strategies beyond standard chemotherapy(5). BsAbs are the preferred treatment in this population, with a median overall survival between 7 and 17 months(12,13). Regarding BsAbs eligibility, recent studies have demonstrated activity in CNS-positive disease, meaning some patients in our cohort would currently qualify(14). Nonetheless, CD20 loss remains a strong adverse predictor of bispecific efficacy, supporting the use of CD20-independent approaches such as Ibru-Len in this setting(15).

In our cohort, the majority of patients had highly aggressive disease, including one-third with HGBL and more than 90% classified as refractory or relapsing within 12 months of first-line therapy. Plus, all experienced failure of prior CAR-T-cell therapy and half received salvage therapy with BsAbs. Despite these adverse baseline characteristics, treatment with Ibru-Len yielded a clinically meaningful OMRR of 52%, with a CMR rate of 37%. The median PFS and OS in our cohort were 5.9 months and 18 months, respectively, with some patients achieving durable responses (median DOR of 11.6 months), and two successfully bridged to stem cell transplantation. These results compare favorably with historical outcomes observed in more favorable patient populations (i.e., nonrelapsed post-CAR-T cohorts) and support the activity of this targeted combination in a setting of unmet clinical need (8–10). Although we recognize left truncation bias (patients who deteriorated before initiation might not have been enrolled) this may limit external generalizability, but internal validity of survival estimates is not compromised.

Consistent with prior reports, responses were enriched in the non-GCB subtype, with an OMRR of 82% versus 29% in the GCB group (p=0,01). This observation aligns with the known biology of non-GCB LBCL, in which chronic active B-cell receptor (BCR) signaling and NF-κB pathway activation confer sensitivity to BCR-targeted agents and lenalidomide(6,8). Despite its retrospective and non-controlled design with a limited cohort, this study suggests that Ibru-Len is particularly promising for non-GCB patients, offering clinically relevant responses

and prolonged survival in a population that otherwise faces very poor outcomes(5).

Exploratorily, HGBL showed no numerical benefit, and prior bispecific exposure or use of Lenalidomide <20mg showed a non-significant trend toward worse outcomes, in small, confounded subgroups. Molecular and genetic data were limited and did not influence treatment selection, particularly in the absence of alternatives; however, unrecognized allocation bias due to the lack of mutational profiling cannot be excluded.

While unsurprising in a retrospective series, some patients received Ibru-Len with additional targeted agents that could have augmented clinical benefit. Despite the small sample size, add-on therapies (particularly anti-CD20 mAbs, the most frequent addition) did not improve outcomes, consistent with heavy prior CD20 exposure and frequent post-bispecific CD20 loss(16). Similarly, Ibru-Len initiation post CAR-T could theoretically promote CAR-T re-expansion and bias results; yet the 6.4-month median interval to initiation (when CAR-T persistence is typically minimal in non-responders) suggests that the observed activity reflects the direct antitumor and immunomodulatory effects of the regimen(17).

The safety profile of Ibru-Len was consistent with the known adverse events of the individual agents, with grade ≥ 3 toxicities primarily related to hematologic events and infections (8). Although 70% of patients experienced at least one grade ≥ 3 adverse event, only 4 patients discontinued either ibrutinib or lenalidomide, and no treatment-related death were observed.

In accordance with the standard recommendations, 89% of patients received ibrutinib at 560 mg. The optimal dose of lenalidomide in combination with ibrutinib for treating LBCL remains under investigation. A phase 1b study identified recommended doses above 15 mg, but also suggested that 15 mg dosing may be associated with clinically meaningful response rates(8). In our cohort, just over half of patients (14/27; 52%) received lenalidomide 20–25 mg. The remainder underwent dose reductions to balance efficacy against tolerability in this heavily pretreated population with cumulative marrow impairment and immunosuppression.

In conclusion, Ibru-len demonstrated encouraging activity with a manageable safety profile in patients with R/R LBCL, particularly those with the non-GCB subtype who had previously received CAR-T-cell therapy and had failed or were ineligible for BsAbs which are now the standard 2nd- and/or 3rd-line therapies. Given the limited therapeutic options in this heavily

pretreated population, Ibru-Len represents a promising treatment strategy. Prospective studies are warranted to confirm these findings and to better identify the patients most likely to benefit from this combination.

1. Neelapu SS, Jacobson CA, Ghobadi A, et al. 5-year follow-up supports curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1). *Blood*. 2023;141(19):2307-2315.
2. Abramson JS, Palomba ML, Gordon LI, et al. Five-year survival of patients (pts) from transcend NHL 001 (TRANSCEND) supports curative potential of lisocabtagene maraleucel (liso-cel) in relapsed or refractory (R/R) large B-cell lymphoma (LBCL). *Blood*. 2024;144(Supplement 1):3125.
3. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2022;387(24):2220-2231.
4. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell-engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II trial. *J Clin Oncol*. 2023;41(12):2238-2247.
5. Di Blasi R, Le Gouill S, Bachy E, et al. Outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy: a DESCAR-T analysis. *Blood*. 2022;140(24):2584-2593.
6. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med*. 2015;21(8):922-926.
7. Yang Y, Shaffer AL, Emre NCT, et al. Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma. *Cancer Cell*. 2012;21(6):723-737.
8. Goy A, Ramchandren R, Ghosh N, et al. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. *Blood*. 2019;134(13):1024-1036.
9. Ramchandren R, Johnson P, Ghosh N, et al. The iR2 regimen (ibrutinib plus lenalidomide and rituximab) for relapsed/refractory DLBCL: a multicentre, non-randomised, open-label phase 2 study. *EClinicalMedicine*. 2023;56:101779.
10. Melani C, Lakhotia R, Pittaluga S, et al. Combination targeted therapy in relapsed diffuse large b-cell lymphoma. *N Eng J Med*. 2024;390(23):2143-2155.
11. Sesques P, Manson G, Dubois S, et al. Large B-cell lymphoma: the LYSA pragmatic guidelines. *Eur J Cancer*. 2026;232:116070.
12. Sesques P, Houot R, Al Tabaa Y, et al. Glofitamab is superior to non a-CD3x20 treatments for patients with diffuse large B-cell lymphoma who are refractory or relapse immediately after anti-CD19 CAR T-cell therapy: final results of the bicar study (LYSA) and indirect comparison with a synthetic control arm from the descart registry. *Blood*. 2025;146(Supplement 1):1958.
13. Cartron G, Houot R, Al Tabaa Y, et al. Glofitamab in refractory or relapsed diffuse large B cell lymphoma after failing CAR-T cell therapy: a phase 2 LYSA study. *Nat Cancer*. 2025;6(7):1173-1183.

14. Gilbert A, Boussen I, Bardet H, et al. Safety and efficacy of CD3xCD20 bispecific antibody for the treatment of primary and secondary central nervous system lymphoma patients: A multicentric retrospective study. *Blood*. 2025;146(Supplement 1):1018..
15. Kyvsgaard ER, Grantzau TL, Sørensen MD, et al. Reduced CD20 expression yields inferior survival in patients with B-cell lymphoma treated with CD20xCD3 antibodies. *Blood Neoplasia*. 2025;2(3):100096.
16. Grigg S, Minson A, Prins E, et al. Relapse after glofitamab has a poor prognosis and rates of CD20 loss are high. *Br J Haematol*. 2024;205(1):122-126.
17. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *Lancet Oncol*. 2019;20(1):31-42.

Characteristics, n (%) or median (range)	All patients, n=27
Male	16 (59%)
Age, years	62 (23 – 83)
Histologic subtypes, Hans algorithm	
GCB DLBCL	14 (52%)
Non-GCB DLBCL	11 (41%)
Unclassifiable	2 (7%)
High-grade B lymphoma ^a	6 (29%)
Missing data	6
Transformed lymphoma ^b	5 (19%)
Median no. of previous therapies	4 (2 – 7)
Previous therapies	
Prior exposure to study agents	12 (50%)
Ibrutinib ^c	2 (8%)
Lenalidomide ^d	7 (29%)
Ibrutinib and Lenalidomide ^e	3 (13%)
Missing data	3
ASCT	1 (4%)
CAR T-cells ^f	27 (100%)
BsAbs ^g	15 (56%)
Primary refractory disease or early relapsers ^h	25 (93%)
Median time between initial diagnosis and onset of IL (months)	16,8 (4 – 150,5)
Median time between last dose of prior therapy and onset of IL (months)	2,1 (0,1 – 18,4)
Median time between CAR-T cells therapy and onset of IL (months)	6,4 (2,1 – 35,2)
Features before IL initiation	
ECOG PS > 1	3 (12%)
Missing data	1
LDH > ULN	17 (71%)
Missing data	3
CRP	21,3 (0,5 – 146)
Missing data	3
Ann Arbor stage before IL initiation	
I-II	4 (15%)
III-IV	22 (85%)
CNS involvement	6 (23%)
Two or more extranodal sites	11 (42%)
Missing data	1

Table 1. Baseline demographics and disease characteristics in the all-treated population

^a This category includes 5 patients with high-grade B-cell lymphoma double hit with *MYC* and *BCL2* rearrangements, and 1 patient with high-grade B-cell lymphoma triple hit with *MYC*, *BCL2* and *BCL6* rearrangements. ^b This category includes 4 patients with transformed follicular lymphoma and one with a Richter's syndrome. ^c This category includes 1 patient who received Ibrutinib in combination with chemotherapy for a fixed duration as bridging to CAR-T-cells; missing data (n=1). ^d This category includes 4 patients who received Lenalidomide in combination with BsAbs (n=3) or chemotherapy (n=1) for a fixed duration; and 2 patients who received lenalidomide post-CAR T with an immunomodulatory intent; missing data (n=1). ^e This category includes 1 patient who received the concomitant Ibru-Len doublet for a fixed duration of one cycle as bridging to CAR-T-cells; and 1 patient who received Lenalidomide in combination with BsAbs, and Ibrutinib post-CAR T with an immunomodulatory intent; missing data (n=1). ^f This category includes 23 patients (85%) who received Axicabtagene ciloleucel (axi-cel) and 4 patients (15%) who received Lisocabtagene maraleucel (liso-cel). CAR T-cells were used in 2nd line (n=8), 3rd line (n=12) or 4th line and above (n=7). ^g This category includes 8 patients who received Epcoritamab, 6 patients who received Glofitamab, and 1 patient who received Plamotamab. ^h Primary refractory or early relapse status was defined as refractory or relapsed disease within 12 months of first-line chemoimmunotherapy.

Abbreviations: ASCT, autologous stem-cell transplantation; BsAbs, bispecific antibodies CD3xCD20; CAR, chimeric antigen receptor; CNS, central nervous system; CRP, C-reactive protein; DLBCL diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; GCB DLBCL, germinal-center B-cell diffuse large B-cell lymphoma; IL, Ibrutinib and Lenalidomide; LDH lactate dehydrogenase; ULN, upper limit of normal.

Figure 1. Treatment exposure in the all-treated population.

^aThis category includes 9 patients treated with Rituximab and 3 patients treated with Obinutuzumab. All patients who didn't receive anti-CD20 monoclonal antibodies but 3, were CD20 negative on the most recent biopsy. ^bThis category includes 4 patients who received Venetoclax, 1 patient who received Tafasitamab and 1 patient who received intrathecal chemotherapy.

Abbreviations: Ibru-Len, Ibrutinib-Lenalidomide; IV, intravenous; PO, per os.

Figure 2. Overall antitumor activity and survival outcomes with ibrutinib–lenalidomide in the entire cohort, with panel-specific analyses by cell-of-origin subtype. (A) Response in the all-treated population; (B) Response in non-GCB LBCL; (C) Response in GCB LBCL; (D) PFS and OS in the entire cohort; (E) PFS by histologic subtype; (F) OS by histologic subtype.

Abbreviations: CMR, complete metabolic response; GCB, germinal center B-cell-like; NR, not reached; OS, overall survival; PFS, progression-free survival; PMR, partial metabolic response.

Treatment cycle of Ibru-Len (28 days)



Ibrutinib, PO continuous daily
Days 1–28 of each cycle

Initial dose (mg)	Patients (n, %)
560	24 (89%)
420	3 (11%)



Lenalidomide, PO Days 1–21
of each cycle

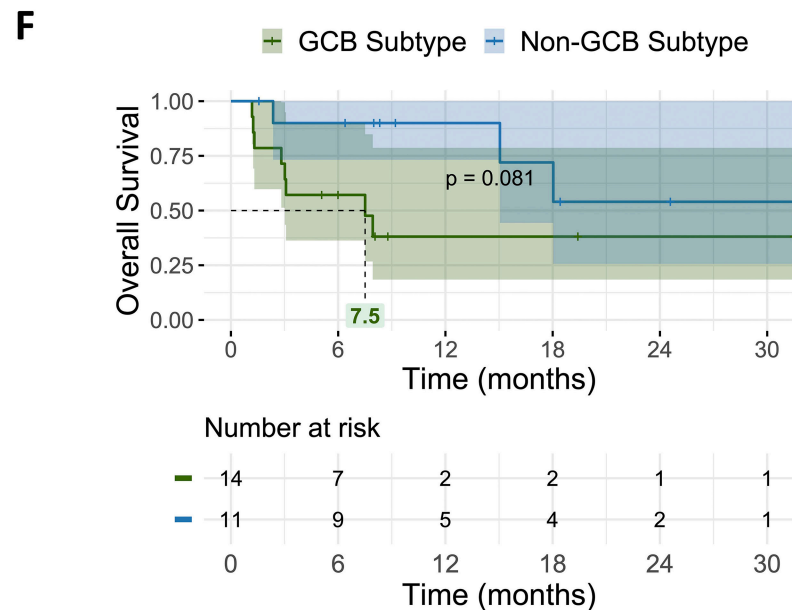
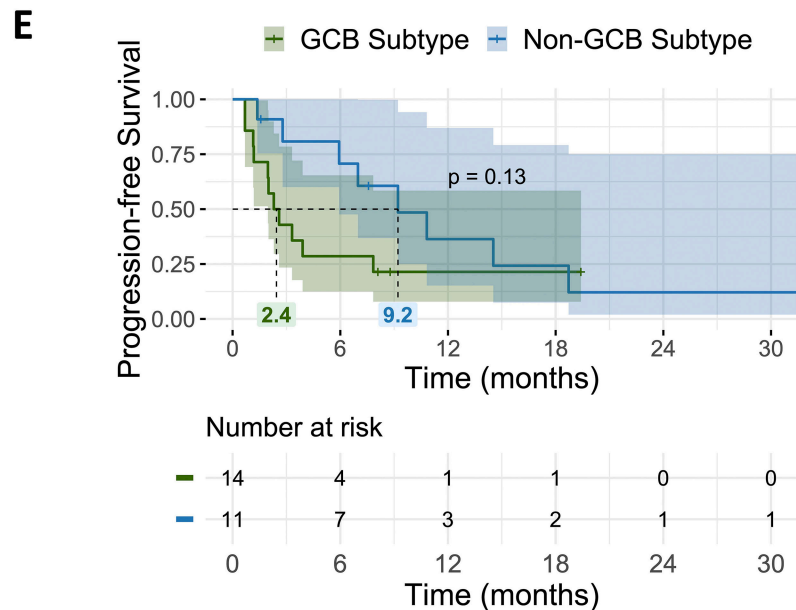
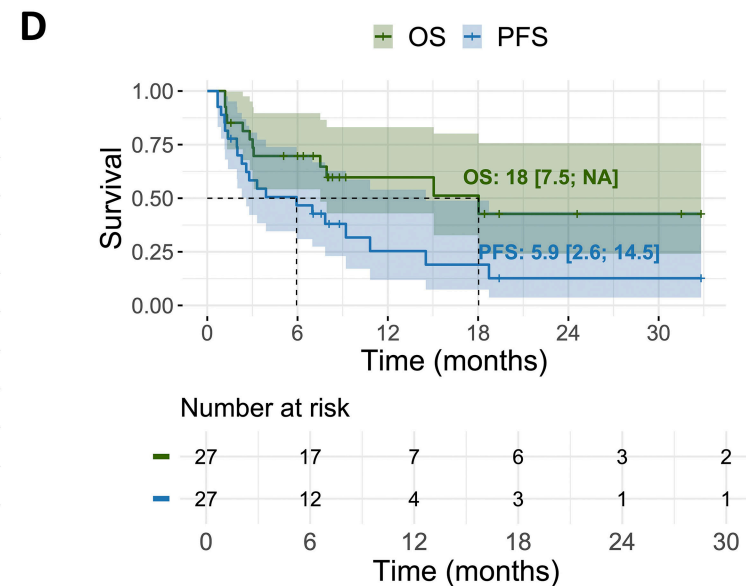
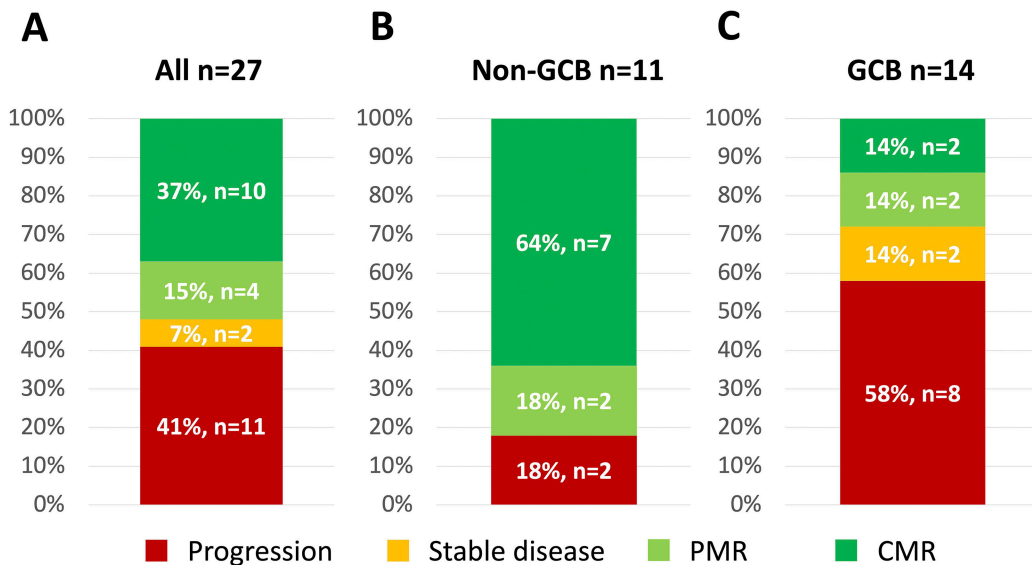
Initial dose (mg)	Patients (n, %)
25	3 (11%)
20	11 (41%)
15	9 (33%)
10	4 (15%)



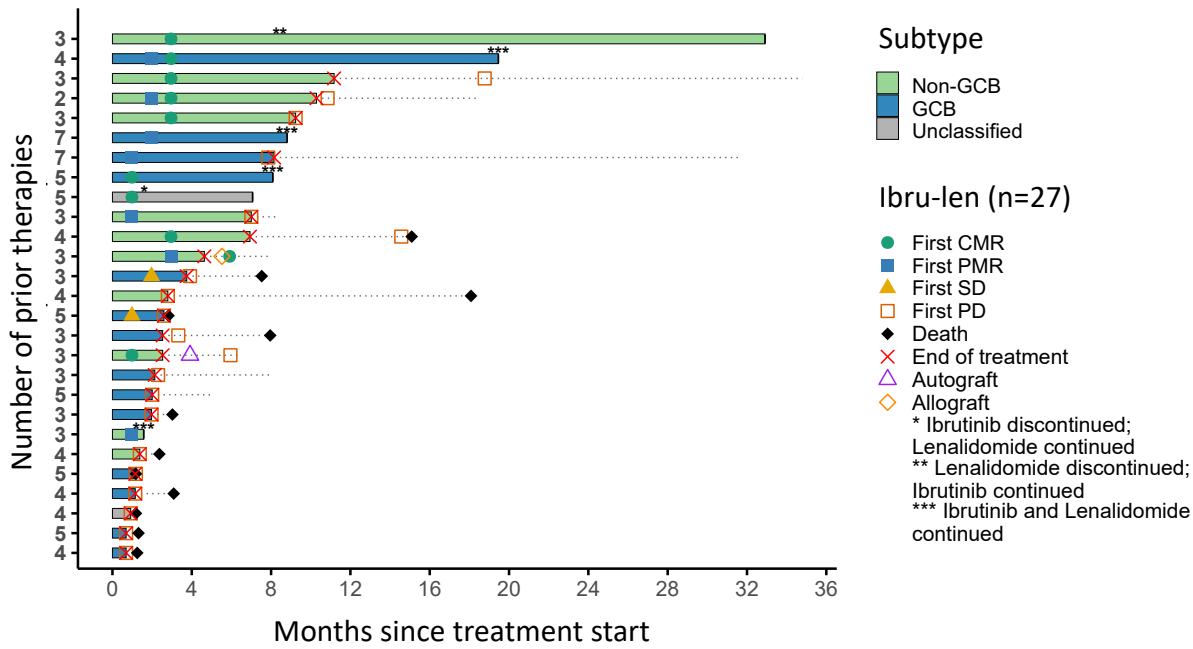
Anti-CD20 monoclonal
antibodies, IV on day 1
of cycle 1–6^a



Additional therapy^b



A

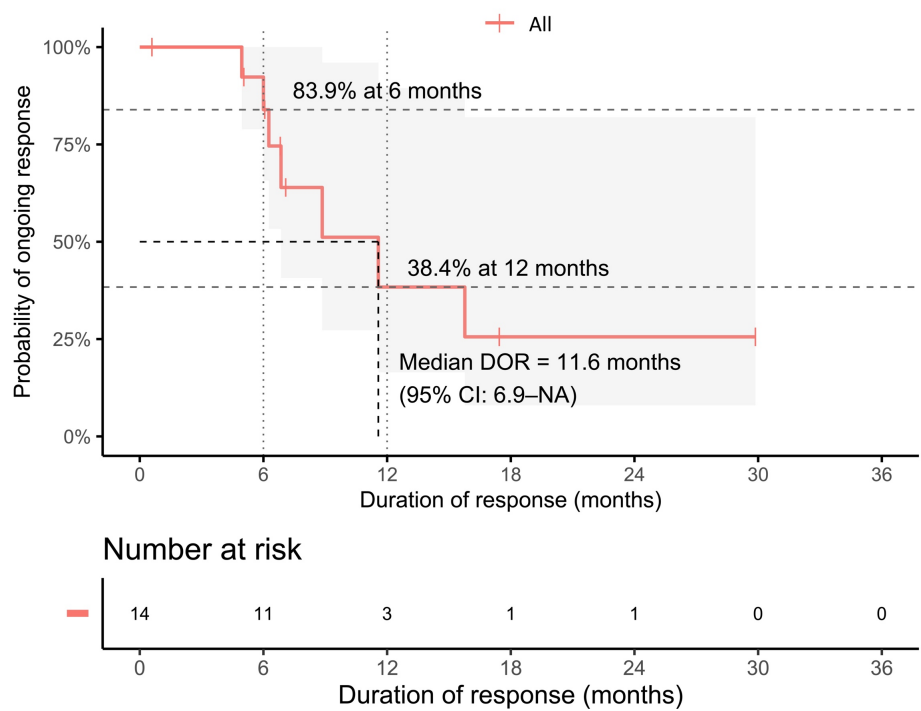


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Patients	Line(s) after Ibru-Len	Regimen(s)	Best outcome per line
1	1	Bendamustine	PD
2	1	Bendamustine	PD
3	1	Rituximab – bendamustine	PD
4	1	Rituximab – bendamustine – polatuzumab vedotin	PD
5	1	Cyclophosphamide-based regimen	CMR
6	1	Rituximab – ifosfamide – etoposide (R-IE)	CMR
7	1	CD3×CD20 bispecific antibody	CMR
8	1	CD3×CD20 bispecific antibody	PD
9	2	Brentuximab vedotin – gemcitabine – vinorelbine – doxorubicin → Lisocabtagene maraleucel	PD → PD
10	2	CD3×CD20 bispecific antibody → Golcadomide	PMR then PD → PD
11	4	Rituximab – bendamustine → R-IE → Rituximab – gemcitabine – oxaliplatin – zilovertamab vedotin → Allogeneic CAR-T cells	PD → PD → PD → PD

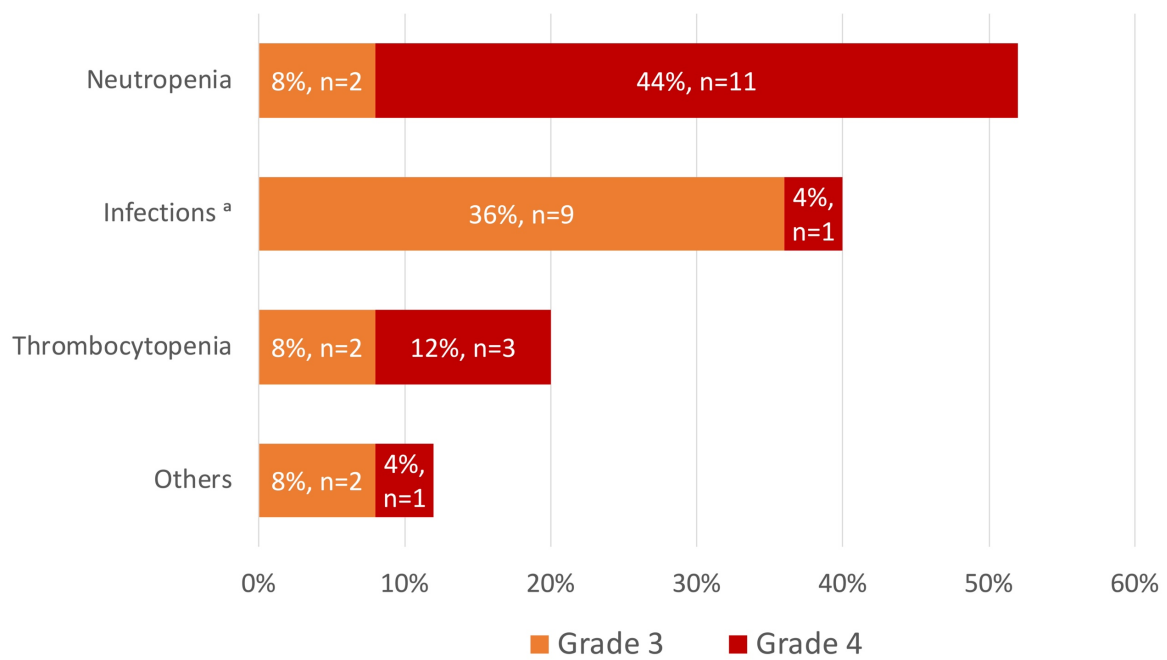
Abbreviations: CMR, complete metabolic response; GCB, germinal center B-cell-like; Ibru-Len, Ibrutinib-Lenalidomide; PD, progressive disease; PMR, partial metabolic response; SD, stable disease.

Supplementary Figure 1. Treatment duration, response, and salvage therapies. (A) Swimlane plot of treatment duration and response in all treated patients (each bar represents one patient, ordered by treatment duration). (B) Salvage therapies after Ibru-Len regimen.



Abbreviations: DOR, duration of response; CI, confidence interval

Supplementary Figure 2. Duration of response in the all-treated population.



^a Grade 3 (n=9): febrile neutropenia without microbiological documentation (n=3); febrile neutropenia with obstructive pyelonephritis due to *Escherichia coli* (n=1); fever without neutropenia requiring broad-spectrum IV antibiotics and without clinical focus/microbiological documentation (n=1); central line infections with *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* in the same patient at different time points (n=1); *Campylobacter jejuni* colitis with bacteremia (n=1); COVID-19 pneumonia (n=1); nocardiosis (n=1). Grade 4 (n=1): ARDS secondary to presumed infectious pneumonia of unknown etiology.

Supplementary Figure 3. Summary of treatment-emergent adverse events with ibrutinib–lenalidomide regimen in the all-treated population

Characteristic	PFS				OS			
	N	HR	95% CI ¹	p-value	N	HR	95% CI ¹	p-value
COO subtype	25				25			
GCB		—	—			—	—	
Non-GCB		0.49	0.19, 1.26	0.14		0.32	0.08, 1.23	0.10
Anti-CD20 mAbs addition	27				27			
Ibru-Len		—	—			—	—	
Ibru-Len-anti CD20 mAbs		0.87	0.35, 2.17	0.8		1.49	0.48, 4.65	0.5
Any additional treatment	27				27			
Ibru-Len		—	—			—	—	
Ibru-Len-based regimen ^a		1.75	0.70, 4.36	0.2		3.05	0.82, 11.3	0.10
Lenalidomide Dose	27				27			
<20 mg		—	—			—	—	
≥20 mg		0.52	0.21, 1.27	0.15		0.41	0.12, 1.36	0.15
Bispecific exposure	27				27			
No Previous Bispecific Antibody		—	—			—	—	
Previous Bispecific Antibody		2.77	0.94, 8.12	0.063		2.25	0.66, 7.65	0.2
High-grade subtype	21				21			
Non-HGBL		—	—			—	—	
HGBL		2.14	0.71, 6.46	0.2		0.82	0.17, 4.11	0.8

^a 14 patients, including 12 receiving anti-CD20 mAbs and 6 receiving other additional therapies (Venetoclax, n=4; Tafasitamab, n=1; intrathecal chemotherapy, n=1).

Abbreviations: CI, confidence interval; COO, cell of origin; GCB, germinal center B-cell-like; HGBL, high-grade B-cell lymphoma; HR, hazard ratio; Ibru-Len, Ibrutinib-Lenalidomide; mAbs, monoclonal antibodies; OS, overall survival; PFS, progression-free survival; CI = Confidence Interval.

Supplementary Table 1. Univariate Cox analyses of PFS and OS across subgroups.