The iR^2 regimen (ibrutinib plus lenalidomide and rituximab) for relapsed/refractory DLBCL: A multicentre, non-randomised, open-label phase 2 study

Radhakrishnan Ramchandren,[a,*] Peter Johnson,[b] Nilanjan Ghosh,[c] Jia Ruan,[d] Kirit M. Ardeshna,[e] Roderick Johnson,[f] Gregor Verhoef,[g] David Cunningham,[h] Sven de Vos,[i] Shireen Kassam,[j] Luis Fayad,[k] John Radford,[l] Sarah Bailly,[m] Fritz Offner,[n] David Morgan,[o] Javier Munoz,[p,s] Jerry Ping,[q] Edith Szafer-Glusman,[q] Karl Eckert,[q] Jutta K. Neuenburg,[q] and Andre Goy[r]

[a]Division of Hematology/Oncology, University of Tennessee Health Science Center, Knoxville, TN, USA
[b]Cancer Research UK Clinical Centre, Southampton General Hospital, Southampton, UK
[c]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA
[d]Division of Hematology and Medical Oncology, Weill Cornell Medicine, New York, NY, USA
[e]University College London/UCL Hospitals, Biomedical Research Centre, London, UK
[f]Leeds Cancer Centre at St. James's University Hospital, Leeds, UK
[g]Department of Haematology, UZ Leuven – Campus Gasthuisberg, Leuven, Belgium
[h]Gastrointestinal and Lymphoma Unit, The Royal Marsden NHS Foundation Trust – Royal Marsden Hospital, London, UK
[i]Division of Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[j]Haematology Department, King's College Hospital, London, UK
[k]Department of Lymphoma-Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX, USA
[l]Division of Cancer Sciences, The University of Manchester and the Christie NHS Foundation Trust, Manchester, UK
[m]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain Brussels, Brussels, Belgium
[n]Department of Clinical Hematology, Universitair Ziekenhuis Gent, Ghent, Belgium
[o]Division of Hematology and Oncology, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA
[p]Department of Hematology, Banner MD Anderson Cancer Center, Gilbert, AZ, USA
[q]Pharmacyclics LLC, an AbbVie Company, South San Francisco, CA, USA
[r]Department of Hematology & Oncology, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA

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Summary

Background This phase 1b/2 PCYC-1123-CA study evaluated efficacy and safety of the combination of ibrutinib, lenalidomide, and rituximab (iR^2 regimen) in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) ineligible for stem cell transplantation.

Methods In phase 2, patients with relapsed/refractory non-germinal centre B-cell–like DLBCL received oral ibrutinib 560 mg once daily and oral lenalidomide 20 mg or 25 mg once daily on Days 1–21 of each 28-day cycle until disease progression or unacceptable toxicity and intravenous rituximab 375 mg/m^2 on Day 1 of Cycles 1–6. The primary endpoint was overall response rate (ORR) in the response-evaluable population (received any study treatment and had ≥1 post-baseline disease assessment). The study was done at 24 academic and community hospitals in Belgium, Germany, United Kingdom, and USA. This study was registered with ClinicalTrials.gov, NCT02077166.

Findings Between March 13, 2014 and October 2, 2018, 89 patients were enrolled with a median time on study of 35.0 months. Best ORR in the response-evaluable population (n = 85) was 49% (95% confidence interval [CI], 38–61) across dose cohorts and 53% (95% CI, 39–67) and 44% (95% CI, 26–62) in the 20 mg and 25 mg lenalidomide cohorts, respectively, with complete responses in 24/85 (28%), 17/53 (32%), and 7/32 (22%) patients, respectively. Grade 3/4 adverse events (AEs) occurred in 81/89 patients (91%), most frequently neutropenia (36/89; 40%), maculopapular rash (16/89; 18%), anaemia (12/89; 13%), and diarrhoea (9/89; 10%). Serious adverse events occurred in 57/89 patients (64%). Fatal AEs occurred in 12/89 patients (13%); causes of death were worsening of DLBCL (n = 7), pneumonia (n = 3), sepsis (n = 1), and cardiac arrest (n = 1).

Interpretation The most frequent AEs (diarrhoea, neutropenia, fatigue, cough, anaemia, peripheral oedema, and maculopapular rash) were consistent with known safety profiles of the individual drugs. The iR^2 regimen demonstrated antitumour activity with durable responses in patients with relapsed/refractory DLBCL.

*Corresponding author. University of Tennessee Health Science Center, 1926 Alcoa Highway, Building F, Suite 410, Knoxville, TN 37920, USA.
E-mail address: RRamchandren@utmck.edu (R. Ramchandren).
[s]Current affiliation: Mayo Clinic, Phoenix, AZ, USA.

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Research in context

Evidence before this study

The team searched PubMed through April 25, 2022 for clinical trials using the search terms "diffuse large B cell lymphoma" OR "DLBCL", AND "relapsed" OR "refractory" with no restrictions for language or date. Search results showed that autologous stem cell transplantation (SCT) and chimeric antigen receptor T-cell (CAR-T) therapies can induce durable remissions in up to 50% of patients with relapsed/refractory DLBCL. However, only a minority of patients are eligible for SCT, and many patients do not respond or are unable to access CAR-T for logistical reasons. The team found that several other novel treatment options for relapsed/refractory DLBCL (polatuzumab vedotin, loncastuximab tesirine, selinexor, and tafasitamab) have reported overall response rates of 24–70%, with complete response rates of 12–58%. However, none of these therapies were specifically evaluated in patients with the poor-prognosis non-germinal centre B-cell–like (non-GCB) DLBCL subtype.

Added value of this study

Here, results from the phase 2 portion of the PCYC-1123-CA study evaluating the combination of ibrutinib, lenalidomide, and rituximab (iR^2 regimen) in patients with relapsed/refractory non-GCB DLBCL ineligible for SCT are reported. Results of the study demonstrated encouraging antitumour activity and durable responses with the iR^2 regimen in patients with relapsed/refractory non-GCB DLBCL. Median duration of response and overall survival appeared promising relative to other novel approved therapies. The iR^2 regimen demonstrated a manageable safety profile consistent with the known safety profiles of the individual drugs.

Implications of all the available evidence

The iR^2 regimen may provide a tolerable therapeutic regimen with encouraging activity for patients who are not candidates for or have relapsed after intensive therapy (SCT or CAR-T), a population with poor outcomes and continued unmet medical need. The regimen could also potentially serve as a bridging therapy to SCT or CAR-T therapy or could be administered prior to T-cell collection based on evidence that ibrutinib can augment CAR-T cell production.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive B-cell lymphoma that accounts for 30–40% of all non-Hodgkin lymphomas.[1] Standard first-line treatment for DLBCL is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[2] However, only ~60% of patients are cured with R-CHOP.[3] Patients with relapsed/refractory DLBCL have poor outcomes, particularly those ineligible for stem cell transplantation (SCT), with life expectancy of a few months and overall survival (OS) rates of 28% at 1 year and 20% at 2 years.[4] Approximately half of the patients eligible for chimeric antigen receptor T-cell (CAR-T) therapy may respond, but unmet medical need remains for non-responders and those unable to access CAR-T for logistical reasons.[5] DLBCL can be further classified according to cell of origin using immunohistochemistry (IHC; Hans method), resulting in germinal centre B-cell–like (GCB) or non-GCB subtypes. By gene expression profiling (GEP), DLBCL can be subdivided into activated B-cell–like (ABC), GCB, and unclassified.[6] The non-GCB subtype by IHC largely overlaps with the ABC subtype by GEP and has inferior prognosis compared to the GCB subtype.[1,7] ABC and GCB subtypes are driven by distinct mechanisms; the ABC subtype is dependent on nuclear-factor kappa-B (NF-κB) activation, whereas the GCB subtype relies on phosphatidylinositol 3-kinase activation.[8] In the ABC subtype, malignant B cells selectively acquire mutations targeting the B-cell receptor (BCR) pathway, resulting in chronic active BCR signaling.[9] Bruton's tyrosine kinase (BTK) plays a critical role in this pathway, leading to downstream activation of NF-κB, and is essential for ABC DLBCL cell survival.[10]

Ibrutinib is a once-daily BTK inhibitor approved globally for the treatment of B-cell malignancies and chronic graft-versus-host disease.[11] A phase 1/2 study in patients with relapsed/refractory DLBCL demonstrated preferential activity with ibrutinib in ABC relative to GCB DLBCL, with response rates of 37% and 5%, respectively.[9] Similarly, lenalidomide has demonstrated higher response rates in non-GCB relative to GCB DLBCL (53% vs 9%).[12] Preclinically, models suggest the

potential for synergy with ibrutinib and lenalidomide in ABC DLBCL by inhibition of BCR and MYD88 pathways, each of which induce NF-κB, via distinct mechanisms.[13] In follicular lymphoma, the combination of ibrutinib, lenalidomide, and rituximab was previously evaluated in a phase 1 study in previously untreated patients.[14] The combination resulted in rash and adverse events (AEs) that led to a 50% discontinuation rate; this was considered unacceptable for a first-line regimen for an indolent lymphoma, despite an overall response rate (ORR) of 95%.[14] However, this combination could prove beneficial in patients with more aggressive lymphomas such as DLBCL, especially in the relapsed/refractory setting, where few treatment options are available.

This phase 1b/2 study evaluated the efficacy and safety of the combination of ibrutinib, lenalidomide, and rituximab (iR^2 regimen) in patients with relapsed/refractory DLBCL ineligible for SCT. In the phase 1b portion of the study, the iR^2 regimen demonstrated promising activity with a manageable safety profile.[15] Here, results for the phase 2 portion are reported.

Methods

Study design and participants

PCYC-1123-CA (ClinicalTrials.gov, NCT02077166) was an international, open-label, multicentre, phase 1b/2 study that evaluated safety and efficacy of the iR^2 regimen. Methods and results for phase 1b were previously reported.[15] Phase 2 was done at 24 sites in 4 countries (Belgium, Germany, United Kingdom, USA; Appendix p 2). For phase 2, eligible patients were ≥18 years with de novo non-GCB DLBCL by IHC (Hans algorithm); relapsed/refractory disease (defined as recurrence after complete response [CR], or residual disease [partial response (PR), stable disease, or progressive disease (PD)] at completion of prior treatment regimen), ≥1 measurable disease site by computed tomography (>1.5 cm), and adequate haematologic, hepatic, and renal function. Patients were transplant-ineligible, defined as one or more of the following criteria: age ≥70 years, diffuse lung capacity for carbon monoxide <50% by pulmonary function test, left ventricular ejection fraction <50%, organ dysfunction or comorbidities precluding transplantation, failure to achieve CR or PR with salvage therapy (prior to stem cell transplant), or patient refusal. Key exclusion criteria included transformed, GCB, or primary mediastinal DLBCL, central nervous system lymphoma or leptomeningeal disease, and prior ibrutinib and/or lenalidomide.

The study was conducted in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice and principles of the Declaration of Helsinki. The protocol was approved by institutional review boards or independent ethics committees of all participating institutions. All patients provided written informed consent. The protocol and statistical analysis plan are available online at ClinicalTrials.gov (NCT02077166).

Procedures

Patients received oral ibrutinib 560 mg once daily throughout each 28-day cycle, oral lenalidomide at 20 mg or 25 mg once daily on Days 1–21 of each 28-day cycle, and intravenous rituximab 375 mg/m^2 on Day 1 of Cycles 1–6.[15] Ibrutinib and lenalidomide were continued until PD or unacceptable toxicity (Fig. 1). Following study closure, eligible patients could continue ibrutinib in a long-term extension study PCYC-1145-LT (NCT03229200). Because of dose-limiting toxicities of neutropenia and rash observed in phase 1b,[15] management guidelines were implemented via protocol amendments (Appendix p 16), including dose holds and/or reductions and management with corticosteroids (no cap) and/or antihistamines for rash and growth factors for neutropenia. Venous thromboembolism risk assessment was performed at baseline, and thromboprophylaxis was given per investigator's discretion.

Outcomes

The primary endpoint was ORR by investigator assessment per Lugano Classification. Secondary endpoints were CR, duration of response (DOR), progression-free survival (PFS), OS, safety, and tolerability. Response was assessed by computed tomography, magnetic resonance imaging, and/or positron emission tomography every 3 months until Cycle 25, then every 6 months thereafter (Fig. 1). Exploratory analyses were performed to evaluate ORR according to DLBCL subtype based on GEP (nanoString Technologies, Seattle, WA). Minimal residual disease (MRD) was assessed by next-generation sequencing (ClonoSEQ NGS Assay; Adaptive Biotechnologies, Seattle, WA) in plasma samples collected at baseline (Day 1 Cycle 1) and at Day 1 of Cycles 2, 3, and 4 and was based on detection of tumour-specific immunoglobulin gene rearrangement clones previously identified in tumour tissue. MRD was measured as tumour clones per millilitre of plasma. Safety was assessed using physical examinations, vital signs, laboratory tests, and AE reporting at each study visit from initiation of study treatment until 30 days after last dose. Major haemorrhage (defined as serious or grade ≥3 haemorrhage, or CNS haemorrhage of any grade) was monitored as an AE of special interest. AEs were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Sample size determination

For phase 2, ~55 patients were required for enrolment of ≥49 response-evaluable patients receiving 20 mg lenalidomide. An interim analysis was planned to include approximately 28 evaluable patients with adequate

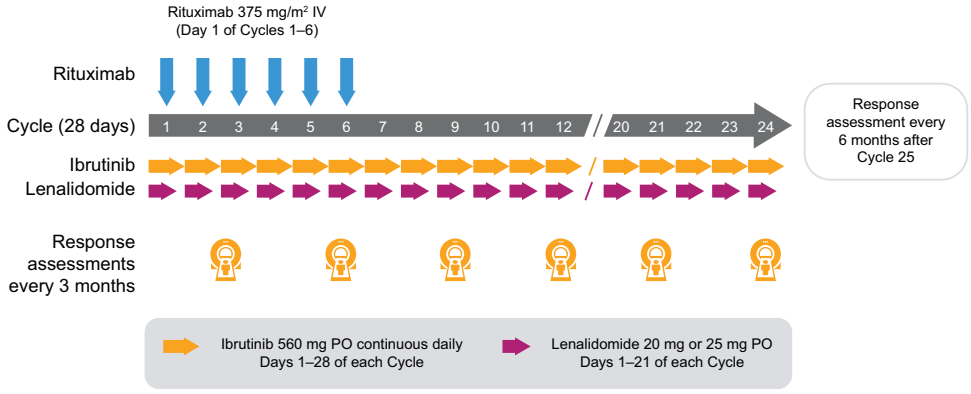

Fig. 1: Phase 2 treatment schema. PO = per oral.

tumour response assessments. If 11 or fewer responders (≤11/28) are observed, the study may be discontinued for futility. The study was designed to test the null hypothesis of an ORR of 40% (based on historic controls) in the response-evaluable population vs the alternative hypothesis that the ORR is 60% (considered clinically meaningful). The null hypothesis will be rejected if 27 or more responses are observed in the 49 patients. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true ORR is 60%. This statistical design including the number of patients and the number of responders follows the statistical framework of Simon's minimax two-stage design (Simon 1989).

In addition, approximately 28 additional patients were planned to be enrolled at 25 mg lenalidomide to explore the efficacy and safety at this higher dose of lenalidomide in phase 2.

Statistical analysis

At the interim analysis, 30 response-evaluable patients treated with 20 mg lenalidomide were enrolled, and 18 responders (60%) were observed. The results were reviewed by a review committee comprising the Sponsor (the medical monitor, a safety physician, and a biostatistician) as well as participating investigators (Appendix p 2). Among the initially enrolled 28 response-evaluable patients, 17 responders (61%) were observed. Per planned interim analysis, if 11 or fewer responders (≤11/28) in 28 response-evaluable patients are observed, the study may be discontinued for futility. Futility requirements were not met, and the review committee unanimously voted to continue the trial as planned with continued enrolment in the 20 mg lenalidomide cohort.

Finally, the study enrolled 55 patients in the 20 mg lenalidomide cohort and 34 patients in the 25 mg lenalidomide cohort (enrolled sequentially following completion of enrolment in the 20 mg cohort).

Among 55 patients in the 20 mg lenalidomide cohort, 53 patients were response evaluable. Among 49 initially enrolled response-evaluable patients, 26 responders (53%) were observed, which is one less responder than the pre-specified responders (27) for rejecting the null hypothesis. In the following 4 response-evaluable patients enrolled, 2 responders were observed. In total, there were 28 responders among 53 response-evaluable patients, and the ORR was 53% (90% CI, 41–65; 95% CI, 39–67).

The primary analysis of ORR was performed in the response-evaluable population, which comprised all patients who received any study treatment and had ≥1 post-baseline disease assessment using imaging, physical examination, and/or laboratory tests. As a sensitivity analysis, the analysis of ORR was also performed in the all-treated population, which comprised all enrolled patients who received any amount of study drug. PFS, OS, and safety were evaluated in the all-treated population. This Phase 2 study was designed for proof of concept, and no adjustments were made to control for bias or to control alpha for multiplicity.

For ORR, two-sided 95% CIs were calculated based on the exact binomial distribution. Medians and 95% CIs for time-to-event endpoints were estimated by the Kaplan–Meier method. For DOR and PFS, patients without PD or death were censored at the date of the last tumour assessment; for OS, patients without death were censored at the last date known to be alive. No imputation was done for missing data. Prespecified subgroup analyses were performed according to DLBCL subtype by GEP and disease status at completion of prior regimen. All analyses were performed using SAS version 9.3.

Role of the funding source

This study was sponsored by Pharmacyclics LLC, an AbbVie Company, and was designed by a representative of the sponsor (J.K.N.) in collaboration with A.G. Data were collected by investigators and their teams and

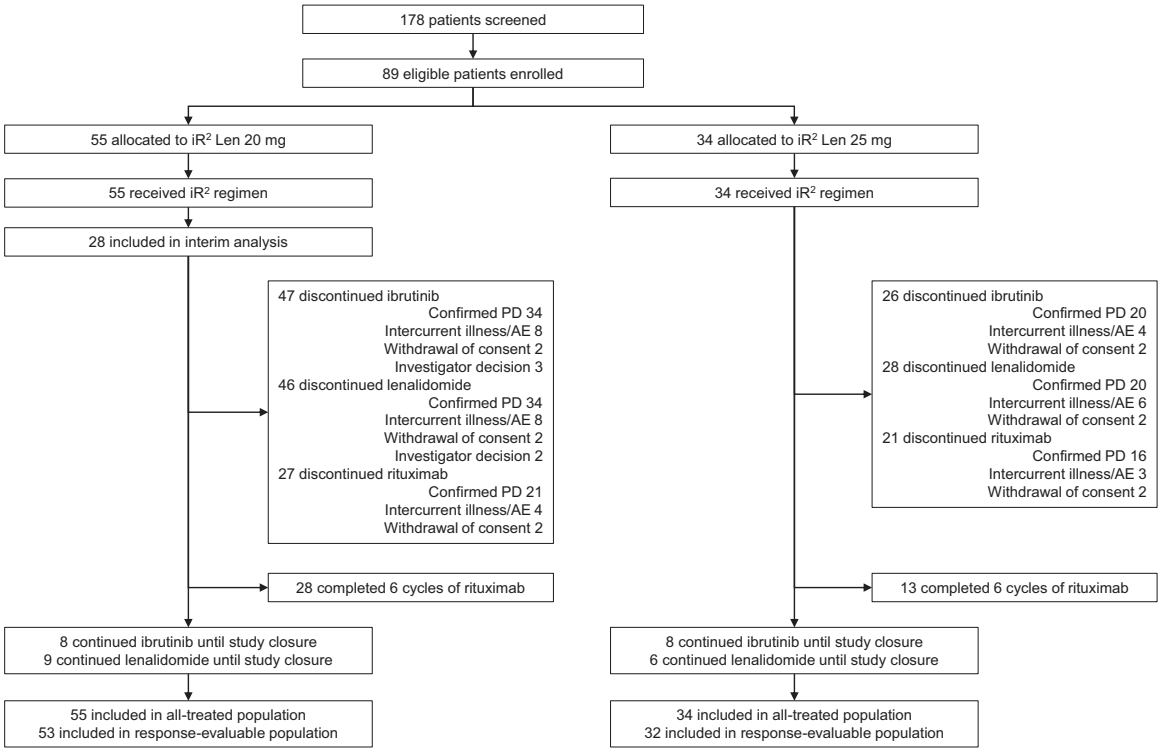

Fig. 2: Trial profile. AE = adverse event; iR^2 = ibrutinib, lenalidomide, and rituximab; Len = lenalidomide; PD = progressive disease.

entered into an electronic database maintained by the sponsor. The sponsor confirmed the data accuracy and compiled them for analysis. All authors had full access to and interpreted the data. Editorial support, funded by the sponsor, was provided by a professional medical writer. R.R., J.K.N., and A.G. collaboratively wrote the first draft, had full access to and verified all study data, and had final responsibility for the decision to submit for publication.

Results

Between March 13, 2014 and October 2, 2018, 55 patients were enrolled at the 20 mg lenalidomide dose, and 34 patients were enrolled at the 25 mg lenalidomide dose (Fig. 2). Median age was 64 years (range, 30–86); 58% were male (Table 1). Median time from initial diagnosis to study treatment was 17.3 months (range, 3–159). Median number of prior regimens was 2 (range, 1–5). Most patients (76%) had received ≥2 prior regimens; 52% were refractory to the prior regimen, and 16% had primary refractory disease (Table 1). No patients received prior CAR-T; prior anticancer treatments are described in the Appendix (p 4). All patients had non-GCB DLBCL by IHC. GEP was conducted on tumour tissue samples from 65 patients (32 ABC subtype, 15 GCB subtype, 18 unclassified).

At the time of analysis, median time on study was 35.0 months (interquartile range [IQR], 32.5–51.4). At study closure, 14/89 patients (16%) were receiving ibrutinib and lenalidomide, 2/89 (2%) ibrutinib only, and 1/89 (1%) lenalidomide only (Fig. 1). Most patients (49/89; 55%) received ≥6 treatment cycles (Table 2). The most common reason for treatment discontinuation was PD (Fig. 2).

Best ORR in the response-evaluable population (n = 85) was 49% (95% CI, 38–61) across dose cohorts and was 53% (95% CI, 39–67) and 44% (95% CI, 26–62) in the 20 mg and 25 mg lenalidomide cohorts, respectively (Fig. 3A; Appendix p 5). CR was achieved in 24/85 (28%) patients across cohorts and in 17/53 (32%) and 7/32 (22%) in the 20 mg and 25 mg lenalidomide cohorts, respectively. Of patients with baseline and ≥1 postbaseline assessments (n = 82), 68% had tumour size reductions (Fig. 3B). Durable responses were observed (Fig. 3C and D). Median DOR was 38.3 months (95% CI, 9.5–not estimable [NE]) across cohorts and was 38.3 months (95% CI, 3.7–NE) and 28.6 months (95% CI, 2.8–28.6) in the 20 mg and 25 mg lenalidomide cohorts, respectively. Median duration of CR was not reached in either cohort (95% CI, 29.8–NE months across cohorts, with 14 patients actively remaining on therapy). Of 24 complete responders, 19 had ongoing response at this analysis; 15 of these had response durations >2 years, including six with response durations >3 years.

Characteristic	iR^2 Len 20 mg n = 55	iR^2 Len 25 mg n = 34	iR^2 Total N = 89
Age, years			
Median	63 (56–72)	67 (60–74)	64 (58–72)
≥65 years	24 (44%)	20 (59%)	44 (49%)
Sex			
Male	32 (58%)	20 (59%)	52 (58%)
Female	23 (42%)	14 (41%)	37 (42%)
Race			
White	51 (93%)	30 (88%)	81 (91%)
Black/African American	2 (4%)	1 (3%)	3 (3%)
Asian	1 (2%)	2 (6%)	3 (3%)
Multiple	0	1 (3%)	1 (1%)
Unknown	1 (2%)	0	1 (1%)
Ethnicity			
Hispanic/Latino	0	5 (15%)	5 (6%)
Non-Hispanic/Latino	55 (100%)	29 (85%)	84 (94%)
Mean BMI, kg/m^2	27.0 (6.1)	27.2 (5.6)	27.1 (5.9)
ECOG PS			
0	25 (45%)	17 (50%)	42 (47%)
1	29 (53%)	15 (44%)	44 (49%)
2	1 (2%)	2 (6%)	3 (3%)
Median time from initial diagnosis, months	19.8 (11.0–51.4)	14.0 (10.8–24.4)	17.3 (11.0–33.3)
DLBCL subtype per GEP			
ABC	25 (45%)	7 (21%)	32 (36%)
GCB	9 (16%)	6 (18%)	15 (17%)
Unclassified	12 (22%)	6 (18%)	18 (20%)
Not available	9 (16%)	15 (44%)	24 (27%)
Ann Arbor staging			
I/IE	3 (5%)	0	3 (3%)
II/IIE	10 (18%)	4 (12%)	14 (16%)
III/IIIE/IIIE,S	5 (9%)	11 (32%)	16 (18%)
IV	37 (67%)	19 (56%)	56 (63%)
Bulky disease	27 (49%)	10 (29%)	37 (42%)
5–10 cm	20 (36%)	8 (24%)	28 (31%)
>10 cm	7 (13%)	2 (6%)	9 (10%)
Extranodal disease	39 (71%)	22 (65%)	61 (69%)
Median number of prior regimens	2 (2–3)	2 (2–3)	2 (2–3)
Number of prior regimens			
1	13 (24%)	8 (24%)	21 (24%)
≥2	42 (76%)	26 (76%)	68 (76%)
Disease status at completion of prior regimen			
Refractory	29 (53%)	17 (50%)	46 (52%)
Relapsed			
Complete response	14 (25%)	9 (26%)	23 (26%)
Partial response	12 (22%)	8 (24%)	20 (22%)
Primary refractory DLBCL	13 (24%)	1 (3%)	14 (16%)
Prior autologous SCT	12 (22%)	8 (24%)	20 (22%)
Median time from last dose of prior therapy to first ibrutinib dose, months	3.4 (1.8–9.4)	4.6 (1.7–8.7)	4.2 (1.8–8.7)

Data are n (%), median (IQR), or mean (SD). ABC = activated B-cell-like; BMI = body mass index; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group performance status; GCB = germinal center B-cell-like; GEP = gene expression profiling; IQR = interquartile range; iR^2 = ibrutinib, lenalidomide, and rituximab; Len = lenalidomide; SCT = stem cell transplantation; SD = standard deviation.

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

	iR² Len 20 mg n = 55	iR² Len 25 mg n = 34	iR² Total N = 89
Median time on study, months	37.3 (35.0–42.6)	31.1 (27.9–32.5)	35.0 (31.3–40.7)
Number of treatment cycles received			
1	5 (9%)	4 (12%)	9 (10%)
2	3 (5%)	5 (15%)	8 (9%)
3–5	14 (25%)	9 (26%)	23 (26%)
6	9 (16%)	4 (12%)	13 (15%)
7–12	5 (9%)	1 (3%)	6 (7%)
>12	19 (35%)	11 (32%)	30 (34%)
Median treatment duration, months			
Ibrutinib	5.5 (2.8–17.5)	4.5 (1.8–26.2)	4.9 (2.3–17.5)
Lenalidomide	5.3 (2.5–26.3)	4.3 (1.6–13.1)	4.7 (2.3–17.5)
Median relative dose intensity, %			
Ibrutinib	95 (76–100)	93 (81–98)	93 (80–100)
Lenalidomide	82 (66–92)	73 (52–92)	75 (65–92)
Rituximab	100 (100–100)	100 (100–100)	100 (100–100)
AE leading to dose hold			
Ibrutinib	38 (69%)	28 (82%)	66 (74%)
Lenalidomide	37 (67%)	26 (76%)	63 (71%)
Rituximab	10 (18%)	6 (18%)	16 (18%)
AE leading to dose reduction			
Ibrutinib	12 (22%)	9 (26%)	21 (24%)
Lenalidomide	21 (38%)	14 (41%)	35 (39%)
Rituximab	NA	NA	NA
AE leading to discontinuation			
Ibrutinib	11 (20%)	5 (15%)	16 (18%)
Lenalidomide	11 (20%)	7 (21%)	18 (20%)
Rituximab	6 (11%)	4 (12%)	10 (11%)

Data are n (%) or median (IQR). AE = adverse event; IQR = interquartile range; iR² = ibrutinib, lenalidomide, and rituximab; Len = lenalidomide; NA = not applicable; PD = progressive disease; SD = standard deviation.

Table 2: **Treatment exposure in the all-treated population.**

In prespecified subgroup analyses, responses were observed across all DLBCL subtypes by GEP, with best ORRs of 55% (95% CI, 36–73) in ABC, 36% (95% CI, 13–65) in GCB, and 61% (95% CI, 36–83) in unclassified (Fig. 4A). Reductions in tumour size were observed in all subtypes (Fig. 4B). Median DOR was 18.4 months (95% CI, 3.2–NE) in ABC, not reached (95% CI, 0.9–NE) in GCB, and 38.3 months (95% CI, 2.2–NE) in unclassified (Appendix p 6). In patients with primary refractory disease (n = 13), ORR was 31% (95% CI, 9–61), with CR in 4/13 (31%) patients. In patients with relapsed disease (n = 42), ORR was 64% (95% CI, 48–78), with CR in 15/42 (36%) patients.

A total of 25 patients who responded to treatment (20 CR, 5 PR) across cohorts had a tumour clone identified in tumour tissue and had plasma samples for MRD available. Among the 20 CR patients evaluated, 13 had detectable MRD in plasma at baseline (Day 1 Cycle 1), while seven had undetectable MRD (uMRD) in plasma at baseline and all timepoints from Day 1 of Cycle 1 through Day 1 of Cycle 4. uMRD was achieved after one cycle in 9/13 patients (69%), and after two cycles in 12/13 (92%). Among the 5 PR patients evaluated, 4 had detectable MRD in plasma at baseline; no durable MRD clearance was observed, with one patient achieving uMRD in plasma at a single time point (Day 1 of Cycle 2). Median DOR was 31.3 months (95% CI, 2.5–68.4) for patients with uMRD at baseline (n = 8), 21.7 months (95% CI, 9.8–31.9) for those who became uMRD on treatment (n = 13), and 7.7 months (95% CI, 1.6–15.9) for those without conversion to uMRD (n = 4).

In the all-treated population (n = 89), median PFS was 5.4 months (95% CI, 3.4–6.3) across dose cohorts and 5.4 months (95% CI, 3.4–11.3) and 4.7 months (95% CI, 2.6–24.8), respectively, in the 20 mg and 25 mg lenalidomide cohorts (Fig. 5A). At the time of analysis, deaths had occurred in 55/89 patients (62%) in the all-treated population and 33/55 patients (60%) and 22/34 patients (65%), respectively, in the 20 and 25 mg lenalidomide cohorts (Appendix p 7). Median OS was 14.2 months (95% CI, 9.7–28.1) across cohorts and 14.7 months (95% CI, 9.7–32.8) and 11.6 months (95% CI, 5.7–NE),

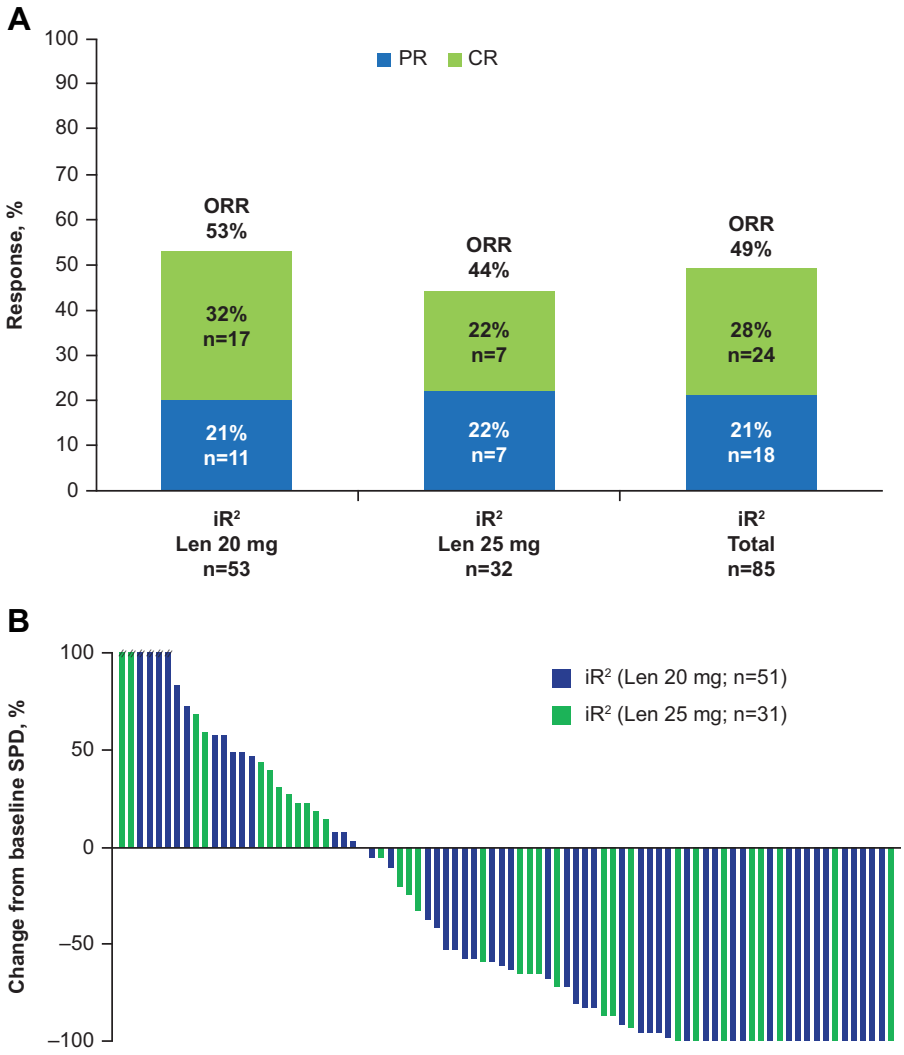

Fig. 3: Response by dose cohort. Best overall response by dose cohort in the response-evaluable population (A); Waterfall plot of maximum percent reduction from baseline in tumour size by dose cohort in the response-evaluable population* (B); Swimlane plot of treatment duration and response in all-treated patients in the lenalidomide 20 mg dose cohort, with each bar representing an individual patient ordered by treatment duration (C); Swimlane plot of treatment duration and response in all-treated patients in the lenalidomide 25 mg dose cohort, with each bar representing an individual patient ordered by treatment duration (D). // indicates values greater than 100% (457%, 315%, 247%, 152%, 146%, and 112%). CR = complete response; iR^2 = ibrutinib, lenalidomide, and rituximab; Len = lenalidomide; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; SPD = sum of the product of diameters. *Three patients with a best response of progressive disease had no post-baseline imaging and are not included in the waterfall plot.

respectively, in the 20 and 25 mg lenalidomide cohorts (Fig. 5B).

Updated analysis of patients from the phase 1b cohort (n = 45) with a median time on study of 59.6 months (IQR, 54.3–70.0) demonstrated durable responses in patients treated with lenalidomide dose levels ≥15 mg (Appendix p 3). Of 40 response-evaluable patients, best response was CR in 11/40 (28%) and PR in 6/40 (15%); this was unchanged from the primary analysis (median time on study, 25.6 months).[15] Median DOR remained 15.9 months (95% CI, 2.8–NE) as in the primary analysis[15]; however, range of DOR increased from 0.9–37.2+ months at primary analysis to 0.9–68.4+ months at updated analysis. Of 11 CRs, six had an ongoing response at updated analysis; 2/6 patients had response durations >5 years including one patient who remained on study for >6 years.

All patients experienced treatment-emergent AEs. The most frequent AEs of any grade were diarrhoea (48/89 patients; 54%), neutropenia (40/89; 45%), fatigue (39/89; 44%), cough (32/89; 36%), anaemia (29/89; 33%), peripheral oedema (29/89; 33%), and

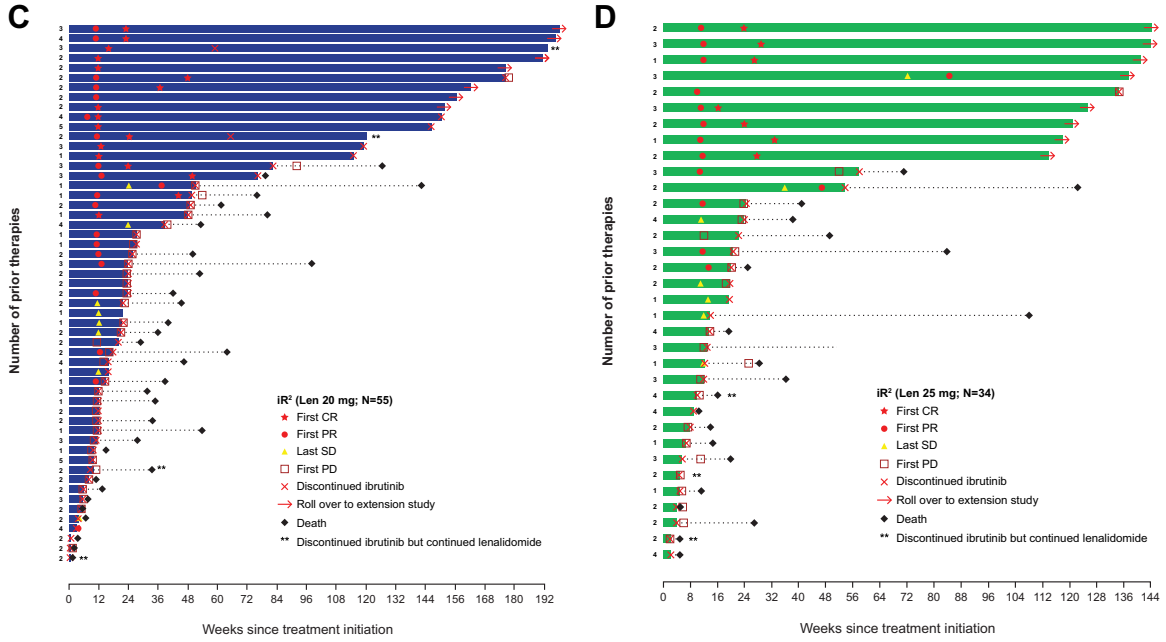

Fig. 3: (continued)

maculopapular rash (28/89; 31%) (Table 3; Appendix p 8). Rates were generally similar between lenalidomide dose cohorts (Table 3). Grade 3/4 AEs occurred in 81/89 patients (91%), most frequently neutropenia (36/89; 40%), maculopapular rash (16/89; 18%), anaemia (12/89; 13%), and diarrhoea (9/89; 10%) (Table 3). Serious AEs occurred in 57/89 patients (64%) (Table 3). Fatal AEs occurred in 12/89 patients (13%); causes of death were worsening of DLBCL (n = 7), pneumonia (n = 3), sepsis (n = 1), and cardiac arrest (n = 1). The most frequent treatment-related AEs are in the Appendix (p 11).

Atrial fibrillation of any grade occurred in 5/89 patients (6%) and was grade ≥3 in 2/89 (2%). Atrial fibrillation resulted in ibrutinib dose holds in 3/89 patients (3%), discontinuation in 1/89 (1%), and no dose reductions. Other cardiac arrhythmias occurred in 22/89 patients (25%) and were grade ≥3 in 10/89 (11%); other cardiac arrhythmias occurring in ≥2 patients were: palpitations (n = 5), syncope (n = 4), sinus bradycardia (n = 3), atrial flutter (n = 3), bradycardia (n = 3), and cardiac arrest (n = 2). Hypertension occurred in 6/89 patients (7%). Bleeding events (identified using Standardised Medical Dictionary for Regulatory Activities [MedDRA] Query for haemorrhage, excluding laboratory terms) of any grade occurred in 38/89 patients (43%); major haemorrhage occurred in 7/89 (8%): petechiae (n = 3), gastrointestinal haemorrhage (n = 2), gastric haemorrhage (n = 1), haematoma infection (n = 1), and purpura (n = 1). Infections of any grade occurred in 55/89 patients (62%) and were grade ≥3 in 14/89 (16%). The most frequent any-grade infections were upper respiratory tract infection (17/89; 19%), urinary tract infection (12/89; 13%), and pneumonia (9/89; 10%). Infections resulted in ibrutinib dose holds in 27/89 patients (30%), dose reductions in 2/89 (2%), and discontinuation in 3/89 (3%). Other malignancies occurred in 4/89 patients (4%), including basal cell carcinoma (n = 2), Bowen's disease (n = 1), squamous cell carcinoma (n = 1), acute myeloid leukaemia (n = 1), and myelodysplastic syndrome (n = 1). Deep vein thrombosis of any grade occurred in 2/89 patients (2%).

AEs led to dose holds of ibrutinib, lenalidomide, or rituximab in 66/89 (74%), 63/89 (71%), or 16/89 (18%) patients, respectively (Table 2, Appendix p 13). AEs led to dose holds of ibrutinib or lenalidomide more frequently in the 25 mg vs 20 mg lenalidomide cohort (Table 2). AEs led to dose reduction of ibrutinib and lenalidomide in 21/89 (24%) and 35/89 (39%) patients, respectively (Table 2, Appendix p 14). AEs led to discontinuation of ibrutinib, lenalidomide, or rituximab in 16/89 (18%), 18/89 (20%), and 10/89 (11%) patients, respectively (Table 2). The most frequent AEs leading to ibrutinib and lenalidomide discontinuation were worsening of DLBCL (n = 4), pneumonia (n = 2), and thrombocytopenia (n = 2).

Discussion

Durable remissions are infrequent with current treatment options in relapsed/refractory DLBCL.[4,5] In this study, the iR^2 regimen (ibrutinib, lenalidomide, and

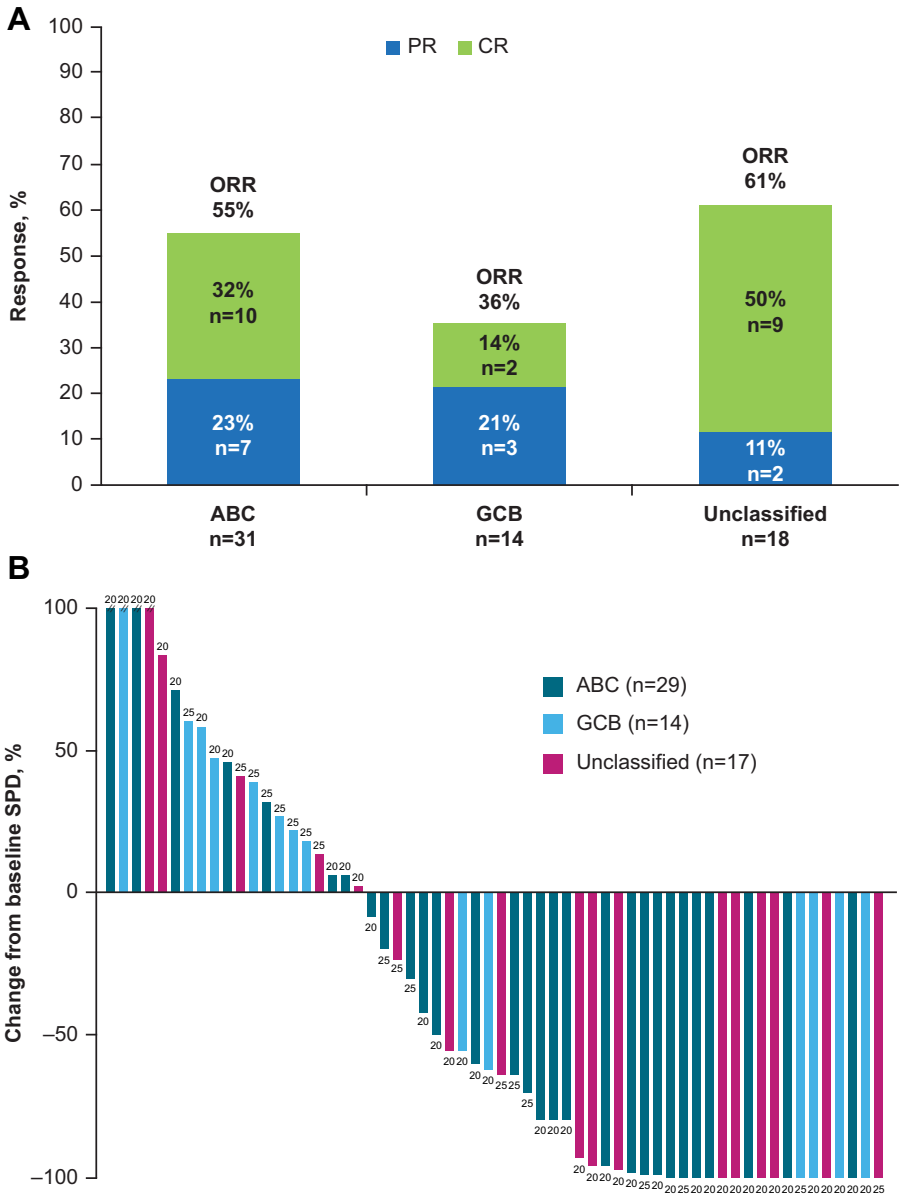

Fig. 4: Response by DLBCL subtype in the response-evaluable population. Best overall response by DLBCL subtype per GEP (A); Waterfall plot of maximum percent reduction from baseline in tumour size by DLBCL subtype per GEP* (B). Numbers next to each bar indicate the dose cohort (ie, lenalidomide dose) for that patient. // indicates values greater than 100% (315%, 247%, 152%, and 146%). ABC = activated B-cell–like; CR = complete response; DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B-cell–like; GEP = gene expression profiling; iR^2 = ibrutinib, lenalidomide, and rituximab; Len = lenalidomide; PR = partial response; SPD = sum of the product of diameters. *Two patients with a best response of progressive disease had no post-baseline imaging and are not included in the waterfall plot.

rituximab) demonstrated durable responses in patients with relapsed/refractory non-GCB DLBCL. ORR was 49% in response-evaluable patients across dose cohorts, with ORRs of 53% and 44% in the 20 mg and 25 mg lenalidomide cohorts, respectively; corresponding CR rates were 28% across dose cohorts, and 32% and 22% in the 20 mg and 25 mg lenalidomide cohorts, respectively. While the null hypothesis cannot be rejected because the lower bound of the 95% CI in the 20 mg lenalidomide cohort is 39%, an ORR of 53% is considered clinically relevant given the limited treatment options for this difficult-to-treat population of patients with relapsed/refractory DLBCL. While indirect comparisons should be interpreted with caution given differences in

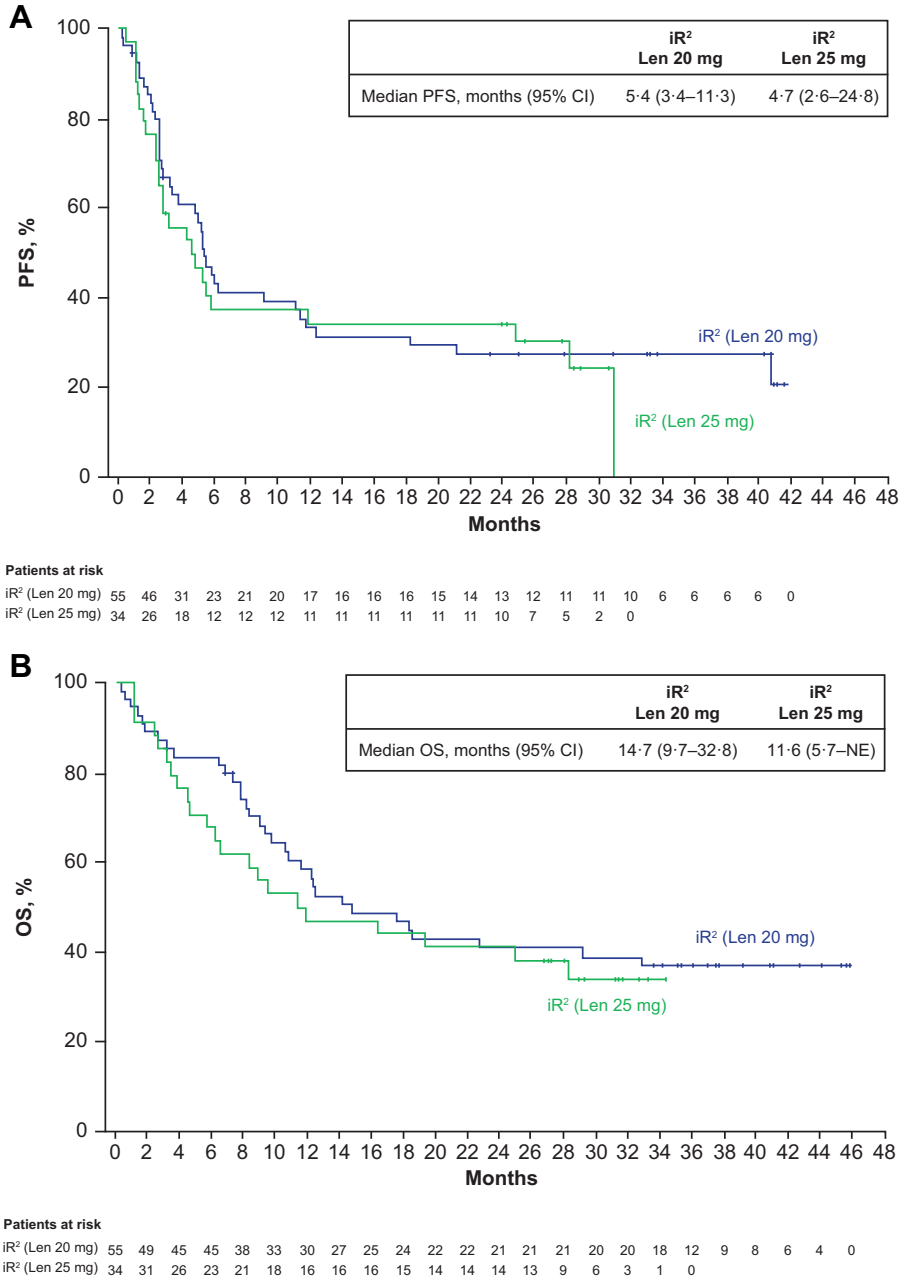

Fig. 5: Progression-free survival and overall survival. Kaplan–Meier curves of progression-free survival (A) and overall survival (B) in the all-treated population. Tick marks indicate patients with censored data. CI = confidence interval; iR^2 = ibrutinib, lenalidomide, and rituximab; Len = lenalidomide; NE = not estimable; OS = overall survival; PFS = progression-free survival.

study design and patient populations, these response rates appear higher than ORRs of 28–35% and similar to CR rates of 22–35% observed in phase 2 studies of lenalidomide plus rituximab in patients with relapsed/refractory DLBCL.[16,17] CRs were durable; with a median follow-up of 35 months, median duration of CR was not yet reached. Furthermore, long-term follow-up from the phase 1b cohort demonstrated impressive durability of CRs, with some patients maintaining responses for >5 years.

The study was not powered to identify differences in efficacy between the 20 and 25 mg lenalidomide cohorts; however, phase 1b data suggested that doses >15 mg lenalidomide demonstrated higher response

AEs	iR^2 Len 20 mg n = 55	iR^2 Len 25 mg n = 34	iR^2 Total N = 89
Any grade 3/4 AE	51 (93%)	30 (88%)	81 (91%)
Any grade 5 AE	8 (15%)	4 (12%)	12 (13%)[a]
Any serious AE	32 (58%)	25 (74%)	57 (64%)
AEs of any grade in ≥20% of patients			
Diarrhoea	34 (62%)	14 (41%)	48 (54%)
Neutropenia	25 (45%)	15 (44%)	40 (45%)
Fatigue	23 (42%)	16 (47%)	39 (44%)
Cough	19 (35%)	13 (38%)	32 (36%)
Anaemia	18 (33%)	11 (32%)	29 (33%)
Oedema peripheral	21 (38%)	8 (24%)	29 (33%)
Rash maculopapular	15 (27%)	13 (38%)	28 (31%)
Dyspnoea	19 (35%)	7 (21%)	26 (29%)
Nausea	17 (31%)	9 (26%)	26 (29%)
Constipation	11 (20%)	10 (29%)	21 (24%)
Thrombocytopenia	11 (20%)	10 (29%)	21 (24%)
Dry skin	13 (24%)	7 (21%)	20 (22%)
Hypokalaemia	16 (29%)	4 (12%)	20 (22%)
Dizziness	11 (20%)	8 (24%)	19 (21%)
Vomiting	12 (22%)	7 (21%)	19 (21%)
Muscle spasms	12 (22%)	7 (21%)	19 (21%)
Peripheral sensory neuropathy	11 (20%)	7 (21%)	18 (20%)
Grade 3/4 AEs in ≥5% of patients			
Neutropenia	22 (40%)	14 (41%)	36 (40%)
Rash maculopapular	9 (16%)	7 (21%)	16 (18%)
Anaemia	9 (16%)	3 (9%)	12 (13%)
Diarrhoea	5 (9%)	4 (12%)	9 (10%)
Neutrophil count decreased	6 (11%)	2 (6%)	8 (9%)
Thrombocytopenia	5 (9%)	3 (9%)	8 (9%)
Hypokalaemia	6 (11%)	1 (3%)	7 (8%)
Fatigue	4 (7%)	1 (3%)	5 (6%)
Serious AEs in ≥5% of patients			
Pyrexia	5 (9%)	4 (12%)	9 (10%)
Worsening of DLBCL	5 (9%)	3 (9%)	8 (9%)
Pneumonia	3 (5%)	2 (6%)	5 (6%)
AEs of special interest			
Major haemorrhage	4 (7%)	3 (9%)	7 (8%)

Data are n (%). AE = adverse event; DLBCL = diffuse large B-cell lymphoma; iR^2 = ibrutinib, lenalidomide, and rituximab; Len = lenalidomide. [a]Includes seven deaths due to worsening of DLBCL that were reported as AEs; other grade 5 AEs were pneumonia (n = 3), cardiac arrest (n = 1), and sepsis (n = 1).

Table 3: **Summary of treatment-emergent adverse events in the all-treated population.**

rates.[15] ORR differences noted between dosing cohorts may reflect the small sample size or clinical differences between treatment populations. Notably, a large proportion of patients on 25 mg lenalidomide discontinued study treatment within the first 16 weeks for various reasons (16 patients discontinued ibrutinib, 12 patients had PD, and 8 patients had died; Fig. 3D) and therefore had limited follow up; more patients had stage III/IV disease, and many were very ill at study entry leading to an early death. Given the small numbers in each cohort, the optimal dose remains unclear; however, based on phase 1b data, a dose >15 mg lenalidomide is recommended. Promising activity observed with the iR^2 regimen in phase 1b[15] also led to initiation of studies in the first-line setting, with the goal to reduce the number of chemotherapy cycles needed. Studies incorporating this strategy include the Smart Start study (NCT02636322), which demonstrated impressive response rates after ibrutinib, lenalidomide, and rituximab lead-in (ORR, 86%) followed by standard combination chemotherapy (ORR, 100%),[18] and the Smart Stop study (NCT04978584), evaluating lead-in with targeted agents and fewer chemotherapy cycles.

Treatment options for patients with relapsed/refractory DLBCL have expanded in recent years with the introduction of CAR-T and other novel approved agents. Indirect comparisons suggest lower response rates but favourable DOR and OS with the iR^2 regimen relative to CAR-T, noting that patients in this iR^2 study were ineligible for SCT, while many CAR-T studies included fit patients who were SCT candidates.[19,20] Additionally, ~50% of patients receiving CAR-T therapy relapse, and many cannot access CAR-T for logistical reasons. Thus, iR^2 may provide a tolerable regimen for individuals who are not candidates for SCT or CAR-T. In particular, the median DOR of 38.3 months and median OS of 12.4 months with the iR^2 regimen compares favourably to other novel approved therapies (Appendix p 15), as described below. Polatuzumab vedotin combined with bendamustine + rituximab demonstrated an ORR of 70% (58% CR rate) with a median DOR of 10.3 months and median OS of 12.4 months in patients treated with 1–7 (median 2) prior regimens.[21] Loncastuximab tesirine provided an ORR of 48% (24% CR) in patients with 2–7 (median 3) prior regimens; median DOR was 10.3 months and median OS was 9.9 months.[22] Selinexor demonstrated a 28% ORR and 12% CR rate in patients with ≥2 (median 2) prior regimens; median DOR was 9.3 months and median OS was 9.1 months.[23] Tafasitamab combined with lenalidomide provided a 58% ORR and 40% CR rate in patients with 1–4 (median 2) prior regimens.[24] Median DOR (43.9 months) and median OS (33.5 months) were longer with tafasitamab + lenalidomide than with the iR^2 regimen; however, patients in this study were less heavily pretreated, and primary refractory patients were excluded.[24] It should also be noted that these trials of novel therapies were conducted in patient populations agnostic of cell-of-origin DLBCL subtype, whereas this iR^2 study only included patients with the poor-prognosis non-GCB subtype.

In a potentially curable disease like DLBCL, monitoring molecular response (eg, MRD) to inform depth of response may prove useful to predict long-term outcomes. MRD monitoring remains technically challenging with respect to identification of clones from tumour tissue at baseline and subsequent identification of these clones in peripheral blood. In the current study, rapid conversion to undetectable MRD after one or two cycles of the iR^2 regimen in 12/13 patients with CR is encouraging in these patients with multiple prior lines of treatment. Results should be interpreted with caution, given that only 22/35 CR patients had a clone identified in tumour tissue at baseline (due to tissue availability).

Enrolment in the phase 2 portion of this study was restricted to patients with non-GCB DLBCL by IHC based on: previously observed preferential activity of ibrutinib in non-GCB subtypes,[9] dependence of the ABC DLBCL subtype on NF-κB activation,[10] and expected synergy of ibrutinib and lenalidomide in ABC DLBCL.[13] Results from the phase 1b of the study also supported greater activity in non-GCB, with notably higher ORR in patients with non-GCB vs GCB (65% vs 29%).[15] Subtyping by GEP in patients with available tissue samples in phase 2 (n = 65), in which all patients had non-GCB subtype of DLBCL by IHC, identified ABC, GCB, and unclassified subtypes in 32, 15, and 18 patients, respectively. The rate of classification of GCB subtype by GEP in 15/65 (23%) samples identified as non-GCB by IHC is consistent with historical rates.[25] Although subgroup numbers were small, responses were seen in patients with all cell-of-origin subtypes, with higher ORRs in ABC and unclassified (55% and 61%, respectively) relative to GCB (36%).

Rash and neutropenia were observed as dose-limiting toxicities with the iR^2 regimen in phase 1b.[15] With management guidelines in place for these AEs, the safety profile in phase 2 was manageable. While maculopapular rash and neutropenia were among the most frequent AEs leading to dose holds and/or dose reductions for both ibrutinib and lenalidomide, rash and neutropenia rarely led to discontinuation. The most frequent AEs were consistent with known safety profiles of the individual drugs, with no new safety signals identified. Rates of atrial fibrillation, hypertension, bleeding, and infections were consistent with those previously reported.[11] However, the incidence of major haemorrhage in the current study appeared higher than that observed in pooled data from randomized ibrutinib trials; this may be at least partly due to the advanced age of patients in this study, a high rate of comorbidities in this transplant-ineligible population, and concomitant use of anticoagulant and antiplatelet agents which are known to increase the risk of major haemorrhage with ibrutinib.[11] Rates of cardiac AEs were consistent with rates from pooled data from randomized ibrutinib trials.[11]

Limitations of the study include the non-randomised phase 2 design and the lack of a control arm. While the study was initially designed to include randomisation to the iR^2 regimen or a comparator arm comprising ibrutinib plus lenalidomide, the protocol was subsequently amended to remove this comparator arm in order to maximise potential efficacy in this population with relapsed/refractory and aggressive DLBCL (Appendix p 16). Additionally, the study was not designed or powered to evaluate potential differences in efficacy between lenalidomide dose cohorts, and modest sample sizes preclude comparisons of outcomes between dose cohorts. Although enrolment in the study was completed before the COVID-19 pandemic, some assessments during 2020 were impacted by the COVID-19 pandemic, resulting in virtual visits or partial assessments for 19 patients.

In conclusion, the combination of ibrutinib, lenalidomide, and rituximab demonstrated encouraging

antitumour activity with durable responses and a manageable safety profile in patients with relapsed/refractory non-GCB DLBCL ineligible for SCT. Prevalence of the non-GCB or ABC subtype is higher in elderly patients (≥50% in patients aged ≥70 years),[26] who are frequently ineligible for SCT or CAR-T therapy. This regimen may be valuable for this non-GCB or ABC DLBCL population and could be used in patients who are ineligible for or have relapsed after SCT or CAR-T therapy. The regimen could also potentially serve as a bridging therapy to SCT or CAR-T therapy, minimizing potential impact for CAR-T therapy by leaving CD19 expression intact, or could be administered prior to T-cell collection based on evidence that ibrutinib can augment CAR-T cell production.[27–29]

Contributors

J.K.N. and A.G. designed the study. R.R., P.J., N.G., J.Ru., K.M.A., R.J., G.V., D.C., S.d.V., S.K., L.F., J.Ra., S.B., F.O., D.M., J.M., and A.G. recruited patients and collected data. J.P. (statistician), E.S.-G., K.E., and J.K.N. performed the data analyses, confirmed the accuracy of the data, and compiled the data for analysis. J.K.N., R.R., and A.G. collaboratively wrote the first draft of the manuscript, had full access to and verified all study data, and had final responsibility for the decision to submit for publication. All authors had access to the data and were involved in the interpretation of data, contributed to the manuscript review and revisions, and approved the final version for submission.

Data sharing statement

Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Declaration of interests

R.R. reports a consulting/advisory role with Pharmacyclics LLC, an AbbVie Company; and research funding from Janssen and Pharmacyclics LLC, an AbbVie Company. P.J. reports honoraria from Bristol-Myers Squibb, Genmab, Incyte, Kymera, MorphoSys, Novartis, and Takeda; a consulting/advisory role for Epizyme and Janssen; and patents/royalties/other intellectual property with the University of Southampton. N.G. reports a consulting/advisory role for AbbVie, ADC Therapeutics, Adaptive Biotech, BeiGene, Bristol Myers Squibb, Genmab, Gilead/Kite, Incyte, Janssen, TG Therapeutics, and Pharmacyclics LLC, an AbbVie Company; research funding from Bristol Myers Squibb, Genentech, TG Therapeutics, and Pharmacyclics LLC, an AbbVie Company; and speakers bureau for AbbVie, Bristol Myers Squibb, Epizyme, Gilead/Kite, Janssen, and Pharmacyclics LLC, an AbbVie Company. JRu reports a consulting/advisory role for Celgene/Bristol Myers Squibb, Daiichi Sankyo, Kite Pharma, Seagen, and Secura Bio; and research funding from AstraZeneca, Celgene/Bristol Myers Squibb, Daiichi Sankyo, and Genentech. K.M.A. reports honoraria from and a consulting/advisory role for BeiGene, Celgene, Gilead, Novartis, and Roche; research funding from ADC Therapeutics, Autolus, Bristol Myers Squibb, Janssen, Novartis, and Pharmacyclics LLC, an AbbVie Company; and travel/accommodations/expenses from Celgene, Gilead, Novartis, and Roche. R.J. reports honoraria from Gilead and Novartis; and a consulting/advisory role for Gilead, Novartis, and Takeda. G.V., S.d.V., S.K., and F.O. have nothing to disclose. D.C. reports a consulting/advisory role with OVIBIO; and research funding from 4SC, Bayer, Celgene, Clovis, Eli Lilly, Leap, MedImmune/AstraZeneca, the National Institute for Health and Care Research Efficacy and Mechanism Evaluation Programme, and Roche. L.F. reports honoraria from and a consulting/advisory role for EUSA Pharma; and research funding from Pharmacyclics LLC, an AbbVie Company. J.Ra. reports stock or other ownership with ADC Therapeutics (self) and AstraZeneca (spouse); honoraria from ADC Therapeutics, Bristol Myers Squibb, and Takeda; a consulting/advisory role and speakers bureau for ADC Therapeutics and Takeda; and research funding from Takeda. S.B. reports a consulting/advisory role for and travel/accommodations/expenses from AbbVie, Gilead, Janssen, Roche, and Takeda. D.M. reports stock or other ownership with Johnson & Johnson, Merck, Pfizer, Regeneron, Roche, and Vertex Pharma. J.M. reports honoraria from Curio, Kyowa, OneView, Physicians' Education Resource, Seagen, and Targeted Oncology; a consulting/advisory role for ADC Therapeutics, Alexion, Bayer, BeiGene, Bristol Myers Squibb, Debiopharm, Epizyme, Fosun Kite, Genmab, Gilead/Kite Pharma, Innovent, Janssen, Juno/Celgene, Kyowa, Karyopharm, Morphosys/Incyte, Novartis, Pfizer, Seagen, Servier, and Pharmacyclics LLC, an AbbVie Company; research funding from Bayer, Celgene, Genentech, Gilead/Kite Pharma, Incyte, Janssen, Merck, Millennium, Portola, Seagen, and Pharmacyclics LLC, an AbbVie Company; and speakers bureau for Acrotech/Aurobindo, AstraZeneca, Bayer, BeiGene, Celgene/Bristol Myers Squibb, Genentech/Roche, Gilead/Kite Pharma, Janssen, Kyowa, Seagen, Verastem, and Pharmacyclics LLC, an AbbVie Company. J.P. reports employment and stock or other ownership with AbbVie. E.S.-G. reports employment and stock or other ownership with AbbVie. K.E. reports employment with Pharmacyclics LLC, an AbbVie Company; and stock or other ownership with AbbVie. J.K.N. reports employment and stock or other ownership with AbbVie. A.G. reports a leadership position with COTA Healthcare, Genomic Testing Cooperative LCA, and Resilience; stock or other ownership with Alloplex, COTA Healthcare, Genomic Testing Cooperative LCA, Resilience, and Vincerx; a consulting/advisory role for Alloplex, AstraZeneca, Bristol Myers Squibb, Celgene, Clinical Advances H&O, Elsevier's Practice Update Oncology, Gilead, Hoffmann-La Roche, Janssen, Kite Pharma, Medscape, Michael J Hennessey Associates, MorphoSys, Novartis, Onclive Peer Exchange, Physicians Education Resource, Roswell Park, Vincerx, and Xcenda-Amerisource; research funding from Acerta, AstraZeneca, Bristol Myers Squibb, Genentech, Hoffmann-La Roche, Infinity, Janssen, Karyopharm, Kite Pharma, MorphoSys, Seagen, Verastem, and Pharmacyclics LLC, an AbbVie Company; travel/accommodations/expenses from Alloplex, AstraZeneca, Bristol Myers Squibb, Celgene, Clinical Advances H&O, COTA Healthcare, Elsevier's Practice Update Oncology, Genomic Testing Cooperative LCA, Gilead, Hoffmann-La Roche, Janssen, Kite Pharma, Medscape, Michael J Hennessey Associates, MorphoSys, Novartis, Onclive Peer Exchange, Physicians Education Resource, Roswell Park, Resilience, Vincerx, and Xcenda-Amerisource; and other relationship with Acerta, Alloplex, AstraZeneca, Bristol Myers Squibb, Celgene, Clinical Advances H&O, COTA Healthcare, Elsevier's Practice Update Oncology, Genentech, Genomic Testing Cooperative LCA, Gilead, Hoffmann-La Roche, Infinity, Janssen, Karyopharm, Kite Pharma, Medscape, Michael J Hennessey Associates, MorphoSys, Novartis, Onclive Peer Exchange, Physicians Education Resource, Resilience, Roswell Park, Seagen, Verastem, Vincerx, Xcenda-Amerisource, and Pharmacyclics LLC, an AbbVie Company.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101779.

References

1 Lenz G, Staudt LM. Aggressive lymphomas. *N Engl J Med*. 2010;362(15):1417–1429.
2 Feugier P, van HA, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23(18):4117–4126.
3 Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol*. 2005;23(22):5027–5033.
4 Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800–1808.
5 Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med*. 2017;377(26):2545–2554.
6 Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000;403(6769):503–511.
7 Scott DW, Mottok A, Ennishi D, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. *J Clin Oncol*. 2015;33(26):2848–2856.
8 Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. *N Engl J Med*. 2018;378(15):1396–1407.
9 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.
10 Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature*. 2010;463(7277):88–92.
11 *Imbruvica (ibrutinib) [package insert]*. Sunnyvale, CA: Pharmacyclics LLC; 2020.
12 Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. *Cancer*. 2011;117(22):5058–5066.
13 Yang Y, Shaffer III AL, Emre NC, et al. Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma. *Cancer Cell*. 2012;21(6):723–737.
14 Ujjani CS, Jung SH, Pitcher B, et al. Phase 1 trial of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma: alliance A051103. *Blood*. 2016;128(21):2510–2516.
15 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.
16 Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. *Leukemia*. 2013;27(9):1902–1909.
17 Zinzani PL, Pellegrini C, Gandolfi L, et al. Combination of lenalidomide and rituximab in elderly patients with relapsed or refractory diffuse large B-cell lymphoma: a phase 2 trial. *Clin Lymphoma Myeloma Leuk*. 2011;11(6):462–466.
18 Westin JR, Nastoupil LJ, Fayad L, et al. Smart start: rituximab, lenalidomide, and ibrutinib alone and in combination with standard chemotherapy for patients with newly diagnosed diffuse large B-cell lymphoma: final phase II results. *Blood*. 2019;134(Supplement_1):1581.
19 Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45–56.
20 Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839–852.
21 Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2020;38(2):155–165.
22 Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2021;22(6):790–800.
23 Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. *Lancet Haematol*. 2020;7(7):e511–e522.
24 Duell J, Maddocks KJ, González-Barca E, et al. Long-term outcomes from the phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. *Haematologica*. 2021;106(9):2417–2426.
25 Balasubramanian S, Wang S, Major C, et al. Comparison of immunohistochemistry and gene expression profiling subtyping for diffuse large B-cell lymphoma in the phase III clinical trial of R-CHOP ± ibrutinib. *Br J Haematol*. 2021;194(1):83–91.
26 Mareschal S, Lanic H, Ruminy P, Bastard C, Tilly H, Jardin F. The proportion of activated B-cell like subtype among de novo diffuse large B-cell lymphoma increases with age. *Haematologica*. 2011;96(12):1888–1890.
27 Fan F, Yoo HJ, Stock S, et al. Ibrutinib for improved chimeric antigen receptor T-cell production for chronic lymphocytic leukemia patients. *Int J Cancer*. 2021;148(2):419–428.
28 Fraietta JA, Beckwith KA, Patel PR, et al. Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia. *Blood*. 2016;127(9):1117–1127.
29 Solman IG, Blum LK, Hoh HY, et al. Ibrutinib restores immune cell numbers and function in first-line and relapsed/refractory chronic lymphocytic leukemia. *Leuk Res*. 2020;97:106432.