Lenalidomide plus R-GDP (R2-GDP) in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Final Results of the R2-GDP-GOTEL Trial and Immune Biomarker Subanalysis

Natalia Palazón-Carrión[1,2], Alejandro Martín García-Sancho[3], Esteban Nogales-Fernández[1,2], Carlos Jiménez-Cortegana[4], Fernando Carnicero-González[5], Eduardo Ríos-Herranz[6], Fátima de la Cruz-Vicente[7], Guillermo Rodríguez-García[7], Rubén Fernández-Álvarez[8], Natividad Martínez-Banaclocha[9], Josep Gumà-Padrò[10], José Gómez-Codina[11], Antonio Salar-Silvestre[12], Delvys Rodríguez-Abreu[13], Laura Gálvez-Carvajal[14], Jorge Labrador[15], María Guirado-Risueño[16], Daniel J. García-Domínguez[1,2,4], Lourdes Hontecillas-Prieto[1,2,4], Pablo Espejo-García[1,2], Isabel Fernández-Román[17], Mariano Provencio-Pulla[18], Margarita Sánchez-Beato[19], Marta Navarro[20], Lejeune Marylene[21], Tomás Álvaro-Naranjo[22], Maria Casanova-Espinosa[23], Victor Sánchez-Margalet[4], Antonio Rueda-Domínguez[23], and Luis de la Cruz-Merino[1,2]

ABSTRACT

Purpose: New therapeutic options are needed in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). Lenalidomide-based schedules can reverse rituximab refractoriness in lymphoma.

Patients and Methods: In the phase II R2-GDP trial, 78 patients unsuitable for autologous stem cell transplant received treatment with the following schedule: lenalidomide 10 mg Days (D)1–14, rituximab 375 mg/m^2 D1, cisplatin 60 mg/m^2 D1, gemcitabine 750 mg/m^2 D1 and D8, and dexamethasone 20 mg D1–3, up to 6 cycles (induction phase), followed by lenalidomide 10 mg (or last lenalidomide dose received) D1–21 every 28 days (maintenance phase). Primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), safety, and monitorization of key circulating immune biomarkers (EU Clinical Trials Register number: EudraCT 2014-001620-29).

Results: After a median follow-up of 37 months, ORR was 60.2% [37.1% complete responses (CR) and 23.1% partial responses (PR)]. Median OS was 12 months (47 vs. 6 months in CR vs. no CR); median PFS was 9 months (34 vs. 5 months in CR vs. no CR). In the primary refractory population, ORR was 45.5% (21.2% CR and 24.3% PR). Most common grade 3–4 adverse events were thrombocytopenia (60.2%), neutropenia (60.2%), anemia (26.9%), infections (15.3%), and febrile neutropenia (14.1%). Complete responses were associated with a sharp decrease in circulating myeloid-derived suppressor cells and regulatory T cells.

Conclusions: R2-GDP schedule is feasible and highly active in R/R DLBCL, including the primary refractory population. Immune biomarkers showed differences in responders versus progressors.

[1]Department of Clinical Oncology, Hospital Universitario Virgen Macarena, University of Seville, Seville, Spain. [2]Department of Medicine, University of Seville, Seville, Spain. [3]Department of Hematology, Hospital Universitario de Salamanca, IBSAL, CIBERONC, Salamanca, Spain. [4]Department of Medical Biochemistry and Molecular Biology and Immunology, Medical School, Hospital Universitario Virgen Macarena, Seville, Spain. [5]Department of Hematology, Hospital San Pedro de Alcántara de Cáceres, Cáceres, Spain. [6]Department of Hematology, Hospital Universitario de Valme, Seville, Spain. [7]Department of Hematology, Hospital Universitario Virgen del Rocío, Seville, Spain. [8]Department of Hematology, Cabueñes Hospital, Gijón, Spain. [9]Department of Clinical Oncology, Hospital General Universitario de Alicante, Alicante, Spain. [10]Department of Clinical Oncology, Hospital Universitari Sant Joan de Reus URV, IISPV, Reus, Spain. [11]Department of Clinical Oncology, Hospital Universitario La Fé, Valencia, Spain. [12]Department of Hematology, Hospital del Mar, Barcelona, Spain. [13]Department of Clinical Oncology, Hospital Universitario Insular, Las Palmas de Gran Canaria, Spain. [14]Department of Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain. [15]Department of Hematology, Research Unit, Hospital Universitario de Burgos, Burgos, Spain. [16]Department of Clinical Oncology, Hospital General Universitario de Elche, Elche, Spain. [17]Department of Hematology, Hospital Universitario Virgen Macarena, Seville, Spain. [18]Department of Medical Oncology, Hospital Universitario Puerta de Hierro-Majadahonda, Facultad de Medicina, Universidad Autónoma de Madrid, IDIPHISA, Madrid, Spain. [19]Department of Medical Oncology, Lymphoma Research Group, Hospital Universitario Puerta de Hierro-Majadahonda, IDIPHISA, CIBERONC, Madrid, Spain. [20]Department of Medical Oncology, Lymphoma Research Group, Hospital Universitario Puerta de Hierro-Majadahonda, IDIPHISA, Madrid, Spain. [21]Department of Pathology, Plataforma de Estudios Histológicos, Citológicos y de Digitalización, Hospital de Tortosa Verge de la Cinta, IISPV, URV, Tortosa, Tarragona, Spain. [22]Department of Pathology, Hospital de Tortosa Verge de la Cinta, Catalan Institute of Health, Institut d'Investigació Sanitària Pere Virgili (IISPV), Tortosa, Tarragona, Spain. [23]Department of Hematology/Clinical Oncology, Hospital Costa del Sol, Marbella, Spain.

Corresponding Authors: Luis de la Cruz-Merino, Hospital Universitario Virgen Macarena and University of Seville, Avenue Doctor Fedriani, 41009 Seville, Spain. Phone: 346-7790-2681; E-mail: ldelacruzmerino@gmail.com; and Antonio Rueda-Domínguez, rueda.dominguez@gmail.com

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Translational Relevance

Diffuse large B-cell lymphoma (DLBCL) is recognized as a heterogeneous disease that can be cured in up to 60%–70% of the cases with upfront therapy. However, indisputably, relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) still represents a great clinical challenge. At this point, we conducted an academic open label multicenter phase 2 trial (R2-GDP-GOTEL) testing the synergism of combination of lenalidomide and rituximab (R2) plus gemcitabine, cisplatin, and dexamethasone (R2-GDP schedule) in R/R DLBCL patients not suitable for autologous stem cell transplantation (ASCT). Results suggest that lenalidomide in combination with R-GDP (R2-GDP schedule) is an immunomodulatory treatment option with manageable toxicity and promising clinical activity, with high proportion of complete responses (CR) and favorable survival outcomes in patients with R/R DLBCL who are ineligible for ASCT. In addition, evolution of myeloid-derived suppressor cells and regulatory T cells in peripheral blood seems an alternative for monitoring immune profiling that is clearly related to clinical outcomes in terms of overall survival and CRs.

Introduction

Patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) who are not candidates for autologous stem cell transplantation (ASCT) show a dismal prognosis and thus new treatment strategies are needed. Results from the SCHOLAR-1 study reflect the poor clinical outcomes especially for those considered refractory to previous therapies, with a median overall survival (OS) of 6.3 months, a 2-year OS of 20%, and an overall response rate (ORR) to subsequent treatments of 26% with just a 7% of complete response (CR) rate (1). At this point, cell immunotherapies with CAR T cells, antibody–drug conjugates (ADC) like polatuzumab, tafasitamab, or bispecific mAbs represent different tools to improve clinical outcomes in these patients. Lenalidomide is a thalidomide analogue considered as an immunomodulatory drug (IMID) with pleiotropic properties, including anti-proliferative, T-cell co-stimulatory, anti-angiogenic, and anti-inflammatory effects (2, 3). Interestingly, lenalidomide in association with rituximab has demonstrated synergism and reversal of rituximab refractoriness (4, 5). Although early studies (6) suggested that combining chemotherapy with lenalidomide and rituximab (R2) could improve outcomes in activated B cells (ABC) DLBCL, final results from the ROBUST (7) and the Eastern Cooperative Oncology Group (ECOG)-ACRIN 1412 trial (E1412; ref. 8) were disappointing, discarding special activity for the lenalidomide plus R-CHOP schedule in ABC DLBCL in the first-line setting.

In this trial, we pursued to test the activity and safety of the combination of the R-GDP schedule, given its favorable toxicity profile, plus lenalidomide (R2-GDP schedule) in a cohort of patients with R/R DLBCL unsuitable for ASCT. Special attention was paid to the primary refractory population. Correlative studies using flow cytometry for immune biomarkers in peripheral blood before, during, and after R2-GDP and genetic subtypes DLBCL classification were performed.

Patients and Methods

Study design

This multicenter, open-label, single-arm phase II study started in April 2015 at 18 centers in Spain. Database was locked in March 2021 for this report.

The study was conducted in compliance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Declaration of Helsinki, good clinical practice guidelines, and local laws. The study protocol and any subsequent amendments were approved by the relevant institutional review boards or independent ethics committee at each institution. All patients provided written informed consent.

Selection of patients

Eligible patients were R/R DLBCL unsuitable for ASCT, aged over 18 years old, Eastern Cooperative Oncology Group performance status of 0–1, and who had previously received at least one prior line of immunochemotherapy, including rituximab. The main exclusion criteria included baseline renal, hepatic, or hematological abnormalities; previous malignancies; and leptomeningeal or central nervous system infiltration.

Procedures

A first run-in phase period was performed with the following schedule: intravenous rituximab 375 mg/m^2 on day (D)1, intravenous cisplatin 80 mg/m^2 D1, intravenous gemcitabine 1,000 mg/m^2 D1 and D8, oral dexamethasone 20 mg D1–3, subcutaneous G-CSF 30 million units international (MUI) D2–6 and D9–14 in combination with oral lenalidomide 1 mg D1–14, in cycles every 3 weeks. If after the 3rd cycle there was no progression of disease (PD), a maximum of 6 induction cycles were administered. Patients that reached clinical benefit (CB) after at least 3 cycles of treatment could enter into a maintenance phase with lenalidomide 10 mg (or the last dose administered in the induction phase) D1–21 in cycles every 4 weeks. The maintenance phase was intended to continue until progression, unacceptable toxicity, patient voluntary withdrawal, or when two PET confirmed metabolic CR after 2 years of treatment.

In a cohort of 6 patients, 3 of them developed a 3–4 grade toxicity and therefore an Independent Safety Committee (ISC) constituted of two hematologists, two clinical oncologists, and two clinical pharmacologists considered the schedule excessively toxic to continue with the recruitment. Consequently, a second run-in phase period was initiated, with the following R2-GDP schedule: intravenous rituximab 375 mg/m^2 D1, intravenous cisplatin 60 mg/m^2 D1, intravenous gemcitabine 750 mg/m2 D1 and D8, oral dexamethasone 20 mg D1–3, subcutaneous G-CSF 30 MUI D2–6 and D9–14 in combination with oral lenalidomide 10 mg D1–14, in cycles of every 3 weeks. After the safety analysis of 2 cohorts of 6 and 12 patients, the ISC deemed the aforementioned schedule safe enough to continue recruitment and complete the phase 2 of the study. Venous thromboembolism prophylaxis was not mandatory (Supplementary Fig. S1).

Tumor response was evaluated according to the International Working Group Criteria (9) using CT after the third induction cycle and PET in the following 4 weeks after the last cycle of the induction phase.

Immune biomarkers were also studied in the patients. Flow cytometry analysis was performed on whole-blood samples. The evolution of myeloid-derived suppressor cells (MDSC), regulatory T (Treg),

$OX40^+PD\text{-}1^-$ T, and $PD\text{-}1^+OX40^+$ T cells (CD4, CD8, and total T cells) from peripheral blood cells were studied before (basal), during (cycle 3), and after (end of induction, EOI) the R2-GDP schedule, and were analyzed by the FACSCanto II flow cytometry system (Becton Dickinson) from EDTA-K3 tubes. Both the mAbs and the gating strategies used were previously described (10). The results of biomarkers studied were divided on the basis of their response to the treatment (CB vs. PD).

COO subtypes were determined in germinal center (GCB) and non-germinal center (non-GCB) by IHC using the Hans algorithm (11). Tissue sections were stained with antibodies against CD10 (clone 56C6), BCL-6 (PG-B6p), and MUM1 (MUM1p), all of which were mouse mAbs, obtained from Agilent Technologies, Glostrup, Denmark. Response, OS, and progression-free survival (PFS) were analyzed according to cell of origin (COO).

To further characterize the samples, we performed targeted massive sequencing in available diagnostic samples from enrolled patients (29 out of 79) and classified them according to the new genetic subtypes previously described by Lacy and colleagues (12), Chapuy and colleagues (13), and Schmitz and colleagues (14) using the LymphGen algorithm (15) and the two-step algorithm developed by our group (16). We have analyzed the ORR, OS, and PFS with respect to their genetic subtype (Methods are detailed in Supplementary "Genetics subtypes").

Outcomes

The primary endpoint was ORR in the intention to treat (ITT) population. Secondary endpoints included median PFS, median OS, safety and response by COO using the Hans algorithm (11), and other microenvironment biomarkers. The ORR was defined as the proportion of patients whose best overall response was CR or partial response (PR). CB was defined as the proportion of patients whose best overall response was CR, PR, or stabilization of disease (SD). PFS was defined as the time from the first dose of R2-GDP schedule to PD or death from any cause. OS was defined as the time from the first R2-GDP schedule dose to death from any cause. Adverse events (AE) were monitored throughout the study period and graded according to the NCI Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

The sample size was determined using a binomial Simon's two-stage design, using ORR as the main variable. To formulate the null hypothesis, we used historical data from studies, including R/R DLBCL that reported ORR of 35% (1). The 1-year survival in these studies was 20%, and the median OS was 6.3 months. Assuming a null hypothesis of 35%–50% ORR being experimental treatment (R2-GDP) not statistically superior to the standard schedule (R-GDP) and an alternative hypothesis of ≥50% ORR (experimental treatment is superior to standard schedule) with two-sided type I error of 5% and power of 80%, the final sample calculation resulted in 79 patients.

All statistical analyses were performed with IBM SPSS Statistics for Windows (Version 22·0). Efficacy statistical analysis was performed per ITT. The OS and PFS were calculated using log-rank test with confidence intervals (CI) at 95%. Safety analysis was performed using all patients who have received at least one dose of the study treatment, both at the time of the interim analysis and at the end of study. The χ^2 test was performed to analyze response according to previous chemotherapy and response according to International Prognostic Index (IPI score).

Data availability

Our DNA-sequencing data have been deposited in the Sequence Read Archive (SRA) database of NCBI. GEO accession number is PRJNA834596.

Results

At the data collection cutoff date (March 2021), the median follow-up period was 37.0 (range, 2.0–56.0) months. Seventy-eight patients were finally considered in the ITT analysis due to the voluntary withdrawal of one patient.

Baseline patient characteristics

Main baseline patients' characteristics are detailed in **Table 1**: median age of 66 (range 23–66) years old, high LDH (80.7%), ECOG 0–1 (97.4%), and Ann Arbor stage III-IV (61.5%). Thirteen (16.6%), 29 (37.2%), 20 (25.7%), and 16 (20.5%) patients had an IPI score of low (0–1), intermediate (2–3), high (4–5), and indeterminated/missing, respectively. Of the total patients enrolled, 43 (55.1%) and 35 (44.9%) patients had received 1 and ≥2 previous lines of treatment, respectively. Thirty-three patients (42.3%) were

Table 1. Key patient characteristics.

	Number of patients (%)
Median age, y (range)	66 (23–86)
Male sex	40 (51.3%)
ECOG	
0	33 (42.3%)
1	43 (55.1%)
Indeterminated/missing	2 (2.6%)
LDH levels	
Within reference range	14 (17.9%)
Beyond reference range (elevated)	63 (80.7%)
Indeterminated/missing	1 (1.2%)
Ann Arbor stage	
I	3 (3.8%)
II	12 (15.3%)
III	10 (12.8%)
IV	38 (48.7%)
Indeterminated/missing	15 (19.2%)
IPI score	
Low (0–1)	13 (16.6%)
Intermediate (2–3)	29 (37.2%)
High (4–5)	20 (25.7%)
Indeterminated/missing	16 (20.5%)
Previous ASCT	
Yes	14 (17.9%)
No	64 (82.1%)
Previous total lines of treatments	
1	36 (46.1%)
2	27 (34.6%)
3	6 (7.6%)
4	2 (2.5%)
5	6 (7.6%)
6	1 (1.2%)
Primary refractory	
Yes	33 (42.3%)
No	45 (57.7%)

Abbreviations: ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

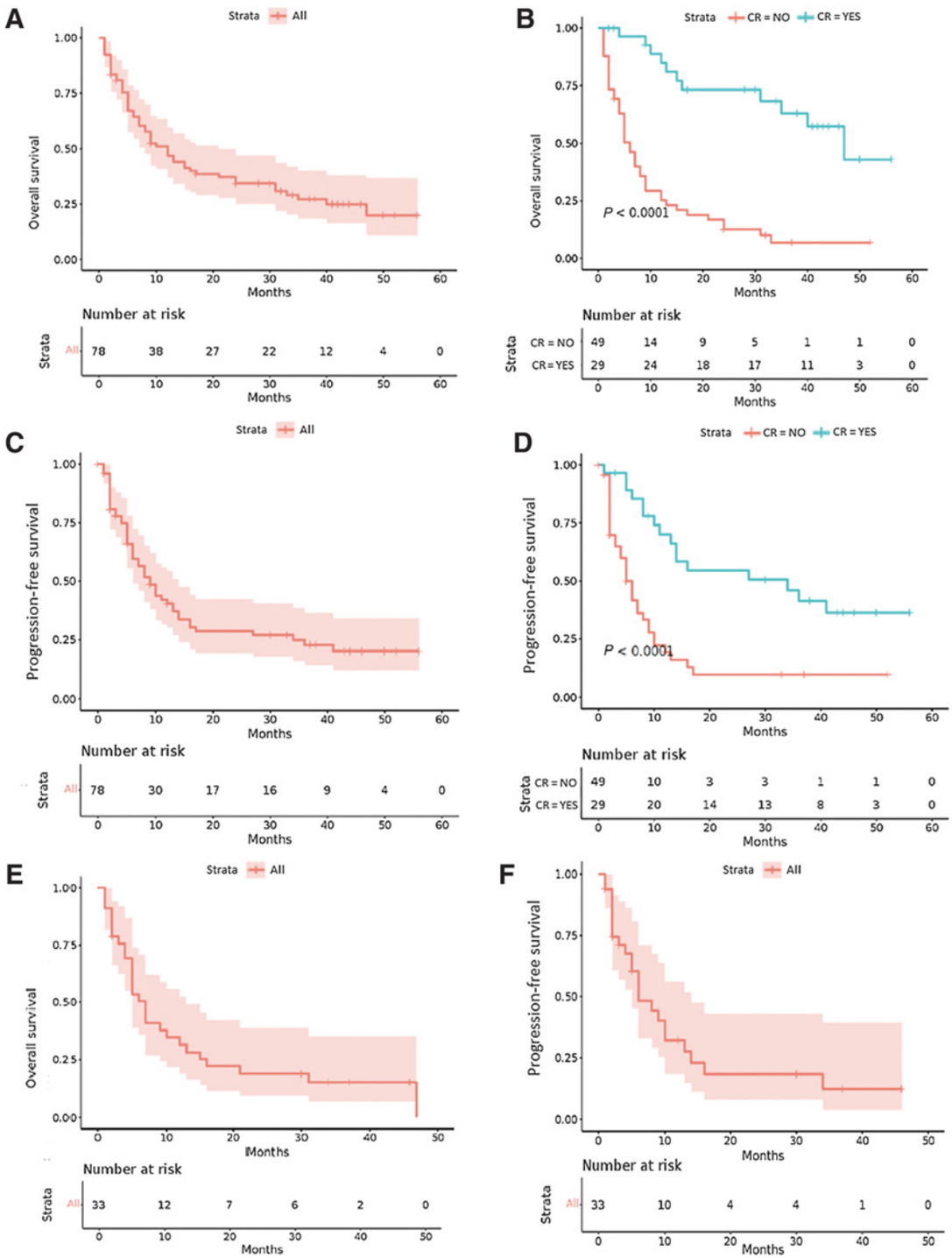

Figure 1.

Kaplan–Meier analysis. **A,** Overall survival (OS); **B,** OS according to response; **C,** Progression-free survival (PFS); **D,** PFS according to response; **E,** OS in the primary refractory population; **F,** PFS in the primary refractory population. CR, complete response.

primary refractory DLBCL defined as in the SCHOLAR-1 study. One hundred percent of patients had previously received rituximab and alkylating agents. The schedules most frequently used in the first line were R-CHOP (80.4%), R-DA-EPOCH (9.7%), high-dose methotrexate (5.1%), and R-CVP (4.8%), whereas the most used in second and subsequent lines were R-ESHAP (26.9%), ASCT (18.9%), R-ICE (14.7%), R-MINE (8.3%), R-DHAP (8.3%), R-GEMOX (7.8%), R-Bendamustine (7.8%), and R-GDP (7.3%).

Efficacy endpoints

ORR was 60.2% (95% CI, 48.5–71.1), with 37.1% CR and 23.1% PR. SD rate was 7.8% and PD rate was 32.0%. In the primary refractory population ($N = 33$), ORR was 45.5% (95% CI, 30.8–66.4), with 21.2% CR and 24.3% PR. SD rate was 12.1% and PD rate was 42.4% (Supplementary Table S1). A total of 3 patients were rescued for ASCT upon reaching CR in the induction phase, one of them considered primary refractory to two previous anti-lymphoma schedules containing rituximab. Response did not differ between subjects depending on the number of lines of chemotherapy previously received in any of the comparisons performed ($P = 0.356$; Supplementary Table S2). The same applies when only patients with primary refractory disease were considered ($P = 0.210$; Supplementary Table S3). Although a trend was observed for worse response within increasing IPI, it did not reach statistical significance, either in the whole population ($P = 0.118$; Supplementary Table S4) or in the subcohort with primary refractory disease ($P = 0.242$; Supplementary Table S5).

Median OS was 12.0 (95% CI, 68.0–24.0) months (**Fig. 1A**). OS rates at 2 and 3 years were 34.4% (95% CI, 25.0–47.2) and 27.2% (95% CI, 18.4–40.2). Furthermore, 23 (29.5%) and 14 (17.9%) patients were alive without evidence of disease at 12 and 24 months. Median OS was better in patients who achieved CR compared with no CR, with a median OS of 47 (95% CI, 35.0 to 72.0) versus 6 (95% CI, 5.0 to 9.0) months, respectively ($P < 0.0001$; **Fig. 1B**). Median PFS was 9.0 (95% CI, 6.0–14.0) months (**Fig. 1C**). Median PFS was better in patients with CR compared with those with no CR, with a median PFS of 34 (95% CI, 14.0–NR) versus 5 (95% CI, 4.0–9.0) months in CR versus no CR, respectively ($P < 0.0001$; **Fig. 1D–F**).

COO subtype

IHC determined COO in 64 samples. Thirty-five samples (54.7%) were classified as GCB and 29 (45.3%) samples as non-GCB subtype. Response did not differ between GCB and non-GCB DLCBL (Supplementary Table S6). Nonsignificant results were found for OS or PFS (Supplementary Fig. S2).

Genetic subtypes

We performed targeted massive parallel sequencing in 29 diagnostic samples. At least one somatic mutation was identified in all the samples (Supplementary Table S3). A total of 206 somatic mutations (SNVs and indels) were detected, considering missense, nonsense, and splicing mutations (Supplementary Table S7). The samples harbored a median of 7.1 mutations (range, 1–24). The most recurrently mutated genes were *KMT2D* (11/29 samples, *38%), TP53* (10/29, 34.5%), *BCL2* (8/29, 27.5%), *CREBBP* and *PIM1* (7/29, 24%), *MYD88, TMSB4X*, and *IGLL5* (6/29, 20.7%). Although the low number of samples precludes reaching significant results, Kaplan–Meier survival analyses revealed better survival probabilities for BN2 cases and a lower risk of relapse for ST2 cases (Supplementary Figs. S4 and S5). We analyzed whether *MYD88* mutation affects the response to treatment. We detected 6 cases with *MYD88* mutation, four of them with the recurrent $MYD88^{L265P}$ mutation, but its presence did not affect ORR, PFS, or OS. Two cases showed concurrent $MYD88^{L265P}$ and $CD79B^{Y93S}$ mutations, but their clinical outcomes did not differ (CR vs. PD, exitus vs. alive, and others).

Safety

Once the dose of R2-GDP schedule was established after a safety analysis by the ISC, 34 patients had a dose reduction of lenalidomide to 5 mg, and 10 patients required dose reduction of cisplatin to 40 mg/m^2 D1 and gemcitabine to 500 mg/m^2. Patients who received a reduced lenalidomide dose (5 mg) had a similar response to those receiving the normal dose (10–15 mg; $P = 0.058$; Supplementary Table S8). Ten patients did not complete the induction phase due to toxicity: 7 subjects receiving full dose of lenalidomide and 3 subjects receiving the reduced lenalidomide dose, although this difference of dose did not relate to dropout rate ($P = 0.353$; Supplementary Table S9).

All patients developed AEs during treatment, with a predominance of hematological AEs. Grade 3 or higher AEs are detailed in **Table 2**. The most common grade (G)3–4 AEs were thrombocytopenia (60.2%), neutropenia (60.2%), anemia (26.9%), and febrile neutropenia (14.1%). The most frequent G3–4 non-hematologic AEs were asthenia (19.2%) and infection (15.3%). There were 4 (5.1%) toxic deaths related to the R2-GDP schedule due to G5 febrile neutropenia with associated septic shock. These G5 AEs occurred in cycle 2 (2 patients) and in cycle 3 (2 patients) of induction phase. Doses of 15, 10, and 5 mg of lenalidomide were received by 1, 2, and 1 subjects, respectively. Only one patient had previously had an event of G3 febrile neutropenia in a prior cycle (Supplementary Table S10).

Table 2. Grade 3 to 4 AEs ocurring in >1 patient.

Hematologic AEs	Patients ($N = 78$)	Overall population (%)
Neutropenia	47	60.2
Thrombocytopenia	47	60.2
Anemia	21	26.9
Febrile neutropenia	11	14.1
Lymphopenia	7	8.9
Leukopenia	6	7.6
Aplasia	2	2.5

Non-hematologic AEs	Patients ($N = 78$)	Overall population (%)
Asthenia	15	19.2
Infections	12	15.3
Renal insufficiency	5	6.4
Sepsis	5	6.4
Fever	4	5.1
Diarrhea	3	3.8
Dyspnea	3	3.8
Pain	3	3.8
Rash	3	3.8
Hypomagnesemia	3	3.8
Cardiac toxicity	3	3.8
AST/ALT increased	2	2.5
Hypocalcemia	2	2.5
Hypophosphatemia	2	2.5
Sickness	2	2.5
Tumor lysis syndrome	2	2.5

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Translational substudy

Low-circulating MDSCs were associated with better responses

In CB, MDSC subsets and total MDSCs were significantly reduced with the R2-GDP schedule ($P = 0.039$ for M-MDSCs, $P < 0.001$ for G-MDSCs, and $P = 0.006$ for total MDSCs), whereas an increase in those cell populations occurred in PD (**Fig. 2A–F**).

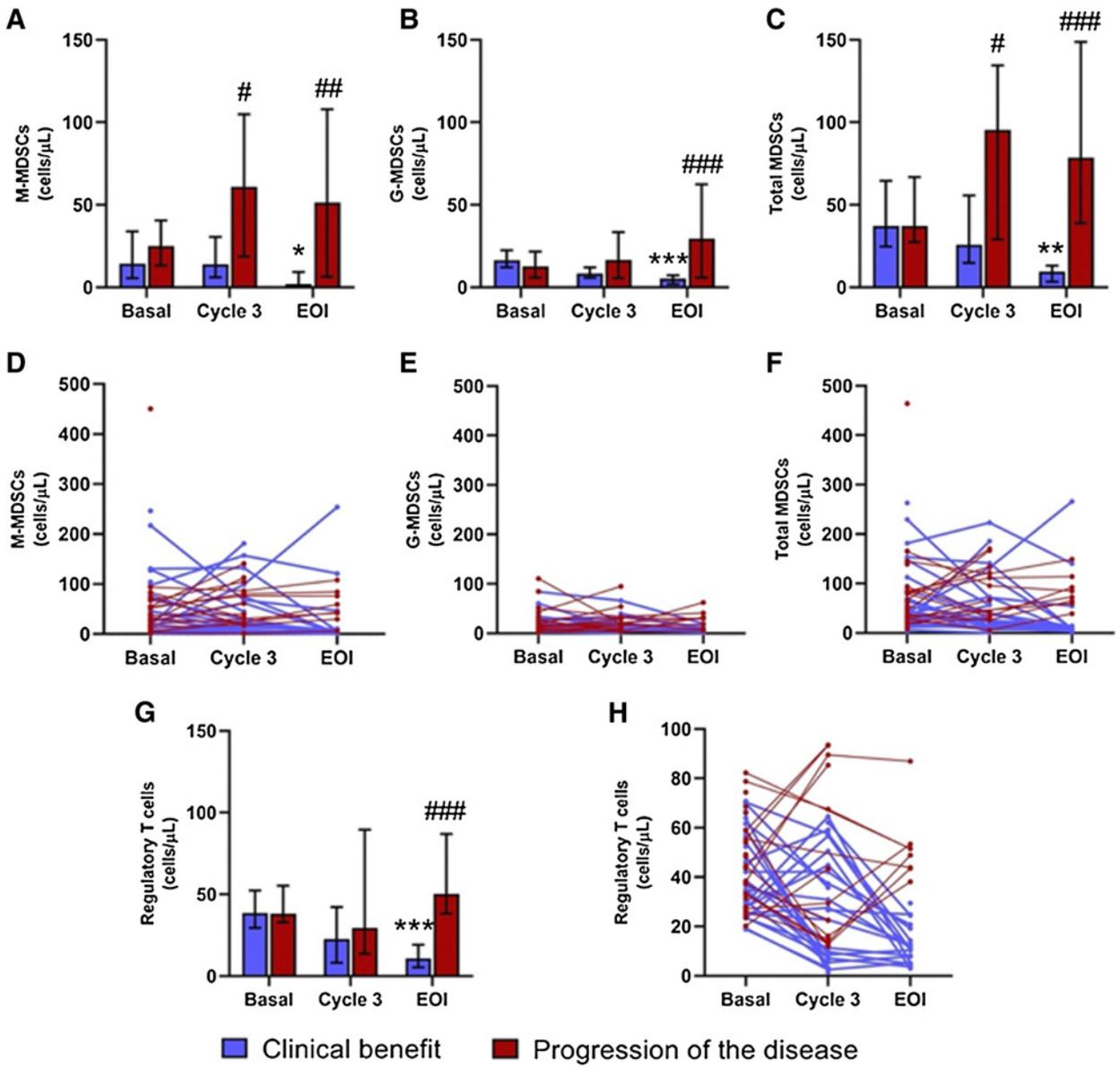

Figure 2.

MDSC populations and Tregs in patients with R/R DLBCL. **A,** M-MDSCs; **B,** G-MDSCs; **C,** Total MDSCs; **D,** Tregs data are represented as median and 95% CI; Spider graphs are **E,** M-MDSCs; **F,** G-MDSCs; **G,** Total MDSCs; and **H,** Tregs. EOI, End of induction. *, $P \le 0.05$; **, $P \le 0.01$; and ***, $P \le 0.001$ compared with basal levels; #, $P \le 0.05$; ##, $P \le 0.01$; and ###, $P \le 0.001$ compared with CB patients.

Decrease in blood Tregs was also associated with CB

Treg concentration was almost 4-fold reduced in CB ($P < 0.001$) and slightly increased in PD. Significant differences were also found in Treg levels between CB and PD after treatment ($P < 0.001$; **Fig. 2G–H**).

High activated CD4$^+$ and total T-cell levels were associated with positive responses

Concentration of CD4$^+$OX40$^+$PD-1–(activated) T cells was significantly increased after the use of R2-GDP compared with basal determination ($P = 0.033$), whereas activated CD8$^+$ T cells slightly improved (**Fig. 3A–F**).

Depletion of inhibited T cells from blood was correlated with CB

Circulating levels of CD4$^+$, CD8$^+$, and total PD-1$^+$OX40-(inhibited) T cells significantly decreased by the R2-GDP schedule in CB patients ($P < 0.001$ for CD4$^+$ and total inhibited T cells, and $P = 0.005$ for the CD8$^+$ subset), whereas inhibited T cells (CD4$^+$, CD8, and total T cells) slightly increased in PD (**Fig. 4A–F**).

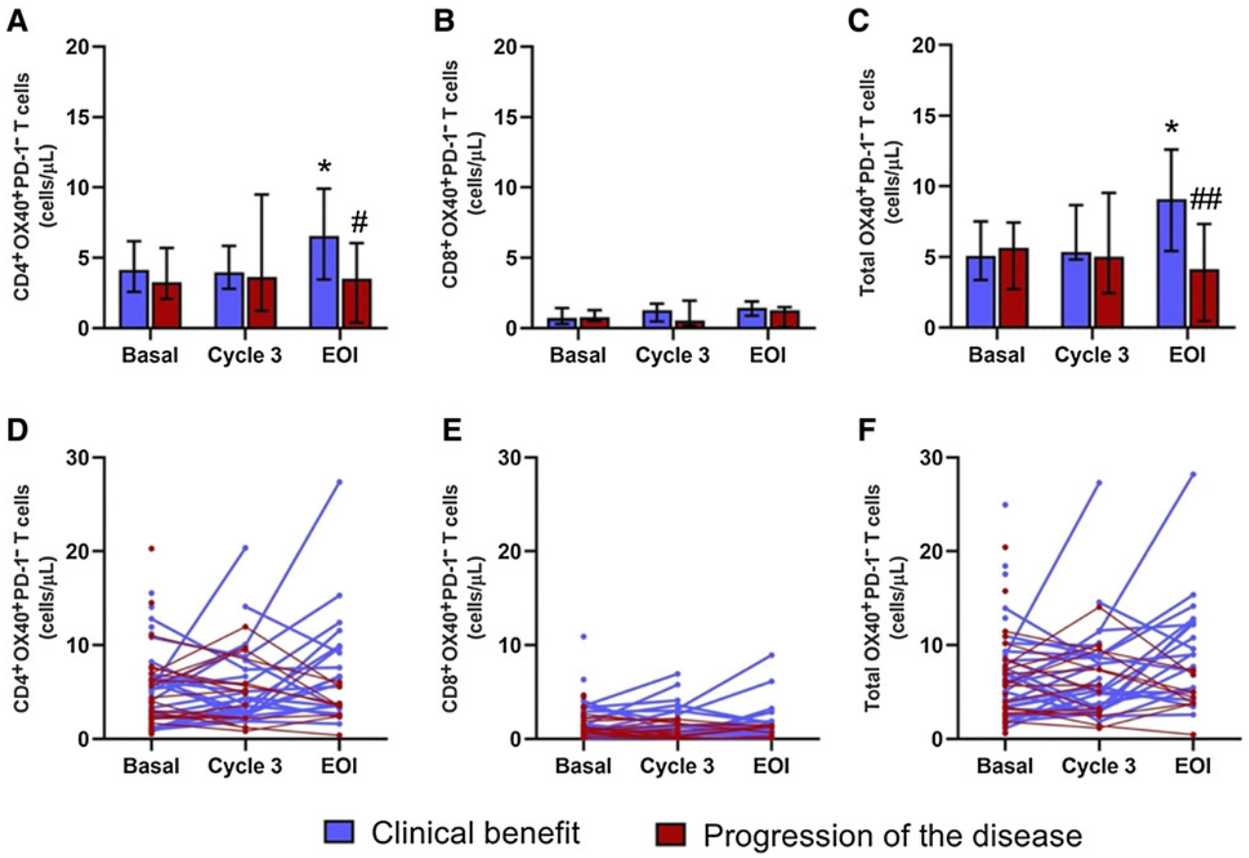

Figure 3.

Activated OX40$^+$PD-1$^-$ T cells in patients with R/R DLBCL. **A,** CD4$^+$; **B,** CD8$^+$; **C,** Total T cells data are represented as median and 95% CI; Spider graphs are **D,** CD4$^+$; **E,** CD8$^+$; and **F,** Total T cells. *, $P \leq 0.05$ compared with basal levels; #, $P \leq 0.05$ and ##, $P \leq 0.01$ compared with CB patients.

Discussion

DLBCL represents the most frequent non-Hodgkin lymphoma, being recognized as a highly heterogeneous disease from a molecular and clinical point of view. When DLBCL recurs, second-line therapies testing chemosensitivity followed by ASCT remain the standard of care. For patients unsuitable for ASCT, and even though new therapeutical strategies have been recently introduced, prognosis is still ominous in most of the cases. The results of the R2-GDP-GOTEL trial suggest that R-GDP plus lenalidomide may represent another alternative to consider due to its favorable results in response and survival rates in this pretreated and poor prognostic population.

The rate of CR achieved with R2-GDP schedule (37%) was related to better survival (OS and PFS). Furthermore, 14 (17.8%) patients were alive with CR and without disease recurrence after 24 months. Because the response did not differ between subjects depending on type and number of lines of chemotherapy previously received, R2-GDP schedule could be useful in R/R DLBCL regardless of treatment previously received. Hence, attending to the R/R DLBCL natural history and aggressiveness, these data suggest that there may be a percentage of patients who could benefit in the long term with the R2-GDP schedule without the need for ASCT or serving as a bridge to CAR T-cell therapy or stem cell transplantation.

Response did not differ between GCB and non-GCB DLCBL in R2-GDP schedule. Data from ROBUST (7) and E1412 trials, (8) with R2-CHOP regimen must be taken into account. At this point, the classification of DLBCL subtypes by COO show different prognostic implications with poor prognosis with standard chemoimmunotherapy in ABC-type DLBCL (17). In an attempt to improve prognosis in ABC-type DLBCL and based on data from retrospective studies (6), indicating a higher response to lenalidomide in ABC R/R DLBCL, the ROBUST and E1412 trials were performed with R2-CHOP schedule. The phase 2 E1412 (8) in previously untreated DLBCL irrespective of COO, showed that R2-CHOP was associated with a 34% reduction in risk of progression or death and an improvement in OS (83% vs. 75%, $P = 0.05$) and in PFS (73% vs. 61%, $P = 0.03$) with PFS HR for R2-CHOP of 0.67 for ABC DLBCL ($P = 0.1$). Finally, the phase 3 ROBUST (7) in previously untreated ABC DLBCL did not meet its primary endpoint. PFS (HR, 0.85; 95% CI, 0.63–1.14; $P = 0.29$), ORR (91%), and OS (80%) were similar for R2-CHOP and placebo/R-CHOP.

To further characterize the samples from R2-GDP, genetic DLBCL subtypes were analyzed. Because of the low number of samples and the multiple groups, no significant association was found between the different genetic DLBCL subtypes analyzed, but better clinical outcomes were shown in ST2 and BN2 subtypes, as

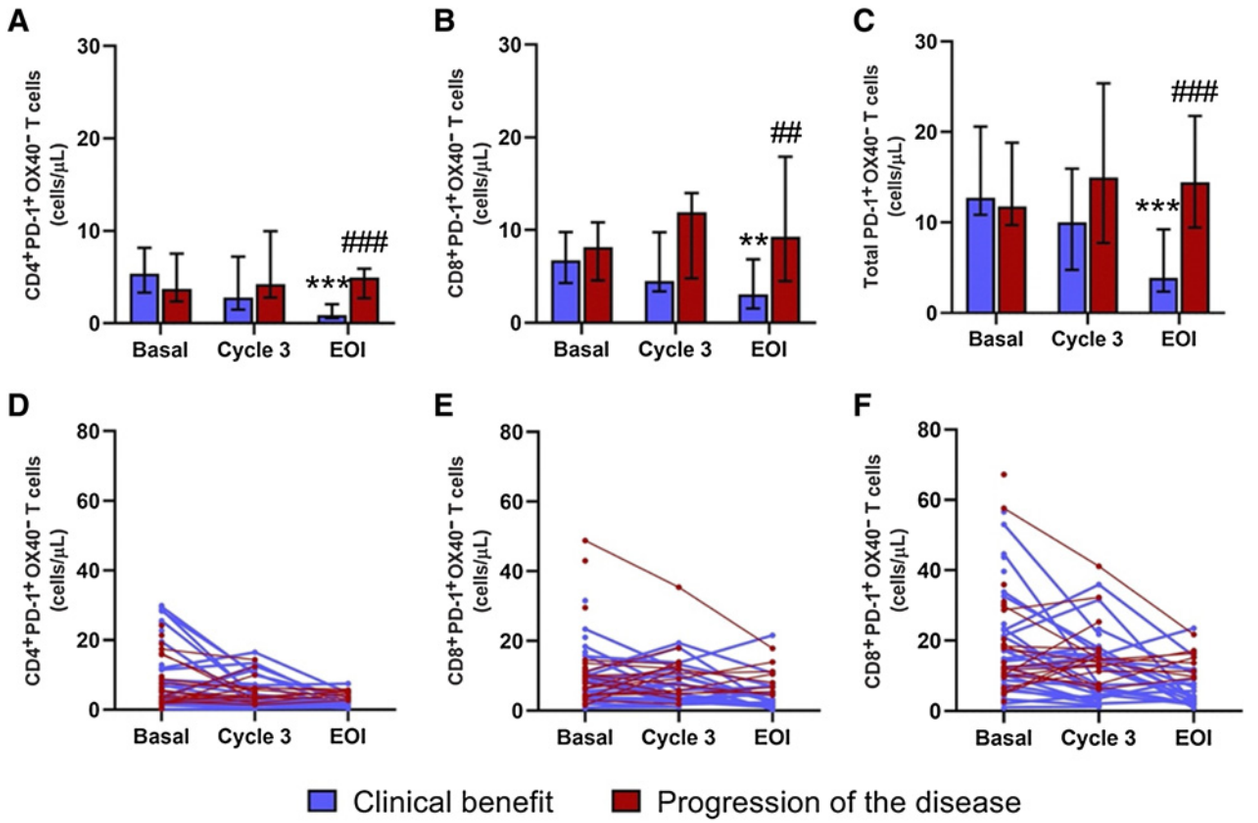

Figure 4.

Inhibited PD-1$^+$OX40$^-$ T cells in patients with R/R DLBCL. **A,** CD4$^+$; **B,** CD8$^+$; **C,** Total T cells data are represented as median and 95% CI; Spider graphs are **D,** CD4$^+$; **E,** CD8$^+$; and **F,** Total T cells. **, $P \le 0.01$ and ***, $P \le 0.001$ compared with basal levels; ##, $P \le 0.01$ and ###, $P \le 0.001$ compared with CB patients.

previously reported by Pedrosa and colleagues (16) and Wright and colleagues (15).

Until now, salvage treatments most commonly used in R/R DLBCL are combinations of rituximab with chemotherapy with ORR of 20%–60%, CR up to 30%, and median OS and PFS of 10 and 6 months, respectively. In the classic combinations with rituximab, the median OS and PFS of the patients who achieved CR were 40 and 22 months, respectively (18, 19). The more recent treatment option with anti-CD20 in combination with anti-CD79b mAb has been previously described. Polatuzumab–rituximab–bendamustine showed an ORR of 45%, CR of 40%, and median OS and PFS of 12 and 9 months, respectively (20). Furthermore, new therapeutic approaches with anti-CD19 mAbs without any anti-CD20 component have been developed, showing promising clinical activity, including patients with disease that was refractory to previous CD20-directed immunochemotherapies (20). Tafasitamab combined with lenalidomide showed an ORR of 57% and a CR of 43%. Median OS was 33 months and median PFS was 11 months (21). Loncastuximab had an ORR of 48% and a CR of 24% (22). Trials with CAR T-cell therapies have reported ORRs of 50%–85% and CRs of 47%; however, 90%–95% of the patients had AEs of grade 3 or worse (up to 95% of patients with cytokine release syndrome) with difficult access and eligibility to CAR T-cell therapy for some patients (23, 24).

The toxicity of R2-GDP at modified doses and schedule was frequent but generally manageable. The most common G3–4 AEs were thrombocytopenia (60.2%), neutropenia (60.2%), anemia (26.9%), asthenia (19.2%), infection (15.3%), and febrile neutropenia (14.1%), with 4 (5.1%) toxic deaths (G5 febrile neutropenia with associated septic shock) as expected from the common toxicity with the use of lenalidomide schedules (7, 25, 26). Chemo-free therapies with R2 combination (rituximab–lenalidomide 20 mg D1–21) used by Wang and colleagues (26) in R/R DLBCL and by Gini and colleagues (25) in front-line DLBCL showed common G3–4 AEs, including neutropenia (52%), thrombocytopenia (36%), anemia (20%), and febrile neutropenia (11%; ref. 26), with 4 (5.9%) deaths (2 patients due to visceral arterial ischemia and 2 due to infectious disease; ref. 25). R2-chemotherapy (CHOP) schedule with lenalidomide 15 mg D1–14 of every 21-day cycle, used by Nowakowski and colleagues (7) in the phase III ROBUST study with previously untreated patients with ABC-type DLBCL describes neutropenia (60%), anemia (22%), thrombocytopenia (17%), and febrile neutropenia (14%) as most common G3–4 AEs, and 3 deaths due to AEs (not otherwise specified), so lenalidomide dose adjustments were planned to manage toxicity. This point is crucial for the heavily pretreated patients with compromised performance status or age from R2-GDP study. Accordingly, reduced doses were used with respect to the classic R-GDP schedule, maintaining its efficacy;

similarly, additional dose reductions in R2-GDP schedule were allowed according to the physician's decision based on toxicity, comorbidities, and age.

It is worthy of note that the R2-GDP-GOTEL trial included a substantial proportion of patients with primary refractory disease (42%). This subgroup treated with the R2-GDP schedule, compared favorably with the data communicated from the SCHOLAR-1 study (1). At this point, the R2-GDP schedule induced an ORR of 45% with 21% of CR, whereas in the SCHOLAR-1 study (1) the primary refractory population showed a very modest ORR of 20% (CR, 3%).

Data from our study highlight the immunomodulatory potential of IMIDs (lenalidomide in this case), especially in combination with other mAbs targeting CD-20 (rituximab), overcoming resistance of lymphomas that were previously rituximab resistant (10, 21, 27, 28). Aforementioned combination seems to exert immunostimulatory effects, like the improvement of antibody-dependent cellular cytotoxicity and restoration of lytic natural killer (NK)-cell immunological synapses (29). Single-agent lenalidomide have shown antiproliferative, anti-angiogenic, and immunomodulatory properties, achieving accordingly inhibition of tumoral cell proliferation as well as modulation of the tumor microenvironment in hematological malignances. Specifically, it alters cytokine production, co-stimulates T cells, and enhances NK and NKT-cell cytotoxicity (30–33).

Immune biomarkers in peripheral blood were analyzed before, during, and after treatment with R2-GDP. In this context, an increase in MDSCs in the tumor microenvironment seems to favor tumor growth and correlates with poorer clinical outcomes (34, 35). In this line, our group (10) previously described that circulating MDSCs and Treg cells could be reliable immunological biomarkers for survival in the patients with R/R DLBCL treated with R2-GDP.

Here, we show the results of monitoring MDSCs and T cells in peripheral blood for response (CB vs. PD) to R2-GDP schedule. In CB patients, MDSCs were significantly reduced with R2-GDP schedule. Decrease of Tregs and total PD-1^{+}OX40-(inhibited) T cells was also associated with CB. In contrast, concentration of CD4^{+}OX40^{+}PD-1– (activated) T cells was significantly increased after the use of R2-GDP, being related to CB.

Therefore, with these results, it can be inferred that lenalidomide in combination with rituximab causes depletion of Tregs in responding patients with B-cell lymphomas (27). In addition, T cells may provide an effective immune response by the activated CD4 and CD8 cells expressing activation markers such as OX-40, whereas T-cell inhibition/exhaustion (expressing PD-1) may contribute to a defective immune response (36). In this sense, the decrease in MDSCs and Tregs observed in patients with a better response may underlie the observed increase in activated T cells and the decrease in inhibited/exhausted T cells. Nevertheless, further studies are needed to elucidate whether the observed changes in MDSCs and Tregs are part of the mechanism underlying the good clinical response or is a consequence of the decrease in tumor burden. In any case, MDSCs and Tregs may be considered as promising biomarkers in the clinical management of patients with R/R DLBCL.

In conclusion, the final results of the R2-GDP-GOTEL trial suggest that lenalidomide in combination with R-GDP is an immunomodulatory treatment option in R/R DLBCL ineligible for ASCT, especially for patients with primary refractory disease. Immune biomarkers are promising, because data from the R2-GDP-GOTEL trial showed differences in responders versus progressors. These results may envision new approaches to restore antitumoral immunity allowing a glimpse of new potential therapeutic targets in lymphoproliferative diseases.

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Authors' Contributions

N. Palazón-Carrión: Conceptualization, writing–original draft, writing–review and editing. **A. Martín García-Sancho:** Investigation. **E. Nogales-Fernández:** Investigation. **C. Jiménez-Cortegana:** Investigation. **F. Carnicero-González:** Investigation. **E. Ríos-Herranz:** Investigation. **F. de la Cruz-Vicente:** Investigation. **G. Rodríguez-García:** Investigation. **R. Fernández-Álvarez:** Investigation. **N. Martínez-Banaclocha:** Investigation. **J. Gumà-Padrò:** Investigation. **J. Gómez-Codina:** Investigation. **A. Salar-Silvestre:** Investigation. **D. Rodríguez-Abreu:** Investigation. **L. Gálvez-Carvajal:** Investigation. **J. Labrador:** Investigation. **M. Guirado-Risueño:** Investigation. **D.J. García-Domínguez:** Data curation, investigation, writing–original draft, writing–review and editing. **L. Hontecillas-Prieto:** Supervision, investigation, writing–original draft, writing–review and editing. **P. Espejo-García:** Investigation. **I. Fernández-Román:** Investigation. **M. Provencio-Pulla:** Investigation. **M. Sánchez-Beato:** Formal analysis. **M. Navarro:** Investigation. **L. Marylene:** Investigation. **T. Álvaro-Naranjo:** Investigation. **M. Casanova-Espinosa:** Investigation. **V. Sánchez-Margalet:** Conceptualization, investigation, writing–original draft, writing–review and editing. **A. Rueda-Domínguez:** Investigation. **L. de la Cruz-Merino:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

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Note

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