VOLUME 35 · NUMBER 31 · NOVEMBER 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma

Umberto Vitolo, Marek Trněný, David Belada, John M. Burke, Angelo Michele Carella, Neil Chua, Pau Abrisqueta, Judit Demeter, Ian Flinn, Xiaonan Hong, Won Seog Kim, Antonio Pinto, Yuan-Kai Shi, Yoichi Tatsumi, Mikkel Z. Oestergaard, Michael Wenger, Günter Fingerle-Rowson, Olivier Catalani, Tina Nielsen, Maurizio Martelli, and Laurie H. Sehn

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on August 10, 2017.

Clinical trial information: NCT01287741.

Corresponding author: Umberto Vitolo, MD, SC Ematologia, Dipartimento di Oncologia ed Ematologia, AOU Città della Salute e della Scienza di Torino, C.so Bramante 88/90, 10126 Torino, Italy; e-mail: uvitolo@cittadellasalute.to.it.

0732-183X/17/3531w-3529w/$20.00

ABSTRACT

Purpose

Rituximab (R) plus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy is the standard of care in previously untreated diffuse large B-cell lymphoma (DLBCL). Obinutuzumab (G) is a glycoengineered, type II, anti-CD20 monoclonal antibody. GOYA was a randomized phase III study that compared G-CHOP with R-CHOP in patients with previously untreated advanced-stage DLBCL.

Methods

Patients (N = 1,418) were randomly assigned to receive eight 21-day cycles of G (n = 706) or R (n = 712), plus six or eight cycles of CHOP. Primary end point was investigator-assessed progression-free survival (PFS).

Results

After median observation of 29 months, the number of investigator-assessed PFS events was similar between G (201; 28.5%) and R (215; 30.2%), stratified hazard ratio was 0.92 (95% CI, 0.76 to 1.11; $P = .39$), and 3-year PFS rates were 70% and 67%, respectively. Secondary end points of independently reviewed PFS, other time-to-event end points, and tumor response rates were similar between arms. In exploratory subgroup analyses, patients with germinal-center B cell–like subtype had a better PFS than did patients with activated B cell–like subtype, irrespective of treatment. Frequencies of grade 3 to 5 adverse events (AEs; 73.7% *v* 64.7%, respectively) and serious AEs (42.6% *v* 37.6%, respectively) were higher with G-CHOP compared with R-CHOP. Fatal AE frequencies were 5.8% for G-CHOP and 4.3% for R-CHOP. The most common AEs were neutropenia (G-CHOP, 48.3%; R-CHOP, 40.7%), infusion-related reactions (G-CHOP, 36.1%; R-CHOP, 23.5%), nausea (G-CHOP, 29.4%; R-CHOP, 28.3%), and constipation (G-CHOP, 23.4%; R-CHOP, 24.5%).

Conclusion

G-CHOP did not improve PFS compared with R-CHOP in patients with previously untreated DLBCL. AEs reported with G were consistent with the known safety profile. Biomarker analyses may help define a future role for G in DLBCL.

J Clin Oncol 35:3529-3537. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma (NHL). Immunochemotherapy with the anti-CD20 monoclonal antibody, rituximab (R), plus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the standard-of-care treatment for previously untreated patients who present with advanced-stage disease.[1-3] Studies have shown a rate of complete response (CR) and unconfirmed CR of 76%,[1] as well as a 2-year failure-free survival rate of 77%.[4] Although first-line treatment of DLBCL is curative for many patients,[5] there is still a need to improve outcome for the 20% to 40% of patients who fail to achieve remission or who experience relapse—and outcomes with salvage therapy remain poor.[6]

Obinutuzumab (Gazyva/Gazyvaro; G) is a glycoengineered, type II anti-CD20 monoclonal antibody with greater direct cell death induction

ASSOCIATED CONTENT

See accompanying Editorial on page 3519

See accompanying article on page 3538

Data Supplements
DOI: https://doi.org/10.1200/JCO.2017.73.3402

DOI: https://doi.org/10.1200/JCO.2017.73.3402

and antibody-dependent cellular cytotoxicity and phagocytosis than R.[7,8] In phase III studies of previously untreated patients with chronic lymphocytic leukemia (CLL) and coexisting conditions (CLL11) or follicular lymphoma (FL; GALLIUM), G proved more effective than R.[9,10] In smaller studies, G monotherapy and G-CHOP have demonstrated promise in the treatment of aggressive forms of NHL, including DLBCL.[11,12] GOYA compared the efficacy and safety of G-CHOP with R-CHOP in previously untreated patients with DLBCL. Results of the final analysis are presented here.

METHODS

Patients

Eligible patients were age ≥ 18 years with the following: previously untreated, histologically documented, CD20-positive DLBCL as assessed by a local pathology laboratory; one or more bidimensionally measurable lesion (> 1.5 cm at the largest dimension on computed tomography [CT] scan); Eastern Cooperative Oncology Group performance status of 0 to 2; adequate hematologic, liver, and kidney function; left ventricular ejection fraction of ≥ 50%; and an International Prognostic Index (IPI) score of ≥ 2—as well as patients with an IPI score of 1 age ≤ 60 years, with or without bulky disease, and those with an IPI score of 0 and bulky disease, that is, one lesion ≥ 7.5 cm. Full inclusion/exclusion criteria are detailed in the Data Supplement. All patients provided written informed consent.

Study Design and Treatments

GOYA is a multicenter, open-label, randomized, phase III study. Patients were randomly assigned in a 1:1 ratio to receive eight 21-day cycles of either G (1,000 mg intravenously [IV] on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2 to 8) or R (375 mg/m^2 IV on day 1 of cycles 1 to 8), plus six or eight cycles of CHOP at the following doses: cyclophosphamide 750 mg/m^2 IV (day 1); doxorubicin 50 mg/m^2 IV (day 1); vincristine 1.4 mg/m^2 IV (day 1, maximum 2.0 mg); and prednisone 100 mg per day orally (days 1 to 5). The number of CHOP cycles for both arms was agreed upon in advance with each study site. If only six CHOP cycles were administered, the antibody was administered as monotherapy during cycles 7 and 8. Preplanned radiotherapy at initial sites of bulky or extranodal disease was permitted within 8 weeks of day 1 of the last antibody cycle and after the completion of end-of-treatment assessments. Details of premedications, permitted concomitant therapies, and permitted reasons for dose delays and/or reductions are provided in the Data Supplement. Random assignment was performed by an interactive voice-response system with stratification according to the number of planned chemotherapy cycles (six or eight cycles of CHOP), IPI score, and geographic region (Western Europe, Eastern Europe, South and Central America, North America, and Asia and others).

GOYA was conducted in accordance with the European Clinical Trial Directive for European centers and the International Conference on Harmonization guidelines for Good Clinical Practice. The protocol was approved by the ethics committees of participating centers.

Study End Points and Assessments

The primary study end point was investigator-assessed progression-free survival (PFS), which was defined as the time from the date of random assignment until the first occurrence of disease progression, relapse, or death from any cause. To rule out bias and support the primary analysis, PFS was also assessed by an independent review committee. Secondary end points included overall survival (OS); event-free survival; CR rate; overall response rate, including CR and partial response; disease-free survival, duration of response, time to next antilymphoma treatment, and safety. PFS was also analyzed in DLBCL cell-of-origin (COO) subgroups: germinal-center B cell–like (GCB), activated B cell–like (ABC), and unclassified subgroups (exploratory analysis). COO classification was based on gene-expression profiling using the NanoString Research Use Only Lymphoma Subtyping Test (NanoString Technologies, Seattle, WA).

Tumor response and progression were assessed by the investigator by using regular clinical and laboratory examinations and CT scans according to the Revised Response Criteria for Malignant Lymphoma.[13] For those patients with [^{18}F]fludeoxyglucose positron emission tomography (FDG-PET) scans (mandatory at sites with a PET scanner), a separate response assessment was performed that incorporated FDG-PET results. Primary end point analysis was based on the assessment of all patients using conventional CT scan. Response was evaluated 4 to 8 weeks (CT) or 6 to 8 weeks (FDG-PET) after the last study treatment or sooner in the case of early discontinuation.

Safety was assessed by monitoring and recording all adverse events (AEs) and serious AEs (SAEs), including abnormalities that were identified from laboratory evaluations, vital sign measurement, and physical examination. AEs were graded by using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Laboratory safety assessments included routine hematology and blood chemistry as well as tests of immunologic parameters. An independent data monitoring committee performed periodic safety reviews.

Statistical Analysis

Sample size was calculated to allow for the detection of a 25% reduction in the risk of disease progression, relapse, or death with G-CHOP versus R-CHOP—that is, a PFS hazard ratio (HR) for G-CHOP compared with R-CHOP of 0.75, with a two-sided α level of .05 and 80% power. To achieve this—and allowing for an annual dropout rate of 5%—405 PFS events were needed for the primary analysis, which required an enrollment of 1,400 patients over 3 years.

Efficacy assessments were performed on the intent-to-treat (ITT) population, which comprised all randomly assigned patients. The safety analysis population included all patients who received any study drug (antibody or CHOP). Treatment comparison of PFS was performed by using a two-sided α level .05 stratified log-rank test. The Kaplan-Meier method was used to estimate PFS distribution for each treatment arm. Estimates of treatment effect were expressed as HRs by using a stratified Cox proportional hazards regression analysis, including 95% CIs.

The independent data monitoring committee evaluated efficacy and safety at three formal interim analyses; two for futility and one for efficacy. Preplanned subgroup analyses assessed the effect of selected baseline patient characteristics, including COO subtype, on PFS.

RESULTS

Patient Characteristics and Treatment

Patients were enrolled at 207 centers in 29 countries. A total of 1,418 patients were randomly assigned between July 2011 and June 2014 to receive either G-CHOP (n = 706) or R-CHOP (n = 712), and 1,188 patients (G-CHOP, n = 587; R-CHOP, n = 601) completed planned treatment (Fig 1). AEs were the main reason for study (antibody) treatment discontinuation in both arms, and this was reported more frequently in the G-CHOP arm. Study (antibody) treatment discontinuation as a result of progressive disease was approximately twice as frequent in the R-CHOP arm compared with the G-CHOP arm.

Demographic and baseline disease characteristics were well balanced between the two arms (Table 1). COO subgroup information was available for 933 patients. Distribution by subtype was well balanced and there were no clinically relevant differences

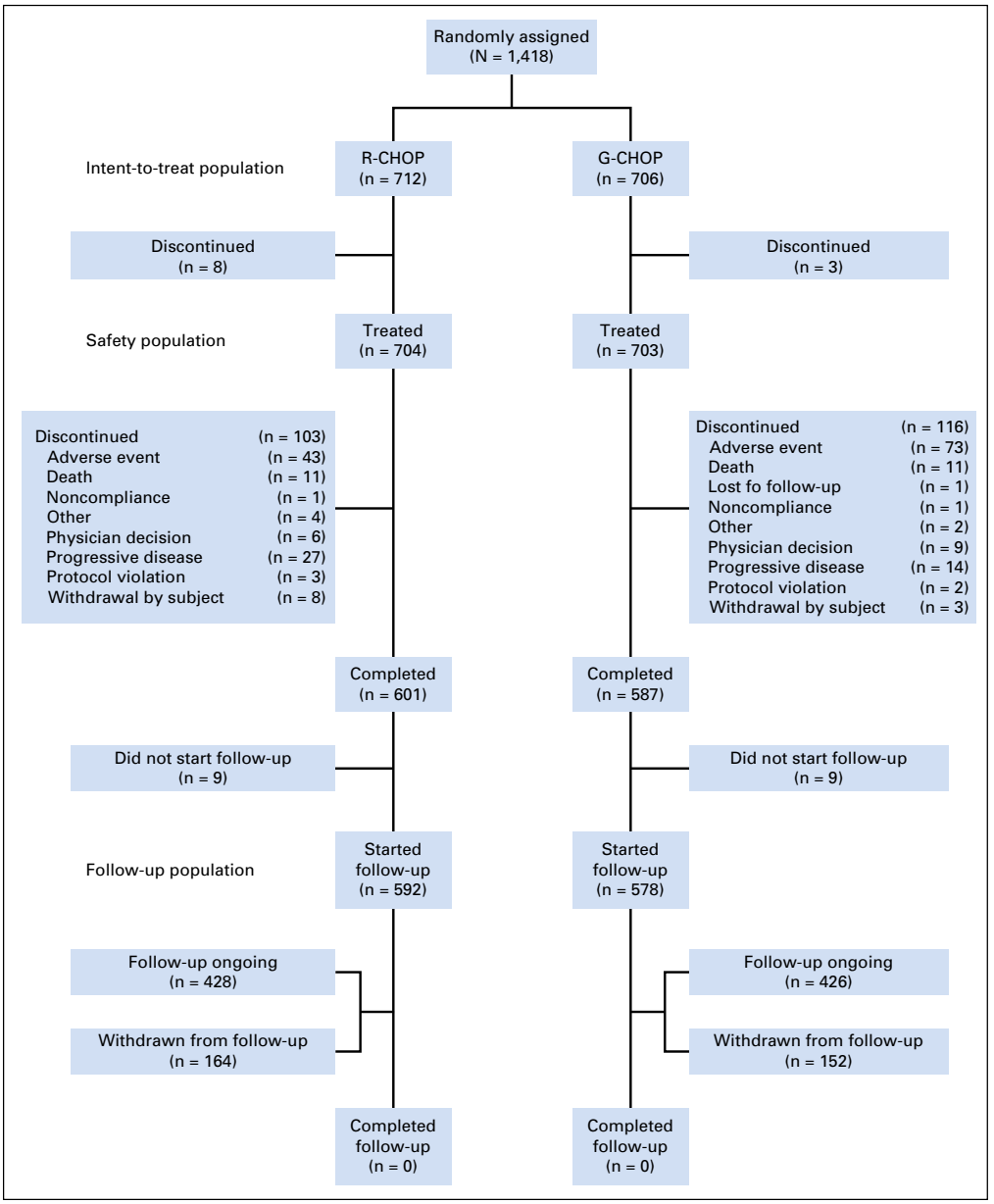


Fig 1. Patient disposition. Discontinued refers to patients who discontinued study (antibody) treatment. Median observation time was 29 months in each group. Completed treatment refers to patients who completed study (antibody) treatment. Patients were stratified at random assignment by International Prognostic Index score (low/low-intermediate, high-intermediate, and high-risk), planned number of CHOP cycles (six *v* eight), and geographic region (Western Europe, Eastern Europe, South and Central America, North America, Asia, and others). G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone.

between arms within COO subtypes. Reasons for missing COO information were as follows: a restricted Chinese sample export license that precluded biomarker assessments (n = 252), CD20-positive DLBCL not confirmed by central laboratory (n = 102; note that these patients were balanced between treatment arms: G-CHOP, n = 53; R-CHOP, n = 49), and missing and/or inadequate tissue (n = 131).

Median duration of exposure was 25.3 weeks (range, 1 to 32 weeks) for G and 25.3 weeks (0 to 32 weeks) for R. Dose intensity of G and R exceeded 90% for 95.3% and 99.1% of patients, respectively. Most patients in both arms (> 88%) received more than 90% of the planned dose of each CHOP component. Antibody dose delays were more common in the G-CHOP arm: at least one delay of ≤ 7 days (G-CHOP, 34.9%; R-CHOP, 30.0%) and of > 7 days (G-CHOP, 13.1%; R-CHOP, 9.1%; Data Supplement). New (unplanned) antilymphoma treatment was received by 103 patients (G-CHOP, n = 49; R-CHOP, n = 54) before disease progression, including radiotherapy for 23 patients with signs of residual disease after study treatment completion (G-CHOP, n = 9; R-CHOP, n = 14) and 227 patients (G-CHOP, n = 102; R-CHOP, n = 125) after disease progression.

Efficacy

As of April 30, 2016, and after median observation of 29 months, the number of investigator-assessed PFS events in the ITT population was similar for G-CHOP (201; 28.5%) and R-CHOP (215; 30.2%), with stratified HR of 0.92 (95% CI, 0.76 to 1.11; $P = .3868$). Estimated 3-year PFS rates were 69.6% and 66.9%, respectively (Fig 2A and Table 2).

Secondary end points were consistent with the primary end point, with no clinically meaningful differences between treatment arms for independent review committee–assessed PFS or any other

Table 1. Baseline Patient and Disease Characteristics (intent-to-treat population)

Characteristic	G-CHOP (n = 706)	R-CHOP (n = 712)
Median age (range), years	62.0 (18-86)	62.0 (18-83)
Male sex	369 (52.3)	383 (53.8)
Geographic region		
Asia	260 (36.8)	258 (36.2)
Western Europe	211 (29.9)	215 (30.2)
North America	109 (15.4)	107 (15.0)
Eastern Europe	97 (13.7)	99 (13.9)
Other	29 (4.1)	33 (4.6)
ECOG PS	n = 705	n = 712
0-1	618 (87.7)	613 (86.1)
2-3	87 (12.3)	99 (13.9)
Ann Arbor stage	n = 706	n = 711
I and II	170 (24.1)	171 (24.0)
III and IV	536 (75.9)	540 (75.8)
IPI risk group		
Low/low intermediate	376 (53.3)	409 (57.4)
High-intermediate	221 (31.3)	192 (27.0)
High	109 (15.4)	111 (15.6)
No. of planned CHOP cycles		
6	523 (74.1)	526 (73.9)
8	183 (25.9)	186 (26.1)
LDH elevated	n = 705	n = 708
Yes	415 (58.9)	401 (56.6)
Extranodal involvement*	484 (68.6)	468 (65.7)
Bulky disease (≥ 7.5 cm)	261/703 (37.1)	262/710 (36.9)
Cell of origin	n = 471†	n = 462†
GCB	271 (57.5)	269 (58.2)
ABC	125 (26.5)	118 (25.5)
Unclassified	75 (15.9)	75 (16.2)

NOTE. Data are presented as No. (%) unless otherwise noted; n = 706 for G-CHOP and n = 712 for R-CHOP for all parameters unless otherwise specified.
Abbreviations: ABC, activated B cell–like (subgroup); ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal-center B cell–like (subgroup); G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PET, positron emission tomography; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone.
*Cases where 'yes' was ticked in the electronic case report form for extranodal involvement; 14 patients with extranodal sites 0 were ticked in error.
†Cell of origin subtype classification was missing for 485 patients (G-CHOP, n = 235; R-CHOP, n = 250), which includes samples from China that could not be analyzed as a result of lack of an export license. Analysis of these samples is planned in the near future.

time-to-event end point (OS, event-free survival, disease-free survival, and time to next antilymphoma treatment; Fig 2B and Table 2; Data Supplement).

Subgroup and Exploratory Analyses. The efficacy of G-CHOP versus R-CHOP—unstratified HR for investigator-assessed PFS—was generally similar across selected patient subgroups, including patients who received six versus eight cycles of CHOP (Fig 3).

Kaplan-Meier analysis of PFS in patients with different COO subtypes—irrespective of study treatment—suggested that the GCB subtype is associated with a better outcome than the ABC or unclassified subtypes. HRs for PFS were as follows: 1.71 (95% CI, 1.31 to 2.23) for the ABC–GCB comparison; 1.57 (95% CI, 1.14 to 2.15) for the unclassified–GCB comparison; and 1.08 (95% CI, 0.77 to 1.52) for the ABC–unclassified comparison (Fig 2C). Three-year PFS rates were 75%, 59%, and 63% for the GCB, ABC, and unclassified subtypes, respectively. In an exploratory analysis of investigator-assessed PFS, the stratified HR for G-CHOP relative to R-CHOP for the 933 patients with available COO data was 0.82 (95% CI, 0.64 to 1.04), which suggests a potential selection bias versus the ITT population. Stratified HR for 540 patients in the GCB COO subgroup was 0.72 (95% CI, 0.51 to 1.03; 3-year PFS, 79% [G-CHOP] *v* 71% [*R*-CHOP]). No clinically meaningful differences in PFS between treatment groups (G-CHOP *v* R-CHOP) were observed in 243 patients with the ABC subtype (HR, 0.86; 95% CI, 0.57 to 1.29; 3-year PFS, 61% *v* 58%, respectively) or in 150 patients with unclassified COO subtype (HR, 1.02; 95% CI, 0.60 to 1.75; 3-year PFS, 62% *v* 64%, respectively; Data Supplement).

Safety

In the safety population, the proportion of patients who experienced at least one AE of any grade was similar in the G-CHOP and R-CHOP arms (97.0% [683 of 704 patients] and 93.5% [657 of 703 patients], respectively; Table 3). The most common AEs in both arms were neutropenia (G-CHOP, 48.3%; R-CHOP, 40.7%), infusion-related reactions (IRRs; G-CHOP, 36.1%; R-CHOP, 23.5%), nausea (G-CHOP, 29.4%; R-CHOP, 28.3%), and constipation (G-CHOP, 23.4%; R-CHOP, 24.5%; Data Supplement). Grade 3 to 5 AEs were more common in the G-CHOP arm (73.7% [519 of 704 patients] *v* 64.7% [455 of 703 patients]), as were SAEs (42.6% [300 of 704 patients] *v* 37.6% [264 of 703 patients]). The most common grade 3 to 5 AEs in both arms were neutropenia (G-CHOP, 46.2%; R-CHOP, 38.1%), infections (G-CHOP, 19.2%; R-CHOP, 15.5%), febrile neutropenia (G-CHOP, 17.5%; R-CHOP, 15.2%), and leukopenia (G-CHOP, 13.6%; R-CHOP, 10.1%; Table 3).

Analyses of AEs of particular interest showed that infections, neutropenia, IRRs, cardiac events, thrombocytopenia, and hemorrhagic events of any grade—as well as grade 3 to 5 AEs and SAEs—were more common with G-CHOP than R-CHOP (Data Supplement). Of note, rates of hepatitis B reactivation were higher with G-CHOP (2.3%) than R-CHOP (0.9%), the majority of events were grade 1 or 2, and grade 3 or 4 events were well balanced between the two arms (G-CHOP, 0.3% *v* R-CHOP, 0.3%). All other AE groups of particular interest, namely opportunistic infections, tumor lysis syndrome, secondary malignancies, and GI perforation (excluding abscesses), occurred at similar frequencies in the two arms (Data Supplement).

A similar proportion of patients in each arm received at least one dose of G-CSF during the study (G-CHOP, 611 patients [86.5%]; R-CHOP, 586 patients [82.3%]).

A higher proportion of patients in the G-CHOP arm than in the R-CHOP arm discontinued one or more components of the study treatment as a result of an AE (84 [11.9%] *v* 60 [8.5%], respectively). Fatal AEs were experienced by 71 patients (G-CHOP, 5.8% [41 of 704 patients]; R-CHOP, 4.3% [30 of 703 patients]) and are listed in Table 3.

DISCUSSION

In the current study of patients with previously untreated DLBCL, G-CHOP and R-CHOP demonstrated similar efficacy for all time-to-event end points, and the primary study end

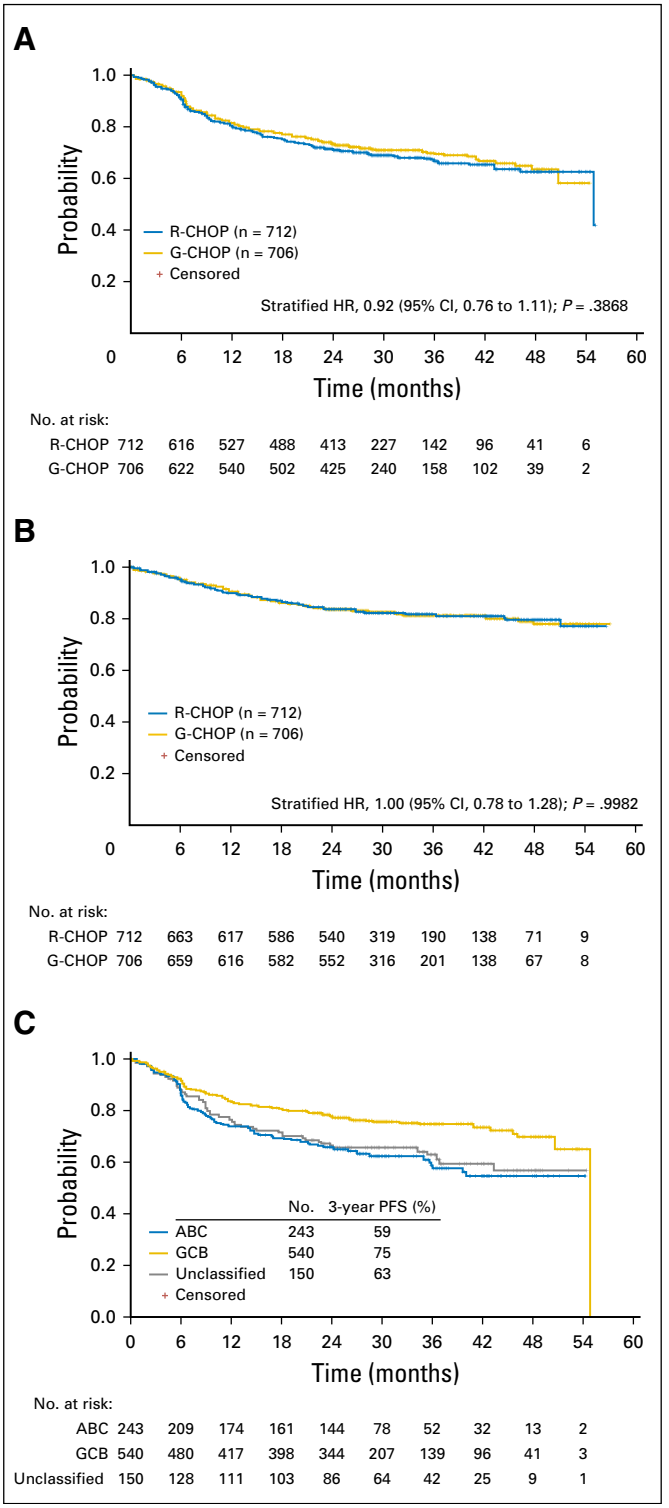


Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS). (A) Investigator-assessed PFS (primary end point) by treatment, intent-to-treat population. (B) OS by treatment, intent-to-treat population. (C) Investigator-assessed PFS by cell-of-origin subtype (irrespective of study treatment) in patients with cell-of-origin data. ABC, activated B cell–like; GCB, germinal-center B cell–like (subtype); G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

point of investigator-assessed PFS was not met. The lack of superiority of G-CHOP over R-CHOP in a population of patients with aggressive NHL contrasts with the results of studies that evaluated G in patients with CLL and FL. In the GALLIUM study, G-based induction and maintenance therapy significantly improved investigator-assessed PFS relative to R-based therapy in 1,202 previously untreated patients with FL.[10] G also prolonged PFS relative to R in untreated patients with CLL (n = 663) when both were combined with chlorambucil in the phase III CLL11 study.[9]

Given the advantages of G-based therapy in patients with FL and CLL, the lack of benefit of G-CHOP in patients with DLBCL in the GOYA study was unexpected, and the reasons for it are unclear. This lack of benefit might simply have resulted from the differences in biologic and clinical profiles between indolent lymphoproliferative diseases, such as FL and CLL, and aggressive ones, such as DLBCL.[14,15] Indeed, G may be more beneficial in lymphomas that are less aggressive or, like FL, are derived from the germinal center. The trend toward a benefit of G-CHOP over R-CHOP in GOYA for the GCB subtype—derived from the germinal center and known to be more similar to FL compared with other DLBCL subtypes,[16,17] with a more favorable prognosis and different immune microenvironment than the ABC and unclassified subtypes—seems to support this finding. The different mode of action of G and R may also play a role in the differential benefit of these agents in patients with FL and DLBCL; however, no data are yet available to support this statement. Ongoing analyses of GOYA biomarker data will provide additional insight into these differences. Of note, dose interruptions and skipped doses in cycle 1 were more frequent with G-CHOP, which reflects a higher rate of AEs (IRRs and cytopenias). This might have contributed to the lack of efficacy benefit compared with R-CHOP.

Since the dramatic improvement in outcomes after R was first added to CHOP,[1] no major advances have been made in the management of patients with DLBCL. Randomized trials have failed to show a benefit of shortening intervals between cycles,[18] or from consolidation with high-dose chemotherapy and autologous stem cell transplantation.[19,20] Addition of bortezomib to R-CHOP also failed to improve outcomes in a randomized trial of patients with non-GCB DLBCL,[21] and maintenance with lenalidomide did not improve OS.[22] Given the aggressive behavior of DLBCL, the substitution of R with a new anti-CD20 antibody with a different mode of action may not be sufficient to overcome refractoriness to chemotherapy. Combinations of drug-conjugated antibody or anti-BCL2 agents with R-CHOP could hold more promise, as shown by preliminary results of recent phase I and II studies.[23,24]

Determination of COO status by using gene-expression profiling has identified biologically distinct subtypes of DLBCL, including GCB and ABC origin subtypes.[25,26] These molecular subtypes have important implications for oncogenesis and treatment outcome, as reflected by their inclusion in the current WHO classification for DLBCL.[27] Patients with the GCB subtype typically have more favorable outcomes, whereas the ABC subtype has been associated with inferior outcomes after chemotherapy or immunochemotherapy, including R-CHOP, and may represent a poor-risk subset of patients with unmet medical need, as shown

Table 2. Summary of Efficacy End Points (intent-to-treat population)

End Point	Investigator Assessment	
	G-CHOP (n = 706)	R-CHOP (n = 712)
Median observation time (range), months	29.0 (0.1-56.6)	28.9 (0.1-56.2)
Investigator-assessed PFS (primary end point)	n = 706	n = 712
Patients with event, No. (%)	201 (28.5)	215 (30.2)
3-year PFS, %	69.6	66.9
Stratified HR (95% CI); *P* (log-rank)*	0.92 (0.76 to 1.11); *P* = .3868	
IRC-assessed PFS	n = 706	n = 712
Patients with event, No. (%)	171 (24.2)	186 (26.1)
3-year PFS, %	72.5	70.6
Stratified HR (95% CI); *P* (log-rank)*	0.89 (0.72 to 1.10); *P* = .2736	
OS	n = 706	n = 712
Patients with event, No. (%)	126 (17.8)	126 (17.7)
3-year OS, % (95% CI)	81.2 (77.9 to 84.1)	81.4 (78.1 to 84.3)
Stratified HR (95% CI)*	1.00 (0.78 to 1.28)	
DFS in patients with investigator-assessed CR	n = 397	n = 369
Patients with event, No. (%)	77 (19.4)	64 (17.3)
Stratified HR (95% CI)*	1.27 (0.91 to 1.77)	
Investigator-assessed EFS	n = 706	n = 712
Events, No. (%)	236 (33.4)	250 (35.1)
Stratified HR (95% CI)*	0.92 (0.77 to 1.11)	
Time to start of new antilymphoma treatment	n = 706	n = 712
Patients with event, No. (%)	213 (30.2)	230 (32.3)
Proportion of EFS at 3 years, % (95% CI)	69.9 (66.2 to 73.2)	66.5 (62.7 to 70.1)
Stratified HR (95% CI)*	0.92 (0.76 to 1.11)	
Investigator-assessed response (with PET) at end of treatment†	n = 669	n = 665
ORR		
Proportion, No. (%)	518 (77.4)	518 (77.9)
Percentage difference (95% CI)	−0.47 (−5.01 to 4.08)	
CR		
Proportion, No. (%)	379 (56.7)	396 (59.5)
Difference (95% CI)	−2.90 (−8.27 to 2.48)	
Investigator-assessed response (without PET) at end of treatment†	n = 706	n = 712
ORR		
Proportion, No. (%)	577 (81.7)	572 (80.3)
Percentage difference (95% CI)	1.39 (−2.76 to 5.54)	
CR		
Proportion, No. (%)	248 (35.1)	241 (33.8)
Difference (95% CI)	1.28 (−3.74 to 6.30)	

Abbreviations: CR, complete response; DFS, disease-free survival; EFS, event-free survival; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; HR, hazard ratio; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone.
*Stratification factors were International Prognostic Index score and planned number of CHOP cycles (6 or 8).
†According to revised response criteria.[13]

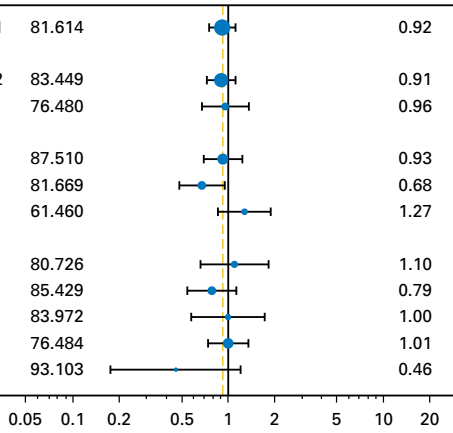
in retrospective studies.[25,26] GOYA is the largest prospective study, to our knowledge, to assess the impact of COO on clinical outcomes. Comparison of PFS by COO subtype was consistent with a better outcome in GCB DLBCL, with an HR indicating a 70% increase in risk of disease progression in patients with the ABC subtype relative to those with the GCB subtype. Outcome for the unclassified subgroup was similar to that of the ABC subgroup, which is in contrast to what has been reported in some prior studies.[26] Of interest, COO classification was not correlated with overall response rate and/or preliminary assessment of PFS in other prospectively defined studies, such as REMoDL-B[28] or PYRAMID,[21] although these studies used different COO assays. Specific treatments that are aimed at COO subtypes of DLBCL may offer an alternative strategy for improving outcomes. Selectively targeting the B-cell receptor or NF-κB pathways, for example, may prove to be beneficial in DLBCL subtypes (ABC or non-GCB), as suggested by the results of phase II studies that evaluated lenalidomide or ibrutinib with R-CHOP.[29-31] These strategies are currently being evaluated in randomized phase III studies.

The profile and nature of the AEs reported among G-CHOP–treated patients was as expected, with no new safety signals. The incidence of grade 3 to 5 AEs, SAEs, and treatment discontinuations as a result of AEs was slightly higher in the G-CHOP group than in the R-CHOP group, which was in keeping with what has been reported in other studies. These discrepancies may be a result of the different structural and biologic properties of G and R.

In conclusion, the current study demonstrated that G-CHOP did not improve PFS in a large population of patients with previously untreated DLBCL compared with R-CHOP, which remains the standard treatment in these patients. No new safety signals were identified and additional analysis of outcomes in biomarker-defined patient subgroups continues. These observations may help to inform and shape the direction of future research activities in patients with advanced-stage DLBCL.

A

Stratification Factors	Total No.	R-CHOP (n = 712) No.	R-CHOP Events	R-CHOP 1-Year KM Rate	G-CHOP (n = 706) No.	G-CHOP Events	G-CHOP 1-Year KM Rate	HR	95% Wald CI
All patients	1,418	712	215	79.778	706	201	81.614	0.92	0.76 to 1.12
No. of planned CHOP cycles									
6	1,049	526	152	80.789	523	142	83.449	0.91	0.73 to 1.15
8	369	186	63	76.949	183	59	76.480	0.96	0.6 to 1.37
IPI									
Low-intermediate	785	409	99	84.168	376	86	87.510	0.93	0.70 to 1.24
High-intermediate	413	192	71	75.013	221	62	81.669	0.68	0.48 to 0.95
High	220	111	45	71.577	109	53	61.460	1.27	0.85 to 1.90
Geographic region									
Eastern Europe	196	99	28	77.354	97	32	80.726	1.10	0.66 to 1.82
Western Europe	426	215	61	79.653	211	51	85.429	0.79	0.54 to 1.14
North America	216	107	27	87.556	109	25	83.972	1.00	0.58 to 1.73
Asia	518	258	87	77.830	260	87	76.484	1.01	0.75 to 1.36
Other	62	33	12	77.047	29	6	93.103	0.46	0.17 to 1.22



B

Baseline Factors	Total No.	R-CHOP (n = 712) No.	R-CHOP Events	R-CHOP 1-Year KM Rate	G-CHOP (n = 706) No.	G-CHOP Events	G-CHOP 1-Year KM Rate	HR	95% Wald CI
All patients	1,418	712	215	79.778	706	201	81.614	0.92	0.76 to 1.12
Sex									
Female	666	329	100	78.126	337	83	85.406	0.75	0.56 to 1.00
Male	752	383	115	81.180	369	118	78.124	1.11	0.86 to 1.43
Age group, years									
< 65	850	432	131	78.198	418	117	82.351	0.88	0.68 to 1.13
≥ 65	568	280	84	82.192	288	84	80.528	0.99	0.73 to 1.34
Race									
Asian	522	258	87	77.830	264	88	76.457	1.00	0.74 to 1.35
White	856	430	121	80.575	426	108	84.355	0.87	0.67 to 1.12
Other	40	24	7	86.542	16	5	93.333	1.10	0.34 to 3.49
ECOG PS									
0–1	1,231	613	180	81.540	618	161	83.774	0.86	0.69 to 1.06
2–3	186	99	35	68.590	87	40	65.750	1.41	0.89 to 2.23
Ann Arbor stage									
I	103	48	8	86.709	55	10	90.338	1.01	0.40 to 2.58
II	238	123	22	87.644	115	25	86.699	1.27	0.71 to 2.25
III	466	255	82	79.663	211	52	85.871	0.71	0.50 to 1.01
IV	610	285	103	75.197	325	114	75.572	0.96	0.73 to 1.25
Bulky disease									
Yes	523	262	94	71.548	261	79	78.333	0.78	0.58 to 1.05
No	890	448	120	84.771	442	122	83.481	1.06	0.82 to 1.36
Extranodal involvement*									
Yes	952	468	147	77.956	484	154	78.661	1.00	0.80 to 1.25
No	466	244	68	83.235	222	47	88.127	0.73	0.50 to 1.06
No. of extranodal sites									
0	14	8	2	75.000	6	1	100.000	0.58	0.05 to 6.40
1	437	221	58	81.552	216	54	87.211	0.94	0.65 to 1.36
> 1	503	240	87	74.793	263	99	71.520	1.02	0.77 to 1.36
Cell of origin									
GCB	540	269	74	81.022	271	55	86.062	0.72	0.5 to 1.01
ABC	243	118	47	73.714	125	45	74.634	0.86	0.57 to 1.29
Unclassified	150	75	27	73.973	75	27	80.572	1.02	0.60 to 1.75
Missing	485	250	627	83.214	235	74	80.634	1.18	0.85 to 1.64

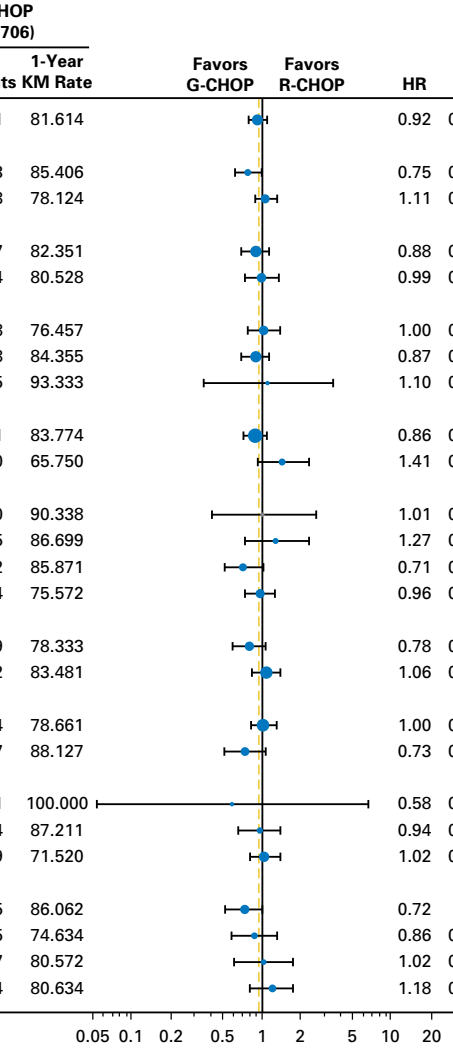


Fig 3. Unstratified hazard ratios (HRs) for investigator-assessed progression-free survival in patients with diffuse large B-cell lymphoma by patient subgroups. (A and B) Random assignment stratification factors (A) and baseline characteristics (B). (*)Cases where "yes" was ticked in the electronic case report form for extranodal involvement; 14 patients with extranodal sites 0 were ticked in error. ABC, activated B cell–like (subtype); ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal-center B cell–like (subtype); G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; IPI, International Prognostic Index; KM, Kaplan-Meier; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 3. Summary of AEs, Including Grade 3 to 5 and Serious AEs Reported by ≥ 5% of Patients in Either Group (at preferred term level; safety population)

Variable	G-CHOP (n = 704), No. (%)		R-CHOP (n = 703), No. (%)	
No. of deaths for any reason	126 (17.9)		122 (17.4)	
No. of patients withdrawn from study as a result of an AE	4 (0.6)		3 (0.4)	
Patients with at least one:				
AE	683 (97.0)		657 (93.5)	
Grade 3-5 AE	519 (73.7)		455 (64.7)	
AE with fatal outcome*	41 (5.8)		30 (4.3)	
Serious AE	300 (42.6)		264 (37.6)	
Treatment-related AE	639 (90.8)		596 (84.8)	
AE leading to withdrawal of any treatment	84 (11.9)		60 (8.5)	
AE leading to dose reduction for any treatment	145 (20.6)		138 (19.6)	
	Grade 3-5 AE	Serious AE	Grade 3-5 AE	Serious AE
Blood and lymphatic system disorders				
Total No. of patients with at least one AE	415 (58.9)	135 (19.2)	348 (49.5)	113 (16.1)
Neutropenia	325 (46.2)	52 (7.4)	268 (38.1)	40 (5.7)
Febrile neutropenia	123 (17.5)	81 (11.5)	107 (15.2)	72 (10.2)
Leukopenia	96 (13.6)	10 (1.4)	71 (10.1)	5 (0.7)
Anemia	51 (7.2)	9 (1.3)	53 (7.5)	6 (0.9)
Infections and infestations				
Total No. of patients with at least one AE	135 (19.2)	121 (17.2)	109 (15.5)	94 (13.4)
Pneumonia	40 (5.7)	40 (5.7)	35 (5.0)	32 (4.6)

Abbreviations: AE, adverse event; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone.

*Fatal AEs that were reported in more than one patient in either group, listed as preferred terms, were as follows: septic shock (six patients [0.9%]), pneumonia (five patients [0.7%]), death (cause unknown; three patients [0.4%]), pulmonary embolism (two patients [0.3%]), and cerebrovascular accident (two [0.3%]) in the G-CHOP group, and pneumonia (six patients [0.9%]), sepsis (three patients [0.4%]), cerebrovascular accident (two patients [0.3%]), and death (cause unknown; two patients [0.3%]) in the R-CHOP group.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Umberto Vitolo, Marek Trněný, Mikkel Z. Oestergaard, Michael Wenger, Günter Fingerle-Rowson, Olivier Catalani, Maurizio Martelli, Laurie H. Sehn

Provision of study materials or patients: Umberto Vitolo, Marek Trněný, David Belada, John M. Burke, Angelo Michele Carella, Neil Chua, Pau Abrisqueta, Judit Demeter, Ian Flinn, Xiaonan Hong, Won Seog Kim, Antonio Pinto, Yuan-Kai Shi, Yoichi Tatsumi, Maurizio Martelli, Laurie H. Sehn

Collection and assembly of data: Marek Trněný, Mikkel Z. Oestergaard, Olivier Catalani, Tina Nielsen

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Coiffier B, Lepage E, Briére J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002

2. Tilly H, da Silva MG, Vitolo U, et al: Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 26:v116-v125, 2015 (suppl 5)

3. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines: Non-Hodgkin's lymphoma, version 3.2016. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

4. Habermann TM, Weller EA, Morrison VA, et al: Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 24:3121-3127, 2006

5. Maurer MJ, Ghesquières H, Jais J-P, et al: Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. J Clin Oncol 32:1066-1073, 2014

6. Sehn LH, Gascoyne RD: Diffuse large B-cell lymphoma: Optimizing outcome in the context of clinical and biologic heterogeneity. Blood 125:22-32, 2015

7. Herter S, Herting F, Mundigl O, et al: Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Mol Cancer Ther 12:2031-2042, 2013

8. Mössner E, Brünker P, Moser S, et al: Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 115:4393-4402, 2010

9. Goede V, Fischer K, Busch R, et al: Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 370:1101-1110, 2014

10. Marcus R, Davies A, Ando K, et al: Obinutuzumab or rituximab immunochemotherapy in previously untreated iNHL. N Engl J Med (in press)

11. Morschhauser FA, Cartron G, Thieblemont C, et al: Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: Results from the phase II GAUGUIN study. J Clin Oncol 31:2912-2919, 2013

12. Zelenetz AD, Mobasher M, Costa LJ, et al: Safety and efficacy of obinutuzumab (GA101) plus CHOP chemotherapy in first-line advanced diffuse large B-cell lymphoma: Results from the phase 2 GATHER study (GAO4915g). Blood 122:1820, 2013

13. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007

14. Lenz G, Staudt LM: Aggressive lymphomas. N Engl J Med 362:1417-1429, 2010

15. Lim SH, Vaughan AT, Ashton-Key M, et al: Fc gamma receptor IIb on target B cells promotes rituximab internalization and reduces clinical efficacy. Blood 118:2530-2540, 2011

16. Morin RD, Mendez-Lago M, Mungall AJ, et al: Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. Nature 476:298-303, 2011

17. Shaffer AL, Rosenwald A, Staudt LM: Lymphoid malignancies: The dark side of B-cell differentiation. Nat Rev Immunol 2:920-932, 2002

18. Cunningham D, Hawkes EA, Jack A, et al: Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: A phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 381:1817-1826, 2013

19. Stiff PJ, Unger JM, Cook JR, et al: Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med 369:1681-1690, 2013

20. Schmitz N, Nickelsen M, Ziepert M, et al: Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: An open-label, randomised, phase 3 trial (DSHNHL 2002-1). Lancet Oncol 13:1250-1259, 2012

21. Leonard JP, Kolibaba K, Reeves JA, et al: Randomized phase 2 open-label study of R-CHOP ± bortezomib in patients with untreated non-germinal center B-cell-like subtype diffuse large cell lymphoma: Results from the PYRAMID trial (NCT00931918). Blood 126: 811, 2015

22. Thieblemont C, Tilly H, da Silva MG, et al: First analysis of an international double-blind randomized phase III study of lenalidomide maintenance in elderly patients with DLBCL treated with R-CHOP in first line, the REMARC study from LYSA. Blood 128:471, 2016

23. Zelenetz AD, Salles GA, Mason KD, et al: Results of a phase 1b study of venetoclax plus R or G-CHOP in patients with B-cell non-Hodgkin lymphoma. ASH 58th Annual Meeting & Exposition, San Diego, CA, December 3-6, 2016 (abstr 3032)

24. Tilly H, Morschhauser F, Bartlett NL, et al: Polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) for patients with previously untreated diffuse large B-cell lymphoma (DLBCL): Updated results of a phase Ib//II study. Blood 128:1853, 2016

25. Lenz G, Wright GW, Emre NC, et al: Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci USA 105:13520-13525, 2008

26. 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 33:2848-2856, 2015

27. Swerdlow SH, Campo E, Pileri SA, et al: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127:2375-2390, 2016

28. Davies AJ, Caddy J, Maishman T, et al: A prospective randomised trial of targeted therapy for diffuse large B-cell lymphoma (DLBCL) based upon real-time gene expression profiling: The Remodl-B study of the UK NCRI and SAKK lymphoma groups. Blood 126:812, 2015

29. Nowakowski GS, LaPlant B, Macon WR, et al: Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: A phase II study. J Clin Oncol 33:251-257, 2015

30. Vitolo U, Chiappella A, Franceschetti S, et al: Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: Results of the REAL07 open-label, multicentre, phase 2 trial. Lancet Oncol 15:730-737, 2014

31. Younes A, Thieblemont C, Morschhauser F, et al: Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: A non-randomised, phase 1b study. Lancet Oncol 15:1019-1026, 2014

Affiliations

Umberto Vitolo, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Turin; **Angelo Michele Carella**, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliera e Universitaria San Martino-IST, Genoa; **Antonio Pinto**, Istituto Nazionale Tumori, Fondazione G. Pascale, IRCCS, Naples; **Maurizio Martelli**, Sapienza University, Rome, Italy; **Marek Trněný**, Charles University, General Hospital, Prague; **David Belada**, Charles University Hospital, Hradec Králové, Czech Republic; **John M. Burke**, Rocky Mountain Cancer Centers, Aurora, CO; US Oncology Research, The Woodlands, TX; **Neil Chua**, Cross Cancer Institute, University of Alberta, Edmonton, Alberta; **Laurie H. Sehn**, British Columbia Cancer Agency and the University of British Columbia, Vancouver, British Columbia, Canada; **Pau Abrisqueta**, University Hospital Vall d'Hebron, Barcelona, Spain; **Judit Demeter**, Semmelweiss University, Budapest, Hungary; **Ian Flinn**, Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; **Xiaonan Hong**, Fudan University Shanghai Cancer Center, Shanghai; **Yuan-Kai Shi**, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China; **Won Seog Kim**, Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul, Republic of Korea; **Yoichi Tatsumi**, Kinki University Hospital, Osaka, Japan; **Mikkel Z. Oestergaard**, **Günter Fingerle-Rowson**, **Olivier Catalani**, and **Tina Nielsen**, F. Hoffman-La Roche, Basel, Switzerland; and **Michael Wenger**, Genentech, South San Francisco, CA.

Support

Supported by F. Hoffman-La Roche with scientific support from the Fondazione Italiana Linfomi.

Prior Presentation

Presented at the American Society of Hematology 58th Annual Meeting & Exposition, San Diego, CA, December 3-6, 2016.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Umberto Vitolo
Consulting or Advisory Role: F. Hoffman-La Roche, Janssen Pharmaceuticals
Speakers' Bureau: F. Hoffman-La Roche, Janssen Pharmaceuticals, Celgene, Gilead Sciences, Takeda
Research Funding: F. Hoffman-La Roche
Travel, Accommodations, Expenses: F. Hoffman-La Roche, Alexion Pharmaceuticals, Janssen Pharmaceuticals

Marek Trněný
Honoraria: F. Hoffmann-La Roche, Takeda, Janssen Pharmaceuticals, Gilead Sciences, Celgene, Bristol-Myers Squibb, NanoString Technologies
Consulting or Advisory Role: F. Hoffmann-La Roche, Celgene, Janssen Pharmaceuticals, Gilead Sciences, Takeda, Bristol-Myers Squibb, NanoString
Research Funding: F. Hoffmann-La Roche, Celgene
Travel, Accommodations, Expenses: Janssen Pharmaceuticals, Gilead Sciences, Takeda, Bristol-Myers Squibb

David Belada
Honoraria: F. Hoffmann-La Roche, Janssen Pharmaceuticals, Takeda, Gilead Sciences
Consulting or Advisory Role: F. Hoffmann-La Roche, Janssen Pharmaceuticals, Takeda, Gilead Sciences
Research Funding: F. Hoffmann-La Roche, Janssen Pharmaceuticals, Takeda, Gilead Sciences

John M. Burke
Consulting or Advisory Role: Incyte, Pfizer, Celgene, Bayer, Genentech, Gilead Sciences
Travel, Accommodations, Expenses: TG Therapeutics

Angelo Michele Carella
No relationship to disclose

Neil Chua
Consulting or Advisory Role: Seattle Genetics, F. Hoffman-La Roche, Celgene, Gilead Sciences, Lundbeck
Research Funding: F. Hoffman-La Roche
Travel, Accommodations, Expenses: Lundbeck

Pau Abrisqueta
Honoraria: F. Hoffman-La Roche, Janssen Pharmaceuticals, Gilead Sciences

Judit Demeter
Consulting or Advisory Role: Amgen, Novartis, Bristol-Myers Squibb, Pfizer, Angelini, F. Hoffman-La Roche, Aramis Pharma, Celgene
Speakers' Bureau: Amgen

Ian Flinn
Stock or Other Ownership: RainTree Oncology Services
Research Funding: Acerta Pharma (Inst), Agios (Inst), Calithera Biosciences (Inst), Celgene (Inst), Constellation Pharmaceuticals (Inst), Genentech (Inst), Gilead Sciences (Inst), Immunogen (Inst), Incyte (Inst), Infinity Pharmaceuticals (Inst), Janssen Pharmaceuticals (Inst), Karyopharm Therapeutics (Inst), Kite Pharma (Inst), Medivation (Inst), Millennium Pharmaceuticals (Inst), Novartis (Inst), OncoMed (Inst), Pharmacyclics (Inst), Portola Pharmaceuticals (Inst), F. Hoffmann-La Roche (Inst), Seattle Genetics (Inst), TG Therapeutics (Inst), Trillium Therapeutics (Inst)

Xiaonan Hong
No relationship to disclose

Won Seog Kim
Consulting or Advisory Role: Celltrion, Takeda, Janssen Pharmaceuticals
Research Funding: Janssen Pharmaceuticals, Takeda, Kyowa-Kirin, Dong-A, Novartis, F. Hoffman-La Roche, Gilead Sciences

Antonio Pinto
Consulting or Advisory Role: F. Hoffman-La Roche, Janssen Pharmaceuticals, Takeda, Bristol-Myers Squibb, Helssin Healthcare, MSD, Servier, Celgene
Speakers' Bureau: Bristol-Myers Squibb, F. Hoffman-La Roche, Janssen Pharmaceuticals, Celgene, Gilead Sciences, Takeda
Research Funding: Takeda

Yuan-Kai Shi
No relationship to disclose

Yoichi Tatsumi
No relationship to disclose

Mikkel Z. Oestergaard
Employment: F. Hoffman-La Roche
Stock or Other Ownership: F. Hoffman-La Roche
Honoraria: F. Hoffman-La Roche

Michael Wenger
Employment: Genentech

Günter Fingerle-Rowson
Employment: F. Hoffman-La Roche
Stock or Other Ownership: F. Hoffman-La Roche

Olivier Catalani
Employment: F. Hoffman-La Roche

Tina Nielsen
Employment: Roche
Stock or Other Ownership: F. Hoffman-La Roche

Maurizio Martelli
Consulting or Advisory Role: F. Hoffman-La Roche, Janssen Pharmaceuticals
Speakers' Bureau: F. Hoffman-La Roche, Janssen Pharmaceuticals, Celgene, Gilead Sciences, Takeda
Research Funding: F. Hoffman-La Roche

Laurie H. Sehn
Honoraria: Celgene, AbbVie, Seattle Genetics, TG Therapeutics, Janssen Pharmaceuticals, Amgen, Genentech, Gilead Sciences, Lundbeck
Consulting or Advisory Role: Celgene, AbbVie, Seattle Genetics, TG Therapeutics, Janssen Pharmaceuticals, Amgen, Genentech, Gilead Sciences, Lundbeck

Acknowledgment

Third-party medical writing assistance, under the direction of U.V. was provided by Cheryl Wright of Gardiner-Caldwell Communications, and was funded by F. Hoffman-La Roche.