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Obinutuzumab plus CHOP is effective and has a tolerable safety profile in previously untreated, advanced diffuse large B-cell lymphoma: the phase II GATHER study

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Abstract

This study investigated the safety and efficacy of obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP) in patients with advanced diffuse large B-cell lymphoma (DLBCL) and explored the impact of cell-of-origin (COO) on patient outcomes. Patients ($N = 100$) received obinutuzumab (1000 mg days 1, 8, and 15 of cycle 1, and day 1 of cycles 2–8) plus CHOP (cycles 1–6). For patients without grade ≥3 infusion-related reactions (IRRs) to standard-rate obinutuzumab infusion, a shorter duration of infusion (SDI) was evaluated. Overall and complete response rates, as determined according to the Cheson 2007 criteria by investigators/independent radiological facility, were 82.0/75.0% and 55.0/58.0%, respectively. SDI of 120 minutes and 90 minutes were well tolerated with no grade ≥3 IRRs. Among all patients, IRRs typically occurred during cycle 1, day 1. G-CHOP is active and has an acceptable safety profile in the first-line treatment of patients with advanced DLBCL.

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Authorship

Contribution: A.D.Z., M.M., and J.P.S. conceived and designed the study; A.D.Z., L.J.C., I.W.F., L.I., K.K., A.B., A.M.E., and M.M. collected and assembled the data; A.D.Z., A.F-T., D.S., L.J.C., I.W.F., K.K., A.B., L.E.F., A.M.E., C.R.F., K.M., T.S., G.F-R., C.V., M.M., and J.P.S were involved with the data analysis and interpretation; all authors contributed to the writing, critical review, and final approval of the manuscript.

Keywords

DLBCL; efficacy; obinutuzumab; safety profile

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma worldwide. Since the 1990s, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy has been the preferred treatment for advanced DLBCL, based on equivalent outcome with less toxicity compared with more intensive regimens [1, 2]. Addition of the type 1 anti-CD20 monoclonal antibody rituximab to CHOP (R-CHOP) resulted in clinically meaningful progression-free survival (PFS) and overall survival (OS) improvements without substantially increasing adverse events (AEs), establishing R-CHOP as the standard of care for patients with advanced DLBCL [3–7].

Despite improvements in outcomes, almost 40% of patients with DLBCL are not cured [8], demonstrating the heterogeneity of this disease; some of which can be captured by prognostic factors. The International Prognostic Index (IPI) [9] has proved a robust predictor of outcome and continues to be clinically useful in the rituximab era [10, 11]. DLBCL subtypes, characterized by cell-of-origin (COO; activated B-cell [ABC] or germinal center B-cell [GCB]), have been identified as an important prognostic factor for patients treated with R-CHOP [12–14]. New therapeutic modalities appear to have selective activity in different subtypes [15, 16].

Obinutuzumab (GA101) is a glycoengineered, humanized, type 2 anti-CD20 monoclonal antibody with increased direct cell death, antibody-dependent cell-mediated cytotoxicity and phagocytosis, and superior anti-tumor activity in human lymphoma xenograft models relative to rituximab [17].

Obinutuzumab demonstrated clinical activity as a single agent in patients with relapsed/refractory DLBCL [18]. Superior PFS was shown for obinutuzumab plus chlorambucil in comparison with rituximab plus chlorambucil and chlorambucil alone in the phase III CLL11 study in patients with previously untreated chronic lymphocytic leukemia and comorbidities [19]. Improved PFS was also demonstrated for obinutuzumab plus chemotherapy (CHOP, cyclophosphamide, vincristine, and prednisone [CVP], or bendamustine) followed by obinutuzumab maintenance (in responders) compared with rituximab plus chemotherapy and rituximab maintenance in the phase III GALLIUM study in patients with previously untreated follicular lymphoma [20].

A large, randomized, phase III comparison of obinutuzumab plus CHOP (G-CHOP) versus R-CHOP in patients with previously untreated advanced-stage DLBCL (GOYA; NCT01287741) showed similar PFS with either treatment [21]. Here, we report the final analysis of the GATHER study [22], which aimed to extensively evaluate the safety and efficacy of G-CHOP, with a minimum of 3 years follow-up post-treatment, in patients with newly diagnosed advanced DLBCL. We also evaluated the impact of COO on the efficacy

and safety of a shorter duration of infusion (SDI) of obinutuzumab, as part of overall safety, and performed a drug–drug interaction (DDI) sub-study.

Methods

Study design

GATHER (Clinical Trials: NCT01414855) is a phase II, open-label, multicenter, single-arm study in previously untreated patients with CD20-positive advanced DLBCL. Eligible patients were aged ≥18 years with: measurable disease; Ann Arbor stage II with bulky disease (mass >7.5 cm), stage III, or stage IV; IPI 1 (low risk) with bulky disease, or 2 to 5 (low-intermediate, high-intermediate, or high risk); Eastern Cooperative Oncology Group performance status 0 to 2; left ventricular ejection fraction >50%; hemoglobin ≥9 g/dL; absolute neutrophil count $\geq 1.5 \times 10^9$ cells/L; and platelet count $\geq 75 \times 10^9$ cells/L unless secondary to documented extensive bone marrow involvement or hypersplenism. Patients with CNS, primary mediastinal large cell, leg-type, primary cutaneous follicular center cell or primary effusion lymphoma, known HIV-associated DLBCL, primary cutaneous DLBCL, or active hepatitis (HBsAg, Hepatitis B-DNA-, or C-RNA-positive) were excluded.

This study was approved by local Institutional Review Boards (IRBs) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients gave written, IRB-approved, informed consent.

Treatment

Patients received eight 21-day cycles (10 doses) of obinutuzumab (1000 mg intravenous [IV] day 1 of cycles 1–8 with additional doses on day 8 and 15 of cycle 1) with six cycles of standard CHOP (cyclophosphamide 750 mg/m^2 IV day 1; doxorubicin 50 mg/m^2 IV day 1; vincristine 1.4 mg/m^2 [that could be capped at 2 mg] IV day 1; and prednisone 100 mg oral days 1–5 [or an equivalent IV dose of methylprednisone]). The obinutuzumab dose in cycle 1 could be split over two days if required by length of infusion duration, or at the investigator's discretion for patients considered at increased risk of an infusion-related reaction (IRR) or tumor lysis syndrome (TLS); CHOP could be administered on the second day if necessitated by a prolonged obinutuzumab administration.

IRR prophylaxis (acetaminophen 650 to 1000 mg and an antihistamine e.g. diphenhydramine 50 to 100 mg) was administered orally 30 to 60 minutes before each obinutuzumab infusion. Prophylactic corticosteroids were considered for patients at high risk of IRRs and when deemed appropriate by the investigator. Granulocyte-colony stimulating factor (filgrastim) was administered to patients ≥60 years old or with comorbidities and was strongly recommended for all patients in cycle 1 based on increased neutropenia in other obinutuzumab studies.

In the event of hematologic and non-hematologic toxicity, dose modifications/delays ≤14 days were permitted per protocol (supplemental material). G-CHOP could be resumed upon resolution of hematologic toxicity to grade ≤2 (platelets to grade ≤1) or baseline for the first episode, or of non-hematologic toxicity to grade ≤1 or baseline. CNS prophylaxis was given according to institutional practice.

Response and safety assessment

Disease responses were assessed using [^{18}F]fludeoxyglucose positron emission tomography and computed tomography scans 6 to 8 weeks after treatment completion according to the 2007 Revised Response Criteria for Malignant Lymphoma [23]. The incidence and severity of AEs and serious AEs (SAEs) were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [24]. AEs of special interest (AESIs) were serious IRRs, serious neutropenia, serious infection, and all TLS.

Shorter duration of infusion

Once safety of obinutuzumab in combination with CHOP was established in the first 20 patients, two SDI infusion times (120 minutes and then 90 minutes) were then tested (see Table S1 for infusion rates). Patients were treated with SDI if they had received ≥3 obinutuzumab doses at the regular infusion rate without any grade ≥3 IRRs and had a lymphocyte count $<5 \times 10^9$/L. SDI safety was assessed based on the incidence of grade 3/4 IRRs.

Cell-of-origin

In the current study, COO was determined by analysis of characteristic mRNA expression signatures in formalin-fixed, paraffin embedded (FFPE) samples in the Fluidigm qPCR platform (Fluidigm Heme V2, Fluidigm, South San Francisco, CA), using a modified version of the signature developed by Wright [25], that was based on 21 genes (see supplemental material for further information and Table S2 for genes analyzed) [26].

Drug–drug interactions

The effect of obinutuzumab on CHOP pharmacokinetics (PK) was evaluated in a DDI sub-study ($n = 20$). In cycle 1, cohort I received CHOP day 1 and obinutuzumab day 2, and cohort II received obinutuzumab day 1 and CHOP day 2. Subsequent cycles were administered as for the main study. Blood was sampled immediately after each drug infusion and at protocol-specified timepoints. Volume of distribution (V), clearance (CL), $t_{1/2}$, t_{max}, C_{max}, and AUC_{last} were derived by non-compartmental methods using Phoenix WinNonLin version 6.2 (Certara, Princeton, NJ). Patients with insufficient data to adequately derive PK parameters were excluded from the analysis.

Efficacy endpoints

Primary endpoints were investigator-assessed overall response rate (ORR; complete response [CR]/partial response) and CR rate at end of treatment (EOT). Patients with stable disease (SD), progressive disease (PD) before EOT, and patients with missing or non-evaluable post-baseline response assessment (for any reason) were considered non-responders.

Secondary endpoints included ORR and CR rate assessed by an Independent Review Facility (IRF), and investigator- and IRF-assessed PFS, defined as time from first dose until disease progression, relapse, or death from any cause. OS, defined as time from first dose until death from any cause, was an exploratory endpoint.

Statistical analyses

Eighty patients were planned to evaluate the primary endpoints (ORR and CR rate) at EOT. A further cohort of approximately 15 patients (depending on the final number enrolled on the DDI sub-study before the 80th patient in the main study was enrolled) was planned to ensure an adequate number in the DDI sub-study. All patients were part of the primary analysis of investigator-assessed response at EOT and the final analysis of investigator-assessed PFS and OS; results from both analyses are presented.

The emphasis in this study was on estimation rather than hypothesis testing. With 80 patients, if the observed CR rate at EOT was 50, then the 95% confidence intervals (CIs) for ORR and CR would be approximately equal to 0.39 to 0.61 using the Clopper-Pearson method [27].

Response rates (95% CIs) were calculated using the Clopper-Pearson method [27]. The proportion and 95% CIs for the response categories (CR, partial response [PR], stable disease [SD], and PD) are also presented. PFS (95% CIs) was assessed at six months, and at one, two, and three years using the Kaplan–Meier approach [28]. In an exploratory analysis, OS (95% CIs) was assessed using the same methodology.

Results

Patient characteristics

Between August 11, 2011 and June 4, 2013, 100 patients from 25 US centers were enrolled, and 87 completed all planned therapy (eight cycles of obinutuzumab and six cycles of CHOP; Figure 1). The clinical cutoff for the primary analysis of investigator-assessed response at EOT was April 8, 2013, and the cutoff for the final analysis of investigator-assessed PFS and OS was December 23, 2016, with a data snapshot date of March 14, 2017. Results from the final analysis are presented. Patient characteristics are shown in Table 1. Median age was 62 years (range, 24–80), with 22% of patients aged >70 years; 48% had high-intermediate/high risk disease (IPI 3–5) and 48% had bulky disease. By the final clinical cutoff date, of 100 patients enrolled, 24 had PD and 6 had died. Overall, 29 patients discontinued the study, either during treatment or during follow-up: 17 died (14 PD, 2 AEs [encephalitis and cardiovascular disorder] in follow-up, and one other reason [dilated congestive cardiomyopathy, which occurred after the AE reporting period had ended and was not related to study treatment]), five were lost to follow-up, and seven withdrew consent (Figure 1). None of the 17 deaths occurred during treatment. One additional patient died from hepatocellular carcinoma following study completion. In the 13 patients who did not complete all planned cycles of study treatment (obinutuzumab and CHOP), the most common reason for non-completion was an AE: eight patients experienced nine events (one each of intra-abdominal hemorrhage, small intestinal obstruction, catheter site cellulitis, herpes zoster infection, febrile neutropenia [FN], left ventricular dysfunction, wound, increased aspartate aminotransferase, and hypoxia). Additional reasons for non-completion of study treatment included PD (two patients), physician decision (one patient), patient withdrawal (one patient), and other undefined reasons (one patient).

Outcomes

Response rates at EOT for the overall study population (N = 100) are shown in Table 2. Investigator-assessed ORR and CR rate were 82.0% and 55.0%, respectively. IRF-assessed ORR and CR rate were similar at 75.0% and 58.0%, respectively.

Median observation time for time-to-event endpoints was 50.7 months (range, 3.5–63.2 months) at the time of the final analysis. Investigator-assessed PFS is shown in Figure 2(A); median PFS was 48.3 months (95% CI: 46.1, 58.2). PFS was 84.2% (95% CI: 76.9, 91.6%) at one year, 76.3% (95% CI: 67.7, 85.0%) at two years, and 71.6% (95% CI: 62.3, 80.9%) at three years. Investigator-assessed PFS did not appear to be impacted by IPI [low/low-intermediate *vs.* high-intermediate/high risk; Figure 2(B)].

IRF-assessed PFS was consistent with investigator assessment: median PFS was 46.1 months (95% CI: 46.1, 58.2), and the PFS rate at three years was 66.6% (95% CI: 57.0, 76.3%) (Figure S1). In an exploratory analysis, OS at two and three years was 87.5% (95% CI: 80.9, 94.1%) and 85.3% (95% CI: 78.2, 92.4%), respectively; median OS was not reached (Figure S2).

Archival FFPE tumor tissue was available from 99 patients: COO was assigned for 78, with insufficient tissue the most common reason for non-assignment. Forty-five (58%) patients had GCB-DLBCL, 19 (24%) ABC-DLBCL, and 14 (18%) were unclassified. Response by COO is shown in Table 2; there was little difference in ORR: GCB, 84.4%; ABC, 78.9%; and unclassified, 71.4%; however, the CR rate was numerically higher in GCB-DLBCL: GCB, 62.2%; ABC, 42.1%; and unclassified, 35.7%. By COO, the investigator-assessed 3-year PFS rate in patients with GCB- or ABC-DLBCL [(Figure 2(C)] was 75.9% (95% CI: 62.9, 89.0%) and 66.5% (95% CI: 44.5, 88.6%), respectively.

Similar findings were obtained when PFS was analyzed retrospectively by COO using an alternative genomic profiling assay (NanoString Lymphoma Subtyping Research-Use-Only Assay, NanoString Technologies, Seattle, WA, USA), as described in the supplemental material.

Obinutuzumab pharmacokinetics and drug–drug interactions

Overall, 76% of patients received all 10 obinutuzumab infusions and only 2% missed two or more doses. The PK of obinutuzumab were analyzed in cycle 1 (100 patients) and 8 (85 patients). C_{max} and AUC_{7day} increased from cycle 1 (297 μg/mL and 1320 day • μg/mL, respectively) to cycle 8 (584 μg/mL and 3300 day • μg/mL, respectively). C_{max} at cycle 8 was in line with that observed at steady state at a dose of 1000 mg. $t_{1/2}$, CL, and V were 23 ± 15.9 days, 143 ± 59.8 mL/day, and 9.21 ± 17.0 L, respectively (Table S3).

The DDI sub-study evaluated the impact of obinutuzumab on the PK of the components of CHOP. There was no difference in exposure to either doxorubicin or vincristine (Figure S1); however, AUC_{last} and C_{max} for the active 4-hydroxy metabolite of cyclophosphamide were slightly higher when obinutuzumab was given prior to CHOP: $AUC_{last,}$ 4310 ± 2730 ng • h/mL and 3000 ± 1590 ng • h/mL, respectively; and $C_{max,}$ 1100 ± 787 ng/mL and 810 ± 587 ng/mL, respectively. There was a minor increase in prednisone exposure with obinutuzumab;

however, there was no difference in exposure to the active metabolite prednisolone (Figure S3).

Adverse events

All patients experienced at least one AE; the most common are listed in Table S4 and a comparison of all AEs with obinutuzumab-related AEs is shown in Figure S4. Fifty-one patients experienced clinically relevant neutropenia: one grade 1, one grade 2, 16 grade 3, and 33 grade 4. Of the 15 patients not receiving filgrastim, four experienced ≥1 neutropenic event, including two who experienced FN. No patients experienced TLS. Hypogammaglobulinemia has been reported with antibodies targeting CD20 and was observed in this study at the EOT assessment [29], with IgM depletion being most common (30% of patients), followed by IgA (9%) and IgG (8%), compared with 8%, 3% and 6%, respectively, at baseline (thresholds: IgM, 0.3 g/L; IgA, 0.5 g/L; and IgG, 5 g/L). SAEs are shown in Table 3; infections were most common (19%), followed by blood and lymphatic system disorders (17%), notably FN (14%), despite 85% of patients receiving filgrastim.

Infusion-related reactions and shorter duration of infusion

Seventy-one patients received corticosteroids for IRR prophylaxis. The safety of SDI after cycle 1 was evaluated. Twenty patients received obinutuzumab at the standard rate (Table S1) to establish baseline safety. Thereafter, three patients who had not experienced an IRR grade ≥3 in prior infusions were treated with SDI 120 as an initial test of SDI; none experienced an IRR grade ≥3 and thus SDI 90 was tested. Once declared safe, remaining patients were treated with SDI 90 after three infusions at the standard rate.

Table 4 summarizes IRRs by infusion rate (defined as AEs related to any study treatment [not specific to obinutuzumab] occurring during/within 24 hours of the end of infusion). Overall, 69 patients (69%) experienced 244 IRRs. The majority occurred in cycle 1 (187/244) and were predominantly grade 2 in intensity (129/244). One grade 4 IRR was reported (FN) and there were no grade 5 IRRs. IRRs of all grades affected 60% of patients infused at the standard rate. No patients receiving SDI 90 experienced IRRs grade ≥3; 3% (2/70) experienced grade 1 to 2 IRRs. No patients withdrew from obinutuzumab treatment as a result of IRRs. Obinutuzumab concentration at the end of infusion was summarized by infusion duration and was as expected, slightly higher for SDI 90 compared with the regular rate. However, when data variability was taken into account, the difference was not marked (Table S5).

Discussion

This study demonstrates that G-CHOP can be safely administered in DLBCL and is efficacious. Although initial obinutuzumab administration is frequently associated with IRRs (69 patients experienced 244 IRR events overall in this study, with 76.6% occurring during cycle 1), after the first infusion they are uncommon, generally mild, and can be managed by premedication with corticosteroids, acetaminophen, and an antihistamine; even on cycle 1 day 8, the risk of IRRs is low. SDI was explored with only 3% of the patients receiving the 90-minute infusion experiencing IRRs, all being grade 1 or 2. Thus, SDI was well tolerated

in this cohort of patients with no grade ≥3 IRRs, showing obinutuzumab can be delivered in 90-minutes in combination with CHOP in a subgroup of carefully selected patients. The feasibility and tolerability of anti-CD20 antibody SDI (over 90 minutes) has been demonstrated previously for rituximab in combination with chemotherapy in untreated DLBCL (R-CHOP) or follicular lymphoma (R-CVP) [29], and is under investigation for obinutuzumab in combination with chemotherapy in Japanese patients with untreated B-cell NHL in the GATS study [30].

In a study by Cunningham et al of patients with DLBCL receiving R-CHOP, the risk of neutropenia and FN was 60% and 11%, respectively, when filgrastim administration was reactive compared with 31% and 5%, respectively, for prophylactic filgrastim administration [31]. In the current study, the rates of neutropenia (41%) and FN (16%) AEs were similar to those with R-CHOP without prophylactic filgrastim. In the phase III GOYA study, where filgrastim was recommended but not mandatory for at-risk patients, rates of neutropenia/FN were 48.3%/18.0% with G-CHOP and 40.7%/15.4% with R-CHOP [21]. Of the 85 patients who received prophylactic filgrastim during at least one cycle in the present study, 36 experienced at least one neutropenic AE in the same cycle. Most patients who received filgrastim and experienced a neutropenic event did so in cycle 1 (24%); this proportion dropped considerably in subsequent cycles (range, 4–7%). Thus, although G-CHOP may be associated with a greater risk of neutropenia than R-CHOP, it can be managed with filgrastim prophylaxis.

Obinutuzumab did not have a major impact on the PK of individual CHOP components, with the exception of higher AUC and C_{max} for the active 4-hydroxy metabolite of cyclophosphamide. However, significant variability in exposure (which is typical for a metabolite) makes the clinical significance of this effect uncertain. Overall, obinutuzumab does not appear to reduce patient exposure to CHOP components and thus does not affect the efficacy of chemotherapy. Although IRF-assessed ORR at EOT (75.0%) was slightly below the expected range, compared with studies of R-CHOP in DLBCL (94% [33] and 88% [32]), the CR rate by IRF (58.0%) was similar to CR rates of 61% and 49% reported in these studies, [32, 33] respectively. Notably, ORRs/CR rates were in line with those reported in the GOYA study with either G-CHOP (77.4%/56.7%) or R-CHOP (77.9%/59.5%) [21].

Determination of COO is controversial because of the lack of concordance between the various algorithms and gene expression profiling (GEP) [34]. For example, a previous study has demonstrated low concordance in patient's COO classification across nine different immunohistochemistry algorithms, where only 4% of DLBCL tumors were classified as GCB and 21% as ABC/non-GCB by all methods [34, 35]. In this study, COO was determined on a multiplex Fluidigm qPCR platform using 21 genes based on a modification of the published DLBCL classifier using a previously reported technique [25, 26]. In post-hoc analyses, the Fluidigm platform demonstrated good concordance with the validated NanoString Lymphoma Subtyping Research-Use-Only GEP assay [36], as described in the supplemental material. COO did not appear to affect ORR; however, the CR rate was numerically superior for GCB-DLBCL compared with ABC-DLBCL. The 3-year PFS rate was also numerically higher in GCB- versus ABC-DLBCL patients (75.9% *vs.* 66.5%, respectively). Similarly, with R-CHOP, outcomes are consistently inferior for ABC-DLBCL

compared with GCB-DLBCL [14]. Our observation must be interpreted cautiously, however, due to the relatively small sample size. Furthermore, the low event rate means the comparison of GCB- and ABC-DLBCL is underpowered. Interestingly, exploratory analyses from the larger GOYA study, which enrolled 1418 DLBCL patients, indicated that the GCB subtype was associated with longer PFS than the ABC or unclassified subtypes. Notably, there was a trend toward a benefit of G-CHOP over R-CHOP in GCB DLBCL (PFS hazard ratio, 0.72; 95% CI: 0.51, 1.03) [21].

In summary, these phase II data indicate that G-CHOP is effective and can be administered with a tolerable safety profile, including the ability to administer obinutuzumab as a short 90-minute infusion after the initial cycle. While data from the separate phase III GOYA study demonstrate that G-CHOP is no more effective than R-CHOP in previously untreated DLBCL [21], exploratory efficacy signals in the GCB subtype suggest that biomarker studies may help to establish a role for obinutuzumab in DLBCL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential conflicts of interest

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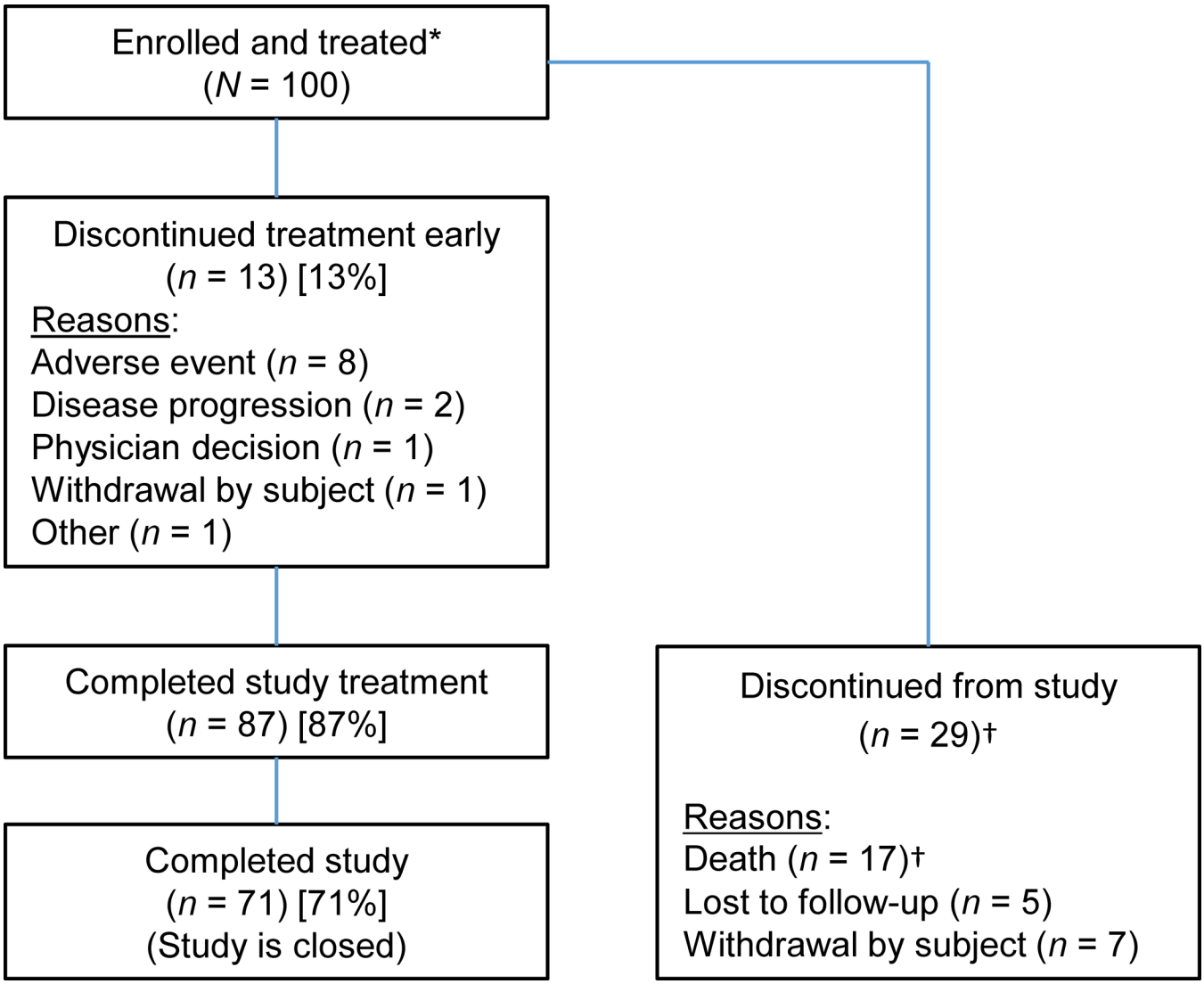

Figure 1.

Patient disposition. *Planned treatment consisted of obinutuzumab administered as 1000 mg IV on day 1 of a 21-day cycle for 8 cycles, with additional doses on days 8 and 15 of cycle 1. †One additional patient completed the study and then died due to a secondary malignancy. AE: adverse event; IV: intravenous; PD: progressive disease.

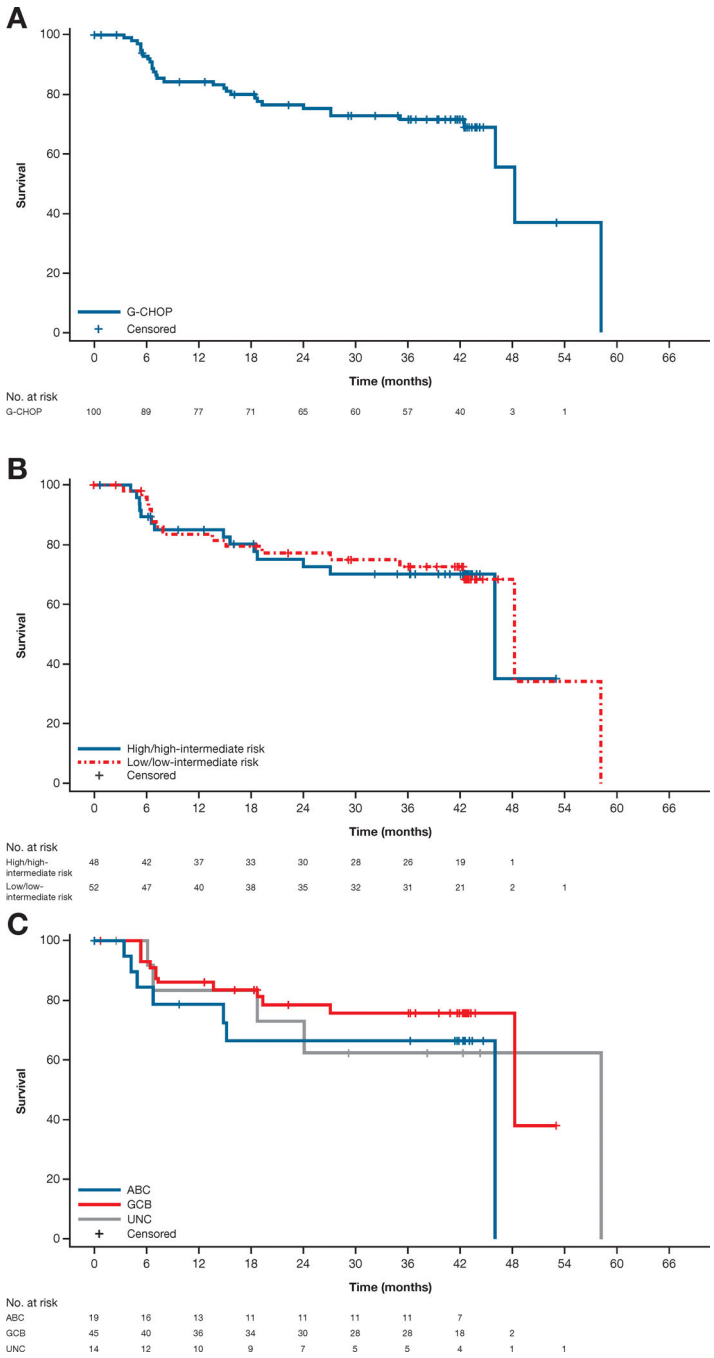

Figure 2.

Progression-free survival. (A) Investigator-assessed PFS of all patients in the study after a median observation time of 50.7 months. Median PFS was 48.3 months. (B) PFS according to IPI: low risk/low-intermediate risk (0–2) versus high risk/high-intermediate risk (3–5). (C) PFS according the COO as determined by a modification of the Wright et al.[25] DLBCL gene expression classifier (see Methods). COO could be assigned in 78 cases: 45 GCB, 19 ABC. ABC: activated B-cell; COO: cell-of-origin; DLBCL: diffuse large B-cell lymphoma;

GCB: germinal center B-cell; IPI: International Prognostic Index; PFS: progression-free survival.

Table 1.

Patient characteristics.

	All	COO*		
		GCB	ABC	Unclassified
Characteristic	***N* = 100**	***N* = 45**	***N* = 19**	***N* = 14**
Age in years, median	62	63	63	56
Range	24–80	24–79	24–76	39–80
<40	12 (12.0%)	7 (15.6%)	2 (10.5%)	1 (7.1%)
40–59	34 (34.0%)	11 (24.4%)	6 (31.6%)	8 (57.1%)
60–70	32 (32.0%)	19 (42.2%)	6 (31.6%)	2 (14.3%)
>70	22 (22.0%)	8 (17.8%)	5 (26.3%)	3 (21.4%)
Male	57 (57.0%)	25 (55.6%)	13 (68.4%)	5 (35.7%)
Race				
Asian	4 (4.0%)	-	-	-
Black or African American	9 (9.0%)	-	-	-
White	81 (81.0%)	-	-	-
Other	6 (6.0%)	-	-	-
Ann Arbor stage				
II	16 (16.0%)	8 (17.8%)	4 (21.1%)	3 (21.4%)
III	32 (32.0%)	16 (35.6%)	5 (26.3%)	5 (35.7%)
IV	52 (52.0%)	21 (46.7%)	10 (52.6%)	6 (42.9%)
B-symptoms	57 (57.0%)	22 (48.9%)	13 (68.4%)	11 (78.6%)
Bulk (>7.5 cm)	48 (48.0%)	24 (53.3%)	9 (47.4%)	6 (42.9%)
ECOG PS				
0	39 (39.0%)	17 (37.8%)	8 (42.1%)	6 (42.9%)
1	54 (54.0%)	26 (57.8%)	9 (47.4%)	6 (42.9%)
2	7 (7.0%)	2 (4.4%)	2 (10.5%)	2 (14.3%)
LDH > ULN	58 (58.0%)	22 (48.9%)	13 (68.4%)	10 (71.4%)
IPI category (score)				
Low (1)	13 (13.0%)	7 (15.6%)	3 (15.8%)	3 (21.4%)
Low-intermediate (2)	39 (39.0%)	16 (35.6%)	6 (31.6%)	5 (35.7%)
High-intermediate (3)	29 (29.0%)	10 (22.2%)	10 (52.6%)	4 (28.6%)
High (4–5)	19 (19.0%)	12 (26.7%)	0	2 (14.3%)
Extranodal involvement	53 (53.0%)	-	-	-

ABC: activated B-cell; COO: cell-of-origin; EGOG PS: Eastern Cooperative Oncology Group performance status; GCB: germinal center B-cell; IPI: international Prognostic Index; LDH: lactate dehydrogenase; ULN: upper limit of normal.

Data are expressed as n (%) unless stated otherwise.

*COO as determined with the Fluidigm qPCR platform using a modified version of the Wright classifier.[23]

Formalin-fixed, paraffin-embedded tumor tissue was available for 99 patients and COO was assigned for 78; the most common reason for non-assignment was insufficient tissue.

Table 2.

Response to G-CHOP therapy and progression-free survival.

Outcome	Investigator	IRF	COO*		
			GCB† *N* = 45	ABC† *N* = 19	Unclassified *N* = 14
EOT‡					
ORR (95% CI)	82 (82.0%) (73.1, 89.0%)	75 (75.0%) (65.3, 83.1%)	38 (84.4%) (70.5, 93.5%)	15 (78.9%) (54.4, 94.0%)	10 (71.4%) (41.9. 91.6%)
CR (95% CI)	55 (55.0%) (44.7, 65.0%)	58 (58.0%) (47.7, 67.8%)	28 (62.2%) (46.5, 76.2%)	8 (42.1%) (20.3, 66.5%)	5 (35.7%) (12.8, 64.9%)
PR (95% CI)	27 (27.0%) (18.6, 36.8%)	17 (17.0%) (10.2, 25.8%)	10 (22.2%) (11.2, 37.1%)	7 (36.8%) (16.3, 61.6%)	5 (35.7%) (12.8, 64.9%)
SD (95% CI)	1 (1.0%) (0.03, 5.5%)	3 (3.0%) (0.6, 8.5%)	1 (2.2%) (0.1, 11.8%)	0 -	0 -
Relapsed/ Progression (95% CI)	11 (11.0%) (5.6, 18.8%)	14 (14.0%) (7.9, 22.4%)	3 (6.7%) (1.4, 18.3%)	4 (21.1%) (6.1, 45.6%)	2 (14.3%) (1.8, 42.8%)
Not evaluable (95% CI)	2 (2.0%) (0.2, 7.0%)	1 (1.0%) (0.03, 5.5%)	-	-	-
Missing (95% CI)	4 (4.0%) (1.1, 9.9%)	7 (7.0%) (2.9, 13.9%)	-	-	-
PFS, 3 years (95% CI) Patients at risk	71.6% (62.3, 80.9%) 57	66.1 (57.0, 76.3) 52	75.9 (62.9, 89.0) 28	66.5 (44.5, 88.6) 11	62.5 (33.0, 92.1) 5

ABC: activated B-cell; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CI: confidence interval; COO: cell-of-origin; CR: complete response; EOT: end of treatment; GCB: germinal center B-cell; G-CHOP: obinutuzumab plus CHOP; IRF: independent review facility; ORR: overall response rate; PFS: progression-free survival; PR: partial response; SD: stable disease.

*COO as determined with the Fluidigm qPCR platform using a modified Wright classifier.[23] Formalin-fixed, paraffin-embedded tumor tissue was available for 99 patients and COO was assigned for 78; the most common reason for non-assignment was insufficient tissue.

†For GCB and ABC subgroups, response values were calculated based on the number of patients with available biomarker data.

‡The first disease response assessment after the last dose of any study treatment and before the start of any new anti-lymphoma treatment.

Table 3.

Summary of serious adverse events (occurring in >1 patient).

Serious adverse events (by system's organ class and preferred term)	Number of events*	Number of patients, N (%)†
Infections	23	19 (19)
Pneumonia		6 (6)
Sepsis		2 (2)
Blood and lymphatic system disorder	24	17 (17)
Febrile neutropenia		14 (14)
Gastrointestinal disorders	10	9 (9)
Diarrhea		2 (2)
Respiratory, thoracic, and mediastinal disorders	5	5 (5)
Hypoxia		2 (2)
Pulmonary embolism		2 (2)
Metabolism and nutrition disorders	3	3 (3)
Dehydration		2 (2)
Psychiatric disorders	5	3
Mental status changes		2 (2)

*For frequency counts of 'number of events', multiple occurrences of the same AE in an individual were counted separately.

†For frequency of counts by preferred term, multiple occurrences of the same AE in an individual were counted only once.

Table 4.

Infusion-related reactions with shorter duration of infusion.

IRRs				
Infusion rate	**Day, cycle**	**Number of AEs**	**Number of AEs ≥ grade 3**	**Patients with ≥1 AE IRR n/N (%)**
Summary of AESIs: all treatment-related IRRs*				
All infusion rates	All	244	7	69/100 (69%)
Summary of AESIs: all treatment-related IRRs*†				
Regular infusion rate	All	193	3	60/100 (60%)
SDI 120	All	1	0	1/5 (20%)
SDI 90	All	3	0	2/70 (3%)
Summary of AESIs: obinutuzumab-related IRRs				
Regular infusion rate	All	150	3	51/100 (51%)
SDI 120 minutes	All	1	0	1/5 (20%)
SDI 90 minutes	All	3	0	2/70 (3%)

AE: adverse event; AESI: adverse event of special interest; IRR: infusion-related reaction; SDI: shorter duration of infusion.

*IRRs are AEs related to any study treatment (not specific to obinutuzumab) which occurred during or within 24 hours of the end of infusion.

†The number of patients with at least one AE in regular infusion, SDI 120, and SDI 90, does not add up to 69 (all infusion rates) because patients can be counted in regular infusion, SDI 120, and SDI 90 outputs, if they received more than one type of infusion during the treatment period.