Combination of Atezolizumab and Obinutuzumab in Patients with Relapsed/Refractory Follicular Lymphoma and Diffuse Large B-Cell Lymphoma: Results from a Phase 1b Study

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Abstract

This Phase 1b study assessed the safety, tolerability, and efficacy of atezolizumab plus obinutuzumab in patients with R/R DLBCL and FL. 49 patients were enrolled. All-grade AEs were reported in 94% of patients The ORRs were 54% (FL cohort) and 17% (DLBCL cohort). Atezolizumab plus tazemetostat was determined to be safe and tolerable, with no new toxicities observed.

Background: This was an open-label, phase 1b study assessing the safety, tolerability, preliminary efficacy and pharmacokinetics of the combination of atezolizumab and obinutuzumab in patients with relapsed/refractory follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL). There is a mechanistic rationale suggesting that this combination may enhance recruitment of both innate and adaptive immunity and be effective against CD20+ B-cell malignancies. **Materials and methods:** The study consisted of a safety evaluation stage and an expansion stage. Patients received obinutuzumab 1000 mg intravenously (IV) in cycle (C) 1, obinutuzumab plus atezolizumab 1200 mg IV for C2–8, and atezolizumab only from C9. Primary endpoints were to identify a recommended phase 2 dose (RP2D) for atezolizumab, and safety and tolerability in the safety and expansion stages. **Results:** A total of 49 patients were enrolled (FL, n = 26; DLBCL, n = 23), with a median of 2 prior lines of treatment. The RP2D for atezolizumab was 1200 mg IV every 3 weeks. Adverse events reported in ≥ 20% of patients were fatigue (15 patients [31%]), nausea (13 patients [27%]), cough, and diarrhea (10 patients [20%] each). Objective response rate was 54% in the FL cohort (complete response [CR] rate: 23%) and 17% in the DLBCL cohort (CR: 4%). Median progression-free survival was 9 months for FL and 3 months for DLBCL. Median overall survival was not estimable for FL and 9 months for DLBCL. **Conclusion:** The combination of obinutuzumab and atezolizumab was determined to be safe and tolerable, with no new toxicities observed.

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Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous malignancy, and is the fifth most common malignancy and eighth most common cause of cancer death in the US.[1] There is no standard treatment for the management of advanced follicular lymphoma (FL), an indolent form of NHL, and data from the National LymphoCare registry suggest that clinical practice varies widely among physicians.[2] Although FL is highly treatable it remains incurable, and responses to therapy are typically shorter with each line of treatment. The current standard of care for diffuse large B cell lymphoma (DLBCL), an aggressive form of NHL, is rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), but the prognosis for patients with relapsed or refractory (R/R) DLBCL is poor, with only a minority of patients cured with autologous stem cell transplantation.[3] As a result, patients with R/R FL and DLBCL represent a significant unmet medical need and novel therapeutic regimens are needed.

Evidence from an *in vitro* study using established cell lines and primary lymphoma specimens has suggested that programmed death-ligand 1 (PD-L1) is expressed in patients with DLBCL primarily presenting as non-germinal center subtypes.[4] Atezolizumab is a humanized IgG2 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Cis-PD-L1/CD80 interaction on antigen-presenting cells can inhibit the function of PD-1 and consequently induce optimal T-cell responses.[5,6] Additionally, induction of lymphoma-directed T-cell responses has been shown to be enhanced by the anti-CD20 antibody, rituximab.[7,8] Obinutuzumab is a humanized, glycoengineered type II anti-CD20 monoclonal antibody that demonstrated an improved response rate compared with rituximab in patients with relapsed FL.[9]

There is a mechanistic rationale to combine tumor-targeted therapies with anti-tumor immunity agents, which may potentially enhance the recruitment of both innate and adaptive immunities and be effective against CD20+ B-cell malignancies. Antibodies targeting T-cell immune checkpoint inhibitors such as PD-L1 and PD-1 have demonstrated the capacity to generate durable responses in patients with multiple cancer types.[10,11] Moreover, nonclinical studies have shown that the combination of targeted therapies and PD-1 inhibitors can lead to durable complete responses (CRs) that are not achieved by either agent alone.[12]

Here, we report results from the final analysis of the first study to evaluate the activity of the chemotherapy-free combination of atezolizumab and obinutuzumab in patients with R/R FL and DLBCL. (NCT02220842; EudraCT: 2014-001812-21).

Materials and Methods

Patients

This was an open-label, multicenter, global phase 1b study assessing the safety, tolerability, preliminary efficacy and pharmacokinetics of atezolizumab and obinutuzumab administered in combination to patients with FL and DLBCL.

Key eligibility criteria included 18 years of age or older with histologically documented, CD20 positive, R/R (refractory defined as having relapsed within 6 months to the previous treatment) FL or DLBCL (including primary mediastinal large B cell lymphoma [PMBCL]), presence of measurable nodal lesion $\geq$ 1.5 cm in its longest diameter by imaging, adequate hematologic and end-organ function, and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. Patients having treatment with any approved systemic anti-cancer therapy within 3 weeks prior to initiation of study treatment, treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to enrollment, or prior treatment with obinutuzumab were excluded.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP). Approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) was obtained before the study started and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. The sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

Study Design and Treatment

The study consisted of 2 stages, a safety evaluation and an expansion stage. The safety evaluation stage (Stage 1) was designed to establish the safety and tolerability of atezolizumab in combination with obinutuzumab. There was no dose-finding component for atezolizumab in combination with obinutuzumab; rather, both drugs were given at their recommended single-agent dose as there were no overlapping safety concerns. This schedule was validated in Stage 1 before a potential recommended phase 2 dose (RP2D) and schedule were investigated in the 2 expansion (Stage 2) cohorts of patients with R/R FL and DLBCL. For all patients, the treatment cycle length was 21 days. Cycle (C) 1 consisted of obinutuzumab alone dosed at 1000 mg intravenous (IV) infusion on Days (D) 1 (the first dose was split and administered over 2 days), 8, and 15. For C2–8, obinutuzumab 1000 mg IV and atezolizumab 1200 mg IV were administered on D1 of each cycle. Starting at C9, only atezolizumab was given on D1. Premedication with acetaminophen/paracetamol, an antihistamine, and 100 mg prednisolone or equivalent (except hydrocortisone) was administered prior to the first infusion of obinutuzumab. If the patient did not experience a Grade $\geq$ 1 infusion-related reaction (IRR) during the first infusion, the glucocorticoid for the subsequent infusion(s) could be omitted; however, premedication with acetaminophen/paracetamol and an antihistamine was still administered prior to subsequent infusions of obinutuzumab.

For all patients participating in Stage 1, dose-limiting toxicities (DLTs) were assessed from the day of first administration of combination treatment (C2D1) through C2D21. Key DLT criteria included any Grade 3 or 4 obinutuzumab- or atezolizumab-related adverse events (AEs), any Grade 4 IRR, recurrence of a Grade 3 IRR at re-challenge despite adequate preventive measures, Grade $\geq$ 4 thrombocytopenia lasting $\geq$ 7 days, or thrombocytopenia associated with bleeding unless due to lymphoma infiltration.

Assessments

The primary endpoint was to establish safety and tolerability of atezolizumab in combination with obinutuzumab at the safety evaluation and expansion stages and to identify an RP2D and schedule for atezolizumab when administered in combination with obinutuzumab at the expansion stage. Secondary endpoints included objective response rate (ORR) (ie, CR or partial response [PR]), as determined by investigator per Lugano 2014 criteria[13] measured by positron emission tomography-computed tomography (PET-CT), and best overall response (BOR; a best response of CR or PR at any time during the study) as determined by investigator per Lugano 2014 criteria measured by PET-CT or CT scan. Additionally, exploratory endpoints included correlative analyses of baseline and pharmacodynamic biomarkers (PD-L1 and CD8 immunohistochemistry [IHC] and interferon-gamma [IFN-γ] measurement by ELISA) relative to response. PD-L1 IHC was measured centrally at Ventana using the SP-142 clone. CD8 IHC was measured at HistoGeneX (Antwerp, Belgium) using the CD8A (clone C8/144B from Dako [Santa Clara, CA, USA]). Both PD-L1 and CD8 are reported as the percentage of positive cells in the tumor area. IFN-γ was measured from plasma at Myriad RBM (Austin, TX, USA) using the SIMOA (single-molecule array) technology and is reported as pg/ml.

The primary analysis was based on patient data collected through study discontinuation or the end of study. All analyses were based on the safety-evaluable population, defined as all patients who received any amount of either study drug. Response was reported by PET-CT or CT scan and time-to-event data were estimated using Kaplan-Meier methods. Duration of response (DOR) was defined as the time from the BOR to the time of disease progression (PD) or death, whichever occurred first. Biomarker results were summarized using box plots.

Results

Patients

The clinical data cut-off date was January 21, 2020. A total of 49 patients (FL, n = 26; DLBCL, n = 23 [none with PMBCL]) were enrolled to receive atezolizumab in combination with obinutuzumab. For the FL cohort, the median age of patients was 59.5 years (range: 41-83) with 8 patients (31%) being ≥ 65 years of age. There were 16 males (62%) and 10 females (38%). The median number of prior lines of therapy was 3 (range: 1-7), and the majority of patients had an ECOG PS of 0 or 1 (ECOG PS 0, n = 12 [46%]; ECOG PS 1, n = 13 [50%]). Based on the Follicular Lymphoma International Prognostic Index (FLIPI), 12 of 26 patients (46%) were classified as high-risk at study entry. For the DLBCL cohort, the median age of patients was 69 years (range: 26-90) with 15 patients (65%) being ≥ 65 years of age. There were 14 males (61%) and 9 females (39%). The median number of prior lines of therapy was 2 (range: 1-4), and the majority of patients had an ECOG PS of 0 or 1 (ECOG PS 0, n = 8 [35%]; ECOG PS 1, n = 15 [65%]). One DLBCL patient (1/23; 4%) was high-risk and 6 of 23 patients (26%) were intermediate-high risk as per International Prognostic Index (IPI) at study entry. Patient characteristics are provided in Table 1.

Median duration of follow-up was 45 months (95% confidence interval [CI]: 32.7, 49.1) for the FL cohort and 35.9 months (95% CI: 35.9, 41.2) for the DLBCL cohort. Among 49 patients who were enrolled and received treatment, 27 patients (55%) died, 8 patients (16%) withdrew from the study, 4 patients (8%) were lost to follow-up, 2 patients (4%) discontinued the study because the study was terminated by the sponsor, 2 patients (4%) discontinued due to physician's decision, and 1 patient (2%) discontinued due to other reasons (*Supplemental Figure 1*). At the time of the data cut, 5 patients (19%) in the FL cohort were still in follow-up.

Safety and Tolerability

No DLTs were reported for the FL cohort. 1 DLT, a Grade 3 thrombocytopenia, was reported for the DLBCL cohort. The patient did not experience any treatment interruption and remained on study treatment. The RP2D of atezolizumab was confirmed to be 1200 mg IV every 3 weeks when given in combination with obinutuzumab. For the FL cohort, the median duration of exposure to atezolizumab was 6.6 months (range: 0-46) and the median duration of exposure to obinutuzumab was 4.8 months (range: 1-5). For the DLBCL cohort, the median duration of exposure to atezolizumab was 1.4 months (range: 0-40) and the median duration of exposure to obinutuzumab was 2.1 months (range: 0-5).

There were a total of 49 safety-evaluable patients, and 46 (94%) reported at least one adverse event (AE; any Grade) (Table 2). The most common AEs reported in ≥ 20% patients were fatigue (15 patients [31%]), nausea (13 patients [27%]) cough, and diarrhea (10 patients [20%] each). Immune-mediated colitis and noninfectious diarrhea (SOC) was reported in 10 patients (20%) and immune-mediated rash (SOC) was reported in 9 patients (18%); these events were all between Grade 1 and Grade 3. A total of 30 patients (61%) reported Grade ≥ 3 AEs. The Grade ≥ 3 AEs reported in ≥ 5% patients were anemia, neutropenia, and pain (3 patients [6%] each).

A total of 18 patients (37%) experienced at least 1 serious AE (SAE). 8 patients (16%) experienced SAEs that were considered related to the study treatment, including 2 neutrophil count decrease (4%), 1 lower respiratory tract infection (2%), 1 pneumonia (2%), 1 neutropenia (2%), 1 pericardial effusion (2%), 1 ileus (2%), 1 hyperthermia (2%), and 1 pleural effusion (2%). A total of 27 patients (55%) died ≤ 30 days from last dose (FL, n = 8; DLBCL, n = 19). Of these, 23 deaths (FL, n = 7/8 [88%]; DLBCL, n = 16/19 [84%]) were due to PD. 1 patient with FL (4%) died due to other causes and 3 patients with DLBCL (6%) died due to an unknown reason. No AE led to a fatal outcome.

Efficacy

A total of 49 patients were efficacy-evaluable (FL, n = 26; DLBCL, n = 23). For the FL cohort, 14 of 26 patients achieved an objective response (ORR of 54%) with 6 patients (23%) achieving a CR and 8 patients (31%) achieving a PR (Table 3). For the DLBCL cohort, 4 of 23 patients achieved an objective response

Table 1 Patient Demographics and Baseline Characteristics

	FL (n = 26)	DLBCL (n = 23)	All patients (n = 49)
Age median (range), years	59.5 (41–83)	69.0 (26–90)	63.0 (26–90)
Age distribution, *n* (%)			
< 65	18 (69.2)	8 (34.8)	26 (53.1)
≥ 65	8 (30.8)	15 (65.2)	23 (46.9)
Male, *n* (%)	16 (61.5)	14 (60.9)	30 (61.2)
Race, *n* (%)			
Asian	1 (3.8)	0 (0)	1 (2.0)
White	22 (84.6)	18 (78.3)	40 (81.6)
Unknown	3 (11.5)	5 (21.7)	8 (16.3)
Ethnicity, *n* (%)			
Hispanic or Latino	3 (11.5)	0 (0)	3 (6.1)
Not Hispanic or Latino	18 (69.2)	16 (69.6)	34 (69.4)
Not reported	5 (19.2)	4 (17.4)	9 (18.4)
Unknown	0 (0)	3 (13.0)	3 (6.1)
Median prior lines of treatment (range)	3 (1–7)	2 (1–4)	2 (1–7)
ECOG PS, *n* (%)			
0	12 (46.2)	8 (34.8)	20 (40.8)
1	13 (50.0)	15 (65.2)	28 (57.1)
2	1 (3.8)	0 (0)	1 (2.0)
Ann Arbor Stage at study entry, *n* (%)			
Stage I	1 (3.8)	2 (8.7)	3 (6.1)
Stage II	5 (19.2)	7 (30.4)	12 (24.5)
Stage III	9 (34.6)	5 (21.7)	14 (28.6)
Stage IV	11 (42.3)	9 (39.1)	20 (40.8)
Bone marrow infiltration, *n* (%)			
Yes	9 (34.6)	1 (4.5)	10 (20.8)
No	17 (65.4)	21 (95.5)	38 (79.2)
Relapsed/refractory, *n* (%)			
Relapsed	11 (42.3)	3 (13.0)	14 (28.6)
Refractory*	13 (50.0)	19 (82.6)	32 (65.3)
Relapsed with unknown refractory status	2 (7.7)	1 (4.3)	3 (6.1)
International Prognostic Index at study entry, *n* (%)			
Low		3 (13.0)	3 (13.0)
Low-intermediate		13 (56.5)	13 (56.5)
Intermediate-high		6 (26.1)	6 (26.1)
High		1 (4.3)	1 (4.3)
FL International Prognostic Index at study entry, *n* (%)			
Low	5 (19.2)		5 (19.2)
Intermediate	9 (34.6)		9 (34.6)
High	12 (46.2)		12 (46.2)

* Defined as having relapsed within 6 months of the previous treatment. DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group performance status; FL = follicular lymphoma.

(ORR of 17%) with 1 patient (4%) achieving a CR and 3 patients (13%) achieving a PR. The BOR was 65% (17/26 patients) with 6 patients (23%) achieving a CR and 11 patients (42%) achieving a PR in the FL cohort. For the DLBCL cohort, the BOR was 17% (4/23 patients) with 1 patient (4%) achieving a CR and 3 patients (13%) achieving a PR.

The median DOR was 12.9 months (95% CI: 6.9, 21.5) for the FL cohort and 3.5 months (95% CI: 2.6, not estimable [NE]) for the DLBCL cohort. For the FL cohort, the median PFS was 9.5 months (95% CI: 7.1, 18.5) (Figure 1A), and for the DLBCL cohort, the median PFS was 2.6 months (95% CI: 2.0, 4.8) (Figure 1B). In terms of overall survival (OS), 8 patients (31%) had died by the time of the analysis in the FL cohort and the median OS was not reached (95% CI: 27.8, NE) (Figure 1C). For the DLBCL cohort, the median OS was 9.0 months (95% CI: 5.5, 12.4) (Figure 1D).

Table 2 Summary of Selective Adverse Events (Safety Evaluable Population)

N (%)	FL (n = 26)		DLBCL (n = 23)		All patients (n = 49)	
	Any grade AEs	Grade 3–5 AEs	Any grade AEs	Grade 3–5 AEs	Any grade AEs	Grade 3–5 AEs
Fatigue	11(42.3)	0	4 (17.4)	1 (4.3)	15 (30.6)	1 (2)
Pyrexia	3 (11.5)	NR	5 (21.7)	NR	8 (16.3)	NR
Cough	8 (30.8)	NR	2 (8.7)	NR	10 (20.4)	NR
Nausea	7(26.9)	NR	6 (26.1)	NR	13 (26.5)	NR
Diarrhea	8 (30.8)	2 (7.7)	2 (8.7)	0	10 (20.4)	2 (4.1)
Abdominal pain	3 (11.5)	NR	5 (21.7)	NR	8 (16.3)	NR
Hyponatraemia	6 (23.1)	1 (3.8)	1 (4.3)	0	7 (14.3)	1 (2)
Decreased appetite	1 (3.8)	NR	5 (21.7)	NR	6 (12.2)	NR
Headache	6 (23.1)	NR	2 (8.7)	NR	8 (16.3)	NR
Anemia	2 (7.7)	1 (3.8)	3 (13)	2 (8.7)	5 (10.2)	3 (6.1)
Neutropenia	3 (11.5)	2 (7.7)	3 (13)	1 (4.3)	6 (12.2)	3 (6.1)
Pain	5 (19.2)	2 (7.7)	3 (13)	1 (4.3)	8 (16.3)	3 (6.1)

AE = adverse event; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; NR = not reported.

Table 3 Patient Response Based on Investigator Assessment

N (%)	FL (n = 26)	DLBCL (n = 23)
ORR		
Total number of patients with response assessment	19	9
Responders	14 (53.8)	4 (17.4)
CR	6 (23.1)	1 (4.3)
PR	8 (30.8)	3 (13.0)
BOR		
Total number of patients with response assessment	25	19
Responders	17 (65.4)	4 (17.4)
CR	6 (23.1)	1 (4.3)
PR	11 (42.3)	3 (13.0)

BOR was defined as a best response of CR or PR during the study, as determined by investigator assessment per Lugano criteria measured by PET-CT or CT scan. Objective response was defined as a CR or PR, as determined by investigator assessment per Lugano criteria measured by PET-CT scan.
BOR = best overall response; CR = complete response; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; ORR = objective response rate; PR = partial response.

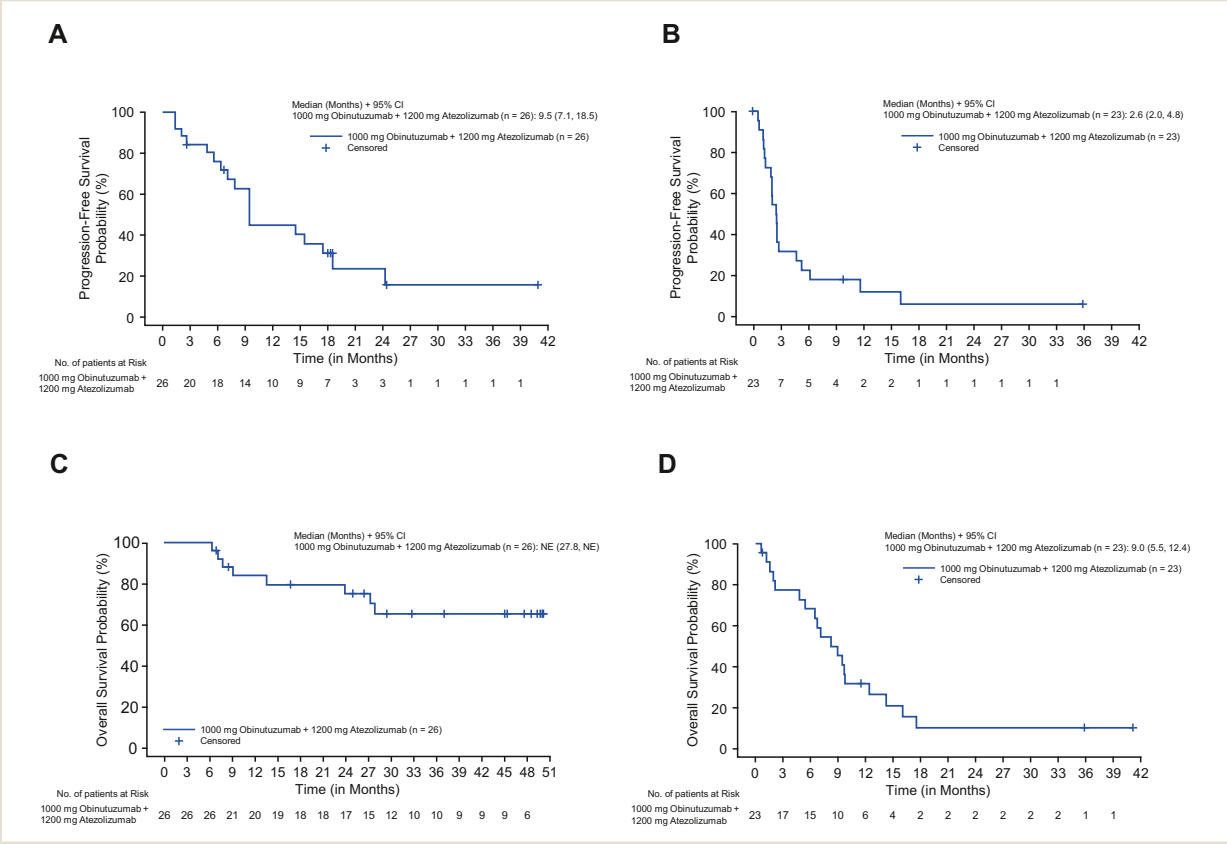
Biomarker Analyses

PD-L1 staining at baseline was similar across histologies (based on PD-L1 positive cells in the tumor area). There was no consistent change in PD-L1 observed on-treatment in paired biopsies from FL patients (n = 8 at C1D15 post-obinutuzumab dosing or at C3D1 post-obinutuzumab and atezolizumab dosing), and no relationships between PD-L1 levels at baseline or changes on-treatment and response were observed (Figure 2A). In contrast, there was a trend towards higher CD8+ cells in the tumor area at baseline in FL compared to DLBCL, and CD8+ cells in the tumor area were elevated in on-treatment biopsies compared to baseline paired biopsies (n = 9). CD8+ cells were elevated at CD15 post-obinutuzumab, and further elevated at C3D1 following administration of atezolizumab. Increased CD8+ cells were consistently observed in patients achieving CR or PR at end of induction (EOI) by PET-CT. 2 out of 3 patients with the lowest CD8+ cells at baseline and who showed little/no increase in CD8+ cells only achieved PD (end of maintenance by PET-CT) or stable disease (SD; mid-induction by CT); however, in the third patient a minor increase was observed on-treatment and the patient achieved a PR at EOI by PET-CT (Figure 2B). Plasma IFN-γ was measured in matched pre-dose (C1D1) and post-dose (atezolizumab + obinutuzumab, C3D1) samples. Baseline levels were higher in DLBCL compared with FL and, generally, IFN-γ increased on treatment in both histologies. For DLBCL (n = 12), the mean increase was 2.64 (95% CI: 1.42, 3.86) and for FL (n = 22) the mean increase was 3.58 (95% CI: 2.17, 4.99). IFN-γ decreased on-treatment in only 5 patients with FL and 3 with DLBCL. IFN-γ levels at baseline and on-treatment were not associated with response (Figure 2C).

Discussion

This was a phase 1b study evaluating the combination of atezolizumab and obinutuzumab in patients with R/R FL and DLBCL. The intent of the analysis was to assess safety, tolerability, preliminary efficacy and pharmacokinetics of atezolizumab and obinutuzumab administered in combination to patients with R/R FL and DLBCL.

Figure 1 PFS KM curves in patients with (A) FL and (B) DLBCL, and OS KM curves in patients with (C) FL and (D) DLBCL. DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival.

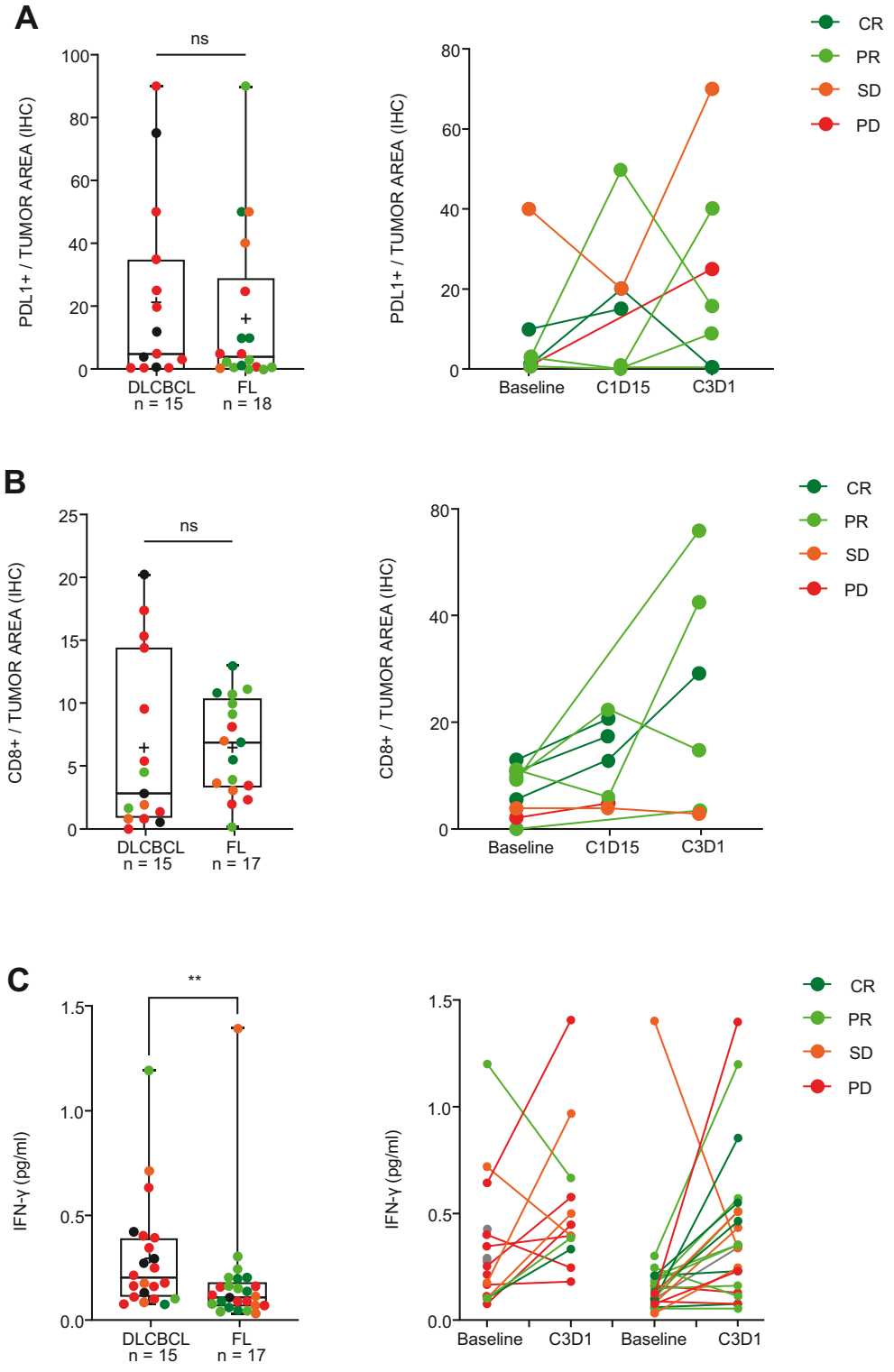


For R/R FL and DLBCL cohorts, the observed safety of the combination was consistent with the single agent toxicity of atezolizumab and obinutuzumab. The safety profile obtained in this study was consistent with observations among 17 patients with incurable or metastatic small cell lung cancer receiving atezolizumab monotherapy,[14] and 87 patients with relapsed CD20+ indolent B cell NHL who received obinutuzumab monotherapy.[9]

Even though it was hypothesized that, given their mechanisms of action, the combination of atezolizumab and obinutuzumab may be effective against CD20+ B-cell malignancies, the combination regimen in this study showed limited activity when compared with the efficacy of obinutuzumab as a single agent. For the FL cohort in this study, the ORR was 54% (including 23% CR) and the median PFS was 9.5 months. The addition of atezolizumab did not show an improvement in PFS for patients with FL. For the DLBCL cohort, ORR was 17% (including 4% CR) and the median DOR was 3.5 months for patients treated with atezolizumab and obinutuzumab. The CR rate observed here is similar to that in SCHOLAR-1, a multi-cohort retrospective analysis, that found a pooled CR rate of 7% in patients with refractory DLBCL.[15] In the phase 2 GAUGUIN study of obinutuzumab monotherapy in 40 patients with R/R indolent NHL, ORR was demonstrated to be 55% (with 9% CR/unconfirmed CR [CRu]) and the median PFS was 11.9 months at the 1600/800 mg dose level.[16] For patients with R/R DLBCL receiving obinutuzumab monotherapy in the 1600/800 mg cohort (n = 15), the end-of-treatment response was 27% with 0% CR/CRu. Specifically, for the 5 DLBCL patients in the 1600/800 mg cohort who experienced a response, the response durations were 3.1, 5.8, and 19.5 months for 3 patients (1 patient was still in response at 26.9+ months, and the remaining patient was censored at 3.1 months).[17] Obinutuzumab monotherapy showed more favorable response durations than the combination regimen evaluated in this study. However, it should be noted that the proportion of patients with refractory DLBCL in GAUGUIN was much lower than in the current analysis (47% [in the 1600/800 mg group][17] vs 83%, respectively), and the combination regimen evaluated in the current study demonstrated a higher CR rate than that of obinutuzumab monotherapy for both the FL and DLBCL cohorts.

The addition of atezolizumab to the combination regimen for patients with FL and DLBCL has limited activity. Without an appropriate comparator arm, it is challenging to compare across studies. However, based on the data that are available, the response to the combination regimen is paradoxically reduced in comparison with each monotherapy. Presently, there are limited data on

Figure 2 Relationships between response and (A) PD-L1, (B) CD8+ and C) plasma IFN-γ at baseline and on-treatment. C = cycle; CR = complete response; D = day; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; IFN-γ = interferon-gamma; IHC = immunohistochemistry; PD = disease progression; PD-L1 = programmed death-ligand 1; PR = partial response; SD = stable disease.



atezolizumab monotherapy in either FL or DLBCL. However, previous studies of nivolumab monotherapy, an anti-PD-1 monoclonal antibody, have demonstrated an ORR of 3%-36% in patients with DLBCL,[18,19] and 40% in patients with FL.[19]

Expression of additional checkpoints such as TIGIT and TIM3 could prevent optimal T-cell activation by atezolizumab.[20] An immunosuppressive tumor microenvironment could also play an important role in preventing checkpoint inhibition from being effective in NHL.[21] Additionally, the lower efficacy observed in this study could be attributed to the high degree of molecular heterogeneity observed in DLBCL.[22] Other combinations of immune checkpoint inhibitors and immune-modulating agents have been investigated; for example nivolumab, lenalidomide and rituximab, which had an ORR of 40% in heavily pretreated patients with R/R DLBCL.[23] Numerous other combinations remain in development; however, the optimal combination is yet to be determined and further studies are needed.[24]

Pharmacodynamic measurements such as IFN-γ-confirmed activation are consistent with the mechanism of action of atezolizumab in both DLBCL and FL, despite differences in response. Baseline levels and increases consistent with tumor infiltration of CD8+ T cells were observed in FL patients and correlated with response. In contrast, neither baseline nor on-treatment levels of PD-L1 correlated with response.

This study has several limitations. Although the finding of higher baseline levels of CD8+ cells in FL may be indicative of greater likelihood of response to atezolizumab, the limited numbers of samples and lack of a control arm in this small, single-arm study make it challenging to conclude whether this observation is prognostic or predictive. Based on the study design, obinutuzumab was administered alone in C1 and was only administered along with atezolizumab from C2–8, with atezolizumab administered alone from C9. It may be beneficial to explore the option of including obinutuzumab as part of maintenance therapy beyond C8. Administering atezolizumab first before introducing obinutuzumab may potentially bring additional benefits for the treatment of R/R FL and DLBCL.

It should be noted that the treatment landscape for DLBCL has changed since this study was initiated in 2014. For example, the final analysis of the phase 3 GOYA study demonstrated that obinutuzumab plus CHOP did not show a PFS benefit over R-CHOP in patients with previously untreated advanced DLBCL,[25] potentially suggesting limited efficacy of obinutuzumab in this setting. Furthermore, chimeric antigen receptor T cell (CAR-T) therapies have since been approved for the treatment of patients with DLBCL or FL after 2 or more lines of therapy. In DLBCL, a number of phase 1 and phase 2 trials have demonstrated that CAR-T treatment results in an ORR of 52%-80%, with a CR rate of 40%-55%,[26-28] and in FL, the phase 2 ZUMA-5 trial of the CAR-T therapy axicabtagene ciloleucel demonstrated an ORR of 94%, with a CR rate of 80%.[29]

Conclusion

The safety profile of atezolizumab plus obinutuzumab was consistent with previous studies and no new safety issues were observed. However, the combination of atezolizumab and obinutuzumab demonstrated limited overall activity in comparison with the individual agents when administered as monotherapy, although for both R/R FL and DLBCL a higher CR rate was observed in patients receiving the combination regimen than in those receiving obinutuzumab monotherapy. While there was a trend towards better response in patients with higher levels of CD8+ tumor-infiltrating lymphocytes and in patients who experienced on-treatment increases in these levels, the limited sample size and minimal observed activity caution over-interpretation. In conclusion, given the results of the current analysis and the evolving treatment landscape, the combination of atezolizumab and obinutuzumab in patients with R/R FL and DLBCL will not be considered for further development.

Clinical Practice Points

- Atezolizumab, a monoclonal antibody targeting PD-L1, has previously demonstrated efficacy in early phase trials in diffuse large B-cell lymphoma (DLBCL), and obinutuzumab, an anti-CD20 monoclonal antibody, has demonstrated reasonable efficacy in patients with relapsed follicular lymphoma (FL).
- The combination of tumor-targeted therapies and anti-tumor immunity agents may potentially enhance the recruitment of both innate and adaptive immunities.
- Here, the combination of atezolizumab and obinutuzumab in patients with R/R DLBCL or R/R FL was found to be safe and tolerable, with no new safety signals observed. However, no significant improvement in overall activity was observed when compared with the individual agents administered as monotherapy.
- There was a trend towards better response in certain patient subgroups, such as those with higher levels of CD8+ tumor-infiltrating lymphocytes, but patient numbers were small, confounding interpretation of these results.
- The combination of atezolizumab and obinutuzumab will not be considered for further development in R/R DLBCL and R/R FL.

Supplementary Material

Supplemental Figure 1. Patient disposition (intent-to-treat patients)

Clinical Trial Registration

This study was registered on ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02220842; the EudraCT number is 2014-001812-21.

Data Availability Statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Ethics Approval Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP). Approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) was obtained before the study started and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. The sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

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Disclosure

MLP or an immediate family member consults for or advises Amgen, Celgene, Evelo Therapeutics, Flagship Biosciences, Gilead Sciences, Jazz Pharmaceuticals, Kite, Merck, Novartis, Seres Therapeutics, and Therakos, has received honoraria from Amgen, Celgene, Evelo Therapeutics, Flagship Biosciences, Jazz Pharmaceuticals, Merck, Novartis, Pharmacyclics, Seres Therapeutics and Therakos and has received research funding from and owns stock in Seres Therapeutics. BGT has received research funding from MustangBio and reports patents and royalties wrt a CD20-targeted chimeric antigen receptor from MustangBio. SIP has no relationships to disclose. FM consults for or advises F. Hoffmann-La Roche Ltd, has received honoraria from Bayer, BMS, Celgene, Epizyme, F. Hoffmann-La Roche Ltd, Gilead Sciences and Janssen, and is a member of advisory boards for Celgene, Bayer, BMS, Epizyme, F. Hoffmann-La Roche Ltd and Gilead Sciences. GC consults for or advises Celgene and F. Hoffmann-La Roche Ltd and has received honoraria from AbbVie, Celgene, Janssen, F. Hoffmann-La Roche Ltd, Gilead, and Sanofi. RM has received honoraria from F. Hoffmann-La Roche Ltd. AR, ACC, EP, W-JH are employees of Genentech, Inc. MS is an employee of Roche Products Ltd. LLP has received honoraria from Spectrum Pharmaceuticals, consults for or advises F. Hoffmann-La Roche Ltd, has received research funding from Genentech, Inc., Janssen, Millennium, Novartis, Pfizer and Pharmacyclics and has received travel expenses from Spectrum Pharmaceuticals.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2021.12.010.

References

1. National Cancer Institute. SurveillanceEpidemiology and End Results (SEER) cancer statistics database. *Cancer Stat Facts: Non-Hodgkin Lymphoma*. 2021;2021:1.
2. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. *J Clin Oncol*. 2009;27:1202–1208.
3. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant*. 2016;51:51–57.
4. Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. *Clin Cancer Res*. 2011;17:4232–4244.
5. Sugiura D, Maruhashi T, Okazaki IM, et al. Restriction of PD-1 function by cis-PD-L1/CD80 interactions is required for optimal T cell responses. *Science*. 2019;364:558–566.
6. Zhao Y, Lee CK, Lin CH, et al. PD-L1:CD80 Cis-heterodimer triggers the co-stimulatory receptor CD28 while repressing the inhibitory PD-1 and CTLA-4 pathways. *Immunity*. 2019;51:1059–1073 e1059.
7. Kim S, Fridlender ZG, Dunn R, et al. B-cell depletion using an anti-CD20 antibody augments antitumor immune responses and immunotherapy in nonhematopoetic murine tumor models. *J Immunother*. 2008;31:446–457.
8. Wahlin BE, Sundstrom C, Holte H, et al. T cells in tumors and blood predict outcome in follicular lymphoma treated with rituximab. *Clin Cancer Res*. 2011;17:4136–4144.
9. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS Study. *J Clin Oncol*. 2015;33:3467–3474.
10. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366:2443–2454.
11. Herbst HS, Gordon MS, Fine GD, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. *J Clin Oncol*. 2013;31:3000.
12. Stagg J, Loi S, Divisekera U, et al. Anti-ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti-PD-1 or anti-CD137 mAb therapy. *Proc Natl Acad Sci U S A*. 2011;108:7142–7147.
13. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–3068.
14. Chiang AC, Sequist LVD, Gilbert J, et al. Clinical activity and safety of atezolizumab in a phase 1 study of patients with relapsed/refractory small-cell lung cancer. *Clin Lung Cancer*. 2020;21:455–463 e454.
15. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130:1800–1808.
16. Salles GA, Morschhauser F, Solal-Celigny P, et al. Obinutuzumab (GA101) in patients with relapsed/refractory indolent non-Hodgkin lymphoma: results from the phase II GAUGUIN study. *J Clin Oncol*. 2013;31:2920–2926.
17. 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*. 2013;31:2912–2919.
18. Ansell SM, Minnema MC, Johnson P, et al. Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study. *J Clin Oncol*. 2019;37:481–489.
19. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J Clin Oncol*. 2016;34:2698–2704.
20. Josefsson SE, Beiske K, Blaker YN, et al. TIGIT and PD-1 mark intratumoral T cells with reduced effector frunction in B-cell non-Hodgkin lymphoma. *Cancer Immunol Res*. 2019;7:355–362.
21. Joshi M, Ansell SM. Activating the antitumor immune response in non-Hodgkin lymphoma using Immune checkpoint inhibitors. *J Immunol Res*. 2020;2020:8820377.
22. Zhang J, Grubor V, Love CL, et al. Genetic heterogeneity of diffuse large B-cell lymphoma. *PNAS*. 2013;110(4):1398–1403.
23. Sethi T, Kovach AE, Mason EF, et al. Combination of nivolumab, lenalidomide and rituximab in relapsed/refractory non-germinal center diffuse large B cell lymphoma: Results from a dose-escalation cohort. *Blood*. 2019;134(Supplement_1) 4100-4100.
24. Zhang J, Medeiros LJ, Young KH. Cancer immunotherapy in diffuse large B-cell lymphoma. *Front Oncol*. 2018;8:351.
25. Sehn LH, Martelli M, Trneny M, et al. A randomized, open-label, Phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-Cell lymphoma: final analysis of GOYA. *J Hematol Oncol*. 2020;13:71.
26. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell Therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377:2531–2544.
27. Abramson JS, Gordon LI, Palomba ML, et al. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocbtagene maraleucel (JCAR017) in R/R aggressive NHL. *J Clin Oncol*. 2018;36:7505.
28. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380:45–56.
29. Jacobson CA, Chavez JC, Sehgal AR, et al. Primary analysis of ZUMA-5: a phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). *Blood*. 2020;136(Supplement 1):40–41.