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# Combination of Atezolizumab and Tazemetostat in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Results From a Phase Ib Study

Maria Lia Palomba,<sup>1</sup> Guillaume Cartron,<sup>2</sup> Leslie Popplewell,<sup>3</sup> Vincent Ribrag,<sup>4</sup> Jason Westin,<sup>5</sup> Ling-Yuh Huw,<sup>6</sup> Shefali Agarwal,<sup>7</sup> Mahesh Shivhare,<sup>8</sup> Wan-Jen Hong,<sup>9</sup> Aparna Raval,<sup>6</sup> Alice C. Chang,<sup>9</sup> Elicia Penuel,<sup>6</sup> Franck Morschhauser<sup>10</sup>

## Abstract

**This phase 1b study assessed the safety, tolerability, and efficacy of atezolizumab plus tazemetostat in patients with R/R DLBCL. A total of 43 patients were enrolled. All-grade adverse events were reported in 95.3% of patients. The ORR was 16% (CR rate: 7%). The combination of atezolizumab and tazemetostat was determined to be safe and tolerable, although anti-tumor activity was modest.**

**Background:** The combination of atezolizumab, a monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, and tazemetostat, an EZH2 inhibitor, may lead to selective epigenetic reprogramming, alter the tumor microenvironment, and provide additive or synergistic response to patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). **Materials and Methods:** This was an open-label, phase Ib study assessing the safety, tolerability, and preliminary efficacy of atezolizumab plus tazemetostat in patients with R/R DLBCL. Atezolizumab (1200 mg) was administered via intravenous (IV) infusion on day 1 of each cycle and tazemetostat (800 mg) was given orally twice daily (BID) on days 1 to 21. Primary endpoints were safety and tolerability, and to identify a recommended phase II dose (RP2D) for atezolizumab. Secondary efficacy endpoints included response rate and duration of response. **Results:** A total of 43 patients were enrolled, receiving a median of 3 prior lines of treatment (range: 1-9). The RP2D for atezolizumab was 1200 mg IV infusion every 3 weeks in combination with tazemetostat 800 mg BID. At the RP2D, adverse events reported in  $\geq 20\%$  patients were anemia (11 patients [26%]), fatigue (10 patients [23%]), and nausea (10 patients [23%]). Overall response rate was 16% (complete response rate: 7%). Median progression-free survival was 2 months (range: 0-24) and median overall survival was 13 months (range: 1-29). **Conclusions:** The combination of atezolizumab and tazemetostat was determined to be safe and tolerable. However, anti-tumor activity of the combination was modest.

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**Keywords:** Non-Hodgkin's lymphoma, Diffuse large B-cell lymphoma, Immunotherapy, EZH2 inhibitor, Epigenetic

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive neoplasm of large B cells and accounts for approximately 25% to 30% of non-Hodgkin lymphomas (NHL).<sup>1</sup> High levels of soluble checkpoint receptor programmed death-1 (PD-1) in patients with relapsed or refractory (R/R) DLBCL have been found to be a predictor of poor outcome after dose-dense immunochemotherapy.<sup>2</sup> Evidence from an *in vitro* study using established cell lines and primary lymphoma specimens suggested that programmed death-ligand 1 (PD-L1) is expressed in DLBCL patients with non-germinal center subtypes, which also indicates a poorer prognosis.<sup>3</sup>

Atezolizumab is a monoclonal antibody that inhibits the interaction between PD-L1 and PD-1 and therefore enhances T-cell

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activity against tumor cells.<sup>4</sup> Atezolizumab has previously demonstrated efficacy in the treatment of patients with NHL when combined with immunotherapy or chemo-immunotherapy,<sup>5</sup> with early phase trials in DLBCL yielding positive results.<sup>6,7</sup>

NHL shows a high propensity for mutations in chromatin-modifying enzymes such as histone methyltransferases (HMTs).<sup>8</sup> As an HMT, enhancer of zeste homolog 2 (EZH2) plays a role in epigenetic modification and is involved in the methylation of H3K27.<sup>9</sup> Gain-of-function mutations in EZH2 can lead to induction in methylation of H3K27 and is observed in about 20% of patients with germinal center-derived follicular lymphoma (FL) and DLBCL.<sup>10-12</sup> As a result, the loss of EZH2 has been proposed to inhibit the function of regulatory T cells as it may contribute to enhancing anti-tumor immunity.<sup>13</sup> Tazemetostat (also known as EPZ6438), an EZH2 inhibitor, inhibits both wild-type and activating mutation-bearing EZH2 and has demonstrated anti-tumor activity in patients with R/R NHL.<sup>14</sup>

The combination of atezolizumab and tazemetostat may bring additive or synergistic effects in patients with R/R DLBCL through addressing both genetic abnormalities and aberrant epigenetic modifications. The possible mechanisms may involve the release of repression of molecules important for immune recognition on tumor cells and increased effector T-cell tumor infiltration, reduction in tumor progression, and enhancement of efficacy of immune checkpoint inhibitors. Additionally, loss of EZH2 may affect T helper cell plasticity<sup>15</sup> and inhibit the function of regulatory T cells,<sup>13</sup> which suggests that inhibition of EZH2 may lead to enhanced anti-tumor immunity.<sup>16</sup>

Here we present data from the final analysis of a phase Ib study evaluating the safety, tolerability and preliminary efficacy of atezolizumab in combination with tazemetostat in patients with R/R DLBCL (NCT02220842; EudraCT: 2014-001812-21). Exploratory biomarker objectives were also investigated.

## Materials and Methods

### Patients

Eligible patients were  $\geq 18$  years of age with histologically documented, R/R (defined as having relapsed within 6 months to one of the previous treatments) DLBCL (including primary mediastinal large B-cell lymphoma [PMBCL]), at least two bi-dimensionally measurable nodal lesions  $\geq 1.5$  cm in its longest diameter by imaging as defined by the Lugano 2014 criteria,<sup>17</sup> European Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, and at least two lines of prior therapy (including rituximab plus chemotherapy), and who were transplant-ineligible, unable to benefit from transplant, or post-transplant. Patients who received treatment with any approved systemic anti-cancer therapy within three weeks prior to initiation of study treatment, received treatment with any other investigational agent or participated in another clinical study with therapeutic intent within 28 days prior to enrollment, or had prior exposure to tazemetostat or other inhibitor(s) of EZH2 were excluded. No eligibility criteria were based on EZH2 mutation status.

The safety evaluation stage was planned to enroll 3 to 6 patients and the expansion stage was planned to enroll approximately 40 patients. The sample size for the expansion stage was calculated

based on increasing the probability of observing an adverse event (AE).

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Approval from the Institutional Review Board/Independent Ethics Committee 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, Treatment, and Objectives

This open-label, multicenter, global, phase Ib study consisted of a safety evaluation stage and an expansion stage. Each treatment Cycle (C) was defined as 21 days. Tazemetostat was administered orally at 800 mg twice daily (BID) on Day (D) 1 to 21 in combination with atezolizumab 1200 mg intravenously (IV) on D1 of each cycle. If tazemetostat 800 mg BID in combination with atezolizumab exceeded the maximum tolerated dose during the safety evaluation stage, other dose levels could be opened to evaluate an alternative dosing regimen.

For all patients that participated in the safety evaluation stage, dose-limiting toxicities (DLTs) were assessed during a DLT assessment window of 21 days (ie, from the day of first administration of combination treatment). Key DLT criteria included Grade  $\geq 3$  infusion-related toxicity that occurred during or within 24 hours after the infusion of atezolizumab, Grade 4 neutropenia for  $\geq 7$  days or Grade 3 neutropenia with fever, Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding or lasting  $\geq 7$  days, and Grade 3 or 4 nausea, vomiting, or diarrhea that persisted despite maximal medical therapy.

The primary objective was to establish the safety and tolerability of atezolizumab in combination with tazemetostat at the safety evaluation and expansion stages, and to identify a recommended phase II dose (RP2D) and schedule for atezolizumab when administered in combination with tazemetostat at the expansion stage. Secondary objectives included objective response rate (ORR) (defined as a complete response [CR] or partial response [PR], as determined by investigator assessment per Lugano 2014 criteria measured by positron emission tomography-computed tomography [PET-CT] scan), best overall response (BOR) (defined as a best response of CR or PR during the study, as determined by investigator assessment per Lugano 2014 criteria measured by PET-CT or CT scan), and duration of response (DOR) (defined as the time from the BOR to the time of progression of disease [PD] or death, whichever occurred first). Biomarker analyses were performed as an exploratory objective.

### Biomarkers

Expression of PD-L1 (H Score; clone SP263 Ventana [Roche Diagnostics Ltd, UK]), CD8 (% of tumor cells; clone 144B [Dako, Glostrup, Denmark]), and FOXP3 (% of tumor cells; clone 236A/E7 [Ebioscience, MA, USA]) was studied by immunohistochemistry using pre-treatment, formalin-fixed, paraffin-embedded tissue samples. Biopsies were collected prior to C1D1 (archival specimens were acceptable if collected within 4 months of

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C1D1 and with no intervening treatment received between study inclusion and biopsy). If these requirements could not be met, biopsies were collected prior to dosing. On-treatment biopsies were collected at C2D1 (+/-3 days) to assess the effect of the atezolizumab and tazemetostat combination. Median cutoff was used to study the association with tumor shrinkage and response, and changes in levels of CD8, FOXP3, and PD-L1 were assessed on-treatment relative to baseline. EZH2 mutation status was studied using FoundationOne Heme (Foundation Medicine, Inc., Cambridge, MA). Flow cytometry was performed using longitudinal blood samples to study changes in the level of regulatory T cells (Tregs; %CD25+FOXP3+[CD3+CD4+]).

## Assessments and Statistical Analysis

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 receive any amount of either study drug. All AEs occurring on or after treatment on D1 were summarized by mapped term and NCI CTCAE v4.0 toxicity grade. The Clopper-Pearson method was used to estimate 95% confidence intervals (CI). Time-to-event data (progression-free survival [PFS] and overall survival [OS]) were estimated using Kaplan-Meier methods. Correlative analysis to study association between the biomarkers evaluated and the end of induction response was performed for exploratory biomarker analyses.

## Results

### Patients

The clinical data cut-off date was January 21, 2020. A total of 45 patients with DLBCL (none with PMBCL) were enrolled and 43 patients received at least 1 dose of either study drug (1 patient discontinued prior to dosing due to low hemoglobin [ $<9$  g/dL] and 1 died prior to starting treatment). The median age of the patients was 65 years (range: 26-86) with 23 patients (53.5%) being  $\geq 65$  years of age (Table 1). There were 32 males (74.4%) and 11 females (25.6%). Patients were diagnosed with either refractory (35 patients, 81.4%) or relapsed (7 patients, 16.3%) disease, except one patient (2.3%) who relapsed with unknown refractory status. There were 16 (37.2%) primary refractory patients. The median number of prior lines of treatment was 3 (range: 1-9). The majority of patients had an ECOG PS of 0 or 1 (ECOG PS 0, 13 patients [30.2%]; ECOG PS 1, 27 patients [62.8%]). Based on the International Prognostic Index, three patients (7.0%) were at high risk and 21 patients (48.8%) were at intermediate-high risk at study entry.

Median follow-up was 23.7 months (95% CI: 19.8, 25.9). Among the 43 patients who received treatment, 28 patients (65.1%) died, seven patients (16.3%) discontinued the study because it was terminated by the sponsor, two patients (4.7%) withdrew from the study, and one patient each (2.3%) discontinued the study due to physician's decision and other reason (Supplemental Figure 1). At the time of the data cut, four patients (9.3%) were still in follow-up.

**Table 1** Patient Demographics and Baseline Characteristics.

	Patients with DLBCL (n = 43)
<b>Age median (range), years</b>	65 (26-86)
<b>Age distribution, n (%)</b>	
<65	20 (46.5)
$\geq 65$	23 (53.5)
<b>Male, n (%)</b>	32 (74.4)
<b>Ethnicity, n (%)</b>	
Hispanic or Latino	1 (2.3)
Not Hispanic or Latino	17 (39.5)
Not stated	24 (55.8)
Unknown	1 (2.3)
<b>Median prior lines of treatment (range)</b>	3 (1-9)
<b>ECOG PS, n (%)</b>	
0	13 (30.2)
1	27 (62.8)
2	3 (7.0)
<b>Ann Arbor Stage at study entry, n (%)</b>	
Stage I	1 (2.3)
Stage II	9 (20.9)
Stage III	4 (9.3)
Stage IV	29 (67.4)
<b>Bone marrow infiltration, n (%)</b>	
Yes	3 (7.0)
No	40 (93.0)
<b>Refractory/relapsed, n (%)</b>	
Refractory	35 (81.4)
Relapsed	7 (16.3)
Relapsed with unknown refractory status	1 (2.3)
<b>Primary refractory, n (%)</b>	16 (37.2)
<b>International Prognostic Index at study entry, n (%)</b>	
Low risk	4 (9.3)
Low-intermediate risk	15 (34.9)
Intermediate-high risk	21 (48.8)
High risk	3 (7.0)

DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group performance status.

### Safety and Tolerability

There were 43 safety-evaluable patients, with 3 patients in the safety evaluation stage and 40 patients in the expansion stage. No DLTs were reported during the assessment window for the first 3 patients in the safety evaluation stage. As a result, no additional dose finding was required. The RP2D of atezolizumab was confirmed to be 1200 mg IV every 3 weeks when administered in combination with 800 mg tazemetostat orally BID. The median duration of exposure to atezolizumab was 1.4 months (range: 0-23), and median duration of exposure to tazemetostat was 2.1 months (range: 0-24).

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

N (%)	Patients with DLBCL (n = 43)	
	Any Grade AEs	Grade 3-5 AEs
Anemia	11 (25.6)	5 (11.6)
Fatigue	10 (23.3)	1 (2.3)
Nausea	10 (23.3)	NR
Pyrexia	8 (18.6)	NR
Diarrhea	8 (18.6)	NR
Platelet count decreased	8 (18.6)	2 (4.7)
Thrombocytopenia	7 (16.3)	5 (11.6)
Decreased appetite	7 (16.3)	NR
Neutropenia	5 (11.6)	4 (9.3)
Febrile neutropenia	3 (7.0)	3 (7.0)

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

Forty-one patients (95.3%) reported at least 1 AE (any Grade). The most common any-Grade AEs reported in ≥15% patients were anemia (11 patients [25.6%]), fatigue (10 patients [23.3%]), nausea (10 patients [23.3%]), pyrexia (8 patients [18.6%]), diarrhea (eight patients [18.6%]), platelet count decreased (8 patients [18.6%]), thrombocytopenia (7 patients [16.3%]), and decreased appetite (7 patients [16.3%]) (Table 2). Eighteen patients (41.9%) were reported with AEs of special interest. Immune-mediated colitis plus noninfectious diarrhea and immune-mediated rash were each reported in 8 patients (18.6% in each System Organ Class). The majority of these patients did not require dose modification for either study drug. One patient with Grade 1 diarrhea experienced interruption of atezolizumab, which was restarted after resolution of the event. Grade ≥3 AEs were reported in 21 patients (48.8%). The Grade ≥3 AEs reported in ≥5% patients were anemia (five patients [11.6%]), thrombocytopenia (five patients [11.6%]), neutropenia (four patients [9.3%]), and febrile neutropenia (three patients [7.0%]).

A total of 17 patients (39.5%) experienced at least 1 serious AE (SAE). The SAEs reported in ≥5% patients were neutropenia (4 patients [9.3%]) and thrombocytopenia (3 patients [7%]). Nine patients (20.9%) experienced SAEs that were considered related to the study treatment, including 3 with neutropenia (7%), 3 with thrombocytopenia (7%), 1 with atrial fibrillation (2.3%), 1 with hyperthyroidism (2.3%), 1 with fungal pneumonia (2.3%), 1 with neutrophil count decreased (2.3%), 1 with hyponatremia (2.3%), and 1 with pneumonitis (2.3%). Twenty-eight patients (65.1%) died within 30 days of last dose. Of those, 25 deaths (89.3%) were due to PD, 2 deaths (7.1%) were due to Grade 5 AEs, and 1 death (3.6%) was due to an unknown reason. Of the 2 patients who experienced Grade 5 AEs, 1 died due to cardiac decompensation secondary to the event of hyponatremia, which was considered by the investigator to be related to atezolizumab and tazemetostat, and 1 died due to septic shock. The septic shock death occurred on study day 51; the patient had discontinued study treatment on study day 22 (atezolizumab) and 29 (tazemetostat) following a diagnosis of PD on study day 22, and had received 1 cycle of immunochemotherapy treatment (rituximab, ifosfamide, carbo-

**Table 3** Response Based on Investigator Assessment.

N (%)	DLBCL (n = 43)
<b>ORR (CR + PR)<sup>a</sup></b>	7 (16.3)
CR	3 (7.0)
PR	4 (9.3)
<b>SD</b>	7 (16.3)
<b>BOR (CR + PR)<sup>b</sup></b>	7 (16.3)
CR	3 (7.0)
PR	4 (9.3)
SD	5 (11.6)

ORR was defined as a CR or PR, as determined by investigator assessment per Lugano criteria measured by PET-CT scan. 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. BOR = best overall response; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ORR = objective response rate; PET-CT = positron emission tomography-computed tomography; PR = partial response; SD = stable disease.

<sup>a</sup> Total number of patients with response assessment: 29  
<sup>b</sup> Total number of patients with response assessment: 37

platin and etoposide) on study days 30 to 32. The investigator considered the event to be unrelated to atezolizumab and tazemetostat but related to the underlying disease and toxicity of the last line of therapy (ifosfamide, carboplatin, and etoposide).

**Efficacy**

The efficacy-evaluable population consisted of 43 patients. The ORR was 16.3% with 3 patients (7%) achieving a CR and 4 patients (9.3%) achieving a PR. Seven patients (16.3%) achieved stable disease (SD) (Table 3). The BOR was also 16.3% (CR, 7%; PR, 9.3%). Five patients (11.6%) achieved SD. The median DOR was 7.4 months (95% CI: 1.4, not estimable [NE]).

The median PFS was 1.9 months (range: 0.0-23.7) (Figure 1A). Additionally, the median OS was 13 months (range: 0.8-29.5) (Figure 1B).

**Biomarker Analyses**

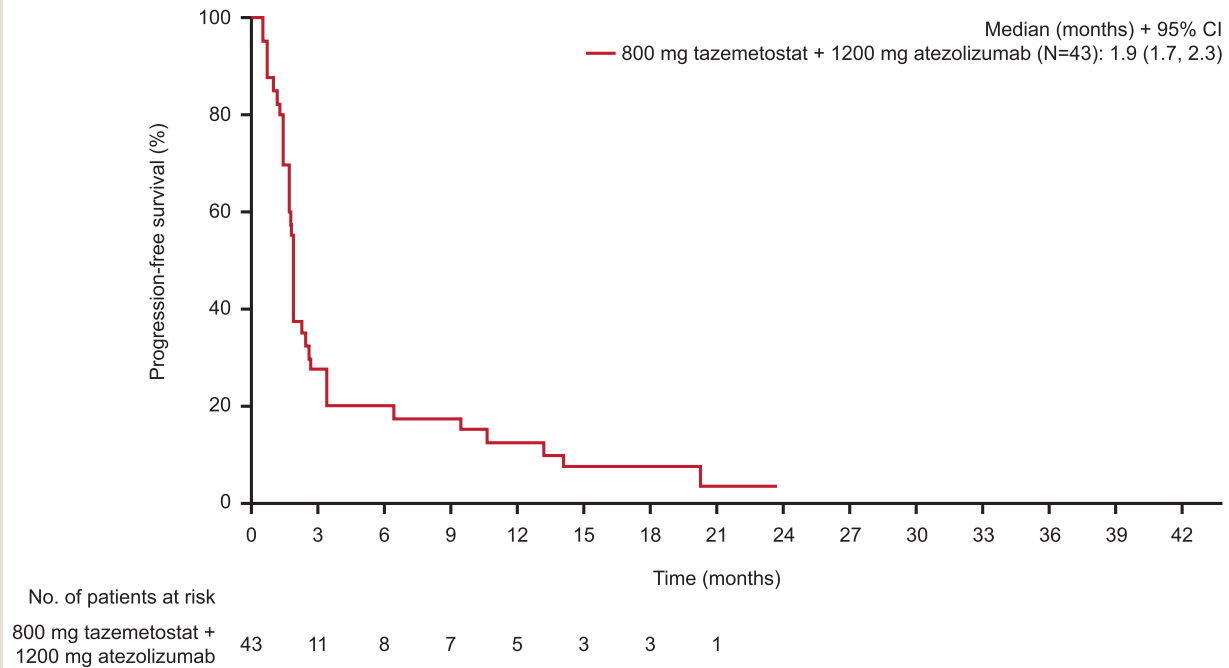
Twenty-eight patients had sufficient tissue for analysis using FoundationOne Heme. Four patients (14.3%) had EZH2 mutation. Three out of those 4 patients (75%) were responders (CR, n = 1; PR, n = 2) while a no response assessment (NA) was recorded for the fourth patient (Table 4). Of the 24 patients without EZH2 mutations, 21 were non-responders and 3 were NA.

No clear association between expression of CD8 (% tumor cells), FOXP3 (% tumor cells), or PD-L1 (H-Score) at baseline and tumor shrinkage or response was observed (Supplemental Figure 2A). Additionally, there was no consistent change in CD8, FOXP3, or PD-L1 immunohistochemistry staining on-treatment (Supplemental Figure 2B). Peripheral assessments by flow cytometry that allowed for additional longitudinal sampling were also evaluated. On-treatment changes in the frequency of Tregs were not observed in responders or non-responders (Supplemental Figure 2C).

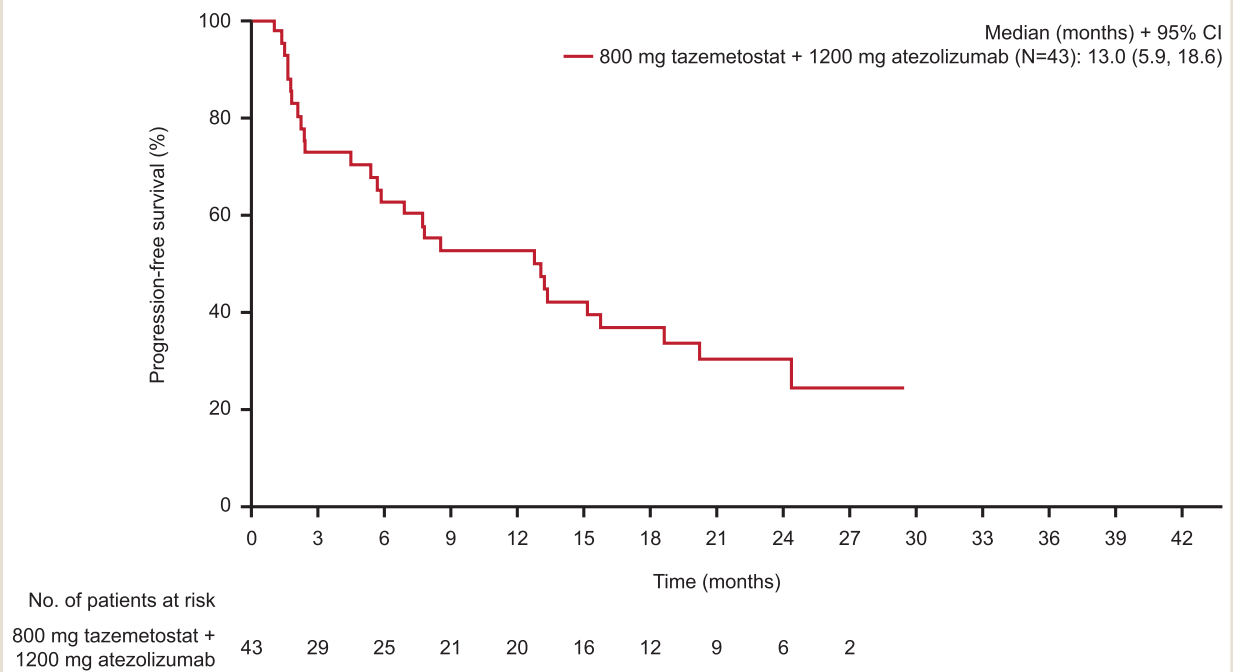
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**Figure 1** PFS KM (A) and OS KM (B) curves. DLBCL = diffuse large B-cell lymphoma; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival.

**A)**



**B)**



**Table 4** EZH2 Mutation Status in 28/43 Patients With DLBCL.

Samples	Variant type	SNV-protein-change	Somatic status / functional impact	BOR based on PET-CT	BOR based on CT scan (any time during the study)
1		WT		PD	-
2		WT		PD	-
3		WT		PD	-
4		WT		PD	-
5	Short-variant	Y646N	Known	CR	-
6		WT		-	NA <sup>a</sup>
7		WT		SD	-
8		WT		SD	-
9		WT		PD	-
10	Short-variant	Y646C	Known	-	NA <sup>a</sup>
11		WT		-	PD
12	Short-variant	V680L	Unknown	PR	-
13	Short-variant	Y646N	Known	PR	-
14		WT		-	NA <sup>a</sup>
15		WT		PD	-
16		WT		SD	-
17		WT		PD	-
18		WT		PD	-
19		WT		PD	-
20		WT		-	PD
21		WT		SD	-
22		WT		PD	-
23		WT		SD	-
24		WT		-	PD
25		WT		SD	-
26		WT		PD	-
27		WT		PD	-
28		WT		PD	-

- = data not available; BOR = best overall response; CR = complete response; NA = not applicable; PD = progressive disease; PET-CT = positron emission tomography-computed tomography; SD = stable disease; SNV = single nucleotide variant; WT = wild-type.

<sup>a</sup> Patient progressed before response assessment

## Discussion

In the current study, which enrolled heavily pretreated and mostly refractory DLBCL patients, the observed safety of the combination of atezolizumab and tazemetostat was generally consistent with their single-agent toxicity. The combination of atezolizumab and tazemetostat demonstrated modest activity, and response was observed in the small number of patients with EZH2 mutation.

The safety profile obtained in this study was consistent with observations among 95 patients with advanced and metastatic urothelial carcinoma who received single agent atezolizumab.<sup>18</sup> It was also consistent with observations in 64 patients with B-cell NHL or advanced solid tumors receiving tazemetostat monotherapy<sup>14</sup> and 99 patients with R/R FL receiving single agent tazemetostat.<sup>19</sup>

The ORR in this study (16%; CR, 7%) was lower than the pooled ORR observed in SCHOLAR-1 (26%; CR, 7%), a retrospective

analysis of outcomes in 636 patients with refractory DLBCL.<sup>20</sup> However, when patients in SCHOLAR-1 were stratified by refractory subgroup, ORR was 20% in primary refractory patients, 26% in those refractory to second-line or later-line therapy, and 34% in those patients who relapsed ≤12 months post-autologous stem cell transplantation, demonstrating poorer outcomes for those patients who relapse earlier. In the current study, more than one-third of patients were primary refractory, a contributing factor to the low response rates observed here.

Despite the hypothesis that the combination of atezolizumab and tazemetostat may mechanistically predict an increase in anti-tumor activity greater than that of either agent alone, the combination regimen in this study provided modest efficacy (ORR, 16.3%; median DOR, 7.4 months) when compared with tazemetostat as a single agent. In a first-in-human, phase I study where 21 patients with B-cell NHL received tazemetostat

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monotherapy,<sup>14</sup> ORR was observed in 8 patients (38%), with CR observed in 3 patients (14.2%; 1 DLBCL and 2 FL) and PR observed in 5 patients (23.8%; 3 DLBCL, 1 FL, and 1 marginal zone lymphoma). The median DOR was 12.4 months. In a phase II study evaluating tazemetostat monotherapy in 157 R/R DLBCL patients with either mutated or wild-type EZH2 tumors,<sup>21</sup> the ORR was the same for both patient cohorts (17%). The median DOR was 44.2 weeks for the mutated EZH2 cohort and 28.0 weeks for the wild-type EZH2 cohort. In the current study, the addition of atezolizumab did not result in an improvement in either ORR or DOR when compared with tazemetostat alone, regardless of EZH2 mutation status. Presently, there are limited data on atezolizumab monotherapy in DLBCL. However, other studies have investigated the efficacy of similar checkpoint inhibitors in this setting. For example, in a study of monotherapy with nivolumab, an anti-PD-1 monoclonal antibody, in R/R B-cell lymphoma, the ORR was 36% (4/11 patients) in the DLBCL cohort.<sup>22</sup> However, in another study of nivolumab monotherapy in patients with R/R DLBCL, the ORR was just 3% (1/34 patients) in those patients ineligible for autologous hematopoietic cell transplantation (auto-HCT), and 10% (9/87 patients) in those who had experienced auto-HCT failure. Of note, the combination of nivolumab, lenalidomide (an immunomodulating agent) and rituximab, (an anti-CD20 monoclonal antibody), has shown promising activity, with an ORR of 40% in heavily pretreated patients with R/R DLBCL.<sup>23</sup> Therefore, further studies investigating different combinations of immune checkpoint inhibitors and immune-modulating agents may be warranted.

In this study, we evaluated heavily pretreated and mostly refractory DLBCL patients with poor prognosis. In a phase II study evaluating 30 R/R DLBCL patients receiving ifosfamide and etoposide plus rituximab, median PFS was reported to be 2.5 months in those who relapsed within 12 months of prior therapy.<sup>24</sup> The median time to response to tazemetostat in patients with B-cell NHL was 3.5 months,<sup>14</sup> which is typical for epigenetic therapies. The time to response may have contributed to the modest efficacy observed in this study, as this highly refractory group of patients with rapidly progressing disease may not have received the combination regimen for long enough to observe a response (median duration of exposure to tazemetostat in this study was just 2.1 months).

In the current study, 75% of patients (3/4) with EZH2 mutation achieved an objective response while 21 patients with wild-type EZH2 were non-responders, suggesting that the activity observed may be attributable to tazemetostat in the EZH2 mutant population. This may also be explained by the high degree of molecular heterogeneity observed in DLBCL, and in particular the high frequency of EZH2 mutation observed in germinal center B-cell DLBCL.<sup>25</sup> The results observed here are in line with previous studies suggesting superior response rates in patients with EZH2 mutations vs. those with wild-type EZH2 treated with tazemetostat.<sup>26</sup> Any additional activity of atezolizumab on top of tazemetostat could not be assessed due to the limited number of patients. EZH2 inhibition has been associated with altered FOXP3

expression resulting in reduced immunosuppressive effects of Tregs.<sup>27</sup> However, the expected reduction in circulating Tregs and an association between FOXP3 expression and tumor shrinkage were not observed. An association between the expression of PD-L1 and CD8 and response to PD-L1/PD-1 inhibitor therapy has been reported in cancer patients.<sup>28,29</sup> Lack of association between PD-L1 and CD8 expression with tumor shrinkage in this study and the relatively modest number of responses observed only in patients with EZH2 mutation suggests that the efficacy is mostly driven by tazemetostat. However, the poor prognosis of this patient population and the small number of patients found to have an EZH2 mutation (n=4) make it difficult to draw any firm conclusions from these data.

This study has several limitations. Firstly, the patient population consisted of heavily pretreated and mostly refractory patients with poor prognosis. This, combined with the limited median duration of exposure in this study, may have contributed to the modest response observed for this combination. Additionally, due to the small number of biomarker-evaluable patients, it is difficult to draw robust conclusions from the biomarker analysis; however, these data suggest further evaluation of patients with EZH2-mutated DLBCL is warranted. Future studies further exploring the potential effects of combination with immune modulating agents may be needed for patients with DLBCL.

### Conclusion

The safety profile of the combination of atezolizumab and tazemetostat was consistent with prior studies and no new major safety signals were reported. Modest activity was observed with this combination regimen, which could in part be attributed to the patient population being heavily pretreated and mostly refractory with poor prognosis. Response to atezolizumab and tazemetostat was observed in patients with EZH2 mutation suggesting that tazemetostat treatment could be reversing the effects of deregulated EZH2 in these patients.

### Clinical Practice Points

Atezolizumab has previously demonstrated efficacy in early phase trials in diffuse large B-cell lymphoma (DLBCL), and tazemetostat has demonstrated anti-tumor activity in relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL).

Here, the combination of atezolizumab and tazemetostat in patients with R/R DLBCL was found to be safe and tolerable, with no new safety signals observed. Responses were modest, although this could be due in part to the heavily pretreated and mostly refractory patient population in this study.

Response to atezolizumab and tazemetostat was observed in patients with EZH2 mutation, suggesting that tazemetostat treatment could potentially reverse the effects of deregulated EZH2 in these patients; however, patient numbers were small.

Further investigation of the atezolizumab plus tazemetostat combination is warranted, particularly in patients with EZH2 mutation.



## Disclosure

MLP or an immediate family member consult 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. 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. 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. VR has received honoraria from AstraZeneca, AZD, Bristol Myers Squibb, Eisai, Epizyme, Gilead, Incyte, Infinity, MSD, Nanostring, Pharmamar, Roche and Servier; consults or advises for Bristol Myers Squibb, Epizyme, Genentech, Gilead, Incyte, Infinity, MSD, Nanostring, Pharmamar, Roche and Servier; has received research funding from argenX, arGEN-X-BVBA and Epizyme; is a member of advisory boards for AstraZeneca, Bristol Myers Squibb, Epizyme, Genentech, Gilead, Immune Design, Incyte, Infinity, MSD, Nanostring, Pharmamar and Roche; holds patents and royalties wrt BAY1000394 studies in MCL; has received travel expenses from Roche; and holds equity in argenX and arGEN-X-BVBA. JW consults for or advises Amgen, AstraZeneca, Bristol Myers Squibb, Curis, Genentech, Janssen, Kite, Morphosys and Novartis; and has received research funding from 47, AstraZeneca, Bristol Myers Squibb, Curis, Genentech, Janssen, Kite, Novartis and Morphosys. SA is an employee of Epizyme Inc. MS is an employee of Roche Products Ltd. AR, ACC, EP, L-YH and W-JH are employees of Genentech, Inc. 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.

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## 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 Statements

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](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.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.cml.2021.12.014](https://doi.org/10.1016/j.cml.2021.12.014).

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