Atezolizumab combined with immunogenic salvage chemoimmunotherapy in patients with transformed diffuse large B-cell lymphoma

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Abstract

Patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) transformed from indolent B-cell lymphomas, including Richter transformation, have a poor prognosis. PD-1/PD-L1 antibodies produce modest objective and complete response rates in B-cell non-Hodgkin lymphoma as monotherapy but may synergize with immunogenic chemotherapies such as gemcitabine and oxaliplatin (GemOx). Thus, we evaluated the safety and efficacy of atezolizumab plus rituximab and GemOx (R-GemOx+Atezo) in R/R transformed DLBCL, including Richter transformation. We conducted a phase I trial including patients with transformed DLBCL after ≥1 prior therapy. Patients received up to four cycles of R-GemOx+Atezo. Patients in complete remission could then proceed to R-Atezo maintenance until progression. A safety lead-in with evaluation of dose-limiting toxicity was performed to confirm the recommended phase II dose; subsequently the treatment was administered to two expansion cohorts: one with transformed follicular lymphoma (FL) and the other with non-FL transformed DLBCL, including Richter transformation. Twenty-seven patients were enrolled. One of the six patients in the safety lead-in had a dose-limiting toxicity attributed to atezolizumab, a grade 4 Stevens-Johnson syndrome. The most common grade ≥3 events were neutropenia (18.5%), lymphopenia (18.5%), and thrombocytopenia (14.8%). The overall and complete response rates were 59% and 33%, respectively. The overall and complete response rates in transformed FL were 79% and 43%, respectively, and 38% and 23% in transformed non-FL, respectively. The median progression-free survival and overall survival of the total population were 4.2 and 7.7 months, respectively. R-GemOx+Atezo was well tolerated and demonstrated promising preliminary efficacy in patients with relapsed/refractory transformed DLBCL.

Introduction

Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma and indolent B-cell non-Hodgkin lymphomas, including follicular lymphoma (FL), can experience histological transformation to diffuse large B-cell lymphoma (DLBCL). Transformed DLBCL can be challenging to manage, especially if patients develop relapsed/refractory (R/R) disease.[1,2] Patients with R/R transformed DLBCL have a poor prognosis, with an estimated 4-year event free survival and overall survival of 27% and 39%, respectively.[3] Standard therapy for patients with R/R DLBCL who have primary refractory disease or relapse within 12 months after initial anthracycline-based chemoimmunotherapy is to proceed to chimeric antigen receptor (CAR) T-cell therapy, while for those who relapse after more than 12 months the standard management is salvage chemoimmunotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) in chemosensitive patients eligible for transplant, or palliative therapies in patients who are not candidates for transplantation.[4-6] Among patients with R/R transformed DLBCL, a minority of patients who undergo autologous HSCT or re-

ceive CAR T cells achieve long-term disease-free survival.[3,5-7] There were small subsets of patients with transformed FL in the pivotal and randomized CAR T-cell studies and there is no clear standard treatment for patients with Richter transformation (RT). Thus, better therapies for transformed DLBCL, including RT, is a clear unmet need.

Atezolizumab is a monoclonal antibody that binds programmed death ligand-1 (PD-L1) to inhibit the interaction between the programmed cell death-1 receptor (PD-1) and PD-L1.[8] PD-1 or PD-L1 is overexpressed in several types of non-Hodgkin lymphoma, including DLBCL[9], FL, and RT.[10-12] Anti-PD-1/PD-L1 monotherapy has demonstrated modest overall response rates ranging from 4-18% in FL and DLBCL.[13] Atezolizumab has been safely combined with several agents in R/R DLBCL, such as polatuzumab vedotin, tazemetostat, and obinutuzumab, but these combinations again demonstrated limited overall response rates ranging from 16-25%.[14-16] Preclinical data suggest synergy between immunogenic chemotherapy with anti-PD-L1 antibodies, leading to eradication of PD-1/PD-L1 blockade-refractory tumor cells.[17] One such immunogenic chemotherapy is oxaliplatin, which increases T- and dendritic cell infiltration, thereby increasing the cytotoxic T-cell:regulatory T-cell ratio and enhancing dendritic cell/macrophage function.[17,18] Another example is gemcitabine, which depletes myeloid-derived suppressor cells, increases tumor cell expression of major histocompatibility complex class I, and shifts the polarity of tumor-associated macrophages.[19-22]

The combination of gemcitabine and oxaliplatin (GemOx) is a commonly used salvage regimen for DLBCL. Transformed DLBCL is an ideal disease in which to evaluate the combination of immunogenic chemotherapy and checkpoint inhibitors given the genomic complexity of transformed FL. PD-1/PD-L1 antibodies exhibit their greatest efficacy in tumors with high genomic instability (i.e., high tumor mutational burden and microsatellite instability).[23,24] Transformed DLBCL, and in particular transformed FL, are more genomically complex than the underlying indolent B-cell non-Hodgkin lymphomas,[25,26] and therefore may provide more neo-antigens ripe for recognition by T cells stimulated by checkpoint inhibitors. We hypothesized that combining PD-L1 blockade with immunogenic R-GemOx would be safe and could enhance the antitumor activity driven by each type of therapy and lead to a higher response rate than chemotherapy or immunotherapy alone. We developed a pilot study to combine immunogenic chemotherapy, R-GemOx, with atezolizumab (R-GemOx+Atezo), to assess the safety and preliminary activity of this combination in patients with R/R transformed DLBCL, including RT, and report our findings here.

Methods

Study design and participants

We conducted a multicenter phase I trial through the National Cancer Institute Experimental Therapeutics Clinical Trials Network (NCI ETCTN). Participating centers included City of Hope, University of California Davis, and Emory University. All participating sites obtained institutional review board approval. The trial was registered at clinicaltrials.gov (NCT03321643). Eligible patients were ≥18 years old with histologically confirmed transformed DLBCL, including histological transformation from any indolent lymphoma, such as FL, marginal zone lymphoma, lymphoplasmacytic lymphoma or RT of chronic lymphocytic leukemia. Additionally, they must have had documented R/R disease after at least one prior treatment regimen (which did not have to be DLBCL-directed therapy), as defined using the 2014 Lugano classification.[27] Other inclusion criteria included an Eastern Cooperative Oncology Group performance status ≤2 and adequate organ function. Exclusion criteria included prior receipt of GemOx, anti-PD1/PD-L1 therapy or allogeneic HSCT; prior chemotherapy, radiotherapy or systemic immunosuppressive therapy (with the exception of acute, low dose, systemic immunosuppressant medications) within 2 weeks of enrollment; active central nervous system lymphoma; history of autoimmune disease; and pregnancy. A full list of eligibility criteria is provided in the *Online Supplementary Appendix*.

The study had a six-patient safety lead-in with a dose-limiting toxicity (DLT) evaluation. Patients were enrolled in the safety lead-in via the traditional 3+3 method to establish the recommended phase II dose (RP2D). We included a dose de-escalation level in the event that excess toxicity was observed at the starting dose level. Once the RP2D had been established, two separate expansion cohorts were enrolled: a cohort of patients with transformed FL and another cohort of patients with transformation of other non-FL indolent lymphomas or RT. The six patients from the safety lead-in portion of the study treated at RP2D were included in the expansion cohort accrual. R-GemOx consisted of rituximab 375 mg/m^2 intravenously (IV), gemcitabine 1000 mg/m^2 IV, and oxaliplatin 100 mg/m^2 on day 1 every 2 weeks. Atezolizumab was given at a fixed dose of 840 mg IV every 2 weeks on day 1 starting with cycle 2. Patients could receive up to a maximum of four 21-day cycles of R-GemOx. Responding patients could then receive maintenance therapy with rituximab 375 mg/m^2 IV plus a fixed dose of atezolizumab 1,200 mg IV (R-Atezo) every 4 weeks until disease progression or unacceptable toxicity (Figure 1A). Patients who achieved a complete response could transition to maintenance therapy after completing at least two cycles. Patients who were transplant candidates were required to complete at least the first two cycles of study therapy before proceeding to HSCT at the discretion of the treating physician. Positron emission tomography/computed tomography (PET/CT) was performed at baseline, followed by PET/CT (or CT scans once a complete response had been confirmed) after cycles 2 and 4. For those receiving maintenance, PET/CT or CT scans were performed every 12 weeks until 2 years from

the start of the study, then every 6 months while receiving maintenance therapy.

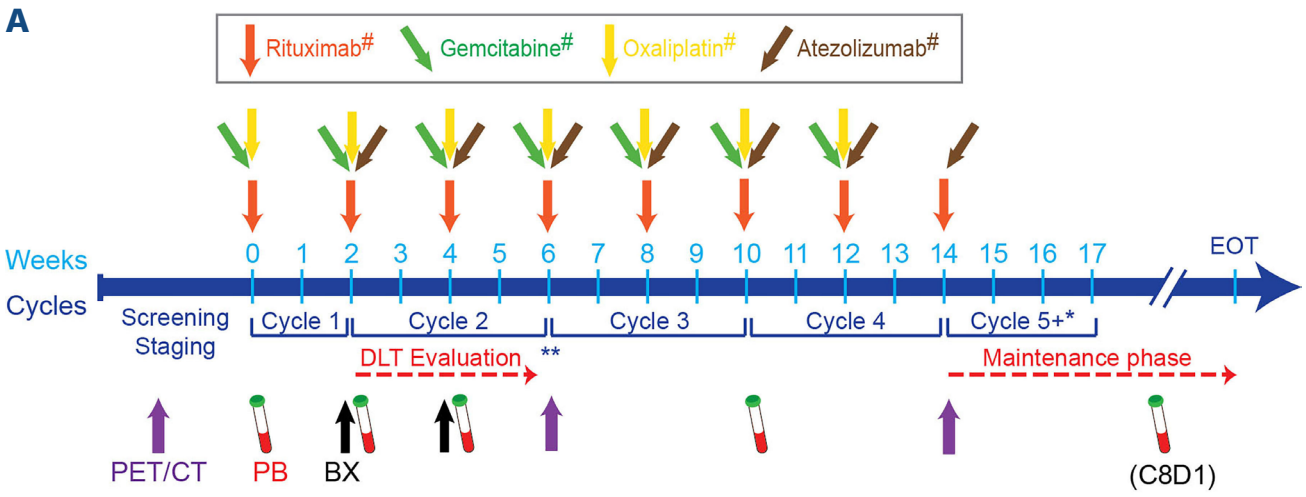
Study outcomes and statistical analyses

The primary endpoint was to establish safety and dosing of R-GemOx+Atezo by documenting adverse events and determining the maximum tolerated dose/RP2D. To be evaluable for DLT, a patient must have either experienced a DLT during the DLT period (i.e., cycle 2), or received the total planned doses of all drugs during the DLT period and not experienced a DLT (which included a therapy delay of >2 weeks due to a treatment-related toxicity). During the safety portion of the study, patients who were not evaluable for DLT were replaced. A list of the full DLT criteria can be found in the *Online Supplementary Appendix*. Toxicity monitoring was continued beyond the 28-day DLT period because of the immune-related adverse events associated with checkpoint inhibitors. Secondary endpoints were overall response rate, complete response rate, duration of response, progression-free survival, and overall survival. Baseline characteristics were summarized using descriptive statistics. Responses were determined using the Lugano 2014 criteria.[27] Duration of response was calculated from the time of first documented response to progression or death. Progression-free survival was calculated as the time from start of treatment to the date of progression or death, whichever came first. Overall survival was calculated as the time from start of treatment until death. Patients who were alive and free of progression were censored at the date of last follow-up. Patients who started another therapy prior to progression were censored at that time. Survival estimates were calculated using the Kaplan-Meier method.

Results

Participants' characteristics

Twenty-seven patients were enrolled and received treatment (Figure 1B). All patients were evaluable for efficacy and safety. The patients' baseline characteristics are listed in Table 1. The median age was 68 years (range, 44-80), 14 patients (52%) had transformed FL, while 13 patients (48%) had transformed non-FL (9 chronic lymphocytic leukemia/



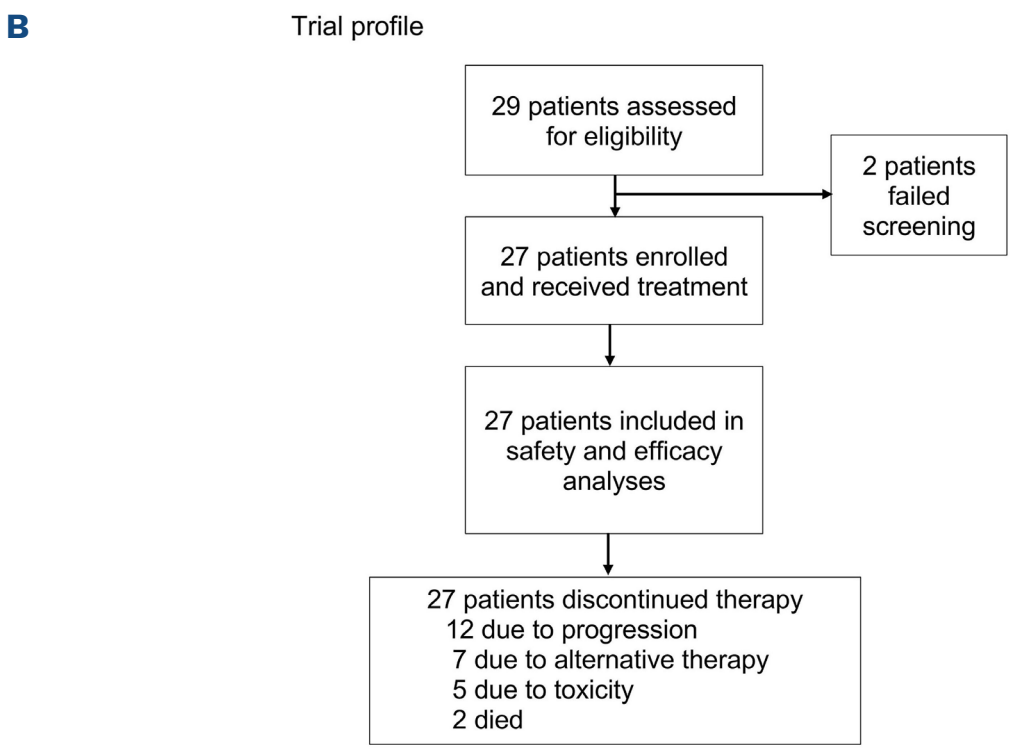


Figure 1. Clinical trial profile of this single-arm trial of rituximab, gemcitabine, oxaliplatin, and atezolizumab. (A) Study schema. (B) CONSORT diagram. EOT: end of treatment; DLT: dose-limiting toxicity; PET/CT: positron emission tomography/computed tomography; PB: peripheral blood; BX: biopsy; C8D1: cycle 8, day 1.

small lymphocytic lymphoma, 3 marginal zone lymphoma, 1 lymphoplasmacytic lymphoma). The median number of prior lines of treatment was 2 (range, 1-7), and two patients had received prior CAR T-cell therapy, one patient had previously received a CD20-CD3 bispecific antibody (mosunetuzumab), and one patient underwent autologous HSCT prior to enrollment.

Safety

During the safety lead-in, eight patients were enrolled. Two patients were replaced because of progressive disease prior to completing the DLT evaluation period but were included in the response rate calculations. One of six patients evaluable for DLT had a DLT attributed to atezolizumab during the safety lead-in, a grade 4 Stevens-Johnson syndrome followed by infectious complications, eventually leading to asystole and death. The maximum tolerated dose/RP2D was dose level 1. The most common adverse events of any grade were fatigue (N=15), raised levels of transaminases (N=14), thrombocytopenia (N=13), nausea/vomiting (N=12), and hypertension (N=10) (Table 2). The most common grade ≥3 events were neutropenia (N=5, 18.5%), lymphopenia (N=5, 18.5%), and thrombocytopenia (N=4, 14.8%) (Table 2). There was only one grade ≥3 immune-related adverse event, which was the grade 4 Stevens-Johnson syndrome previously mentioned. There were two treatment-related deaths: the patient with Stevens-Johnson syndrome and one patient who experienced an infusion reaction that led to respiratory failure who simultaneously had progressive disease. Eleven patients (40.7%) proceeded to R-Atezo maintenance, and the most common grade ≥3 adverse events during maintenance were lymphopenia (N=3), hypertension (N=2), leukopenia (N=2), and thrombocytopenia (N=2) (*Online Supplementary Table S1*).

Six deaths occurred either during treatment or within 30 days of last treatment: disease progression (N=4), disease progression with concurrent sepsis during maintenance (N=1), and COVID-19 pneumonia (N=1). Other non-lymphoma related deaths include infection after coming off treatment for progressive disease (N=2) and respiratory failure from pneumonia after autologous HSCT. All patients have discontinued or completed protocol therapy. Reasons for discontinuing treatment included lack of objective response or progression of lymphoma (N=12), switching to an alternative therapy (N=7) (5 patients underwent autologous HSCT, 2 patients received CAR T cells), non-fatal adverse events (N=4), and death on study (N=3).

Table 1. Baseline characteristics of the patients.

Characteristics	All patients N=27
Age in years, median (range)	68 (44-80)
Male, N (%)	16 (59)
Race/Ethnicity, N (%) Asian Black Non-Hispanic White Hispanic or Latino Pacific Islander	 2 (7) 1 (4) 18 (67) 5 (19) 1 (4)
Subgroup, N (%) Transformed follicular lymphoma Other transformed indolent lymphoma	 14 (52) 13 (48)
Performance status, N (%) ECOG 0-1 ECOG 2	 26 (96) 1 (4)
Extra-nodal involvement, N (%)	10 (37)
MYC rearranged, N (%)	4 (15)
Double/triple-hit, N (%) Unknown	7 (25.9) 1 (4)
Prior lines of therapy, median (range)	2 (1-7)
Refractory to last line of therapy, N (%)	8 (30)
Underlying Indolent lymphoma, N (%) Follicular lymphoma CLL/SLL Marginal zone lymphoma Lymphoplasmacytic lymphoma	 14 (52) 9 (33) 3 (11) 1 (4)

ECOG: Eastern Cooperative Oncology Group; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma.

Efficacy

The overall and complete response rates in all patients were 59% (N=16) and 33% (N=9), respectively. Seven patients (26%) had a partial response, one patient (4%) had stable disease, nine patients (33%) had progressive disease, and one patient (4%) was not assessed for a response. A waterfall plot demonstrating the maximum change in tumor size from baseline of all patients is shown in *Online Supplementary Figure S2*. The median duration of response in all responders was 4.0 months (Figure 2A), whereas that in patients achieving a complete response or a partial response was 42.6 *versus* 3.0 months, respectively (Figure 2B). Of the nine patients who achieved a complete response, five (55.6%) in complete remission proceeded to autologous HSCT, one (11.1%) proceeded to maintenance, two discontinued treatment due to toxicity (peripheral neuropathy and an inflammatory reaction), and one died of a myocardial infarction, which was unrelated to treatment, after 42 months of maintenance therapy. The duration of therapy for each patient is summarized in Figure 2C. We note that durable remissions were observed irrespective of response to last therapy prior to enrollment and time elapsed from last line of treatment to enrollment. Table 3 lists the response to R-GemOx+Atezo for each individual patient based on prior lines of therapy. We did not discern any clear correlation between prior receipt of and response to an anthracycline-containing regimen, response to CAR T cells, and time from last line of treatment to enrollment. Among the 14 patients with FL, the overall and complete

Table 2. Adverse events.

Adverse events related to treatment with at least two grade ≥ 2 events, N (%)	Transformed follicular lymphoma			Other transformed lymphomas		
	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
Cardiac arrest	-	1 (7)	-	-	-	1 (8)
White blood cell count decreased	-	3 (21)	-	2 (15)	1 (8)	-
Lymphocyte count decreased	-	4 (29)	-	2 (15)	1 (8)	-
Neutrophil count decreased	1 (7)	3 (21)	-	2 (15)	2 (15)	-
Fever	3 (21)	-	-	3 (31)	1 (8)	-
Dyspnea	-	-	-	1 (8)	1 (8)	-
Acute kidney injury	-	1 (7)	-	-	1 (8)	-
Atrial fibrillation	-	-	-	-	1 (8)	-
Hyperkalemia	-	-	-	-	1 (8)	-
Hypernatremia	1 (7)	-	-	-	1 (8)	-
Respiratory failure	-	1 (7)	-	-	1 (8)	-
Platelet count decreased	3 (21)	3 (21)	-	6 (46)	1 (8)	-
Maculo-papular rash	2 (14)	-	-	-	1 (8)	-
Aspergillosis	-	1 (7)	-	-	-	-
Multi-organ failure	-	1 (7)	-	-	-	-
Sepsis	-	1 (7)	-	-	-	-
Stevens-Johnson syndrome	-	1 (7)	-	-	-	-
Hypertension	6 (43)	2 (14)	-	-	2 (15)	-
Infusion related reaction	2 (14)	-	-	1 (8)	1 (8)	-
Increased alanine transaminase	6 (43)	-	-	7 (54)	1 (8)	-
Dizziness	-	-	-	-	1 (8)	-
Febrile neutropenia	-	1 (7)	-	-	1 (8)	-
Anemia	3 (21)	1 (7)	-	3 (31)	-	-
Hypokalemia	2 (14)	1 (7)	-	-	-	-
Hypocalcemia	1 (7)	1 (7)	-	-	-	-
Nausea/vomiting	5 (36)	-	-	7 (54)	-	-
Fatigue	7 (50)	-	-	8 (62)	-	-
Peripheral sensory neuropathy	2 (14)	-	-	3 (31)	-	-

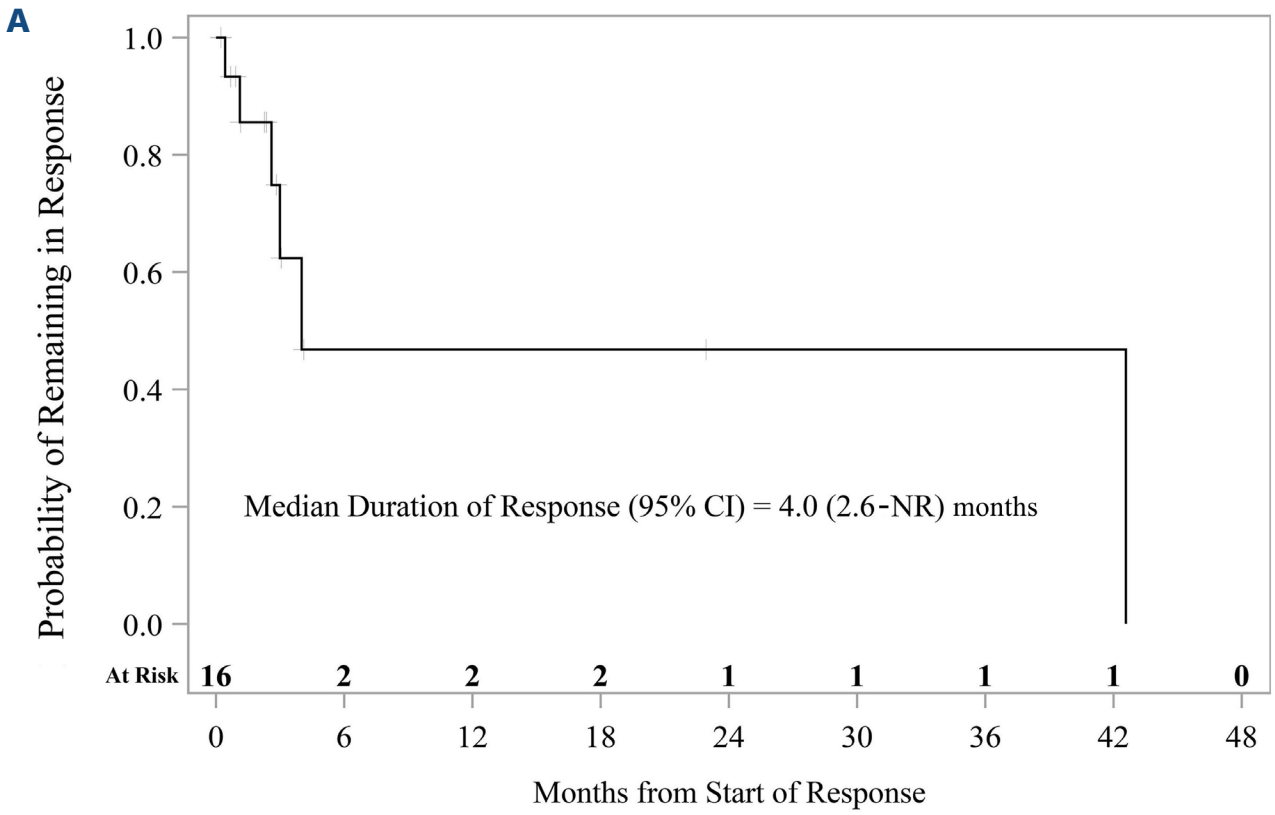
response rates were 79% and 43%, respectively. In non-FL transformed lymphomas, the overall and complete response rates were 38% and 23%, respectively. There were three patients with transformed marginal zone lymphoma, of whom two achieved a complete response, while one patient achieved a partial response. There were nine patients with RT; the overall and complete response rates were 22% and 11%, respectively. The median progression-free survival and overall survival of the total population were 3.7 and 7.7 months, respectively (Figure 3A). The median progression-free survival in patients with transformed FL or non-FL were 3.7 and 3.1 months, respectively (P=0.4) (Figure 3B), and the median overall survival for the two groups were 22.5 and 7.3 months, respectively (P=0.4) (Figure 3C). Notably, one patient who received both an autologous HSCT and CAR T cells prior to enrollment had a partial response to R-GemOx+Atezo, while another patient who had been treated with mosunetuzumab and CAR T cells had progressive disease during treatment with R-GemOx+Atezo.

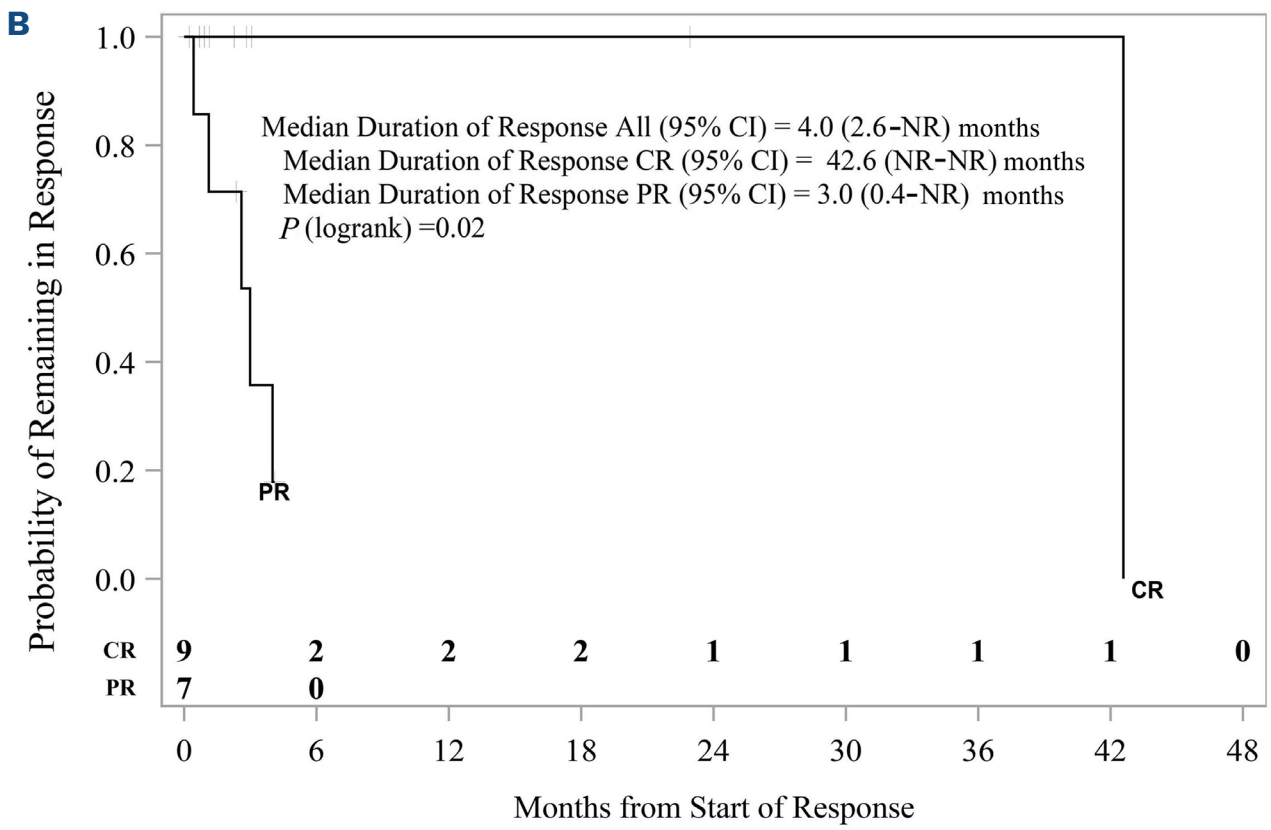
Discussion

R-GemOx+Atezo was tolerable and effective in R/R transformed DLBCL. The starting dose was the RP2D, and most

toxicities were manageable. With the caveat of the small sample size, response rates were numerically higher in the FL cohort than in the non-FL cohort, although progression-free survival and overall survival were similar in the two groups. Durable responses were observed and appeared to be longer for those who achieved a complete response than in those who had a partial response. Notably, over a quarter of patients enrolled were successfully transitioned to autologous HSCT or CAR T-cell therapy. However, there was a rare but fatal complication with this regimen, Stevens-Johnson syndrome, which is known to occur with PD-1/PD-L1 blockade.[28] Although uncommon, severe immune toxicities are an important limitation of using regimens that incorporate PD-1 blockade into therapy for DLBCL.

Although R-GemOx previously demonstrated overall and complete response rates of 61% and 44%, respectively, in DLBCL,[29] the patient population in that study is not directly comparable to ours: in the previous study the cohort predominately consisted of *de novo* DLBCL patients receiving second-line therapy, and none had RT. Moreover, the management of R/R DLBCL has evolved significantly since the original R-GemOx studies were conducted. Our trial was carried out more recently, with some patients having re-





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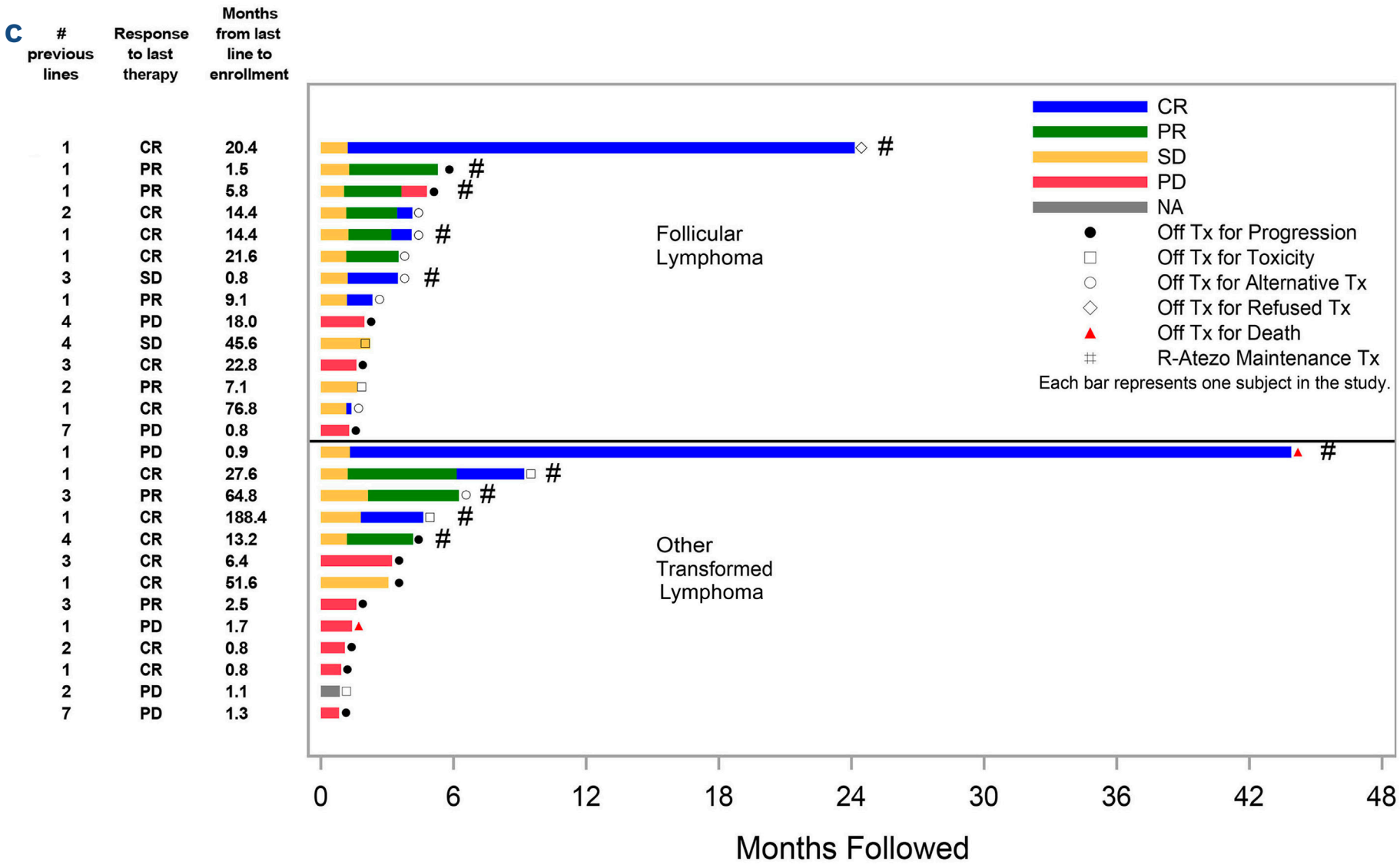

Figure 2. Duration of response in patients treated with rituximab, gemcitabine, oxaliplatin, and atezolizumab. (A) Duration of response in all treated patients. (B) Duration of response in patients achieving complete or partial response. (C) Swimmer plot of patients enrolled. 95% CI: 95% confidence interval; NR: not reached; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NA: not available; Tx: treatment; R-Atezo: rituximab and atezolizumab.

ceived prior, novel therapies. Recently, the phase III NIVEAU study showed no benefit in progression-free survival from the addition of nivolumab to R-GemOx in R/R DLBCL, and a median progression-free survival similar to that in our study.[30] However, these patients were not restricted to transformed DLBCL and patients enrolled in the NIVEAU study had received only one prior line of therapy, which limits direct comparisons with our study. Regardless, the short progression-free survival we observed suggests that our regimen serves best as a bridge to more definitive therapy, such as autologous HSCT or CAR T cells. In contrast to the efficacy of R-GemOx-Atezo that we observed in R/R transformed FL, the treatment was not very effective in RT. This finding parallels the results seen in KEYNOTE-170,[31] in which the response rate to pembrolizumab in R/R RT with DLBCL histology was only 6%, but differs from those of prior studies conducted by Ding *et al*. and Jain *et al.*, which utilized pembrolizumab and nivolumab, leading to response rates of 44% and 42%, respectively.[32,33] The striking difference in efficacy between these two studies and ours may be related to the use of a BTK inhibitor. The two prior studies included patients with recent or concurrent BTK inhibition, which may have immunomodulatory effects that possibly enhance the efficacy of PD-1/PD-L1 blockade.[34,35] A third study of venetoclax, obinutuzumab, and atezolizumab demonstrated overall and complete response rates of 100% and 71%, respectively, in six patients.[36]

The responses we observed may have been due to chemotherapy sensitizing lymphoma cells to PD-1/PD-L1 blockade, possibly due to the immunogenic effects of certain chemotherapeutic agents. This apparent chemosensitization by PD-1 blockade has been observed in non-Hodgkin lymphoma, with several studies demonstrating improved response rates to chemotherapy in previously chemorefractory patients after PD1 blockade was given.[37] Our study, as well as those conducted in RT by others, support the idea that PD1 combined with chemotherapy may be effective in non-Hodgkin lymphoma, but the types of chemotherapy or other concurrent/subsequent therapies may be important, as well as the immunogenicity of that particular agent.

We note several important limitations to our study, such as the small sample size and lack of a comparator arm to determine whether the addition of atezolizumab affects the response rate to the immunogenic chemotherapy. At the time this study was conceived, there was a significant dearth of trials studying transformed indolent lym-

Table 3. Responses to the rituximab, gemcitabine, oxaliplatin and atezolizumab treatment regimen based on prior lines of therapy.

Patient ID	N of prior lines	N of prior lines for transformed lymphoma	Prior anthracycline	Response to R-CHOP or DA-EPOCH-R	Last line of therapy	Response to last line of therapy	Last line treating indolent or transformed lymphoma	Response to CAR T cells	Time from last line of therapy to enrollment	Response to R-GemOx+ Atezo
1	2	1	Yes	CR	Bendamustine/ Obinutuzumab	PR	Indolent	N/A	7.1 months	PR
2	1	1	Yes	PD	DA-EPOCH-R	PD	Transformed	N/A	27 days	CR
3	1	1	Yes	CR	R-CHOP	CR	Transformed	N/A	15.7 years	CR
4	3	0	No	N/A	Venetoclax/ obinutuzumab	CR	Indolent	N/A	6.4 months	PD
5	2	0	No	N/A	Ibrutinib	CR	Indolent	N/A	19 days	PD
6	1	1	Yes	SD	R-CHOP	CR	Transformed	N/A	25 days	PD
7	7	1	Yes	PD	DA-EPOCH-R	PD	Transformed	N/A	1.3 months	PD
8	4	4	Yes	CR	Axicabtagene ciloleucel	CR	Transformed	CR	1.1 years	PR
9	2	0	No	N/A	Venetoclax	PD	Indolent	N/A	1.1 months	N/A
10	1	1	No	N/A	Bendamustine/ rituximab	CR	Indolent	N/A	4.3 years	SD
11	3	1	Yes	PR	Bendamustine/ rituximab	SD	Indolent	N/A	23 days	CR
12	3	1	Yes	PR	R-CHOP	PR	Transformed	N/A	2.5 months	PD
13	1	1	Yes	PR	R-CHOP	PR	Transformed	N/A	1.5 months	PR
14	1	1	Yes	PR	R-CHOP	PR	Transformed	N/A	9.1 months	CR
15	7	4	Yes	PD	Clinical Trial	PD	Transformed	CR	23 days	PD
16	1	1	Yes	CR	R-CHOP	CR	Transformed	N/A	1.7 years	CR
17	1	1	Yes	CR	DA-EPOCH-R	CR	Transformed	N/A	2.3 years	CR
18	3	1	Yes	CR	Bendamustine/ Obinutuzumab	CR	Indolent	N/A	1.9 years	PD
19	4	2	Yes	SD	ICE	PD	Transformed	N/A	1.5 months	PD
20	3	1	Yes	PR	DA-EPOCH-R	PR	Transformed	N/A	5.4 months	PR
21	1	1	Yes	PD	R-CHOP	PD	Transformed	N/A	1.7 months	PD
22	1	1	Yes	CR	R-CHOP	CR	Transformed	N/A	1.2 years	CR
23	1	1	Yes	PR	DA-EPOCH-R	PR	Transformed	N/A	5.8 months	PR
24	4	1	Yes	CR	Bendamustine/ rituximab	SD	Indolent	N/A	3.8 years	PR
25	2	1	Yes	CR	R-CHOP	CR	Transformed	N/A	1.2 years	CR
26	1	1	Yes	CR	R-CHOP	CR	Transformed	N/A	1.8 years	PR
27	1	1	Yes	CR	R-CHOP	CR	Transformed	N/A	6.4 years	CR

ID. Identity; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; DA-EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; CAR: chimeric antigen receptor; R-GemOx+Atezo: rituximab, gemcitabine, oxaliplatin, and atezolizumab; CR: complete response; PR: partial response; N/A: not applicable; PD: progressive disease; SD: stable disease; ICE: ifosfamide, carboplatin, and etoposide.

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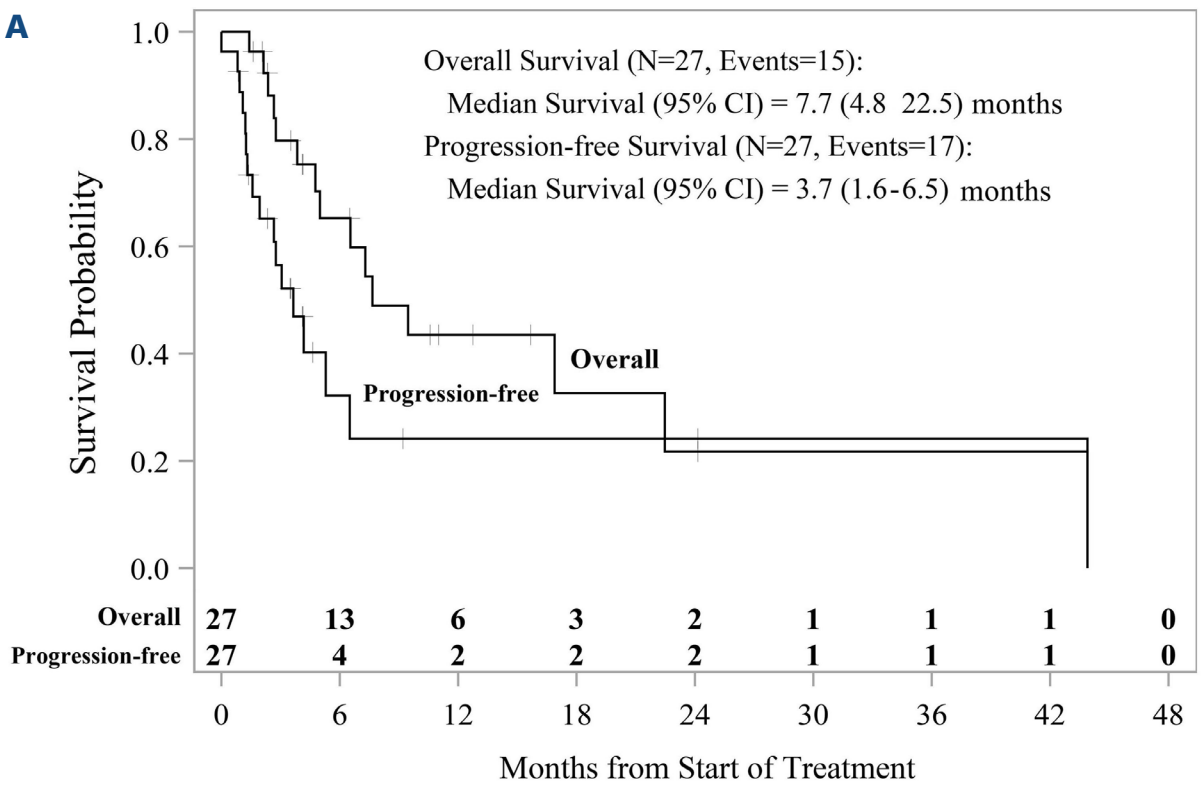

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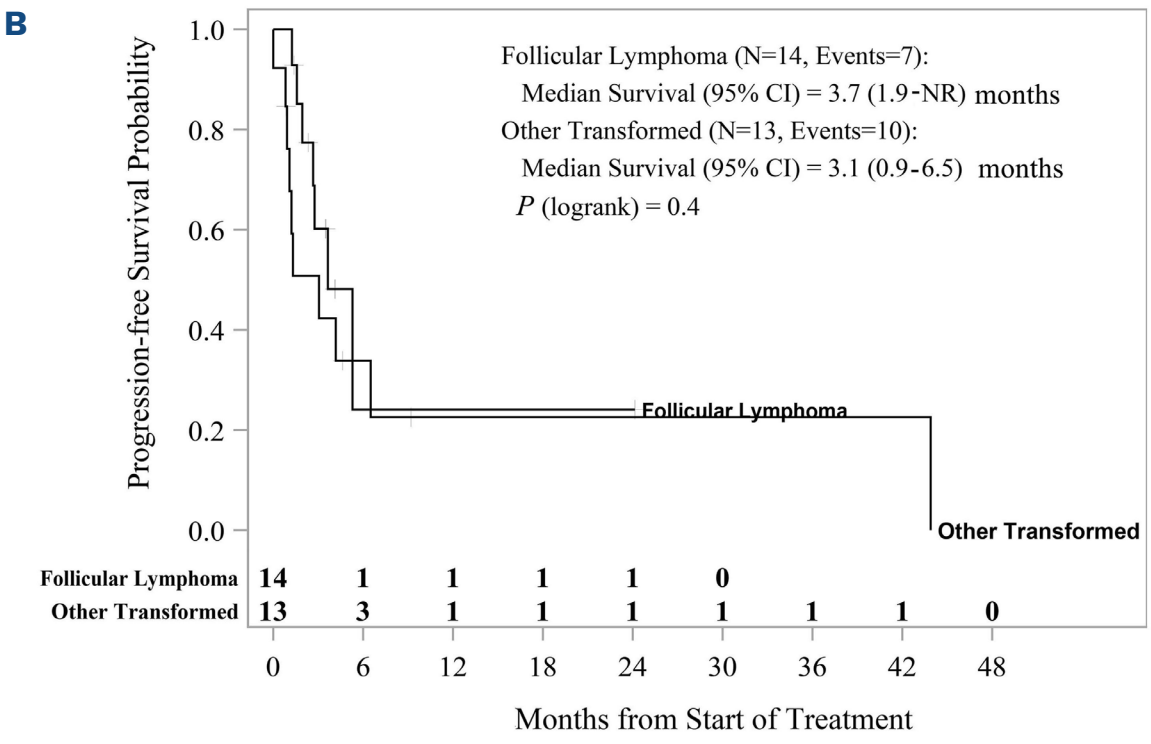

C

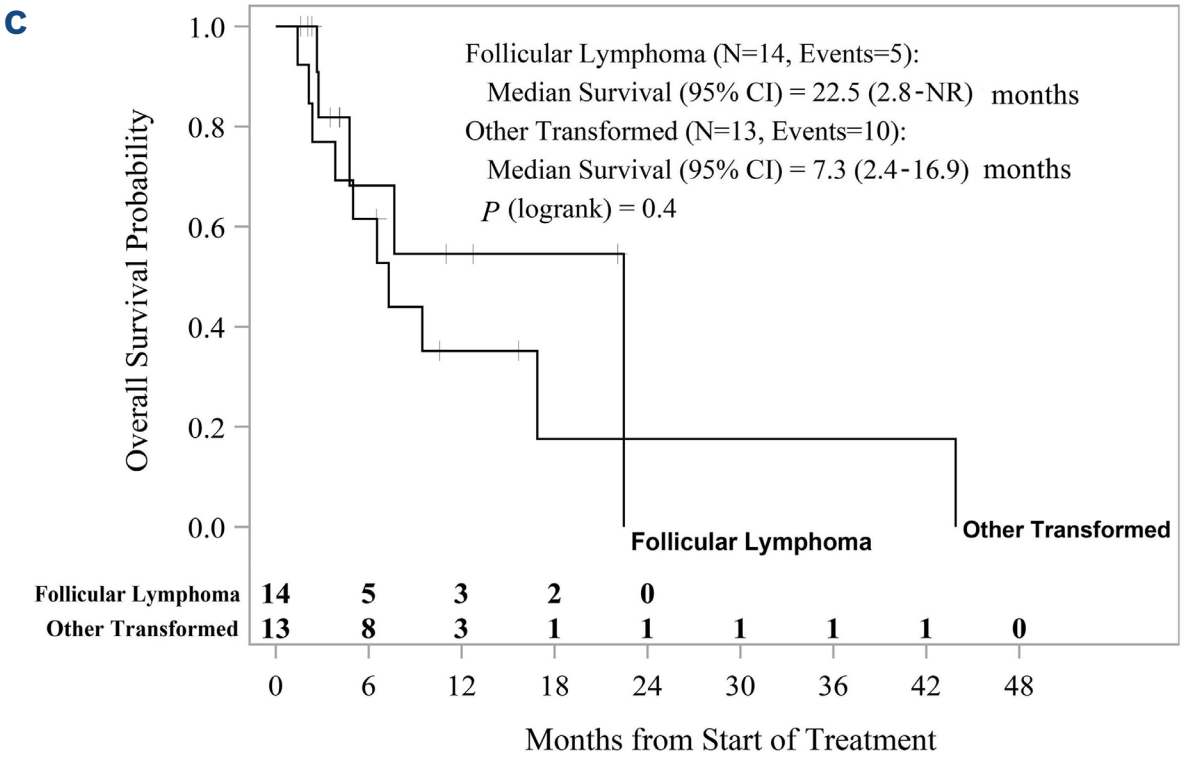

Figure 3. Survival outcomes in patients treated with rituximab, gemcitabine, oxaliplatin, and atezolizumab. (A) Progression-free and overall survival for all treated patients. (B) Progression-free survival for patients with follicular lymphoma or non-follicular lymphoma. (C) Overall survival for patients with follicular lymphoma or non-follicular lymphoma. 95% CI: 95% confidence interval; NR: not reached.

phomas. Over the past few years, however, the Food and Drug Administration has approved newer agents such as CAR T-cell therapy and bispecific antibodies, which have all shown promising efficacy in transformed indolent lymphomas.[6,38-40] Since the study was conducted primarily in the era before these therapies were available, our study cohort included a small number of patients receiving CAR T cells and bispecific antibodies. Moreover, we note that four patients did not receive an anthracycline-containing therapy for transformed DLBCL prior to enrollment, a standard-of-care treatment for this disease. The reasons for the treating investigators' choice to forego a standard anthracycline-containing therapy for DLBCL were not collected during the trial.

With further validation, the R-GemOx-Atezo regimen could be considered as an option for patients who relapse after CAR T-cell and bispecific antibody therapy. There may be appeal from using a PD-1/PD-L1 blocking antibody after these immunotherapies as there may be augmentation or re-sensitization of the prior immunotherapy. Moreover, this regimen has potential use as a bridging regimen for those intended to receive CAR T cells, for patients with late relapses after initial chemoimmunotherapy with an indication for autologous HSCT, or for allogeneic HSCT. The immunogenic and/or chemosensitizing effects of R-GemOx and PD-1/PD-L1 blockade may possibly impact the efficacy of subsequent immunotherapies, such as CAR T cells or bispecific antibodies, as has previously been observed with PD-1/PD-L1 blockade.[37]

In conclusion, R-GemOx+Atezo was tolerable and effective in transformed DLBCL. The highest response rate to R-GemOx+Atezo was in patients with transformed FL. The response rate in patients with RT was lower than what has been described in some prior studies employing checkpoint inhibitors. Our results support future evaluation of immunogenic chemotherapy combined with checkpoint inhibitors to improve outcomes in R/R transformed DLBCL.

Disclosures

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Contributions

TO and MV interpreted the analyses and wrote the manuscript. PF, NR, and CR conducted the statistical analyses. PA, LLP, GS, TS, AVD, and STR enrolled patients and edited the manuscript. SD, LP, and SK collected data and edited the manuscript. ES designed the study and edited the manuscript. JT designed the study, enrolled patients, and edited the manuscript. AFH designed the study, enrolled patients, interpreted the analyses, and wrote the manuscript.

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Data-sharing statement

Original data and the protocol are available upon request. Please contact the corresponding author.

References

1. Smith S. Transformed lymphoma: what should I do now? Hematology Am Soc Hematol Educ Program. 2020;2020(1):306-311.
2. Ding W. Richter transformation in the era of novel agents. Hematology Am Soc Hematol Educ Program. 2018;2018(1):256-263.
3. Kuruvilla J, MacDonald DA, Kouroukis CT, et al. Salvage chemotherapy and autologous stem cell transplantation for transformed indolent lymphoma: a subset analysis of NCIC CTG LY12. Blood. 2015;126(6):733-738.
4. Zelenetz AD, Gordon LI, Chang JE, et al. NCCN Guidelines® insights: B-cell lymphomas, version 5.2021. J Natl Compr Canc Netw. 2021;19(11):1218-1230.
5. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.
6. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022;399(10343):2294-2308.
7. Herrera AF, Ahn KW, Litovich C, et al. Autologous and allogeneic hematopoietic cell transplantation for diffuse large B-cell lymphoma-type Richter syndrome. Blood Adv. 2021;5(18):3528-3539.
8. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220-2229.
9. Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res. 2013;19(13):3462-3473.
10. Carreras J, Lopez-Guillermo A, Roncador G, et al. High numbers of tumor-infiltrating programmed cell death 1-positive

regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. J Clin Oncol. 2009;27(9):1470-1476.
11. Xerri L, Chetaille B, Serriari N, et al. Programmed death 1 is a marker of angioimmunoblastic T-cell lymphoma and B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia. Hum Pathol. 2008;39(7):1050-1058.
12. Behdad A, Griffin B, Chen Y-H, et al. PD-1 is highly expressed by neoplastic B-cells in Richter transformation. Br J Haematol. 2019;185(2):370-373.
13. Armengol M, Santos JC, Fernández-Serrano M, Profitós-Pelejà N, Ribeiro ML, Roué G. Immune-checkpoint inhibitors in B-cell lymphoma. Cancers (Basel). 2021;13(2):214.
14. Topp MS, Eradat H, Florschütz A, et al. Anti-CD20-atezolizumab-polatuzumab vedotin in relapsed/refractory follicular and diffuse large B-cell lymphoma. J Cancer Res Clin Oncol. 2023;149(2):811-817.
15. Palomba ML, Cartron G, Popplewell L, et al. Combination of atezolizumab and tazemetostat in patients with relapsed/refractory diffuse large B-cell lymphoma: results from a phase Ib study. Clin Lymphoma Myeloma Leuk. 2022;22(7):504-512.
16. Palomba ML, Till BG, Park SI, et al. Combination of atezolizumab and obinutuzumab in patients with relapsed/refractory follicular lymphoma and diffuse large B-cell lymphoma: results from a phase 1b study. Clin Lymphoma Myeloma Leuk. 2022;22(7):e443-e451.
17. Pfirschke C, Engblom C, Rickelt S, et al. Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy. Immunity. 2016;44(2):343-354.
18. Wang W, Wu L, Zhang J, Wu H, Han E, Guo Q. Chemoimmunotherapy by combining oxaliplatin with immune checkpoint blockades reduced tumor burden in colorectal cancer animal model. Biochem Biophys Res Commun. 2017;487(1):1-7.
19. Noguchi T, Ward JP, Gubin MM, et al. Temporally distinct PD-L1 expression by tumor and host cells contributes to immune escape. Cancer Immunol Res. 2017;5(2):106-117.
20. Parra ER, Behrens C, Rodriguez-Canales J, et al. Image analysis-based assessment of PD-L1 and tumor-associated immune cells density supports distinct intratumoral microenvironment groups in non-small cell lung carcinoma patients. Clin Cancer Res. 2016;22(24):6278-6289.
21. Pham CD, Flores C, Yang C, et al. Differential immune microenvironments and response to immune checkpoint blockade among molecular subtypes of murine medulloblastoma. Clin Cancer Res. 2016;22(3):582-595.
22. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell. 2015;28(6):690-714.
23. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348(6230):124-128.
24. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014;371(23):2189-2199.
25. Casulo C, Burack WR, Friedberg JW. Transformed follicular non-Hodgkin lymphoma. Blood. 2015;125(1):40-47.
26. Scherer F, Kurtz DM, Newman AM, et al. Distinct biological subtypes and patterns of genome evolution in lymphoma revealed by circulating tumor DNA. Sci Transl Med. 2016;8(364):364ra155.
27. 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(27):3059-3068.
28. Zhu J, Chen G, He Z, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis in patients treated with immune checkpoint inhibitors: a safety analysis of clinical trials and FDA pharmacovigilance database. EClinicalMedicine. 2021;37:100951.
29. Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica. 2013;98(11):1726-1731.
30. Held G, Altmann B, Kerkhoff A, et al. R-GemOx plus nivolumab vs R-GemOx as second-line therapy for large B-cell lymphoma in transplant-ineligible patients: interim analysis of the Niveau trial, an international, randomized phase 3 study of the AGMT, GLA, HOVON, Lysa and PLRG. Blood. 2023;142(Supplement 1):435.
31. Armand P, Murawski N, Molin D, et al. Pembrolizumab in relapsed or refractory Richter syndrome. Br J Haematol. 2020;190(2):e117-e120.
32. Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. Blood. 2017;129(26):3419-3427.
33. Jain N, Senapati J, Thakral B, et al. A phase 2 study of nivolumab combined with ibrutinib in patients with diffuse large B-cell Richter transformation of CLL. Blood Adv. 2023;7(10):1958-1966.
34. Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood. 2013;122(15):2539-2549.
35. Sagiv-Barfi I, Kohrt HE, Czerwinski DK, Ng PP, Chang BY, Levy R. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. Proc Natl Acad Sci U S A. 2015;112(9):E966-E972.
36. Jain N, Ferrajoli A, Thompson PA, et al. Venetoclax, obinutuzumab and atezolizumab (PD-L1 checkpoint inhibitor) for treatment for patients with Richter transformation. Blood. 2021;138 (Supplement 1):1550.
37. Carreau NA, Armand P, Merryman RW, et al. Checkpoint blockade treatment sensitises relapsed/refractory non-Hodgkin lymphoma to subsequent therapy. Br J Haematol. 2020;191(1):44-51.
38. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021;398(10306):1157-1169.
39. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2022;387(24):2220-2231.
40. Neelapu SS, Dickinson M, Munoz J, et al. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. Nat Med. 2022;28(4):735-742.