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

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AUTHOR'S CONTRIBUTION

TO – interpreted the analyses, wrote the manuscript

PF, NR, CR – conducted the statistical analyses

PA, LLP, GS, TS, AVD, STR – enrolled patients, edited the manuscript

SD, LP, SK – collected data, edited the manuscript

ES – designed the study, edited the manuscript

MV – interpreted analyses, wrote manuscript

JT – designed the study, enrolled patients, edited the manuscript

AFH – designed the study, enrolled patients, interpreted the analyses, wrote the manuscript

DATA SHARING STATEMENT

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

ABSTRACT

Patients with relapsed/refractory (R/R) transformed diffuse large B-cell lymphoma (DLBCL) from indolent B-cell lymphomas, including Richter transformation (RT), have a poor prognosis. PD-1/PD-L1 antibodies produce modest objective and complete response rates (ORR and CRR) in B-NHL as monotherapy but may synergize with immunogenic chemotherapies like 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 RT. We conducted a phase I trial including patients with transformed DLBCL after ≥1 prior therapy. Patients received up to 4 cycles of R-GemOx-+Atezo. Patients in CR could then proceed to R-atezo maintenance until progression. A safety lead-in with dose-limiting toxicity (DLT) evaluation was enrolled to confirm the recommended phase 2 dose (RP2D), followed by 2 expansion cohorts: one for transformed follicular lymphoma (FL) and another for non-FL transformed DLBCL, including RT. Twenty-seven patients were enrolled. One of the 6 safety lead-in patients had a DLT attributed to atezolizumab, a grade 4 Stevens-Johnson syndrome (SJS). The most common grade ≥3 events were neutropenia (18.5%), lymphopenia (18.5%), and thrombocytopenia (14.8%). The overall and complete response rates (ORR and CRR) were 59% and 33%, respectively. The ORR and CRR in transformed FL were 79% and 43%, and 38% and 23% in transformed non-FL, respectively. The median PFS and OS 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 R/R transformed DLBCL.

INTRODUCTION

Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and indolent B-cell non-Hodgkin lymphomas (B-NHL), including follicular lymphoma (FL), can experience histologic 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 (EFS) and overall survival (OS) of 27% and 39%, respectively.[3] Standard therapy for patients with R/R DLBCL who have primary refractory disease to or relapse within 12 months after initial anthracycline-based chemoimmunotherapy is to proceed to chimeric antigen receptor (CAR) T-cell therapy, while those who relapse >12 months is salvage chemoimmunotherapy followed by autologous hematopoietic cell transplantation (autoHCT) 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 autoHCT or receive CAR T-cells achieve long-term disease-free survival.[3,5-7] Additionally, 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 PD-1 and PD-L1.[8] PD-1 or PD-L1 are overexpressed in several types of NHL, including DLBCL[9], FL, and RT.[10,11,12] Anti-PD-1/PD-L1 monotherapy has demonstrated modest overall response rates (ORR) 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 ORR ranging from 16-25%.[14-16] Preclinical data suggests 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 (MDSC), increases tumor cell expression of MHC class I, and shifts tumor-associated macrophages (TAMs) polarity.[19-22]

The combination of gemcitabine and oxaliplatin (GemOx) is a commonly used salvage regimen for DLBCL. Transformed DLBCL is an ideal disease to evaluate the combination of immunogenic chemotherapy and checkpoint inhibitors (CPIs) 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 when compared to the underlying indolent B-NHL,[25,26] and therefore may provide more neo-antigens ripe for recognition by T-cells stimulated by CPI. We hypothesized that combining PD-L1 blockade with immunogenic R-GemOx would be safe and could enhance the anti-tumor 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 1 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 (IRB) approval. The trial was registered at clinicaltrials.gov (NCT03321643). Eligible patients were ≥18 years old with histologically confirmed transformed DLBCL, including histologic transformation from any indolent lymphoma, such as FL, marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL) or RT of CLL. Additionally, they must have had documented R/R disease after at least 1 prior regimen (which did not have to be DLBCL-directed therapy), as defined using the 2014 Lugano classification.[27] Other inclusion criteria include an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and adequate organ function. Exclusion criteria include prior receipt of GemOx, anti-PD1/PD-L1 therapy or allogeneic hematopoietic cell transplantation (alloHCT); 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 (CNS) lymphoma; history of autoimmune disease, and pregnant women. A full list of eligibility criteria is provided in the Supplementary Appendix.

The study had a 6 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 we observed excess toxicity at starting dose level. Once the RP2D was established, 2 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 6 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/m2 intravenously (IV), gemcitabine 1000 mg/m2 IV, and oxaliplatin 100 mg/m2 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/m2 IV plus a fixed dose of atezolizumab 1200 mg IV (R-atezo)

maintenance therapy every 4 weeks until disease progression or unacceptable toxicity (Figure 1A). Patients who achieved a CR could transition to maintenance therapy after completing at least 2 cycles. Patients who were transplant candidates were required to complete at least the first 2 cycles of study therapy before proceeding to HCT 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 CR was 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 study, then every 6 months while receiving maintenance.

Study outcomes and statistical analyses

The primary endpoint was to establish safety and dosing of R-GemOx+Atezo by documenting adverse events (AEs) and determining the MTD/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 includes a delay due to a treatment-related toxicity >2 weeks). During the safety portion, patients who were not evaluable for DLT were replaced. A list of the full DLT criteria can be found in the Supplementary Appendix. Toxicity monitoring was continued beyond the 28-day DLT period because of the immune-related adverse events AEs (irAEs) associated with CPIs. Secondary endpoints were ORR, CRR, duration of response (DOR), progression-free survival (PFS), and OS. Baseline characteristics were summarized using descriptive statistics. Responses were determined via the Lugano 2014 criteria.[27] DOR was calculated from time of first documented response to progression or death. PFS was calculated as the time from start of treatment to the date of progression or death, whichever came first. OS 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

Participant characteristics

Twenty-seven patients were enrolled and received treatment (Figure 1B). All patients were evaluable for efficacy and safety. Baseline patient 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 CLL/SLL, 3 MZL, 1 LPL). The median number of prior lines were 2 (range, 1-7), and 2 patients had received prior CAR T-cells, one patient previously received a CD20-CD3 bispecific antibody (mosunetuzumab), and one patient underwent autoHCT prior to enrollment, respectively.

Safety

During the safety lead-in, 8 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 6 patients evaluable for DLT had a DLT attributed to atezolizumab during the safety lead-in, a grade 4 Stevens-Johnson syndrome (SJS) followed by infectious complications, eventually leading to asystole and death. The MTD/RP2D was dose level 1. The most common AEs, all grades were: fatigue (n=15), transaminitis (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 irAE, which was the grade 4 SJS previously mentioned. There were 2 treatment-related deaths: the patient with SJS 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 AEs during maintenance were lymphopenia

(n=3), hypertension (n=2), leukopenia (n=2), and thrombocytopenia (n=2) (Supplementary Table 1).

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 autoHCT. All patients have discontinued or completed protocol therapy. Reasons for discontinuing treatment include lack of objective response or progression of lymphoma (n=12), switching to an alternative therapy (n=7) (5 patients underwent autoHCT, 2 patients received CAR T-cells), and non-fatal AE (n=4), death on study (n=3).

Efficacy

The ORR and CRR in all patients were 59% (n=16) and 33% (n=9), respectively. Seven patients (26%) had a partial response (PR), 1 patient (4%) had stable disease, 9 patients (33%) had progressive disease (PD), and 1 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 Supplemental Figure 2. The median DOR in all responders was 4.0 months (Figure 2A). The median DOR in patients achieving CR vs PR was 42.6 vs 3.0 months (Figure 2B). Of the 9 patients who achieved CR, 5 patients (55.6%) in CR proceeded to autoHCT, 1 patient (11.1%) proceeded to maintenance, 2 patients discontinued treatment due to toxicity (peripheral neuropathy and an inflammatory reaction), and 1 who died of a myocardial infarction, which was unrelated to treatment, after 42 months of therapy on maintenance. 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 note no clear correlation between prior receipt of and response to an anthracycline-containing regimen, response to CAR T, and time from last line of treatment to enrollment.

Among the 14 patients with FL, the ORR and CRR were 79% and 43%, respectively. In non-FL transformed lymphomas, the ORR and CRR were 38% and 23%, respectively. There were 3 patients with transformed marginal zone lymphoma, 2 patients achieved a CR while one patient achieved a PR. There were 9 patients with RT; the ORR and CRR were 22% and 11%. The median PFS and OS of the total population were 3.7 and 7.7 months, respectively (Figure 3A). The median PFS in patients with transformed FL vs non-FL were 3.7 vs 3.1 months, respectively (*P*=0.4) (Figure 3B), and the median OS for the 2 groups were 22.5 vs 7.3 months, respectively (*P*=0.4) (Figure 3C). Notably, one patient who received both an autoHCT and CAR T-cells prior to enrollment had a PR to R-GemOx+Atezo, while another patient who had mosunetuzumab and CAR T-cells had PD to 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 vs the non-FL cohort, although PFS and OS were similar between the 2 groups. Durable responses were observed and appeared to be longer for those achieved a CR vs PR. Notably, over a quarter of patients enrolled were successfully transitioned to autoHCT or CAR-T. However, there was a rare but fatal complication with this regimen, SJS, that 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 an ORR and CRR of 61% and 44% respectively in DLBCL,[29] the patient population in that study is not directly comparable to ours – that 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 conducted in a more modern era with some patients having received prior novel therapies. Recently, the phase 3 NIVEAU study showed no benefit in PFS with the addition of nivolumab with R-GemOx in R/R DLBCL, and a median PFS similar to our study.[30] However, these patients were not restricted to transformed DLBCL and patients enrolled in the NIVEAU had received only 1 prior line of therapy, which limits direct comparisons with our study. Regardless, the short PFS we observed suggests that our regimen serves best as a bridge to more definitive therapy, such as autoHCT or CAR T-cells. In contrast to the efficacy we observed in R/R transformed FL, R-GemOx-atezo was not very effective in RT. This finding parallels the results seen in KEYNOTE-170,[31] where the response rate of pembrolizumab in R/R RT with DLBCL histology was only 6%, but differs from 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 vs 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 an ORR and CRR of 100% and 71% in 6 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 NHL, 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 NHL, 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 is impacting the response rate to the immunogenic chemotherapy. At the time this study was conceived, there was a significant dearth of trials studying transformed indolent lymphomas. Over the past few years however, the FDA 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 it was conducted primarily in the era before these therapies were available, our study cohort included a small number of patients receiving CAR T 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 reason for the treating investigator's choice to forego standard anthracycline-containing therapy for DLBCL were not collected during trial conduct

Thus, with further validation the R-GemOx-Atezo regimen could be considered as an option in patients who relapse post-CAR T-cell and bispecific antibody therapy. There may be appeal to 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 relapse after initial chemoimmunotherapy with an indication for autoHCT, or for allogeneic HCT. The immunogenic and/or chemosensitizing effects of R-GemOx and PD-1/PD-L1 blockade may possibly impact the efficacy of subsequent immunotherapies like CAR T-cells or bispecific

antibodies as has been observed with PD-1/PD-L1 blockade previously.[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 CPI. Our results support future evaluation of immunogenic chemotherapy combined with CPIs to improve outcomes in R/R transformed DLBCL.

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Table 1: Baseline patient characteristics

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

Table 2: Adverse events

	Treatment Arm					
Adverse Events Related to Treatment with at least two grade 2 or higher events	**Transformed Follicular Lymphoma**			**Other Transformed**		
Adverse Event	**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%)	---
RASH MACULO-PAPULAR	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%)	---	---

Table 3: Responses to R-GemOx+Atezo based on prior lines of therapy

Patient ID	# of prior lines	# 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	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

FIGURE LEGEND

Figure 1: Clinical trial profile of this single-arm trial of R-GemOx+Atezo, including:
Panel A: Study schema

Panel B: Consort diagram

Figure 2: Duration of response in patients treated with R-GemOx+Atezo, including:

Panel A: Duration of response in all treated patients

Panel B: Duration of response in patients achieving CR vs PR

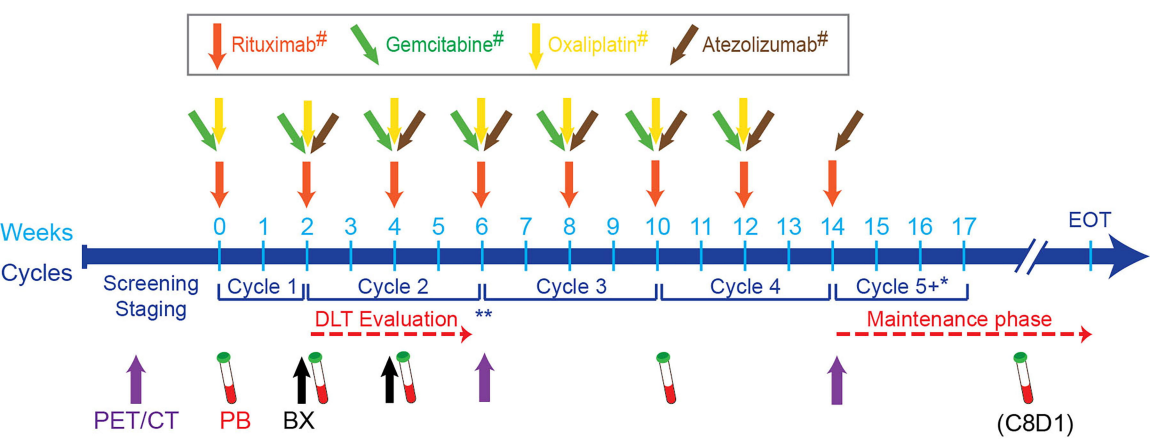
Panel C: Swimmer's plot of patients enrolled

Figure 3: Survival outcomes in patients treated with R-GemOx+Atezo, including:

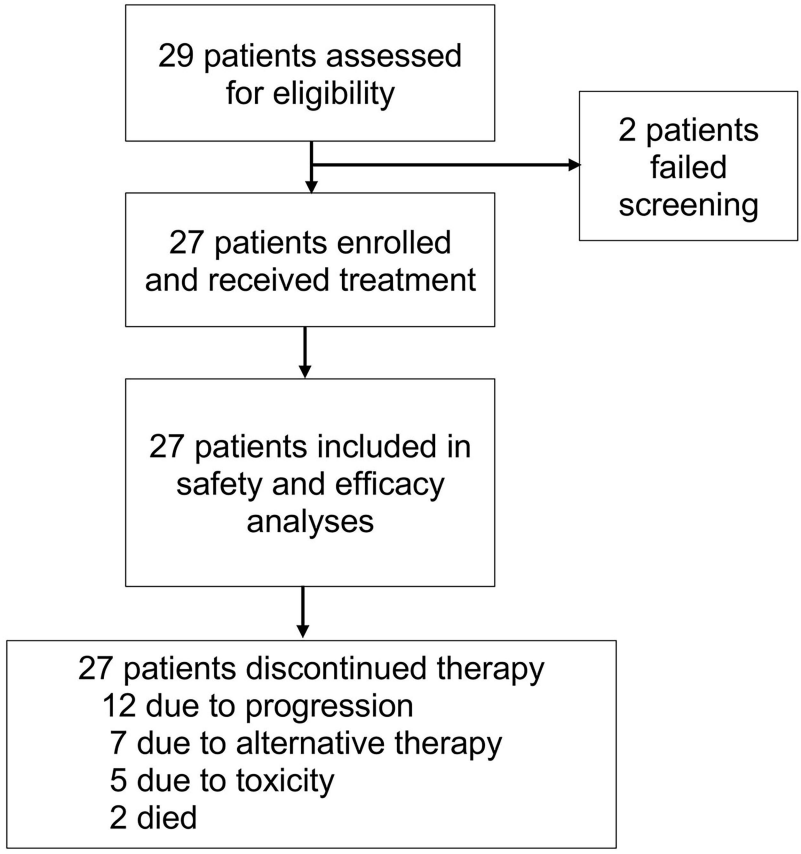
Panel A: Progression-free and overall survival for all treated patients

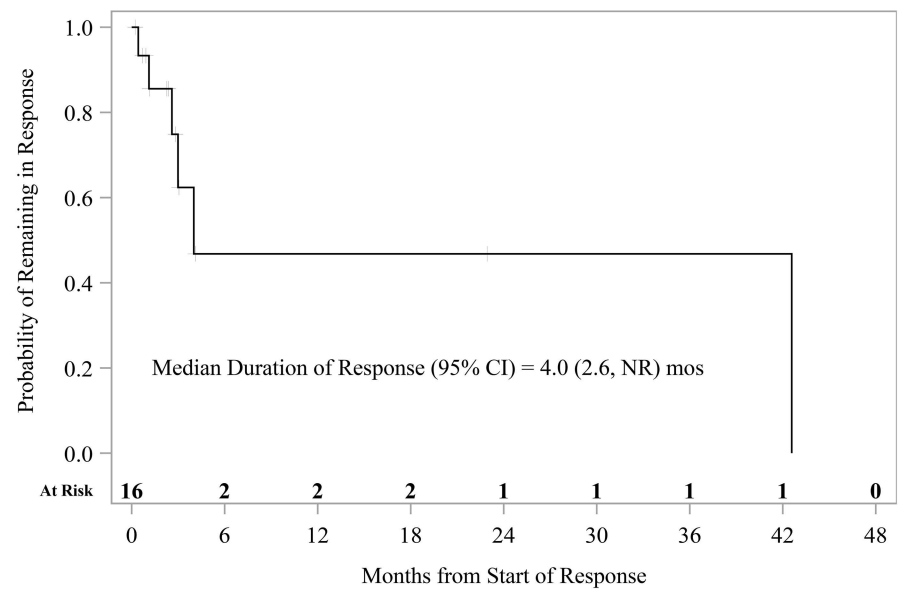
Panel B: Progression-free survival for follicular lymphoma vs non-follicular lymphoma

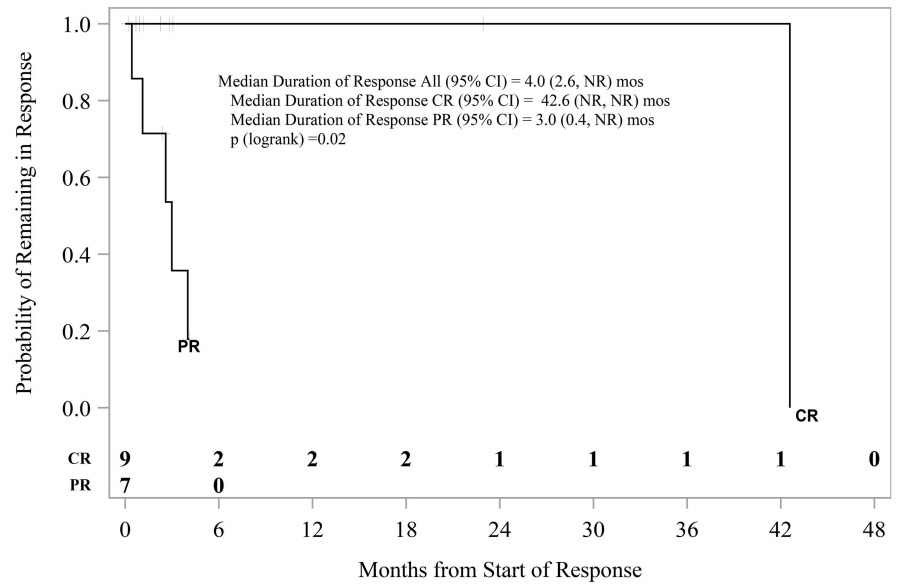
Panel C: Overall survival for follicular lymphoma vs non-follicular lymphoma

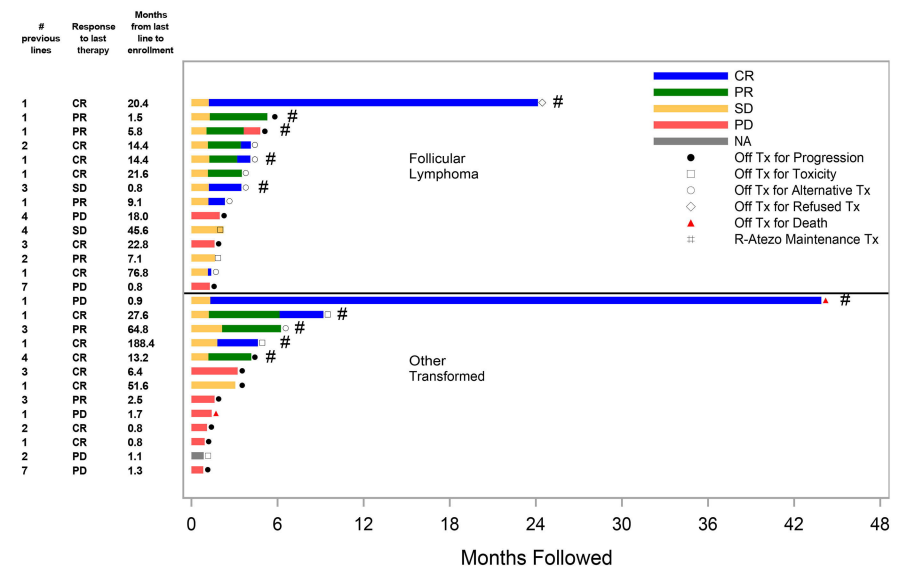


B. Trial profile

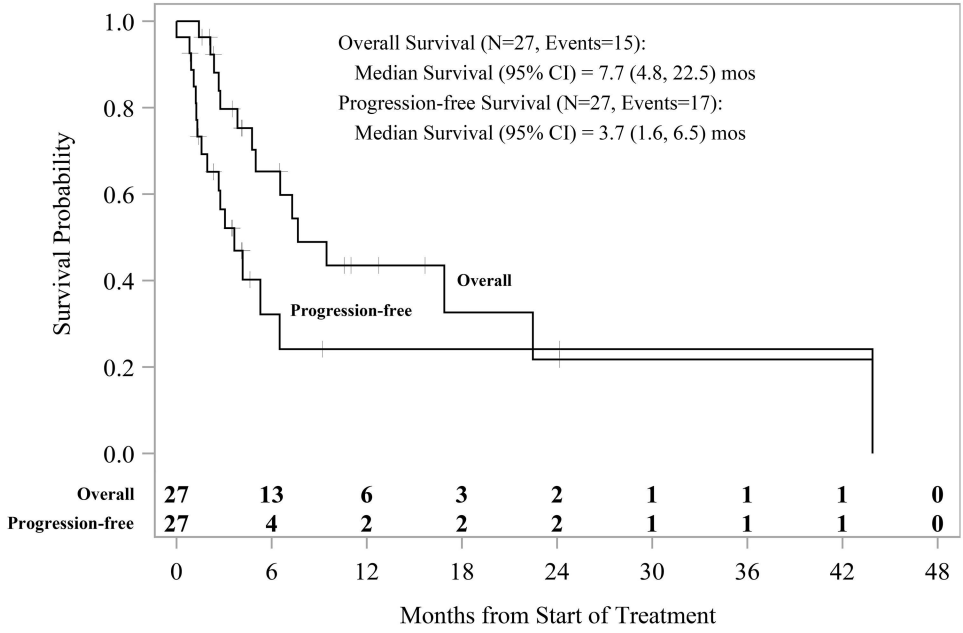


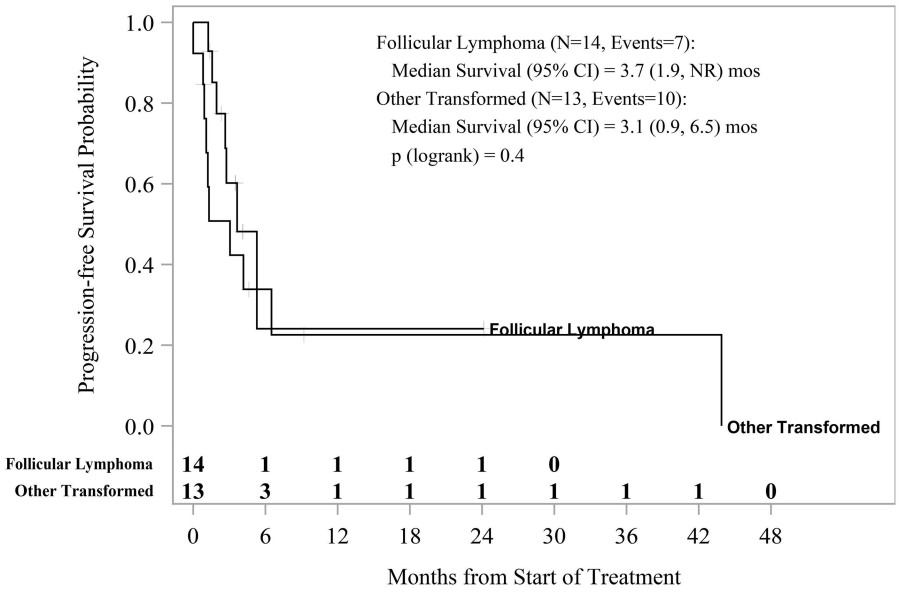


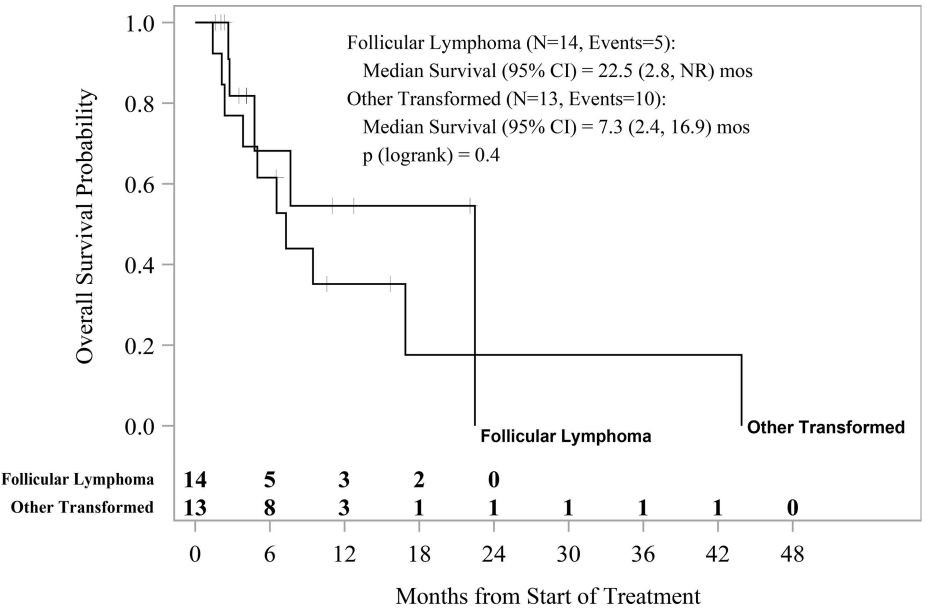




Each bar represents one subject in the study.


Overall Survival (N=27, Events=15):
Median Survival (95% CI) = 7.7 (4.8, 22.5) mos
Progression-free Survival (N=27, Events=17):
Median Survival (95% CI) = 3.7 (1.6, 6.5) mos
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Overall
Progression-free
Overall 27 13 6 3 2 1 1 1 0
Progression-free 27 4 2 2 2 1 1 1 0
0 6 12 18 24 30 36 42 48
Months from Start of Treatment


Follicular Lymphoma (N=14, Events=7):
Median Survival (95% CI) = 3.7 (1.9, NR) mos
Other Transformed (N=13, Events=10):
Median Survival (95% CI) = 3.1 (0.9, 6.5) mos
p (logrank) = 0.4
Progression-free Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Follicular Lymphoma
Other Transformed
Follicular Lymphoma 14 1 1 1 1 0
Other Transformed 13 3 1 1 1 1 1 1 0
0 6 12 18 24 30 36 42 48
Months from Start of Treatment


Follicular Lymphoma (N=14, Events=5):
Median Survival (95% CI) = 22.5 (2.8, NR) mos
Other Transformed (N=13, Events=10):
Median Survival (95% CI) = 7.3 (2.4, 16.9) mos
p (logrank) = 0.4
Overall Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Follicular Lymphoma
Other Transformed
Follicular Lymphoma 14 5 3 2 0
Other Transformed 13 8 3 1 1 1 1 1 0
0 6 12 18 24 30 36 42 48
Months from Start of Treatment

Supplementary Table 1: Adverse events through all courses for the 11 patients who proceeded to maintenance

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
WHITE BLOOD CELL COUNT DECREASED	---	---	1(9%)	1(9%)	---
NEUTROPHIL COUNT DECREASED	---	1(9%)	---	1(9%)	---
LYMPHOCYTE COUNT DECREASED	1(9%)	---	3(27%)	---	---
HYPERTENSION	---	2(18%)	2(18%)	---	---
PLATELET COUNT DECREASED	4(36%)	---	2(18%)	---	---
ALT	3(27%)	1(9%)	1(9%)	---	---
ANEMIA	1(9%)	1(9%)	1(9%)	---	---
PERIPHERAL SENSORY NEUROPATHY	2(18%)	1(9%)	---	---	---
COUGH	1(9%)	1(9%)	---	---	---
FEVER	---	1(9%)	---	---	---
GASTROESOPHAGEAL REFLUX DISEASE	---	1(9%)	---	---	---
INFUSION RELATED REACTION	---	1(9%)	---	---	---
FATIGUE	5(45%)	---	---	---	---
HYPERGLYCEMIA	3(27%)	---	---	---	---
NAUSEA\VOMITING	3(27%)	---	---	---	---
PRURITUS	3(27%)	---	---	---	---
ALKALINE PHOSPHATASE INCREASED	2(18%)	---	---	---	---
BLOOD LACTATE DEHYDROGENASE INCREASED	2(18%)	---	---	---	---
COLD INTOLERANCE	2(18%)	---	---	---	---
CONSTIPATION	2(18%)	---	---	---	---
GGT INCREASED	2(18%)	---	---	---	---
MYALGIA	2(18%)	---	---	---	---
BLOOD BILIRUBIN INCREASED	1(9%)	---	---	---	---
CREATININE INCREASED	1(9%)	---	---	---	---
DIARREHA	1(9%)	---	---	---	---
DRY SKIN	1(9%)	---	---	---	---
DYSGEUSIA	1(9%)	---	---	---	---
FLATULENCE	1(9%)	---	---	---	---
GENERALIZED MUSCLE WEAKNESS	1(9%)	---	---	---	---
HEADACHE	1(9%)	---	---	---	---
HYPOALBUMINEMIA	1(9%)	---	---	---	---
HYPONATREMIA	1(9%)	---	---	---	---
HYPOPHOSPHATEMIA	1(9%)	---	---	---	---

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
INSOMNIA	1(9%)	---	---	---	---
MALAISE	1(9%)	---	---	---	---
PALPITATIONS	1(9%)	---	---	---	---
PROTEINURIA	1(9%)	---	---	---	---
TREMOR	1(9%)	---	---	---	---

Supplemental Figure 1: Maximum % change in baseline lesion dimension