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Loncastuximab in high-risk and heavily pretreated relapsed / refractory diffuse large B-cell lymphoma: a real-world analysis from 21 US centers

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Abstract:
Outcomes in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) are poor. Loncastuximab-teserine (Lonca) is an antibody drug conjugate (ADC) which was FDA approved for R/R DLBCL patients who have received at least 2 prior lines of therapy based on the LOTIS-2 trial. However, there are limited data regarding its efficacy in the real-world setting (RWS). This retrospective study included 21 US centers and evaluated outcomes of patients with R/R DLBCL treated with Lonca. Our analysis includes 187 patients with notably higher risk baseline features compared to LOTIS-2 including a higher proportion of patients with bulky disease (17% vs 0%), high-grade B-cell histology (HGBL) (22% vs 8%), and increased number of prior lines of therapy (median 4 vs 3). The complete response (CR) rate was 14% and overall response rate (ORR) was 32%. Median event free (EFS) and overall survival (OS) were 2.1 and 4.6 months, respectively. Those with bulky disease and HGBL had significantly worse outcomes, and those with non-germinal center cell of origin and CR to most recent line of therapy demonstrated superior outcomes. In summary, in this largest retrospective cohort study of Lonca in the RWS, the response rates, EFS, and OS were lower than those reported in LOTIS-2, which is likely reflective of its use in higher risk and more heavily pre-treated patients within the real world compared to those enrolled on clinical study.

Introduction:
Patients with relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) have a poor prognosis, with particularly dismal outcomes seen in those who progress following autologous stem cell transplantation (ASCT) and/or chimeric antigen receptor T-cell therapy (CAR T-cell)[1–3]. In recent years, there have been several advances in novel therapies including antibody-drug conjugates (ADC) and bispecific antibodies that offer promising results for these patients[4–11].

Loncastuximab-teserine (Lonca) is one such therapy. Lonca is an ADC targeting CD19 paired to a pyrrolobenzodiazepine (PBD) payload that crosslinks DNA upon internalization within the tumor cell[12,13]. Lonca received FDA approval in 2021 following the LOTIS-2 trial, a multicenter single-arm phase 2 study of 145 patients with R/R DLBCL having received 2 or more prior systemic therapies[4,14]. The LOTIS-2 study reported an overall response rate (ORR) of 48% and a complete response rate (CRR) of 25% with a median progression-free survival (mPFS) and median overall survival (mOS) of 4.9 months and 9.5 months, respectively.

Routinely seen following the commercial approval of new therapies, the efficacy-effectiveness gap is a well-documented phenomenon wherein real-world outcomes fall short of those reported in prospective clinical trials[15,16]. While retrospective studies are often subject to many widely recognized limitations, these data are still meaningful to inform treating clinicians across a broader base and to generate hypotheses which further advance prospective research. Here, we present the first large-scale analysis of outcomes among patients receiving Lonca in a real-world setting.

Methods

Study design and patient population
Patient data from 21 US centers was collected retrospectively and transferred to the University of Virginia (UVA) in a de-identified manner. Patients were 18 years of age or older diagnosed with R/R DLBCL who were treated with Lonca from April 2021 to December of 2022 as standard of care. Patients with incomplete data and those using Lonca as a bridge to consolidative treatment with transplantation or CAR T-cell therapy were excluded from the primary analysis. The study protocol was approved by the University of Virginia Institutional Review Board (IRB) as well as each contributing institutional IRB. All pathologic analysis and treatment decisions were determined according to each institutional standard of care.

Outcomes
The primary endpoint for this analysis was CRR according to Lugano criteria[17]. Secondary endpoints included ORR, event-free survival (EFS), defined as the time from start of Lonca therapy to disease progression or change in therapy (censored at death or last follow-up), and overall survival (OS) as defined by time from start of Lonca therapy to death from any cause.

Statistical Methods
Baseline characteristics were summarized using descriptive statistics. The impact of categorical variables on CRR and ORR were analyzed using Fishers exact test. EFS and OS curves were

constructed using Kaplan-Meier estimates and compared via the log-rank test. A Cox proportional-hazard model was used to analyze the impact of the same clinicopathologic characteristics on EFS and OS. Statistical significance was defined as a p-value of ≤0.05 for all analyses. R version 1.4.1106 (Boston, MA) was used for analysis.

Results

Patients

A total of 187 patients from 21 US centers were deemed eligible and included in the final analysis. Eighty-seven patients (47%) would have been ineligible for LOTIS-2 on the basis of renal function, bulky disease, CNS involvement, CD19 status, or performance status. As listed in **Table 1**, the age distribution included 39% ≤65 years of age and 21% ≥75 years, and 64% were male. Eighty-six percent had advanced stage disease (stage III or IV) and 65% had an International Prognostic Index score (IPI) ≥3. Seven percent of patients had an ECOG performance status >2, 19% with an eGFR <60, and 17% with bulky disease as defined by tumor ≥10 cm in longest dimension at time of Lonca start.

With regards to prior treatments, the majority of patients (81%) had >3 prior lines of therapy for LBCL, with a median of 4 (IQR;1-7). One-quarter had primary refractory disease as defined by stable or progressive disease after first-line therapy. Sixteen percent received prior ASCT and 60% had prior CAR T-cell therapy. The median time from CAR T-cell therapy to Lonca was 7.7 months. Seventy-seven percent of patients experienced progressive disease as the best response to the most recent line of therapy prior to Lonca.

A total of 160 patients had full histopathologic data available for analysis. Twenty-two percent of patients had HGBL as defined by the 5th Edition of the WHO Classification, with the majority (89%) of the HGBL patients being double hit (DH) with MYC and BCL2 rearrangements or triple hit (TH) with BCL6, BCL2, and MYC.[18] Thirty-eight percent of patients were classified as non-germinal center B-cell (non-GCB) by the Hans algorithm[19].

CD19 status was available for 128 patients. The majority (85%) were CD19-positive prior to Lonca. Eighty percent of patients with prior CAR T-cell therapy had a known CD19 status and 78% were positive. Of the 98 patients with CAR T-cell therapy as their only anti-CD19 therapy, 81 (83%) had known CD19 status, and 67 (83%) were CD19-positive. Among the 19 patients who received Tafasitamab/lenalidomide as the only anti-CD19 therapy, 4 (21%) had known CD19 status, and all were CD19-positive. Fourteen patients had received both tafasitamab/lenalidomide and CAR-T cell therapy prior to Lonca, 9 of whom had known a CD19 status, and 4 (45%) were CD19-positive.

Outcomes

Median follow up time was 12.5 months (range 0.1 – 24.1 months). The CRR was 14% (95% CI:10- 20%) and ORR was 32% (95% CI:26-39%) with median duration of treatment of 42 days. Among evaluated clinicopathologic characteristics, HGBL and bulky disease were significantly

associated with inferior response rates. Those with HGBL demonstrated a CRR and ORR of 3% and 8%, respectively, compared to 15% and 34% in patients without HGBL (**Table 2**). There was no statistically significant difference in CRR or ORR between BCL-2/MYC and BCL-6/MYC patients. Similarly, patients with bulky disease had a CRR and ORR of 0% and 16% compared to 16% and 35% in those patients without bulky disease. Elevated LDH at time of Lonca start was also associated with statistically significant inferior response with CRR/ORR of 8/25% compared to CRR/ORR of 30/51% in patients with normal LDH. A complete response to the last therapy prior to Lonca therapy (CR 63% vs 9% and ORR 75% vs 28%) and a non-GCB subtype (CR 25% vs 6% and ORR 43% vs 24%) were associated with significantly superior response to Lonca. When accounting for double-hit patients, non-GCB subtype remained significant with CR/ORR of 23%/40% compared to 7%/26% in the germinal center B-cell (GCB) cohort (p-value 0.04 for CR). These findings are visually summarized in Figure 1. Aside from the higher proportion of HGBL among the GCB subtype, there were no statistically significant differences in baseline characteristics according to GCB vs non-GCB subtype. However, a higher proportion of non-GCB patients had a CR as best response to therapy prior to Lonca (15% vs 5%, p = 0.04). Multivariate logistic regression corroborated these findings **(Table 3)**.

Notably, in our cohort, CD19 status as assessed by institutional standards. Prior CAR T-cell therapy, number of prior lines of therapy, and age (< or ≥ 75 years) were not significantly associated with response rates. Patients with CD19-negative disease had an ORR and CR rate of 26% and 21%, respectively. However, with respect to *time* from CAR T-cell therapy to Lonca, those who received Lonca within 100-days had significantly lower CRR (0% vs 13%, p-value: 0.04) and ORR (15% vs 35%). Of note, patients requiring Lonca within 100 days were almost uniformly refractory to CAR T-cell therapy (18/20, 90%).

The median EFS and OS were 2.1 and 4.6 months, respectively (**Figure 2**). Similar high-risk features including HGBL, bulky disease, and elevated LDH were associated with significantly inferior survival (**Table 4**). Both a complete response prior to Lonca (median not reached vs 1.9 months, p <0.01) and non-GCB subtype (median 2.8 vs 1.8 months, p-value: 0.04) were associated with significantly superior EFS. However, when accounting for enrichment of the GCB subgroup with double hit patients, the difference was no longer significant with median EFS of 2.7 vs 2.1 months (p-value: 0.2) in patients with non-GCB and GCB subtypes, respectively. Multivariate cox regression for EFS and OS is displayed in **Supplementary Table 1.**

Again, CD19 status and prior CAR T-cell therapy were not associated with a significant difference in EFS or OS. Stratified by response to Lonca, patients achieving a CR to Lonca demonstrate significantly superior survival compared to those patients who fail to achieve CR (median EFS not reached vs 1.8 months, p-value <0.001 and median OS 12.6 vs 3.9 months, p <0.001) (**Figure 3**).

Data was collected for 5 pre-specified adverse events (AEs) including pleural and pericardial effusion, edema, rash, and cytopenia of any kind (**Table 5**). Thirty-five percent of patients were reported to experience at least one AE with 14% discontinuing due to an AE. Cytopenias were

both most commonly reported (17%) and the most cited cause of discontinuation (7%). Peripheral edema was reported in 11% of patients.

Data was obtained for 53 (28%) patients who received additional therapies after Lonca. The most common subsequent therapy was immunochemotherapy (31%). Six (10%) patients received CAR T-cell therapy with a CR in 3 (CRR 50%), and 10 (17%) received tafasitamab/lenalidomide with a CRR of 10%. Additionally, 4 patients received Lonca as bridge to CAR T-cell therapy and were excluded from all other analyses. In these 4 patients, the ORR to Lonca was 25% and CR rate to subsequent CAR T-cell therapy was 50% with a median OS of 6.0 months.

Discussion

In our study, we found outcomes were inferior compared to those reported in the pivotal LOTIS-2 study. Our cohort was enriched with higher risk and more heavily pretreated patients including HGBL, bulky disease, and >3 lines of prior therapy which likely contributed to the inferior outcomes reported here. Although small in numbers, our analysis also included patients who would have been excluded from the prospective clinical trial according to ECOG performance status, renal function, bulky disease and CD19-negative status, accounting for 47% of our cohort. A retrospective analysis which included 40 patients treated with Lonca in the real world setting has demonstrated comparable outcomes in the real world setting with a mEFS and mOS of 3.0 and 4.7 months, respectively (Nastoupil et al, ASH 2023).

We performed a subset analysis of those patients who would have been potentially LOTIS-2 eligible. This analysis included 100 (53%) patients with an ORR/CRR of 34%/16% and a mEFS/mOS of 2.1/4.9 months, similar to the overall cohort described above. While these subjects were "eligible" according to available data in the electronic health records collected for this analysis, the similarly poor outcomes here likely reflect the high-risk features often prevalent in patients treated in the standard of care setting who do not make it onto prospective clinical trials such as rapidly progressive disease and need for urgent therapy which are not easily captured objectively within the medical record.

We found consistent clinicopathologic factors which were predictive of both poor response and inferior survival. Specifically, HGBL, bulky disease, and elevated LDH were predictive of poor response and inferior EFS and OS compared to patients without these characteristics. A prior subset analysis of the LOTIS-2 study did report a higher CRR of 33% in patients with HGBL-DH/TH although there were only 15 patients in this category included on the prospective study, making this data hard to interpret[20]. Notably, no patient with bulky disease in our study obtained a complete response. This is in line with initial findings in the LOTIS-1/2 study in which patients with bulky disease of ≥10cm were excluded due to lack of benefit with Lonca. While these well-accepted high-risk features should not warrant dismissal of Lonca as a potential therapy on their own, this finding should be taken into consideration when choosing the optimal candidate for Lonca.

In contrast, there were also consistent factors which predicted improved response and survival with Lonca. As one might expect, those patients who achieved a CR to the last therapy prior to Lonca demonstrated persistently favorable outcomes. Of particular interest here, seems to be the improved outcomes among those with non-GCB subtype even after accounting for the enrichment of the GCB subgroup with DH lymphoma patients. This finding is of unclear significance at this time without any clear biologic rationale, but it certainly merits further thought. Interestingly, similar observations have been noted with various polatuzumab-based regimens as well for reasons that remain not-fully elucidated[21,22].

Our current analysis is of particular importance due to the high proportion of patients receiving multiple CD19 directed therapies, with prior CAR T-cell exposure in 60% of patients compared to only 9% of those in the LOTIS-2 study. Although prior CAR T-cell therapy was associated with higher rates of CD19-negative disease (22% v 0%, p value – 0.005), the majority of patients still maintained CD19 positivity following CAR T-cell failure, as has been documented previously[23]. Similarly, a higher proportion of CD19 negativity was seen in tafasitamab-exposed patients and even more marked among patients having received both CAR T-cell therapy and tafasitamab. However, there was no significant difference in outcomes according to CD19 status prior to Lonca, consistent with other published data[24]. Regardless of CD19 status, neither prior CAR T-cell nor tafasitamab/lenalidomide exposure demonstrated statistically significant differences in outcomes. While patients should still be biopsied following progression on any CD19 directed therapy, the importance of the results remain unclear.

It should be emphasized that, while overall prior CAR T-cell exposure did not portend inferior outcomes, time from CAR T-cell treatment to Lonca is important. Patients receiving Lonca within 100 days of CAR T-cell experience poor outcomes, likely reflective of the highly aggressive nature of large B-cell lymphoma that is refractory to CAR-T therapy. This finding should inform practice in treating clinicians trying to choose therapies in this clinical setting. Alternatively, outcomes among patients >100 days from CAR T-cell therapy mirrored those of the general cohort.

Our study is limited by the often-cited and well-recognized limitations of retrospective studies including, but not limited to, unmeasured confounders and selection bias. Lonca treatment was determined according to the treating physician and was variable both between institutions and clinicians. Furthermore, treatment response was determined according to institutional protocol with either PET-CT scan or CT scan alone. Details regarding adverse events were imperfectly collected as these were extracted from clinic notes and electronic documentation and were not regulated in a prospective manner. As such, the likely rate of adverse events is potentially higher than reported here.

In addition, CD19 status was not uniformly collected or standardized. Our data reflects CD19 status collected by both flow cytometry and immunohistochemistry (IHC) and, at this time, it remains unclear if the method of detection matters[24]. Prior data demonstrates that CD19 status by IHC is not predictive of response to Lonca, but the importance of CD19 status by flow cytometry is unknown.

There continue to be gaps in clinical data regarding the proper sequencing of therapies in relapsed DLBCL as we have no prospective, direct comparisons between many of the newly approved novel agents. As is seen with other agents, real-world outcomes here fall short of those reported on the clinical trial examining Lonca in R/R DLBCL. However, this study offers insight into the appropriate patients who may derive durable remissions with this overall well-tolerated therapy. It is possible that with better patient selection and with combination therapies currently under investigation with Lonca, we will see better outcomes in the future.

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Table 1. Baseline demographic and clinicopathologic characteristics.

Factor	N (%)	LOTIS-2	Factor	N (%)	LOTIS-2
Age, years (N=177)			Histology (N=160)		
<65	72 (39)	65 (45)	HGBL	36 (22)	11 (8)
65-75	66 (33)	59 (41)	DH/TH	32 (20)	15 (10)*
>75	39 (21)	21 (14)	De novo DLBCL	85 (53)	--
			Transformed DLBCL	28 (18)	29 (20)
Sex (N=187)			Cell of Origin – Hans (N=157)		
Female	68 (36)	60 (41)	GCB	96 (61)	48 (33)
Male	119 (64)	85 (59)	Non GCB	61 (38)	23 (16)
Race (N=169)		--	Double Expressor (N=155)		
African American	14 (8)		Yes	61 (39)	20 (14)
Asian	11 (7)		No	94 (61)	
White	144 (85)				
Disease Stage (N=184)			CD19 Status (N=128)		
I-II	23 (14)	33 (23)	Positive	109 (85)	145 (100)
III-IV	161 (86)	112 (77)	Negative	19 (15)	0 (0)
			Post CAR-T cell Therapy (N=90)		
			Positive	70 (78)	
			Negative	20 (22)	
IPI (N=111)		--	Lonca Line of Therapy (N=187)		
<3	39 (35)		2-3rd	36 (19)	98 (68)
3-5	72 (65)		4th and beyond	151 (81)	47 (32)
ECOG (N=150)			Primary Refractory Disease (N=187)		
0-2	111 (74)	145	Yes	47 (25)	29 (20)
3-5	39 (26)	(100)	No	140 (140)	
		0 (0)			
Bulky Disease (N=186)			Prior ASCT (N=187)		
<10cm	154 (83)	137 (94)	Yes	31 (16)	21 (14)
≥10cm	32 (17)	8 (6)	No	156 (84)	
			Median time from ASCT (months)	26	
CNS Involvement (N=169)			Prior CAR-T Cell Therapy (N=187)		
Yes	12 (7)	0 (0)	Yes	112 (60)	13 (9)
No	157 (93)	145	No	75 (40)	132 (91)
		(100)	CAR T as second line	11 (10)	
			Median time from CAR T (months)	7.7	
			Last best response prior to Lonca (N=187)		--
			CR	16 (9)	
			PR	15 (8)	
			SD	12 (6)	
			PD	144 (77)	

*Includes former BCL-6/MYC definition of double hit

Table 2. Response rates by baseline characteristics.

Factor	ORR (%)	p	CR (%)	p
Overall	32	-	14	-
HGBL				
Yes	8	0.003	3	0.05
No	34		15	
COO				
nonGCB	43	0.02	25	0.001
GCB	24		6	
Bulky Disease				
Yes	16	0.04	0	0.009
No	35		16	
Elevated LDH				
Yes	25	0.001	8	0.0001
No	51		30	
Response prior to lonca				
CR	75	<0.001	63	<0.001
<CR	28		9	
CD19 Status				
Positive	32	0.62	14	0.48
Negative	26		21	
Prior CAR T-cell				
Yes	30	0.54	15	0.54
No	35		12	
Prior Tafasitamab				
Yes	27	0.65	6	0.24
No	33		16	
# Prior Therapies				
>3	33	0.74	14	0.83
≤3	30		13	
Age >75				
Yes	32	0.08	14	0.89
No	26		21	

HBGL: high grade B cell lymphoma, COO: cell of origin, nonGCB: non-germinal center B-cell, GCB: germinal center B-cell, LDH: lactate dehydrogenase, CR: complete response, ORR: overall response rate. Bulky disease defined as <10cm.

Table 3. Multivariate logistic regression of response rates

Factor	CR Adjusted Odds Ratio	p	ORR Adjusted Odds Ratio	p
nonGCB	4.2	0.05	1.7	0.22
Elevated LDH	0.3	0.08	0.5	0.11
HGBL	0.3	0.14	0.4	0.04
Bulky disease	NA (no patients with CR)	-	0.3	0.10
CR prior to Lonca	4.0	0.002	15.2	0.01

HBGL: high grade B cell lymphoma, nonGCB: non-germinal center B -ell, GCB: germinal center B cell, LDH: lactate dehydrogenase, CR: complete response, ORR: overall response rate. Bulky disease defined as <10cm.

Table 4. Survival by baseline characteristics.

Factor	Median EFS (mo)	p	Median OS (mo)	p
HGBL				
Yes	0.7	<0.001	1.9	0.002
No	2.2		4.8	
Cell of origin				
nonGCB	2.8	0.04	5.7	NS
GCB	1.8		3.7	
Bulky disease				
Yes	1.1	0.004	3.1	0.004
No	2.2		5.4	
Elevated LDH				
Yes	1.8	<0.001	3.7	<0.001
No	5.5		9.8	
Response prior to lonca				
CR	NR	<0.001	10.8	0.008
<CR	1.9		4.5	

HBGL: high grade B cell lymphoma, nonGCB: non-germinal center B-cell, GCB: germinal center B cell, LDH: lactate dehydrogenase, CR: complete response, mo: months. Bulky disease defined as <10cm

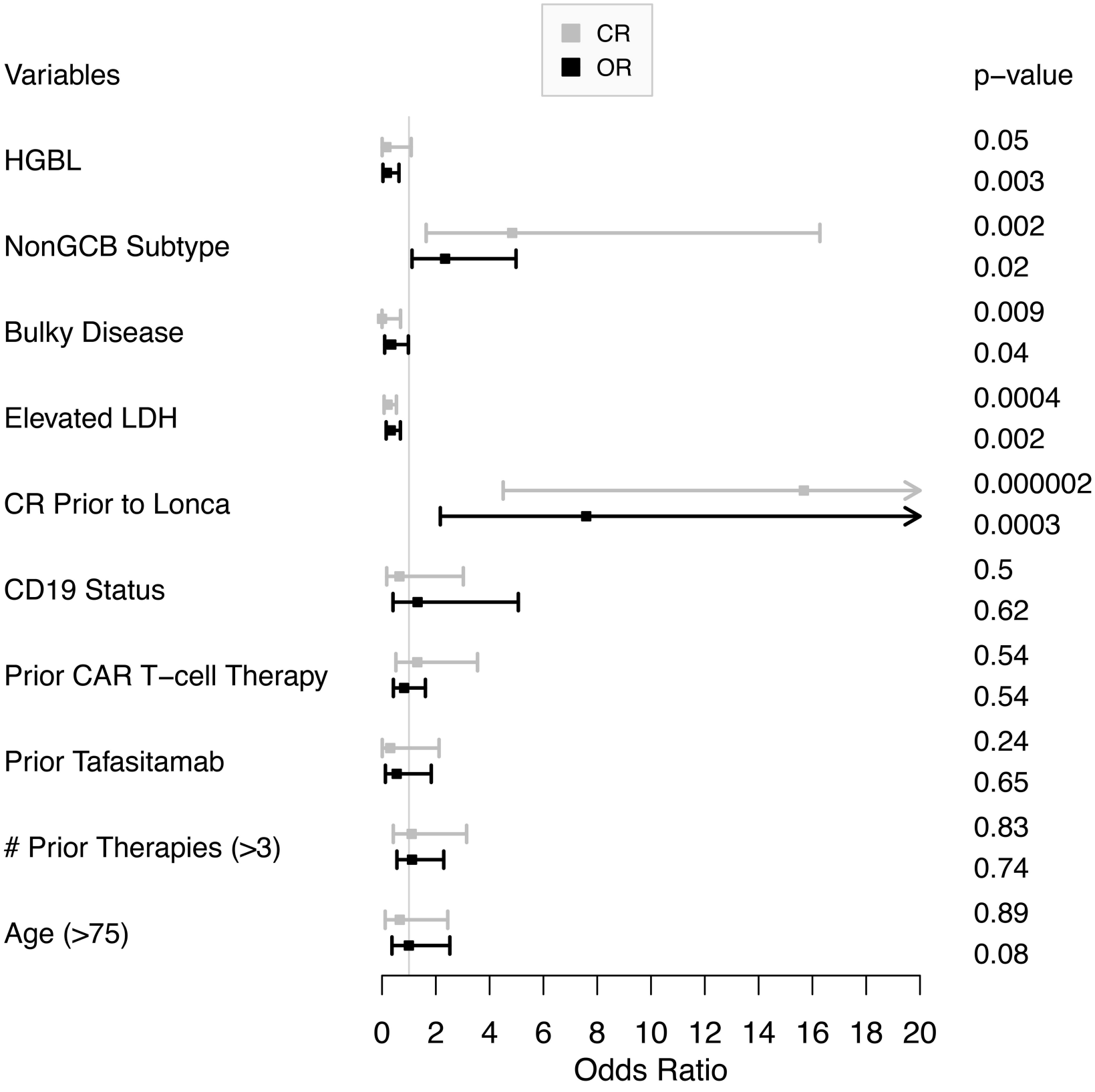
Table 5. Adverse events of interest.

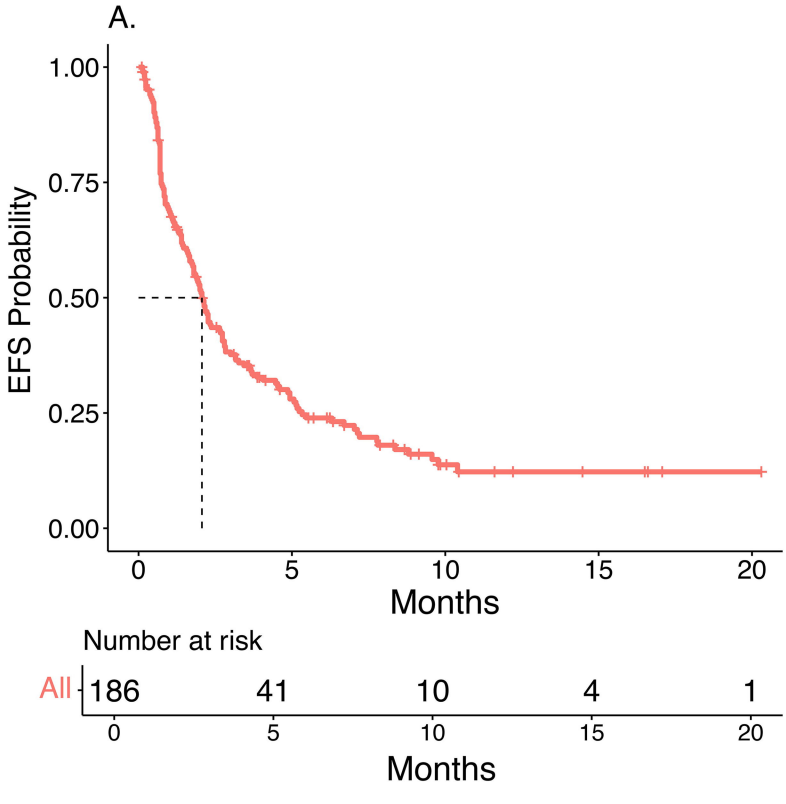
Adverse Event	Incidence (%)	Main reason for discontinuation
Pleural effusion	6 (3)	1(<1)
Peripheral edema	21 (11)	7 (4)
Pericardial effusion	1 (<1)	0 (0)
Rash	18 (10)	7 (4)
Cytopenia	31 (17)	13 (7)

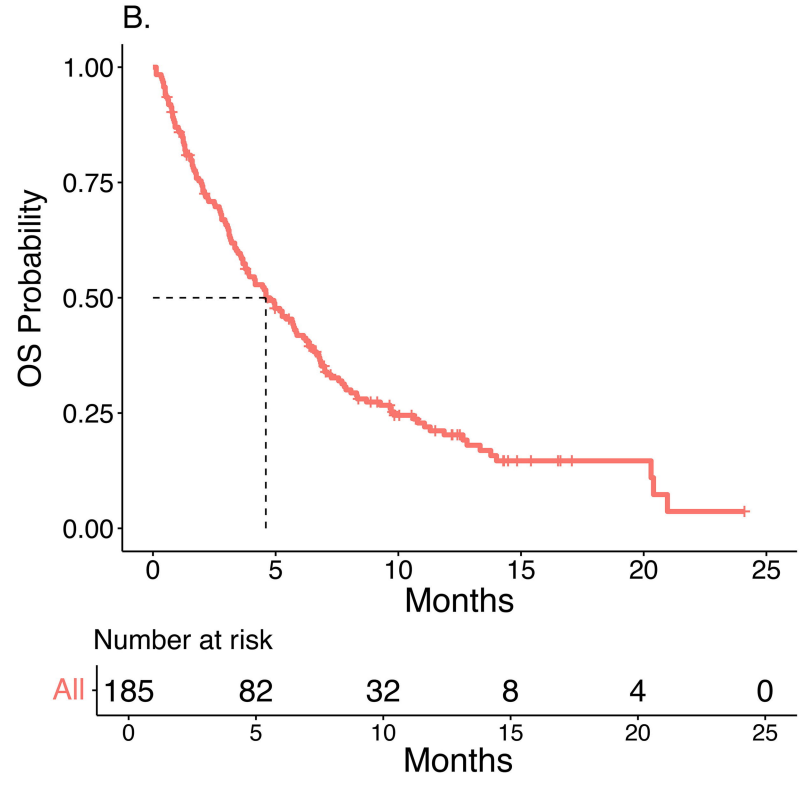
Figure Legends:
Figure 1: Forest plot for CR/OR by clinicopathologic features at treatment start. (CR: complete response, OR: overall response)

Figure 2. Outcome analysis. (A) EFS for all patients. (B) OS for all patients. (EFS: event free survival, OS: overall survival)

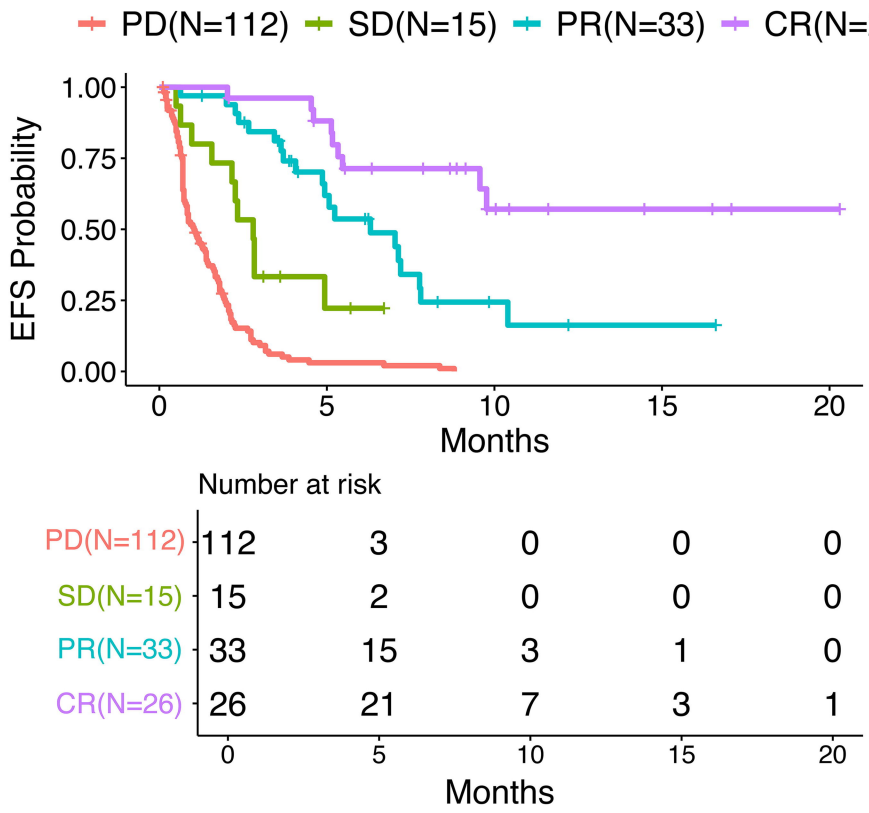
Figure 3. Outcomes stratified by response to Lonca. EFS (A) and OS (B). Median EFS for CR, PR, SD, and PD is not reached (NR) (9.6-NR), 6.3(4.9-10.4), 2.8(2.2-NR), and 0.9(0.7-1.4) months respectively. Median OS for CR, PR, SD, and PD is 12.6 (10.6-NR), 7.6 (6.2-NR), 5.3 (3.6-NR), and 2.8(2.0-3.3) months respectively. (EFS: event free survival, OS: overall survival, PD: progression of disease, SD: stable disease, PR: partial response, CR: complete response)


CR
OR
Variables
p−value
HGBL
0.05
0.003
NonGCB Subtype
0.002
0.02
Bulky Disease
0.009
0.04
Elevated LDH
0.0004
0.002
CR Prior to Lonca
0.000002
0.0003
CD19 Status
0.5
0.62
Prior CAR T−cell Therapy
0.54
0.54
Prior Tafasitamab
0.24
0.65
Prior Therapies (>3)
0.83
0.74
Age (>75)
0.89
0.08
0 2 4 6 8 10 12 14 16 18 20
Odds Ratio

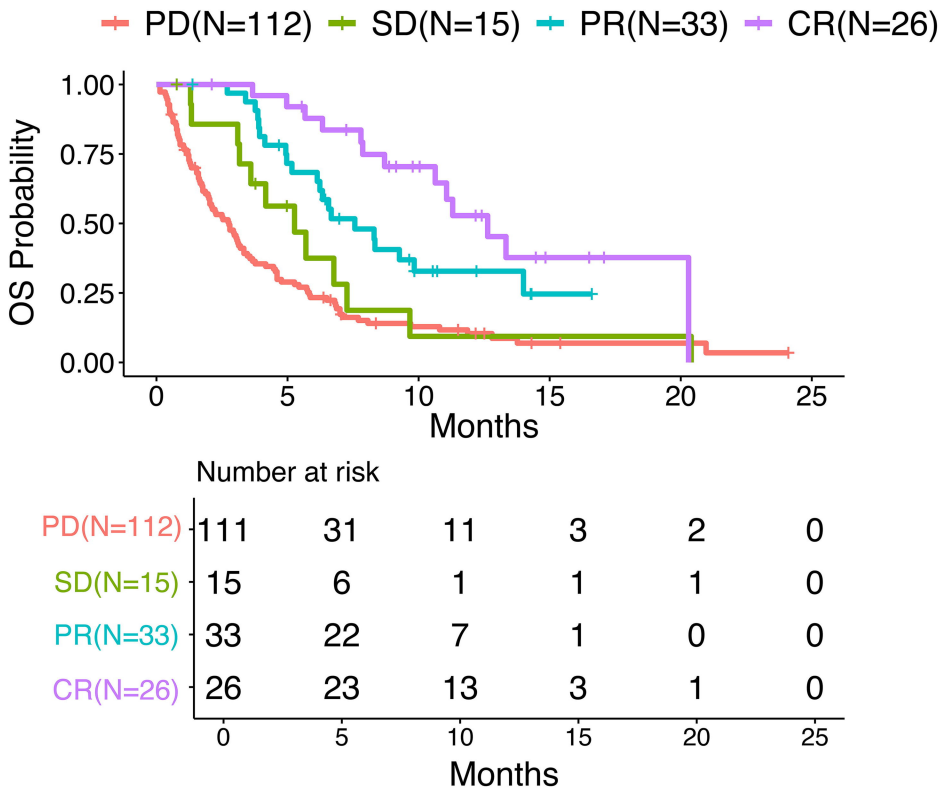

A.
1.00
0.75
0.50
0.25
0.00
EFS Probability
0
5
10
15
20
Months
Number at risk
All
186
41
10
4
1
0
5
10
15
20
Months


B.
1.00
0.75
0.50
0.25
0.00
OS Probability
0
5
10
15
20
25
Months
Number at risk
All
185
82
32
8
4
0
0
5
10
15
20
25
Months

A.


PD(N=112)
SD(N=15)
PR(N=33)
CR(N=26)
EFS Probability
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
Months
Number at risk
PD(N=112) 112 3 0 0 0
SD(N=15) 15 2 0 0 0
PR(N=33) 33 15 3 1 0
CR(N=26) 26 21 7 3 1
0
5
10
15
20
Months

B.


PD(N=112)
SD(N=15)
PR(N=33)
CR(N=26)
OS Probability
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
Months
Number at risk
PD(N=112) 111 31 11 3 2 0
SD(N=15) 15 6 1 1 1 0
PR(N=33) 33 22 7 1 0 0
CR(N=26) 26 23 13 3 1 0
0
5
10
15
20
25
Months

Supplementary Table 1. Univariate and multivariate cox regression for OS and EFS

Factor	OS Univariate		OS Multivariate		EFS Univariate		EFS Multivariate	
	HR	p	HR	p	HR	p	HR	p
HGBL	1.92	0.001	2.71	<0.001	2.62	<0.001	2.08	0.003
nonGCB	0.73	0.10			0.68	0.04	0.82	0.34
Bulky disease	1.83	0.005	1.78	0.48	1.91	0.002	1.67	0.03
Elevated LDH	2.57	<0.001	1.62	0.05	2.27	<0.001	1.82	0.02
CR prior to Lonca	0.40	0.01	0.16	0.01	0.23	<0.001	0.16	0.01
CD19 status (+)	0.89	0.75			0.62	0.18		
Prior CAR T-cell	1.40	0.06			0.95	0.75		
Prior Tafasitamab	1.79	0.03	0.82	0.48	1.24	0.41		
# Prior therapies (>3)	1.28	0.27			1.20	0.42		
Age > 75	0.77	0.22			0.67	0.06		
OS: overall survival, EFS: event free survival, nonGCB: non-germinal B-cell								