Loncastuximab tesirine versus glofitamab for the treatment of relapsed/refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy: a matching-adjusted indirect comparison

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CONCLUSIONS

To our knowledge, this is the first comparative analysis between loncastuximab tesirine and glofitamab. While accounting for the known matching-adjusted indirect comparison (MAIC) limitations, in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) after ≥2 systemic therapies, these analyses show no evidence of a difference between the treatments for all assessed efficacy endpoints (overall response rate [ORR], duration of response [DOR], duration of complete response [DOCR], progression-free survival [PFS], overall survival [OS]), except complete response (CR) which was higher with glofitamab, but this did not lead to differences in long term endpoints such as PFS and OS. Safety comparisons show few differences between the treatments, in line with their known safety profiles.

INTRODUCTION

- Diffuse large B-cell lymphoma (DLBCL) is the most prevalent type of malignant lymphoma with up to 40% of patients experiencing R/R disease after initial treatment (1).
- There are limited treatment options for patients with R/R DLBCL who have previously received two or more lines of systemic treatment, and hence prognosis remains poor in this population (2-4).
- Loncastuximab tesirine and glofitamab are two novel treatments recently approved in third-line R/R DLBCL (5, 6).
  - Loncastuximab tesirine is a CD19-targeted antibody drug conjugate (ADC), delivering a potent and cytotoxic pyrrolobenzodiazepine (PBD) dimer alkylating agent through a stable and protease-cleavable linker (7).
  - Glofitamab is a T-cell engaging bispecific antibody (Ab) with a novel 2:1 configuration that enables bivalent binding to CD20 on B cells and monovalent binding to CD3 on T cells (8).

OBJECTIVE

- Given that there are no head-to-head trials of loncastuximab tesirine versus glofitamab in adult patients with R/R DLBCL after two or more systemic therapies, the objective of this analysis was to conduct a MAIC to evaluate their relative efficacy and safety.

METHODS

- A systematic literature review identified LOTIS-2 (loncastuximab tesirine trial, NCT03589469) and NP30179 (glofitamab trial, NCT03075696) for inclusion in an indirect comparison.
- Both trials were single-arm and had similar inclusion criteria, and therefore unanchored MAICs were conducted to compare the relative effect of the treatments.
- Baseline variables that were identified as having the potential to impact patient outcome included age, histology (high-grade B-cell lymphoma [HGBL] vs non-HGBL), disease stage (I–II vs III–IV), Eastern Cooperative Oncology Group status (0 vs 1), previous systemic therapy (<3 vs ≥3 lines) and refractory status. Baseline characteristics are summarised in Table 1.
- To reduce potential bias associated with the cross-study comparisons, baseline variables with potential prognostic impact were adjusted to ensure more closely matched patient characteristics for both efficacy and safety comparisons.
- This was done by re-weighting the available individual patient data (IPD) for loncastuximab tesirine to match the average baseline characteristics of glofitamab for which only aggregate data are reported.
- Hazard ratios (HRs) were calculated for survival outcomes and odds ratios (ORs) for response and safety outcomes. The standard error for HR and OR MAIC estimates were calculated using a bootstrap or sandwich estimator, respectively.
- Endpoints of interest were response rates (ORR, CR and partial response [PR]), DOR, DOCR, PFS, OS, and key safety outcomes.

Table 1: Summary of baseline characteristics included in the MAIC analyses

Characteristic	Description	LOTIS-2	NP30179
Treatment (N)	-	Loncastuximab tesirine (N = 145)	Glofitamab (N = 154)†
Line of treatment data is for	-	3L+	3L+
Age, median years [IQR] <range>	-	66 [56, 71] <23, 94>	66 [NR] <21, 90>
Gender, n (%)	Male	85 (59)	100 (65)
Histology, n (%)	DLBCL, not o/w specified	127 (88)	110 (71)
	HGBL	11 (8)	11 (7)
GCB or ABC DLBCL, n (%)	GCB	48 (33)	NR
	ABC/non-GCB	23 (16)	NR
	Unknown	74 (51)	NR
Double-hit or triple-hit DLBCL, n (%)	-	15 (10)	NR
Double-expressor or triple-expressor DLBCL, n (%)	-	20 (14)	NR
Bulky disease, n (%)	Yes	≥10 cm: 8 (6)	>6 cm: 64 (42); >10 cm: 18 (12)
	No	137 (94)	NR
Extranodal disease, n (%)	-	50 (34.5)	95 (61.3)
Disease stage (Ann Arbor), n (%)	I–II	33 (23)	35 (23)
	III–IV	112 (77)	116 (75)
ECOG PS, n (%)	0	58 (40)	69 (45)
	1	78 (54)	84 (55)
	2	9 (6)	NA
IPI score, n (%)	≤2	70 (48)	NR
	>2	75 (52)	NR
Previous systemic therapy, n (%)	Median [IQR] <range>	3 [1, 4]	3 <2, 7>
	2 lines	63 (43)	62 (40)
	3 lines	35 (24)	≥3 lines: 92 (60)
	4 lines	47 (32)	
Response to 1st line, n (%)	Relapse	99 (68)	NR
	Refractory	29 (20)‡	90 (58)¶
	Other	17 (12)	NR
Response to most recent line of systemic therapy, n (%)	Relapse	43 (3)	NR
	Refractory	84 (58)‡	132 (86)
	Other	18 (12)	NR
Previous HSCT, n (%)	Allogeneic	2 (1)	NA
	Autologous	21 (14)	28 (18)
	Both	1 (1)	NA
Previous CAR T-cell therapy, n (%)	Yes	13 (9)	51 (33)
	No	132 (91)	NR

†Only reported for safety population of 154/155 patients enrolled; ‡Defined as no response to treatment; ¶Defined as no response or progression or relapse within 6 months of anti-lymphoma therapy end date.

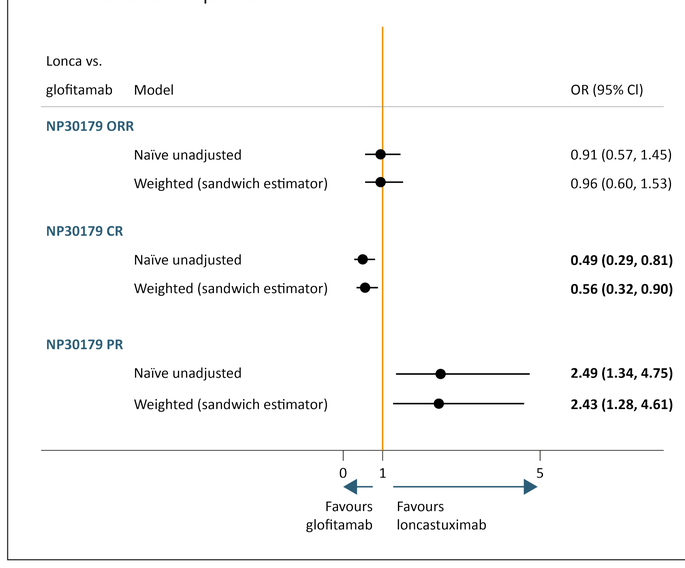
Abbreviations: 3L+, third- or later-line; ABC, activated B-cell; CAR T, Chimeric antigen receptor T; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal centre B-cell; HGBL, high grade B-cell lymphoma; HSCT, haematopoietic stem-cell transplantation; IPI, International Prognostic Index; IQR, interquartile range; MAIC, matching-adjusted indirect comparison; NA, not applicable; NR, not reported; o/w, otherwise.

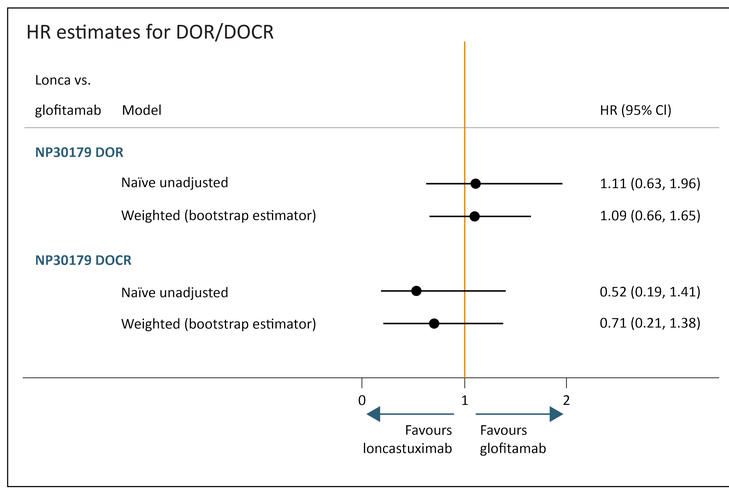
RESULTS

Efficacy results

- The results of the naïve unadjusted and weighted efficacy comparisons and MAIC analyses comparing loncastuximab tesirine and glofitamab are summarised in Figure 1, Figure 2, and Table 2.
- No statistically significant treatment differences were observed between loncastuximab and glofitamab for ORR, DOR, DOCR, PFS, and OS (Table 2).
- Patients treated with glofitamab had significantly greater odds of achieving a CR, but this did not lead to significant differences in long term endpoints such as PFS and OS.
- Results from the naïve unadjusted and weighted analyses were very similar.

Figure 1: Forest plots showing OR estimates for response and HR estimates for DOR/DOCR, for naïve unadjusted and weighted (sandwich or bootstrap) estimators

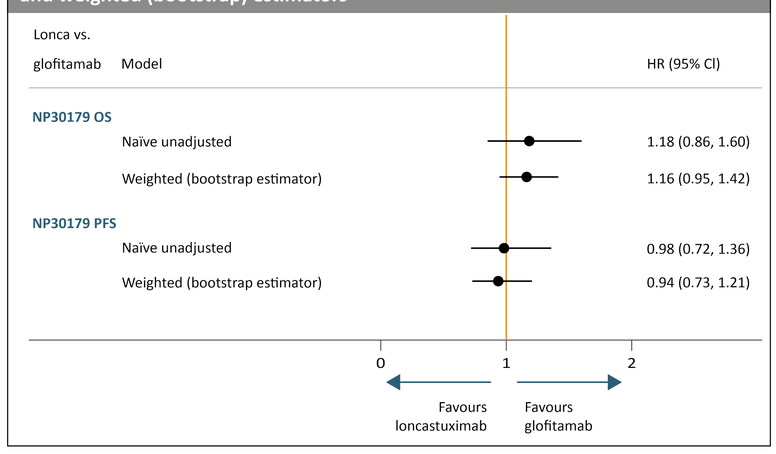




Bold font = statistically significant benefit for patients receiving glofitamab. HR<1.0 favours loncastuximab tesirine, with a reduced hazard of an event (loss of response) and OR>1.0 favours loncastuximab tesirine, with higher odds of achieving a response.

Abbreviations: CI, confidence interval; CR, complete response; Lonca, loncastuximab tesirine; DOCR, duration of complete response; DOR, duration of response; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PR, partial response.

Figure 2: Forest plots showing HR estimates for OS and PFS, for naïve unadjusted and weighted (bootstrap) estimators



HR<1.0 favours loncastuximab tesirine, with a reduced hazard of an event (progression or death).
Abbreviations: CI, confidence interval; HR, hazard ratio; Lonca, loncastuximab tesirine; OS, overall survival; PFS, progression-free survival.

Table 2: Efficacy results of the MAIC analyses (loncastuximab tesirine vs glofitamab)

Outcome	Loncastuximab tesirine unadjusted†			Glofitamab			Loncastuximab tesirine versus glofitamab	
	N	Events, n (%)	Median (months)	N	Events, n (%)	Median (months)	Naïve unadjusted	Weighted comparison‡¶
Response outcomes: OR (95% CI)								
ORR	134	66 (49)	NA	155	80 (52)	NA	0.91 (0.57, 1.45)	0.96 (0.60, 1.53)
CR	134	33 (25)	NA	155	62 (40)	NA	**0.49 (0.29, 0.81)**	**0.56 (0.32, 0.90)**
PR	134	33 (25)	NA	155	18 (12)	NA	**2.49 (1.34, 4.75)**	**2.43 (1.28, 4.61)**
Time-to-event outcomes: HR (95% CI)								
DOR (event = PD/death)	66	21 (32)	13.4 (6.9, NE)	80	NR	18.4 (13.7, NE)	1.11 (0.63, 1.96)	1.09 (0.66, 1.65)
DOCR (event = PD/death)	33	5 (15)	NE (13.4, NE)	62	NR	26.9 (19.8, NE)	0.52 (0.19, 1.41)	0.71 (0.21, 1.38)
PFS (event = recurence/ PD/death)	134	65 (49)	6.0 (2.9, 11.2)	155	NR	4.9 (3.4, 8.1)	0.98 (0.72, 1.36)	0.94 (0.73, 1.21)
OS (event = death)	134	89 (66)	9.9 (6.7, 11.6)	155	NR	11.5 (7.9, 15.7)	1.18 (0.86, 1.60)	1.16 (0.95, 1.42)

Bold font = statistically significant difference between treatments. HR<1.0 favours loncastuximab tesirine; OR>1.0 favours loncastuximab tesirine for efficacy and OR<1.0 favours loncastuximab tesirine for safety outcomes.

†Two patients with ECOG PS 2 and nine patients with prior alloSCT were excluded from the LOTIS-2 ITT population (n=145) for the comparison with glofitamab; ‡Bootstrap or sandwich estimate for variance; ¶ESS for efficacy for loncastuximab tesirine group: 129.4 / DOR: 63.3 / DOCR: 29.9 / safety: 133.5.

Abbreviations: AlloSCT, allogenic stem cell transplant; CI, confidence interval; CR, complete response; DOCR, duration of complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; HR, hazard ratio; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; N, sample size; NA, not applicable; NE, not evaluable; NR, not reported; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response.

Safety results

- Safety results significantly favoured loncastuximab for serious adverse event (SAE): cytokine release syndrome (CRS), and significantly favoured glofitamab for treatment discontinuation due to treatment-emergent adverse events (TEAEs); Grade 3–4: any adverse events (AEs), gamma glutamyl transferase (GGT) elevation and thrombocytopenia.
- Numerically higher odds of Grade 3–4: anaemia and febrile neutropenia were observed with loncastuximab treatment, and numerically higher odds of any grade infections; Grade 3–4: infections, neutropenia, and tumour lysis syndrome were observed with glofitamab treatment, although none of these differences were statistically significant.
- There were no notable differences between treatments for fatal AEs and SAEs.

Table 3: Comparison of safety outcomes: loncastuximab tesirine (LOTIS-2) vs glofitamab (NP30179)

Outcome	Loncastuximab tesirine, n (%)		Glofitamab, n (%) (N=154)	Loncastuximab tesirine versus glofitamab, odds ratio (95% CI)		
	Unadjusted (N=134)	Weighted (N=133.5)		Naïve unadjusted	Weighted comparison‡¶	Weighted comparison (sandwich estimator)
Treatment discontinuation due to TEAEs	35 (26.1)	35.3 (26.4)	14 (9.1)	**3.54 (1.84, 7.12)**	**3.59 (1.87, 7.22)**	**3.59 (1.82, 7.06)**
Any grade infection	44 (33)	44.2 (33.1)	59 (38)	0.79 (0.48, 1.28)	0.80 (0.49, 1.29)	0.80 (0.49, 1.30)
AE Grade 3–4						
Any AE, Grade 3–4	97 (72.4)	95.7 (71.7)	87 (56.5)	**2.02 (1.23, 3.31)**	**1.95 (1.20, 3.21)**	**1.95 (1.18, 3.21)**
Anaemia	12 (9.0)	11.3 (8.5)	10 (6.5)	1.42 (0.59, 3.39)	1.33 (0.55, 3.28)	1.33 (0.55, 3.21)
Cytokine release syndrome†	0 (0)‡	0 (0)‡	6 (3.9)	0.08 (0.005, 1.52)¶	0.09 (0.005, 1.53)¶	-
Febrile neutropenia	4 (3.0)	4.0 (3.0)	4 (2.6)	1.15 (0.28, 4.71)	1.15 (0.27, 4.95)	1.15 (0.28, 4.74)
GGT elevation	28 (20.9)	27.3 (20.4)	4 (3)	**9.91 (3.75, 34.2)**	**9.64 (3.64, 33.3)**	**9.64 (3.26, 28.5)**
Infections	11 (8.2)	11.3 (8.4)	23 (15)	0.51 (0.23, 1.07)	0.52 (0.24, 1.09)	0.52 (0.24, 1.13)
Neutropenia	35 (26.1)	34.0 (25.5)	41 (26.6)	0.97 (0.58, 1.65)	0.94 (0.55, 1.59)	0.94 (0.55, 1.60)
Thrombocytopenia	23 (17.2)	21.9 (16.4)	12 (7.8)	**2.45 (1.17, 5.14)**	**2.32 (1.12, 5.04)**	**2.32 (1.10, 4.90)**
Tumour lysis syndrome	0 (0)	0 (0)	2 (1.3)	0.23 (0.01, 4.77)¶	0.23 (0.01, 4.78)¶	-
SAEs						
Any SAE	49 (36.6)	48.3 (36.2)	73 (47.4)	0.64 (0.40, 1.03)	0.63 (0.39, 1.01)	0.63 (0.39, 1.01)
Cytokine release syndrome†	0 (0)	0 (0)	32 (20.8)	**0.01 (0.001, 0.23)¶**	**0.01 (0.001, 0.23)¶**	-
Fatal AEs	5 (3.7)	4.9 (3.7)	8 (5.2)	0.71 (0.23, 2.22)	0.70 (0.21, 2.16)	0.70 (0.22, 2.21)
Sepsis	0 (0)	0 (0)	6 (3.9)	0.08 (0.005, 1.52)¶	0.09 (0.005, 1.53)¶	-

Bold font = statistically significant difference between treatments: OR<1.0 favours loncastuximab tesirine; OR>1.0 favours glofitamab.

†Graded according to the approach of ASTCT; ‡Only 1 patient experienced this AE and this event was Grade 1; ¶Zero loncastuximab events make it difficult to accurately estimate the OR; OR estimated using a continuity correction of 0.5 for patients with events / without events in both treatment arms.

Abbreviations: AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CI, confidence interval; GGT, gamma glutamyl transferase; OR, odds ratio; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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