Loncastuximab tesirine versus polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL after ≥2 lines of therapy: matching-adjusted indirect comparison

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SUPPLEMENTARY INFORMATION

Methods

Systematic literature review

A systematic literature review (SLR) was conducted in October 2022 to identify clinical data on loncastuximab tesirine (Lonca) and polatuzumab vedotin + bendamustine and rituximab (Pola+BR), including randomized controlled trials (RCTs), single-arm trials and real-world evidence (RWE) related to the treatment of patients with diffuse large B-cell lymphoma (DLBCL). The Ovid platform was used to search Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) on October 25, 2022. The database searches were complemented by hand-searching of conference proceedings (2019-2022), clinical trial registries, and previous health technology assessment (HTA) submissions. The bibliographic reference lists of included studies and relevant SLRs and HTA documents were screened. Additional databases including EQ-5D (www.euroqol.org), HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA [http://www.inahta.org/]), and NIHR Health Technology Assessment (NIHR HTA [http://www.hta.ac.uk/]) were also hand-searched in November 2021. The pre-specified population, intervention, comparator, outcomes, and study design (PICOS) elements used to assess study eligibility are detailed in Table S1, and Table S2 summarizes the inclusion/exclusion criteria in the studies included in the matching-adjusted indirect comparison (MAIC) analyses. Full details of the SLR search strategy are provided in Table S3 to Table S5.

All publications were screened against the predefined selection criteria in Covidence® by two independent reviewers (Table S1). Any conflicts were resolved via dialogue between the two reviewers, or arbitration was provided by a third reviewer. Data from included publications were extracted into standardized data extraction tables (DETs) in Microsoft® Excel by one reviewer, with all information checked and validated by a second independent reviewer. Quality assessment of eligible studies was performed using Cochrane Risk of Bias (RoB) 2 tool for RCTs (1) and the Risk Of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool for comparative cohort studies (2). Studies were limited to those in the English language. The SLR was performed in accordance with best practice guidelines from the Cochrane Collaboration, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the Centre for Reviews and Dissemination (CRD) (3-5).

Table S1: Summary of inclusion/exclusion criteria for SLR

Characteristics	Inclusion criteria	Exclusion criteria
Population	Patients aged 18 years or older with relapsed or refractory DLBCL or HGBL who have received two or more previous lines of systemic therapy	Patients aged <18 years Mixed populations containing <80% of the relevant population, where outcomes are not disaggregated by relevant subgroups
Intervention/ comparators	Loncastuximab tesirine (Zynlonta®) Chemoimmunotherapy regimens: ○ R-GemOx (rituximab, gemcitabine oxaliplatin) ○ R-Gem (rituximab gemcitabine) ○ R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine) ○ (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine) ○ BR (bendamustine, rituximab) ○ DHAP (cisplatin, cytarabine, dexamethasone) ○ GDP (cisplatin, gemcitabine, dexamethasone) ○ ICE (ifosfamide, carboplatin, etoposide) ○ IVE (ifosfamide, epirubicin and etoposide) ○ Selinexor (Xpovio®) (combination therapy or monotherapy) Tafasitamab (Minjuvi®) (in combination with lenalidomide or monotherapy) Polatuzumab vedotin-piiq (POLIVY®) + bendamustine + rituximab CAR-T cell therapies: ○ Axicabtagene ciloleucel (Yescarta®) ○ Tisagenlecleucel (Kymriah®) ○ Lisocabtagene maraleucel (Breyanzi®) Pixantrone monotherapy Glofitamab (combination therapy or monotherapy)	Interventions/ comparators not listed
Outcomes	Efficacy Overall survival Progression-free survival	Outcomes not listed

Characteristics	Inclusion criteria	Exclusion criteria
	Response rates Duration of response Time to response Time to progression Safety Discontinuations due to AEs Serious AEs Treatment related mortality Grade 3/4 AEs Grade 3/4 atrial fibrillation Grade 3/4 hepatotoxicity Grade 3/4 elevations in liver enzymes ALT/AST Grade 3/4 diarrhea Grade 3/4 colitis Grade 3/4 effusion Grade 3/4 oedema Hospitalizations Need for transfusions Need for growth factors	
Study design	RCTs (Phase II and above) † Multi-arm non-randomized trials Single-arm clinical trials Open label extensions or long-term follow-up trials Real-world evidence Retrospective or prospective observational studies, including cohort studies Medical record review/chart review studies Claims database analyses Patient registry analyses Case series	Phase I trials Pharmacokinetic studies Reviews/editorials/commentaries/letters SLRs/(N)MAs‡ *In vitro*/animal studies/pre-clinical studies Case reports

Characteristics	Inclusion criteria	Exclusion criteria
Date limits	No restriction	–
Countries	No restriction	–
Languages	English language publications	Non-English language publications

† Phase 1/2 trials should be included.
‡ Relevant SLRs/NMAs will be included at title/abstract screening stage so their bibliographic reference lists can be hand-searched for relevant studies.
Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B cell lymphoma; HGBL, High Grade B-cell lymphoma; NMA, network meta-analysis; PICOS, Population, Intervention, Comparison, Outcomes and Study design; RCT, randomized controlled trial; SLR, systematic literature review.

Table S2: Summary of inclusion/exclusion criteria in the studies included in the MAIC analyses

Study name [Author (Year)]	Age	DLBCL definition	Prior lines of systemic therapy	Previous chemotherapy	ECOG PS	Transplant status	Other
LOTIS-2 [Caimi 2021 (6)]	≥18	Pathologic diagnosis of R/R DLBCL by the 2016 WHO classification, to include: DLBCL not otherwise specified; primary mediastinal large B-cell lymphoma; and high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	≥2	Excluded patients if they had major surgery, radiotherapy, chemotherapy or other anti-neoplastic therapy within 14 days prior to start of study drug	0-2	Excluded patients with ASCT within 30 days prior to start of study drug or AlloSCT within 60 days prior to start of study drug	Measurable disease as defined by the 2014 Lugano Classification Availability of FFPE tumor tissue block or minimum 10 freshly cut unstained slides if block is not available
GO29365 extension study [Sehn 2022 (7)]	≥18	Histologically confirmed R/R DLBCL (excluding transformed follicular lymphoma)	≥1	No restriction	0-2	Patients were considered transplant ineligible by the treating physician or experienced treatment failure with prior ASCT	Enrolled in GO29365 RCT
Hamadani 2022b COTA database (8)	≥18	A diagnosis of DLBCL was determined based on pathologic documentation/confirmation of an initial DLBCL diagnosis	≥2	No restriction	No restriction	With or without HSCT (treatments initiated 6 months prior to HSCT or 100 days after with no progression were defined as the same line as therapy as the HSCT)	Patients were grouped by the type of treatment received in their 3L. This analysis included patients with Pola+BR or Tafa+Len in the 3L

Study name [Author (Year)]	Age	DLBCL definition	Prior lines of systemic therapy	Previous chemotherapy	ECOG PS	Transplant status	Other
Dal 2023 (9)	≥18	Histologically-evaluated R/R DLBCL	≥2	Including R-CHOP	No restriction	Ineligible for subsequent HSCT	Prior BR exposure was permitted if the patient's duration of response to BR was ≥12 months; patients with Grade ≥2 peripheral neuropathy were excluded

Abbreviations: alloASCT, allogeneic autologous stem cell transplant; ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, Formalin-fixed paraffin-embedded; HSCT, hematopoietic stem cell transplantation; MAIC, matching adjusted indirect comparison; Pola+BR, polatuzumab + bendamustine +rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RCT, randomized controlled trial; R/R, relapsed/refractory; Tafa+Len, tafasitamab + lenalidomide; WHO, World Health Organization.

Embase search strategy

Platform: Ovid

Date searched: 25/10/2022

Hits: 3,273

Table S3: Embase search string

#	Searches	Results
1	exp diffuse large b cell lymphoma/	22508
2	(DLBCL or HGBL* or HGBCL*).tw,hw,ot,kw.	22941
3	((large cell* or large-cell or b-cell or bcell or lymphoid* or histiocytic* or plasmablastic* or centroblastic* or immunoblastic*) adj3 lymphom*).tw,hw,ot,kw.	111354
4	or/1-3	111639
5	exp tumor recurrence/ or exp recurrent disease/ or exp retreatment/	281946
6	(relapse* or refractor* or "relapsed/refractory" or recur* or pretreated or pre-treated or (previously adj1 treated) or (prior adj1 therap*) or ((third or 3rd or previous or prior) adj1 line*) or 3L or 3-L).tw,hw,ot,kw.	1795120
7	or/5-6	1803778
8	4 and 7	27326
9	exp loncastuximab tesirine/	182
10	(Zynlonta* or lonca* or ADCT-402 or 1879918-31-6 or DB16222 or 7K5O7P6QIU or D11338).mp.	238
11	exp pixantrone/	279
12	(pixantron* or Pixuvri* or DB06193 or DB-06193 or BBR 2778 or BBR2778 or 144510-96-3).mp.	316
13	exp glofitamab/	120
14	(glofitamab* or DB16371 or DB-16371 or RG-6026 or RG6026 or RO-7082859 or RO7082859).mp.	137
15	exp Selinexor/	1370
16	(selinexor* or Xpovio* or DB11942 or DB-11942 or KPT-330 or KPT330 or a619044).mp.	1500
17	(chemoimmunotherap* or CIT or R-GemOx or R-Gem or (rituximab and gemcitabine) or (rituximab and oxaliplatin) or R-P-MitCEBO or (rituximab and prednisolone and mitoxantrone and cyclophosphamide and (etoposide or bleomycin) and vincristine) or R-DECC or (rituximab and dexamethasone and etoposide and chlorambucil and lomustine) or BR or R-Benda* or (bendamustine and rituximab) or DHAP or (cisplatin and cytarabine and dexamethasone) or GDP or (cisplatin and gemcitabine and dexamethasone) or ICE or (ifosfamide and carboplatin and etoposide) or IVE or (ifosfamide and epirubicin and etoposide)).mp.	151746
18	exp tafasitamab/	234
19	(Monjuvi* or Minjuvi* or tafasitamab or tafasitamab-cxix or MOR208 or Xmab5574 or L01FX12 or 1422527-84-1 or DB15044 or QQA9MLH692 or D11601).mp.	291
20	exp polatuzumab vedotin/	596

21	(Polivy* or polatuzumab* or DCDS4501A or RG7596 or polatuzumab vedotin-piiq or a619039 or L01FX14 or 1313206-42-6 or "347911301" or DB12240 or KG6VO684Z6 or D10761).mp.	758
22	exp Lisocabtagene maraleucel/	389
23	(Lisocabtagene or maraleucel or Breyanzi* or liso-cell or DB16582 or JCAR-017 or JCAR017).mp.	442
24	exp tisagenlecleucel T/	2021
25	(Tisagenlecleucel* or Kymriah* or CTL019 or CART-19 or a617053 or L01XX71 or 1823078-37-0 or DB13881 or Q6C9WHR03O or D11386).mp.	2311
26	exp axicabtagene ciloleucel/	1666
27	(Axicabtagene ciloleucel or Yescarta* or KTE-C19 or Axi-cel or a618003 or L01XX70 or DB13915 or U2I8T43Y7R or D11144).mp.	1885
28	or/9-27	156985
29	8 and 28	5275
30	exp Clinical Trial/	1744164
31	exp RANDOMIZATION/	95670
32	Single Blind Procedure/	48019
33	Double Blind Procedure/	199982
34	Crossover Procedure/	71825
35	PLACEBO/	386931
36	randomi?ed controlled trial*.tw.	298311
37	rct.tw.	49150
38	(random$ adj3 (allocat$ or assign*)).tw.	221912
39	((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.	269245
40	placebo$.tw.	350431
41	(clinical adj trial*).tw.	647861
42	((phase 2? or phase 3? or phase 4? or phase ii? or phase iii? or phase iv?) adj2 (study or studies or trial*)).tw.	174842
43	or/30-42	2632728
44	Case Study/	89326
45	case report.tw.	502701
46	letter/	1166686
47	Editorial.pt.	740747
48	Letter.pt.	1243525
49	Note.pt.	910722
50	or/44-49	3475031
51	43 not 50	2505847
52	29 and 51	2444
53	Clinical study/	160767
54	case control study/	194410

55	Family study/	25709
56	Longitudinal study/	180278
57	Retrospective study/	1327875
58	Prospective study/ not Randomized controlled trials/	794626
59	Cohort analysis/	911592
60	(Cohort adj (study or studies)).mp.	426570
61	((Case control adj (study or studies)) or case series).tw.	293175
62	(follow up adj (study or studies)).tw.	70707
63	(observational adj (study or studies)).tw.	229147
64	(epidemiologic$ adj (study or studies)).tw.	117925
65	(cross sectional adj (study or studies)).tw.	306124
66	(real adj (world or life)).tw.	154401
67	(RWE or RWD).tw.	2246
68	((single centre or single center or multi centre or multi center or multicentre or multicenter) adj2 experience).tw.	39835
69	audit.tw.	86703
70	(registry or registries).ti.	62945
71	clinical practice.ti.	48898
72	exp registries/	185190
73	exp databases/	505905
74	or/53-73	4415097
75	29 and 74	1846
76	52 or 75	3404
77	limit 76 to english language	3380
78	limit 77 to abstracts	3305
79	animal/	1591255
80	nonhuman/	7071741
81	exp animal experiment/	2913124
82	exp experimental animal/	779675
83	animal model/	1598248
84	exp rodent/	3883849
85	(rat or rats or mouse or mice).ti.	1566821
86	or/79-85	9531762
87	human/ and 86	2628814
88	86 not 87	6902948
89	78 not 88	3273

Medline search strategy

Platform: Ovid

Date searched: 25/10/2022

Hits: 570

Table S4: Medline search string

#	Searches	Hits
1	exp Lymphoma, Large B-Cell, Diffuse/	22780
2	(DLBCL or HGBL* or HGBCL*).tw,hw,ot,kf.	9496
3	((large cell* or large-cell or b-cell or bcell or lymphoid* or histiocytic* or plasmablastic* or centroblastic* or immunoblastic*) adj3 lymphom*).tw,hw,ot,kf.	75492
4	or/1-3	75711
5	exp Recurrence/ or exp Neoplasm Recurrence, Local/ or exp Retreatment/	344352
6	(relapse* or refractor* or "relapsed/refractory" or recur* or pretreated or pre-treated or (previously adj1 treated) or (prior adj1 therap*) or ((third or 3rd or previous or prior) adj1 line*) or 3L or 3-L).tw,hw,ot,kf.	1168836
7	or/5-6	1176755
8	4 and 7	12589
9	(Zynlonta* or lonca* or ADCT-402 or 1879918-31-6 or DB16222 or 7K5O7P6QIU or D11338).mp.	60
10	(pixantron* or Pixuvri* or DB06193 or DB-06193 or BBR 2778 or BBR2778 or 144510-96-3).mp.	123
11	(glofitamab* or DB16371 or DB-16371 or RG-6026 or RG6026 or RO-7082859 or RO7082859).mp.	16
12	(selinexor* or Xpovio* or DB11942 or DB-11942 or KPT-330 or KPT330 or a619044).mp.	400
13	(chemoimmunotherap* or CIT or R-GemOx or R-Gem or (rituximab and gemcitabine) or (rituximab and oxaliplatin) or R-P-MitCEBO or (rituximab and prednisolone and mitoxantrone and cyclophosphamide and (etoposide or bleomycin) and vincristine) or R-DECC or (rituximab and dexamethasone and etoposide and chlorambucil and lomustine) or BR or R-Benda* or (bendamustine and rituximab) or DHAP or (cisplatin and cytarabine and dexamethasone) or GDP or (cisplatin and gemcitabine and dexamethasone) or ICE or (ifosfamide and carboplatin and etoposide) or IVE or (ifosfamide and epirubicin and etoposide)).mp.	108247
14	(Monjuvi* or Minjuvi* or tafasitamab or tafasitamab-cxix or MOR208 or Xmab5574 or L01FX12 or 1422527-84-1 or DB15044 or QQA9MLH692 or D11601).mp.	64
15	(Polivy* or polatuzumab* or DCDS4501A or RG7596 or polatuzumab vedotin-piiq or a619039 or L01FX14 or 1313206-42-6 or "347911301" or DB12240 or KG6VO684Z6 or D10761).mp.	189
16	(Lisocabtagene or maraleucel or Breyanzi* or liso-cell or DB16582 or JCAR-017 or JCAR017).mp.	68
17	(Tisagenlecleucel* or Kymriah* or CTL019 or CART-19 or a617053 or L01XX71 or 1823078-37-0 or DB13881 or Q6C9WHR03O or D11386).mp.	548
18	(Axicabtagene ciloleucel or Yescarta* or KTE-C19 or Axi-cel or a618003 or L01XX70 or DB13915 or U2I8T43Y7R or D11144).mp.	419

19	or/9-18	109690
20	8 and 19	1028
21	Randomized Controlled Trials as Topic/	158345
22	randomized controlled trial/	579481
23	Random Allocation/	106889
24	Double Blind Method/	173391
25	Single Blind Method/	32254
26	exp clinical trial/	954177
27	exp Clinical Trials as topic/	377823
28	PLACEBOS/	35924
29	(clinical adj trial*).tw.	452503
30	((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.	192224
31	placebo$.tw.	240206
32	(random$ adj2 allocat$).tw.	41775
33	randomi?ed controlled trial*.tw.	231284
34	rct.tw.	28984
35	((phase 2? or phase 3? or phase 4? or phase ii? or phase iii? or phase iv?) adj2 (study or studies or trial*)).tw.	83802
36	or/21-35	1765349
37	case report.tw.	375936
38	letter/	1197292
39	historical article/	368847
40	or/37-39	1923797
41	36 not 40	1724364
42	20 and 41	414
43	Epidemiologic studies/	9190
44	exp case control studies/	1363549
45	exp cohort studies/	2408608
46	Cross-sectional studies/	444106
47	multicenter study/ not exp clinical trial/	191545
48	Case control.tw.	147468
49	(cohort adj (study or studies or analy*)).tw.	298627
50	(follow up adj (study or studies)).tw.	54650
51	(observational adj (study or studies)).tw.	147992
52	Longitudinal.tw.	303783
53	Retrospective.tw.	693334
54	Cross sectional.tw.	473726
55	(epidemiologic$ adj (study or analy*)).tw.	29095
56	(real adj (world or life)).tw.	92098

57	(RWE or RWD).tw.	893
58	((single centre or single center or multi centre or multi center or multicentre or multicenter) adj2 experience).tw.	17232
59	audit.tw.	39030
60	(registry or registries).ti.	35618
61	clinical practice.ti.	36185
62	Databases, Factual/	96136
63	exp registries/	115002
64	or/43-63	3939166
65	20 and 64	289
66	42 or 65	605
67	limit 66 to english language	584
68	limit 67 to abstracts	571
69	animals/	7185864
70	exp animals, laboratory/	944654
71	exp animal experimentation/	10228
72	exp models, animal/	633952
73	exp rodentia/	3490918
74	(rat or rats or mouse or mice).ti.	1415227
75	or/69-74	7292663
76	humans/ and 75	2168955
77	75 not 76	5123708
78	68 not 77	570

Cochrane search strategy

Platform: Ovid

Database: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews

Date searched: 25/10/2022

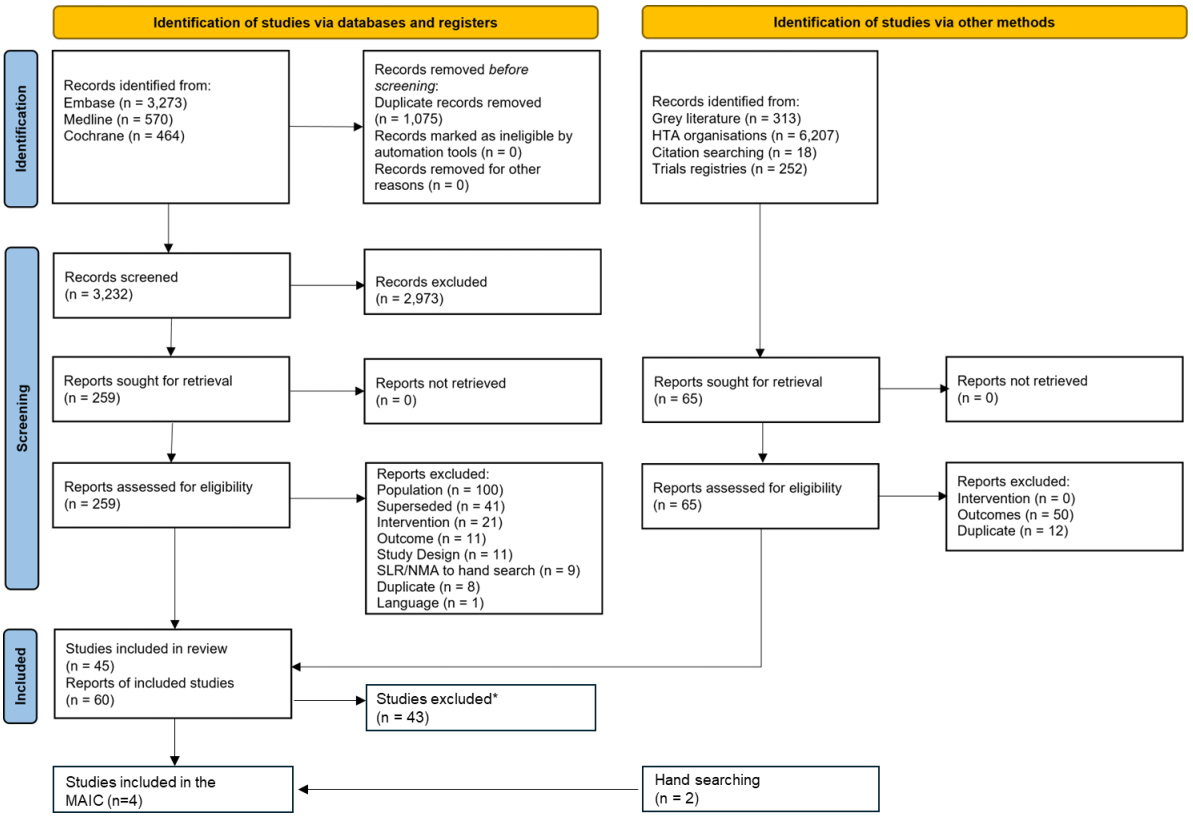
Hits: 464

Table S5: Cochrane search string

#	Searches	Hits
1	exp Lymphoma, Large B-Cell, Diffuse/	480
2	(DLBCL or HGBL* or HGBCL*).tw,hw,ot,kf.	1307
3	((large cell* or large-cell or b-cell or bcell or lymphoid* or histiocytic* or plasmablastic* or centroblastic* or immunoblastic*) adj3 lymphom*).tw,hw,ot,kf.	3386
4	or/1-3	3416

5	exp Recurrence/ or exp Neoplasm Recurrence, Local/ or exp Retreatment/	18156
6	(relapse* or refractor* or "relapsed/refractory" or recur* or pretreated or pre-treated or (previously adj1 treated) or (prior adj1 therap*) or ((third or 3rd or previous or prior) adj1 line*) or 3L or 3-L).tw,hw,ot,kf.	144597
7	or/5-6	145267
8	4 and 7	1601
9	(Zynlonta* or lonca* or ADCT-402 or 1879918-31-6 or DB16222 or 7K5O7P6QIU or D11338).mp.	23
10	(pixantron* or Pixuvri* or DB06193 or DB-06193 or BBR 2778 or BBR2778 or 144510-96-3).mp.	45
11	(glofitamab* or DB16371 or DB-16371 or RG-6026 or RG6026 or RO-7082859 or RO7082859).mp.	8
12	(selinexor* or Xpovio* or DB11942 or DB-11942 or KPT-330 or KPT330 or a619044).mp.	152
13	(chemoimmunotherap* or CIT or R-GemOx or R-Gem or (rituximab and gemcitabine) or (rituximab and oxaliplatin) or R-P-MitCEBO or (rituximab and prednisolone and mitoxantrone and cyclophosphamide and (etoposide or bleomycin) and vincristine) or R-DECC or (rituximab and dexamethasone and etoposide and chlorambucil and lomustine) or BR or R-Benda* or (bendamustine and rituximab) or DHAP or (cisplatin and cytarabine and dexamethasone) or GDP or (cisplatin and gemcitabine and dexamethasone) or ICE or (ifosfamide and carboplatin and etoposide) or IVE or (ifosfamide and epirubicin and etoposide)).mp.	7949
14	(Monjuvi* or Minjuvi* or tafasitamab or tafasitamab-cxix or MOR208 or Xmab5574 or L01FX12 or 1422527-84-1 or DB15044 or QQA9MLH692 or D11601).mp.	33
15	(Polivy* or polatuzumab* or DCDS4501A or RG7596 or polatuzumab vedotin-piiq or a619039 or L01FX14 or 1313206-42-6 or "347911301" or DB12240 or KG6VO684Z6 or D10761).mp.	98
16	(Lisocabtagene or maraleucel or Breyanzi* or liso-cell or DB16582 or JCAR-017 or JCAR017).mp.	10
17	(Tisagenlecleucel* or Kymriah* or CTL019 or CART-19 or a617053 or L01XX71 or 1823078-37-0 or DB13881 or Q6C9WHR03O or D11386).mp.	46
18	(Axicabtagene ciloleucel or Yescarta* or KTE-C19 or Axi-cel or a618003 or L01XX70 or DB13915 or U2I8T43Y7R or D11144).mp.	53
19	or/9-18	8287
20	8 and 19	464

Figure S1: PRISMA flow diagram



Abbreviations: HTA, health technology assessment; Lonca, loncastuximab; MAIC, matching adjusted indirect comparison; NMA, network meta-analysis; Pola+BR, polatuzumab + bendamustine +rituximab; SLR, systematic literature review; Tafa+Len, tafasitamab + lenalidomide.

Notes: *The Phase 1 study, LOTIS-1, was superseded by the Phase 2, LOTIS-2 study; in addition, 36 studies did not report data for Lonca or Pola; the remaining six Pola+BR studies either had very small sample size (<25 patients) or did not report subgroup data for the relevant line of treatment.

Overview of MAIC methodology

As LOTIS-2 is a single-arm study, standard techniques for indirect treatment comparisons (ITC), such as Bucher ITCs and network meta-analyses (NMA), are not possible because they rely on a common comparator to connect studies in the network. MAIC is one method that can be used to estimate treatment effects when a connected network is not possible and individual patient data (IPD) are available for one treatment and published aggregate data available for comparator interventions.

The MAIC approach can minimize the bias of unadjusted indirect treatment effect estimates by adjusting for observed baseline characteristics that differ between the studies and which influence patient outcomes. The patient characteristics from the IPD are adjusted, using a logistic propensity score matching, so that the mean baseline characteristics from the IPD match those of the aggregate data and comparison of outcomes can be made between balanced populations. The weighting process allows calculation of an effective sample size (ESS) for the IPD arm. The ESS represents the number of non-weighted individuals needed

to give an estimate with the same precision as the weighted sample estimate. A larger ESS is preferable to a small ESS, as the larger sample has greater power to detect any potential differences between treatments.

RStudio software version 4.0.2 (10) was used to conduct the MAIC analyses and standard packages, including the survival package (version 3.2.7), were used to make the calculations. The methods applied for the current analyses are in line with the published guidance in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 and Phillippo et al (11, 12).

Estimation of MAIC weights

The weights in a MAIC are derived using a non-parametric likelihood reweighting method, which allows the propensity score logistic regression model to be estimated without patient-level data in one of the treatment arms. Weights were assigned to patients in LOTIS-2 to adjust for their over- or underrepresentation relative to the average prognostic factors and treatment effect modifiers observed in each comparator study and wereestimated using the following equation:

$$w_i = exp(\alpha + x_i^r \beta)$$

where w_i is the patient weight for the *ith* patient receiving Lonca, x_i^r is the vector of baseline variables included for matching, and α is a constant value. A method of moments was used to ensure the weights exactly balanced the mean covariate values between the weighted Lonca IPD and the comparator population. The weighted average baseline characteristics were calculated and compared with the target values from each comparator study.

The ESS achieved after weighting LOTIS-2 patients was defined as:

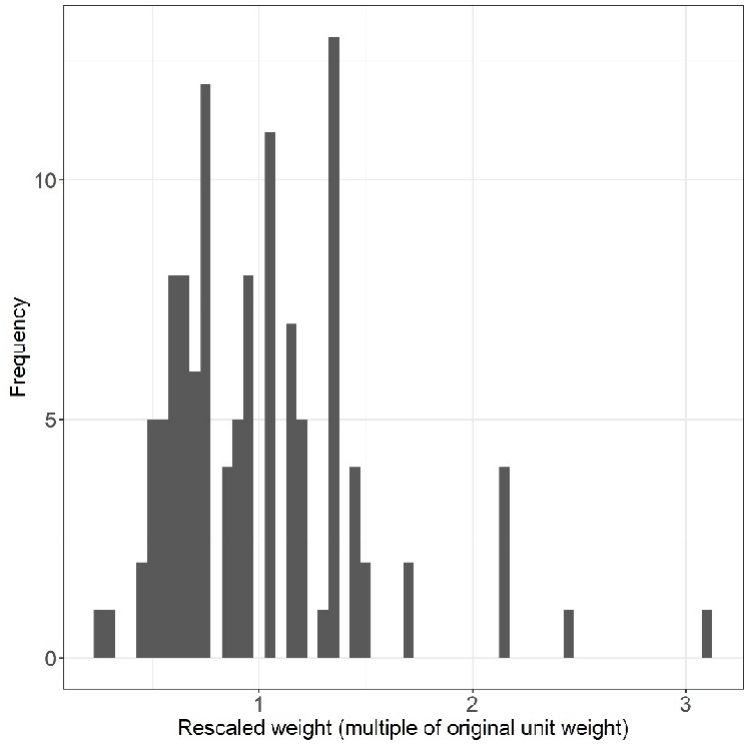
$$ESS = (\sum wi)^2 / \sum (wi^2)$$

The weights were also re-scaled to aid their interpretation and explore their distribution. Re-scaled weights are defined as:

$$\text{Rescaled weighting} = (\sum wi)^2 / \sum (wi^2) \times N$$

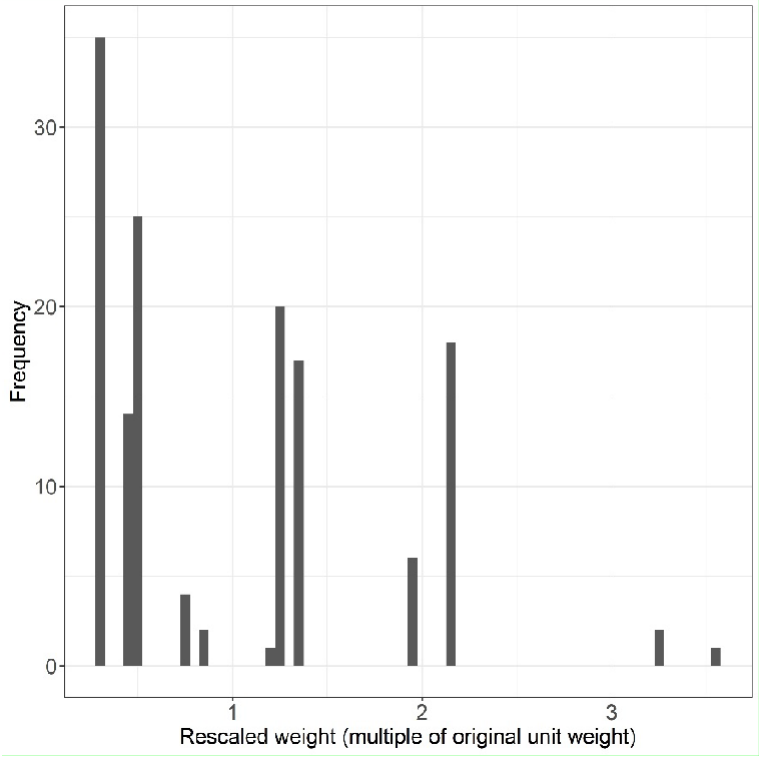
The rescaled weights were plotted using histograms (Figure S2 to Figure S4) with the histograms showing whether specific patient(s) have extremely low or large weights and are therefore over- or underrepresented in the analysis. A rescaled weight of >1 means that an individual carries more weight in the re-weighted sample than in the original sample, and a rescaled weight of <1 means that an individual carries less weight.

Figure S2: Histogram of rescaled weights (efficacy outcomes) – Lonca vs Pola + BR (GO29365 extension study)



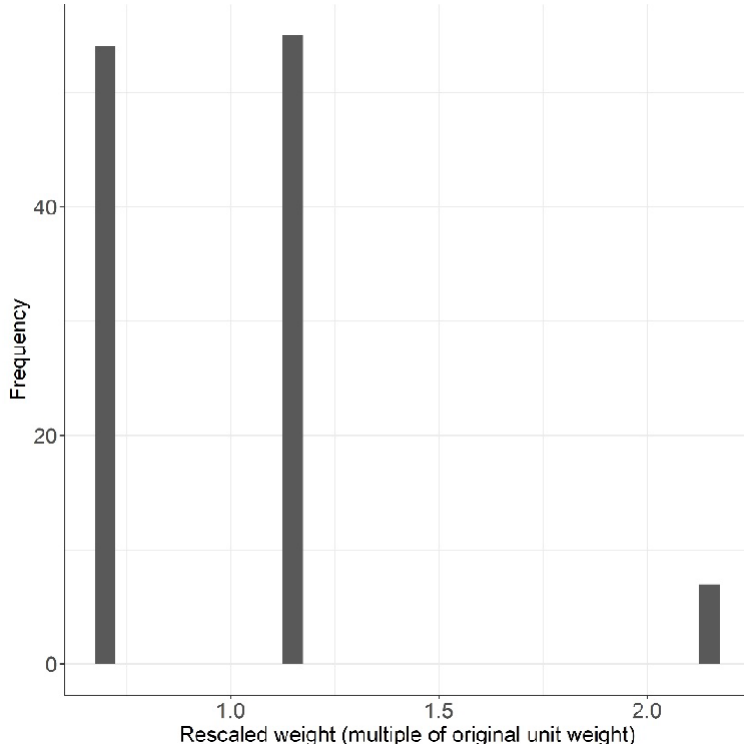
Abbreviations: Lonca, loncastuximab tesirine; Pola+BR, polatuzumab vedotin plus bendamustine plus rituximab.

Figure S3: Histogram of rescaled weights (efficacy outcomes) – Lonca vs Pola + BR (COTA database)



Abbreviations: Lonca, loncastuximab tesirine; Pola+BR, polatuzumab vedotin plus bendamustine plus rituximab.

Figure S4: Histogram of rescaled weights (safety outcomes) – Lonca vs Pola + BR (GO29365 extension study)



Abbreviations: Lonca, loncastuximab tesirine; Pola+BR, polatuzumab vedotin plus bendamustine plus rituximab.

Estimation of variance

To account for the fact that weights are estimated rather than fixed and known, standard errors for the MAIC estimates were calculated using a bootstrap estimator (11). The use of a bootstrap estimator can help quantify sampling uncertainty in the estimates. This procedure was repeated 1,000 times to obtain a distribution of estimates for which the 2.5th and 97.5th percentiles were used to generate the lower and upper confidence interval limits.

Additional assumptions and data calculations

Patient baseline characteristics were available for the third- or later-line population in the COTA database(13) and Dal 2023 (9). In the GO29365 extension study (7), patient baseline characteristics were reported for the second- or later-line population and the majority of patients were third- or later-line (102/152 patients).

Individual patient data were only available from LOTIS-2 (14), with aggregate data available from the three comparator studies. Where available, the percentage of patients receiving comparator treatment who were progression-free or alive/alive over time were extracted from the published KM curves for PFS and OS, respectively. Digitizing software, Engauge Digitizer version 12.1, was used to extract the data, and pseudo individual patient-level data

were reconstructed from the extracted survival (supplemented by the number of patients at risk over time, if reported) using the algorithm published by Guyot et al. 2012 (15).

In addition, where KM curves were not available for survival outcomes in the relevant subgroup of third- or later-line patients from the GO29365 extension study (7), and only median PFS or OS were reported, these data were used to make a crude estimate of the HR and associated 95% CI for Lonca vs Pola+BR, using methods described in Tierney et al 2007 (16). This involved estimating the HR from:

$$\textit{Median survival time for Lonca/Median survival time for Pola+BR}$$

and the corresponding standard error (SE) using the formula

$$SE\ log\ HR = \sqrt{(1/E1+1/E2)}$$

where *E1* and *E2* were the number of events in each treatment arm, respectively.

As is typical with MAIC estimates, standard errors were calculated using either a bootstrap estimate or a robust sandwich estimator; these were subsequently used to calculate the 95% CIs.

Identification of prognostic factors and treatment effect modifiers

The clinical experts confirmed the appropriateness of the initial list of matching variables while cautioning about the potential unreliability of results when adjusting for certain variables. Double/triple hit LBCL was noted as challenging to adjust for due to variability in risk levels among patients. Similarly, considering cell of origin (activated B-cell like [ABC] vs germinal center B-cell-like [GCB]) was deemed difficult due to conflicting outcomes and the presence of double hits in GCB patients. There is some evidence that patients with transformed lymphoma may have improved outcomes compared with de novo DLBCL (17); however, the clinical experts considered this less critical due to challenges in aligning prior therapies for follicular lymphoma. Regarding prior ASCT, while there was some debate among clinicians, the majority leaned towards exclusion since it doesn't necessarily reflect disease characteristics. Bulky disease was suggested as a predictive variable, but inconsistencies in its definition across studies posed challenges. Additionally, scrutiny of published evidence (18, 19) proposed additional covariates such as elevated LDH, neutropenia, and anemia. However, these were not considered key variables for adjustment by clinicians and were not available for any comparator studies.

Due to differences in the list of reported baseline characteristics across the trials, the set of characteristics that were matched were specific to each Pola+BR study. Where individual components of the IPI were available, including age, Ann Arbor disease stage and ECOG

PS, the individual components were included to provide higher granularity of the matching. Individual components and IPI score were not both included in the analyses to avoid double adjustment of correlated variables. Extranodal disease was not identified as an important prognostic factor in its own right, however as it is one of the risk factors included as part of the IPI calculation and was available for the LOTIS-2 and Dal 2023 studies, this characteristic was included in a sensitivity analysis.

The definition of refractory to primary treatment and refractory to last treatment differed between the studies, with the GO29365 extension study reporting the proportion of refractory patients as a group combined with those who had relapse or progression within six months of completion of therapy. In LOTIS-2, the definition of refractory was stable disease or progressive disease following treatment. For the primary refractory definition, data were available to enable the criteria from GO29365 extension study to be extended to LOTIS-2 to match the definitions. However, although refractory to last line of treatment was also identified as an important predictor of outcome, it was not possible to match the definition for this variable between LOTIS-2 and the GO29365 extension study due to the different approach taken to collection of this variable for LOTIS-2.

Predictive factors for safety outcomes are generally less well established, with clinicians indicating that only age and Eastern Cooperative Oncology Group performance status (ECOG PS) were relevant.

Efficacy outcomes

GO29365

Matching was conducted based on the aggregate prognostic baseline characteristics for all patients, and after matching, the adjusted characteristics for the trial populations were well-balanced (Table S6).

Table S6: Comparison of baseline characteristics Lonca (LOTIS-2) vs Pola+BR (GO29365 extension study)

Treatment (study)	N/ ESS	Age <65 (%)	Male (%)	HGBL (%)	ECOG 0-1 (%)	Disease stage ≥3 (%)	Prior lines ≥3 (%)	Primary refractory or progression / relapse <6 months (%)
Lonca unadjusted (LOTIS-2)	116.0	46.6	62.9	6.0	94.0	78.4	56.9	62.9
Lonca weighted (LOTIS-2)	96.5	32.0	55.0	3.0	87.0	80.0	58.8	64.0

Treatment (study)	N/ ESS	Age <65 (%)	Male (%)	HGBL (%)	ECOG 0-1 (%)	Disease stage ≥3 (%)	Prior lines ≥3 (%)	Primary refractory or progression / relapse <6 months (%)
Pola+BR (GO29365 extension)	102.0	32.0	55.0	3.0	87.0	80.0	58.8	64.0

Abbreviations: ESS, effective sample size; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table S7: Odds ratio for response outcomes – Lonca vs Pola+BR (GO29365 extension study)

Outcome	Method	Lonca ORR, n/N (%)	Pola+BR ORR, n/N (%)	Lonca vs Pola+BR Odds ratio (95% CI)
ORR	Naïve comparison (unadjusted)	57/116 (49.1)	51/102 (50)	0.97 (0.57, 1.65)
	Weighted GLM model†	50.7/105.9 (47.9)		0.92 (0.53, 1.59)
	Weighted sandwich estimator			0.92 (0.52, 1.62)
CR	Naïve comparison (unadjusted)	29/116 (25.0)	43/102 (42.2)	***0.46 (0.26, 0.81)***
	Weighted GLM model†	26.9/105.9 (25.4)		***0.47 (0.26, 0.85)***
	Weighted sandwich estimator			***0.47 (0.25, 0.89)***

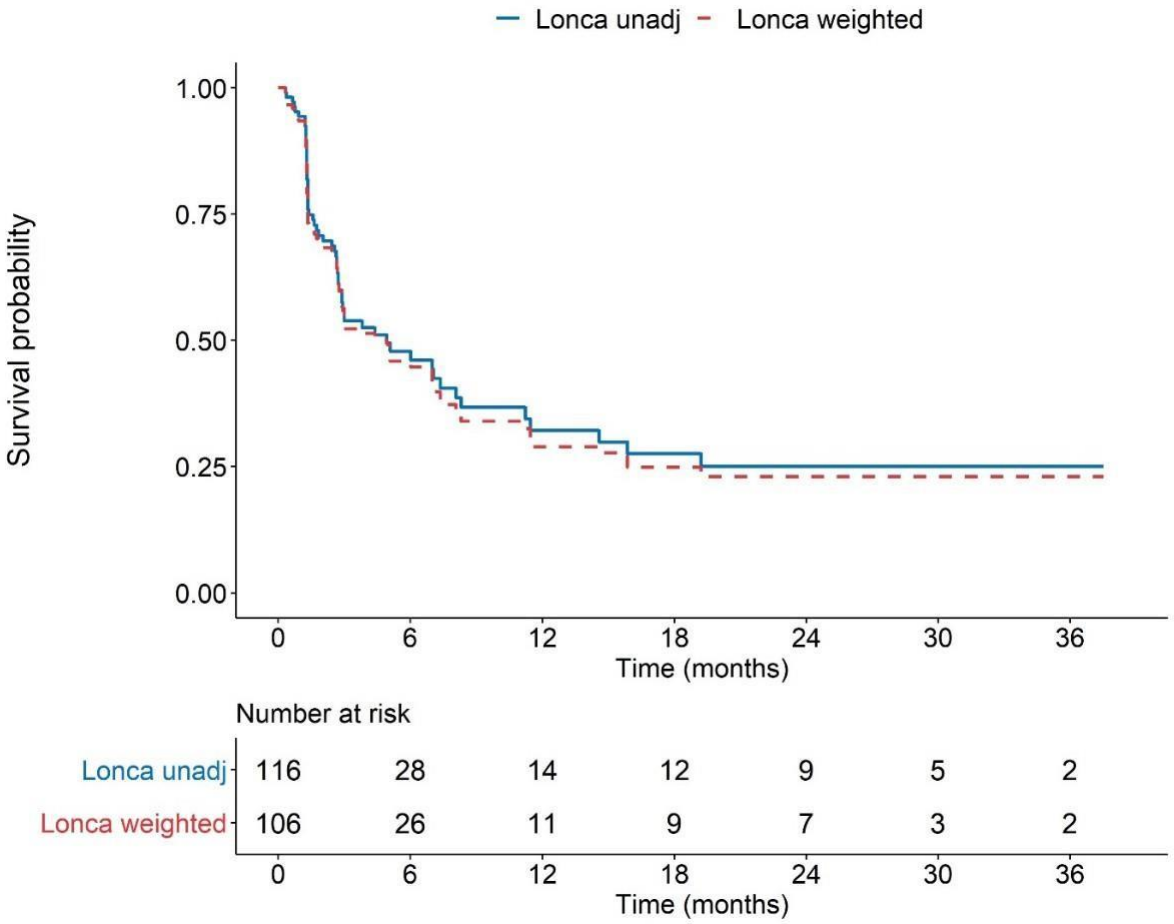
OR>1.0 favors Lonca.
Text in bold and italics indicates significantly higher odds of response with Pola+BR
†Logistic regression
Abbreviations: CI, confidence interval; CR, complete response; GLM, generalized linear model; Lonca, loncastuximab tesirine; OR, odds ratio; ORR, overall response rate; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table S8: Summary of PFS comparison – Lonca vs Pola+BR (GO29365 extension study)

Treatment (study)	N/ ESS	Events	Median PFS (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve comparison (LOTIS-2)	116.0	60	4.93 (2.76, 8.08)	1.24 (0.88, 1.73)
Lonca weighted (LOTIS-2)	96.5	57	4.93 (2.73, 7.36)	1.24 (0.88, 1.74)
Pola+BR (GO29365 extension)	102.0	79	6.1 (4.5, 8.0)	Comparator

HR<1.0 favors Lonca.
Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Figure S5: Kaplan-Meier plot for PFS – Lonca matched to Pola+BR GO29365 extension study characteristics†



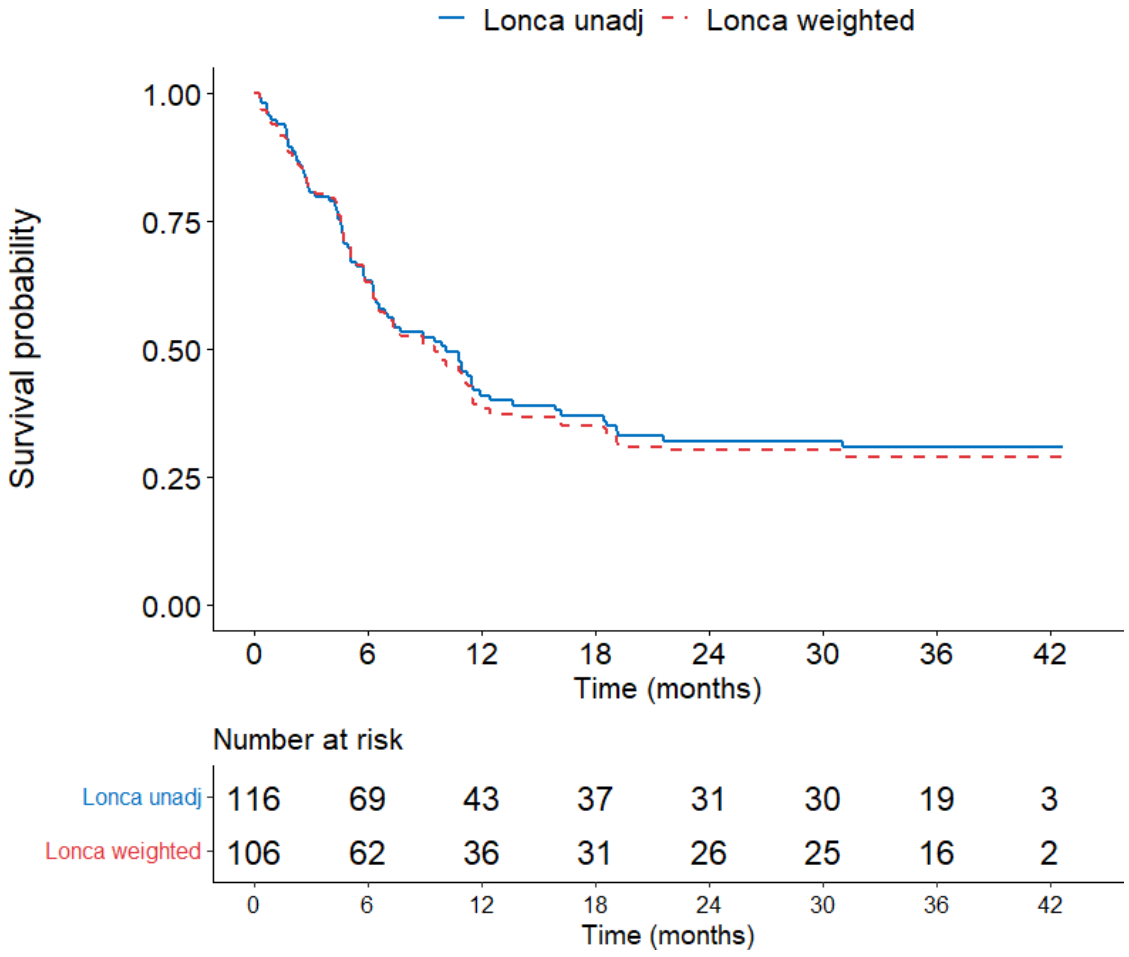
†Only median survival reported from GO29365 extension study, no KM curve available for Pola+BR in the 3L+ subgroup.
Abbreviations: Lonca, loncastuximab tesirine; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted.

Table S9: Summary of OS comparison – Lonca vs Pola+BR (GO29365 extension study)

Treatment (study)	N/ ESS	Events	Median OS (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	116.0	75	10.12 (6.47, 11.93)	0.94 (0.67, 1.31)
Lonca weighted (LOTIS-2)	96.5	70	9.53 (6.34, 11.56)	1.00 (0.71, 1.40)
Pola+BR (GO29365 extension)	102.0	63	9.5 (7.6, 14.2)	Comparator

HR<1.0 favors Lonca.
Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Figure S6: Kaplan-Meier plot for OS – Lonca matched to Pola+BR GO29365 extension study characteristics†



†Only median survival reported from GO29365 extension study, no KM curve available for Pola+BR in the 3L+ subgroup.
Abbreviations: 3L+, third- or later-line; Lonca, loncastuximab tesirine; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted.

COTA database

After matching, the adjusted prognostic baseline characteristics for the trial populations were well-balanced (Table S10).

Table S10: Comparison of baseline characteristics Lonca (LOTIS-2) vs Pola+BR (COTA database)

Treatment (study)	N/ ESS	Age <65 (%)	Male (%)	Prior lines ≥3 (%)	HGBL (%)
Lonca unadjusted (LOTIS-2)	145.0	44.8	58.6	56.6	7.6
Lonca weighted (LOTIS-2)	95.0	50.0	60.0	26.0	12.0
Pola+BR (COTA database)	43.0	50.0	60.0	26.0	12.0

Abbreviations: ESS, effective sample size; HGBL, high grade B-cell lymphoma; Lonca, loncastuximab tesirine; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table S11: Odds ratio for response outcomes – Lonca vs Pola+BR (COTA database)

Outcome	Method	Lonca ORR, n/N (%)	Pola+BR ORR, n/N (%)	Lonca vs Pola+BR Odds ratio (95% CI)
ORR	Naïve comparison (unadjusted)	70/145 (48.3)	25/43 (58)	0.67 (0.33, 1.33)
	Weighted GLM model†	55/114 (48.2)		0.68 (0.33, 1.38)
	Weighted sandwich estimator			0.68 (0.32, 1.43)
CR	Naïve comparison (unadjusted)	36/145 (24.8)	7/43 (16.3)	1.70 (0.73, 4.46)
	Weighted GLM model†	27.4/113.6 (24.1)		1.63 (0.68, 4.36)
	Weighted sandwich estimator			1.63 (0.63, 4.23)

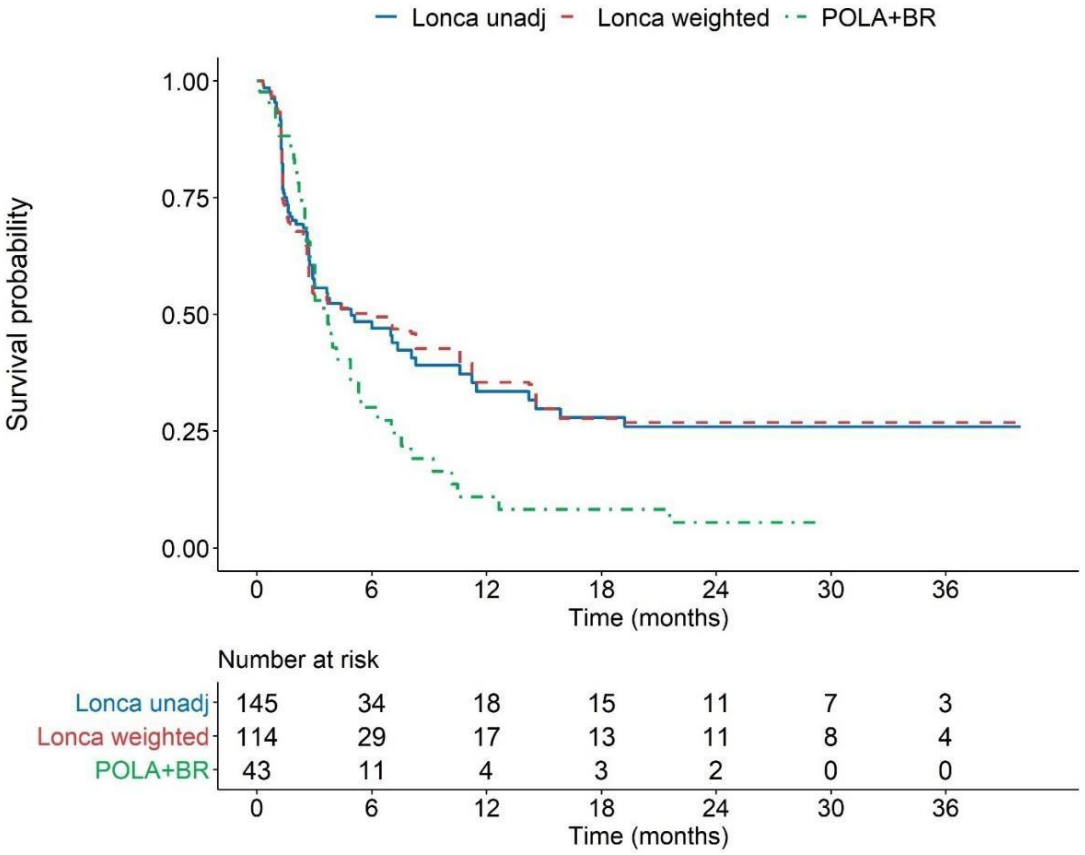
OR>1.0 favors loncastuximab tesirine.
†Logistic regression
Abbreviations: CI, confidence interval; CR, complete response; GLM, generalized linear model; Lonca, loncastuximab tesirine; OR, odds ratio; ORR, overall response rate; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table S12: Summary of PFS comparison – Lonca vs Pola+BR (COTA database)

Treatment (study)	N/ ESS	Events	Median PFS (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	145.0	73	4.93 (2.89, 8.31)	0.67 (0.45, 1.00)
Lonca weighted (LOTIS-2)	95.0	58	6.01 (2.66, 11.24)	Standard: ***0.66 (0.44, 0.97)*** Bootstrap: ***0.66 (0.48, 0.89)***
Pola+BR (COTA database)	43.0	37	3.70 (2.59, 4.89)	Comparator

HR<1.0 favors Lonca.
Text in bold and italics indicates significantly higher odds of response with loncastuximab tesirine
Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Figure S7: Kaplan-Meier plot for PFS – Lonca matched to Pola+BR patient characteristics (COTA US database)



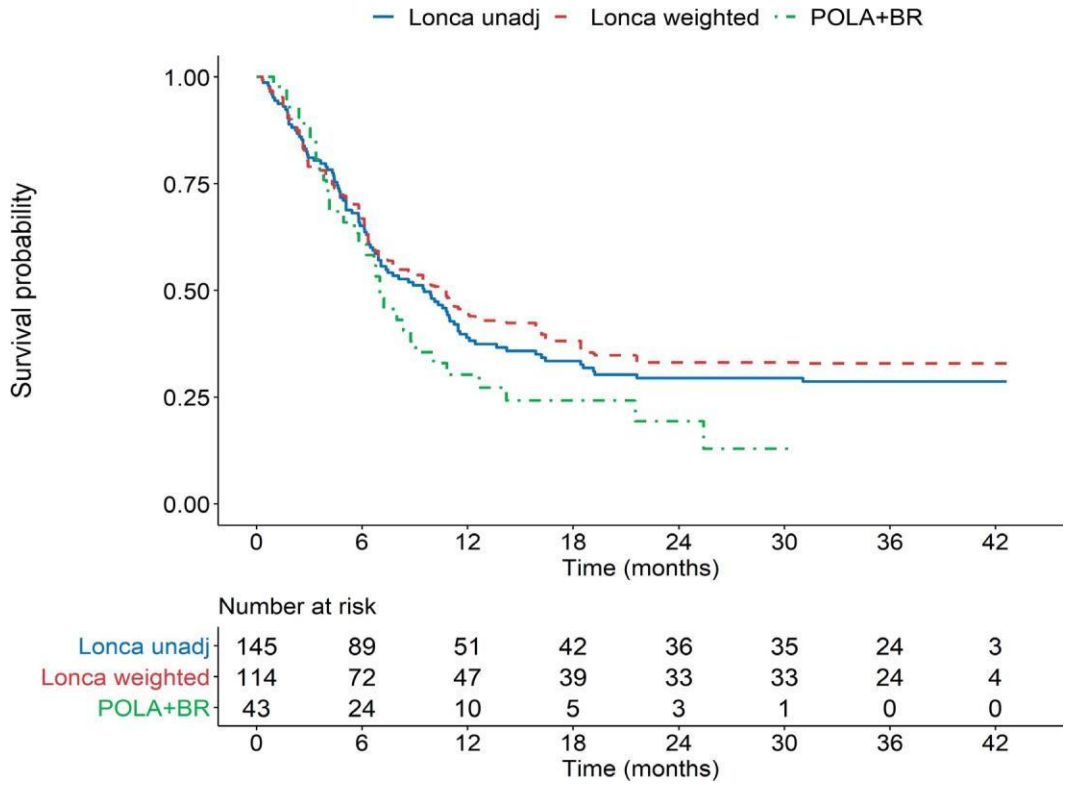
Abbreviations: Lonca, loncastuximab tesirine; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted.

Table S13: Summary of OS comparison – Lonca vs Pola+BR (COTA database)

Treatment (study)	N/ ESS	Events	Median OS (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	145.0	97	9.53 (6.74, 11.47)	0.75 (0.50, 1.12)
Lonca weighted (LOTIS-2)	95.0	72	10.78 (6.60, 16.20)	Standard: 0.69 (0.46, 1.04) Bootstrap: ***0.69 (0.53, 0.90)***
Pola+BR (COTA database)	43.0	32	7.00 (4.95, 10.05)	Comparator

HR<1.0 favors Lonca.
Text in bold and italics indicates significantly higher odds of response with loncastuximab tesirine
Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Figure S8: Kaplan-Meier plot for OS – Lonca matched to Pola+BR patient characteristics (COTA database)



Abbreviations: Lonca, loncastuximab tesirine; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted.

Dal 2023

After matching, the adjusted prognostic baseline characteristics for the trial populations were well-balanced (Table S14).

Table S14: Comparison of baseline characteristics Lonca (LOTIS-2) vs Pola+BR (Dal 2023 study)

Treatment (study)	N/ ESS	ECOG ≥2 (%)	Age <55 (%)	Stage ≥3 (%)
Lonca unadjusted (LOTIS-2)	143.0	5.6	22.4	76.9
Lonca weighted (LOTIS-2)	40.4	36.6	50.0	73.0
Pola+BR (Dal 2023, base case)	71.0	36.6	50.0	73.0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; Lonca, loncastuximab tesirine; N, sample size; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table S15: Odds ratios for response outcomes – Lonca vs Pola+BR (Dal 2023)

Outcome	Method	Lonca ORR, n/N (%)	Pola+BR ORR, n/N (%)	Lonca vs Pola+BR Odds ratio (95% CI)
ORR	Naïve comparison (unadjusted)	69/143 (48.3)	34/71 (47.9)	1.01 (0.57, 1.80)
	Weighted GLM model†	28.2/60.2 (46.9)		0.99 (0.48, 2.07)
	Weighted sandwich estimator			0.99 (0.40, 2.46)
CR	Naïve comparison (unadjusted)	35/143 (24.5)	23/71 (32.4)	0.68 (0.36, 1.27)
	Weighted GLM model†	15.0/60.2 (24.9)		0.67 (0.29, 1.51)
	Weighted sandwich estimator			0.67 (0.21, 2.09)

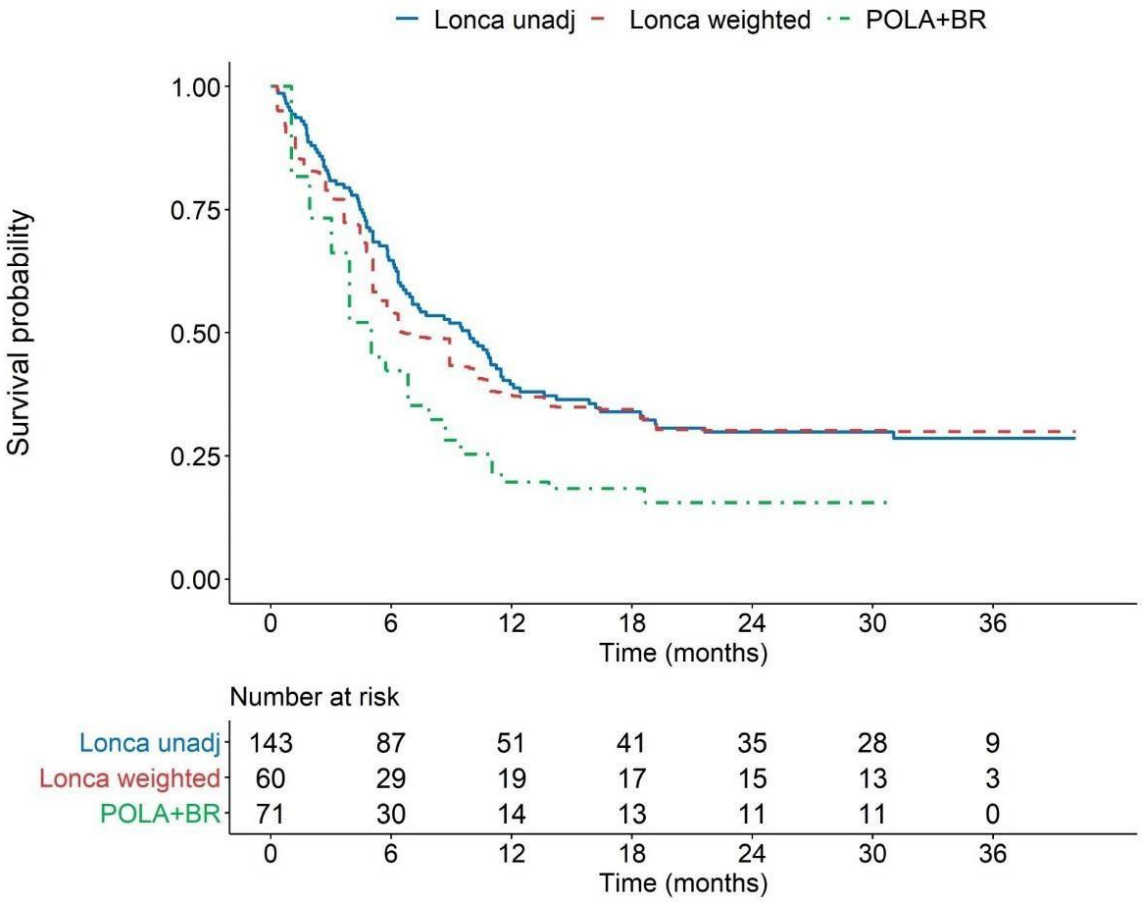
OR>1.0 favors Lonca.
†Logistic regression
Abbreviations: CI, confidence interval; CR, complete response; GLM, generalized linear model; Lonca, loncastuximab tesirine; OR, odds ratio; ORR, overall response rate; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table S16: Summary of OS comparison – Lonca vs Pola+BR (Dal 2023)

Treatment (study)	N/ ESS	Events	Median OS (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	143.0	95	9.89 (6.74, 11.47)	***0.58 (0.42, 0.81)***
Lonca weighted (LOTIS-2)	40.4	39	6.60 (4.76, 13.63)	Standard: 0.65 (0.41, 1.04) Bootstrap: ***0.65 (0.42, 0.98)***
Pola+BR (Dal 2023)	71.0	60	5.00 (3.92, 6.83)	Comparator

Text in bold and italics indicates significantly higher odds of response with Lonca.
Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Figure S9: Kaplan-Meier plot for OS – Lonca matched to Pola+BR patient characteristics (Dal 2023 study)



Abbreviations: Lonca, loncastuximab tesirine; OS, overall survival; Pola+BR, polatuzumab plus bendamustine

Dal 2023, Sensitivity analysis

Table S17: Comparison of baseline characteristics Lonca (LOTIS-2) vs Pola+BR (Dal 2023 study), sensitivity analysis

Treatment (study)	N/ ESS	ECOG ≥2 (%)	Age <55 (%)	Stage ≥3 (%)	EN disease (%)
Lonca unadjusted (LOTIS-2)	143.0	5.6	22.4	76.9	33.6
Lonca weighted (LOTIS-2)	29.4	36.6	50.0	73.0	63.4
Pola+BR (Dal 2023, sensitivity analysis)	71.0	36.6	50.0	73.0	63.4

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EN, extranodal; ESS, effective sample size; Lonca, loncastuximab tesirine; N, sample size; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table S18: Summary of OS comparison – Lonca vs Pola+BR (Dal 2023 study), sensitivity analysis

Treatment (study)	N/ ESS	Events	Median OS (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	143.0	95	9.89 (6.74, 11.47)	***0.58 (0.42, 0.81)***
Lonca weighted (LOTIS-2)	29.4	27	10.12 (5.09, NE)	Standard: ***0.54 (0.31, 0.94)*** Bootstrap: ***0.52 (0.33, 0.92)***
Pola+BR (Dal 2023)	71.0	60	5.00 (3.92, 6.83)	Comparator

Text in bold and italics indicates significantly higher odds of response with Lonca.
Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Safety outcomes

GO29365

Follow-up time and treatment duration differed between the trials. However, an exposure-adjusted analysis was not deemed appropriate as this requires the strong assumption that patients have a constant hazard of experiencing an AE over the follow-up period, which could not reliably be made. This was due to challenges in identifying which Pola+BR patients from the subgroups in the cohort experienced events in order to estimate exposure times, and lack of detail regarding the length of time AEs were considered to be treatment-emergent. Moreover, in LOTIS-2, a treatment-emergent AE (TEAE) was defined as an AE occurring or worsening from the first dose until 30 days post last dose or initiation of new anti-cancer therapy/procedure, whichever came first. This resulted in most TEAEs occurring early in the trial.

Table S19: Comparison of safety outcomes in the unadjusted population: Lonca (LOTIS-2) vs Pola+BR (GO29365 extension study)

Outcome	Lonca, n (%) (N=116)	Pola+BR, n (%) (N=151)	Lonca vs Pola+BR Odds ratio (95% CI)
Treatment discontinuations due to AEs	30 (25.9)	31 (20.5)	1.35 (0.76, 2.40)
AE Grade 3–4			
Any AE, Grade 3–4	85 (73.3)	122 (80.8)	0.65 (0.37, 1.16)
Anemia	12 (10.3)	19 (12.6)	0.80 (0.37, 1.73)
Infections and infestations	9 (7.8)	33 (21.9)	***0.30 (0.14, 0.66)***
Neutropenia	27 (23.3)	49 (32.5)	0.63 (0.36, 1.09)
Thrombocytopenia	18 (15.5)	31 (20.5)	0.71 (0.38, 1.35)
SAEs, any grade			
Any SAE	46 (39.7)	86 (57)	***0.50 (0.30, 0.81)***
Fatal AEs	7 (6.0)	17 (11.3)	0.51 (0.20, 1.26)
Febrile neutropenia	3 (2.6)	15 (9.9)	***0.24 (0.07, 0.85)***

Pneumonia	1 (0.9)	14 (9.3)	***0.09 (0.01, 0.66)***
Pyrexia	2 (1.7)	13 (8.6)	***0.19 (0.04, 0.84)***
Sepsis	1 (0.9)	15 (9.9)	***0.08 (0.01, 0.61)***

Text in bold and italics indicates significantly lower odds for Lonca. OR<1.0 favors Lonca.
Abbreviations: AE, adverse event; Lonca, loncastuximab tesirine; OR, odds ratio; Pola+BR, polatuzumab plus bendamustine plus rituximab; SAE, serious adverse event.

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