Clinical outcomes of patients with relapsed/refractory large B-cell lymphoma receiving second-line therapy in England: A multicenter, retrospective, real-world study

Christopher P Fox[1], Farah Toron[2], Emma Tyas[3], Miranda Cooper[3], Joshua Rickards[3] and Paula Williams[2]

[1]School of Medicine, University of Nottingham, UK; [2]Bristol Myers Squibb, Uxbridge, UK; [3]Lumanity, London, UK

CO15

Objectives

- Large B-cell lymphoma (LBCL) refers to several distinct subtypes of non-Hodgkin lymphoma (NHL). Diffuse LBCL is the most common form of the disease, with around 5,500 people diagnosed per year in the UK[1]
- LBCL is treated with anti-CD20 chemoimmunotherapy at first line (1L). 1L treatment is curative in approximately 60% of cases.[2] However, in 10–15% of patients, the disease is refractory to treatment, and a further 20-30% of patients relapse[3]
- Standard-of-care at second line (2L) includes platinum-based multi-agent chemoimmunotherapy, followed by high-dose chemotherapy and autologous stem-cell transplant (ASCT)[4]
- However, fewer than half of patients are considered eligible for ASCT due to inadequate physiological fitness or response to prior lines of therapy[5,6]
- Real-world studies have demonstrated that non-receipt of ASCT is associated with poor survival.[7-9] However, outcomes have not been stratified by transplant eligibility status
- We describe the real-world clinical outcomes of patients with relapsed or refractory (R/R) LBCL initiating 2L treatment in the UK, stratified by transplant eligibility

Methods

- This retrospective, observational study was conducted across six centers in England
- Patients were included if they met the following inclusion criteria:
  - Aged ≥ 18 years at diagnosis
  - Aggressive B-cell NHL of one of the following histological subtypes:
    - DLBCL not otherwise specified (NOS) (de novo or transformed follicular lymphoma)
    - High-grade B-cell lymphoma with MYC and BCL2 or BCL6 rearrangement with DLBCL histology
    - Primary mediastinal B-cell lymphoma (PMBCL)
    - LBCL with follicular lymphoma grade 3B (FL3B)
  - R/R disease after one prior line of therapy that included treatment with an anthracycline and rituximab (or another CD20-targeting agent)
- Patients were excluded if they had prior receipt of chimeric antigen receptor T-cell (CAR T) therapy or prior receipt of ASCT at 1L
- Eligible patients were stratified by transplant-eligibility, defined as:
  - Receipt of ASCT, or
  - Receipt of one of six chemotherapy regimens: DHAP, GDP, ICE, IVE, ESHAP, or DHAX, as part of the 2L regimen
- Ineligibility was defined as:
  - Non-receipt of above chemotherapy regimens, or DHAC, MATRIx, MINE, IVAC, IGEV or BEAM
  - At least one of: age ≥ 70 years, ECOG performance status (PS) ≥ 2, diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60%, left ventricular ejection fraction (LVEF) ≤ 50%, creatine clearance (Cr/Cl) < 60 mL/min, or alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN)
- Overall survival (OS) was calculated from the 2L therapy start date to the date of death due to any cause. Patients were censored at their last observation date if death did not occur
- Progression-free survival (PFS) was calculated from 2L therapy start date to the date of first documented progressive disease or death due to any cause. Progressive disease was recorded when the disease had grown or spread beyond the previous assessment, as assessed by laboratory, radiologic or pathologic testing, or physician assessment from electronic medical records. Patients with no events were censored at last observation date
- Event-free survival (EFS) was defined as for PFS, but initiation of third-line (3L) therapy or failure to achieve complete or partial response also constituted an event

Results

- In total, 299 patients met eligibility criteria, of these 223 were defined as ASCT-eligible, 49 ineligible, and 27 unclassified
- ASCT-eligible patients were younger than ineligible patients (mean age 56.5 vs. 74.7 years), with lower ECOG scores (60.1% vs. 42.8% with ECOG 0-1) **(Table 1)**

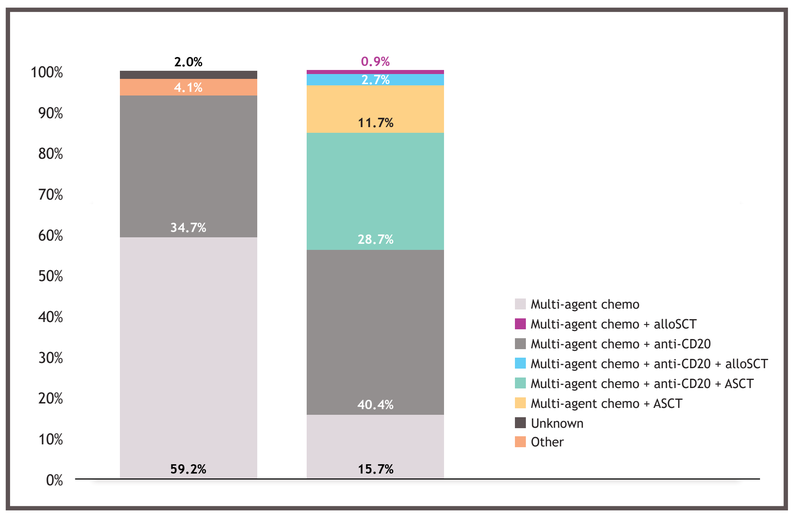
Table 1. Baseline characteristics

PATIENT CHARACTERISTICS		OVERALL[a] (N = 299)	TRANSPLANT ELIGIBLE (N=223)	TRANSPLANT INELIGIBLE (N=49)
Months from initial diagnosis to index date, median (IQR)		10.8 [6.9, 23.1]	10.2 [6.6, 19.0]	17.3 [8.7, 41.0]
Age (years), mean (SD)		59.8 (13.4)	56.5 (11.8)	75.24 (11.61)
Age (years), n (%)	< 70	235 (78.6)	201 (90.1)	7 (14.3)
	≥ 70	64 (21.4)	22 (9.9)	42 (85.7)
Sex, n (%)	Male	187 (62.5)	137 (61.4)	29 (59.2)
ECOG PS, n (%)	0	94 (31.4)	79 (35.4)	8 (16.3)
	1	79 (26.4)	55 (24.7)	13 (26.5)
	2	25 (8.4)	15 (6.7)	10 (20.4)
	3	10 (3.3)	4 (1.8)	6 (12.2)
	4	1 (0.3)	1 (0.4)	0 (0.0)
	Unknown	90 (30.1)	69 (30.9)	12 (24.5)
Disease histology, n (%)	DLBCL NOS	203 (67.9)	146 (65.5)	39 (79.6)
	DLBCL NOS (tFL)	19 (6.4)	13 (5.8)	5 (10.2)
	FL3B	5 (1.7)	3 (1.3)	0 (0.0)
	HGBCL	14 (4.7)	11 (4.9)	1 (2.0)
	Not verified[c]	58 (19.4)	50 (22.4)	4 (8.2)
Refractory[d] or relapsed to last therapy, n (%)	Refractory	164 (54.8)	120 (53.8)	26 (53.1)
	Relapsed	117 (39.1)	91 (40.8)	20 (40.8)
	Missing[b]	18 (6.0)	12 (5.4)	3 (6.1)
Best response to prior therapy, n (%)	CR	117 (39.1)	91 (40.8)	20 (40.8)
	PD	46 (15.4)	34 (15.2)	7 (14.3)
	PR	103 (34.4)	72 (32.3)	18 (36.7)
	SD	15 (5.0)	14 (6.3)	1 (2.0)
	Missing	18 (6.0)	12 (5.4)	3 (6.1)

CR, complete response; IQR, interquartile range; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; SD, stable disease or standard deviation; TE, transplant eligible; TNE, transplant non-eligible.
aUnclassified patients were included in the patient characteristics for the overall patient cohort, but were not included in later analyses; bStatus was missing for all patients with no response data recorded between 1L and 2L; cHigh grade B-cell NHL subtype not verified; dStatus was defined as relapsed if a patient achieved a complete response after the start date of last prior therapy and had clinical outcome records with stable disease, progressive disease or no response after CR but before the 2L start date, otherwise status was refractory.

- The proportion of the cohort that was transplant-ineligible was lower than expected.[5,6] This may represent a selection bias, given participating study sites were tertiary referral centers; nevertheless, clinical characteristics are consistent with other 2L populations[7,9]
- Of the transplant-eligible group, only 98 patients (40.4%) underwent ASCT (**Figure 1**). In some patients, this may have been due to inadequate response to 2L therapy, as patients who do not achieve at least a partial response (PR) to 2L chemotherapy are generally considered unsuitable to undergo ASCT[10]
- In the transplant-eligible group, the most common 2L treatment was multi-agent chemotherapy with an anti-CD20 monoclonal antibody (mAb), with 40.4% of these patients then undergoing ASCT (**Figure 1**)
- In the transplant-ineligible group, the most common 2L treatment was multi-agent chemotherapy without an anti-CD20 mAb (**Figure 1**). This may be reflective of the higher ECOG PS scores in the in ASCT-ineligible population (**Table 1**), as NICE guidelines recommend that chemoimmunotherapy should be offered to "people with relapsed or refractory DLBCL who are fit enough to tolerate intensive therapy"[11]

Figure 1. 2L treatment regimens in transplant-ineligible and transplant-eligible subgroups



- The overall response rate (ORR) to 2L therapy was substantially lower in the transplant-ineligible population (25.7%) compared with the transplant-eligible population (63.5%) (**Table 2**)
- This is despite both groups having a similar best response to 1L therapy (**Table 1**), and may be indicative of the poorer physiological health and more advanced age in the ASCT-ineligible group

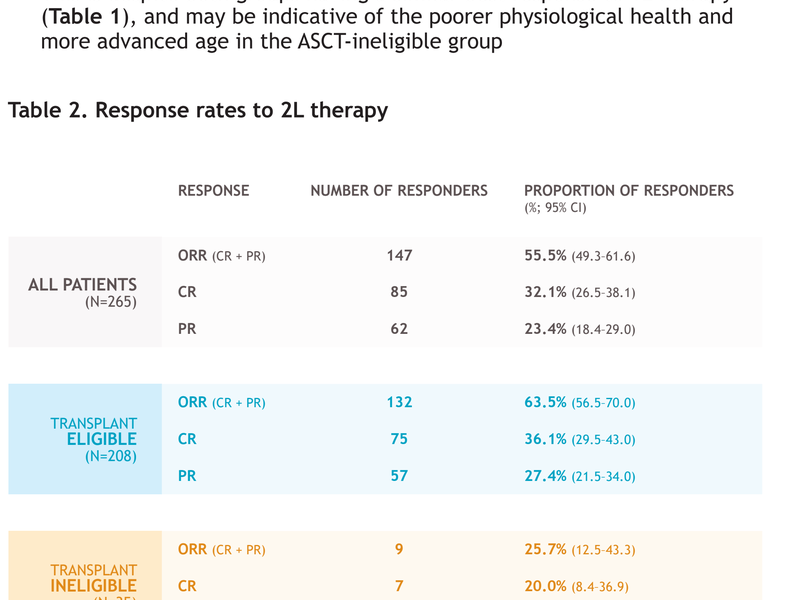
Table 2. Response rates to 2L therapy

	RESPONSE	NUMBER OF RESPONDERS	PROPORTION OF RESPONDERS (%; 95% CI)
ALL PATIENTS (N=265)	ORR (CR + PR)	147	55.5% (49.3-61.6)
	CR	85	32.1% (26.5-38.1)
	PR	62	23.4% (18.4-29.0)
TRANSPLANT ELIGIBLE (N=208)	ORR (CR + PR)	132	63.5% (56.5-70.0)
	CR	75	36.1% (29.5-43.0)
	PR	57	27.4% (21.5-34.0)
TRANSPLANT INELIGIBLE (N=35)	ORR (CR + PR)	9	25.7% (12.5-43.3)
	CR	7	20.0% (8.4-36.9)
	PR	2	5.7% (0.0-19.2)

Data available for 265 of 299 patients. Best overall response based on response assessments which occurred following initiation of 2L therapy and prior to progression or the start of subsequent therapy for patients who satisfy the required inclusion criteria.
CI, confidence interval

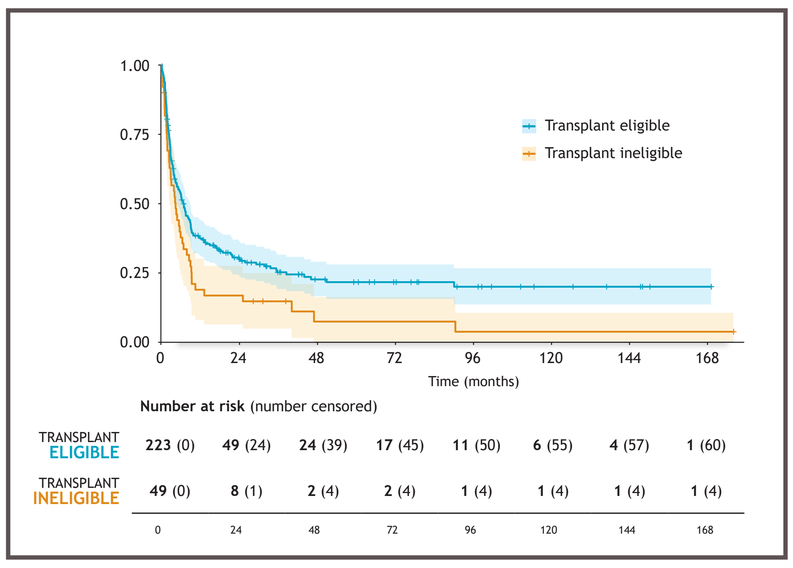
- Median OS for transplant-ineligible patients was considerably shorter than for eligible patients (6.94 months versus 18.71 months; **Figure 2**), and transplant-ineligible patients had a significantly greater risk of death (HR 2.39 [95% CI: 1.70–3.37])

Figure 2. Kaplan-Meier curve for overall survival



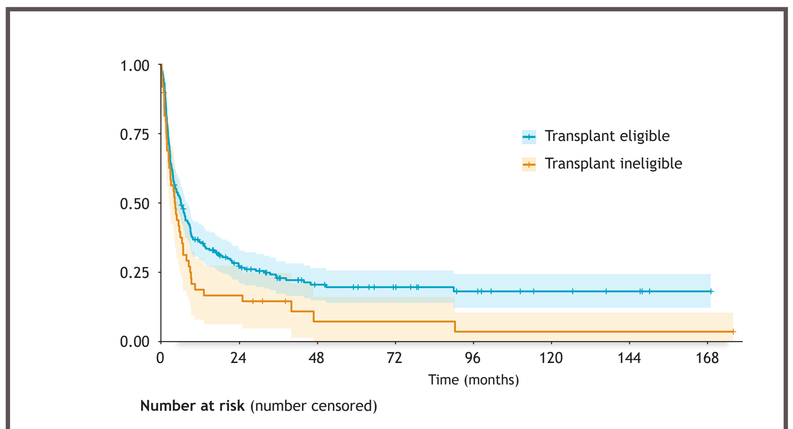
	PATIENTS	EVENTS	CENSORS	MEDIAN (months; 95% CI)	HAZARD RATIO (95% CI)
TRANSPLANT ELIGIBLE	223	136	87	18.71 (13.15-33.44)	Reference
TRANSPLANT INELIGIBLE	49	44	5	6.94 (4.77-9.11)	2.39 (1.70-3.37)

Figure 3. Kaplan-Meier curve for progression-free survival



	PATIENTS	EVENTS	CENSORS	MEDIAN (months; 95% CI)	HAZARD RATIO (95% CI)
TRANSPLANT ELIGIBLE	223	162	61	6.67 (4.67-8.71)	Reference
TRANSPLANT INELIGIBLE	49	44	5	4.27 (2.40-6.35)	1.54 (1.10-2.15)

Figure 4. Kaplan-Meier curve for event-free survival



	PATIENTS	EVENTS	CENSORS	MEDIAN (months; 95% CI)	HAZARD RATIO (95% CI)
TRANSPLANT ELIGIBLE	223	171	52	6.08 (3.95-7.99)	Reference
TRANSPLANT INELIGIBLE	49	44	5	4.27 (2.40-6.35)	1.46 (1.05-2.04)

- Median PFS and EFS were also considerably shorter for transplant-ineligible patients compared with the transplant-eligible group (**Figure 3, Figure 4**). PFS and EFS were both 4.27 months in the transplant-ineligible group, compared with 6.67 and 6.08 respectively in the transplant-eligible group. Transplant-ineligible patients also had a significantly greater risk of progression or death (HR 1.54 [95% CI: 1.10–2.15]) and of an EFS event occurring (HR 1.46 [95% CI: 1.05–2.04]) compared with the transplant-eligible group
- Despite the majority of transplant-eligible patients not undergoing ASCT, the survival outcomes in this group were still improved compared with the transplant-ineligible group, indicating that transplant-eligibility is correlated with survival, irrespective of whether transplant was received

Conclusions

- This study provides insight into UK clinical practice and survival outcomes in R/R LBCL when considering transplant-eligibility
- Transplant-ineligible patients, who were older with higher ECOG PS scores than transplant-eligible patients, were less likely to receive immunotherapy at 2L and had considerably lower response rates
- Overall, progression-free and event-free survival were shorter in the transplant-ineligible group versus the transplant-eligible group, despite fewer than half of eligible patients undergoing transplant
- This suggests that transplant eligibility is associated with survival, even when patients do not undergo transplant
- Therefore, there is a substantial unmet need in the transplant-ineligible population for alternative therapies to improve survival in the 2L setting

References

1. NICE. Available at: https://www.nice.org.uk/News/Article/more-than-400-people-set-to-benefit-after-nice-approves-ground-breaking-car-t-therapy-to-treat-aggressive-form-of-blood-cancer. Published 26 January 2023. Accessed 05 September 2023.
2. Coiffier et al. Blood. 2010;116(12):2040-5
3. Chaganti et al. Br J Haematol. 2016;174(1):43-56.
4. Tilly et al. Ann Oncol. 2015;26 Suppl 5:v116-25
5. Sarkozy et al. Best Pract Res Clin Haematol. 2018;31(3):209-16
6. Crump et al. Blood. 2017;130(16):1800-8.
7. Vardhana et al. Biol Blood Marrow Transplant. 2018;24(10):2133-8
8. Rassy et al. Clin Lymphoma Myeloma Leuk. 2021;21(4):e373-e80
9. Harrysson, et al. Br J Haematol. 2022;198(2):267-77.
10. Frontzek et al. Ther Adv Hematol. 2022;13:20406207221103321.
11. NICE guideline NG52. Available at: https://www.nice.org.uk/guidance/ng52/chapter/Recommendations

Acknowledgements

We would like to acknowledge Lumanity, London, UK for data analysis support which was funded by Bristol Myers Squibb

This study was supported by Bristol Myers Squibb

All authors contributed to and approved the presentation; writing and editorial assistance were provided by Alice Bedwell and Emma Crouch-Baker of HEOR Ltd and design assistance by Hayley Thomson of HEOR Ltd, Cardiff, UK, funded by Bristol Myers Squibb.

Presented at ISPOR Europe 2023; November 12-15, 2023; Copenhagen, Denmark

Email: christopher.fox@nottingham.ac.uk