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Letter to the Editor

Outcomes after chimeric antigen receptor T-cell therapy across large B-cell lymphoma subtypes

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Authorship Contributions

C.B., C.R., A.A.K., A.K.: designed the research, collected the data, analysed the data, and wrote the manuscript; Other authors: contributed to collecting the data and reviewed the manuscript.

Conflict of interest disclosures

A.K. has served on advisory boards and received honoraria from Kite/Gilead, Novartis, Abbvie, Roche and BMS. C.R. has served on advisory boards and received honoraria from Kite/Gilead, Novartis and BMS. A.A.K. received honoraria from Kite/Gilead. R.S. and M.O.R. have served on advisory boards and received honoraria from Kite/Gilead and Novartis. S.C. has served on advisory boards, provided consultancy services, and received meeting attendance support from Takeda, Novartis, Celgene/BMS, Kite/Gilead, Atara Bio, Incyte, and Roche. J.N. received travel funds from Kite/Gilead. A.G. has served on advisory boards for Takeda and received honoraria from Kite/Gilead and Takeda. W.O. has received honoraria from Roche, Takeda, Pfizer, Servier, Kite/Gilead, MSD, Novartis, Beigene, Astra Zeneca, Syneos, Autolus, Kyowa Kirin, Abbvie, Incyte, BMS, Janssen. C.G.A has served on advisory boards and received honoraria from Kite/Gilead and Novartis, received research funding from Kite/Gilead, and received conference sponsorship from Kite/Gilead, Novartis and BMS/Celgene. The remaining authors declare no conflict of interest.

Data sharing

Anonymised data may be shared on reasonable request and ethical approval.

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CD19 CAR T-cell therapy has significantly improved treatment options for large B-cell lymphoma (LBCL) and has become a new standard-of-care for relapsed or refractory (r/r) disease. The licence includes histological subtypes of primary mediastinal B-cell lymphoma (PMBCL) and transformed LBCL from follicular lymphoma (t-FL) or non-FL background (t-NFL), such as marginal zone lymphoma (MZL) or chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), i.e. Richter's syndrome (RS).

Efficacy of CD19 CAR T in r/r LBCL has been confirmed in long-term follow-up of the registrational trials,[1,2] as well as several large retrospective CAR T real-world cohorts.[3–7] However, the clinical benefit of CAR T within histological subgroups is less clear. T-NFL have been excluded from the clinical trials and patients with PMBCL or t-FL have been underrepresented.[1,2] In the real-world setting, incidences ranged between 3-6% for PMBCL, 14-26% for t-FL, and 1-6% for t-NFL within national CAR T cohorts, but subtype-specific outcomes were not provided.[4–9]

In a single-centre retrospective analysis of 21 patients with t-NFL, CAR T response rates and long-term survival were similar to other subgroups, but with potentially higher rates of Immune effector cell-associated neurotoxicity syndrome (ICANS).[10] Regarding r/r PMBCL, multi-centre retrospective analyses suggested better long-term survival with axicabtagene ciloleucel (axi-cel) compared to other LBCL.[11–13] Subtype-specific CAR T outcome data will be key to understand the relative benefit of CAR T vs alternative treatments such as CD20 x CD3 bispecific antibodies in each subgroup in order to guide decision-making in daily practice.

Herein, we report outcomes of patients intended to be treated with CD19 CAR T in the UK according to histological subtypes. We included 760 consecutive patients with r/r LBCL approved for ≥3rd line treatment with axi-cel or tisagenlecleucel (tisa-cel) between December 2018 and October 2022 across 12 CAR T centres as part of a National Service Evaluation (not requiring separate consent). The UK National CAR T Clinical Panel approval process, toxicity grading and response assessment have been previously described.[6]

Among 760 cases, 529 (70%) had *de novo* diffuse large B-cell lymphoma (DLBCL), 27 (4%) PMBCL, 157 (21%) t-FL and 47 (6%) t-NFL (23 t-MZL, 15 RS, 5 t-NLPHL (nodular lymphocyte predominant Hodgkin lymphoma), 4 t-LPL (lymphoplasmacytic lymphoma)). No significant differences were seen in baseline characteristics when comparing the t-NHL group to *de novo* DLBCL. PMBCL patients were significantly younger and t-FL patients showed significant differences compared to *de novo* DLBCL for CHOP refractory disease and bridging response (Table 1). 720 (94.7%) of patients proceeded with leukapheresis and 614 (81%) received CAR T, with similar rates across subgroups. Of 614 infused patients, 485 received axi-cel and 129 tisa-cel. Bridging therapy was given to 89.9% of apheresed patients.

Median follow-up from the time of CAR T approval was 18.2 months (IQR 13.6-23.6). The best overall response rate (ORR) was 77% (57% CR), with no significant differences between groups, but a trend towards better response in t-FL (ORR 84%/CR 70%; p = 0.054). The 12-month progression-free survival (PFS) for the different subgroups was as follows: 53% (33-70) for PMBCL, 42% (37-47) for *de novo* DLBCL, 54% (45-63) for t-FL and 39% (24-54) for t-NFL. The intention-to-treat (ITT) 12-month OS rates were 84% (63-94), 50% (45-54), 58% (50-66) and 50% (34-63), respectively (Figure 1). We did not observe significant differences in PFS or OS between subtypes of t-NFL (PFS: RS vs t-MZL 0.80 (0.31 – 2.04); t-other vs t-MZL 0.51 (0.16 – 1.59); RS vs t-other 0.64 (0.19 – 2.18); p=0.49, OS: RS vs t-MZL 1.06 (0.37 – 3.07); t-other vs t-MZL 0.67 (0.18 – 2.54); RS vs t-other 0.63 (0.16 – 2.53); p=0.79). PFS was significantly better for t-FL vs *de novo* DLBCL (HR 0.75 (0.57-0.99); p=0.043), in both the ITT and infused cohorts; OS was significantly better for PMBCL and t-FL (for infused: PMBCL: HR (0.34 (0.16-0.72), p=0.005; t-FL: HR 0.73 (0.57-0.94), p=0.017). There was no evidence of a different effect by CAR T product (p value for interaction (Cox model): 0.29 PFS and 0.89 OS (infused cohort)).

Grade ≥3 cytokine release syndrome (CRS) occurred in 5% and grade ≥3 ICANS in 15% of patients and was similar between subgroups. No significant differences were seen according to tocilizumab and corticosteroid use, ICU admission, and non-relapse mortality (see Supplement).

In this large national dataset, we show that safety and efficacy of CD19 CAR T in t-NFL patients are comparable to the main LBCL cohort, indicating that CAR T is a suitable and curative treatment for these rare subgroups. Given the generally poor outcomes of r/r patients with t-MZL or RS with conventional therapies, the relative benefit of CAR T might indeed be higher than in *de novo* DLBCL. For subtypes such as RS, which characteristically show aggressive disease kinetics, it is particularly important to provide ITT outcomes and account for patients dropping out during the prolonged CAR T pathway due to fast disease progression. In this regard, the infusion rate of 87% seen in our RS cohort is very encouraging, although numbers are too small to draw firm conclusions. Due to the heterogeneity of RS, larger studies with more detailed analyses of prior CLL-directed therapy and baseline T-cell function are warranted.[14,15] Efficacy of bispecific antibodies and other novel treatments in t-NFL is not yet known. Our data provide a useful benchmark for future comparison of CAR T against novel immunotherapies in t-MZL and RS.

We observed similar drop-out rates across all LBCL subtypes. However, PMBCL and t-FL had significantly better long-term survival compared to other subgroups. The favourable results seen in PMBCL are in line with previous reports. Our 2-year PFS of 53% for PMBCL is almost identical to the 54% reported in the German series.[12] The survival difference was highly significant in their cohort, but did not reach significance in our analysis, probably explained by the unexpectedly short PFS of the German comparator cohort (DLBCL NOS) of only 26% at 2 years.[12]

A numerically higher response rate was seen in t-FL in the ZUMA-1 and JULIET trials,[1,2] but to our knowledge, this is the first study suggesting superior long-term outcomes of t-FL vs *de novo* DLBCL. CAR T-cell toxicities and non-relapse mortality were similar between subgroups which is an important finding, suggesting a similar risk/benefit profile of CAR T in rare subtypes.

In conclusion, our data provide evidence for a clinical benefit of CAR T across rare subgroups of r/r LBCL such as t-NFL. We further show particularly favourable CAR T outcomes in patients with PMBCL as well as t-FL, highlighting the important role of CD19 CAR T against alternative treatment options for these patients, which should be confirmed in larger datasets.

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Figures and Tables

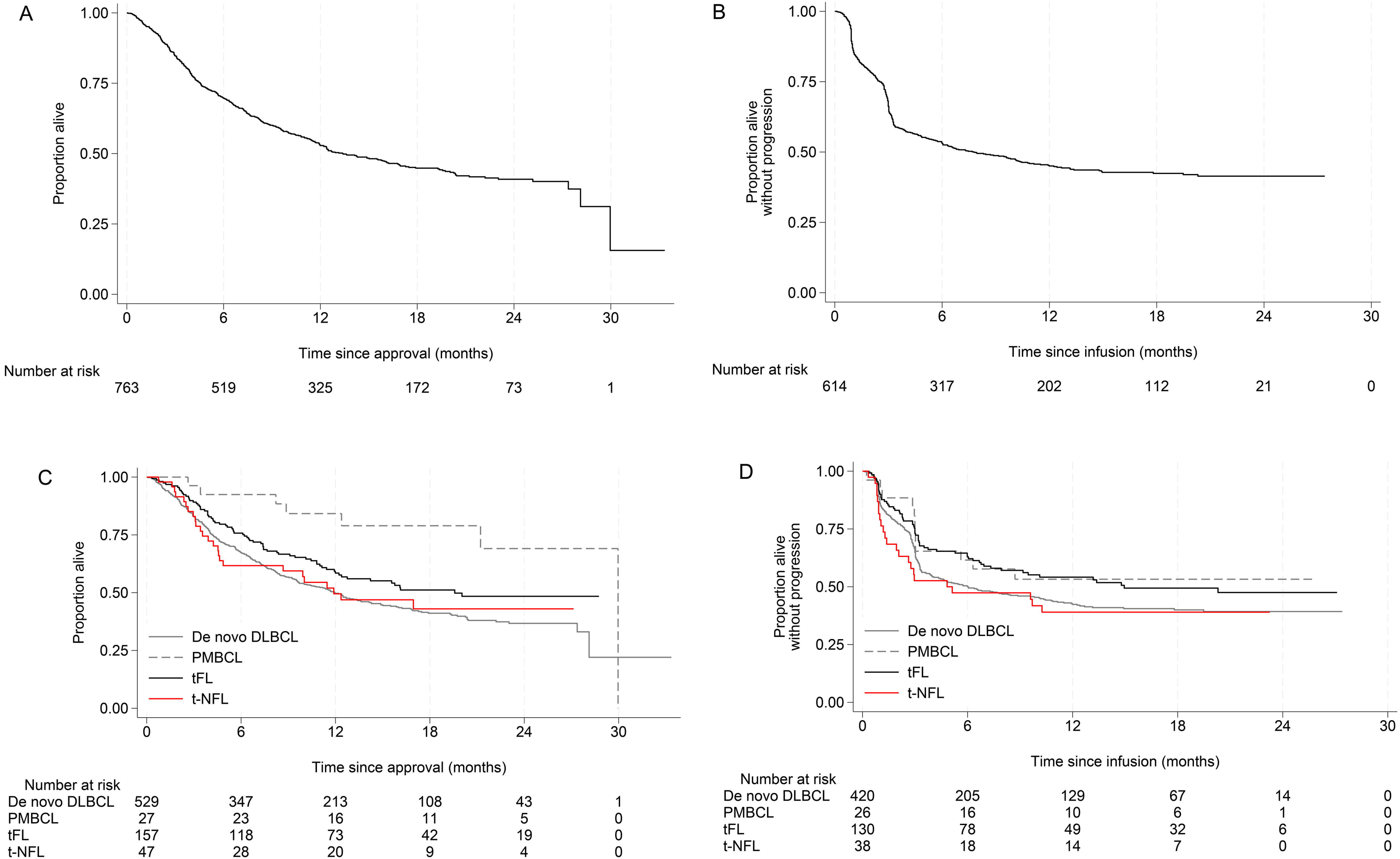
Table 1. Baseline characteristics across subgroups.

	De novo DLBCL N=529	PMBCL N=27	t-FL N=157	t-NFL N=47	p-value[1]	t-MZL N=23	RS N=15	t-other N=9
Product, N (%)								
Axi-cel	323 (61.1)	26 (96.3)[2]	104 (66.2)	32 (68.1)	0.48[2]	14 (60.9)	12 (80.0)	6 (66.7)
Tisa-cel	97 (18.3)	0	26 (16.6)	6 (12.8)		3 (13.0)	1 (6.7)	2 (22.2)
Not infused	109 (20.6)	1 (3.7)	27 (17.2)	9 (19.1)	0.15[3]	6 (26.1)	2 (13.3)	1 (11.1)
Age (years), median (IQR)	62.0(53 - 69)	32.0(29 - 41)	63.0(56 - 69)	59.0(51 - 67)	0.0001[4]	59.0(54 - 64)	62.0(52 - 69)	40.0(35 - 65)
Sex, N (%)								
Male	334 (63.1)	15 (55.6)	85 (54.1)	27 (57.4)	0.19	12 (52.2)	8 (53.3)	7 (77.8)
Female	195 (36.9)	12 (44.4)	72 (45.9)	20 (42.6)		11 (47.8)	7 (46.7)	2 (22.2)
Stage at approval, N (%)								
Stage 0-2	77 (21.3)	8 (36.4)	24 (24.7)	5 (18.5)	0.35	3 (15.8)	0	2 (33.3)
Stage 3-4	285 (78.7)	14 (63.6)	73 (75.3)	22 (81.5)		16 (84.2)	2 (100.0)	4 (66.7)
Missing/unknown	167	5	60	20		4	13	3
ECOG at approval, N (%)								
0	127 (43.3)	10 (45.5)	34 (38.2)	9 (40.9)	0.84	6 (37.5)	1 (100.0)	2 (40.0)
1	166 (56.7)	12 (54.5)	55 (61.8)	13 (59.1)		10 (62.5)	0	3 (60.0)
Missing/unknown	236	5	68	25		7	14	4
Bulk>7.5cm, N (%)								
No	231 (66.2)	16 (66.7)	75 (75.8)	20 (76.9)	0.25	15 (78.9)	0	5 (83.3)
Yes	118 (33.8)	8 (33.3)	24 (24.2)	6 (23.1)		4 (21.1)	1 (100.0)	1 (16.7)
Missing/unknown	180	3	58	21		4	14	3
Extranodal sites, N (%)								
0-2 sites	315 (88.2)	23 (95.8)	95 (95.0)	24 (92.3)	0.18	19 (100.0)	1 (100.0)	4 (66.7)
3+	42 (11.8)	1 (4.2)	5 (5.0)	2 (7.7)		0	0	2 (33.3)
Missing/unknown	172	3	57	21		4	14	3
LDH at approval, N (%)								
<ULN	43 (15.5)	3 (16.7)	9 (11.2)	5 (23.8)	0.84	4 (26.7)	0	1 (20.0)
>ULN	147 (52.9)	9 (50.0)	46 (57.5)	11 (52.4)		7 (46.7)	0	4 (80.0)
>2ULN	88 (31.7)	6 (33.3)	25 (31.2)	5 (23.8)		4 (26.7)	1 (100.0)	0
Missing/unknown	251	9	77	26		8	14	4
IPI, N (%)								

	De novo DLBCL N=529	PMBCL N=27	t-FL N=157	t-NFL N=47	p-value[1]	t-MZL N=23	RS N=15	t-other N=9
0-2	139 (47.3)	15 (75.0)	43 (50.0)	12 (54.5)	0.11	7 (46.7)	1 (100.0)	4 (66.7)
3+	155 (52.7)	5 (25.0)	43 (50.0)	10 (45.5)		8 (53.3)	0	2 (33.3)
Missing/unknown	235	7	71	25		8	14	3
More than 2 lines of therapy, N (%)								
No	236 (66.1)	16 (66.7)	57 (57.6)	12 (46.2)	0.11	10 (52.6)	0	2 (33.3)
Yes	121 (33.9)	8 (33.3)	42 (42.4)	14 (53.8)		9 (47.4)	1 (100.0)	4 (66.7)
Missing/unknown	172	3	58	21		4	14	3
Previous SCT, N (%)								
No	263 (83.8)	20 (100.0)	66 (73.3)	21 (87.5)	0.030[5]	15 (88.2)	1 (100.0)	5 (83.3)
Auto	46 (14.6)	0	23 (25.6)	2 (8.3)		2 (11.8)	0	0
Allo	5 (1.6)	0	1 (1.1)	1 (4.2)		0	0	1 (16.7)
Missing/unknown	215	7	67	23		6	14	3
Refractory to CHOP, N (%)								
No	111 (40.7)	4 (21.1)	44 (55.7)	10 (52.6)	0.017[4]	8 (57.1)	0	2 (50.0)
Yes	162 (59.3)	15 (78.9)	35 (44.3)	9 (47.4)		6 (42.9)	1 (100.0)	2 (50.0)
Missing/unknown	256	8	78	28		9	14	5
HCT CI 3+, N (%)								
0	254 (91.7)	18 (94.7)	78 (92.9)	19 (86.4)	0.74	13 (81.2)	1 (100.0)	5 (100.0)
1	23 (8.3)	1 (5.3)	6 (7.1)	3 (13.6)		3 (18.8)	0	0
Missing/unknown	252	8	73	25		7	14	4
Response to bridging, N (%)								
CR/PR	236 (60.5)	14 (60.9)	50 (43.5)	26 (66.7)	0.007[4]	11 (68.8)	11 (73.3)	4 (50.0)
SD/PD	154 (39.5)	9 (39.1)	65 (56.5)	13 (33.3)		5 (31.2)	4 (26.7)	4 (50.0)
Missing/unknown/no bridging	139	4	42	8		7	0	1

[1]p-value comparing *de novo* DLBCL, PMBCL, t-FL and t-NFL. [2]Compares product in those infused and excludes PMBCL (only approved for axi-cel). [3]Compares infusion rates. [4]No significant differences between *de novo* DLBCL and t-NFL; PMBCL significantly younger than *de novo* DLBCL (p=0.0001); t-FL significantly less likely to have been refractory to R-CHOP (p=0.021) and less likely to have responded to bridging (p=0.001) when compared to *de novo* DLBCL. [5]No pairwise comparison with *de novo* DLBCL was significant.

Figure 1. Overall survival (OS) and progression-free survival (PFS). (A) OS total cohort, (B) PFS total cohort. (C) OS by lymphoma subgroups. (D) PFS by lymphoma subgroups. DLBCL: Diffuse large B-cell lymphoma,; PMBCL: Primary mediastinal B-cell lymphoma. T-FL: Transformed follicular lymphoma; T-NFL: Transformed non-follicular lymphoma.


A
1.00
0.75
0.50
0.25
0.00
Proportion alive
0
6
12
18
24
30
Time since approval (months)
Number at risk
763
519
325
172
73
1
B
1.00
0.75
0.50
0.25
0.00
Proportion alive without progression
0
6
12
18
24
30
Time since infusion (months)
Number at risk
614
317
202
112
21
0
C
1.00
0.75
0.50
0.25
0.00
Proportion alive
De novo DLBCL
PMBCL
tFL
t-NFL
0
6
12
18
24
30
Time since approval (months)
Number at risk
De novo DLBCL 529 347 213 108 43 1
PMBCL 27 23 16 11 5 0
tFL 157 118 73 42 19 0
t-NFL 47 28 20 9 4 0
D
1.00
0.75
0.50
0.25
0.00
Proportion alive without progression
De novo DLBCL
PMBCL
tFL
t-NFL
0
6
12
18
24
30
Time since infusion (months)
Number at risk
De novo DLBCL 420 205 129 67 14 0
PMBCL 26 16 10 6 1 0
tFL 130 78 49 32 6 0
t-NFL 38 18 14 7 0 0

Data Supplement

Outcomes after chimeric antigen receptor T-cell therapy across large B-cell lymphoma subtypes

Table S1. CAR T toxicity across subgroups

Best response	*De novo* DLBCL N=420	PMBCL N=26	t-FL N=130	t-NFL N=38	p-value[1]	t-MZL N=17	RS N=13	t-other N=8
Grade 3+ CRS	20/420 (4.8%)	3/26 (11.5%)	7/130 (5.4%)	2/38 (5.3%)	0.43	2/17 (11.8%)	0/13 (0%)	0/8 (0%)
Any grade CRS[2]	272/319 (85.3%)	22/26 (84.6%)	75/98 (76.5%)	19/26 (73.1%)	0.11	11/13 (84.6%)	4/6 (66.7%)	4/7 (57.1%)
Grade 3+ ICANS	66/420 (15.7%)	5/26 (19.2%)	21/130 (16.2%)	3/38 (7.9%)	0.55	1/17 (5.9%)	2/13 (15.4%)	0/8 (0%)
Any grade ICANS[2]	132/319 (41.4%)	9/26 (34.6%)	35/98 (35.7%)	5/26 (19.2%)	0.13	2/13 (15.4%)	3/6 (50.0%)	0/7 (0%)
Steroids used	119/274 (43.4%)	9/23 (39.1%)	36/77 (46.8%)	3/19 (15.8%)	0.088	3/13 (23.1%)	0/1 (0%)	0/5 (0%)
Tocilizumab used	199/274 (72.6%)	16/23 (69.6%)	53/78 (68.0%)	11/19 (57.9%)	0.48	7/13 (53.9%)	1/1 (100%)	3/5 (60.0%)
ICU admission	69/244 (28.3%)	7/23 (30.4%)	16/73 (21.9%)	3/18 (16.7%)	0.55	3/13 (23.1%)	0/1 (0%)	0/4 (0%)
Grade 3+ thrombocytopenia 1 month[3]	57/146 (39.0%)	6/17 (35.3%)	26/54 (48.2%)	5/10 (50.0%)	0.59	4/6 (66.8%)	-	1/4 (25.0%)
Grade 3+ neutropenia 1 month[3]	68/145 (46.9%)	7/16 (43.8%)	26/53 (49.1%)	5/9 (55.6%)	0.94	3/5 (60.0%)	-	2/4 (50.0%)
Grade 3+ thrombocytopenia 3 months[3]	9/81 (11.1%)	2/11 (18.2%)	6/37 (16.2%)	2/5 (40.0%)	0.23	1/3 (33.3)	-	1/2 (50.0%)
Grade 3+ neutropenia 3 months[3]	15/81 (18.5%)	2/11 (18.2%)	7/37 (18.9%)	2/5 (40.0%)	0.63	1/3 (33.3)	-	1/2 (50.0%)

[1]Fisher's exact test comparing rates in de novo DLBCL/PMBCL/t-FL and t-NFL groups. [2]Any grade: chi-squared for trend 0.13 (CRS), 0.036 (ICANS: lower grades in t-NFL patients, p=0.30 if these patients are excluded). [3]Thrombocytopenia and Neutropenia rates exclude patients who have relapsed by each timepoint.