

New therapies for relapsed or refractory aggressive B-cell lymphoma increase survival: Analysis from the RELINF registry of the GELTAMO group

Mariana Bastos-Oreiro¹  | Pau Abrisqueta² | Antonio Gutierrez³ | Ana Jiménez Ubieto⁴ | Maria Poza⁴ | Paula Fernandez-Caldas¹ | María José LLacer¹ | Sonia Gonzalez de Villambrosia⁵ | Raúl Córdoba⁶ | Alberto López⁶ | Elena Ceballos⁷ | Belen Navarro⁸ | Ana Muntañola⁹ | Eva Donato¹⁰ | Eva Diez-Baeza¹¹ | Lourdes Escoda¹² | Hugo Luzardo¹³ | María José Peñarrubia¹⁴ | Daniel García Belmonte¹⁵ | Emilia Parda¹⁶ | Claudia Lozada¹⁷ | Alejandro Martín García-Sancho¹¹

Correspondence: Mariana Bastos-Oreiro (marianabeatriz.bastos@salud.madrid.org)

Aggressive B-cell lymphomas (ABCL) represent a heterogeneous group of biologically different diseases with variable clinical outcomes.^{1,2} Around one-third of patients are not cured with frontline treatment, and outcomes for this relapse/refractory (R/R) group are extremely poor with conventional treatments.^{3–5} However, during the last years, several promising new therapies (NTs) have been progressively incorporated into the treatment arsenal, such as new monoclonal antibodies (MAs), cellular therapy with T cells with chimeric antigen receptor (CAR-T cells), or, in a lesser extent, bispecific antibodies (BiMAs). Polatuzumab vedotin–bendamustine–rituximab⁶ was approved in Europe since 2019 and funded in Spain since September 2019. Tafasitamab–lenalidomide⁷ was approved for European Medicines Agency (EMA) in August 2021 and funded in Spain in 2023. CAR-T cell was approved for EMA in 2018,^{8–10} and funded in Spain in 2019. BiMAs are still only available in clinical trials.^{11,12}

Our study aims to assess to what extent these new treatments have been incorporated into the clinical practice and how this has impacted patient survival.

This is a multicentre retrospective study based on the GELTAMO RELINF platform, which has been active since January 2014 and

includes only essential variables such as histological subtype, age, gender, and current situation. From 60 centers actively registering on the platform invited to participate, 17 centers accepted. All of these centers are university hospitals, and five are CAR-T cell therapy providers. Participating centers completed a short questionnaire on disease relapse and the use of NTs in their registered patients. Conventional treatments only include chemotherapy ± anti-CD20 antibodies ± autologous transplant. Investigators in each center were required to report relapses with histological confirmation of large B-cell lymphoma (LBCL). For refractory patients, histological confirmation was not mandatory. The histologies included were diffuse LBCL (DLBCL) and high-grade B-cell lymphoma (HGBCL) not otherwise specified (NOS) and double hit. Early relapse was defined as within 12 months of completion of induction therapy, and late relapse was defined as more than 12 months.

The present analysis was based on a January 2023 data cut-off. Overall survival (OS) and progression-free survival (PFS) were determined from diagnosis. OS was also calculated since the date of the first relapse (OS2). All reported *p* values were two-sided, and statistical significance was set at *p* < 0.05. Analyses were performed using SPSS version 29 (SPSS).

¹Hospital Universitario Gregorio Marañón. Instituto de investigación Sanitaria Gregorio Marañón (IISGM), Madrid, Spain

²Hospital Vall d Ebron, Barcelona, Spain

³Hospital Son Espases, IIdISBa, Palma de Mallorca, Spain

⁴Hospital Universitario 12 de Octubre, Madrid, Spain

⁵Hospital Universitario de Valdecillas, Santander, Spain

⁶Hospital Fundación Jiménez Díaz, Madrid, Spain

⁷Hospital Morales Meseguer, Murcia, Spain

⁸Hospital Universitario Puerta de Hierro, Madrid, Spain

⁹Hospital Mutua Tarrasa, Barcelona, Spain

¹⁰Hospital Dr Peset, Valencia, Spain

¹¹Hospital Universitario de Salamanca, IBSAL, CIBERONC, Universidad de Salamanca, Salamanca, Spain

¹²Hospital Juan XXIII, Tarragona, Spain

¹³Hospital Universitario Dr Negrin, Gran Canaria, Spain

¹⁴Hospital Universitario de Valladolid, Valladolid, Spain

¹⁵Hospital de La Zarzuela, Madrid, Spain

¹⁶Hospital Virgen del Puerto, Cáceres, Spain

¹⁷Hospital IVO, Valencia, Spain

From 3270 patients with ABCL registered, 2853 patients were included in the present analysis; exclusion reasons are described in Supporting Information S1: Table 1.

Supporting Information S1: Table 2 shows patients' characteristics. Three hundred fifty-three patients (47.8%) were identified as primary refractory, whereas 139 patients (19%) relapsed between 3 months and 1 year after completion of induction treatment. These 492 patients were analyzed together as the "early relapse group" (67% of R/R patients). Two hundred and forty-six patients had a late relapse (33%). The distribution was 132 (54%) during the second year, 51 (21%) during the third year, 24 (10%) during the fourth, 16 (6%) during the fifth year, and 23 (10%) from the sixth year onward.

Supporting Information S1: Table 3 describes the characteristics and outcomes of patients who relapsed early and late. A third of relapses were in patients older than 80 years. Regarding histologies, early relapses were most common in double/triple hit HGL (34%) and T-cell rich DLBCL (29%) compared to DLBCL or HGL NOS (16%) ($p < 0.001$).

Of 738 patients with detailed information on the type of salvage treatments, 236 received NT: 144 received CAR-T (90 as the only NT), 68 BiMAs (27 as the only NT), 92 polatuzumab-based (46 as the only TN), 14 tafasitamab-lenalidomide (12 as the only NT), and 61 received multiple NTs. Specific information on the number of treatment lines was available in 730 of the 738 patients. The median number of lines among R/R patients was 2.¹⁻¹⁰ The use of NT was much more frequent in patients who received three or more lines of treatment. The immense majority of patients who received only two treatment lines ($n = 376$) were treated with conventional treatments (90%), and only 38 (10%) received NT. By contrast, among 354 patients who received more than two lines of treatment, 194 (55%) received NT: 130 (67%) received CAR-T cell therapy (80 as the only NT), 75 (21%) polatuzumab (35 as the only NT), nine (2%) tafasitamab-lenalidomide (seven as the only NT), 55 (15%) BiMA (18 as the only NT), 54 (30%) received multiple NTs, whereas 160 (45%) of these patients did not receive any NT. While 175 (74%) patients received just one NT, 50 (21%) received two combined NTs, and 11 (5%) received three. As shown in Supporting Information S1: Table 4, there were no differences in the timing of relapse (early vs. late) between patients treated with conventional treatments versus NT.

With a median follow-up of 49 months (95% confidence interval, CI: 47–51), the median PFS for the entire cohort was 54 months (95% CI: 48–61), and the median OS was 82 months (95% CI: 74–90) (Supporting Information S1: Figure 1A).

Supporting Information S1: Table 5 shows factors identified as related to OS, since diagnosis. In multivariate analysis, early relapse (hazard ratio, HR 2.91 [95% CI: 2.35–3.6]; $p < 0.001$), number of total lines (HR 1.4 [95% CI: 1.14–1.71]; $p = 0.018$), age over 65 years (HR 1.83 [95% CI: 1.17–2.86]; $p = 0.008$), age over 75 years (HR 2.86 [95% CI: 1.84–4.46]; $p < 0.001$), use of CAR-T cell therapy (HR 0.67 [95% CI: 0.47–0.96]; $p = 0.029$), and BiMAs (HR 0.5 [95% CI: 0.37–0.68]; $p < 0.001$) impacted on OS.

Considering the 738 R/R patients only, with a median follow-up of 40 months, the median OS (mOS2) was 16.8 (95% CI: 14.5–19) months (Supporting Information S1: Figure 1B). It was longer for the group of patients treated with more than two lines (19 months [95% CI: 16–22]) than in patients treated with only two lines (11 months [95% CI: 6–17]; $p < 0.001$) (Figure 1A).

Median OS2 was significantly shorter ($p < 0.001$) in the early relapse group (13.5 months [95% CI: 11.5–15.5]) than in late relapses (31.1 months [95% CI: 22.5–39.8]; $p < 0.001$) (Figure 1B). Median OS2 for relapsed patients treated with NT was 31.1 months (95% CI: 22.5–39.7) compared with 11.9 months (95% CI: 9.2–14.6) for the group of standard treatment ($p < 0.001$) (Figure 1C). Patients who received CAR-T cell therapy had better OS2 than those who did not

($p < 0.001$) (Figure 1D). Among early relapses, the median OS2 for patients who received CAR-T cell therapy was 32.2 months (95% CI: 16–48.4) versus 10.5 (95% CI: 7.6–13.4) for those who did not ($p < 0.001$) (Figure 1E).

When analyzing whether the patients initially belonged to a CAR-T provider center, we identified better mOS2 for patients from CAR-T cell centers than non-CAR-T provider centers, both among early relapses (25 months [95% CI: 20.6–29.3] vs. 14.9 months [95% CI: 12.2–17.5]; $p < 0.001$) and late ones (80.7 months [95% CI: 60.1–101.4] vs. 57.7 months [95% CI: 42.4–72.9]; $p = 0.011$) (Supporting Information S1: Figure 2). Characteristics of both groups are present in Supporting Information S1: Table 6. Interestingly, NT was significantly more commonly used in CAR-T provider centers, especially CAR-T cell therapy.

Factors related to OS2 are described in Table 1. The multivariable analysis identified early relapse (HR 1.68 [95% CI: 1.37–2.06]; $p < 0.001$), age over 65 years (HR 1.91 [95% CI: 1.23–2.98]; $p = 0.004$), treatment with CAR-T cell therapy (HR 0.68 [95% CI: 0.51–0.90]; $p = 0.007$), and to belong to a CAR-T cell center (HR 0.7

TABLE 1 Univariate analysis of OS since the first relapse.

	Median OS2 (95% CI)	p Value
Sex		0.72
Male	16 (13–20)	
Female	18 (15–21)	
Age		<0.001
<40	31 (17–45)	
40–64	26 (18–34)	
65–74	14 (10–19)	
>74	8 (6–10)	
Diagnosis		0.23
DLBCL	18 (15–20)	
DLBCL T-cell rich	26 (12–41)	
HGL NOS	19 (12–28)	
HGL double/triple hit	8 (4–11)	
Type of relapse		<0.001
Late relapse	31 (22–40)	
Early relapse	13 (11–15)	
Treatment lines (all)		0.018
2	11 (6–16)	
>2	19 (16–22)	
CAR-T cell center		<0.001
Yes	24.7 (18.1–31.3)	
No	11.3 (8.9–13.7)	
New immunotherapies if relapse		
No	12 (9–15)	
CAR-T	37 (31–44)	<0.001
BiAB	23 (17–29)	0.024

Note: Bold values indicate statistical significant at $p \leq 0.05$.

Abbreviations: BiAB, bispecific antibodies (glofitamab, epcoritamab, blinatumumab); CAR-T, T cells with chimeric antigen receptor; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HGL, high-grade lymphoma; MA, monoclonal antibodies (polatuzumab, tafasitamab, loncastuximab); NOS, not otherwise specified; OS, overall survival.

[95% CI: 0.58–0.85]; $p < 0.001$) as the variables independently related with OS2.

The advent of NTs in recent years is improving the prognosis of R/R ABCL patients.^{13,14} Here, we evaluated how these NTs have been used and how much this has impacted patient survival.

Regarding the time until the first relapse, early relapses during the first year after induction therapy were significantly more frequent, as described previously,^{15,16} representing 67% of relapses. Likewise, adverse histologies such as HGBCL and T-cell-rich B-cell lymphoma showed a higher frequency of early relapses than DLBCL NOS. Although the greater aggressiveness of these histologies is well known,^{17,18} these data have not been previously reported to the best of our knowledge. Moreover, we were also able to find a remarkable difference in terms of survival of suffering early versus late relapses, with mOS2 of 13 versus 31 months, respectively. This fact is well known, as previously described in the CORAL and the ORCHARRD trials,^{15,16} but here, with a median follow-up of more than 4 years, we have demonstrated it in a real-life registry population.

Regarding age, the proportion between early and late relapses is maintained through the different age ranges but relapses in patients older than 75 years are less frequent. Despite this, as previously described,¹⁹ patients older than 75 have worse OS than younger ones, among other reasons because they receive in most cases adjusted treatments of less intensity.²⁰

In our series, globally, 32% of the patients received NT. The use of NT has been infrequent in the first relapse. However, it must be considered that only polatuzumab and tafasitamab would be available for this indication. The impact of the use of NT, more

widespread from the third line, is reflected in the improvement in the OS2 of these patients compared to those who only receive two lines, as shown in Figure 1A.

We obtained exciting results regarding how introducing NT has globally improved survival for patients with ABCL. Considering the results of the pivotal trials of NT on this population^{8–12} and the real-world data,^{21–23} it was expected. In this sense, we found that BiMA and CAR-T were related to better outcomes. However, only CAR-T was maintained as an independent variable in the multivariate analysis for those patients who relapsed, although it is important to consider that this therapeutic group was the most represented.

Finally, we found that patients treated in CAR-T cell centers showed superior survival compared with those treated in non-CAR-T cell centers, which was maintained as an independent variable in the multivariate analysis. These results could be related to several factors. It could represent the advantage of easier or faster access to CAR-T cell therapy but also could be related to the quickest access to new drugs in clinical trials, more common in centers of high complexity. However, with the available data, we cannot rule out that patients treated in CAR centers represent a more selected group with better biology that could explain the improved OS in this group.

We acknowledge certain limitations in our study. Being a registry study, we do not have detailed data on patient's characteristics or biological features. The total relapse rate is lower than expected, which has to do with patients being diagnosed, especially in large centers, who are finally treated in other centers. On the other hand, we do not have details of the characteristics of the relapse or the complete treatments received. However, this simple analysis has

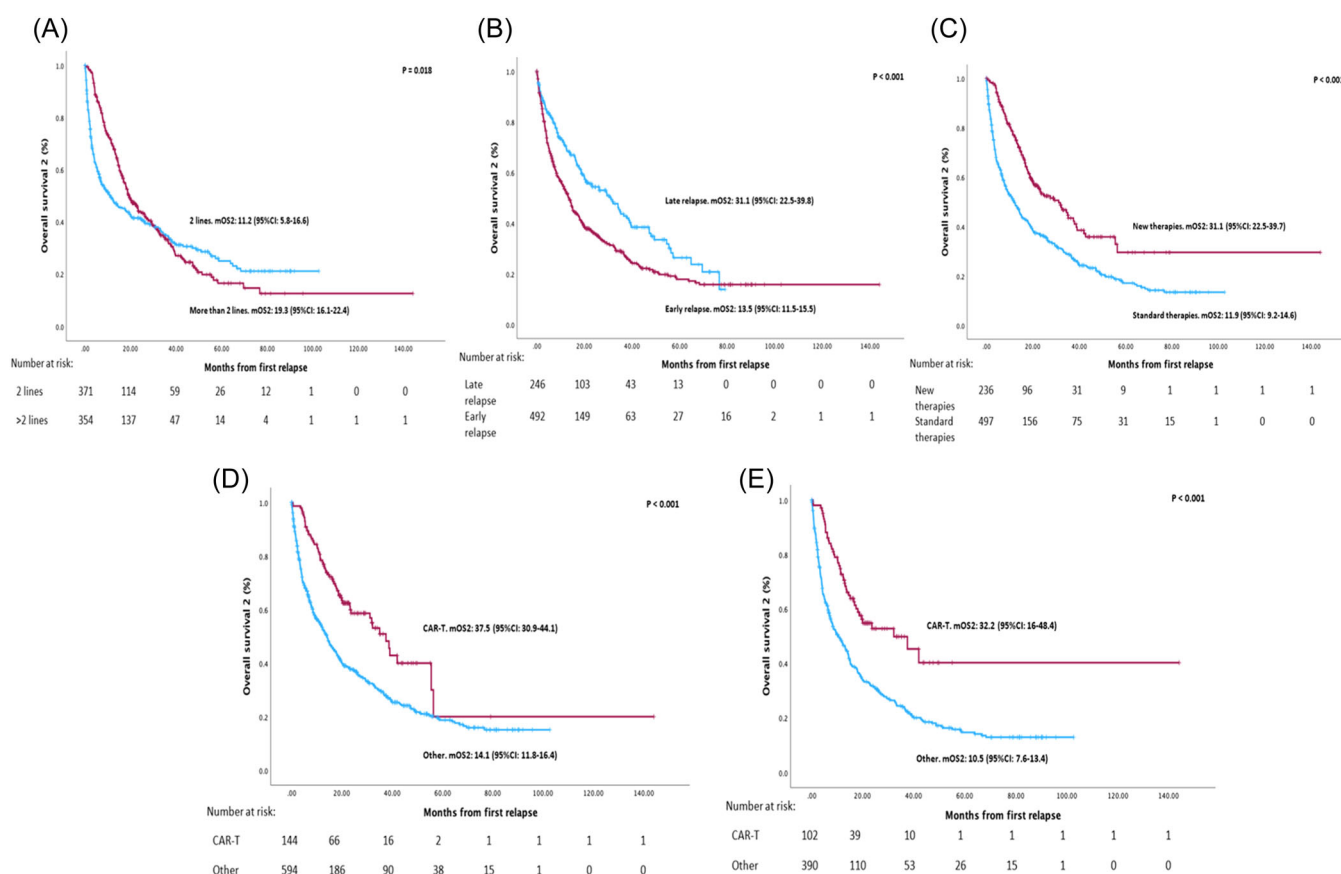


FIGURE 1 Overall survival according to (A) lines of treatment; (B) timing of relapse; (C) use of new treatments; (D) treatment with T cells with chimeric antigen receptor (CAR-T) cell therapy; (E) treatment with CAR-T cell therapy in early relapses.

allowed us to analyze a considerable number of patients in a real-world population, and despite the limitations, we have managed to extract precious information.

In conclusion, our analysis confirms, in a real-world setting, the negative impact of age and timing of relapse on the survival of patients with ABCL. In this regard, histologies such as HGBCL presented more frequent early relapses. Moreover, according to our results, the introduction in recent years of NT has markedly improved survival, especially CAR-T cell therapy.

ACKNOWLEDGMENTS

We thank all the patients and their families. We also thank the Geltamo technical secretariat, especially Angel Cedillo and Silvia Filafarro.

AUTHOR CONTRIBUTIONS

Mariana Bastos-Oreiro designed research, performed research, contributed vital new reagents or analytical tools, analyzed data, and wrote the paper. Pau Abrisqueta, Ana Jiménez Ubieto, María Poza, María José LLacer, Sonia Gonzalez de Villambrosia, Raúl Córdoba, Alberto López, Elena Ceballos, Belen Navarro, Ana Muntañola, Eva Donato, Eva Díez-Baeza, Lourdes Escoda, Hugo Luzardo, María José Peñarribia, Daniel García Belmonte, Emilia Pardo, and Claudia Lozada collected data and performed research. Antonio Gutierrez collected data, performed research, and did the statistical analysis. Alejandro Martín García-Sancho designed research analyzed and interpreted data, and wrote the paper.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FUNDING

This research received no funding.

ORCID

Mariana Bastos-Oreiro  <http://orcid.org/0000-0002-9431-4646>

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

REFERENCES

- Sehn LH, Salles G. Diffuse large B-cell lymphoma. *N Engl J Med*. 2021;384(9):842-858. doi:10.1056/NEJMra2027612
- Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720-1748. doi:10.1038/s41375-022-01620-2
- Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346(4):235-242. doi:10.1056/NEJMoa011795
- Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23(18):4117-4126. doi:10.1200/JCO.2005.09.131
- Bartlett NL, Wilson WH, Jung SH, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *J Clin Oncol*. 2019;37(21):1790-1799. doi:10.1200/JCO.18.01994
- Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2020;38(2):155-165. doi:10.1200/JCO.19.00172
- Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020;21(7):978-988. doi:10.1016/S1470-2045(20)30225-4
- Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544. doi:10.1056/NEJMoa1707447
- Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56. doi:10.1056/NEJMoa1804980
- Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0
- Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2022;387(24):2220-2231. doi:10.1056/NEJMoa2206913
- Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *Lancet*. 2021;398(10306):1157-1169. doi:10.1016/S0140-6736(21)00889-8
- Roschewski M, Longo DL, Wilson WH. CAR T-cell therapy for large B-cell lymphoma—who, when, and how? *N Engl J Med*. 2022; 386(7): 692-696.
- Bastos-Oreiro M, Gutierrez A, Reguera JL, et al. Best treatment option for patients with refractory aggressive B-cell lymphoma in the CAR-T cell era: real-world evidence From GELTAMO/GETH Spanish Groups. *Front Immunol*. 2022;13:855730. doi:10.3389/fimmu.2022.855730
- van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARD study. *J Clin Oncol*. 2017;35(5):544-551. doi:10.1200/JCO.2016.69.0198
- Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184-4190. doi:10.1200/JCO.2010.28.1618
- El Weshi A, Akhtar S, Mourad WA, et al. T-cell/histiocyte-rich B-cell lymphoma: clinical presentation, management and prognostic factors: report on 61 patients and review of literature. *Leuk Lymphoma*. 2007; 48(9):1764-1773. doi:10.1080/10428190701559124
- Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: double hit and triple hit lymphomas and double expressing lymphoma. *Blood Rev*. 2017; 31(2):37-42. doi:10.1016/j.blre.2016.09.004
- Hounsborne L, Eyre TA, Ireland R, et al. Diffuse large B cell lymphoma (DLBCL) in patients older than 65 years: analysis of 3 year real world data of practice patterns and outcomes in England. *Br J Cancer*. 2022;126(1):134-143. doi:10.1038/s41416-021-01525-4
- Morrison VA, Hamilton L, Ogbonnaya A, Raju A, Hennenfent K, Galaznik A. Treatment approaches for older and oldest patients with diffuse large B-cell lymphoma—use of non-R-CHOP alternative therapies and impact of comorbidities on treatment choices and outcome: a Humedica database retrospective cohort analysis, 2007–2015. *J Geriatr Oncol*. 2020;11(1):41-54. doi:10.1016/j.jgo.2019.07.025

21. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2020; 38(27):3119-3128. doi:10.1200/JCO.19.02104
22. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. *J Clin Oncol*. 2020;38(27):3095-3106. doi:10.1200/JCO.19.02103
23. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med*. 2022;28(10): 2145-2154. doi:10.1038/s41591-022-01969-y