HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2020 April ; 26(4): e77–e85. doi:10.1016/j.bbmt.2019.12.771.

Cellular immunotherapy for refractory DLBCL in the CART era: still a role for allogeneic transplantation?

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Abstract

Chimeric antigen receptor-engineered T (CART) cells are a promising new treatment option for patients with multiply relapsed and refractory (R/R) diffuse large B-cell lymphoma (DLBCL). Because of the favourable outcome data reported for CART cells, uncertainty is emerging if there is still a role for allogeneic hematopoietic cell transplantation (alloHCT) in the treatment of R/R DLBCL. This paper provides an overview of available evidence and theoretical considerations to put these two types of cellular immunotherapy (CI) into perspective. Altogether, current data suggest that CART cells are preferred now over transplantation as first choice CI in many clinical situations. However, the majority of patients will fail CART therapy, resulting in an unmet medical

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Author contributions

P.D., A.S., and M.H. designed the concept and wrote the manuscript. All other authors contributed to further development of the concept, helped writing the manuscript, and approved the final version of the manuscript.

Conflict of Interest Disclosure

P Dreger: consultancy for AbbVie, AstraZeneca, Gilead, Janssen, Novartis, Riemser, Roche; speakers bureau for AbbVie, Gilead, Novartis, Riemser, Roche; research support from Neovii and Riemser.

T Fenske: consultancy for Genetech, Adaptive Biotechnologies, AbbVie; speakers bureau for Genentech, Sanofi, Seattle Genetics, Astrazeneca, Celgene; research support to institution from Millennium, Kyowa, TG Therapeutics, Portola, Curis.

S Montoto: Data Monitoring Committee Services for Bayer; travel grant from Gilead.

M Pasquini: consultancy for Amgen, Medigene, Pfizer; speakers bureau for Celgene; research support from BMS, Celgene, Kite/Gilead, Novartis

A Sureda: consultancy for BMS, Celgene, Gilead, Janssen, MSD, Novartis, Sanofi, Takeda; speakers bureau for BMS, MSD, Takeda; travel grants from BMS, Celgene, Janssen, Roche, Sanofi, Takeda

M Hamadani: consultancy for ADC Therapeutics, Celgene, Cellerant Therapeutics, Incyte, Janssen, Magenta Therapeutics, Medimmune LLC, Pharmacyclics; speakers bureau for Celgene (inactive), Sanofi Genzyme; research support from Astellas, Otsuka, Spectrum, Takeda; research support to institution from Celgene, Janssen, Medimmune, Merck, Millenium, Seattle Genetics

need where alloHCT could be beneficial. In contrast, employing alloHCT instead of CART cells as 1st CI should be presently restricted to situations where CART cell therapy deems not feasible or useful, such as patients with refractory cytopenia or incipient MDS. However, alloHCT remains a standard treatment option as 1st CI for patients with in chemosensitive R/R DLBCL when CARTs are not available, or transplantation is preferred by the patient. Continuous collection and analysis of CI outcome data by professional registries appear to be of key importance for developing rational strategies of CI allocation and sequencing.

Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative cellular immunotherapy (CI) for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), and used to be considered as a standard therapeutic option in this setting for eligible patients (1–4). However, the recent approval of CD19-directed chimeric antigen receptor-engineered T cells (CART cells) for treatment of patients with DLBCL having failed two lines of therapy has added a promising new immunotherapeutic tool to the treatment armory of R/R DLBCL. Because of the favourable outcome data reported for CART cells, uncertainty is emerging if there is still a role for alloHCT in the management of multiply R/R DLBCL. As a result, in some recently proposed treatment algorithms, alloHCT has completely disappeared (5).

While CART cell treatment is increasingly used as first CI in patients with multiply R/R DLBCL, the aim of this effort was to identify settings where alloHCT promises to be beneficial in this new treatment landscape. Based on a comprehensive summary of mode of action, efficacy, toxicity, outcome predictors, rescue options, and strengths and limitations of both modalities, a Task Force appointed by the EBMT Lymphoma Working Party and the CIBMTR Lymphoma Working Group (see Supplements for details) developed this proposal for a rational approach to alloHCT at the dawn of the CART era when valid evidence is still sparse.

Scientific basis / current evidence

Mode of action

CART cells: In contrast to alloHCT, where the immunotherapeutic effect relies on a polyclonal immune reaction against multiple undefined target antigens (graft-versus-lymphoma activity; GVL), CART cells exert monoclonal immune activity against defined antigens, such as CD19, thereby avoiding the unspecific graft-versus-host reactions linked to alloHCT efficacy. This immune effect is mediated by the chimeric antigen receptor (CAR) unique to CART cells, thereby combining the HLA-independent antigen-binding properties of the B cell receptor with the potent activating and effector functions inherent to T cells (6, 7).

An essential part of CART therapies is lymphodepleting conditioning which is administered to the patient prior to infusion of the CART product (8–10). Although not fully understood, this lymphodepletion enhances CART cell expansion and has been associated with efficacy, possibly by promoting a pro-inflammatory cytokine milieu, eradicating regulatory T cells,

abrogating endogenous T cell responses against the transgene product, and/or simply creating space for the re-infused cells to expand (6, 7, 11, 12).

AlloHCT: Similar to other lymphoid malignancies, the basis of alloHCT in DLBCL is graft-versus-lymphoma activity (GVL). Evidence for GVL efficacy in DLBCL derives from observations showing that (1) alloHCT but not autoHCT can overcome pretransplant metabolic chemoresistance (13–15), (2) reduced-intensity conditioning (RIC) alloHCT can provide long-term disease control in patients who have failed myeloablative treatment with autoHCT(16–21), (3) T-cell depletion of the graft has detrimental effects on the relapse risk (22) and (4) withdrawal of immune suppression or donor lymphocyte infusion can induce remissions in DLBCL patients progressing after alloHCT (23). Similar to CART cells, successful engraftment of allogeneic hematopoietic cells requires immunosuppressive conditioning (24, 25). Another aim of conditioning in rapidly proliferating neoplasms is to control the disease until the immunotherapeutic potential of the donor immune system can become effective after immunosuppression tapering, i.e. bridging to GVL. This is the rationale for using intensive conditioning in DLBCL (26). However, the superiority of myeloablative conditioning over reduced-intensity conditioning (RIC) in DLBCL is not supported by retrospective studies (3, 16–18, 25, 27), again arguing that the GVL effects are key to disease eradication in DLBCL.

Efficacy

CART cells: The approval trials for both labeled constructs (Axicabtagene ciloleucel, Axicel; Tisagenlecleucel, Tisacel) were largely restricted to patients with DLBCL who had failed >=2 lines of chemoimmunotherapy and/or autoHCT and had active disease at the time of enrolment. Overall response rates (ORR) for those patients who were actually infused with the CART product were consistently high with 52%−83% including 40%−55% complete responses (CR). Whereas partial responses were largely transient, the majority of CRs were sustained, resulting in 12-month progression-free survival (PFS) and overall survival (OS) rates of 34%−44% and 49%−59%, respectively(8, 28, 29) (Table 1a). Considerable differences regarding the turnaround time between apheresis and reinfusion existed, partly explaining why outcomes differed between the trials when calculated by intent-to-treat (ITT)(ORR 75% and 30%, for Axicel and Tisacel, respectively)(30). Preliminary “real-world” experience with commercial CART therapy roughly confirms the response data from the approval trials (31–35)(Table 1b).

AlloHCT: The only recent published prospective trial on alloHCT for R/R DLBCL is DSHNHL 2004-R3 (NCT00785330) for aggressive lymphoma, which enrolled 84 patients including 42 patients with DLBCL (26). Although the trial was formally following an ITT design, patients were eligible only after donor search was completed successfully, resulting in positive patient selection similar to the CART approval trials. With 55% of the patients being chemorefractory at alloHCT, PFS and OS were 45% and 52% at 1 year and 39% and 42% at 3 years post transplant. 1-year relapse/progression incidence was 29% with no relapse event occurring thereafter (26). These results are in keeping with registry studies, consistently showing 3-year PFS rates of 30%−40%(3, 16–18, 20) (Table 2). By design, these studies only included patients who actually received an alloHCT.

Safety

CART cells: The major toxicities of the CD19 constructs discussed here consist of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS)(36), and cytopenias. CRS is associated with mild to severe constitutional symptoms and usually develops within the first week after infusion (37). In the pivotal trials, grade ≥3 CRS has been observed in 11% and 22% of patients receiving Axicel or Tisacel, respectively, but the different grading systems used have to be taken into account (Table 1a).

ICANS is characterized by impaired vigilance, apraxia, confusion and aphasia, which can evolve to severe central symptoms such as seizures and coma (38). Higher grade ICANS is observed in up to 40% of Axicel-treated patients (less after Tisacel), usually within the first 2 weeks after CART cell infusion (8, 9, 29, 31, 32) (Table 1a+b). Upon standard treatment with high-dose steroids ICANS is mostly transient with a median duration of 5–11 days but can follow a prolonged course in individual patients (39, 40), and can contribute to NRM after CART which has ranged thus far from 0 to 9% (41). More than 20% of CD19 CART-treated patients suffer from protracted or recurrent neutropenia and/or thrombocytopenia beyond 4 weeks after reinfusion (28, 29, 42). Persistent neutropenia, along with B cell aplasia and hypogammaglobulinemia, contributes to the increased risk of infections observed in patients treated with CART cells (43).

AlloHCT: Although early mortality has substantially decreased in recent years following the introduction of lower-intensity conditioning regimens, NRM still can be as high as 30% at two years (Table 2). This is largely due to complications of acute and chronic graft-versus-host disease (GVHD). In fact, grade 3–4 acute GVHD can occur in 10–15% of patients allografted for DLBCL, and up to one third of surviving patients at least transiently suffers from quality-of-life-impairing chronic GVHD (3, 17, 26). Other complications which can contribute to mortality and morbidity after alloHCT include neutropenic and opportunistic infections, transplant-related microangiopathy, and veno-occlusive disease (44, 45).

Eligibility and outcome predictors

CART cells: Preliminary data suggest that poor performance status (PS), comorbidity, bulky disease, high tumor load, and high-risk IPI could be associated with inferior outcome of CD19-directed CART therapy (31, 32, 46–48). In contrast, older age (65–75) and chemorefractory disease were not associated with significant outcome disadvantages in the studies available to date (28, 29, 49, 50), although refractory patients tended to do worse in the approval trials. Of note, the presence of a rearrangement of *myc* along with *bcl2* and/or *bcl6* rearrangements (double/triple hit lymphomas; DHL), known to confer a poor prognosis, does not seem to affect CD19 CART therapy efficacy (29, 31, 32). More recently, “Real-World” data suggested that patients receiving Axicel as standard of care had a significantly poorer outcome on multivariate analysis when bridging treatment was needed (which had been an exclusion criterion for ZUMA-1)(51). Similarly, need for bridging was associated with inferior outcome in the JULIET trial (52). Finally, molecular indicators of pretreatment tumor activity and/or early response may emerge as sensitive outcome predictors (53).

Because of a potentially increased risk of neurotoxicity, patients with CNS involvement were excluded from ZUMA-1 and JULIET. Preliminary experience from commercial application of Axicel and Tisacel in patients with secondary CNS lymphoma, however, does not support this concern, while response rates appear to be comparable to patients without CNS involvement (54, 55). With the advent of other CD19-directed targeted therapies (56), CD19 CART therapy efficacy might be compromised by CD19-negative R/R DLBCL, even though an effect of CD19 expression on the response rate was not observed in the pivotal trials(8, 29).

Taken together, although the “usual suspects” PS and tumor aggressiveness seem to play a role, valid predictors of response and response duration after CART therapy have not been proven with the limited body of evidence available to date. However, patients with poor marrow function do not appear to be good candidates for successful CART therapy given that these were excluded from the pivotal trials but may be particularly susceptible to CART-associated cytopenias. This even more if impaired hematopoietic function is associated with morphological or clonal marrow abnormalities suspicious of impending or manifest myelodysplasia.

AlloHCT: Patient-related factors associated with an increased risk of NRM after alloHCT for lymphoma include age 65 years or older, comorbidities, and resistant disease (57–60). The most consistent predictors of poor disease control after alloHCT for lymphoma appear to be refractory disease at transplant and short remission duration after a preceding autoHCT. Based on a study including 503 patients allografted for DLBCL recurrence after autoHCT, investigators from the CIBMTR proposed a score considering disease status at HCT, interval from autoHCT to alloHCT, and PS. Three-year PFS of patients with low risk (chemosensitive disease, good PS, and >12 months between auto- and alloHCT) was 40%, whereas it was <10% in patients meeting none of these criteria (3). In addition, a (mismatched) unrelated donor emerged as significant adverse predictor of PFS in larger cross-sectional studies of the main NHL subtypes (57, 59, 60). Only limited data exist on the efficacy of alloHCT in DHL (61).

Rescue options in case of failure

CART cells: First real-world data obtained in patients with DLBCL progressing or relapsing after CART treatment indicate that the prognosis of these patients is poor, independently of the rescue strategy used (2nd CART infusion, targeted therapy, chemotherapy), in particular if progression occurs within the first 3 months after dosing (62–64). Innovative strategies currently being explored include kinase inhibitors (65), polatuzumab (66), bispecific antibodies (67), lenalidomide (64), and, particularly promising, checkpoint inhibitors (63, 64, 68).

Since all of these agents will mostly provide only short-lived responses, investigating alloHCT consolidation for sensitive post-CART relapse in eligible patients appears to be worthwhile. However, it seems that in DLBCL this approach may often not be feasible if considered at all. In a real-world study, only 5 of 61 patients underwent alloHCT at any time

post CART failure, with 2 of these patients being among 9 patients achieving sustained lymphoma control (62).

AlloHCT: Although chemotherapy, immunomodulation, donor lymphocyte infusion, and second alloHCT could be considered for DLBCL recurrence post alloHCT, the efficacy of all these approaches appears to be limited (69–71), resulting in a generally poor prognosis of patients with DLBCL who progress after alloHCT (72). Preliminary data suggest that CART administration in this setting can be safe and effective, provided that there is no active GVHD and/or no need for immunosuppression (12, 73). At the University of Heidelberg, eight patients received CD19-directed CART therapy for lymphoma relapse after a preceding alloHCT. Safety and efficacy outcomes appeared to be comparable to that of similarly treated patients without prior alloHCT except for reactivation of chronic GVHD in 1 of 8 patients (ML Schubert, abstract submitted). Moreover, novel agents selectively targeting lymphoma cells while sparing GVL activity might improve the outlook of DLBCL relapse after alloHCT, alone or as a bridge to CART therapy (56, 66).

Strengths and limitations

CART cells: The major strengths of CART (relative to alloHCT) are (a) an immediate anti-tumor effect upon infusion of the product, conferring immunotherapeutic activity even against actively proliferating DLBCL; (b) the avoidance of GVHD; and (c) a considerably lower NRM. The majority of CAR-T recipients relapse, but since CART treatment is only at the beginning of its evolution, it can be expected that further development of the methodology will likely improve treatment results of CART cells in DLBCL and other diseases (68, 74, 75).

Regarding limitations, it has to be taken into account that the population of patients included in published CART trials represent a favorable selection, e.g. by excluding patients with poor PS, cytopenias, CNS involvement, and those who deteriorate in the interval between apheresis and planned reinfusion (76). Due to the limited follow-up available to date, long-term safety and efficacy outcomes of CD19 CART therapies are still uncertain, and valid predictors of treatment success still need to be defined. Moreover, there is only very limited data on the efficacy of CD19 CARTs in the absence of active tumor, i.e. if used as consolidating treatment in patients with chemosensitive DLBCL (77). A major disadvantage of commercial CART therapies are their costs and the resulting limited availability in countries with less well equipped health systems.

AlloHCT: Although mostly based on registry studies, available evidence regarding alloHCT in DLBCL appears to be robust in terms of case and study numbers, patient heterogeneity, risk factor characterization, and, in particular, long-term follow-up. Another strength of alloHCT is that it does not depend on a functioning patient T-cell system and can be readily performed in cytopenic patients.

On the other side, similar to CART trials, lymphoma alloHCT studies are positively biased because they are restricted to patients who were actually able to undergo transplantation, thereby disregarding transplant-ineligble patients and early progressors. A recent single-center analysis showed that only two thirds of all patients with DLBCL for whom a donor

search was initiated finally were transplanted, resulting a long-term survival rate of 25% if calculated by intent-to-transplant (78). More importantly, despite significant improvement over time (79), alloHCT is still associated with substantial procedure-related mortality and morbidity. In addition, older age, comorbidities, and PS restrictions may affect alloHCT feasibility in patients with lymphoma. Furthermore, the limited efficacy of alloHCT in unresponsive DLBCL is another point to consider.

A rational approach to alloHCT in the CART era

The advent of CARTs has undoubtedly opened new perspectives for patients with R/R DLBCL. However, due to efficacy limitations and selection effects, the currently commercially available CARTs will address only a small portion of the unmet clinical need of patients with multiply relapsed DLBCL. AlloHCT thus should be actively explored as a rescue strategy for eligible patients failing CART cell therapy, both in clnical trials and by registry analyses. (Given the fact that in particular partial responses to CARTs are often not durable, a field of future research might be investigating alloHCT for consolidating incomplete DLBCL responses obtained with CART therapy, as currently being studied in ALL (80, 81). This approach could be refined by employing additional outcome predictors, such as circulating tumor DNA (53).) Hence, these two cellular immunotherapies could be complementary rather than mutually exclusive. Accordingly, pre-emptive donor search for all potentially transplant-eligible patients treated with CART cells appears worth considering. Bridging into alloHCT after CART failure remains a critical issue, but options for inducing remissions in chemorefactory DLBCL are steadily increasing (12, 64–67).

In patients with DLBCL who have failed two or more lines, both alloHCT and CARTs are available options. Although in the absence of comparative studies published survival rates do not clearly favor the currently approved CART cell therapies over alloHCT (Tables 1a & 2), treatment reality is that they are now the preferred option as first choice CI because of their safety and documented efficacy in refractory disease. Exceptions may consist in circumstances that limit the feasibility of CART therapy, such as refractory cytopenia with or without signs of therapy-related myelodysplasia, where considering alloHCT rather than CART therapy as first CI appears to be reasonable in eligible patients. Also autologous HCT (autoHCT) could still be an option beyond the 2nd line (82). Since its successful application requires transplant eligibility, being autoHCT-naïve, and chemosensitivity, however, it will be a possibility only in selected cases.

In the absence of controlled studies, real-world outcome information addressing the effectiveness of CI approaches is crucial. The transplant field evolved utilizing real-world evidence through the use of outcomes databases for research. The contributions from the EBMT and CIBMTR registries have been invaluable to the field and helped to answer a multitude of questions to improve transplantation results. Similarly, EBMT and CIBMTR are now capturing outcomes of CART cell therapies allowing for quality control and research activities. Furthermore, collecting outcome data of transplants and CART therapies in the same registry appear to be of key importance for developing rational strategies of CI allocation and sequencing.

Conclusions

While CART cells are currently the preferred option as first CI for multiply R/R DLBCL, the natural role of alloHCT appears to be consolidation of ~~sensitive~~ relapses/ progressions after CART treatment in eligible patients who respond to (targeted) salvage therapy. Therefore using alloHCT as rescue strategy for CART failures should be actively explored in clinical trials and by registry analyses. Another potential field of research might be pre-emptive treatment of incomplete responses to CART cells with allotransplantation. In contrast, employing alloHCT instead of CART cells as 1st CI should be presently restricted to situations where CART cell therapy deems not feasible or useful, such as patients with refractory cytopenia or incipient MDS. However, alloHCT remains a standard treatment option as 1st CI for patients with in chemosensitive R/R DLBCL when CARTs are not available, or transplantation is preferred by the patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Tilly H, Gomes da SM, Vitolo U, et al.: Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26 Suppl 5:v116–v125, 2015 [PubMed: 26314773]
2. Majhail NS, Farnia SH, Carpenter PA, et al.: Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 21:1863–1869, 2015 [PubMed: 26256941]
3. Fenske TS, Ahn KW, Graff TM, et al.: Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. Br J Haematol 174:235–248, 2016 [PubMed: 26989808]
4. Duarte RF, Labopin M, Bader P, et al.: Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. Bone Marrow Transplant, 2019
5. Chow VA, Shadman M, Gopal AK: Translating anti-CD19 CAR T-cell therapy into clinical practice for relapsed/refractory diffuse large B-cell lymphoma. Blood 132:777–781, 2018 [PubMed: 29914976]
6. Maus MV, Grupp SA, Porter DL, et al.: Antibody-modified T cells: CARs take the front seat for hematologic malignancies. Blood 123:2625–2635, 2014 [PubMed: 24578504]
7. Schubert ML, Huckelhoven AG, Hoffmann JM, et al.: Chimeric antigen receptor (CAR) T cell therapy targeting CD19 positive leukemia and lymphoma in the context of stem cell transplantation. Hum Gene Ther, 2016
8. Neelapu SS, Locke FL, Bartlett NL, et al.: Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 377:2531–2544, 2017 [PubMed: 29226797]
9. Schuster SJ, Svoboda J, Chong EA, et al.: Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N Engl J Med 377:2545–2554, 2017 [PubMed: 29226764]
10. Schuster SJ, Bishop MR, Tam C, et al.: Sustained Disease Control for Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma: An Updated Analysis of Juliet, a Global Pivotal Phase 2 Trial of Tisagenlecleucel. Blood (ASH Annual Meeting Abstracts):1684, 2018 (abstr)
11. Geyer MB, Brentjens RJ: Review: Current clinical applications of chimeric antigen receptor (CAR) modified T cells. Cytotherapy, 2016
12. Jain T, Bar M, Kansagra AJ, et al.: Utilization of Chimeric Antigen Receptor (CAR) T Cell Therapy in Clinical Practice for Relapsed/Refractory Aggressive B cell non-Hodgkin Lymphoma:

An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant, 2019

13. Spaepen K, Stroobants S, Dupont P, et al.: Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. Blood 102:53–59, 2003 [PubMed: 12609836]
14. Schot BW, Pruim J, van Imhoff GW, et al.: The role of serial pre-transplantation positron emission tomography in predicting progressive disease in relapsed lymphoma. Haematologica 91:490–495, 2006 [PubMed: 16533726]
15. Lambert JR, Bomanji JB, Peggs KS, et al.: Prognostic role of PET scanning before and after reduced-intensity allogeneic stem cell transplantation for lymphoma. Blood 115:2763–2768, 2010 [PubMed: 20124510]
16. van Kampen RJ, Canals C, Schouten HC, et al.: Allogeneic Stem-Cell Transplantation As Salvage Therapy for Patients With Diffuse Large B-Cell Non-Hodgkin's Lymphoma Relapsing After an Autologous Stem-Cell Transplantation: An Analysis of the European Group for Blood and Marrow Transplantation Registry. J Clin Oncol 29:1342–1348, 2011 [PubMed: 21321299]
17. Rigacci L, Puccini B, Dodero A, et al.: Allogeneic hematopoietic stem cell transplantation in patients with diffuse large B cell lymphoma relapsed after autologous stem cell transplantation: A GITMO study. Ann Hematol 91:931–940, 2012 [PubMed: 22245922]
18. Robinson SP, Boumendil A, Finel H, et al.: Autologous stem cell transplantation for relapsed/refractory diffuse large B-cell lymphoma: efficacy in the rituximab era and comparison to first allogeneic transplants. A report from the EBMT Lymphoma Working Party. Bone Marrow Transplant 51:365–371, 2016 [PubMed: 26618550]
19. Urbano-Ispizua A, Pavletic SZ, Flowers ME, et al.: The Impact of Graft-versus-Host Disease on the Relapse Rate in Patients with Lymphoma Depends on the Histological Subtype and the Intensity of the Conditioning Regimen. Biol Blood Marrow Transplant 21:1746–1753, 2015 [PubMed: 25981509]
20. Dreger P, Sureda A, Ahn KW, et al.: PTCy-based haploidentical vs matched related or unrelated donor reduced-intensity conditioning transplant for DLBCL. Blood Adv 3:360–369, 2019 [PubMed: 30723110]
21. Gonzalez-Barca E, Boumendil A, Blaise D, et al.: Outcome in patients with diffuse large B-cell lymphoma who relapse after autologous stem cell transplantation and receive active therapy. A retrospective analysis of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant, 2019
22. Glass B, Nickelsen M, Dreger P, et al.: Reduced-intensity conditioning prior to allogeneic transplantation of hematopoietic stem cells: the need for T cells early after transplantation to induce a graft-versus-lymphoma effect. Bone Marrow Transplant 34:391–397, 2004 [PubMed: 15273707]
23. Bishop MR, Dean RM, Steinberg SM, et al.: Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation. Ann Oncol 19:1935–1940, 2008 [PubMed: 18684698]
24. Bacigalupo A, Ballen K, Rizzo D, et al.: Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 15:1628–1633, 2009 [PubMed: 19896087]
25. Kharfan-Dabaja MA, El-Jurdi N, Ayala E, et al.: Is myeloablative dose intensity necessary in allogeneic hematopoietic cell transplantation for lymphomas? Bone Marrow Transplant 52:1487–1494, 2017 [PubMed: 28368373]
26. Glass B, Hasenkamp J, Wulf G, et al.: Rituximab after lymphoma-directed conditioning and allogeneic stem-cell transplantation for relapsed and refractory aggressive non-Hodgkin lymphoma (DSHNHL R3): an open-label, randomised, phase 2 trial. Lancet Oncol 15:757–766, 2014 [PubMed: 24827808]
27. Bacher U, Klyuchnikov E, Le-Rademacher J, et al.: Conditioning regimens for allotransplants for diffuse large B-cell lymphoma: myeloablative or reduced intensity? Blood 120:4256–4262, 2012 [PubMed: 23007405]

28. Locke FL, Ghobadi A, Jacobson CA, et al.: Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol 20:31–42, 2019 [PubMed: 30518502]
29. Schuster SJ, Bishop MR, Tam CS, et al.: Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 380:45–56, 2019 [PubMed: 30501490]
30. Jacobson CA: CD19 Chimeric Antigen Receptor Therapy for Refractory Aggressive B-Cell Lymphoma. J Clin Oncol 37:328–335, 2019 [PubMed: 30557517]
31. Nastoupil LJ, Jain MD, Spiegel JY, et al.: Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Real World Experience. Blood (ASH Annual Meeting Abstracts):91, 2018 (abstr)
32. Jacobson CA, Hunter B, Armand P, et al.: Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance and Toxicity. Blood (ASH Annual Meeting Abstracts):92, 2018 (abstr)
33. Pasquini MC, Locke FL, Herrera AF, et al.: Post-Marketing Use Outcomes of an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, Axicabtagene Ciloleucel (Axi-Cel), for the Treatment of Large B Cell Lymphoma (LBCL) in the United States. Blood (ASH Annual Meeting Abstracts):764, 2019 (abstr)
34. Riedell PA, Walling C, Nastoupil LJ, et al.: A Multicenter Retrospective Analysis of Clinical Outcomes, Toxicities, and Patterns of Use in Institutions Utilizing Commercial Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B-Cell Lymphomas. Blood (ASH Annual Meeting Abstracts) 134:1599, 2019 (abstr)
35. Jaglowski S, Hu ZH, Zhang Y, et al.: Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Adults with Diffuse Large B-Cell Lymphoma (DLBCL): Real World Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry. Blood (ASH Annual Meeting Abstracts) 134:766, 2019 (abstr)
36. Lee DW, Santomasso BD, Locke FL, et al.: ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant, 2018
37. Neelapu SS, Tummala S, Kebriaei P, et al.: Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 15:47–62, 2018 [PubMed: 28925994]
38. Gajra A, Zettler ME, Phillips E, et al.: Neurological Adverse Events Following CAR-T Cell Therapy: A Real-World Analysis of Adult Patients Treated with Axicabtagene Ciloleucel or Tisagenlecleucel. Blood (ASH Annual Meeting Abstracts) 134:1952, 2019 (abstr)
39. Gust J, Hay KA, Hanafi LA, et al.: Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. Cancer Discov 7:1404–1419, 2017 [PubMed: 29025771]
40. Hirayama AV, Turtle CJ: Toxicities of CD19 CAR-T cell immunotherapy. Am J Hematol 94:S42–S49, 2019 [PubMed: 30784102]
41. Burns E, Anand K, Westin JR, et al.: Comparative Review of 30 Day Non-Relapse Mortality (NRM) in B-Cell Lymphomas Associated with Anti-CD19 Chimeric Antigen Receptor T-Cells (CAR-T) from FDA Database, Clinical Studies, and MD Anderson. Blood (ASH Annual Meeting Abstracts):1931, 2019 (abstr)
42. Fried S, Avigdor A, Bielorai B, et al.: Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant 54:1643–1650, 2019 [PubMed: 30809033]
43. Hill JA, Li D, Hay KA, et al.: Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood 131:121–130, 2018 [PubMed: 29038338]
44. Khosla J, Yeh AC, Spitzer TR, et al.: Hematopoietic stem cell transplant-associated thrombotic microangiopathy: current paradigm and novel therapies. Bone Marrow Transplant 53:129–137, 2018 [PubMed: 28967899]
45. Carreras E, Diaz-Beya M, Rosinol L, et al.: The incidence of veno-occlusive disease following allogeneic hematopoietic stem cell transplantation has diminished and the outcome improved over the last decade. Biol Blood Marrow Transplant 17:1713–1720, 2011 [PubMed: 21708110]

46. Locke FL, Ghobadi A, Lekakis LJ, et al.: Axicabtagene Ciloleucel (Axi-Cel) in Patients With Refractory Large B Cell Lymphoma: Outcomes by Prior Lines of Therapy in ZUMA-1. HemaSphere 2:801, 2018 (abstr)
47. Dean E, Lu H, Lazaryan A, et al.: Association of high baseline metabolic tumor volume with response following axicabtagene ciloleucel in refractory large B-cell lymphoma. J Clin Oncol 37:abstr 7562, 2019 (abstr)
48. Kittai AS, Gordon MJ, Mian A, et al.: Comorbidities Predict Inferior Survival in Patients Receiving CAR T-Cell Therapy for Relapsed/Refractory DLBCL: A Multicenter Retrospective Analysis. Blood (ASH Annual Meeting Abstracts) 134:780, 2019 (abstr)
49. Neelapu SS, Jacobson CA, Oluwole OO, et al.: Outcomes of patients >= 65 years of age in ZUMA-1, a pivotal phase ½ study of axicabtagene ciloleucel in refactory large B cell lymphoma. Hematological Oncol 37 Suppl. 2:303–394, 2019 (abstr)
50. Lin RJ, Lobaugh SM, Pennisi M, et al.: Impact and Safety of Chimeric Antigen Receptor T Cell Therapy in Vulnerable Older Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma. Blood (ASH Annual Meeting Abstracts):1603, 2019 (abstr)
51. Jain MD, Jacobs MT, Nastoupil LJ, et al.: Characteristics and Outcomes of Patients Receiving Bridging Therapy While Awaiting Manufacture of Standard of Care Axicabtagene Ciloleucel CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Results from the US Lymphoma CAR-T Consortium. Blood (ASH Annual Meeting Abstracts):245, 2019 (abstr)
52. Andreadis C, Tam CS, Borchmann P, et al.: Correlation of Bridging and Lymphodepleting Chemotherapy with Clinical Outcomes in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma Treated with Tisagenlecleucel. Blood (ASH Annual Meeting Abstracts):2883, 2019 (abstr)
53. Sworder B, Kurtz DM, Macaulay C, et al.: Circulating DNA for Molecular Response Prediction, Characterization of Resistance Mechanisms and Quantification of CAR T-Cells during Axicabtagene Ciloleucel Therapy. Blood (ASH Annual Meeting Abstracts) 134:550, 2019 (abstr)
54. Frigault MJ, Dietrich J, Martinez-Lage M, et al.: Tisagenlecleucel CAR-T Cell Therapy in Secondary CNS Lymphoma. Blood 134:860–866, 2019 [PubMed: 31320380]
55. Bennani NN, Maurer MJ, Nastoupil LJ, et al.: Experience with Axicabtagene Ciloleucel (Axi-cel) in Patients with Secondary CNS Involvement: Results from the US Lymphoma CAR T Consortium. Blood (ASH Annual Meeting Abstracts) 134:763, 2019 (abstr)
56. Jurczak W, Zinzani PL, Gaidano G, et al.: Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. Ann Oncol 29:1266–1272, 2018 [PubMed: 29444231]
57. McClune BL, Ahn KW, Wang HL, et al.: Allotransplantation for patients age >/=40 years with non-hodgkin lymphoma: encouraging progression-free survival. Biol Blood Marrow Transplant 20:960–968, 2014 [PubMed: 24641829]
58. Raimondi R, Tosetto A, Oneto R, et al.: Validation of the Hematopoietic Cell Transplantation-Specific Comorbidity Index: a prospective, multicenter GITMO study. Blood 120:1327–1333, 2012 [PubMed: 22740454]
59. Kyriakou C, Boumendil A, Finel H, et al.: The impact of advanced patient age on mortality after allogeneic hematopoietic Cell Transplantation for Non-Hodgkin's Lymphoma: A retrospective study by the EBMT Lymphoma Working Party. Biol Blood Marrow Transplant 25:86–93, 2019 [PubMed: 30219698]
60. Shah NN, Ahn KW, Litovich C, et al.: Outcomes of Medicare-age eligible NHL patients receiving RIC allogeneic transplantation: a CIBMTR analysis. Blood Adv 2:933–940, 2018 [PubMed: 29685953]
61. Herrera AF, Rodig SJ, Song JY, et al.: Outcomes after Allogeneic Stem Cell Transplantation in Patients with Double-Hit and Double-Expressor Lymphoma. Biol Blood Marrow Transplant 24:514–520, 2018 [PubMed: 29196080]
62. Chow VA, Gopal AK, Maloney DG, et al.: Outcomes of patients with large B-cell lymphomas and progressive disease following CD19-specific CAR T-cell therapy. Am J Hematol 94:E208–E213, 2019

63. Spiegel JY, Dahiya S, Jain MD, et al.: Outcomes in large B-cell lymphoma progressing after axicabtagene ciloleucel (Axi-cel): Results from the U.S. Lymphoma CAR-T Consortium. J Clin Oncol 37:abstr 7517, 2019 (abstr)
64. Byrne M, Oluwole OO, Savani B, et al.: Understanding and Managing Large B Cell Lymphoma Relapses after Chimeric Antigen Receptor T Cell Therapy. Biol Blood Marrow Transplant 25:e344–e351, 2019 [PubMed: 31279751]
65. Landsburg DJ, Hughes ME, Koike A, et al.: Outcomes of patients with relapsed/refractory double-expressor B-cell lymphoma treated with ibrutinib monotherapy. Blood Adv 3:132–135, 2019 [PubMed: 30651281]
66. Sehn LH, Herrera AF, Flowers CR, et al.: Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol:, 2019
67. Schuster SJ, Bartlett NL, Assouline S, et al.: Mosunetuzumab Induces Complete Remissions in Poor Prognosis Non-Hodgkin Lymphoma Patients, Including Those Who Are Resistant to or Relapsing After Chimeric Antigen Receptor T-Cell (CAR-T) Therapies, and Is Active in Treatment through Multiple Lines. Blood (ASH Annual Meeting Abstracts) 134:6, 2019 (abstr)
68. Chong EA, Svoboda J, Nasta SD, et al.: Sequential Anti-CD19 Directed Chimeric Antigen Receptor Modified T-Cell Therapy (CART19) and PD-1 Blockade with Pembrolizumab in Patients with Relapsed or Refractory B-Cell Non-Hodgkin Lymphomas. Blood (ASH Annual Meeting Abstracts):4198, 2018 (abstr)
69. Wudhikarn K, Brunstein CG, Bachanova V, et al.: Relapse of Lymphoma after Allogeneic Hematopoietic Cell Transplantation: Management Strategies and Outcome. Biol Blood Marrow Transplant 17:1497–1504, 2011 [PubMed: 21338707]
70. Ram R, Gooley TA, Maloney DG, et al.: Histology and Time to Progression Predict Survival for Lymphoma Recurring after Reduced-Intensity Conditioning and Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 17:1537–1545, 2011 [PubMed: 21536145]
71. Horstmann K, Boumendil A, Finke J, et al.: Second Allogeneic Stem Cell Transplantation in Patients with Lymphoma Relapse after a First Allogeneic Transplantation. A Retrospective Study of the EBMT Lymphoma Working Party. Bone Marrow Transplant 50:790–794, 2015 [PubMed: 25751644]
72. Epperla N, Hamadani M, Ahn KW, et al.: Survival of Lymphoma Patients Experiencing Relapse or Progression after an Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 24:983–988, 2018 [PubMed: 29410340]
73. Jain T, Sauter CS, Shah GL, et al.: Safety and feasibility of chimeric antigen receptor T cell therapy after allogeneic hematopoietic cell transplantation in relapsed/ refractory B cell non-Hodgkin lymphoma. Leukemia 33:2540–2544, 2019 [PubMed: 31114023]
74. Fraietta JA, Lacey SF, Orlando EJ, et al.: Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med 24:563–571, 2018 [PubMed: 29713085]
75. Brudno JN, Kochenderfer JN: Chimeric antigen receptor T-cell therapies for lymphoma. Nat Rev Clin Oncol 15:31–46, 2018 [PubMed: 28857075]
76. Smith SD, Reddy P, Sokolova A, et al.: Eligibility for Car T-cell Therapy: An Analysis of Selection Criteria and Survival Outcomes in Chemorefractory DLBCL. Am J Hematol, 2019
77. Bishop MR, Maziarz RT, Waller EK, et al.: Tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma patients without measurable disease at infusion. Blood Adv 3:2230–2236, 2019 [PubMed: 31332046]
78. Selberg L, Stadtherr P, Dietrich S, et al.: The Impact of Allogeneic Hematopoietic Cell Transplantation (alloHCT) on the Outcome of Poor-Risk Non-Hodgkin Lymphoma (NHL): A Retrospective Intent-to-Transplant (ITT) Analysis. Blood (ASH Annual Meeting Abstracts) 134:3328, 2019 (abstr)
79. Hahn T, McCarthy PL Jr., Hassebroek A, et al.: Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. J Clin Oncol 31:2437–2449, 2013 [PubMed: 23715573]
80. Kansagra AJ, Frey NV, Bar M, et al.: Clinical utilization of Chimeric Antigen Receptors T-cells (CAR-T) in B-cell acute lymphoblastic leukemia (ALL) - an expert opinion from the European

Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT). Biol Blood Marrow Transplant, 2018

81. Maude SL, Laetsch TW, Buechner J, et al.: Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 378:439–448, 2018 [PubMed: 29385370]
82. Van Den Neste E, Schmitz N, Mounier N, et al.: Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant 51:51–57, 2016 [PubMed: 26367239]
83. Abramson JS, Palomba ML, Gordon LI, et al.: Pivotal Safety and Efficacy Results from Transcend NHL 001, a Multicenter Phase 1 Study of Lisocabtagene Maraleucel (liso-cel) in Relapsed/Refractory (R/R) Large B Cell Lymphomas. Blood (ASH Annual Meeting Abstracts):241, 2019 (abstr)
84. Hamadani M, Saber W, Ahn KW, et al.: Impact of Pretransplantation Conditioning Regimens on Outcomes of Allogeneic Transplantation for Chemotherapy-Unresponsive Diffuse Large B Cell Lymphoma and Grade III Follicular Lymphoma. Biol Blood Marrow Transplant 19:746–753, 2013 [PubMed: 23380340]

Highlights

- This paper addresses the possible role of alloHCT for R/R DLBCL in the CART era
- AlloHCT should be explored for patients failing CART therapy
- AlloHCT should be considered when CART therapy is not feasible or available
- AlloHCT and CART outcome data should be collected and analysed in registries

Table 1a.

Results of clinically approved or far developed CD19 CARTs in DLBCL: Prospective trials

	ZUMA-1 NCT02348216 (8,28)	JULIET NCT02445248 (29)	TRANSCEND NHL-001 NCT02631044 (83)
Study type	Phase 1/2 prospective	Phase 2 prospective	Phase 1 prospective
Indication	DLBCL or PMBCL or tFL; PD/SD and/or autoHCT failure <12mo	DLBCL; failed 2 lines and/or autoHCT	DLBCL, PMBCL, FL3B; failed 2 lines
N (enrolled/infused)	119 / 108	165 / 115	268/342
Data reported using intent-to- treat principle?	No	No	No
Age (years; median (range)	58 (23–76)	56 (22–76)	63 (18–86)
PS >1 (ECOG)	0%	0%.	n.a.
Prior autoHCT	21%	49%	34% *
Disease status refractory	79%	55%	67%
Construct (Costimulatory domain)	Axicabtagene ciloleucel (CD28)	Tisagenlecleucel (4–1BB)	Lisocabtagene maraleucel (4–1BB)
Bridging therapy permitted * (% patients administered)	No	Yes (90%)	Yes (56%)
Median turnaround time between leukapheresis and reinfusion (d)	17	54	24
Lymphodepleting regimen	FC	FC or bendamustine	FC
Response rate of infused patients (ORR/CR)	83% / 58%	52% / 38%	73%/53%
ORR by ITT	75%	36%	57%
Non-relapse mortality			
	3%	0	1.5%
Progression-free survival (of infused patients)			
1y	44%	35%	6.8 mo median
2y	38%		
Overall survival (of infused patients)			
1y	59%	49%	19.9 mo median
1.5y	52%	40%	
2y	51%		
Risk factors for response	Tumor load	Need for bridging	none
Grade ≥3 neutropenia (overall/> d +28)	80%/26%	33%/25%	60%/n.a. §
Grade ≥3 thrombopenia (overall/> d +28)	40%/24%	28%/39%	27%/n.a.
CRS (grade ≥3)	11% ¶	22% ‡	2%
Grade ≥3 neurotoxicity	32%	11%	10%
Follow-up (months)	27 (IQR 26–29)	14 (0–26)	11

* salvage therapy before leukapheresis or between leukapheresis and infusion

§ 37% had grade ≥3 cytopenia beyond day 28

¶ by Lee criteria (36)

[≠] by Penn criteria (36)

CR, complete response; FC, fludarabine/cyclophosphamide; ITT, intent-to-treat; NA, not available; ORR, overall response rate.

Table 1b.

Results of clinically approved CD19 CARTs in DLBCL: Real-World data

	US Academic center "Real World" (31)	Boston/Seattle "Real World" (32)	CIBMTR Axi-cel (33)	US Academic centers (34)	US Academic centers (34)	CIBMTR Tisa-cel (35)
Study type	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Indication	DLBCL,PMBCL,tFL	DLBCL,PMBCL,tFL, DLBCL transformed from non-FL	DLBCL or PMBCL or transforme d lymphoma	DLBCL, PMBCL, tFL, HGBL	DLBCL, tFL, HGBL	DLBCL or transformed lymphoma
N (enrolled/infus ed)	211 / 165	87 / 76	n.a./ 295	163/149	79/75	70
Data reported using intent-to-treat principle?	NA	NA	No	No	No	No
Age (years;median (range)	59 (21–82)	64	61 (19–81)	58 (18–85)	67 (36–88)	65 (19–89)
PS >1 (ECOG)	19%	n.a.	5%	14%.	6%	4%.
Prior HCT (auto/ allo)	31%/NA	≈30%	34%/NA	29%/NA	23%/NA	23%/6%
Disease status refractory	NA	NA	66%	NA	NA	NA
Construct	Axicabtagene ciloleucel	Axicabtagene ciloleucel	Axicabtagene ciloleucel	Axicabtagene ciloleucel	Tisagenlecleucel	Tisagenlecleucel
Bridging therapy permitted* (%patients administered)	Yes	Yes (40%)	NA	Yes (61%)	Yes (72%)	Yes
Median turnaround time between leukapheresis and reinfusion (d)	27	n.a.	NA	28	44	NA
Lymphodepleting regimen	FC	FC	FC	FC	FC	FC
Response rate of infused patients (ORR/CR)	79% / 50%	64% / 41%	70% / 52%	72% / 43%$	59%/44%$	59% / 38%
ORR by ITT	62%	56%	NA	NA	NA	NA
Non-relapse mortality	2%	7%	NA	8%	6%	0
Progressionfree survival (of infused patients)	NA	NA	NA	NA	NA	NA
1y						
2y						
Overall survival				NA		
(of infused patients)	n.a.	n.a.	NA		NA	NA
1y						
1.5y						
2y						

	US Academic center "Real World" (31)	Boston/Seattle "Real World" (32)	CIBMTR Axi-cel (33)	US Academic centers (34)	US Academic centers (34)	CIBMTR Tisa-cel (35)
Risk factors for response	ECOG >1; bulk; refractory disease; male sex	ECOG >1; bulk; IPI >2; CRP; prior ibrutinib	NA	NA	NA	NA
Grade ≥3 neutropenia (overall/> d+28)	n.a.	n.a.	NA/ 7%§	NA	NA	NA
Grade ≥3 thrombopenia (overall/> d+28)	n.a.	n.a.	NA/ 7%§	NA	NA	NA
CRS (grade ≥3)	7%	16%	10%	13%	1%	4%
Grade ≥3 neurotoxicity	33%	39%	NA	41%	3%	4%
Follow-up (months)	<3	4	6 (1–14)	NA	NA	6 (1–9)

*salvage therapy before leukaoheresis or between leukapheresis and reinfusion

§grade ≥3 cytopenia beyond day 28

$d30 responses

CR, complete response; FC, fludarabine/cyclophosphamide; ITT, intent-to-treat; n.a., not available; ORR, overall response rate.

Table 2.

Studies on alloHCT for DLBCL

	EBMT 2011 (16)	GITMO 2012 (17)	CIBMTR 2013 (84) MAC/RIC	CIBMTR 2016 (3)	EBMT 2010-R-12 (18) MAC / RIC	CIBMTR/EBMT LY16-03 (20) MRD / MUD TCD+ / MUD TCD-/ haplo	DSHNHL 2004-R3 NCT007853 30 (26)
Study type	Registry retrospective	Registry retrospective	Registry retrospective	Registry retrospective	Registry retrospective	Registry retrospective	Phase 2 Prospective
Indication	autoHCT failure	autoHCT failure	Refractory disease	autoHCT failure	DLBCL,alloHCT as 1st HCT (prior autoHCT excluded)	DLBCL, 1st alloHCT (prior autoHCT permitted)	PIF, early relapse, autoHCT failure
N	101	165	533 (incl.80 FL3)	503	132 / 98	1306 525 / 403 / 378/132	84 *
Period	1997–2006	1995–2008	1998–2010	2000–2012	2002–2010	2008–2015	2004–2009
Age (years; median (range))	46 (19–66)	43 (16–65)	46 (19–66) / 53 (20-70)	52 (19–72)	42 (31–50) / 52 (43-57)	55 (19–75)	48 (38–57)
PS >1 (ECOG) or <90% (Karnofsk y)	2%	n.a.	n.a.	10% §	16% / 19%	38%/38%/43% /27%	8% §
Prior autoHCT	100%	100%	15% / 38%	100%	0%	55%/59%/61% /42%	46%
Disease status refractory	26%	33%	100%	21%	46% / 32%	21%/18%/17% /17%	55%
Unrelated donor	29%	35%	34% / 53%	50%	37% / 34%	0%/100%/ 100%/0%	57%
Conditioning regimen RIC or NMA	64%	70%	43%	100%	0% / 100%	100%	0%
Nonrelapse mortality	16%	n.a.	38% / 25%	12%	10% / 5%	n.a.	12%
100	25%			23%	20% / 16%	13%/21%/20% /16%	35%
d	28%		47% / 36%	30%			
1y 3y			53% / 42%		23% / 17%	17%/26%/30% /22%	
Relapse incidence			27% /		46% /	39%/33%/28% /3	
1y	24%	n.a.	32%	33%	46%	4%	29%
3y	30%		28% / 35%	38%	47% / 51%	47%/38%/34% /4 1%	29%
Progressi on-free survival	52%	48%	26% / 32%	44%	34% / 38%	48%/46%/52% /50%	45%
1y	42%	34%		31%			39%
3y	23%	27%	19% / 23%	HR 2.04 (vs CR)	30% / 33%	37%/36%/37% /38%	
3y (if refractory at HCT)			19% / 23%			n.a.	
Overall survival							

	EBMT 2011 (16)	GITMO 2012 (17)	CIBMTR 2013 (84) MAC/RIC	CIBMTR 2016 (3)	EBMT 2010-R-12 (18) MAC / RIC	CIBMTR/EBMT LY16-03 (20) MRD / MUD TCD+ / MUD TCD-/ haplo	DSHNHL 2004-R3 NCT007853 30 (26)
1y	65%	55%	31% / 42%	54%	39% / 50%	65%/56%/63% /66%	52%
3y	52%	42%	19% / 28%	37%	32% / 40%	50%/43%/46% /46%	42%
Risk factors for PFS/OS	Time to rel after auto <12mo / =	Time to rel after auto <12mo / Refractory at HCT, MUD	DLBCL (vs FL3)	Refractory at HCT, poor PS, MAC / Refractory at HCT, poor PS, MAC, Time auto_allo <12mo	n.a.	Refractory at HCT, poor PS / Refractory at HCT, poor PS, age, HCT-CI	n.a. / refractory at HCT, no ATG, >4 lines of pretreatment, mismatched donor
Grade 2-4 (3-4) acute GVHD	33% (n.a.)	29% (10%)	29% / 31%	36% (15%)	n.a.	32%/32%/42% /34% (11%/13%/19%/7%)	30% (n.a.)
Extensive chronic GVHD	17%	n.a.	n.a.	33%	n.a.	n.a.	33%-41% (3y)
1y							
Follow-up (months)	36 (3–112)	39 (1–144)	35 / 30	55 (11–49)	36 (9–68)	49 (12–73)	48 (29–71)

[*] includes 27% patients with T cell lymphoma

[§] Karnofky <80%

ATG, anti-thymocyte globuline; DLBCL, diffuse large B-cell lymphoma; GVHD, graft-versus-host disease; HCT-CI, hematopoietic cell transplantation comorbidity index; MAC, myeloablative conditioning; MUD, matched unrelated donor, n.a., not available; PS, performance status; RIC, reduced intensity conditioning; TCD, T-cell depletion