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Sequencing of cellular therapy and bispecific antibodies for the management of diffuse large B-cell lymphoma

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Running Head: Sequencing therapy in DLBCL

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Abstract

Historically, management of relapsed or refractory (R/R) Diffuse large B-cell (DLBCL) following first-line chemoimmunotherapy has been second-line chemotherapy, followed by high-dose chemotherapy and consolidative autologous hematopoietic stem cell transplantation (auto-HSCT), resulting in durable remissions in approximately 40% of patients. In 2017, chimeric antigen receptor (CAR) T-cell therapy changed the landscape of treatment for patients with R/R DLBCL, with complete response rates ranging from 40-58% and long-term disease-free survival of >40% in the highest risk subgroups, including patients who relapsed after auto-HSCT. Since that time further studies have demonstrated improved overall response rates (ORRs) and survival outcomes in patients with primary refractory or early-relapse (relapse <1 year) DLBCL treated with CAR T-cell therapy compared with auto-HSCT, advancing CAR T-cell therapy into the second-line setting. However, >50% of patients will relapse in the post-CAR T-cell setting. In the past two years, two CD20 x CD3 bispecific antibodies (BsAbs) were FDA approved for the treatment of R/R DLBCL after two or more lines of systemic therapy. These BsAbs have demonstrated ORRs exceeding 50% and durable remissions at > 2yrs of follow-up. Additionally, a notable treatment advantage of BsAbs is their ability to be administered in the community setting, making treatment more accessible for patients. The development and advancement of these novel therapies raise questions regarding the ongoing role of HSCT in the management of relapsed and refractory DLBCL and how to best sequence cellular and Bi-specific therapies to optimize patient outcomes.

Introduction

Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of lymphoid neoplasms that originate from B-cells, T-cells, or natural killer cells[1]. Mature B-cell Lymphomas rank as the 11th most common cancer worldwide, with more than 80,000 new cases diagnosed in the United States each year, and accounting for >60% of all hematopoietic neoplasms[2,3]. Diffuse Large B-cell Lymphoma (DLBCL) is the most common and prototypical aggressive B-cell lymphoma accounting for approximately 30% of cases [1]. In the rituximab era, treatment with anti-CD20 containing chemoimmunotherapy regimens such as R-CHOP, DA-R-EPOCH, or POLA-R-CHP has become the standard of care (SOC) front-line treatment for DLBCL with complete response (CR) rates ranging from 75-80%[4-6]. However, 30-40% of these patients will be refractory to front-line treatment or experience relapse within 5 years[7]. Since 1995, management for relapsed or refractory (R/R) DLBCL has been second-line chemotherapy, followed by high-dose chemotherapy and consolidative autologous (auto) hematopoietic stem cell transplant (HSCT) resulting in durable remission rates in 30-40% of patients[8,9]. However, auto-HSCT is associated with acute and long-term treatment-related toxicities and many patients are thought not to be good candidates for transplant due to advanced age or other preexisting comorbid conditions[10]. Novel therapies such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies (BsAbs) have demonstrated durable treatment responses in the management of R/R DLBCL with tolerable side effect profiles, even for those patients of advanced age or with comorbidities. These advances in cellular therapy raise questions regarding the role of HSCT in the management of R/R DLBCL going forward and how to integrate these novel therapies into clinical practice.

Autologous Stem Cell Transplantation

The PARMA study, published by Philip, et al in the NEJM in 1995 demonstrated superior overall response rates (ORR) for patients treated with intensive chemotherapy followed by consolidative auto-HSCT vs 4 additional cycles of chemotherapy (84% vs 44%). Long term follow-up data showed a superior 5 year (yr.) overall survival (OS) of 53% in the auto-HSCT group compared with 32% with intensive chemotherapy alone, and established auto-HSCT as the SOC for chemotherapy-sensitive, relapsed NHL[9]. The CORAL study further validated these findings in 2010, albeit in the post-rituximab era, and demonstrated a 3-yr progression free survival (PFS) of 37% and 3-yr OS of 49% in patients with R/R DLBCL treated with second-line chemotherapy followed by auto-HSCT. However, this study showed an inferior 3-year PFS of 23% in those patients with early relapsed disease, defined as relapse less than 12 months after diagnosis, treated with second-line chemotherapy followed by auto-HSCT[8,11]. Hamadani et al further investigated the use of auto-HSCT in those patients with early relapsed disease in a large, multi-center retrospective analysis of 516 patients with R/R DLBCL treated with second-line chemotherapy followed by auto-HSCT. This study demonstrated inferior PFS and OS in those patients with early relapsed compared with those patients who relapsed >12 months after diagnosis [12]. In addition, studies examining the use of auto-HSCT in those patients with DLBCL harboring *MYC* gene rearrangement with *BCL2* and/or *BCL6* gene rearrangements, also referred to as high-grade B-cell lymphomas (HGBCL), have demonstrated particularly bad outcomes with 2 year OS <10% [13]. These studies highlight the limitations of second-line chemotherapy + auto-HSCT for the management of R/R DLBCL in higher risk groups.

Chimeric Antigen Receptor T-Cell Therapy

In 2017, CAR T-cell therapy changed the landscape of treatment for patients with refractory DLBCL or relapse following auto-HSCT. The ZUMA-1, JULIET, and TRANSCEND NHL 001 clinical trials, targeting patients who progressed after at least 2 lines of therapy, including auto-HSCT, demonstrated an ORR in 52-83% of patients, CR in 40-58%, and long term OS ranging from 36-42% [14-16]. These studies led to the approval of axicabtagene ciloleucel (axi-cel; Yescarta), tisagenlecleucel (tisa-cel; Kymriah), and lisocabtagene maraleucel (liso-cel; Breyanzi) by the US Food and Drug Administration (FDA) in the third- or later-line setting for R/R DLBCL. The subsequent ZUMA-7 and TRANSFORM clinical trials evaluated CAR T-cell therapy as an earlier line of therapy for patients with primary refractory DLBCL or early relapsed disease compared with SOC chemoimmunotherapy + auto-HSCT. The ZUMA-7 clinical trial enrolled 359 patients with DLBCL, 74% with primary refractory, and 26% with early relapsed disease[17]. Only 64 patients (36%) in the SOC arm achieved at least a PR after second line chemotherapy and went on to receive auto-HSCT compared with 170 patients (94%) who received axi-cel infusion[17]. ZUMA-7 demonstrated superior ORR (83% vs. 50%), CR (65% vs 32%), and median EFS (8.3 months vs 2 months) with axi-cel compared with SOC treatment[17]. The TRANSFORM study randomized patients to SOC chemotherapy followed by auto-HSCT vs liso-cel and enrolled 184 patients. Ninety-one (99%) of the patients randomized to liso-cel received liso-cel infusion while only 43 (46.7%) patients in the SOC arm received auto-HSCT, with progression of disease cited as the most common reason for inability to proceed with auto-HSCT. The TRANSFORM study produced similar results to ZUMA-7. Patients who were randomized to liso-cel compared with SOC chemoimmunotherapy + auto-HSCT had an ORR of 86% vs 46%, CR 66% vs 39%, and median EFS of 10.1 months vs 2.3 months, respectively[18]. Recent long-term follow-up data from the ZUMA-7 study showed superior OS at a median follow-up of 47.2 months with axi-cel when compared with the SOC treatment arm [19]. These studies led to FDA approval of axi-cel and liso-cel for patients in second line who relapsed within 1 year of remission or who never achieved remission after first line therapy.

Auto-HSCT compared with Chimeric Antigen Receptor T-Cell Therapy

Auto-HSCT is associated with treatment related toxicities such as febrile neutropenia, opportunistic infections, and cardiovascular events, with ≥ grade 3 cardiovascular toxicity occurring in 29% of patients within the first 100-day post auto-HSCT and in nearly 60% of patients 70 years of age or older[9,10,20]. Although CAR T-cell therapies are associated with their own unique toxicity profile, namely cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and hypogammaglobulinemia, the PILOT study (a phase II, open-label, multi-center clinical trial) demonstrated the safety and efficacy of liso-cel as second-line therapy in patients who were did not experience early relapse (relapsed > 1 year) but were considered not to be candidates for auto-HSCT based on age or other co-morbid conditions[21]. In this study, the ORR was 80% and CR was 54% with liso-cel [21]. Long-term follow-up data show that with a median follow-up of 18.5 months, the median duration of response was 23 months, and for patients in CR the median duration of response was not reached[21]. Taken together, these studies establish CAR T-cell therapy as the second-line treatment option for those patients with primary refractory or early relapsed disease and those patients who relapse any time after remission but are deemed

to be poor candidates for auto-HSCT based on advanced age or the presence of co-morbid medical conditions.

When considering treatment for R/R DLBCL it is important to consider the financial implications associated with each subsequent line of therapy. In the USA, the estimated cost of anti-CD 19 CAR T-cell therapy ranges from $373,000-1,600,000 compared with $140,000-150,000 with auto-HSCT[22-25]. Several financial analyses have justified the high price tag of CAR T-cell therapy, finding that when accounting for life-years gained due to improved overall survival with the use of CAR T-cell over intensive chemotherapy for R/R DLBCL, the cost of each quality-adjusted life year ranged from $58,146- $82,400[22,25,26]. Nevertheless, it is important to acknowledge that the cost of CAR T-cell therapy may preclude the adoption of this novel therapy over auto-HSCT for management of R/R DLBCL world-wide.

CAR T-cell therapy has also demonstrated remarkable efficacy for the treatment of HGBCL in both the third-, second-, and more recently the first-line setting. The TRANSCEND NHL-001 and ZUMA-1 included 13% and 15% of patients with HGBCL with CR rates of 60.6% and 67%, respectively[14,15]. The ZUMA-7 and TRANSFORM clinical trials also demonstrated superior clinical EFS in patients with primary refractory or early relapsed HGBCL treated with CAR T-cell therapy compared with SOC chemoimmunotherapy + auto-HSCT [17-19]. A subsequent multi-center, phase II clinical trial, ZUMA-12, which examined the use of axi-cel following 2 cycles of chemoimmunotherapy for the front-line treatment of HGBCL demonstrated superior response rates to those historically reported in the literature with ORR of 89% and CR rates of 78% [27]. Randomized trials (e.g. ZUMA 23) of first line CAR T therapy vs standard chemotherapy in high-risk patients are ongoing.

Recently, the FDA announced an investigation into reports of increased rates of subsequent malignant neoplasms (SMN), in particular T-cell lymphomas, following CAR T-cell therapy [28]. Historically rates of SMN after auto-HSCT for the treatment of R/R DLBCL have been reported to range from 6-20% [20]. Following the FDA's announcement multiple large, multi-center, retrospective analyses have demonstrated similar rates of SMN in the post-CAR T-cell setting ranging from 0.9-12.9%, including rates of T-cell neoplasms <0.2% [28-30]. Thus, it is not clear yet if SMNs are a result of CAR-T or the extensive prior therapy these patients have received. Further investigation is needed to evaluate the presence of remnant viral vector genes and CAR transgenes in SMNs arising in the post-CAR T-cell setting.

Is There Still a Role for Autologous Stem Cell Transplantation in B-Cell Lymphoma?

The superior outcomes demonstrated with the use of axi-cel and liso-cel compared with SOC chemoimmunotherapy +auto-HSCT in ZUMA-7 and TRANSFORM raise the question as to whether there is still a role for auto-HSCT for the management of R/R DLBCL. The current literature and consensus guidelines support the use of auto-HSCT in patients with chemotherapy-sensitive disease (able to achieve at least a PR to second line chemotherapy) who relapse >12 months after completion of first-line chemoimmunotherapy and are deemed fit enough to proceed with auto-HSCT[31]. This approach allows for a curative treatment option in about 40% of patients treated with auto-HSCT[11]. In addition, it is important to note that ZUMA-1, TRANSCEND NHL-001, and JULIET included 25-49% of patients who were previously treated with auto-HSCT, and a subgroup analysis of these

studies demonstrated the efficacy of CAR T-cell therapy after treatment failure with auto-HSCT with ORRs ranging from 52- 78%[14-16]. Conversely, there are few data available regarding the role of auto-HSCT following CAR T-cell relapse. Speigel et al reported particularly bad outcomes with salvage chemotherapy in patients who progressed following axi-cel therapy with 29% ORR, 17% CR, and median PFS of only 55 days[32]. Therefore, for those patients who are deemed candidates and proceed with auto-HSCT for the management of R/R DLBCL in the second-line setting, CAR T-cell therapy remains a viable third-line treatment option. It is partly for this reason that auto-HSCT remains a viable approach for those patients who relapse > 1 year post front-line chemotherapy and are fit enough to proceed with transplant.

Bispecific Antibodies

CD20 x CD3 bispecific T-cell engaging monoclonal antibodies (BsAbs) are immunologic agents that cross-link the CD20 surface marker expressed on malignant B-cells to the CD3 surface marker expressed on both cytotoxic and helper T-cells to induce potent T-cell-mediated cytotoxic activity against the CD20 positive malignant B-cells. Both epcoritamab and glofitamab (two novel BsAbs) have demonstrated remarkable efficacy for the management of heavily pre-treated DLBCL.

The phase I/II, multi-institutional study of epcoritamab for the management of large B-cell lymphoma following at least two prior lines of chemoimmunotherapy included 157 patients previously treated with a median of 3 prior lines of therapy and 61.1% of patients who had primary refractory disease[33]. Patients received CRS prophylaxis with prednisone, diphenhydramine, and acetaminophen and epcoritamab was dosed via step-up dosing at 0.16-mg priming dose on day 1 of the first 21-day cycle (C1D1), followed by a 0.8-mg intermediate dose on C1D8, full 48-mg dose on C1D15 and day 1 of all subsequent cycles until disease progression or unacceptable toxicity[33]. Treatment with epcoritamab produced an ORR in 63.1% and a CR in 38.9% with a median duration of response of 12 months. Treatment was well tolerated with 4 patients experiencing grade 3 CRS following epcoritamab infusions (no patients experienced grade 4 or 5 CRS) and 10 patients experiencing all grade ICANS, with only 1 patient with possible ≥ grade 3 ICANS (this patient was also noted to have multiple brain infarcts, making it unclear if neurological changes were related to Epcoritamab)[33].

The phase 2 study of glofitamab included 155 heavily pre-treated patients with DLBLC, 60% of whom had received ≥ 3 prior lines of therapy and 90% who had refractory disease[34]. Patients included in this study received B-cell depleting therapy with 1000mg of obinutuzumab 7 days prior to initial glofitamab infusion. Glofitamab was then administered via step-up doses on day 8 (2.5 mg) and day 15 (10 mg) of the first 21-day cycle, followed by a dose of 30 mg on day 1 of cycles 2 through 12[34]. Treatment with glofitamab resulted in an ORR of 52% and a CR rate of 39%. Of those patients who achieved a CR, 67% remained in CR at 18 months of follow-up[35]. Although only 4% of patients developed ≥ grade 3 CRS, 44 patients required hospitalization for management of CRS. The rate of ICANS was low, occurring in only 12 patients, and ≥ grade 3 ICANS occurred in 3% of patients[34]. Similar findings were also reflected in real-world data of patients treated with glofitamab via compassionate use in Turkey, published by Birtas Atesoglu et al. This study included 43

patients who received at least 1 dose of glofitamab and showed an ORR in 37% of patients and 21% of patients were able to achieve a CR[36]. Based on these studies, in the late spring of 2023, both epcoritamab and glofitamab were approved by the FDA as additional treatment options for patients with R/R DLBCL.

How to Sequence These Therapies

Despite overall response rates > 80% with CAR T-cell therapy in the 2nd line setting, more than 30% of patients will not achieve a CR, and at a median follow-up of 12.9 months nearly 36% of patients who do achieve a CR will experience progression after CAR T-cell therapy[32,37]. Historically, patients relapsing after CAR T-cell therapy have had poor outcomes with a median OS of 5-6 months; however, BsAbs have demonstrated efficacy in the treatment of this heavily pre-treated patient population[33,34].

The phase I-II clinical trial, published by Thieblemont et al., examining the use of epcoritamab for the management of R/R DLBCL included 61 patients previously treated with CAR T-cell therapy (75.4% of whom progressed within 6 months following CAR T-cell infusion)[33]. The subset analysis of this patient population showed an ORR of 54.1% and CR rate of 34.3%, similar to response rates seen in the overall study population. In addition, of those patients who achieved a CR, 88% remained in CR at both 6- and 9-month follow-up [33]. The phase 2 study of glofitamab included 52 patients previously treated with CAR T-cell therapy and reported CR rates of 35%, like those reported with Epcoritamab[34]. Although the efficacy of BsAbs following CAR T-cell therapy progression has been documented in both prospective and retrospective studies, the efficacy of CAR T-cell therapy following treatment of BsAbs is unknown as none of the prospective studies examining CAR T-cell therapy in either the third-, second-, or first-line setting have included patients previously treated with BsAbs [33,34].

In addition, studies have suggested that the lymphoma microenvironment and T-cell activity play a vital role in the efficacy of CAR T-cell therapy for the management of DLBCL [38]. Although data are limited, there is a theoretical concern that continuous BsAbs can lead to T-cell exhaustion, decreasing the proliferative capacity and anti-tumor activity of CAR T-cells in patients previously treated with BsAbs [39]. By contrast, a retrospective analysis by Rentsch, et al. monitored the kinetics of CAR T-cell-specific DNA in peripheral blood before, during, and after glofitamab treatment in 9 patients previously treated with CAR T-cell therapy [40]. Of these patients, 5 patients had detectable CAR T-cell-specific DNA prior to glofitamab infusions. Two patients had a continued decrease in CAR T-cells following glofitamab; however, three patients experienced a re-expansion of CAR T-cells in the peripheral blood after glofitamab with peak expansion occurring a median of 35 days following the start of glofitamab infusions [40]. These data suggest that treatment with BsAbs following CAR T-cell therapy may not only be an effective treatment modality but may also enhance residual CAR T-cell activity.

When to Consider Allogenic Stem Cell Transplantation for B-Cell Lymphoma

Allogeneic (allo) HSCT was the first form of immunotherapy to demonstrate clinical efficacy and potential cure in the treatment of leukemia and lymphoma, and indeed, can be

considered the first cellular therapy and forerunner for the cellular therapy we have been discussing. In 1957, Thomas et. al first described the ability to harness the T-cells and natural killer cells of the donor immune system against a recipient patient's leukemia[41]. This graft-versus-tumor (GVT) effect has served as the foundation for the development of alternative cellular and immunotherapies, such as CAR T-cell therapy. However, despite the efficacy of allo-HSCT and the benefits of GVT effect in the management of R/R DLBLC, resulting in CR in 50-60% of patients, it has historically been used in the 3rd+ line setting, following auto-HSCT, due to the increased treatment related morbidity and mortality when compared with auto-HSCT[42,43]. However, in the post-CAR T-cell therapy setting, Speigel et al. reported particularly poor outcomes in patients treated with salvage chemotherapy alone, suggesting that there may not be a role for consolidative auto-HSCT following CAR T-cell therapy and raising the question of whether patients may benefit from the GVT effect from allo-HSCT following CAR T-cell failure[32].

One multi-center retrospective analysis of 88 patients who received allo-HSCT after anti-CD19 CAR T-cell therapy failure demonstrated a one-year PFS of 45% and OS of 59% [44]. The median number of lines of therapy between CAR T-cell infusion and allo-HSCT was one (with a range of 1-7 lines). Multivariate analysis showed that receiving <2 lines of therapy between CAR T and allo-HSCT and the ability to achieve a complete response at time of allo-HSCT were associated with better transplant related outcomes[44]. These findings suggest that if a patient can achieve a CR with subsequent lines of therapy after CAR T-cell failure, one should consider early allo-HSCT if the patient is deemed to be a candidate for stem cell transplantation.

Given the novelty of CD20 x CD30 BsAbs, there is a paucity of data surrounding the use of allo-HSCT post-BsAbs. Each of the phase II clinic trials that examined the use of either Glofitamab or Epcoritamab for the treatment of R/R DLBCL included 7 patients that went on to receive allo-HSCT after treatment with BsAbs, however, the outcomes of these patient subgroups have not yet been published[33,34]. Additionally, a single-center retrospective analysis from Spain reported 8 patients who received allo-HSCT after treatment with CD20 x CD3 BsAbs (3 patients treated with Epcoritamab and 5 with glofitamab). Patients received a median of 10 doses of BsAbs and 6 patients (75%) were in CR at the time of transplant[45]. Five patients received haploidentical transplants, 2 patients matched unrelated donor, and one matched related donor. All patients received graft-versus-host disease (GVHD) prophylaxis with post-transplant cyclophosphamide. At a median follow-up of 30 months (range 23–37 months) from allo-HSCT, 2-year OS was only 25%. Of the 6 patients who died during follow-up 1 patient died from disease relapse, 3 patients died from infections, and 2 from complications of GVHD[45]. Only 2 of the patients included in this analysis had previously been treated with CAR T-cell therapy[45].

Summary/Conclusion

Based on the current literature, auto-HSCT should still be considered for a subset of patients with chemotherapy-sensitive, relapsed DLBCL who are deemed medically fit for auto-HSCT. Patients with primary refractory DLBCL or early relapsed disease, relapsed disease following auto-HSCT, or who are deemed not to be a candidate for auto-HSCT should be offered potentially curative and definite treatment with CAR T-cell therapy (Figure 1). BsAbs should

be utilized as a line of therapy following CAR T-cell therapy and as an earlier line of therapy in select patients on a case-by-case basis. These situations include those patients in the community who are unwilling or unable to travel to a larger academic center to receive auto-HSCT or CAR T-cell therapy, or those patients who do not wish to receive intensive cellular therapy. In addition, higher rates of severe neurological toxicity have been noted in patients with underlying neurological deficits treated with CAR T-cell therapy [46]. In this subset of patients who are deemed to be at a higher risk for severe complications or toxicities with CAR T-cell therapy, it may be reasonable to consider treatment with BsAbs without prior treatment with CAR T-cell therapy. However, these decisions should be based on a risks vs benefits conversation between physician and patient on an individualized basis. There are limited data to support the use of auto-HSCT after CAR T-cell treatment failure; however, allo-HSCT should be considered for those patients who are able to achieve a CR after CAR T-progression with subsequent lines of therapy (either CD20 X CD3 BsAbs or alternative regimens as suggested in NCCN guidelines)[31]. Ongoing clinical trials are currently investigating the use of both BsAbs and CAR T-cell therapy in combination with chemoimmunotherapy in the front-line setting. As patients are exposed to these cellular therapies earlier in their disease and treatment course, it will be even more important to establish objective criteria and guidelines for the sequencing of these novel therapies.

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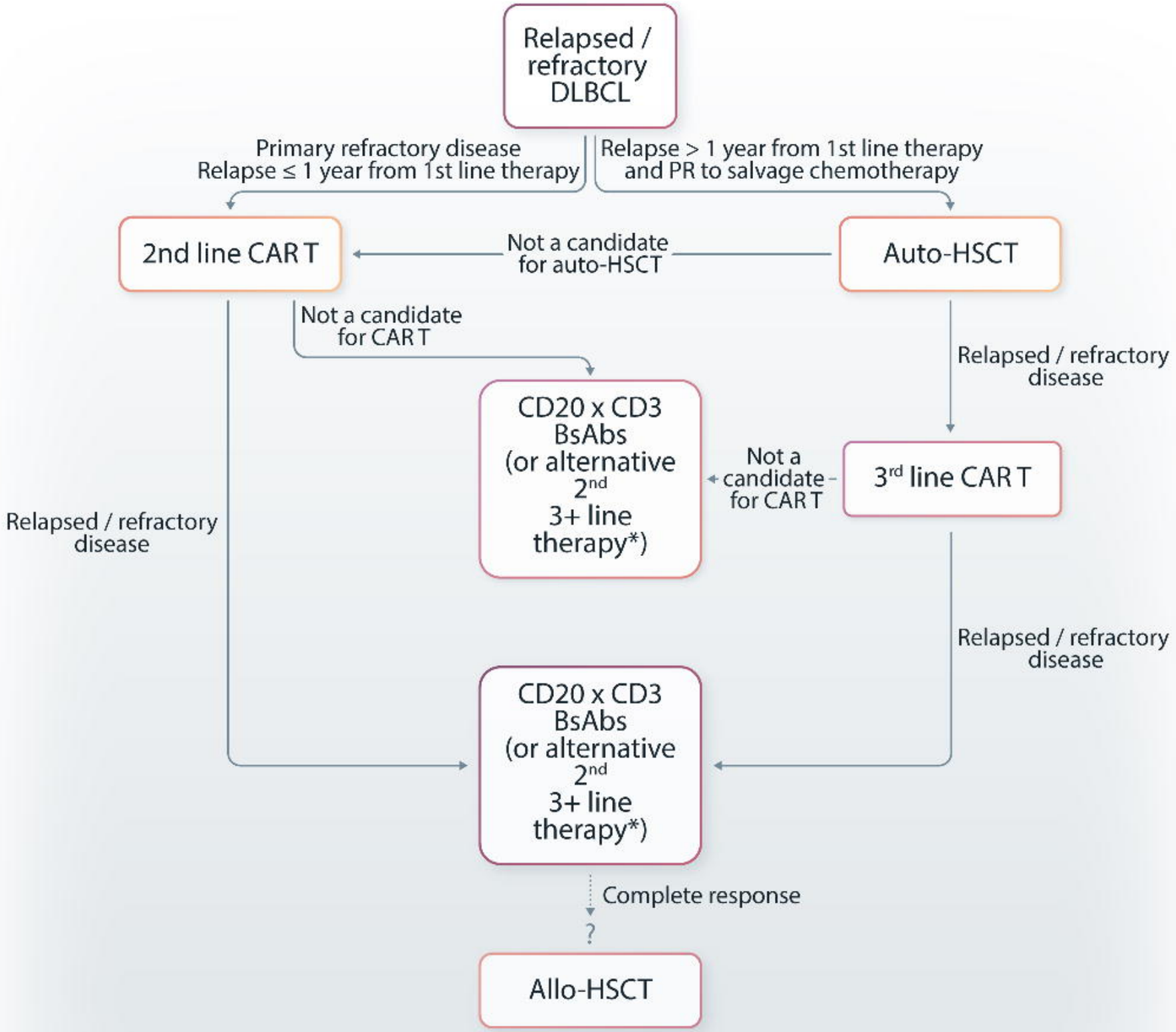
Figure 1. Proposed Treatment Algorithm for the Management of R/R DLBCL

Abbreviations- DLBCL: diffuse large B-cell lymphoma, CAR T: chimeric antigen receptor T-cell therapy, PR: partial response, Auto-HSCT: autologous hematopoietic stem cell transplantation, BsAbs: bispecific antibodies, Allo-HSCT: allogeneic-hematopoietic stem cell transplantation

Figure Legend: Patients with relapsed disease > 1 year following 1st line chemoimmunotherapy with chemotherapy sensitive disease (able to achieve at least a PR to 2nd line therapy) should be considered for auto-HSCT. Those patients who are deemed not to be a candidate for auto-HSCT or patients with primary refractory DLBCL or early relapsed disease should be considered for CAR T-cell therapy in the second line setting. For those patients deemed not to be a candidate for CAR T-cell therapy (due to underlying neurological condition or other comorbid condition) or who are unwilling to travel to a tertiary center to receive care, 2nd or 3rd line treatment options per the NCCN guidelines version 1.2024, including BsAbs should be considered on a case-by-case basis. Patients who experience disease relapse after auto-HSCT should be considered for CAR T-cell therapy, and those patients who are thought not to be a candidate for CAR T-cell therapy should proceed with 3rd line treatment options per NCCN guidelines until treatment related toxicity or disease progression. Those patients who experience disease relapse following CAR T-cell therapy in either the second- or third-line setting should be considered for treatment with BsAbs or an alternative 3+ line treatment option per NCCN guidelines. If patients can achieve a CR with these subsequent lines of therapy, patients should be considered for allo-HSCT.



*2nd and 3rd line treatment options per NCCN guidelines version 1.2024

DLBCL: Diffuse large B-cell lymphoma
CAR T: Chimericantigen receptor T-cell therapy
PR: Partial response
Auto-HSCT: Autologous hematopoietic stem cell transplantation
BsAbs: Bispecific antibodies
Allo-HSCT: Allogenic-hematopoietic stem cell transplantation