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CLINICAL TRIALS AND OBSERVATIONS

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Two years later: CD19 CAR-T going the distance

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In this issue of *Blood*, Abramson et al[1] present follow-up data from TRANSCEND, redemonstrating robust and ongoing responses from the largest pivotal cohort of CD19 chimeric antigen receptor (CAR)-T–treated patients to date. As was seen in prior publications, the authors observed a 73% overall response rate (ORR) and a 53% complete response rate in their efficacy evaluable cohort of 257 patients.[2] These updated data also demonstrated impressive progression-free survival (PFS) and overall survival (OS) of 40.6% and 50.5%, respectively, at 2 years (previously 44.1% and 57.9%, respectively, at 12 months[2]). With all but 2 evaluable patients having completed the 2-year study period, this translates to a median OS of 27.3 months, with median follow-up for survival of 29.3 months. Although direct comparison between clinical trials is difficult because of differing patient populations and design, these results compare favorably to contemporary pivotal trials of CD19-directed CAR-T for non-Hodgkin lymphoma (NHL) with axicabtagene ciloleucel (axi-cel) in the ZUMA-1 trial[3] and tisagenlecleucel (tisa-cel) in the JULIET trial.[4]

TRANSCEND continues to represent the broadest array of lymphoma histologies and largest patient sample among registrational trials of CD19 CAR-T cell therapy for NHL. The 2-year follow-up data presented by Abramson et al highlight data relevant to current day standard-of-care (SOC) clinical use of lisocabtagene maraleucel (liso-cel). More important, the authors present outcomes for patients with secondary central nervous system lymphoma, patients with grade 3B follicular lymphoma, and patients with a history of allogeneic stem cell transplant, with encouraging outcomes in these subgroups. Furthermore, Abramson et al indicate outcomes for the 8% of patients treated with nonconforming product are consistent with previously reported findings indicating slightly inferior ORR (60% vs 70%) and PFS (4.6 vs 6.8 months) compared with those receiving standard liso-cel.[2] As nonconforming product manufacturing has been a continued phenomenon in real-world use of liso-cel, anticipated data from the American Society of Hematology 2023 will be useful to guide clinical decision-making when a nonconforming product is received in SOC use.

Abramson et al helpfully delineate the incidence of cytokine release syndrome (CRS) and immune cell–associated neurotoxicity syndrome (ICANS) during the treatment period by each grade. They report a low rate (CRS, 2%; and ICANS, 10%) of severe (grade ≥3) toxicities during the treatment-emergent period. As the authors note, it is difficult to compare adverse events (AEs) across trials given design and grading system differences. With this caveat, from available contemporary trials with axi-cel[3] and tisa-cel,[4] the authors of TRANSCEND report a favorable toxicity profile for liso-cel. More important, of the 42% of patients treated with liso-cel who experienced CRS, most (58%) of these were grade 1. Low incidence of grade ≥2 CRS is increasingly important as the field considers future outpatient administrations of liso-cel and other CAR-T products to expand access to these therapies. The rate of grade ≥2 ICANS (20%) remains a potential barrier to outpatient administration, although it remains lower than that observed in ZUMA-1.[5] Although prevention and management of CAR-T toxicities have steadily improved, recent efforts to prevent ICANS with prophylactic interleukin 1 receptor antagonist[6] or corticosteroids[7] highlight an ongoing need for more effective ICANS prophylaxis. Overall, the data presented at 2-year follow-up demonstrate a favorable safety profile for liso-cel, although, as with other CD19 CAR products, additional prophylactic approaches may be necessary to facilitate truly universal outpatient administration of CAR-T cell products.

The data presented by Abramson et al continue to highlight prolonged cytopenias and hypogammaglobulinemia as potential complications of CD19-directed CAR-T therapy in a subset of patients, as has been described in other CD19 CAR-T constructs. Most recent analysis of data from the phase 3 trial of liso-cel in second-line treatment of large B-cell lymphoma (LBCL) reported 43% of patients treated with liso-cel had prolonged cytopenias compared with 3% treated with SOC autologous stem cell transplant.[8] This discrepancy implies a potentially CAR-intrinsic process driving prolonged cytopenias and warrants the need of additional studies. Systemic grading of immune effector cell–associated hematotoxicity (ICAHT) has been developed to stratify patients by

risk for long-term aplastic phenotypes and subsequent infection.[9] Clinical stratification of ICAHT risk may be useful in optimal selection of CAR-T product and infusion setting (outpatient vs inpatient) as CAR-T cell therapies continue to expand.

Alongside risk for prolonged cytopenias and hypogammaglobulinemia, Abramson et al provide valuable data regarding long-term infectious complications of liso-cel treatment. As highlighted in recent work,[10] infection remains the primary cause of death aside from disease progression in patients with hematologic malignancies treated with CAR-T. Three of the 11 liso-cel–treated patients who died >23 months after infusion died of infectious causes, highlighting infectious complications as a significant long-term toxicity.

Overall, the authors present favorable data from 2-year follow-up of TRANSCEND, indicating continued efficacy, durability of responses, and a manageable toxicity profile for liso-cel in the treatment of NHL. As evidenced by data from the phase 3 trial of liso-cel as second-line therapy for LBCL (TRANSFORM), efficacy rates for CAR-T are improved with second-line use, and the most recent evaluation of this study appears to demonstrate a potential trend toward an OS benefit compared with prior SOC.[8] Prolonged cytopenias and/or hypogammaglobulinemia stemming from CAR-T therapy, leading to immunosuppression and risk for infection, is an ongoing challenge across all commercially available CAR-T products. Continual improvement in risk stratification and prophylaxis, particularly of neurologic AEs, will be essential to efforts to move CAR-T cell infusion into the outpatient setting. With improved risk stratification, prophylaxis, and management of cytopenias in patients treated with CAR-T, we expect OS to only increase further with time. Regardless, these data, among other data, confirm that CAR-T cells will continue racing, pacing, and plotting the course for the treatment of NHL.

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Old rivals become new friends

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In this issue of *Blood*, Jabbour et al report on the use of inotuzumab ozogamicin (InO) in the setting of measurable residual disease (MRD) in patients with B-cell acute lymphoblastic leukemia (ALL).[1] InO (Besponsa) is an antibody-drug conjugate approved for the treatment of relapsed/refractory B-cell ALL (R/R B-ALL) in adults.[2] InO consists of a CD22-targeting immunoglobulin G4 humanized monoclonal antibody conjugated to calicheamicin, similar to the anti-CD33 antibody-drug conjugate gemtuzumab ozogamicin (GO, Mylotarg).

After initial development in R/R aggressive B-cell non-Hodgkin lymphoma, InO moved to $CD22^+$ R/R B-ALL. Important points emerged from phase 2 studies of InO such as the dosing regimen and increased sinusoidal obstruction syndrome (SOS) rate when combined with chemotherapy despite a better response rate. As seen with GO, splitting the dose into 2 to 3 days of administration per cycle (0.8, 0.5, 0.5 mg/m^2; day 1, day 8, and day 15) resulted in a better tolerance without affecting efficacy, which was a major step forward. In 2016, the results of the registration phase 3 study, the INO-VATE (INotuzumab Ozogamicin trial to inVestigAte Tolerability and Efficacy) study were reported.[3] Although the benefit in survival was not significantly different between the 2 arms,