blood® commentary

CLINICAL TRIALS AND OBSERVATIONS

Comment on Dreyling et al, page 1713

A promising step for high-risk FL

Kai Hübel | University Hospital of Cologne

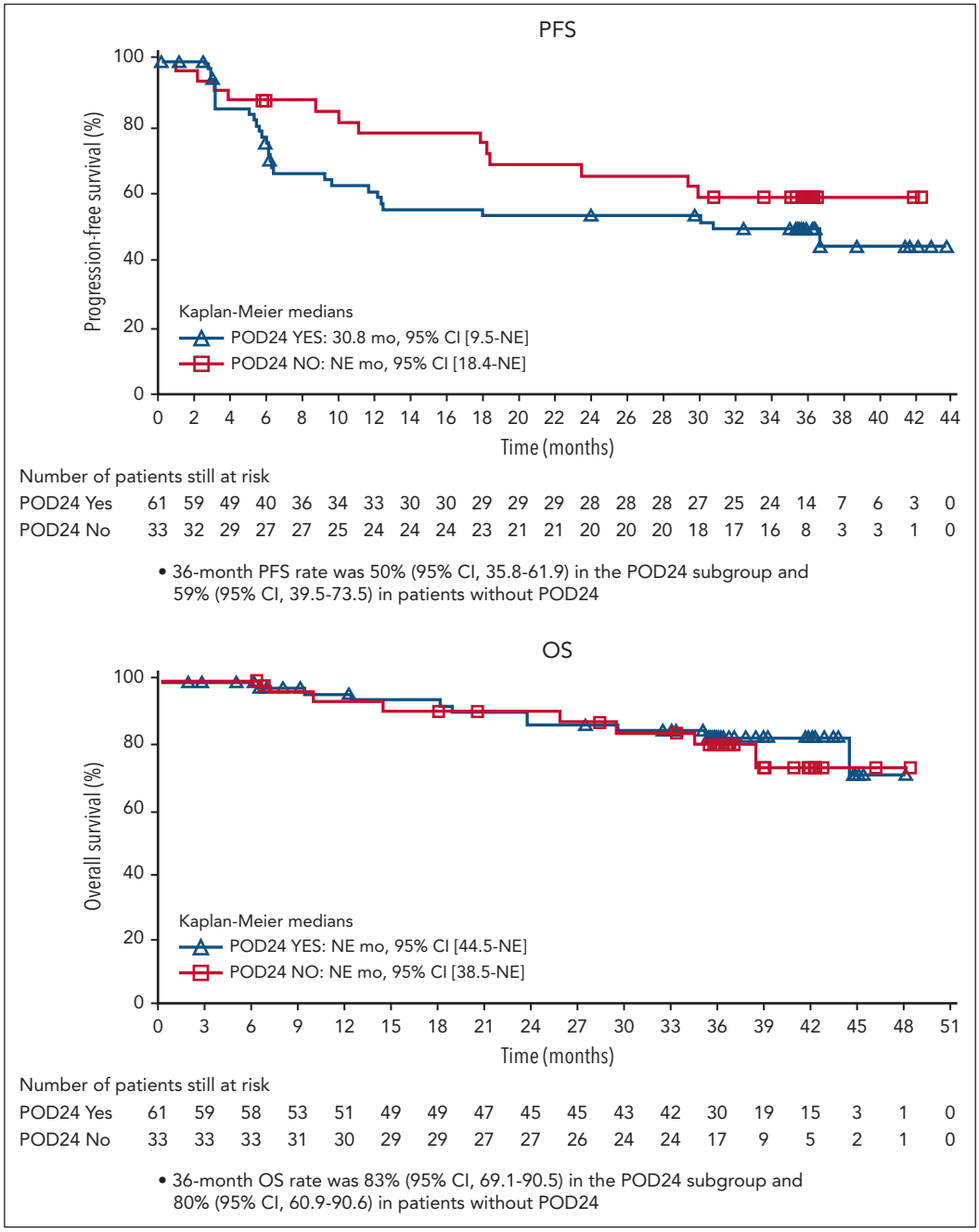
In this issue of *Blood*, Dreyling et al[1] reported the long-term follow-up of the ELARA trial, a phase 2 study of tisagenlecleucel (tisa-cel) in relapsed and refractory follicular lymphoma (FL). After a median follow-up of 29 months, tisa-cel continued to demonstrate a high and durable response rate without new or unexpected safety signals. These data indicated that tisa-cel may be an important treatment option in relapsed FL.

The overall prognosis of patients with FL has substantially improved over the last decades, making FL a chronic disease for the majority of patients. However, for most patients, FL is still a relapsing and remitting disease. Furthermore, response duration and survival shorten after each relapse,[2] and certain subsets of patients still have a poor outcome. This includes patients with high tumor burden by total metabolic tumor volume, bulky disease, high Follicular Lymphoma International Prognostic Index score, double refractoriness (refractory to CD20 and alkylating therapy), and early relapses within 24 months from first immunochemotherapy (POD24), with POD24 as a robust indicator of poor survival.[3]

With the expanding knowledge of the biology and pathogenesis of B-cell malignancies, a plethora of new treatment approaches have been investigated and approved in relapsed FL, allowing movement away from chemotherapy into an era of targeted and cellular therapy. In 2019, the combination of rituximab and lenalidomide was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) based on the AUGMENT trial,[4] quickly acknowledged as a new standard in relapsed FL. Tazemetostat, an enhancer of zeste homolog 2 (EZH2) inhibitor, received FDA license in 2020. A significant milestone was achieved by the approval of 2 autologous anti-CD19 chimeric antigen receptor (CAR) T-cell products and a bispecific antibody in 2021/2022. Tisa-cel is available following 2 lines of therapy based on the phase 2 ELARA trial,[1] and axicabtagene ciloleucel was approved after ≥3 lines of therapy based on the phase 2 ZUMA-5 trial.[5] Mosunetuzumab, a CD20 × CD3 bispecific antibody, documented significant efficacy following 2 lines of therapy in a phase 2 trial.[6] In this trial, the median duration of response (DOR) was 36 months, and the median progression-free survival (PFS) was 24 months. Moreover, mosunetuzumab documented high efficacy in high-risk subgroups (eg, patients with POD24). Recently, the combination of zanubrutinib and obinutuzumab achieved EMA approval for use after 2 relapses based on the ROSEWOOD data.[7] There is no doubt this armamentarium of new compounds will change the treatment landscape in relapsed FL; however, the implementation of these compounds in treatment algorithms for different risk categories is still needed.

Dreyling et al analyzed a total of 97 patients receiving tisa-cel after ≥2 lines of therapy. They reported an overall response rate of 86.2% and a complete response rate of 68.1%. Estimated 24-month PFS, DOR, and overall survival (OS) were 57.4%, 66.4%, and 87.7%, respectively. Patients achieving a complete remission had a significantly longer PFS compared with the overall ELARA population. More important, tisa-cel also induced a high rate of durable responses in patients with high-risk disease characteristics, including POD24. The 3-year PFS and OS for POD24 patients compared with patients without POD24 have been presented at the recent American Society of Hematology meeting[8] (see figure), showing no significant differences between both groups. Furthermore, Dreyling et al reported a correlation between the overall outcome and the levels of $LAG3^{+}CD3^{+}$ exhausted T cells in the lymphoma microenvironment and between outcome and baseline levels of naïve $CD8^{+}$ cells. They also reported that patients with POD24 had a reduced CAR T-cell expansion, which, however, did not substantially affect PFS and OS. These exploratory biomarker analyses are important steps for the understanding of factors affecting the long-term prognosis of patients with FL.

There is an ongoing discussion on the use of CARs and bispecific antibodies in relapsed FL. Both treatment approaches are effective not only in the general population with FL but also in patients with high-risk features. Bispecifics are available off the shelf and may be used in the community setting and mostly outpatient setting, without the need of lymphodepleting chemotherapy. However, treatment with bispecifics requires repeated infusions over a longer period, and response is dependent on the target antigen expression. CARs require just a single infusion, response is irrespective of the target antigen expression, and data show a stable and long-term PFS for ≈60% of patients. However, the use of CARs is limited to specialized accredited



The 36-month PFS and OS of patients with or without POD24; subgroup analysis of the ELARA trial presented at the American Society of Hematology meeting 2023[8] (with permission). CI, confidence interval; NE, not estimated; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 2 years of frontline systemic therapy.

centers, and they are used mostly in the inpatient setting and require a substantial upfront commitment.

The ELARA trial update clearly emphasizes the therapeutic significance of CARs in relapsed FL. The authors not only confirmed the response data following 2 relapses but also demonstrated the role of CARs in high-risk subgroups. This supports evaluation of CARs to earlier lines of treatment, with trials exploring this question already underway. Determining the optimal therapeutic sequence for the individual patient based on risk features will be a major challenge for the near future.

Conflict-of-interest disclosure: K.H. has received advisory honoraria from Roche, Bristol Myers Squibb, Incyte, AbbVie, Novartis, Gilead, and BeiGene; and research funding from Roche, Gilead, and Incyte. ■

REFERENCES

1. Dreyling M, Fowler NH, Dickinson M, et al. Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update. *Blood.* 2024; 143(17):1713-1725.

2. Rivas-Delgado A, Magnano L, Moreno-Velazquez M, et al. Response duration and survival shorten after each relapse in patients

with follicular lymphoma treated in the rituximab era. *Br J Haematol*. 2019;184(5):753-759.

3. Casulo C, Dixon JG, Le-Rademacher J, et al. Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 33 clinical trials. *Blood*. 2022; 139(11):1684-1693.

4. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2019;37(14):1188-1199.

5. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2022;23(1):91-103.

6. Schuster SJ, Sehn LH, Bartlett NL, et al. Mosunetuzumab monotherapy continues to demonstrate durable responses in patients with relapsed and/or refractory follicular lymphoma after ≥2 prior therapies: 3-year follow-up from a pivotal phase II study [abstract]. *Blood*. 2023;142(suppl 1):603.

7. Zinzani PL, Mayer J, Flowers CR, et al. ROSEWOOD: a phase II randomized study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma. *J Clin Oncol*. 2023;41(33):5107-5117.

8. Schuster SJ, Fowler N, Dickinson M, et al. Clinical outcomes of patients with relapsed/refractory follicular lymphoma treated with tisagenlecleucel: phase 2 Elara 3-year follow-up [abstract]. *Blood*. 2023;142(suppl 1):601.

https://doi.org/10.1182/blood.2023023686

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Leung et al, page 1726

T cells take aim in AML: targeting IDH2

Marion Subklewe | Ludwig-Maximilians-Universität München

In this issue of *Blood*, Leung et al[1] present preclinical findings demonstrating the potential of neoantigen-specific T cells to recognize acute myeloid leukemia (AML) driver mutations. The study assessed the immunogenicity of 14 recurrent driver mutations over 8 genes, confirming their ability to provoke an immune response in donors with varied HLA types. Notably, IDH2^{R140Q} was identified as an immunodominant neoantigen, discernible in both in vitro and in vivo models, thereby enabling selective targeting of malignant over normal hematopoietic cells. This research paves the way for AML-specific immunotherapy, leveraging T-cell-specific activity to target AML cells while sparing healthy counterparts.

Currently employed chimeric antigen receptor (CAR) T cells, but also bispecific antibodies, are engineered to bind to surface antigens presented on the neoplastic cells. In B-cell malignancies, CD19 has been commonly targeted by CAR T cells and bispecifics and has limited toxicity, partially due to the possibility of mitigating toxicity due to B-cell depletion through immunoglobulin replacement. However, in the context of AML, targeting of lineage-restricted antigens, like CD33, CD123, and CLEC12A, has been hampered by increased toxicity due to on-target, off-leukemia toxicity against normal healthy hematopoiesis.[2] In addition the ubiquitous expression of these myeloid antigens might contribute to antigen sink and T-cell exhaustion.[3]

For this reason, there is an increasing effort to target intracellular tumor antigens in AML and other hematologic malignancies. Intracellular tumor antigens are degraded into peptides that are presented on the cell surface by defined major histocompatibility complex (MHC) class I molecules and recognized by T cells though their T-cell receptor (TCR).[4] T cells recognizing overexpressed leukemia-associated antigens, such as WT1, PRAME, and NY-ESO-1, have been described and already successfully transferred into patients with AML. Early clinical trial data demonstrated safety and signs of efficacy.[5] Targeting neoantigens that arise from nonsynonymous mutations should enhance specificity and reduce the probability of the emergence of antigen escape variants, resulting in more precise AML targeting.

In the study, detecting neoantigen-specific T cells from healthy individuals required 25 days of ex vivo stimulation, indicating the low frequency of these T cells in the circulation and the need for amplification for detection. These T cells responded to a range of neoantigens including nonsynonymous mutations derived from KRAS, NRAS, IDH1/2 and FLT3, with IDH2^{R140Q} emerging as an immunodominant epitope. Further characterization of IDH2^{R140Q}-specific T cells led to the identification of a 15-mer peptide that elicited responses mainly in the CD8$^+$ T cells, but few donors also had responses in the CD4$^+$ T-cell subset. The unique immunogenic epitopes were found to be HLA-B*15:01* and *B*35:43 restricted. When primary AML samples harboring an IDH2 mutation were employed as targets, they confirmed the presentation of the neoepitope on the cell surface. Finally, in an NSG-SGM3 mouse model using HLA-modified AML cell lines (Kg1A), the specificity of the response was validated in vivo.

In this article, the authors successfully elicited T-cell responses against neoantigens that originate from mutations driving AML. Specifically, the study demonstrated the strong efficacy of IDH2-specific T cells in vitro and in vivo against AML cell lines and primary cells. This approach offers substantial hope for addressing several challenges in developing immunotherapy in AML. First, this strategy might minimize the risk of on-target, off-leukemia toxicity and might also circumvent adverse effects that arise from direct interactions with monocytes and macrophages that contribute to cytokine release syndrome, persistent antigen stimulation, and antigen sink. Moreover, the technique's potential could be enhanced by isolating and inserting the specific TCR into T cells, paving the way for the development of more potent, engineered T cells.[6]

A barrier to the clinical development of neoantigen-specific T cells is the restriction of genetic mutations within the HLA system. The IDH2^{R140Q} mutation, for instance, appears in roughly 10% of AML cases and is specific to HLA types B15:01 and B35:43, effectively narrowing the