Abstract: P1458

Title: LONG-TERM DURABLE RESPONSES IN PATIENTS WITH R/R ALL, DLBCL, AND FL TREATED WITH TISAGENLECLEUCEL AND ITS ASSOCIATION WITH PERSISTENCE OF CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELLS

Abstract Type: Poster Presentation

Topic: Gene therapy, cellular immunotherapy and vaccination - Clinical

Background:

Monitoring of CAR transgene levels in peripheral blood after tisagenlecleucel (tisa-cel) infusion provides information on expansion and persistence of CAR T-cells. In adult patients (pts) with DLBCL and FL, CAR T-cells expansion was similar among responders and non-responders. However, higher expansion was observed responding pediatric and young adult pts with ALL.

Aims:

This analysis aimed to delineate the impact of CAR persistence and B-cell aplasia on duration of remission (DOR) using long-term follow-up data from tisa-cel treated pts.

Methods:

Transgene levels in blood, measured by qPCR, were available from pivotal phase II/III studies in pts with r/r ALL (ELIANA [N=79], ENSIGN [N=64], NCT03123939 [N=69], NCT01626495 [N=60]), r/r DLBCL (JULIET [N=115]), and r/r FL (ELARA [N=97]), along with the long-term follow-up study (NCT02445222). The loss of persistence of CAR T-cells (Tloss) was defined as the time when transgene levels first dropped below 50 transgene copies/µg DNA (approximates to lower limit of quantification [LLOQ] of the assay) after maximal expansion. The impact of Tloss duration and time of the last quantifiable level (Tlast) on DOR/relapse was investigated. The impact of time to B-cell recovery (>1% CD19+ B-cells/WBCs or >3% CD19+ B-cells/lymphocytes for ALL, and 80-616 cells/µL for DLBCL and FL), on DOR/relapse was also examined.

Results:

Long-term CAR persistence in tisa-cel treated pts has been observed for up to 9, 6, and 2.5 years for ALL, DLBCL, and FL pts, respectively, reflecting differing length of follow up based on initiation of trials in respective indications. Pts who lost transgene ≤6 months (mo) or between 6-12 mo had shorter DOR relative to pts with persistent transgene (**Figure**, ALL pts). In ALL, the median Tloss was 27.4, 18.2, 9.7, and 18.0 mo for ongoing complete response (CR) >12 mo, CR pts between 6-12 mo, relapsed pts <12 mo, and relapsed pts >12 mo, respectively. However, of the pts who lost transgene ≤6 mo, some pts maintained durable responses for ≥12 mo — ALL: 29%; DLBCL: 15%; FL: 50%. Among ALL relapsed pts, majority (17/26, 65%) of the pts with Tloss <6 mo showed B-cell recovery; however, 6 pts had Tloss at <6 mo as well as B-cell recovery but maintained response for ≥12 mo. In ALL, NGS MRD ≤6 mo to 1 year post infusion may be a more reliable predictor of potential relapse than B-cell recovery (Pulsipher *et al.,* 2022). The median time to B-cell recovery was 266 days in pts who relapsed/censored ≤12 mo but was not reached for pts with ongoing response at 12 mo. On the contrary, B-cell recovery seems to have no association with relapse in DLBCL or FL pts.

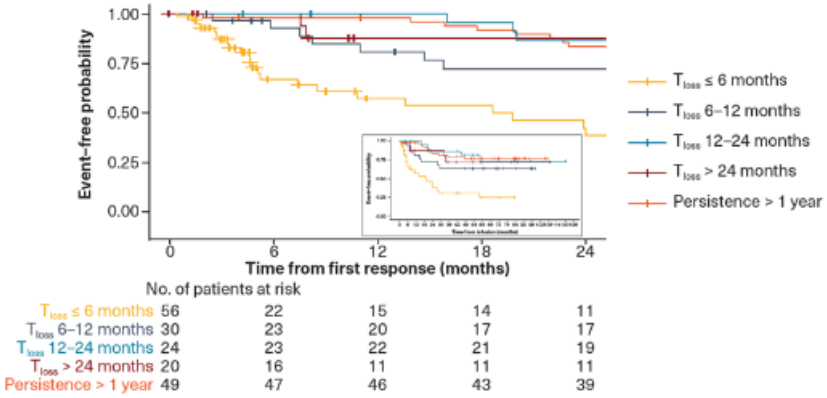
Of ALL pts with CAR persistence, longer DOR observed in pts (with <50% blasts) at any time prior to infusion of tisa-cel vs pts with ≥50% blasts, reflecting more resistant high risk ALL at study entry or greater potential for stochastic loss of CD19 in pts with the higher disease burden.

Summary/Conclusion:

Long-term sustained remission was observed in tisagenlecleucel-treated pts in the pivotal trials. The analyses show a positive association between CAR persistence and durable clinical responses across indications. However, some pts maintained durable responses despite early loss of transgene and/or early B-cell recovery

(<6 mo post infusion; Myers *et al.,* 2021). In DLBCL and FL, the transgene levels in blood may not represent the levels at target sites including lymph nodes. Furthermore, Tlast and Tloss are dependent on the duration of follow up and LLOQ. Further research is needed to identify potential factors or patient characteristics that result in durable responses despite early transgene loss.

Figure: Association between DOR and time corresponding to persistence or T_{loss} of CAR-T cells in pts with ALL.[a,b] Main panel, up to 24 months; inset panel, full follow-up available.



No. of patients at risk

T_{loss} ≤ 6 months	56	22	15	14	11
T_{loss} 6–12 months	30	23	20	17	17
T_{loss} 12–24 months	24	23	22	21	19
T_{loss} > 24 months	20	16	11	11	11
Persistence > 1 year	49	47	46	43	39

[a]Persistence >1 year includes patients who have had at least 1 year follow-up with observable transgene and no T_{loss} event has been observed at any time point. [b]Not included in the figure: patients with persistence <1 year with limited follow-up as patients discontinued due to relapse/new therapy (possibly due to B-cell recovery)/loss to follow-up/withdrew consent. ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; DOR, duration of response; T_{loss}, time corresponding to persistence or loss.

Keywords: DLBCL, ALL, CAR-T, Follicular lymphoma