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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Duvelisib for Cytokine Release Syndrome Prophylaxis during CD19-Targeted CAR T Cell Therapy

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Chimeric antigen receptor (CAR) T-cell therapy has transformed the treatment of patients with advanced non-Hodgkin lymphoma (NHL). However, treatment toxicity, including cytokine release syndrome (CRS) and immune cell-associated neurotoxicity syndrome (ICANS), can be significant. Effective prophylactic strategies may reduce the frequency and/or severity of CAR T cell therapy while also expanding the pool of patients eligible for such therapy. Duvelisib is an oral inhibitor of the gamma and delta isoforms of phosphoinositide 3-kinases (PI3K), which is an active therapy for CLL/NHL with an established safety profile. In addition, prior work from our group and others has demonstrated that PI3K inhibition can prevent CRS in an in vitro model (Amatya et al. ASH 2022) and can enhance antitumor cytotoxicity of CAR-T cells. Consequently, we performed a trial of duvelisib for CRS prophylaxis in patients undergoing standard-of-care (SoC) CAR T-cell therapy for NHL (NCT05044039).
This was a phase I trial with a 3 + 3 dose escalation and two-arm dose expansion phase. The trial enrolled patients with NHL eligible for SoC CAR T-cell therapy and adequate organ function. Herein, we report data from the dose escalation cohort and the first dose expansion cohort, treated with duvelisib BID from day -2 to +28. The primary outcome was safety and tolerability. Secondary outcomes included the incidence and severity of CRS and ICANS, overall response rate (ORR), and progression-free survival (PFS).
17 patients are included in this analysis, including 6 patients in dose escalation and 11 of 14 planned patients in dose expansion cohort A, with full enrollment of cohort A expected prior to presentation. Median age was 68 years (range: 28 - 79) and 53% were male. Diagnoses included DLBCL (n = 13), MCL (2), FL (1) and PBMCL (1). For CAR-T cell therapy, patients received axi-cel (10), liso-cel (4), brexu-cel (2) and tisa-cel (1).
3 patients were enrolled on dose level 1 (15 mg BID) and 3 patients were enrolled on dose level 2 (25 mg BID). No patients experienced a dose-limiting toxicity (DLT) during dose escalation and consequently, 25 mg BID was selected as the recommended dose for expansion.
75 adverse events (AEs) were considered possibly (73) or probably (2) related to duvelisib by study investigators, including 14 severe (grade $\geq$3) AEs. The most common AEs were blood count abnormalities (41), liver function test abnormalities (12), fatigue (8) and nausea (6). The majority of severe AEs were cytopenias (13) and one patient had grade 3 hypokalemia. 13 patients (77%) had AEs attributed to duvelisib, including 6 patients (35%) with severe AEs.
76% of patients (13/17) experienced CRS at a median of 5 days following cell infusion (range 2 - 9) (Figure 1A). In 71% of patients (12/17), the onset of CRS was after day 3. Most were grade 1 (65%) and no patients experienced severe (grade 3 - 4) CRS. The median duration of CRS was 1 day (range: 1 - 7). ICANS occurred in 41% of patients (7/17) at a median of 7 days (range 4 - 10) and 12% of patients experienced severe (grade 3-4) ICANS. The median duration of ICANS was 5.5 days (range: 4 - 11 days). Toclizumab was given to 65% of patients for treatment of CRS and 53% received steroids for CRS and/or ICANS.
All 17 patients were evaluable for disease response. At day +30, the overall response rate (ORR) was 71% (12/17) with 47% achieving complete response (CR) rate. At day +100, the ORR was 64% (9/14) with 50% CR. Best response was CR in 71% of patients and stable disease in 18% of patients. No patients had progressive disease (PD) as best response. CAR T cell expansion by flow cytometry was robust at all dose levels, consistent with prior reports (Figure 1B).
With a median follow up of 93 days (range: 28 - 406), 53% of patients were alive and in remission. PD occurred in 6/17 (35%) patients with a median time to progression of 89 days (range: 28 - 182). Three patients enrolled on the study have died. One died from disease progression on day +266. Two died in remission from neutropenic sepsis (day +50) and vaping-induced lung injury (day +144).

Data from this ongoing phase I study suggests that duvelisib with SoC CAR T-cell therapy is safe and tolerable. Preliminary data from this study suggest that the addition of duvelisib to CAR T-cell therapy may prevent grade 3-4 CRS and also delay the onset of CRS. Although limited follow-up is available, the depth and duration of response is similar to published data for CAR T-cells in this setting.

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Figure 1