ELSEVIER

Blood 142 (2023) 4466–4468

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Phase 1 Dose Escalation Study of Pembrolizumab in Combination with Rituximab and Lenalidomide for Relapsed/Refractory Large B-Cell or Follicular Lymphoma Following Progression after Anti-CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy

Dustin McCurry, MD[1], *Jason Westin, MD*[2], *Lei Feng, MS*[3], *Sairah Ahmed, MD*[2], *Ranjit Nair, MD*[4], *Raphael Eric Steiner, MD*[5], *Lauren Wynn*[6], *Jennifer Thomas*[7], *Ly Huynh Dsouza, PA-C*[6], *Felipe Samaniego, MD*[8], *Sattva S. Neelapu, MD*[2], *Loretta J. Nastoupil, MD*[2]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX
[2]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX
[3]Biostatistics, UT MD Anderson Cancer Center, Houston, TX
[4]Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX
[5]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston
[6]Lymphoma/Myeloma, UT MD Anderson Cancer Center, Houston, TX
[7]UT MD Anderson Cancer Center, Houston, TX
[8]M.D. Anderson Cancer Center, Houston, TX

Introduction: While autologous CD19-targeting chimeric antigen receptor T-cells (CAR T) can induce high complete response (CR) rates in relapsed and refractory (r/r) large B-cell lymphoma (LBCL) and follicular lymphoma (FL), over 50% of patients experience progressive disease. Survival following CAR T failure is dismal, with only 1 in 5 patients living >2 years. Multiple studies indicated that resistance to CAR T therapy may be driven by CAR T cell intrinsic and/or tumor intrinsic mechanisms. Here, we evaluated the combination of PD-1 blockade with rituximab (R) and lenalidomide (len) with the rationale that it would restore the function of exhausted T cells, enhance CAR T function with len and target the tumor and its immunosuppressive microenvironment.

Methods: In this single center, phase I dose-escalation study, eligible patients included adults with r/r LBCL or FL who progressed following CD19 CAR T. Treatment consisted of R (375 mg/m2/day) on days 1, 8, and 15 of cycle 1 and day 1 of cycle 2. Pembrolizumab (200 mg/day) was administered on day 1 of each 21-day cycle with the cycles repeated for up to 2 years (those who attain an investigator-determined CR could stop pembrolizumab after 24 weeks). A standard 3+3 dose escalation of len was pursued to determine the recommended phase 2 dose (RP2D), starting at 2.5 mg and escalated up to 10 mg on days 1-14 of each cycle for up to 12 cycles. The primary endpoint was overall response rate (ORR). Secondary endpoints included safety, CR rate, progression-free survival (PFS), and overall survival (OS). Exploratory objectives sought to determine the effect of combination therapy on peripheral blood T cells and evaluate baseline tumor characteristics that associated with clinical outcomes.

Results: Fourteen patients initiated study treatment, 13 had LBCL (high grade B-cell lymphoma n=4; non-GCB DLBCL n=4; GCB DLBCL n=3; transformed FL n=2), 1 had FL. 12 progressed following axicabtagene ciloleucel, 1 progressed after lisocabtagene maraleucel, and 1 following an investigational allogeneic CAR T. The median time from CAR (day 0) to enrollment was 171 days (range 60-1134). The median time to progression following prior CAR T was 104 days (range 22-280). Median age was 57.5 years (range 41-73), 64% were male, all had advanced stage disease (stage III n=1, stage IV n=13), 79% had high-risk IPI, and 79% had an ECOG performance status of 1. Patients had a median of 3 prior lines of therapy (range 2-5), 86% were refractory to their last therapy. Four were treated at dose level 1 (2.5 mg len), 7 at dose level 2 (5 mg len), and 3 at dose level 3 (10 mg len). Five DLTs were observed, 3 at dose level 2 (3 gr 4 neutropenia > 7 days) and 2 at dose level 3 (1 gr 4 neutropenia > 7 days and 1 gr 3 febrile neutropenia). The RP2D was determined to be 2.5 mg of len. The most common all grade treatment-emergent non-hematologic adverse events (TEAEs) included rash (n=6, 43%), hyperglycemia (n=6, 43%), arthralgia/myalgia (n=5, 36%), diarrhea (n=4, 29%), and AST/ALT elevation (n=3, 21%). Grade 3 or higher TEAEs included 79% neutropenia (gr3 n=2; gr4 n=9), 29% lung infection (gr3 n=3; gr5 n=1), 21% febrile neutropenia (gr3 n=3), 21% lymphopenia (gr3 n=3), 21% anemia (gr3 n=3), and 14% thrombocytopenia (gr3 n=1; gr 4 n=1). With a median follow up of 37.5 months, the most common reason for discontinuation was progressive disease (n=7). Four patients (all LBCL) responded

with all achieving a CR (ORR and CR rates were 29%) and all 4 patients remain in CR beyond 2 years, Figure 1. Median time to CR was 39.5 days. Median PFS was 2.3 months (95% CI: 1.6 mos-NR). Six patients died due to progressive lymphoma. Two patients died as a result of treatment-related AEs, 1 due to COVID19 infection, and 1 due to pneumonia/respiratory failure. Median OS was 21.3 months (95% CI:4.7 mos-NR).

Conclusion: In these heavily pre-treated patients who progressed following CAR T-cell therapy, neutropenia was the dose limiting toxicity that prevented escalation of lenalidomide beyond 2.5 mg when combined with pembrolizumab and R. Four durable CRs were observed, none were observed at the RP2D. Risk mitigating strategies to reduce the incidence of febrile or grade 4 neutropenia and biomarker exploration to identify those likely to achieve a durable response are needed to explore this combination further.

Disclosures Westin: *Genentech:* Consultancy, Research Funding; *SeaGen:* Consultancy; *Kymera:* Research Funding; *AstraZeneca:* Consultancy, Research Funding; *BMS:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *MonteRosa:* Consultancy; *ADC Therapeutics:* Consultancy, Research Funding; *Abbvie:* Consultancy; *Morphosys/Incyte:* Consultancy, Research Funding; *Nurix:* Consultancy; *Calithera:* Research Funding; *Kite/Gilead:* Consultancy, Research Funding. **Ahmed:** *ADC Therapeutics:* Consultancy; *Servier:* Consultancy; *Kite/Gilead:* Consultancy; *Chimagen:* Research Funding; *Genmab:* Research Funding; *Merck:* Research Funding; *Seagen:* Research Funding; *Tessa Therapeutics:* Research Funding. **Neelapu:** *Fosun Kite:* Consultancy, Other: Advisory board member; *Kite, A Gilead Company:* Consultancy, Other: Advisory Board Member, Research Funding; *Incyte:* Consultancy, Other: Advisory board member; *Sellas Life Sciences:* Consultancy, Other: Advisory board member; *Takeda:* Consultancy, Other: Advisory board member; *Chimagen:* Consultancy, Other: Advisory board member; *Allogene:* Consultancy, Other: Advisory board member, Research Funding; *Janssen:* Consultancy, Other: Advisory board member; *Bristol Myers Squibb:* Consultancy, Other: Advisory Board Member, Research Funding; *Morphosys:* Consultancy, Other: Advisory board member; *Immunoadoptive Cell Therapy Private Limited:* Consultancy, Other: Scientific Advisory Board; *Merck:* Consultancy, Other: Advisory Board Member; *Precision Biosciences:* Research Funding; *Synthekine:* Consultancy, Other: Advisory board member; *Adicet Bio:* Consultancy, Other: Advisory board member, Research Funding; *Sana Biotechnology:* Consultancy, Other: Advisory board member, Research Funding; *Caribou:* Consultancy, Other: Advisory board member; *Astellas Pharma:* Consultancy, Other: Advisory board member; *Athenex:* Consultancy, Other: Advisory board member; *Longbow Immunotherapy:* Current holder of *stock options* in a privately-held company; *N/A:* Patents & Royalties: Related to cell therapy and the safety switch described (intellectual property); *Carsgen:* Consultancy; *Orna Therapeutics:* Consultancy, Other: Advisory board member; *Bluebird Bio:* Consultancy, Other: Advisory board member. **Nastoupil:** *Gilead Sciences/Kite Pharma:* Honoraria, Research Funding; *AstraZeneca:* Honoraria; *Regeneron:* Honoraria; *Genentech, Inc., Genmab, Gilead/Kite, Janssen, Merck, Novartis, Takeda:* Honoraria, Research Funding; *Daiichi Sankyo:* Honoraria, Research Funding; *DeNovo:* Honoraria; *Caribou Biosciences:* Honoraria, Research Funding; *Bristol Myers Squibb/Celgene:* Honoraria, Research Funding; *AbbVie:* Honoraria; *ADC Therapeutics:* Honoraria.

OffLabel Disclosure: pembrolizumab in combination with rituximab and lenalidomide in R/R LBCL and FL

Figure 1. PFS

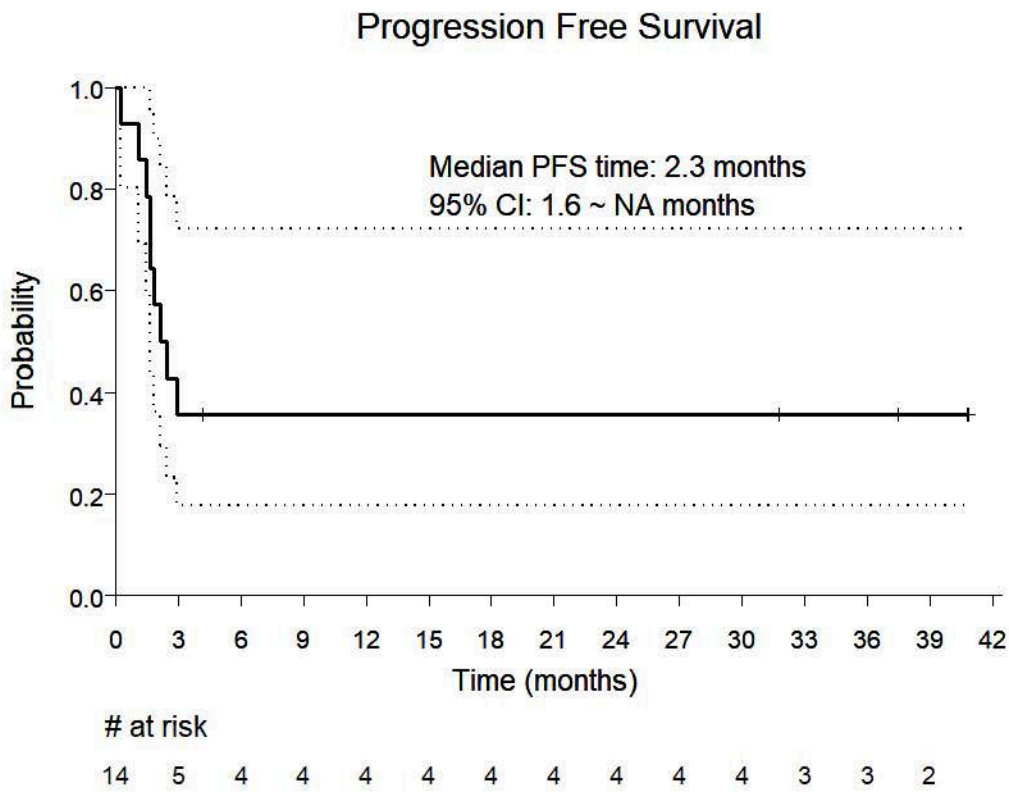

Figure 1

https://doi.org/10.1182/blood-2023-182978