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ORAL ABSTRACTS

614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Blinatumomab in Combination with Immune Checkpoint Inhibitors (ICIs) of PD-1 and CTLA-4 in Adult Patients with Relapsed/Refractory (R/R) CD19 Positive B-Cell Acute Lymphoblastic Leukemia (ALL): Results of a Phase I Study

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Background: Blinatumomab (blina) improves outcomes in R/R CD19+ ALL compared to chemotherapy. However, the overall response rate to blina was 44%, and median overall survival (OS) is just 7.7 mos (Kantarjian. *NEJM*. 2017). Preclinical studies show increased PD-L1 expression on leukemic blasts potentially contributes to relapse after blina. The addition of PD-1 +/- CTLA-4 blockade to blina leads to increased *in vitro* T cell proliferation and enhanced cytotoxicity (Feucht. *Oncotarget* 2016). Thus, blockade of co-inhibitory pathways may enhance blina efficacy *in vivo*. We describe results of a multi-center phase I study combining blina with immune checkpoint inhibitors (ICIs) targeting PD-1 (nivolumab) +/- CTLA-4 (ipilimumab).
Methods: In a dose-escalation study, we evaluated the safety, tolerability, and preliminary efficacy of blina with nivolumab (nivo) +/- ipilimumab (ipi) using a 3+3 design. Pts ³16 years-old with R/R CD19+ B-ALL or mixed phenotype acute leukemia (MPAL) were eligible. Pts ³60 years could be untreated. Table 1 presents the dose escalation schema. Expansion cohorts of 6 pts were planned at the maximum tolerated dose (MTD) for blina + nivo AND blina + nivo + ipi. Pts received up to 5 cycles of blina and 1 year of ICIs. Pts removed from the study during the blina lead-in (days 1-10) were replaced. Dose-limiting toxicities (DLTs) were defined as grade 3+ non-hematologic toxicities requiring the permanent discontinuation of treatment in the first 42 days. Primary endpoints were toxicities and MTD. Secondary endpoints included complete remission (CR), MRD-negativity at a sensitivity of 0.01%, duration of response and OS from treatment initiation.
Results: Twenty-seven pts were enrolled to 3 dose levels (14 DLA1, 3 DLB1, and 10 DLB-1) from September 2017-December 2022. Six pts were replaced (4 prior to ICI dosing and 2 requiring subsequent therapy in the DLT window). The median age of enrolled pts was 55 (range 24-84), 14 were male (52%), and median baseline BM blasts were 60% (range 0.2-98%). Baseline characteristics are presented in Table 2. A single DLT (G4 infusion reaction and G3 hypotension) occurred among 6 pts at DLA1. Based on this safety and efficacy data, blina + nivo was expanded to include 6 additional pts without additional DLTs. There were 2 DLTs at DLB1 (G5 pneumonitis and G2 GVHD), which led to de-escalation to DLB-1, where there was 1 DLT (G3 delirium). Grade 2+ immune-related adverse events attributable to ICIs included pneumonitis (G2+G5), rash (G2+G3), transaminitis (G2+G3), colitis (G3), and hypothyroidism (G2). Grade 3+ adverse events attributable to blina included neutropenia (5-G4+3-G3), dysphasia (2-G3), weakness (G3), seizure (G4), and transaminitis (1-G4+4-G3). Among 22 pts evaluable for response, the CR rate was 68% (100% MRD-negative). Among 13 pts with >50% BM blasts at baseline, 62% achieved CR. Pts with B-myeloid MPAL (0/2) and a history of extramedullary disease (1/4) were less likely to respond. Nine responders subsequently relapsed including 3 with isolated extramedullary disease and 2 with CD19-negative disease. As shown in Figure 1, relapse-free survival

(RFS) at 1 year was 27% (95% CI 10-46), while OS at 1 year was 63% (95% CI 38-79). Twelve pts underwent allogeneic blood or marrow transplant (alloBMT) following study treatment. At 1 year for alloBMT pts, RFS was 51% (95% CI 19-76) and OS was 61% (95% CI 26-83). Ongoing analyses of changes in T cell subpopulations, co-signaling molecule expression, and single cell RNA seq results will be presented.

Conclusions: Combination therapy with blina and ICIs in R/R ALL is safe, feasible, and associated with a high MRD-negative response rate. Long-term survival was promising in comparison to prior results with blina monotherapy, especially following consolidation with alloBMT. A randomized trial of blina +/- nivolumab is needed to confirm the benefit of this combination.

Disclosures Webster: *Servier:* Consultancy; *Pfizer:* Consultancy. **Luskin:** *Novartis:* Honoraria; *Novartis:* Research Funding; *Pfizer:* Honoraria; *Jazz:* Honoraria; *AbbVie:* Research Funding. **Rimando:** *Merck:* Current equity holder in publicly-traded company. **Zeidan:** *Notable:* Consultancy, Honoraria; *Orum:* Consultancy, Honoraria; *Daiichi Sankyo:* Consultancy, Honoraria; *Mendus:* Consultancy, Honoraria; *Otsuka:* Consultancy, Honoraria; *Seattle Genetics:* Consultancy, Honoraria; *Servier:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *Boehringer-Ingelheim:* Consultancy, Honoraria; *Jazz:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *BeyondSpring:* Consultancy, Honoraria; *Celgene/BMS:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *Zentalis:* Consultancy, Honoraria; *Taiho:* Consultancy, Honoraria; *Geron:* Consultancy, Honoraria; *BioCryst:* Consultancy, Honoraria; *ALX Oncology:* Consultancy, Honoraria; *Chiesi:* Consultancy, Honoraria; *Kura:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *Syndax:* Consultancy, Honoraria; *Schrödinger:* Consultancy, Honoraria; *Regeneron:* Consultancy, Honoraria; *Lox Oncology:* Consultancy, Honoraria; *Syros:* Consultancy, Honoraria; *Tyme:* Consultancy, Honoraria; *Astex:* Research Funding; *Shattuck Labs:* Research Funding; *Foran:* Consultancy, Research Funding; *Ionis:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Genentech:* Consultancy, Honoraria; *Epizyme:* Consultancy, Honoraria; *Incyte:* Consultancy, Honoraria; *Agios:* Consultancy, Honoraria. **DeAngelo:** *Gilead:* Honoraria; *Incyte:* Honoraria; *Pfizer:* Honoraria; *Takeda:* Honoraria; *AbbVie:* Research Funding; *Servier:* Honoraria; *Jazz:* Honoraria; *Kite:* Honoraria; *Autolus:* Honoraria; *Novartis:* Research Funding; *Novartis:* Honoraria; *Amgen:* Honoraria; *Blueprint:* Honoraria; *GlycoMimetics:* Research Funding; *Blueprint:* Research Funding. **Luznik:** *Talaris Therapeutics:* Consultancy; *Precision Biosciences:* Consultancy; *WindMiL therpeutics:* Patents & Royalties; *Genentech:* Research Funding; *Gilead Sciences:* Consultancy; *Rubius Therapeutics:* Consultancy. **Gojo:** *Gilead:* Research Funding; *Scimentum:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Merck:* Research Funding; *Incyte:* Research Funding; *Clearview:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *MJH Healthcare Holdings:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Nkarta:* Consultancy, Membership on an entity's Board of Directors or advisory committees.

OffLabel Disclosure: Immune checkpoint inhibitors are off-label for R/R B ALL and the subject of this trial

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Table 1: Dose Escalation

Dose Level	Dose		
	Blinatumomab[1]	Nivolumab[2]	Ipilimumab[2]
A-1	9 µg/day IV on D1-7 28 µg/day IV on D8-28	80 mg IV q 2wks	(none)
A1	(same)	240 mg IV q 2wks	(none)
B-1	(same)	80 mg IV q 2wks	1 mg/kg IV q6wks
B1	(same)	240 mg IV q 2wks	1 mg/kg IV q6wks

[1] After cycle 1, blinatumomab is given at 28 µg/day IV on D1-28 of a 42-day cycle
[2] Drug to start day #11 following blinatumomab

Table 2: Demographics

	All (N=27)	DL A1 (N=14)	DL B1 (N=3)	DL B-1 (N=10)
Median Age (Range)	55 (24-84)	56 (24-84)	57 (28-70)	53 (33-78)
Female Gender (%)	13 (48%)	6 (43%)	1 (33%)	6 (60%)
Median % BM Blasts (Range)	60 (0.2-98)	72 (10-98)	54 (43-95)	12 (0.2-95)
Median ECOG PS (Range)	1 (0-2)	1 (0-2)	1 (1-2)	1 (0-2)
Disease				
Ph- B ALL	20 (74%)	9 (64%)	3 (100%)	8 (80%)
Ph+ B ALL/LBC CML	4 (15%)	3 (21%)		1 (10%)
B-Myeloid MPAL	2 (7%)	1 (7%)		1 (10%)
B/T MPAL	1 (4%)	1 (7%)		
Disease Status				
Relapsed	19 (70%)	8 (57%)	3 (100%)	8 (80%)
Primary Refractory	6 (22%)	5 (36%)		1 (10%)
MRD+	1 (4%)	0		1 (10%)
Newly Diagnosed	1 (4%)	1 (7%)		
Prior Blinatumomab	7 (26%)	3 (21%)	0	1 (10%)
Prior Inotuzumab	3 (11%)	0	0	3 (30%)
Prior AlloBMT	9 (33%)	4 (29%)	1 (33%)	4 (40%)
Prior EM Disease	4 (15%)	0	0	4 (40%)

Figure 1: Survival by Patient

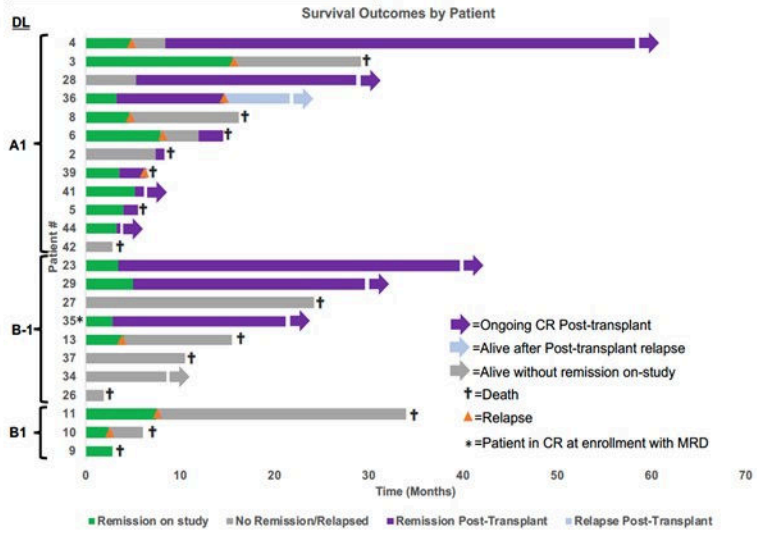

Figure 1