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POSTER ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

Acalabrutinib in Combination with Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy in Relapsed/Refractory B-Cell Lymphoma: A Phase I/II Study of Safety, Efficacy and Immune Correlative Analysis

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Introduction
Limitations of effective CD19-targeted chimeric antigen receptor T-cell therapy (CAR-T) in relapsed/refractory (R/R) B-cell lymphoma include inability to control disease prior to CAR-T, lack of sustained remissions following CAR-T and the potential for life-threatening adverse effects such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). BTK inhibitors, ibrutinib and acalabrutinib are immunomodulatory and may enhance CAR-T expansion, engraftment and tumor clearance while decreasing the frequency and severity of CRS in chronic lymphocytic leukemia (Qin, et al. J Immunother 2020). Based on this, we hypothesized that acalabrutinib, when combined with CD19-targeted CAR-T, could enhance its efficacy and safety and may also serve as an effective bridging strategy. We report the initial safety, efficacy and correlative analysis of acalabrutinib in combination with axicabtagene ciloleucel (axi-cel) in R/R B-cell lymphoma.
Methods
We conducted a phase I/II, open-label trial (NCT04257578) involving adult patients meeting FDA-approved criteria for axi-cel; this included patients with R/R CD19+ large B-cell (LBCL) and follicular lymphoma (FL) with measurable disease. Acalabrutinib was continuously administered at 100 mg twice daily over the 3 study phases: 1) Bridging: Starting between 3 weeks and 24 hours prior to leukapheresis until lymphodepletion (LD), 2) Cell therapy: From LD to 30 days after axi-cel infusion, 3) Maintenance: From 30 days to 1 year after axi-cel infusion or until unacceptable toxicity or disease progression (Figure 1). Axi-cel was administered per institutional practice. The primary endpoint was safety based on rates of grade ≥3 CRS or ICANS within 30 days of axi-cel infusion. We also assessed bridging success rate (defined as receipt of axi-cel without any additional required treatment), overall response rate (ORR) and complete response (CR) rate following axi-cel infusion, progression-free survival, overall survival and immune response biomarkers.
Results
As of July 28, 2023, 17 patients have enrolled, 14 have received axi-cel infusion and are evaluable for response to CAR-T and 3 are earlier in treatment. Fourteen patients had LBCL (12 DLBCL [4 with double/triple hit, 3 with double/triple expressor, 1 with only MYC translocation] and 2 PMBCL) and 3 had FL (Table 1). Median age was 58 (range 34-74) years, largest lesion diameter was a median of 3.75 (1.7-7.1) cm and the median number of prior regimens was 3 (range 1-5). Of LBCL patients, 6 (43%) had primary refractory disease and 5 (38%) had relapsed within 12 months of initial therapy; 4 (31%) patients had previous autologous stem cell transplant. Fourteen of 15 patients (93%) who underwent axi-cel infusion were successfully bridged from prior to leukapheresis to LD with single agent acalabrutinib and no additional therapy; 1 received added radiation. After cell infusion, 13 (93%) and 8 (57%) patients had any grade CRS and ICANS, respectively. Three (20%) patients had grade 3 ICANS which resolved with dexamethasone and anakinra or tocilizumab. No patients received prophylactic dexamethasone. No patients experienced grade ≥3 CRS or any grade hemorrhage or tachyarrhythmia. No patients discontinued acalabrutinib at any time due to toxicity, meeting an interim safety endpoint. The ORR and CR rate at day 30 post axi-cel infusion was 93% and 71%, respectively. Through post axi-cel maintenance, there were no drug holds. One of the 3 patients with partial remission (PR) at day 30 converted to CR at day 180 post infusion while 2 suffered disease progression at day 90 post axi-cel infusion. No treatment related deaths were observed by time of data cutoff. At a median follow-up of 13.8 (range 1.7-29.1) months, 10 (73%) patients are alive and 9 are progression-free. Post axi-cel cytokines peaked at a median of day 6 [median IL-6 196

pg/ml (range 20-11803), ferritin 425 ng/ml (156-2051), CRP 52.9 mg/L (7.7-239.7), Table 1]. Impact of acalabrutinib on myeloid derived suppressor cells and the immunosecretome profile are underway and will be reported at time of presentation.

Conclusions

Acalabrutinib successfully bridged most patients in this trial when given concurrently with axi-cel and safely maintained high CR rates. CRP and ferritin levels were typically only modestly elevated after cell infusion. Severe CRS was not observed and high-grade ICANS was uncommon.

Disclosures Poh: *BeiGene:* Consultancy; *Seattle Genetics:* Consultancy; *Incyte:* Research Funding; *Acrotech:* Consultancy. **Chow:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Lynch:** *Merck:* Research Funding; *Abbvie:* Consultancy; *Genentech:* Research Funding; *Cyteir:* Research Funding; *SeaGen:* Consultancy; *Foresight Diagnostics:* Consultancy; *Bayer:* Research Funding; *Incyte:* Research Funding; *TG Therapeutics:* Research Funding; *Seagen Inc.:* Research Funding; *Rapt:* Research Funding; *Cancer Study Group:* Consultancy. **Ujjani:** *Genentech:* Consultancy, Honoraria; *Beigene:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria, Research Funding; *Atara:* Consultancy; *Pharmacyclics:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria; *Lilly:* Consultancy, Honoraria, Research Funding; *Epizyme:* Consultancy; *Astrazeneca:* Consultancy, Honoraria, Research Funding; *Kite, a Gilead Company:* Consultancy, Other: Travel expenses , Research Funding; 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OffLabel Disclosure: Acalabrutinib is approved for chronic lymphocytic leukemia and mantle cell lymphoma

Figure 1: Treatment Schema

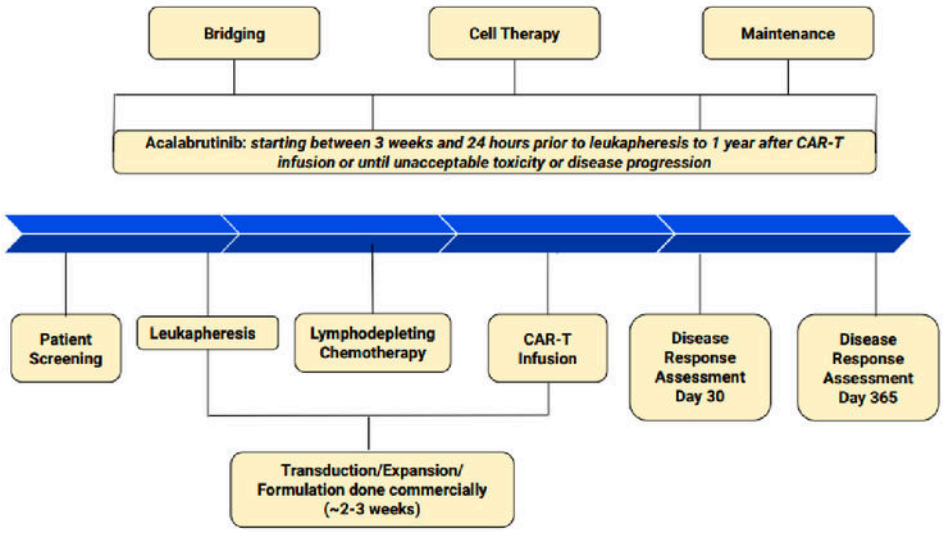

Table 1: Patient characteristics, response to acalabrutinib and axicabtagene ciloleucel treatment and correlative cytokine profile

Age	Diagnosis	Best response	CRS (grade)	Neurotoxicity (grade)	CRP (mg/L) (baseline/peak)*	Ferritin (ng/mL) (baseline/peak)*	IL-6 (pg/mL) (baseline/peak)*	LDH (U/L) (baseline/peak)*
57	PMBCL	CR	2	2	4.7/55.2	97/156	4/305	162/173
67	DLBCL**	CR	2	none	2.5/128.8	211/436	2/252	147/213
66	DLBCL**	CR	1	none	3.8/30.4	243/334	5/20	187/212
39	DLBCL, DE**	PR	1	none	9.9/41.4	321/348	8/31	128/194
34	DLBCL, DH	CR	1	none	2.1/176.7	225/1115	2/135	127/141
57	DLBCL, TH	PR	2	3	4.3/96.8	1065/2051	8/195	148/248
38	FL	CR	2	2	18.6/154.8	100/229	11/11803***	137/277
48	DLBCL, DH**	CR	1	none	1.2/32.6	93/177	2/34	168/127
74	DLBCL	CR	2	2	16.4/38.2	380/1458	8/199	260/207
36	DLBCL	SD	none	none	4.5/7.7	371/414	13/26	156/145
58	FL	CR	2	3	11.6/239.7	210/1076	4/267	160/212
58	DLBCL, TE	CR	2	3	10.2/43.6	227/231	4/1362	118/184
67	DLBCL, DE	CR	2	2	13.7/93.8	296/611	8/358	818/159
67	DBCL, DH	CR	2	2	2.7/50.6	241/972	8/1200	133/137
70	FL	TBD	TBD	TBD	TBD	TBD	23/TBD	TBD
28	PMBCL**	TBD	TBD	TBD	TBD	TBD	TBD	TBD
59	DLBCL, MYC translocation*	TBD	TBD	TBD	TBD	TBD	TBD	TBD

PMBCL: primary mediastinal B-cell lymphoma; DLBCL: diffuse large B-cell lymphoma; DE: double expressor; DH: double hit; TH: triple hit; TE: triple expressor; FL: follicular lymphoma; CR: complete response; PR: partial response; SD: stable disease; TBD: to be determined; CRP: c-reactive protein; IL-6: interleukin-6

** Baseline levels drawn within 24 hours prior to axicabtagene ciloleucel infusion on acalabrutinib. Peak levels drawn between axicabtagene ciloleucel infusion and 1 month thereafter.*
*** Patient had primary refractory disease.*
**** Patient had COVID-infection at time of peak IL-6 draw.*

Figure 1

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