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ORAL ABSTRACTS

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

A Phase I Study of Asciminib (ABL001) in Combination with Dasatinib and Prednisone for BCR-ABL1-Positive ALL and Blast Phase CML in Adults

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Introduction:Oral ABL1 kinase inhibitors rapidly produce deep remissions in *BCR::ABL1*+ acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia in lymphoid blast crisis (CML-LBC). Second generation TKIs such as dasatinib (DAS) are more effective than imatinib (Foa et al. *Blood* 2011) but patients may develop resistance. Asciminib (ASC), previously ABL001, is a STAMP (Specifically Targeting the ABL Myristoyl Pocket) allosteric ABL1 inhibitor that binds to a site spatially distinct from ATP-competitive TKIs. Combination treatment with an allosteric and an ATP-competitive TKI may deepen clinical responses and limit mutational resistance as supported by a cell line xenograft model of CML (Wylie et al. *Nature* 2017) and patient-derived xenograft models of *BCR::ABL1*+ ALL. We hypothesized that dual ABL blockade with catalytic domain and allosteric inhibitors would be tolerable and active in *BCR::ABL1*+ ALL and CML-LBC.
Methods: This investigator initiated, phase I study (NCT03595917) of asciminib (ASC) in combination with DAS plus prednisone (pred) for *BCR::ABL1*+ ALL studied ASC in escalating doses in a 3+3 design with the primary objective to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D); a 10 patient (pt) expansion cohort was then accrued. Secondary objectives define the depth and durability of responses. Pts with *BCR::ABL1*+ ALL or CML-LBC newly diagnosed $\geq$ 50 years (yrs), or unfit; or relapsed/refractory (no prior DAS or ASC) were eligible in dose escalation; all pts $\geq$18 yrs were eligible in dose expansion. Pts received DAS 140 mg/day(d) and pred 60 mg/m ^{2}/d 1-24 (max 120 mg/d, tapered d 25-32) with escalating daily doses of ASC (DL1: 40 mg; DL2: 80 mg; DL3: 160 mg). DAS and ASC were given in 28-d cycles indefinitely in setting of clinical benefit, with allogeneic stem cell transplant (SCT) consolidation after d85 per treating physician. Dose-limiting toxicity (DLT) was initially defined as CTCAEv4 non-heme toxicity grade (gr) 3+; the study was amended to assess DLT via CTCAEv5. Correlative science efforts seek to define biomarkers of response and resistance to dual ABL1 blockade.
*Results:*The study enrolled 25 pts (48% female), with 14 in dose escalation (13 evaluable), and 11 in expansion (10 evaluable). Most (92%) had new ALL (p190: 15/23, p210: 8/23; 8% had CML-LBC. Median age was 65 yrs (range 33 - 85; 8 pts 70+). Median WBC was 15.1 K/μL (range 0.9 - 251.9 K/μL). No pt had CNS disease. DL1 and DL2 enrolled 3 pts each without DLT. Two of 3 pts at DL3 developed asymptomatic CTCAEv4 gr 3 amylase elevation during C1 meeting original DLT criteria. A 4 th pt enrolled on re-opened DL3 under an amendment defining asymptomatic CTCAEv4 gr 3 amylase/lipase elevations persisting $\leq$5d to not be a DLT. This pt experienced an asymptomatic CTCAEv4 gr 3 lipase elevation meeting DLT criteria. Thus, the study de-escalated to DL2, re-opening under an amendment assessing DLTs via CTCAEv5. Of note, all DLTs at DL3 would be gr <3 per CTCAEv5. Four more pts (3 evaluable) enrolled at DL2 without a DLT. Thus, ASC 80 mg/d was declared the RP2D, and 11 pts age $\geq$18 yrs enrolled in an expansion cohort, 10 of whom initiated study treatment. No pt had symptomatic pancreatitis. Rates of molecular response after 3 cycles among all evaluable patients were 58.3% (14/24) for MRD 3.0 and 25.0% (6/24) for MRD 4.0. Evaluable pts with new ALL treated at the RP2D achieved molecular response rates after 3 cycles of

78.6% (11/14) for MRD 3.0 and 42.9% (6/14) for MRD 4.0. Both patients with imatinib-refractory CML-LBC progressed (C9, C3). Of those with ALL, 8 bridged to SCT after 2-8 cycles; 2 elected local care (C5, C7); 1 transitioned to ponatinib for inadequate response plus recurrent DAS pulmonary toxicity (C4); 6 remained on study treatment until disease progression (C4 - MRD+, C45, C11, C11); 3 remain on study. Correlative science evaluation of serial pt biospecimens in pursuit of predictive biomarkers will be shared at the meeting.
Conclusion: Dual ABL1 kinase inhibition with ASC and DAS plus pred in *BCR::ABL1*+ ALL and CML-LBC is feasible and tolerable in adults with *BCR::ABL1*+ ALL and CML-LBC. DLTs at ASC 160 mg/d were asymptomatic amylase and lipase elevation, without clinical sequelae. ASC 80 mg/day was declared the RP2D, and an expansion cohort of 10 pts was completed. High rates of molecular response and bridging to transplant highlight encouraging preliminary activity. A phase II expansion cohort incorporating blinatumomab is now open.

Disclosures Luskin: *Novartis:* Honoraria; *Pfizer:* Honoraria; *Jazz:* Honoraria; *AbbVie:* Research Funding; *Novartis:* Research Funding. **Murakami:** *Novartis AG:* Membership on an entity's Board of Directors or advisory committees; *imCORE (Genentech/Roche):* Research Funding. **Winer:** *Curis Inc:* Consultancy; *Abbvie:* Consultancy. **Garcia:** *Gilead:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Astellas:* Consultancy; *AbbVie:* Consultancy, Research Funding; *Prelude:* Research Funding; *Pfizer:* Research Funding; *New Wave:* Research Funding; *Genentech:* Consultancy, Research Funding; *Servier:* Consultancy; *AstraZeneca:* Research Funding. **Stahl:** *Kymera:* Membership on an entity's Board of Directors or advisory committees; *Rigel:* Membership on an entity's Board of Directors or advisory committees; *Clinical care options:* Other: GME activity ; *Haymarket Media:* Other: GME activity ; *Boston Consulting:* Consultancy; *Dedham group:* Consultancy; *GSK:* Membership on an entity's Board of Directors or advisory committees; *Curis Oncology:* Other: GME activity ; *Sierra Oncology:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Other: GME activity . **Neuberg:** *Madrigal Pharmaceuticals:* Current equity holder in private company. **Stone:** *Ligand Pharma:* Consultancy; *Hermavant:* Consultancy; *Lava Therapeutics:* Consultancy; *AvenCell:* Consultancy; *Takeda:* Other: DSMB; *Cellularity:* Consultancy; *Abbvie:* Consultancy; *Kura One:* Consultancy; *Rigel:* Consultancy; *Syntrix:* Other: DSMB; *CTI Biopharma:* Consultancy; *BerGenBio:* Consultancy; *Epizyme:* Other: DSMB; *Aptevo:* Other: DSMB; *GSK:* Consultancy; *Amgen:* Consultancy; *Jazz:* Consultancy. **Wang:** *Pfizer:* Consultancy, Speakers Bureau; *Takeda:* Consultancy; *PharmaEssentia:* Consultancy; *Dava oncology:* Speakers Bureau; *Kite:* Consultancy, Speakers Bureau; *Jazz:* Consultancy; *Novartis:* Consultancy, Speakers Bureau; *GlaxoSmithKline:* Consultancy; *Kura Oncology:* Speakers Bureau; *Gilead:* Consultancy; *BMS:* Consultancy; *Astellas:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy. **Stock:** *Amgen:* Honoraria; *Kite:* Consultancy; *Kura:* Research Funding; *Servier:* Other: Data Safety Monitoring Board/Advisory Board; *Newave:* Honoraria; *Jazz Pharmaceuticals:* Consultancy, Honoraria; *Glaxo Smith Kline:* Consultancy. **DeAngelo:** *Jazz:* Honoraria; *Amgen:* Honoraria; *Servier:* Honoraria; *Takeda:* Honoraria; *Blueprint:* Research Funding; *AbbVie:* Research Funding; *Pfizer:* Honoraria; *Novartis:* Honoraria; *Gilead:* Honoraria; *Novartis:* Research Funding; *GlycoMimetics:* Research Funding; *Kite:* Honoraria; *Incyte:* Honoraria; *Autolus:* Honoraria; *Blueprint:* Honoraria.

	1 month	3 months
Flow Negative	60% (9/14)	80% (12/14)
BCR-ABL qPCR		
MRD 3.0	30.8% (4/13)	78.6% (11/14)
MRD 4.0	23.1% (3/13)	42.9% (6/14)

Table 1. Summary of clinical responses for study participants with newly diagnosed acute lymphoblastic leukemia (ALL) treated at the recommended phase 2 dose (RP2D) of asciminib (80 mg daily) after 1 and 3 months of study treatment. Data shown reflect the numbers of participants who achieved the indicated response metric of those who had a valid test result at that time point (patients not tested or technical assay failures are excluded). Data current as of 7/14/2023.

	Dose Level	Patient	Onc Diagnosis	Prior Therapy	Isoform	Age/Sex	Flow Cytometry (%)		BCR-ABL mRNA (%)		Last Cycle Completed	Evaluable for AEs	Disposition	Off Study Reason
							Month 1	Month 3	Month 1	Month 3				
Dose Escalation	1 (40 mg)	01	ALL	-	p190	67 F	1.1	0*	0.145†	0.0522*	4	Y	Off	Patient discretion
		02	ALL	-	p210	53 M	0	0	3.0018	0.0500	5	Y	Off	SCT
		03	ALL	-	p190	66 M	0.8	0	4.2955	0.0802	5	Y	Off	SCT
	2 (80 mg)	04	ALL	-	p190	83 F	0	0	failed	< LOD	45	Y	Off	Progression
		05	ALL	-	p210	73 F	16	0.7	> 50	6.2937	3	Y	Off	Dasatinib toxicity
		06	ALL	-	p190	65 M	0	0	1.5762	0.0775	10	Y	Off	Progression
	3 (160 mg)	07	ALL	-	p210	85 M	-	-	-	-	0	Y	Off	DLT (amylase increased)
		08	ALL	-	p190	57 F	0	-	0.0171	-	1	Y	Off	Dasatinib toxicity
		09	ALL	-	p190	57 F	-	-	-	-	0	Y	Off	DLT (amylase increased)
		10	ALL	-	p190	65 M	0.1	-	1.5398	-	2	Y	Off	DLT (lipase increased) > dose reduction > blinatumomab and SCT
	2 (80 mg)	11	ALL	-	p190	80 M	0	0	0.0278	0.0481	6	**N**	Off	Patient discretion
		12	ALL	-	p190	62 M	0.1	0	8.3336	0.0056	9	Y	Off	Progression
		13	ALL	-	p190	76 F	0	0	0.002	< LOD	22	Y	Continues	-
		14	ALL	-	p190	70 M	0.04	0	0.1933	0.0069	3	Y	Off	Blinatumomab and SCT
Dose Expansion	2 (80 mg)	15	ALL	-	p210	33 F	0	0	4.3973	0.0342	3	Y	Off	Blinatumomab and SCT
		16	ALL	-	p210	57 M	0.07	0	0.0082	< LOD	3	Y	Off	Blinatumomab and SCT
		17	ALL	-	p190	64 M	0	0	0.0058	0.0031	4	Y	Off	SCT
		18	ALL	-	p190	67 M	missing	missing	missing	missing	14	Y	Off	Dasatinib toxicity
		19	ALL	-	p190	75 F	-	-	-	-	0	**N**	Off	Death before study treatment
		20	CML-LBP	Imatinib	p210	44 M	0	0	0.0059	0.0386	9	Y	Off	Progression
		21	ALL	-	p210	44 F	0	0	0.1500	0.0461	11	Y	Continues	-
		22	ALL	-	p190	77 F	0	0	1.073	0.5693	10	Y	Continues	-
		23	ALL	-	p190	66 F	0.06	0.075*	3.5822	0.1849*	8	Y	Off	SCT
		24	ALL	-	p190	53 F	0	0	0.3601	0.0682	4	Y	Off	Progression
		25	CML-LBP	Imatinib	p210	53 M	0	0*	0.9500	0.2936*	3	Y	Off	Progression

Table 2. Patient outcomes and disposition for all diagnoses, dose phases, and dose levels. Abbreviations: ALL (acute lymphoblastic leukemia), CML-LBP (chronic myelogenous leukemia in lymphoid blast crisis), SCT (allogeneic hematopoietic stem cell transplantation).
* Data shown were obtained during month 2 in lieu of data from month 3 in the event of technical failure or patient declining aspirate at month 3.
† Data shown are from peripheral blood in lieu of valid bone marrow test result at this time point (n.b. excluded from summary statistics in Table 1).
Data current as of 7/14/2023.

Figure 1

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