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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Results from a Phase (Ph) 1 Clinical Study of the All-Oral Regimen of CC-486 and Venetoclax for Relapsed and Refractory Acute Myeloid Leukemia

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Background: Venetoclax (Ven) with azacitidine (Aza) is the standard of care for newly diagnosed AML patients who are unfit for intensive induction chemotherapy. It is well known that this treatment also has activity in the relapsed and refractory (R/R) setting. However, this regimen requires 7 consecutive daily subcutaneous or intravenous doses of Aza each month, which continues indefinitely. The relative inconvenience of this, and its negative impact on quality of life, may lead to its early discontinuation, which may decrease the efficacy or durability of this regimen. A more convenient all-oral regimen may decrease visits to an infusion center, improve quality of life, and potentially increase the efficacy of the regimen due to improved compliance. CC-486 is the oral formulation of Aza that is currently approved for post-induction chemotherapy maintenance in AML.
Methods: This is a single center open label, Ph I study investigating CC-486 and Ven in R/R AML patients. In the dose escalation phase, subjects received CC-486 at one of two cohorts (200 mg PO days 1-14 and 300 mg PO days 1-14). Ven was given at the 400 mg/day PO regimen, for 28 days, after an initial intra-patient dose escalation per the standard of care. Using a 3+3 study design for these two cohorts, we aimed to determine the maximum tolerated dose (MTD) of CC-486 in combination with Ven. An expansion cohort is planned for 10 additional patients treated at the MTD. To assess whether CC-486 exerts similar effects in the leukemia stem cell population (LSCs) compared to conventional IV Aza, we retrospectively analyzed patient samples from cohort 1 with a patient sample treated with Ven/IV Aza outside of the study. We performed mass spectrometry-based metabolomics analyses in LSCs isolated from patient samples as well as single-cell RNA sequencing.
Results: A total of 9 patients were accrued for this Ph I study (Figure 1A). The average age at the time of enrolment was 66, and median prior treatment regimens was 1 (range 1-3). Five patients had received Ven/Aza in prior treatments. There were no dose-limiting toxicity (DLT) events and the MTD was determined to be 300mg. The most common hematologic toxicities were Gr 3-4 neutropenia (n = 8, 89%), Gr 3-4 anemia (n = 7, 78%), and Gr 3-4 thrombocytopenia (n = 5, 56%). The most common non-hematologic toxicities were Gr 1-2 nausea (n = 5, 56%), fatigue (n = 2, 22%), and diarrhea (n = 2, 22%). Febrile neutropenia was also seen in two subjects (Gr 1-2 n = 1, 11%, Gr 3-4 n= 1, 11%). Best responses were complete remission (CR) (n = 2, 22%) partial remission (PR) (n = 1, 11%), and stable disease (SD) (n= 3, 33%). Three patients proceeded to an allogeneic stem cell transplant. Overall survival was 288 days, 95% CI: (39 days, 424 days). To determine whether CC-486/Ven exerts similar effects on the LSC population compared to conventional IV Aza/Ven, LSCs were isolated from the bone marrow of a responder and non-responder, and these were compared to LSCs from a patient who underwent treatment and responded to conventional IV Aza/Ven. Given subjects who achieved a CR in the study cleared their blasts by day 4 rendering no leukemia cells for analyses, samples used were from Subject 1 (stable disease with unchanged blasts), and Subject 2 (stable disease with significant blast reduction). Metabolomics assays performed in LSCs at day 4 and day 28 suggested mitochondrial dysfunction, decreased electron transport chain complex II activity and decreased glutathione levels in Subject 2 and conventional IV Aza/Ven but not on Subject 1. These findings are consistent with Pollyea et al. 2018 suggesting CC-486/Ven targets LSCs by perturbing complex II activity and OXPHOS in LSCs. Further, scRNA seq performed in Subject 1 and 2 showed gene expression patterns similar to those seen in patients who respond to Aza/Ven vs not, including a significant shift of BCL-2 to MCL-1 expression in the cell population harboring LSCs (Figure 1B).

Conclusion: CC-486 and Ven is an all-oral regimen currently being investigated for the treatment of R/R AML. Our Ph I dose escalation demonstrated a favorable safety profile for this regimen with a MTD of 300mg CC-486. Responses were seen in both dose cohorts including 2 CRs and 1 PR, and patients have been successfully bridged to hematopoietic stem cell transplant. Analyses performed in patient samples from this study suggested a similar effect in LSCs in CC-486/Ven compared to conventional IV Aza/Ven.

Disclosures McMahon: *Arcellx:* Membership on an entity's Board of Directors or advisory committees; *Syros Pharmaceuticals:* Research Funding; *Kura Oncology:* Membership on an entity's Board of Directors or advisory committees; *Syndax Pharmaceuticals:* Research Funding. **Schwartz:** *Novartis:* Consultancy; *Jazz Pharmaceuticals:* Consultancy. **Smith:** *AML JV:* Consultancy; *OncoVerity:* Current Employment, Current holder of *stock options* in a privately-held company. **Jordan:** *AML JV:* Consultancy. **Pollyea:** *AbbVie, Bristol Myers Squibb, Syros, Novartis, Beigene, Bergen Bio, Arcellx, Jazz, Genentech, Immunogen, AstraZeneca, Kura, Ryvu, Magenta, Qihan, Zentalis, Medivir, Hibercell, LINK, Daiichi Sankyo, Aptevo, Rigel, Sumitomo, Adicet, Seres, Gilead, OncoVerit:* Consultancy; *Teva, Karyopharm, Bristol Myers Squibb, and AbbVie.:* Research Funding.

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Patient	Cohort	Age	Blast%	ENL Risk	Molecular	# Prior lines of therapy	Prior Ven/Aza Exposure	DLT	Best Response	Number of cycles received	Transplant Y/N	Reason for Trial Discontinuation
Subject 1	1	80	20%	Adverse	DNMT3A, TP53, SF3B1, TET2, SETBP1	3	Yes	No	Stable Disease	3	N	Progression
Subject 2	1	81	>80%	Adverse	DNMT3A, TET2, U2AF1, BCOR, FLT3-ITD	1 + transplant	Yes	No	Stable Disease	2	N	Stable disease - presence of FLT-3 mutation
Subject 3	1	53	10-13%	Favorable	No mutations detected	1	No	No	CR	1	Y	Transplant
Subject 4	2	92	10%	Adverse	SF3B1, RUNX1, DNMT3A	2	Yes	No	Disease Progression	1	N	Disease Progression
Subject 5	2	70	60%	Adverse	TP53, NF1	1+ transplant	Yes	No	Disease Progression	2	N	Disease Progression
Subject 6	2	62	20%	Intermediate	DNMT3A, NRAS, TET2	1	No	No	CR	2	Y	Transplant
Subject 7	2	40	60-70%	Adverse	JAK2, DDX41	1 + transplant	No	No	Partial Remission	2	Y	Transplant
Subject 8	2	36	30%	Favorable	RAD21, ETV6	1	No	No	Disease Progression	1	N	Disease Progression
Subject 9	2	80	10-15%	Adverse	ASXL1, GATA2	1	Yes	No	Stable Disease	2	N	On Trial

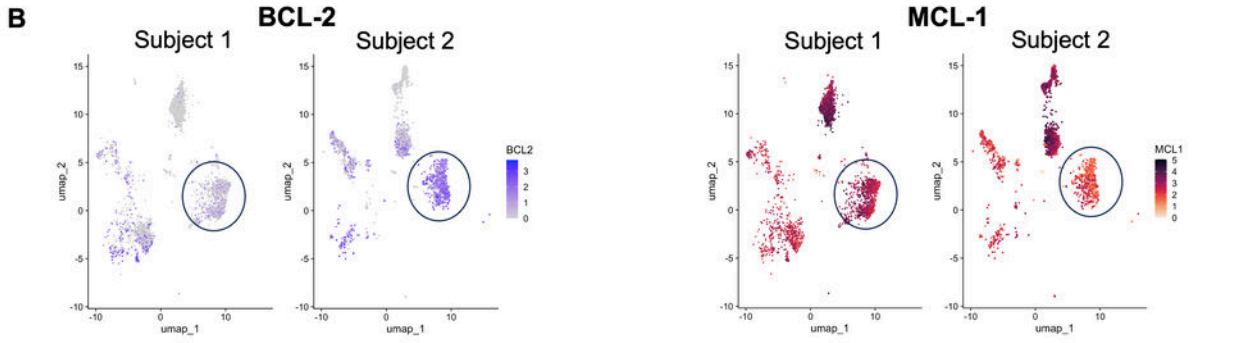

Figure 1. CC-486 in combination with Venetoclax shows safety and efficacy in R/R AML patients. (A) Baseline characteristics and responses in subjects from cohorts 1 and 2. (B) scRNA seq from day 4 bone marrow samples from Subject 1 (non-responder, stable 20% blasts) and Subject 2 (responder, blast reduction from 90 to 10% blasts) show a difference in expression of BCL-2 and MCL-1 in the population harboring LSCs (circled).

Figure 1

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