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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Results of a Phase 1 Trial Testing the Novel Combination Therapy of Venetoclax and Ruxolitinib in Relapsed/Refractory Acute Myeloid Leukemia Patients

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Introduction : A functional small molecule screen on a large cohort of primary AML patient samples revealed that the combination of Ruxolitinib (Rux) and Venetoclax (Ven) exhibited *ex vivo* efficacy and synergy in both newly diagnosed and R/R AML. This observation motivated a Phase I multi-center trial to evaluate Rux+Ven in R/R AML, for which we now report complete toxicity and efficacy data for 30 subjects.

Methods: This study was designed to identify a maximum tolerated or recommended Phase II dose (RP2D) and evaluate the overall safety and preliminary efficacy of Rux+Ven therapy. Eligible subjects were ≥18 years old with R/R AML. There was no restriction on the number of previous therapies or prior exposure to Ven or Rux. We included subjects with prior allogeneic transplant if GVHD was controlled and prior MDS (≥75 years old or having poor cardiac or kidney function) who progressed on a hypomethylating agent (HMA) but had no primary AML therapy. In cohorts of 3 to 4, subjects were assigned to receive Rux+Ven at 1 of 6 dose levels according to the "keyboard" Bayesian toxicity probability interval design applied to a target dose-limiting toxicity (DLT) rate of 30%. DLTs were defined as non-disease-related, Grade ≥3 non-hematologic toxicities, with exceptions for nausea, vomiting, infections, febrile neutropenia episodes, and electrolyte abnormalities that resolved within 48 hours. Hematologic DLT was specified as Grade 4 neutropenia after 42 days in the absence of disease. The DLT evaluation period covered the first cycle. Subjects could continue study therapy after two 28-day cycles if they had a response (ie, CR/CRi or MLFS) or were otherwise deriving clinical benefit.

Results : This Phase 1 study has completed enrollment (n=30), with all but one patient off-treatment as of June 2023. Baseline patient characteristics are summarized in Table 1. Median age was 69 (range 29-84), 40% of subjects had ≥3 prior therapies, and 43% had prior Ven. At enrollment, 30% had prior MDS, 24% had mutated TP53 (of 25 patients with available data), and

47% had CD56+ blasts. The numbers of patients treated by dose level (DL) were: 3 on DL0 (200 mg qd Ven; 10 mg bid Rux), 4 on DL1 (400 mg qd Ven; 10 mg bid Rux), 3 on DL2 (400 mg qd Ven; 20 mg bid Rux), and 20 on DL3 (400 mg qd Ven; 30 mg bid Rux), the highest dose level of the study. Per prescribing guidelines, the cycle 1 Rux doses of 15 subjects and Ven doses of 20 subjects were reduced because of a concomitant CYP3A inhibitor.
The regimen was well-tolerated. As no DLTs were observed, DL3 is the RP2D. The median (interquartile range) duration of therapy was 55 (36-93) days. The most common grade ≥3 hematologic AEs, regardless of attribution, were thrombocytopenia (50%; which was 30% at study enrollment), anemia (40%; 40% at enrollment), neutropenia (37%; 10% at enrollment), febrile neutropenia (33%), and leukopenia (33%; 7% at enrollment). Six subjects had a Grade 5 AE: 4 were unrelated to study drug (2 death NOS, 1 lung infection, 1 respiratory failure) and 2 were potentially related to Ven (1 sepsis, 1 neutropenic pneumonia). Over the first 2 cycles of study therapy, the Clinical Benefit Rate (CBR; defined as the proportion of subjects obtaining at least stable disease) was 63% (95% CI: 44%-80%). Morphologic leukemia-free state (MLFS) was achieved in 20% (95% CI: 8%-39%) and Composite Complete Remission in 10% (95% CI: 2%-27%). Median overall survival (OS) was 3.7 months (95% CI: 2.3-6.5), with 23% (95% CI: 10%-39%) alive 1 year after commencing Rux+Ven. Two participants were exceptional responders: the first achieving MLFS and receiving 16 cycles of study therapy and the second having a complete remission and remaining on-treatment after 31 cycles. Pre-Rux+Ven CD56 expression on blasts correlated with worse response (all 6 ≥MLFS patients were CD56-; Fig 1) and overall survival (HR=2.37, p=0.044; Table 1). Correlative studies such as *ex vivo* drug assessment, genomic analysis, CyTOF, and single-cell imaging will be presented to enhance this finding.
Conclusion: The novel, all-oral combination of Rux+Ven in R/R AML patients was well-tolerated with no DLTs and an encouraging 63% CBR over cycles 1-2. Negative CD56 was a biomarker of response, although additional work is required to determine if this is a broad association with Ven-based therapies or unique to the Rux+Ven combination. The tolerable toxicity profile of Rux+Ven makes it a promising combination to test with HMAs in high-risk AML patients.

Disclosures Borate: *Incyte:* Other; *Abbvie:* Membership on an entity's Board of Directors or advisory committees, Other: Research; *Jazz:* Other: Research; *Pfizer:* Other: Research; *Genentech:* Membership on an entity's Board of Directors or advisory committees; *Agios:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Blueprint:* Membership on an entity's Board of Directors or advisory committees; *Astellas:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Kura:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Membership on an entity's Board of Directors or advisory committees; *RUNX1 Foundation:* Honoraria. **Madanat:** *GERON:* Consultancy; *Blueprint Medicines:* Consultancy, Honoraria, Other: travel reimbursement; *Sierra Oncology:* Honoraria; *Morphosys:* Honoraria, Other: travel reimbursement; *Stemline therapeutics:* Honoraria; *Taiho oncology:* Honoraria; *Novartis:* Honoraria; *OncLive:* Honoraria; *MD Education:* Honoraria; *Rigel Pharmaceuticals:* Honoraria. **Tognon:** *Notable Labs:* Research Funding. **Patel:** *Servier LLC:* Current Employment. **Vasu:** *Sanofi Inc:* Research Funding; *Omeros Inc:* Research Funding. **Vu:** *Kronos Bio:* Research Funding. **Leonard:** *Pfizer:* Consultancy; *Takeda:* Consultancy; *Kite/Gilead:* Consultancy; *Adaptive Biotechnologies:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel, accommodations, expenses. **Maziarz:** *Orca Therapeutics:* Research Funding; *Kite:* Consultancy; *AlloVir:* Consultancy, Research Funding; *Gamida:* Research Funding; *Novartis:* Consultancy, Research Funding; *Athersys:* Other: Patent holder. **Traer:** *Schrodinger:* Research Funding; *Prelude Therapeutics:* Research Funding; *Incyte:* Research Funding; *Daiichi-Sankyo:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Membership on an entity's Board of Directors or advisory committees; *Rigel:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Astellas:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Research Funding. **Swords:** *Kronos Bio:* Research Funding. **Tyner:** *Incyte:* Research Funding; *Genentech:* Research Funding; *Kronos:* Research Funding; *Constellation:* Research Funding; *Petra:* Research Funding; *AstraZeneca:* Research Funding; *Acerta:* Research Funding; *Meryx:* Research Funding; *Aptose:* Research Funding; *Schrodinger:* Research Funding; *Tolero:* Research Funding; *Recludix Pharma:* Membership on an entity's Board of Directors or advisory committees. **Druker:** *Blueprint Medicines:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Aptose Biosciences:* Consultancy, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Adela, Inc.:* Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Burroughs Wellcome Fund:* Membership on an entity's Board of Directors or advisory committees; *Cepheid:* Membership on an entity's Board of Directors or advisory committees; *GRAIL:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Iterion Therapeutics:* Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Labcorp:* Membership on an entity's Board of Directors or advisory committees; *Nemucore Medical Innovations, Inc.:* Membership on an entity's Board of Directors or advisory committees; *Recludix Pharma, Inc.:* Consultancy, Current holder of *stock options* in a privately-held company; *The RUNX1 Research Foundation:* Membership on an entity's Board of Directors or advisory committees; *VB Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Vincerx Pharma, Inc.:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Beat AML LLC:* Membership on an entity's Board of Directors or advisory committees; *Multicancer Early Detection (MCED) Consortium:* Membership on an entity's Board of Directors or advisory committees; *Aileron Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Therapy Architects, LLC:* Membership on an entity's

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OffLabel Disclosure: Novel Rux+VEN in R/R AML

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Table 1: Patient Characteristics and correlation with outcomes, N=30

			≥MLFS rate (C12) = 20.0%	CBR (C12) = 63.3%	OS median = 3.7 months
Features	**Categories**	**Counts (%)**	**OR (95% CI); p-value**	**OR (95% CI); p-value**	**HR (95% CI); p-value**
Sex	female^	12 (40.0%)			
	male	18 (60.0%)	0.60 (0.09 - 3.86); 0.578	0.79 (0.16 - 3.58); 0.757	0.83 (0.39 - 1.76); 0.620
Race	white^	25 (83.3%)			
	other	4 (13.3%)	1.33 (0.06 - 13.3); 0.819	0.47 (0.05 - 4.50); 0.488	1.39 (0.47 - 4.08); 0.554
	<NA>	1 (3.3%)			
Ethnicity	Hispanic^	3 (10.0%)			
	Non-Hisp.	26 (86.7%)	No LR; Fisher test p=1.00	0.94 (0.04 - 11.2); 0.965	0.50 (0.15 - 1.72); 0.273
	<NA>	1 (3.3%)			
Prior VEN	no^	17 (56.7%)			
	yes	13 (43.3%)	0.59 (0.07 - 3.65); 0.583	0.87 (0.19 - 4.01); 0.858	1.02 (0.48 - 2.17); 0.959
Prior BMT	no^	24 (80.0%)			
	yes	6 (20.0%)	0.76 (0.04 - 6.36); 0.820	1.20 (0.19 - 9.94); 0.850	1.14 (0.42 - 3.08); 0.801
Number of Prior Lines	1L^	11 (36.7%)			
	2L	7 (23.3%)	0.44 (0.02 - 4.54); 0.525	1.11 (0.16 - 8.07); 0.914	0.82 (0.29 - 2.32); 0.710
	3+L	12 (40.0%)	0.53 (0.06 - 3.99); 0.541	2.50 (0.44 - 16.3); 0.309	0.90 (0.38 - 2.12); 0.808
Complex karyotype	no^	19 (63.3%)			
	yes	10 (33.3%)	No LR; Fisher test p=0.068	0.24 (0.04 - 1.16); 0.084	4.26 (1.55 - 11.7); **0.005***
	<NA>	1 (3.3%)			
TP53 mutation	no^	19 (63.3%)			
	yes	6 (20.0%)	No LR; Fisher test p=0.278	0.58 (0.09 - 3.92); 0.568	6.57 (1.78 - 24.2); **0.005***
	<NA>	5 (16.7%)			
CD56 expression	negative^	16 (53.3%)			
	positive	14 (46.7%)	No LR; Fisher test **p=0.019**	1.08 (0.24 - 4.95); 0.919	2.37 (1.02 – 5.49); **0.044**
Age	< 70^	15 (50.0%)			
	≥ 70	15 (50.0%)	2.36 (0.38 - 19.5); 0.369	2.41 (0.54 - 12.0); 0.260	0.90 (0.42 - 1.90); 0.780

Table 1: Correlation of baseline clinical and molecular features with clinical response (≥MLFS), Clinical Benefit Rate (CBR; ≥SD), and Overall Survival (OS). ORs estimated from univariable logistic regression; when these models yield unstable estimates, Fisher exact test p-values are provided. HRs estimated from univariable Cox models. ^ denotes the reference group for ORs and HRs. * Cox proportional hazards assumption is violated. **Abbreviations**: <NA> = missing patient data, BMT = allogeneic Bone Marrow Transplantation, CI = Confidence Interval, HR = Hazards Ratio, LR = Logistic Regression, MLFS = Morphologic Leukemia-Free State, OR = Odds Ratio, SD = Stable Disease.

Figure 1: Response, CD56, Prior Lines

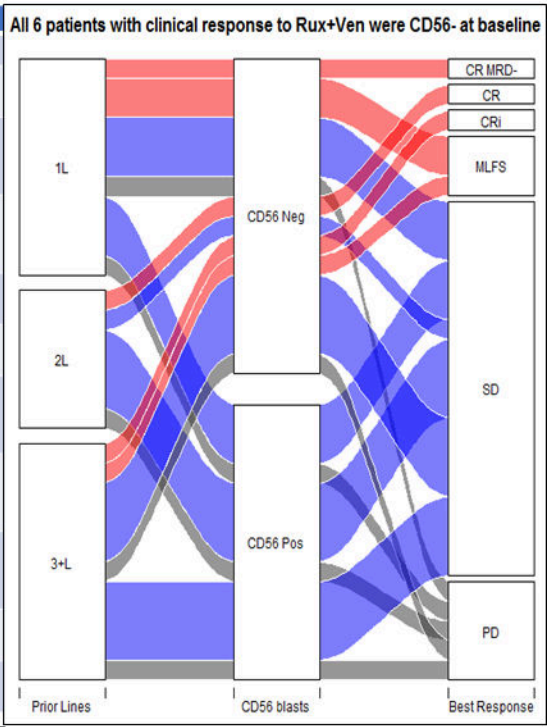

Figure 2: Sankey plot showing relationship between prior lines, pre-Rux+Ven CD56 blast expression, and clinical response over cycles 1-2 in 30 trial patients. Responders are colored RED and patients who achieved Stable Disease are BLUE. All responders were CD56-.

Figure 1