

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES**E7820, an Anti-Cancer Sulfonamide, in Combination with Venetoclax in Patients with Splicing Factor Mutant Myeloid Malignancies: A Phase II Clinical Trial**

Jan Philipp Bewersdorf, MD¹, Namrata Sonia Chandhok, MD², Justin M. Watts, MD³, Andriy Derkach, PhD⁴, Omar Abdel-Wahab, MD⁵, Eytan M. Stein, MD⁶, Justin Taylor, MD⁷

¹ Memorial Sloan Kettering Cancer Center, New York, NY

² Division of Hematology, University of Miami Miller School of Medicine/ Sylvester Comprehensive Cancer Center, Miami, FL

³ Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, MIAMI, FL

⁴ Department of Biostatistics and Epidemiology, Memorial Sloan Kettering Cancer Center, New York, NY

⁵ Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, NY

⁶ Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY

⁷ Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL

*JPB and NSC contributed equally.

Background and Significance: Mutations in RNA splicing factor genes (*SF3B1*, *SRSF2*, *U2AF1* and *ZRSR2*) are common in patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). We and others have previously shown that pharmacologic degradation of the RNA splicing factor RBM39 preferentially kills splicing factor mutant cells. These preclinical data provided the rationale for a recently completed phase II clinical trial (NCT05024994) of the oral RBM39 degrader E7820 in patients with relapsed or refractory splicing factor mutant MDS or AML. The safety and efficacy data of this trial have been presented previously (Bewersdorf *et al* ASH 2022). The generally favorable safety profile and correlative studies confirming target engagement and induction of mis-splicing events support the further exploration of E7820 in the context of combination therapies. Recent clinical data show that treatment with venetoclax can overcome the negative prognostic impact of splicing factor mutations in AML (Senapati *et al*, Blood 2023). Additionally, preclinical data from our laboratory show synergy between E7820 and venetoclax in *SF3B1*-mutant isogenic cell lines leading to enhanced RBM39 degradation and blunting of MCL-1 expression, a common cause of venetoclax resistance (**Figure 1**). Dynamic BH3 profiling of E7820 in myeloid leukemia cell lines suggests an E7820 dose-dependent priming for BAD which implies forced reliance on BCL2. Furthermore, adding venetoclax to E7820 further increased mitochondrial priming. Preclinical animal modeling with patient-derived xenografts (PDX) is ongoing. Based on these preclinical data, we are amending the study to include a separate arm of E7820 in combination with venetoclax.

Methods and Study Design: This is an investigator-initiated, phase II trial (NCT05024994) that is being conducted at Memorial Sloan Kettering Cancer Center and Sylvester Comprehensive Cancer Center at the University of Miami of adult (≥ 18 years) patients with relapsed or refractory AML, MDS, or chronic myelomonocytic leukemia (CMML). Patients must have a hotspot splicing factor mutation in *SF3B1*, *SRSF2*, *U2AF1* or *U2AF2* (with hotspot mutations as defined by OncoKB) or a nonsense or frameshift mutation in *ZRSR2* detected within 6 months of study screening for enrollment. Patients are required to have adequate end-organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 3 . Prior treatment with venetoclax is permitted.

Patients enrolled in the new combination arm will receive E7820 100mg by mouth once daily + venetoclax orally once daily on days 1-28 of cycle 1 on days 1-21 of subsequent cycles. The study design is shown in **Figure 2**. As this combination has never been studied in human AML and MDS patients previously, the study will include a 6-patient safety run-in phase with an optional dose de-escalation of E7820 to 70mg orally once daily. The sample size is based on a Minimax Simon 2-stage design. Assuming a type I error rate of 0.05, power of 0.8, a response rate of 10% in the historical control group and 30% with E7820 + venetoclax, 15 patients will be enrolled in stage 1. If there are at least 2 responses among the first 15 patients, we will enroll another 10 patients. The null hypothesis will be rejected if there are at least 6 responses in the 25 patients. The primary endpoint of this trial is to evaluate the efficacy of E7820 + venetoclax in patients with relapsed/refractory myeloid malignancies

with mutations in splicing factor genes as measured by the response rate within 6 cycles of therapy (AML: complete remission (CR) + complete remission with partial hematologic recovery (CRh); MDS: CR + CRh + CR with limited hematologic recovery (CR-L) + partial remission (PR); CMML: CR + PR). Secondary endpoints include overall and event-free survival. Correlative biomarker and pharmacodynamic parameters will be assessed as exploratory endpoints including effects on RBM39 protein levels, changes in global and key target splicing events, and evaluation of DCAF15 mRNA levels and response to therapy.

Disclosures Watts: *Reven Pharma:* Consultancy; *Rafael Pharma:* Consultancy; *Aptose:* Consultancy; *Takeda:* Consultancy, Research Funding; *BMS:* Consultancy; *Daiichi Sankyo:* Consultancy; *Servier:* Consultancy; *Rigel:* Consultancy; *Immune Systems Key:* Research Funding. **Abdel-Wahab:** *Harmonic Discovery:* Current holder of stock options in a privately-held company; *AsstraZeneca:* Consultancy; *Amphista Therapeutics:* Consultancy; *Minovia Therapeutics:* Research Funding; *Nurix Therapeutics:* Research Funding; *Loxo/Lilly:* Consultancy; *AbbVie, Inc.:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Stein:** *Foghorn:* Consultancy; *PinotBio:* Consultancy; *Janssen:* Consultancy; *Syndax:* Consultancy; *Abbvie:* Consultancy; *Genentech:* Consultancy; *Eisai:* Research Funding; *Jazz:* Consultancy; *Menarini:* Consultancy; *Neoleukin:* Consultancy; *Genesis:* Consultancy; *Gilead:* Consultancy; *Servier:* Consultancy; *CTI Biopharma:* Consultancy; *On-Cusp:* Consultancy; *Bristol Myers Squibb:* Consultancy, Research Funding; *Novartis:* Consultancy; *Calithera:* Consultancy; *Agios:* Consultancy; *Daiichi:* Consultancy; *Blueprint:* Consultancy; *Aptose:* Consultancy; *Syros:* Consultancy; *Astellas:* Consultancy; *Ono Pharma:* Consultancy.

Figure 1: Preclinical data supporting synergy of E7820 and venetoclax

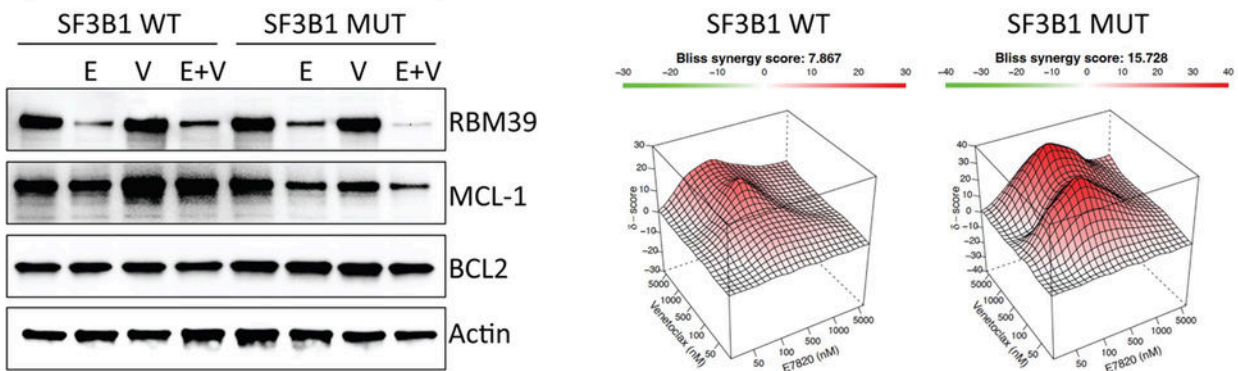


Figure 1: Combination of E7820 (E) and venetoclax (V) has synergistic effects in *SF3B1*-mutant cell lines as demonstrated by greater levels of RBM39 degradation and blunting of MCL1 expression with combination therapy and higher Bliss Synergy Score (>10) in the mutant.

Figure 2. Study schema

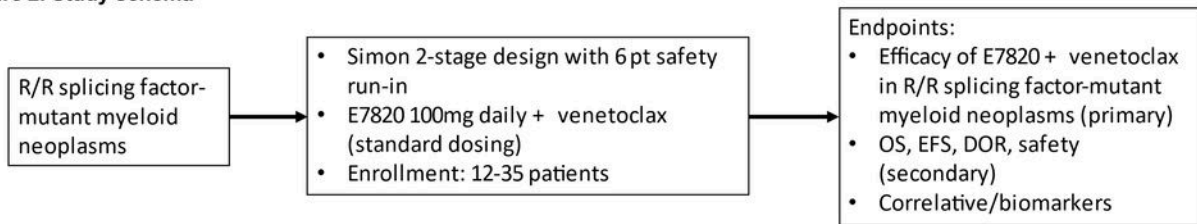


Figure 2. This is a single-arm, non-randomized, open-label phase II trial of E7820 in combination with venetoclax in patients with R/R splicing factor-mutant myeloid neoplasms.

Figure 1

<https://doi.org/10.1182/blood-2023-182369>

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement_1/1547/2027289/blood-8150-main.pdf by guest on 21 May 2024