



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES**Tagraxofusp in Combination with Azacitidine and Venetoclax in Newly Diagnosed CD123+ Acute Myeloid Leukemia, Expansion Cohort of a Phase 1b Multicenter Trial**

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Background: CD123 is a subunit of the interleukin 3 (IL3) receptor expressed on the surface of blasts in most acute myeloid leukemias (AMLs). Tagraxofusp (TAG), a CD123-directed therapy, is a recombinant protein drug consisting of IL3 fused to a truncated diphtheria toxin payload approved for treatment of blastic plasmacytoid dendritic cell neoplasm. We found TAG resistance in AML cells was mediated by DNA methylation and silencing of diphthamide genes (e.g., *DPH1*), which causes resistance to diphtheria toxin (Togami, JCI 2019). The hypomethylating agent azacitidine (AZA) reversed TAG resistance, and TAG plus AZA prolonged survival vs. either alone in xenograft models. TAG-exposed AML cells were also sensitized to the BCL2 inhibitor venetoclax (VEN). We performed a phase 1b trial combining these agents in myeloid malignancies and reported acceptable safety in dose escalation of TAG with AZA-VEN (ASH 2021). Here, we report an expansion cohort in newly diagnosed AML treated with TAG-AZA-VEN.

Methods: Patients (pts) were adults with AML ineligible or declining intensive induction chemotherapy. CD123+ blasts were required (tested locally by flow or IHC, any level). Eligibility included albumin >3.2 g/dL and normal cardiac ejection fraction. Pts were treated on 28-day cycles with AZA 75 mg/m² d1-7, VEN 400 mg d1-21 with ramp up in cycle 1, and TAG 12 µg/kg d4-6 (Fig A), with cycle 1 hospitalization to mitigate risks of capillary leak syndrome (CLS). Also included are 3 pts who received TAG 7 µg/kg (n=2) or 9 µg/kg (n=1) in escalation. TAG was given on d4 to avoid VEN ramp up overlap and because preclinical data showed AZA pretreatment can sensitize AML cells to TAG.

Results: 26 pts with AML were treated; median age 71 (range 60-81). All were adverse risk per ELN 2022 criteria, including 13 (50%) with a mutation in *TP53* and others with 1 or more of *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, or *U2AF1*. Eight (31%) had complex karyotype, 8 (31%) secondary AML, and 5 (19%) therapy-related AML. Adverse events (AEs) were like those seen with TAG or AZA/VEN, without evidence of exacerbation by combination. Grade 3+ AEs occurring in >15% of pts regardless of attribution included thrombocytopenia (54%), leukopenia (54%), febrile neutropenia (35%), and anemia (31%). CLS, a known TAG side effect, occurred in 19% (n=5; three grade 2, one gr 3, one gr 4; all in cycle 1) and was manageable by albumin supplementation and diuresis. Mortality at 30 days was 11.5%, with causes of death of sepsis (n=2), multiorgan system failure (n=1).

18 of 26 pts (69%) achieved a best response of CR (10; 39%), CRi (5; 19%), or MLFS (3; 12%). Of the 13 with *TP53* mutation, 7 (54%) achieved CR/CRi/MLFS (CR=4, CRi=2, or MLFS=1). Bone marrow blasts decreased in all pts who had a biopsy after starting treatment (Fig A). For the 18 achieving CR/CRi/MLFS, the median duration of response was 12.4 months (mo) (95% CI, 6.1-NA). 13 of 26 (50%) proceeded to allogeneic stem cell transplantation, which included 6/13 (46%) with *TP53* mutation.

The median number of cycles was 3 for both pts who did (range 1-15) and did not (range 2-4) proceed to transplant. The median follow-up was 10.7 mo, including post-transplant timepoints.

Median overall survival (OS) was 14 mo (95% CI, 9.5-NA) and progression-free survival (PFS) was 8.5 mo (95% CI, 5.1-NA). In pts with *TP53* mutation, median OS was 9.5 mo (95% CI, 1.8-NA); and not reached (NR) without (**Fig B**). PFS for pts with *TP53* mutation was 5.1 mo (95% CI, 1.8-NA), and 13.3 mo (95% CI, 8.6-NA) without. Measurable residual disease (MRD) was assessed by flow cytometry in 17 pts who achieved CR/CRi/MLFS; 12/17 (71%) were MRD negative (<0.1%). 4/7 (57%) with *TP53* mutation achieving CR/CRi/MLFS were MRD negative. Median OS for pts who became MRD negative was NR. Median OS for the 13 pts who received allogeneic transplant was 18.2 mo (95% CI, 14.0-NA). Median PFS for the transplanted pts was 13.3 mo (95% CI, 8.2-NA).

Conclusions: Treatment of AML with triplet TAG-AZA-VEN is feasible and shows encouraging activity as up-front therapy in adverse risk AML, including in pts with *TP53* mutation. These data (OS 14 mo; *TP53* mutant OS 9.5 mo) compare favorably to HMA/VEN in ELN adverse risk (OS 12 mo; Lachowiec, BloodAdv 2023) or *TP53* mutant AML with poor risk cytogenetics (OS 5.2 mo; Pollyea, CCR 2022), albeit with some differences between populations. No new safety signals were observed. Further development of this combination is warranted, including directly compared to AZA-VEN.

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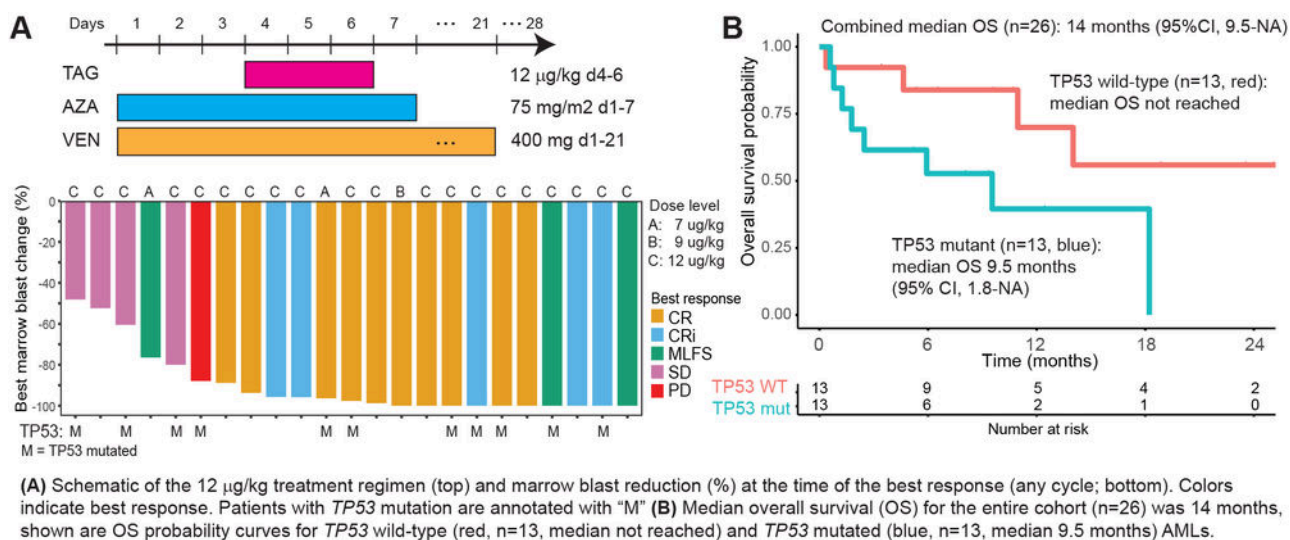


Figure 1

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