ELSEVIER

Blood 142 (2023) 4277–4279

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

Andrew A. Lane, MD PhD[1], *Jacqueline S. Garcia, MD*[1], *Evangeline G. Raulston*[1], *Jada L. Garzon*[1], *Ilene Galinsky, ANP*[1], *Emilie W. Baxter*[1], *Rebecca Leonard*[1], *Daniel J. DeAngelo*[2], *Marlise R. Luskin, MD*[3], *Christopher R. Reilly, MD*[1], *Maximilian Stahl, MD*[4], *Richard M Stone, MD*[2], *Rahul Vedula, MD*[1], *Martha Wadleigh, MD*[2], *Eric S. Winer, MD*[2], *Tariq Mughal, MD*[5], *Christopher Brooks*[5], *Ira V. Gupta, MD*[5], *Kristen E. Stevenson, MS, PhD*[6], *Donna S. Neuberg, ScD*[6], *Siyang Ren, MS*[6], *Marina Y. Konopleva, MD PhD*[7,8], *Anthony Stein, MD*[9], *Naveen Pemmaraju, MD*[7]

[1] Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
[2] Dana-Farber Cancer Institute, Boston, MA
[3] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
[4] Dana Farber Institute, Boston, MA
[5] Stemline Therapeutics, New York, NY
[6] Department of Data Science, Dana-Farber Cancer Institute, Boston, MA
[7] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[8] Department of Oncology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY
[9] City of Hope Cancer Center, Duarte, CA

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.

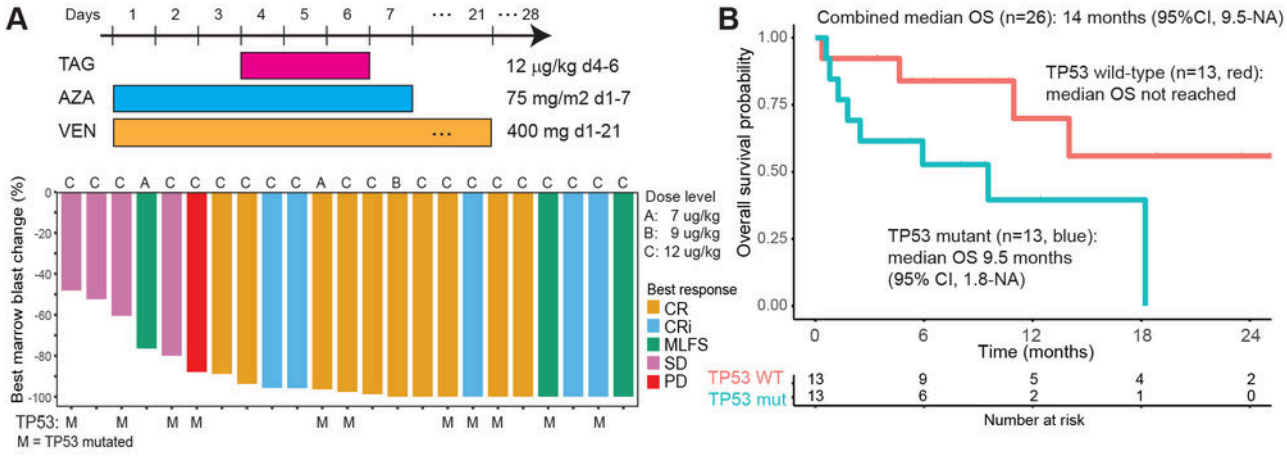
The median number of cycles was 3 for both pts who did (range 1-15) and did not (range 2-4) proceed to transplant. The median follow-up was 10.7 mo, including post-transplant timepoints.

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; Lachowiez, 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.

Disclosures Lane: *AbbVie:* Research Funding; *Cimeio Therapeutics:* Consultancy; *IDRx:* Consultancy; *Jnana Therapeutics:* Consultancy; *ProeinQure:* Consultancy; *Qiagen:* Consultancy; *Medzown:* Current equity holder in private company; *Stemline Therapeutics:* Research Funding. **Garcia:** *Astellas:* Consultancy; *Genentech:* Consultancy, Research Funding; *AstraZeneca:* Research Funding; *AbbVie:* Consultancy, Research Funding; *Bristol Myers Squibb:* Consultancy; *Gilead:* Consultancy; *Servier:* Consultancy; *Pfizer:* Research Funding; *New Wave:* Research Funding; *Prelude:* Research Funding. **DeAngelo:** *Novartis:* Research Funding; *Blueprint:* Research Funding; *AbbVie:* Research Funding; *Gilead:* Honoraria; *Jazz:* Honoraria; *Autolus:* Honoraria; *Amgen:* Honoraria; *GlycoMimetics:* Research Funding; *Blueprint:* Honoraria; *Incyte:* Honoraria; *Kite:* Honoraria; *Novartis:* Honoraria; *Pfizer:* Honoraria; *Servier:* Honoraria; *Takeda:* Honoraria. **Luskin:** *Novartis:* Research Funding; *Novartis:* Honoraria; *Jazz:* Honoraria; *Pfizer:* Honoraria; *AbbVie:* Research Funding. **Reilly:** *RenBio:* Consultancy. **Stahl:** *Rigel:* Membership on an entity's Board of Directors or advisory committees; *Kymera:* Membership on an entity's Board of Directors or advisory committees; *Clinical care options:* Other: GME activity ; *Dedham group:* Consultancy; *Curis Oncology:* Other: GME activity ; *GSK:* Membership on an entity's Board of Directors or advisory committees; *Boston Consulting:* Consultancy; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Other: GME activity ; *Sierra Oncology:* Membership on an entity's Board of Directors or advisory committees; *Haymarket Media:* Other: GME activity . **Stone:** *GSK:* Consultancy; *Kura One:* Consultancy; *Jazz:* Consultancy; *Cellularity:* Consultancy; *BerGenBio:* Consultancy; *Takeda:* Other: DSMB; *Amgen:* Consultancy; *AvenCell:* Consultancy; *Rigel:* Consultancy; *Syntrix:* Other: DSMB; *Lava Therapeutics:* Consultancy; *Hermavant:* Consultancy; *Ligand Pharma:* Consultancy; *Epizyme:* Other: DSMB; *Aptevo:* Other: DSMB; *CTI Biopharma:* Consultancy; *Abbvie:* Consultancy. **Winer:** *Curis Inc:* Consultancy; *Abbvie:* Consultancy. **Mughal:** *Stemline Therapeutics:* Current Employment. **Brooks:** *Stemline Menarini Oncology:* Current Employment. **Gupta:** *Stemline Therapeutics:* Current Employment. **Neuberg:** *Madrigal Pharmaceuticals:* Current equity holder in private company. **Konopleva:** *AbbVie, Forty Seven, Precision Biosciences, Gilead Sciences, Genentech, Janssen, Sanofi, MEI Pharma, Daiichi Sankyo Pharmaceutical, AstraZeneca Co., Menarini.:* Consultancy; *Reata Pharmaceuticals.:* Current holder of *stock options* in a privately-held company, Patents & Royalties; *Abbvie, Allogene Therapeutics, Cellectis, Forty Seven, Gilead Sciences, Genentech, Sanofi, MEI Pharma, Rafael Pharmaceuticals, Daiichi Sankyo Pharmaceutical, AstraZeneca Co., Menarini, Precision BioSciences.:* Research Funding. **Stein:** *Sanofi:* Current Employment, Current holder of *stock options* in a privately-held company. **Pemmaraju:** *CareDx:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Incyte:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Pacylex:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *OncLive:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Harborside Press:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Celgene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ClearView Healthcare Partners:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Aplastic Anemia & MDS International Foundation:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Dava Oncology:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Magdalen Medical Publishing:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Medscape:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Menarini Group:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Karger Publishers:* Other: Licenses; *ASCO Cancer.Net Editorial Board:* Other: Leadership; *ASH Committee on Communications:* Other: Leadership; *Physician Education Resource (PER):* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Neopharm:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Imedex:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *CancerNet:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Stemline:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *EUSA Pharma:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Curio Science:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Intellisphere:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Dan's House of Hope:* Membership on an entity's Board of Directors or advisory committees; *Protagonist Therapeutics, Inc.:* Consultancy, Member-

ship on an entity's Board of Directors or advisory committees; *PharmaEssentia:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Cimeio Therapeutics AG:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ImmunoGen:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *CTI BioPharma:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novartis Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Patient Power:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *PeerView Institute for Medical Education:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *United States Department of Defense (DOD):* Research Funding; *National Institute of Health/National Cancer Institute (NIH/NCI):* Research Funding; *Blueprint:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Astellas:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Aptitude Health:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AbbVie:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *HemOnc Times/Oncology Times:* Other: Uncompensated; *Bristol Myers Squibb Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau.



(A) Schematic of the 12 μg/kg treatment regimen (top) and marrow blast reduction (%) at the time of the best response (any cycle; bottom). Colors indicate best response. Patients with *TP53* mutation are annotated with "M" **(B)** Median overall survival (OS) for the entire cohort (n=26) was 14 months, shown are OS probability curves for *TP53* wild-type (red, n=13, median not reached) and *TP53* mutated (blue, n=13, median 9.5 months) AMLs.

Figure 1

https://doi.org/10.1182/blood-2023-180010