Tagraxofusp plus venetoclax and azacitidine in patients ineligible for intensive chemotherapy with previously untreated CD123+ acute myeloid leukemia: a phase 2 multicenter trial

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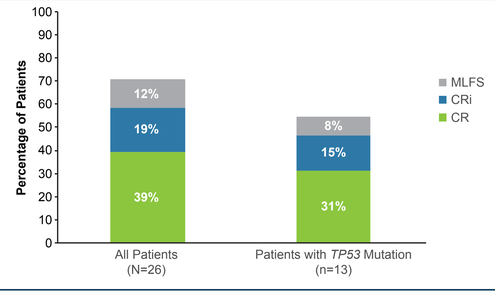
BACKGROUND

- Although complete remission (CR) rates after first-line therapy in acute myeloid leukemia (AML) are relatively high, some patients cannot tolerate high-intensity treatments or have a high risk of relapse with standard therapies.
- Venetoclax + azacitidine (VEN/AZA), a less intensive regimen, is the current standard of care for untreated patients unfit for or declining intensive chemotherapy for AML (CR 36.7%; minimal residual disease negative [MRD-] 23.4% in composite CR; median overall survival [OS] 14.7 months).[1]
- Maintaining a prolonged duration of remission and long-term overall survival with VEN/AZA is challenging in AML patients with negative prognostic factors, including older age, comorbidities, unfavorable cytogenetics, and high-risk genetic aberrations (eg, *TP53* mutations).
- AML patients with *TP53* mutations often have very poor responses, as observed in an exploratory post-hoc analysis of VEN/AZA in patients with *TP53*-mutated AML, where the CR rate was 22% and the median OS was 5.5 months.[2] Moreover, only 17.5% of AML patients with poor-risk cytogenetics and *TP53*-mutated AML achieved MRD negativity.[3]
- Adding an agent with a non-overlapping mechanism of action and safety profile may improve outcomes for patients in this difficult-to-treat condition and address an unmet medical need for this population.

RATIONALE

- Interleukin 3 receptor alpha chain (CD123) is present on the surface of most AML blasts and is enriched on leukemia stem cells (LSCs).
- In adult AML patients, CD123 expression has been associated with higher rates of chemoresistance and high-risk genetic alterations, particularly FLT3 ITD.[4] Additional studies have demonstrated that high levels of $CD34^{+}CD38^{low/-}CD123^{+}$ blasts are predictive of an adverse outcome[5] and that high expression of CD123 is strongly associated with several high-risk genetic abnormalities in childhood AML.[6]
- Tagraxofusp (TAG), a first-in-class CD123-targeted therapy, is a recombinant fusion protein consisting of human interleukin-3 conjugated to a truncated diphtheria toxin payload.
- Preclinical studies show synergistic efficacy with TAG and AZA in patient-derived xenografts treated in vivo.[7]
- TAG may overcome AZA resistance by targeting the CD123-high escape clone, and AZA overcomes TAG resistance by upregulating *DPH1* and thus re-sensitizing cells to the payload.
- In a phase 1b expansion cohort of CD123+ patients with untreated adverse-risk AML, TAG/VEN/AZA induced 39% CR, and 71% of responders were MRD-, consistent with clinical activity not only against blasts but LSCs as well; in patients with *TP53* mutations, 54% achieved CR/CR with incomplete hematologic recovery (CRi)/morphologic leukemia-free state (MLFS), 57% were MRD- (**Figure 1**),[8] consistent with TAG's likely *TP53*-independent mechanism of action as a protein synthesis inhibitor.[9]
- Based on promising early data and high unmet need, we have initiated a phase 2 trial to evaluate the addition of TAG to standard VEN/AZA to reduce overall disease burden and contribute to elimination of therapy-resistant leukemia cells.

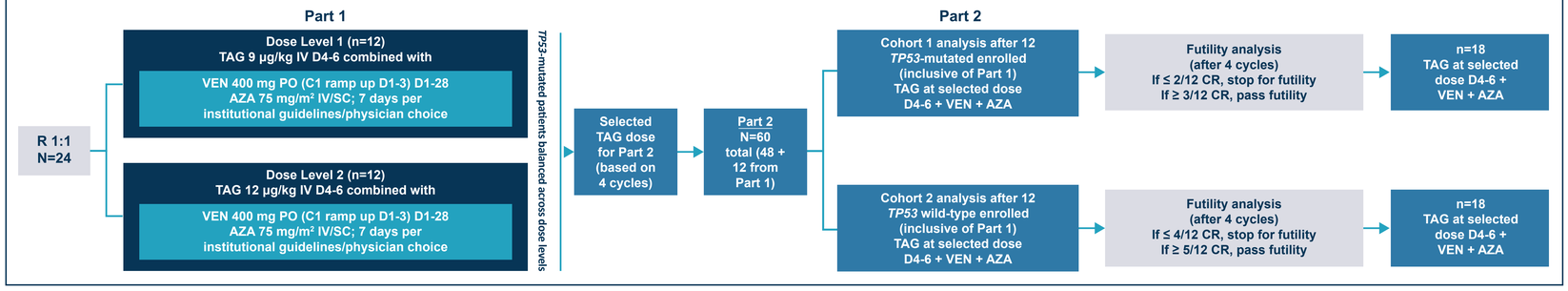
Figure 1. Bone marrow response in the previously untreated AML cohort that received TAG/AZA/VEN (Lane et al. 2024)



STUDY DESIGN

- This is a two-part, multicenter, open-label phase 2 study (NCT06456463) designed to evaluate the combination of TAG with VEN/AZA in adults with previously untreated CD123+ AML ineligible for intensive chemotherapy (**Figure 2**).
- Part 1 will evaluate two doses of intravenous (IV) TAG (9 µg/kg/day and 12 µg/kg/day) in combination with VEN/AZA.
- Part 2 will evaluate the preliminary clinical efficacy of TAG at the Selected Dose in combination with VEN/AZA in two cohorts (Cohort 1: *TP53*-mutated; and Cohort 2: *TP53* wild type).

Figure 2. Study Schema



ENDPOINTS

Primary Endpoints

Part 1
- Optimal TAG dose determination

Part 2
- CR rate

Key Secondary Endpoints

Part 1
- Safety
- CR rate
- Time to response (TTR)
- Composite CR rate
- CR/CRi rate
- Duration of response (DOR)
- Event-free survival (EFS)
- MRD negativity
- OS
- Pharmacokinetics/Pharmacodynamics (PK/PD)
- Rate of hematopoietic stem cell transplant (SCT)
- Exposure-response

Part 2
- Safety
- TTR
- Composite CR rate
- CR/CRi rate
- DOR
- EFS
- MRD negativity
- OS
- PK/PD
- Rate of SCT
- Exposure-response

ELIGIBILITY CRITERIA

Key Inclusion Criteria
- Previously untreated AML per World Health Organization (WHO) 2022
- CD123 expression (central or local)
- Age ≥ 75 years or 18-74 years with one qualifying comorbidity*
- Eastern Cooperative Oncology Group (ECOG) 0 to 2 (0 to 3 if age 18-74)
- Creatinine clearance (CrCl) ≥ 45 mL/min (≥ 30 mL/min if age 18-74)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x upper limit of normal (ULN)
- Total bilirubin (TBil) ≤ 1.5 x ULN (≤3.0 x ULN if age 18-74)†
- White blood cell count (WBC) ≤ 20 × 10^3/µL‡
- Serum albumin ≥ 3.2 g/dL§

Key Exclusion Criteria
- Willing and able to receive standard induction therapy
- Received prior therapy for AML (exception: hydroxyurea)
- Acute promyelocytic leukemia (APL)
- Central nervous system (CNS) involvement
- Mixed phenotype acute leukemia
- Received any of the following for antecedent hematologic disease: hypomethylating agent, VEN, TAG, purine analogue, cytarabine, intensive chemotherapy, CAR-T therapy, or other experimental therapies
- Experienced Grade 3 or 4 capillary leak syndrome (CLS) in the past for any reason

*ECOG Score of 2 or 3, diffusing capacity of the lungs for carbon monoxide (DLCO) ≤ 65% or forced expiratory volume in one second (FEV1) ≤ 65%, CrCl ≥ 30 ml/min to < 45 ml/min, TBil > 1.5 to ≤ 3.0 × ULN; †Unless due to known history of Gilbert's disease; ‡Note: hydroxyurea and/or leukapheresis is permitted prior to Cycle 1 Day 1 to reduce the WBC count to ≤ 20 × 10^3/µL and to satisfy eligibility; §Administration of serum albumin is not permitted to achieve albumin eligibility.

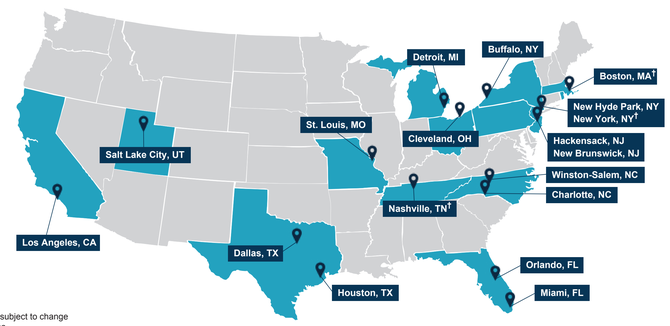
TREATMENT ADMINISTRATION

Tagraxofusp	▪ Administered IV on Days 4, 5, and 6 of each 28-day cycle. ▪ TAG must be administered inpatient in Cycle 1. Subsequent cycles of TAG may be administered in the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped for intensive monitoring of patients. ▪ Infusions may be delayed; dose delays that extend beyond 10 days from the first TAG infusion require discussion with the Medical Monitor.
Azacitidine	▪ Administered subcutaneous (SC) or IV at 75mg/m² of BSA over 7 days (ie, days 1 through 7, 5-on-2-off-2-on schedule, 4-on-2-off-3-on, or other similar modified schedule as required) of each 28-day cycle, per institutional guidelines and physician's choice.
Venetoclax	▪ During Cycle 1, the PO dose of VEN on Cycle 1 Day 1 (C1D1) is 100 mg, C1D2 is 200 mg, C1D3 is 400 mg (target dose) and should be continued at target dose for the remainder of Cycle 1 and subsequent cycles. ▪ Note: Dose reductions per local labeling for subjects taking azoles, CYP3A inhibitors, or P-gp inhibitors. ▪ The goal is to administer 28 days of VEN in Cycle 1 unless marrow remission with concomitant marrow hypocellularity and/or myelosuppression is confirmed earlier than Cycle 1 Day 28. ▪ For Cycle 2 and beyond, VEN may be reduced to Days 1-21 or less after PI approval.

STUDY INFORMATION

- Part 1 will enroll patients from the United States (**Figure 3**), South Korea, and Australia.
- This phase 2 study (NCT06456463) is currently open for enrollment.
- Study contact: clinicaltrials@menarinistemline.com

Figure 3. US sites participating in the study*



*Study sites subject to change
†Multiple sites

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ABBREVIATIONS ALT, alanine transaminase; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AST, aspartate transaminase; AZA, azacitidine; C, cycle; CD123, interleukin 3 receptor alpha chain; CNS, central nervous system; CLS, capillary leak syndrome; CR, complete remission; CrCl, creatinine clearance; CRi, complete remission with incomplete hematologic recovery; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FEV1, forced expiratory volume in one second; IV, intravenous; LSCs, leukemia stem cells; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; OS, overall survival; PK/PD, pharmacokinetic/pharmacodynamic; PO, by mouth; SC, subcutaneous; SCT, stem cell transplant; TAG, tagraxofusp; TBil, total bilirubin; TTR, time to response; ULN, upper limit of normal; VEN, venetoclax; WBC, white blood cell; WHO, World Health Organization.

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