# TUSCANY Study Demonstrates Safety and Efficacy of Tuspetinib plus Standard of Care Venetoclax and Azacitidine in Patients with Newly Diagnosed AML Ineligible for Induction Chemotherapy

*Gabriel Mannis[1], Nikolai A. Podoltsev[2], Deepa Jeyakumar[3], Justin M. Watts[4], Pankit Vachhani[5], Brian A. Jonas[6], Uma Borate[7], Eric L. Tam[8], Harry P. Erba[9], Yuling Shi[10], Donna Nguyen Haney[10], William Rice[10], Rafael Bejar[10], Naval Daver[11]*

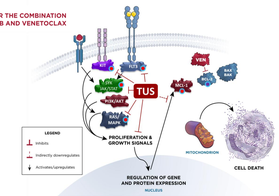
[1]Stanford Cancer Center, Stanford University, [3]Palo Alto, CA, [2]Yale School of Medicine, New Haven, CT, [3]UC Irvine Health, Chao Family Comprehensive Cancer Center, Irvine, CA, [4]Miller School of Medicine, University of Miami, Miami, FL, [5]University of Alabama at Birmingham, Birmingham, AL, [6]UC Davis Comprehensive Cancer Center, Sacramento, CA, [7]The James Cancer Hospital and Solove Research Institute, Ohio State University, Columbus, OH, [8]USC Norris Comprehensive Cancer Center, Los Angeles, CA, [9] Duke Cancer Institute, Durham, NC, [10]Aptose Biosciences, Del Mar, CA,[11]The University of Texas MD Anderson Cancer Center, Houston, TX

## BACKGROUND

The combination of venetoclax (VEN) with azacitidine (AZA) improves response rates and overall survival in newly diagnosed AML patients. However, outcomes remain poor, particularly in those with adverse *FLT3-ITD*, *RAS*, or *TP53* mutations that drive VEN resistance and early relapse. The addition of a well-tolerated, broadly active, targeted agent to VEN/AZA is needed to enhance response, increase survival, and decrease resistance.

Tuspetinib (TUS) is a potent, once-daily oral kinase inhibitor that targets SYK, FLT3, JAK1/2, RSK1/2 of the RAS/MAPK pathway, and mutant KIT kinases that drive dysregulated proliferation in AML and has been shown to indirectly inhibit MCL-1 expression. In the prior global APTIVATE study in relapsed/refractory (R/R) AML, both TUS monotherapy (93 pts) and TUS in combination with VEN (79 pts) produced objective responses in patients with diverse mutations with no dose-limiting toxicities (DLTs) observed at the 40-160 mg dose levels, supporting the combination of TUS with VEN/AZA in the TUSCANY study.

## TUS TARGETS VEN-RESISTANCE MECHANISMS

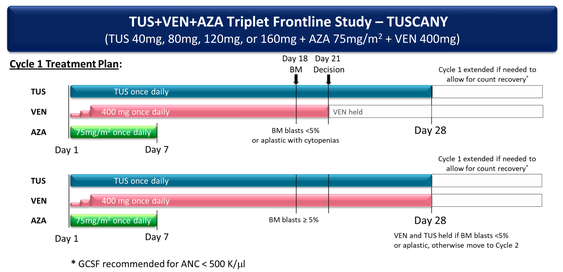



- TUS inhibits kinase-driven abnormal signaling
- TUS reduces MCL-1 protein expression
- TUS/VEN combine to avoid VEN resistance
- TUS can deliver responses in *RAS* and *TP53* mutated patients

## STUDY DESIGNS AND OBJECTIVES

**TUSCANY** is a phase 1/2, open-label dose escalation study of TUS in combination with VEN and AZA (TUS/VEN/AZA) in subjects with previously untreated AML ineligible for intensive chemotherapy.

**Objective:** To evaluate the safety, tolerability, response rates, measurable residual disease (MRD) status, and pharmacokinetics (PK) of TUS at various dose levels in combination with VEN/AZA in newly diagnosed AML ineligible for induction chemotherapy.




## BASELINE PATIENT CHARACTERISTICS

**As of the datacut of 27 Oct 2025:** 12 subjects have been treated across 4 TUS dose levels ( 40, 80, 120 and 160 mg daily) in combination with standard-of-care doses of VEN (400 mg on Days 1-28) and AZA (75 mg/m² on Days 1-7)

| TUS+VEN+AZA Triplet | |
|---|---|
| **Demographics and AML Features** | **N=12** |
| Median Age (Range), years | 78 (69-81) |
| **Sex** | |
| Male | 5 (41.7%) |
| Female | 7 (58.3%) |
| **FLT3 Mutation Status** | |
| FLT3-ITD | 2 (16.7%) |
| FLT3-unmutated | 10 (83.3%) |
| **TP53 Mutation or Complex Karyotype** | 3 (25.0%) |

## TUS+VEN+AZA SAFETY / TOLERABILITY

### TUS+VEN+AZA Triplet

- Treatment was well tolerated with no DLTs across all TUS dose levels (40-160 mg once daily) combined with standard dosing of VEN/AZA.
- Febrile neutropenia reported in 2 subjects (16.7%) with 1 subject related to TUS.
- No Dose Limiting Toxicities including no prolonged myelosuppression for subjects in remission in Cycle 1.
- No drug-related deaths, differentiation syndrome, QTc prolongation, or CPK elevation reported
- 8/10 subjects experienced red cell and platelet transfusion independence for >8 weeks after their best response

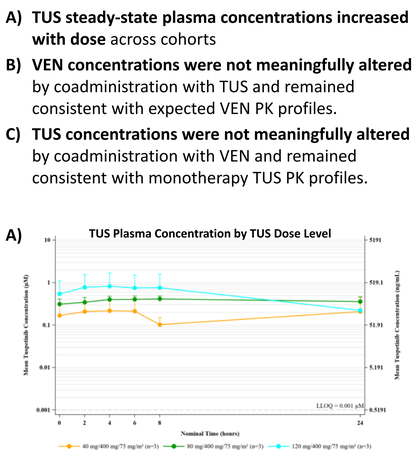
| Treatment Emergent Adverse Events | All | Related to TUS | Related to VEN | Related to AZA |
|---|---|---|---|---|
| **Any** | **11 (91.7%)** | **7 (58.3%)** | **10 (83.3%)** | **11 (91.7%)** |
| **Most Frequent AEs ≥10%** | | | | |
| Platelet count decreased | 9 (75.0%) | 6 (50.0%) | 8 (66.7%) | 8 (66.7%) |
| Diarrhoea | 6 (50.0%) | 2 (16.7%) | 3 (25.0%) | 3 (25.0%) |
| Neutrophil count decreased | 6 (50.0%) | 2 (16.7%) | 5 (41.7%) | 6 (50.0%) |
| White blood cell count decreased | 6 (50.0%) | 2 (16.7%) | 5 (41.7%) | 6 (50.0%) |
| Hypokalaemia | 5 (41.7%) | 1 (8.3%) | 1 (8.3%) | 1 (8.3%) |
| Constipation | 5 (41.7%) | 1 (8.3%) | 11 (8.3%) | 1 (8.3%) |
| Anaemia | 5 (41.7%) | 4 (33.3%) | 4 (33.3%) | 4 (33.3%) |
| Decreased appetite | 4 (33.3%) | 1 (8.3%) | 2 (16.7%) | 2 (16.7%) |
| Nausea | 4 (33.3%) | 3 (25.0%) | 3 (25.0%) | 3 (25.0%) |
| Hyponatraemia | 3 (25.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Aspartate aminotransferase increased | 3 (25.0%) | 2 (16.7%) | 2 (16.7%) | 2 (16.7%) |
| Blood alkaline phosphatase increased | 3 (25.0%) | 0 (0.0%) | 1 (8.3%) | 1 (8.3%) |
| Vomiting | 3 (25.0%) | 2 (16.7%) | 2 (16.7%) | 2 (16.7%) |
| Blood creatinine increased | 3 (25.0%) | 1 (8.3%) | 1 (8.3%) | 1 (8.3%) |
| Neutropenia | 3 (25.0%) | 3 (25.0%) | 3 (25.0%) | 0 (0.0%) |
| Fall | 3 (25.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pruritus | 3 (25.0%) | 1 (8.3%) | 1 (8.3%) | 1 (8.3%) |
| Back pain | 3 (25.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dry Mouth | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Proctalgia | 2 (16.7%) | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) |
| Blood bilirubin increased | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dehydration | 2 (16.7%) | 1 (8.3%) | 1 (8.3%) | 1 (8.3%) |
| Hypocalcaemia | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hypophosphataemia | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Chills | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Oedema Peripheral | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Febrile neutropenia | 2 (16.7%) | 1 (8.3%) | 0 (0.0%) | 1 (8.3%) |
| Contusion | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dysgeusia | 2 (16.7%) | 1 (8.3%) | 1 (8.3%) | 1 (8.3%) |
| Headache | 2 (16.7%) | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) |
| Skin infection | 2 (16.7%) | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) |
| Urinary tract infection | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Epistaxis | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hypotension | 2 (16.7%) | 0 (0.0%) | 0 (0.0% | 0 (0.0%) |
| **Grade ≥ 3 AEs (≥10%)** | **10 (83.3%)** | **7 (58.3%)** | **9 (75.0%)** | **10 (83.3%)** |
| Platelet count decreased | 7 (58.3%) | 5 (41.7%) | 7 (58.3%) | 7 (58.3%) |
| Neutrophil count decreased | 6 (50.0%) | 2 (16.7%) | 4 (33.3%) | 5 (41.7%) |
| White blood cell count decreased | 6 (50.0%) | 2 (16.7%) | 5 (41.7%) | 6 (50.0%) |
| Anaemia | 4 (33.3%) | 4 (33.3%) | 4 (33.3%) | 4 (33.3%) |
| Neutropenia | 3 (25.0%) | 3 (25.0%) | 3 (25.0%) | 3 (25.0%) |
| Diarrhoea | 2 (16.7%) | 1 (8.3%) | 1 (8.3%) | 1 (8.3%) |
| Febrile neutropenia | 2 (16.7%) | 1 (8.3%) | 1 (8.3%) | 1 (8.3%) |
| Hypophosphataemia | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **SAEs** | **5 (41.7%)** | **1 (8.3%)** | **1 (8.3%)** | **1 (8.3%)** |
| Leading to treatment termination | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Leading to death | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

## PHARMACOKINETICS

**A) TUS steady-state plasma concentrations increased with dose** across cohorts

**B) VEN concentrations were not meaningfully altered** by coadministration with TUS and remained consistent with expected VEN PK profiles.

**C) TUS concentrations were not meaningfully altered** by coadministration with VEN and remained consistent with monotherapy TUS PK profiles.



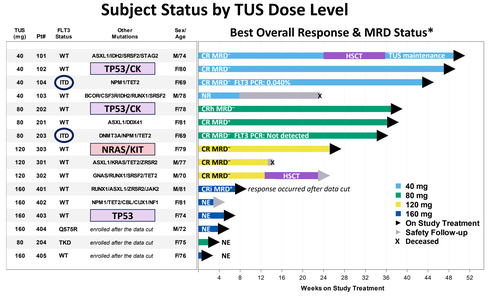

## RESPONSE RATES AND STUDY STATUS

| AML Category | TUSCANY (TUS-VEN-AZA) | | VIALE-A (VEN-AZA) | |
|---|---|---|---|---|
| | CR/CRh n/N (%) | MRD$^{NEG}$ n/N (%) | CR/CRi (%) | MRD$^{NEG}$ (%) |
| **Overall** | **9/10 (90%)** | **7/9 (78%)** | **66%** | **41%** |
| FLT3-ITD | 2/2 (100%) | 2/2 (100%) | 63.3% | 53% |
| FLT3$^{WT}$ | 7/8 (88%) | 5/7 (71%) | | |
| NPM1$^{MUT}$ | 2/2 (100%) | 2/2 (100%) | 66.7% | 88% |
| TP53$^{MUT}$/CK | 2/2 (100%) | 1/2 (50%) | 47.6% | 14.5% |
| AML-MR | 4/5 (80%) | 2/4 (50%) | | |
| **AZA-VEN Benefit Group** | | | | |
| Higher | 4/5 (80%) | 2/4 (50%) | 77.2% | 33.1% |
| Intermediate | 3/3 (100%) | 3/3 (100%) | 59.2% | 27.9% |
| Lower | 2/2 (100%) | 2/2 (100%) | 47.6% | 14.5% |

**At 40, 80, and 120 mg TUS dose levels:**

- CR/CRh as best response observed in 9/10 evaluable subjects (8 CR, 1 CRh)
- MRD-levels <0.1% by central flow cytometry observed in 7/9 (78%) responding subjects
- Two subjects transitioned to stem cell transplantation with one returned for TUS maintenance

**160 mg dose escalation and 80 mg expansion TUS dose levels are currently enrolling**

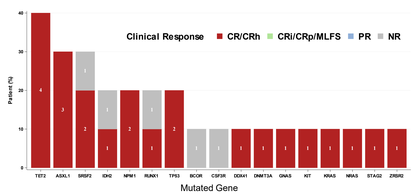



* MRD is assessed by central flow cytometry of bone marrow mononuclear cells with values of <0.1% considered negative

**Abbreviations**: CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; NE, not yet evaluable; MRD, measurable residual disease; ITD, FLT3 internal tandem duplication; TKD, tyrosine kinase domain mutation; WT, FLT3 unmutated; CK, complex karyotype

## MUTATION PROFILES

A)




A) Incidence of mutations at baseline in the first 10 subjects treated, coded by response.

B) Mutation grid showing somatic mutations in the first 10 subjects treated coded by whether mutations were present at baseline and at time of best response (persists), at baseline only (cleared), or at time of best response or end of treatment only (gained).

B)

| Gene Name | Study Subjects by Patient # | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 104 | 203 | 101 | 103 | 301 | 302 | 201 | 303 | 102 | 202 |
| *FLT3* | | | | | | | | | | |
| *NPM1* | | | | | | | | | | |
| *IDH1* | | | | | | | | | | |
| *IDH2* | | | | | | | | | | |
| *TET2* | | | | | | | | | | |
| *DNMT3A* | | | | | | | | | | |
| *ASXL1* | | | | | | | | | | |
| *SRSF2* | | | | | | | | | | |
| *RUNX1* | | | | | | | | | | |
| *BCOR* | | | | | | | | | | |
| *STAG2* | | | | | | | | | | |
| *EZH2* | | | | | | | | | | |
| *ZRSR2* | | | | | | | | | | |
| *SF3B1* | | | | | | | | | | |
| *U2AF1* | | | | | | | | | | |
| *TP53* | | | | | | | | | | |
| *JAK2* | | | | | | | | | | |
| *MPL* | | | | | | | | | | |
| *KRAS* | | | | | | | | | | |
| *NRAS* | | | | | | | | | | |
| *CSF3R* | | | | | | | | | | |
| *KIT* | | | | | | | | | | |
| *DDX41* | | | | | | | | | | |
| *GNAS* | | | | | | | | | | |

- mutation cleared - mutation persists - mutation gained
- AML target mutation - AML-MR mutation

## CONCLUSIONS

- In newly diagnosed AML, **TUS+VEN+AZA shows promising safety, tolerability, and robust efficacy**, including **MRD-negative remissions** across a broad mutational spectrum
- **CR/CRh rates:**
  - **90%** across 40, 80, and 120 mg dose levels
- **MRD negativity: 78%** by central flow cytometry in responding subjects
- Responses observed in **FLT3-WT, FLT3-ITD, NPM1c, biallelic TP53/complex karyotype, RAS**, and **MDS-related** mutations
- The **160 mg TUS cohort** is fully enrolled, and the **80 mg TUS expansion cohort** is enrolling

We thank our principal investigators, clinical site staff, and most importantly, our patients and their families for their participation in this clinical trial. ASH2025 Poster 1645

Disclosures: This clinical study is sponsored by Aptose Biosciences. The following authors are current or prior employees of Aptose Biosciences: DN Haney, R Bejar, W Rice, and Y Shi