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

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BACKGROUND

Combination of venetoclax (VEN) with a hypomethylating agent (HMA) improves outcomes in newly diagnosed AML patients. Yet, overall survival remains poor, particularly in cases with adverse *FLT3*-ITD, *RAS*, or *TP53* mutations. Addition of a well-tolerated, broadly active agent to HMA/VEN is needed to enhance response, increase survival, and prevent resistance.

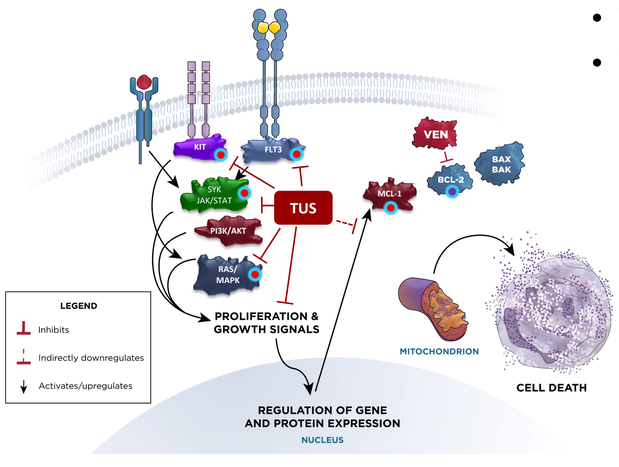
Tuspetinib (TUS) is a potent, once-daily oral kinase inhibitor targeting SYK, FLT3, JAK1/2, RSK1/2 of the RAS/MAPK pathway, and mutant KIT kinases that drive dysregulated proliferation in AML. Combination of TUS with HMA/VEN is supported by early phase safety and efficacy results in relapsed/refractory (R/R) AML, as monotherapy and in combination with VEN.

Dissociation and inhibition constants for TUS against key kinases operative in AML

Assay Methodology	Kinase	Mutation Status	Activity
Binding Affinity (K_D, nM)	FLT3	WT	0.58
		ITD	0.37
		D835Y	0.29
		D835H	0.4
		ITD/D835V	0.48
		ITD/F691L	1.3
Inhibition of Kinase Enzyme Activity (IC_{50}, nM)	FLT3	WT	1.1
		ITD	1.8
		D835Y	1.0
	SYK	WT	2.9
	JAK	JAK1	2.8
		JAK2	6.3
		JAK2 V617F	9.9
	c-KIT	WT	> 500
		D816H	3.6
		D816V	3.5
	RSK	RSK2	9.7
	TAK1-TAB1	TAK1-TAB1	7.0

TUS TARGETS VEN-RESISTANCE MECHANISMS

RATIONALE FOR THE COMBINATION OF TUSPETINIB AND VENETOCLAX



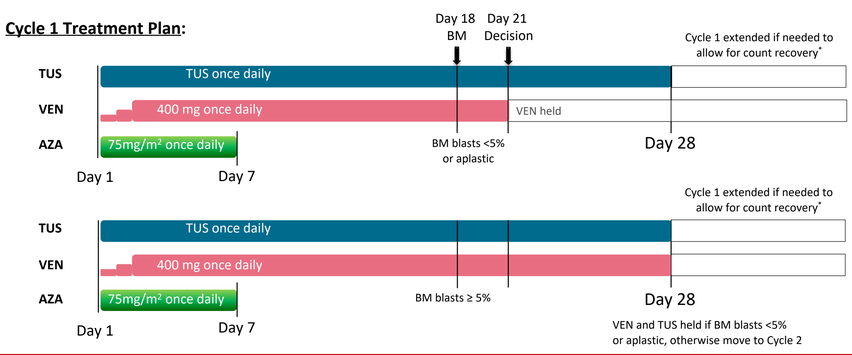
- TUS inhibits kinase-driven abnormal signaling
- TUS reduces MCL-1 protein expression
- TUS/VEN combine to avoid VEN resistance
- TUS can deliver responses in *RAS* and *TP53* mutated patients

SCAN ME

STUDY DESIGN & 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

- To assess the safety, tolerability, activity, and PK of TUS, at various dose levels, in combination with AZA and VEN in newly diagnosed AML patients ineligible for induction chemotherapy.



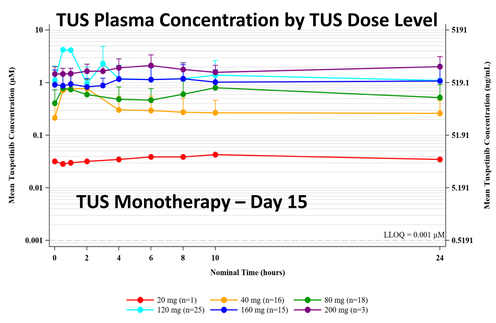
DEMOGRAPHICS

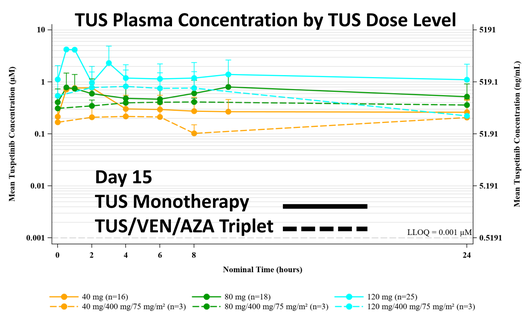
As of 15 Sep 2025: 10 subjects have been treated across 3 TUS dose levels (40, 80, & 120 mg daily) in combination with standard-of-care doses of VEN (400 mg on Days 1-28) and AZA (75 mg/m^2 on Days 1-7)

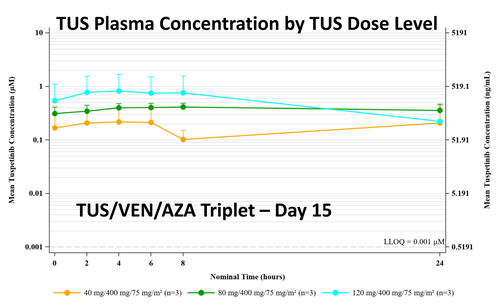
Baseline Subject and Disease Characteristics	
	TUS/VEN/AZA
Subject Demographics and AML Features	**N=10**
Median Age (Range), years	77.5 (69-81)
Sex	
Male	4 (40%)
Female	6 (60%)
FLT3 Mutation Status	
FLT3-ITD	2 (20%)
FLT3-unmutated	8 (80%)
TP53 Mutation or Complex Karyotype	2 (20%)

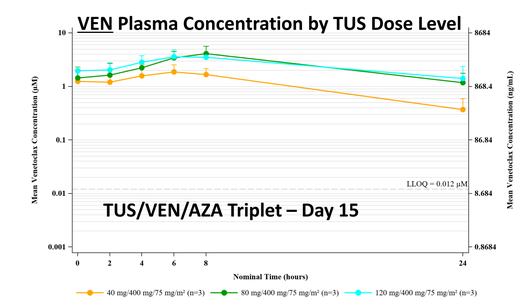
PHARMACOKINETICS

- TUS plasma concentrations increased with dose from 40 to 80 to 120 mg in combination with AZA/VEN
- TUS plasma concentrations are not increased when given with VEN compared to TUS as monotherapy
- VEN plasma concentrations are not significantly altered by coadministration with increasing doses of TUS and are consistent with published results for VEN monotherapy







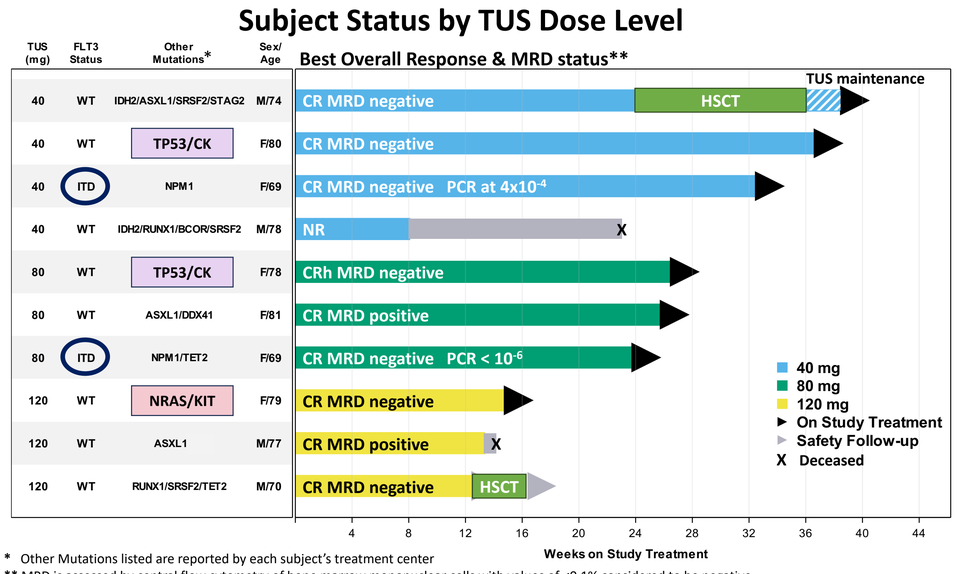


We thank our principal investigators, clinical site staff, and most importantly, our patients and their families for their participation in this clinical trial.

CLINICAL EFFICACY AND MRD STATUS

- CR/CRh as best response observed in 9/10 (8 CR, 1 CRh) subjects
- 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

Subject Status by TUS Dose Level



* Other Mutations listed are reported by each subject's treatment center
** MRD is assessed by central flow cytometry of bone marrow mononuclear cells with values of <0.1% considered to be negative
Abbreviation: CR, complete remission; CRh, complete remission with partial hematologic recovery; MRD, measurable residual disease; ITD, FLT3 internal tandem duplication; WT, FLT3 unmutated; CK, complex karyotype

AML Category	TUSCANY (TUS-VEN-AZA) CR/CRh n/N (%)	TUSCANY (TUS-VEN-AZA) MRD^{NEG} n/N (%)	VIALE-A (VEN-AZA) CR/CRi (%)	VIALE-A (VEN-AZA) 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				
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%

SAFETY

TUS/VEN/AZA Triplet:

- Treatment was well tolerated across all TUS dose levels (40, 80, and 120 mg once daily) combined with standard dosing of VEN/AZA.
- Febrile neutropenia reported in only 2 subjects (20%).
- No Dose Limiting Toxicities including no prolonged myelosuppression for subjects in remission in Cycle 1.
- No drug-related deaths, differentiation syndrome, QT_c prolongation, or CPK elevation reported
- 8/10 subjects experienced red cell and platelet transfusion independence for >8 weeks after their best response

Treatment-emergent AEs (TEAEs) TUS/VEN/AZA (Part D)	
Subjects Experiencing TEAEs	TUS/VEN/AZA (N=10, n[%])
Any	10 (100%)
Most Frequent TEAEs (>15% of subjects)	
Platelet count decreased	9 (90%)
Neutrophil count decreased	6 (60%)
White blood cell count decreased	6 (60%)
Constipation	5 (50%)
Diarrhea	5 (50%)
Hypokalaemia	5 (50%)
Nausea	4 (40%)
Decreased appetite	4 (40%)
Anaemia	4 (40%)
Vomiting	3 (30%)
Blood alkaline phosphatase increased	3 (30%)
Blood creatinine increased	3 (30%)
Hyponatremia	3 (30%)
Headache	3 (30%)
Neutropenia	3 (30%)
Fall	3 (30%)
Blood bilirubin increased	2 (20%)
Hypophosphataemia	2 (20%)
Hypocalcaemia	2 (20%)
Febrile neutropenia	**2 (20%)**
Dysgeusia	2 (20%)
Chills	2 (20%)
Pruritus	2 (20%)
Skin infection	2 (20%)
Urinary tract infection	2 (20%)
Hypotension	2 (20%)
≥ Grade 3	9 (90%)
SAEs	4 (40%)
Leading to treatment termination	0 (0%)
Leading to death	0 (0%)

Subjects Experiencing TUS-related TEAEs	Related to TUS	Related to VEN	Related to AZA
Any	6 (60%)	8 (80%)	9 (90%)
Most Frequent Related TEAEs (>10% of subjects)			
Platelet count decreased	6 (60%)	6 (60%)	6 (60%)
Neutrophil count decreased	2 (20%)	3 (30%)	4 (40%)
Anaemia	4 (40%)	4 (40%)	4 (40%)
Neutropenia	3 (30%)	3 (30%)	3 (30%)
Nausea	3 (30%)	3 (30%)	3 (30%)
White blood cell count decreased	2 (20%)	4 (40%)	5 (50%)
Vomiting	2 (20%)	2 (20%)	2 (20%)
Diarrhea	1 (10%)	2 (20%)	2 (20%)
Decreased appetite	1 (10%)	2 (20%)	2 (20%)
Grade ≥ 3	6 (60%)	7 (26%)	7 (70%)
Platelet count decreased	5 (50%)	5 (50%)	5 (50%)
Neutrophil count decreased	2 (20%)	3 (30%)	4 (40%)
WBC count decreased	2 (20%)	4 (40%)	5 (50%)
Neutropenia	3 (30%)	3 (30%)	3 (30%)
Anaemia	4 (40%)	4 (40%)	4 (40%)
Febrile neutropenia	1 (10%)	1 (10%)	1 (10%)
SAEs	0 (0%)	1 (10%)	0 (0%)
Leading to death	0 (0%)	0 (0%)	0 (0%)
Dose Limiting Toxicity (DLT)	0 (0%)	0 (0%)	0 (0%)

CONCLUSIONS

- TUS in combination with standard dosing of VEN/AZA has been well tolerated in newly diagnosed AML across 3 TUS dose levels.
- TUS+VEN+AZA CR/CRh = 100% with ≥ 80 mg TUS
- TUS+VEN+AZA CR/CRh = 90% across all dose levels
- TUS+VEN+AZA MRD-negativity = 78% by central flow cytometry
- CR/CRh achieved across diverse mutational subtypes including: FLT3-unmutated, FLT3-ITD, NPM1c, biallelic *TP53* with complex karyotype, RAS, and myelodysplasia related mutations.
- Dosing at the TUS 160 mg dose level is now ongoing.

Disclosures: This clinical study is sponsored by Aptose Biosciences. The following authors are employed by Aptose Biosciences: W Rice, D Nguyen, Y Shi, and R Bejar