Phase 1 Safety and Efficacy of Tuspetinib Plus Venetoclax Combination Therapy in Study Participants with Relapsed or Refractory Acute Myeloid Leukemia (AML) Support Exploration of Triplet Combination Therapy of Tuspetinib Plus Venetoclax and Azacitidine for Newly Diagnosed AML

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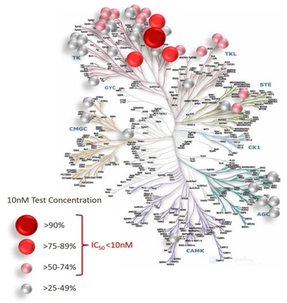
INTRODUCTION

Tuspetinib (TUS) is being developed for frontline AML therapy as part of the TUS+VEN+AZA triplet (tuspetinib+venetoclax+azacitidine) for newly diagnosed AML patients ineligible for intensive chemotherapy. TUS is a once daily, oral, multi-kinase inhibitor selectively targeting FLT3, SYK, JAK1/2, RSK2, and mutant forms of KIT that drive AML cell proliferation. In a Phase 1/2 trial of relapsed/refractory (R/R) AML patients (NCT03850574), **TUS** single agent and the **TUS+VEN** doublet demonstrated **excellent safety and broad efficacy across AML genetic subgroups**, supporting advancement of the TUS+VEN+AZA triplet in frontline therapy. **TUS targets known VEN resistance mechanisms**, and in combination with VEN, could prevent emergence of resistance to both agents. Ongoing clinical investigation with tuspetinib is being conducted as the **TUS+VEN+AZA triplet in newly diagnosed AML patients** with clinical findings from the front-line triplet study expected during Q4'2024.

Kinome Inhibition Tree for Tuspetinib



Kinase Inhibition Profile

Method	Kinase	Mutation	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	JAK-1	2.8
		JAK-2	6.3
		JAK-2 (V617F)	9.9
	c-KIT	WT	> 500
		D816H	3.6
		D816V	3.5
	RSK	RSK-2	9.7

STUDY DESIGN (DATA CUT 5 NOV 2024)

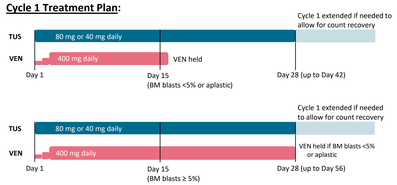
TUS Single Agent Dose Escalation and Exploration — **Total n=93**

Cohort 1: 20 mg QD	2
Cohort 2: 40 mg QD	17
Cohort 3: 80 mg QD	22
Cohort 4: 120 mg QD	32
Cohort 5: 160 mg QD	16
Cohort 6: 200 mg QD	4

Doses with CR & no DLT

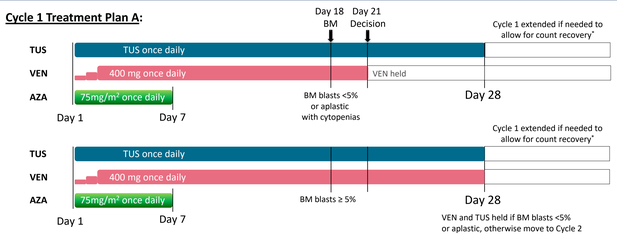
TUS+VEN Doublet Study
(TUS 80mg or 40mg + VEN 400mg)
n=**79** dosed | n=65 in 80 mg/400 mg | n=14 in 40 mg/400 mg

Cycle 1 Treatment Plan:



TUS+VEN+AZA Triplet Frontline Study – Currently Enrolling
(TUS 40mg, 80mg, or 120mg + AZA 75mg/m^2 VEN 400mg)

Cycle 1 Treatment Plan A:



* GCSF recommended for ANC < 500 K/µl

BASELINE PATIENT CHARACTERISTICS

TUS Single Agent

- **93 patients** dosed as of Nov 5, 2024
- Median **age ≥ 61 years**: Older population
- Over **35% failed Prior-transplant**
- **49% of FLT3^{MUT} failed Prior-FLT3i**
- Population included **FLT3^{WT}** and **FLT3^{MUT}**
- Population included **17% TP53^{MUT}/CK** and **25% NKRAS^{MUT}**
- Over **58% failed Prior-VEN** : Correlates with poor outcome

Patient Characteristics (n=93)	FLT3^{MUT}	FLT3^{WT}
Patient number (n)	35	58
Median Age Years (Range)	61 (21-84)	66 (18-84)
Female n (%)	14 (40.0%)	25 (43.1%)
Lines prior therapy Mean (Range)	3.2 (1-11)	2.4 (1-6)
Prior-VEN	19 (54.3%)	35 (60.3%)
Prior FLT3 Inhibitor	17 (48.6%)	3 (5.1%)
Prior Cytotoxic Chemotherapy	27 (77.1%)	38 (65.5%)
Prior HMAs	22 (62.9%)	39 (67.2%)
Prior HSCT	14 (40.0%)	19 (32.8%)

TUS+VEN Doublet

- **79 patients** dosed as of Nov 5, 2024
- Median **age ≥ 69 years**: Older than TUS single agent trial
- Over **24% failed Prior-transplant**
- Over **85% of FLT3^{MUT} failed Prior-FLT3i**
- Population included **FLT3^{WT}** and **FLT3^{MUT}**
- Population included **32% TP53^{MUT}/CK** and **22% NKRAS^{MUT}**
- Over **74% failed Prior-VEN** : Correlates with poor outcome

Patient Characteristics (n=79)	FLT3^{MUT}	FLT3^{WT}
Patient number (n)	20	58
Median Age Years (Range)	70 (39-84)	69 (31-86)
Female n (%)	11 (55.0%)	27 (46.6%)
Prior lines of therapy Mean (Range)	2.8 (1-5)	2.3 (1-7)
Prior-VEN	16 (80.0%)	42 (72.4%)
Prior FLT3 Inhibitor	17 (85.0%)	6 (10.3%)
Prior Cytotoxic Chemotherapy	12 (60.0%)	30 (51.7%)
Prior HMAs	15 (75.0%)	46 (79.3%)
Prior HSCT	7 (35.0%)	12 (20.7%)

TUS & TUS+VEN SAFETY / TOLERABILITY

TUS Single Agent

- No drug-related myelosuppression in remission
- No treatment related QTc prolongation or CPK elevations
- No drug-related discontinuations or deaths
- No drug-related non-hematologic SAEs
- No differentiation syndrome

TUS+VEN Doublet

- No new or unexpected safety signals with TUS+VEN
- No treatment related CPK elevations
- No differentiation syndrome
- No drug-related deaths

Adverse Events	*TUS Single Agent* n(%) (n=93)		*TUS+VEN Doublet* n(%) (n=79)		
	Treatment Emergent AEs	Treatment Related AEs	Treatment Emergent AEs	Treatment Emergent AEs Related to TUS	Treatment Emergent AEs Related to VEN
Any	**89 (95.7%)**	**29 (31.2%)**	**77 (97.5%)**	**40 (50.6%)**	**37 (46.8%)**
Most Frequent AEs ≥10%					
Pneumonia	32 (34.4%)	0 (0%)	19 (24.1%)	2 (2.5%)	3 (3.8%)
Nausea	20 (21.5%)	9 (9.7%)	21 (26.6%)	14 (17.7%)	10 (12.7%)
Pyrexia	19 (20.4%)	9 (9.7%)	10 (12.7%)	1 (1.3%)	1 (1.3%)
Diarrhea	18 (19.4%)	9 (9.7%)	15 (19.0%)	5 (6.3%)	4 (5.1%)
Alanine aminotransferase increased	13 (14.0%)	2 (2.2%)	12 (15.2%)	3 (3.8%)	3 (3.8%)
Hypokalaemia	13 (14.0%)	0 (0%)	11 (13.9%)	2 (2.5%)	1 (1.3%)
Epistaxis	12 (12.9%)	0 (0%)	4 (5.1%)	0 (0%)	0 (0%)
Decreased appetite	11 (11.8%)	2 (2.2%)	11 (13.9%)	1 (1.3%)	4 (5.1%)
Hypomagnesaemia	11 (11.8%)	0 (0%)	4 (5.1%)	1 (1.3%)	1 (1.3%)
Febrile neutropenia	11 (11.8%)	1 (1.1%)	21 (26.6%)	2 (2.5%)	4 (5.1%)
Fatigue	10 (10.8%)	2 (2.2%)	16 (20.3%)	7 (8.9%)	6 (7.6%)
Abdominal pain	10 (10.8%)	0 (0%)	4 (5.1%)	1 (1.3%)	1 (1.3%)
Constipation	10 (10.8%)	2 (2.2%)	6 (7.6%)	0 (0%)	0 (0%)
Dyspnoea	10 (10.8%)	0 (0%)	8 (10.1%)	0 (0%)	0 (0%)
Headache	10 (10.8%)	1 (1.1%)	7 (8.9%)	0 (0%)	0 (0%)
Cough	8 (8.6%)	0 (0%)	10 (12.7%)	0 (0%)	0 (0%)
Anaemia	7 (7.5%)	0 (0%)	10 (12.7%)	3 (3.8%)	3 (3.8%)
Neutrophil count decreased	5 (5.4%)	2 (2.2%)	8 (10.1%)	6 (7.6%)	5 (6.3%)
Platelet count decreased	5 (5.4%)	1 (1.1%)	10 (12.7%)	4 (5.1%)	3 (3.8%)
White blood cell count decreased	4 (4.3%)	2 (2.2%)	10 (12.7%)	6 (7.6%)	7 (8.9%)
Aspartate aminotransferase increased	4 (4.3%)	1 (1.1%)	11 (13.9%)	2 (2.5%)	2 (2.5%)
Leukocytosis	4 (4.3%)	0 (0%)	8 (10.1%)	1 (1.3%)	0 (0%)
Vomiting	7 (7.5%)	2 (2.2%)	8(10.1%)	3 (3.8%)	4 (5.1%)
Grade ≥ 3 AEs (≥10%)	**67 (72.0%)**	**9 (9.7%)**	**68 (86.1%)**	**22 (27.8%)**	**22 (27.8%)**
Pneumonia	27 (29.0%)	0 (0%)	17 (21.5%)	2 (2.5%)	3 (3.8%)
Febrile neutropenia	11 (11.8%)	1 (1.1%)	20 (25.3%)	2 (2.5%)	3 (3.8%)
Anaemia	6 (6.5%)	0 (0%)	9 (11.4%)	2 (2.5%)	2 (2.5%)
Platelet count decreased	4 (4.3%)	0 (0%)	10 (12.7%)	4 (5.1%)	3 (3.8%)
Neutrophil count decreased	5 (5.4%)	2 (2.2%)	8 (10.1%)	6 (7.6%)	5 (6.3%)
SAEs					
Leading to treatment termination	12 (12.9%)	1(1.1%)	10 (12.7%)	0 (0%)	10 (12.7%)
Leading to death	17 (18.3%)	0 (0%)	18 (22.8%)	0 (0%)	0 (0%)

TUS & TUS+VEN RESPONSE RATES

TUS Single Agent

- Includes 40, 80, 120, and 160 mg TUS dose as a single agent
- Includes those who failed prior therapy with Venetoclax
- Includes those with mutated or unmutated FLT3, those who failed prior-HSCT, prior-FLT3i, prior-chemotherapy, prior-HMA
- **33% CRc & 42% ORR** (CR, CRp, CRh, CRi or PR) in FLT3 mutated and Ven-Naïve patients

R/R AML Population	TUS Single Agent (40, 80, 120, 160 mg)			
	All Comers		Ven Naive	
	CRc	ORR	CRc	ORR
All Comers	15% (10/65)	22% (14/65)	27% (8/30)	30% (9/30)
FLT3-Mutated	16% (4/25)	28% (7/25)	33% (4/12)	**42% (5/12)**
FLT3-Wildtype	15% (6/40)	18% (7/40)	22% (4/18)	**42 % (5/12)**
TP53MUT/ CK	25% (3/12)	25% (3/12)	40% (2/5)	40% (2/5)
N/KRASmut	11% (2/18)	17% (3/18)	17% (1/6)	17% (1/6)
Prior VEN	6% (2/35)	14% (5/35)	NA	NA
Prior FLT3i	6% (1/16)	13% (2/16)	33% (1/3)	33% (1/3)

TUS+VEN Doublet

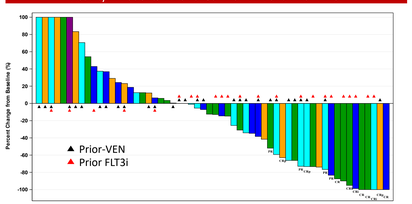
- TUS+VEN Achieved Responses Among Diverse R/R AML with Adverse Mutations in VEN-naïve, Prior-VEN, FLT3WT, FLT3MUT, Prior-FLT3i
- Blast reductions achieved in patients who failed prior therapies with FLT3 inhibitors and VEN
- 40% ORR was observed at 80 mg TUS + 400 mg VEN in FLT3 mutated patients. Among these 83% (5/6) had failed prior-VEN treatment and 50% (3/6) had failed both Prior-VEN and FLT3i treatment.

40 mg TUS + 400 mg VEN		80 mg TUS + 400 mg VEN	
CRc	ORR	CRc	ORR
7% (1/14)	7% (1/14)	19% (12/65)	26% (17/65)
20% (1/5)	20% (1/5)	27% (4/15)	**40% (6/15)**
0% (0/9)	0% (0/9)	16% (8/49)	**22% (11/49)**
0% (0/5)	0% (0/5)	20% (4/20)	20% (4/20)
0% (0/1)	0% (0/1)	12% (2/16)	31% (5/16)
9% (1/11)	9% (1/11)	19% (9/48)	27% (13/48)
25% (1/4)	25% (1/4)	26% (5/19)	32% (6/19)

TUS & TUS+VEN BONE MARROW BLAST REDUCTIONS AND RESPONSES

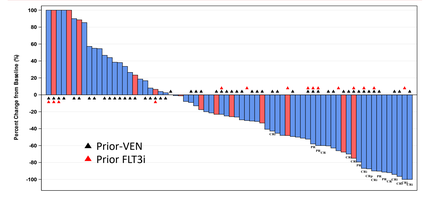
TUS Single Agent

Reductions Demonstrate Activity Across 4 Dose Levels
Activity in Patients Who Failed Prior-VEN and Prior-FLT3i



TUS-VEN Doublet

Blast Reductions in VEN-Naive and Prior-VEN R/R AML
Blast Reductions in Most R/R AML Patients Treated with Prior-FLT3i



Note: Blast percent change was calculated as 100 X (the lowest post-baseline bone marrow blast - baseline bone marrow blast)/baseline bone marrow blast. Patients with blast percent change >=100% are shown as 100%. Only patients who reported both baseline and any post-baseline bone marrow blast results are included in the figure.
Black triangle indicates patients who received prior Ven before starting HM43239. Red triangle indicates prior FLT3i.

CONCLUSION

TUS+VEN+AZA Triplet Trial Proceeding

- **In preparation for triplet studies in newly diagnosed AML, extensive dose exploration studies were conducted** with **TUS** (93 patients) and **TUS+VEN** (79 patients) in **highly treatment experienced R/R AML patients** (prior VEN, FLT3i, HMA, chemo, HSCT)

TUS Monotherapy

- Complete remissions achieved at 40, 80, 120, and 160 mg with no DLT
- 33% CRc and 42% ORR achieved in VEN naïve and FLT3-mutation harboring patients.
- Responses achieved in patients harboring highly adverse genetics (TP53^{MUT}, RAS^{MUT}, other)

TUS+VEN Doublet

- Remains safe and well tolerated (40mg TUS + 400mg VEN | 80mg TUS + 400mg VEN)
- Achieves bone marrow blast reductions and responses among diverse R/R AML patients with adverse mutations and prior failure of VEN

Resistance Avoidance: TUS targets known VEN resistance mechanisms *in vitro* and is clinically active in both FLT3^{MUT} & FLT3^{WT} R/R AML populations

TUS+VEN+HMA TRIPLET for AML 1L UNMET NEED

Tuspetinib Maintains Orphan Drug Designation and Fast Track Status

Critical Unmet Medical Need for Improved Frontline Therapy in Newly Diagnosed AML

- **VEN+HMA in 1L therapy:** 1/3 do not respond; median OS <15 months; <25% alive at 3-years; 9% survival after 5 years if patient > 65 years of age
  - Response rates and OS need improvement, especially in adverse genetic subgroups
  - Emergence of VEN resistance via RAS/MAPK, TP53, and FLT3 clonal expansion, among other mechanisms, compromises salvage therapies in R/R setting
- **A safe and broadly active 3rd agent** is needed to boost responses with VEN+HMA standard of care therapy and avoid rapid emergence of drug resistance

TUS is an Ideal 3rd Agent for Addition to VEN+AZA to Treat Newly Diagnosed AML

- TUS has **excellent safety** alone and in combination with **VEN** when co-administered
- TUS has **broad activity** across genetic subgroups including TP53, RAS/MAPK, & FLT3 mutants
- TUS mechanism **may minimize drug resistance to VEN via inhibition of key AML kinases**

TUS+VEN+AZA is Now Enrolling to Address the Needs of Newly Diagnosed AML Patients

We thank our principal investigators, clinical site staff, and most importantly, our patients and their families for their participation in this clinical trial. ASH2024 Abstract 4255

Disclosures: This clinical study is sponsored by Aptose Biosciences. The following authors are current or prior employees of Aptose Biosciences: R Sinha, J Hu, N Khan, W Rice, and R Bejar