Safety and Efficacy of Tuspetinib (TUS) and Tuspetinib+Venetoclax (TUS+VEN) in a Phase 1/2 Trial of R/R Acute Myeloid Leukemia (AML) Patients Support TUS+VEN+AZA Triplet Strategy for Front Line AML

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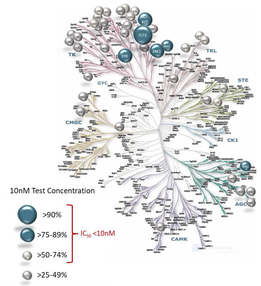
INTRODUCTION

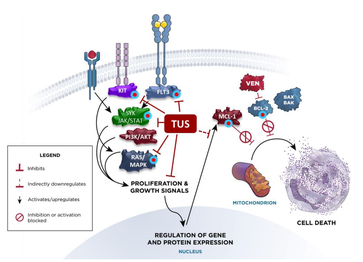
Tuspetinib (TUS) is a once daily, oral, multi-kinase inhibitor designed to selectively target SYK, RSK, FLT3$^{WT/MUT}$, JAK1/2$^{WT/MUT}$, KIT^{MUT} that drive AML cell proliferation. **Tuspetinib is being developed for frontline AML therapy as part of the TUS+VEN+AZA triplet (tuspetinib + venetoclax + azacitidine) for newly diagnosed AML patients ineligible for intensive chemotherapy.** 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 (See EHA ePoster# P1756). 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 2H'2024.

Kinome Tree of Tuspetinib Kinase Inhibition Profile



Tuspetinib Maintains Orphan Drug Designation and Fast Track Status

Rationale for the combination of TUS and VEN



BASELINE PATIENT CHARACTERISTICS

TUS Single Agent

- **93 patients** dosed as of April 26, 2024
- Median **age > 63 years**: Older population
- Over 35% **failed Prior-transplant**
- 49% of FLT3^{MUT} **failed Prior-FLT3i**
- Population included **FLT3^{WT}** and **FLT3^{MUT}**
- Population included 13% **TP53^{MUT}**/CK and 14% **N/KRAS^{MUT}**
- Over 58% **failed Prior-VEN** : Correlates with poor outcome

Patient Characteristics (n=93)	FLT3^{MUT}	FLT3^{WT}
Patient number n (%)[1]	35	57
Median Age Years (Range)	61 (21-84)	66 (18-84)
Female n (%)	14 (40.0%)	25 (43.9%)
Lines prior therapy Mean (Range)	3.2 (1-11)	2.3 (1-6)
Prior-VEN	19 (54.2%)	34 (59.6%)
Prior FLT3 Inhibitor	17 (48.6%)	3 (5.3%)
Prior Cytotoxic chemotherapy	27 (77.1%)	37 (64.9%)
Prior HMAs	22 (62.9%)	38 (66.7%)
Prior HSCT	14 (40%)	19 (33.3%)

TUS+VEN Doublet

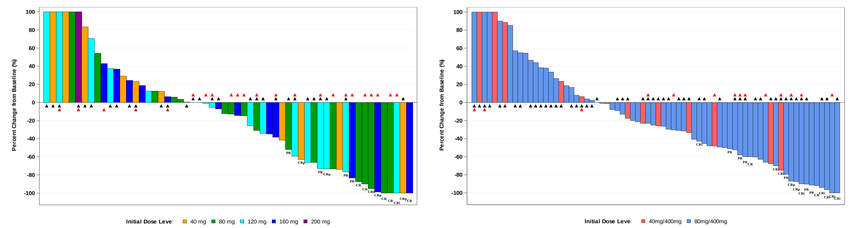
- **79 patients** dosed as of April 26, 2024
- Median **age > 69 years**: Older than TUS single agent trial
- Over 24% **failed Prior-transplant**
- Over 84% of FLT3^{MUT} **failed Prior-FLT3i**
- Population included **FLT3^{WT}** and **FLT3^{MUT}**
- Population included **29% TP53^{MUT}**/CK and 15% **N/KRAS^{MUT}**
- Over 75% **failed Prior-VEN** : Correlates with poor outcome

Patient Characteristics (n=79)	FLT3^{MUT}	FLT3^{WT}
Patient number n (%)[2]	19	58
Median Age Years (Range)	65.4 (39-84)	66.6 (31-86)
Female n (%)	10 (52.6%)	28 (48.3%)
Prior lines of therapy Mean (Range)	2.8 (1-5)	2.2 (1-7)
Prior-VEN	15 (78.9%)	42 (72.4%)
Prior FLT3 Inhibitor	16 (84.3%)	7 (12.0%)
Prior Cytotoxic chemotherapy	11 (57.9%)	31 (53.4%)
Prior HMAs	14 (73.7%)	46 (79.3%)
Prior HSCT	7 (36.8%)	12 (20.7%)

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-Naïve and Prior-VEN R/R AML
Blast Reductions in Most R/R AML Patients Treated with Prior-FL3i



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.

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 observed
- No drug-related deaths

Adverse Events	*TUS Single Agent*		*TUS+VEN Doublet*		
			Related to TUS/VEN, 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%)	41 (51.9%)	38 (48.1%)
Most Frequent AEs ≥10%					
Pneumonia	31 (33.3%)	0 (0%)	16 (20.3%)	2 (2.5%)	3 (3.8%)
Nausea	20 (21.5%)	9 (9.7%)	21 (26.6%)	14 (17.7%)	10 (12.7%)
Diarrhea	18 (19.4%)	9 (9.7%)	14 (17.7%)	5 (6.3%)	4 (5.1%)
Pyrexia	18 (19.4%)	0 (0%)	11 (13.9%)	1 (1.3%)	1 (1.3%)
Alanine aminotransferase increased	13 (14.0%)	2 (2.2%)	12 (15.2%)	3 (3.8%)	3 (3.8%)
Hypokalaemia	13 (14.0%)	0 (0%)	10 (12.7%)	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%)	4 (5.1%)	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%)	20 (25.3%)	3 (3.8%)	4 (5.1%)
Fatigue	10 (10.8%)	2 (2.2%)	15 (19.0%)	6 (7.6%)	5 (6.3%)
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%)	9 (11.4%)	0 (0%)	0 (0%)
Headache	10 (10.8%)	1 (1.1%)	6 (7.6%)	0 (0%)	0 (0%)
Cough	8 (8.6%)	0 (0%)	10 (12.7%)	0 (0%)	0 (0%)
Anaemia	6 (6.5%)	0 (0%)	11 (13.9%)	4 (5.1%)	4 (5.1%)
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%)	7 (8.9%)	7 (8.9%)
Aspartate aminotransferase increased	4 (4.3%)	1 (1.1%)	11 (13.9%)	2 (2.5%)	2 (2.5%)
Grade ≥ 3 AEs (≥10%)	66 (71.0%)	9 (9.7%)	67 (84.8%)	23 (29.1%)	23 (29.1%)
Pneumonia	26 (28.0%)	0 (0%)	14 (17.7%)	2 (2.5%)	3 (3.8%)
Febrile neutropenia	10 (10.8%)	1 (1.1%)	19 (24.1%)	2 (2.5%)	3 (3.8%)
Anaemia	5 (5.4%)	0 (0%)	11 (13.9%)	3 (3.8%)	3 (3.8%)
Platelet count decreased	4 (4.3%)	0 (0%)	11 (13.9%)	4 (5.1%)	3 (3.8%)
SAEs					
Leading to treatment termination	12 (12.9%)	1 (1.1%)	11 (13.9%)	1 (1.3%)	3 (3.8%)
Leading to death	18 (19.4%)	0(0%)	17 (21.5%)	0(0%)	0(0%)

CONCLUSIONS

- **Extensive dose exploration** 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
  - 42% CRc and 50% ORR was observed 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
- **TUS targets known VEN resistance mechanisms** *in vitro* and is clinically active in both FLT3^{MUT} & FLT3^{WT} R/R AML populations

STUDY DESIGN

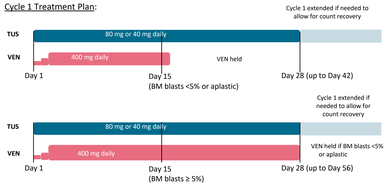
Data Cut 26 April 2024

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

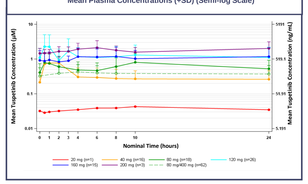
TUS+VEN Doublet Study
(TUS 80mg or 40mg + VEN 400mg)
n=**79** dosed | n=65 in 80 mg/400 mg | n=14 in 40 mg/400 mg

Cycle 1 Treatment Plan:



TUS Steady State PK by Dose Cohort

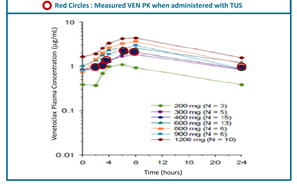
Mean Plasma Concentrations (+SD) (Semi-log Scale)



Note: the time 0 of single dose PK is the dosing time on Cycle 1 Day 1, whereas the time 0 of multiple dose PK is the dosing time of Cycle 1 Day 15 and Day 17 in Part C (dose expansion) Combo. The number of patients in legend reflect the number of patients reported any Venetoclax PK data at each dose cohort in the PK population.
Timepoints where all concentrations are below LLOQ are excluded from this plot.

VEN PK in the Absence (Historical) of TUS and Co-administered with TUS

Blue Symbols : 400mg VEN PK from FDA Venetoclax NDA 208573 Review Package
Red Circles : Measured VEN PK when administered with TUS



Notes: Mean venetoclax plasma concentration-time profile at steady state in the patient's reported for single agent VEN dosing in the published FDA Venetoclax NDA 208573 Review Package.
Steady state PK properties of Venetoclax from our AFTIVATE study dosed as the TUS/VEN doublet (red spheres) appear roughly the same as the PK properties of Venetoclax reported for single agent VEN dosing in the published FDA Venetoclax NDA 208573 Review Package.

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
- **42% CRc** (CR, CRp, CRh, or CRi) & **50% ORR** (CRc or PR) in FLT3^{MUT} and Ven Naïve patients

R/R AML Patient Population	TUS Single Agent (40, 80, 120, 160 mg)			
	All Comers		Ven Naive	
	CRc	ORR	CRc	ORR
All Comers	17% (11/65)	23% (15/65)	30% (9/30)	33% (10/30)
FLT3-Mutated	20% (5/25)	32% (8/25)	**42% (5/12)**	**50% (6/12)**
FLT3-Wildtype	15% (6/40)	18% (7/40)	22% (4/18)	22% (4/18)
TP53MUT/ CK	29% (2/7)	29% (2/7)	67% (2/3)	67% (2/3)
N/KRASmut	20% (2/10)	30% (3/10)	67% (2/3)	67% (2/3)
Prior VEN	6% (2/35)	14% (5/35)	0% (0/0)	0% (0/0)
Prior FLT3i	13% (2/16)	19% (3/16)	67% (2/3)	67% (2/3)

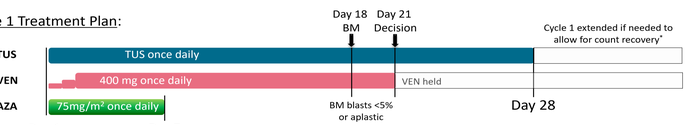
Data Cut 26 April 2024

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)	28% (18/65)
25% (1/4)	25% (1/4)	**27% (4/15)**	**40% (6/15)**
0% (0/9)	0% (0/9)	16% (8/49)	25% (12/49)
0% (0/6)	0% (0/6)	18% (3/17)	18% (3/17)
0% (0/1)	0% (0/1)	9% (1/11)	27% (3/11)
9% (1/11)	9% (1/11)	19% (9/48)	27% (13/48)
25% (1/4)	25% (1/4)	26% (5/19)	32% (6/19)

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



Significant Unmet Medical Need in Frontline Newly Diagnosed AML

- Progress made with **VEN+HMA in 1L therapy** but 1/3 do not respond and median OS <15 months with <25% alive at 3-years.
  - 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 3rd agent** is needed to boost responses with VEN+HMA standard of care therapy

TUS is 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 does **not require a change** to the TUS administered **with or without food** allowing co-administration with VEN

TUS+VEN+AZA is Being Developed 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. EHA2024 Abstract# P557

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