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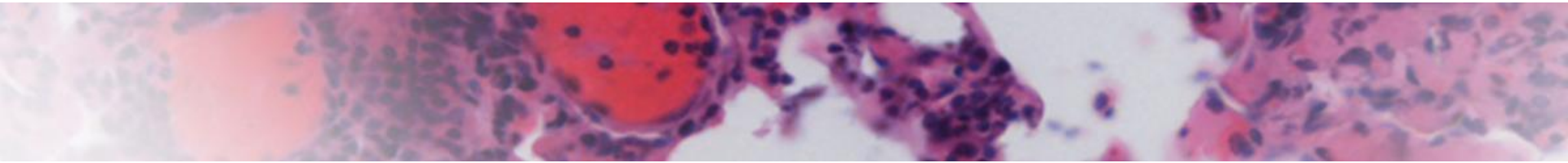

TUSCANY Study of Safety and Efficacy of Tuspetinib plus Standard of Care Venetoclax and Azacitidine in Study Participants with Newly Diagnosed AML Ineligible for Induction Chemotherapy

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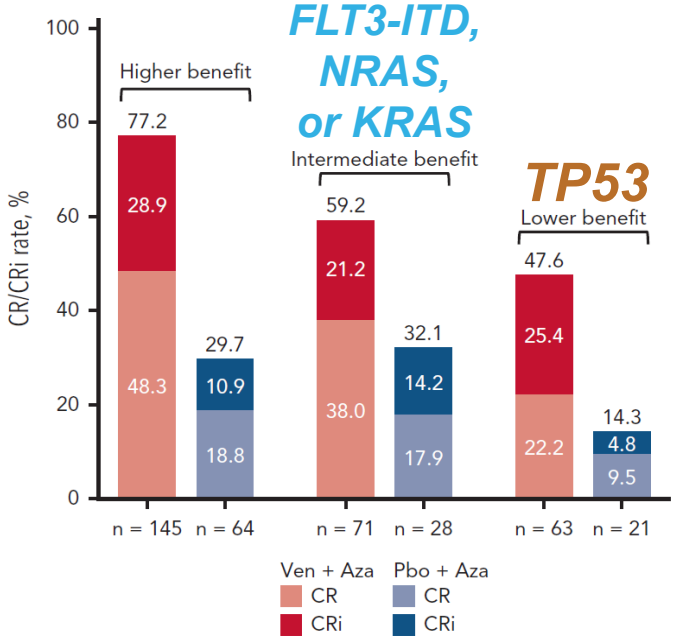
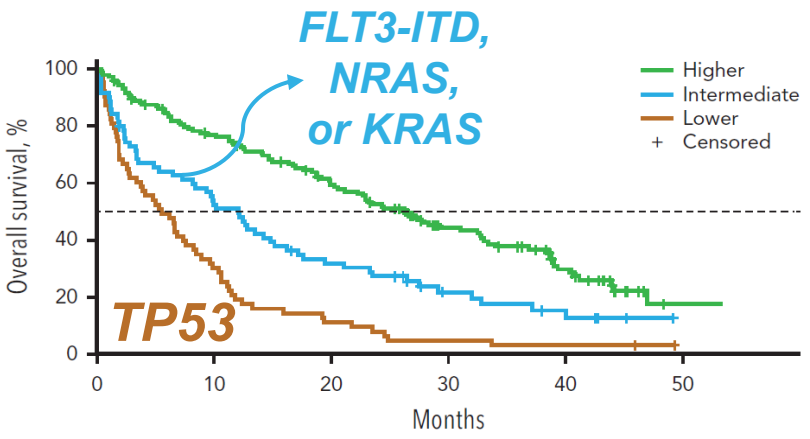
TUS : Tuspetinib ; **VEN** : Venetoclax ; **HMA** : Hypomethylating agent ; **AZA** : Azacitidine ; **CK** : Complex Karyotype ; **AML** : Acute Myeloid Leukemia ; **SOC** : Standard of Care

Unmet Medical Needs in Newly Diagnosed AML Patients Unfit for Intensive Chemotherapy in the Age of Venetoclax + HMA Therapy





Patients at Risk

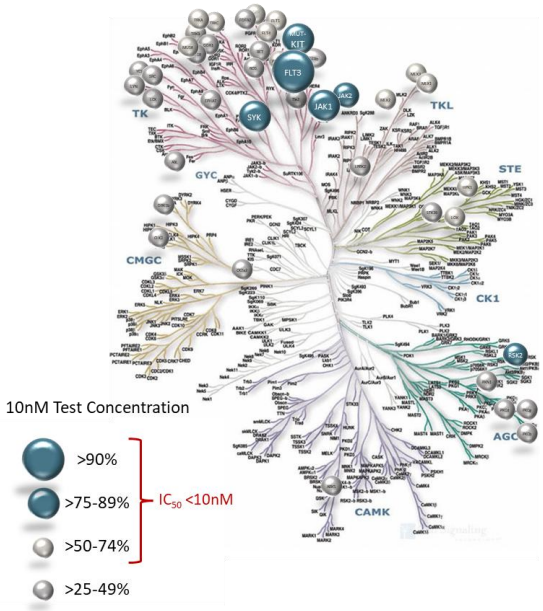
145	107	79	47	25	2
71	36	21	10	6	0
63	19	7	3	2	0

Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher benefit	145	96	26.5 (20.2, 32.7)
Intermediate benefit	71	57	12.1 (7.3, 15.2)
Lower benefit	63	61	5.5 (2.8, 7.6)

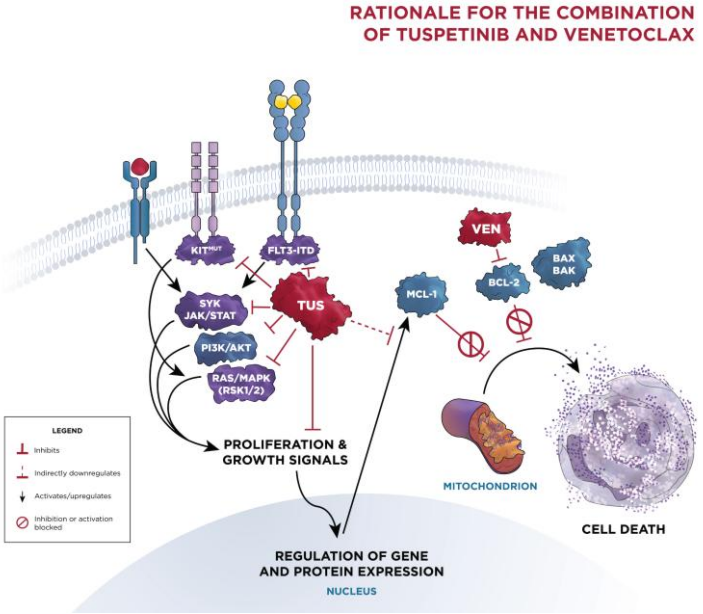
TP53

Döhner et al. *Blood*. 2024 Nov 21;144(21):2211-2222.

Tuspetinib (TUS) Targets AML Oncogenic Signaling and Venetoclax Resistance Mechanisms



Assay	Kinase	Mutation Status	Activity
K_D Binding Affinity (nM)	FLT3	WT	0.58
		ITD	0.37
		D835Y	0.29
		D835H	0.4
		ITD/D835V	0.48
		ITD/F691L	1.3
IC_{50} Inhibition of Kinase Enzyme Activity (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
	TAK1-TAB1	TAK1-TAB1	7.0



Sonowal et al. *Cancer Res Commun*. 2025 Jan 1;5(1):74-83.

Tuspetinib Single Agent Phase 1/2 Study in R/R AML

Dose Escalation + Exploration + Expansion (93 subjects treated)	Total n	VEN-Naïve n	Prior-VEN n
Cohort 1: 20 mg QD	2	1	1
Cohort 2: 40 mg QD	17	8	9
Cohort 3: 80 mg QD	22	16	6
Cohort 4: 120 mg QD	32	5	27
Cohort 5: 160 mg QD	16	8	8
Cohort 6: 200 mg QD	4	1	3

71% Prior-VEN

Data filtered through 26APR2025

Safety Profile of Tuspetinib R/R AML

- CRs with 40, 80, 120, 160 mg and no DLTs
- No QT_c prolongation, differentiation syndrome, muscle damage, or non-hematologic SAEs related to TUS
- No treatment related adverse events leading to death

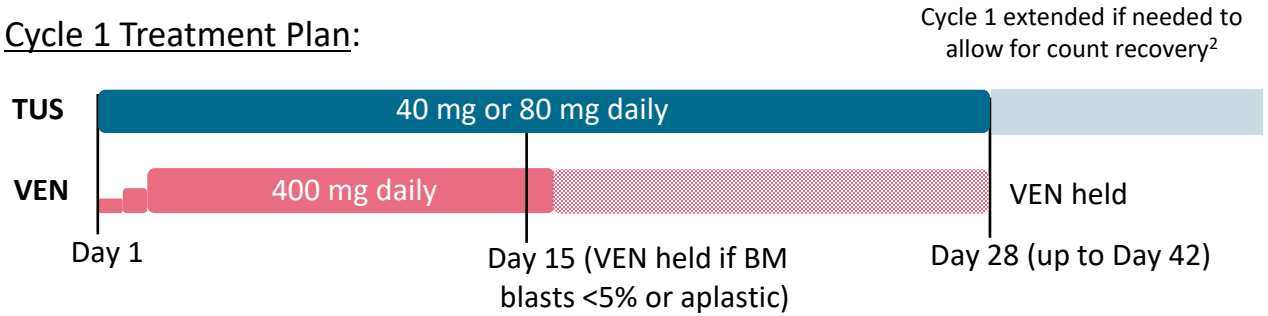
Composite Complete Remission (CRc) in 80-160 mg Patients[1]

FLT3 Status	ALL	VEN-Naïve	VEN-Prior	FLT3i-Prior
ALL	11.4% (8/70)	24.1% (7/29)	0% (1/41)	NA
$FLT3^{WT}$	9.8% (4/41)	18.8% (3/16)	4% (1/25)	NA
$FLT3^{MUT}$	13.8% (4/29)	30.8% (4/13)	0% (0/16)	7% (1/14)

[1]All patients treated at active dose levels 80 mg, 120 mg, 160 mg

80mg selected as R2PD for VEN-naïve R/R AML

Tuspetinib + Venetoclax in R/R AML (APTIVATE Study)



Safety Profile of Tuspetinib in Evaluable Patients

- **79 R/R AML subjects, 65 treated at 80 mg**
- 75% with Prior-VEN exposure
- No QT_c prolongation, differentiation syndrome, muscle damage, or treatment related deaths
- No apparent DDI between TUS and VEN
- **Low rate of febrile neutropenia (26.6%)**

Composite Complete Remission (CRc) in Evaluable Patients[1]

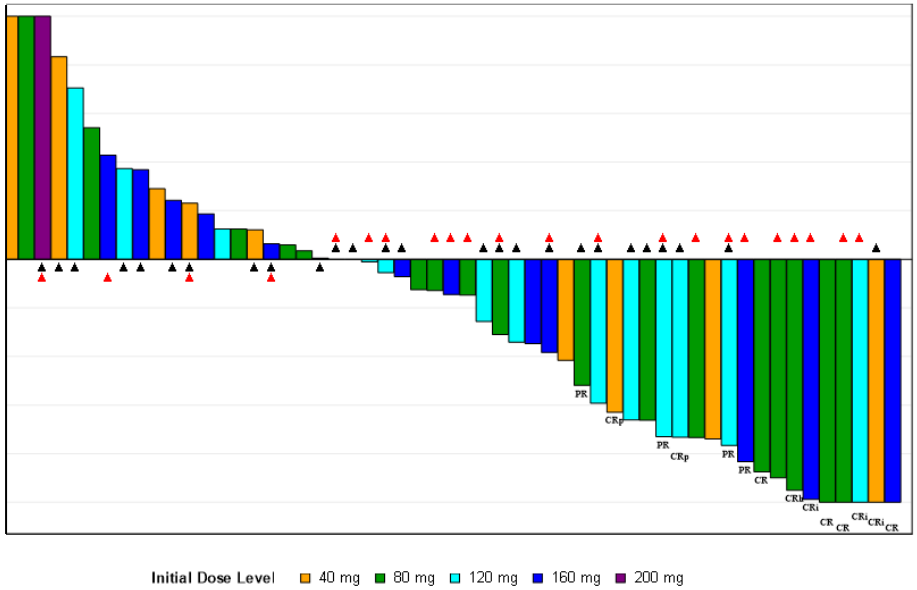
FLT3 Status	ALL	VEN-Naïve	VEN-Prior	FLT3i-Prior
ALL	18.5% (12/65)	17.6% (3/17)	18.8% (9/48)	NA
$FLT3^{WT}$	16.3% (8/49)	14.3% (2/14)	17.1% (6/35)	NA
$FLT3^{MUT}$	26.7% (4/15)	33.3% (1/3)	25% (3/12)	30.8% (4/13)

[1]All patients at the 80 mg active dose level

Data filtered through 26APR2025

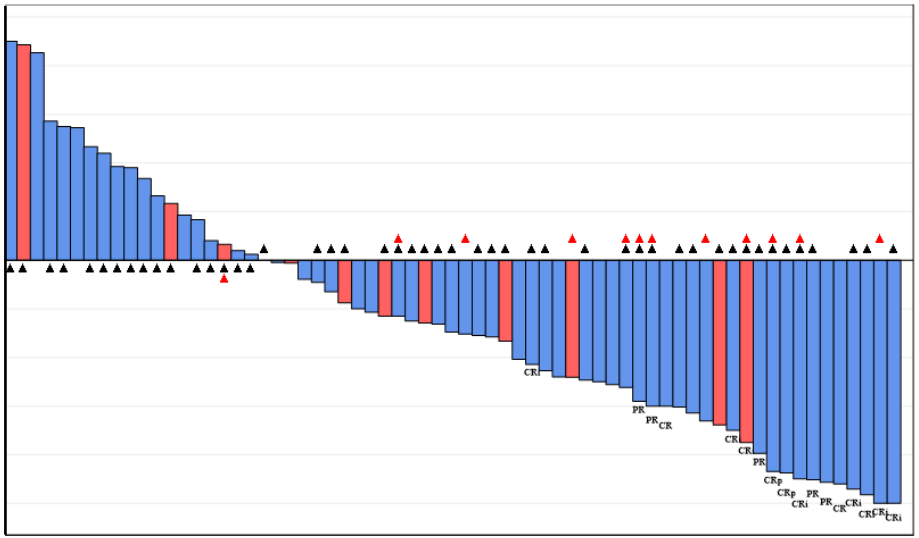
TUS and TUS+VEN Bone Marrow Blast Reductions in R/R AML

Bone Marrow Blast – Percent Change from baseline
Tuspetinib Single Agent



Initial Dose Level 40 mg 80 mg 120 mg 160 mg 200 mg

Bone Marrow Blast – Percent Change from baseline
Tuspetinib with Venetoclax



Initial Dose Leve 40mg/400mg 80mg/400mg

Data filtered through 26APR2025

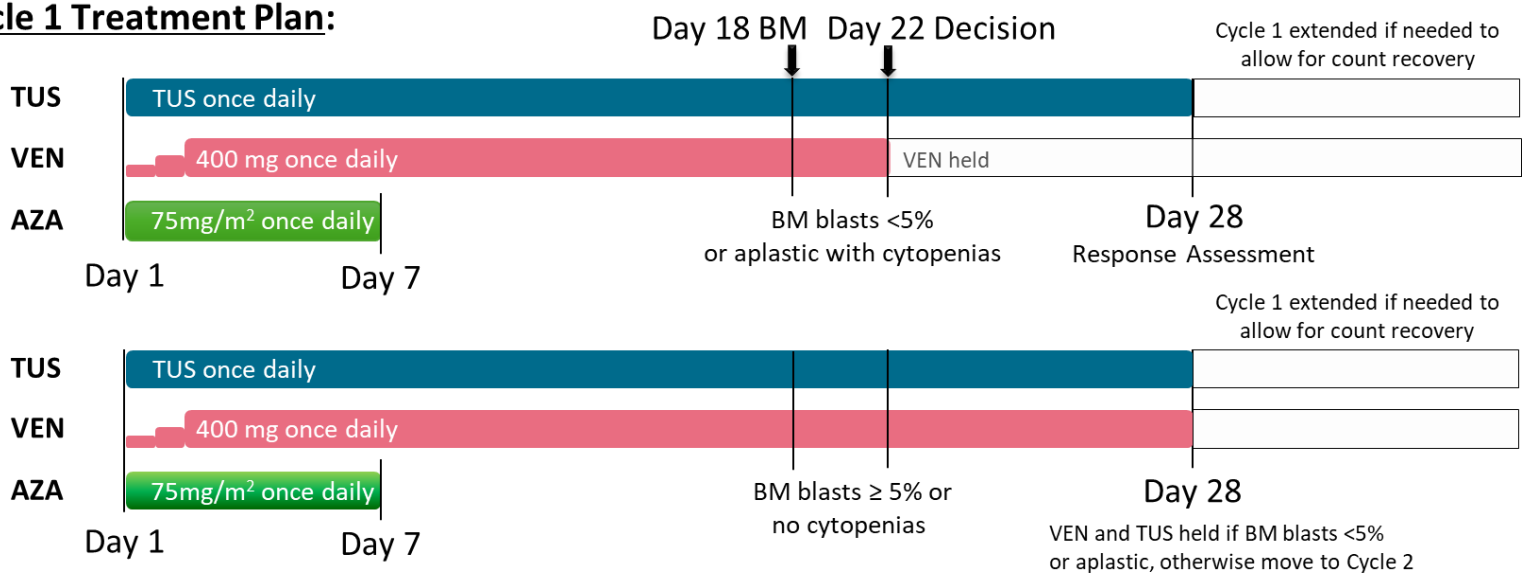
▲ Prior-FLT3i ▲ Prior-VEN

TUS/VEN/AZA Phase 1/2 Study (TUSCANY Trial – Ongoing) in Newly Diagnosed AML

Tuspetinib (40/80/120 mg) + Venetoclax (400 mg) + Azacitidine (75 mg/m²)

Newly Diagnosed AML Ineligible for Intensive Chemotherapy

Cycle 1 Treatment Plan:



TUSCANY: TUS/VEN/AZA Eligibility Criteria and Baseline Patient Characteristics

Key Eligibility Criteria

- Newly diagnosed 1^{o} or 2^{o} AML
- No prior HMA or VEN treatment
- Age 75 or over, *or*
- Age <75 and 1 or more co-morbidity that would preclude the use of intensive chemotherapy
- No APML or *BCR-ABL1*

Similar to VIALE-A eligibility criteria

Baseline Patient Characteristics	
Measure	**N = 10 Patients**
Age, yrs (range)	75.5 (69-81)
Female, n (%)	6 (60%)
White, n (%)	7 (70%)
Hispanic or Latino	3 (30%)
Mean BMI (kg/m2), Mean Weight (Kg)	31.5, 85.4
ECOG 0, n (%)	3 (30%)
ECOG 1, n (%)	3 (30%)
ECOG 2, n (%)	4 (40%)
Mean Baseline BM Blasts, %	44.3
FLT3-ITD, n (%)	2 (20%)
TP53 mutated or CK, n (%)	3 (30%)
Median Duration of Study (months)	2.7
Median Treatment Duration (months)	2.5

TUS/VEN/AZA Phase 1/2 Study (TUSCANY Trial - Ongoing) in Newly Diagnosed AML

Dose Escalation Phase

B-Dose Levels available with planned 21 days of tuspetinib

Dose Level A2
TUS: **120 mg** 28 days
VEN: 400 mg 21-28 days
AZA: 75 mg/m^2 7 days

3 Subjects - 3 ongoing
- 77 yo M with *ASXL1* mutation
- 70 yo M with CK + *RUNX1*, *SRSF2*, *TET2 muts*
- 79 yo F with *KIT* and two *NRAS* mutations

Dose Level A1
TUS: **80 mg** 28 days
VEN: 400 mg 21-28 days
AZA: 75 mg/m^2 7 days

3 Subjects - 3 ongoing
- 81 yo F with *ASXL1* and two *DDX41* mutations
- 78 yo F with *TP53* mutation and CK
- 69 yo F with *FLT3-ITD*, *NPM1*, *TET2* mutations

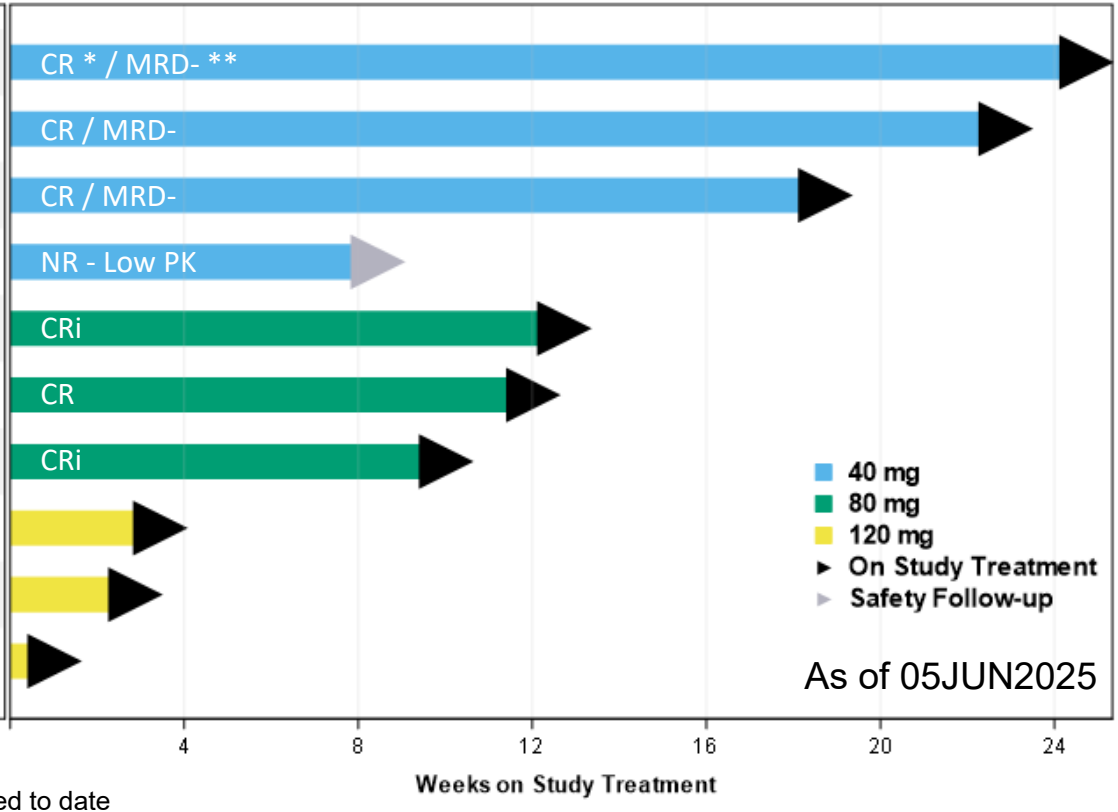
Dose Level A0
TUS: **40 mg** 28 days
VEN: 400 mg 21-28 days
AZA: 75 mg/m^2 7 days

4 Subjects - 3 ongoing
- 80 yo F with *TP53* mutation and CK
- 69 yo F with *FLT3*-ITD and *NPM1* mutations
- 74 yo M with *IDH2, STAG2, ASXL1, SRSF2* mutations → HSCT planned
- 78 yo M with *IDH2, RUNX1, BCOR, SRSF2* mutations - *discontinued*

As of 05JUN2025

TUS/VEN/AZA: Duration and Clinical Responses in Newly Diagnosed AML

Dose (mg)	FLT3 Status	Other Mutations	Sex/ Age
40/400/75	WT	IDH2/ASXL1/SRSF2/STAG2	M/74
40/400/75	WT	TP53/CK	F/80
40/400/75	ITD	NPM1	F/69
40/400/75	WT	IDH2/RUNX1/BCOR/SRSF2	M/78
80/400/75	WT	TP53/CREBBP/LAG3/CK	F/78
80/400/75	WT	ASXL1/DDX41/CBFA2T3/IL2RB	F/81
80/400/75	ITD	NPM1/TET2	F/69
120/400/75	WT	ASXL1	M/77
120/400/75	WT	CK	M/70
120/400/75	WT	NRAS/KIT	F/79



* Response indicates Best Overall Response achieved to date

** MRD Flow Cytometry results are either from the Central Lab assay or Local Site assay

Abbreviations: CR-complete remission; CRi-CR with incomplete hematologic recovery; NR-no response; PK-pharmacokinetic exposure to TUS

TUS/VEN/AZA: Safety Data

All TEAEs (n=136)	n (%)
Any	**7 (100%)**
Most Frequent TEAEs (>15% of subjects)	
Constipation	5 (71.4%)
Platelet count decreased	5 (71.4%)
Anemia	4 (57.1%)
White blood cell count decreased	4 (57.1%)
Blood alkaline phosphatase increased	3 (42.9%)
Blood creatinine increased	3 (42.9%)
Diarrhea	3 (42.9%)
Hypokalemia	3 (42.9%)
Neutropenia	3 (42.9%)
Blood bilirubin increased	2 (28.6%)
Fatigue	2 (28.6%)
Nausea	2 (28.6%)
Hypophosphatemia	2 (28.6%)
Neutrophil count decreased	2 (28.6%)
Pruritus	2 (28.6%)
Vomiting	2 (28.6%)
Decreased appetite	2 (28.6%)
Grade ≥ 3	**7 (100.0%)**
SAEs	**3 (42.9%)**
Leading to treatment termination	**0 (0%)**
Leading to death	**0 (0%)**

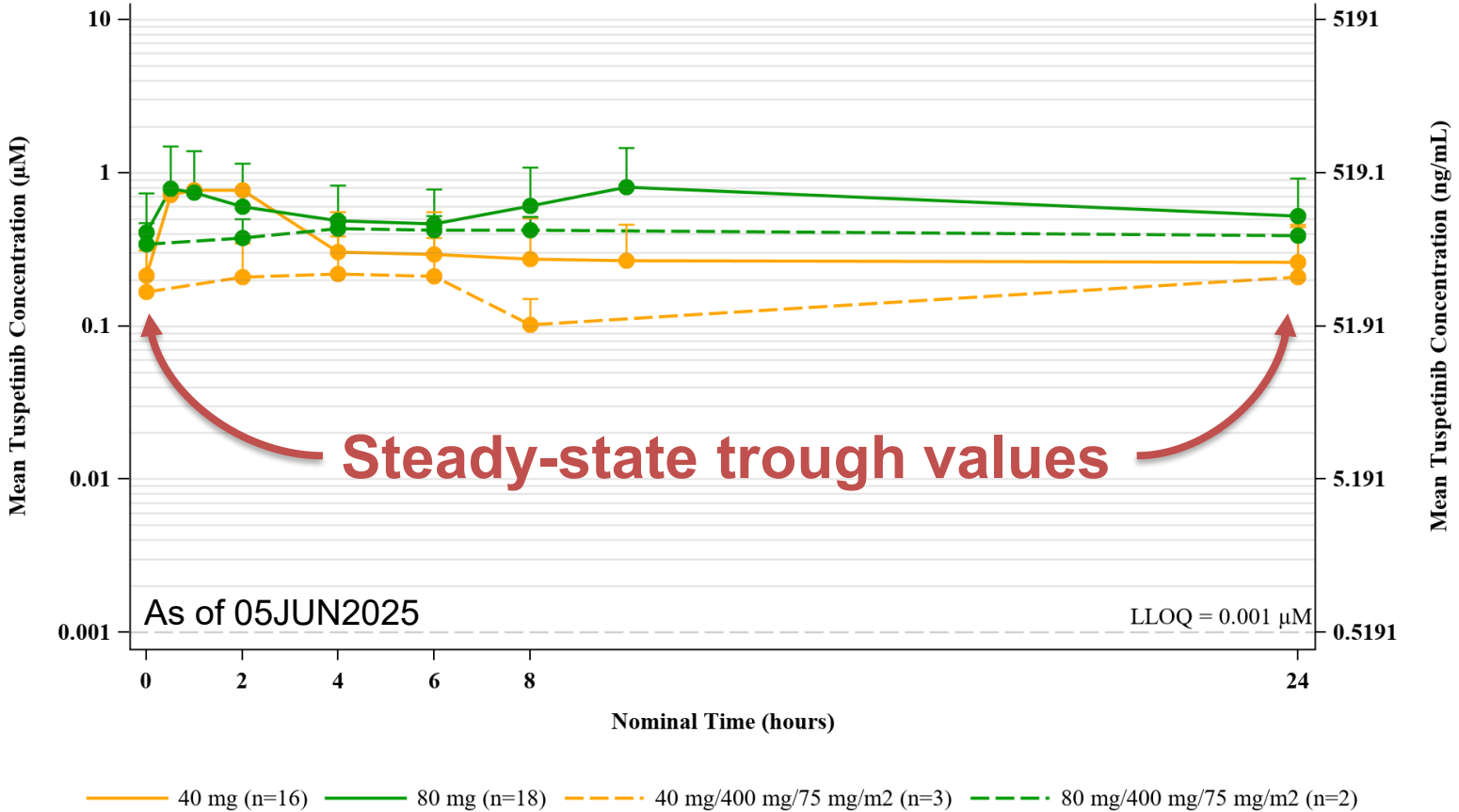
Treatment Related AEs Evaluable Patients (n=7)	TUS	VEN	AZA
Any	**5 (71.4%)**	**7 (100%)**	**7 (100%)**
Most Frequent Related Non-Heme TEAEs (>15% of subjects)			
Diarrhoea	2 (14.3%)	2 (28.6 %)	1 (14.3%)
Grade ≥ 3 (n≥ 2 subjects)			
Platelet count decreased	4 (57.1%)	4 (57.1%)	4 (57.1%)
Anemia	4 (57.1%)	4 (57.1%)	4 (57.1%)
White blood cell count decreased	1 (14.3%)	4 (57.1%)	4 (57.1%)
Neutropenia	3 (42.9%)	3 (42.9%)	3 (42.9%)
Neutrophil count decreased	1 (14.3%)	2 (28.6%)	2 (28.6%)
SAEs			
Leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dose Limiting Toxicity (DLT)	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**

- No treatment related QT_c prolongation, CPK elevations, differentiation syndrome, or non-hematologic SAEs
- No prolonged myelosuppression in Cycle 1 in the absence of AML
- No treatment related deaths or discontinuations

Data filtered through 26APR2025

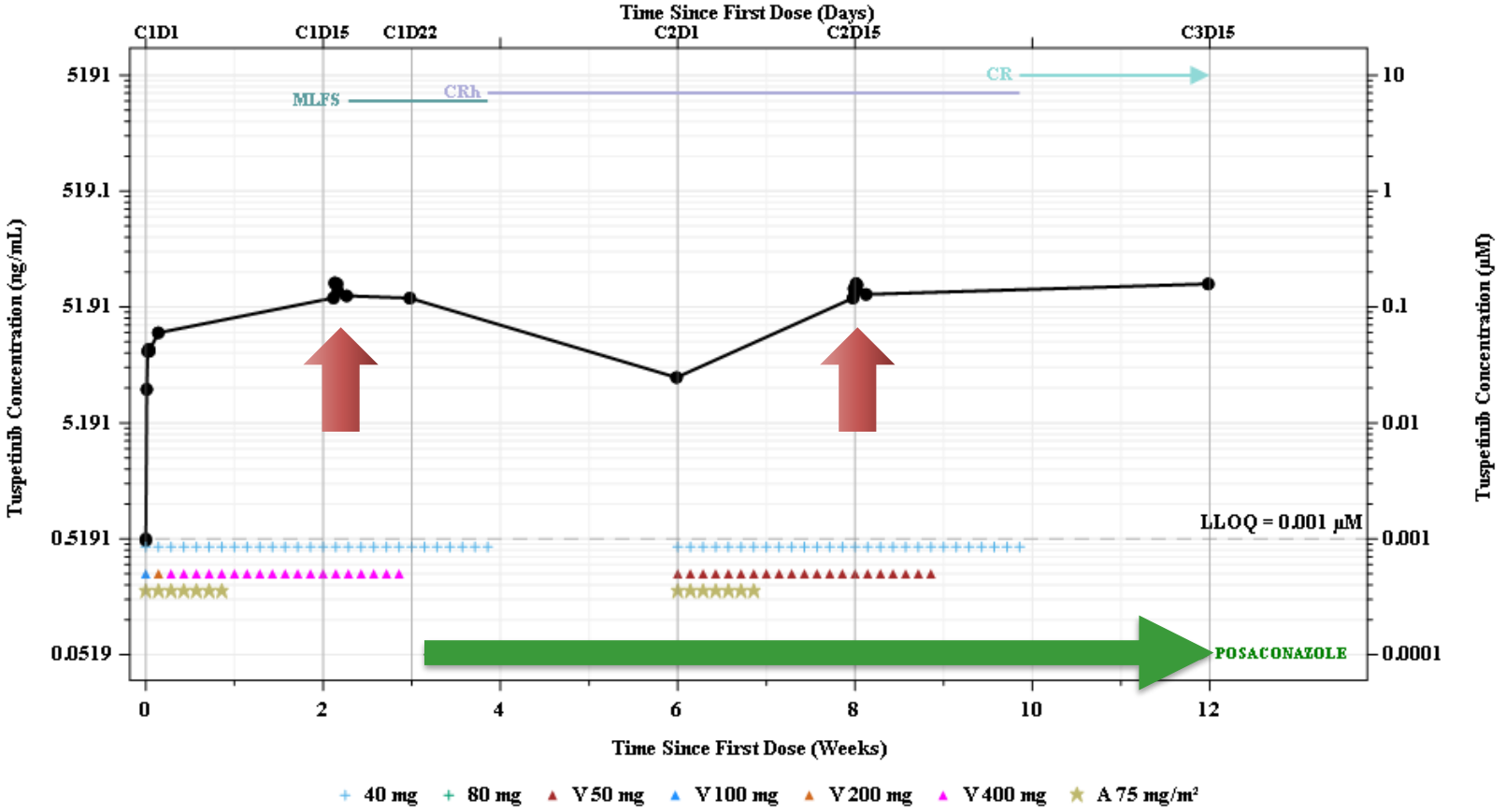
TUS PK in TUS/VEN/AZA: Relative to TUS Single Agent

No significant effect on TUS PK in combination with VEN and AZA



TUS PK in TUS/VEN/AZA: Before and After Posaconazole Use

No significant effect on TUS PK in combination with VEN and AZA and antifungals



TUS/VEN/AZA: Response Rates by Dose Level

(40-80 mg/400 mg/ 75 mg/m², n=7 as of 26APR2025)

Response Rates by Dose and Mutation Groups			
Mutation Group	**TUS 40 mg/ 400 mg/75 mg/m²**	**TUS 80 mg/ 400 mg/75 mg/m²**	**Total**
ORR (MLFS + CRi + CRh + CR)			
Overall	3/4 (75.0%)	3/3 (100%)	6/7 (85.7%)
FLT3-Mut	1/1 (100%)	1/1 (100%)	2/2 (100%)
NPM1-Mut	1/1 (100%)	1/1 (100%)	2/2 (100%)
FLT3-WT	2/3 (66.7%)	2/2 (100%)	4/5 (80.0%)
TP53-Mut/CK	1/1 (100%)	1/1 (100%)	2/2 (100%)
CRc (CRi + CRh + CR)			
Overall	3/4 (75.0%)	3/3 (100%)	**6/7 (85.7%)**
FLT3-Mut	1/1 (100%)	1/1 (100%)	2/2 (100%)
FLT3-WT	2/3 (66.7%)	2/2 (100%)	4/5 (80.0%)
CR/CRh			
Overall	2/4 (50.0%)	1/3 (33.3%)	3/7 (42.9%)
FLT3-Mut	0/1 (0%)	0/1 (0%)	0/2 (0%)
FLT3-WT	2/3 (66.7%)	1/2 (50.0%)	3/5 (60.0%)

Preliminary Efficacy Data:

- Overall CRc Rate is 85.7%
- 6 of 7 patients remain on study
- Responses continue to evolve

At the 40 mg dose level:

- Three subjects were MRD-negative including:
  - Subject with *FLT3*-ITD
  - Subject with *FLT3*-WT
  - Subject with *TP53*/CK
- Subject with *TP53* mutation + CK cleared *TP53* mutations by NGS

CONCLUSIONS

TUS/VEN/AZA is being developed as well tolerated and mutation agnostic 1L therapy for newly diagnosed AML

TUS Single Agent

- Convenient once daily oral tablet administered with or without food
- Responses achieved in **FLT3^{WT}**, **FLT3^{MUT}** with prior FLT3i exposure, **TP53^{MUT}**, and **RAS^{MUT}** AML
- Responses achieved with no DLTs at 40, 80, 120 and 160mg once daily – Single agent RP2D = 80 mg QD
- Well tolerated and more active in VEN-naïve R/R AML

TUS/VEN Doublet

- Well tolerated and active in broad populations of R/R AML
- TUS has no apparent drug-drug interactions with VEN or CYP3A4 inhibitors (e.g., azole antifungals)

TUS/VEN/AZA Frontline Triplet

- Well tolerated and active in newly diagnosed AML patients who are ineligible for intensive chemotherapy and regardless of mutation status
- TUS can be administered with standard-of-care dosing VEN/AZA without prolonged myelosuppression or undue toxicity
- MRD-negative responses achieved across diverse patient populations – including adverse *TP53* mutations and CK

Acknowledgements

We are grateful to the clinical trial teams, investigators, staff, and most of all, to the patients and their families for their participation in this study, and for their dedication to improving the lives of patients with AML

This study was sponsored by Aptose Biosciences.
https://www.aptose.com/clinical-trials/tuspetinib