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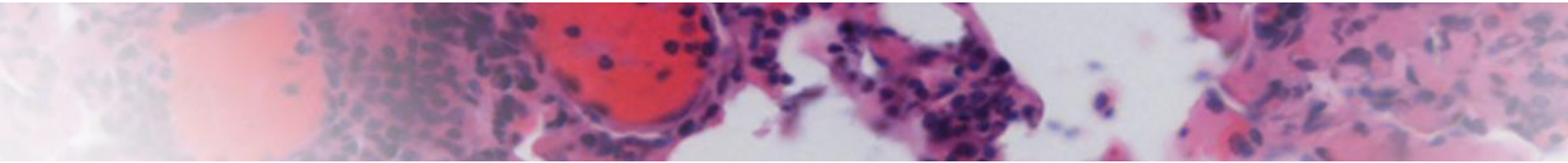

TUSCANY Study of Safety and Efficacy of Tuspetinib plus Standard of Care Venetoclax and Azacitidine in Study Participants with Newly Diagnosed AML Ineligible for Induction Chemotherapy

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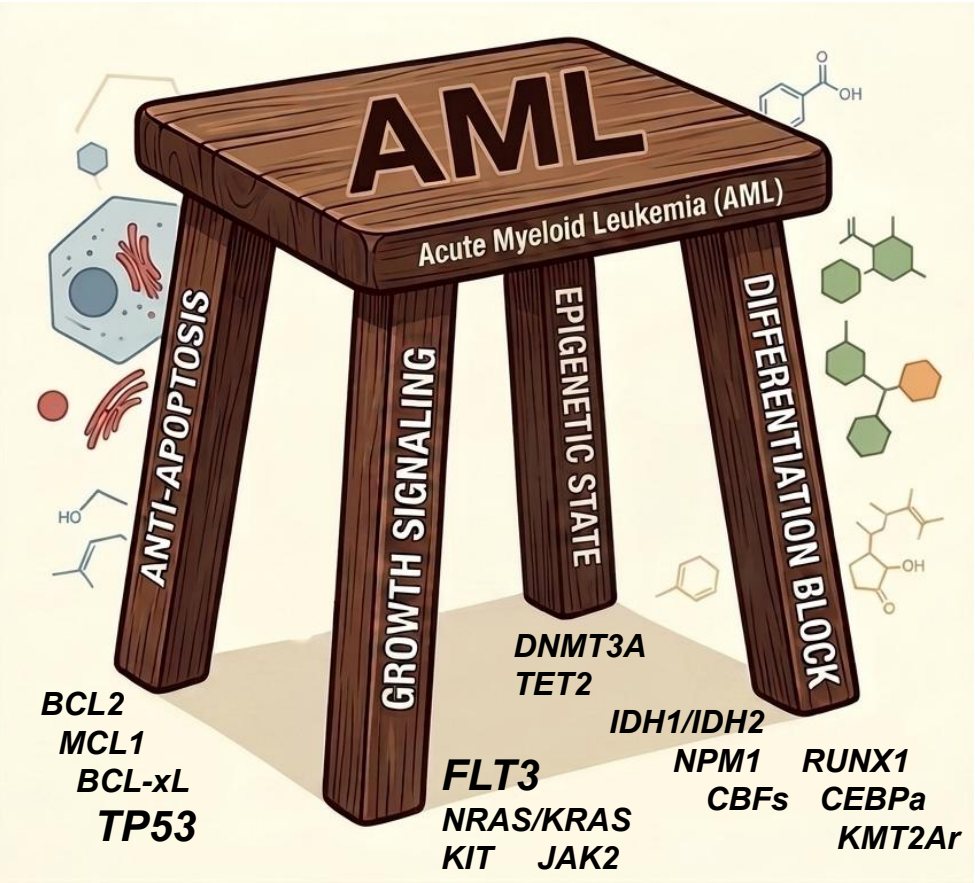
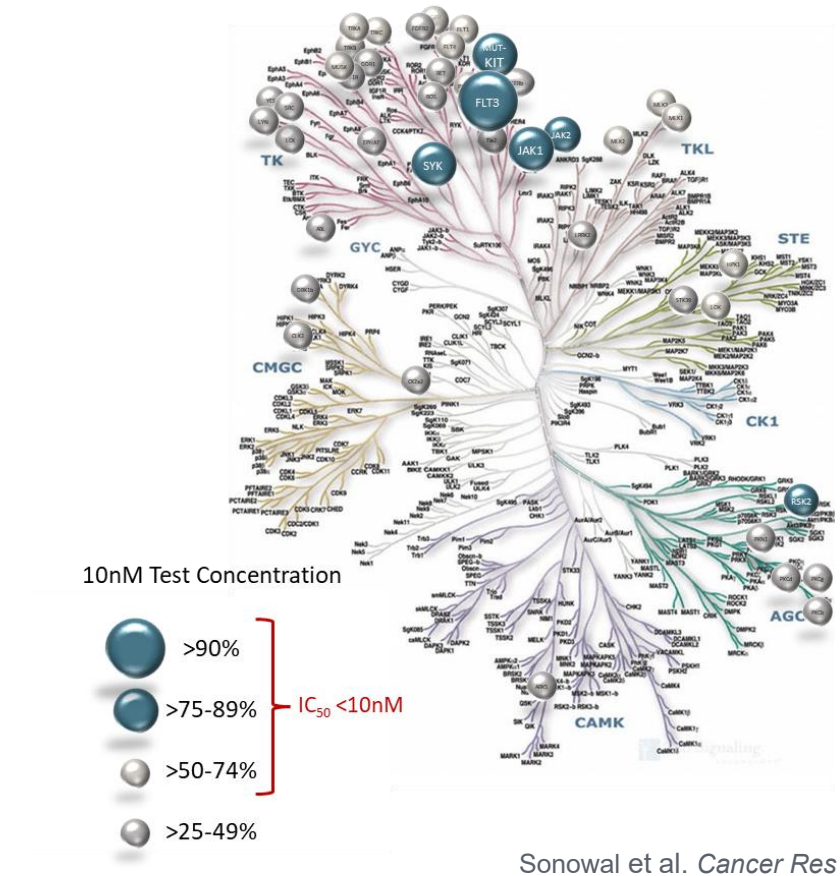
TUS : Tuspetinib ; **VEN** : Venetoclax ; **HMA** : Hypomethylating agent ; **AZA** : Azacitidine ; **CK** : Complex Karyotype ; **AML** : Acute Myeloid Leukemia ; **SOC** : Standard of Care

Combination Therapy in Newly Diagnosed AML – Adding to Venetoclax + HMA Therapy



- Leukemic cells rely on multiple pathways to survive and proliferate
- Targeting multiple pathways can produce greater treatment efficacy
- Most combination therapies have focused on growth factor signaling pathways only when targetable mutations like *FLT3*-ITD are present
- However, all acute leukemias up regulate multiple growth factor signaling pathways even when marker mutations are absent
- ***Safe and effective inhibitors of multiple growth factor signaling pathways that are amenable to combination therapy could improve AML outcomes in a mutation agnostic manner.***

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



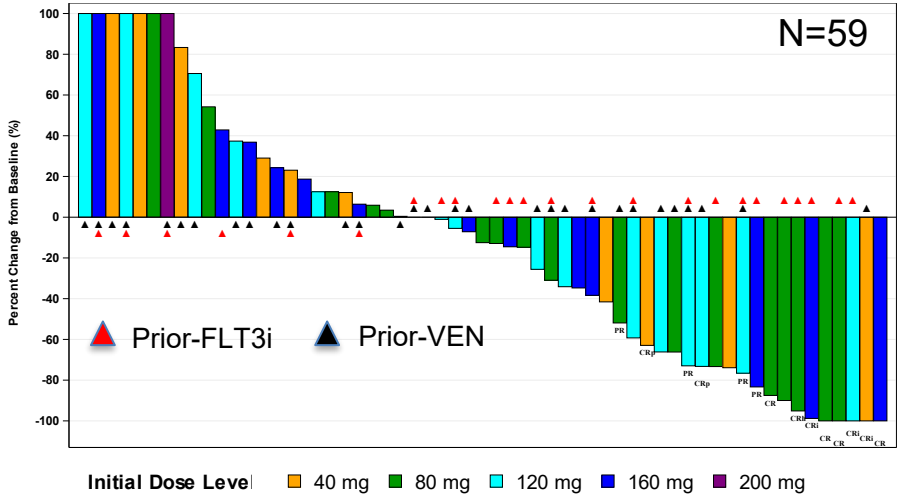
Assay	Kinase	Mutation Status	Activity
K_D Binding Affinity (nM)	FLT3	WT	0.58
		ITD	0.37
		D835Y	0.29
		D835H	0.4
		ITD/D835V	0.48
		ITD/F691L	1.3
IC_{50} Inhibition of Kinase Enzyme Activity (nM)	FLT3	WT	1.1
		ITD	1.8
		D835Y	1.0
	SYK	WT	2.9
	JAK	JAK-1	2.8
		JAK-2	6.3
		JAK-2 (V617F)	9.9
	c-KIT	WT	> 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.

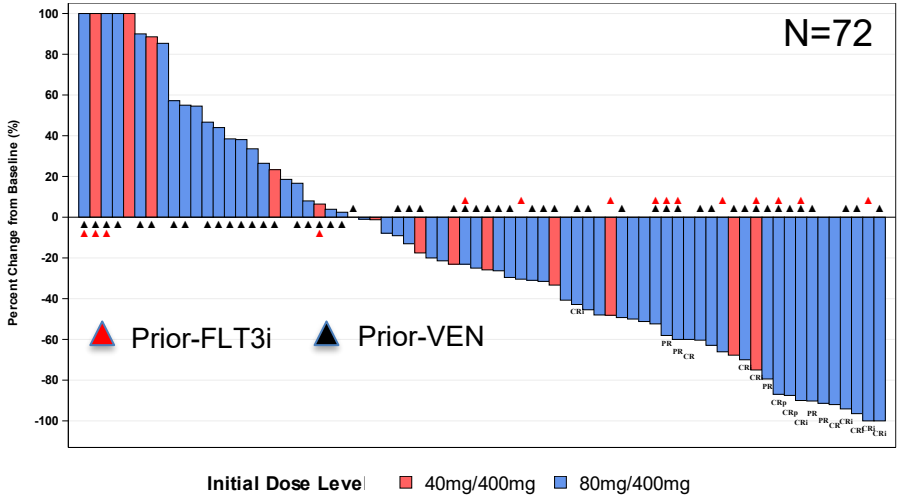
TUS and TUS+VEN Bone Marrow Blast Reductions in R/R AML

(Completed Study Arms)

Bone Marrow Blast – Percent Change from baseline
Tuspetinib Single Agent



Bone Marrow Blast – Percent Change from baseline
Tuspetinib + Venetoclax



Tuspetinib monotherapy CRc rate at target dose levels (80-160 mg) in VEN-naïve R/R AML: **28.0% (7/25)**

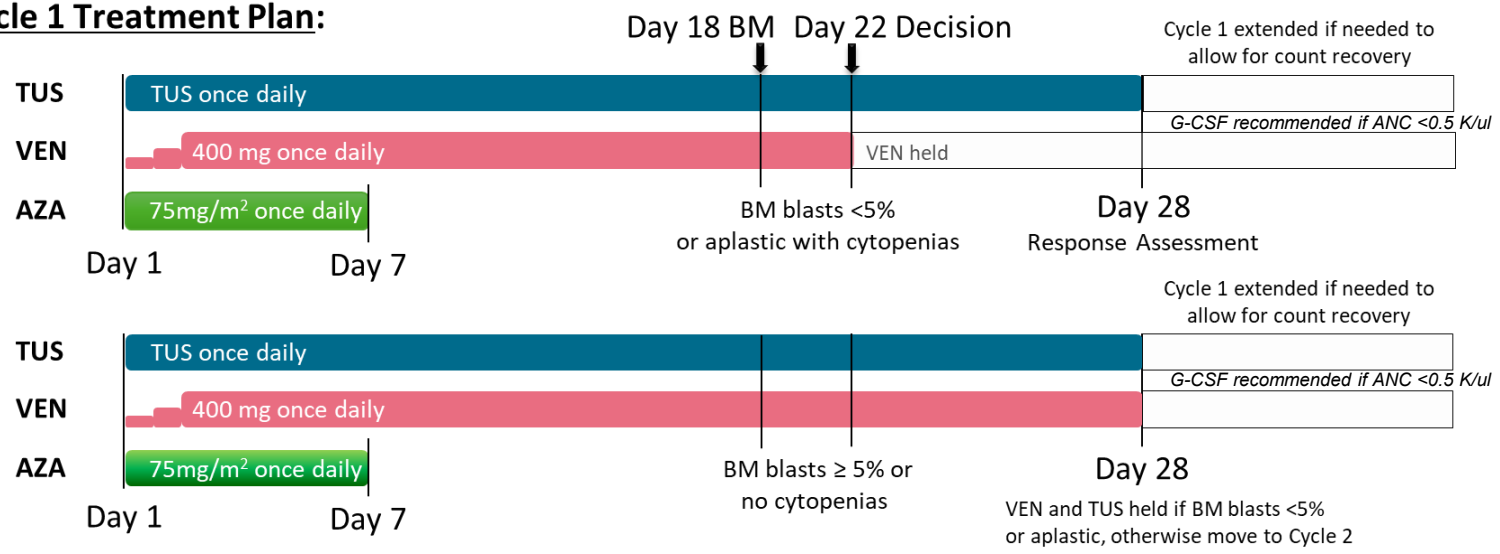
Tuspetinib + venetoclax CRc rate at 80 mg TUS in evaluable R/R AML: **25.0% (9/36)**

TUS+VEN improves responses in VEN-prior AML subjects

TUS/VEN/AZA Phase 1/2 Study (TUSCANY Trial – Ongoing) for Newly Diagnosed AML Ineligible for Intensive Chemotherapy

Tuspetinib (40/80/120/160 mg) + Venetoclax (400 mg) + Azacitidine (75 mg/m^2)

Cycle 1 Treatment Plan:



Subjects in remission can resume tuspetinib as monotherapy 30-90 days after HSCT

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

Key Eligibility Criteria

- Newly diagnosed 1° or 2° 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*

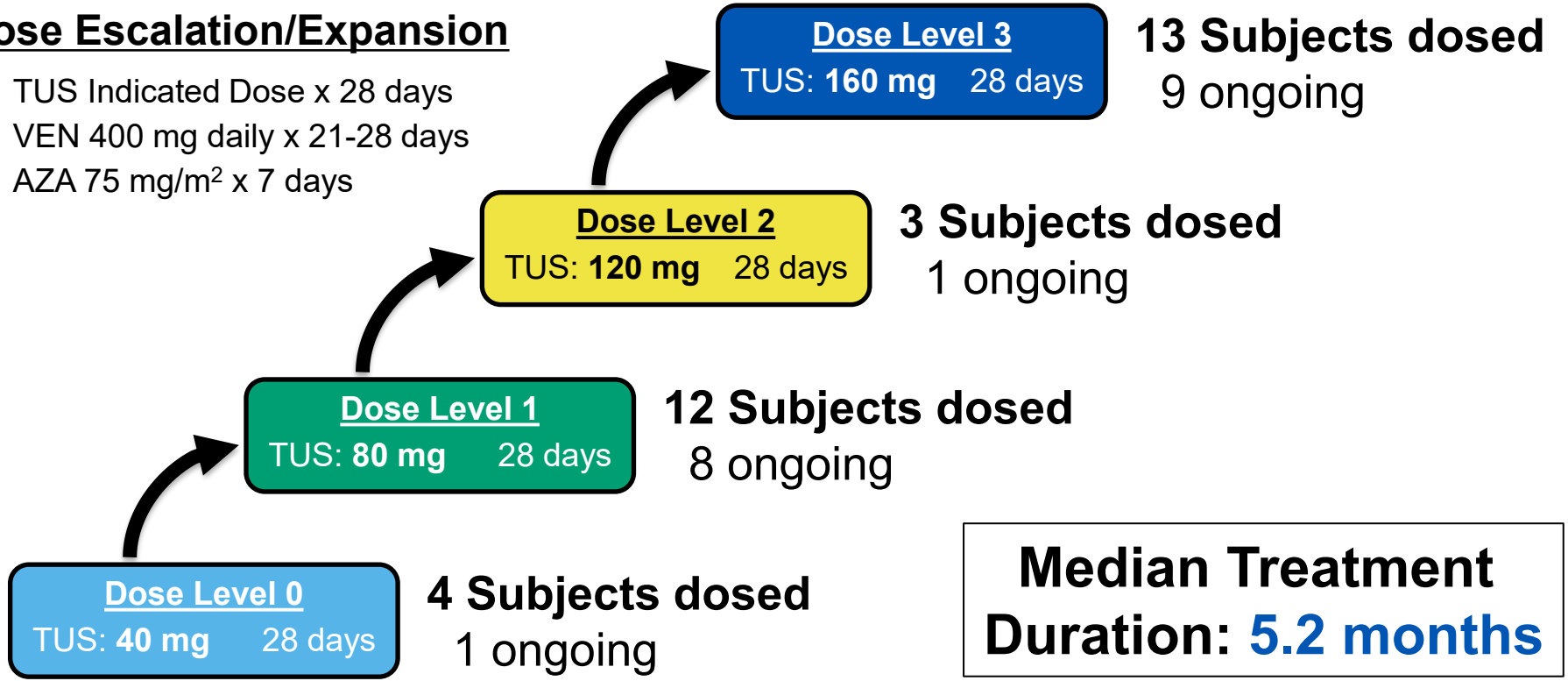
Similar to VIALE-A eligibility criteria

Baseline Patient Characteristics	
Measure	**N = 32 Patients**
Age, mean yrs (range)	75.7 (63-82)
Female, n (%)	17 (53.1%)
White, n (%)	25 (78.1%)
Hispanic or Latino, n (%)	4 (12.5%)
ECOG ≥ 2, n (%)	8 (25.0%)
Mean Baseline BM Blasts, %	50.2%
FLT3-ITD, TKD, or other mut, n (%)	9 (28.1%)
TP53 mutated or CK, n (%)	10 (31.3%)
NPM1 mutated, n (%)	5 (15.6%)
NRAS or *KRAS* mutated, n (%)	2 (6.3%)
AML with MR mutations, n (%)	18 (56.3%)

TUS/VEN/AZA Phase 1/2 Study (TUSCANY Trial) Dose Levels

Dose Escalation/Expansion

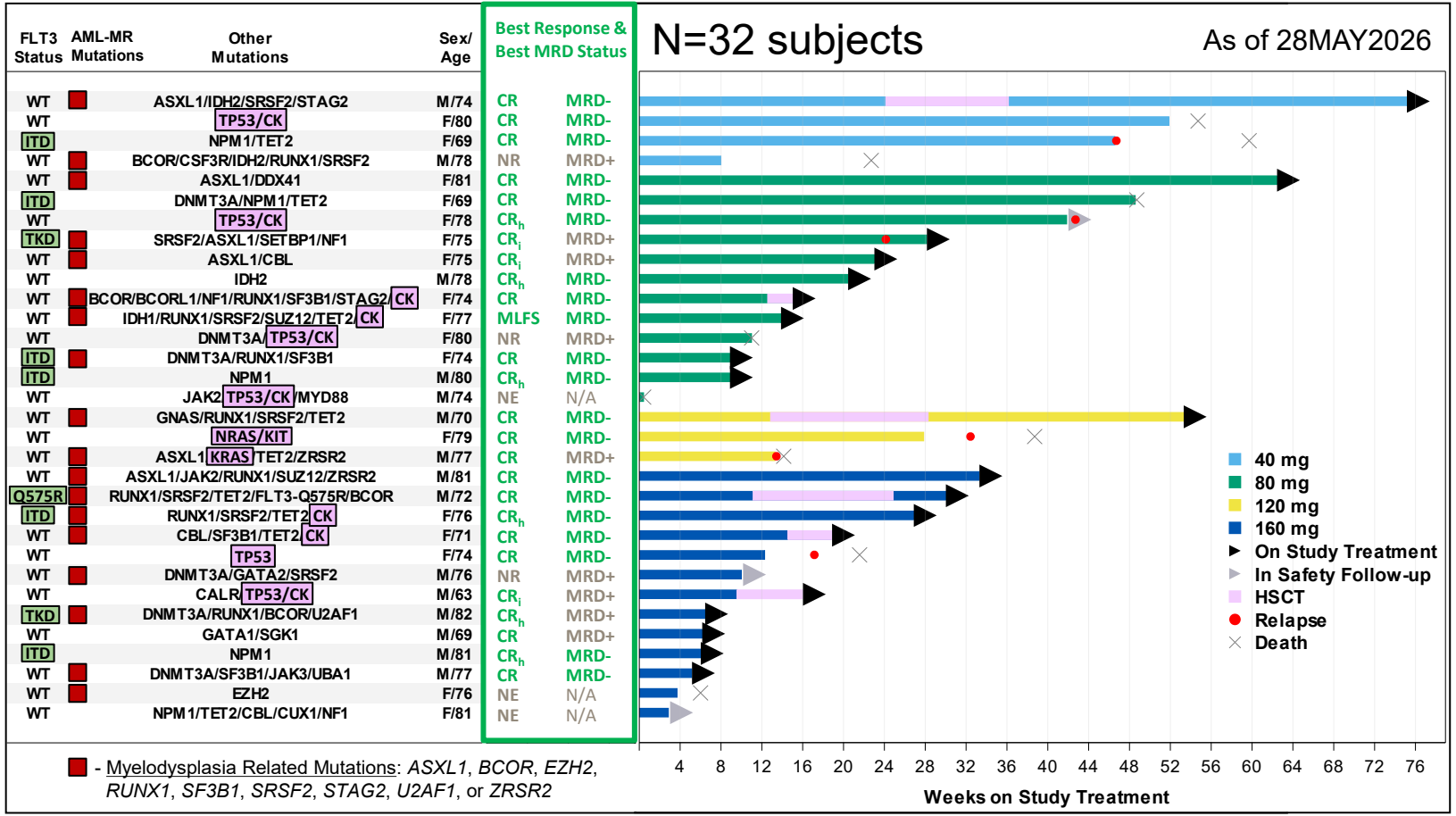
- TUS Indicated Dose x 28 days
- VEN 400 mg daily x 21-28 days
- AZA 75 mg/m^2 x 7 days



Median Treatment Duration: 5.2 months

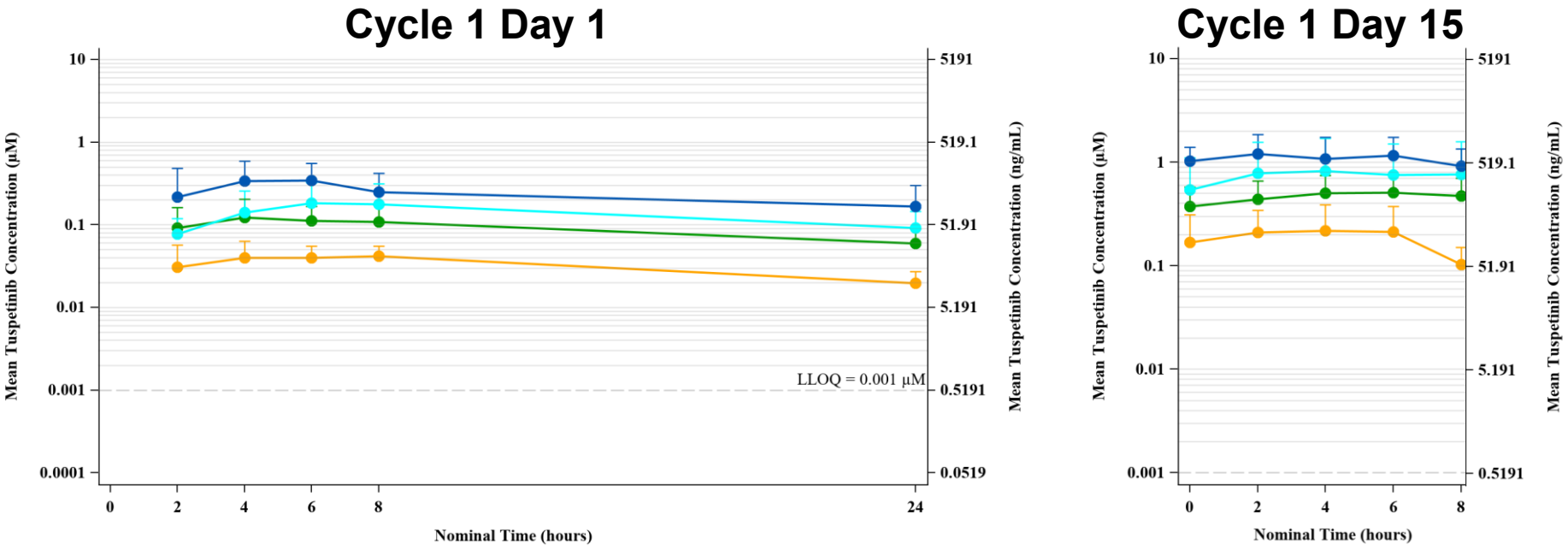
As of 28MAY2026

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



TUS PK in TUS/VEN/AZA Triplet

Dose proportional exposure from 40-160 mg once daily



TUS/VEN/AZA: Safety Data

Data filtered through 26-APR 2026

All TEAEs (n=982)	n (%)
Any	**30 (93.8%)**
Most Frequent TEAEs (> 15% of Subjects)	
Platelet count decreased	21 (65.6%)
White blood cell count decreased	19 (59.4%)
Anemia	18 (56.3%)
Neutrophil count decreased	17 (53.1%)
Diarrhea	15 (43.8%)
Nausea	12 (37.5%)
Constipation	12 (37.5%)
Vomiting	9 (28.1%)
Hypophosphatemia	9 (28.1%)
Hypokalemia	9 (28.1%)
Hyponatremia	8 (25.0%)
Aspartate aminotransferase increased	8 (25.0%)
Hypocalcaemia	8 (25.0%)
Febrile neutropenia	7 (21.9%)
Alanine aminotransferase increased	6 (18.8%)
Blood creatinine increased	6 (18.8%)
Decreased appetite	6 (18.8%)
Blood alkaline phosphatase increased	5 (15.6%)
Lymphocyte count decreased	5 (15.6%)
Back pain	5 (15.6%)
Muscular Weakness	5 (15.6%)
Pain in extremity	5 (15.6%)
Oedema Peripheral	5 (15.6%)
Pruritus	5 (15.6%)
Dizziness	5 (15.6%)
Fall	5 (15.6%)
Grade ≥ 3	**29 (90.6%)**
SAEs	**19 (59.4%)**
Leading to treatment termination	1 (3.1%)
Leading to death	0 (0%)

Treatment Related AEs Evaluable Patients (n=28)	TUS	VEN	AZA
Any	**22 (68.8%)**	**27 (84.4%)**	**28 (87.5%)**
Most Frequent Related Non-Heme TEAEs (>15% of Subjects)			
Nausea	8 (25.0%)	8 (25.0 %)	7 (21.9%)
Diarrhea	8 (25.0%)	8 (25.0%)	7 (21.9%)
Vomiting	5 (15.6%)	5 (15.6%)	6 (18.8%)
Grade ≥ 3 (≥ 25% of Subjects)			
Platelet count decreased	13 (40.6%)	15 (46.9%)	15 (46.9%)
White blood cell count decreased	11 (34.4%)	14 (43.8%)	15 (46.9%)
Neutrophil count decreased	11 (34.4%)	14 (43.8%)	15 (46.9%)
Anemia	8 (25.0%)	9 (28.1%)	9 (28.1%)
Related SAEs			
Leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dose Limiting Toxicity (DLT)	**2 (0.0%)**	**1 (0.0%)**	**1 (0.0%)**

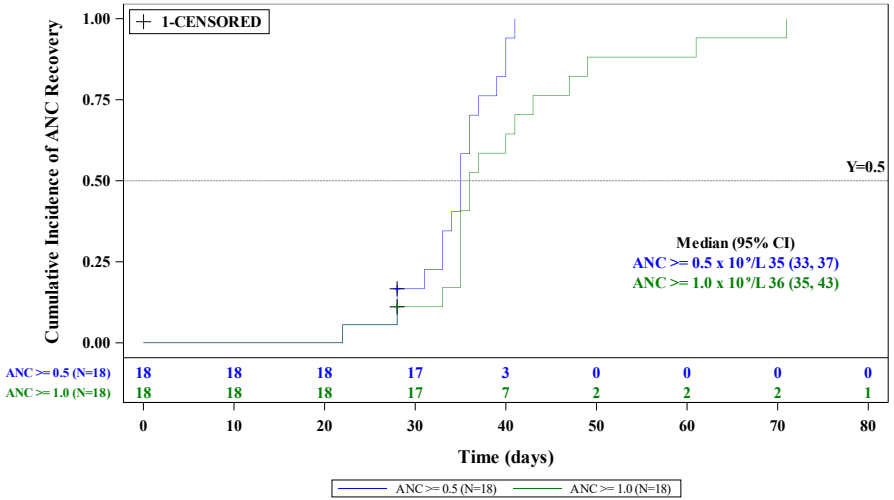
Two DLTs occurred at the 160 mg dose level:

- #1 was reversible Gr3 myositis and weakness with normal CPK and aldolase levels in the setting of sepsis and low [Na^+]
- #2 was persistent Gr4 neutropenia at Cycle 1 Day 42

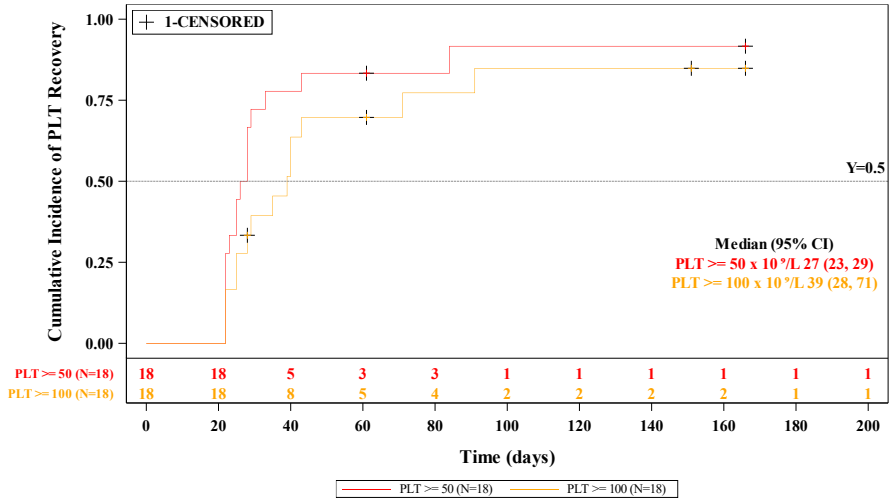
No related QTc prolongation, differentiation syndrome, or CPK elevations & no treatment-related deaths

TUS/VEN/AZA: Count Recovery in Cycle 1 Remissions

Days to ANC Recovery



Days to Platelet Recovery



Median time to ANC ≥0.5 K/μl: **35 days**

Median time to ANC ≥1.0 K/μl: **36 days**

Median time to platelets ≥50 K/μl: **27 days**

Median time to platelets ≥100 K/μl: **39 days**

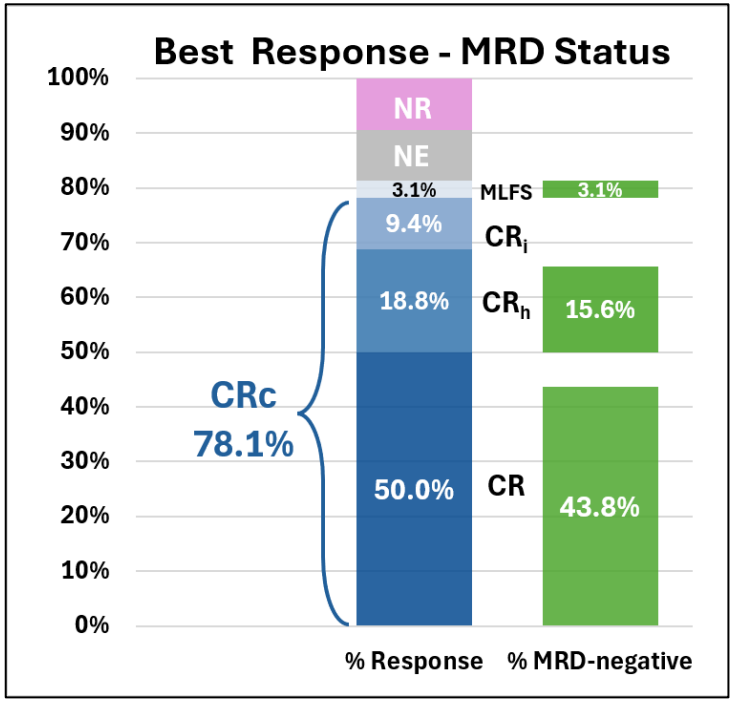
TUS/VEN/AZA: Response Rates by Dose Level

(40-160 mg/400 mg/75 mg/m², n=32 as of 28MAY2026)

ITT Response Rates by Dose and Mutation Groups

Mutation Group	TUS 40 mg	TUS 80 mg	TUS 120 mg	TUS 160 mg	Total
ORR (MLFS + CR_i + CR_h + CR)					
Overall	3/4 (75.0%)	10/12 (83.3%)	3/3 (100%)	10/13 (76.9%)	**26/32 (81.3%)**
CR_c (CRi + CRh + CR)					
Overall	3/4 (75.0%)	9/12 (75.0%)	3/3 (100%)	10/13 (76.9%)	**25/32 (78.1%)**
***FLT3*-Unmutated**	2/3 (66.7%)	5/8 (62.5%)	3/3 (100%)	8/11 (72.7%)	18/25 (72.0%)
***FLT3*-Mutated**	1/1 (100%)	4/4 (100%)	0/0	2/2 (100%)	7/7 (100%)
***NPM1*-Mutated**	1/1 (100%)	2/2 (100%)	0/0	1/2 (50.0%)	4/5 (80.0%)
***TP53*-Mut/CK**	1/1 (100%)	2/5 (40%)	0/0	4/4 (100%)	7/10 (70.0%)
MRD Negativity in CRc Subjects	3/3 (100%)	7/9 (77.8%)	2/3 (66.7%)	7/10 (70%)	**19/25 (76.0%)**
CR/CR_h					
Overall	3/4 (75.0%)	7/12 (58.3%)	3/3 (100%)	9/13 (69.2%)	**22/32 (68.8%)**
CR					
Overall	3/4 (75.0%)	4/12 (33.3%)	3/3 (100%)	6/13 (46.2%)	**16/32 (50.0%)**

CR_c rate in ***response evaluable*** *(n=29)* subjects: **86.2%**



MRD^{NEG} rate in all subjects: 62.5%

MRD^{NEG} rate in CR/CR_h: 86.4%

CONCLUSIONS

*TUS/VEN/AZA is being developed as a safe, **mutation agnostic** 1L therapy for newly diagnosed AML*

TUS Single Agent

- Responses achieved in VEN-naïve **FLT3^{WT}**, **FLT3^{MUT}** with prior FLT3i exposure, **TP53^{MUT}**, and **RAS^{MUT}** AML

TUS/VEN Doublet

- Well tolerated and active in broad populations of R/R AML including prior-VEN treated subjects

TUS/VEN/AZA Frontline Triplet

- Well tolerated and active in newly diagnosed AML patients who are ineligible for intensive chemotherapy
- TUS can be administered with standard-of-care dosing of VEN/AZA without unacceptable myelosuppression or dose-limiting toxicities
- High rates of MRD-negative responses achieved across diverse AML populations regardless of mutation status – including adverse *TP53* mutations and those with CK
- Several TUS dose levels will be carried into a controlled, randomized Phase 2 study

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

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https://www.aptose.com/clinical-trials/tuspetinib