

Tuspetinib Myeloid Kinase Inhibitor Safety and Efficacy as Monotherapy and Combined with Venetoclax in Phase 1/2 Trial of Patients with Relapsed or Refractory (R/R) Acute Myeloid Leukemia (AML)

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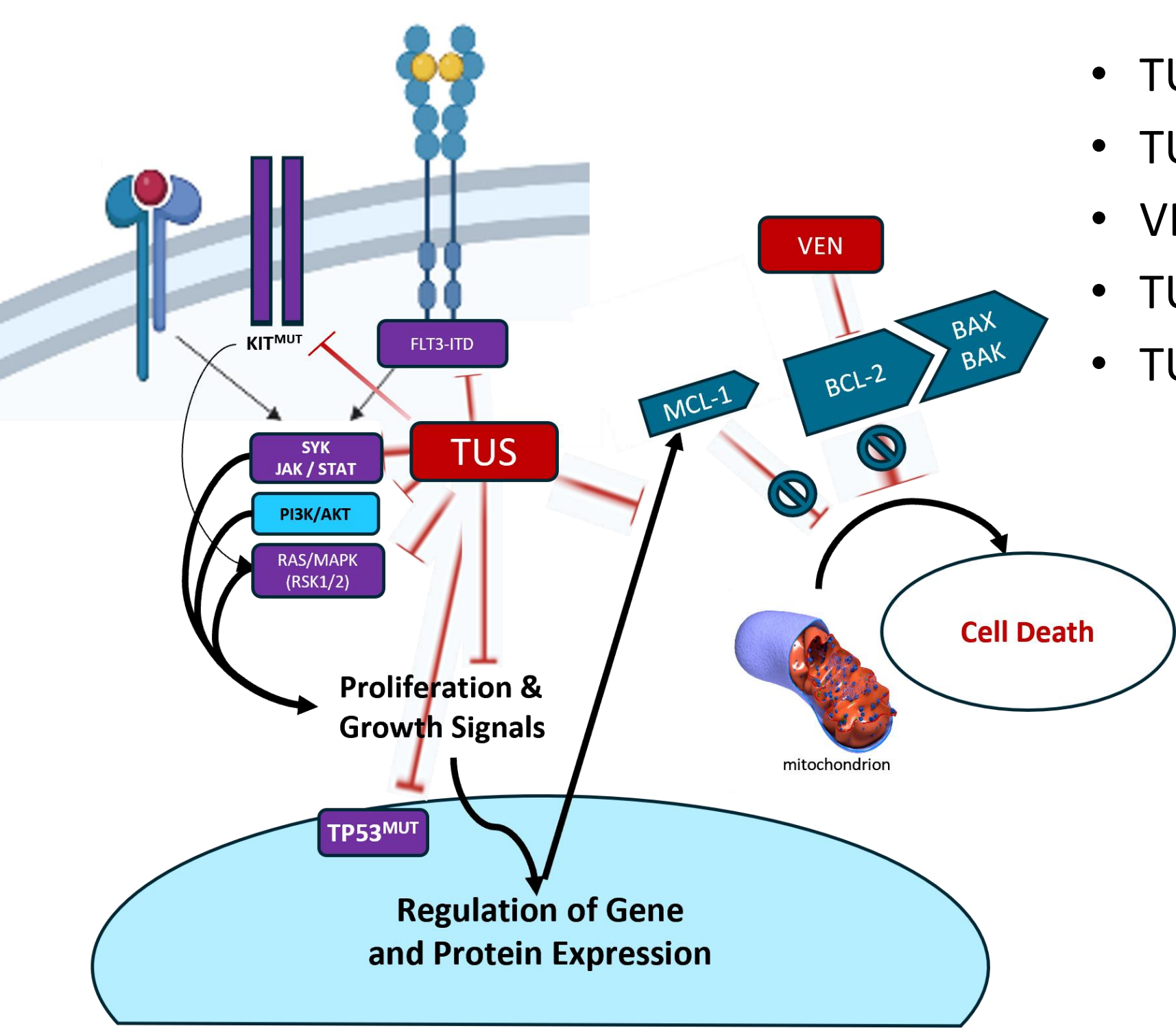
BACKGROUND

Tuspetinib (HM43239; TUS) is a potent, once daily, oral myeloid kinase inhibitor of SYK, FLT3, RSK2, JAK1/2, mutant KIT, and TAK1-TAB1 kinases that mediate dysregulated cellular proliferation in AML. In AML animal models, tuspetinib exhibited greater potency than gilteritinib and entospletinib when given as single agents and combined favorably with venetoclax (VEN) and azacitidine (AZA). Tuspetinib is being evaluated as monotherapy (TUS) and in combination (TUS/VEN) in a global Phase 1/2 trial of patients with R/R AML (NCT03850574) and in a study examining the food effect on PK of a single oral dose in healthy volunteers.

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	JAK-1
	JAK-2		6.3
	JAK-2 (V617F)		9.9
	c-KIT	WT	> 500
		D816H	3.6
		D816V	3.5
	RSK	RSK2	9.7
		TAK1-TAB1	TAK1-TAB1

TUS TARGETS VEN-RESISTANCE MECHANISMS



- TUS inhibits kinase-driven abnormal signaling
- TUS reduces MCL-1 protein expression
- VEN continues to inhibit BCL-2 block on cell death
- TUS/VEN combine to kill AML cells
- TUS can deliver responses in TP53^{MUT} patients



STUDY DESIGN & OBJECTIVES

Global phase 1/2, open-label, first-in-human, dose escalation, exploration, and expansion clinical study of TUS as a single agent and in combination with VEN (TUS/VEN) for the treatment of relapsed or refractory (R/R) AML

- Tuspentinib tablets administered once daily in ~ 28-day cycles for exploration and expansion
- Broad eligibility includes FLT3-mutated and FLT3-unmutated R/R AML
- No restriction on prior therapy received including allogeneic transplantation
- Dose Expansion includes single agent TUS and in TUS/VEN combination

Primary objectives:

- Assess the safety, tolerability, and PK parameters of TUS and TUS/VEN in patients with R/R AML
- Establish the recommended phase 2 dose of tuspetinib based on safety, efficacy, PK, and PD data

STUDY STATUS

As of September 1, 2023: 117 patients have been treated across 6 dose levels (20, 40, 80, 120, 160, and 200 mg QD) with TUS single agent (Part A, B, & C) and TUS/VEN combination (Part C)

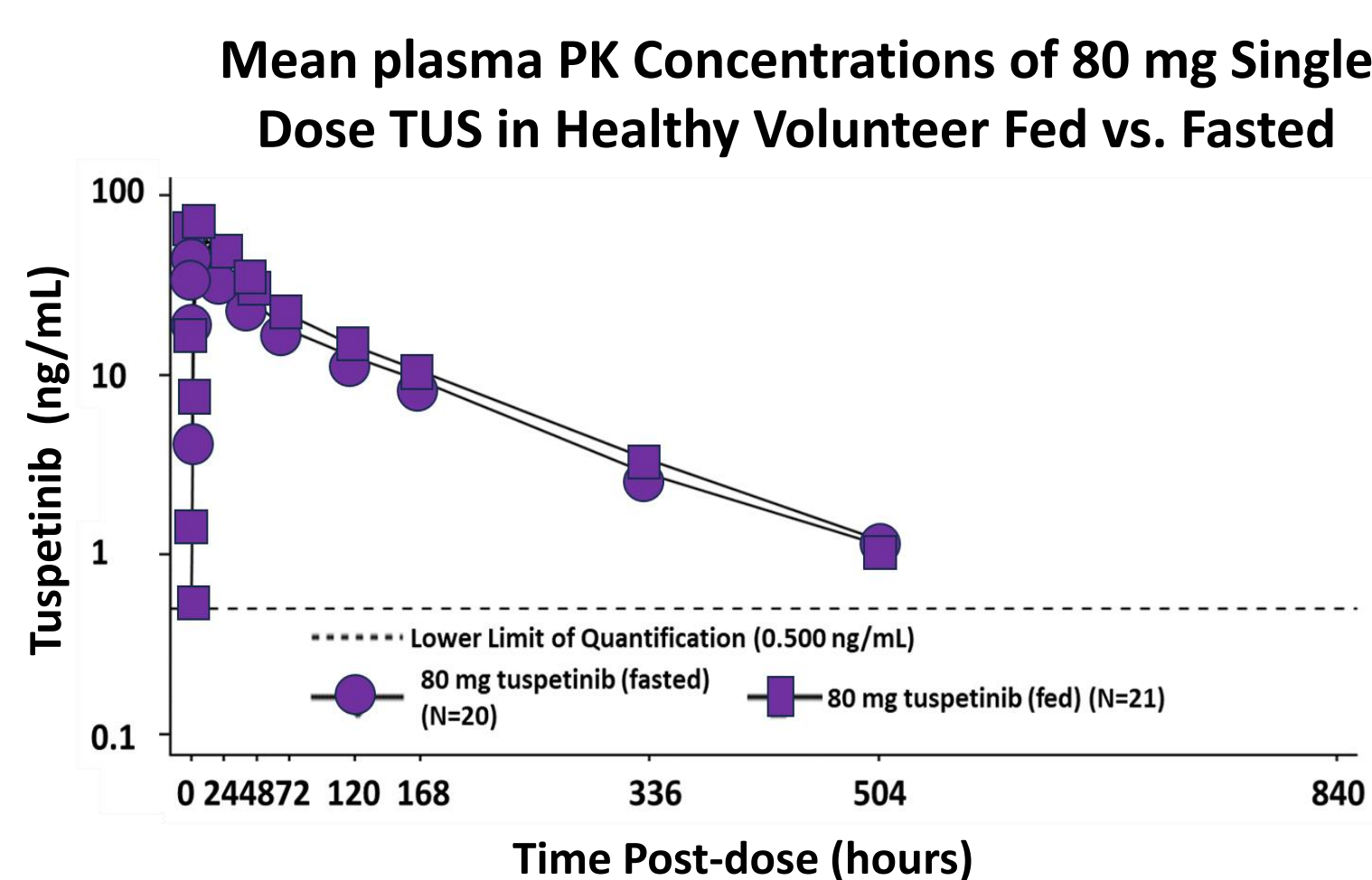
Patient Disease Characteristics		
	TUS	TUS/VEN
Patient Demographics	N=91	N=26
Median Age (Range), years	60.9 (18-84)	66.3 (31-86)
Gender		
Male	53 (58.2%)	11 (42.3%)
Female	38 (41.8%)	15 (57.7%)
FLT3 Mutation Status	N (%)	
FLT3+	34 (37.4%)	8 (30.8%)
FLT3-	56 (61.5%)	18 (69.2%)
Unknown	1 (1.1%)	0 (0%)
Prior AML Therapy		
Lines of prior therapy - Mean (Range)	2.6 (1-6)	2.6 (1-7)
Type of Prior AML Therapy	N (%)	
Cytotoxic chemotherapy	63 (69.2%)	17 (65.4%)
HSCT	33 (36.3%)	6 (23.1%)
FLT3 Inhibitor	20 (22.0%)	10 (38.4%)
Venetoclax	53 (58.2%)	21 (80.8%)
HMA's	60 (65.9%)	19 (73.1%)

PHARMACOKINETICS

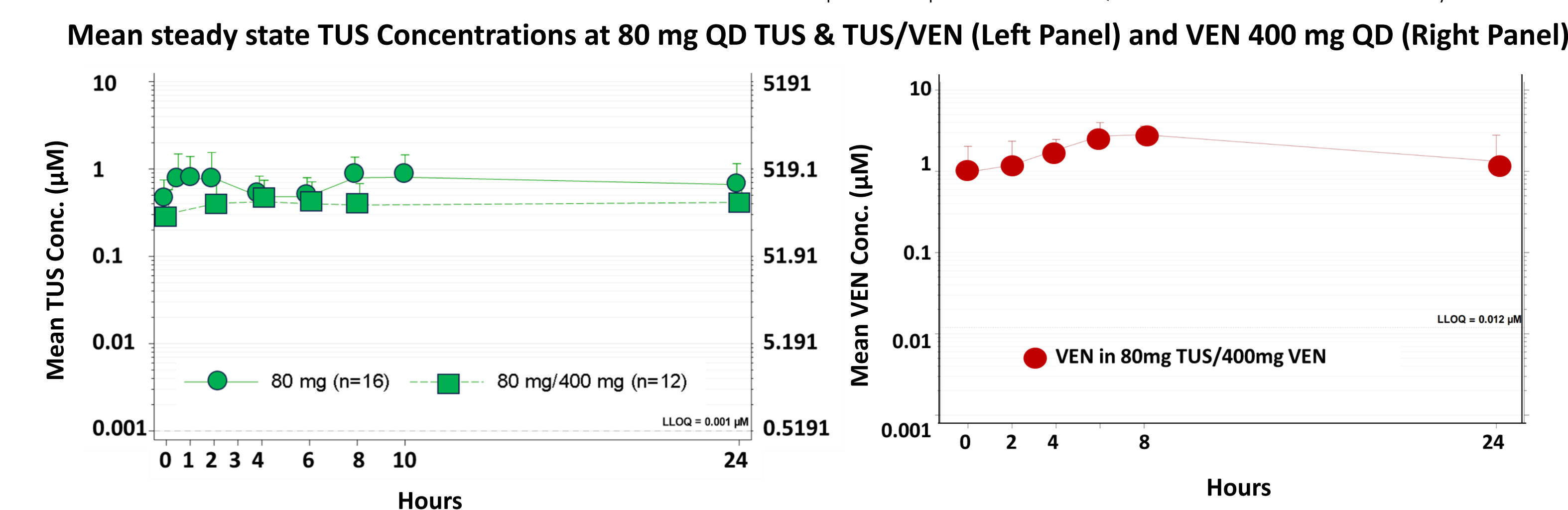
- TUS PK in Fed and Fasting state shows no clinically significant difference in exposure, allowing TUS to be administered in either condition and together with VEN

- TUS steady state PK similar as TUS and TUS/VEN
- No significant drug-drug interaction observed on TUS steady state exposure in TUS/VEN

- VEN steady state C_{min} exposure in TUS/VEN in preliminary analysis is similar to published VEN PK



Note: N= Number of subjects; The Period 1 504-hour post-dose samples was also the Period 2 pre-dose sample. Values that are BLQ were set to 0 for the calculation of summary statistics.

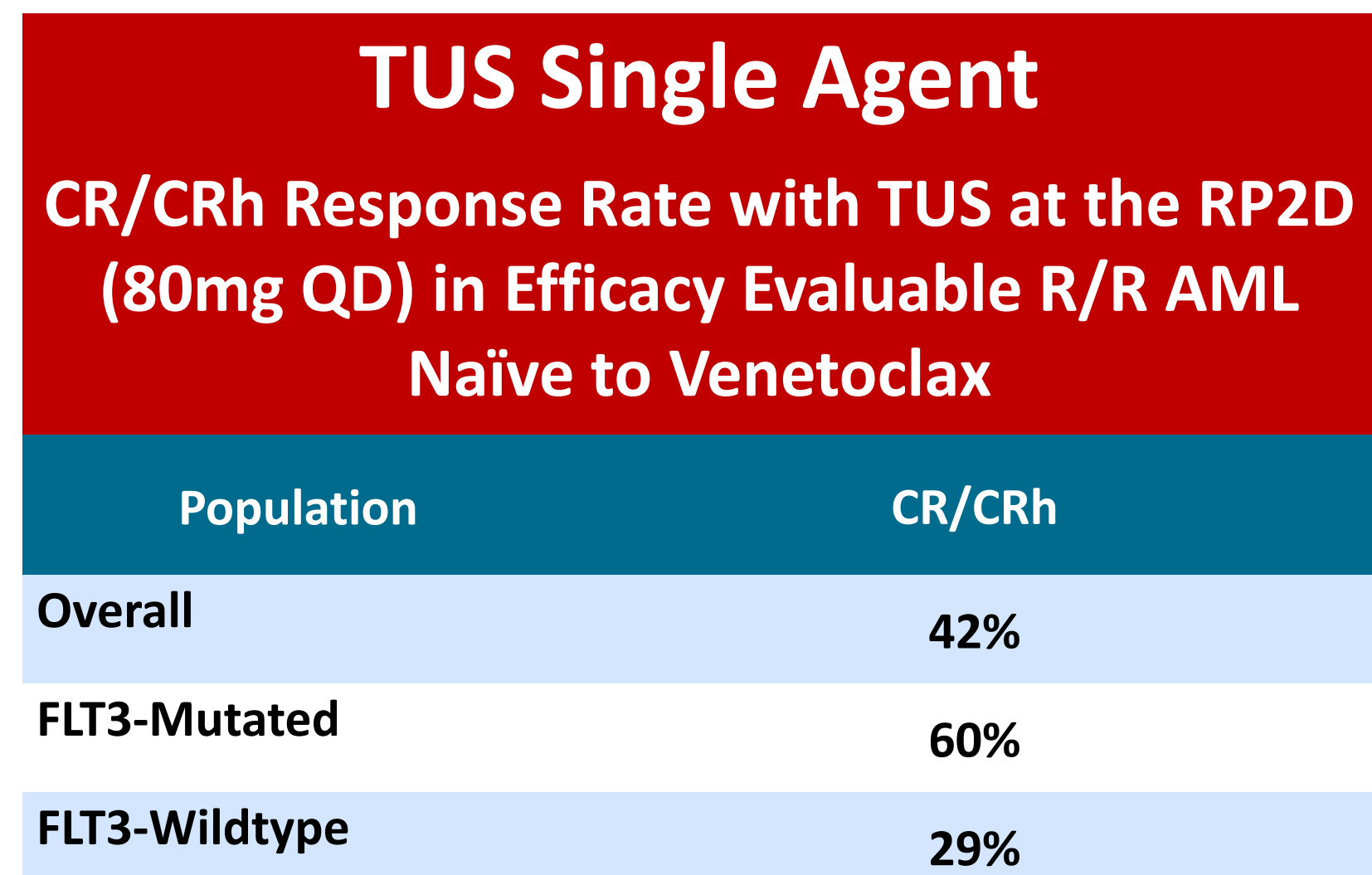
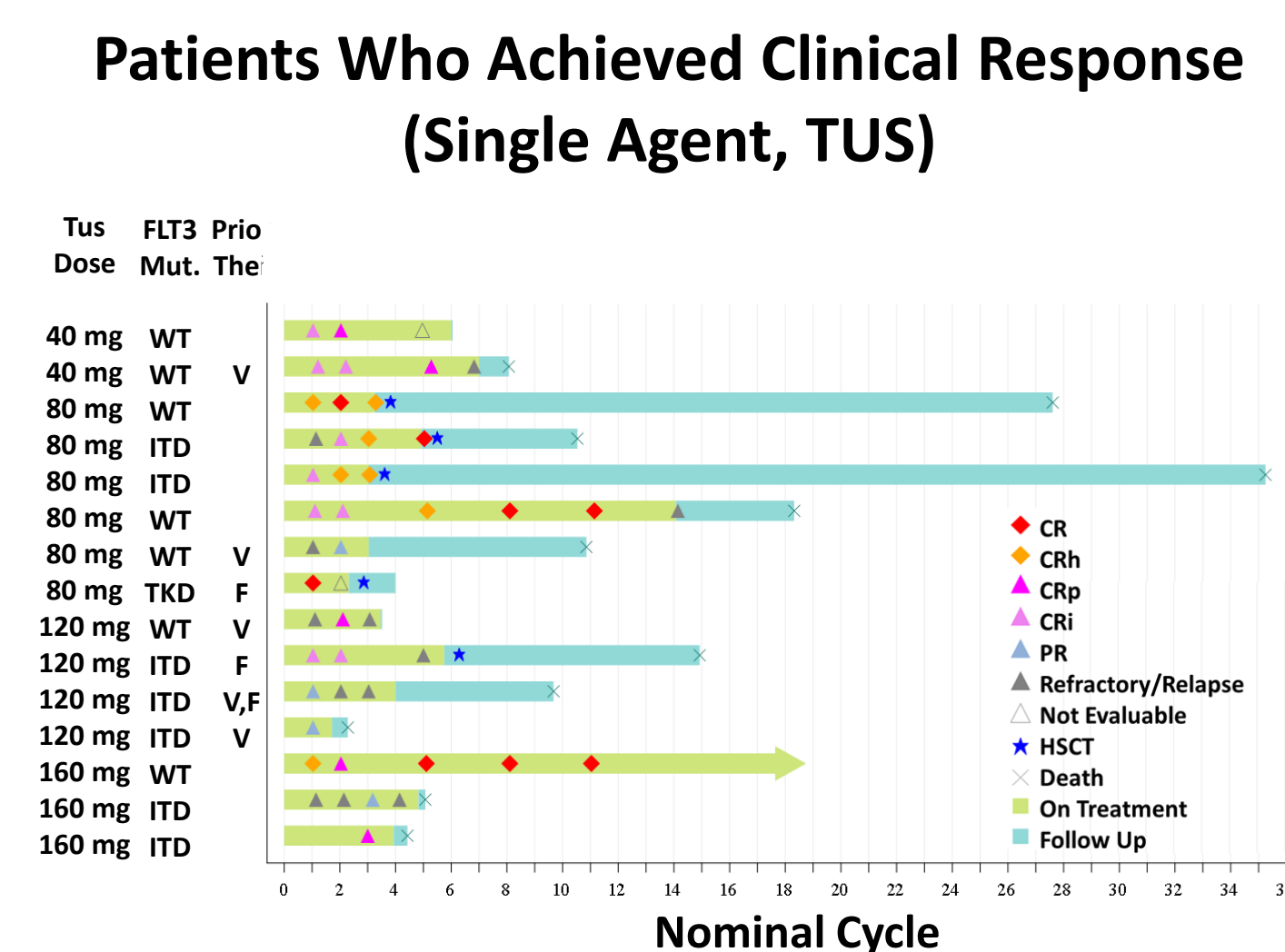


We thank our principal investigators, clinical site staff, and most importantly, our patients and their families for their participation in this clinical trial. ESH2023 Abstract# 6046059

CLINICAL RESPONSES

- TUS single agent achieved clinical responses in 40, 80, 120, and 160mg QD cohorts
- **TUS in VEN naïve R/R AML pts: CR/CRh 42%, 60%, 29% in Overall, FLT3-MUT, FLT3-WT, respectively**
- TUS/VEN achieved responses in patients who previously failed VEN and refractory to other therapies
- **TUS/VEN in Prior-VEN failure pts : CRc = 38%, 60%, 25% in Overall, FLT3-MUT, FLT3-WT, respectively**

Clinical Response Rates with TUS and TUS/VEN



TUS and TUS/VEN

CRc Response Rates in Efficacy Evaluable R/R AML Patients

Composite Complete Remission (CRc)		
Subgroups	TUS % CRc (N=63)	TUS /VEN % CRc (N=15)
Overall	17.5% (11/63)	46.7% (7/15)
VEN Naïve	31.0% (9/29)	100% (2/2)
Prior VEN	5.9% (2/34)	38.5% (5/13)
FLT3-Mutated	20.8% (5/24)	66.7% (4/6)
VEN Naïve	45.5% (5/11)	100% (1/1)
Prior VEN	0% (0/13)	60.0% (3/5)
Prior FLT3i	14.3% (2/14)	66.7% (4/6)
FLT3-Unmutated	15.4% (6/39)	33.3% (3/9)
VEN Naïve	22.2% (4/18)	100% (1/1)
Prior VEN	9.5% (2/21)	25.0% (2/8)

SAFETY

TUS as Single Agent:

- Tuspentinib is well tolerated as TUS single agent and as the TUS/VEN combination
- TUS RP2D = 80mg once daily as single agent

TUS/VEN Doublet:

- 80 mg TUS / 400 mg VEN
- Only one VEN-related SAE (pneumonia) was observed

Treatment-emergent AEs (TEAEs), Safety Analysis Set, Monotherapy (Parts A+B+C) and TUS/VEN (Part C)				
Patients Experiencing TEAEs		Monotherapy (N=91, n[%])	TUS/VEN (N=26, n[%])	
Any		87 (95.6%)	23 (88.5%)	
Most Frequent TEAEs (>15% of patients)				
Pneumonia		30 (33.0%)	3 (11.5%)	
Nausea		18 (19.8%)	5 (19.2%)	
Diarrhea		17 (18.7%)	3 (11.5%)	
Pyrexia		17 (18.7%)	1 (3.8%)	
Anaemia		5 (5.5%)	4 (15.4%)	
Febrile neutropenia		11 (12.1%)	7 (26.9%)	
White blood cell count decreased		4 (4.4%)	4 (15.4%)	
≥ Grade 3		66 (72.5%)	16 (61.5%)	
SAEs		52 (57.1%)	12 (46.2%)	
Leading to treatment termination ¹		12 (13.2%)	1 (3.8%)	
Leading to death		18 (19.8%)	0 (0%)	
Patients Experiencing related TEAEs		Related to TUS	Related to TUS	Related to VEN
Any		29 (31.9%)	11 (42.3%)	11 (42.3%)
Most Frequent Related TEAEs (>10% of patients)				
Diarrhea		10 (11.0%)	2 (7.7%)	1 (3.8%)
Nausea		8 (8.8%)	4 (15.4%)	3 (11.5%)
White blood cell count decreased		2 (2.2%)	3 (11.5%)	3 (11.5%)
Grade ≥ 3		9 (9.9%)	6 (23.1%)	7 (26.9%)
Neutrophil count decreased or Neutropenia		3 (3.3%)	2 (7.7%)	2 (7.7%)
Muscle weakness		2 (2.2%)	0 (0%)	0 (0%)
White blood cell count decreased or Leukopenia		3 (3.3%)	1 (3.8%)	2 (7.7%)
Nausea		1 (1.1%)	0 (0%)	0 (0%)
Febrile neutropenia		1 (1.1%)	0 (0%)	0 (0%)
Hyperttransaminasaemia		1 (1.1%)	0 (0%)	0 (0%)
Platelet count decreased or Thrombocytopenia		1 (1.1%)	1 (3.8%)	1 (3.8%)
Pneumonia		0 (0%)	0 (0%)	1 (3.8%)
Vomiting		0 (0%)	1 (3.8%)	1 (3.8%)
SAEs		1 (1.1%)	0 (0%)	1 (3.8%)
Leading to death		0 (0%)	0 (0%)	0 (0%)
Dose Limiting Toxicity (DLT) ²		1 (1.1%)	NA	NA

1. SAE leading to treatment termination is for both drug; VEN & TUS
2. A DLT of G3 muscle weakness was experienced by a patient at the 200 mg QD dose level
NA: Not Applicable

NA: Not Applicable

FUTURE PLANS

- Explore TUS/VEN in mutationally defined subsets of treated patients
- Explore TUS and TUS/VEN in R/R myelodysplastic syndromes with 10-19% blasts (HR-MDS) and chronic myelomonocytic leukemia (CMML)
- Open TUS/VEN/AZA triplet therapy cohort for 1L newly diagnosed AML

CONCLUSIONS

- TUS/VEN is highly active in emerging Prior-Ven failure AML population, including FLT3^{WT} and FLT3^{MUT} who failed prior VEN and prior FLT3i
- TUS targets VEN-resistance mechanisms and appears to re-sensitize Prior-VEN failure patients to VEN
- TUS and TUS/VEN are broadly active across difficult-to-treat AML with adverse mutations and MDS-like AML mutation profiles
- TUS and TUS/VEN well tolerated with no drug related non-hematologic SAEs, QT_c prolongation, CPK elevations, differentiation syndrome, or deaths
- TUS single agent achieved CR's in heavily pretreated R/R AML with highest response rates observed in VEN naïve patients
- TUS provides a unique opportunity to treat FLT3-WT AML with an oral kinase inhibitor as TUS/VEN in the R/R setting
- TUS will be studied as part of a TUS/VEN/HMA triplet in 1L newly diagnosed AML patients unfit for chemotherapy with or without FLT3-mutations

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