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# Oral Presentation Delivered by Naval Daver, MD To the 65th ASH Annual Meeting & Exposition Saturday 09Dec2023



**Naval G. Daver, MD** is Professor, Director Leukemia Research Alliance Program, in the Department of Leukemia at the University of Texas MD Anderson Cancer Center. He completed his medical school from Grant Medical College and Sir J group of Hospitals Mumbai, followed by a residency and fellowship in hematology-oncology from Baylor College of Medicine. He is a clinical investigator with a focus on molecular and immune therapies in AML and Myelofibrosis and is principal investigator on >25

ongoing institutional, national and international clinical trials in these diseases. These trials focus on developing a personalized therapy approach by targeting specific mutations or immune pathways expressed by patients with AML, evaluating novel combinations of targeted, immune and cytotoxic agents, and identifying and overcoming mechanism of resistance. He is especially interested in developing monoclonal and bispecific antibodies, immune checkpoint and vaccine based approaches in AML, MDS, and myelofibrosis and is leading a number of these trials at MDACC. Dr. Daver has published >150 peer-reviewed manuscripts and is on the editorial board of numerous hematology specific journals. He has also authored numerous abstracts at national and international conferences.



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## Tuspetinib Oral 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)

**Naval Daver**<sup>1</sup>, Kyoo-Hyun Lee<sup>2</sup>, Yunsuk Choi<sup>2</sup>, Brian Jonas<sup>3</sup>, Martha Arellano<sup>4</sup>, Justin M Watts<sup>5</sup>, Pau Montesinos<sup>6</sup>, Uma Borate<sup>7</sup>, Paul B. Koller<sup>8</sup>, Chul-Won Jung<sup>9</sup>, Sang Kyun Sohn<sup>10</sup>, Pankit Vachhani<sup>11</sup>, Amir T. Fathi<sup>12</sup>, Sung-Soo Yoon<sup>13</sup>, Jeong-Ok Lee<sup>14</sup>, Ho-Jin Shin<sup>15</sup>, Gabriel Mannis<sup>16</sup>, Nikolai A. Podoltsev<sup>17</sup>, Tan Shuhying<sup>18</sup>, Harry P. Erba<sup>19</sup>, Eric Tam<sup>20</sup>, Mar Tormo Diaz<sup>21</sup>, Jia Hu<sup>22</sup>, Ranjeet Kumar Sinha<sup>22</sup>, Nawazish Khan<sup>22</sup>, William Rice<sup>22</sup>, Rafael Bejar<sup>22</sup>

<sup>1</sup>The University of Texas MD Anderson Cancer Center Houston, TX, <sup>2</sup>Asan Medical Center, Seoul, SK, <sup>3</sup>UC Davis Comprehensive Cancer Center, Davis, CA, <sup>4</sup>Emory University, Atlanta, GA, <sup>5</sup>University of Miami, FL, <sup>6</sup>Hospital Universitari i Politècnic La Fe, Valencia, ESP, <sup>7</sup>The James Cancer Hospital and Solove Research Institute, The Ohio State University, OH, <sup>8</sup>Department of Hematology/HCT, City of Hope, Duarte, CA, <sup>9</sup>Samsung Medical Center, Seoul, SK, <sup>10</sup>Kyungpook National University Hospital Daegu, SK, <sup>11</sup>University of Alabama, AL, <sup>12</sup>Massachusetts General Hospital Boston, MA, <sup>13</sup>Seoul National University Hospital, Seoul, SK, <sup>14</sup>Seoul National University Bundang Hospital, Seongnam, SK, <sup>15</sup>Pusan National University Hospital, Busan, SK, <sup>16</sup>Stanford Cancer Center, Stanford, Palo Alto, <sup>17</sup>Yale School of Medicine, New Haven, CT, <sup>18</sup>St. Vincent's Hospital, Melbourne, AUS, <sup>19</sup>Duke Cancer Center, Durham, NC, <sup>20</sup>USC Norris Comprehensive Cancer Center, Los Angeles, CA, <sup>21</sup>Hospital Clínico Universitario, Valencia, ESP, <sup>22</sup>Aptose Biosciences Inc, San Diego, CA

# Investment Highlights

## Precision oncology company developing oral targeted agents to treat hematologic malignancies

### Tuspetinib (TUS) lead agent | Once daily oral kinase inhibitor for R/R acute myeloid leukemia (R/R AML)

- Highly active as a single agent with an excellent safety record
- Targets FLT3<sup>WT/MUT</sup>, SYK, KIT<sup>MUT</sup>, JAK1/2, RSK2, TAK1-TAB1 kinases and suppresses MCL-1 expression
- CR/CRh=36% All-comers | CR/CRh=50% FLT3<sup>MUT</sup> | CR/CRh=25% FLT3<sup>WT</sup> at the RP2D 80mg in VEN-naïve R/R AML

### AML care shifted to Venetoclax (VEN) based combinations | Emergence of difficult-to-treat Prior-VEN failure population

- Prior-Ven failure R/R AML patients have dismal response to salvage therapy: CR/CRh = 4-15% | mOS = 2.8 months
- Any new drug needs to combine well with VEN and treat Prior-VEN failure AML patients

### Opportunities | Tuspetinib is ideal for combination therapy with VEN-containing regimens and treating Prior-VEN failures

- TUS directly targets VEN resistance mechanisms | Re-sensitizes VEN failures to VEN | TUS/VEN successfully treats these VEN failures

**TUS/VEN doublet planned for registrational trial in R/R Prior-VEN AML → Estimated \$400 million market<sup>1</sup>**

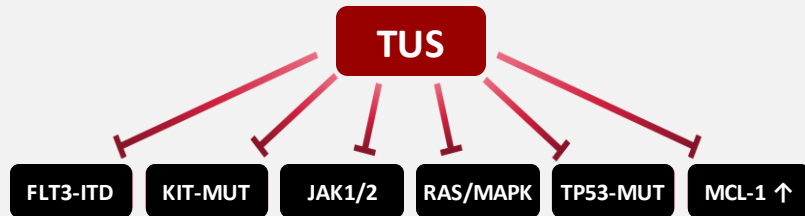
**TUS/VEN/AZA triplet planned for pilot study in 1L Newly Diagnosed AML → Estimated \$1 billion market<sup>1</sup>**

### Multiple value-creating milestones ahead

- TUS/VEN further data on duration of response in R/R AML planned: 1Q & 2Q 2024
- TUS/VEN/HMA planned initiation of pilot study in 1L AML: 1H 2024
- Extension into HR-MDS and CMML planned

# Tuspetinib Directly and Indirectly Targets Venetoclax Escape Mechanisms

Tuspetinib targets pathways involved in resistance to Venetoclax

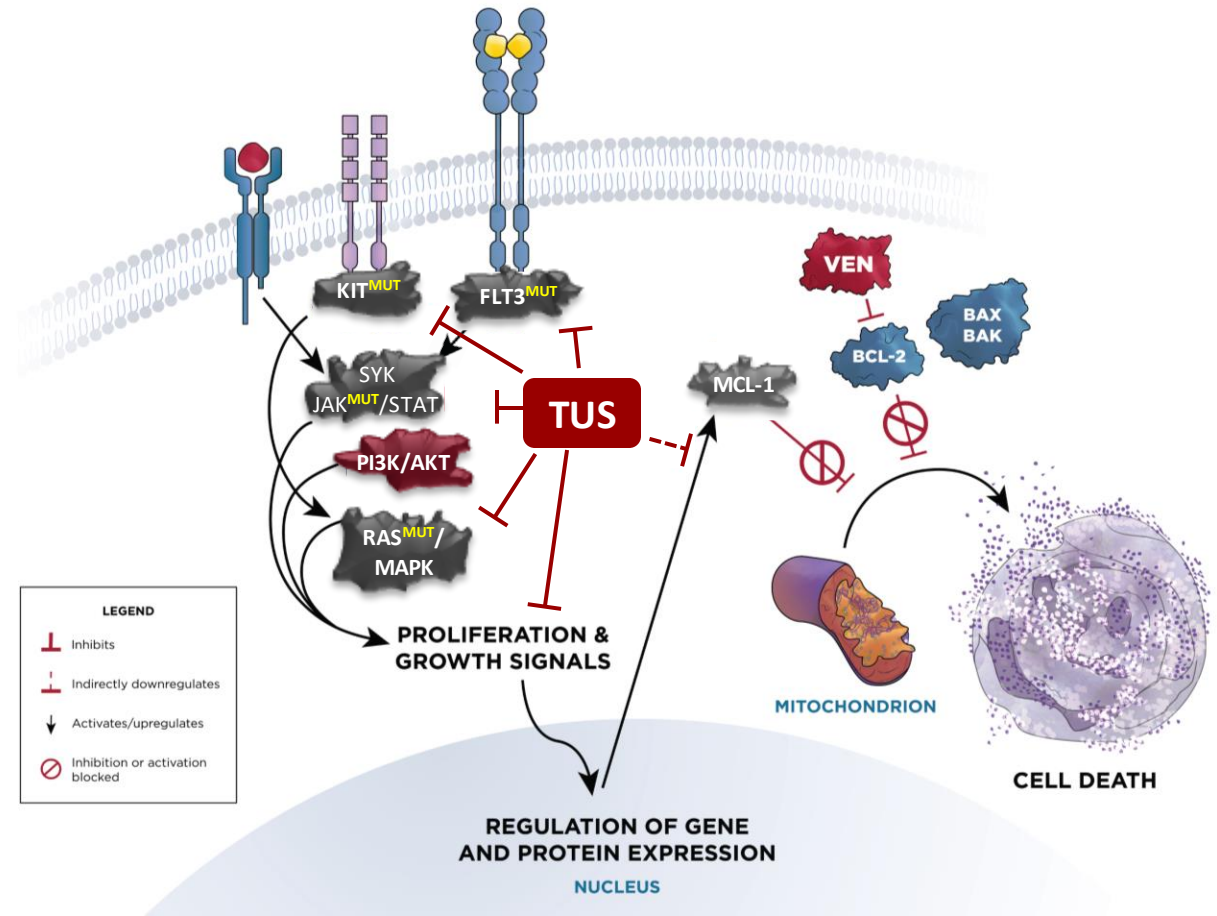


VEN BCL-2i resistance involves mutations in multiple pathways to evade BCL-2 blockade

By shutting down escape pathways, TUS may re-sensitize prior-VEN failures to venetoclax

- Strong evidence for combination therapy with tuspetinib and venetoclax
- ESH Poster: *Tuspetinib oral myeloid kinase inhibitor creates synthetic lethal vulnerability to venetoclax*

RATIONALE FOR THE COMBINATION OF TUSPETINIB AND VENETOCLAX



# TUS/VEN May be Ideal Doublet Therapy in R/R Prior-VEN Failure AML

R/R AML Setting: AML care shifted toward Venetoclax (VEN) containing combination regimens and a new population of difficult-to-treat VEN failures is emerging

After failing venetoclax, AML is highly refractory to salvage therapy<sup>(1,2,3,4)</sup>

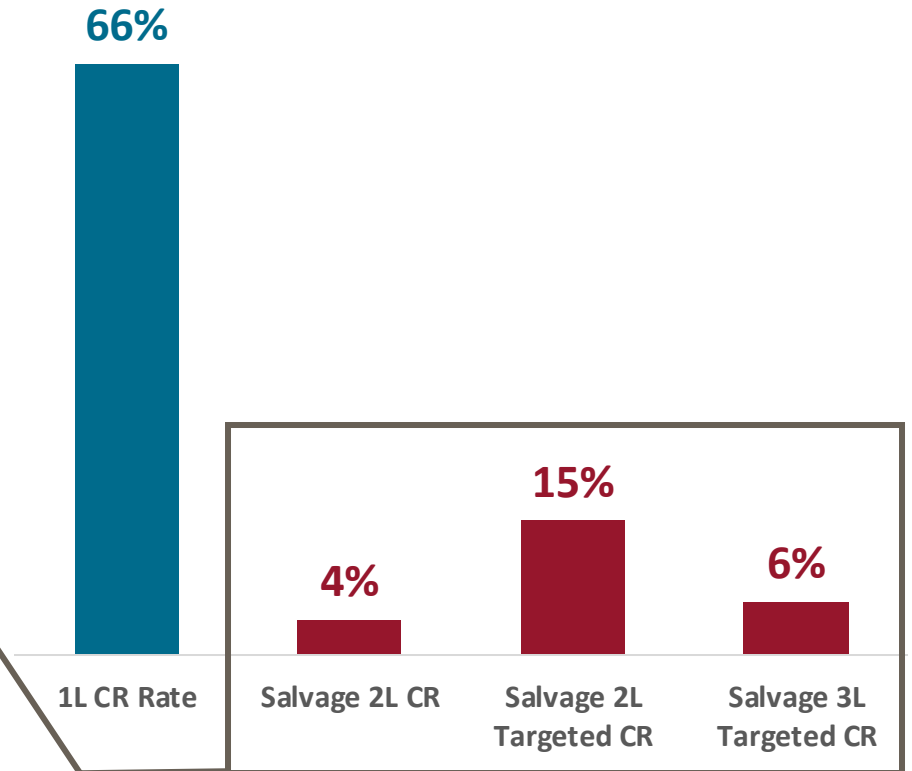
- Prior-VEN failures have “dismal” response rates to salvage therapy
- Resistance involves alterations in multiple pathways (FLT3, NRAS, KIT, TP53, JAK1/STAT5, MCL-1)

**Need Improved Therapy for R/R Prior-VEN Failures**

**TUS/VEN combination is safe & active in Prior-VEN**

**Potential first-to-market in R/R Prior-VEN setting**

**<sup>1</sup>Estimated \$400 Mn opportunity forecast to treat the majority of R/R AML patients**



1 Pei, Cancer Discov 2020; 2 DiNardo, Blood 2020; 3 (Maiti et al., Haematologica 2021); 4 (Mannis et al., Leukemia Research 2023); 5 Datamonitor Healthcare AML forecast July 2023; Also, Bewersfor et al., Leukemia Research 2022; 122: 106942.

# TUS/VEN/HMA May be Ideal Triplet Therapy in 1L Newly Diagnosed AML

1L Newly Diagnosed Setting: Venetoclax (VEN/HMA) in “Unfit” patients dramatically increased response rates (CRc = 66%) and mOS (14.7 mos)

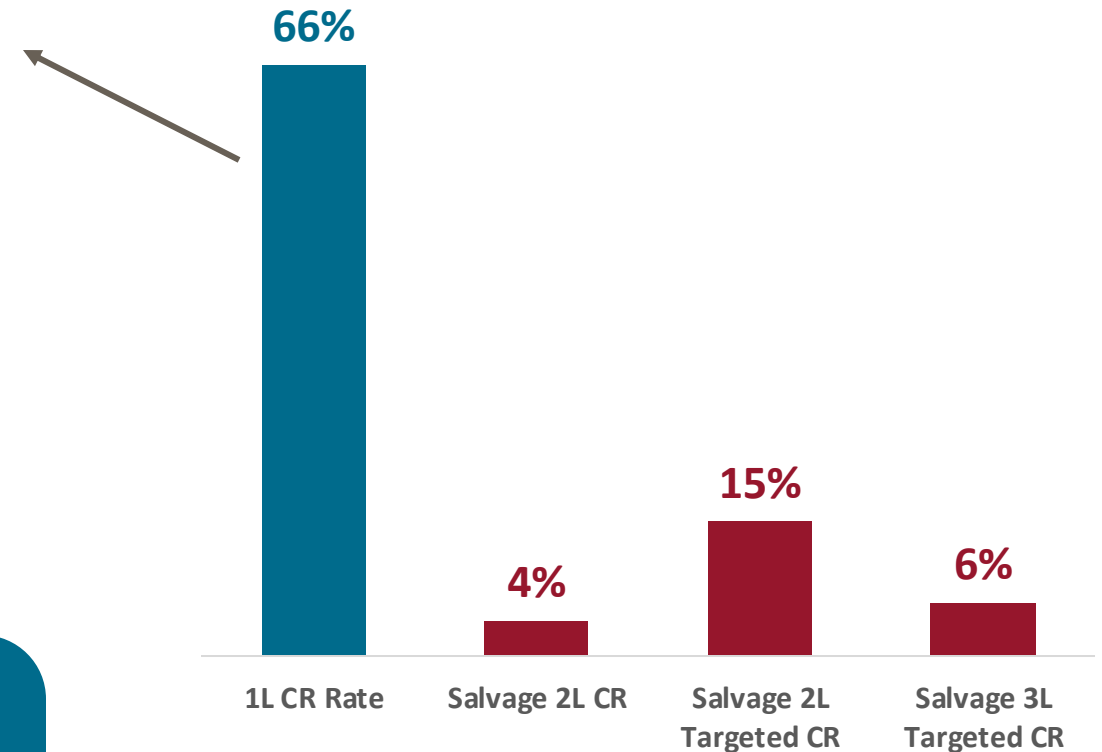
## Problem: Need Improved 1L Therapy

- 1L chemo and VEN/HMA not universally curative
- VEN containing regimens are highly successful and will further revolutionize 1L therapy
- Proof of Concept: Gilt/VEN/HMA triplet delivered high response rates, but Gilt limited to FLT3+ population (~30%) and limited by AEs

## Need Improved 1L Triplet Therapy

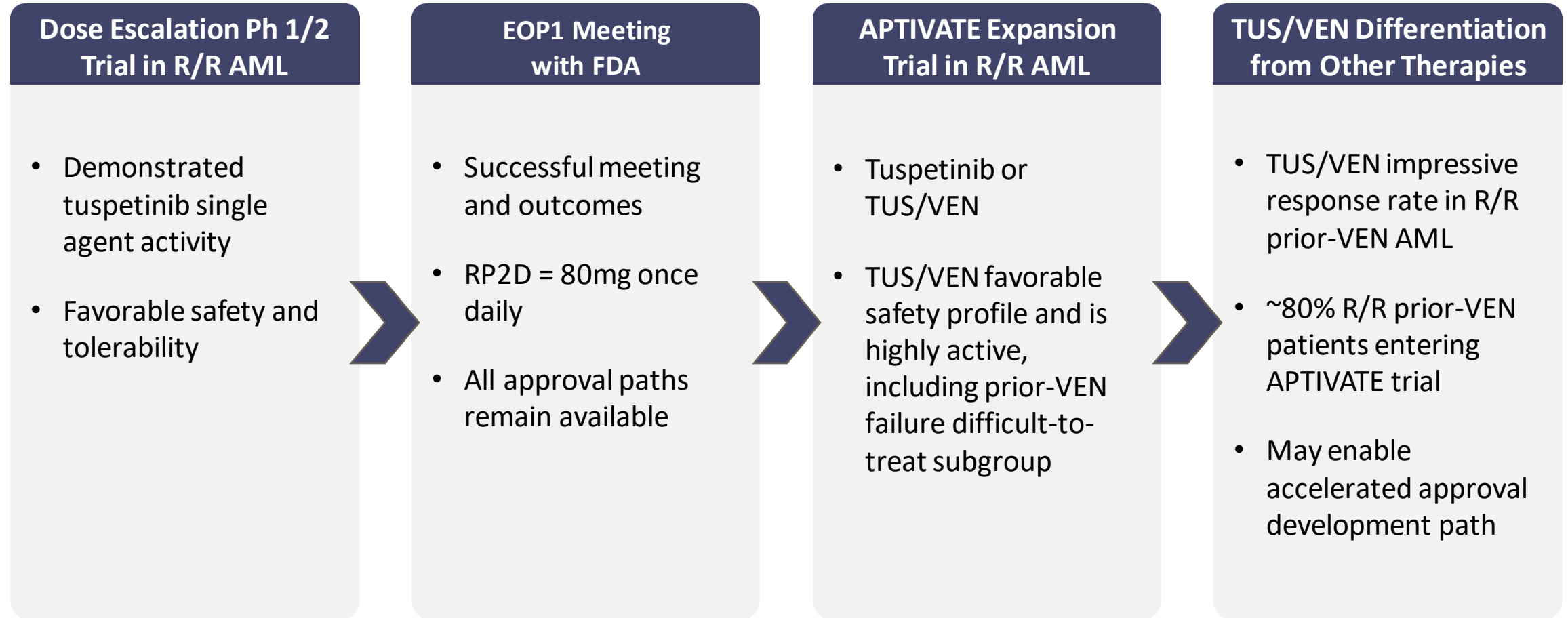
**TUS/VEN/HMA Triplet may expand treatable 1L populations (improved safety; fit and unfit ; FLT3 agnostic)**

**<sup>1</sup>Estimated \$1Bn opportunity forecasted in front-line AML**



1 Pei, Cancer Discov 2020; 2 DiNardo, Blood 2020; 3 (Maiti et al., Haematologica 2021); 4 (Mannis et al., Leukemia Research 2023); 5 Datamonitor Healthcare AML forecast July 2023; Also, Bewersfor et al., Leukemia Research 2022; 122: 106942.

# Clinical Path to Support Clinical Development and Registrational Plans



# Tuspetinib Single Agent Phase 1/2 Clinical Study



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

- TUS is dosed orally once daily in 28-day cycles without interruption
- Safety and efficacy analyses include all dosed patients<sup>1</sup>
- $CR_c = CR + CR_h + CR_p + CR_i$  (incl MLFS)
- Extensive dose exploration | 91 patients dosed
- Proportion of Prior-VEN patients increased over time, resulting in lower response rates at 120mg & 160mg
- Therapeutic window 80 mg – 160 mg
- CRs with no DLTs
- CRs in patients with highly adverse genetics
- RP2D = 80 mg once daily

## Dose Escalation + Exploration + Expansion

	Total n=	VEN- Naïve n=	Prior- VEN n=	
<b>Cohort 1: 20 mg QD</b>	2	1	1	
<b>Cohort 2: 40 mg QD</b>	17	8	9	
<b>Cohort 3: 80 mg QD</b>	20	14	6	
<b>Cohort 4: 120 mg QD</b>	32	6	26	} 71% Prior- VEN
<b>Cohort 5: 160 mg QD</b>	16	8	8	
<b>Cohort 6: 200 mg QD</b>	4	1	3	

<sup>1</sup>Data cut Oct 23, 2023

# Tuspetinib Single Agent Patient Baseline Characteristics

Highly treatment experienced and representative of current R/R AML patient population

Patient Characteristics (n=91)	FLT3 <sup>MUT</sup>	FLT3 <sup>WT</sup>
Patient number n (%) <sup>1</sup>	<b>34</b>	<b>56</b>
<b>Median Age Years (Range)</b>	<b>60 (21-84)</b>	<b>65.5 (18-83)</b>
Female n (%)	14 (41.2%)	24 (42.9%)
Lines prior therapy Mean (Range)	3.3 (1-11)	2.4 (1-6)
<b>Prior-VEN</b>	<b>19 (55.9%)</b>	<b>33 (58.9%)</b>
Prior FLT3 Inhibitor	17 (50.0%)	3 (5.4%)
Prior Cytotoxic chemotherapy	26 (76.5%)	36 (64.3%)
Prior HMAs	22 (64.7%)	37 (66.1%)
Prior HSCT	14 (41.2%)	19 (33.9%)

← Population included FLT3<sup>WT</sup> & FLT3<sup>MUT</sup>

← Older: Median age > 60 years

- Prior-VEN represented > 50% of patients
- Percentage increased as trial proceeded
- ← • Higher dose levels had higher percentages of Prior-VEN patients

← Over 50% failed Prior-FLT3i

← Over 1/3 failed Prior-transplant

<sup>1</sup> One patient had an indeterminant status for FLT3

# Tuspetinib Single Agent Safe and Well Tolerated

No treatment related QT<sub>c</sub> prolongation, CPK elevations, differentiation syndrome, non-hematologic SAEs, discontinuations or deaths | Avoids typical toxicities observed with other FLT3, IDH1/2 and menin inhibitors

All TEAEs (n=91)	n (%)	Treatment Related AEs (n=91)	n (%)
Any	87 (95.6%)	Any	29 (31.9%)
Most Frequent TEAEs (>12% of patients)		Most Frequent Related TEAEs (>10% of patients)	
Pneumonia	30 (33.0%)	Diarrhea	10 (11.0%)
Nausea	18 (19.8%)	Grade ≥ 3 (N≥2 patients)	9 (9.9%)
Diarrhea	17 (18.7%)	Neutrophil count decreased	2 (2.2%)
Pyrexia	17 (18.7%)	White blood cell count decreased	2 (2.2%)
Alanine aminotransferase increased	13 (14.3%)	Muscle weakness	2 (2.2%)
Hypokalaemia	12 (13.2%)	SAEs	1 (1.1%)
Epistaxis	11 (12.1%)	Leading to death	0 (0%)
Decreased appetite	11 (12.1%)	Dose Limiting Toxicity (DLT)	1 (1.1%)
Febrile neutropenia	11 (12.1%)		
≥ Grade 3	66 (72.5%)		
SAEs	52 (57.1%)		
Leading to treatment termination	12 (13.2%)		
Leading to death	18 (19.8%)		

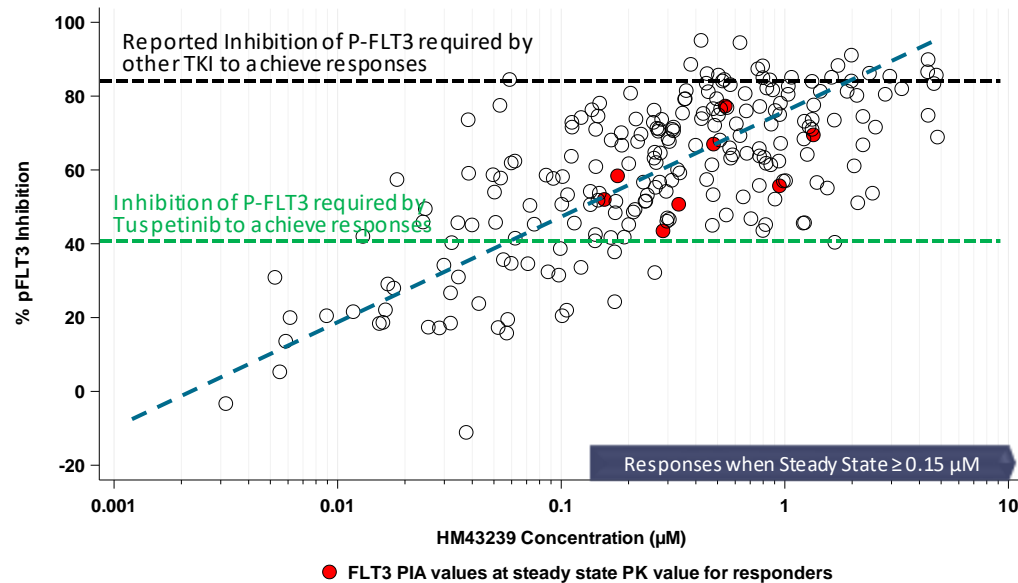
\* DLT of muscle weakness occurred at the 200mg dose level in a study participant with high drug exposure.  
No CPK elevation. No CNS abnormality.

# Tuspetinib in Patient Plasma Inhibits Multiple Kinase Targets

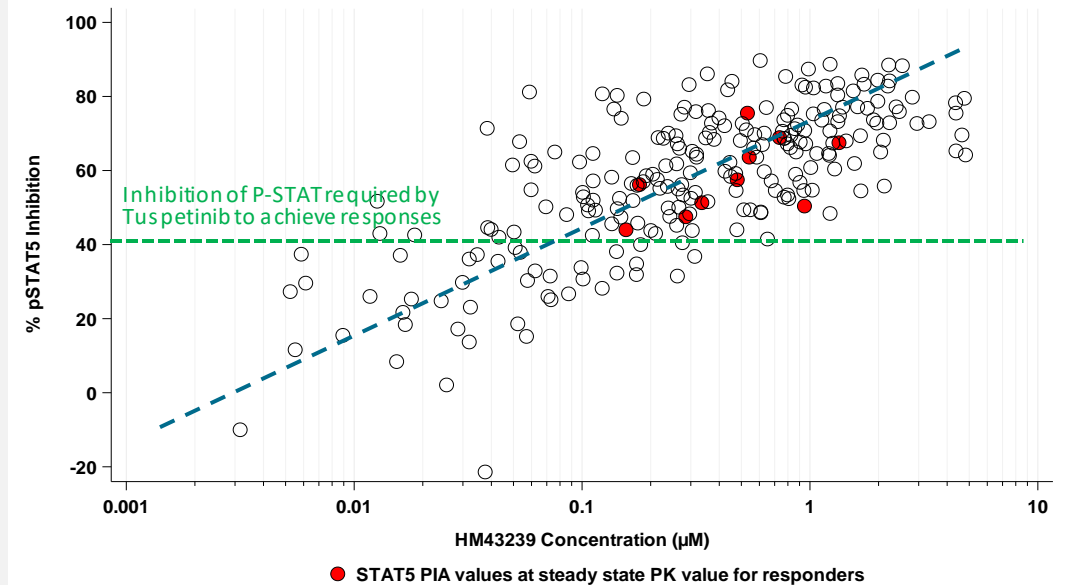
## Full inhibition of each target is not required to achieve response

*Lower doses needed for responses = fewer toxicities*

### Inhibition of FLT3 activity Measure P-FLT3 in MOLM-14 AML Cells By Patient Plasma in PIA Assay

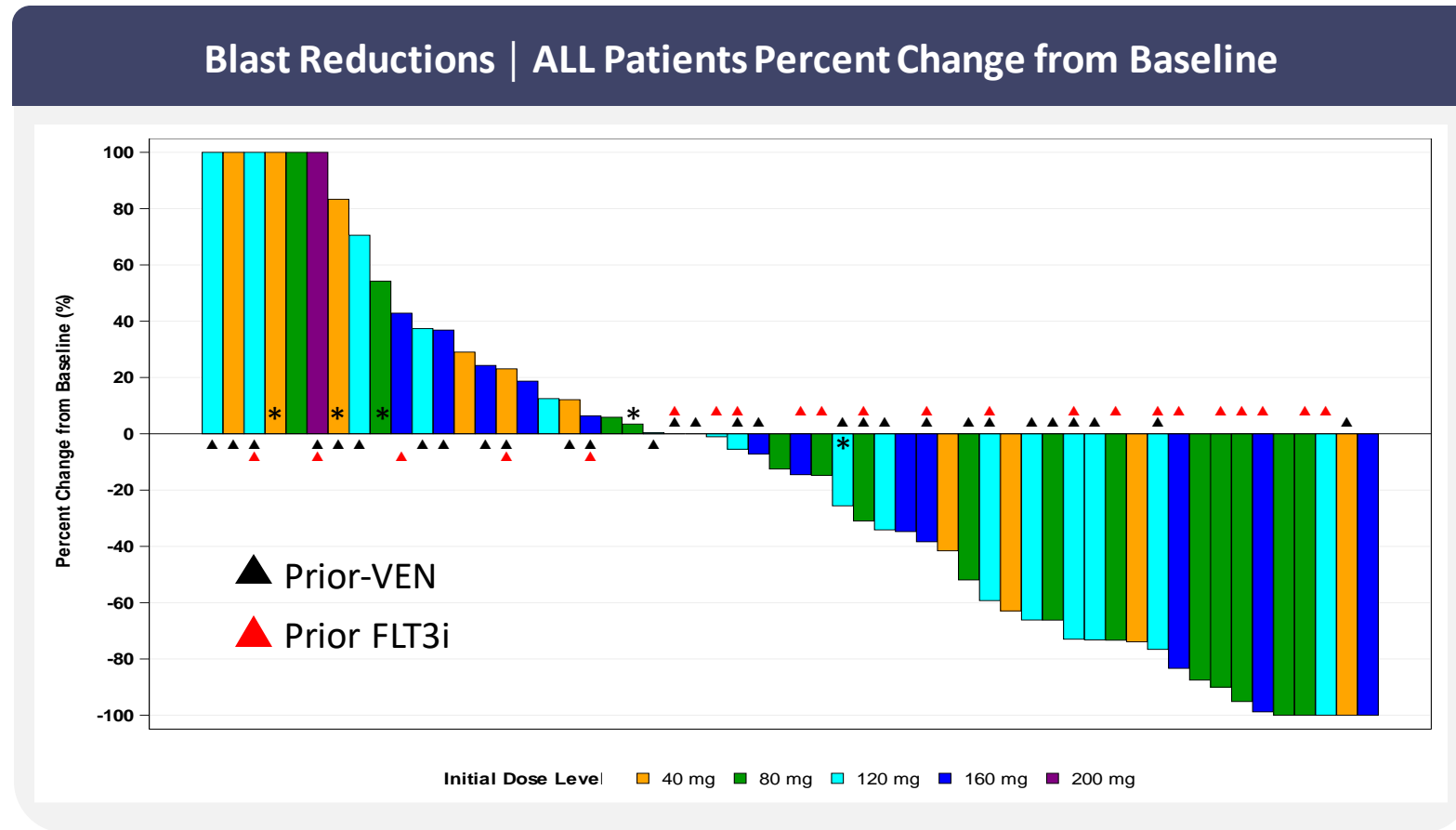


### Inhibition of JAK activity Measure P-STAT5 in MOLM-14 AML Cells Patient Plasma in PIA Assay



Abbreviations: PIA, plasma inhibitory activity; PK, pharmacokinetics; PKAS, pharmacokinetics analysis set.  
Note: available PIA values with corresponding PK values at the same time points from patients in PKAS are plotted in these figures.

# Tuspetinib Single Agent Bone Marrow Blast Reductions in R/R AML Patients



- Significant blast reductions with 40mg, 80mg, 120mg, 160mg single agent tuspetinib
- More consistent blast reductions with 80mg, 120mg, 160mg therapeutic window
- Blast reductions observed across AML subgroups with tuspetinib

Note: Blast percent change was calculated as  $100 \times \frac{(\text{the lowest post-baseline bone marrow blast} - \text{baseline bone marrow blast})}{\text{baseline bone marrow blast}}$ . Patients with blast percent change  $\geq 100\%$  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 Tuspetinib. ▲ Red triangle indicates prior FLT3i.

\* Black asterisk indicates patients who administered hydroxyurea within 7 days prior to the lowest marrow blast value

# Tuspetinib Single Agent Activity at Therapeutic Doses (80-160 mg; n=68)

- Impressive response rates: only agent being developed across all AML populations
- More active in VEN-Naive R/R AML population

## TUS Response Rate Analysis (ITT)

TUS active in FLT3<sup>WT</sup> and FLT3<sup>MUT</sup> AML

TUS CR<sub>c</sub> in VEN-Naïve AML (80-160mg)

- **29% CR<sub>c</sub>** in all patients (n=8/28)
- **42% CR<sub>c</sub>** in FLT3<sup>MUT</sup> (n=5/12)
- **19% CR<sub>c</sub>** in FLT3<sup>WT</sup> (n=3/16)

**TUS CR/CR<sub>h</sub> in VEN-Naïve AML at 80 mg RP2D:**

- **36% CR/CR<sub>h</sub>** in all patients (n=5/14)
  - 50% CR/CR<sub>h</sub> in FLT3<sup>MUT</sup> (n=3/6)
  - 25% CR/CR<sub>h</sub> in FLT3<sup>WT</sup> (n=2/8)

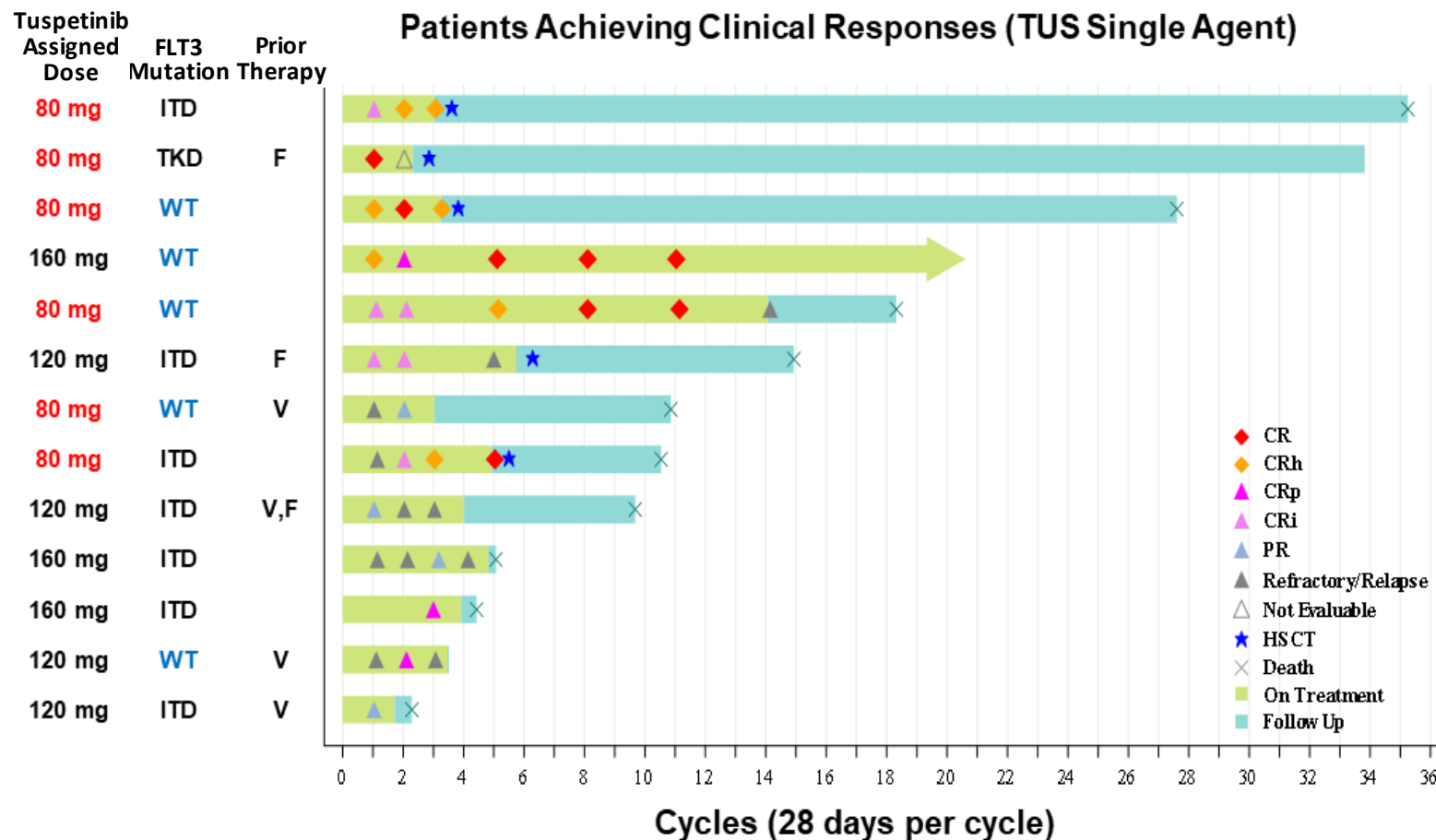
## Composite Complete Remission (CR<sub>c</sub>)

Subgroups	% CR <sub>c</sub> (n=68)
<b>Overall</b>	13% (9/68)
VEN Naïve	<b>29% (8/28)</b>
Prior VEN	3% (1/40)
<b>FLT3-Mutated</b>	18% (5/28)
VEN Naïve	<b>42% (5/12)</b>
Prior VEN	0% (0/16)
Prior FLT3i	14% (2/14)
<b>FLT3-Unmutated (WT)</b>	10% (4/39)
VEN Naïve	<b>19% (3/16)</b>
Prior VEN	4% (1/23)

# TUS Single Agent Efficacy: Clinical Responses

## TUS Responder Analysis

- Responses in **FLT3<sup>WT</sup>** and **FLT3<sup>MUT</sup>** (ITD and TKD) AML
- Responses and blood counts improve with continuous dosing
- Many bridged to allogeneic transplant (HSCT ☆ )
- Durability observed when HSCT not performed
- **80 mg selected as RP2D**



'V' indicates Prior-Venetoclax  
'F' indicates prior FLT3 inhibitor

# Tuspetinib Single Agent Response Rates Compare Favorably to GILT FLT3i

Compare\* RP2D of Each | No Prior-VEN Therapy | FLT3-Mutated and FLT3-Wildtype

	FLT3-Mutated R/R AML	
	Tuspetinib 80mg Phase 1/2 Trial (R/R, n=5)	GILT 120mg Admiral Phase 3 Trial <sup>1,2</sup> (2L, n=243)
<b>CR/CRh</b>	<b>60%</b>	<b>23%</b>

**FLT3-Mutated R/R AML**

- Tuspetinib appears highly active in FLT3-mutated AML

	FLT3-Wildtype R/R AML	
	Tuspetinib 80mg Phase 1/2 Trial (R/R, n=7)	GILT 120mg Phase 1b Trial <sup>3</sup> (R/R, n=14)
<b>CR/CRh</b>	<b>29%</b>	<b>0%</b>

**FLT3-Wildtype R/R AML**

- Tuspetinib also active in FLT3-wildtype AML
- Important data that unlock the potential for tuspetinib to treat additional 70-75% of the AML population (FLT3<sup>WT</sup>) not available to GILT

\*Inter-trial comparison

1 Pulte, and Pazdur and colleagues, FDA Approval Summary: Gilteritinib for Relapsed or Refractory Acute Myeloid Leukemia with a FLT3 Mutation. Clinical Cancer Research 2021;27(13):3515; 2 Gilteritinib US package insert May 2019; 3 Perl and colleagues, Selective Inhibition of FLT3 by Gilteritinib in Relapsed/Refractory Acute Myeloid Leukemia: a Multicenter, First-in-human, Open-label, Phase 1/2 Study. Lancet Oncol. 2017;18(8):1061.



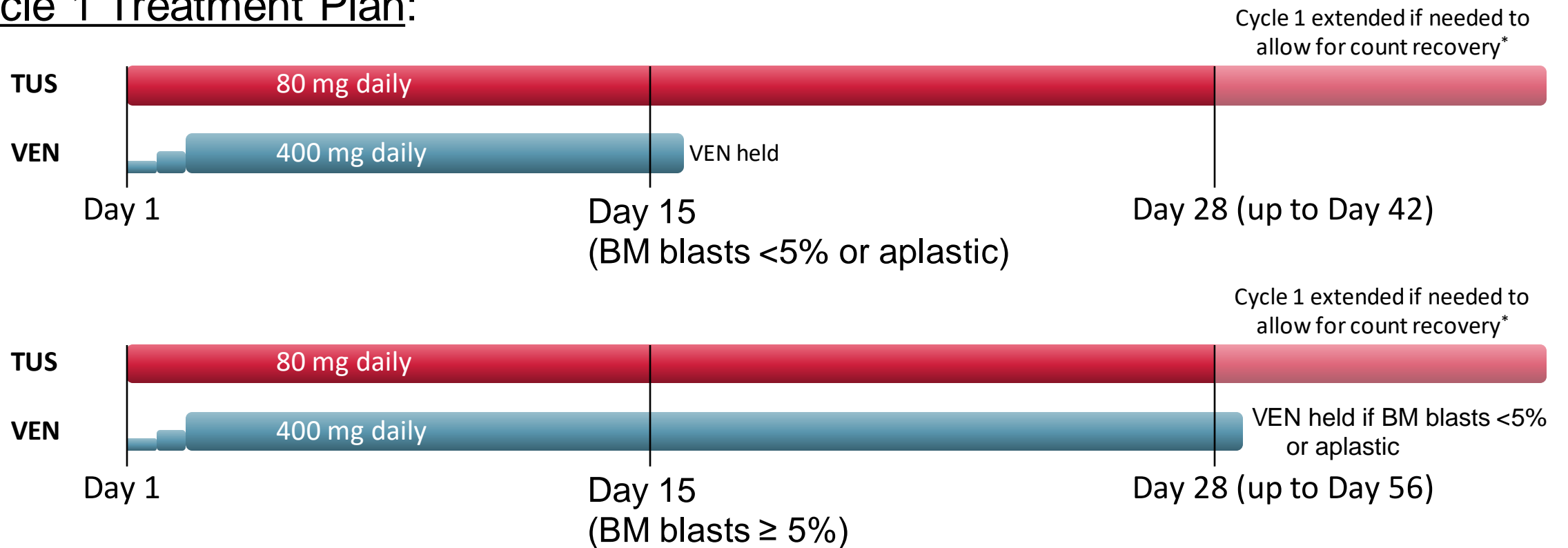
**APTIVATE Trial**

**TUS/VEN Expansion Trial in R/R AML**

# TUS/VEN Phase 1/2 Global Study (APTIVATE Trial)

**Tuspetinib (80 mg) + Venetoclax (400 mg) Doublet Study**  
(n=49 patients dosed as of Oct 23, 2023) (n=31 evaluable, 32 ongoing)

## Cycle 1 Treatment Plan:



\* GCSF permitted anytime per protocol

# TUS/VEN Patient Baseline Characteristics: Even More Treatment Experienced Primarily Older with Prior-VEN Failure

Patient Characteristics (n=49)	FLT3 <sup>MUT</sup>	FLT3 <sup>WT</sup>
Patient number n (%) <sup>1,2</sup>	<b>13</b>	<b>32</b>
<b>Median Age Years (Range)</b>	<b>74 (39-84)</b>	<b>68 (31-81)</b>
Female n (%)	7 (53.8%)	15 (46.9%)
Prior lines of therapy Mean (Range)	2.9 (1-5)	2.4 (1-7)
<b>Prior-VEN</b>	<b>11 (84.6%)</b>	<b>21 (65.6%)</b>
<b>Prior FLT3 Inhibitor</b>	<b>11 (84.6%)</b>	<b>3 (9.4%)</b>
Prior Cytotoxic chemotherapy	7 (53.8%)	20 (62.5%)
Prior HMAs	10 (76.9%)	21 (65.6%)
Prior HSCT	4 (30.8%)	7 (21.9%)

← Population included FLT3<sup>WT</sup> & FLT3<sup>MUT</sup>

← Older than single agent trial  
 • Median age > 68 years

← More Prior-VEN than single agent trial  
 • Prior-VEN represented majority of patients and increased as trial proceeded

← 85% failed Prior-FLT3i

<sup>1</sup>Four patients had an indeterminant status for FLT3

<sup>2</sup>Data cut Oct 23 2023

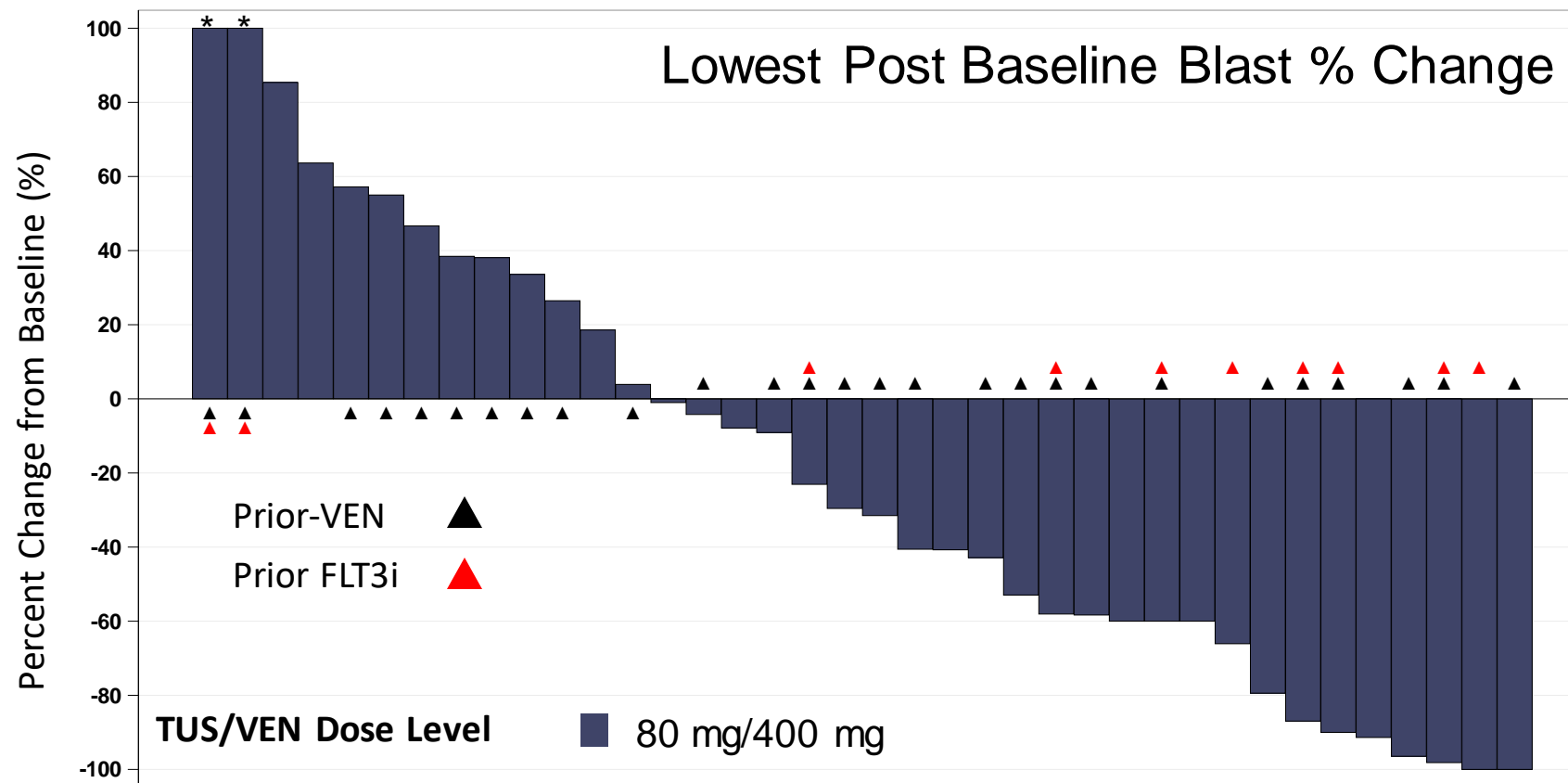
# TUS/VEN Safety: Favorable Safety and Tolerability

No new or unexpected safety signals observed with the TUS/VEN, no drug related AE of QTc prolongation, no observed differentiation syndrome, no drug related deaths

All TEAEs (n=49)	TUS/VEN n (%)
Any	41 (83.7%)
<b>Most Frequent TEAEs (≥10% of patients)</b>	
Febrile neutropenia	12 (24.5%)
Nausea	11 (22.4%)
Diarrhoea	6 (12.2%)
Hypokalaemia	6 (12.2%)
Fatigue	6 (12.2%)
Anaemia	5 (10.2%)
Platelet count decreased	5 (10.2%)
White blood cell count decreased	5 (10.2%)
≥ Grade 3	31 (63.3%)
SAEs	26 (53.1%)
Leading to treatment termination	1 (2%)
Leading to death	2 (4.1%)

Treatment Related AEs (n=49)	TUS/VEN n (%)	
	Related to TUS	Related to VEN
Any	24 (49.0%)	22 (44.9%)
<b>Most Frequent Related TEAEs (≥10% of patients)</b>		
Nausea	8 (16.3%)	4 (8.2%)
<b>Grade ≥ 3 (N ≥ 2 patients)</b>	16 (32.7%)	15 (30.6%)
Neutrophil count decreased	3 (6.1%)	3 (6.1%)
Febrile neutropenia	3 (6.1%)	2 (4.1%)
Platelet count decreased	2 (4.1%)	3 (6.1%)
White blood cell count decreased	2 (4.1%)	2 (4.1%)
Fatigue	2 (4.1%)	2 (4.1%)
SAEs	7 (14.3%)	7 (14.3%)
Leading to death	0 (0%)	0 (0%)

# TUS/VEN: Bone Marrow Blast Decreases Achieved in Both VEN-Naïve and Prior-VEN R/R AML



Blast percent change was calculated as  $100 \times (\text{the lowest post-baseline bone marrow blast} - \text{baseline bone marrow blast}) / \text{baseline bone marrow blast}$ .

\*Patients with blast percent change  $\geq 100\%$  are shown as 100%.

Only patients who reported both baseline and any post-baseline bone marrow blast results are included in the figure.

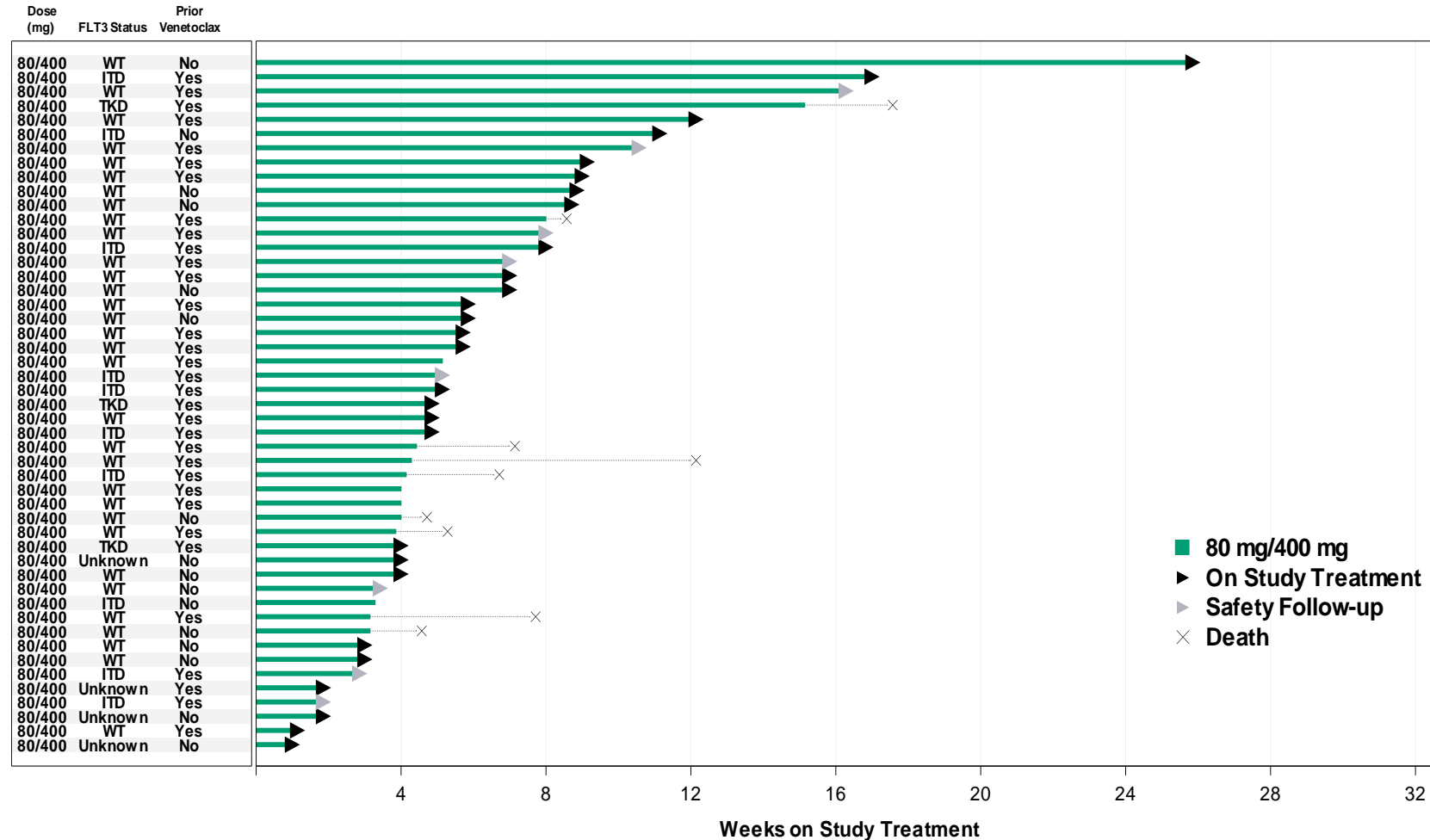
Red triangle indicates patients who received prior FLT3 inhibitors before starting tuspetinib, including gilteritinib, midostaurin, and/or sorafenib

Data cut Oct 23, 2023

# TUS/VEN Swimmer Plot of Patient Status by Weeks on Study Treatment

Overview of Time on Study and Early Patient Follow-up

- As of 23 Oct 2023 data cut:
  - 49 patients dosed with TUS/VEN
  - 36 evaluable patients completed C1 or discontinued prior to C1
  - 13 too early to assess – in C1 and still on study
  - 81% failed Prior-VEN
- Rapid accrual over prior 2 months
- Short median follow up time of only 1.6 months
- Majority of patients remain on treatment



<sup>1</sup>Data cut Oct 23, 2023

# TUS/VEN Active in Both VEN-Naïve and Prior-VEN R/R AML: Evaluable Patient Population (APTIVATE Ongoing)

## Key Findings

- TUS/VEN is active across broad populations of R/R AML
- TUS/VEN is active in FLT3<sup>WT</sup>, representing ~70% of AML patients
- TUS/VEN retains activity in difficult-to-treat Prior-VEN & Prior-FLT3i AML populations

## Composite Complete Remission (CRc) in Evaluable Patients<sup>1</sup>

FLT3 Status	ALL	VEN-Naïve	VEN-Prior	FLT3i-Prior
ALL	<b>25% (9/36)</b>	<b>43% (3/7)</b>	<b>21% (6/29)</b>	
FLT3 <sup>WT</sup>	20% (5/25)	33% (2/6)	16% (3/19)	
FLT3 <sup>MUT</sup>	<b>36% (4/11)</b>	<b>100% (1/1)</b>	<b>30% (3/10)</b>	<b>44% (4/9)</b>

<sup>1</sup>Data cut Oct 23, 2023

## Patient Status

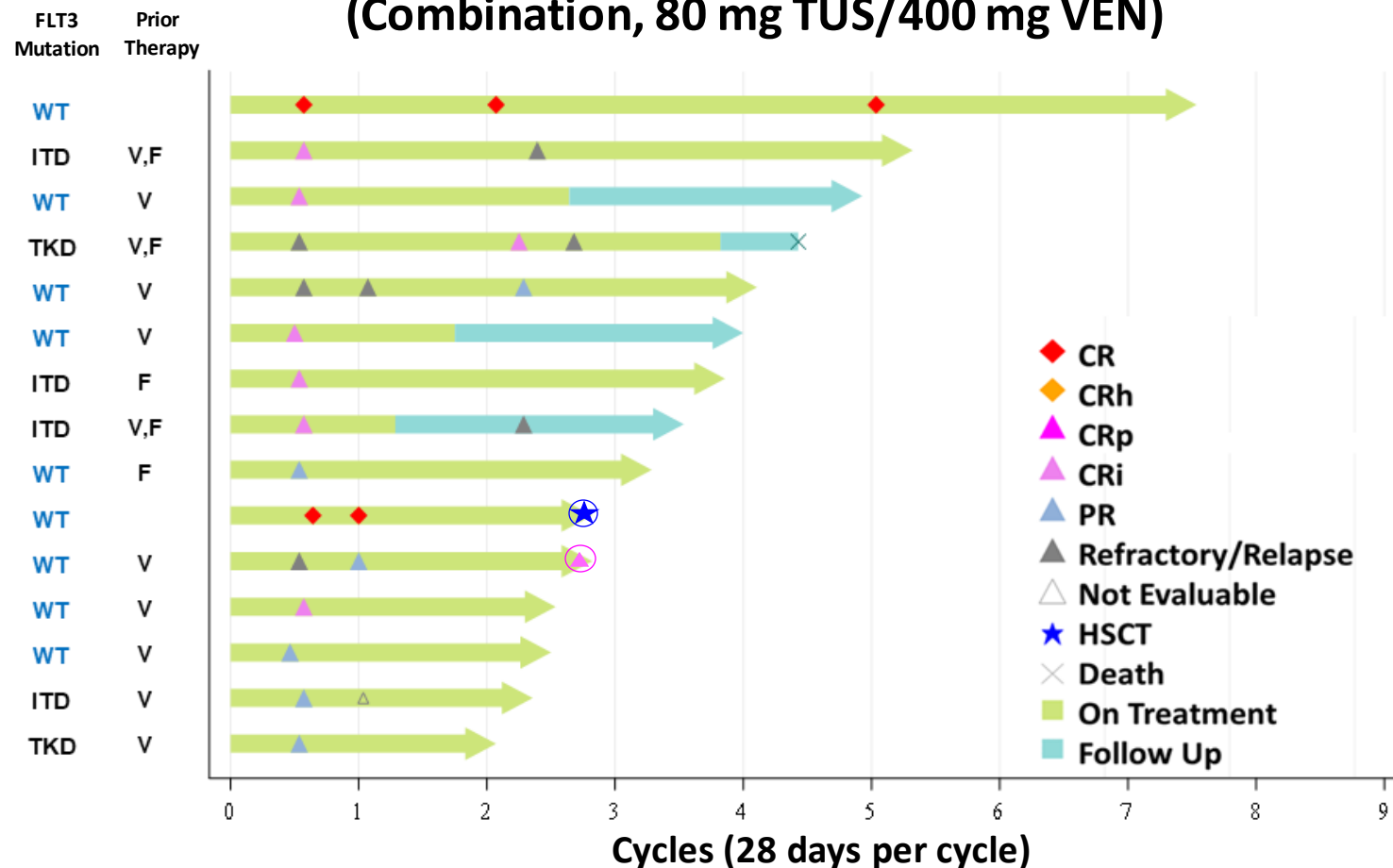
**49** : Patients dosed with TUS/VEN  
**36** : Evaluable patients who completed C1 or discontinued prior to C1  
*81% Prior-VEN failure*  
**13** : Too early to assess (in C1 and still on study)

# TUS/VEN Treats Both VEN-Naïve and Prior-VEN R/R AML

## TUS/VEN Responder Analysis

- Responses in heavily pretreated R/R AML Patients
- Responses in FLT3<sup>WT</sup> & FLT3<sup>MUT</sup> AML
- Notable responses in difficult-to-treat Prior-VEN (V) failure AML
- Most patients achieving a response remain on treatment
- Responses beginning to mature and bridge to HSCT

### Patients Who Achieved Clinical Response<sup>1</sup> (Combination, 80 mg TUS/400 mg VEN)



'V' indicates Prior-Venetoclax  
'F' indicates prior FLT3 inhibitor

<sup>1</sup>Data cut Oct 23, 2023

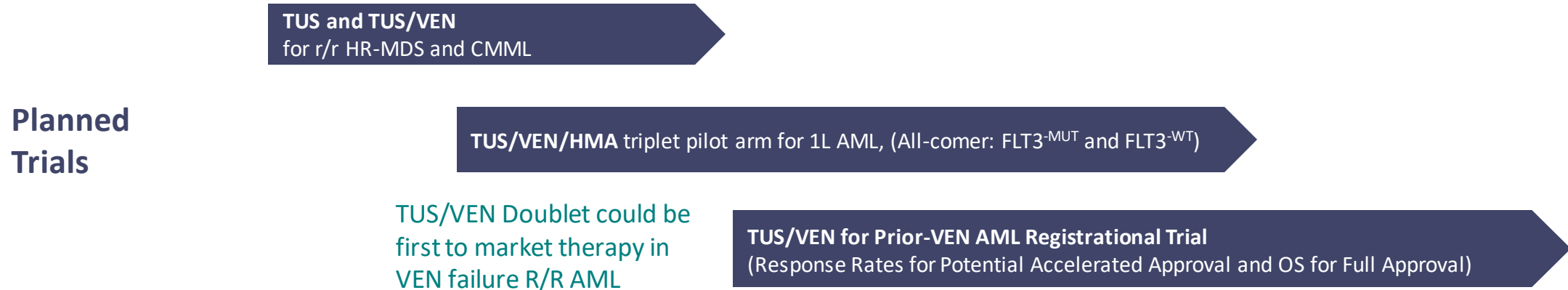
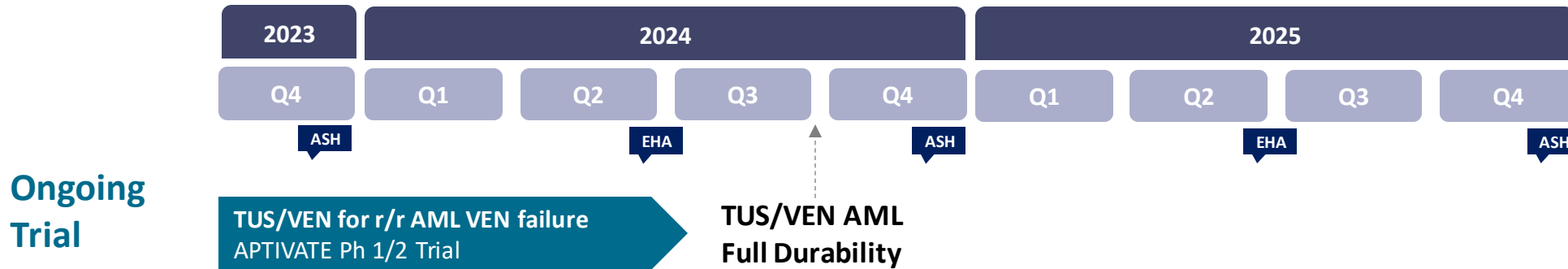


# Summary of Tuspetinib Clinical Findings

- **TUS single agent well tolerated and more active in VEN-naïve R/R AML**
  - Active in FLT3<sup>WT</sup> AML and FLT3<sup>MUT</sup> AML with prior FLT3i
  - TUS RP2D 80mg: Overall CR/CR<sub>h</sub>=36% | FLT3<sup>MUT</sup> CR/CR<sub>h</sub>=50% | FLT3<sup>WT</sup> CR/CR<sub>h</sub>=25%
- **TUS/VEN doublet well tolerated and active in broad range of R/R AML**
  - TUS/VEN active in **FLT3<sup>WT</sup>** AML and **FLT3<sup>MUT</sup>** AML with prior FLT3i
  - TUS directly and indirectly **targets VEN-resistance** mechanisms
  - TUS/VEN active in VEN-Naïve and **Prior-VEN R/R AML**
- **TUS/VEN provides a unique opportunity to treat Prior-VEN AML (FLT3<sup>MUT</sup> and FLT3<sup>WT</sup>) in the R/R setting**
- **TUS/VEN/HMA triplet will be studied in 1L newly diagnosed AML patients unfit for chemotherapy with or without FLT3-mutations**
- **TUS is ideal for combination therapy to treat R/R AML and 1L AML, as well as hr-MDS, and an estimated deliver commercial forecast >\$3 billion annually by 2035<sup>1</sup>**

# Tuspetinib Development Plan

\$10M financing combined with the \$4M 2<sup>nd</sup> tranche from Hanmi extends cash runway to the end of Q3/2024 and delivers data from TUS/VEN Doublet in AML by 2Q/2024.





THANK YOU

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