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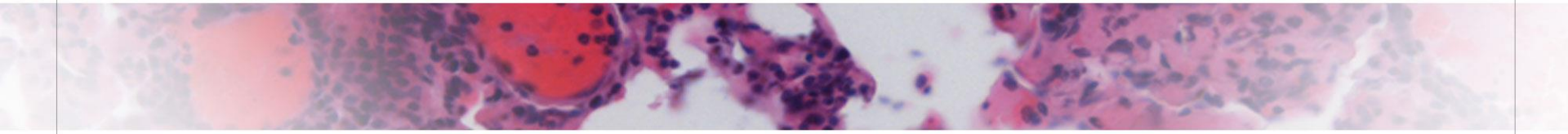

# Tuspetinib Oral Myeloid Kinase Inhibitor Safety and Efficacy As Monotherapy and Combined with Venetoclax in Phase 1/2 Trial of Patients with Relapsed or Refractory (R/R) Acute Myeloid Leukemia (AML)

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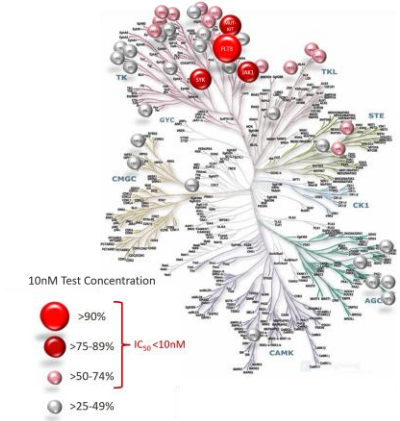
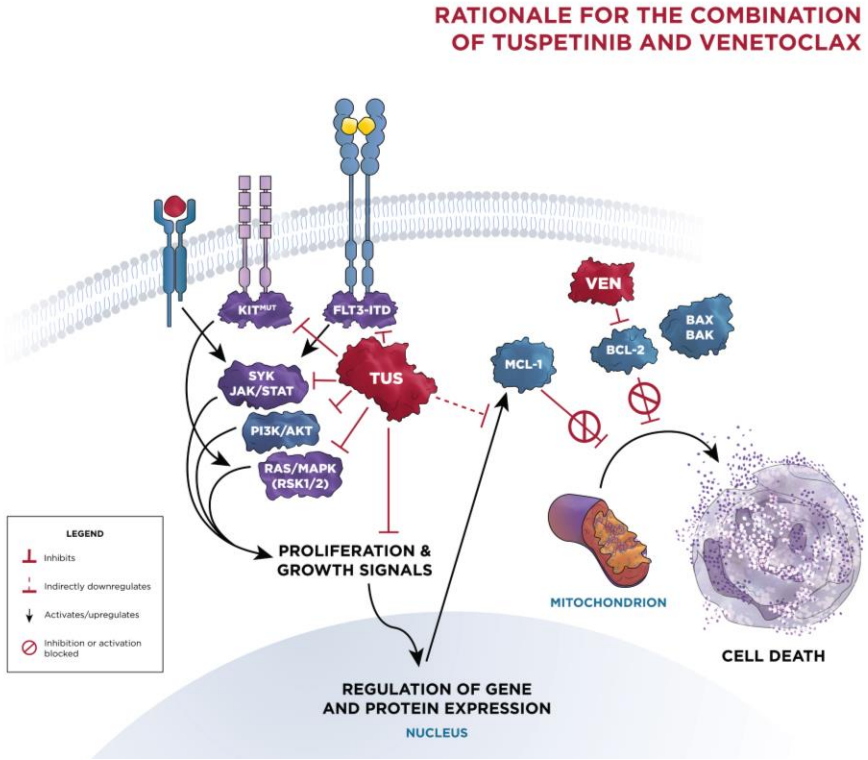
# Tuspetinib (TUS) Targets AML Oncogenic Signaling and Venetoclax Resistance Mechanisms

**Multi-kinase inhibitor suppresses**

- **SYK**, **FLT3$^{MUT/WT}$**, **KIT$^{MUT}$** (not KIT-WT)
- **JAK1/2** in the JAK/STAT pathway
- **RSK2** in the RAS/MAPK pathway
- **MCL1** expression (indirect suppression)



# 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[1]
- $CR_c = CR + CR_h + CR_p + CR_i$ (incl MLFS)
- 91 patients dosed with TUS single agent
- Therapeutic window 80 – 160 mg
- RP2D = 80 mg once daily

[1]Data cut Oct 23, 2023

**Dose Escalation + Exploration + Expansion**

| | Total n | VEN-Naïve n | Prior-VEN[2] n |
|---|---|---|---|
| **Cohort 1:** 20 mg QD | 2 | 1 | 1 |
| **Cohort 2:** 40 mg QD | 17 | 8 | 9 |
| **Cohort 3: 80 mg QD** | 20 | 14 | 6 |
| **Cohort 4: 120 mg QD** | 32 | 6 | 26 |
| **Cohort 5: 160 mg QD** | 16 | 8 | 8 |
| **Cohort 6:** 200 mg QD | 4 | 1 | 3 |

**71% Prior-VEN**

[2]Proportion of Prior-VEN patients increased over time

# Tuspetinib Single Agent Baseline Characteristics: Representative of Current R/R AML Patient Population

| Patient Characteristics (n=91) | FLT3$^{MUT}$ | FLT3$^{WT}$ |
|---|---|---|
| Patient number [1] | n=34 | n=56 |
| Age Years, Median (Range) | 60 (21-84) | 65.5 (18-83) |
| Female, n (%) | 14 (41.2%) | 24 (42.9%) |
| Lines prior therapy, Mean (Range) | 3.3 (1-11) | 2.4 (1-6) |
| Prior-VEN | 19 (55.9%) | 33 (58.9%) |
| 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%) |

[1]One patient had an indeterminant status for FLT3

# Tuspetinib Single Agent Well Tolerated

No treatment related $QT_c$ prolongation, CPK elevations, differentiation syndrome, non-hematologic SAEs, or deaths

| All TEAEs (n=91) | n (%) |
|---|---|
| Any | 87 (95.6%) |
| Most Frequent TEAEs (>12% of patients) | |
| Pneumonia | 30 (33.0%) |
| Nausea | 18 (19.8%) |
| Diarrhea | 17 (18.7%) |
| Pyrexia | 17 (18.7%) |
| Alanine aminotransferase increased | 13 (14.3%) |
| Hypokalaemia | 12 (13.2%) |
| Epistaxis | 11 (12.1%) |
| Decreased appetite | 11 (12.1%) |
| 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%) |

| Treatment Related AEs (n=91) | n (%) |
|---|---|
| Any | 29 (31.9%) |
| Most Frequent Related TEAEs (>10% of patients) | |
| Diarrhea | 10 (11.0%) |
| Grade ≥ 3 (N≥2 patients) | 9 (9.9%) |
| Neutrophil count decreased | 2 (2.2%) |
| White blood cell count decreased | 2 (2.2%) |
| Muscle weakness | 2 (2.2%) |
| SAEs | 1 (1.1%) |
| Leading to death | 0 (0.0%) |
| Dose Limiting Toxicity (DLT) | 1 (1.1%) |

***** 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 Single Agent at Therapeutic Doses (**80-160 mg, n=68**): More Active in VEN-Naive R/R AML Patients

## TUS Response Rate Analysis (ITT)

**TUS active in FLT3$^{WT}$ and FLT3$^{MUT}$ AML**

**TUS $CR_c$ in VEN-Naïve AML (80-160mg)**

- **29% $CR_c$** in all patients (n=8/28)
- **42% $CR_c$** in FLT3$^{MUT}$ (n=5/12)
- **19% $CR_c$** in FLT3$^{WT}$ (n=3/16)

**TUS CR/$CR_h$ in VEN-Naïve AML at 80 mg RP2D:**

- **36% CR/$CR_h$** in all patients (n=5/14)
  - 50% CR/$CR_h$ in FLT3$^{MUT}$ (n=3/6)
  - 25% CR/$CR_h$ in FLT3$^{WT}$ (n=2/8)

## Composite Complete Remission ($CR_c$)

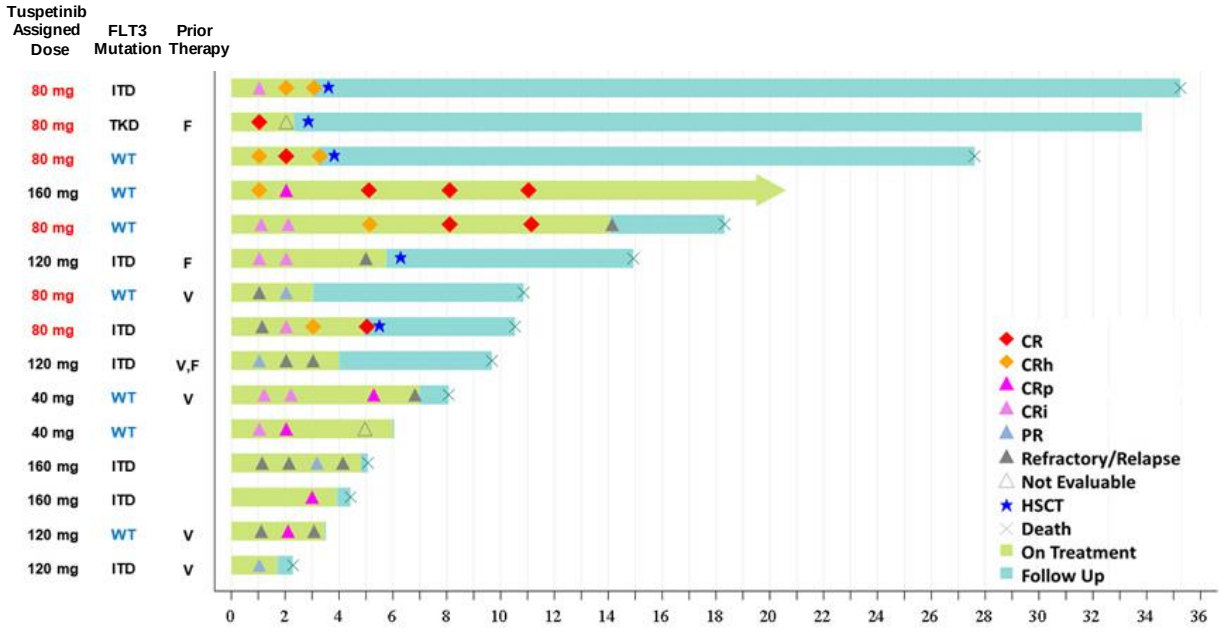
| Subgroups | % $CR_c$ (n=68) |
|---|---|
| **Overall** | 13% (9/68) |
| VEN Naïve | **29% (8/28)** |
| Prior VEN | 3% (1/40) |
| **FLT3-Mutated** | 18% (5/28) |
| VEN Naïve | **42% (5/12)** |
| Prior VEN | 0% (0/16) |
| Prior FLT3i | 14% (2/14) |
| **FLT3-Unmutated (WT)** | 10% (4/39) |
| VEN Naïve | **19% (3/16)** |
| Prior VEN | 4% (1/23) |

# TUS Single Agent Efficacy: Clinical Responses

## TUS Responder Analysis

- Responses in **FLT3$^{WT}$** and **FLT3$^{MUT}$** (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**

### Patients Achieving Clinical Responses (TUS Single Agent)

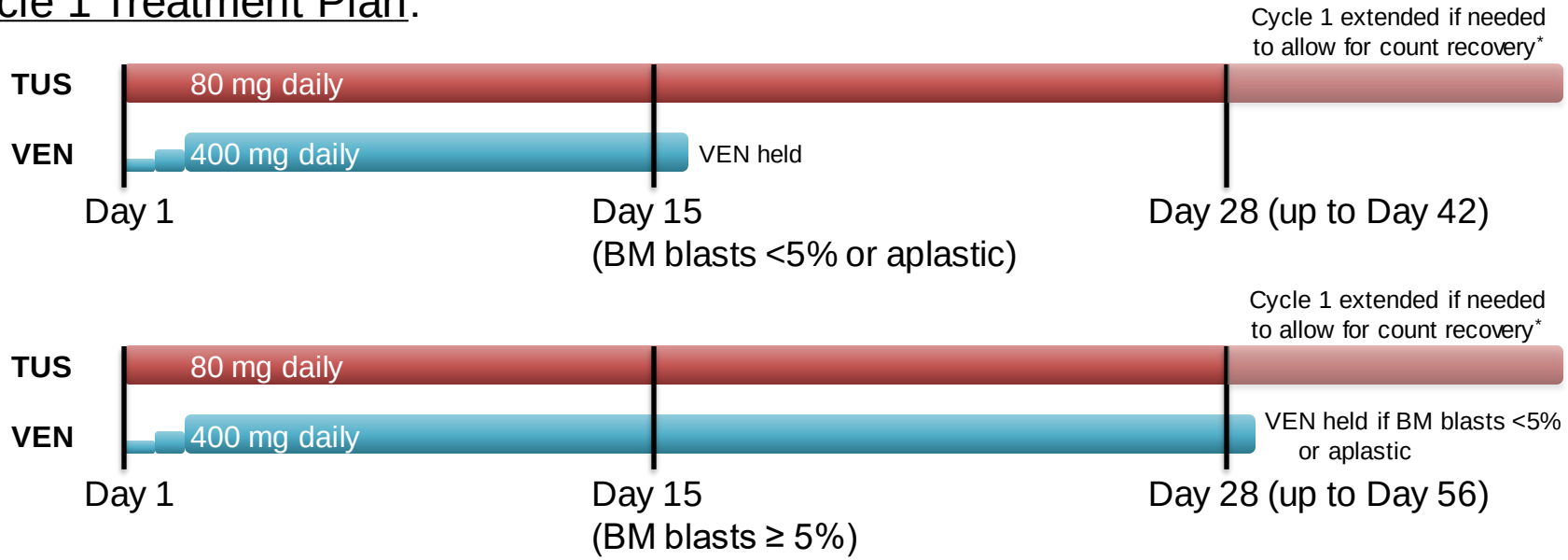



'**V**' indicates Prior-Venetoclax
'**F**' indicates prior FLT3 inhibitor

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

**Tuspetinib (80 mg) + Venetoclax (400 mg) Doublet Study**
**(n=49 patients dosed as of Oct 23, 2023) (n=36 evaluable, 32 ongoing)**

## Cycle 1 Treatment Plan:




*GCSF permitted anytime per protocol

# TUS/VEN Patient Baseline Characteristics: Older Heavily Prior-VEN and Prior FLT3i Exposed

| Patient Characteristics (n=49) | FLT3$^{MUT}$ | FLT3$^{WT}$ |
|---|---|---|
| Patient number [1,2] | n=13 | n=32 |
| Age Years, Median (Range) | 74 (39-84) | 68 (31-81) |
| Female, n (%) | 7 (53.8%) | 15 (46.9%) |
| Prior lines of therapy, Mean (Range) | 2.9 (1-5) | 2.4 (1-7) |
| Prior-VEN | 11 (84.6%) | 21 (65.6%) |
| Prior FLT3 Inhibitor | 11 (84.6%) | 3 (9.4%) |
| 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%) |

[1]Four patients had an indeterminant status for FLT3

[2]Data cut Oct 23, 2023

# TUS/VEN Safety: Favorable Tolerability Profile

| All TEAEs (n=49)[1] | TUS/VEN n (%) |
|---|---|
| Any | 41 (83.7%) |
| Most Frequent TEAEs (≥10% of patients) | |
| 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%) |

[1]Data cut Oct 23, 2023

| Treatment Related AEs (n=49) | TUS/VEN n (%) | |
|---|---|---|
| | Related to TUS | Related to VEN |
| Any | 24 (49.0%) | 22 (44.9%) |
| Most Frequent Related TEAEs (≥10% of patients) | | |
| Nausea | 8 (16.3%) | 4 (8.2%) |
| Grade ≥ 3 (N ≥2 patients) | 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 Active in Both VEN-Naïve and Prior-VEN R/R AML: Evaluable Patient Population (APTIVATE Ongoing), N=49

## Key Findings

- TUS/VEN is active across broad populations of R/R AML
- TUS/VEN is active in FLT3$^{WT}$, representing ~70% of AML patients
- TUS/VEN has activity in difficult-to-treat Prior-VEN AML population

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

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

[1]Data cut Oct 23, 2023

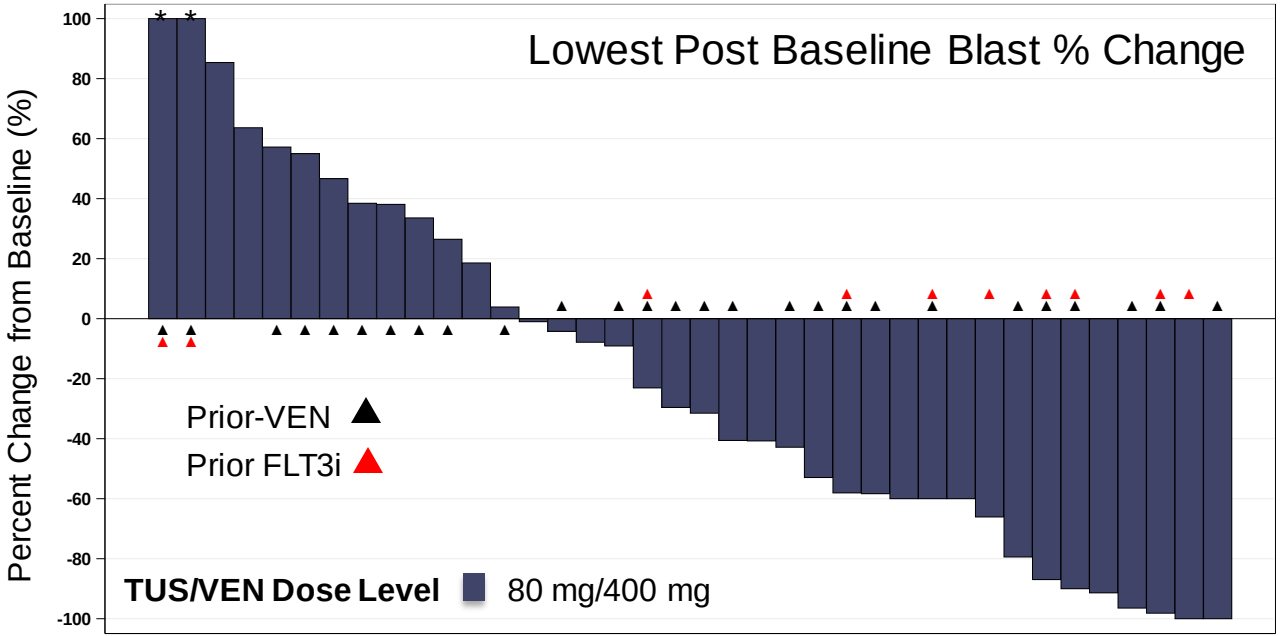
## Patient Status

**49** : Patients dosed with TUS/VEN

**36** : Evaluable patients who completed C1 or discontinued prior to C1

**13** : Too early to assess (in C1 and still on study)

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




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.

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

Data cut Oct 23, 2023

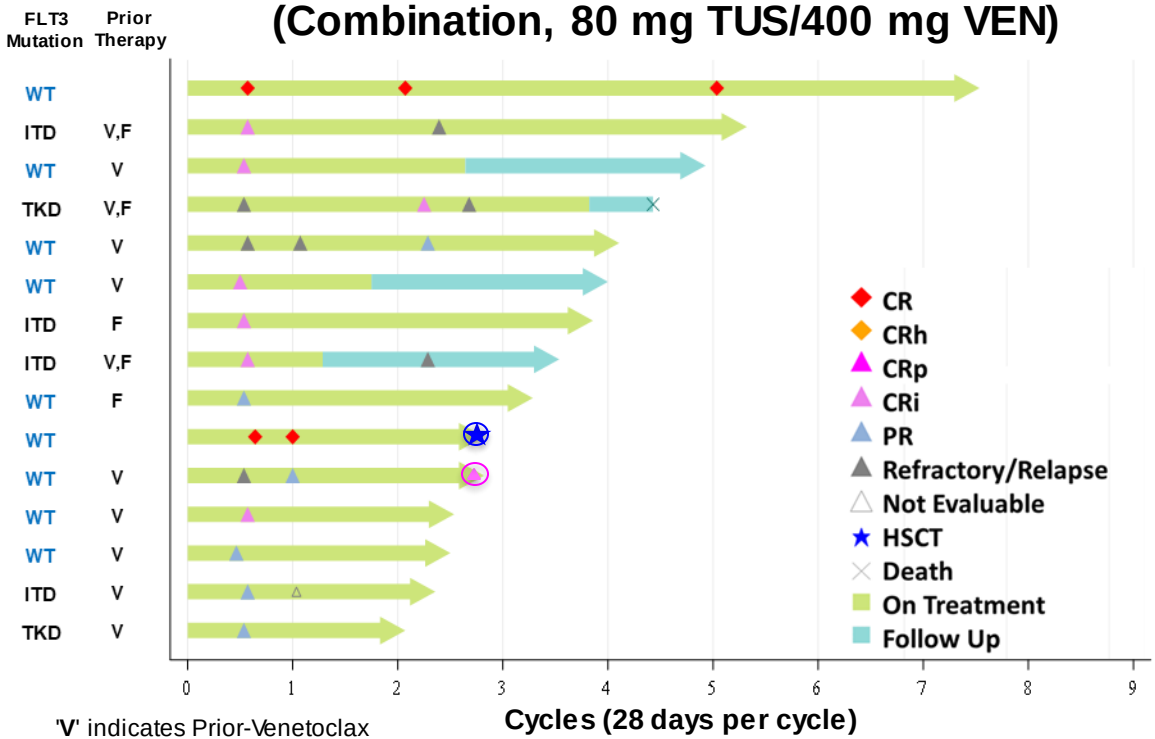
# TUS/VEN Treats Both VEN-Naïve and Prior-VEN R/R AML

## TUS/VEN Responder Analysis

- Responses in heavily pretreated R/R AML Patients
- Responses in $FLT3^{WT}$ & $FLT3^{MUT}$ 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

[1]Data cut Oct 23, 2023

**Patients Who Achieved Clinical Response[1] (Combination, 80 mg TUS/400 mg VEN)**




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

# CONCLUSIONS

- **TUS single agent is well tolerated and more active in VEN-naïve R/R AML**
  - TUS is active in **FLT3$^{WT}$** AML and **FLT3$^{MUT}$** AML with prior FLT3i
  - TUS RP2D 80mg: Overall CR/CR$_h$=36% | FLT3$^{MUT}$ CR/CR$_h$=50% | FLT3$^{WT}$ CR/CR$_h$=25%
- **TUS/VEN doublet is well tolerated and active in broad populations of R/R AML**
  - TUS/VEN is active in **FLT3$^{WT}$** AML and **FLT3$^{MUT}$** AML with prior FLT3i
  - TUS directly and indirectly **targets VEN-resistance** mechanisms
  - TUS/VEN is active in VEN-Naïve and **Prior-VEN R/R AML**
- **TUS/VEN may provide an important opportunity to treat Prior-VEN AML, including both FLT3$^{MUT}$ and FLT3$^{WT}$ AML in the R/R setting**
- **TUS/VEN/HMA triplet will be studied in 1L newly diagnosed FLT3$^{MUT}$ and FLT3$^{WT}$ AML patients ineligible for induction chemotherapy**

Data cut Oct 23, 2023

# Acknowledgements

**We are grateful to the clinical trial team, 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