Tuspetinib clinical strategy as a triplet frontline therapy to treat newly diagnosed AML

Earnings Call Presentation
14 May 2024

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PRECISION ONCOLOGY FOR THERAPIES OF TOMORROW

Tuspetinib
Aptose's Lead Clinical Asset

- **TUS+VEN+HMA triplet** is being developed as frontline therapy to treat newly diagnosed AML
- Bolting TUS on VEN+HMA Frontline Standard of Care
- Expect clinical data from our frontline triplet 2H 2024

AML Highly Aggressive Cancer of Blood and Bone Marrow

Unmet Need for Superior Frontline (1L) Therapy in AML

- Progress made with **VEN+HMA (SOC)**
  - **Response rates** too low and **survival** too short
  - **Resistance to VEN** compromises subsequent R/R therapies
- **A 3rd agent** is needed to boost responses with VEN+HMA SOC
- Current 3rd agents in development only address specific genetic subtypes and are limited by toxicities

Tuspetinib Opportunity | Addressing 1L Unmet Needs

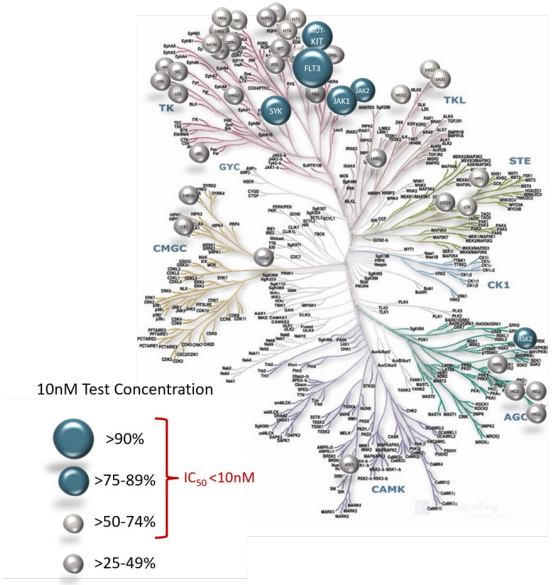
- **TUS** is a natural **3rd agent** for addition to VEN and HMA
- **TUS** has **excellent safety** in combination with VEN and HMA
- **TUS increases efficacy** in combination with VEN and HMA
- **TUS** has **broad scope** of activity across AML genetic subgroups
- **TUS targets known VEN resistance** mechanisms to minimize resistance

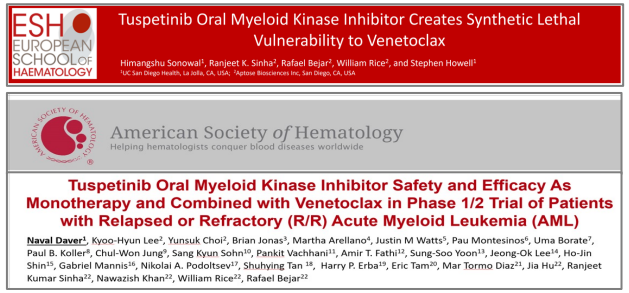
TUS+VEN+HMA … creating a new SOC addressing safety, scope, and survival needs of newly diagnosed AML patients

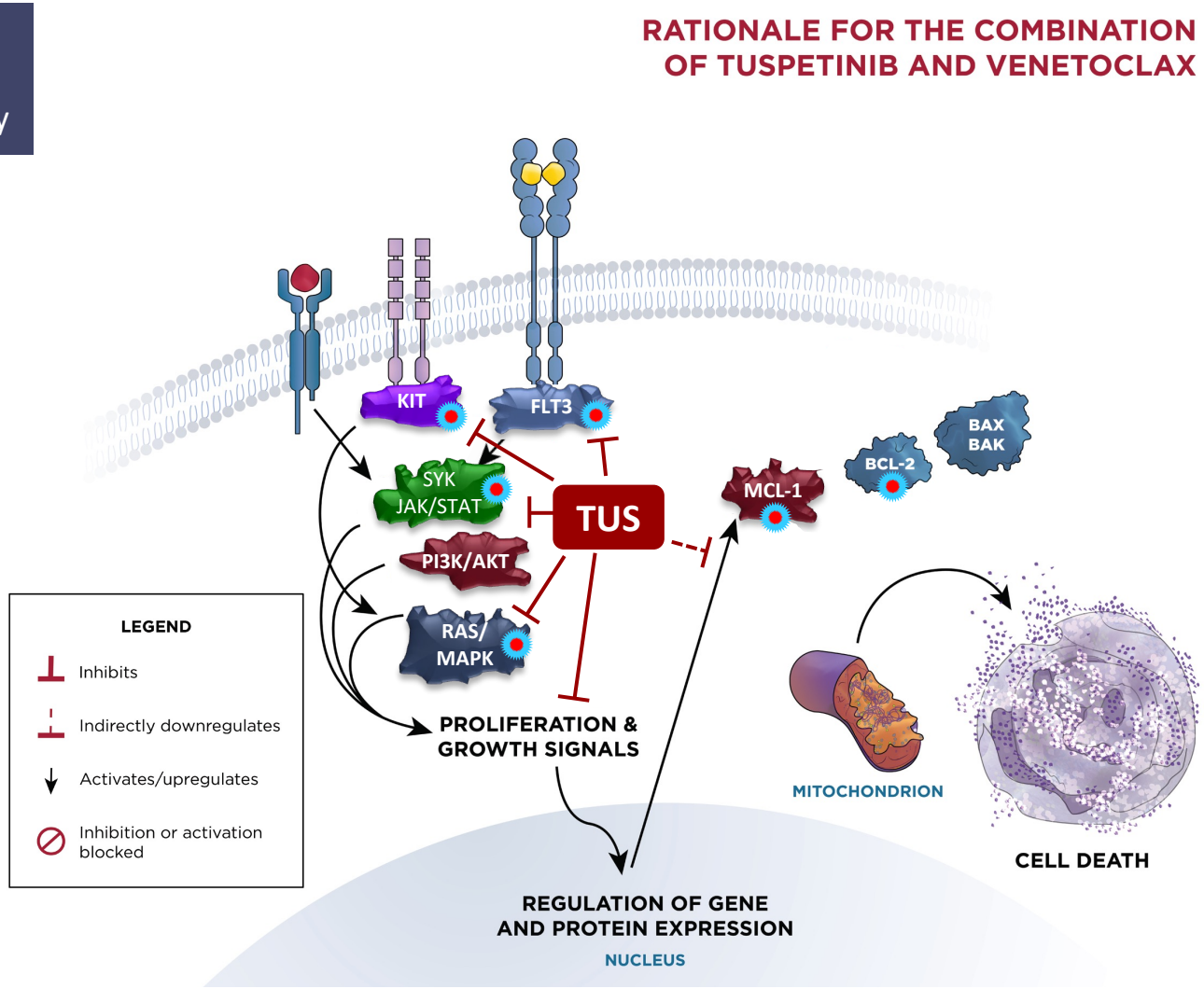
TUS : Tuspetinib ; **VEN** : Venetoclax ; **HMA** : Hypomethylating agent
AML : Acute Myeloid Leukemia ; **SOC** : Standard of Care

TUS Targets Known VEN-Resistance Mechanisms and May Minimize Drug Resistance

Tuspetinib suppresses:
SYK, KIT^{MUT}, FLT3$^{MUT/WT}$, JAK/STAT, RAS/MAPK oncogenic signaling directly and MCL-1 anti-apoptotic signaling indirectly

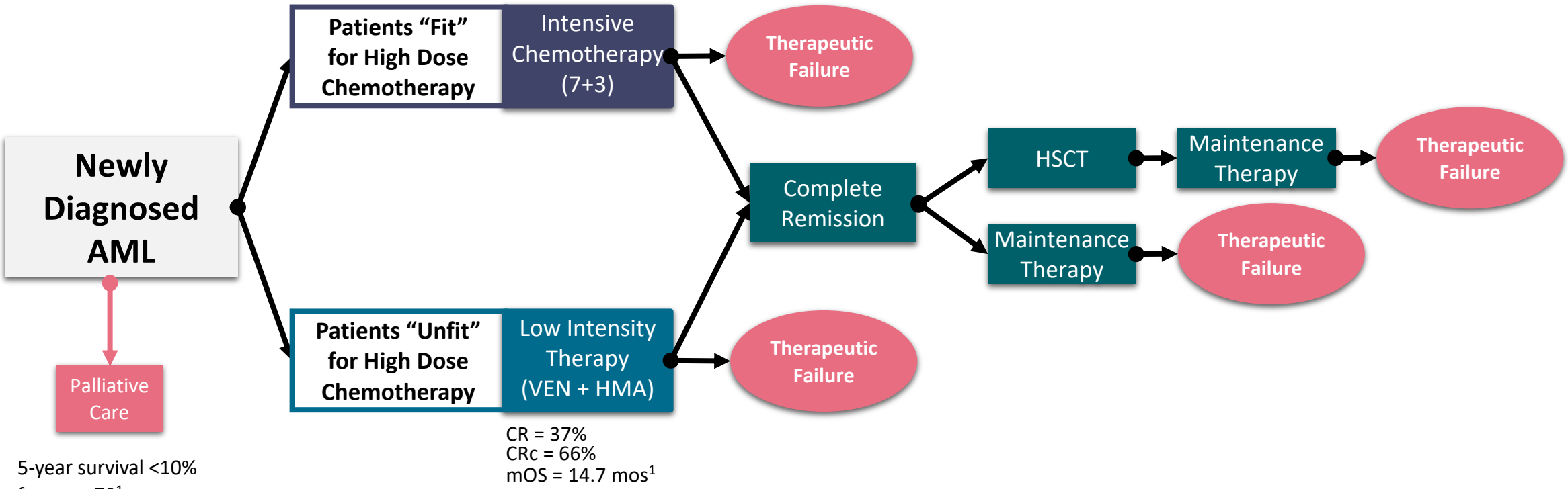






AML Patient Journey | 1L Therapy High-Level Overview

Current Standard-of-Care (SOC) treatment options leading to therapeutic failure……



1 Pei, Cancer Discos 2020); DiNardo, Blood 2020); (Maiti et al., Haematologica 2021); (Mannis et al., Leukemia Research 2023); Bewersforf et al., Leukemia Research 2022; 122: 106942

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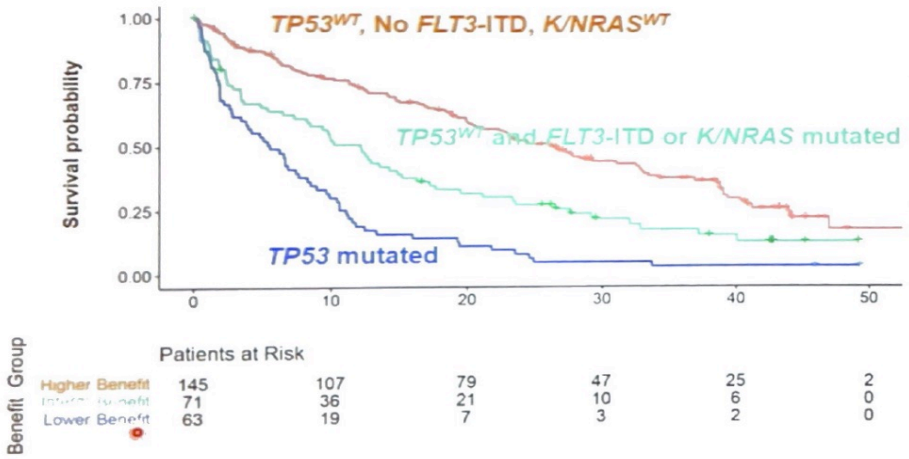
TUS+VEN+HMA May Increase Survival in High-risk Frontline (1L) Newly Diagnosed AML Patients with Adverse Mutations

- VEN+AZA combo delivers less benefit in "high-risk AML" with $FLT3^{ITD}$, RAS^{MUT}, and $TP53^{MUT}$
- **Tuspetinib retains activity in high-risk AML with the adverse FLT3, RAS and TP53 mutations**
- **Tuspetinib added to VEN+AZA (HMA) may uniquely benefit the most challenging 1L populations**

Frontline AML patients receiving VEN+AZA separate into three efficacy subgroups by OS benefit

- First a higher benefit group was identified, with a median OS > 24 months
- Subsequently a lower benefit group was determined, with a median OS < 6 months
- Patients fitting neither criteria were categorized as the intermediate benefit group, with a median OS of 12 months



Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	**26.51** (20.24, 32.69)
Intermediate Benefit	71	57	**12.12** (7.26 – 15.15)
Lower Benefit	63	61	**5.52** (2.79 – 7.59)

- **Majority of patients in the Ven+Aza arm are in the higher benefit group: 52% (145/279)**
- The remainder of the patients are distributed equally between the intermediate and lower benefit groups: 25.4% (71/279) and 22.6% (63/279), respectively

Dohner et al. ASH 2022

Greatest Need in AML Therapy Today

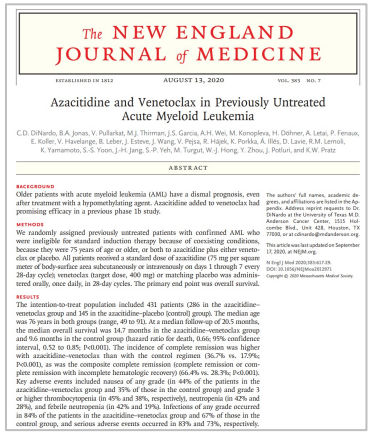
"We are making progress but are not curing our patients[1]."

Annual new cases in U.S. ≈ 21,000[2] | Median age at diagnosis 68[2]
Annual deaths in U.S. ≈ 11,200[2] | 5-yr survival ≈ 30% in Adults[2] | 5-yr Survival 9% for Age >65[2]

Age[2]	5-year survival rate
Children < 14	65-70%
Ages 15 to 34	52%
Ages 35 to 54	37%
Ages 55 to 64	20%
Ages 65 to 74	9%

Frontline therapies are making progress but leave substantial room for improvement

- Younger "Fit" patients achieve >50% CR, but only 30-50% of patients are "Fit" and many relapse[3]
- Older "Unfit" patients achieve improved efficacy with *VEN+HMA doublet* but many relapse
  - VEN+HMA(AZA): CR = 37%, CR/CRi = 66%, median OS = 14.7 months[4]
- Patients with adverse FLT3, N/KRAS, and TP53 mutations correlated with poor response/outcomes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Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

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ABSTRACT

BACKGROUND
Older patients with acute myeloid leukemia (AML) have a dismal prognosis, even after treatment with a hypomethylating agent. Azacitidine added to venetoclax had promising efficacy in a previous phase 1b study.

METHODS
We randomly assigned previously untreated patients with confirmed AML who were ineligible for standard induction therapy because of coexisting conditions, because they were 75 years of age or older, or both to azacitidine plus either venetoclax or placebo. All patients received a standard dose of azacitidine (75 mg per square meter of body-surface area subcutaneously or intravenously on days 1 through 7 every 28-day cycle); venetoclax (target dose, 400 mg) or matching placebo was administered orally, once daily, in 28-day cycles. The primary end point was overall survival.

RESULTS
The intention-to-treat population included 431 patients (286 in the azacitidine–venetoclax group and 145 in the azacitidine–placebo [control] group). The median age was 76 years in both groups (range, 49 to 91). At a median follow-up of 20.5 months, the median overall survival was 14.7 months in the azacitidine–venetoclax group and 9.6 months in the control group (hazard ratio for death, 0.66; 95% confidence interval, 0.52 to 0.85; P<0.001). The incidence of complete remission was higher with azacitidine–venetoclax than with the control regimen (36.7% vs. 17.9%; P<0.001), as was the composite complete remission (complete remission or complete remission with incomplete hematologic recovery) (66.4% vs. 28.3%; P<0.001). Key adverse events included nausea of any grade (in 44% of the patients in the azacitidine–venetoclax group and 35% of those in the control group) and grade 3 or higher thrombocytopenia (in 45% and 38%, respectively), neutropenia (in 42% and 28%), and febrile neutropenia (in 42% and 19%). Infections of any grade occurred in 84% of the patients in the azacitidine–venetoclax group and 67% of those in the control group, and serious adverse events occurred in 83% and 73%, respectively.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. DiNardo at the University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 428, Houston, TX 77030, or at cdinardo@mdanderson.org.

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Current triplets can deliver better efficacy, but increased toxicity requires dose reductions

- Studies have shown upper ranges of response at CRc >90%
- Current 3rd agents with VEN+HMA have been more toxic, requiring dose reductions of all agents
- Current 3rd agents with VEN+HMA do not deliver broad activity across AML genotypes

Urgent need for safer and more effective 1L triplet therapies to improve outcomes for AML patients of all genetic subtypes

1 Catherine E. Lai, MD, MPH, of the University of Pennsylvania
2 NIH; Yale Medicine; American Cancer Society; NIH; Healthline
3 Kantarjian, Blood Canc J 2021
4 DiNardo, NEJM 2020; Pei, Cancer Discos 2020; DiNardo, Blood 2020; Maiti, Haematologica 2021; Mannis, Leukemia Research 2023; Bewersforf, Leukemia Research 2022

***CR** : Complete Remission ; **CRc** : composite Complete Remission ; **OS** : Overall Survival*

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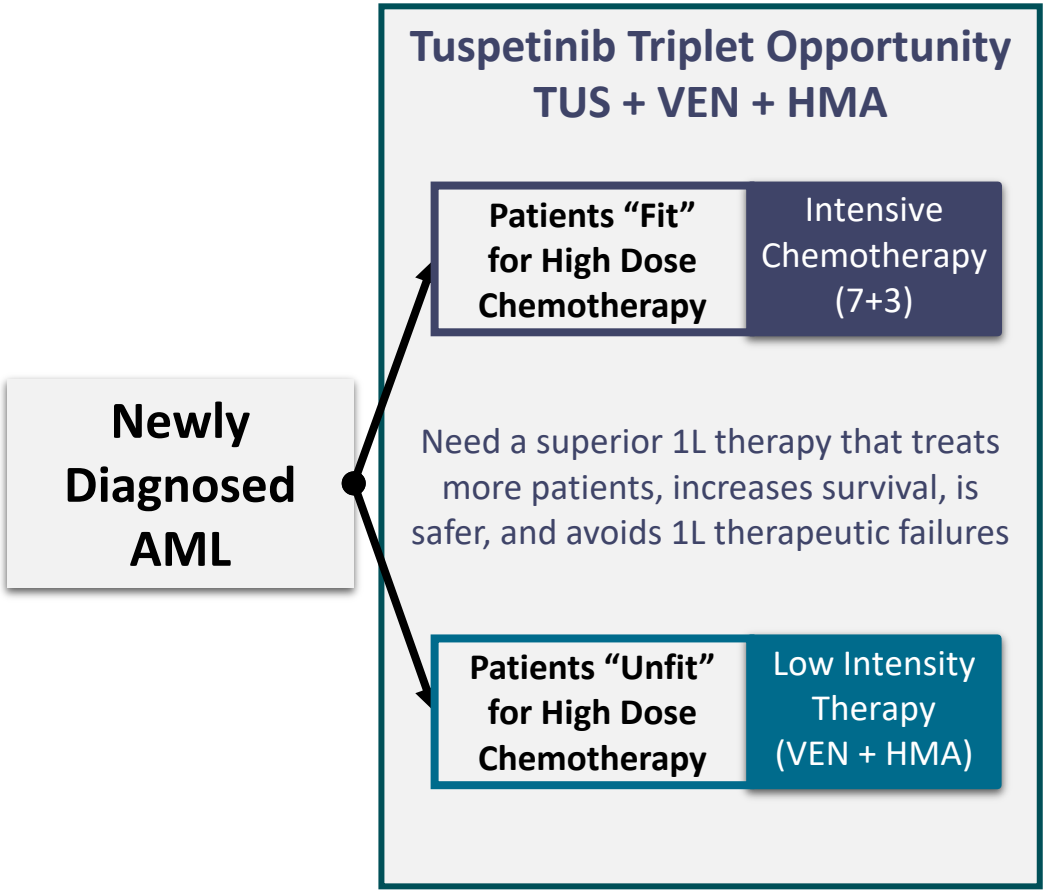
AML Patient Journey | 1L Therapy High-Level Overview

Tuspetinib-containing triplet can become a new 1L SOC to increase survival



Tuspetinib Frontline Triplet Opportunities

- **Potential to increase CR rates and survival of *FLT3 ^{MUT}* patients without the need to dose reduce SOC drugs**
- **TUS is the only agent being developed in combination with VEN+HMA for *FLT3 ^{WT}* AML patients (70% of AML)**
- **TUS is the only agent being developed in combination with VEN+HMA for high-risk AML subtypes with highly adverse *TP53 and N/KRAS mutations***
- **TUS+VEN+HMA expected to be a *safer* therapy for "unfit" patients than other triplets**

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New Paradigm in Frontline Therapy to Treat Newly Diagnosed AML

Deploying Triplet Combinations of Targeted Drugs | Building on VEN + HMA Backbone for 1L Therapy

Proof for Triplets : Addition of a 3rd Targeted Agent Boosts VEN+HMA Responses in 1L AML

Addition of gilteritinib (Gilt) FLT3i to VEN+HMA boosts CR rate 2.4X in newly diagnosed FLT3+ AML patients[1]

Problem: Current 3rd Agents for Triplets have Limitations

Gilt is not active in FLT3-Wildtype AML (70% of patients) and toxicities of Gilt with VEN+HMA require SOC dose reductions

Solution: TUS Fulfills Ideal Profile as 3rd Agent for 1L Triplet

TUS clean safety is ideal for addition to VEN+HMA backbone

- TUS shows no QTc prolongation, differentiation syndrome, muscle damage, or prolonged myelosuppression in remission
- TUS is not expected to require dose reductions or interruptions to SOC drugs

TUS clinical efficacy broader than Gilt and achieves CR in high-risk AML

- TUS achieves clinical responses in patients who failed prior therapy with Gilt
- TUS achieves clinical responses at lower and better-tolerated doses than Gilt
- TUS achieves clinical responses in $FLT3^{WT}$ patients (70% of AML population), a population not addressable by Gilt FLT3i

TUS preclinical safety, antitumor, mechanistic findings superior to Gilt

- TUS MOA targets VEN-resistance mechanisms and re-sensitizes cells to VEN
- TUS suppresses more oncogenic signaling pathways than Gilt and at lower doses
- TUS potent antitumor activity in animal models of human AML resistant to Gilt
- TUS+VEN & TUS+HMA safe and effective in animal models of human AML

1 Short et al. J Clin Oncol. 2024 Jan 26:JCO2301911. Epub ahead of print. PMID: 38277619.

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FDA Requirements for TUS to Enter Frontline Therapy in Newly Diagnosed AML

Tuspetinib has Met the FDA Requirements to Perform the Triplet Pilot Study

What Does the FDA Want? Begin in **R/R AML** with **TUS** and **TUS+VEN**	Aptose Completed
TUS Single Agent Study in R/R AML	
Thorough Single Agent **Dose Exploration**	√
Demonstrate Single Agent **Responses**	√
Demonstrate Single Agent **Safety**	√
Tus+Ven Doublet Study in R/R AML	
Characterize **Safety** of TUS+VEN Doublet	√
Characterize **PK** of TUS and VEN in Doublet	√

Next Step: TUS+VEN+AZA Triplet Pilot Study

Initiate dosing and collect data from
Triplet Pilot Study in Newly Diagnosed AML Patients

Protocol implemented and clinical sites being prepared

- Select optimal dose of TUS that allows for SOC dosing
- Characterize safety and mitigate myelosuppression
- Characterize activity in $TP53^{MUT}$ and $N/KRAS^{MUT}$
- Characterize activity in $FLT3^{MUT}$ and $FLT3^{UNMUT}$
- Characterize PK of TUS and VEN in triplet
- Determine CR, CRh, CRc, MRD rates
- Characterize duration of dosing
- Characterize mOS

Tuspetinib Achieved Orphan Drug Designation and Fast Track Status

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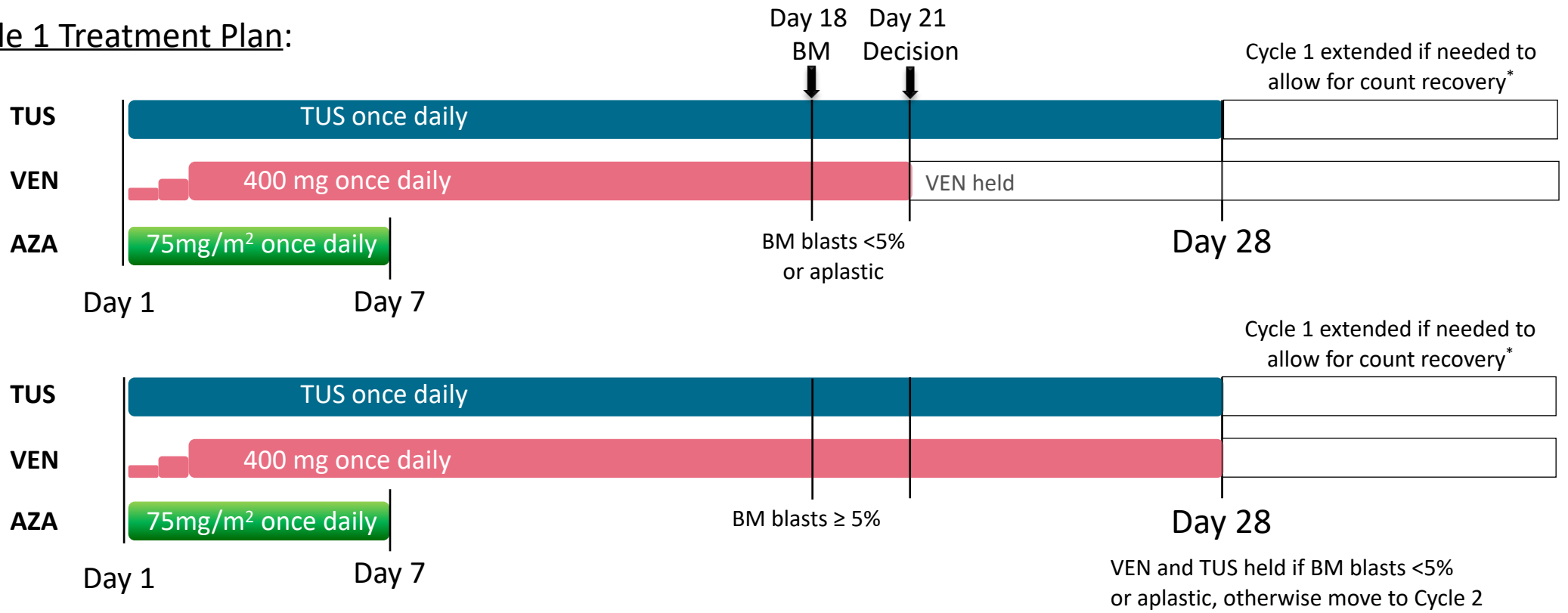
TUS+VEN+AZA TRIPLET Pilot Study: Design, Patient Populations, Dose Selection, Goals

Patient Populations | 20-36 Pts Total | 50% FLT3-MUT | <20% TP53+/CK

Trial Goals | Safety, CR rate, MRD negativity and OS across AML subtypes ($FLT3^{MUT/WT}$, $TP53^{MUT}$, RAS^{MUT})

Dose Selection | Explore 80, 120, 160mg Doses for Optimal Phase 2 Dose of TUS and Avoid SOC Dose Reductions

Cycle 1 Treatment Plan:



** GCSF permitted after D28 per protocol*

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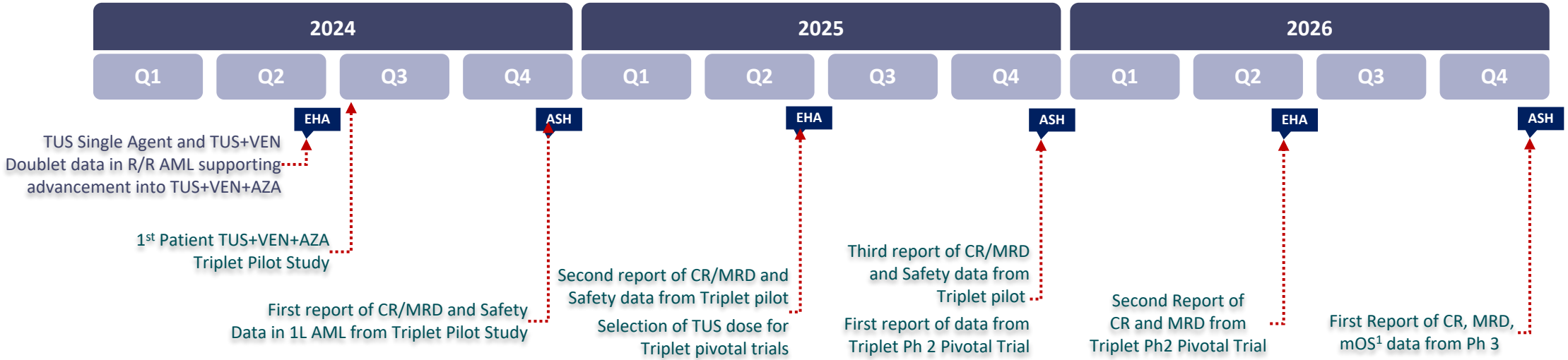
TUS+VEN+HMA Planned Clinical Development Plan, Timelines and Milestones



Triplet Frontline Therapy Newly Diagnosed AML

TUS+VEN+HMA[1] Triplet Pilot Study/Arm
Frontline Therapy for Newly Diagnosed AML
Dose selection for Ph 2 and Ph3 pivotal trial

TUS+VEN+HMA Triplet Phase 2 Portion of Pivotal Frontline Therapy for Newly Diagnosed AML

Ph 3 Portion of Pivotal

1 MRD = Measurable Residual Disease; mOS = Median Overall Survival

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Tuspetinib (TUS) Single Agent and TUS+VEN Doublet Clinical Findings Support TUS+VEN+HMA Triplet

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TUS and TUS+VEN Safe and Well Tolerated in Highly Treatment Experienced R/R AML

TUS Single Agent

- No drug-related myelosuppression in remission
- No treatment related QTc prolongation or CPK elevations
- No drug-related discontinuations or deaths
- No drug-related non-hematologic SAEs
- No differentiation syndrome

TUS+VEN Doublet

- No new or unexpected safety signals with TUS+VEN
- No drug related AE of QTc prolongation
- No differentiation syndrome observed
- No drug related deaths

Treatment Related AEs	*TUS Single Agent, n (%) (n=91)*	TUS+VEN, n (%) (n=77)	
	Related to TUS	Related to TUS	Related to VEN
Any	29 (31.2%)	39 (50.6%)	37 (48.1%)
Most Frequent Related TEAEs [1]			
Nausea	8 (8.6%)	13 (16.9%)	9 (11.7%)
Fatigue	2 (2.2%)	7 (9.1%)	6 (7.8%)
White blood cell count decreased	2 (2.2%)	6 (7.8%)	7 (9.1%)
Diarrhea	10 (10.8%)	5 (6.5%)	4 (5.2%)
Decreased appetite	2 (2.2%)	5 (6.5%)	4 (5.2%)
Neutrophil count decreased	2 (2.2%)	4 (5.2%)	3 (3.9%)
Platelet count decreased	1 (1.1%)	3 (3.9%)	4 (5.2%)
Vomiting	2 (2.2%)	3 (3.9%)	4 (5.2%)
Muscle Weakness	2 (2.2%)	0	0
Grade ≥ 3 (≥5% of patients in TUS+VEN)	9 (9.7%)	23 (29.9%)	24 (31.2%)
White blood cell count decreased	2 (2.2%)	5 (6.5%)	6 (7.8%)
Neutrophil count decreased	2 (2.2%)	4 (5.2%)	3 (3.9%)
Platelet count decreased	0	3 (3.9%)	4 (5.2%)
SAEs	1 (1.1%)	7 (9%)	10 (13.0%)
Leading to treatment termination	1 (1.1%)	0	1 (1.3%)
Leading to death	0	0	0

Data as of Feb 09, 2024

[1] Most frequent related TEAEs in TUS + VEN treatment arm are listed by descending order of frequency. Incidence of corresponding related TEAEs in TUS Single Agent arm is listed for comparison. Muscle weakness is included as it was identified as a DLT in Tus Single Agent (ie, only one DLT of muscle weakness occurred at the Tus Single Agent 200mg dose level in a study participant with high drug exposure, with no CPK elevation or CNS abnormality).

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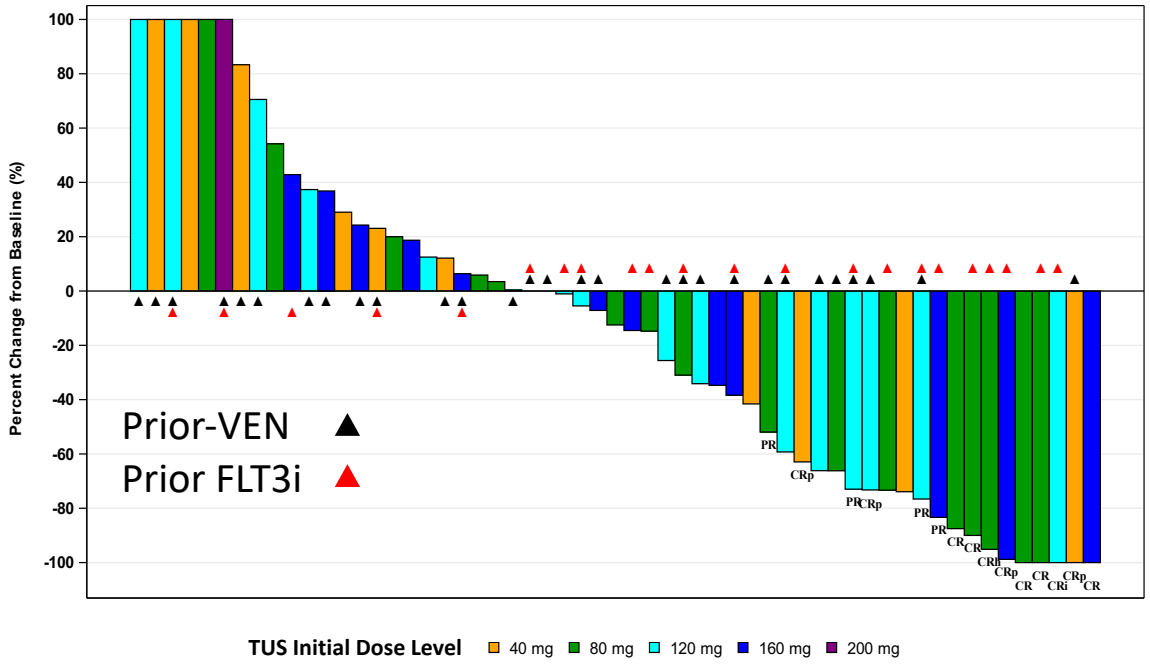
TUS and TUS+VEN : Bone Marrow Blast Reductions and Responses in R/R AML Patients

TUS Single Agent

Bone Marrow Leukemic Blasts | Percent Change from Baseline

Blast Reductions Demonstrate Activity Across 4 Dose Levels

Activity in Patients Who Failed Prior-VEN and Prior-FLT3i

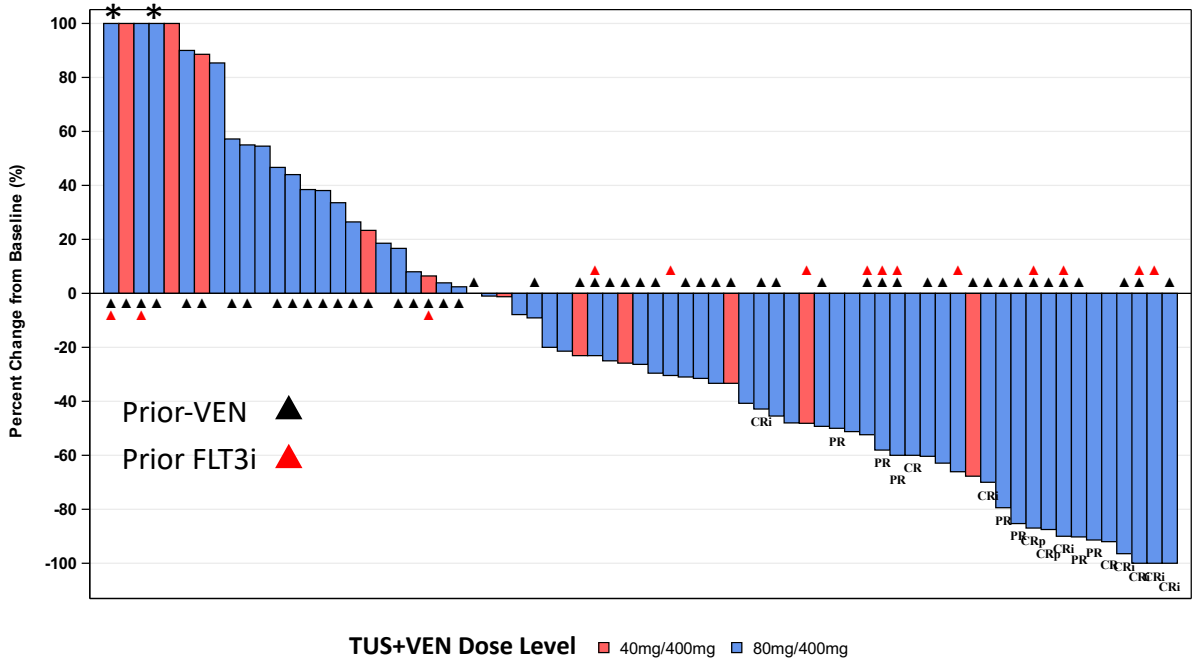


TUS-VEN Doublet

Bone Marrow Leukemic Blasts | Percent Change from Baseline

Blast Reductions in VEN-Naïve and Prior-VEN R/R AML

Blast Reduction in R/R AML Who Failed Prior-VEN and Prior-FL3i



Note: 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.

▲ Black triangle indicates patients who received prior Ven before starting Tuspetinib.

▲ Red triangle indicates prior FLT3i.

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

Data cut Feb 09, 2024

Investment Thesis

- **Highest unmet medical needs in frontline AML**
  - Need to safely increase survival across all subgroups
- **KOLs support TUS as the ideal 3rd agent for 1L triplet**
- **TUS emerging as ideal agent to combine with VEN+HMA**
  - Excellent safety profile
  - Broad activity on $FLT3^{MUT}$ and $FLT3^{WT}$ AML
  - Activity on high-risk TP53 and RAS mutated AML
  - Extended patent life and premium pricing
- **Near-term milestones can create shareholder value**

Near-Term Milestones

2024: EHA

- Report TUS Single Agent and TUS+VEN Doublet data in R/R AML supporting TUS+VEN+AZA Triplet trial in newly diagnosed AML

2024: Summer

- Initiate dosing of TUS+VEN+AZA Triplet in newly diagnosed AML

2024: ASH

- Report of CR/MRD/Safety data from TUS+VEN+AZA Triplet pilot

2025: 1H

- Complete enrollment in TUS+VEN+AZA Triplet pilot and report CR/MRD/Safety data

2025: EHA

- Data readout TUS+VEN+AZA Triplet pilot
- Select TUS dose for TUS+VEN+HMA Triplet PIVOTAL trials

2025: ASH

- Initiate Ph 2 portion of Ph 2 / Ph 3 PIVOTAL program

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Thank you

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