PEVONEDISTAT (TAK-924): A POTENTIAL NEW TREATMENT FOR HR-MDS AND AML

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BUILDING ON THE TAKEDA ONCOLOGY FOUNDATION IN HEMATOLOGIC MALIGNANCIES
HIGH RISK MYELODYSPLASTIC SYNDROME (HR-MDS) AND ACUTE MYELOID LEUKEMIA (AML) HAVE LIMITED TREATMENT OPTIONS

CONTINUUM OF HR-MDS AND AML

- HR-MDS and AML are both rare bone marrow-related cancers that share foundational biology, clinical features, and genetic mutations*
- Incidence highest in elderly (>70 years old)
- Overall survival several months to a few years, depending on risk category

* 30% of HR-MDS patients progress to AML

CLINICAL TREATMENT

BM failure → cytopenias
- Fatigue (anemia)
- Infection (neutropenia)
- Bleeding (thrombocytopenia)

Clinical treatment goals:
- Alleviate cytopenias
- Improve patient quality of life
- Improve survival

Fit Patients
Younger
Fewer co-morbidities
Better performance status

Intensive Chemotherapy

Stem Cell Transplant
(Only curative treatment)
≤ 10% HR-MDS, ~45% AML

Unfit Patients
Older
Unfit for intensive chemotherapy and/or stem cell transplant

Chemotherapy
azacitidine
decitabine
Low dose ara-c
Targeted therapies
AML only
- BCL2
- IDH1/2
- FLT3

CURRENT STANDARD OF CARE IS INADEQUATE FOR HR-MDS PATIENTS

- No new treatments have been approved for MDS in over a decade
- Transplant ineligible patients treated with first line therapy: Median OS = 15mo; 2yr OS rate 35%
- Economic burden is substantial - hospitalizations are common among patients and many are transfusion dependent

MDS SURVIVAL BY PROGNOSTIC RISK

Very good (n = 81; events, 34)
Very good (n = 1,809; events, 880)
Intermediate (n = 529; events, 312)
Poor (n = 148; events, 109)
Very poor (n = 187; events, 158)
P (log-rank) < .001

Median survival ~6 months to 5 years
PEVONEDISTAT: A UNIQUE FIRST-IN-CLASS NAE INHIBITOR

- Pevonedistat is a small molecule inhibitor of NAE (NEDD-8 activating enzyme), a protein involved in the ubiquitin-proteasome system
- NAE acts upstream of the proteasome and catalyzes the first step in the neddylation pathway

ENCOURAGING RESPONSES IN AML PATIENTS TREATED WITH PEVONEDISTAT + AZACITIDINE

- 60% ORR with a trend towards improved survival in secondary AML
- Response rates not influenced by AML genetic risk or leukemia burden
- Initial data drove interest to move to registration
A PHASE 2 STUDY IN HR-MDS TO CONFIRM THE RISK / BENEFIT PROFILE OBSERVED IN AML

Phase 2, Randomized, Open-label, Global, Multicenter Study
Comparing Pevonedistat Plus Azacitidine vs. Azacitidine in Patients with Higher-Risk MDS, CMML, or Low-Blast AML

- Mature OS data will be available in November
- Data will be presented in upcoming congress
- Potential approval in FY21*

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<table>
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<th>Randomization</th>
<th>n = 117</th>
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| Pevonedistat + Azacitidine | Pevo: 20 mg/m² on Days 1, 3, 5
| Aza: 75 mg/m² on Days 1-5, 8, 9 |
| Repeat every 28 days |
| Azacitidine | Aza: 75 mg/m² on Days 1-5, 8, 9 |
| Primary endpoint: | OS |
| Secondary endpoints: | EFS, ORR |
```

* Projected approval date assumes filing on Phase 2 data

THE PHASE 3 PANTHER STUDY WAS INITIATED AT RISK TO ACCELERATE DEVELOPMENT

Phase 3, Randomized controlled trial of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine as First-Line Treatment for Patients with Higher risk-MDS/CMML, or Low-blast AML

- Completed global enrollment 10 months earlier than originally projected*
- Indicative of demand for new innovative therapies

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</table>
| Pevonedistat + Azacitidine | Pevo: 20 mg/m² on Days 1, 3, 5
| Aza: 75 mg/m² Days 1-5, 8, 9 |
| Repeat every 28 days |
| Azacitidine | Aza: 75 mg/m² Days 1-5, 8, 9 |
| Primary endpoint: | EFS |
| Secondary endpoints: | OS |
```

* Closed to global enrollment; Open for extended enrollment in China
EXPANDING PATIENT-CENTRIC DEVELOPMENT OF PEVONEDISTAT

Continuum of disease

HR-MDS

Ph2 (P2001)  Ph3 (P3001)
Potential approval in FY21*

NEW STUDIES IN UNFIT AML

Ph3 PEVOLAM
pevo + aza vs. aza
Currently enrolling patients

Ph2 (P2002) Combo
pevo + venetoclax + aza vs. venetoclax + aza
Study will open in 2020

Utilizing partnership (PETHEMA) for efficient development

Unique MOA and biologic hypothesis to support combination

SUMMARY

1
Unmet need in High-risk MDS and AML remain high with few treatment options

2
Pevonedistat is a selective first-in-class inhibitor with potential to be first new therapy in over a decade for HR-MDS

3
The Ph2 HR-MDS trial has reached the updated OS endpoint data readout and the PANTHER Ph3 trial has completed global enrollment

* Projected approval date assumes filing on Phase 2 data