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

Phil Rowlands, PhD
Head Oncology Therapeutic Area Unit
Takeda Pharmaceutical Company Limited
New York, NY
November 14, 2019

BUILDING ON THE TAKEDA ONCOLOGY FOUNDATION IN HEMATOLOGIC MALIGNANCIES

GROWING LEADERSHIP POSITION IN HEMATOLOGIC MALIGNANCIES

Next Generation I/O
Cell therapies
Type I IFN
Novel checkpoints

MDS/AML
Phase 3
pevonedistat

Lymphoma
Chronic Myeloid Leukemia

Improve Patient Outcomes in Multiple Myeloma

VELCADE
NINLARO
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

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

Intensive Chemotherapy

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

Takeda

CURRENT STANDARD OF CARE IS INADEQUATE FOR HR-MDS PATIENTS

MDS SURVIVAL BY PROGNOSTIC RISK

- 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

Median survival ~6 months to 5 years

Schanzet al., J Clin Oncol. 2012, 30:820-829
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*

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

* Projected approval date assumes filing on Phase 2 data

* 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

Utilizing partnership (PETHEMA) for efficient development

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

Unique MOA and biologic hypothesis to support combination

* Projected approval date assumes filing on Phase 2 data

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