Panobinostat, a pan-deacetylase inhibitor, has been shown to have anti-leukemic activity in Acute Myeloid Leukemia (AML) preclinical models. Additionally, early clinical studies of panobinostat as a single-agent confirmed a modest anti-leukemic activity and established the Maximum Tolerated Dose (MTD) as 60 mg of panobinostat three times per week (TIW) as single agent in weekly and biweekly schedules.

Richard Schlenk et al. from the National Center for Tumor Diseases, Heidelberg, Germany, in a Letter to the Editor of Haematologica, discussed results from two of their clinical studies which evaluated the tolerability and clinical efficacy of panobinostat when given as a monotherapy or in combination with intensive chemotherapy in patients with AML.

Schlenk et al. first discussed a phase II study (EU Clinical Trials Register: 2008-002983-32), which evaluated the safety and efficacy of oral panobinostat monotherapy given at the previously established MTD (60 mg TIW for 28 days; one cycle) in patients with refractory de novo AML or refractory AML secondary to precedent Antecedent Hematologic disorder (AHD) or Myelodysplastic Syndrome (MDS). Fifty-nine patients with a median age of 66 years (range, 37–84) were enrolled in this study. A two-stage design was applied to this phase II trial and patients were split into two strata including stratum A (refractory de novo AML, n = 32) and stratum B (refractory AML secondary to AHD/MDS, n = 27).

The key findings from this phase II study were:

- All patients discontinued treatment due to death (n = 6) disease progression (n = 24); Adverse Events (AEs [n = 19]), withdrawal of consent (n = 7) and other reasons (n = 3)
- Treatment-related AEs occurred in 89.9% (53/59) of patients and the most frequent all grade included diarrhea (62.7%), nausea (40.7%), thrombocytopenia (30.5%), decreased appetite (27.1%) and vomiting (23.7%)
- Serious AEs (SAEs) occurred in 88.1 % of patients and 38.9% of these were treatment related
- Complete Remission (CR) in patients in strata A and B were 3.1% and 7.4% respectively
- Overall survival after one and two years were 12% and 0% respectively

Due to the lack of clinical response in this phase II study, enrollment was halted in this study. As a single-agent, panobinostat was not well-tolerated in patients with refractory AML and showed no clinical benefit.

Schenk et al. then discussed a phase I dose-escalation study (EU Clinical Trials Register: 2008-002986-30), which aimed to evaluate whether panobinostat could be safely administered in escalating doses with cytarabine (Ara-C) and mitoxantrone as salvage therapy for patients with Relapsed/Refractory (R/R) AML.
Fifty-nine R/R AML patients with a median age of 60 years (range, 19–76) were enrolled into this phase I study. Patients were administered oral doses of panobinostat via five cohorts including 20 mg (n = 5), 30 mg (n = 8), 40 mg (n = 10), 50 mg (n = 30) and 60 mg (n = 6) with a fixed dose of Ara-C (0.5 g/m² IV twice daily, Days 1–6) and mitoxantrone (5mg/m² IV, Days 1–5).

The key findings from the phase I study were:

- **Safety**
  - At dose level 1 (20 mg) and 2 (30 mg), there were no Dose Limiting Toxicities (DLTs) detected with DLTs detected in one patient at dose level 3 (40 mg)
  - At dose level 4 (50 mg) and 5 (60 mg), DLTs occurred in two and three patients respectively
  - MTD was determined at 50 mg panobinostat thrice weekly
  - Treatment-related AEs occurred in 93% of patients and the most common grade ≥ 3 non-hematologic treatment-related AEs include diarrhea (20%), nausea (5%), hypokalemia (7%) and sepsis (5%)
  - Death occurred in patients during or within 28 days of completing treatment due to sepsis (n = 5), septic shock (n = 2), fungal infection (n = 1), candidiasis (n = 1), acute respiratory distress syndrome (n =1) and intracranial hemorrhage (n = 1)

- **Response**
  - Overall Response Rate (ORR); 56%
  - ORR at MTD; 50%

In summary, addition of panobinostat to Ara-C and mitoxantrone did not significantly increase the rate of AEs. However, the response rate from this combination therapy does not indicate encouraging efficacy in patients with R/R AML.

Overall, the results of these two studies did not show any clinical benefit for panobinostat monotherapy or in combination with intensive chemotherapy in AML patients. Although, clinical studies of panobinostat in combination with idarubicin and cytarabine have shown promising efficacy in AML patients.

**References**