ACY-1215, a selective histone deacetylase (HDAC) 6 inhibitor, in combination with lenalidomide and dexamethasone (DEX), is well tolerated without dose limiting toxicity (DLT) in patients (PTS) with multiple myeloma (MM) at doses demonstrating biologic activity: interim results of a phase 1b trial.

**Background**

ACY-1215 (ricalinostat) is the first orally bioavailable selective HDAC6 inhibitor in clinical trials and is well-tolerated as monotherapy up to 360 mg/day, the maximum dose examined. Cmax ≥1.5 μM was achieved at doses ≥30 mg (Raje, Blood, 202(21):4061). Unlike nonselective HDAC inhibitors, which are associated with severe fatigue, vomiting, diarrhea and myelosuppression, DLTs have not been observed with ACY-1215. ACY-1215 synergizes in vitro with both lenalidomide and dexamethasone in MM cell lines (Quayle et al., Poster #A192, ASH 2013) providing the rationale to conduct a phase 1b trial of ACY-1215 in combination with these agents.

**Aims**

The aims of the study are to characterize the safety, pharmacokinetics and pharmacodynamics of ACY-1215 in combination with lenalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma and to establish a recommended phase 2 dose and schedule.

**Methods**

Relapsed and refractory MM patients who progressed on at least one prior treatment regimen, who have creatinine clearance >50 ml/min, adequate bone marrow and hepatic function, and who gave informed consent were enrolled. In Part A, patients were treated with escalating doses of oral ACY-1215 on days 1-5 and 8-12 of a 28 day cycle with lenalidomide 15-25 mg once daily and dexamethasone 40 mg weekly. In Part B, the schedule also includes ACY-1215 on days 15-19. Subsequent cohorts will explore twice daily dosing based on emerging clinical, pharmacokinetic (PK) and pharmacodynamic (PD) data. Peripheral blood samples were obtained for PK and PD analysis. PD assessment measured the fold increase of acetylated tubulin (a marker of HDAC6 inhibition) and acetylated histones (a marker of class 1 HDAC inhibition) in peripheral blood mononuclear cells (PBMC).

**Results**

**Safety**

- No dose limiting toxicity up to 240 mg (days 1-5, 6-12) and 160 mg (days 1-5, 6-12, 15-19) weeks (n=2)
- 1 SAE due to disease progression
- Most common treatment emergent adverse events were fatigue (50%), URI (38.9%), neutropenia (27.8%), headache, diarrhea, and muscle spasm (22.2%)
- Most were grade 1 and 2, with no dose relationships

**Most Common Treatment Emergent Adverse Events (≥15%)**

- Fatigue
- Headache
- Diarrhea
- Anemia
- Nausea
- Vomiting

**Pharmacodynamics**

- Pharmacodynamics data was available at the time of data cut-off.

**Pharmacodynamics: Monotherapy and Lenalidomide Combination**

- Most events were grade 1 and not considered related to ACY-1215.
- Dose dependence was observed in the PBMC in the cell culture for the combination of ACY-1215 and lenalidomide.

**Conclusion**

- ACY-1215 is well tolerated in combination with lenalidomide and dexamethasone at doses up to 160 mg QO (days 1-5, 6-12 & 15-19) and dose escalation is ongoing.
- PD demonstrates inhibition of HDAC6 at lower exposures than Class 1 HDACs.
- Most AEs were low grade and no dose relationship was observed.
- Two grade 3 AEs of neutropenia were considered possibly related to ACY-1215.
- No DLTs have been observed to date.
- Responses were observed in 13 out of 16 patients evaluable for response including one CR and three VGPR.

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