Oral Session (Oral presentations categorized by each organ)

PHASE I STUDY OF RESMINOSTAT, AN ORAL HDAC INHIBITOR, IN JAPANESE PATIENTS WITH SOLID TUMORS

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Background: Resminostat, an oral pan-inhibitor of class I and II histone deacetylases, exhibits antitumor activity in various cancer cell lines, and clinical trials are currently underway in Europe. We conducted a phase I study of single agent resminostat in Japanese patients with solid tumors. Primary objective of the study was to determine the maximum tolerated dose (MTD). The secondary objectives were evaluation of its safety, tolerability, pharmacokinetics, pharmacodynamics and antitumor activity.

Methods: This was an open-label, 3 + 3 designed, dose-escalation study. The eligibility criteria stipulated i.a. solid tumors refractory to standard therapy. Resminostat was administered orally once-daily on days 1 to 5 every 14 days. Three dose levels (400, 600, 800 mg/day) were planned. Pharmacodynamic activity of resminostat was evaluated by quantification of acetylated histone H4 in peripheral blood mononuclear cells.

Results: Twelve patients (3 at 400 mg/day, 3 at 600 mg/day, and 6 at 800 mg/day) were enrolled, including 4 with colon cancer, 3 with pancreatic cancer, 2 with lung cancer, and 3 other cancers. No dose limiting toxicity (DLT) was observed and the MTD was not reached. The most frequent adverse events were anorexia (10/12 pts, 83.3%), thrombocytopenia (10/12 pts, 83.3%) and lymphocytopenia (9/12 pts, 75.0%). In the pharmacokinetic profile, plasma exposure characteristics Cmax and AUC demonstrated a dose-proportional increase. Histone H4 acetylation increased at all the dose levels studied.

Conclusion: Up to 800 mg/day resminostat was well tolerated in Japanese patients. These findings warrant further clinical studies with resminostat in Japan.