Plenary session 7: Epigenetics and chaperones

O7.2 PHASE 1 FIRST-IN-HUMAN STUDY OF THE ENHANCER OF ZESTE-HOMOLOG 2 (EZH2) HISTONE METHYL TRANSFERASE INHIBITOR E7438

V. Ribrag1, J.-C. Soria1, L. Reyderman2, R. Chen3, P. Salazar4, N. Kumar3, G. Kuznetsov5, H. Keilhack6, L. H. Ottesen4, A. Italiano7
1Institute Gustave Roussy, Paris, France
2Eisai, Woodcliff Lake, NJ, USA
3Eisai Inc, Woodcliff Lake, NJ, USA
4Eisai Ltd, Hatfield, United Kingdom
5Eisai, Andover, MA, USA
6Epizyme, Cambridge, MA, USA
7Institut Begonie, Bordeaux, France

E7438 (EPZ-6438) is a selective, small molecule inhibitor of EZH2, the catalytic subunit of the polycomb repressive complex 2 that methylates H3K27. Hypertrimethylation of H3K27 (H3K27Me3) appears tumorigenic in various malignancies, including subsets of Non-Hodgkin Lymphoma (NHL) with mutant EZH2. Inhibition of H3K27Me3 with E7438 leads to killing of EZH2 mutant lymphoma cells. Tumors with loss of INI1, a subunit of the SWI-SNF chromatin remodelling complex, also appear dependent on EZH2. E7438 induces apoptosis and differentiation of INI1-deleted malignant rhabdoid tumor (MRT) models in vitro and in vivo.

E7438 was administered PO BID to cohorts of 3 to 6 pts up to a maximum feasible dose of 1600 mg BID. Blood samples for PK and skin biopsies for PD analysis were collected. PD samples were stained with H3K27me3 specific antibody and change from baseline was determined. PK/PD relationship was analysed. Tumour assessments were performed every 8 weeks.

As of 14 August 2014, 21 patients (pts) have been enrolled and treated at 5 dose levels of 100, 200, 400, 800, and 1600 mg BID. B cell NHL patients included follicular lymphoma (FL, n = 4), DLBCL (n = 4, including 1 pt with primary mediastinal lymphoma [PMBL] and marginal zone lymphoma (n = 1)). Solid tumour (ST) pts included 1 pt with MRT. 11 pts (7 ST, 4 B-cell NHL) had at post-treatment tumour assessment. Median age was 59 yrs (range 23-83). 1 DLT of thrombocytopenia was reported at 1600mg BID. Frequently occurring AEs independent of causality were asthenia (8 pts), anaemia (4 pts), decreased appetite and diarrhoea (3 pts each), pulmonary embolism, insomnia, muscle spasms, thrombocytopenia, nausea, and vomiting (2 pts each). 5/21 pts experienced Grade 3/4 AE.

E7438 PK exhibit rapid absorption, dose related increase in exposure and rapid elimination (half-life ~ 4hr). There was an exposure-related decrease in H3K27Me3 positive cells in skin. Partial responses were demonstrated in 2 of 4 evaluable NHL pts and in 1 pt with MRT with INI1 deficiency. Cohort expansion is ongoing. Updated data will be presented.

E7438 is well tolerated up to 1600 mg BID with preliminary evidence of activity in NHL and MRT and exposure related inhibition of H3K27Me3. MTD has not been reached.