Abstract: P2080

Title: PHASE II STUDY OF EZH2 INHIBITOR TAZEMETOSTAT PLUS AMDIZALISIB, A PI3K INHIBITOR, IN PATIENTS WITH RELAPSED/REFRACTORY LYMPHOMAS

Abstract Type: e-Poster Presentation

Topic: Aggressive Non-Hodgkin lymphoma - Clinical

Background:

Tazemetostat (TAZ) is the first approved enhancer-of-zeste-homolog-2 (EZH2) inhibitor by FDA in 2021. Amdizalisib (HMPL-689) is a novel and highly potent selective inhibitor of phosphatidylinositol 3-kinase p110δ isoform (PI3Kδ). Both agents showed satisfactory efficacies and controllable safety for relapsed or refractory (R/R) lymphomas in phase I/II clinical trials. Preclinical studies demonstrated synergistic antitumor effects of TAZ plus amdizalisib in vitro and vivo

Aims:

To investigate the safety, efficacy and pharmacokinetics (PK) of TAZ plus amdizalisib in R/R lymphomas.

Methods:

Patients with histologically confirmed R/R lymphoma were eligible. Two cohorts of amdizalisib (20mg, or 30mg QD) plus fixed dosage of TAZ (800mg BID) in phase IIa were observed to identify the recommended Phase IIb dosage (RP2D). Amdizalisib and TAZ were orally dosed until disease progression, intolerable toxicity or withdrawal from the study. Safety was evaluated according to CTCAE v5.0. Tumor assessments were performed according to LUGANO 2014.

Results:

A total of 21 R/R lymphoma patients (pts) were enrolled, including 10 in 20mg and 11 in 30mg cohort. Pts were at a median age of 60 (range 34-74) years old, 52.4% were male, 85.7% had ECOG performance status score of 0 or 1. The median line of prior systemic therapy was 3 (range 1-7), with 47.6% refractory to CD20 antibody and 81.0% refractory to last therapy. No obvious baseline differences were observed between 20mg and 30mg cohorts.

18 pts had evaluated response, including 5 follicular lymphoma (FL), 3 diffuse large B cell lymphoma (DLBCL), 8 peripheral T cell lymphoma (PTCL), 1 marginal zone lymphoma (MZL) and 1 mantle cell lymphoma (MCL). In 20mg cohort, 7 (7/9, 77.8%) pts achieved partial response (PR) (2 PTCL [1 of them was primary cutaneous PTCL and not shown in Figure], 2 DLBCL and 3 FL), and 2 pts were stable disease (SD) (1 MZL and 1 FL). In 30mg cohort, 5 (5/9, 55.6%) pts achieved PR (1 DLBCL, 1 FL and 3 PTCL), 3 pts were SD (1 MCL and 2 PTCL) and 1 PTCL had progression disease (PD) (see Figure). The median duration of response, progression-free and overall survival had not reached. Efficacy seems similar in two cohorts.

All pts experienced at least one treatment related adverse events (TRAE).11 (52.4%) pts experienced grade≥3 TRAE, and the most common (≥10%) events included anemia, leukopenia, lymphopenia, thrombocytopenia (each 4 pts, 19.0%), and neutropenia (3 pts, 14.3%). 5 (23.8%) pts had dose reduction due to TEAE (2 pts from 20mg cohort and 1 pt from 30mg cohort had TAZ dose reduction, 2 pts from 30mg cohort had amdizalisib and TAZ dose reduction). 4 (36.4%) pts experienced TRSAE in 30mg cohort, while 1 (10%) pt at 20mg cohort experienced TRSAE. Pts in 30mg cohort experienced more grade≥3 TRAEs, TRSAEs, and TEAEs leading to dose reduction, compared to 20mg cohort. However, the majority were manageable and recoverable. Compared with C1D1, an obvious decrease (around 45%) occurred on C1D15 in terms of AUC0-12h for TAZ, while the AUC0-24h for amdizalisib on C1D15 was decreased by 20% with combined administration, which was consistent with the induction potential of CYP3A4 by TAZ.

The RP2D was recommended by SRC as amdizalisib 20mg QD combined with TAZ 800mg BID on the basis of safety, efficacy, and PK properties.

Summary/Conclusion:

The combination of amdizalisib and TAZ showed promising efficacy with manageable safety profile in R/R lymphoma, especially in PTCL and DLBCL. However, larger sample and long-term follow-up are needed to further validate efficacy and safety.

Figure: Best change in tumor size of target lesions, assessed by investigator

One patient with primary cutaneous PTCL lymphoma in the 20 mg Cohort was not included in the waterfall plot, as the patient only had skin lesions, and the response was PR at C3D1.

Keywords: Non-Hodgkin's lymphoma, Diffuse large B cell lymphoma, Targeted therapy, Peripheral T-cell lymphoma