Abstract: P722

Title: OLVEREMBATINIB OVERCOMES PONATINIB AND ASCIMINIB RESISTANCE IN PATIENTS (PTS) WITH HEAVILY PRETREATED CHRONIC MYELOID LEUKEMIA (CML) AND PHILADELPHIA-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (PH^+ ALL)

Abstract Type: Poster Presentation

Topic: Chronic myeloid leukemia - Clinical

Background:

Olverembatinib (HQP1351), an investigational, novel, potent BCR::ABL1 tyrosine kinase inhibitor (TKI), has strong antitumor activity in pts with CML or Ph^+ ALL.

Aims:

Assess the safety, efficacy, and pharmacokinetic (PK) profiles of olverembatinib in pts with heavily TKI pretreated CML or Ph+ ALL.

Methods:

Olverembatinib was administered orally QOD at randomly assigned doses of 30, 40, or 50 mg in repeated 28-day cycles.

Results:

As of January 2, 2024, 80 pts were enrolled and provided informed consent; 62 (77.5%) had chronic-phase (CP)-CML; the median (range) age was 54.0 (21-80) years; and 46 (57.5%) were male. Fourteen (17.5%) pts had received 2 prior lines of TKI therapy; 22 (27.5%), 3 lines; and 43 (53.8%), ≥ 4 lines. Forty-six (57.5%) pts were previously treated with ponatinib (32 [40.0%] resistant and 10 [12.5%] intolerant), and 25 pts (31.3%) received asciminib (19 [23.8%] resistant and 4 [5.0%] intolerant). Fifty-eight (72.5%) pts had BCR::ABL1 IS ≥ 10%. At baseline, 25 (31.3%) pts with CP-CML or advanced leukemia harbored *T315I* mutations including 4 (5%) pts with other mutations; 34 (42.5%) had hypertension; and 12 (15.0%) other cardiovascular comorbidities. Median (range) follow-up duration was 48.9 (4-179) weeks; the PK profiles were similar compared with PK data on Chinese CML pts. Fifteen pts with CML and 12 with advanced leukemia discontinued treatment: 4 because of adverse events (AEs); 7, disease progression; and 16, other reasons (6 transplantation, 3 no response, 3 pt withdrawals, 2 deaths, and 2 noncompliance). Sixty (75%) pts experienced treatment-related AEs (TRAEs; most grade 1/2 and clinically manageable) 32 (40%) grade 3/4 TRAEs, and 12 (15%) treatment-related serious AEs. Per investigators, common (≥ 20% incidence) TRAEs were blood creatine phosphokinase increased (30%) and thrombocytopenia (23%). Common treatment-related grade 3/4 TRAEs (≥10% incidence) were thrombocytopenia and blood creatine phosphokinase increased; treatment-related SAEs that occurred in ≥ 2 (2.5%) patients included neutropenia and blood creatine phosphokinase increased in 2 pts (2.5%) each; no treatment-related AE led to death. Three (3.8%) pts had treatment-related arterial occlusive events that were non-SAEs: one each with angina pectoris, brachiocephalic arteriosclerosis, and embolism. Olverembatinib showed robust antileukemic activity. A total of 31/51 (60.8%) evaluable pts with CP-CML achieved complete cytogenetic response (CCyR), and 25/59 (42.4%), major molecular response (MMR); similar response rates were observed despite *T315I* mutation status. Of 26 cytogenetic response-evaluable pts with ponatinib-failed CP-CML, 15 (57.7%) achieved CCyR, including pts with prior ponatinib resistance (10/19 [52.6%]) or intolerance (3/4 [75.0%]). A total of 11/30 (36.7%) evaluable pts previously treated with ponatinib achieved MMR, including those with prior resistance (9/21 [42.9%]) or intolerance (1/6 [16.7%]) to this agent. Half (n = 4/8) of evaluable pts with asciminib-resistant disease achieved CCyR and 4 of 12 (33.3%) MMR. In all, 3/14 (21.4%) evaluable pts with advanced leukemia achieved CCyR and 3/17 (17.6%), MMR. A total of 1/6 (16.7%) pts with advanced leukemia and *T315I* mutations achieved MMR and/or CCyR; 2 pts without the *T315I* mutation, who had MMRs with olverembatinib, had ponatinib-resistant disease.

Conclusion:

Olverembatinib was efficacious and well tolerated at doses up to 50 mg QOD in pts with heavily pretreated CP-CML and advanced leukemias, including ponatinib- or asciminib-resistant/intolerant disease. (ClinicalTrial.gov registration: NCT04260022; Internal study HQP1351CU101)

Keywords: Chronic myeloid leukemia, Philadelphia chromosome, Tyrosine kinase inhibitor, Acute lymphoblastic leukemia