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POSTER ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

A Phase I/II Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of BTK Inhibitor HZ-a-018 in Adult Patients with Relapsed and/or Refractory Central Nervous System Lymphoma

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Background: HZ-A-018 is a highly selective and potent covalent BTK inhibitor with CNS-penetrating profile, which was previously reported (Abstract 5501, ASH 2022). Phase I/II study is ongoing in China, and here we present preliminary results of HZ-A-018 monotherapy of the phase I part in central nervous system lymphoma.
Methods: HZ-A-018-102 is an ongoing phase I/II study (CTR20210181) to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of HZ-A-018 in central nervous system lymphoma. The primary objective for phase I monotherapy was to determine the safety and tolerability and the recommended phase 2 dose (RP2D), and secondary objectives included preliminary antitumor activity and pharmacokinetics in patients with relapsed/refractory primary/secondary CNS lymphoma (R/R PCNSL/SCNSL) and primary vitreoretinal lymphoma (PVRL) who had received ≥1 prior therapy. HZ-A-018 was administered orally once daily in 28-day cycles until disease progression or unacceptable toxicity.
Results: At the data cutoff date of 30 May 2023, 21 pts from the phase I monotherapy were analyzed, including 18 R/R PCNSL and 3 R/R SCNSL. 3 pts received 300mg/d, 12 pts received 450mg/d and 6 pts received 600mg/d. 600mg was the highest dose pre-defined in the study and MTD was not reached. Pts were with a median age of 62 years (range: 36-80), median KPS 80 (range: 60-90) and a median of 2 prior systemic therapies (range: 1-5). 20 pts (95.2%) presented with brain parenchyma, and 1 pt (4.8%) presented with intraocular (IO) involvement. All patients had received HD-MTX based chemotherapy, 19 pts (90.5%) had received rituximab and 1 pt had received whole brain radiation therapy (WBRT). 16 of 21 pts (76.2%) experienced a treatment related adverse event (TRAE). The most common TRAEs (≥10%) were thrombocytopenia (42.9%), neutropenia (23.8%), leukopenia (23.8%), and hypokalemia (14.3%), majority of which were grade 1 to 2. DLTs occurred in 1 pt at 450 mg/d and 1 pt at 600 mg/d. 4 pts (19.0%) had dose interruption, no pts had dose reductions, and no pts discontinued from the study due to TRAEs. The plasma and cerebrospinal fluid (CSF) pharmacokinetics showed HZ-A-018 was rapidly absorbed and could cross the blood-brain barrier with CSF HZ-A-018 concentration ranged from 5.94 to 17.5 ng/mL two hours post-dose. Of 19 pts available for tumor assessment (16 PCNSL with brain parenchyma, 1 PCNSL with IO and 2 SCNSL with brain parenchyma) and 2 pts not evaluable (1 PCNSL with brain parenchyma, and 1 SCNSL with brain parenchyma), the overall response rate (ORR) was 52.4% (95%CI: 29.8, 74.3), including 23.8% (5 pts) complete response(CR)/unconfirmed complete response(CRu), 28.6% (6 pts) partial response (PR), and 19.0% (4 pts) stable disease (SD), contributing to an 71.4% (95%CI: 47.8, 88.7) disease control rate (DCR). At 600mg/d, all 6 pts had achieved high and deep responses, contributing to 100% ORR and 50% CRR, with the 3-month duration of response (DOR) rate not reached. Dose expansion was ongoing at 600mg QD.
Conclusions: These results demonstrated that HZ-A-018 was efficacious and well-tolerated in CNS lymphoma patients with high CNS penetrating profile. The monotherapy RP2D for R/R PCNSL was determined as 600 mg QD and a phase 2 R/R PCNSL registration study in China is currently planned.

Disclosures No relevant conflicts of interest to declare.

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