P1237 PRELIMINARY RESULTS OF A PHASE II STUDY OF ZANUBRUTINIB COMBINED WITH IMMUNOCHEMOTHERAPY IN PATIENTS WITH CD79A/CD79B-MUTANT DIFFUSE LARGE B-CELL LYMPHOMA

Topic: 19. Aggressive Non-Hodgkin lymphoma - Clinical

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Background:
Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous hematologic malignancy with highly variable genetic abnormalities and clinical outcomes, highlighting the importance of individualized treatment. Previous studies showed that CD79B mutation was associated with higher risk of relapse and shorter survival after standard treatment (2020 ASH Abstract 2923), and both CD79B- or CD79A-mutant lymphoma cells were sensitive to BTKi in vitro (Nat Med. 2015;21:922-926). Moreover, a recent pooled analysis revealed that CD79B-mutant lymphoma patients (pts) treated with Zanubrutinib alone or in combination with anti-CD20 antibody had better response (2020 EHA Abstract EP1246). Thus, we inferred that BTKi combined with immunochemotherapy might be a favorable option for pts with CD79A/CD79B-mutant DLBCL. Here, we present preliminary data from the phase 2 trial of Zanubrutinib combined with immunochemotherapy in pts with CD79A/CD79B-mutant DLBCL (NCT04668365).

Aims:
To investigate the efficacy of Zanubrutinib combined with immunochemotherapy in pts with CD79A/CD79B-mutant DLBCL. The primary objective is complete response rate (CRR).

Methods:
Pts aged 18-80 years with CD79A/CD79B-mutant DLBCL and adequate organ function are being enrolled. This study consisted of treatment naïve (TN) cohort and relapsed/refractory (R/R) cohort. Zanubrutinib (160 mg po bid) plus R-CHOP (ZR-CHOP) was administered in TN cohort, and Zanubrutinib (160 mg po bid) combined with investigator-determined conventional salvage chemotherapy (CSC, including ICE, DHAP, GDP, or GemOx, +/- rituximab) was administered in R/R cohort. A total of 7 cycles of treatment was planned for TN patients. After 5 cycles of induction treatment, responders in R/R cohort undergo autologous stem cell transplantation (ASCT) or Zanubrutinib maintenance for 12 months, based on the patient’s fitness and preference.

Results:
From July 2020 to 22 February 2022, 91 pts had been screened, including 65 TN pts and 26 R/R pts. CD79A/CD79B mutation was identified in 14 (21.5%) TN pts and in 11 (42.3%) R/R pts, of which 7 TN pts and 8 R/R pts agreed to participate in this trial. Their baseline characteristics are displayed in Table 1.

By 22 February 2022, 6 TN pts and 7 R/R pts had been evaluated for response. All of the 6 (100%) TN pts achieved CR. In the R/R cohort, the responses were CR in 4 (51.7%) pts, partial response (PR) in 2 (28.6%) pts, and progression disease (PD) in 1 (14.3%) patient. The median follow-up time was 9.7 (1.2 – 19.2) months for the TN cohort and 3.8 (0.3 – 9.6) months for the R/R cohort. None of the patients had PD in the TN cohort. Two pts (1R/R and 5R/R) in the R/R cohort experienced PD and subsequently succumbed to lymphoma, both of which harbored TP53

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mutations.

The most common adverse events in both cohorts were hematologic toxicities. Grade 3/4 AEs occurred in ≥20% pts were neutropenia, leukopenia, anemia, and thrombocytopenia. Bleeding events and cardiac events were not observed.

Image:

| Parameter | Treatment naive cohort | Relapsed/refractory cohort |
|-----------|------------------------|---------------------------|
| Grade 2-4 toxicity (%) | 20.2% | 20.2% |
| Grade 3-4 toxicity (%) | 41.0% | 41.0% |
| Hematologic toxicity (%) | 
| Neutropenia | 4 (7.5%) | 10 (15.9%) |
| Leukopenia | 6 (9.8%) | 14 (21.7%) |
| Anemia | 10 (15.9%) | 28 (44.4%) |
| Thrombocytopenia | 10 (15.9%) | 28 (44.4%) |
| Blinded adverse events (%) | 
| Nausea | 7 (11.3%) | 18 (27.9%) |
| Vomiting | 6 (9.8%) | 14 (21.7%) |
| Diarrhea | 1 (1.6%) | 5 (7.8%) |
| Infusion reactions | 1 (1.6%) | 2 (3.1%) |
| Total | 3 (4.8%) | 11 (16.8%) |

Summary/Conclusion:

CD79A/CD79B mutation was frequent in DLBCL patients, especially in R/R cases. Zanubrutinib combined with immunochemotherapy showed encouraging activity and acceptable tolerance in pts with CD79A/CD79B-mutant DLBCL. TP53 mutation seems to be a detrimental factor. The study is still ongoing and it is worth looking forward to updating the long-term survival data.