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626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Safety Results of a Phase I Study of Zandelisib + R-CHOP in Newly Diagnosed Diffuse Large B Cell Lymphoma (DLBCL)

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Introduction:
Emerging data have identified distinct genetic subtypes of DLBCL based on the diverse oncogenic molecular drivers with varying clinical outcomes when treated with standard R-CHOP. Relapse post frontline treatment could be curbed by integrating novel agents upfront. The phosphatidylinositol 3 kinase (PI3K) signalling pathway contributes to the oncogenesesis of both germinal center derived and activated B-cell (ABC) DLBCL subtypes (Wright, et al Cancer Cell, 2020). Zandelisib, a highly selective oral PI3Kδ inhibitor has proven efficacy in B cell lymphoma with a favorable toxicity profile when administered in intermittent dosing schedule (Pagel, et al Lancet Oncol 2022). We conducted a phase I/2 trial to evaluate the safety and efficacy of zandelisib in combination with R-CHOP chemotherapy in newly diagnosed DLBCL. The study enrollment was closed in 12/2022 after the development of zandelisib was discontinued. We present the results of the phase I (P1) trial.
Methods:
In this investigator-initiated trial, patients (pts) with untreated DLBCL with ECOG performance status (PS) $\leq$ 2, adequate bone marrow (BM) and organ function were enrolled from 08/2021-12/2022 at Cleveland Clinic (NCT04517435). ECOG PS 3 was allowed if it was attributed to the lymphoma diagnosis. The study was supported by the MEI Pharma. The P1 study had 2 dose escalation cohorts in combination with standard doses of R-CHOP every 21 days for 6 cycles; zandelisib was dosed 60 mg daily on days 1-4 in cohort 1 and daily on days 1-7 in cohort 2. If the 3 subjects in dose level 1 (D1) did not experience any dose limiting toxicity (DLT) during cycle 1 (C1), pts were enrolled into D2. In phase 2 (P2), a cycle of R-CHOP prior to the study treatment was allowed, if clinically deemed. All pts received pneumocystis jirovecii (PJP) and viral prophylaxis. Disease response was assessed after C3 and C6. Primary end point for P1 was to assess safety and tolerability of the combination and to determine recommended P2 dose (RP2D) of zandelisib. Pts who received at least 1 cycle of study treatment were included in the safety analysis. Primary objective of P2 is progression free survival (PFS) at 1 year. Pt and disease characteristics were analyzed using descriptive statistics.
Results:
We enrolled a total of 13 pts (P1: 9 and P2: 4) in the study prior to termination. The median age was 67 (range 46-79) years, with majority being female (53.8%), with an ECOG PS of 0-2 (100%). Most pts had stage III-IV disease 10/13 (77%), IPI $\geq$3 in 8/15 (62%), elevated LDH 9/13 pts (69%), and extranodal involvement 7/13 (54%). 3 pts had BM involvement. DLBCL was germinal center (GC) subtype in 77% of the pts. FISH studies revealed translocations in BCL2 (46%), BCL6 (8%) and c-myc (0%). There was no DLT observed in cohort 1 and zandelisib 60 mg daily on D1-7 was the RP2D. 12 of 13 enrolled pts completed 6 cycles of the study regimen prior to study closure. Of the 12 evaluable pts, the ORR was 100% with 9 pts (75%) achieving CR and 3 PR (25%). No pt experienced disease progression prior to study closing. Median time from treatment start to response was 165 (range 48-189) days. The most common adverse events were diarrhea (38%), neutropenia and anemia (31% each), fatigue, constipation, leukopenia and thrombocytopenia (23% each). Other AEs include colitis, nausea, hypoalbuminemia and hypokalemia (15% each). Of the 2 pts who developed colitis, 1 pt had G1 colitis which resolved, while the other pt discontinued the study after 2 cycles due to G3 colitis and bowel obstruction. Another pt experienced G3 jejunal perforation

after completing cycle 6. Other G≥3 AE observed were neutropenia and leukopenia each (23% each), lung infection and lymphopenia (8% each). All pts were alive at the time of study closure.

Conclusion:

In this phase 1/II study, encouraging efficacy was observed with zandelisib + R-CHOP, but this should be interpreted with caution as the study was incomplete. There is a potential signal for increased gastrointestinal toxicity (one G3 colitis, one G3 bowel perforation) in this small sample size and larger prospective trials are needed to further assess the toxicity profile of the combination of oral PI3K inhibitors with R-CHOP.

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