(PB3606) MRD-DRIVEN TRIPLET THERAPY WITH ORELABRUTINIB, POMALIDOMIDE, AND ZUBERITAMAB FOR NEWLY DIAGNOSED INTERMEDIATE/HIGH-RISK MANTLE CELL LYMPHOMA

Topic: 18. Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

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Background

Bruton's tyrosine kinase inhibitor (BTKi)-based regimens have improved outcomes in mantle cell lymphoma (MCL), addressing the poor prognosis and toxicity associated with traditional immunochemotherapy. Current research focuses on chemo-free multi-agent combinations to deepen responses and enable fixed-duration strategies (fixed-cycle/MRD-guided). The OASIS2 trial demonstrated that adding venetoclax to ibrutinib and rituximab yields superior complete response (CR) and undetectable minimal residual disease (uMRD) rates, supporting the potential of BTKi + CD20 monoclonal antibody (mAb) + X regimens, particularly for high-risk MCL. Orelabrutinib exhibits potent efficacy with a favorable safety profile in relapsed/refractory MCL; pomalidomide provides immunomodulatory and pro-apoptotic effects; and zuberitamab, an innovative recombinant human-mouse chimeric anti-CD20 mAb, mediates tumor clearance via antibody-dependent cellular cytotoxicity (ADCC). We hypothesized that the triplet combination of orelabrutinib, pomalidomide, and zuberitamab (POZ) would synergistically inhibit tumor proliferation, achieve high uMRD rates, and prolong progression-free survival (PFS). Here, we present preliminary findings from the study (NCT07257510), evaluating this regimen in newly diagnosed intermediate/high-risk MCL with treatment de-escalation guided by post-induction MRD status.

Methods

Eligible patients receive six cycles of induction therapy with the POZ regimen. Post-induction, patients achieving uMRD proceed to 18 cycles of maintenance therapy with orelabrutinib plus zuberitamab, while those with MRD positivity discontinue study treatment (Figure 1). The primary endpoint is the uMRD rate following induction therapy. Key secondary endpoints include CR rate, objective response rate (ORR), duration of response (DOR), PFS, overall survival (OS), and safety.

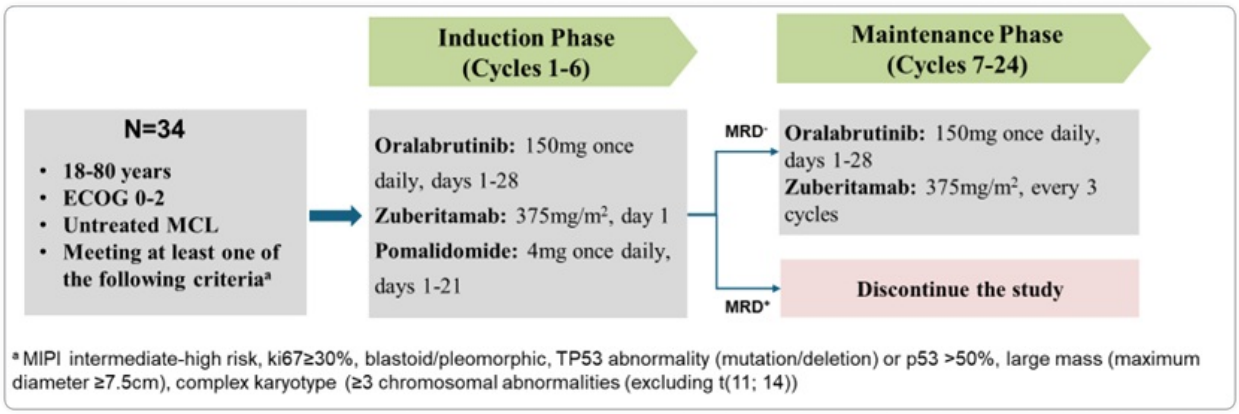
Results

As of the data cutoff date (March 26, 2026), 10 patients were enrolled. The median age was 58.5 years (mean, 58.6 ± 6.8). According to MIPI scoring, 7 patients were low-risk and 3 were intermediate-risk. High proliferative activity (Ki-67 ≥30%) was observed in 6 patients. Among 6 patients evaluable for genetic profiling, TP53 mutations were detected in 3 (50%). With a median follow-up of 4.1 months (95% CI: 3.5-5.9), efficacy was assessed in 10 evaluable patients. The ORR was 100%, comprising 9 CRs (90%) and 1 partial response (PR). All patients remained on treatment with no reported disease progression or death. The safety profile was manageable. No treatment discontinuations occurred due to adverse events (AEs), and only one patient required a dose delay. The most common AEs were dermatologic: grade 1 rash (n=4) and grade 1 pruritus (n=1). Other reported AEs included grade 2 pulmonary infection (n=1), grade 3 leukopenia (n=2), and grade 4 neutropenia (n=1). No grade ≥5 AEs were observed.

Summary/Conclusion

Although no patients have yet completed induction therapy and MRD data remain immature, this preliminary analysis demonstrates that the chemo-free POZ regimen induces deep and rapid responses (100% ORR, 90% CR) in newly diagnosed intermediate/high-risk MCL, including patients with high-risk features such as TP53 mutations. The safety profile is favorable and manageable. Continued follow-up is warranted to assess the primary endpoint of uMRD and long-term durability of response.

Figure 1. Study Design



[a] MIPI intermediate-high risk, ki67≥30%, blastoid/pleomorphic, TP53 abnormality (mutation/deletion) or p53 >50%, large mass (maximum diameter ≥7.5cm), complex karyotype (≥3 chromosomal abnormalities (excluding t(11; 14))