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43 Co-Inhibition of IL-2, IL-9 and IL-15 By the Novel Immunomodulator, Bnz-1, Provides Clinical Efficacy in Patients with Refractory Cutaneous T Cell Lymphoma in a Phase 1/2 Clinical Trial

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Hematology Disease Topics & Pathways:
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Saturday, December 5, 2020: 8:30 AM

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Background: Cutaneous T cell lymphoma is incurable with current standard therapies and there is an urgent need for more effective therapies. BNZ-1 is a pegylated peptide antagonist that binds to the common gamma chain signaling receptor for cytokines IL-2, IL-9 and IL-15. We hypothesized that inhibition of these 3 cytokines could generate a therapeutic benefit to CTCL patients through a multipronged mechanism: **1)** IL-2 and IL-15 inhibition blocks cytokine-driven propagation/survival of tumor cells **2)** IL-2 and IL-9 inhibition lowers the activity of regulatory T-cells that may impede the anti-lymphoma immune response **3)** IL-15 inhibition may provide an additional anti-inflammatory effect.

Methods: A multicenter, open-label Phase 1/2 study was completed to characterize the safety and efficacy of BNZ-1 (NCT03239392). Refractory patients, who have failed FDA-approved or investigational treatments appropriate for the stage of their disease, with a diagnosis of mycosis fungoides (MF) of any stage or Sézary syndrome (SS) were eligible for this trial. In part I of the study, Pts were enrolled in sequential dose cohorts of 0.5 mg/kg, 1mg/kg, 2 mg/kg, and 4 mg/kg to receive weekly intravenous dose of BNZ-1 to characterize safety, pharmacokinetics, pharmacodynamics, and evidence of antitumor activity. Thereafter, patients were enrolled on an extension phase for 3 months of weekly dosing of BNZ-1. Patients who achieved a response were eligible for a long-term extension arm. Blood samples were collected to assess the impact of BNZ-1 on PD biomarkers including Treg numbers and activation markers of cytotoxic T lymphocytes using FACS analysis.

Results: In the dose ranging part of the study, 15 patients (stages IB and IVB) were enrolled across the 4 dose cohorts. All patients completed the first 4 weeks for safety of the study and 9 enrolled in the 3-month extension period and 3 continued in the long term extension (LTE) period for over a year. BNZ-1 showed activity in all doses as it was determined by early signs of clinical efficacy and PD biomarkers.

Subsequently, we selected the 2 mg/kg based on PK/PD relationship and clinical efficacy and expanded to a total of 19 patients. Clinical efficacy was measured by mSWAT and Global Response Score (GRS) as defined previously (Olsen E. et al. 2011). Based on the best response, one patient (5%) achieved a complete response, eleven (58%) patients achieved a partial response (50% reduction over baseline) by the end of the study. 7 patients (37%) showed stable disease during the study period. No disease recurrence was observed during the study period. For those patients who responded to the therapy in the dose ranging part of the study, the mean duration of response was calculated to be 9.2 months. Overall, BNZ-1 was well tolerated and showed no serious treatment-related adverse events in this patient population. Furthermore, PD analysis revealed that BNZ-1 discernibly suppressed the inflammatory nature of CTLs in majority of patients that respond to BNZ-1 treatment as measured by reduction in their mSWAT scores.

Conclusion: BNZ-1, an IL-2, IL-9, and IL-15 inhibitor, may provide a novel treatment option for CTCL patients who relapsed or were refractory with conventional therapies with a favorable toxicity profile. The multifaceted approach of BNZ-1 leads to direct inhibition of malignant cells, activation of tumor immunity, and suppression of inflammation. Since BNZ-1 showed safety and efficacy in challenging rCTCL patient population, its further development in a phase 3 trial is planned.

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