2943 A Phase II Trial of Combined Bendamustine, Bortezomib and Dexamethasone in Newly Diagnosed Multiple Myeloma (MM) Patients Who Are Not Candidates for High-Dose Chemotherapy: Results of a Planned Interim Safety Analysis

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Background

Despite significant advances, multiple myeloma is an incurable plasma cell disorder with an eventual fatal outcome. In newly diagnosed MM, combinations of bortezomib, steroids and alkylating agents, such as melphalan and prednisone, have achieved response rates in excess of 70% and have been established as a standard of care in patients (pts) who are ineligible for high dose chemotherapy. Bendamustine is a bi-functional alkylating agent with a purine-like benzimidazole ring effective as single agent and in combination with steroids, thalidomide and bortezomib for the treatment of MM. **Pönisch et al** reported an overall response of 61% and CR of 15% in pts with relapsed/refractory MM using the combination of bendamustine, bortezomib and prednisone. In this study, the combination of bendamustine, bortezomib and dexamethasone (BVD) was tested for efficacy and safety in newly diagnosed pts with active MM who are not candidates for high-dose chemotherapy.

Methods

Patients with newly diagnosed active multiple myeloma who were not candidates for high-dose chemotherapy and met standard eligibility criteria with regards to renal, hepatic and hematologic function were enrolled. Pts were treated with bendamustine 80 mg/m^2 on days 1,4, bortezomib 1.3 mg/m^2 on days 1,4,8,11 and dexamethasone 40 mg on days 1,2,3,4 every 28 days for a total of 8 cycles or 2 cycles beyond documented CR, whichever occurred first. Responses were assessed using the IMWG criteria. We report on the preliminary efficacy and safety results of a planned interim analysis of the BVD combination.

Results

Between May 2010 and February 2011, 18 pts were enrolled, all evaluable for toxicity. The median age was 75 (range 56-82); nine (50%) pts were DS stage III; seven (39%) pts had a B2M ≥ 5mg/L. Cytogenetics and FISH analysis for 13 del, t4;14, t14;16, and 17p del were available for all but 1 pt; 8 (44%) pts had at least 1 chromosomal abnormality , while 9 (50%) pts had none. At the time of data cut off, pts completed a median of 5.5 cycles (range 1-8); with 11 (61 %) receiving at least 4 cycles; and 5 (28%) receiving 8 cycles. Seven (39%) pts remain on study and 10 have discontinued therapy (1 disease progression and 3 deaths on study [2 cardiac arrest, 1 pulmonary

emboli; all 3 determined to be unrelated to treatment], 1 MD discretion, 1 non-compliance, 1 pt request, 2 poor tolerance, 1 intercurrent illness) and 1 completed treatment. The most common grade 3 /4 adverse events, occurring in more than 10% of pts, were leucopenia (17%), neutropenia (11%), myalgia (17%) and sensory neuropathy (11%). Twelve pts had treatment emergent sensory neuropathy: 5 (28%) grade 1, 5 (28%) grade 2 and 2 (11%) grade 3. Of the 17 patients evaluable for response, 15 had at least a PR for an ORR of 88% (9 (53%) VGPR, 6 (35%) PR, 2 (12%) SD). The presence of cytogenetic abnormalities did not seem to have a strong impact on response rates, with 88% of pts with 1 or more abnormalities responding compared to 88% with none. The median time to best response was 9 weeks.

Conclusions

In this planned interim analysis, the combination of BVD produced a high ORR, however the current schedule is relatively toxic in this pt population. The majority of the non-hematological toxicities appear to be related to bortezomib and dexamethasone. For this reason, the protocol was amended where bortezomib and dexamethasone are now dosed weekly (days 1, 8, and 15). The amended trial is currently accruing.

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