

A Phase 2 Study of Bortezomib as First Line Therapy In Patients with Multiple Myeloma

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Session Type: Oral Session (Abstract #333)

Introduction

The proteasome is an important therapeutic target in multiple myeloma (MM). Bortezomib, a first-in-class proteasome inhibitor that inhibits proliferation and induces apoptosis, is approved for the treatment of relapsed and refractory MM. We present results in patients (pts) who have completed a phase 2 trial evaluating bortezomib as first-line therapy for MM.

Methods

Newly diagnosed adult pts with measurable disease and a Karnofsky performance status (KPS) $\geq 50\%$ were included. Eligible pts received bortezomib 1.3 mg/m² twice weekly for the first 2 weeks of a 3-week cycle for a maximum of 6 cycles. Pts achieving < partial response (PR) after 2 cycles or < complete response (CR) after 4 cycles received oral dexamethasone 40 mg on the day of and day after each bortezomib dose. Response evaluation criteria were based on modified EBMT criteria, with the addition of a near CR (nCR) category (nondetectable M-protein by electrophoresis but positive immunofixation with normal marrow). The primary endpoint was response rate. Neurologic assessments,

including nerve conduction tests, were performed, and stem cells for transplantation-eligible candidates were harvested at the discretion of the physician.

Results

As of August 2004, 38 pts were accrued. The first 23 pts (44% males, median age 63 yrs) who have now completed the study presented at baseline with IgG (61%), IgA (26%), Freelite (9%), or kappa light chain (4%) disease, with a median KPS of 90 (range, 50-100). The majority of pts were Durie-Salmon stage II (36%) or IIIA (36%). 19 (83%) pts achieved major responses (CR+nCR+PR): CR in 3 pts (13%), nCR in 4 (17%), and PR in 12 pts (53%). A minimal response (MR) was observed in 3 (13%) pts. 43% of pts reached their best response after cycle 2, 39% after cycle 4, and 13% after cycle 6. 14 pts (61%) received dexamethasone combination therapy (8 pts after cycle 2 and 6 pts after cycle 4), and the combination resulted in improved response in 9 pts: 6 pts improved from MR to PR, and 3 pts from stable disease to PR. Five of 5 pts had successful stem cell harvest, and 2 pts who underwent transplantation had complete hematologic recovery. Ten pts discontinued early: 7 due

to adverse events, 1 due to progressive disease, and 2 pts withdrew. One pt with relapsing disease died of sepsis shortly after coming off study. The most common adverse events (grades 1-3) were neuropathy (56%), fatigue (56%), diarrhea (44%), constipation (38%), and neuropathic pain (12%). Neuropathic pain abbreviated therapy for 2 pts, with subsequent resolution of symptoms. One grade 4 neutropenia and one episode of each of the following grade 3 events occurred: abdominal pain, diarrhea, dizziness, dyspnea, fever, neuropathic pain, neutropenia, syncope, and vomiting.

Conclusion

Bortezomib is a promising addition to the treatment armamentarium of initial therapies for previously untreated pts with MM. Major responses were seen in 83% of the pts at the time of this analysis, and combination bortezomib + dexamethasone provided additional benefit. Toxicities, including peripheral neuropathy, were manageable and reversible. Stem cell harvest and engraftment were feasible. Study accrual is ongoing, and final results of the full complement of 42 pts will be available in November 2004. *Abstract #333 appears in Blood, Volume 104, issue 11, November 16, 2004 OA*

PAD Combination Therapy (PS-341/Bortezomib, Adriamycin and Dexamethasone) for Previously Untreated Patients with Multiple Myeloma

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Session Type: Poster Session 632-I (Abstract # 1478)

Background

The most favorable outcomes for patients with MM are seen in those achieving a complete or near complete response following initial

therapy. Therefore, it is logical to explore strategies aimed at improving initial response rates. Bortezomib has shown significant activity in patients with advanced MM and has been shown to be superior to pulsed dexamethasone in this setting. Additional efficacy is seen when dexamethasone is

combined with bortezomib and in vitro synergy is observed with cytotoxic agents such as adriamycin. On this basis, the PAD regimen was investigated as front line therapy for patients with MM. Aims: The primary objective of this Phase I/II study was to assess the feasibility of harvesting