

Bortezomib in Patients with Relapsed or Refractory Mantle Cell Lymphoma (MCL)

Preliminary results of the PINNACLE study

[6563]

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Background: Bortezomib (VELCADE, Vc, Millennium Pharmaceuticals) is a novel proteasome inhibitor effective in relapsed multiple myeloma (MM) and is now being explored in MCL.

Methods: Patients (pts) with relapsed or refractory MCL with a maximum of 2 prior therapies received Vc 1.3 mg/m² IV bolus on days 1, 4, 8, and 11 of a 21-day cycle for 4 cycles beyond complete response (CR) or up to 1 year unless there was disease progression or toxicity. 102 patients have been enrolled (June 2003 through Nov 2004) in this 3-stage, phase 2 study at 29 sites (28 US, 1 UK). Response was assessed by the investigators using International Workshop criteria, while final results will be

based on central radiology review.

Results: 48 pts were evaluable for response at the second stage. Baseline characteristics included median age 66 y, 85% male, 88% International Prognostic Index ≥ 2 , 40% lactic dehydrogenase > normal, 92% Karnofsky performance score $\geq 70\%$, 77% ≥ 1 extranodal site, and 57% with 2 prior lines of therapy. Median time from diagnosis was 2.3 y (range 0.2-9.0). A median of 4 cycles was administered. Median follow-up was 6.2 mo. Response rate (CR + unconfirmed CR [Cru] + partial response) was 40% (19/48) with CR + CRu 6% (3/48). Evaluation of time to progression, response duration, and survival is ongoing. Vc was well tolerated. 34% of 102 pt experienced a serious adverse

event (SAE); however, only 21 of 46 events were considered related to Vc by the investigator. The most common Vc related SAEs included vomiting, abdominal pain, dehydration, and asthenia. Mean platelet (plt) counts followed a cyclical pattern, decreasing during treatment and recovering to baseline by the next cycle, as seen in MM. Only 9.3% of patients had a nadir plt count < 25,000 cells/ μ L.

Conclusions: These data confirm the activity of Vc in MCL, and an update on the 152 pts scheduled for enrollment in this trial will be presented at the meeting. These results support the rapid development of Vc as a new treatment option for MCL. ●

Bortezomib Appears to Overcome Poor Prognosis Conferred by Chromosome 13 Deletion

In Phase 2 and 3 Trials

[6501]

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Background: Deletion of chromosome 13 [del(13)] by conventional cytogenetics is an important adverse prognostic factor for survival in multiple myeloma (MM) patients (pts) regardless of treatment (conventional chemotherapy and autologous or mini-allogeneic transplantation). However, in a phase 2 trial with bortezomib (VELCADE) (SUMMIT), del(13) did not adversely affect survival or response rate (RR). Therefore, we wanted to support this observation in the recently concluded large phase 3 trial, APEX, which allowed us the opportunity to evaluate the prognostic value of del(13) in both the conventional treatment arm (dexamethasone, dex) and the bortezomib arm.

Methods: The APEX trial was a randomized multi-center international phase 3 trial comparing bortezomib and high-dose dex in 669 pts with relapsed MM. This study demonstrated improved survival of pts on bortezomib vs those on dex. Metaphase cytogenetics (MCG) in 168 evaluable pts showed del(13) in 24 (14%). A match-paired analysis of 21 of the 24 evaluable del(13) pts with 41 pts with wild type chromosome 13 balanced for adverse prognostic factors (treatment, age, lines of prior therapy, β_2 M, and albumin) was performed to analyze the impact of del(13) on survival.

Results: A significant decrease in survival was found in 21 evaluable pts with del(13)

compared with 41 pts without this deletion [HR (95% CI) = 3.24 (1.27, 8.23), $P=0.0090$]. Detection of del(13) was associated with markedly decreased survival in the dex arm [HR (95% CI) = 5.72 (1.65, 19.81), $P=0.0020$]. In contrast, in the bortezomib arm, del(13) was not associated with a difference in survival [HR (95% CI) = 1.23 (0.26, 5.74), $P=NS$] or RR [25% del(13) vs 35%, $P=NS$].

Conclusions: Bortezomib therapy appears to overcome the adverse impact of del(13) on survival or response rate consistent with findings in SUMMIT. Del(13) by metaphase cytogenetics appears to remain an adverse prognostic factor for survival in the dex arm. ●