

Bortezomib Demonstrates Superior Efficacy to High-Dose Dexamethasone

In Relapsed Multiple Myeloma: Final Report of the APEX Study

Paul Richardson, P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. Facon, J. Harousseau, D. Ben-Yehuda, S. Lonial, H. Goldschmidt, D. Reece, J. San Miguel, J. Blade, M. Boccadoro, J. Cavenagh, W. Dalton, A. Boral, D. Schenkein, K. Anderson. Med Onc/Hem Malig, Dana-Farber Cancer Inst, MA, USA; Univ Hosp Rotterdam, Netherlands; NY-Presbyterian Hosp, NY, USA; Alta Bates Cancer Ctr, CA, USA; Univ PA Cancer Ctr, PA, USA; Hosp Claude Huriez, France; Hotel Dieu Hosp, Canada; Hadassah Univ Hosp, Israel; Emory Univ, GA, USA; Univ Heidelberg, Germany; Princess Margaret Hosp, Canada; Hosp Univ Salamanca, Spain; Univ Barcelona, Spain; Univ Torino, Italy; St.Bartholomew's Hosp, United Kingdom; H.Lee Moffitt Cancer Ctr, FL, USA; Millennium Pharmaceuticals, Inc., MA, USA

Session Type: Oral Session

Abstract #336.5

Introduction/Methods

This international phase 3 study conducted at 93 sites is the largest randomized study to date in relapsed multiple myeloma (MM). Patients (pts) had to have received 1-3 prior therapies and those with dexamethasone (Dex) refractory disease were excluded. Pts were randomized to bortezomib (VELCADE®) 1.3mg/m² IV d 1, 4, 8, 11 q3wk for 8 cycles followed by 3 cycles on d 1, 8, 15, 22 q5wk, or Dex 40mg PO d 1-4, 9-12, 17-20 q5wk for 4 cycles followed by 5 cycles on d 1-4 every 28 d. The 1^o endpoint was time to progression (TTP); 2^o endpoints included survival, response rate (CR+PR) using EBMT criteria, duration of response, time to response (TTR), time to skeletal events, infections ≥gr 3 and safety; exploratory endpoints included pharmacogenomics and quality of life. Pts with progressive disease



on Dex were eligible to crossover to bortezomib in a companion study.

Results

669 pts were randomized and baseline characteristics were balanced in both arms. Based on a median follow-up of 8.3 mo, bortezomib demonstrated a 78% improvement in median TTP (hazard ratio 0.55, P<0.0001) and a significant 1-y and overall survival benefit over Dex (hazard ratio 0.53, P=0.0005; hazard ratio 0.57,

P=0.0013, respectively). The response rate (CR+PR) was significantly higher (P<0.0001) with CR/nCR rates of 13% for bortezomib vs 2% for Dex. 132 (40%) and 119 (35%) pts received bortezomib or Dex 2nd line, respectively. Importantly, in 2nd-line bortezomib vs Dex, median TTP was 7.0 v 5.6 mo, 1-y survival was 89% vs 72%, and CR+PR rate was 45% vs 26%, respectively. The incidence of ≥gr 3 adverse events and the discontinuation rate were similar across treatments in all pts.

Conclusion

This is the first and largest randomized study demonstrating a survival advantage in relapsed MM, with single-agent bortezomib proving superior to Dex based on TTP, survival, and response. Superiority was also observed in 2nd line and later salvage therapy. The safety profiles of bortezomib and Dex were predictable and toxicities were manageable.

Efficacy	Bortezomib (n=333)	Dex (n=336)	P
Median TTP, mo	6.2	3.5	<0.0001
1 prior line	7.0 (n=132)	5.6 (n=119)	0.0021
> 1 prior line	4.9 (n=200)	2.9 (n=217)	<0.0001
1-year survival, %	80	66	0.0005
1 prior line	89	72	0.0098
> 1 prior line	73	62	0.0109
CR, % (n/N)	6 (20/315)	1 (2/312)	0.0001
1 prior line	6 (8/128)	2 (2/110)	0.0842
> 1 prior line	6 (12/187)	0 (0/202)	0.0002
CR/PR, % (n/N)	38 (121/315)	18 (56/312)	<0.0001
1 prior line	45 (57/128)	26 (29/110)	0.0035
> 1 prior line	34 (64/187)	13 (27/202)	<0.0001
Median TTR (CR/PR), d	43	43	NC

NC = not calculated.