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# Bortezomib: introduction

**Alessandro Corso**
Division of Hematology,
Istituto Scientifico Policlinico
San Matteo, University of Pavia,
Italy

Bortezomib (Velcade®), an inhibitor of 20S proteasome, represents the second attempt in multiple myeloma of a drug interfering with the malignant clone through a new mechanism of interaction with the cellular signaling and cell-to-cell network. The proteasome, in fact, is essential for proper turnover of cellular proteins involved in apoptosis, proliferation, angiogenesis, and metastasis. Bortezomib (Velcade®) has demonstrated both *in vitro* and *in vivo* models to inhibit MM cell growth and adhesion, favor neoplastic cell apoptosis and decrease growth factor secretion and angiogenesis in the bone marrow. Clinical studies has shown as well the efficacy of Bortezomib (Velcade®) in different setting of patients. The first study SUMMIT[1] (*Study of Uncontrolled Myeloma Management with proteasome Inhibition Therapy*) was performed in heavily pretreated patients refractory or relapsed after a median of 6 previous lines of therapies. In this study Bortezomib (Velcade®) used as single agent at the standard schedule (1.3 mg/m$^2$ twice weekly for 2 of 3 weeks for up to 8 cycles), produced a response rate (CR+PR) of 27%. The phase II Crest[2] (*Clinical Response and Efficacy Study of bortezomib in the Treatment of refractory myeloma*) trial of 2 doses of single agent bortezomib showed a response rate of 38% at 1.3 mg/m$^2$ and 30% at 1 mg/m$^2$ in patients refractory or relapsed after 1 line of therapy. Responses were improved when dexamethasone was added in patients with suboptimal response to Bortezomib (Velcade®). The extension of treatment beyond 8 cycles in SUMMIT trial produced a median duration of response of 12.7 months and a median survival of 17 months.[3]

The international multicenter phase III APEX[4] (*Assessment of Proteasome inhibition for Extending Remission*) trial aimed to compare Bortezomib (Velcade®) with the standard high-dose dexamethasone. This trial demonstrated the superiority of Bortezomib (Velcade®) either in terms of response rate, progression free survival and overall survival particularly in patients who had been treated with only 1 line of therapy.

Basing of these results and keeping into account the additive anti-myeloma activity showed by Bortezomib (Velcade®) in preclinical studies with other agents, several Bortezomib (Velcade®)-based combinations have been designed in order to improve response and survival in myeloma patients. Moreover, although the more relevant evidences are reported on refractory/ relapsed patients, there are also some preliminary results on the efficacy of Bortezomib (Velcade®) used as single agent or in combination with other drugs even as front-line therapy.

The aim of this publication is to summarize the bulk of information available on Bortezomib (Velcade®) updated with the recent results presented at the last ASH meeting in Atlanta. Clearly, only the more significant and consistent studies will be reported, since more than 100 abstracts have been brought at the meeting on bortezomib. In particular, in this review on Bortezomib (Velcade®) will be included: 1) an updating on APEX study, 2) an overview on the more interesting and effective combination regimens adopted in relapsed/refractory patients or at onset, 3) a look on the results of the study of Bortezomib (Velcade®) as front-line therapy, and 4) a review on the side effects focusing on the management of the more frequent, namely thrombocytopenia and peripheral neuropathy.

## References

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