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## Bortezomib in lymphoma

Goy A

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**B**ortezomib, the first of its class of new agents called proteasome inhibitors, was approved by the FDA initially as third line therapy in multiple myeloma (MM) in May 2003 and added early 2005 as second line option in this disease. In parallel activity of bortezomib has been shown in a variety of lymphomas especially in mantle cell and follicular lymphoma subtypes. Though inhibitors of the proteasome can be considered as targeted agents (i.e. affecting a discrete enzymatic subunit in the UPP pathway), the antitumor effect of proteasome inhibitors results from the disruption of multiple pathways in cancer cells (cell cycle, cell survival, growth and differentiation) as well as on microenvironment (adhesion molecules and angiogenesis). Multiple studies now have confirmed the activity of bortezomib as single agent especially in MCL with an ORR of 42% across all phase II studies done including the multicenter pivotal trial. Additional activity was suggested also in the early trials in other

subtypes of NHL such as follicular lymphoma, marginal zone lymphoma and Waldenstrom's Macroglobulinemia, all being tested further in ongoing trials. Pre-clinical studies also suggest that bortezomib can help overcome chemoresistance partly through a synergy with a variety of other anticancer agents including cytotoxics, monoclonal antibodies and radiation induced cell damages, providing a rationale for combination studies. Bortezomib plus rituximab was just completed in relapsed FL or MZL while other combinations with chemotherapy (R-CHOP, R-CVP, R-Fludara-bine, R-HyperCVAD or radioimmunotherapy) are still ongoing or underway.

Proteasome inhibition is not only a novel anti-cancer therapy approach but it also represents an excellent example of the impact of the continuous improvement of our understanding of cancer cells biology, leading the field toward a new era of rational therapeutics.