The transcription factor NF-κB serves as a central mediator of inflammatory and immune processes and is constitutively activated in many solid and hematopoietic malignancies. Although gain- or loss-of-function mutations directly leading to NF-κB activation are rare, genetic alterations of upstream signal and receptor kinases and extracellular signals from a proinflammatory tumor microenvironment can contribute to constitutive NF-κB activity (1). Activation of canonical and noncanonical NF-κB transcriptional activity relies upon proteasome-mediated degradation of ubiquitinated cytoplasmic inhibitor-κB, which sequesters NF-κB into the cytoplasm and away from the nucleus. In response to different upstream stimuli, inhibitor-κB kinases phosphorylate inhibitor-κB, leading to its ubiquitination and degradation by the proteasome, freeing NF-κB to translocate into the nucleus. Introduction of a mutant dominant-negative inhibitor-κB, which sequesters NF-κB in the cytoplasm and away from the nucleus, can demonstrate enhanced cytotoxicity in an HNSCC cell line relatively resistant to NF-κB inhibition alone with the addition of MAPK or STAT3 pathway blockade (5). Together, these data provided early evidence in HNSCC of targeted therapeutic resistance due to lack of inhibition of coactivated progrowth and prosurvival signaling pathways, a phenomenon now well recognized as a common mechanism of resistance to single-modality targeted therapy in solid tumors.

Exploration of upstream genetic alterations or microenvironmental factors leading to the coactivation of NF-κB, MAPK, and STAT3 pathways led many researchers to investigate the potential role of cell surface kinase receptors such as the EGFR. Given existing preclinical and clinical evidence suggesting an additive...
or synergistic cytotoxic effect with the combination of NF-κB and EGFR targeted therapies, a phase I trial combining bortezomib, the anti-EGFR monoclonal antibody cetuximab, and radiation in patients with previously untreated, advanced-stage HNSCC was initiated (6). However, this clinical trial was halted before accrual was completed because of an unexpectedly high rate of early disease progression in these patients. Molecular evidence from patient tumor biopsies revealed enhanced activation of NF-κB and MAPK pathway elements downstream of EGFR, potentially due to antagonism of radiation-induced EGFR degradation following proteasome inhibition. Given that *in vitro* and *in vivo* murine models can be powerful screening tools for different therapies, this result highlights the caution that must be used when extrapolating information gleaned from preclinical work into the rational design of human clinical trials.

Evaluation of bortezomib in patients with non-small cell lung cancer (20) has shown similar results. Several early phase I and II trials combining bortezomib with standard chemotherapeutic or kinase receptor–targeted therapies failed to demonstrate improved disease control or survival (7). In addition, more recent work has demonstrated that initial sensitivity of RAS- and p53-mutant NSCLC cells to bortezomib-induced NF-κB inhibition was subsequently lost due to the development of NF-κB-independent resistance mechanisms *in vitro* (8). Similar to what has been observed in HNSCC, these reports establish a consistent trend of acquired therapeutic resistance to proteasome inhibition alone through unaltered signaling of coactivated pro-growth and pro-survival signaling pathways.

The story of limited activity of bortezomib monotherapy in the treatment of solid tumors contrasts with the remarkable success bortezomib has shown in the treatment of hematologic malignancies. Given the known role of NF-κB in immune signaling, bortezomib was evaluated early by others as a therapy for different forms of leukemia and lymphoma, and these studies demonstrated constitutive NF-κB activation. Following large, multicenter advanced-phase clinical trials demonstrating improved outcomes compared with existing standard therapies, bortezomib, marketed as Velcade (Millennium), was FDA approved as second-line therapy for refractory mantle cell lymphoma and as first-line therapy for multiple myeloma in 2006 and 2008, respectively (9). Similarly, carfilzomib, marketed as Kyprolis (Onyx), was FDA approved in 2012 for the treatment of multiple myeloma that has not shown a response to at least two prior therapies after demonstrating significant single-agent activity in clinical trials. Mechanistically, the differential success of bortezomib in treating these malignancies may lie, in part, in its ability to effectively modulate the bcl-2 family of apoptosis-regulating proteins, known to be critical for transformed leukocyte proliferation and survival (7).

Beginning with the article by Sunwoo and colleagues (2) in 2001 and in work from others, the story of bortezomib in solid and hematologic malignancies has taken divergent courses. Although bortezomib alone demonstrates significant single-agent activity in some hematopoietic cancers, the development of therapeutic resistance due to unaltered signaling through coactivated signaling pathways observed following single-agent bortezomib treatment in solid tumors has mirrored observations made with many different targeted therapies. Nevertheless, this work investigating novel combinations of existing targeted therapies, including bortezomib, holds promise. Enhanced recognition of the ability of bortezomib and its newer analogues to induce altered protein folding responses, and endoplasmic reticulum stress, with subsequent enhancement of tumor cell antigenicity, places proteasome inhibitors in an ideal position to be combined with immunotherapies (10). However, more investigation is needed, given the potential immunosuppressive effects proteasome inhibition may exert on cells of adaptive immunity. Although second-generation proteasome inhibitors are FDA approved for clinical use and also being evaluated for their effectiveness in the treatment of solid tumors, bortezomib remains the subject of continued research given its remarkable clinical activity in hematopoietic malignancies, FDA approval, and encouraging preclinical data as a component of combination therapy in various solid tumor models.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

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