# Session VII: Novel Agents for Treatment of

# Waldenström's Macroglobulinemia

# Abstract 144

## Special Guest Lecturer: K. Anderson

**Applying the Lessons Learned from the Treatment of Multiple Myeloma to Waldenström's Macroglobulinemia.** Kenneth C. Anderson, Dana Farber Cancer Institute. Boston, MA, USA.

As a result of advances in oncogenomics on the one hand and increased understanding of the role of the BM in the pathogenesis of MM on the other, a new treatment paradigm targeting the tumor cell and its BM microenvironment to overcome drug resistance and improve patient outcome has now been developed in MM, which has already and will continue to facilitate development of similar novel treatment options in WM. Thalidomide, lenalidomide, and Bortezomib are three agents which target the tumor cell in its microenvironment in both laboratory and animal models which have rapidly translated from the bench to the bedside, first used effectively to treat relapse refractory disease and then combined with dexamethasone in the transplant candidates and melphalan and prednisone in the elderly patients to achieve increased frequency and extent of response, as well as prolonged progression free and overall survival, when used as initial therapy for newly diagnosed MM. Ongoing and future efforts are identifying next generation therapies in MM on the one hand, and using oncogenomics to inform the design of combination trials on the other. Profiling and array comparative genomic hybridization (aCGH) are allowing for RNA and DNA based, respectively, classifications of patient. Examples of promising novel targeted therapies include agents targeting the tumor cell surface include CD40, which is expressed on MM and malignant B cells and triggers tumor cell growth and survival. Already clinical trials of humanized anti- CD40 antibody, both alone and with lenalidomide to enhance antibody dependent cellular cytotoxicity (ADCC), are ongoing. FGFR 3 is expressed on the 10-15% of MM patient cells with t4:14 translocation and is being targeted clinically with both small molecule tyrosine kinase inhibitors. CS-1 represents a novel cell surface MM antigen targeted with HuLuc63 humanized monoclonal antibody, which mediates selective ADCC in vitro and is now under evaluation in phase I clinical trials. Cytokines are also being targeted in MM therapeutics. Vascular endothelial growth factor (VEGF) mediates modest growth, survival and migration of MM cells; the small-molecule VEGF receptor inhibitor pazopanib, which targets both tumor and endothelial cells, is under evaluation in a clinical trial. B cell activating factor mediates MM cell growth in the BM milieu, which can be abrogated by either a small molecule inhibitor or monoclonal antibody. Within the MM cell, exciting intracellular targets MEK, PKC, NF-kB, Akt, and proteasomes. The Ras/Raf MAPK cascade mediates growth of MM cells, and a novel MEK inhibitor AZD664 can block phosphorylation of ERK triggered by IL-6, IGF-1, and CD40 with associated inhibition of MM cell growth. Importantly, it can also inhibit RANKL and MCSF induced differentiation of osteoclasts from peripheral blood mononuclear cells as well. Therefore a derived clinical trial of AZD 2664 in MM will determine its efficacy in abrogating both tumor cell growth and bone disease. Enzastaurin is a Protein kinase C inhibitor which inhibits MM cell proliferation, survival, and migration, as well

as induces synergistic cytotoxicity with Bortezomib, and a derived clinical trial of the combination is starting in MM. Recent studies have defined mutations in NF-kB signaling cascades; moreover, adhesion of MM cells to BM upregulates NF-kB in MM cells with resultant tumor cell survival and drug resistance; therefore targeted therapies inhibiting NF-kB activation via these cascades hold great promise, ie . MLN120B, a novel IkB kinase b inhibitor. Akt activation in MM mediates growth and drug resistance; moreover, Bortezomib upregulates Akt in MM cells, and blockade of this effect with Akt inhibitor perifosine induces synergistic cell death. Already a clinical trial of single agent perifosine is completed, and a combination bortezomib-perifosine trial ongoing based upon these preclinical studies. Finally Bortezomib has established the therapeutic efficacy of targeting proteasomes in MM. Two next generation proteasome inhibitors are NPI0052 and Carfilzomib, both of which can overcome Bortezomib resistance in preclinical in vitro and in vivo studies. NPI 0052 will examine whether more broad proteasome inhibition is useful as it inhibits chymotryptic, tryptic, and caspase-like activities of the proteasome, wherease Bortezomib targets primarily chymotrypic activity. In contrast, Carlfizomib more potently targets the chymotrpytic proteasome activity than does Bortezomib. Phase I/II clinical trials of both are ongoing. Oncogenomics is not only useful for identify novel therapeutic targets and validating targeted therapies, but also is useful for informing the design of clinical trials. For example, bortezomib inhibits DNA repair and can sensitize or overcome resistance to DNA damaging agents including alkylating agents and anthracyclines. Already a large randomized clinical trial showed that Bortezomib and doxil resulted increased extent and frequency of response, as well as prolonged progression free and overall survival, resulting in its FDA approval to treat relapsed myeloma. Heat shock protein 90 is overexpressed in MM and is a chaperone for kinases mediating growth, survival, drug resistance, and migration of MM cells on the one hand and for ubiquinated protein to the proteasome and aggresome for its degradation. HSP 90 tanespimycin coupled with Bortezomib can sensitize or overcome resistance to Bortezomib and an international randomized phase III clinical trial is comparing Bortezomib with Bortezomib and tanespimycin in relapsed MM. Lenalidomide mediates caspase 8 and Bortezombi primarily caspaxe 9 mediated apoptosis of MM cells, and the combination trigger synergistic cytotoxicity in vitro. Excitingly, combined lenaldiomide and bortezomib induce responses in the majority of patients with relapsed refractory MM unresponse to one or both of these agents when give alone. Perhaps the most exciting ongoing combination clinical trial is of the histone deacetylase inhibitor LBH 589 and the proteasome inhibitor Bortezomib, which mediate synergistic MM cytotoxicity in vitro by block both the aggresome/autophagy and proteasome cascades of protein degradation, respectively. In conclusion, combination therapies have been curative in acute lymphocytic leukemia, Hodgkins disease, and testicular cancer. In MM and WM, future progress in will also be based upon using science to inform the design of the optimal combined treatments, and high throughput assays can now assess the ability of combination therapies to induce death of tumor cells, both alone and in the BM microenvironment. This new paradigm targeting the tumor cell in its microenvironment has great promise not only to change the natural history of MM, but also to serve as a model for targeted therapeutics directed to improve outcome of patients with other hematologic malignancies such as WM, and solid tumors as well.