ATL313, A Potent, and Selective A2A Agonist as a Novel Drug Candidate for the Treatment of Multiple Myeloma

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Abstract
Adenosine A2A receptor agonists, in combination with standard of care Multiple Myeloma (MM) therapeutics, demonstrate potent and highly synergistic anti-proliferative effects in 8-cell malignancies. We have previously reported that A2A agonists show significant anti-tumor synergy with established MM drugs in several anti-tumor models including: tumor cell lines, in vivo xenograft models and in primary human MM tumor cells vs. vivo. While these initial studies robustly demonstrate the proof of concept for this unexpected synergistic interaction, they were conducted with research compounds at doses and routes of administration resulting in exposure above therapeutically relevant levels. Here we describe the preclinical evaluation of ATL313, a potent and highly selective adenosine A2A receptor agonist that synergizes with established anti-MM agents resulting in enhanced efficacy in pre-clinical models of MM. ATL313 shows binding affinity for the human A2A receptor in the low single digit nM range and shows at least 80-fold selectivity for A2A compared to other adenosine receptor subtypes. As with other agonists examined, the activity of ATL313 is dependent on expression of the A2A receptor in the target cell and demonstrates single agent inhibition of proliferation in MM cell lines with an IC50 of 0.5-1 nM in the MM.1S cell line. ATL313 potently synergizes with glucocorticoids (dexamethasone and prednisolone), bortezomib, lenalidomide, melphalan and doxorubicin as well as emerging drug classes including HDAC inhibitors and HSPI90 inhibitors. Substantial increases in inhibition of proliferation and cell killing and 2 to 10 fold potency shifts are observed with ATL313 combinations in MM cell lines including those both sensitive and resistant to current MM agents. In MM.1S cells, addition of 0.5 nM ATL313 to 100 nM Dexamethasone results in 95% inhibition of proliferation as compared to approximately 45% and 70% inhibition with either ATL313 or dexamethasone alone respectively. This combination results in a 30 fold shift in the dexamethasone IC50 and a combination index of 0.1 indicating high levels of synergy. Furthermore, the combination results in nearly complete cell killing as compared to reductions in number of 50% and 70% by ATL313 or dexamethasone respectively. Importantly, we have observed that A2A agonists are effective in combination in cells resistant to dexamethasone. Evaluation of A2A agonist combinations in a panel of 83 cell lines including solid tumor types and hematological malignancies demonstrates that synergy is highly selective for B-cell malignancies with little to no activity in solid tumor cell lines. We have now translated these in vitro results with ATL313 to a mouse xenograft model where the ATL313 is delivered using continuous infusion osmotic pumps. Doses of 10, 33, 100 and 330 nM were evaluated in addition to Q2 subcutaneous bolus dosing at 0.1 mg/kg and demonstrate synergistic anti-proliferative effects with no significant body weight loss. Mice bearing subcutaneous MM.1S tumors show a 43% reduction in tumor volume after treatment with the combination of dexamethasone (1 mg/kg, s.c. QD) and ATL313 (100 mg/kg/min) for 24 days as compared to a 500% or 700% increase after treatment with either ATL313 or dexamethasone, respectively. Furthermore, treatment with ATL313 in combination with dexamethasone confers a statistically significant survival advantage as compared to either agent alone. In summary, we report the preclinical evaluation of ATL313, a potent and highly druggable A2A agonist as a novel, selective and synergistic drug candidate for the treatment of MM. Our preclinical data provides compelling evidence in support of the further development of ATL313 for use in multi-drug combination therapy of MM.