INTRODUCTION
Inhibitor of apoptosis (IAP) antagonists are being tested in the clinic for the treatment of cancer as they can switch cancer cell TNF-α signaling from being pro-survival to being pro-apoptotic, and relieve the block on effector caspase activation. Astex has used fragment-based-drug discovery to develop a second generation of IAP antagonists, which are non- peptidomimetic and do not contain an alanine as a warhead. Melanoma is a highly aggressive malignancy with an exceptional ability to develop resistance to targeted therapies. Here we report data from models of melanoma in which our IAP antagonists have demonstrated potent activity in vivo and in vitro activity. Using a predictive biomarker strategy, we have also demonstrated activity in a patient-derived xenograft (PDX) model. Cancer Stem Cell (CSC) fractions within melanoma cell lines are more apoptosis-resistant than the bulk cell population and they have been associated with resistance to cancer therapy, relapse and disease progression. We have demonstrated that our compounds induce enhanced levels of apoptosis in such CD133+ cancer stem cell (CSC) populations, thereby demonstrating the potency of our dual antagonists.

IAAP ANTAGONISTS DERIVED FROM FRAGMENT-BASED DRUG DISCOVERY

AT-IAP ACTIVITY IN MELANOMA CELL LINES AND EX VIVO PDX CELLS

A375 MELANOMA XENOGRAFT PK/PD DATA

* Reduced levels of cIAPs were decreased in A375 xenograft tumour spheres up to 24 h after dosing, and elevated levels of apoptosis markers (cleaved PARP and cleaved caspase-3) were evident

** Significant tumour concentrations of AT-IAP were measured at 6 and 24 h, suggesting daily 50 mg/kg p.o. dosing achieves good coverage of cIAP1 and XIP antagonists

SUMMARY AND CONCLUSIONS
* AT-IAP represents a novel class of IAP antagonist with a potent dual cIAP1 and XIAP antagonist profile
* In vitro cell line testing suggested that AT-IAP has significant activity against a panel of melanoma cell lines and ex vivo PDX cells, which was enhanced on addition of exogenous TNF-α
* Significant in vivo activity has been seen in A375 melanoma cell line xenograft model after oral dosing with AT-IAP, and also in a melanoma PDX model predicted to be sensitive by Astex’s dual biomarker selection strategy
* Our preliminary studies have shown that AT-IAP has potent apoptosis-inducing capacity in melanoma CSC fractions

REFERENCES

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