Targeting Multiple Myeloma: Using Translational Research to Inform the Development Path for the KSP inhibitor ARRY-520

The discovery of novel mitosis-specific targets, such as the kinesin spindle protein (KSP, eg5), offered the promise of next-generation anticancer agents that could improve on the activity and safety profile of existing drugs. The clinical history of these agents, however, has not lived up to that promise: KSP inhibitors have shown disappointing activity in multiple clinical trials, predominantly in solid tumors.

ARRY-520 is a next-generation KSP inhibitor, with improved potency and superior preclinical activity. Given the poor clinical history of KSP inhibitors, it was critical to apply a rational approach to the identification of clinical indications that might enable successful development of ARRY-520.

By focusing on mechanisms of cell death in response to ARRY-520, we found that many cell lines require prolonged (>72h) and continuous exposure to ARRY-520 to elicit apoptosis. However, a subset of cell lines - predominantly hematological cells - underwent cell death within 24h of treatment. Investigation of the biological mechanisms underlying cell death in response to ARRY-520 showed that 1) cells undergoing rapid apoptosis express the short-lived survival protein Mcl1, a member of the BCL2 family and 2) the rapid degradation of Mcl1 following mitotic arrest by ARRY-520 is required for early cell death. These data suggest that tumors that rely on Mcl1 for survival may be clinically more sensitive to ARRY-520. Such tumor types include myeloma and lymphomas as well as subsets of other hematological and solid tumors. We have seen that *in vivo* myelomas are amongst the most sensitive models to ARRY-520. Further, the *in vivo* activity of ARRY-520 has shown striking additivity and synergy with both bortezomib and lenalidomide, which are standards of care in myeloma. In particular, the combination activity with bortezomib has been observed in several models that are resistant or poorly responsive to bortezomib as a single agent.

These data supported clinical investigation of ARRY-520 in multiple myeloma. In a phase 1 dose-escalation study of single agent ARRY-520 in relapsed and refractory multiple myeloma, ARRY-520 was well-tolerated, with reversible neutropenia the most common dose-limiting adverse effect. Clinical activity of ARRY-520, as evidenced by partial and minor responses and prolonged stable disease, have also been seen in this patient population, all of whom have been pretreated with both IMiDs (lenalidomide, thaldomid) and bortezomib. ARRY-520 is currently undergoing investigation in a phase 2 single agent study and a phase1b study in combination with bortezomib.

In summary, while multiple clinical studies of KSP inhibitors have shown negative data, by employing translational research, we have identified multiple myeloma as a preferred indication for development of KSP inhibitors and demonstrated a clinical proof-of-concept for ARRY-520 in this indication.