ARRY-162, A Potent and Selective MEK 1/2 Inhibitor, Shows Enhanced Efficacy in Combination with Other Targeted Kinase Inhibitors and with Chemotherapy

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Abstract

MAPK kinase-pathway activation is implicated in uncontrolled cell proliferation and tumor growth in numerous tumor types. Targeting MAPK, an attractive strategy for the treatment of cancers driven by elevated MAPK activity, is complicated by the fact that MAPK signaling crosstalk between the pathways is a major contributor to treatment resistance. Optimal therapeutic strategies will therefore require the development of agents that inhibit multiple MAPK pathway components. In this study, we evaluated the activity of the MEK 1/2 inhibitor ARRY-162, in combination with inhibitors of mTOR and the EGFR receptor family as well as standard-of-care chemotherapeutics, in various tumor xenograft models.

ARRY-162 is a novel, potent and selective alternate MEK inhibitor that has entered clinical development for the treatment of cancer. In vitro, ARRY-162 is efficacious in numerous tumor xenograft models that harbor BRAF or KRAS mutations. ARRY-162 activity, alone and in combination with an mTOR inhibitor (ARRY-mTOR-1) was evaluated in A549 (KRAS mutant) and in COLO 205 (KRAS mutant) and constitutively active PI3K models. In A549, both ARRY-162 and ARRY-mTOR-1 as single agents, demonstrated significant efficacy, with ARRY-162 showing a more pronounced effect on tumor growth inhibition, consistent with a MEK-specific mechanism. In COLO 205, neither ARRY-162 alone nor with ARRY-mTOR-1 showed significant activity. Combination of these treatments enhanced TGI and produced significant tumor growth delay confirming recent reports that MEK pathway activation confers resistance to MEK inhibitors. The L61R-CRC model (KRAS mutant and pEGFR overexpression) had demonstrated resistance to EGFR-targeted therapies (i.e., cetuximab). In L61R xenografts, ARRY-162 produced modest TGI (33%) as did ARRY-543, an AKT inhibitor (57% TGI), with no tumor regressions in either single agent group. Combination treatment produced 80% TGI with 3 partial responses (90% tumor regression). Thus, combining ARRY-162 with agents that inhibit pathways downstream of MEK appears to enhance efficacy and may warrant further exploration.

The MAPK, PI3K and EGFR signaling pathways are frequently deregulated in cancer. These two pathways interact and share inputs and outputs, leading to pathway redundancy and resistance to single-targeted therapy. One approach to limiting drug resistance is to use combination treatments, thus inhibiting multiple nodes in these pathways. The MAPK, PI3K and EGFR signaling pathway all have crosstalk interactions at multiple levels. In A549, both ARRY-162 and ARRY-mTOR-1 alone produced 80% TGI and gemcitabine or paclitaxel alone achieved 90% and 45% TGI in A549 or COLO 205 xenografts, respectively. When dosed as combination treatments in either model, TGI was enhanced and regressions were achieved. Thus, ARRY-162 has demonstrated significant single agent activity as well as promoting additivity with anti-cancer agents. The added activity in these wide-ranging models with many different chemotherapeutics suggests a large versatility may be expected when this drug is used in combination in the clinic.

Methods

QuickTime Video

Activity in Combination with an mTOR Inhibitor

Activity in Combination with Cytotoxics

Summary

ARRY-162 demonstrates significant single agent activity and enhances the activity of targeted therapies and standard cytotoxic agents

- is effective against KRAS and BRAF mutant tumors (A498, LoVo, COLO 205, MapCa2-2), on continuous and intermittent dosing schedules
- enhances the activity of an mTOR inhibitor in a tumor with mutant KRAS and constitutively active PI3K pathway (COLO 4601)
- enhances the activity of EGFR and ErbB2 targeted agents
- enhances the activity of standard cytotoxic agents (paclitaxel and gemcitabine) in p53 mutant tumors with an activated MAPK pathway (COLO 205, MapCa2-2), on continuous and intermittent dosing schedules

ARRY-162, alone and in combination, was well-tolerated in these experiments.

These data suggest that ARRY-162 will be a versatile agent in combination with a variety of antitumor agents in the clinic.

ARRY-162 is currently in a phase 1 dose escalation trial in patients with solid tumors.