

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 MEK may inhibit cancer cell signaling mediated by a wide variety of signals, making MEK an attractive target for the treatment of cancer. Recent data suggest that some cancers are resistant/refractory to MEK inhibitors due to activation of alternate pathways. Optimal efficacy may require inhibition of additional pathways. We report activity of the MEK inhibitor ARRY-162, in combination with inhibitors of mTOR and the ErbB receptor family as well as standard-of-care chemotherapeutics, in various tumor xenograft models.

ARRY-162 is a novel, potent and selective allosteric MEK inhibitor that has entered clinical development for the treatment of cancer. *In vivo*, 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 (ARR-mTOR-1) was evaluated in A549 (KRAS mutant) and in NCI-H460 (KRAS mutant and constitutively active PI3K) models. In A549, both ARRY-162 and ARR-mTOR-1, as single agents, produced significant tumor growth inhibition (TGI; 71 and 82%, respectively). Enhanced inhibition (89% TGI) and regressions were seen when these agents were given in combination. In NCI-H460, ARRY-162 alone was inactive while ARR-mTOR-1 showed moderate activity (64 %TGI). Combination of these treatments enhanced TGI and produced significant tumor growth delay confirming recent reports that mTOR pathway activation confers resistance to MEK inhibitors. The LoVo CRC model (KRAS mutant and pEGFR overexpression) has demonstrated resistance to EGFR-targeted therapies (i.e., cetuximab). In LoVo xenografts, ARRY-162 produced modest TGI (50%) as did ARRY-543, a pan-ErbB TKI (57% TGI), with no tumor regressions in either single agent group. Combination treatment produced 83% TGI with 3 partial responses (>50% tumor regression). Thus, combining ARRY-162 with agents that inhibit signaling through the ErbB pathway produced additive efficacy and significant regressions. Lastly, the activity of ARRY-162 in combination with gemcitabine or paclitaxel was determined. ARRY-162 alone produced 40 and 79% TGI while gemcitabine or paclitaxel alone achieved 16% and 43% TGI in MiaPaCa or COLO 205 xenografts, respectively. When dosed as combinations in either model, TGI was enhanced and regressions were achieved. Thus, ARRY-162 has demonstrated significant single agent activity as well as promising 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.

Array's company policy is to not disclose exact structure until the compound is in Phase 2 trials. Disclosure of the structure should not impact the importance or the interpretation of the data we wish to present.

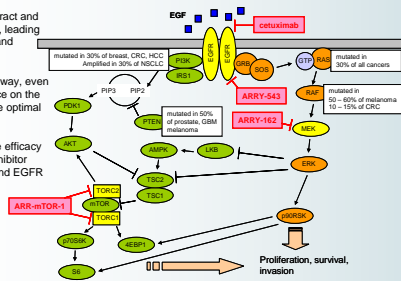
MAPK, PI3K and EGFR signaling

The MAPK and PI3K pathways are frequently deregulated in cancer

These two pathways interact and share inputs and outputs, leading to pathway redundancy and resistance

Inhibition of a single pathway, even when there is dependence on the pathway, may not provide optimal therapeutic benefit

We have investigated the efficacy of combining the MEK inhibitor ARRY-162 with mTOR and EGFR inhibitors



Methods

All *in vivo* studies were performed in accordance with IACUC guidelines and in harmony with the Guide for Laboratory Animal Care and Use

In vivo tumor growth experiments

NCI-H460

- human large cell lung carcinoma
- tumors grown in female nude mice by implanting 4.7 x 10⁶ cells subcutaneously in the right flank
- mice randomized into groups of 7, based on tumor size, 8 days after implantation

A549

- human lung carcinoma
- tumors grown in female nude mice by implanting 5 x 10⁶ cells subcutaneously in the right flank
- mice randomized into groups of 6, based on tumor size, 10 days after implantation

LoVo

- human colon adenocarcinoma
- tumors grown in female nude mice by implanting 3 x 10⁶ cells subcutaneously, with Matrigel, in the right flank
- mice randomized into groups of 7-8, based on tumor size, 10-12 days after implantation

COLO 205

- human large intestine adenocarcinoma
- tumors grown in female nude mice by implanting 5 x 10⁶ cells subcutaneously in the right flank
- mice randomized into groups of 4, based on tumor size, 14 days after implantation

MiaPaCa-2

- human pancreatic carcinoma
- tumors grown in female nude mice by implanting 5 x 10⁶ cells subcutaneously, with Matrigel, in the right flank
- mice randomized into groups of 8, based on tumor size, 10 days after implantation

Tumor Volume Measurements

Tumors were measured 2 or 3 times a week after initiation of treatment. Volumes were determined using the formula: volume = (length x width)²/2

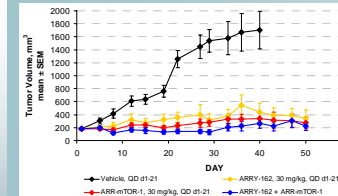
Compounds and Dosing Regimens

Compound	Source	Dose	Frequency
ARRY-162	Array BioPharma	30 or 300 mg/kg, PO	QD d1-3 x 2 cycles Q4d x 4 cycles
ARR-mTOR-1	Array BioPharma	30 mg/kg, PO	QD, d1-21
ARRY-543	Array BioPharma	50 or 100 mg/kg PO	BD, d1-21
cetuximab	Imclone	2 mg/kg, IP	Q4D, d1-21
paclitaxel	Astrotech	30 mg/kg, IP	d1, d8
gemcitabine	Lilly	120 mg/kg, IP	Q4d x 4

Mutation status of tumor lines

	A549	NCI-H460	LoVo	MiaPaCa-2	COLO 205
KRAS	G12S	Q61H	G13D	G12C	
BRAF					V600E
PIK3CA		E545K			
p53				R248W	Y103 L111>L
FBXW7			R505C		
SMAD4					1_904del904
APC			M1431fs*42 R1114*		T1556fs*3
p16	M1 *157del	1_457del457		M1 *157del	
STK11	Q37*	Q37*			

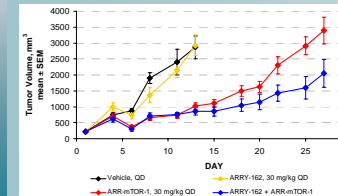
Activity in Combination with an mTOR Inhibitor



A549

ARRY-162 and mTOR inhibitors are both potent inhibitors of tumor growth in a KRAS mutant tumor

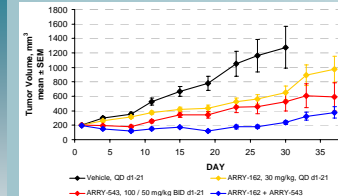
Slight benefit for combination



NCI-H460

Activity of mTOR inhibitor enhanced by the addition of ARRY-162 in a KRAS + PI3K mutant tumor

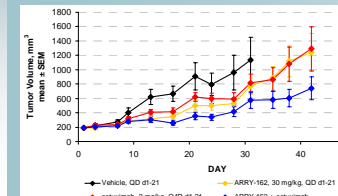
Activity in Combination with dual EGFR/ErbB2 or selective EGFR Inhibitors



LoVo

Moderate inhibition of tumor growth when combined with a KRAS mutant tumor

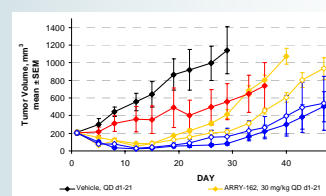
Additive inhibition of tumor growth when combined with a dual EGFR/ErbB2 inhibitor



LoVo

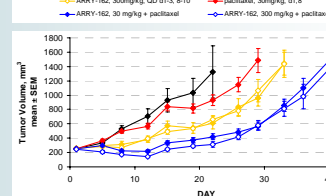
Additive inhibition of tumor growth when combined with the EGFR mAb cetuximab

Activity in Combination with Cytotoxics



COLO 205

Additive inhibition of tumor growth, on continuous and intermittent dosing schedules, when combined with paclitaxel in a BRAF + p53 mutant tumor



MiaPaCa-2

Additive inhibition of tumor growth, on continuous and intermittent dosing schedule, when combined with gemcitabine in a KRAS + p53 mutant tumor

Summary

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

- is efficacious against KRAS and BRAF mutant tumors (A549, LoVo, COLO 205, MiaPaCa-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 (NCI-H460)
- enhances the activity of EGFR and EGFR / ErbB2 targeted agents
- enhances the activity of standard cytotoxic agents (paclitaxel and gemcitabine) in p53 mutant tumors with an activated MAPK pathway (COLO 205, MiaPaCa-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