A Phase 1 Study of MEK Inhibitor MEK162 (ARRY-438162) in Patients with Biliary Tract Cancer


Background: The RAS/RAF/MEK/ERK pathway plays a major role in cell growth and survival, and is often aberrantly activated in many cancers. MEK162 is an orally bioavailable, potent, selective, ATP-uncompetitive inhibitor of MEK1/2 that: has nanomolar activity against purified MEK enzyme (IC50 = 12 nM) exhibits both in vitro and in vivo efficacy with submillimolar levels of ERK phosphorylation in numerous cancer cell lines (IC50 values ≥ 5 μM) has demonstrated efficacy in several xenograft tumor models in mice, including those harboring KRAS or BRAF mutations enhances the activity of targeted therapies and standard phototherapy agents in nonclinical tumor models.

Methods: The objectives of this expansion cohort trial were to characterize the safety profile, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of MEK162 in pts with advanced or metastatic, unresectable biliary tract cancer, with 1 prior systemic anticancer therapy (including adjuvant therapy) and 1 prior surgical treatment; also with the intent to collect biomarker data (oncoCarta panel, archival sample).

Results: Sixty-five (65) pts were enrolled at 45 dose levels. The most frequent AE that led to dose reduction was Gr 1/2 central serous-like retinopathy (1 pt each) and ocular irritation (1 pt each).

Treatment-related AEs in > 10% of Patients:

- Grade 1
  - Anorexia
  - Fatigue
  - Rash erythematous
- Grade 2
  - Anorexia
  - Fatigue
  - Rash maculo-papular
  - Rash papular
  - Rash pruritic
  - Rash pustular
- Grade 3
  - Anorexia

Pharmacokinetics:

- MEK162 was absorbed quickly, reaching maximum concentrations in plasma within 2 hrs of dosing.
- MEK162 exhibits linear PK with modest accumulation on repeat dosing (68% increase, 44% CV).
- Median half-life of 3.63 hrs, geometric mean CL/F of 21.9 L/hr, V/F of 145 L were consistent with those observed in a healthy subject population.
- Maximum reductions in TNFα, IL6 and IL8 relative to baseline are seen.

Pharmacodynamics:

- 5 pts were evaluable for efficacy response evaluations.
- MEK162 was initiated at 80 mg BID and was dose-reduced due to AEs. Total duration of treatment ≥ 6 weeks; 46%); median duration 5.0 months (range 1.8 to 10.0 months).
- Overall response: 2 of 26 pts (8%).

Summary

- MEK162 was well-tolerated, with most AEs being Grade (Gr) 1 or 2 and reversible.
- No Grade 4 or 5 events were reported.
- The most common AEs were fatigue, rash, and diarrhea.
- MEK162 has an acceptable safety profile at 60 mg BID.
- Central sensitivity-related toxicities were manageable with dose modifications.
- MEK162 has desirable PK properties that are equivalent to that observed in prior studies.

We Thank the Patients and Their Families