A Phase 1 Dose-Escalation Study of MEK Inhibitor MEK162 (ARRY-438316) in Patients with Advanced Solid Tumors

Abstract # B243
Sarah Cannon Research Institute (SCRI), Nashville, TN; START-South Texas Accelerated Research Therapeutics, San Antonio, TX; Array BioPharma Inc., Boulder, CO

**MEK162 (ARRY-438316): A Potent MEK1/2 Inhibitor**

- MEK162 is an orally bioavailable, potent, selective, ATP-competitive inhibitor of MEK1/2.
- MEK162 has nanomolar activity against purified MEK enzyme (IC50 = 12 nM) and inhibits both basal and induced levels of ERK phosphorylation in xenograft tumor cell lines (IC50 values ≤ 3 ng/mL).
- In vivo, MEK162 has demonstrated efficacy in several xenograft tumor models in mice, including those harboring KRAS or BRAF mutations.
- In vivo, MEK162 enhances the activity of targeted therapies and standard cytotoxic agents in xenograft tumor models.

**Methods**

- The objectives of the completed Phase 1 open-label, dose-escalation study were to determine the maximum tolerated dose (MTD) and characterize the safety profile, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of MEK162 in patients with advanced solid tumors.

**Dose and Schedule of MEK162**

- Three dose-escalation phases (3 + 3 design)
- 21-day cycles
- *Single QD dose on Cycle 1 Day 1 only*

**Patient Demographics**

- N = 19
- Gender (male/female), n 15/4
- Median age (range), years 57 (33-75)
- ECOG (0-1), n (%) 7/12
- Median lines of previous chemotherapy for advanced disease (range), n 2 (0-4)
- Race (Asian/Black/ Caucasian), n (%) 1/1/17
- Tumor type, n
  - Colorectal 7
  - Pancreatic 2
  - Cholangiocarcinoma 2
- Mutation status, n (%) Wild type on all loci tested
  - BRAF V600E 7
  - MET 2

**Pharmacokinetics**

- **Pharmacokinetics of MEK162**: Mean plasma concentrations of MEK162 were maintained above the in vitro IC50 for cell growth inhibition (~2 hours of dosing).

**Most Common Treatment-related AEs (> 2 Patients)**

<table>
<thead>
<tr>
<th>AE</th>
<th>30 mg BID</th>
<th>45 mg BID</th>
<th>60 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All AEs</strong></td>
<td>20 (52.4)</td>
<td>23 (50)</td>
<td>20 (47.6)</td>
</tr>
<tr>
<td><strong>Grade &gt; 3</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.3)</td>
</tr>
</tbody>
</table>

**安全管理 of MEK162 Adverse Effects**

- **Diarrhea, nausea and vomiting**: Treated with standard antiemetics and anti-diarrheal medications; prophylactic treatment was not required.
- **Rash events**: Generally G1/G2, not requiring dose modification and frequently treated with oral antihistamines and anti-inflammatory agents, topical and oral antibiotics and corticosteroids. No specific treatment other than dose modifications.
- **Creatine kinase (CK) elevations**: Elevations in CK were asymptomatic, reversible, and did not require dose modifications.
- **Retinal events**: Symptomatic, reversible central serous-like retinal eye disorders were managed without specific treatment other than dose modifications. There was no evidence of retinopathy as measured by changes in multiple visual parameters and visual field.
- **Rash/retinopathy findings observed on funduscopic examination were consistent with general criteria and determined dose-limiting**.
- **Deep venous thrombosis**: Deep venous thrombosis was managed without specific treatment other than dose modifications.

**Summary**

- MEK162 had an acceptable safety profile at doses up to the MTD of 60 mg BID and showed preliminary signs of clinical activity.
- MEK162 demonstrated activity across multiple solid tumor types.
- MEK162 is being further studied in multiple Phase 2 studies.

**We Thank the Patients and Their Families**