A Phase Ia study to evaluate the MEK inhibitor cobimetinib in combination with the ERK1/2 inhibitor GDC-0949 in patients with advanced solid tumors

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**BACKGROUND**

Dysregulation of the MAPK pathway, initiated by mutations in the RAS or BRAF oncogenes or MEK, is involved in the development of many human cancers through upregulated mitogen-activated protein kinase (MAPK) signaling. Studies have suggested that single-agent kinase inhibitors targeting one or more components of the MAPK pathway can be ineffective or suboptimal because of acquired resistance or insensitivity to the therapies used. Combination therapy for patients with advanced solid tumors that harbor activating mutations in MAPK pathway components has demonstrated limited clinical benefit outside of metastatic melanoma.

**METHODOLOGY**

**Study Design**

- This open-label, multicenter, global Phase Ib dose-escalation study was designed to assess the safety, tolerability, and pharmacokinetics (PK) of oral combination dosing of cobimetinib and GDC-0994.

**Patient Characteristics**

In total, 23 patients were enrolled (Schedule A, n=8; Schedule B, n=15). As of 14 April 2016, 1 patient remained active on study.

**RESULTS**

- The majority of adverse events (AE) attributed to cobimetinib and/or GDC-0994 were Grade 1 or 2. The most common Grade 3 AEs related to treatment were rash, peripheral edema, and vision.

- The safety profile of this combination of MEK and ERK inhibition demonstrated classic MAPK-activated adverse events involving rash, peripheral edema, and visual disturbances.

**CONCLUSIONS**

- The safety profile of the combination of MEK and ERK inhibition demonstrated classic MAPK-activated adverse events.

- No new safety signals were identified. However, overlapping Grade 1-2 AEs and cumulative toxicity may be of concern and may affect either dosing strategies or further development of this combination.

- There was no evidence of DDIs between the study drugs.

- Metabolic response (FDG-PET) did not predict tumor responses by RECIST.

- Of 11 patients that underwent at least one tumor assessment, best responses included stable disease in 5 patients (45%) and 1 patient with partial response (9%).

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**REFERENCES**


**Figures**

- Figure 1. Schematic Overview of the Role of MEK and ERK Proteins in Mediating Signals

- Figure 2. Dose Schedules

- Figure 3. Cobimetinib Steady State Exposure in Combination with GDC-0949: Comparison to Historic, Monotherapy Data

- Figure 4. Cobimetinib + GDC-0949 Anti-Tumor Activity and mSiNOS (FDG-PET).

- Figure 5. Tumor Assessments.