Phase 1a Study of the Safety, Pharmacokinetics, and Pharmacodynamics of GDC-0919 in Patients with Recurrent/Advanced Solid Tumors

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BACKGROUND
• Indoleamine 2,3 dioxygenase 1 (IDO1) is a cytosolic enzyme that catalyzes the oxidation of L-tryptophan to kynurenine. It is over-expressed in many human tumors, particularly melanoma, and functions in immune tolerance in the tumor microenvironment. Immunotherapies that inhibit IDO1 show promise in preclinical models.
• GDC-0919 (RO 7077339; previously known as MLN0028) is an oral inhibitor of IDO1 that has been extensively evaluated in preclinical models. Its safety and pharmacokinetics have been evaluated in a Phase 1 clinical trial (Holmgaard et al. J Exp Med. 2013 Jul 1;210(7):1389-402) and a Phase 1b study in patients with recurrent/advanced melanoma (Mautino et al.; Cancer Res October 1, 2014 74;5023).

OBJECTIVES

Primary Objectives
• Evaluate the safety and tolerability of GDC-0919 in patients with advanced solid tumors
• Define maximum tolerated dose (MTD) or maximum biologically effective dose (MBED), and recommended phase 2 dose (RP2D) in patients with advanced solid tumors

Secondary Objectives
• Characterize the plasma pharmacokinetics (PK) of GDC-0919
• Evaluate pharmacodynamic (PD) modulation of plasma Kyn and Trp by GDC-0919

METHODS

Patients
• Eligible patients were aged ≥18 years with histologically or cytologically confirmed solid tumor that is relapsed/refractory to standard therapies or for which no approved or curative therapy exists. Tumors included melanoma, renal cell carcinoma, small cell lung cancer, gastric cancer, ovarian cancer, and colorectal cancer.

Study Design
• Open label, single and multiple dose exposures from 50 to 800 mg GDC-0919 increased in approximately dose-proportional manner.

Pharmacokinetics
• Pharmacokinetic analyses were performed on plasma samples obtained during treatment phases. Pharmacokinetic parameters were determined using non-compartmental methods. Key pharmacokinetic parameters included terminal half-life, area under the curve (AUC) at steady state, and maximum concentration (Cmax).

Pharmacodynamics
• Plasma kynurenine concentrations were measured using liquid chromatography/tandem mass spectrometry. The pharmacodynamic effects of GDC-0919 on plasma kynurenine concentration were evaluated using the percentage decrease in plasma kynurenine as compared to baseline.

RESULTS

Safety
• All patients achieved at least one AE during the study regarding toxicity of GDC-0919.
• No new safety concerns were identified in this study.

Clinical Activity/Efficacy
• No objective responses were observed in this study.

CONCLUSIONS
• Overall, GDC-0919 was well tolerated up to 800 mg BID in a 21-day cycle.
• No significant reductions in plasma kynurenine at higher doses by ~30%, 4 hrs post-dose was observed.

ACKNOWLEDGMENTS
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REFERENCES
1. Mautino A, Immuno. 2014 74;5023

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Pharmacokinetics: Fig. 4. Plasma Concentrations of GDC-0919 Following a Single Oral Dose

Pharmacodynamics: Fig. 1. Changes in Plasma Kyn and Tryp Relative to CD11b Pre-Doses Levels After Oral Exposure to GDC-0919 (50-800 mg)