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Selective Oral MEK1/2 Inhibitor Pimasertib: A Phase I Trial in Patients with Advanced Solid Tumors

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Abstract

Background: The Ras/Raf/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (Ras/Raf/MEK/ERK) signaling cascade is frequently constitutively activated in human cancers. Pimasertib is a selective and potent adenosine triphosphate non-competitive MEK1/2 inhibitor.

Objective: Our objectives were to describe the results of a phase I, first-in-human, dose-escalation trial of pimasertib that investigated the maximum tolerated dose, recommended phase II dose, and safety, as well as other endpoints.

Patients and methods: Four dosing schedules of pimasertib (once daily [qd], 5 days on, 2 days off; qd, 15 days on, 6 days off; continuous qd; continuous twice daily [bid]) were evaluated in patients with advanced solid tumors. Each treatment cycle lasted 21 days. The primary objective was to determine the maximum tolerated dose based on dose-limiting toxicities (DLTs) evaluated during cycle 1, and the recommended phase II dose (RP2D). Secondary objectives included safety, pharmacokinetics, pharmacodynamics, and antitumor activity.

Results: Overall, 180 patients received pimasertib (dose range 1-255 mg/day). DLTs were mainly observed at doses ≥ 120 mg/day and included skin rash/acneiform dermatitis and ocular events, such as serous retinal detachment. The most common drug-related adverse events were consistent with class effects, including diarrhea, skin disorders, ocular disorders, asthenia/fatigue, and peripheral edema. The median time to maximum pimasertib concentration was 1.5 h across dosing schedules, and the apparent terminal half-life was 5 h across qd dosing schedules. Pimasertib decreased ERK phosphorylation within 2 h of administration, which was maintained for up to 8 h at higher doses and prolonged with bid dosing.

Conclusions: Based on the safety profile and efficacy signals, a continuous bid regimen was the preferred dosing schedule and the RP2D was defined as 60 mg bid.

Trial registration: ClinicalTrials.gov, NCT00982865.

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