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Abstract CT016: First-in-human (FIH) phase 1 trial of the oral first-in-class covalent Werner helicase (WRN) inhibitor RO7589831 in patients with microsatellite instable (MSI) and/or mismatch repair deficient (dMMR) advanced solid tumors FREE

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Cancer Res (2025) 85 (8_Supplement_2): CT016.

https://doi.org/10.1158/1538-7445.AM2025-CT016

Abstract

Background:

WRN is an enzyme critical for DNA repair and genome stability and is a promising synthetic lethal target for MSI cancers. 40-70 % of patients (pts) with MSI/dMMR solid tumors do not respond to immune checkpoint inhibitors (ICI) or develop resistance, representing an unmet need in MSI cancers. RO7589831 is a novel first-in-class covalent, irreversible WRN inhibitor that induces dose-dependent DNA damage and tumor growth inhibition in MSI preclinical models, supporting its clinical evaluation in MSI pts.

Methods:

This open-label, multi-center, FIH study assesses the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary anti-tumor activity of RO7589831 in pts with MSI and/or dMMR advanced solid tumors (NCT06004245). The primary objective is to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D). 14 paired tumor biopsies were collected for translational analysis.

Results:

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As of Nov 25, 2024, 44 pts (24 F, 20 M; median age 62y (32-77y)) were enrolled in six dose cohorts at RO7589831 daily doses from 150 mg to 2000 mg. Based on clinical first dose PK data

(rapid absorption, mean Tmax 2.6 h [± 1.3h] and half-life 4.4 h [±1.8h], n=41), RO7589831 was dosed orally once (QD) or twice (BID) daily. Among the 44 pts (22 colorectal (CRC) and 22 non-CRC), median prior treatment lines were 3 (range 1-12); 89% had received ICIs. 35 pts had MSI tumors (18 CRC and 17 non-CRC). No dose-limiting toxicities (DLTs) have been reported and the MTD has not been reached. The most common treatment-emergent AEs across all doses were nausea (52.3%), diarrhea (34.1%), and vomiting (31.8%). Grade (G)3 treatment related AEs (TRAE) were nausea and increased AST/ALT in 2 pts each (4.3%) as well as fatigue and anemia in 1 pt each (2.1%). No G4 or worse TRAEs were observed. Of the efficacy evaluable MSI pts (n= 32), four RECISTv1.1 partial responses (PRs) (2 confirmed and 2 ongoing unconfirmed PRs) were observed in post-ICI-treated MSI CRC (n=1), ovarian (n=1), and endometrial cancer (n=2) for up to 9.5+ mths. Disease control rate (DCR) was 68.8% (95%CI 51.13, 86.37) and 20 (62.5%) pts achieved RECISTv1.1 stable disease (SD). 48.4% (15/31) of FDG-PET scan evaluable pts across all dose levels showed metabolic responses to RO7589831. All pts with RECIST PR showed pronounced metabolic responses (-50% to -90%). ctDNA molecular responses were observed in 2/2 pts with RECISTv1.1 PR, 8/9 pts with SD and 0/5 pts with disease progression.

Conclusions:

RO7589831 is generally safe and well tolerated, with promising DCR, durable RECISTv1.1, FDG-PET metabolic and ctDNA molecular responses in pts with advanced MSI cancers, including ICI-treated pts, providing the first early clinical proof-of-concept for effectively drugging WRN. Dose optimization cohorts are ongoing to establish the RP2D.

Citation Format:

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Online ISSN 1538-7445 **Print ISSN** 0008-5472