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Abstract CT019: Preliminary safety and antitumor activity of zoldonrasib (RMC-9805), an oral, RAS(ON) G12D-selective, tri-complex inhibitor in patients with KRAS G12D non-small cell lung cancer (NSCLC) from a phase 1 study in advanced solid tumors FREE

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Abstract

Background:

Patients with previously treated NSCLC have a high unmet medical need, with a median reported overall survival (OS) of <1 year. In NSCLC, KRAS G12D oncogenic mutations occur in approximately 4% of patients, but there are currently no RAS-targeted therapies approved for this population. Zoldonrasib (RMC-9805) is a potent, oral, RAS(ON) G12D-selective, covalent, tri-complex inhibitor targeting the active, GTP-bound state of oncogenic RAS G12D isoforms.

Methods:

In this Phase 1 study (NCT06040541), patients with previously treated, advanced KRAS G12D solid tumors received escalating zoldonrasib doses (150-1200 mg once daily [QD] or 300-600 mg twice daily [BID]). Antitumor activity was assessed every 6 weeks for the first 24 weeks then every 9 weeks. Additional patients were enrolled at doses that cleared the dose-limiting toxicity (DLT) evaluation to further characterize pharmacokinetics, safety, and antitumor activity of zoldonrasib.

Results:

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As of a December 2, 2024 data cutoff, 211 patients with KRAS G12D solid tumors received 5 escalating dose levels of zoldonrasib monotherapy (150-1200 mg daily). No DLTs or Grade 4 or 5 treatment-related adverse events (TRAEs) were reported, and the maximum tolerated dose

was not reached. Among patients who received a candidate recommended Phase 2 dose (RP2D) of 1200 mg QD (n=90), the most common (≥10% of patients) TRAEs were nausea (39%), diarrhea (24%), vomiting (18%), and rash (12%). TRAEs were primarily Grade 1 or 2 in severity with the exception of 1 patient with Grade 3 diarrhea and 1 patient with Grade 3 ALT elevation. Both Grade 3 TRAEs resolved following dose interruption. Among patients who received 1200 mg QD, 1 patient (1%) discontinued treatment, 4 patients (4%) had dose reductions, and 8 patients (9%) had dose interruptions due to a TRAE. At daily doses ≥600 mg, exposures to zoldonrasib were within the range of preclinical exposures that induced tumor regressions in mice. In patients with NSCLC (n=18) receiving 1200 mg QD zoldonrasib who enrolled at least 8 weeks prior to the data cutoff, the objective response rate (confirmed response or pending confirmation) was 61% (95% CI: 36, 83). Median time to onset of initial response was 1.4 months (range, 1.2-2.8) and the disease control rate was 89% (95% CI: 65, 99).

Conclusions:

Zoldonrasib showed encouraging initial antitumor activity in patients with KRAS G12D NSCLC. Tolerability was manageable across all dose levels in the Phase 1 study, which enrolled various tumor types. This overall safety profile and antitumor activity support continued evaluation as monotherapy in patients with KRAS G12D NSCLC, and in combination with immunotherapy, chemotherapy, and targeted therapies (NCT06162221).

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