CK-101 (RX518), a Third Generation Mutant-Selective Inhibitor of EGFR in NSCLC: Results of an Ongoing Phase I/II Trial

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Background: CK-101 (also known as RX518) is a novel, oral, third-generation, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitizing and resistance mutations, with minimal activity on wild-type EGFR. CK-101 is being studied in an ongoing first-in-human, multicenter, Phase I/II trial in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations and other advanced malignancies in the US, Australia, New Zealand and Thailand (NCT02926768). Following dose escalation in which 18 pts received CK-101 in dose groups ranging from 100 mg to 1200 mg/day, a first dose-expansion cohort was enrolled at 400 mg bid.

Methods: Eligible pts in dose escalation had a confirmed diagnosis of NSCLC or any advanced solid tumor where targeting EGFR was reasonable. Eligible pts in dose-expansion had a confirmed diagnosis of either (1) EGFR mutation-positive advanced or metastatic NSCLC without prior exposure to EGFR-TKI therapy, or (2) T790M-positive advanced or metastatic NSCLC with disease progression on previous EGFR-TKI therapy, with no limit on number of prior lines of systemic therapy.

Results: As of 25 June 2018, 37 pts were treated in dose escalation and expansion and evaluable for safety; median age 59 years, 51% male, 51% Asian, 84% ECOG PS 1. No DLTs or treatment-related SAEs were reported. Most common treatment-emergent adverse events: nausea (16%), diarrhea (14%), lacrimation increased (14%) and vomiting (11%), all grade 1/2 except one grade 3 diarrhea; no grade 4. In dose-expansion, 19 pts were treated with CK-101 at a dose of 400 mg bid and evaluable for response; 8/19 (42%) pts were treatment-naïve, 6/19 (32%) pts had brain metastases; 16/19 (84%) pts remained on treatment. Disease control rate was 100% (19/19), with 16/19 pts (84%) experiencing target lesion reduction versus baseline and 8 pts achieving a partial response (7 confirmed, 1 pending confirmation). In treatment-naïve pts, 6/8 (75%) pts achieved a partial response. In pts with brain metastases, 3/6 (50%) pts achieved a partial response. Higher drug exposures were associated with higher response rate with a confirmed ORR of 55% (6/11) in pts achieving Cmax >400 ng/mL. Median duration of response and progression-free survival were not reached as of the data cutoff.

Conclusions: CK-101 was well tolerated with a manageable safety profile. Durable anti-tumor activity was observed, particularly in treatment-naïve pts. Further study is ongoing to establish the optimal dose to maximize therapeutic effect in a planned Phase 3 study in treatment-naïve EGFR-mutant NSCLC pts.