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CK-101 (RX518), a mutant-selective inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC

Short Title:

CK-101 (RX518) EGFR inhibitor

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Abstract:

Patients with non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations initially respond to small molecule inhibitors of the EGFR tyrosine kinase such as gefitinib and erlotinib. However, secondary mutations in the kinase domain lead to acquired resistance to these inhibitors and limited clinical efficacy, with the EGFR T790M mutation being the most common mechanism of acquired resistance in more than half the patients that experience disease progression. CK-101 (also known as RX518) is a novel, irreversible, orally administered EGFR kinase inhibitor that specifically targets the mutant forms of EGFR, including T790M, while exhibiting minimal activity toward the wild-type (WT) EGFR. WT EGFR inhibition is believed to drive the commonly observed side effects of skin rash and diarrhea. The 50% inhibitory concentrations (IC50s) of CK-101 and 2 reference compounds, afatinib and AZD-9291, were determined in cell proliferation assays in human cancer cell lines in vitro after incubation for 72 hours. Xenograft studies were conducted in BALB/c nude mice or SCID/Beige mice using once daily oral administration of CK-101 or afatinib for 14 or 21 days. CK-101 selectively inhibited cell proliferation of cell lines expressing both the activating (e.g. HCC827, IC50 <0.015 μ M) and resistance mutations (NCI-H1975, IC50 <0.005 μ M), but was much less potent at inhibiting proliferation of cell lines expressing the WT form of the receptor (e.g. A431, IC50 >0.5 μ M; i.e., CK-101 was over 100 fold less potent against A431 than against NCI-H1975). Single agent CK-101 significantly inhibited tumor growth in EGFR-mutated NSCLC tumor xenograft models, with no activity in a WT EGFR tumor xenograft model. In a xenograft study of PC-9 cells (exon 19 deletion) in SCID/Beige mice, CK-101 inhibited tumor growth by up to 90% (p <0.001). In a xenograft study of NCI-H1975 cells (L858R/T790M double mutant) in BALB/c nude mice, CK-101 inhibited tumor growth by up to 95% (p <0.001). The pre-clinical findings from this work strongly supported the clinical development of CK-101, and a first-in-human study of CK-101 was initiated in September 2016.

Author Disclosure Information:

X. Qian: ; NeuPharma, Inc. **Y. Zhu:** ; NeuPharma, Inc. **E. Cullen:** ; Checkpoint Therapeutics, Inc. **R.M. Niecestro:** ; Checkpoint Therapeutics, Inc. **J.F. Oliviero:** ; Checkpoint Therapeutics, Inc..