CK-101 (RX518), a Mutant-Selective Inhibitor of EGFR that Overcomes T790M-Mediated Resistance in Non-Small Cell Lung Cancer (NSCLC)

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Abstract

Introduction

- 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.

Experimental procedures

- The 50% inhibitory concentrations (IC50s) of CK-101 and 2 reference compounds, afatinib and osimertinib (AZD9291), 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.

Results

- CK-101 selectively inhibited cell proliferation of cell lines expressing both the activating (e.g. HCC827 [exon 19 deletion]) and resistance mutations (NCI-H1975 [L858R/T790M double mutation]), but was much less potent at inhibiting proliferation of cell lines expressing the WT form of the receptor (e.g. A431; i.e., CK-101 was over 100-fold less potent against WT EGFR than against L858R/T790M double mutation).
- Single agent CK-101 significantly inhibited tumor growth in EGFR-mutated NSCLC tumor xenograft models, with no activity in a A431 (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).

Conclusions

- The pre-clinical findings from this work strongly supported the clinical development of CK-101 (RX518), and a first-in-human study was initiated in September 2016.

CK-101 (RX518) selectively inhibits mutant EGFR including T790M

Inhibition of Cancer Cell Proliferation (IC_{50}, nM)

Cell Line	EGFR Mutation	CK-101	osimertinib (AZD9291)	afatinib
NCI-H1975	L858R/T790M	5	2	23
HCC827	Exon 19 del	10	3	1
A431	WT	689	280	34

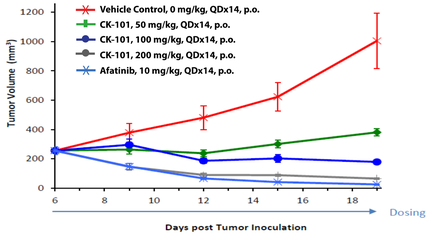
The 50% inhibitory concentrations (IC50s) of CK-101 and 2 reference compounds, afatinib and osimertinib (AZD9291), were determined in cell proliferation assays in human cancer cell lines in vitro after incubation for 72 hours.

- CK-101 selectively inhibits cancer cell proliferation of cell lines expressing mutant EGFR, with the most sensitive being cell lines with EGFR exon 19 deletions or L858R/T790M double mutations.
- CK-101 was over 100-fold less potent against WT EGFR than against L858R/T790M double mutation.

CK-101 (RX518) inhibits mutant EGFR tumor growth; while sparing wild-type EGFR

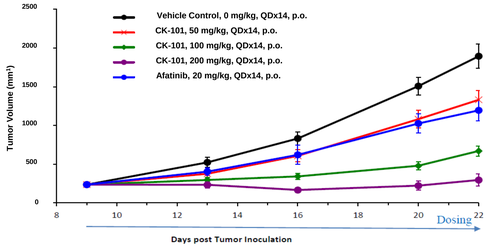
Evaluation of Efficacy in Human Xenograft Models

PC-9 NSCLC xenograft model



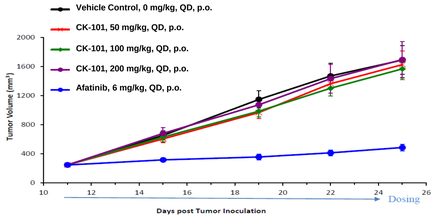
- In a xenograft study of PC-9 cells (exon 19 deletion) in SCID/Beige mice, CK-101 selectively inhibited tumor growth at all 3 dose levels and in a dose-dependent manner.
- CK-101 inhibited tumor growth by up to 90% (p <0.001).

H1975 NSCLC xenograft model



- In a xenograft study of NCI-H1975 cells (L858R/T790M double mutant) in BALB/c nude mice, CK-101 selectively inhibited tumor growth at all 3 dose levels and in a dose-dependent manner.
- CK-101 inhibited tumor growth by up to 95% (p <0.001).

A431 xenograft model



- In a xenograft study of A431 cells (WT EGFR) in BALB/c nude mice, CK-101 was orally administered at 3 dose levels (50, 100, and 200 mg/kg) once daily for 14 days, and compared against afatinib (positive control), orally administered at 6 mg/kg once daily for 14 days.
- The growth of A431 tumor was not inhibited by any of the 3 dose levels of CK-101.
- Afatinib, the positive control in the study, inhibited A431 (WT EGFR) tumor growth.

Phase 1/2 Clinical Trial

- CK-101 is currently in a first-in-human Phase 1/2 clinical trial, with the Phase 1 portion ongoing (clinicaltrials.gov: NCT02926768).
- The Phase 2 portion, expected to initiate in 2H 2017 at both U.S. and ex-U.S. sites, will test CK-101 at the recommended Phase 2 dose in previously treated mutant EGFR T790M-positive NSCLC patients who have failed treatment with a first-line EGFR inhibitor.

Summary

- CK-101 (also known as RX518) is a potent, mutant-selective inhibitor of both the activating (exon 19 deletion) and resistance mutations (L858R/T790M double mutation).
- CK-101 inhibited tumor growth as a single agent in a NSCLC model (PC-9) with a single activating mutation (exon 19 deletion)
- CK-101 showed dose-dependent inhibition of tumor growth as a single agent in a L858R/T790M double mutant NSCLC model (NCI-H1975).
- CK-101 has little inhibitory potency toward WT EGFR (i.e., CK-101 was over 100 fold less potent against WT EGFR than against L858R/T790M double mutation).
- A Phase 1/2 clinical trial is ongoing (clinicaltrials.gov: NCT02926768).

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