**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.

**Results**

- CK-101, also known as RX518, is a potent, mutant-selective inhibitor of both the activating (exon 19 deletion) and resistance (L858R/T790M double mutation). CK-101 was over 100-fold less potent against WT EGFR than against mutant EGFR, with the most sensitive being cell lines with EGFR exon 19 deletions or L858R/T790M double mutations.

**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.

**Inhibition of Cancer Cell Proliferation (IC50, nM)**

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>EGF Stimulation</th>
<th>CK-101</th>
<th>AFK-TKI</th>
<th>CK-101 afatinib (AZD2911)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC827</td>
<td>Untreated</td>
<td>IC50</td>
<td>IC50x</td>
<td>IC50</td>
</tr>
<tr>
<td>PC-9</td>
<td>Untreated</td>
<td>IC50</td>
<td>IC50x</td>
<td>IC50</td>
</tr>
</tbody>
</table>

**Experimental procedures**

- The 50% inhibitory concentrations (IC50s) of CK-101 and 2 reference compounds, afatinib and osimertinib (AZD2911), were determined in cell proliferation assays in human cancer cell lines in vitro after incubation for 72 hours.

**Evaluation of Efficacy in Human Xenograft Models**

- 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).

**CK-101 (RX518) selectively inhibits mutant EGFR expressing tumors, while sparing wild-type EGFR**

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