Abstract #2708

BPI-7711, a Covalent Mutant-Selective EGFR Inhibitor, Inhibits the Growth of NSCLC Lines with EGFR Activating and T790M Resistance Mutations

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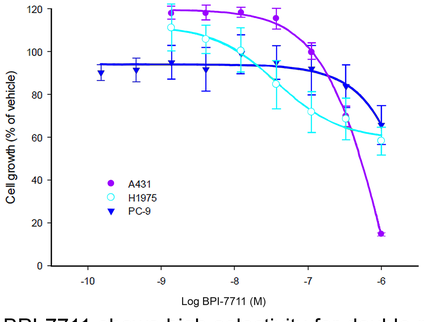
BACKGROUND

First generation EGFR TKIs, erlotinib, gefitinib and icotinib, have shown excellent clinical efficacy in non-small-cell lung cancer (NSCLC) patients with activating EGFR mutations. However, patients eventually encounter disease progression due to acquired resistance in the form of a T790M point mutation. This mutation occurs in about 50-60% of EGFR TKI treated patients. Second generation, irreversible EGFR TKIs, afatinib and dacomitinib, express even higher kinase potency in the activating mutation as well as potency against the acquired resistance mutation. Clinical efficacy of these TKIs is reduced due to the dose limiting toxicities of the drugs, attributed to wild type EGFR inhibition by the compounds. In order to improve clinical efficacy against the activating and double mutant EGFR tumor cells, it is important to build in selectivity against wild type EGFR to avoid dose-limiting toxicities. Here, we present BPI-7711, a novel, irreversible EGFR inhibitor with high potency against the activating mutant EGFR and the T790M resistance mutation with good selectivity over wild type EGFR.

METHODS

BPI-7711 was evaluated in biochemical and in vitro assays against mutant EGFR (L858R, del ex19, del ex19/T790M) and WT EGFR. In vivo anti-tumor activity was evaluated in xenografts of HCC827 (del ex19) and H1975 (del ex19/T790M) NSCLC cells. (All animal experiments were completed at Molecular Imaging, Inc. Ann Arbor, MI)

CELLULAR ASSAY



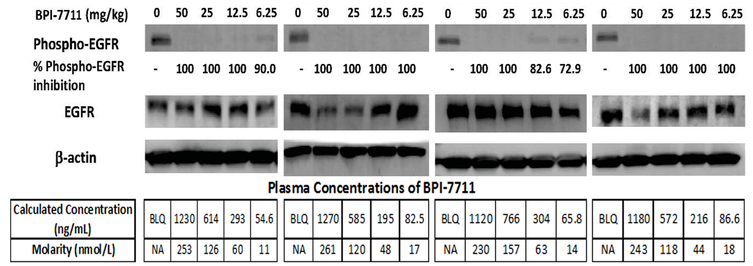
EC50 (nM)

Cell Type	BPI-7711
H1975	22
A431	>1000
PC-9	133
HCC827	

• BPI-7711 shows high selectivity for double mutant NSCLC cells (H1975) against wild type EGFR epithelial cells (A431).
• BPI-7711 is potent against cell lines harboring common activating mutations, HCC827 (L585R) and PC-9 (del ex19).

PHARMACODYNAMICS

BPI-7711 Dose Response in H1975 Xenografts



Plasma Concentrations of BPI-7711

Calculated Concentration (ng/mL)	BLQ	1230	614	293	54.6	BLQ	1270	585	195	82.5	BLQ	1120	766	304	65.8	BLQ	1180	572	216	86.6
Molarity (nmol/L)	NA	253	126	60	11	NA	261	120	48	17	NA	230	157	63	14	NA	243	118	44	18

• Nude mice with H1975 tumor xenografts were exposed to 0, 6.25, 12.5, 25, 50 mg/kg of BPI-7711. Mice were sacrificed at the 2-hour post-dose time point and plasma and tumor samples were collected. Tumor powders were evaluated by Western blotting for phosphorylated EGFR and total EGFR.

• BPI-7711 inhibited pEGFR in a dose-dependent manner, with concentrations higher than 20 nmol/L resulting in 100% inhibition.

BPI-7711 Time Course in H1975 Xenografts

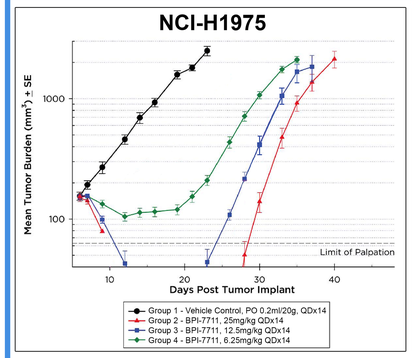
Time Point	2 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr	2 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr
Calculated Concentration (ng/ml)	BLQ	1130	1120	525	573	92.3	7.59	31.3	BLQ	349	391	98.4	54.6	3.01	1.2	BLQ
Molarity (nmol/L)	NA	2320	2300	1080	1180	190	15.6	64.2	NA	717	804	202	112	6.18	2.46	NA

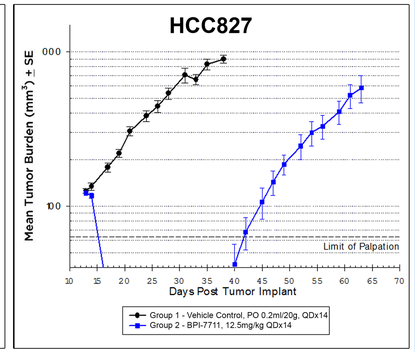
• Nude mice with H1975 tumor xenografts were exposed to single doses of 12.5 and 50 mg/kg of BPI-7711. Tumor and plasma samples were collected over a 24-hour period. Tumor powders were evaluated by Western blotting for phosphorylated EGFR and total EGFR.

• BPI-7711 induced inhibition of EGFR phosphorylation in H1975 tumor xenografts for 24 after initial dosing of the animal. Inhibition of H1975 EGFR phosphorylation was determined to be irreversible and long-lasting *in vivo*.

• Results of the dose response and time course experiment suggest a dose of 12.5 mg/kg, once per day, will completely inhibit EGFR phosphorylation in the H1975 tumor xenografts.

in vivo TUMOR GROWTH INHIBITION





• BPI-7711 induces significant tumor regression in the NCI-H1975 (T790M/L858R) xenograft model when administered orally at doses of 6.25, 12.5 and 25 mg/kg QD.
• Treatment at 25 mg/kg QD produced significant anticancer activity, based on 100% TGI. Time to evaluation was 34.3 days, resulting in a tumor growth delay of 19.3 days. Treatment produced a 100% incidence of complete regressions and 10% of the mice were tumor free survivors.
• BPI-7711 was also found to be highly potent in the activating mutant cell line model, HCC827 xenograft (L858R). At a dose of 6.25 mg/kg, BPI-7711 produced a 100% incidence of complete regressions.
• Treatment with BPI-7711 was well-tolerated, resulting in no treatment-related mortality and was associated with nominal body weight loss between 0.6-2.4%.

CONCLUSIONS

• BPI-7711 is a small molecule EGFR TKI that inhibits the growth of cancer cells with EGFR activating mutations, as well as the T790M resistance mutation.
• BPI-7711 has minimal inhibitory activity against human epithelial cells containing WT EGFR.
• BPI-7711 inhibits EGFR phosphorylation in NCC-H1975 (L858R/T790M) and HCC827 (L858R) cells in a dose-dependent manner.
• BPI-7711 has shown dose-dependent efficacy (tumor regression) in NCI-H1975 and HCC827 *in vivo* xenograft models.

Results from the nonclinical studies described in this poster, as well as preclinical DMPK and toxicology studies, support the investigation of BPI-7711 in patients with NSCLC whose tumors harbor EGFR mutations, including the T790M resistance mutation.