Poster No. - PB01

Preclinical evidence of BPI-7711 activity in EGFR-mutant non-small cell lung cancer (NSCLC) in orthotopically implanted human tumor xenografts in the lung and brain

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Abstract

Background: BPI-7711 is a highly selective and potent, irreversible epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor with high potency against the common activation EGFR and the resistance T790M mutations.

Aims: To determine the efficacy of BPI-7711 in orthotopic non-small cell lung cancer (NSCLC) xenografts, implanted in either the lung or brain.

Methods: Preclinical blood-brain barrier penetration of BPI-7711 was evaluated in rats to determine the plasma, brain and CSF concentration after oral dosing. In vivo efficacy of BPI-7711 was assessed in a lung orthotopic TGI/TGD study in mouse utilizing luciferase-enabled H1975 (H1975-luc, EGFRm+ exon 19 deletion, T790M) cells. Data was gathered using bioluminescence imaging (BLI) and computed tomography (CT) scans. Efficacy of BPI-7711 against EGFRm+ brain metastases (BM) was tested via an intracranial tumor growth inhibition study utilizing H1975-luc human NSCLC xenograft cells.

Results: In preclinical studies, BPI-7711 had significant exposure in the brain. Pharmacokinetic analysis of brain, tumor and plasma samples showed that BPI-7711 accumulated in the brain and tumor tissue, with highest concentrations seen at the 4 hour time point. In the H1975-luc lung model, BPI-7711, dosed orally at 12.5 mg/kg, showed significant tumor regression with a 70% incidence of partial regressions and a 30% incidence of complete regressions. When compared to the vehicle control group, those animals treated with BPI-7711 survived an average of 112% longer (53 days vs. 25 days). In the H1975-luc BM model, BPI-7711 showed significant tumor regressions at 50 mg/kg.

Conclusion: Preclinical studies show that BPI-7711 has significant exposure in the brain and activity against EGFRm+ BM. Clinical studies are planned to determine the efficacy of BPI-7711 in patients with EGFRm+ NSCLC BM.

Introduction

- BPI-7711 is a potent, irreversible, small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) selective for EGFR activating mutations and the T790M gatekeeper mutation.
- Epidermal growth factor receptor (EGFR) activating mutations (EGFRm+) occur in 50% of non-small cell lung cancers (NSCLCs) in Asian patients.
- EGFR-TKIs are approved as first-line therapy for patients who have advanced NSCLC with tumours that carry an EGFR activating mutation.
- Approximately 60% of patients will progress on 1st line therapy with a secondary EGFR mutation, T790M.
- Patients harboring EGFRm+ often progress due to growth of secondary brain metastases. Currently available EGFR TKIs have poor penetration across the blood brain parrier and have had poor clinical use for patients with brain metastases.
- We researched the potential efficacy of BPI-7711 against EGFRm+ NSCLC brain metastases in a preclinical mouse model.

Figure 1. Anti-tumor efficacy of BPI-7711 in HCC827 mouse subcutaneous xenografts
(Mean Tumor Burden - Group comparison with standard error)

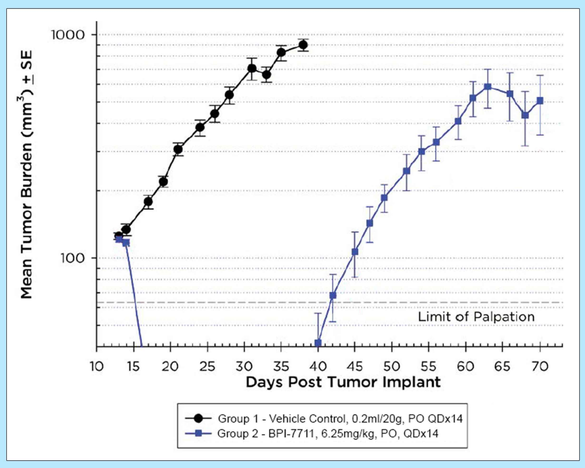
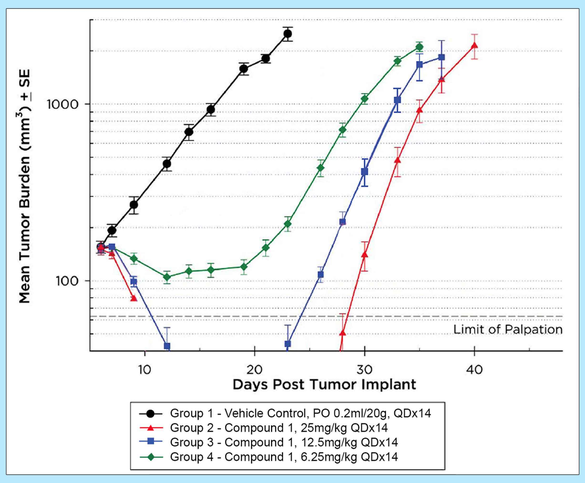


Figure 2. Anti-tumor efficacy of BPI-7711 in H1975 mouse subcutaneous xenografts
(Mean Tumor Burden - Group comparison with standard error)



Results

BPI-7711 efficacy against orthotopically implanted H1975-luc human NSCLC in mice

- BPI-7711, 12.5 mg/kg PO, showed significant tumor regression with a 70% incidence of partial regressions and a 30% incidence of complete regressions.
- When compared to the vehicle control group, those animals treated with BPI-7711 survived an average of 112% longer (Figure 3., 53 days vs. 25 days).
- Computed tomography (CT) scans show rapid regression of orthotopically implanted EGFRm+ NSCLC xenografts (Figure 4).

Figure 3. BPI-7711 tumor growth inhibition in H1975-luc NSCLC, orthotopic lung model

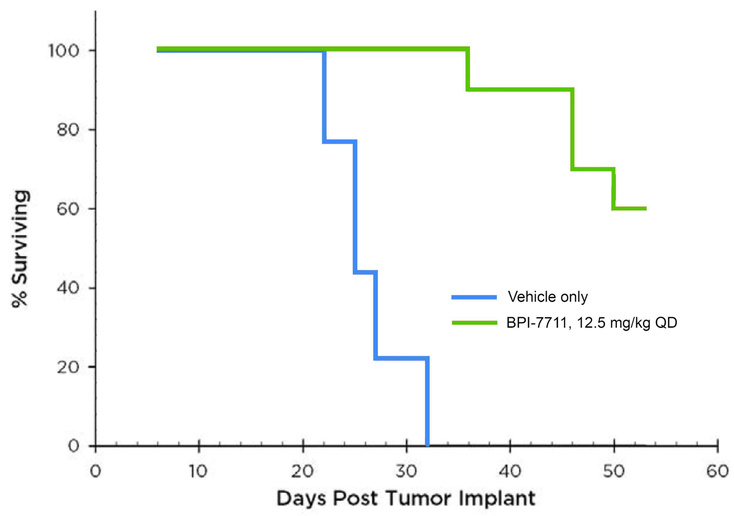
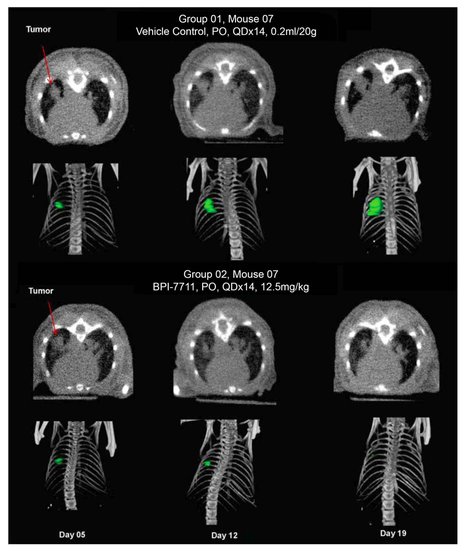


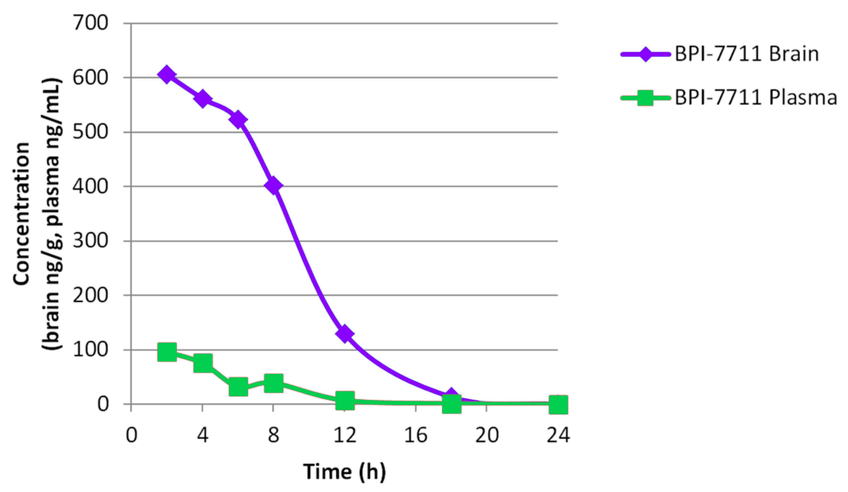
Figure 4. Computed tomography (CT) generated high resolution 3D images



BPI-7711 rat brain exposure

- In preclinical studies, BPI-7711 showed significant exposure in the brain (Figure 5).
- Following a single oral dose of 5 mg/kg to fasted male Sprague Dawley rats, BPI-7711 showed relatively higher brain exposure ($AUC_{0\text{-last}}$) compared with its exposure in plasma and CSF.
- The mean $AUC_{0\text{-last}}$ ratio value of brain to plasma was 9.44.

Figure 5. Total brain and plasma concentrations in rat for BPI-7711 (5 mg/kg) after oral dosing



BPI-7711 efficacy against intracranial H1975-luc human NSCLC in nude mice

- BPI-7711 is efficacious in H1975-luc (EGFRm+) BM model (Figure 6).
- Sustained tumor shrinkage was achieved at 50 mg/kg daily dose.
- 50 mg/kg in mouse approximates a 240 mg/day clinical dose (based on body surface area calculation).
- BPI-7711 was well tolerated at the doses used in this study.
- Anti-tumor efficacy correlated to improved average overall survival of the animals of 115% (Figure 7, 28 days vs. 13 days).

Figure 6. Intracranial H1975-luc tumor xenograft model (treatment = Day 5-19)

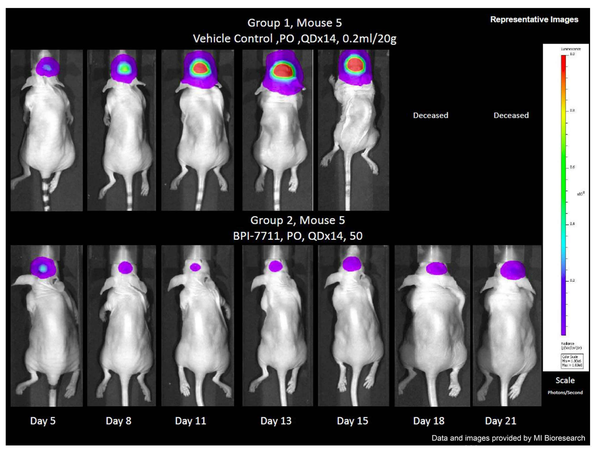
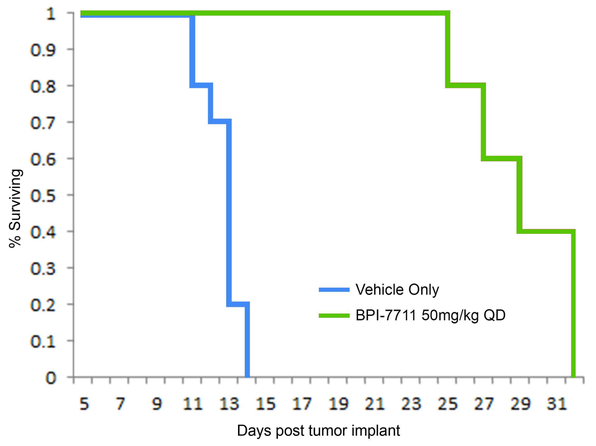


Figure 7. BPI-7711 tumor growth inhibition in H1975-luc mouse brain metastases model - overall survival



Conclusions

- In pre-clinical models, BPI-7711 shows significant exposure in the brain and is efficacious in treating EGFRm+ NSCLC brain metastases.
- In the orthotopic lung model, 100% of the animals treated with 12.5 mg/kg showed either partial regression or complete regression of the tumors.
- Sustained intracranial tumor shrinkage was achieved when dosed at 50 mg/kg.
- BPI-7711 was well tolerated at the doses tested and has been shown to be safe at much higher doses in rat and dog repeat dose toxicity studies.
- The anti-tumor efficacy of BPI-7711 correlated with an improved overall survival of the animals, both in the lung orthotopic (112%) and intracranial (115%) studies.
- BPI-7711 is expected to enter phase 1 clinical trials in China in Q3 2016, in collaboration with Betapharma Inc. (Shanghai) Co. Ltd.

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