Poster #357

A Phase I Study to Evaluate Safety, Tolerability, Pharmacokinetics and Antineoplastic Activity of BPI-7711 in Patients with EGFR/T790M Mutation Advanced or Recurrent NSCLC

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BACKGROUND

- BPI-7711 is a 3rd generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that is selectively against EGFR TKI–sensitizing mutations and the T790M resistance mutations. We are conducting a phase I study to determine the safety and efficacy of BPI-7711 in patients with advanced or recurrent EGFRm+ /T790M+ non-small cell lung cancer (NSCLC).

METHODS

- NSCLC patients who had documented disease progression after 1st/2nd generation EGFR-TKI treatment and with EGFRm+/T790M+ confirmed by central lab were enrolled in the multicenter trial (NCT03386955) into "3+3" dose escalation or expansion cohorts.
- BPI-7711 was orally administered at doses of 30~300 mg in capsules.
- Patients in dose-escalation cohorts firstly received a single dose of BPI-7711 followed by a 7-day pharmacokinetic (PK) evaluation period then received the same dose daily until disease progression or intolerable toxicity(ies) per CTCAE V4.03.
- Treatment efficacy per RECIST 1.1 was evaluated every 6 weeks since daily treatment commence. Once efficacy was observed in a dose, its expansion cohort was opened to enroll patients for daily treatment.
- The data cut-off date for this analysis was 15 April 2019.

RESULTS

Baseline Characteristics

- A total of 119 patients were enrolled and treated with BPI-7711 by 15 April 2019.
- 17 patients were enrolled into 6 dose escalation cohorts (30/60/120/180/240/300 mg) and 102 were into dose expansion cohorts (30/60/120/180/240 mg).
- The median age was 56. 82 were female and 37 were male patients.
- 44.5% patients were with brain metastases (BM) and 44.5% were with bone metastases.

Table 1. Baseline Characteristics

	30 mg (n=11)	60 mg (n=6)	120 mg (n=26)	180 mg (n=51)	240 mg (n=24)	300 mg (n=1)	Total (n=119)
Age, yr, median (range)	54.0 (34, 68)	52.5 (47, 73)	51.0 (34, 73)	59.0 (43, 74)	58.5 (37, 72)	54.0 (54, 54)	56.0 (34, 74)
Female, n (%)	7 (63.6)	5 (83.3)	16 (61.5)	39 (76.5)	14 (58.3)	1 (100.0)	82 (68.9)
Number of prior chemotherapy, median (range)	1 (0, 3)	0 (0, 1)	1 (0, 4)	0 (0, 4)	1 (0, 5)	3 (3, 3)	1 (0, 5)
Number of prior EGFR-TKIs, median (range)	1 (1, 2)	1 (1, 1)	1 (1, 2)	1 (1, 3)	1 (1, 2)	1 (1, 1)	1 (1, 3)
Regimen, n (%)							
Gefitinib	6 (54.4)	2 (33.3)	12 (46.2)	25 (49.0)	10 (41.7)	0 (0)	55 (46.2)
Icotinib	3 (27.3)	4 (66.7)	12 (46.2)	20 (39.2)	10 (41.7)	1 (100.0)	50 (42.0)
Erlotinib	2 (18.2)	0 (0)	2 (7.7)	9 (17.6)	6 (25.0)	0 (0)	19 (16.0)
Brain metastasis, n (%)	5 (45.5)	2 (33.3)	12 (46.2)	22 (43.1)	12 (50.0)	0 (0)	53 (44.5)
Bone metastasis, n (%)	3 (27.3)	5 (83.3)	11 (42.3)	21 (41.2)	12 (50.0)	1 (100.0)	53 (44.5)

Efficacy

- For all efficacy-evaluable patients (n=101), the overall objective response rate (ORR) of all doses was 55.4% per investigator review.
- Per independent radiological review committee (IRRC) review, the overall ORR was 61.0% (n=100).
- For patients in 180 mg cohort, the overall ORR was 68.1% and disease control rate (DCR) was 95.7% per IRRC review.
- The ORR for BM was 38.8% across all doses and 45.8% in 180 mg cohort, and the DCR for BM was 98.0% and 100.0% for overall and 180 mg groups.
- The median progression-free survival (PFS) was 9.92 months (Kaplan-Meier estimates, not mature).

Table 2. Summary of Antineoplastic Efficacy

Per Investigator Review*	30 mg (n=10)	60 mg (n=6)	120 mg (n=26)	180 mg (n=48)	240 mg (n=11)	Overall (n=101)
Best response#, n (%)						
Confirmed CR	1 (10.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)
Confirmed + unconfirmed CR	1 (10.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)
Confirmed PR	2 (20.0)	2 (33.3)	15 (57.7)	18 (37.5)	0 (0)	37 (36.6)
Confirmed + unconfirmed PR	3 (30.0)	2 (33.3)	16 (61.5)	30 (62.5)	4 (36.4)	55 (54.5)
SD	5 (50.0)	3 (50.0)	9 (34.6)	16 (33.3)	4 (36.4)	37 (36.6)
PD	0 (0)	1 (16.7)	1 (3.8)	2 (4.2)	0 (0)	4 (4.0)
NE	1 (10.0)	0 (0)	0 (0)	0 (0)	3 (27.3)	4 (4.0)
Confirmed ORR, n (%)	3 (30.0)	2 (33.3)	15 (57.7)	18 (37.5)	0 (0)	38 (37.6)
Overall ORR, n (%)	4 (40.0)	2 (33.3)	16 (61.5)	30 (62.5)	4 (36.4)	56 (55.4)
DCR, n (%)	9 (90.0)	5 (83.3)	25 (96.2)	46 (95.8)	8 (72.7)	93 (92.1)
Per IRRC Review	**30 mg (n=10)**	**60 mg (n=6)**	**120 mg (n=26)**	**180 mg (n=47)**	**240 mg (n=11)**	**Overall^ (n=100)**
Best response#, n (%)						
Confirmed CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Confirmed + unconfirmed CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Confirmed PR	5 (50.0)	1 (16.7)	16 (61.5)	26 (55.3)	0 (0)	48 (48.0)
Confirmed + unconfirmed PR	5 (50.0)	2 (33.3)	17 (65.4)	32 (68.1)	5 (45.5)	61 (61.0)
SD	2 (20.0)	3 (50.0)	7 (26.9)	13 (27.7)	3 (27.3)	28 (28.0)
PD	2 (20.0)	1 (16.7)	2 (7.7)	2 (4.3)	0 (0)	7 (7.0)
NE	1 (10.0)	0 (0)	0 (0)	0 (0)	3 (27.3)	4 (4.0)
Confirmed ORR, n (%)	5 (50.0)	1 (16.7)	16 (61.5)	26 (55.3)	0 (0)	48 (48.0)
Overall ORR, n (%)	5 (50.0)	2 (33.3)	17 (65.4)	32 (68.1)	5 (45.5)	61 (61.0)
DCR, n (%)	7 (70.0)	5 (83.3)	24 (92.3)	45 (95.7)	8 (72.7)	89 (89.0)

* Evaluable patients: Patients who have baseline and at least one post-baseline assessment.
# CR=complete response; PR=partial response; SD= stable disease; PD=progression disease; ORR=objective response rate; DCR=disease control rate;
^ One subject's baseline imaging data in evaluable patients set was not available to IRRC by data cut-off day.

Figure 1. Duration of Treatment and Response (per Investigator Review)

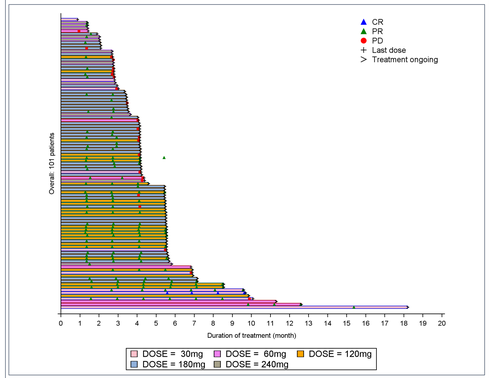


Figure 2. Best Percentage Change in Target Lesion Size (per Investigator Review)

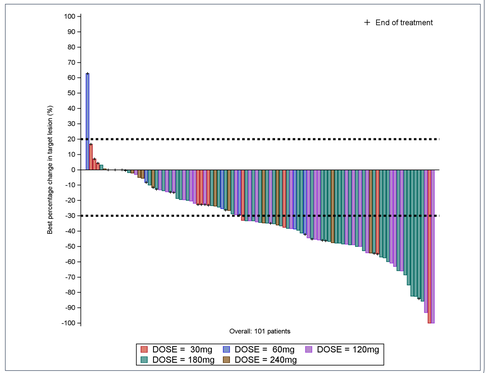


Table 3. Summary of Antineoplastic Efficacy on Brain Metastases (per IRRC Review)

Per IRRC Review*	30 mg (n=5)	60 mg (n=2)	120 mg (n=13)	180 mg (n=24)	240 mg (n=5)	Overall (n=49)
Best response, n (%)						
CR	1 (20.0)	1 (50.0)	0 (0)	1 (4.2)	0 (0)	3 (6.1)
PR	0 (0)	0 (0)	5 (38.5)	10 (41.7)	1 (20.0)	16 (32.7)
SD	3 (60.0)	1 (50.0)	8 (61.5)	13 (54.2)	4 (80.0)	29 (59.2)
PD	1 (20.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)
ORR, n (%)	1 (20.0)	1 (50.0)	5 (38.5)	11 (45.8)	1 (20.0)	19 (38.8)
DCR, n (%)	4 (80.0)	2 (100.0)	13 (100.0)	24 (100.0)	5 (100.0)	48 (98.0)

* The analysis was performed in patients with baseline brain metastases of evaluable patients set, based on radiographical response criteria from Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM).

Safety

- No dose-limiting toxicity (DLT) was observed and maximum tolerated dose (MTD) was not reached.
- For all safety-evaluable patients, most common treatment related treatment emergent adverse events (TEAEs) (≥10%) were neutrophil count decreased (17.6%), white blood cell count decreased (17.6%), leukopenia (11.8%) and platelet count decreased (10.1%).
- Grade 3~5 TEAEs were occurred in 16.0% patients and 8.4% of them were treatment-related per investigators' judgement.
- Serious adverse events (SAEs) were reported in 8.4% of patients, and 1.7% were treatment-related.
- The TEAEs leading to dose reduction, dose interruption and discontinuation were reported in 2.5%, 9.2% and 2.5% of overall patients, respectively.
- There were no dose-dependently increased TEAEs.

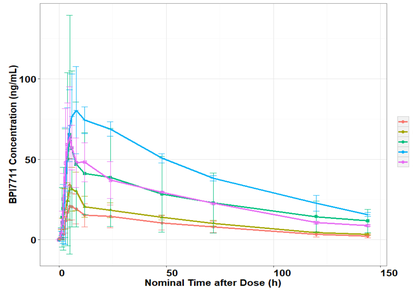
Table 4. Safety Overview of TEAEs

Patients with TEAEs, n (%)	30 mg (n=11)	60 mg (n=6)	120 mg (n=26)	180 mg (n=51)	240 mg (n=24)	300 mg (n=1)	Overall (n=119)
TEAEs	11 (100.0)	6 (100.0)	21 (80.8)	43 (84.3)	11 (45.8)	1 (100.0)	93 (78.2)
Treatment related TEAEs	8 (72.7)	3 (50.0)	17 (65.4)	36 (70.6)	10 (41.7)	0 (0)	74 (62.2)
Serious TEAEs	1 (9.1)	1 (16.7)	2 (7.7)	4 (7.8)	2 (8.3)	0 (0)	10 (8.4)
Treatment related serious TEAEs	0 (0)	0 (0)	1 (3.8)	1 (2.0)	0 (0)	0 (0)	2 (1.7)
Grade ≥3 TEAEs	2 (18.2)	1 (16.7)	4 (15.4)	10 (19.6)	2 (8.3)	0 (0)	19 (16.0)
Treatment related grade ≥3 TEAEs	0 (0)	1 (16.7)	2 (7.7)	7 (13.7)	0 (0)	0 (0)	10 (8.4)
TEAEs leading to							
Dose reduction	0 (0)	0 (0)	0 (0)	2 (3.9)	1 (4.2)	0 (0)	3 (2.5)
Dose interruption	1 (9.1)	0 (0)	2 (7.7)	7 (13.7)	1 (4.2)	0 (0)	11 (9.2)
Discontinuation	1 (9.1)	0 (0)	0 (0)	2 (3.9)	0 (0)	0 (0)	3 (2.5)
Death	1 (9.1)	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)	2 (1.7)

Pharmacokinetics

- Median $T_{max,ss}$ of BPI-7711 were 4.0~8.2h across all dose groups.
- Mean terminal elimination half-life of BPI-7711 were 41.0~63.1h across all dose groups.
- Steady state was achieved by 8~15 days after first dosing, and mean AUC accumulation ratio was 3.8~5.4 across all dose groups.
- Exposures of BPI-7711 increased dose dependently at steady state between 30 mg and 180 mg.

Figure 3. Plasma Concentrations of BPI-7711*



* 300 mg data was not available to central lab by data cut-off day.

CONCLUSIONS

- BPI-7711 was well tolerated and highly effective in acquired T790M+ NSCLC patients, with an overall ORR of 61.0% per IRRC review.
- BPI-7711 demonstrated a promising efficacy on brain metastases with a DCR of 98.0% per IRRC review.
- 180 mg was determined as recommended phase 2 dose and phase 2 trials are under preparation.

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