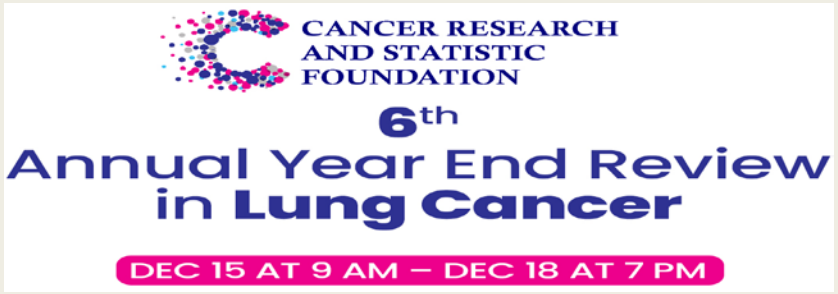
BBT-176- A 4TH GENERATION EGFR TKI, FOR PROGRESSED NSCLC AFTER EGFR TKI THERAPY: PK, SAFETY AND EFFICACY FROM PHASE 1 STUDY

Dr Dilip Harindran Vallathol
Consultant
Medical Oncology
MVRCCRI, Calicut



DISCLOSURE

Abstract presented by S.M. Lim at IASLC-WCLC 2022 conducted at Vienna, Austria

INTRODUCTION

- EGFR TKIs are the standard of care for EGFR mutated, advanced-stage NSCLC.
- Various mechanisms contribute to their resistance, among which a tertiary point mutation in the C797 residue of EGFR is the most well-known.
- C797S mutations develop in between 7% to 24% of patients treated with third-generation EGFR TKIs
- Currently, there is no approved drug for NSCLC in patients harboring the EGFR C797S resistance mutation

INTRODUCTION

- BBT- 176, a reversible, ATP-competitive inhibitor was developed to target complex EGFR mutations like C797S triple mutations and after progression on third-generation EGFR inhibitors such as Osimertinib
- It was shown to exhibit low nanomolar IC50 values in cell and animal efficacy models.
- Preclinical data showed BBT-176’s efficacy in NSCLC with EGFR double mutations and triple mutations and showed efficacy in inhibiting brain metastases
- Antitumor activity was presumed to be at a dose of 200 mg to 800 mg in humans

MATERIALS AND METHODS

- A phase 1 study to determine the PK parameters, safety profile, recommended phase 2 dose and explore efficacy
- Patients with EGFR mutation previously treated with at least one EGFR TKI were enrolled
- Followed up with imaging study and underwent Guardant liquid biopsy every 6 weeks
- BBT-176 was orally administered once daily continuously from 20 mg to 600 mg until progressive disease or intolerability
- Intra-patient dose escalation was allowed
- Bayesian linear regression model was employed to guide dose escalation

RESULTS

- A total of 18 patients were enrolled
- Triple mutant EGFR gene mutation was detected in the blood of five patients.
- Drug exposure was apparently dose-proportional and within the therapeutic range with QD dosing

RESULTS

- Reduction in EGFR mutation allelic frequency was observed in three patients, including non-classical exon 19 deletion and T790M.
  - These changes were correlated with tumor shrinkage in two of the patients.
  - Two patients harboring triple mutations of exon 19 del/ T790M/C797S showed radiological improvements in both target and non-target lesions

RESULTS

- Common treatment-related adverse events (TRAEs) were nausea (n=5), vomiting (n=3), diarrhea (n=3), rash (n=4), pruritus (n=2), amylase increase (n=2), and lipase increase (n=2).
- No dose-limiting toxicity or discontinuation of treatment due to TRAE were reported so far.

RESULTS

Table. Clinical outcomes of representative patients

Dose	Age/Gender/Race	*EGFR* allelic frequency at baseline	EGFR allelic frequency at nadir	Target lesion size change by RECIST	Investigator's Assessment of Overall Response
160→ 320 mg	43/F/Asian	L747_K754delinsSPQ (30.6%)	L747_K754delinsSPQ (4.1%)	-30.3%	PR
320 mg	39/M/Asian	E746_A750del (39.7%), T790M (13.8%)	E746_A750del (25.7%), T790M (9.7%)	0.0%	SD
320 mg	52/F/Asian	E746_A750del (1.7%), T790M (0.4%), C797S* (0.5%) * in cis relation with T790M	E746_A750del (3.0%), T790M (1.5%), C797S (1.4%) From the second follow-up. All values increased from baseline, with no nadir	-12.1%	SD
480 mg	67/F/Asian	L858R (0.08%)	L858R (0.04%)	-11.8%	SD
480 mg	54/M/Asian	E746_A750del (56.8%), T790M (37.0%), L792H* (34.6%), C797S** (2.9%) *,** mutually exclusive and in cis relation with T790M	Not available at the time of submission	-26.3%	SD

CONCLUSION

- Continuous daily dosing of BBT-176 was well-tolerated with manageable toxicities.
- The effectiveness of BBT-176 may be further enhanced by molecular selection of the patients and dynamic monitoring with liquid biopsy.
- Further exploration at recommended phase 2 Dose study is planned

THANK YOU