Gene fusions are oncogenic drivers and potential therapeutic targets across a broad range of tumor types. Fusion events in the neurotrophic tyrosine kinase receptor (NTRK) gene lead to constitutive kinase activation of the NTRK fusion protein, which may be enriched in non-small cell lung cancer (NSCLC). An unmet need exists for effective treatments with central nervous system (CNS) activity for patients with NTRK and ROS1 fusion-positive NTRK+ cancers and ROS1-fusion-positive (ROS1+) NSCLC, many of whom will have brain metastases or diagnosis of disease progression in the CNS. Overall, up to 50% of NSCLC patients may have brain metastases.

Entrectinib is a potent inhibitor of NTRK and ROS1, Entrectinib has systemic activity and is also able to cross the blood-brain barrier and achieve therapeutic levels by effectively reaching the CNS.

Entrectinib has antitumor effects in mouse and human tumor cell lines and patient-derived xenograft models across several tumor types, both systemically and intracranially.

We report integrated data from three phase 1/2 entrectinib clinical trials for a large cohort of adults with NTRK+ solid tumors or ROS1+ NSCLC to baseline CNS metastases.

### INTRODUCTION

- Gene fusions are oncogenic drivers and potential therapeutic targets across a broad range of tumor types.
- Fusions in the neurotrophic tyrosine kinase receptor (NTRK) gene lead to constitutive kinase activation of the NTRK fusion protein, which may be enriched in non-small cell lung cancer (NSCLC).
- An unmet need exists for effective treatments with central nervous system (CNS) activity for patients with NTRK and ROS1 fusion-positive NTRK+ cancers and ROS1-fusion-positive (ROS1+) NSCLC, many of whom will have brain metastases or diagnosis of disease progression in the CNS. Overall, up to 50% of NSCLC patients may have brain metastases.

### OBJECTIVE

- To describe the efficacy of entrectinib for adult patients with ROS1+ NSCLC or NTRK+ solid tumors with and without CNS metastases from phase 1/2 trials.

### METHODS

- This analysis (data cut off May 31, 2018) includes adult patients with locally advanced or metastatic ROS1+ NSCLC or NTRK+ solid tumors confirmed via FISH or IHC.
- Inclusion criteria included measurable disease at baseline, no previous therapy with NTRK/ROS1-targeted treatments, and receipt of 21 cycles of entrectinib dose at or above the recommended phase 2 dose (i.e., 600 mg daily).
- Stable CNS involvement was permitted with or without prior CNS-directed therapy.
- Baseline CNS metastases were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) at screening, after cycle 1 (4 weeks), and every 8 weeks thereafter.

- Efficacy

  - The ORR was 57% (95% confidence interval (CI) 43.3–74.8%) in patients with NTRK+ solid tumors and 77% (95% CI 63.8–87.7%) in patients with ROS1+ NSCLC.
  - Response according to baseline CNS disease status is summarized in Table 2.
  - ORR was similar in patients with and without baseline CNS disease and was higher in patients with baseline CNS disease.

- Conclusions

  - Entrectinib induced clinically meaningful durable responses in patients with NTRK+ solid tumors or ROS1+ NSCLC.
  - Entrectinib was tolerable with a manageable safety profile.

### RESULTS

- Baseline characteristics are summarized in Table 1.
- CNS metastases at baseline were seen in 22% and 43% of patients in NTRK+ solid tumor and ROS1+ NSCLC cohorts, respectively.

### CONCLUSIONS

- Entrectinib induced clinically meaningful durable responses in patients with NTRK+ solid tumors or ROS1+ NSCLC.
- Entrectinib was tolerable with a manageable safety profile.

The results from this integrated analysis of entrectinib clinical trials indicate that entrectinib has systemic and intracranial activity and is a potential treatment option for patients with NTRK+ solid tumors and ROS1+ NSCLC with metastatic CNS disease, which is a current unmet need in these populations.

### ACKNOWLEDGMENTS & DISCLOSURES

- All authors are employees of Blueprint Medicines or Blueprint Medicine. The authors thank the patients, families, investigators, and sites throughout the trial.

### REFERENCES