Intracranial Efficacy of Pralsetinib in Patients With *RET* Fusion-Positive NSCLC: ARROW Study Subanalysis

Emma St. Martin, MD[1*]; Aaron S. Mansfield, MD[1]; Gilberto de Lima Lopes, MD, MBA[2]; Vivek Subbiah, MD[3,4]; Stephen V. Liu, MD[5]; Robert C. Doebele, MD, PhD[6]; Christina S. Baik, MD, MPH[7]; Matthew H. Taylor, MD[8]; Makenzi Evangelist, MD[9]; Sophia Wang, MS[10]; Francois Di Trapani, PharmD[10]; Justin F. Gainor, MD[11]

[1]Department of Oncology, Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA; [2]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA; [3]UT MD Anderson Cancer Center, Houston, TX, USA; [4]Sarah Cannon Research Institute, Nashville, TN, USA; [5]Georgetown University, Washington, DC, USA; [6]Division of Medical Oncology, Department of Medicine, University of Colorado Cancer Center, Aurora, CO, USA; [7]Division of Medical Hematology and Oncology, Department of Medicine, University of Washington, Seattle, WA, USA; [8]Earle A. Chiles Research Institute, Providence Medical Center, Portland, OR, USA; [9]Albany Cancer Center, Albany, NY, USA; [10]Rigel Pharmaceuticals, Inc., South San Francisco, CA, USA; [11]Department of Medicine, Center for Thoracic Cancers, Massachusetts General Hospital Cancer Center, Boston, MA, USA

*Presenting Author

ABSTRACT 477/500 words

Background: *RET* fusions are targetable oncogenic drivers in 1%-2% of non-small cell lung cancers (NSCLCs). Approximately 25% of patients with Stage 4 *RET* fusion-positive NSCLC will also have brain metastases at baseline, and nearly half will experience brain metastases in their lifetime. Pralsetinib is an oral, selective RET inhibitor FDA approved in adults with metastatic *RET* fusion-positive NSCLC and in adults and children aged ≥12 years with advanced or metastatic *RET* fusion-positive thyroid cancer, based on results from the global, open-label phase 1/2 ARROW trial (NCT03037385). We report final intracranial efficacy and safety results in ARROW patients with *RET* fusion-positive NSCLC**.**

Methods: Phase 2 ARROW patients received pralsetinib 400 mg once daily. Patients did not receive radiation therapy during pralsetinib treatment or within 14 days before starting therapy. Intracranial overall response rate (CNS ORR), duration of response, disease control rate, progression-free survival, and overall survival were assessed in patients with measurable central nervous system (CNS) metastases (per RECIST 1.1) at baseline. Cumulative incidence rates (CIRs) of progressive disease (PD) were evaluated in all patients with and without CNS metastases at baseline.

Results: Seventy-eight patients with *RET* fusion-positive NSCLC had CNS metastases at baseline, 20 of whom had measurable lesions, while 184 patients did not have baseline CNS metastases. Baseline characteristics were relatively similar between patients with and without CNS metastases, though those with CNS disease had poorer ECOG performance status (0 in 19% vs 35%; 1 in 76% vs 63%, respectively). Among patients with CNS metastases, 55% had received prior platinum chemotherapy, 21% received multikinase inhibitors, and 27% received PD-(L)1 inhibitors. The **Table** summarizes efficacy outcomes for patients with measurable baseline CNS metastases (n=20). CNS ORR was 55% (11/20), including 5 complete responses. Among patients with posttreatment response assessments, CNS ORR was 73% (11/15). In patients without CNS metastases at baseline, the 12-month CIR for CNS progression was 3% vs 13% in those with baseline CNS metastases. The 12-month CIR for non-CNS progression was 26% in patients without baseline CNS metastases and 23% in those with CNS metastases. No new safety signals were observed.

Conclusions: Pralsetinib demonstrated a CNS ORR of 55%, including 5 CRs, and a median response duration of 14.8 months, supporting its clinical utility in the treatment of *RET* fusion-positive NSCLC with CNS involvement.

Table. Intracranial Efficacy Summary in Patients With *RET* Fusion-Positive NSCLC and Measurable CNS Metastases at Baseline

	CNS Measurable Population (n=20)
CNS ORR, % (95% CI)	55 (31.5, 76.9)
CR, n (%)	5 (25)
PR, n (%)	6 (30)
CNS DOR, median, mo (95% CI)	14.8 (4.1, 45.6)
CNS DCR, % (95% CI)	75 (50.9, 91.3)
CNS PFS	
Median, mo (95% CI)	5.9 (3.6, 47.3)
Mean, mo (SD)	13.4 (18.3)
OS, median, mo (95% CI)	16.2 (3.6, 47.3)

CNS, central nervous system; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

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