Landscape of Genomic Mechanisms of Resistance to Selective RET Inhibitors in *RET*-Altered Solid Tumors: Analysis of the RETgistry Global Consortium

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Background: Rearranged during transfection (*RET*) alterations are oncogenic drivers across solid tumors. Selective RET inhibitors (SRIs) selpercatinib and pralsetinib have transformed outcomes for patients with *RET*-altered malignancies. However, resistance invariably emerges, curtailing therapeutic benefit. Limited knowledge exists on the genomic landscape of resistance to SRIs.

Methods: We established 'RETgistry,' a global consortium across 20 institutions of patients with advanced *RET*-altered solid tumors who received SRI(s) and underwent post-progression tissue or plasma biopsies assessed by next-generation sequencing. Frequencies of secondary *RET* mutations and acquired non-*RET* alterations were determined. Progression-free survival (PFS) and time to treatment discontinuation (TTD) on first SRI were estimated with Kaplan-Meier method.

Results: RETgistry included 109 patients with *RET*-altered solid tumors (lung, n=94; thyroid, n=15) with 143 post-SRI progression biopsies (tissue, 91; plasma, 52). Median PFS and TTD were 13.9 months (95% CI 10.1-16.6) and 17.3 months (95% CI 14.0-20.2), respectively. Secondary *RET* mutations were detected in 20 (14.0%) biopsies overall (lung, 12.4%; thyroid, 22.7%). Among 99 paired pre/post-SRI biopsies (79 patients; Figure 1A), with pre-SRI biopsies obtained immediately before SRI and after prior multikinase inhibitors (if received), acquired *RET* mutations (on-target resistance) were identified in 2.0% of post-SRI biopsies, non-*RET* alterations only (off-target resistance) in 60.6%, both in 10.1%, and no acquired alterations in 27.3%. Common acquired off-target alterations (Figure 1B) involved *MET* (18.2%; amplification: 15.0%), *TP53* (8.2%), *APC* (7.6%), *KRAS* (7.1%), and *KEAP1* (5.9%). *MET* alterations were enriched in post-SRI versus pre-SRI tumors (17.6% vs 2.0%, p=0.022; lung only: 19.1% vs 2.1%, p=0.022).

Conclusions: In RETgistry, secondary *RET* mutations after SRIs were uncommon, underscoring predominance of off-target resistance. Recurrent acquired alterations involving tumor suppressor genes or upstream MAPK and PI3K regulators were identified, with *MET* amplification being the most common. Continued efforts to characterize SRI resistance biology are critical to guide development of novel therapeutic strategies.

Figure 1: Acquired genomic alterations following selective RET inhibitor therapy