First results from the RETgistry:

A global consortium for the study of resistance to RET inhibitors in *RET*-altered tumors

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Background

- Rearranged during transfection (*RET*) gene alterations are the oncogenic driver in diverse tumor types. RET-selective tyrosine kinase inhibitors (TKIs) selpercatinib and pralsetinib are effective, but acquired drug resistance remains a challenge.
- Here, we report the initial results from the RETgistry, an international consortium aimed at elucidating mechanisms of resistance to RET TKIs across *RET*-altered solid tumors.

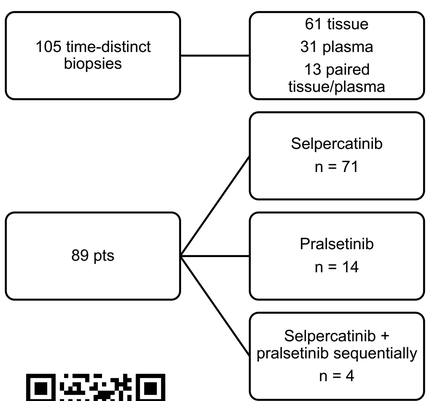
Methods

- This was a retrospective analysis performed across 16 institutions.
- Patients (pts) were eligible if they had an advanced solid tumor harboring an oncogenic *RET* alteration, received ≥1 RET TKI with disease progression, and underwent resistant tumor or liquid biopsy for next-generation sequencing (NGS).

Table 1. Characteristics of enrolled pts.

Characteristic	n (%), n=89
Age at diagnosis, median (range)	58 (21-86)
Male	42 (47)
Never or light smoker	79 (89)
Tumor type	*n=89*
Non-small cell lung cancer (NSCLC)	73 (82)
Medullary thyroid cancer (MTC)	13 (15)
Papillary thyroid cancer	2 (2)
Anaplastic thyroid cancer	1 (1)
NSCLC, RET fusion	*n=73*
KIF5B-RET	51 (70)
CCDC6-RET	15 (21)
Other or unknown	7 (10)
MTC, RET mutation	*n=13*
M918T	7 (54)
Other	6 (46)
RET TKI line of therapy	*n=105*
First-line	34 (32)
Second-line	42 (40)
Third- or greater-line	29 (28)
Resistant biopsy obtained, median (range)	15.4 mos (1.8-58.8)
Baseline co-mutations, pre-RET TKI	*n=93*
TP53	27 (29)
CDKN2A/B loss	12 (13)

Fig. 1. Summary of samples collected from the enrolled pts.



Results

- 105 time-distinct biopsies were included in analysis, obtained from 89 pts with progression on a RET-selective TKI (**Fig. 1**). 97% of samples had baseline NGS.
- Acquired *RET* mutations were detected in 13% (G810X, in 10%) (**Fig. 2, 3**).
- Potential off-target resistance gene alterations identified in 46 cases (44%) included *MET* amplification (12%), *BRAF* V600E or fusion (3%), *KRAS* gain or mutation (5%), *ERBB2* amplification (2%), *EGFR* amplification (3%), *ROS1* fusion (1%), *ALK* fusion (1%) , and activating *PIK3CA* mutation or *PTEN* loss (5%) (**Fig. 2, 4**).

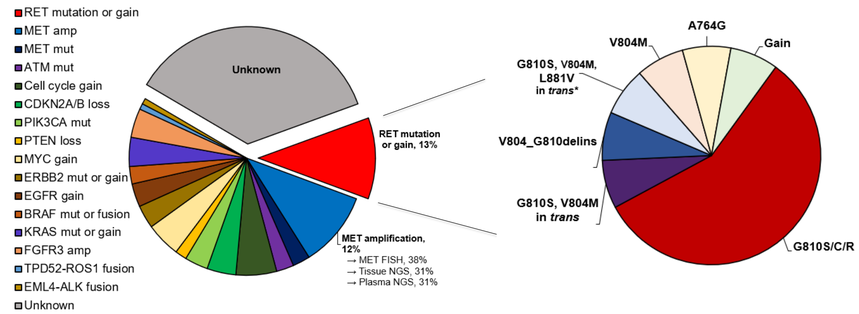


Fig. 2. Putative on- and off-target resistance mechanisms detected in post-RET TKI biopsies. The diagnostic method used for *MET* amplification detection is listed.

Fig. 3. On-target (*RET*) resistance alterations detected in post-RET TKI biopsies. *G810 and V804M mutations known to be in *trans.*

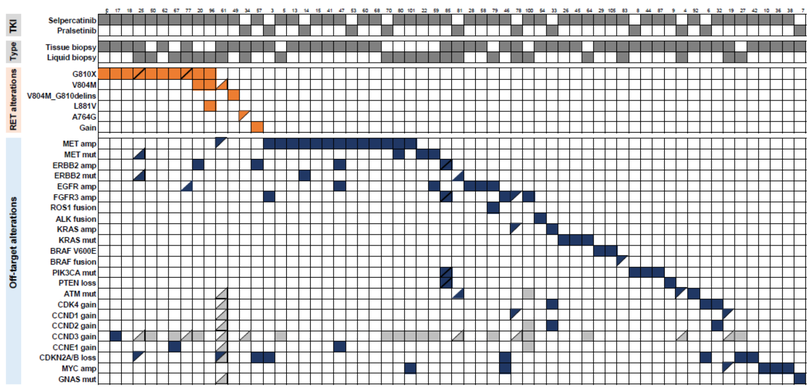


Fig. 4. Heatmap depicting gene alterations detected in post-RET-selective TKI biopsies (n=60/105 with putative on- or off-target resistance mechanisms, as in Fig. 2). Light gray = samples in which the NGS assay did not probe the indicated genes. For samples with paired tissue/liquid biopsies (n=10), findings are shown using the upper (tissue) and lower (liquid) triangle, respectively.

Results

- On-target mutations were detected in 15% of thyroid cancer samples and 12.9% of NSCLC samples; off-target alterations, in 40% of thyroid cancer and 44.7% of NSCLC samples.
- Median duration of RET TKI preceding biopsies [first-line, n=34 (32%); second-line, n=42 (40%); third-/greater-line, n=29 (28%)] was 16.5 months (mos) (95% CI, 14.0-20.0).
- Median PFS was 13.0 mos (95% CI, 9.3-15.88).
- The duration of TKI therapy (HR 0.87, p=0.64) or PFS (HR 0.79, p=0.42) (**Fig. 5**) did not differ according to the presence of on-target vs off-target resistance.

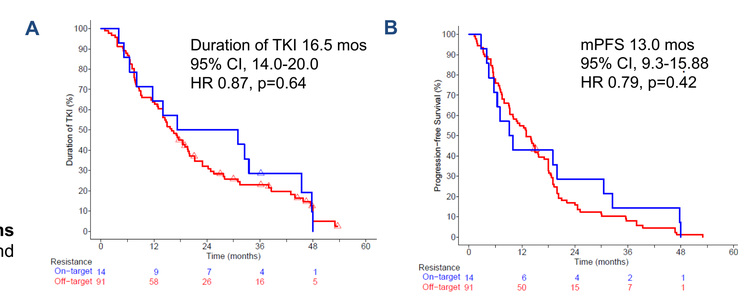


Fig. 5. A) Median duration of RET TKI by the status of *RET* mutation in post-TKI biopsies. B) Median progression-free survival by the status of *RET* mutation in post-TKI biopsies. Blue = *RET* mutation present, red = no *RET* mutation present.

Conclusions

- On-target resistance to RET inhibition due to acquired *RET* mutations was less common than off-target resistance, identified in 13% of the analyzed cases.
- Several potentially actionable off-target gene alterations were detected in post-treatment biopsies, (e.g., *MET* amplification, *BRAF* or *KRAS* alterations, *ALK* or *ROS1* fusion).
- Further studies are warranted to enable the development of strategies to address resistance in pts with *RET*-altered tumors.

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