72P Pan-tumor survey of *RET* fusions as detected by next-generation RNA sequencing identified *RET+* colorectal carcinoma as a unique molecular subset of CRC

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Background

Two selective RET tyrosine kinase inhibitors have been approved to treat RET fusion positive (RET+) non-small cell lung cancer and well-differentiated thyroid cancer. However, *RET* fusions have been reported in other solid tumors.

Methods

To identify the full spectrum of *RET+* solid tumors using next-generation RNA sequencing and to evaluate their molecular characteristics, a retrospective analysis was executed on *RET+* solid malignancies identified by targeted RNA sequencing and whole transcriptome sequencing of clinical tumor samples performed at Caris Life Science (Phoenix, AZ).

Results

Table 1- Patient demographics and cancer type distribution for RET positive tumors.

		NSCLC	**Thyroid	Colorectal	Breast	CUP	Pancreatic
	N	253	42	38	10	10	8
Age	Median (range)	66 (27->89)	81.0 (9-84)	72.5 (34-88)	59.5 (35-75)	71.5 (41-87)	68.5 (55-81)
	Mean (SD)	64.7 (12.02)	51.1 (21.1)	67.9 (12.7)	58.8 (15.7)	68.8 (13.9)	67.3 (9.0)
Gender	Male	113	14	15	0	6	5
	Female	140	28	23	10	4	3
Platform	Targeted RNA (Archer)	44	3	2	3	2	0
	WTS	209	39	36	7	8	8
	Mean junction read (SD)	45.2 (42.6)	18.7 (35.9)	22.7 (26.8)	16.7 (10.8)	48.8 (52.1)	38.4 (80.9)

**Breakdown of RET+ thyroid tumors

RET+ Thyroid tumors	N
Papillary carcinoma	38
Medullary carcinoma	1
None of These Apply	3
Total	42

Figure 1-Distribution of RET+ tumors by cancer type (N=378)

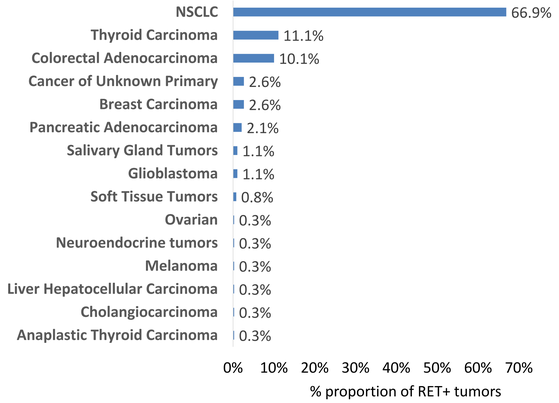
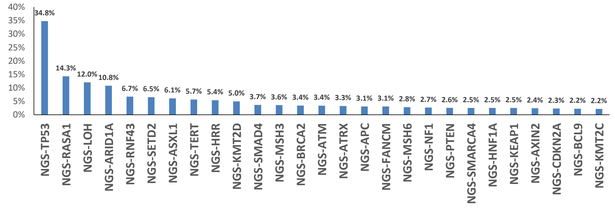


Figure 3-Most prevalent co-alterations for RET+ tumors.

A. co-mutations (pathogenic/likely pathogenic)



B. co-amplifications (copy number ≥6)

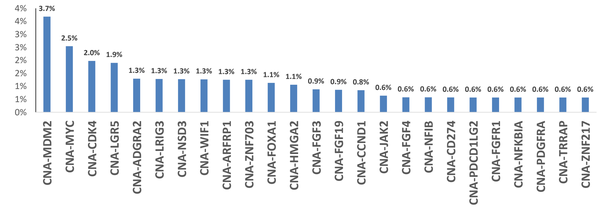


Figure 2-RET fusion partners among cancer types

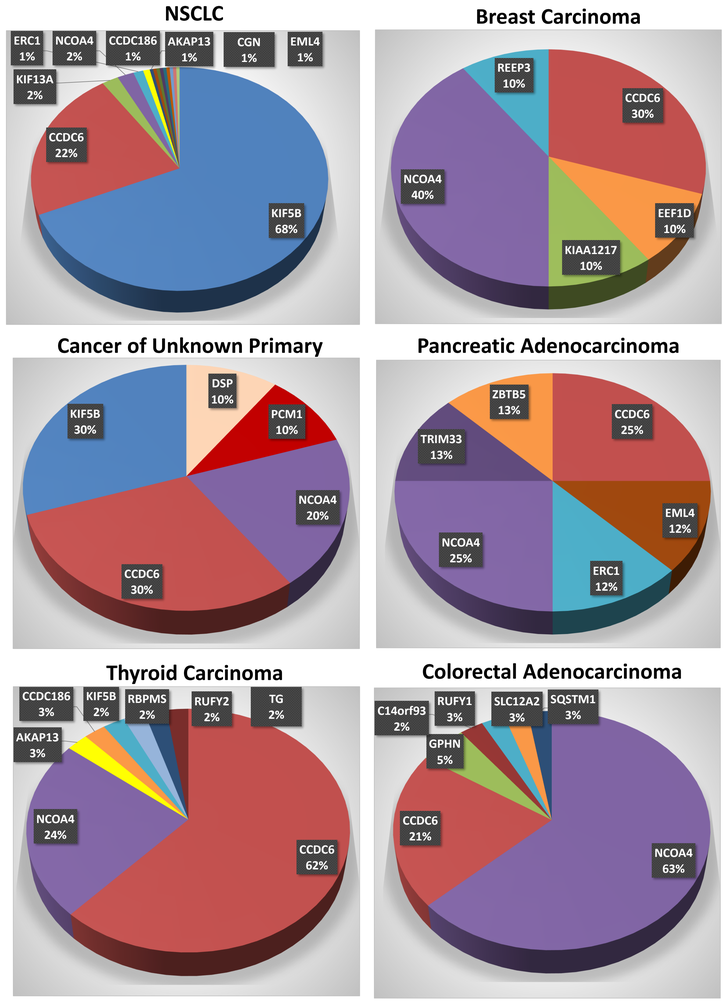
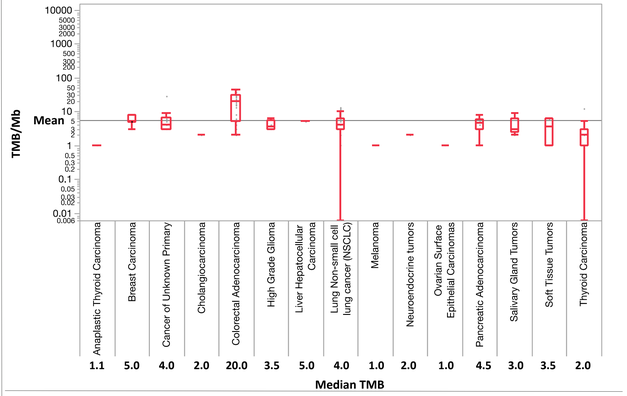


Figure 4- TMB per Mb distribution in RET+ tumors



Conclusions

- A total of 378 RET+ solid malignancies were identified in 15 different tumor types and carcinoma of unknown primary (CUP) that underwent next-generation RNA sequencing.
- RET+ NSCLC and RET+ thyroid cancer constituted 66.9% and 11.1% of the RET+ solid malignancies with CRC and breast adenocarcinoma constituting 10.1% and 2.6% respectively.
- KIF5B (46.8%) is the most common fusion partner followed by CCDC6 (28.3%) and NCOA4 (13.8%).
- The most common single gene alterations in RET+ tumors were TP53 (34.8%), ARID1A (10.8%) and RNF43 (6.7%).
- RET+ CRC had a median TMB of 20 Mt/Mb with MSI-H seen in 63%.
- Outside of approved indications of NSCLC and thyroid cancers, *RET* fusions were identified in multiple tumor types such as colorectal, breast, cancer of unknown primary and pancreatic cancer.

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