case reports

Real-World Experience of *NTRK* Fusion–Positive Thyroid Cancer

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Introduction

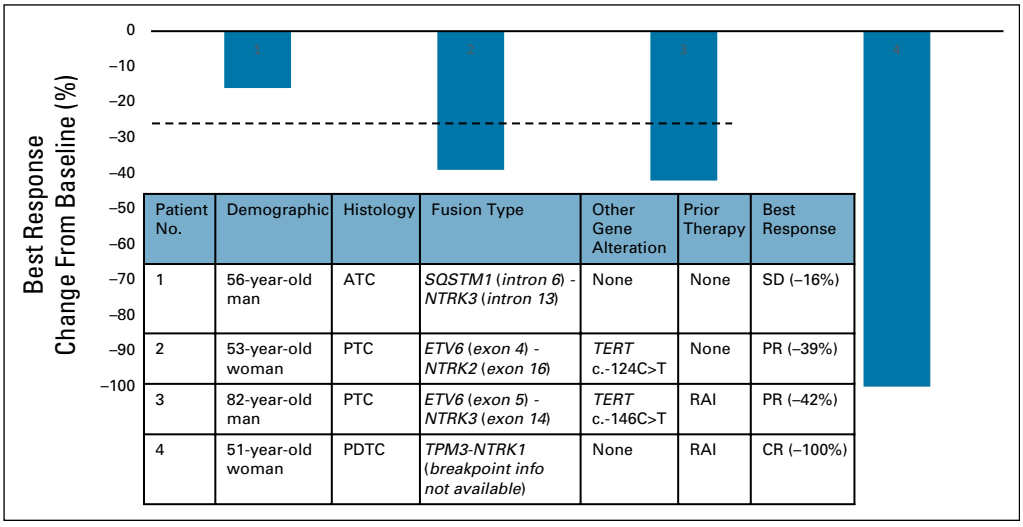
The tropomyosin receptor kinase (Trk) receptors, TrkA, TrkB, and TrkC, encoded by the *NTRK1*, *NTRK2,* and *NTRK3* genes, respectively, are transmembrane proteins that play an important role in the normal development and function of the nervous system. Aberrant fusions of *NTRK* genes lead to the production of chimeric Trk receptors, which are constitutively activated with subsequent activation of downstream signaling pathways including mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways.[1] Such *NTRK* fusions have been found to be oncogenic drivers in multiple solid tumors including thyroid cancer.[2]

Selective Trk inhibitors, larotrectinib and entrectinib, demonstrated excellent efficacies with high and durable responses across the *NTRK* fusion–positive pediatric and adult solid tumors in several small basket trials.[3,4] Only a few patients with thyroid cancer were included in the published studies because of the rarity of the *NTRK* fusions in thyroid cancer. Furthermore, the frequencies and the types of *NTRK* fusions in thyroid cancer are widely variable in different studies.[5-10] Herein, we describe our real-world experience from four patients with *NTRK* fusion–positive thyroid cancer treated with larotrectinib. We also report the frequencies and the types of *NTRK* gene alterations in thyroid cancer from available public databases and a real-world data set from Tempus.

Case Presentations

A case series of four patients with *NTRK* fusion–positive thyroid cancer treated with larotrectinib is summarized in Figure 1. One patient had anaplastic thyroid cancer (ATC), one patient had poorly differentiated thyroid cancer (PDTC), and two patients had papillary thyroid cancer (PTC). The study was approved by the institutional review board of University of California, San Francisco (IRB #20-31865). Patient consent for the study was waived as the study did not involve any identifiable data. Consent to publish images was obtained from patient 2.

Patient 1 with ATC harboring *SQSTM1-NTRK3* presented with a rapidly enlarging neck mass and multiple lung nodules. He underwent total thyroidectomy and central neck dissection; pathology showed small



Patient No.	Demographic	Histology	Fusion Type	Other Gene Alteration	Prior Therapy	Best Response
1	56-year-old man	ATC	*SQSTM1* (*intron 6*) - *NTRK3* (*intron 13*)	None	None	SD (–16%)
2	53-year-old woman	PTC	*ETV6* (*exon 4*) - *NTRK2* (*exon 16*)	*TERT* c.-124C>T	None	PR (–39%)
3	82-year-old man	PTC	*ETV6* (*exon 5*) - *NTRK3* (*exon 14*)	*TERT* c.-146C>T	RAI	PR (–42%)
4	51-year-old woman	PDTC	*TPM3-NTRK1* (*breakpoint info not available*)	None	RAI	CR (–100%)

FIG 1. Baseline clinicopathologic characteristics of four patients with *NTRK* fusion harboring thyroid cancer who were treated with larotrectinib, and waterfall plot for best response. ATC, anaplastic thyroid cancer; CR, complete response; PDTC, poorly differentiated thyroid cancer; PR, partial response; PTC, papillary thyroid cancer; RAI, radioactive iodine; SD, stable disease.

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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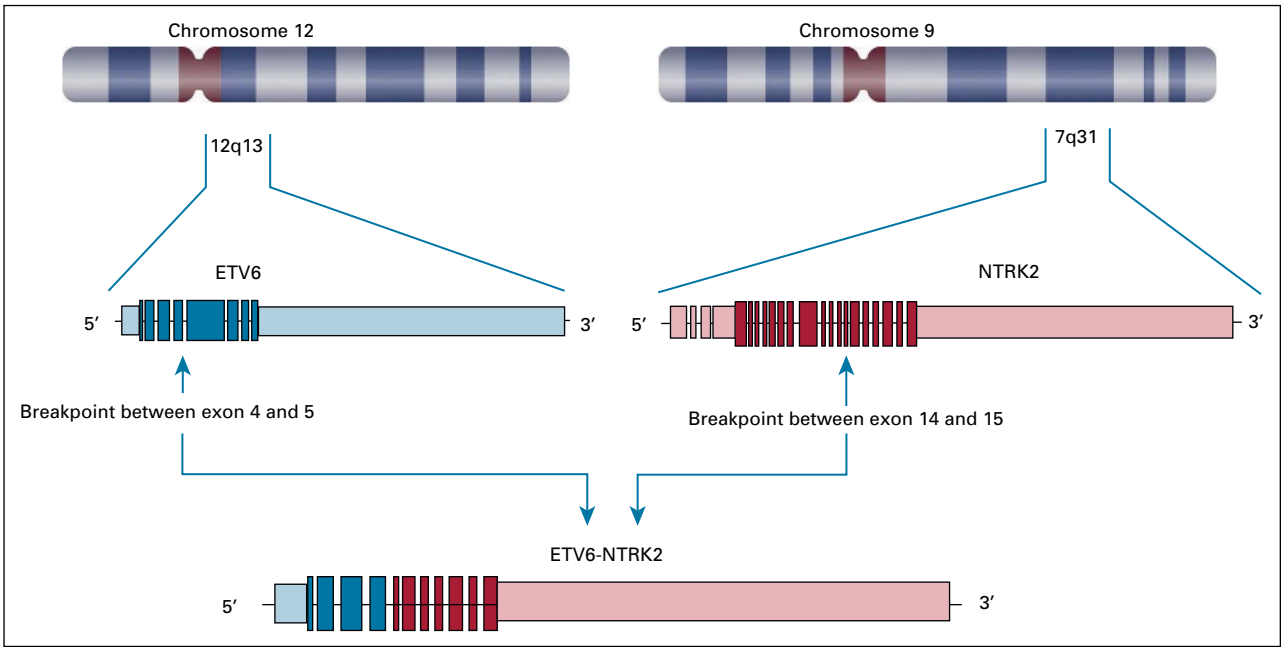

FIG 2. Novel fusion between 5′ breakpoint in *ETV6* exon 4-5 and 3′ breakpoint in *NTRK2* exon 14-15. This fusion preserves the *ETV6* PNT domain and the *NTRK2* kinase domain, leading to constitutive activation of the *NTRK2* kinase.

multifocal PTCs in thyroid and 9.5-cm mixed anaplastic and PDTC in left central neck. Because of complicated postoperative course, larotrectinib was initiated instead of intensive chemoradiation. The patient had 16% reduction in tumor burden after 2 months but progressed with enlarging parotid and neck masses after 6 months. Biopsy of the progressing lesion showed no gatekeeper mutations[11] or additional alterations.

Patient 2 with PTC harbored novel *ETV6-NTRK2* fusion not previously described in other solid tumors. The novel fusion has breakpoints in *ETV6* exon 4 and *NTRK2* exon 16 with preserved *ETV6* PNT domain and *NTRK2* kinase domain leading to constitutive activation of TrkB kinase (Fig 2). The patient has a remote history of PTC treated with surgery. She was found to have multiple brain metastases, obstructive hydrocephalus caused by a cerebellar mass, and pleural effusion with pleural masses. Pleural biopsy and cerebellar resection specimens confirmed metastatic PTC with *ETV6-NTRK2* fusion and *TERT* c.-124C>T mutation. Thyrogen-stimulated I-123 scan showed uptake only in the chest. After receiving stereotactic body radiation to brain metastases and cerebellar resection bed, larotrectinib was initiated, resulting in ongoing partial response (PR) in the pleural metastases for more than 18 months (Fig 3) without evidence of recurrence in the brain.

Patient 3 with PTC harboring *ETV6-NTRK3* fusion and *TERT* c.-146C>T mutation presented with a spine metastasis. He underwent total thyroidectomy, neck dissection, and metastasectomy of the spine lesion, followed by radioactive iodine treatment (RAI-T; 100 mCi) and radiation to the spine and neck lymph nodes. After 2 years, he developed multiple new bone and pulmonary metastases with a recurrence in the ipsilateral neck. He started larotrectinib and achieved PR ongoing for 7 months.

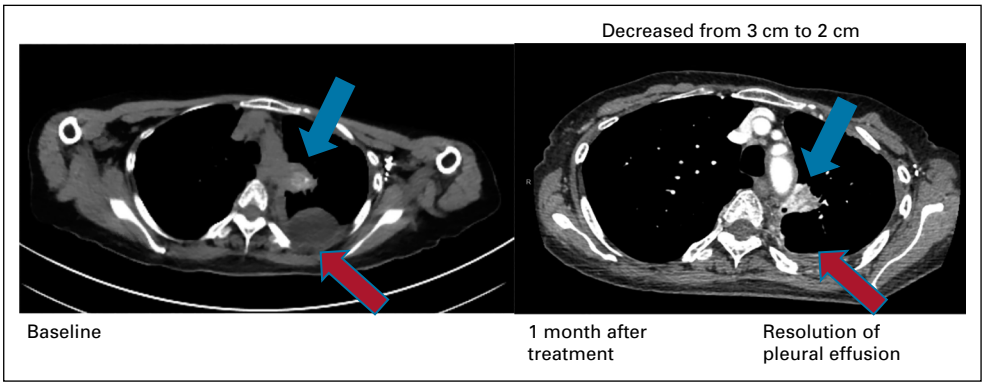

FIG 3. Patient 2 with metastatic PTC harboring *ETV6-NTRK2*. Computed tomography chest images demonstrate dramatic response after 1 month treatment with larotrectinib. PTC, papillary thyroid cancer.

TABLE 1. Identified *NTRK* Gene Fusion Alterations in Thyroid Cancers From GENIE, TCGA, and Tempus Databases

Histology	*NTRK* Fusion	Coaltered Genes	Overexpressed Genes	Data Source
PTC	*ETV6-NTRK3*	*FGFR4*, *ATM*, *TSC*	NA	GENIE
PTC	*ETV6-NTRK3*	*BRCA2*, *ATRX*, *ARID1B*	NA	GENIE
PTC	*ETV6-NTRK3*	*TERT* promoter	NA	GENIE
PTC	*ETV6-NTRK3*	*TSC*	NA	GENIE
PTC	*ETV6-NTRK3*	*NOTCH2*	NA	GENIE
PTC	*ETV6-NTRK3*	None	NA	GENIE
PTC	*ETV6-NTRK3*	None	NA	GENIE
PTC	*ETV6-NTRK3*	None	NA	GENIE
PTC	*ETV6-NTRK3*	None	NA	GENIE
PTC	*ETV6-NTRK3*	None	NA	GENIE
PTC	*ETV6-NTRK3*	None	NA	GENIE
PDTC	*ETV6-NTRK3*	None	NA	GENIE
PTC	*ETV6-NTRK3*	None	NA	TCGA
PTC	*ETV6-NTRK3*	None	NA	TCGA
PTC	*ETV6-NTRK3*	None	NA	TCGA
PTC	*ETV6-NTRK3*	None	NA	TCGA
PTC	*ETV6-NTRK3*	None	NA	TCGA
PTC	*ETV6-NTRK3* (*ETV6* intron 4: *NTRK3* intron 12)	*TERT* promoter, *TP53*	*MET*	Tempus
PTC	*ETV6-NTRK3* (*ETV6* intron 4: *NTRK3* intron 13)	*TERT* promoter	None	Tempus
PTC	*ETV6-NTRK3* (*ETV6* intron 4: *NTRK3* intron 13)	*TERT* promoter	None	Tempus
PTC	*ETV6-NTRK3* (*ETV6* intron 4: *NTRK3* intron 13)	None	*BRAF*	Tempus
ATC	*ETV6-NTRK3* (*ETV6* intron 4: *NTRK3* intron 13)	None	None	Tempus
PTC	*TPM3-NTRK1*	*TERT* promoter, *SMARCB1*	NA	GENIE
PTC	*TPM3-NTRK1*	*TERT* promoter	NA	GENIE
ATC	*TPM3-NTRK1*	*TERT* promoter, *TP53*, *CDKN2A*, *CDKN2B*	NA	GENIE
Medullary thyroid cancer	*TPM3-NTRK1*	*CDKN2A*	NA	GENIE
PTC	*TPM3-NTRK1*		NA	TCGA
PTC	*TPM3-NTRK1* (*TPM3* 3′ UTR: *NTRK1* exon 8)	*TERT* promoter, *SMARCB1*	*MAPK1*, *MET*	Tempus
PTC	*TPM3-NTRK1* (*TPM3* exon 10: *NTRK1* intron 9)	None	None	Tempus
ATC	*TPM3-NTRK1* (*TPM3* 3′ UTR: *NTRK1* intron9)	*TERT* promoter, *TP53*, *ARID2*	*FGFR1*, *CDK4*, *NRAS*	Tempus
ATC	*TPM3-NTRK1* (*TPM3* 3′ UTR: *NTRK1* exon 8)	*TERT* promoter, *TP53*	None	Tempus
PTC	*TPR-NTRK1*	*TERT* promoter, *NOTCH1*, *ARID1B*	NA	GENIE
PTC	*TPR-NTRK1*	*BRCA2*	NA	GENIE
PTC	*TPR-NTRK1*	*ARID1A*	NA	GENIE
PTC	*TPR-NTRK1*	None	NA	GENIE
PTC	*TPR-NTRK1*	None	NA	GENIE
PTC	*TPR-NTRK1*	None	NA	GENIE

(Continued on following page)

TABLE 1. Identified *NTRK* Gene Fusion Alterations in Thyroid Cancers From GENIE, TCGA, and Tempus Databases (Continued)

Histology	*NTRK* Fusion	Coaltered Genes	Overexpressed Genes	Data Source
PTC	*TPR-NTRK1* (*TPR* intron 21 *NTRK1* intron 8)	None	*CCND1*	Tempus
ATC	*IRF2BP2-NTRK1*	*TERT* promoter, *CDKN2A*, *CDKN2B*	NA	GENIE
PTC	*IRF2BP2-NTRK1*	None	NA	TCGA
PTC	*IRF2BP2-NTRK1*	None	NA	TCGA
PTC	*SQSTM1-NTRK3*	None	NA	GENIE
PTC	*SQSTM1-NTRK3*	None	NA	GENIE
PTC	*SQSTM1-NTRK1*	None	NA	TCGA
PDTC	*EML4-NTRK3*	*TERT* promoter	NA	GENIE
PTC	*EML4-NTRK3* (*EML4* intron 2: *NTRK3* intron 13)	*TERT* promoter, *MEN1*	*MAPK1*, *BRAF*	Tempus
PTC	*RBPMS-NTRK3*	*TERT* promoter, *NOTCH1*, *ARID2*	NA	TCGA
PDTC	*RBPMS-NTRK3*	None	NA	GENIE
PTC	*DIAPH1-NTRK1*	None	NA	GENIE
PTC	*SSBP2-NTRK1*	None	NA	TCGA
PTC	*TFG-NTRK1*	None	NA	TCGA

Abbreviations: ATC, anaplastic thyroid cancer; NA, not available; PDTC, poorly differentiated thyroid cancer; PTC, papillary thyroid cancer; TCGA, The Cancer Genome Atlas.

Patient 4 with PDTC harboring *TPM3-NTRK1* fusion developed mediastinal nodal metastases after initial thyroidectomy. She received RAI-T (155 mCi) after Thyrogen stimulation following surgery, and the post-treatment scan did not show any iodine uptake. After another year, she developed multiple hilar, mediastinal, and pulmonary metastases and started larotrectinib. She achieved complete resolution of enlarged lymph nodes and pulmonary nodules consistent with complete response (CR) in 2 months. Thyroglobulin (TG) rose from 329 to 1,588 ng/mL within 1 month of larotrectinib associated with a radiographic response. TG gradually decreased over the next 8 months but remained higher than the baseline before larotrectinib.

Types and frequencies of NTRK gene alterations. Of 2,362 thyroid cancer specimens identified in the American Association for Cancer Research (AACR) Genie, The Cancer Genome Atlas (TCGA), and Tempus databases, *NTRK1* or *NTRK3* gene fusions were found in 51 patients (2.2%): 28 of 1,133 in the AACR Genie data set (2.4%), 12 of 482 in the TCGA data set (2.5%), and 11 of 747 (1.5%) in the Tempus data set. No *NTRK2* gene fusions were identified in any of the databases (Table1).

We identified 10 different 5′ fusion partner genes; *ETV6-NTRK3* fusion was the most common, accounting for 43% of all *NTRK* fusions identified in thyroid cancer, followed by *TPM3-NTRK1* fusion (18%) and *TPR-NTRK1* fusion (14%). *TERT* promoter mutations were the most frequent coalteration, found in 15 cases (29%), followed by *TP53* (8%). Among cases from the Tempus cohort whose RNA expression data are available, overexpression of genes related to MAPK/ERK signaling pathway and cell-cycle regulation, and receptor tyrosine kinase genes were observed. We explored other relevant genomic alterations of *NTRK* genes and identified 24 cases of *NTRK1/2/3* single-nucleotide alterations, two cases of *NTRK1* amplification, and a splice variant of *NTRK1* in both differentiated and medullary thyroid cancers (Table2). More than half (58%) of the point mutations were predicted to be pathogenic,[12] but the majority of non–fusion-altered *NTRK* cases also harbored well-established driver mutations such as *BRAF/KRAS/HRAS* mutations or *RET/ALK* gene fusions.

Discussion

We report a single-institution experience of four consecutive patients with advanced thyroid cancer harboring *NTRK* gene fusions, treated with larotrectinib, a selective Trk inhibitor. Three patients with PTC or PDTC achieved durable radiographic responses, and all of them have remained on larotrectinib. This is consistent with the data from prior phase I and II Trk inhibitor studies in solid tumors, demonstrating lower overall response rate (ORR) in patients with ATC compared to patients with DTC. In the combined analysis of phase I/II basket trials of larotrectinib including 28 patients with *NTRK* fusion–positive advanced thyroid cancer (22 DTCs and six ATCs), the ORR was 75% with two CRs and 19 PRs, 90% in DTC and 29% in ATC.[13] Entrectinib was designed to cross the blood-brain barrier[14] and demonstrated an ORR of 55% among patients with known brain metastases.[3] Patient 2 with brain metastases started larotrectinib before approval of entrectinib. In the pooled analysis, two in four larotrectinib-treated thyroid

TABLE 2. Identified *NTRK* Gene Nonfusion Alterations in Thyroid Cancers From GENIE and TCGA Databases

	***NTRK* Nonfusion Alteration**			
Histology	**Missense mutation**	**FATHMN Prediction**	**Coaltered Genes**	**Data Source**
PTC	*NTRK1* S256N	Pathogenic (0.71)	*BRAF* V600E, *TERT* promoter	GENIE
PTC	*NTRK1* R214W	Neutral (0.36)	*BRAF* V600E	GENIE
PTC	*NTRK1* P407L	Pathogenic (0.95)	*BRAF* V600E	GENIE
PTC	*NTRK1* R507C	Pathogenic (0.88)	*BRAF* V600E	GENIE
PTC	*NTRK1* E581K	Pathogenic (0.95)	*BRAF* V600E	GENIE
PTC	*NTRK1* R153L	Pathogenic (0.78)	*BRAF* V600E	TCGA
PTC	*NTRK1* V511M	Pathogenic (0.96)	*NCOA4-RET* fusion	GENIE
PTC	*NTRK1* R686H	Neutral (0.44)		GENIE
PTC	*NTRK1* R85S	Neutral (0.06)		GENIE
PDTC	*NTRK1* G368V	Pathogenic (1.00)	*KRAS G12C*, *TERT* promoter	GENIE
PDTC	*NTRK1* V715M	Pathogenic (0.99)	*ATM*, *PTEN*, *SMARCD1*, *MSH6*	GENIE
PTC	*NTRK2* A203T	Neutral (0.13)	*BRAF* V600E	GENIE
PTC	*NTRK2* T34A	Neutral (0.16)	*BRAF* V600E	GENIE
PDTC	*NTRK2* H430Y	Unknown	*PTEN*, *TP53*	GENIE
PTC	*NTRK2* D474Y	Unknown	*RET M918T*, *ATM*, *KRAS* G12D	GENIE
PTC	*NTRK3* Q177L	Pathogenic (0.93)	*BRAF* V600E, *TERT* promoter	GENIE
PTC	*NTRK3* G104R	Pathogenic (0.91)	*BRAF V600E*, *ATM*, *TERT* promoter	
Follicular thyroid cancer	*NTRK3* H825R	Unknown	*RET* V438I	GENIE
PTC	*NTRK3* V451I	Neutral (0.27)	*HRAS*, *PTEN*	GENIE
PTC	*NTRK3* H349Y	Pathogenic (0.98)	*ALK-THSD4* fusion	GENIE
PTC	*NTRK3* P739A	Unknown		GENIE
PTC	*NTRK3* N294T	Pathogenic (0.99)	*ERC1-RET* fusion	TCGA
Medullary thyroid cancer	*NTRK3* T93M	Pathogenic (0.92)	*RET* M918T	GENIE
Medullary thyroid cancer	*NTRK3* A689V	Pathogenic (0.95)	*TP53*	GENIE
	Amplification			
PTC	*NTRK1*			GENIE
PTC	*NTRK1*			GENIE
	Splice variant			
Medullary thyroid cancer	*NTRK1* T256 = splice		*RET* M918T	GENIE

Abbreviations: PDTC, poorly differentiated thyroid cancer; PTC, papillary thyroid cancer; TCGA, The Cancer Genome Atlas.

cancer patients with CNS metastases had decreases in measurable brain lesions.[13]

Notably, the *ETV6-NTRK2* fusion found in patient 2 is a novel gene fusion not previously reported for a solid tumor. The fusion was described in a patient with acute myeloid leukemia and was found to have transforming potential in a murine hematopoietic cell line.[15] The patient did not have any abnormal blood counts, and germline sequencing performed on peripheral blood cells did not demonstrate abnormal findings. A good response to larotrectinib in patient 2 adds to the evidence that a selective Trk inhibitor has an efficacy in a tissue-agnostic manner, across the spectrum of *NTRK* fusion types. Another interesting observation was a rise in serum TG in patient 4 with PDTC harboring *TPM3-NTRK1* fusion and durable CR. This suggests a potential role of larotrectinib in redifferentiation, similar to other tyrosine kinase inhibitors that have been used to restore iodine avidity.[16] A recent case report demonstrated enhanced radioactive iodine uptake in a patient with PTC with *EML4-NTRK3* fusion after larotrectinib.[17] Among seven patients with thyroid cancer treated with larotrectinib in clinical trials, one patient with *PPL-NTRK1* fusion achieved CR.[18] TrkA encoded by *NTRK1* is not expressed in normal thyroid tissue, but overexpression was observed in thyroid cancer, with activated Rous sarcoma oncogene and extracellular signal-regulated kinase pathways.[19] Exceptional responses may be related to TrkA's oncogenic role in thyroid cancer.

In search for *NTRK* alterations in thyroid cancer using AACR Genie, TCGA, and Tempus databases, we identified

various alterations in *NTRK1* and *NTRK3*, but none in *NTRK2*. These fusions were found mostly in PTC, but also in PDTC, MTC, and ATC. *ETV6-NTRK3* was the most common fusion found in 22 of 55 cases (40%). The actual frequency of *NTRK* fusions in thyroid cancer is not known, as some targeted exome sequencing can easily miss fusion event involving introns of certain genes. Studies on frequency of *NTRK* fusions from a single institution and from the TCGA found *NTRK* fusion in 10 of 451 (2.2%; four *NTRK1* and six *NTRK3* fusions) and 12 of 498 (2.4%; five *NTRK1* and seven *NTRK3* fusions) patient with thyroid cancer, respectively.[20,21] In our study cohort, *TERT* promoter mutations were found in 29% of the cases: 10 in 42 (23.8%) PTCs and four in five (80%) ATCs. It is not known whether *TERT* promoter coalteration has any impact on prognosis or response to Trk inhibitor in *NTRK*-altered thyroid cancers. *TERT* promoter mutation has been reported in various frequencies in different histologies ranging from 10% in PTD up to 50% in ATC.[22] It is associated with more advanced stage and poor prognosis.[22-24]

We also explored other genetic alterations of *NTRK* genes including nonrecurring missense single-nucleotide variations in *NTRK1/2/3* and *NTRK1* gene amplification. Interestingly, most cases with a missense mutation of *NTRK1/2/3* also harbored well-described oncogenic alterations in genes encoding for RAS/RAF pathways, suggesting that these mutations are not likely the main driver for these tumors.

AFFILIATIONS

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Tempus supported data analyses of the Tempus cohort.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX 1. SUPPLEMENTARY TEXT

Materials and Methods

Patients with advanced thyroid cancer harboring *NTRK1/2/3* gene fusions were identified through retrospective review of clinical records at the University of California, San Francisco (UCSF). Presence of *NTRK* fusions was confirmed with commercially available oncology genomic profiling assays, including the UCSF500 DNA-based next-generation sequencing (NGS) test, which uses capture-based NGS and analyzes the exons of 529 cancer-related genes, as well as select intron of 47 genes, and the Tempus xT DNA, which is a targeted NGS test that detects single-nucleotide variants, indels, and copy-number variants of 648 genes and chromosomal rearrangements in 22 genes, supplemented by whole-transcriptome RNA sequencing for enhanced fusion detection.[25] Demographic data, molecular analysis data, treatment history, and treatment responses were obtained from the patient records. The radiographic responses to the treatment were collected from each patient. Patient consent for the study was waived as the study did not involve any identifiable data.

To describe the landscape of *NTRK* gene alterations in thyroid cancer, the public data generated from American Association for Cancer Research (AACR) Project Genie cohort version 9.0[26] and The Cancer Genome Atlas (TCGA) research network[27] were reviewed. Among 40 patients identified in AACR Genie and TCGA, median age was 39 years, and 53% of the patients were women. Additionally, a retrospective analysis on deidentified data from the Tempus real-world database was conducted to identify patients with thyroid cancer with *NTRK* fusions and discern the prevalence of these fusions. For Tempus specimens, gene expression was generated through RNA-seq of formalin-fixed paraffin-embedded tumor samples using an exome capture–based protocol as previously described.[28] Demographic information was not available for patients in the Tempus database.

