Real-World Experience of NTRK Fusion–Positive Thyroid Cancer

Jong Chul Park, MD1; Arya Ashok, PhD2; Chienying Liu, MD3; and Hyunseok Kang, MD, MPH3

JCO Precis Oncol 6:e2100442. © 2022 by American Society of Clinical Oncology
Creative Commons Attribution Non-Commercial No Derivatives 4.0 License

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. Such NTRK fusions have been found to be oncogenic drivers in multiple solid tumors including thyroid cancer. 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. 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. 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

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.
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\textsuperscript{11} or additional alterations.

Patient 2 with PTC harbored novel \textit{ETV6-NTRK2} fusion not previously described in other solid tumors. The novel fusion has breakpoints in \textit{ETV6} exon 4 and \textit{NTRK2} exon 16 with preserved \textit{ETV6} PNT domain and \textit{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 \textit{ETV6-NTRK2} fusion and \textit{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 \textit{ETV6-NTRK3} fusion and \textit{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 2.** Novel fusion between 5' breakpoint in \textit{ETV6} exon 4-5 and 3' breakpoint in \textit{NTRK2} exon 14-15. This fusion preserves the \textit{ETV6}PNT domain and the \textit{NTRK2} kinase domain, leading to constitutive activation of the \textit{NTRK2} kinase.

**FIG 3.** Patient 2 with metastatic PTC harboring \textit{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       |
| ATC             | 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 | B Raf | 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 9) | 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)
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 (Table 1).

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 (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 (Table 2). More than half (58%) of the point mutations were predicted to be pathogenic, 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. Entrectinib was designed to cross the blood-brain barrier and demonstrated an ORR of 55% among patients with known brain metastases. Patient 2 with brain metastases started larotrectinib before approval of entrectinib. In the pooled analysis, two in four larotrectinib-treated thyroid

### Table 1

| Histology | NTRK Fusion | Coalterated Genes | Overexpressed Genes | Data Source |
|-----------|-------------|-------------------|---------------------|-------------|
| PTC       | TPR-NTRK1   | None              | CCND1               | Tempus      |
| ATC       | IRF2BP2-NTRK1 | TERT promoter, CDKN2A, CDKN2B | NA | GENIE |
| PTC       | IRF2BP2-NTRK1 | None              | NA | TCGA |
| PTC       | SQSTM1-NTRK3 | None              | NA | GENIE |
| PTC       | SQSTM1-NTRK3 | None              | NA | GENIE |
| PDTC      | EML4-NTRK3  | TERT promoter     | NA | GENIE |
| PTC       | EML4-NTRK3  | 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.
cancer patients with CNS metastases had decreases in measurable brain lesions.\textsuperscript{13}

Notably, the ETV6-\textit{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.\textsuperscript{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 \textit{NTRK} fusion types. Another interesting observation was a rise in serum TG in patient 4 with PDTC harboring TPM3-\textit{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.\textsuperscript{16} A recent case report demonstrated enhanced radioactive iodine uptake in a patient with \textit{PTC} harboring EML4-\textit{NTRK3} fusion after larotrectinib.\textsuperscript{17} Among seven patients with thyroid cancer treated with larotrectinib in clinical trials, one patient with PPL-\textit{NTRK1} fusion achieved CR.\textsuperscript{18} TrkA encoded by \textit{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.\textsuperscript{19} Exceptional responses may be related to TrkA’s oncogenic role in thyroid cancer.

In search for \textit{NTRK} alterations in thyroid cancer using AACR Genie, TCGA, and Tempus databases, we identified

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
Histology & Nonfusion Alteration & FATHMN Prediction & Coaltered Genes & Data Source \\
\hline
PTC & \textit{NTRK}1 S256N & Pathogenic (0.71) & \textit{BRAF} V600E, TERT promoter & GENIE \\
PTC & \textit{NTRK}1 R214W & Neutral (0.36) & \textit{BRAF} V600E & GENIE \\
PTC & \textit{NTRK}1 P407L & Pathogenic (0.95) & \textit{BRAF} V600E & GENIE \\
PTC & \textit{NTRK}1 R507C & Pathogenic (0.88) & \textit{BRAF} V600E & GENIE \\
PTC & \textit{NTRK}1 E818K & Pathogenic (0.95) & \textit{BRAF} V600E & GENIE \\
PTC & \textit{NTRK}1 R153L & Pathogenic (0.78) & \textit{BRAF} V600E & TCGA \\
PTC & \textit{NTRK}1 V511M & Pathogenic (0.96) & \textit{NCOA4-RET} fusion & GENIE \\
PTC & \textit{NTRK}1 R686H & Neutral (0.44) & \textit{BRAF} V600E & GENIE \\
PTC & \textit{NTRK}1 R85S & Neutral (0.06) & \textit{BRAF} V600E & GENIE \\
PDTC & \textit{NTRK}1 G368W & Pathogenic (1.00) & \textit{KRAS} G12C, TERT promoter & GENIE \\
PDTC & \textit{NTRK}1 V715M & Pathogenic (0.99) & \textit{ATM}, \textit{PTEN}, \textit{SMARCD1}, \textit{MSH6} & GENIE \\
PTC & \textit{NTRK}2 A203T & Neutral (0.13) & \textit{BRAF} V600E & GENIE \\
PTC & \textit{NTRK}2 T34A & Neutral (0.16) & \textit{BRAF} V600E & GENIE \\
PDTC & \textit{NTRK}2 H430Y & Unknown & PTEN, TP53 & GENIE \\
PTC & \textit{NTRK}2 D474Y & Unknown & RET M918T, ATM, KRAS G12D & GENIE \\
PTC & \textit{NTRK}3 Q177L & Pathogenic (0.93) & \textit{BRAF} V600E, TERT promoter & GENIE \\
PTC & \textit{NTRK}3 G104R & Pathogenic (0.91) & \textit{BRAF} V600E, ATM, TERT promoter & GENIE \\
Follicular thyroid cancer & \textit{NTRK}3 H825R & Unknown & RET V438I & GENIE \\
PTC & \textit{NTRK}3 V451I & Neutral (0.27) & \textit{HRAS}, \textit{PTEN} & GENIE \\
PTC & \textit{NTRK}3 H349Y & Pathogenic (0.98) & \textit{ALK-THSD4} fusion & GENIE \\
PTC & \textit{NTRK}3 P739A & Unknown & \textit{RET} M918T & GENIE \\
PTC & \textit{NTRK}3 N294T & Pathogenic (0.99) & \textit{ERC1-RET} fusion & TCGA \\
Medullary thyroid cancer & \textit{NTRK}3 T93M & Pathogenic (0.92) & \textit{RET} M918T & GENIE \\
Medullary thyroid cancer & \textit{NTRK}3 A689V & Pathogenic (0.95) & \textit{TP53} & GENIE \\
Medullary thyroid cancer & \textit{NTRK}3 T256 = splice & \textit{RET} M918T & GENIE \\
\hline
\end{tabular}
\caption{Identified \textit{NTRK} Gene Nonfusion Alterations in Thyroid Cancers From GENIE and TCGA Databases}
\end{table}

Abbreviations: PDTC, poorly differentiated thyroid cancer; PTC, papillary thyroid cancer; TCGA, The Cancer Genome Atlas.
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.\textsuperscript{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.\textsuperscript{22} It is associated with more advanced stage and poor prognosis.\textsuperscript{23-24}

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.
7. Seethala RR, Chiosea SI, Liu CZ, et al: Clinical and morphologic features of ETV6-NTRK3 translocated papillary thyroid carcinoma in an adult population without radiation exposure. Am J Surg Path 41:446, 2017
8. Prasad ML, Vyas M, Horne MJ, et al: NTRK fusion oncogenes in pediatric papillary thyroid carcinoma in northeast United States. Cancer 122:1097-1107, 2016
9. Gatalica Z, Xiu J, Swensen J, et al: Molecular characterization of cancers with NTRK gene fusions. Mod Pathol 32:147-153, 2019
10. Amatu A, Sartore-Bianchi A, Siena S: NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open 1:e000023, 2016
11. Drioln A, Nagasubramanian R, Blake JF, et al: A next-generation TRK kinase inhibitor overcomes acquired resistance to prior TRK kinase inhibition in patients with TRK fusion-positive solid tumors. Cancer Discov 7:963-972, 2017
12. Shihab HA, Gough J, Cooper DN, et al: Predicting the functional consequences of cancer-associated amino acid substitutions. Bioinformatics 29:1504-1510, 2013
13. Cabanillas ME, Drioln A, Farago AF, et al: Larotrectinib treatment of advanced TRK fusion thyroid cancer. Ann Oncol 31:S10862020, 2016
14. Fischer H, Ullah M, de la Cruz CC, et al: Entrectinib, a TRK/ROS1 inhibitor with anti-CNS tumor activity: Differentiation from other inhibitors in its class due to weak interaction with P-glycoprotein. Neuro Oncol 22:819-829, 2020
15. Taylor J, Pavlick D, Yoshimi A, et al: Oncogenic TRK fusions are amenable to inhibition in hematologic malignancies. J Clin Invest 128:3819-3825, 2018
16. Ho AL, Grewal RK, Leboeuf R, et al: Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer, N Engl J Med 368:623-632, 2013
17. Groussin L, Clerc J, Huillard O: Larotrectinib-enhanced radioactive iodine uptake in advanced thyroid cancer. N Engl J Med 383:1686-1687, 2020
18. Broshe MS, Albert CM, Waguespack SG, et al: Activity of larotrectinib in patients with advanced TRK fusion thyroid cancer. 88th Annual Meeting of the American Thyroid Association. Washington, DC, 2018
19. Faulkner S, Jobling P, Rowe CW, et al: Neurotrophin receptors TrkA, p75(NTR), and sortilin are increased and targetable in thyroid cancer. Am J Pathol 188:229-241, 2018
20. Rosen EY, Goldman DA, Hechtman JF, et al: TRK fusions are enriched in cancers with uncommon histologies and the absence of canonical driver mutations. Clin Cancer Res 26:1624-1632, 2020
21. Agrawal N, Akbani R, Aksoy BA, et al: Integrated genomic characterization of papillary thyroid carcinoma. Cell 159:676-690, 2014
22. Bournaud C, Descotes F, Decaussin-Petrucci M, et al: TERT promoter mutations identify a high-risk group in metastasis-free advanced thyroid carcinoma. Eur J Cancer 108:41-49, 2019
23. Su X, Jiang X, Wang W, et al: Association of telomerase reverse transcriptase promoter mutations with clinicopathological features and prognosis of thyroid cancer: A meta-analysis. Onco Targets Ther 9:6965, 2016
24. Liu R, Xing M: TERT promoter mutations in thyroid cancer. Endocr Relat Cancer 23:R143-R155, 2016
25. Beaubier N, Tell R, Lau D, et al: Clinical validation of the tempus xT next-generation targeted oncology sequencing assay. Oncotarget 10:2384-2396, 2019
26. AACR Project GENIE Consortium: AACR Project GENIE: Powering precision medicine through an international consortium. Cancer Discov 7:818-831, 2017
27. Cancer Genome Atlas Research Network: Integrated genomic characterization of papillary thyroid carcinoma. Cell 159:676-690, 2014
28. Brueffer C, Vallon-Christersson J, Grabau D, et al: Clinical value of RNA sequencing-based classifiers for prediction of the five conventional breast cancer biomarkers: A report from the population-based multicenter Sweden cancerome analysis network-breast initiative. JCO Precis Oncol 2:1-18, 2018
APPENDIX 1. SUPPLEMENTARY TEXT

Materials and Methods

Patients with advanced thyroid cancer harboring \textit{NTRK1/2/3} gene fusions were identified through retrospective review of clinical records at the University of California, San Francisco (UCSF). Presence of \textit{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.\textsuperscript{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 \textit{NTRK} gene alterations in thyroid cancer, the public data generated from American Association for Cancer Research (AACR) Project Genie cohort version 9.0\textsuperscript{26} and The Cancer Genome Atlas (TCGA) research network\textsuperscript{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 \textit{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.\textsuperscript{28} Demographic information was not available for patients in the Tempus database.