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Efficacy and Safety of NTRK Inhibitors in Patients With *NTRK* Fusion–Positive Lung and Thyroid Cancers

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Abstract: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are implicated in various cancers, including those of the lung and thyroid. The prevalence of *NTRK* fusions is 0.1 to 0.3% in non–small cell lung cancer (NSCLC) and as high as 26% in pediatric papillary thyroid carcinoma. Detection methods include immunohistochemistry, fluorescence in situ hybridization, reverse transcription polymerase chain reaction, and next-generation sequencing. Management of *NTRK* fusion–positive lung cancer primarily involves targeted therapies, notably the tyrosine receptor kinase (TRK) inhibitors larotrectinib and entrectinib. Both agents demonstrate high response rates and durable disease control, particularly in metastatic adenocarcinoma of the lung. They are preferred as first-line treatments because of their efficacy over immunotherapy. Possible adverse events include dizziness, weight gain, neuropathy-like pain, and liver enzyme elevation. Larotrectinib and entrectinib also produce robust and durable responses in *NTRK* fusion–positive thyroid cancer that is refractory to radioactive iodine. Second-generation TRK inhibitors that have been designed to overcome acquired resistance are under investigation.

Diagnosing *NTRK* Fusions in Lung and Thyroid Cancer

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Note: This Roundtable was conducted before the accelerated approval of repotrectinib on June 13, 2024, for NTRK *fusion–positive solid tumors.*

Overview of *NTRK* Gene Fusions

The neurotrophic tropomyosin receptor tyrosine kinase (*NTRK*) genes 1, 2, and 3 include 3 closely related tropomyosin receptor kinase (TRK) proteins—TRKA, TRKB, and TRKC, respectively.[1,2] Normally, these proteins signal downstream of neurotrophins via phospholipase-C gamma (PLCγ), Ras/mitogen-activated protein (Ras/MAP) kinase, and the phosphoinositide 3-kinase (PI3K)-protein kinase B (PKB) and AKT pathways to stimulate cell proliferation and survival. These proteins are first of all important for neuronal development in utero, and they also retain some normal postnatal function within the nervous system, including the regulation of appetite, proprioception, and pain.

NTRK rearrangements, and more specifically gene fusions, are the most common mechanism of TRK oncogene activation.[3] *NTRK* fusions are reminiscent of *BCR-ABL* fusions in leukemia, in which an unrelated 5′ upstream gene partner is fused to 1 of the 3 kinase domains within the *NTRK* gene. The results of this fusion are constitutive expression, with the chimeric protein driven by the promoter from the 5′ partner and ligand-independent activation of the resulting kinase domain. *NTRK* fusions can be oncogenic. Like other driver mutations, *NTRK* fusions tend to be mutually exclusive, with one notable exception. *NTRK* fusion–positive colorectal cancer (CRC) appears to be a unique subset of CRC that has a high tumor mutational burden (TMB) and is microsatellite instability-high (MSI-H).[4]

Numerous *NTRK* gene fusions have been reported across a broad range of tumors in both adults and children. The frequency of *NTRK* gene fusions is variable and appears highly dependent on the tumor type, with some tumors appearing to be nearly pathognomonic for *NTRK* fusions. The frequencies of *NTRK* fusions are often classified in 3 broad categories (Table 1).[5,6] The high-frequency category includes tumors in which *NTRK* fusions are defining molecular features, with frequencies of 85% or higher. The low-frequency category includes tumors in which the frequency of *NTRK* fusions tends to be less than 5% (and most often <1%). An intermediate category includes somewhat common tumors in which *NTRK* fusions occur at frequencies between approximately 5% and 25%.

Prevalence of *NTRK* Fusions in Lung Cancer

The prevalence of *NTRK* fusions in non–small cell lung cancer (NSCLC) is estimated to be between 0.1% and 0.3%, on the basis of data from multiple studies.[7] For example, in a study published in 2023, Overbeck and

Table 1. Frequencies of *NTRK* Fusions in Various Solid Tumors

Frequency	Tumor Type
High (≥85%)	• Infantile fibrosarcoma • MASC • Secretory carcinoma (breast and salivary gland) • Cellular and mixed-type congenital mesoblastic nephroma
Intermediate (~5%-25%)	• Pediatric papillary thyroid carcinoma • Spitz tumors • Pediatric high-grade gliomas • *KIT/PDGFRA/RAS* wild-type gastrointestinal mesenchymal tumors
Low (<5%)	• All other solid tumors including but not limited to the following: o NSCLC o CRC o Adult soft-tissue sarcomas o Adult gliomas o Melanoma

CRC, colorectal cancer; MASC, mammary analogue secretory carcinoma; NSCLC, non–small cell lung cancer. Sources: Nguyen MA et al. *Pathology*. 2023;55(5):596-609[5] and Shulman DS, DuBois SG. *Paediatr Drugs*. 2020;22(2):189-197.[6]

colleagues used real-world screening of 1068 unselected patients in Germany over an 18-month period to report on the frequency of *NTRK* gene fusions.[8] Overall, 982 of 1068 samples were successfully evaluated. The overall prevalence of *NTRK* fusions in this population was 0.2% (2 cases among 982). Frequencies of 0.1% and 0.16% in NSCLC were reported in 2 large studies,[9,10] whereas a frequency of 0.23% was identified in another study of 4872 patients with NSCLC.[11]

The frequency of *NTRK* fusions in NSCLC is markedly less than the frequencies of other canonical gene fusions in this tumor type—namely, those involving *ALK*, *ROS1*, or *RET*. Although the frequency is highest in adenocarcinoma NSCLC, *NTRK* fusions have also been identified in patients with squamous cell NSCLC as well as neuroendocrine carcinoma of the lung and sarcomatoid carcinoma of the lung.

The clinicopathologic features of *NTRK* fusion–positive NSCLC were reported from a study of 11 patients.[11] The median age at diagnosis in this group was 48 years, with a range from 25 to 86 years. The percentages of male and female patients were 55% and 45%, respectively. Patients reported either a no or low smoking history (0-5 pack-years; 73%) or a high smoking history (>20 pack-years; 27%); however, overall there was no smoking history (median of 0 pack-years; range, 0-58). Of the 11 patients, the majority had adenocarcinoma histology (82%), followed by squamous cell carcinoma (9%) and neuroendocrine carcinoma (9%). Although *NTRK* fusions, like other gene fusions, were shown to occur most typically in patients of middle age with no smoking history, this study demonstrated that *NTRK* fusions can occur across age groups and smoking status, prompting the recommendation to screen all patients with NSCLC for *NTRK* fusion.

Prevalence of *NTRK* Fusions in Thyroid Cancer

The prevalence of *NTRK* fusions in thyroid cancer differs across studies and in different tumor types, with the highest prevalence observed in pediatric papillary thyroid cancers and in radiation-induced thyroid cancer. Across various studies of sporadic thyroid cancer in adults, the frequencies of *NTRK* fusions reported were 2.22% (of 451 tumors), 2.28% (of 571 tumors), 2.34% (of 513 tumors), 5.7% (of 70 tumors), 2.9% (of 243 tumors), and 3.1% (of 351 tumors).[9,12-16] In comparison, the frequency of *NTRK* fusions in post-Chernobyl cases of thyroid cancer was 14.5% of 62 cases.[13] *NTRK* fusions occur at a much higher rate in pediatric papillary thyroid carcinoma, reported at a frequency of 26% in a study of 27 cases.[17] In a study of 93 cases of pediatric papillary thyroid carcinoma, *NTRK* fusions were identified in 17 patients (18.3%).[18]

Clinicopathologic features of *NTRK* fusion–positive thyroid cancers in 11 patients with primary thyroid cancer (10 adults and 1 adolescent) were reported.[12] Of the 11 patients, 8 were female. All patients were radiation-naive except 1 patient who had received low-dose radiotherapy for acne during adolescence 30 years prior. At initial presentation, each patient had a large, infiltrative mass that was pathologically staged as T2 (9%) or T3 (91%), and all patients had cervical lymph node involvement. At presentation, 3 patients (27%) had pulmonary metastases; in 3 additional patients, pulmonary metastases developed over the course of their disease.

In a study of pediatric patients with papillary thyroid carcinoma, of 14 patients identified with *NTRK* fusion–positive tumors, nearly all (11 patients) were female.[18] The mean age at diagnosis was 15.9 (±2.4) years, and the mean tumor size was 20.1 (±10.4) mm. The tumor histology was identified as classic (14.3%), follicular (57.1%), a mixture of classic and follicular (21.4%), or other (7.1%). Multifocality was identified in 50.0% and extrathyroidal extension in 42.9%.

Detection of *NTRK* Fusions

Several methods are available to identify *NTRK* fusions in solid tumors.[15,19,20] Each of these methods has benefits and

Table 2. Comparison of the Various Methods Used to Test for *NTRK* Gene Fusions

	IHC	FISH	RT-PCR	NGS
Advantages	• Widely used • Cost-effective • ~1- to 2-d turnaround time	• Widely available • ~3- to 5-d turnaround time • Can detect the presence of a fusion event involving a target gene without prior knowledge of the fusion partner	• Highly specific • Sensitive • ~1-wk turnaround time • Multiplexing capabilities	• Most comprehensive and inclusive • Can be used for the analysis of either DNA or RNA • ctDNA NGS can serve as a surrogate method when a tissue specimen is not available
Disadvantages	• Pan-TRK antibody does not discriminate between expression of the wild-type and fusion proteins • May be used as initial screening, but requires confirmation with secondary method	• Can be labor- and cost-intensive, as individual analyses must be performed for each of the 3 *NTRK* genes	• Requires prior knowledge of the fusion partners	• Costly • RNA NGS requires optimal tissue fixation • Technically complex • DNA NGS risks false negatives • ~1- to 3-wk turnaround time • Sensitivity varies among partner genes • ctDNA NGS requires adequate tumor cell shedding for detection in the circulation

ctDNA, circulating tumor DNA; d, day; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcription-polymerase chain reaction; TRK, tropomyosin receptor kinase; wk, week.
Source: Repetto M et al. *Cancer Treat Rev*. 2024;127:102733. (http://creativecommons/org/licenses/by/4.0)[20]

drawbacks that drive their utility in the clinic (Table 2).

Immunohistochemistry (IHC) offers a widely available, inexpensive method with a rapid turnaround to identify *NTRK* fusions. IHC results in antibody-based visualization of TRK protein expression and staining patterns that correlate with the TRK fusion partner. Although powerful in its relative simplicity, IHC can be associated with false-positive results and therefore is often used as an initial screening test.

Fluorescence in situ hybridization (FISH) uses probes to track anomalous *NTRK* gene fusion partners. Benefits of FISH include high sensitivity, relatively rapid turnaround time, and ability to work with limited tumor content, particularly in formalin-fixed, paraffin-embedded specimens. Drawbacks revolve around the low throughput of this technique, particularly because it must be repeated for all 3 *NTRK* genes.

Reverse transcription polymerase chain reaction (RT-PCR) begins with primer-specific reverse transcription of RNA to complementary DNA. This DNA is then amplified and detected via a fluorogenic probe. The use of sequence-specific primers requires knowledge of both fusion partners, limiting the use of RT-PCR for the detection of *NTRK* fusions.

Next-generation sequencing (NGS) implements either a targeted approach (focusing on a panel of genes) or whole-genome sequencing to examine multiple genomic alterations simultaneously. Either DNA sequencing or RNA sequencing can be used. The RNA sequencing approach is considered the more useful because it allows detection of larger fusion partners that may not be detected by DNA NGS.

Who Should Be Tested for *NTRK* Fusions?

Clinical decisions for testing can vary across institutions. Some *NTRK* fusion testing is histology-driven, with routine testing used for tumor types in which it facilitates the diagnosis (eg, infantile fibrosarcoma, secretory breast carcinoma, and MASC, among others). For other tumor types, the decision to test may be driven by the history. For example, *NTRK* fusion testing should be considered when a patient's tumor is negative for other oncogenic drivers or a patient has relapsed/refractory disease.

In cases of advanced or metastatic NSCLC specifically, the National Comprehensive Cancer Network (NCCN) guidelines include *NTRK* fusion testing in the list of broad molecular profiling tests recommended for cases with adenocarcinoma histology.[21] Additionally, it is recommended that broad molecular profile testing include *NTRK* fusions in cases of squamous cell carcinoma.

The NCCN guidelines for thyroid cancer recommend

molecular diagnostics in all cases of advanced thyroid cancer.[22] *NTRK* fusions are seen in papillary thyroid cancer as well as in the cancers that differentiate from papillary thyroid cancer and become more aggressive, such as high-grade papillary thyroid cancer and anaplastic thyroid cancer. The fusions are typically not seen in purely follicular thyroid cancers or in medullary thyroid cancers.

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Management of Patients with *NTRK* Fusion–Positive Lung Cancer

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The Current Standard of Care

To best understand the current standard of care for the treatment of *NTRK* fusion–positive lung cancer, it is first important to point out that these fusions are most frequently found in adenocarcinoma NSCLC. However, they can also be detected in squamous cell lung carcinomas and neuroendocrine lung cancers. Thus, the standard of care can change from one histology to another. For the purposes of this discussion, we will focus on the treatment of metastatic adenocarcinoma of the lung, the most frequent type of lung cancer with *NTRK* fusions.

If an *NTRK* fusion is not immediately identified in the tumor tissue, patients with metastatic NSCLC are generally treated in the first-line setting with either immunotherapy alone or chemoimmunotherapy.[1] However, there is a growing recognition from the IMMUNOTARGET

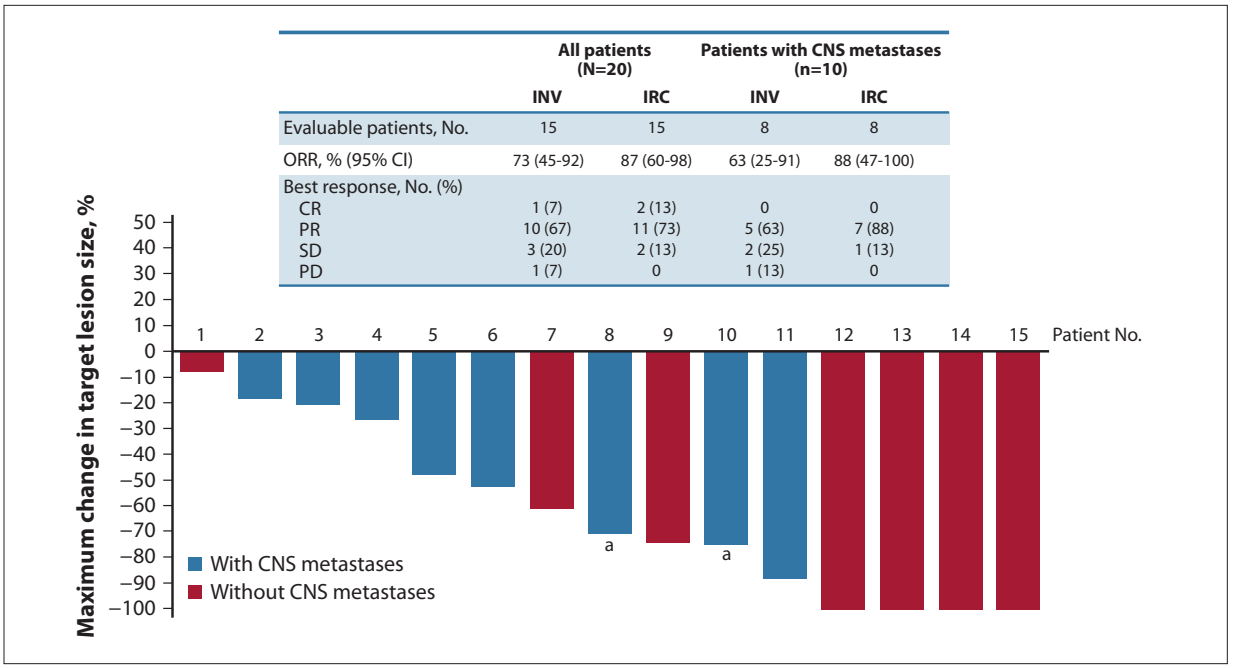

Figure 1. Waterfall plot of the maximum change in target lesions following treatment with larotrectinib in patients with advanced *TRK* fusion–positive lung cancer. [a]Two patients had CNS metastases included as target lesions with a 100% and 59% reduction observed by cycle 4, respectively. CR, complete response; CNS, central nervous system; INV, investigator; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. Source: Drilon A et al. *JCO Precis Oncol.* 2022;6(6):e2100418. (http://creativecommons.org/licenses/by/4.0)[6]

Registry that NSCLC tumors harboring oncogenic drivers (such as *NTRK* fusions) do not have a high likelihood of response to immunotherapy.[2] This may be because such cancers are less genomically complex and thus less immunogenic. Most providers avoid the use of immunotherapy in driver-positive NSCLC, even in the background of high programmed death ligand 1 (PD-L1) levels.

Therefore, for an *NTRK* fusion–positive NSCLC, recognizing that the level of activity of targeted therapies like larotrectinib and entrectinib is high, the preference is to start with the best drug up front (ie, the targeted agent), then later move to chemotherapy in the second line.[1] In cases in which some form of lung cancer is initially diagnosed, then an *NTRK* fusion is found later after a first-line treatment has already been started, it is perfectly reasonable to continue that therapy if it is working. However, if the patient shows a suboptimal response or continues to experience cancer-associated symptoms, it makes sense to switch to a TRK inhibitor even in the absence of formal progression.

Notably, in addition to the treatment of metastatic solid tumors, the indications for both larotrectinib and entrectinib approved by the US Food and Drug Administration (FDA) allow their use in earlier stages of disease. Specifically, the label for both agents states that they can be used in patients either with metastatic disease or in whom surgical resection is likely to result in severe morbidity (eg, stage IIIb NSCLC).[3,4]

Clinical Data Supporting NTRK Inhibitors in Lung Cancer

Larotrectinib

Data from patients with lung cancer were gathered from 2 global, multicenter, registrational clinical trials: a phase 1 adult trial (NCT02122913) and a phase 2 basket trial (NAVIGATE) of adolescents older than 12 years and adults.[5] A total of 20 patients with *NTRK* fusion–positive lung cancer were included in this combined analysis.[6]

Adult patients were treated with larotrectinib (100 mg twice daily), and treatment beyond progression was allowed if they continued to benefit. The median patient age was 48.5 years (range, 25.0-76.0), and the percentages of male and female patients were the same (50%/50%). Patient races included White (45%), Asian (40%), American Indian or Alaska Native (5%), and other (10%). Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (40%) or 1 (50%), although 1 patient (5%) had an ECOG performance status of 2 and 1 patient an ECOG performance status of 3. Half of the patients (50%) had central nervous system (CNS) metastasis at baseline. The

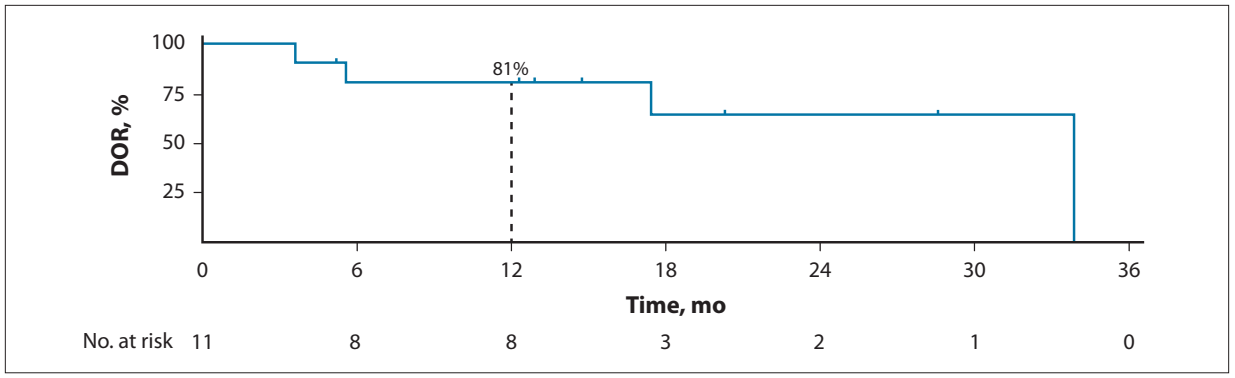

Figure 2. Kaplan-Meier curve for the duration of response (DOR) among 11 patients with *TRK* fusion–positive lung cancer treated with larotrectinib. The median DOR at a median follow-up of 17.4 months was 33.9 months (95% CI, 5.6-33.9), the DOR rate at 12 months was 81%, and the DOR rate at 24 months was 65%. DOR, duration of response; mo, months. Source: Drilon A et al. *JCO Precis Oncol*. 2022;6(6):e2100418. (http://creativecommons.org/licenses/by/4.0)[6]

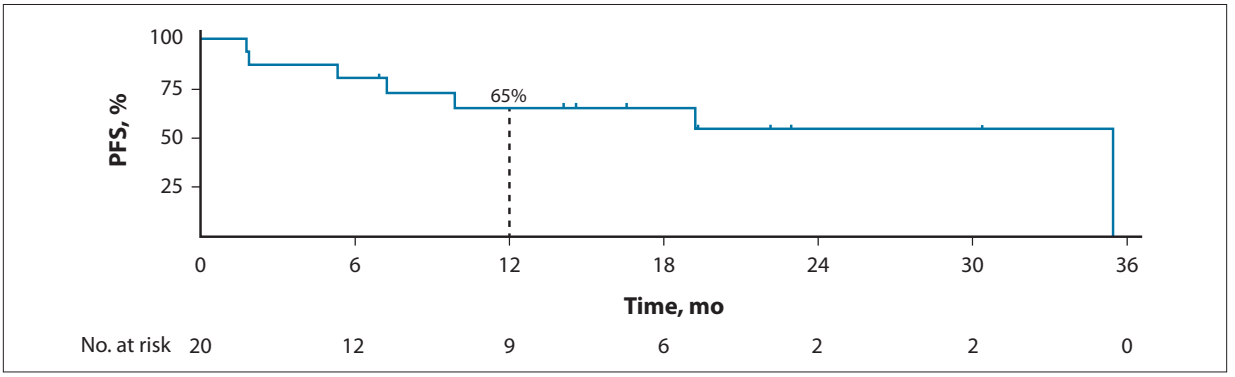

Figure 3. Kaplan-Meier curve for progression-free survival (PFS) among 20 patients with *TRK* fusion–positive lung cancer treated with larotrectinib. The median PFS at a median follow-up of 16.6 months was 35.4 months (95% CI, 5.3-35.4), the PFS rate at 12 months was 65%, and the PFS rate at 24 months was 55%. mo, months; PFS, progression-free survival. Source: Drilon A et al. *JCO Precis Oncol*. 2022;6(6):e2100418. (http://creativecommons.org/licenses/by/4.0)[6]

vast majority of *NTRK* gene fusions identified involved *NTRK1* (80%), 20% involved *NTRK3*, and no *NTRK2* gene fusions were found. Patients were heavily pretreated, and all but 1 patient (95%) had received prior systemic therapy for their disease, with 50% of patients having received 3 or more prior systemic treatments.

The primary endpoint, investigator-assessed objective response rate (ORR) in 15 evaluable patients, was 73% (95% CI, 45-92). Of these responses, 1 (7%) was a complete response and 10 (67%) were partial responses. In addition, 3 patients (20%) had stable disease as the best response. All patients with measurable disease showed a reduction in target tumor size (Figure 1). Larotrectinib appeared to show CNS activity, and although intracranial response was not a study endpoint, CNS metastases were included as target lesions for 2 patients. By cycle 4, reductions in their CNS metastases of 59% and 100% were noted in these 2 patients.

For patients with an objective response, the median time to response was 1.8 months (range, 1.6-1.9), which was approximately the time to the first follow-up imaging examination in the trial. At a median follow-up of 17.4 months, the median duration of response (DOR) was 33.9 months (95% CI, 5.6-33.9) (Figure 2). At 12 months and 24 months, the DOR rates were 81% and 65%, respectively.

The secondary endpoint of median progression-free survival (PFS) was 35.4 months (95% CI, 5.3-35.4) at a median follow-up of 16.6 months (Figure 3). The 12- and 24-month PFS rates were 65% and 55%, respectively. In 11 of the 19 patients who had received at least one prior systemic therapy (58%), PFS was 2-fold longer with larotrectinib than their time to progression or treatment failure on their most recent prior therapy.

At a median follow-up of 16.2 months, the median overall survival (OS) was 40.7 months (95% CI, 17.2 to not estimable). The 12-month OS rate was 86%, and the 24-month OS rate was 75% (Figure 4).

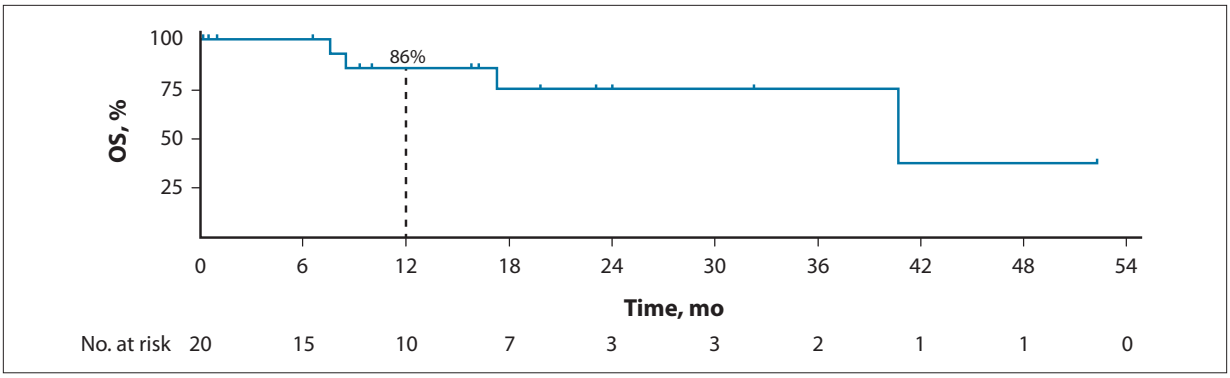

Figure 4. Kaplan-Meier curve for overall survival (OS) among 20 patients with *TRK* fusion–positive lung cancer treated with larotrectinib. The median OS at a median follow-up of 16.2 months was 40.7 months (95% CI, 17.2 to not estimable), the OS rate at 12 months was 86%, and the OS rate at 24 months was 75%. mo, months; PFS, progression-free survival. Source: Drilon A et al. *JCO Precis Oncol.* 2022;6(6):e2100418. (http://creativecommons.org/licenses/by/4.0)[6]

Entrectinib

Similarly, a patient dataset from 3 clinical studies (the phase 1 ALKA-372-001 trial, the phase 1 STARTRK-1 trial, and the phase 2 STARTRK-2 basket trial) was used to evaluate entrectinib. All these studies enrolled patients aged 18 years or older with metastatic or locally advanced *NTRK* fusion–positive solid tumors.[7] Patients were included in a prespecified integrated analysis if they had an *NTRK* fusion–positive solid tumor, had measurable disease, and had received at least one dose of entrectinib at or above the recommended phase 2 dose (600 mg once daily). In the first report of this integrated analysis, which had a data cutoff of May 31, 2018, and included 54 patients, NSCLC was the primary tumor type in 10 patients (19%). An objective response was achieved with entrectinib in 7 of these patients (70%; 95% CI, 35%-93%).

A subsequent update, with a data cutoff of August 31, 2020, included 22 patients with NSCLC, of whom 13 had CNS metastases at baseline.[8] In this update, an objective response was reported in 14 patients (63.6%; 95% CI, 40.7%-82.8%). The median DOR in the responding patients was 19.9 months (95% CI, 10.4-29.4). Additional endpoints reported among the subset of patients with NSCLC were median PFS (14.9 months; 95% CI, 6.5-30.4) and median OS (not estimable; 95% CI, 20.8 to not estimable).

Selecting *NTRK* Inhibitors for Patients With Lung Cancer

Both larotrectinib and entrectinib are FDA-approved TRK inhibitors,[3,4] but subtle differences underscore the different contexts in which they may be used. Larotrectinib is a selective TRK inhibitor of 3 different TRK proteins: TRKA, TRKB, and TRKC. In an evaluation of a broad panel of enzymes, only one other non-TRK kinase (TNK2) was inhibited, at an approximately 100-fold higher concentration. In contrast, entrectinib is a multikinase inhibitor that inhibits the 3 TRK proteins as well as ROS1 and ALK at similar potencies. Because of this more extensive kinase inhibition, entrectinib is also indicated in the treatment of *ROS1* fusion–positive NSCLC.

Both agents are associated with high response rates and very durable disease control. Entrectinib was initially perceived to be a more CNS-penetrant drug. In practice, however, CNS responses have been observed with both entrectinib and larotrectinib. In the absence of a head-to-head trial comparing the 2 agents, it is difficult to know if one agent or the other is better for our NSCLC patients.

Managing Adverse Events

Several on-target adverse events (AEs) have been described with larotrectinib and entrectinib, and these indeed appear to be class effects resulting from TRK inhibition.[9,10] One of the more well-recognized on-target (or TRK inhibition–related) AEs associated with either larotrectinib or entrectinib is dizziness. Often, the AE will decrease over time, as the patient's body seemingly adjusts to the agent. However, in rare cases, the dizziness can be overwhelming, so that either a dose reduction or permanent discontinuation is required. Alternatively, supportive care agents like meclizine may be useful for vertigo, or midodrine for orthostatic hypotension.

Another common side effect is weight gain. Early in the clinical trials, the weight gain was initially attributed to the improved health of the patients. However, when it was determined that even patients with stable disease continued to gain weight, this AE was truly recognized as being attributable to the TRK inhibitor. The cause of the

weight gain may be related to increased appetite modulation due to TRK inhibition. For weight gain, patients may benefit from seeing weight gain specialist partners in endocrinology, who may choose to intervene with weight loss drugs.

A third common and somewhat perplexing AE associated with TRK inhibitors is neuropathy-like or myalgia-mimicking withdrawal pain, likely due to inhibition of the TRK proteins regulating neurosympathetic processes in the body. This pain often occurs as withdrawal or rebound pain when a dose of the drug is missed—for example, one of the twice-daily doses of larotrectinib. This pain syndrome can occur in patients who have an underlying pain issue (eg, pre-existing knee arthritis), but this is not always the case. Support with pain medication may be needed for the pain flares, although amazingly, the pain can disappear in the first hour after the patient restarts the treatment.

Finally, the most common grade 3 AE that tends to occur is elevation of liver function enzymes. Although its occurrence as a grade 3 or higher event is relatively uncommon (approximately 2% to 3% of patients treated in clinical trials), either dose reduction or discontinuation is required.[3,4]

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Management of Patients with *NTRK* Fusion–Positive Thyroid Cancer

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The Current Standard of Care

Most well-differentiated thyroid cancers are cured by surgery alone, with thyrotropin suppression and radioactive iodine (RAI) added for patients with intermediate- or high-risk disease.[1] However, RAI-refractory thyroid cancer eventually develops in a small subset of patients. In general, patients have indolent disease at their first presentation of recurrent and/or metastatic thyroid cancer and may not immediately require systemic therapy.

Because most cases of RAI-refractory thyroid cancer are relatively indolent, with a low, slow-growing tumor burden, there are typically no time constraints for gathering the molecular diagnostic information needed before the initiation of therapy.[1] Often, a period of disease monitoring is planned to gain a better understanding of the rate of disease progression. Patients can have very slow disease progression and may not need systemic therapy immediately. Criteria to initiate systemic therapy include disease progression in the prior 6 to 14 months, symptomatic disease, anatomically threatening disease, and bulky disease. One exception is anaplastic thyroid cancer, a rare histologic subtype of thyroid cancer that is more

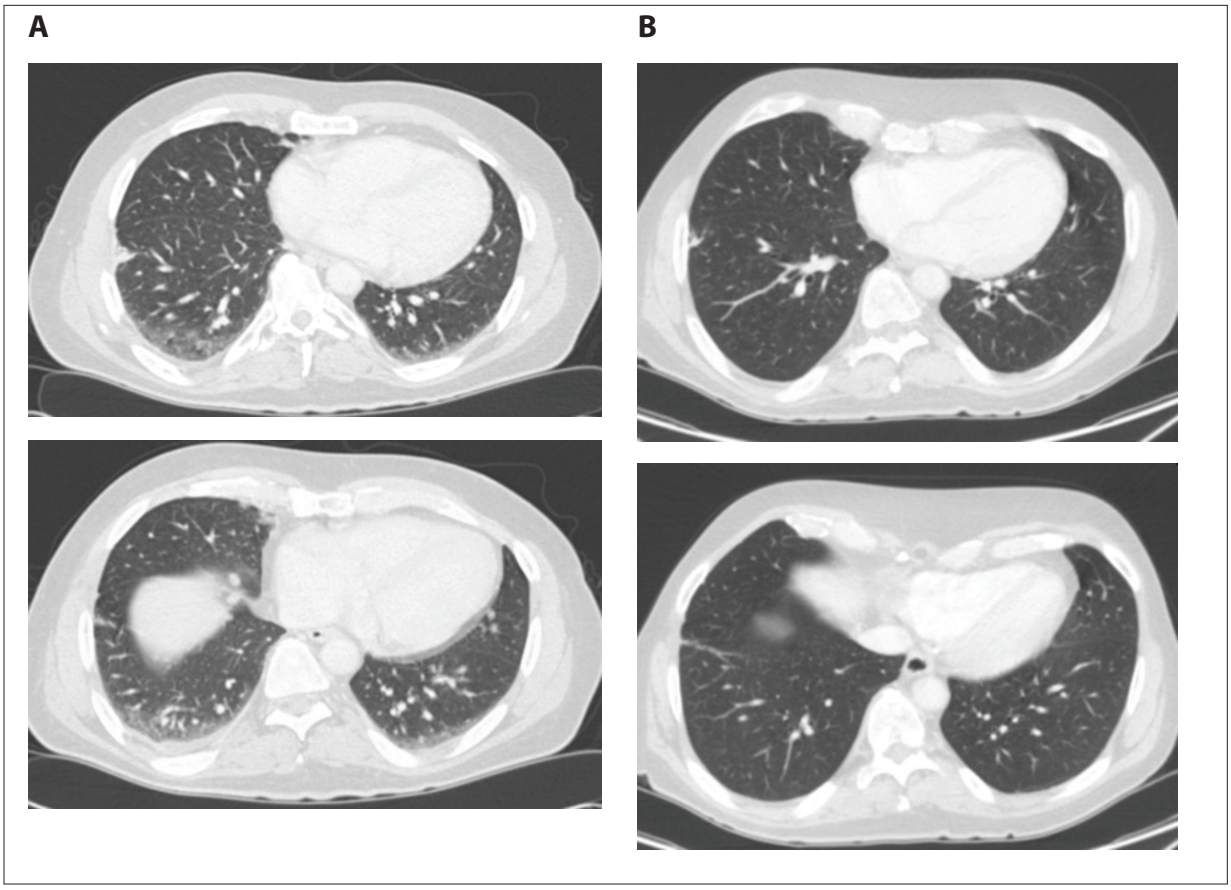

Figure 5. A 62-year-old patient with thyroid cancer had multiple new and increasing lung nodules on positron emission tomography/computed tomography (PET/CT) following surgery and radiation treatment. After testing positive for an *NTRK1* exon 13 fusion, the patient was enrolled in a phase 2 basket trial of larotrectinib in December 2016. The patient experienced a complete remission, as seen in the CT images above, with the thyroglobulin (Tg) level decreasing from 1185 ng/mL at the beginning of the study (A) to 66 ng/mL 4 months later (B). The patient experienced grade 1 fatigue but remained in complete remission as of May 2024, with a Tg level of 33 ng/mL.

Photos courtesy of Lori J. Wirth, MD.

aggressive and requires immediate treatment. However, turnaround times for testing have greatly improved, particularly when in-house testing is available. As a result, we generally can wait for the molecular diagnostics as well as *BRAF* status by IHC to make clinical decisions. Cases found to be positive for a *BRAF* V600E mutation will not harbor oncogenic kinase fusions, whereas those cases found to be *BRAF* wild-type may benefit from additional molecular diagnostic studies to identify *NTRK* fusions, *RET* fusions, tumor mutational burden-high (TMB-H) status, or MSI-H or defective mismatch repair (dMMR) status, all of which can be targeted with NCCN-recommended regimens.

Traditional chemotherapeutic agents (including paclitaxel and doxorubicin) generally have minimal efficacy in patients with metastatic differentiated thyroid cancer. Alternatively, targeted agents have been demonstrated to be effective and are recommended for patients with locally recurrent, advanced, and/or metastatic disease that is not amenable to RAI therapy.[2] Although effective, none of these agents is curative, and their toxic effects may limit their use in some patients. Targeted agents used in this setting include anti-angiogenic multitargeted kinase inhibitors: sorafenib, lenvatinib, and cabozantinib, as well as selpercatinib or pralsetinib (for patients with *RET* gene fusion–positive tumors), dabrafenib/trametinib (for patients with *BRAF* V600E mutation–positive tumors), and pembrolizumab (for patients with TMB-H tumors or with MSI-H or dMMR tumors that have progressed following prior treatment and for which no satisfactory alternative options are available. The TRK inhibitors larotrectinib and entrectinib are recommended for

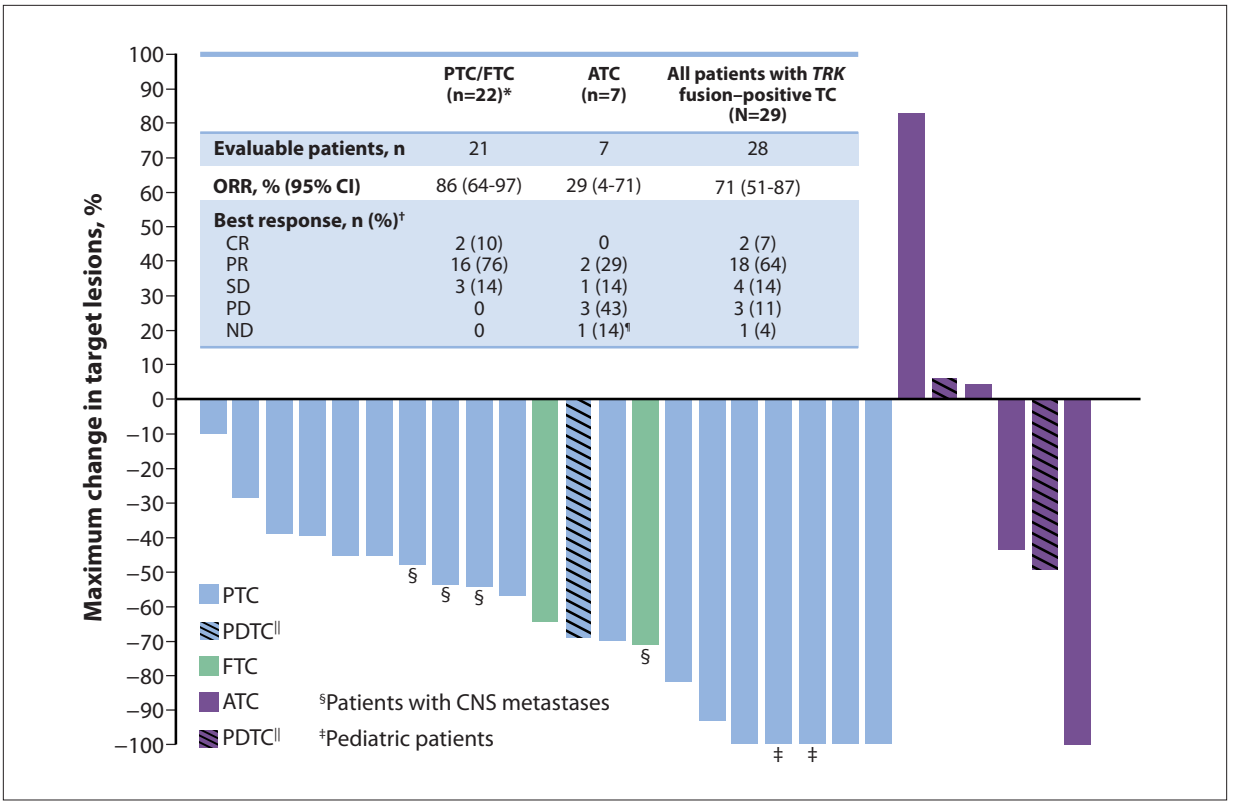

Figure 6. Waterfall plot of the maximum change in target lesions following treatment with larotrectinib in patients with advanced *TRK* fusion–positive thyroid carcinoma. *One patient with papillary thyroid carcinoma was not evaluable for tumor response. †Investigator assessment based on RECIST version 1.1. ¶One patient with ATC was evaluable, but the response could not be determined because the patient had clinical disease progression before the first tumor response assessment. ||Three PDTCs, 2 in the anaplastic group and 1 in the papillary group. ATC, anaplastic thyroid carcinoma; CR, complete response; FTC, follicular thyroid carcinoma; ND, not determined; ORR, objective response rate; PD, progressive disease; PDTC, poorly differentiated thyroid carcinoma; PR, partial response; PTC, papillary thyroid carcinoma; SD, stable disease; TC, thyroid carcinoma; TRK, tropomyosin receptor kinase. Source: Waguespack SG et al. *Eur J Endocrinol*. 2022;186(6):631-643. (http://creativecommons.org/licenses/by/4.0)[4]

patients with *NTRK* gene fusion–positive tumors that are not amenable to RAI therapy. Responses to TRK inhibitors can be robust and durable, with long-term remission achievable (Figure 5).

It is difficult to compare these options in the absence of head-to-head trials. However, it is clear that the AE profiles of these agents differ significantly. In particular, larotrectinib and entrectinib tend to be better tolerated than the multitargeted kinase inhibitors, so that patients can remain on the full dose without dose modifications and without discontinuation for a much longer period of time.

Clinical Data Supporting TRK Inhibitors in Thyroid Cancer

Larotrectinib

A pooled data analysis from 3 clinical studies (a phase 1 adult trial [NCT02122913], a phase 1/2 pediatric trial [SCOUT] in patients younger than 21 years of age, and a phase 2 basket trial [NAVIGATE] of adolescents older than 12 years and adults) demonstrated the durable antitumor efficacy of larotrectinib across a population comprising 159 patients with multiple types of *NTRK* fusion–positive solid tumors.[3] In 2022, Waguespack and colleagues reported a subset analysis of 29 adult and pediatric patients identified from this pooled dataset.[4]

All patients included had measurable locally advanced or metastatic thyroid carcinoma harboring an *NTRK* gene fusion and were treated with larotrectinib (100 mg twice daily in adults, 100 mg/m^2 twice daily in pediatric patients). Larotrectinib was administered until disease progression, unacceptable toxicity, or study withdrawal, although patients could continue treatment beyond disease progression if the study investigator judged they were still benefitting from treatment. Among the 29 patients, the primary tumor histology was papillary thyroid carcinoma

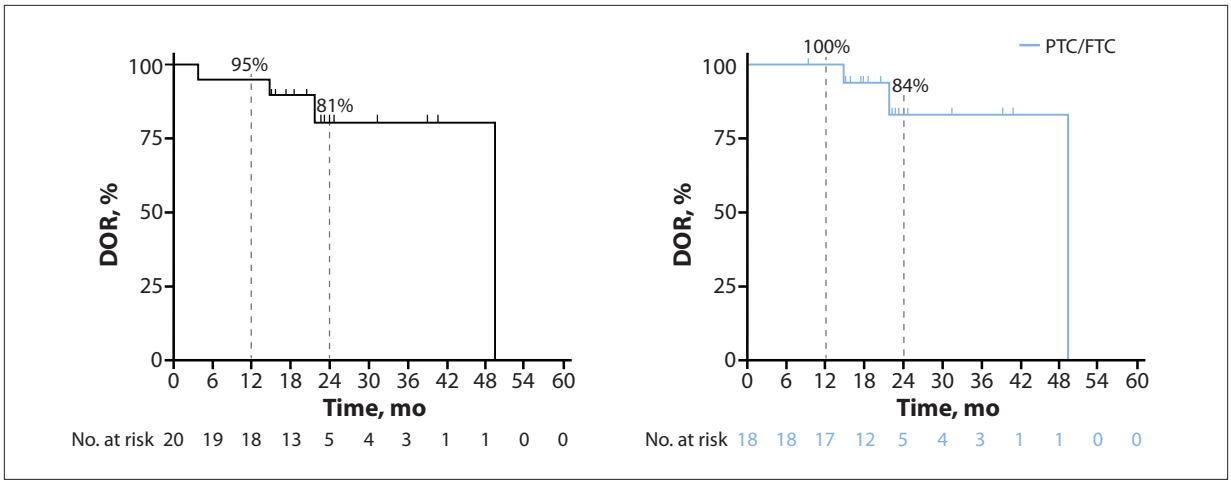

Figure 7. Kaplan-Meier curve for the duration of response (DOR) among patients with advanced *TRK* fusion–positive thyroid cancer treated with larotrectinib. The estimated DOR rate is given for the entire study group (left) and on the basis of histology (right). The DOR Kaplan-Meier curve includes only the patients who experienced a response. The ATC DOR Kaplan-Meier curve is not shown because there were too few patients. ATC, anaplastic thyroid carcinoma; DOR, duration of response; FTC, follicular thyroid carcinoma; mo, months; PTC, papillary thyroid carcinoma. Source: Waguespack SG et al. *Eur J Endocrinol*. 2022;186(6):631-643. (http://creativecommons.org/licenses/by/4.0)[4]

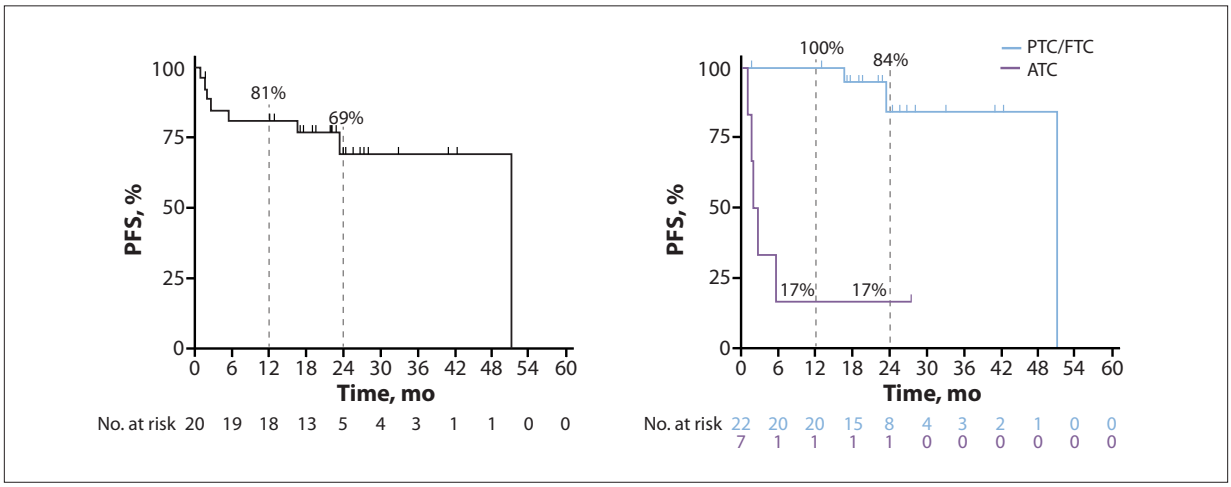

Figure 8. Kaplan-Meier curve for progression-free survival (PFS) among 20 patients with advanced *TRK* fusion–positive thyroid cancer treated with larotrectinib. The estimated PFS rate is given for the entire study group (left) and on the basis of histology (right). The one patient in the ATC group with a durable response had poorly differentiated thyroid carcinoma. ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; mo, months; PFS, progression-free survival; PTC, papillary thyroid carcinoma. Source: Waguespack SG et al. *Eur J Endocrinol*. 2022;186(6):631-643. (http://creativecommons.org/licenses/by/4.0)[4]

(69%), followed by anaplastic thyroid carcinoma (24%) and follicular thyroid carcinoma (7%). The median age was 60 years, although the ages ranged widely from 6 to 80 years (2 patients were children). At baseline, 4 patients showed evidence of CNS metastases. All *NTRK* fusions involved either *NTRK1* (45%) or *NTRK3* (55%), with no *NTRK2* gene fusions identified. A total of 45% of the patient set had received no prior systemic therapies, whereas 24%, 24%, and 7% had received 1, 2, or 3 or more prior systemic therapies, respectively. The prior systemic therapy most often given was a tyrosine kinase inhibitor (38%).

The primary endpoint, ORR, was 71% (95% CI, 51%-87%) among the 28 evaluable patients in this subset; this included 2 complete responses (7%) and 18 partial responses (64%; Figure 6). An additional 4 patients

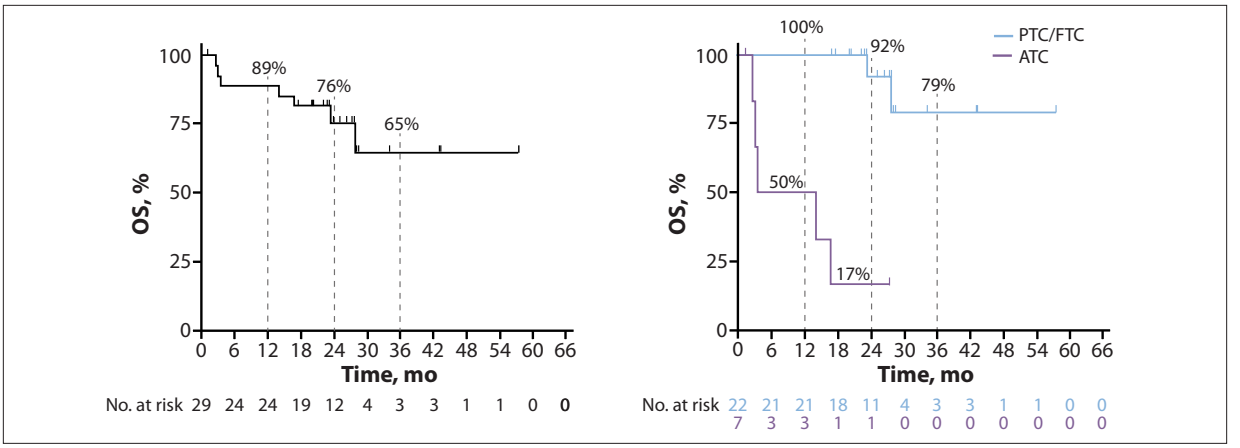

Figure 9. Kaplan-Meier curve for overall survival (OS) among 29 patients with advanced *TRK* fusion–positive thyroid cancer treated with larotrectinib. The estimated OS rate is given for the entire study group (left) and on the basis of histology (right). The one patient in the ATC group with a durable response had poorly differentiated thyroid carcinoma. ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; mo, months; OS, overall survival; PTC, papillary thyroid carcinoma. Source: Waguespack SG et al. *Eur J Endocrinol*. 2022;186(6):631-643. (http://creativecommons.org/licenses/by/4.0)[4]

(14%) had stable disease. Among the patients who achieved an objective response, the median time to that response was 1.87 months (range, 1.64-3.68), which in most cases corresponded to the first post-baseline assessment. A large difference was noted between the degrees of response in anaplastic and other thyroid carcinoma histologies (eg, papillary and follicular). Indeed, all 3 patients who showed evidence of disease progression had anaplastic thyroid carcinoma. The 4 patients with CNS metastases at baseline had a partial response as their best response; 2 patients showed intracranial tumor reductions of 14% and 46%.

Secondary efficacy endpoints included DOR, PFS, and OS. In the 20 responding patients, the estimated DOR rate at 12 months was 95% and at 24 months was 81% (Figure 7). In patients with either papillary or follicular histology, the DOR rates at 12 and 24 months were 100% and 84%, respectively. For patients with anaplastic thyroid carcinoma, the 12-month estimated DOR rate was 50%.

Overall, the PFS rate was 81% at 12 months and 69% at 24 months (Figure 8). PFS was markedly better in patients with differentiated thyroid carcinoma (either papillary or follicular histology: 100% and 84% at 12 and 24 months, respectively) than in patients with anaplastic histology (17%) at each time point. In patients with anaplastic thyroid carcinoma, after a median follow-up of 27.4 months, the median PFS was relatively short, at 2.2 months (95% CI, 0.9 to not estimable).

In the overall patient population, the estimated OS rates at 12, 24, and 36 months were 89%, 76%, and 65%, respectively (Figure 9). Again, these outcomes were markedly better in patients with either papillary or follicular thyroid carcinoma, with OS rates of 100% (12 months), 92% (24 months), and 79% (36 months). Comparatively, the OS rate in patients with anaplastic thyroid carcinoma was 50% at 12 months and 17% at 24 months, with patients reaching a median OS of 8.8 months (95% CI, 2.6 to not estimable) over a median follow-up of 27.4 months.

Entrectinib

As was described in the section on lung cancer, a patient dataset from 3 clinical studies (the phase 1 ALKA-372-001 trial, the phase 1 STARTRK-1 trial, and the phase 2 STARTRK-2 basket trial) was used to evaluate entrectinib. All these studies enrolled patients aged 18 years or older with metastatic or locally advanced *NTRK* fusion–positive solid tumors.[5] This prespecified integrated analysis enrolled patients with an *NTRK* fusion–positive solid tumor if they had measurable disease and had received at least one dose of entrectinib at or above the recommended phase 2 dose (600 mg once daily).

The initial report of this integrated analysis, with a data cutoff of May 31, 2018, included 54 patients, of whom 5 were identified as having thyroid cancer. An objective response was achieved in 1 of these 5 patients. A subsequent update, with a data cutoff of August 31, 2020, included 13 patients with thyroid cancer.[6] An objective response was achieved with entrectinib in 7 of these patients (53.8%; 95% CI, 25.1%-80.8%). The median DOR in the responding patients was 13.2 months (95% CI, 7.9 to not estimable). Additional endpoints reported among the subset of patients with thyroid cancer were

median PFS (19.9 months; 95% CI, 6.5-33.8) and median OS (19.9 months; 95% CI, 14.5 to not estimable).

Selecting TRK Inhibitors for Patients With Thyroid Cancer

Both larotrectinib and entrectinib carry indications under accelerated approval for the treatment of patients with *NTRK* fusion–positive cancer if the cancer is metastatic or if surgical resection is likely to result in severe morbidity and the cancer has either progressed following treatment or no satisfactory alternative therapy is available.[7,8] The clinical data reported thus far with the use of TRK inhibitors in thyroid cancer are limited to 29 patients treated with larotrectinib and 13 patients treated with entrectinib.[4,6] Although both of these are relatively small numbers, given the rarity of the disease, it is fair to say that we have more experience with larotrectinib in patients with differentiated thyroid cancer. In general in these patients, larotrectinib was associated with a higher response rate and a longer PFS than was entrectinib, although the results cannot be directly compared. On the basis of these findings, although both agents are FDA-approved options, I tend to select larotrectinib when treating patients outside a clinical trial.

One important caveat is that initially the impression was that entrectinib was designed specifically to penetrate and remain in the CNS (later, larotrectinib was demonstrated to have excellent CNS activity as well).[9-11] As a result, patients presenting with brain metastases tended to be enrolled in the entrectinib clinical trials; indeed, of the 13 patients with thyroid cancer included in the integrated analysis of entrectinib, 7 had CNS metastases. This is a high rate of CNS metastasis for thyroid cancer, suggesting that the patient population in the entrectinib studies probably was not the same thyroid cancer patient population that was enrolled in the larotrectinib studies.

Adverse Events Reported in Patients With Thyroid Cancer

AEs occurring with either larotrectinib or entrectinib are relatively similar, and both are very well tolerated; however, only larotrectinib has reported specific AE data in patients with thyroid cancer. Among the 29 patients with thyroid carcinoma included from the pooled analysis of 3 clinical trials, the most frequent treatment-related AEs were myalgia (28%), fatigue (28%), dizziness (28%), and elevated liver transaminases (28% with increased aspartate aminotransferase and 28% with increased alanine aminotransferase).[4] These AEs were primarily grade 1 or 2 and were consistent with those reported in the full pooled analysis dataset.[3] Just 2 patients experienced a grade 3 AE—one with anemia and the other with a decreased lymphocyte count. No patients permanently discontinued larotrectinib because of an AE.

Emerging Roles for TRK Inhibitors in Thyroid Cancer

TRK inhibition has also been explored in novel roles for thyroid cancer treatment. Accumulating evidence suggests that TRK inhibition with larotrectinib may cause a tumor to concentrate RAI more effectively. Case reports have begun to demonstrate a potential role of larotrectinib in RAI redifferentiation, which may further extend to its use as neoadjuvant therapy before initial RAI treatment.[4,12,13] An open-label, phase 2 study is currently recruiting patients with *NTRK* fusion–positive differentiated thyroid cancer to evaluate larotrectinib followed by RAI therapy.[14]

One case study has been reported that showed a dramatic response of an anaplastic thyroid cancer to entrectinib.[15] However, given the generally low response rate in patients with anaplastic histology in the larotrectinib pooled clinical trials, TRK inhibition should not yet replace chemoradiotherapy for patients with this more aggressive form of thyroid cancer.

Compared with papillary thyroid cancers in adult patients, those in pediatric patients tend to present as larger primary tumors with more extensive extrathyroidal involvement and an increased prevalence of both local and distant metastatic disease.[16] Given the tolerability of these agents, it would be reasonable to consider using larotrectinib or entrectinib in patients who present with initially bulky disease that would be difficult to resolve with an R0 or R1 resection.

Resistance to TRK Inhibitors

Acquired resistance to the TRK inhibitors larotrectinib and entrectinib has been documented, primarily resulting from *NTRK* gene mutations that involve amino acid substitutions in the solvent-front region, gatekeeper residues, and xDFG motif substitutions.[17,18] In addition, genomic alterations in complementary pathways, such as those involving MAPK, BRAF, KRAS, and MET, may also be implicated in acquired mechanisms of resistance to TRK inhibitors.[19] The second-generation TRK inhibitors repotrectinib and selitrectinib were designed to overcome TRK inhibitor resistance and are currently under clinical investigation.[20]

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Q&A: Barriers to Testing for *NTRK* Fusions in Metastatic Lung and Thyroid Cancer

David S. Hong, MD; Alexander Drilon, MD; and Lori J. Wirth, MD

Why is it important to test patients for any driver with an FDA-approved therapy?

Dr Drilon: Lung cancer is a type of cancer that is enriched for the following targets: *EGFR*, *ALK*, *RET*, *ROS1*, and *NTRK*, in addition to others. The approach should be to use a comprehensive test that captures all these different drivers. Even though some of them are much less common than others, given the high response rates and durable benefit associated with the use of targeted agents, testing is worthwhile because you hit the jackpot for a patient if you find the appropriate target.

What are some of the barriers to testing?

Dr Drilon: One of the barriers is education. Doctors' insights will depend on when they were in medical school and their level of continuing education. Doctors need to be aware of targeted therapies, the associated molecular biology, how these newer treatments work, how the targets are detected, and how the tests work. For *NTRK* fusions, RNA-based NGS testing is preferred over DNA-based testing because of its superior sensitivity.

Can you discuss treatment of *NTRK* fusion–positive lung cancer according to stage?

Dr Drilon: In the stage IV setting, the targeted therapies larotrectinib and entrectinib really beat everything else in terms of response and durability. They are our best drugs for patients with *NTRK* fusions, and they should be used up front whenever possible. In the earlier-stage setting, perhaps a stage II NSCLC, obviously the intent is curative. If someone can get the surgery and then adjuvant chemotherapy, that is the recommended approach. There is no approval for adjuvant TRK inhibitor therapy, but one could consider a clinical trial.

Are there limits to how long treatment with a TRK inhibitor can last?

Dr Hong: I think treatment can last for as long as the patient continues to benefit. We know that patients on long-term larotrectinib have tolerated it fairly well. The primary mechanism of resistance occurs at the binding site of larotrectinib and entrectinib. Right now, the most relevant drugs currently under investigation for TRK inhibitor resistance are repotrectinib and selitrectinib. Repotrectinib is not particularly effective against the TRK xDFG resistance mutation, but it can overcome other mechanisms of resistance, including the solvent-front and gatekeeper mutations.

Are insurers reimbursing for TRK inhibitor agents?

Dr Wirth: Copays associated with these drugs vary. But fortunately, patient assistance programs that are generous are available to most patients with typical incomes so that most patients in the United States are able to access these therapies.

Slide Library

NTRK Gene Fusions

- The *NTRK* genes 1, 2, and 3 include 3 closely related TRK proteins—TRKA, TRKB, and TRKC, respectively.[1,2]
- *NTRK* rearrangements, and more specifically gene fusions, are the most common mechanism of TRK oncogene activation.[3]
- The frequencies of *NTRK* fusions are often classified in 3 broad categories.[4,5]

NTRK, neurotrophic tropomyosin receptor tyrosine kinase; TRK, tropomyosin receptor kinase.
1. Okamura R et al [published online November 15, 2018]. *JCO Precis Oncol.* 2. Laetsch TW, Hong DS. *Clin Cancer Res.* 2021;27(18):4974-4982. 3. Cocco E et al. *Nat Rev Clin Oncol.* 2018;15(12):731-747. 4. Nguyen MA et al. *Pathology.* 2023;55(5):596-609. 5. Shulman DS, DuBois SG. *Paediatr Drugs.* 2020;22(2):189-197.

Prevalence of *NTRK* Fusions

- The prevalence of *NTRK* fusions in NSCLC is estimated to be between 0.1% and 0.3%.[1]
- The prevalence of *NTRK* fusions in thyroid cancer differs across studies and in different tumor types, with the highest prevalence observed in pediatric papillary thyroid cancers and in radiation-induced thyroid cancer.

NSCLC, non–small cell lung cancer; NTRK, neurotrophic tropomyosin receptor tyrosine kinase.
1. Liu F et al. *Front Oncol.* 2022;12:864666.

Detection of *NTRK* Fusions

- IHC offers a widely available, inexpensive method with a rapid turnaround to identify *NTRK* fusions.
- FISH uses probes to track anomalous *NTRK* gene fusion partners.
- RT-PCR begins with primer-specific reverse transcription of RNA to complementary DNA.
- NGS implements either a targeted approach or whole-genome sequencing to examine multiple genomic alterations simultaneously.

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NTRK, neurotrophic tropomyosin receptor tyrosine kinase; RT-PCR, reverse transcription polymerase chain reaction.

NCCN Guidelines

- In cases of advanced or metastatic NSCLC, include *NTRK* fusion testing in the list of broad molecular profiling tests recommended for cases with adenocarcinoma histology.[1]
- Broad molecular profile testing should include *NTRK* fusions in cases of squamous cell carcinoma.
- The NCCN guidelines for thyroid cancer recommend molecular diagnostics in all cases of advanced thyroid cancer.[2]

NCCN, National Comprehensive Cancer Network; NTRK, neurotrophic tropomyosin receptor tyrosine kinase.
1. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. Version 5.2024. 2. NCCN Clinical Practice Guidelines in Oncology. Thyroid carcinoma. Version 2.2024.

Treatment of Metastatic Adenocarcinoma of the Lung

- The most frequent type of lung cancer with *NTRK* fusions.
- Growing recognition from the IMMUNOTARGET Registry that NSCLC tumors harboring driver mutations do not show a good response to immunotherapy.[1]
- Start with the best drug up front (ie, larotrectinib or entrectinib), then later move to chemotherapy in the second line.[2]
- Larotrectinib and entrectinib can be used in earlier stages of disease.[3,4]

NSCLC, non–small cell lung cancer; NTRK, neurotrophic tropomyosin receptor tyrosine kinase.
1. Mazieres J et al. *Ann Oncol.* 2019;30(8):1321-1328. 2. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. Version 5.2024. 3. Larotrectinib [prescribing information]. November 2023. 4. Entrectinib [prescribing information]. January 2024.

Clinical Data on TRK Inhibitors in Lung Cancer

Larotrectinib

- A total of 20 patients with *NTRK* fusion–positive lung cancer were included in a combined analysis of a phase 1 adult trial and the phase 2 NAVIGATE basket trial.[1,2]

Entrectinib

- A patient dataset from 3 clinical studies (the phase 1 ALKA-372-001 trial, the phase 1 STARTRK-1 trial, and the phase 2 STARTRK-2 basket trial) was used to evaluate entrectinib.[3]
- A subsequent update included 22 patients with NSCLC, of whom 13 had CNS metastases at baseline.[4]

NSCLC, non–small cell lung cancer; NTRK, neurotrophic tropomyosin receptor tyrosine kinase.
1. Drilon A et al. *N Engl J Med.* 2018;378(8):731-739. 2. Drilon A et al. *JCO Precis Oncol.* 2022;6(6):e2100418. 3. Doebele RC et al. *Lancet Oncol.* 2020;21(2):271-282. 4. Demetri GD et al. *Clin Cancer Res.* 2022;28(7):1302-1312.

AEs in Patients With Lung Cancer

- **Common adverse effects with TRK inhibitors include dizziness, weight gain, and neuropathy-like pain.[1,2]**
- **The most common grade 3 AE that tends to occur is elevation of liver function enzymes.[3,4]**

AE, adverse event; NTRK, neurotrophic tropomyosin receptor tyrosine kinase; TRK, tropomyosin receptor kinase.
1. Liu D et al. *Ann Oncol*. 2020;31(9):1207-1215. 2. Liguori V et al. *Biomedicines*. 2023;11(9):2538. 3. Larotrectinib [prescribing information]. November 2023. 4. Entrectinib [prescribing information]. January 2024.

Treatment of Well-Differentiated Thyroid Cancers

- **Most well-differentiated thyroid cancers are cured by surgery alone, with thyrotropin suppression and RAI added for patients with intermediate- or high-risk disease.[1]**
- **Traditional chemotherapeutic agents (including paclitaxel and doxorubicin) generally have minimal efficacy in patients with metastatic differentiated thyroid cancer.**
- **The TRK inhibitors larotrectinib and entrectinib are recommended for patients with *NTRK* gene fusion–positive tumors that are not amenable to RAI therapy.**

NTRK, neurotrophic tropomyosin receptor tyrosine kinase; RAI, radioactive iodine; TRK, tropomyosin receptor kinase.
1. Boucai L et al. *JAMA*. 2024;331(5):425-435.

Clinical Data on TRK Inhibitors in Thyroid Cancer

Larotrectinib

- **A pooled data analysis from 3 clinical studies (NCT02122913, SCOUT, and NAVIGATE) demonstrated the durable antitumor efficacy of larotrectinib in *NTRK* fusion–positive solid tumors.[1]**
- **In 2022, Waguespack and colleagues reported a subset analysis of 29 adult and pediatric patients identified from this pooled dataset.[2]**

Entrectinib

- **A patient dataset from 3 clinical studies (ALKA-372-001, STARTRK-1, and STARTRK-2) was used to evaluate entrectinib.[3,4]**

NTRK, neurotrophic tropomyosin receptor tyrosine kinase; TRK, tropomyosin receptor kinase.
1. Hong DS et al. *Lancet Oncol*. 2020;21(4):531-540. 2. Waguespack SG et al. *Eur J Endocrinol*. 2022;186(6):631-643. 3. Doebele RC et al. *Lancet Oncol*. 2020;21(2):271-282. 4. Demetri GD et al. *Clin Cancer Res*. 2022;28(7):1302-1312.

AEs in Patients With Thyroid Cancer

- **AEs occurring with either larotrectinib or entrectinib are relatively similar, and both are very well tolerated**
- **The most frequent treatment-related AEs with larotrectinib in thyroid cancer were myalgia, fatigue, dizziness, and elevated liver transaminases.[1]**
- **Two patients experienced a grade 3 AE—one with anemia and the other with a decreased lymphocyte count.**

AE, adverse event; NTRK, neurotrophic tropomyosin receptor tyrosine kinase.
1. Waguespack SG et al. *Eur J Endocrinol*. 2022;186(6):631-643.

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