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Larotrectinib and Entrectinib: TRK Inhibitors for the Treatment of Pediatric and Adult Patients With *NTRK* Gene Fusion

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Author's disclosure of conflict of interest is found at the end of this article.

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Abstract

Two new targeted agents have been approved for pediatric and adult patients with advanced or metastatic solid tumors with neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without an acquired resistance mutation. Larotrectinib and entrectinib are the second and third agents to be approved as tissue agnostic treatments, respectively. *NTRK* gene fusion is now a targetable biomarker for patients who may otherwise be devoid of satisfactory alternative treatment options. In this article, the safety and efficacy trials of each medication, and the initial and ongoing monitoring required for patients on these treatments will be discussed.

Tropomyosin-related kinase (TRK) transmembrane proteins TRKA, TRKB, and TRKC are encoded by neurotrophic tyrosine receptor kinase (*NTRK*) genes *NTRK1*, *NTRK2*, and *NTRK3*, respectively (Amatu, Sartore-Bianchi, & Siena, 2016; Vaishnavi, Le, & Doebele, 2015). When the kinase domains are bound by neurotrophins, this leads to dimerization and intracellular activation. Signaling cascades then result in cellular growth and differentiation. However, DNA damage to *NTRK* genes can lead to fusion proteins. This results in unregulated dimerization of TRK proteins and consequently uncontrolled cellular growth.

NTRK gene fusions are rare but have been found in multiple tumor types. *NTRK* fusions occur at lower frequencies (< 5% for adults) in common cancers such as lung, melanoma, and colon cancer but are detected at high frequencies (> 75% for adults) in rare cancers, including secretory carcinoma of the breast and salivary gland (Bayer, 2019). In pediatric patients, *NTRK* gene fusions occur at high rates (> 75%) in

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infantile fibrosarcoma and secretory breast carcinoma. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) are considered selective inhibitors for TRKA, TRKB, and TRKC (Cocco, Scaltriti, & Drilon, 2018). Entrectinib has additional activity against proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and anaplastic lymphoma kinase (ALK; Genentech USA, Inc., 2019). Larotrectinib and entrectinib were granted accelerated approval by the FDA in November 2018 and August 2019, respectively (FDA.gov, 2018, 2019). Both approvals were based on tumor response rates and duration of response (Bayer HealthCare Pharmaceuticals, Inc., 2019; Genentech USA Inc., 2019).

MECHANISM OF ACTION

Larotrectinib and entrectinib are first-generation pan-tropomyosin-related kinase (TRK) inhibitors with activity against TRKA, TRKB, and TRKC. Inhibition of TRK receptor domains exerts antitumor effects by decreasing cellular proliferation and survival of cancers positive for *NTRK* fusions (Bhangoo & Sigal, 2019; Lange & Lo, 2018). Larotrectinib and entrectinib are approved for patients with solid tumors that have *NTRK* gene fusion without a known resistance mutation, are metastatic or where resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or have progression following treatment (Bayer Healthcare Pharmaceuticals, Inc., 2019). These highly selective, tumor-agnostic agents have been approved in both adult and pediatric patients (Bayer HealthCare Pharmaceuticals, Inc., 2019; FDA.gov, 2018). Entrectinib has an additional indication for adult patients with metastatic, *ROS1*-positive non–small cell lung cancer (NSCLC; Genentech USA, Inc., 2019).

CLINICAL TRIALS

Larotrectinib was studied in 176 patients across three single-arm trials that lead to an accelerated FDA approval in November 2018 (Bayer HealthCare Pharmaceuticals, Inc., 2019). The LOXO-TRK-14001 (NCT02122913) trial assessed the safety of the medication in adult patients, SCOUT (NCT026376687) tested the safety and efficacy of larotrectinib in children, and the basket trial NAVIGATE (NCT02576431) evaluated efficacy in both adult and adolescent patients (Bayer HealthCare Pharmaceuticals Inc., 2019; Drilon et al., 2018). The primary endpoint of overall response rate evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was assessed in the first 55 patients of the 176 enrolled across all three studies. Patients who met inclusion criteria were those with confirmed TRK fusion (identified by next-generation sequencing [n = 50] or fluorescence in situ hybridization [n = 5]), a noncentral nervous system primary tumor, and had received at least one dose of larotrectinib. The most common tumor types in the analyzed patient population included salivary gland (22%), a variety of other soft-tissue sarcoma subtypes (20%), and infantile fibrosarcoma (13%). The age range of patients included in the trials was 4 months to 76 years old. The overall response rate was 75%, with a median time to response of 1.8 months. The duration of response was not reached at the time of data cutoff. Table 1 stratifies patients based on level and duration of response (Drilon et al., 2018).

Entrectinib was studied in four dose-finding and activity-estimating trials: ALKA (n = 55), STARTRK-1 (n = 76), STARTRK-NG (n = 16), and STARTRK-2 (n = 206). The most prevalent tumor types studied were lung (56%), sarcoma (8%), and colon (5%). Efficacy analysis for *NTRK* gene fusion tumors was based on the first 54 adult patients enrolled in the trials. The overall response rate of entrectinib was 57% (7.4% complete response, 50% partial response). The duration of response ranged from 2.8 to 26.0 months (with results ongoing). The efficacy and safety of entrectinib in ado-

Table 1. Treatment Responses to Larotrectinib

Patient response	**Rate (n = 55)**
Complete response	13%
Partial response	62%
Stable disease	13%
Progression	9%
Unevaluable patients	4%
Duration of response	**Rate (n = 41)**
6 months or greater	73%
9 months or greater	63%
12 months or greater	39%

Note. Information from Bayer HealthCare Pharmaceuticals, Inc. (2019); Drilon et al. (2018).

lescent patients was extrapolated from adult data and the 30 pediatric patients in the STARTRK-NG trial (Genentech USA, Inc., 2019).

The most recent NCCN Guidelines update for NSCLC includes larotrectinib and entrectinib as first-line and subsequent treatment options for patients with advanced or metastatic disease with *NTRK* gene fusion. Entrectinib has also been added as a therapeutic option for patients positive for *ROS1* rearrangement (NCCN, 2019a). Recommendations for larotrectinib can also be found in the NCCN Guidelines for patients with soft tissue sarcoma subtypes with nonspecific histologies (NCCN, 2019b).

DOSING AND ADMINISTRATION

Larotrectinib

The recommended dose of larotrectinib is 100 mg orally twice daily for adult and pediatric patients (28 weeks and older) with a body surface area (BSA) greater than or equal to 1.0 m^2. For pediatric patients with a BSA less than 1.0 m^2, the recommended dose is 100 mg/m^2 orally twice daily. Larotrectinib can be taken with or without food. The medication is available as 25-mg and 100-mg gelatin capsules, as well as a 20-mg/mL oral solution. Both dosage forms may be used interchangeably (Bayer Healthcare Pharmaceuticals, Inc., 2019).

Larotrectinib undergoes hepatic metabolism primarily via CYP3A4. Concurrent administration of strong CYP3A4 inhibitors and inducers should be avoided. If coadministration is necessary with strong CYP3A4 inhibitors (e.g., itraconazole), the dose of larotrectinib should be reduced by 50%. The dose of larotrectinib should be doubled if given in combination with strong CYP3A4 inducers (e.g., rifampin). Moderate and weak CYP3A4 inhibitors and inducers have not been studied in combination with larotrectinib. The prescribing information states that no renal dose adjustments are recommended; however, pharmacokinetics analysis with creatinine clearance less than or equal to 60 mL/min has not been studied. For moderate/severe hepatic impairment (Child-Pugh B and C), the package insert recommends reducing the starting dose of larotrectinib by 50%. The half-life of larotrectinib is 2.9 hours. The medication is primarily excreted in feces (58%) and 39% in urine (Bayer HealthCare Pharmaceuticals, Inc., 2019).

Entrectinib

The recommended adult dose of entrectinib for both *NTRK* gene fusion–positive solid tumors and *ROS1*-positive NSCLC is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity. For pediatric patients (age 12 years or older) with *NTRK* gene fusion–positive solid tumors, the recommended daily dose is based on BSA: 600 mg (BSA greater than 1.50 m^2), 500 mg (BSA 1.11–1.50 m^2) and 400 mg (BSA 0.91–1.10 m^2). Entrectinib is available as 100-mg and 200-mg capsules that are to be swallowed whole (Genentech USA, Inc., 2019).

Entrectinib is primarily metabolized hepatically via CYP3A4. Therefore, concomitant administration with moderate and strong CYP3A4 inhibitors should be avoided. For patients receiving the 600-mg dose, entrectinib should be decreased to 200 mg once daily and 100 mg once daily if taken concurrently with moderate and strong CYP3A4 inhibitors, respectively. For moderate and strong CYP3A4 inducers, coadministration with entrectinib should be avoided. There are no dose adjustments recommended for mild to moderate renal impairment (creatinine clearance 30–89 mL/min). Severe renal impairment (creatinine clearance < 30 mL/min) has not been studied. No dose adjustments are recommended for mild hepatic impairment (total bilirubin ≤ 1.5 × upper limit of normal). Moderate and severe hepatic impairment (total bilirubin > 1.5 x upper limit of normal) have not been studied. The half-life of entrectinib is 20 hours (40 hours for active metabolite). It is excreted primarily in feces (83%; Genentech USA, Inc., 2019).

ADVERSE EVENTS

In comparison to other tyrosine kinase inhibitors (TKI), larotrectinib is well tolerated, with over 90% of adverse events observed as grade 1 or 2. The adverse events seen most frequently in the larotrectinib trials of any grade include increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST), fatigue, and vomiting. Median time of onset of hepatotoxicity was 2 months. Table 2 shows the rates of adverse events in patients who received larotrectinib (n = 176). Warnings and precautions for larotrectinib include neurotoxicity, hepatotoxicity, and embryo-fetal toxicity (Bayer HealthCare Pharmaceuticals, Inc., 2019).

Of the 55 patients analyzed, only 15% of them required a dose reduction. Adverse events leading to dose reductions included increased ALT/AST, dizziness, and decreased absolute neutrophil count (ANC). Medication discontinuation due to adverse events did not occur in patients who demonstrated a response to treatment (Drilon et al., 2018). However, 53% of all the patients who received larotrectinib (n = 176) experienced neurologic adverse reactions (most occurring within the first 3 months), including delirium, dysarthria, and dizziness. Among these neurologic side effects, dizziness was the most prevalent at 31% of the 55 patients in the final analysis (Cocco et al., 2018; Drilon et al., 2018).

Unlike larotrectinib, entrectinib is implicated with additional warnings and precautions, including congestive heart failure, central nervous system effects, and skeletal fractures. Table 3 contains a complete list. In addition, Table 4 lists the most common adverse events observed with entrectinib for all grades. Sixty percent of patients experienced a grade 3 or 4 reaction, including lung infection (5%), dyspnea (6%), cognitive disorders (4.5%), syncope (2.5%), pulmonary embolism (3.4%), and pleural effusions (3.1%). Adverse reactions resulting in death included dyspnea (0.6%), pneumonia (0.6%), sepsis (0.6%), suicide (0.3%), large intestine perforation (0.3%), and tumor lysis syndrome (0.3%; Genentech USA, Inc., 2019). Due to entrectinib's adverse event profile and ability to affect many laboratory values, close monitoring

Table 2. Adverse Events of Larotrectinib (n = 176)

Adverse event	All grades (%)	Grade 3 or 4 (%)
Increased ALT or AST level	45	6
Anemia	42	10
Fatigue	37	3
Nausea	29	1
Dizziness	28	1
Vomiting	26	1
Cough	26	0
Neutropenia	23	7
Constipation	23	1
Diarrhea	22	2
Dyspnea	18	2
Pyrexia	18	1
Weight gain	15	4
Arthralgia	14	1
Headache	14	0
Back pain	12	1
Falls	10	1

Note. Information from Bayer HealthCare Pharmaceuticals, Inc. (2019).

Table 3. Warnings and Precautions for Entrectinib (n = 355)

Adverse event	All grades, %	Median time to onset
Hepatotoxicity	42 (increased AST) 36 (increased ALT)	2 weeks (AST) 2 weeks (ALT)
Dizziness	38	–
Cognitive impairment	27	3 months
Skeletal fractures	5 (adult) 23 (pediatric)	3.8 months (adult) 4 months (pediatric)
Vision changes	21	–
Sleep disturbances	14	–
Mood disorders	10	1 month
Hyperuricemia	9	–
Congestive heart failure[a]	3.4	2 months
QT interval prolongation (> 500 ms)	0.6	–

Note. Information from Genentech USA, Inc. (2019)
[a]Patients with baseline symptomatic congestive heart failure, myocardial infarction, unstable angina, and coronary artery bypass graft within 3 months of study entry were excluded in clinical trials.

Table 4. Adverse Events of Entrectinib (≥ 30% Occurrence; n = 355)

Adverse event	All grades (%)	Grade 3 or higher (%)
Fatigue	48	5.0
Constipation	46	0.6
Dysgeusia	44	0.3
Edema	40	1.1
Dizziness	38	0.8
Diarrhea	35	2.0
Nausea	34	0.3
Dysesthesia	34	0.3
Dyspnea	30	6.0

Note. Information from Genentech USA, Inc. (2019)

for dose adjustments and hold parameters are recommended in the package insert.

PATIENT MONITORING AND COUNSELING

For larotrectinib, it is recommended to monitor liver function every 2 weeks during the first month, then monthly thereafter (Bayer HealthCare Pharmaceuticals, Inc., 2019). Patients should be counseled to avoid grapefruit and St. John's wort. The oral solution should be refrigerated and discarded after 90 days from opening. Oral capsules should be swallowed whole, not crushed or chewed. Missed doses should not be taken if they are within 6 hours of the next scheduled dose. If patients vomit a dose, that dose should not be repeated. Females of reproductive age and males should be counseled to use effective contraception during larotrectinib treatment and for 1 week after the final dose. Additionally, females should avoid breastfeeding during treatment and for 1 week after the final dose.

For entrectinib, left ventricular ejection fraction should be monitored at baseline in patients with congestive heart failure risk factors (e.g., hypertension, cigarette use, diabetes, being overweight; Genentech USA, Inc., 2019; He et al., 2001). Liver function tests should be monitored every 2 weeks during the first month, then monthly thereafter. Serum uric acid levels should be monitored at baseline then as clinically indicated throughout treatment. Finally, QT interval and electrolytes should be monitored at baseline then as clinically indicated throughout treatment. Patients should be counseled to avoid grapefruit, and oral capsules should be swallowed whole. Missed doses should not be taken if they are within 12 hours of the next scheduled dose. If a dose is vomited immediately after taking the dose, the patient should repeat the dose. Females of reproductive age should be counseled to use effective contraception during entrectinib treatment and for 5 weeks after the final dose. Males with female partners of reproductive potential should use effective contraception during treatment and continue for 12 weeks after the final dose. Females should avoid breastfeeding during treatment and for 1 week after the final dose.

SUMMARY

Larotrectinib and entrectinib have received expedited approval for patients with solid tumors that have *NTRK* gene fusion without a known resistance mutation, are metastatic or where resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or have progression following treatment. In the final trial analysis, larotrectinib produced an overall response rate of 75% and entrectinib generated 57% with sustained duration of responses in 39% and 45% of patients at 12 months, respectively (Bayer Healthcare Pharmaceuticals, Inc., 2019; Genentech USA, Inc., 2019).

Conveniently, both medications are formulated as oral capsules; additionally, larotrectinib is available as an oral solution. Since these treatments are given in the outpatient setting, prescribers should be aware of the differences in monitoring parameters for safety between the two agents and the potential for drug-drug and drug-food interactions. Patients and/or caregivers should receive extensive counseling on administration and possible side effects prior to the initiation of treatment.

The estimated wholesale acquisition cost of larotrectinib treatment has been estimated at $393,600 per year compared with $204,560 per year for entrectinib (Hofland, 2018; Maddipatla, 2019). For patients in need of financial assistance with larotrectinib and entrectinib, both Bayer and Genentech have copay and foundation assistance programs.

Disclosure

The author has no conflicts of interest to disclose.

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