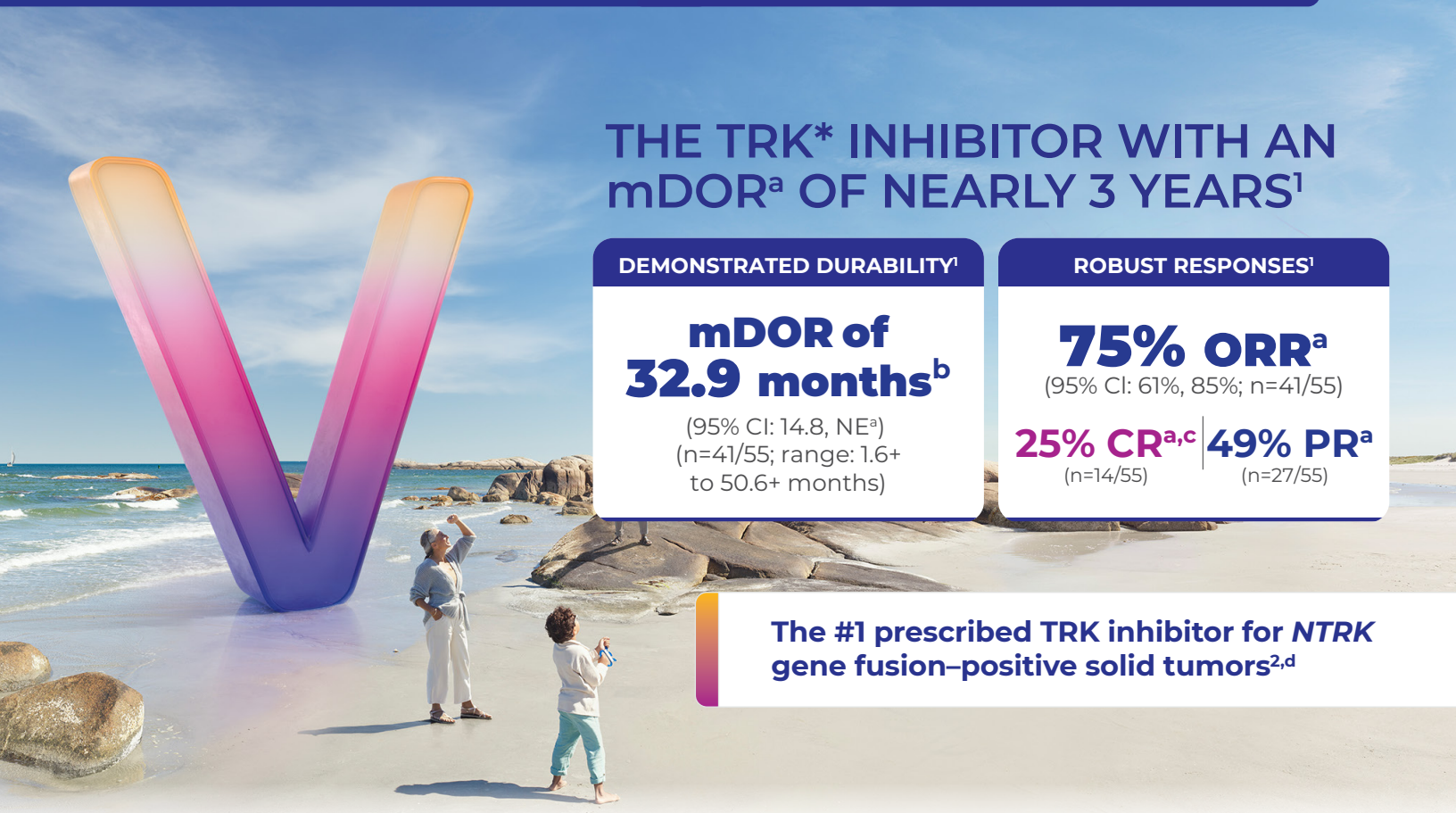


THE TRK* INHIBITOR WITH AN mDOR[a] OF NEARLY 3 YEARS[1]

DEMONSTRATED DURABILITY[1]

mDOR of 32.9 months[b]

(95% CI: 14.8, NE[a])
(n=41/55; range: 1.6+ to 50.6+ months)

ROBUST RESPONSES[1]

75% ORR[a]

(95% CI: 61%, 85%; n=41/55)

25% CR[a,c] (n=14/55) | **49% PR[a]** (n=27/55)

The #1 prescribed TRK inhibitor for *NTRK* gene fusion–positive solid tumors[2,d]

Study design: Pooled efficacy analysis based on 3 open-label, single-arm clinical studies in adult and pediatric patients with unresectable or metastatic solid tumors with an *NTRK* gene fusion.[1]

Indication

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase *(NTRK)* gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information

Warnings and Precautions

- **Central Nervous System Effects:** Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

  In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

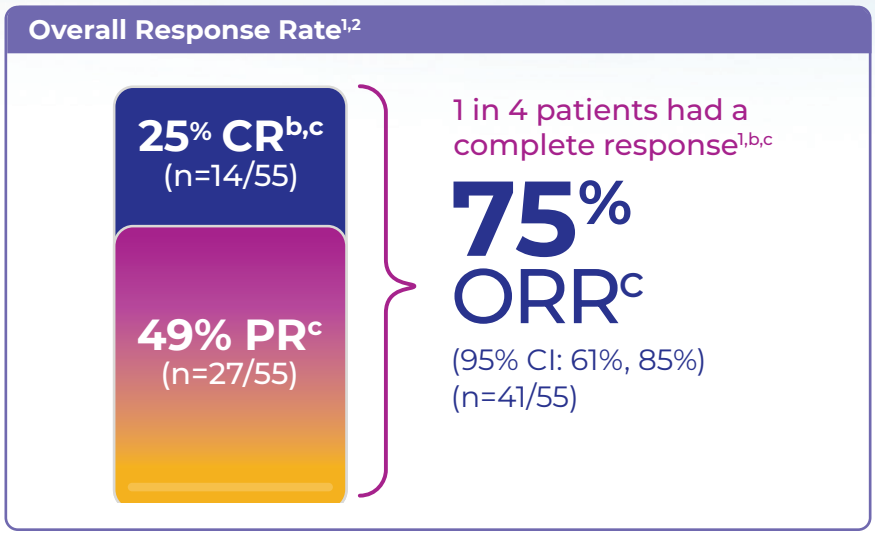
+denotes ongoing response.[1]
*TRK, tropomyosin receptor kinase.
[a]CR, complete response; mDOR, median duration of response; NE, not evaluable; *NTRK*, neurotrophic receptor tyrosine kinase; ORR, overall response rate; PR, partial response.
[b]Kaplan-Meier estimate.
[c]5% were pathological complete response. Patients undergoing a surgical resection whose postoperative pathologic assessment showed no viable tumor cells and negative margins were pathological complete responders provided that no other sites of disease were present.
[d]Based on medical claims and prescription data claims for the period January 2019 through July 2024. Validated by IQVIA in September 2024.[2]

Please see Important Safety Information throughout and click here for full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

3 OUT OF 4 PATIENTS RESPONDED TO TREATMENT WITH VITRAKVI®[1]

Remarkable Overall Response Rate[1]



Rapid response

Median time to best response was 1.84 months (25/75 percentile: [1.81, 5.49]).[2]

Study design: A pooled efficacy analysis based on 3 multicenter, open-label, single-arm clinical studies in adult and pediatric patients with unresectable or metastatic solid tumors with an *NTRK*[c] gene fusion. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. Major efficacy outcome measures were ORR and DOR[c], as determined by a BIRC[c] according to RECIST[c] v1.1.[1]

VITRAKVI is approved under accelerated approval based on overall response rate and duration of response. Continued approval for VITRAKVI may be contingent upon verification and description of clinical benefit in confirmatory trials.[1]

[a]July 2019 cutoff.[1]

[b]5% were pathological complete response. Patients undergoing a surgical resection whose postoperative pathologic assessment showed no viable tumor cells and negative margins were pathological complete responders provided that no other sites of disease were present.

[c]BIRC, blinded independent review committee; CR, complete response; DOR, duration of response; *NTRK*, neurotrophic receptor tyrosine kinase; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors.

Important Safety Information (continued)

- **Central Nervous System Effects (continued):** Cognitive impairment occurred in 11% of patients. The median time to onset of cognitive impairment was 5.6 months (range: 2 days to 41 months). Cognitive impairment occurring in ≥ 1% of patients included memory impairment (3.6%), confusional state (2.9%), disturbance in attention (2.9%), delirium (2.2%), cognitive disorders (1.4%), and Grade 3 cognitive adverse reactions occurred in 2.5% of patients. Among the 30 patients with cognitive impairment, 7% required a dose modification and 20% required dose interruption.

  Mood disorders occurred in 14% of patients. The median time to onset of mood disorders was 3.9 months (range: 1 day to 40.5 months). Mood disorders occurring in ≥1% of patients included anxiety (5%), depression (3.9%), agitation (2.9%), and irritability (2.9%). Grade 3 mood disorders occurred in 0.4% of patients.

  Dizziness occurred in 27% of patients, and Grade 3 dizziness occurred in 1.1% of patients. Among the 74 patients who experienced dizziness, 5% of patients required a dose modification and 5% required dose interruption.

  Sleep disturbances occurred in 10% of patients. Sleep disturbances included insomnia (7%), somnolence (2.5%), and sleep disorder (0.4%). There were no Grade 3-4 sleep disturbances. Among the 28 patients who experienced sleep disturbances, 1 patient each (3.6%) required a dose modification or dose interruption.

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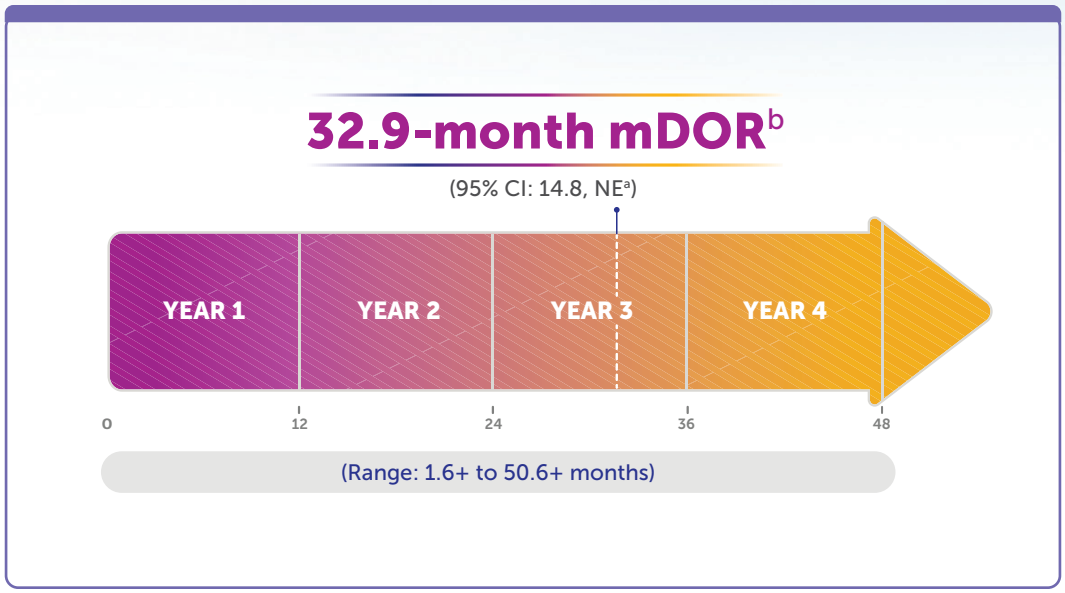
VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

LONG-LASTING DURABILITY: mDOR[a] OF NEARLY 3 YEARS[1]

Duration of Response (n=41/55)[1,2]



Observed DOR[a] rates[1]

- 63% of patients with a response had an observed DOR >1 year
- 49% of observed responses lasted longer than 2 years

VITRAKVI is approved under accelerated approval based on overall response rate and duration of response. Continued approval for VITRAKVI may be contingent upon verification and description of clinical benefit in confirmatory trials.[1]

+ denotes ongoing response.[1]
[a]DOR, duration of response; mDOR, median duration of response; NE, not evaluable.
[b]Kaplan-Meier estimate.

Important Safety Information (continued)

- **Central Nervous System Effects (continued):** Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.
- **Skeletal Fractures:** Among 187 adult patients who received VITRAKVI across clinical trials, fractures were reported in 7% and among 92 pediatric patients, fractures were reported in 9% (N=279; 8%). Median time to fracture was 11.6 months (range 0.9 to 45.8 months) in patients followed per fracture. Fractures of the femur, hip or acetabulum were reported in 4 patients (3 adult, 1 pediatric). Most fractures were associated with minimal or moderate trauma. Some fractures were associated with radiologic abnormalities suggestive of local tumor involvement. VITRAKVI treatment was interrupted due to fracture in 1.4% patients.

  Promptly evaluate patients with signs or symptoms of potential fracture (e.g., pain, changes in mobility, deformity). There are no data on the effects of VITRAKVI on healing of known fractures or risk of future fractures.
- **Hepatotoxicity:** Hepatotoxicity including drug induced liver injury (DILI) has been reported in patients taking VITRAKVI.

Please see Important Safety Information throughout and click here for full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

THE MAJORITY OF ADVERSE REACTIONS IN ≥ 10% OF ADULT AND PEDIATRIC PATIENTS WERE GRADE 1 OR 2[1]

Adverse Reactions Occurring in ≥ 10% of patients treated with VITRAKVI®[1]

ADVERSE REACTION[a]	VITRAKVI (N=279)	
	ALL GRADES[b] (%)	GRADES 3-4[c] (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE		
Musculoskeletal pain[d]	42	3.9
Muscular weakness	10	0.7
GENERAL		
Fatigue[e]	36	2.5
Pyrexia	24	1.8
Edema[f]	19	0.7
RESPIRATORY, THORACIC, AND MEDIASTINAL		
Cough[g]	32	0.4
Dyspnea[h]	17	3
Upper respiratory tract infection	13	0
Nasal congestion	11	0
NERVOUS SYSTEM		
Dizziness[i]	27	1.1
Headache	15	0.4
Cognitive impairment[j]	11	2.5
GASTROINTESTINAL		
Constipation	27	0.4
Diarrhea	27	1.4
Nausea	25	0.7
Vomiting	25	0.7
Abdominal pain[k]	21	2.2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash[l]	19	0.4
PSYCHIATRIC		
Mood disorders[m]	14	0.4
Sleep disturbance[n]	10	0
INVESTIGATIONS		
Increased weight	14	3.6
METABOLISM AND NUTRITION		
Decreased appetite	12	1.4
INFECTIONS AND INFESTATIONS		
Urinary tract infection[o]	12	1.4

Low incidence of Grade 3 or 4 adverse reactions occurring in ≥ 10% of patients[1]

- **9%** of patients permanently discontinued treatment due to adverse reactions[1]

NO CARDIAC MONITORING REQUIRED WITH VITRAKVI.[1]

Obtain liver function tests (ALT,[p] AST,[p] ALP,[p] and bilirubin) before initiation of treatment and every 2 weeks during the first 2 months of treatment, then monthly thereafter or more frequently following the occurrence of Grade 2 or greater AST or ALT elevation.[1]

Clinically relevant adverse reactions occurring in ≤10% of patients include fractures (8%).

The safety of VITRAKVI was evaluated in 279 patients, irrespective of *NTRK*[p] gene fusion status, in 3 clinical trials.[1]

To learn more about laboratory abnormalities, please see Table 4 in the Prescribing Information.

[a]The adverse reaction identifies a composite term.
[b]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.
[c]One Grade 4 adverse reaction of pyrexia.
[d]Includes: arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, noncardiac chest pain, and pain in extremity.
[e]Includes: fatigue, asthenia.
[f]Includes: face edema, generalized edema, lip edema, localized edema, edema, edema genital, edema peripheral, periorbital edema, and swelling.
[g]Includes: cough, productive cough, and upper-airway cough syndrome.
[h]Includes: dyspnea and dyspnea exertional.
[i]Includes: dizziness, dizziness postural, and vertigo.
[j]Includes: amnesia, aphasia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, memory impairment, mental impairment, and mental status changes.
[k]Includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
[l]Includes: dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative generalized, eczema, eczema asteatotic, palmar-plantar erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, and rash pustular.
[m]Includes: agitation, anxiety, depression, depressed mood, euphoric mood, and irritability.
[n]Includes: insomnia, sleep disorder, and somnolence.
[o]Includes: cystitis, escherichia urinary tract infection, pyelonephritis acute, and urinary tract infection.
[p]ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; *NTRK*, neurotrophic receptor tyrosine kinase.

Please see Important Safety Information throughout and click here for full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

ORAL DOSING WITH 2 FORMULATIONS[1]

Available in capsules and an oral solution for both adults and children[1]

100-mg and 25-mg capsules[1]

20-mg/mL oral solution[1]

- VITRAKVI® capsules and oral solution may be used interchangeably[1]

VITRAKVI® (larotrectinib) is taken twice daily[1]

VITRAKVI can be taken with or without food[1]

Adult[1]

- 100 mg taken orally twice daily, until disease progression or until unacceptable toxicity

Pediatric[1]

- **Recommended dosage in pediatric patients with body surface area of ≥1.0 m^2:** 100 mg taken orally twice daily until disease progression or until unacceptable toxicity
- **Recommended dosage in pediatric patients with body surface area <1.0 m^2:** 100 mg/m^2 taken orally twice daily until disease progression or until unacceptable toxicity

Important Safety Information (continued)

- **Hepatotoxicity (continued):** In patients who received VITRAKVI, increased AST of any grade occurred in 52% of patients and increased ALT of any grade occurred in 45%. Grade 3-4 increased AST or ALT occurred in 3.1% and 2.5% of patients, respectively. The median time to onset of increased AST was 2.1 months (range: 1 day to 4.3 years). The median time to onset of increased ALT was 2.3 months (range: 1 day to 4.2 years). Increased AST and ALT leading to dose modifications occurred in 1.4% and 2.2% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 3 (1.1%) of patients.
  There have been reports in adult patients from clinical studies and post-marketing cases of Grade ≥ 2 increases in ALT and/or AST with increases in bilirubin ≥ 2 x ULN.
  Obtain liver function tests (ALT, AST, ALP and bilirubin) before initiation of VITRAKVI and monitor every 2 weeks during the first two months of treatment, then monthly thereafter, or more frequently following the occurrence of Grade 2 or greater AST or ALT elevation.
  Temporarily withhold, reduce the dose, or permanently discontinue VITRAKVI based on severity.
- **Embryo-Fetal Toxicity:** VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the last dose of VITRAKVI.

Adverse Reactions

- The most common adverse reactions (≥20%), including laboratory abnormalities, were: increased AST (52%), increased ALT (45%), anemia (42%), musculoskeletal pain (42%), fatigue (36%), hypoalbuminemia (36%), neutropenia (36%), increased alkaline phosphatase (34%), cough (32%), leukopenia (28%), constipation (27%), diarrhea (27%), dizziness (27%), hypocalcemia (25%), nausea (25%), vomiting (25%), pyrexia (24%), lymphopenia (22%) and abdominal pain (21%).

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VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

RECOMMENDED DOSE MODIFICATIONS

Recommended dose reductions for adverse reactions[1]

DOSE REDUCTIONS	ADULT AND PEDIATRIC PATIENTS WITH BODY SURFACE AREA OF 1 m^2 OR GREATER	PEDIATRIC PATIENTS WITH BODY SURFACE AREA <1 m^2
1st Dose Reduction	75 mg twice daily	75 mg/m^2 twice daily
2nd Dose Reduction	50 mg twice daily	50 mg/m^2 twice daily
3rd Dose Reduction	100 mg once daily	25 mg/m^2 twice daily[a]

[a]Pediatric patients on 25 mg/m^2 orally twice daily should remain on this dosage even if body surface area becomes greater than 1 m^2 during the treatment. Maximum dose should be 25 mg/m^2 orally twice daily at the third dosage modification.

For Grade 2 and higher liver function test abnormalities, refer to the Recommended Dose Modifications for Hepatotoxicity table below.[1]

- For Grade 3 or 4 adverse reactions[1]:
  - Withhold VITRAKVI until adverse reaction resolves or improves to baseline or Grade 1. Resume at the next lower dose if resolution occurs within 4 weeks
  - Permanently discontinue VITRAKVI if an adverse reaction does not resolve within 4 weeks
  - Permanently discontinue VITRAKVI in patients who are unable to tolerate VITRAKVI after 3 dose modifications[1]
- For CTCAE[b] Grade 2 ALT[b] and/or AST[b] elevation, monitor liver function frequently as clinically indicated to establish whether a dose interruption or reduction is required.[1]

Recommended Dose Modifications for Hepatotoxicity[1]

SEVERITY[c]	DOSAGE MODIFICATION
AST or ALT ≥5 x ULN with bilirubin ≤2 x ULN[b]	• Withhold VITRAKVI until recovery to ≤ Grade 1 or return to baseline • Resume VITRAKVI at the next lower dose level • Permanently discontinue if a Grade 4 AST and/or ALT elevation occurs after resuming VITRAKVI
AST or ALT >3 x ULN with total bilirubin >2 x ULN in the absence of alternative causes	• Permanently discontinue VITRAKVI

[b]ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; ULN, upper limit of normal.
[c]Grading defined by NCI[b]-CTCAE version 4.03.[1]

Dose modification for coadministration with strong or moderate CYP3A4 inhibitors or inducers[1]

- Avoid coadministration of strong CYP3A4 inhibitors with VITRAKVI. If coadministration of a strong CYP3A4 inhibitor cannot be avoided, reduce the VITRAKVI dose by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the VITRAKVI dose taken prior to initiating the CYP3A4 inhibitor. For coadministration with moderate CYP3A4 inhibitors, monitor for adverse reactions more frequently and reduce the dosage based on severity of emergent adverse reactions
- Avoid coadministration of strong CYP3A4 inducers with VITRAKVI. If coadministration of a strong CYP3A4 inducer cannot be avoided, double the VITRAKVI dose. After the inducer has been discontinued for 3 to 5 elimination half-lives, resume the VITRAKVI dose taken prior to initiating the CYP3A4 inducer. For coadministration with moderate CYP3A4 inducers, modify dose as recommended

Dose modifications for patients with hepatic impairment[1]

- Reduce the starting dose of VITRAKVI by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment

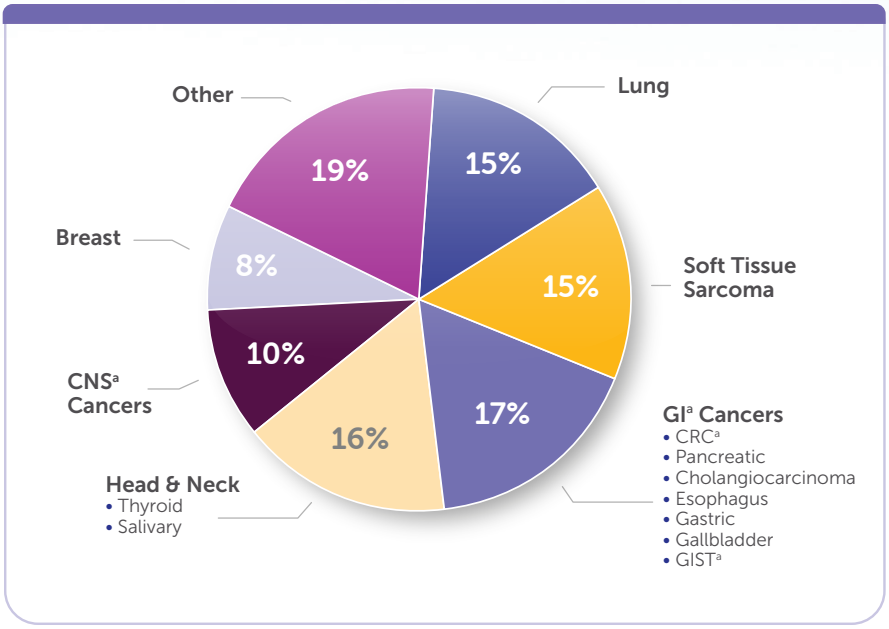
References: 1. VITRAKVI [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; November 2023. **2.** Data on file. Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ. **3.** Hechtman JF, Benayed R, Hyman DM, et al. Pan-Trk immunohistochemistry is an efficient and reliable screen for the detection of NTRK fusions. *Am J Surg Pathol.* 2017;41(11):1547-1551. **4.** Park HS, Park S-J, Kim JY, et al. Next-generation sequencing of BRCA1/2 in breast cancer patients: potential effects on clinical decision-making using rapid, high-accuracy genetic results. *Ann Surg Treat Res.* 2017;92(5):331-339.

Please see Important Safety Information throughout and click here for full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

TEST EARLY AND COMPREHENSIVELY TO UNCOVER ACTIONABLE ONCOGENIC DRIVERS, INCLUDING *NTRK*[a] GENE FUSIONS[1,3]

VITRAKVI® has been prescribed in >20 tumor types as of December 2023[2]



[a]CNS, central nervous system; CRC, colorectal cancer; FDA, United States Food and Drug Administration; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; NGS, next-generation sequencing, *NTRK*, neurotrophic receptor tyrosine kinase.

Test for *NTRK* gene fusions as part of your broad molecular testing

NGS

NGS[a] allows for efficient multiplex testing, with the ability to find *NTRK* gene fusions as well as other key oncogenic drivers.[3,4]

FDA[a]-approved *NTRK* gene fusion companion diagnostic test

Select patients for treatment with VITRAKVI based on the presence of an NTRK gene fusion in tumor specimens as detected by an FDA-approved test. Information on FDA-approved tests is available at www.fda.gov/companiondiagnostics.[1]

Important Safety Information (continued)

Drug Interactions

- Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John's wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs. For coadministration with moderate CYP3A4 inhibitors, monitor for adverse reactions more frequently and reduce the dosage based on severity. For coadministration with moderate CYP3A4 inducers, modify dose as recommended.

Please see Important Safety Information throughout and click here for full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

THE TRK* INHIBITOR WITH AN mDOR[a] OF NEARLY 3 YEARS[1]

In *NTRK*[a] gene fusion–positive solid tumors, inhibit what's driving the tumor with VITRAKVI® (larotrectinib) for:

DEMONSTRATED DURABILITY[1]

mDOR of 32.9 months[b]

(95% CI: 14.8, NE[a])
(n=41/55; range: 1.6+ to 50.6+ months)

ROBUST RESPONSES[1]

75% ORR[a]
(95% CI: 61%, 85%; n=41/55)

25% CR[a,c] (n=14/55) | **49% PR[a]** (n=27/55)

Study design: Pooled efficacy analysis based on 3 open-label, single-arm clinical studies in adult and pediatric patients with unresectable or metastatic solid tumors with an *NTRK* gene fusion.[1]

Indication

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Find the oncogenic driver early and act with VITRAKVI for appropriate patients.

Select Safety Information

Serious adverse events occurred with VITRAKVI treatment. Warnings and precautions include central nervous system effects, skeletal fractures, hepatotoxicity, and embryo-fetal toxicity. The most common adverse reactions (≥20%), including laboratory abnormalities, were: increased AST[a] (52%), increased ALT[a] (45%), anemia (42%), musculoskeletal pain (42%), fatigue (36%), hypoalbuminemia (36%), neutropenia (36%), increased alkaline phosphatase (34%), cough (32%), leukopenia (28%), constipation (27%), diarrhea (27%), dizziness (27%), hypocalcemia (25%), nausea (25%), vomiting (25%), pyrexia (24%), lymphopenia (22%) and abdominal pain (21%).[1]

+ denotes ongoing response.[1]
*TRK, tropomyosin receptor kinase.
[a]ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete response; mDOR, median duration of response; NE, not evaluable; *NTRK*, neurotrophic receptor tyrosine kinase; ORR, overall response rate; PR, partial response.
[b]Kaplan-Meier estimate.
[c]5% were pathological complete response. Patients undergoing a surgical resection whose post-operative pathologic assessment showed no viable tumor cells and negative margins were pathological complete responders provided that no other sites of disease were present.

Important Safety Information (continued)

Use in Specific Populations

- Lactation: Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the last dose.

Please see Important Safety Information throughout and click here for full Prescribing Information.

PP-VIT-US-1433-1 11/2024

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION