אוקטובר 2024

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון:

Vitrakvi 25 mg capsules
Vitrakvi 100 mg capsules
Vitrakvi 20 mg/ml oral solution
Larotrectinib (as sulfate) 25 mg, 100 mg, 20 mg/ml

אנו מבקשים להודיעכם שהעלונים לרופא של התכשירים שבנדון עודכנו.

ההתוויה המאושרת לתכשיר:
Vitrakvi as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,
• Who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
• Who have no satisfactory treatment options

בהודעה זו כלולים העידכונים המהותיים בלבד, בפירוט שלהלן מופיע, רק המידע שהתעדכן. תוספת טקסט מודגש בצבע אדום ומסומן בקו תחתון.
המידע במלואו מופיע בעלונים לרופא אשר נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug
כמו כן, ניתן לקבלם מודפסים ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700

בברכה,
באייר ישראל

העדכונים בעלון לרופא:

4.7 Effects on ability to drive ~~or~~and use machines

VITRAKVI has a moderate influence on the ability to drive and use machines. Dizziness and fatigue have been reported in patients receiving larotrectinib, mostly grade 1 and 2 during the first 3 months of treatment. This may influence the ability to drive and use machines during this time period. Patients should be advised not to drive and use machines, until they are reasonably certain VITRAKVI therapy does not affect them adversely (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were increased ALT (35%), increased AST (~~31~~32%), vomiting (~~28~~29%),anaemia (~~27~~28%), constipation (27%), diarrhoea (~~25~~26%), nausea (23%), fatigue (22%), and dizziness (20%).
The majority of adverse reactions were grade 2 or 3. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (2%) ALT increased (1%) , AST increased, leucocyte count decreased, platelet count decreased, muscular weakness and blood alkaline phosphatase increased (each in <1%).The highest reported grade was grade 3 for adverse reactions anaemia (~~7~~6%),

weight increased (4%), diarrhoea (3%), gait disturbance and vomiting (each 1%), and fatigue, dizziness, paraesthesia, nausea, myalgia, and constipation~~vomiting~~ (each in < 1%).

Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions occurred in 2% of patients (2 cases each of neutrophil count decreased, ~~1 case each of~~ALT increased, and AST increased, 1 case each of gait disturbance, ~~vomiting~~and muscular weakness~~, fatigue, and nausea~~). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

Tabulated list of adverse reactions

The safety of VITRAKVI was evaluated in ~~335~~361 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 ("NAVIGATE"), and 3 ("SCOUT") and post-marketing. The safety population, characteristics were comprised of patients with a median age of 39.0 years (range: 0~~.1~~, 90) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=~~335~~361) was ~~14.5~~13.1 months (range: 0.1~~0~~, 7~~65~~.4~~2~~).
The adverse drug reactions reported in patients (n=~~335~~361) treated with VITRAKVI are shown in Table 2 and Table 3.

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Table 2: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population n=~~335~~361) and post-marketing

System organ class	Frequency	All grades	Grades 3 and 4
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	
	Common	Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia)[a] Leukocyte count decreased (Leukopenia)[a, b]
	Uncommon		~~Leukocyte count decreased (Leukopenia)[a, b]~~ Platelet count decreased (Thrombocytopenia)[a,b]
Nervous system disorders	Very common	Dizziness	
	Common	Gait disturbance Paraesthesia	Gait disturbance
	Uncommon		Dizziness Paraesthesia
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	
	Common	Dysgeusia[c]	Diarrhoea
	Uncommon		Vomiting Nausea Constipation
Hepatobiliary	Not known	Liver injury[d]	~~Liver injury[a]~~

disorders			
Musculoskeletal and connective tissue disorders	Very common	Myalgia	
	Common	Muscular weakness	
	Uncommon		Myalgia Muscular weakness[a, b]
General disorders and administration site conditions	Very common	Fatigue	
	Uncommon		Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)	
	Common	Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased[a] Aspartate aminotransferase (AST) increased[a] Weight increased (Abnormal weight gain)
	Uncommon		Blood alkaline phosphatase increased[a, b]

Table 3: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=~~124~~135); all grades

System organ class	Frequency	Infants and toddlers (n=~~42~~43)[a]	Children (n=~~59~~67)[b]	Adolescents (n=~~23~~25)[c]	Paediatric patients (n=~~124~~135)
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)

	Common		Platelet count decreased (Thrombocytopenia)	Platelet count decreased (Thrombocytopenia)	
Nervous system disorders	Very common			Dizziness	
	Common	Dizziness	Dizziness Paraesthesia Gait disturbance	Paraesthesia Gait disturbance	Dizziness Paraesthesia Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea
	Common		Dysgeusia		Dysgeusia
Musculoskeletal and connective tissue disorders	Very common		Myalgia	Myalgia	Myalgia
	Common		Muscular weakness	Muscular weakness	~~Myalgia~~ Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	Fatigue	Fatigue	Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline Phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased
	~~Common~~		~~Blood alkaline phosphatase increased~~	~~Weight increased (Abnormal weight gain)~~	

[a] Infant/toddlers (28 days to 23 months): 5 grade 4 Neutrophil count decreased (Neutropenia) reactions and 2 Blood alkaline phosphatase increased reported. Grade 3 reactions included ~~1~~2~~1~~1 cases of Neutrophil count decreased (Neutropenia), 4 cases of ALT increased, 3 cases each of Anaemia,~~ALT increased~~ and Weight increased (Abnormal weight gain), and 2 cases each of Blood alkaline phosphatase increased, Diarrhoea, and Vomiting and 1 case of AST increased.

[b] Children (2 to 11 years): 1 grade 4 Leucocytes count decreased reported. ~~6~~8 reported grade 3 cases of Neutrophil count decreased (Neutropenia), 2 cases each of Anaemia, ~~and~~Diarrhoea, and Vomiting and 1 case each of ALT increased, AST increased, Gait disturbance, ~~Vomiting~~Weight increased (Abnormal weight gain), Paraesthesia and Myalgia

[c] Adolescents (12 to <18 years): no grade 4 reactions were reported. Grade 3 reactions were reported in 1 case each of ALT increased, AST increased, Fatigue, Gait disturbance, and Muscular weakness.

Description of selected adverse reactions

Neurologic reactions

In the overall safety database (n=~~335~~361), the maximum grade neurologic adverse reaction observed was grade 3 or 4 which was observed in 10 (3%) patients and included gait disturbance (4 patients, 1%), dizziness (3 patients, <1%), and paraesthesia (3 patients, <1%). The overall incidence was 20% for dizziness, ~~7~~6% for paraesthesia and 5% for gait disturbance. Neurologic reactions leading to dose modification or interruptions included dizziness (~~<~~1%),gait disturbance (<1%), and paraesthesia (<1%). One patient permanently discontinued the treatment due to grade 3 gait disturbance. In all cases except of one, patients with evidence of anti-tumour activity who required a dose reduction were able to continue dosing at a reduced dose and/or schedule (see section 4.4).

Hepatotoxicity

Abnormalities of liver function tests including ALT, AST, ALP and bilirubin have been observed in patients treated with VITRAKVI.

In the overall safety database (n=~~335~~361), the maximum grade transaminase elevation observed was grade 4 ALT increase in ~~6~~7 patients (2%) and AST increase in ~~3~~4 patients (1%). Grade 3 ALT and AST increases in ~~17~~25 (~~5~~7%) and ~~16~~22 (~~5~~6%) of patients, respectively. Majority of grade 3 elevations were transient appearing in the first three months of treatment and resolving to grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in ~~34~~35 (10%) and 32 (~~10~~9%) of patients, respectively, and grade 1 ALT and AST increases were observed in ~~157~~173 (~~47~~48%) and ~~157~~177 (~~47~~49%) of patients, respectively.

ALT and AST increases leading to dose modifications or interruptions occurred in ~~13~~24 (~~5~~7%) patients and ~~12~~21 (~~5~~6%) patients, respectively (see section 4.4). ~~One~~Two patients permanently discontinued the treatment with 1 patient due to grade 3~~4~~ ALT and grade 3 AST increases.

Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported in adult patients. In some cases, the dose of VITRAKVI was withheld and restarted at a reduced dose, while in other cases treatment was permanently discontinued (see section 4.4).

Additional information on special populations

Paediatric patients

Of the ~~335~~361 patients treated with VITRAKVI, ~~124~~135 (37%) patients were from birth to <18 years of age (n=13 from birth to < 3 months, n=4 ≥ 3 months to < 6 months, n=17 ≥ 6 months to < 12 months, n=~~8~~9≥ 12 months to < 2 years, n=~~27~~31 ≥ 2 years to < 6 years, n=~~32~~36 ≥ 6 years to < 12 years, n= ~~23~~25 ≥ 12 years to < 18 years). The majority of adverse reactions were grade 1 or 2 in severity and were resolved without VITRAKVI dose modification or discontinuation. Adverse reactions of grade 3 or 4 in severity were generally observed more frequently in patients < 6 years of age. They were reported in 69% of patients from birth to < 3 months and in ~~48~~44% of patients ≥ 3 months to < 6 years. Decreased neutrophil count has been reported to have led to study drug discontinuation, dose modification and dose interruption.

Elderly

Of the ~~335~~361 patients in the overall safety population who received VITRAKVI, ~~65~~69 (19%) patients were 65 years or older and ~~20~~22 (6%) patients were 75 years or older. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients. The adverse reaction dizziness (~~32~~30% versus 28% in all adults), anaemia (~~32~~35% versus ~~25~~27% in all adults), diarrhoea (25% versus 22% in all adults), muscular weakness (~~14~~13% versus ~~11~~10% in all adults), platelet count decreased (12% versus 6% in all adults), ~~and~~gait disturbance (~~8~~9% versus 5% in all adults), and dysgeusia (9% versus 6% in all adults) were more frequent in patients of 65 years or older.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Clinical efficacy

Overview of studies

The efficacy and safety of VITRAKVI were studied in three multicentre, open-label, single-arm clinical studies in adult and paediatric cancer patients (Table 4). The studies are still ongoing Patients with and without documented *NTRK* gene fusion were allowed to participate in Study 1 and Study 3 ("SCOUT"). Patients enrolled to Study 2 ("NAVIGATE") were required to have TRK fusion-positive cancer. The pooled primary analysis set of efficacy includes ~~272~~302 patients with TRK fusion-positive cancer enrolled across the three studies that had measurable disease assessed by RECIST v1.1, a non-CNS primary tumour and received at least one dose of larotrectinib as of July ~~2022~~2023. These patients were required to have received prior standard therapy appropriate for their tumour type and stage of disease or who, in the opinion of the investigator, would have had to undergo radical surgery (such as limb amputation, facial resection, or paralysis causing procedure), or were unlikely to tolerate, or derive clinically meaningful benefit from available standard of care therapies in the advanced disease setting. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC). In addition, ~~41~~55 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 ("NAVIGATE") and in Study 3 ("SCOUT"). Forty of the ~~41~~55 primary CNS tumour patients had received prior cancer treatment (surgery, radiotherapy and/or previous systemic therapy). Tumour responses were assessed by the investigator using RANO or RECIST v1.1 criteria.

Identification of *NTRK* gene fusions relied on tissue samples for the molecular test methods: next generation sequencing (NGS) used in ~~276~~320 patients, polymerase chain reaction (PCR) used in 14 patients, fluorescence *in situ* hybridization (FISH) used in 18 patients, and other testing methods (Sequencing, Nanostring, Sanger sequencing, or Chromosome Microarray) used in 5 patients.

Table 4: Clinical studies contributing to the efficacy analyses in solid and primary CNS tumours

Study name, design and patient population	Dose and formulation	Tumour types included in efficacy analysis	n
Study 1 NCT02122913 • Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours with an *NTRK* gene fusion • Adult patients (≥ 18 years) with advanced solid tumours with an *NTRK* gene fusion	Doses up to 200 mg once or twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Thyroid (n=4) Salivary gland (n=3) GIST (n=2)[a] Soft tissue sarcoma (n=2) NSCLC (n=1)[b],[c] Unknown primary cancer (n=1)	13
Study 2 "NAVIGATE" NCT02576431 • Phase 2 multinational, open label, tumour "basket" study • Adult and paediatric patients ≥ 12 years with advanced solid tumours with an *NTRK* gene fusion	100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	NSCLC (n=29)[b, c] Soft tissue sarcoma (n=~~27~~28) Thyroid (n=~~25~~26)[b] ~~NSCLC (n=24)[b, c]~~ Salivary gland (n=~~22~~24) Colon (n=~~22~~24) Primary CNS (n=~~15~~19) Melanoma (n=~~8~~10)[b] Breast, non-secretory (n=9)[b] Pancreas (n=~~6~~7) ~~Breast, non-secretory (n=6)[b]~~ Breast, secretory (n=~~4~~5) Cholangiocarcinoma (n=4) GIST (n=3)[a] Gastric (n=3) Prostate (n=2) Appendix, Atypical carcinoid lung cancer, Bone sarcoma , Cervix, Hepatic[e] Duodenal, External auditory canal[b],~~Gastric,~~ Oesophageal, SCLC[b, d], Rectal, Testes[b], Thymus, Unknown primary cancer, Urothelial, Uterus (n=1 each)	~~179~~ 208
Study 3 "SCOUT" NCT02637687 • Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours with an *NTRK*	Doses up to 100 mg/m^2 twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Infantile fibrosarcoma (n=49) Soft tissue sarcoma (n=~~39~~42)[b] Primary CNS (n=~~26~~36) Congenital mesoblastic nephroma (n=2)	~~121~~ 136

gene fusion, including locally advanced infantile fibrosarcoma • Paediatric patients from birth ~~>1 month~~ to 21 years with advanced cancer or with primary CNS tumours		Bone sarcoma (n=2) ~~Thyroid (n=1), melanoma (n=1)~~ Breast, secretory, Cervix, Lipofibromatosis, Melanoma, Thyroid (n=1 each)	
Total number of patients (n)*			~~313~~ 357

* consist of ~~272~~302 patients with IRC tumour response assessment and ~~41~~55 patients with primary CNS tumours (including astrocytoma, ganglioglioma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, and primitive neuro-ectodermal tumour, not specified) with investigator tumour response assessment

[a] GIST: gastrointestinal stromal tumour

[b] brain metastases were observed in some patients in the following tumour types: lung (NSCLC, SCLC), thyroid, melanoma, breast (non-secretory) , external auditory canal, ~~and~~soft tissue sarcoma and testes

[c] NSCLC: non-small cell lung cancer

[d] SCLC: small cell lung cancer

[e] hepatocellular carcinoma

Baseline characteristics for the pooled ~~272~~302 patients with solid tumours with an *NTRK* gene fusion were as follows: median age ~~41~~44 years (range 0-90 years); ~~35~~33% < 18 years of age, and ~~65~~67% ≥ 18 years; ~~57~~55% white and ~~49~~47% male; and ECOG PS 0-1 (~~89~~88%), 2 (~~9~~10%), or 3 (2%). Ninety-twoone percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. Of these, ~~72~~71% had received prior systemic therapy with a median of 1 prior systemic treatment regimen. Twenty-six percent of all patients had received no prior systemic therapy. Of those ~~272~~302 patients the most common tumour types represented were soft tissue sarcoma (~~25~~24%), infantile fibrosarcoma (1816%), lung cancer (11%), thyroid cancer (~~11~~10%), ~~lung cancer (10%), and~~ salivary gland tumour (9%) and colon cancer (8%).
Baseline characteristics for the ~~41~~55 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 11 years (range 0~~1~~-79 years); ~~28~~38 patients < 18 years of age, and ~~13~~17 patients ≥ 18 years, and ~~28~~36 patients white and ~~20~~27 patients male; and ECOG PS 0-1 (~~36~~47 patients), or 2 (~~4~~5 patients). ~~Forty~~Fifty-two (~~98%~~95%) patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. There was a median of 1 prior systemic treatment regimen received.

Efficacy results
The pooled efficacy results for overall response rate, duration of response and time to first response, in the primary analysis population (n=~~272~~302) and with post-hoc addition of primary CNS tumours (n=~~41~~55) resulting in the pooled population (n=~~313~~357), are presented in Table 5 and Table 6.

Table 5: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

Efficacy parameter	Analysis in solid tumours excluding primary CNS tumours (n=~~272~~302)[a]	Analysis in solid tumours including primary CNS tumours (n=~~313~~357)[a, b]
Overall response rate (ORR) % (n) [95% CI]	~~67~~65% (~~182~~195) [~~61~~59, ~~72~~70]	~~61~~59% (~~191~~210) [~~55~~54, ~~66~~64]
Complete response (CR)	~~23~~22% (~~62~~65)	~~20~~19% (~~63~~68)
Pathological complete response[c]	~~5~~6% (~~13~~17)	~~4~~5% (~~17~~3)
Partial response (PR)	~~39~~37% (113)	~~37~~35% (~~115~~125)
Time to first response (median, months) [range]	1.84 [0.89, 22.90]	1.84 [0.89, 22.90]
Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months % with duration ≥ 36 months % with duration ≥ 48 months	43.3 [0.0+, ~~65.4~~73.7+] ~~80~~79% ~~66~~67% ~~54~~55% 48%	43~~1~~.~~5~~3 [0.0+, ~~65.4~~73.7+] 78~~9~~% 65~~4~~% 54~~2~~% 47%

+ denotes ongoing

[a] Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (~~272~~302 patients).

[b] Investigator assessment using either RANO or RECIST v1.1 criteria for primary CNS tumours (~~41~~55 patients).

[c] A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumour cells and negative margins on post-surgical pathology evaluation. The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v.1.1

Table 6: Overall response rate and duration of response by tumour type*

Tumour type	Patients (n=3573 13)	ORR[a]		DOR			
		%	95% CI	months			Range (months)
				≥ 12	≥ 24	≥ 36	
Soft tissue sarcoma	6872	68%	5556%, 7879%	8480 %	7072 %	4955%	0.03+, 65.572.7
Primary CNS	55	27%	16%, 41%	63%	32%	32%	5.8, NE
Infantile fibrosarcoma	49	9294%	8083%, 9899%	8081 %	6064 %	5355%	1.6+, 64.273.7+
Lung	32	66%	47%, 81%	73%	59%	47%	1.9+, 56.2+
Thyroid	3031	6365%	4445%, 8081%	8985 %	6563 %	54%	3.7, 64.372.4+
Salivary gland	2527	8481%	6462%, 9594%	90%	86%	7475 %	7.45.5, 65.359.1+
Colon	1824	5046%	26%, 674%	816 %	816%	403%	5.23.9, 39.445.2+
Breast	115						
Non-secretory[c]	69	5033%	127% 8870%	67%	67% NR	NR 67%	7.4 45.312.5+
Secretory[b]	56	803%	3628%, 10099%	75 80%	75 80%	NR80%	11.1, 31.5 58.2+
Melanoma	911	445%	174% 779%	50%	NR	NR	1.9+, 23.2+
Pancreas	67	147	0%, 5864%	0%	0%	0%	5.8, 5.8
Gastrointestinal stromal tumour	5	80%	28%, 99%	75%	38%	38%	9.5, 50.4+
Bone sarcoma	3	33%	1%, 91%	0%	0%	0%	9.5, 9.5
Congenital mesoblastic nephroma	2	100%	16%, 100%	100 %	100%	50100%	29.432.9, 44.5
Cervix	2	50%	1%, 99%	NR	NR	NR	2.1+, 2.1+
Unknown primary cancer	2	100%	16%, 100%	0	0	0	5.6, 7.4
External auditory canal	1	100%	3%, 100%	100 %	100%	NR	33.8+, 33.8+

DOR: duration of response
NE: not evaluable
NR: not reached
* no data are available for the following tumour types: cholangiocarcinoma (n=4); gastric (n=3); prostate unknown primary cacner(n=2 each); appendix, cervixhepatic, duodenal,external auditory canal lipofibromatosisgastric, oesophageal, rectal, testes, thymus, urothelial, uterus (n=1 each)
+ denotes ongoing response
[a] evaluated per independent review committee analysis by RECIST v1.1 for all tumour types except patients with a primary CNS tumour who were evaluated per investigator assessment using either RANO or RECIST v1.1 criteria
b with 3 complete, 2 partial response

[c] with 1 complete, 2 partial response

Due to the rarity of TRK fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

In the adult sub-population (n=~~178~~220), the ORR was ~~58~~50%. In the paediatric sub-population (n=~~94~~137), the ORR was ~~84~~72%.

In ~~238~~247 patients with wide molecular characterisation before larotrectinib treatment, the ORR in ~~218~~117 patients who had other genomic alterations in addition to *NTRK* gene fusion was ~~52~~54%, and in ~~110~~130 patients without other genomic alterations ORR was ~~7~~68%.

Pooled primary analysis set

The pooled primary analysis set consisted of ~~272~~302 patients and did not include primary CNS tumours. Median time on treatment before disease progression was ~~19.6~~14.4 months (range: 0.1~~0~~ to ~~75.2~~87.4 months) based on July ~~2022~~2023 cut-off. Fifty-three~~seven~~ percent of patients had received VITRAKVI for 12 months or more, 3~~6~~4% had received VITRAKVI 24 months or more, and 2~~4~~1% had received VITRAKVI 36 months or more, with follow-up ongoing at the time of the analysis.
At the time of analysis, the median duration of response is 43.3 months (range: 0.0+ to 73.7+), an estimated ~~80~~79% [95% CI: 72~~4~~, 85~~6~~] of responses lasted 12 months or longer, ~~66~~67% [95% CI: ~~58~~60, 74] of responses lasted 24 months or longer, and 55~~1~~% [95% CI:47~~2~~, 64~~0~~] of responses lasted 36 months or longer. Eighty-three~~six~~ percent (83~~6~~%) [95% CI: ~~82~~79, ~~90~~87] of patients treated were alive one year after the start of therapy 74~~7~~% [95% CI: ~~72~~68, ~~82~~79] after two years after the start of therapy, and ~~72~~70% [95% CI: ~~66~~64, ~~78~~75] after three years with the median for overall survival not yet being reached. Median progression free survival was ~~30~~28.1 months at the time of the analysis, with a progression free survival rate of ~~65~~62% [95% CI: ~~59~~56, ~~71~~68] after 1 year 54~~6~~% [95% CI: ~~49~~48, 60~~2~~] after 2 years, and 43% [95% CI: 37~~6~~, 50] after 3 years.
The median change in tumour size in the pooled primary analysis set was a decrease of ~~79~~65%.

Patients with primary CNS tumours

At the time of data cut-off, of the ~~41~~55 patients with primary CNS tumours confirmed response was observed in ~~9~~15 patients (~~22~~27%) with ~~1~~3 of the ~~41~~55 patients (~~2~~5%) being complete responders and ~~8~~12 patients (~~20~~22%) being partial responders. Further ~~20~~24 patients (~~49~~44%) had stable disease. Twelve patients (~~29~~22%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.~~7~~2 to ~~50~~62.9 months and was ongoing in ~~13~~16 out of ~~41~~55 patients with ~~one~~15 of these patients receiving post-progression treatment.