Entrectinib (Rozlytrek®) as monotherapy for the treatment of solid tumours with a NTRK gene fusion

General information

Drug description [1]

Entrectinib (Rozlytrek®) is an inhibitor of the tropomyosin receptor tyrosine kinases TRKA, TRKB and TRKC (encoded by the NTRK genes NTRK1, NTRK2 and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS (ROS1), and anaplastic lymphoma kinase (ALK).

Indication [2]

Rozlytrek® as monotherapy is indicated for the treatment of adult and paediatric patients older than one month with solid tumours that have a 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 not received a prior NTRK inhibitor
- ❖ who have no satisfactory treatment options.

Incidence [3]

- ❖ NTRK1, NTRK2, or NTRK3 fusions, encoding TRKA, TRKB, and TRKC, respectively, occur
  - at high frequency (>90%) in some rare paediatric tumours, including infantile fibrosarcoma, congenital mesoblastic nephroma, and secretory breast carcinoma;
  - at low frequency (5%-25%) in a subset of paediatric gliomas, gastrointestinal stromal tumours, melanoma, and papillary thyroid cancer; and
  - rarely (<5%) in most common tumours, including adenocarcinoma, gastrointestinal carcinoma, acute leukaemia, or soft tissue sarcoma, including inflammatory myofibroblastic tumours.

Current treatment

- ❖ Currently, no Onkopedia or ESMO guideline is available for treating solid tumours with a NTRK gene fusion.

Regulatory status

EMA [2]

Approval status for this indication: On 25 April 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Rozlytrek®.

The CHMP adopted a new pharmaceutical form, 50 mg film-coated granules, a new gastroenteral route of administration for the 100 and 200 mg hard capsules, and an extension to an existing indication for film-coated granules and hard capsules, as follows:

- ❖ Rozlytrek® as monotherapy is indicated for the treatment of adult and paediatric patients older than one month with solid tumours that have a 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 not received a prior NTRK inhibitor
  - who have no satisfactory treatment options.

Other indications:
Rozlytrek® as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

FDA [4, 5]

Approval status for this indication: On 20 October 2023, the FDA granted accelerated approval to entrectinib (Rozlytrek®) for paediatric patients older than one month with solid tumours that have a NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy.

The FDA also approved a new oral pellet formulation for entrectinib, and the prescribing information now includes instructions for making an oral suspension from the capsules.

- ✓ Indication is approved under accelerated approval based on the overall response rate and duration of response.
- ✓ Priority review
- ✓ Breakthrough designation
- ✓ Orphan drug designation

Other indications: Rozlytrek® is indicated for:

✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[1]	❖ Adult patients with ROS1-positive metastatic NSCLC as detected by an FDA-approved test.

Manufacturer

Rozlytrek® is manufactured by Roche.

Costs [6]

30 Rozlytrek® hard capsules 100 mg = € 772.50 (ex-factory price)

Posology [1]

- ❖ NTRK gene fusion-positive solid tumours
  - A validated assay is required for the selection of patients with NTRK gene fusion-positive solid tumours. NTRK gene fusion-positive status must be established prior to initiation of Rozlytrek® therapy.

Warnings and precautions [1]

- ❖ **Efficacy across tumour types**
  - The benefit of Rozlytrek® has been established in single-arm trials encompassing a relatively small sample of patients whose tumours exhibit NTRK gene fusions. Favourable effects of Rozlytrek® have been shown based on overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genomic alterations.
  - For these reasons, Rozlytrek® should only be used if there are no satisfactory treatment options (i.e., for which clinical benefit has not been established or where such treatment options have been exhausted).
- ❖ **Cognitive disorders**
  - Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with Rozlytrek®.
  - Patients over the age of 65 years experienced a higher incidence of these events than younger patients. Patients should be monitored for signs of cognitive changes.
  - Based on the severity of cognitive disorders, Rozlytrek® treatment should be modified as described in Product Information.
  - Patients should be counselled on the potential for cognitive changes with Rozlytrek® treatment. Patients should be instructed not to drive or use machines until symptoms resolve if they experience cognitive disorders.
- ❖ **Fractures**
  - Fractures have been reported in 25.0% of paediatric patients treated with Rozlytrek® in clinical trials.
  - Bone fractures mainly occurred in paediatric patients less than 12 years of age and were localised in the lower extremity (with a predilection for femur, tibia, foot and fibula). In both adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area. Thirteen paediatric patients had more than one occurrence of a fracture, and three paediatric patients had Rozlytrek treatment interrupted due to a fracture. The majority of fracture events experienced by the paediatric patients were resolved. Five paediatric patients discontinued treatment due to fractures.
  - Patients with signs or symptoms of fractures (e.g., pain, abnormal gait, changes in mobility, deformity) should be evaluated promptly.
- ❖ **Hyperuricemia**
  - Hyperuricemia has been observed in patients treated with entrectinib. Serum uric acid levels should be assessed prior to initiating Rozlytrek® and periodically during treatment. Patients should be monitored for signs and symptoms of hyperuricemia. Treatment with urate-lowering medicinal products should be initiated as clinically indicated, and Rozlytrek® withheld for signs and symptoms of hyperuricemia.
  - Rozlytrek® dose should be modified based on severity as described in Product Information.
- ❖ **Congestive heart failure (CHF)**

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- CHF has been reported in less than 5% of patients across clinical trials with Rozlytrek®. These reactions were observed in patients with or without a history of cardiac disease and resolved in 70% of those patients upon institution of appropriate clinical management and/or Rozlytrek® dose reduction/interruption.
- For patients with symptoms or known risk factors of CHF, left ventricular ejection fraction should be assessed prior to initiation of Rozlytrek® treatment. Patients receiving Rozlytrek® should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or oedema, should be evaluated and treated as clinically appropriate.
- Based on the severity of CHF, Rozlytrek® treatment should be modified as described in Product Information.

❖ **QTc interval prolongation**

- QTc interval prolongation has been observed in patients treated with Rozlytrek® in clinical trials.
- Use of Rozlytrek® should be avoided in patients with a baseline QTc interval longer than 450 ms, in patients with congenital long QTc syndrome, and in patients taking medicinal products that are known to prolong the QTc interval.
- Rozlytrek® should be avoided in patients with electrolyte imbalances or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias. If in the opinion of the treating physician, the potential benefits of Rozlytrek® in a patient with any of these conditions outweigh the potential risks, additional monitoring should be performed and a specialist consultation should be considered.
- Assessment of ECG and electrolytes at baseline and after 1 month of treatment with Rozlytrek® are recommended. Periodic monitoring of ECGs and electrolytes as clinically indicated throughout Rozlytrek® treatment, are also recommended.
- Based on the severity of QTc prolongation, Rozlytrek® treatment should be modified as described in Product Information.

❖ **Women of childbearing potential**

- Rozlytrek® may cause foetal harm when administered to a pregnant woman. Women of childbearing potential must use highly effective contraception methods during treatment and up to 5 weeks after the last dose of Rozlytrek®.
- Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment with Rozlytrek® and for 3 months after the last dose.

❖ **Drug interactions**

- Co-administration of Rozlytrek® with a strong or moderate CYP3A inhibitor increases entrectinib plasma concentrations, which could increase the frequency or severity of adverse reactions. In adult and paediatric patients 12 years and older, co-administration of Rozlytrek® with a strong or moderate CYP3A inhibitor should be avoided. For adult patients, if co-administration is unavoidable, the Rozlytrek® dose should be reduced.
- During treatment with Rozlytrek®, the consumption of grapefruit and grapefruit products should be avoided.
- Co-administration of Rozlytrek® with a strong or moderate CYP3A or P-gp inducer decreases entrectinib plasma concentrations, which may reduce efficacy of Rozlytrek®, and should be avoided.

❖ **Lactose intolerance**

- Rozlytrek® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

❖ **Sunset yellow FCF (E110)**

- Rozlytrek® 200 mg hard capsules contain sunset yellow FCF (E110), which may cause allergic reactions.

Study characteristics: STARTRK-NG trial [3, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
STARTRK-NG NCT02650401	43	**Phase 1:** Definition of MTD[2] **Phase 2:** MTD[3] was administered to patients enrolled in cohorts B-D[4]	-	**Phase 1:** RP2D based on toxicity; **Phase 2:** ORR in patients harbouring target	-	**ongoing**[5], multicentre, non-randomised, open-label, single-arm phase 1-2 trial	NTRK	F. Hoffmann-La Roche Ltd	STARTRK-NG [3]

[2] Patients were enrolled using a 3 + 3 design to evaluate up to 4 entrectinib doses (250, 400, 550, 750 mg/m^2).
[3] Daily entrectinib 550 mg/m^2 was established as the MTD in paediatric patients.

				fusions					

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline
❖ Disease status • Phase 1 portion (closed): Participants must have measurable or evaluable disease, as defined by RECIST v1.1 • Phase 2 portion: o Part B: Participants must have measurable or evaluable disease, as defined by RANO. o Part C (closed): Participants must have measurable or evaluable disease, as defined by RECIST v1.1 ± Curie Scale. o Part D: Participants must have measurable or evaluable disease, as defined by RECIST v1.1. o Part E (closed): Participants must have measurable or evaluable disease, as defined by RECIST v1.1 ± Curie Scale or RANO. ❖ Tumor type: • Phase 1 portion: Part A: Relapsed or refractory extracranial solid tumours • Phase 2 portion: o Part B: Primary brain tumours with NTRK1/2/3 or ROS1 gene fusions; gene fusions are defined as those predicted to translate into a fusion protein with a functional TRKA/B/C or ROS1 kinase domain, without a concomitant second oncodriver as determined by a nucleic acid-based diagnostic testing method. o Part D: Extracranial solid tumours (including NB) with NTRK1/2/3 or ROS1 gene fusions; gene fusions are defined as those predicted to translate into a fusion protein with a functional TRKA/B/C or ROS1 kinase domain without a concomitant second oncodriver as determined by a nucleic acid-based diagnostic testing method. ❖ Histologic/molecular diagnosis of malignancy at diagnosis or the time of relapse. ❖ Archival tumour tissue from diagnosis or, preferably, at relapse. ❖ Performance status: Lansky or Karnofsky score ≥ 60% and minimum life expectancy of at least 4 weeks. ❖ Prior therapy: Participants must have a disease that is locally advanced,	❖ Receiving other experimental therapy. ❖ Known congenital long QT syndrome. ❖ History of recent (3 months) symptomatic congestive heart failure or ejection fraction ≤50% at screening. ❖ Known active infections. ❖ Familial or personal history of congenital bone disorders, bone metabolism alterations or osteopenia. ❖ Enzyme-inducing antiepileptic drugs should be received within 14 days of the first dose. ❖ Prior treatment with approved or investigational TRK or ROS1 inhibitors. ❖ Known hypersensitivity to entrectinib or any of the other excipients of the investigational medicinal product. ❖ Patients with NB with bone marrow space-only disease. ❖ Incomplete recovery from acute effects of any surgery prior to treatment. ❖ Active gastrointestinal disease or other malabsorption syndromes that would impact drug absorption. ❖ Other severe acute or chronic medical or psychiatric conditions or lab abnormalities that may increase the risk associated with study participation drug administration or may interfere with the interpretation of study results.	❖ Median age, years: 7 (2 months-20 years) ❖ Female sex: 48.8% ❖ Race: • White: 86.0% • Black or African American: 11.6% • Other: 2.3% ❖ Ethnicity: • Hispanic or Latino: 9.3% • Non-Hispanic or Latino: 83.7% • Not stated: 2.3% • Unknown: 4.7% ❖ Karnofsky/Lansky score: • 60: 4.8% • 70: 4.8% • 80: 23.8% • 90: 31.0% • 100: 35.7% ❖ Prior systemic therapies: • Chemotherapy: 76.7% • Immunotherapy: 25.6% • Targeted therapy: 7.0% • Monoclonal antibody: 27.9% • Radiation: 55.8% ❖ Tumour type/histology: • Extracranial solid tumour: 27.9% • Infantile fibrosarcoma: 4.7% • IMT: 11.6% • Melanoma: 2.3% • Salivary gland adenocarcinoma: 2.3% • Spindle cell sarcoma: 2.3% • Myofibroblastic tumour: 2.3% • Infantile myofibroma: 2.3% • Primary CNS (brain) tumour: 37.2% • Glioblastoma: 7.0% • Astrocytoma: 9.3% • Ganglioglioma: 4.7% • Epithelioid glial neoplasm: 2.3%

[4] Patients in cohort E received 1 dose level below the MTD during cycle 1 and could then escalate to the MTD.
[5] The STARTRK-NG trial is currently ongoing; estimated study completion date is 06/2025.

metastatic, or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options for solid tumors and primary CNS tumors that are NTRK or ROS1 fusion-positive. ❖ Participants must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrolment. ❖ Adequate organ and neurologic function. ❖ Females of childbearing potential must have a negative serum pregnancy test during screening and be neither breastfeeding nor intending to become pregnant during study participation. Agreement to remain abstinent or use use combined contraceptive methods prior to study entry, for the duration of study participation and in the following 90 days after discontinuation of study treatment. ❖ For male participants with a female partner of childbearing potential or a pregnant female partner: Agreement to remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study drug.		• Medulloblastoma: 3.7% • High-grade glioma NOS: 7.0% • Glioma NOS: 2.3% • Ganglioneuroblastoma: 2.3% • Neuroblastoma 2: 34.9% ❖ Target gene fusion: • NTRK1/2/3: 34.9% • ROS1: 18.6% • ALK: 7.0% ❖ Non-fusion target gene alteration: • NTRK1c: 4.7% • ROS1: 0 • ALK 0: 4.7% ❖ Any target gene alteration • NTRK1/2/3: 39.5% • ROS1: 18.6% • ALK: 11.6%

Efficacy	**Safety** (n=43)
Data cutoff: 17 September 2020; median duration of treatment 10.6 months Efficacy according to the presence or absence of target gene fusion (n = 26)[6] **Confirmed ORR**: 57.7% (15/26; 95% CI 36.9-76.7), including 7 CRs (26.9%) and 8 PRs (30.8%) **ORR in the non-fusion population** (n = 17): 5.9% (1/17; 95% CI 0.15-28.7) **Reductions in measurable target lesions**: in 80.9% of patients **Median DoR (95% CI) among responders in the target fusion population (BICR-assessed)**: not reached (14.3 months-NE) due to patients still receiving therapy. **Median PFS** (95% CI): not reached (12.8 months-NE) in the target fusion population and 1.9 months (1.7-5.7) in the non-fusion population (p< .0001) Efficacy according to the type of target gene fusion (n = 26)[7]: **Confirmed ORR**: 60.0% (9/15; 95% CI 32.3-83.7), 62.5% (5/8; 95% CI 24.5-91.5), and 33.3% (1/3; 95% CI 0.84-90.6) in patients with NTRK1/2/3, ROS1, and ALK fusions, respectively. Efficacy in CNS tumors (n=16): **ORR:** 50.0% (95% CI 24.7-75.4) **ORR per BICR in cohort B (phase 2; n = 11)**: 54.5% (n = 6/11; 95% CI 23.4-83.3) Efficacy in extracranial solid tumours (n=10) **Confirmed objective responses**: 70.0% (95% CI 34.8-93.3)	**≥1 AE:** 100% **AEs of grade 3 and 4**: 76.7% **TRAEs of any grade**: 97.7% **TRAEs of grade 3 and 4**: 53.5% **Fracture events that were considered related to entrectinib**: 61.5% **Discontinuation of entrectinib due to AEs**: 18.6%[8] **AE or TRAE leading to death**: 0
Patient-reported outcomes	

[6] 16 patients with primary CNS tumours and 10 with extracranial solid tumours.
[7] 15 patients with NTRK1/2/3 fusions, 8 patients with ROS1 fusions, and 3 patients with ALK fusions.
[8] Fractures (n = 3); dyspnoea, encephalitis, pancreatitis, increased alanine aminotransferase, and pulmonary edema (n = 1 each).

The measurement of patient-reported outcomes is not provided in the STARTRK-NG trial.

ESMO-MCBS version 1.1 [8]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 60.0%	-	ORR (PR+CR) ≥ 60%	3	≥30% grade 3-4 toxicities	-	1[9]	2

Due to the low level of evidence (single-arm study design) the adapted scale was not applied.

Risk of bias - study level (case series) [9]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	no[10]	yes	unclear[11]	yes	partial[12]
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	no[13]	no	yes	yes	unclear[14]	yes

Overall risk of bias: Moderate

Ongoing trials [10]

NCT number/trial name	Description	Estimated study completion date
NCT02650401 / STARTRK-NG	Please see above.	06/2025
NCT02568267 / STARTRK-2	An open-label, multicentre, global phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbour NTRK1/2/3, ROS1, or ALK gene rearrangements.	04/2025

Available assessments

- Canada´s Drug Agency (CDA-AMC, formerly CADTH) published a Reimbursement Recommendation for entrectinib in November 2022 [11].
- IQWIG conducted an efficacy assessment for entrectinib in November 2020 [13].
- In August 2020, NICE published a Technology appraisal guidance, "Entrectinib for treating NTRK fusion-positive solid tumours" [11].

[9] Toxicity adjustment.
[10] Heterogenous characteristics at baseline.
[11] No information available.
[12] Open-label trial design. Blinded independent central review was performed for patients with a target gene fusion.
[13] Currently, there is no information available regarding the length of follow up.
[14] Since the trial is currently ongoing; there is no final analysis data available.

- No further assessments were identified via ICER and NIHR.

Other aspects and conclusions

- In April 2024, the **CHMP** adopted a **new pharmaceutical form**, 50 mg film-coated granules, a **new gastroenteral route of administration** for the 100 and 200 mg hard capsules, and an **extension to an existing indication** for film-coated granules and hard capsules for Rozlytrek®, as follows: Rozlytrek® as monotherapy is indicated for the treatment of adult and paediatric patients older than one month with solid tumours that have a 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 not received a prior NTRK inhibitor, who have no satisfactory treatment options. In October 2023, the **FDA granted accelerated approval to Rozlytrek®** for paediatric patients older than one month with solid tumours that have a NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy.
- **STARTRK-NG (NCT02650401)** is an **ongoing**, multicentre, non-randomised, open-label, single-arm phase 1-2 trial of entrectinib in paediatric patients with extracranial solid tumours or primary CNS tumours, with or without target gene fusions in NTRK1/2/3, ROS1, or ALK. Eligible patients were aged <22 years with relapsed or refractory disease and had Lansky or Karnofsky performance score of ≥60%; life expectancy of ≥4 weeks; adequate bone marrow, liver, renal, cardiac, and neurologic function. Patients previously treated with TRK, ROS1, or ALK inhibitors were only eligible for phase 1. Following protocol amendment, enrolment was restricted to patients aged <18 years and included patients without satisfactory treatment options or where surgical resection was likely to result in severe morbidity, including newly diagnosed patients. Patients with active infections or who were pregnant, breastfeeding, or receiving enzyme-inducing antiepileptic medication were excluded.
- **Primary endpoints** were **RP2D** based on toxicity (in phase 1) and **ORR** in patients harbouring target fusions (in phase 2). In patients with fusion-positive tumours, ORR was 57.7%; confirmed ORR was 60.0% (95% CI 32.3-83.7), 62.5% (95% CI 24.5-91.5), and 33.3% (95% CI 0.84-90.6) in patients with NTRK1/2/3, ROS1, and ALK fusions, respectively.
- Patient-reported outcomes were **not evaluated** in STARTRK-NG trial.
- The **original ESMO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit of **3**. Due to the low level of evidence (single-arm study design) the adapted scale was not applied.
- Since the trial is currently ongoing and final analysis data is lacking, the **risk of bias** was considered **unclear**. However, it is **increased** by the heterogeneous characteristics of the patients at baseline, the open-label trial design, and the industry-funded background of the trial.
- Besides the STARTRK-NG trial, one further ongoing phase 2 study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbour NTRK1/2/3, ROS1, or ALK gene rearrangements was identified via ClinicalTrials.gov.
- Due to the **small number and heterogenous characteristics** of trial patients, **evidence** for entrectinib in the assessed patient population is **rare.** Final analysis data and patient-reported outcome data, proven by phase 3 data, are required.

First published: 05/2024

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, BICR=blinded independent central review, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHF=chronic heart failure, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, DoR=duration of response, ECG=electrocardiogram, EMA=European Medicines Agency, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, MTD= maximum tolerated dose, n=number of patients, NICE=National Institute for Health Care Excellence, NSCLC=non–small-cell lung cancer, NTRK=neurotrophic tyrosine receptor kinase, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RANO=Response Assessment in Neuro-Oncology criteria, RECIST=Response Evaluation Criteria in Solid Tumours, RP2D=recommended phase 2 dose, SAE=serious adverse event, ST=standard treatment, TRAEs=treatment-related adverse events

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