Supplementary appendix

Supplementary methods

Briefly, this study included patients with histologically or cytologically confirmed locally advanced or metastatic solid tumours harbouring a neurotrophic receptor tyrosine kinase (*NTRK)1/2/3*, ROS proto-oncogene 1 (*ROS1)*, or anaplastic lymphoma kinase *(ALK)* gene fusion (with and without central nervous system [CNS] involvement) and an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Any previous therapy, except tropomyosin receptor kinase (TRK), ROS1, or ALK inhibitors, was permitted, and patients with *ALK* or *ROS1* fusion-positive non-small cell lung cancer who had previously been treated with crizotinib and had experienced CNS-only progression were permitted to enrol. As a basket trial, patients enrol in one of several single arms and receive entrectinib; there is no comparator arm. All patients received oral entrectinib 600 mg once daily in 4-week cycles, remaining on treatment until documented radiographic progression, as assessed by blinded independent central review (BICR), development of unacceptable toxicity, or withdrawal of consent. The primary endpoint was BICR-assessed overall response rate. Secondary efficacy endpoints include best overall response, duration of response, time to response, progression-free survival (PFS), clinical benefit rate, intracranial tumour response, intracranial PFS, and overall survival. STARTRK-2 is ongoing at >150 sites (including cancer and medical centres, research institutes, hospitals, and universities) in 15 countries.

Supplementary Table S1. PRO instruments: functional/symptom domains and single items

QLQ-C30		
Functional domains	**Symptom domains and single items**	**Additional scale**
Physical	Fatigue	GHS/QoL
Role	Pain	
Cognitive	Nausea/vomiting	
Emotional	Dyspnoea	
Social	Loss of appetite	
	Insomnia	
	Constipation	
	Diarrheal	

EORTC QLQ-CR29	
Symptom domains	**Single Items**
Body image	Urinary frequency
Anxiety	Blood and mucus in stool
Weight	Stool frequency
Sexual interest (men)	Urinary incontinence
Sexual interest (women)	Dysuria
	Abdominal pain
	Buttock pain
	Bloating
	Dry mouth
	Hair loss
	Taste
	Flatulence
	Faecal incontinence

	Sore skin
	Embarrassment
	Stoma care problems
	Impotence
	Dyspareunia

EORTC QLQ-LC13

Symptom domain	**Single items**
Dyspnoea	Coughing
	Haemoptysis
	Sore mouth
	Dysphagia
	Peripheral neuropathy
	Alopecia
	Pain in chest
	Pain in arm/shoulder
	Pain in other parts

EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; PRO, patient-reported outcomes; QoL, quality of life.

Supplementary Table S2. Baseline characteristics of the *NTRK* and *ROS1* SA-PRO populations

Characteristic	***NTRK* fusion-positive solid tumours (N=88)**	***ROS1* fusion-positive NSCLC (N=180)**
Median age, years (range)	57 (21–83)	54 (15–86)
Sex, n (%)		
Female	47 (53.4)	108 (60.0)
Male	41 (46.6)	72 (40.0)
Race, n (%)		
Asian	15 (17.0)	80 (44.7)
Black – African American	3 (3.4)	10 (5.6)
White	60 (68.2)	76 (42.5)
Other/unknown	-	3 (1.7)
Not reported	10 (11.4)	10 (5.6)
ECOG PS, n (%)		
0	33 (37.5)	76 (42.2)
1	41 (46.6)	84 (46.7)
2	12 (13.6)	18 (10.0)
3	2 (2.3)	1 (0.6)
4	0	1 (0.6)
Baseline CNS lesions (INV), n (%)		
Measurable	8 (9.1)	23 (12.8)
Present	20 (22.7)	51 (28.3)
Absent	60 (68.2)	106 (58.9)

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator-assessed; NSCLC, non-small-cell lung cancer; *NTRK*, neurotrophic receptor tyrosine kinase; PRO, patient-reported outcomes; *ROS1*, *ROS* proto-oncogene 1; SA, safety analysis.

Supplementary Table S3. Baseline characteristics of the *NTRK* and *ROS1* EA-PRO populations

Characteristic	*NTRK* fusion-positive solid tumours (N=71)	*ROS1* fusion-positive NSCLC (N=145)
Median age, years (range)	57 (21–83)	54 (20–86)
Sex, n (%)		
Female	37 (52.1)	93 (64.1)
Male	34 (47.9)	52 (35.9)
Race, n (%)		
Asian	13 (18.3)	68 (46.9)
Black – African American	2 (2.8)	7 (4.8)
White	49 (69.0)	60 (41.4)
Other	–	2 (1.4)
Not reported	6 (8.5)	8 (5.5)
ECOG PS, n (%)		
0	30 (42.3)	61 (42.1)
1	31 (43.7)	69 (47.6)
2	10 (14.1)	15 (10.3)
Baseline CNS lesions (INV), n (%)		
Measurable	1 (1.4)	11 (7.6)
Present	17 (23.9)	40 (27.6)
Absent	53 (74.6)	94 (64.8)

CNS, central nervous system; EA, efficacy analysis; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator-assessed; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic receptor tyrosine kinase; PRO, patient-reported outcomes; *ROS1*, *ROS* proto-oncogene 1.

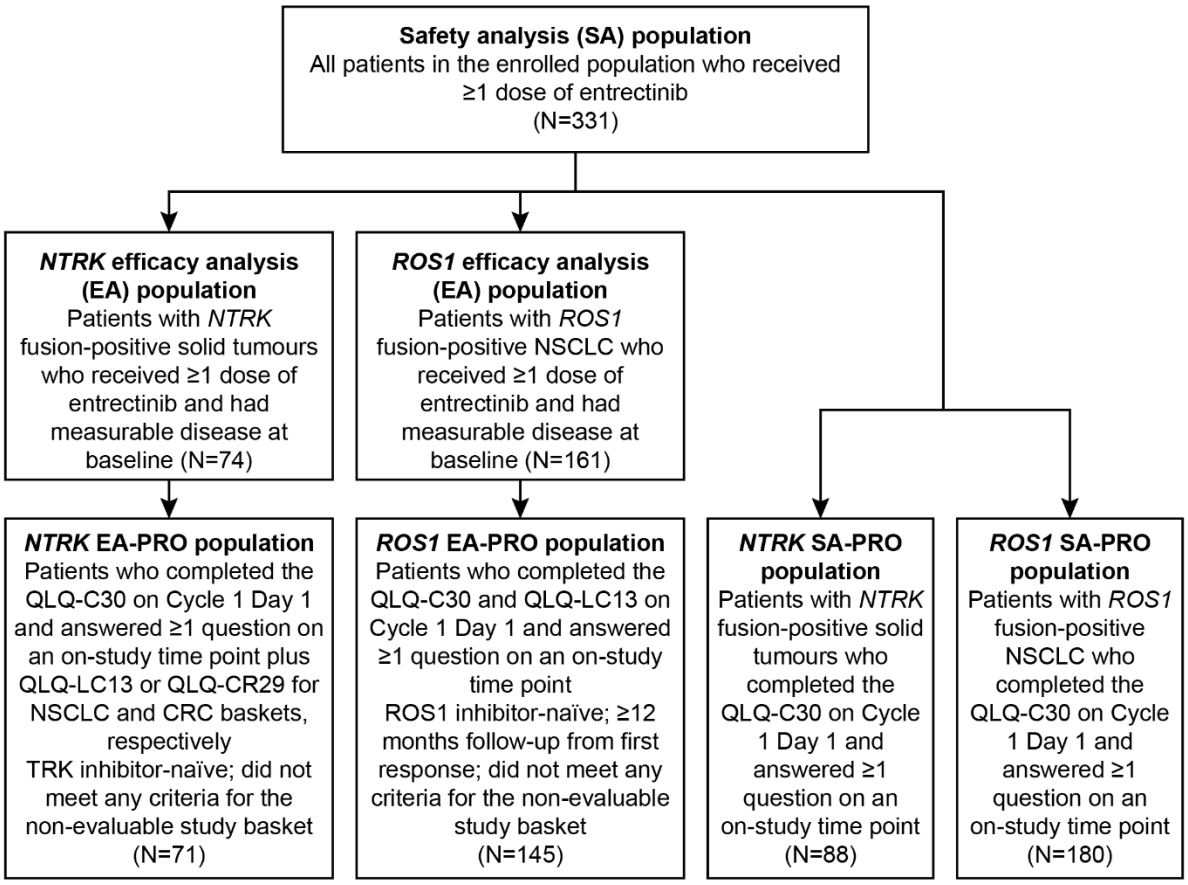
Supplementary Table S4. Categorical responses of selected treatment-related symptoms over time in the *NTRK* SA-PRO population (N=88) and *ROS1* SA-PRO population (N=180) according to QLQ-C30 and QLQ-LC13.

Categorical response provided by patients with *NTRK* fusion-positive solid tumours								
Symptom, n (%)	**"Not at all"**		**"A little"**		**"Quite a bit"**		**"Very much"**	
	BL	**C12**	**BL**	**C12**	**BL**	**C12**	**BL**	**C12**
Diarrhoea*	65 (79.3)	8 (36.4)	13 (15.9)	12 (54.5)	3 (3.7)	2 (9.1)	1 (1.2)	0
Nausea*	65 (79.3)	19 (86.4)	12 (14.6)	1 (4.5)	4 (4.9)	2 (9.1)	1 (1.2)	0
Vomiting*	73 (89.0)	18 (81.8)	8 (9.8)	4 (18.2)	0	0	1 (1.2)	0
Appetite loss*	46 (56.1)	18 (81.8)	24 (29.3)	4 (18.2)	8 (9.8)	0	4 (4.9)	0
Constipation*	52 (63.4)	11 (50.0)	23 (28.0)	10 (45.5)	4 (4.9)	1 (4.5)	3 (3.7)	0
Trouble sleeping*	34 (41.5)	18 (81.8)	31 (37.8)	2 (9.1)	13 (15.9)	2 (9.1)	4 (4.9)	0
Hair loss†	9 (69.2)	3 (75.0)	2 (15.4)	1 (25.0)	1 (7.7)	0	1 (7.7)	0
Tingling hands / feet†	10 (76.9)	2 (50.0)	2 (15.4)	2 (50.0)	0	0	1 (7.7)	0
Sore mouth†	13 (100.0)	4 (100.0)	0	0	0	0	0	0
Categorical response provided by patients with *ROS1* fusion-positive NSCLC								
	BL	**C18**	**BL**	**C18**	**BL**	**C18**	**BL**	**C18**
Diarrhoea*	140 (79.5)	31 (63.3)	34 (19.3)	16 (32.7)	1 (0.6)	1 (2.0)	1 (0.6)	1 (2.0)
Nausea*	113 (64.2)	41 (83.7)	51 (29.0)	6 (12.2)	11 (6.3)	2 (4.1)	1 (0.6)	0

Vomiting*	146 (83.0)	48 (98.0)	25 (14.2)	1 (2.0)	2 (1.1)	0	3 (1.7)	0
Appetite loss*	80 (45.5)	38 (77.6)	59 (33.5)	11 (22.4)	22 (12.5)	0	15 (8.5)	0
Constipation*	109 (61.9)	21 (42.9)	51 (29.0)	18 (36.7)	11 (6.3)	9 (18.4)	5 (2.8)	1 (2.0)
Trouble sleeping*	56 (31.8)	36 (73.5)	81 (46.0)	12 (24.5)	29 (16.5)	1 (2.0)	10 (5.7)	0
Hair loss‡	110 (78.6)	31 (83.8)	22 (15.7)	5 (13.5)	6 (4.3)	1 (2.7)	2 (1.4)	0
Tingling hands / feet‡	97 (69.3)	22 (59.5)	31 (22.1)	15 (40.5)	8 (5.7)	0	4 (2.9)	0
Sore mouth‡	120 (85.7)	31 (83.8)	17 (12.1)	6 (16.2)	3 (2.1)	0	0	0

*QLQ-C30, †QLQ-LC13 (*NTRK* NSCLC SA-PRO population [N=13]). ‡QLQ-LC13 (*ROS1* SA-PRO population [N=145]; 35 patients were excluded from this analysis based on enrolment in a sub-study in Japan, prior treatment with crizotinib (CNS progression only), or being non-evaluable). BL, baseline; C18, Cycle 18 Day 1; C12, Cycle 12 Day 1; CNS, central nervous system; *NTRK,* neurotrophic receptor tyrosine kinase; PRO, patient-reported outcomes; *ROS1,* ROS protooncogene 1 fusion positive; SA, safety analysis.

Supplementary Figure S1. Schematic of the SA-PRO and EA-PRO populations



NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic receptor tyrosine kinase; PRO, patient-reported outcomes; *ROS1*, ROS proto-oncogene 1; TRK, tropomyosin receptor kinase.