RESEARCH ARTICLE

Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1)

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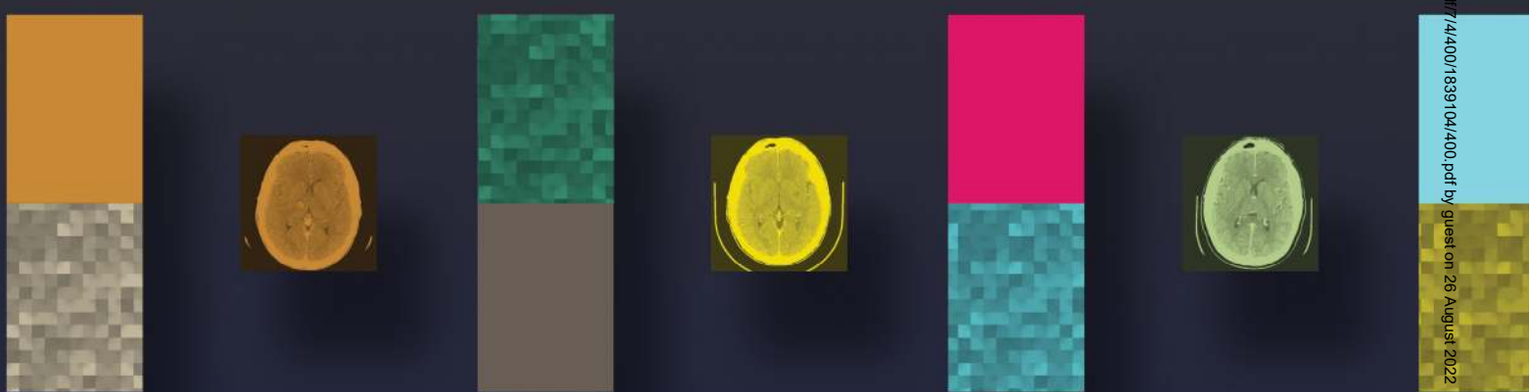

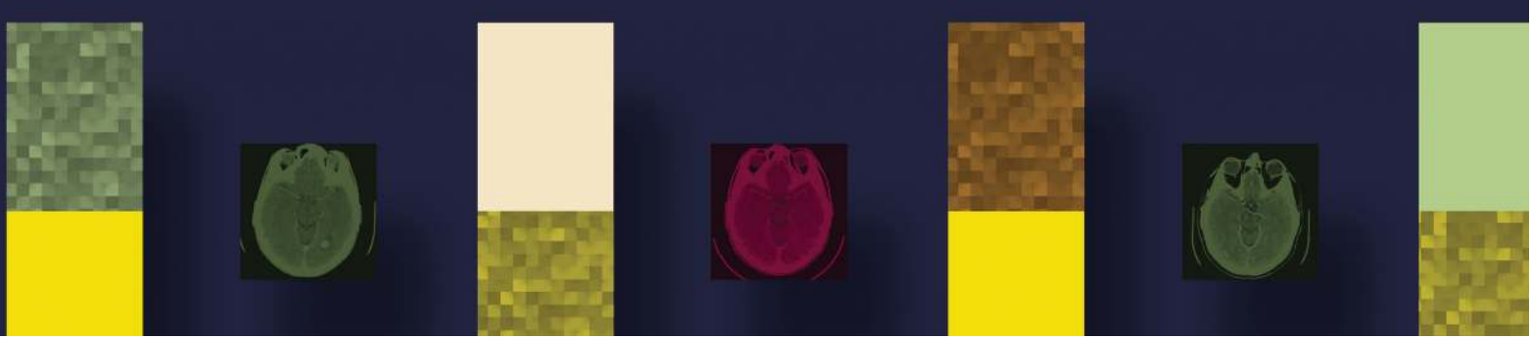

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ABSTRACT Entrectinib, a potent oral inhibitor of the tyrosine kinases TRKA/B/C, ROS1, and ALK, was evaluated in two phase I studies in patients with advanced or metastatic solid tumors, including patients with active central nervous system (CNS) disease. Here, we summarize the overall safety and report the antitumor activity of entrectinib in a cohort of patients with tumors harboring *NTRK1/2/3, ROS1*, or *ALK* gene fusions, naïve to prior TKI treatment targeting the specific gene, and who were treated at doses that achieved therapeutic exposures consistent with the recommended phase II dose. Entrectinib was well tolerated, with predominantly Grades 1/2 adverse events that were reversible with dose modification. Responses were observed in non–small cell lung cancer, colorectal cancer, mammary analogue secretory carcinoma, melanoma, and renal cell carcinoma, as early as 4 weeks after starting treatment and lasting as long as >2 years. Notably, a complete CNS response was achieved in a patient with *SQSTM1–NTRK1*-rearranged lung cancer.

SIGNIFICANCE: Gene fusions of *NTRK1/2/3, ROS1,* and *ALK* (encoding TRKA/B/C, ROS1, and ALK, respectively) lead to constitutive activation of oncogenic pathways. Entrectinib was shown to be well tolerated and active against those gene fusions in solid tumors, including in patients with primary or secondary CNS disease. *Cancer Discov; 7(4); 400–9. ©2017 AACR.*

INTRODUCTION

Recurrent gene fusions are oncogenic drivers of tumor growth and survival across a variety of malignancies (1). Structurally, many of these fusions retain an intact tyrosine kinase domain fused to an upstream gene partner that promotes ligand-independent dimerization. The resultant chimeric oncoprotein initiates and sustains downstream signaling, resulting in tumor growth and proliferation (2). As molecular profiling of tumors continues to migrate toward more comprehensive platforms, such as DNA-based next-generation sequencing and RNA-based anchored multiplex PCR, the number of these fusion events that are detectable in the clinic continues to rise substantially (3, 4).

Most importantly, a significant proportion of recurrent gene rearrangements are clinically actionable. In patients with advanced *ALK*- and *ROS1*-rearranged non–small cell lung cancer (NSCLC), three targeted therapies [crizotinib (Xalkori), ceritinib (Zykadia), and alectinib (Alecensa)] have been approved based on dramatic improvements in response rate and progression-free survival (5–9). Beyond NSCLC, *ALK* rearrangements have also been identified in a variety of malignancies, including anaplastic large cell lymphoma and renal cell, breast, esophageal, and colorectal cancers, as have *ROS1* rearrangements in colorectal, gastric, and ovarian cancers, glioblastoma multiforme, and cholangiocarcinomas (2).

Similar to *ALK* and *ROS1* rearrangements, recurrent gene fusions involving the genes *NTRK1, NTRK2*, and *NTRK3* are actionable drivers of tumor growth (10, 11). These genes encode the proteins TRKA, TRKB, and TRKC, respectively, and play roles in neuronal development, cell survival, and cellular proliferation (12). In the rearranged state, the activated fusion kinases signal through the RAS–RAF–MEK–ERK, PI3K–AKT–mTOR, and PLCγ–PKC pathways, driving the initiation and progression of malignancy. These fusions have been detected in a variety of tumors, including lung (13), gastrointestinal (14–16), head and neck (1), thyroid (17–19), and spitzoid cancers (20, 21), sarcomas (22–24), primary brain tumors (25–27), and acute myeloid leukemia (28, 29). Although many of these events are found at a lower incidence in tumors such as lung and gastrointestinal cancers, they are found in the majority of rare tumors such as secretory breast carcinoma (30), mammary analogue secretory carcinoma (MASC; refs. 31, 32), and congenital infantile fibrosarcoma (33), where the identification of an *NTRK* fusion is a defining factor for diagnosis.

The presence of recurrent gene fusions involving *NTRK1, NTRK2, NTRK3, ROS1*, and *ALK* across different tumor histologies and the growing number of events that are detected in patient samples underscore the ongoing need for routine diagnostic testing to identify gene fusions.

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Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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Equally critical is the need for clinical trials that afford access to effective targeted agents regardless of histology, in what is commonly referred to as a "basket" trial design. Phase I trials have rapidly evolved to meet this challenge, not only establishing the recommended phase II dose (RP2D) of a promising agent, but also providing meaningful efficacy data in molecularly defined subsets of patients (34). Here, we present the combined results of two phase I trials of entrectinib (16), a highly potent, orally available, ATP-competitive tyrosine kinase inhibitor with low- to sub-nanomolar enzymatic efficacy against TRKA, TRKB, TRKC, ROS1, and ALK (IC_{50} values of 1.7, 0.1, 0.1, 0.2, and 1.6 nmol/L, respectively; ref. 35). Furthermore, the drug was specifically designed to cross the blood–brain barrier in an effort to address both primary brain tumors and brain metastases in patients with *NTRK1-, NTRK2-, NTRK3-, ROS1-*, and *ALK*-rearranged cancers (36).

RESULTS

Demographics

Between October 2012 and March 2016, a total of 119 patients with advanced solid tumors were treated with entrectinib: 54 on ALKA-372-001 and 65 on STARTRK-1. The demographic features of these patients are summarized in Table 1. The median age was 55 years (range, 18–80 years). The majority of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 (96%; n = 114/119) and had received 3 or more prior treatments for their cancer (83%; n = 98/119), including prior ALK/ROS1 inhibitors (27%; n = 32/119) and checkpoint inhibitors (3%; n = 4/119). Patients with a wide range of solid tumors, including primary brain, head and neck, sarcoma, breast, melanoma, renal cell, and ovarian tumors, were treated. The most predominant tumor type was NSCLC (60%; n = 71/119), followed by tumors of the gastrointestinal tract (15%; n = 18/119).

The 54 patients on ALKA-372-001 were treated on the following dosing schedules: 19 on Schedule A (fasted, 4 days on entrectinib and 3 days off entrectinib for 21 of 28 days), 29 on Schedule B (fed, continuous daily dosing for 28 days), and 6 on Schedule C (fed, 4 days on entrectinib and 3 days off entrectinib for 28 days). All 65 patients on STARTRK-1 received continuous daily dosing with entrectinib (daily for 28 days).

Safety Profile

The most common treatment-related adverse events of any grade were fatigue/asthenia (46%; n = 55/119), dysgeusia (42%; n = 50/119), paresthesias, (29%; n = 34/119), nausea (28%; n = 33/119), and myalgias (23%; n = 27/119; Table 2). The majority of treatment-related adverse events were Grade 1 or 2 in severity; all related adverse events were reversible with dose modifications. Dose reduction occurred in 15% (n = 18/119) of patients.

Table 1. Demographics: The clinical and pathologic features of 119 patients with advanced solid tumors who received entrectinib on either phase I trial (ALKA-372-001 or STARTRK-1) are summarized

	ALKA-372-001 (n = 54)	STARTRK-1 (n = 65)	Total (n = 119)
Age, years, median (range)	53 (22–77)	57 (18–80)	55 (18–80)
Sex, male/female (%)	44/56	48/52	46/54
ECOG performance status, *n* (%)			
0	30 (56)	22 (34)	52 (44)
1	21 (39)	41 (63)	62 (52)
2	2 (4)	2 (3)	4 (3)
Unknown	1 (2)	0	1 (1)
Prior systemic therapies, *n* (%)			
0	0	6 (9)	6 (5)
1–2	0	15 (23)	15 (13)
3–4	3 (6)	25 (39)	28 (24)
>4	51 (94)	19 (29)	70 (59)
Prior ROS1/ALK inhibitors, *n* (%)	10 (19)	22 (34)	32 (27)
Prior immunotherapy, *n* (%)	0	4 (6)	4 (3)
Tumor type, *n* (%)			
NSCLC	35 (65)	36 (56)	71 (60)
Gastrointestinal tract	9 (17)	9 (14)	18 (15)
CNS	4 (7)	1 (2)	5 (4)
Head and neck	1 (2)	4 (6)	5 (4)
Other[a]	5 (9)	15 (23)	20 (17)

NOTE: Most patients had an ECOG performance status of 0 or 1 and were heavily pretreated with three or more prior anticancer therapies. Patients with a wide range of solid tumors were treated.

Abbreviation: CNS, central nervous system.

[a]Other tumor types: breast, cholangiocarcinoma, melanoma, neuroblastoma, neuroendocrine ovarian, pancreatic, prostate, renal cell carcinoma, sarcoma, squamous skin cancer, unknown primary.

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Table 2. Adverse events: Listed below are adverse events reported in at least 10% of the patients ($n = 119$) with advanced solid tumors who received entrectinib on either phase I trial (ALKA-372-001 or STARTRK-1) and that were deemed by the investigators to be related to study drug

Adverse event, *n* (%)	Grade 1	Grade 2	Grade 3	All grades ($n = 119$)
Fatigue/asthenia	28 (24)	22 (19)	5 (4)	55 (46)
Dysgeusia	47 (40)	3 (3)	0	50 (42)
Paresthesia	34 (29)	0	0	34 (29)
Nausea	29 (24)	4 (3)	0	33 (28)
Myalgia	23 (19)	4 (3)	0	27 (23)
Diarrhea	19 (16)	3 (3)	1 (1)	23 (19)
Vomiting	19 (16)	1 (1)	0	20 (17)
Arthralgia	12 (10)	6 (5)	1 (1)	19 (16)
Dizziness	14 (12)	5 (4)	0	19 (16)
Constipation	12 (10)	2 (2)	0	14 (12)
Weight increase	4 (3)	6 (5)	2 (2)	12 (10)

NOTE: There was only one Grade 4 treatment-related adverse event: eosinophilic myocarditis on STARTRK-1. No treatment-related Grade 5 events were reported.

No dose-limiting toxicities (DLT) were observed on ALKA-372-001; two DLTs occurred on STARTRK-1 at a daily dose of 800 mg: Grade 3 cognitive disturbance and Grade 3 fatigue, both resolved with dose interruption. At the 800 mg dose level, one additional patient experienced Grade 4 eosinophilic myocarditis, which was the only Grade 4 treatment-related adverse event reported on either study. This event occurred after two doses of entrectinib; the patient was subsequently discontinued from the study and fully recovered from the event. No Grade 5 treatment-related adverse events were reported.

There were no significant differences in toxicity between patients who received intermittent dosing (Schedules A and C on ALKA-372-001) and continuous dosing (Schedule B on ALKA-372-001 and STARTRK-1) despite numerical differences between these two groups, such as a higher incidence of dysgeusia, increased blood creatinine, and weight increase in patients on continuous dosing. These are detailed in Supplementary Table S1.

The number of patients and treatment-related adverse events observed at each dose level on either trial are summarized in Supplementary Tables S2 and S3. A continuous dose of 400 mg/m^2 was designated as the body surface area (BSA)–based RP2D based upon a review of safety and pharmacokinetics (PK). Per protocol, the next dose tested was 800 mg (fixed dosing), which resulted in two DLTs as described above; a continuous dose of 600 mg daily was then tested and identified as the fixed-dose MTD and RP2D in adults. The treatment-related adverse events in patients who received entrectinib at the RP2D are summarized in Supplementary Table S4.

Pharmacokinetics

In the ALKA-372-001 study, Schedule A, when entrectinib was administered in the fasted state, exposure (C_{max} and AUC) appeared to increase in a dose-proportional manner across the dose range of 100 to 800 mg/m^2 with no appreciable increase in exposure observed at higher doses of 1,200 or 1,600 mg/m^2. In Schedules B and C, entrectinib exposure increased in a less than dose-proportional manner when it was coadministered with food. In the STARTRK-1 study, entrectinib was administered with food and exposure increased in a linear manner from 100 to 400 mg/m^2, and from 600 to 800 mg flat dosing (Fig. 1). Steady state was reached within 2 weeks of continuous dosing, with average accumulation of approximately 2-fold. The plasma half-life of entrectinib was estimated to be between 20 and 22 hours and compatible with a once-daily, continuous dosing regimen (Supplementary Table S5). At the RP2D, the mean steady-state C_{trough} of 1,590 nmol/L was greater than 4-fold higher than that of trough concentrations observed in animal tumor models with complete tumor inhibition (corrected for plasma protein binding differences across species; refs. 36, 37).

Antitumor Activity

Of the 119 patients treated on either trial, 60 had a gene rearrangement involving *NTRK1/2/3, ROS1*, or *ALK*. Of the remaining 59 patients, 53 had other molecular alterations, broadly categorized as point mutations, amplifications, copy-number variants, or insertions/deletions, and 6 patients were enrolled without a known alteration of *NTRK1/2/3, ROS1*, or *ALK* (Supplementary Table S6). No objective responses (per RECIST v1.1; ref. 38) were observed in patients whose tumors did not harbor gene fusions involving *NTRK1/2/3, ROS1*, or *ALK*, with the exception of 1 patient with an *ALK*^{F1245V} mutant neuroblastoma for whom a durable, confirmed partial response (PR) lasted 8.3 months; this patient remained on study treatment for more than 3.5 years due to clinical benefit. Furthermore, no responses were observed in the 25 patients with recurrent gene rearrangements involving *ROS1* ($n = 6$) or *ALK* ($n = 19$) who had previously received a ROS1 inhibitor (crizotinib) or ALK inhibitors (crizotinib, ceritinib, or alectinib), respectively, prior to entrectinib. Thirteen of the 19 *ALK* patients had received

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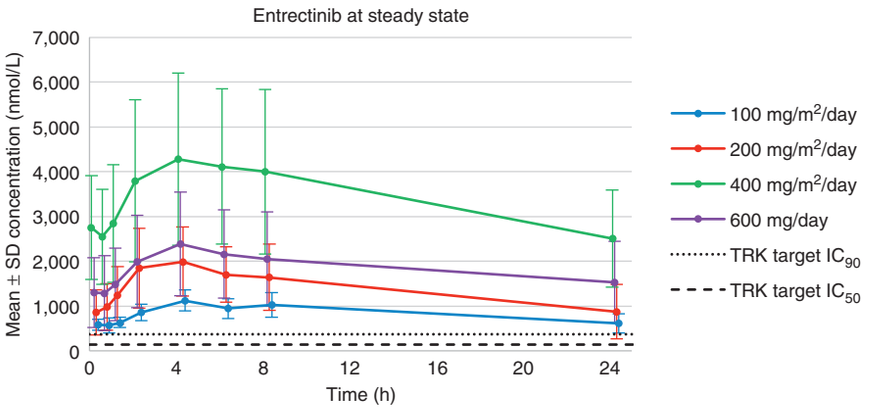

Figure 1. PK of entrectinib at steady state (continuous daily dosing). Mean steady-state (day 28) patient plasma concentration profiles at escalating dose levels were plotted over the dosing interval following once-daily continuous dosing. The target IC_{50} and IC_{90} values are based on entrectinib-induced tumor growth inhibition in mouse xenograft models of *NTRK1*-rearranged colorectal cancer.

more than one prior ALK inhibitor, including 2 patients who had received more than two prior ALK inhibitors.

"Phase II–Eligible Population"

Given that responses were observed only in TKI treatment–naïve patients with a fusion involving *NTRK1/2/3, ROS1*, or *ALK*, the population that would serve as the focus of later-phase development of entrectinib, an analysis was performed of patients treated on either phase I trial who met criteria for what was defined as a "Phase II–eligible population." This included patients whose tumors harbored a recurrent gene fusion involving any of the 5 genes of interest, with a history of no prior TKI treatment targeting the fusion of interest, and who were treated on ALKA-372-001 or STARTRK-1 at doses that achieved therapeutic exposures consistent with the RP2D of 600 mg of entrectinib daily (Supplementary Fig. S1).

Of the 60 patients with gene rearrangements, 5 patients were treated with doses that were below those which achieved therapeutic exposures consistent with the RP2D. Of the remaining 55 patients, 25 were previously treated with a TKI targeted to one of the fusions of interest (45%; $n = 25/55$). For the purposes of this analysis, crizotinib was not considered a significant inhibitor of TRKA/B/C (IC_{50} values of 580 and 399 nmol/L toward TRKA and TRKB, respectively; ref. 39), and 1 patient with an *NTRK3* fusion who had received this drug in the past was classified as "Phase II–eligible."

Of the resulting 30 patients comprising the "Phase II–eligible" patient population as defined above, 25 patients were evaluable (Table 3), of whom 24 patients had extracranial solid tumors and 1 patient had a glioneuronal tumor. The waterfall plot for the 24 patients with extracranial solid tumors is shown in Fig. 2. In three *NTRK1/2/3*-rearranged advanced solid tumors with RECIST-measurable disease, the objective response rate (ORR) was 100% [95% confidence interval (CI): 44–100]. These included patients with NSCLC (*SQSTM1–NTRK1*; ref. 40), MASC (*ETV6–NTRK3*; ref. 31), and colorectal cancer (*LMNA–NTRK1*; ref. 16). An additional patient with a *BCAN–NTRK1*-rearranged glioneuronal tumor experienced stable disease by RECIST, but further analysis via three-dimensional volumetric assessment demonstrated a 60% reduction in total tumor burden (41). This radiographic response was accompanied by a clinical response to therapy with diminished ataxia and diplopia.

In 14 *ROS1*-rearranged solid tumors, the ORR was 86% (95% CI: 60–96). These confirmed responses included 2 complete responses (CR). With the exception of 1 patient with a *GOPC–ROS1*-rearranged melanoma, all other patients who responded had *ROS1*-rearranged NSCLC. In seven *ALK*-rearranged solid tumors, the ORR was 57% (95% CI: 25–84), and responses were observed in *ALK*-rearranged NSCLC, renal cell carcinoma, and colorectal cancer.

Initial responses to entrectinib were demonstrated within Cycle 1 (scans performed at 4 weeks) or Cycle 2 (scans performed at 8 weeks). Responses to entrectinib therapy were also durable, with the longest duration of clinical benefit observed in a patient with *ROS1*-rearranged lung cancer who remains on therapy at 32 months as of the data cutoff date (Fig. 3). Recognizing that different tumor types were treated, the median duration of response for *ROS1*- and *ALK*-rearranged cancers was 17.4 months (95% CI: 12.7–not reached) and 7.4 months (95% CI: 3.7–not reached), respectively. For the 3 responding patients with *NTRK*-rearranged cancers, the durations of response were 2.6 months, 4.6 months, and 15.1 months (patient ongoing as of data cutoff date), respectively.

With a median duration of follow-up of 15 months, a number of exploratory secondary endpoints were analyzed. Considering the variety of tumor types evaluated in this study, each with a different natural history, the median progression-free survival for patients harboring *NTRK1/2/3*- ($n = 4$), *ROS1*- ($n = 14$), and *ALK*- ($n = 7$) rearranged malignancies was not reached (95% CI: 3.6–not reached), 19.0 months (95% CI: 6.5–not reached), and 8.3 months (95% CI: 4.6–12), respectively. Among all 25 patients, the median overall survival has not been reached (95% CI: 19 months–not reached). The proportion of patients surviving at 12 months was 89.4% (95% CI: 75.5%–100%).

Intracranial Activity

Among the 25 evaluable "Phase II–eligible population," 32% ($n = 8/25$) of patients had known primary or metastatic disease involving the brain prior to treatment with entrectinib. Responses were noted in 5 of the 8 (63%) patients: 4 patients with *NTRK1*- ($n = 1$), *ROS1*- ($n = 2$), and *ALK*- ($n = 1$) rearranged NSCLC and 1 additional patient with *ALK*-rearranged colorectal cancer; among the responders, 4 patients have had prior radiotherapy to the brain. Of note, the patient with *SQSTM1–NTRK1*-rearranged NSCLC had 15 to 20 brain metastases identified at baseline not previously irradiated; a complete intracranial response was achieved with entrectinib therapy that is ongoing at 15 months as of the data cutoff date (Fig. 4; ref. 40).

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Table 3. Molecular characteristics of the "Phase II–eligible" patients: The specific molecular profile of 25 patients with advanced solid tumors who received entrectinib on either phase I trial (ALKA-372-001 or STARTRK-1) is summarized

Number	Gene	Tumor type	Molecular alteration	Diagnostic method
1	*NTRK*	NSCLC	*SQSTM1–NTRK1*	NGS
2	*NTRK*	Glioneuronal	*BCAN–NTRK1*	NGS
3	*NTRK*	MASC	*ETV6–NTRK3*	NGS
4	*NTRK*	mCRC	*LMNA–NTRK1*	NGS
5	*ROS1*	NSCLC	*ROS1+*	FISH
6	*ROS1*	NSCLC	*ROS1+*	FISH
7	*ROS1*	NSCLC	*CD74–ROS1*	NGS
8	*ROS1*	NSCLC	*ROS1+*	FISH
9	*ROS1*	NSCLC	*ROS1+*	FISH
10	*ROS1*	NSCLC	*EZR–ROS1*	NGS
11	*ROS1*	NSCLC	*ROS1+*	FISH
12	*ROS1*	Melanoma	*GOPC–ROS1*	NGS
13	*ROS1*	NSCLC	*ROS1+*	FISH
14	*ROS1*	NSCLC	*ROS1+*	FISH
15	*ROS1*	NSCLC	*ROS1+*	FISH
16	*ROS1*	NSCLC	*ROS1+*	FISH
17	*ROS1*	NSCLC	*ROS1+*	FISH
18	*ROS1*	NSCLC	*SDC4–ROS1*	NGS
19	*ALK*	NSCLC	*ALK+*	FISH
20	*ALK*	NSCLC	*ALK+*	FISH
21	*ALK*	RCC	*VCL–ALK*	NGS
22	*ALK*	NSCLC	*ALK+*	FISH
23	*ALK*	mCRC	*CAD–ALK*	NGS
24	*ALK*	NSCLC	*ALK+*	FISH
25	*ALK*	Unknown primary	*D5F3–ALK*	NGS

Abbreviations: mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; RCC, renal cell carcinoma.

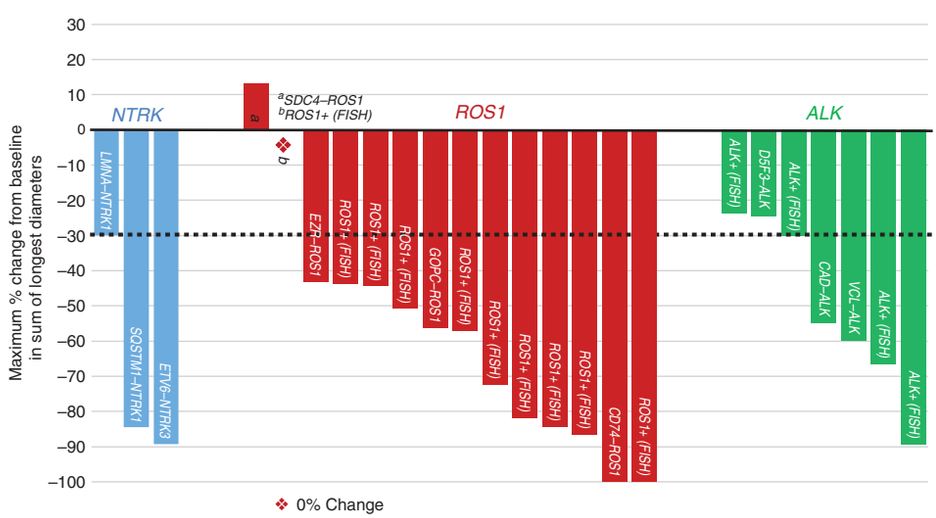

Figure 2. Best response to entrectinib in patients with TKI treatment–naïve extracranial solid tumors. Each bar represents maximal tumor regression from baseline based upon the sum of the longest diameters of target lesions (per RECIST 1.1) in the 24 "Phase II–eligible" patients with extracranial solid tumors. The dashed line at −30% indicates the threshold for partial response. Specific molecular alterations are shown for each patient. The red diamond indicates 1 patient with *ROS1*-rearranged NSCLC, who experienced no change in tumor burden during treatment with entrectinib.

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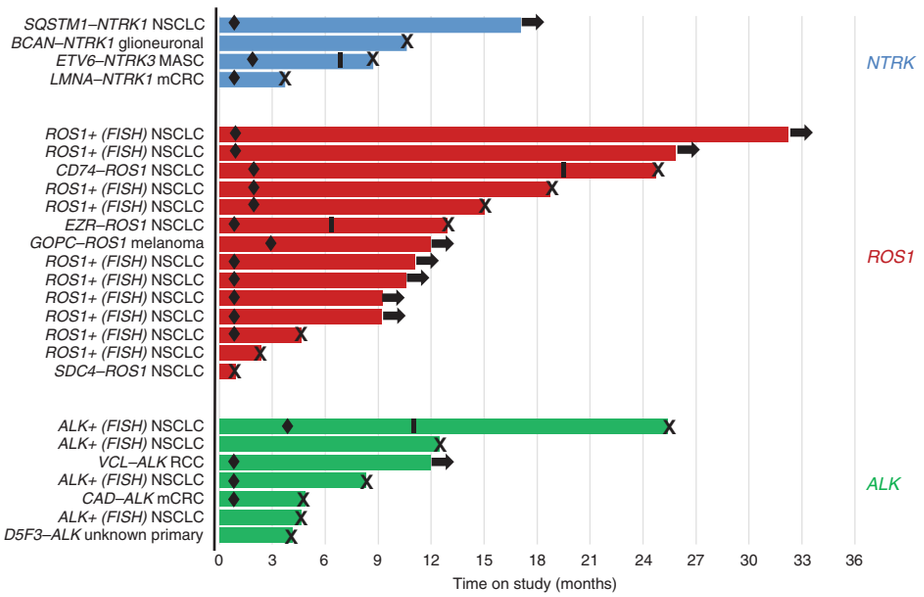

Figure 3. Duration of treatment. Each bar indicates the duration of treatment for the 25 "Phase II–eligible" patients at the time of data cutoff. Specific molecular alterations are shown next to each patient. Arrows indicate patients who were ongoing on study; X denotes patients who discontinued the study (all due to disease progression); black diamonds represent time of first response; black bars represent 4 patients who experienced disease progression but remained on study due to clinical benefit.

DISCUSSION

Here, we present a large multicenter safety experience in 119 patients treated with the pan-TRK, ROS1, and ALK inhibitor entrectinib on two phase I trials. We demonstrated that the drug is safe and well tolerated. No responding patients discontinued the study due to adverse events. The majority of treatment-related adverse events were Grade 1 or 2 in severity, and all were reversible with dose interruption and/or modification. Dose reduction was required in only 15% of patients. Specific adverse events, such as dysgeusia, sensory neuropathy, cognitive changes, and weight gain, are thought to be on-target toxicities of entrectinib mediated by TRK receptor inhibition (42). Forty-five patients were treated at the identified RP2D of 600 mg daily with continuous dosing. Given that no significant differences in toxicity were observed between continuous daily dosing and intermittent dosing schedules, continuous dosing was chosen due to its ability to enable 24-hour continuous exposures above those required for complete tumor inhibition in animal tumor models, resulting in sustained target inhibition.

Entrectinib demonstrated robust antitumor activity in TKI-naïve patients harboring gene rearrangements involving *NTRK*, *ROS1*, or *ALK*. Responses were fast and durable, and clinical benefit was observed across a broad range of solid tumors regardless of histology, including NSCLC, MASC, melanoma, glioneuronal tumor, colorectal cancer, and renal cell carcinoma. The majority of responses were observed within Cycle 1 or 2, and several patients continued treatment beyond a year, with the longest response approaching 2.5 years as of the time of the data cutoff. Intriguingly, the responses in patients with *NTRK*-rearranged tumors are particularly notable, as these provide proof-of-principle that *NTRK* rearrangements are clinically actionable drivers of tumor growth. We thus strongly encourage that clinicians continue to test for these alterations

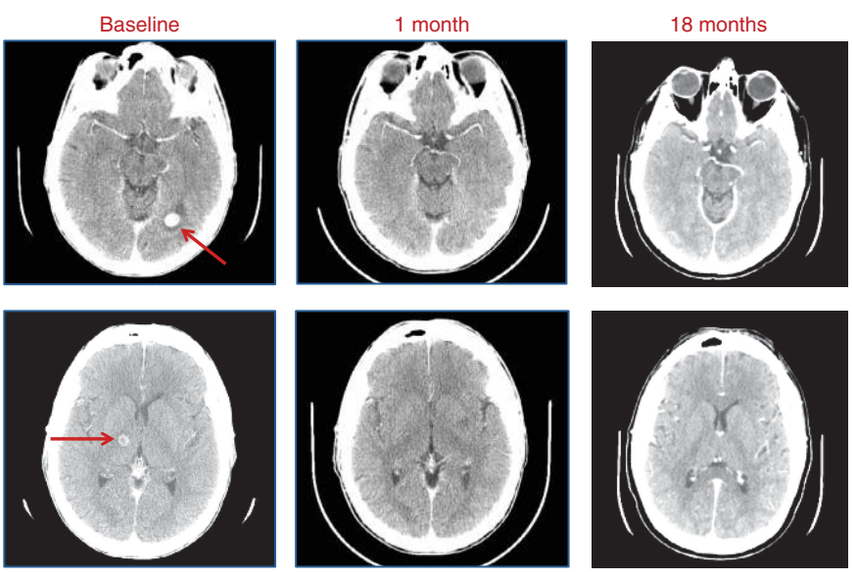

Figure 4. Baseline and on-study brain MRI images for a patient with *SQSTM1–NTRK1*-rearranged lung cancer. Baseline head CT scans show metastases (red arrows) in the left occipital lobe (top) and in the right thalamus (bottom). Restaging head CT scans show CR at 1 month and 18 months on entrectinib (at the time of data cutoff).

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using comprehensive molecular profiling platforms that are poised to identify these alterations, preferably with a strategy that combines testing at both the DNA level and, potentially, the RNA level, when feasible (13). Although no responses were observed in patients with recurrent gene rearrangements who had previously received ROS1 or ALK inhibitors, further investigation will be required to determine the activity of this drug in TKI-pretreated patients, considering that the drug is active preclinically against potential resistance mutations, such as the ALK^{L1196M} mutation, that can emerge after crizotinib therapy in *ALK*-rearranged lung cancers.

Of note, entrectinib showed promising antitumor activity in the central nervous system (CNS). This becomes particularly important when we consider that cancers that can harbor *NTRK, ROS1,* or *ALK* rearrangements such as lung cancers and melanomas have a proclivity for CNS metastasis. Moreover, many primary adult and pediatric brain tumors, such as astrocytoma, glioblastoma, and pediatric gliomas, harbor *NTRK1, NTRK2, NTRK3*, or *ROS1* fusions (10). On STARTRK-1, a CR was achieved in the brain in a patient with *SQSTM1–NTRK1*-rearranged lung cancer with an ongoing response at 15 months at the time of the data cutoff (40). Substantial reduction in disease burden was likewise noted by volumetric analysis in a *BCAN–NTRK1*-rearranged glioneuronal tumor (41). These cases highlight the intracranial activity of entrectinib against both metastatic disease and primary brain tumors that can otherwise result in substantial morbidity and mortality. As has been observed in *ALK*-rearranged lung cancers, the use of a CNS-penetrant drug like entrectinib in the first-line setting in patients with *ROS1*-rearranged lung cancers may potentially improve outcomes for patients compared with treatment with crizotinib, which is thought to be less CNS-penetrant.

Lastly, these studies emphasize the utility of clinical trial strategies that focus on molecular enrichment independent of tumor histology as a model for the development of promising targeted therapies, especially in patients with rare genomic aberrations. Over the last decade, expansion cohorts on phase I trials have driven the accelerated approval of targeted therapies such as crizotinib for *ALK*- and *ROS1*-rearranged lung cancers (6, 34). The same model can potentially be applied to establish preliminary efficacy across a variety of cancer types, especially as actionable drivers of interest such as *NTRK* rearrangements are detected at a lower frequency across multiple histologies, precluding the ability to easily accrue histology-specific cohorts on ongoing trials. Later-phase clinical trials, so called "basket studies," provide a complementary approach that utilizes this paradigm. For entrectinib, a global, multicenter, phase II basket study (STARTRK-2, NCT02568267) is currently accruing patients with *NTRK-, ROS1-,* and *ALK*-rearranged cancers with the intent of confirming the results generated by STARTRK-1 and ALKA.

METHODS

Patients with locally advanced or metastatic solid tumors harboring *NTRK1/2/3, ROS1*, or *ALK* molecular alterations were enrolled in one of two phase I studies aimed at determining the MTD or RP2D of entrectinib: Study ALKA-372-001 ("ALKA"; EudraCT 2012-000148-88; 2 sites, Italy) and Study RXDX-101-01 ("STARTRK-1"; NCT02097810; 10 sites, United States, Korea, and Spain). Patients were enrolled in the ALKA study between October 2012 and November 2015, and in the STARTRK-1 study between July 2014 and February 2016, respectively.

Study Design

Patients were assigned sequentially to escalating dose levels of entrectinib following a standard 3+3 design. All patients received entrectinib orally and remained on study treatment until disease progression (with allowance to remain on study if the treating physician deemed the patient as continuing to derive clinical benefit), development of unacceptable toxicity, or withdrawal of consent. Fasted and fed, BSA-based and flat dosing, as well as intermittent and continuous daily dosing regimens were evaluated. Entrectinib was initially dosed by BSA (doses ranging from 100 mg/m^2 to 1,600 mg/m^2) and later transitioned to flat dosing (doses ranging from 600 mg to 800 mg). In addition, intermittent dosing regimens were evaluated in addition to once-daily, continuous dosing. In the ALKA study, patients were enrolled across three dosing regimens: Schedule A (fasted, 4 days on/3 days off for 3 of 4 weeks), Schedule B (fed, continuous daily dosing), and Schedule C (fed, 4 days on/3 days off). In the STARTRK-1 study, all patients received entrectinib on a fed, continuous daily dosing regimen (Supplementary Fig. S2). Patients were enrolled into STARTRK-1 and ALKA Schedules B and C simultaneously after Schedule A was completed.

On both studies, the starting dose was 100 mg/m^2. At least 3 patients at each dose level were monitored for DLTs through Cycle 1 (day 28 for ALKA and day 42 for STARTRK-1). DLTs were defined as any Grade ≥2 CNS, Grade ≥3 nonhematologic, Grade ≥3 and/or lasting >7 days hematologic (as well as febrile neutropenia) toxicities according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; v4.03). Failure to recover (except alopecia) to Grade ≤1 or baseline after delaying the initiation of next cycle by a maximum of 14 (ALKA) or 28 (STARTRK-1) days was also considered a DLT. Patients were eligible for DLT evaluation if they experienced a DLT after at least one dose of study drug or did not experience a DLT having taken a minimum of 75% (ALKA) or 80% (STARTRK-1) of doses expected during Cycle 1. Patients who did not fulfill these requirements or who discontinued the study prior to completing the DLT evaluation period were to be replaced. The MTD was defined as the highest dose associated with first-cycle DLT in <33% of patients. If an MTD was not reached, RP2D was to be selected based on available safety, tolerability, PK, and pharmacodynamics data from different dose levels and dosing regimens tested.

Study Population

All patients had a histologically or cytologically confirmed diagnosis of relapsed or refractory advanced/metastatic solid tumor for which no alternative effective standard therapy was available or for which standard therapy was considered unsuitable or intolerable, ECOG PS ≤2, a life expectancy of ≥3 months, and adequate organ function. Patients with stable asymptomatic CNS involvement were eligible.

TRKA/B/C, ROS1, or ALK molecular alterations were detected via immunohistochemistry, FISH, or RNA/DNA-based methods [e.g., next-generation sequencing (NGS), NanoString] performed at the various local institutions or through third-party commercial diagnostic providers.

Institutional Review Boards and/or ethics committees of all participating institutions approved the study, which was conducted according to the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice. Data were anonymized to protect the identities of subjects involved in the research. All patients provided written informed consent.

Safety Assessments

Safety was assessed from the first dose until 30 days after the last dose of entrectinib or until the resolution or stability of any drug-related toxicity. Clinical and laboratory assessments were performed

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at least once weekly during the first two cycles of treatment: weekly and biweekly after ≥1 year of treatment (ALKA) or biweekly (STARTRK-1), at the end of treatment visit, and approximately 28 to 30 days after discontinuing study drug. Laboratory assessments included routine hematology and chemistry panels, coagulation parameters, and urinalysis. Twelve-lead single ECGs (triplicate in STARTRK-1) were obtained at baseline and around the anticipated maximal and steady-state entrectinib plasma concentrations (e.g., between 3 and 6 hours after dose) with time-matched PK samples (various time points on Cycles 1 through 4), at the end of treatment visit, as well as whenever clinically indicated, to assess for potential QTc changes as a result of treatment with entrectinib.

Pharmacokinetics

Depending on dosing regimens, serial blood samples for PK analyses were obtained at various time points throughout Cycle 1. Samples were shipped frozen to Accelera (ALKA) and InVentiv (STARTRK-1) for analysis of entrectinib (and its metabolites) using a validated liquid chromatography–tandem mass spectrometry assay. PK analysis for all parameters was performed using Phoenix WinNonlin software (version 6.4.0.768; Pharsight Corporation). Parameters analyzed included maximum observed plasma concentration (C_{max}) and minimum observed plasma concentration (C_{24h}), time of maximum observed plasma concentration (T_{max}), effective half-life ($t_{1/2}$), and area under the plasma concentration–time curve (AUC).

Pharmacodynamics

For all patients who provided consent, archival tumor tissue, if available, was submitted for retrospective and/or additional exploratory genomic profiling. Tissue (if clinically feasible) and blood at the time of progression in addition to monthly blood samples were collected to gain insights into potential mechanisms of resistance. Molecular alteration status of the *NTRK1/2/3, ROS1*, and *ALK* genes, among others, was collected in nucleic acids isolated from plasma using NGS for future analyses.

Tumor Assessments

CT/MRI of the brain, chest, abdomen, and pelvis, as clinically indicated, were initially performed at the end of Cycle 2 and every 8 weeks thereafter. For both studies, a protocol amendment later modified the first assessment time point to the end of Cycle 1 and every 8 weeks thereafter. All scans were read locally and tumor response evaluated according to RECIST v1.1 (38).

Statistical Analysis

Patients who received at least one dose of entrectinib were included in the efficacy and safety analyses, irrespective of molecular alteration. In addition, patients with evidence of a gene fusion were analyzed as a subset. Demographics, baseline characteristics, adverse events, vital signs, and clinical laboratory evaluations were summarized with descriptive statistics. Objective response was defined as confirmed CR or PR that persisted on repeat imaging ≥4 weeks after initial documentation of response. ORR was calculated as the proportion of responders out of the population of patients with measurable disease at baseline. The Kaplan–Meier method was used to estimate the median, 25th, and 75th percentiles for time-to-event endpoints (duration of response, progression-free survival, and overall survival), with corresponding 95% CIs. The data cutoff date for safety and efficacy analyses for both studies was September 20, 2016.

Disclosure of Potential Conflicts of Interest

A. Drilon has received honoraria from Ignyta. S. Siena is a consultant/advisory board member for Amgen, Bayer, Eli Lilly, Merck, Merrimack, and Roche. S.-H.I. Ou has received honoraria from the Speakers Bureaus of AstraZeneca and Genentech, and is a consultant/advisory board member for ARIAD, AstraZeneca, Genentech, and Novartis. S.V. Liu is a consultant/advisory board member for Ariad, Boehringer Ingelheim, Celgene, Genentech, Lilly, and Pfizer. R. Doebele reports receiving a commercial research grant from Ignyta. A. Amatu is a consultant/advisory board member for Amgen, Bayer, and Lilly. A. Sartore-Bianchi has received honoraria from the Speakers Bureaus of Amgen and Bayer, and is consultant/advisory board member for Amgen, Bayer, and Sanofi. A. Vanzulli has received honoraria from the Speakers Bureau of Bracco SpA. D. Luo has ownership interest (including patents) in Ignyta. Z. Hornby has ownership interest (including patents) in Ignyta. P.S. Multani has ownership interest (including patents) in Ignyta. A.T. Shaw is a consultant/advisory board member for Ariad, Blueprint Medicines, Daiichi-sankyo, Ignyta, Genentech/Roche, LOXO, Novartis, Pfizer, and Taiho. No potential conflicts of interest were disclosed by the other authors.

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