Clinical Trial Protocol

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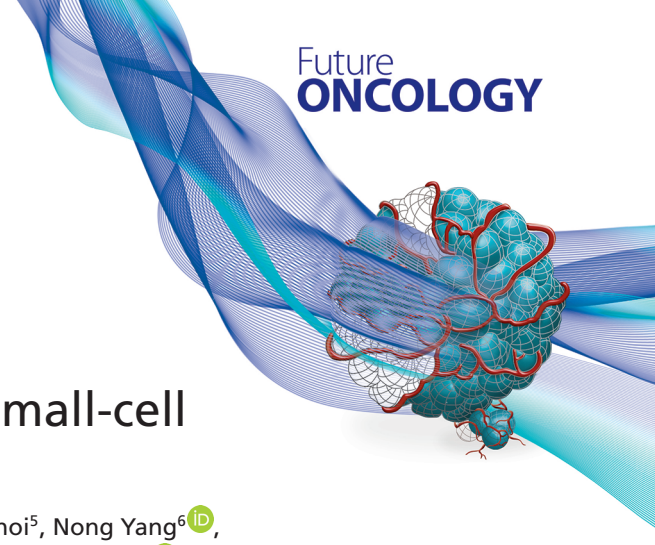

TRUST-II: a global phase II study of taletrectinib in *ROS1*-positive non-small-cell lung cancer and other solid tumors

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Crizotinib and entrectinib have been approved to treat *ROS1* fusion-positive (ROS1$^+$) non-small-cell lung cancer. However, unmet needs remain, including treatment of patients with resistance mutations, efficacy in brain metastasis and avoidance of neurological side effects. Taletrectinib was designed to: improve efficacy; overcome resistance to first-generation ROS1 inhibitors; and address brain metastasis while conferring fewer neurological adverse events. All of these features are demonstrated and supported by the interim data from the regional phase II TRUST-I clinical study. Here we describe the rationale and design of TRUST-II, a global phase II study of taletrectinib in patients with locally advanced/metastatic ROS1$^+$ non-small-cell lung cancer and other ROS1$^+$ solid tumors. The primary end point is confirmed objective response rate. Secondary end points include duration of response, progression-free survival, overall survival and safety. This trial is enrolling patients in North America, Europe and Asia.

Plain language summary: The targeted therapies crizotinib and entrectinib are the first options available to treat a type of lung cancer called *ROS1* fusion-positive non-small-cell lung cancer (ROS1$^+$ NSCLC). However, not all patients with ROS1$^+$ NSCLC respond to these drugs. In addition, most patients who take these drugs find their cancer eventually develops resistance and begins to grow again. Patients with disease that has spread (metastasized) to the brain have worse outcomes. Taletrectinib is a new type of targeted therapy that is being developed to treat people who have metastatic ROS1$^+$ NSCLC. Data from a regional phase II clinical trial showed that taletrectinib is well tolerated, effective for patients who have never taken a ROS1 targeted therapy and inhibits ROS1$^+$ NSCLC for patients whose cancer has developed some types of resistance to these drugs. It has also been shown to treat ROS1$^+$ NSCLC tumors that have spread to the brain. This article discusses the rationale and design of a new trial called TRUST-II, which is a

global phase II clinical trial looking at how well taletrectinib works and how safe it is. TRUST-II is actively enrolling patients in North America, Europe and Asia.

Clinical Trial Registration: NCT04919811 (ClinicalTrials.gov)

First draft submitted: 28 October 2022; Accepted for publication: 5 January 2023; Published online: 6 March 2023

Keywords: brain metastasis • brain penetration • intracranial antitumor activity • neoplasm drug resistance • non-small-cell lung cancer • *ROS1*$_{G2032R}$ • *ROS1* kinase fusion • taletrectinib • TRKB • tyrosine kinase inhibitors

ROS1 tyrosine kinase inhibitor (TKI) therapy is the current standard-of-care for patients with *ROS1* fusion-positive non-small-cell lung cancer (ROS1$^+$ NSCLC). Patients with ROS1$^+$ NSCLC account for about 1–2% of NSCLC patients and generally respond well to ROS1-targeted therapy [1].

Crizotinib was the first ROS1 inhibitor approved and marketed in multiple countries worldwide for the treatment of ROS1$^+$ NSCLC. Crizotinib has shown an objective response rate (ORR) of 72% and a median progression-free survival (PFS) of 15.9–19.2 months in advanced/metastatic ROS1$^+$ NSCLC in clinical trials [2,3]. However, many patients develop resistance to crizotinib within 2 years of treatment due to the emergence of secondary mutations within the ROS1 kinase domain, or activation of alternative signaling pathways. The most common on-target resistance mutation is the solvent-front mutation G2032R, which sterically impedes drug binding [4]. Several other resistance mutations within *ROS1* have also been reported, at lower frequencies [4]. Furthermore, crizotinib has limited CNS penetration, leading to frequent emergence of brain metastases and a limited intracranial activity for patients with brain metastases [5].

Entrectinib was the second ROS1 TKI approved for the treatment of ROS1$^+$ NSCLC in the USA, Europe and Japan and is preferred by many oncologists over crizotinib due to its perceived CNS activity. In an integrated analysis with 168 ROS1 TKI-naive NSCLC patients, the reported ORR was 68% (95% CI: 60.2–74.8) with a median PFS of 15.7 months, which is comparable to or shorter than the PFS reported for crizotinib despite its better CNS activity. The intracranial ORR of entrectinib was 80% (95% CI: 59.3–93.2) in 25 patients with measurable CNS metastases [6]. However, entrectinib is not effective against tumors with the G2032R resistance mutation [4]. Among six patients who had previously received crizotinib, none experienced an objective response, although no mutation status following crizotinib failure was reported [7]. Furthermore, entrectinib has neurological side effects likely attributable to its TRKB inhibitory activity (dysgeusia, dizziness, paresthesia), and many patients require dose reduction or discontinuation [6,7]. Thus a strong unmet medical need remains for patients who are refractory to or intolerant of the ROS1 inhibitors crizotinib and entrectinib.

Introduction to the TRUST-II study

Here we describe the rationale and study design for the TRUST-II study (NCT04919811, AB 106 G208), an open-label, multicenter, single-arm, global, phase II study designed to evaluate the efficacy and safety of taletrectinib in patients with advanced or metastatic ROS1$^+$ NSCLC and other solid tumors. The study is sponsored by AnHeart Therapeutics, Inc. (NY, USA).

Background & rationale

Taletrectinib (previously named AB106 or DS-6051b) is a highly potent, selective, orally available next-generation ROS1 inhibitor. It is not only highly potent against tumors with primary fusions in ROS1, but also for those with ROS1 resistance mutations, such as the secondary solvent-front mutation G2032R [8]. Taletrectinib potently inhibited G2032R tumors (Table 1) with IC_{50} in the subnanomolar range in the presence of 10 μM ATP in the *in vitro* kinase assay. The IC_{50} of taletrectinib against G2032R is more than 400-times lower than that of the approved ROS1 inhibitors crizotinib and entrectinib. In addition, taletrectinib demonstrated a superior capability to cross the blood–brain barrier (BBB). In rats, the brain-to-plasma ratio of taletrectinib ranged from 0.40 to 3.11 following a single dose at 30 mg/kg. Even after 24 h of dosing, the brain concentrations were still measurable at 26 ng/g (Table 2), indicating that taletrectinib sufficiently penetrated into and sustained in the CNS. By comparison, repotrectinib, another next-generation ROS1 inhibitor in development, showed significantly weaker brain penetration ability, with the brain-to-plasma ratio ranging from 0 to 0.53 and undetectable at 24 h after dosing (Table 2). In an intracranial mouse patient-derived xenograft tumor model of SDC4 ROS1$^+$ NSCLC, seven out of eight mice survived for 60 days when treated with 100 mg/kg of taletrectinib daily starting on day 6 post

Table 1. Summary of IC_{50} in the kinase assay.

Kinase	IC_{50} (nM)			
	Taletrectinib	Crizotinib	Entrectinib	Repotrectinib
ROS1	0.07	0.66	0.71	<0.05
$ROS1_{G2032R}$	0.20	86.22	88.00	0.09
TRKA	1.26	8.46	1.63	0.53
TRKB	1.47	6.75	0.15	<0.05
TRKC	0.18	0.53	0.19	0.07

Biochemical IC_{50} data were generated by Reaction Biology Corp., comparing taletrectinib, repotrectinib, entrectinib and crizotinib side by side in the presence of ATP at a concentration of 10 μM.

Table 2. Total drug concentrations in the brain and plasma in the rat pharmacokinetics study.

Time points (h)	Taletrectinib			Repotrectinib		
	Total conc. in brain (ng/g)	Total conc. in plasma (ng/ml)	Brain/plasma ratio	Total conc. in brain (ng/g)	Total conc. in plasma (ng/ml)	Brain/plasma ratio
4	220	550	0.40 ± 0.10	32	475	0.07 ± 0.01
10	145	170	0.90 ± 0.19	15	28	0.53 ± 0.15
24	26	8	3.11 ± 1.20	0	2	0

Drugs were administered orally at 30 mg/kg.
Conc.: Concentration.

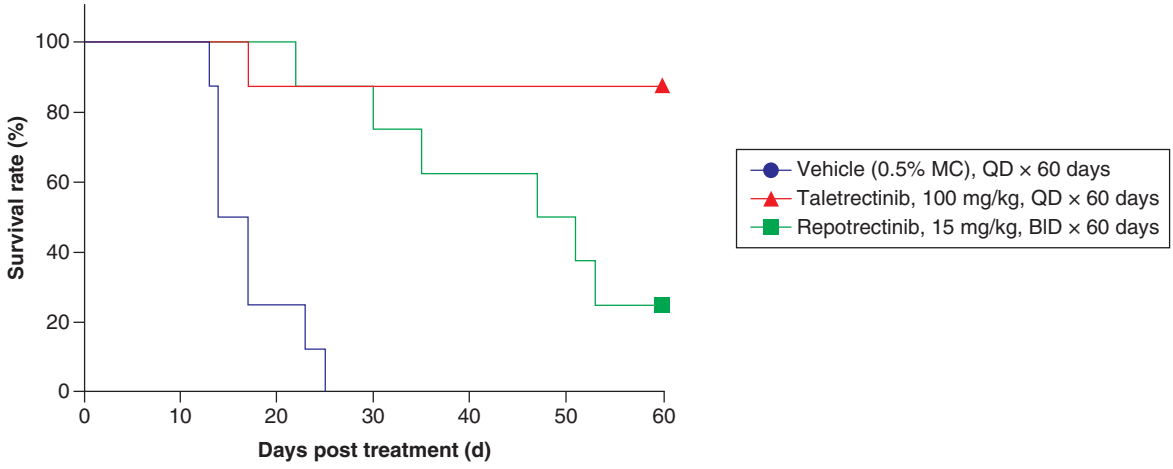
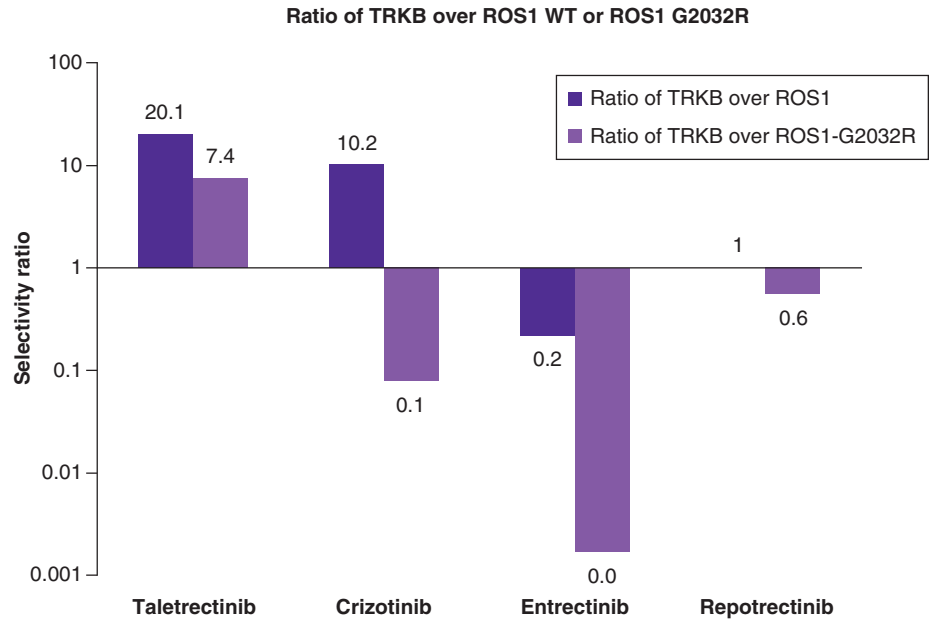


Figure 1. Intracranial antitumor activity of ROS1 inhibitors in mouse patient-derived xenograft model. The intracranial antitumor activity of taletrectinib and repotrectinib on survival times of BALB/C nude mice bearing non-small-cell lung cancer patient-derived tumor xenografts (SCD4 – ROS1 fusion) is presented.
BID: Twice a day; MC: Methyl cellulose; QD: Once daily.

inoculation, while all eight mice treated with vehicle died on day 25. In contrast, six out of eight mice treated with 15 mg/kg twice a day of repotrectinib died between day 25 and day 60 (Figure 1). The prolonged survival benefit of taletrectinib compared with repotrectinib suggested its better intracranial antitumor activity. While entrectinib and repotrectinib do show some intracranial antitumor activity, it comes at a cost of neurological side effects, potentially due to nonselective inhibition of TRKB in the CNS [9,10]. In contrast, taletrectinib was shown to be selective for ROS1 and $ROS1_{G2032R}$ over TRKB in the kinase assay (Figure 2 & Table 1). The data showed that taletrectinib is seven- to 20-times more selective against $ROS1_{G2032R}$ and ROS1 wild-type (i.e., only $ROS1^{+}$ without other point mutation) over TRKB.

In the taletrectinib regional phase II trial (TRUST-I, NCT04395677), the interim data showed ORRs of 92.5 (95% CI: 83.4–97.5) and 50.0% (95% CI: 33.4–66.6) in 67 ROS1 TKI-naive patients and 38 ROS1 TKI-pretreated patients, respectively [11]. Among five patients with the $ROS1_{G2032R}$ resistance mutation, four achieved partial response and one achieved stable disease. In 12 patients with measurable baseline CNS metastases,



TRKB	1.47	6.75	0.15	0.05
ROS1	0.07	0.66	0.71	0.05
	20.1	10.2	0.2	1
ROS1-G2032R	0.2	86.2	88	0.09
	7.4	0.1	0.0	0.6

Figure 2. Selectivity of taletrectinib, crizotinib, entrectinib and repotrectinib on ROS1 wild-type and ROS1$_{G2032R}$ over TRKB. The higher the ratio, the more active for ROS1/ROS1$_{G2032R}$ and the less inhibition of TRKB. 'ROS wild-type' means *ROS1* fusion only, with no other point mutation.
WT: Wild-type.

the intracranial ORR was 91.7% (95% CI: 61.5–99.8). Taletrectinib was well tolerated. The most common treatment-emergent adverse events (TEAEs) of any grade reported in a total of 190 patients (incidence ≥15%) were diarrhea (61.6%), increased aspartate aminotransferase (55.8%), increased alanine aminotransferase (49.5%), nausea (47.4%), vomiting (45.3%), anemia (27.4%), dizziness (18.4%), decreased appetite (17.4%) and decreased white blood cell count (15.3%). No grade 4 or 5 event was reported for these common TEAEs. The only grade 3 treatment-related adverse events (AEs) to occur in >5% of patients were increased aspartate aminotransferase (7.4%) and increased alanine aminotransferase (6.3%). No grade 3 dizziness was observed. In all, 27 patients (14.2%) had TEAEs requiring dose reduction, and ten (5.3%) had TEAEs requiring discontinuation of taletrectinib [11]. Based on the clinical data accumulated to date, taletrectinib has been granted Breakthrough Therapy Designation by the US FDA for the treatment of adult patients with advanced or metastatic ROS1$^+$ NSCLC who are either TKI treatment naive or previously treated with crizotinib.

Inhibition of TRKB in the brain is one of the potential reasons for the high incidence of CNS-related AEs associated with entrectinib. An ideal next-generation ROS1 TKI should be able to cross the BBB and exert its intracranial antitumor activity while sparing TRKB in the CNS. By comparing the relationship between intracranial objective response and one of the CNS-related AEs, dizziness, among four different ROS1 TKIs (Figure 3), we found that taletrectinib was the most desirable ROS1 TKI, with encouraging clinical benefit and a unique balance of excellent intracranial antitumor activity and low CNS AEs [11,12]. The differentiating property of taletrectinib demonstrated by *in vivo* and *in vitro* studies and promising clinical data from the regional study TRUST-I warrant further investigation of taletrectinib in patient populations with a more diverse ethnic background.

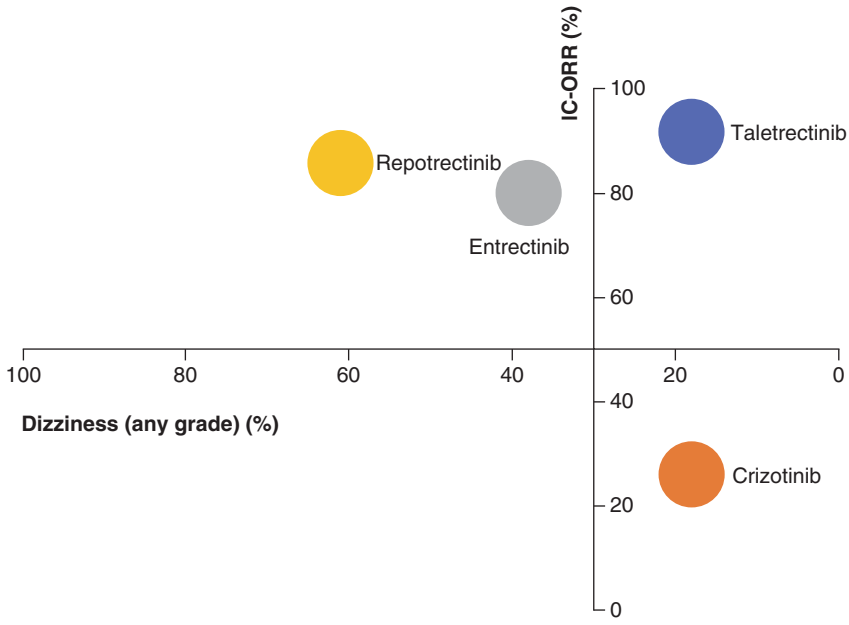


Figure 3. Taletrectinib has a unique balance of excellent intracranial antitumor activity and low CNS adverse events (dizziness). By comparing the relationship between intracranial objective response and one of the CNS-related adverse events, dizziness, among four different ROS1 tyrosine kinase inhibitors (TKIs), we found that taletrectinib was the most desirable ROS1 TKI, with encouraging clinical benefit and a unique balance of excellent intracranial antitumor activity and low CNS adverse events [6,9–11,13]. Note that the intracranial antitumor activity of crizotinib was from clinical data in TKI-naive ALK$^+$ non-small-cell lung cancer patients [14].
IC-ORR: Intracranial objective response rate.

Study objectives & design

The TRUST-II trial is a global, multicenter, open-label, single-arm, phase II study to evaluate the efficacy and safety of taletrectinib in the treatment of advanced or metastatic NSCLC and other solid tumors which are ROS1$^+$. An overview of the study design is provided in Figure 4.

This study will be conducted at approximately 80 investigational sites in countries in Asia, Europe and North America, including but not limited to Canada, China, France, Italy, Japan, Korea, Poland, Spain and the USA.

A total of 119 patients will be enrolled in this study, and the study population will consist of four cohorts:

- Cohort 1: systemic chemotherapy naive or pretreated with one prior line of chemotherapy, but never treated with any ROS1 TKI in ROS1$^+$ NSCLC;
- Cohort 2: prior treatment with one ROS1 TKI (crizotinib or entrectinib) and disease progression. The subject could be either chemotherapy naive or have received one line of platinum- and/or pemetrexed-based chemotherapy for the locally advanced or metastatic NSCLC;
- Cohort 3: prior treatment with two or more ROS1 TKIs and disease progression. The patient could be either chemotherapy naive or have received two or more lines of platinum- and/or pemetrexed-based chemotherapy for the locally advanced or metastatic NSCLC;
- Cohort 4: systemic chemotherapy naive or pretreated with two or more prior lines of chemotherapy, but never treated with any ROS1 TKI. ROS1$^+$ solid tumor types other than NSCLC will be enrolled.

The primary objective of this study is to evaluate the efficacy of taletrectinib, as evidenced by confirmed ORR according to Response Evaluation Criteria In Solid Tumors v. 1.1 (RECIST 1.1), assessed by an independent radiology review committee (IRC) in patients with advanced or metastatic ROS1$^+$ NSCLC (cohorts 1 and 2). The secondary objectives are: to evaluate the efficacy by duration of response (DOR), PFS, time to failure and time to response, as assessed by IRC; to evaluate the efficacy by ORR, DOR and PFS, as assessed by the investigators; to assess the intracranial activity, as evidenced by confirmed intracranial ORR, intracranial DOR, intracranial PFS and time to intracranial progression according to RECIST 1.1 and assessed by IRC; to evaluate overall survival

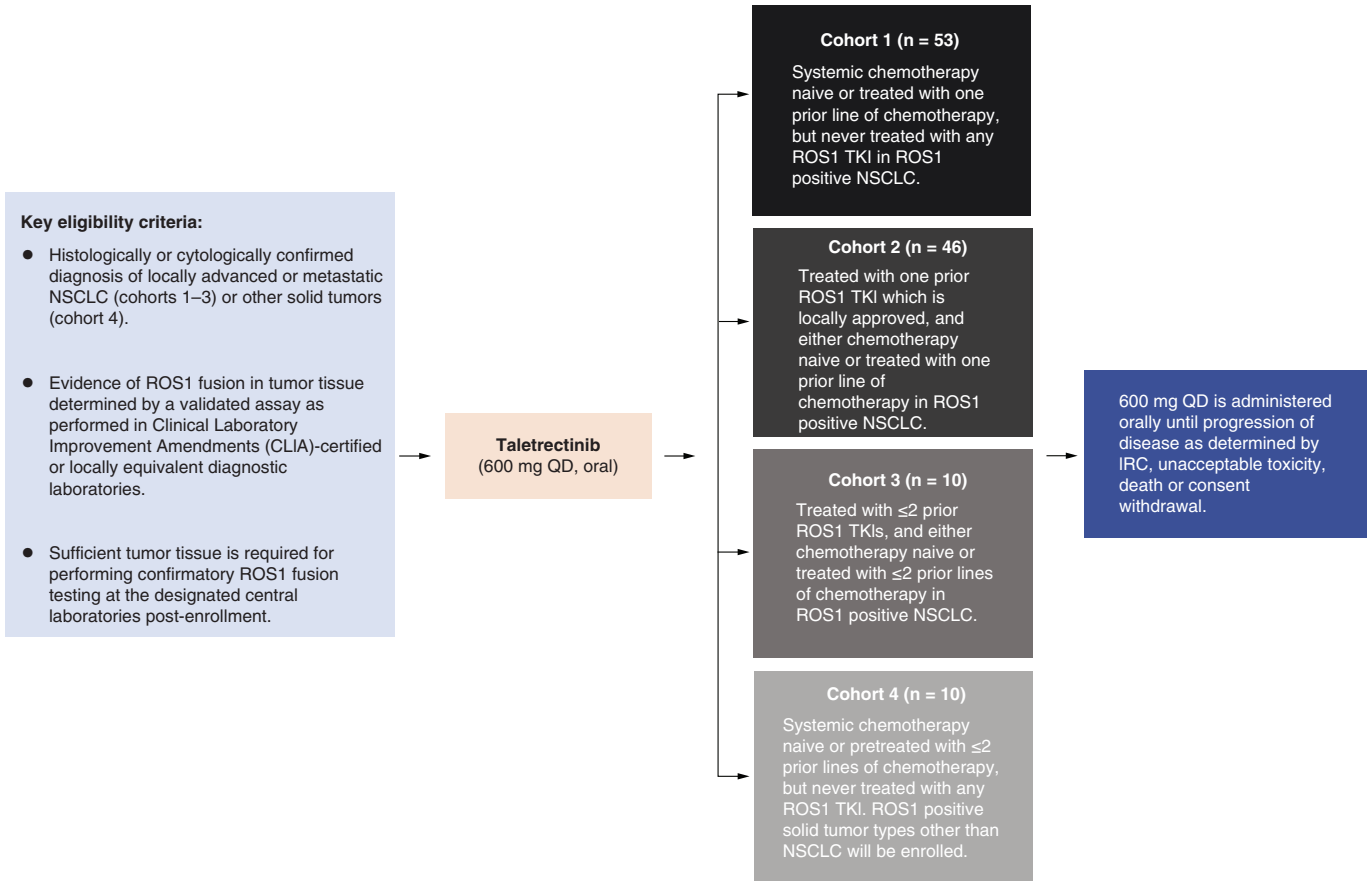


Figure 4. Schematic study design of TRUST-II. The study is a phase II study of taletrectinib in *ROS1* fusion-positive non-small-cell lung cancer and other solid tumors.
CLIA: Clinical Laboratory Improvement Amendments; IRC: Independent radiology review committee; NSCLC: Non-small-cell lung cancer; QD: Once daily; TKI: Tyrosine kinase inhibitor.

for patients enrolled in cohorts 1 and 2; to assess safety and tolerability of taletrectinib for all cohorts; and to characterize the pharmacokinetic profile of taletrectinib. The exploratory objectives include: to assess intracranial efficacy per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria by IRC (cohorts 1 and 2); to assess the efficacy in cohort 2 patients with specific *ROS1* secondary mutations; to assess the efficacy of taletrectinib in patients previously treated with two or more TKIs (cohort 3) and patients with non-NSCLC solid tumors (cohort 4); and to evaluate biomarkers of sensitivity or resistance to taletrectinib in tumor tissue and/or peripheral blood.

Eligibility criteria

The study population will consist of patients with advanced or metastatic ROS1$^+$ NSCLC and other solid tumors. Patients must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria for study entry (Table 3).

Study treatment

All patients will be treated with 600 mg taletrectinib, administered orally, once daily (q.d.) at approximately the same hour every day according to the dosing schedule, at least 2 h before a meal or at least 2 h after a meal. Because the MTD of taletrectinib identified in patients enrolled from the USA in the phase I study DS6051-A-U101 (NCT02279433) was 800 mg q.d., which was higher than 600 mg q.d., the MTD identified in patients enrolled from Japan in phase I study DS6051-A-J102 (NCT02675491) was used to further optimize the dose that can be used in patients enrolled in western countries [12]. The study allows intra-patient dose escalation for the patients in cohorts 2 and 3 (excluding patients in Asian countries): the dose of taletrectinib can be increased from 600 to

Table 3. Key eligibility criteria for TRUST-II.

Key inclusion criteria	Exclusion criteria
• Age ≥18 years (or ≥20 years if required by local regulations) • Histologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC (cohorts 1–3) or other solid tumor (cohort 4) • Evidence of *ROS1* fusion in tumor tissue determined by a validated assay as performed in a CLIA-certified or locally equivalent diagnostic laboratory. The molecular assays (RT-PCR, NGS) are highly recommended • Sufficient tumor tissue is required for performing confirmatory *ROS1* fusion testing at the designated central laboratories post-enrollment. For patients in cohort 1, an archival tumor tissue specimen should be available and collected prior to enrollment. If archival tumor tissue is unavailable, then a fresh biopsy must be performed. For patients in cohort 2, a fresh biopsy for tumor tissue is highly recommended before enrollment even if the archival tumor tissue is available. For patients in cohorts 3 and 4, either an archival sample or fresh tumor tissue must be available before enrollment • Patients with CNS involvement (including leptomeningeal carcinomatosis) which is either asymptomatic or previously treated and controlled are allowed; the use of seizure prophylaxis is allowed as long as patients are taking non-EIAEDs. If corticosteroid treatment is required, it should be a stable or decreasing dose of ≤10 mg prednisone or equivalent. If patients have neurological symptoms or signs due to CNS metastasis, they need to complete whole-brain or gamma-knife irradiation treatment at least 14 days before enrollment and be clinically stable • The patient is either ROS1 TKI treatment naive, or treated with prior ROS1 TKI(s): ◦ Cohort 1: systemic chemotherapy naive or pretreated with one prior line of chemotherapy, but never treated with any ROS1 TKI ◦ Cohort 2: prior treatment with one ROS1 TKI (crizotinib or entrectinib) and disease progression. The patient could be either chemotherapy naive or has received one line of platinum- and/or pemetrexed-based chemotherapy for the locally advanced or metastatic NSCLC ◦ Cohort 3: prior treatment with two or more prior ROS1 TKIs and disease progression. The patient could be either chemotherapy naive or has received two or more lines of platinum- and/or pemetrexed-based chemotherapy for the locally advanced or metastatic NSCLC ◦ Cohort 4: systemic chemotherapy naive or pretreated with two or more prior lines of chemotherapy, but never treated with any ROS1 TKI. ROS1^{+} solid tumor types other than NSCLC will be enrolled • At least one measurable disease per RECIST 1.1 assessed by investigator • ECOG performance status: 0 or 1 • Patients with adequate organ function (bone marrow, hepatic, renal)	• Treatment with other investigational agents or anticancer therapy within 2 weeks (or five half-lives of the compound, whichever is longer) prior to study enrollment. In addition, no concurrent anticancer therapy is permitted • Previously treated with IO therapy including immune checkpoint inhibitors within 12 weeks before enrollment • Major surgery within 4 weeks prior to enrollment • Radiation therapy with a limited field for palliation within 1 week before study treatment • AEs due to prior therapy are unresolved to ≤CTCAE grade 1 except for AEs not constituting a safety risk to the patient in the judgment of investigators • Patients with spinal cord compression caused by tumor and/or cancerous meningitis • History or evidence of interstitial fibrosis, interstitial lung disease or TKI-induced pneumonitis (excluding clinically insignificant or asymptomatic post-radiation pneumonitis) • Any gastrointestinal disorders that may affect absorption of oral medications • Active and clinically significant bacterial, fungal or viral infection including HBV, HCV or SARS-CoV-2, known HIV and AIDS-related illness • Clinically significant cardiovascular diseases within 3 months prior to the first dose of investigational drug: myocardial infarction, severe/unstable angina, coronary/peripheral endovascular treatment, heart failure or cerebrovascular disorder including transient ischemic attack • Ongoing cardiac dysrhythmias of ≥ CTCAE grade 2, uncontrolled atrial fibrillation of any grade, or QTcF >470 milliseconds, or symptomatic bradycardia <45 beats per min

AE: Adverse event; CLIA: Clinical Laboratory Improvement Amendments; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Co-operative Oncology Group; EIAED: Enzyme-inducing anti-epileptic drugs; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IO: Immuno-oncology; NSCLC: Non-small-cell lung cancer; NGS: Next-generation sequencing; QTcF: QT interval corrected for heart rate by Fredericia's formula; RECIST 1.1: Response Evaluation Criteria In Solid Tumors version 1.1; TKI: Tyrosine kinase inhibitor.

800 mg q.d. on the condition that the patient has completed at least one cycle of initial treatment of taletrectinib 600 mg q.d. with good tolerability (no AEs > grade 2) in the clinical judgment of the investigator.

Taletrectinib will be administered in 21-day cycles. The study treatment will continue until disease progression as per RECIST 1.1 (determined by IRC), unacceptable toxicity, death or consent withdrawal. Patients may continue study treatment after disease progression if they continue to experience clinical benefit, in the opinion of the investigator, and after discussion with the sponsor.

Planned sample size & interim analysis

Approximately 119 patients will be enrolled in this study at approximately 80 sites in North America, Europe and the Asia-Pacific region; 53 patients will be enrolled in cohort 1 and 46 in cohort 2 to ensure sufficient patients for response evaluation (at least 47 and 41 response-evaluable patients for cohort 1 and cohort 2, respectively). Approximately ten patients are planned to be enrolled in each of cohorts 3 and 4. For cohort 1, an interim analysis is planned after 18 response-evaluable patients are enrolled and first tumor response is due for assessment based on Fleming's two-stage method. For cohort 2, an interim analysis is planned after 22 response-evaluable patients are enrolled and first tumor response is due for assessment based on Fleming's two-stage method. The two planned interim analyses will be conducted independently of each other and will be triggered whenever cohort 1 or 2 has met the predefined criteria. The purpose of the planned interim analysis is to evaluate the safety of the dosing regimen

and modification schemes for study population, as well as to stage-gate the study for achieving its anticipated efficacy. No interim analysis is planned for cohorts 3 and 4.

Planned study duration

The trial was opened for enrollment in September 2021, and it is estimated that final data analysis for the primary outcome measure will likely occur in June 2024.

Study procedures

Disease assessments

Tumor response and disease progression will be assessed using diagnostic imaging (contrast-enhanced computed tomography [CT] of the chest, abdomen and pelvis; MRI of the brain). Fluorodeoxyglucose-PET and bone scan are not required unless clinically indicated. Contrast-enhanced CT of the brain is allowed in patients for whom brain MRI is contraindicated. Plain CT or MRI is allowed when contrast imaging cannot be performed for reasons such as bronchial asthma or contrast media allergy. Diagnostic imaging within 4 weeks and bone scan within 12 weeks before screening are accepted in this study. These images will be used as baseline.

Tumor evaluation post-treatment should be started at cycle 3, day 1 (C3D1) for all patients and performed every two cycles in the first eight cycles (C3D1, C5D1, C7D1 and C9D1), then every three cycles for cycles 9–26 (C12D1, C15D1, C18D1, C21D1, C24D1 and C27D1) and every four cycles thereafter. A time window of ±7 days is acceptable. The imaging examination method and examination site of the follow-up cycle should be the same as those used at baseline. If there are clinical indications, appropriate imaging methods to examine the additional site may be required by investigators. For any patient who has bone metastases at baseline, a bone scan will be performed every 12 weeks; otherwise, a bone scan is only required when new symptoms (e.g., bone pain) are present during the treatment period which suggest new or previously unknown bone metastases. CT/MRI brain scans are performed at every tumor assessment in patients with baseline brain metastases; and as clinically indicated in patients without baseline brain metastases. For patients who achieve complete or partial response for the first time, the efficacy confirmation must be conducted at least 4 weeks later. For patients who discontinue treatment for reasons other than disease progression, the tumor evaluation should be performed every 6 or 12 weeks after the last dose until either disease progression or commencement of a new anticancer therapy. Meanwhile, patients who have measurable brain metastases prior to the start of treatment will continue tumor evaluation until progression of IRC-confirmed brain metastases.

Safety assessments

Safety assessments include physical and laboratory examinations, vital signs, ECG and ophthalmological examination. Laboratory examinations include hematology, coagulation, biochemistry and urinalysis. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v. 5.0.

Tumor tissue collection

Mandatory pre-treatment tumor tissue will be collected for the central laboratory to confirm the *ROS1* fusion status by a validated next-generation sequencing assay. Central *ROS1* confirmation via next-generation sequencing will not delay treatment initiation, which will be acceptable provided that a site's local qualified laboratory or independent reference lab (i.e., a Clinical Laboratory Improvement Amendments-certified laboratory) has returned positive results. If it can be safely performed, a fresh biopsy of tumor tissue should be obtained at disease progression to identify genetic alterations associated with upfront or acquired resistance to taletrectinib.

Blood sample collection

Blood samples for pharmacokinetic analysis will be collected from approximately ten patients from each of cohorts 1 and 2 with an extensive pharmacokinetic sampling approach at the prespecified time points: 0 (pre-dose), 1 (±15 min), 2 (±15 min), 4 (±24 min), 6 (±36 min), 8 (±48 min) and 24 h (±2 h) post-dose on C1D1 and C1D15; and pre-dose on C1D8 and C2D1. Sparse pharmacokinetic samples will be collected from other patients (cohorts 1–4) pre-dose and at 2–7 h post-dose on C1D1, C1D15 and C2D1; and pre-dose on C1D8. Pharmacokinetic blood sampling is not required after C2D1. Whole blood samples (20 ml) will be collected for exploratory biomarker studies at screening, once per cycle in the first eight cycles starting from cycle 3 (C3D1, C4D1, C5D1, C6D1, C7D1, C8D1 and C9D1), then once every two cycles (C11D1, C13D1, C15D1 etc.) until the end of treatment.

Table 4. Efficacy outcome measures/end points for TRUST-II.

Efficacy end points
Primary
• Confirmed ORR according to RECIST 1.1 assessed by an IRC (cohorts 1 and 2)
Secondary
• DOR according to RECIST 1.1 assessed by IRC (cohorts 1 and 2) • PFS according to RECIST 1.1 assessed by IRC (cohorts 1 and 2) • TTF according to RECIST 1.1 assessed by IRC (cohorts 1 and 2) • TTR according to RECIST 1.1 assessed by IRC (cohorts 1 and 2) • OS (cohorts 1 and 2) • ORR, DOR and PFS according to RECIST 1.1 assessed by investigators (cohorts 1 and 2) • Confirmed IC ORR, IC DOR, IC PFS and TTiP according to RECIST 1.1 assessed by IRC (cohorts 1 and 2)
Exploratory
• Confirmed IC ORR, IC DOR, IC PFS and TTiP per RANO-BM criteria assessed by IRC (cohorts 1 and 2) • IRC response rate in patients with specific *ROS1* secondary mutations (cohort 2) • ORR, DOR, PFS, TTF, TTR and OS according to RECIST 1.1 assessed by investigators (cohort 3) • ORR, DOR, PFS, TTF, TTR and OS according to RECIST 1.1 assessed by investigators (cohort 4) • Biomarkers in tumor tissue and peripheral blood circulating tumor DNA including *ROS1* fusion gene and/or *ROS1* kinase domain mutations

DOR: Duration of response; IC: Intracranial; IRC: Independent radiology review committee; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RANO-BM: Response Assessment in Neuro-Oncology Brain Metastases; RECIST 1.1: Response Evaluation Criteria In Solid Tumors version 1.1; TTF: Time-to-failure; TTiP: Time-to-intracranial-progression; TTR: Time-to-response.

Efficacy outcome measures/end points

As shown in Table 4, the primary and secondary end points are defined for cohorts 1 and 2, but not for cohorts 3 and 4, which are included in the study for exploratory purposes only.

Statistics

All eligible patients who have received at least one dose of taletrectinib will be the population for primary safety analysis. All response-evaluable patients will be the population for primary efficacy analysis.

Sample size determination

Cohort 1: with a threshold ORR of 55% (null hypothesis H0: ORR ≤55%) and expected ORR of 75% (alternative hypothesis H1: ORR >55%), the necessary sample size was calculated by using Fleming's two-stage method with assumptions of a one-sided type I error rate of 0.025 and 80% power. The required sample size is 47 response-evaluable patients. To ensure enough response-evaluable patients, the target number of enrolled patients is increased to 53.

Cohort 2: with a threshold ORR of 20% (null hypothesis H0: ORR ≤20%) and expected ORR of 40% (alternative hypothesis H1: ORR >20%), the necessary sample size was calculated by using Fleming's two-stage method with assumptions of a one-sided type I error rate of 0.025 and 80% power. The required sample size is 41 response-evaluable patients. To ensure enough response-evaluable patients, the target number of enrolled patients is increased to 46.

Cohorts 3 and 4: approximately ten patients for each cohort are planned to be enrolled. The results will be used for exploratory purposes. The sample size of cohorts 3 and 4 is not based on statistical assumption.

Primary analysis of the primary efficacy end point

The ORR will be determined as the proportion of patients with a confirmed objective response of complete or partial response. The decision rule will be based on Fleming's two-stage method. The frequencies and proportions of ORR will be summarized by cohort, and 95% CIs for the ORR will be calculated by cohort using the Clopper–Pearson method for both interim analysis and final analysis. The disease control rate will be defined as the proportion of patients with complete or partial response or stable disease and will be summarized descriptively. The overall response at each tumor assessment visit will be listed for each patient. The swimmer plot will be presented to show individual treatment status and objective response for each patient. Waterfall plots will be created to show the individual response based on tumor reduction. The spider plot will be presented to show the tumor change from baseline for each patient by visit.

Discussion & future perspective

The TRUST-II study was designed in 2020 and began enrolling patients in September 2021. During that time, crizotinib and entrectinib were approved by the FDA as treatment options for patients with ROS1$^+$ NSCLC. However, crizotinib has limited penetration to the brain and is ineffective against tumors with *ROS1* secondary resistance mutations [4]. While entrectinib has improved CNS penetration, it is often ineffective against tumors with *ROS1* secondary resistance mutations and is intolerable by many patients, as manifested by its high dose-reduction rate of 29% and high incidence of CNS-related AEs such as dysgeusia, dizziness and paresthesia [6,7].

Taletrectinib has shown clinically meaningful efficacy and a favorable safety profile in the phase I [12] and regional phase II studies and has the potential to improve PFS based on its greater potency against tumors with *ROS1* fusions and its broad *in vitro* coverage against those with known crizotinib-resistant mutations [11]. Additionally, taletrectinib has excellent BBB penetration and prolonged survival benefit compared with repotrectinib in animal models, corroborating the promising intracranial activity of taletrectinib and potentially improved efficacy in patients with brain metastasis [11,12]. Furthermore, taletrectinib selectively inhibits ROS1 wild-type and its resistant mutations over TRKB, which greatly improves its safety profile with minimal CNS-related AEs. The ongoing TRUST-II study is actively enrolling patients globally. Cohorts 1 and 2 are the main cohorts with the registrational intention. Cohorts 3 and 4 are exploratory in nature, and further exploratory cohorts (e.g., patients with NTRK$^+$ solid tumors) can be included pending the emerging supportive preclinical and clinical data. Given the rarity of ROS1$^+$ NSCLC, which is a severe and life-threatening disease, the current study was designed as a single-arm study to expedite the development and regulatory approval of, and timely patient access to, a potential effective treatment option. However, the study did not mandate patients without brain metastasis at baseline to follow regular brain imaging to measure the cumulative incidence rate of CNS progression. Nevertheless, the result of the TRUST-II study, if positive, may reshape the treatment paradigm for ROS1$^+$ NSCLC regardless of treatment-naive patients or patients who failed first-generation TKIs.

Conclusion

The current standard-of-care TKI for ROS1$^+$ NSCLC patients is crizotinib or entrectinib in many parts of the world; treatment standard after progression on crizotinib or entrectinib has yet to be established. The TRUST-II study is investigating the efficacy and tolerability of taletrectinib as second-line and first-line therapy for ROS1$^+$ NSCLC. The results of this study will help define the role of taletrectinib in the treatment of ROS1$^+$ NSCLC treatment.

Author contributions

Conception and design of the clinical trial by S Ou and all AnHeart authors (Z Hu, M Pan, W Wang, S Li). Provision of patients contributed by M Nagasaka, Y Ohe, C Zhou, C Choi, N Yang, G Liu, E Felip, M Pérol, B Besse, J Nieva, L Raez, N Pennell, A Dimou, F de Marinis, F Ciardiello. Collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of the manuscript were contributed by all authors. All authors take accountability for all aspects of the work.

Acknowledgments

The authors thank the patients, their families and their caregivers, as well as the investigators and their team members, for participation in the TRUST-II trial. Relevant team members from AnHeart Therapeutics, especially F Fan, M Chen, Q Zhao, H Zheng and Y Hou, are acknowledged for data collecting, data analysis and editorial assistance.

Financial & competing interests disclosure

Anheart provided the publication fee and editorial assistance. M Nagasaka: consulting (Caris Life Science), advisory boards honoraria (Astra Zeneca, Daiichi-Sankyo, Novartis, EMD Serono, Pfizer, Lilly, Genentech, Mirati), speaker's bureau (JNJ/Janssen, Takeda, Blueprint Medicine), travel support (AnHeart Therapeutics). Y Ohe: consulting or advisory role (AstraZeneca, Chugai, ONO, BMS, Kyorin, Celltrion, Amgen, Nippon Kayaku, Boehringer Ingelheim, AnHeart Therapeutics), honoraria (AstraZeneca, Chugai, Eli Lilly, ONO, BMS, Boehringer Ingelheim, Bayer, Pfizer, MSD, Taiho, Nippon Kayaku, Kyowa Hakko Kirin, Eisai), research funding (AstraZeneca, Chugai, Lilly, ONO, BMS, Kyorin, Dainippon-Sumitomo, Pfizer, Taiho, Novartis, Takeda, Kissei, Daiichi-Sankyo, Janssen). C Zhou: consulting or advisory role (Innovent Biologics, Hengrui, Qilu, TopAlliance Biosciences, Inc.), honoraria (Lily China, Sanofi, BI, Roche, MSD, Qilu, Hengrui, Innovent Biologics, C-Stone, LUYE Pharma, TopAlliance Biosciences, Inc., Amoy Diagnositics, AnHeart Therapeutics). G Liu: consulting or advisory role (Pfizer, Takeda, Amgen, AstraZeneca, END Serono, Merck, Jazz, Novartis, Roche, BMS), research funding (Pfizer, Takeda, Amgen, AstraZeneca, Boehringer Ingelheim). E Felip: consulting or advisory role

(Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly, F. Hoffmann-La Roche, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Peptomyc, Pfizer, Sanofi, Takeda), honoraria (Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Roche, Janssen, Medical Trends, Medscape, Merck Serono, Merck Sharp & Dohme, Peervoice, Pfizer, Sanofi, Takeda, Touch Oncology), research funding, all to institution (Grant for oncology innovation [Merck healthcare KGAa], foundation Merk Salud), others (GRÍFOLS, an independent member of the board). M Pérol: consulting or advisory role (Roche, Eli Lilly, Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, AstraZeneca, Takeda, Gritstone, Sanofi, GlaxoSmithKline, Amgen, Daiichi-Sankyo, Janssen-Cilag, Ipsen, AnHeart Therapeutics, Esai), honoraria (Eli Lilly, Roche, AstraZeneca, Pfizer, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Takeda, Merck Sharp & Dohme, Chugai, Illumina, Sanofi, AnHeart Therapeutics, Esai, Ipsen), research funding (Roche, AstraZeneca, Chugai, Takeda, Boehringer Ingelheim). B Besse: research funding, all to institution (4D Pharma, Abbvie, Amgen, Aptitude Health, AstraZeneca, BeiGene, Blueprint Medicines, Boehringer Ingelheim, Celgene, Cergentis, Chugai Pharmaceutical, Cristal Therapeutics, Daiichi-Sankyo, Eli Lilly, Eisai, Genzyme Corporation, GSK, Inivata, IPSEN, Janssen, Onxeo, OSE Immunotherapeutics, Pfizer, Roche-Genentech, Sanofi, Takeda, Tolero Pharmaceuticals, Turning Point Therapeutics). J Nieva: consulting or advisory role (Ypsomed, Aadi, Fujirebio, Naveris, AstraZeneca, Western Oncolytics, Kalivir), research funding (Genentech, Merck), stock and other ownership interests (Cansera, Indee Bio, Epic Sciences, Quantgene). L Raez: consulting or advisory role (BMS, Roche, Merck, Guardant Health, Nant Health, Natera, AstraZeneca, Pfizer, Mirati, Turning Point). N Pennell: consulting or advisory role (Merck, Eli Lilly/LOXO, Mirati, Novartis, Pfizer, Sanofi Genzyme, Genentech, Janssen, ResistanceBio), research funding (LOXO, Merck, Heat Bio, WindMIL, Genentech, Astrazeneca, Spectrum, Mirati, Altor, Jounce, Sanofi, Navire). A Dimou: research funding, clinical trial support (AnHeart Therapeutics). F de Marinis: consulting or advisory role (Merck, Roche, AstraZeneca), honoraria (MSD, Novartis, BMS). F Ciardiello: consulting or advisory role (Roche, Merck KGaA, Servier, Pierre Fabre, MSD, Bayer), research funding (Merck KGaA, Amgen). T Seto: honoraria (AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical, Covidien Japan, Daiichi-Sankyo, Eli Lilly Japan, Kyowa Hakko Kirin, MSD, Mochida Pharmaceutical, Nippon Boehringer Ingelheim, Novartis Pharma, Ono Pharmaceutical, Pfizer Japan, Taiho Pharmaceutical, Takeda, Towa Pharmaceutical), research funding, all to institution (Abbvie, Chugai Pharmaceutical, Daiichi-Sankyo, Eli Lilly Japan, Kissei Pharmaceutical, MSD, Novartis, Pfizer Japan, Takeda), employment (Precision Medicine Asia). Z Hu: employment (AnHeart Therapeutics). M Pan: employment (AnHeart Therapeutics). W Wang: employment (AnHeart Therapeutics). S Li: employment (AnHeart Therapeutics). S Ou: consulting or advisory role (JNJ/Janssen, Lilly, Daiichi Sankyo, BlossomHill Therapeutics, AnHeart Therapeutics, Elevation Oncology), honoraria (Pfizer, JNJ/Janssen, Lilly, Daiichi-Sankyo, Elevation Oncology, Caris Life Science, Astra Zeneca, DAVA Oncology LLP), research funding, all to institution (Pfizer, JNJ/Janssen, Nuvalent, Merus, Genentech, Mirati, Daiichi Sankyo, Merch, Merus), stock and other ownership interests (BlossomHill Therapeutics, MBrace Therapeutics, Turning Point Therapeutics [stock prior to 17 August 2022], Elevation Oncology [stock prior to 30 September 2022], AnHeart Therapeutics). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical conduct of research

The authors have confirmed appropriate institutional review board approval and have followed the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline for good clinical practice. Informed consent has been obtained from all participants enrolled in the study.

Data sharing statement

The datasets, including the redacted study protocol, redacted statistical analysis plan and individual participant data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after deidentification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

Open access

Executive summary

Background

- *ROS1* oncogenic fusions are observed in 1–2% of patients with non-small-cell lung cancer (NSCLC) as well as in ovarian, gastric and colorectal cancers, cholangiocarcinoma and glioblastoma.
- CNS metastasis occurs in 20–30% of ROS1 tyrosine kinase inhibitor (TKI)-naive patients and in up to 50% of crizotinib-pretreated ROS1$^+$ NSCLC patients.
- Resistance to first-generation ROS1 inhibitors often occurs with secondary mutations, predominantly the solvent-front mutation ROS1$_{G2032R}$.
- Taletrectinib, a next-generation, potent, selective ROS1 TKI, is being developed to further improve the efficacy and safety profile in ROS1$^+$ NSCLC patients.
- Taletrectinib has the following differentiating properties: 1) potently inhibits ROS1 wild-type; 2) overcomes resistance to first-generation ROS1 inhibitors; 3) addresses CNS metastasis; 4) confers fewer CNS adverse events by selectively inhibiting ROS1 over TRKB.
- Efficacy and safety data of taletrectinib from a regional phase II study (TRUST-I, NCT04395677) showed very good results.

The TRUST-II study

- The TRUST-II is a phase II, multicountry, multicenter, open-label, nonrandomized, single-arm study designed to evaluate the efficacy and safety of taletrectinib in the treatment of advanced or metastatic NSCLC and other solid tumors which are ROS1$^+$.
- Eligible patients will be treated with taletrectinib at 600 mg (three capsules) once daily, administered until disease progression and/or unacceptable toxicity.
- A total of 119 patients will be enrolled into four different cohorts, with cohorts 1 (n = 53) and 2 (n = 46) as the main cohorts with the registrational intention.
- The TRUST-II study is currently actively enrolling patients in North America, Europe and Asia.
- The primary end point for cohorts 1 and 2 is the confirmed objective response rate (ORR), as assessed by an independent review committee (IRC), per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1).
- Secondary end points include confirmed ORR by investigators; duration-of-response (DOR); progression-free survival (PFS); time to failure; time to response assessed by IRC and by investigators; overall survival; confirmed intracranial ORR, intracranial DOR, intracranial PFS and time to intracranial progression according to RECIST 1.1 for cohorts 1 and 2 assessed by IRC; safety and tolerability; and pharmacokinetic parameters.
- Exploratory end points include confirmed intracranial ORR, intracranial DOR, intracranial PFS and time to intracranial progression per Response Assessment in Neuro-Oncology Brain Metastases criteria assessed by IRC for cohorts 1 and 2; IRC response rate in patients with specific secondary mutations for cohort 2; ORR, DOR, PFS, time-to-failure, time-to-response and overall survival according to RECIST 1.1 assessed by investigators for cohorts 3 and 4; and biomarker analyses.

Conclusion

- The TRUST-II study is mainly investigating the efficacy and tolerability of taletrectinib as second- and first-line ROS1 TKI therapy for ROS1$^+$ NSCLC. The results of this study will help define the role of taletrectinib in ROS1$^+$ NSCLC treatment.

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