TRIDENT-1 (TurningPoint)

A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients With Advanced Solid Tumors Harboring ROS1 or NTRK1-3 Rearrangements.

This is the trial summary as assessed on clinicaltrials.gov on 11/02/2021.

Minor changes in the protocol may occur. You can check this on this direct link: https://clinicaltrials.gov/ct2/show/NCT03093116

Trial Design:

Arm	Intervention
Experimental 6 distinct expansion cohorts • EXP-1: ROS1 TKI-naïve ROS1+ NSCLC • EXP-2: 1 Prior ROS1 TKI and 1 Platinum based chemo ROS1+ NSCLC • EXP-3: 2 Prior ROS1 TKIs ROS1+ NSCLC (No Chemo or IO) • EXP-4: 1 Prior ROS1 TKI ROS1+ NSCLC (No Chemo or IO) • EXP-5: TRK TKI-naïve NTRK+ solid tumors • EXP-6: TRK TKI-pretreated NTRK+ solid tumors	Repotrectinib (TPX-0005) - oral

Inclusion criteria:

Histologically or cytologically confirmed diagnosis of locally advanced, or metastatic solid tumor (including primary CNS tumors) that harbors a ROS1, or NTRK1-3 gene fusion.

1. Subject must have a documented ROS1 or NTRK1-3 gene fusion determined by tissue-based local testing using either:
    a. a next-generation sequencing (NGS) or quantitative polymerase chain reaction (qPCR) test will be accepted to determine molecular eligibility.

    • Adequate tumor tissue needs to be sent to the Sponsor designated central diagnostic laboratory for retrospective confirmation by a central diagnostic laboratory test selected by the Sponsor.

    OR

    b. a fluorescence in situ hybridization (FISH) test AND prospective confirmation of fusion status by a central diagnostic laboratory test selected by the Sponsor PRIOR to enrollment will be accepted to determine molecular eligibility.

- Adequate tumor tissue must be sent to the Sponsor designated central diagnostic laboratory for prospective confirmation by a central diagnostic laboratory test selected by the Sponsor PRIOR to enrollment.

2. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.
3. Age ≥12 (or age ≥ 20 as required by local regulation).
4. Willing and able to provide written institutional review board (IRB)/institutional ethics committee-approved Informed Consent or an Assent signed by a parent or legal guardian for subjects age 12 to 17.
5. At least 1 measurable target lesion according to RECIST (v1.1) prospectively confirmed by Blinded Independent Central Radiology Review (BICR), selected by Sponsor, PRIOR to enrollment. Subjects with CNS-only measurable disease ≥10 mm as defined by RECIST (v1.1) are eligible.
6. Subjects with advanced solid tumors harboring ROS1, NTRK1, NTRK2, or NTRK3 rearrangement will be assigned into 6 distinct expansion (EXP) cohorts provided all inclusion and exclusion criteria are met.

   i. EXP-1: ROS1 TKI-naïve ROS1+ NSCLC ii. EXP-2: 1 Prior ROS1 TKI and 1 Platinum based chemo ROS1+ NSCLC iii. EXP-3: 2 Prior ROS1 TKIs ROS1+ NSCLC (No Chemo or IO) iv. EXP-4: 1 Prior ROS1 TKI ROS1+ NSCLC (No Chemo or IO) v. EXP-5: TRK TKI-naïve NTRK+ solid tumors vi. EXP-6: TRK TKI-pretreated NTRK+ solid tumors
7. Subjects with asymptomatic CNS metastases (treated or untreated) and/or asymptomatic leptomeningeal carcinomatosis are eligible to enroll if they satisfy the protocol specified criteria.
8. Baseline laboratory values fulfilling the following requirements:Absolute neutrophils count (ANC) ≥1500/mm3 (1.5 × 109/L); Platelets (PLTs) ≥100,000/mm3 (100 × 109/L); Hemoglobin ≥ 9.0 g/dL transfusions are allowed; Serum creatinine or creatinine clearance > 40 mL/min; Total serum bilirubin < 1.5 × ULN; Liver transaminases (ASTs/ALTs) < 2.5 × ULN; < 5 × ULN if liver metastases are present Alkaline phosphatase (ALP); < 2.5 × ULN; < 5 × ULN if liver and/or bone metastasis are present; Serum calcium, magnesium, and potassium Normal or CTCAE grade ≤ 1 with or without supplementation
9. Life expectancy ≥ 3 months.

Exclusion criteria:

1. Concurrent participation in another therapeutic clinical trial.
2. Symptomatic brain metastases or leptomeningeal involvement.
3. History of previous cancer, except for squamous cell or basal-cell carcinoma of the skin, or any in situ carcinoma that has been completely resected, requiring therapy within the previous 2 years.
4. Major surgery within 4 weeks of start of repotrectinib treatment. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (≤10 fractions) must have been completed at least 48 hours prior to study entry
5. Clinically significant cardiovascular disease (either active or within 6 months prior to enrollment): myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Classification Class ≥ II), cerebrovascular accident or transient ischemic attack, symptomatic bradycardia, requirement for anti-arrhythmic medication. Ongoing cardiac dysrhythmias of NCI CTCAE grade ≥2

6. Any of the following cardiac criteria:

   Mean resting corrected QT interval (ECG interval measured from the onset of the QRS complex to the end of the T wave) for heart rate (QTcF) > 470 msec obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or any concomitant medication known to prolong the QT interval.

7. Known active infections (bacterial, fungal, viral including HIV positivity).
8. Gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact drug absorption.
9. Peripheral neuropathy of CTCAE ≥grade 2.
10. History of extensive, disseminated, bilateral, or presence of CTCAE grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis. Subjects with history of prior radiation pneumonitis are not excluded.