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Newcastle University

Health Technology Briefing
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Repotrectinib for treating advanced or metastatic non-small-cell lung cancer with ROS1-postive mutation

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 35982	NICE TSID: 11851	UKPS ID: 668001

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Repotrectinib is currently in clinical development for treating advanced or metastatic non-small-cell lung cancer (NSCLC) with ROS1-positive mutation. NSCLC is the most common type of lung cancer. Metastatic and advanced cancer means that the cancer has spread and curative treatment with surgery is unsuitable. A ROS1-positive lung cancer refers to any lung cancer that tests positive for a mutation in the ROS1 gene. ROS1-positive lung cancer tends to be aggressive and can spread to the brain and the bones which can lead to increased mortality. Current treatment options tend to cause acquired resistant mutations which make the treatment of ROS1-positive lung cancers more challenging.

Repotrectinib is a type of targeted therapy. It means that it identifies and attacks specific types of cancer cells while causing less damage to normal cells. In the phase I/II clinical trial, repotrectinib is administered orally. Preclinical and clinical data suggest that repotrectinib may be more effective than current standard treatments. If licensed, repotrectinib will offer an additional treatment option for patients with NSCLC with ROS1-positive mutation.

Proposed Indication

Treatment for adults with advanced or metastatic non-small cell lung cancer (NSCLC) with ROS1-postive mutation.[1]

Technology

Description

Repotrectinib (TPX-0005) is a small (low molecular weight), macrocyclic tyrosine kinase inhibitor of ROS1, tyrosine kinase (TRK) and anaplastic lymphoma kinase (ALK). Repotrectinib was designed to efficiently bind with the active kinase conformation and avoid steric interference from a variety of clinically resistant mutations.[2]

Oral repotrectinib is currently in clinical development (NCT03093116) for NSCLC with ROS1-postive mutation at the target dose of 160mg twice a day.[1,3]

Key Innovation

Despite new targeted therapies for the treatment of NSCLC ROS1-positive mutation, there continues to be a growing number of acquired resistant mutations in patients with previously treated tyrosine kinase inhibitors (TKIs), such as first-line crizotinib treatment, particularly solvent-front mutations. Existing TKIs can show susceptibility to acquired mutations, and toxicities that can limit duration of treatment. There continues to be a high unmet medical need to develop novel therapies that overcome intrinsic and acquired resistance, treat brain metastases, and prolong duration of response, with a more tolerable overall safety profile.[2,4]

The compact and rigid structure of repotrectinib is believed to enable it to precisely and efficiently bind deep into the ATP binding pocket of the kinase, and potentially circumvent the steric interference that results in resistance to bulkier kinase inhibitors, especially the solvent-front and gatekeeper mutations of ROS1, TRK and ALK kinases.[2] The ability to target the ATP-binding site of ROS1 and overcome steric interference created by different mutations meant repotrectinib showed activity against multiple resistance mechanisms, including metastasis, bypass pathways and different mutations.[5] If licensed, repotrectinib will offer an additional treatment option for patients with NSCLC with ROS1-positive mutation.

Regulatory & Development Status

Repotrectinib does not currently have marketing authorisation in the EU/UK for any indication.

Repotrectinib is in phase II/III clinical development for:[6]

- Locally advanced solid tumors
- Metastatic solid tumors
- Lymphoma
- Primary central nervous system (CNS) tumors
- Advanced cancer
- Solid tumours that harbor KRAS-, ALK-, or NTRK1-3-mutations

Repotrectinib has the following regulatory designations/awards:

- Fast Track designation by Food and Drug Administration (FDA) for NTRK-positive advanced solid tumors in August 2020[7]

- Breakthrough Therapy Designation by FDA for ROS1-positive metastatic NSCLC who have been previously treated with one ROS1 TKI and who have not received prior platinum-based chemotherapy in May 2022[8]

Patient Group

Disease Area and Clinical Need

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. Metastatic cancer occurs when the disease has spread, either to both lungs, the chest or beyond.[9] Advanced cancer normally means a cancer that cannot be cured.[10] Certain factors can increase the risk of developing lung cancer, including; smoking tobacco, exposure to radiation (by exposure to radon gas and previous radiotherapy treatment), exposure to certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes), previous lung disease (e.g. tuberculosis and COPD), family history of lung cancer and certain genetic mutations and lowered immunity (e.g. due to certain conditions e.g. HIV/AIDS, rheumatoid arthritis and systemic lupus erythematosus, or immunosuppressive medications).[11] Symptoms of lung cancer include a persistent cough, shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[12] A ROS1-positive lung cancer, also known as a ROS1 rearrangement in lung cancer, refers to any lung cancer that tests positive for a fusion in the ROS1 gene. ROS1-positive lung cancer tends to be aggressive and can spread to the brain and the bones.[13]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017.[14] According to the National Cancer Registration and Analysis Service (NCRAS), there were 25,777 diagnosed cases of stage III-IV lung cancer in 2017 in England.[15] In the UK, it is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage III-IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 21,910 cases diagnosed with stage III-IV in 2017 were NSCLC.[16] ROS1 is a rare mutation that occurs in less than 1-2% of people with NSCLC predominantly with adenocarcinoma.[17] Thus, according to the numbers above, there were approximately 438 people with NSCLC ROS1-postive mutation in England (2017).

Recommended Treatment Options

National Institute for Health and Care Excellence (NICE) recommends crizotinib and entrectinib for advanced or metastatic ROS1-positive NSCLC.[18,19]

Clinical Trial Information

Trial	**TRIDENT-1; NCT03093116; EudraCT 2016-003616-13;** 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 ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1) **Phase I/II –** Recruiting **Location(s):** 9 EU countries, UK, USA, Canada, and other countries **Primary completion date:** June 2024
Trial Design	Single group assignment, open-label
Population	N=patients 12 years and older who have histologically or cytologically confirmed diagnosis of locally advanced, or metastatic solid tumor (including

	primary CNS tumors) (Stage IV, American Joint Committee on Cancer v.7) that harbours an ALK, ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement by protocol specified tests
Intervention(s)	Phase 1: Oral repotrectinib Phase 2: Oral repotrectinib (TPX-0005): 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
Comparator(s)	No comparator
Outcome(s)	**Primary outcome measures:** • Dose limiting toxicities (DLTs) (Phase 1) [Time frame: Within 28 days of the first repotrectinib dose] • Recommended Phase 2 Dose (RP2D) (Phase 1) [Time frame: Within 28 days of the last patient dosed in escalation] • Overall Response Rate (ORR) Phase 2 [Time frame: Two to three years after first dose of repotrectinib dose] See trial record for full list of other outcomes
Results (efficacy)	"Median number of prior TKI treatment was 1 (0-3) with all of TKI naïve and 83% of TKI pre-treated patients (pts) received prior chemotherapy. Among 10 evaluable TKI-naïve ROS1+ NSCLC patients, confirmed ORR by Blinded Central Review (BCR) was 90% (95% CI 56 - 100) with median duration of response (DOR) not reached ((range 5.5+ – 14.9+ months (months, mo)). Among 18 TKI-pretreated patients, confirmed ORR by BCR was 28% (95% CI 10 – 54) with DOR of 10.2 mos. Subgroup analysis showed confirmed ORR 44% (95% CI 14 - 79) in 9 prior TKI pts and treated at dose levels of 160 mg daily or above. In 7 pts with measurable target CNS lesions at baseline, the intracranial ORR was 3/3 (100%) with DOR (5.5+; 7.2+; 14.85+ mos) in TKI-naïve patients and 2/4 (50%) with DOR (5.5+;14.8+, mo) in TKI-pretreated patients, respectively."[20]
Results (safety)	"Most AEs (adverse events) were manageable and grade (Gr) 1-2. Common (> 20%) treatment-related AEs were dizziness (49%), dysgeusia (48%), paresthesia (28%), and constipation (20%). Four dose limiting toxicities (Gr3 dyspnea/hypoxia (n = 1); Gr2 (n = 1) and Gr3 (n = 1) dizziness at 160 mg twice daily, and Gr3 dizziness (n = 1) at 240 mg daily) occurred and were managed with dose modifications."[20]

Estimated Cost

The cost of repotrectinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology guidance. Entrectinib for treating ROS1-positive advanced non-small-cell lung cancer (TA643). August 2020.
- NICE technology guidance. Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (TA529). July 2018.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). Updated September 2022.
- NICE quality standard. Lung cancer in adults (QS17). Updated March 2019.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- European Society of Medical Oncology (ESMO). ESMO Guideline. Early and locally advanced non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow up. 2020.[21]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[22]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137). 2014.[23]

Additional Information

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