NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Datopotamab deruxtecan for previously treated advanced non-small-cell lung cancer

Company/Developer	Daiichi Sankyo Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30937	NICE TSID: 11840	UKPS ID: 666402

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Datopotamab deruxtecan is being developed to treat advanced stage non-small-cell lung cancer (NSCLC). NSCLC is diagnosed at an advanced stage in nearly 50% of patients and often has a poor prognosis with worsening outcomes after each line of subsequent therapy. While initial treatment consisting of immunotherapy with or without chemotherapy has improved outcomes for patients with NSCLC without actionable genomic alterations, disease progression still occurs in the majority of patients and additional treatment strategies in this setting are needed. Currently in phase III clinical trials.

Datopotamab deruxtecan is a specifically designed precision cancer medicine known as an antibody drug conjugate (ADC). ADCs are proteins designed to harness the targeting ability of monoclonal antibodies (a type of protein) by linking them to cell-killing agents. Datopotamab deruxtecan is administered intravenously. The drug binds to a protein (TROP2) expressed on tumour cells. This causes the DNA to break. In turn, there is no more DNA reproduction, resulting in cell death. There are currently no TROP2-directed therapies or ADCs approved for the treatment of NSCLC. If licensed, datopotamab deruxtecan would offer an additional treatment option for patients with advanced NSCLC, whose disease has progressed following previous treatment.

Proposed Indication

For previously treated advanced or metastatic non-small cell lung cancer.[1]

Technology

Description

Datopotamab deruxtecan (Dato-DXd; DS-1062) is an ADC composed of a humanised anti-TROP2 IgG1 monoclonal antibody conjugated to a topoisomerase I inhibitor via a tetrapeptide-based cleavable linker. [2] TROP2 is expressed in many normal tissues, though in contrast, it is overexpressed in many cancers and the overexpression of TROP2 is associated with poor prognostic outcomes.[3] Upon administration of datopotamab deruxtecan, the anti-TROP2 antibody targets and binds to TROP2 expressed on tumour cells. Upon cellular uptake and lysosomal degradation of the linker, deruxtecan (DXd) targets and binds to DNA topoisomerase I, thereby stabilising the cleavable complex between topoisomerase I and DNA, resulting in DNA breaks, inhibition of DNA replication and apoptosis. This inhibits tumour cell proliferation of TROP2-expressing tumour cells. The ADC allows for reduced systemic exposure and enhanced delivery of the cytotoxic agent DXd. [4]

In a phase III clinical trial (NCT04656652), 6.0mg/kg of datopotamab deruxtecan will be administered as an intravenous (IV) infusion on day 1 of each 3-week cycle. [1]

Key Innovation

Treatment options are limited for patients with advanced NSCLC without driver genomic alterations after failure of a platinum-based chemotherapy and immunotherapy. The prognosis for these patients is poor with a median survival time of less than one year.[5] ADC is a rapidly growing cancer therapeutic class which has a broader therapeutic window compared with conventional cancer chemotherapeutic drugs. Datopotamab deruxtecan has a highly potent payload with a short systemic half-life, and a cleavable linker designed to be tumour selective which is stable in circulation. These features enable a wide therapeutic window with high anti-tumour potency and less systemic toxicity.[6] Datopotamab deruxtecan demonstrates potent anti-tumour activity and an acceptable safety profile in pre-clinical models suggesting it could be a valuable additional therapeutic option with a potential benefit to patients.[7]

Regulatory & Development Status

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

Datopotamab deruxtecan is also in phase II/III clinical development for other indications, including:[8]

- Locally recurrent inoperable or metastatic triple-negative breast cancer.
- Inoperable or metastatic HR-positive, HER2-negative breast cancer.
- Previously untreated advanced or metastatic PD-L1 tumour proportion score (TPS) <50%, non-squamous NSCLC without actionable genetic mutations.
- Advanced solid tumours.

Patient Group

Disease Area and Clinical Need

Primary lung cancers are divided into two main groups: small cell lung cancer (SCLC) and NSCLC. NSCLC is a heterogeneous class of tumours and makes up to around 80-85% of lung cancers in the UK.[9] Advanced lung cancer means that the cancer has spread from where it started in the lung, metastatic cancer means the cancer has spread to another region in the body.[10,11] The leading environmental cause of lung cancer in the UK is smoking tobacco. The risk of lung cancer can also be higher with a close relative who has had lung cancer.[12] The most common symptoms of lung cancer are having a cough, unusual breathlessness, coughing up sputum with blood and an aching chest or shoulder. [13]

In England (2021-22), there were 119,396 finished consultant episodes (FCE) and 99,551 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34), resulting in 75,969 day cases and 206,640 FCE bed days.[14] In England (2017), there were 38,888 newly diagnosed cases of malignant neoplasm of bronchus and lung (ICD-10 code C34) and 28,170 registered deaths.[15] 7,564 of the newly diagnosed cases were stage 3, and 18,213 were stage 4.[16] In England, for patients diagnosed with stage 3 lung cancer between 2013 and 2017 (followed up to 2018), the age-standardised 1-year and 5-year survival rate was 48.7% and 12.6% respectively. For patients diagnosed with stage 4 lung cancer, the age-standardised 1-year and 5-year survival rate was 19.3% and 2.9% respectively.[17]

Recommended Treatment Options

NICE recommends pharmacological treatment options for advanced or metastatic NSCLC that has progressed following previous treatment based on whether the cancer is squamous or non-squamous, and based on if there are any actionable mutations. Further details and a comprehensive list of treatment options can be found in the interactive pathway for advanced NSCLC and the NICE clinical guideline for lung cancer diagnosis and management.[18,19]

Examples of pharmacological therapies for patients with advanced or metastatic NSCLC with no actionable mutations who have progressed following previous treatment include, but are not limited to:

- Atezolizumab
- Pembrolizumab
- Nivolumab
- Docetaxel
- Platinum doublet chemotherapy
- Docetaxel and nintedanib
- Pemetrexed and carboplatin
- Pemetrexed and cisplatin

Examples of pharmacological therapies for patients with advanced or metastatic NSCLC with an actionable mutation who have progressed following previous treatment include, but are not limited to:

- Amivantamab
- Atezolizumab
- Ceritinib
- Erlotinib
- Crizotinib
- Lorlatinib
- Nivolumab
- Osimertinib
- Pembrolizumab
- Selpercatinib

- Sotorasib
- Tepotinib
- Docetaxel
- Docetaxel and nintedanib
- Platinum doublet chemotherapy
- Brigatinib
- Pemetrexed and cisplatin
- Pemetrexed and carboplatin
- Entrectinib

Clinical Trial Information

Trial	**TROPION-LUNG01,** NCT04656652 , EudraCT-2020-004643-80 Study of DS-1062a Versus Docetaxel in Previously Treated Advanced or Metastatic Non-small Cell Lung Cancer With or Without Actionable Genomic Alterations (TROPION-LUNG01). **Phase III**: Active, recruiting. **Location(s):** 10 EU countries, UK, USA and other countries. **Primary Completion Date:** September 2023.
Trial Design	Randomised, open label, parallel assignment.
Population	N = 590 (actual); in adults and elderly, previously treated advanced or metastatic NSCLC with or without Actionable Genomic Alterations.
Intervention(s)	Datopotamab deruxtecan 6.0mg/kg will be administered as an intravenous (IV) infusion on Day 1 of each 3-week cycle.
Comparator(s)	Docetaxel 75 mg/m^2 (IV infusion)
Outcome(s)	Primary outcome measures: • Progression-free survival (PFS) as assessed by blinded independent central review (BICR) per response evaluation criteria in solid tumours (RECIST) [Time Frame: From randomisation up to approximately 43 months] • Overall Survival (OS) [Time Frame: From randomisation until date of death due to any cause, up to approximately 43 months] See trial record for full list of other outcome measures.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of datopotamab deruxtecan is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pembrolizumab with pemetrexed and platinum-based chemotherapy for previously TKI-treated EGFR-positive metastatic non-squamous non-small-cell lung cancer [ID3873] Expected date of issue to be confirmed..
- NICE technology appraisal in development. Cimavax for treating wild-type EGFR-positive non-small-cell lung cancer. [GID-TA10225] Expected date of issue to be confirmed.
- NICE technology appraisal in development. Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851] Expected date of issue: May 2023.
- NICE technology appraisal in development. Mobocertinib for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3984] Expected date of issue: January 2023.
- NICE technology appraisal guidance. Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [TA850]. December 2022.
- NICE technology appraisal guidance. Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [TA789] May 2022.
- NICE technology appraisal guidance. Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [TA781] March 2022
- NICE technology appraisal guidance. Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer [TA760] January 2022.
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- NICE technology appraisal guidance. Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [TA628] May 2020.
- NICE technology appraisal guidance. Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer [TA529] July 2018.
- NICE technology appraisal guidance. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. [TA520] May 2018.
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- NICE technology appraisal guidance. Nintedanib for previously treated locally advanced, metastatic or locally recurrent non-small-cell lung cancer [TA347]. July 2015
- NICE quality standard. Lung cancer in adults [QS17] December 2019.
- NICE diagnostic guidance. EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer [DG9] August 2013.
- NICE clinical guideline. Lung cancer: diagnosis and management. [NG122] September 2022.

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

- National Comprehensive Cancer Network (NCCN). Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. 2022.[20,21]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020 update.[22]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[23]

Additional Information

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