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Health Technology Briefing
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Datopotamab deruxtecan with durvalumab and carboplatin for previously untreated, locally advanced, unresectable non-small cell lung cancer

Company/Developer	AstraZeneca UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 36642	NICE ID: Not Available	UKPS ID: 670184

Licensing and Market Availability Plans

The company's regulatory procedure with the MHRA is currently unknown. The company anticipate submitting a Marketing Authorisation Application (MAA) to the MHRA in **Q1 2026**, with a final licence expected in **Q4 2026** and a UK launch expected in **Q4 2026**.

Summary

Datopotamab deruxtecan in combination with durvalumab and carboplatin is in clinical development for the treatment of previously untreated, locally advanced, or metastatic non-small cell lung cancer (NSCLC), without actionable genomic alterations. NSCLC is the most common lung cancer. Locally advanced cancer has grown outside the body part it started in but has not yet spread to other parts of the body. Metastatic cancer is a cancer that has spread from the part of the body where it started (the primary site) to other parts of the body. Actionable genomic alterations refer to a DNA change that, if detected in a patient's tumour, would be expected (or predicted) to affect a patient's response to treatment. 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 therefore additional treatment options are needed in this setting.

Datopotamab deruxtecan is type of drug called an antibody-drug conjugate (ADC). This means there are two parts to the drug, these are: datopotamab a monoclonal antibody (type of protein with an attachment site) and deruxtecan, a chemotherapy drug. Datopotamab attaches to the TROP2 protein on the cancer cell. Datopotamab then releases deruxtecan into the cancer cell which will damage or kill the cancer cell, stopping the cancer from growing. If licensed, datopotamab deruxtecan in combination with durvalumab and carboplatin (a chemotherapy drug) will provide an additional first-line treatment option for patients with locally advanced or metastatic NSCLC, without actionable genomic alterations.

Proposed Indication

Treatment of adult patients with TROP2 advanced non-small cell lung cancer without actionable genomic alterations, first-line.[a]

Technology

Description

Datopotamab deruxtecan (Dato-DXd; DS-1062) is an trophoblastic cell surface antigen-2 (TROP2)-directed antibody–drug conjugate (ADC) composed of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to a topoisomerase I inhibitor via a tetrapeptide-based cleavable linker.[2-4] ADCs are antibodies conjugated with cytotoxic drugs via a chemical linker. ADCs bind to cancer-associated cell-surface antigens and internalise into cancer cells. Then the cytotoxic drugs are released into the cytoplasm leading to the target cell death.[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.[5] 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 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 deruxtecan.[6]

In the phase III clinical trial (NCT05687266), datopotamab deruxtecan will be administered in combination with durvalumab and carboplatin via intravenous (IV) infusion every 3 weeks on day 1 of each 21-day cycle.[1]

Key Innovation

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for the highest mortality rates among both men and women.[8] While first-line treatment with immune checkpoint inhibitors with or without chemotherapy has improved outcomes for patients with NSCLC without actionable genomic alterations, most patients eventually experience disease progression.[9-12] TROP2 is a protein broadly expressed in a large majority of NSCLC tumours.[12,13] There are currently no TROP2-directed ADCs approved for the treatment of patients with lung cancer.[12,14,15] ADCs are a rapidly growing cancer therapeutic class which has a broader therapeutic window compared with conventional cancer chemotherapeutic drugs.[2] Datopotamab deruxtecan combined with durvalumab and carboplatin has previously demonstrated manageable safety and encouraging antitumor activity in advance NSCLC.[16,17] If licensed, datopotamab deruxtecan in combination with durvalumab and carboplatin will offer an additional treatment option for patients with locally advanced or metastatic NSCLC without actionable genomic alterations not amenable to surgical resection or definitive chemoradiation.

Regulatory & Development Status

Datopotamab deruxtecan does not currently have Marketing Authorisation in the EU/UK for any indication.

Durvalumab is currently marketed in the EU/UK in combination with other technologies for the following indications :[18]

[a] Information from UK PharmaScan

- NSCLC
- Small cell lung cancer (SCLC)
- Biliary tract cancer
- Hepatocellular carcinoma

Durvalumab is also currently marketed in the EU/UK as a monotherapy for NSCLC.[18]
Carboplatin is currently marketed in the EU/UK as combination with other technologies for the following indications:[19-21]

- NSCLC
- Ovarian Cancer
- SCLC

Carboplatin is currently marketed in the EU/UK as a monotherapy for the treatment of ovarian carcinoma of epithelial origin and SCLC.[7]

Datopotamab deruxtecan in combination with durvalumab and carboplatin is in phase III/II clinical development for breast cancer.[22]

Patient Group

Disease Area and Clinical Need

NSCLC is the most common lung cancer, there are three main types. Adenocarcinoma is the most common type of NSCLC, developing from cells that make mucus. It is more often found in the outer area of the lung. Squamous cell carcinoma develops in the cells that line the airways and is more often found in the main airways in the centre of the lungs. Large cell lung cancer is a very uncommon type that usually starts in the centre of the lungs.[23] Locally advanced means that cancer has grown outside the body part it started in but has not yet spread to other parts of the body.[24] Cancer that spreads from where it started to a distant part of the body is called metastatic cancer.[25] Unresectable NSCLC cannot be removed with surgery.[26] Actionable mutation or actionable genomic event refers to a DNA change that, if detected in a patient's tumour, would be expected (or predicted) to affect a patient's response to treatment. [28,29] The majority of patients with NSCLC still lack targetable genomic alterations.[30] Lung cancer may not always have symptoms early on. Sometimes it is found by chance when a person is having tests for another condition. Symptoms of lung cancer include a cough, repeated chest infections, breathlessness, unexplained pain, weight loss or tiredness and coughing up blood.[31] Smoking tobacco is the cause of most lung cancers and the biggest risk factor. People who do not smoke can still develop lung cancer, but their risk is much lower.[23]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (2017-2019). 48% of lung cancer cases in the UK are in females, and 52% are in males.[32] The one-year survival rate in England was 40.6%, dropping to 16.2% over five years, and 9.5% over ten years (2013-17).[33] In England between 2017- 2019, the 1-year age-standardised net survival for stage III lung cancer was 48.7% and the 5-year age-standardised net survival was 12.6%.[34] In England (2022-23) there were 122,866 finished consultant episodes (FCE) for malignant neoplasm of the bronchus and lung (ICD-10 code: C34), with 104,232 hospital admissions, that resulted in 80,131 day cases and 217,569 FCE bed days.[33]

Recommended Treatment Options

There is no treatment option recommended by NICE for patients with Treatment of adult patients with previously untreated, locally advanced or metastatic NSCLC, without actionable genomic alterations.

NICE guidelines recommend the following combination treatment options for untreated, locally advanced, or metastatic NSCLC:[35,36]

- Pemetrexed with cisplatin
- Pembrolizumab with pemetrexed and platinum chemotherapy

Clinical Trial Information

Trial	**AVANZAR;** NCT05687266; 2021-004606-21; A Phase III, Randomised, Open-label, Multicentre, Global Study of Datopotamab Deruxtecan (Dato-DXd) in Combination With Durvalumab and Carboplatin Versus Pembrolizumab in Combination With Platinum-based Chemotherapy for the First-line Treatment of Patients With Locally Advanced or Metastatic NSCLC Without Actionable Genomic Alterations (D926NC00001; AVANZAR) **Phase III:** Recruiting **Location(s):** Eleven EU countries, UK, USA, Canada, and other countries **Primary completion date:** February 2027
Trial Design	Randomised, parallel-assignment, open-label
Population	N = 1280 (estimated); subjects with stage IIIB, IIIC, or IV TROP2 positive NSCLC without actionable genomic alterations not amenable to surgical resection or definitive chemoradiation.
Intervention(s)	• 6.0mg/kg datopotamab deruxtecan IV • 1120 mg durvalumab IV • 5 mg/mL/minute carboplatin IV
Comparator(s)	• 5 mg/mL/minute carboplatin IV • 200 mg pembrolizumab IV • 75 mg/m2 cisplatin IV • 500 mg/m2 pemetrexed IV • 200 mg/m2 paclitaxel IV
Outcome(s)	• Progression-Free Survival (PFS) in the TROP2 biomarker positive population. PFS is defined as time from randomisation until progression per Response Evaluation Criteria in solid tumours, Version 1.1 (RECIST 1.1) as assessed by blinded independent central review, or death due to any cause. • Overall Survival (OS) in the TROP2 biomarker positive population. OS is defined as the time from randomisation until the date of death due to any cause.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of datopotamab deruxtecan is not yet known.

Durvalumab is already marketed in the UK for the treatment of NSCLC, SCLC, biliary tract cancer and hepatocellular carcinoma. A 120mg/2.4ml concentrate vial costs £592.00 (NHS indicative price).[18,37]

Carboplatin is already marketed in the UK for the treatment of ovarian carcinoma of epithelial origin small cell lung carcinoma. A 50mg/5ml solution for infusion vial costs £22.86 (NHS indicative price).[7,38]

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA683). March 2021
- NICE technology appraisal. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009.

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) Guidelines Insights: Non–Small Cell Lung Cancer, Version 2. 2021.[39]
- The European Society for Medical Oncology. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. September 2020.[40]
- NHS Northern Cancer Alliance. Lung Cancer Clinical Guidelines. May 2018.[41]
- Scottish Intercollegiate Guidelines Network. SIGN 137 – Management of lung cancer. February 2014.[42]
- London Cancer Alliance. LCA Lung Cancer Clinical Guidelines. March 2013.[43]

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