Health Technology Briefing
May 2024

Patritumab deruxtecan for previously treated metastatic or locally advanced EGFR mutated non-small-cell lung cancer

Company/Developer	Daiichi Sankyo Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30856	NICE ID: Not available	UKPS ID: 669921

Licensing and Market Availability Plans

Currently in clinical development.

Summary

Patritumab deruxtecan is currently in clinical development for treatment of metastatic or locally advanced epidermal growth factor receptor-mutated (EGFRm) non-squamous non-small cell lung cancer (NSCLC) after failure of several therapy options. NSCLC is the most common type of lung cancer. EGFR is protein involved in the growth and division of healthy cells. For some NSCLC sufferers, there is a mutation to the gene coding for this protein which means it can be significantly over expressed. This can cause cells to grow out of control and lead to cancer. The most common symptoms of lung cancer include cough, breathlessness, coughing up phlegm with blood, pain in the chest or shoulder, recurrent chest infections, loss of appetite, weight loss and fatigue.

Patritumab deruxtecan is an investigational antibody-drug conjugate (ADC). ADC's work by using antibodies to selectively deliver drugs to cancer cells while sparing healthy cells. The ADC is created by joining a cancer payload , in this case patritumab, to an antibody, in this case anti-HER3 monoclonal antibody, which acts as a guidance system that propels the drug to the surface of the tumour cells. The ADC is then taken up by the cell and the drug is released, leading to the destruction of the cancer cells whilst minimising the damage to the healthy cells. If licensed patritumab deruxtecan will offer a new treatment option to patients with metastatic or locally advanced EGFR mutated NSCLC.

Proposed Indication

Patients with locally advanced epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) after failure of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy.[1]

Technology

Description

Patritumab deruxtecan (HER3-DXd) is a type of medication known as an antibody drug conjugate (ADC). It is comprised of 3 components: an anti-HER3 IgG1 monoclonal antibody, Patritumab (HY-P99275), attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker.[2] The ADC targets the HER3 receptor and delivers the chemotherapy payload to destroy the cancer cell.[3] EGFR-mutated NSCLC is associated with higher expression of HER3 compared with EGFR wild-type NSCLC.[4]

Patritumab deruxtecan is currently in phase 2 and 3 clinical development (NCT04619004: HERTHENA-Lung01, NCT05338970: HERTHENA-Lung02) for previously treated adults with metastatic or locally advanced EGFRm NSCLC.[1,5] The phase 2 trial will initially randomise participants to one of 2 arms in a 1:1 ratio to receive either a 5.6 mg/kg fixed dose regimen as an intravenous (IV) infusion or an up-titration dose regimen of patritumab deruxtecan IV every 3 weeks.[5] The phase 3 trial involved administering patritumab deruxtecan intravenously at a dose of 5.6mg/kg every 3 weeks.[1]

Key Innovation

For patients with EGFRm advanced NSCLC that has progressed after treatment with EGFR tyrosine kinase inhibitors (TKI) and platinum-based chemotherapy, current treatment options provide only limited clinical benefit. Salvage therapies after disease progression on platinum-based chemotherapy have limited efficacy.[6] In the phase I study, patritumab deruxtecan once every 3 weeks was effective in patients with diverse mechanisms of resistance to EGFR TKIs, including *EGFR*-dependent and -independent mechanisms.[3]

If licensed, patritumab deruxtecan will offer a new treatment option for patients with metastatic or locally advanced EGFR mutated NSCLC.

Regulatory & Development Status

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

Patritumab deruxtecan is also in phase II clinical development for:[7]

- Breast cancer
- Colorectal cancer
- Solid tumours
- Gastric cancer
- Head and neck cancer
- Melanoma
- Angiosarcoma

Patritumab deruxtecan has been awarded the following regulatory designations:

- FDA breakthrough therapy designation in 2021 for patients with metastatic EGFRm NSCLC.[8]

Patient Group

Disease Area and Clinical Need

Around 80 to 85 out of 100 lung cancers (around 80 to 85%) are NSCLC. The three main types are adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[9] Metastatic NSCLC (stage 4) is when the cancer spreads to other parts of the body such as the bones, lungs, brain, liver or adrenal glands.[10] Locally advanced NSCLC (Stage 3) is cancer that has spread into tissues around the lungs, or is larger than 7cm.[11] EGFR mutations are most common in people with lung adenocarcinoma which accounts for 40% of all lung cancers and is the most common type of NSCLC. EGFR is protein involved in the growth and division of healthy cells. For some NSCLC sufferers, there is a mutation to the gene coding for this protein which means it can be significantly over expressed. This can cause cells to grow out of control and lead to cancer. An EGFR mutation is more common in women than men, and in people who have never smoked or have been light smokers. These mutations are not hereditary but develop later in life as a part of the process of a healthy cell becoming a cancer cell.[12] The most common symptoms of lung cancer include cough, breathlessness, coughing up phlegm with blood, pain in the chest or shoulder, recurrent chest infections, loss of appetite, weight loss and fatigue.[13]

Approximately 39,000 people are diagnosed with lung cancer each year in the UK and around 10-15% of these lung cancers have sensitising EGFR mutations.[12] Lung cancer is the 3rd most common cancer in the UK, accounting for 13% of all new cancer cases (2016-18).[14] In England (2022-23), there were 122,866 finished consultant episodes (FCEs) and 104,232 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34), which resulted in 80,131 day cases and 217,569 FCE bed days.[15] In England (2017) there were 38,888 patients diagnosed with malignant neoplasm of bronchus and lung, and 28,170 deaths registered with this being the underlying cause.[16] In 2013-2017 in England, the 1 year survival rate for all stages of lung cancer was 40.6% , with 19.3% being specifically for stage 4 lung cancer. The 5 year survival rate for all stages of lung cancer was 16.2%, with 2.9% also for stage 4 in particular.[17]

Recommended Treatment Options

NICE recommends platinum-based chemotherapy, and atezolizumab in combination with chemotherapy in adult patients with metastatic or locally advanced EGFRm non-squamous NSCLC after receiving a TKI therapy.[18,19] For people who have disease progression after initial treatment with platinum doublet chemotherapy, recommended treatment options for metastatic or locally advanced EGFRm non-squamous NSCLC is afatinib.[20]

Clinical Trial Information

Trial	**HERTHENA-Lung02;** NCT05338970, 2021-005879-40; A Phase 3, Randomized, Open-label Study of Patritumab Deruxtecan Versus Platinum-based Chemotherapy in Metastatic or Locally Advanced Epidermal Growth Factor Receptor-mutated (EGFRm) Non-small Cell Lung Cancer (NSCLC) After Failure of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) Therapy **Phase 3** - Active, not recruiting **Locations:** UK, USA, Australia, Canada and 11 EU countries **Primary completion date:** August 2024
Trial Design	Randomised, Parallel assignment, open label, active comparator-controlled

Population	N=586 (actual); patients diagnosed with locally advanced or metastatic non-squamous NSCLC who has an EGFR-activating mutation and has received 1 or 2 prior line(s) of an approved EGFR TKI treatment in the metastatic or locally advanced setting, which must include a third -generation EGFR TKI; aged 18 years and over.
Intervention(s)	Patritumab Deruxtecan (Intravenous (IV) administration, 5.6 mg/kg every 3 weeks)
Comparator(s)	Platinum-based chemotherapy (IV, pemetrexed 500 mg/m^2 plus either cisplatin (75 mg/m^2) or carboplatin) every 3 weeks
Outcome(s)	Primary outcome measures: • Progression-free survival (PFS) as assessed by blinded independent central review based on RECIST v1.1 [Time frame: baseline up to approximately 49 months] See trial record for full outcomes list.
Results (efficacy)	-
Results (safety)	-

Trial	**HERTHENA-Lung01**; NCT04619004, EudraCT2020-000730-17; A Phase 2 Randomized Open-Label Study of Patritumab Deruxtecan (U3-1402) in Subjects With Previously Treated Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer (NSCLC). **Phase 2 -** Active, not recruiting **Locations:** UK, USA, Australia and 8 EU countries **Primary completion date:** June 2024
Trial Design	Randomised, Parallel assignment, open label, active comparator-controlled
Population	N=420 (estimated); patients diagnosed with locally advanced or metastatic NSCLC. Previously treated with Osimertinib and at least 1 platinum-based therapy. Documentation of an EGFR-activating mutation; aged 18 years and over.
Intervention(s)	Patritumab Deruxtecan (Fixed dose) administered intravenously at 5.6mg/kg on day 1 of each 21 day cycle.
Comparator(s)	Patritumab Deruxtecan (Up-Titration) administered intravenously at 3.2mg/kg on cycle 1, 4.8mg/kg on cycle 2 and 6.4mg/kg on cycle 3 onwards.
Outcome(s)	Primary outcome measures: • Objective response rate (ORR) as assessed by blinded independent central review (BICR) [Time frame: Data collected from screening until time of disease progression, death, study discontinuation, or other protocol-defined reasons, whichever occurs first, assessed up to approximately 26 months] See trial record for full outcome list.
Results (efficacy)	HER3-DXd once every 3 weeks treatment yielded clinically meaningful responses in NSCLC CNS metastases which have been reported in 70% of

	patients with advanced *EGFR*-mutated NSCLC. HER3-DXd once every 3 weeks elicited tumour responses in a diverse group of *EGFR*-mutated NSCLC tumours, including clinical efficacy across a broad range of pretreatment tumor HER3 membrane expression, consistent with previous observations.[3]
Results (safety)	HER3-DXd once every 3 weeks had a manageable safety profile with a low rate of treatment-related discontinuation due to AEs. Thrombocytopenia was the most frequent grade ≥3 TEAE, and it typically occurred early in treatment and was transient; bleeding events in the setting of thrombocytopenia were rare. Grade ≥3 neutropenia was also transient and was rarely associated with fever and/or infection.[3]

Estimated Cost

The cost of Patritumab deruxtecan is currently unknown.

Relevant Guidance

NICE Guidance

- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE Technology appraisal guidance. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. (TA584). June 2019.
- NICE Technology appraisal guidance. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer. (TA310). April 2014.
- NICE quality standard. Lung cancer in adults (QS17). December 2017

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- National Comprehensive Cancer Network (NCCN) Guidelines Insights: Non–Small Cell Lung Cancer, Version 2. 2021.[21]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up 2019.[22]

Additional Information

References

1 ClinicalTrials.gov. *A Phase 3, Randomized, Open-label Study of Patritumab Deruxtecan Versus Platinum-based Chemotherapy in Metastatic or Locally Advanced Epidermal Growth Factor*

Receptor-mutated (EGFRm) Non-small Cell Lung Cancer (NSCLC) After Failure of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) Therapy (HERTHENA-Lung02). *Trial ID: NCT05338970*. 2021. Status: ACTIVE, NOT RECRUITING. Available from: https://clinicaltrials.gov/study/NCT05338970 [Accessed 25 April 2024].

2 MedChemExpress. *Patritumab deruxtecan* 2022. Available from: https://www.medchemexpress.com/patritumab-deruxtecan.html?utm_source=bing&utm_medium=CPC&utm_campaign=Europe&utm_term=HY-P99813&utm_content=Patritumab%20deruxtecan [Accessed 25 April 2024].

3 Yu HA, Goto Y, Hayashi H, Felip E, Yang JC-H, Reck M, et al. HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor–Mutated Non–Small-Cell Lung Cancer After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy. *Journal of Clinical Oncology*. 2023;41(35):5363-75. Available from: https://doi.org/10.1200/jco.23.01476.

4 Kawano O, Sasaki H, Endo K, Suzuki E, Haneda H, Yukiue H, et al. ErbB3 mRNA expression correlated with specific clinicopathologic features of Japanese lung cancers. *J Surg Res*. 2008;146(1):43-8. Available from: https://doi.org/10.1016/j.jss.2007.05.030.

5 ClinicalTrials.gov. *HERTHENA-Lung01: A Phase 2 Randomized Open-Label Study of Patritumab Deruxtecan (U3-1402) in Subjects With Previously Treated Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer (NSCLC)*. *Trial ID: NCT04619004*. 2020. Status: ACTIVE, NOT RECRUITING. Available from: https://clinicaltrials.gov/study/NCT04619004 [Accessed 25 April 2024].

6 ESMO. *Efficacy and Safety of Patritumab Deruxtecan in Patients with EGFR-mutated NSCLC that Progressed to EGFR TKI and Platinum-Based Chemotherapy*. Available from: https://www.esmo.org/oncology-news/efficacy-and-safety-of-patritumab-deruxtecan-in-patients-with-egfr-mutated-nsclc-that-progressed-to-egfr-tki-and-platinum-based-chemotherapy [Accessed 25 April 2024].

7 ClinicalTrials.gov. *Search Results - Paritumab deruxtecan* 2023. Available from: https://clinicaltrials.gov/search?intr=Patritumab%20deruxtecan%20&aggFilters=phase:2 [Accessed 25 April 2024].

8 Daiichi-Sankyo. *Patritumab Deruxtecan Granted U.S. FDA Breakthrough Therapy Designation in Patients with Metastatic EGFR-Mutated Non-Small Cell Lung Cancer*. Press release. Available from: https://www.daiichisankyo.com/files/news/pressrelease/pdf/202112/20211223_E1.pdf [Accessed 25 April 2024].

9 Cancer Research UK. *Types of lung cancer*. 2022. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 25 April 2024].

10 Cancer Research UK. *Stage 4 lung cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stage-4 [Accessed 25 April 2024].

11 Cancer Research UK. *Stage 3 lung cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stage-3 [Accessed 25 April 2024].

12 EGFR+ UK. *Non-Small Cell Lung Cancer and EGFR*. Available from: https://www.egfrpositive.org.uk/what-is-egfr [Accessed 25 April 2024].

13 Cancer Research UK. *Symptoms of lung cancer*. 2022. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/symptoms [Accessed 25 April 2024].

14 Cancer Research UK. *Lung cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 25 April 2024].

15 National Health Service Digital. *Hospital Admitted Patient Care Activity, 2022-23 National statistics*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23.

16 Office of National Statistics. *Cancer registration statistics, England*. 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland.

17 Office of National Statistics. *Dataset Cancer survival in England - adults diagnosed*. 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed.

18 National Institiue of Health and Care Excellence (NICE). *Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer* (*TA584)*. Available from: https://www.nice.org.uk/guidance/ta584 [Accessed 25 April 2024].

19 National Institiue of Health and Care Excellence (NICE). *Lung cancer: diagnosis and management* (*NG122)*. Last Update Date: 2024. Available from: https://www.nice.org.uk/guidance/ng122 [Accessed 25 April 2024].

20 National Institiue of Health and Care Excellence (NICE). *Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer* (*TA310)*. Available from: https://www.nice.org.uk/guidance/TA310 [Accessed 25 April 2024].

21 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2.2021: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*. 2021;19(3):254-66. Available from: https://doi.org/10.6004/jnccn.2021.0013.

22 Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up††FootnotesApproved by the ESMO Guidelines Committee: February 2002, last update September 2018. This publication supersedes the previously published version—Ann Oncol 2016; 27 (Suppl 5): v1–v27. *Annals of Oncology*. 2018;29:iv192-iv237. https://doi.org/10.1093/annonc/mdy275.

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