Health Technology Briefing
November 2021

Sintilimab in combination with pemetrexed and platinum chemotherapy for advanced or metastatic non-small cell lung cancer

Company/Developer	Eli Lilly and Company Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31193	NICE ID: 10653	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

The combination of sintilimab and pemetrexed and platinum chemotherapy is in clinical development for the treatment of advanced or metastatic non-squamous non-small cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK. Advanced cancers can be locally advanced or metastatic. Locally advanced NSCLC is when the cancer has grown into the tissues surrounding the lung and at the metastatic stage, the disease has already spread from the lungs to other parts of the body. There are currently a number of first line therapies to control advanced or metastatic NSCLC however additional treatment options are needed to improve patient survival.

Some cancer cells produce proteins (PD-L1) that switch off cancer-killing cells of the immune system called T cells by attaching to a target on the T-cells called PD-1. This prevents the T cells from attacking the cancer. Sintilimab is a monoclonal antibody, a type of protein, administered intravenously (IV) and is designed to attach to PD-1 without switching the T cells off itself. This blocks the cancer cell proteins from attaching and switching the cells off, thereby increasing the ability of the immune system to kill cancer cells. If licensed, the combination of sintilimab, pemetrexed and platinum chemotherapy will provide an additional first line treatment option for adults with advanced or metastatic non-squamous NSCLC.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

First-line treatment of advanced or metastatic (IIIB-IV phase) non-squamous NSCLC.[1]

Technology

Description

Sintilimab (Tyvyt, IBI-308) is a type of immunoglobulin G4 monoclonal antibody, which binds to programmed death 1 (PD-1) molecules on the surface of T-cells, blocks the PD-1/ PD-Ligand 1 (PD-L1) pathway and reactivates T-cells to kill cancer cells.[2,3]

In the phase III trial (NCT03607539), sintilimab IV 200mg was administered on day 1 of each cycle, once every 3 weeks (Q3W), in combination with pemetrexed (500 mg/m^2 IV on day 1 Q3W) and either cisplatin (75 mg/m^2 IV on day 1 Q3W) or carboplatin (area under the concentration–time curve, 5 mg/mL/min IV on day 1 Q3W) for four cycles as induction therapy, followed by sintilimab 200mg in combination with pemetrexed (500 mg/m^2) as maintenance therapy Q3W for up to 24 months. The treatment was continued until disease progression, intolerable toxicity, initiation of new treatment, or withdrawal of consent.[1,4]

Key Innovation

PD-1 and PD-L1 antibodies are effective therapies for previously untreated patients with metastatic non-squamous NSCLC who do not harbour driver gene mutations. Anti–PD-1 antibody monotherapy prolongs overall survival (OS) compared to the standard chemotherapy among patients with a PD-L1 tumour proportion score (TPS) of 1% or greater. However, the benefit is more remarkable in patients with a PD-L1 TPS of 50% or greater, who only represents a minority of those with non-squamous NSCLC. Of note, first-line combination regimens that include a PD-1 or PD-L1 inhibitor and chemotherapy result in longer OS than chemotherapy alone in patients with any level of PD-L1 expression.[4]

Compared with other anti-PD-1 antibodies, sintilimab has a different binding site and potentially greater affinity against PD-1 as per the preclinical data. In a phase Ib study, sintilimab plus pemetrexed and platinum has been found to have tolerable safety profile and promising efficacy in previously untreated patients with non-squamous NSCLC.[4]

If approved, the combination of sintilimab, pemetrexed and platinum chemotherapy will provide a new first-line treatment option for adults with advanced or metastatic non-squamous NSCLC.

Regulatory & Development Status

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

Sintilimab in combination with chemotherapy is in phase II clinical development various cancer indications including: soft tissue sarcoma, triple negative breast cancer and head and neck squamous cell carcinoma.[5] Sintilimab in combination with chemotherapy is in phase III clinical development for oesophageal squamous cell carcinoma, classic Hodgkin's lymphoma and gastric cancer.[6]

Sintilimab was granted orphan designation in the EU in 2020 for the treatment of peripheral T-cell lymphoma.[7]

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Patient Group

Disease Area and Clinical Need

Lung cancer is the uncontrolled growth of abnormal cells in one or both lungs. There are two major types of lung cancer: NSCLC and small cell lung cancer. NSCLC accounts for about 85% of lung cancers. Non-squamous NSCLC is a non-small cell lung carcinoma without evidence of squamous differentiation (squamous cells are the flat cells that cover the surface of the airways).[8,9] Locally advanced is cancer that has grown outside the body part it started in but has not yet spread to other parts of the body and at the metastatic stage, the disease has already spread from the lungs to other sites.[10] A person's risk of developing lung cancer depends on many factors including age, genetics and exposure to risk factors including: smoking, workplace chemicals (e.g., asbestos, silica), air pollution and ionising radiation.[11] There are usually no signs or symptoms in the early stages. Symptoms of lung cancer develop as the condition progresses. The main symptoms of lung cancer include a continuous or persistent worsening cough, recurrent chest infections, coughing up blood, an ache or pain when breathing or coughing, persistent breathlessness, persistent tiredness or lack of energy, loss of appetite or unexplained weight loss.[12]

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; this represents 66% of the overall number of lung cancer cases diagnosed for that year.[13] In the UK it is estimated that 85% of lung cancers 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 were stage III/IV NSCLC.[13,14] In 2020/21 there were 86,043 hospital admissions with a primary diagnosis of malignant neoplasm of bronchus and lung (ICD-10 code C34) resulting in 103,856 finished consultant episodes (FCEs) and 170,030 FCE bed days.[15] In England (2013-2017, followed up to 2018), for people with stage III lung cancer, the 1-year survival rate was 48.7% and the 5-year survival rate was 12.6%. For stage IV (metastatic) cancer it was 19.3% at one year and 2.9% at five.[16] In 2020, there were 28,730 registrations of deaths in England and Wales for malignant neoplasms of the trachea, bronchus and lung in England (ICD-10 code C34).[17]

Recommended Treatment Options

The main treatment option for the locally advanced or metastatic disease includes surgery, chemotherapy, chemoradiation, targeted therapy, immunotherapy and radiotherapy.[18]

Current treatment options for advanced NSCLC include:[19]

Current first-line treatment for adults with advanced non-squamous NSCLC with PD-L1 under 50% are:

- Atezolizumab combination
- Pembrolizumab with pemetrexed and platinum chemotherapy
- Pemetrexed with cisplatin

Current first-line treatment for adults with advanced non-squamous NSCLC with PD-L1 over 50% are:

- Atezolizumab monotherapy
- Pembrolizumab
- Pembrolizumab with pemetrexed and platinum chemotherapy

Trial	**CIBI308C302; NCT03607539;** A Randomised, Double-blinded, Phase III Study of Pemetrexed Plus Platinum Chemotherapy With or Without Sintilimab (IBI308) in

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	First Line Advanced or Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (Orient-11) **Phase III** - Active, not recruiting **Location(s):** China **Study completion date:** July 2021
Trial Design	Randomised, parallel assignment and quadruple-blinded.
Population	N = 397; subjects with histologically or cytologically confirmed stage IIIB to IV non squamous NSCLC; aged 18 to 75 years.
Intervention(s)	Sintilimab IV (200mg) in combination with pemetrexed and platinum chemotherapy Q3W.
Comparator(s)	Matched comparator.
Outcome(s)	Primary outcome measure; • Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 as Assessed by Independent Radiographic Review Committee (IRRC) [Time frame: trough database cut-off date of 15-Nov-2019 (Up to approximately 16 months)] See trial record for full list of other outcomes.
Results (efficacy)	• The median PFS was significantly longer in the sintilimab-combination group than that in the placebo-combination group (8.9 versus 5.0 months; hazard ratio, 0.482, 95% confidence interval [CI]: 0.362-0.643; p < 0.00001). • The confirmed objective response rate was 51.9% (95% CI: 45.7%-58.0%) in the sintilimab-combination group and 29.8% (95% CI: 22.1%-38.4%) in placebo-combination group.[20]
Results (safety)	The incidence of grade 3 or higher adverse events was 61.7% in sintilimab-combination group and 58.8% in placebo-combination group.[20]

Estimated Cost

The cost of sintilimab is not yet known.

Pemetrexed is already marketed in the UK; a 100mg/4ml vial costs £160, and a 500mg/20ml vial costs £800.[21]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer [GID-TA10248]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer [TA724]. September 2021.
- NICE technology appraisal. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [TA705]. June 2021.

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- 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. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. [TA584]. June 2019.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. [TA192]. July 2010.
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- NICE Guideline. Lung cancer: diagnosis and management [NG122]. 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

- National Comprehensive Cancer Network (NCCN). Non–small cell lung cancer, Version 5. 2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[22]
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[23]
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- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[25]

Additional Information

Eli Lilly and Company Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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