NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
October 2022

Nivolumab with chemotherapy neoadjuvant followed by nivolumab adjuvant for treating early stage non-small-cell lung cancer

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28137	NICE TSID: 10543	UKPS ID: 661058

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Neoadjuvant nivolumab in combination with chemotherapy followed by adjuvant nivolumab is currently in clinical development for early stage non-small-cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. Early-stage lung cancer is typically treated with surgery consisting of removing either part of or the whole of the lung, followed by chemotherapy and/or radiotherapy. However, the long-term outlook for patients undergoing this treatment pathway is still poor. Treatment with medicines prior to surgery (neoadjuvant) and after surgery (adjuvant) may provide better long term survival prospects and reduce the risk of disease recurrence for patients with resectable NSCLC.

Nivolumab is an antibody that is designed to help the immune system fight tumour cells and slow tumour growth, helping to stop recurrence of cancer once it has been removed. Nivolumab is administered via intravenous (IV) injection. If licensed, neoadjuvant treatment of nivolumab in combination with chemotherapy followed by nivolumab adjuvant will offer an additional treatment option for patients with early-stage NSCLC who currently have few effective therapies available.

Proposed Indication

Neoadjuvant treatment of chemotherapy in combination with nivolumab followed by adjuvant nivolumab for adult patients with resectable stage II- IIIB non-small-cell lung cancer (NSCLC).[1]

Technology

Description

Nivolumab (Opvido) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[2]

Neoadjuvant nivolumab in combination with chemotherapy followed by adjuvant nivolumab is currently in clinical development for patients with early-stage NSCLC. In the phase III clinical trial (NCT04025879), nivolumab in combination with chemotherapy is given at specified dose on specified days.[1]

Key Innovation

For patients diagnosed with early stage NSCLC, surgery is the primary curative treatment in patients where resection is possible. However, 5-year survival rates for patients with early-stage NSCLC remain poor, with survival rates in resected patients of 61.7% (Stage IA) to 43.0% (Stage IIB) being reported. Postoperative recurrence remains a key concern, and additional treatment options are required.[3]

In a 2018 study, neoadjuvant administration of two doses of nivolumab was associated with major pathological response in nine (45%) of 20 evaluable patients with NSCLC tumours, with two (10%) of 20 patients achieving a complete pathological response.[4] Furthermore, in a 2020 study of neoadjuvant chemoimmunotherapy, 17 (57%) of 30 patients achieved a major pathological response, with ten (33%) of 30 patients achieving a complete pathological response.[5] Finally, intratumoral immunotherapy minimises the potential for toxicities and allows for greater development of combination therapies.[6] If licensed, neoadjuvant nivolumab in combination with chemotherapy followed by adjuvant nivolumab will offer an additional treatment option for patients with early stage resectable NSCLC who currently have few effective therapies available.

Regulatory & Development Status

Nivolumab as monotherapy and in combination is licensed in the UK for the treatment of a range of advanced cancers including melanoma, renal carcinoma, NSCLC, etc. Nivolumab in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable (tumours ≥ 4 cm or node positive) non-small cell lung cancer in adults.[2]

Nivolumab is in phase II and phase III clinical development for a number of conditions including:[7]

- Gastric cancer
- Stomach cancer
- Urothelial cancer
- Colorectal cancer
- Pancreatic cancer
- Various advanced solid tumours

Patient Group

Disease Area and Clinical Need

Lung cancer is classified into two main histologic types: SCLC or NSCLC.[8] A stage IIA cancer describes a tumour larger than 4 cm but 5 cm or less in size that has not spread to the nearby lymph nodes. Stage IIB lung cancer describes a tumour that is 5 cm or less in size that has spread to the lymph nodes within the lung, called the N1 lymph nodes. A stage IIB cancer can also be a tumour more than 5 cm wide that has not spread to the lymph nodes. Stage III lung cancers are classified as either stage IIIA, IIIB, or IIIC. The stage is based on the size of the tumour and which lymph nodes the cancer has spread to. Stage III cancers have not spread to other distant parts of the body.[9] 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).[10] Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[11]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017. According to the National Cancer Registration and Analysis Service (NCRAS), there were 10,519 diagnosed cases of stage II-III lung cancer in 2017 in England.[12] In the UK, it is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage II-III lung cancer cases diagnosed in 2017, it can be estimated that approximately 8,941 cases diagnosed with stage II-III in 2017 were NSCLC.[8] In 2020/21 there were 86,043 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days and 62,688 day cases.[13] In England between 2013 and 2017, the age-standardised net lung cancer survival for stage II was 73.0% at one year and 34.1% at five years and for stage III, 48.7% at one year and 12.6% at five years.[14] There are around 34,800 lung cancer deaths in the UK every year (based on data from 2017-2019). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035, to 58 deaths per 100,000 people by 2035.[15]

Recommended Treatment Options

There are currently no recommended neoadjuvant treatments for stages IIA to IIIB patients with NSCLC. Adjuvant chemotherapy should be offered with resected stage II and III. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board.[16]

Clinical Trial Information

Trial	NCT04025879, EudraCT 2019-000262-38; A Phase 3, Randomized, Double-blind Study of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy Plus Placebo, Followed by Surgical Resection and Adjuvant Treatment With Nivolumab or Placebo for Participants With Resectable Stage II-IIIB Non-small Cell Lung Cancer **Phase III –** Recruiting **Location(s):** 10 EU countries, UK, USA, Canada and other countries **Primary completion date:** December 2023
Trial Design	Randomised, parallel-assignment, double-blinded

Population	N=452 (estimated); adult participants with suspected or histologically confirmed stage IIA (> 4 cm) to IIIB (T3N2) NSCLC with disease that is considered resectable
Intervention(s)	• Nivolumab • Carboplatin • Cisplatin • Paclitaxel • Pemetrexed • Docetaxel
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: event-free survival (EFS) as assessed by blinded independent central review (BICR) [Time frame: 5 years from randomisation] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Nivolumab is already marketed in the UK. The NHS indicative price for nivolumab solution for infusion is as follows:[17]

- Nivolumab 100mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £1,097.00 (Hospital only)
- Nivolumab 120mg/12ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £1,317.00 (Hospital only)
- Nivolumab 240mg/24ml concentrate for solution for infusion (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £2,633.00 (Hospital only)
- Nivolumab 40mg/4ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £439.00 (Hospital only).

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer (ID3907). Expected June 2023.
- NICE technology appraisal in development. Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer (ID3757). Expected June 2023.
- NICE technology appraisal in development. Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (ID3852). Expected September 2022.
- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019. Last updated: August 2022.
- NICE quality standard. Lung cancer in adults (QS17). March 2012. Last updated: December 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.
- NHS England. Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. 16024/P. 2016.

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.[16]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[18]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137). 2014.[19]

Additional Information

No information was received from Bristol-Myers Squibb Pharmaceuticals Ltd

References

1 ClinicalTrials.gov. *A Study of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy Plus Placebo, Followed by Surgical Removal and Adjuvant Treatment With Nivolumab or Placebo for Participants With Surgically Removable Early Stage Non-small Cell Lung Cancer.* 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT04025879 [Accessed 24 August 2022].

2 Electronic Medicines Compendium (EMC). *OPDIVO 10 mg/mL concentrate for solution for infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/6888/smpc#PRODUCTINFO [Accessed 24 August 2022].

3 Heymach JV, Mitsudomi T, Harpole D, Aperghis M, Jones S, Mann H, et al. Design and Rationale for a Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III non-small-cell Lung Cancer: The AEGEAN Trial. *Clinical Lung Cancer*. 2022;23(3):e247-e51. Available from: https://doi.org/10.1016/j.cllc.2021.09.010.

4 Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *New England Journal of Medicine*. 2018;378(21):1976-86. Available from: https://doi.org/10.1056/NEJMoa1716078.

5 Shu CA, Gainor JF, Awad MM, Chiuzan C, Grigg CM, Pabani A, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. *The Lancet Oncology*. 2020;21(6):786-95. Available from: https://doi.org/10.1016/S1470-2045(20)30140-6.

6 Hong WX, Sagiv-Barfi I, Czerwinski DK, Sallets A, Levy R. Neoadjuvant Intratumoral Immunotherapy with TLR9 Activation and Anti-OX40 Antibody Eradicates Metastatic Cancer. *Cancer Research*. 2022;82(7):1396-408. Available from: https://doi.org/10.1158/0008-5472.CAN-21-1382.

7 ClinicalTrials.gov. *nivolumab | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3.* Available from:

https://clinicaltrials.gov/ct2/results?cond=&term=nivolumab&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 24 August 2022].

8 Cancer Reasearch UK. *Types of lung cancer.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 23 August 2022].

9 Cancer.Net. *Lung Cancer - Non-Small Cell: Stages.* 2021. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/stages [Accessed 23 August 2022].

10 Cancer Reasearch UK. *Lung cancer: risks and causes.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes [Accessed 23 August 2022].

11 Cancer Reasearch UK. *Lung cancer symptoms.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/symptoms [Accessed 23 August 2022].

12 Park K, Vansteenkiste J, Lee KH, Pentheroudakis G, Zhou C, Prabhash K, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with locally-advanced unresectable non-small-cell lung cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. *Annals of Oncology*. 2020;31(2):191-201. Available from: https://doi.org/10.1016/j.annonc.2019.10.026.

13 National Cancer Registration and Analysis Service (NCRAS). *Survival by stage.* Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 23 August 2022].

14 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 23 August 2022].

15 Office for National Statistics. *Cancer survival in England - adults diagnosed.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 23 August 2022].

16 Cancer Reasearch UK. *Lung cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 23 August 2022].

17 Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2017;28:iv1-iv21. Available from: https://doi.org/10.1093/annonc/mdx222.

18 National Insitute for Health and Care Excellence (NICE). *Nivolumab: Medicinal forms.* Available from: https://bnf.nice.org.uk/drugs/nivolumab/medicinal-forms/ [Accessed 31 August 2022].

19 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2017;15(4):504-35. Available from: https://doi.org/10.6004/jnccn.2017.0050.

20 Scottish Intercollegiate Guidelines Network (SIGN). *Management of lung cancer.* 2014. Available from: https://www.sign.ac.uk/our-guidelines/management-of-lung-cancer/ [Accessed 23 August 2022].

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.