Health Technology Briefing
December 2022

Nivolumab with ipilimumab for previously untreated locally advanced non-small-cell lung cancer

Company/Developer	Bristol-Myers Squibb

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28595	NICE ID: 10631	UKPS ID: 661089

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Nivolumab in combination with ipilimumab is in clinical development for the treatment of previously untreated locally advanced non-small-cell lung cancer (NSCLC). NSCLC is the most common form of lung cancer. Locally advanced NSCLC means the cancer is in more than one lobe of the lung, or it has spread to lymph nodes or nearby structures in the chest. Smoking tobacco is the cause of most lung cancers and the biggest risk factor. Other risk factors include second-hand smoke, exposure to workplace carcinogens, radiation exposure, environmental pollution, and family history of lung cancer. Current standard of care treatment can help to control the cancer for some time and reduce symptoms, however, there can still be poor long-term outcomes for these NSCLC patients despite chemotherapy and immunotherapy.

Nivolumab is a monoclonal antibody, a type of protein that has been designed to attach to a receptor called PD-1 found on cells of the immune system called T cells. By attaching to PD-1, nivolumab prevents cancer cells from switching off the activity of the T cells, thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab is a monoclonal antibody designed to increase the number and the activity of T cells which can kill cancer cells. Ipilimumab acts on T cells by attaching to and blocking the activity of CTLA-4, a protein that controls the activity of T cells. If licensed, nivolumab with ipilimumab, administered intravenously, could provide an additional effective treatment option.

Proposed Indication

Previously untreated stage III non-small-cell lung cancer (NSCLC) that is unable or not planned to be removed by surgery.[1]

Technology

Description

Nivolumab (Opdivo) 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. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[2]

Ipilimumab (Yervoy) is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoural T-effector/ T-regulatory cell ratio which drives tumour cell death.[3]

Nivolumab in combination with ipilimumab is currently in clinical development for the treatment of previously untreated stage III NSCLC. In the phase III clinical trial (CheckMate73L, NCT04026412) patients are given nivolumab in combination with ipilimumab intravenously (IV) and concurrent chemoradiotherapy (CCRT).[1]

Key Innovation

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.[2] Nivolumab plus ipilimumab has shown durable overall survival benefit in several tumours, including melanoma, renal cell carcinoma, metastatic NSCLC, and mesothelioma. In CheckMate 227, this combination provided statistically significant and clinically meaningful overall survival improvements compared to chemotherapy in patients with tumour PD-L1 expression ≥1%. These findings support the potential use of nivolumab plus ipilimumab in stage III NSCLC not amenable for definitive resection.[4]

If licenced, nivolumab in combination with ipilimumab would provide an additional treatment option with improvements to overall survival for patients with previously untreated stage III NSCLC.

Regulatory & Development Status

Nivolumab in combination with ipilimumab has Marketing Authorisation in the UK/EU for the following indications:[2]

- The treatment of advanced (unresectable or metastatic) melanoma in adults
- With 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation

- The first-line treatment of adult patients with unresectable malignant pleural mesothelioma
- The first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma
- The treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy
- The first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥1%

The combination of nivolumab with ipilimumab is in phase II and III trials for various cancer indications, some of which include:[5]

- Renal cell carcinoma
- Melanoma
- Colon cancer
- Hepatocellular carcinoma

Patient Group

Disease Area and Clinical Need

NSCLC is the most common form of lung cancer, accounting for between 80 to 85% of lung cancer cases in the UK. The three main types are adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[6] Smoking tobacco is the cause of most lung cancers and the biggest risk factor. Other risk factors include second-hand smoke, exposure to workplace chemicals, radiation exposure, air pollution and family history of lung cancer.[7] Symptoms of lung cancer include a cough, repeated chest infections, breathlessness, unexplained pain, weight loss or tiredness. However, lung cancer may not always have symptoms early on. Sometimes it is found by chance when a person is having tests for another condition.[8] Stage III lung cancer means the cancer is in more than one lobe of the lung, or it has spread to lymph nodes or nearby structures in the chest.[9]

Lung cancer is the 3rd most common cancer in the UK, accounting for 13% of all new cancer cases (2016-18).[10] The age standardised incidence rate of lung cancer in England is 88.4 and 67.4 per 100,000 amongst males and females respectively.[11] In England (2021-22), there were 119,396 finished consultant episodes (FCEs) and 99,551 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34), which resulted in 75,969 day cases and 206,640 FCE bed days.[12] In England (2017), there were 38,888 patients diagnosed with malignant neoplasm of bronchus and lung and 28,170 deaths registered where malignant neoplasm of bronchus and lung was the underlying cause.[13] In England, there were 7,564 newly diagnosed cases of stage III lung cancer.[14] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for stage III lung cancer were 48.7% and 12.6% respectively.[15]

Recommended Treatment Options

Treatment for lung cancer includes surgery, chemotherapy, radiotherapy, immunotherapy, and other targeted therapy drugs. People may be offered one or more different treatments depending on the stage, histology, and type of lung cancer as well as their general health. Systemic anti-cancer treatments are increasingly used to treat advanced NSCLC.[16]

The following treatment options are licensed in the UK for the treatment of previously untreated locally advanced NSCLC:[17,18]

- Gefitinib (only recommended for treatment if they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation)

- Pemetrexed in combination with cisplatin

The National Institute for Health and Care Excellence (NICE) recommends that chemoradiotherapy should be considered for people with stage III NSCLC when surgery isn't suitable or is declined.[19]

Recommendations by NICE include the following systemic anti-cancer treatments for people with:[20]

- Squamous NSCLC with no targetable mutations and PD-L1 <50%
  - Platinum doublet chemotherapy
  - Pembrolizumab with carboplatin and paclitaxel

- Squamous NSCLC with no targetable mutations and PD-L1 ≥50%
  - Atezolizumab
  - Pembrolizumab
  - Pembrolizumab with carboplatin and paclitaxel

- Non-squamous NSCLC with no targetable mutations and PD-L1 <50%
  - Platinum doublet chemotherapy
  - Pemetrexed and cisplatin
  - Pemetrexed and carboplatin
  - Atezolizumab and bevacizumab, carboplatin and paclitaxel
  - Pembrolizumab and pemetrexed and platinum chemotherapy

- Non-squamous NSCLC with no targetable mutations and PD-L1 ≥50%
  - Pembrolizumab and pemetrexed and platinum chemotherapy
  - Pembrolizumab
  - Atezolizumab

Clinical Trial Information	
Trial	**CheckMate73L**, NCT04026412, 2019-001222-98; A Phase 3, Randomized, Open Label Study to Compare Nivolumab Plus Concurrent Chemoradiotherapy (CCRT) Followed by Nivolumab Plus Ipilimumab or Nivolumab Plus CCRT Followed by Nivolumab vs CCRT Followed by Durvalumab in Previously Untreated, Locally Advanced Non-small Cell Lung Cancer (LA NSCLC) **Phase III** – Active, not recruiting **Locations:** 11 EU countries, UK, USA, Canada and other countries **Primary completion date:** July 2025
Trial Design	Randomised, parallel assignment, open-label
Population	N=888 (planned); locally advanced stage IIIA, IIIB, or IIIC pathologically-confirmed NSCLC; newly diagnosed and treatment-naïve, with no prior local or systemic anticancer therapy given as primary therapy for locally advanced disease; aged 18 years and older
Intervention(s)	• Arm A: nivolumab + ipilimumab + concurrent chemoradiotherapy • Arm B: nivolumab + concurrent chemoradiotherapy

Comparator(s)	• Arm C: durvalumab + concurrent chemoradiotherapy
Outcome(s)	Primary outcome measure: • Progression-free survival (PFS) by RECIST 1.1 per blinded independent central review (BICR) for arm A vs arm C [Time frame: up to 7 years] See trial record for full list of other outcome measures
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Nivolumab is already marketed in the UK as follows:[21]

- 100mg/10ml concentrate for solution for infusion (1 vial) costs £1,097.00
- 120mg/12ml concentrate for solution for infusion (1 vial) costs £1,317.00
- 240mg/24ml concentrate for solution for infusion (1 vial) costs £2,633.00
- 40mg/4ml concentrate for solution for infusion (1 vial) costs £439.00

Ipilimumab is already marketed in the UK as follows:[22]

- 200mg/40ml concentrate for solution for infusion (1 vial) costs £15,000.00
- 50mg/10ml concentrate for solution for infusion (1 vial) costs £3,750.00

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Durvalumab with chemoradiation for treating unresectable locally advanced non-small-cell lung cancer (GID-TA10783). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Durvalumab with tremelimumab for untreated EGFR- and ALK-negative locally advanced and metastatic non-small-cell lung cancer (GID-TA10422). Expected date of issue to be confirmed.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019. Last updated September 2022.
- NICE quality standard. Lung cancer in adults (QS17). 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) Guidelines Insights: Non–Small Cell Lung Cancer, Version 2. 2021.[23]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2019.[24]

- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[25]

Additional Information

References

1 Clinicaltrials.gov. *A Phase 3, Randomized, Open Label Study to Compare Nivolumab Plus Concurrent Chemoradiotherapy (CCRT) Followed by Nivolumab Plus Ipilimumab or Nivolumab Plus CCRT Followed by Nivolumab vs CCRT Followed by Durvalumab in Previously Untreated, Locally Advanced Non-small Cell Lung Cancer (LA NSCLC)*. *Trial ID: NCT04026412*. 2019. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04026412 [Accessed 21 November 2022].

2 Electronic Medicines Compendium. *OPDIVO 10 mg/mL concentrate for solution for infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/6888/smpc [Accessed 18 November 2022].

3 Electronic Medicines Compendium. *YERVOY 5 mg/ml concentrate for solution for infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/4683/smpc [Accessed 18 November 2022].

4 De Ruysscher D, Ramalingam S, Urbanic J, Gerber DE, Tan DSW, Cai J, et al. CheckMate 73L: A Phase 3 Study Comparing Nivolumab Plus Concurrent Chemoradiotherapy Followed by Nivolumab With or Without Ipilimumab Versus Concurrent Chemoradiotherapy Followed by Durvalumab for Previously Untreated, Locally Advanced Stage III Non-Small-Cell Lung Cancer. *Clin Lung Cancer*. 2022;23(3):e264-e8. Available from: https://doi.org/10.1016/j.cllc.2021.07.005.

5 Clinicaltrials.gov. *Search of: Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | nivolumab + ipilimumab | Phase 2, 3.* 2022. Available from: https://clinicaltrials.gov/ct2/results?cond=nivolumab+%2B+ipilimumab&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&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 21 November 2022].

6 Cancer Research UK. *Types of lung cancer.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 21 November 2022].

7 Macmillan Cancer Support. *Causes and risk factors of lung cancer.* 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/causes-and-risk-factors-of-lung-cancer [Accessed 21 November 2022].

8 Macmillan Cancer Support. *Signs and symptoms of lung cancer.* 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/signs-and-symptoms-of-lung-cancer [Accessed 21 November 2022].

9 Cancer Research UK. *Treatment for non small cell lung cancer (NSCLC).* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/non-small-cell-lung-cancer [Accessed 11 October 2022].

10 Cancer Research UK. *Lung cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer [Accessed 11 October 2022].

11 Cancer Research UK. *Lung cancer incidence statistics.* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence [Accessed 11 October 2022].

12 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22.* 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 11 October 2022].

13 Office for National Statistics. *Cancer registration statistics, England.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 21 November 2022].

14 National Cancer Registration and Analysis Service. *Survival by stage.* Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 24 November 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 21 November 2022].

16 National Institute for Health and Care Excellence. *Treatment for lung cancer.* Available from: https://www.nice.org.uk/about/what-we-do/into-practice/measuring-the-use-of-nice-guidance/impact-of-our-guidance/niceimpact-lung-cancer/ch4-treatment-for-lung-cancer [Accessed 21 November 2022].

17 National Insititute for Health and Care Excellence. *Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer* (*TA192)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta192 [Accessed 21 November 2022].

18 National Insititute for Health and Care Excellence. *Pemetrexed for the first-line treatment of non-small-cell lung cancer* (*TA181)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta181 [Accessed 15 December 2022].

19 National Insititute for Health and Care Excellence. *Treatment for lung cancer.* Available from: https://www.nice.org.uk/about/what-we-do/into-practice/measuring-the-use-of-nice-guidance/impact-of-our-guidance/niceimpact-lung-cancer/ch4-treatment-for-lung-cancer [Accessed 15 December 2022].

20 National Institute for Health and Care Excellence. *Systemic anti-cancer therapy for advanced non-small-cell lung cancer: treatment options.* 2022. Available from: https://www.nice.org.uk/guidance/ng122/resources/interactive-pdf-of-all-treatment-pathways-for-squamous-and-nonsquamous-advanced-nonsmallcell-lung-cancer-pdf-11189888174 [Accessed 17 November 2022].

21 British National Formulary (BNF). *Medicinal Forms: Nivolumab.* Available from: https://bnf.nice.org.uk/drugs/nivolumab/medicinal-forms/ [Accessed 21 November 2022].

22 British National Formulary (BNF). *Medicinal Forms: Ipilimumab.* Available from: https://bnf.nice.org.uk/drugs/ipilimumab/medicinal-forms/ [Accessed 21 November 2022].

23 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.

24 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. *Ann Oncol*. 2018;29(4):iv192-iv237. Available from: https://doi.org/10.1093/annonc/mdy275.

25 Scottish Intercollegiate Guidelines Network. *Management of lung cancer* (*137)*. Last Update Date: Available from: https://www.sign.ac.uk/media/1075/sign137.pdf [Accessed 11 October 2022].

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