National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: October 2017

Nivolumab (Opdivo) in combination with platinum doublet chemotherapy for Non-Small Cell Lung Carcinoma – first line

NIHRIO (HSRIC) ID: 13775 NICE ID: 9711

LAY SUMMARY

Lung cancer is the third most common cancer in the UK. There are two types: Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). The majority of lung cancers are NSCLCs. The condition can be further classified into several stages based on site, involvement of surrounding structure and spread of disease. Stage IV disease is also called advanced lung cancer and it means the disease has spread from where it started in the lung.

Nivolumab is an intravenous drug under development for the management of advanced (Stage IV) NSCLC. The drug acts on specific proteins (receptors) on immune cells, allowing the defence system of the body to decrease the growth of cancer cells. If licensed, Nivolumab in combination with the current standard of care (platinum doublet chemotherapy) may offer an additional treatment option for patients with advanced NSCLC who currently have failed to respond to standard of care chemotherapy alone.

TARGET GROUP

Non-small cell lung carcinoma (Stage IV) – first line; monotherapy and/or combined therapy

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo,) is a fully human monoclonal antibody directed against cell surface receptor PD-1 (programmed death-1 or programmed cell death-1/PCD-1). PD-1 has an inhibitory action on the immune system. The drug therefore has an immunostimulatory effect. The PD-1 antibody binds to and blocks the activation of PD-1, by its ligands PD-L1 and PD-L2, resulting in the activation of T-cells and cell-mediated immune responses against cancer cells.[1] PD-L1 is the primary PD-1 ligand expressed on hematopoetic, non-hematopoetic cells, T and B cells, and on macrophages along with endothelial and muscle cells.[2] It is expressed in many cancers, including NSCLC.[3]

A doublet chemotherapy, generally cisplatin or carboplatin-based, is the standard of care in the management of advanced NSCLC patients.[4] Carboplatin possesses antineoplastic activity derived from cisplatin.[5] Both are metallic compounds that cause DNA damage, and induce apoptosis in cancer cells.[6] Gemcitabine is an antineoplastic agent that prevents DNA synthesis and induces apoptosis in tumour cells.[7] Pemetrexed is an antifolate drug that targets enzymes involved in folate metabolism, and purine and pyrimidine synthesis, thus disrupting DNA synthesis.[8] Paclitaxel has antineoplastic activity as well and acts by disrupting the normal cell cycle, interfering with mitosis.[9]

The combination of nivolumab with a doublet chemotherapy is being developed as an additional treatment option for non-small cell lung cancer who currently have failed to respond to standard chemotherapy. In the phase III trial (NCT02477826), patients in the experimental arm that received the drug combination were administered nivolumab 10 mg/ml IV plus platinum doublet chemotherapy (IV) dose as carboplatin 10 mg/ml, cisplatin 1 mg/ml, gemcitabine 1000 mg, pemetrexed 500 mg.[1]

In the EU, Nivolumab has been authorised since June 2015 and is being used for the following conditions:[10]

- Advanced melanoma
- Non-Small Cell Lung Cancer
- Renal Cell Carcinoma
- Hodgkin's lymphoma
- Squamous cell cancer of the head and neck
- Urothelial cancer

Common side effects that have been reported with nivolumab include abdominal pain; alopecia; arthralgia; blurred vision; colitis; constipation; cough; decreased appetite; diarrhoea; dizziness; dry eyes; dry mouth; dry skin; dyspnoea; erythema; headache; hyperglycaemia; hypertension; infusion-related reactions; malaise; musculoskeletal pain; nausea; oedema; peripheral neuropathy; pneumonitis; pruritus; pyrexia; rash; stomatitis; thyroid disorders; upper respiratory tract infection; vitiligo and vomiting.[11]

Besides NSCLC, Nivolumab is also undergoing phase III trials for the following indications:[12]

- Gastric or gastroesophageal junction cancer
- Esophageal or gastroesophageal cancer
- Unresectable advanced or recurrent esophageal cancer
- Small cell lung cancer
- Advanced stage melanoma
- Metastatic and localized renal cell carcinoma
- Mesothelioma
- Recurrent or metastatic head and neck carcinoma
- Recurrent or metastatic squamous cell carcinoma of the head and neck
- Bladder or upper and lower urinary tract cancer
- Advanced Stage Classical Hodgkin Lymphoma
- Glioblastoma
- Advanced hepatocellular carcinoma
- Urothelial cancer
- Unresectable pleural mesothelioma
- Multiple myeloma
- Acute myeloid leukaemia or high risk myelodysplastic syndrome

INNOVATION and/or ADVANTAGES

If licensed, Nivolumab in combination with platinum doublet chemotherapy will offer an additional treatment option for non-small cell lung cancer who currently have failed to respond to standard chemotherapy.

DEVELOPER

Bristol-Myers Squibb Pharmaceuticals Ltd (BMS)

PATIENT GROUP

BACKGROUND

Lung cancer is the third most common cancer in the UK and accounts for 13% of all new cancer cases.[13] It is the most common cause of death among both sexes. It is divided into small cell lung cancer (SCLC) and non-small cell lung cancers (NSCLC).[14] 80% of all lung cancers are NSCLC.[15] These are further subdivided into three types; adenocarcinomas, squamous cell carcinomas and large cell carcinomas.[14]

Smoking appears to be the main risk factor for all lung cancers (accounting for 85% of all cases), however, non-smokers may also develop the condition.[16] Other risk factors include exposure to radioactive gas (radon), asbestos, silica, diesel engine exhaust fume, air pollution, previous lung disease such as tuberculosis (TB) and chronic obstructive pulmonary disease (COPD, family history of lung cancer, previous radiotherapy treatment and lowered immunity due to HIV/AIDS.[17] Symptoms include a persistent cough, blood in sputum, persistent breathlessness, tiredness and weight loss and chest pain, loss of appetite, weight loss and on-going chest infections.[18]

Lung cancer is divided into several stages based on site, involvement of surrounding structure and spread of disease. Stage IV disease is also called advanced lung cancer and it means the disease has spread from where it started in the lung to other parts of the body.[19] Unfortunately advanced cancer

can usually not be cured. Treatment aims to control the cancer for as long as possible and help to reduce symptoms.[19] The relative survival of NSCLC varies by subtype, where adenocarcinoma has the highest survival, followed by squamous cell carcinoma, and large cell carcinoma.[20]

In order to explore the potential patient population who could benefit from anti PD-1/PD-L1 mono or combination therapies, trials have been conducted in patients with solid tumours and non-small cell lung cancer to assess the response to treatment in both PD-1 positive and negative expressors.[21,22]

CLINICAL NEED and BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK.[13] The survival in the UK has changed little in the last 40 years.[13] In 2014, 24,800 cases of lung cancer among males and 21,600 among females were reported. The incidence rates are highest among people in the age group 85-89. Most cases are diagnosed in the late stage.[13]

Only 5% of patients survive lung cancer for 10 or more years in England and Wales.[23] The Hospital Episodes Statistics for England 2015/2016 recorded 48,066 finished consultant episodes (FCE), 37,205 hospital admissions and 123,915 FCE beds due to malignant neoplasm in bronchus or lung (unspecified) (ICD-10 code C34.9).[24]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for previously treated locally advanced or metastatic non-squamous non-small cell lung cancer [ID900] (GID TAG524). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab monotherapy for non-small-cell lung cancer [ID1088] (GID TA10148). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811] (GID-TAG506). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab in combination with ipilimumab for untreated PD-L1-positive non-small-cell lung cancer (ID1187) (GID-TA10234). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab in combination with platinum-doublet chemotherapy for untreated PD-L1-negative non-small-cell lung cancer (ID1135) (GID-TA10233). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900] (GID-TAG524). Expected date of issue to be confirmed.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.
- NICE diagnostic guidance. EGFR‑TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer (DG9). August 2013.
- NICE public health guidance. Smoking: harm reduction (PH45). June 2013.

NHS ENGLAND and POLICY 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: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). NHSCB/B01/P/a. April 2013.

OTHER GUIDANCE

- Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Giaj Levra M, Kerr K, Popat S, Reck M, Senan S, Simo GV, Vansteenkiste J, Peters S. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; 27 (5): v1-v27.[25]

CURRENT TREATMENT OPTIONS

Since advanced lung cancer cannot be cured therefore treatment aims to control the cancer for as long as possible and help to reduce symptoms.[19] At the moment there are no treatment options specifically for PD-L1 negative patients.

Standard treatment options for Stage IV NSCLC include the following:[26]

- Surgery
- Chemotherapy
- Radiotherapy
- Chemoradiotherapy

Chemotherapy is considered the option for advanced (Stage IV) NSCLC while surgery and radiotherapy and reserved for less advanced conditions.[27]

EFFICACY and SAFETY

Trial	Opdivo, NCT02477826, CA209-227; EudraCT-2014-003630-23. Nivolumab with platinum doublet chemotherapy (Experimental Arm C)
Sponsor	Bristol-Myers Squibb Pharmaceuticals Ltd (BMS)
Status	Ongoing
Source of Information	Trial Registry,[28] Global Data[29]
Location	EU (15 countries) including the UK and USA
Design	Randomized, Parallel Assignment, Open Label
Participants	n=2,220 (planned); > = 18 years old; Subjects with histologically confirmed Stage IV or recurrent NSCLC squamous or non-squamous histology, with no prior systemic anticancer therapy; Subjects must have programmed death-ligand 1 (PD -L1) immunohistochemical (IHC) testing, with results, performed

	by the central lab during the Screening period; Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1; Measurable disease by CT or MRI per response evaluation criteria in solid tumors version 1.1 (RECIST 1.1) criteria;
Schedule	One of the four groups (Experiment Arm C) was given nivolumab 10 mg/ml IV plus platinum doublet chemotherapy (IV) dose as carboplatin 10 mg/ml, cisplatin 1 mg/ml, gemcitabine 1000 mg, pemetrexed 500 mg.
Follow-up	Not reported
Primary Outcomes	Overall survival (OS) (Up to 48 months) Progression-free survival (PFS) (Up to 40 months)
Secondary Outcomes	• Objective response rate (ORR) (Up to 48 months) ORR of nivolumab monotherapy and nivolumab in combination with ipilimumab to platinum-doublet chemotherapy in subjects with advanced lung cancer • Disease related symptom improvement as measured by the Lung Cancer Symptom Score (LCSS) in all subjects (Up to 48 months) Disease related symptom improvement assessed at each dosing for 6 months, then every 6 weeks while on treatment
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Not reported

ESTIMATED COST and IMPACT

COST

The cost of Nivolumab for this indication is not yet known.

However, nivolumab is already licenced in the UK for the treatment of unresectable or metastatic advanced melanoma, locally advanced or metastatic non-small cell lung cancer and advanced renal cell carcinoma. The cost for nivolumab infusion vials is cited in the BNF as: 10 mg per 1 ml, 1 vial (100mg/10ml) = £1097.00; 1 vial (40mg/4ml) = £439.00.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) declined to provide information.

UK PharmaScan ID number 645029.

REFERENCES

[1] Global Data. An Investigational Immuno-therapy Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum-doublet Chemotherapy, Compared to Platinum Doublet Chemotherapy in Patients with Stage IV Non-Small Cell Lung Cancer (NSCLC) (CheckMate 227). Available at: https://pharma.globaldata.com/ClinicalProductsView.aspx?id=Drug&ClinicalID=YhaEvkMptbiEqLv62xJOfg== [Accessed on: 28th September 2017]

[2] Festino L, Botti G, Lorigan P, Masucci GV, Hipp JD, Horak CE, Melero I, Ascierto PA. Cancer treatment with anti-PD-1/PD-L1 agents: Is PD-L1 expression a biomarker for patient selection? Drug. 2016; 76(9), 925-945. Available at: https://link.springer.com/article/10.1007%2Fs40265-016-0588-x#citeas [Accessed on: 4th October 2017]

[3] Velcheti V, Schalper KA, Carvajal DE, Anagnostou VK, Syrigos KN, Sznol M, Herbst RS, Gettinger SN, Chen L, Rimm DL. Programmed death ligand-1 expression in non-small cell lung cancer. Lab Invest. 2014;94(1):107-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24217091/ [Accessed on: 4th October 2017]

[4] B. Besse, J. C. Soria and T. Le Chevalier. Front-line doublets in advanced non-small cell lung cancer: The golden age for second line chemotherapy. Ann Oncol (2005) 16 (7) 997-998. Available at: https://academic.oup.com/annonc/article/16/7/997/167484/Front-line-doublets-in-advanced-non-small-cell [Accessed on: 2nd October 2017]
[5] Global Data. Carboplatin. Available at: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=6798 [Accessed on: 2nd October 2017]
[6] Shaloam Dasari and Paul Bernard Tchounwou. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 2014 Oct 5; 0: 364–378. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4146684/ [Accessed on: 2nd October 2017]
[7] LS Cavalcante, G Monteiro. Gemcitabine: Metabolism and molecular mechanisms of action, sensitivity and chemoresistance in pancreatic cancer. Eur J Pharmacol. 2014 Oct 15;741:8-16. Available at: http://www.sciencedirect.com/science/article/pii/S0014299914005780 [Accessed on: 3rd October 2017]
[8] Alex A. Adjei. Pharmacology and Mechanism of Action of Pemetrexed. Clin Lung Cancer. 2004 Mar; 5(2): S51-S55. Available at: http://www.sciencedirect.com/science/article/pii/S1525730411701929?via%3Dihub [Accessed on: 3rd October 2017]
[9] Global Data. Paclitaxel. Available at: https://pharma.globaldata.com/ProductsView.aspx?id=PD&ProductId=6977&ProductType=0,1 [Accessed on: 3rd October 2017]
[10] European Medicines Agency. Opdivo. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003985/wapp/Post-authorisation/human_wapp_000238.jsp&mid=WC0b01ac058001d128 [Accessed on: 28th September 2017]
[11] BNF. Nivolumab. Available at: https://www.medicinescomplete.com/mc/bnf/current/PHP202754-nivolumab.htm [Accessed on: 2nd October 2017]
[12] Global Data. Nivolumab. Available from: https://pharma.globaldata.com/AdvancedProductsData.aspx [Accessed on: 23rd October, 2017]
[13] Cancer Research UK. Lung cancer statistics. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer [Accessed on: 28th September 2017]
[14] Cancer Research UK. Lung Cancer Types. Available from: http://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed on: 2nd October 2017]
[15] NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/08/b01-p-a.pdf [Accessed on: 28th September 2017]
[16] NHS Choices. Lung Cancer. Available at: http://www.nhs.uk/Conditions/Cancer-of-the-lung/Pages/Introduction.aspx [Accessed on: 2nd October 2017]
[17] Cancer Research UK. Risks and causes. Available from: http://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes [Accessed on: 23rd October, 2017]
[18] Cancer Research UK. Symptoms. Available from: http://about-cancer.cancerresearchuk.org/about-cancer/lung-cancer/symptoms [Accessed on: 23rd October, 2017]
[19] Cancer Research UK. Lung cancer Stage 4. Available at: http://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stage-4 [Accessed on: 2nd October 2017]
[20] Global Data. Epicast Report: Non-Small Cell Lung Cancer (NSCLC)-Epidemiology Forecast to 2025. Available at: https://pharma.globaldata.com/Reportsview.aspx?DocID=49829 [Accessed on: 2nd October 2017]
[21] Topalian SL, Sznol M, Brahmer JR, McDermott DF, Smith DC, Gettinger SN, Taube JM, Drake CG, Pardoll DM, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Antonia SJ, Spigel DR, Lawrence DP, Kollia G, Gupta AK, Wigginton JM, Hodi FS. Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with advanced solids tumours: Survival and long-term safety in a phase I trial. *J Clin Oncol*. 2013;31(15):3002. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2013.31.15_suppl.3002 [Accessed on: 4th October 2017]
[22] Sacher AG and Gandhi L. PD-1 and PD-L1 inhibitors in advanced non-small cell lung cancer-promising agents and evolving questions. Oncology & Hematology Review, 2015;11(1):36–42. Available at: http://www.touchoncology.com/articles/pd-1-and-pd-l1-inhibitors-advanced-non-small-cell-lung-cancer-promising-agents-and-evolving/page/3/0 [Accessed on: 4th October 2017]
[23] Cancer Research UK. Lung cancer survival statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival [Accessed on: 2nd October 2017]

[24] Hospital Episode Statistics 2015-2016. Primary diagnosis: 4 character. NHS Digital. Available at: http://content.digital.nhs.uk/catalogue/PUB22378/hosp-epis-stat-admi-diag-2015-16-tab.xlsx [Accessed on: 2nd October 2017]

[25] Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Giaj Levra M, Kerr K, Popat S, Reck M, Senan S, Simo GV, Vansteenkiste J, Peters S. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; 27 (5): v1-v27. Available from: http://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer [Accessed on: 2nd October, 2017]

[26] NICE. Lung cancer: diagnosis and management. Available from: https://www.nice.org.uk/guidance/cg121/ifp/chapter/treatments-for-non-small-cell-lung-cancer [Accessed on: 23rd October, 2017]

[27] NICE clinical guidelines. Lung cancer: diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg121/chapter/1-Guidance#treatment [Accessed on: 28th September 2017]

[28] Clinicaltrials.gov. An investigational immune-therapy trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy, compared to platinum doublet therapy in patients with stage IV non-small cell lung cancer (NSCLC) (Checkmate 227). Available at: https://clinicaltrials.gov/ct2/show/NCT02477826?term=NCT02477826&rank=1 [Accessed on: 28th September 2017]

[29] Global Data. Clinical Trial Profile Overview. An investigational immune-therapy trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy, compared to platinum doublet therapy in patients with stage IV non-small cell lung cancer (NSCLC) (Checkmate 227). Available at: https://pharma.globaldata.com/ClinicalProductsView.aspx?ClinicalID=YhaEvkMptbiEqLv62xJOfg== [Accessed on: 28th September 2017]