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Pembrolizumab (Keytruda®) for non-small cell lung cancer

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LAY SUMMARY

Lung cancer is the third most common cancer in the UK and non-small cell lung cancer is the most common cancer within this type. Lung cancer is often diagnosed at an advanced stage and cannot usually be cured. However, treatment can control cancer progression and relieve symptoms.

Pembrolizumab is a type of immunotherapy. It stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-L1 on the surface of certain immune cells called T-cells. Blocking the PD-L1 protein triggers the T-cells to find and kill cancer cells. It is administered as a drip into a vein for 30 minutes every three weeks for up to 35 cycles.

Clinical trials suggest that when treated with pembrolizumab as opposed to platinum-based chemotherapies, those advanced NSCLC patients who have not yet received treatment (treatment naïve) may survive for longer and achieve a better quality of life.

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TARGET GROUP

Non-Small Cell Lung Cancer PD-L1 expression (>=1%): previously untreated stage IV; first line; monotherapy

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda®; MK-3475; SCH-900475) is a humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signalling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumour cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on APCs. Activated PD-1 negatively regulates T-cell activation and plays a key role in in tumour evasion from host immunity.[1] Keytruda® is the branded name for this drug.

The following are recommended as first line treatment options for NSCLC: pemetrexed (in combination with cisplatin), platinum based chemotherapy in combination with a third generation drug, single agent chemotherapy with a third generation drug. For Epidermal Growth Factor Receptor (EGFR) positive tumours: Erlotinib, Gefitinib, Afatinib.

In the Phase III trial (NCT02220894) currently recruiting pembrolizumab as monotherapy that will compared with standard of care in PD-L1 positive patients. This study is planned to be conducted in up to thirty different locations across different countries and is planned to be competed in 2018. Participants will be administered pembrolizumab 200 mg intravenous (IV) on Day 1 of every 21-day cycle (every 3 weeks, or Q3W) for up to 35 treatments.

Pembrolizumab is currently licensed in the EU under its commercial name Keytruda for the following indications:

- Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- Keytruda as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Keytruda.
- Keytruda as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

The most common side effects with Keytruda (which may affect more than 1 in 10 people) are diarrhoea, nausea (feeling sick), itching, rash, joint pain and tiredness, most of which are mild to

moderate in severity. Other common side effects of Keytruda related to the activity of the immune system causing inflammation of body organs. Most will resolve following appropriate treatment or on stopping Keytruda.[2]

Additional Phase III trials of pembrolizumab are registered for the following indications:

- Head/Neck 1L: NCT02358031;
- Head/Neck 2L: NCT02252042;
- Gastroesophageal /Gastric 1L: NCT02678572;
- 2L Gastric/Gastroesophageal NCT02370498
- Colorectal 1L: NCT02563002;
- Esophageal/Esophagogastric 2L: NCT 02564263;
- Multiple Myeloma 1L: NCT 02579863;
- Multiple Myeloma 3L or beyond: NCT 02576977;
- Bladder/Renal 1L: NCT 02853305;
- Bladder/Renal 2L: NCT 02256436;
- Mesothelioma 2L: NCT 02991482;
- Liver 2L: NCT 03062358;
- Small Cell Lung Cancer 1L: NCT 03066778.

INNOVATION and/or ADVANTAGES

When treated with pembrolizumab as opposed to platinum-based chemotherapies, treatment naïve NSCLC patients may have a longer progression free survival and overall survival.

Pembrolizumab may also result in less adverse events than alternative platinum-based chemotherapy.

DEVELOPER

Merck Sharp & Dohme Corp.

AVAILABILITY, LAUNCH or MARKETING

Pembrolizumab was designated as a breakthrough therapy and given priority review designation for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumours express PD-L1 by FDA in 2016.[3]

PATIENT GROUP

BACKGROUND

Non-Small Cell Lung Cancer (NSCLC) is a type of primary lung cancer. About 87 per cent of lung cancers in the UK are NSCLC. There are three common types that are grouped together because they respond to treatment in a similar way. The three types are: adenocarcinoma, squamous cell cancer and large cell carcinoma[4]. Smoking is by far the leading risk factor for lung cancer with other risk factors being air pollution, exposure to some chemicals, radon and asbestos.[5] NSCLC is often insidious, producing no symptoms until the disease is well advanced. Surgery, chemotherapy, and radiation are the main treatment options for NSCLC. Because most lung cancers cannot be cured with currently available

therapeutic modalities, the appropriate application of skilled palliative care is an important part of the treatment of patients with NSCLC.

The system used most often to stage NSCLC is the American Joint Committee on Cancer (AJCC) TNM system, which is based on: size of the main Tumour, existence of lymph Nodes and whether the cancer has spread or Metastasized.[6] The prognosis for patients diagnosed with NSCLC depends on the stage of the disease at diagnosis. Patients who are diagnosed in the earliest stages can have a 5 year survival rate between 53-78% however; those diagnosed at the latest stage may be looking at a 5 year survival rate of 2-13%.[7]

CLINICAL NEED and BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK (2014). In England, it is more common in people living in the most deprived areas. There were around 46,400 new cases of lung cancer in the UK in 2014. Over the last decade, lung cancer incidence rates have increased by four per cent in the UK, this includes a decrease (8%) for males and an increase (18%) for females. However, incidence rates are projected to fall by seven per cent in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035. This includes a larger decrease for males than for females. For males, lung cancer European age standardised incidence rates in the UK are projected to fall by 14% between 2014 and 2035, to 97 cases per 100,000 by 2035. For females, rates are projected to fall by less than 1% between 2014 and 2035, to 80 cases per 100,000 by 2035.[8]

Around three-quarters of lung cancer cases are diagnosed at a late stage in England (2014), Scotland (2014-2015) and Northern Ireland (2010-2014). Is estimated that around 22% of cancer deaths in 2014 were lung cancer related deaths. Lung cancer mortality is strongly related to age, with the highest mortality rates being in older males and females. In the UK in 2012-2014, on average each year almost half (48%) of deaths were in people aged 75 and over.[9]

Survival rates are low. Only about five per cent of patients survive lung cancer for more than 10 years. In England, those aged between 15 and 39 are more likely to survive.[10]

Non-Small Cell Lung Cancer patients represent the majority of the lung cancer patients, however, the population likely to be eligible to receive pembrolizumab (Keytruda) could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology Appraisal. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428). Jan 2017.
- NICE Technology Appraisal. Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA422). Dec 2016.
- NICE Technology Appraisal. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (TA416). Oct 2016.
- NICE Technology Appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). Sept 2016.

- NICE Technology Appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). Sept 2016.
- NICE Technology Appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). Aug 2016.
- NICE Technology Appraisal. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (TA403). Aug 2016.
- NICE Technology Appraisal. Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer (TA395). Jun 2016.
- NICE Technology Appraisal. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). Feb 2016.
- NICE Technology Appraisal. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (TA374). Dec 2015.
- NICE Technology Appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non‑small‑cell lung cancer (TA347). Jul 2016.
- NICE Technology Appraisal. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343) Jun 2015.
- NICE Technology Appraisal. Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small-cell lung cancer (TA310). Apr 2014.
- NICE Technology Appraisal. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (TA258). Jun 2012.
- NICE Technology Appraisal. Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer (TA227). Jun 2011.
- NICE Technology Appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). Jul 2010.
- NICE Technology Appraisal. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (TA190). Jun 2010.
- NICE Technology Appraisal. Topotecan for the treatment of relapsed small-cell lung cancer (TA184). Nov 2009.
- NICE Technology Appraisal. Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated appraisal) (TA175). Jul 2009.
- NICE Technology Appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). Nov 2007.

- NICE guidelines. Lung cancer: diagnosis and management (CG121). April 2011

- Quality Standard. Lung cancer in adults. March 2012.

- Diagnostics guidance. EGFR‑TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer. August 2013.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013 Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small Cell Lung Cancer (Adult). B01/P/a
- NHS England. 2016 Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. 16024/P
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2014.[11]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (137). 2014.[12]
- National Comprehensive Cancer Network. The NCCN clinical practice guidelines in oncology. Non-small cell lung cancer. 2013.[13]
- American College of Chest Physicians. Treatment of stage IV non-small cell lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. 2013.[14]
- American Society of Clinical Oncology. 2011 focused update of 2009 American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small cell lung cancer. 2011[15]

CURRENT TREATMENT OPTIONS

The aim of treatment for locally advanced or metastatic NSCLC is to prolong survival, improve quality of life, and control disease-related symptoms.[16] Treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient's age, performance status, comorbidities, and preferences. Patients who smoke should be encouraged to cease, as cessation improves treatment outcomes.[17] Current NICE Pathways reflect this recommendations.[18]

For the UK, NICE clinical guideline 121 (CG121) recommends platinum-based chemotherapy as an option for people with previously untreated stage III or IV NSCLC and good performance status.

For people with locally advanced or metastatic NSCLC whose disease has progressed after non-targeted chemotherapy, NICE recommends chemotherapy combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. [18]

Treatment choices may be influenced by the presence of genetic markers (such as mutations in EGFR-TK), histology (squamous or non-squamous) and previous treatment experience. Supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated.[19]

EFFICACY and SAFETY

Trial	NCT02142738, KEYNOTE-024; pembrolizumab *vs.* platinum-based chemotherapies; phase III	NCT02220894, KEYNOTE-042; pembrolizumab *vs.* platinum-based chemotherapies; phase III
Sponsor	Merck & Co Inc	Merck & Co Inc
Status	Stopped early due to superiority for both endpoints	Ongoing, not recruiting
Source of Information	Trial registry[20]	Trial registry[21]
Location	Not reported	Argentina, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Estonia, Guatemala, Hong Kong, Hungary, Japan,

		Korea, Republic of, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russian Federation, South Africa, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine
Design	Randomized, open-label, active-controlled, cross- over phase for those randomised to control.	Randomized, open-label, active-controlled.
Participants	N=305 recruited; aged <18 (upper limit not specified) years; previously untreated stage IV, programmed cell death ligand 1 (PD-L1) strong expressing Non-Small Cell Lung Cancer (NSCLC).	N=1240; aged <18 (upper limit not specified) years; previously untreated stage IV, programmed cell death ligand 1 (PD-L1) expressing Non-Small Cell Lung Cancer (NSCLC).
Schedule	Randomised to pembrolizumab 200 mg, administered as intravenous (IV) infusion on Day 1 of each 21-day cycle for up to 35 cycles; or paclitaxel 200 mg/m^2 and carboplatin Area Under the Curve (AUC) 5 or 6, administered as IV infusion on Day 1 of each 21-day cycle for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 every three weeks (Q3W) maintenance for participants with non-squamous histologies for the remainder of the study; or pemetrexed 500 mg/m^2 and carboplatin AUC 5 or 6, IV infusion on Day 1 of each 21-day cycle for 4-6 cycles; participants with non-squamous histologies may then receive pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle as maintenance therapy for the remainder of the study; or pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, administered as IV infusion on Day 1 of each 21-day cycle for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W maintenance for the remainder of the study; or gemcitabine 1250 mg/m^2, administered as IV infusion on Days 1 and 8 of each 21-day cycle and carboplatin AUC 5 or 6, administered as IV infusion on Day	Randomised to pembrolizumab 200 mg intravenous (IV) on Day 1 of every 21-day cycle (every 3 weeks, or Q3W) for up to 35 treatments; or carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m^2 IV on Day 1 of every 21-day cycle (Q3W) for a maximum of 6 cycles OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m^2 IV on Day 1 Q3W for a maximum of 6 cycles; participants with non-squamous histologies may go on to receive optional treatment with pemetrexed 500 mg/m^2 IV on Day 1 Q3W.

	1 of a 21-day cycle, for 4-6 cycles; or gemcitabine 1250 mg/m^2, administered as IV infusion on Days 1 and 8 of each 21-day cycle and cisplatin 75 mg/m^2, administered as IV infusion on Day 1 of each 21-day cycle for 4-6 cycles.	
Follow-up	Active treatment for 35 cycles, follow-up not specified.	Active treatment for 35 cycles, follow-up not specified.
Primary Outcomes	Progression Free Survival (PFS) timeframe 2 years	Overall survival (OS) timeframe 2.5 years
Secondary Outcomes	Overall Survival (OS), Objective Response Rate (ORR) timeframe 2 years	Progression-free Survival (PFS) timeframe 2.5 years
Key Results	Median PFS was 10.3 mths (95% CI 6.7 to not reached) in intervention versus 6.0 mths (95% CI, 4.2 to 6.2); rate of OS at 6 mths was 80.2% in the intervention versus 72.4% in the controls (hazard ratio for death 0.60; 95% CI, 0.41 to 0.89, p=0.005); response rate was higher in the intervention group than in the control (44.8% vs. 27.8%); median duration of response was longer (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+]).	-
Adverse effects (AEs)	Treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%)	-
Expected reporting date	Trial stopped early because intervention shown superiority in both primary and secondary outcomes.	Estimated primary completion date February 2018

ESTIMATED COST and IMPACT

COST

The cost of pembrolizumab for this indication is not yet known. However, pembrolizumab is approved for use in the UK for the treatment of advanced melanoma.

Furthermore, in December 2016, NICE released a news item in which they state the price of pembrolizumab for second line treatment of lung cancer as follows “the average cost of a course of

treatment with pembrolizumab is £29,114 at its full list price but the company offered the NHS a confidential discount".[22]

The current medicinal product price registered in the NHS is for Keytruda 100mg/4ml concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) 1 vial at £2,630.00[23] and for Keytruda 50mg powder for concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) 1 vial is £1,315.00.[24]

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: *specify, e.g. new staff training requirements, requirement for new facilities, specialist laboratory testing, etc.*	☒ 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

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