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Pembrolizumab in addition to standard of care chemotherapy for extensive stage small cell lung cancer – first line

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LAY SUMMARY

Small-cell lung cancer (SCLC) is a type of lung cancer. There are two stages of SCLC; limited (where the cancer has not yet spread to other areas of the body) and extensive (where the cancer has spread to other areas in the body). SCLC is strongly linked with smoking and the risk of developing SCLC increases with increased duration and frequency of smoking. The most common symptoms include cough, chest pain, coughing up blood, difficulty breathing and weight loss. Symptoms of lung cancer usually become apparent when the cancer has already spread, so the outlook for patients with lung cancer is usually worse than other cancers. Treatment for extensive SCLC usually includes chemotherapy, radiotherapy or a combination of the two.

Pembrolizumab is a drug administered by injection which stimulates the body's own 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. If licenced, pembrolizumab in combination with usual chemotherapy treatment for extensive SCLC could provide an additional or alternative treatment option to standard chemotherapy alone. This is important as there are limited treatment options for those with extensive SCLC and relapse rates after treatment are high.

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TARGET GROUP

Small cell lung cancer (newly diagnosed; extensive) – first line; in combination with standard of care treatment (etoposide/platinum: cisplatin or carboplatin)

TECHNOLOGY

DESCRIPTION

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands 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. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to 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.[1]

Pembrolizumab is in phase III clinical development (KEYNOTE-604; NCT03066778) in addition to standard of care chemotherapy (etoposide/platinum: cisplatin or carboplatin) for patients with newly diagnosed extensive stage small cell lung cancer. The proposed dose of pembrolizumab for this indication is 200mg pembrolizumab administered by IV every three weeks alongside 100mg/m^2 etoposide by IV on days 1, 2 and 3 of each three week (21 day) cycle, plus the investigators choice of platinum based chemotherapy (cisplatin or carboplatin).[2]

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:[1]

- advanced (unresectable or metastatic) melanoma in adults
- 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 – first line
- locally advanced or metastatic NSCLC in adults whose tumour express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen
- 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
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy

The most common side effects of pembrolizumab (affecting more than one in ten people) include diarrhoea, nausea, rash, pruritus and fatigue.[1]

Pembrolizumab is currently in phase III clinical trials for the treatment of:[3]

- breast cancer
- colorectal cancer
- oesophageal cancer
- gastric cancer
- head and neck cancer
- liver cancer

- nasopharyngeal cancer
- renal cancer

INNOVATION and/or ADVANTAGES

Therapeutic options for SCLC remain limited with (etoposide/platinum: cisplatin or carboplatin) as the standard first-line chemotherapy regime. However patients with extensive stage SCLC experience high relapse rates within months after initial therapy.[4]

Numerous clinical studies and licence/marketing authorisations have demonstrated the efficacy and safety of pembrolizumab in a range of cancer indications. If pembrolizumab in combination with standard of care chemotherapy is licenced as a first line treatment, this may provide an additional, alternative treatment option for patients with extensive SCLC.

DEVELOPER

Merck Sharp & Dohme Ltd (MSD)

PATIENT GROUP

BACKGROUND

There are two types of primary lung cancer: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). SCLC is less common than NSCLC, making up approximately 12% of lung cancer cases and usually spread earlier than NSCLC.[5] SCLC gets its name from how the cells look when examined under the microscope.[6] There are two main types of SCLC which are named after the types of cells which make up the cancer and how they look under the microscope: small cell carcinoma (oat cell cancer) and combined small cell carcinoma.[7]

There are two stages of SCLC; limited-stage SCLC (where the cancer is in the original location within the lung which may have spread to the area between the lungs or to the lymph nodes above the collarbone) and extensive stage SCLC (where the cancer has spread beyond the lung or the area between the lungs or the lymph nodes above the collarbone to other places in the body).[8]

The main risk factor for SCLC is smoking (past or current). The risk of lung cancer is greater with earlier onset of smoking, higher frequency of smoking and longer duration of smoking. Other risk factors for SCLC include; exposure to second-hand smoke, exposure to asbestos, arsenic, chromium, beryllium, nickel, soot or tar in the workplace, exposure to radiation, exposure to air pollution, family history of lung cancer, HIV infection and increased age. When smoking is combined with other risk factors, this increases the risk of lung cancer.[7]

Symptoms of SCLC include chest pain, cough which does not go away or gets worse over time, trouble breathing, wheezing, blood in sputum, hoarseness, trouble swallowing, loss of appetite, weight loss, fatigue, swelling in the face and/or veins in the neck.[7]

Lung cancer does not usually cause noticeable symptoms until it has spread throughout the lungs or into other parts of the body, which means the outlook for this condition is not as good as other types of cancer.[9]

CLINICAL NEED and BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases.[10] In 2015, the age-standardised incidence rate for lung cancer in England was 75.9 per 100,000 (equivalent to 37,637 persons). Of all lung cancer cases, 10-15% of lung cancer cases are classed as SCLC. If this figure is applied to the statistics above, the age-standardized incidence of SCLC in England in 2015 would be between 7.6 and 11.4 per 100,000 (equivalent to 3,764 – 5,646 persons).[11]

Survival for lung cancer is strongly related to stage of disease at diagnosis. One year survival for adults aged 15-99 years in England in 2014 for those diagnosed with stage IV lung cancer was 14.6% for males and 19.3% for females.[12] A cohort study of 18,513 patients diagnosed with SCLC from 2004-2011 in England showed that median survival was 4 months for those with extensive stage SCLC.[13]

Lung cancer is the most common cause of cancer death in the UK, accounting for 21% of all cancer deaths. In 2015, the age-standardised mortality rate for lung cancer in England was 56.6 per 100,000 (equivalent to 28,566 people).[14]

In 2015, there were 91,902 admissions, 112,905 finished consultant episode and 64,257 day cases for malignant neoplasm of bronchus and lung (ICD10: C34).[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE quality standard. Lung cancer in adults (QS17). March 2012.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011.

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.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 137 Management of lung cancer. February 2014.[16]
- European Society for Medical Oncology (ESMO). Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. October 2013.[17]
- European Society for Medical Oncology (ESMO). ESMO Consensus Guideline: Small-Cell Lung Cancer. 2011.[18]

CURRENT TREATMENT OPTIONS

SCLC is usually treated with chemotherapy, either on its own or in combination with radiotherapy. Surgery is not usually used to treat SCLC, especially in extensive disease where the cancer has spread to other areas of the body.[19] The aim of treatment is to control the cancer for as long as possible and help with symptoms.

Treatments for extensive stage SCLC include:[20]

- Combination chemotherapy
- Radiation therapy to the brain, spine, bone, or other parts of the body where the cancer has spread and as palliative therapy to relieve symptoms and improve quality of life
- Radiation therapy to the chest for patients who respond to chemotherapy
- Radiation therapy to the brain for patients who have a complete response to prevent spread of cancer to the brain

There are several different types and regimes of radiotherapy which are used for the treatment of SCLC, including; [19]

- Prophylactic cranial irradiation (PCI) - delivers a low dose of radiotherapy to the brain
- External beam radiotherapy - machine directs beams of radiation at affected parts of the body
- Internal radiotherapy (- catheter filled with radioactive material is inserted into the lung and positioned against the tumour before being removed after several minutes. Internal therapy is usually only used as palliative care when the cancer is blocking the airway.
- Radical radiotherapy is usually given 5 days a week (with each session lasting 10-15 minutes) with a break at weekends for a total of 12 days in a row.
- Continuous hyper fractionated accelerated radiotherapy (CHART) is an alternative method of delivering radical radiotherapy and is given 3 times a day for 12 days in a row.
- Palliative radiotherapy is usually given over 1-5 sessions to control sessions.

Chemotherapy combinations for SCLC usually include:[21]

- EP (cisplatin and etoposide)
- Carboplatin and etoposide
- Gemcarbo (gemcitabine and carboplatin)

EFFICACY and SAFETY

Trial	NCT03066778, KEYNOTE-604, EudraCT: 2016-004309-15; pembrolizumab vs placebo, both in combination with standard of care chemotherapy: etoposide plus investigators choice of platinum treatment (carboplatin or cisplatin); phase III trial
Sponsor	Merck Sharp & Dohme
Status	Ongoing
Source of Information	Trial registry[2]
Location	7 EU countries (including UK), USA, Australia, Canada, Chile, Israel, Japan, New Zealand, Russian Federation, Taiwan, Turkey and Switzerland

Design	Randomised, placebo-controlled,
Participants	n=430 (planned); aged 18 years or older; small-cell lung cancer; newly diagnosed; extensive (stage IV); in combination with standard of care chemotherapy
Schedule	Participants are randomised to one of two treatment arms: 1. Experimental arm: during a 21 day cycle, participants receive 200mg IV pembrolizumab on day 1, 100mg/m^2 IV etoposide on days 1, 2 and 3 plus investigators choice of platinum chemotherapy (carboplatin titrated to an area under the plasma drug concentration time curve 5 IV on day 1 or 75mg/m^2 IV cisplatin on day 1) 2. Active comparator: during a 21 day cycle, participants receive placebo (normal saline solution) IV on day 1 plus 100mg/m^2 IV etoposide on days 1, 2 and 3 plus investigators choice of platinum chemotherapy (carboplatin titrated to an area under the plasma drug concentration time curve 5 IV on day 1 or 75mg/m^2 IV cisplatin on day 1)
Follow-up	Follow up for up to 2 years
Primary Outcomes	• Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) [Time Frame: Up to approximately 2 years] • Overall Survival (OS) [Time Frame: Up to approximately 2 years]
Secondary Outcomes	• Objective Response Rate (ORR) per RECIST 1.1 as Assessed by BICR [Time Frame: Up to approximately 2 years] • Duration of Response (DOR) per RECIST 1.1 as Assessed by BICR [Time Frame: Up to approximately 2 years] • Percentage of Participants Experiencing an Adverse Event (AE) [Time Frame: Up to approximately 27 months] • Percentage of Participants Discontinuing Study Treatment Due to an AE [Time Frame: Up to approximately 2 years] • Percentage of Participants Experiencing Any Grade 3 to 5 AE as Assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE 4.0) [Time Frame: Up to approximately 27 months] • Change from Baseline at Weeks 12 and 24 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale [Time Frame: Baseline and Week 12, Week 24] • Time to True Deterioration in the Composite Endpoint of Cough, Chest Pain, and Dyspnea Using the EORTC Quality of Life Questionnaire and Lung Cancer Module 13 (QLQ-LC13) [Time Frame: Time frame: Day 1 of Cycles 1-9, Day 1 of every other cycle for Cycles 10-17 and 30 days after last dose of study treatment (Up to approximately 13 months)]
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Study primary completion date reported as January 2019.

ESTIMATED COST and IMPACT

COST

Pembrolizumab is already marketed in the UK; 100mg/4ml concentrate for solution for infusion vials (25mg/mL) costs £2,630 vial.[22]

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 – increased use of clinics for IV drug administration

☐ 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: additional costs for IV administration in clinic

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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