Nivolumab (Opdivo) for relapsed small-cell lung cancer – second line

NIHR HSRIC ID: 11262

Lay summary

Nivolumab is a new drug to treat small-cell lung cancer that has returned after first being treated with chemotherapy. Small-cell lung cancer is a fast growing and rare type of lung cancer which is usually caused by smoking. Nivolumab is given straight into the bloodstream and stimulates the body’s immune system to fight the cancer cells.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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

- Small-cell lung cancer (SCLC): relapsed; second line – after platinum-based first line therapy.

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo; anti-PD-1 monoclonal antibody - Medarex/Ono; BMS936558; MDX1106; ONO4538) is a fully human IgG4 monoclonal antibody which targets the programmed cell death-1 (PD-1) receptor expressed on the surface of activated lymphocytes. PD-1 blockage by nivolumab activates T-cell responses and promotes an anti-tumour immune response. In phase III clinical trials, nivolumab is administered every 14 days at 240mg via intravenous (IV) infusion over 30 minutes.

Nivolumab is pre-registration in the EU for recurrent metastatic head and neck cancer. It is licensed for the treatment of advanced melanoma in adults (alone or in combination with ipilimumab), locally advanced or metastatic non-small cell lung cancer after prior chemotherapy, and advanced renal cell carcinoma after prior therapy. Very common adverse effects (>10%) associated with nivolumab include: rash, pruritus, fatigue, decreased appetite, increased amylase, hypocalcaemia, lymphopenia, leukopenia, thrombocytopenia, anaemia, hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, and increased: AST, ALT, alkaline phosphatase, lipase, and creatinine. Common adverse effects associated with nivolumab include: upper respiratory tract infection, infusion related reaction and hypersensitivity, hypothyroidism, hyperthyroidism, hyperglycaemia, peripheral neuropathy, headache, dizziness, blurred vision, dry eye, hypertension, pneumonitis, dyspnoea, cough, colitis, stomatitis, vomiting, abdominal pain, constipation, dry mouth, vitiligo, dry skin, erythema, alopecia, mycosis, peripheral oedema, increased total bilirubin, neutropenia, hypermagnesaemia, hyponatraemia, and decreased weight.

Nivolumab is in phase III clinical trials for gastric cancer, glioblastoma, hepatocellular carcinoma, multiple myeloma, oesophageal cancer and urogenital cancer. It is also in phase II clinical trials for acute myeloid leukaemia, breast cancer, chronic lymphocytic leukaemia, diffuse large B cell lymphoma, follicular lymphoma, myelodysplastic syndromes, ovarian cancer and uveal melanoma.

INNOVATION and/or ADVANTAGES

If licensed, nivolumab will offer an additional treatment option for patients with relapsed SCLC.

DEVELOPER

Bristol-Myers Squibb Pharmaceuticals Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.
PATIENT GROUP

BACKGROUND

SCLC originates from neuroendocrine-cell precursor cells and is characterised by rapid growth, high initial response rates to both chemotherapy and radiotherapy, and development of treatment resistance in patients with metastatic disease. SCLC is so called because of its histological appearance; the cells appear very small and are mostly filled by the nucleus. This type of cancer occurs mainly in middle-aged individuals (median age 69 years), and is usually caused by smoking. Symptoms may include chest pain, persistent cough, dyspnoea, wheezing, hoarseness, haemoptysis, loss of appetite, weight loss, and neurological and endocrine paraneoplastic syndromes.

SCLC is staged into limited or extensive disease. Limited disease is defined as disease that can be encompassed within a radical radiotherapy field. In practice, this means the cancer is only in one lung; it may also be in lymph nodes which are close to the lung or there may be cancer cells in the fluid around the lung (pleural effusion). Extensive disease means the cancer has spread into lymph nodes outside the lung or into other organs.

CLINICAL NEED and BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK (2013), accounting for 13% of all new cancer cases. In 2013, there were 45,525 new cases of lung cancer in the UK. SCLC represents approximately 10-15% of all lung cancers. The majority of patients who initially respond to first line therapy will subsequently relapse. An estimated 40% of patients who relapse or do not respond will receive second-line chemotherapy. The two-year cumulative recurrence rate is 75% in patients with limited disease and nearly 100% in patients with extensive disease. Patients with SCLC have a median overall survival of 12-20 months with only 6-12% of patients surviving for 5 years after diagnosis. Patients who relapse have a median survival of only 4 to 5 months when treated with further chemotherapy.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


NHS England Policies and Guidance

CURRENT TREATMENT OPTIONS

Patients with relapsed SCLC have an extremely poor prognosis. Patients receiving second-line therapy are divided into refractory (if the interval is less than 3 months) or relapsed (if more than 3 months after the end of first-line therapy). Patients who have relapsed benefit the most from second-line chemotherapy.

First-line treatment for SCLC may include: cisplatin-based chemotherapy (4-6 cycles), platinum-based chemotherapy, and radiotherapy (prophylactic cranial irradiation). For patients with limited-stage SCLC and good performance status (0–2), the recommended treatment is chemotherapy with concurrent thoracic radiotherapy; for patients with extensive-stage disease, chemotherapy alone is recommended, although radiotherapy may be used for palliation of symptoms.

Current second-line treatment options for patients with SCLC that have relapsed after first-line treatment include:

- **Chemotherapy:**
  - Anthracycline - containing regimen or further platinum chemotherapy (maximum 6 cycles).
  - Topotecan – only for people with relapsed SCLC for whom treatment with the first line regimen is not considered appropriate and the combination of cyclophosphamide, doxorubicin and vincristine (CAV) is contraindicated.

- **Radiotherapy for palliation of local symptoms.**

Expert opinion states that oncologists are generally prepared to give immunotherapy (such as nivolumab) to patients who would not tolerate further standard chemotherapy because of their poorer performance status. An expert further suggests that the majority of patients with relapsed SCLC will have poor performance status (WHO 2-4), the role of nivolumab in these patients should be explored.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>CheckMate33, NCT02481830, CA209-331, EudraCT2015-001097-18; nivolumab vs chemotherapy with topotecan or amrubicin; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Bristol-Myers Squibb.</td>
</tr>
<tr>
<td>Status</td>
<td>On-going.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
</tr>
</tbody>
</table>

* Expert personal opinion.
Location: EU (incl UK), USA and other countries.

Design: Randomised, active-controlled.

Participants: n = 480 (planned); age ≥ 18 yrs; small-cell lung cancer; limited or extensive disease; recurrence or progression after platinum-based first-line chemotherapy or chemoradiation; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

Schedule: Randomised to nivolumab 240mg IV on day 1 of a 14 day cycle; or chemotherapy with one of topotecan 1.5mg/m² IV or 2.3mg/m² oral once daily on days 1 to 5 of a 21-day cycle, or amrubicin (investigator’s choice where locally approved) 40mg/m² IV once daily on days 1 to 3 of a 21 day cycle.

Follow-up: For up to 5 yrs.

Primary outcome/s: Overall survival.

Secondary outcome/s: Progression free survival; objective response rate. No quality of life measures included in reported trial outcomes.

Expected reporting date: Primary completion date reported as Mar 2018.

ESTIMATED COST and IMPACT

COST

The cost of nivolumab is not known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

☑ Reduced mortality/increased length of survival: expert opinion state that if the trial shows a significant survival benefit, it is likely that oncologists may see this as a new standard of care for relapsed SCLC.

☐ Other

☑ Reduced symptoms or disability: expert opinion state that the toxicity of nivolumab is generally much better than the standard chemotherapy.

☐ 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: expert opinion notes the high cost of nivolumab compared to standard chemotherapy.

☐ Other increase in costs

☐ Reduced drug treatment costs

☐ Other

☐ Other reduction in costs

☐ None identified

b Expert personal opinion.
Other Issues

- Clinical uncertainty or other research question
- None identified

REFERENCES


