NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer ID5094

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of pembrolizumab with chemotherapy and then pembrolizumab monotherapy within its marketing authorisation for neoadjuvant and adjuvant treatment of resectable stage 2 to 3B non-small cell lung cancer (NSCLC).

Background

Lung cancer is the third most common cancer and the most common cause of cancer death in the UK, accounting for 13% of all new cancer cases and 21% of all cancer deaths between 2017 to 2019.[1] Most lung cancers are diagnosed at an advanced stage when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage 3) or to other parts of the body (metastatic disease; stage 4). Less than 30% of lung cancers are diagnosed at an early stage (stage 1 or 2).[2]

In 2021, 91% (31,374) of people diagnosed with lung cancer in England had NSCLC.[2] Of these people, 17% (5,333) had surgical treatment for their cancer.[2] Despite the curative intent of treatment for early-stage lung cancer, survival is poor, with only about 57% people with stage 1, 34% with stage 2 and 13% with stage 3 surviving for 5 years after diagnosis.[3] It is estimated that over half of all NSCLCs express the programmed cell death ligand-1 (PD-L1) biomarker.[4] Cancer cells expressing PD-L1 are believed to suppress certain immune responses which results in a weaker anti-tumour response.[4,5]

The treatment pathway for NSCLC can be divided into interconnected decision points based on the number staging system and line of therapy. Treatment choices are influenced by the presence of biological markers (including programmed cell death 1 ligand PD-L1 status), oncogenic driver genetic alterations, histology (squamous or non-squamous) and previous treatment. NICE's Technology Appraisal Pathway Pilot scope for treatments for non-small-cell lung cancer outlines in more detail the NSCLC treatment pathway.

NICE guideline 122 (NG122) 'Lung cancer: diagnosis and management' recommends surgery, radiotherapy, chemotherapy or a combination of these for stage 1 to 2 NSCLCPeople may be offered a neo-adjuvant (before surgical removal of cancerous tumour) treatment which could be platinum based chemotherapy, or nivolumab with chemotherapy as recommended by NICE TA876. Neoadjuvant chemotherapy has shown equivalent outcomes in terms of survival to adjuvant chemotherapy.[6]

For stage 3 NSCLC, surgery is carried out if the surgeon deems the tumour to be resectable. Before surgery, chemoradiotherapy (chemotherapy with radiotherapy) may be used or surgery may potentially be followed by chemotherapy. If well enough,

people may be offered a cisplatin-based chemotherapy (adjuvant treatment) after surgery.

People who have had surgery may have an adjuvant treatment. NICE TA761 recommends osimertinib in the Cancer Drugs Fund as adjuvant treatment for people whose cancer has an EGFR exon 19 deletion or an exon 21 (L858R) substitution mutation. For people whose cancer does not have an EGFR mutation, platinum chemotherapy may be offered as adjuvant treatment. NICE TA823 recommends atezolizumab in the Cancer Drugs Fund as an option for maintenance treatment after complete tumour resection in adults with stage 2 to 3a NSCLC and adjuvant chemotherapy.

The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) with chemotherapy then pembrolizumab monotherapy does not currently have a marketing authorisation in the UK for neoadjuvant and adjuvant treatment of resectable NSCLC. It is currently being studied in a clinical trial compared with placebo in people with previously untreated and pathologically confirmed resectable stage 2, 3A, or 3B NSCLC.

Pembrolizumab is currently licenced as a monotherapy for several indications including but not limited to:

- locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a greater than or equal to 1% tumour proportion score (TPS) and who have received at least one prior chemotherapy regimen. People with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

- first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a greater than or equal to 50% TPS with no EGFR or ALK positive tumour mutations

Pembrolizumab is also currently licenced as combination therapy with:

- pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.

- carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.

Intervention	Pembrolizumab with chemotherapy
Population	People with untreated resectable NSCLC which is PD-L1 positive
Subgroups	If the evidence allows subgroups will be considered based on: • Whether pembrolizumab is used before and after surgery • PD-L1 tumour proportion score • Disease stage
Comparators	Established CM without durvalumab, which may include • Neoadjuvant nivolumab with chemotherapy • Neoadjuvant chemoradiotherapy • Platinum based chemotherapy • Active monitoring For people whose tumours express PD-L1 with at least a 50% tumour proportion score • Atezolizumab after adjuvant cisplatin… (subject to NICE appraisal)

Outcomes	The outcome measures to be considered include: • disease-free survival • event-free survival • pathological complete response • overall survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related technology appraisals:** Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer (2023). NICE technology appraisals guidance 876 Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (2022). NICE technology appraisals guidance 823 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (2022). NICE technology appraisals guidance 761. **Related technology appraisals in development:**

	Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer. NICE Technology Appraisals guidance [ID3907]. Publication date to be confirmed Durvalumab with chemotherapy for neoadjuvant and adjuvant treatment of resectable non-small-cell lung cancer NICE Technology Appraisals guidance [ID6220]. Publication date to be confirmed Atezolizumab with chemotherapy for neoadjuvant and adjuvant treatment of resectable non-small-cell lung cancer [ID3894] Publication date to be confirmed Nivolumab for adjuvant treatment of resected non-small-cell lung cancer [ID4053] Publication date to be confirmed Durvalumab for adjuvant treatment of resectable non-small-cell lung cancer NICE Technology Appraisals guidance ID1263. Publication date to be confirmed **Related NICE guidelines:** 'Lung cancer: diagnosis and management' (2019). NICE guideline NG122. **Related quality standards:** 'Lung cancer in adults' (2019). NICE quality standard 17
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2018) NHS manual for prescribed specialist services (2018/2019) Chapter 105: Specialist cancer services (adults).

Questions for consultation

Have all relevant comparators for pembrolizumab for neoadjuvant and adjuvant treatment of resectable non-small-cell lung cancer been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for resectable NSCLC? How does this differ by stage?

Would all patients with resectable NSCLC that receive neoadjuvant treatment with pembrolizumab continue to receive adjuvant treatment? Are there any clinical features post-surgery that may make patients less likely to benefit from adjuvant treatment?

Are there any patients with resectable NSCLC who would not have a neo-adjuvant treatment but who would have an adjuvant treatment after surgery? If so, what might the reasons be for this and which treatments would they have?

If a patient had nivolumab with chemotherapy as a neo-adjuvant treatment, would they have any chemotherapy regimens as an adjuvant treatment?

What considerations are made in determining whether pembrolizumab is used before or after neoadjuvant chemoradiotherapy or adjuvant chemotherapy?

Is there a routine test to detect the biomarker PD-L1 in resectable samples?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

References

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3. Office for National Statistics. Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed. Accessed October 2023
4. Skov, B., Rørvig, S., Jensen, T. et al. (2020) The prevalence of programmed death ligand-1 (PD-L1) expression in non-small cell lung cancer in an unselected, consecutive population. Mod Pathol 33, 109–117
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6. European Society for Medical Oncology (ESMO). Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2017;28(Supplement 4):iv1–iv21. Available from: https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/. Accessed October 2023