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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

Pembrolizumab in combination with olaparib for treatment of metastatic squamous non-small cell lung cancer

NIHRIO ID	27277	**NICE ID**	10541
Developer/Company	Merck Sharp & Dohme	**UKPS ID**	662433

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Pembrolizumab in combination with olaparib is in clinical development for the treatment of metastatic squamous non-small cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK and squamous NSCLC is where the cancer begins in the flat cells that cover the surface of the airway. Metastatic (advanced) NSCLC refers to when the cancer has spread from the lung to other parts of the body most often to the brain, bones, liver, and adrenal glands. Advanced squamous NSCLC is not usually curable and currently there are currently limited treatment options available for these patients.

Pembrolizumab is an immunotherapy drug given by intravenous (IV) infusion and works by blocking a protein called PD-L1, which results in an increased ability of the patient's immune system to attack and kill cancer cells. Olaparib is taken orally and belongs to a class of drugs called poly-ADP-ribose polymerase inhibitors (PARPi) which increase the anti-cancer effect of immunotherapy drugs. The combined effect of both treatments may offer improved therapeutic benefits and an acceptable safety profile and if licenced, will offer an additional therapy option for metastatic squamous NSCLC patients.

PROPOSED INDICATION

Treatment of patients with metastatic squamous NSCLC.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-3475) 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.[2]

Olaparib (Lynparza) is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3). It works through the inhibition of single-stranded DNA repair leading to DNA damage, increased tumour mutational burden, enhanced PD-L1 expression and promotion of neoantigen release to make the tumour a more attractive target for immunotherapy.[3,4] Olaparib has been shown to inhibit the growth of selected tumour cell lines *in vitro* and tumour growth *in vivo*, either as a standalone treatment or in combination with established chemotherapies.[4]

Pembrolizumab in combination with olaparib is in clinical development for the treatment of metastatic squamous non-small cell lung cancer (NSCLC). In the phase III clinical trial (NCT03976362, EudraCT 2018-004721-88) participants are given 200mg pembrolizumab, administered through IV infusion, on day one of each 21-day cycle for up to 31 cycles in combination with maintenance oral olaparib 300mg twice daily. The participants continue to receive maintenance olaparib until centrally verified progressive disease, physician decision or intolerable toxicity.[1,5]

INNOVATION AND/OR ADVANTAGES

Poly(ADP-ribose) polymerase inhibitors (PARPi), including olaparib have been shown to upregulate PD-L1 (the target of pembrolizumab treatment) expression in preclinical studies. Pre-clinical studies and preliminary evidence suggest a synergistic effect when combining PARPi inhibitors such as olaparib with anti-PD-L1 immunotherapy such as pembrolizumab resulting in therapeutic benefits and an acceptable safety profile.[3,6,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The combination of pembrolizumab and olaparib does not currently have marketing authorisation in the EU/UK for any indication.

Pembrolizumab as a monotherapy is currently licenced as a monotherapy for the following indications:[2]

- advanced (unresectable or metastatic) melanoma in adults
- adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection

- first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ⩾ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
- 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 pembrolizumab.
- treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option
- treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ⩾ 10
- treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ⩾ 1
- treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ⩾ 50% TPS and progressing on or after platinum-containing chemotherapy
- first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults

The very common adverse effects (occurring in ≥10% patients) associated with pembrolizumab monotherapy are pneumonia, anaemia, infusion-related reaction, hypothyroidism, decreased appetite, dry eye headache, dyspnoea, cough, pruritus, arthralgia, muscoskeletal pain, fatigue, asthenia, oedema, pyrexia and gastrointestinal complaints.[2]

Olaparib as a monotherapy is currently licensed for the following indications:
- maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy
- maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
- treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen
- treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent

Olaparib has been associated with adverse reactions generally of mild or moderate severity (common terminology criteria for adverse events grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving Lynparza monotherapy (⩾ 10%) were nausea, fatigue, anaemia, vomiting, diarrhoea, decreased appetite, headache, dysgeusia, cough, neutropenia, dyspnoea, dizziness, dyspepsia, leukopenia and thrombocytopenia.[4]

Pembrolizumab in combination with olaparib is currently in phase III development for the treatment of non-squamous NSCLC and small cell lung cancer (SCLC). This combination is also

in phase II development for metastatic melanoma, and several other advanced solid tumour indications including: breast cancer, cervical cancer, prostate cancer, head and neck cancer, cholangiocarcinoma, and gastric cancer.[8]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: SCLC and NSCLC. NSCLC comprises approximately 80 to 85% of lung cancers in the UK and can be classified into three different types (adenocarcinoma, squamous cell, and large cell carcinoma) according to how the cancer behaves. Approximately 30% of NSCLC cases are classified as squamous cell, where the cancer develops in the flat cells that cover the surface of the airways and tends to grown near the centre of the lung.[9,10] Metastatic (stage IV) lung cancer is the most advanced form of lung cancer where the cancer has spread from the site of origin in the lung to other parts of the body - most commonly the brain, bones, liver and adrenal glands, via the blood or lymphatic system.[11]

Tobacco smoking is the primary cause of lung cancer and the biggest risk factor; approximately 90% of people who develop lung cancer are smokers or ex-smokers. Squamous cell lung cancers are more commonly associated with smoking that any other type of lung cancer.[12,13] Other risk factors include passive smoking, increasing age, exposure to high levels of radon gas, exposure to chemicals e.g. asbestos, previous cancer treatment, lowered immunity and family history of lung cancer.[13] Lung cancer does not always result in symptoms in the early stages of the disease and many of the signs and symptoms can also be caused by other medical conditions. Symptoms of advanced (metastatic) lung cancer include: a persistent cough; a change in cough that has been present for a long time; breathlessness; unexplained weight loss; ongoing chest infections; coughing up blood; a hoarse voice; difficulty swallowing; finger clubbing; swelling of the face; and loss of appetite.[14,15]

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 in 2017.[16] In England (2017), the European-age standardised incidence rates of lung cancer was 86.9 per 100,000 amongst males and 67.0 per 100,000 amongst females.[17] Lung cancer incidence rises with increasing age; 44% of all new lung cancer cases in the UK were diagnosed in those aged 75 and over, and the highest incidence rate occurs amongst those aged 85-89 (2015-2017). Incidence rates for lung cancer in the UK are predicted to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.[16]

In 2019/20 there were 111,188 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 132,969 finished consultant episodes (FCEs), resulting in 243,883 FCE bed days.[18]According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,213 diagnosed cases of stage IV lung cancer in 2017, this represents 47% of the overall number of lung cancer cases diagnosed for that year.[19] In the UK it is estimated that up to 85% of lung cancer cases are NSCLC, and 30% of these are classified as squamous cell NSCLC. Applying this figure to the number of stage IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 4,644 lung cancer cases diagnosed at stage IV are squamous cell NSCLC.

In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV was 19.3% at one year and 2.9% at five years.[20] In England and Wales (2017) there were 30,139 deaths where malignant neoplasm of trachea bronchus and lung (ICD-10 code C33-34) were recorded as the underlying cause.[21] Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The type of treatment given will depend on several factors including: the stage of the cancer; the type of cancer and the general health of the patient.[23] For patients with metastatic NSCLC, treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally include chemotherapy, targeted drugs, radiotherapy and other drugs to improve symptoms associated with lung cancer.[24]

CURRENT TREATMENT OPTIONS

NICE currently recommends pembrolizumab, with carboplatin and paclitaxel, for use within the Cancer Drugs Fund as a first-line treatment option for adults if pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if the disease progresses.[25,26]

NICE also recommends atezolizumab monotherapy (TA705) and pembrolizumab monotherapy as fist-line treatment for metastatic squamous NSCLC patients whose tumours express PD-L1 ≥50%.[27,28]

There are no therapies currently recommended by NICE as maintenance therapy for patients whose disease has not progressed following initial first-line treatment.[25]

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in combination with olaparib would be the first medical product approved in the first-line maintenance setting of adults with metastatic squamous NSCLC.[1,25]

CLINICAL TRIAL INFORMATION

Trial	**KEYLYNK-008/MK-7339**, NCT03976362, 2018-004721-88; A phase 3 study of pembrolizumab in combination with carboplatin/taxanes (paclitaxel or nab-paclitaxel) followed by pembrolizumab with or without maintenance Olaparib in the first-line treatment of metastatic squamous non-small cell lung cancer **Phase III** – recruiting **Locations:** 6 EU countries, UK, USA, Canada, and other countries **Estimated primary completion date:** May 2024
Trial design	Randomised, parallel assignment, triple masked,

Population	N=735; histology or cytologically confirmed diagnosis of squamous NSCLC; have not received prior systemic treatment for their advanced/metastatic NSCLC; have a life expectancy of at least 3 months
Intervention(s)	Induction phase: • 200mg pembrolizumab (IV) on day 1 of each 21 day cycle • Carboplatin (IV) • Taxane; either paclitaxel or nab-paclitaxel (IV) Maintenance Phase: • 200mg pembrolizumab on day 1 of each 21-day cycle (IV) • 300mg olaparib twice daily (oral administration)
Comparator(s)	Induction phase: • 200mg pembrolizumab (IV) on day 1 of each 21 day cycle • Carboplatin (IV) • Taxane; either paclitaxel or nab-paclitaxel (IV) Maintenance Phase: • 200mg pembrolizumab on day 1 of each 21-day cycle (IV) • 300mg olaparib placebo twice daily (oral administration)
Outcome(s)	Primary outcome measure: • Progression-free survival (PFS) from the date of randomisation until either documented disease progression or death due to any cause, whichever comes first. Per response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) [Time frame: Up to approximately 3 years] • Overall survival (OS) from the date of randomisation do death due to any cause [Time frame: Up to approximately 5 years] For full list of other outcomes, see trial registry
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Whilst pembrolizumab and olaparib are not licensed as a combination therapy, both are licensed as monotherapies. The NHS indicative price of pembrolizumab is £2630.00 for one 25mg/mL vial and the NHS indicative price of olaparib is £2317.50 for 56x100mg tablets; £2317.50 for 56x150mg tablets; and £3,550 for 448x50 mg capsules.[29,30]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small cell lung cancer (TA600). September 2019

- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018
- NICE technology appraisal. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer (TA705). June 2021NICE clinical guideline. Lung cancer: diagnosis and management (MG122). March 2019
- NICE quality standard. Lung cancer in adults (QS17). March 2012. Last updated December 2019.

NHS ENGLAND (POLICY/COMMISSIONING) 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

- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018, updated 2020.[31]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[32]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[33]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. *A Phase 3 Study of Pembrolizumab in Combination With Carboplatin/Taxane (Paclitaxel or Nab-paclitaxel) Followed by Pembrolizumab With or Without Maintenance Olaparib in the First-line Treatment of Metastatic Squamous Non-small Cell Lung Cancer (NSCLC). Trial ID: NCT03976362*. 2019. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03976362 [Accessed 25 August 2021].

2 Electronic Medicines Compendium (EMC). *KEYTRUDA 25 mg/mL concentrate for solution for infusion.* 2021. Available from: https://www.medicines.org.uk/emc/product/2498/smpc [Accessed 27 August 2021].

3 Vikas P, Borcherding N, Chennamadhavuni A, Garje R. Therapeutic Potential of Combining PARP Inhibitor and Immunotherapy in Solid Tumors. *Frontiers in Oncology*. 2020;10:570-. Available from: https://doi.org/10.3389/fonc.2020.00570.

4 Electronic Medicines Compendium (EMC). *Lynparza 100mg Film-Coated Tablets.* 2021. Available from: https://www.medicines.org.uk/emc/product/9204/smpc [Accessed 26 August 2021].

5 EU Clinical Trials Register. *A Phase 3 Study of Pembrolizumab in Combination with Carboplatin/Taxane (Paclitaxel or Nab-paclitaxel) Followed by Pembrolizumab with or without Maintenance Olaparib in the First-line Treatment of Metastatic Squamous Non-small Cell Lung Cancer (NSCLC). Trial ID: 2018-004721-88*. 2019. Status: Recruitng. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-004721-88/GB [Accessed 26 August 2021].

6 Gray JE, Owonikoko TK, Kato T, Cardona Zorrilla AF, Wagman J, Chen X, et al. Randomized phase III study of first-line pembrolizumab plus pemetrexed/platinum followed by pembrolizumab and maintenance olaparib versus pemetrexed in patients with metastatic nonsquamous non-small cell lung cancer (NSCLC): KEYLYNK-006. *Journal of Clinical Oncology*. 2020 2020/05/20;38(15_suppl):TPS9632-TPS. Available from: https://doi.org/10.1200/JCO.2020.38.15_suppl.TPS9632.

7 American Cancer Society. *Immune Checkpoint Inhibitors and Their Side Effects.* 2021. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html [Accessed 25 August 2021].

8 Clinicaltrials.gov. *Search for pembrolizumab in combination with olaparib clinical studies: phase II and III.* 2021. Available from: https://clinicaltrials.gov/ct2/results?intr=Pembrolizumab+in+combination+with+olaparib&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 27 August 2021].

9 Cancer Research UK. *Types of lung cancer.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 27 August 2021].

10 McKeage MJ, Jameson MB, Investigators ASSG. Comparative outcomes of squamous and non-squamous non-small cell lung cancer (NSCLC) patients in phase II studies of ASA404 (DMXAA) - retrospective analysis of pooled data. *Journal of Thoracic Disease*. 2010;2(4):199-204. Available from: https://doi.org/10.3978/j.issn.2072-1439.2010.02.04.1.

11 Cancer Treatment Centers of America. *What is stage 4 lung cancer?* 2021. Available from: https://www.cancercenter.com/cancer-types/lung-cancer/stages/stage-iv-lung-cancer [Accessed 27 August 2021].

12 Lungevity. *Types of Lung Cancer: Squamous Cell Lung Cancer.* 2021. Available from: https://www.lungevity.org/for-patients-caregivers/lung-cancer-101/types-of-lung-cancer/squamous-cell-lung-cancer [Accessed 27 August 2021].

13 Macmillan Cancer Support. *Causes and risk factors of lung cancer.* 2018. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/causes-and-risk-factors-of-lung-cancer [Accessed 27 August 2021].

14 Cancer Research UK. *Lung Cancer Symptoms.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/symptoms [Accessed 27 August 2021].

15 Cancer Research UK. *Symptoms of advanced lung cancer.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/advanced/symptoms [Accessed 27 August 2021].

16 Cancer Research UK. *Lung cancer incidence.* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 27 August 2021].

17 Cancer Research UK. *Lung cancer incidence by sex and UK country.* 2020. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Zero [Accessed 27 August 2021].

18 NHS Digital. *Hospital Admitted Patient Care Activity 2019-20*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Downloaded 17 September 2020].

19 National Cancer Registration and Analysis Service (NCRAS). *Stage breakdown by CCG 2017.* 2017. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 27 August 2021].

20 Office for National Statistics (ONS). *Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Downloaded 12 August 2019].

21 Office for National Statistics (ONS). *Deaths registered in England and Wales – 21st century mortality*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Downloaded 01 July 2020].

22 Cancer Research UK. *Lung cancer statistics: mortality.* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-One [Accessed 27 August 2021].

23 Macmillan Cancer Support. *Treatment for lung cancer.* 2018. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/treatment-for-lung-cancer [Accessed 27 August 2021].
24 Cancer Research UK. *Treatment for non small cell lung cancer (NSCLC).* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/non-small-cell-lung-cancer [Accessed 27 August 2021].
25 National Institute for Health and Care Excellence (NICE). *Lung cancer – everything NICE says in an interactive flowchart.* 2021. Available from: https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/advanced-squamous-non-small-cell-lung-cancer-systemic-anti-cancer-therapy.xml&content=view-node%3Anodes-first-line-treatment-under-50 [Accessed 27 August 2021].
26 National Institute for Health and Care Excellence (NICE). *Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer* (*TA600).* Last Update Date: Available from: https://www.nice.org.uk/guidance/TA600/chapter/1-Recommendations [Accessed 27 August 2021].
27 National Institute for Health and Care Excellence (NICE). *Atezolizumab monotherapy for untreated advanced nonsmall-cell lung cancer* (*TA705).* Last Update Date: June 2021. Available from: https://www.nice.org.uk/guidance/ta705/resources/atezolizumab-monotherapy-for-untreated-advanced-nonsmallcell-lung-cancer-pdf-82611074786245 [Accessed 27 September 2021].
28 National Institute for Health and Care Excellence (NICE). *Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer* (*TA531).* Last Update Date: July 2018. Available from: https://www.nice.org.uk/guidance/ta531/resources/pembrolizumab-for-untreated-pdl1positive-metastatic-nonsmallcell-lung-cancer-pdf-82606895901637 [Accessed 27 September 2021].
29 National Institute for Health and Care Excellence (NICE). *Olaparib.* 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/olaparib.html [Accessed 22 September 2021].
30 National Institute for Health and Care Excellence (NICE). *Pembrolizumab.* 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html [Accessed 22 September 2021].
31 Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2016 Sep;27(suppl 5):v1-v27. Available from: https://doi.org/10.1093/annonc/mdw326.
32 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2017 01 Apr. 2017;15(4):504-35. Available from: https://doi.org/10.6004/jnccn.2017.0050.
33 Scottish Intercollegiate Guidelines Network. *Management of lung cancer (SIGN 137). .* 2014. Available from: https://www.sign.ac.uk/media/1075/sign137.pdf [Accessed 27 August 2021].

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