Health Technology Briefing
December 2021

Tislelizumab with chemotherapy for previously untreated advanced squamous or non-squamous non-small-cell lung cancer

Company/Developer	Novartis Pharmaceuticals UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29666	NICE ID: 10708	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Tislelizumab is in clinical development to treat patients with advanced non-squamous or squamous non-small cell lung cancer (NSCLC) who have not received previous treatment. NSCLC makes up the majority of lung cancers in the UK. In locally advanced NSCLC, the cancer has spread beyond the lung which was initially affected. Symptoms of lung cancer include a persistent cough, shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue. Most patients with NSCLC are diagnosed at the advanced stage where curative treatment with surgery is unsuitable.

Tislelizumab is a drug, administered intravenously, that has been designed to recognise and block a target called PD-1 found on certain cells of the immune system. Some cancers make a protein that attaches to PD-1 and switches off the immune cells' ability to attack the cancer. By blocking PD-1, tislelizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. If licenced, tislelizumab will provide an additional first-line treatment option for adult patients with either non squamous or squamous advanced NSCLC.

Proposed Indication

For the first-line treatment of adults with non-squamous or squamous non-small cell lung cancer.[1,2]

Technology

Description

Tislelizumab (BGB-A317) is a humanised IgG4 anti–PD-1 (programmed death-1) monoclonal antibody specifically designed to minimise binding to FcγR on macrophages. Binding to FcγR on macrophages compromises the anti-tumour activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells. PD-1 is a cell surface receptor that plays an important role in allowing tumour cells to evade the immune system. Many types of cancer cells have hijacked the PD-L1 expression system that normally exists in healthy cells. By expressing PD-L1, cancer cells can interact with PD-1 expressing cytotoxic T-lymphocytes (CTLs) and protect themselves from being killed by these CTLs. Tislelizumab can potentially restore the ability of CTLs to kill cancer cells by binding to PD-1, without activating the receptor, thereby preventing PD-L1 from engaging PD-1.[3]

Tislelizumab in combination with pemetrexed and platinum chemotherapy is currently in phase III clinical development for the first-line treatment of adult patients with advanced non-squamous NSCLC.[1] Tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel is also currently in phase III clinical development for the first-line treatment of adult patients with advanced squamous NSCLC.[2] In both clinical trials (NCT03663205; NCT03594747), 200 mg of tislelizumab is administered intravenously every 3 weeks for 4 to 6 cycles in combination with intravenously administered chemotherapy.[1,2]

Key Innovation

Tislelizumab, as an antagonist to PD-L1/PD-L2 mediated cell signalling, leads to increased cytokine production and restoration of T-cell activation, resulting in immune-mediated tumour cell death. Tislelizumab has a higher affinity to PD-1 than other anti-PD-1 antibodies, potentially due to its differential PD-1 binding orientation. In early clinical research, tislelizumab has demonstrated promising efficacy results, a manageable safety profile and longer duration of response.[4]

Regulatory & Development Status

Tislelizumab in combination with chemotherapy does not currently have Marketing Authorisation in the EU/UK for any indication.

Tislelizumab is in phase II and III clinical development for the treatment of various types of cancers, some of which include:[5]

- Hepatocellular carcinoma
- Oesophageal squamous cell carcinoma
- Muscle-invasive bladder cancer
- Classical Hodgkin lymphoma
- Diffuse large B-cell lymphoma

Patient Group

Disease Area and Clinical Need

NSCLC comprises approximately 80 to 85% of lung cancers in the UK. There are three common types of NSCLC: adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways); squamous cell cancer (develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung) and large cell carcinoma (cancer cells which appear large and round under the microscope).[6] Advanced cancer occurs when the cancer is not localised to one site and has developed to nearby tissue, lymph nodes, or distant parts of the body.[7] Tobacco smoking remains the main cause of lung cancer.[8] Several other factors have been described as lung cancer risk factors including exposure to radiation, certain chemicals (e.g., asbestos, silica and diesel engine exhaust fumes) and previous lung disease (e.g., tuberculosis and chronic obstructive pulmonary disease). Other factors include family history of lung cancer and certain genetic mutations. [9]

Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[10]

There are around 48,000 new lung cancer cases in the UK yearly.[11] In the UK, it is estimated that up to 85% of lung cancer cases are NSCLC, which would mean around 40,800 of the annual new lung cancer cases are NSCLC.[6] Lung cancer is the most common cause of cancer death in the UK. There are around 35,100 lung cancer deaths in the UK every year, and the mortality rates are highest in people aged 85 to 89 (2016-2018).[11] In 2020/21 there were 86,043 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days.[12]

Recommended Treatment Options

Treatment for NSCLC usually depends on the stage, grade and general health of the patient. For advanced NSCLC, treatment aims to control the cancer for as long as possible and help with symptoms. Treatment options include chemotherapy, targeted drugs, immunotherapy, radiotherapy and symptom control treatment.[13]

NICE recommends the following first-line treatment options for squamous NSCLC:[14-16]

- Atezolizumab as a monotherapy for tumours with PDL1 expression on at least 50% or 10% of tumour invading immune cells.
- Pembrolizumab, or pembrolizumab with carboplatin and paclitaxel for tumours with PDL1 at 50% or above
- Nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy except in adults whose tumours have no ALK or EGFR mutations
- Gemcitabine or vinorelbine and cisplatin or carboplatin, for tumours with PDL1 below 50%

For first-line treatment for advanced non-squamous NSCLC, NICE recommends:[14,17,18]

- Atezolizumab as a monotherapy for tumours with PDL1 expression on at least 50% or 10% of tumour invading immune cells.
- Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel for tumours with PDL1 score between 0% and 49%
- Pembrolizumab or pembrolizumab with pemetrexed and platinum chemotherapy, for tumours with PDL1 at 50% or above
- Pembrolizumab with pemetrexed and platinum chemotherapy, or pemetrexed with cisplatin, for tumours with PDL1 below 50%
- Nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy except in adults whose tumours have no ALK or EGFR mutations

Clinical Trial Information	
Trial	NCT03663205; Phase III Open Label First Line Therapy Study of Tislelizumab With Chemotherapy Versus Chemotherapy in Untreated Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) **Phase III** – Active, not recruiting **Location(s)**: China **Primary completion date:** December 2021
Trial Design	Randomised, open label, parallel assignment
Population	N= 334; Subjects aged 18-75 years with untreated advanced non-squamous NSCLC
Intervention(s)	Tislelizumab 200mg (IV) + cisplatin 75mg (IV) or carboplatin AUC 5 (IV) + pemetrexed 500mg (IV) every 3 weeks for 4 to 6 cycles
Comparator(s)	Cisplatin or carboplatin and pemetrexed
Outcome(s)	Primary outcome measure: Progression Free Survival (PFS) assessed by Independent Review Committee (IRC) [Time Frame: approximately 2 years] See trial record for full list of all outcomes
Results (efficacy)	With a median study follow-up of 9.8 months, progression-free survival (PFS) was significantly longer with tislelizumab plus chemotherapy compared with chemotherapy alone (median PFS: 9.7 versus 7.6 months; hazard ratio = 0.645 [95% confidence interval: 0.462–0.902], p = 0.0044). In addition, response rates were higher and response duration was longer with combination therapy versus chemotherapy alone.[19]

Results (safety)	Hematologic adverse events (AEs) were common in both treatment arms; the most reported AEs were grades 1 to 2 in severity. The most common grade greater than or equal to 3 AEs were associated with chemotherapy and included neutropenia (44.6% [A]; 35.5% [B]) and leukopenia (21.6% [A]; 14.5% [B]).[19]

Trial	NCT03594747; A Phase III, Multicentre, Randomised Open-Label Study to Compare the Efficacy and Safety of Tislelizumab (BGB A317, Anti-PD1 Antibody) Combined With Paclitaxel Plus Carboplatin or Nab Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Carboplatin Alone as First-Line Treatment for Untreated Advanced Squamous Non Small Cell Lung Cancer **Phase III** – Active, not recruiting **Location(s)**: China **Primary completion date:** September 2020
Trial Design	Randomised, open label, parallel assignment, multicentre
Population	N= 360; Subjects aged 18-75 years with untreated advanced squamous NSCLC
Intervention(s)	Tislelizumab 200mg (IV) + carboplatin AUC 5 (IV) + paclitaxel 175mg or nab-paclitaxel 100mg (IV) every 3 weeks for 4 to 6 cycles
Comparator(s)	Carboplatin AUC 5 + paclitaxel 175mg (IV)
Outcome(s)	Primary outcome measure: Progression Free Survival (PFS) [Time Frame: 2 years] See trial record for full list of all outcomes
Results (efficacy)	After a median study follow-up of 8.6 months (95% CI, 8.1-9.0 months), independent review committee (IRC)-assessed PFS was significantly improved with tislelizumab plus chemotherapy (arm A, 7.6 months; arm B, 7.6 months) vs chemotherapy alone (arm C, 5.5 months; hazard ratios were 0.524 (95% CI, 0.370-0.742; P < .001 [A vs C]) and 0.478 (95% CI, 0.336-0.679; P < .001 [B vs C]). Higher IRC-assessed objective response rate (ORR) and longer IRC-assessed duration of response were observed in arms A (72.5%; 8.2 months) and B (74.8%; 8.6 months) vs C (49.6%; 4.2 months). No association was observed between PD-L1 expression and IRC-assessed PFS or ORR.[20]
Results (safety)	Discontinuation of any treatment because of adverse events (AEs) was reported in 15 (12.5%; arm A), 35 (29.7%; arm B), and 18 (15.4%; arm C) patients. In each arm, the most common grade of 3 or greater AE was decreased neutrophil levels,

	which aligned with known chemotherapy toxic effects. Six treatment-related AEs leading to death occurred; however, no deaths were solely attributed to tislelizumab.[20]

Estimated Cost

The cost of tislelizumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Sugemalimab with chemotherapy for untreated metastatic non-small-cell lung cancer (ID4001). Expected date of issue to be confirmed.
- NICE technology appraisal. Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer (TA724). September 2021.
- NICE technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA683). March 2021.
- NICE technology appraisal. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA600). September 2019.
- NICE technology appraisal. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy (TA655). October 2020.
- NICE technology appraisal. Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer (TA724). September 2019.
- NICE technology appraisal. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). June 2019.
- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE technology appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009.
- NICE technology appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). 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.
- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). B01/P/a. April 2013.

Other Guidance

- European Society for Medical Oncology. Metastatic Non-Small-Cell Lung Cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.[8]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[21]
- European Society for Medical Oncology. ESMO Consensus Conference on Lung Cancer: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[22]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[23]

Additional Information

References

1 Clinical Trials.gov. *A Study Evaluating the Efficacy and Safety of Tislelizumab Versus Chemotherapy in Advanced Non-Squamous NSCLC. Trial ID: NCT03663205*. 2018. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03663205 [Accessed 04 November 2021].

2 Clinical Trials.gov. *A Study Tislelizumab in Combination With Chemotherapy Versus Chemotherapy in Advanced Lung Cancer. Trial ID: NCT03594747*. 2018. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03594747 [Accessed 04 November 2021].

3 BeiGene. *Tislelizumab.* Available from: https://www.beigene.com/en-eu/science-and-product-portfolio/pipeline/tislelizumab [Accessed 4 November 2021].

4 Liu S-Y, Wu Y-L. Tislelizumab: an investigational anti-PD-1 antibody for the treatment of advanced non-small cell lung cancer (NSCLC). *Expert Opinion on Investigational Drugs*. 2020;29(12):1355-64. Available from: https://www.tandfonline.com/doi/full/10.1080/13543784.2020.1833857.

5 Clinical Trials.gov. *Tislelizumab | Phase 2, 3.* Available from: https://clinicaltrials.gov/ct2/results?cond=tislelizumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 8 November 2021].

6 Cancer Research UK. *Types of lung cancer.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 8 November 2021].

7 National Cancer Institute. *Advanced cancer.* Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/advanced-cancer [Accessed 9 November 2021].

8 Planchard D, Popat S, Kerr K, Novello S, Smit E, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2018;29:iv192-iv237. Available from: https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer.

9 Cancer Research UK. *Risks and causes.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes [Accessed 9 Novemer 2021].

10 National Institute for Health and Care Excellence. *Advanced squamous non-small-cell lung cancer: systemic anti-cancer therapy* 2020. Available from: https://pathways.nice.org.uk/pathways/lung-cancer/advanced-squamous-non-small-cell-lung-cancer-systemic-anti-cancer-therapy.pdf [Accessed 9 November 2021].

11 Cancer Research UK. *Lung cancer statistics.* 2017. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 9 November 2021].

12 NHS Digital. *Hospital Admitted Patient Care Activity.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity [Accessed 9 November 2021].

13 Cancer Research UK. *Treatment for non small cell lung cancer (NSCLC).* Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/non-small-cell-lung-cancer [Accessed 12 November 2021].

14 National institute for Health and Care Excellence. *Lung cancer: diagnosis and management* 2019. Available from: https://www.nice.org.uk/guidance/ng122/resources/lung-cancer-diagnosis-and-management-pdf-66141655525573 [Accessed 9 November 2021].

15 National Institute for Health and Care Excellence Guidance. *Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer.* 2019. Available from: https://www.nice.org.uk/guidance/ta600/chapter/1-Recommendations [Accessed 9 December 2021].

16 National Institute for Health and Care Excellence Pathways. *Advanced squamous non-small-cell lung cancer: systemic anti-cancer therapy.* Available from: https://pathways.nice.org.uk/pathways/lung-cancer/advanced-non-squamous-stages-iiib-and-iv-non-small-cell-lung-cancer-pd-l1-50-or-over-no-gene-mutation-fusion-protein-or-biomarker#content=view-node%3Anodes-first-line-treatment-under-50&path=view%3A/pathways/lung-cancer/advanced-squamous-non-small-cell-lung-cancer-systemic-anti-cancer-therapy.xml [Accessed 9 December 2021].

17 National Institute for Health and Care Excellence Pathways. *Advanced non-squamous (stages IIIB and IV) non-small-cell lung cancer: PD-L1 50% or over (no gene mutation, fusion protein or biomarker).* Available from: https://pathways.nice.org.uk/pathways/lung-cancer/advanced-non-squamous-stages-iiib-and-iv-non-small-cell-lung-cancer-pd-l1-50-or-over-no-gene-mutation-fusion-protein-or-biomarker#content=view-node:nodes-first-line-treatment [Accessed 9 December 2021].

18 National Institute for Health and Care Excellence Guidance. *Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer.* 2019. Available from: https://www.nice.org.uk/guidance/ta584/chapter/1-Recommendations [Accessed 9 December 2021].

19 Lu S, Wang J, Yu Y, Yu X, Hu Y, Ai X, et al. Tislelizumab Plus Chemotherapy as First-line Treatment for Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer (RATIONALE 304): A Randomized Phase 3 Trial. *Journal of Thoracic Oncology*. 2021. Available from: https://www.jto.org/article/S1556-0864(21)02176-6/fulltext.

20 Wang J, Lu S, Yu X, Hu Y, Sun Y, Wang Z, et al. Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non–Small-Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. *JAMA oncology*. 2021;7(5):709-17. Available from: https://jamanetwork.com/journals/jamaoncology/fullarticle/2777901.

21 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*. 2017;15(4):504-35. Available from: https://jnccn.org/view/journals/jnccn/15/4/article-p504.xml.

22 Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of

treatment in advanced disease. *Annals of Oncology*. 2014;25(8):1475-84. Available from: https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer/consensus-guidelines-non-small-cell-lung-cancer-first-line-second-and-further-lines-in-advanced-disease.

23 Scottish Intercollegiate Guidelines Network. *Management of lung cancer.* 2014. Available from: https://www.sign.ac.uk/our-guidelines/management-of-lung-cancer/ [Accessed 9 November 2021].

NB: 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.