Health Technology Briefing
July 2023

Niraparib with pembrolizumab maintenance therapy for metastatic stage III or IV non-small cell lung cancer

Company/Developer	GlaxoSmithKline

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30216	NICE ID: Not available	UKPS ID: 667617

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Niraparib with pembrolizumab is in clinical development for the maintenance therapy of patients with later stages of non-small cell lung cancer (NSCLC) after first-line platinum-based chemotherapy with pembrolizumab. Lung cancer is the third most common cancer in the UK and about 47,000 people are diagnosed with it each year. When cancer starts in the lungs, it is called primary lung cancer and when the cancer cells spread from the lungs to other organs, it is referred to as metastatic lung cancer. There are different kinds of lung cancer including NSCLC which is the most common type; it grows slowly and has often spread to other parts of the body by the time it is diagnosed. Some symptoms include a cough, repeated chest infections, breathlessness, unexplained pain, weight loss or tiredness.

The active substance in Zejula, niraparib, blocks the action of enzymes called PARP-1 and PARP-2, which help to repair damaged DNA in cells when the cells divide to make new cells. By blocking PARP enzymes, the damaged DNA in cancer cells cannot be repaired, and, as a result, the cancer cells die. Niraparib is administered orally, and pembrolizumab is administered into the vein (intravenously). Previous research has shown the combination of both might be safe and effective. If licensed niraparib with pembrolizumab will offer an additional maintenance therapy option for patients with metastatic NSCLC after first-line platinum-based chemotherapy with pembrolizumab.

Proposed Indication

Maintenance therapy for stage IIIB/IIIC or IV non-small cell lung cancer (NSCLC) after first-line platinum based chemotherapy with pembrolizumab.[1]

Technology

Description

Niraparib (Zejula) is targeted therapy drug that inhibits poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1, and PARP-2, which play a role in DNA repair.[2,3] By blocking PARP enzymes, the damaged DNA in cancer cells cannot be repaired, and, as a result, the cancer cells die.[4] Niraparib also increases formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death.[2]

Niraparib with pembrolizumab is currently in clinical development for the maintenance treatment of patients with stage IIIB/IIIC or IV NSCLC after first-line platinum based chemotherapy with pembrolizumab. In the phase III clinical trial, ZEAL-1L (NCT04475939), niraparib will be administered as an oral tablet once daily. Pembrolizumab will be administered as an infusion every 3 weeks (on day 1 of each treatment cycle).[5]

Key Innovation

Poly (ADP-ribose) polymerase (PARP) inhibitors may synergize with programmed cell death receptor-1 (PD-1) inhibitors to enhance adaptive and innate antitumor immune responses. The phase II clinical trial JASPER (NCT04475939) found that more than 50% of patients with advanced NSCLC who had high levels of the tumour marker (programmed cell death ligand tumour proportion score (PD-L1 TPS) ≥ 50%), and one-fifth of patients with lower levels of the tumour marker (PD-L1 TPS 1%-49%), responded to the combination. The primary end point was investigator-assessed objective response rate (ORR). Secondary end points included duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety, and pharmacokinetics. Overall, niraparib plus pembrolizumab showed clinical activity in patients with advanced and/or metastatic NSCLC. In addition, the types of side effects from combining both were similar to side effects from either drug alone.[6]

If licensed, niraparib in combination with pembrolizumab will provide an additional chemotherapy-free maintenance therapy option for patients with stage III or IV NSCLC.

Regulatory & Development Status

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

In the EU/UK, niraparib as a monotherapy has a Marketing Authorisation for the following:[2]

- Maintenance treatment of adult patients with advanced epithelial International Federation of Gynaecology and Obstetrics (FIGO) Stages III and IV high-grade 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 serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Niraparib in combination with pembrolizumab is in clinical development for breast cancer and ovarian cancer.[7]

Patient Group

Disease Area and Clinical Need

Lung cancer starts in the windpipe (trachea), the main airway (bronchus) or the lung tissue. Cancer that starts in the lung is called primary lung cancer. Metastatic lung cancer means the cancer has spread from where it started in the lung to other parts of the body.[8] Lung cancer is divided into two main groups: small cell lung cancer (SCLC) and NSCLC. NSCLC is the most common, accounting for 80-85% of lung cancer cases.[9] In Stage III, the cancer is larger and may have spread to surrounding tissues while in stage IV, the cancer has spread to other body organs.[10] Symptoms of lung cancer include: chronic cough, a chest infection that does not get better, repeated chest infections, breathlessness or wheezy breathing, coughing up blood, chest or shoulder pain, persistent hoarse voice, loss of appetite, weight loss and prolonged tiredness.[11] Smoking cigarettes is the single biggest risk factor for lung cancer, it is responsible for more than 7 out of 10 cases.[12] Other risk factors include exposure to radon (a natural radioactive gas that comes from tiny amounts of uranium present in all rocks and soils), occupational exposure to radiation and chemicals (e.g., arsenic, asbestos, and silica), old age, previous cancer treatment, lowered immunity and family history of lung cancer.[13]

In England (2021-22), there were 119,396 finished consultant episodes (FCE) and 99,551 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34), resulting in 75,969 day cases and 206,640 FCE bed days.[14] In England (2017), there were 38,888 newly diagnosed cases of malignant neoplasm of bronchus and lung (ICD-10 code C34) and 28,170 registered deaths.[15] 57,564 of the newly diagnosed cases were stage III, and 18,213 were stage IV.[16] In England, for patients diagnosed with stage III lung cancer between 2013 and 2017, the age-standardised 1-year and 5-year survival rate was 48.7% and 12.6% respectively. For patients diagnosed with stage IV lung cancer, the age-standardised 1-year and 5-year survival rate was 19.3% and 2.9% respectively.[17]

Recommended Treatment Options

Options for maintenance therapy of NSCLC include maintaining response to initial therapy by continuing the initial combination chemotherapy regimen, continuing only single agent chemotherapy, or by introducing a new agent.[18] NICE recommends the following for maintenance therapy of NSCLC after chemotherapy:[19]

- Pemetrexed
- Durvalumab
- Pembrolizumab

Clinical Trial Information

Trial	**ZEAL-1L,** NCT04475939; A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicentre Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants Whose Disease Has Remained Stable or Responded to First-Line Platinum Based Chemotherapy With Pembrolizumab for Stage IIIB/IIIC or IV Non-Small Cell Lung Cancer

	Phase III: Active, not recruiting **Locations**: 13 EU countries, UK, USA, and other countries **Primary completion date**: December 2024
Trial Design	Randomised, parallel assignment, triple masking.
Population	N=666 (actual); Patients with Stage IIIB/IIIC or IV NSCLC; aged 18 years and older whose disease has remained stable or responded to first-line platinum-based chemotherapy with pembrolizumab.
Intervention(s)	• Niraparib • Pembrolizumab
Comparator(s)	• Pembrolizumab • Matched placebo
Outcome(s)	Primary outcomes: • Progression-free survival (PFS) assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 in overall population (time frame: up to approximately 3 years). • Overall survival (OS) in overall population (time frame: up to approximately 5 years). See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative cost of 56 capsules of niraparib 100mg is £4,500.[20]
The NHS indicative cost of one vial of pembrolizumab 25mg/ml is £2,630.[21]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Tislelizumab for treating advanced non-small-cell lung cancer after platinum-based chemotherapy [ID6161] (GID-TA11099) Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with olaparib for maintenance treatment of advanced squamous non-small-cell lung cancer [ID4006] (GID-TA10906). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with lenvatinib for treating EGFR, ALK or ROS1-negative metastatic non-small-cell lung cancer after a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy [ID5109] (GID-TA11024). Expected date of issue to be confirmed.
- NICE technology appraisal. Mobocertinib for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy (TA855). January 2023.

- NICE technology appraisal. Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy (TA850). December 2022.
- NICE technology appraisal. Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (TA798). June 2022.
- 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. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy (TA655). October 2020.
- NICE technology appraisal. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (TA190). August 2017.
- NICE technology appraisal. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428). January 2017.
- NICE technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). August 2016.
- NICE technology appraisal. Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer (TA227). June 2011.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

NHS England (Policy/Commissioning) Guidance

NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- European Society of Medical Oncology (ESMO). ESMO Guideline. Early and locally advanced non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow up. 2020.[22]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017,
- NCCN Clinical Practice Guidelines in Oncology. 2017.[23]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137).
- 2014.[24]

Additional Information

References

1 Clinicaltrials.gov. *Placebo-controlled Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants With Advanced/Metastatic Non-small Cell Lung Cancer (ZEAL-1L). Trial ID: NCT04475939*. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04475939 [Accessed 22 May 2023].

2 Electronic Medicines Compendium (eMC). *Zejula 100 mg hard capsules*. 2023. Available from: https://www.medicines.org.uk/emc/product/8828/smpc [Accessed 22 May 2023].

3 Macmillan Cancer Support. *Niraparib (Zejula®)*. 2023. Available from: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/niraparib [Accessed 20 June 2023].

4 European Medicines Agency. *Zejula*. 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zejula [Accessed 22 May 2023].
5 National Health Service (NHS). *213400 Niraparib in Stage IIIB/IV NSCLC*. 2020. Available from: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/213400-niraparib-in-stage-iiibiv-nsclc/ [Accessed 22 May 2023].
6 Ramalingam SS, Thara E, Awad MM, Dowlati A, Haque B, Stinchcombe TE, et al. JASPER: Phase 2 trial of first-line niraparib plus pembrolizumab in patients with advanced non-small cell lung cancer. *Cancer*. 2022;128(1):65-74. Available from: https://doi.org/10.1002/cncr.33885.
7 Clinicaltrials.gov. *Niraparib in Combination With Pembrolizumab in Patients With Triple-negative Breast Cancer or Ovarian Cancer (TOPACIO)*. 2020. Status: Completed. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02657889 [Accessed 23 May 2023].
8 Cancer Reasearch UK. *Lung cancer*. 2022. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer [Accessed 23 May 2023].
9 City of Hope. *Lung cancer types*. 2022. Available from: https://www.cancercenter.com/cancer-types/lung-cancer/types#:~:text=The%20two%20key%20types%20of,to%2015%20percent%20of%20cases. [Accessed 5 June 2023].
10 Macmillan Cancer Support. *Staging of lung cancer*. 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/staging-of-lung-cancer [Accessed 5 June 2023].
11 Macmillan Cancer Support. *Signs and symptoms of lung cancer*. 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/signs-and-symptoms-of-lung-cancer [Accessed 23 May 2023].
12 National Health Service (NHS). *Causes-Lung cancer*. 2022. Available from: https://www.nhs.uk/conditions/lung-cancer/causes/ [Accessed 23 May 2023].
13 Macmillan Cancer Support. *Causes and risk factors of lung cancer*. 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/causes-and-risk-factors-of-lung-cancer [Accessed 23 May 2023].
14 National Health Service(NHS) Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 23 May 2023].
15 Office for National Statistics. *Dataset Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 23 May 2023].
16 National Cancer Registration and Analysis Service. *Survival by stage*. 2017. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 23 May 2023].
17 Office for National Statistics. *Cancer survival in England - adults diagnosed*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 23 May 2023].
18 Coate LE, Shepherd FA. Maintenance Therapy in Advanced Non-small Cell Lung Cancer. *Journal of thoracic oncology*. 2010;5(5):723-34. Available from: https://doi.org/https://doi.org/10.1097/JTO.0b013e3181d86e8b.
19 National Institute for Health and Care Excellence(NICE). *The maintenance treatment of non-small-cell lung cancer*. 2023. Available from:

https://www.nice.org.uk/search?q=+the+maintenance+treatment+of+non-small-cell+lung+cancer [Accessed 24 May 2023].
20 British National Formulary. *Niraparib medicinal forms*. 2023. Available from: https://bnf.nice.org.uk/drugs/niraparib/medicinal-forms/ [Accessed 24 May 2023].
21 British National Formulary. *Pembrolizumab Medicinal forms*. 2023. Available from: https://bnf.nice.org.uk/drugs/pembrolizumab/medicinal-forms/ [Accessed 24 May 2023].
22 Postmus P, Kerr K, Oudkerk M, Escriu C, Peters S. Early and locally advanced non-small-cell lung cancer (NSCLC):ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *ESMO*. 2017;28:IV1-IV21. https://www.annalsofoncology.org/article/S0923-7534(19)42150-9/fulltext.
23 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;15(4):504-35. Available from: https://doi.org/10.6004/jnccn.2017.0050.
24 Healthcare Improve Scotland. *Management of Lung Cancer*. 2014. Available from: https://www.sign.ac.uk/media/1075/sign137.pdf [Accessed 24 May 2023].

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