NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
March 2023

Neoadjuvant nivolumab with gemcitabine and cisplatin followed by adjuvant nivolumab for previously-untreated muscle-invasive bladder cancer

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26508	NICE TSID: 10542	UKPS ID: 647618

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Neoadjuvant (before surgery) nivolumab in addition to gemcitabine and cisplatin followed by adjuvant (additional) nivolumab is in clinical development for muscle-invasive bladder cancer (MIBC). MIBC is when the cancer has spread beyond the lining of the bladder and into the muscle layer. The most well-known risk factor for MIBC is smoking, and the most common symptom is blood in the urine. A common treatment option for patients with MIBC treated with curative intent is a radical cystectomy, a surgery where parts or all of the bladder is removed. Therefore, other treatment approaches with long disease control additional to surgery are needed.

Nivolumab is a type of protein (a monoclonal antibody) designed to recognise and bind to a protein called PD-1, which is present on the surface of many cancer cells and reduces the immune system's ability to attack cancer cells. Nivolumab therefore increases the body's ability to kill cancer cells and slow down progression of the disease. A recent study into nivolumab has shown encouraging results for disease-free survival duration in MIBC. Therefore, if licensed, nivolumab (in addition to gemcitabine and cisplatin) would offer an additional treatment option for patients with previously-untreated MIBC.

Proposed Indication

First line treatment for adult participants with previously untreated muscle-invasive bladder cancer.

Technology

Description

Nivolumab (Opdivo, BMS-936558) is a human immunoglobulin G4 (IgG4) monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. Engagement of PD-1 with the ligands PD-L1 and PD-L2 results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[1]

Nivolumab with gemcitabine and cisplatin is in phase III clinical development (ENERGIZE; NCT03661320) for the treatment of adults with previously untreated MIBC.[2]

Key Innovation

The recommended standard of care for MIBC is radical cystectomy (RC) with bilateral pelvic lymph node dissection, preceded by the administration of neoadjuvant chemotherapy in patients who are eligible to receive cisplatin. However, neoadjuvant chemotherapy has failed to become a widely used treatment, as it is administered in only 20% of eligible patients.[3]

Nivolumab binds to PD-L1, a receptor which switches off immune cells that would otherwise attack the cancer cells[4]. By blocking its effects, nivolumab increases the ability of the immune system to attack the cancer cells and thereby slow down the progression of the disease. In a recent trial (NCT02632409) involving patients with high-risk MIBC who had undergone radical surgery, disease-free survival was longer with adjuvant nivolumab than with placebo in the intention-to-treat population and among patients with a PD-L1 expression level of 1% or more.[5] Therefore, if licensed, nivolumab with gemcitabine and cisplatin would offer an additional therapy option for people with previously untreated MIBC.

Regulatory & Development Status

Nivolumab monotherapy currently has Marketing Authorisation in the EU/UK for the following indications:[1]

- melanoma
- non-small cell lung cancer
- renal cell carcinoma
- classical Hodgkin lymphoma
- squamous cell cancer of the head and neck
- urothelial carcinoma
- oesophageal squamous cell carcinoma
- oesophageal or gastro-oesophageal junction cancer

Nivolumab is also licensed in combination with other technologies. For example, nivolumab, in combination with ipilimumab, is indicated for:

- malignant pleural mesothelioma

- renal cell carcinoma
- melanoma
- colorectal cancer

Nivolumab, in combination with fluoropyrimidine- and platinum-based combination chemotherapy, is indicated for gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.[1]

Nivolumab with gemcitabine and cisplatin is also in phase II/III clinical development for several indications, some of which are:[6]

- non-squamous non-small cell lung carcinoma
- metastatic urothelial cancer
- untreated metastatic pancreatic ductal adenocarcinoma
- nasopharyngeal carcinoma

Patient Group

Disease Area and Clinical Need

Bladder cancer is when a growth of abnormal tissue, known as a tumour, develops in the bladder lining. When the cancerous cells spread beyond the lining into the surrounding bladder muscle, it is known as MIBC. MIBC is caused by changes to the cells of the bladder. It is often linked with exposure to certain chemicals, but the cause is not always known.[7] There are certain factors that can increase the risk for bladder cancer. These include smoking, exposure to chemicals such as arylamines and polycyclic aromatic hydrocarbons, exposure to water disinfection chemicals such as chlorine and trihalomethanes, treatment for some other cancers, other medical conditions such as diabetes and spinal cord injury, infection and chronic irritation of the bladder, diet and alcohol intake, previous bladder cancer and family history.[8] The most common symptom of bladder cancer is blood in the urine that is usually painless. Less common symptoms include a need to urinate on a more frequent basis, sudden urges to urinate and a burning sensation when passing urine. Other symptoms include pelvic pain, bone pain, unintentional weight loss, and swelling of the legs.[9]

Bladder cancer is the 11th most common cancer in the UK, accounting for 3% of all new cancer cases (2016-18).[10] Approximately 25% of bladder cancers are MIBC. Applying this estimate to the average number of cases per year, for 2016-2018, it could be approximated that there were 2,573 cases of MIBC per year in the UK. The age standardised incidence rate of malignant neoplasm of bladder in England is 27.6 and 8.2 per 100,000 amongst males and females respectively.[11] In England (2021-22) there were 68,614 finished consultant episodes (FCEs) and 64,548 admissions for malignant neoplasm of the bladder (ICD-10 code C67), which resulted in 40,978 day cases and 88,955 FCE bed days.[12] In England (2017), there were 8,686 patients diagnosed with malignant neoplasm of bladder (ICD-10 code C67) and 4,736 deaths registered where this was the underlying cause.[11] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 68.8% and 41.2% respectively.[13]

Recommended Treatment Options

NICE recommends the following treatments for MIBC:[14]

- Cisplatin combination regimen for people with newly diagnosed muscle-invasive urothelial bladder cancer for whom cisplatin-based chemotherapy is suitable – neoadjuvant treatment
- Radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable

- Adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive urothelial bladder cancer for whom neoadjuvant chemotherapy was not suitable

Clinical Trial Information

Trial	**ENERGIZE,** NCT03661320, A Phase 3, Randomized, Study of Neoadjuvant Chemotherapy Alone Versus Neoadjuvant Chemotherapy Plus Nivolumab or Nivolumab and BMS-986205, Followed by Continued Post-Surgery Therapy With Nivolumab or Nivolumab and BMS-986205 in Participants With Muscle-Invasive Bladder Cancer **Phase III:** active, not recruiting **Location:** 11 EU countries, UK, USA, Canada and other countries **Primary completion date:** November 2023
Trial Design	Randomised, parallel assignment, open label
Population	N = 861 (estimated). Participants must ≥18 years old and deemed eligible for Radial Cystectomy by his/her oncologist and/or urologist, and must agree to undergo Radial Cystectomy after completion of neoadjuvant therapy. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
Intervention(s)	Nivolumab + Gemcitabine + Cisplatin will be administered as a specified dose on specified days.
Comparator(s)	Gemcitabine + Cisplatin will be administered as a specified dose on specified days.
Outcome(s)	Primary outcome measures: • Pathological Complete Response rate, in all randomized participants. Time frame: approximately 43 months • Event-Free Survival, in all randomized participants. Time frame: approximately 51 months See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Nivolumab is already marketed in the UK. The NHS indicative price is:[15]

- For 100 mg/10 ml concentrate for solution for infusion vials £1,097.00
- For 120mg/12ml concentrate for solution for infusion vials £1,317.00
- For 240mg/24ml concentrate for solution for infusion vials £2,633.00
- For 40mg/4ml concentrate for solution for infusion vials £439.00

Relevant Guidance

NICE Guidance

- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS106). December 2015.
- NICE technology appraisal in development. Durvalumab for neoadjuvant and adjuvant treatment of muscle-invasive bladder cancer (GID-TA11115). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of cisplatin-eligible muscle-invasive bladder cancer (GID-TA11137/ GID-TA11122). Expected date of issue to be confirmed.

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: Robotic Assisted Surgery for Bladder Cancer. July 2016. 16033/P
- NHS England. Guidelines for the Management of Bladder Cancer. December 2016.

Other Guidance

- European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer. 2022.[16]
- Powles T, Bellmunt J, Comperat E, et al., Bladder cancer: European Society for Medical Oncology (ESMO) Clinical Practice Guideline for diagnosis, treatment and follow-up. 2021.[17]
- Official Journal of the National Comprehensive Cancer Network (JNCCN). Bladder Cancer, Version 3. NCCN Clinical Practice Guidelines in Oncology. March 2020.[18]

Additional Information

References

1 Electronic Medicines Compendium. *OPDIVO 10 mg/mL concentrate for solution for infusion*. 2022. Available from: https://www.medicines.org.uk/emc/product/6888#PHARMACODYNAMIC_PROPS [Accessed 1 February 2023].

2 Clinicaltrials.gov. *A Study to Compare Chemotherapy Alone Versus Chemotherapy Plus Nivolumab or Nivolumab and BMS-986205, Followed by Continued Therapy After Surgery With Nivolumab or Nivolumab and BMS-986205 in Participants With Muscle Invasive Bladder Cancer*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03661320 [Accessed 1 February 2023].

3 Necchi A et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. *Journal of Clinical Oncology*. 2018;36(34):3353-60. Available from: https://doi.org/10.1200/JCO.18.01148.

4 Sonpavde S et al. ENERGIZE: a Phase III study of neoadjuvant chemotherapy alone or with nivolumab with/without linrodostat mesylate for muscle-invasive bladder cancer. *Clinical Trial Protocol*. 2019;16(2). Available from: https://doi.org/10.2217/fon-2019-0611.

5 Bajorin DF et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *New England Journal of Medicine*. 2021;384:2102-14. Available from: https://doi.org/10.1056/NEJMoa2034442.

6 Clinicaltrials.gov. *Nivolumab Gemcitabine Cisplatin | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Interventional Studies | Phase 2, 3 | Industry*. Available from: https://clinicaltrials.gov/ct2/results?term=nivolumab+Gemcitabine++Cisplatin&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=Intr&rslt=&phase=1&phase=2&fund=2&Search=Apply [Accessed 15 February 2023].

7 National Health Service (NHS). *Bladder cancer*. 2021. Available from: https://www.nhs.uk/conditions/bladder-cancer/ [Accessed 1 February 2023].

8 Cancer Research UK. *Risks and Causes*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/risks-causes [Accessed 1 February 2023].

9 National Health Service (NHS). *Bladder Cancer-Symptoms*. 2021. Available from: https://www.nhs.uk/conditions/bladder-cancer/symptoms/ [Accessed 2 February 2023].

10 Cancer Research UK. *Bladder cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer [Accessed 2 February 2023].

11 Office for National Statistics (ONS). *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 16 February 2023].

12 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/2020-21 [Accessed 15 February 2023].

13 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdia [Accessed 16 February 2023].

14 National Institute for Health and Care Excellence (NICE). *Bladder cancer: diagnosis and management*. 2015. Available from: https://www.nice.org.uk/guidance/ng2/chapter/1-recommendations#treating-muscle-invasive-bladder-cancer-2 [Accessed 16 February 2023].

15 British National Formulary. *Nivolumab: solution for infusion*. 2023. Available from: https://bnf.nice.org.uk/drugs/nivolumab/medicinal-forms/ [Accessed 15 February].

16 European Association of Urology (EAU). *Muscle-invasive and Metastatic Bladder Cancer*. 2022. Available from: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer [Accessed 16 February 2023].

17 Powles T et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*. 2022;33(3):244-58. Available from: https://doi.org/10.1016/j.annonc.2021.11.012.

18 Flaig T et al. Bladder Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2020;18(3):329-54. Available from: https://doi.org/10.6004/jnccn.2020.0011.

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