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Newcastle University

# Health Technology Briefing
# February 2022

# Nivolumab in combination with chemotherapy for previously untreated unresectable or metastatic urothelial cancer

| Company/Developer | Bristol-Myers Squibb Pharmaceuticals Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 29667 | NICE ID: 10439 | UKPS ID: 656801 |
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## Licensing and Market Availability Plans

Currently in phase III clinical development.

## Summary

Nivolumab in combination with chemotherapy is in development for the treatment of patients with previously untreated, unresectable or metastatic urothelial cancer (UC). UC occurs on the lining of the renal pelvis, ureter, bladder and urethra, and other parts of the urinary system. Metastatic UC occurs when the cancer has spread to other parts of the body. Durable responses are rare with current standard of care treatments. Common symptoms of UC include pain or a burning sensation when passing urine, weight loss and back/lower tummy/bone pain. Therefore, treatment approaches with longer-term disease control and extending to broader metastatic UC patient populations are needed.

Nivolumab is an immune checkpoint inhibitor. This is a type of protein (monoclonal antibody) administered by intravenous (IV) infusion It works by improving the activity of white blood cells (T-cells), thereby increasing the ability of the immune system to kill cancer cells. Nivolumab blocks the activity of a receptor called programmed death-1 (PD-1). If licensed, nivolumab in combination with chemotherapy may offer an additional first line treatment option for patients with previously untreated, unresectable or metastatic UC.

## Proposed Indication

Treatment of adults with previously untreated, cisplatin-eligible, unresectable or metastatic urothelial cancer (UC)[1]

## Technology

### Description

Nivolumab (Opdivo) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the PD-1 receptor and blocks its interaction with 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. Engagement of PD-1 with the ligands 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, 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. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[2]

Nivolumab is currently in phase III clinical development for the treatment of cisplatin-eligible patients with previously untreated, unresectable or metastatic UC.[1]. In this trial, nivolumab 360 mg is administered in combination with chemotherapy (gemcitabine-cisplatin) every 3 weeks for up to 6 cycles, followed by nivolumab 480 mg (arm C) every 4 weeks.[3]

### Key Innovation

Currently, the standard first line treatment for patients with untreated, cisplatin-eligible unresectable or metastatic UC is cisplatin-based chemotherapy.[4] Regimens containing cisplatin have been the standard of care for metastatic UC for nearly 40 years, but durable response is rare with such treatment regimens. Furthermore, a large proportion of patients with unresectable or metastatic UC are ineligible for cisplatin-based chemotherapy. There is a need for treatment approaches conferring longer-term disease control that extend to patients with metastatic UC.[3] In recent studies, nivolumab in combination with chemotherapy has shown promising antitumour activity and an acceptable toxicity profile in other cancers such as advanced non-small cell lung cancer (NSCLC),[5] as well an induction of durable responses, in patients with unresectable or metastatic UC progressing regardless of platinum-based chemotherapy.[3]

### Regulatory & Development Status

Nivolumab currently has Marketing Authorisation in the UK for the following indications:[2]

- as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults
- as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy
- as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
- in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation.
- as monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults
- in combination with ipilimumab for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma

- as monotherapy for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults
- in combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC
- in combination with cabozantinib for the first-line treatment of adult patients with advanced RCC
- as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin
- as monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy
- in combination with ipilimumab for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy
- as monotherapy for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.
- as monotherapy for the adjuvant treatment of adult patients with completely resected oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy
- in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5

Nivolumab in combination with chemotherapy is also currently in phase II and/or III development for the treatment of a number of other types of cancers including: squamous cell lung cancer, pleural mesothelioma malignant, and neuroendocrine tumours.[6]

## Patient Group

### Disease Area and Clinical Need

Urothelial cancer (UC), also called transitional cell carcinoma (TCC), begins in the transitional cells that line the renal pelvis, ureters, bladder and urethra, and some other organs. These cells can change shape and stretch without breaking apart.[7] Metastatic urothelial cancer occurs when cancer cells break away from where they began (the primary tumour) and travel through the lymph system or blood to other parts of the body, such as the liver or bones.[8] The main risk factors for bladder cancer include: smoking, bladder infections, medical conditions such as systemic sclerosis, as well as prior bladder cancer and family history, being overweight, and exposure to certain chemicals.[9] The symptoms include blood in the urine, increased frequency/urgency of urine passing, pain or a burning sensation when passing urine, weight loss, back/lower tummy/bone pain, fatigue and illness.[10]

UC is the most common type of bladder cancer.[11] UC accounts for about 90% of all bladder cancers and 12% of kidney cancers (of which 7% begin in the renal pelvis, and 5% in the ureter).[12] In England in 2017, there were 8,686 new registrations for malignant neoplasm of bladder (ICD-10 code C67), 692 for malignant neoplasm of renal pelvis (ICD-10 code C65), and 596 for malignant neoplasm of ureter (ICD-10 code C66).[13] The 2020-2021 Hospital Episodes Statistics for England recorded a total of 56,069 finished consultant episodes (FCE) for malignant neoplasm of bladder, resulting in 52,437 hospital admissions, 73,087 FCE bed days and 30,679 day cases. There were 1,512 FCE for malignant neoplasm of renal pelvis, resulting in 1,385 hospital admissions, 2,572 FCE bed days and 768 day cases. The FCE for malignant

neoplasm of ureter were 2,159, resulting in 1,942 hospital admissions, 4,241 FCE bed days and 1,003 day cases.[14]

## Recommended Treatment Options

For metastatic UC, treatment options may include chemotherapy, immunotherapy or treatment to relieve cancer symptoms.[15] The current treatment options recommended by NICE for first-line unresectable or metastatic UC in adults include:[4]

- a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine)
- atezolizumab for untreated locally advanced or metastatic UC in adults whose tumours express PD-L1 at a level of 5% or more and when cisplatin-containing chemotherapy is unsuitable

## Clinical Trial Information

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| Trial | NCT03036098; **EudraCT**2016-003881-14; A Phase 3, Open-label, Randomized Study of Nivolumab Combined With Ipilimumab, or With Standard of Care Chemotherapy, Versus Standard of Care Chemotherapy in Participants With Previously Untreated Unresectable or Metastatic Urothelial Cancer<br>**Phase III –** Recruiting<br>**Location(s):** EU, USA, Canada, Australia, China and other countries<br>**Primary completion date:** May 2021 |
| Trial Design | Randomised, open label, parallel assignment |
| Population | N= 897 (estimated), Subjects aged 18 and over with histological or cytological evidence of metastatic or surgically inoperable transitional cell cancer (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra; No prior systemic chemotherapy for metastatic or surgically inoperable urothelial cancer (UC) |
| Intervention(s) | 360 mg of nivolumab + gemcitabine-cisplatin every 3 weeks for up to 6 cycles, followed by 480 mg of nivolumab.There is a 120mg vial available. |
| Comparator(s) | - |
| Outcome(s) | **Primary outcome measure:**<br>- Overall Survival (OS) in cisplatin-ineligible randomized participants [Time Frame: Up to 55 months]<br>- Overall survival (OS) in PD-L1 positive (>=1%) randomized participants by immunohistochemistry (IHC) [Time Frame: Up to 52 months]<br>- Progression-free survival (PFS) by blinded independent central review (BICR) (using RECIST 1.1) in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC [Time Frame: Up to 64 months]<br>- Overall survival (OS) in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC [Time Frame: Up to 64 months]<br><br>See trial record for full list of all outcomes |

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| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

Nivolumab is already marketed in the UK. One vial of nivolumab Opdivo 100mg/10ml concentrate for solution for infusion costs £1097.00, one vial of nivolumab Opdivo 240mg/24ml concentrate for solution for infusion costs £2633.00, and one vial of nivolumab Opdivo 40mg/4ml concentrate for solution for infusion vials costs £439.00.[16]

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal awaiting development. Durvalumab with tremelimumab and chemotherapy for treating unresectable or advanced urothelial cancer (GID-TA 10748). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Nivolumab with ipilimumab for untreated PD-L1 positive unresectable or metastatic urothelial cancer (GID-TA 10707). Expected date of issue to be confirmed.
- NICE Technology appraisal. Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable (TA739). October 2021.
- NICE technology appraisal guidance. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272). Jan 2013.
- NICE guidance. Bladder cancer: diagnosis and management (NG2). Feb 2015

### NHS England (Policy/Commissioning) Guidance

- NHS England. Specialised kidney, bladder and prostate cancer services (Adults). Service Specification (170114S). February 2019.
- 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

- Powles T, Bellmunt J, Comperat E, et al., Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up.2021.[17]
- European Association of Urology. Guidelines on muscle-invasive and metastatic bladder cancer. 2020.[18]

## Additional Information

## References


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***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.***