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HEALTH TECHNOLOGY BRIEFING
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Nivolumab in combination with ipilimumab for previously untreated unresectable or metastatic urothelial cancer – first-line

NIHRIO ID	13753	**NICE ID**	9838
Developer/Company	Bristol-Myers Squibb	**UKPS ID**	645155

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Nivolumab in combination with ipilimumab is in clinical development for PD-L1 positive patients with previously untreated unresectable or metastatic urothelial cancer regardless of cisplatin eligibility. Urothelial cancer, a subset of bladder cancer, occurs on the lining of the renal pelvis, ureter, bladder and urethra, and other parts of the urinary system. In some cases, the tumour spreads into the surrounding muscles or other parts of the body which means that it cannot be cured by surgery. Metastatic urothelial cancer occurs when the cancer has spread to other parts of the body, such as the liver or bones. The symptom of urothelial cancer is blood in the urine, but symptoms may only appear once the cancer grows larger or into the deeper layers of the bladder wall for both men and women. Other symptoms may include increased frequency/urgency/pain of urine passing, weight loss, back/lower tummy/bone pain, fatigue and illness.

Nivolumab and ipilimumab, both administered by intravenous infusion, are immune therapy medicinal products that are currently licensed as a combination treatment of advanced cancers such as melanoma and kidney cancer. Nivolumab is a medicinal product called an immune checkpoint inhibitor. It works by improving the activity of white blood cells (T-cells), thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab has a different mode of action but also increases the activity of T-cells against the cancer cells. If licensed, nivolumab in combination with ipilimumab may offer an additional first-line treatment option for PD-L1 positive patients with previously untreated, unresectable or metastatic urothelial cancer.

PROPOSED INDICATION

Nivolumab in combination with ipilimumab for PD-L1 positive patients with previously untreated, unresectable or metastatic urothelial cancer regardless of cisplatin eligibility.[1]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo, BMS-936558) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (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]

Ipilimumab (Yervoy, BMS-734016) is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoral T-effector/ T-regulatory cell ratio which drives tumour cell death.[3]

Nivolumab in combination with ipilimumab is in phase III clinical development for adults with previously untreated, unresectable or metastatic urothelial cancer. In the phase III clinical trial (CheckMate901; NCT03036098), patients will receive a specified dose of 10mg/kg of nivolumab combined with either 5mg/kg of ipilimumab or standard of care (SOC) chemotherapy by intravenous (IV) infusion.[1,4]

INNOVATION AND/OR ADVANTAGES

Urothelial carcinoma of the ureter or renal pelvis is typically managed with nephroureterectomy, but despite surgery with or without neo/adjuvant chemotherapy many patients with invasive urothelial carcinoma are at high risk of recurrence and death. Nivolumab is a PD-1 inhibitor that has proven efficacious for metastatic or unresectable urothelial carcinoma progressing despite chemotherapy.[5]

According to a phase I/II clinical trial, although some patients with platinum-pretreated metastatic urothelial cancer (mUC) demonstrated good responses to nivolumab monotherapy, the response rate and survival were higher with combined nivolumab plus ipilimumab therapy.[6] These results provide a strong rationale by which to evaluate nivolumab plus ipilimumab in the first-line setting for mUC in the current ongoing phase III randomized clinical trial (CheckMate 901; NCT03036098).[6,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab is currently indicated in the UK in combination with ipilimumab for the following:[2,3]

- Treatment of advanced (unresectable or metastatic) melanoma
- First-line treatment of intermediate/poor-risk advanced renal cell carcinoma in adults

The most common adverse reactions (affecting more than one in ten people) associated with treatment with nivolumab in combination with ipilimumab are: hypothyroidism,

hyperthyroidism, decreased appetite, headache, dyspnoea, colitis, diarrhoea, vomiting, nausea, abdominal pain, rash, pruritus, arthralgia, fatigue and pyrexia.[2]

Nivolumab in combination with ipilimumab is currently in phase II and phase III clinical development for the treatment of various types of cancers including renal, ovarian, cervix, and prostate.[8]

PATIENT GROUP

DISEASE BACKGROUND

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 (the lining is called the urothelium).[9] These cells can change shape and stretch without breaking apart.[9] When the bladder is empty, the transitional cells are all bunched together. As the bladder fills with urine the cells stretch out into a single layer. These cells come into contact with waste products in the urine that may cause cancer, such as chemicals from cigarette smoke.[10] Of all kidney cancers, only about 7 out of 100 (7%) begin in the renal pelvis, and 5 out of 100 (5%) in the ureter. About 9 in 10 cancers of the ureter and renal pelvis (90%) start in transitional cells.[11]

Locally advanced indicates the cancer has spread to the wall of the pelvis or abdomen, or there are cancer cells in more than one lymph node in, or just outside, the pelvis. 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.[10,12]

Levels of PD-L1 expression have been shown to correlate with bladder cancer severity and outcome. It has been found that tumours that express higher levels of PD-L1 (on tumour cells) are more likely to be considered high-grade, and patients experience higher frequencies of postoperative recurrence and poorer survival in organ-confined disease.[13]

Each year around 60% of new bladder cancer cases are in people 75 years and over and 34% of all new kidney cases in the UK are in people aged 75 and over (2015-2017).[14,15] The main risk factors for UC include: smoking, bladder infections, medical conditions such as systemic sclerosis, as well as prior bladder cancer and family history.[16] The symptom of UC is blood in the urine, but symptoms may only appear once the cancer grows larger or into the deeper layers of the bladder wall for both men and women. Other symptoms may include increased frequency/urgency/pain of urine passing, weight loss, back/lower tummy/bone pain, fatigue and illness.[17]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK 7% of kidney cancers are in the renal pelvis, 6% in the ureter, and 1% in the urethra and paraurethral gland.[18] Between 2015 and 2017, there were around 10,200 new bladder cancer cases and 13,056 new kidney cancer cases in the UK every year. In the UK, about 90% of bladder cancers are urothelial cancer type.[10] Incidence rates for bladder cancer and kidney cancer in the UK were highest in people aged 85 to 89 (2015-2017).[15,19]

In England in 2017, there were 8,686 new registrations for malignant neoplasm of bladder, 692 for malignant neoplasm of renal pelvis (ICD-10 code C65), and 596 for malignant neoplasm of ureter (ICD-10 code C66). The direct age-standardised rates per 100,000 population were 27.6 among males and 8.2 among females for malignant neoplasm of bladder. The direct age-standardised rates were low for malignant neoplasm of renal pelvis (1.8 for males and 1.0 for females) and malignant neoplasm of ureter (1.7 for males and 0.7 for females).[20]

In 2018-2019, the finished consultant episodes (FCEs) in England for malignant neoplasm of the bladder as primary diagnosis were 73,789, resulting in 69,198 admissions and 100,777 FCE bed days. There were 1,533 FCEs for malignant neoplasm of renal pelvis (1,386 admissions and 3,219 bed days); and 2,445 FCEs for malignant neoplasm of ureter (2,157 admission and 5,579 bed days).[21]

The European age-standardised incidence rate of bladder and kidney cancer in the UK is projected to decrease by 2035 to 21.07 per 100,000 (7,531 projected cases) and 43.88 per 100,000 (14,258 projected cases), respectively.[22]

The European age-standardised mortality rate in the UK is projected to decrease by 2035 to 9.39 per 100,000 (7,771 projected deaths) for bladder cancer and 7.61 per 100,000 (5,739 projected deaths) for kidney cancer.[23] Between 2015 and 2017, there were around 4,500kidney cancer deaths in the UK every year.[15] In 2017, there were 5,014 deaths (3,441 male and 1,573 female) in England and Wales recorded with malignant neoplasm of bladder as the cause (ICD-10 code C67).[24] The one-year age-standardised net cancer survival for stage IV bladder cancer in adults was 35.7% (2013-2017). The one-year age-standardised net cancer survival for stage IV kidney cancer was 38.7% and 5-year age-standardised survival was 12.4%.[25]

Based on current published literature, the number of adults in England and Wales with PD L1 positive urothelial cancer could not be found.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment options for urothelial cancer depends on how advanced the cancer is. A specialist urology multidisciplinary team (composing of urologists, pathologists, radiologists and a specialist clinical nurse) is normally employed throughout the treatment. Treatment options for muscle-invasive bladder cancer include radical cystectomy or radical radiotherapy. Surgery is often followed by chemotherapy.[26]

For locally advanced or metastatic urothelial cancer, treatment may include chemotherapy, immunotherapy or treatment to relieve cancer symptoms. If the cancer is too advanced, palliative care may be offered to manage pain.[26] The role of first-line chemotherapy should be discussed with patients who have locally advanced or metastatic bladder cancer. For people having first-line chemotherapy for locally advanced or metastatic bladder cancer: regular clinical and radiological monitoring ought to be carried out, symptoms of disease and treatment-related toxicity need to be actively managed and chemotherapy needs to be stopped if excessive toxicity or disease progression.[27]

CURRENT TREATMENT OPTIONS

According to the current NICE treatment pathway, current first-line treatment options for locally advanced or metastatic bladder cancer include:[28]

- Cisplatin-based chemotherapy regimen
- Carboplatin in combination with gemcitabine chemotherapy if cisplatin-based chemotherapy is unsuitable
- Pembrolizumab or atezolizumab (via Cancer Drugs Fund) if treatment with cisplatin is unsuitable and the tumour is PD-L1 positive.

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with ipilimumab will offer an additional first-line treatment for cisplatin-ineligible patients with previously untreated, unresectable or metastatic urothelial cancer.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**CheckMate901; NCT03036098, CA209-901, EudraCT Number 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 **Phase III - ongoing** **Location(s):** EU (not UK), USA, Canada and other countries.
Trial design	Randomised, parallel assignment, open-label
Population	N=1290 (planned); 18 years and older with metastatic or inoperable urothelial cancer involving the renal pelvis, ureter, bladder or urethra, at least 1 lesion with measurable disease, and no prior systemic chemotherapy treatment in the metastatic setting
Intervention(s)	Specified dose of 10mg/kg of nivolumab and 5mg/kg of ipilimumab on specified days followed by nivolumab only on specified days, administered by IV infusion
Comparator(s)	SOC chemotherapy alone: • Gemcitabine-cisplatin or gemcitabine-carboplatin
Outcome(s)	Primary outcomes: • OS in PD-L1 positive (>=1%) randomised participants by immunohistochemistry (IHC) [Time frame: Up to 52 months] • Overall survival (OS) in PD-L1 positive (>=1%) randomized participants by immunohistochemistry (IHC) [Time Frame: Up to 52 months] • 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] • Overall survival (OS) in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC [Time Frame: Up to 64 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 prices for nivolumab solution for infusion vials are as follows:[29]

- Nivolumab 100mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £1097.00 (Hospital only)
- Nivolumab 240mg/24ml concentrate for solution for infusion (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £2633.00 (Hospital only)
- Nivolumab 40mg/4ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £439.00 (Hospital only).

Ipilimumab is already marketed in the UK. The NHS indicative prices for ipilimumab solution for infusion vials are as follows:[30]

- Ipilimumab 200mg/40ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £15000.00 (Hospital only)
- Ipilimumab 50mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £3750.00 (Hospital only).

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Atezolizumab with gemcitabine and carboplatin for treating metastatic urothelial bladder cancer (TA10202). Expected July 2021.
- NICE technology appraisal in development. Pembrolizumab with chemotherapy for untreated metastatic urothelial cancer (TA10418). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Durvalumab for untreated PD-L1 positive metastatic urothelial bladder cancer (TA10324). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Durvalumab with tremelimumab for untreated PD-L1-positive urothelial bladder cancer (TA10315). Expected date of issue to be confirmed.
- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA522). July 2018.
- NICE technology appraisal. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA492). July 2018.
- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS106). December 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

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- ESMO bladder cancer practice guidelines for diagnosis, treatment and follow-up. 2014.[32]

ADDITIONAL INFORMATION

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