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HEALTH TECHNOLOGY BRIEFING JANUARY 2021

Nivolumab in combination with ipilimumab for cisplatin-ineligible patients with untreated, unresectable or metastatic urothelial cancer– first line

NIHRIO ID	29787	NICE ID	10476
Developer/Company	Bristol-Myers Squibb	UKPS ID	657697

Licensing and market availability plans	In phase III clinical trial.

SUMMARY

Nivolumab in combination with ipilimumab is in development for cisplatin-ineligible 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. Therefore, treatment approaches with longer-term disease control and extending to broader metastatic UC patient populations are needed.

Nivolumab and ipilimumab, administered IV, are immune therapy medicinal products that are currently licensed as a combination treatment of advanced cancers. Nivolumab is 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 cancer cells. If licensed, nivolumab in combination with ipilimumab may offer an additional first line treatment option for cisplatin-ineligible patients with previously untreated, unresectable or metastatic UC.

PROPOSED INDICATION

Nivolumab in combination with ipilimumab for cisplatin-ineligible patients with previously untreated, unresectable or metastatic urothelial cancer (UC).[1,a]

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 intratumoural T-effector/ T-regulatory cell ratio which drives tumour cell death.[3]

In the phase III clinical trial (CheckMate901; NCT03036098), cisplatin ineligible patients in treatment arm A received nivolumab 1mg/kg and ipilimumab 3mg/kg every 3 weeks for up to 4 cycles. This was then followed by nivolumab 480mg every 4 weeks until unacceptable toxicity or a maximum of 2 years.[1,4,b]

INNOVATION AND/OR ADVANTAGES

Cisplatin-containing regimens have been standard of care for metastatic UC for nearly 40 years, but durable responses are rare with such treatments. Furthermore, a large proportion of patients with unresectable or metastatic UC are ineligible for cisplatin therapy. Treatment approaches conferring longer-term disease control and extending to broader metastatic UC patient populations are urgently needed.[4]

Recently, the programmed death-1 (PD-1) inhibitor, nivolumab, induced durable responses in patients with unresectable or metastatic UC progressing despite platinum-based chemotherapy, and nivolumab combined with ipilimumab (a CTLA-4 inhibitor) demonstrated acceptable safety and clinical activity.[4] According to a phase I/II clinical trial, although some patients with platinum-pretreated metastatic UC demonstrated good responses to nivolumab monotherapy, the response rate and survival were higher with combined nivolumab plus ipilimumab therapy. These results support the ongoing phase III CheckMate901 (NCT03036098) trial of nivolumab (in combination with ipilimumab or chemotherapy) compared to standard chemotherapy in patients with previously untreated metastatic UC.[5,6]

[a] Information provided by Bristol-Myers Squibb on UK Pharma Scan
[b] Information provided by Bristol-Myers Squibb

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

- Advanced melanoma in adults
- 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, 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 lung, renal, ovarian, and prostate.[7]

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). These cells can change shape and stretch without breaking apart.[8] UC is by far the most common type of bladder cancer.[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]

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.[12]

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).[13,14] 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.[15] 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.[16]

CLINICAL NEED AND BURDEN OF DISEASE

For each year between 2015 and 2017 in the UK there were around 10,200 new bladder cancer cases. In the UK, about 90% of bladder cancers are urothelial cancers.[10] Incidence rates for bladder cancer and kidney cancer in the UK were highest in people aged 85 to 89 (2015-2017).[17]

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). 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).[18]

The 2019-2020 Hospital Episodes Statistics for England recorded a total of 73,189 finished consultant episodes (FCE) for malignant neoplasm of bladder, resulting in 68,480 hospital admissions, 99,476 FCE bed days and 41,883 day cases. There were 1,596 FCE for malignant neoplasm of renal pelvis, resulting in 1,477 hospital admissions, 2,898 FCE bed days and 801 day cases. The FCE for malignant neoplasm of ureter were 2,521, resulting in 2,205 hospital admissions, 5,551 FCE bed days and 1,154 day cases.[19]

For males, the European age-standardised incidence rate of bladder cancer is projected to decrease by 38% between 2014 and 2035, to 21.07 cases per 100,000 (7,531 projected cases) by 2035. For females, the rates are projected to fall by 31% between 2014 and 2035, to 7 cases per 100,000 by 2035. Kidney cancer in the UK is projected to increase by 28% for males and 18% for females between 2014 and 2035, to 43.88 per 100,000 (14,258 projected cases) and 20.42 per 100,000 (7,473 projected cases) by 2035 respectively.[20]

The European age-standardised mortality rate in the UK is projected to decrease between 2014 and 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.[21] Between 2015 and 2017, there were around 4,500 kidney cancer deaths in the UK every year.[14] 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).[22] 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%.[23]

The European Association of Urology guidance estimates 50% of patients with UC are unfit for cisplatin-based chemotherapy.[24]

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.[25]

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.[25] 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.[26]

CURRENT TREATMENT OPTIONS

According to the current NICE treatment pathway, current first-line treatment options for cisplatin-ineligible locally advanced or metastatic bladder cancer include:[27]

- 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 option for cisplatin-ineligible patients with previously untreated, unresectable or metastatic UC.

CLINICAL TRIAL 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=445 (planned);[c] cisplatin-ineligible patients (randomized 1:1 to Arms A and B) 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; 18 years and older
Intervention(s)	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks up to 4 doses, followed by nivolumab 480 mg every 4 weeks until unacceptable toxicity or a maximum of 2 years[4,c]
Comparator(s)	Gemcitabine-carboplatin every 3 weeks for up to 6 cycles.[4,c]
Outcome(s)	Primary outcomes: Overall survival (OS) in cisplatin-ineligible randomized participants [Time frame: up to 55 months] Secondary outcome: Progression-free survival (PFS) by blinded independent central review (BICR) (using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1) in cisplatin-ineligible randomized participants [Time frame: up to 55 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:[28]

[c] Information provided by Bristol-Myers Squibb

- Nivolumab 100mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £1,097.00 (Hospital only)
- Nivolumab 240mg/24ml concentrate for solution for infusion (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £2,633.00 (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:[29]

- Ipilimumab 200mg/40ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £15,000.00 (Hospital only)
- Ipilimumab 50mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £3,750.00 (Hospital only).

RELEVANT GUIDANCE

NICE GUIDANCE

- 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 in development. Atezolizumab with gemcitabine and carboplatin for treating metastatic urothelial bladder cancer (TA10202). Expected July 2021.
- 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

- European Association of Urology. Guidelines on muscle-invasive and metastatic bladder cancer. 2020.[30]
- ESMO bladder cancer practice guidelines for diagnosis, treatment and follow-up. 2014.[31]

ADDITIONAL INFORMATION

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