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Durvalumab in combination with Tremelimumab for locally advanced or metastatic urothelial bladder cancer – first line

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LAY SUMMARY

Urothelial bladder cancer (UBC) is the most common type of bladder cancer. It originates from the cells that lines the walls (urothelial cells) of the bladder. In advanced or metastatic UBC, the cancer has spread past the bladder into neighbouring or distant organs. Men are up to three times more likely than women to be diagnosed with UBC and risk increases with age in both genders. Other risk factors include tobacco smoking, exposure to some environmental/industrial chemicals, chronic bladder infection and some genetic factors. The most common symptom of UBC is blood in the urine. Advanced/metastatic UBC may present for the first time as an emergency admission, and this is frequently associated with a poor prognosis.

Durvalumab with tremelimumab is being developed as a combination therapy administered intravenously for the treatment of locally advanced or metastatic UBC. Both drugs act in different unique ways to stimulate the body's natural defences that fight the cancer cells. The combined effect of this produces a stronger and more targeted immune response against the cancer cells when compared to current treatment. This has the potential to increase survival rates and reduce side effects when compared to current treatment options.

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TARGET GROUP

Urothelial bladder cancer (locally advanced or metastatic) – first line

TECHNOLOGY

DESCRIPTION

Durvalumab (Imfinzi) in combination with tremelimumab is under development as a first line therapy for the treatment of patients with locally advanced or metastatic urothelial bladder cancer (UBC).[1]

Durvalumab is a fully human IgG monoclonal antibody that blocks PD-L1 (anti-PDL1), a protein expressed on the surface of nearly all types of human cancer cells.[2] PD-L1 can bind to its receptors PD-1 and B7.1 on activated T cells, which can result in the inactivation of tumour-specific T cells. Anti-PDL1 is designed to inhibit the interactions of PD-L1 with PD-1 and B7.1. This activity would relieve the inhibition on T-cell activity, allowing T cells to kill tumour cells. T cell activation has been shown to be a key component of a successful anti-tumour response.[2, 3]

Tremelimumab is a human IgG2 monoclonal antibody that binds to and inhibits the activity of the T-cell receptor protein - cytotoxic T-lymphocyte-associated protein 4 (CTLA4).[4] Tremelimumab binds to CTLA4 and blocks the binding of the antigen-presenting cell ligands B7-1 and B7-2 to CTLA4, resulting in inhibition of B7-CTLA4-mediated down regulation of T-cell activation. This increases proliferation of T cells and prolongs their activation, thus enhancing the anti-tumour response.[4, 5]

The combination of durvalumab and tremelimumab allows for simultaneous inhibition of two independent pathways that act to suppress T cell responses to tumours. Targeting both checkpoint pathways provides the potential for additive or synergistic effects as the mechanisms of activation for PD-1 and CTLA-4 are non-redundant.[6]

In the ongoing phase III study of durvalumab with or without tremelimumab versus Standard of Care Chemotherapy in Urothelial Cancer (DANUBE), subjects in the combination therapy experimental arm will receive intravenous infusions of durvalumab (1500 mg) and tremelimumab (75 mg) for four times per week, followed by durvalumab (1500 mg) every 4 weeks for up to 12 months.[7, 8]

Durvalumab monotherapy and/or in combination with tremelimumab does not currently have Marketing Authorisation in the EU for any indication. The US Food and Drug Administration (FDA) granted accelerated approval to durvalumab (Imfinzi) for the treatment of patients with locally advanced or metastatic urothelial carcinoma in May 2017.[9, 10]

The combination of durvalumab with tremelimumab is also under development for the treatment of the following conditions;[1]

- Non-Small Cell Lung Cancer
- Recurrent Head and Neck Cancer Squamous Cell Carcinoma
- Adenocarcinoma of the gastroesophageal junction
- Bladder Cancer
- Dysgerminoma
- Gastric Cancer

- Germ Cell Tumours
- Germinomatous (Seminomatous) Germ Cell Tumours
- Hepatocellular Carcinoma
- Malignant Pleural Mesothelioma
- Metastatic Breast Cancer
- Neuroendocrine Gastroenteropancreatic Tumours (GEP-NET)
- Non-Small Cell Lung Cancer
- Non-germinomatous (Non-seminomatous) Germ Cell Tumours
- Small-Cell Lung Cancer
- Ureter Cancer
- Urethral Cancer
- Urinary Tract Cancer

INNOVATION and/or ADVANTAGES

The combination of durvalumab and tremelimumab, through its mechanism of action (simultaneous inhibition of two independent pathways that acts to suppress T cell responses to tumours), provides the potential for additive or synergistic effects when compared with current therapies for advanced/metastatic UBC.

DEVELOPER

AstraZeneca Plc

AVAILABILITY, LAUNCH or MARKETING

Durvalumab was designated a breakthrough therapy in February 2016, approved for a Priority Review in December 2016 and received an Accelerated Approval from the FDA in May 2017 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.[9]

PATIENT GROUP

BACKGROUND

Bladder cancer is a urinary tract system malignancy arising primarily from epithelial cells lining the bladder. In the vast majority of cases (>90%), bladder cancer manifests as transitional (urothelial) cell carcinoma (TCC), also referred to as urothelial bladder cancer (UBC).[11, 12] The remaining cases manifest as squamous cell carcinoma, adenocarcinoma, and in rare instances, carcinosarcoma. Bladder cancer is classified under the International Classification of Diseases, Tenth Revision (ICD-10) code C67. Men are up to three times more likely than women to be diagnosed with bladder cancer, and risk increases with age in both genders.[12]

Urothelial bladder cancer (UBC) can be grouped into three stages of increasing severity:

1. Early stage, most commonly referred to as non-muscle-invasive bladder cancer (NMIBC) where the cancerous cells are contained inside the lining of the bladder
2. Advanced stage, referred to as muscle-invasive bladder cancer (MIBC) where the cancerous cells spread to the surrounding muscle
3. Metastatic bladder cancer, where the cancer has spread past the bladder into neighbouring or distant organs.[12]

In addition to the male and female reproductive organs, the most common metastatic sites for bladder cancer are the lymph nodes in the pelvis, abdomen, and neck, as well as the lungs, liver and bones.[13]

The aetiology of bladder cancer is complex; the main risk factor is increasing age (most common in people aged 60 years and over), but smoking and exposure to some industrial chemicals also increase risk.[14] Tobacco use has been identified as the main known environmental contributor to bladder cancer development, with smoking implicated in over half of cases in men and in one third of cases in women.[15] Exposure to certain chemicals, such as polycyclic aromatic hydrocarbon (PAH), has also been linked to increased risk of bladder cancer. Populations of workers who have occupational exposure to these carcinogenic chemicals, including metal workers, leather workers, hairdressers, mechanics, miners, painters, and bus and taxi drivers, have been reported to have increased incidence of bladder cancer.[16] Chronic inflammation resulting from infection is also suspected to be linked to bladder cancer; schistosomiasis, a chronic parasitic infection commonly found in residents of rural areas, has been shown to increase the risk of bladder cancer.[17] Recently, several genetic variants that modify prognosis in bladder cancer patients have been identified with results suggesting a potential for gene variants/short nucleotide polymorphisms (SNPs) to be used to predict recurrence and thus better inform practitioners on the treatment regimens most suitable for individual bladder cancer patients.[18]

Bladder cancer is usually identified on the basis of visible blood in the urine or blood found by urine testing. It often presents for the first time as an emergency admission, which is frequently associated with a poor prognosis. In approximately 90% of cases, the first indicator of bladder cancer is haematuria (blood in the urine).[11] The urine can vary in colour, depending on the amount of blood, from yellow-red to dark red. Dysuria (frequent urination in small amounts), frequent urinary tract infections (UTIs), abdominal pain, incontinence, urinary urgency and fatigue are other symptoms of early-stage bladder cancer.[12] If bladder cancer reaches an advanced stage and begins to spread, the symptoms can include pelvic pain, bone pain, unexplained weight loss and swelling of the legs.[12]

Bladder cancer can significantly affect the quality of life of patients and their families/carers in so many ways. Diagnosis is usually made via cystoscopy, which involves examination of the bladder using a thin instrument called a cystoscope. Although it is an unpleasant procedure, it normally occurs without any complications. The immediate side effects of cystoscopy that affect the patient's quality of life include a mild burning sensation during urination, the urge to urinate more frequently and a pink hue to the urine, which can be due to mild bleeding. Occasionally, UTIs can develop as a result of cystoscopy, which can cause fever and increased pain during urination.[12] Some patients may require radical cystectomy which involves the removal of the entire bladder and nearby lymph nodes. In women, the ovaries, fallopian tubes, uterus, and a portion of the vaginal wall may also be removed, causing infertility and a potential reduction in sexual sensitivity. In men, the prostate may be removed, which can result in erectile dysfunction.

The general consensus is that the urinary and sexual domains of health-related quality of life are the greatest concerns for bladder cancer patients in regards to quality of life.[19] The involvement of the urogenital tract and the nature of the treatments give bladder cancer a strong psychological impact,

in addition to the physical impact of the disease and its treatments, which is often profound. There is thought to be considerable variation across the UK National Health Service (NHS) in the diagnosis and management of bladder cancer and the provision of care to people who have it. There is evidence that the patient experience for people with bladder cancer is worse than that for people with other cancers.[20]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, bladder cancer was the tenth most common cancer in 2014, with around 10,100 new cases diagnosed that year.[21] Bladder cancer is three to four times more common in men than in women in the UK; it was the eight most common cancer in males and 14th most common cancer in females in 2014.[21] Bladder cancer was the seventh most common cause of cancer death in the UK in 2014, accounting for approximately 5,400 deaths in that year.[21]

The prevalence of the condition and the nature of its management make bladder cancer one of the most expensive cancers for the NHS.[20] According to the 2015/2016 hospital episode statistics for England, bladder cancer (ICD-10 Code – C67) accounted for 71,702 finished consultant episodes (FCEs), 67,422 hospital admissions and 115,082 FEC bed days.[22]

An estimated 69,100 people who had been diagnosed with bladder cancer between 1991 and 2010 were alive in the UK at the end of 2010.[21] Overall, the five-year survival rates for bladder cancer for men and women are 57% and 46%, respectively in England and Wales according to 2010-2011 data.[21]

As with most cancers, survival is greatly dependent upon the stage in which the cancer has been diagnosed. Approximately 70−80% of bladder cancer patients are diagnosed while they are still considered to have early-stage NMIBC, with relatively good prognosis.[12] In locally advanced and/or metastatic disease however, the prognosis is less optimistic with the five-year survival rate dipping to 15%.[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939] (GID-TA10111). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab for urothelial cancer [ID1019] (GID-TA10113). Expected date of publication: 22 November 2017
- NICE technology appraisal in development. Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy [ID995] (GID-TA10163). Expected date of publication: 28 February 2018.
- NICE Technology appraisal guidance. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272). January 2013.
- NICE clinical guideline. Bladder Cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder Cancer (QS106). December 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- British Uro-oncology Group (BUG), British Association of Urological Surgeons (BAUS) Section of Oncology and Action on Bladder Cancer (ABC). Multi-disciplinary Team (MDT) Guidance for Managing Bladder Cancer 2nd Edition (January 2013).

CURRENT TREATMENT OPTIONS

Most bladder cancers (75–80%) do not involve the muscle wall and are usually treated with telescopic removal of the cancer (transurethral resection of bladder tumour [TURBT]). This may be followed by instilling chemotherapy or vaccine-based therapy into the bladder, with prolonged telescopic checking of the bladder (cystoscopy) as follow-up.

Some people with non-muscle-invasive bladder cancer who are at higher risk of poor prognosis are treated with major surgery to remove the bladder (cystectomy).[14] Adults with cancer in or through the bladder muscle wall may be treated with intent to cure using chemotherapy, cystectomy or radiotherapy and those who have cancer too advanced to cure may have palliative radiotherapy and chemotherapy.[14]

For locally advanced or metastatic muscle-invasive bladder cancer, the following options are available according to NICE clinical guidelines:[20]

<u>First-line chemotherapy</u>

- The role of first-line chemotherapy with people who have locally advanced or metastatic bladder cancer should be discussed. These discussions should include:
    - Prognosis of their cancer and
    - Advantages and disadvantages of the treatment options, including best supportive care.
- Offer a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [high-dose] MVAC in combination with granulocyte-colony stimulating factor [G-CSF]) to people with locally advanced or metastatic urothelial bladder cancer who are otherwise physically fit (have an Eastern Cooperative Oncology Group [ECOG] performance status of 0 or 1) and have adequate renal function (typically defined as a GFR of 60 ml/min/1.73m2 or more).
- Offer carboplatin in combination with gemcitabine, to people with locally advanced or metastatic urothelial bladder cancer with an ECOG performance status of 0-2 if a cisplatin-based chemotherapy regimen is unsuitable, for example, because of poor ECOG performance

status, inadequate renal function (typically defined as GFR of less than 60 ml/min/1.73m2) or comorbidity.

- For people having first-line chemotherapy for locally advanced or metastatic bladder cancer:
    - Carry out regular clinical and radiological monitoring and
    - Actively manage symptoms of disease and treatment-related toxicity and
    - Stop first-line chemotherapy if there is excessive toxicity or disease progression

Second-line chemotherapy

- Discuss second-line chemotherapy with people who have locally advanced or metastatic bladder cancer. Include in your discussion:
    - The prognosis of their cancer
    - Advantages and disadvantages of treatment options, including best supportive care.
- Consider second-line chemotherapy with gemcitabine in combination with cisplatin, or accelerated (high-dose) MVAC in combination with G-CSF for people with incurable locally advanced or metastatic urothelial bladder cancer whose condition has progressed after first-line chemotherapy if:
    - Their renal function is adequate (typically defined as a GFR of 60 ml/min/1.73m2 or more) and
    - They are otherwise physically fit (have an ECOG performance status of 0 or 1).
- Consider second-line chemotherapy with carboplatin in combination with paclitaxel or gemcitabine in combination with paclitaxel for people with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it.
- For recommendations on vinflunine as second‑line chemotherapy for people with incurable locally advanced or metastatic urothelial bladder cancer, see NICE's technology appraisal guidance.[23]
- For people having second-line chemotherapy for locally advanced or metastatic bladder cancer:
    - Carry out regular clinical and radiological monitoring and
    - Actively manage symptoms of disease and treatment-related toxicity and
    - Stop second-line chemotherapy if there is excessive toxicity or disease progression.

Managing symptoms of locally advanced or metastatic bladder cancer

- Bladder symptoms
    - Offer palliative hypofractionated radiotherapy to people with symptoms of haematuria, dysuria, urinary frequency or nocturia caused by advanced bladder cancer that is unsuitable for potentially curative treatment.
- Loin pain and symptoms of renal failure
    - Discuss treatment options with people who have locally advanced or metastatic bladder cancer with ureteric obstruction. Include in your discussion:
        - Prognosis of their cancer and
        - Advantages and disadvantages of the treatment options, including best supportive care.
    - Consider percutaneous nephrostomy or retrograde stenting (if technically feasible) for people with locally advanced or metastatic bladder cancer and ureteric

obstruction who need treatment to relieve pain, treat acute kidney injury or improve renal function before further treatment.
    - If facilities for percutaneous nephrostomy or retrograde stenting are not available at the local hospital, or if these procedures are unsuccessful, discuss the options with a specialist urology multidisciplinary team for people with bladder cancer and ureteric obstruction.
- Intractable bleeding
    - Evaluate the cause of intractable bleeding with the local urology team.
    - Consider hypofractionated radiotherapy or embolisation for people with intractable bleeding caused by incurable bladder cancer.
    - If a person has intractable bleeding caused by bladder cancer and radiotherapy or embolisation are not suitable treatments, discuss further management with a specialist urology multidisciplinary team.
- Pelvic pain
    - Evaluate the cause of pelvic pain with the local urology team.
    - Consider, in addition to best supportive care, 1 or more of the following to treat pelvic pain caused by incurable bladder cancer:
        - Hypofractionated radiotherapy if the person has not had pelvic radiotherapy
        - Nerve block
        - Palliative chemotherapy.

EFFICACY and SAFETY

Trial	DANUBE, NCT02516241, EudraCT-2015-001633-24; Adults aged 18 years and above; durvalumab monotherapy vs durvalumab in combination with tremelimumab vs standard of care chemotherapy; phase III
Sponsor	AstraZeneca Plc
Status	Ongoing, not reported.
Source of Information	Trial registry[7, 8]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active control, open-label trial
Participants	n=1005; aged 18 years and older; patients with histologically or cytologically documented, unresectable, Stage IV transitional cell carcinoma of the urothelium who have not been previously treated with first-line chemotherapy.
Schedule	Participants are randomized into three arms in a 1:1:1 ratio: 1) Experimental (Durvalumab Monotherapy): Subjects undergo treatment with durvalumab at a dose of 1500 mg every 4 weeks for up to 12 months

	2) Experimental (Durvalumab in combination with tremelimumab): Subjects undergo treatment with durvalumab at a dose of 1500 mg through IV infusion and doses of tremelimumab 75 mg IV for four times per week, followed by durvalumab 1500 mg IV every 4 weeks for up to 12 months 3) Active comparator (Standard of care): Subjects undergo treatment with standard of care includes cisplatin, carboplatin and gemcitabine through IV infusion for up to 6 months 6 cycles)
Follow-up	Two years
Primary Outcomes	Progression-Free Survival (PFS) and Overall Survival (OS) in patients with Urothelial Cancer (UC) [Time Frame: Up to 4 years]
Secondary Outcomes	The efficacy of durvalumab monotherapy compared to SoC in terms of PFS and OS in patients with UC [Time Frame: 4 years] Health related quality of life (HRQoL) in patients treated with durvalumab + tremelimumab or durvalumab compared to SoC using the Functional Assessment of Cancer Therapy - Bladder Cancer (FACT-BL) questionnaire [Time Frame: 4 years] The pharmacokinetics (PK) - Peak concentration (Cmax) of durvalumab + tremelimumab combination therapy and durvalumab monotherapy [Time Frame: up to 6 months] The pharmacokinetics (PK) - Trough concentration (Ctrough) of durvalumab + tremelimumab combination therapy and durvalumab monotherapy [Time Frame: up to 6 months] The immunogenicity of durvalumab and tremelimumab combination therapy and durvalumab monotherapy [Time Frame: 4 years] The efficacy of durvalumab + tremelimumab combination therapy compared to SoC in terms of Objective Response Rate (ORR) [Time Frame: 4 years] The efficacy of durvalumab monotherapy compared to SoC in terms of ORR [Time Frame: 4 years] The safety and tolerability profile of durvalumab + tremelimumab combination therapy and durvalumab monotherapy compared to SoC will be determined using vital signs, laboratory data, electrocardiograms (ECGs), and physical examination [Time Frame: 4 years]

Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated Primary completion date: April 2018 Estimated completion date: July 2019

ESTIMATED COST and IMPACT

COST

The cost of durvalumab in combination with tremelimumab is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services (increased treatment duration compared to chemotherapy)

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other

☐ None identified

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