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Newcastle University

Health Technology Briefing
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Durvalumab with gemcitabine-cisplatin neoadjuvant treatment and durvalumab adjuvant treatment for muscle-invasive bladder cancer

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27013	NICE ID: 10554	UKPS ID: 665475

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Neoadjuvant treatment of durvalumab in combination with gemcitabine-cisplatin and adjuvant treatment of durvalumab alone are currently in clinical development for patients with muscle-invasive bladder cancer (MIBC). Bladder cancer is where 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 referred to as MIBC. However, limited treatment options exist for patients with MIBC.

Durvalumab is a type of protein designed to recognise and attach to a protein called 'programmed death-ligand 1' (PD-L1), which is present on the surface of many cancer cells. PD-L1 acts to switch off immune cells that would otherwise attack the cancer cells. Durvalumab is administered intravenously (IV). Durvalumab increases the ability of the immune system to attack the cancer cells and thereby slow down the progression of the disease. Furthermore, multiple studies have demonstrated that blocking PD-L1 result in encouraging rates of anti-tumour activity in patients with metastatic urothelial cancer (a type of bladder cancer) who had disease progression following standard chemotherapy. Therefore, if licensed, durvalumab will offer an additional treatment option for patients with MIBC.

Proposed Indication

Neoadjuvant treatment (durvalumab in combination with gemcitabine-cisplatin) and adjuvant treatment (durvalumab alone) for patients with muscle-invasive bladder cancer (MIBC).[1]

Technology

Description

Durvalumab (Imfinzi, MEDI4736) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed cell death ligand-1 (PD-L1) and CD80. Expression of PDL1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation.[2]

Durvalumab in combination with gemcitabine-cisplatin (neoadjuvant treatment) and durvalumab alone (adjuvant treatment) is currently in phase III clinical development for patients with MIBC. In the phase III clinical trial NIAGARA (NCT03732677), participants were randomised to neoadjuvant durvalumab in combination with gemcitabine-cisplatin followed by adjuvant durvalumab (Arm 1) or neoadjuvant gemcitabine-cisplatin (Arm 2).[1,3]

Key Innovation

Durvalumab attaches to PD- L1, which acts to switch off immune cells that would otherwise attack the cancer cells, and thus by blocking its effects, durvalumab increases the ability of the immune system to attack the cancer cells and thereby slow down the progression of the disease.[4]

Furthermore, multiple studies have demonstrated that blocking PD-L1 result in encouraging rates of anti-tumour activity in patients with metastatic urothelial cancer (a type of bladder cancer) who had disease progression following standard chemotherapy.[5] Therefore, if licensed, durvalumab will offer an additional treatment option for patients with MIBC.

Regulatory & Development Status

Durvalumab as monotherapy is licensed for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. It is also approved in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).[2]

Durvalumab is in phase III/II clinical development for several indications, some of which include:[6]

- Non-small cell lung cancer
- SCLC
- Bladder cancer
- Ovarian cancer
- Urothelial cancer

Patient Group

Disease Area and Clinical Need

Bladder cancer is where 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 referred to

as muscle-invasive bladder cancer (MIBC) (or invasive bladder cancer). Bladder cancer 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, bladder infections and chronic bladder irritation, diet and alcohol intake, previous bladder cancer, and family history.[8] The most common symptom of bladder cancer is blood in urine that is usually painless. Less common symptoms of bladder cancer include a need to urinate on a more frequent basis, sudden urges to urinate, and a burning sensation when passing urine.[7]

Bladder cancer accounted for 3% of all new cancer cases in 2016-2018 in the UK.[9] In England in 2017, newly diagnosed registered cases of malignant neoplasms of bladder (ICD 10 code: C67) were 8,686 and directly age standardised incidence rate in males was 27.6 per 100,000 and in females was 8.2 per 100,000.[10] Bladder cancer incidence rates are projected to fall by 34% in the UK between 2014 and 2035, to 13 cases per 100,000 people by 2035.[11] At diagnosis, 30% of bladder cancers are MIBC.[12] This would be equivalent to 2,605 of the newly diagnosed cases in England in 2017. In 2020-21, there were 52,437 hospital admissions and 30,679 day cases (ICD 10 code: C67) in England for malignant neoplasm of bladder.[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
- 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	**NIAGARA, NCT03732677, EudraCT 2018-001811-59;** A Phase III, Randomized, Open-Label, Multi-Center, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With Gemcitabine+Cisplatin for Neoadjuvant Treatment Followed by Durvalumab Alone for Adjuvant Treatment in Patients With Muscle-Invasive Bladder Cancer. **Phase III** - Active, not recruiting **Location(s):** Eight EU countries, UK, USA, Canada and other countries **Primary completion date:** June, 2023
Trial Design	Randomised, parallel assignment, open-label
Population	N= 1063 (actual); adults (18 years and older) with resectable muscle-invasive bladder cancer with clinical stage T2-T4aN0/1M0 with transitional and mixed transitional cell histology
Intervention(s)	Durvalumab with gemcitabine- cisplatin
Comparator(s)	Gemcitabine- cisplatin
Outcome(s)	Primary outcome measures:

	• Pathologic complete response rates at time of cystectomy [time frame: up to 6 months] • Event-free survival per central review defined as time from randomisation to event [time frame: up to 48 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	NCT03912818; Phase 2 Open Label Study of Durvalumab With Neoadjuvant Chemotherapy in Variant Histology Bladder Cancer **Phase II** - Active, not recruiting **Location(s):** USA **Primary completion date:** September, 2022
Trial Design	Non-randomised, parallel assignment, open-label
Population	N= 24 (estimated); adults (18 years and older) who have Eastern Collaborative Oncology Group (ECOG) performance status score of 0 or 1; histologically proven carcinoma of the bladder
Intervention(s)	• Durvalumab (IV) at 1500 mg fixed dose administered over 60 minutes • Cisplatin (IV) 70 mg/m2 on cycle day 2 • Gemcitabine 1,000 mg/m2 on cycle day 1 and day 8 • Cystectomy within 6 weeks
Comparator(s)	• Durvalumab (IV) at 1500 mg fixed dose administered over 60 minutes • Carboplatin (IV) AUC 5 on cycle day 1 • Gemcitabine (IV) 1,000 mg/m2 on cycle day 1 and day 8 • Cystectomy within 6 weeks
Outcome(s)	Primary outcome measure: incidence of grade 3-5 adverse events [time frame: at 120 days] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Durvalumab is already marketed in the UK for various indications; a 120mg/2.4ml concentrate for solution for infusion vial costs £592.00 and a 500mg/10ml concentrate for solution for infusion vial costs £2,466.[15]

Relevant Guidance

NICE Guidance

- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.

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 Society for Medical Oncology (ESMO). Bladder Cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. November 2021.[16]
- European Association of Urology (EAU). EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS). March 2021.[17]
- Official Journal of the National Comprehensive Cancer Network (JNCCN). Bladder Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. March 2020.[18]

Additional Information

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