NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Durvalumab with Bacillus Calmette-Guerin for treating non-muscle invasive bladder cancer

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24212	NICE ID: 10737	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Durvalumab is in clinical development for the treatment of non-muscle invasive bladder cancer (NMIBC). Bladder cancer is when cancerous cells develop in the lining of the bladder. NMIBC is the most common type of bladder cancer and is categorised by risk. High risk NMIBC is when cancerous cells are likely to persist or return after treatment, this means people with this type might require additional treatment and monitoring. Current treatment for patients with high risk NMIBC is surgery to remove the bladder and a course of the Bacillus Calmette-Guerin (BCG) vaccine. NMBIC recurrence rate is high when treated with BCG alone, and surgical removal of the bladder is an invasive procedure.

Durvalumab is in clinical development as a combination therapy with BCG, and it is designed to attach to a protein called programmed death-ligand 1 (PD-L1) which is found on the surface of many cancer cells. PD-L1 acts to switch off immune cells that would otherwise attack the cancer cells. By attaching to PD-L1 and 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. Durvalumab is administered intravenously every four weeks. If licenced, durvalumab in addition to BCG will offer an additional first line treatment option, which could reduce recurrence rate compared to BCG alone, for patients with high risk NMIBC.

Proposed Indication

Adult patients who are Bacillus Calmette-Guerin (BCG) naïve and with a histologically confirmed high-risk non-muscle invasive bladder cancer (NMIBC) who have undergone complete resection of papillary tumours.[1]

Technology

Description

Durvalumab (Imfinzi) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Selective blockade of PD-L1/PD1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation. Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals and can be expressed on both tumour cells and tumour-associated immune cells in the tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80. By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production.[2]

Durvalumab is in clinical development for induction and maintenance treatment of adults with high risk, BCG-naïve NMIBC. In the phase III clinical trial (POTOMAC, NCT03528694), participants received durvalumab 1500mg via intravenous (IV) infusion once every 4 weeks for 13 cycles in addition to BCG induction therapy six times per week via instillation, followed by 2 years of BCG maintenance therapy (3 doses given once per week, on the first week of month 3, 6, 12, 18 and 24). Participants could also be assigned to receive durvalumab in addition to BCG as an induction therapy only.[1]

Key Innovation

Durvalumab with BCG is a combination therapy that combines a PD-L1 human monoclonal antibody concurrently administered with standard of care intravesical BCG. PD-L1 inhibition with durvalumab in combination with other immunotherapies, including standard of care BCG, may improve response rate and duration of tumour response. The rates of recurrence in NMIBC with BCG alone are 50% in the first 3 years.[1]

Regulatory & Development Status

Durvalumab is licensed in EU/UK for the following indications:[2]

- As a monotherapy 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.
- 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).

Durvalumab as a monotherapy and in addition to various other medicinal products is in phase II and phase III clinical development for indications including but not limited to, biliary tract neoplasms, solid tumours and haematological malignancies.[3]

Patient Group

Disease Area and Clinical Need

Bladder cancer is the growth of cancerous cells within the bladder. If the growth of these cells is contained within the lining of the bladder, this is described as NMIBC, whereas if the cells spread beyond the lining into the surrounding bladder muscle, this is muscle-invasive bladder cancer (MIBC). NMIBC is the most common type of bladder cancer. The most prevalent symptom of bladder cancer is blood in the urine, which is often painless. Causes include exposure to harmful substances, with tobacco smoke accounting for more than 1 in 3 cases of bladder cancer.[4] NMIBC is divided into three risk groups: low, intermediate (medium) and high. High risk NMIBC means the cancer is most likely to spread or return after treatment, so may require more treatment and closer monitoring.[5] NMIBC patients have a significantly lower quality of life (QoL) compared with the general population, especially in fatigue, physical and role functioning, and mental health.[6]

Approximately 75% of bladder cancers are NMIBC.[7] From this estimate, in England (2020-21), there were approximately 42,052 finished consultant episodes (FCE) for NMIBC within the malignant neoplasm of bladder categorisation (ICD-10 C67), accounting for 39,328 hospital admissions, 23,009 day cases and 54,815 FCE bed days.[8]

In 2020, in England and Wales, there were 5,054 deaths (3,495 male and 1,559 female) caused by malignant neoplasm of bladder (ICD-10 C67). With a crude total death rate of 11.8 per 100,000 in men, and 5.2 per 100,000 in women.[9]

Recommended Treatment Options

The currently recommended treatments for high risk NMIBC are transurethral resection of a bladder tumour (TURBT), cystectomy (operation to remove the bladder), and a course of BCG.[4,10]

Clinical Trial Information

Trial	**POTOMAC; NCT03528694, 2017-002979-26;** A Phase III Randomized, Open-Label, Multi-Center, Global Study of Durvalumab and Bacillus Calmette-Guerin (BCG) Administered as Combination Therapy Versus BCG Alone in High-Risk, BCG Naïve Non-Muscle Invasive Bladder Cancer Patients **Phase III –** Active, not recruiting **Location(s):** 8 EU countries, UK , Canada, Australia, Russia and Japan **Primary completion date:** October 2024
Trial Design	Randomised, open label, parallel assignment.
Population	N=1020 (actual); aged 18-130 years old; BCG-naïve high risk bladder cancer; complete resection of all papillary disease; no prior exposure to radiotherapy or immunotherapy
Intervention(s)	• Durvalumab plus BCG (induction + maintenance):

	1500mg durvalumab every 4 weeks for 13 cycles, BCG induction (6 times every 1 week instillation) and 2 years of maintenance (3 doses every 1 week at 3, 6, 12, 18, and 24 months)[1] • Durvalumab plus BCG (induction only): 1500mg durvalumab every 4 weeks for 13 cycles, and BCG induction (6 times every 1 week instillation)[1]
Comparator(s)	BCG therapy
Outcome(s)	**Primary outcome measures:** The efficacy of Durvalumab + BCG (induction plus maintenance) combination therapy compared to SoC in terms of Disease-free survival (DFS) in patients with NMIBC [Time Frame: Up to 4 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Durvalumab 500mg/10ml concentrate for solution for infusion vials (POM) has an NHS indicative price of £2466.00.[11]

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.[12]
- European Association of Urology (EAU). EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS). March 2021.[13]

Additional Information

AstraZeneca UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 Santis MD, Abdrashitov R, Hegele A, Kolb M, Parker S, Redorta JP, et al. A phase III, randomized, open-label, multicenter, global study of durvalumab and bacillus calmette-guérin (BCG) versus BCG alone in high-risk, BCG-naïve non-muscle-invasive bladder cancer (NMIBC) patients (POTOMAC). *Journal of Clinical Oncology*. 2019;37(7_suppl):TPS500-TPS. Available from: https://doi.org/10.1200/JCO.2019.37.7_suppl.TPS500.

2 Electronic Medicines Compendium (emc). *Imfinzi 50 mg/mL concentrate for solution for infusion.* 2021. Available from: https://www.medicines.org.uk/emc/product/9495 [Accessed 16 Dec 2021].

3 Clinicaltrials.gov. *Phase II/III clinical development for durvalumab.* Available from: https://clinicaltrials.gov/ct2/results?term=durvalumab%2C+AstraZeneca&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 16 Dec 2021].

4 NHS. *Bladder cancer - Overview.* 2021. Available from: https://www.nhs.uk/conditions/bladder-cancer/ [Accessed 16 Dec 2021].

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6 Jung A, Nielsen ME, Crandell JL, Palmer MH, Bryant AL, Smith SK, et al. Quality of Life in Non-Muscle-Invasive Bladder Cancer Survivors: A Systematic Review. *Cancer Nursing*. 2019;42(3):E21-E33. Available from: https://doi.org/10.1097/ncc.0000000000000606.

7 European Association of Urology (EAU). *EAU Guidelines Non-muscle-invasive Bladder Cancer presented at the EAU Annual Congress Milan 2021 (ISBN 978-94-92671-13-4)*. Last Update Date: Available from: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/#3 [Accessed 04 Jan 2022].

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9 Office for National Statistics (ONS). *Deaths registered in England and Wales, 2020 edition.* 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables [Accessed 16 Dec 2021].

10 National Institute for Health and Care Excellence (NICE). *Bladder cancer: diagnosis and management - Treating non-muscle-invasive bladder cancer (NG2)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ng2/ifp/chapter/treating-non-muscle-invasive-bladder-cancer [Accessed 16 Dec 2021].

11 British National Formulary (BNF). *Durvalumab solution for infusion.* Available from: https://bnf.nice.org.uk/medicinal-forms/durvalumab.html [Accessed 16 Dec 2021].

12 Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Loriot Y, et al. Bladder Cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*. 2021 2021/11/30/. Available from: https://doi.org/10.1016/j.annonc.2021.11.012.

13 European Association of Urology (EAU). *EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS)* Last Update Date: Mar 2021. Available from: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Non-muscle-invasive-Bladder-Cancer-TaT1-2021V2.pdf [Accessed 16 Dec 2021].

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