AstraZeneca: Leading the science of immunotherapy in bladder cancer

Immunotherapy is becoming the cornerstone for oncology therapeutics with agents now approved or being considered for approval across an array of different tumours. Immunotherapeutic agents, through their ability to inhibit a tumour's evasion of the body's immune system lead to the enhancement of immune-mediated antitumour response. AstraZeneca , and its global biologics research and development arm, MedImmune, is developing new immunotherapeutic approaches as part of its clinical development programme that targets both the immune system and the tumour microenvironment. AstraZeneca's clinical research programme aims to identify novel immunotherapy targets and develop treatment approaches that combine different immunotherapies, each with a unique mechanism of action with the goal of providing precision medicine options for clinicians and patients.

Immunotherapy for bladder cancer

Despite being the sixth most common cancer in the United States[1], research for novel treatments for bladder cancer has been neglected. Recent research has led to a resurgence of interest in both the pathogenesis and treatment of bladder cancer resulting in drug approvals of immunotherapy agents. Immunotherapy offers a promising alternative to chemotherapy for bladder cancer.

Bladder cancer is a logical target for immunotherapy as it is characterized by a high tumour mutational burden that is thought to result in increased neoantigen expression, which may aid the immune system in recognizing and mounting an immune response to the tumour. Early evidence of the potential effectiveness of immunotherapy treatment in bladder cancer can be found by use of Bacillus Calmette-Guérin vaccine in non–muscle invasive bladder cancer, which appears to achieve its effect by activating a local antitumour immune reaction.

Metastatic bladder cancer is uniformly a fatal disease with a 5-year survival rate of 5% and the mortality rate in the United States remaining unchanged for more than 20 years[1]. Platinum-based chemotherapy containing cisplatin is the preferred first-line therapy for patients with inoperable locally advanced or metastatic bladder cancer with a median overall survival of 14–16 months[2]. However, when patients progress despite receiving platinum-containing chemotherapy, the median overall survival decreases to 5–7 months[3].

Checkpoint inhibitors in bladder cancer

AstraZeneca's late-stage immunotherapy research has been directed at potentiating the ongoing or existing antitumour response through the use of checkpoint inhibitors. Programmed death ligand 1 (PD-L1), expressed on a variety of normal cells, binds to programmed death 1 (PD-1) to inhibit effector T-cell activity, and reverses T-cell exhaustion. Tumour cells can increase expression of PD-L1 and evade the cytotoxic effect of tumour-directed T cells[4]. Durvalumab, AstraZeneca's PD-L1 inhibitor, was approved for previously treated patients ,which blocks the interaction of PD-L1 with PD-1 and CD80. with locally advanced or metastatic bladder cancer based on its clinical activity and survival benefits shown in the bladder cohort of study 1108, an ongoing phase 1/2 clinical trial in advanced solid tumours [5].

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), another checkpoint inhibitor, is a negative regulatory receptor that prevents T-cell activation and suppresses the tumour immune response via CTLA-4-expressing regulatory T cells (Tregs) [4]. Both CTLA-4 and PD-L1 may bind to CD80 on antigen-presenting cells and reduce CD80's ability to activate T cells through binding to CD28. Tremelimumab is a CTLA-4 inhibitor also being developed by AstraZeneca as an immunotherapeutic agent that enhances T-cell activation, amplifies T-cell proliferation and promotes differentiation into memory T cells.

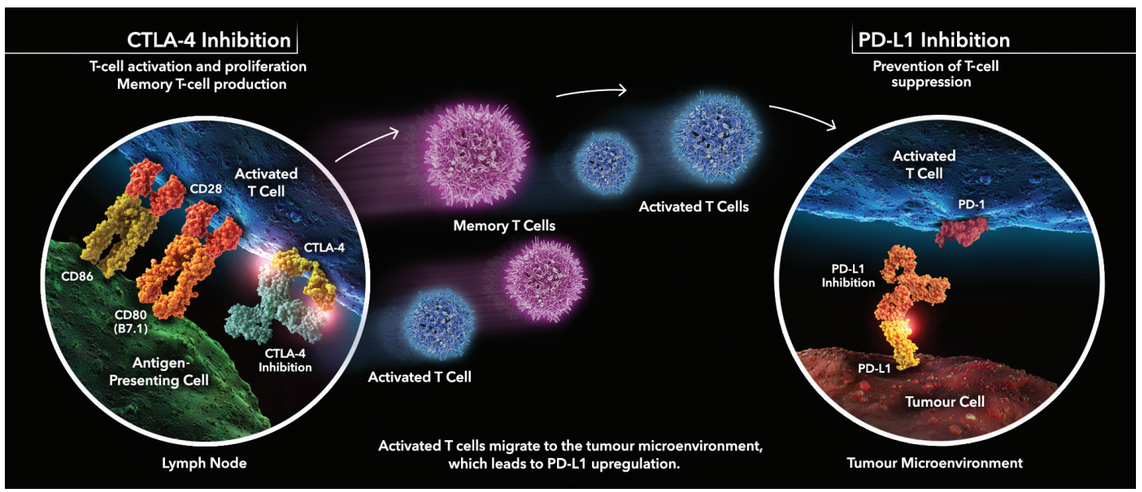

Figure 1. Disrupting the non-redundant PD-1/PD-L1 and CTLA-4 pathways may have complementary biological effects by acting at different stages of the antitumour response. APC = antigen-presenting cell; CTLA-4 = T-lymphocyte-associated protein 4; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1.

Rational, combinatory immunotherapy for bladder cancer

By combining different therapeutic agents, AstraZeneca can take advantage of different mechanisms of action that disrupt non-redundant pathways to inhibit complementary immunosuppressive pathways, resulting in synergistic immune effects with the potential for enhanced treatment outcomes. The DANUBE trial is examining the simultaneous inhibition of PD-L1 and CTLA-4 pathways in a phase 3, randomized, open-label, multicentre, global study (NCT02516241). DANUBE compares both durvalumab + tremelimumab and durvalumab monotherapy to standard platinum-based combination chemotherapy in treatment-naive patients with unresectable, stage IV transitional cell carcinoma of the urothelium.

Currently, the only commercially available biomarker in bladder cancer is PD-L1. Testing for PD-L1 expression may aid clinicians to predict response to PD-1/PD-L1 immunotherapies and help establish treatment expectations with patients. Other putative biomarkers, such as interferon-γ expression signature, are being explored to help develop assays to identify patients with bladder cancer who are most likely to benefit from immunotherapeutic approaches. The continuing identification of new biomarkers will enhance the selection of therapeutic regimens that will enable clinicians to offer each specific patient (or patient subpopulation) the most beneficial treatment. AstraZeneca is currently conducting BISCAY, a phase 1b, biomarker-directed, modular, open-label, randomized multi-arm study to evaluate durvalumab and small molecule targeted therapies in patients with metastatic muscle-invasive bladder cancer (NCT02546661). Patients are assigned to the appropriate study module based on specific gene mutations in the tumours relevant to the compounds under investigation. One module pairs durvalumab with AZD4547, which is a potent, selective FGFR-1, -2, and -3 tyrosine kinase inhibitor for patients with *FGFR3* mutation or *FGFR1, 2, 3* fusion. Another module studies durvalumab combined with olaparib, a PARP-1, -2, and -3 inhibitor with activity in cancers with *ATM* and/or *BRCA1/2* alterations that affect DNA repair. Patients with *MYC/MYCL1/MYCN/CCNE* amplification, *CKDN2A*, and/or *RB1* alteration will be assigned to a module that adds AZD1775, a Wee1 protein tyrosine kinase inhibitor, to durvalumab.

AstraZeneca's commitment to immunotherapy

AstraZeneca's clinical programme has three therapeutic aims: priming a new antitumour immune response; potentiating an existing antitumour response; and reversing tumour suppression during antitumour responses. Each aim addresses specific tumour immunologic states with the goal of achieving a highly active and sustained antitumour immune response (see Figure 2).

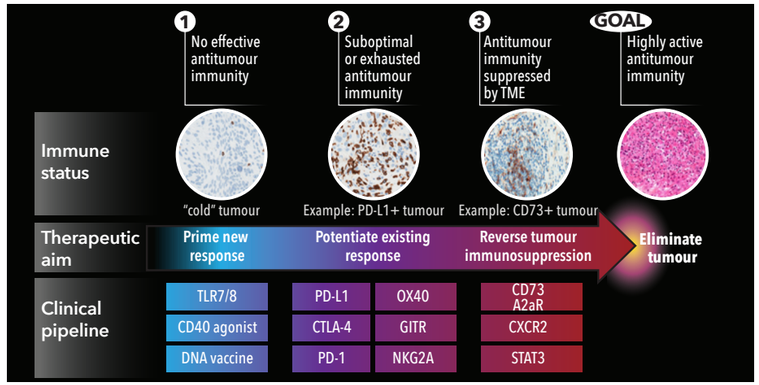

Figure 2. AstraZeneca's clinical development pipeline for immunotherapies spans key immune tumour states to enhance antitumour immunity by generating new immune responses against tumours, sustaining ongoing immune responses, and reversing immune suppression within the tumour microenvironment.
A2aR = adenosine A2A receptor; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; GITR = glucocorticoid-induced (tumour necrosis factor receptor) related protein; NK = natural killer; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; STAT = signal transducer and activator of transcription; TME = tumour microenvironment; TLR = Toll-like receptor.

In a "cold" tumour, in which there is little or no antitumour immune activity, it is crucial to initiate T-cell activation to induce a new immune response against the tumour. MEDI9197, targets the Toll-like receptor 7/8 (TLR-7/8), and activates predominantly dendritic cells to create a pro-inflammatory tumour microenvironment supporting the antitumour response. MEDI9197 is being studied in combination with durvalumab as a part of a phase 1 safety and tolerability trial in patients with solid tumours or cutaneous T-cell lymphoma (NCT02556463). Another agent, MEDI4920, stimulates CD40 to activate dendritic cells, promoting antigen-presentation and priming of T cells.

MEDI0562, an agonist of OX40, a molecule expressed by both CD4 and CD8 T cells, is being developed to strengthen T-cell activation, as well as possibly impair inhibitory Tregs. MEDI0562 is being studied in combination with durvalumab, as well as with tremelimumab, as part of a phase 1 study evaluating safety and antitumour activity in patients with solid tumours (NCT02705482). NKG2A is expressed predominately on natural killer (NK) cells, and reduces the cytotoxic activity of these cells. IPH2201 will inhibit NKG2A is being tested to maintain NK cell functions within the tumour microenvironment. Reversing tumour immunosuppression is key for sustained antitumour activity. MEDI9447 will block CD73, a cell-surface 5'-nucleotidase that increases extracellular levels of adenosine, which can impair T-cell effector function including NK cell activity, is being evaluated to reduce immunosuppression within the tumour.

By harnessing the power of four scientific platforms–Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response, and Antibody Drug Conjugates–AstraZeneca together with its global biologics research and development arm MedImmune, is championing the development of personalized oncology combinations. This demonstrable commitment to bladder cancer is highlighted by its expansive and robust clinical trial programme that will help redefine the treatment of bladder cancer. AstraZeneca is advancing new, innovative therapies that will deliver deeper and more durable responses for patients and significantly reduce early mortality in bladder cancer.

Authors:

Ashok K. Gupta, MBBS, MD, PhD, Vice President, Immuno-Oncology Clinical Development

Marnie L. Boron, PharmD, Director, Medical Alignment, Immuno-Oncology

Doris Makari, MD, Senior Medical Director, Immuno-Oncology, US Medical Affairs

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