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 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, 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(46,537),(93,573) of 5% and the mortality rate in the United States remaining unchanged for more than 20 years. Platinum-based chemotheraphy 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. However, when patients progress despite receiving platinum-containing chemotherapy, the median overall survival decreases to 5-7 months.

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-1) expressed on a variety of normal and tumour-infiltrating immune cells, binds to programmed death 1 (PD-1) on T cells 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. 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 1180, an ongoing phase 1/2 clinical trial in advanced solid tumours.

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). Both CTLA-4 and PD-L1 may bind to CD80 on antigen-presenting cells and reduce the ability to activate T cells through binding to CD80. Tregmimumab 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 pathway may have complementary biological effects by acting at different stages of the antitumour response: 4PCL = antigen-presenting cell; CTLA-4 + T lymphocyte-associated protein 4; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1.

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 overcoming tumour evasion within the tumour microenvironment. A2AR = adenosine A2A receptor; CTLA-4 = cytotoxic T lymphocyte-associated protein 4; GPR1 = 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.

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 efficacious treatments (or patient subpopulation) the most beneficial treatment. AstraZeneca is currently conducting BSC05, a phase 1b, biomarker-directed, modified, open-label, parallel-group, multi-arm study to evaluate durvalumab and small molecule targeted therapies in patients with metastatic muscle-invasive bladder cancer (NCT02546611). Patients are assigned to the appropriate study module based on specific gene mutations in the tumours relevant to the compounds under investigation. One module develops new immunotherapeutic approaches for patients with PD-L1 expression signature, are being explored to help develop cancer (NCT02546611). Patients are assigned to the appropriate study module based on specific gene mutations in the tumours relevant to the compounds under investigation. One module develops new immunotherapeutic approaches for patients with PD-L1 expression signature, are being explored to help.