AstraZeneca's Imfinzi (durvalumab) receives US FDA accelerated approval for previously treated patients with advanced bladder cancer

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Approval granted regardless of PD-L1 status, based on tumour response rate and duration of response

Imfinzi is the cornerstone in an extensive Immuno-Oncology programme across multiple cancer types and stages of disease

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AstraZeneca and its global biologics research and development arm, MedImmune, today announced that the US Food and Drug Administration (FDA) has granted accelerated approval to *Imfinzi* (durvalumab). *Imfinzi* is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who have disease progression during or following platinum-containing chemotherapy, or whose disease has progressed within 12 months of receiving platinum-containing chemotherapy before (neoadjuvant) or after (adjuvant) surgery. *Imfinzi* is approved under the FDA's accelerated approval pathway, based on tumour response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Pascal Soriot, Chief Executive Officer of AstraZeneca, said: "We are excited to offer *Imfinzi* as a breakthrough therapy for patients with locally-advanced or metastatic bladder cancer. *Imfinzi* is the cornerstone of our extensive Immuno-Oncology programme, in development across many tumour types, as monotherapy and in combination. This first approval for *Imfinzi* is an important milestone in our return to growth and brings us another step closer to our goal of redefining the way cancer is treated."

Imfinzi is also under investigation in the Phase III DANUBE trial as 1st- line treatment in urothelial carcinoma as monotherapy and in combination with tremelimumab.

Nicholas J. Vogelzang, MD, FACP, FASCO, Clinical Professor at the University of Nevada School of Medicine; SWOG GU Vice Chair; US Oncology Research GU Chair; Comprehensive Cancer Centers of Nevada, said: "The usual course of treatment for patients with advanced bladder cancer begins with a standard platinum-containing chemotherapy. Patients who have disease progression during or following chemotherapy are left with few other treatment options. The approval of *Imfinzi* to treat this population of select patients signifies hope for those who are currently suffering, or may find themselves with limited options in the future."

The recommended dose of *Imfinzi* is 10 mg/kg body weight administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity.

The accelerated FDA approval of *Imfinzi*, a human monoclonal antibody that blocks PD-L1, is based on data from Study 1108. This Phase I/II trial evaluated the safety and efficacy of *Imfinzi* in patients with locally-advanced or metastatic urothelial carcinoma of the bladder. Patients had progressed while on or after a platinum-containing chemotherapy, including those who progressed within 12 months of receiving therapy in a neoadjuvant or adjuvant setting.

In the trial, *Imfinzi* demonstrated rapid and durable responses, with an objective response rate (ORR) of 17.0% (95% confidence interval [CI]: 11.9; 23.3) in all evaluable patients, regardless of PD-L1 status, and 26.3% (95% CI: 17.8; 36.4) in patients with PD-L1 high-expressing tumours (as determined by the VENTANA PD-L1 (SP263) Assay, Ventana Medical Systems Inc., a member of the Roche Group). PD-L1 high was defined as ≥25% of tumour cells (TC) or tumour-infiltrating immune cells (IC) expressing membrane PD-L1 if ICs involved >1% of the tumour area, or TC≥25% or IC=100% if ICs involved ≤1% of the tumour area. Additionally, approximately 14.3% of all evaluable patients achieved partial response and 2.7% achieved complete response. Of patients who had received only neoadjuvant or adjuvant therapy prior to trial entry, 24% (n=9) responded. Based on a secondary endpoint in this single-arm trial, median time to response was six weeks. Among the total 31 responding patients, 14 patients (45%) had ongoing responses of six months or longer and five patients (16%) had ongoing responses of 12 months or longer.

Efficacy results for Study 1 (bladder cancer cohort of Study 1108

	All Patients (N=182)	**PD-L1 High (N=95)**	**PD-L1 Low/Negative (N=73)**	**PD-L1 Not Evaluable (N=14)**
Objective Response Rate (ORR) by BICR*, n (%) (95% confidence interval [CI])	31 (17.0%) (11.9; 23.3)	25 (26.3%) (17.8; 36.4)	3 (4.1%) (0.9; 11.5)	3 (21.4%) (4.7; 50.8)

	All Patients (N=182)	**PD-L1 High (N=95)**	**PD-L1 Low/Negative (N=73)**	**PD-L1 Not Evaluable (N=14)**
Complete Response (CR)	5	3	1	1
Partial Response (PR)	26	22	2	2
Median Duration of Response (DoR), months (range)	Not reached (0.9+; 19.9+)	Not reached (0.9+; 19.9+)	12.3 (1.9+; 12.3)	Not reached (2.3+; 2.6+)
*BICR=Blinded Independent Central Review + Denotes a censored value				

Patients should be monitored for immune-mediated adverse reactions including pneumonitis, hepatitis, colitis, endocrinopathies (including adrenal insufficiency, hypophysitis, or Type 1 diabetes mellitus), nephritis, rash, thrombocytopenic purpura, infection, infusion-related reactions, or embryo-fetal toxicity. Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions (>2%) were acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain, and pyrexia/tumour associated fever (2.7% each). Eight patients (4.4%) who were treated with *Imfinzi* experienced Grade 5 adverse events of cardiorespiratory arrest, general physical health deterioration, sepsis, ileus, pneumonitis, or immune-mediated hepatitis. Three additional patients were experiencing infection and disease progression at the time of death. *Imfinzi* was discontinued for adverse reactions in 3.3% of patients.

Clinical trials have demonstrated that patients with PD-L1 high-expressing tumours have a higher likelihood of response through blockade of the PD-1/PD-L1 pathway. PD-L1 expression testing may be a useful tool to help guide physicians in their treatment decisions, but it is not required for use of *Imfinzi*.

NOTES TO EDITORS

About *Imfinzi (durvalumab)*

Imfinzi (durvalumab, previously known as MEDI4736) is a human monoclonal antibody directed against PD-L1, which blocks the interaction of PD-L1 with PD-1 and CD80.

Durvalumab is also being tested in the 1st-line treatment of patients with unresectable and metastatic bladder cancer as a monotherapy and in combination with tremelimumab, a checkpoint inhibitor that targets CTLA-4, as part of the DANUBE Phase III trial, which had the last patient commenced dosing during the first quarter of 2017 (global trial, excluding China). Additional clinical trials are ongoing to investigate durvalumab as monotherapy or in combination in multiple solid tumours and blood cancers.

About bladder cancer

Urothelial bladder cancers arise from the epithelium of the bladder and are the ninth most common form of cancer worldwide. It is estimated that in 2016, about 430,000 people were diagnosed with bladder cancer around the world and 165,000 did not survive. Metastatic bladder cancer remains an area of unmet medical need in particular; among patients treated with standard-of-care chemotherapy, the five-year survival rate is below 15%.

The tumour microenvironment of urothelial carcinoma (UC) significantly impairs lymphocyte function, helping the cancer to evade immune detection by exploiting inhibitory checkpoint pathways, such as PD-L1/PD-1. PD-L1 is widely expressed in tumour and immune cells in UC patients and helps tumours to evade detection from the immune system through binding to the PD-1 receptor on cytotoxic T lymphocytes.

About AstraZeneca's approach to Immuno-Oncology (IO)

Immuno-Oncology (IO) is a therapeutic approach designed to stimulate the body's immune system to attack tumours. At AstraZeneca and MedImmune, our biologics research and development arm, our IO portfolio is anchored by immunotherapies that have been designed to overcome anti-tumour immune suppression. We believe that IO-based therapies will offer the potential for life-changing cancer treatments for the vast majority of patients.

We are pursuing a comprehensive clinical trial program that includes durvalumab (anti-PD-L1) monotherapy and in combination with tremelimumab (anti-CTLA-4) in multiple tumour types, stages of disease, and lines of therapy, using the PD-L1 biomarker as a decision-making tool to define the best potential treatment path for a patient. In addition, the ability to combine our IO portfolio with small, targeted molecules from across our oncology pipeline, and with those of our research partners, may provide new treatment options across a broad range of tumours.

About AstraZeneca in Oncology

AstraZeneca has a deep-rooted heritage in Oncology and offers a quickly growing portfolio of new medicines that has the potential to transform patients' lives and the Company's future. With at least six new medicines to be launched between 2014 and 2020, and a broad pipeline of small molecules and biologics in development, we are committed to advance New Oncology as one of AstraZeneca's five Growth Platforms focused on lung, ovarian, breast and blood cancers. In addition to our core capabilities, we actively pursue innovative partnerships and investments that accelerate the delivery of our strategy as illustrated by our majority investment in Acerta Pharma in haematology.

By harnessing the power of four scientific platforms – Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response and Antibody Drug Conjugates – and by championing the development of personalised combinations, AstraZeneca has the vision to redefine cancer treatment and one day eliminate cancer as a cause of death.

About MedImmune

MedImmune is the global biologics research and development arm of AstraZeneca, a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialisation of small molecule and biologic prescription medicines. MedImmune is pioneering innovative research and exploring novel pathways across Oncology; Respiratory, Cardiovascular & Metabolic Diseases; and Infection and Vaccines. The MedImmune headquarters is located in Gaithersburg, Md., one of AstraZeneca's three global R&D centres, with additional sites in Cambridge, UK, and Mountain View, CA. For more information, please visit www.medimmune.com.

About AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three main therapy areas - Oncology, Cardiovascular & Metabolic Diseases and

Respiratory. The Company also is selectively active in the areas of Autoimmunity, Neuroscience and Infection. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information, please visit www.astrazeneca.com and follow us on Twitter @AstraZeneca.

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