News Release

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Imfinzi plus chemotherapy further improved overall survival benefit in advanced biliary tract cancer in the TOPAZ-1 Phase III trial, reducing the risk of death by 24% in additional follow-up

HIMALAYA Phase III trial exploratory results support the benefit of tremelimumab added to Imfinzi in unresectable liver cancer regardless of aetiology

Updated results from the TOPAZ-1 Phase III trial showed AstraZeneca's *Imfinzi* (durvalumab), in combination with standard-of-care chemotherapy demonstrated a clinically meaningful and durable overall survival (OS) benefit as a treatment for patients with advanced biliary tract cancer (BTC).

These results from TOPAZ-1, the first Phase III trial to show improved OS with an immunotherapy combination in this setting, will be presented today at the European Society for Medical Oncology (ESMO) Congress 2022 in Paris (abstract #56P).

The updated results for *Imfinzi* plus chemotherapy (gemcitabine plus cisplatin) showed enhanced clinical efficacy after an additional 6.5 months of follow-up, demonstrating a 24% reduction in the risk of death versus chemotherapy alone (based on a hazard ratio [HR] of 0.76; 95% confidence interval [CI], 0.64–0.91). Updated median OS was 12.9 months versus 11.3 with chemotherapy. More than two times as many patients were estimated to be alive at two years versus chemotherapy alone (23.6% versus 11.5%). Results were seen across all prespecified subgroups, regardless of disease status, tumour location or PD-L1 expression. In addition, OS benefit was observed in patients whose tumours stayed the same size (stable disease) as well as in patients whose tumours got smaller or disappeared (responders).

The safety profile of *Imfinzi* plus chemotherapy continued to be well-tolerated, with no new safety signals observed with longer follow-up. Grade 3 or 4 treatment-related AEs were experienced by 60.9% of patients treated with *Imfinzi* and chemotherapy, and by 63.5% of patients receiving chemotherapy alone. *Imfinzi* plus chemotherapy did not increase the discontinuation rate due to adverse events (AEs) compared to chemotherapy alone (8.9% for the *Imfinzi* combination versus 11.4% for chemotherapy).

Do-Youn Oh, MD, PhD, Professor, Division of Medical Oncology, Department of Internal Medicine at Seoul National University Hospital and Seoul National University College of Medicine, and principal investigator in the TOPAZ-1 Phase III trial, said: "It's exciting to see the improved overall survival delivered by durvalumab plus chemotherapy over the current standard of care for patients with advanced biliary tract cancer after a median follow-up of nearly two years. With limited treatment advances over the past decade, these patients have long faced a dismal prognosis. For the first time, an immunotherapy-based combination has shown the ability to alter the course of treatment for this disease.

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: “These longer-term data reinforce the survival benefit and well-tolerated safety profile of *Imfinzi* added to standard-of-care chemotherapy for patients with advanced biliary tract cancer. With these results, the exploratory data from the HIMALAYA trial and the recent FDA approval based on the TOPAZ-1 trial, we are continuing to advance our commitment to extend survival for patients with gastrointestinal tumours who desperately need new treatment options.”

Summary of updated results: TOPAZ-1

	***Imfinzi* + chemotherapy (N=341)**	**Chemotherapy (n=344)**
OS[i,ii]		
Median OS (95% CI) (in months)	12.9	11.3
HR (95% CI)[iii]	0.76 (0.64, 0.91)	
OS rate at 12 months (95% CI) (%)[iv]	54.3	47.1
OS rate at 24 months (95% CI) (%)	23.6	11.5
OS by BoR[v,vi]		
Median OS (95% CI), responders, months	19.5	15.7
HR (95% CI) responders[iii]	0.69 (0.46, 1.04)	
Median OS (95% CI), stable disease (SD), months	13.6	11.5
HR (95% CI) SD[iii]	0.77 (0.62, 0.96)	
12-month OS rate in responders (95% CI) (%)[iv]	75.8	75.0
12-month OS rate in SD (95% CI) (%)[iv]	57.5	48.0
24-month OS rate in responders (95% CI) (%)[iv]	40.6	20.5
24-month OS rate in SD (95% CI) (%)[iv]	20.7	10.6

OS, overall survival; HR, hazard ratio; CI, confidence interval; BoR, best overall response; SD, stable disease

i. 6.5 months of additional follow-up (data cut-off: 25 February 2022) after the primary analysis, with 76.9% overall OS event maturity
ii. At data cut-off for this analysis, median (95% CI) follow-up time (calculated using the inverse Kaplan-Meier techniques with the censoring indicator of OS reversed) was 23.4 (20.6–25.2) months for *Imfinzi* plus chemotherapy and 22.4 (21.4–23.8) months for chemotherapy
iii. HRs were calculated using a Cox proportional hazards model
iv. OS rates calculated using Kaplan-Meier techniques
v. To avoid immortal time bias, only participants surviving ≥ 3 months were included in this OS by best objective response analysis
vi. BoR was assessed by the investigator per Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 in all randomised participants with measurable disease at baseline and defined as response (complete response or partial response), SD or progressive disease (PD); BoR was determined based on the IA data cut-off (11 August 2021)

Earlier this month, *Imfinzi* in combination with chemotherapy was granted approval in the US as a treatment for adults with locally advanced or metastatic BTC based on results from TOPAZ-1. Regulatory applications are also currently under review in Europe, Japan and several other countries based on the TOPAZ-1 results.

In October 2021, the TOPAZ-1 trial met the OS primary endpoint at a predefined interim analysis, reducing the risk of death by 20% versus chemotherapy (based on a HR of 0.80; 95% CI, 0.66-0.97; 2-sided p=0.021).

HIMALAYA Phase III trial exploratory analysis by aetiology in unresectable hepatocellular carcinoma at ESMO

Also at ESMO, an exploratory analysis from the HIMALAYA Phase III trial evaluated the impact of disease causes on outcomes for patients with unresectable hepatocellular carcinoma (abstract #714P). Data from HIMALAYA suggest a trend for OS benefit over sorafenib with the STRIDE regimen regardless of the underlying disease cause (hepatitis B virus [HBV], hepatitis C virus [HCV] or nonviral). Similar trends were observed with *Imfinzi* versus sorafenib across subsets.

In 2021, positive results from the HIMALAYA Phase III trial showed a single priming dose of tremelimumab, an anti-CTLA4 antibody, added to *Imfinzi* (STRIDE regimen) demonstrated a statistically significant and clinically meaningful improvement in OS versus sorafenib as a 1st-line treatment for patients with unresectable hepatocellular carcinoma (HCC) who had not received prior systemic therapy and were not eligible for localised treatment. Patients treated with the STRIDE regimen experienced a 22% reduction in the risk of death versus sorafenib (based on a HR of 0.78, 96.02% CI 0.65-0.93; p=0.0035).

When subsets were adjusted for prognostic factor imbalances (exploratory analysis), patients with HBV treated with the STRIDE regimen experienced a 36% reduction in the risk of death versus sorafenib (based on a HR of 0.64, 95% CI 0.47-0.86). Median duration of response was 25.69 months versus 17.00 months for sorafenib. Patients with HCV treated with the STRIDE regimen experienced an 11% reduction in the risk of death versus sorafenib (based on a HR of 0.89; 95% CI 0.63-1.25). Median duration of response was 13.5 months versus 15.7 months for sorafenib. Nonviral patients treated with the STRIDE regimen experienced a 23% reduction in the risk of death versus sorafenib (based on a HR of 0.77; 95% CI 0.59-1.00). Median duration of response was 13.21 months versus 6.01 months for sorafenib. The safety profiles of STRIDE and durvalumab were consistent across aetiology subgroups.

In the past, viral HCC (disease associated with cirrhosis related to chronic hepatitis B or hepatitis C) has been the primary aetiology of the disease. Over the last two decades, the prevalence of non-viral HCC (disease associated with non-viral factors including liver disease, obesity and diabetes) has significantly increased.

The STRIDE regimen is under review by global regulatory authorities in first line treatment for unresectable HCC based on the results of the HIMALAYA trial.

Notes

Biliary tract cancer

Biliary tract cancer (BTC) is a group of rare and aggressive gastrointestinal (GI) cancers that form in the cells of the bile ducts (cholangiocarcinoma), gallbladder or ampulla of Vater (where the bile duct and pancreatic duct connect to the small intestine).[3,4] Approximately 50,000 people in the US, Europe and Japan and about 210,000 people worldwide are diagnosed with BTC each year.[5-7] These patients have a poor prognosis, with approximately 5% to 15% of patients with BTC surviving five years.[8]

Cholangiocarcinoma is more common in China and Thailand and is on the rise in Western countries.[3,8] Gallbladder cancer is more common in certain regions of South America, India and Japan.[9]

Early-stage BTC affecting the bile ducts and gallbladder often presents without clear symptoms and most new cases of BTC are therefore diagnosed at an advanced stage, when treatment options are limited and the prognosis is poor.[8-10]

Liver cancer

About 75% of all primary liver cancers are HCC.[11] Between 80-90% of all patients with HCC also have cirrhosis, which is primarily caused by infection with the hepatitis B or C viruses. Chronic liver diseases are associated with inflammation that over time can lead to the development of HCC.[12]

More than half of HCC patients are diagnosed at advanced stages of the disease, often when symptoms first appear.[13] A critical unmet need exists for patients with HCC who face limited treatment options. The unique immune environment of liver cancer provides clear rationale for investigating medications that harness the power of the immune system to treat HCC.[13]

TOPAZ-1

TOPAZ-1 is a randomised, double-blind, placebo controlled, multicentre, global Phase III trial of *Imfinzi* in combination with chemotherapy (gemcitabine plus cisplatin) versus placebo in combination with chemotherapy as a 1st-line treatment in 685 adult patients with unresectable, locally advanced or metastatic BTC including intrahepatic and extrahepatic cholangiocarcinoma, and gallbladder cancer. Patients with ampullary carcinoma were excluded.

The primary endpoint is overall survival and key secondary endpoints included progression-free survival, objective response rate and safety. The trial was conducted in 105 centres across 17 countries including in the US, Europe, South America and several countries in Asia including South Korea, Thailand, Japan and China.

HIMALAYA

HIMALAYA was a randomised, open-label, multicentre, global Phase III trial of *Imfinzi* monotherapy and the STRIDE regimen, comprising a single priming dose of tremelimumab 300mg added to *Imfinzi* 1500mg followed by *Imfinzi* every four weeks versus sorafenib, a standard-of-care multi-kinase inhibitor.

The trial included a total of 1,324 adult patients with unresectable HCC who had not been treated with prior systemic therapy and were not eligible for locoregional therapy (treatment localised to the liver and surrounding tissue).

The trial was conducted in 190 centres across 16 countries, including in the US, Canada, Europe, South America and Asia. The primary endpoint was OS for STRIDE versus sorafenib and key secondary endpoints included OS for *Imfinzi* versus sorafenib, objective response rate and progression-free survival (PFS) for STRIDE and for *Imfinzi* alone.

Imfinzi

Imfinzi (durvalumab) is a human monoclonal antibody that binds to the PD-L1 protein and blocks the interaction of PD-L1 with the PD-1 and CD80 proteins, countering the tumour's immune-evading tactics and releasing the inhibition of immune responses.

Imfinzi is the only approved immunotherapy in the curative-intent setting of unresectable, Stage III non-small cell lung cancer (NSCLC) in patients whose disease has not progressed after chemoradiation therapy, and is the global standard of care in this setting based on the PACIFIC Phase III trial.

Imfinzi is currently approved in a number of countries in multiple tumour types including for the treatment of extensive-stage small cell lung cancer (ES-SCLC); for previously treated patients with advanced bladder cancer and for locally advanced or metastatic BTC in combination with chemotherapy (gemcitabine plus cisplatin).

Since the first approval in May 2017, more than 100,000 patients have been treated with *Imfinzi*.

As part of a broad development programme, *Imfinzi* is being tested as a single treatment and in combination with other anti-cancer treatments for patients with SCLC, NSCLC, bladder cancer, several GI cancers, cervical cancer, ovarian cancer, endometrial cancer, and other solid tumours.

Imfinzi combinations have demonstrated clinical benefit in multiple additional cancer settings with positive Phase III trials in unresectable advanced liver cancer (HIMALAYA), metastatic NSCLC (POSEIDON) and resectable NSCLC (AEGEAN). The data from HIMALAYA and POSEIDON are under review with global health authorities.

Tremelimumab

Tremelimumab is a human monoclonal antibody and potential new medicine that targets the activity of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Tremelimumab blocks the activity of CTLA-4, contributing to T-cell activation, priming the immune response to cancer and fostering cancer cell death.

Beyond HIMALAYA, tremelimumab is being tested in combination with *Imfinzi* across multiple tumour types including in bladder cancer (VOLGA and NILE), locoregional HCC (EMERALD-3) and SCLC (ADRIATIC).

Tremelimumab is also under review by global regulatory authorities in combination with *Imfinzi* in metastatic NSCLC based on the results of the POSEIDON Phase III trial.

AstraZeneca in GI cancers

AstraZeneca has a broad development programme for the treatment of GI cancers across several medicines and a variety of tumour types and stages of disease. In 2020, GI cancers collectively represented approximately 5.1 million new cancer cases leading to approximately 3.6 million deaths.[14]

Within this programme, the Company is committed to improving outcomes in gastric, liver, BTC, oesophageal, pancreatic, and colorectal cancers.

Imfinzi is being assessed in combinations in liver, BTC, oesophageal and gastric cancers in an extensive development programme spanning early to late-stage disease.

The Company aims to understand the potential of *Enhertu* (trastuzumab deruxtecan), a HER2-directed antibody drug conjugate, in the two most common GI cancers, colorectal and gastric cancers. *Enhertu* is jointly developed and commercialised by AstraZeneca and Daiichi Sankyo.

Lynparza (olaparib) is a first-in-class PARP inhibitor with a broad and advanced clinical trial programme across multiple GI tumour types including pancreatic and colorectal cancers. *Lynparza* is developed and commercialised in collaboration with MSD (Merck & Co., Inc. inside the US and Canada).

AstraZeneca in immuno-oncology (IO)
Immunotherapy is a therapeutic approach designed to stimulate the body's immune system to attack tumours. The Company's Immuno-Oncology (IO) portfolio is anchored in immunotherapies that have been designed to overcome evasion of the anti-tumour immune response. AstraZeneca is invested in using IO approaches that deliver long-term survival for new groups of patients across tumour types.

The Company is pursuing a comprehensive clinical-trial programme that includes *Imfinzi* as a single treatment and in combination with tremelimumab and other novel antibodies in multiple tumour types, stages of disease, and lines of treatment, and where relevant 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 the IO portfolio with radiation, chemotherapy, and targeted small molecules from across AstraZeneca's oncology pipeline, and from research partners, may provide new treatment options across a broad range of tumours.

AstraZeneca in oncology
AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

AstraZeneca
AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal &

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Contacts

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