Imfinzi improves survival in biliary tract cancer

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Imfinzi plus chemotherapy reduced risk of death by 20% in 1st-line advanced biliary tract cancer

TOPAZ-1 is the first Phase III trial to show improved survival with an immunotherapy combination in this setting

Combination did not increase discontinuations due to adverse events vs. chemotherapy alone

Positive results from the TOPAZ-1 Phase III trial showed AstraZeneca's *Imfinzi* (durvalumab), in combination with standard-of-care chemotherapy, demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS) versus chemotherapy alone as a 1st-line treatment for patients with advanced biliary tract cancer (BTC).

These results will be presented on 21 January at the 2022 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium.

BTC is a group of rare and aggressive cancers that occur in the bile ducts and gallbladder.[1,2] Approximately 50,000
[6]

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: "After minimal progress for more than a decade in advanced biliary tract cancer, the TOPAZ-1 results are a tremendous advance for our patients, showing a clear survival benefit for *Imfinzi* added to chemotherapy compared to standard of care with a remarkable safety profile. This combination will provide a desperately needed and potentially practice-changing new treatment option in a setting where the current prognosis is devastating."

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "The results from the TOPAZ-1 trial challenge treatment expectations in advanced biliary tract cancer and provide compelling evidence that longer-term survival is possible. Overall survival improves over time with an estimated one in four patients on *Imfinzi* plus chemotherapy alive at two years compared to one in ten on chemotherapy alone. This is a potential new standard of care for patients in this setting and we remain committed to making advances in gastrointestinal cancers with high unmet need."

In a predefined interim analysis, patients treated with *Imfinzi* in combination with standard-of-care chemotherapy experienced a 20% reduction in the risk of death versus chemotherapy alone (based on a hazard ratio [HR] of 0.80; 95% confidence interval [CI], 0.66-0.97; 2-sided p=0.021). Median OS was 12.8 months versus 11.5 for chemotherapy. An estimated 25% of patients were still alive at two years versus 10% for chemotherapy.

Results also showed a 25% reduction in the risk of disease progression or death with *Imfinzi* plus chemotherapy (HR, 0.75; 95% CI, 0.64-0.89; 2-sided p=0.001). Median PFS was 7.2 months for the combination versus 5.7 for chemotherapy. Patients treated with *Imfinzi* plus chemotherapy achieved an objective response rate (ORR) of 26.7% versus an ORR of 18.7% for patients treated with chemotherapy alone.

Summary of efficacy results[i]:

	***Imfinzi* + chemotherapy(n=341)**	**Placebo + chemotherapy(n=344)**
OS[ii,iii]		
Percentage of patients with event	58.1	65.7
Median OS (95% CI) (in months)	12.8 (11.1, 14.0)	11.5 (10.1, 12.5)

HR (95% CI)2-sided p-value	0.80 (0.66, 0.97)0.021	
OS rate at 18 months (95% CI) (%)	35.1 (29.1, 41.2)	25.6 (19.9, 31.7)
OS rate at 24 months (95% CI) (%)	24.9 (17.9, 32.5)	10.4 (4.7, 18.8)
PFS[iv,v]		
Percentage of patients with event	80.9	86.3
Median PFS (95% CI) (in months)	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)
HR (95% CI)2-sided p-value	0.75 (0.64, 0.89)0.001	
ORR (%)	26.7	18.7

i. Analysis was done at 62% maturity in OS data.

ii. Investigator-assessed OS data cut-off date was 11 August 2021.

iii. Median follow-up in censored patients at DCO: 13.7 months (range 0.4-27.2) for *Imfinzi* plus chemotherapy, 12.6 months (range 0.7-26.0) for chemotherapy alone.

iv. Investigator-assessed PFS data cut-off date was 11 August 2021.

v. Median follow-up in censored patients at DCO: 9.2 months (range 0.0-24.0) for *Imfinzi* plus chemotherapy, 6.9 months (range 0.0-20.4) for chemotherapy alone.

Imfinzi plus chemotherapy did not increase the discontinuation rate due to adverse events (AEs) compared to chemotherapy alone. Grade 3 or 4 treatment-related AEs were experienced by 62.7% of patients treated with *Imfinzi* and chemotherapy, and by 64.9% of patients receiving chemotherapy alone. Treatment-related AEs led to discontinuation in 8.9% of patients treated with the *Imfinzi* combination versus 11.4% of patients receiving chemotherapy.

In December 2020, *Imfinzi* was granted Orphan Drug Designation in the US for the treatment of BTC. In October 2021, an Independent Data Monitoring Committee recommended the TOPAZ-1 Phase III trial to be unblinded at an interim analysis due to clear evidence of efficacy for *Imfinzi* plus chemotherapy.

An additional presentation featured during the ASCO Gastrointestinal Cancers Symposium will showcase *Imfinzi* data from the HIMALAYA Phase III trial, demonstrating the potential of this medicine in the treatment of unresectable liver cancer.

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).[1,2]

Cholangiocarcinoma is more common in China and Thailand and is on the rise in Western countries.[1,6] Gallbladder cancer is more common in certain regions of South America, India and Japan.[7]

Apart from ampullary cancer, early-stage BTC 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]

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 patients with unresectable advanced or metastatic BTC including intrahepatic and extrahepatic cholangiocarcinoma, and gallbladder cancer (ampullary carcinoma was excluded).

The primary endpoint was OS 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.

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 also approved in the US, EU, Japan, China and many other countries around the world for the treatment of extensive-stage small cell lung cancer (ES-SCLC) based on the CASPIAN Phase III trial.

Imfinzi is also approved for previously treated patients with advanced bladder cancer in several countries.

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 combinations with other anti-cancer treatments for patients with small cell lung cancer, NSCLC, bladder cancer, several GI cancers, cervical cancer, ovarian cancer, endometrial cancer, and other solid tumours.

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.[11]

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 colorectal and gastric cancers - the two most common GI 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 immunotherapy
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 anti-tumour immune suppression. 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 & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

Contacts
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