

Imfinzi plus transarterial chemoembolisation (TACE) and bevacizumab reduced the risk of disease progression or death by 23% vs. TACE in liver cancer eligible for embolisation

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DETAILED NEWS

EMERALD-1 is first global Phase III trial to show improved clinical outcome for systemic therapy in combination with TACE in this setting. Positive results from the EMERALD-1 Phase III trial showed AstraZeneca's Imfinzi (durvalumab) in combination with TACE and bevacizumab demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS) compared to TACE alone in patients with hepatocellular carcinoma (HCC) eligible for embolisation. These results will be presented today at the 2024 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI) in San Francisco, California (#LBA432). Approximately 20-30% of patients with HCC, the most common type of liver cancer, are eligible for embolisation, a procedure that blocks the blood supply to the tumour and can also deliver chemotherapy or radiation therapy directly to the liver.¹⁻⁸ Despite being the standard of care in this setting, most patients who receive embolisation experience disease progression or recurrence within eight months.⁹⁻¹¹ In EMERALD-1, treatment with Imfinzi plus TACE and bevacizumab reduced the risk of disease progression or death by 23% compared to TACE alone (based on a hazard ratio [HR] of 0.77; 95% confidence interval [CI] 0.61-0.98; $p=0.032$).

Median PFS was 15 months in patients treated with the Imfinzi combination versus 8.2 months with TACE.

The PFS benefit observed was generally consistent across key prespecified subgroups.

The secondary endpoint of time to progression (TTP) further supports the clinical benefit of Imfinzi plus TACE and bevacizumab in this setting, with a median TTP of 22 months versus 10 months for TACE (HR 0.63; 95% CI 0.48-0.82). The trial will continue as planned to assess the key secondary endpoint of overall survival (OS).

Bruno Sangro, MD, PhD, Director of the Liver Unit and Professor of Medicine at Clínica Universidad de Navarra, Pamplona, Spain and a lead investigator in the EMERALD-1 trial, said: "In this earlier liver cancer setting, embolisation alone has been the standard of care for more than 20 years, and rates of disease progression have remained high.

- Adding durvalumab and bevacizumab to TACE reduced the risk of disease progression or death by twenty-three per cent for patients with liver cancer eligible for embolisation, showing for the first time that combining a systemic treatment with TACE meaningfully improves this clinically relevant outcome in earlier-stage disease.” Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: “With Imfinzi-based treatment, patients with liver cancer eligible for embolisation lived nearly seven additional months before their disease progressed.

We are discussing these positive EMERALD-1 data with global regulatory authorities while awaiting the final overall survival results from the trial.”

Summary of results:
EMERALD-1i Imfinzi plus TACE and bevacizumab (n=204) Placebo plus TACE (n=205)Median PFS (months; 95% CI)ii, iii 15.0 (11.1-18.9) 8.2 (6.9-11.1)PFS HR (95% CI)ii, iv 0.77 (0.61-0.98)p-valuev 0.032PFS rate at 12 months (%)iii 55.5 39.8 PFS rate at 18 months (%)iii 43.1 28.3Median TTP (months; 95% CI)iii 22.0 (16.6-24.9) 10.0 (7.1-13.6)TTP HR (95% CI)iv, v 0.63 (0.48-0.82)Subjects with measurable disease Imfinzi plus TACE and bevacizumab (n=202) Placebo plus TACE (n=203) Objective Response Rate (ORR) (%)ii 43.6 29.6i The data cut-off date was 11 Sep 2023. ii PFS, TTP and ORR by Blinded Independent Central Review (BICR) per RECIST v1.1 iii Calculated using Kaplan-Meier method iv Calculated from stratified Cox proportional hazards method v The threshold of significance for this analysis was 0.0435 based on the alpha spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

- Imfinzi plus TACE and bevacizumab(n=204) Placebo plus TACE(n=205)Median PFS (months; 95% CI)ii, iii15.0 (11.1-18.9)8.2 (6.9-11.1)PFS HR (95% CI)ii, iv0.77 (0.61-0.98)p-valuev0.032PFS rate at 12 months (%)iii55.539.8PFS rate at 18 months (%)iii43.128.3Median TTP (months; 95% CI)iii22.0 (16.6-24.9)10.0 (7.1-13.6)TTP HR (95% CI)iv, v0.63 (0.48-0.82)Subjects with measurable diseaseImfinzi plus TACE and bevacizumab(n=202)Placebo plus TACE (n=203)Objective Response Rate (ORR) (%)ii43.629.6i The data cut-off date was 11 Sep 2023.ii PFS, TTP and ORR by Blinded Independent Central Review (BICR) per RECIST v1.1iii Calculated using Kaplan-Meier methodiv Calculated from stratified Cox proportional hazards methodv The threshold of significance for this analysis was 0.0435 based on the alpha spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.The safety profile for Imfinzi plus TACE and bevacizumab was generally manageable and consistent with the known profile of each medicine.

- The number of TACE procedures was consistent across arms.

- No new safety signals were observed.

Grade 3 and 4 adverse events due to any cause occurred in 45.5% of patients treated with Imfinzi plus TACE and bevacizumab and 23% of patients treated with TACE alone.

NotesLiver cancer Liver cancer, of which HCC is the most common type, is the third-leading cause of cancer death, with an estimated 900,000 people worldwide diagnosed each year and a high prevalence in certain regions of Asia.12-14 An estimated 80-90% of all patients with HCC also have cirrhosis.15 Chronic liver diseases such as cirrhosis are associated with inflammation that over time can lead to

- the development of HCC.15 Immunotherapy is a proven treatment modality in HCC with approved options available for patients in later-line settings.16EMERALD-1 EMERALD-1 is a randomised, double-blind, placebo-controlled, multicentre, global Phase III trial of Imfinzi plus TACE concurrently, followed by Imfinzi with or without bevacizumab until progression versus TACE alone in a total of 616 patients with unresectable HCC eligible for embolisation.The trial was conducted in 157 centres across 18 countries, including in North America, Australia, Europe, South America and Asia.

→ The primary endpoint was PFS for Imfinzi plus TACE and bevacizumab versus TACE alone, and secondary endpoints include PFS for Imfinzi plus TACE, OS, patient-reported outcomes and ORR. 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 approved in combination with chemotherapy (gemcitabine plus cisplatin) in locally advanced or metastatic biliary

tract cancer (BTC) and in combination with Imjudo (tremelimumab) in unresectable HCC in the US, EU, Japan, China and many other countries based on the TOPAZ-1 and HIMALAYA Phase III trials, respectively.

→ Following HIMALAYA in the advanced setting, EMERALD-1 is AstraZeneca's second positive Phase III trial in HCC. In non-small cell lung cancer (NSCLC), Imfinzi is approved in combination with a short course of Imjudo and chemotherapy for the treatment of metastatic NSCLC in the US, EU and Japan based on the POSEIDON Phase III trial.

→ Imfinzi is also the only approved immunotherapy and the global standard of care in the curative-intent setting of unresectable, Stage III NSCLC in patients whose disease has not progressed after chemoradiation therapy based on the PACIFIC Phase III trial, the results of which have been confirmed in the real-world setting in the PACIFIC-R study.

→ In 2023, AstraZeneca announced positive results from the AEGEAN Phase III trial evaluating Imfinzi in combination with neoadjuvant chemotherapy before surgery and as adjuvant monotherapy after surgery in resectable NSCLC. 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 (SCLC) based on the CASPIAN Phase III trial.

→ Imfinzi is approved in previously treated patients with advanced bladder cancer in a small number of countries. Since the first approval in May 2017, more than 200,000 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 SCLC, NSCLC, bladder cancer, several GI cancers, breast cancer and other solid tumours.

→ In 2023, AstraZeneca announced positive results for several Phase III trials evaluating Imfinzi in various combinations, including in ovarian (DUO-O) and endometrial (DUO-E) cancers with Lynparza (olaparib). In GI cancers specifically, AstraZeneca has an extensive clinical development programme further assessing Imfinzi across multiple settings.

→ In addition to EMERALD-1, Imfinzi is also being investigated in combination with bevacizumab in adjuvant HCC (EMERALD-2), in combination with Imjudo, lenvatinib and TACE in embolisation-eligible HCC (EMERALD-3), in resectable gastric and gastroesophageal junction cancers (MATTERHORN) and in locally advanced oesophageal cancer (KUNLUN).

→ In June 2023, Imfinzi added to standard-of-care neoadjuvant chemotherapy met a key secondary endpoint of pathologic complete response in the MATTERHORN 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.¹⁷ Within this programme, the Company is committed to improving outcomes in gastric, liver, biliary tract, oesophageal, pancreatic and colorectal cancers. In addition to its indications in BTC and with Imjudo in HCC, Imfinzi is being assessed in combinations, including with Imjudo, in liver, oesophageal and gastric cancers in an extensive development programme spanning early to late-stage disease across settings. Enhertu

(trastuzumab deruxtecan), a HER2-directed antibody drug conjugate, is approved in the US and several other countries for HER2-positive advanced gastric cancer and is being assessed in colorectal cancer.

↪ Enhertu is jointly developed and commercialised by AstraZeneca and Daiichi Sankyo. Lynparza, a first-in-class PARP inhibitor, is approved in the US and several other countries for the treatment of BRCA-mutated metastatic pancreatic cancer.

↪ Lynparza is developed and commercialised in collaboration with MSD (Merck & Co., Inc. inside the US and Canada). AstraZeneca is advancing multiple modalities that provide complementary mechanisms for targeting Claudin 18.2, a promising therapeutic target in gastric cancer.

↪ These include AZD0901, a potential first-in-class antibody drug conjugate licensed from KYM Biosciences Inc., currently in Phase II development, AZD5863, a novel Claudin 18.2/CD3 T-cell engager bispecific antibody, licensed from Harbour Biomed, that is in Phase I development, and AZD6422, an armoured autologous chimeric antigen receptor T-cell (CAR-T) therapy, currently being evaluated in an Investigator Initiated Trial (IIT) in collaboration with AbelZeta in China. In early development, AstraZeneca is developing two Glypican 3 (GPC3) armoured CAR-Ts in HCC.

↪ AZD5851, currently in Phase I development, is being developed globally, and C-CAR031 / AZD7003 is being co-developed with AbelZeta in China where it is under evaluation in an IIT. AstraZeneca in immuno-oncology (IO) AstraZeneca is a pioneer in introducing the concept of immunotherapy into dedicated clinical areas of high unmet medical need.

↪ The Company has a comprehensive and diverse IO portfolio and pipeline anchored in immunotherapies designed to overcome evasion of the anti-tumour immune response and stimulate the body's immune system to attack tumours. AstraZeneca aims to reimagine cancer care and help transform outcomes for patients with Imfinzi as a single treatment and in combination with Imjudo as well as other novel immunotherapies and modalities.

↪ The Company is also exploring next-generation immunotherapies like bispecific antibodies and therapeutics that harness different aspects of immunity to target cancer. AstraZeneca is boldly pursuing an innovative clinical strategy to bring IO-based therapies that deliver long-term survival to new settings across a wide range of cancer types.

↪ With an extensive clinical programme, the Company also champions the use of IO treatment in earlier disease stages, where there is the greatest potential for cure. 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 (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 social media @AstraZeneca. For details on how to contact the Investor Relations Team, please click [here](#).
- For media contacts, click [here](#).
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INSIGHTS

- ↪ 1.
The EMERALD-1 Phase III trial showed AstraZeneca's Imfinzi (durvalumab) in combination with TACE and bevacizumab achieved a statistically significant improvement in the primary endpoint of progression-free survival (PFS) compared to TACE alone in patients with hepatocellular carcinoma (HCC) eligible for embolisation.
- ↪ 2.
About 20-30% of patients with HCC, the most common type of liver cancer, are eligible for embolisation, but most patients who receive embolisation experience disease progression or recurrence within eight months.
- ↪ 3.
The trial demonstrated that treatment with Imfinzi plus TACE and bevacizumab reduced the risk of disease progression or death by 23% compared to TACE alone, with median PFS of 15 months in patients treated with the Imfinzi combination versus 8.2 months with TACE.
- ↪ 4.

- ↪ The secondary endpoint of time to progression (TTP) further supports the clinical benefit of Imfinzi plus TACE and bevacizumab in this setting, with a median TTP of 22 months versus 10 months for TACE.
- ↪ 5.
- ↪ The EMERALD-1 trial will continue as planned to assess the key secondary endpoint of overall survival (OS).
- ↪ AstraZeneca is in discussions with global regulatory authorities about these positive EMERALD-1 data while awaiting the final overall survival results from the trial.



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