A randomised Phase 3 study of tremelimumab plus durvalumab with or without lenvatinib combined with concurrent transarterial chemoembolisation (TACE) versus TACE alone in patients with locoregional hepatocellular carcinoma: EMERALD-3

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Plain language summary

Why are we performing this research?

- Some people with hepatocellular carcinoma (HCC) that cannot be removed by surgery or other techniques receive transarterial chemoembolization (TACE), which delivers direct chemotherapy and reduces blood flow to the tumor, as a standard therapy
- Tremelimumab plus durvalumab (types of immunotherapy) and a medication called lenvatinib can allow people with HCC to live longer
- EMERALD-3 aims to find out if tremelimumab plus durvalumab with lenvatinib and TACE, or tremelimumab plus durvalumab with TACE, can improve outcomes better than TACE alone

How are we performing this research?

- Participants will be treated with either tremelimumab plus durvalumab with lenvatinib and TACE, tremelimumab plus durvalumab with TACE, or TACE alone
- The main analysis will measure the length of time it takes for participants to experience cancer growth, spreading, or worsening, as well as the length of time that participants live

Who will participate in this study?

- Approximately 525 people with intermediate-stage HCC will be enrolled from 21 countries across the globe

Where can I access more information?

- This study is ongoing; no results are available. Expected completion is January 2027
- More information about this study can be found at: https://clinicaltrials.gov/ct2/show/NCT05301842. You may also speak to your doctor about clinical studies

Background

- Primary liver cancer is the sixth most diagnosed cancer and third leading cause of cancer death worldwide, with over 900,000 new cases and 830,000 deaths in 2020[1,2]
- HCC is the most common form of primary liver cancer and accounts for 75–85% of cases[2]; most people with HCC present with disease that is not eligible for curative therapy[3]
- TACE is standard of care for people with HCC amenable to embolization[4,5]
- While TACE results in tumor responses in most people, progression or recurrence are common within 1 year[6] of TACE, with median overall survival (OS) up to approximately 30 months[6,7]
- There is a need to assess novel treatment options for people with HCC amenable to embolization

Study rationale

- TACE induces tumor cell death, which may cause the release of tumor antigens to stimulate anti-tumor T-cell activation; however, programmed cell death ligand-1 (PD-L1) / programmed cell death-1 and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) can promote immunosuppression in the tumor microenvironment, enabling immune escape[8–10]
- TACE increases vascular endothelial growth factor (VEGF) expression, which may have immunosuppressive effects and promote neovascularization, potentially supporting the survival of residual HCC tissue[10,11]
- In the Phase 3 HIMALAYA study, the STRIDE (Single Tremelimumab Regular Interval Durvalumab) regimen, which combines a single priming dose of tremelimumab (anti-CTLA-4) with durvalumab (anti-PD-L1), significantly improved OS versus sorafenib in participants with unresectable HCC not amenable to embolization[12]
- Lenvatinib is a multikinase inhibitor of VEGF receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT that is used for the first-line treatment of unresectable HCC not amenable to embolization[4,13,14]; promising clinical activity has also been reported for TACE plus lenvatinib in the Phase 2 TACTICS-L study in HCC[15]
- Combining STRIDE and lenvatinib with concurrent TACE may enhance the anti-tumor response and provide synergistic benefit in people with HCC amenable to embolization

EMERALD-3 (NCT05301842) study design:

A Phase 3, randomized, open-label, sponsor-blind, multicenter study to assess the efficacy and safety of STRIDE, with or without lenvatinib, combined with concurrent TACE, versus TACE alone in participants with HCC amenable to embolization

Participants with intermediate-stage HCC not amenable to curative therapy

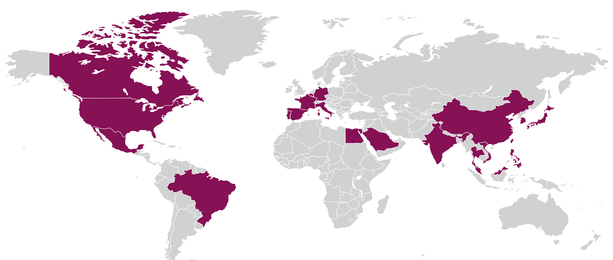
Approximately 525 participants randomized 1:1:1

- **Arm A:** STRIDE + lenvatinib 8 mg or 12 mg* QD + TACE†
- **Arm B:** STRIDE + TACE†
- **Arm C:** TACE alone†

*Based on body weight: 8 mg for participants <60 kg; 12 mg for participants ⩾60 mg; †Drug eluting bead or conventional TACE; the first procedure will occur no earlier than 7 days following the first administration of tremelimumab and durvalumab (Arms A and B) and lenvatinib (Arm A) or within 7 days following randomization (Arm C)

HCC, hepatocellular carcinoma; QD, once daily; STRIDE, Single Tremelimumab (priming 300 mg dose) Regular Interval Durvalumab (1500 mg Q4W); TACE, transarterial chemoembolization

Enrollment start: March 2022 | Expected study end: January 2027



Study enrollment is ongoing; enrollment is intended at 188 sites across 21 countries

Key inclusion criteria

- Pathologically or radiologically confirmed HCC
- Not amenable to curative therapy (e.g. surgical resection, transplantation, ablation) but eligible for TACE
- No evidence of extrahepatic disease
- Child-Pugh score class A
- Eastern Cooperative Oncology Group performance status of 0 to 1
- Measurable disease by modified Response Evaluation Criteria in Solid Tumors (mRECIST)
- Adequate organ and marrow function

Key exclusion criteria

- History of symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardia arrythmia or hepatic encephalopathy
- Baseline major portal vein thrombosis (Vp3 / Vp4)
- Uncontrolled hypertension
- Co-infection with hepatitis B and D virus

Study endpoints

1°

- Progression-free survival (PFS) for Arm A versus Arm C (blinded independent central review [BICR], RECIST v1.1)

2°

- PFS for Arm B versus Arm C (BICR, RECIST v1.1)
- OS for Arm A or Arm B versus Arm C
- PFS for Arm A or Arm B versus Arm C (BICR or Investigator, mRECIST)
- Objective response rate
- Duration of response
- Time to progression
- Time from randomization to second progression or death
- Health-related quality of life
- Safety

Disclosures

Angela Zeng, Brent Evans, Kerry Parsons, and Gordon Cohen are employees and shareholders of AstraZeneca. Ghassan K. Abou-Alfa received grants from AstraZeneca and consulting fees from AstraZeneca. Riccardo Lencioni has received consulting fees from AstraZeneca. Jia Fan served as a Steering Committee member for AstraZeneca. Zhenggang Ren received consulting fees from and participated on Data Safety Monitoring Board / Advisory Board for AstraZeneca. Joseph Erinjeri received consulting fees from AstraZeneca. Christiane Kuhl, Jeong Heo, Masatoshi Kudo and Yasuaki Arai report no conflicts of interest related to AstraZeneca. Full author disclosures are available with the published abstract.

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Acknowledgements

This study is sponsored by AstraZeneca. Medical writing support, under the direction of the authors, was provided by Eilidh McLachlan, PhD, of CMC Connect, a division of IPG Health Medical Communications, and was funded by AstraZeneca, in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015).

Study sponsored by: AstraZeneca

Previously presented at European Society for Medical Oncology, Final Publication Number: 727TiP,
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Poster presented at: Symposium on Clinical Interventional Oncology, September 23–25, 2022, Miami, FL, USA. Corresponding author email address: Ghassan K. Abou-Alfa (abou-alg@mskcc.org)