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Durvalumab With or Without Bevacizumab as Adjuvant Therapy for HCC Patients at Risk of Recurrence After Curative Therapy: EMERALD-2

P-06

Jennifer Knox,[1] Riccardo Lencioni,[2] Ann-Lii Cheng,[3] Sean Cleary,[4] Peter Galle,[5] Norihiro Kokudo,[6] Joong-Won Park,[7] Jian Zhou,[8] Philip He,[9] Shethah Morgan,[10] Gordon Cohen,[9] Jia Fan[8]

[1]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [2]University of Pisa School of Medicine, Pisa, Italy; [3]National Taiwan University, Taipei City, Taiwan; [4]Mayo Clinic, Rochester, MN, USA; [5]University Medical Center Mainz, Mainz, Germany; [6]National Center for Global Health and Medicine, Tokyo, Japan; [7]National Cancer Center, Gyeonggi-do, South Korea; [8]Zhongshan Hospital, Fudan University, Shanghai, China; [9]AstraZeneca, Gaithersburg, MD, USA; [10]AstraZeneca, Cambridge, United Kingdom

Summary

- The EMERALD-2 study will expand the understanding of the efficacy and safety of durvalumab with or without bevacizumab as adjuvant HCC therapy for patients who are at high risk for recurrence after curative hepatic resection or ablation.

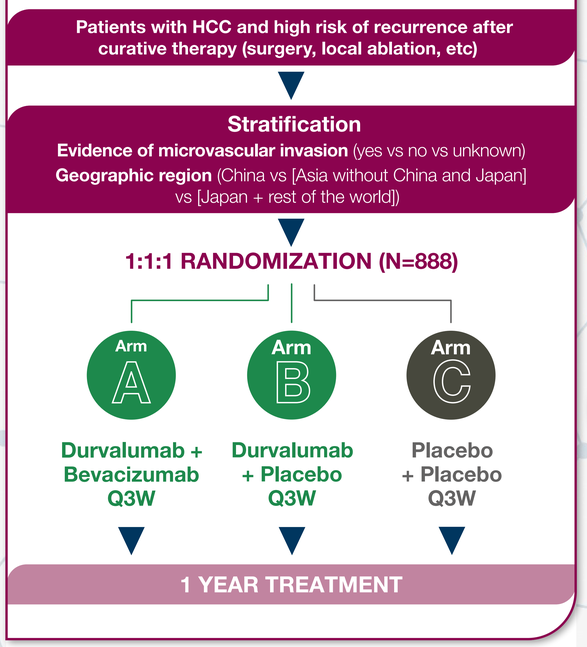
Introduction

- Many patients with early-stage HCC undergo hepatic resection or ablation as standard of care, but while potentially curative, **the risk of cancer recurrence following resection is as high as 44%–79% at 5 years.**[1–3]
- Effective adjuvant therapy has not been identified to date, and the **prevention and/or delay of recurrence of HCC after curative treatment presents a high unmet medical need.**
- Adjuvant therapy given after resection or ablation has the potential to reduce the risk of relapse and is an effective therapeutic approach in the treatment of many solid tumors.
- Encouraging clinical evidence shows that **adjuvant therapy involving agents that engage the immune response can prolong RFS in patients with early-stage HCC.**[4–7]
- In addition, data suggest that **inhibiting the VEGF pathway may enhance activity of programmed death ligand-1 blockade** in patients with more advanced HCC.[8–10]

Methods

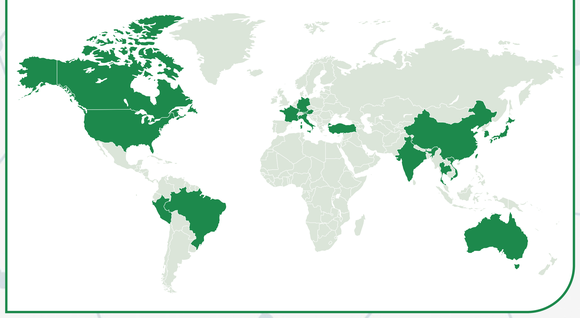
- **EMERALD-2 (NCT03847428)** is a Phase 3 randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of durvalumab monotherapy and durvalumab combined with bevacizumab as adjuvant therapy in patients with HCC within 12 weeks of completion of curative hepatic resection or final curative ablation procedure (which may include embolization) who are at high risk of recurrence.
- Following hepatic resection and ablation, approximately 888 patients will be randomized 1:1:1 to Arm A, B, or C (**Figure 1**).

Figure 1. EMERALD-2 study design



- A tumor tissue sample is mandatory for biomarker analysis.
- Patients with HBV or HCV alone may be enrolled, but patients who are HBV+ must have adequately controlled viral suppression prior to enrollment, and HBV/HCV replication will be monitored during the study and treated if appropriate.
- Patients are required to have an upper endoscopy (or contrast-enhanced cross-sectional imaging) performed within 6 months of randomization; patients with varices at risk of bleeding should be excluded.
- There are currently 18 countries and regions participating in the EMERALD-2 study (**Figure 2**).

Figure 2. EMERALD-2 participating regions



Study Endpoints

1. **Assess RFS of Arm B vs Arm C (by BICR using RECIST v 1.1)**

2.
- Assess RFS of Arm A vs Arm C (by BICR using RECIST v 1.1)
- Evaluate 24-month RFS for all arms (by BICR using RECIST v 1.1)
- Measure time to relapse for all arms (by BICR using RECIST v 1.1)
- Evaluate overall survival for all arms
- Investigate the relationship between a patient's baseline PD-L1 expression and efficacy outcomes
- Assess disease-related symptoms, impacts, and HRQoL for all arms
- Evaluate safety and tolerability profile of all arms

Key exploratory objectives
- Investigate the association of candidate biomarkers with efficacy measures using blood and tissue samples
- Explore the impact of treatment and disease state on health care utility and resources (EQ-5D-5L, HOSPAD)

Key Inclusion Criteria

- Aged ≥18 years
- Successful completion of curative therapy (resection or ablation) with imaging to confirm disease-free status ≤28 days prior to randomization
- Histologically or cytologically confirmed HCC
- No prior systemic therapy for HCC
- Child-Pugh score of 5 or 6
- ECOG PS of 0 or 1 at enrollment

Key Exclusion Criteria

- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Any evidence of metastatic, macrovascular invasion, or co-existing malignant disease on baseline imaging
- Evidence of portal vein thrombosis
- Prior systemic anticancer therapy for HCC
- Patients with varices at risk of bleeding
- Patients who are candidates for liver transplantation

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Abbreviations

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EQ-5D-5L, EuroQol 5-dimension, 5-level, health state utility index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HOSPAD, hospital admission form; HRQoL, health-related quality of life; PD-L1, programmed death ligand-1; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; RFS, recurrence-free survival; VEGF, vascular endothelial growth factor.

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Contact Information

Shethah.Morgan@astrazeneca.com