A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Transarterial Chemoembolization Combined With Durvalumab or Durvalumab Plus Bevacizumab Therapy in Patients With Locoregional Hepatocellular Carcinoma (HCC): EMERALD-1

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Introduction

Curative therapy is not always an option for patients with intermediate-stage HCC and a standard approach for treatment is locoregional therapy such as TACE. TACE therapy achieves tumor responses, but progression and recurrence are common and often occur within 1 year.

Checkpoint inhibitors have shown promising efficacy with durable response as treatment for advanced HCC when combined with TACE. Checkpoint inhibitors combined with VEGF inhibitors have also been approved in advanced HCC.

Combining durvalumab with VEGF inhibitors and TACE therapies warrants evaluation in patients with locoregional HCC.

Methods

EMERALD-1 (NCT03778957) is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study assessing efficacy and safety for durvalumab when given concurrently with either DEB-TACE or conventional TACE followed by durvalumab ± bevacizumab in patients with locoregional HCC not amenable to curative therapy.

600 patients will be randomized 1:1:1 to Arm A, B, or C (Figure 1).

Durvalumab (or its matched placebo) will begin at least 7 days following the initial TACE procedure. Bevacizumab (or its matched placebo) will be added to durvalumab (or its matched placebo) at least 14 days after the last TACE procedure.

Study Endpoints

1. Assess PFS (by BICR using RECIST v 1:1)
2. Evaluate PFS for all arms using modified RECIST (by BICR)
3. Evaluate overall survival for all arms
4. Investigate the relationship between baseline PD-L1 expression and efficacy outcomes
5. Measure time to progression for all arms
6. Evaluate objective response, duration of response, and disease control rate
7. Assess disease-related symptoms, impacts, and HRQoL for all arms
8. 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

Summary

- The EMERALD-1 study will expand the understanding of the efficacy and safety of durvalumab combined with TACE therapy followed by durvalumab with or without bevacizumab in patients with locoregional HCC who cannot undergo curative therapy.

Key Inclusion Criteria

- Aged ≥18 years
- Histologically or radiologically confirmed HCC not amenable to curative therapy
- No prior TACE or systemic therapy for HCC
- Child-Pugh Score class A to B7
- ECOG PS of 0 or 1 at enrollment
- 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 performed to evaluate varices and risk of bleeding within 6 months of randomization.

Key Exclusion Criteria

- A history of nephrotic or nephritic syndrome
- Clinically significant cardiovascular disease
- Extrahepatic disease
- Evidence of main portal vein thrombosis (Vp3/Vp4)
- Prior or current evidence of bleeding diathesis, within 28 days following surgery, or GI perforation or active GI bleeding within 6 months of enrollment

- A tumor tissue sample is mandatory and may either be taken during the 1st TACE procedure or a sample taken ≥3 months prior to randomization.
- There are currently 18 countries and regions participating in the EMERALD-1 study (Figure 2).

EMERALD-1 study design and participating regions

Figure 1

Patients with HCC who are unsuitable for curative therapy with no prior TACE or systemic therapy

1:1:1 RANDOMIZATION (N=600)

ARM A
TACE + Durvalumab
Durvalumab + Placebo

ARM B
TACE + Durvalumab
Durvalumab + Bevacizumab

ARM C
TACE + Placebo
Placebo + Placebo

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References

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