財團法人明日醫學基金會研究計畫申請書

計畫名稱	（中文）晚期肝細胞癌患者 atezolizumab 合併 bevacizumab 與 durvalumab 合併 tremelimumab 的比較療效：真實世界臨床應用的觀察性研究	
	（英文）Comparative effectiveness of atezolizumab plus bevacizumab versus durvalumab plus tremelimumab in patients with advanced hepatocellular carcinoma: an observational study based on real-world practice	
計畫類別	☑個別型	☐整合型
計畫歸屬	☐基礎醫學☐生物醫學☑臨床醫學☐資訊系統☐醫院管理☐整合性醫學研究	
計畫主持人	姓名：許耀峻 Yao-Chun Hsu	機關：**義守大學、義大醫院**
	職稱：**教授**	單位：**醫學研究所**
通訊地址	**高雄市左營區重化街六號 13 樓**	
聯絡電話	**(02)6150011, 0988687726**	
計畫執行期限	自 **114** 年 1 月 **1** 日起至 **114** 年 **12** 月 **31** 日止	
共同主持人（一）	姓名： 曾政豪	機關：
	職稱：	單位：
共同主持人（二）	姓名：陳子皓	機關：
	職稱：	單位：
共同主持人（三）	姓名：李穎儒	機關：
	職稱：	單位：

研究計畫摘要

一、試驗目的：

本研究將比較晚期肝細胞癌患者使用 atezolizumab 合併 bevacizumab，相較於 durvalumab 合併 tremelimumab，在真實世界中臨床應用的療效結果

二、研究背景：

免疫檢查哨抑制劑為基礎的治療已被核准用於罹患晚期肝細胞癌的病人，其中 atezolizumab 合併 bevacizumab 與 durvalumab 合併 tremelimumab 分別在第三期臨床試驗中都顯示出顯著優於標靶藥物 sorafenib 的療效，也已經被健保列為晚期肝癌第一線治療藥物，但是兩者在常規診療中的相對療效仍不明確。

三、研究方法：

這是一項多中心世代研究，我們將系統地檢視義大醫療體系中，所有接受 atezolizumab 合併 bevacizumab 或者 durvalumab 合併 tremelimumab 的晚期肝癌患者，從各醫院癌症登錄系統與電子病歷中取得資料，經過去識別化處理後，我們將收集人口學資料（例如年齡、性別）、肝病病因（B 型肝炎、C 型肝炎、代謝異常脂肪肝、酒精等）、體能狀態(ECOG)、肝功能檢查及 Child-Pugh 參數、腫瘤特徵（初診斷時與使用免疫治療時的腫瘤大小、病灶數目、血管侵犯、肝外轉移）、以及先前治療史（如手術切除、局部消融術或 TACE）。此外，我們將從病歷記錄擷取 atezo/bev 或 durva/trem 治療開始日期。治療期間，治療給藥資料（劑量、療程、任何中斷情況）、腫瘤反應評估及不良事件發生情況。患者將追蹤至死亡或最後的就診時間。

關鍵詞: 晚期肝癌；免疫檢查哨抑制劑；比較療效；真實世界研究

研究計畫目的及背景說明

Hepatocellular carcinoma (HCC) is a major health burden, ranking as the fourth most common malignancy and the second leading cause of cancer-related death in Taiwan. Advanced HCC carries a poor prognosis, historically managed with multi-kinase inhibitors (e.g. sorafenib or lenvatinib) that provide modest survival benefit. The median overall survival on sorafenib is around 10–13 months in advanced disease, reflecting the aggressive nature of HCC and the need for more effective therapies.

Significant advances have been made with immune checkpoint inhibitor-based combinations. In 2020, the IMbrave150 trial demonstrated that atezolizumab (anti–PD-L1 antibody) plus bevacizumab (anti-VEGF antibody) markedly improved patient outcomes compared to sorafenib. In that study, median overall survival was 19.2 months with atezolizumab–bevacizumab versus 13.4 months with sorafenib, and median progression-free survival was 6.9 vs 4.3 months. This established atezolizumab–bevacizumab as a new first-line standard of care for unresectable HCC, with superior efficacy and a favorable quality-of-life profile.

Separately, the HIMALAYA trial introduced a different immunotherapy approach: a single high priming dose of tremelimumab (CTLA-4 inhibitor) combined with durvalumab (PD-L1 inhibitor), often termed the STRIDE regimen. Durvalumab plus tremelimumab also demonstrated a significant survival benefit over sorafenib, with a median OS of 16.4 months vs 13.8 months on sorafenib (hazard ratio 0.78). This regimen achieved durable long-term responses in a subset of patients, with 4-year survival rates of about 25% in the combination arm.

By 2023, international guidelines recognize both atezolizumab–bevacizumab and

tremelimumab–durvalumab as first-line options for advanced HCC. Despite their successes, these two regimens have distinct mechanisms and toxicity considerations, and they have not been compared head-to-head in a randomized trial. Atezolizumab–bevacizumab combines immunotherapy with an antiangiogenic drug, which can reduce tumor vascularization but carries risks such as bleeding and hypertension. In contrast, durvalumab–tremelimumab entails dual immune checkpoint blockade, which can provoke immune-related adverse events (e.g. hepatitis, colitis, endocrinopathies) especially early after the CTLA-4 inhibitor dose.

Clinicians currently must choose a first-line regimen based on clinical judgment in the absence of direct comparative evidence. Real-world comparative effectiveness data are needed to inform these decisions. Taiwan's National Health Insurance (NHI) began reimbursing the atezolizumab–bevacizumab combination in August 2023, greatly expanding patient access to this therapy. Likewise, durvalumab plus tremelimumab was reimbursed by the NHI for advanced HCC after February 2025 and has become available in practice.

The NHI reimbursement along with the standardized criteria are instrumental for comparing the effectiveness of these two regimens, given the high cost of the medications and the potential differences in patient selection. This study will leverage the cancer registry in the E-Da Healthcare Group to compare survival outcomes and safety between atezolizumab–bevacizumab and durvalumab–tremelimumab in routine practice, hopefully providing evidence on whether these treatments are equally effective in the real world and guide treatment selection for patients with advanced HCC in Taiwan.

Methods and Materials:

Design and setting

This study is designed as a multicenter observational cohort (registry-based) study. We will collect data on patients with advanced HCC treated in real-world practice at three hospitals in the E-Da Healthcare Group (Kaohsiung, Taiwan): E-Da Hospital, E-Da Cancer Hospital, and E-Da Dachang Hospital, which share an integrated electronic medical record system, facilitating a unified registry. Patients who initiate first-line systemic therapy with either atezolizumab–bevacizumab or durvalumab plus tremelimumab between August 1, 2023 and December 31, 2026 will be enrolled. There will be no randomization or intervention assignment by investigators; the choice of regimen is determined by treating oncologists according to clinical indication and patient preference. This design allows an assessment of comparative effectiveness in routine clinical practice (pragmatic, non-interventional study).

Study patients

We will include adult patients (age ≥18) with unresectable or advanced HCC who meet the criteria for first-line immunotherapy-based treatment under Taiwan NHI policy.

Inclusion Criteria

To mirror real-world reimbursement criteria, all the following criteria must be satisfied:

1. Advanced disease not amenable to curative therapy: Patients must have HCC that is metastatic or unresectable, and not suitable for curative locoregional treatments (or have failed prior local therapies).
2. Adequate liver function: Child-Pugh class A liver function reserve.
3. Extrahepatic spread: presence of distant metastasis or nodal spread beyond the

liver, or macrovascular invasion: tumor invasion into major vasculature (e.g. portal vein trunk or first-/second-order branches), or TACE failure: inadequate response to transarterial chemoembolization, defined as ≥3 sessions of TACE within 12 months without tumor control (evidence of progression).

4. No prior systemic therapy: Patients must not have received any previous systemic chemotherapy, targeted therapy (e.g. sorafenib or lenvatinib), or immunotherapy for HCC.

5. Treatment with atezolizumab plus bevacizumab, or durvalumab plus tremelimumab: at least one dose of either regiments

Exclusion Criteria

1. Organ transplant history: Previous liver transplantation (due to risk of graft rejection with immunotherapy).

2. Concurrent immunosuppressive therapy: Requirement for systemic immunosuppressants (e.g. for autoimmune disease) which could both contraindicate checkpoint inhibitors and confound outcomes.

3. Uncontrolled bleeding risk: Active gastrointestinal bleeding or high-risk esophageal varices that have not been treated. All patients must have recent endoscopic evaluation (within 6 months) with appropriate management of potential bleeders.

4. Poor physical condition (Eastern Cooperative Oncology Group ECOG performance status ≥2)

5. Poor cardiopulmonary function (New York Heart Association NYHA Class III or IV)

6. Poor renal function (estimated glomerular filtration rate eGFR ≤60 ml/min/1.73m^2)

Study outcomes

The primary outcome of this study is overall survival, defined as the time from initiation of first-line therapy (atezolizumab–bevacizumab or durvalumab–tremelimumab start date) to death from any cause. Surviving patients will be censored at the last follow-up date. Given the observational period, patients will be followed for survival through at least December 31, 2026, with additional follow-up in 2027 as needed to capture mature outcomes.

Secondary outcomes include progression-free survival (PFS) and serious adverse events (SAEs). PFS is defined as the time from treatment initiation to radiographic disease progression or death, whichever occurs first. Disease progression will be assessed based on imaging (contrast-enhanced CT or MRI) interpreted according to RECIST 1.1 criteria during routine follow-up visits (typically every 8–12 weeks) or as clinically indicated. Patients alive without progression at last imaging assessment will be censored at that time. SAEs will encompass Grade 3 or higher treatment-related adverse events, or any adverse event leading to hospitalization, permanent therapy discontinuation, life-threatening outcome, or death, as defined by Common Terminology Criteria for Adverse Events (CTCAE v5.0). Key adverse events of interest include bleeding complications (for the atezolizumab–bevacizumab group) and immune-mediated toxicities (for the durvalumab–tremelimumab group), among others. We will compare the frequency and profiles of SAEs between the two treatment cohorts.

Statistical analyses

We plan to collect data from 200 patients with advanced HCC (n=100 for each treatment arm) and will conduct a preliminary analysis when data from at least 100 patients (at least 50 patients in each arm) are available.

With available data, we will perform a comparative analysis between the two treatment cohorts (atezolizumab–bevacizumab vs durvalumab–tremelimumab). Baseline patient characteristics will be summarized and compared using chi-square (or Fisher's exact) tests for categorical variables and Mann-Whitney U tests for continuous variables, to identify any significant differences in patient profiles between treatment groups. If imbalances are present (for example, if patients receiving one regimen have more advanced disease or different liver function), these factors will be accounted for in the outcome analysis.

For the primary endpoint of overall survival, we will use the Kaplan-Meier method to estimate survival curves for each treatment group and compare them with the log-rank test. Median OS and survival rates at 6, 12, and 18+ months will be reported per group. We will also construct multivariable Cox proportional hazards models to estimate the hazard ratio (HR) for death with durvalumab–tremelimumab versus atezolizumab–bevacizumab, adjusting for potential confounders (such as age, tumor burden, performance status, viral etiology, etc.).

In addition, we may employ propensity score methods (matching or weighting) as a sensitivity analysis to further control for indication bias in this non-randomized comparison. For secondary endpoints, Kaplan-Meier analysis and Cox models will similarly be used for PFS comparison between regimens. Patients who switch therapy or receive subsequent lines will be censored at the time of a new systemic treatment when analyzing PFS to focus on first-line regimen efficacy. Objective response rates (if evaluable) will be summarized, although tumor response is not a primary endpoint. Rates of serious adverse events will be compared using Fisher's exact test or chi-square, as appropriate. We will specifically compare incidence of key SAEs (e.g. grade ≥3

bleeding, grade ≥3 immune-related events) between the two cohorts. All statistical tests will be two-sided, with a significance level of $\alpha = 0.05$. The analysis will be primarily descriptive and hypothesis-generating, given the observational design; however, the study is expected to have adequate power to detect large differences in survival if they exist, given an anticipated sample size of hundreds of patients across the study period (we expect enrollment of approximately 150–200 patients, based on HCC incidence and referral patterns). Analyses will be performed using STATA or R statistical software.

REFERENCES:

1. Llovet, J. M. et al. Hepatocellular carcinoma. Nat. Rev. Dis. Prim. 7, 7 (2021).
2. Finn, R. S. et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N. Engl. J. Med. 382, 1894–1905 (2020).
3. Singal, A. G. et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 78, 1922–1965 (2023).
4. Galle, P. R. et al. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J. Hepatol. 69, 182–236 (2018).
5. Omata, M. et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol. Int. 11, 317–370 (2017).
6. Qin, S. et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave 050): a randomised, open-label, multicentre, phase 3 trial. Lancet 402, 1835–1847 (2023).
7. Jardim, D. L., Goodman, A., de Melo Gagliato, D. & Kurzrock, R. The challenges of tumor mutational burden as an immunotherapy biomarker. Cancer Cell 39, 154–173 (2021).
8. Haber, P. K. et al. Molecular markers of response to anti-PD1 therapy in advanced hepatocellular carcinoma. Gastroenterology 164, 72–88.e18 (2023).

9. Montironi, C. et al. Inflamed and non-inflamed classes of HCC: a revised immunogenomic classification. Gut 72, 129–140 (2023).
10. Llovet, J. M. et al. Trial design and endpoints in hepatocellular carcinoma: AASLD consensus conference. Hepatology 73, 158–191 (2021).
11. Abou-Alfa, G. K. et al. Phase 3 randomized, open-label, multicenter study of tremelimumab and durvalumab as first-line therapy in patients with unresectable hepatocellular carcinoma: HIMALAYA. J. Clin. Oncol. 40, 379 (2022).
12. Lau G, Abou-Alfa GK, Cheng AL, et al. Outcomes in the Asian subgroup of the phase III randomised HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. J Hepatol. 2025 Feb;82(2):258-267.