CALL FOR STAKEHOLDER COMMENTS ON THE PRELIMINARY RECOMMENDATION OF THE HEALTH TECHNOLOGY ASSESSMENT (HTA) COUNCIL ON (1) ATEZOLIZUMAB + BEVACIZUMAB AND (2) LENVATINIB FOR ADULTS DIAGNOSED WITH ADVANCED OR UNRESECTABLE HEPATOCELLULAR CANCER (HCC)

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As of 01 December 2025, the Health Technology Assessment Council has completed the evidence appraisal on the assessment of **(1) Atezolizumab [60 mg/mL, 20 mL vial for intravenous (IV) infusion] + Bevacizumab [25 mg/mL, 4 mL or 16 mL vial for IV infusion] and (2) Lenvatinib [4 mg/10 mg capsule] for adults diagnosed with advanced or unresectable HCC,** for possible government financing**.** The HTA Council hereby releases its **preliminary recommendation** on the said health technologies **for stakeholder feedback and comments from 01 to 16 December 2025.**

The population, interventions, comparators, and outcome (PICO) set by the HTA Council for the said evaluation are shown in the table below, for your reference:

Population	Adults diagnosed with advanced or unresectable hepatocellular carcinoma (HCC)	
Intervention/ Comparator	• Atezolizumab + Bevacizumab *(anti-Programmed Death-Ligand 1 [PD-L1] + anti-Vascular Endothelial Growth Factor [VEGF] combination)* • Lenvatinib *(oral multikinase inhibitor)* • Sorafenib *(oral multikinase inhibitor)* • Durvalumab *(anti-PD-L1)* • Durvalumab + Tremelimumab *(anti-PD-L1 + anti-Cytotoxic T-Lymphocyte-Associated Protein 4 [CTLA-4] combination)* • Placebo	
Outcome	*Efficacy Outcomes:*	*Safety Outcomes:*
	• Overall survival (OS) • Progression-free survival (PFS) • Time-to-progression (TTP) • Overall response rate • Objective response rate (ORR) • Duration of response • Health-related quality of life (HRQoL)	• Serious adverse events (SAEs) • Discontinuation due to adverse events

This health technology was also reviewed against the Philippine Food and Drug Administration (FDA) requirements for authorization, clinical evidence from systematic review with network meta-analysis (SRNMA) of randomized controlled trials (RCTs) and systematic reviews of observational studies, clinical practice guidelines (CPGs) *[local and approved by the Department of Health (DOH), such as the DOH Omnibus Health Guidelines (OHG); and/or international, but locally adopted guidelines*], and existing recommendations by the World Health Organization (WHO). Further, a costing analysis of this health technology was performed.

As a preliminary recommendation, **the HTA Council <u>recommends</u> the following for government financing:**

(1) Atezolizumab [60 mg/mL, 20 mL vial for intravenous (IV) infusion] **+ Bevacizumab** [25 mg/mL, 4 mL or 16 mL vial for IV infusion] **as preferred first-line treatment for adults diagnosed with advanced or unresectable HCC;** and,

(2) Lenvatinib [4 mg/10 mg capsule] **as first-line treatment for adults diagnosed with advanced or unresectable HCC who are not candidates for immunotherapy.**

Overall, based on current evidence, Atezolizumab + Bevacizumab shows superior overall survival compared to the other reviewed comparators (i.e., Lenvatinib, Sorafenib, Durvalumab, and Durvalumab + Tremelimumab) and, in terms of progression-free survival, both Atezolizumab + Bevacizumab and Lenvatinib are superior to Sorafenib and Durvalumab-based regimens. Generally, current guidelines recommend Atezolizumab + Bevacizumab as the first-line treatment for unresectable HCC, while Lenvatinib is also recommended for those who are not candidates for immunotherapy. Given the significant burden of HCC in the country and the absence of listed health technologies for HCC in the Philippine National Formulary (PNF), recommending Atezolizumab + Bevacizumab and Lenvatinib as first-line treatments for government financing ensures access to comprehensive unresectable HCC interventions. Both treatments, however, incur significant costs; hence, the Department of Health (DOH) should strongly consider conducting price negotiation to ensure affordability and sustainable access of these treatments.

This HTA Council preliminary recommendation is based on the following evidence:

Disease Magnitude and Severity

Globally and in the Philippines, liver cancer ranked as the sixth top cancer in terms of incidence and third top cause of cancer-related mortality (GLOBOCAN 2022). Hepatocellular carcinoma (HCC) is the predominant type of liver cancer caused by hepatitis B or C infection, alcoholic liver disease, non-alcoholic steatohepatitis/non-alcoholic fatty liver disease. In the Philippines, 67.37% of patients with liver cancer from 2007 to 2016 were diagnosed with HCC. According to a local study by Prieto & Jamias (2016) involving patients with HCC at the National Kidney and Transplant Institute (NKTI) from January 2008 to December 2014, most HCC cases were diagnosed at late stages *(43.5% were Barcelona Clinic Liver Cancer [BCLC] stage B and 43.81% had advanced stage on presentation [BCLC C/D])*. At these stages, HCC becomes unresectable because surgical removal of the tumor is no longer feasible. In terms of Child Pugh classification, local evidence has shown that more than half of patients with HCC (51.8%) are classified as Child Pugh B. This is followed by Child Pugh A at 23% and Child Pugh C at 17.6% (Ong, 2019). In the Philippines, the median overall survival of patients with HCC is 13.7 months. Globally, the late detection and ineligibility for resection contribute to its low five-year survival rate of approximately 18% (Kim, 2024).

Clinical Efficacy/Effectiveness and Safety

- **Clinical Efficacy/Effectiveness**

  There is limited evidence available for the drugs included in this assessment, with only one RCT for each direct comparison evaluating outcomes such as overall survival, progression-free survival, and objective response rate for Atezolizumab + Bevacizumab, Lenvatinib, Durvalumab, and Durvalumab + Tremelimumab against the common comparator, Sorafenib. Indirect comparisons from the adopted SRNMA were used to determine how each intervention of interest compares with the others.

  Overall, evidence consistently shows that Atezolizumab + Bevacizumab generally provides the best outcomes in terms of overall survival, progression-free survival, and objective response rate among the drugs assessed. Lenvatinib also demonstrates better progression-free survival and objective response rate compared with Sorafenib, and performs comparably to, or better than, Durvalumab-based regimens in indirect comparisons.

  The detailed results for each clinical outcome are summarized below.

  In terms of **overall survival**, direct comparisons with moderate to high certainty evidence show that combination therapies, specifically Atezolizumab + Bevacizumab and Durvalumab + Tremelimumab, are **superior** to Sorafenib. Furthermore, indirect comparisons indicate that Atezolizumab + Bevacizumab is **superior** to Lenvatinib, Durvalumab, and Durvalumab + Tremelimumab based on low to moderate certainty evidence.

  For **progression-free survival**, Atezolizumab + Bevacizumab and Lenvatinib are **superior** to Sorafenib in direct comparisons with high certainty evidence, while Durvalumab-based regimens showed varying results (i.e., as good as or better and inconclusive) compared to Sorafenib based on moderate certainty evidence. Meanwhile, indirect comparisons show that both Atezolizumab + Bevacizumab and Lenvatinib are **better** than Durvalumab-based regimens based on low certainty evidence, and when compared with each other, results show that Atezolizumab + Bevacizumab is **better** than Lenvatinib based on moderate certainty evidence.

  Regarding **objective response rate**, all four interventions/comparators (i.e., Atezolizumab + Bevacizumab, Lenvatinib, Durvalumab, and Durvalumab + Tremelimumab) **perform better** than Sorafenib in direct comparisons with high certainty evidence. However, indirect comparisons with moderate to low certainty evidence show **inconclusive evidence** on how these four treatments perform relative to each other.

- **Clinical Safety**

  Across the three (3) RCTs, the most common reported any-grade adverse effects (AEs) vary by intervention which are as follows:

  - Hemorrhage (25.0%), hypertension (23.7%), proteinuria (18.8%), fatigue (15.2%), and elevated liver enzymes Aspartate aminotransferase [AST] (14.0%) and Alanine aminotransferase [ALT] (10.3%) for **Atezolizumab + Bevacizumab** based on one (1) RCT with a total of 329 participants in the Atezolizumab + Bevacizumab arm

- Hypertension (42.0%), diarrhea (39.0%), decreased appetite (34.0%), and weight loss (31.0%) for **Lenvatinib** based on one (1) RCT with a total of 476 participants in the Lenvatinib arm
- Palmar-plantar erythrodysesthesia (hand-foot syndrome) (49.55%), diarrhea (45.17%), and hypertension (24.18%) for Sorafenib based on three (3) RCTs with a total of 1,005 participants in the Sorafenib arm
- Diarrhea (26.5%), pruritus (22.9%), rash (22.4%), fatigue (17.0%), decreased appetite (17.0%), elevated AST (12.4%), and elevated ALT (9.3%) for Tremelimumab + Durvalumab based on one (1) RCT with a total of 388 participants in the Tremelimumab + Durvalumab arm
- Diarrhea (14.9%), pruritus (14.4%), elevated AST (14.4%), decreased appetite (13.7%), elevated ALT (11.3%), rash (10.3%), and fatigue (9.8%) for Durvalumab based on one (1) RCT with a total of 388 participants in the Durvalumab arm.

Findings from 11 observational studies further indicate that Atezolizumab+Bevacizumab and Lenvatinib each carry adverse events when compared to each other. Atezolizumab + Bevacizumab has a **higher risk** of liver injury compared with Lenvatinib, while Lenvatinib is **associated with** hand–foot skin reactions, anorexia, diarrhea, fatigue, and rash. Pooled results from five (5) observational studies (*very low certainty of evidence*) show that overall adverse events occur **significantly lower** with Atezolizumab + Bevacizumab than with Lenvatinib [(OR 0.54 (95% CI 0.36 to 0.79)]. Similarly, the pooled results of four (4) studies (*very low certainty of evidence*) demonstrate that grade ≥3 adverse events are **significantly lower** for Atezolizumab + Bevacizumab than for Lenvatinib [OR 0.43 (95% CI 0.36 to 0.51)].

Other Evidence Considered

Seven (7) out of 13 guidelines reviewed provide positive recommendations for Atezolizumab + Bevacizumab, Lenvatinib, Sorafenib, and Durvalumab + Tremelimumab. In general, combination therapies such as Atezolizumab + Bevacizumab and Durvalumab + Tremelimumab are considered as the preferred first-line agents, while Lenvatinib and Sorafenib are considered as alternative options. Specific to the two (2) health technologies of interest, the recommendations are as follows:

1. **Atezolizumab + Bevacizumab as preferred first-line treatment for adults diagnosed with advanced or unresectable HCC**
   The combination therapy of Atezolizumab + Bevacizumab is **recommended as a first-line treatment** over Sorafenib for advanced-stage HCC in selected patients according to the DOH-approved Clinical Practice Guidelines for the Diagnosis and Management of Hepatocellular Carcinoma (2021) *(conditional recommendation, low certainty of evidence)*. It is also identified as the preferred first-line treatment for unresectable HCC in the Japan Guidelines on Systemic Therapy in Unresectable HCC (2021), the American Association for the Study of Liver Diseases (AASLD, 2023), the American Society of Clinical Oncology (ASCO, 2024), National Comprehensive Cancer Network Guidelines (NCCN, 2025), Clinical and Molecular Hepatology Review Summary of Asian Guidelines for HCC (2023), and the European Association for the Study of the Liver Guidelines (EASL, 2024). The ASCO (2024) and NCCN (2025) guidelines further specified that Atezolizumab + Bevacizumab is **recommended** for patients with good liver function (Child-Pugh A) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.

2. **Lenvatinib as first-line treatment for adults diagnosed with advanced or unresectable HCC who are not candidates for immunotherapy**
   The AASLD Guidelines (2023), NCCN Guidelines (2025), and Japan Guidelines on Systemic Therapy in Unresectable HCC (2021) recommend Lenvatinib for those who are not candidates for immunotherapy.

Costing Analysis

1. **Atezolizumab + Bevacizumab as preferred first-line treatment for adults diagnosed with advanced or unresectable HCC**
   The estimated annual treatment cost per patient with unresectable HCC using Atezolizumab + Bevacizumab is **Php 3,660,309.72 to Php 3,901,294.80**. Of this amount, Atezolizumab accounts for Php 1,759,824.00, while Bevacizumab accounts for Php 1,900,485.72 for patients weighing < 60 kg (assumed weight: 55 kg) and Php 2,141,470.80 for patients weighing ≥ 60 kg (assumed weight: 65 kg). The total annual cost is based on the cost of the drugs alone. Other cost components (i.e., cost of administration, cost of AE monitoring and management) were not considered in the analysis.

2. **Lenvatinib as first-line treatment for adults diagnosed with advanced or unresectable HCC who are not candidates for immunotherapy**
   The estimated annual treatment cost per patient with unresectable HCC using Lenvatinib ranges from **Php 2,737,500.00** (for patients weighing < 60 kg) **to Php 4,106,250.00** (for patients weighing ≥ 60 kg). The total annual cost is based on the cost of the drug alone. Other cost components (i.e., cost of administration, cost of AE monitoring and management) were not considered in the analysis.

For the supporting evidence reviewed and discussed by the HTA Council in coming up with this preliminary recommendation, please refer to: https://tinyurl.com/EvidenceAtezoBevaLenva. All comments, inputs, and/or appeals on the above preliminary recommendation may be submitted until **01 to 16 December 2025**, for the consideration of the HTA Council, through email at hta@dost.gov.ph. Please use the prescribed form for appeals indicated on the official HTA Philippines website [https://hta.dost.gov.ph/appeals-2/]. **Appeals not following the prescribed format and those submitted beyond the deadline, shall not be entertained**.

Should you have any questions or concerns regarding the preliminary recommendation, please do not hesitate to contact us through the same email address.

Thank you very much and best regards.

On behalf of the HTA Philippines:

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