# ASSESSMENT OF ATEZOLIZUMAB PLUS BEVACIZUMAB AND LENVATINIB IN THE TREATMENT OF PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC)

Health Technology Assessment Philippines

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# Policy Question

***Should atezolizumab + bevacizumab (60 mg/mL-25 mg/mL) IV infusions and/or lenvatinib (4 mg) capsule be financed by the government for adults with unresectable hepatocellular carcinoma (uHCC)?***

# PICO Table

| | |
|---|---|
| **Population** | Adults diagnosed with advanced or unresectable hepatocellular carcinoma (HCC) |
| **Intervention/ Comparator** | • Atezolizumab + Bevacizumab *(anti-PD-L1 + anti-VEGF combination)*<br>• Lenvatinib *(oral multikinase inhibitor)*<br>• Sorafenib *(oral multikinase inhibitor)*<br>• Durvalumab *(anti-PD-L1)*<br>• Durvalumab + Tremelimumab *(anti-PD-L1 + anti-CTLA-4 combination)*<br>• Placebo |
| **Outcome** | **Efficacy Outcomes:**<br>• Overall survival (OS)*<br>• Progression-free survival (PFS)*<br>• Time-to-progression (TTP)<br>• Overall response rate**<br>• Objective response rate (ORR)<br>• Duration of response<br>• Health-related quality of life (HRQoL)<br><br>**Safety Outcomes:**<br>• Serious adverse events (SAEs)<br>• Discontinuation due to adverse events |

*Ideal outcomes to be reported based on expert consultation:*
**Advanced stages: PFS and OS*
***Onco standard: Overall response rate (ORR)*

**Green:** health technologies that were nomination and prioritized
**Blue:** Comparators during the clinical assessment but are not priority topics
**Black:** included in the HTAC PICO and with results reported
**Purple:** No evidence found (included in the HTAC PICO but without results from evidence)

# Research Questions

## C1: Responsiveness to Magnitude and Severity

**RQ1.** What is the magnitude and severity of unresectable hepatocellular carcinoma (uHCC) as a public health concern?

## C2: Clinical efficacy, effectiveness and safety

**RQ2.1.** Among patients with uHCC, what is the effectiveness/efficacy of atezolizumab + bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?

**RQ2.2.** Among patients with uHCC, what is the safety of atezolizumab + bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?

## Other evidence considered

What are the recommendations and guidelines of ministries of health, HTA agencies and medical societies on the use of atezolizumab + bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo for uHCC?

# Regulatory status and WHO, PNF listing of the I/C drugs

| Drug | Drug Class | PH FDA registration | WHO EML Listing | PNF Listing |
|---|---|---|---|---|
| **Sorafenib** | TKI | Initial | Not listed in the WHO EML | **Not listed**<br><br>*Note: No other PNF-listed drugs specifically indicated for unresectable HCC.* |
| **Atezolizumab** | ICI (PD-L1 inhibitor) | Monitored-release | Rejected in WHO EML for a different indication (Lung cancer, rationale for rejection: uncertainty in clinical benefit, prohibitive cost) | |
| **Bevacizumab** | Anti-VEGF | Initial | Listed in the WHO EML but for age related macular degeneration | |
| **Lenvatinib** | TKI | Monitored release | Not listed in the WHO EML | |
| **Durvalumab*** | ICI (PD-L1 inhibitor) | No CPR found in the FDA verification portal | Rejected in WHO EML in 2023 for "*Other specified malignant neoplasms of bronchus or lung*" | |
| **Tremelimumab*** | ICI (CTLA-4) | Monitored-release | Not listed in the WHO EML | |

**Not in the approved HTAC PICO but added by the EAG after expert consultation*

# Outline of Presentation of Evidence

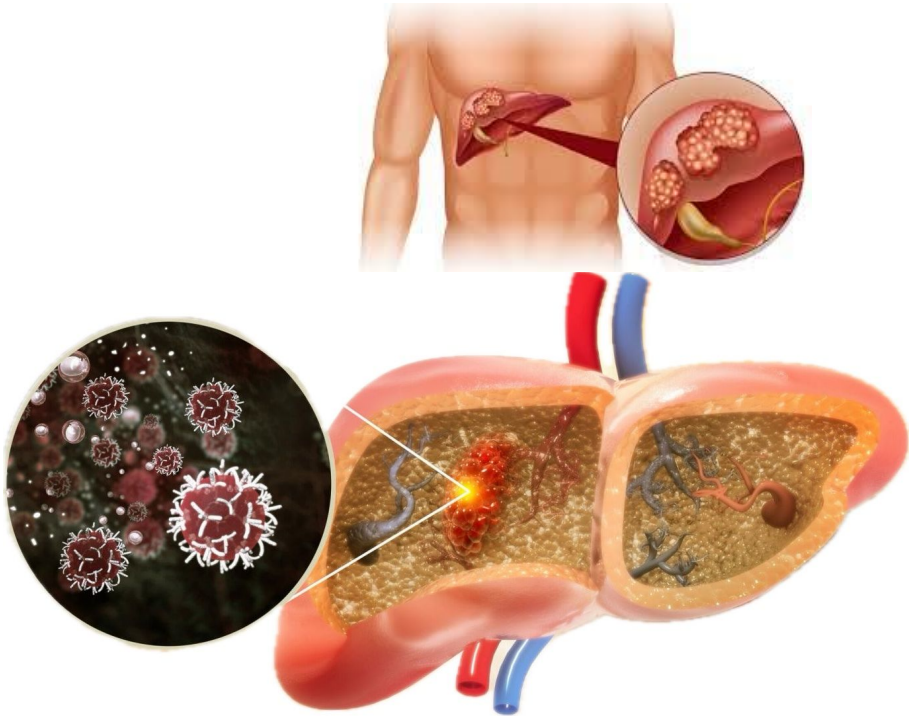
I. Burden of Disease
II. aHTA
    A. aHTA eligibility
    B. Review of Guidelines
    C. Review of Clinical Evidence
    D. aHTA Costing
    E. Overall judgment

# BURDEN OF DISEASE

*(Evidence on C1: Disease Magnitude and Severity)*

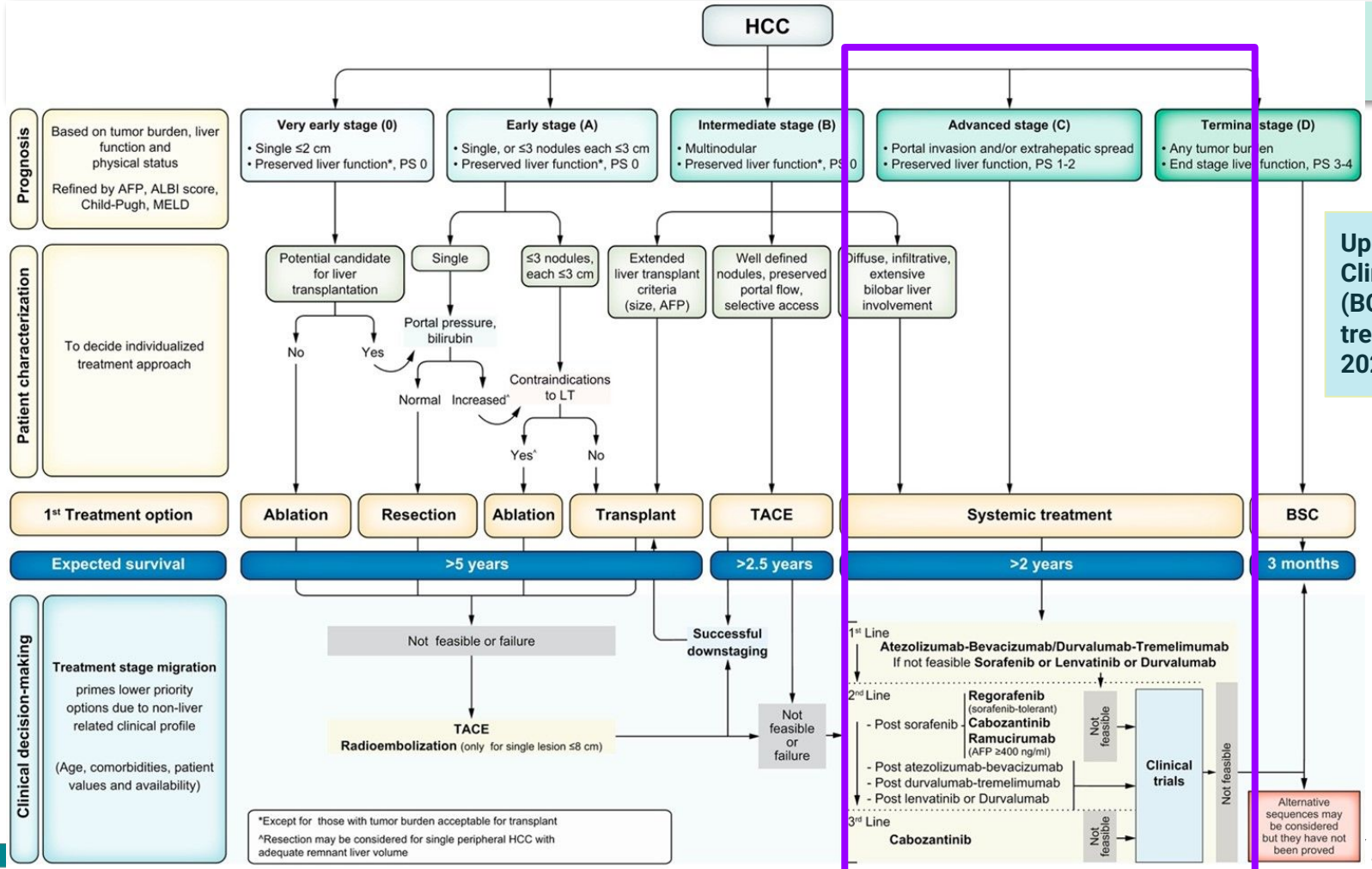
# Unresectable hepatocellular carcinoma (HCC)

- Hepatocellular carcinoma (HCC) is a primary tumor of the liver
- Caused by the following:
  - Hepatitis B
  - Hepatitis C
  - Alcoholic liver disease
  - Non-alcoholic liver steatohepatitis /non-alcoholic fatty liver disease
- Most patients are diagnosed at an advanced, unresectable stage due to the lack of noticeable clinical symptoms in the early phases



**Reference:** Asafo-Agye, 2023

*Atezo+Bev / Lenva*




**Updated Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy in 2022 ( *AASLD, 2023*)**

Lenva

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# Unresectable hepatocellular carcinoma (HCC): Child-Pugh Classification

| 2 Minute Medicine® | Child-Pugh Score | | 2minutemedicine.com |
|---|---|---|---|
| **Factor** | **1 point** | **2 points** | **3 points** |
| **Total bilirubin (µmol/L)** | <34 | 34-50 | >50 |
| **Serum albumin (g/L)** | >35 | 28-35 | <28 |
| **PT INR** | <1.7 | 1.71-2.30 | >2.30 |
| **Ascites** | None | Mild | Moderate to Severe |
| **Hepatic encephalopathy** | None | Grade I-II (or suppressed with medication) | Grade III-IV (or refractory) |

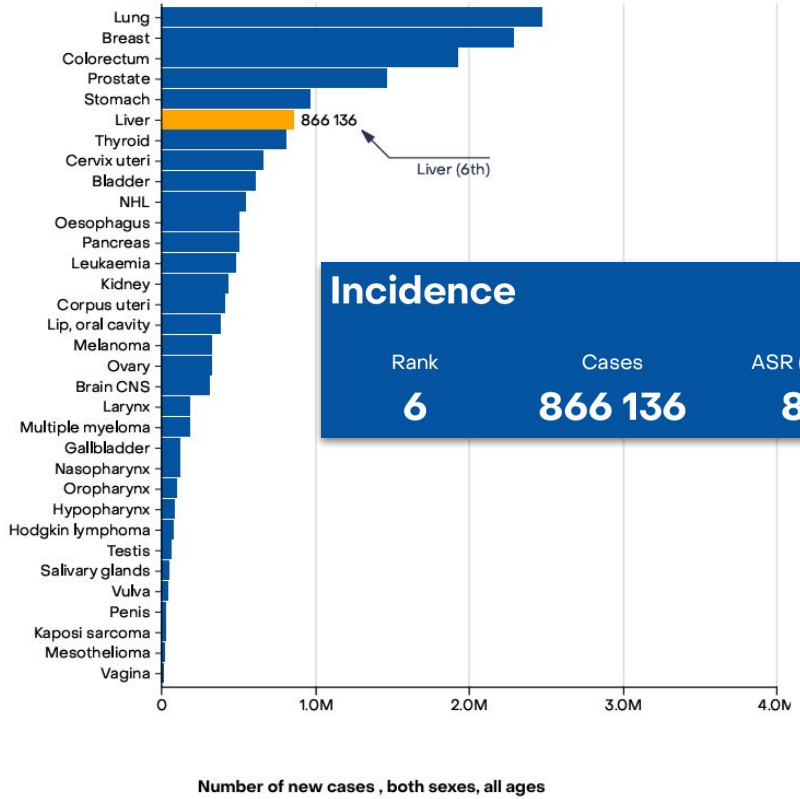
| | **Class A** | **Class B** | **Class C** |
|---|---|---|---|
| **Total points** | 5-6 | 7-9 | 10-15 |
| **1-year survival** | 100% | 80% | 45% |

Table I. Child-Pugh score.

**Reference:** Cheung (2025)

# C1: Disease Magnitude and Severity - Global Data [1 of 3]

**Incidence**

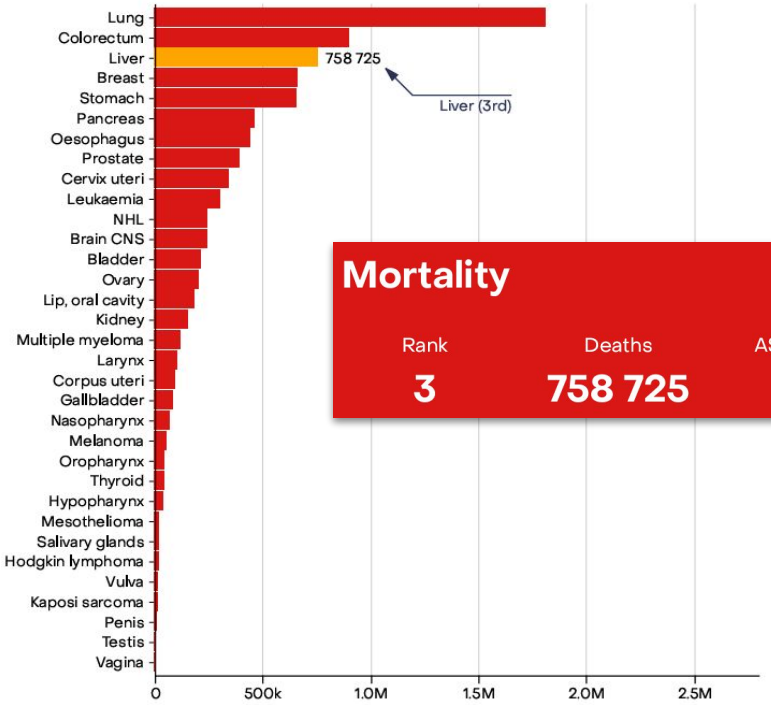



**Incidence**

| Rank | Cases | ASR (World) |
|---|---|---|
| 6 | 866 136 | 8.6 |

Number of new cases , both sexes, all ages

**Mortality**




**Mortality**

| Rank | Deaths | ASR (World) |
|---|---|---|
| 3 | 758 725 | 7.4 |

Number of deaths , both sexes, all ages

**Reference**: GLOBOCAN 2022

*Atezo+Bev / Lenva*

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# C1: Disease Magnitude and Severity - Global Data [2 of 3]

**Hepatocellular Carcinoma or HCC** *(Kim, 2024)*: ***Asia and worldwide***

- accounts for 80-90% of primary liver cancer cases
- 3rd leading cause of cancer-related death globally, with an only ~18% 5-year survival rate
- 2nd leading cause of malignant deaths in Asia
- 2nd most significant contributor to years of life lost due to cancer globally from 2005 to 2015 (a 4.6% increase in absolute years of life lost.)
- An estimated 80% of HCC cases arise in sub-Saharan Africa and Eastern Asia, aligning with the high prevalence of chronic hepatitis B virus (HBV) carriers in these regions.

# C1: Disease Magnitude and Severity - Global Data [3 of 3]

## Liver cancer incidence, mortality, and MIR in 2022 (GLOBOCAN,2022)

| Country | New cases | Incidence (per 100,000) | | Percent (%) | Liver cancer-related death cases | Mortality (per 100,000) | | Percent (%) | Mortality-to-incidence ratio | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Crude rate | ASR (World) | | | Crude rate | ASR (World) | | Crude rate | ASR (World) |
| Asia | 607,361 | 13.1 | 10.0 | 70.12 | 530,928 | 11.4 | 8.7 | 69.98 | 0.87 | 0.87 |
| China | 367,657 | 26.0 | 15.0 | 42.45 | 316,544 | 22.4 | 12.6 | 41.72 | 0.86 | 0.84 |
| India | 38,703 | 2.8 | 2.7 | 4.47 | 36,953 | 2.6 | 2.6 | 4.87 | 0.93 | 0.96 |
| Indonesia | 23,805 | 8.5 | 8.0 | 2.75 | 23,383 | 8.4 | 7.9 | 3.08 | 0.99 | 0.99 |
| Japan | 41,388 | 33.0 | 9.2 | 4.78 | 26,420 | 21.0 | 4.3 | 3.48 | 0.64 | 0.47 |
| Korea, Republic of | 14,791 | 28.8 | 13.7 | 1.71 | 12,595 | 24.5 | 10.7 | 1.66 | 0.85 | 0.78 |
| Korea, Democratic People Republic of | 6180 | 23.8 | 16.4 | 0.71 | 5791 | 22.3 | 15.3 | 0.76 | 0.94 | 0.93 |
| Mongolia | 2668 | 79.0 | 96.1 | 0.31 | 2164 | 64.1 | 80.2 | 0.29 | 0.81 | 0.83 |
| Thailand | 27,936 | 39.9 | 22.7 | 3.23 | 27,143 | 38.7 | 22.0 | 3.58 | 0.97 | 0.97 |
| Turkey | 5039 | 5.9 | 4.7 | 0.58 | 4929 | 5.8 | 4.4 | 0.65 | 0.98 | 0.94 |
| Viet Nam | 24,502 | 24.8 | 20.2 | 2.83 | 23,333 | 23.6 | 19.3 | 3.08 | 0.95 | 0.96 |

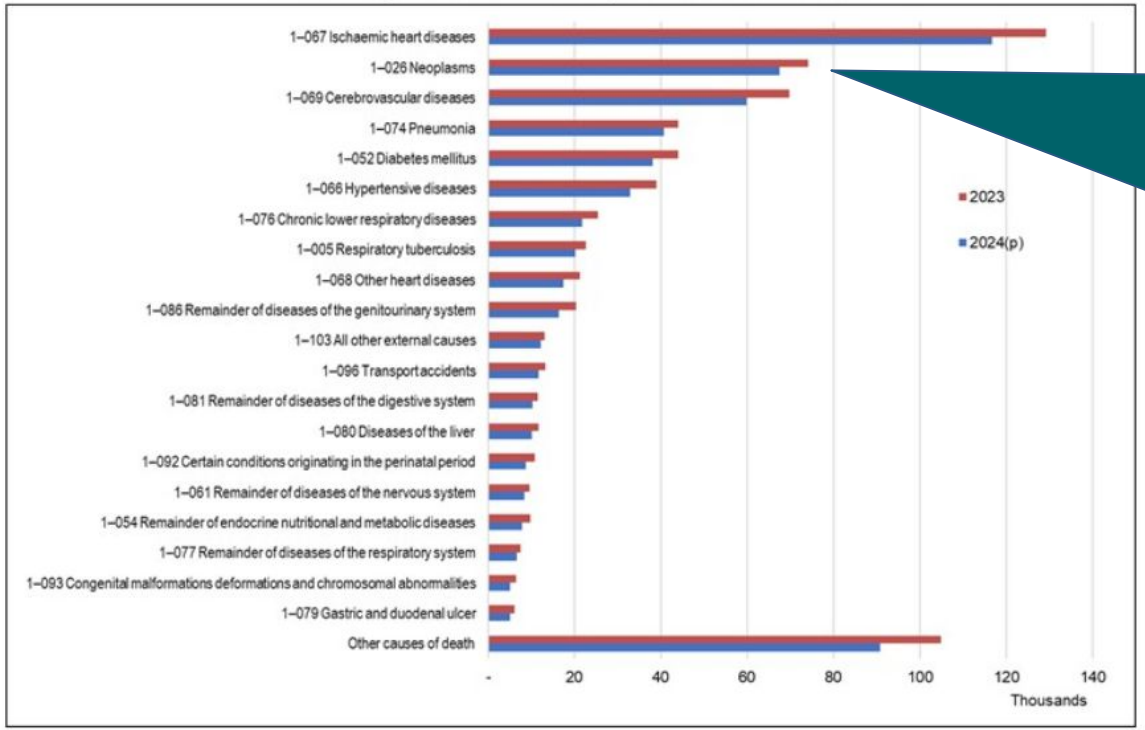
ASR, age-standardized rate per 100,000

- **Asia has the highest incidence of liver cancer cases** (70.12%) with an age-standardized incidence rates (ASIR) of 10.0 per 100,000
- The ASIRs were consistently higher among males than among females in the selected countries

Reference: Li, 2024

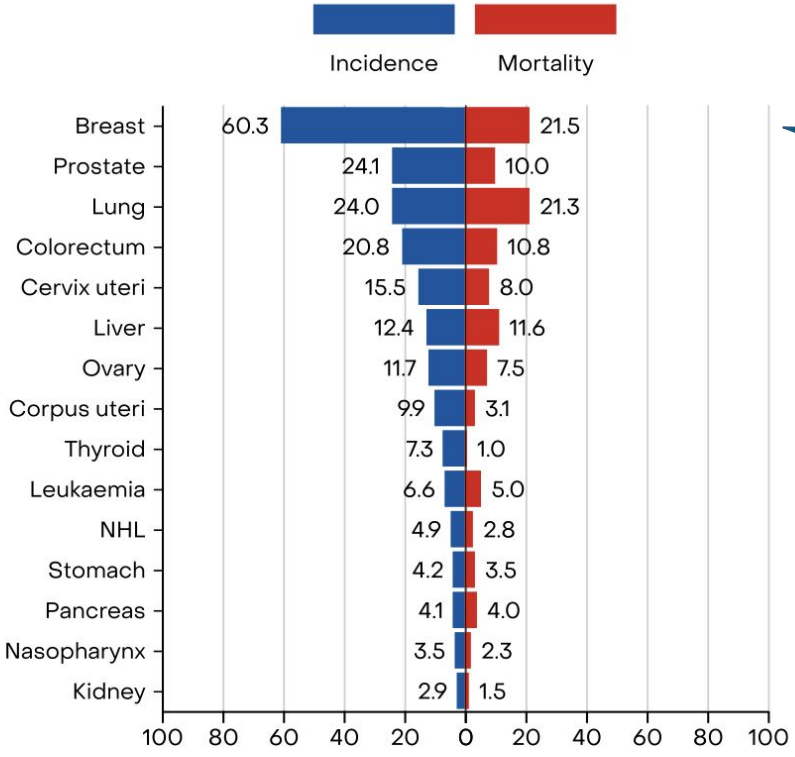
# C1: Disease Magnitude and Severity - Local Data [1 of 3]

Figure 1. Top 20 Causes of Mortality, Philippines:
January to December, 2023 and 2024




**PH MORTALITY DATA:**
HCC with an ICD code of C22.0 belongs to neoplasm which is the 2nd leading cause of death in the Philippines (PSA, 2024)

# C1: Disease Magnitude and Severity - Local Data [2 of 3]




**ASR (World) incidence and mortality rates, top 15 cancers****

**Liver Cancer in PH:**
Incidence: Top 6
Mortality: Top 3

**67.37%** of liver cancer patients hospitalized from 2007 to 2016 belong to the hepatocellular carcinoma group (Fausto et al., n.d.)

**Reference**: GLOBOCAN 2022

# C1: Disease Magnitude and Severity - Local Data [3 of 3]

| **Prognostic features, treatment outcomes and survival of hepatocellular carcinoma patients in National Kidney and Transplant Institute**<br><br>*(Cross-sectional study by Prieto & Jamias 2016)* | |
|---|---|
| Age (SD) | 61.47+13.08 years |
| Most common risk factors: | HBV infection |
| Stage of most HCC diagnosis | 43.5% were barcelona clinic liver cancer (BCLC) stage B and 43.81% had advanced stage on presentation (BCLC C/D); |
| Median survival | 13.7 months |

# C1: Disease Magnitude and Severity

- **Philippines:** Retrospective study (2019)
  - Total N = 1,260 patients with HCC from St. Luke's Medical Center, Quezon City (SLMC-QC) and Cardinal Santos Medical Center (CSMC) (2018-2020)
    - Patients with Child–Pugh A: 290 (23.0%)
    - Patients with Child–Pugh B: 653 (51.8%)
    - Patients with Child–Pugh C: 222 (17.6%)

- **Philippines:** Cross-sectional study (2014)
  - Total N = 20 patients with HCC among them, 11 patients were assessed with Child-Pugh score
    - Patients with Child–Pugh A: 4 (36.4%)
    - Patients with Child–Pugh B: 5 (45.5%)
    - Patients with Child–Pugh C: 2 (18.2%)

- **Pakistan:** Retrospective study (2025)
  - Total N = 104 patients with advanced HCC (BCLC stage C)
    - Patients with Child–Pugh A: 62 (59.6%)
    - Patients with Child–Pugh B: 36 (34.6%)
    - Patients with Child–Pugh C: 6 (5.8%)

# C1: Disease Magnitude and Severity

- **Taiwan:** Epid study (2023) → investigates secular trends of Child-Pugh among patients with HCC
  - Total N = 73,817 HCC cases identified between 2011 and 2019
    If we divided the study period into 2011–2014 and 2015–2019:
    - Proportion of Child–Pugh class A increased from 75.6% to 77.9%
    - Proportions of Child–Pugh B and C decreased from 18.1% to 16.8%

- **Taiwan:** Retrospective study (2024)
  - Total N= 72 patients with advanced hepatocellular carcinoma treated with lenvatinib-based therapy
    - Patients with Child–Pugh A: 69 (95.8%)
    - Patients with Child-Pugh B: 3 (4.2%)

- **Korea:** Retrospective study (2020)
  - Total N= 92 patients with advanced HCC treated with lenvatinib (September 2018 and January 2020)
    - Patients with Child–Pugh A: 74 (80.4%)
    - Patients with Child-Pugh B: 18 (19.6%)

# C1. Responsiveness to Magnitude and Severity

## RQ.1. What is the magnitude and severity of unresectable HCC as a public health concern?

**HTAC Judgment:**

Globally and in the Philippines, liver cancer ranked as the 6th most common cancer in terms of incidence and 3rd leading 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 liver steatohepatitis/non-alcoholic fatty liver disease. In the Philippines, 67.37% of patients from 2007 to 2016 with liver cancer are diagnosed with HCC .

According to a local study by Prieto & Jamias (2016), which included patients with HCC in 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)]. HCC becomes unresectable when 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). The median overall survival of patients with HCC in the Philippines is 13.7 months. Globally, the late detection and ineligibility for resection has contributed to its low 5-year survival rate of approximately 18% (Kim, 2024).

# aHTA OF ATZ+BEV & LENVATINIB

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# aHTA ELIGIBILITY

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# Atezolizumab + Bevacizumab in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (uHCC)

| | |
|---|---|
| **Is there a DOH-approved/ local society CPG recommending this HT?** | Recommended in the DOH-approved CPG for the Diagnosis and Management of Hepatocellular Carcinoma 2021 *"We suggest the use of combination therapy (at Atezolizumab plus bevacizumab) over sorafenib as a first-line treatment for advanced-stage hepatocellular carcinoma in selected patients." (conditional recommendation, low certainty of evidence)* |
| **Is the HT in the WHO EML?** | Bevacizumab: Listed in the WHO EML but for age related macular degeneration<br>Atezolizumab: Rejected in WHO EML for a different indication (Lung cancer, rationale for rejection: uncertainty in clinical benefit, prohibitive cost) |
| **Is there an international CPG adopted by the local medical society recommending this HT?** | Not assessed |
| **Is there a local society certifying the HT as standard of care?** | Recommendation from the same DOH-approved CPG for the Diagnosis and Management of Hepatocellular Carcinoma 2021 which is also a joint statement from relevant medical societies:<br>*-Philippine Association of Hepato-pancreato Biliary Surgeons*<br>*-Hepatology Society of the Philippines*<br>*-Philippine Society of Medical Oncology*<br>*-Surgical Oncology Society of the Philippines*<br>*-Philippine Society of Gastroenterology*<br>*-Philippine Society of General Surgeons*<br>*-Philippine Society of Vascular and Interventional Radiology* |

# Lenvatinib in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (uHCC)

| | |
|---|---|
| **Is there a DOH-approved/ local society CPG recommending this HT?** | Not included in any of the DOH OHGs<br>Mentioned in the DOH-approved CPG for the Diagnosis and Management of Hepatocellular Carcinoma 2021 but no strong recommendation due to insufficient evidence:<br>"*There is insufficient evidence to recommend the addition of targeted therapy (eg., sorafenib, lenvatinib) to transarterial chemoembolization in BCLC B hepatocellular carcinoma. (no recommendation, low certainty of evidence)*" |
| **Is the HT in the WHO EML?** | Not listed in the WHO EML |
| **Is there an international CPG adopted by the local medical society recommending this HT?** | **Yes**.<br><br>Local medical society (i.e., Hepatology Society of the Philippines): *In the Philippine context, HSP recommends lenvatinib as first-line systemic therapy for unresectable or advanced HCC (BCLC C) with good performance status and Child–Pugh A liver function and as alternative systemic option for patients who are intolerant to or unsuitable for sorafenib.*<br><br>HSP follows and adopts the two international guidelines: (1) EASL 2024/2025 and (2) AASLD 2023 (See review of guidelines) |
| **Is there a local society certifying the HT as standard of care?** | |

# Review of Guidelines

# Overview of Country Recommendations Reviewed

| | |
|---|---|
| **United States** (n=3) | 2024 American Society of Clinical Oncology (ASCO) Guideline Update for systemic therapy in unresectable hepatocellular carcinoma (HCC |
| | NCCN 2025 Guideline Summary: Systemic Therapy in Unresectable Hepatocellular Carcinoma (HCC) |
| | American Association for the Study of Liver Diseases (AASLD) |
| **Europe** (n=1) | European Association for the Study of the Liver |
| **Japan** (n=1) | Japan Society of Hepatology (JSH) 2021 Guidelines: Systemic Therapy in Unresectable HCC |
| **Philippines** (n=1) | 2021 Philippine Clinical Practice Guideline for the Diagnosis and Management of Hepatocellular Carcinoma |
| **Asian Countries** (i.e., China, Hong Kong, Taiwan, Japan, and South Korea, n=1) | Asian Guidelines Summary on Systemic Therapy for Unresectable Hepatocellular Carcinoma (HCC) |
| **Asia Pacific Region** | Asian Pacific Association for the Study of the Liver (APASL) (2024) |

# Review of Guidelines [1 of 4]

**Positive recommendations**

| Country/Agency | Recommendation |
|---|---|
| **United States**<br>• American Society of Clinical Oncology (ASCO) 2024 | • **Atezolizumab + bevacizumab is listed as a preferred first-line regimen** for patients with good liver function (Child-Pugh A) and ECOG 0–1<br>• **Durvalumab + Tremelimumab is recommended as an alternative first-line** option for patients with unresectable HCC who are eligible for immunotherapy. Particularly useful when anti-VEGF therapy (e.g., bevacizumab) is contraindicated. |
| **US**<br>National Comprehensive Cancer Network (NCCN) 2025 | **Preferred first-line regimen:**<br>• **Atezolizumab plus bevacizumab** for patients with Child-Turcotte-Pugh (CTP) Class A liver function, good performance status, and no contraindications to immunotherapy or anti-VEGF therapy.<br>• **Durvalumab plus tremelimumab** (STRIDE regimen) is another preferred first-line immunotherapy-based combination. For patients who cannot tolerate immunotherapy, tyrosine kinase inhibitors such as **lenvatinib** remain viable options.<br>**Other Recommended regimen:**<br>• **Lenvatinib** remains a preferred oral option for patients who are not candidates for immunotherapy or in centers where infusion access is limited.<br>• Considered for patients with bleeding risks or autoimmune conditions where atezolizumab–bevacizumab may be contraindicated.<br>• Durvalumab is recommended for who have not been previously treated with ICI |

# Review of Guidelines [2 of 4]

**Positive recommendations**

| Country/Agency | Recommendation |
|---|---|
| **United States**<br>• American Association for the Study of Liver Diseases (AASLD) | **Preferred first-line regimen:**<br>• IMbrave150 trial established the combination of **atezolizumab,** an immunotherapy targeting PD-L1, **plus bevacizumab,** a monoclonal antibody targeting VEGF, as the preferred first-line treatment option for patients with advanced HCC.<br>**Other Recommended regimen:**<br>• **Durvalumab plus tremelimumab** is another preferred option for patients in the first-line setting, particularly for patients who are not candidates for anti-VEGF therapy.<br>• Both **sorafenib and lenvatinib** remain first-line treatment options for patients with advanced HCC who are not candidates for newer first-line combination therapies.<br>• **Durvalumab alone** may be a treatment option for select patients in the first-line setting who are not candidates for combination therapies. |
| **Europe**<br>• European Association for the Study of the Liver | **Preferred first-line regimen:**<br>• Combination therapy containing PD-1 or PD-L1 inhibitors should be considered first-line standard of care for those without contraindications to immune checkpoint inhibitor (ICIs) (and bevacizumab).<br>**Other recommended regimen:**<br>• Sorafenib and lenvatinib remain first-line options in these patients and both single agent durvalumab and tislelizumab may also be considered. |

# Review of Guidelines [3 of 4]

**Positive recommendations**

| Country/Agency | Recommendation |
|---|---|
| **Japan**<br>• Japan Society of Hepatology: 2021 Guidelines on Systemic Therapy in Unresectable HCC: | First-Line Systemic Therapy Recommendations:<br>• For systemic therapy-naïve patients who are not candidates for resection, transplantation, ablation, or TACE, the combination of **atezolizumab plus bevacizumab is the preferred first-line regimen.**<br>• **If contraindications to immunotherapy exist, monotherapy with lenvatinib or sorafenib is advised.**<br>Lenvatinib as an Alternative First-Line Option<br>• **Lenvatinib,** a multikinase inhibitor, is **indicated for patients ineligible for atezolizumab–bevacizumab.** It is especially considered for patients with autoimmune disease or bleeding risk, or where infusion access is limited. |
| **Asian Countries (i.e., China, Hong Kong, Taiwan, Japan, South Korea)**<br>• 2023 Clinical and Molecular Hepatology review summary of Asian guidelines for hepatocellular carcinoma (HCC) | • China (2019): Atezolizumab + bevacizumab, donafenib, sintilimab + biosimilar, FOLFOX<br>• Hong Kong (2021): Atezolizumab + bevacizumab, sorafenib, lenvatinib, nivolumab<br>• Taiwan (2020): Atezolizumab + bevacizumab, sorafenib, lenvatinib<br>• Japan (2021): Atezolizumab + bevacizumab, sorafenib, lenvatinib<br>• Korea (2022): Atezolizumab + bevacizumab, durvalumab + tremelimumab, sorafenib, Lenvatinib |
| **Asia-Pacific Region**<br>• Asian Pacific Association for the Study of the Liver (APASL) (2024) | First-Line Systemic Therapy Recommendations:<br>• The first choice of systemic therapy should be anti-VEGF + anti-PD-1/anti-PD-L1* **(in those without risk of bleeding)** or dual ICIs with anti CTLA-4 and anti-PD1/anti-PDL1 or anti-PD-1/anti-PD-L1 |

# Review of Guidelines [4 of 4]

**Positive recommendations**

| Country/Agency | Recommendation |
|---|---|
| **Philippines**<br>The Philippine Clinical Practice Guidelines for the Diagnosis and Management of Hepatocellular Carcinoma 2021<br>**Joint statement from:**<br>• Philippine Association of Hepato-Pancreato-Biliary Surgeon (PAHBS)<br>• Hepatology Society of the Philippines (HSP)<br>• Philippine Society of Medical Oncology (PSMO)<br>• Surgical Oncology Society of the Philippines (SOSP)<br>• Philippine Society of Vascular and And Interventional Radiology (PSVIR)<br>• Philippine Society of General Surgeons (PSGS)<br>• Philippine Society of Gastroenterology (PSG) | *"We suggest the use of combination therapy (atezolizumab plus bevacizumab) over sorafenib as a first-line treatment for advanced-stage hepatocellular carcinoma in selected patients (conditional strength, low certainty of evidence)"* |

# Review of Guidelines

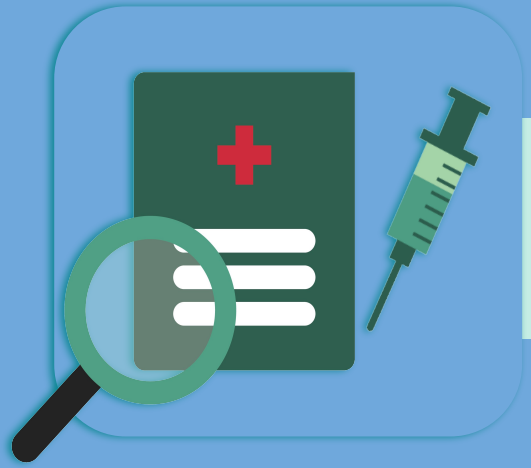
**What are the recommendations and guidelines of ministries of health, HTA agencies and medical societies on the use of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo for uHCC?**

**[HTAC Judgment]**

Eight out of fourteen guidelines scoped had positive recommendations for atezolizumab+bevacizumab, lenvatinib, sorafenib and durvalumab + tremelimumab. In general, Atezolizumab+Bevacizumab and Durvalumab+ Tremelimumab are considered the preferred first line agents while Lenvatinib and Sorafenib are considered alternatives.

Specifically, the 2021 Philippine Clinical Practice Guideline for the Diagnosis and Management of Hepatocellular Carcinoma, 2021 Japan Guidelines on Systemic Therapy in Unresectable HCC, the 2023 American Association for the Study of Liver Diseases (AASLD), The American Society of Clinical Oncology (ASCO) 2024, National Comprehensive Cancer Network (NCCN) 2025 guidelines, 2023 Clinical and Molecular Hepatology review summary of Asian guidelines for hepatocellular carcinoma (HCC), 2024 European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver (APASL) recommend Atezolizumab + Bevacizumab as the preferred first line treatment for unresectable HCC. Two guidelines, (i.e., ASCO 2024 and NCCN 2025) specified that combination therapy of atezolizumab+bevacizumab is recommended for patients with good liver function (Child-Pugh A) and ECOG performance status 0–1.

Recommendations for the use of monotherapy such as lenvatinib was stated in the 2021 Japan Guidelines on Systemic Therapy in Unresectable HCC, 2023 AASLD and NCCN 2025 guidelines for patients who are not candidates for immunotherapy.



# **Review of Clinical Evidence** *(Evidence on C2: Clinical Efficacy/ Effectiveness and Safety)*

# Review of Clinical Evidence *(Evidence on C2: **Clinical Efficacy/ Effectiveness** and Safety)*

# Summary of efficacy outcomes: Direct comparison

| DIRECT COMPARISON: OVERALL SURVIVAL | | | |
|---|---|---|---|
| **I and C** | **HR (95% CI)** | **jSC interpretation** | **Certainty of Evidence** |
| Atz+Bev vs Sorafenib | 0.66 (0.52 to 0.85) | Favors I | High |
| Lenvatinib vs Sorafenib | 0.92 (0.79 to 1.06) | As good as or better | Moderate |
| Durv+Trem vs Sorafenib | 0.78 (0.65 to 0.92) | Favors I | High |
| Durvalumab vs Sorafenib | 0.86 (0.73 to 1.03) | As good as or better | Moderate |

**Key findings:**

- Based on the direct comparisons, the **combination therapies (i.e., Atezo+Bev and Durv+Trem) are superior over sorafenib;**
- **Other monotherapies (i.e., Lenvatinib and Durvalumab) are as good as or better than sorafenib** in terms of overall survival.

# Summary of efficacy outcomes: Indirect comparison

| INDIRECT COMPARISON: OVERALL SURVIVAL | | | |
|---|---|---|---|
| **I and C** | **HR (95% CI)** | **jSC interpretation** | **Certainty of Evidence** |
| Atz+Bev vs Lenvatinib | 0.51 (0.50, 0.53) | Favors Atz+Bev | Low |
| Atz+Bev vs Durvalumab | 0.59 (0.57, 0.61) | Favors Atz+bev | Moderate |
| Atz+Bev vs Durv+Trem | 0.72 (0.69, 0.74) | Favors Atz+bev | Low |
| Durvalumab vs Lenva | 0.87 (0.85 to 0.90) | Favors Durvalumab | Low |
| Durv+Trem vs Lenva | 0.72 (0.70, 0.74) | Favors Durv+Trem | Low |
| Durv+Trem vs Durva | 0.82 (0.80, 0.85) | Favors Durv+Trem | Moderate |

**Key findings:**

- Based on the indirect comparisons, **Atz+Bev is superior over lenvatinib, durvalumab and durvalumab + tremelimumab**

# Summary of efficacy outcomes: Direct comparison

| DIRECT COMPARISON: PROGRESSION FREE SURVIVAL | | | |
|---|---|---|---|
| **I and C** | **HR (95% CI)** | **jSC interpretation** | **Certainty of Evidence** |
| Atz+Bev vs Sorafenib | 0.59 (0.47 to 0.76) | Favors I | High |
| Lenvatinib vs Sorafenib | 0.66 (0.57 to 0.77) | Favors I | High |
| Durv+Trem vs Sorafenib | 0.90 (0.77 to 1.05) | As good as or better | Moderate |
| Durvalumab vs Sorafenib | 1.02 (0.88 to 1.19) | Inconclusive | Moderate |

**Key findings:**

- Based on the direct comparisons, the combination therapy of **Atz+Bev and Lenvatinib are superior over sorafenib.** Durvalumab-based regimens showed varying results (i.e., as good as or better and inconclusive) compared to sorafenib.

# Summary of efficacy outcomes: Indirect comparison

| INDIRECT COMPARISON: PROGRESSION FREE SURVIVAL | | | |
|---|---|---|---|
| **I and C** | **HR (95% CI)** | **jSC interpretation** | **Certainty of Evidence** |
| Atz+Bev vs Lenvatinib | 0.80 (0.78 to 0.82) | Favors Atz+Bev | Moderate |
| Atz+Bev vs Durvalumab | 0.33 (0.33 to 0.34) | Favors Atz+Bev | Low |
| Atz+Bev vs Durv+Trem | 0.43 (0.42 to 0.44) | Favors Atz+Bev | Low |
| Lenvatinib vs Durvalumab | 0.42 (0.41 to 0.42) | Favors Lenvatinib | Low |
| Lenvatinib vs Durv+Trem | 0.54 (0.53 to 0.55) | Favors Lenvatinib | Low |
| Durvalumab vs Durv+Trem | 0.78 (0.77 to 0.79) | Favors Durvalumab | Moderate |

**Key findings:**

- Based on the indirect comparisons, **Atz+Bev and Lenvatinib is better compared to durvalumab-based regimen. When compared with each other, Atz+Bev is better than lenvatinib in terms of PFS**

# Summary of efficacy outcomes: Direct comparison

| DIRECT COMPARISON: OBJECTIVE RESPONSE RATE (ORR) | | | | |
|---|---|---|---|---|
| **I and C** | **% response (I vs C)** | **OR (95% CI)** | **jSC interpretation** | **Certainty of Evidence** |
| Atz+Bev vs Sorafenib | 27.0% vs 12.0% | 2.77 (1.62 to 4.73) | Favors I | High |
| Lenvatinib vs Sorafenib | 24.1% vs 9.2% | 3.11 (2.13 to 4.54) | Favors I | High |
| Durv+Trem vs Sorafenib | 20.1% vs 5.1% | 4.65 (2.82 to 7.68) | Favors I | High |
| Durvalumab vs Sorafenib | 17.0% vs 5.1% | 3.77 (2.25 to 6.32) | Favors I | High |

**Key findings:**

- Based on the direct comparisons, **Atz+Bev, Lenvatinib, Durvalumab and Durv+Trem are better than sorafenib.**

# Summary of efficacy outcomes: Indirect comparison (3 of 3)

| INDIRECT COMPARISON: OBJECTIVE RESPONSE RATE | | | |
|---|---|---|---|
| **I and C** | **OR (95% CI)** | **jSC interpretation** | **Certainty of Evidence** |
| Lenva vs Atz+Bev | 1.01 (0.29, 3.52) | Inconclusive | **Low** |
| Durva vs Atz+bev | 1.44 (0.41, 5.03) | Inconclusive | **Low** |
| Durv+Trem vs Atz+Bev | 2.19 (0.63, 7.63) | Inconclusive | **Low** |
| Durva vs Lenva | 1.43 (0.41, 4.98) | Inconclusive | **Low** |
| Durv+Trem vs Lenva | 2.17 (0.62, 7.55) | Inconclusive | **Low** |
| Durv+Trem vs Durva | 1.52 (0.43, 5.29) | Inconclusive | **Moderate** |

**Key findings: There is inconclusive evidence** on the effect of Atezo+Bev, Lenva, Durva, Durv+Trem on objective response rate when compared to each other

# C2. Efficacy, Effectiveness, and Safety [1 of 6]

**RQ.2.1. Among patients with uHCC, what is the efficacy/effectiveness of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

**[HTAC Judgment]**

Overall, there is limited evidence for the drug topics appraised in this assessment with only one RCT available per direct comparison. The following efficacy outcomes: overall survival, progression-free survival and objective response rate came from direct comparisons of atezolizumab+bevacizumab, lenvatinib, durvalumab, durvalumab+tremelimumab with the common comparator sorafenib. Indirect comparisons from the adopted SR-NMA were used to determine how each intervention of interest compares with each other.

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 other drugs assessed. Lenvatinib also showed better clinical effects in terms of progression-free survival and objective response rate when compared with Sorafenib; and performs comparably to, or better than Durvalumab-based regimens in indirect comparisons.

# C2. Efficacy, Effectiveness, and Safety [1 of 6]

**RQ.2.1. Among patients with uHCC, what is the efficacy/effectiveness of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

**[HTAC Judgment]**

*(1.1) Overall survival: Direct comparison*

**Based on the direct comparisons, the combination therapies (i.e., Atezo+Bev and Durv+Trem) are superior over sorafenib. Other monotherapies (i.e., Lenvatinib and Durvalumab) are as good as or better than sorafenib in terms of overall survival.**

- Based on 1 RCT with high certainty of evidence, the direct comparison of ATZ+BEV and sorafenib show that ATZ+BEV increases overall survival compared to sorafenib [HR 0.66 (0.52 to 0.85)].
- Based on 1 RCT with moderate certainty of evidence, the direct comparison of lenvatinib and sorafenib show that lenvatinib is as good as or better than sorafenib in increasing overall survival [HR 0.92 (0.79 to 1.06)].
- Based on 1 RCT with moderate certainty of evidence, the direct comparison of DURV+TREM and sorafenib show that DURV+TREM increases overall survival compared to sorafenib [HR 0.78 (0.65 to 0.92)].
- Based on 1 RCT with high certainty of evidence, the direct comparison of durvalumab and sorafenib show that durvalumab is as good as or better than sorafenib in increasing overall survival [HR 0.86 (0.73 to 1.03)].

**Hazard ratio of death from any cause*

# C2. Efficacy, Effectiveness, and Safety [2 of 6]

**RQ.2.1. Among patients with uHCC, what is the efficacy/effectiveness of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

**[HTAC Judgment]**

*(1.2) Overall survival: Indirect comparison*

**Based on the indirect comparisons, Atz+Bev is superior over lenvatinib, durvalumab and durvalumab + tremelimumab.**

- Based on 2 RCTs with low certainty of evidence, the indirect comparison of ATZ+BEV and lenvatinib show that ATZ+BEV increases overall survival compared to lenvatinib [HR 0.51 (0.50, 0.53)].
- Based on 2 RCTs with moderate certainty of evidence, the indirect comparison of ATZ+BEV and durvalumab show that ATZ+BEV increases overall survival compared to durvalumab [HR 0.59 (0.57, 0.61)].
- Based on 2 RCTs with low certainty of evidence, the indirect comparison of ATZ+BEV and DURV+TREM show that ATZ+BEV increases overall survival compared to DURV+TREM [HR 0.72 (0.69, 0.74)].
- Based on 2 RCTs with low certainty of evidence, the indirect comparison of durvalumab and lenvatinib show that durvalumab increases overall survival compared to lenvatinib [HR 0.87 (0.85 to 0.90)].
- Based on 2 RCTs with low certainty of evidence, the indirect comparison of DURV+TREM and lenvatinib show that DURV+TREM increases overall survival compared to lenvatinib [HR 0.72 (0.70, 0.74)].
- Based on 2 RCTs with moderate certainty of evidence, the indirect comparison of DURV+TREM and durvalumab show that DURV+TREM increases overall survival compared to durvalumab [HR 0.82 (0.80, 0.85)].

**Hazard ratio of death from any cause*

# C2. Efficacy, Effectiveness, and Safety [3 of 6]

**RQ.2.1. Among patients with uHCC, what is the efficacy/effectiveness of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

**[HTAC Judgment]**

*(2.1) Progression free survival: Direct comparison*

**Based on the direct comparisons, the combination therapy of Atz+Bev and Lenvatinib are superior over sorafenib. Durvalumab-based regimens showed varying results (i.e., as good as or better and inconclusive) compared to sorafenib.**

- Based on 1 RCT with high certainty of evidence, the direct comparison of ATZ+BEV and sorafenib show that ATZ+BEV increases progression free survival compared to sorafenib [HR 0.59 (0.47 to 0.76)].
- Based on 1 RCT with high certainty of evidence, the direct comparison of lenvatinib and sorafenib show that lenvatinib increases progression free survival compared to sorafenib [HR 0.66 (0.57 to 0.77)].
- Based on 1 RCT with moderate certainty of evidence, the direct comparison of DURVA+TREM and sorafenib show that DURVA+TREM is as good as or better than sorafenib in terms of progression free survival [HR 0.90 (0.77 to 1.05)].
- Based on 1 RCT with moderate certainty of evidence, the direct comparison of durvalumab and sorafenib show there is an inconclusive evidence between the two in terms of progression free survival [HR 1.02 (0.88 to 1.19)].

**Hazard ratio of progression based on RECIST 1.1. Or mRECIST criteria or death*

# C2. Efficacy, Effectiveness, and Safety [4 of 6]

**RQ.2.1. Among patients with uHCC, what is the efficacy/effectiveness of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

**[HTAC Judgment]**

*(2.2) Progression free survival: Indirect comparison*

**Based on the indirect comparisons, Atz+Bev and Lenvatinib is better compared to durvalumab-based regimen. When compared with each other, Atz+Bev is better than lenvatinib in terms of PFS.**

- Based on 2 RCTs with moderate certainty of evidence, the indirect comparison of ATZ+BEV and lenvatinib show that ATZ+BEV increases progression free survival compared to lenvatinib [HR 0.80 (0.78 to 0.82)].
- Based on 2 RCTs with low certainty of evidence, the indirect comparison of ATZ+BEV and durvalumab show that ATZ+BEV increases progression free survival compared to durvalumab [HR 0.33 (0.33 to 0.34)].
- Based on 2 RCTs with low certainty of evidence, the indirect comparison of ATZ+BEV and DURV+TREM show that ATZ+BEV increases progression free survival compared to DURV+TREM [HR 0.43 (0.42 to 0.44)].
- Based on 2 RCTs with low certainty of evidence, the indirect comparison of lenvatinib and durvalumab show that lenvatinib increases progression free survival compared to durvalumab [HR 0.42 (0.41 to 0.42)].
- Based on 2 RCTs with low certainty of evidence, the indirect comparison of lenvatinib and DURV+TREM show that lenvatinib increases progression free survival compared to DURV+TREM [HR 0.54 (0.53 to 0.55)].
- Based on 2 RCTs with moderate certainty of evidence, the indirect comparison of durvalumab and DURV+TREM show that Durvalumab increases progression free survival compared to DURV+TREM [HR 0.78 (0.77 to 0.79)].

**Hazard ratio of progression based on RECIST 1.1. Or mRECIST criteria or death*

# C2. Efficacy, Effectiveness, and Safety [5 of 6]

**RQ.2.1. Among patients with uHCC, what is the effectiveness/efficacy of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

**[HTAC Judgment]**

*(3.1) Objective response rate (ORR): Direct comparison*

**Based on the direct comparisons, Atz+Bev, Lenvatinib, Durvalumab and Durv+Trem are better than sorafenib.**

- Based on 1 RCT with high certainty of evidence, the direct comparison of ATZ+BEV and sorafenib show that approximately, tumor response is thrice higher when patients are given ATZ+BEV compared to those given sorafenib [OR 2.77 (1.62 to 4.73)].
- Based on 1 RCT with high certainty of evidence, the direct comparison of lenvatinib and sorafenib show that approximately, tumor response is thrice higher when patients are given lenvatinib compare to those given sorafenib [OR 3.11 (2.13 to 4.54)].
- Based on 1 RCT with high certainty of evidence, the direct comparison of DURV+TREM and sorafenib show that approximately, tumor response is five times higher when patients are given DURV+TREM compared to those given sorafenib [OR 4.65 (2.82 to 7.68)]
- Based on 1 RCT with high certainty of evidence, the direct comparison of durvalumab and sorafenib show that approximately, tumor response is four times higher when patients are given durvalumab compared to those given sorafenib [OR 3.77 (2.25 to 6.32)].

**Odds ratio of proportion with confirmed complete response or partial response per RECIST 1.1.*

# C2. Efficacy, Effectiveness, and Safety [6 of 6]

**RQ.2.1. Among patients with uHCC, what is the effectiveness/efficacy of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

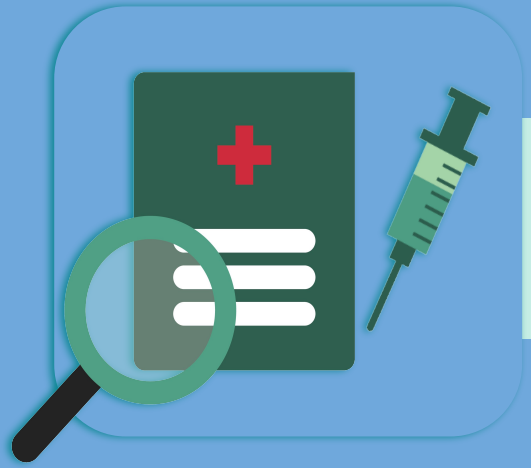
**[HTAC Judgment]**

*(3.2) Objective response rate: Indirect comparison*

**There is inconclusive evidence on the effect of Atezo+Bev, Lenvatinib, Durvalumab, Durv+Trem on objective response rate when compared to each other.**

- Based on 2 RCTs with moderate to low certainty of evidence, the indirect comparison of the different treatments showed inconclusive evidence:
  - Lenvatinib and ATZ+BEV: OR = 01 (95%CI: 0.29, 3.52)
  - Durvalumab and ATZ+BEV: OR = 1.44 (95%CI: 0.41, 5.03)
  - DURV+TREM and ATZ+BEV: OR = 2.19 (95%CI: 0.63, 7.63)
  - durvalumab and lenvatinib: OR = 1.43 (95%CI: 0.41, 4.98)
  - DURV+TREM and lenvatinib: OR = 2.17 (95%CI: 0.62, 7.55)
  - DURV+TREM and durvalumab OR = 1.52 (95%CI: 0.43, 5.29)

**Odds ratio of proportion with confirmed complete response or partial response per RECIST 1.1.*



# **Review of Clinical Evidence** *(Evidence on C2: Clinical Efficacy/ Effectiveness and **Safety**)*

# Notable Adverse Events (AEs) from RCTs

| Trial | Treatment Arm(s) | Any-Grade AEs (most common) |
|---|---|---|
| **IMbrave150** | Atezolizumab + Bevacizumab (n=329) | hemorrhage (25.0%), hypertension (23.7%), proteinuria (18.8%), ↑AST (14.0%) /ALT (10.3%), fatigue (15.2%) |
| | Sorafenib (n=156) | Palmar-plantar erythrodysesthesia (48.1%), diarrhea (42.9%), hypertension (19.9%), anorexia (19.9%) |
| **REFLECT** | Lenvatinib (n=476) | Hypertension (42%), diarrhea (39%), ↓appetite (34%), ↓weight (31%) |
| | Sorafenib (n=475) | Palmar-plantar erythrodysesthesia (52%), diarrhea (46%), hypertension (30%), ↓appetite (27%) |
| **HIMALAYA** | STRIDE: Tremelimumab (300mg x1) + Durvalumab (1500mg q4w) (n=388) | diarrhea (26.5%), pruritus (22.9%), rash (22.4%),, fatigue (17%), ↓appetite (17%) ↑AST (12.4%) /ALT (9.3%) |
| | Durvalumab monotherapy (n=388) | Diarrhea (14.9%), pruritus (14.4%), ↑AST (14.4%), ↓appetite (13.7%), ↑ALT (11.3%), rash (10.3%), fatigue (9.8%) |
| | Sorafenib (n=374) | Palmar-plantar erythrodysesthesia (46.5%), diarrhea (44.7%), fatigue (19.0%), hypertension (18.2%) |

# Notable Specific Adverse Events (AEs) from RWEs

| Specific AEs | No. of studies | Rate of events | | Heterogeneity | | Pooled analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | ATZ+BEV | LEN | $I^2$ | p-value | OR | 95% CI | p-value |
| Liver injury | 8 | 1.99% | 1.05% | 0% | 0.70 | 2.05 | 1.16, 3.65 | 0.01 |
| Hand-foot skin reaction | 9 | 0.36% | 2.37% | 0% | 1.00 | 0.23 | 0.12, 0.47 | <0.01 |
| Anorexia | 8 | 1.87% | 5.87% | 0% | 0.65 | 0.30 | 0.20, 0.44 | <0.01 |
| Diarrhea | 7 | 0.68% | 2.22% | 15% | 0.32 | 0.35 | 0.19, 0.67 | <0.01 |
| Fatigue | 8 | 2.17% | 4.61% | 0% | 0.80 | 0.46 | 0.31, 0.68 | <0.01 |
| Rash | 4 | 1.67% | 0.49% | 0% | 0.48 | 2.44 | 0.71, 8.39 | 0.16 |
| Hypertension | 10 | 6.38% | 6.36% | 65% | 0.02 | 1.10 | 0.60, 2.00 | 0.76 |
| Hypothyroidism | 5 | 0.59% | 0.95% | 0% | 0.81 | 0.63 | 0.28, 1.41 | 0.26 |
| Thrombocytopenia | 6 | 1.08% | 2.45% | 11% | 0.34 | 0.56 | 0.25, 1.24 | 0.15 |
| Proteinuria | 9 | 6.49% | 7.61% | 0% | 0.61 | 0.80 | 0.62, 1.04 | 0.10 |

# EAG GRADE Rating of Safety Outcomes from RWEs

| ATZ+BEV vs Lenvatinib | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | |
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Point Estimate | Certainty | Interpretation of result |
| Overall AEs | | | | | | | | | |
| 5 | Obs study | Serious[a] | Not serious | Not serious | Not serious | N/A | OR 0.54 (0.36 to 0.79) | Very Low | Favors I |
| Serious AEs | | | | | | | | | |
| 4 | Obs study | Serious[a] | Not Serious | Not serious | Not serious | N/A | OR 0.43 (0.36 to 0.51) | Very Low | Favors I |

(a) Serious overall rating for the studies included

# C2. Efficacy, Effectiveness, and Safety [1 of 2]

**RQ.2.1. Among patients with uHCC, what is the safety of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

**[Draft Judgment]**

Based on three RCTs, the most common reported any-grade adverse events (AEs) specific for each intervention are as follow:

- Based on 1 RCT with a total of 329 participants under the Atezolizumab + Bevacizumab arm, the most common AEs for Atezolizumab + Bevacizumab (ATZ+BEV) are the following: hemorrhage (25.0%), hypertension (23.7%), proteinuria (18.8%), fatigue (15.2%), increased AST (14.0%), increased ALT (10.3%)
- Based on 1 RCT with a total of 476 participants under the Lenvatinib arm, the most common AEs for Lenvatinib are the following: Hypertension (42%), diarrhea (39%), decreased appetite (34%), weight loss (31%)
- Based on 3 RCTs with a total of 1,005 participants under the Sorafenib arm, the most common AEs for Sorafenib are the following: palmar-plantar erythrodysesthesia (hand-foot syndrome) (49.55%), diarrhea (45.17%), hypertension (24.18%)
- Based on 1 RCT with a total of 388 participants under the Tremelimumab + Durvalumab arm, the most common AEs for Tremelimumab + Durvalumab are the following: diarrhea (26.5%), pruritus (22.9%), rash (22.4%), fatigue (17%), decreased appetite (17%), increased AST (12.4%), and increased ALT (9.3%)
- Based on 1 RCT with a total of 388 participants under the Durvalumab arm, the most common AEs for Durvalumab are the following: Diarrhea (14.9%), pruritus (14.4%), increased AST (14.4%), decreased appetite (13.7%), increased ALT (11.3%), rash (10.3%), fatigue (9.8%)

# C2. Efficacy, Effectiveness, and Safety [2 of 2]

**RQ.2.1. Among patients with uHCC, what is the safety of atezolizumab+bevacizumab, lenvatinib, sorafenib, durvalumab, durvalumab + tremelimumab , and placebo?**

**[Draft Judgment]**

Similar AEs were also noted from eleven (k=11) observational studies showing that ATZ+BEV and lenvatinib have higher risk of some adverse events when compared with each other: ATZ+BEV had higher risk of liver injury versus lenvatinib. Lenvatinib was associated with hand and foot skin reaction, anorexia, diarrhea, fatigue, and rash.

Meanwhile, based on the pooled result of five (k=5) observational studies with very low certainty of evidence, overall adverse events are significantly lower in the ATZ+BEV vs lenvatinib [(OR 0.54 (0.36 to 0.79)]. Similarly, the pooled result of four studies with very low certainty of evidence showed that GRADE ≥3 AEs are significantly lower in the ATZ+BEV group than that of the lenvatinib group [OR 0.43 (0.36 to 0.51)].

# aHTA COSTING

*Note: Comparative costing was not performed as there is no drugs in the PNF specific to the applied indication. Further, Atezo+Bev and Lenvatinib are current standard of care.*

**Atezolizumab [60 mg/mL, 20 mL vial for intravenous (IV) infusion] + Bevacizumab [25 mg/mL, 4 mL or 16 mL vial for IV infusion] in the treatment of patients with unresectable hepatocellular carcinoma (uHCC)**

| Cost components | Cost of treatment regimen | |
|---|---|---|
| | Atezolizumab + | Bevacizumab |
| Unit cost of health technology | *[Redacted, confidential information]* | *[Redacted, confidential information]* |
| | | *[Redacted, confidential information]* |
| Dosage per day or **per treatment course [every 3 weeks]** | 1200 mg | 825 mg<br>< 60 kg (55 kg) |
| | | 975 mg<br>≥ 60 kg (65 kg) |
| Number of dosage units per day or **per treatment course [every 3 weeks]** | 1 vial | Two (2) 400 mg vials + one (1) 100 mg vial<br>< 60 kg (55 kg) |
| | | Two (2) 400 mg vials + two (2) 100 mg vial<br>≥ 60 kg (65 kg) |
| Number of days or treatment course per year | 18 | 18 |
| Total cost of treatment regimen per patient per year | *[Redacted, confidential information]* | *[Redacted, confidential information]* |
| | | *[Redacted, confidential information]* |
| **Total cost of treatment regimen per patient per year: combination of ATZ+BEV** | **₱3,660,309.72 - ₱3,901,294.80** | |

# Lenvatinib [4 mg / 10 mg capsule] in the treatment of Patients with Unresectable Hepatocellular Carcinoma (uHCC)

| Cost components | Cost of treatment regimen |
|---|---|
| | **Lenvatinib** |
| Unit cost of health technology | *[Redacted, confidential information]* |
| Dosage per day or **per treatment course** | 8 mg (<60 kg) |
| | 12 mg (≥60 kg) |
| Number of dosage units per day or **per treatment course** | Two (2) 4 mg capsule (<60 kg) |
| | Three (3) 4 mg capsule (≥60 kg) |
| Number of days or treatment course per year | 365<br>*(Assumption based on the PSMO response and review of other data)* |
| Total cost of treatment regimen per patient per year | *[Redacted, confidential information]* |
| | *[Redacted, confidential information]* |
| **Total cost of treatment regimen per patient per year** | **₱2,737,500.00 - 4,106,250.00** |

# OVERALL JUDGMENT

# Summary of judgment per criterion

| Domain | Direction of Judgment |
|---|---|
| **Responsiveness to Disease Magnitude and Severity** | Significant burden |
| **aHTA eligibility** | ATZ+BEV: YES<br>Lenvatinib: YES<br>Other guidelines review<br>- **ATZ+BEV:** Recommended by **six guidelines (out of 7)** as first-line treatment<br>- **Lenvatinib:** Recommended as **alternative to ATZ+BEV by three guidelines** (Japan, AASLD and NCCN); recommended as first-line in the Asian guidelines |
| **Efficacy/ Effectiveness** | *Please see next slides* |
| **Safety** | - **Overall AEs:** ATZ+BEV > Lenvatinib<br>- **Serious AEs:** ATZ+BEV > Lenvatinib<br>*No data on these outcomes were available for durvalumab and DURV+TREM.* |
| **aHTA costing** | **ATZ+BEV:** Significantly high cost per patient per year<br>**Lenvatinib:** Significantly high cost per patient per year |

# Summary of efficacy outcomes: Direct comparison

| DIRECT COMPARISON | | | |
|---|---|---|---|
| **I and C** | **Overall Survival** [HR (95% CI)] | **Progression Free Survival** [HR (95% CI)] | **Objective response rate** [OR (95% CI)] |
| **Atz+Bev vs Sorafenib** | Favors Atz+Bev<br>0.66 (0.52 to 0.85) | Favors Atz+Bev<br>0.59 (0.47 to 0.76) | Favors Atz+Bev<br>2.77 (1.62 to 4.73) |
| **Lenvatinib vs Sorafenib** | As good as or better<br>0.92 (0.79 to 1.06) | Favors I Lenvatinib<br>0.66 (0.57 to 0.77) | Favors Lenvatinib<br>3.11 (2.13 to 4.54) |
| **Durv+Trem vs Sorafenib** | Favors I Durv+Trem<br>0.78 (0.65 to 0.92) | As good as or better<br>0.90 (0.77 to 1.05) | Favors Durv+Trem<br>3.77 (2.25 to 6.32) |
| **Durvalumab vs Sorafenib** | As good as or better<br>0.86 (0.73 to 1.03) | Inconclusive<br>1.02 (0.88 to 1.19) | Favors Durvalumab<br>4.65 (2.82 to 7.68) |

# Summary of efficacy outcomes: Indirect comparison

| INDIRECT COMPARISON | | |
|---|---|---|
| **I and C** | **Overall Survival [HR (95% CI)]** | **Progression free survival [HR (95% CI)]** |
| Atz+Bev vs Lenvatinib | Favors Atz+Bev<br>0.51 (0.50, 0.53) | Favors Atz+Bev<br>0.80 (0.78 to 0.82) |
| Atz+Bev vs Durvalumab | Favors Atz+Bev<br>0.59 (0.57, 0.61) | Favors Atz+Bev<br>0.33 (0.33 to 0.34) |
| Atz+Bev vs Durv+Trem | Favors Atz+Bev<br>0.72 (0.69, 0.74) | Favors Atz+Bev<br>0.43 (0.42 to 0.44) |
| Durvalumab vs Lenva | Favors Durvalumab*<br>0.87 (0.85 to 0.90) | Favors Lenvatinib<br>0.42 (0.41 to 0.42) |
| Durv+Trem vs Lenva | Favors Durv+Trem*<br>0.72 (0.70, 0.74) | Favors Lenvatinib<br>0.54 (0.53 to 0.55) |
| Durv+Trem vs Durva | Favors Durv+Trem<br>0.82 (0.80, 0.85) | Favors Durvalumab**<br>0.78 (0.77 to 0.79) |

*Lenvatinib is the comparator
** Durvalumab is the intervention

# Summary of efficacy outcomes: Indirect comparison

| INDIRECT COMPARISON | |
|---|---|
| **I and C** | **Objective response rate [OR (95% CI)]** |
| Lenvatinib vs Atz+bev | Inconclusive<br>1.01 (0.29, 3.52) |
| Durva vs Atz+bev | Inconclusive<br>1.44 (0.41, 5.03) |
| Durv+Trem vs Atz+Bev | Inconclusive<br>2.19 (0.63, 7.63) |
| Durva vs Lenva | Inconclusive<br>1.43 (0.41, 4.98) |
| Durv+Trem vs Lenva | Inconclusive<br>2.17 (0.62, 7.55) |
| Durv+Trem vs Durva | Inconclusive<br>1.52 (0.43, 5.29) |

# Summary of safety outcomes:

| I and C | Overall AEs (RR 95% CI) | Serious AEs (OR 95% CI) |
|---|---|---|
| Atz+Bev vs Lenvatinib | Favors Atz+Bev<br>0.54 (0.36 to 0.79) | Favors Atz+Bev<br>0.43 (0.36 to 0.51) |

*No data on these outcomes were available for durvalumab and DURV+TREM.*

# Thank you!