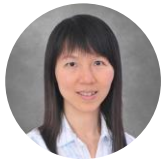
LEAD 2024 Dinner Symposium

25th October 2024, 6 pm to 7 pm GMT+8

Zhuhai People's Hospital, Hong Kong

Chairperson



Prof. Grace Wong

Speakers and panelists:

Dr Yao Liu

Dr Bing Liu

Dr Qing Yang

Objectives

01 Engage in discussions with a multidisciplinary team of experts in Hong Kong and China

02 Discuss end-to-end care and management for patients with HCC

Forefront of Innovation: End-to-end Liver Disease Management

Dr Yao Liu, Guangzhou First People's Hospital, China

Project Pearl: A collaboration between Zhuhai People's Hospital Medical Group and Roche to develop two digital solutions, the LDP and OH systems, to support comprehensive end-to-end management of liver disease

Screening | Diagnosis

LDP system: For HCC screening and diagnosis

Comprises six functions:

- On-premise servers to **facilitate intra-hospital connection** and **meet safety standards**
- Multiple built-in risk stratification models
- Complete CRF fields that can be customized to **fit research requirements**
- Integration of GAAD to **improve detection of early-stage HCC**
- Intelligent real-time analysis for **scientific research and operation**
- Mobile platform for **out-of-hospital follow-up**

The use of LDP and OH in Project Pearl led to a marked increase in detection of early-stage HCC, with **95% (39/41) of patients diagnosed in the early stages***

Treatment | Follow-up

OH system: For management and follow-up in HCC

Comprises three modules:

1. Liver cancer database, which consists of patient information
2. MDT module (performed before treatment)
   - Automatically captures patient information and generates presentation documents **with one click**
   - Efficiently displays information across different systems **in one page**
3. HCC patient follow-up module (performed after treatment)
   - Still under development; aims to provide **comprehensive follow-up information** on perioperative period, outcomes, complications and QoL across different treatment types

A total of 164 patients have used the **OH platform for MDT consultations†**

*A total of 5,122 patients screened as of 22 October 2024. †As of 25 September 2024.

Panel Discussion

Moderated by Prof. Grace Wong, The Hong Kong Association for the Study of Liver Diseases, Hong Kong
Panelists: Dr Bing Liu, Guangzhou First People's Hospital, China; Dr Qing Yang, Zhuhai People's Hospital, China; Dr Yao Liu, Zhuhai People's Hospital

Barriers to implementation of Project Pearl

Clinical inertia was a barrier to the adoption of digital tools in Project Pearl, as doctors were accustomed to the previous liver cancer management system

- To overcome this, actions were taken to increase awareness among HCPs of the **enhanced efficiency and convenience** of the new system

As HCPs and laboratory stakeholders have vastly different backgrounds, **extensive discussions** were held to facilitate **successful collaborations** and **project development**

MDT discussions

To ensure **effective collaboration between MDTs**, the following recommendations were suggested:

- Regular MDT meetings to **discuss follow-up measures** for patients with HCC; in Zhuhai People's Hospital, MDT meetings are held twice weekly
- Ensure MDT recommendations **comply with guidelines and scientific consensus**
- Use **digital tools**, such as the MDT module in the OH system

Role of patients and families

Patient education and awareness is a key contributor for the **success of HCC screening**, and was done through:

- eBooks and scientific visuals/infographics
- Public dissemination of information through WeChat
- Community clinics

The patient and family members play a **crucial role in MDT discussions** as they provide additional information to guide treatment decisions

Interim outcomes of Project Pearl

In >5,000 patients screened under Project Pearl, the most common HCC etiology was **viral hepatitis**

The diagnosis rate of 95% for early-stage HCC is **much higher than the national average of 30%**

Engaging stakeholders in HCC management

Apart from the main stakeholders (hospital, patients, and government), collaboration with other stakeholders aid in advancing liver care and HCC management

- **Pharmaceutical companies**: Develop new treatment options to improve patient outcomes
- **Diagnostic companies**: Develop new diagnostic tools and techniques to detect more patients with early-stage HCC
- **Policy makers**: Support, monitor, and evaluate liver cancer programs

LEAD 2024 APAC HCC Expert Meeting

26th October 2024, 9 am to 5 pm GMT+8

Speakers/panelists

- Prof. Albert Chan
- Dr Bing Liu
- Dr Chien An Liu
- Dr Chien Huai Chuang
- Prof. Rong Fan
- Prof. Henry Chan
- Prof. Masatoshi Kudo
- Dr Michael Ko
- Prof. Pisit Tangkijvanich
- Asst. Prof. Rashid Lui
- Prof. Ronnie Poon
- Clin. Asst Prof. Shuting Han
- Prof. Tawesak Tanwandee
- Prof. Teerha Piratvisuth
- Asst Prof. Wei Fan Hsu

Objectives

01 Discuss the use of novel biomarkers, digital algorithms, and treatment modalities for comprehensive management of HCC

02 Address critical gaps in HCC awareness, clinical practices, policy frameworks, funding, and access across APAC

03 Facilitate insights from diverse practices to advance end-to-end patient care for HCC

The Big Picture: Comprehensive HCC Management in Japan

Prof. Masatoshi Kudo, Kindai University Faculty of Medicine, Japan

HCC surveillance in Japan

Due to the comprehensive HCC surveillance program in Japan, which involves screening of three tumor markers (**AFP, AFP-L3, and PIVKA-II**), a higher proportion of patients are **diagnosed at early stages and receive curative therapy**, and have **prolonged survival**

Patient population	HCC surveillance
Medium risk: Non-cirrhotic MASH/MASLD*	AFP, AFP-L3, PIVKA-II, US, Fibrosis-4 index, and platelet count every 12 months
High risk: Chronic hepatitis B/C; liver cirrhosis	AFP, AFP-L3, PIVKA-II, and US every 6 months
Very high risk: Cirrhotic hepatitis B/C	AFP, AFP-L3, PIVKA-II, and US every 3–4 months, with optional dynamic CT/MRI every 6–12 months

HCC treatment in Japan

	Early stage	Intermediate stage	Advanced stage
Criteria	Tumor number 1–3 and tumor size ≤3 cm	Tumor number >3 or tumor size >3 cm	Extrahepatic metastasis or vascular invasion
Recommended treatment	Both surgery and RFA are equally recommended as they lead to similar outcomes	**TACE-eligible patients†:** LEN-TACE **TACE-ineligible patients†:** Atezolizumab-bevacizumab • If tumor shrinkage is observed: curative conversion is performed via resection, ablation, TACE, or a combination (**ABC conversion therapy**) • If SD: Administer TACE + LEN, followed by atezolizumab-bevacizumab again (**ABC LEN-TACE sandwich therapy**)	**In patients suitable for combination IO:** • **Patients who are anti-VEGF suitable**: Atezolizumab-bevacizumab • **Patients who are anti-VEGF unsuitable**: Durvalumab-tremelimumab • If patient shows no response after 3 weeks, **as assessed by AFP, AFP-L3, and PIVKA-II**, patients should switch to an alternative regimen HAIC is effective for HCC with **PVTT or Vp4 involvement**

*Not yet included in JSH clinical guidelines. †Based on up-to-7 criteria.

HCC Surveillance in High-Risk Chinese Population: Preliminary Results with PIVKA-II and GAAD

Prof. Rong Fan, Nanfang Hospital, China

HCC surveillance challenges and solutions in China

Challenge 1: Poorly defined HCC surveillance population due to:

- Unclear HCC risk and surveillance strategy
- Unequal distribution of medical resources

Solution: Use risk models to identify high-risk populations

aMAP score[1]

- Validated in Asian and Caucasian ethnicities across different HCC etiologies
- **Performed modestly in patients with cirrhosis,** who are at high risk for HCC

aMAP-2 score[2]

- By modelling longitudinal biomarker profiles, **AFP was incorporated into aMAP** to develop the aMAP-2 score
- Able to **further identify patients at higher risk of HCC** compared with the aMAP score; however, it still performed modestly among **patients with cirrhosis**, with an AUC of <0.8

aMAP-2 Plus score[2]

- Developed by incorporating **cfDNA** into the aMAP-2 score
- **Better performance** in predicting HCC risk than aMAP-2, aMAP, and other HCC risk scores
- Better discrimination of HCC risk in **patients with cirrhosis** than aMAP and aMAP-2

Stepwise application of aMAP scores (aMAP ⇨ aMAP-2 ⇨ aMAP-2 Plus) may be a cost-effective approach to guide HCC surveillance in China

Challenge 2: Inaccurate surveillance methods as AFP + US only perform modestly in detecting HCC, especially for early-stage HCC

Solution: Novel serum markers and algorithms

PIVKA-II

High sensitivity and specificity for detection of HCC in both global and Chinese cohorts, and can **detect ~80% of AFP-negative HCC**

GAAD

Demonstrated **good sensitivity and specificity in detecting all- and early-stage HCC**, and has been validated in China's population

Interim results of a multicenter study in China in patients with CHB receiving antiviral treatment (N=6,110)

- In patients with HCC, the proportion of patients with AFP >20 ng/mL and PIVKA-II >28.4 ng/mL **progressively increased prior to diagnosis**
- GAAD algorithm **performed significantly better** in detecting all- and early-stage HCC than PIVKA-II or AFP

GAAD is recommended by China guidelines for early diagnosis of HCC due to its comparable performance with GALAD

1. Fan R, et al. J Hepatol 2020;73(6):1368-1378. 2. Fan R, et al. J Hepatol 2023;79(4):933-944.

Chronic Liver Disease Comprehensive Management: The Introduction of Project Pearl

Dr Bing Liu, Guangzhou First People's Hospital, China

Characteristics of liver cancer in China

- **55% of patients are diagnosed with HCC at Stage III or IV,** higher than America (15%) and Japan (5%)
- **5-year survival rate is 12%,** lower than America (21%) and Japan (44%)

Project Pearl

- Project Pearl was established to **improve liver cancer staging and prognosis through risk stratification** and **standardize HCC management processes**
- High-risk patients underwent screening with US, AFP, PIVKA-II, and/or GAAD; those with normal results will **undergo risk stratification with the Zhuhai risk assessment model to determine follow-up procedures**

The Zhuhai risk assessment model evaluates 12 parameters and has a total score of 230

Risk stratification	Score	Follow-up
Low	<50	Every year
Medium	50 (inclusive) to 90	Every 6 months
High	90 (inclusive) to 170	Every 3 months
Very high	≥170	Every 3 months

Outcomes of Project Pearl (From March 2023 to October 2024)

All patients (N=3,952)

HCC diagnosis rate
0.8%, higher than the national incidence

Follow-up rate
64% versus the national average of 30%

Early diagnosis rate
94% versus the national average of 30%

Patient subgroup that underwent GAAD assessment (n=1,831)

Early diagnosis rate
94% versus the national average of 30%

Diagnostic performance
AUC 0.84 versus PIVKA-II (0.67) and AFP (0.66)

Panel Discussion: Unlock Early HCC Detection – Perspectives from Leading Experts

Moderated by Prof. Henry Chan, The Chinese University of Hong Kong, Hong Kong
Panelists: Prof. Rong Fan; Dr Bing Liu

Evaluation of PIVKA-II and GAAD

The PIVKA-II cut-off values differ across populations and represents the best **compromise between sensitivity and specificity.** The different PIVKA-II cut-off values should not affect GAAD assessment as PIVKA-II is entered as a **continuous variable** during calculations

Limitations of US

The 6-monthly interval for US in HCC screening is constrained by **resource limitations**. Further risk stratification is needed to identify low-risk patients, optimizing the use of US for those with higher risks

- One suggestion is to evaluate patients with **negative tumor markers but positive US findings** within the large database of patients in China, to identify the subgroup that would benefit most from US screening

Surveillance in patients with MAFLD

It is impractical to provide US screening for all **non-cirrhotic patients with MAFLD** due to the high patient volume; hence, evaluating the performance of **biomarker testing** in this patient subgroup is crucial

- The use of biomarker testing (AFP, AFP-L3, and PIVKA-II) for this patient subgroup is currently under discussions to be included in **Japan HCC guidelines**
- In China, MAFLD makes up a **small percentage of HCC cases**, with the dominant etiology being hepatitis B. Most MAFLD cases will not progress to cirrhosis or HCC, although it will be intriguing to evaluate the use of biomarker testing in this large cohort

HCC surveillance strategies in APAC countries

GAAD may soon be reimbursed for HCC surveillance in **Thailand**, as a HECON analysis showed that **GAAD was the most cost-effective** among other HCC surveillance modalities (AFP, PIVKA-II, US)

In **China**, establishing a national consensus on a HCC surveillance strategy is **challenging** due to the vast area and unequal distribution of medical resources

Applications of aMAP score

The aMAP Plus score is currently used for **research purposes** only. Although it is intended for risk stratification, it may potentially be used for **early diagnosis** of HCC in the future

Coordinating Care in Advanced HCC: How to Select the Right Treatment for the Right Patient?

Clin. Asst Prof. Shuting Han, National Cancer Centre Singapore, Singapore

Guidelines and clinical trials in advanced HCC

- Guidelines recommend **atezolizumab-bevacizumab as 1L treatment in advanced HCC**; durvalumab-tremelimumab is also recommended in the BCLC guidelines. The table on the right shows recent Phase III trials that evaluated advanced HCC treatments
  - IMbrave150 is the only trial of the three to include patients with **macrovascular invasion Vp4**

Treatment	Efficacy	Safety
Atezolizumab-bevacizumab Evaluated in IMbrave150[1]	• ORR 30% • Significant OS and PFS benefit	Well-tolerated overall; more AEs that led to treatment discontinuation, but lower corticosteroid use than the other trials
Durvalumab-tremelimumab Evaluated in HIMALAYA[2]	• ORR 20% • Significant OS benefit, but not PFS	Higher rate of imAEs in the doublet-IO arm
Nivolumab-ipilimumab Evaluated in CheckMate 9DW[3]	• ORR 36% • Significant OS benefit, but not PFS	Higher rate of imAEs in the doublet-IO arm

RWD on atezolizumab-bevacizumab

- **Similar OS and better PFS** compared with that of IMbrave150, and **good ORR**[4,*]
- Good OS and PFS in patients with HCC etiologies of **ALD** and **MASLD**[5,†]
- Efficacy in **Child-Pugh B disease** supported by RWD[6,‡]

Considerations in treatment selection

CV risk

- **Not an absolute contraindication;** assess CVD type, severity, stability, as well as number of CV drugs
- Aim for **DBP <85–90 mmHg**
- Involve **cardiologists** when in the decision-making process when necessary

High-risk patients contraindicated for anti-VEGF:
Severe uncontrolled hypertension with end-organ damage; recent ischemic/hemorrhagic CV event

Bleeding

- Results from IMbrave150 and RWD indicate **manageable bleeding risks** with atezolizumab-bevacizumab
- Assess bleeding risks with an **OGD** before initiating treatment; patients with **minor bleeds** may still use anti-VEGF treatment

High-risk patients contraindicated for anti-VEGF:
Ruptured HCC; intra-tumoral bleeding; recurrent and/or uncontrolled variceal bleeding despite optimal management

Autoimmune risk

- Ranges from good prognosis (such as hypothyroidism) to those with potentially life-threatening complications (such as lupus)
- Treatment is **individualized**; high-risk patients may receive either IO + anti-VEGF or anti-VEGF alone

High-risk patients contraindicated for immunotherapies:
Solid tumor organ transplant recipients; organ- or life-threatening autoimmune disease

*Systematic review and meta-analysis of 2,179 patients with Child-Pugh A disease. †Prospective multicentre study of 545 patients in France. ‡Meta-analysis of 5,400 patients.

1. Cheng AL, et al. J Hepatol 2022;76(4):862-873. 2. Chan S, et al. Ann Oncol 2023;34(S4):S1520-S1555 (147P). 3. Galle PR, et al. JCO 2024;42(17). LBA4008. 4. Manfredi GF, et al. Presented at EASL Congress 2024. 5. Allaire M, et al. J Hepatol 2024;80(S1):S444. 6. Kulkarni AV, et al. EClinicalMedicine 2023;63:102179.

Synergies with Immunotherapies Towards Cancer-Free, Drug-Free Status in Intermediate HCC: Myth or Reality?

Dr Chien An Liu, Taipei Veterans General Hospital, Taiwan

Combining systemic and locoregional therapy in intermediate stage HCC

- Systemic therapy is playing an **increasingly important role** in treatment of intermediate-stage HCC, especially in patients who are **unsuitable for TACE**
- Combining locoregional treatment with systemic therapies may have a synergistic effect to **enhance the efficacy of treatment**, as locoregional treatment induces immunological responses that **increases the patient's susceptibility to IO treatment**

RCTs evaluating the combination of TACE + systemic therapy*

	EMERALD-1 study[1]	LEAP-012 study[2]
Baseline characteristics	• ~60% received conventional TACE • ~50% were unsuitable for TACE†	• ~60% BCLC Stage B • ~50% were unsuitable for TACE†
Key findings	• **Durvalumab + bevacizumab + TACE** led to significant PFS benefit vs **placebo + TACE**, but **durvalumab + TACE** did not, suggesting that **anti-VEGF is required to drive PFS benefit** • Longer follow-up needed for OS results	• **Levatinib + pembrolizumab + TACE** led to significant PFS benefit vs **placebo + TACE** (14.6 vs 10.0 months; p=0.0002) • OS data still immature • Grade 3–5 AEs occurred in >70% of patients, but were **mostly manageable**

Note: Longer follow-up is needed to confirm the findings

Achieving cancer-free and/or drug-free status in intermediate HCC

Superselective TACE should be used for patients who are suitable for TACE‡ if curative conversion is the treatment goal

Nearly 30% of patients are **eligible to receive curative therapy** after treatment with atezolizumab-bevacizumab[3]

Adding locoregional therapy to atezolizumab-bevacizumab in intermediate-stage disease may induce a **deeper and more sustained response**

Combination of Y90-TARE with IO

Y90-TARE + IO can provide a high radiation dose and induce **potent antitumor activity**

Y90-TARE has **potential synergistic effect with atezolizumab-bevacizumab** to increase the proportion of resectable HCCs

Preliminary data on the combination has shown **significant OS benefits** in advanced-stage disease. Investigator-initiated STRATUM trial (NCT05377034) is currently assessing the efficacy and safety of Y90-TARE + IO vs Y90-TARE in **locally advanced HCC without extrahepatic metastases**

*This combination should only be used in patients who are eligible candidates for TACE. †Based on up-to-7 criteria. ‡Patients unsuitable for TACE include those with tumors beyond up-to-7 criteria or with complex tumor types.

1. Lencioni R, et al. JCO 2024;42. LBA432. 2. Llovet J, et al. Ann Oncol 2024;35(S2):1-72 (LBA3). 3. Kudo M, et al. Liver Cancer 2023;12(4):321-338.

Unlocking the Potential of Collaborative Care: Can Immunotherapies Enhance Surgical Outcomes in HCC?

Prof. Albert Chan, The University of Hong Kong, Hong Kong

Adjuvant IO treatment

- Adjuvant treatment may **minimize the early risk of HCC recurrence** and **improve patient prognosis**
- Ideal duration and OS benefit of adjuvant therapy is unknown
- In addition to tumor size/number and MVI, more biomarkers are needed to **accurately select** the high-risk populations for adjuvant treatment

Data on adjuvant IO treatment

- A China study reported **significant RFS benefit** with adjuvant sintilimab (PD-1 inhibitor),[1] but longer follow-up is needed to fully assess the benefit
- Atezolizumab-bevacizumab adjuvant therapy showed RFS benefit in the interim analysis of IMbrave050, which was **not maintained in the longer-term follow-up** (HR 0.90; 95% CI 0.72–1.12)[2]

Neoadjuvant IO treatment

Advantages

May **reduce recurrence** and **improve OS and surgical outcomes**

Disadvantages

Potential **toxicities** and **delay of surgery**

- MORPHEUS study is currently ongoing to evaluate the **efficacy and safety of neoadjuvant treatment** in resectable HCC

Conversion therapy for unresectable HCC

Conversion therapy can **increase surgical opportunities** for unresectable HCC, and has been included in China HCC guidelines

Conversion surgery is associated with **better survival benefits** than palliative care or upfront surgery in intermediate- or advanced-stage HCC

Interim results from an ongoing study showed that atezolizumab-bevacizumab led to **high conversion and response rates** in patients with HCC and MVI (N=201)

A unique trimodal strategy of **TACE, SBRT and IO** is used in Queen Mary Hospital

- In unresectable tumors, this approach led to **~40% CR**, with an **additional 12% opting for curative treatment**[3]

Downstaging for liver transplantation

Use of pre-transplant IOs **increases patient eligibility for liver transplantation**, which may be beneficial for high-risk patients who require downstaging

Patients who received IOs pre-liver transplantation (N=117) had **high downstaging rates (76%)** and **survival rates (3-year ITT OS 71%)**[4]

1. Wang K, et al. Nat Med 2024;30(3):708-715. 2. Yopp A, et al. Ann Oncol 2024;35(S2):1-72 (LBA39). 3. Chiang CL, et al. Lancet Gastroenterol Hepatol 2023;8(2):169-178. 4. Tabrizian P, et al. J Hepatol 2024;doi: 10.1016/j.jhep.2024.09.003.

Addressing Funding Challenges Through HTA HECON Data and MOH engagement

Prof. Pisit Tangkijvanich, Chulalongkorn University, Thailand

HCC surveillance in Thailand

- Early HCC detection is a major challenge in Thailand, with only **2.5% of patients with HCC receiving curative treatment**
- US-based screening faces **several limitations**, including modest performance in early-stage HCC, operator dependence, and poor adherence. New biomarkers are needed to **improve the standard HCC surveillance approach of AFP + US** in Thailand.
- The GAAD score **significantly improves early-stage HCC detection** compared with AFP or PIVKA-II alone, making it a viable tool for HCC surveillance

HCC HECON study in Thailand

Study objectives and design

- Conducted to guide decision-making and **reimbursement of GAAD** in public healthcare
- Outcomes were simulated using a **Markov model** to reflect disease progression in cirrhosis
- Sensitivity and specificity of each surveillance method must be **balanced** to determine cost-effectiveness
  - Higher sensitivity indicates **increased early HCC detection** and **better survival**
  - Higher specificity indicates **lower false positive rates**, as well as **lower number and costs of unnecessary procedures** (such as CT/MRI)

Population
Patients aged 40–60 years with compensated liver cirrhosis

Comparators
No surveillance, US, US + AFP, GAAD, GAAD + US, GALAD

Findings

Compared with "no surveillance":
US alone and GAAD were cost-effective

Compared with US + AFP (SoC in Thailand):
GAAD is the dominant strategy, with lower costs and increased QALYs compared with US + AFP

Compared with GALAD:
Although GALAD has a higher true positive rate of 2.5%, it is associated with **increased false positive and overall costs of >25%** compared with GAAD

GAAD is likely the dominant strategy in most simulations, primarily due to its lower associated costs for false positive cases

Limitations

The diagnostic accuracy of the surveillance methods **cannot be directly compared** as no head-to-head comparisons exist

Survival outcomes were based on **treatment modalities received**, not the BCLC stage

Real-world compliance and diagnostic performance may differ from the simulation, **especially in rural areas**

The disease burden from false positive results **could not be completely evaluated** as it does not account for emotional and psychological costs

Informing National Policies & Reimbursement and the Role of Liver Cancer Surveillance Consensus

Asst. Prof. Rashid Lui, Prince of Wales Hospital, Hong Kong

HCC surveillance in Hong Kong

- In Hong Kong, **49.4%** of HCC cases are diagnosed at the early-stage and **43.0%** are diagnosed at the advanced stage
- Recently, experts from Hong Kong recommended the use of **AFP + PIVKA-II** for HCC surveillance, and the use of PIVKA-II to **select patients for US** to minimize wait times
  - Additionally, PIVKA-II can clarify HCC diagnosis in **difficult or borderline cases**, as well as **monitor recurrence** in patients who had undergone HCC resection
- The **cost-utility** of PIVKA-II-based surveillance strategies (PIVKA-II + AFP, GAAD, GAAD + US) were evaluated against the SoC (US + AFP) in Hong Kong in two separate models[1,*]

Liver cirrhosis model	PIVKA-II + AFP, GAAD, and GAAD US were all **dominant** against US + AFP, with lower costs and increased QALYs
Hepatitis B model	• PIVKA-II + AFP and GAAD were **dominant** against US + AFP, with lower costs and increased QALYs • GAAD + US had higher costs and higher QALYs than US + AFP, and was considered a **cost-effective** option

PIVKA-II-based surveillance strategies detect more early-stage HCC cases than US + AFP, and are viable options for the Hong Kong healthcare system

Rise of MAFLD-related HCC

- In the United States, MASH is the **fastest-growing cause of HCC** in liver transplant candidates
- As the MAFLD prevalence approaches 30–40% in certain APAC countries, **MAFLD-related HCC** will likely be a problem in APAC as well
- PIVKA-II has **better diagnostic performance** than AFP in patients with MAFLD-related HCC, who are typically more likely to be **AFP-negative** than those with viral HCCs

HCC surveillance in APAC

In APAC, only Japan and South Korea have a national HCC surveillance program:

Japan is the only country in APAC that uses three tumor markers (AFP, AFP-L3 and PIVKA-II) for HCC surveillance. **Early HCC detection and survival improved drastically** after the introduction of the national HCC surveillance program

In South Korea, the national HCC surveillance program led to several benefits, including **lower mortality and medical costs**, **earlier HCC detection**, and **increased uptake of curative treatment**

The combination of **PIVKA-II + AFP** for surveillance and monitoring of HCC is recommended in an APAC expert consensus

Although not yet reimbursed, the use of **GAAD score** for HCC surveillance is included in the latest China guidelines

*Simulation of 100,000 patients for each model. 1. Leung MK, et al. Presented at APASL 2023 (PPP-280).

Panel Discussion: Complementing Innovation Through Patient-Centric Policies

Moderated by: Dr Michael Ko, Queen Mary Hospital, Hong Kong
Panelists: Prof. Pisit Tangkijvanich; Asst. Prof. Rashid Lui

Considerations in the HECON studies

- In the Thailand HECON study, GAAD was considered cost-effective while PIVKA-II + AFP was not, due to the **low WTP threshold**. Additionally, GAAD could have detected more cases than PIVKA-II + AFP as it included age and gender in its calculations
- The data used in the Markov model may be **outdated** and consist of a **heterogeneous population.** This may affect the study's findings, especially since treatment options have evolved over time
- Each country should conduct their own HECON study as the data used in the model are **country-specific**

Application of GAAD in clinical practice

Dynamic changes in AFP and PIVKA-II levels raise clinical suspicions of HCC; however, as **GAAD score increases with age**, some clinicians find it challenging to interpret and apply it in clinical practice

Need for early screening

Despite rapid advancements in the treatment landscape for advanced HCC, including developments in curative transplants, RFAs, and resections, **major breakthroughs** have been limited over the past decade. There is an urgent need to emphasize the importance of **early HCC screening** to administrators

Lack of prospective data on GAAD and GALAD

Most of the data in APAC for GAAD and GALAD are derived from **retrospective case-control studies**, as few countries have a national surveillance program to support prospective research. Hence, Roche can consider performing an APAC prospective study on the performance of GAAD and GALAD

Healthcare policies for HCC screening

Due to the high prevalence of viral hepatitis and the emergence of MAFLD in the region, there is an **urgent need** to implement healthcare policies to address these issues, which can potentially lead to **cost savings** in the future

Interdisciplinary Management and the Role of Tumor Boards

Dr Chien Huai Chuang, National Taiwan University Cancer Center, Taiwan

The need for MTBs

- **Improves decision making**
- **Enhances communication among stakeholders**
- **Facilitates a patient-centered approach**
- **Considers all treatment modalities**
- **Provides access to latest treatments and trials**

Implementation of MTBs in Taiwan

In NTU Hospital, Taiwan, a multi-disciplinary clinic for liver cancer is held every Tuesday morning, enabling patients to **consult various specialties in the same visit**. This **reduces wait time** and **enhances workflow efficiency**

MTB case in NTU Hospital

- 63-year-old male
- BCLC Stage C HCC with left portal vein invasion
- Child-Pugh A5

- The MTB discussion reached a consensus to **enrol the patient in the MORPHEUS trial** to receive atezolizumab-bevacizumab, as the regimen was not reimbursed at that time
- After 12 weeks, the patient demonstrated **good CT and AFP response**

Role of NGS in HCC

Genomic sequencing has **potential applications** for targeted treatment in patients with advanced disease or who have received extensive treatment, as they may be unsuitable for available treatment options or clinical trials

- In these patients, performing a liver biopsy and NGS may provide insights into **additional treatment options** and **inform future trial designs for targeted therapies**

Preliminary results from an ongoing Taiwan study showed that patients with HCC have **gene alterations of interest**, such as *TSC*, *HER2*, and *MET*

Case studies have shown that patients with ***TSC* alterations** may derive benefit from everolimus, a mTOR inhibitor. Additional research is required on the utility of gene sequencing and targeted therapy in HCC

Digital tumor boards can potentially evolve to include the patient's **trial eligibility**, **predicted outcomes**, and **molecular report**, with AI assistance to guide management of challenging HCC cases

Live MDT Case Discussion: Role of Immunotherapy in Locally Advanced uHCC and Curative Conversion

Moderated by: Prof. Teerha Piratvisuth, NKC Institute of Gastroenterology and Hepatology, Thailand
Panelists: Prof. Tawesak Tanwandee, Mahidol University, Thailand; Asst Prof. Wei Fan Hsu, China Medical University Hospital, Taiwan; Clin. Asst Prof. Shuting Han; Dr Chien An Liu; Prof. Ronnie Poon, Hong Kong Liver Cancer and Gastrointestinal Cancer Foundation, Hong Kong

Patient characteristics

- 57-year-old male with underlying hypertension
- Newly-diagnosed HCC cT4N0M1 (peritoneal invasion)
- Stage IVB, BCLC Stage C, CLIP 1
- AFP 46,158 ng/mL
- Tumor number 1; maximum size 6.47 cm
- Suspected omental invasion; no obvious hepatic or portal venous invasion and lymph node involvement

1L treatment

Patient underwent treatment with atezolizumab-bevacizumab

Considerations:

- Perform EGD prior to treatment to **ensure no GI bleeding**
- Monitor for **CV side effects**, especially since patient has hypertension
- Aim for **DBP <90 mm Hg**

Alternative treatment options

- If patient's disease is confirmed to be localized, **upfront resection** without any systemic therapy is also an option. Neoadjuvant therapy is typically not administered due to the lack of data and modest response rates
- Upfront locoregional therapy is not preferred due to the patient's high AFP levels, which could indicate potential **extrahepatic spread**

Monitoring response and follow-up treatment

Three cycles of atezolizumab-bevacizumab was administered, with the following responses:

- Tumor size: 6.47 cm → **4.85 cm**
- AFP: 46,158 ng/mL → **18,082 ng/mL**

AFP + PIVKA-II were used to monitor the patient's response

Curative treatment with resection was then performed

- Curative treatment provides the best chance for the patient to achieve drug-free status

As of 3 years after treatment, patient remains free of disease
The patient has a high risk for recurrence as the disease was locally advanced; however, there is a lack of consensus on the use of systemic therapy after resection

Live MDT Case Discussion: The Role of GAAD in Surveillance Strategies

Moderated by: Prof. Teerha Piratvisuth

Panelists: Prof. Tawesak Tanwandee; Asst Prof. Wei Fan Hsu; Clin. Asst Prof. Shuting Han; Dr Chien An Liu; Prof. Ronnie Poon

Patient characteristics

- 66-year-old male with chronic hepatitis C (SVR achieved) and cirrhosis
- Comorbidities: Diabetes, hypertension, dyslipidemia

Regular HCC surveillance

Patient underwent regular surveillance of PIVKA-II + AFP + US every 6 months

- During a regular surveillance, the following findings were reported:
  - **PIVKA-II: 1,376 ng/mL**
  - AFP: 5.35 ng/mL
  - **GAAD score: 9.31**
  - US: Cirrhosis with no definite mass

Due to the abnormal PIVKA-II level and GAAD score, the patient underwent an MRI which detected HCC of 6.1 cm at the caudate lobe

1L treatment

Patient underwent resection

- The surgeon may evaluate whether the patient has **adequate liver reserve** to determine the patient's eligibility for resection
- **Liver transplantation** is also an option, but the waiting time is lengthy

1.5 years later, new lesions were detected with primary defects observed in multiple liver lobes

2L treatment

Patient underwent TACE

- Systemic therapy is preferred in the case of recurrent satellite lesions; however, due to **financial concerns**, the patient opted for TACE
- After TACE, a right hepatic vein thrombosis was observed in the MRI images. **Close surveillance with MRI** is currently ongoing as the patient has minimal and stable disease

Panel Discussion: A Look into the Future – A Step Closer to the Cure in HCC

Moderated by: Prof. Teerha Piratvisuth

Panelists: Prof. Tawesak Tanwandee; Prof. Masatoshi Kudo; Clin. Asst Prof. Shuting Han; Dr Chien An Liu; Prof. Ronnie Poon; Dr Chien Huai Chuang

Future directions for IO downstaging/conversion treatment

In Japan, clinical use of ABC conversion therapy with peri-operative IO treatment has been shown to **improve recurrence rates and prolong survival**. Additional prospective studies should be performed to confirm this benefit

The optimal approach and duration in stopping IO treatment before switching to surgical/locoregional treatments are **still under debate**. Oncologists and surgeons must **collaborate** to ensure the timing of the next line of treatment aligns with the discontinuation of IO treatment

Future directions for prevention and surveillance of HCC

Risk factors for HCC, such as hepatitis B and C, should be addressed early to **minimize cirrhosis and HCC risk**

An affordable biomarker that can **replace US** for HCC surveillance would be clinically valuable. Complex new biomarkers involving the use of liquid biopsies are **impractical to implement** in low-to-middle income regions in APAC and Africa

Potential imaging biomarkers

Tumors that are isointense or hyperintense during imaging may indicate **poorer response** to IO treatment. Additional studies should be performed to evaluate the use of AI in this area

Effect of gut microbiota on HCC

Ongoing studies are assessing whether **altering gut microbiota** may facilitate IO response in head and neck cancers; however, no such experience exist for HCC cases currently

Abbreviations

1L, first-line
2L, second-line
ABC, atezolizumab-bevacizumab followed by curative treatment
AE, adverse event
AFP, alpha-fetoprotein
AI, artificial intelligence
aMAP, HCC risk score that considers age, male, albumin-bilirubin and platelets
APAC, Asia Pacific
AUC, area under the curve
BCLC, Barcelona Clinic Liver Cancer
cfDNA, cell-free deoxyribonucleic acid
CHB, chronic hepatitis B
CI, confidence interval
CLIP, Cancer of the Liver Italian Program
CRF, Case Report Form
CT, computed tomography
CV, cardiovascular
CVD, cardiovascular disease
DBP, diastolic blood pressure
EGD, esophagogastroduodenoscopy
GAAD, HCC detection assay that considers gender, age, AFP and DCP (PIVKA-II)
GALAD, HCC detection assay that considers gender, age, AFP-L3, AFP and DCP (PIVKA-II)
GI, gastrointestinal
HCC, hepatocellular carcinoma
HCP, healthcare professional
HECON, health economics;
HER2, human epidermal growth factor receptor 2
HR, hazard ratio
HTA, health technology assessment
imAE, immune-mediated adverse even
IO, immunotherapy
ITT, intention-to-treat
irAE, immune-related adverse events
JSH, Japan Society of Hepatology
LDP, Liver Disease Pathway
LEAD, Liver Experts for Advancing Liver Disease Diagnosis and Management
LEN, lenvatinib
MAFLD, metabolic dysfunction-associated fatty liver disease
MASH, metabolic dysfunction-associated steatohepatitis;
MASLD, metabolic dysfunction-associated steatotic liver disease
MDT, multidisciplinary team
MET, mesenchymal-epithelial transition factor
MOH, Ministry of Health
MRI, magnetic resonance imaging
MTB, molecular tumor board;
mTOR, mammalian target of rapamycin;
MVI, microvascular invasion
NTU, National Taiwan University
OGD, oesophago-gastro-duodenoscopy
OH, Oncology Hub
ORR, objective response rate
OS, overall survival
PFS, progression-free survival
PIVKA-II, protein induced by vitamin K absence or antagonist-II
PVTT, portal vein tumor thrombosis
QALY, quality-adjusted life-year
QoL, quality of life
RCT, randomized controlled trial
RFA, radiofrequency ablation
RFS, recurrence-free survival
RWD, real-world data
SBRT, stereotactic body radiation therapy
SD, stable disease
SoC, standard of care
SVR, sustained virologic response
TACE, transarterial chemoembolization
TARE, transarterial radioembolization
TSC, tuberous sclerosis complex
uHCC, unresectable hepatocellular carcinoma
US, ultrasound
VEGF, vascular endothelial growth factor
Vp4, tumor thrombus in main portal trunk
WTP, willingness-to-pay