APPLE ACADEMY 2025

Friday, July 11, 2025
Kobe Portopia Hotel, Kobe, Japan

Download the
APPLE Academy 2025
Highlights

The Asia-Pacific Primary Liver Cancer Expert Association
APPLE

APPLE Academy Luncheon Symposium

Future treatment strategies for hepatocellular carcinoma from basic and clinical perspectives

Chair

Masafumi Ikeda MD, PhD
Department of Hepatobiliary & Pancreatic Oncology, National Cancer Center Hospital East

Speakers

1. **Naoto Fujiwara MD, PhD**
Department of Gastroenterology and Hepatology, Graduate School of Medicine, Mie University

Future Treatment Strategies for Hepatocellular Carcinoma in the Era of Combined Immunotherapy.
-Toward Optimal Post-IO Sequencing: Insights from Multicenter Studies -

2. **Kaoru Tsuchiya, MD, PhD**
Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo, Japan

Advances in Systemic Therapy for uHCC
- How to use LEN-TACE in the Era of Combination Immunotherapy -

2025 7/11 Friday

Friday, July 11, 2025
11:50～12:50
KOBE PORTOPIA HOTEL
Room B (Main Building B1F Kairaku3)

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APPLE ACADEMY 2025

Friday, July 11, 2025 [Kobe Portopia Hotel, Kobe, Japan]

PROGRAM

09:20-09:30	Opening	**Pierce Chow** *(Singapore)*	
SESSION 1	**CHANGES IN THE LANDSCAPE OF HCC** **Chairperons: Pierce Chow** *(Singapore)*, **Takumi Fukumoto** *(Kobe)*		
09:30-09:55	Changing Etiology and Epidemiology of HCC in Asia	**Wonseok Kang** *(Seoul)*	6
09:55-10:20	Real World Data on the Management of HCC in the Asia-Pacific	**Kaina Chen** *(Singapore)*	8
10:20-10:45	Adaptation of Practice Guidelines: When East Meets West	**Do Young Kim** *(Seoul)*	13
10:45-11:00	Q&A		
11:00-11:15	Break		
SESSION 2	**APPLE ACADEMY: THE ROADS BEFORE US** **Chairperons: Do Young Kim** *(Seoul)*, **Masafumi Ikeda** *(Kashiwa)*		
11:15-11:50	Promoting the Next-Generation Asian Liver Cancer Experts to the Global Arena	**Pierce Chow** *(Singapore)* **& Chiun Hsu** *(Taipei)*	21 26
11:50-12:50	Luncheon Symposium [by Eisai]		
SESSION 3	**UNMET CLINICAL NEEDS IN HCC AND CURRENT CLINICAL RESEARCH DIRECTIONS** **Chairperons: Jong Young Choi** *(Gwangmyeong)*, **Chiun Hsu** *(Taipei)*		
12:50-13:15	Challenges of Biomarker Development: Pathologist's View	**Young Nyun Park** *(Seoul)*	31
13:15-13:40	Challenges of Biomarker Development: Clinician's View	**Han Chong Toh** *(Singapore)*	37
13:40-14:05	Advanced HCC: Novel Approaches beyond IMbrave150, HIMALAYA, and Checkmate 9DW	**Yi-Hsiang Huang** *(Taipei)*	45
14:05-14:30	Integrating Systemic and Liver-Directed Therapy: Current Evidence and Future Development	**Stephen L Chan** *(Hong Kong)*	52
14:30-14:45	Q&A		
14:45-15:00	Break		

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PROGRAM

SESSION 4	FROM APPLE ACADEMY INTO THE FUTURE Chairperons: Pierce Chow *(Singapore)*, Chiun Hsu *(Taipei)*		
15:00-15:25	How to Promote Investigator-Initiated Trials for HCC in the Asia-Pacific Region?	**Ryosuke Tateishi** *(Tokyo)*	60
15:25-15:50	Translational Research of New Drug Development for HCC: Scientist's View	**Alfred Cheng** *(Hong Kong)*	66
15:50-16:25	Panel Discussion: The APPLE Association as a Platform for Future International Research Collaboration		
16:25-16:30	Closing Remark	**Jian Zhou** *(Shanghai)*	

Introduction to APPLE Academy

APPLE Academy is a prestigious educational initiative by the Asia-Pacific Primary Liver Cancer Expert Association (APPLE), designed to nurture the next generation of liver cancer experts.

This intensive program brings together young clinicians and researchers from across the Asia-Pacific region for in-depth learning, case discussions, and networking with world-renowned faculty in the field of liver cancer.

With strong support from leading industry partners, APPLE Academy offers a unique platform to share real-world clinical insights, explore the latest advancements, and build long-lasting professional collaborations.

Program planned by the Education Chairs

Professor Pierce Chow and Professor Chiun Hsu

APPLE
ACADEMY 2025

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SESSION 1.

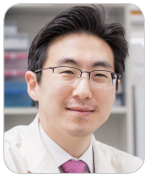
CHANGES IN THE LANDSCAPE OF HCC

Chairperons: **Pierce Chow** *(Singapore)*, **Takumi Fukumoto** *(Kobe)*

Changing Etiology and Epidemiology of HCC in Asia
Wonseok Kang *(Seoul)*

Real World Data on the Management of HCC in the Asia-Pacific
Kaina Chen *(Singapore)*

Adaptation of Practice Guidelines: When East Meets West
Do Young Kimn *(Seoul)*



Changing Etiology and Epidemiology of HCC in Asia

Wonseok Kang *(Seoul)*

Wonseok Kang is an Associate Professor of Medicine at Sungkyunkwan University School of Medicine, and the Chief of Digestive Disease Center at Samsung Medical Center, Seoul, Korea.

He graduated from Yonsei University with his medical degree in 2004 and completed his residency at the Department of Internal Medicine in Severance Hospital in 2009. After completing his clinical training, he pursued a Ph.D. in Medical Science and Engineering at Korea Advanced Institute of Science and Technology (KAIST) in 2013.

Recently, he spent a year as a Visiting Research Scholar at The Jackson Laboratory for Genomic Medicine and Yale School of Medicine in Connecticut, USA. After returning from his sabbatical, he is currently focusing on translational research in the field of hepatology in relation to his clinical practice.

Research Interests

Hepatocellular Carcinoma, Immunotherapy, Biomarkers, Viral hepatitis, Autoimmune liver disease

Representative Publications

1. Molecular landscape of tumor-associated tissue-resident memory T cells in tumor microenvironment of hepatocellular carcinoma. Cell Commun Signal 2025.
2. Unraveling the immune-activated tumor microenvironment correlated with clinical response to atezolizumab plus bevacizumab in advanced HCC. JHEP Rep. 2024.
3. Hepatocellular carcinoma patients with high circulating cytotoxic T cells and intra-tumoral immune signature benefit from pembrolizumab: results from a single-arm phase 2 trial. Genome Med 2022.

MEMO

Real World Data on the Management of HCC in the Asia-Pacific

Kaina Chen *(Singapore)*

Dr. Kaina Chen, M.D., MRCP (UK), MMed (Int Med), FAMS, is an Associate Consultant in the Department of Gastroenterology and Hepatology at Singapore General Hospital. She obtained her Master of Medicine in Internal Medicine from the National University of Singapore and is a Member of the Royal College of Physicians (UK). She is also a Fellow of the Academy of Medicine, Singapore.

Dr. Chen's clinical interests include liver diseases such as chronic hepatitis B and C, cirrhosis, and hepatocellular carcinoma, as well as general gastrointestinal disorders and endoscopy. Her research focuses on improving early detection strategies for liver cancer, particularly in the Asian population.

She is actively involved in medical education as a clinical tutor at Duke-NUS Medical School and mentors junior residents in internal medicine and gastroenterology. Dr. Chen is also a regular speaker at continuing medical education programs and liver disease workshops.

Real World Data on the Management of HCC in the Asia-Pacific

Dr. Chen Kaina
Associate Consultant
Department of Gastroenterology and Hepatology
Singapore General Hospital
Date: 2025 July 11, Kobe, APPLE Academy

Why Real-World Data?

RCT outcomes ≠ real-world outcomes

- Patient populations
  - More co-morbidites, borderline liver function
  - Child Pugh Score is a key inclusion criterion for phase 3 trials
- Practice differ from guidelines
- Real-world data: guide public health strategies and future therapeutic decisions

Phase 3 Trials	Child-Pugh Score Inclusion
IMBrave150	A5-6
HIMALAYA	A5-6
CheckMate 9DW	A5-6
COSMIC-312	A5-6
REFLECT	A5-6
SHARP	A5-6
CARES-310	A5-6
RATIONALE-301	A5-6
ORIENT-32	A5-6 and B7
LEAP-012	A5-6
EMERALD-1	A5-6 and B7

Ntellas et al., ASCO 2024

Liver INTERNATIONAL

Liver International ISSN 14

LIVER CANCER

Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study

Joong-Won Park[1], Minshan Chen[2], Massimo Colombo[3], Lewis R. Roberts[4], Myron Schwartz[5], Pei-Jer Chen[6], Masatoshi Kudo[7], Philip Johnson[8], Samuel Wagner[9], Lucinda S. Orsini[10] and Morris Sherman[11]

- Real-world, multi-regional, longitudinal cohort study
- Objective: global patterns of HCC therapy and outcomes across real-world clinical practice
- 1 Jan 2005 – 30 June 2011
  N = 18,031

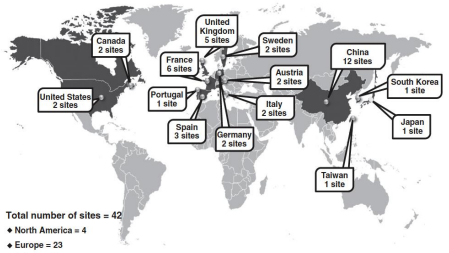
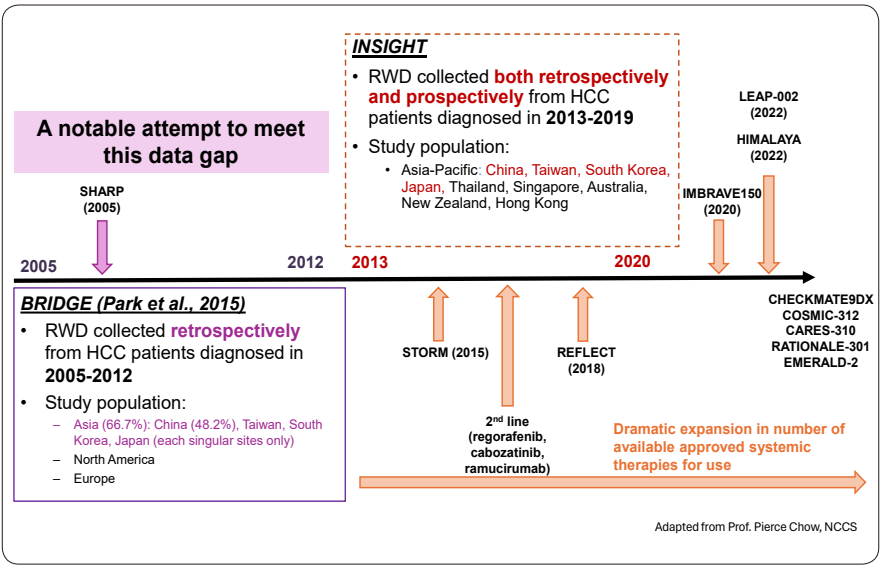


Fig. 1. Distribution of sites participating in the HCC BRIDGE study by country.

Post-BRIDGE
Rapid evolution in the Treatment Paradigm of HCC

2005-2012 (Before INSIGHT)		2013-2019 (During INSIGHT)		After 2019 (After INSIGHT) till 2022	
Setting	**Design**	**Setting**	**Design**	**Setting**	**Design**
Advanced	Sorafenib vs placebo (SHARP)	Adjuvant	Sorafenib vs placebo (STORM)	Adjuvant	Nivolumab vs placebo (CHECKMATE9DX)
		Advanced 2nd line	Regorafenib vs placebo (RESORCE)	Adjuvant	Durvalumab ± Bevacizumab vs placebo (EMERALD-2)
		Advanced 2nd line	Cabozantinib vs placebo (CELESTIAL)	Adjuvant	Atezolizumab + bevacizumab vs placebo (IMbrave050)
		Advanced 2nd line	Ramucirumab vs placebo (REACH-2)	Advanced 1st line	Sorafenib vs lenvatinib (REFLECT)
		Advanced 2nd line	Nivolumab vs placebo (CheckMate040)	Advanced 1st line	Sorafenib vs. atezolizumab + bevacizumab (IMbrave150)
		Advanced 2nd line	Pembrolizumab vs placebo (KEYNOTE-224)	Advanced 1st line	Sorafenib vs. durvalumab + tremelimumab vs. durva (HIMALAYA)
				Advanced 1st line	Sorafenib vs. tislelizumab (Rationale-301)
				Advanced 1st line	Lenvatinib vs. lenvatinib + pembrolizumab (LEAP-002)

Sim et al., Liver Cancer 2024



Adapted from Prof. Pierce Chow, NCCS

BRIDGE vs INSIGHT real-world cohort studies

Characteristic	BRIDGE (2005-2012)	INSIGHT (2013-2019)
Age, gender, etiology	No difference	
BCLC Stage at Diagnosis – late stage (BCLC C) diagnosis	47.3% Particularly in South Korea: 53%	31.5% Particularly in South Korea: 26.5%
Prevalence of HBV	72.5%	64.8%
T2DM	Not reported	20%
Preferred first line treatment in BCLC A	Resection (~45%); TACE (~35%)	Ablative/surgical therapy (82.5%)
Preferred first line treatment in BCLC B	Resection (~15%); TACE (~65%)	Locoregional therapy (53.6%); Resection (38.5%) Particularly in Singapore: Radiation therapy (Y90): 57.4%
Preferred first line treatment in BCLC C ***Reflects greater market entry of sorafenib and increase in state subsidies for use of such therapy***	Low utility of sorafenib (<5% in China and Taiwan, 10% in South Korea, <10% in Japan)	High utility of sorafenib (48.2% in Taiwan, 38.2% in South Korea) Other regions not included in BRIDGE: 50% in Singapore, 62.5% in Australia + New Zealand
Median OS in months ***Lower OS recorded in INSIGHT than BRIDGE***	Not reached (0), 80 (A), 27 (B), 15 (C), 4 (D)	68.53 (0+A), 20.99 (BCLC B), 5.68 (BCLC C), 1.81 (D)

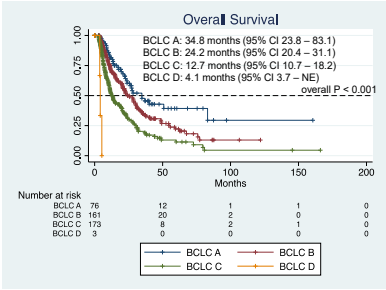
Sim et al., Liver Cancer 2024; slide Courtesy from Prof. Pierce Chow, NCCS

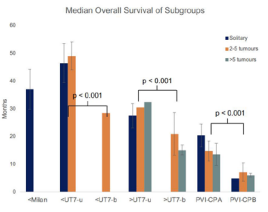
OPTIMIS Conclusions – Real-world TACE for uHCC

- In the real world practice, not uncommon to perform TACE in patients that are not adequately indicated
  - 39% ineligible for first TACE by protocol
  - 86% BCLC stage C or D
- Patient selection is important for better outcome
  - Complete radiologic response: 8% in TACE-ineligible patients and 17% in TACE-eligible patients
  - Median OS: 16.3 months in TACE-ineligible patients and 40.1 months in TACE-eligible patients
- Liver function deterioration was noted in the acute and chronic periods
  - Adequate monitoring liver function before and after TACE treatment

Radioembolisation – real-world outcomes in Singapore

mOS of entire cohort: 20.9 months (95% CI 18.2 – 24.0)
Majority were BCLC C (42%), BCLC B (39%)





Subgroups	N (413)	median OS (months)	95% CI
<Milan	14	37	19.6 – NE
<UT7-u	28	46.4	23.9 – 59.5
Solitary	16	46.4	10.6 – NE
2-5 tumours	11	49.0	20.2 – NE
<UT7-b	3	28.5	13.5 – NE
>UT7-u	110	31.2	23.8 – 40.1
Solitary	56	27.6	22.6 – 34.8
2-5 tumours	16	30.4	20.2 – NE
>5 tumours	38	32.4	20.6 – 73
>UT7-b	104	15.2	11.5 – 20.9
PVI-CPA	133	14.8	11.3 – 20.9
Solitary	40	20.4	10.5 – 38.3
2-5 tumours	19	14.8	10.2 – 21.4
>5 tumours	71	13.5	9.5 – 24.0
PVI-CPB	21	8.1	4.1 – 8.1

Best outcomes: unilobar HCC within Up-to-seven
MVI/Child A: mOS 14.8 months

Chen et al., Liver Cancer 2024

Adaptation of Practice Guidelines: When East Meets West

Do Young Kim *(Seoul)*

Do Young Kim is now a professor of Internal Medicine at Yonsei University College of Medicine, Seoul, Korea, and a hepatologist in the Severance Hospital where he has been a faculty member since 2007. He graduated Yonsei University in 1996, and completed training course in Severance Hospital from 1996 to 2001. He studied proteomics and microRNA in hepatocellular carcinoma (HCC) at Fred Hutchinson Cancer Research Center as a research associate between 2011 and 2012.

Research Interests

Hepatocellular carcinoma
Biomarker

Representative Publications

1. Nam H, Kim DY, Kim DY, et al. [Co-corresponding author] Development and validation of a risk prediction model for patients with hepatocellular carcinoma receiving atezolizumab-bevacizumab. Hepatology [Online ahead of print].
2. Lee HJ, Kim MJ, Kim DY, et al. [Co-corresponding author] Non-contrast resonance imaging versus ultrasonography for hepatocellular carcinoma surveillance: A randomized, single-center trial. Gastroenterology 2025;168:1170-1177.
3. Choi M, ..., Kim DY, Choi GH. [Co-corresponding author] Is liver resection still required for patients who have predictive factors for complete pathological necrosis after downstaging treatments of locally advanced hepatocellular carcinoma? Eur J Surg Oncol 2025;51(1):109349
4. Chon YE, ..., Kim DY. [Corresponding author] Sorafenib vs. lenvatinib in advanced hepatocellular carcinoma after atezolizumab/bevacizumab failure: A real-world study. Clin Mol Hepatol 2024;30:345-359.
5. Cho KJ, ..., Kim DY. [Corresponding author] YAP/TAZ suppress drug penetration into hepatocellular carcinoma via stromal activation. Hepatology 2021;74:2605-2621.

2025 APPLE Academy in Kobe

Adaptation of Practice Guidelines: When East Meets West

Do Young Kim

Department of Internal Medicine,
Yonsei University College of Medicine

EASL as well as AASLD finally included AFP in HCC surveillance

Recommendation

- An ultrasound examination of the liver every 6 months is recommended for screening of HCC. The combined use of ultrasound with AFP increases sensitivity while decreasing specificity and is a reasonable option. There is limited data to support the use of other promising imaging modalities such as abbreviated MR or serum biomarkers **(LoE 3, strong recommendation, consensus).**

EASL

10. HCC surveillance should be performed using ultrasound and AFP at semiannual (approximately every 6 months) intervals (**Level 2, Strong Recommendation**).

AASLD

2. Surveillance test for HCC should be performed with liver US plus serum AFP measurement every 6 months (A1).

KLCA

Extremely High-Risk Group (Cirrhosis Type B and C):
Ultrasound every 3-4 months + Tumor marker every 3-4 months
Dynamic CT/MRI every 6-12 months (optional)
High-risk group (chronic hepatitis B/C, non-viral cirrhosis):
Ultrasound every 6 months + Tumor marker every 6 months

JSH

Statement 1-1: Surveillance for HCCs should be performed using both ultrasonography and tumor markers such as alpha-fetoprotein (AFP) and/or PIVKA-II in clinical settings for HCC surveillance (A: 100%; E: 2; R: B).

TLCA

Target population for HCC surveillance

Eastern			Western	
Korea	Japan	Taiwan	EASL	AASLD
Chronic hepatitis B	Chronic hepatitis B	Chronic hepatitis B	Chronic hepatitis B	Chronic hepatitis B
Chronic hepatitis C	Chronic hepatitis C	Chronic hepatitis C	Cirrhosis	Cirrhosis
Cirrhosis	Cirrhosis	Cirrhosis	Chronic hepatitis C without cirrhosis is not target for surveillance	Chronic hepatitis C without cirrhosis is not target for surveillance

Recommendation

- Patients with chronic liver disease and advanced fibrosis without cirrhosis have a higher risk of HCC than the general population, but HCC surveillance cannot currently be recommended in this group owing to insufficient evidence **(LoE 3, weak recommendation, strong consensus).**

Insufficient risk and in need of risk stratification models/biomarkers

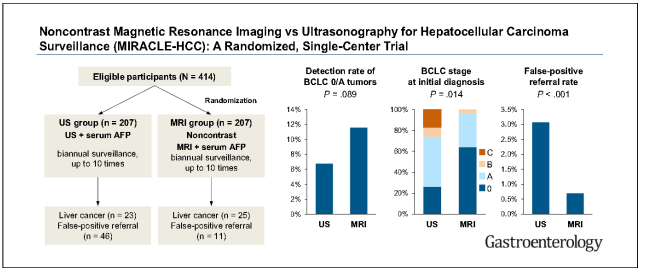
Hepatitis C and stage 3 fibrosis < 0.2% per year

Noncirrhotic NAFLD

Noncontrast Magnetic Resonance Imaging vs Ultrasonography for Hepatocellular Carcinoma Surveillance: A Randomized, Single-Center Trial

Hyungjin Rhee,[1] Myeong-Jin Kim,[1] Do Young Kim,[2] Chansik An,[1] Wonseok Kang,[2] Kyunghwa Han,[1] Yun Ho Roh,[3] Kwang-Hyub Han,[2] Sang Hoon Ahn,[2] Jin-Young Choi,[1] Jun Yong Park,[2] Yong Eun Chung,[1] Seung Up Kim,[2] Beom Kyung Kim,[2] Sunyoung Lee,[1] Hye Won Lee,[2] and Jae Seung Lee[2]

[1]Department of Radiology, Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; [2]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; and [3]Biostatistics Collaboration Unit, Medical Research Center, Yonsei University College of Medicine, Seoul, South Korea



Gastro. 2025

Comparison of diagnostic algorithm between Eastern and Western

Eastern			Western	
Korea	Japan	Taiwan	EASL	AASLD
Imaging study: Multiphasic contrast-enhanced CT or MRI	Imaging study: Multiphasic contrast-enhanced CT or MRI	Imaging study: Multiphasic contrast-enhanced CT or MRI	Imaging study: Multiphasic contrast-enhanced CT or MRI or CEUS	Imaging study: multiphasic contrast-enhanced CT or MRI
APHE and washout is the rule of HCC diagnosis. Ancillary features are permitted.	APHE and washout is the rule of HCC diagnosis. Ancillary features are permitted.	APHE and washout is the rule of HCC diagnosis. Ancillary features are permitted.	LI-RADS is the standard algorithm.	LI-RADS is the standard algorithm.
CEUS can be used as the second-line exam.	CEUS can be used as the second-line exam.	CEUS can be used as the second-line exam.	CEUS can be used as a first-line examination.	CEUS is not allowed as imaging study.

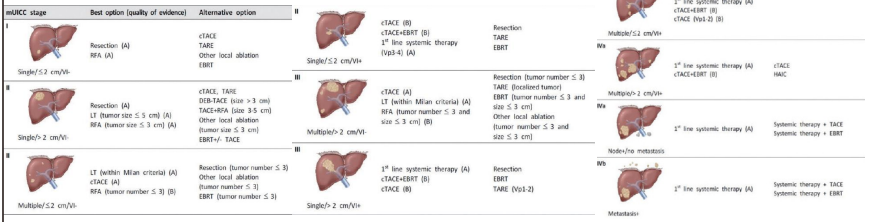
HCC staging and treatment allocation - KLCA

Table 5. Modified UICC stage

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IV A	T4	N0	M0
	T1, T2, T3, T4	N1	M0
IV B	T1, T2, T3, T4	N0, N1	M1

[Recommendations]

1. This guideline adopts the mUICC stages as the primary staging system, with the BCLC staging system and the AJCC/UICC TNM staging system serving as complementary systems (B1).



Surgical technique – minimally invasive surgery

KLCA

5. LLR for HCC located in the left lateral section and anterolateral segments can be selectively performed (B2).
6. LLR for HCC located in the posterosuperior segments or caudate lobe can be selectively performed depending on the location and size of the tumor (C2).

EASL

Recommendation

- In properly trained centres, liver resection should be performed via laparoscopic or minimally invasive approaches whenever feasible, especially for tumours in anterolateral and superficial locations **(LoE 3, strong recommendation, strong consensus).**

AASLD

30. Minimally invasive liver resection (laparoscopic and robotic) may be performed to enhance recovery and lower risk of perioperative morbidity in selected patients (**Level 3, Weak Recommendation**).

- Japan, Taiwan guidelines did not deal with surgical technique.

TARE – An alternative to ablative therapy for single HCC in West

KLCA

5. Compared with cTACE, TARE results in a better quality of life and lower occurrence of PES; therefore, it can be considered an alternative treatment to cTACE when the remnant liver function is expected to be sufficient after the TARE treatment (B2).

EASL

Recommendation

- Radiation segmentectomy can be considered an alternative to percutaneous ablation for single tumours within Milan criteria that are unsuitable for resection or transplantation, when there is a significant risk of post-ablation recurrence based on size (>3 cm) or location (v.g. in contact with large vessels) **(LoE 3, weak recommendation, strong consensus).**

AASLD

40. Targeted radioembolization (radiation segmentectomy) or EBRT may be used as alternative therapies to thermal ablation for patients with BCLC stage A HCC who are not candidates for surgical resection, including those with tumors >3 cm in size (**Level 3, Strong Recommendation**).

With accumulating evidences

Research Article
Hepatic and Biliary Cancer

JOURNAL OF HEPATOLOGY

Stereotactic body radiation therapy *vs.* radiofrequency ablation in Asian patients with hepatocellular carcinoma

Nalee Kim[1], Jason Cheng[2], Inkyung Jung[3], Ja Der Liang[4], Yu Lueng Shih[5], Wen-Yen Huang[6], Tomoki Kimura[7], Victor H.F. Lee[8], Zhao Chong Zeng[9], Ren Zhenggan[10], Chul Seung Kay[11], Seok Jae Heo[3], Jong Yoon Won[12], Jinsil Seong[1,*]

J Hepatol 2020.

Research Article
Hepatic and Biliary Cancer

JOURNAL OF HEPATOLOGY

Proton beam radiotherapy *vs.* radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial

Tae Hyun Kim[1,2,†], Young Hwan Koh[1,3,†], Bo Hyun Kim[1], Min Ju Kim[3], Ju Hee Lee[1,3], Boram Park[4], Joong-Won Park[1,*]

J Hepatol 2021.

EBRT – An alternative to ablation based on size and location

Recommendation

- EBRT can be considered an alternative to percutaneous ablation for single tumours within Milan criteria unsuitable for resection or transplantation, when there is a significant risk of post-ablation recurrence based on size (>3 cm) or location (v.g. in contact with large vessels) **(LoE 4, weak recommendation, consensus).**

EASL

40. Targeted radioembolization (radiation segmentectomy) or EBRT may be used as alternative therapies to thermal ablation for patients with BCLC stage A HCC who are not candidates for surgical resection, including those with tumors >3 cm in size (**Level 3, Strong Recommendation**).

AASLD

Summary

- Surveillance
  - The West finally accepted serum AFP in surveillance program
  - The role of aMRI will be increase both in the East and West
- Diagnosis
  - The East is still adopting traditional APHE and washout in contrast-enhanced CT or MRI.
  - The West accepts LIRAD classification for HCC diagnosis.
  - EASL accepts CEUS as the 1st line diagnostic modality.
- Staging
  - The West keeps BCLC guidelines with subclassficiation of BCLC-B.
  - The East allocates various treatment modalities to a specific stage.
- Treatment
  - Minimally invasive surgery, role of TARE, EBRT as an alternative to ablation highlighted
  - Similar recommendation of 1st line systemic therapy for advanced HCC

APPLE ACADEMY 2025

Friday, July 11, 2025 [Kobe Portopia Hotel, Kobe, Japan]

SESSION 2.

APPLE ACADEMY: THE ROADS BEFORE US

Chairperons: Do Young Kim *(Seoul)*, Masafumi Ikeda *(Kashiwa)*

Promoting the Next-Generation Asian Liver Cancer Experts to the Global Arena
Pierce Chow *(Singapore)* & Chiun Hsu *(Taipei)*

Promoting the Next-Generation Asian Liver Cancer Experts to the Global Arena

Pierce Chow *(Singapore)*

Pierce Chow is Professor and Program Director at the Duke-NUS Medical School and Senior Consultant Surgeon at the National Cancer Centre Singapore (NCCS) and the Singapore General Hospital. He is concurrently a National Medical Research Council (NMRC) funded Senior Clinician-Scientist and was the founding President of the College of Clinician Scientists, Academy of Medicine Singapore. Prof Chow was conferred the Chapter of Surgeon's Gold Medal in the conjoint FRCSE/MMed examination in 1995, and after completing his surgical residency and PhD, he trained in liver transplantation with Professor Russell Strong in Australia. Pierce leads the multi-disciplinary NMRC TCR National Flagship Program in Liver Cancer, which in 2022, has been successfully renewed under the NMRC Open Fund-Large Collaborative Grant. In 2020, he was awarded an A*STAR IAF-ICP grant to conduct a nation-wide 2000-patient cohort study to develop diagnostics for early detection of hepatocellular carcinoma in high-risk patients. Pierce is also a faculty member at the Genome Institute of Singapore, the SingHealth Duke-NUS Global Health Institute and Research Director at the Institute of Cell and Molecular Biology Singapore. In recognition of his outstanding work in clinical and translational liver cancer research, Pierce was conferred the NMRC Outstanding Clinician Scientist Award in 2012 and the NMRC Singapore Translational Research (STaR) Investigator Award in 2025. In 2023, he was inducted into Duke-NUS Medical School's Hall of Master Academic Clinicians. He has authored more than 300 peer-reviewed papers on PubMED and has published in the Lancet, Cell, JCO, Nature Cancer, Journal of Hepatology, Gut and others.

Research Interests

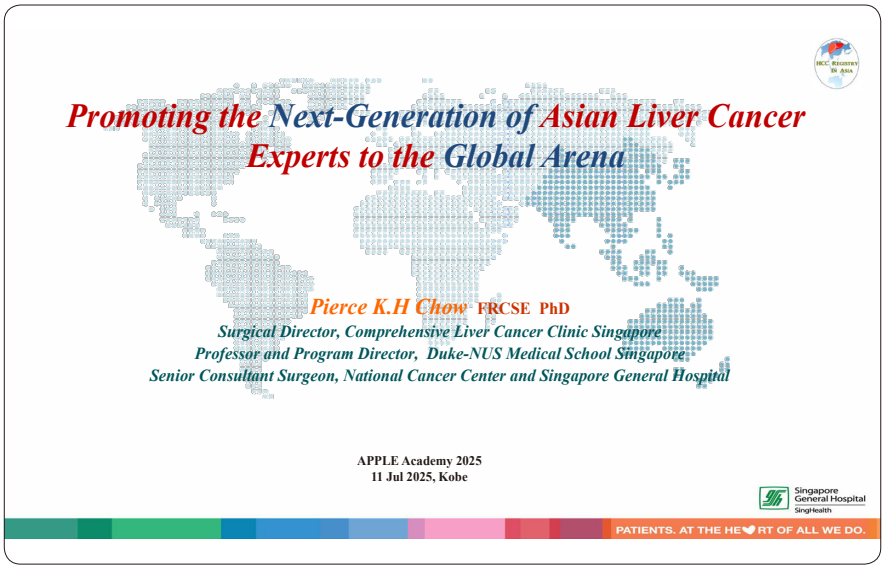
- Prospective Clinical Trials and Translational Research in hepatocellular carcinoma.
- Downstaging of HCC to curative resection and transplantation
- Genomics, immunomics, metabolomics as applied to Precision Medicine in Hepatocellular Carcinoma
- Epidemiology and health services outcomes research in hepatocellular carcinoma
- Clinical and pre-clinical molecular and functional imaging with patient derived xenografts

Representative Publications

1. Led research that established intra-tumoral heterogeneity (ITH) in HCC with profound clinical relevance.
   - Chen JB, Kaya NA, Zhang Y, et. al. A multimodal atlas of hepatocellular carcinoma revelas convergent evolutionary paths and 'bad apple' effect on clinical trajectory. J Hep. May 2024; doi.org/10.1016/j.jhep.2024.05.017

- Li Z, Pai R, Gupta S, et al. Presence of onco-fetal neighborhoods in hepatocellular carcinoma is associated with relapse and response to immunotherapy. Nat Cancer. Jan 2024;5(1):167-186. doi:10.1038/s43018-023-00672-2
- Jeon AJ, Teo YY, Sekar K, Chong SL, Wu L, Chew SC, Chen J, Kendarsari RI, Lai H, Ling WH, Kaya NA, Lim JQ, Ramasamy A, Oguz G, …, Goh BKP, Tucker-Kellogg G, Foo RSY, Chow PKH. (2023) Multi-region sampling with paired sample sequencing analyses reveals sub-groups of patients with novel patient-specific dysregulation in Hepatocellular Carcinoma. BMC Cancer, 23(1):118. https://doi.org/10.1186/s12885-022-10444-3
- Zhai W, Chow PK, et al. (2021) Dynamic phenotypic heterogeneity and the evolution of multiple RNA subtypes in Hepatocellular Carcinoma: the PLANET study, National Science Review, 2021;, nwab192, https://doi.org/10.1093/nsr/nwab192
- Zhai W, Chow PK, et al. (2017) The spatial organization of intra-tumour heterogeneity and evolutionary trajectories of metastases in hepatocellular carcinoma. Nat. Commun. 8:4565. https://doi.org/10.1038/ncomms14565
- Nguyen PHD, Chow PKH, Chew V, et al. (2021) Intratumoural immune heterogeneity as a hallmark of tumour evolution and progression in hepatocellular carcinoma. Nat Commun., 12(1):227. https://doi.org/10.1038/s41467-020-20171-7. PMID: 33431814.

2. Led research that identified a novel immune-escape mechanism in HCC which is highly relevant to the field of HCC therapeutics
   - Sharma A, Chow PKH, DasGupta R, et al. (2020) Onco-fetal Reprogramming of Endothelial Cells Drives Immunosuppressive Macrophages in Hepatocellular Carcinoma. Cell, 183(2):377-394. e21. https://doi.org/10.1016/j.cell.2020.08.040. PMID: 32976798
3. Chaired the IMbrave050 Scientific Steering Committee, which demonstrated early efficacy as adjuvant therapy for patients with HCC
   - Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet. Nov 18 2023;402(10415):1835-1847. doi:10.1016/S0140-6736(23)01796-8
4. Led the multi-national IIT to study the clinical efficacy of SIRT Y90 and the parallel translational study to understand the immune response related to SIRT Y90.
   - PKH Chow, Say-Beng Tan, et al. (2018) SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J. Clin. Oncol., JCO2017760892. https://doi.org/10.1200/JCO.2017.76.0892.
   - Chew, V., Chow, P.K.H., et al. (2018). Immune Activation Underlies a Sustained Clinical Response to Yttrium-90 Radioembolisation in Hepatocellular Carcinoma. Gut. pii: gutjnl-2017-315485. https://doi.org/10.1136/gutjnl-2017-315485.
   - o Results gave rise to a patent filed for SingHealth (International Pub. No.: WO/2019/108135 A1)
5. Provided a realistic analysis of the usefulness of NCCS guidelines on the clinical management of HCC.
   - Chew XH, Chow PKH, et al. (2021) Real-World Data on Clinical Outcomes of Patients with Liver Cancer: A Prospective Validation of the National Cancer Centre Singapore Consensus Guidelines for the Management of Hepatocellular Carcinoma. Liver Cancer. https://doi.org/10.1159/000514400



Disclosures

Personal financial interests:

Advisory role: Sirtex Medical, Ipsen, BMS, Oncosil, Bayer, New B Innovation, MSD, BTG Plc, Guerbet, Roche, AUM Bioscience, L.E.K. Consulting, AstraZeneca, Eisai, Genentech, IQVIA, Abbott

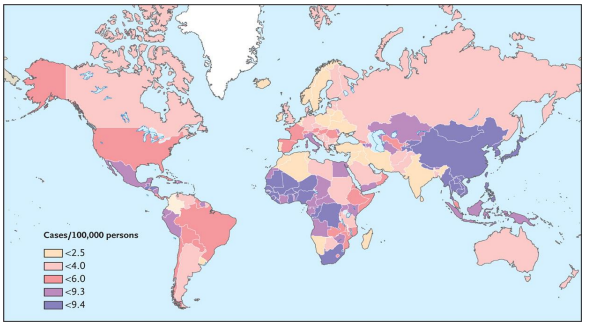
Research funding: Sirtex Medical, Ipsen, IQVIA, New B Innovation, AMiLi, Perspectum, MiRXES, Roche, NMRC, ASTAR, Duke-NUS

Leadership roles:

Academic Vice-Chair (Research), Surgery Academic Clinical Program, Singhealth-Duke-NUS
Founding President, College of Clinician Scientists, Academy of Medicine Singapore
Protocol Chair, The Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group
Chief Medical Officer, AVATAMED PTE LTD

National Cancer Centre Singapore
SingHealth
PATIENTS. AT THE HEART OF ALL WE DO.

HCC is mainly an Asia-Pacific Cancer



El-Serag HB. N Engl J Med 2011;365:1118-1127

Regional variation in the estimated age-standardized incidence rates of HCC

Restricted, Non-Sensitive

6th most common cancer worldwide, 3rd most common cause of cancer death *(Sung et al., 2021)*

- 80% of HCC is found in the **Asia-Pacific**
- The prevalence of HCC is expected to increase

Asia-Pacific Hepatocellular Carcinoma Study Group

National Cancer Centre Singapore SingHealth

3

PATIENTS. AT THE HEART OF ALL WE DO.

Peculiarities in Key Opinion Leadership in HCC

- The Barcelona Clinic for Liver Cancer (**BCLC**) guidelines is the predominant set of guidelines cited
- Most **Key Opinion leaders** in HCC are not from Asia
- Until recently most international randomized controlled trials are not led by PIs from Asia
- Few randomized controlled trials originate from Asia
- Until recently few high-quality translational research studies are published from Asia

National Cancer Centre Singapore SingHealth

4

PATIENTS. AT THE HEART OF ALL WE DO.

Translational and Clinical Science is the predominant requirement for Expertise

Promotion of the Next-Generation of Asian Liver Cancer Experts to the Global Arena cannot happen in the absence of scientific expertise

Singapore General Hospital SingHealth

PATIENTS. AT THE HEART OF ALL WE DO.

Promoting the Next-Generation of Asian Liver Cancer Experts to the Global Arena

- Encouraging the next generation of leaders to conduct strong translational and clinical research
  - encourage collaborative research
  - support each another's research across the Asia-Pacific
- Create Forums where the next generation of leaders can brainstorm research
  - ***APPLE***
  - ***China Liver Cancer Study Group Young Investigators***

National Cancer Centre Singapore SingHealth

6

PATIENTS. AT THE HEART OF ALL WE DO.

Promoting the Next-Generation Asian Liver Cancer Experts to the Global Arena

Chiun Hsu *(Taipei)*

Dr. Chiun Hsu received his medical degree from College of Medicine, National Taiwan University (NTUCM) in 1992 and his PhD degree from the Graduate Institute of Clinical Medicine, NTUCM in 2004. He serves as an Editorial Board member for Journal of Hepatology since 2020. He serves as Associate Dean and Director of Center of Faculty Development, NTUCM since 2024.

Research Interests

Clinical and Translational Research of New Drug Development for Hepatobiliary Cancers

Representative Publications

1. Hsu C*, Chang YF, Yen CJ, Xu YW, Dong M, Tong YZ. Combination of GT90001 and nivolumab in patients with advanced hepatocellular carcinoma: a multicenter, single-arm, phase 1b/2 study. BMC Med 2023; 21: 395. doi: 10.1186/s12916-023-03098-w.
2. Hsu C*, Ducreux M, Zhu AX, Qin S, Ikeda M, Kim TY, Galle PR, Finn RS, Chen E, Ma N, Hu Y, Li L, Cheng AL. Hepatic events and viral kinetics in hepatocellular carcinoma patients treated with atezolizumab plus bevacizumab. Liver Cancer 2023; 12: 44-56.
3. Ou DL, Chen CW, Hsu CL, Chung CH, Feng ZR, Lee BS, Cheng AL, Yang MH, Hsu C*. Regorafenib enhances antitumor immunity via inhibition of p38 kinase/Creb1/Klf4 axis in tumor-associated macrophages. J ImmunoTher Cancer 2021; 9: e001657. doi:10.1136/jitc-2020-001657.
4. Yau T, Kang YK , Kim TY , El-Khoueiry A, Santoro A, Sangro B, Melero I, Kudo M, Hou MM, Matilla A, Tovoli F, Knox J, He AR, El-Rayes B, Acosta-Rivera M, Lim H, Neely J, Shen Y, Wisniewski T, Anderson J, Hsu C. Nivolumab plus ipilimumab in advanced hepatocellular carcinoma previously treated with sorafenib (CheckMate 040): a randomized clinical trial. JAMA Oncol 2020; 6(11): e204564. doi: 10.1001/jamaoncol.2020.4564.
5. Yang HC, Tsou HH, Pei SN, Chang CS, Chen JH, Yao M, Lin SJ, Lin J, Yuan Q, Xia N, Liu TW, Chen PJ, Cheng AL, Hsu C*, and Taiwan Cooperative Oncology Group. Quantification of HBV core antibodies may help predict HBV reactivation in lymphoma patients with resolved HBV infection. J Hepatol 2018; 69: 286-92.


APPLE Academy
11 July 2025
What an academy may look like
Chiun Hsu（許駿）, MD, PhD
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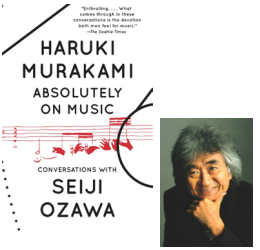
National Science and Technology Council (Taiwan), Bristol-Myers Squibb/ ONO, Eureka Therapeutics, GoldenBiotech (Taiwan), IPSEN, Roche
Advisory board:
AstraZeneca
Honorarium/ consultation:
AstraZeneca, Bristol-Myers Squibb/ONO, Eisai, MSD, Roche

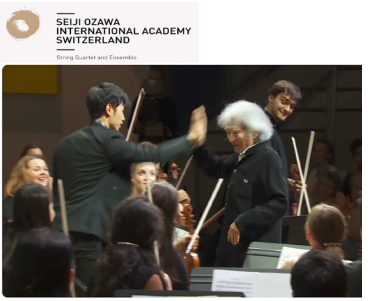
Example 1: the School of Athens

- thought leaders
- multi-disciplinary
- dialogues

Example 2: the Seiji Ozawa International Academy

'If (the students) study chamber music as closely as they do here,
they're going to last longer as musicians.'





Concert Seiji Ozawa International Academy Switzerland

Example 3: the ILCA Liver Cancer Preceptorship

APPLE ACADEMY 2025

Friday, July 11, 2025 [Kobe Portopia Hotel, Kobe, Japan]

SESSION 3.

UNMET CLINICAL NEEDS IN HCC AND CURRENT CLINICAL RESEARCH DIRECTIONS

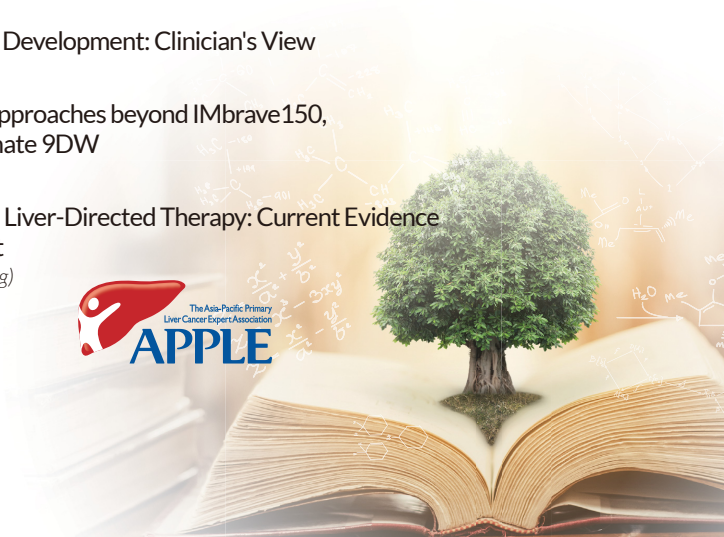
Chairperons: **Jong Young Choi** *(Gwangmyeong)*, **Chiun Hsu** *(Taipei)*

Challenges of Biomarker Development: Pathologist's View
Young Nyun Park *(Seoul)*

Challenges of Biomarker Development: Clinician's View
Han Chong Toh *(Singapore)*

Advanced HCC: Novel Approaches beyond IMbrave150, HIMALAYA, and Checkmate 9DW
Yi-Hsiang Huang *(Taipei)*

Integrating Systemic and Liver-Directed Therapy: Current Evidence and Future Development
Stephen L Chan *(Hong Kong)*



Challenges of Biomarker Development: Pathologist's View

Young Nyun Park *(Seoul)*

Prof. Young Nyun Park is Professor of Pathology at Yonsei University College of Medicine in Seoul, South Korea. She received her M.D. (1982) and Ph.D. (1992) from Yonsei University, and completed her residency and fellowship in pathology at Severance Hospital. She has since dedicated her career to academic medicine and diagnostic pathology.

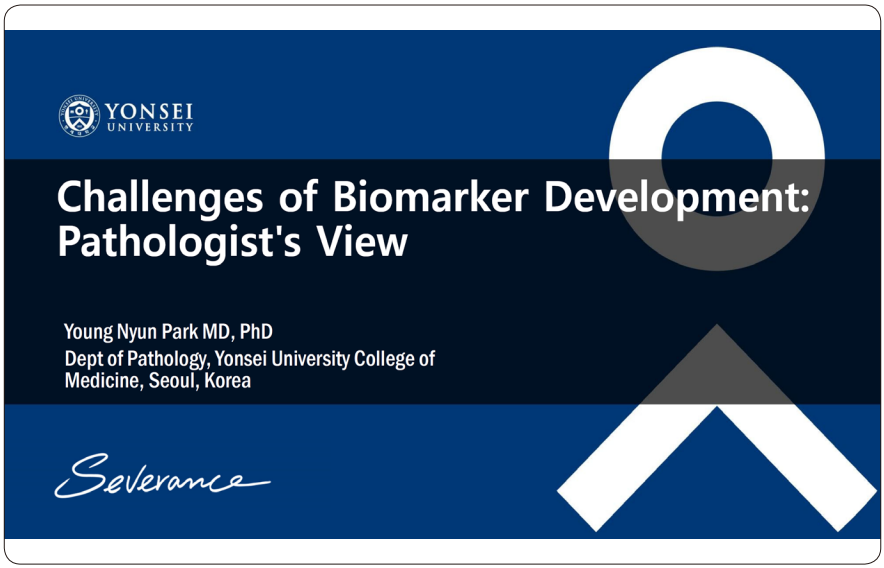
An expert in hepatobiliary pathology, Prof. Park is internationally recognized for her contributions to liver cancer research. She has held key leadership roles, including Vice Dean for Research Affairs and Chair of the Department of Pathology at Yonsei University. She has also served as editor and corresponding author for the WHO Classification of Tumours (Blue Book). Her work has significantly advanced the understanding and classification of hepatocellular carcinoma and related diseases.

Research Interests

Hepatocarcinogenesis, Cholangiocarcinoma, Cancer stem cell, Tumor microenvironment

Representative Publications

1. Chung T, Oh S, Won J, Park J, Yoo JE, Hwang HK, Choi GH, Kang CM, Han DH, Kim S, Park YN. Genomic and transcriptomic signatures of sequential carcinogenesis from papillary neoplasm to biliary tract cancer. J Hepatol. 2025 Jan 18:S0168-8278(25)00013-3. doi: 10.1016/j.jhep.2025.01.007. Online ahead of print. PMID: 39832657
2. Jeon Y, Kwon SM, Rhee H, Yoo JE, Chung T, Woo HG, Park YN. Molecular and radiopathologic spectrum between HCC and intrahepatic cholangiocarcinoma. Hepatology. 2023;77(1):92-108.
3. Yoon JG, Kim MH, Jang M, Kim H, Hwang HK, Kang CM, Lee WJ, Kang B, Lee CK, Lee MG, Chung HC, Choi HJ, Park YN. Molecular Characterization of Biliary Tract Cancer Predicts Chemotherapy and PD-1/PD-L1 Blockade Responses. Hepatology. 2021;74(4):1914-1931.
4. Rhee H, Cho ES, Nahm JH, Jang M, Chung YE, Baek SE, Lee S, Kim MJ, Park MS, Han DH, Choi JY, Park YN. Gadoxetic acid-enhanced MRI of macrotrabecular-massive hepatocellular carcinoma and its prognostic implications. J Hepatol. 2021;74(1):109-121.
5. Renne SL, Woo HY, Allegra S, Rudini N, Yano H, Donadon M, Viganò L, Akiba J, Lee HS, Rhee H, Park YN, Roncalli M, Di Tommaso L. VETC (vessels encapsulating tumor clusters) is a powerful predictor of aggressive hepatocellular carcinoma. Hepatology. 2020;71(1):183-195.



Prognostic factors in HCC (WHO 2025 update)

✓ **Morphological features**

- Tumour grade
- Vascular invasion and intrahepatic metastasis
- Tumour stage
- Tumour subtype
- Tumor vascular pattern: vessels encapsulating tumor clusters pattern
- IHC expression of CK19

✓ **Molecular features**

- *p53* mutation
- *FGF19* amplification
- Gene expression profiling: proliferative vs non-proliferative subclasses

WHO 2025 update in HCC is supported by novel molecular findings.

–35% of HCCs can be further subclassified into distinct subtypes with morphomolecular and clinical features.

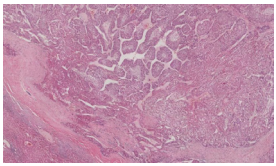
- 9 subtypes

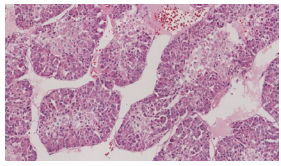
Macrotrabecular massive (MTM) HCC Neutrophil rich HCC Sarcomatoid HCC	Worse Px
Scirrhous HCC	Variable Px (Worse > 5cm)
Steatohepatitic HCC Fibrolamellar HCC Chromophobe HCC	Similar Px
Lymphocyte rich HCC Clear cell HCC	Better Px
√ **K19** is a IHC marker for poor prognosis.	IHC marker for poor Px

Macrotrabecular massive (MTM) HCC

✓Predominant macrotrabecular growth pattern (> 50%)

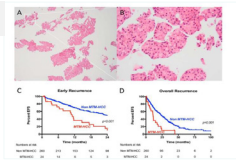
- The thickened cords > 6-10 cells thick tumor cells





- Incidence: 5%~20% of HCC (Calderaro J, *et al.* J Hepatol 2017, Rhee H, *et al.* J Hepatol 2020)
- HBV infection
- High alpha-fetoprotein serum level
- Frequent vascular invasion
- Early relapse and poor survival
- *TP53* mutations, *FGF19* amplifications
- Angiogenesis activation (high *ANGPT2* mRNA levels)
- G3 (Calderaro J, *et al*, J Hepatol 2017)

Bx

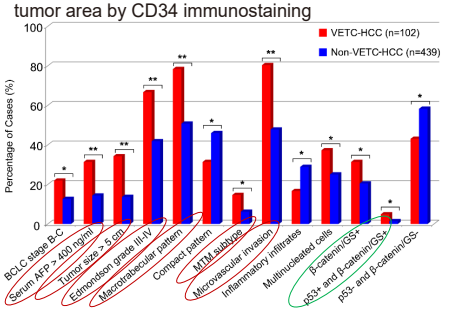


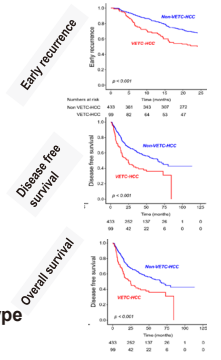
Ziol M, *et al.* Hepatology 2018

VETC- HCC vs non-VETC-HCC

- Multi-institutional HCC cohort (n=541)
  Korean (n=316), Japanese (n=127), Italian (n=98)

✓ VETC phenotype is defined as VETC in more than 55% of tumor area by CD34 immunostaining

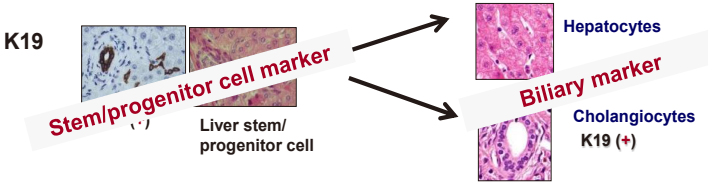




- **VETC phenotype is related to vascular permeation.**
- **MTM/ macrotrabecular pattern is enriched in VETC phenotype**
  ✓ **(MTM and VETC are not the same).**

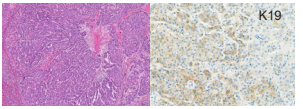
YONSEI UNIVERSITY

HCC with K19 expression



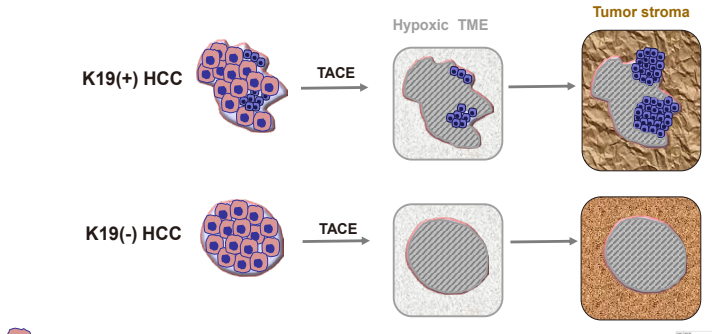
✓ **Incidence of K19+ HCCs**
- 4-28% of HCC

✓ **Clinical features**
- Frequent association with HBV
- High serum AFP levels
- More invasive growth
- LN metastasis
- Poor prognosis



Predictive biomarker: Locoregional treatment

✓**K19: Prediction of HCC treatment response (resistance to TACE)**



Poor outcome of hepatocellular carcinoma with stemness marker under hypoxia: resistance to transarterial chemoembolization

Clinico-Radio-Pathological and Molecular Features of Hepatocellular Carcinomas with Keratin 19 Expression

Predictive biomarker: Chemotherapy

✓**VETC HCC: predictor of sorafenib benefit**

Sorafenib is effective in prolonging the survival of VETC+, but not VETC– patients (Fang JH *et al*. Hepatology 2019;70:824-839).

√ **K19-Positive HCC**: **related to sorafenib resistance**

– Sorafenib resistance was associated with the gene signature of K19-positive HCC, and with EMT and a hypoxic microenvironment. (Tovar V, et al. Gut 2017; 66: 530; Zhu YJ, et al. Acta Pharmacol Sin 2017; 38: 614)

Predictive biomarker: immunotherapy

- Only 15% to 20% of advanced hepatocellular carcinoma treated with anti-PD1 exhibit a strong benefit.
- Regarding anti-PD1 therapy, the only biomarkers approved by the FDA
  - High tumor mutational burden and microsatellite-instability.
  - **< 3% of HCCs**
- Molecular mechanisms determining response are unknown.

✓ Predictive markers for immunotherapy in HCC are not well known.

✓ Evolution of intratumor heterogeneity over the course of tumor progression.
: The need for biopsies of advanced HCC before Tx.

- Over the past 2 decades, molecular profiling of HCC tissue has been performed using surgically resected early-stage HCCs.
- Limited access to tumor tissue specimens in patients with unresectable advanced-stage HCCs.

Challenges of Biomarker Development: Clinician's View

Han Chong Toh *(Singapore)*

Dr. Toh Han Chong is Deputy CEO (Strategic Partnerships), National Cancer Centre Singapore and Professor at Duke NUS Medical School. He then obtained his BSc (Intercalated) from the University of London in 'Infection and Immunity' and his medical degree from the University of Cambridge, UK. His oncology and translational research fellowships were at the Singapore General Hospital, Massachusetts General Hospital, Harvard Medical School and at the Center for Cell and Gene Therapy, Baylor College of Medicine, Houston Texas, USA. Dr Toh is alumni of the Harvard Business School General Management Program. He is Principal Lead, Cellular Immunotherapy at the Singhealth Duke NUS Cell Therapy Centre. Dr Toh received the National Senior Clinician Scientist Award in 2017, National Medical Excellence Award (NMEA) in 2018 and the NMRC STaR Award in 2022.

Dr. Toh is co-founder of the Asia-Pacific Gastrointestinal Cancer Summit (APGCS).

He is European Society for Medical Oncology (ESMO) Scientific Faculty for Cancer Immunology & Immunotherapy and chair of Investigational Immunotherapy at ESMO Annual Congress 2026 in Madrid, Spain. Dr. Toh has published over 160 peer review journal papers.

Research Interests

My laboratory focuses on studying cancer immunology and developing immunotherapies for solid tumours. we have developed immunotherapies and tested their efficacy in first-in-human, Phase I to Phase III clinical trials. These include an allogeneic peripheral blood stem cell transplantation following non-myeloablative conditioning for chemo refractory nasopharyngeal carcinoma (NPC) patients, cancer antigen-specific dendritic cell vaccines for advanced colorectal cancer, and adoptive transfer of Epstein Barr Virus (EBV)-specific T cells for NPC. We have been studying the underlying immune regulatory mechanisms within the tumour microenvironment, and identifying biomarkers for predicting treatment efficacy and resistance especially in hepatocellular carcinoma (HCC). We are also actively studying a deeper mechanistic understanding of the evolution of MASLD to HCC. Our current focus is in developing cell-based and combination immunotherapies against HCC and establishing HCC 3D organoids to better understand the role of immunity in oncogenesis and for testing our therapies.

Representative Publications

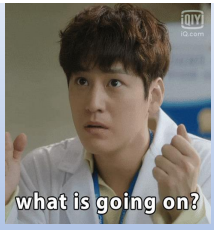
1. Chia JWK, Segelov E, Deng Y, Ho GF, Wang W, Han S, Sharma A, Ding K, Chen G, Jeffery MG, Tham CK, Ahn JB, Nott L, Zielinski R, Chao TY, van Hagen T, Wei PL, Day F, Mehta S, Yau T, Peng J, Hayes TM, Li Y, Gandhi M, Foo EMJ, Rahman N, Rothwell P, Ali R, Simes J, Toh HC. Aspirin after completion of standard adjuvant therapy for colorectal cancer (ASCOLT): an international, multicentre,

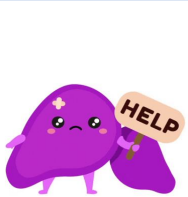
phase 3, randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2025 Mar;10(3):198-209. doi: 10.1016/S2468-1253(24)00387-X. Epub 2025 Jan 14. PMID: 39824200.

2. Chen K, Tong AKT, Moe FNN, Ng DCE, Lo RHG, Gogna A, Yan SX, Thang SP, Loke KSH, Venkatanarasimha NK, Huang HL, Too CW, Ong TSK, Yeo EX, Peh DYY, Ng AWY, Yang L, Chan WY, Chang JPE, Goh BKP, Toh HC, Chow PKH. The Impact of Radiation Dose and Tumour Burden on Outcomes in Hepatocellular Carcinoma: 11-Year Experience in a 413-Patient Cohort Treated with Yttrium-90 Resin Microsphere Radioembolisation. Liver Cancer. 2024 Sep 19;14(2):158-179. doi: 10.1159/000541539. PMID: 40255874; PMCID: PMC12005707.
3. Toh HC, Yang MH, Wang HM, Hsieh CY, Chitapanarux I, Ho KF, Hong RL, Ang MK, Colevas AD, Sirachainan E, Lertbutsayanukul C, Ho GF, Nadler E, Algazi A, Lulla P, Wirth LJ, Wirasorn K, Liu YC, Ang SF, Low SHJ, Tho LM, Hasbullah HH, Brenner MK, Wang WW, Ong WS, Tan SH, Horak I, Ding C, Myo A, Samol J. Gemcitabine, carboplatin, and Epstein-Barr virus-specific autologous cytotoxic T lymphocytes for recurrent or metastatic nasopharyngeal carcinoma: VANCE, an international randomized phase III trial. Ann Oncol. 2024 Sep 4:S0923-7534(24)03923-1. doi: 10.1016/j.annonc.2024.08.2344. Epub ahead of print. PMID: 39241963.
4. Qin S, Chen M, Cheng AL, Kaseb AO, Kudo M, Lee HC, Yopp AC, Zhou J, Wang L, Wen X, Heo J, Tak WY, Nakamura S, Numata K, Uguen T, Hsiehchen D, Cha E, Hack SP, Lian Q, Ma N, Spahn JH, Wang Y, Wu C, Chow PKH; IMbrave050 investigators including Toh HC. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023 Nov 18;402(10415):1835-1847. doi: 10.1016/S0140-6736(23)01796-8. Epub 2023 Oct 20. PMID: 37871608.
5. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators including Toh HC. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745. PMID: 32402160.

CHALLENGES OF BIOMARKER DEVELOPMENT CLINICIAN'S VIEW

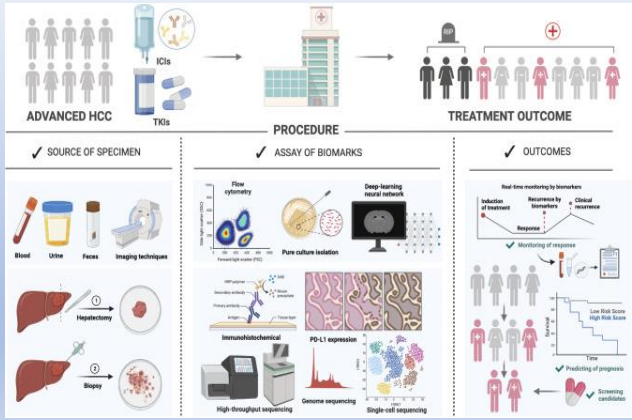
National Cancer Centre Singapore
SingHealth





DR TOH HAN CHONG
DEPUTY CEO
NATIONAL CANCER CENTRE SINGAPORE (NCCS)
SENIOR CONSULTANT DIVISION OF MEDICAL ONCOLOGY
NCCS
PROFESSOR DUKE NUS MEDICAL SCHOOL

WHERE BIOMARKERS COME FROM



AFP

IMbrave150 trial :

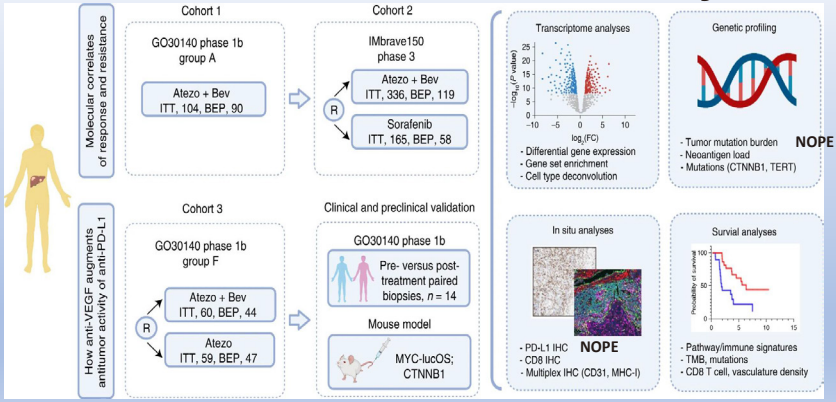
Serum AFP responses at 6 wks is a potential surrogate biomarker of prognosis in patients with HCC receiving atezo + bev

Non-IO Phase III trials :

Raised serum AFP levels associated with a poor prognosis in landmark TKI phase III sorafenib, lenvatinib, regorafenib, cabozantinib and antibody ramucirumab

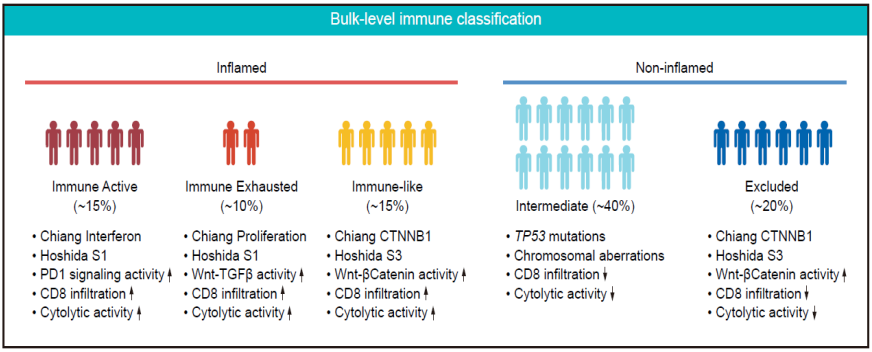
CRAFITY Score : AFP + CRP

IMBRAVE 150 Translational Study



Zhu AX et al. Nature Med Aug 2022

Different Approaches of Microenvironmental Classification Bulk Level

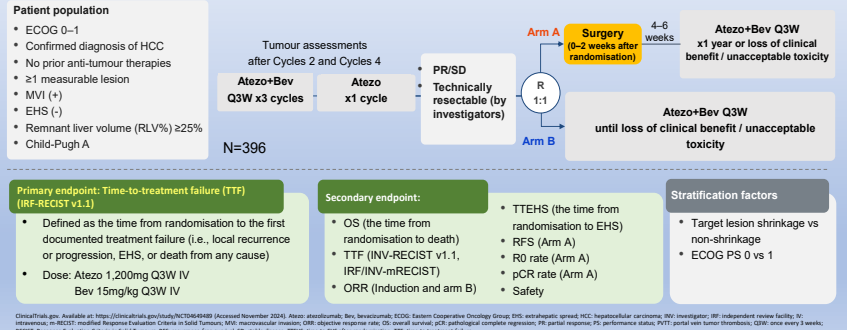


Yang X et al.. Precision treatment in advanced hepatocellular carcinoma. Cancer Cell. 2024 Feb 12;42(2)

TALENTop IIS: Hepatic resection with peri-operative Atezo/Bev in HCC
This study will give us valuable information on therapeutic biomarkers

patients with MVI

A multicentre, randomised, open-label study evaluating the efficacy and safety of hepatic resection for HCC with macrovascular invasion after initial atezolizumab plus bevacizumab therapy



ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT04649489 (Accessed November 2024). Atezo: atezolizumab; Bev, bevacizumab; ECOG: Eastern Cooperative Oncology Group; EHS: extrahepatic spread; HCC: hepatocellular carcinoma; INV: investigator; IRF: independent review facility; IV: intravenous; m-RECIST: modified Response Evaluation Criteria in Solid Tumours; MVI: macrovascular invasion; ORR: objective response rate; OS: overall survival; pCR: pathological complete regression; PR: partial response; PS: performance status; PVTT: portal vein tumor thrombosis; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumours; RFS: recurrence-free survival; SD: stable disease; TTEHS: time to EHS after randomisation; TTF: time to treatment failure.

Potential Therapeutic Biomarkers for Approved HCC Therapies

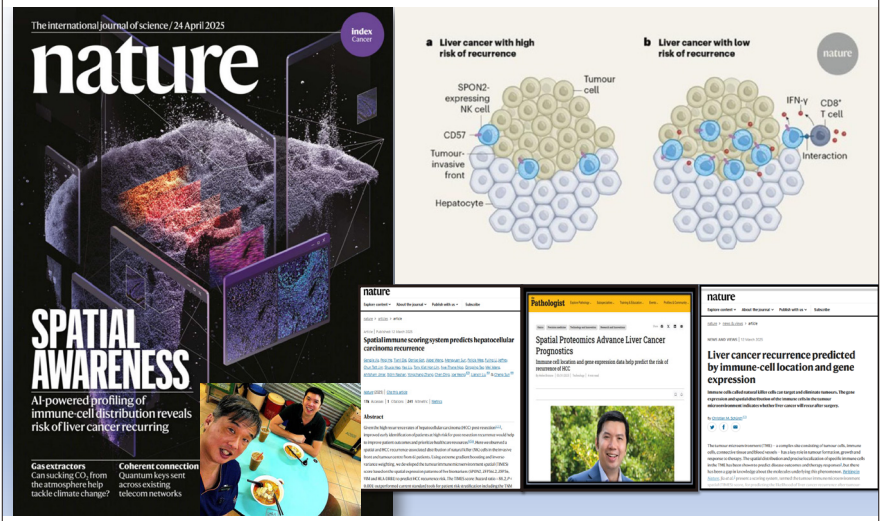
Sorafenib	Lenvatinib	Rogerafenib	Cabozantinib
• **p-ERK:** Not reached vs. ~20.0 months (mRFS) (n=188) • **Serum DKK1:** ~15.0 vs. 10.0 months (mOS) (n=54) • **Serum VEGF:** 30.9 vs. 14.4. months (mOS) (n=49)	• **Serum FGF19 + ANG2** 12.0 vs. ~4.0 months (mPFS) (n=74) • **Baseline serum FGF+ VEGF level** 23.2 vs. 8.4. months (mOS) (n=279) • **CRP** Not reached vs. 6.7 months (mOS) (n=53)	• **ALBI score** (n=138) • **LAP TGF-β1** (n=499)	• **AFP response at 8 weeks after treatment** 16.1 vs. 9.1 months (mOS) (n=236) • **AFP≥ 400 ng/mL at baseline** (n=260)

Yang X et al. Precision treatment in advanced hepatocellular carcinoma. Cancer Cell. 2024 Feb 12;42(2):180-197.

Potential Therapeutic Biomarkers for Approved HCC Therapies

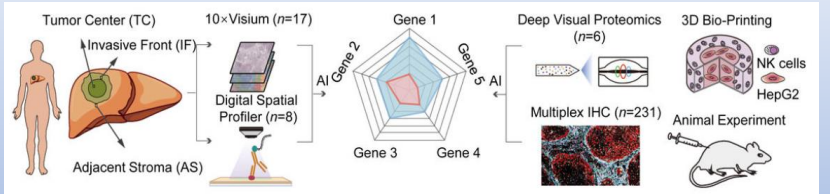
Atezolizumab + Bevacizumab	Durvalumab + Tremelimumab	Ramucirumab	Camrelizumab + Apatinib
• **AFP response at 3 weeks after treatment** 15.63 vs. 5.73 months (mOS) (n=75) • **AFP response at 6 weeks after treatment** Not reached vs. 14.2 months (mOS) (n=150) • **CRAFITY score** 27.6 vs. 11.3 vs. 6.4 months (mOS) (n=204) • **CRAFITY score** Not reached vs. 14.3 vs. 11.6 months (mOS) (n=297) • **Pre-existing immunity Indicators** (n=358)	• **irAEs** 23.2 vs. 14.1 months (mOS) (n=388)	• **AFP≥ 400 ng/mL at baseline** 8.5 vs. 7.3 months (mOS) (n=292)	• **RCCEP reactive cutaneous capillary endothelial proliferation** 17.0 vs. 5.8 months (mOS) (n=217)

Yang X, et al. Precision treatment in advanced hepatocellular carcinoma. Cancer Cell. 2024 Feb 12;42(2):180-197



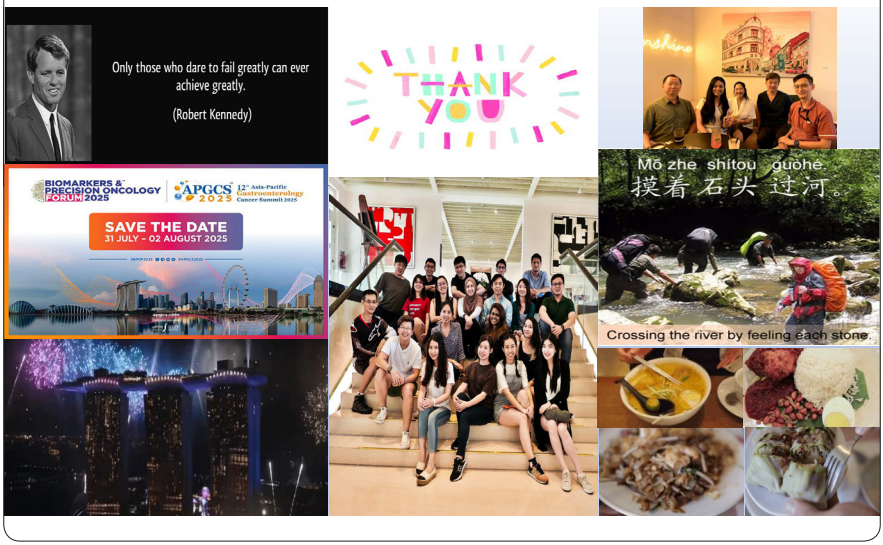
Nature Cover Story Volume 640 Issue 8060, 24 April 2025

Spatial Awareness: AI-powered profiling of immune-cells distribution reveals risk of liver cancer recurring



AI-powered TIMES score outperformed known prognostic factors in predicting recurrence

Jia et al. Nature 2025


Only those who dare to fail greatly can ever achieve greatly.
(Robert Kennedy)
THANK YOU
BIOMARKERS & PRECISION ONCOLOGY FORUM 2025
APGCS 2025 12th Asia-Pacific Gastroenterology Cancer Summit 2025
SAVE THE DATE
31 JULY – 02 AUGUST 2025
Mō zhe shítou guòhé.
摸着石头过河。
Crossing the river by feeling each stone.

Advanced HCC: Novel Approaches beyond IMbrave150, HIMALAYA, and Checkmate 9DW

Yi-Hsiang Huang *(Taipei)*

Professor Yi-Hsiang Huang is a distinguished hepatologist currently serving as President (2023–2027) of the Taiwan Liver Cancer Association (TLCA) and Director of Medical Research at Taipei Veterans General Hospital. He is also a Chair Professor at the Institute of Clinical Medicine, National Yang Ming Chiao Tung University (NYCU).

Prof. Huang completed his medical degree and PhD at National Yang Ming University. He further honed his research expertise as a fellow at the Vaccine Branch of the National Cancer Institute, National Institutes of Health (NIH), USA, from 2006 to 2007. In 2011, he was appointed full professor at NYCU's Institute of Clinical Medicine and has held the position of Chair Professor since August 2022.

Prof. Huang holds several key leadership roles, including:
Council Member, Asia-Pacific Primary Liver Cancer Expert Association (APPLE) since July 2023
Executive Committee Member, Taiwan Association for the Study of the Liver (TASL) since September 2023
Chairman, 2025 Asia Pacific Association for the Study of the Liver (APASL) Single Topic Conference (STC) on Oncology

Research Interests

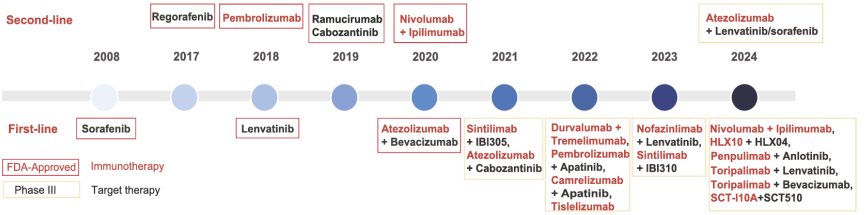
Prof. Huang's research focuses on the virology and immunology of viral hepatitis and hepatocellular carcinoma (HCC), including HBV reactivation associated with immunosuppressive and immune checkpoint inhibitor therapies, as well as comprehensive HCC treatment strategies spanning locoregional to systemic therapies.

Representative Publications

1. Lee PC, Wu CJ, Hung YW, Lee CJ, Mon HC, Chi CT, Lee IC, Juo YL, Chou SH, Luo JC, Hou MC, Huang YH*. Distinct gut microbiota but common metabolomic signatures between Viral and MASLD HCC contribute to outcomes of combination immunotherapy. Hepatology 2025 Publish Ahead of Print DOI:10.1097/HEP.0000000000001446 (*corresponding author)
2. Lee PC, Wu CJ, Lee IC, Lee CJ, Hou MC, Huang YH*. Serum fibrosis marker M2BPGi-based novel score predicts survival of unresectable HCC undergoing immunotherapy. JHEP reports 2025 https://doi.org/10.1016/j.jhepr.2025.101491 (in press) (*corresponding author)
3. Mon HC, Lee PC, Hung YP, Hung YW, Wu CJ, Lee CJ, Chi CT, Lee IC, Hou MC, Huang YH*. Functional cure of hepatitis B in patients with cancer undergoing immune checkpoint inhibitor therapy. J Hepatol 2025 Jan; 82(1): 51-61. (*corresponding author)

4. Hung YW, Lee IC, Chi CT, Lee RC, Liu CA, Chiu NC, Hwang HE, Chao Y, Hou MC, Huang YH*. Radiologic Patterns Determine the Outcomes of Initial and Subsequent Transarterial Chemoembolization in Intermediate-Stage Hepatocellular Carcinoma. Liver Cancer. 2024 Feb;13 (1): 29-40 (*corresponding author)
5. Lee PC, Wu CJ, Hung YW, Lee CJ, Chi CT, Lee IC, Yu-Lun K, Chou SH, Luo JC, Hou MC, Huang YH.*. Gut microbiota and metabolites associate with outcomes of immune checkpoint inhibitors-treated unresectable hepatocellular carcinoma. J Immunother Cancer 2022 Jun;10(6):e004779 (*corresponding author)

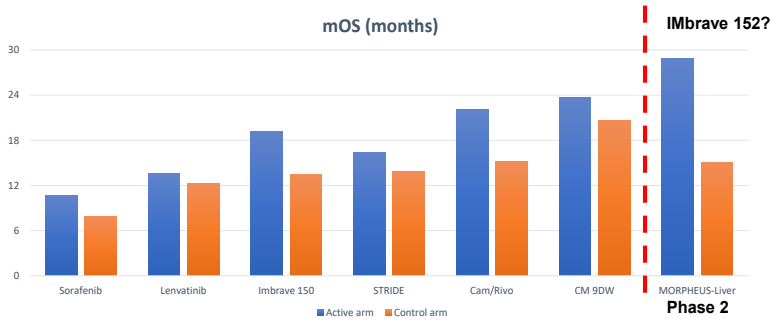
First-line and second-line therapy in HCC during 2007–2024



Zheng J, et al. Signal Transduction and Targeted Therapy 2025;10:35

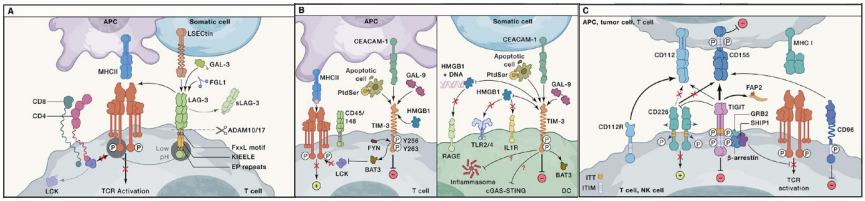
1

Trends of overall survivals in uHCC



2

LAG-3, TIM-3, and TIGIT: the next generation of immune checkpoint receptors

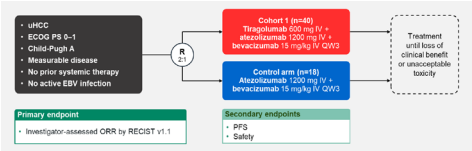


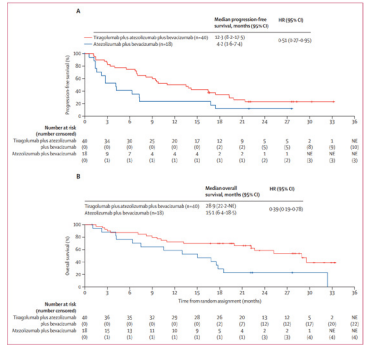
- LAG-3, a structural homolog of CD4, is induced upon T cell stimulation, and its expression is maintained in settings of sustained antigenic stimulation
- TIM-3 was identified as a coinhibitory receptor that regulates type I immunity due to its expression on differentiated interferon (IFN)-γ-secreting CD4+ and CD8+ T cells in both mice and humans.
- Identified in 2009, TIGIT is a new co-inhibitory receptor. TIGIT expression is transiently induced on T cells upon TCR stimulation and is stably expressed on a subset of NK cells and several T cell populations

Joller M, et al. Immunity 2024;57:206-222

3

MORPHEUS-Liver: a phase Ib/II, open-label, multicenter, randomized study





	RECIST version 1.1		Hepatocellular carcinoma-modified RECIST	
	Tiragolumab plus atezolizumab plus bevacizumab (n=40)	Atezolizumab plus bevacizumab (n=18)	Tiragolumab plus atezolizumab plus bevacizumab (n=40)	Atezolizumab plus bevacizumab (n=18)
Responders, n	17	2	22	3
Objective response rate	43% (27–59)*	11% (1–35)*	55% (38–71)†	17% (4–41)†
Complete response	0	0	4 (10%)	1 (6%)
Partial response	17 (43%)	2 (11%)	18 (45%)	2 (11%)
Stable disease	17 (43%)	8 (44%)	11 (28%)	8 (44%)
Progressive disease	3 (8%)	5 (28%)	2 (5%)	2 (11%)
Missing or not evaluable	3 (8%)	3 (17%)	5 (13%)	5 (28%)
Disease control rate	34 (85%, 62–89)	8 (44%, 22–69)	37 (88%, 66–91)	9 (50%, 26–74)
Median duration of response, months (95% CI)	NE (13·8–NE)	NE (NE–NE)	15·2 (12·6–NE)	NE (14·4–NE)

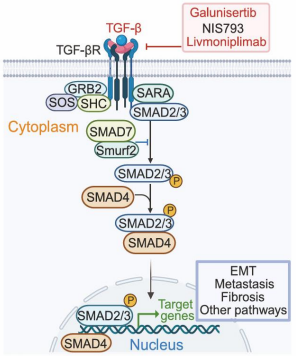
Data are n (%), % (95% CI), or n (%, 95% CI), unless otherwise specified. NE=not estimable. RECIST=Response Evaluation Criteria in Solid Tumours. *Difference in objective response rate 31% (95% CI 16–57). †Difference in objective response rate 38% (95% CI 11–65).

Table 2: Best confirmed overall response rates by investigator per RECIST version 1.1

Finn R, et al. Lancet Oncol 2025: 26; 214–26

4

TGF-β pathway



- ABBV-151 (Livmoniplimab) is a monoclonal antibody that targets the glycoprotein A repetitions predominant (GARP)-transforming growth factor β1 (TGFβ1) complex, prevents release of active TGF-β1, potentially leading to antitumor activity
- Budigalimab is a monoclonal antibody that targets PD-1 (PDCD1) and inhibits binding of the PD-L1 (CD274) ligand.
- Livmoniplimab + Budigalimab as 1L setting for uHCC
- A phase 1 study in HCC showed an overall response rate (ORR) of 42% (5/12) when combining livmoniplimab with the programmed cell death 1 inhibitor budigalimab (ABBV-181)

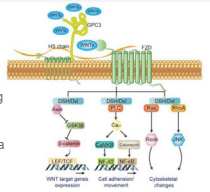
Zheng J, et al. Signal Transduction and Targeted Therapy 2025;10:35

5

Glypican-3 (GPC3) as a Target for HCC

GPC3 biology

- GPC3 is a GPI-linked heparan sulfate proteoglycan
- GPC3 stabilizes the Wnt-FZD interaction, stimulating Wnt signaling → Wnt pathway promotes hepatocellular carcinoma (HCC) growth



Antibody-Drug Conjugates

GPC3 is highly expressed in HCC

Adjacent non-tumor liver:
0% GPC3+

Grade 3:
75% GPC3+

GPC3 Expression

Low — High

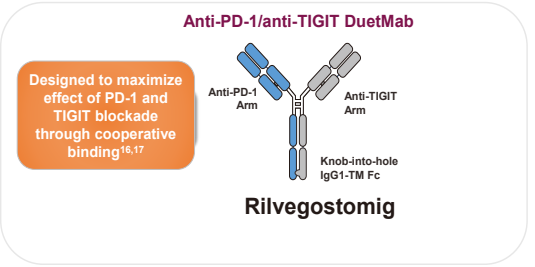
GPC3 membrane staining; GC33 mAb. AZ/Innovation China Center (ICC).

	Incidence in HCC	Incidence in sqNSCLC
GPC3$^{lo+hi(\geq 10\%)}$	81%	40%
GPC3$^{hi(\geq 50\%)}$	54%	20%

6

Rilvegostomig

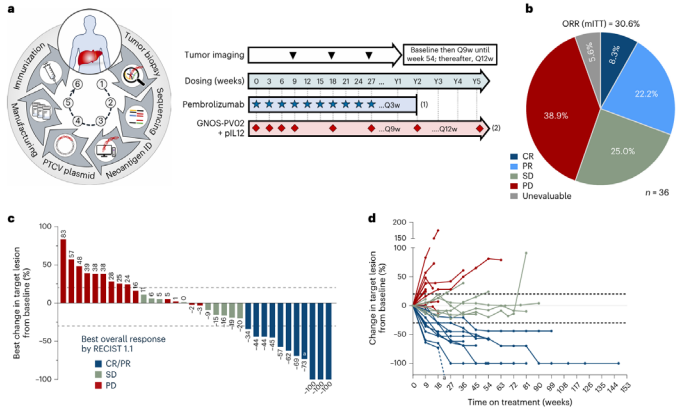
a Monovalent Bispecific Antibody for anti-PD-1 and anti-TIGIT



TIGIT and PD-1 dual blockade enhances CD8 T cell activation and cytotoxicity against tumor cells

7

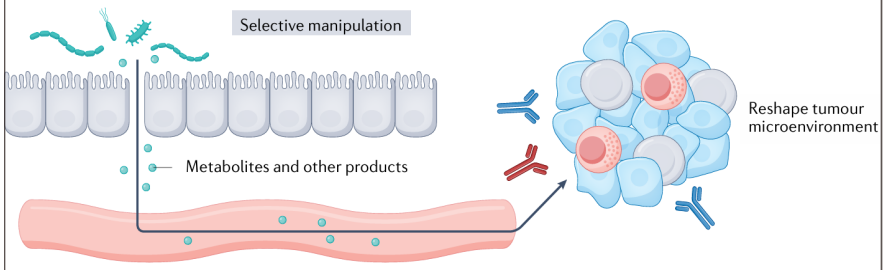
Neoantigen vaccine plus pembrolizumab in HCC failed by TKI



Yarchoan M, et al. Nature Medicine. 2024;30:1044–1053

8

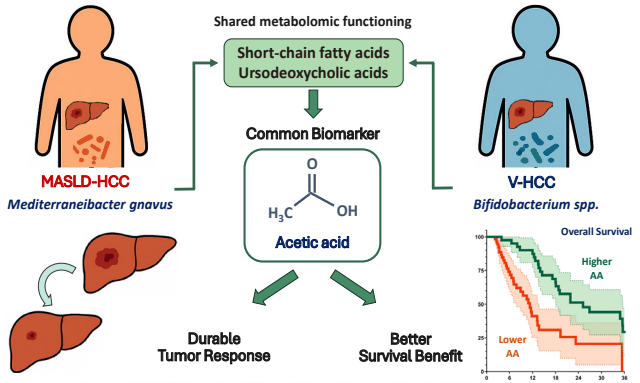
Gut microbiota



Yang C, et al. Nat Rev Gastroenterol Hepatol. 2023 Apr;20(4):203-222

9

Distinct gut microbiota but common metabolomic signatures between Viral and MASLD HCC contribute to outcomes of combination immunotherapy



Lee PC, Huang YH* Hepatology 2025 Publish Ahead of Print DOI:10.1097/HEP.0000000000001446

AASLD Lee, et al | HEPATOLOGY. 2025.

HEPATOLOGY

Integrating Systemic and Liver-Directed Therapy: Current Evidence and Future Development

Stephen L Chan *(Hong Kong)*

Stephen Lam CHAN is the Clinical Professor at the Department of Clinical Oncology of the Chinese University of Hong Kong. His main interest of research is clinical and translational studies on hepatobiliary-pancreatic and neuroendocrine cancers. Prof. Chan has published over 200 papers in peer reviewer journals.

Internationally, Prof. Chan is serving as the President Elect of the Executive Committee of the International Liver Cancer Association (ILCA). He has also been invited to be Associate Editors in several journals including Journal of Hepatology, Liver Cancer, and Therapeutic Advances in Medical Oncology.

Locally, Prof. Chan is the Panel Member of Biology and Medicine Panel for the General Research Fund in Hong Kong. He has also established a charity hand in hand cancer foundation to serve patients in need.

Research Interests

Principal investigator for clinical and translation research on hepatocellular carcinoma and pancreatobiliary cancers at the Chinese University of Hong Kong

Representative Publications

1. Qin, S. K.*, Chan, S. L.*, Gu, S., Bai, Y., Ren, Z., Lin, X., Chen, Z., Jia, W., Jin, Y., Guo, Y., Hua, X., Meng, Z., Liang, J., Cheng, Y., Xiong, J., Ren, H., Fang, Y., Li, W., Chen, Y., Zeng, Y., Sultanbaev, A., Pazgan-Simon, M., Pisetska, M., Melisi, D., Ponomarenko, D., Osypchuk, Y., Sinielnikov, I., Yang, T. S., Liang, X., Chen, C., Wang, L., Cheng, A. L., Kaseb, A., Vogel, A. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. Lancet. 2023. Published Online July 24, 2023 https://doi.org/10.1016/S0140-6736(23)00961-3 (* As co-first author)
2. Chan, S. L., Chotipanich, C., Choo, S. P., Kwang, S. W., Mo, F., Worakitsitisatorn, A., Tai, D., Sundar, R., Ng, D. C. E., Loke, K. S. H., Li, L., Ng, K. K. C., Peng, Y. W., Yu, S. C. H. Selective Internal Radiation Therapy with Yttrium-90 Resin Microspheres Followed by Gemcitabine plus Cisplatin for Unresectable Intrahepatic Cholangiocarcinoma: A Phase 2 Single-Arm Multicenter Clinical Trial. Liver Cancer. 2022. doi: 10.1159/000525489. PMID: 36158588.
3. Chan, S. L., Schuler, M., Kang, Y. K., Yen, C. J., Edeline, J., Choo, S. P., Lin, C. C., Okusaka, T, Weiss, K. H., Macarulla, T., Cattan, S., Blanc, J. F., Lee, K. H., Maur, M., Pant, S., Kudo, M., Assenat, E., Zhu, A. X., Yau, T., Lim, H. Y., Bruix, J., Geier, A., Guillén-Ponce, C., Fasolo, A., Finn, R. S., Fan, J., Vogel, A., Qin, S., Riester, M., Katsanou, V., Chaudhari, M., Kakizume, T., Gu, Y., Porta, D. G., Myers, A., Delord, J. P. A first-in-

human phase 1/2 study of FGF401 and combination of FGF401 with spartalizumab in patients with hepatocellular carcinoma or biomarker-selected solid tumors. Journal of Experimental & Clinical Cancer Research. 2022; 41(1): 189. doi: 10.1186/s13046-022-02383-5. PMID: 35655320.

4. Xiong, Z*., Chan, S. L.*, Zhou, J., Vong, J. S. L., Kwong, T. T., Zeng, X., Wu, H., Cao, J., Tu, Y., Feng, Y., Yang, W., Wong, P. P., Si-Tou, W. W., Liu, X., Wang, J., Tang, W., Liang, Z., Lu, J., Li, K. M., Low, J. T., Chan, M. W., Leung, H. H. W., Chan, A. W. H., To, K. F., Yip, K. Y., Lo, Y. M. D., Sung, J.J., Cheng, A. S. Targeting PPAR-gamma counteracts tumour adaptation to immune-checkpoint blockade in hepatocellular carcinoma. Gut. 2023: gutjnl-2022-328364. doi: 10.1136/gutjnl-2022-328364. Epub ahead of print. PMID: 37019619. (* as co-first author)
5. Abou-Alfa, G. K*., Lau, G*. Kudo, M*. Chan, S.L.*, Kelley, R. K., Furuse, J., Sukeepaisarnjaroen, W., Kang, Y. K., Dao, T. V., Toni, E. N., Rimassa, L., Breder, V., Vasilyev, A., Heurgué, A., Tam, V. C., Mody, K., Thungappa, S, C., Ostapenko, Y., Yau, T., Azevedo, S., Varela, M., Cheng, A. L., Qin, S.K., Galle, P. R., Ali, S., Michelle Marcovitz, M., Makowsky, M., He, P., Kurland, J.F., Negro, A., Sangro, B. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid. 2022; 1(8). DOI: 10.1056/EVIDoa2100070. (As co-first author)

香港中文大學
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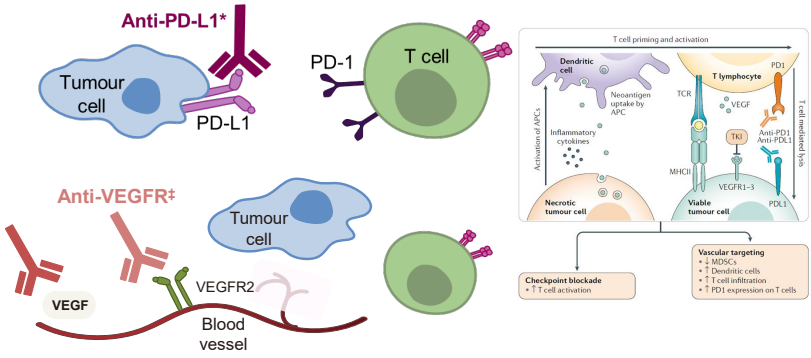
Faculty of Medicine
The Chinese University of Hong Kong

Integrating Systemic and LiverDirected Therapy: Current Evidence and Future Development

Stephen L. Chan
MD, FRCP

Ip's Family Trust Professor of Oncology,
Assistant Dean, Faculty of Medicine

New Rationale



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The Chinese University of Hong Kong
Faculty of Medicine

3

EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)

R 1:1:1 N=616

- **Arm A: Durvalumab‡** (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ placebo** for bevacizumab (Q3W)
- **Arm B: Durvalumab†** (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ bevacizumab** (15 mg/kg Q3W)
- **Arm C: Placebo** for durvalumab (Q4W) **+ TACE§** → **Placebo** for durvalumab (Q3W) **+ placebo** for bevacizumab (Q3W)

Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

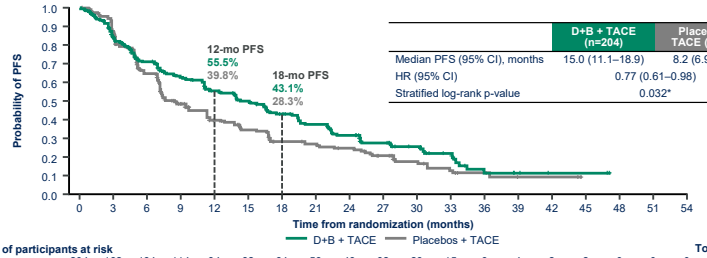
Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.
BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

4

PFS with D+B + TACE versus placebos + TACE: primary endpoint

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

No. of participants at risk																			Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	149

Median (range) duration of follow-up in censored participants, D+B + TACE 16.7 (0.03–47.1) months, Placebos + TACE 10.3 (0.03–44.3) months. Median (95% CI) duration of follow-up in all participants using the reverse Kaplan-Meier method, D+B + TACE 22.2 (16.7–27.3) months, Placebos + TACE 26.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1).
*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.
B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

LEAP-012: Study design[1,2]

- LEAP-012 is a phase 3, prospective, double-blind, randomised study[1,2]

Stratification criteria:
Study site
AFP ≤400 vs AFP >400 ng/mL
ECOG PS 0 vs 1
ALBI grade 1 vs 2 or 3
Tumour burden (6 and 12 rule)*

Key inclusion criteria:
- HCC localised to the liver (not amenable to curative treatment)
- ECOG PS 0-1
- Child-Pugh A

Key exclusion criteria:
- Prior systemic therapy for HCC
- Macrovascular invasion
- Candidate for liver transplant
- Extrahepatic disease
- Oesophageal or gastric variceal bleeding in the past 6 months

N=450 estimated (2 arms) Randomised 1:1

Lenvatinib 8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) PO QD + **pembrolizumab** 400 mg IV Q6W + TACE (cTACE or DEB-TACE)†
Hold **lenvatinib** 2 days pre and at least 7 days post TACE
Pembrolizumab + **lenvatinib** for up to 2 years or until PD or intolerable toxicity‡
(2-year limit applied to pembrolizumab but not lenvatinib)‡

Placebo **PO** QD + saline placebo **IV** Q6W + TACE (cTACE or DEB-TACE)†
Hold placebo **PO** 2 days pre and at least 7 days post TACE
IV + **PO** placebo for up to 2 years or until PD or intolerable toxicity‡

Primary endpoints:
PFS by ***RECIST 1.1*** and OS

Secondary endpoints:
PFS/ORR/DOR/DCR/TTP
mRECIST
ORR/DOR/DCR/TTP
by RECIST 1.1
Safety/AE

AE: adverse event, **AFP:** alpha-fetoprotein, **ALBI:** albumin-bilirubin, **BW:** body weight, **cTACE:** conventional transarterial chemoembolisation, **DCR:** disease control rate, **DEB-TACE:** drug-eluting bead TACE, **DOR:** duration of response, **ECOG PS:** Eastern Cooperative Oncology Group performance status, **HCC:** hepatocellular carcinoma, **IV:** intravenous, **LI-RADS:** Liver Imaging Reporting and Data System, **mRECIST:** modified Response Evaluation Criteria In Solid Tumours, **ORR:** objective response rate, **OS:** overall survival, **PD:** progressive disease, **PFS:** progression-free survival, **PO:** orally, **Q6W:** every 6 weeks, **QD:** once daily, **TTP:** time to progression.

*3 categories: ≤6 versus >6 but ≤12 versus >12. Tumour burden = (largest tumour size in cm) + (number of tumours). † For this study, RECIST 1.1 has been modified to define new intrahepatic lesions as meeting LI-RADS 5 criteria. ‡TACE is limited to 2 treatments per lesion.‡ §Lenvatinib or oral placebo were administered QD until PD or unacceptable toxicity; continuation of lenvatinib beyond 2 years of therapy required consultation with the sponsor. Pembrolizumab or IV saline placebo were administered Q6W for up to 2 years or until PD or unacceptable toxicity.‡

References: 1. ClinicalTrials.gov. NCT04246177. https://clinicaltrials.gov/study/NCT04246177?tab=table (accessed May 2024). 2. Llovet J *et al. Cardiovasc Interv Radiol* 2022;45:405–412.

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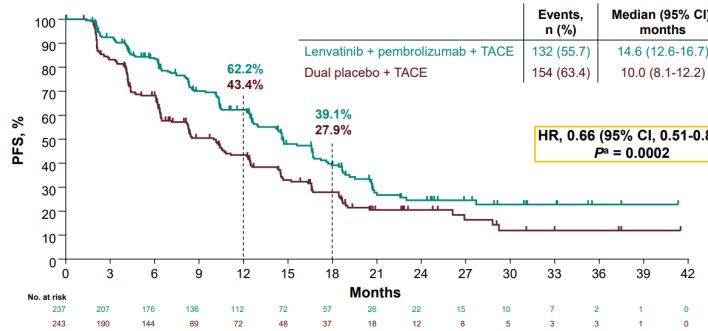
Progression-Free Survival per RECIST v1.1 by BICR



	Events, n (%)	Median (95% CI), months
Lenvatinib + pembrolizumab + TACE	132 (55.7)	14.6 (12.6-16.7)
Dual placebo + TACE	154 (63.4)	10.0 (8.1-12.2)

HR, 0.66 (95% CI, 0.51-0.84)
P[a] = 0.0002

*One-sided *P* from re-randomization test; threshold *P* = 0.025. Data cutoff date for IA1: January 30, 2024.

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Llovet J et al. ESMO 2024

TALENTACE Study Design

A prospective, phase III, open-label, multicenter, randomized study (NCT04712643)

Key eligibility criteria
- Confirmed unresectable HCC
- Eligible for TACE treatment, incl. unresectable BCLC-A, BCLC-B, and BCLC-C for Vp 1/2, and BCLC-C for ECOG PS 1
- Sum of tumor maximum diameter plus tumor number ≥6
- No prior systemic therapy or locoregional therapy to the target lesions
- Child-Pugh A
- No extrahepatic spread
- ECOG PS 0-1

R 1:1, N=342

A: On-demand TACE + Atezolizumab 1200 mg + bevacizumab 15 mg/kg IV q3w

B: On-demand TACE + Control (Observation)

Primary endpoints
- Investigator (INV)-assessed TACE-PFS
- Overall survival (OS)

Stratification factors
- Baseline AFP (< 400 ng/ml vs. ≥ 400 ng/ml)
- Prior locoregional therapy (except curative resection and ablation) (Yes, TACE vs. Yes, other locoregional therapy vs. No)
- Baseline Vp1/2 (Yes vs. No)[a]
- Geographic region(China vs. Japan)[b]

Secondary endpoints
- INV-assessed PFS per RECIST v1.1
- Time to untreatable (unTACEable) progression (TTUP), TTP, EHS per RECICL
- ORR, DOR per RECICL and RECIST v1.1

ECOG PS: Eastern Cooperative Oncology Group performance status; q3W, every three weeks; TACE: transarterial chemoembolization; Vp: Vp classification system; BCLC: Barcelona Clinic Liver Cancer; RECICL: Response Evaluation Criteria in Cancer of the Liver
a This stratification was used on or after Protocol V5; b This stratification was used before Protocol V5

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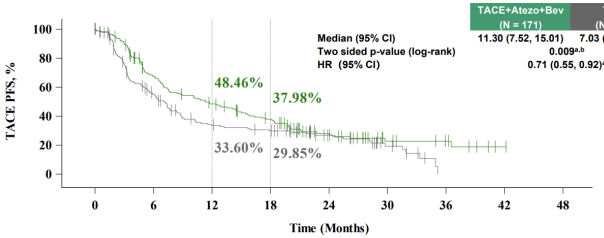
Primary Endpoint: INV-assessed TACE-PFS



	TACE+Atezo+Bev (N = 171)	TACE (N = 171)
Median (95% CI)	11.30 (7.52, 15.01)	7.03 (5.32, 8.41)
Two sided p-value (log-rank)	0.009[a,b]	
HR (95% CI)	0.71 (0.55, 0.92)[a]	

No. of Patients at Risk									
	171	104	73	52	26	11	7	1	0
	171	81	46	39	22	9	0		

[a]HR and *P* value were from Cox model and log-rank test and were stratified by AFP level (< 400 vs ≥ 400 ng/mL) at baseline per IxRS. [b] The 2-sided *P* value boundary is 0.05. Data cutoff, 28 Feb 2025.

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Additional analyses

- Subgroup of patients who received subsequent treatment of curative intent
  - ? More early-stage disease
  - ? Unifocal tumour
- Await the ABC study: TACE vs. Atezo-bevacizumab in high-risk BCLC B
- ? Personalized/Stratified approach
  - Chance of downstaging for surgery/ablation: TACE + IO
  - Advanced disease: sequential TACE followed by IO

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CU Medicine Faculty of Medicine The Chinese University of Hong Kong

APPLE ACADEMY 2025

Friday, July 11, 2025 [Kobe Portopia Hotel, Kobe, Japan]

SESSION 4.

FROM APPLE ACADEMY INTO THE FUTURE

Chairperons: Pierce Chow *(Singapore)*, Chiun Hsu *(Taipei)*

How to Promote Investigator-Initiated Trials for HCC in the Asia-Pacific Region?
Ryosuke Tateishi *(Tokyo)*

Translational Research of New Drug Development for HCC: Scientist's View
Alfred Cheng *(Hong Kong)*

Panel Discussion: The APPLE Association as a Platform for Future International Research Collaboration

How to Promote Investigator-Initiated Trials for HCC in the Asia-Pacific Region?

Ryosuke Tateishi *(Tokyo)*

Dr. Ryosuke Tateishi is an Associate Professor and Vice-Chair in the Department of Gastroenterology at the Graduate School of Medicine, The University of Tokyo. He received his M.D. in 1995 and Ph.D. in 2005 from the University of Tokyo. His research focuses on hepatocellular carcinoma (HCC), liver fibrosis, and the use of AI and digital pathology in liver disease diagnostics.

He serves as a councilor of the Japan Society of Hepatology and Japan Society of Gastroenterology, and a board member of the Japan Liver Cancer Association. He is also on the editorial boards of Liver Cancer and Hepatology International, and currently serves as Vice-Chair of the JSH Clinical Practice Guidelines for Primary Liver Cancer.

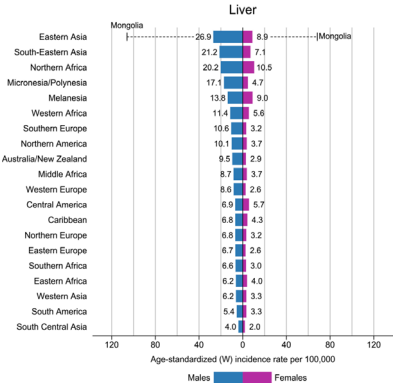
Dr. Tateishi has received several honors, including the Young Investigator Award from the Japan Society of Gastroenterology and the High Citation Award from the Journal of Gastroenterology. His recent work includes high-impact publications on machine learning in liver cancer prediction and comparative studies of HCC treatments.

Representative Publications

1. Nakatsuka T, Tateishi R*, et al. Deep learning and digital pathology powers prediction of HCC development in steatotic liver disease. Hepatology 2024 ePub ahead of print.
2. Dalbeni A, Tateishi R, et al. Diagnostic accuracy of AGILE 3+ score for advanced fibrosis in patients with NAFLD: A systematic review and meta-analysis. Hepatology 2024;79:1107-1116.
3. Sekino Y, Tateishi R*, et al. Proton Beam Therapy Versus Radiofrequency Ablation for Patients with Treatment-Naïve Single Hepatocellular Carcinoma: A Propensity Score Analysis. Liver Cancer 2023;12(4): 297-308.
4. Minami T, Tateishi R*, et al. Machine Learning for Individualized Prediction of Hepatocellular Carcinoma Development after the Eradication of Hepatitis C Virus with Antivirals. J Hepatol 2023;79:1006-14.
5. Nakatsuka T, Tateishi R*, et al. Agile Scores Are a Good Predictor of Liver-Related Events in Patients with Nafld. J Hepatol 2023;79(3): e126-e27.

Epidemiology of HCC in Asia-Pacific

- The Asia-Pacific region accounts for the highest global burden of hepatocellular carcinoma (HCC), largely due to the high prevalence of chronic hepatitis B virus (HBV) infection.
- This dominant etiology highlights the need for region-specific research and treatment strategies.

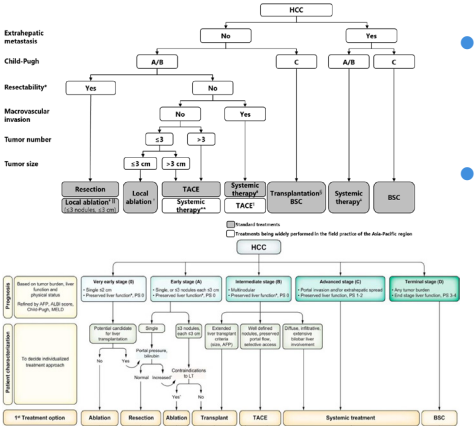


Sung et al., CA Cancer J Clin, 2021

Limitations of Current Standard Therapies

- Current global treatment guidelines were mainly developed in Western populations and may not reflect the clinical realities of Asia.
- There is a need for region-specific evidence to improve the applicability and effectiveness of standard therapies.

Eest vs West



- In the Asia-Pacific region, surgical resection plays a greater role than in Western countries.
- Specifically, resection is often selected even for multifocal disease or cases with portal vein tumor invasion, as many HBV-related HCC cases occur without cirrhosis.

Reig M, et al. J Hepatol 2022;76:681-693.
Omata M, et al. Hepatol Int 2017;11:317-370

Importance of IITs

- Help answer region-specific clinical questions often overlooked by industry trials.
- Support pragmatic designs that fit local healthcare systems.
- Enable development of tailored treatment strategies for diverse patient populations

Kong NH,Chow PKH, et al. Contemp Clin Trials 2013;36:682-6.

Current Challenges

- Limited funding mechanisms specifically designated for investigator-initiated trials in the Asia-Pacific region.
- Insufficient clinical trial infrastructure and expertise at many participating sites.
- Complex, multi-layered regulatory and ethical approval processes across different countries.
- Limited collaboration and inconsistent standards among institutions and nations.

Kong NH,Chow PKH, et al. Contemp Clin Trials 2013;36:682-6.

Funding and Infrastructure

- Leverage public research grants and international academic funding opportunities.
- Build sustainable infrastructure to support high-quality IIT execution.
- Foster academia-industry partnerships while ensuring scientific independence.

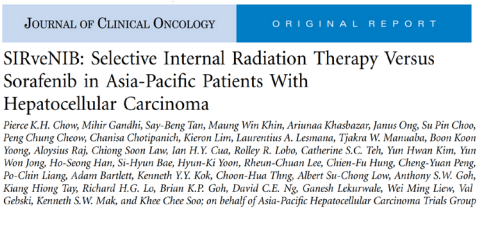
Collaboration and Standardization

- Establish regional collaborative research networks.
- Introduce standardized protocols and ethical approval templates.
  - CONSORT
  - SPIRIT
  - PRECIS-2
  - Trial Forge

Education and Training

- Develop and deliver training in clinical trial design, Good Clinical Practice (GCP), data management, and biostatistics.
- Build capacity through workshops and online courses tailored to local needs.
- Support mentorship and career development pathways for emerging researchers and clinicians.

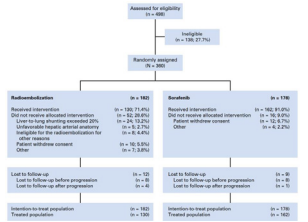
Successful Example



JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma

Pierce K.H. Chow, Mihir Gandhi, Say-Beng Tan, Maung Win Khin, Ariunaa Khasbazar, Janus Ong, Su Pin Choo, Peng Chung Cheow, Chanisa Chotipanich, Kieron Lim, Laurentius A. Lesmana, Tjakra W. Mamuaba, Boon Koon Yoong, Aloysius Raj, Chiong Soon Law, Ian H.Y. Cua, Rolley R. Lobo, Catherine S.C. Teh, Yun Hwan Kim, Yun Won Jong, Ho-Seong Han, Si-Hyun Bae, Hyun-Ki Yoon, Rheun-Chuan Lee, Chien-Fu Hung, Cheng-Yuan Peng, Po-Chin Liang, Adam Bartlett, Kenneth Y.Y. Kok, Choon-Hua Thng, Albert Su-Chong Low, Anthony S.W. Goh, Kiang Hiong Tay, Richard H.G. Lo, Brian K.P. Goh, David C.E. Ng, Ganesh Lekurwale, Wei Ming Liew, Vai Gebski, Kenneth S.W. Mak, and Khee Chee Soo; on behalf of Asia-Pacific Hepatocellular Carcinoma Trials Group



- Investigator-initiated, multicenter, randomized phase III study in 11 Asia-Pacific countries.
- Compared selective internal radiation therapy (SIRT) vs sorafenib in locally advanced HCC.
- Enrolled 360 patients, demonstrating feasibility of large IIT in the region.

Chow PKH, et al. J Clin Oncol 2018;36:1913-1921.

Future Directions

- Strengthen international collaborations among Asia-Pacific research institutions.
- Expand training and mentorship programs to develop the next generation of clinical investigators.
- Advocate for policy reforms that facilitate and fund IITs across diverse healthcare systems.

Translational Research of New Drug Development for HCC: Scientist's View

Alfred Cheng *(Hong Kong)*

Alfred Cheng is a Professor of the School of Biomedical Sciences and Assistant Dean in Research of the Faculty of Medicine at The Chinese University of Hong Kong (CUHK). He completed his Ph.D. under the mentorship of Prof. Joseph Sung at CUHK and his postdoctoral training in the laboratory of Prof. Tim Huang at The Ohio State University. His research aims at advancing the basic understanding and precision immunotherapy of hepatocellular carcinoma. His multi-disciplinary collaborative team has employed the cutting-edge single-cell multi-omics and AI innovation to understand tumor adaptation to immune-checkpoint blockade and identify the cellular and molecular mechanisms of immunotherapeutic resistance. He is the recipient of the Most Promising Young Investigator Award by the HK Government (2014) and CUHK (2015, 2019), the 10th HMRF Anniversary Award in Breakthrough Research by the Food and Health Bureau of HK Government (2021), and the Top 10 Innovation and Technology News, Hong Kong 2023.

Research Interests

Cancer epigenetics, HCC immunology and immunotherapy

Representative Publications

1. Zhou J, Liu M, Sun H, Feng Y, Xu L, Chan AWH, Tong JH, Wong J, Chong CCN, Lai PBS, Wang HK, Tsang SW, Goodwin T, Liu R, Huang L, Chen Z, Sung JJ, Chow KL, To KF, Cheng AS*. Hepatoma-intrinsic CCRK inhibition diminishes myeloid-derived suppressor cell immunosuppression and enhances immune-checkpoint blockade efficacy. Gut. 2018;67(5):931-944. https://gut.bmj.com/content/67/5/931.long [IF: 23.0] [citation = 206]
2. Liu M, Zhou J, Liu X, Feng Y, Yang W, Wu F, Cheung OK, Sun H, Zeng X, Tang W, Mok MT, Wong J, Yeung PC, Lai PB, Chen Z, Jin H, Chen J, Chan SL, Chan AW, To KF, Sung JJ, Chen M, Cheng AS*. Targeting monocyte-intrinsic enhancer reprogramming improves immunotherapy efficacy in hepatocellular carcinoma. Gut. 2020;69(2):365-379. https://gut.bmj.com/content/69/2/365.long [IF: 23.0] [citation = 169]
3. Yang W, Feng Y, Zhou J, Cheung OK, Cao JQ, Wang J, Tang WS, Tu YL, Xu LL, Wu F, Tan Z, Sun H, Tian Y, Wong J, Lai PB, Chan SL, Chan AW, Tan P, Chen Z, Sung JJ, Yip KYL, To KF, Cheng AS*. A selective HDAC8 inhibitor potentiates antitumor immunity and efficacy of immune checkpoint blockade in hepatocellular carcinoma. Science Translational Medicine. 2021;13(588):eaaz6804. https://www.science.org/doi/10.1126/scitranslmed.aaz6804 [IF: 15.8] [citation = 116]
4. Xiong Z, Chan SL, Zhou J, Vong JSL, Kwong TT, Zeng X, Wu H, Cao J, Tu Y, Feng Y, Yang W, Wong PP,

Si-Tou WW, Liu X, Wang J, Tang W, Liang Z, Lu J, Li KM, Low JT, Chan MW, Leung HHW, Chan AWH, To KF, Yip KY, Lo YMD, Sung JJ*, Cheng AS*. Targeting PPAR-gamma counteracts tumour adaptation to immune-checkpoint blockade in hepatocellular carcinoma. Gut 2023 Sep;72(9):1758-1773. https://gut.bmj.com/content/72/9/1758 [IF: 23.0] [citation = 62]

5. Tu Y, Wu H, Zhong C, Liu Y, Xiong Z, Chen S, Wang J, Wong PP, Yang W, Liang Z, Lu J, Chen S, Zhang L, Feng Y, Si-Tou WW, Yin B, Lin Y, Liang J, Liang L, Vong JSL, Ren W, Kwong TT, Leung H, To KF, Ma S, Tong M, Sun H, Xia Q, Zhou J, Kerr D, La Thangue N, Sung JJY, Chan SL*, Cheng AS*. Pharmacological activation of STAT1-GSDME pyroptotic circuitry reinforces epigenetic immunotherapy for hepatocellular carcinoma. Gut 2025 Mar 6;74(4):613-627. https://gut.bmj.com/content/74/4/613 [IF: 23.0] [citation = 9]

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Faculty of Medicine
The Chinese University of Hong Kong

Transforming our Passion into Perfection

Translational Research of New Drug Development for HCC: Scientist's View

Alfred Cheng PhD
Professor and Assistant Dean (Research)
School of Biomedical Sciences
The Chinese University of Hong Kong

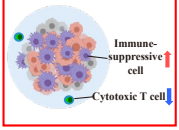
SCHOOL OF BIOMEDICAL SCIENCES CUHK

APPLE ACADEMY 2025

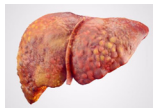
Friday, July 11, 2025
Kobe Portopia Hotel, Kobe, Japan

Challenges of ICB therapy in HCC

Immune excluded tumor

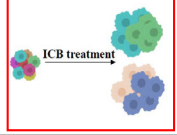


Liver immune microenvironment



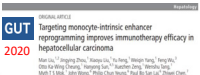
Inter-patient heterogeneity

Therapy-induced adaptation




GUT 2018
Hepatoma-intrinsic CCRK inhibition diminishes myeloid-derived suppressor cell immunosuppression and enhances immune-checkpoint blockade efficacy


2018
An inflammatory-CCRK circuitry drives mTORC1-dependent metabolic and immunosuppressive reprogramming in obesity-associated hepatocellular carcinoma


GUT 2020
Targeting monocyte-intrinsic enhancer reprogramming improves immunotherapy efficacy in hepatocellular carcinoma


Molecular Therapy 2023
Fibrotic immune microenvironment remodeling mediates superior anti-tumor efficacy of a nano-PD-L1 trap in hepatocellular carcinoma


CANCER 2021
A selective HDAC8 inhibitor potentiates antitumor immunity and efficacy of immune checkpoint blockade in hepatocellular carcinoma


2022
Aberrant cholesterol metabolic signaling impairs antitumor immunosurveillance through natural killer T cell dysfunction in obese liver


GUT 2023
Targeting PPAR-gamma counteracts tumour adaptation to immune-checkpoint blockade in hepatocellular carcinoma

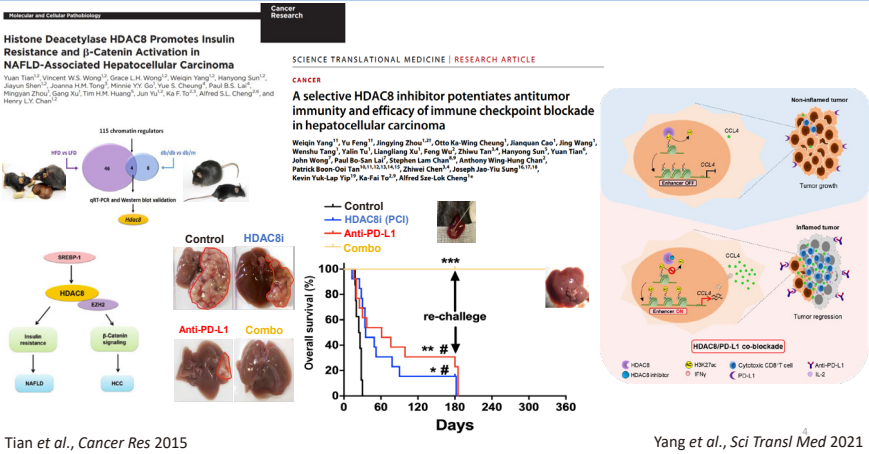

Molecular Therapy 2025
Overcoming Immunotherapy Resistance in Hepatocellular Carcinoma by Targeting Myeloid IL-6–CXCR2 Signaling

Precision Immunotherapy for HCC

Developing preclinical candidates that can target "tolerance" in the tumor microenvironment (TME)

1. Enhancing ICB through epigenetics
2. Myeloid-targeted ICB therapy

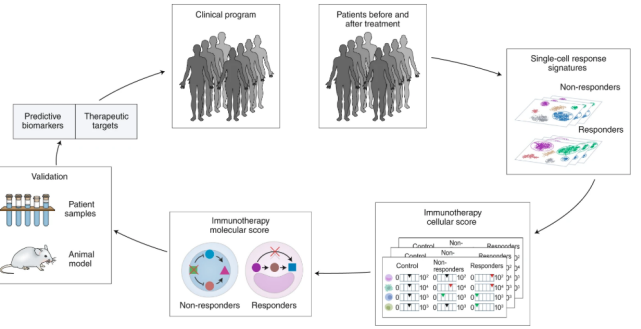
Identification of HDAC8 as new epigenetic immunotherapeutic target for HCC



Tian *et al.*, *Cancer Res* 2015

Yang *et al.*, *Sci Transl Med* 2021

Single-cell genomic approaches for developing the next generation immunotherapies



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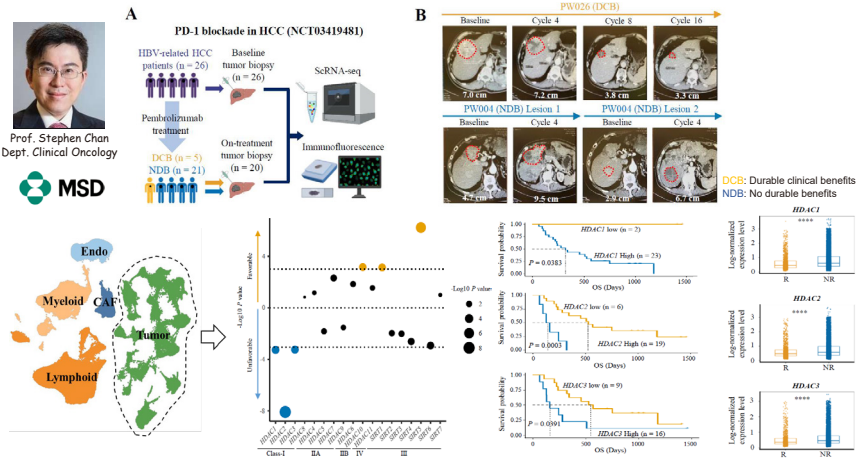
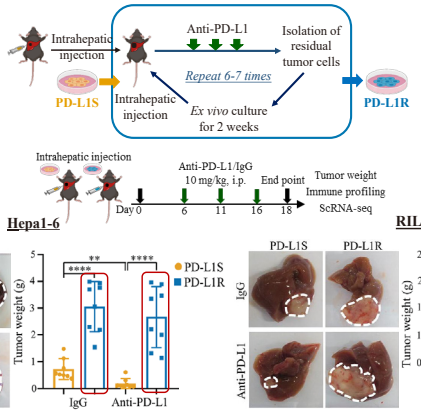
Yofe *et al.*, *Nat Med* 2020

scRNA-seq of tumor biopsies from a phase-II study of pembrolizumab



Establishment of ICB-resistant HCC mouse models

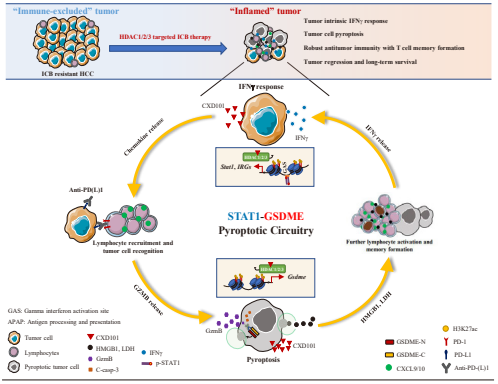
Zhewen Xiong



Hepa1-6: C57L-derived hepatoma cell lines, high immunogenecity
RIL-175: C57BL/6-derived hepatoma cell lines, low immunogenecity

Xiong, Chan, Zhou *et al*,[7] *Gut* 2023

Immuno-epigenetic activation of an antitumor pyroptotic circuitry



- HCC patients with HDAC1/2/3^{high} tumors exhibited lower levels of IFNγ and T-cell exclusion gene signatures and poorer survival upon ICB therapy.
- A selective class-I HDAC inhibitor CXD101 re-sensitized HDAC1/2/3^{high} tumors to ICB by concomitant restoration of multiple rate limiting steps of the cancer-immunity cycle.
- CXD101 synergized with ICB to stimulate STAT1-driven antitumor immunity through enhanced chromatin accessibility and H3K27 hyperacetylation of IFNγ-responsive genes.
- CXD10I-ICB combination therapy induced tumor cell pyroptosis by cooperative functions of CXD101-induced GSDME expression and IFNγ/STAT1-mediated cleavage by cytotoxic lymphocytes.

Tu and Wu *et al.*, *Gut* 2025

Clinical trial of epigenetic immunotherapy for HCC patients

GUT 2025

GI cancer

Original research

Pharmacological activation of STAT1-GSDME pyroptotic circuitry reinforces epigenetic immunotherapy for hepatocellular carcinoma

Commentary

Combining epigenetic modulation: the next step for HCC immunotherapy?

Chi Ma [1], Bertram Bengsch [2]

U.S. National Library of Medicine
ClinicalTrials.gov
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Non-responders to mono-ICB therapy

Experimental arm
CXD101 + Anti-PD-1
(n=20 patients)

Drug treatment
Baseline
6-week on-treatment
Tumor biopsy
PBMC

Control arm
TKI (Sorafenib or Lenvatinib)
(n=20 patients)

Endpoint
Progress-free survival
Identification of biomarkers
scMulti-omics
Single-cell spatial omics

nature reviews clinical oncology

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News & Views | Published: 30 June 2025

Liver cancer

Role of novel immunotherapy combinations in the management of advanced-stage hepatocellular carcinoma

Josep M. Llovet

Nature Reviews Clinical Oncology (2025) | article

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Immune-checkpoint inhibitors have revolutionized the management of hepatocellular carcinoma. Currently, anti-PD-(L)-1 antibodies combined with either bevacizumab or anti-CTLA4 antibodies are the standard of care for advanced-stage tumours. Now, two phase III studies (CheckMate 9DW and APOLLO) have reported positive survival results in the first-line setting, although with distinct implications for clinical practice.

In conclusion, CheckMate 9DW and APOLLO might be the last phase III trials comparing combination therapies with single-TKI regimens. Whereas the former trial provides a new armamentarium for the management of patients with advanced-stage HCC, the latter will need international validation before entering clinical practice in Europe and North America. The near future is expected to be dominated by triplet therapies, biomarker-driven studies and novel therapeutic approaches.