APPLE ACADEMY 2023

Thursday, July 6, 2023

Grand InterContinental Seoul Parnas, Seoul, Korea

The Asia-Pacific Primary Liver Cancer Expert Association

APPLE

Response that matters with the power of LENVIMA®

in first-line uHCC therapy

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Maximum change in tumour size by mRECIST[1]*

For Healthcare Professionals Only
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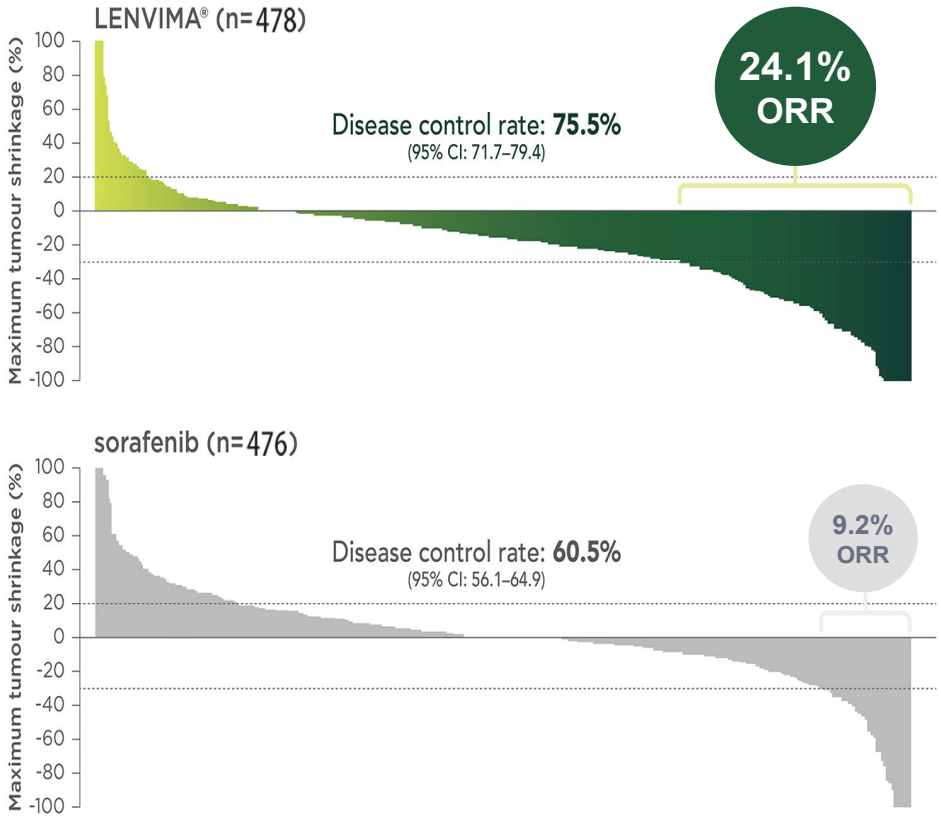


~1 in 4 patients achieved **>30% tumour shrinkage** with **LENVIMA®** compared to ~1 in 10 with sorafenib

[ORR: LENVIMA 24.1%(95% CI 20.2-27.9) vs Sorafenib 9.2%(6.6-11.8) OR 3.13(95% CI 2.15-4.56), p<0.0001, investigators' review according to mRECIST]

【Study Design】This was an open-lavel, phase 3, multicenter, non-inferiority trial that recruited patients with uHCC. Patients were randomly assigned (1:1) via an interactive voice-web response system-with region; macroscopic portal vein invasion, extrahepatic spread, or both; Eastern Cooperative Oncology Group performance status; and body weight as stratification factors-to receive oral Lenvatinib (12mg/day for bodyweight≥60kg or 8mg/day for bodyweight <60kg)or Sorafenib 400mg twice-daily in 28-days cycles. The Primary endpoint was overall survival, measured from the date of randomization until the date of death from any cause. The efficacy analysis followed the intention-to-treat principle, and only patients who received treatment were include in the safety analysis. Lenvatinib(median OS 13.6month,95%CI12.1-14.9)was non-inferior to Sorafenib (median OS 12.3month, 95%CI 10.4-13.9) in overall survival in untreated advanced HCC(HR 0.92, 95%CI 0.79-1.06)1

Change in tumour size truncated at 100%. Disease control rate and tumour shrinkage are % of total study groups, including unknown/not evaluable patients not included on these graphs.
*By investigator assessment.
CI: confi dence interval,**mRECIST**: modifi ed Response Evaluation Criteria In Solid Tumours, **ORR:** objective response rate.
uHCC : unresectable hepatocellular carcinoma
Reference 1 : Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018 Mar 24;391(10126):1163-1173.

Eisai

AR-LV-SN-22A-02 / KR-LV-MK-22A-03

LENVIMA® (lenvatinib) capsules

RESPONSE THAT MATTERS

APPLE ACADEMY 2023

Thursday, July 6, 2023 [ROOM C (Grand Ballroom 3)]

SCIENTIFIC PROGRAM

08:50-09:00	Opening Remarks — **Pierce Chow** *(National Cancer Centre Singapore, Singapore)*	
09:00-10:35	**Session 1: Changes in the Landscape of HCC** **Chairs: Kwang-Hyub Han** *(CHA Univ., Seoul)*, **Kengo Yoshimitsu** *(Fukuoka Univ., Fukuoka)*	
09:00-09:20	Changing Etiology and Epidemiology of HCC: Asia and Worldwide **Do Young Kim** *(Yonsei Univ., Seoul)*	6
09:20-09:40	New Concepts in the Imaging Diagnosis of HCC: Can Artificial Intelligence Help? **Chih-Horng Wu** *(National Taiwan Univ., Taipei)*	20
09:40-10:00	Molecular Heterogeneity in HCC and the Challenge of Identifying Predictive Biomarkers **Irene Oi-Lin Ng** *(The Univ. of Hong Kong, Hong Kong)*	34
10:00-10:20	Adaptation of Practice Guidelines: When East Meets West **Li-Tzong Chen** *(Kaohsiung Medical Univ., Kaohsiung)*	42
10:20-10:35	Q&A	
10:35-10:50	Coffee Break	
10:50-12:25	**Session 2: Translational and Basic Research That May Impact on the Clinical Management of HCC** **Chairs: Pierce Chow** *(National Cancer Centre Singapore, Singapore)*, **Chiun Hsu** *(National Taiwan Univ., Taipei)*	
10:50-11:10	Biomarker-Based Precision Pharmacotherapy in HCC **Takahiro Kodama** *(Osaka Univ., Osaka)*	44
11:10-11:30	Translational Research: The Impact from Research in Epigenomics **Ah-Jung Jeon** *(Mirxes, Singapore)*	52
11:30-11:50	Translational Research: The Impact from Research in Spatial Transcriptomics **Ankur Sharma** *(Harry Perkins Institute of Medical Research, Perth)*	58
11:50-12:10	The Promise of Immuno-Neoadjuvant Therapy in HCC **Han Chong Toh** *(National Cancer Centre Singapore, Singapore)*	74
12:10-12:25	Q&A	
12:25-13:30	Luncheon Symposium & Networking [Eisai]	

APPLE ACADEMY 2023

Thursday, July 6, 2023 [ROOM C (Grand Ballroom 3)]

SCIENTIFIC PROGRAM

13:30-15:05	**Session 3. Unmet Clinical Need in and Current Clinical Research Directions** **Chairs: Etsuro Hatano** *(Kyoto Univ., Kyoto)*, **Thomas Yau** *(The Univ. of Hong Kong, Hong Kong)*	
13:30-13:50	Early HCC and Treatment with Curative Intent - Has Adjuvant Therapy Opened a New Paradigm? **Linda Wong** *(Univ. of Hawaii, Honululu)*	*89*
13:50-14:10	Intermediate-Stage HCC: Re-Defining the Role of Liver-Directed Therapy **Hyo-Cheol Kim** *(Seoul National Univ., Seoul)*	*95*
14:10-14:30	Intermediate-Stage HCC: Expanding the Role of Systemic Therapy **Masafumi Ikeda** *(National Cancer Center Hospital East, Kashiwa)*	*100*
14:30- 14:50	Advanced HCC: Beyond IMbrave150 and HIMALAYA **Chih-Hung Hsu** *(National Taiwan Univ., Taipei)*	*108*
14:50-15:05	Q&A	
15:05-15:20	Coffee Break	
15:20-16:40	**Session 4. From APPLE Academy into the Future** **Chairs: Masatoshi Kudo** *(Kindai Univ., Osaka)*, **Jian Zhou** *(Fudan Univ., Shanghai)*	
15:20-15:45	Investigator-Initiated Trials for HCC in the Asia-Pacific Region **Pierce Chow** *(National Cancer Centre Singapore, Singapore)*	*119*
15:45-16:05	APPLE Association as a Platform for Future International Research Collaboration **Kwang-Hyub Han** *(CHA Univ., Seoul)*	*120*
16:05-16:25	Promoting the Next-Generation Liver Cancer Experts to the Global Arena **Ann-Lii Cheng** *(National Taiwan Univ., Taipei)*	*128*
16:25-16:40	Q&A	
16:40-16:45	Closing Remark — **Norihiro Kokudo** *(National Center for Global Health and Medicine, Tokyo)*	

APPLE ACADEMY 2023

Thursday, July 6, 2023 [ROOM C (Grand Ballroom 3)]

Session 1.

Changes in the Landscape of HCC

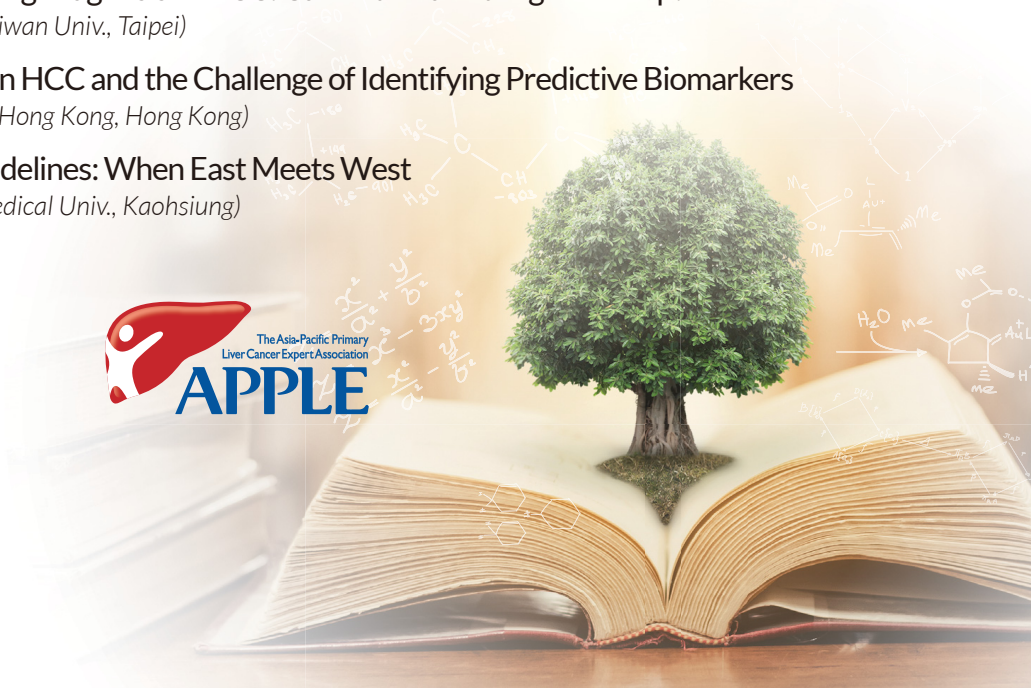
Chairs: **Kwang-Hyub Han** *(CHA Univ., Seoul)*
Kengo Yoshimitsu *(Fukuoka Univ., Fukuoka)*

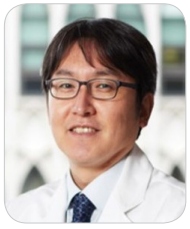
Changing Etiology and Epidemiology of HCC: Asia and Worldwide
Do Young Kim *(Yonsei Univ., Seoul)*

New Concepts in the Imaging Diagnosis of HCC: Can Artificial Intelligence Help?
Chih-Horng Wu *(National Taiwan Univ., Taipei)*

Molecular Heterogeneity in HCC and the Challenge of Identifying Predictive Biomarkers
Irene Oi-Lin Ng *(The Univ. of Hong Kong, Hong Kong)*

Adaptation of Practice Guidelines: When East Meets West
Li-Tzong Chen *(Kaohsiung Medical Univ., Kaohsiung)*





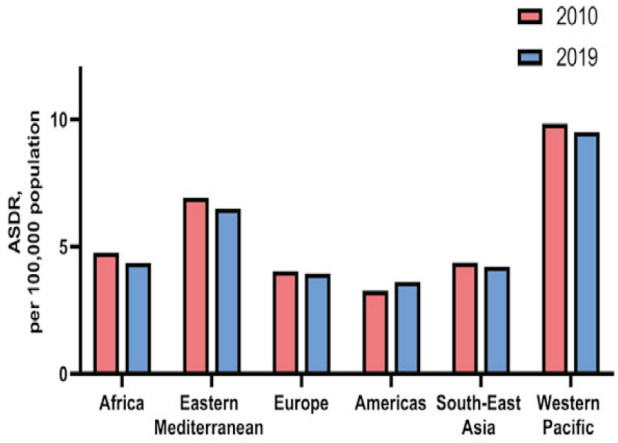
Changing Etiology and Epidemiology of HCC: Asia and Worldwide

Do Young Kim *(Yonsei Univ., Seoul)*

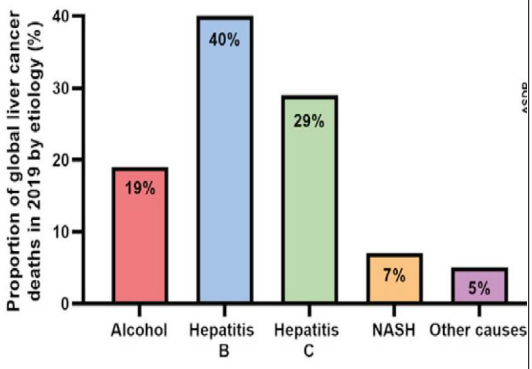
Burden of HCC in Asia and in the global

- Globally,
  - HCC remains the sixth most common cancer.
  - It is the third leading cause of cancer-related death worldwide, representing more than 8% of all cancer-related deaths.
- In Asia,
  - HCC is the fifth most common cancer.
  - It is the second leading cause of malignant death in Asia.
  - HCC cases in Asia account for 72.5% of the world's cases in 2020.

Changing global epidemiology of live cancer: From 2010 to 2019



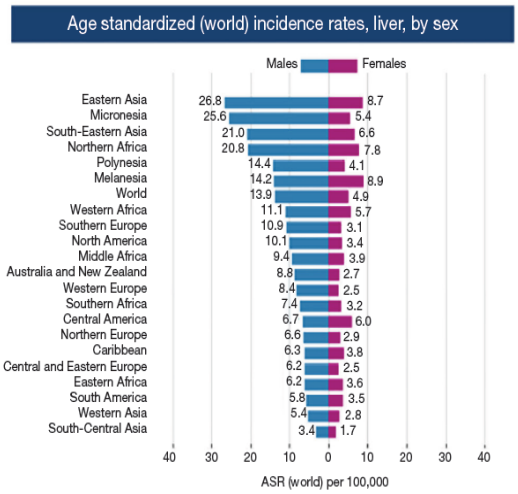
Frequency of liver cancer deaths in 2010 versus 2019, global and by WHO region

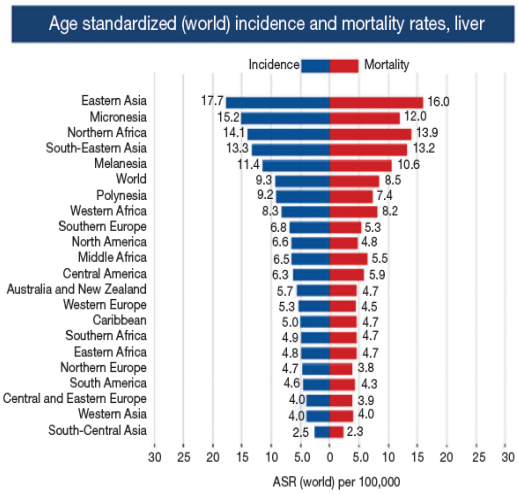


Proportion of deaths in 2019 by etiology

Huang D, et al. Cell Metabolism 2022.

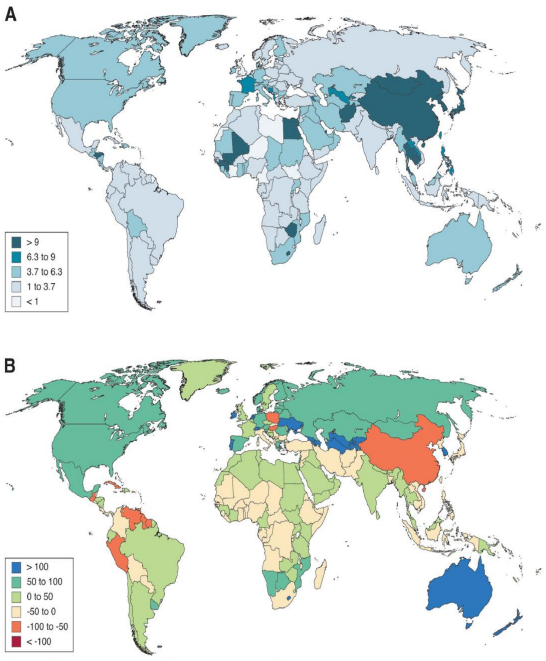
A geographic variation of HCC incidence and mortality





Data source: GLOBOCAN 2018.

Regional variations of HCC between 1990 and 2019



Yang J, et al. Cancer Med 2022.

Shifting of overall trends in HCC incidence over time

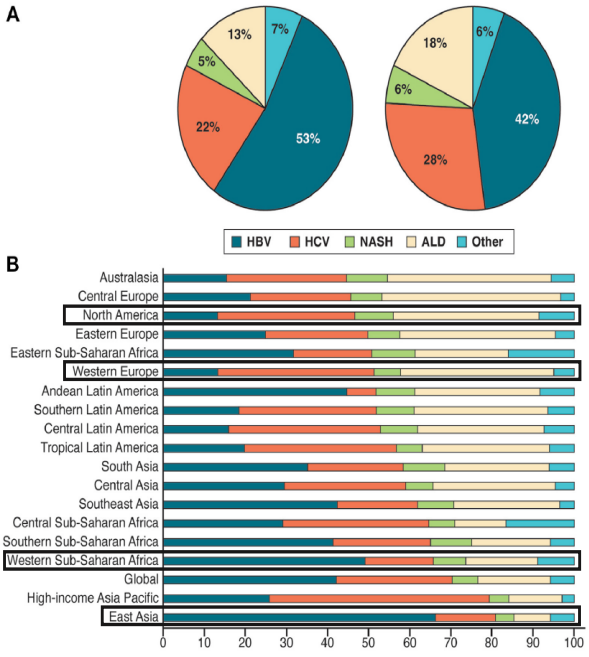
- Worldwide vaccination program against hepatitis B virus (HBV)
- Active antiviral treatment using nucleos(t)ide analogue
- Introduction of direct-acting antiviral agent (DAA) for chronic hepatitis C
- Global effort to eliminate viral hepatitis
- Rates of alcohol use and obesity, influencing the prevalence of alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD)

HCC incidence is rising worldwide

- Despite a slowly decreasing trend in global age-standardized incidence rates (ASIRs) of HCC since the late 1990, the total number of HCC cases has been increasing owing to aging and population growth.
- In 2019, there were approximately 747,000 cases of HCC worldwide, representing a 70% rise since 1990.
- While ASIRs have been minimally decreasing globally since 2000, ASIRs have been increasing for high sociodemographic index countries since 1990.
  - The incidence rates of HCC in the USA have increased 2-folds to 3-folds over the past three decades due to high HCV prevalence of HCV infection and NAFLD.

Yang JD. Nature Reviews Gastroenterol & Hepatol 2019.

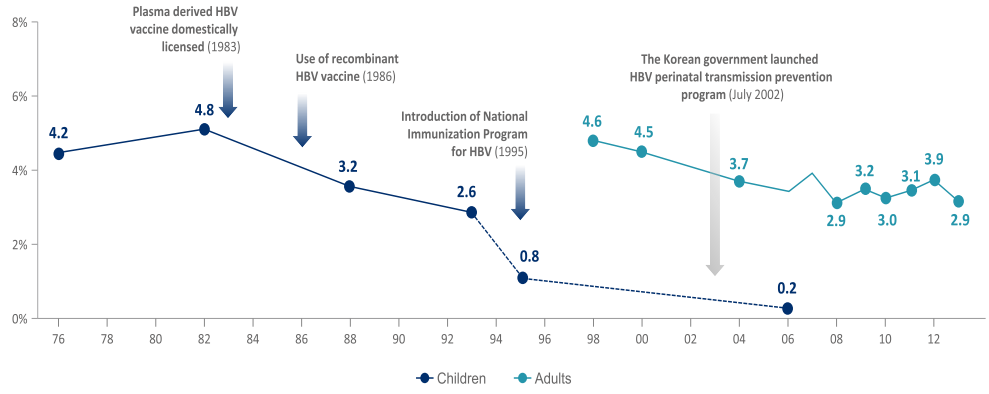
Temporal and geographical differences in HCC etiologies



Toh MR, et al. Gastroenterology 2023.

Change of HBsAg seroprevalence in Korea

Percentage of HBsAg-positive adults adults and children in Korea before and after the implementation of a national HBV vaccination programme*

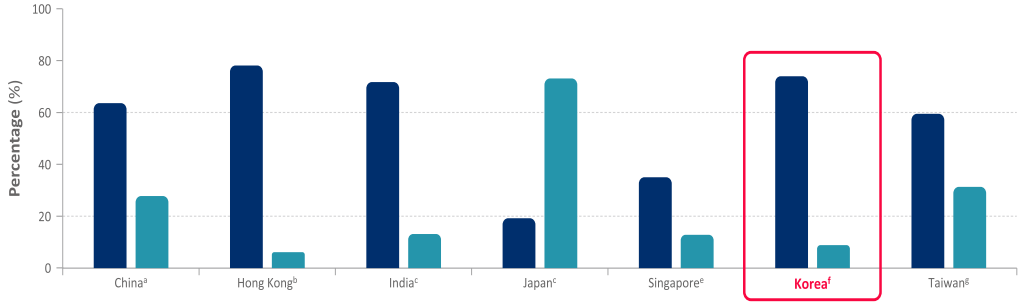


Decrease of HBsAg positive rate due to introduction of HBV vaccination

HBV is still the most common etiology of HCC

- In 1990, HBV caused more than half of all cases of HCC globally.
- In 2019, that number has decreased to 41%
- Nevertheless, it still remains the most common cause of HCC worldwide.

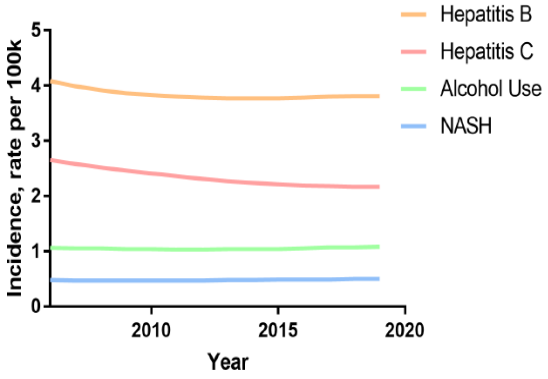
Proportion of HBV- and HCV-related HCC in different Asia-Pacific countries



- **HBV is the main cause of HCC in Asia-Pacific region.[1]**
- **In Korea, HBV infection is the cause of HCC in 74.2%, and HCV infection is in 8.6%.[1]**

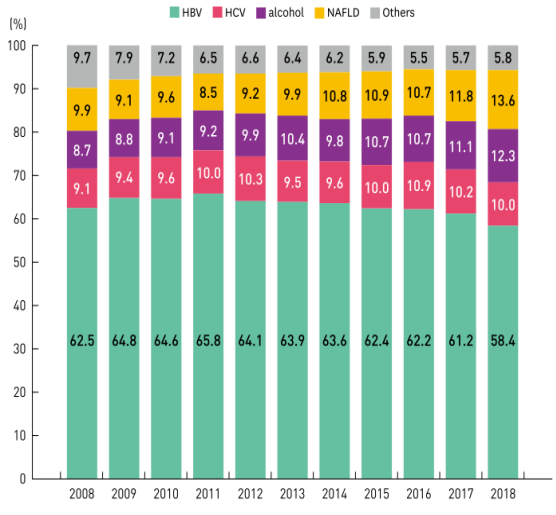
Changing incidence of HCC by etiology in Asia

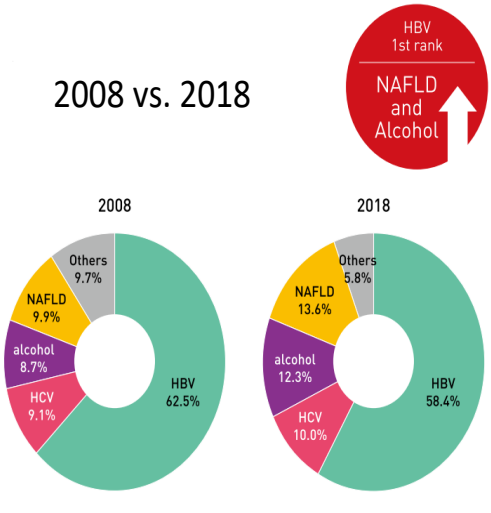
- The incidence of HBV-related HCC declines due to vaccination and antiviral therapy.
- The incidence of HCV-related HCC also declines due to prevention of HCV horizontal transmission and treatment of chronic hepatitis.



Zhang C, et al. Liver Int 2022.

Changing etiology of HCC in Korea





2021 HCC factsheet in Korea

Geographical variation of HCC incidence and mortality in Asia

	Incidence (ASR, per 100000)			Mortality (ASR, per 100000)		
Population	2018	2020	Change (%)	2018	2020	Change (%)
Mongolia	93.7	85.6	−8.64	75.4	80.6	6.90
Lao People's Democratic Republic	22.4	24.4	8.93	22.4	22.9	2.23
Cambodia	21.8	24.3	11.47	21.9	22.9	4.57
Vietnam	23.2	23	−0.86	23.2	21.9	−5.60
Thailand	21	22.6	7.62	20.9	21.9	4.78
China	18.3	18.2	−0.55	17.1	17.2	0.58
Democratic Republic of Korea	16.5	15.5	−6.06	15	14.4	−4.00
Republic of Korea	17.3	14.3	−17.34	11.8	9.9	−16.10
Singapore	12.3	12.2	−0.81	11.4	11.4	0.00
Philippines	11.5	11.4	−0.87	11.4	10.8	−5.26
Brunei Darussalam	9.9	10.5	6.06	8.3	8.8	6.02
Japan	7.6	10.4	36.84	5.4	4.8	−11.11

Zhang C, et al. Liver Int 2022.

Global burden of alcohol-associated HCC

- In 2019, alcohol was associated with an estimated 19% of death from liver cancer globally.
- The age-standardized death rate (ASDR) for alcohol-associated cirrhosis declined between 2012 and 2017, whereas the ASDR for alcohol-associated liver cancer increased.
- Given the projected increase in global alcohol exposure, the burden of alcohol-associated liver disease (ALD), cirrhosis and HCC might increase in parallel.

Huang D, et al. Nature Reviews Gastroenterol & Hepatol 2023.

Regional variation of deaths from alcohol-associated HCC

Location	Number of deaths (95% UI)	Deaths* in 2019 associated with alcohol (%)
Alcohol-associated liver cancer		
Global	90,741 (73,349–109,402)	19
Africa	4,237 (3,193–5,456)	20
Eastern Mediterranean	2,814 (1,939–4,087)	10
Europe	22,215 (18,146–26,413)	35
Americas	15,019 (12,424–17,533)	33
Southeast Asia	18,581 (14,371–23,435)	27
Western Pacific	27,623 (21,296–34,686)	11

Huang D, et al. Nature Reviews Gastroenterol & Hepatol 2023.

NASH is the fastest growing cause of age-adjusted HCC death

Table 1. Incident cases and age-standardized incidence rates of liver cancer in 2010 and 2019 and the temporal trend of age-standardized incident rates from 2010 to 2019

	2010		2019		
	No. incident cases (95% UI)	ASIR per 100,000 (95% UI)	No. incident cases (95% UI)	ASIR per 100,000 (95% UI)	Annual percentage change of ASIR (95% CI)
Global	420,196 (398,639–440,763)	6.50 (6.15–6.81)	534,364 (486,550–588,639)	6.51 (5.95–7.16)	0.03 (−0.01 to 0.05)
Sex					
Male	292,049 (276,249–310,447)	9.54 (9.03–10.13)	376,483 (421,982–335,003)	9.71 (8.69–10.84)	0.21 (0.20–0.23)
Female	128,147 (119,003–134,959)	3.76 (3.49–3.96)	157,881 (140,436–176,052)	3.63 (3.23–4.05)	−0.39 (−0.41 to −0.37)
Socio-demographic index					
Low SDI	16,006 (14,421–17,603)	3.90 (3.53–4.28)	19,279 (16,951–21,648)	3.69 (3.27–4.11)	−0.62 (−0.64 to −0.59)
Low-middle SDI	41,378 (38,129–44,607)	3.89 (3.55–4.20)	55,345 (50,136–61,558)	4.05 (3.67–4.51)	0.49 (0.42–0.55)
Middle SDI	152,103 (141,917–165,051)	7.85 (7.33–8.49)	185,567 (162,261–210,710)	8.28 (7.24–9.47)	0.68 (0.52–0.84)
High-middle SDI	89,077 (83,223–95,370)	5.46 (5.10–5.84)	106,792 (94,151–120,908)	5.34 (4.70–6.05)	−0.25 (−0.40 to −0.10)
High SDI	121,477 (112,975–126,370)	8.01 (7.54–8.29)	140,145 (125,500–154,013)	7.61 (6.88–8.36)	−0.58 (−0.74 to −0.42)
Etiology					
Alcohol	74,377 (61,771–88,219)	1.16 (0.96–1.37)	98,463 (79,034–120,127)	1.19 (0.96–1.45)	0.34 (0.33–0.36)
Hepatitis B	172,897 (154,745–192,114)	2.57 (2.30–2.86)	218,855 (186,488–254,887)	2.62 (2.24–3.05)	0.23 (0.17–0.29)
Hepatitis C	123,598 (108,700–128,172)	2.00 (1.75–2.24)	152,225 (131,581–174,627)	1.90 (1.64–2.17)	−0.60 (−0.67 to −0.54)
NASH	26,220 (21,628–31,705)	0.41 (0.34–0.50)	36,339 (29,494–44,855)	0.45 (0.37–0.55)	0.88 (0.79–0.98)
Other causes	23,104 (19,666–26,849)	0.35 (0.30–0.41)	28,482 (23,574–34,082)	0.35 (0.29–0.42)	0.12 (0.01–0.24)

ASIR, age-standardized incidence rate; SDI, socio-demographic index; NASH, nonalcoholic steatohepatitis.

Huang D, et al. Cell Metabolism 2022.

Changing incidence of liver cancer by each etiology in Asia

Year	Liver cancer owing to hepatitis B	Liver cancer owing to hepatitis C	Liver cancer owing to alcohol use	Liver cancer owing to NASH
2006	4.08	2.65	1.06	0.48
2007	3.99	2.58	1.05	0.47
2008	3.92	2.52	1.05	0.47
2009	3.86	2.46	1.04	0.47
2010	3.83	2.41	1.04	0.47
2011	3.8	2.36	1.03	0.47
2012	3.78	2.31	1.03	0.47
2013	3.77	2.27	1.04	0.48
2014	3.77	2.24	1.04	0.48
2015	3.77	2.21	1.04	0.49
2016	3.78	2.19	1.05	0.49
2017	3.8	2.18	1.07	0.49
2018	3.81	2.17	1.07	0.5
2019	3.81	2.17	1.08	0.5
	↓	↓	↑	↔

Zhang C, et al. Liver Int 2022.

Epidemiologic characteristics of NAFLD-associated HCC

- NAFLD is the most common liver disease in the world.
  - Its global prevalence in 2016 was approximately 25%, with a projected 15% - 56% rise by 203.
- Compared with the other etiologies, people with NASH-related HCC
  - Are older (mean difference, 5.6 years).
  - Have higher body mass index (mean difference, 3 kg/m^2).
  - Have higher rates of type 2 diabetes mellitus (odds ratio, 4.3), hypertension, hyperlipidemia, and cardiovascular disease.
- Noncirrhotic HCC is more common in NASH than the other etiologies.

Toh MR, et al. Gastroenterology 2023.

ORIGINAL ARTICLE

Clinical and survival outcomes after hepatectomy in patients with non-alcoholic fatty liver and hepatitis B-related hepatocellular carcinoma

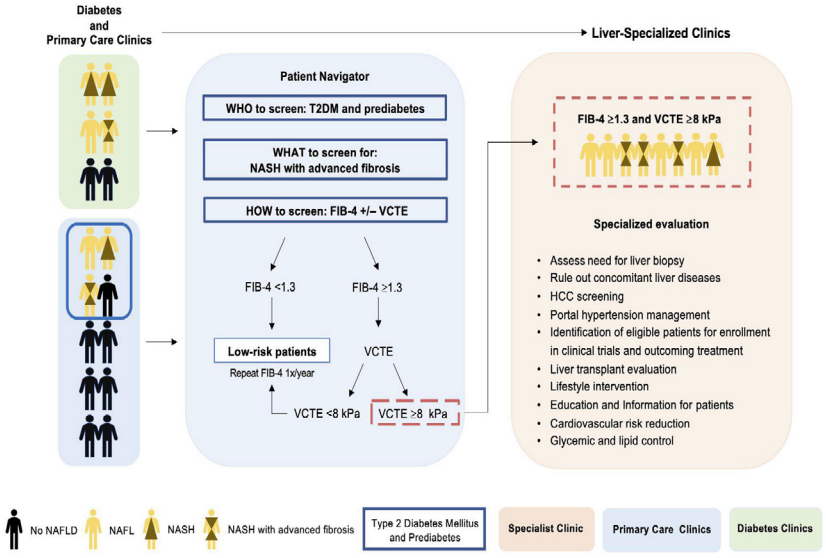
Yoon Bin Jung[1], Jeong Eun Yoo[2], Dai Hoon Han[1], Kyung Sik Kim[1], Jin Sub Choi[1], Do Young Kim[3], Young Nyun Park[2*] & Gi Hong Choi[1*]

Table 2 Demographics and clinical characteristics of study populations after matched analysis

Variables	Entire cohort			Matched cohort		
	HBV-HCC (n = 200)	NAFLD-HCC (n = 32)	p	HBV-HCC (n = 32)	NAFLD-HCC (n = 32)	p
Demographics						
Age (years)	54 ± 10	61 ± 11	<0.001	61 ± 8	61 ± 11	0.846
≥60 years (n, %)	66 (33)	19 (60)	0.004	21 (66)	19 (60)	0.606
Sex (Male, n, %)	146 (73)	25 (78)	0.339	26 (81)	25 (78)	0.756
BMI (kg/m^2)	23.2 ± 2.7	26.6 ± 7.1	<0.012	24.2 ± 2.4	26.6 ± 7.1	0.117
Overweight (n, %)	47 (24)	16 (50)	0.002	10 (31)	16 (50)	0.127
Obese (n)	2	1	0.359[a]	0	1	1.000[a]
Alcohol (g/week) (Median, IQR)	34 (0–52)	27 (0–52)	0.770	35 (0–61)	27 (0–52)	0.505
Metabolic risk factors						
Metabolic SD (n, %)	24 (11)	19 (60)	<0.001	9 (28)	19 (60)	0.012
AC (cm)	83 ± 8	90 ± 9	<0.001	87 ± 8	90 ± 9	0.261
Triglyceride (mg/dL)	81 ± 35	136 ± 84	0.004	79 ± 31	136 ± 84	0.003
HDL (mg/dL)	52 ± 16	44 ± 13	0.063	50 ± 14	44 ± 13	0.156
Glucose (mg/dL)	125 ± 30	152 ± 53	0.009	145 ± 38	152 ± 53	0.557
Hypertension (n, %)	46 (23)	20 (63)	<0.001	15 (47)	20 (63)	0.209
Diabetes (n, %)	21 (11)	15 (47)	<0.001	11 (34)	15 (47)	0.121
Cirrhosis (n, %)	110 (55)	5 (16)	<0.001	9 (28)	5 (16)	0.226

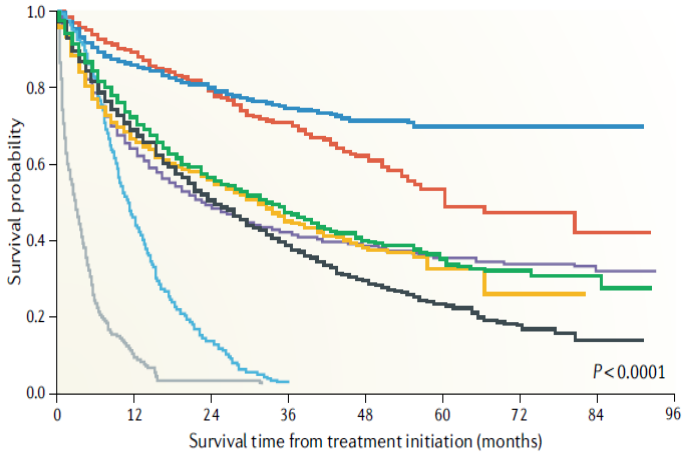
Jung YB, et al. HBP 2021.

American and European Diabetes Association recommend screening for NAFLD in patients with type 2 diabetes



Barbosa JV, et al. Hepatol Commun 2021.

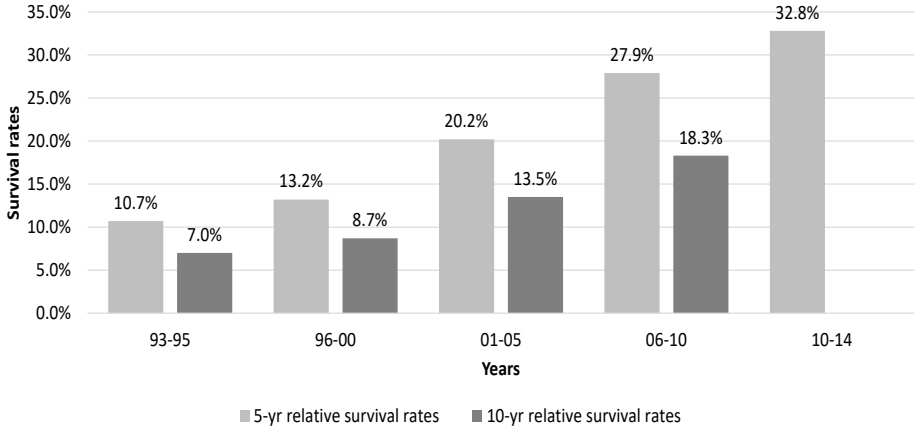
Global variation in the overall survival of patients with HCC



Countries	Median survival (months)
Taiwan	Not reached
Japan	60
North America	33
South Korea	31
Europe	24
China	23
Egypt	11
Other African countries	3

Park JW, et al. Liver Int 2015.

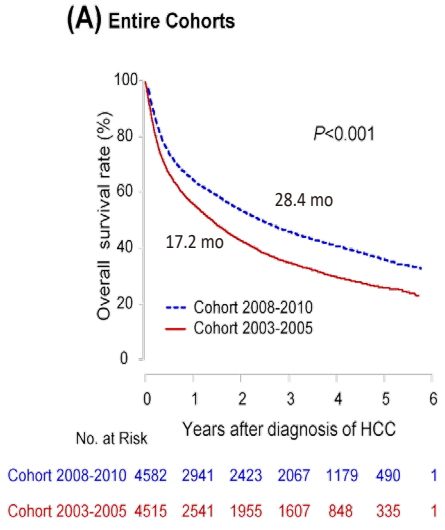
Trends in primary liver cancer survival in Korea



Korea Central Cancer Registry, Annual report of cancer statistics in Korea in 2014
Kim BH, Park JW. Clin Mol Hepatol 2018;24:1-9

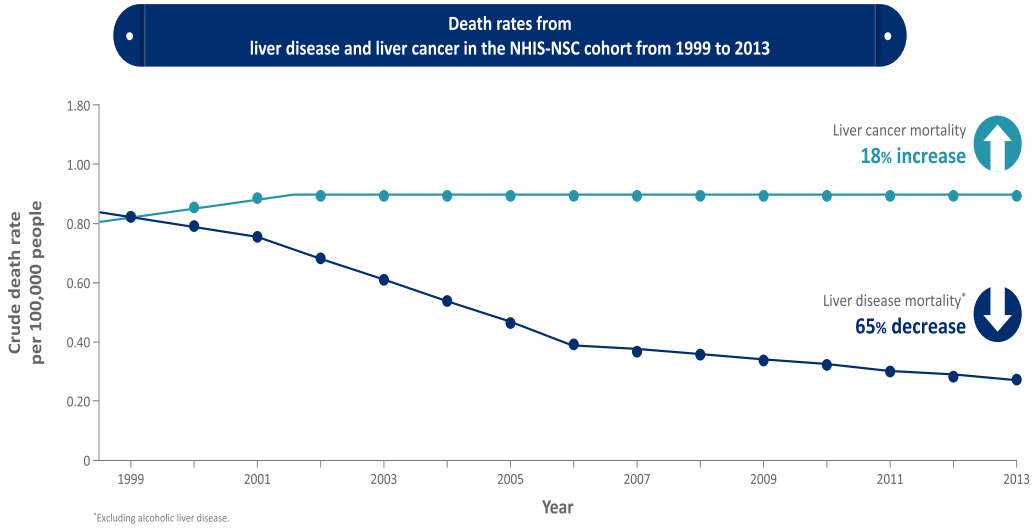
Improvement of HCC patient survival in Korea

- Based on the data from Korea Central Cancer Registry, a nationwide, prospective, population-based database for cancer incidence
- Randomly selected by a systematic sampling method



Kim BH et al. J Gastroenterol Hepatol 2018.

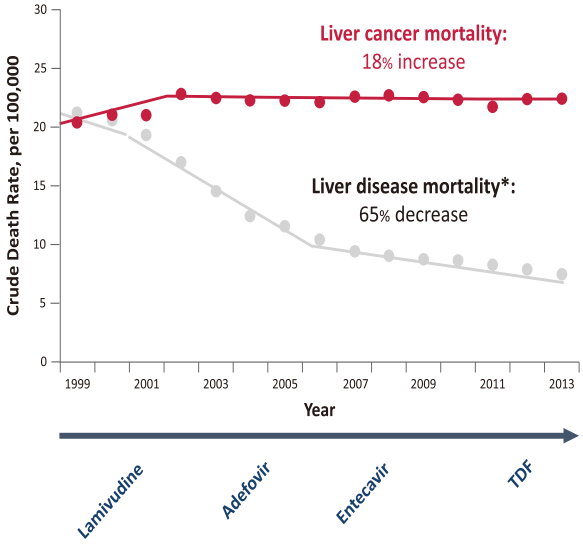
HCC mortality in Korea



Mortality data and population estimates were obtained from Korean Statistical Information Service (KOSIS)
NHIS-NSC, Korean National Health Service-National Sample Cohort (representative sample cohort from the entire Korean population since 2002).

1. Choi J, *et al. Hepatology* 2017;66;1454-63

Increasing death rate by liver cancer in Korea



HEPATOLOGY
HEPATOLOGY, VOL., 66, NO. 5, 2017

Increasing Burden of Liver Cancer Despite Extensive Use of Antiviral Agents in a Hepatitis B Virus-Endemic Population

Jonggi Choi,[1] Seungbong Han,[2] Namkug Kim,[3] and Young-Suk Lim[1]

Calendar Year	Liver Disease		Liver Cancer	
	Deaths	% of total death	Deaths	% of total death
1999	10,004	4.1%	9,682	3.9%
2001	9,243	3.8%	10,127	4.2%
2003	7,018	2.9%	10,916	4.5%
2005	5,633	2.3%	10,877	4.5%
2007	4,580	1.9%	11,144	4.6%
2009	4,311	1.7%	11,246	4.6%
2011	4,159	1.6%	10,946	4.3%
2013	3,773	1.4%	11,405	4.3%
Change between 1999 and 2013	−62.3%	−65.2%	17.8%	8.6%

Excluding alcoholic liver disease
Data sources: KOSIS
Choi J, Lim YS, *et al.* Hepatology 2017;66:1454-1463.

Changing epidemiology of HCC in Asia

Regions	Main Factor	Trends of HCC
Singapore	HBV	Male incidence decreased from 27.4 cases per 100,000 population in 1973–1977 to 17.2 cases in 2008–2012; Female incidence decreased from 6.9 cases per 100,000 population in 1973–1977 to 4.8.
Taiwan	HBV	The mortality rate decreased from 0·81 deaths per 100,000 to 0·05 per 100,000.
Hong Kong	HBV	The incidence has declined over the past 25 years.
Japan	HCV	The incidence and death have increased exponentially since 1970 and peaked in the early 2000s. After a plateau in 2002–2004, the number of deaths began to decline, reaching 28,889 in 2015.
India	HBV	The incidence has increased over the past two decades.
China	NAFLD	The incidence increased from 3.8% in 2001−2005 to 12.2% in 2006–2010.
Korea	NAFLD	The incidence increased from 3.8% in 2001−2005 to 12.2% in 2006–2010
Philippines	Aflatoxin	The incidence of HCC was reduced.
Qidong	Aflatoxin	A significant decrease in the incidence of HCC in men (ASR = 89.9 from 1983 to 1987, ASR = 60.9 from 2008 to 2012, −32.3%) and a slight decrease in women (ASR = 24.5 from 1983 to 1987, ASR = 21.5 from 2008 to 2012, −12.2%) were observed.
Asia-Pacific region	Alcohol	The increase in alcohol intake across the Asia-Pacific region between 2006 and 2016 May have contributed to an increase in age-standardized liver cancer rates.

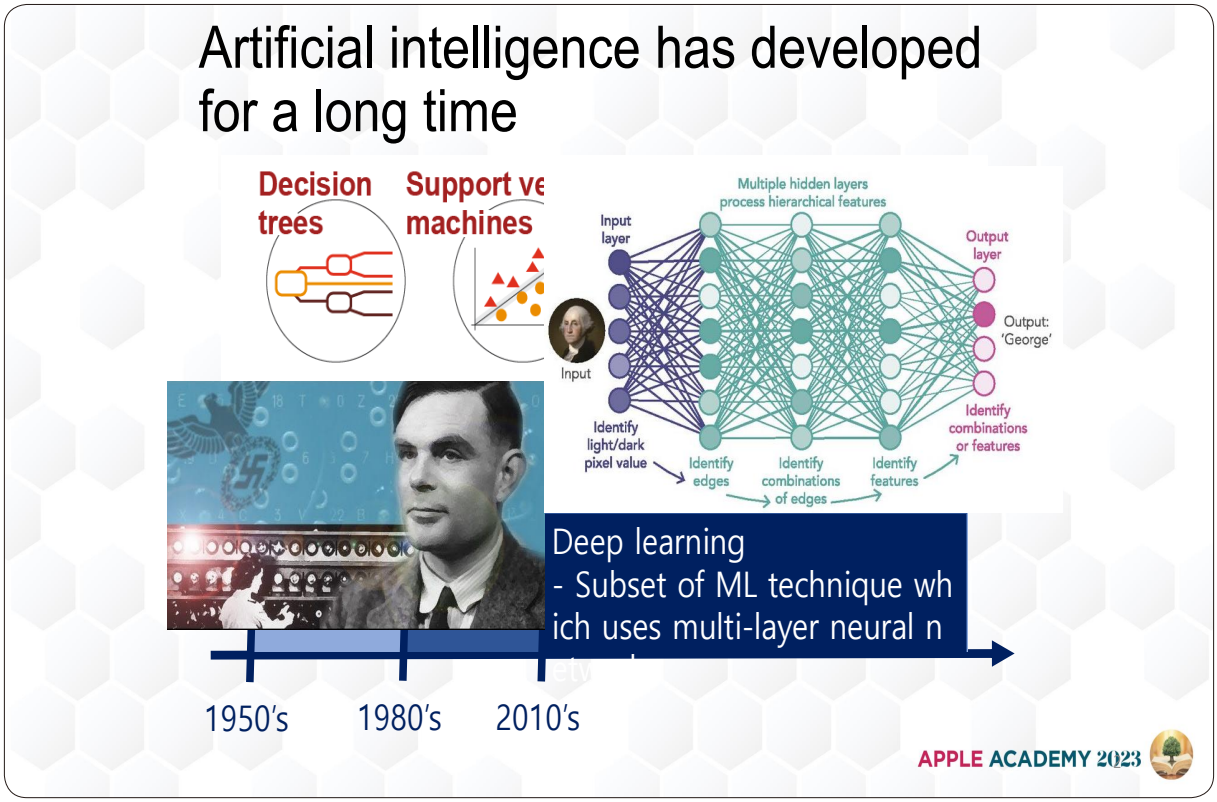
Liu Y et al. Cancers 2022.

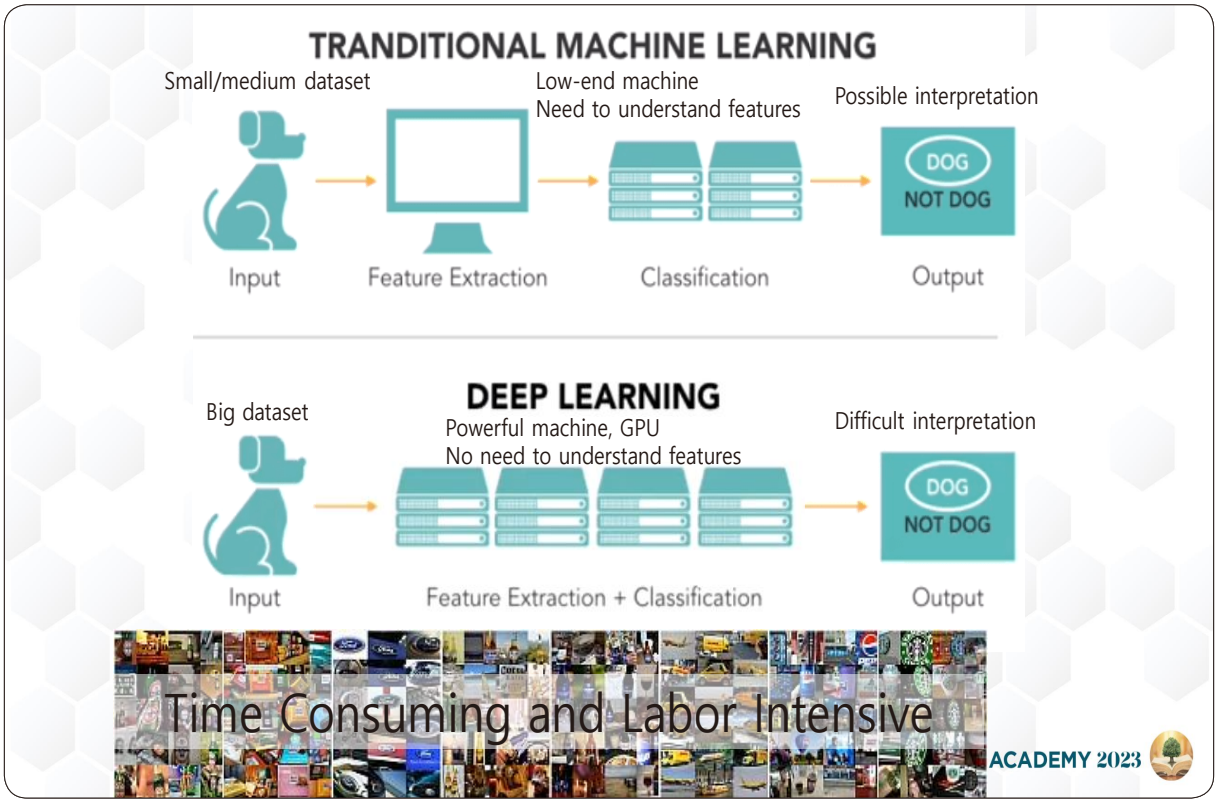
Summary

- Despite vaccination and treatment, HBV and HCV remain the most common etiologies in both Asia and the world.
- Alcohol and NAFLD are more common etiologies in non-Asian regions.
- HCC incidence is still rising worldwide due to increasing consumption of alcohol and prevalence of NAFLD in spite of decreasing prevalence of HBV and HCV infection.
- NASH is the fastest growing etiology of HCC in both Asia and World.
- The survival of Asian HCC patients is significantly prolonged in the past decades with the progress of surveillance, diagnosis and treatment modalities. There are geographical differences in the HCC-related mortality.

New Concepts in the Imaging Diagnosis of HCC: Can Artificial Intelligence Help?

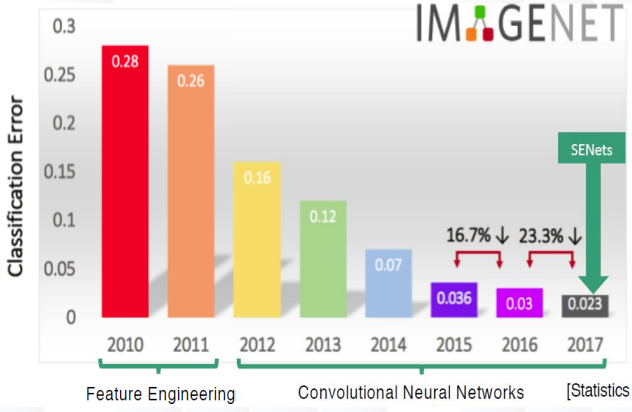
Chih-Horng Wu *(National Taiwan Univ., Taipei)*





ImageNet (Prof. Li Fei-Fei, Stanford University)

- Labeling image database for machine learning
  - 14,197,122 images, 21841 synsets
- ImageNet Large Scale Visual Recognition Challenge (ILSVRC)



Imaging Diagnosis of HCC

- Ultrasound:
  - **Screening,** Monitoring
- Computed tomography:
  - Diagnosis, **Segmentation**
- Magnetic resonance imaging:
  - Diagnosis, Segmentation, **Quantification**

APPLE ACADEMY 2023

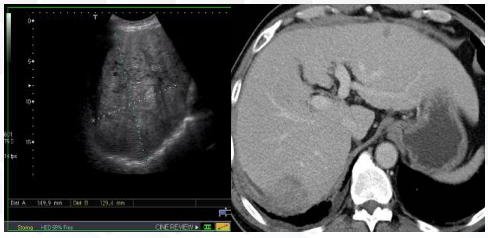
Input x → AI → Output y

$$x = \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_p \end{pmatrix}$$

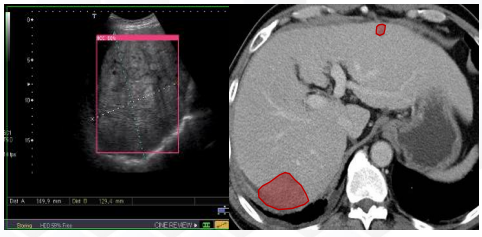
Vector

$$x = \begin{pmatrix} x_{11} & x_{12} & \cdots & x_{1n} \\ x_{21} & x_{22} & \cdots & x_{2n} \\ \cdots & \cdots & \cdots & \cdots \\ x_{m1} & x_{m2} & \cdots & x_{mn} \end{pmatrix}$$

Matrix

$x =$ 

y = Value, Probability

$y =$ 

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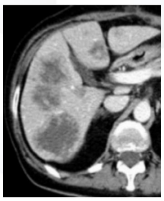
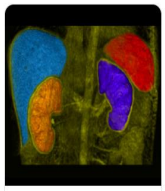
Three major developments in AI
Nowadays, it's easy to access medical AI



LiTS - Liver Tumor Segme...

MICCAI 2017 codalab.org 2017

CT



CHAOS

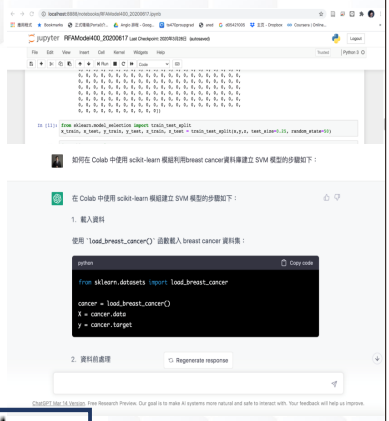
Accepting submissions for Challenge

1,949 1,033 ISBI 2019 Article 2019

MRI

Big Data

AI (⊃ ML)



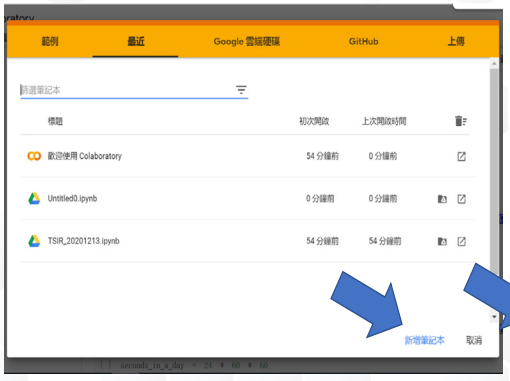
Cloud
(Computing Power)

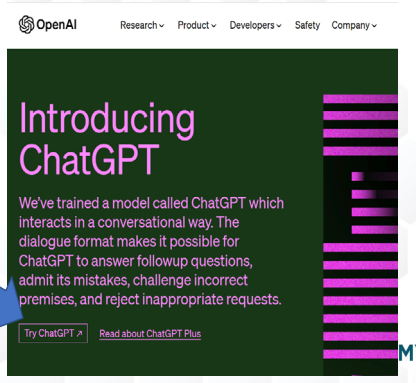
Algorithms
(Availability via
Open Source)

Let's Start Our First AI Project !! APPLE ACADEMY 2023

Preparation – Code yourself

- Connect to Wifi
- Google account
- https://colab.research.google.com
- ChatGPT account
- https://openai.com/blog/chatgpt





MY 2023

Language, Plugins and Algorithms

python 3

Interpreter language
Easy learning

NumPy

Converting vector, matrix and image to array

scikit learn

Machine Learning with Scikit-Learn

Pandas

Dataframe to read excel file

matplotlib

Plugin for drawing image

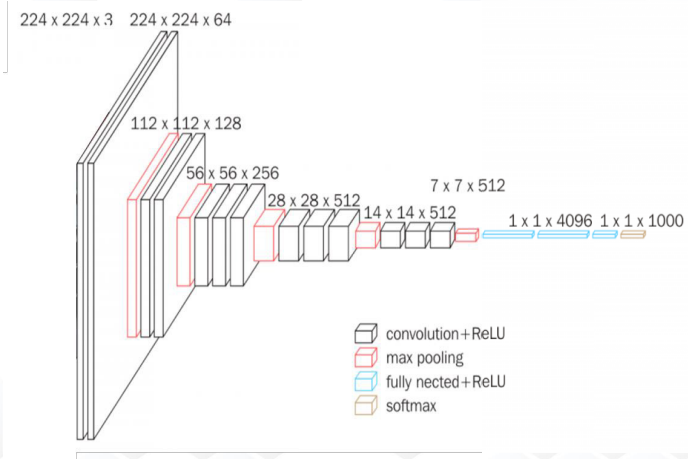
TensorFlow

K Keras

Deep learning algorithms

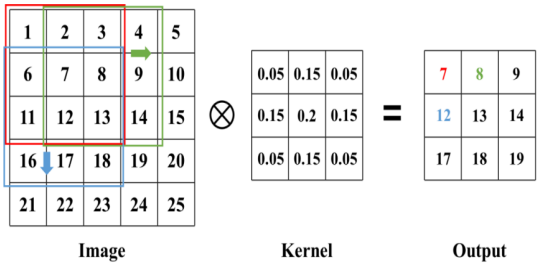
APPLE ACADEMY 2023

Public algorithm: VGG-16 (ILSVRC 2014)

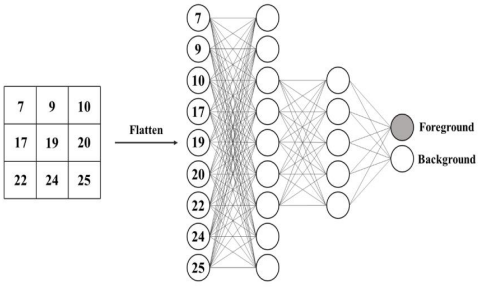


APPLE ACADEMY 2023

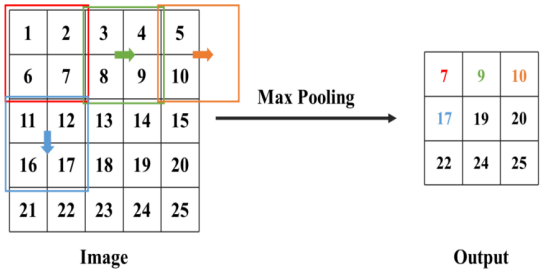
Convolution layer



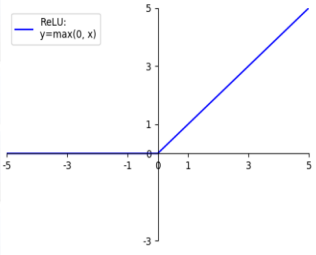
Connection layer



Pooling layer



Activation function



APPLE ACADEMY 2023

Interaction

- Code: MI_DL_20230325.ipynb
- Import Plugin and Keras

Press me

```
import tensorflow as tf
from tensorflow.keras import datasets, models, layers, utils, activations, losses, optimizers, metrics
import numpy as np
import matplotlib.pyplot as plt
from keras.utils import np_utils
from ipywidgets import interact, IntSlider, BoundedIntText
```

Press me

- Check tensorflow version

```
[2] tf.__version__

'2.4.1'
```

APPLE ACADEMY 2023

Import MNIST dataset
Matrix: 28x28, 10 categories

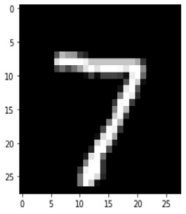
▾ Prepare Data

```
[4] # Load Data from Dataset function
    (x_train, y_train), (x_test, y_test) = datasets.mnist.load_data()
    # Data shape
    x_train.shape, y_train.shape, x_test.shape, y_test.shape

    ((60000, 28, 28), (60000,), (10000, 28, 28), (10000,))
```

```
# Define Parameters
num_classes = 10
img_size = 28
```

- Show one example

```
[5] plt.imshow(x_test[0], cmap=plt.cm.gray)

    <matplotlib.image.AxesImage at 0x7f6b177b5910>
```



MY 2023

Normalization 28x28 image
to standardize 28x28x1 array

```
[6] # add channel
    x_train = np.expand_dims(x_train, axis=3)
    x_test = np.expand_dims(x_test, axis=3)
    print(x_train.shape)
    print(x_test.shape)
    x_train_normalized = x_train / 255
    x_test_normalized = x_test / 255

    (60000, 28, 28, 1)
    (10000, 28, 28, 1)
```

APPLE ACADEMY 2023

Build model

Build Model

```
# Model
from keras.utils import *
from keras.models import Sequential
from keras.layers import Dense, Activation, Flatten, Dropout
from keras.layers import Conv2D, MaxPooling2D
from keras.optimizers import Adam
from keras.preprocessing.image import ImageDataGenerator
model = Sequential()
model.add(Conv2D(16, (5,5), activation="relu", padding="same", data_format="channels_last", input_shape=(28,28,1)))
model.add(MaxPooling2D(pool_size=(2,2), data_format="channels_last"))
model.add(Conv2D(36, (5,5), activation="relu", padding="same", data_format="channels_last"))
model.add(MaxPooling2D(pool_size=(2,2), data_format="channels_last"))
model.add(Flatten())
model.add(Dense(128, activation="relu"))
model.add(Dropout(0.5))
model.add(Dense(10, activation="softmax"))
```

Compile model

```
[8] model.compile(loss='categorical_crossentropy', optimizer=Adam(), metrics=['accuracy'])
```

APPLE ACADEMY 2023

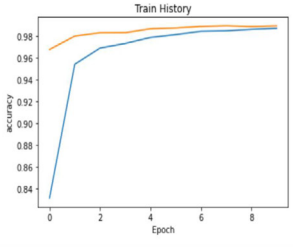
Wait for a long time

Training

```
# 開始訓練
y_train_onehot = np_utils.to_categorical(y_train)
train_history = model.fit(x_train_normalized, y_train_onehot, validation_split=0.2, epochs=10, batch_size=300, verbose=1)

Epoch 1/10
160/160 [==============================] - 53s 326ms/step - loss: 1.0214 - accuracy: 0.6738 - val_loss: 0.1150 - val_accuracy: 0.9678
Epoch 2/10
160/160 [==============================] - 52s 322ms/step - loss: 0.1662 - accuracy: 0.9502 - val_loss: 0.0708 - val_accuracy: 0.9803
Epoch 3/10
160/160 [==============================] - 52s 323ms/step - loss: 0.1138 - accuracy: 0.9669 - val_loss: 0.0547 - val_accuracy: 0.9833
Epoch 4/10
160/160 [==============================] - 51s 320ms/step - loss: 0.0905 - accuracy: 0.9731 - val_loss: 0.0533 - val_accuracy: 0.9833
```

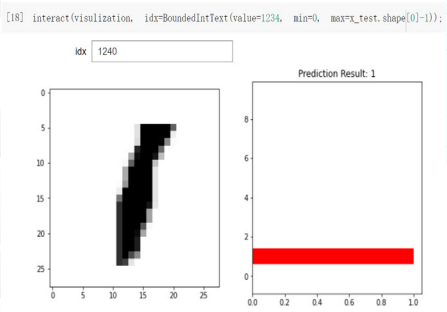
Visualization

```
show_train_history(train_history, "accuracy", "val_accuracy")
```



MY 2023

Our goal



ACADEMY 2023

Ultrasound: **Screening**

- **Ultrasound** is the most common screening tool for **hepatocellular carcinoma (HCC).**
- However, the diagnostic performance of ultrasound is highly **operator-dependent**.
- We aimed to develop **deep learning models** to **diagnose and detect** hepatic lesion in a larger dataset with **HCC** as the dominant malignancy.

APPLE ACADEMY 2023

A retrospective single-center study

- Patients diagnosed with hepatic tumors by the abdominal US from January 2002 to December 2020
- with the diagnosis of
  - **malignant (HCC, cholangiocarcinoma, and metastasis)** and
  - **benign lesions (cysts, hemangiomas, focal fatty sparing, FNH, & other benign findings).**
- Finally,
  - **1,576 patients** with **4,600 images**, and **6,001 lesions** were analyzed.

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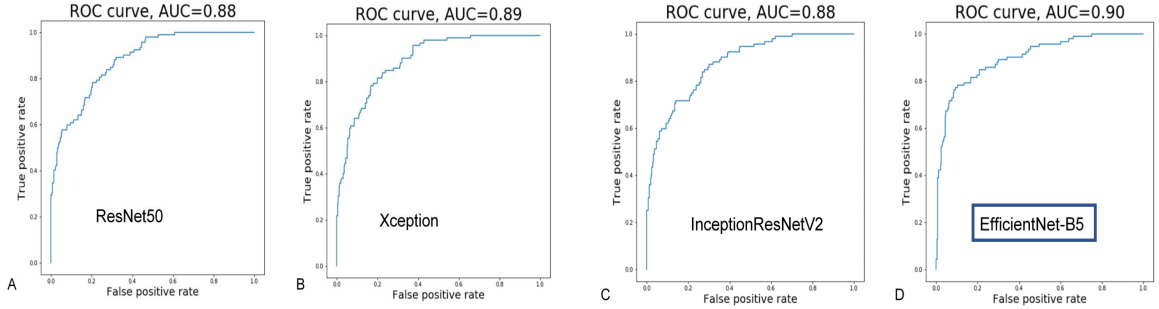
Deep learning models

- **ResNet50, Xception, InceptionResnetV2, and EfficientNet-B5** for diagnosis
  - For EfficientNet-B5, we also performed Swin Transformed, with **small (0.5x), large (2x), tiny (0.25x) and base (1x)** complexity
- **YOLO v6** for lesion detection
  - **Yolo-d6** use deeper CNN layers to provide **higher accuracy**
  - **Yolo-w6** use wider CNN layers to achieve **high speed training**
- **ROC** curve analysis to determine the diagnostic performance
- **Mean Average Precision (mAP) score** for lesion detection

APPLE ACADEMY 2023

Diagnostic performance of differentiation between malignant and benign lesions



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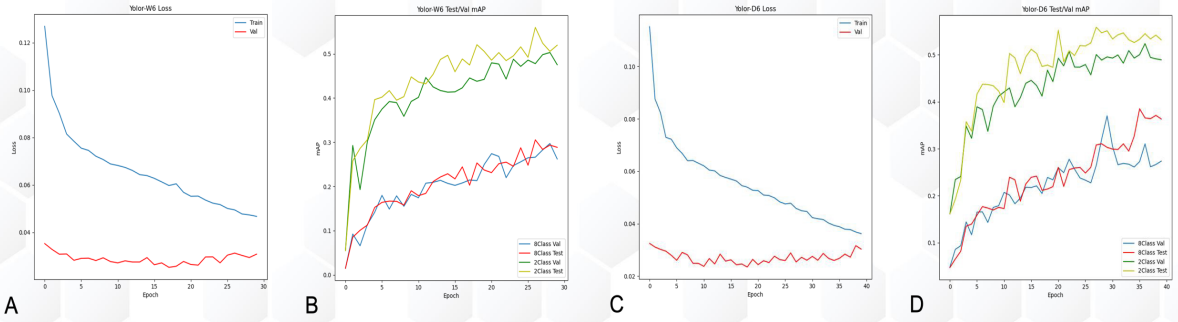
Diagnostic performance of classifying 8 kinds of hepatic lesions

	Transformer type	Total Acc.	HCC Acc.	Cho Acc.	Met Acc.	Cys Acc.	Hem Acc.	FFS Acc.	FNH Acc.	Oth Acc.
Validation set	EfficientNetV2_s	0.694	0.922	0.036	0.000	0.964	0.300	0.032	0.136	0.000
	EfficientNetV2_l	0.700	0.909	0.000	0.000	0.929	0.300	0.290	0.091	0.000
	Swin_t	0.727	0.914	0.071	0.000	0.964	0.300	0.419	0.182	0.000
	Swin_b	0.735	0.881	0.286	0.000	1.000	0.200	0.645	0.091	0.000
Testing set	EfficientNetV2_s	0.755	0.944	0.000	0.071	1.000	0.359	0.000	0.061	0.000
	EfficientNetV2_l	0.757	0.930	0.045	0.107	1.000	0.462	0.333	0.030	0.000
	Swin_t	0.766	0.944	0.136	0.143	1.000	0.385	0.167	0.030	0.000
	Swin_b	0.744	0.920	0.045	0.107	1.000	0.385	0.333	0.030	0.000

APPLE ACADEMY 2023

Lesion detection on ultrasound images

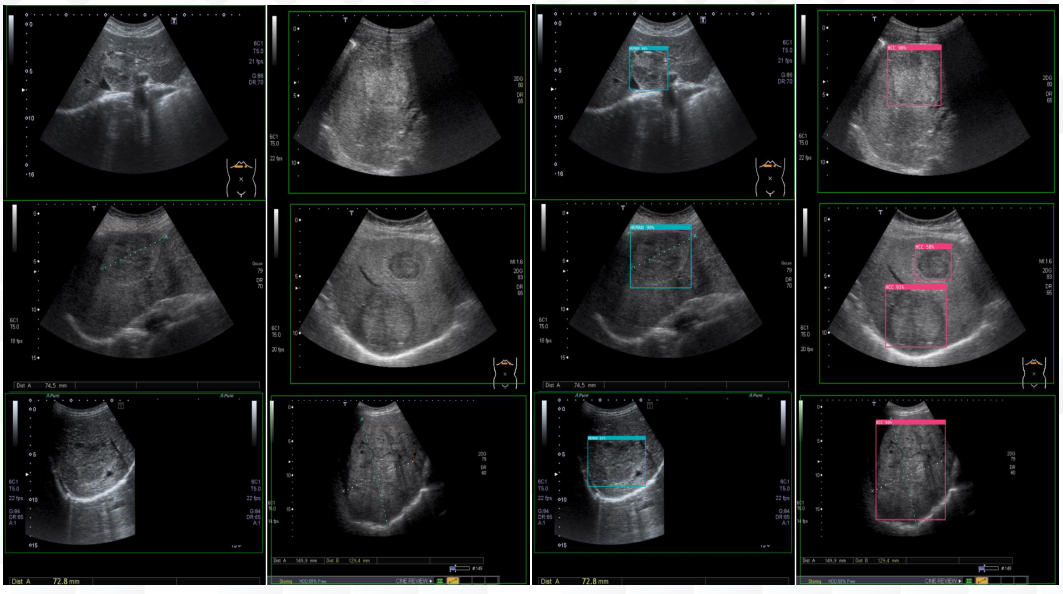


A B C D

Yolo-w6/Yolo-d6 in validation and testing sets were **0.561/0.628** and **0.390/0.397**

APPLE ACADEMY 2023

Real-time lesion detection on US images
Blue: benign, Pink: malignant



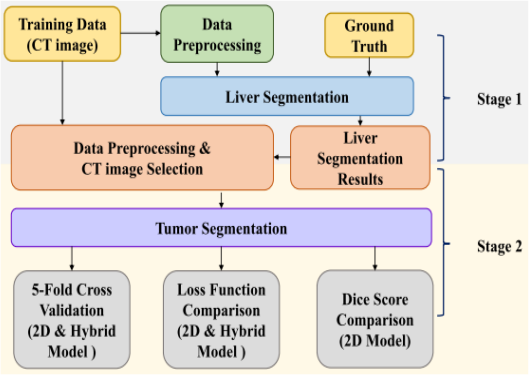
2023

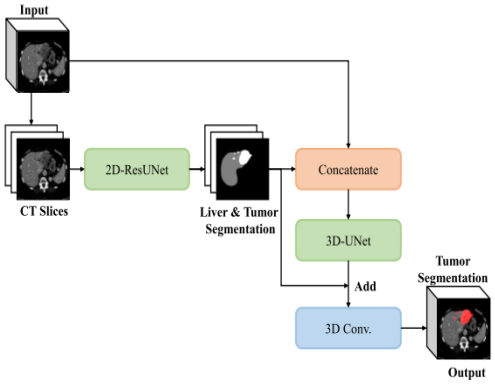
Computed tomography: **Segmentation**

- **Segmentation** of liver tumors on CT images is **challenging**
- Contrast-enhanced studies typically reveal **hyperdense** contrast enhancement during the **HAP** and **hypodense** contrast washout during the **PVP or delayed phase**
- Difficulty identifying small tumors because they have grayscale **intensities similar** to that of the surrounding liver tissue
- Lack of sufficient data for training models is another challenge. A possible solution is **federated learning**
- We aimed to design **FL** algorithms globally to balance and enhance segmentation results without sharing local datasets while achieving high model accuracy and efficiency

APPLE ACADEMY 2023

Two-stage and 2.5D Hybrid-ResUNet liver segmentation and tumor identification approach

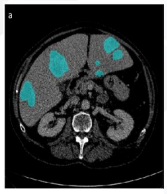


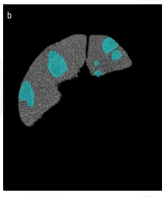


High model accuracy and efficiency

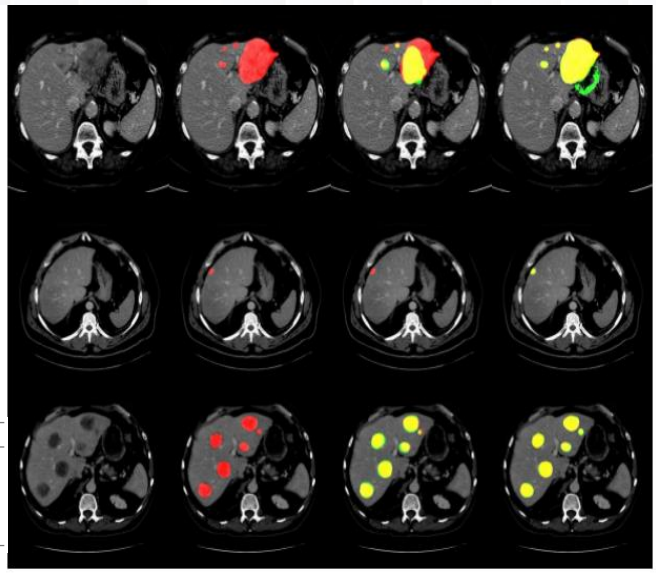
APPLE ACADEMY 2023

Two-stage and 2.5D Hybrid-ResUNet liver segmentation and tumor identification approach





Windowing range	Liver Dice score	Tumor Dice score
(-200, 250)	0.8984	**0.6661**
(-20, 220)	0.8956	0.6461
(50, 250)	0.8901	0.6172
(-200, 400)	**0.9010**	0.6654
(-79, 304)	0.8908	0.6424



Single large and multiple small

Single small

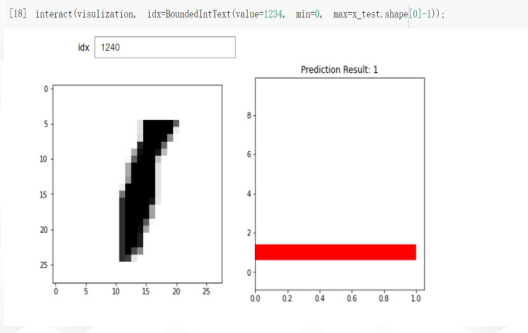
Multiple tumors

True Positive
False Positive
False Negative

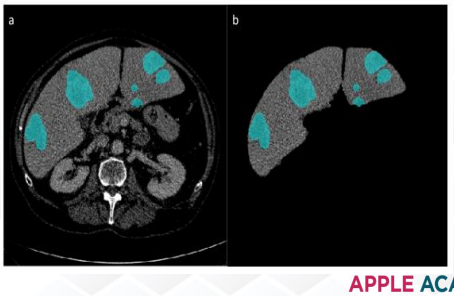
Image Label 2D-Unet Hybrid-ResUNet

2023

Back to our example and Summary



US screening



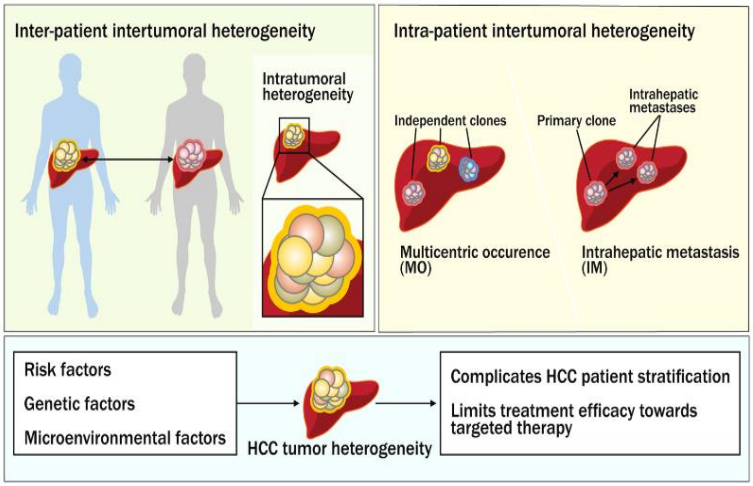
CT segmentation

Can Artificial Intelligence Help?
Of course !!

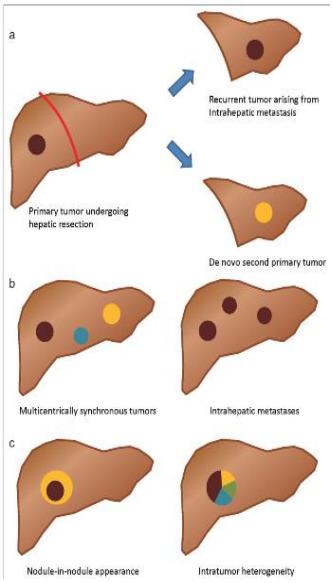
APPLE ACADEMY 2023

Molecular Heterogeneity in HCC and the Challenge of Identifying Predictive Biomarkers

Irene Oi-Lin Ng *(The Univ. of Hong Kong, Hong Kong)*



(Chan LK et al. Sem Cancer Biol 2021)

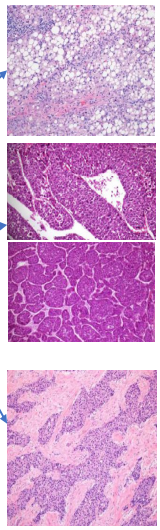


(Lu LC et al. Liver Cancer 2016)

Summary on HCC

1. Associated clinical features 2. Prognosis 3. Genetic alterations

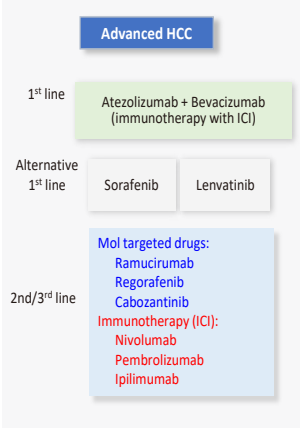
Subtype	Relative frequency	Key clinical correlates	Prognosis[a]	Key histological features	Key molecular features
Steatohepatitic[b] {2835}	5–20%	Steatohepatitis may be in the background liver from metabolic syndrome or alcohol abuse	Similar	Tumour shows histological steatohepatitis	IL-6/JAK/STAT activation; lower frequency of *CTNNB1*, *TERT*, and *TP53* mutations {461}
Clear cell {1888}	3–7%	None to date	Better	> 80% of tumour[c] shows clear cell morphology from glycogen accumulation; some steatosis is acceptable	None to date
Macrotrabecular massive {461}	5%	High serum AFP; poor prognosis	Worse	Macrotrabecular growth pattern in > 50% of tumour; vascular invasion common	*TP53* mutations and *FGF19* amplifications
Scirrhous {2086}	4%	Often mimics cholangiocarcinoma on imaging	Variable, no consensus in the literature	> 50% of tumour shows dense intratumoural fibrosis	*TSC1/2* mutations {461}; TGF-β signalling activation {2953}
Chromophobe {3600}	3%	None to date	Similar	Light, almost clear cytoplasm (chromophobe); mainly bland tumour nuclei, but focal areas of more striking nuclear atypia	Alternative lengthening of telomeres
Fibrolamellar carcinoma (synonym: fibrolamellar HCC) {1085}	1%	Young median age (25 years); no background liver disease	Similar to that of HCC in non-cirrhotic livers	Large eosinophilic tumour cells with prominent nucleoli; dense intratumoural fibrosis	Activation of PKA via a *DNAJB1-PRKACA* fusion gene
Neutrophil-rich {3327}	< 1%	Elevated white blood cell count, CRP, and IL-6	Worse	Numerous and diffuse neutrophils within tumour; can have sarcomatoid areas	Tumour produces G-CSF
Lymphocyte-rich {3327}	< 1%	None to date	Better	On H&E staining, lymphocytes outnumber tumour cells in most fields	None to date; not EBV-related

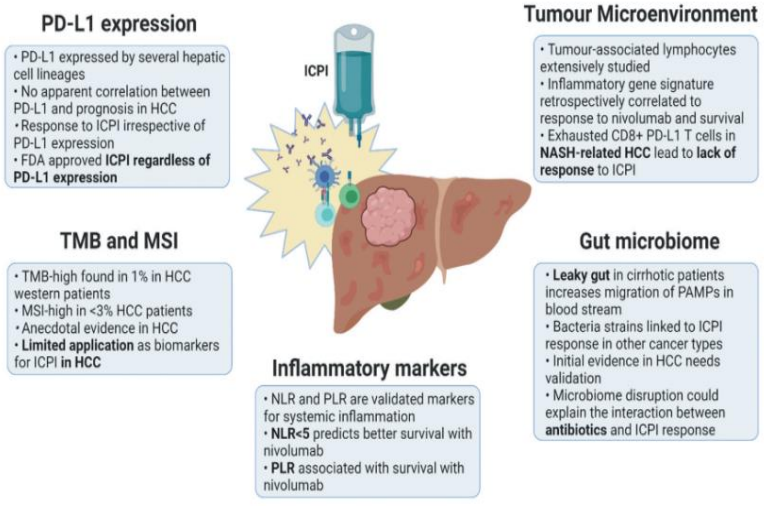


Morpho-molecular correlations -

- Allow better understanding of pathogenesis, predict patient outcome, and facilitate development of targeted therapy
- Importantly, identification of histopathological variants suggests histopathology has important role in HCC management

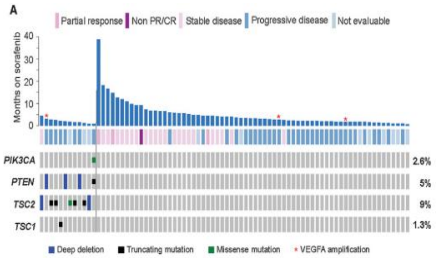
Biomarkers of response to immune checkpoint inhibitors in HCC



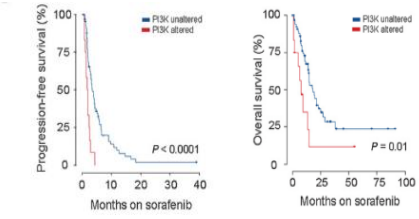


(Muhammed A et al. Exp Rev Mol Diagn 2022)

Genomic determinants of response to sorafenib in advanced HCC



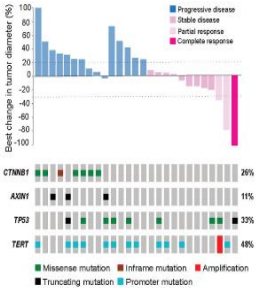
Shorter PFS and OS in PI3K–mTOR activated HCCs (N = 12) versus non-PI3K–mTOR tumors (N = 67)



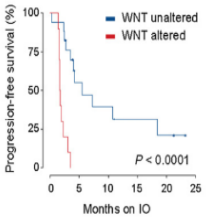
Prospective Genotyping of Hepatocellular Carcinoma: Clinical Implications of Next-Generation Sequencing for Matching Patients to Targeted and Immune Therapies

(Harding et al. Clin Cancer Res 2019)

Genomic determinants of response to immune checkpoint blockade in advanced HCC



Shorter PFS in WNT-activated HCCs



- None of the 10 patients with HCC with activating mutations in CTNNB1 had response to anti-PD-1 or anti-PD-L1 therapy
- Whereas 50% of CTNNB1 WT patients had a response

β-Catenin Activation Promotes Immune Escape and Resistance to Anti–PD-1 Therapy in Hepatocellular Carcinoma

Genetically engineered mouse model of HCC (Hydrodynamic tail vein injection):

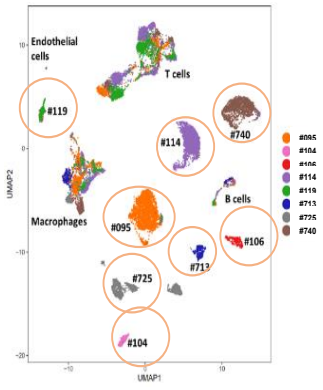
- β-catenin activation promotes immune escape and resistance to anti–PD-1
- Could represent a novel biomarker for HCC patient exclusion

(Ruiz de Galarreta et al. Cancer Discov 2019)

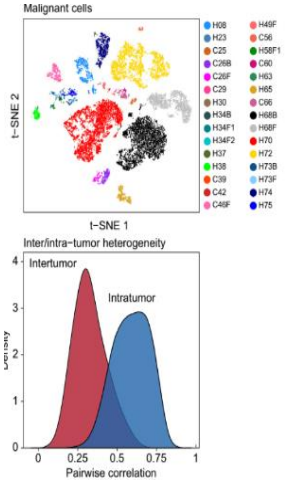
ScRNA-seq on patient HCC tumors – Inter and intratumoral heterogeneity

ITH: Patient prognosis and treatment failure

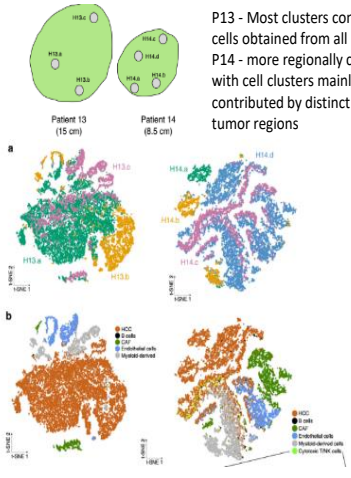
HCC - A high degree of intertumoral heterogeneity



(Ho D…Ng IO. Nat Commun, 2021)



(Ma L… Wang XW. J Hepatol 2021)

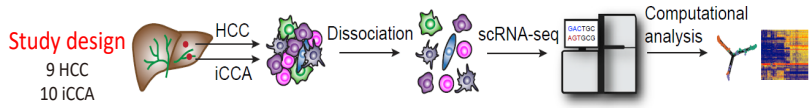


P13 - Most clusters contributed by cells obtained from all 3 regions.
P14 - more regionally clustered, with cell clusters mainly contributed by distinct single tumor regions

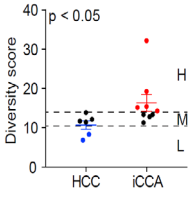
The resulting differential expression signatures were computed to derive a score. The resulting ITH signatures were found to correlate with early tumor recurrence.

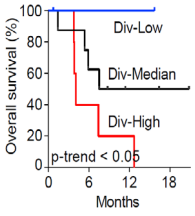
(Losic B et al. Nat Commun 2020)

Tumor cell biodiversity in liver cancer by scRNA-seq – associated with patient survival



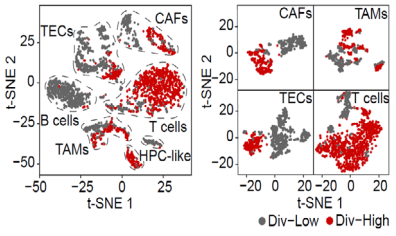
Biodiversity
(Tumor cell transcriptional heterogeneity ~ ITH)



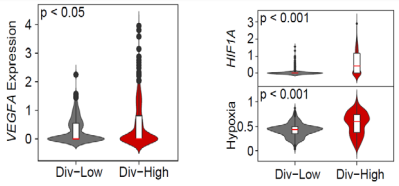


Tumors with higher biodiversity is associated with poorer overall survival of patients

Combining HCC and iCCA



VEGFA expression is higher in Div-high tumor cells



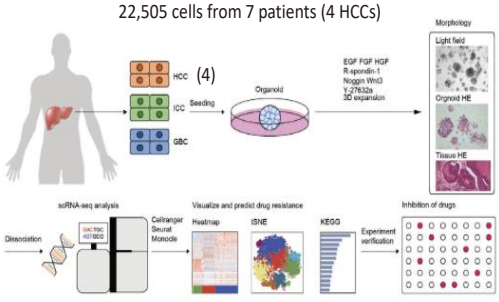
→ May regulate possible reprograming of tumor microenvironment

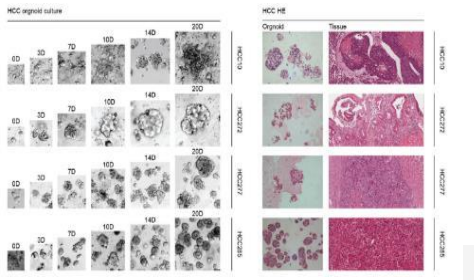
(Combining HCC and iCCA cases)

(Ma L....Wang XY.. Cancer Cell 2020)

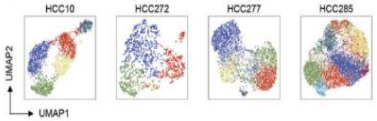
Intratumoral heterogeneity – using HCC organoids

22,505 cells from 7 patients (4 HCCs)

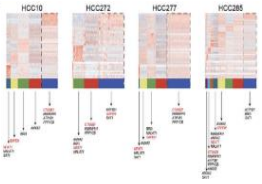




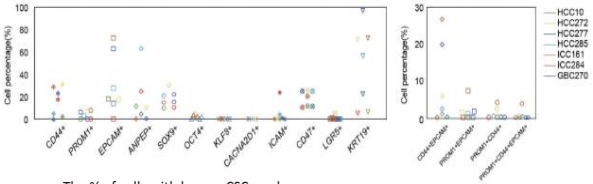
Heterogeneous clusters with diverse gene expression patterns in each HCC organoid



Genes differentially expressed in individual organoid clusters



Cancer stemness within the tumor organoids



The % of cells with known CSC markers varied greatly among individual organoids

Double and triple positive CSC markers were found in individual organoids- PROM1 (CD133), EPCAM, and CD44

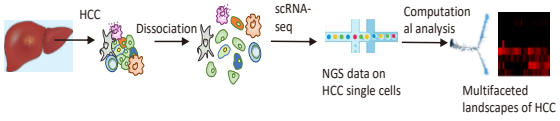
Findings implicate the basis of drug resistance of individual tumors

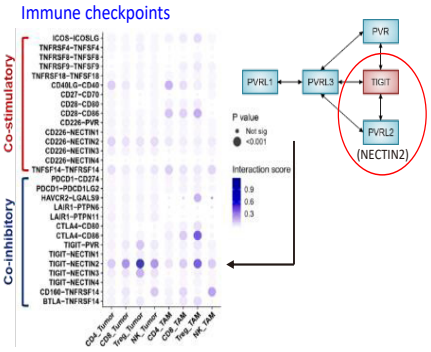
(Zhao Y...Chen L.. Adv Sci 2021)

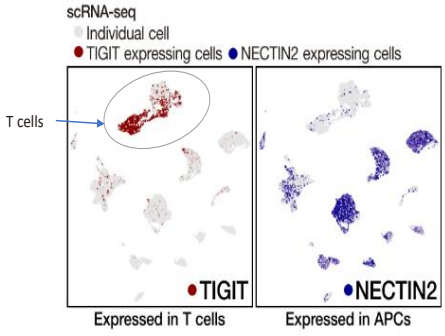
sc-RNA seq identifies novel immune checkpoint axis TIGIT-NECTIN2 in HCC

nature COMMUNICATIONS

Daniel Wai-Hung Ho[1,2✉], Yu-Man Tsui[1,2], Lo-Kong Chan[1,2], Karen Man-Fong Sze[1,2], Xin Zhang[1,2], Jacinth Wing-Sum Cheu[1], Yung-Tuen Chiu[1,2], Joyce Man-Fong Lee[1,2], Albert Chi-Yan Chan[2,3], Elaine Tin-Yan Cheung[4], Derek Tsz-Wai Yau[4], Nam-Hung Chia[5], Irene Lai-Oi Lo[5], Pak-Chung Sham[6], Tan-To Cheung[2,3], Carmen Chak-Lui Wong[1,2] & Irene Oi-Lin Ng[1,2✉] (2021)

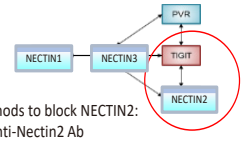




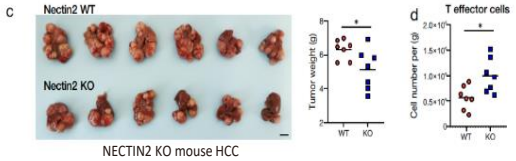


(Ho DW…Ng IO. Nat Commun 2021)

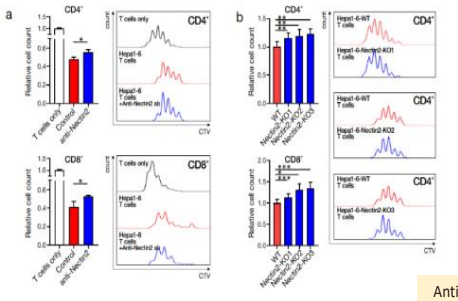
TIGIT and NECTIN2 immune checkpoint axis in human HCC



Two methods to block NECTIN2:
1. Anti-Nectin2 Ab
2. Knockout (KO) of Nectin2

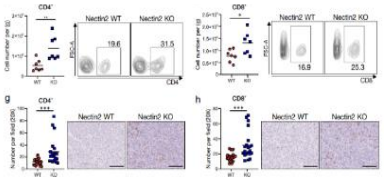


NECTIN2 KO mouse HCC



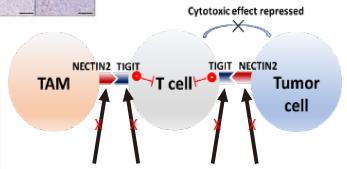
Co-culturing system - mouse splenic T cells co-cultured with mouse HCC Hepa1-6 cells

Tumor-infiltrating lymphocytes by flow cytometry



Anti-Nectin2 Ab and KO of Nectin2 restored both CD4 and CD8 T cell proliferation, suggesting Nectin2 suppressed T cell proliferation

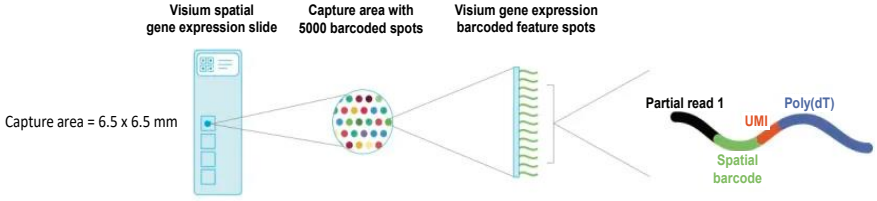
NECTIN2 KO – smaller tumor size and increased infiltration of T effector, CD4+, and CD8+ cells in HCC



Blocking TIGIT-NECTIN2 axis as novel and promising therapeutic target for treating HCC

(Ho DW…Ng IO. Nat Commun 2021)

Spatial transcriptomics



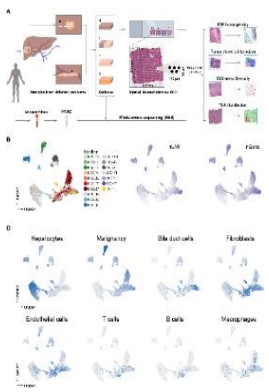
Key advantages of ST

- Endogenous spatial organization of cells and their whole-transcriptome profiles are preserved
- Coupling of histological, molecular and cellular information
- Applicable to both frozen and FFPE samples
- Less amount of tissue input

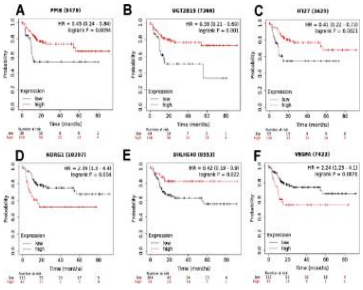
Limitation of ST

- Not yet at single-cell resolution

Comprehensive analysis of spatial architecture in primary liver cancer
(Wu et al. Sci Adv. 2021)

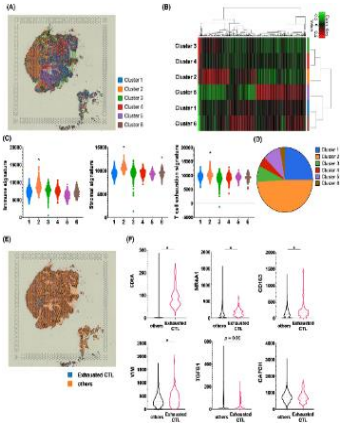


PROM1+ and CD47+ cancer stem cell niches are related to TME remodeling and tumor metastasis



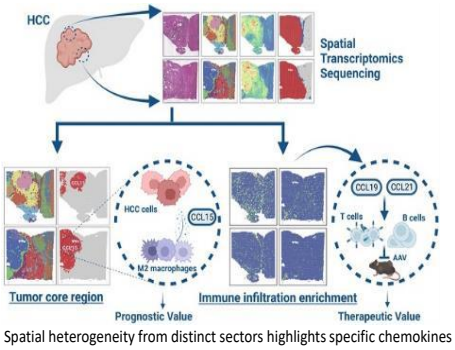
Tumour clusters-specific marker gene signature model (6 genes) for HCC prognosis

Spatial maps of HCC transcriptomes highlight an unexplored landscape of heterogeneity and a novel gene signature for survival
(Zhao et al. Cancer Cell Int. 2022)



M2 macrophages and CAFs may be in close proximity to exhausted CD8+ T cells in steatotic HCC

Multiomics identifies the link between intratumor steatosis and the exhausted tumor immune microenvironment in HCC
(Murai et al. Hepatology 2023)

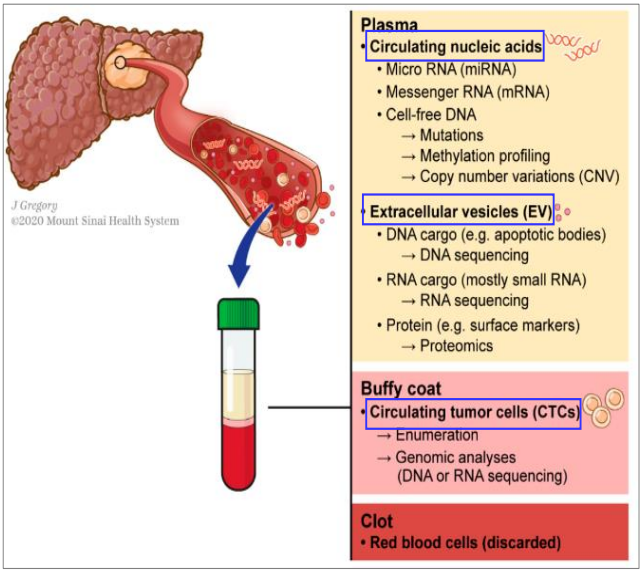


Spatial heterogeneity from distinct sectors highlights specific chemokines

Spatial maps of HCC transcriptomes reveal spatial expression patterns in tumor immune microenvironment
(Wang et al. Theranostics 2022)

Liquid biopsy

Molecular analysis of tumor-byproducts released into the bloodstream



(Labgaa I et al. Cancers 2021)

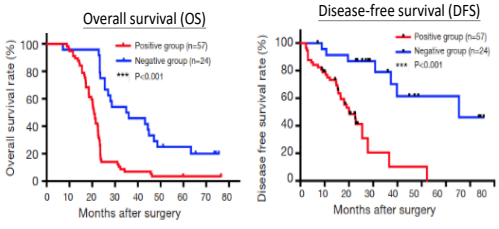
Cell-free nucleic acid-based methods for HCC prognosis

Somatic gene mutations/ SNV

Circulating tumor DNA correlates with microvascular invasion and predicts tumor recurrence of hepatocellular carcinoma

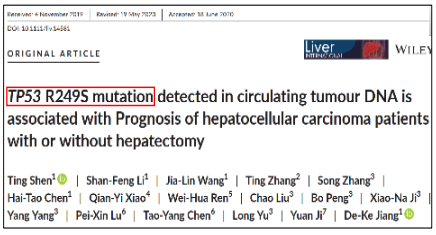
Jian Wang[1#], Ao Huang[1#], Yu-Peng Wang[1#], Yue Yin[1], Pei-Yao Fu[1], Xin Zhang[1], Jian Zhou[1,2,3]

- ctDNA: 4 mutation hotspots in TP53, TERT and CTNNB1 were studied
- Presence of pre-operative ctDNA predicts poorer survival



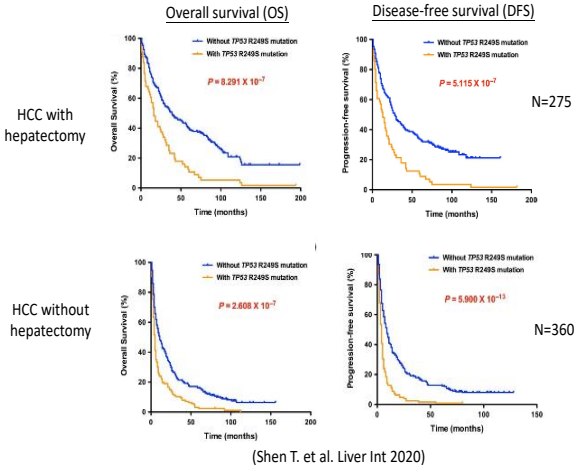
N=81

(Wang J, et al. Ann Transl Med 2020)



TP53 R249S mutation detected in circulating tumour DNA is associated with Prognosis of hepatocellular carcinoma patients with or without hepatectomy

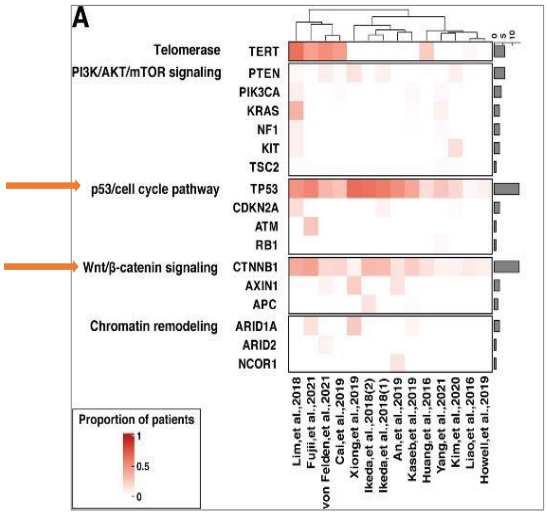
Ting Shen[1] | Shan-Feng Li[1] | Jia-Lin Wang[1] | Ting Zhang[2] | Song Zhang[3] | Hai-Tao Chen[3] | Qian-Yi Xiao[4] | Wei-Hua Ren[5] | Chao Liu[3] | Bo Peng[3] | Xiao-Na Ji[3] | Yang Yang[3] | Pei-Xin Lu[6] | Tao-Yang Chen[6] | Long Yu[3] | Yuan Ji[7] | De-Ke Jiang[1]



(Shen T. et al. Liver Int 2020)

Studies on cell-free DNA in HCC

Recurrent SNVs and related pathways identified



Mutations could be detected in 35- 96% in HCC patients' plasma

- Continued investigation into this area of liquid biopsy is of interest; but increased sensitivity and specificity is needed

(Lyu et al. CMGH 2022)

Summary

- Omics analyses in HCC has allowed significant advancement in the understanding of the pathogenesis of HCC at unprecedented levels
- They have enabled the identification of potential/ candidate molecular biomarkers in HCC for both treatment targets and prognostication
- Analysis of immunosuppressive landscape and intercellular interactions using omics analysis can provide mechanistic information for treatments for HCC and enables identification of potential / candidate molecular biomarkers
- However, with regard to ICI or TKI treatment, there is still a lack of validated biomarkers to guide clinical decision-making; identification of determinants in drug response is much warranted
- Newer technologies (e.g. ST) are emerging and may allow refined analysis of spatial arrangement of cells and their interaction

Adaptation of Practice Guidelines: When East Meets West

Li-Tzong Chen *(Kaohsiung Medical Univ., Kaohsiung)*

APPLE ACADEMY 2023

Thursday, July 6, 2023 [ROOM C (Grand Ballroom 3)]

Session 2.

Translational and Basic Research That May Impact on the Clinical Management of HCC

Chairs: **Pierce Chow** *(National Cancer Centre Singapore, Singapore)*
Chiun Hsu *(National Taiwan Univ., Taipei)*

Biomarker-Based Precision Pharmacotherapy in HCC
Takahiro Kodama *(Osaka Univ., Osaka)*

Translational Research: The Impact from Research in Epigenomics
Ah-Jung Jeon *(Mirxes, Singapore)*

Translational Research: The Impact from Research in Spatial Transcriptomics
Ankur Sharma *(Harry Perkins Institute of Medical Research, Perth)*

The Promise of Immuno-Neoadjuvant Therapy in HCC
Han Chong Toh *(National Cancer Centre Singapore, Singapore)*

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Session 2. Translational and Basic Research That May Impact on the Clinical Management of HCC

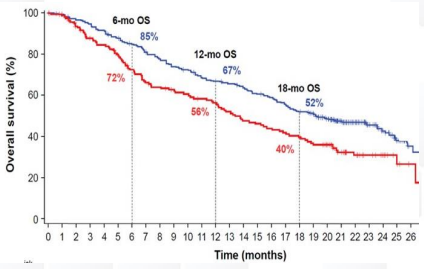
Biomarker-Based Precision Pharmacotherapy in HCC

Takahiro Kodama *(Osaka Univ., Osaka)*

anti-PD-L1 + anti-VEGF therapy for advanced HCC

- In 2020, anti-PD-L1 + anti-VEGF therapy (Atez/Bev) became the first-line ch emotherapy for advanced HCC.
- Its response rate is about 30% but 20% of patients showing initial resistance.

Phase III Clinical Trial IMbrave150 Atesolizumab + Bevacizumab vs Sorafenib



Median OS: 19.2 vs 13.4 mo
HR: 0.66 (*P* = .0009)

	Atezo + Bev n = 326 RECIST 1.1	Sor n = 159 RECIST 1.1
Confirmed ORR (95% CI), %	29.8 (24.8, 35.0)	11.3 (6.9, 17.3)
CR, n (%)	25 (7.7)	1 (0.6)
PR, n (%)	72 (22.1)	17 (10.7)
SD, n (%)	144 (44.2)	69 (43.4)

(Finn RS, et al. New Eng J Med. 2020)

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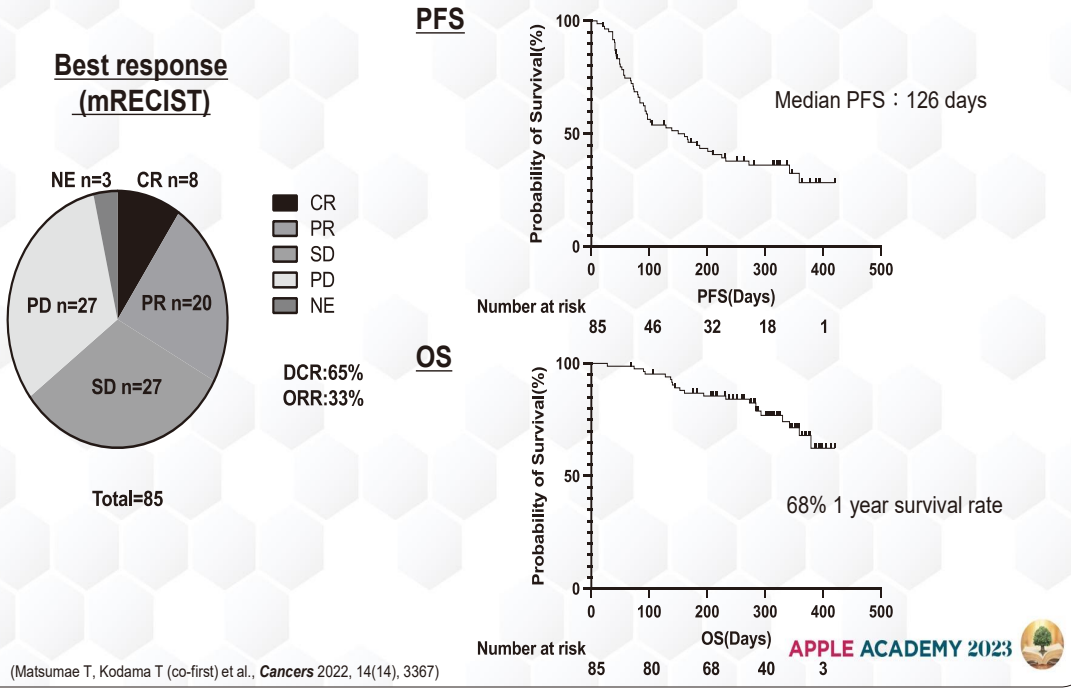
Real-world clinical outcomes of 85 HCC patients treated with Atezo/Bev



(Matsumae T, Kodama T (co-first) et al., ***Cancers*** 2022, 14(14), 3367)

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Aim

To explore predictors of therapeutic response and clinical outcomes upon Atezo/Bev therapy in HCC

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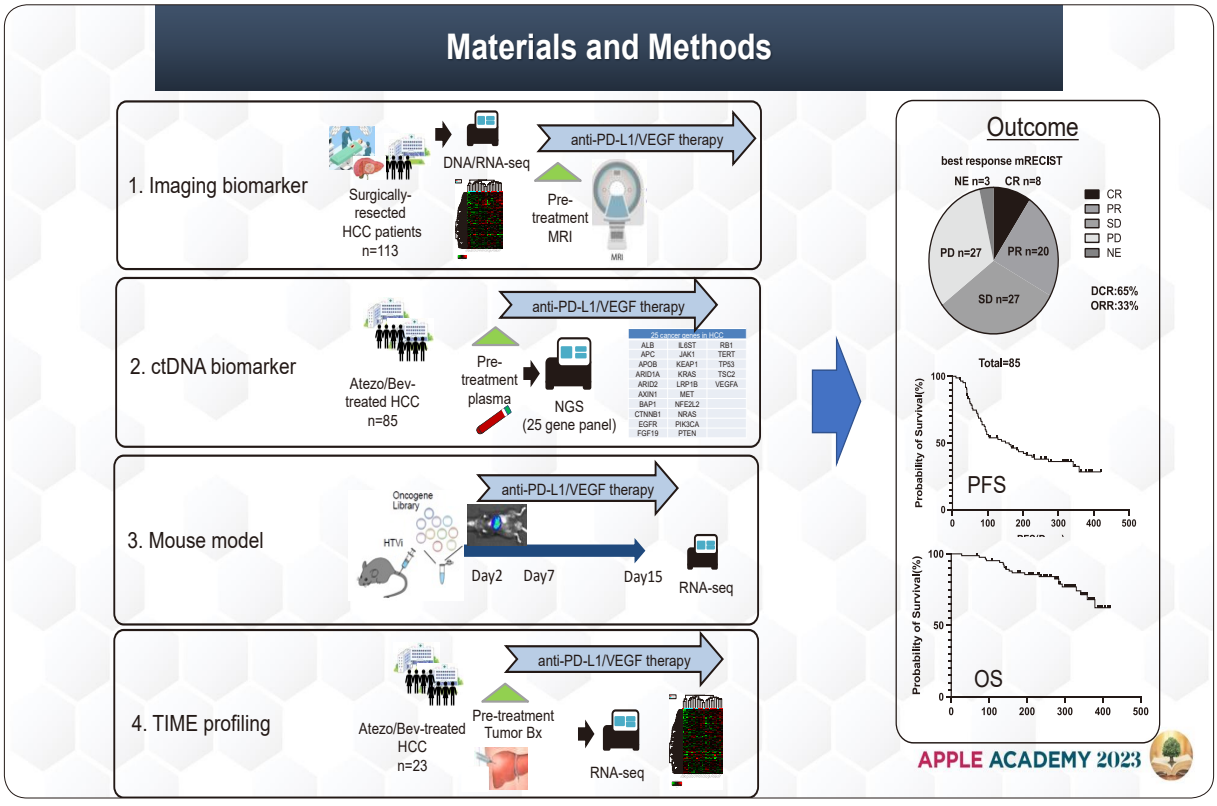
Materials and Methods
1. Imaging biomarker
Surgically-resected HCC patients n=113
DNA/RNA-seq
Pre-treatment MRI
anti-PD-L1/VEGF therapy
2. ctDNA biomarker
Atezo/Bev-treated HCC n=85
Pre-treatment plasma
NGS (25 gene panel)
anti-PD-L1/VEGF therapy
3. Mouse model
Oncogene Library
HTVI
Day2
Day7
Day15
RNA-seq
anti-PD-L1/VEGF therapy
4. TIME profiling
Atezo/Bev-treated HCC n=23
Pre-treatment Tumor Bx
RNA-seq
anti-PD-L1/VEGF therapy
Outcome
best response mRECIST
NE n=3
CR n=8
PD n=27
PR n=20
SD n=27
CR
PR
SD
PD
NE
DCR:65%
ORR:33%
Total=85
Probability of Survival(%)
PFS
OS
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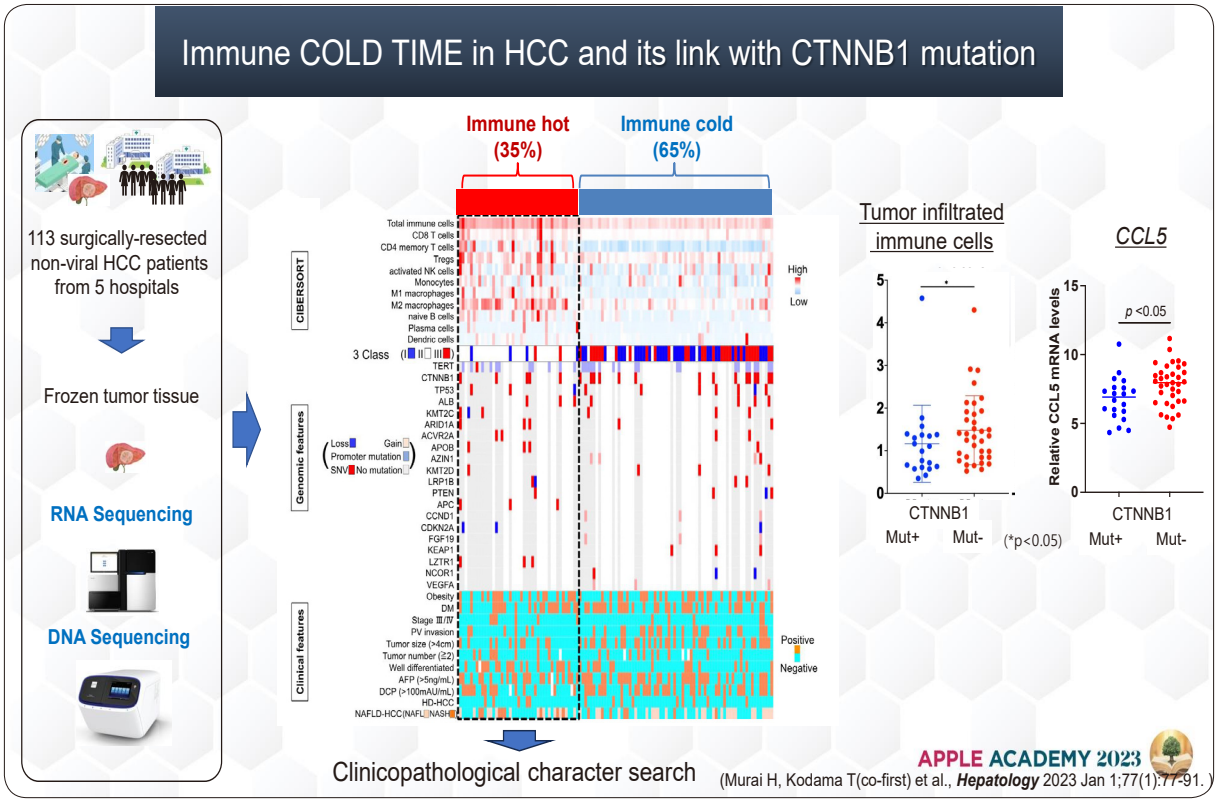
Immune COLD TIME in HCC and its link with CTNNB1 mutation
113 surgically-resected non-viral HCC patients from 5 hospitals
Frozen tumor tissue
RNA Sequencing
DNA Sequencing
Immune hot (35%)
Immune cold (65%)
CIBERSORT
Genomic features
Clinical features
High
Low
Positive
Negative
Clinicopathological character search
Tumor infiltrated immune cells
CCL5
Relative CCL5 mRNA levels
p <0.05
CTNNB1
Mut+
Mut-
(*p<0.05)
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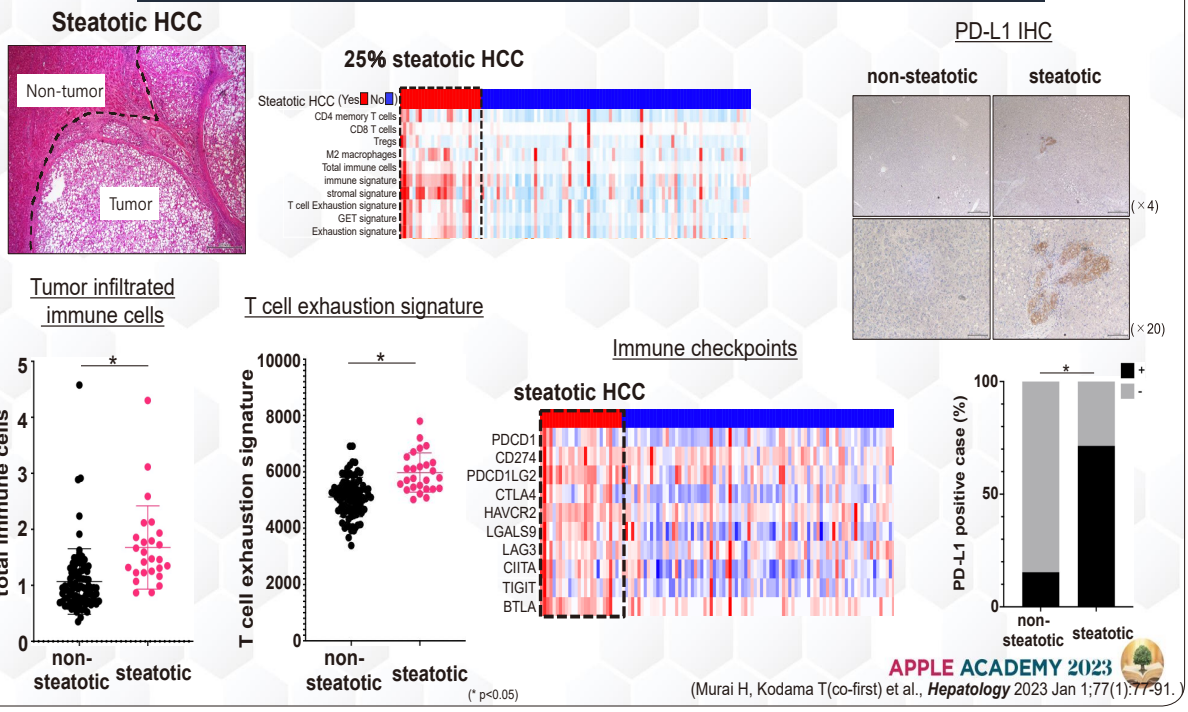
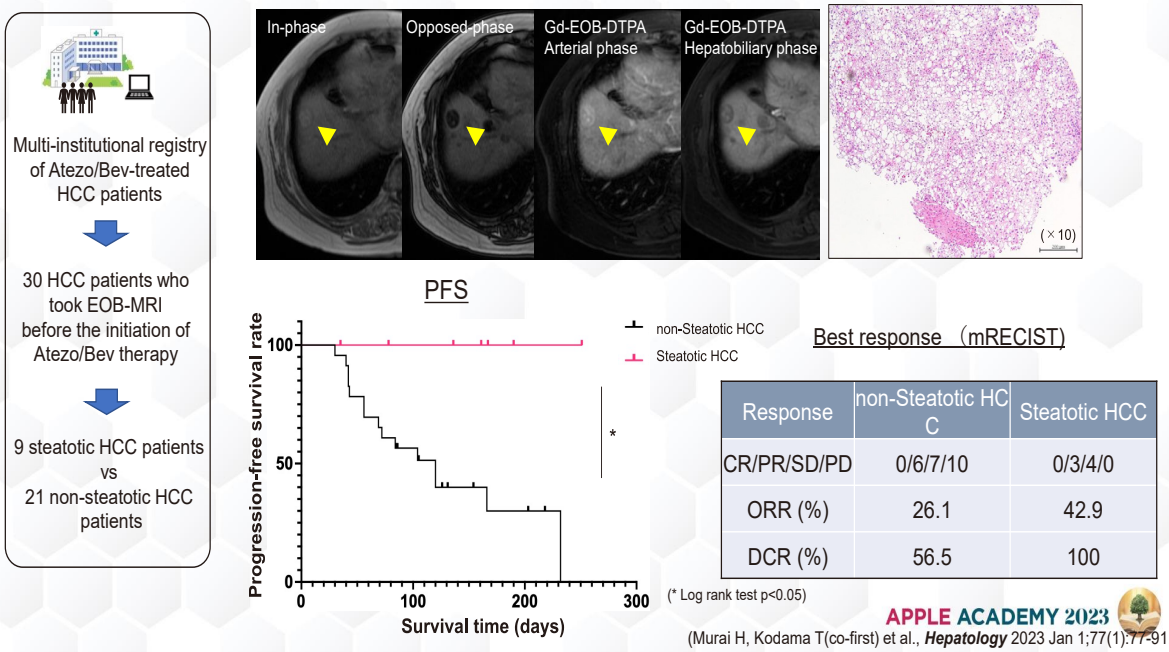
(Murai H, Kodama T(co-first) et al., Hepatology 2023 Jan 1;77(1):77-91.)

Steatotic HCC showed immune-HOT but exhausted microenvironment



(Murai H, Kodama T(co-first) et al., ***Hepatology*** 2023 Jan 1;77(1):77-91.)

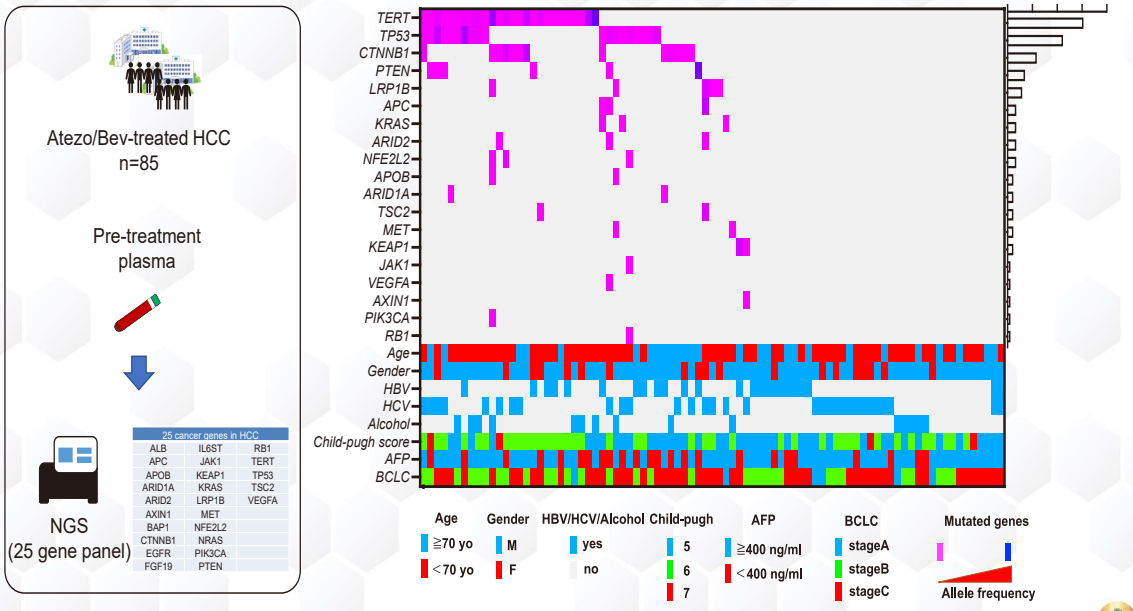
Staeatotic HCC patients identified by MRI chemical shift imaging were susceptible to Atezo/Bev therapy



Response	non-Steatotic HCC	Steatotic HCC
CR/PR/SD/PD	0/6/7/10	0/3/4/0
ORR (%)	26.1	42.9
DCR (%)	56.5	100

(Murai H, Kodama T(co-first) et al., ***Hepatology*** 2023 Jan 1;77(1):77-91.)

ctDNA profiling of HCC patients treated with Atezo/Bev



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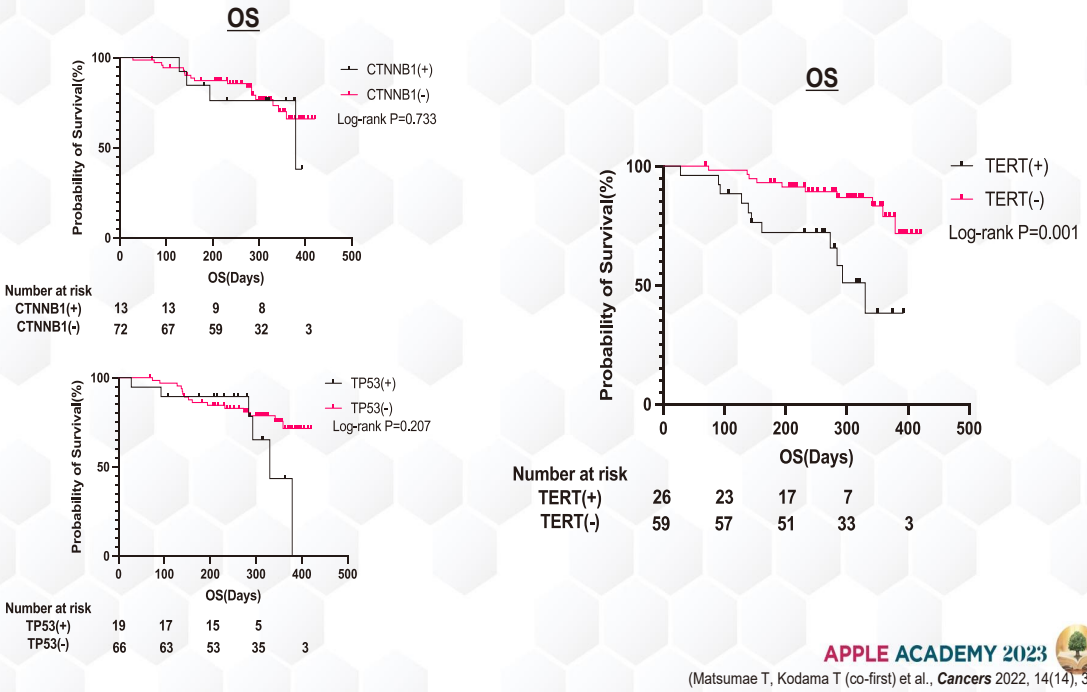
(Matsumae T, Kodama T (co-first) et al., ***Cancers*** 2022, 14(14), 3367)

HCC patients with TERT ctDNA had significantly shorter OS upon Atezo/Bev therapy



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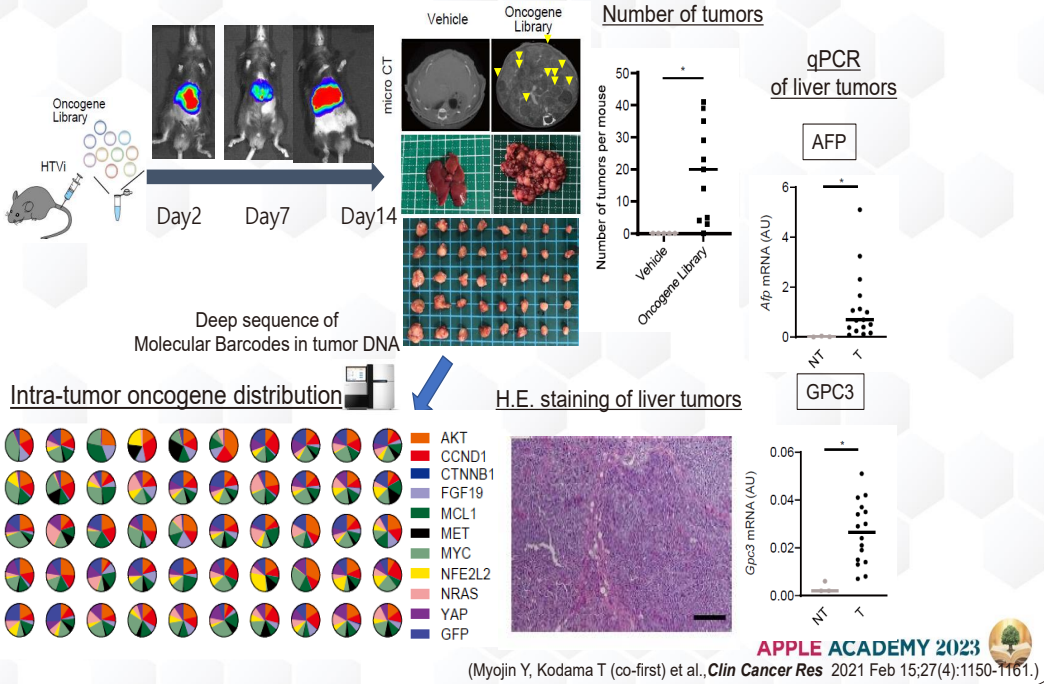
(Matsumae T, Kodama T (co-first) et al., ***Cancers*** 2022, 14(14), 3367)

Liver tumor mouse model mimicking Inter-tumor heterogeneity by transposon-based intrahepatic oncogene library delivery



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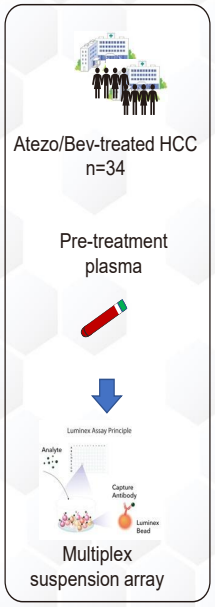
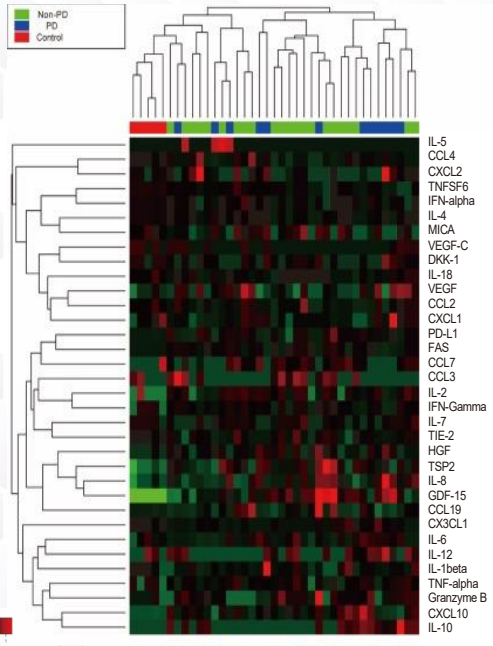
(Myojin Y, Kodama T (co-first) et al., ***Clin Cancer Res*** 2021 Feb 15;27(4):1150-1161.)

High plasma IL-6 levels were associated with initial PD response of Atezo/Bev therapy



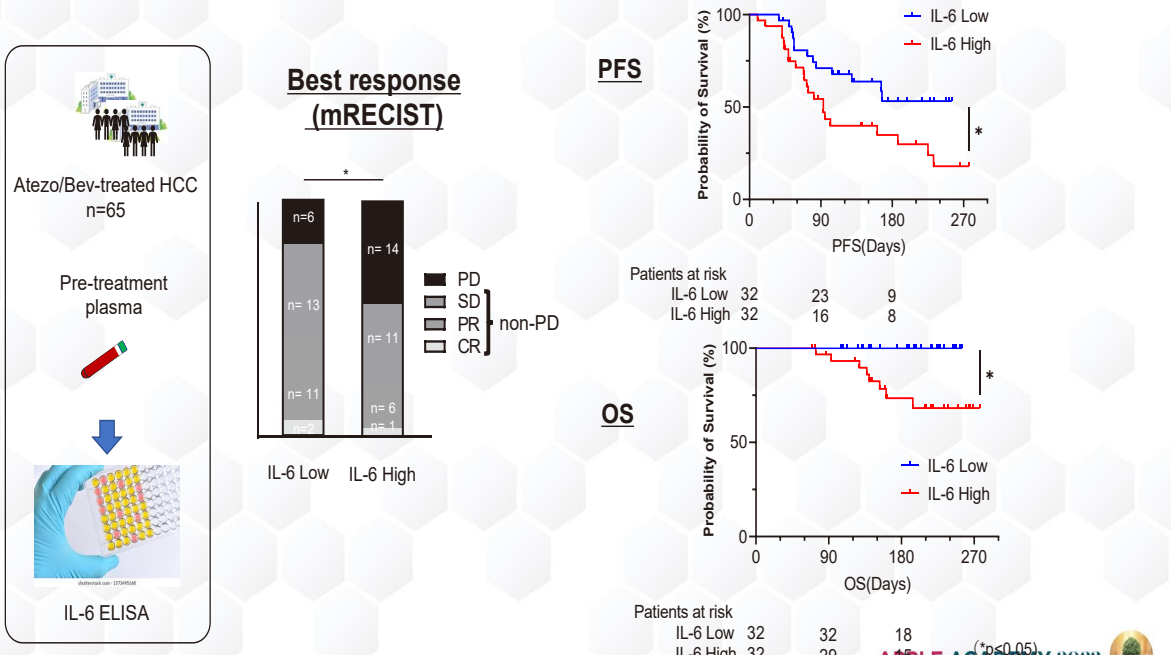
Hierarchical clustering using 34 plasma proteins



Plasma proteins related to initial PD

Variable	ODDs ratio	95% CI	FDR p value
CCL2	0.6	0.144-2.467	0.64
CCL3	0.2	0.035-1.132	0.41
CCL4	0.6	0.144-2.467	0.64
CCL7	0.9	0.139-5.811	1.00
CCL19	0.6	0.144-2.467	0.64
CX3CL1	1.7	0.4054-6.962	0.64
CXCL1	2.9	0.664-12.57	0.50
CXCL2	0.6	0.144-2.467	0.64
CXCL10	0.3	0.080-1.507	0.50
DKK1	1.7	0.405-6.962	0.64
Fas Ligand	1.0	0.245-4.08	1.00
Fas Receptor	0.6	0.144-2.47	0.64
GDF15	1.0	0.245-4.083	1.00
Granzyme B	1.0	0.245-4.083	1.00
HGF	1.0	0.245-4.083	1.00
IFNα	13.3	2.24-79.44	0.02
IFNγ	5.3	1.093-25.21	0.32
IL1β	2.9	0.663-12.57	0.50
IL2	1.4	0.339-5.79	0.81
IL4	3.5	0.795-15.40	0.50
IL5	2.0	0.244-16.36	0.68
IL6	13.3	2.234-79.438	0.02
IL7	0.6	0.144-2.467	0.64
IL8	1.7	0.405-6.962	0.64
IL10	2.0	0.475-8.434	0.64
IL12	1.7	0.405-6.962	0.64
IL18	1.7	0.405-6.962	0.64
MICA	1.0	0.245-4.08	1.00
PD-L1	0.3	0.080-1.507	0.50
TIE2	0.3	0.065-1.257	0.50
TNFα	0.6	0.137--2.445	0.64
TSP2	1.7	0.405-6.962	0.64
VEGF	1.7	0.405-6.962	0.64
VEGF-C	1.0	0.245-4.08	1.00

HCC patients with high plasma IL-6 levels had significantly shorter survival after Atezo/Bev therapy



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(Myojin Y, Kodama T(co-first) et al., ***Cancers*** 2022,10;14(4):883.)

Conclusion

Biomarkers based on TIME and/or liquid biopsy may be helpful to predict

treatment response and prognosis of HCC patients who underwent Atezo/Bev therapy

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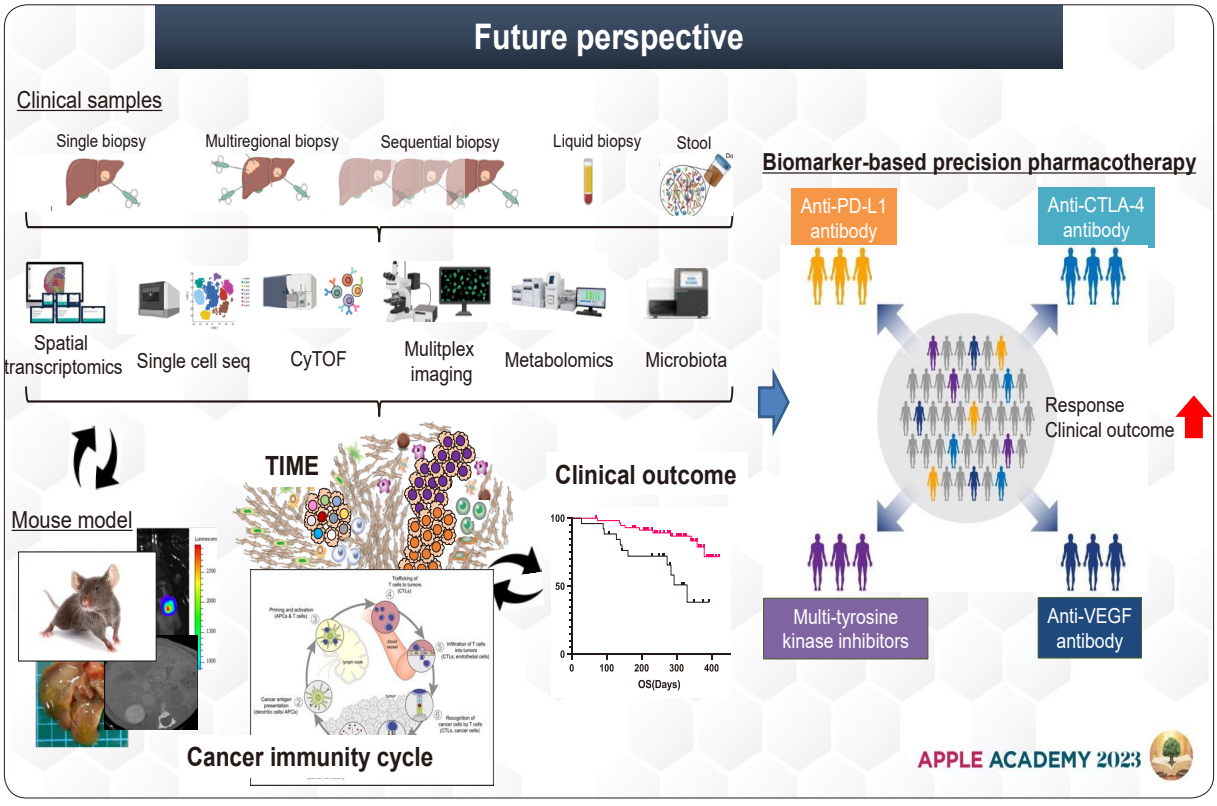
Future perspective
Clinical samples
Single biopsy
Multiregional biopsy
Sequential biopsy
Liquid biopsy
Stool
Spatial transcriptomics
Single cell seq
CyTOF
Mulitplex imaging
Metabolomics
Microbiota
Mouse model
TIME
Cancer immunity cycle
Clinical outcome
100
50
0
0
100
200
300
400
OS(Days)
Biomarker-based precision pharmacotherapy
Anti-PD-L1 antibody
Anti-CTLA-4 antibody
Response
Clinical outcome
Multi-tyrosine kinase inhibitors
Anti-VEGF antibody
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Translational Research: The Impact from Research in Epigenomics

Ah-Jung Jeon *(Mirxes, Singapore)*

The evolving definition of epigenetics/epigenomics

EVOLUTION

INTERNATIONAL JOURNAL OF ORGANIC EVOLUTION

PUBLISHED BY

THE SOCIETY FOR THE STUDY OF EVOLUTION

Vol. X MARCH, 1956 No. 1

GENETIC ASSIMILATION OF THE *BITHORAX* PHENOTYPE

C. H. WADDINGTON [1]

Institute of Animal Genetics, Edinburgh University, Scotland

Recieved March 17, 1955

INTRODUCTION

Some years ago it was suggested (Waddington, 1942) that if selection was practised for the readiness of a strain of organisms to respond to an environmental stimulus in a particular manner, genotypes might eventually be produced which would develop into the favoured phenotype even in the absence of the environmental stimulus. A character which had originally been an "acquired" one might then be said to have become genetically assimilated. An experimental investigation of the suggestion was carried out on *Drosophila melanogaster*, using a heat

fore thought desirable to investigate the genetic assimilation of other characters, so as to broaden the observational basis on which the theory rests. Mrs. K. G. Bateman in this laboratory has studied a number of rather mild developmental modifications, produced by temperature shocks applied to the pupa. These can perhaps be considered as of the same general type as the crossveinless phenotype previously investigated. The present communication deals with experiments on a phenocopy of a rather different character. This is the bithorax-like modification which can be produced by ether

"The fact that such a bizarre phenotype as bithorax can be assimilated, … suggests that the genetic assimilation mechanism is a very powerful one, which could have far-reaching effects during evolution."

Epigenetics is a field of study focused on changes in gene functions that do not involve alterations to the underlying DNA sequence.

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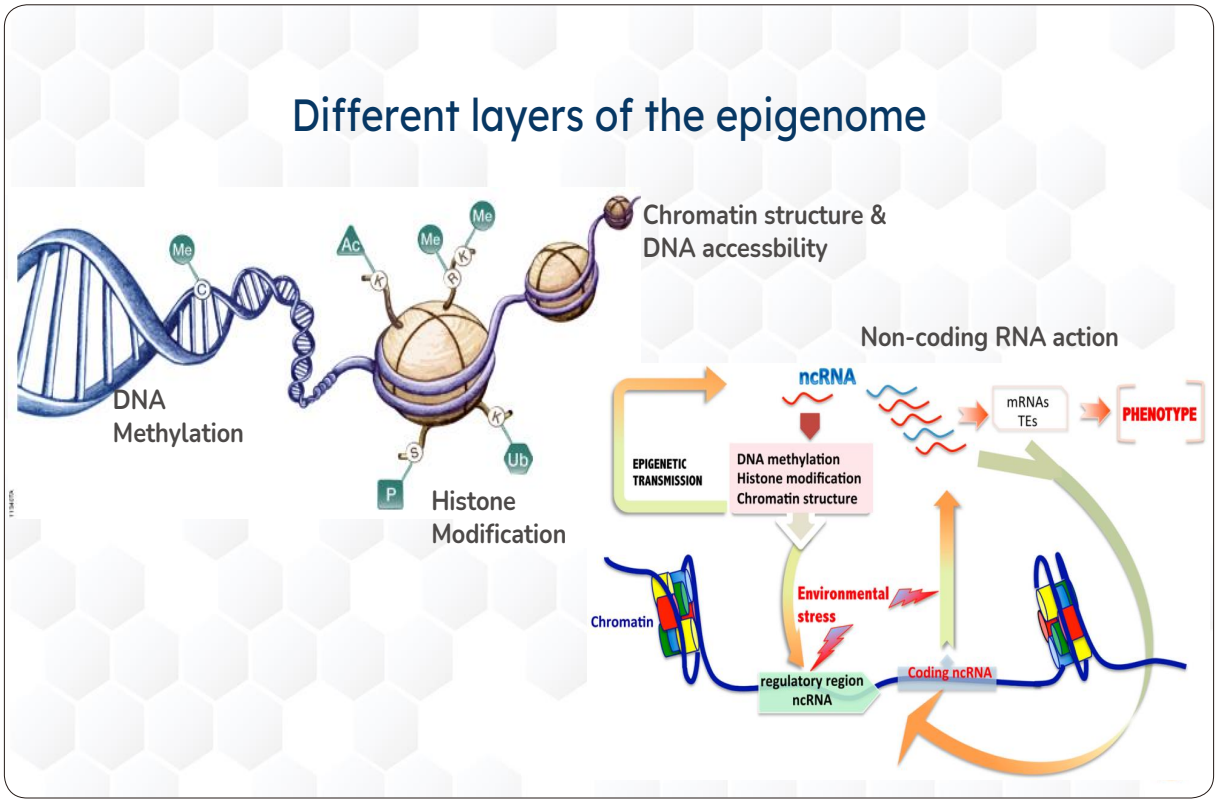
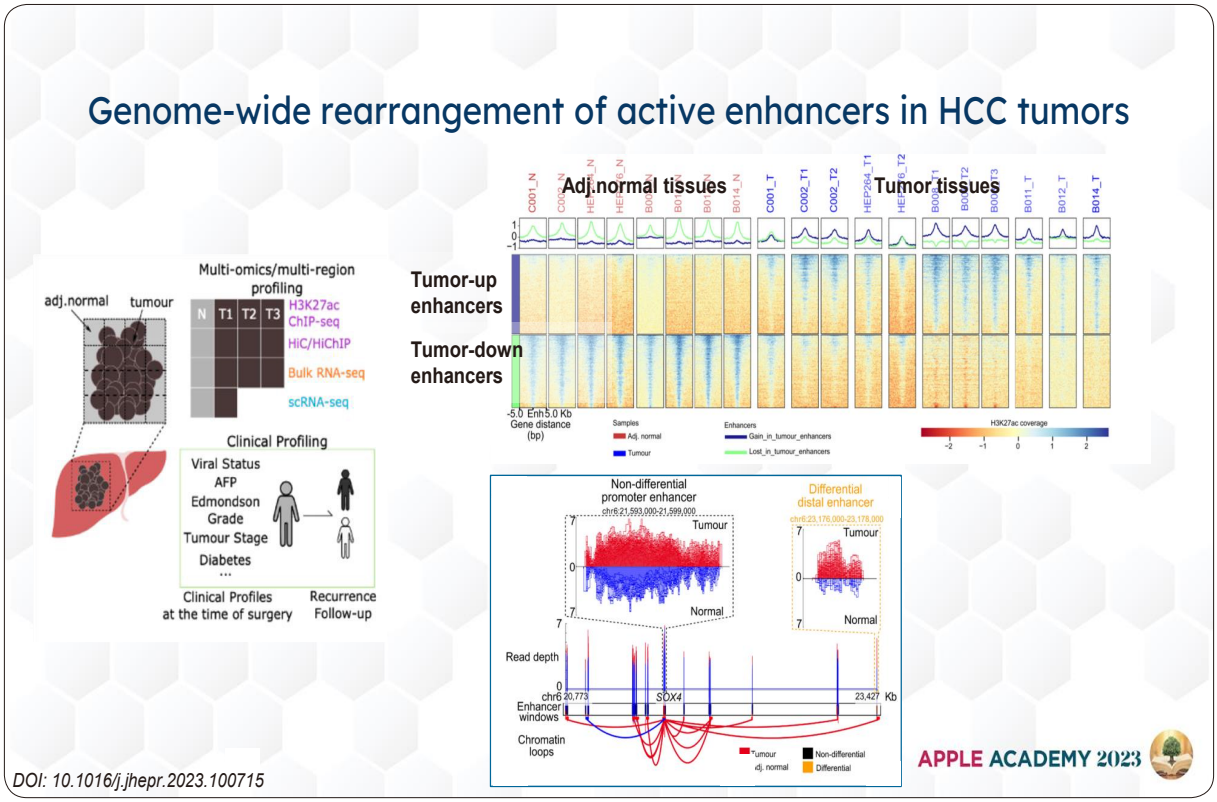
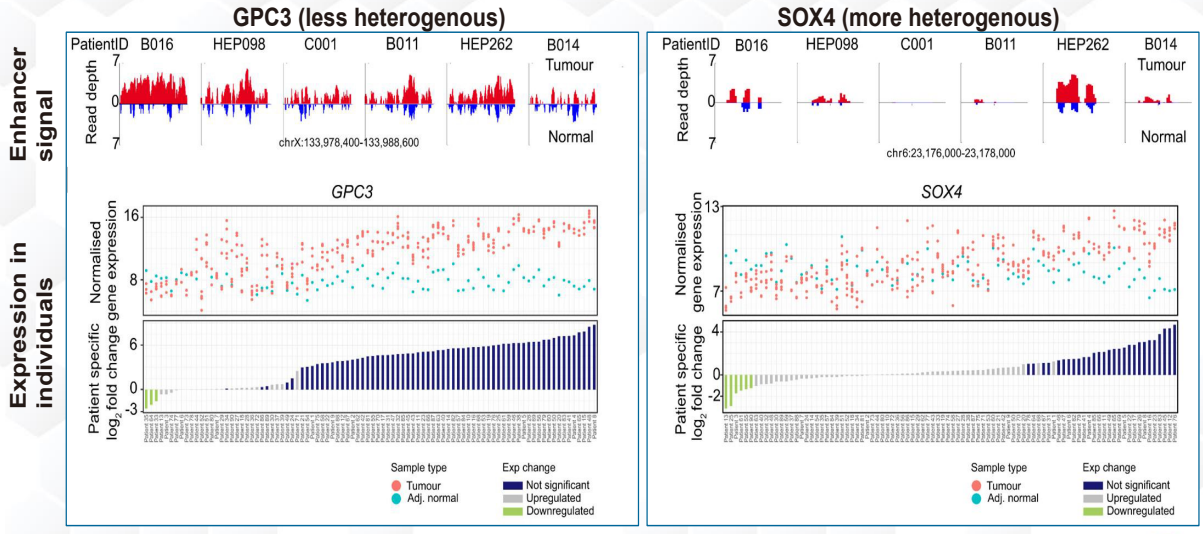




DOI: 10.1016/j.jhepr.2023.100715

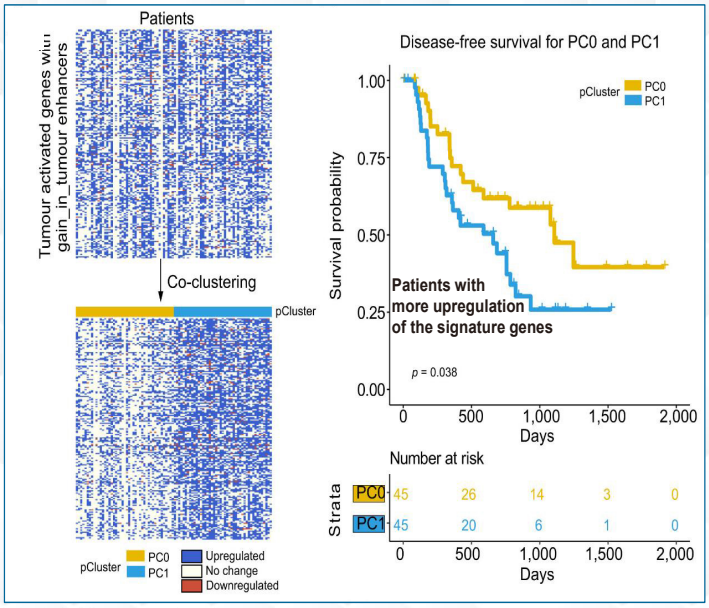
Genes with differential enhancers show high degree of heterogeneity in both H3K27ac signal and gene expression

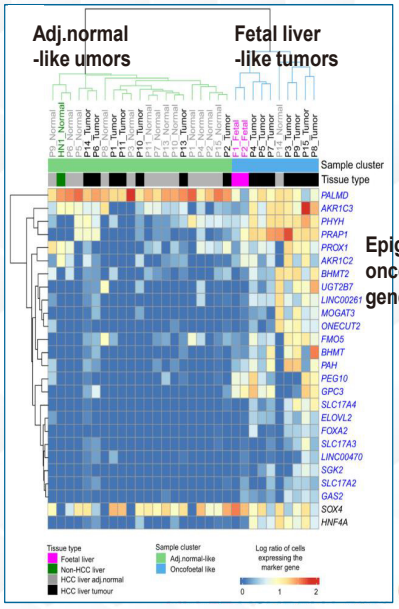


APPLE ACADEMY 2023

DOI: 10.1016/j.jhepr.2023.100715

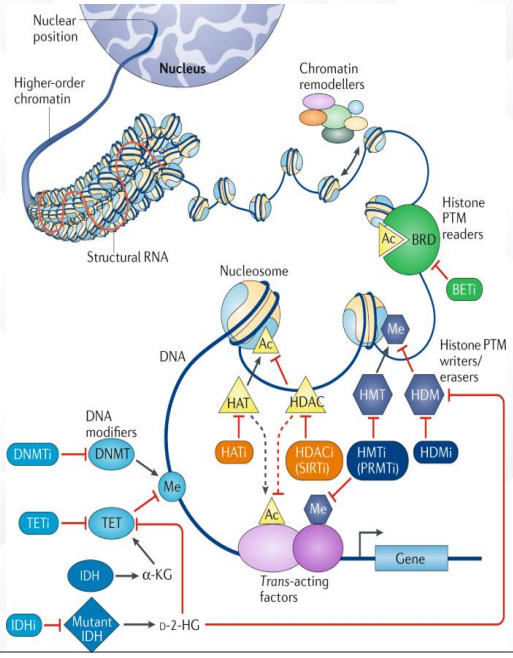
Gain-in-tumour enhancer associated genes, which were upregulated in some patients' tumours, showed prognostic value





DOI: 10.1016/j.jhepr.2023.100715

Applications - therapeutic biomarkers



E.g. HDAC inhibitors

- The first results are promising.
- Heterogeneity in the histone acetylation in HCC means varying patient response to treatment.
- Strong need for biomarkers to identify optimal clinical applications and patient subgroup who will most likely benefit from the treatment.
- Advised to establish HDACi as a targeted therapeutic approach against HCC

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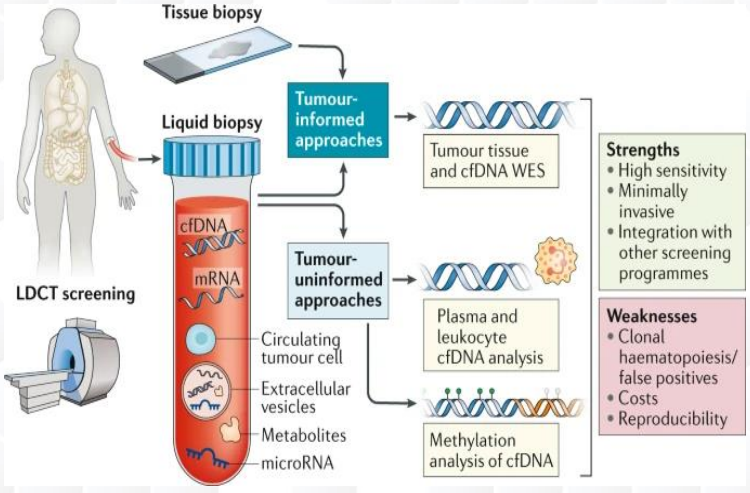
Applications - diagnostic biomarkers



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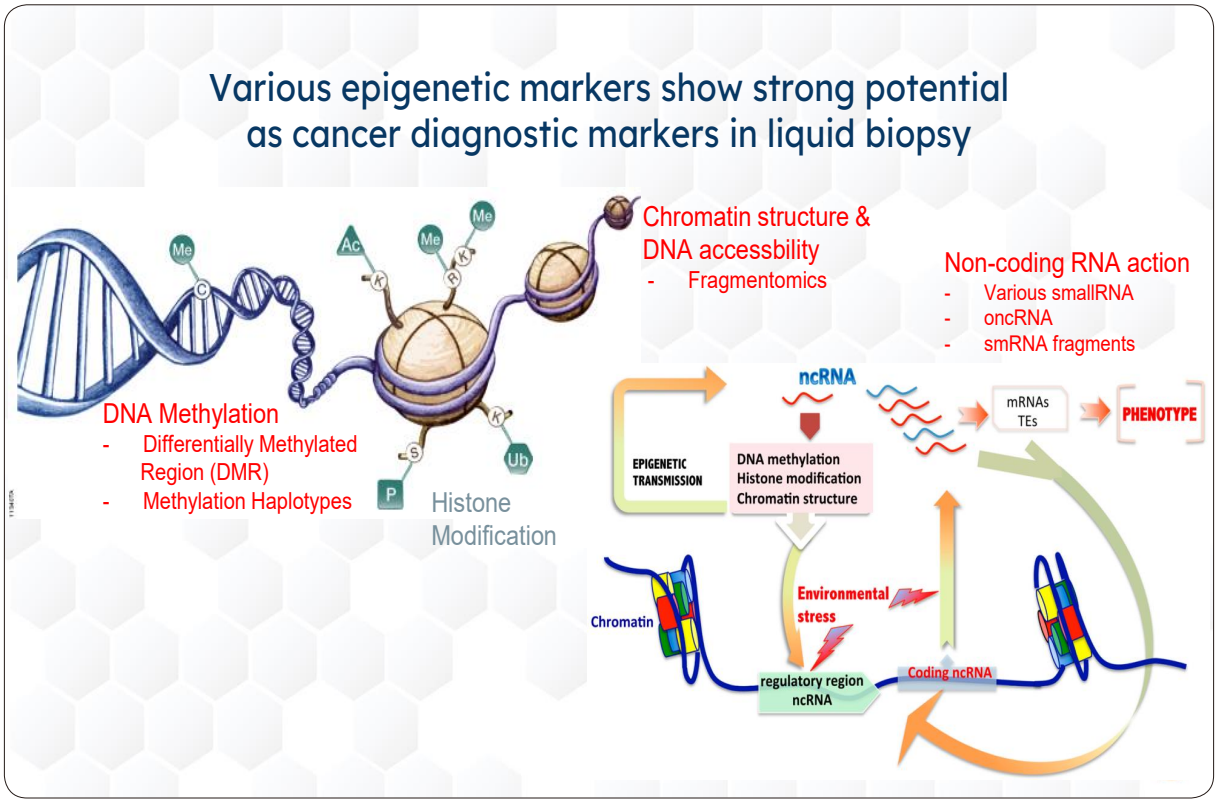
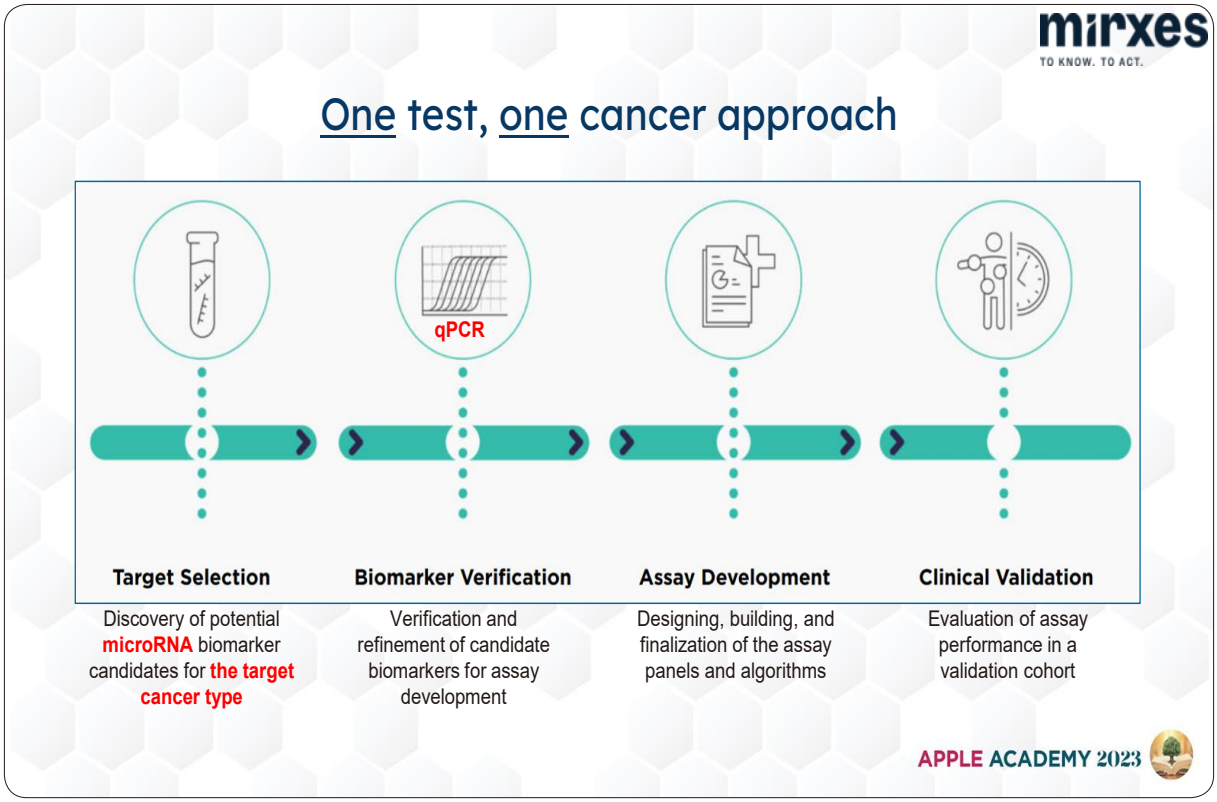

Various epigenetic markers show strong potential as cancer diagnostic markers in liquid biopsy
DNA Methylation
- Differentially Methylated Region (DMR)
- Methylation Haplotypes
Histone Modification
Chromatin structure & DNA accessbility
- Fragmentomics
Non-coding RNA action
- Various smallRNA
- oncRNA
- smRNA fragments
ncRNA
mRNAs TEs
PHENOTYPE
EPIGENETIC TRANSMISSION
DNA methylation
Histone modification
Chromatin structure
Environmental stress
Chromatin
regulatory region ncRNA
Coding ncRNA


mirxes
TO KNOW. TO ACT.
One test, one cancer approach
qPCR
Target Selection
Discovery of potential microRNA biomarker candidates for the target cancer type
Biomarker Verification
Verification and refinement of candidate biomarkers for assay development
Assay Development
Designing, building, and finalization of the assay panels and algorithms
Clinical Validation
Evaluation of assay performance in a validation cohort
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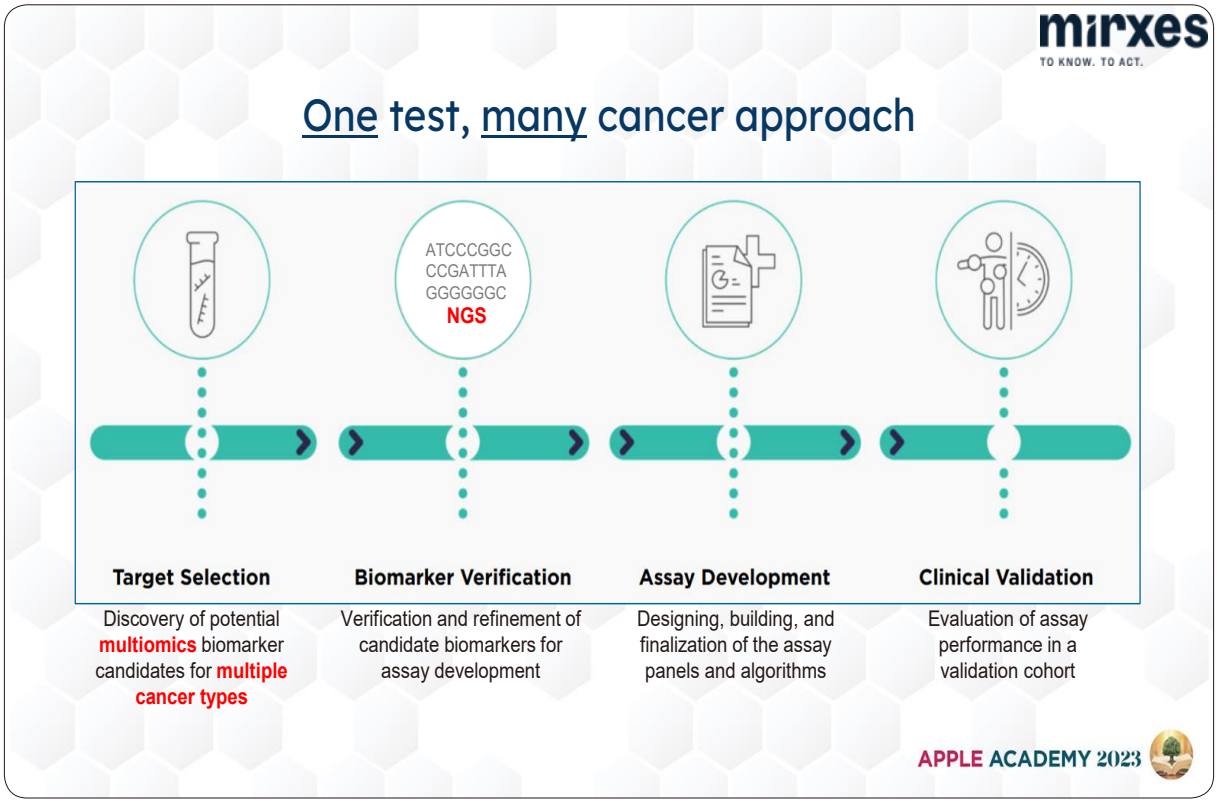
mirxes
TO KNOW. TO ACT.
One test, many cancer approach
ATCCCGGC
CCGATTTA
GGGGGGC
NGS
Target Selection
Biomarker Verification
Assay Development
Clinical Validation
Discovery of potential multiomics biomarker candidates for multiple cancer types
Verification and refinement of candidate biomarkers for assay development
Designing, building, and finalization of the assay panels and algorithms
Evaluation of assay performance in a validation cohort
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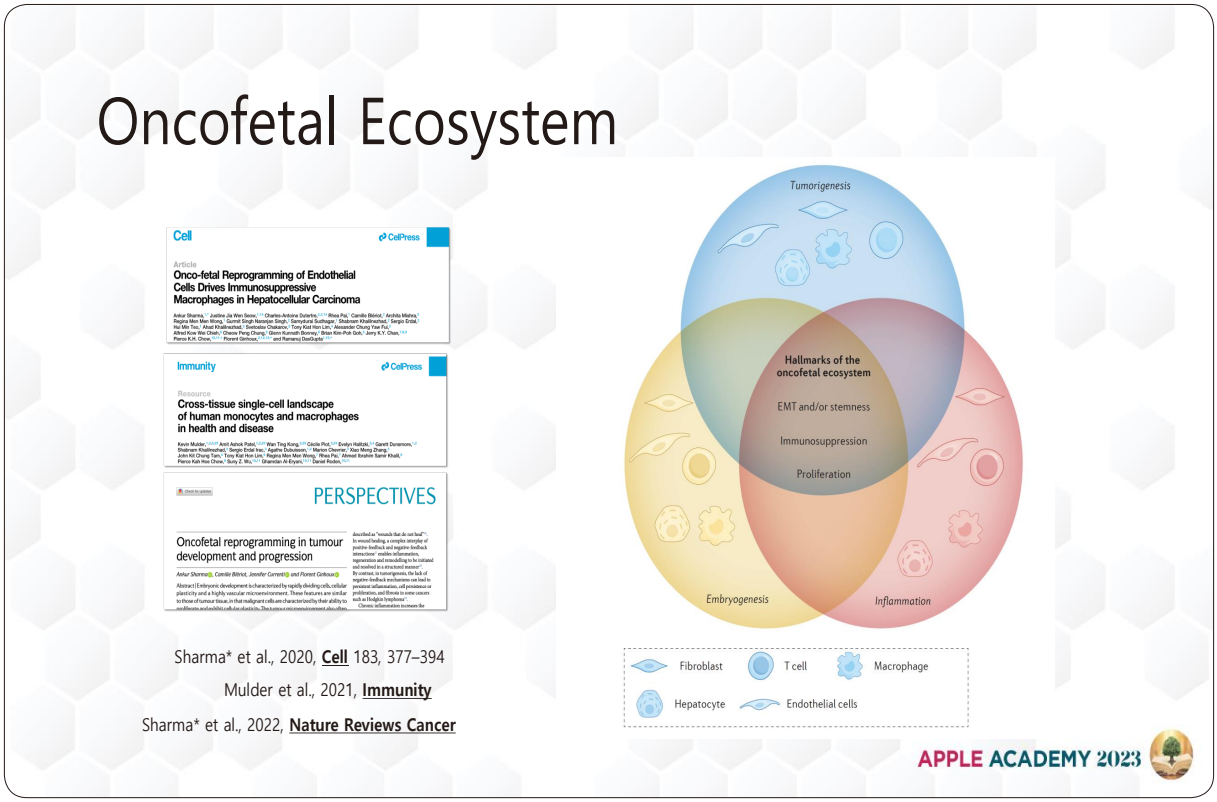
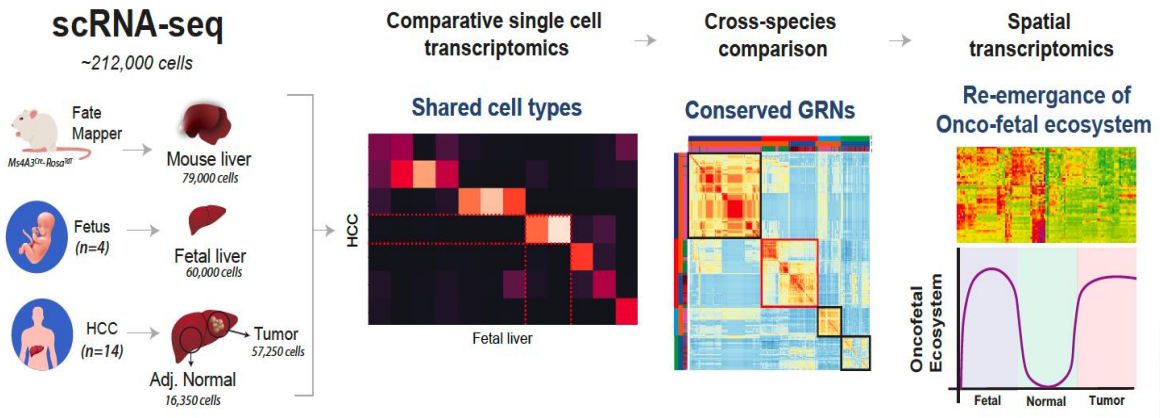
Translational Research: The Impact from Research in Spatial Transcriptomics

Ankur Sharma *(Harry Perkins Institute of Medical Research, Perth)*



scRNA-seq atlas of Liver from Development to Disease



Sharma et al., 2020, Cell 183, 377–394

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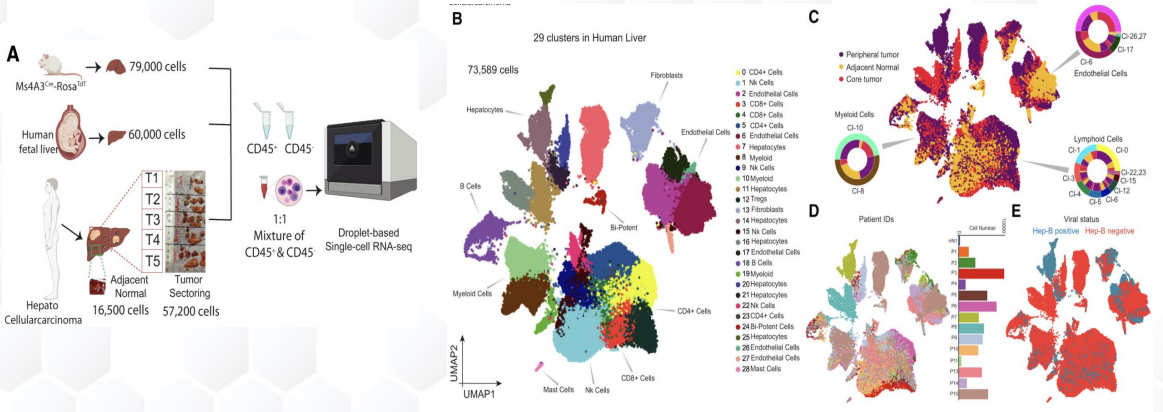
scRNA-seq atlas of Liver from Development to Disease



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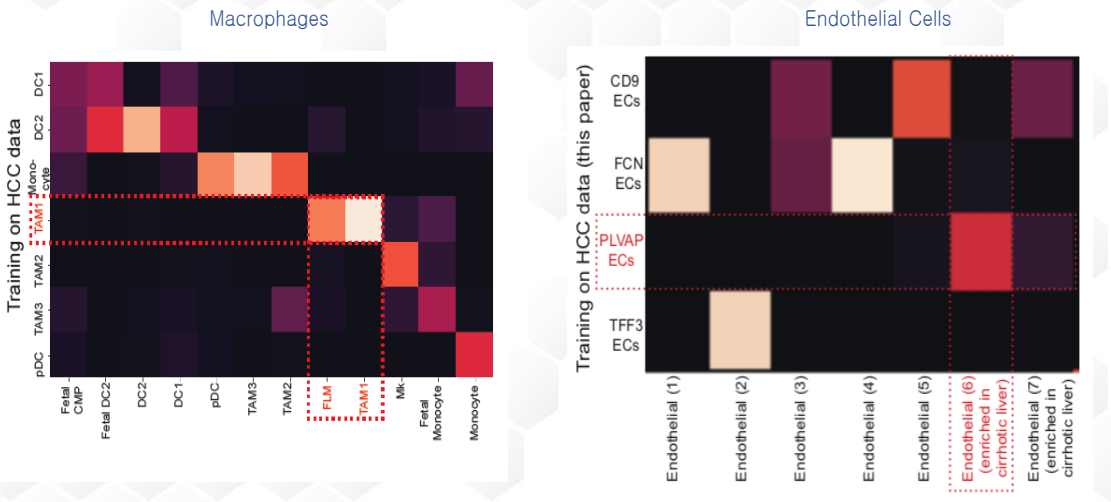
Oncofetal ecosystem: Fetal-like macrophages and endothelial cells in HCC



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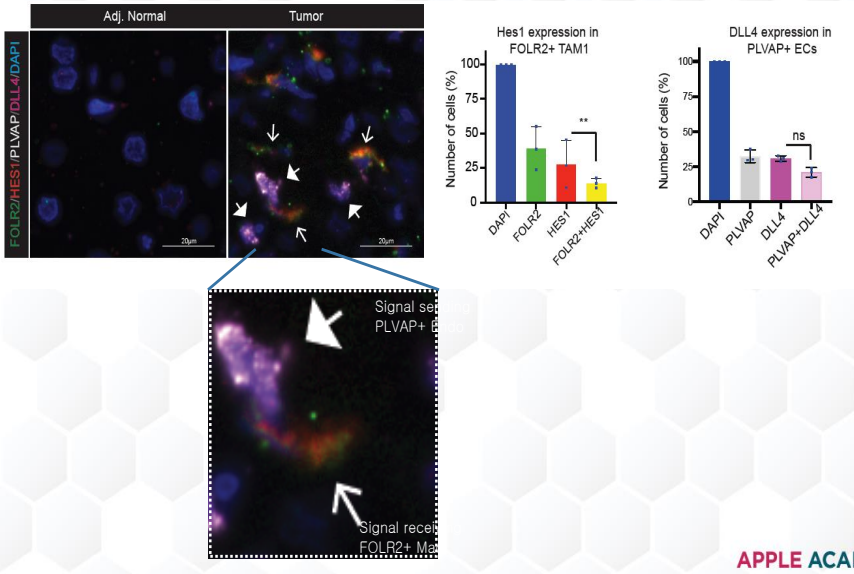
DLL4-Notch communication leads to oncofetal reprogramming of TAMs



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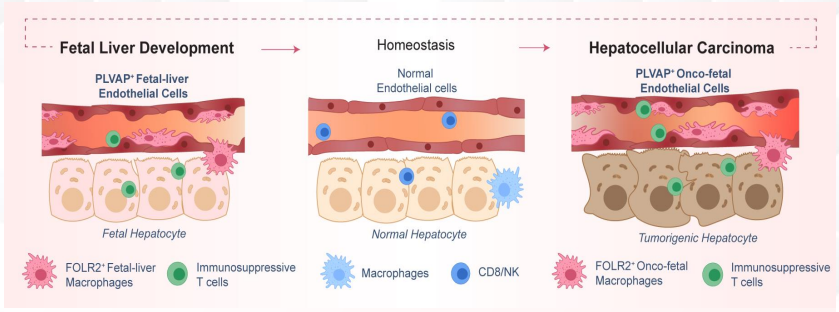

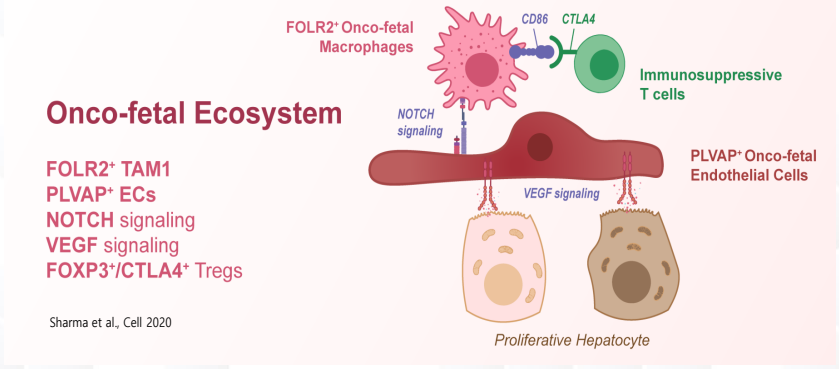

Onco-fetal Ecosystem

FOLR2⁺ TAM1
PLVAP⁺ ECs
NOTCH signaling
VEGF signaling
FOXP3⁺/CTLA4⁺ Tregs

Sharma et al., Cell 2020

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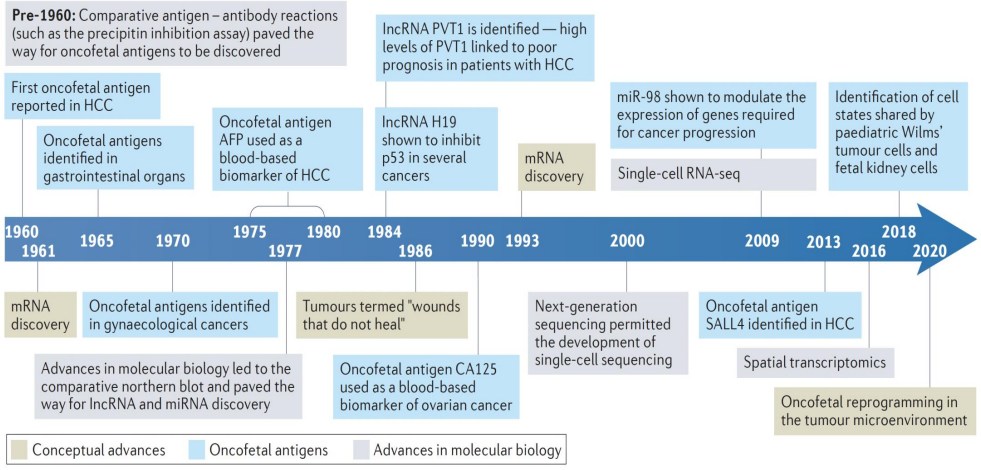

Sharma* et al., 2022, **Nature Reviews Cancer**

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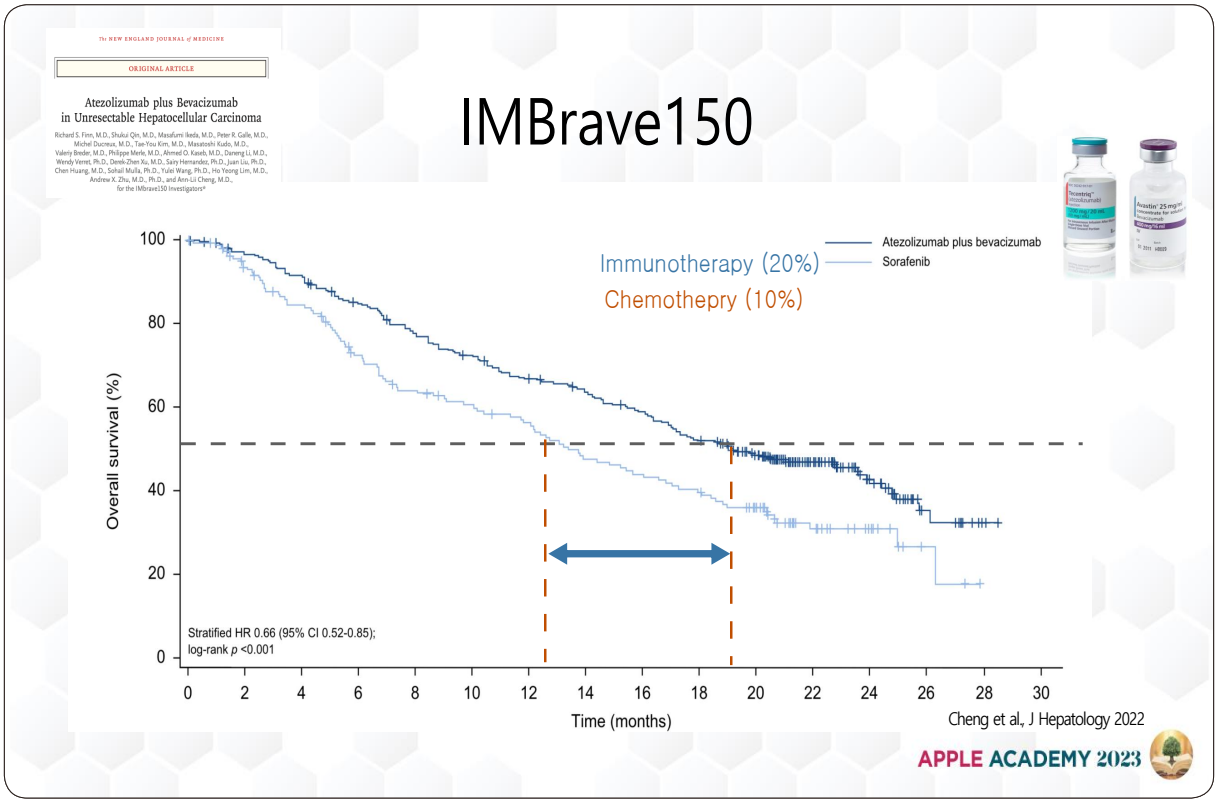
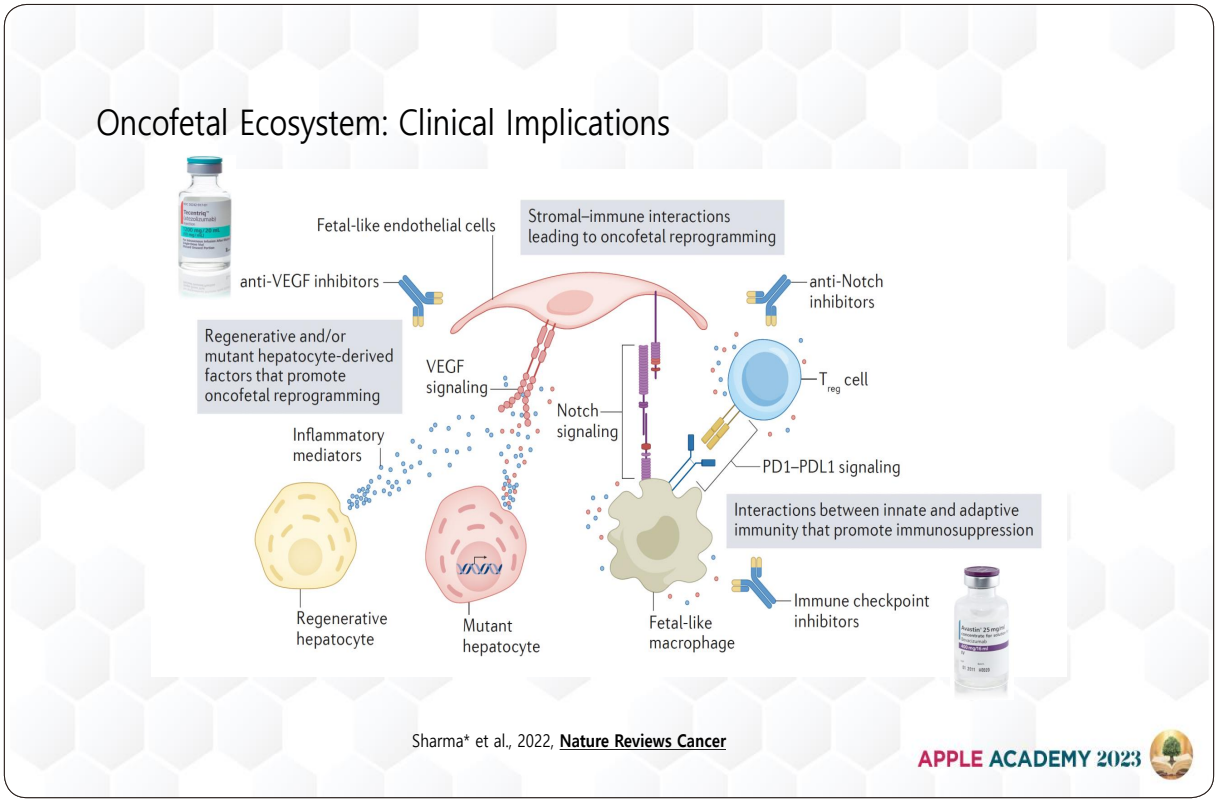
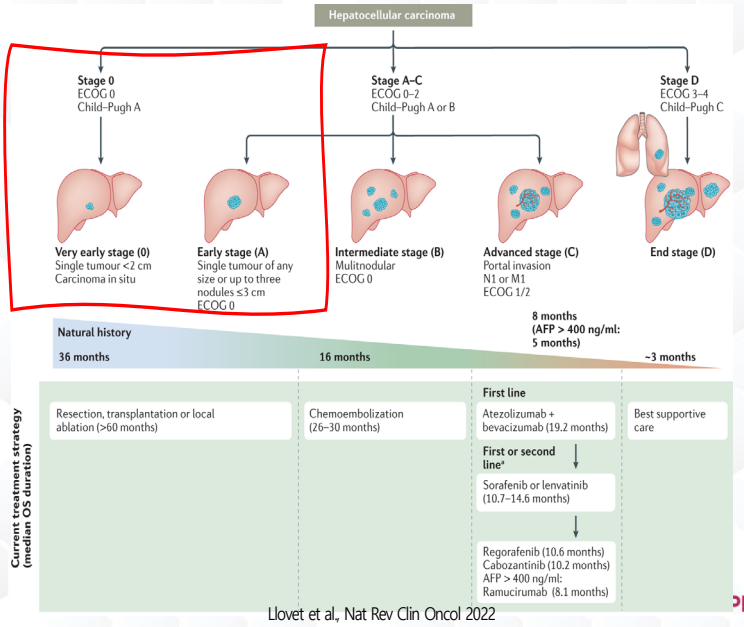

IMBrave150
Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma
Immunotherapy (20%)
Chemotheprу (10%)
Atezolizumab plus bevacizumab
Sorafenib
Overall survival (%)
Time (months)
Stratified HR 0.66 (95% CI 0.52-0.85); log-rank p <0.001
Cheng et al, J Hepatology 2022
APPLE ACADEMY 2023

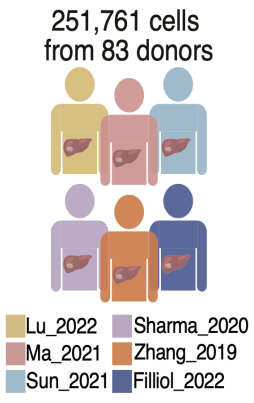

Oncofetal Ecosystem: Clinical Implications
Fetal-like endothelial cells
Stromal–immune interactions leading to oncofetal reprogramming
anti-VEGF inhibitors
anti-Notch inhibitors
Regenerative and/or mutant hepatocyte-derived factors that promote oncofetal reprogramming
VEGF signaling
Notch signaling
T reg cell
Inflammatory mediators
PD1–PDL1 signaling
Interactions between innate and adaptive immunity that promote immunosuppression
Immune checkpoint inhibitors
Regenerative hepatocyte
Mutant hepatocyte
Fetal-like macrophage
Sharma* et al., 2022, Nature Reviews Cancer
APPLE ACADEMY 2023

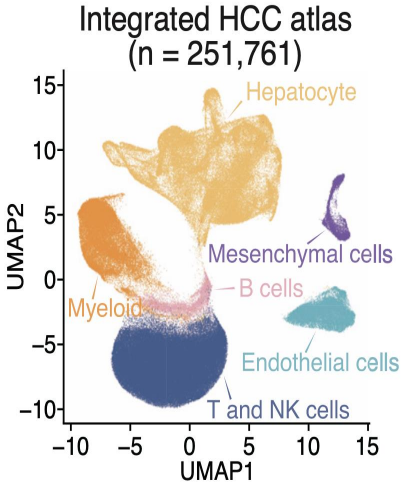
Heterogeneity of HCC and treatment strategies



Llovet et al., Nat Rev Clin Oncol 2022

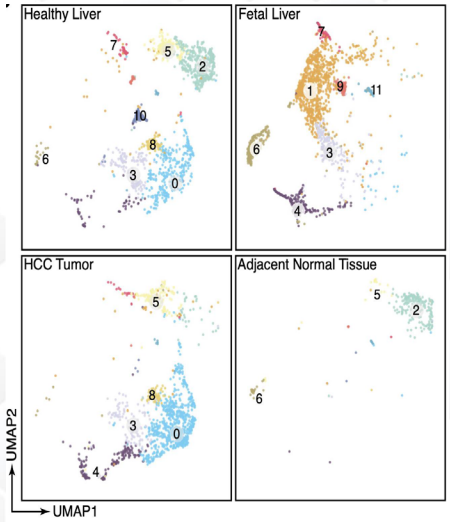
Integrating HCC scRNA-seq datasets to identify new oncofetal cell type





Ziyi,..Chow*, Ginhoux*, Sharma*, *(pending minor revisions)*

Identification of new oncofetal stromal cells



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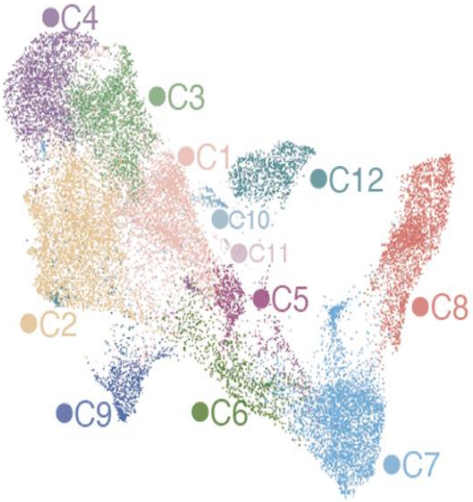
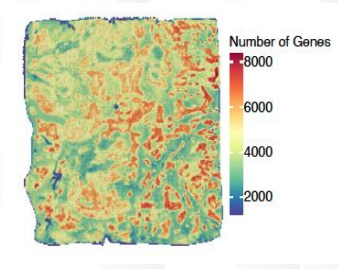
Spatial Transcriptomics

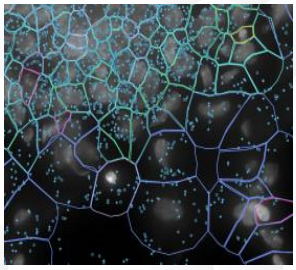


APPLE ACADEMY 2023

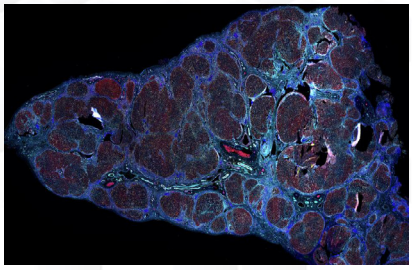
Spatial Transcriptomics



Whole Genome
STOMics (BGI)



Targeted probes
Xenium (10x)



30-100 protein markers
Photocycler (AKOYA)

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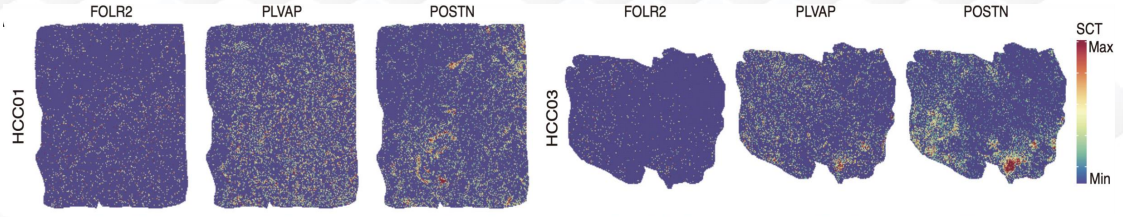
Oncofetal cells are localized in specific 'ecozones' in liver tissue



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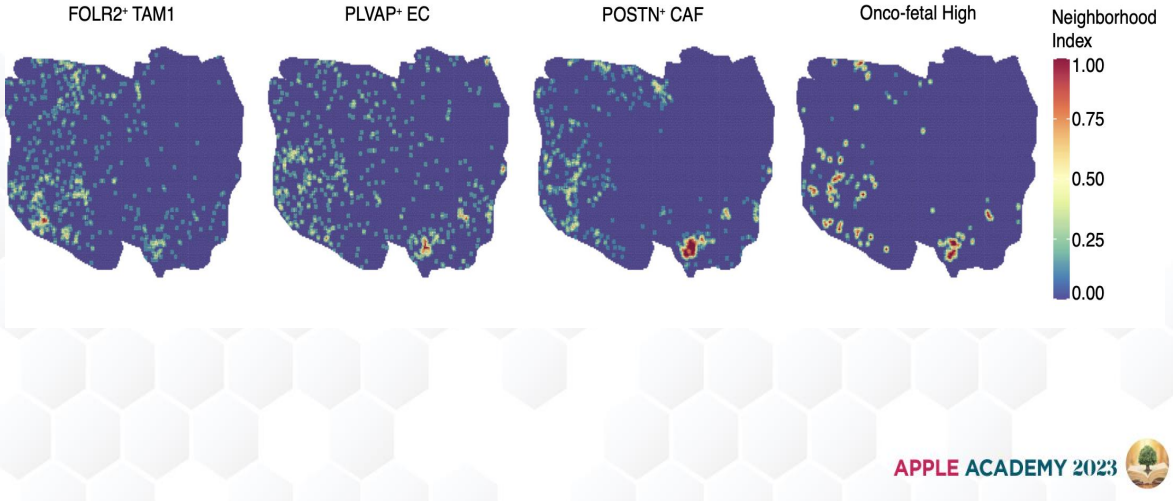
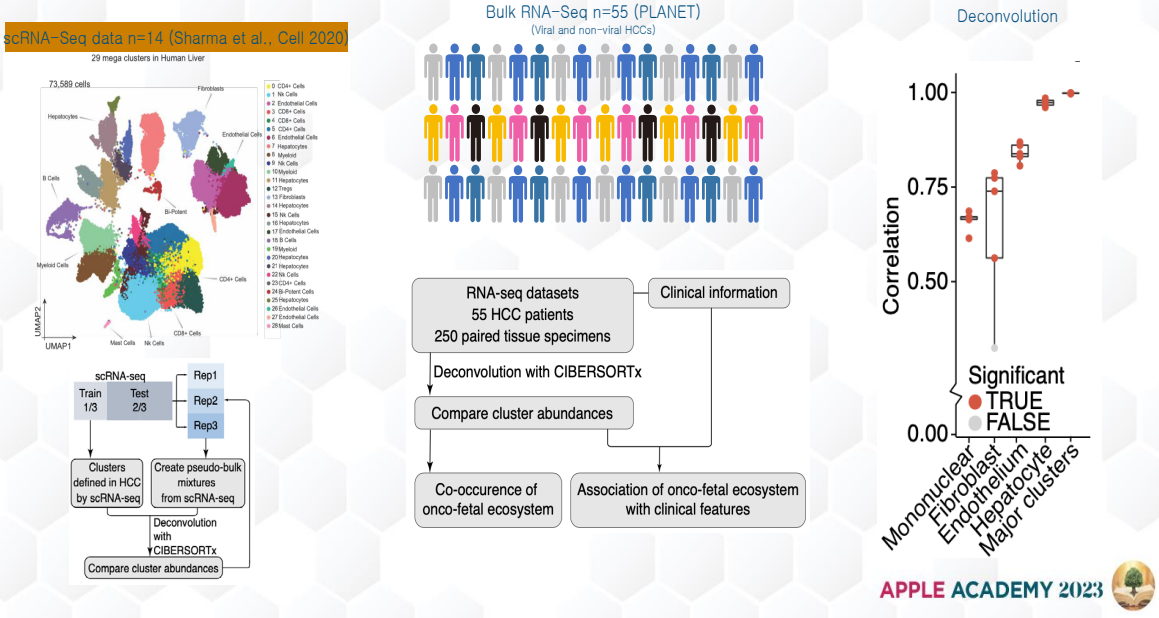
Oncofetal Neighbourhood: A suburb of immunosuppressive activities

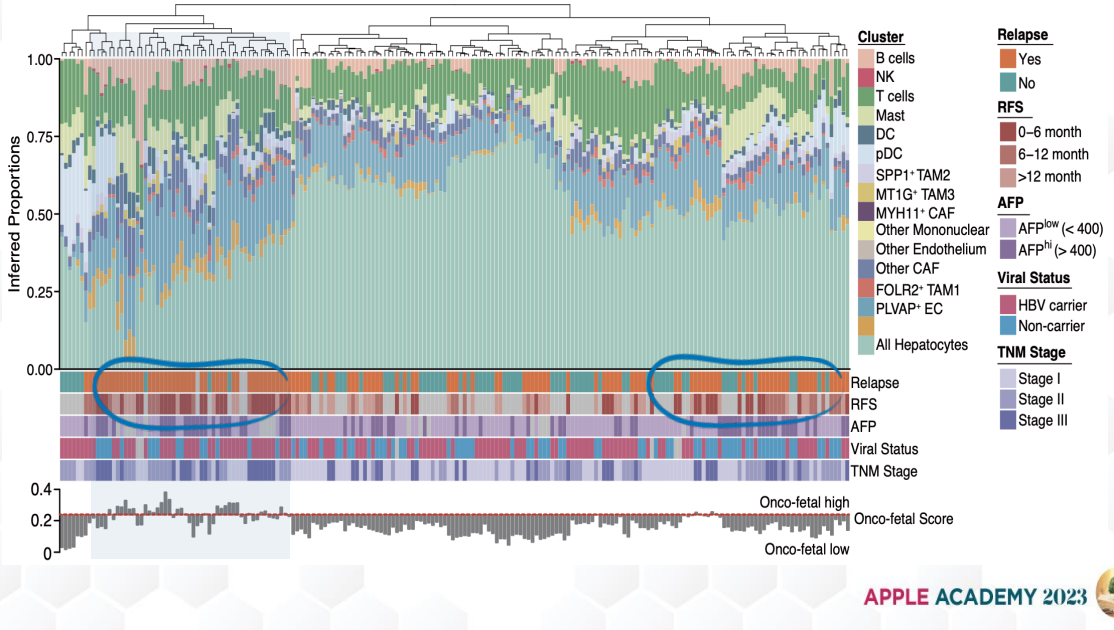
Oncofetal Neighbourhood: A suburb of immunosuppressive activities



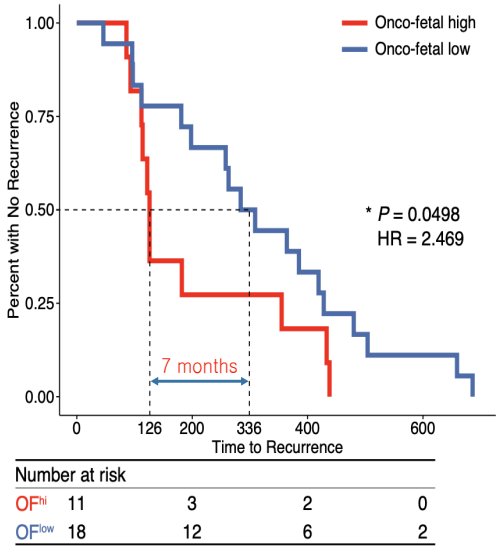
Lessons from PLANET1.0 cohort- Oncofetal score for precision oncology



Lessons from PLANET1.0 cohort- Oncofetal score for precision oncology

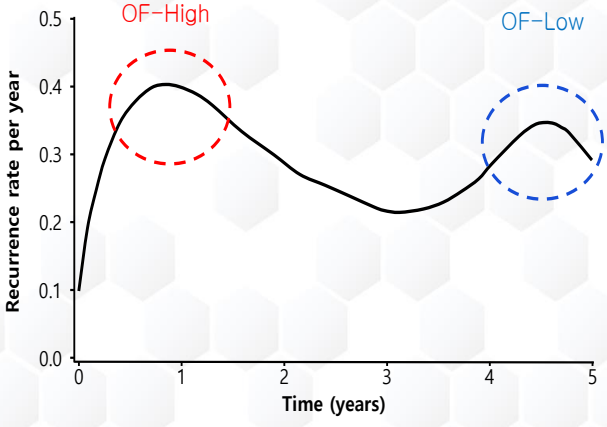


Oncofetal ecosystem score can stratify therapy response in HCC

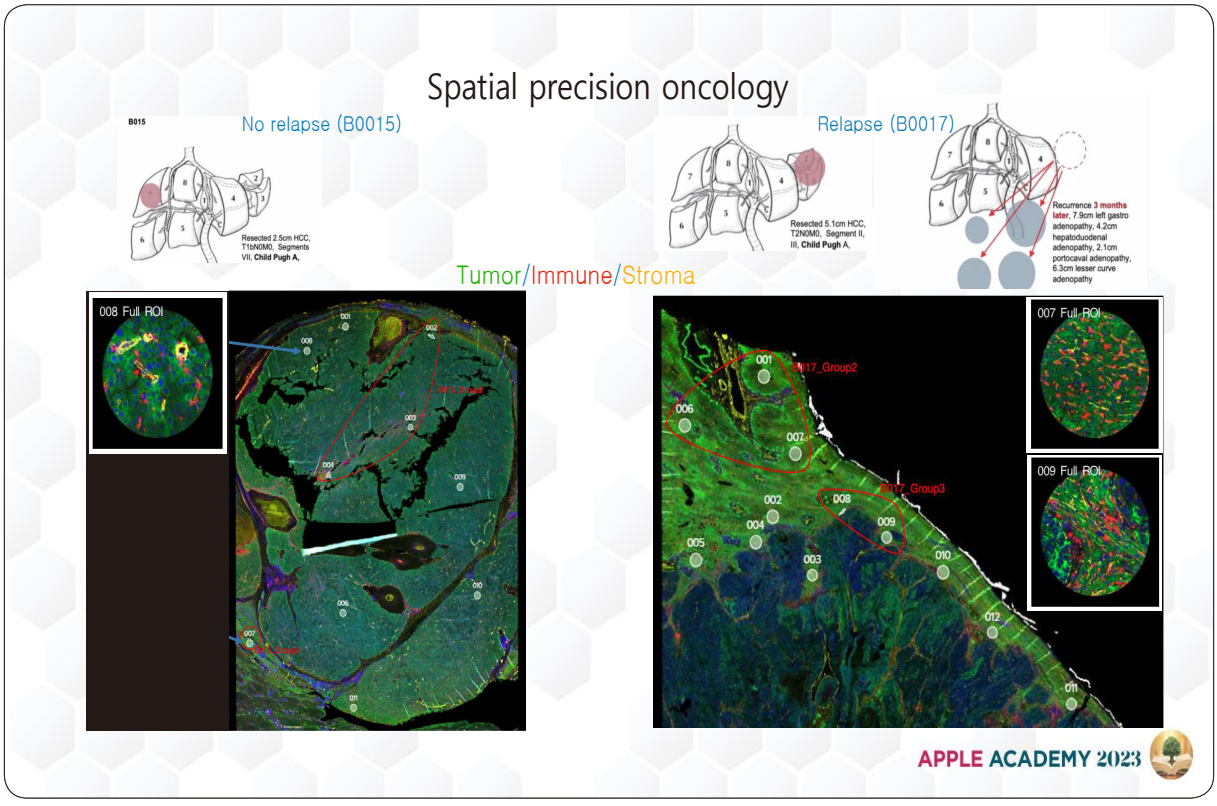


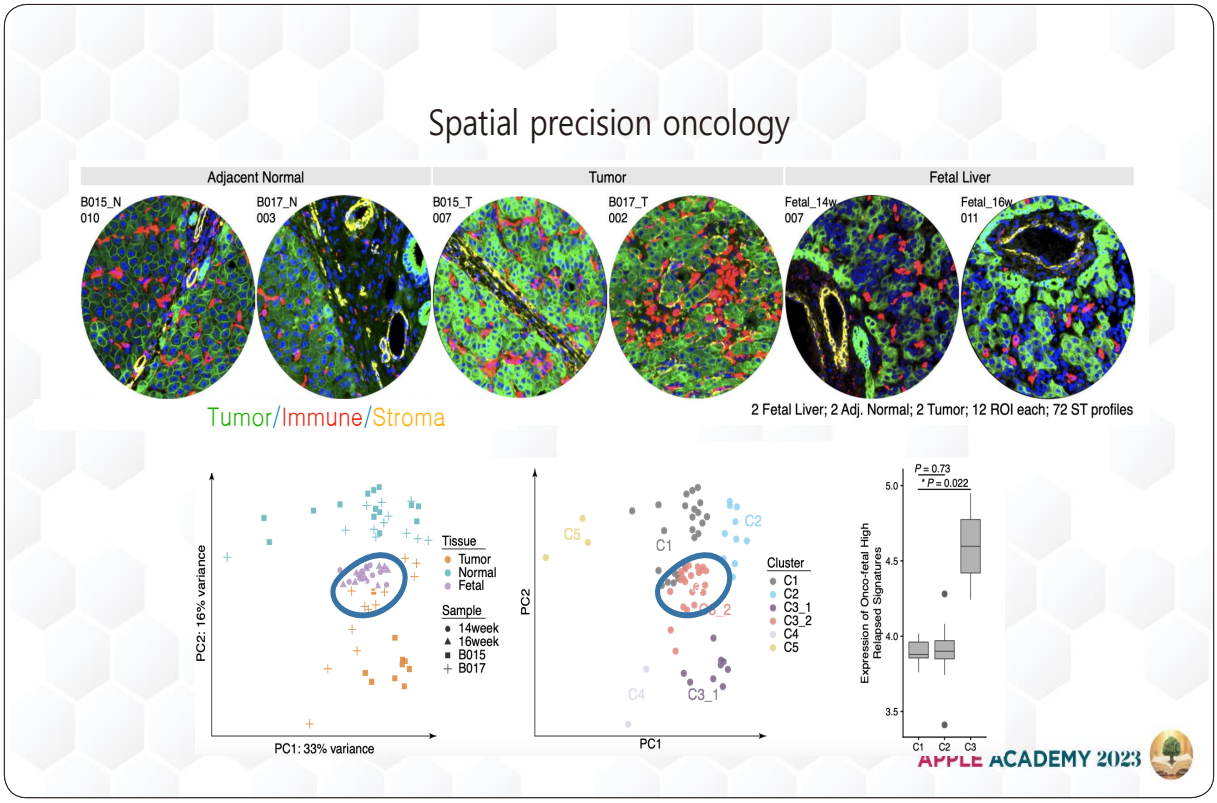
APPLE ACADEMY 2023

Oncofetal ecosystem score can stratify therapy response in HCC



APPLE ACADEMY 2023


Spatial precision oncology
No relapse (B0015)
Relapse (B0017)
Resected 2.5cm HCC, T1bN0M0, Segments VII, Child Pugh A,
Resected 5.1cm HCC, T2N0M0, Segment II, III, Child Pugh A,
Recurrence 3 months later, 7.9cm left gastro adenopathy, 4.2cm hepatoduodenal adenopathy, 2.1cm portocaval adenopathy, 6.3cm lesser curve adenopathy
Tumor/Immune/Stroma
008 Full ROI
007 Full ROI
009 Full ROI
B017_Group2
B017_Group3
APPLE ACADEMY 2023


Spatial precision oncology
Adjacent Normal
Tumor
Fetal Liver
B015_N 010
B017_N 003
B015_T 007
B017_T 002
Fetal_14w 007
Fetal_16w 011
Tumor/Immune/Stroma
2 Fetal Liver; 2 Adj. Normal; 2 Tumor; 12 ROI each; 72 ST profiles
PC2: 16% variance
PC1: 33% variance
Tissue
Tumor
Normal
Fetal
Sample
14week
16week
B015
B017
PC2
PC1
Cluster
C1
C2
C3_1
C3_2
C4
C5
P = 0.73
* P = 0.022
Expression of Onco-fetal High Relapsed Signatures
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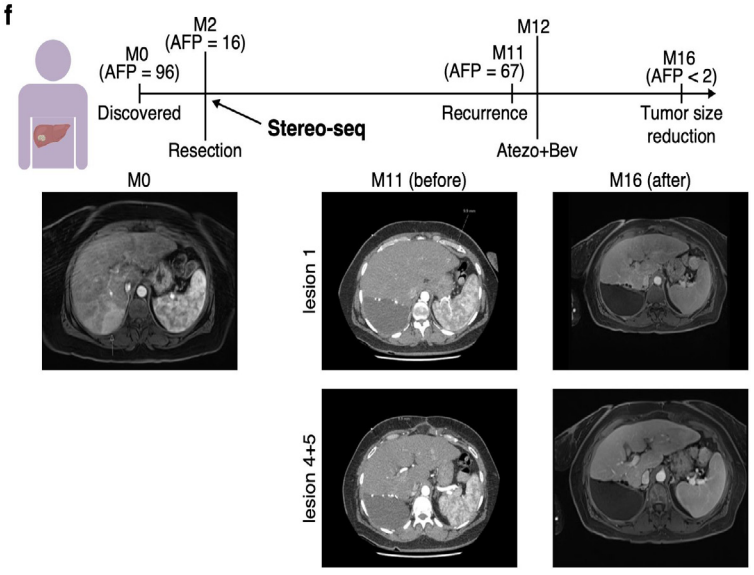
Spatial precision oncology for companion diagnostics



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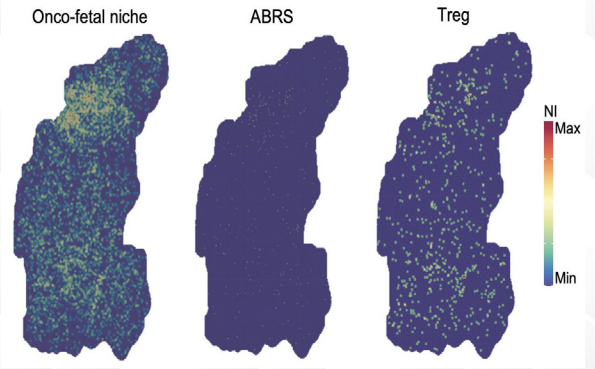
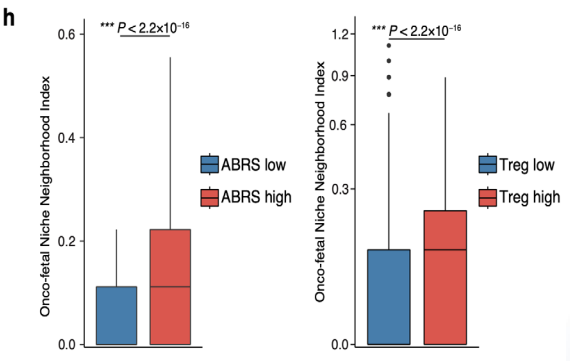
Spatial precision oncology for companion diagnostics





Ziyi,..Chow*, Ginhoux*, Sharma*, *(pending minor revisions)*

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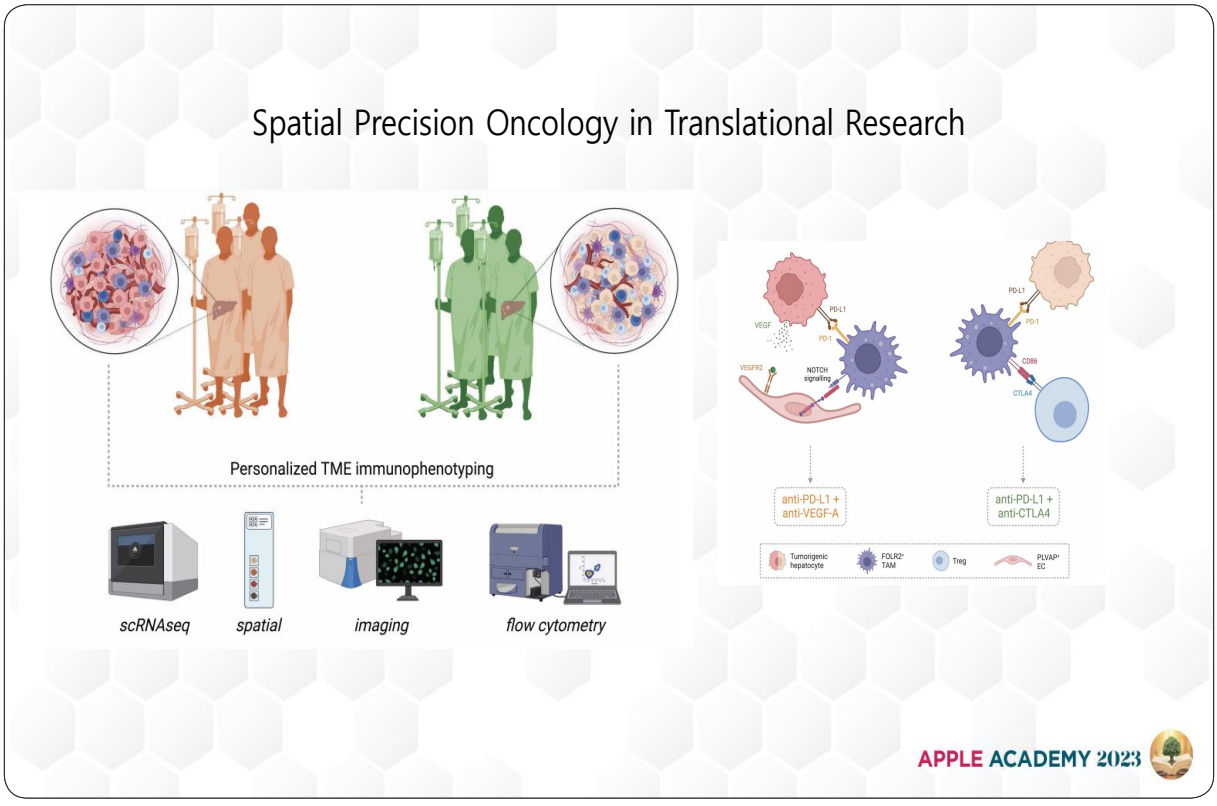
Spatial Precision Oncology in Translational Research
Personalized TME immunophenotyping
scRNAseq
spatial
imaging
flow cytometry
anti-PD-L1 + anti-VEGF-A
anti-PD-L1 + anti-CTLA4
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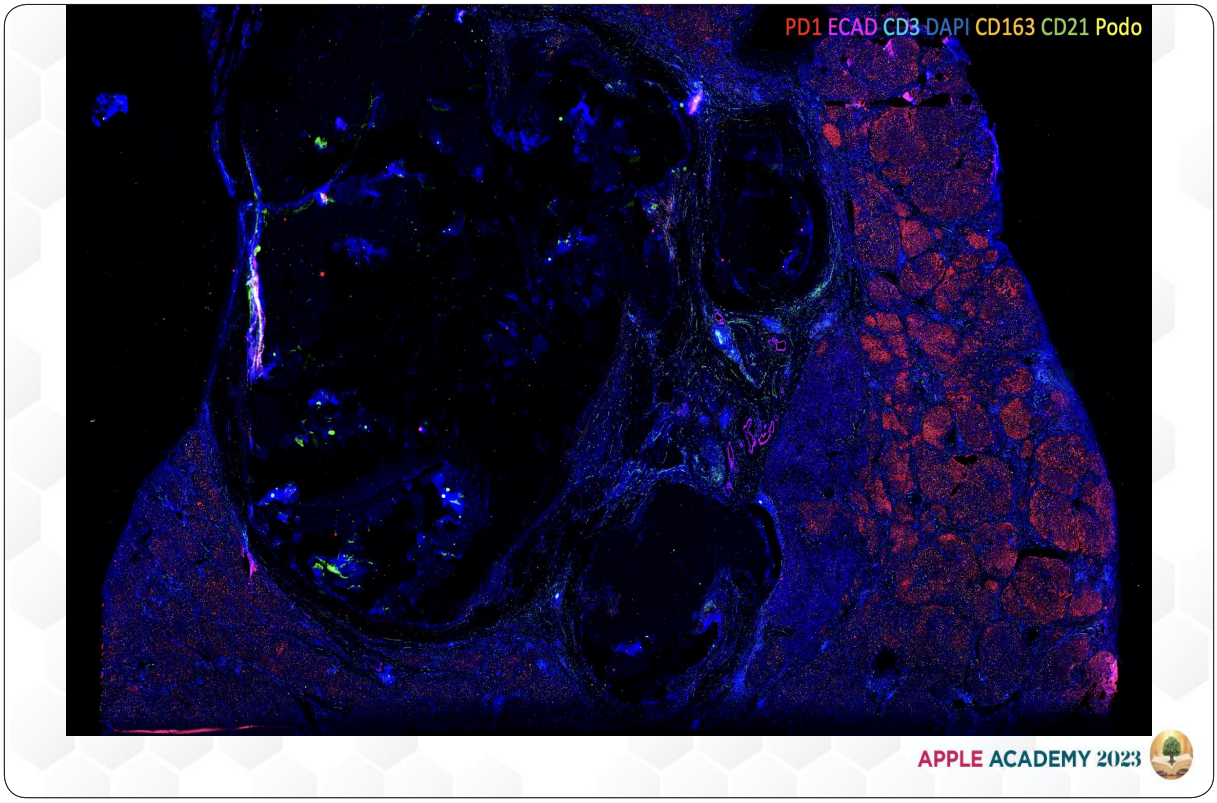
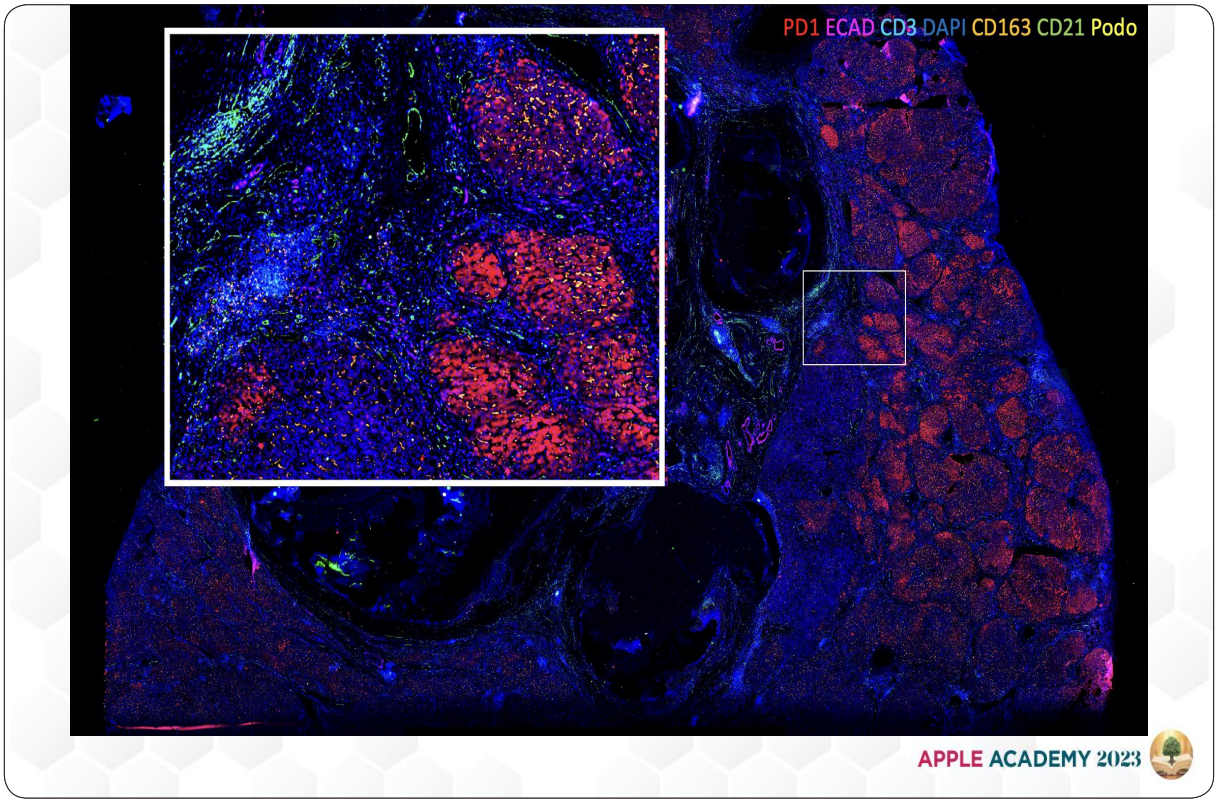
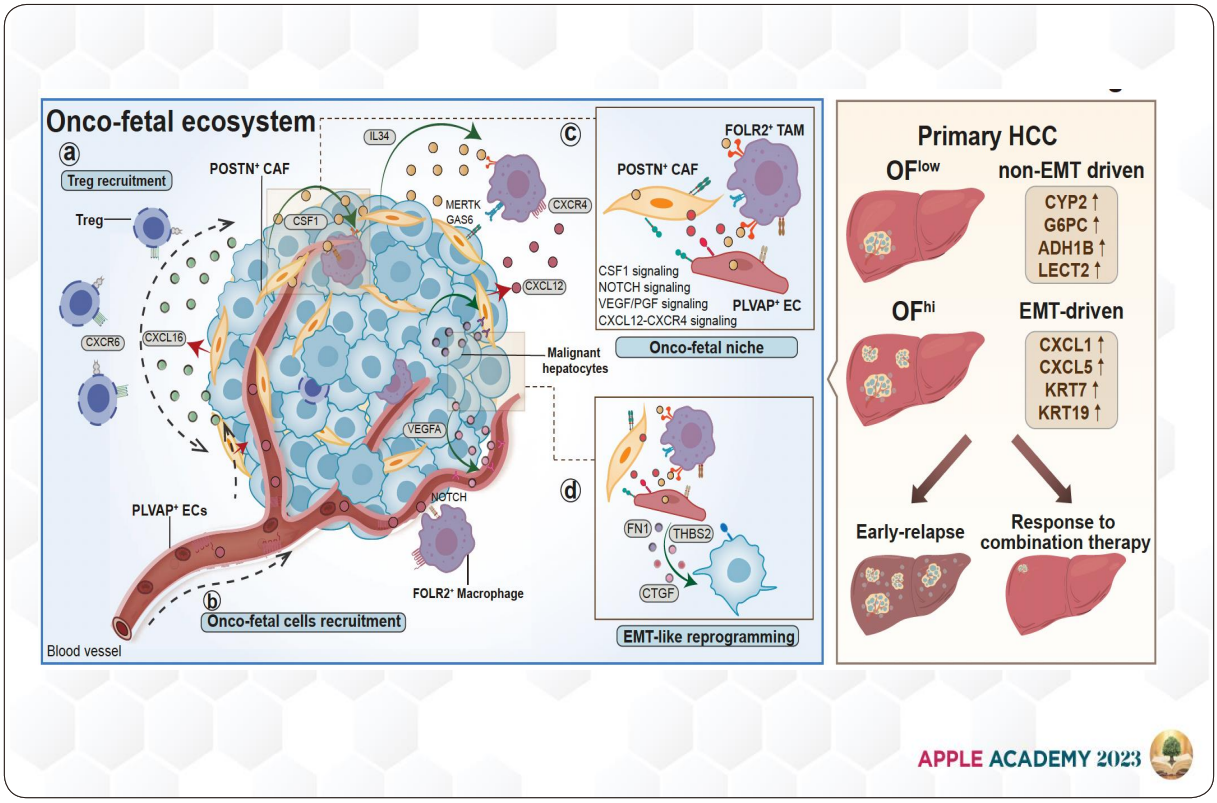

PD1 ECAD CD3 DAPI CD163 CD21 Podo
APPLE ACADEMY 2023


PD1 ECAD CD3 DAPI CD163 CD21 Podo
APPLE ACADEMY 2023


Onco-fetal ecosystem
a
Treg recruitment
POSTN+ CAF
Treg
CSF1
IL34
MERTK
GAS6
CXCR4
CXCL12
CXCR6
CXCL16
VEGFA
NOTCH
PLVAP+ ECs
FOLR2+ Macrophage
b
Onco-fetal cells recruitment
Blood vessel
Malignant hepatocytes
c
FOLR2+ TAM
POSTN+ CAF
CSF1 signaling
NOTCH signaling
VEGF/PGF signaling
CXCL12-CXCR4 signaling
PLVAP+ EC
Onco-fetal niche
d
FN1
THBS2
CTGF
EMT-like reprogramming
Primary HCC
OFlow
non-EMT driven
CYP2 ↑
G6PC ↑
ADH1B ↑
LECT2 ↑
OFhi
EMT-driven
CXCL1 ↑
CXCL5 ↑
KRT7 ↑
KRT19 ↑
Early-relapse
Response to combination therapy
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TRACKERx
Single Cell Precision Oncology

Medical Research Future Fund

Partner organisations

Curtin University · Perkins · LCC Liver Cancer Collaborative · BGI · MGI

Academic Institutions

Curtin University · Perkins · The Westmead Institute for Medical Research · Imperial College London · ilbs Institute of Liver and Bili Sciences · National Cancer Centre Singapore SingHealth · Peter Mac Peter MacCallum Cancer Centre Victoria Australia · Telethon Kids Institute

Harry Perkins Institute of Medical Research
Curtin University

Sharma Lab
Rhea Pai
Jennifer Currenti
Saurabh Gupta
Ashley Seot
Soumi Chaterjee
Shaohi Hou
Abhishek Singh
Merrin Eapen
Danamma Kalavikatte
Joren Regan
Chaki Ramesh
Celest Ong

Liver Cancer Collaborative WA
Michael Wallace
Louise Winteringham
Peter Leedman
Nina Tirnitz-Parker

National Cancer Centre Singapore SingHealth
Pierce Chow

A*STAR SIgN
Florent Ginhoux
Ziyi Li (SII)

The Westmead Institute for Medical Research
Jacob George
Liang Qiao

Telethon Kids Institute
Archita Mishra

KK Women's and Children's Hospital SingHealth
Jerry Chan

BGI 华大
Longqi Liu
Bicheng Yang

Opening for Computational Postdoc
Twitter @asharmaiisc
ankur.Sharma@perkins.org.au
ankur.sharma@curtin.edu.au
http://www.oncofetal.com/

10x Genomics Clinical Translational Research Network · nanoString · Spatio Temporal Omics Consortium

Australian Government National Health and Medical Research Council · NHMRC · Harry Perkins Institute of Medical Research · Curtin University · NMRC National Medical Research Council Singapore

LCC Liver Cancer Collaborative · Minderoo Foundation · CRT Cancer Research Trust · Cancer Council

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The Promise of Immuno-Neoadjuvant Therapy in HCC

Han Chong Toh *(National Cancer Centre Singapore, Singapore)*

CLINICAL CANCER RESEARCH | REVIEW

Neoadjuvant Approaches in Hepatocellular Carcinoma: There's No Time Like the Present

Joseph W. Franses[1] and Andrew X. Zhu[1,2]

Franses and Zhu 2022 *Clin Can Res*

VERY DIVERSE ENDPOINTS

Table 1. Ongoing neoadjuvant trials for HCC.

Identifier	Phase	Intervention(s)	Primary clinical endpoint
NCT04181931	N/A	TACE + HAIC (FOLFOX)	PFS
NCT04424043	N/A	TACE + HAIC (FOLFOX)	PFS
NCT04777942	N/A	TACE + HAIC (FOLFOX)	PFS
NCT03591705	N/A	HAIC (FOLFOX) ± TACE	PFS
NCT04967482	N/A	DEB-TACE vs. TACE	Conversion rate to resectability
NCT04587739	1	SBRT	Drop-out rate prior to resection
NCT03469479	3	HAIC (FOLFOX)	OS
NCT03851913	3	TACE	OS
NCT03368651	3	TACE	OS
NCT04425226	N/A	Pembrolizumab + lenvatinib	4-year RFS
NCT04443322	N/A	Durvalumab + lenvatinib	1) PFS, 2) RFS
NCT04224480	1	Pembrolizumab	2-year RFS
NCT04658147	1	Nivolumab ± relatlimab	Completion of pre-op treatment and proceeding to surgery
NCT03867370	1–2	Toripalimab + lenvatinib	1) Complete pathologic response, 2) Major pathologic response
NCT04888546	1–2	TQB2450 (PD-L1 inhibitor) + anlotinib	1) Pathologic complete response rate, 2) ORR
NCT03630640	2	Nivolumab	2-year local RFS
NCT04727307	2	Atezolizumab + bevacizumab	2-year RFS
NCT03510871	2	Nivolumab + ipilimumab	ORR (4 cycles)
NCT03916627	2	Cemiplimab	Significant tumor necrosis
NCT04615143	2	Tislelizumab	Major pathologic response
NCT04930315	2	Camrelizumab + apatinib	1-year RFS
NCT04123379	2	Nivolumab + (BMS-813160 CCR2/CCR5 antagonist or BMS-986253 IL8 antagonist)	1) Major pathologic response, 2) Significant tumor necrosis
NCT04297202	2	Camrelizumab + apatinib	Major pathologic response
NCT04701060	2	Camrelizumab + apatinib	ORR
NCT04241523	2	Lenvatinib	R0 resection rate
NCT04521153	N/A	Camrelizumab + apatinib + TACE	1) 3-year EFS, 2) Major pathologic response
NCT04857684	1	SBRT + atezolizumab + bevacizumab	Proportion of patients with grade 3–4 TRAEs
NCT04653389	2	TACE + sintilimab + SBRT	EFS
NCT04814043	2	Sintilimab + lenvatinib + TACE + HAIC (FOLFOX)	1) Complete pathologic response, 2) Major pathologic response
NCT04174781	2	TACE + sintilimab	PFS

Locoregional approaches are highlighted with a white background, systemic therapy approaches with a light gray background, and combined approaches with a dark gray background.

Neoadjuvant Immunotherapy Trials for HCC

NCT	Drug Name	Year	enrolled	Result
NCT05471674	nivolumab	2023	20	pathologic response
NCT04297202	camrelizumab plus apatinib	2023	18	DC infiltration might be a predictive marker of response, ctDNA as biomarker to predict pathological response and relapse
NCT03916627	cemiplimab	2022	20 (cohort B)	35% (tumor necrosis≥50%)
NCT03222076	nivo VS nivo+ ipi	2022 2019	13+14 1case report	Increase in CD8+ T cells and Higher CD8 -to-Treg ratio in response tumor
NCT03299946	cabozantinib+ nivo	2021	15	42% (5/12) Major Pathological Rrsponse

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Multimodal integrative genomics and pathology analyses in neoadjuvant nivolumab treatment for intermediate and locally-advanced HCC

Short Title: Multimodal integrative analysis for nivolumab treatment in liver cancer

Primary endpoint was pathologic response and safety of nivolumab

NIVO 3 mg/kg x 3 cycles pre-op

30 cases screened for HKLC staging criteria for intermediate or locally advanced HCC*

*ECOG 0-1, Child A-B and no EVM. Intermediate tumor: 1) 5 cm, either >3 tumor nodules or with intrahepatic venous invasion, or 2) >5 cm, 3 tumor nodules and no intrahepatic venous invasion; and Locally-advanced tumor: 1) 5 cm, >3 tumor nodules and with intrahepatic venous invasion, or 2) >5 cm, >3 tumor nodules or/and with intrahepatic venous invasion, or 3) diffuse tumor.

70% Hepatitis B+

20 cases enrolled and treated with nivolumab

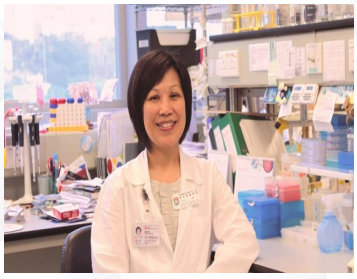
1 case received additional systemic therapy off-trial

19 cases undergone surgical resection on-trial

12 cases had no major pathological tumor response

7 cases had major pathological tumor response

Pre-nivolumab biopsy and post-nivolumab resected tumor for RNA-seq; Pre- and post-nivolumab plasma cell-free DNA for target-panel seq



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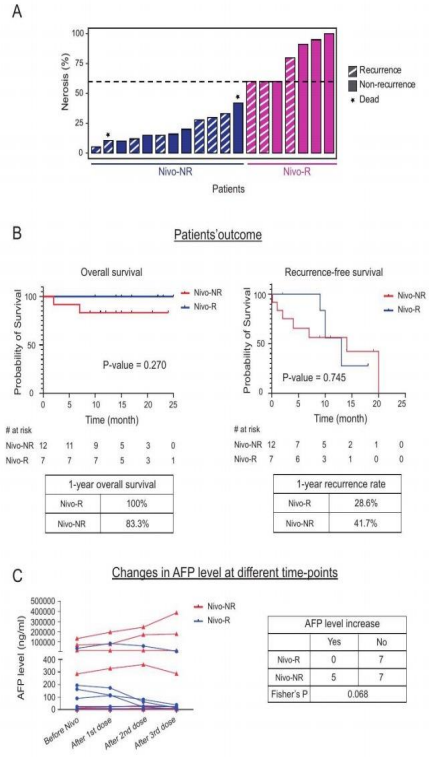
CHEUNG TT et al Liver Cancer, May 2023



1-year overall survival	
Nivo-R	100%
Nivo-NR	83.3%

1-year recurrence rate	
Nivo-R	28.6%
Nivo-NR	41.7%

AFP level increase		
	Yes	No
Nivo-R	0	7
Nivo-NR	5	7
Fisher's P	0.068	

Nivo-R : 36.8% (7/19) had significant tumor necrosis(≥60%)
3 had almost complete tumor necrosis(>90%)
1 had complete pathologic response (100%)

1-year OS: 89.5% (100% VS 83.3%)
higher in nivo-R group

1-year tumor recurrence rate : 36.8% (28.6% VS 41.7%)
lower in nivo-R group

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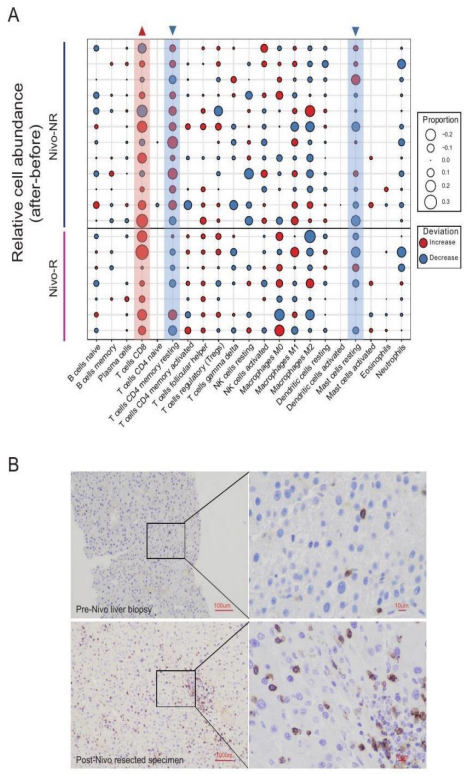

In Nivo-R :

CD8 T cells increase after treatment

CD4 memory (activated) T cells increased but resting T cells and resting mast cells declined.

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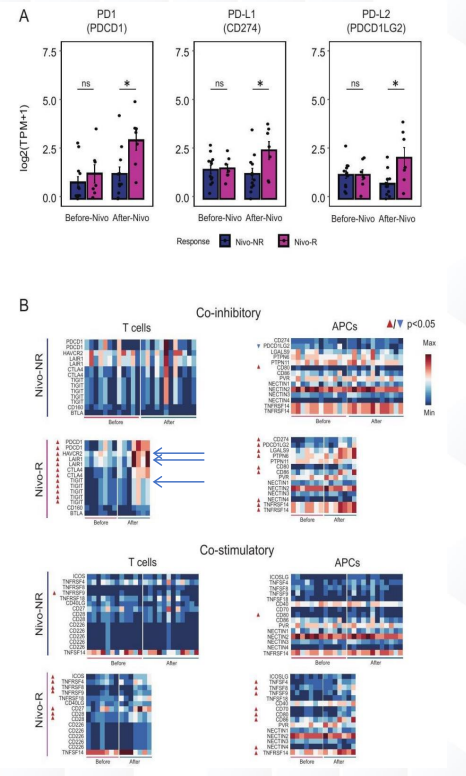

RNA seq Analysis

In Nivo-R, upregulation of co-inhibitory checkpoint molecules : CTLA-4, HAVCR2 (TIM-3), LAIR1 (myeloid checkpoint) and TIGIT

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Conclusion

- n=20 intermediate and locally advanced 19 underwent surgical resection
- Follow up from 2 to 25 months
- Preop nivolumab at 3 mg/kg for 3 cycles prior to surgical resection. No adjuvant nivo given
- Tumor necrosis was hemorrhagic often accompanied with increased or dense immune cell infiltrate at the border of the tumours.
- No patient developed AEs that prevented hepatectomy. TRAE in 1 of 20 patients : Grade 2 hypocortisolism treated with steroids.
- RNA-seq analysis : proportion of CD8 T cells predominantly increased after tx in cases with major pathologic necrosis
- CNV-based anti-PD1 score derived by target-panel sequencing of patient plasma cfDNA, correlated with the extent of tumor necrosis and validated in a Korean patient cohort who received anti-PD1 treatment. Might be non invasive predictor of IO response

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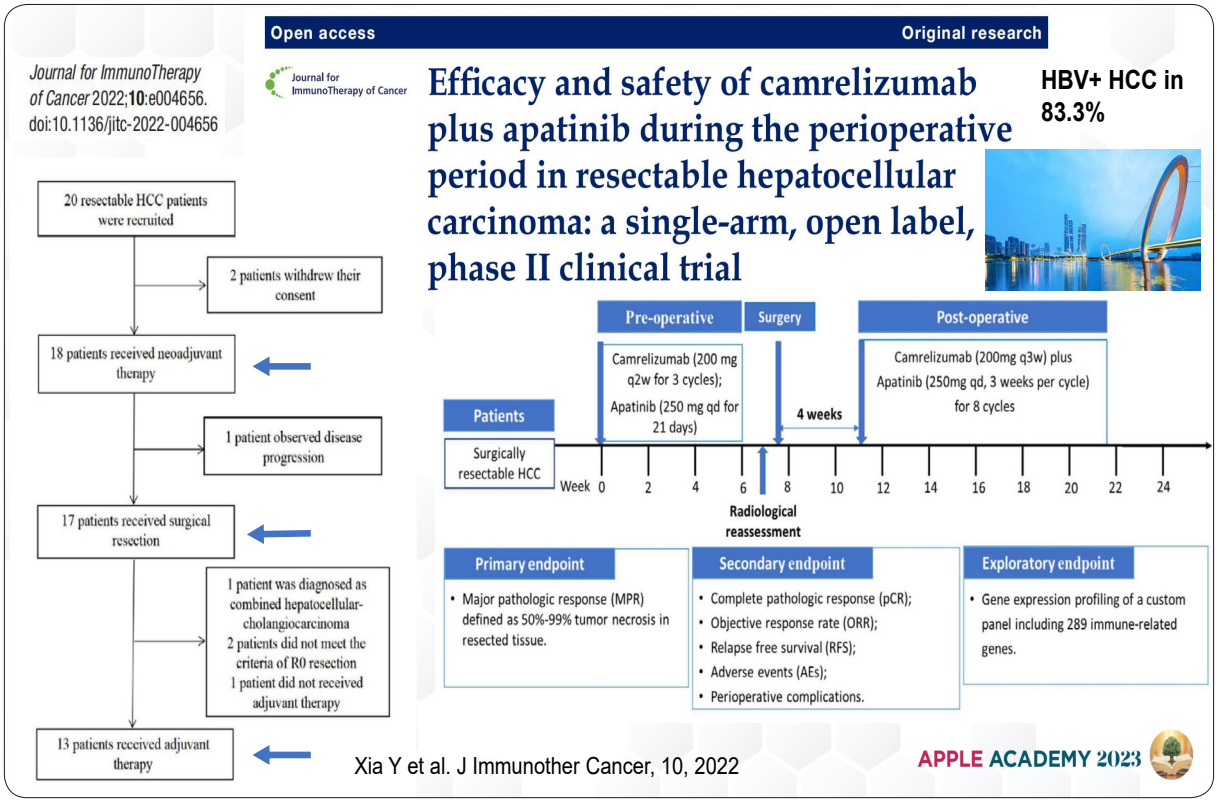

Xia Y et al. J Immunother Cancer, 10, 2022

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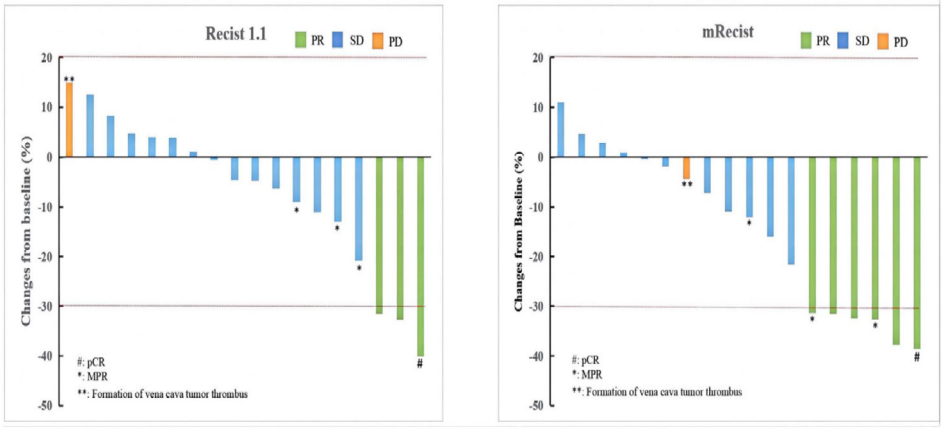
RESPONSE TO TREATMENT

Primary endpoint was MPR defined as 90%–99% tumour necrosis in resected tissue

3 (16.7%) and 6 (33.3%) of 17 resection HCC patients reached ORR on RECIST V.1.1 and modified RECIST criteria respectively.

Of 17 surgical resections, 3 (17.6%) reported MPR and 1 (5.9%) patient achieved pCR.



Tumour diameter was significantly higher in the non-pCR group than in the pCR group

≥ Gd 3 TRAEs in 3 (16.7%) of the 18 patients, most common AE : rash, hypertension, drug-induced liver damage, and neutropenia

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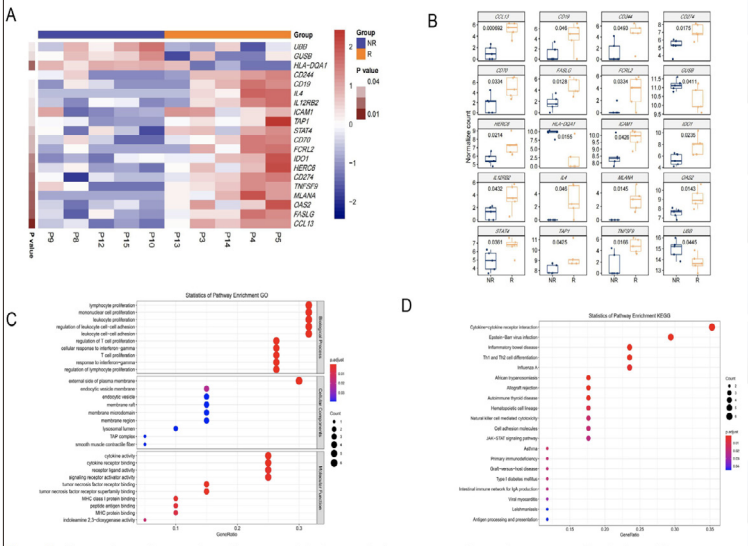

Figure 3 Comparison of expression of immune-related genes between responding and non-responding lesions. (A–B) Expression of immune-related genes per pretreatment sample of response and non-response groups. In the heatmap (A), red indicates an increased gene expression and blue indicates a decreased gene expression. (C–D) GO (C) and Kyoto Encyclopedia of Genes and Genomes (D) pathway analysis of the pretreatment samples. The count represents the number of genes in each pathway and dot size corresponds to 'count'. GO, gene ontology.

In responding tumours :

higher transcriptional level of CCL13, MLANA, T NFSF9, IDO1, CD70, IL12RB2, CD19 and IL4

lower transcriptional levels of HILA-DQ1 and GU SB (figure 3A,B).

Genes significantly enriched in 'lymphocyte proliferation', 'mononuclear cell proliferation' and so on (figure 3C).

Dendritic cell infiltration may be a key predictive marker of response to camrelizumab and apatinib and patient recurrence.

Circulating tumor DNA as biomarker can predict pathological response and relapse.

Abnormal **glucose metabolism** in patients with multifocal HCC may be related to different sensitivity of treatment in different lesions.

Cemiplimab (an anti-PD-1) (NCT03916627, Cohort B)

Primary endpoint was significant tumour necrosis on pathological examination (defined as >70% necrosis of the resected tumour)

Neoadjuvant cemiplimab for resectable hepatocellular carcinoma: a single-arm, open-label, phase 2 trial

Thomas U Marron, Maria Isabel Fiel, Pauline Hamon, Nathalie Fiaschi, Edward Kim, Stephen C Ward, Zhen Zhao, Joel Kim, Paul Kennedy, Ganesh Gunasekaran, Parissa Tabrizian, Deborah Doroshow, Meredith Legg, Ashley Hammad, Assaf Magen, Alice O Kamphorst, Muhammed Shareef, Namita T Gupta, Raquel Deering, Wei Wang, Fang Wang, Pradeep Thanigaimani, Jayakumar Mani, Leanna Troncoso, Alexandra Tabachnikova, Christie Chang, Guray Akturk, Mark Buckup, Steven Hamel, Giorgio Ioannou, Clotilde Hennequin, Hajra Jamal, Haley Brown, Antoinette Bonaccorso, Daniel Labow, Umut Sarpel, Talia Rosenbloom, Max W Sung, Baijun Kou, Siyu Li, Vladimir Jankovic, Nicola James, Sara C Hamon, Hung Kam Cheung, Jennifer S Sims, Elizabeth Miller, Nina Bhardwaj, Gavin Thurston, Israel Lowy, Sacha Gnjatic, Bachir Taouli, Myron E Schwartz, Miriam Merad

Summary

Background Surgical resection of early stage hepatocellular carcinoma is standard clinical practice; however, most tumours recur despite surgery, and no perioperative intervention has shown a survival benefit. Neoadjuvant immunotherapy has induced pathological responses in multiple tumour types and might decrease the risk of postoperative recurrence in hepatocellular carcinoma. We aimed to evaluate the clinical activity of neoadjuvant cemiplimab (an anti-PD-1) in patients with resectable hepatocellular carcinoma.

Lancet Gastroenterol Hepatol 2022; 7: 219–29

Published Online January 19, 2022 https://doi.org/10.1016/S2468-1253(21)00385-X

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Translational analysis

- In 8 patients with adequate tumour samples for analysis by mass cytometry, 4 patients with 50% or greater necrosis (three with 100% necrosis and one with 50% necrosis) had significantly higher $CD8^+$ T-cell infiltration in the tumour vs 4 patients with little to no necrosis (p=0·0010; two-way ANOVA followed by multiple-comparison Sidak test).
- Multiplex IHC showed greater numbers of immune cells at baseline, which further increased after therapy in patients who had 50% or greater necrosis
- Bulk RNA-Seq shows signatures of $CD8^+$ T cells, activated or dysfunctional cells, cytotoxic cells, monocyte-derived macrophages, and B cells at baseline in patients with 50% or greater necrosis
- All but B-cell and naive T-cell signatures (neither of which was enriched at baseline) increased following therapy in responding patients

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Conclusion

- N = 20 (received cemiplimab)
- 20% patients had significant tumour necrosis (> 70% necrosis of resected HCC)
- 15% patients had radiologic partial response
- All other patients maintained stable disease
- Post-surgery, patients continued to receive 8 cycles of adjuvant IV cemiplimab
- Then the largest neoadjuvant IO trial in HCC

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Intratumoral dendritic cell-CD4⁺ T helper cell niches enable CD8⁺ T cell differentiation following PD-1 blockade in hepatocellular carcinoma

Magen A et al. Nature Med June 2023

IO Responders (Nivolumab, Cemiplimab) :

Clonal expansion of intratumoral CXCL13⁺CH25H⁺IL-21⁺PD-1⁺CD4⁺ T helper cells ("CXCL13⁺ T_H") and Granzyme K⁺ PD-1⁺ effector-like CD8⁺ T cells

IO Non Responders

Terminally exhausted $CD39^{hi}TOX^{hi}PD\text{-}1^{hi}CD8^{+}$ T cells

Progenitor CD8⁺ T cells interact with CXCL13⁺ T_H within cellular triads around dendritic cells enriched in maturation and regulatory molecules, or "mregDC". Progenitor CD8+ T cells were enriched in close proximity to mregDC in responders compared with nonresponders.

Suggests that mregDC and CXCL13⁺ T_H control the differentiation of tumour-specific Progenitor exhausted CD8⁺ T cells following ICB.

β-catenin-activating mutations enriched in T cell low lesions (P = 0.001), p53 (TP53) mutations enriched in responders

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FIRST PERI-OPERATIVE IO TRIAL IN HCC TO BE REPORTED

Perioperative nivolumab monotherapy versus nivolumab plus ipilimumab in resectable hepatocellular carcinoma: a randomised, open-label, phase 2 trial

Ahmed Omar Kaseb, Elshad Hasanov, Hop Sanderson Tran Cao, Lianchun Xiao, Jean-Nicolas Vauthey, Sunyoung S Lee, Betul Gok Yavuz, Yehia I Mohamed, Aliya Qayyum, Sonali Jindal, Fei Duan, Sreyashi Basu, Shalini S Yadav, Courtney Nicholas, Jing Jing Sun, Kanwal Pratap Singh Raghav, Asif Rashid, Kristen Carter, Yun Shin Chun, Ching-Wei David Tzeng, Divya Sakamuri, Li Xu, Ryan Sun, Vittorio Cristini, Laura Beretta, James C Yao, Robert A Wolff, James Patrick Allison, Padmanee Sharma

Lancet Gastroenterol Hepatol 2022; 7: 208–18

Published Online January 19, 2022 https://doi.org/10.1016/

Summary

Background Hepatocellular carcinoma has high recurrence rates after surgery; however, there are no approved standard-of-care neoadjuvant or adjuvant therapies. Immunotherapy has been shown to improve survival in advanced hepatocellular carcinoma; we therefore aimed to evaluate the safety and tolerability of perioperative immunotherapy in resectable hepatocellular carcinoma.

- Post-surgery, patients received either IV Nivolumab 480 mg monthly x 2 years and in Ipi + Nivo arm received added Ipi every 6 weeks x 4
- Nivolumab monotherapy : 33% (3/9) patients had major pathological response (≥70% necrosis)
- Nivolumab plus ipilimumab : 27% (3/11) patients had major pathological response
- This neoadjuvant study identified a major pathological response predictor : CD8+T-cell/Treg ratio increased in the tumour microenvironment in nivo-response patients

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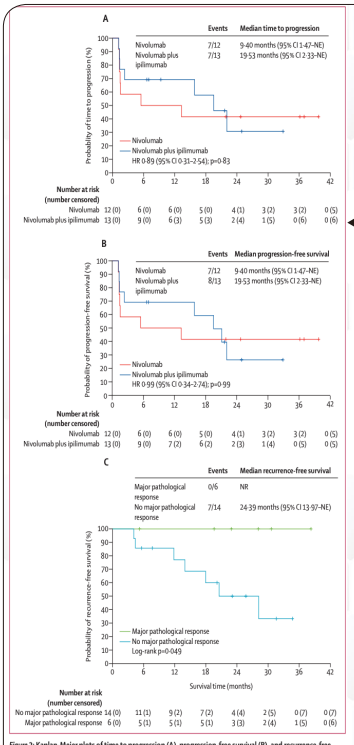

Figure 3: Kaplan-Meier plots of time to progression (A), progression-free survival (B), and recurrence-free survival (C)
Kaplan–Meier estimates are shown according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Stratified hazard ratios (HRs) for progression or death are reported. Significant differences are denoted by p values less than 0·05. Tick marks indicate censored data. NE=not estimable. NR=not reached.

CLINICAL OUTCOMES TO NIVO AND IPI NIVO AND TO MAJOR PATH RESPONSE

IHC AND CYTOF OF MPR VS NO MPR

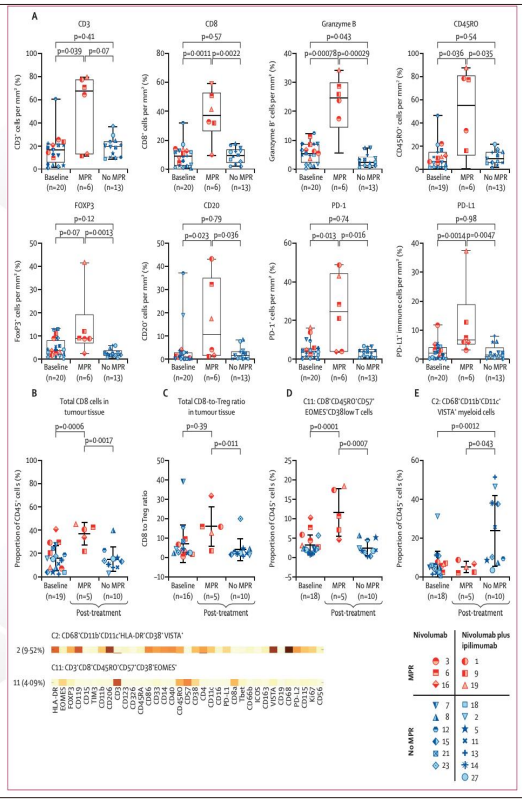

Figure 4: Immunohistochemistry and CyTOF analysis of tissue samples
Immune cell density box plots with whiskers and IQRs are shown (A). Categorical scatter plots showing frequency of CD8 T cells (B), the CD8-to-Treg ratio (C), the T-cell cluster (D), and the myeloid cell cluster (E) are shown. Plots depict means (SD). CyTOF=mass cytometry by time-of-flight. MPR=major pathological response.

Immune microenvironment analysis

- Post-treatment tissue of patients with major pathological responses vs baseline
  - Increase in CD8+ T cells
  - Higher CD8-to-Treg ratio (but no difference in Treg)
- Major pathological response vs without response
  - More activated CD8+ effector T cells in post-treatment tissue
    - CD8+ CD45RO+CD57+Eomes+CD38low
  - Lesser VISTA+ CD68+ macrophage in post-treatment tissue
    - CD68+CD11b+CD11c+VISTA+

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Conclusion

- n=13 (nivo), n=14 (nivo+ipi)
- No patients had surgery delayed due to grade 3 or worse AEs. Primary endpoint was safety and tolerability.
- Estimated median PFS
  - 9·4 months (95% CI 1·47–not estimable [NE]) with nivolumab
  - 19·53 months (2·33–NE) with nivolumab plus ipilimumab (hazard ratio [HR] 0·99, 95% CI 0·31–2·54)
- Median TTP
  - 9·4 months (95% CI 1·47–NE) in the nivolumab group
  - 19·53 months (2·33–NE) in the nivolumab plus ipilimumab group (HR 0·89, 95% CI 0·31–2·54).
- Overall responses:
  - 23% patients with nivolumab monotherapy,
  - none with nivolumab plus ipilimumab.
- Major pathological response (ie, ≥70% necrosis in the resected tumour area):
  - 33% with nivolumab monotherapy
  - 27% with nivolumab plus ipilimumab.

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MD Anderson perioperative HCC nivo-pCR

Cancer Immunology Miniatures

Cancer Immunology Research

Immunologic Correlates of Pathologic Complete Response to Preoperative Immunotherapy in Hepatocellular Carcinoma

CASE REPORT OF A PATIENT WHO ACHIEVED SURGICAL RESECTION SHOWING COMPLETE PATHOLOGICAL RESPONSE TO NEOADJUVANT IPI + NIVO x 3 CYCLES
66 YR OLD HCV+ , AFP 681

Clinical Response correlates :
Increase in CD8+ T-cell infiltration
Increase in two effector T-cell clusters.
11-fold increase in CD3+CD8+CD45RO+Eomes +
6-fold increase in CD3+CD8+CD45RO+Eomes+CD57+CD38low clusters.
Also paradoxical increase in $CD3^{+}CD4^{+}CD45RO^{+}$ $Foxp3^{+}ICOS^{+}$ cells

KASEB AO et al. Cancer Immunol Res Dec 2020

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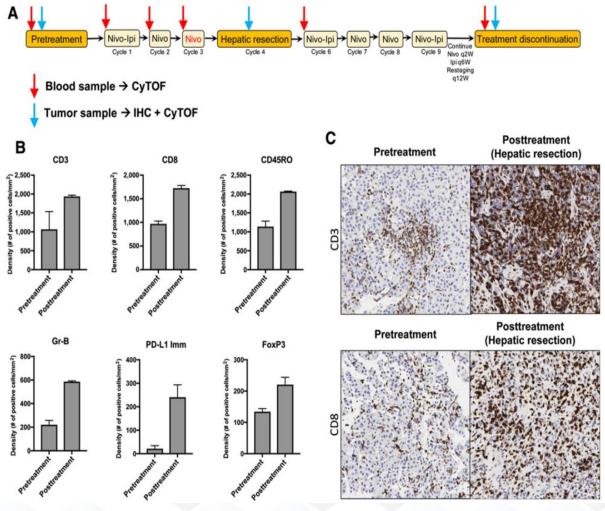

Results

A total of 9 patients have been enrolled at the time of analysis, 5 in arm A and 4 in arm B. There were no delays in surgery related to immunotherapy treatment. Pathologic complete response was observed in 3 of 9 patients (33.3%). The case presented here is the first of these responders.

Figure 2.
Clinical trial schema and IHC analysis showing favorable immune infiltration posttreatment in the responder. **A,** Clinical trial NCT03222076 arm A schema indicating when samples were collected. The dose of nivolumab (indicated in red) was not given due to hepatotoxicity. Time points for blood and tumor tissue collection and the assays performed are indicated by red and blue arrows. q2w, every 2 weeks; q6w, every 6 weeks; q12w, every 12 weeks. **B** and **C,** IHC analysis of pre- and posttreatment hepatic tissues from the HCC patient. **B,** IHC analysis of total T cells ($CD3^{+}$), $CD8^{+}$ T cells, CD45RO-expressing cells, granzyme B (Gr-B)–expressing cells, FoxP3-expressing cells (regulatory T cells), and PD-L1–expressing immune cells (PD-L1 Imm). Mean density + SD is shown for five different regions in the liver at each timepoint. **C,** Representative IHC images of $CD3^{+}$ and $CD8^{+}$ T cells pre- and posttreatment (after resection) from one representative region is shown at a maginification of 20×.

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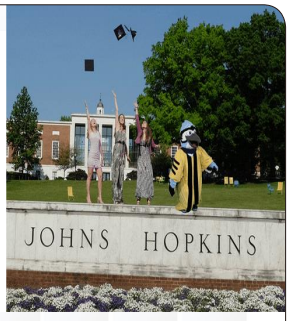
Published in final edited form as:
Nat Cancer. 2021 September ; 2(9): 891–903. doi:10.1038/s43018-021-00234-4.



Neoadjuvant cabozantinib and nivolumab convert locally advanced hepatocellular carcinoma into resectable disease with enhanced antitumor immunity

- n=15 upfront unsuitable for HCC surgery, 12 (80%) had surgery. 20% HBV+
- Included high-risk features such as portal vein invasion, multifocality or advanced tumor size > 10 cm
- 5/12 (42%) major or complete pathologic responses - 1 complete pathologic response – that translates to improved PFS
- no significant AEs from neoadjuvant therapy on the perioperative period after surgery, no perioperative deaths.
- responders demonstrated an enrichment in T effector cells, tertiary lymphoid structures, CD138+ plasma cells
- distinct spatial arrangement of B cells indicating an orchestrated B-cell contribution to antitumor immunity in HCC.

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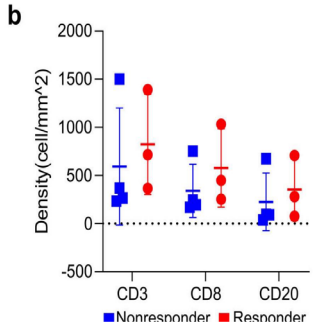
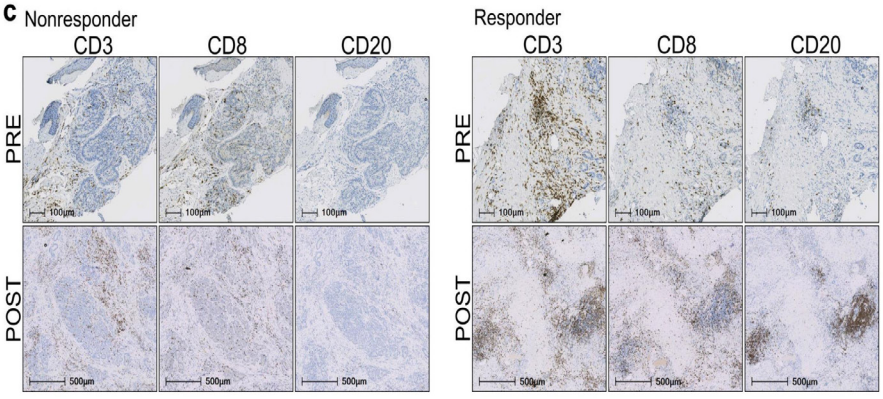


Quantification of TLS along with CD3+, CD8+ and CD20+ cells per tumor area (mm2) in nonresponders (n= 7) and responders (n= 5) by IHC



ONE FROM 7 NON RESPONDERS AND ONE FROM 5 RESPONDERS

Extended Data Fig. 3. Immunohistochemistry (IHC) analysis of immune cells.

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Johns Hopkins Cabo - Nivo Neoadjuvant Trial

Trial design : cabozantinib monotherapy 2w prior to nivolumab
8 week neoadjuvant treatment period. No post-op adjuvant

➢Grade 3 TRAE 13.3%. One case of myasthenia gravis and one autoimmune hepatitis

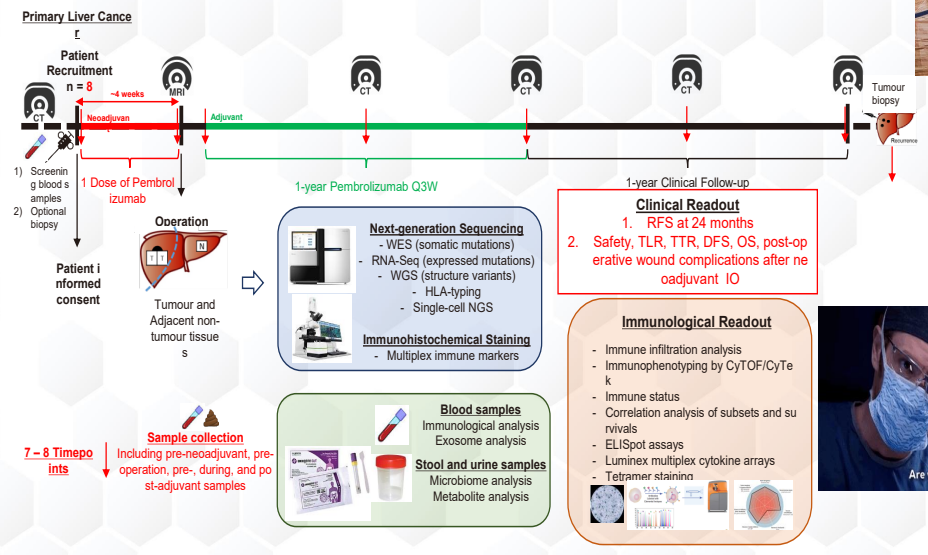
~1.5–2-fold increases in abundance of most **effector and memory CD4+ and CD8+ T cells** including subtypes + for IFNγ, granzyme B, and Ki-67, important signatures of activation and functionally involved in antitumor immunity

Enhanced B cell infiltration, higher TNF-α, CD138+ plasma cell infiltration and TLS consisting of B cells and T cells in responders

Ki-67+CD163+ macrophages as a subtype of macrophages that neighbor T cells within the nonresponder HCC TME

APPL

Investigator-initiated trial (IIT) – Neoadjuvant and adjuvant treatment of Pembrolizumab before/after surgical resection



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APPLE ACADEMY 2023

Thursday, July 6, 2023 [ROOM C (Grand Ballroom 3)]

Session 3.

Unmet Clinical Need in and Current Clinical Research Directions

Chairs: Etsuro Hatano *(Kyoto Univ., Kyoto)*
Thomas Yau *(The Univ. of Hong Kong, Hong Kong)*

Early HCC and Treatment with Curative Intent - Has Adjuvant Therapy Opened a New Paradigm?
Linda Wong *(Univ. of Hawaii, Honululu)*

Intermediate-Stage HCC: Re-Defining the Role of Liver-Directed Therapy
Hyo-Cheol Kim *(Seoul National Univ., Seoul)*

Intermediate-Stage HCC: Expanding the Role of Systemic Therapy
Masafumi Ikeda *(National Cancer Center Hospital East, Kashiwa)*

Advanced HCC: Beyond IMbrave150 and HIMALAYA
Chih-Hung Hsu *(National Taiwan Univ., Taipei)*

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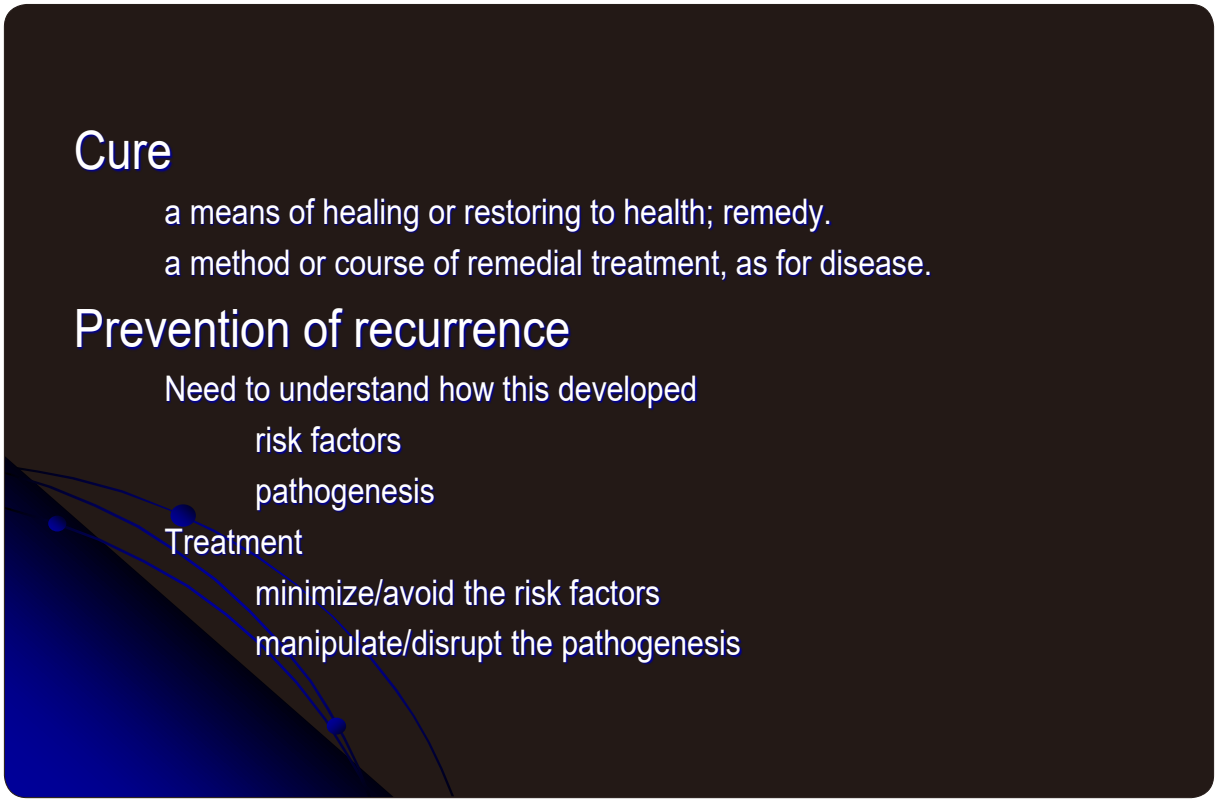
Session 3. Unmet Clinical Need in and Current Clinical Research Directions

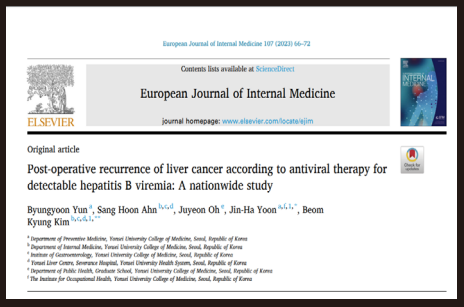
Early HCC and Treatment with Curative Intent - Has Adjuvant Therapy Opened a New Paradigm?

Linda Wong *(Univ. of Hawaii, Honululu)*



Use of antivirals for HBV after resection

- Yun et al, Eur J of Int Med 2023
- Nationwide study, Korea
- N=3034 patients, curative resection for HBV-HCC
- Follow up 2.7 years
- Compared those on antiviral therapy vs not based on serum HBV-DNA
- Initiating antivirals based on detectable HBV-DNA provided similar risk of recurrence.
- *antivirals should be used based on HBV-DNA


European Journal of Internal Medicine 107 (2023) 66–72

Contents lists available at ScienceDirect

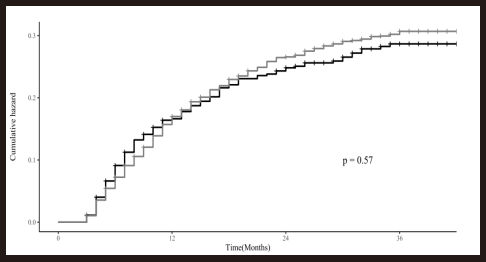
European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Post-operative recurrence of liver cancer according to antiviral therapy for detectable hepatitis B viremia: A nationwide study

Byungyoon Yun, Sang Hoon Ahn, Juyeon Oh, Jin-Ha Yoon, Beom Kyung Kim



Treatment of HCV increases survival of those with HCC

- *Singal AG, Gastroenterology, 2019*
- N=797 HCC pts with HCV
- All patients had achieved complete response of HCC to treatment with resection, local ablation, TACE, radiation or radioembolization
- 383 DAA, 414 untreated
- DAA treatment was associated with reduction in death risk

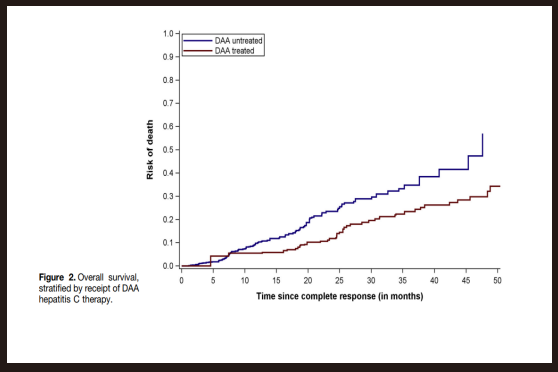
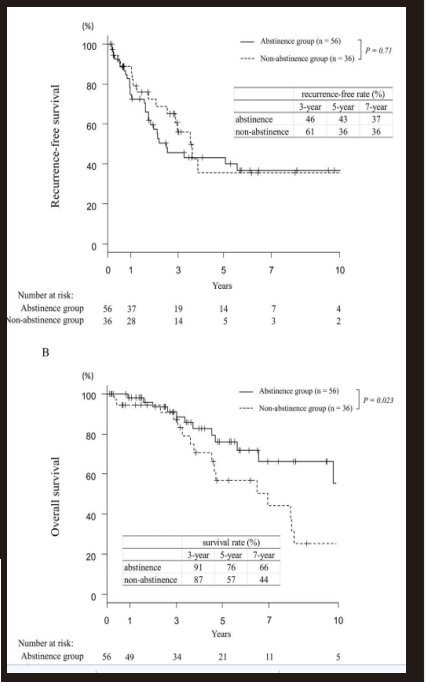
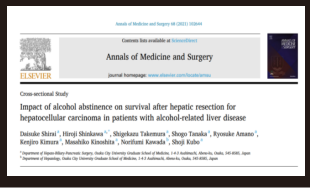


Figure 2. Overall survival, stratified by receipt of DAA hepatitis C therapy.

Does drinking alcohol after surgery affect recurrence?

- Shirai et al. Ann of Med Surg, 2021
- N=92, curative hepatic resection
- 56 were abstinent, 36 using alcohol
- Liver related death 41.9% in those using alcohol and 19.6% in abstinent
- Recurrence free 3, 5 and 7 year survival as significantly worse in those who were not abstinent



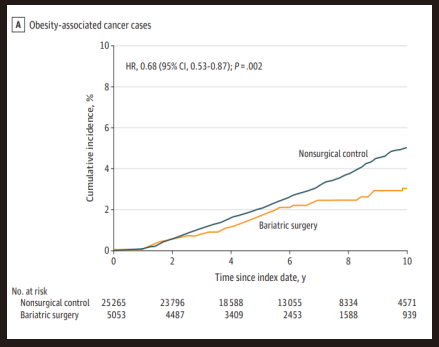

Annals of Medicine and Surgery

Cross-sectional Study

Impact of alcohol abstinence on survival after hepatic resection for hepatocellular carcinoma in patients with alcohol-related liver disease

Can we reduce liver cancer in NAFLD?

- Aminian et al. JAMA 2022
- SPLENDID trial (Surgical Procedures and Long Term Effectiveness in Neoplastic Disease Incidence and Death)
- 30,318 patients
  - Bariatric surgery 5053
  - Non-surgical care 25,265
- 10 yrs of follow up
- Determine the incidence of obesity associated cancer
  - Esophageal, renal breast, gastric, colorectal, liver, gallbladder uterus, ovary thyroid, multiple myeloma
- Cumulative incidence of cancer
  - Bariatric surgery – 2.9%
  - Nonsurgical group – 4.9%
- Among obese adults, bariatric surgery significantly lowed obesity associated cancer and cancer related mortality

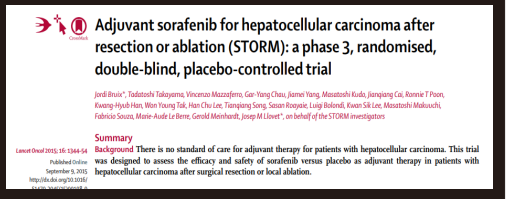


Current approach to promote cure for HCC

- Early detection
- Curative therapies – liver resection, RFA, transplant
- After treatment
  - Surveillance
  - Treat viral hepatitis B, C
  - Avoid alcohol
  - Weight loss, exercise, diet change

STORM trial

- Bruix et al, Lancet Onc 2015.
- Phase 3, double blind , placebo controlled, 202 sites, 28 countries
- Use of sorafenib after treatment for HCC
- HCC pts who had complete response after resection (n=900) or ablation (n=214)
- Median follow up was 8.5 months
- No difference in recurrence free survival in those who received sorafenib vs placebo
- Sorafenib did not prevent recurrence

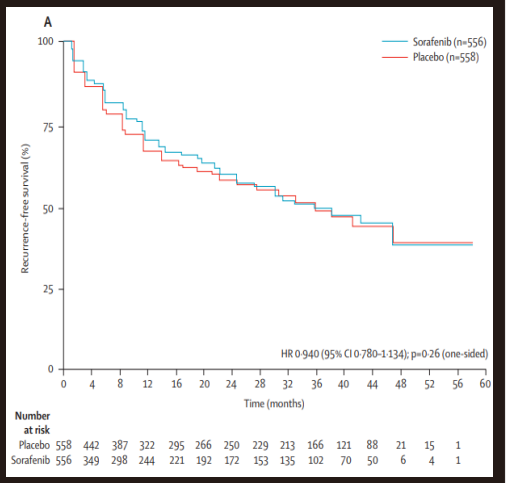


Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial

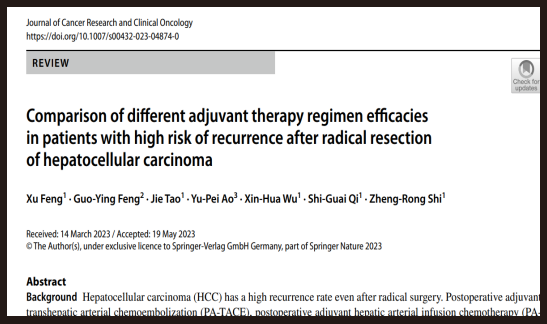
Jordi Bruix*, Tadatoshi Takayama, Vincenzo Mazzaferro, Gar-Yang Chau, Jiamei Yang, Masatoshi Kudo, Jianqiang Cai, Ronnie T Poon, Kwang-Hyub Han, Won Young Tak, Han Chu Lee, Tianqiang Song, Sasan Roayaie, Luigi Bolondi, Kwan Sik Lee, Masatoshi Makuuchi, Fabricio Souza, Marie-Aude Le Berre, Gerold Meinhardt, Josep M Llovet*, on behalf of the STORM investigators

Summary

Background There is no standard of care for adjuvant therapy for patients with hepatocellular carcinoma. This trial was designed to assess the efficacy and safety of sorafenib versus placebo as adjuvant therapy in patients with hepatocellular carcinoma after surgical resection or local ablation.



- Feng et al. J Can Res and clin Onc 2023.
- Meta-analysis, 38 studies, 7079 patients
- Compared 3 postoperative adjuvant therapies after radical resection of HCC:
  - PA-Sorafenib
  - PA-radiation
  - PA-TACE
  - PA-Hep art Chemo
- Both sorafenib and radiation improved OS and DFS compared to TACE and HAIC
- PA-Radiation was superior for disease free survival



Journal of Cancer Research and Clinical Oncology
https://doi.org/10.1007/s00432-023-04874-0

REVIEW

Comparison of different adjuvant therapy regimen efficacies in patients with high risk of recurrence after radical resection of hepatocellular carcinoma

Xu Feng[1] · Guo-Ying Feng[2] · Jie Tao[1] · Yu-Pei Ao[3] · Xin-Hua Wu[1] · Shi-Guai Qi[1] · Zheng-Rong Shi[1]

Received: 14 March 2023 / Accepted: 19 May 2023
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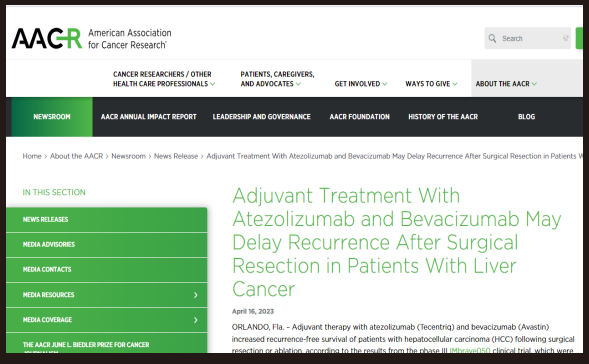
Abstract
Background Hepatocellular carcinoma (HCC) has a high recurrence rate even after radical surgery. Postoperative adjuvant transhepatic arterial chemoembolization (PA-TACE), postoperative adjuvant hepatic arterial infusion chemotherapy (PA-

Imbrave 050

- April 2023, Dr Pierce Chow
- Randomized, controlled, Phase III
- Atezolizumab/Bevacizumab after successful liver resection or ablation.
- Median follow up 17.4 months
- Atezo/Bev increased recurrence free survival
- 28% reduction in recurrence or death



AACR American Association for Cancer Research

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THE AACR JUNE L. BIEDLER PRIZE FOR CANCER

Adjuvant Treatment With Atezolizumab and Bevacizumab May Delay Recurrence After Surgical Resection in Patients With Liver Cancer

April 16, 2023

ORLANDO, Fla. – Adjuvant therapy with atezolizumab (Tecentriq) and bevacizumab (Avastin) increased recurrence-free survival of patients with hepatocellular carcinoma (HCC) following surgical resection or ablation, according to the results from the phase III IMbrave050 clinical trial, which were

Unanswered questions

- Can underlying liver fibrosis, cirrhosis be reversed?
  - Immunotherapy
  - aspirin
- Does improvement of fibrosis decrease the likelihood of recurrence?
- Can we decrease recurrence with systemic therapy?
  - Antifibrotics?
  - Immunotherapy?
  - Chemoprevention agents?

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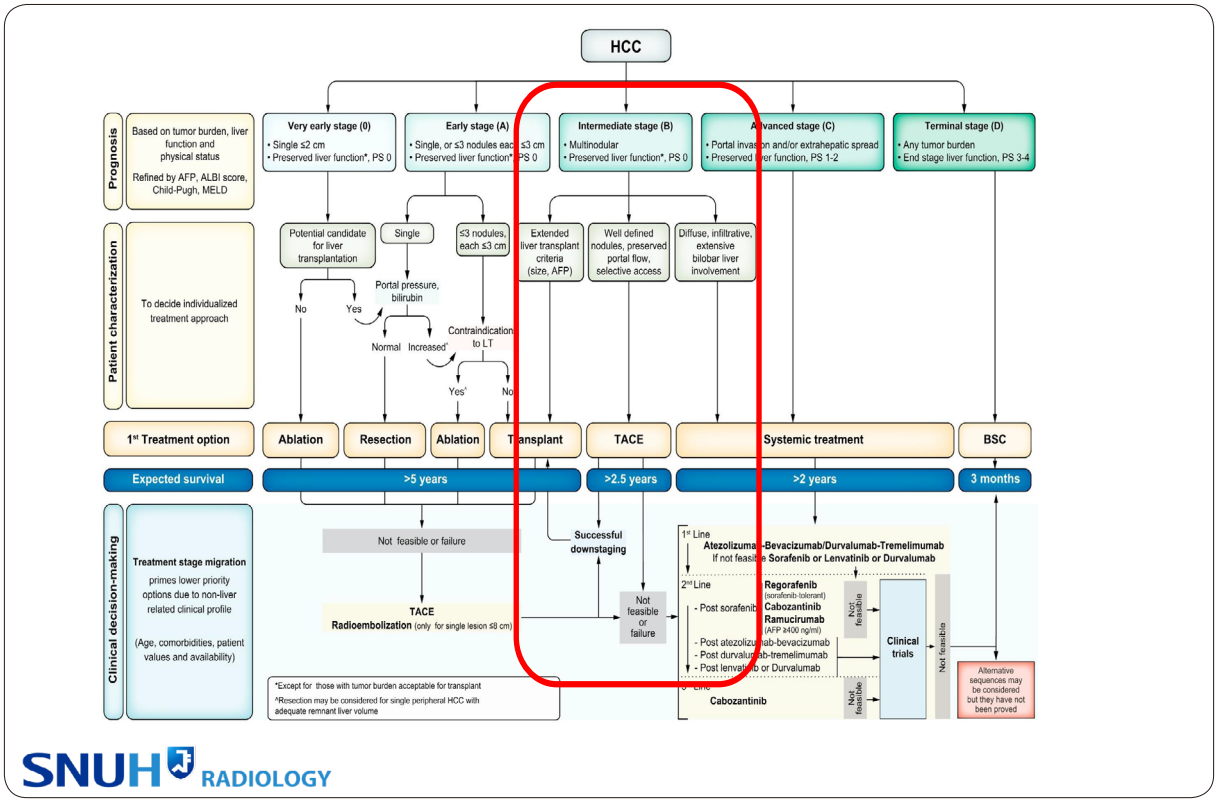
Session 3. Unmet Clinical Need in and Current Clinical Research Directions

Intermediate-Stage HCC: Re-Defining the Role of Liver-Directed Therapy

Hyo-Cheol Kim *(Seoul National Univ., Seoul)*



SNUH RADIOLOGY

Intermediate-stage HCC

① Oligonodular (2 ~ 5)
② Countable Multinodular
③ Uncountable Multinodular
④ Infiltrative type without vascular invasion

✓Child-Pugh A or B
✓ECOG 0
✓No vascular invasion

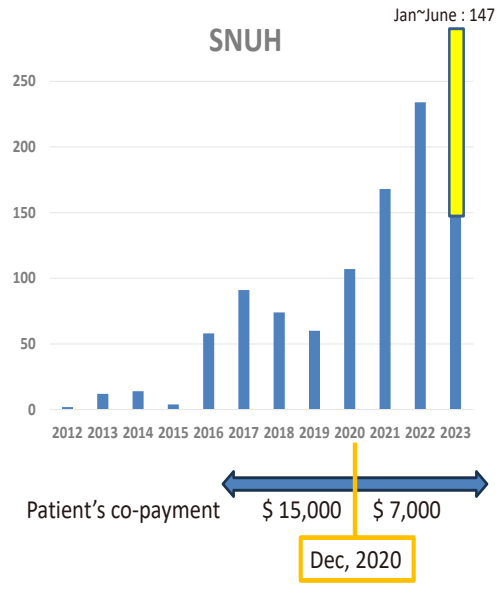
SNUH RADIOLOGY

Intermediate-stage HCC

	Y-90	cTACE
Overall survival	***	***
Progression free survival	****	**
Downstaging to TPL	****	**
Post-embolization syndrome	*	****
Hospitalization	*	****
Repeated visit hospital	*	***
Quality of life	****	*
Patients' co-payment in Korea	$7,000	$200

SNUH RADIOLOGY

Y-90 in SNUH



Unresectable HCC > 5cm
Unilobar HCC with seg/lobar PVT
→ Y-90 is primary option!

3 ~ 5 cm HCC
→ Y-90 is getting priority

SNUH RADIOLOGY

Y-90 vs cTACE

Y-90		cTACE
Curative	Intent	Palliative
Child-Pugh A	Liver Function	Child-Pugh A or B
Large	Size	Small
Oligonodular	Number	Multinodular
Nodular/Infiltrative	Tumor type	Nodular

SNUH RADIOLOGY

Oliogonodular

- 2 ~ 5 in number
- Superselective TACE/TARE is always attempted.
- TARE can be used with curative intent.
- Repeated TACE is commonly required.
- Bridge to TPL

SNUH RADIOLOGY

Countable Multinodular

- 6 ~ 30 in number
- Uni-lobar disease
  - TARE can be used with palliative intent
  - ✓ Repeated TACE is commonly required.
- Bi-lobar disease
  - TACE/TARE may be used as a debulking tool for large dominant tumor, if present.
  - Early conversion to systemic therapy.

SNUH RADIOLOGY

Uncountable Multinodular

- >30 in number
- Bilobar disease
- TACE/TARE may be used as a debulking tool for large dominant tumor, if present.
- Early conversion to systemic therapy.

SNUH RADIOLOGY

Infiltrative type without vascular invasion

- Rare
- Most infiltrative HCC have vascular invasion (BCLC C)
- Rapid progression is common.
- TACE/TARE may be used as a debulking tool prior to systemic therapy.

SNUH RADIOLOGY

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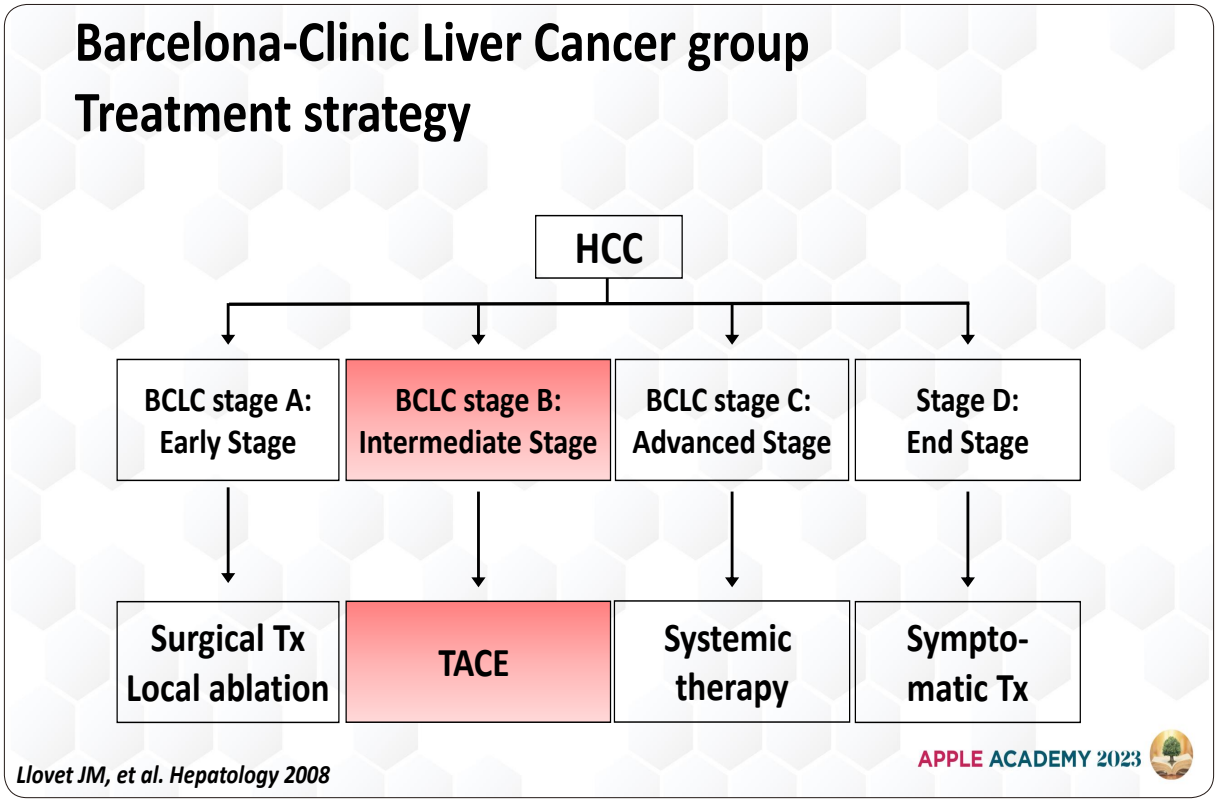
Session 3. Unmet Clinical Need in and Current Clinical Research Directions

Intermediate-Stage HCC: Expanding the Role of Systemic Therapy

Masafumi Ikeda *(National Cancer Center Hospital East, Kashiwa)*



Proportion of pts with Intermediate stage HCC in pivotal trials of Systemic therapies

		Proportion of Intermediate stage HCC (%)
SHARP	Sorafenib	18.0%
Asia-Pacific	Sorafenib	4.7%
REFLECT	Lenvatinib	22.0%
IMBrave150	Atezo+Bev	15.0%
HIMALAYA	Durva+Treme	19.6%
RESORCE	Regorafenib	14.0%
CELESTIAL	Cabozantinib	15.0%
REACH-2	Ramucirumab	17.0%

In the pivotal studies, 10-20% of the patients has initiated systemic ther apy at the Intermediate stage.

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Intermediate stage HCC

Single large n odule (>5 c m) or multifo

The main treatments for intermediate stage HCC are

- TACE
- Systemic therapy

Intermediate stage HCC is heterogeneous.

Forner A, et al. 2012; Piscaglia F, et al. 2010

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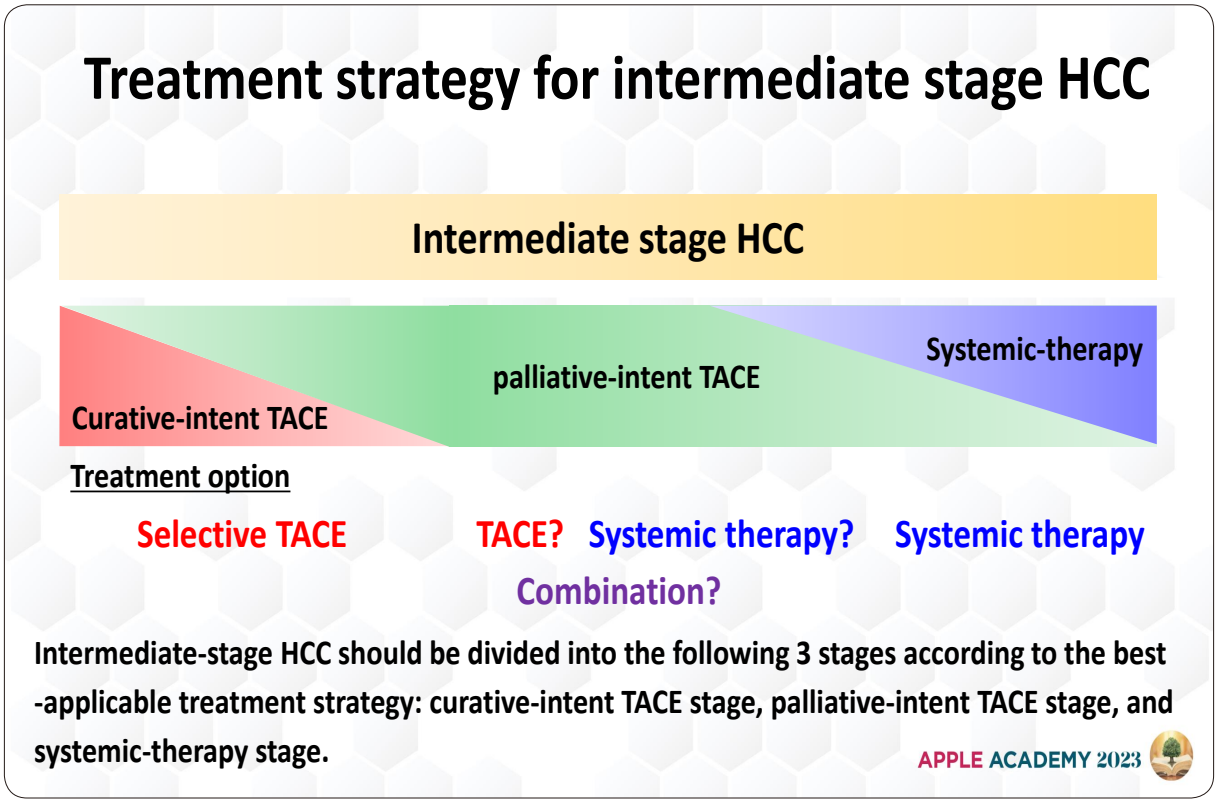
Treatment strategy for intermediate stage HCC
Intermediate stage HCC
Curative-intent TACE
palliative-intent TACE
Systemic-therapy
Treatment option
Selective TACE
TACE?
Systemic therapy?
Systemic therapy
Combination?
Intermediate-stage HCC should be divided into the following 3 stages according to the best -applicable treatment strategy: curative-intent TACE stage, palliative-intent TACE stage, and systemic-therapy stage.
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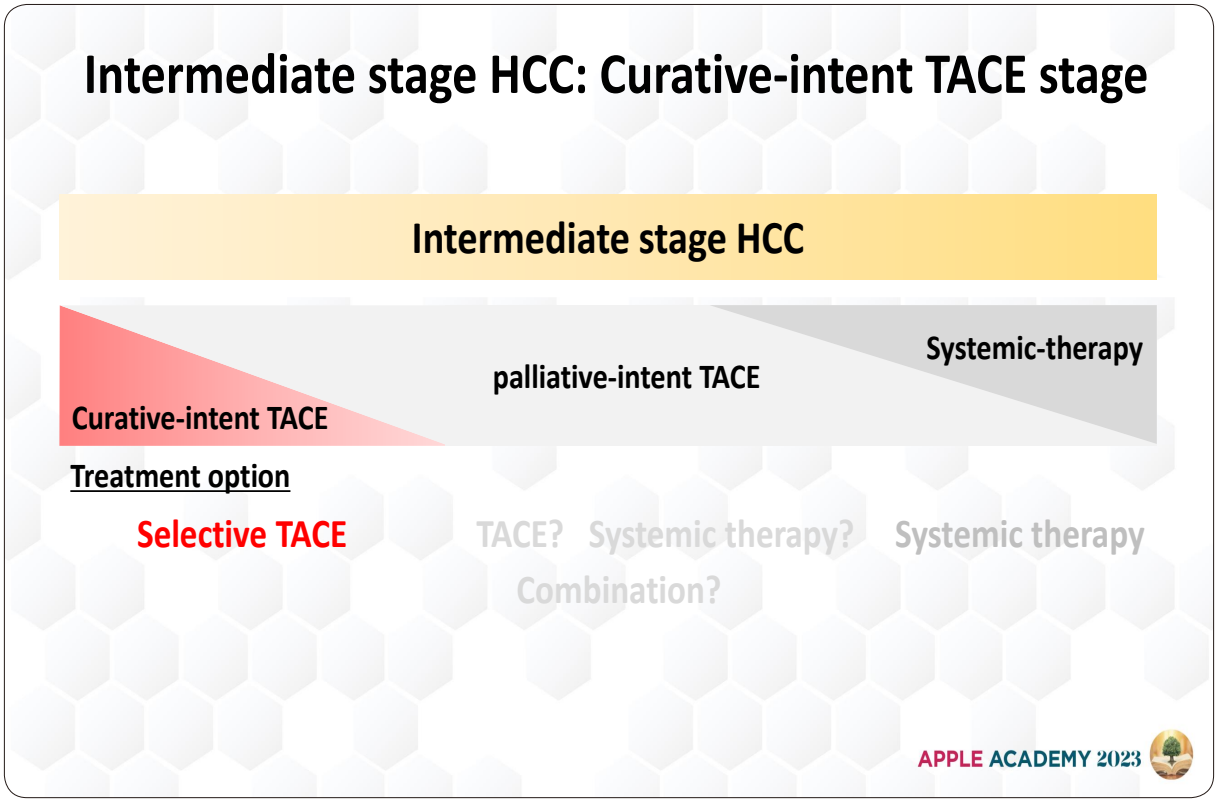
Intermediate stage HCC: Curative-intent TACE stage
Intermediate stage HCC
Curative-intent TACE
palliative-intent TACE
Systemic-therapy
Treatment option
Selective TACE
TACE?
Systemic therapy?
Systemic therapy
Combination?
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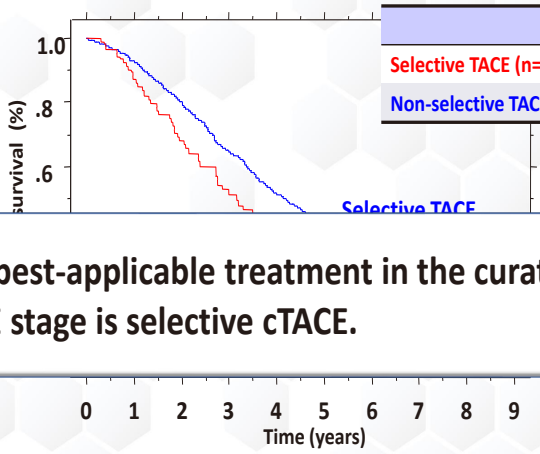
Selective TACE vs. Non-selective TACE

Study subjects: HCC patients with 7 cm or smaller in size and 5 or less nodules

	1 yr	3 yrs	5 yrs	7 yrs
Selective TACE (n=703)	93	65	41	28
Non-selective TACE (n=112)	87	51	27	13



- The best-applicable treatment in the curative-intent TACE stage is selective cTACE.

Significantly favorable OS has been reported in patients undergoing Selective TACE.

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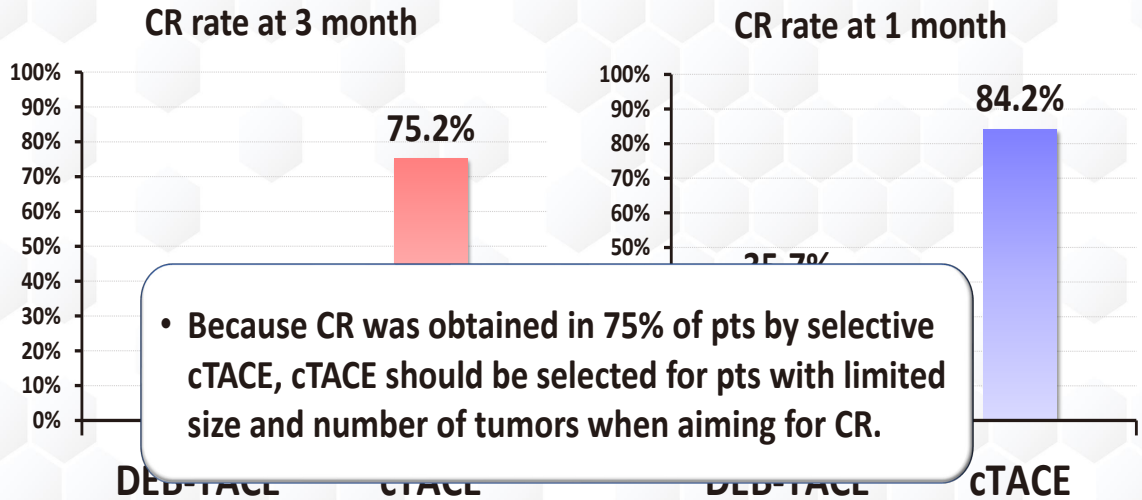
JIVROSG-1302 PRESIDENT study: CR rate (Independent review assessment)



- Because CR was obtained in 75% of pts by selective cTACE, cTACE should be selected for pts with limited size and number of tumors when aiming for CR.

Ikeda M, et al. Liver Cancer 2023

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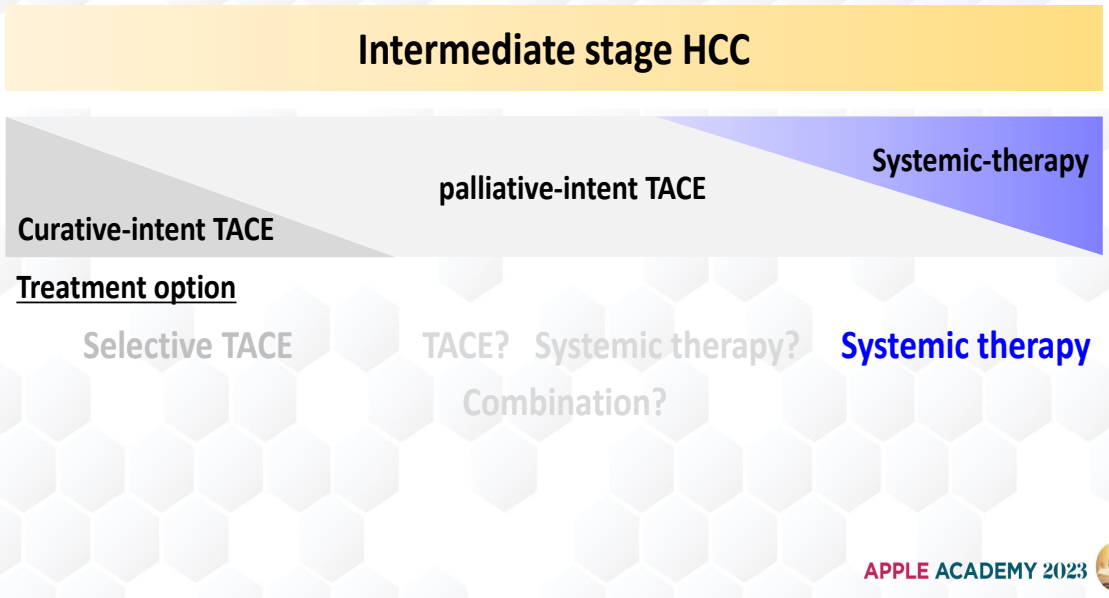
Intermediate stage HCC: Systemic therapy stage



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Definition of TACE refractoriness: JSH criteria

(1) Intrahepatic lesion

I. Two or more consecutive insufficient responses of the treated tumor (viable lesion >50%) even after changing the chemotherapeutic agents and/or reappearance of the feeding artery on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE

II. Two or more consecutive progressions in the liver (tumor number increases as compared to that before the previous TACE procedure) even after change of the chemotherapeutic agents and/or reappearance of the feeding artery on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE

(2) Continuous elevation of tumor markers immediately after TACE even though slight transient decrease is observed

(3) Appearance of vascular invasion

(4) Appearance of extrahepatic spread

Kudo M, et al. 2011

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Definition of TACE unsuitable: APPLE consensus

TACE unsuitable is defined as either of the following 3 clinical conditions that do not appreciate survival benefit from TACE:

i) Unlikely to response to TACE:
Resistant to TACE (confluent multinodular type to massive type, simple nodular type with extranodular growth, poorly-differentiated, intrahepatic multiple disseminated nodules, sarcomatous change after TACE, etc.)

ii) Likely to become TACE failure/refractoriness:
Up-To-Seven out

iii) Likely to become Child Pugh B or C by TACE:
ALBI grade 2

APPLE Expert Consensus members proposed the TACE unsuitable criteria. Further investigation is needed to clarify if the criteria is appropriate.

Kudo M, et al. Liver Cancer 2020

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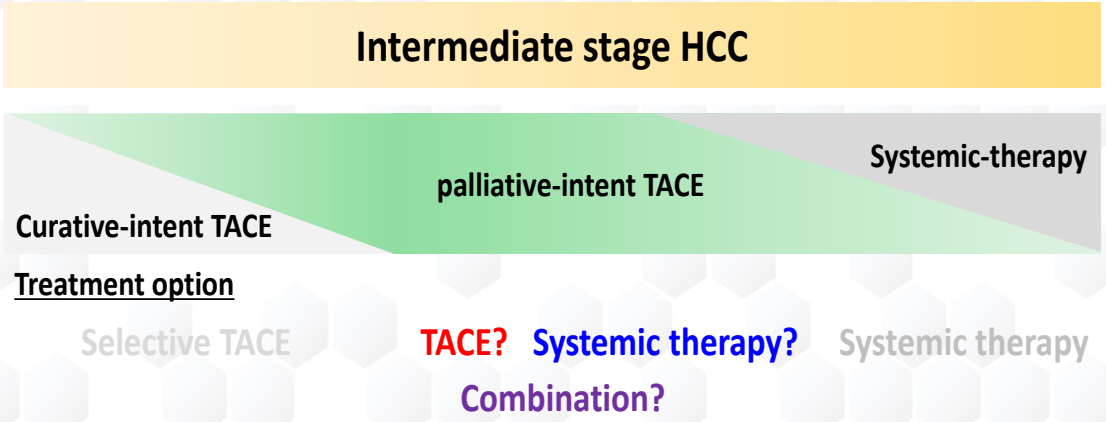
Intermediate stage HCC: Palliative-intent TACE stage



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Randomized trials of TACE plus systemic therapy vs. TACE alone

	Post-TACE		SPACE		TACE-2		TACTICS		BRISK-TA		ORIENTAL	
	Sorafenib (n=229)	Placebo (n=227)	Sorafenib (n=154)	Placebo (n=153)	Sorafenib (n=157)	Placebo (n=156)	Sorafenib (n=80)	None (n=76)	Brivanib (n=249)	Placebo (n=253)	Orantinib (n=444)	Placebo (n=444)
Phase	Phase III		Phase II		Phase III		Phase II		Phase III		Phase III	
OS(median)	29.7mo	NR	NR	NR	21.1mo	19.7mo	36.2mo	30.8mo	26.4mo	26.1mo	31.1mo	32.3mo
HR (95%CI)	1.06 (0.69-1.64)		0.898 (0.606-1.330)		0.91 (0.67-1.24)		0.861 (0.607-1.223)		0.90 (0.66-1.23)		1.090 (0.878-1.352)	
p-value	0.79		0.295		0.57		0.40		0.528		0.435	
PFS(median)	5.4mo	3.7mo	5.6mo	5.5mo	7.9mo	7.8mo	25.2mo	13.5mo	8.4mo	4.9mo	2.9mo	2.5mo
HR (95%CI)	0.87 (0.70-1.09)		0.797 (0.588-1.080)		0.99 (0.77-1.27)		0.59 (0.41-0.87)		0.61 (0.48-0.77)		0.858 (0.744-0.990)	
p-value	0.252		0.072		0.94		0.006		<0.0001		0.0356	
ORR	-	-	35.70%	28.10%	54%	52%	71.3%	61.8%	48	42	-	-
p-value	-		-		-		0.23		-		-	
Tx duration (median)	17.1wks	20.1wks	21.0wks	27.3wks	17.1wks	23.1wks	38.7wks	-	24.0wks	26.4wks	43.6wks	49.2wks

TACE plus systemic therapy did not significantly delay the TTP or prolong the OS in comparison to TACE alone, except TACTICS trial.

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Kudo M, et al. 2011; Lencioni R, et al. 2016; Meyer T, et al. 2017; Kudo M, et al. 2019; Kudo M, et al. 2014; Kudo M, et al. 2018.

Ongoing clinical trials in intermediate stage HCC

Trial name	Test arm	Comparator	Primary endpoint
EMERALD-1	TACE+Durva or TACE+Durva+Bev	TACE+Placebo	PFS
EMERALD-3	TACE+Durva+Treme+Lenva or TACE+Durva+Treme	TACE	PFS
LEAP-012	TACE+Lenva+Pembro	TACE+Placebo	PFS/OS
CheckMate-74W	TACE+Ipi+Nivo	TACE+Placebo	Time to TACE progression/OS
TACE-3	TACE+Nivo	TACE alone	OS/Time to TACE progression
TALENT-ACE	TACE+Atezo+Bev	TACE alone	TACE PFS/OS

A lot of phase III trials of TACE plus systemic therapy vs. TACE are ongoing now.

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Intermediate-Stage HCC: Expanding the Role of Systemic Therapy

Conclusions

- Intermediate-stage HCC should be divided into the following 3 stages according to the best-applicable treatment strategy: curative-intent TACE stage, palliative-intent TACE stage, and systemic-therapy stage.
- The best-applicable treatment
  - Curative-intent TACE stage: Selective cTACE
  - Palliative-TACE stage: TACE plus systemic therapy
  - Systemic-therapy stage: Systemic therapy

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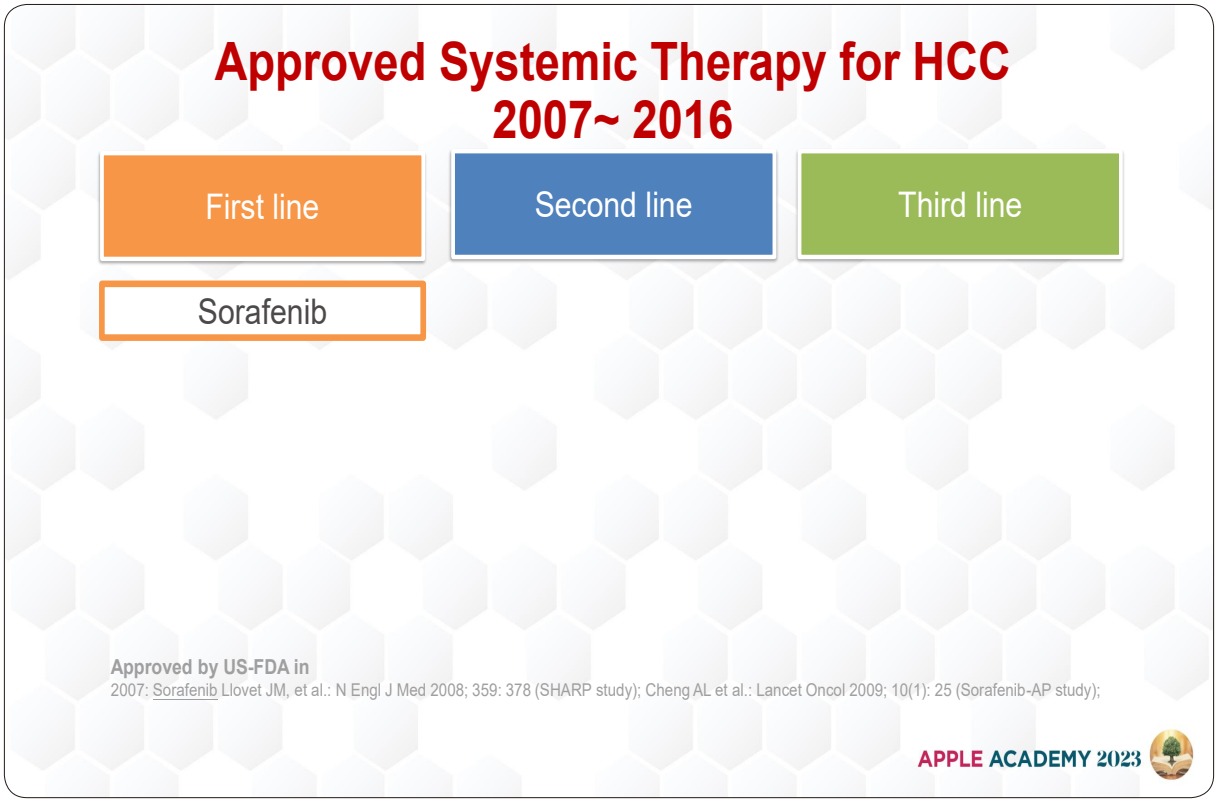
Session 3. Unmet Clinical Need in and Current Clinical Research Directions

Advanced HCC: Beyond IMbrave150 and HIMALAYA

Chih-Hung Hsu *(National Taiwan Univ., Taipei)*



Approved Systemic Therapy for HCC Since Oct of 2022

First line	Second line	Third line
Sorafenib	Regorafenib	
Lenvatinib	Cabozantinib	
Atezolizumab + Bevacizumab	Ramucirumab*	
Tremelimumab + Durvalumab	Nivolumab (Nivo)	
	Pembrolizumab	
	Nivo+ Ipilimumab	

Approved by US-FDA in
2007: Sorafenib Llovet JM, et al.: N Engl J Med 2008; 359: 378 (SHARP); Cheng AL et al.: Lancet Oncol 2009; 10(1): 25 (Sorafenib-AP study);
2017: Regorafenib El-KhoBruix J, et al. Lancet. 2017;389:56-66 (RESORCE); Nivolumab El-Khoueiry AB et al: Lancet 2017; 389: 2492-2502 (CheckMate-040) [2021 Apr ODAC voted 5 to 4 against accelerated approval]
2018: Lenvatinib Kudo M et al. Lancet. 2018;391:1163-1173 (REFLECT); Pembrolizumab Zhu AX et al: Lancet Oncol. 2018;19:940-952 (KEYNOTE-224);
2019: Cabozantinib Abou-Alfa GK et al. N Engl J Med. 2018;379:54-63 (CELESTIAL); Ramucirumab Zhu AX et al: Lancet Oncol 2019; 20: 282–96 (REACH-2) (*for AFP ≥ 400 ng/mL and previously treated with sorafenib).
2020: Atezo+Bev Finn RS et al. N Engl J Med. 2020;382:1894-1905 (IMbrave150); Nivo+Ipi Yau T et al: JAMA Oncol. 2020;6:e204564 (CheckMate-040, cohort 4)
2022: Treme+Durva (STRIDE) Abou-Alfa GK et al. NEJM Evid 2022; 1 (8) DOI:https://doi.org/10.1056/EVIDoa2100070(HIMALAYA)

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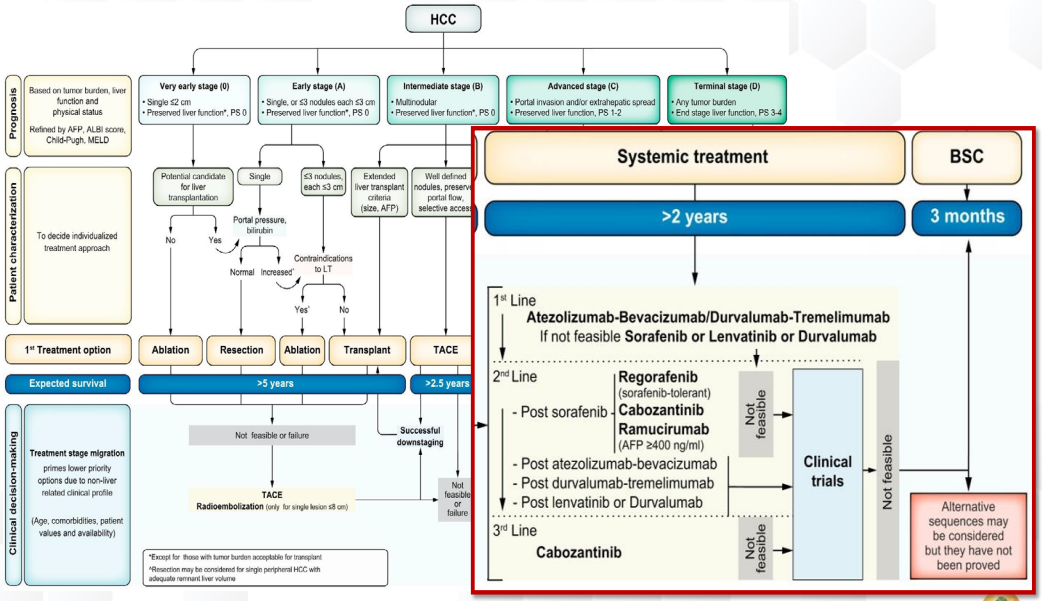
BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update



~ Reig M et al: J Hepatol 2022;76:681-693. DOI: (10.1016/j.jhep.2021.11.018)

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Advanced HCC
Combination therapy as new 1L standard

- **Higher RR (20-30%), longer PFS and OS (median > 18 months)**

	Sorafenib [SHARP]	Sorafenib [AP]	Sorafenib#	Atezo + Bev	Durva + Treme
Response Rate (%)	2%	3.3%	5.1-11%	30%	20.1%
Median PFS (months)	5.5	2.8	4.0-4.3	6.9	3.8
Median OS (months)	10.7	6.5	13.4-13.8	19.2	16.4
1-year OS (%)	44%	30%	56%	67%	~60%
2-year OS (%)			20.2%	~40%	30.7%

[Sorafenib] Llovet JM, et al: *N Engl J Med* 2008; 359: 378 (SHARP); Cheng AL et al: *Lancet Oncol* 2009; 10: 25 (Sorafenib-AP study); # Control arms of IMbrave150 and HIMALAYA A are summarized.
[Atezo + Bev] Finn RS et al: *N Engl J Med.* 2020;382:1894-1905 Cheng AL et al: *J Hepatol* 2022: 76, 862–87. (IMbrave150);
[Durva + Treme (STRIDE)] Abou-Alfa GK et al: *NEJM Evid* 2022; 1 (8) DOI:https://doi.org/10.1056/EVIDoa2100070(HIMALAYA)

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A New Era of 1L Therapy for Advanced HCC

Combination therapy (options superior to sorafenib):

- **Anti-PD-1/PD-L1 + antiangiogenic**
  - Atezolizumab/Bevacizumab
  - Sintilimab/Bev-biosimilar
  - Camrelizumab/Rivoceranib
- **Anti-PD-1/PD-L1 + anti-CTLA4**
  - Durvalumab/Tremelimumab

High RR: the more the better
=> Triplet or more combinations

Monotherapy (options non-inferior to sorafenib):

- **Lenvatinib**
- **Durvalumab**
  – Other anti-PD-1 mAbs (?)

Modest RR with good tolerability
=> Sequencing of all available agents

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New era of 1L therapy for advanced HCC
Unanswered Questions

- **Multiple 1L therapy options:**
  - Combination therapy vs. monotherapy
  - Atezo/Bev or Treme/Durva (STRIDE) as combination therapy
  - Multikinase inhibitors (sorafenib vs lenvatinib) vs anti-PD-L1 (durvalumab) as monotherapy
- **Subsequent therapies (2L and beyond)** for individual 1L therapy options.

~Modified from "Liu TH, Shao YY, Hsu CH: It takes two to tango: breakthrough advanced hepatocellular carcinoma treatment that combines anti-angiogenesis and immune checkpoint blockade. Journal of the Formosan Medical Association 2021; 120:1~4".

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1L Combination Therapy for Advanced HCC: Atezo/Bev, STRIDE
What's next?

- **To add:**
  - Triplet, quadruplet..
    - Need to take the balance of toxicities and effects into account.
- **To select:**
  - Biomarkers for effectiveness or resistance of Atezo/Bev?
  - Biomarkers for effectiveness of resistance of STRIDE?

~Modified from "Liu TH, Shao YY, Hsu CH: It takes two to tango: breakthrough advanced hepatocellular carcinoma treatment that combines anti-angiogenesis and immune checkpoint blockade. Journal of the Formosan Medical Association 2021; 120:1~4".

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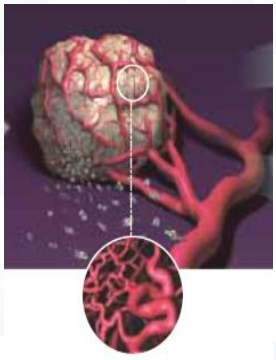
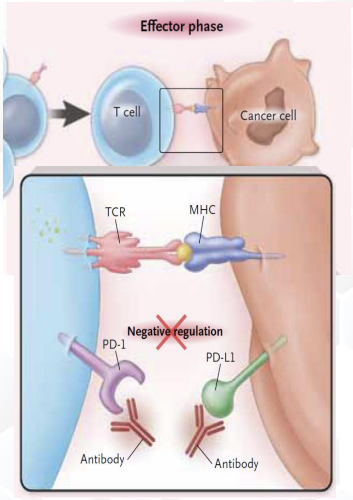
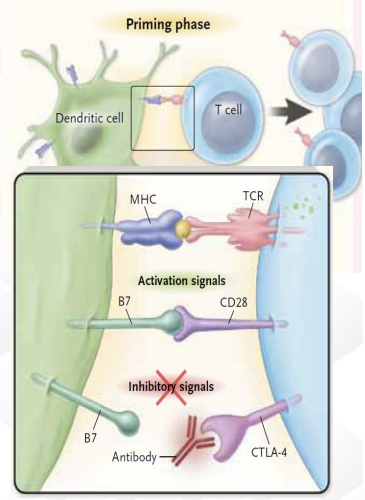
Combination 1L Therapy for Advanced HCC
Anti-angiogenic targeted therapy vs Immune checkpoint blockade







Anti-VEGF/VEGFR | **Anti-PD-1/PD-L1** | **Anti-CTLA-4**

RR~ 30%; mPFS~ 7 months; mOS~19 months

RR~ 20%; mPFS~ 4 months; mOS~16 months

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Systemic Therapy for Advanced HCC
Triplet combinations (1)

- **Anti-VEGF/VEGFR + anti-PD-1/PD-L1 + anti-CTLA-4**
  - Cabozantinib + Nivolumab + Ipilimumab [CheckMate040] (Yau T et al: J Clin Oncol 2023; 41:1747-1757)
  - Lenvatinib + Coformulated Pembrolizumab/Quavonlimab (MK-1308A) [MK-1308A-004] (NCT04740307)
  - Bevacizumab or Lenvatinib + MEDI5752 (a bispecific Ab targeting PD-1 and CTLA4) (NCT05775159)

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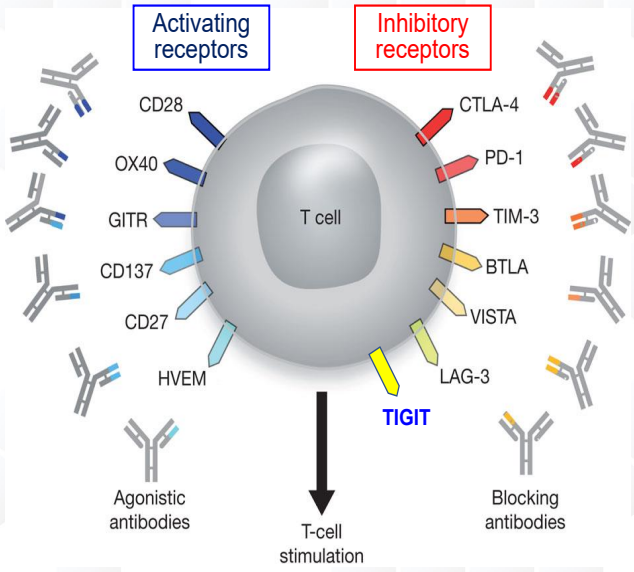
Multiple stimulatory and inhibitory signals to modulate T cell activation



~ Mellman I et al. Nature 2011; 480: 480-489 (with modifications).

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Systemic Therapy for Advanced HCC
Triplet combinations (2)

- **Atezolizumab (or an anti-PD-1/PD-L1) + bevacizumab (or an anti-VEGFR) + another ICI**
  - Phase Ib/II study [Morpheus-Liver] (NCT04524871)
    - Atezolizumab + bevacizumab + **tocilizumab** (anti-IL6R)
    - Atezolizumab + bevacizumab + **tiragolumab** (anti-TIGIT)
    - Anti-PD-1/**LAG-3** bispecific Ab + bevacizumab
    - …..
  - Phase I/II study [RELATIVITY-106] (NCT05337137)
    - Nivolumab + bevacizumab + **relatlimab** (anti-LAG-3)

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2023 ASCO ANNUAL MEETING

Results from the MORPHEUS-Liver study: Phase Ib/II randomized evaluation of tiragolumab in combination with atezolizumab and bevacizumab in patients with unresectable, locally advanced or metastatic hepatocellular carcinoma (uHCC)

Richard S. Finn MD,[1] Baek-Yeol Ryoo MD PhD,[2] Chih-Hung Hsu MD PhD,[3] Daneng Li MD,[4] Adam Burgoyne MD PhD,[5] Christopher Cotter PhD,[6] Shreya Badhrinarayanan MD,[6] Yulei Wang PhD,[6] Anqi Yin PhD,[7] Tirupathi Rao Edubilli MSc,[8] Ed Gane MBChB MD[9]

[1]University of California Los Angeles, Los Angeles, USA; [2]Asan Medical Center, Seoul, South Korea; [3]National Taiwan University Hospital, Taipei, Taiwan; [4]City of Hope Comprehensive Cancer Center, Los Angeles, USA; [5]UC San Diego, San Diego, USA; [6]Genentech, Inc., South San Francisco, USA; [7]Roche (China) Holding Co., Ltd., Shanghai, P. R. China; [8]Roche Products Ltd., Welwyn Garden City, UK; [9]University of Auckland, Auckland, New Zealand

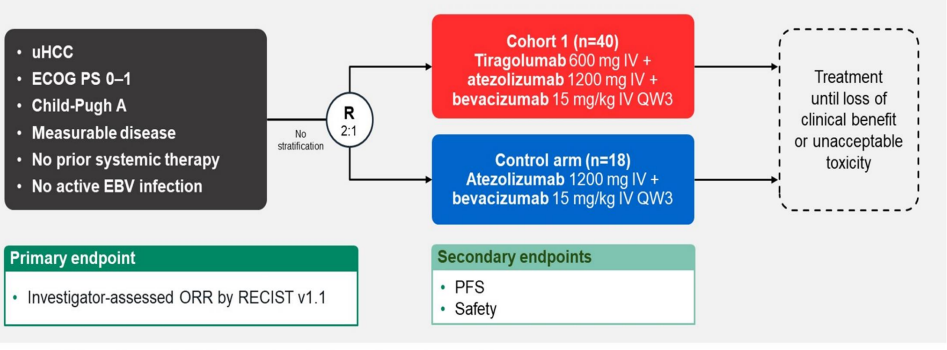
2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Richard S. Finn, MD

~ Finn RS et al: ASCO 2023 Abstract 4010

APPLE ACADEMY 2023

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

- MORPHEUS-Liver is an umbrella study evaluating multiple immunotherapy-based treatment combinations in participants with uHCC who have not yet received prior systemic therapy
- Cohort 1 investigated the addition of tiragolumab to atezolizumab + bevacizumab



Q3W, every 3 weeks; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status
IV, intravenous; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

NCT04524871

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Richard S. Finn, MD

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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~ Finn RS et al: ASCO 2023 Abstract 4010

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Atezo + Bev + Tiragolumab: 1L in uHCC
Phase Ib/II MORPHEUS-Liver Study

- Tiragolumab: an anti-TIGIT mAb
  - TIGIT: a co-inhibitory molecule expressed activated T cells, NK cells, and Treg cells.
- In MORPHEUS-Liver study, the Atezo/Bev/Tira triplet combo showed:
  - Improved treatment efficacy:
    - RR= 42.5%; mPFS= 11. 1 months
  - No significant increase of TRAEs and AESIs
- A planned phase III trial (IMbrave 152/SKYSCRAPER-14), comparing Atezo/Bev/Tira triplet with Atezo/Bev, is expected to begin soon.

~ Finn RS et al: ASCO 2023 Abstract 4010

APPLE ACADEMY 2023

Systemic Therapy for Advanced HCC
Triplet combinations (3)

- **Atezolizumab (or an anti-PD-1/PD-L1) + bevacizumab (or an anti-VEGFR) + an immune modulator**
  - Phase II study (NCT05359861)
    - Atezolizumab + bevacizumab + **SRF388** (anti-IL27)

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1L Combination Therapy for Advanced HCC: Atezo/Bev, STRIDE

What's next?

- To add:
  - Triplet, quadruplet..
    - Need to take the balance of toxicities and effects into account.

- **To select:**
  - Biomarkers for effectiveness or resistance of Atezo/Bev?
  - Biomarkers for effectiveness of resistance of STRIDE?

~Modified from "Liu TH, Shao YY, Hsu CH: It takes two to tango: breakthrough advanced hepatocellular carcinoma treatment that combines anti-angiogenesis and immune checkpoint blockade. Journal of the Formosan Medical Association 2021; 120:1~4".

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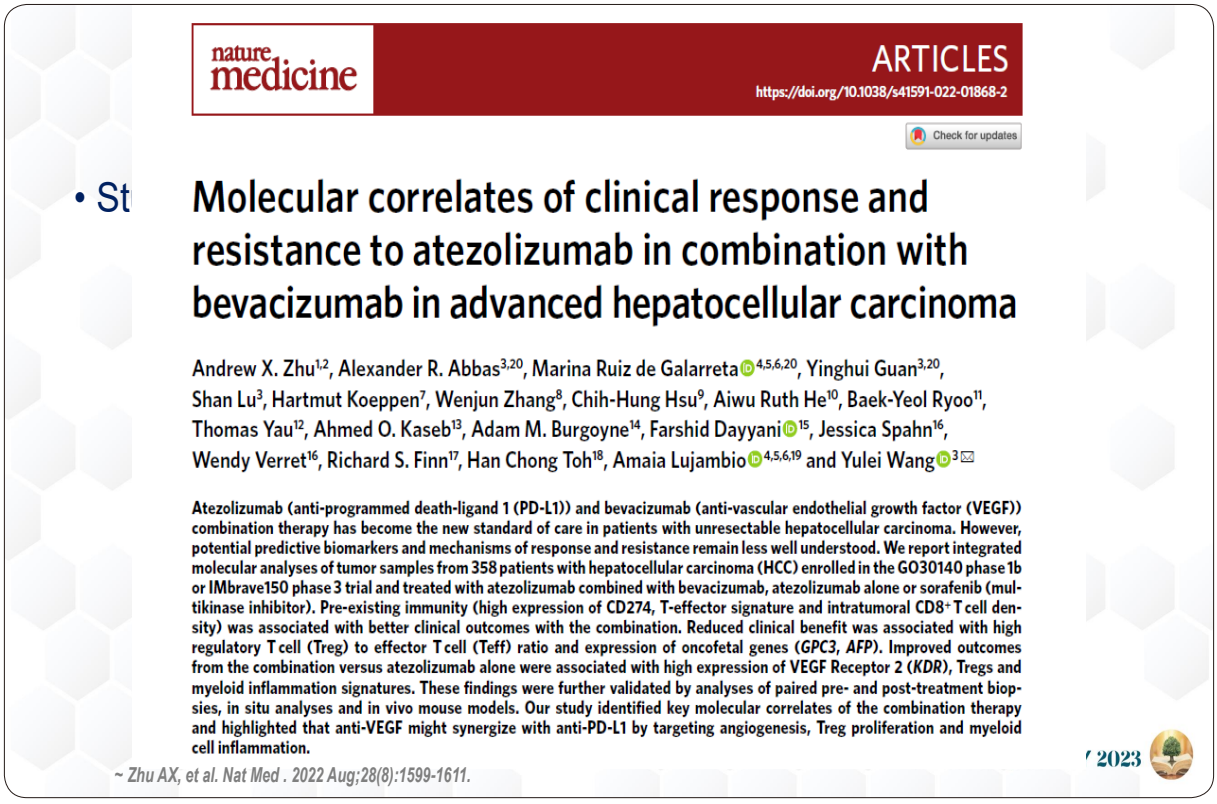

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01868-2

Check for updates

• St

Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma

Andrew X. Zhu[1,2], Alexander R. Abbas[3,20], Marina Ruiz de Galarreta[4,5,6,20], Yinghui Guan[3,20], Shan Lu[3], Hartmut Koeppen[7], Wenjun Zhang[8], Chih-Hung Hsu[9], Aiwu Ruth He[10], Baek-Yeol Ryoo[11], Thomas Yau[12], Ahmed O. Kaseb[13], Adam M. Burgoyne[14], Farshid Dayyani[15], Jessica Spahn[16], Wendy Verret[16], Richard S. Finn[17], Han Chong Toh[18], Amaia Lujambio[4,5,6,19] and Yulei Wang[3]✉

Atezolizumab (anti-programmed death-ligand 1 (PD-L1)) and bevacizumab (anti-vascular endothelial growth factor (VEGF)) combination therapy has become the new standard of care in patients with unresectable hepatocellular carcinoma. However, potential predictive biomarkers and mechanisms of response and resistance remain less well understood. We report integrated molecular analyses of tumor samples from 358 patients with hepatocellular carcinoma (HCC) enrolled in the GO30140 phase 1b or IMbrave150 phase 3 trial and treated with atezolizumab combined with bevacizumab, atezolizumab alone or sorafenib (multikinase inhibitor). Pre-existing immunity (high expression of CD274, T-effector signature and intratumoral CD8⁺ T cell density) was associated with better clinical outcomes with the combination. Reduced clinical benefit was associated with high regulatory T cell (Treg) to effector T cell (Teff) ratio and expression of oncofetal genes (*GPC3*, *AFP*). Improved outcomes from the combination versus atezolizumab alone were associated with high expression of VEGF Receptor 2 (*KDR*), Tregs and myeloid inflammation signatures. These findings were further validated by analyses of paired pre- and post-treatment biopsies, in situ analyses and in vivo mouse models. Our study identified key molecular correlates of the combination therapy and highlighted that anti-VEGF might synergize with anti-PD-L1 by targeting angiogenesis, Treg proliferation and myeloid cell inflammation.

~ Zhu AX, et al. Nat Med . 2022 Aug;28(8):1599-1611.

' 2023

1L Systemic Therapy for Advanced HCC
Conclusions

- Multiple 1L therapy options, including combinations and monotherapies, are available.
  - Individualized approach:
    - Biomarkers?
    - Clinical parameters?
- The "next-generation" combination 1L therapy for advanced HCC needs to take the balance of effect and toxicity into account.
  - Triplet combinations including inhibitors of additional immune checkpoint or immune modulators are emerging.
  - Other novel approaches.

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Systemic Therapy for Advanced HCC: beyond Atezo/Bev, STRIDE
What else?

- **To know HCC better:**
  - **HCC-specific markers**
    - CAR-T therapy
    - Antibody-drug conjugates
    - T-cell engagers
  - **HCC molecular/genetic alterations**
    - TERT promoter mutation
    - WNT/beta-catenin
    - Others….

APPLE ACADEMY 2023

APPLE ACADEMY 2023

Thursday, July 6, 2023 [ROOM C (Grand Ballroom 3)]

Session 4.

From APPLE Academy into the Future

Chairs: Masatoshi Kudo *(Kindai Univ., Osaka)*
Jian Zhou *(Fudan Univ., Shanghai)*

Investigator-Initiated Trials for HCC in the Asia-Pacific Region
Pierce Chow *(National Cancer Centre Singapore, Singapore)*

APPLE Association as a Platform for Future International Research Collaboration
Kwang-Hyub Han *(CHA Univ., Seoul)*

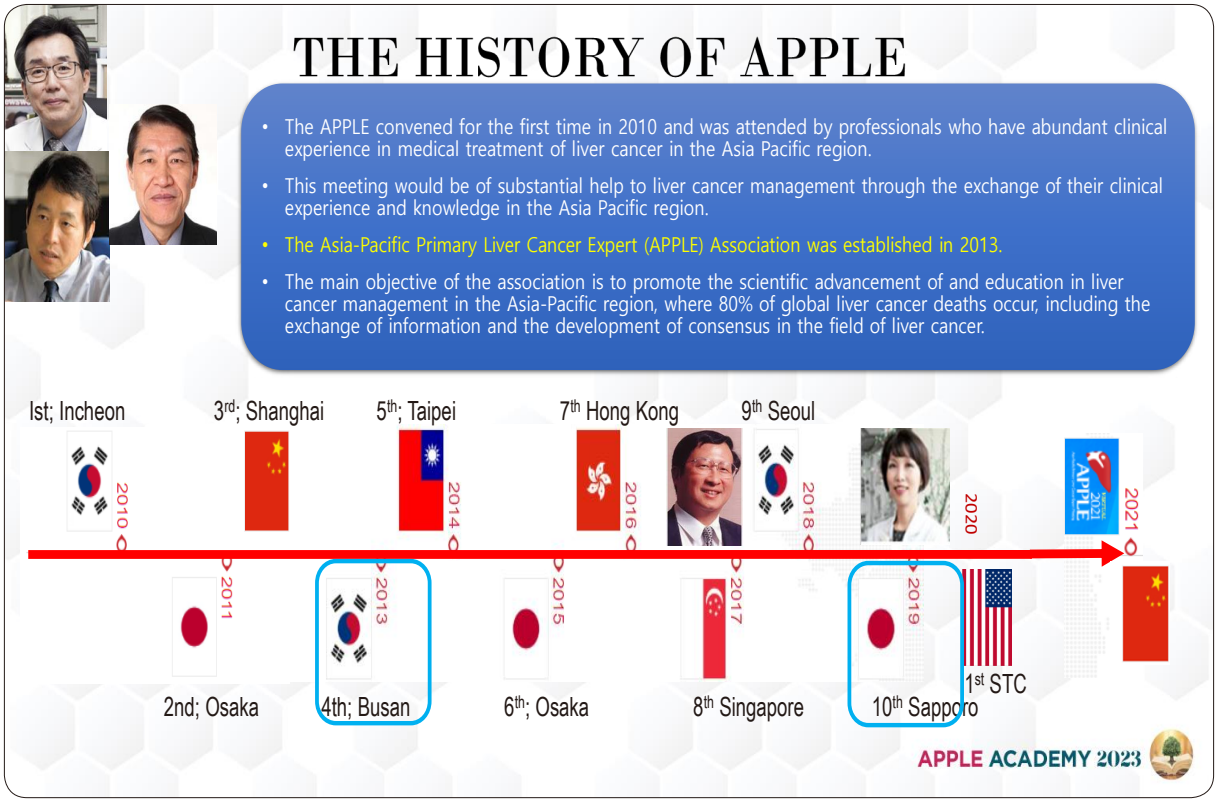
Promoting the Next-Generation Liver Cancer Experts to the Global Arena
Ann-Lii Cheng *(National Taiwan Univ. Cancer Center,Taipei)*

Investigator-Initiated Trials for HCC in the Asia-Pacific Region

Pierce Chow *(National Cancer Centre Singapore, Singapore)*

APPLE Association as a Platform for Future International Research Collaboration

Kwang-Hyub Han *(CHA Univ., Seoul)*



Our Mission and Vision

- To ensure a coherent standpoint concerning liver cancer treatment and its patients, a broad representation drawn from the Asia-Pacific region including its national and international experts have come together to lay a bridge and form a consensus among them.
- We plan to invite renowned experts from all over the world to have in-depth discussions about clinical experiences and share knowledge, and problems associated with liver cancer treatment not only in the Asia-Pacific region but also globally in the long run.

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Challenge : Global Heterogeneity for the management of HCC

APPLE ACADEMY 2023

APPLE Academy

- To commence the Educational Program, 2019, the first APPLE Academy meeting is set on Aug 29, 2019 in Sapporo, Japan.
- This program is expected to become a stepping stone for our next generation of doctors and non-expert doctors who are interested in liver cancer.
- To offer a summary of the state of the art knowledge of research and clinical management of HCC to doctors and researchers in Asia-Pacific Area
- To establish a **platform** for communication, experience sharing and exploring the opportunity of collaboration in Asia-Pacific Area

APPLE ACADEMY 2023

Key difference between East and West

- Experience > Evidence in East
- Experience < Evidence in West

If the only tool you have is a hammer, **you tend to see every problem as a nail**

Abraham Maslow

APPLE ACADEMY 2023

Grading evidence and recommendations

- Grading is a simplified adaptation of the GRADE system[1]

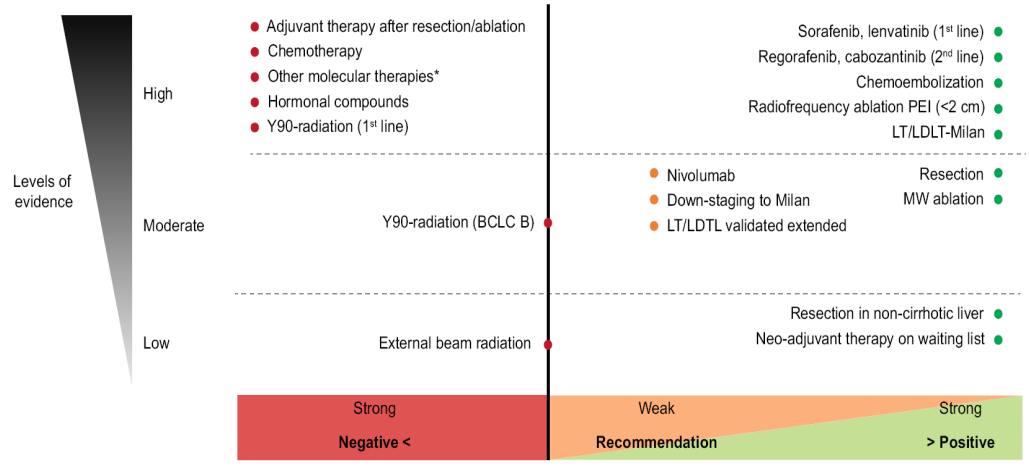
Level of evidence*		*Confidence in the evidence*
High	Data derived from meta-analyses or systematic reviews or from (multiple) RCTs with high quality	*Further research is unlikely to change our confidence in the estimate of benefit and risk*
Moderate	Data derived from a single RCT or multiple non-randomized studies	*Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate*
Low	Small studies, retrospective observational studies, registries	*Any estimate of effect is uncertain*
Grade of recommendation† *(wording associated with the grade of recommendation)*		
Strong	*"Must", "should", or "EASL recommends"*	
Weak	*"Can", "may", or "EASL suggests"*	

*Level was downgraded if there was poor quality, strong bias or inconsistency between studies; level was upgraded if there was a large effect size; †Recommendations were reached by consensus of the panel and included the quality of evidence, presumed patient-important outcomes and costs

1. Guyatt GH, et al. BMJ 2008:336:924–6;

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Overview of EASL recommendations for treatment



- **Other molecular therapies: sunitinib, linifanib, brivanib, tivantinig, erlotinib, everolimus*
- *Weak recommendation: more evidence needed*

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

NECA

Next Generation Healthcare in Asia Pacific:
Where Technology Meets Patients to Improve Care

National Evidence-based Healthcare Collaborating Agency

How to improve sustainable healthcare system in AP region; A new way forward

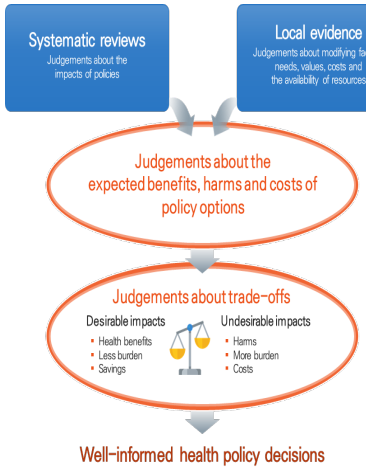
Dr. Kwang-Hyup Han
President
National Evidence-based healthcare Collaborating Agency

Virtual ISPOR Asia Pacific 2020
14-16 September

Conventional HTA & Evidence-based Medicine | Value and evidence in Heath Technology | Current Issue in HTA at NECA, Korea | Role of HTA for Sustainable Healthcare System

Conventional HTA & Evidence-based Medicine

Policy decision-making and EBH



"Robust Evidence" is essential for evidence-based healthcare policy

01 Exploring global evidence through systematic review

02 Applying through analysis of local evidence such as demand, cost, and available resources

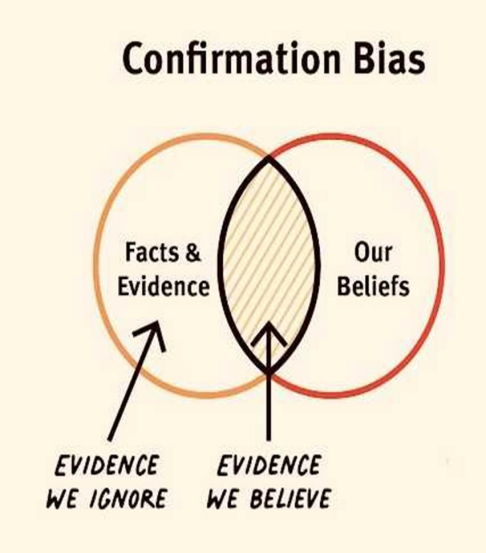
Source: Oxman, SUPPORT Tools for evidence-informed health Policy making (STP) 1: What is evidence-informed policy making? Health research policy and systems,2009

10

NECA National Evidence-based Healthcare Collaborating Agency

Why EBM(P) in Healthcare

- Information overload
- Rising patient expectations
- New and advanced technologies
- Aging populations



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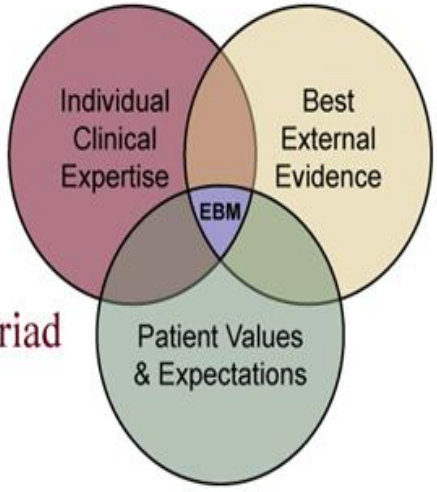
What is Evidence-Based Medicine?
Evidence-Based Medicine is a systematic approach to clinical problem-solving which allows the integration of the best available research evidence with clinical expertise and patient values.



The EBM Triad

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Evolution of new systemic treatment for ad. HCC

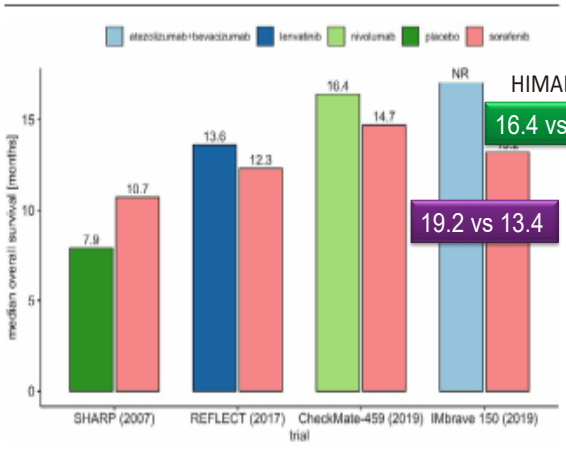


FIGURE 2 Positive phase III first-line trials evaluating tyrosine kinase inhibitor therapy and phase III trials evaluating checkpoint immunotherapy. NR = not reached.

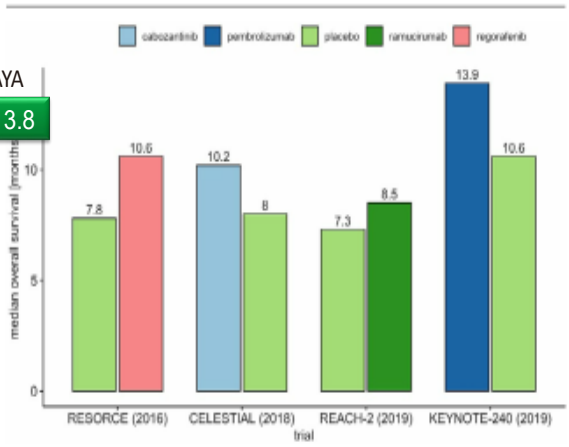
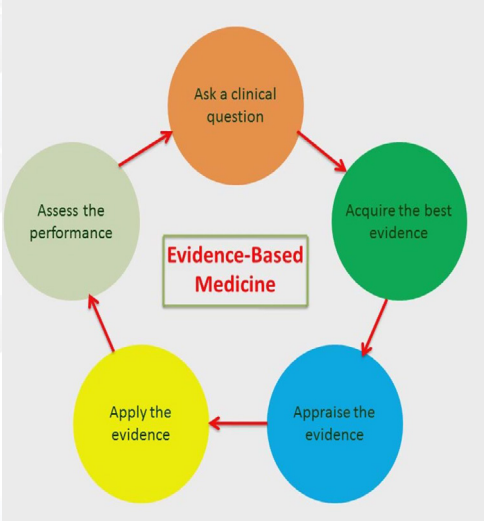


FIGURE 3 Positive phase III second-line trials evaluating tyrosine kinase inhibitor therapy and phase III trials evaluating checkpoint immunotherapy

APPLE Association as a Platform for Future International Research Collaboration

- To establish the EBM, communication, collaboration, and consensus are needed



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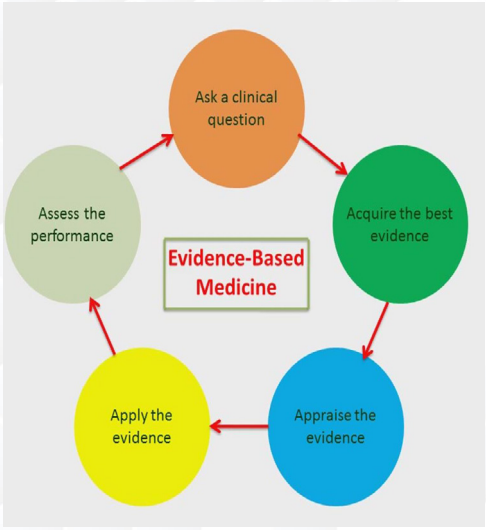
APPLE Association as a Platform for Future International Research Collaboration

- Ask **unmet clinical questions** such as role of biomarkers, LRT in advanced HCC, combination therapies, radiation therapy in IO era. Guideline for aged patients
- Collaborate to conduct IIT in Asia
- Collect the RWD and appraise RWE.
- Support CR in low-income countries



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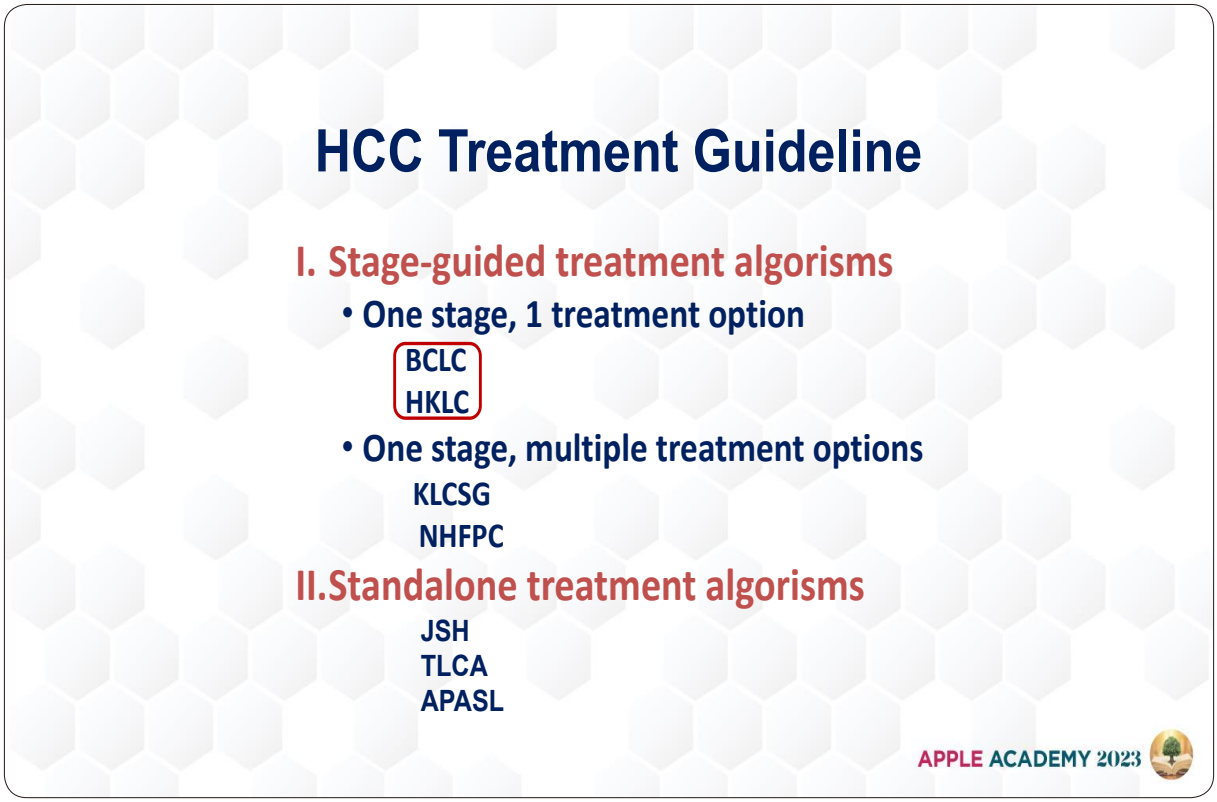
Promoting the Next-Generation Liver Cancer Experts to the Global Arena

Ann-Lii Cheng *(National Taiwan Univ., Taipei)*



Guideline harmonization

Very complicated issues for the future

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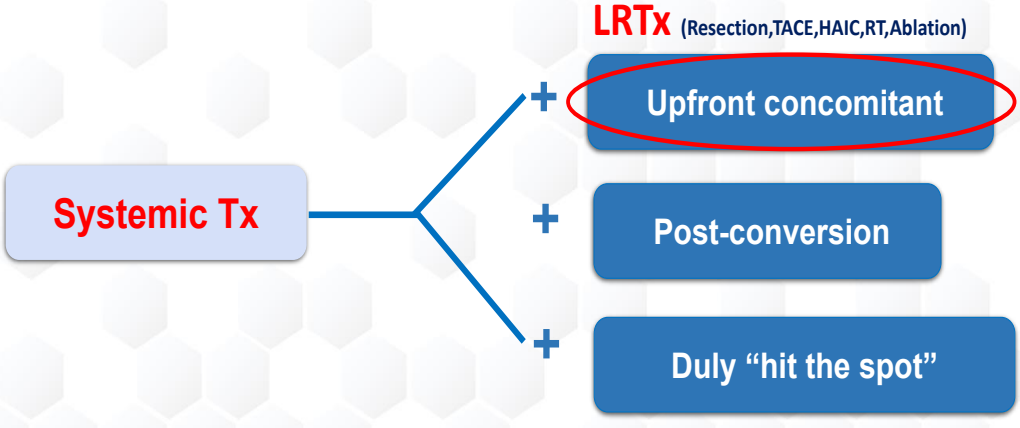
Versatile SysTx / LRTx in BCLC-C



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Lenvatinib plus TACE versus lenvatinib alone as 1L treatment for advanced HCC: phase III, randomized (LAUNCH study)

- N=336, **BCLC-C** (with TACEable primary lesions)
- Single lesion size < 10cm
  Number of lesions < 10
  Tumor burden < 50%
- Primary endpoint = OS

TACE to all TACEable

	LEN-TACE	LEN	P
ORR (RECIST1.1) (CR)	45.9% (0.6%)	20.8% (0.6%)	<0.001
mOS	17.8m	11.5m	<0.001
mPFS	10.6m	6.4m	<0.001

Peng ZW et al ASCO-GI 2022, and JCO 2023;41:117-127

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Sorafenib plus FOLFOX-HAIC vs Sorafenib for HCC with Portal Vein Invasion — A randomized trial

N = 247

FOLFOX-HAIC
Oxa 85 mg/m², D1 5-FU bolus 400mg/m² ,then 2400 mg/m², 46hrs Leucovorin 400mg/m², D1

Results:

	mOS(m)	PFS(m)	RR(%)
HAIC + Sor	13.4	7.0	40.8
Sor	7.1	2.6	2.5
P	<0.001	<0.001	<0.001

He M et al JAMA Oncol 2019(5):953-60

APPLE ACADEMY 2023

Adding Radiation to Systemic Therapy Extends OS for Advanced Liver Cancer

- N = 177, not suitable for resection or locoregional Tx
- SBRT+Sorafenib vs Sorafenib
- OS 15.8 vs 12.3 months (P=0.042, adjusted)
  PFS 9.2 vs 5.5 months (P < 0.001)

Dawson L et al, ASTRO 2022

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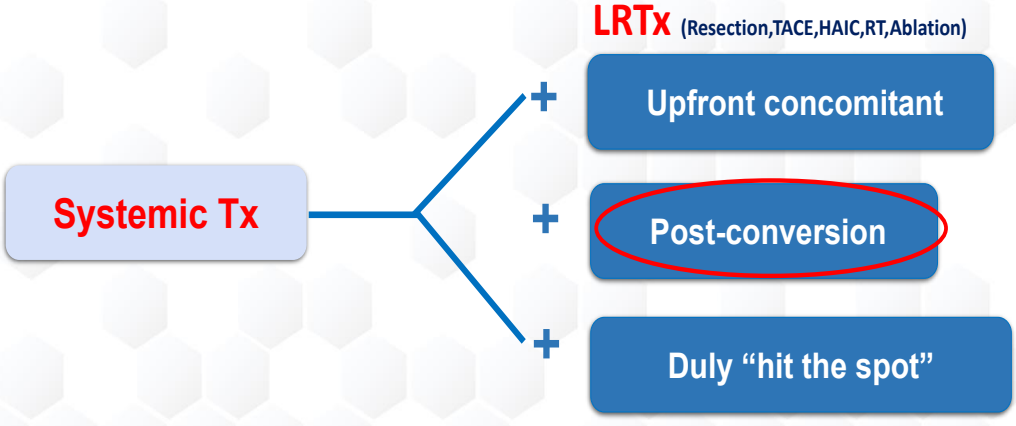
Versatile SysTx / LRTx in BCLC-C



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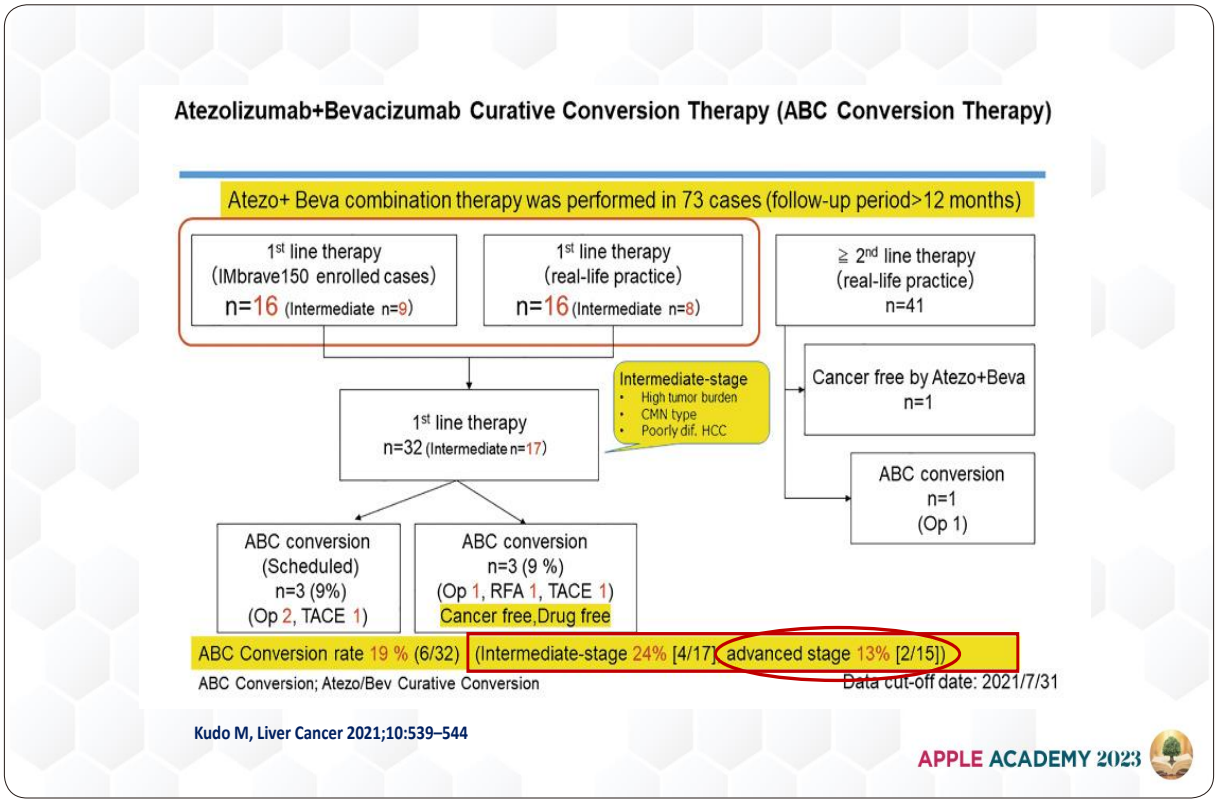
Atezolizumab+Bevacizumab Curative Conversion Therapy (ABC Conversion Therapy)
Atezo+ Beva combination therapy was performed in 73 cases (follow-up period>12 months)
1st line therapy (IMbrave150 enrolled cases) n=16 (Intermediate n=9)
1st line therapy (real-life practice) n=16 (Intermediate n=8)
≧ 2nd line therapy (real-life practice) n=41
Cancer free by Atezo+Beva n=1
ABC conversion n=1 (Op 1)
Intermediate-stage
High tumor burden
CMN type
Poorly dif. HCC
1st line therapy n=32 (Intermediate n=17)
ABC conversion (Scheduled) n=3 (9%) (Op 2, TACE 1)
ABC conversion n=3 (9 %) (Op 1, RFA 1, TACE 1) Cancer free,Drug free
ABC Conversion rate 19 % (6/32) (Intermediate-stage 24% [4/17], advanced stage 13% [2/15])
ABC Conversion; Atezo/Bev Curative Conversion
Data cut-off date: 2021/7/31
Kudo M, Liver Cancer 2021;10:539–544
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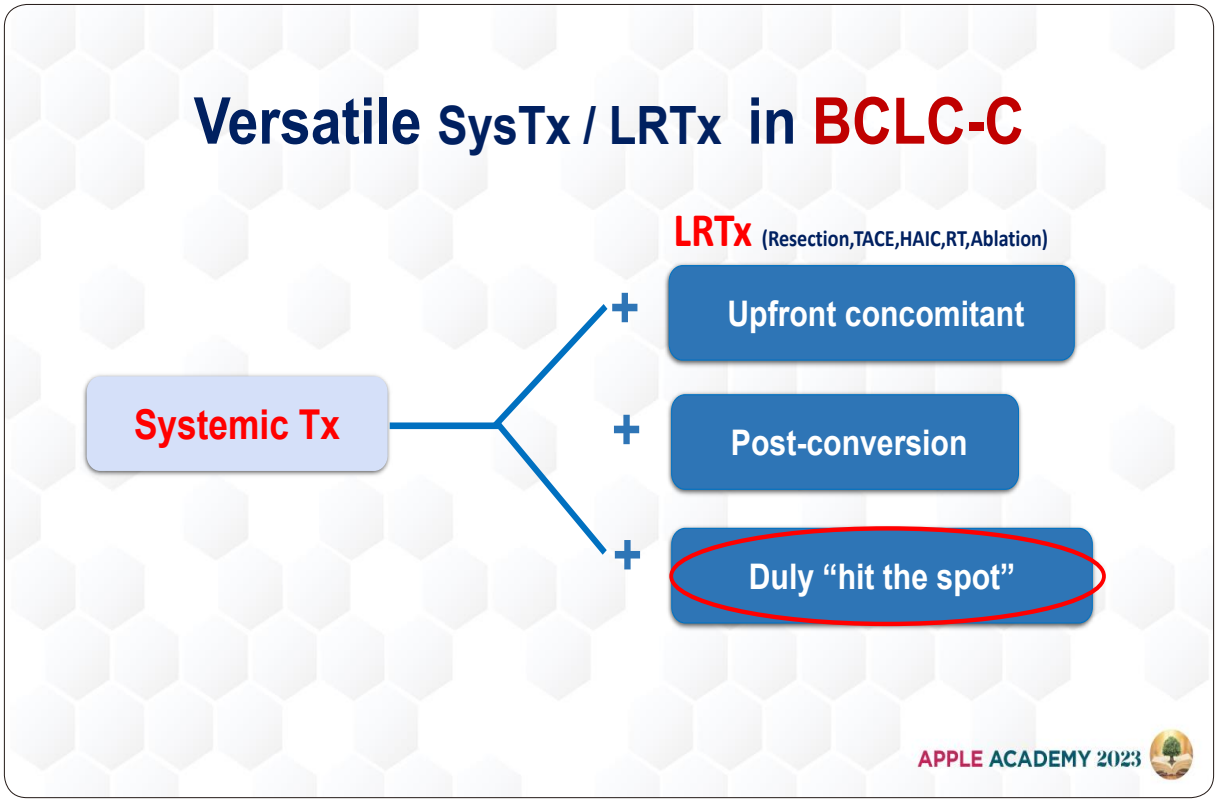
Versatile SysTx / LRTx in BCLC-C
LRTx (Resection,TACE,HAIC,RT,Ablation)
Systemic Tx
+
Upfront concomitant
+
Post-conversion
+
Duly "hit the spot"
APPLE ACADEMY 2023

Reverse Immunoediting

CR

Immune Elimination

PR mR dSD

Immune Enhancement

Immune Escape

- Size shrinking
- Markers decrease
- Growth slowdown
- Clinical improvent

LRTx

- Destroy escaping clones.
- Tilt immune balance toward tumor elimination

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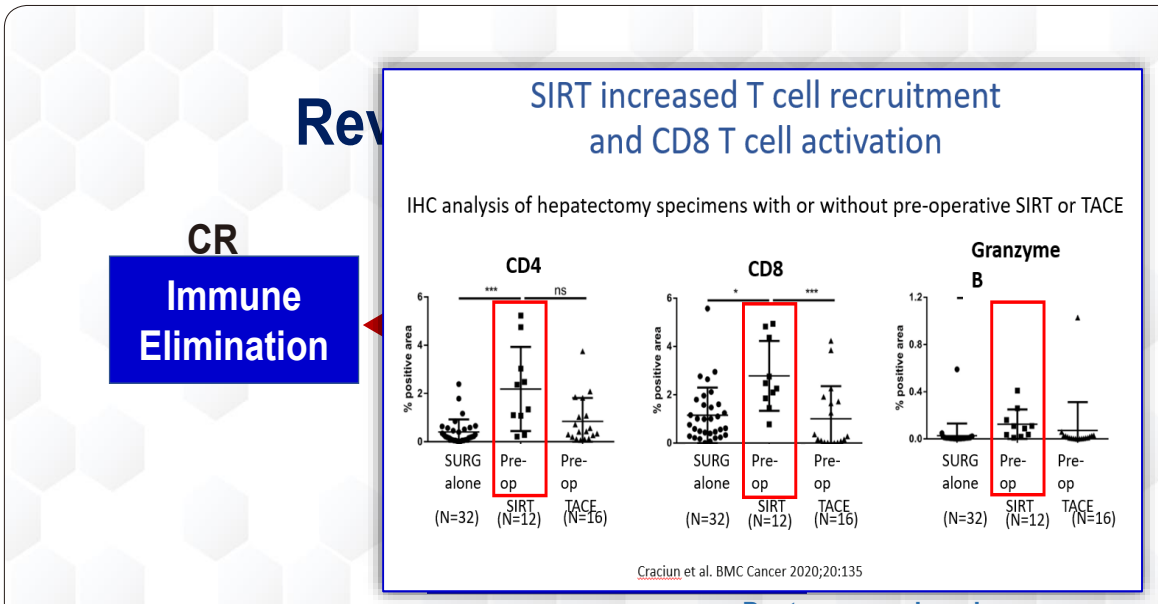
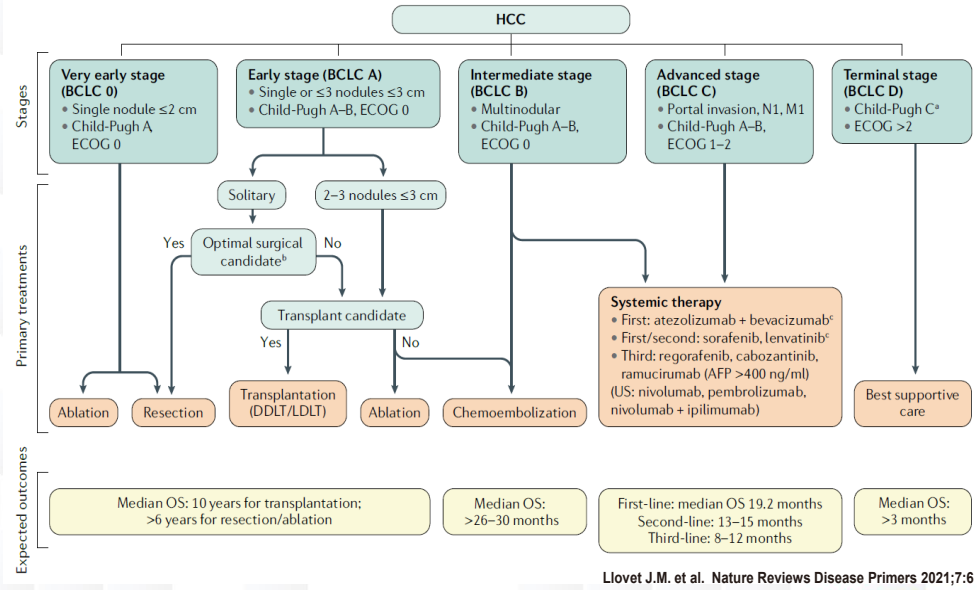


Evolving Treatment Strategy for Locally-advanced HCC



Llovet J.M. et al. Nature Reviews Disease Primers 2021;7:6

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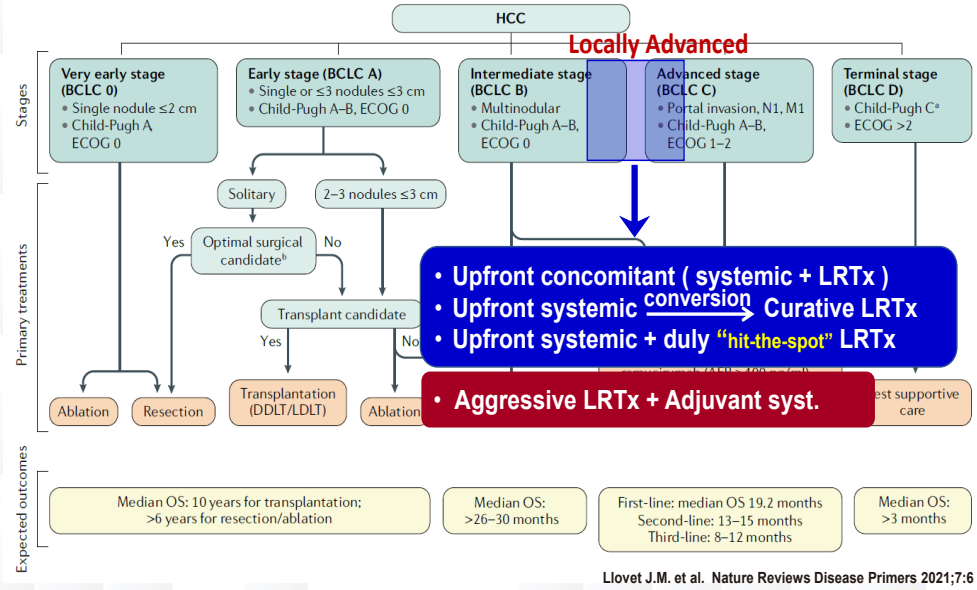
Evolving Treatment Strategy for Locally-advanced HCC



Llovet J.M. et al. Nature Reviews Disease Primers 2021;7:6

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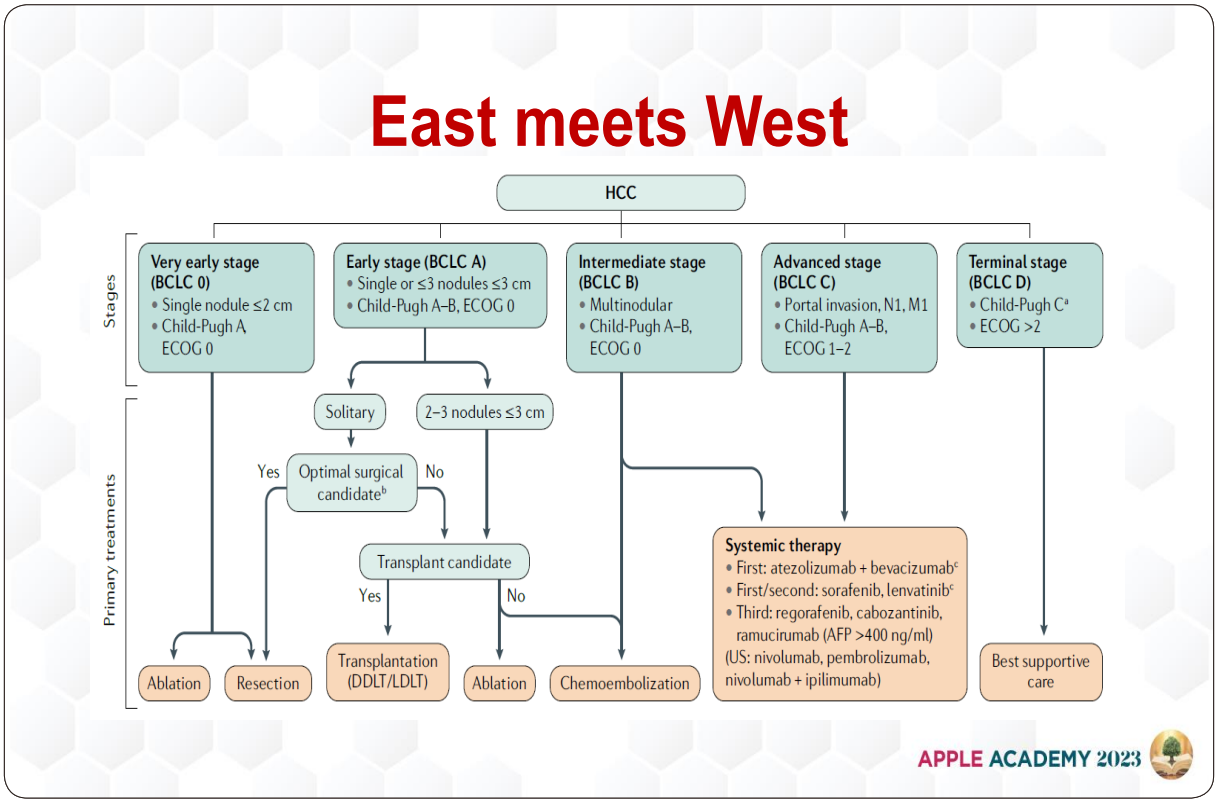
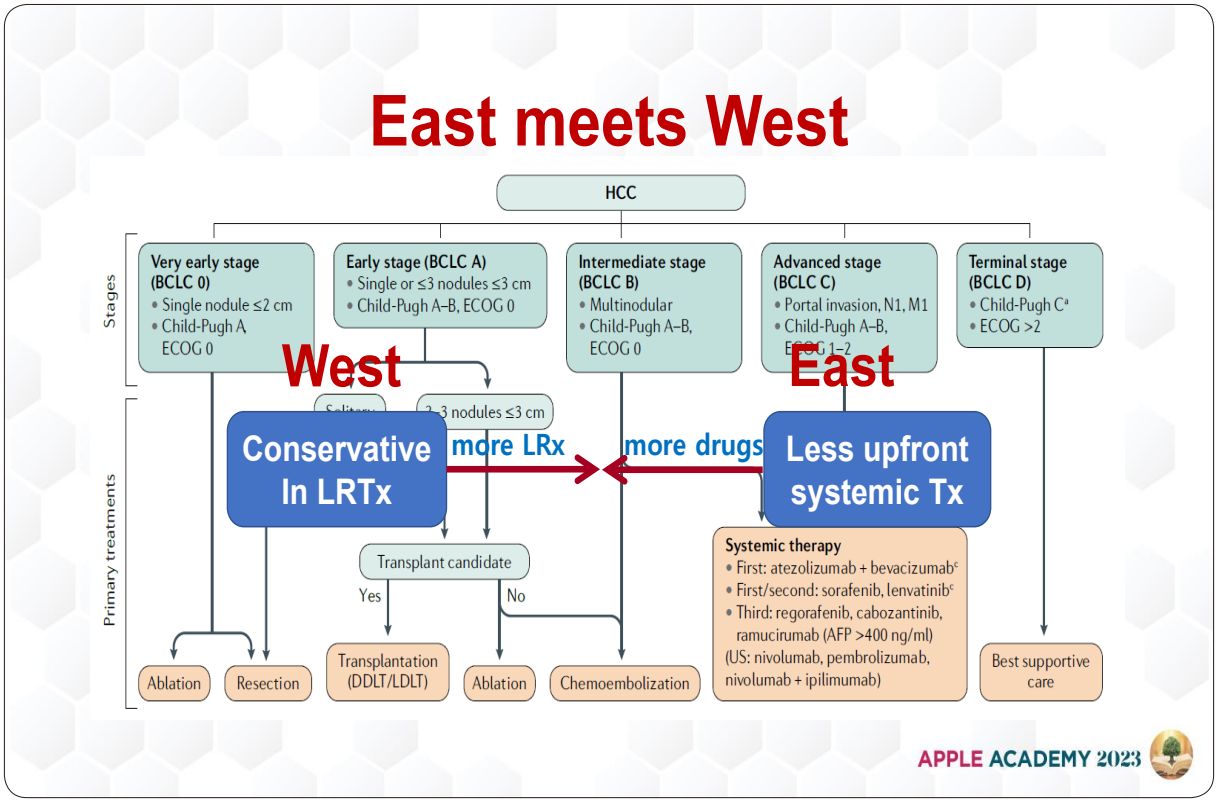

East meets West
HCC
Stages
Very early stage (BCLC 0)
• Single nodule ≤2 cm
• Child-Pugh A
ECOG 0
Early stage (BCLC A)
• Single or ≤3 nodules ≤3 cm
• Child-Pugh A–B, ECOG 0
Intermediate stage (BCLC B)
• Multinodular
• Child-Pugh A–B, ECOG 0
Advanced stage (BCLC C)
• Portal invasion, N1, M1
• Child-Pugh A–B, ECOG 1–2
Terminal stage (BCLC D)
• Child-Pugh C[a]
• ECOG >2
Primary treatments
Solitary
2–3 nodules ≤3 cm
Yes
Optimal surgical candidate[b]
No
Transplant candidate
Yes
No
Systemic therapy
• First: atezolizumab + bevacizumab[c]
• First/second: sorafenib, lenvatinib[c]
• Third: regorafenib, cabozantinib, ramucirumab (AFP >400 ng/ml)
(US: nivolumab, pembrolizumab, nivolumab + ipilimumab)
Ablation
Resection
Transplantation (DDLT/LDLT)
Ablation
Chemoembolization
Best supportive care
APPLE ACADEMY 2023


East meets West
HCC
Stages
Very early stage (BCLC 0)
• Single nodule ≤2 cm
• Child-Pugh A
ECOG 0
Early stage (BCLC A)
• Single or ≤3 nodules ≤3 cm
• Child-Pugh A–B, ECOG 0
Intermediate stage (BCLC B)
• Multinodular
• Child-Pugh A–B, ECOG 0
Advanced stage (BCLC C)
• Portal invasion, N1, M1
• Child-Pugh A–B,
Terminal stage (BCLC D)
• Child-Pugh C[a]
• ECOG >2
West
East
Conservative In LRTx
more LRx
more drugs
Less upfront systemic Tx
Primary treatments
2–3 nodules ≤3 cm
Transplant candidate
Yes
No
Systemic therapy
• First: atezolizumab + bevacizumab[c]
• First/second: sorafenib, lenvatinib[c]
• Third: regorafenib, cabozantinib, ramucirumab (AFP >400 ng/ml)
(US: nivolumab, pembrolizumab, nivolumab + ipilimumab)
Ablation
Resection
Transplantation (DDLT/LDLT)
Ablation
Chemoembolization
Best supportive care
APPLE ACADEMY 2023

Summary

- Effective systemic therapy is changing our practice of all stages of HCC.
- Complicated treatment plans are necessary for most locally advanced HCC.
- APPLE may play a pivotal role in forging new guidelines that allow upfront planning of multimodality treatments.

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Eisai

ONCOLOGY WITH SOUL

We give our first thoughts to patients and their families and helping to increase the benefits that health care provides.

Eisai Co., Ltd.(www.eisai.com)
4-6-10, Koishikawa, Bunkyo-ku,
Tokyo 112-8088, Japan
Tel: 81-3-3817-3700

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