Perspective on the Management for HCC

Toward Global Harmonization of Staging and Etiology

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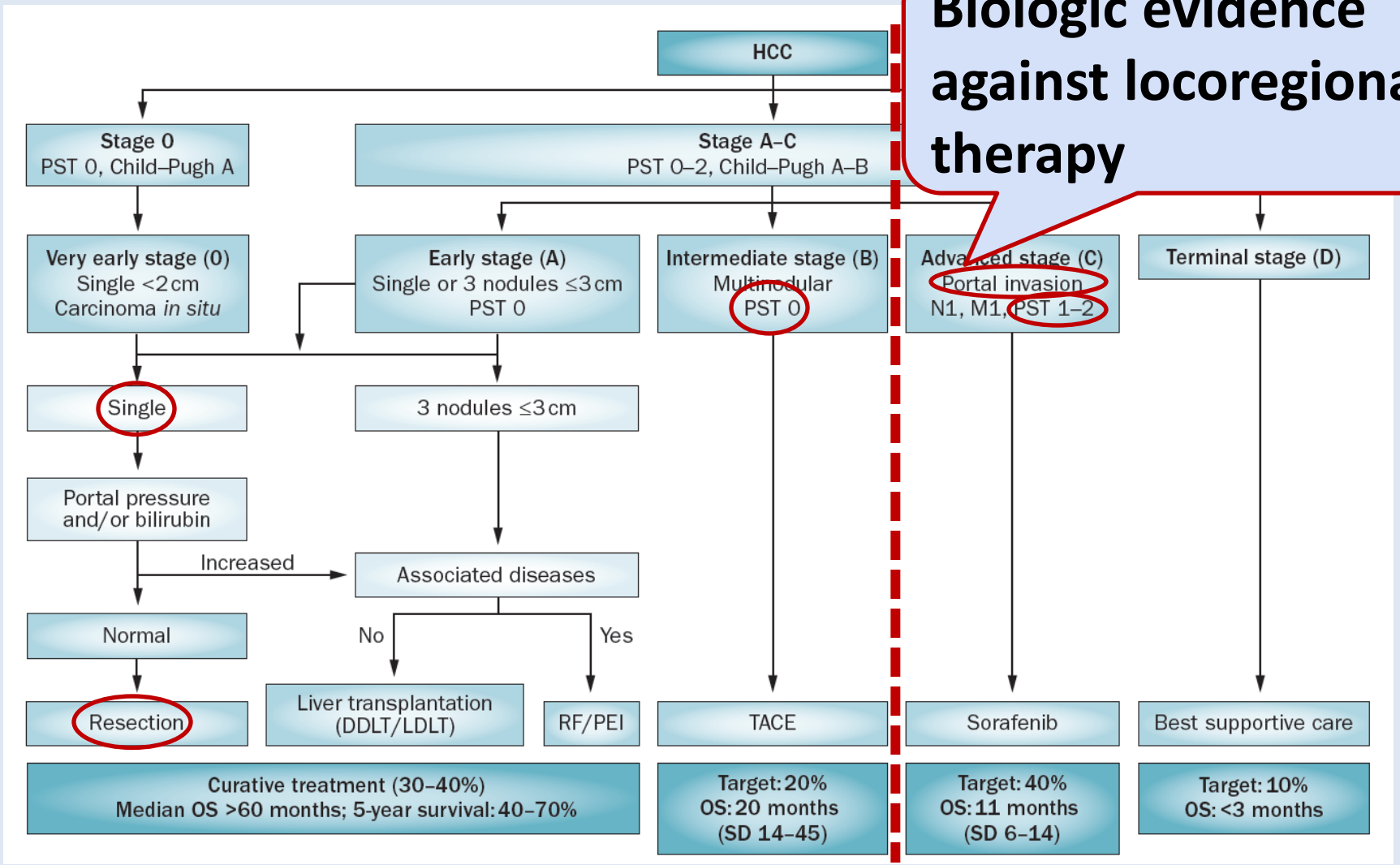
Controversies on Treatment-guiding HCC Staging Systems

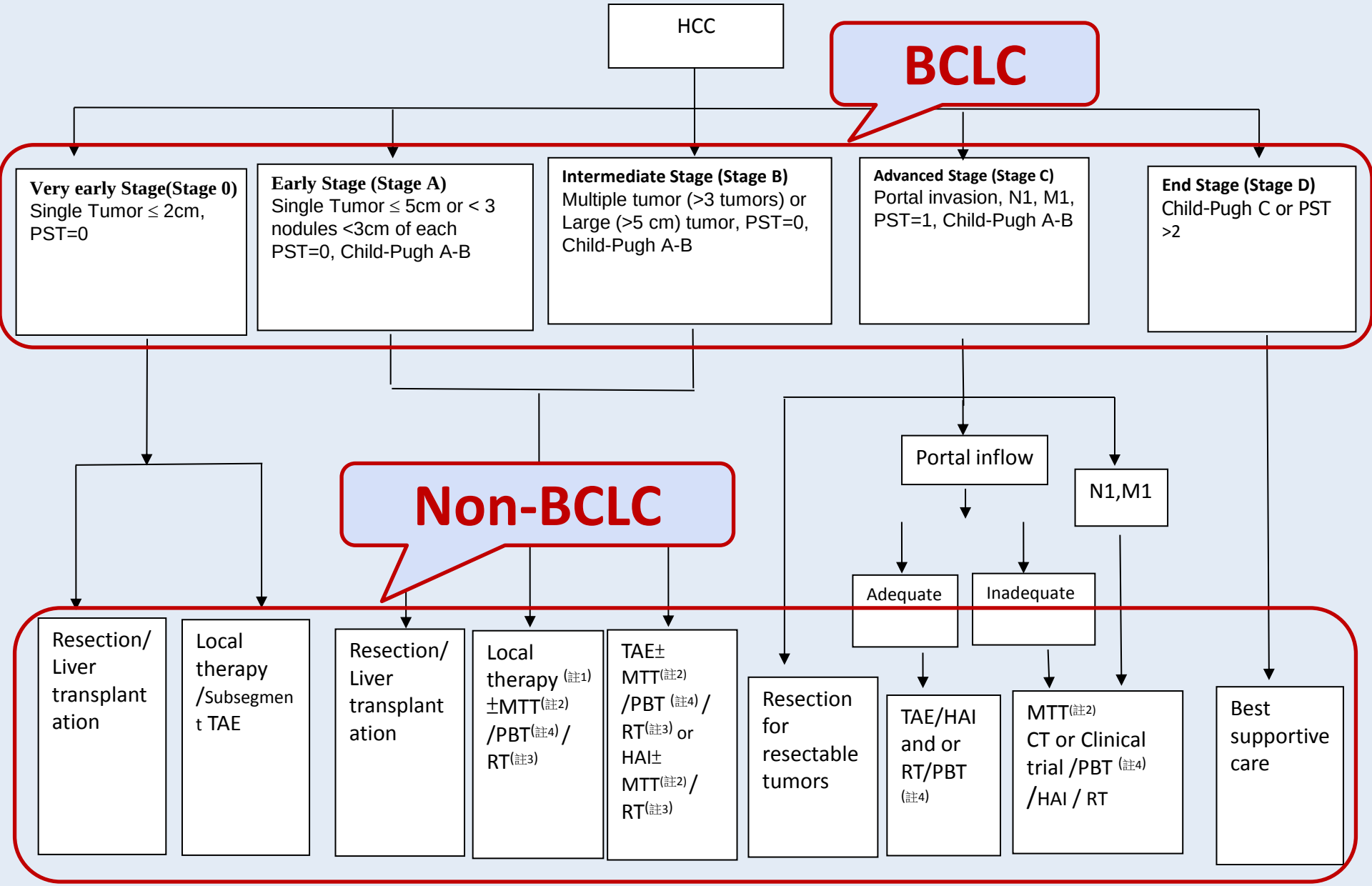
: Toward global harmonization

BCLC Staging System and Therapeutic Strategy According to EASL–EORTC Guidelines

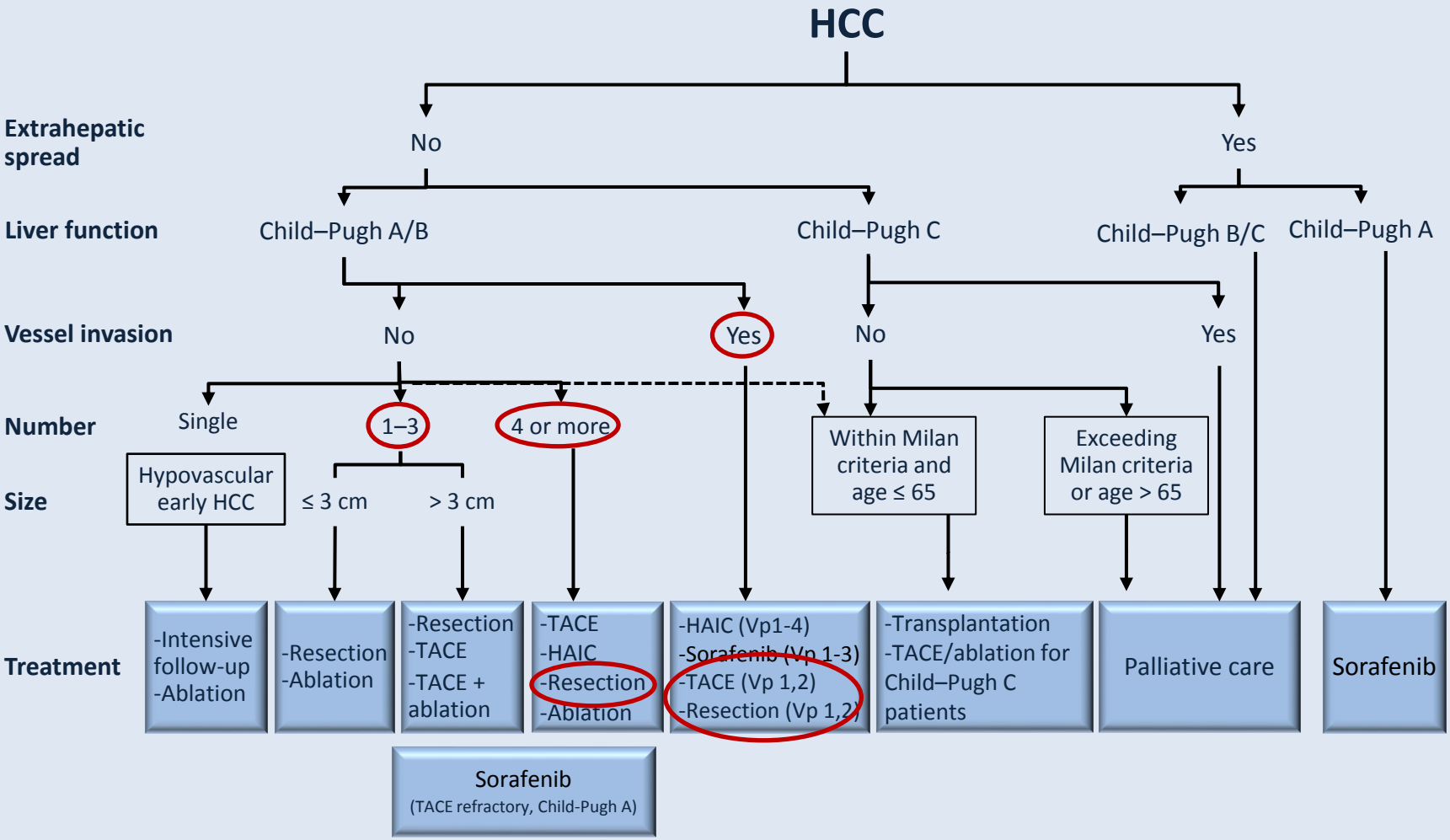


J. Hepatol. 56, 908–943 (2012).

Treatment Guidelines for HCC in an Asian Medical Center



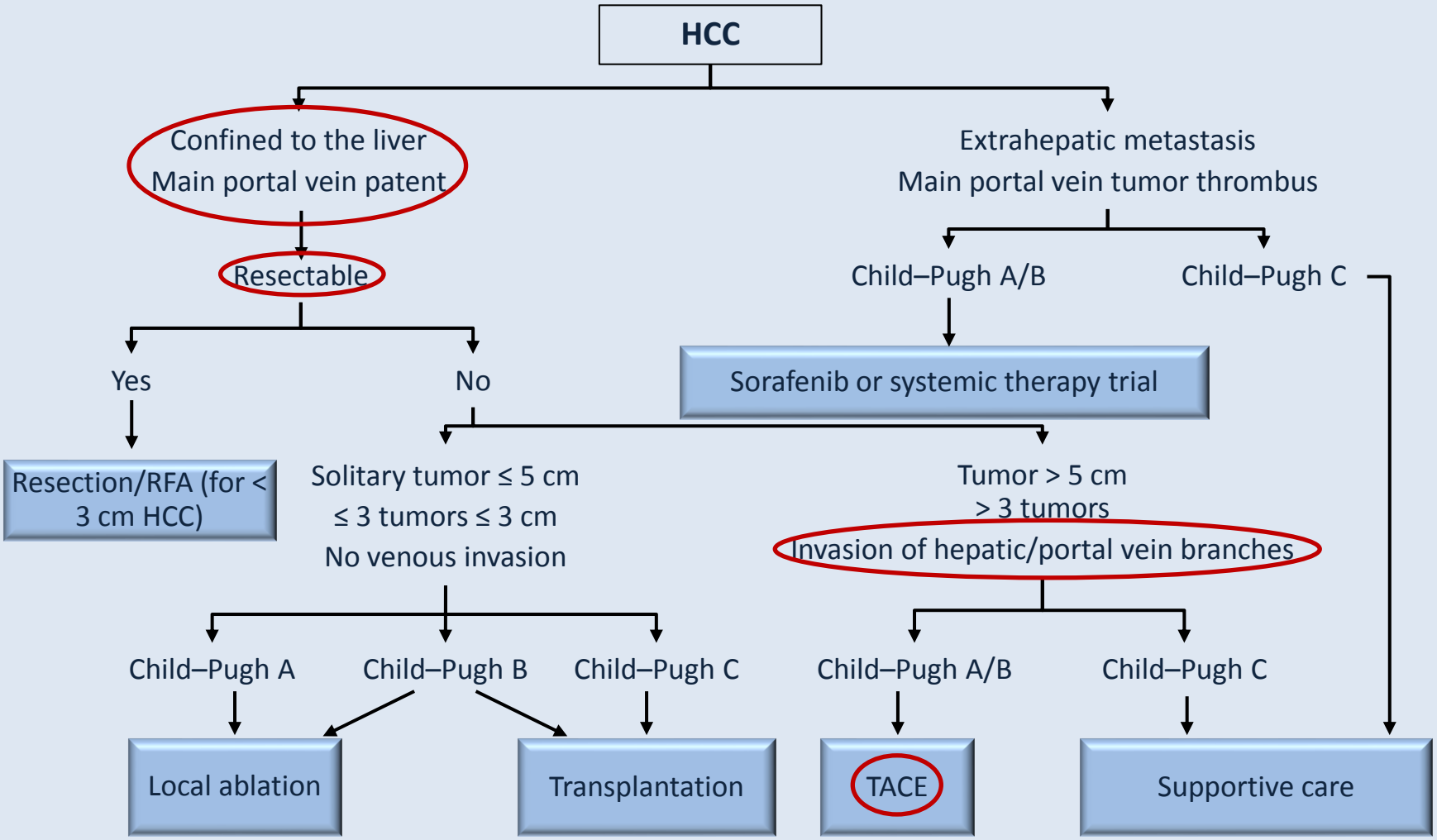
Japan Society of Hepatology: consensus-based treatment algorithm



HAIC = hepatic arterial infusion chemotherapy.

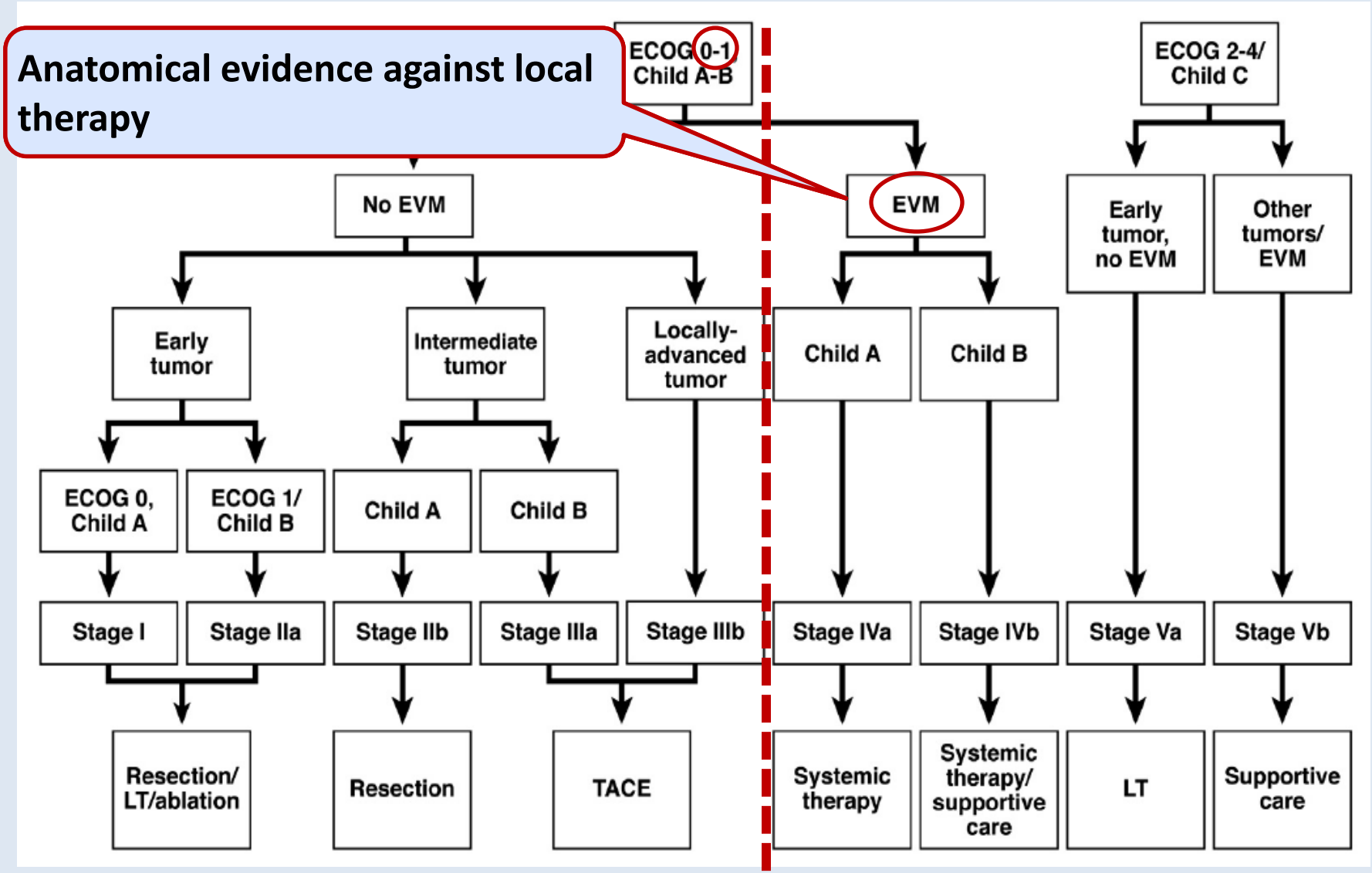
Kudo M, et al. Liver Cancer 2014;3:458–468

APASL guidelines



APASL recommendations on HCC. Omata M, et al. Hepatol Int. 2010;4:439–74.

Hong Kong Liver Cancer Staging System



Yau T et al. Gastroenterology 2014;146:1691–1700

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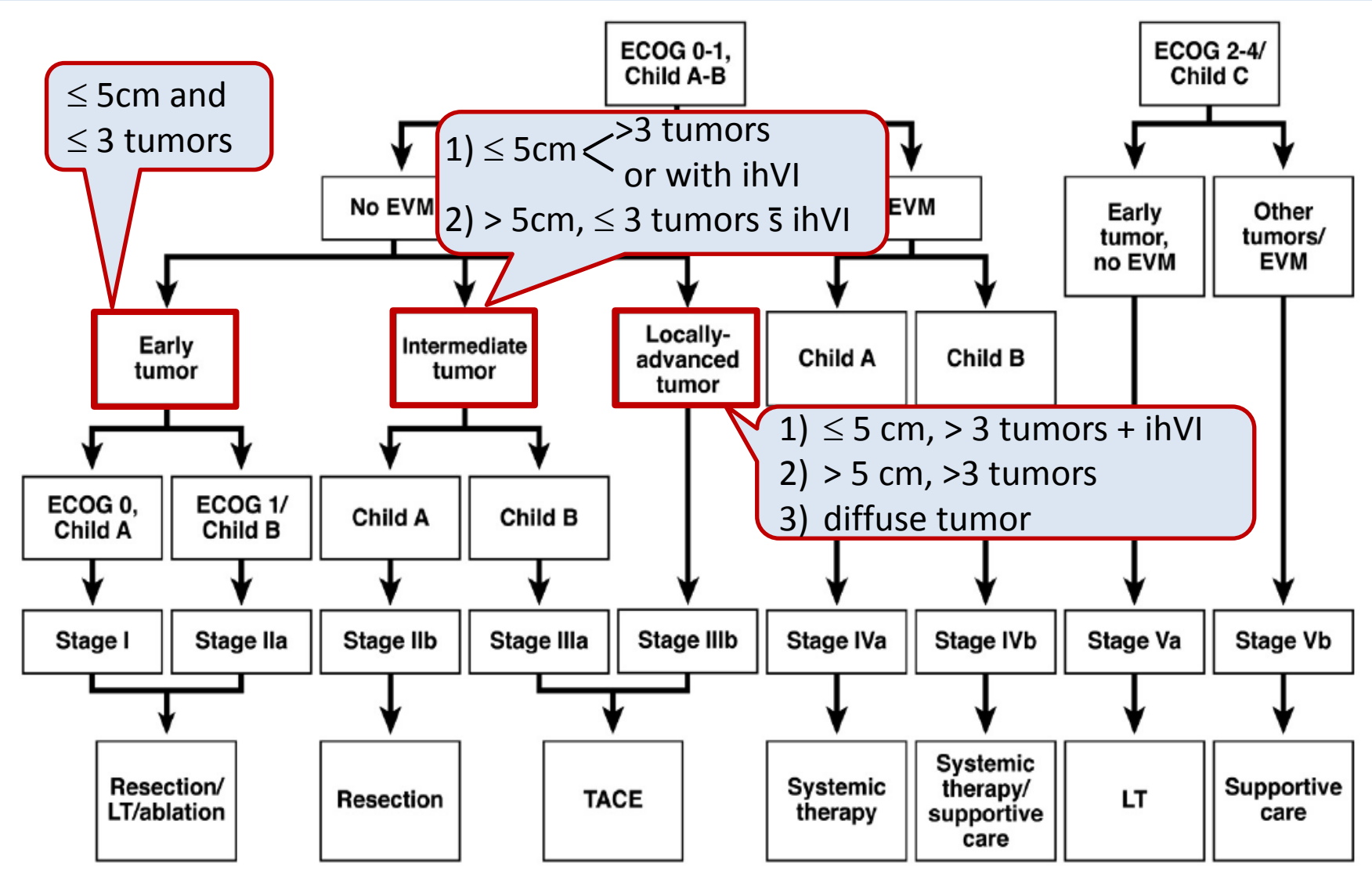


Yau T et al. Gastroenterology 2014;146:1691–1700

Number of Patients Under Three-Way Cross-Classification by BCLC Staging, HKLC Staging, and First Treatment in Test Set

	First treatment					
HKLC stage	Resection	LT	Ablation	TACE	Systemic therapy	Supportive care
BCLC stage A						
I	178	6	103	51	2	9
IIa	3	8	15	16	4	2
BCLC stage B						
I	10	0	5	14	1	1
IIa	2	1	0	0	0	1
IIb	171	1	6	82	5	17
IIIa	4	0	0	14	10	9
IIIb	41	1	0	69	9	11
BCLC stage C						
IIa	16	14	19	26	4	12
IIb	22	1	4	40	6	12
IIIa	3	1	0	5	6	6
IIIb	28	2	1	114	54	50
IVa	12	0	0	21	108	62
IVb	0	0	0	4	37	31
Va	3	1	0	2	1	2
Vb	0	1	0	10	37	54
BCLC stage D						
Va	0	15	2	9	6	18
Vb	2	2	1	8	35	76

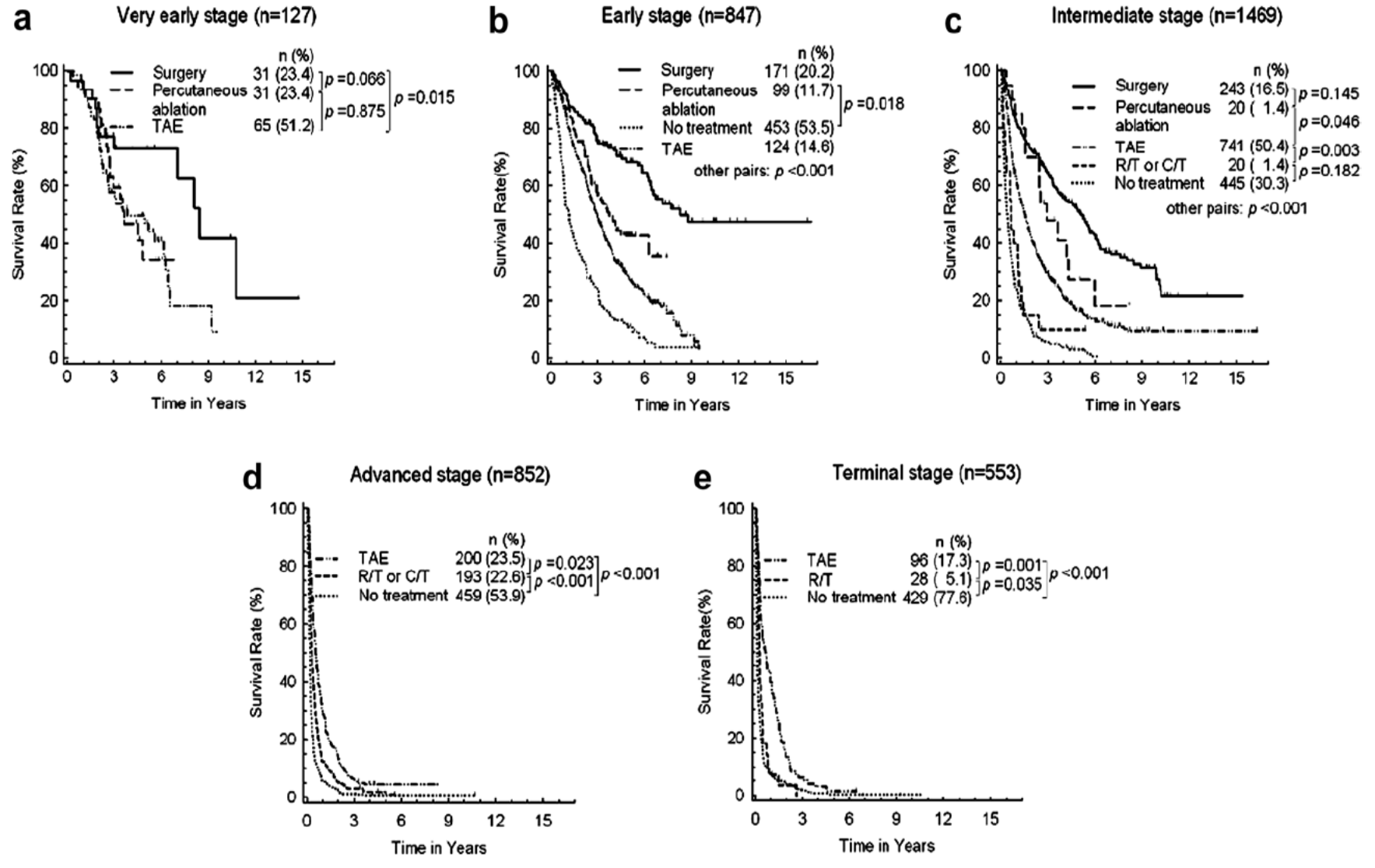
Yau T et al. Gastroenterol 2014;146:1691–1700

The efficacy of treatment schedules according to BCLC for HCC – Survival analysis of 3892 patients

BCLC Stage Treatment Schedule	Total *n* (%)	Survival Rate (%)			Median Survival (month)	*p* value for linear trend
		1 Yr	3 Yr	5Yr		
Very early stage	134 (3.4)	93.3	60.6	47.9	57.7 ± 10.5	
1. Surgery	31 (23.1)	93.5	73.1	73.1	100.8 ± 11.7	0.048
2. Percutaneous ablation	31 (23.1)	93.5	59.5	34.3	43.1 ± 9.0	
3. TAE	65 (48.5)	93.8	57.9	47.0	45.4 ± 14.1	
4. No treatment[a]	7 (5.2)	85.7	38.1	–	27.9 ± 12.7	
Early stage	847 (21.8)	81.2	51.0	35.0	36.9 ± 1.7	
1. Surgery	171 (20.2)	91.8	75.0	68.6	98.6 ± –	<0.001
2. Percutaneous ablation	99 (11.7)	86.9	56.6	42.8	44.0 ± 6.3	
3. TAE	453 (53.5)	83.9	48.2	27.2	35.4 ± 1.9	
4. No treatment	124 (14.6)	52.4	23.4	10.9	13.7 ± 2.0	
Intermediate stage	1469 (37.7)	53.7	27.9	18.2	13.8 ± 0.8	
1. Surgery	243 (16.5)	81.5	64.4	50.5	60.4 ± 6.1	<0.001
2. Percutaneous ablation	20 (1.4)	85.0	47.9	27.4	35.1 ± 8.7	
3. TAE	741 (50.4)	61.9	29.1	16.4	18.2 ± 1.1	
4. RT	20 (1.4)	40.0	10.0	10.0	7.9 ± 1.1	
5. No treatment	445 (30.3)	23.8	5.8	2.9	4.5 ± 0.4	
Advanced stage	878 (22.6)	13.7	3.3	1.9	2.9 ± 0.2	
1. Surgery[a]	14 (1.6)	57.1	28.6	28.6	13.2 ± 2.2	<0.001
2. Percutaneous ablation[a]	12 (1.4)	25.0	16.7	–	3.8 ± 0.5	
3. TAE	200 (22.8)	29.5	6.0	4.4	6.8 ± 0.5	
4. RT	193 (22)	12.4	3.1	0.9	3.8 ± 0.3	
5. No treatment	459 (52.3)	5.7	1.1	0.7	1.9 ± 0.1	
Terminal stage	564 (14.5)	13.3	2.6	0.7	1.6 ± 0.1	
1. Percutaneous ablation[a]	11 (2)	18.2	9.1	–	3.9 ± 1.3	<0.001
2. TAE	96 (17)	39.6	6.3	1.6	7.8 ± 1.8	
3. RT	28 (5)	7.1	–	–	3.0 ± 0.5	
4. No treatment	429 (76)	7.7	1.8	0.4	1.2 ± 0.1	
Total	3892 (100)	46.2	24.8	16.6	10.0 ± 0.4	

Wang JH et al. Eur J Cancer 2008;44:1000-1006

The efficacy of treatment schedules according to BCLC for HCC
Survival analysis of 3892 patients



Wang JH et al. Eur J Cancer 2008;44:1000-1006

Toward Global Harmonization of HCC Staging

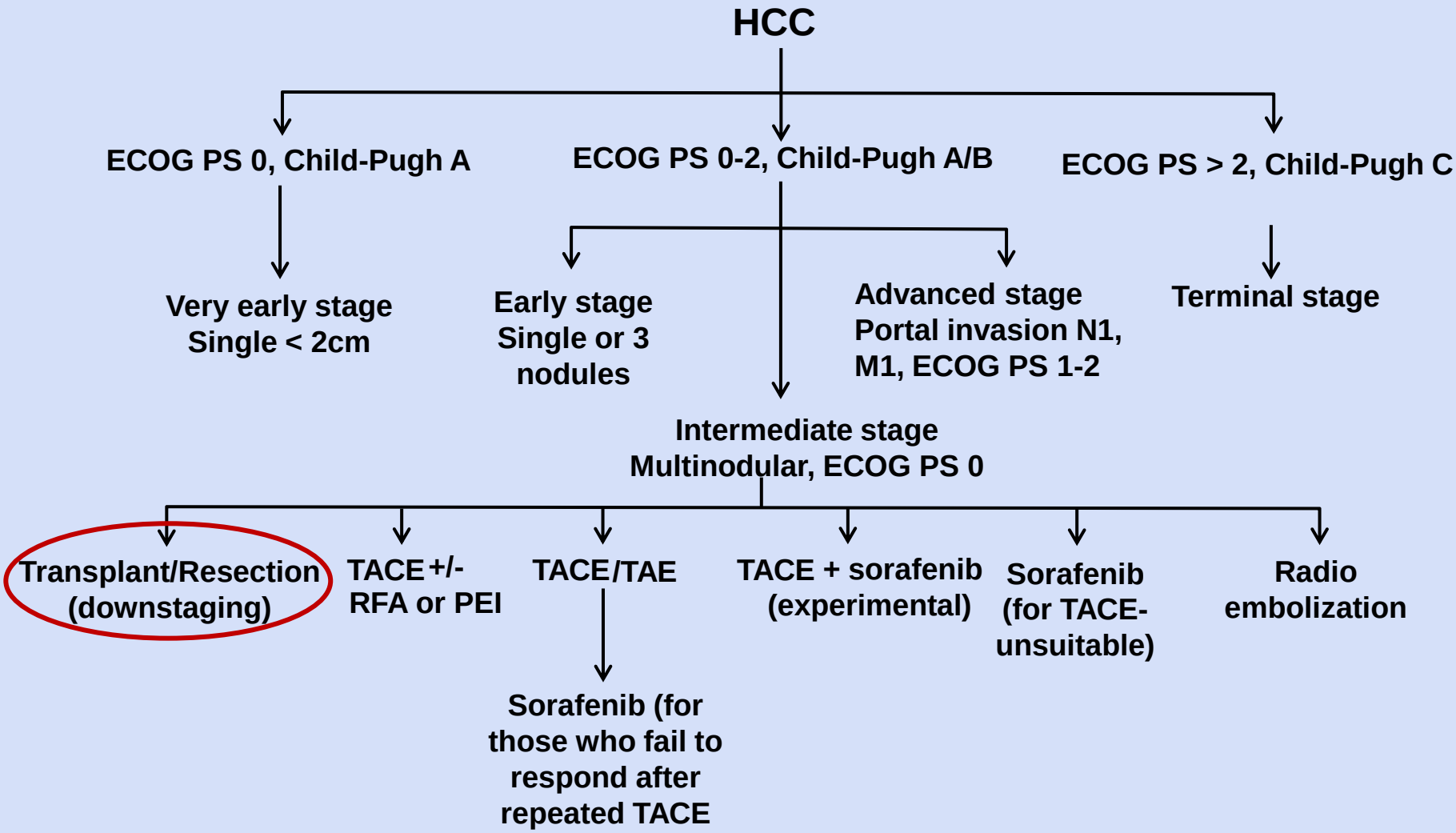
- **Globally accepted treatment-guiding staging systems are needed and should be pursued.**

Heterogeneity of Intermediate HCC (BCLC Stage B) and the Estimated Probability of Total Tumor Necrosis according to the Most Likely Potential Treatment

	Examples of Patients with Intermediate HCC			
	Patient 1	Patient 2	Patient 3	Patient 4
Bilirubin (mg/dl)	0.9	1.6	2.6	1.9
Albumin (g/dl)	4.8	3.6	3.0	2.7
Ascites	No	Mild	Mild	Refractory
Hepatic encephalopathy	No	No	No	No
Child–Pugh class	A	A	B	B
Number of HCC tumors	2	4	1	4
Diameter of the 2 largest HCC	35–16 mm	60–45 mm	110 mm	19–18 mm
Potential treatment	Surgery versus combined TACE + ablation	TACE	TACE (?)	None
Potential for cure (estimated probability of total tumor necrosis)†	65%	20%	<5%	0%

Bolondi L et al. Semin Liver Dis 2012;32:348–359

Treatment Options in Intermediate HCC



Bolondi L et al. Semin Liver Dis 2012;32:348–359

Global Harmonization of HCC Staging

- **The problem of lack of motivation**

  More aggressive locoregional therapy is believed to be ethical

  Conservative approach is considered evidence-based

- **The problem of validation methodology**

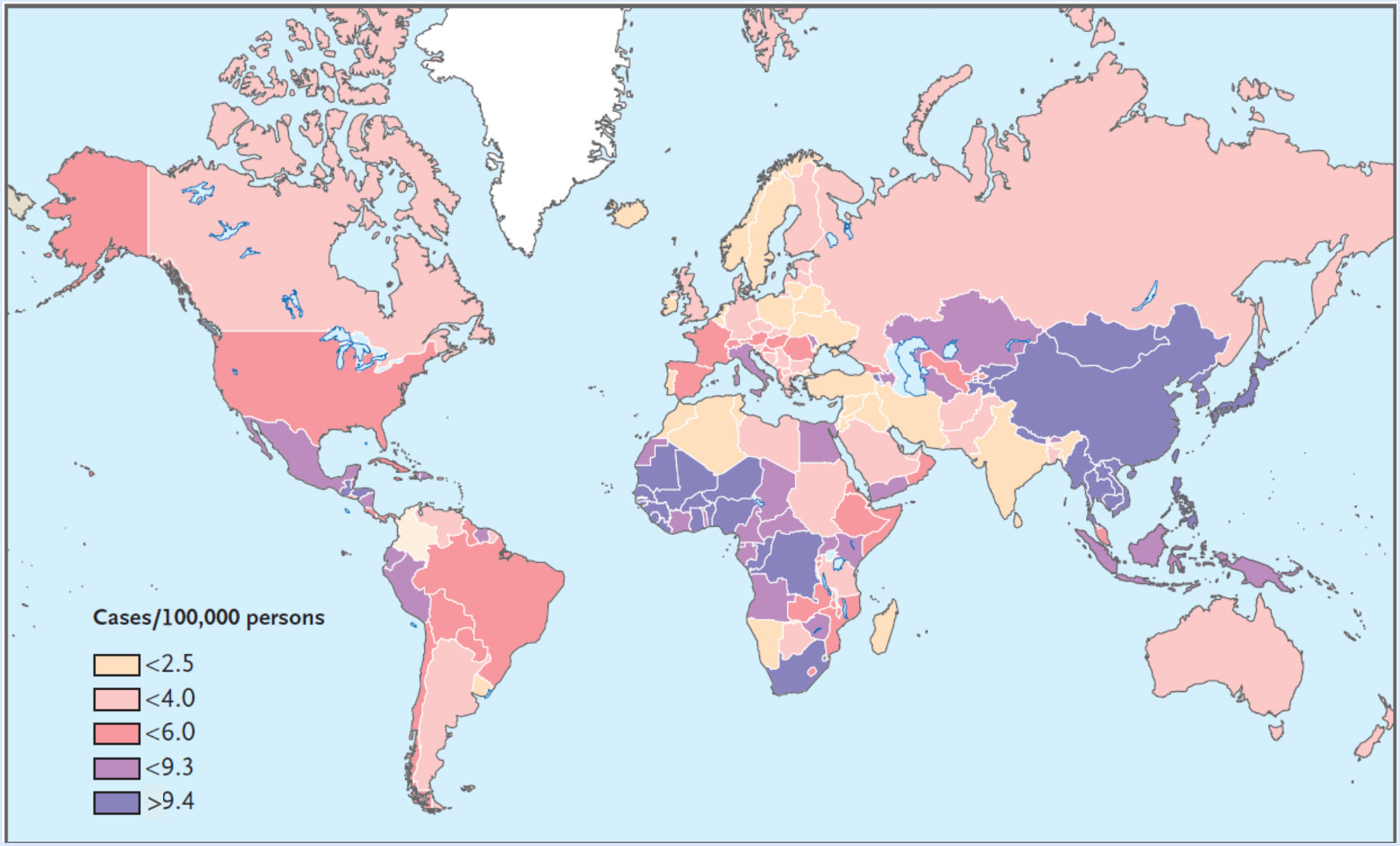
  More aggressive therapy demands higher level of technique and experience

  Prospective randomization is very difficult, if not impossible

Heterogeneity of the Etiology of HCC

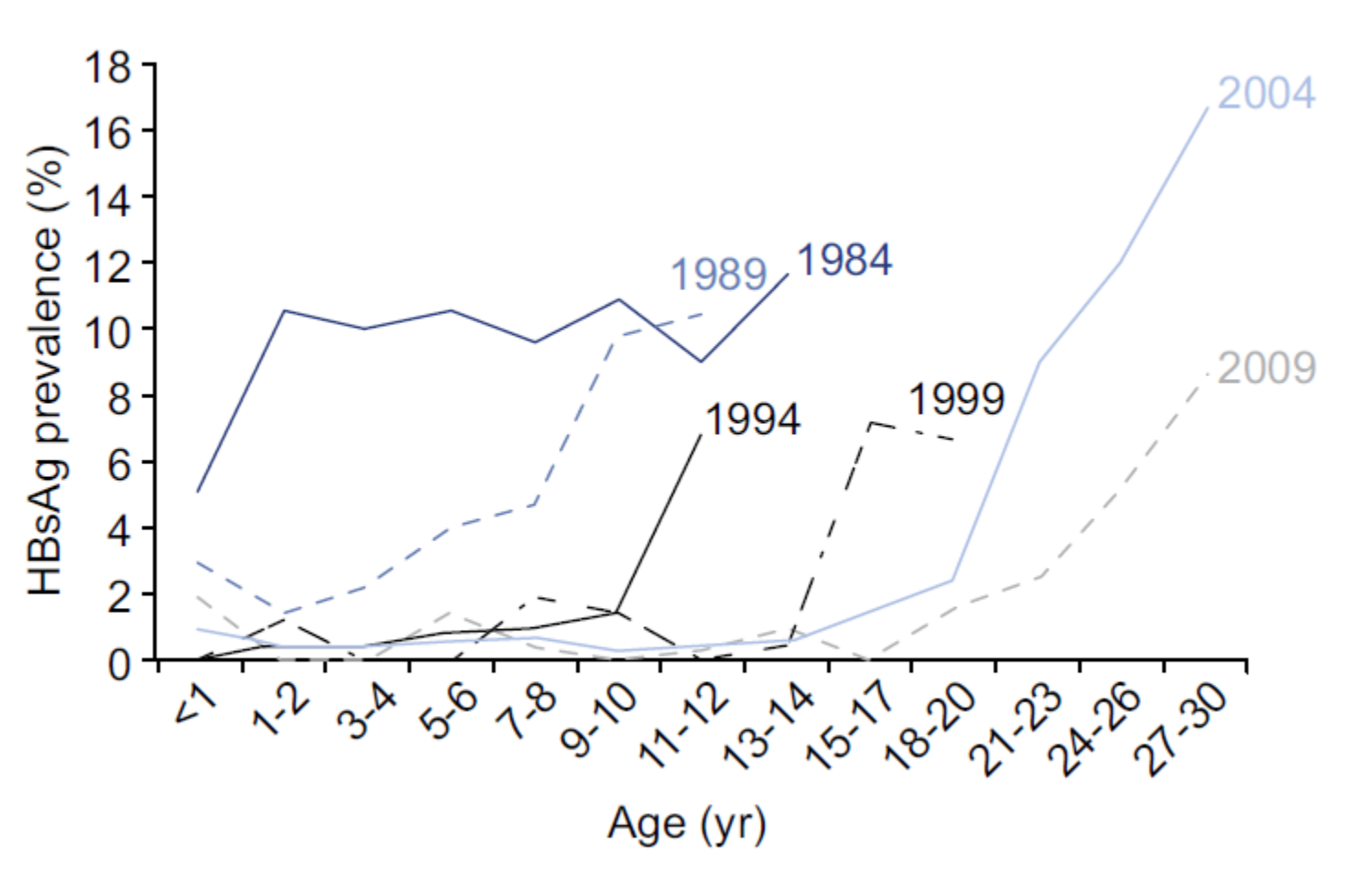
:Toward Global Harmonization

Regional Variation in the Estimated Age-Standardized Incidence Rates of Liver Cancer.



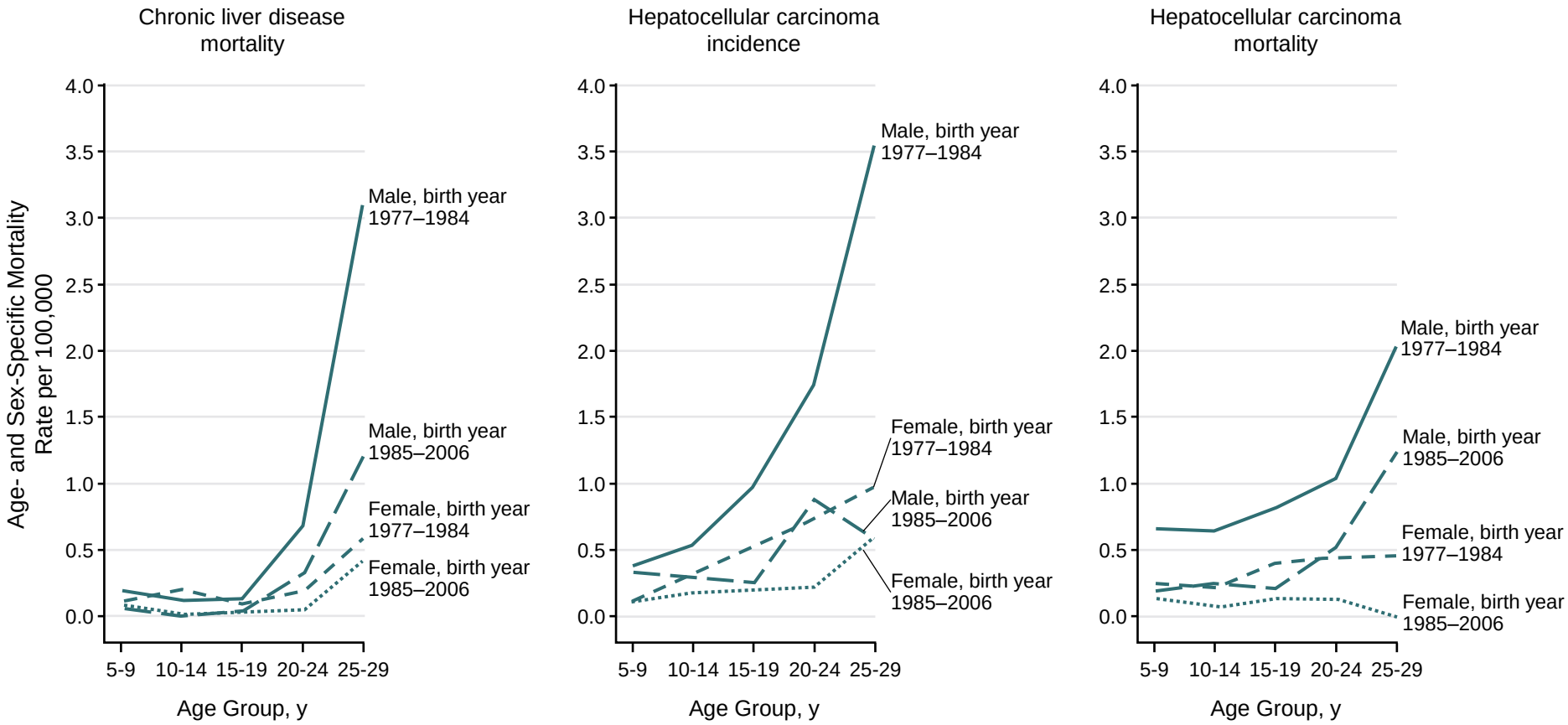
El-Serag H.B. et al. N Engl J Med 2011;365:1118-27

Minimization of HBV infection by a 25-Year Universal Vaccination Program in Taiwan



Ni YH et al J Hepatol 2012;57:730–735

Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan

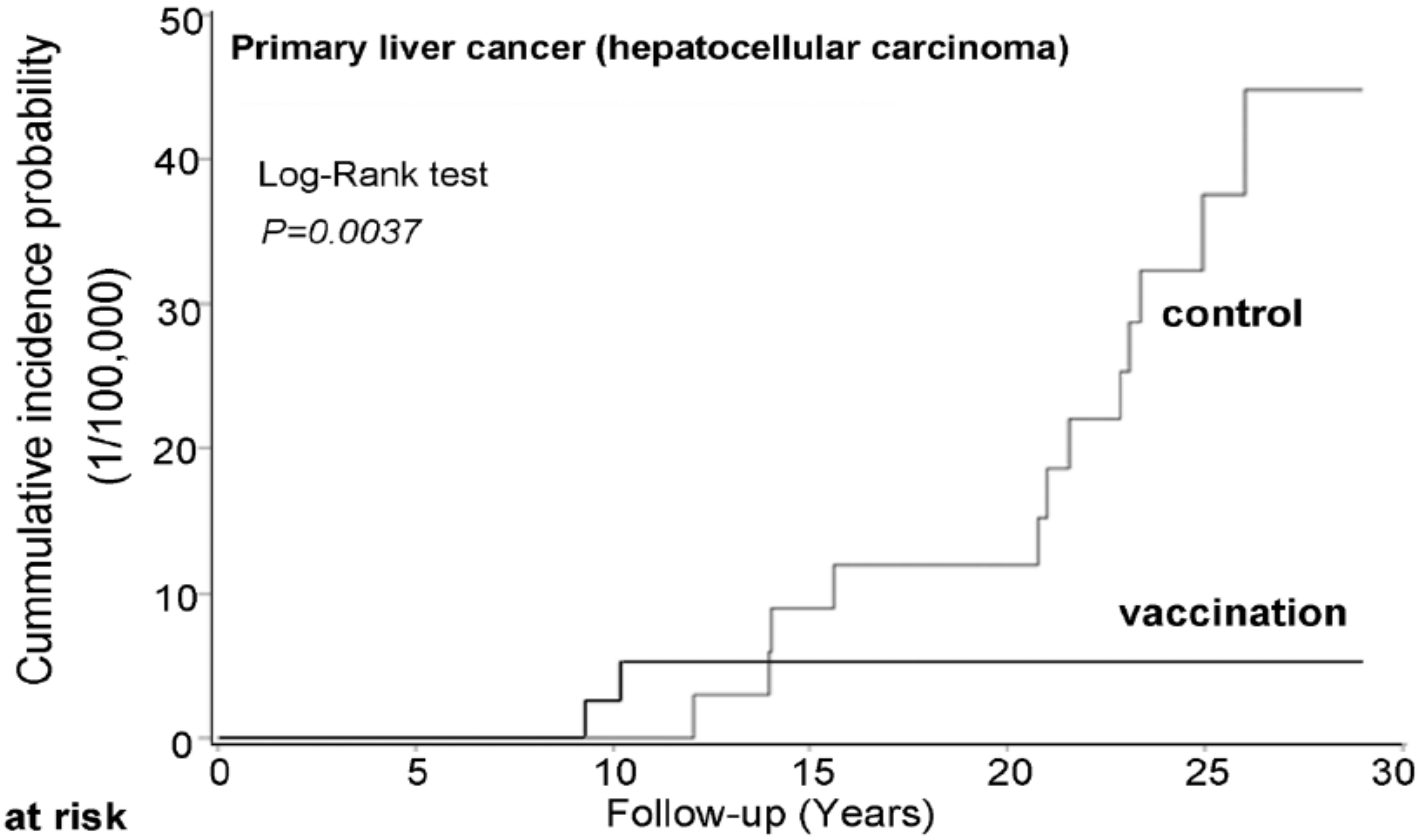


In Taiwan, incidence and mortality of HCC has decreased from 1977 to 2006 – this may be due in part to hepatitis B immunization efforts

HCC=hepatocellular carcinoma.

Chiang CJ et al. *JAMA.* 2013;310(9):974-976.

Efficacy of Neonatal HBV Vaccination on Liver Cancer and Other Liver Diseases over 30-Year Follow-up of the Qidong Hepatitis B Intervention Study: A Cluster Randomized Controlled Trial



Number at risk

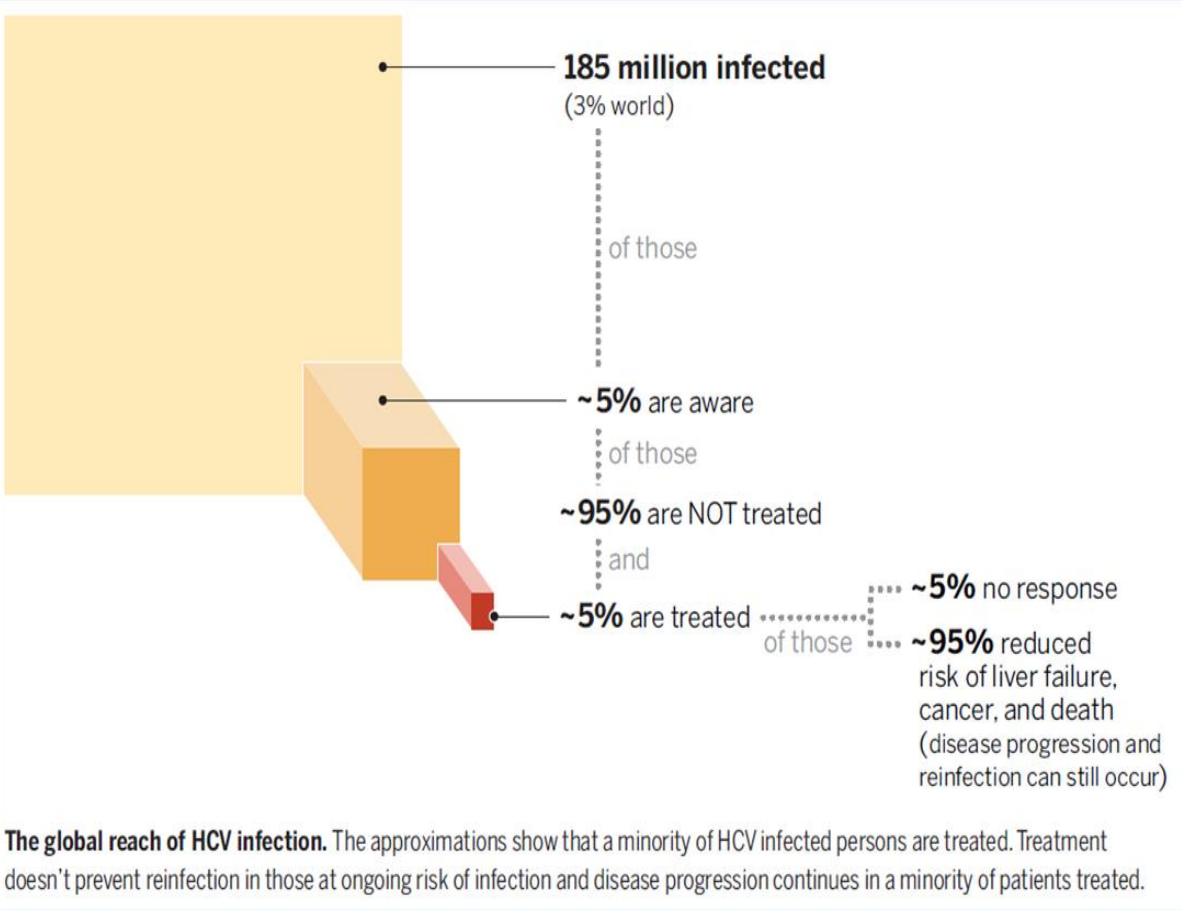
Control group	34441(0)	33665(0)	33605(3)	33570(1)	33561(7)	18985(1)	0
Vaccination group	38366(0)	37989(1)	37880(1)	37858(0)	37841(0)	21283(0)	0

Qu C et al. PLOS Med 2014;11: e1001774

Preven

- Primary
  - Preven
    transfu
    abuser
- Seconda
  - Antivir
- Tertiary
  - Adjuva

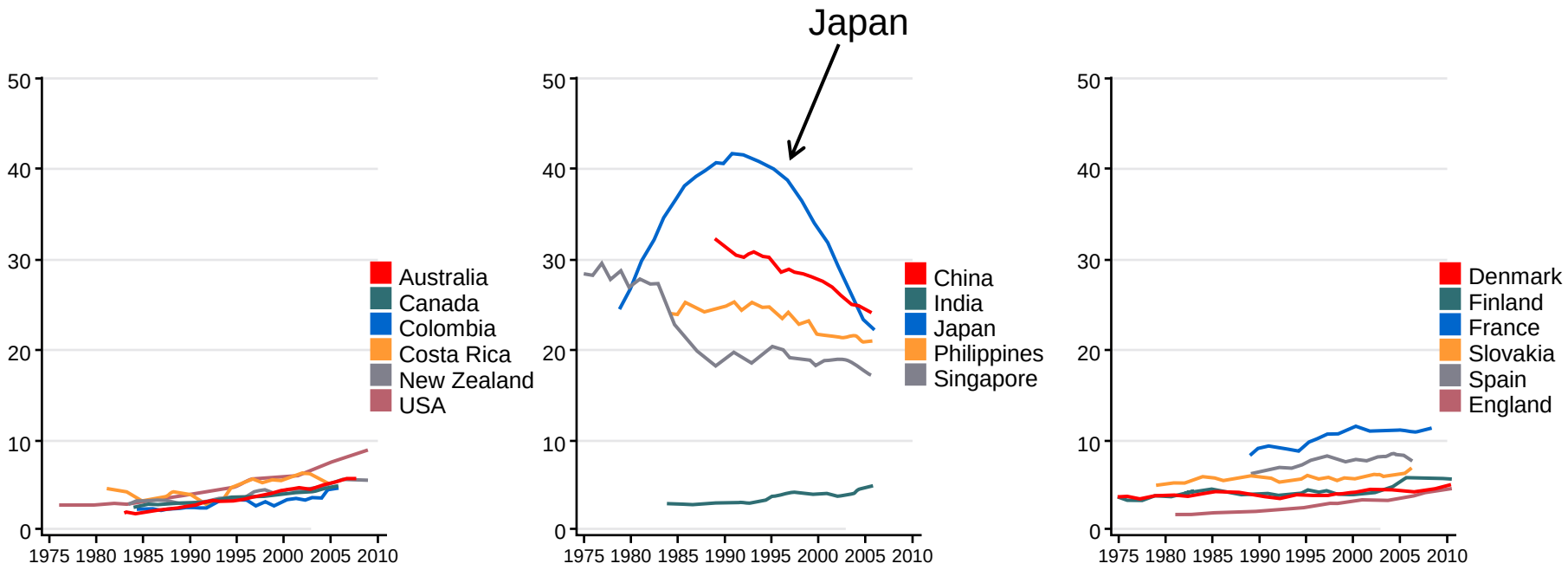
Global control of hepatitis C virus



The global reach of HCV infection. The approximations show that a minority of HCV infected persons are treated. Treatment doesn't prevent reinfection in those at ongoing risk of infection and disease progression continues in a minority of patients treated.

Andrea L. Cox SCIENCE 2015;349:790-791

Global Incidence of HCC in Men (Per 100,000)



HCC incidence is decreasing in Japan – this may be due in part to decreases in HCV-related HCC

Regional data from: CI5.iarc.fr; Australia: www.aihw.gov.au; New Zealand: www.health.govt.nz; USA: seer.cancer.gov; NORDCAN: www.ancr.nu; European Cancer Observatory: eco.iarc.fr; England: www.ons.gov.uk.

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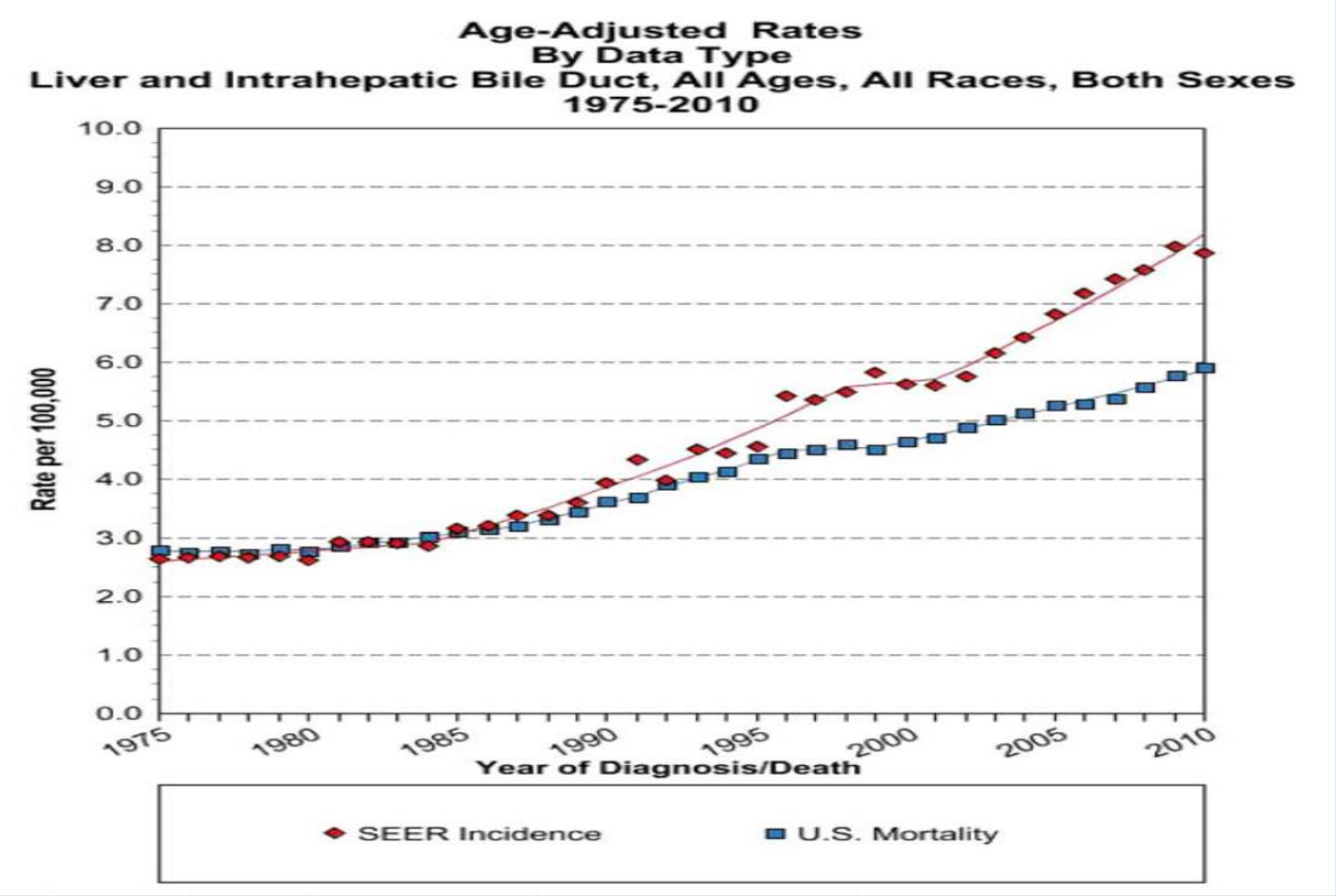
Kudo M. *Liver Cancer.* 2015;4(1):39–50.

HCC in USA



El-Serag HB et al, Hepatol, 2014;60(5):1767-1775

Association of NAFLD with HCC in the United States From 2004 to 2009

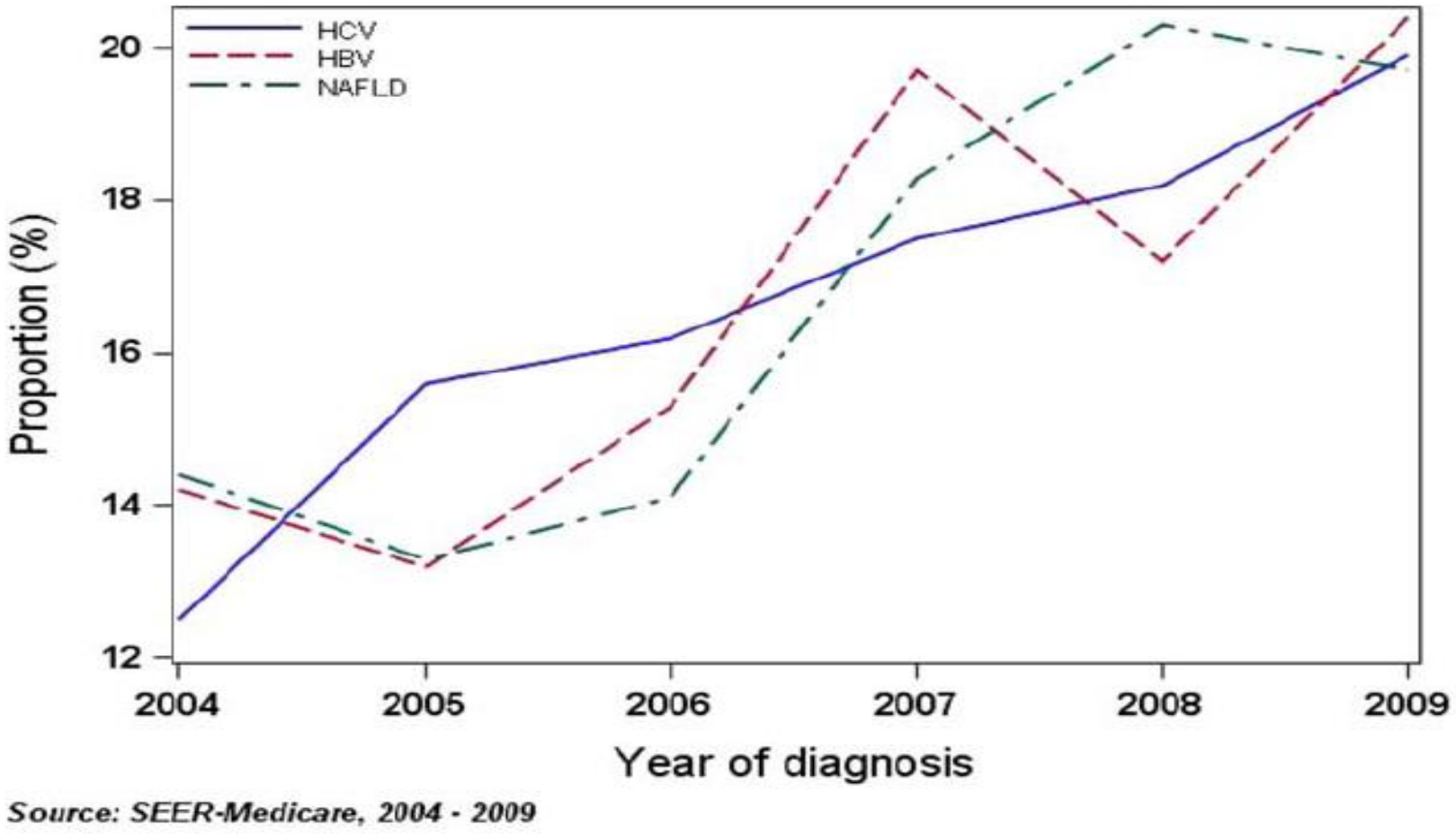


Fig. 2. Trends in proportion of HCC, by liver disease status: 2005-2009, SEER-Medicare.

Younossi ZM et al. Hepatol 2015;62:1723-1730

Liver Disease in the UK: Startling Findings & Urgent Need for Action

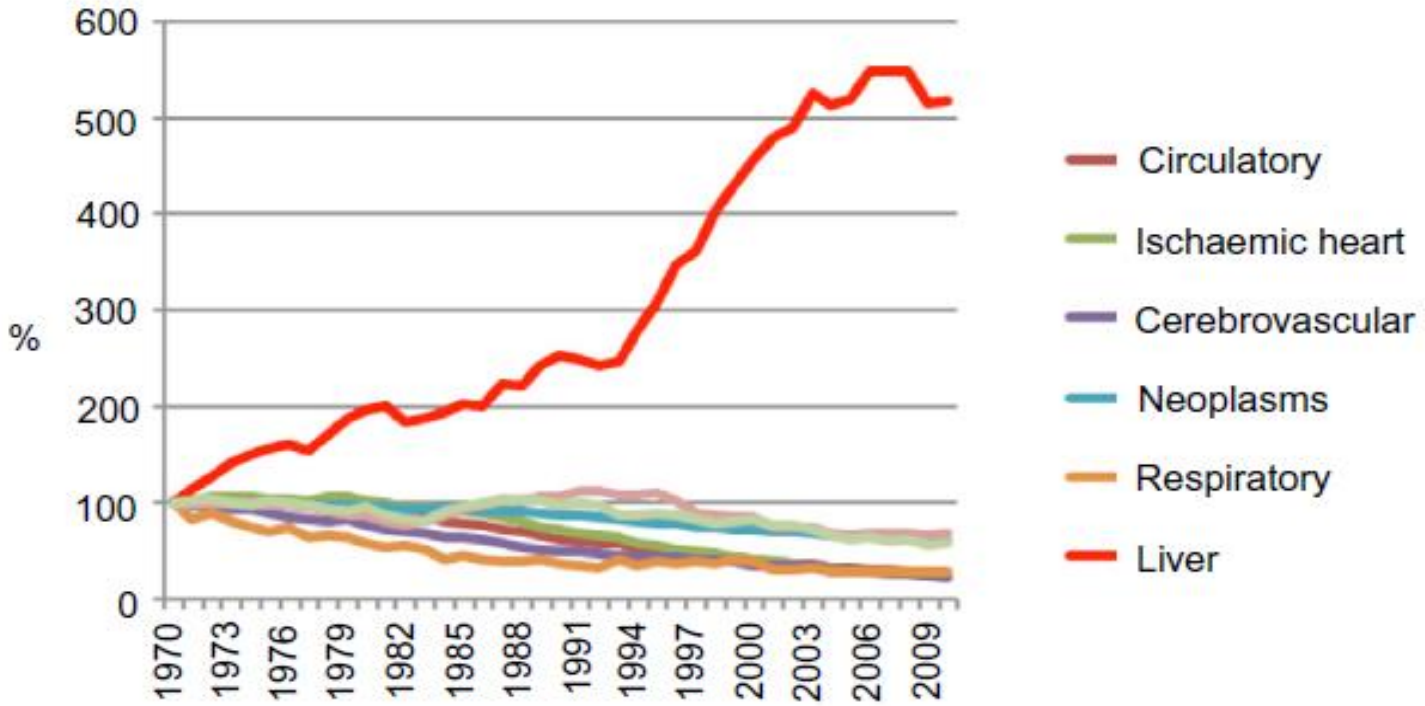
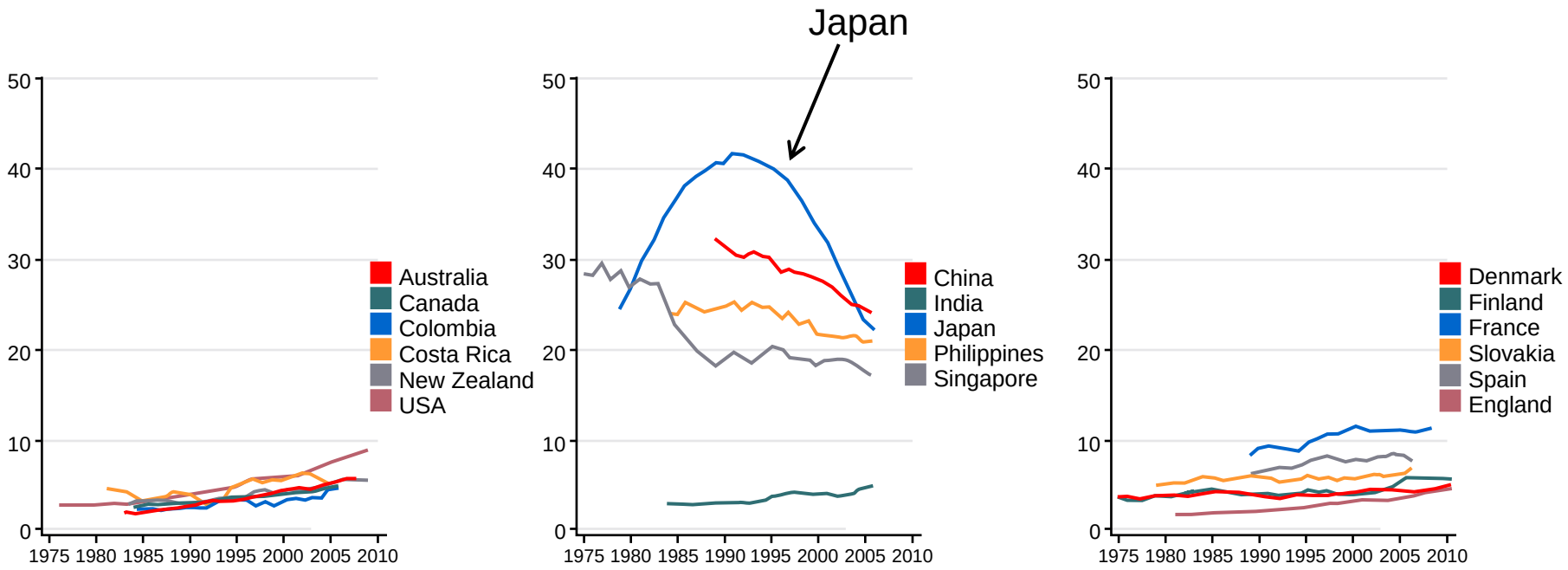


Fig. 1. Percentage changes in standardised UK mortality rates (age 0–64) normalised to 100% in 1980. Standardised Mortality Rate data for the UK was downloaded from the World Health Organisation Health for All Database (http://data.euro.who.int/hfadb/) and normalised to 100% in 1980. (Nick Sheron, October 2013).

Roger W. J Hepatol 2015;63:297–299

Global Incidence of HCC in Men (Per 100,000)



HCC incidence is decreasing in Japan – this may be due in part to decreases in HCV-related HCC

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HCC=hepatocellular carcinoma.

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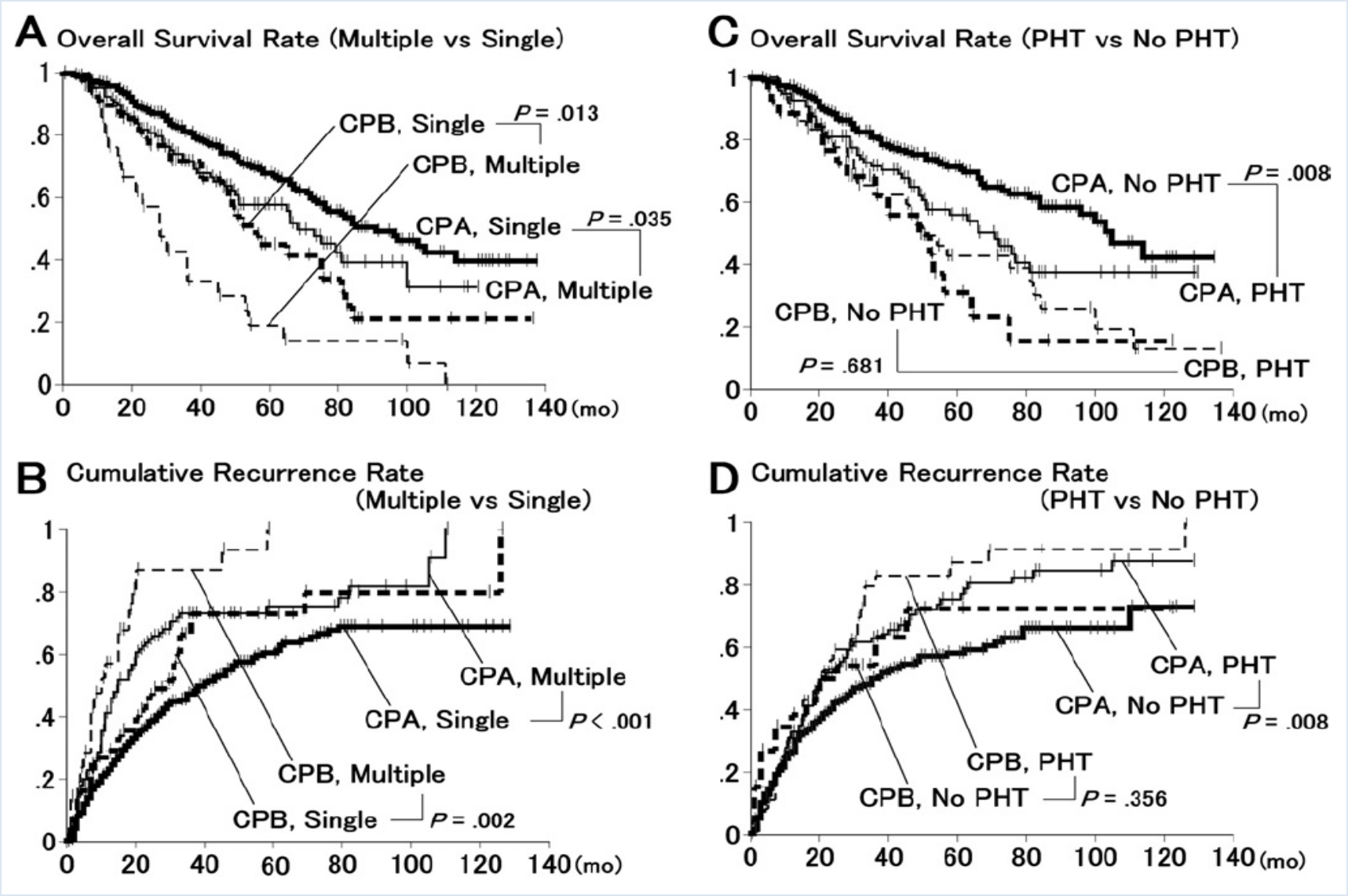
Summary

Toward Global Harmonization of HCC Staging and Etiology

- **Globally accepted treatment-guiding staging systems of HCC should be pursued.**

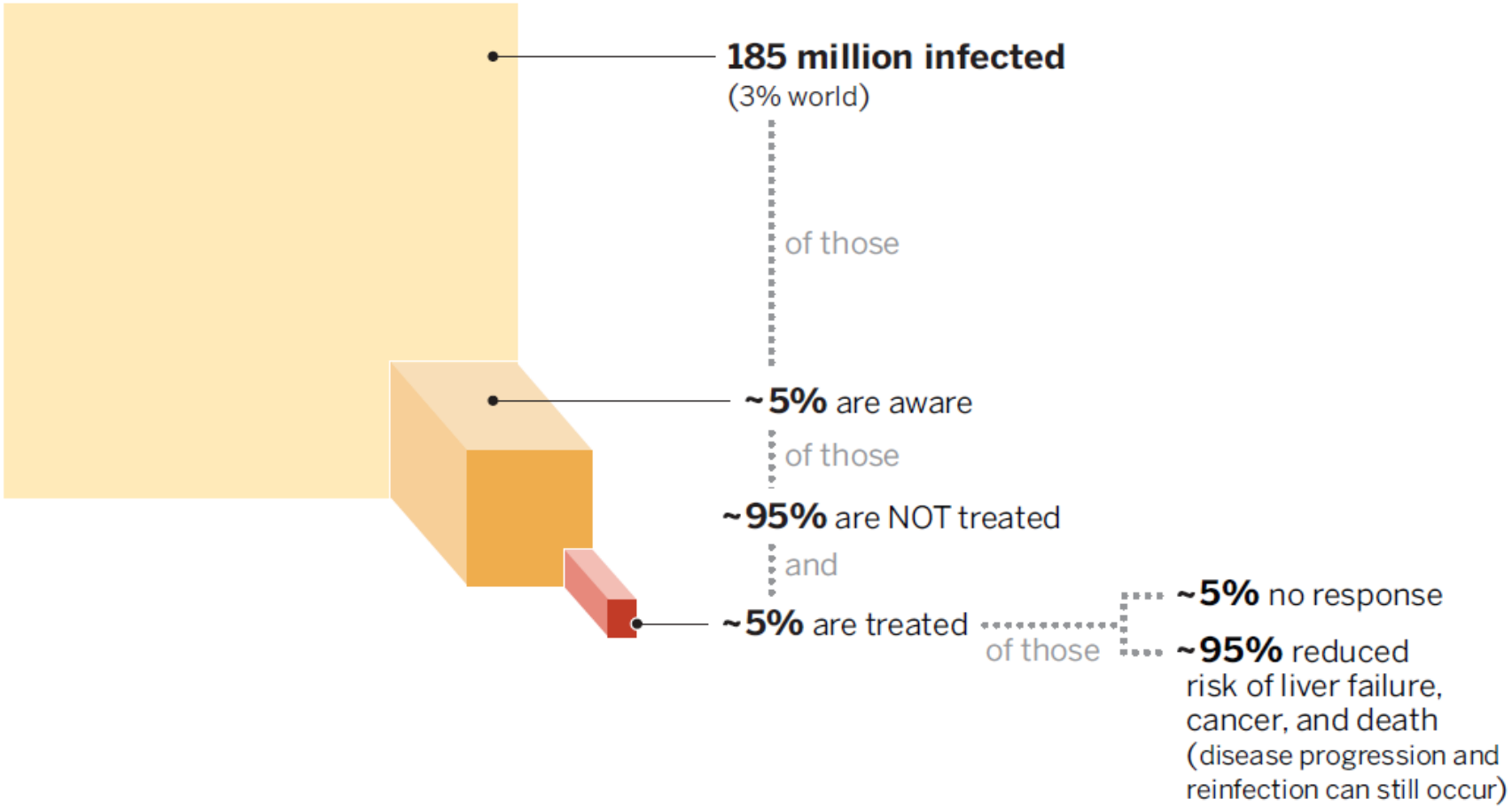
- **Etiology of HCC will reach global harmonization 3 decades from now. Virus will become minor, while metabolic/alcoholic will become major causes, and the incidence will be 10-20 new cases/100,000 population/year around the world.**

Neither Multiple Tumors Nor Portal Hypertension Are Surgical Contraindications for HCC



Ishizawa T et al. Gastroenterol 2008;134:1908–1916

Global control of hepatitis C virus



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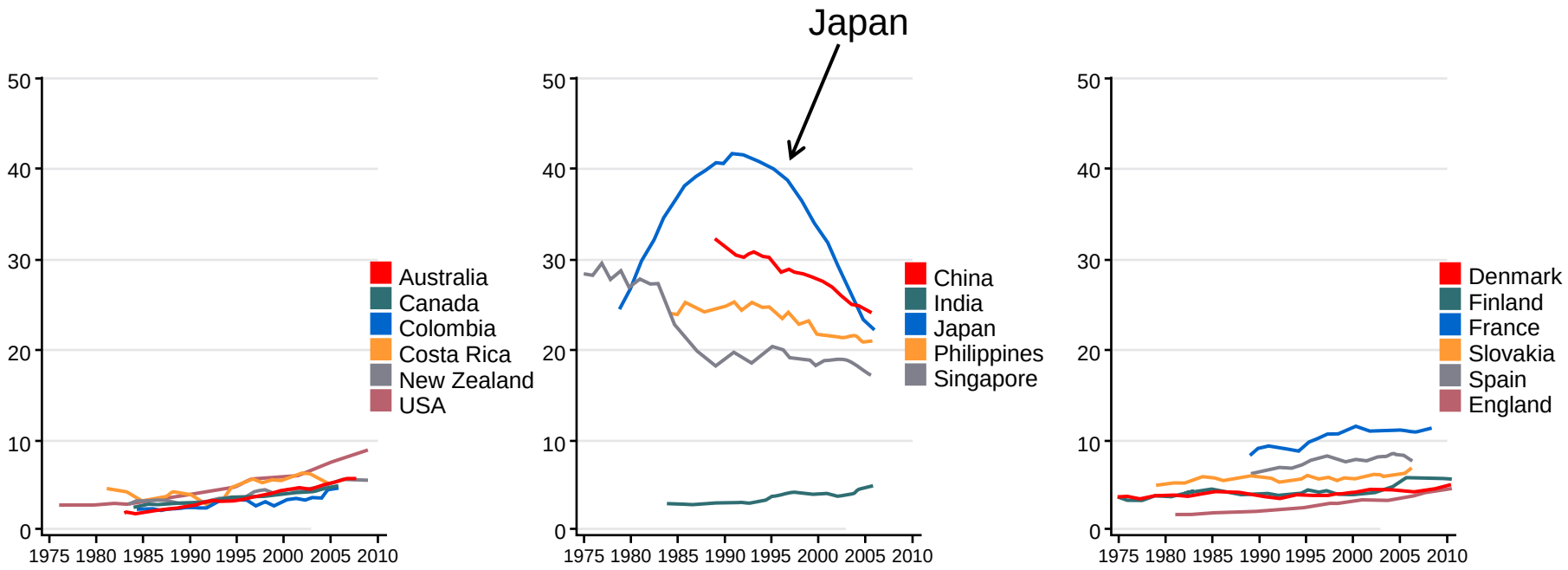

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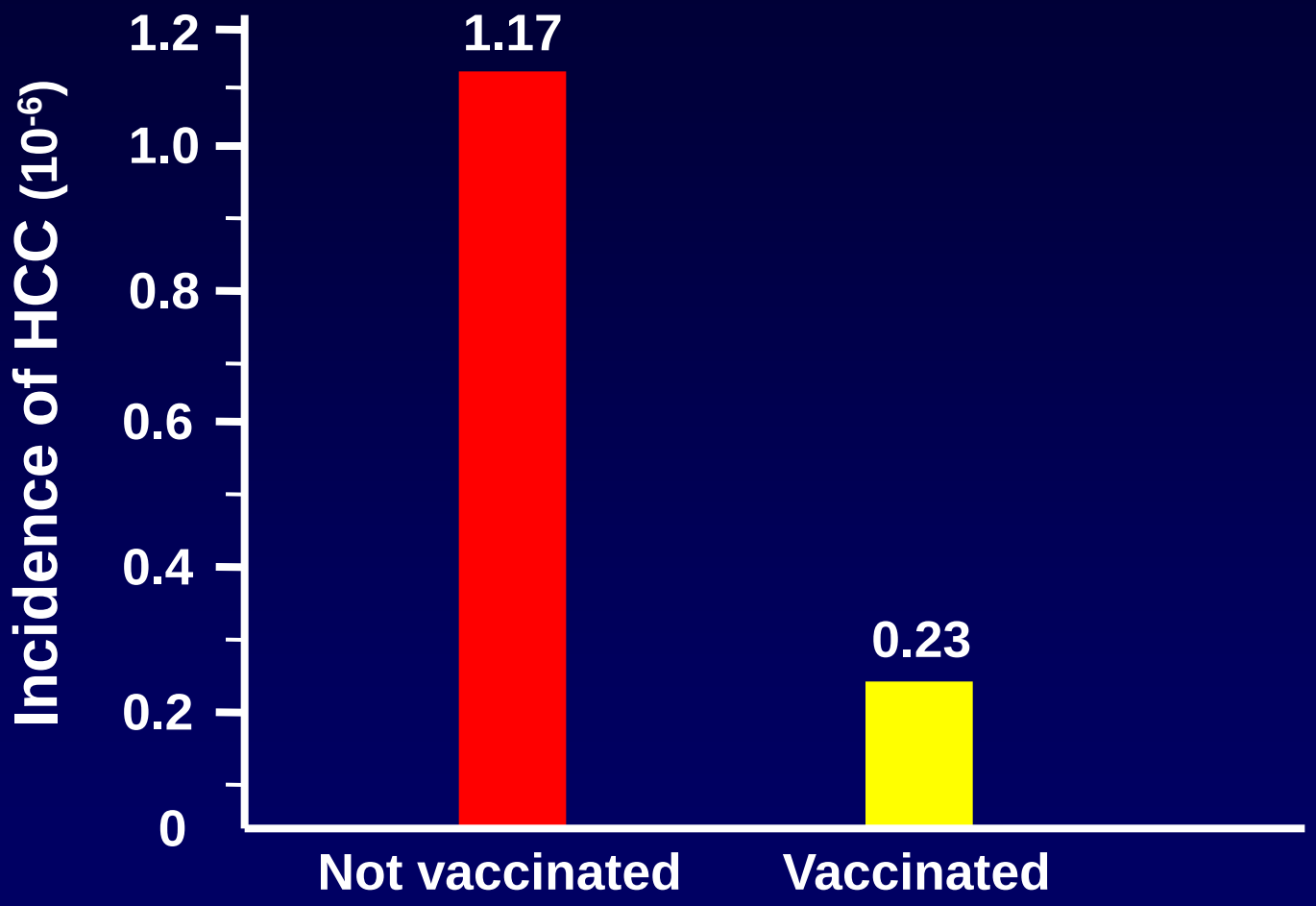
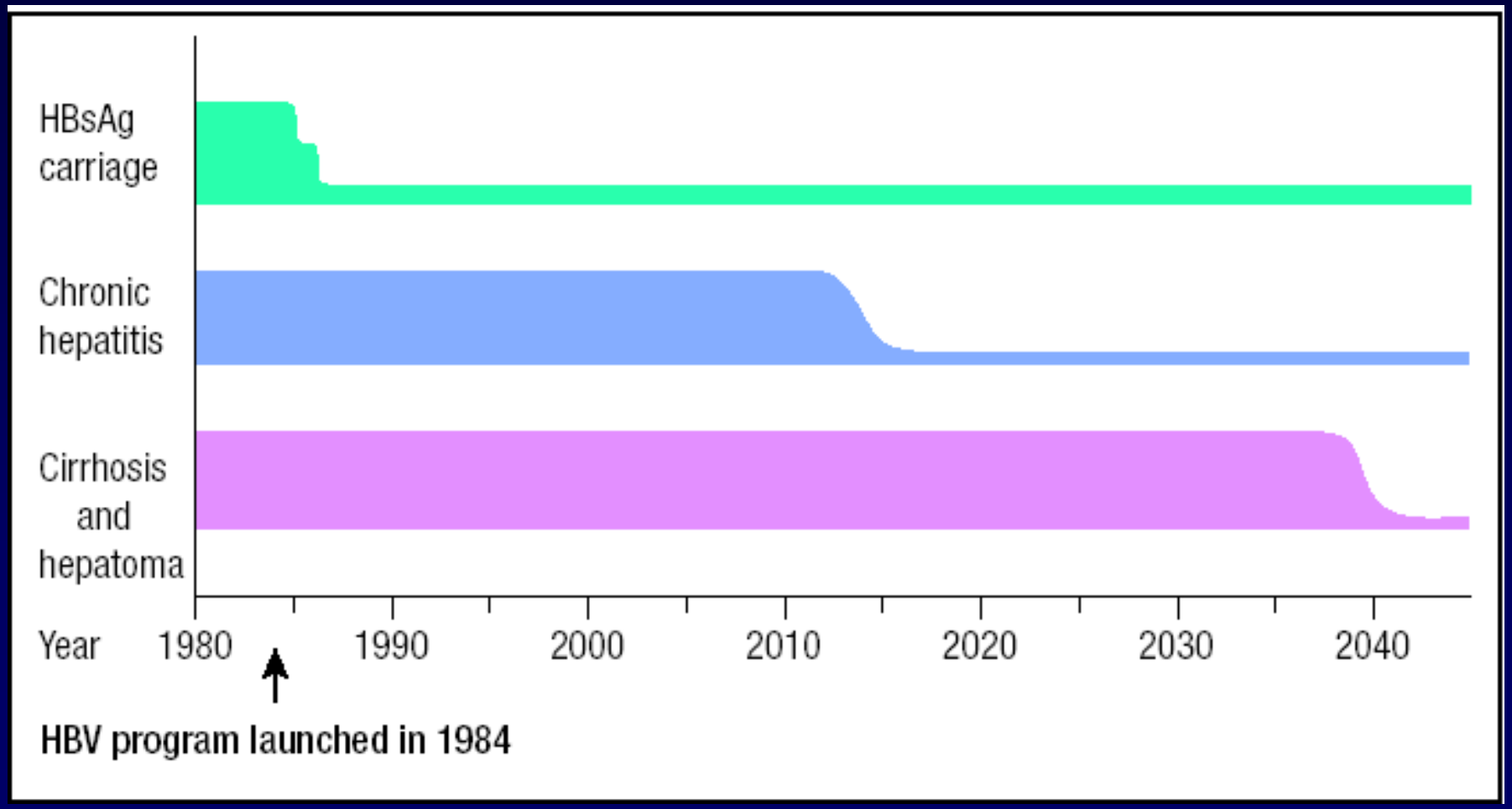
Incidence of HCC in 5~18-yr olds Khon Kaen*, Thailand, 1985~2007



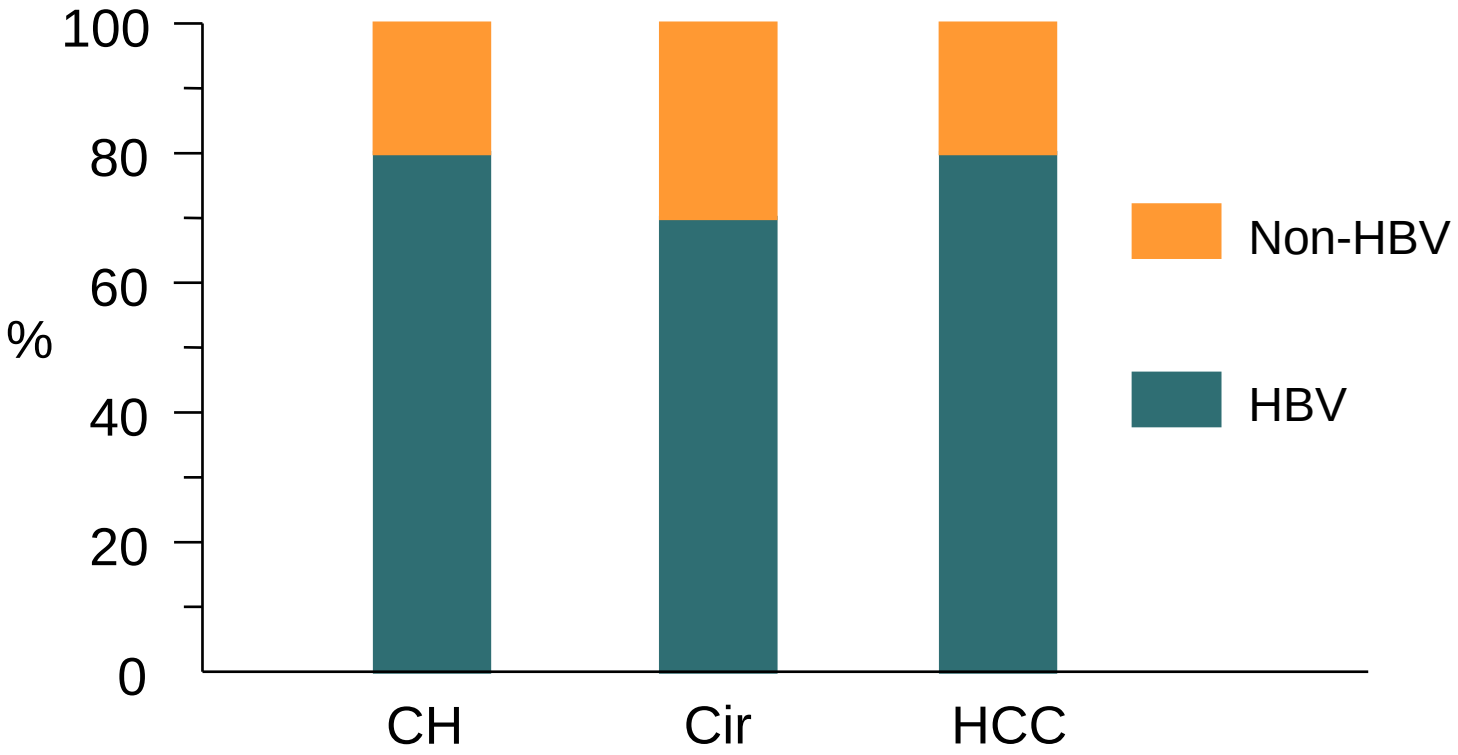
*Hepatitis B vaccination since 1990

Wichajarn, et al. Asian Pac J Cancer Prev 2008; 9:507-510

Projection on the Decrease of Chronic Liver Disease and HCC after HB Vaccination in Taiwan



Etiology of Chronic Hepatitis, Cirrhosis, and HCC in Taiwan Before 1984*



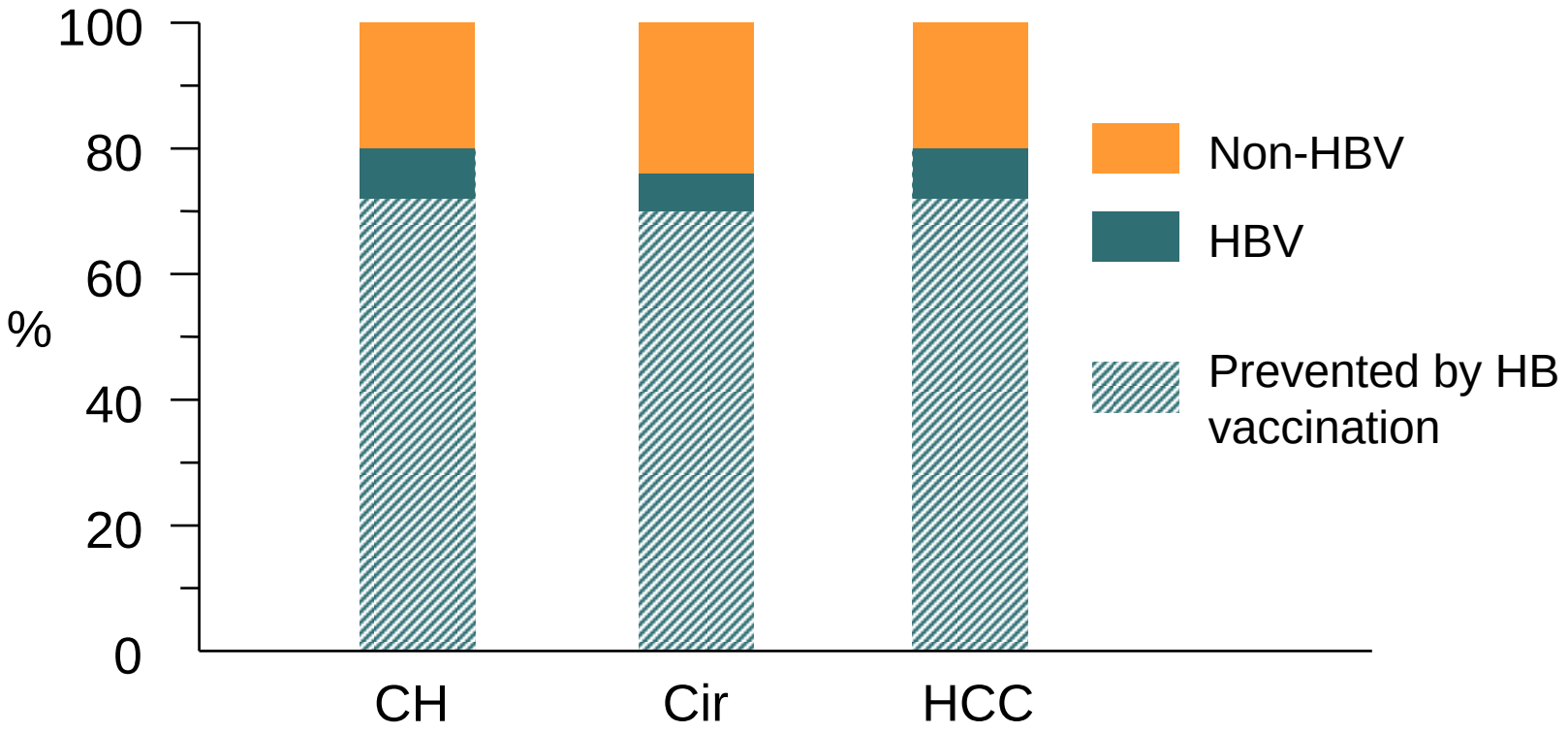
*Hepatitis B vaccination was implemented in 1984.

HBV was a dominant etiological factor for liver disease (including HCC) in Taiwan prior to implementation of HBV vaccination

CH=chronic hepatitis; Cir=cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma.

Chen DS. *Hepatology*. 2011;54(2):381-392.

Etiology of Chronic Hepatitis, Cirrhosis, and HCC in Taiwan Around 2040*



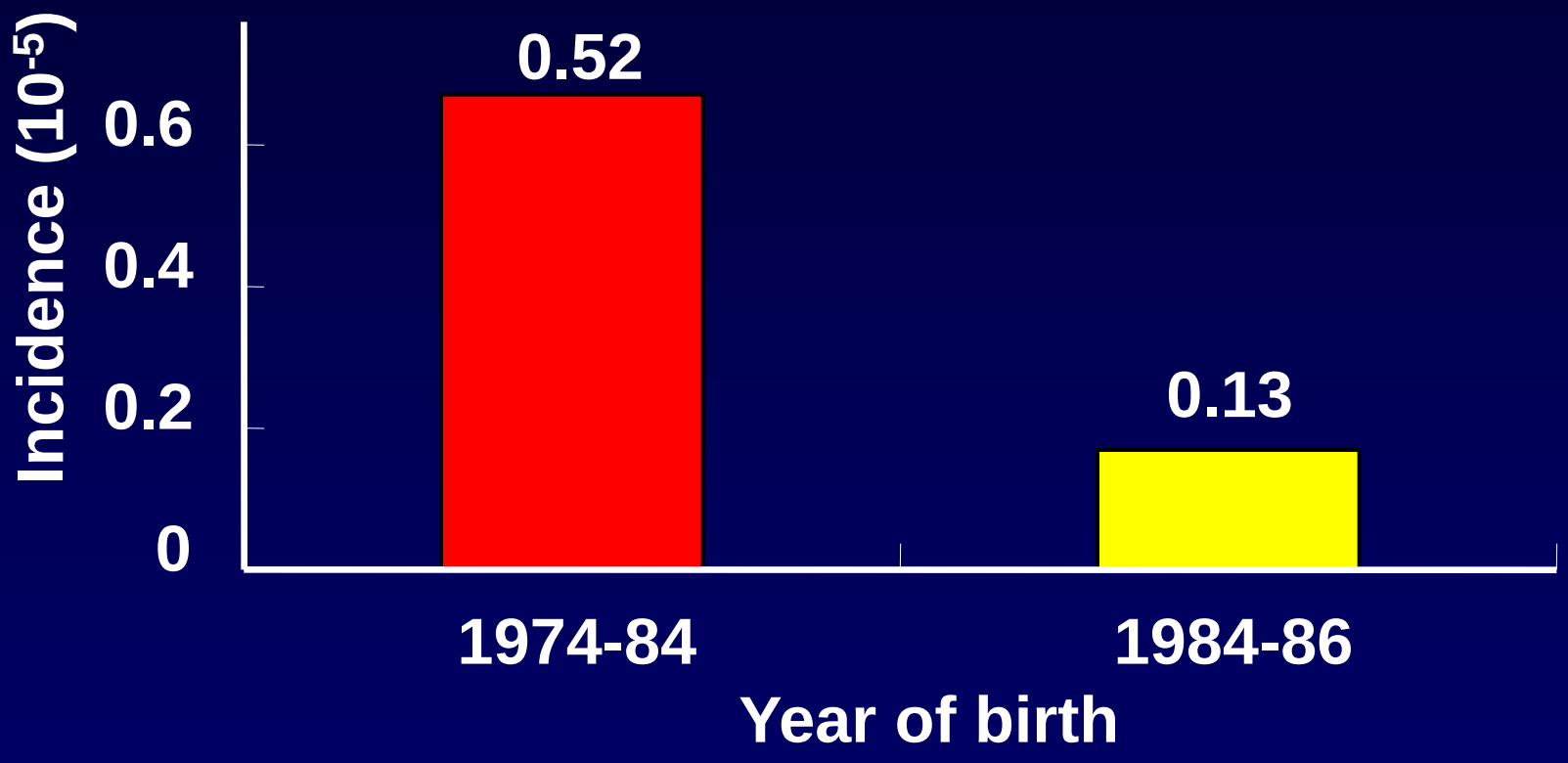
*40~50 years after hepatitis B vaccination was implemented.

By 2040, HBV vaccination efforts in Taiwan are expected to greatly reduce HBV-related liver disease (including HCC)

CH=chronic hepatitis; Cir=cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma.

Chen DS. *Hepatology*. 2011;54(2):381-392.

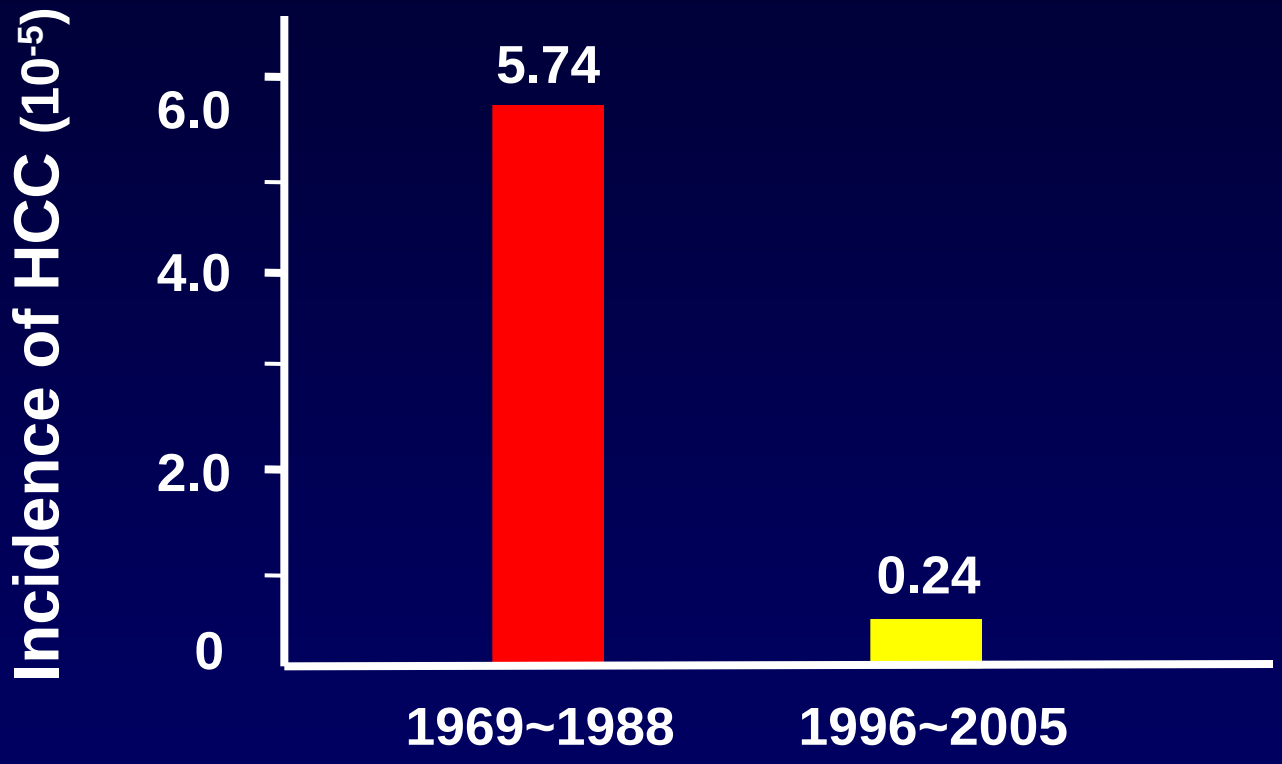
Incidence of HCC in Children (6-9 yr) in Taiwan Born before and after 1984*



* Mass HBV immunization since 1984.

Chang et al, N Engl J Med 1997; 336: 1855-9

Incidence of HCC in 10~19-yr olds Long-An*, Guanxi, China



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Zhuang H, 2008

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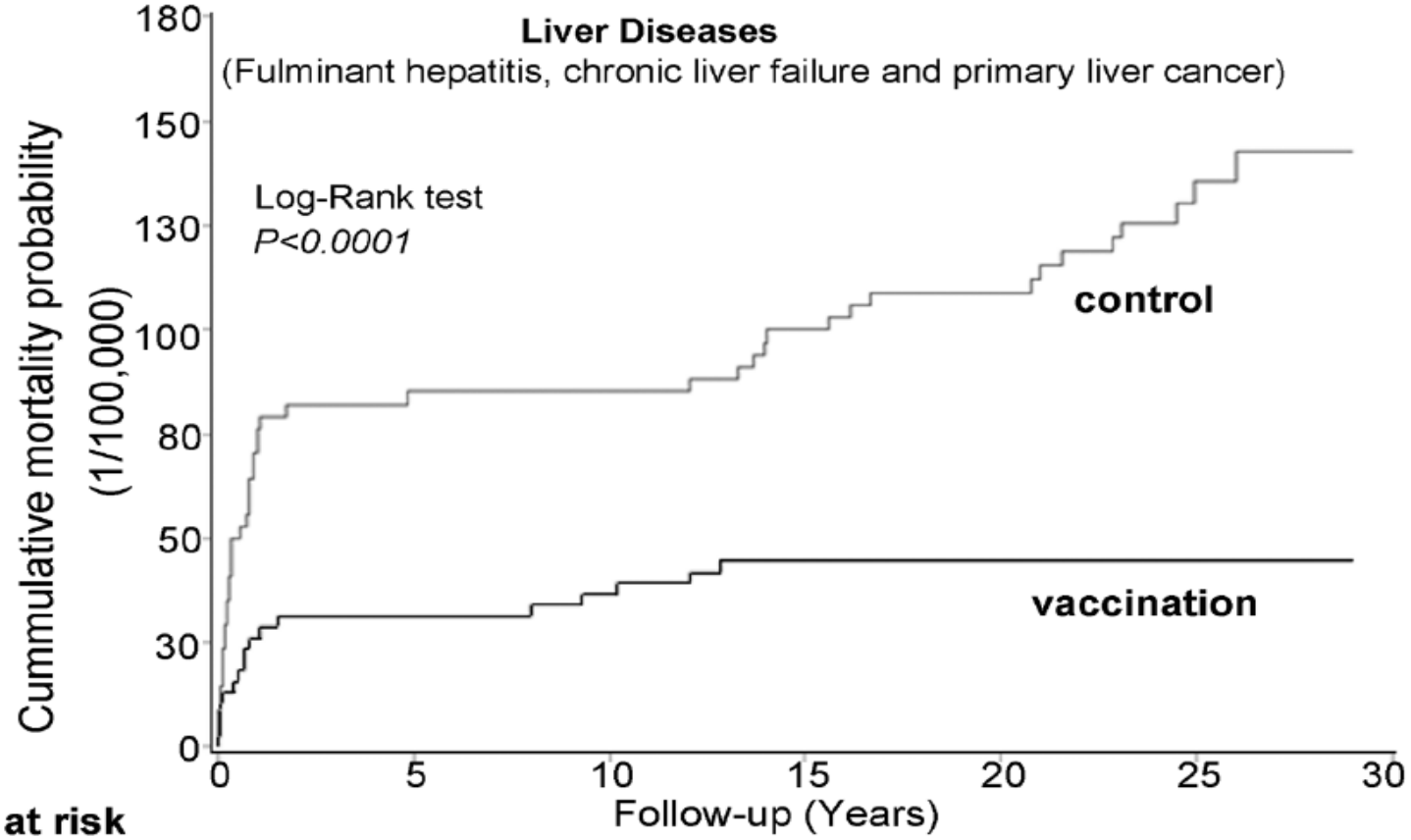

Number at risk

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Qu C et al. PLOS Med 2014;11: e1001774

Changing Incidence Patterns of HCC Among Age Groups in Taiwan

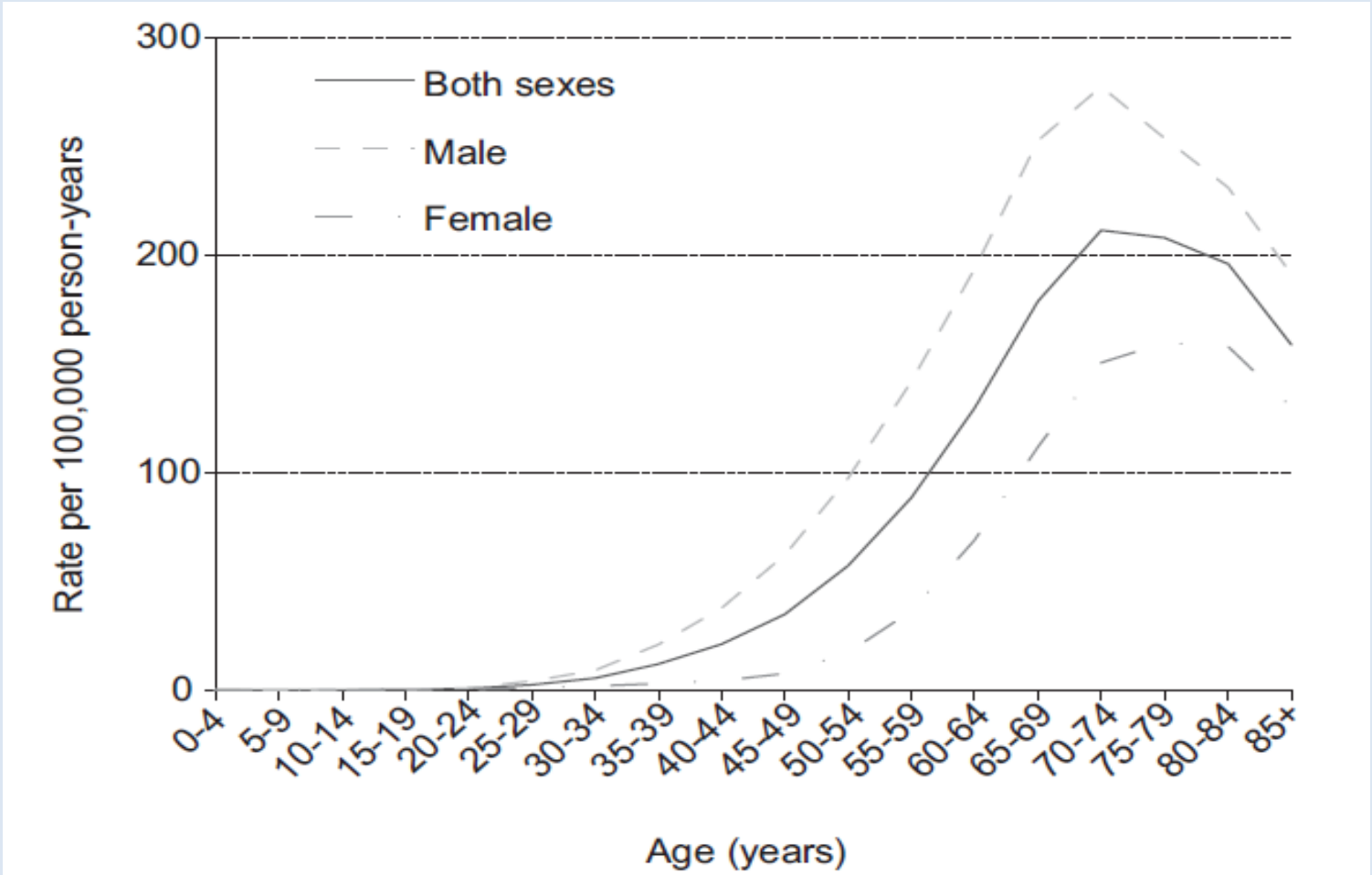


Fig. 1. Age-specific incidence rates of hepatocellular carcinoma by sex in Taiwan (2003–2011).

Hung GY et al. J Hepatol 2015;63:1390–1396

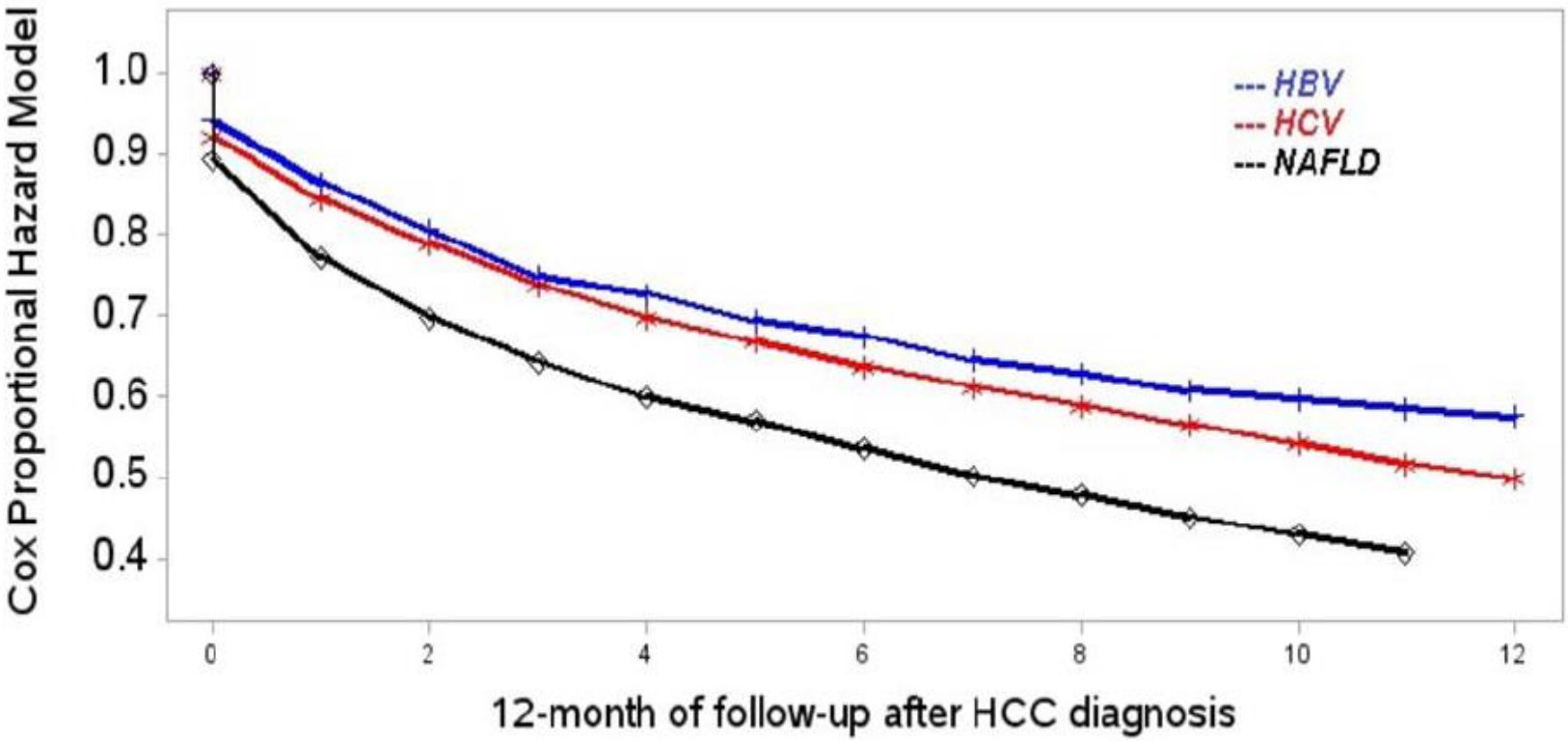
Age-standardized Incidence Rates (per 100,000 person-years) of Primary Liver Cancer According to Cities and Counties, Taiwan (2003–2011).

City/county (n = 22)	n	(%)	Crude rate	ASR[a]	(95% CI)	SRR[b]	(95% CI)
Northern region							
Taipei city	8766	(9)	37.1	26.5[−]	(26.0-27.1)	0.66	(0.64-0.67)
New Taipei city	12,562	(12.9)	36.7	34.3[−]	(33.7-34.9)	0.87	(0.85-0.89)
Hsinchu city	1549	(1.6)	42.9	39.1	(37.1-41.1)	1.01	(0.96-1.07)
Hsinchu county	1428	(1.5)	32.2	26.9[−]	(25.5-28.3)	0.69	(0.66-0.72)
Keelung city	1776	(1.8)	50.8	40.6	(38.6-42.5)	1.05	(1.00-1.10)
Taoyuan city	5371	(5.5)	30.9	30.1[−]	(29.3-30.9)	0.77	(0.75-0.79)
Yilan county	2202	(2.3)	53.1	40.3	(38.6-42.0)	1.04	(1.00-1.09)
Miaoli county	2535	(2.6)	50.2	36.7[-]	(35.2-38.1)	0.95	(0.91-0.99)
Central region							
Taichung city	9512	(9.8)	40.6	38.6	(37.8-39.4)	1.00	(0.98-1.02)
Changhua county	5735	(5.9)	48.5	38.7	(37.7-39.7)	1.00	(0.97-1.03)
Nantou county	2171	(2.2)	45.3	32.9[−]	(31.5-34.3)	0.85	(0.81-0.88)
Yunlin county	5516	(5.7)	84.3	58.5[++]	(56.9-60.1)	1.54	(1.49-1.60)
Southern region							
Chiayi city	1839	(1.9)	75.1	61.3[++]	(58.5-64.2)	1.60	(1.51-1.69)
Chiayi county	3920	(4)	79.1	53.2[++]	(51.5-54.9)	1.39	(1.34-1.45)
Tainan city	10,582	(10.9)	62.9	49.2[++]	(48.3-50.2)	1.31	(1.28-1.34)
Kaohsiung city	14,140	(14.6)	56.9	47.1[++]	(46.4-47.9)	1.26	(1.23-1.28)
Pingtung county	4152	(4.3)	52.0	39.1	(37.9-40.3)	1.01	(0.98-1.04)
Eastern region							
Hualien county	1402	(1.4)	45.3	33.8[−]	(32.0-35.6)	0.87	(0.83-0.92)
Taitung county	1025	(1.1)	48.5	35.6[-]	(33.4-37.9)	0.92	(0.87-0.98)
Offshore islands							
Penghu county	664	(0.7)	78.6	54.8[++]	(50.5-59.1)	1.42	(1.29-1.56)
Kinmen county	242	(0.2)	33	24.5[−]	(21.4-27.6)	0.63	(0.57-0.70)
Lienchiang county	40	(0.04)	45.5	36.3	(24.9-47.8)	0.94	(0.69-1.28)
Total	97,129	(100)	47	38.6	(38.4-38.9)		

[a]ASRs were age adjusted to the 2000 world standard population. [b]SRR: ASR of the city/county *vs.* ASR of the rest area of Taiwan. [++]: indicates significantly higher in comparison with the rest area of Taiwan, $p < 0.01$. [−(−)]: indicates significantly lower in comparison with the rest area of Taiwan, $p < 0.01$ ($p < 0.05$).
ASR, Age-standardized incidence rate; CI, confidence interval; SRR, standardized rate (ASR) ratio.

Hung GY et al. J Hepatol 2015;63:1390–1396

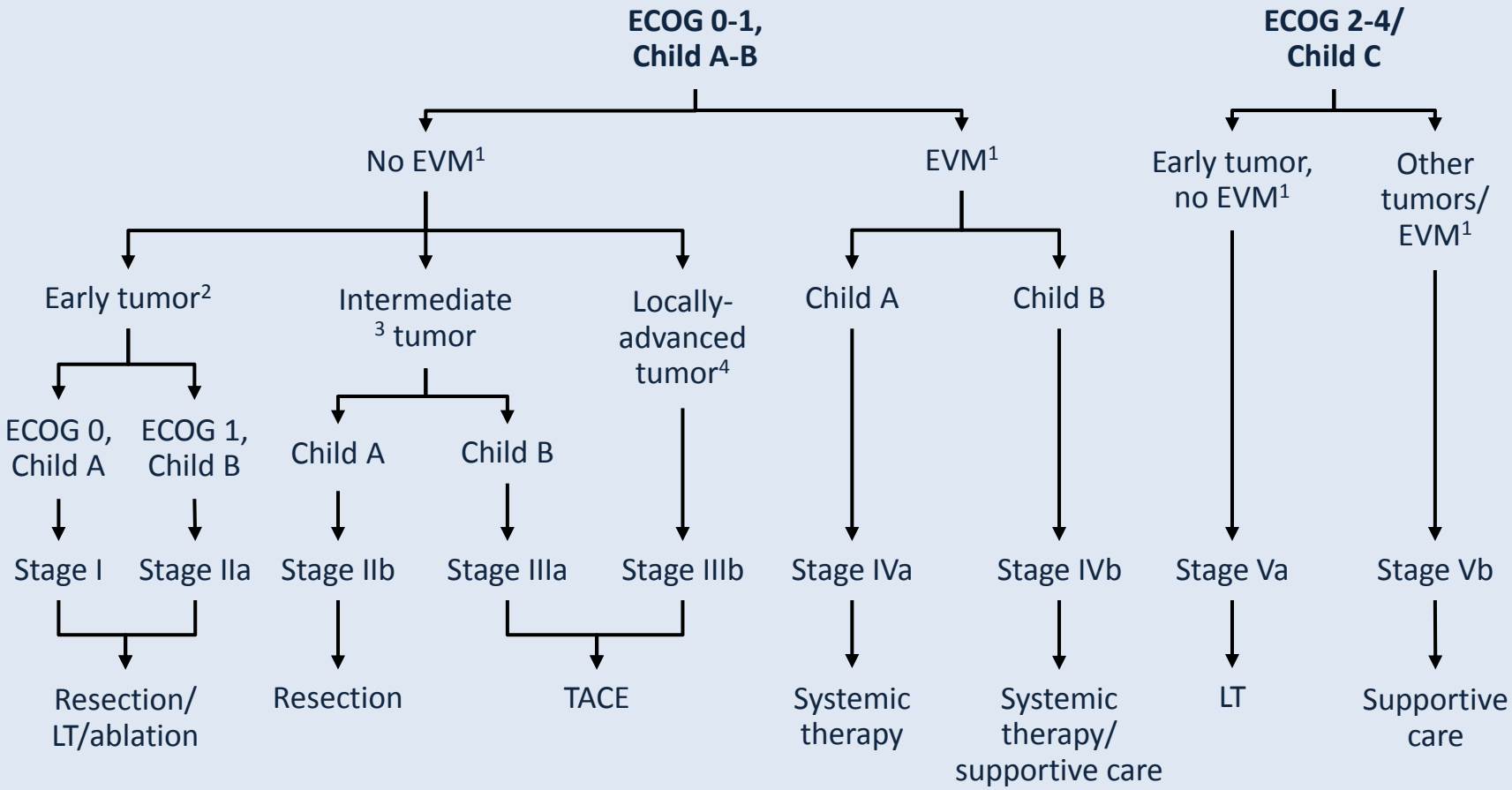
Adjusted Survival Curves by Liver Disease



** Adjusted for age (years) at HCC diagnosis and tumor stage;*
Source: SEER-MEdicare, 2004 - 2009

Younossi ZM et al. Hepatol 2015;62:1723-1730

Hong Kong Algorithm



[1]EVM, extrahepatic vascular invasion/metastasis. [2]Early tumor: 5 cm, 3 tumor nodules and no intrahepatic venous invasion;
[3]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;
[4]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.

Yau. Gastroenterology. 2014 Feb 25. pii: S0016-5085(14)00243-1.
doi:10.1053/j.gastro.2014.02.032.://www.sciencedirect.com/science/article/pii/S0016508514002431

Changing Incidence Patterns of HCC Age Groups in Taiwan

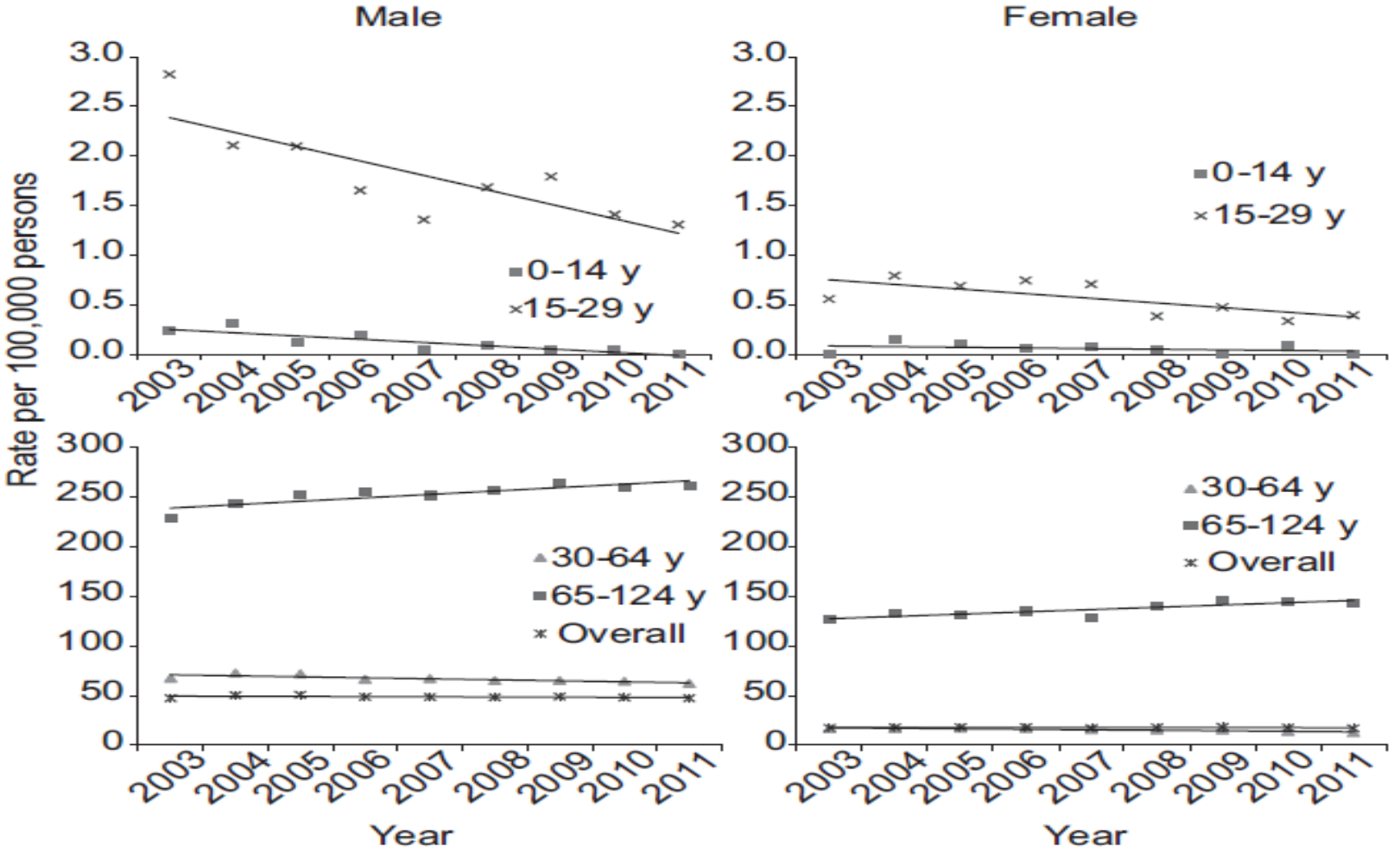


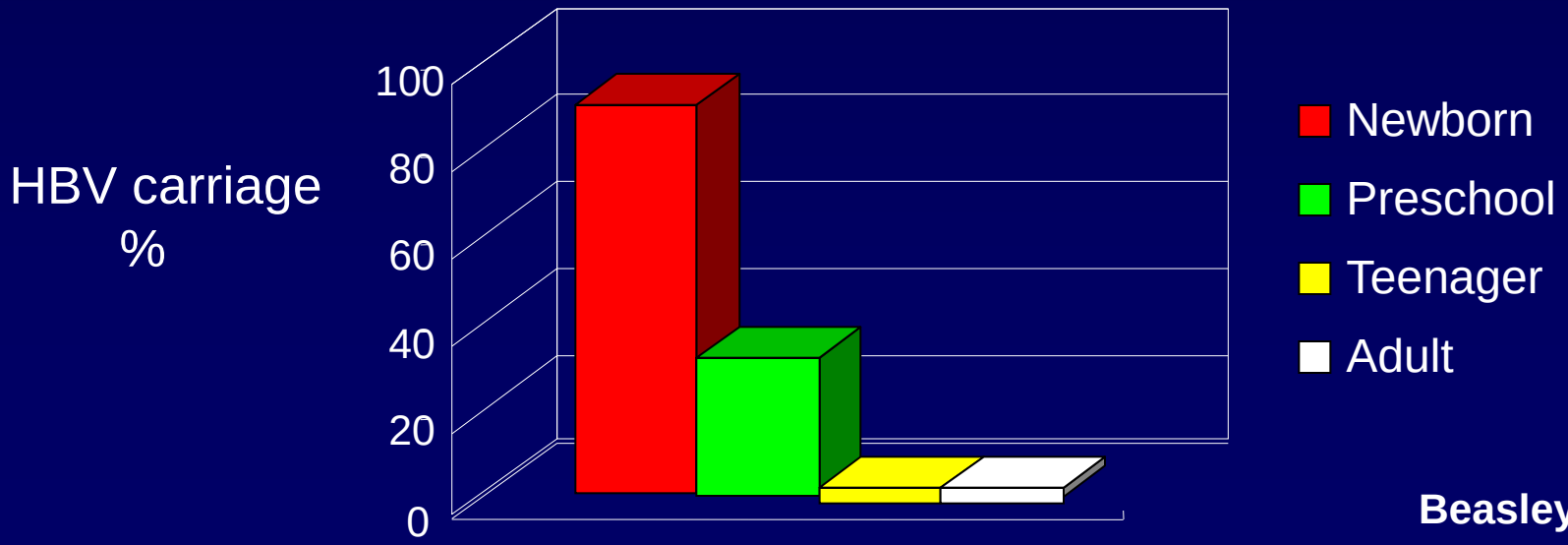
Fig. 2. Temporal trends in the incidence rates of hepatocellular carcinoma by sex and age group in Taiwan (2003–2011).

Hung GY et al. J Hepatol 2015;63:1390–1396

Chronicity and age at infection

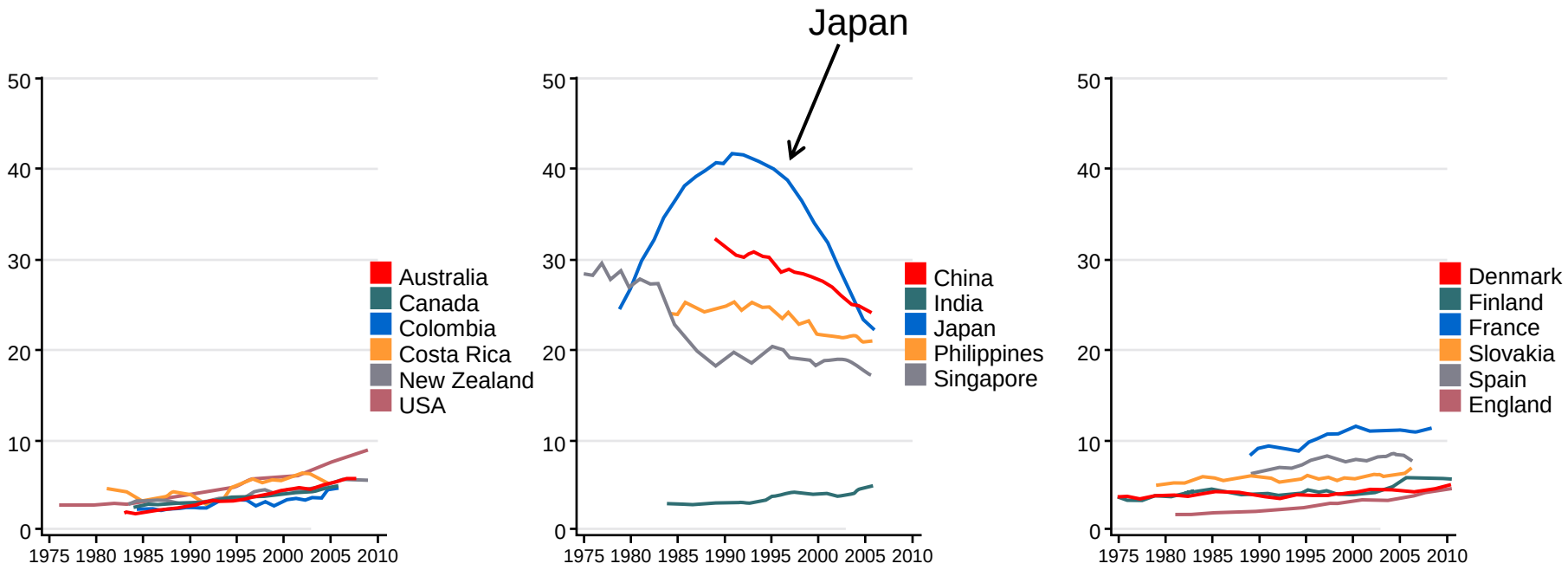
Chronicity is related with age when HBV infection occurs.

Age at infection	Chronicity	Symptomatic
• Perinatal infection:	90%	rare
• Infection at preschool age:	25%	~10%
• Infection at adulthood:	< 3%	~30%



Beasley et al.

Global Incidence of HCC in Men (Per 100,000)



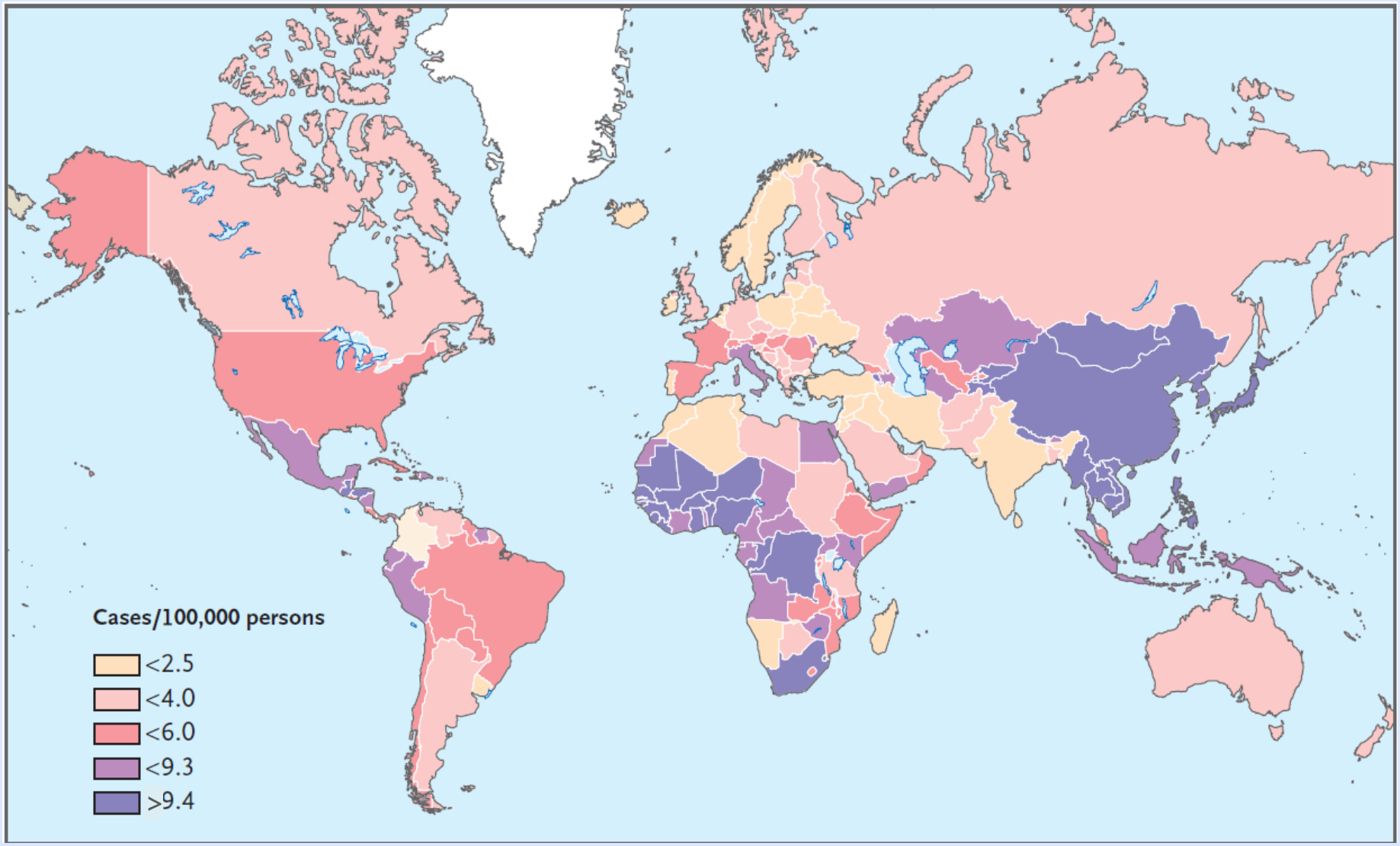
HCC incidence is decreasing in Japan – this may be due in part to decreases in HCV-related HCC

Regional data from: CI5.iarc.fr; Australia: www.aihw.gov.au; New Zealand: www.health.govt.nz; USA: seer.cancer.gov; NORDCAN: www.ancr.nu; European Cancer Observatory: eco.iarc.fr; England: www.ons.gov.uk.

HCC=hepatocellular carcinoma.

Kudo M. *Liver Cancer.* 2015;4(1):39–50.

Regional Variation in the Estimated Age-Standardized Incidence Rates of Liver Cancer.



El-Serag H.B. et al. N Engl J Med 2011;365:1118-27

Future Perspective of Targeted Therapy for HCC

At the Crossroad

KASL, Nov. 26, 2015, Seoul

Ann-Lii Cheng M.D., Ph.D.

Distinguished Professor, Director, NTU Cancer Center,
National Taiwan University, Taipei, Taiwan.

8 Years On - - -

- Results of SHARP was presented in June 2007. Sorafenib was approved by FDA (Dec. 2007) and EMEA (Oct. 2007).
- Up to 80 other compounds have been tested in more than 190 trials. None has succeeded.

Drug Dev

Multi-targeted

sorafenib, sun
linifanib

Linifanib Versus Sorafenib in Patients With Advanced HCC: Results of a Randomized Phase III Trial

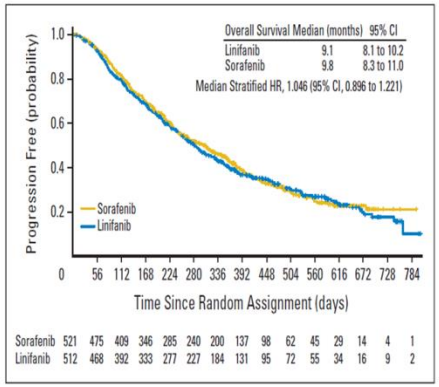


Fig 2. Kaplan-Meier analysis of overall survival with a cutoff point at the 667th patient death. HR, hazard ratio.

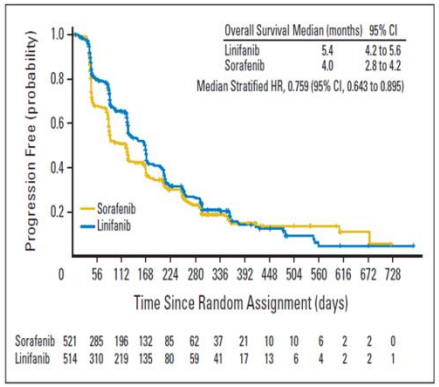


Fig 4. Kaplan-Meier analysis of time to progression. HR, hazard ratio.

Cainap C, et al. J Clin Oncol 2015; 33:172-179

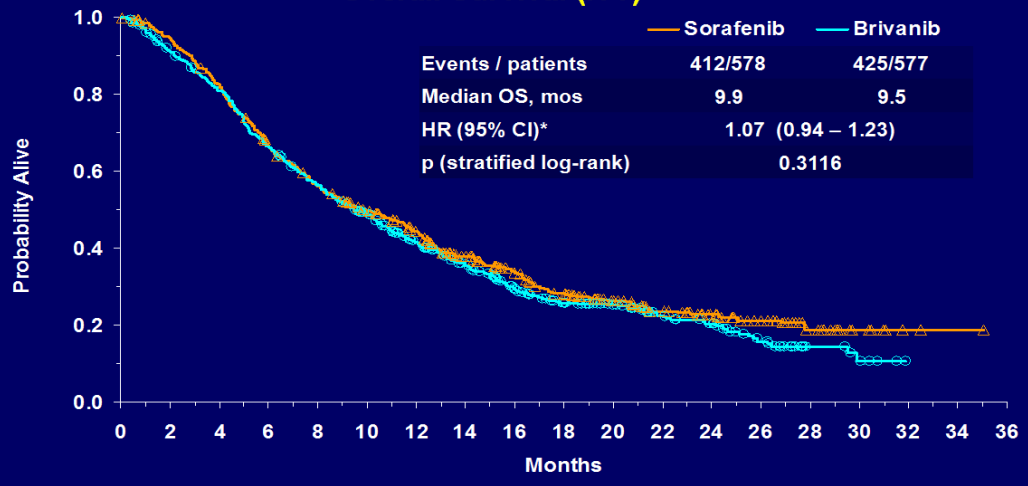
Phase III, R … S …

	Briva… (n = 2…
Median OS	9.4 n…
Median TTP*	4.2 n…
DCR*	71.2…
ORR*	11.5…

CI, confidence interval; HR …
*Modified RECIST for HCC
‡Cochran-Mantel-Haenszel …

Phase III, …

Overall Survival (ITT)



*HR (95% CI) for per-protocol population (575 patients in each arm) was 1.06 (0.93-1.22)

BMS Highly Confidential - Not for Distribution

Johnson P et al. J Clin Oncol. 2013 Oct 1;31(28):3517-24

… CI: 7.4–9.2)

… % CI: 8.9–11.4)

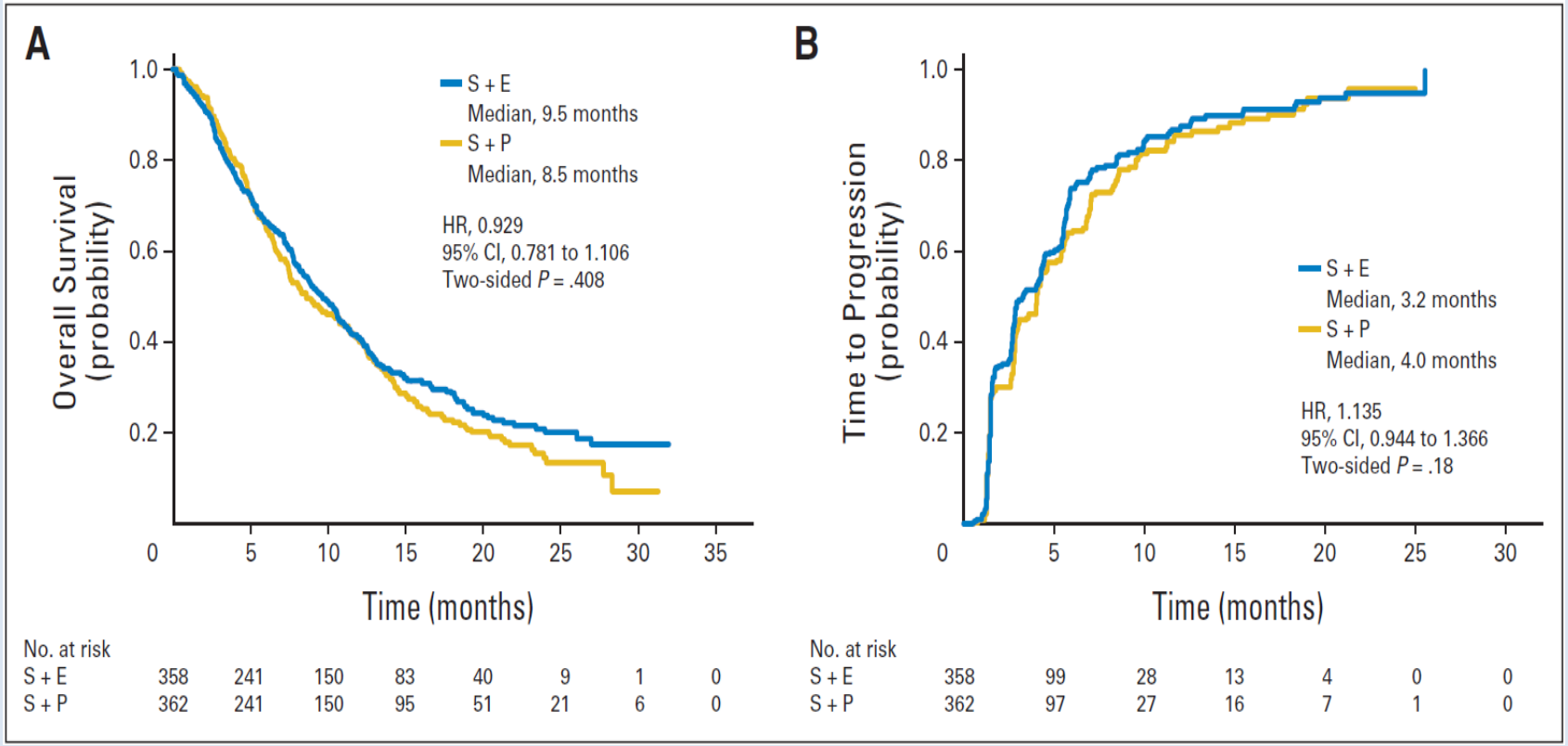
… .50)

… 35 40

… al; HR: hazard ratio

… c ASCO 2011, #4000

SEARCH: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Sorafenib Plus Erlotinib in Patients With Advanced HCC



Zhu A X. et al J Clin Oncol 2015;33:559-566

Ramucirumab Versus Placebo as Second-line Treatment in

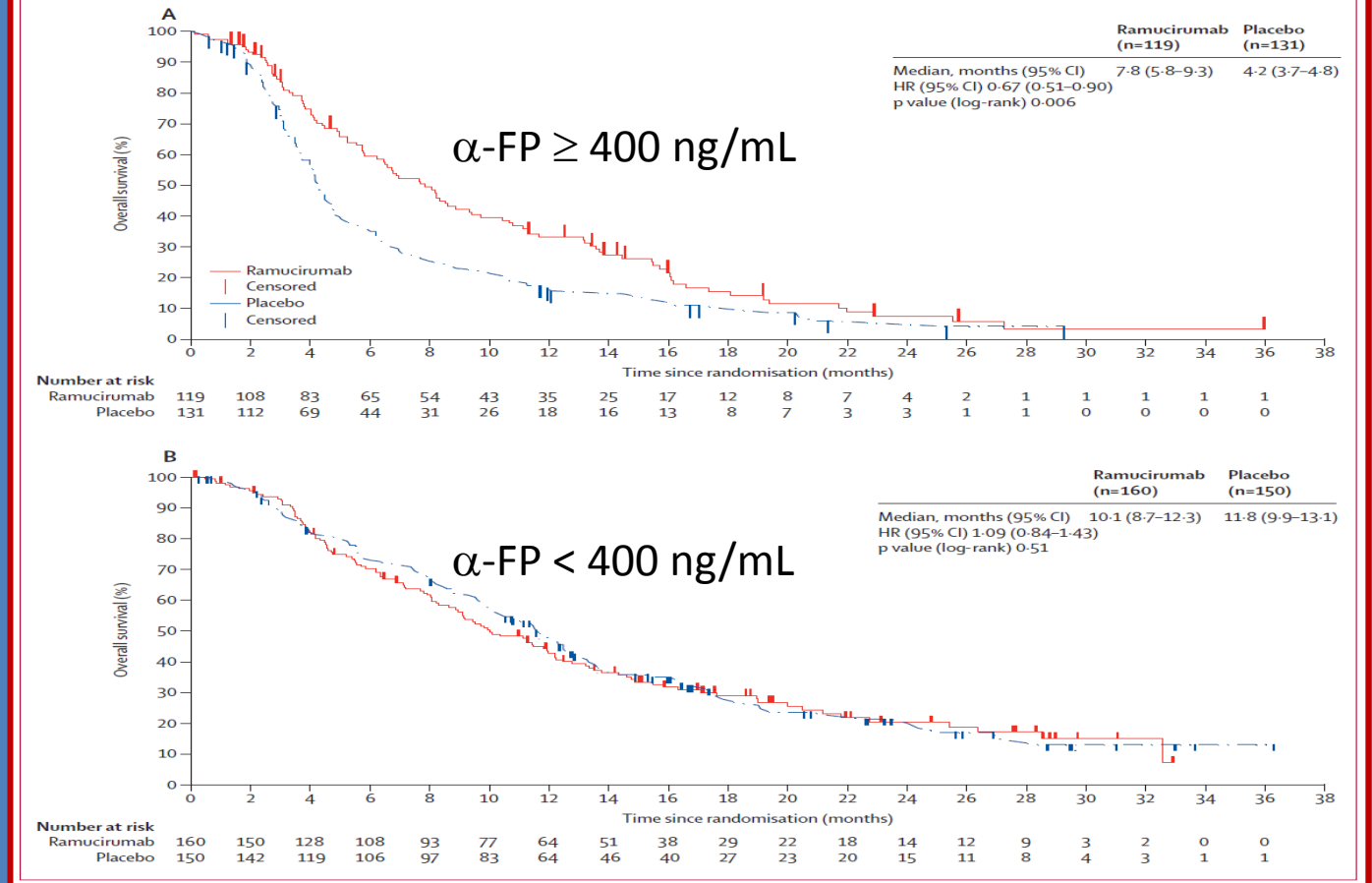
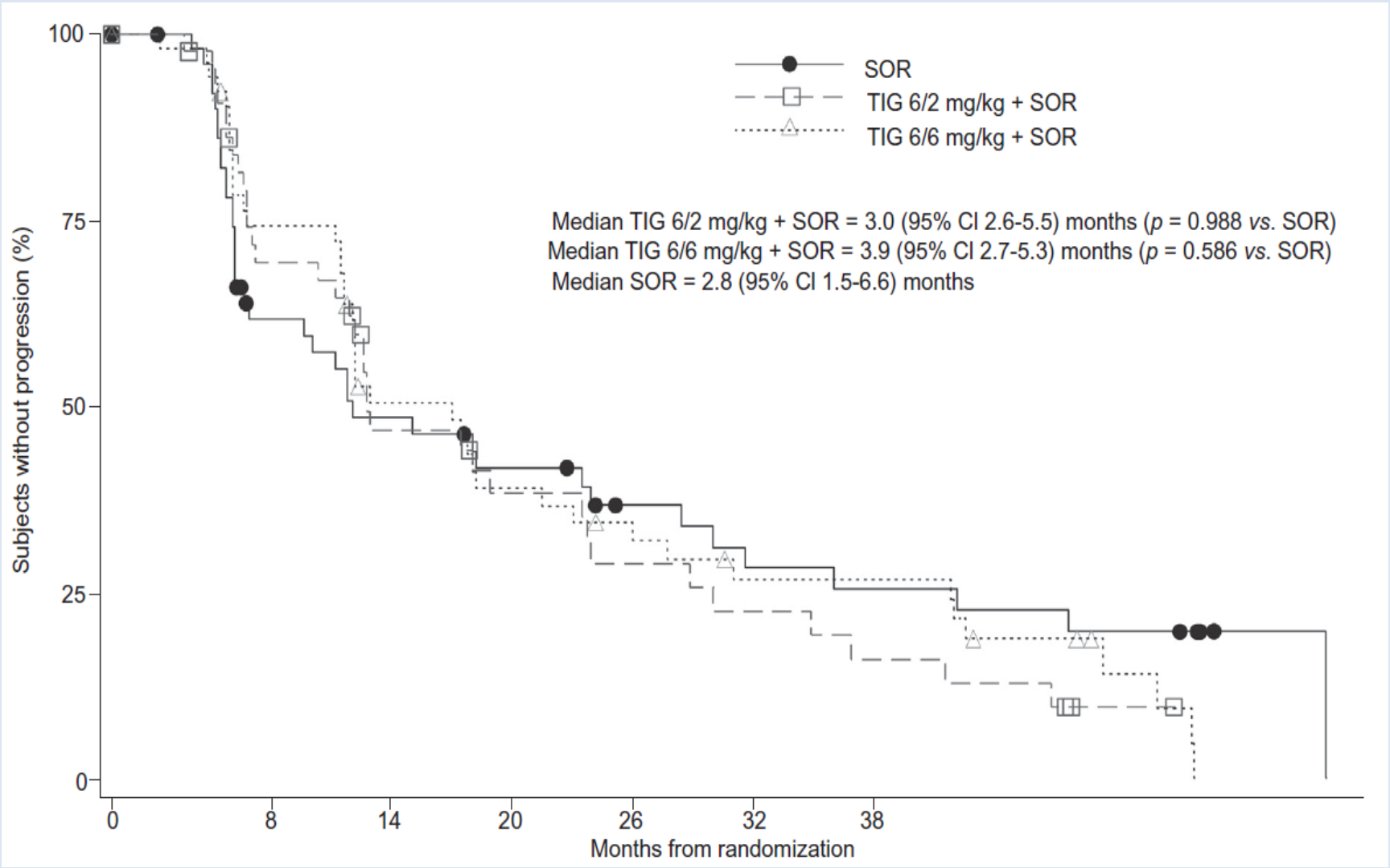


Figure 4: Kaplan-Meier plot of overall survival in patients with baseline α-fetoprotein concentration of 400 ng/mL or greater (A) and in patients with baseline α-fetoprotein less than 400 ng/mL (B)
HR=hazard ratio.

Zhu AX et al. Lancet Oncol 2015; 16: 859–70

Safety and Efficacy of Tigatuzumab Plus Sorafenib as First-line Therapy in Subjects With Advanced HCC: A phase 2 randomized study



Cheng AL et al J Hepatol 2015;63:896–904

Two Groups of Front-runners

EVOLVE-1 (Phase III, Placebo-controlled, 2nd-line) failed to meet its primary end point (OS)

3. mTOR inhibitors

Drug Development for HCC (2010-2015)

FGFR inhibitors

anti-angiogenic TKI

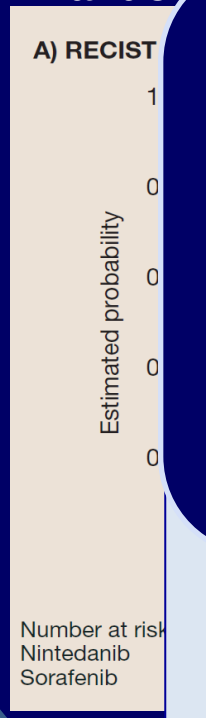
sorafenib, sunitinib, vandetanib, linifanab, brivanib, nintedanib, dovitinib, orantinib, lenvatinib, [illegible] axitinib

Phase II TAC

Novel cat

mTORi, M PI3K/Akt inhibitors anti-PD1, A3 adenc

Random



Did not meet primary end point in the randomized phase II study, 1st line vs sorafenib

Cheng AL et al, ASCO-GI 2015

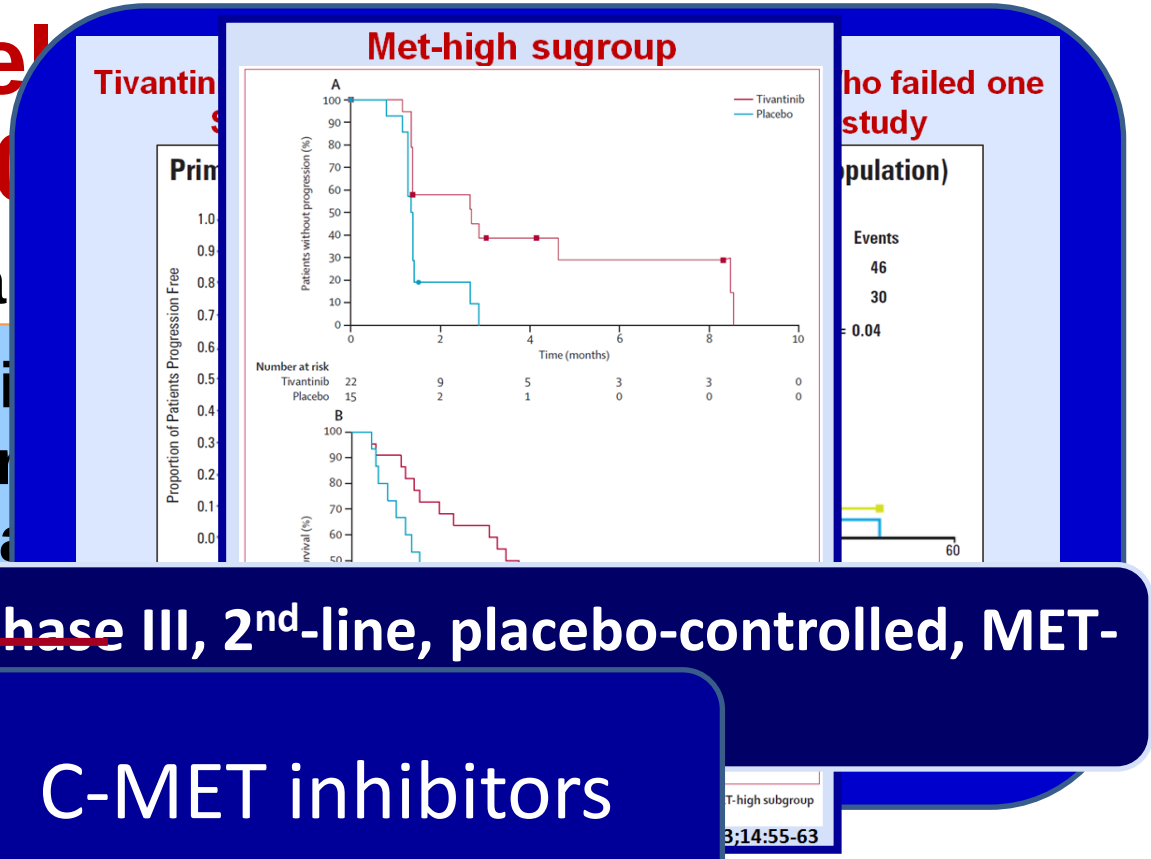
Bruix J et al. Eur J Cancer 49 (2013) 3412–3419

Yen CJ et al ECCO/ESMO 2013

Drug Devel
(20

Multi-targeted a

sorafenib, suni
linifanib, brivar
orantinib, lenva
apatinib, for



Phase III, 2nd-line, placebo-controlled, MET-

Phase III, 2nd-line,

C-MET inhibitors

- ≦1 systemic Tx (51% sorafenib)
- Cabozantinib 100 mg/day x12 wks, lead-in.
- 2/36 PR (RR=5%, DCR=68%) at lead-in.
- One more PR after randomization.

Verslype C et al Proc. ASCO 2012;#4007

Molecular Alterations Of HGF/MET In Human HCC

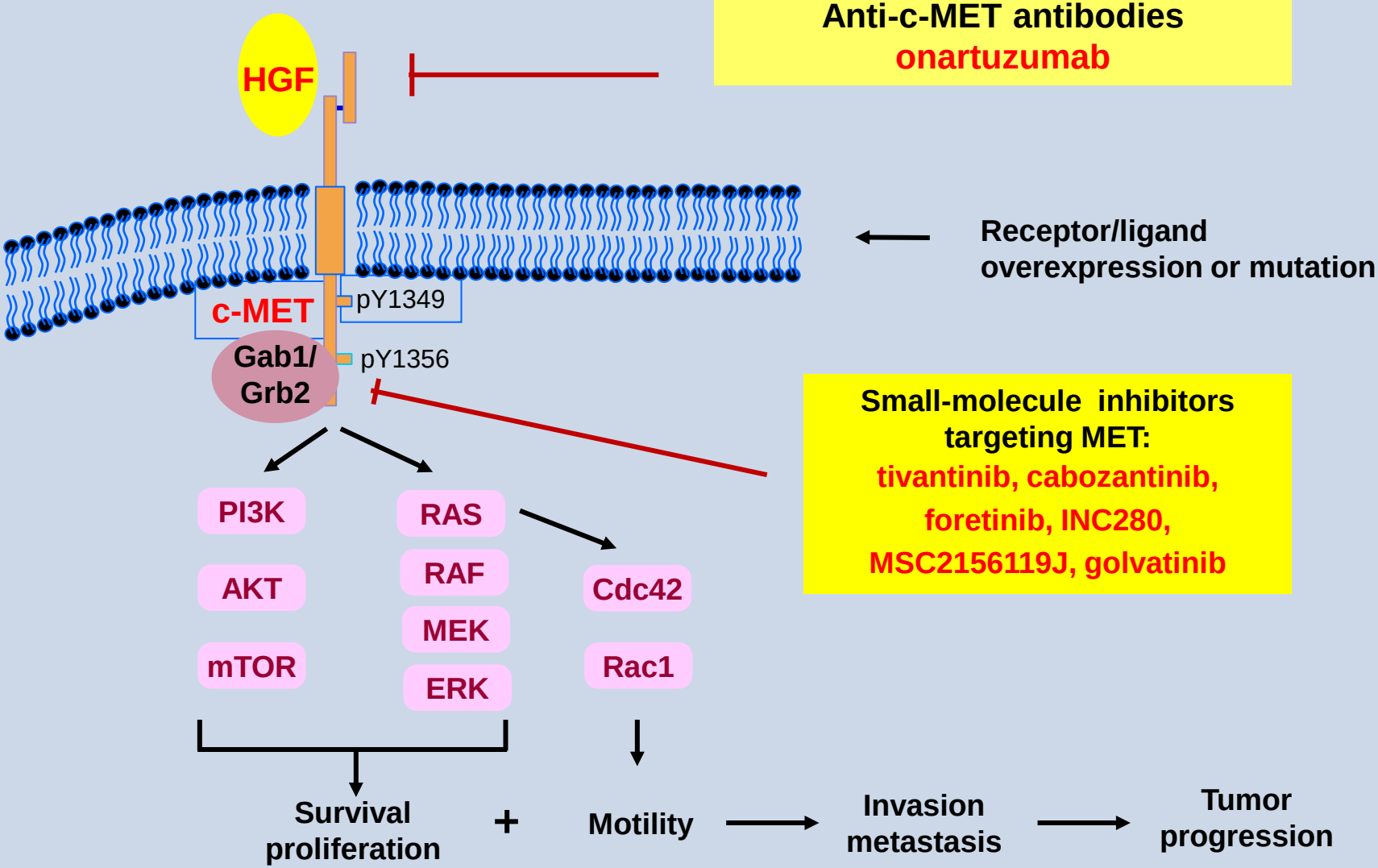
MET alteration	Findings	[Ref.]
Amplification	1/20 cases; 3.8 fold amplification	Takeo *et al.*, 2001 [39]
Amplification	1/59 cases; 22/59 chromosome 7 aneuploidy	Kondo *et al.*, 2013 [40]
Amplification	4-5% in 286 patien	*t al.*, 2013 [41]
Point mutations	0/24 patients	*et al.*, 2012 [42]
Overexpression	Northern blot ana with the surroundi	*l.*, 1994 [45].
Overexpression	Northern blot anal HCC differentiatio	*t al.*, 1994 [46]
Overexpression	Competitive RT-P	*et al.*, 1996 [47]
Overexpression	Northern blot analysis. Met overexpression in some cases and underexpression in others. HGF downregulation	Selden *et al.*, [89]
Overexpression	Western blot analysis. 52% of 62 patients with Met overexpression, correlating with increased incidence of intrahepatic metastases and shorter 5-yr OS	Ueki *et al.*,1997 [44]
Overexpression	IHC in 86 patients. MET overexpression in 20% and downregulation in 32%. HGF overexpression in 33% and downregulation in 20%	Kiss *et al.*, 1997 [48]
Overexpression	IHC and qRT-PCR in 24 HCC. MET overexpression in most of the cases. Underexpression of HGF	Tavian *et al.*, 2000 [49]
Overexpression	qRT-PCR in 15 patients. Overexpression of MET in poorly differentiated tumors	Daveau *et al.*, 2003 [50]

IHC, immunohistochemistry; OS, overall survival; qRT PCR, quantitative Reverse Transcription Polymerase Chain Reaction.

Amplification: 2-5%
Point mutation: 0%
Over-expression: 30-40% (Northern)
40-50% (Western)
20-30% (IHC)

Giordano S et al. J Hepatol 2014;60:442–452

c-MET Targeted Agents in HCC



Ongoing Trials of c-MET Inhibitors for HCC

Drug/ (Identifier)	Design	Patients	Primary outcome	Site	Start date/ Status
Tivantinib (NCT01755767)	III, randomized Placebo-controlled	Failed systemic therapy, c-MET high	OS	International	2012-Dec Recruiting
Tivantinib (NCT02029157)	III, randomized Placebo-controlled	Failed systemic therapy, c-MET high	PFS	Japan	2014-Jan Recruiting
INC280 (NCT01737827)	II, single arm	1st line, c-MET dysregulation	TTP	China, Hong-Kong, Singapore, Thailand	2013-Mar Recruiting
INC280 (NCT01964235)	II, randomized Placebo-controlled	Failed sorafenib, c-MET dysregulation	TTP	Europe, USA, Hong-Kong, Australia	2014-Mar Suspended
Cabozantinib (NCT01908426)	III, randomized Placebo-controlled	Failed sorafenib	OS	International	2013-Aug Recruiting
MSC2156119J (NCT02115373)	I/II, single arm	Failed sorafenib, Phase II: c-MET+	No. of DLT in cycle 1	International	2014-May Recruiting
MSC2156119J (NCT01988493)	I/II, randomized Sorafenib-controlled	First-line c-MET+ Asian	No. of DLT in cycle 1; TTP	Germany	2014-Jan Recruiting

New Targets for HCC

- **Wnt/β-Catenin**
- **JAK/STAT**
- **FGF19/FGFR4**
- **VEGF-A**
- **c-MET**
- **TSC-2**

FGF19-FGFR4 Signaling Is Important in HCC Carcinogenesis and Survival

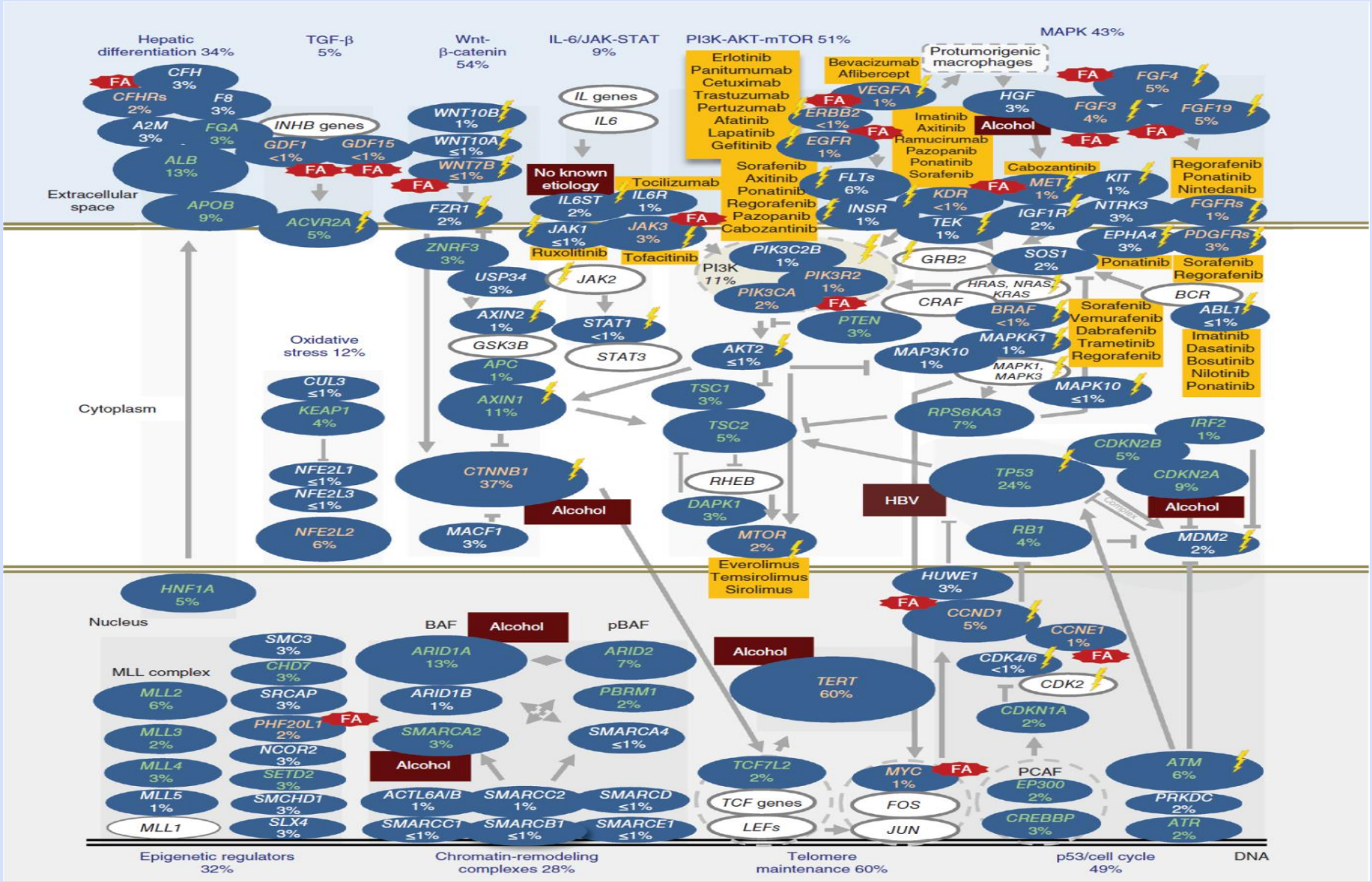
- FGF19-FGFR4 drives hepatocarcinogenesis in preclinical studies.
- FGF19-FGFR4 cross-talks with Wnt/β-catenin pathway.
- Inhibition of FGF19-FGFR4 signaling has shown *in vitro* and *in vivo* anti-cancer activities against HCC.

Ho HK, et al: J Hepatol 2009;50:118-27
Sawey ET et al: Cancer Cell 2011;19:347-358
French DM, et al: PLos One 2012;7:e36713
Miura S, et al: BMC Cancer 2012;12:56
Pai R, et al: Cancer Res 68:5086-95

FGFR4 inhibitors for HCC

- **FGFR4 specific inhibitors**
  - Blue print (phase I)
  - Novartis (phase I)
  - Sanofi
- **Pan-FGFR inhbitors**
  - Eisai (lenvatinib, phase III)
  - Astellas (phase I)
  - Johnson and Johnson (phase I)

The landscape of altered genes and pathways in HCC

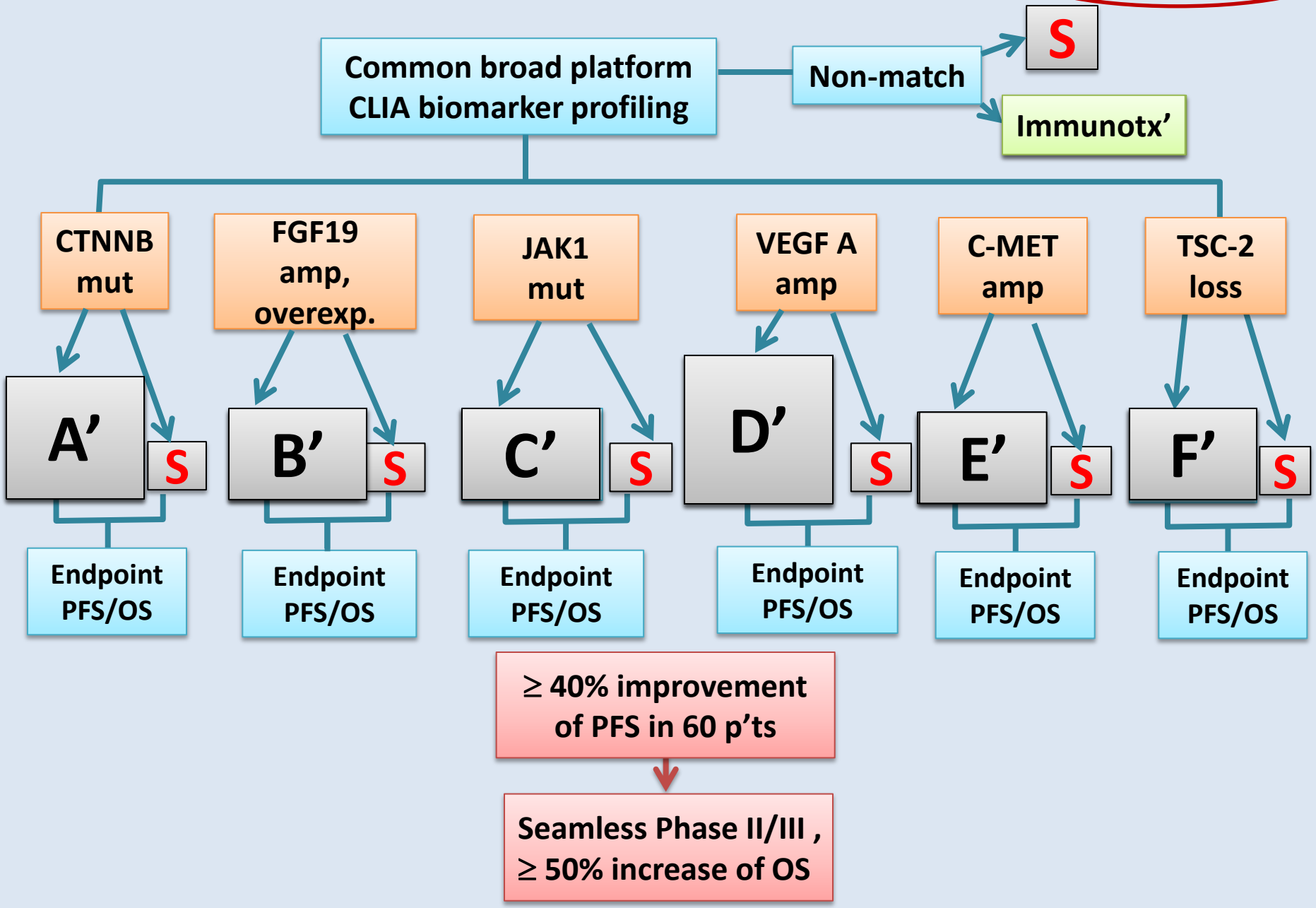


Schulze K et al. Nature Genetics 2015; Published online 30 March 2015

New Targets for HCC

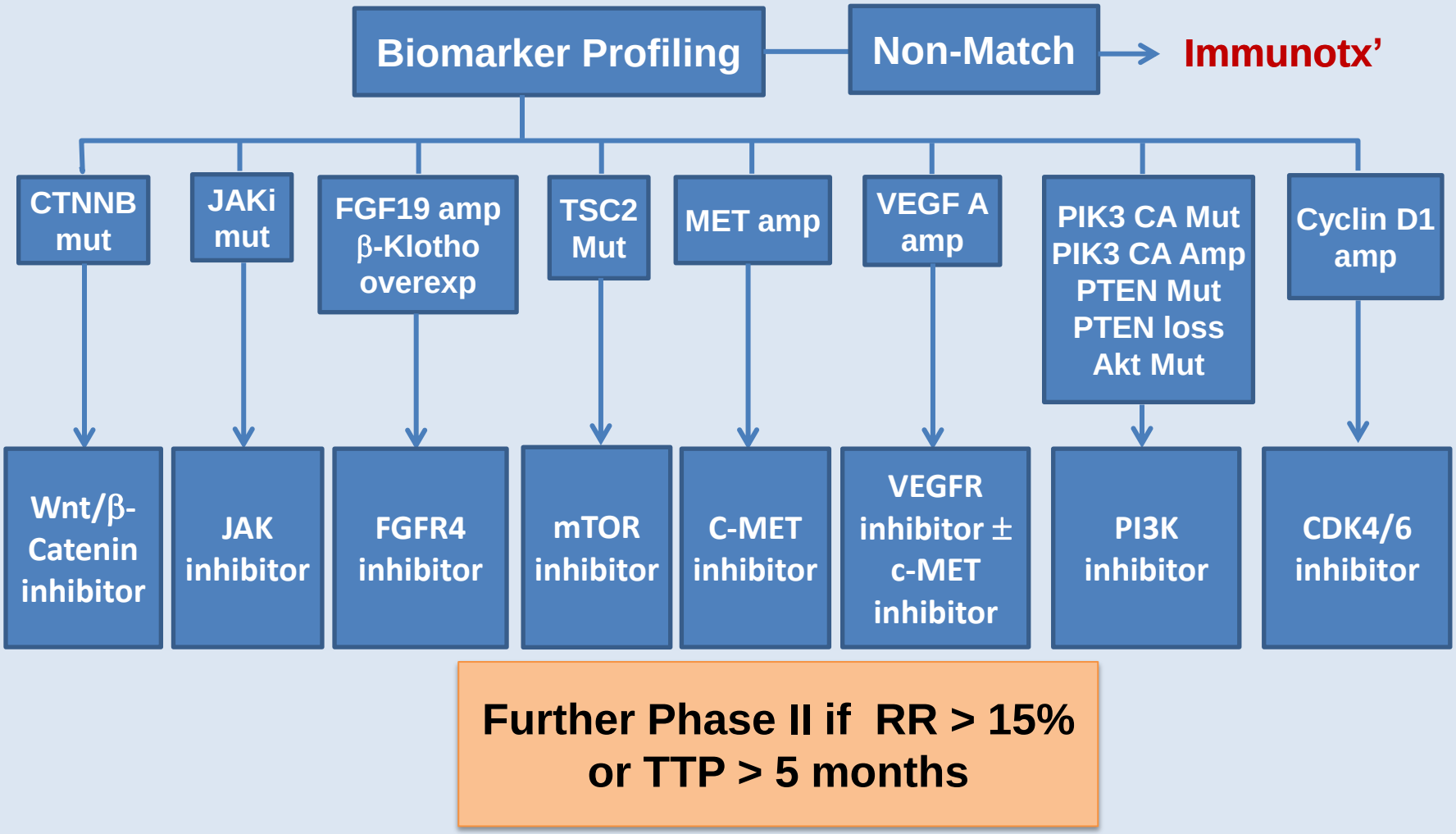
- **Wnt/β-Catenin**
- **JAK/STAT**
- **FGF19/FGFR4**
- **VEGF-A**
- **c-MET**
- **TSC-2**

Master Protocol for 1st-line HCC – Adaptive, confirmatory



Master Protocol for 2nd-line HCC

- Exploratory, single-arm



Further Phase II if RR > 15% or TTP > 5 months

At the Crossroad

Molecular Targeted Therapy at the Era of Immunotherapy

- **While we are about to cash our long years of hard work on MTTs, the promise of immunotherapy has rapidly emerged ---**

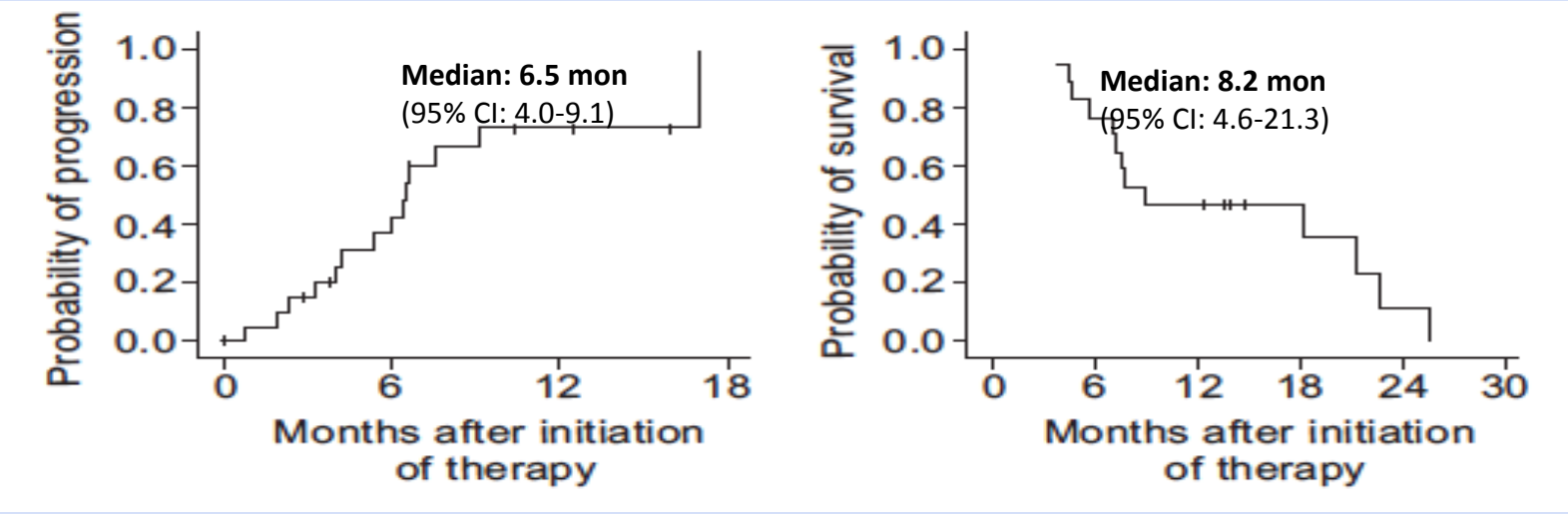
- **How can we make the most out of the two modalities of treatment ?**

Rationale of Using Immune Checkpoint Blockade (anti-CTLA-4, anti-PD1) in HCC

- **Increased CTLA-4(+) or PD-1(+) T cells in patients with chronic viral hepatitis and HCC**
  - Hsu PN et al. *Liver Int* 2010; 30: 1379-86
  - Shi F, et al. *Int J Cancer* 2011; 128: 887-96
  - Kalathil S et al. Cancer Res 2013; 73: 2435-44
- **Anti-CTLA-4 or anti-PD-1 may restore T cell function and have anti-viral effects**
  - Nakamoto N et al. *PLoS Pathog* 2009; 5: e1000313
  - Tzeng HT et al. *PLoS One* 2012; 7: e39179
  - Fuller MJ, et al. *Proc Natl Acad Sci USA* 2013; 110: 15001-6
- **Preliminary anti-tumor effects in HCC patients**
  - Sangro B et al. *J Hepatol* 2013; 59: 81-8
  - El-Khoueiri A et al. ASCO 2015

Tremelimumab (Anti-CTLA-4) for HCV-HCC

- 21 pts with HCV-HCC which was not amenable to locoregional therapy (* 40% were BCLC stage C; 57.5% were untreated)
- Tremelimumab 15 m/kg iv every 90 days for up to 4 cycles
- ORR: 17.6% (3 PRs, lasting for 3.6, 9.2 and 15.8 months)
- DCR: 76.4% (half of them lasting >6 months)



Sangro B, et al: J Hepatol 2013 Mar 4

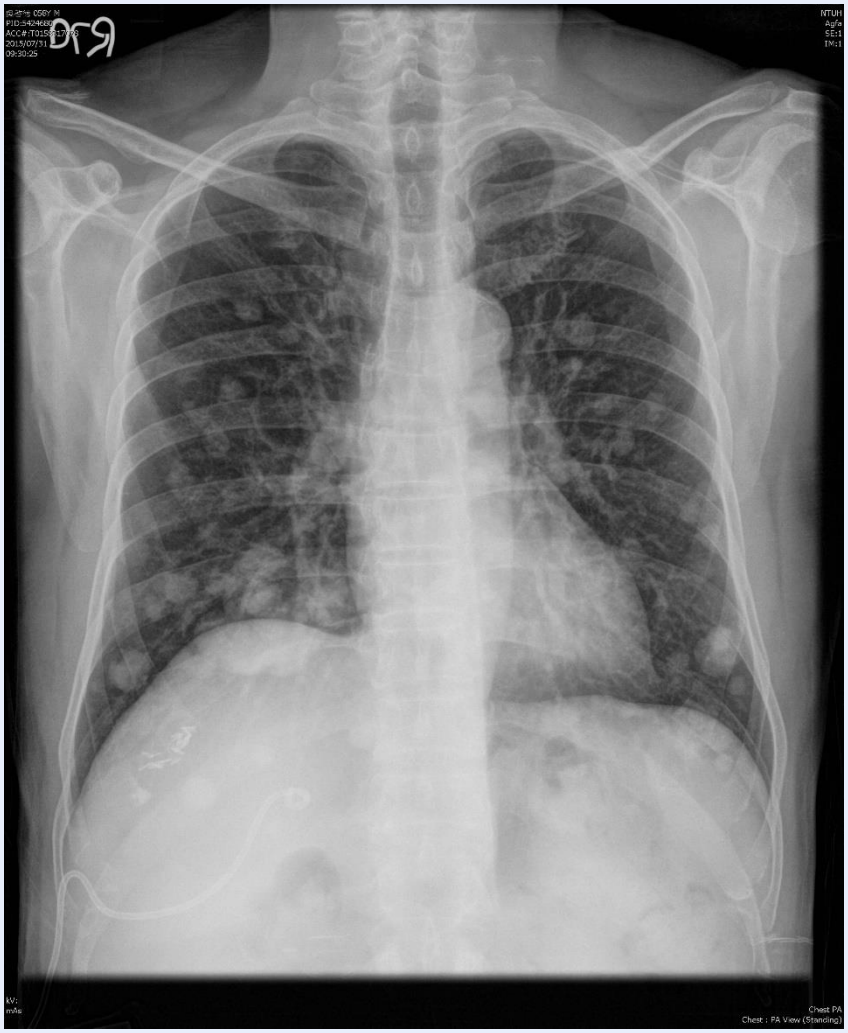
Phase I/II Study of Nivolumab for Advanced Hepatocellular Carcinoma

Investigator-Assessed Best Overall Response

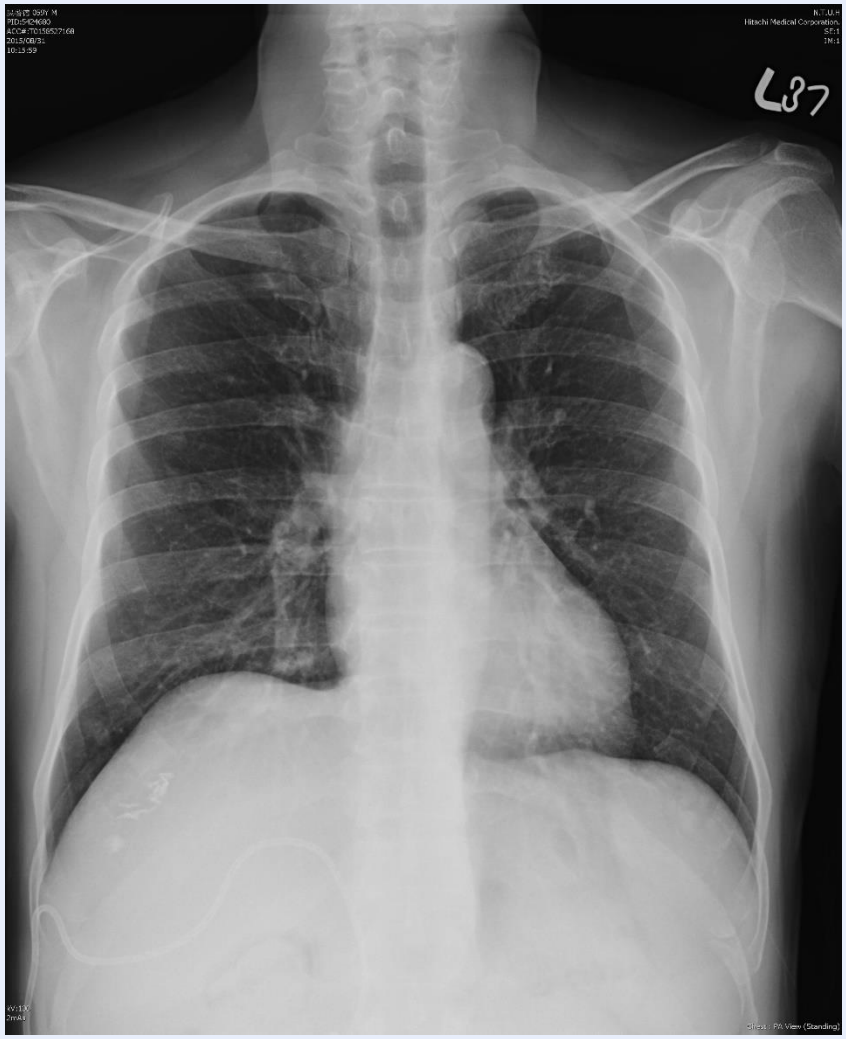
	Uninfected (n=21)	HCV (n=11)	HBV (n=10)	Total Evaluable* (n=42)
Objective response, n (%)	3 (14)	4 (36)	1 (10)	8 (19)
Complete response	2 (10)	0	0	2 (5)
Partial response	1 (5)	4 (36)	1 (10)	6 (14)
Stable disease	10 (48)	5 (45)†	5 (50)	20 (48)
Progressive disease	8 (38)	2 (18)	4 (40)	14 (33)
Ongoing response, n (%)	3/3 (100)	3/4 (75)	0	6/8 (75)

Responses assessed by RECIST 1.1
*5 patients not evaluable: first disease assessment not yet performed in 4 patients, 1 patient died from clinical progression before disease assessment
†Patient with resolved HCV infection

Presented By Anthony El-Khoueiry at 2015 ASCO Annual Meeting



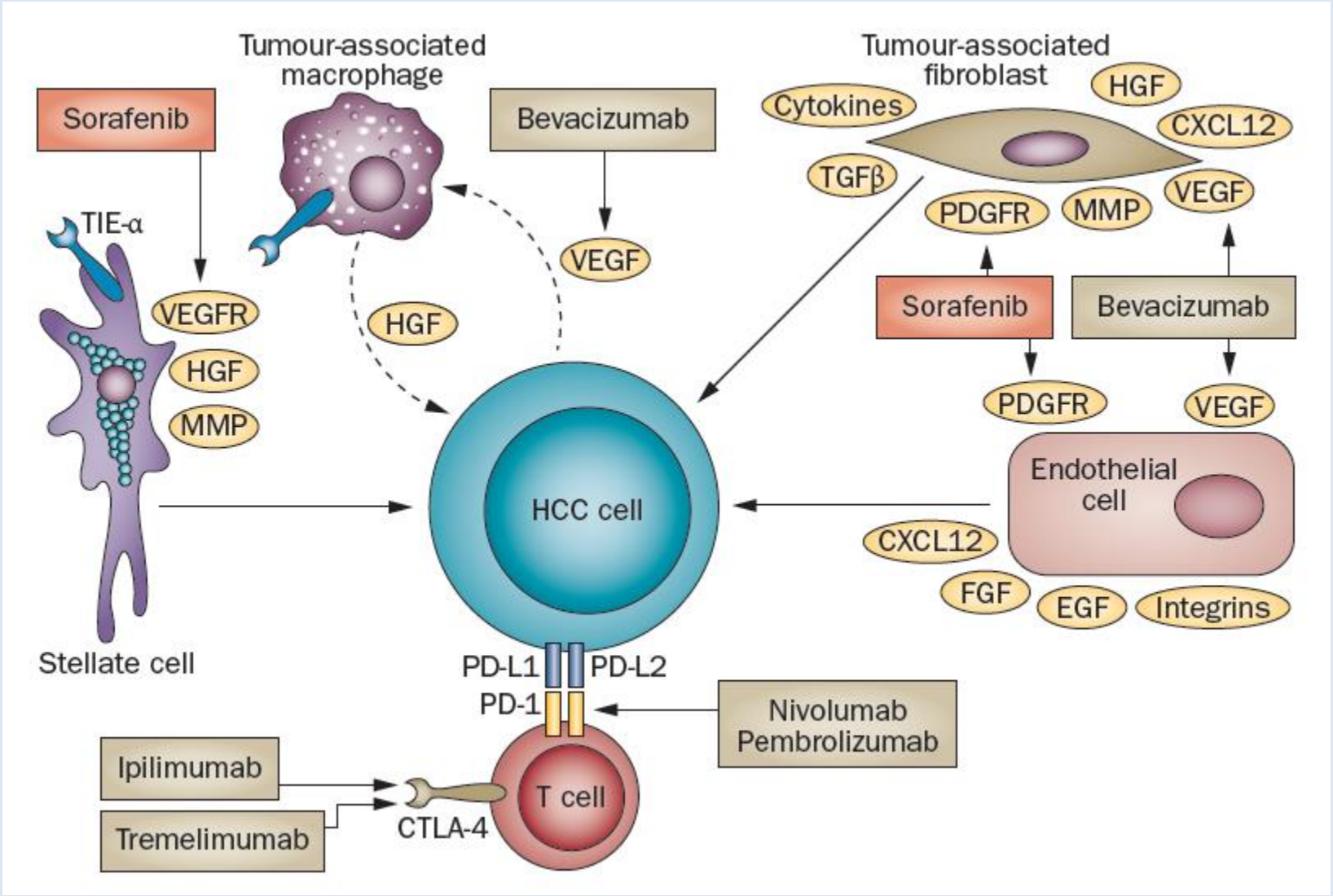
Baseline
(31 July 2015)



After 2 doses of nivolumab
(31 August 2015)

Combination of Immune Checkpoint Inhibitors and Targeted Therapy

Molecular Therapies Acting on Immune Checkpoints and The Microenvironment



Llovet, J. M. et al. Nat. Rev. Clin. Oncol. 2015;12:408–424

Sorafenib Relieves Cell-intrinsic and Cell-extrinsic Inhibitions of Effector T Cells in Tumor Microenvironment to Augment Antitumor Immunity

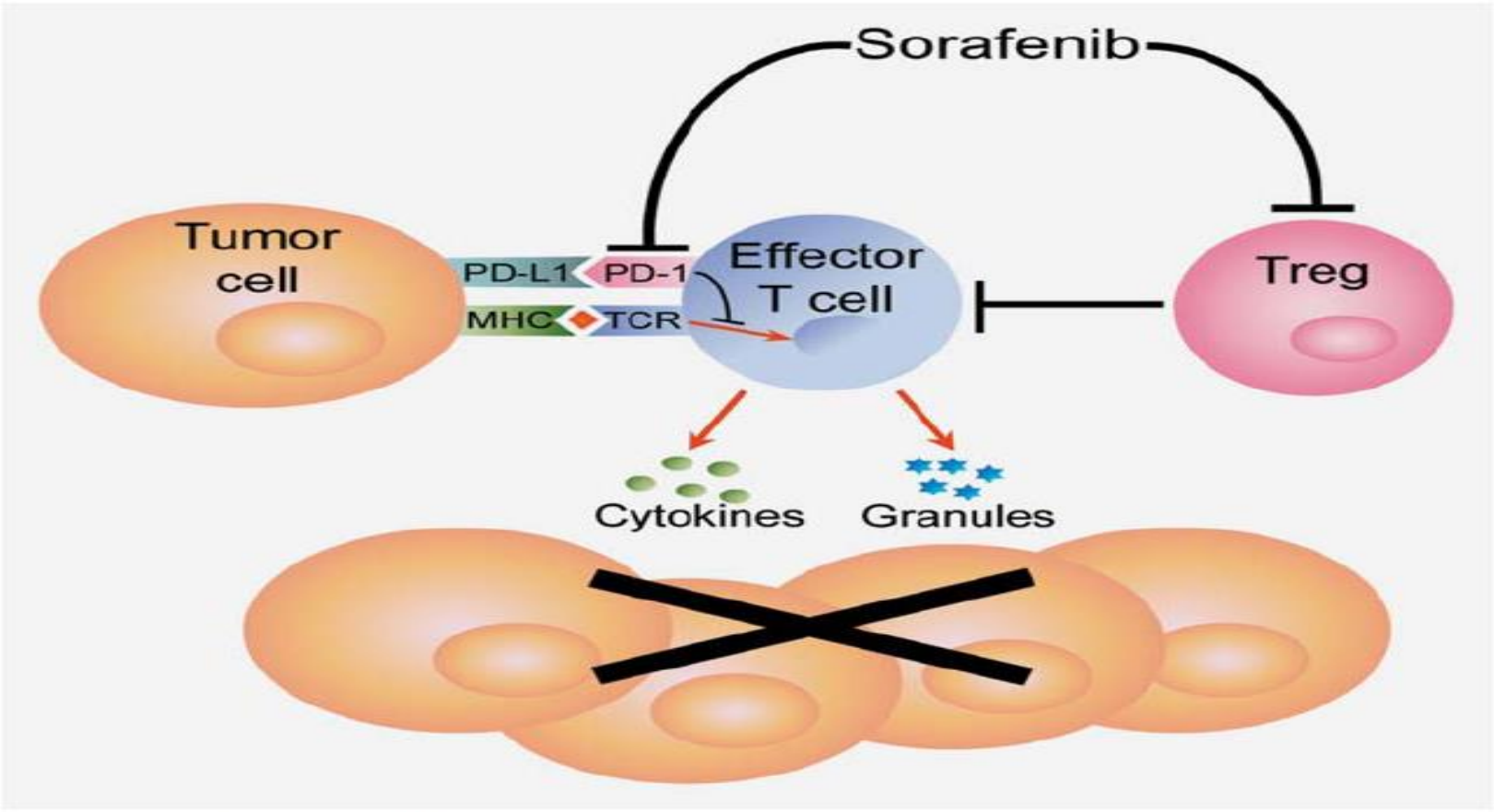
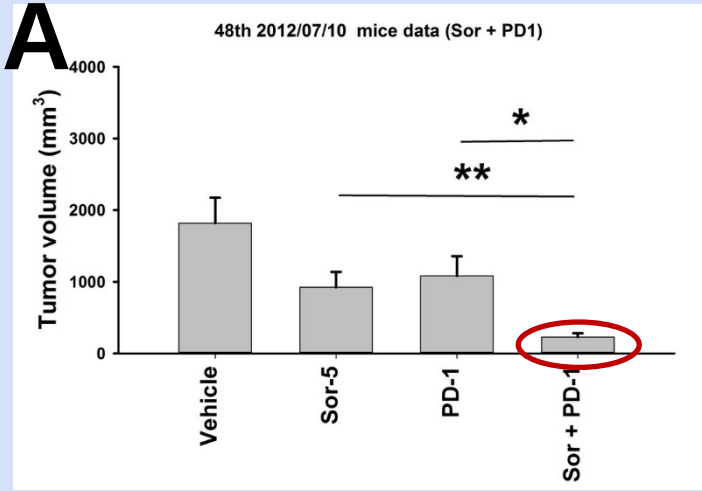


Figure 6. A model illustrating the mechanisms by which sorafenib augments antitumor immunity through relieving PD-1- and Treg-mediated inhibitions in tumor microenvironment.

Chen ML et al. Int. J. Cancer 2014;134:319-331

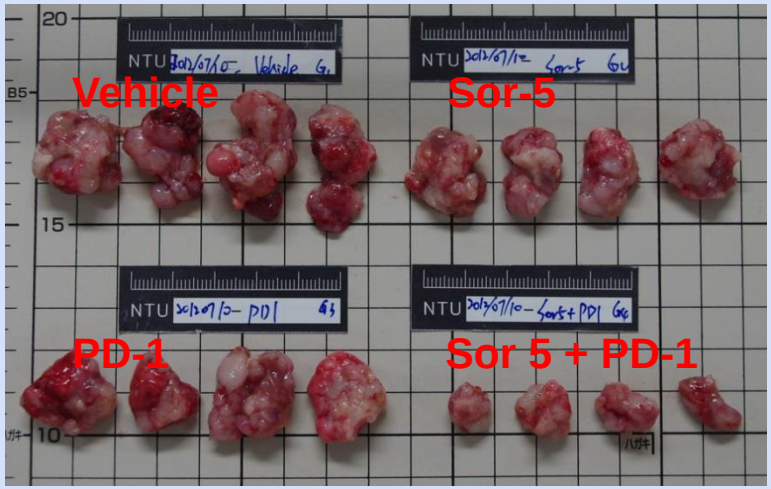
Potential Anti-tumor Synergy Between Sorafenib and Anti-PD-1 (Hsu C et al, 2015)

A



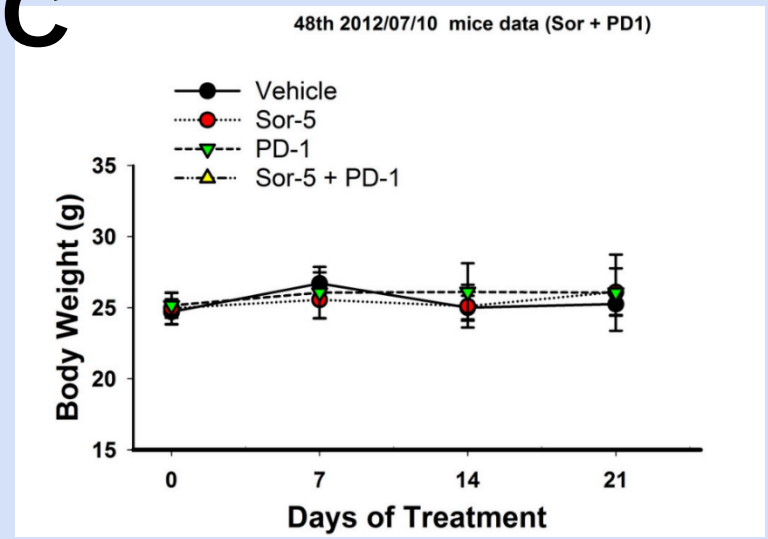
P < 0.05, ** P < 0.01
Treatment time: 22 days

B

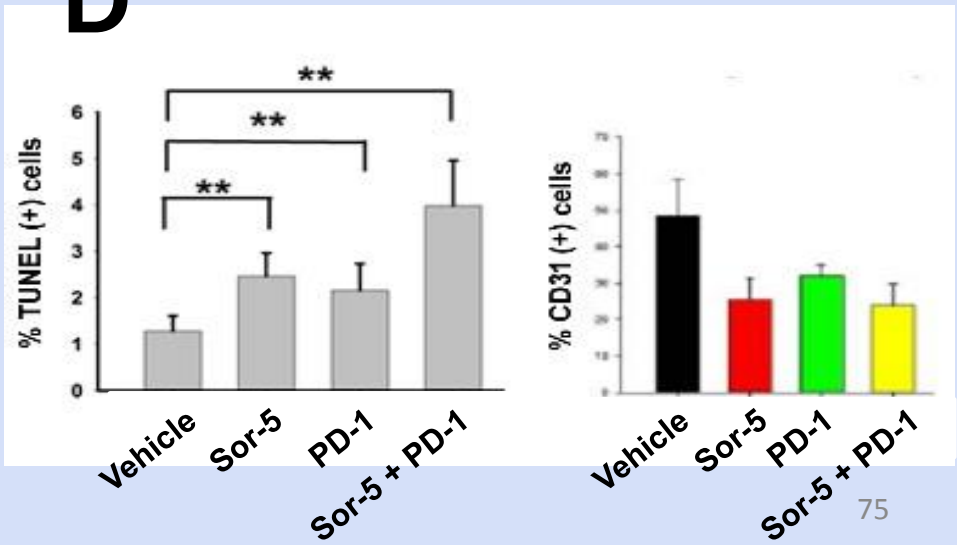


- anti-PD1: 200 μg/ i.p. × 5 doses (days 5, 7, 9, 14, 21)

C

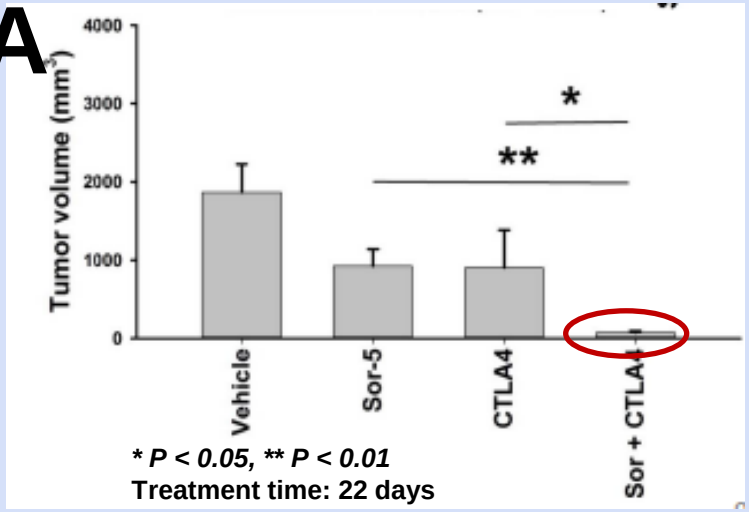


D

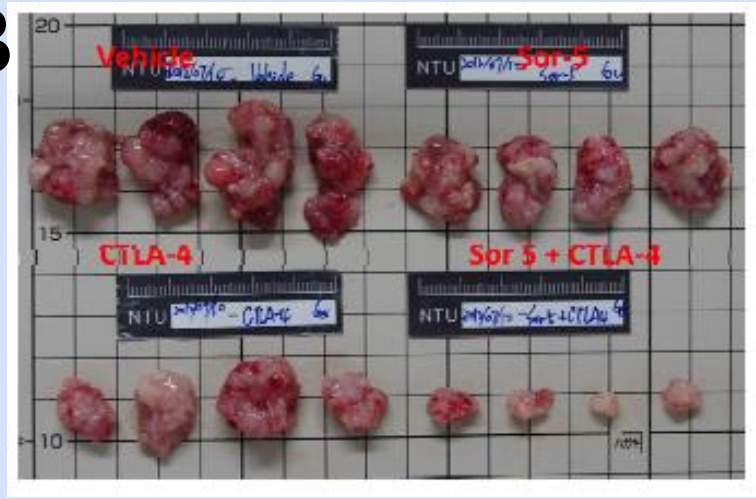


Potential Anti-tumor Synergy Between Sorafenib and Anti-CTLA4

A

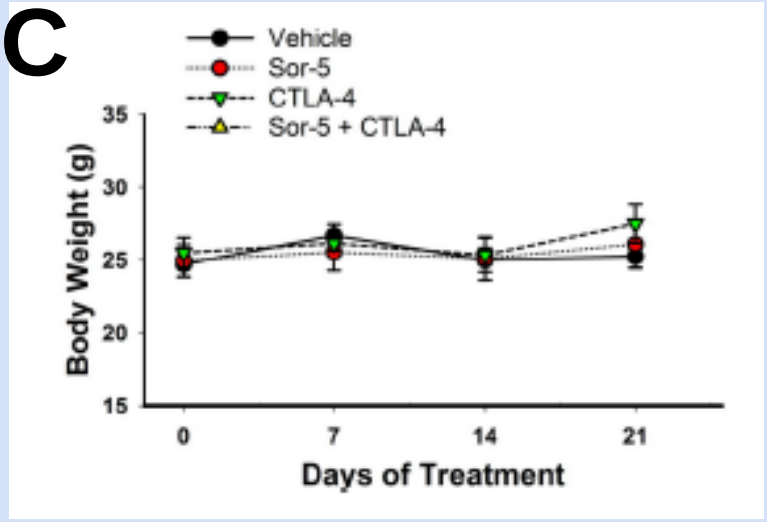


B

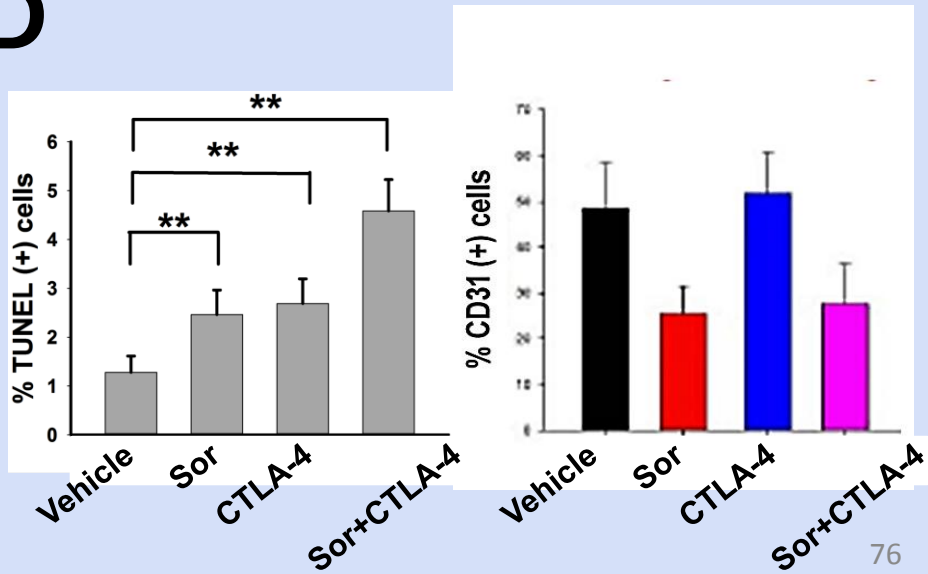


➢ anti-CTLA4: 100 μg/ i.p. × 5 doses (days 5, 7, 9, 14, 21)

C



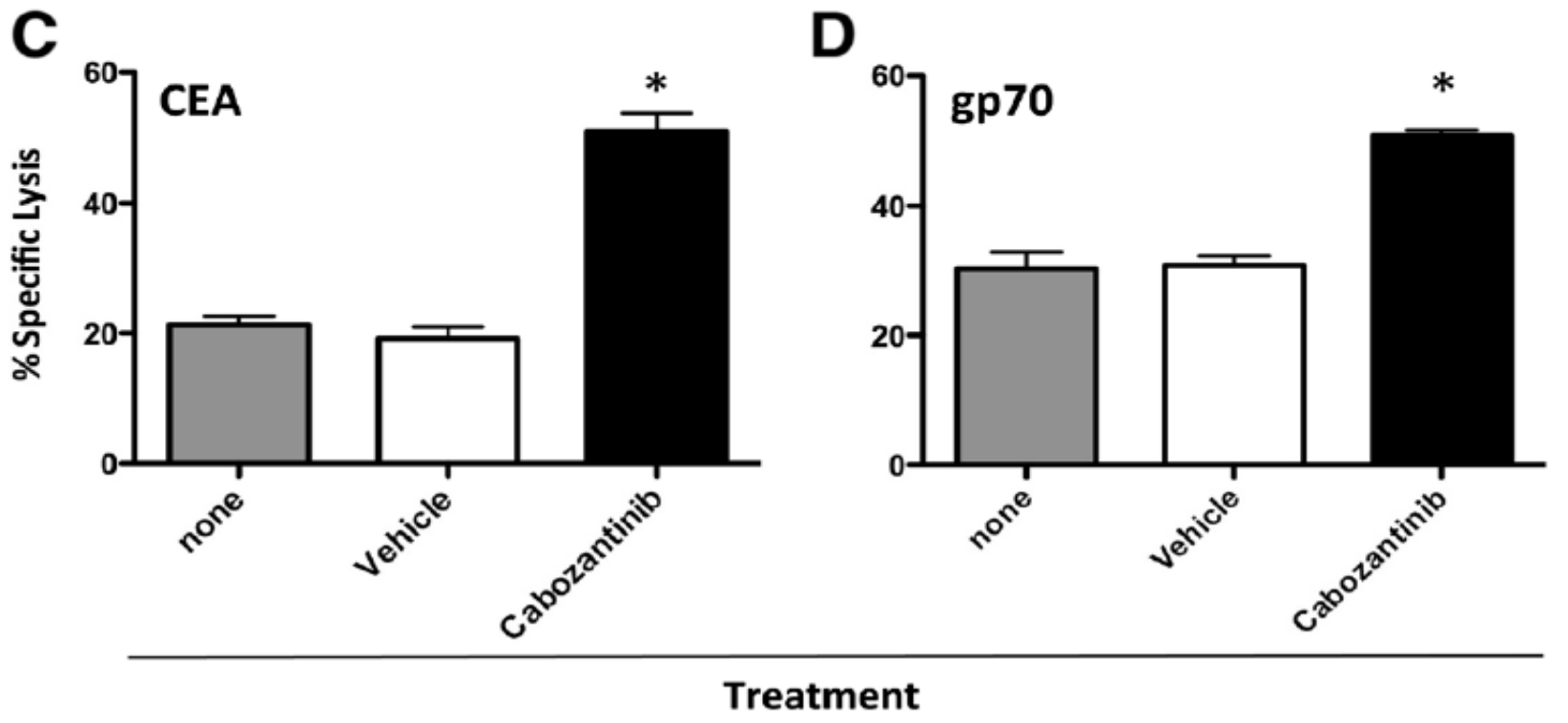
D



Cabozantinib Alters The Phenotype And Increases The Sensitivity of MC38-CEA Cells to T cell-mediated killing

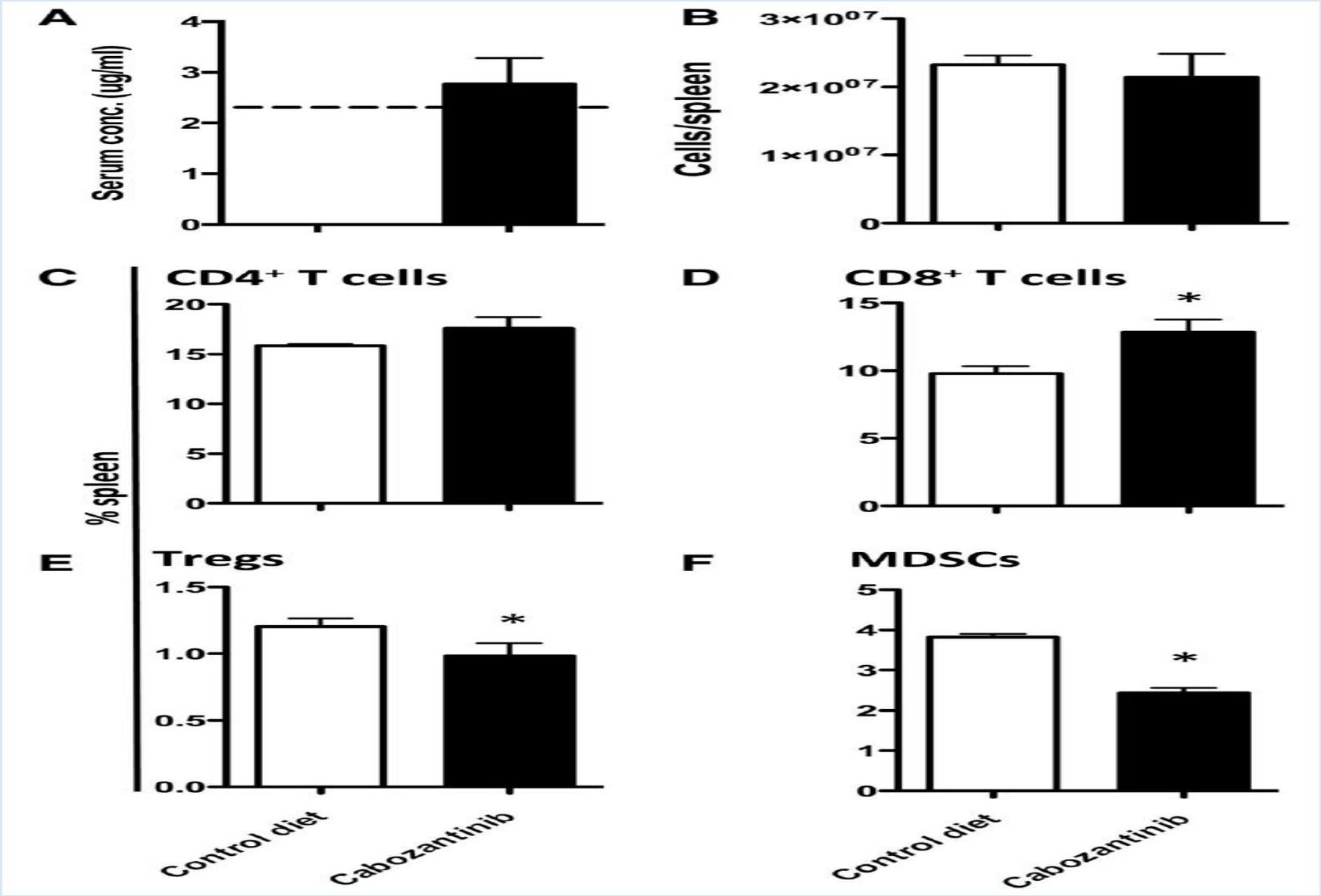
Phenotypic changes in MC38-CEA cells after cabozantinib treatment

	CEA	H-2Kb	H-2Db	ICAM-1	Fas	Calreticulin
Vehicle	68.1 (6665)	91.7 (4458)	19.2 (254)	0.7 (301)	6.1 (578)	4.2 (141)
Cabozantinib	69.1 (7070)	95.0 (**8139**)	**40.5** (302)	**14.6** (239)	**36.0** (565)	**20.3** (168)



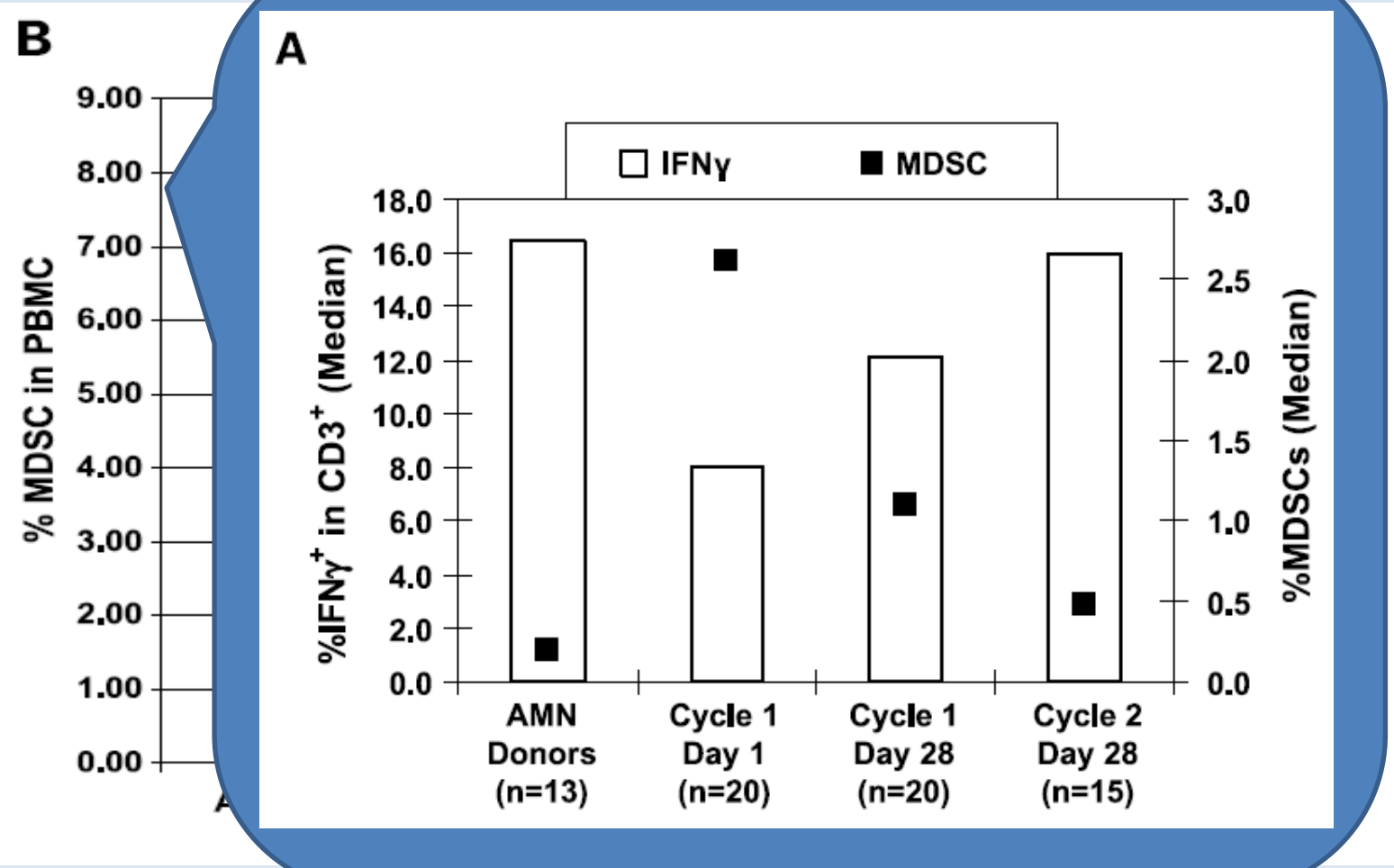
Kwilas et al. J Transl Med 2014;12:294

Cabozantinib Alters The Immune-cell Repertoire of C57BL/6 Mice



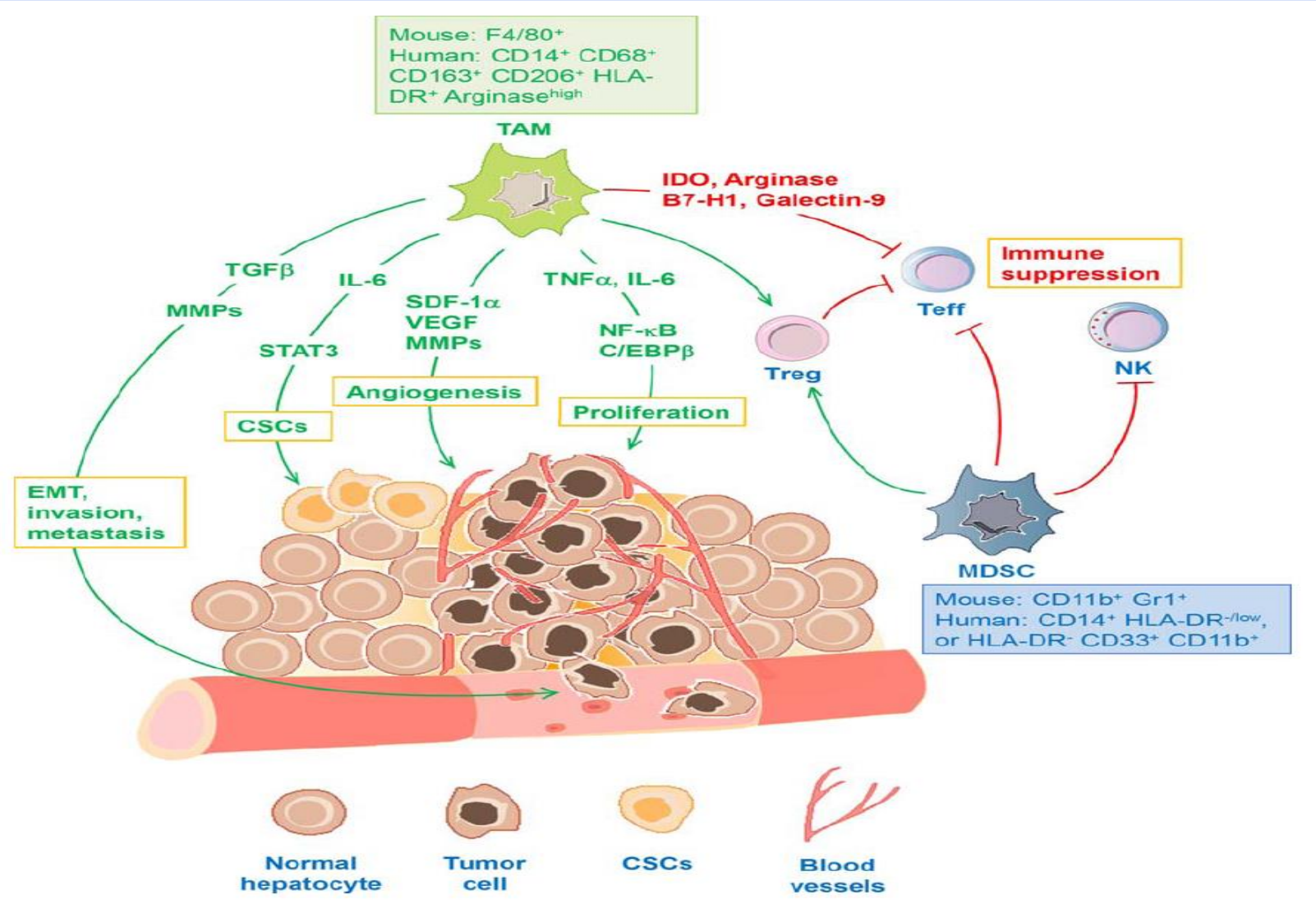
Kwilas et al. J of Transl Med 2014;12:294

Sunitinib Mediates Reversal of MDSC Accumulation in Renal Cell Carcinoma



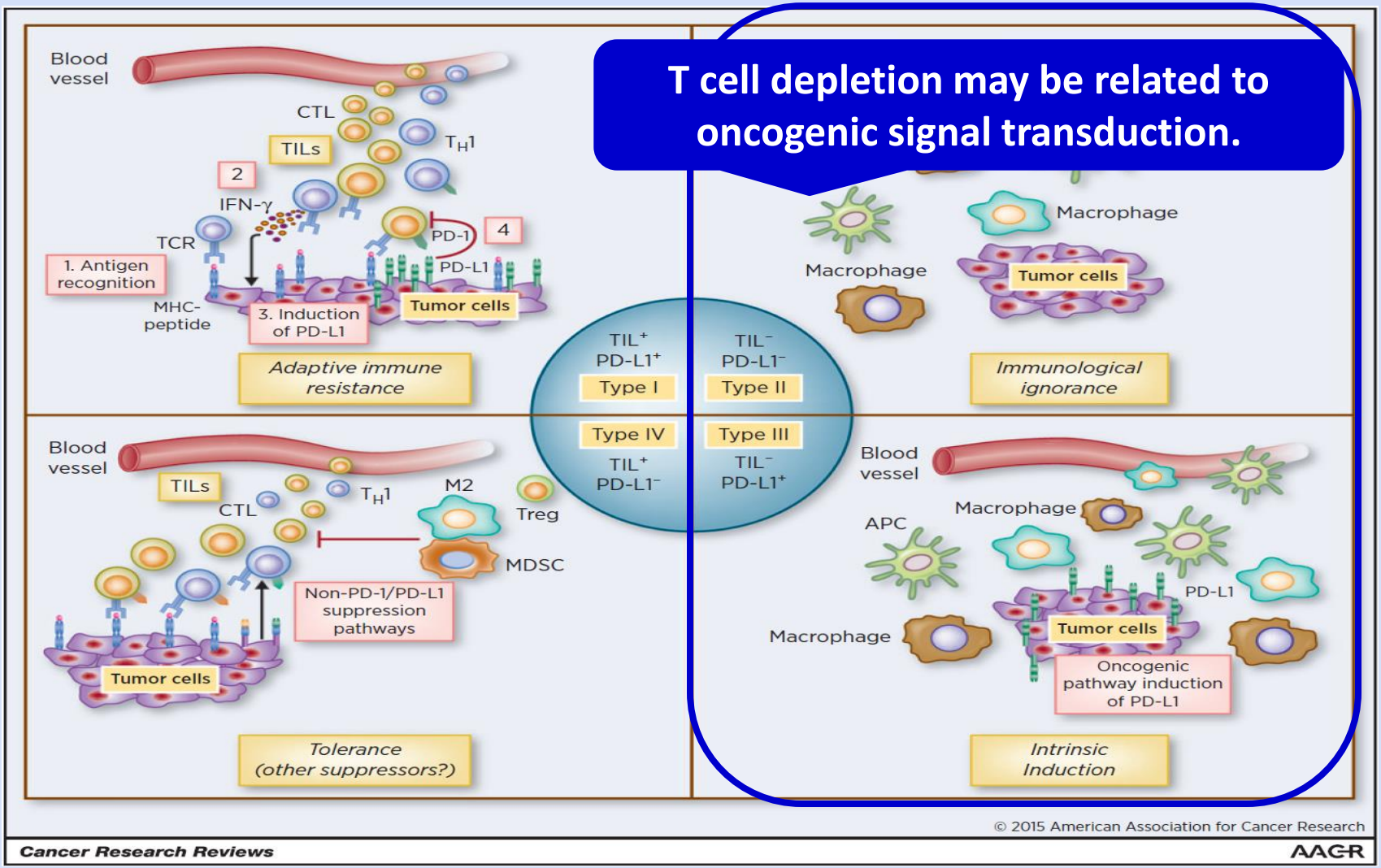
Ko JS et al. Clin Cancer Res 2009;15(6):2148-2157

Immunosuppressive and Tumor-Promoting Functions of TAMs and MDSCs in HCC



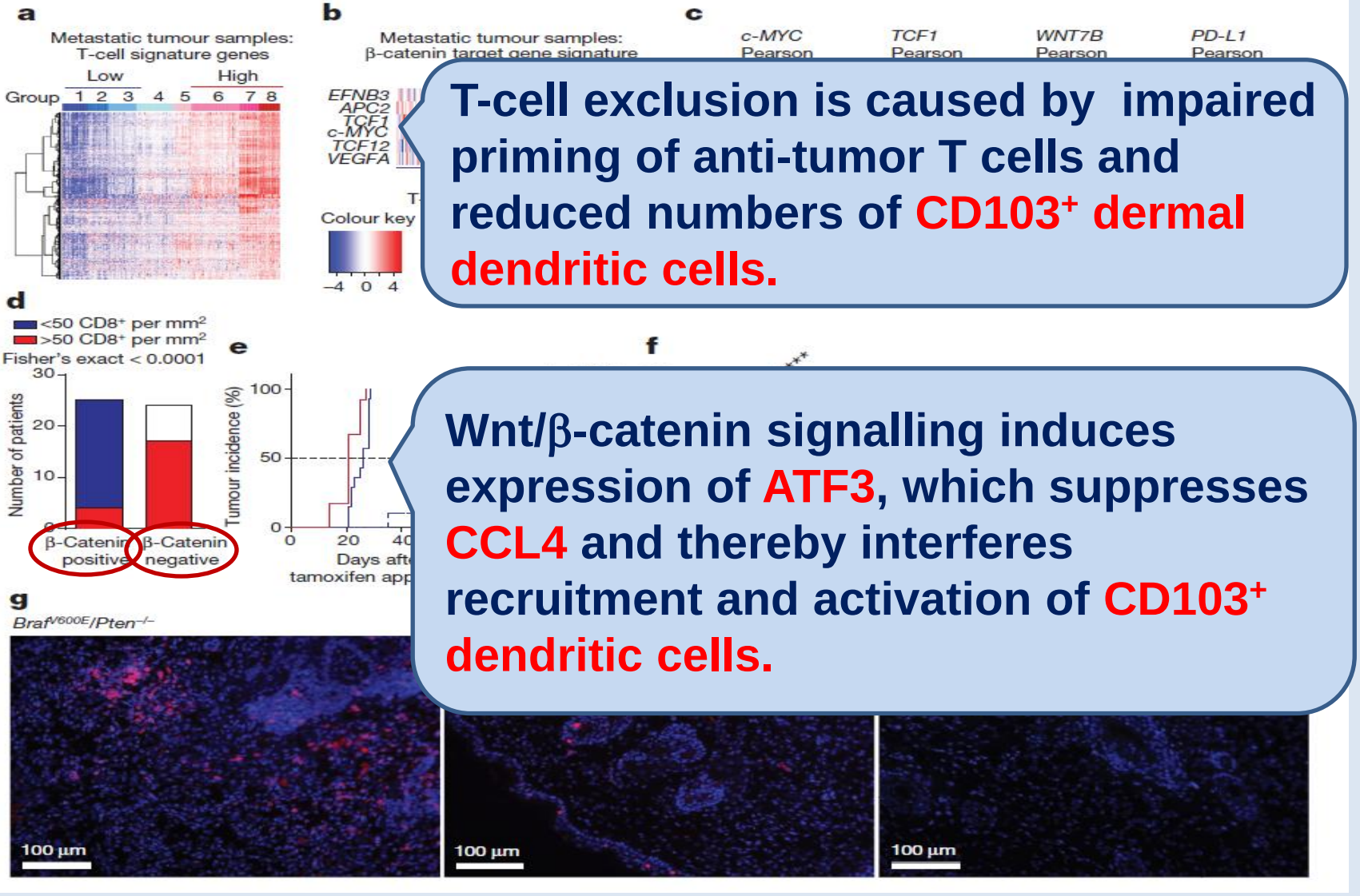
Wan S, et al. Hepatology 2015; ePub

Classifying Cancers Based on T-cell Infiltration and PD-L1



Teng MW, et al. Cancer Res. 2015;75(11):2139-2145.

Melanoma-intrinsic β-catenin Pathway Activation Correlates with T-cell Exclusion



T-cell exclusion is caused by impaired priming of anti-tumor T cells and reduced numbers of CD103⁺ dermal dendritic cells.

Wnt/β-catenin signalling induces expression of ATF3, which suppresses CCL4 and thereby interferes recruitment and activation of CD103⁺ dendritic cells.

Spranger S. et al Nature 2015;523:231-235

Small-molecules Targeting Wnt Signaling

IWP (Inhibitors of Wnt production)

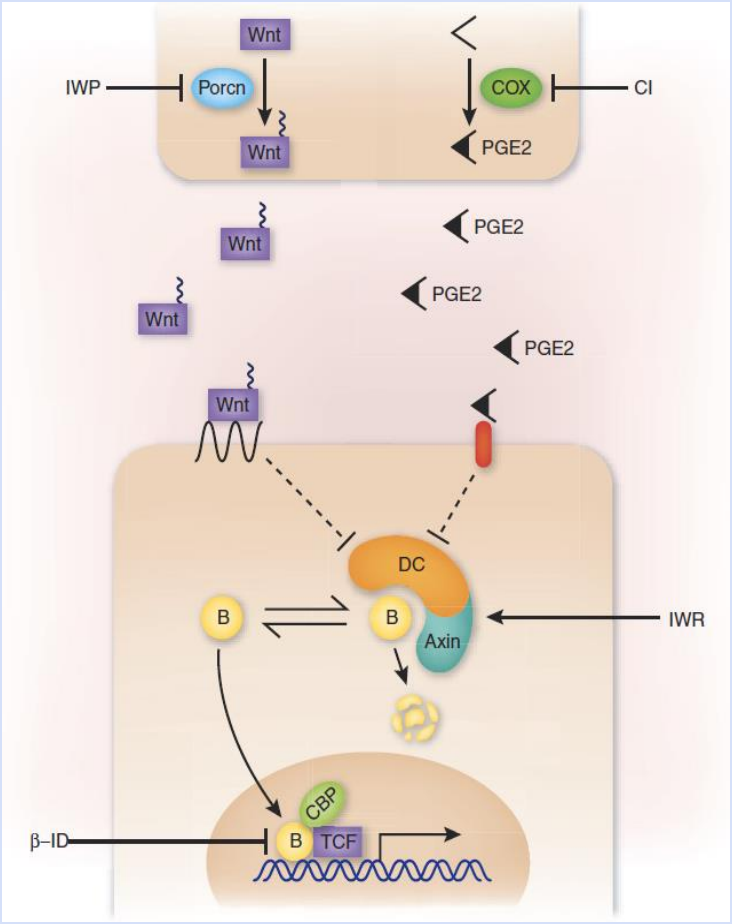
- LGK974

IWR (Inhibitors of Wnt response)

- XAV939
- Other Tankyrase inhibitors

β-ID (β-catenin interaction disruptors)

- ICG-001
- PRI-724



~ Yeh JY & Peterson RT: Nature Chem Biol 2009;5:74 (News) &
~ Chen B et al: Nature Chem Biol 2009;5:100-.

Phase I/II Study of Nivolumab for Advanced Hepatocellular Carcinoma

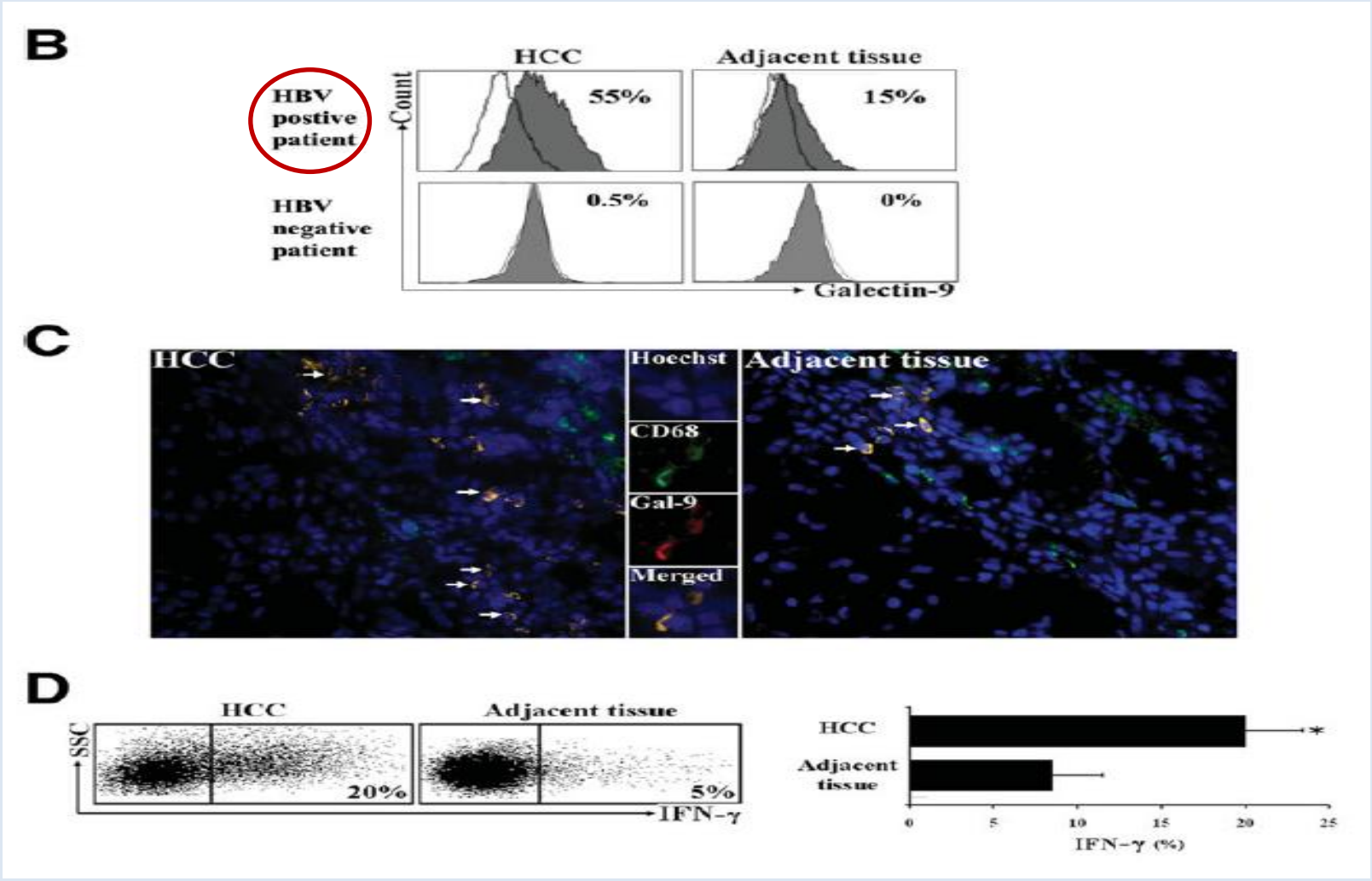
Investigator-Assessed Best Overall Response

	Uninfected (n=21)	HCV (n=11)	HBV (n=10)	Total Evaluable* (n=42)
Objective response, n (%)	3 (14)	4 (36)	1 (10)	8 (19)
Complete response	2 (10)	0	0	2 (5)
Partial response	1 (5)	4 (36)	1 (10)	6 (14)
Stable disease	10 (48)	5 (45)†	5 (50)	20 (48)
Progressive disease	8 (38)	2 (18)	4 (40)	14 (33)
Ongoing response, n (%)	3/3 (100)	3/4 (75)	0	6/8 (75)

Responses assessed by RECIST 1.1
*5 patients not evaluable: first disease assessment not yet performed in 4 patients, 1 patient died from clinical progression before disease assessment
†Patient with resolved HCV infection

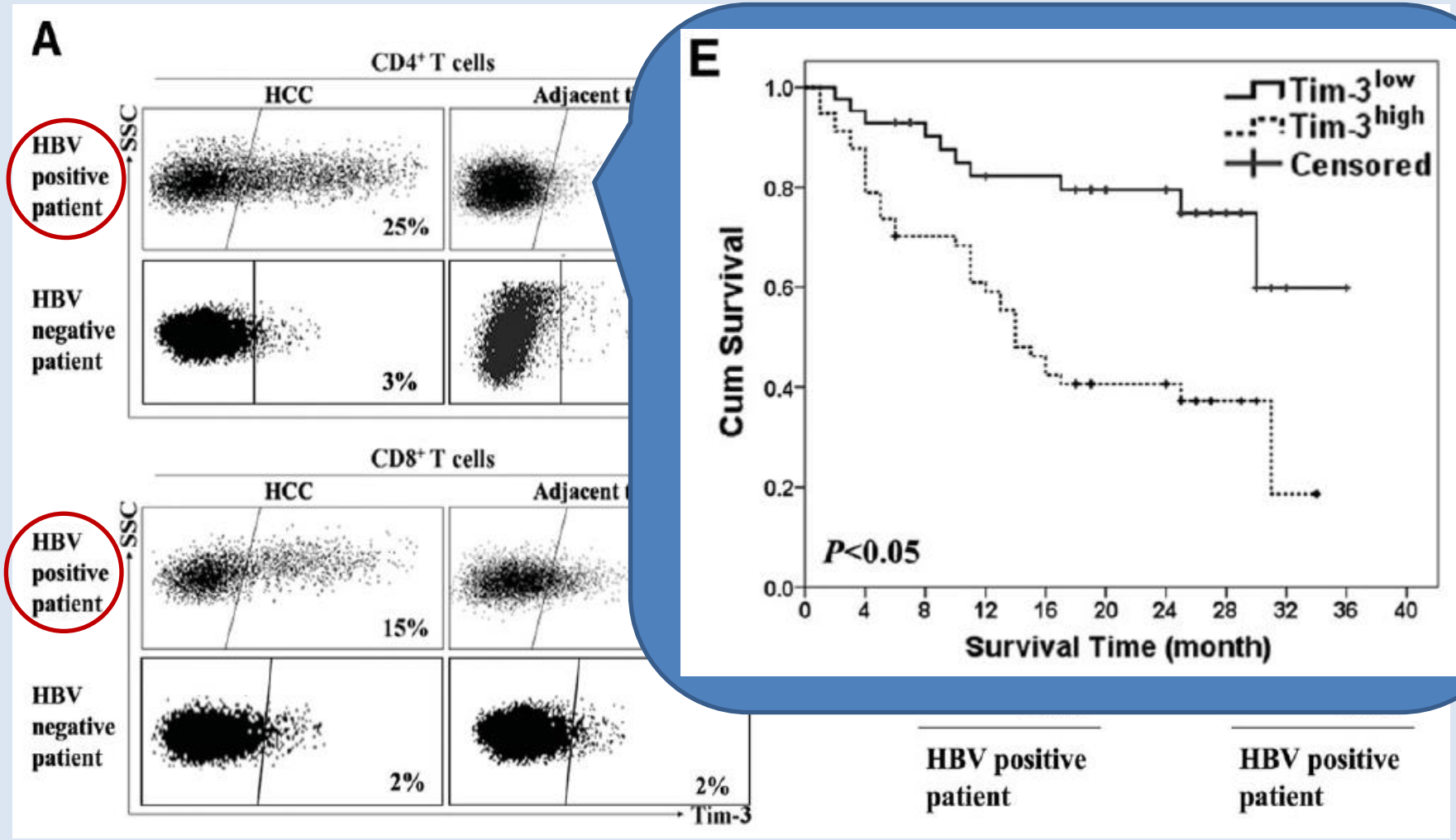
Presented By Anthony El-Khoueiry at 2015 ASCO Annual Meeting

Kupffer Cells of HBV-HCC Express High Level of Galectin-9



Li H et al. Hepatology 2012;56:1342-1351

HBV-HCC is Associated with Higher Expression of Tim-3 of Infiltrating T cells

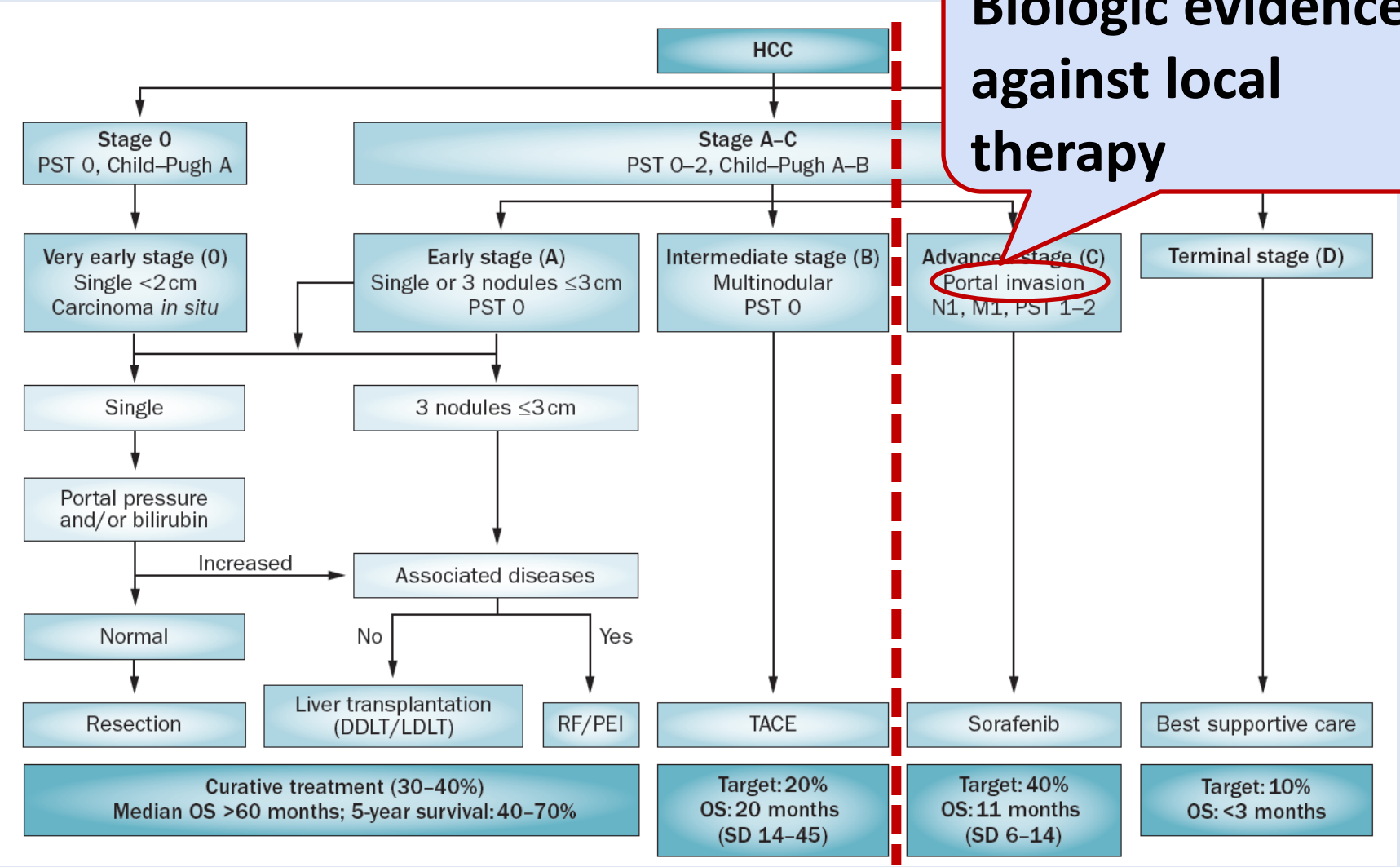


Li H et al. Hepatology 2012;56:1342-1351

Conclusions

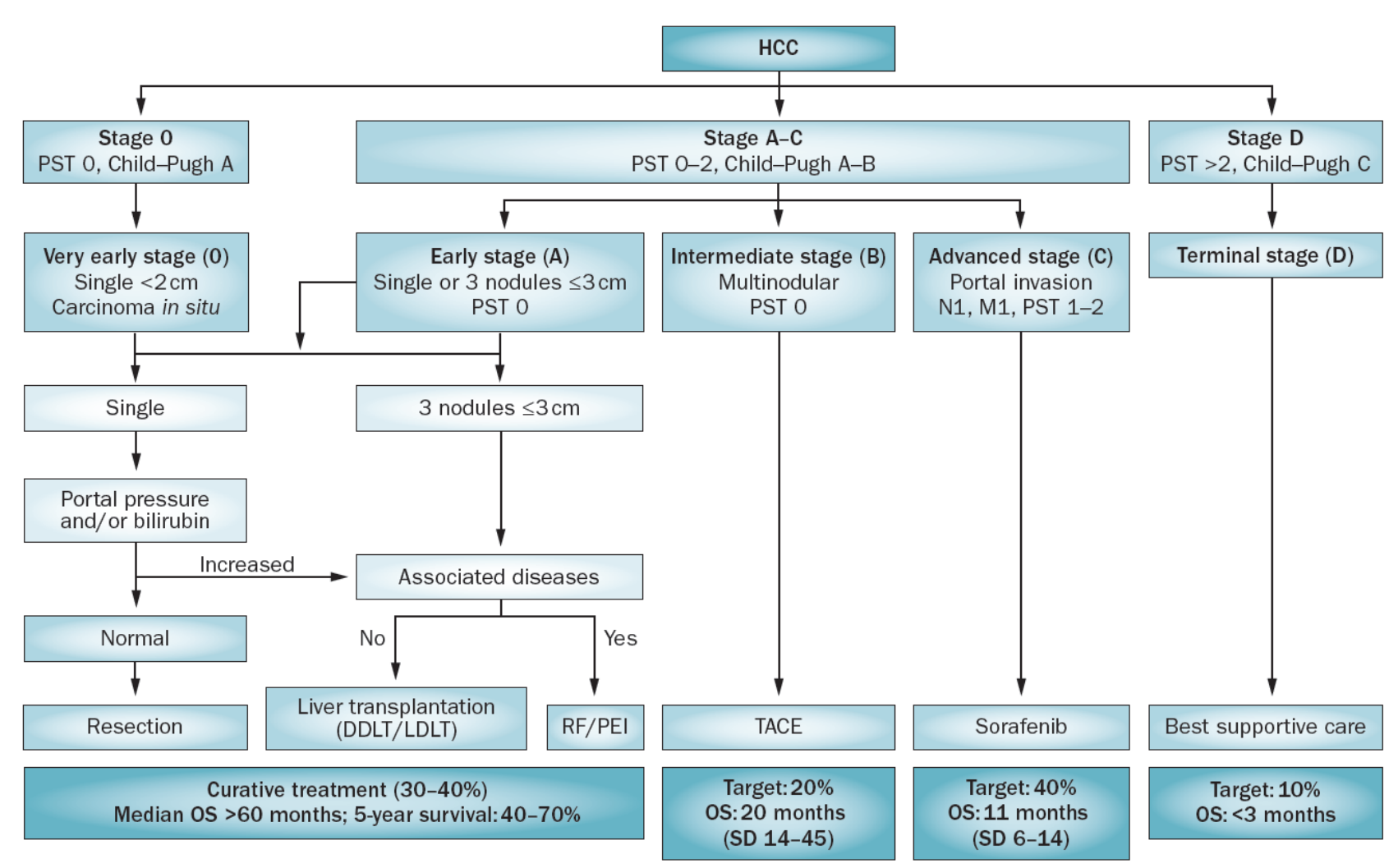
- Novel molecular target therapy beyond sorafenib , such as lenvatinib, regorafenib, cabozantinib, c-MET inhibitors, and FGFR4 inhibitors are being investigated.
- Immunotherapy holds promise, but needs to be refined by better patient enrichment.
- Combination of MTT and immunotx. is an important direction for research.
- Exploration of unique immunobiologic features of HCC is mandatory for personalized targeted and/or immunotherapy.

BCLC Staging System and Therapeutic Strategy According to EASL–EORTC Guidelines



J. Hepatol. 56, 908–943 (2012).

BCLC Staging System and Therapeutic Strategy According to EASL–EORTC Guidelines



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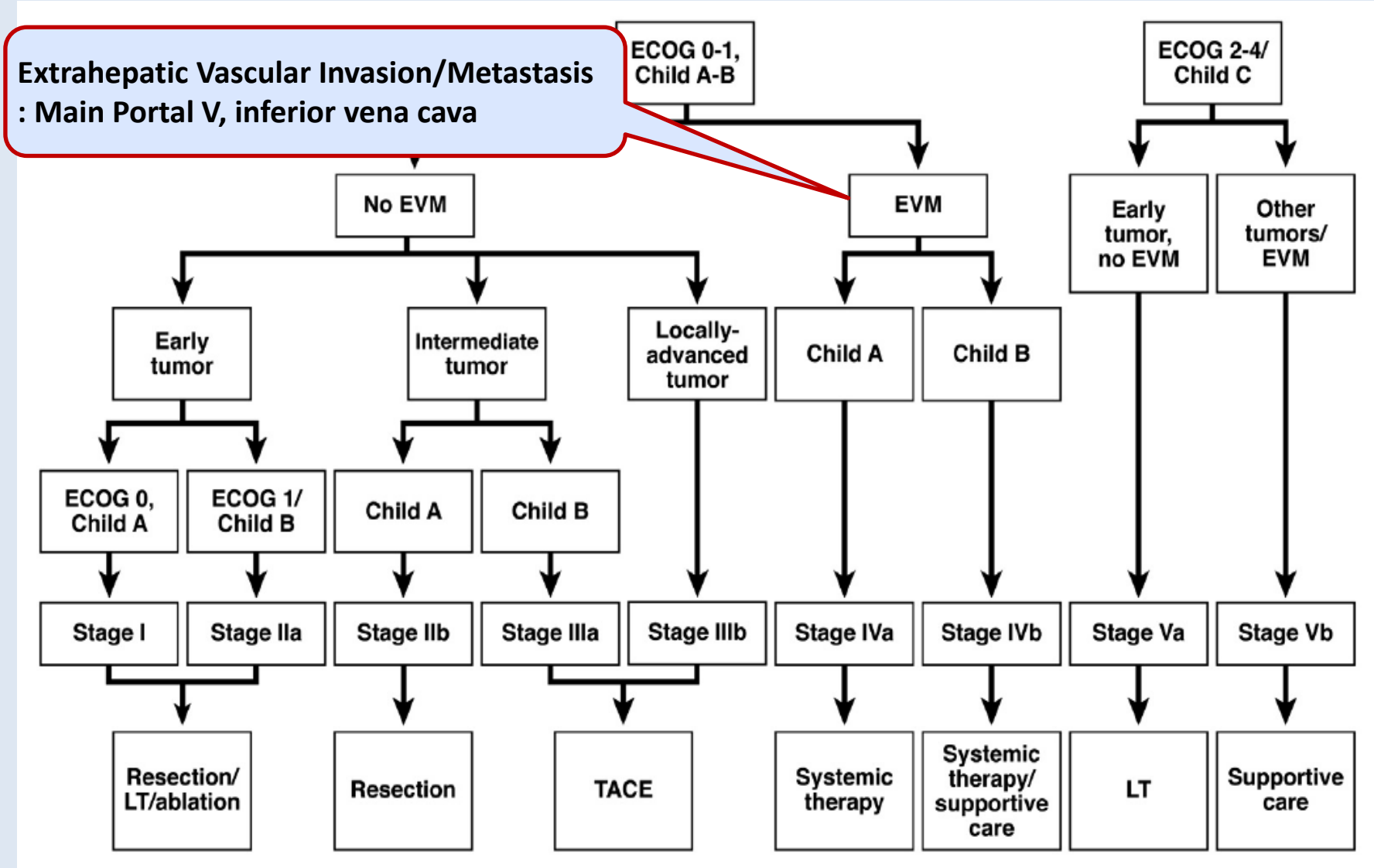
Hong Kong Liver Cancer Staging System

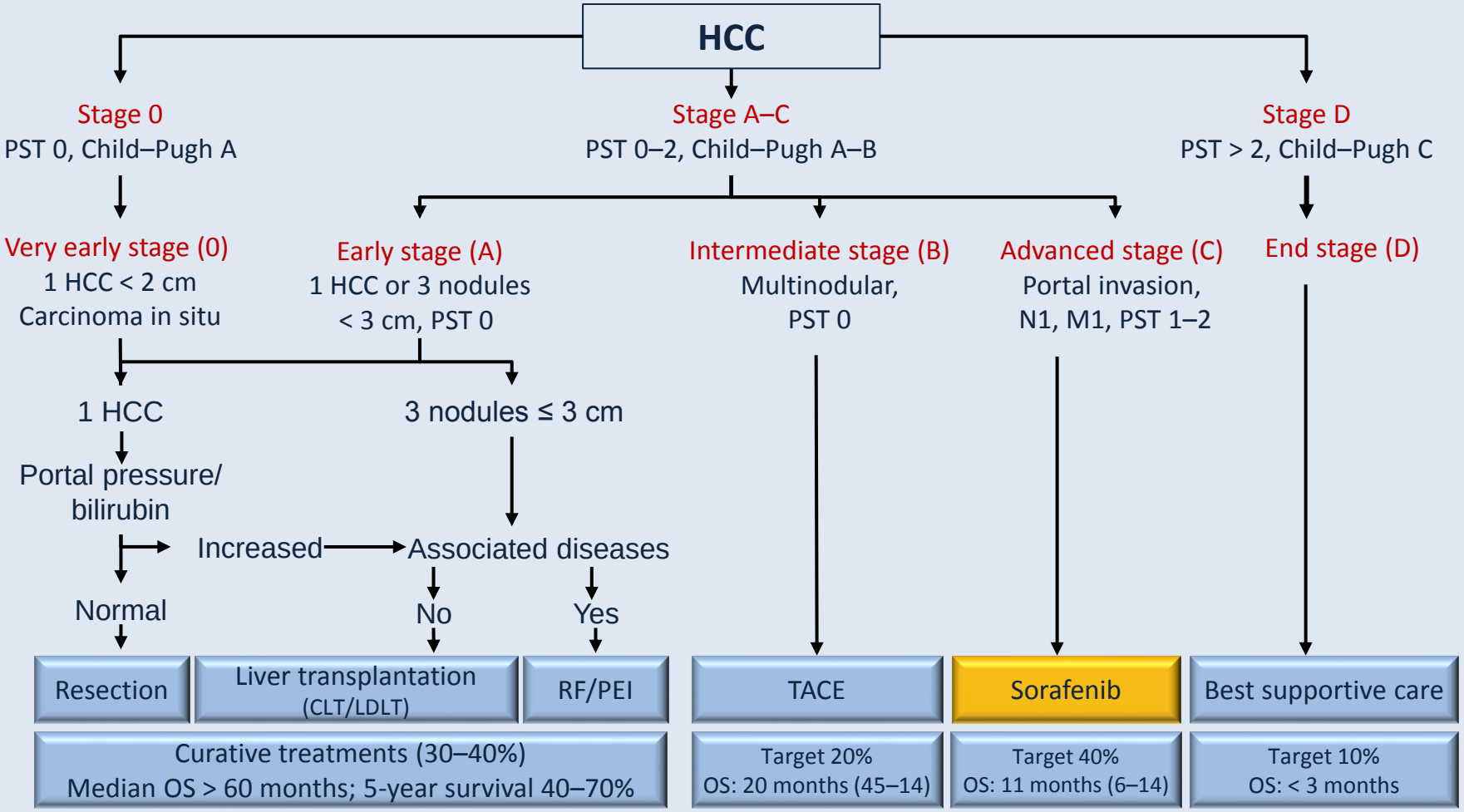


Yau T et al. Gastroenterology 2014;146:1691–1700

Notable ongoings:

Lenvatinib – phase III, 1st-line (vs sorafenib)
Tivantinib – phase III, 2nd-line (c-met enriched)
Cabozantinib – phase III, 2nd-line
Regorafenib – phase III, 2nd-line

EASL-EORTC guidelines (updated 2012)



CLT, cadaveric liver transplantation; EASL, European Association for the Study of the Liver;
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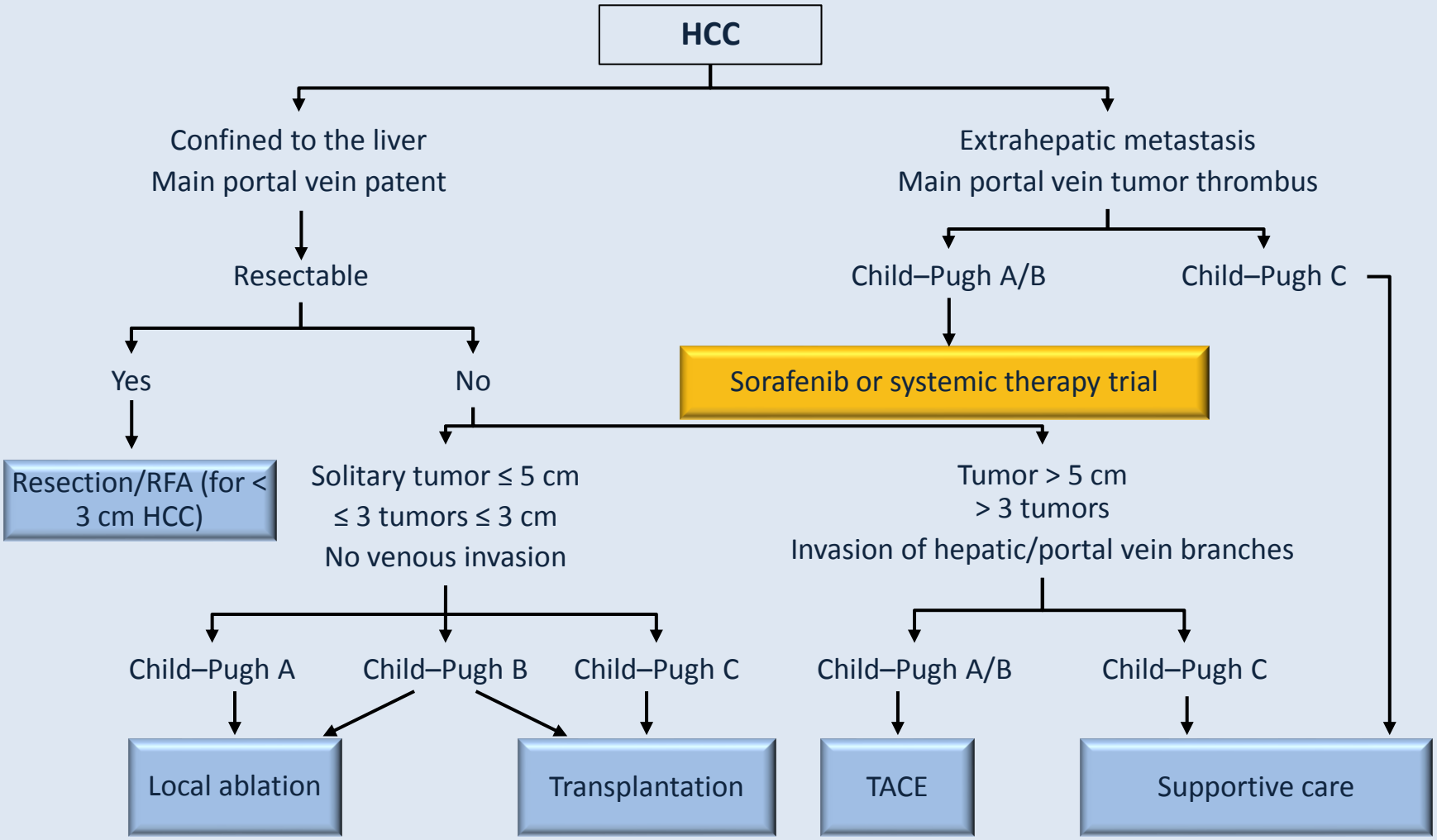
LDLT, living donor liver transplantation

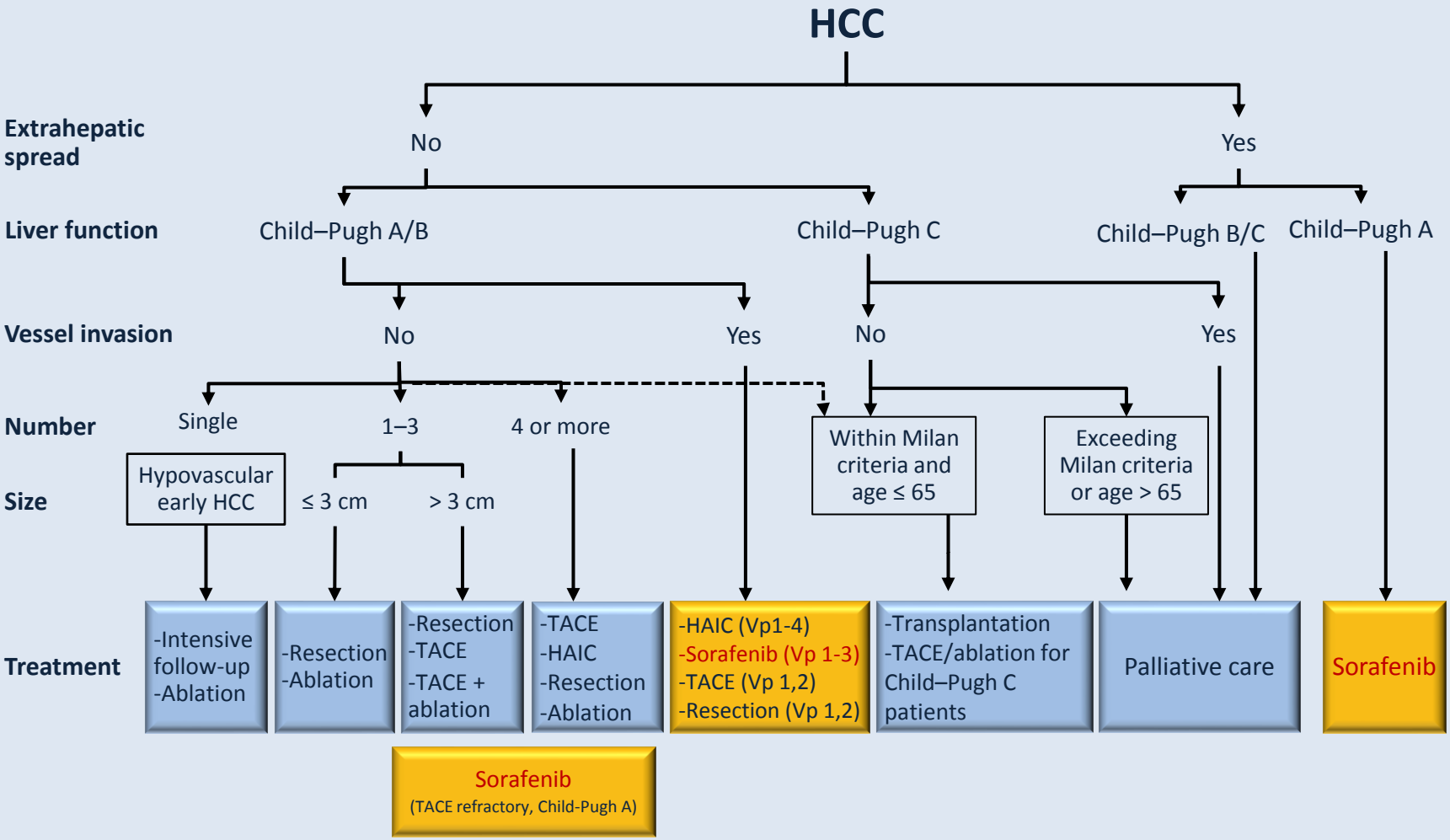
EASL–EORTC. J Hepatol. 2012;56:908–43.

APASL guidelines



APASL recommendations on HCC. Omata M, et al. Hepatol Int. 2010;4:439–74.

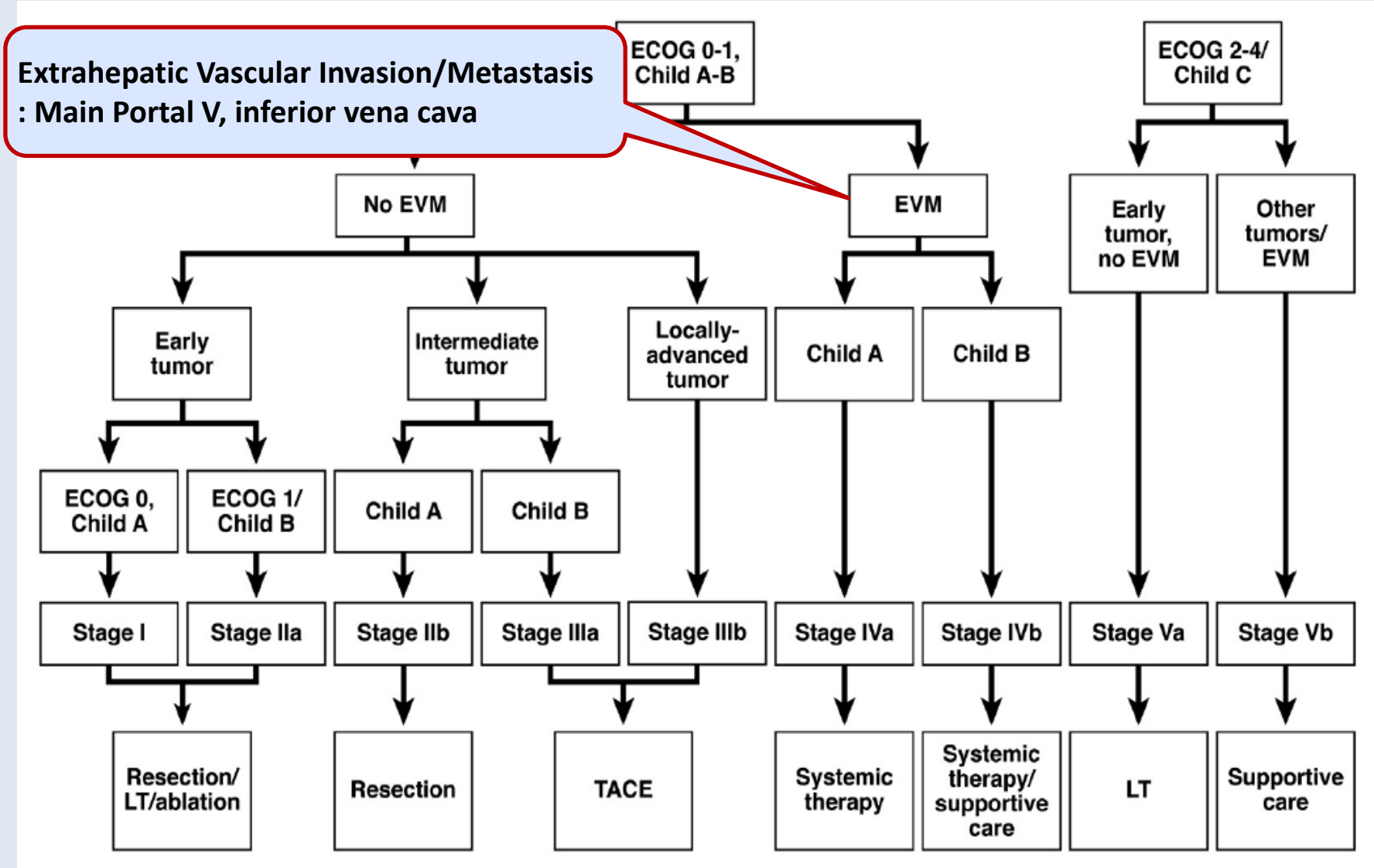
Japan Society of Hepatology: consensus-based treatment algorithm



HAIC = hepatic arterial infusion chemotherapy.

Kudo M, et al. Liver Cancer 2014;3:458–468

Hong Kong Liver Cancer Staging System



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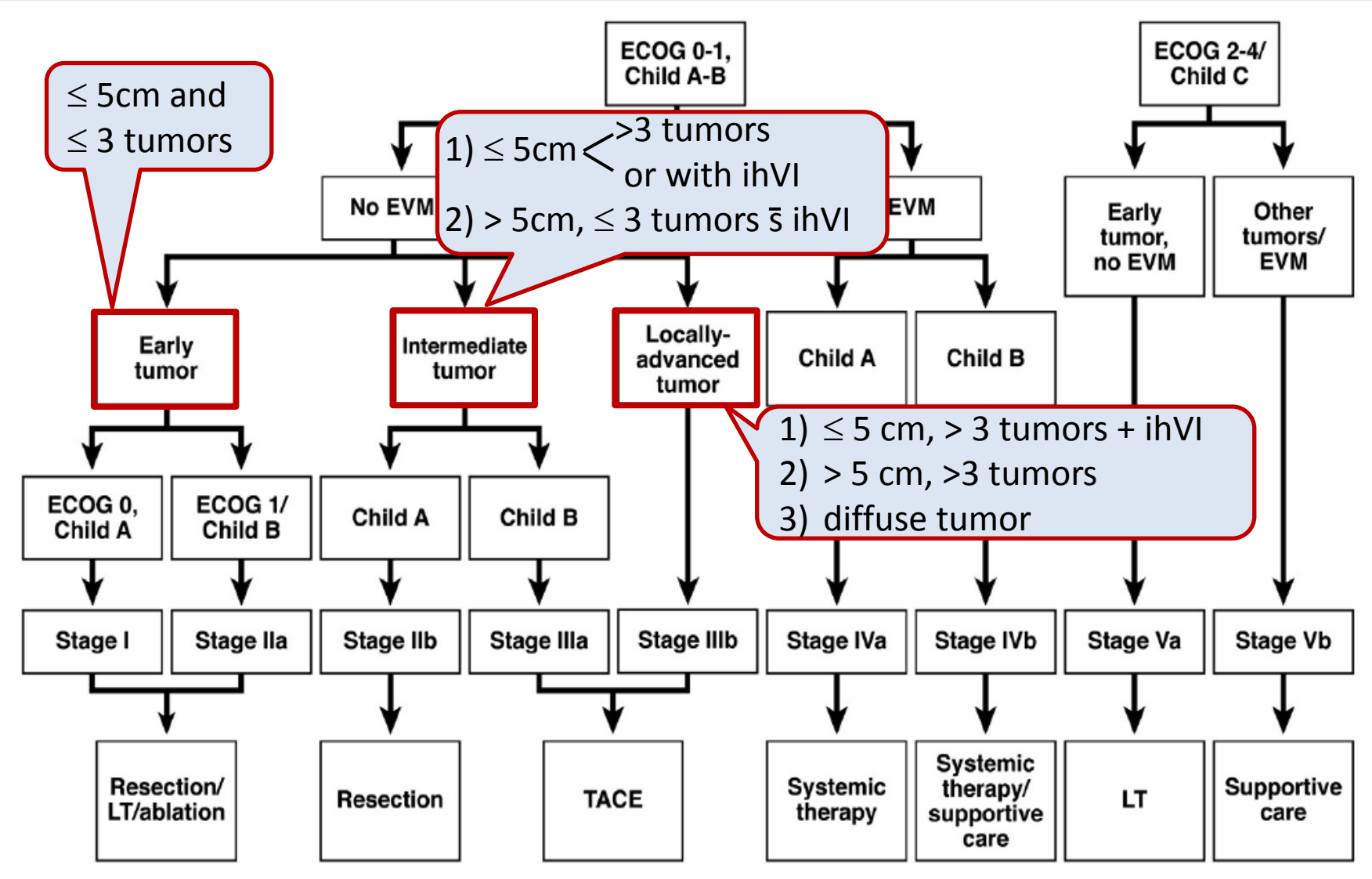
Hong Kong Liver Cancer Staging System



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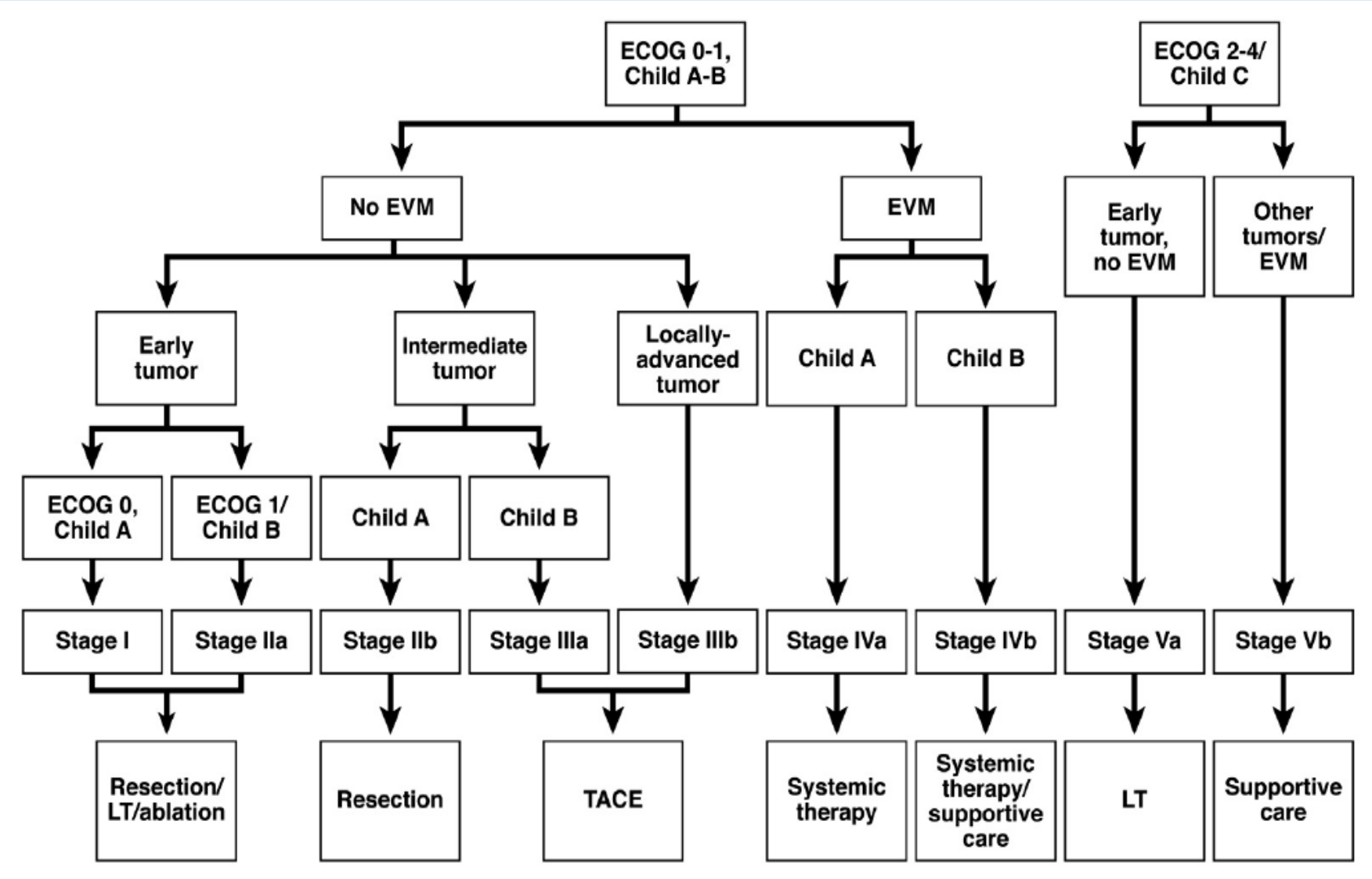

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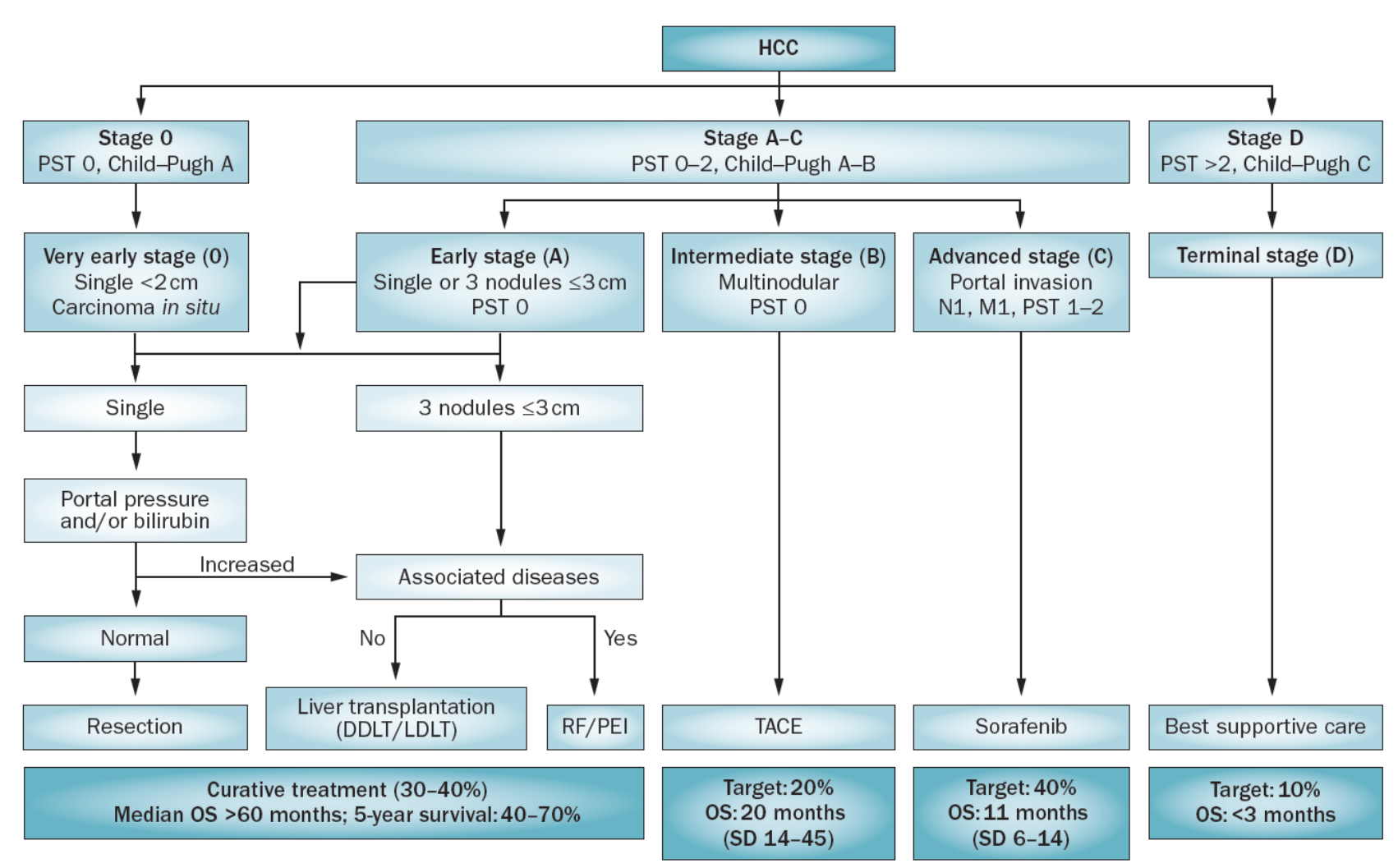
BCLC Staging System and Therapeutic Strategy According to EASL–EORTC Guidelines



J. Hepatol. 56, 908–943 (2012).

TACE Outcomes

Tumor remission

- WHO, RECIST, EASL, m-RECIST
- “Lipiodol retention”

Tumor progression

- TACE failure
- TACE refracotry
- TACE unsuitable
- TACE unrepeatable
- TACE contraindicated
- Untreatable progression
- ……

TACE Failure/Refi

Evaluated by Size? Lipiodol ? or Enhancement/necrosis?

1. **TACE ineffective in controlling TACEed tumors**
   - ≥ 2 , 3 in 6 months , or 4 in 6 months → **TACE Refractory**

2. **Hepatic recurrence after effective TACE** → **Non-TACEable hepatic recurrence**
   - Further TACE not possible (e.g. sustained as
     invasion, deteriorated liver function, bleedi
     problems such as AP/AV shunt, small arteries, poor tumor stain)
   - Further TACE possible (progression of TACEed tumors or emergence of new tumors)

3. **TACE not recommended due to systemic condition**
   - Distant metastases – significant vs
   - Deteriorated performance status
   - (α-FP)

} **TACE not recommended**

TTUP

Time to untreatable progre
nab
fit from TACE:
- Failure to [illegible] objective response after at least two TACE [illegible]ule
- Appearance of c
  - Vascular invasion
  - Extrahepatic spread
  - Sustained ascites
  - Sustained Child-Pugh B
  - Clinical progression to ECOG P
  - Platelet count < 60,000/μL

Minor branch invasion is not considered contraindication

No maximum number, Asian Drs tend to do more

Insignificant mets is not considered contraindication.

Subjective, may overlap with post-TACE syndrome

Can be managed by transfusion

mRECIST for HCC

A target lesion should meet all the following criteria:

- The lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI.

It is important to point out that only well-delineated, arterially enhancing lesions can be selected as target lesions for mRECIST.

Lencioni R et al. Semin Liver Dis 2010; 30(1): 052-060

Which Response Criteria Best Help Predict Survival of Patients with HCC Following Chemoembolization?

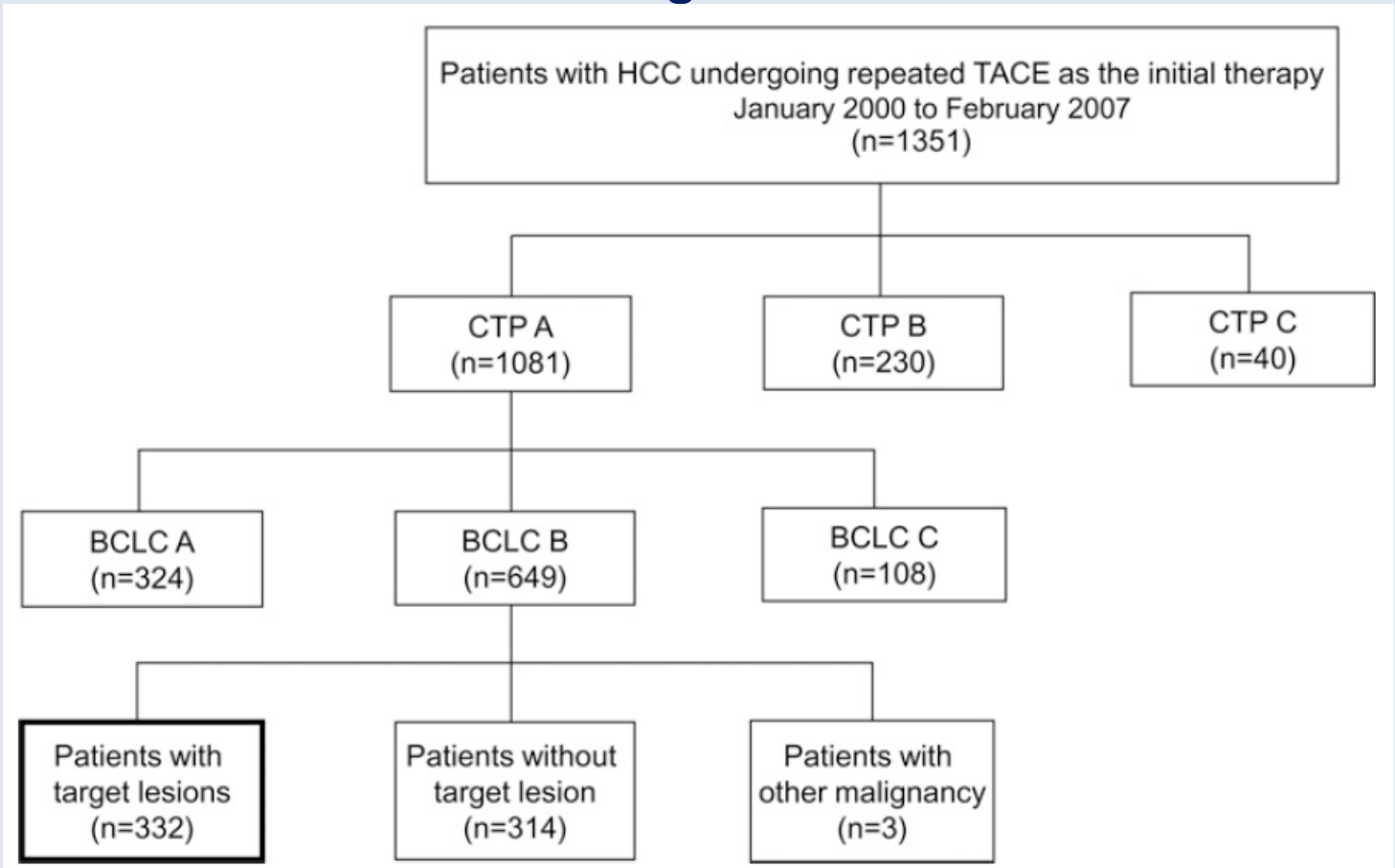
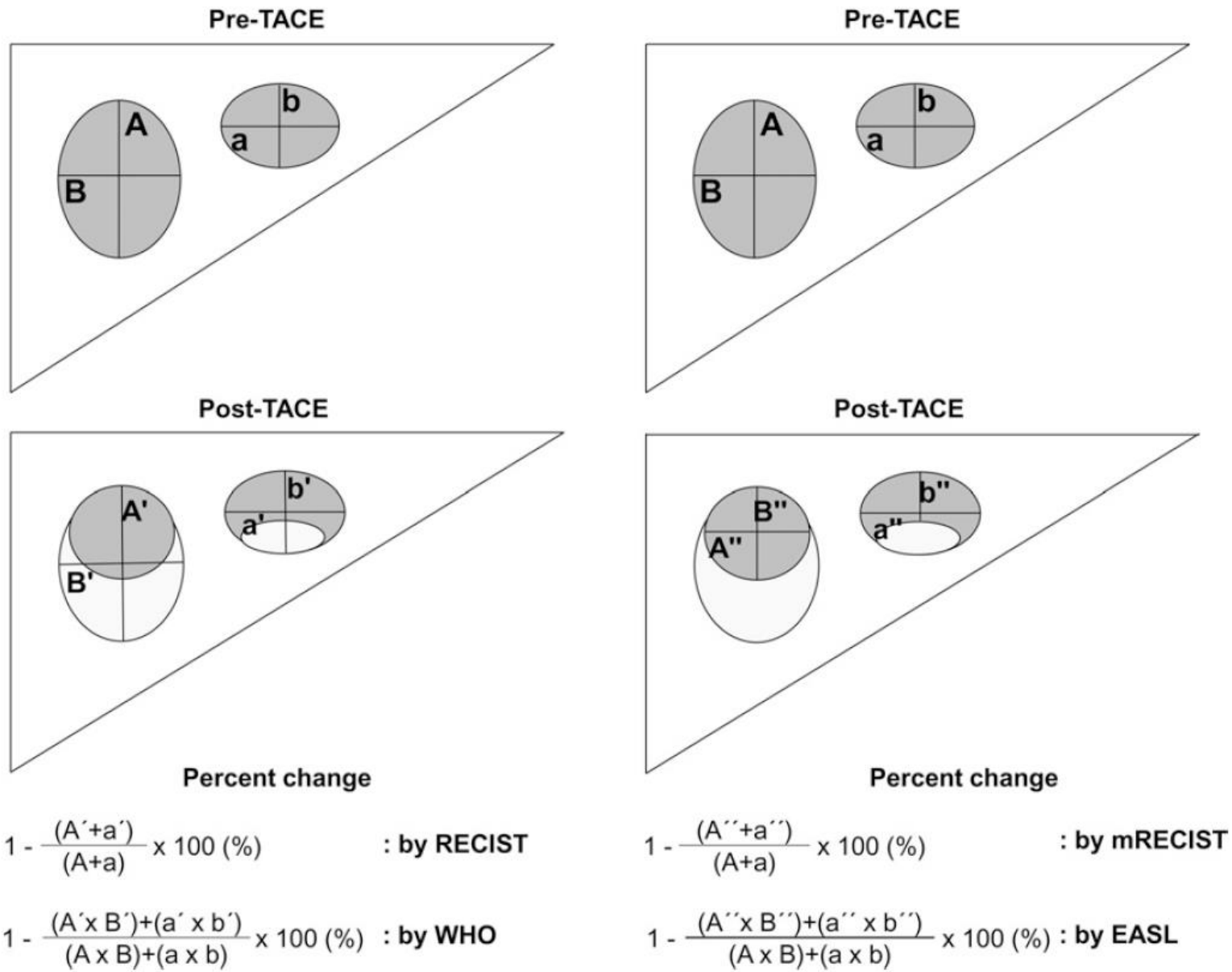


Figure 1: Flowchart of the patient selection process. *CTP A* = Child-Turcotte-Pugh class A, *CTP B* = Child-Turcotte-Pugh class B, *CTP C* = Child-Turcotte-Pugh class C, TACE = transarterial chemoembolization.

Shim JH et al. Radiology 2010;262(2):708-718.

Figure 3



Shim JH, et al. *Radiology* 2012; 262: 708

Definition of TACE Failure/Refractoriness (LCSGJ)

(1) Intrahepatic lesion

i. Two or more consecutive ineffective responses seen within the treated tumors (viable lesion >50%), even after changing the chemotherapeutic agents and/or reanalysis of feeding artery, on response evaluation CT/MRI after 1–3 months following adequately performed selective TACE

ii. Two or more consecutive progressions in the liver (including an increase in the number of tumors compared to that before the previous TACE procedure), even after changing the chemotherapeutic agents and/or reanalysis of feeding artery, on response evaluation CT/MRI after 1–3 months following adequately performed selective TACE

(2) Tumor marker

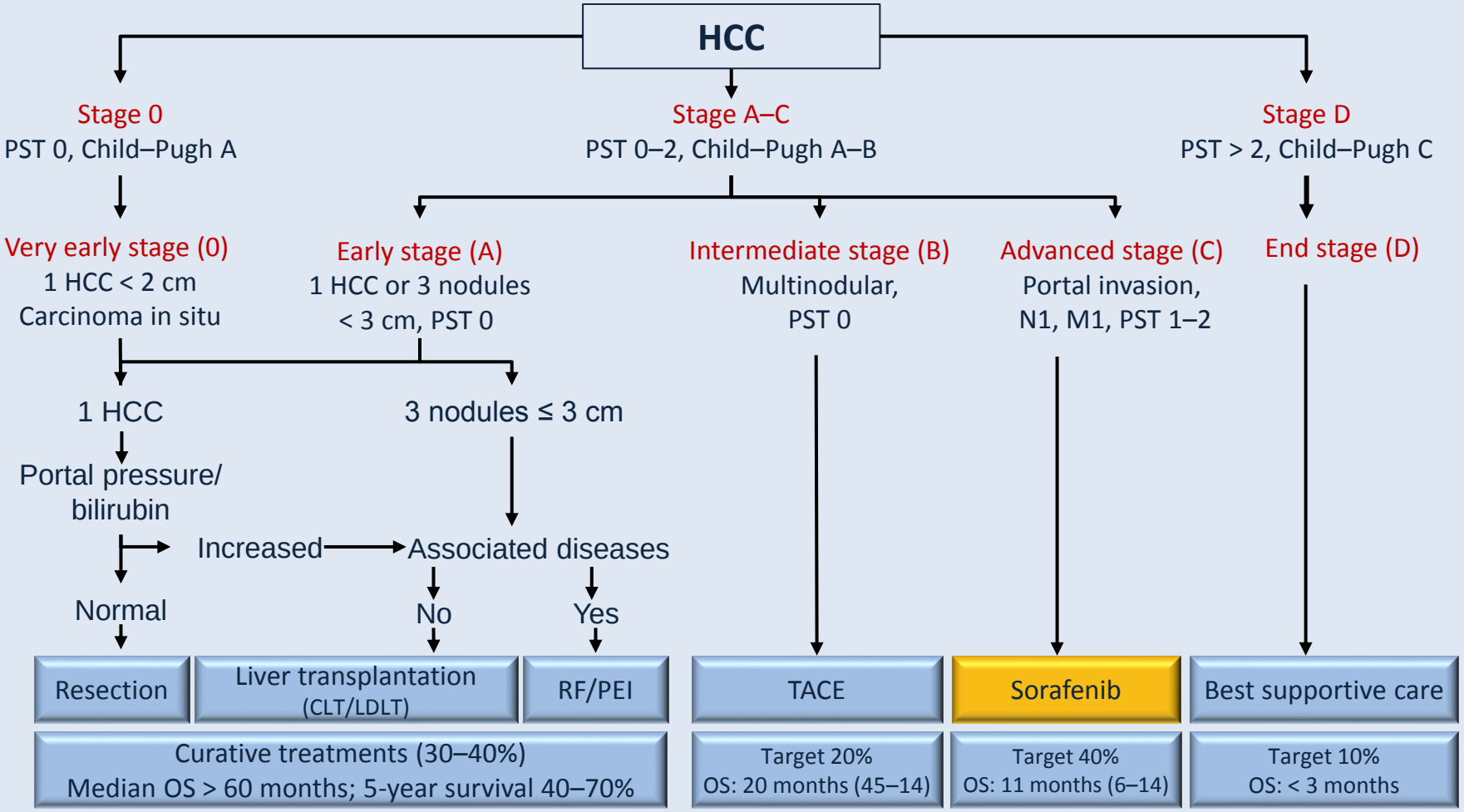
Continuous elevation of tumor markers right after TACE even though transient minor reduction is observed.

(3) Appearance of vascular invasion

(4) Appearance of extrahepatic spread

Kudo M et al. Liver Cancer 2014;3:458–468

EASL-EORTC guidelines (updated 2012)



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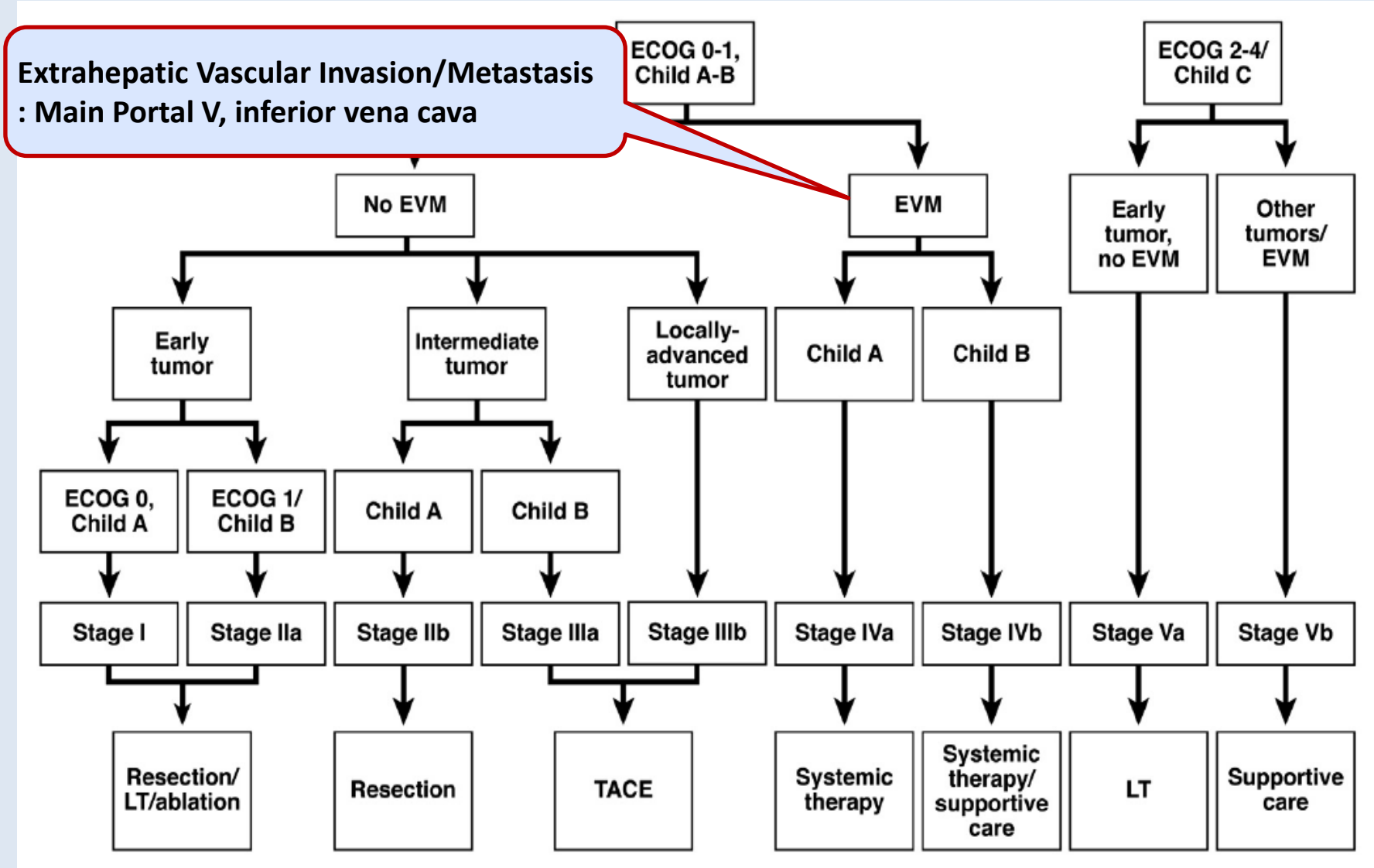
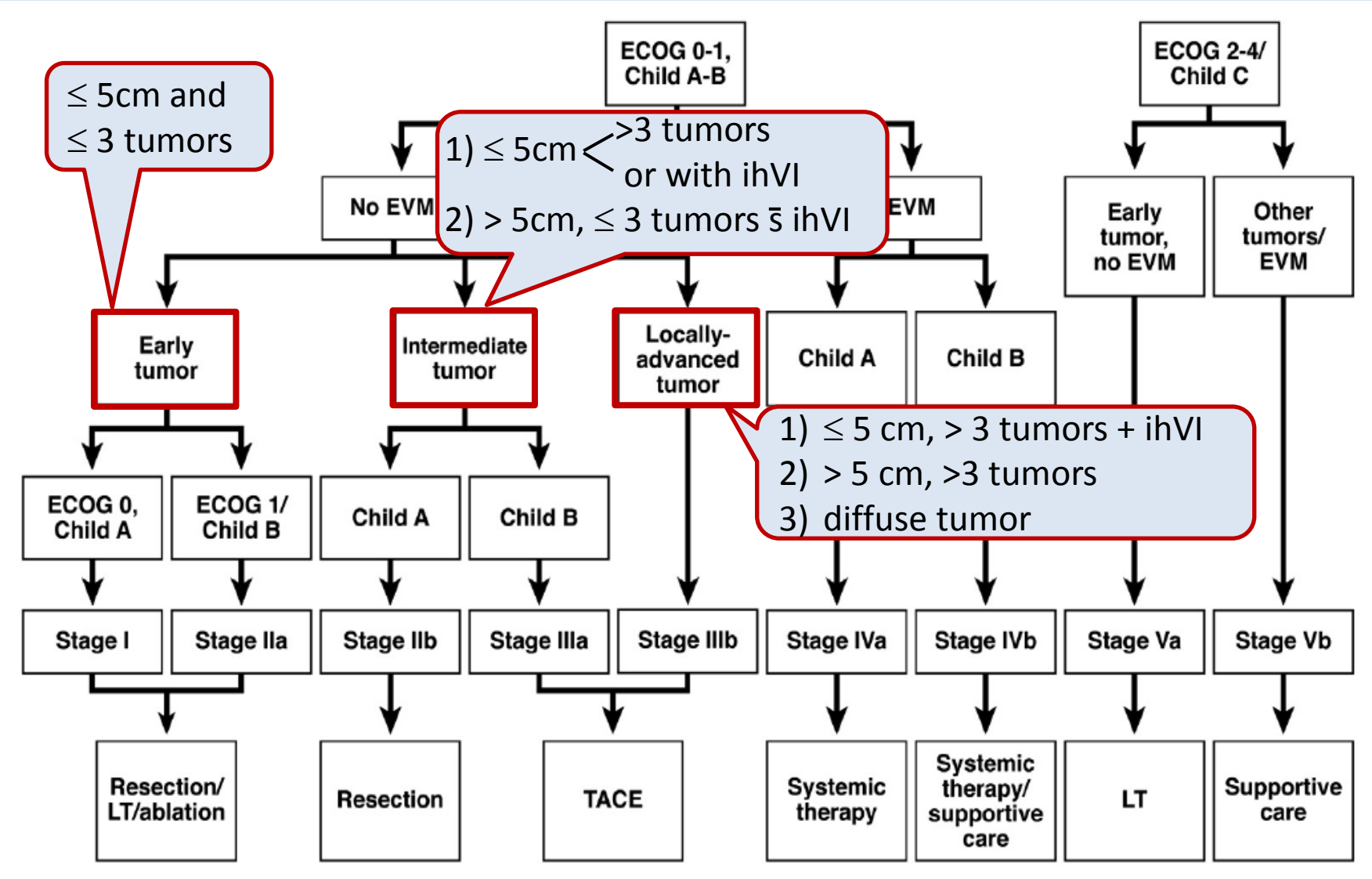
Hong Kong Liver Cancer Staging System



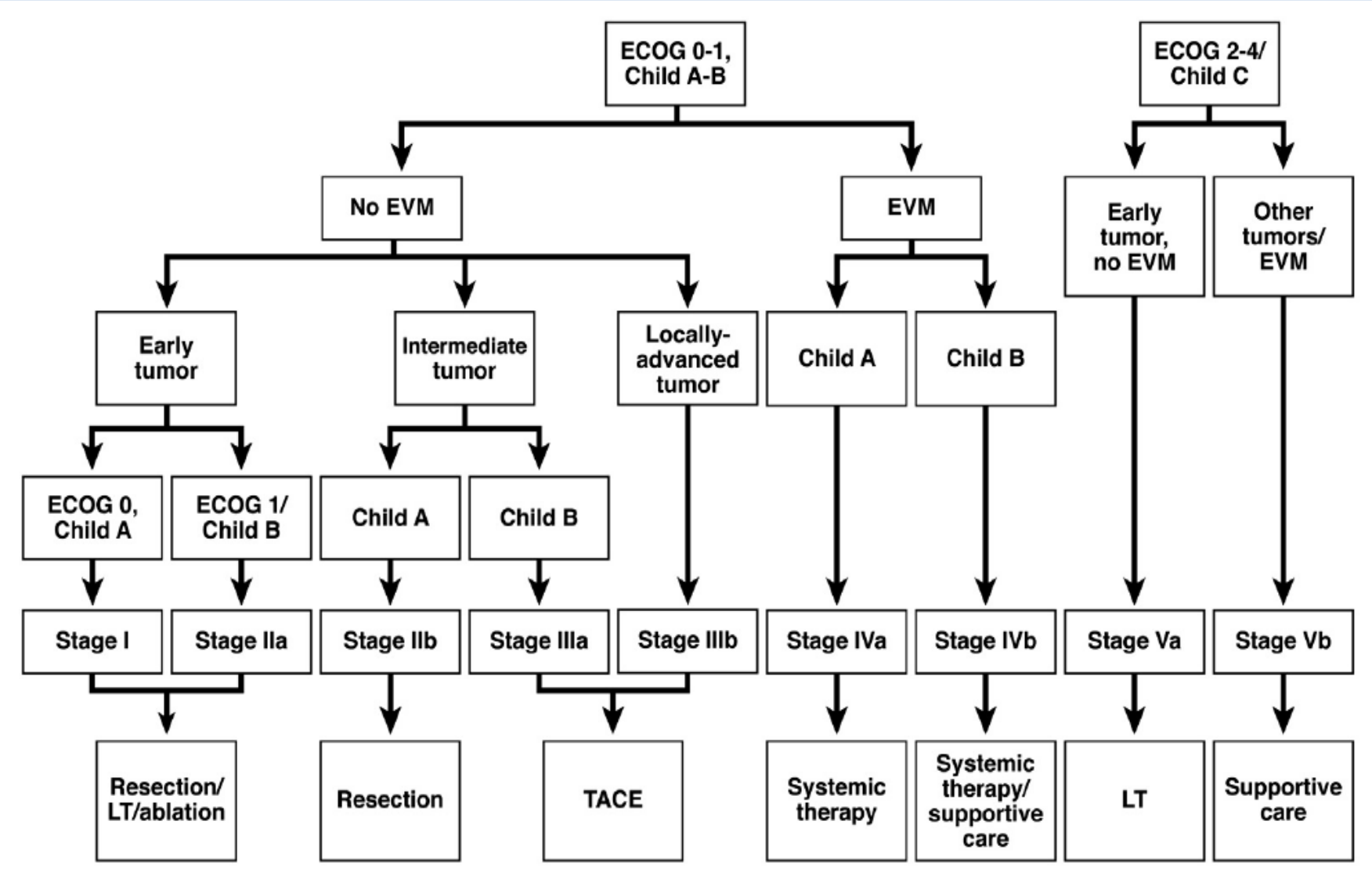
Yau T et al. Gastroenterology 2014;146:1691–1700

Hong Kong Liver Cancer Staging System



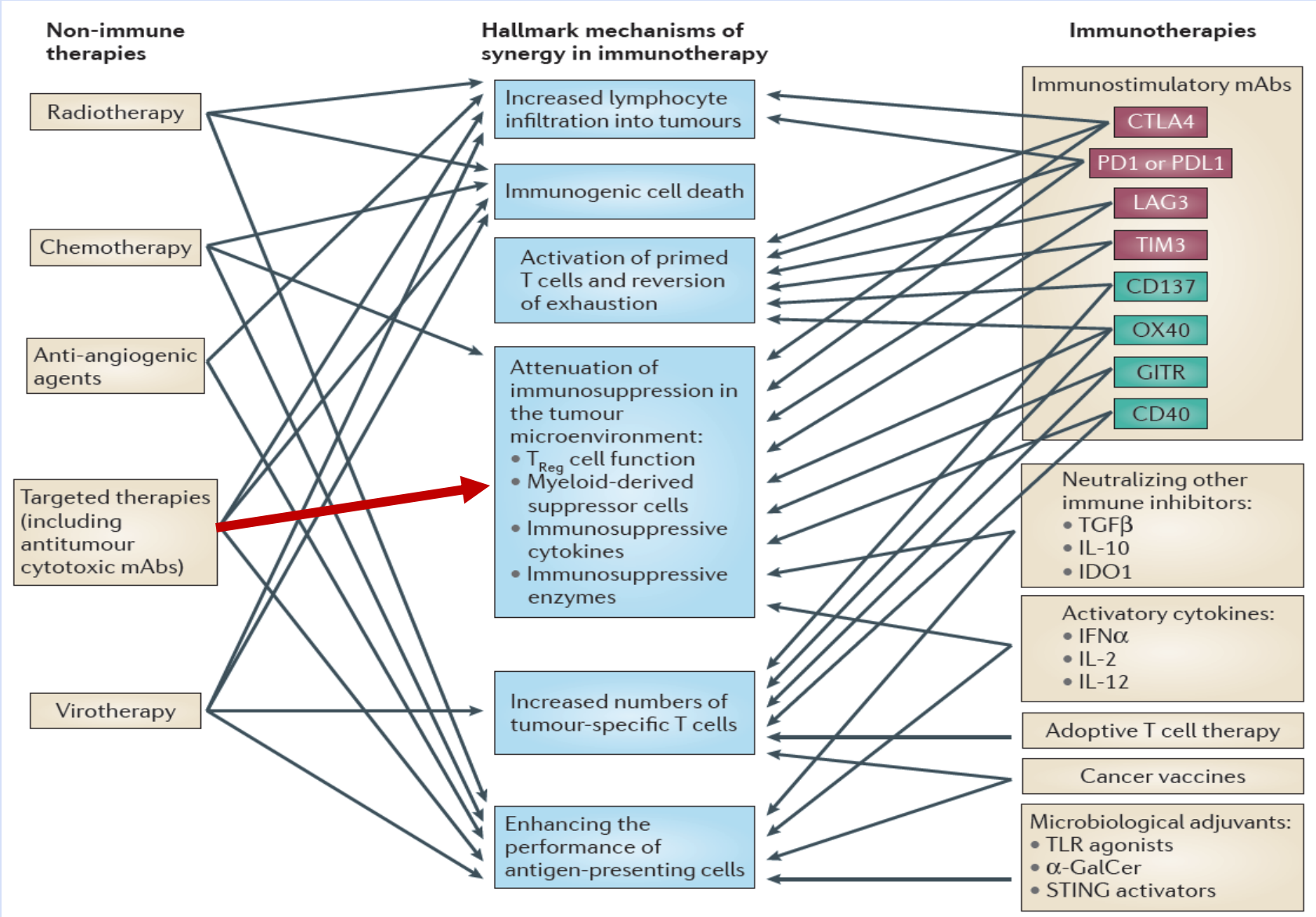
Yau T et al. Gastroenterology 2014;146:1691–1700

Hong Kong Liver Cancer Staging System



Yau T et al. Gastroenterology 2014;146:1691–1700

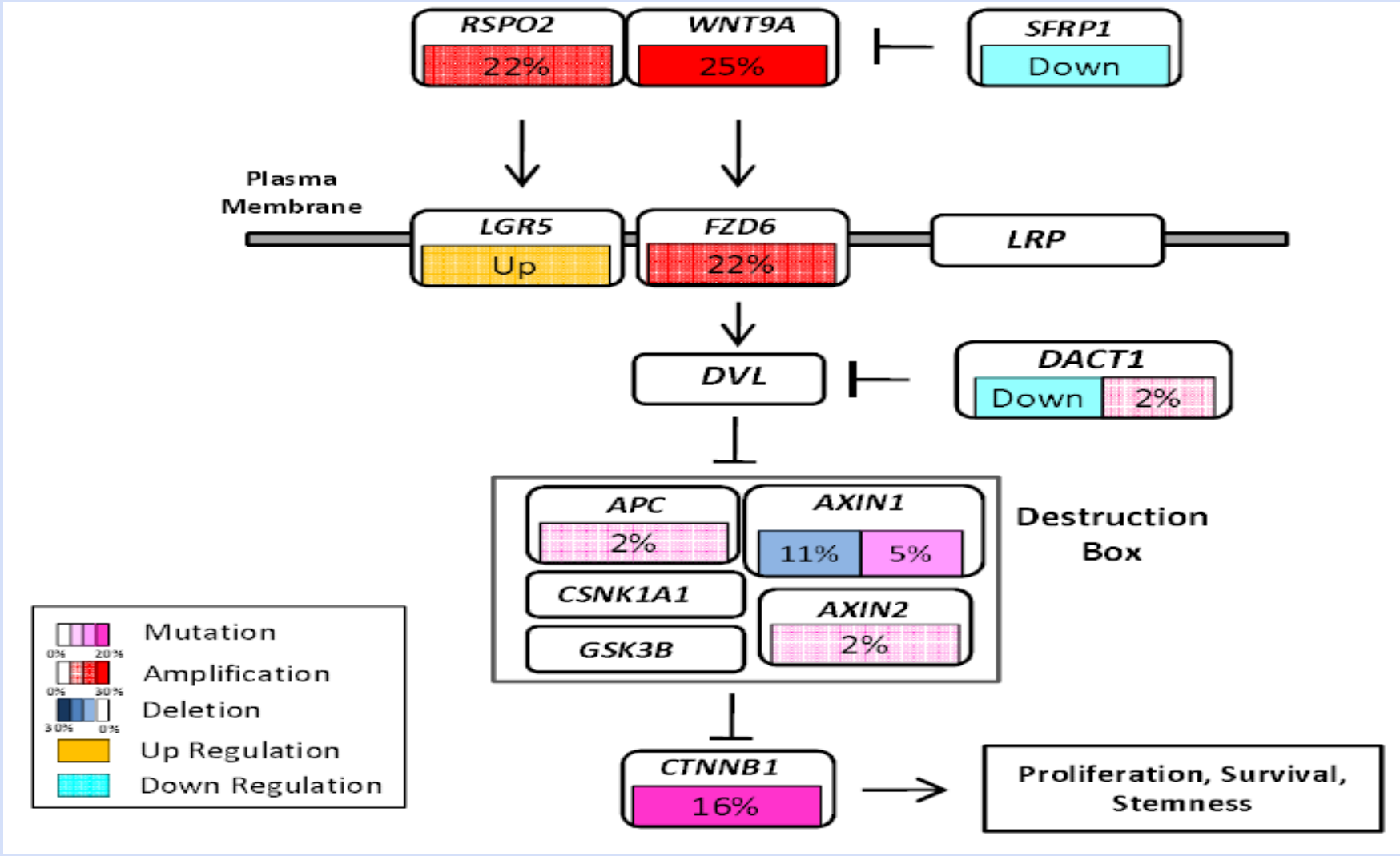
Multi-modality Combined Immunotherapy



Melero I et al. Nat Rev Cancer. 2015 Jul 24;15(8):457-72

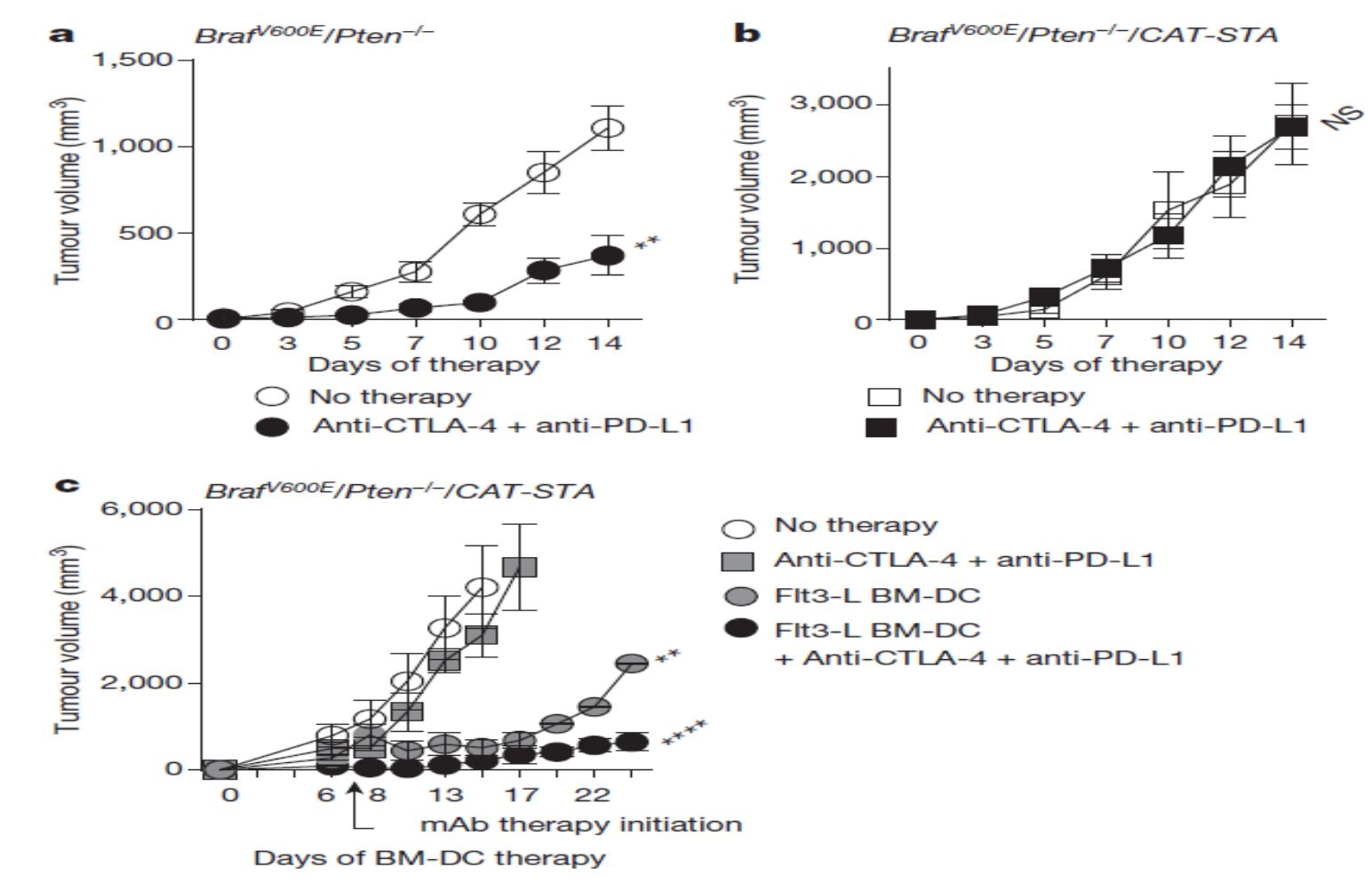
Whole Genome Sequencing Identifies Recurrent Mutations in HCC

Wnt Pathway Genomic Alterations in 62.5% of HCC



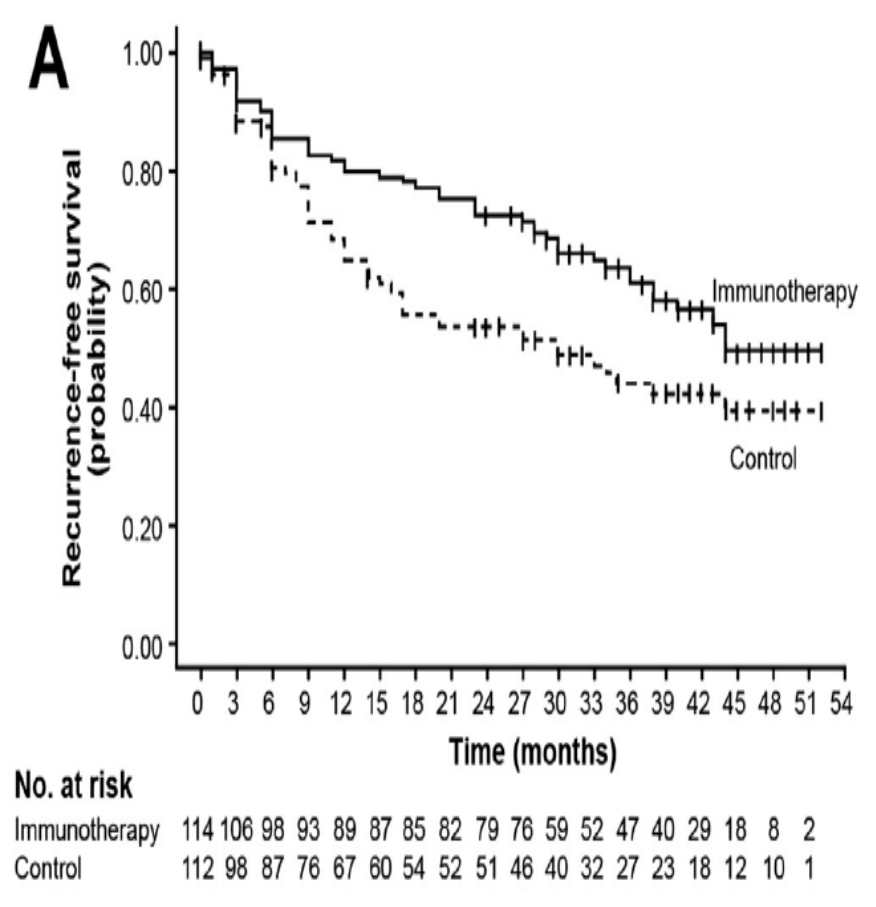
Kan Z, et al. Genome Res. 2013 Jun 20. [Epub ahead of print]

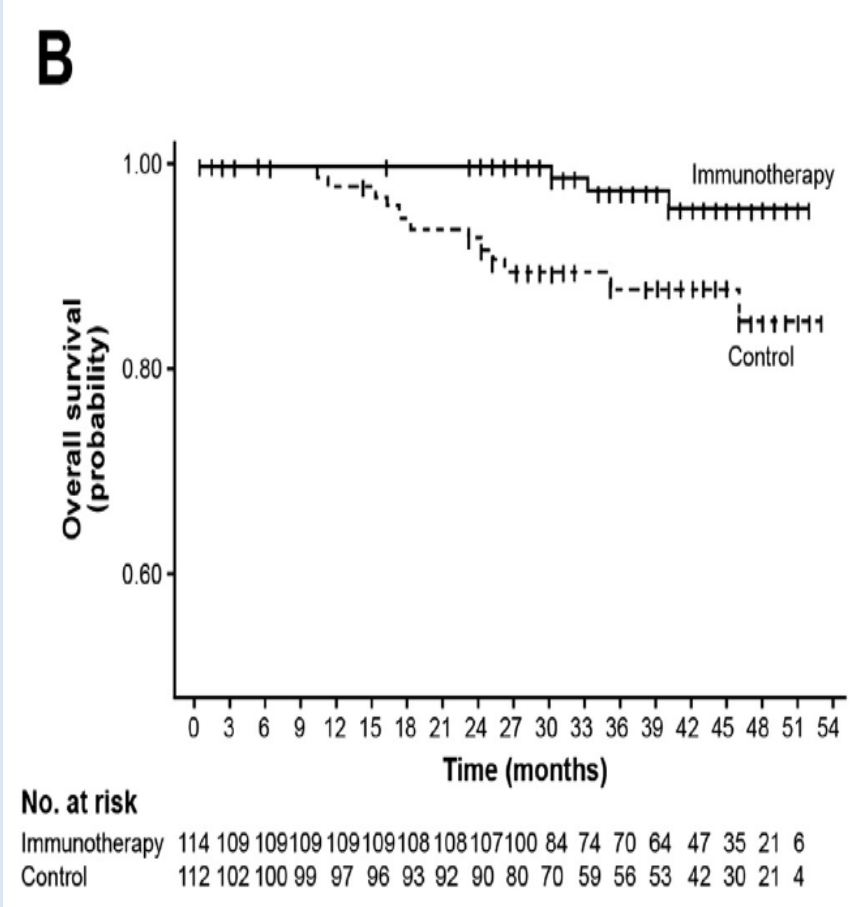
Reconstitution with Flt3 Ligand Dendritic Cells Reverses Resistance to Immunotherapy



Spranger S. et al Nature 2015;523:231-235

Adjuvant Immunotherapy With Autologous Cytokine-Induced Killer Cells for HCC





Lee JH et al. Gastroenterol 2015;148:1383–1391

Preliminary Results From a Phase I/II Study of Epacadostat (incb024360), an IDO inhibitor, in Combination With Pembrolizumab in Patients With Selected Advanced Cancers

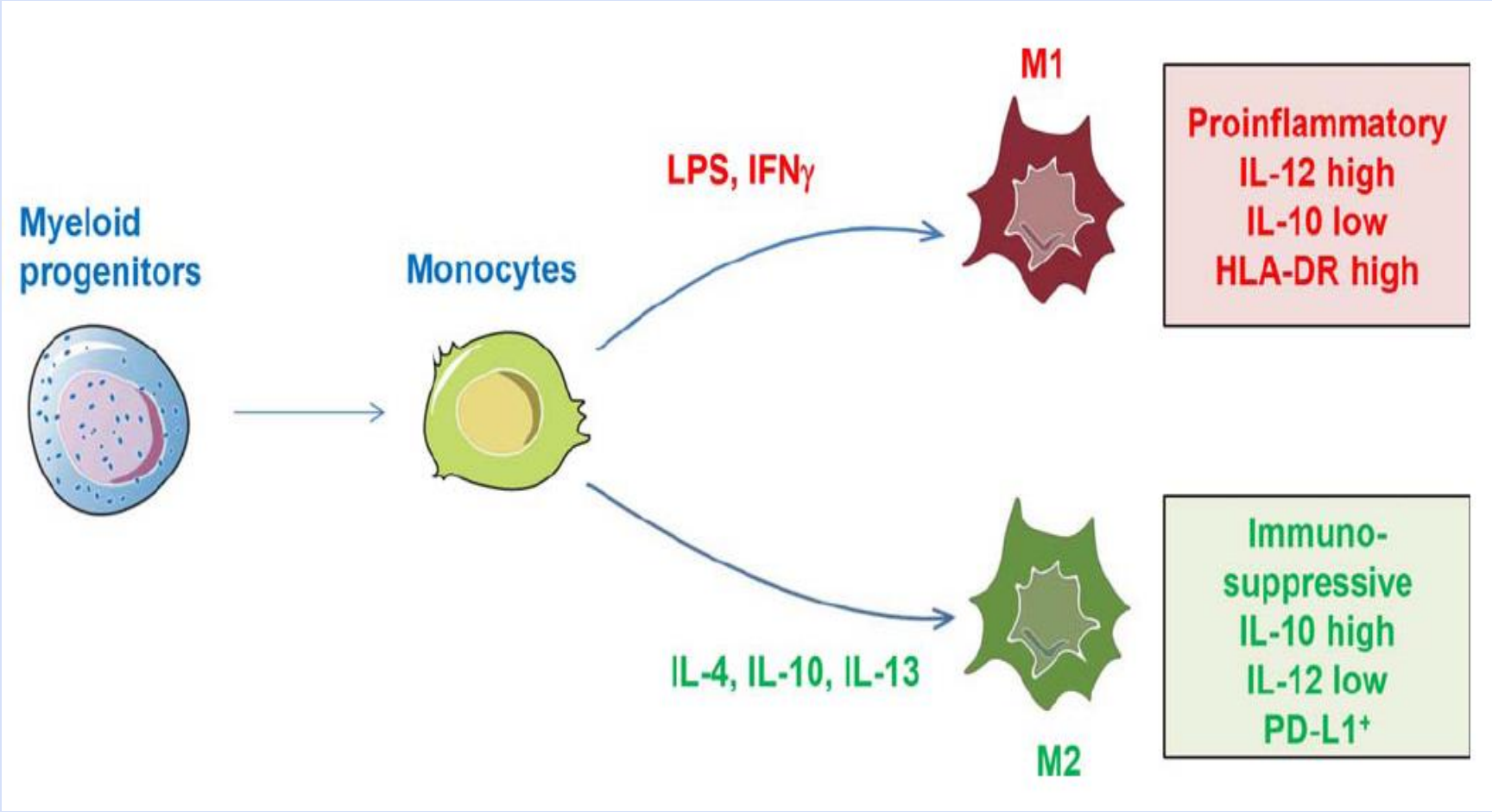
Table 1

Evaluable patients* n(%)	Melanoma (n=7)	RCC (n=5)	TCC (n=2)	NSCLC (n=2)	EA (n=2)	SCCHN (n=1)
ORR (CR+PR)	**4 (57)**	**2 (40)**	**1 (50)**	**1 (50)**	**1 (50)**	**1 (100)**
CR	2 (29)	0	0	0	0	0
PR	2 (29)	2 (40)	1 (50)	1 (50)	1 (50)	1 (100)
SD	2 (29)	2 (40)	0	1 (50)	0	0
DCR (CR+PR+SD)	**6 (86)**	**4 (80)**	**1 (50)**	**2 (100)**	**1 (50)**	**1 (100)**
PD	1 (14)	0	1 (50)	0	0	0
Not assessable	0	1 (20)	0	0	1 (50)	0

*Patients with ≥ 1 post-baseline response assessment or discontinued from study or died before response could be assessed.

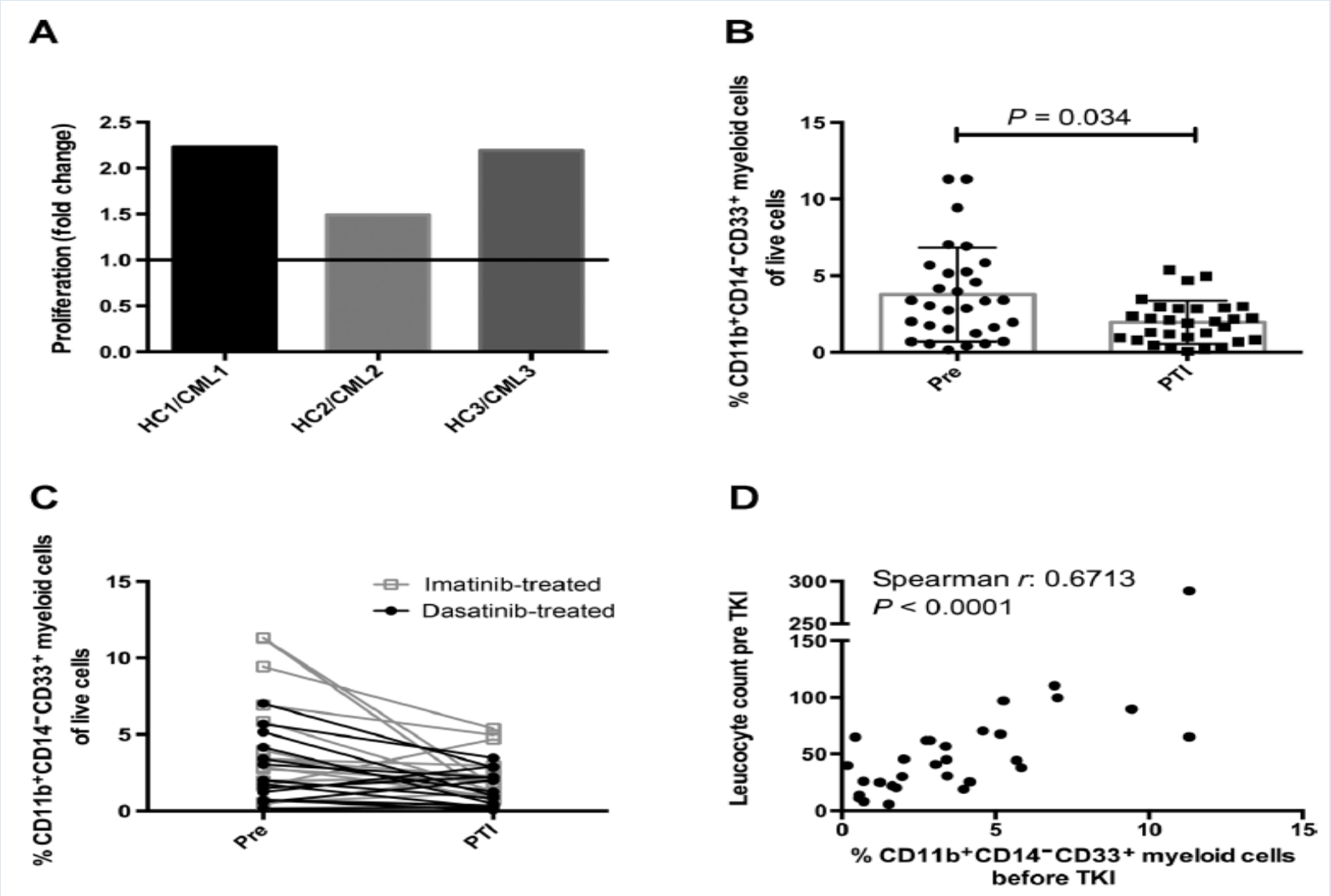
Gangadhar et al. J ImmunoTher Cancer 2015, 3(Suppl 2):O7

Classically Activated M1 and Alternatively Activated M2 Macrophages



Wan S, et al. Hepatology 2015; ePub

Imatinib and Dasatinib Reduce MDSC and Release Effector Lymphocyte Responses



Christiansson L et al. Mol Cancer Ther; 2015, 14(5); 1181–91

Emerging Biomarkers for Cancer Immunotherapy

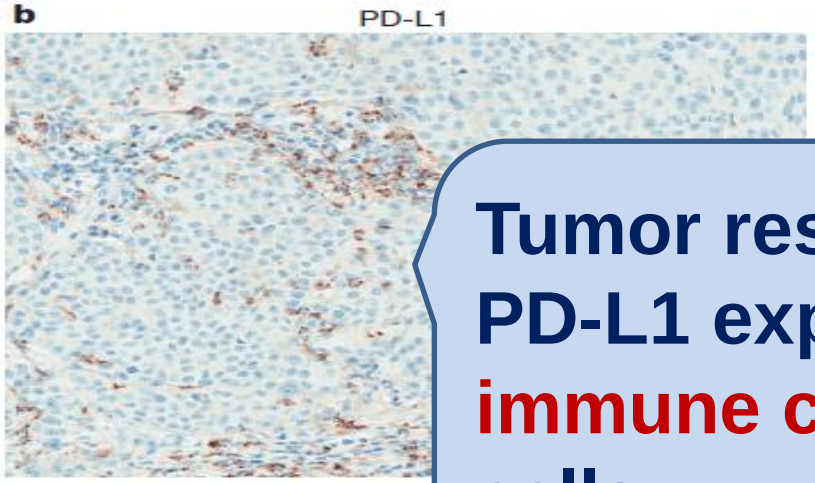
- Mutation burden, neo-antigen burden, mismatch-repair deficiency
- Tumor infiltrating lymphocyte(TIL), Immunoscore
- PDL1 expression
- Tumor associated macrophage (TAM), myeloid-derived suppressor cell (MDSC)

Immunotherapy Biomarkers in the Tumor Microenvironment

Immunohistochemistry	Flow cytometry and functional assay	RNA and DNA
Baseline		
• Ipilimumab: higher levels of IDO1 and FOXP3 at baseline were associated with clinical activity[156]. • Pembrolizumab: density of $CD8^+$ T cells at the invasive margin was associated with response. Other potential predictors include $PD1^+$ T cells in proximity to $PDL1^+$ cells, and clonal T cell repertoire observed in responders[138].	NA	• Ipilimumab: high expression of immune-related genes (including *IDO1*) was associated with clinical activity[157]. • Atezolizumab: expression of CTLA4 and fractalkine was associated with response and progression, respectively. Expression of IFNγ-inducible genes in melanoma was associated with response[45].
Post-treatment		
• Tremelimumab: increased infiltration of $CD8^+$ T cells; increased numbers of HLA-DR^+ and $CD45RO^+$ memory T cells. No change in $FOXP3^+$ T cells or IDO1-expressing cells post-treatment versus pretreatment[158]. • Ipilimumab: possible association between clinical activity and an increase in total TILs by week 4 relative to baseline; $CD8^+$ T cell/$FOXP3^+$ T cell ratio post-treatment is associated with the degree of necrosis[156,160]. • Pembrolizumab: a significantly higher level of expression of the IFNγ-inducible protein STAT1 was seen in responders at baseline and after PD1 inhibition[138]. • Atezolizumab: a decrease in tumour size seems to be associated with an increase in PDL1 expression on tumour and immune cells. Progressing lesions seem to have no intratumoural inflammation and no PDL1 expression[45].	• Tremelimumab: one patient had >40% $CD3^+$; TILs were $CD4^-$ with HLA-DR^+, $CD45RO^+$, $CD27^{2+}$ and $CCR7^-$ (memory phenotype)[158]. • Ipilimumab: one patient with a regressing lesion had a higher number of a subset of NK cells ($CD56^+CD16^-$) than of lymphocytes[159]. One patient showed an autologous T cell (TIL) response to neoantigens that increased after treatment[144]. • An expansion of the $CD8^+$ T cell population specific for shared tumour antigens in peripheral blood was found after treatment[107]. • Pembrolizumab: in blood from a patient with NSCLC, a neoantigen-specific T cell response was observed that increased during tumour regression[145].	• Ipilimumab: general increase in the expression of immune-related genes associated with clinical activity; general increase in the expression of IFNγ and T_H1 cell-associated markers[157]. • Nivolumab: there was an increase in the expression of MIG and IP10 (REF. 161). • Atezolizumab: the RNA expression pattern from regressing lesions was consistent with $CD8^+$ T cell and T_H1 cell phenotypes, but there was no change in FOXP3 expression[45].

Melero I et al. Nat Rev Cancer. 2015 Jul 24;15(8):457-72

MPDL3280A (anti-PD-L1) Treatment Leads to Clinical Activity in Metastatic Bladder Cancer



Tumor response correlates with PD-L1 expression on infiltrating immune cells but not tumor cells.

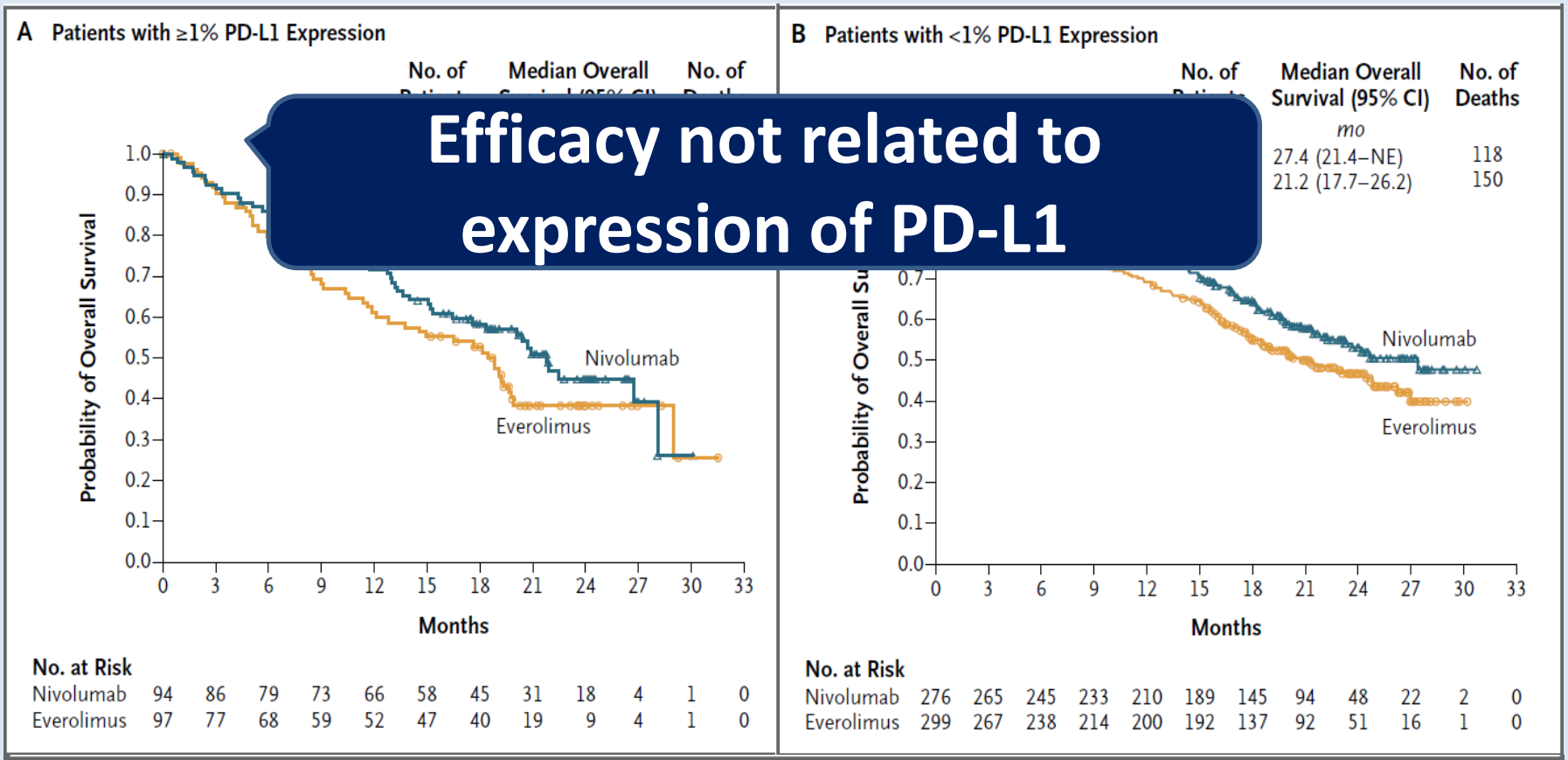
c

Tumour-infiltrating immune cells and objective response rates

	Objective response rate *n* (%)	Stable disease *n* (%)	Progressive disease *n* (%)
IHC 2/3 ($n = 30$)	13 (43.3) (95% CI: 25.5–62.6)	8 (26.7)	8 (26.7)
IHC 3 ($n = 10$)	5 (50.0) (95% CI: 22.2–77.8)	2 (20.0)	3 (30.0)
IHC 2 ($n = 20$)	8 (40.0) (95% CI: 20.9–63.9)	6 (30.0)	5 (25.0)
IHC 0/1 ($n = 35$)	4 (11.4) (95% CI: 4.0–26.3)	13 (37.1)	13 (37.1)
IHC 1 ($n = 23$)	3 (13.0) (95% CI: 3.7–31.7)	8 (34.8)	8 (34.8)
IHC 0 ($n = 12$)	1 (8.3) (95% CI: 0.4–34.9)	5 (41.7)	5 (41.7)

Powles T et al. Nature 2015;515:558-562

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

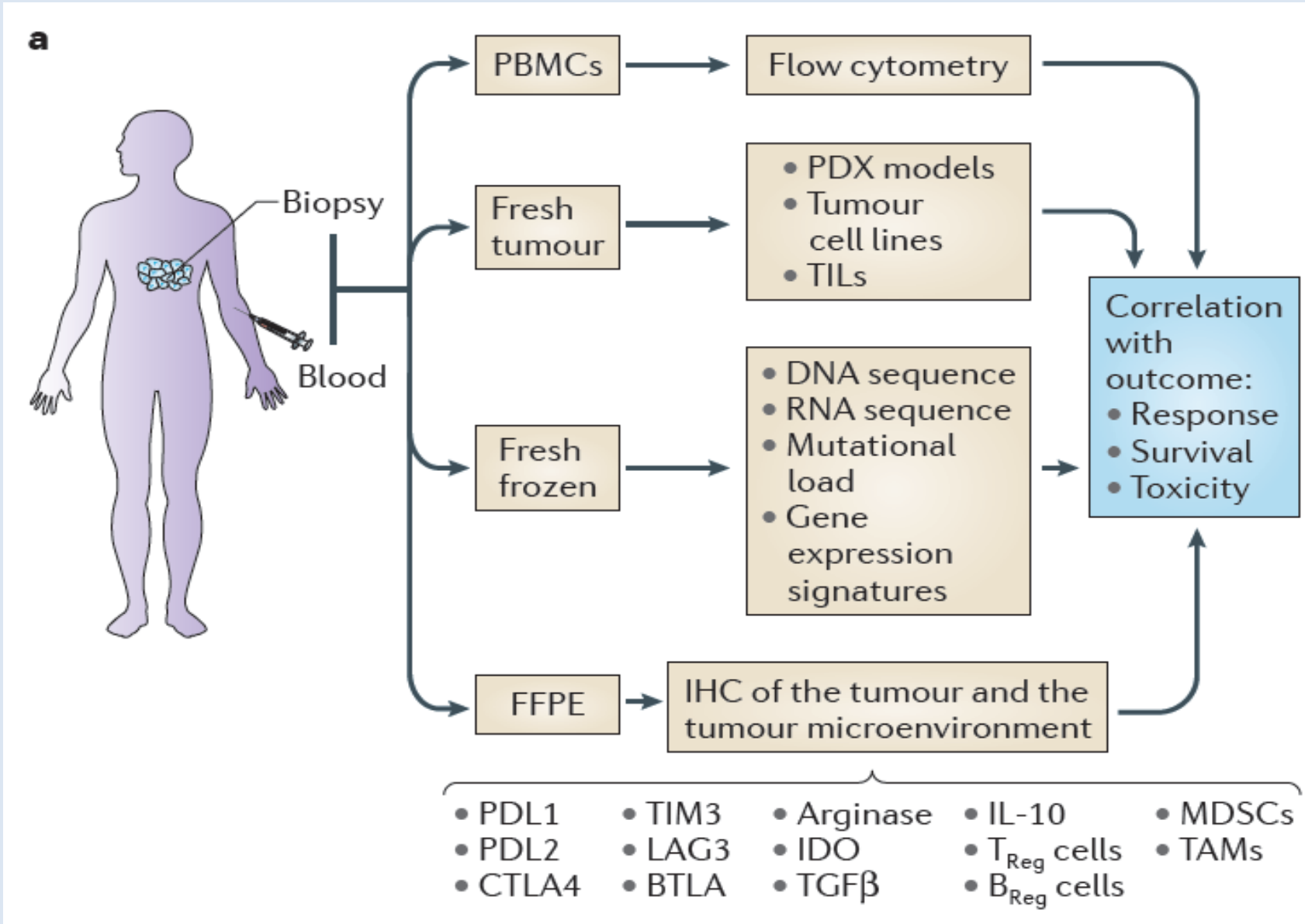


Efficacy not related to expression of PD-L1

Figure 3. Kaplan–Meier Curve for Overall Survival, According to Programmed Death 1 Ligand (PD-L1) Expression Level.

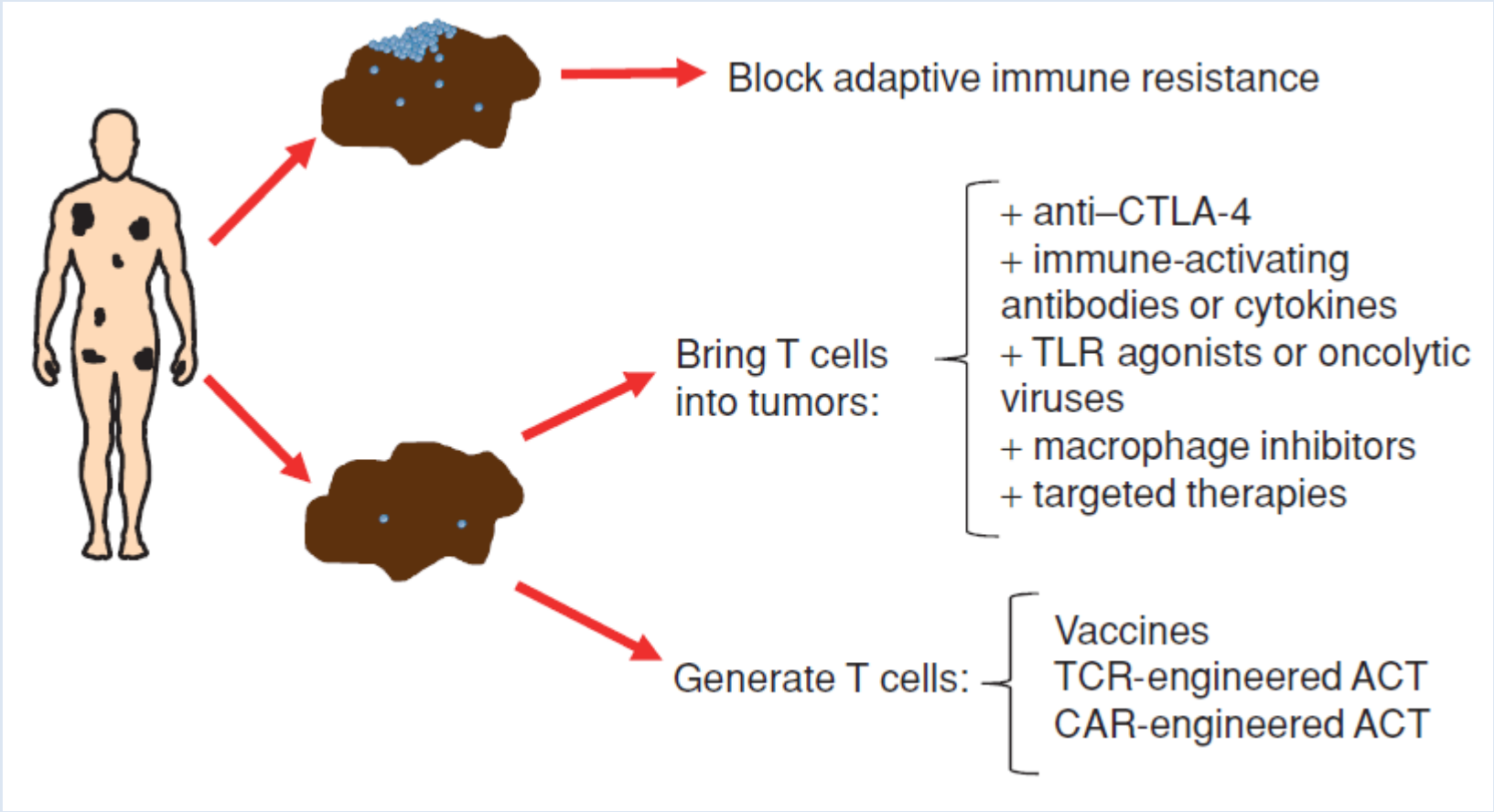
Motzer RJ et al. N Engl J Med. 2015 Sep 25. [Epub]

Biomarker Discovery for Combination Immunotherapy



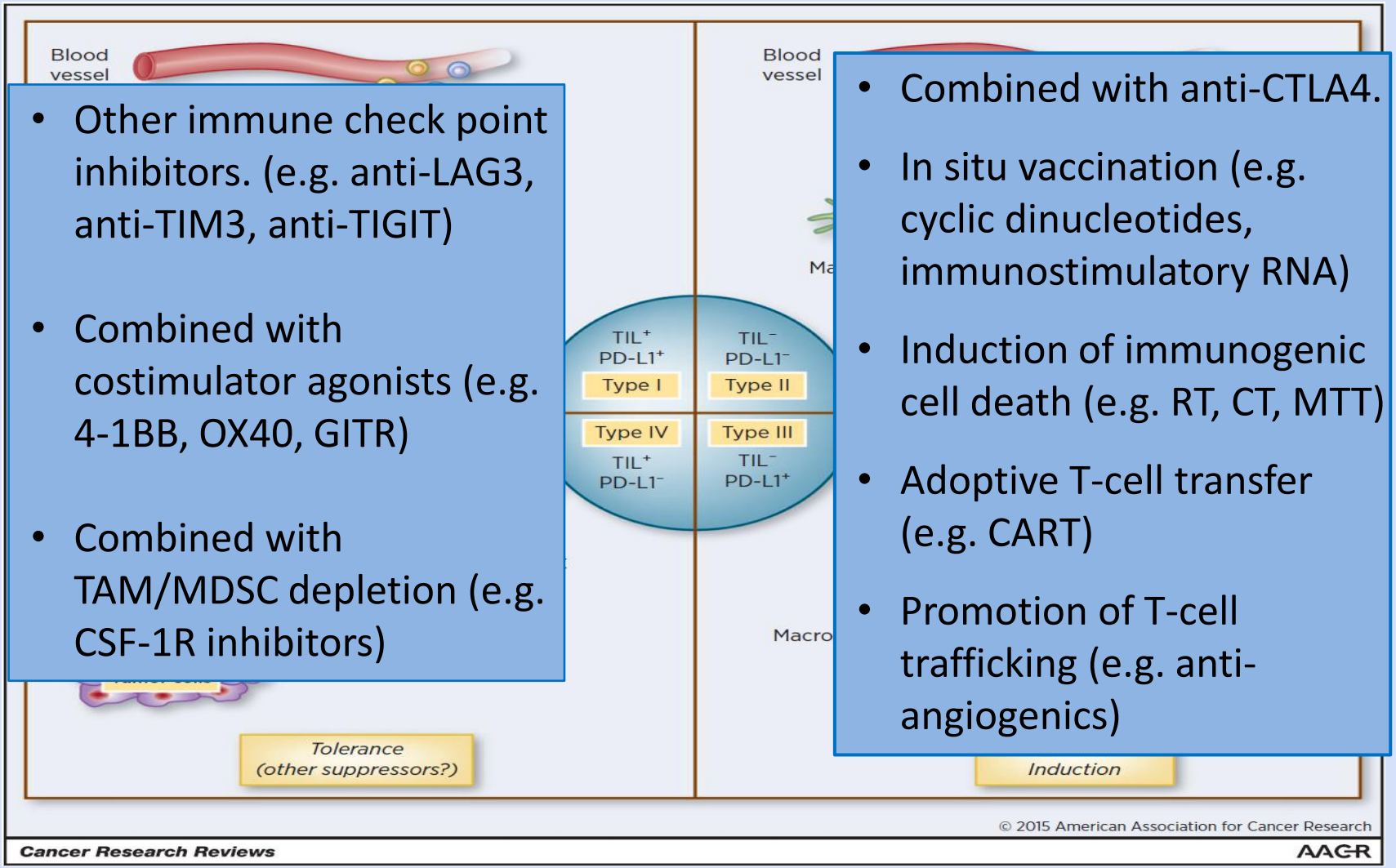
Melero I et al. Nat Rev Cancer. 2015 Jul 24;15(8):457-72

Treatment Selection Based on Detecting Adaptive Immune Resistance



Ribas A *Cancer Discovery 2015;5(9); 915–9.*

Classifying Cancers Based on T-cell Infiltration and PD-L1



- Other immune check point inhibitors. (e.g. anti-LAG3, anti-TIM3, anti-TIGIT)
- Combined with costimulator agonists (e.g. 4-1BB, OX40, GITR)
- Combined with TAM/MDSC depletion (e.g. CSF-1R inhibitors)

- Combined with anti-CTLA4.
- In situ vaccination (e.g. cyclic dinucleotides, immunostimulatory RNA)
- Induction of immunogenic cell death (e.g. RT, CT, MTT)
- Adoptive T-cell transfer (e.g. CART)
- Promotion of T-cell trafficking (e.g. anti-angiogenics)

Teng MW, et al. Cancer Res. 2015;75(11):2139-2145.

Combination of Immune Checkpoint Inhibitors

- PDR001 (αPD-1) + LAG525 (αLAG-3)
  * This concept is also under investigation by BMS
  * LAG525: effects on Treg?
- PDR001 (αPD-1) + MBG453 (αTIM-3)
  * MBG453: first-in-class? Effects on TAM, Treg?

Innate Immunity Modulator w/wo Immune Checkpoint Inhibitor

- BLZ945 (selective CSF-1R RTKi) ± PDR001

  *BLZ945: first-in-class? The other competitors are αCSF1R

- MCS110 (αCSF-1) ± PDR001

  *MCS110: first-in-class

- CDNs (STING agonist) ± PDR001

  *CDNs: first-in-class; usually combined with vaccines as adjuvant and administered via intra-tumor injection in preclinical studies

Immune Checkpoint Inhibitor Plus Costimulatory Receptor Activator

- PDR001 (αPD-1) + LKZ145 (agonistic αGITR)

  * Similar concept is currently under investigation by BMS:

    αPD-1 + α4-1BB

  * LKZ145: not first-in-class

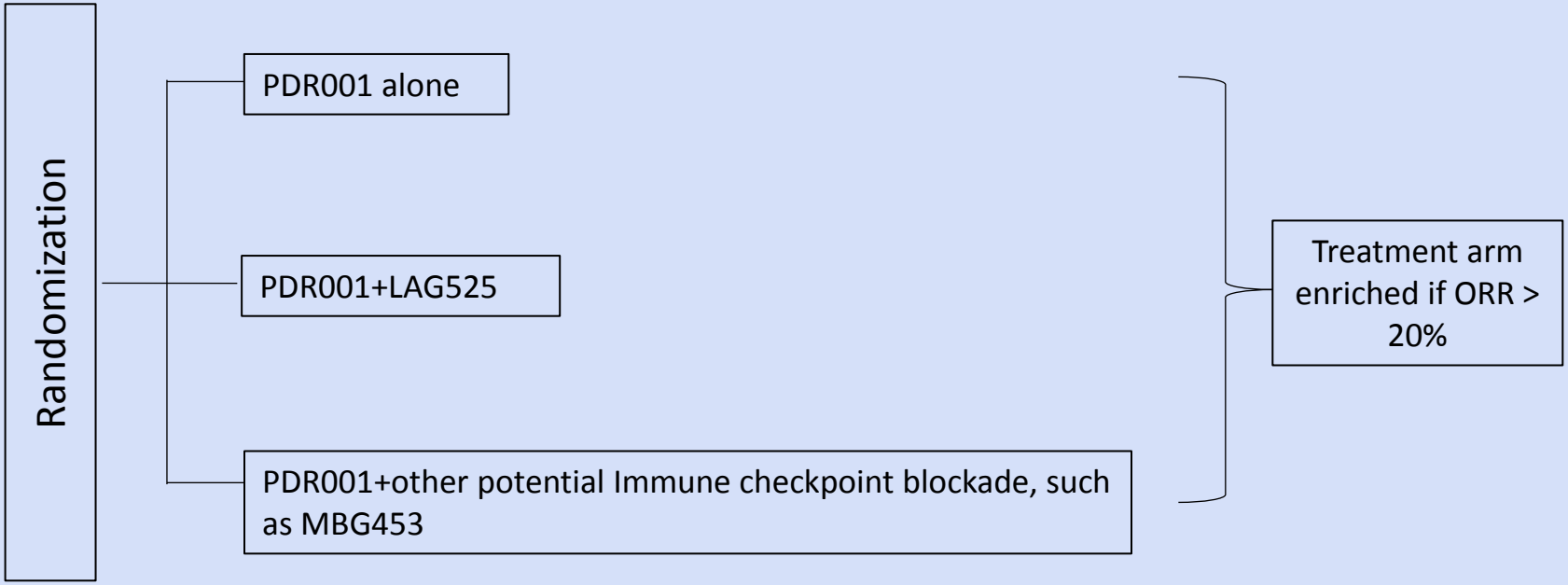
Potential partners (drug x) of PDR001

Drug/ MoA	Pre-clinical synergy with anti-PD1	HCC pre-clinical studies	Human studies	Human HCC studies
LAG525/ anti-LAG3	Yes [1]	Yes [2]	Ongoing	No
MCS110/ anti-CSF-1	No	Yes [3,4]	Ongoing	No
BLZ945/ CSF-1Ri	No	Yes [3,4]	Ongoing	No
MBG453/ anti-TIM3	Yes [5]	Yes [6*]	Planned	No
LKZ145/ GITR agonist	Yes [7]	No	No	No
STING/ in situ vaccine	No	No	Planned	No

1. Woo SR, Turnis ME, Goldberg MV, et al. Cancer Res 2012; 72: 917-27
2. Pedroza-Gonzalez A, Zhou G, Vargas-Mendez E, et al. Oncoimmunology 2015; 4(6):e1008355.
3. Sprinzl MF, Puschnik A, Schlitter AM, et al. J Hepatol 2015; 62: 863-70.
4. Schaer DA, Hirschhorn-Cymerman D, Wolchok JD. *J Immunother Cancer* 2014, 2:7
5. Sakuishi K, Apetoh L, Sullivan JM, et al. J Exp Med 2010; 207: 2187-94.
6. Yan W, Liu X, Ma H, et al. Gut 2015 (E pub)
7. Lu L, Xu X, Zhang B, et al. J Transl Med 2014 Feb 7;12:36

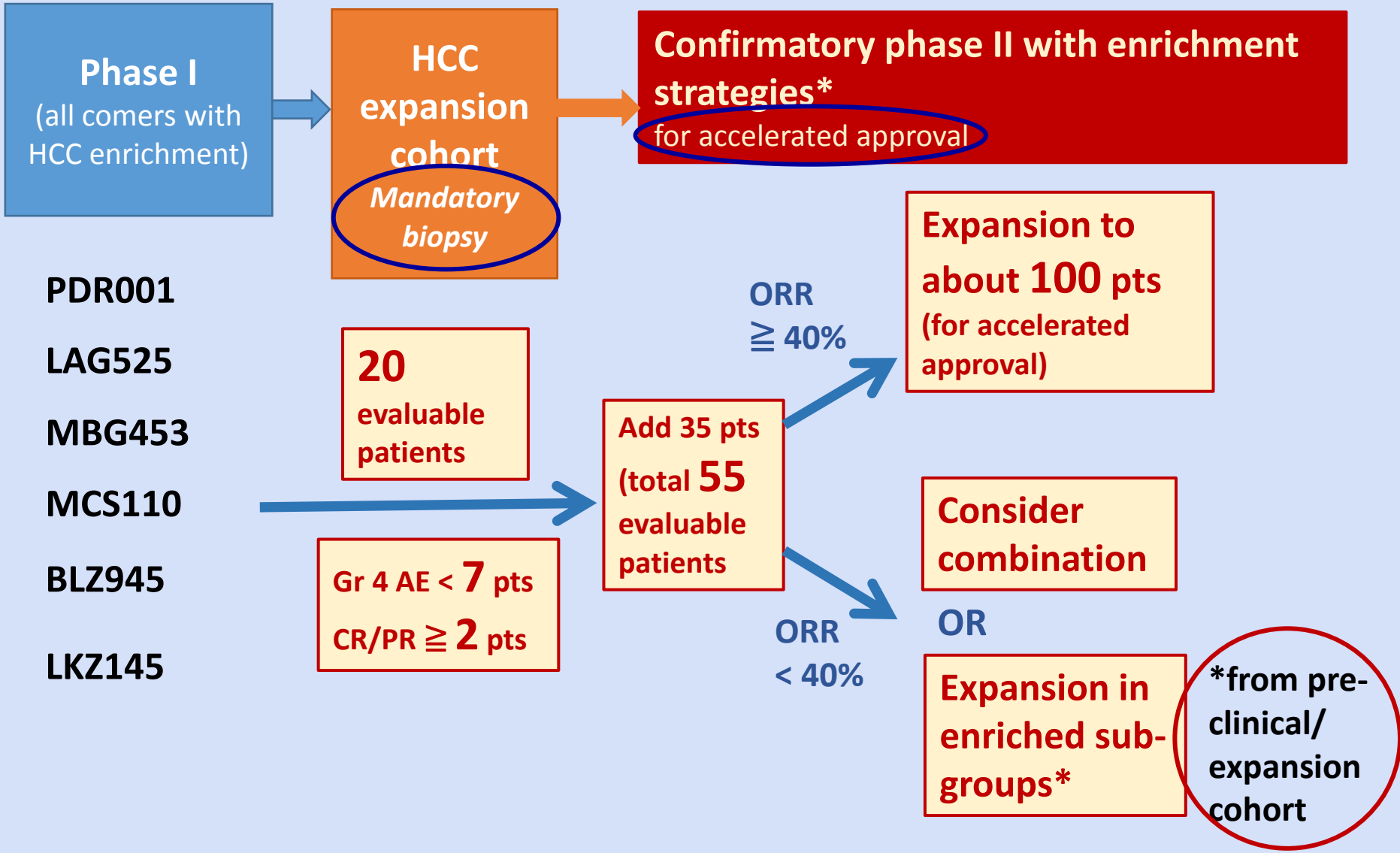
Cluster protocol of immunotherapy for advanced HCC

Open-label, randomized phase II study

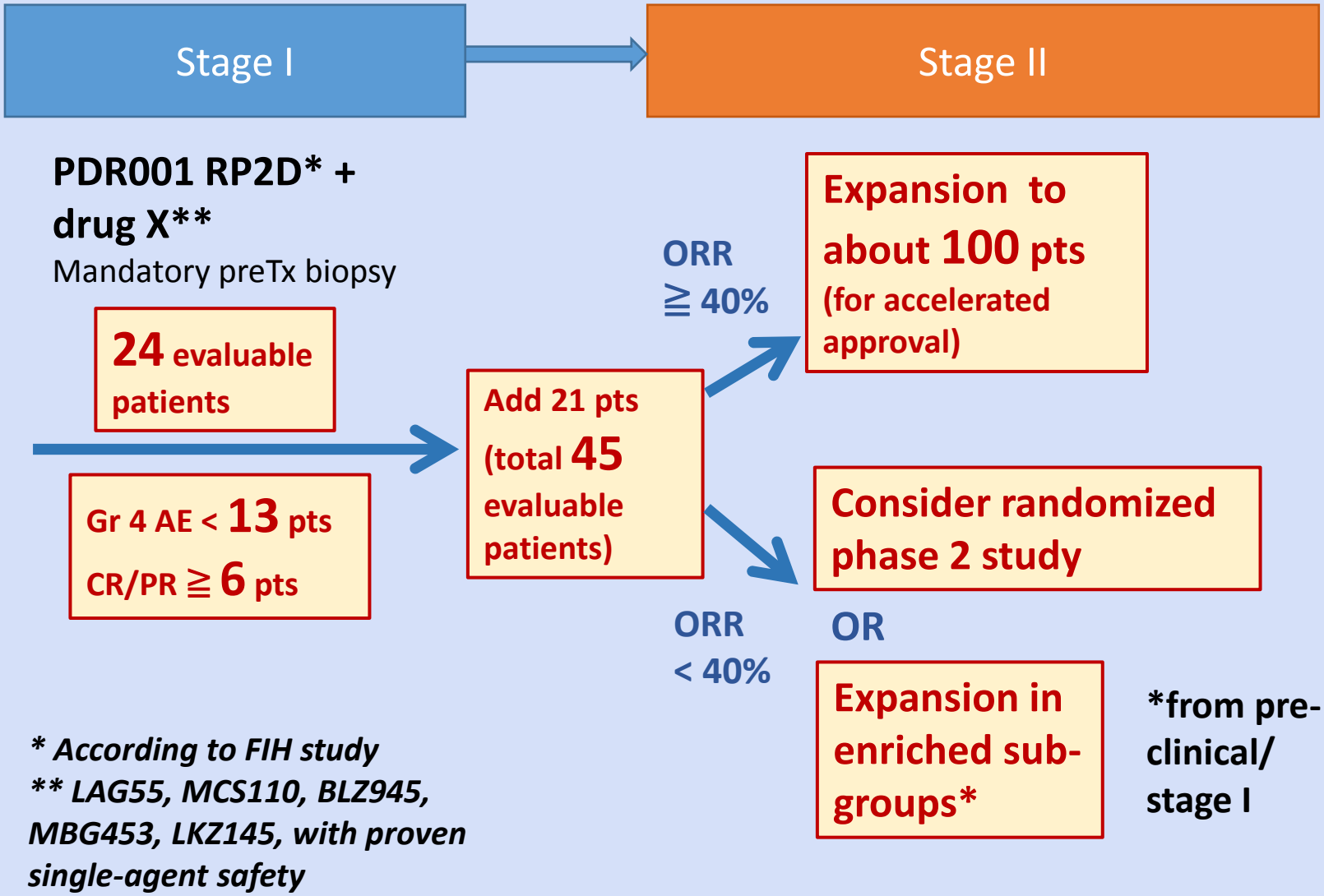


- RP2D: depends on phase I results of individual compound studies (LAG525X2101, MBG453X2101)
- If phase II is in the enriched patient group based on 1) immune score and 2) mutation load, and with ORR >40% and/or OS >15mths in extended cohorts (10-20 patients on the same dose), it is possible to explore fast track approval in Asian countries, such as Taiwan

Immunotherapy for advanced HCC (1): single agent



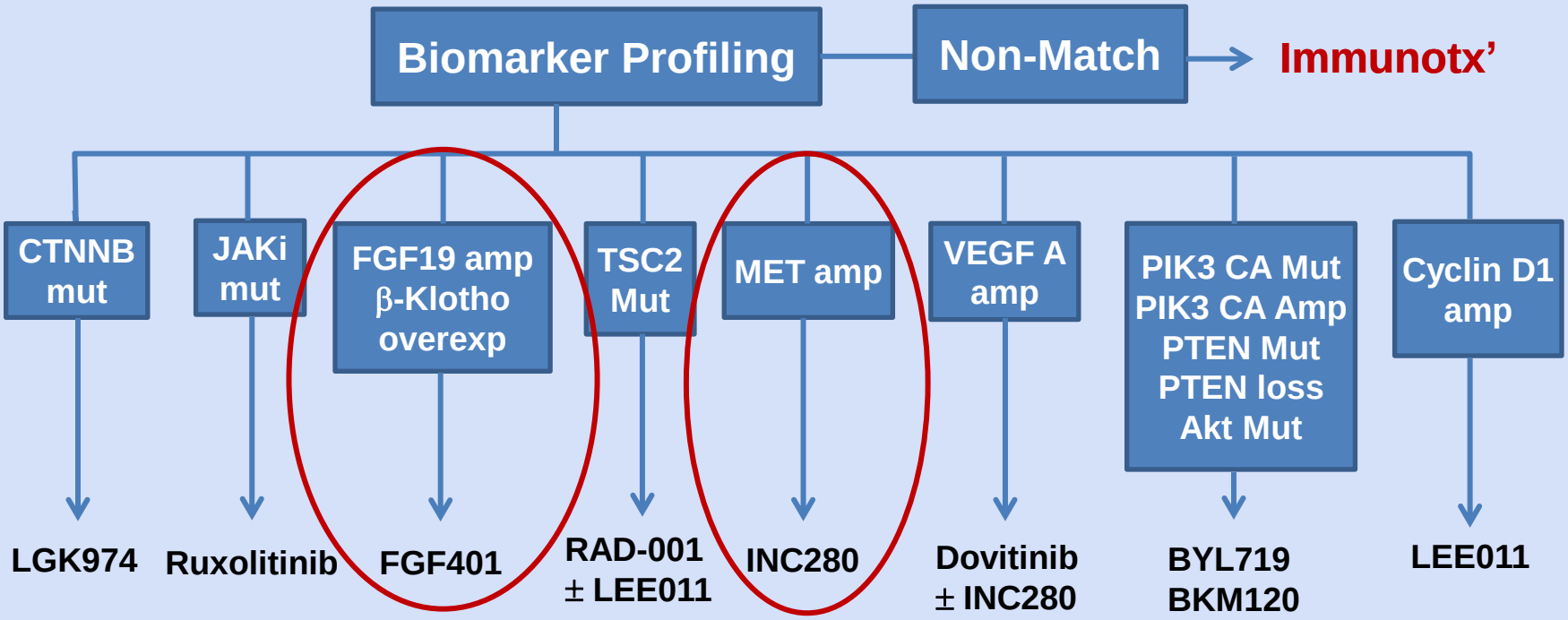
Immunotherapy for advanced HCC (2): PDR001 plus drug X combinations



** According to FIH study*
*** LAG55, MCS110, BLZ945, MBG453, LKZ145, with proven single-agent safety*

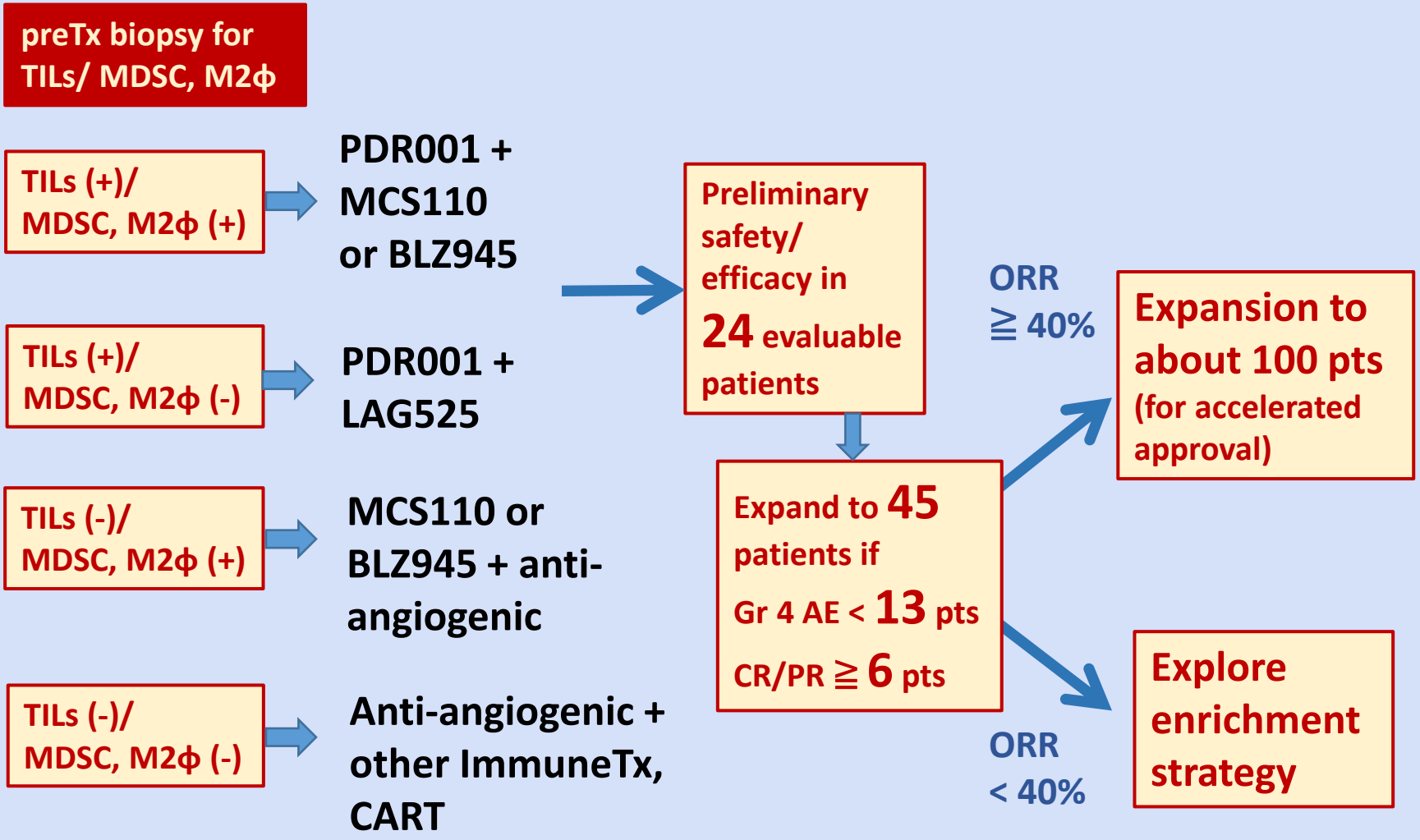
Master Protocol for Novartis 2nd-line HCC

- Exploratory, single-arm

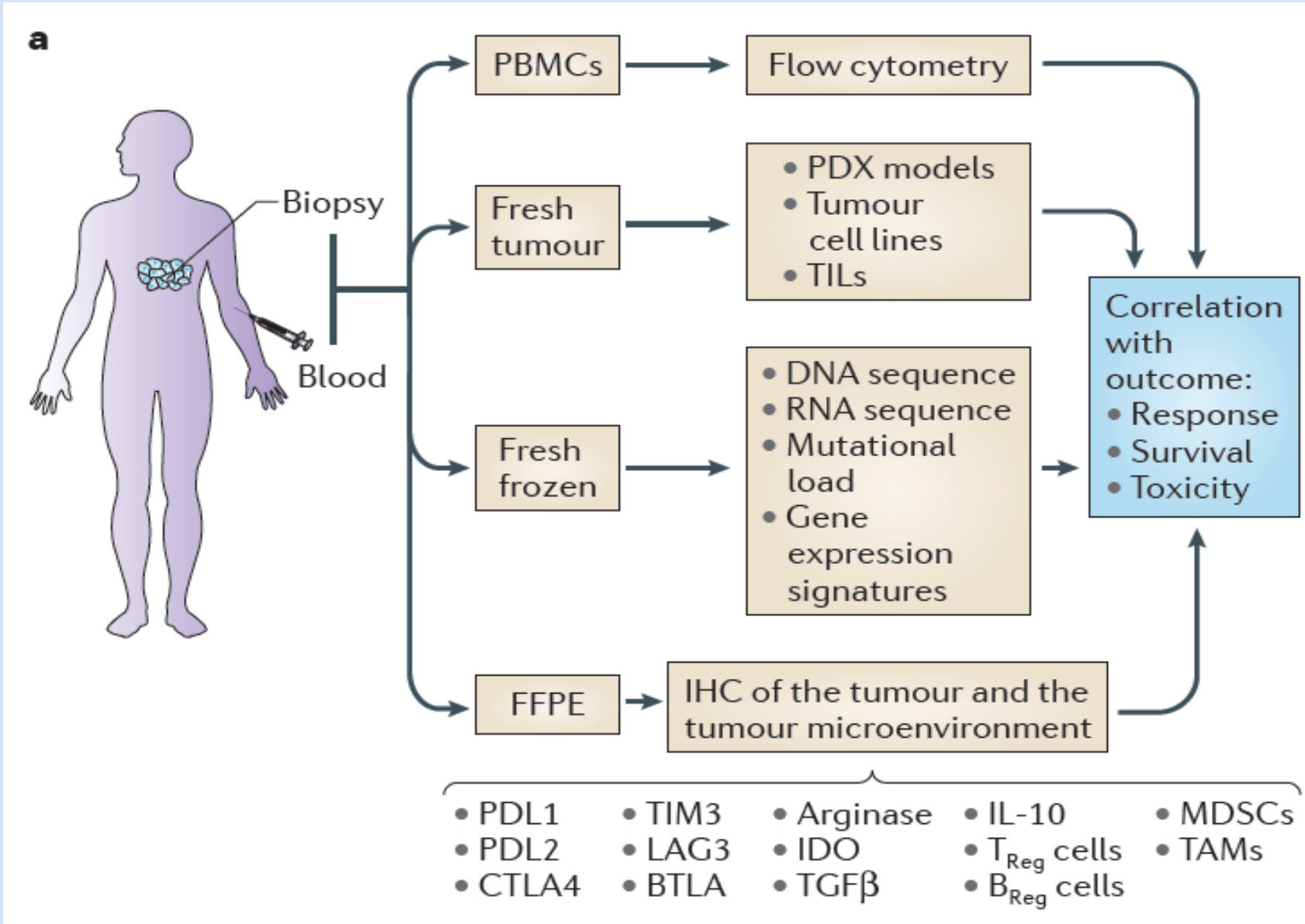


Further Phase II if RR > 15% or PFS > 5 months

A ‘cluster’ protocol of immunotherapy for HCC



Biomarker Discovery for Combination Immunotherapy



Melero I et al. Nat Rev Cancer. 2015 Jul 24;15(8):457-72

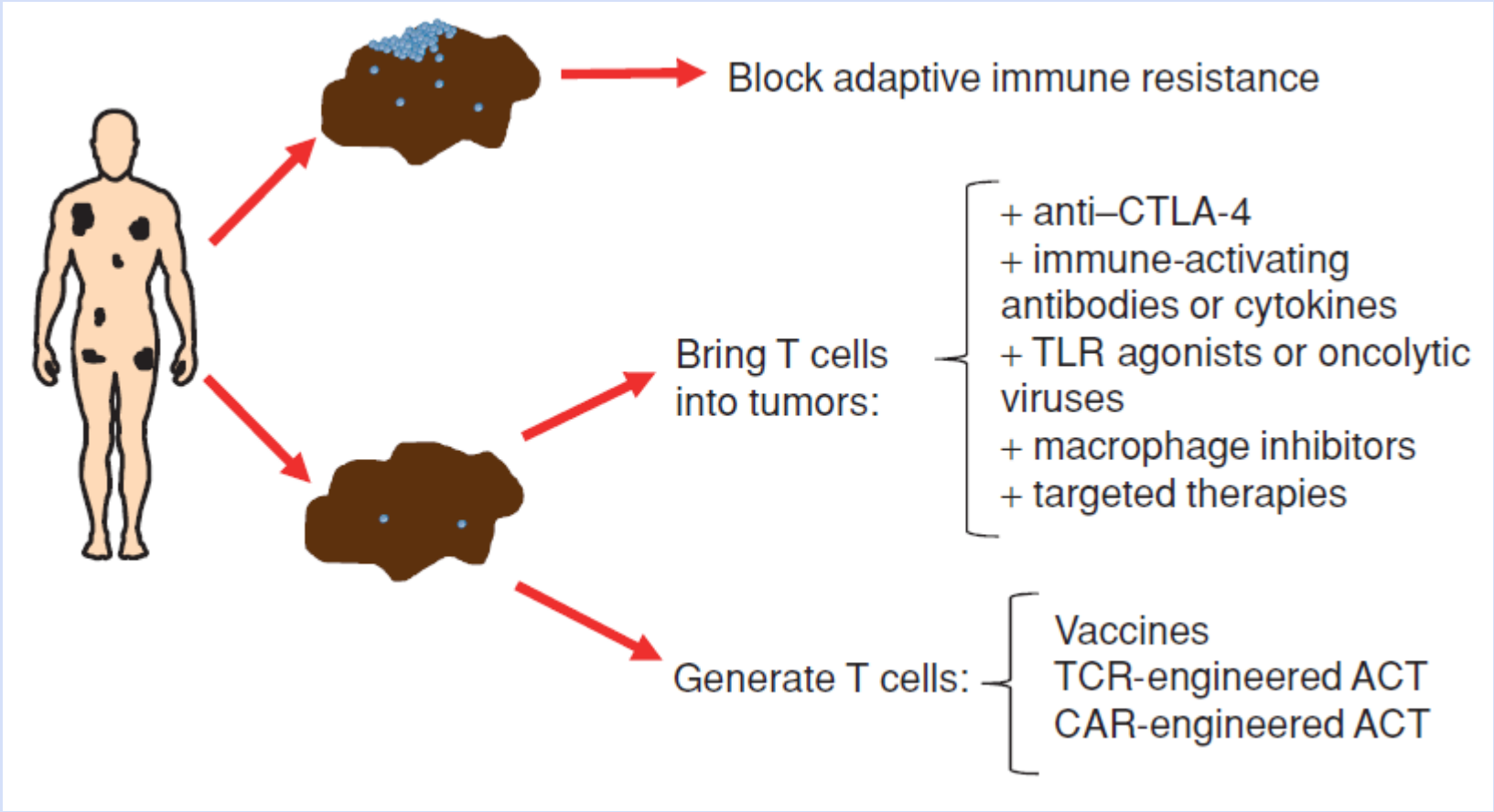
Whole Genome Sequencing Identifies Recurrent Mutations in HCC – 88 cases from HBV-endemic area

Table 1 Significantly mutated genes in primary HCC

Gene	Description	Mutation Frequency	Confidence Interval (95%)	# COSMIC Matched	# Recurrence	FDR
TP53	tumor protein p53	35.2% (31)	±10.0%	29	1	0
CTNNB1	catenin (cadherin-associated protein), beta 1, 88kDa	15.9% (14)	±7.6%	12	1	0
JAK1	Janus kinase 1	9.1% (8)	±6.0%	2	2	0.001
AXIN1	axin 1	4.5% (4)	±4.4%	0	0	0.043
EPS15	epidermal growth factor receptor pathway substrate 15	4.5% (4)	±4.4%	0	0	0.043
SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	3.4% (3)	±3.6%	0	0	0.047
CACNA2D4	calcium channel, voltage-dependent, alpha 2/delta subunit 4	5.7% (5)	±4.8%	0	0	0.066
ADCY2	adenylate cyclase 2 (brain)	5.7% (5)	±4.8%	0	0	0.067
LRP1B	low density lipoprotein receptor-related protein 1B	11.4% (10)	±6.6%	0	0	0.073
FAM5C	family with sequence similarity 5, member C	5.7% (5)	±4.8%	0	0	0.077
COL11A1	collagen, type XI, alpha 1	6.8% (6)	±5.3%	0	0	0.093

Kan Z, et al. Genome Res. 2013 Jun 20. [Epub ahead of print]

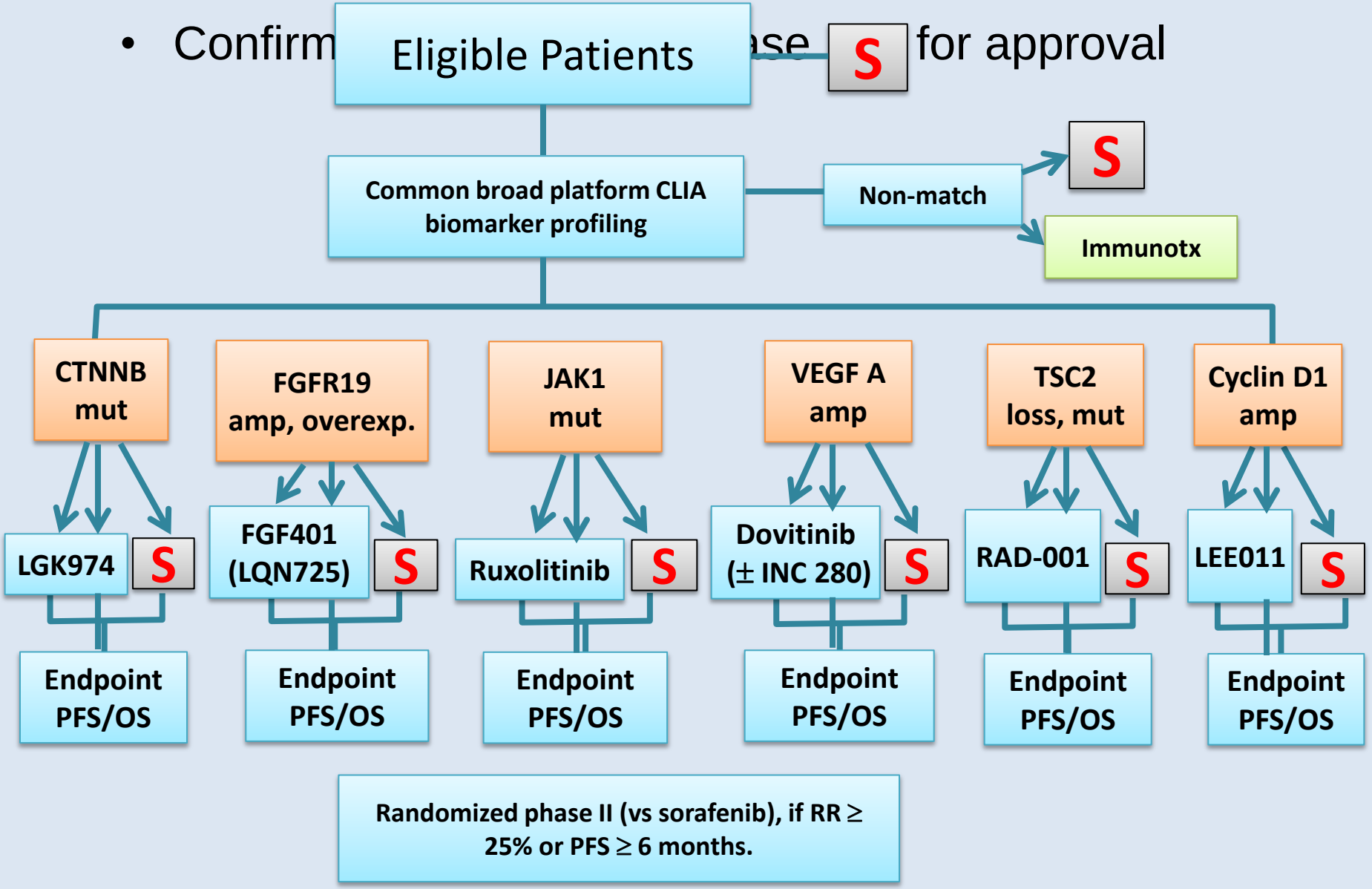
Treatment Selection Based on Detecting Adaptive Immune Resistance



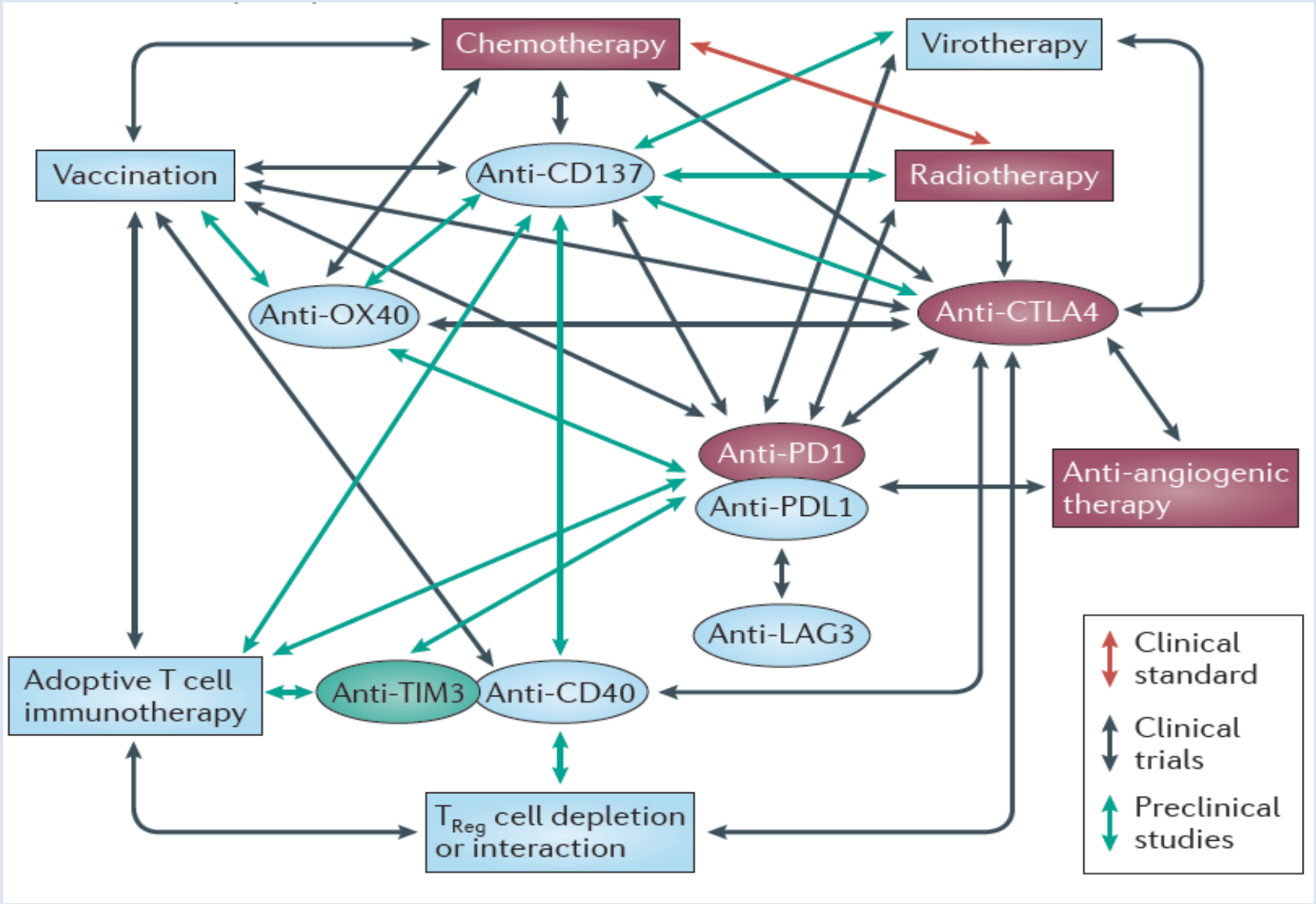
Ribas A *Cancer Discovery 2015;5(9); 915–9.*

Master Protocol for Novartis 1st-line HCC

- Confirm … ase S for approval



Combined Immunotherapy (2015)



Melero I et al. Nat Rev Cancer. 2015 Jul 24;15(8):457-72

Single agent drug X
Go vs. no-go in stage I

Safety

P: subjects without Gr 4 AE
P1: 0.8, P0: 0.6
$\alpha = 0.05, \beta = 0.1$ (optimal)

n1	r1	Probability of No-Go at P0
19	12	0.69

Efficacy

P: subjects with CR/PR
P1: 0.25, P0: 0.1
$\alpha = 0.05, \beta = 0.1$

	n1	r1	n	r	Probability of No-Go at P0
optimal	21	2	66	10	0.65
minimax	31	3	55	9	0.62

PDR001 plus drug X
Go vs. no-go in stage I

Safety

P: subjects without Gr 4 AE
P1: 0.7, P0: 0.5
$\alpha = 0.05, \beta = 0.1$ (optimal)

n1	r1	Probability of No-Go at P0
24	13	0.73

Efficacy

P: subjects with CR/PR
P1: 0.4, P0: 0.2
$\alpha = 0.05, \beta = 0.1$ (minimax)

n1	r1	n	r	Probability of No-Go at P0
24	5	45	13	0.66

Prognostic Immune Markers in HCC

	Good prognosis	Poor prognosis
Intratumoral	CCL2	B7H3
	CCL22	$CD3^+CD56^+$ (↓)
	$CD3^+$	IDO (↓)
	$CD4^+$	iNKT
	IL-6	NKG2D (↓)
	LTA	PDL1
	NCR3	$Tim3^+$
	TNF-α	IFN-γ
	TLR3	$CD15^+$
	TLR4	Tc17
		$PD\text{-}L1^+CD68^+$
Peripheral blood		$CD14^+HLA\text{-}DR^{lo}$ (↑)
		IL-10 (↑)

NOTE: These markers have been shown to correlate with better or poor prognosis in patients with hepatocellular carcinoma.

[a]Prognostic markers, which are increased (↑) or decreased (↓), are marked accordingly.

Greten TF et al, Clin Cancer Res 2013; 19(24); 6678–85.

Immune Markers Changed in HCC

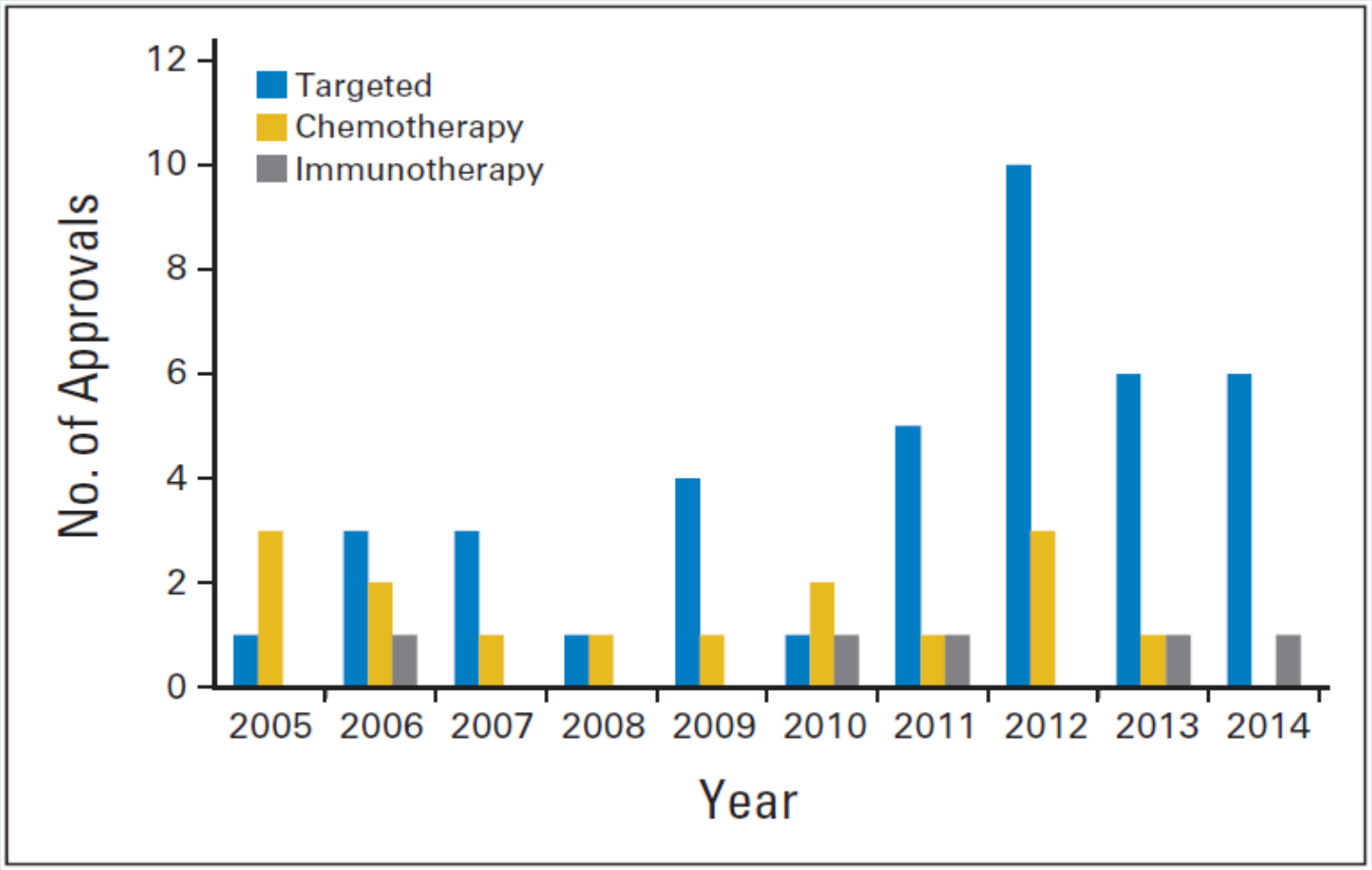
	Elevated	Reduced
Intratumoral	Treg Th17 $PD1^{+}CD8^{+}$	$CD8^{+}$ $CD8^{+}FoxP3^{+}$ γδ T cell $CD56^{dim}CD16^{+}$ NK MHC I CD80/CD86
Peripheral blood	IL-1α, IL-3, IL-6 IL-8, IL-12p40 CCL27, CXCL1, CXCL10 CXCL12, IFN-α2, M-CSF GM-CSF, CXCL9, β-NGF SCF, SCGF-β, TNF-β sCD25, TGF-β $CD11b^{+}CD14^{-}CD33^{+}$ Treg, Th17	$CD1c^{+}Lin^{-}$

NOTE: These markers have been shown to be elevated or reduced in patients with hepatocellular carcinoma in comparison with healthy controls, without known correlation to outcome.

Greten TF et al, Clin Cancer Res 2013; 19(24); 6678–85.

FDA approvals by cancer drug class and year

(2014 is through October)



Masters GA. et al . J Clin Oncol 2015,33:786-809.

Abstract LBA 101

Phase 1/2 Safety and Antitumor Activity of Nivolumab in Patients With Advanced Hepatocellular Carcinoma (HCC): CA209-040

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PRESENTED AT: ASCO Annual '15 Meeting

Treatment-Related Adverse Events

	Total (N=47)		
	Any Grade	Grade 3	Grade 4
Patients with any treatment-related adverse event, n (%)	**32 (68)**	**8 (17)**	**1 (2)**
Treatment-related adverse events reported in ≥5% of patients			
AST increased	9 (19)	5 (11)	0
Lipase increased	8 (17)	3 (6)	1 (2)
Rash	8 (17)	0	0
ALT increased	7 (15)	4 (9)	0
Amylase increased	7 (15)	0	0
Pruritus	6 (13)	0	0
Hypoalbuminemia	4 (9)	0	0
Anemia	3 (6)	1 (2)	0
Fatigue	3 (6)	1 (2)	0
Asthenia	3 (6)	0	0
Diarrhea	3 (6)	0	0
Hyponatremia	3 (6)	0	0

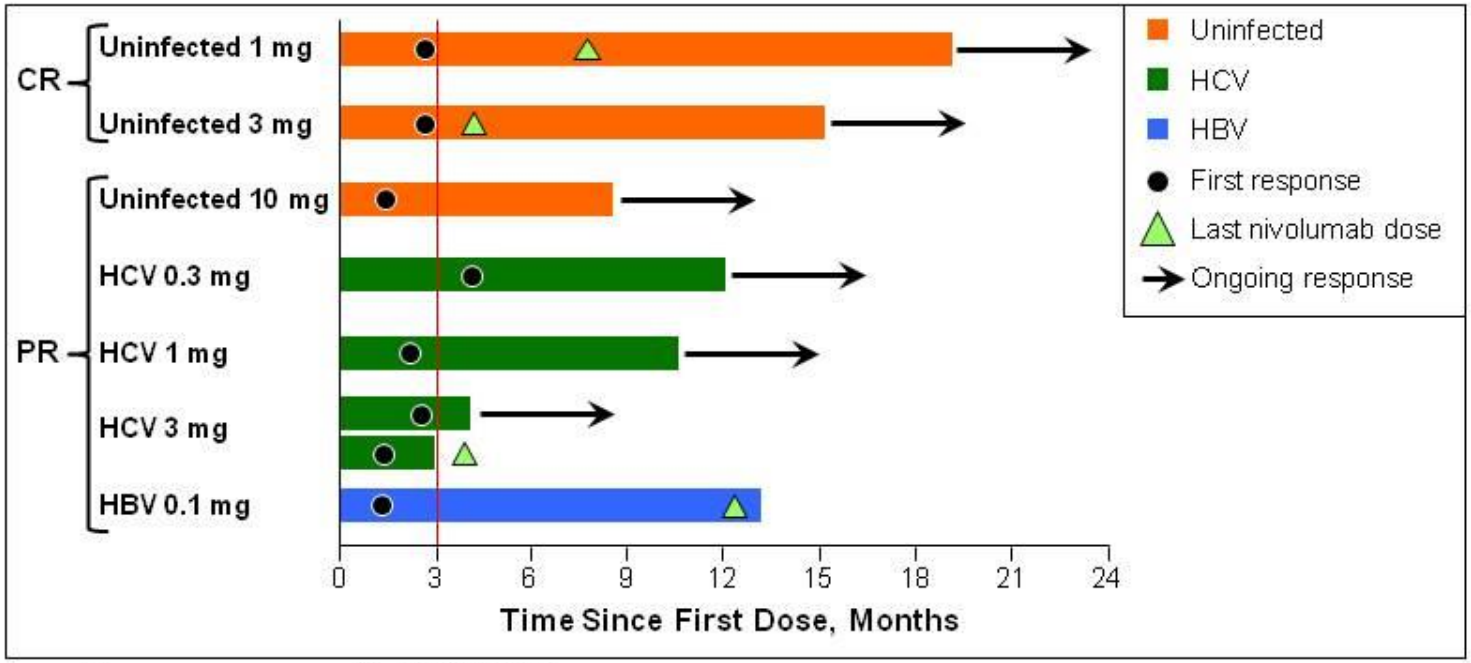
- There were no grade 5 treatment-related AEs

Investigator-Assessed Best Overall Response

	Uninfected (n=21)	HCV (n=11)	HBV (n=10)	Total Evaluable* (n=42)
Objective response, n (%)	3 (14)	4 (36)	1 (10)	8 (19)
Complete response	2 (10)	0	0	2 (5)
Partial response	1 (5)	4 (36)	1 (10)	6 (14)
Stable disease	10 (48)	5 (45)†	5 (50)	20 (48)
Progressive disease	8 (38)	2 (18)	4 (40)	14 (33)
Ongoing response, n (%)	3/3 (100)	3/4 (75)	0	6/8 (75)

Responses assessed by RECIST 1.1
*5 patients not evaluable: first disease assessment not yet performed in 4 patients, 1 patient died from clinical progression before disease assessment
†Patient with resolved HCV infection

Time to and Durability of Response



- 7/8 patients responded within 3 months of beginning treatment
- Responses ongoing in 6/8 patients, including 2 patients who discontinued treatment due to CR

Responses assessed by RECIST 1.1

Immunotherapy for hepato-biliary cancers

Anti-PD1 therapy and beyond

Anti-PD1 for advanced hepatocellular carcinoma (HCC)

- **Nivolumab** 0.1-10 mg/kg every 2 weeks
- Progression/intolerance/refusal to sorafenib
  - 3 cohorts: un-infected, HBV (+), HCV (+)
- 2 CR (5%), 6 PR (15%) in 39 evaluated patients
  - un-infected (21) 2 CR/ 1 PR
  - HBV (+) (10) 1 PR
  - HCV (+) (11) 4 PR
- 12-month overall survival: 62%.

- El-Khoueiry AB, et al. J Clin Oncol 33, 2015 (suppl; abstr LBA101)

Anti-PD1 for advanced biliary tract carcinoma (BTC)

- **Pembrolizumab** 10 mg/kg every 2 weeks
- Progression/intolerance to standard systemic therapy
- PD-L1 (+)
  - ≥1% of cells in tumor and stroma
  - QualTek IHC assay, 22C3 antibody clone (Merck)
- 37 of 89 (42%) patients screened were PD-L1-(+); 24 (65%) enrolled.
- ORR (confirmed and unconfirmed): 17% (95%CI, 5%-39%)
  - 0 CR, 4 PR, 4 SD

- Bang YJ, et al. ESMO 2015, P259

Future trials of anti-PD1/anti-PD-L1 therapy for HCC

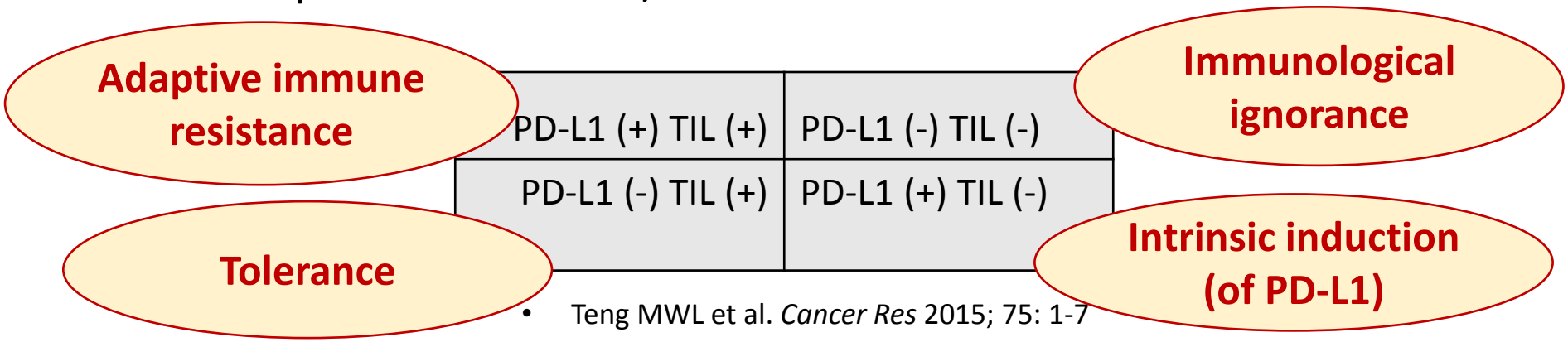
- **Advanced stage disease**
  - First-line:
    - Head-to-head comparison of anti-PD1/anti-PD-L1 with sorafenib
  - Second-line:
    - Head-to-head comparison of anti-PD1/anti-PD-L1 with placebo
    - Exploration of anti-PD1/ anti-PD-L1 based combination
      - NCT02519348 (MEDI4736 + tremelimumab)
- **Early/ Intermediate stage disease**
  - Combination with ablation therapy/TACE

Future trials of immunotherapy for BTC

- **Recurrent/metastatic disease**
  - First-line:
    - Combination of anti-PD1/anti-PD-L1 with chemotherapy
      - NCT02268825 (pembrolizumab + FOLFOX)
  - Second-line:
    - Head-to-head comparison of anti-PD1/anti-PD-L1 with placebo
    - Exploration of anti-PD1/ anti-PD-L1 based combination
      - NCT01938612 (MEDI4736 +/- tremelimumab)
- **Post surgical therapy**
  - Combination with adjuvant chemoradiation (for margin (+) or LN (+) diseases)

Potential predictive biomarkers for anti-PD-1/ anti-PD-L1 therapy

- PD-L1 expression in tumor/immune cells



- Teng MWL et al. *Cancer Res* 2015; 75: 1-7

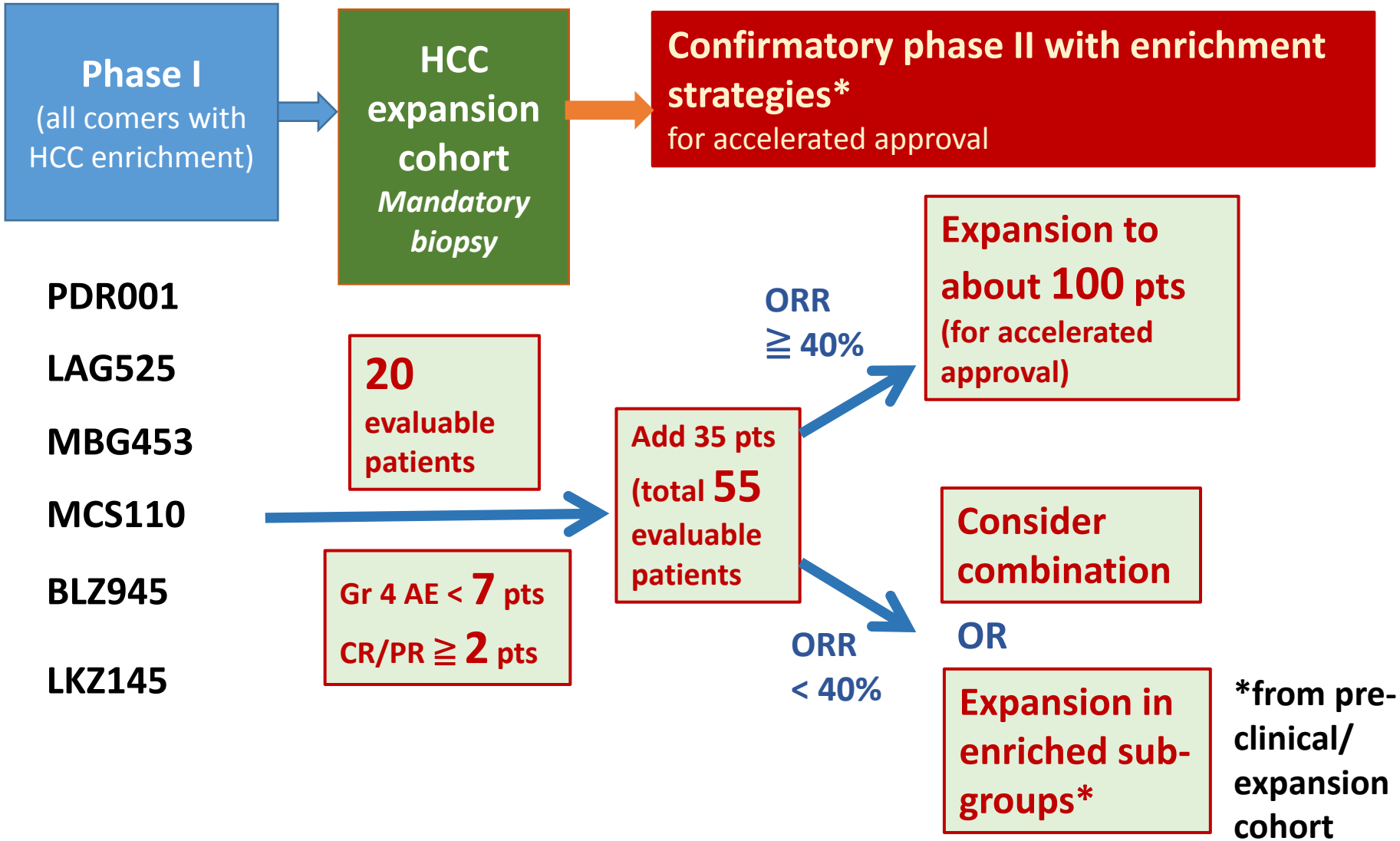
- The potential roles of PD-L2?
  - Yearley J et al. ESMO 2015 (
- Other immune cells in the micro-environment
  - TAM, MDSC
- Mutational loads
  - Melanoma, lung cancers, MMR deficient cancers
- Host immune response
  - Cytokines, No./function of T cell subpopulations
- Incorporation of genomic and immune profiling studies

Combination with other immune modulatory agents

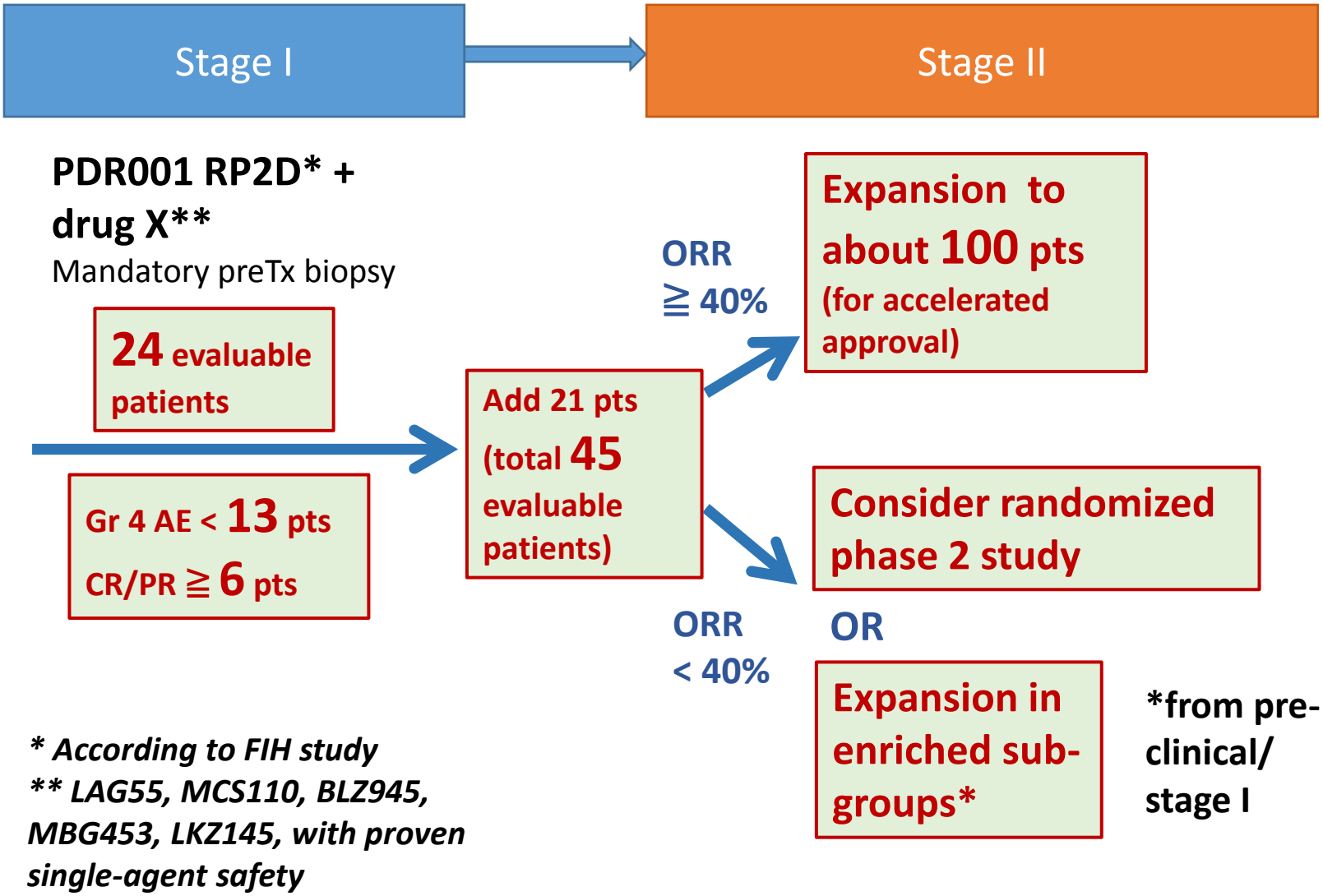
- **For TILs (+) tumors**
  - Combined with other checkpoint inhibitors (anti-LAG3, anti-TIM3, etc.)
  - Combined with co-stimulator agonists
  - Combined with inhibitors of TAM/MDSC (e.g., CSF-1Ri)
- **For TILs (-) tumors**
  - Combined with anti-CTLA4
  - Induction of immunogenic cell death (RT, chemo, MTT, etc.)
  - Improve T cell trafficking (e.g., anti-angiogenic)
  - CART
  - In situ vaccination

Back-up

Immunotherapy for advanced HCC (1): single agent

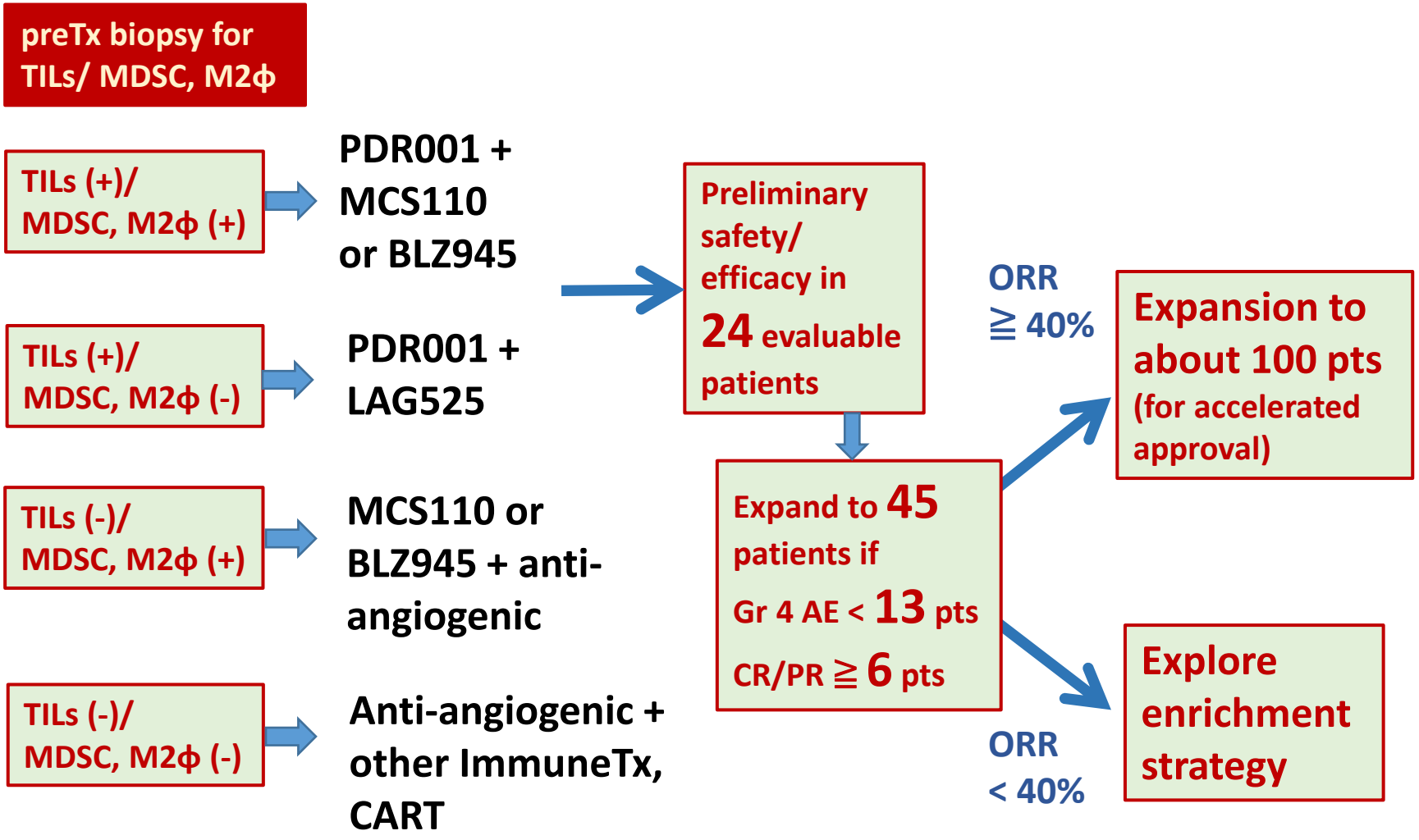


Immunotherapy for advanced HCC (2): PDR001 plus drug X combinations



** According to FIH study*
*** LAG55, MCS110, BLZ945, MBG453, LKZ145, with proven single-agent safety*

A ‘cluster’ protocol of immunotherapy for HCC



Potential partners of PDR001 (anti-PD1)

Drug/ MoA	Pre-clinical synergy with anti-PD1	HCC pre-clinical studies	Human studies	Human HCC studies
Tremelimumab/ anti-CTLA4	Yes	Yes	Yes	Yes
LAG525/ anti-LAG3	Yes [1]	Yes [2]	Ongoing	No
MBG453/ anti-TIM3	Yes [3]	Yes [4*]	Planned	No
LKZ145/ GITR agonist	Yes [5]	No	No	No
MCS110/ anti-CSF-1	No	Yes [6]	Ongoing	No
STING/ in situ vaccine	No	No	Planned	No
Istradefylline/ A2aR antagonist	Yes [7,8]	No	On market (Japan)	No

Strategies of Immunotherapy for Solid Tumors

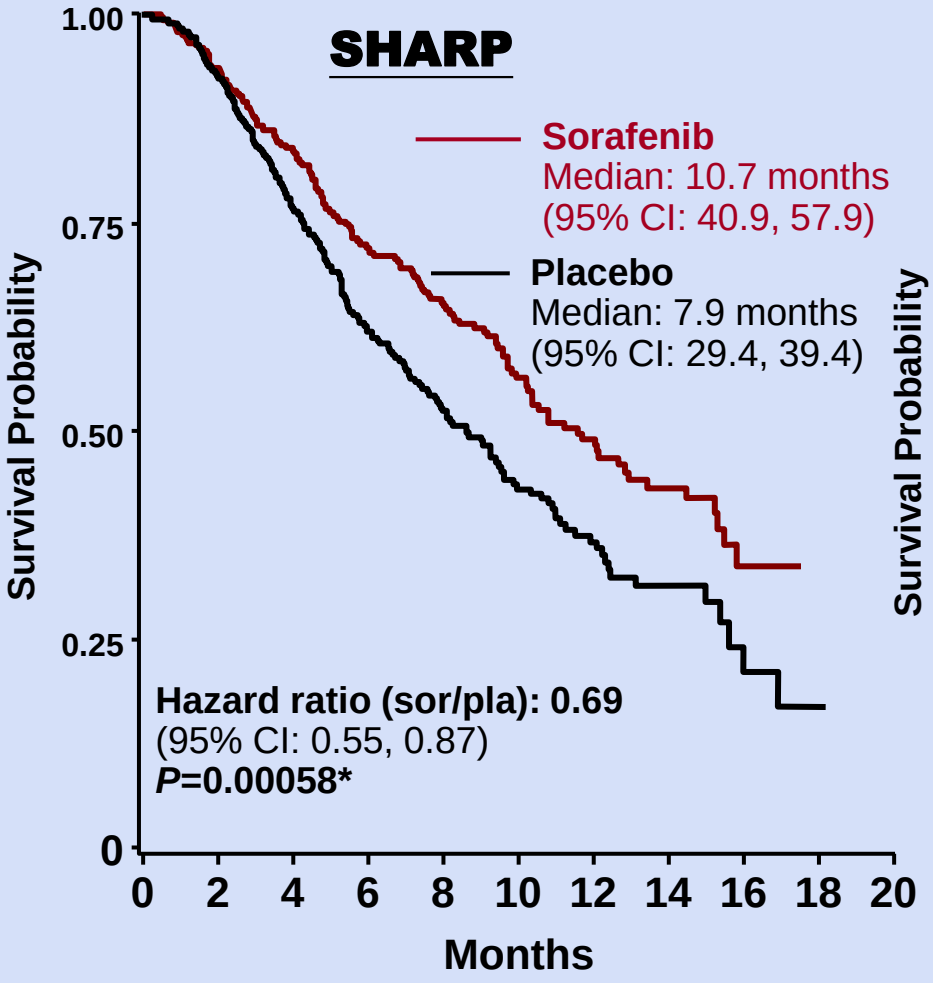
- **TIL abundance (+)**

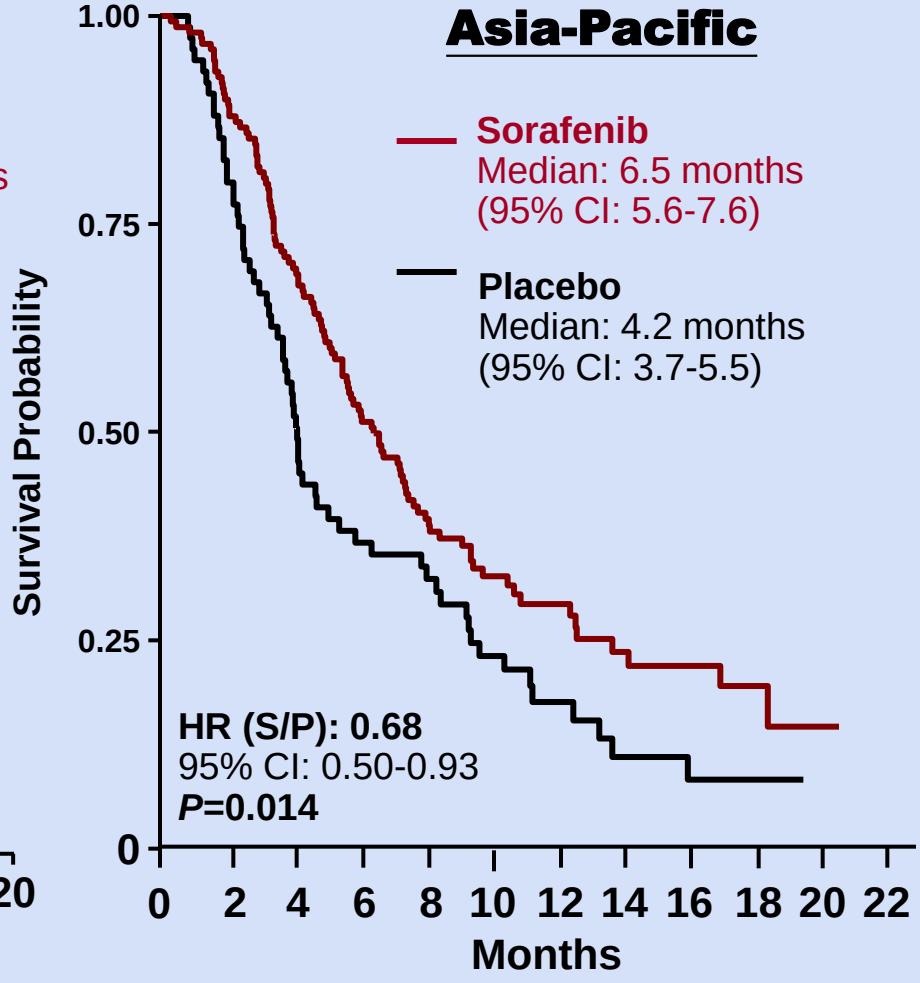
1. Single immune checkpoint inhibitor
2. Combination of immune checkpoint inhibitors
3. Immune checkpoint inhibitor + costimulatory receptor activator
4. Immune checkpoint inhibitor + innate immunity modulator

- **TIL abundance (-)**

1. CAR T cells
2. Vaccine
3. Oncolytic virus
4. Immune checkpoint inhibitor + VEGF/VEGFR inhibitor
5. Innate immunity modulator ± immune checkpoint inhibitor

Phase III SHARP and Asia-Pacific
Overall Survival





Llovet JM, et al. N Engl J Med 2008:359:378-90

Cheng AL, et al. Lancet Oncol 2009;10:25-34.

ASCO 2011

Phase 3 Trial of Sun… orafenib in Advanc… …noma

A-L Cheng,[1] Y-K Kan… …,[5] S Qin,[6]
M Omata,[7] S Pitman Lowen… MJ Lechuga,[9]
E Raymond[10] for th… …oup

[1]National Taiwan University Hospital, Taipei, Taiwan… …of Korea; [3]Chang Gung Memorial Hospital, Chang Gung University, Taiwa… …ncer Center, Goyang, Republic of Korea; [5]Kinki University Hospital, Os… …ing, Jiangsu, China; [7]Yamanashi Prefecture Central Hospital, Kofu, Ya… …lla, California, USA; [9]Pfizer Italia Srl, Milan, Italy; [10]Service Inter H… …n, Clichy, France

- Sunitinib
- Brivanib
- Vandetanib
- Nintedanib
- Dovitinib
- Axitinib
- Orantinib
- Anti-Glypican 3
- Tigatuzumab
- Lenvatinib
- Regorafenib
- ……

8 Years On - - -

- Results of SHARP was presented in June 2007. Sorafenib was approved by FDA (Dec. 2007) and EMEA (Oct. 2007).
- Up to 80 other compounds have been tested in more than 190 trials. None has succeeded.

Drug Dev

Multi-targeted

sorafenib, sun
linifanib

Linifanib Versus Sorafenib in Patients With Advanced HCC: Results of a Randomized Phase III Trial

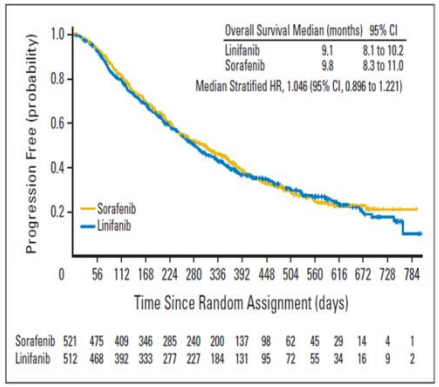


Fig 2. Kaplan-Meier analysis of overall survival with a cutoff point at the 667th patient death. HR, hazard ratio.

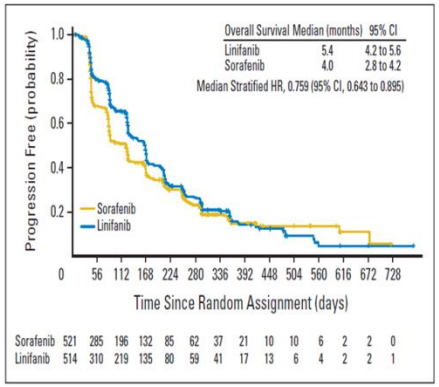


Fig 4. Kaplan-Meier analysis of time to progression. HR, hazard ratio.

Cainap C, et al. J Clin Oncol 2015; 33:172-179

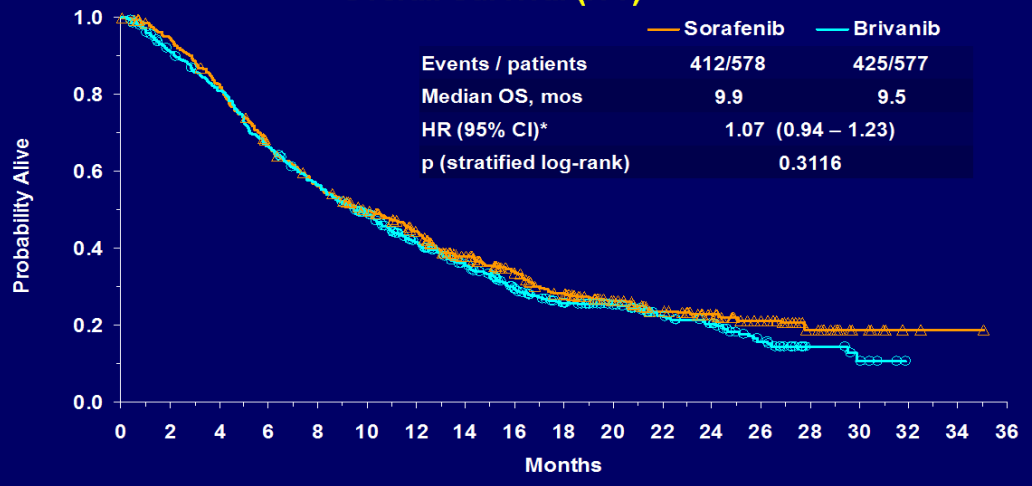
Phase III, R … S …

	Briva… (n = 2…
Median OS	9.4 n…
Median TTP*	4.2 n…
DCR*	71.2…
ORR*	11.5…

CI, confidence interval; HR …
*Modified RECIST for HCC
‡Cochran-Mantel-Haenszel …

Phase III, …

Overall Survival (ITT)



*HR (95% CI) for per-protocol population (575 patients in each arm) was 1.06 (0.93-1.22)

BMS Highly Confidential - Not for Distribution

Johnson P et al. J Clin Oncol. 2013 Oct 1;31(28):3517-24

… CI: 7.4–9.2)
… CI: 8.9–11.4)
…50)
35 40
…al; HR: hazard ratio
…c ASCO 2011, #4000

Two Groups of Front-runners

EOLVE-1 (Phase III, Placebo-controlled, 2nd-line) failed to meet its primary end point (OS)

3. mTOR inhibitors

Drug Development for HCC (2010-2015)

FGFR inhibitors

anti-angiogenic TKI

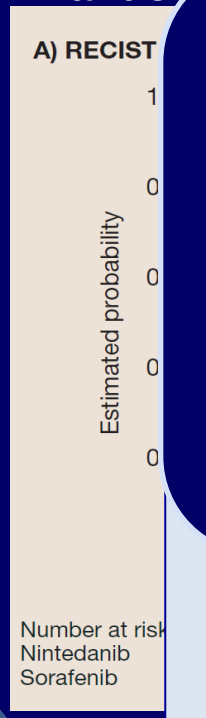
sorafenib, sunitinib, vandetanib, linifanab, brivanib, nintedanib, dovitinib, orantinib, lenvatinib, [illegible] axitinib

Phase II TAC

Novel cat

mTORi, M PI3K/Akt inhibitors anti-PD1, A3 adenc

Random



Did not meet primary end point in the randomized phase II study, 1st line vs sorafenib

Cheng AL et al, ASCO-GI 2015

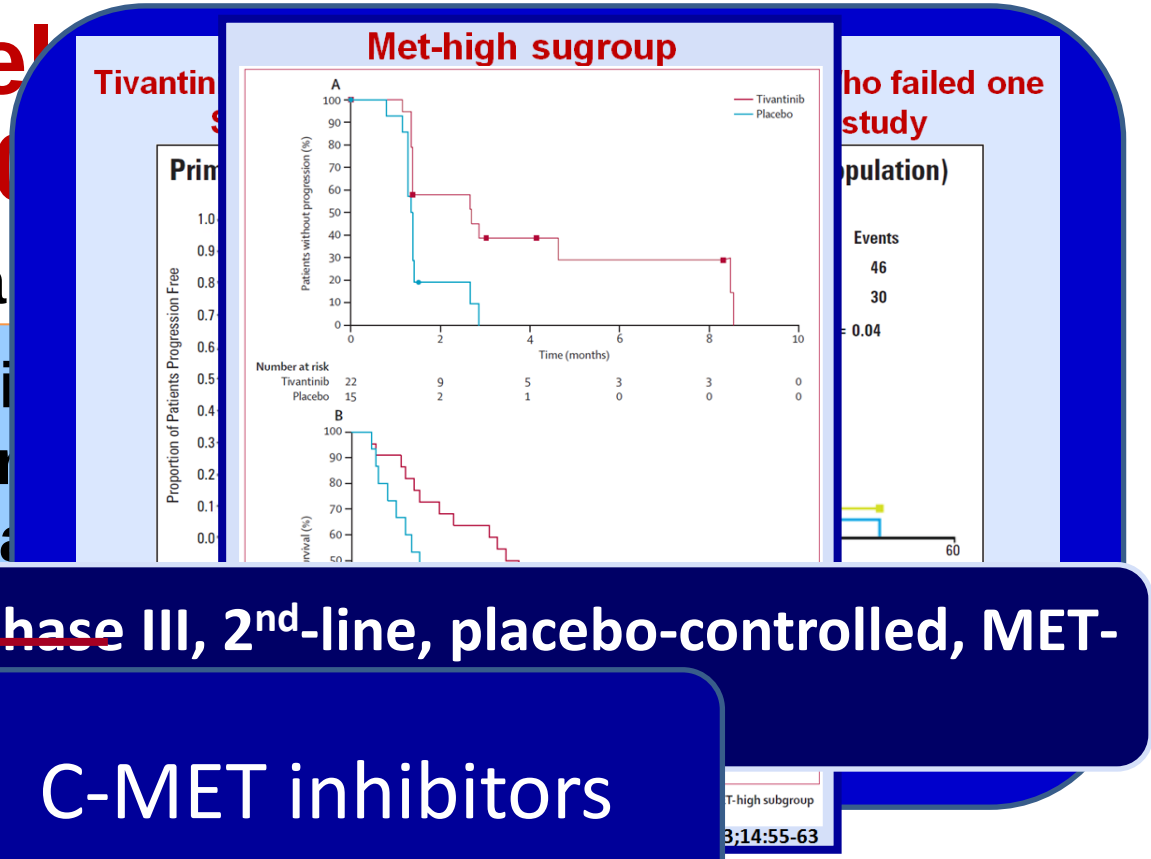
Bruix J et al. Eur J Cancer 49 (2013) 3412–3419

Yen CJ et al ECCO/ESMO 2013

Drug Devel
(20

Multi-targeted a

sorafenib, suni
linifanib, brivar
orantinib, lenva
apatinib, for



Phase III, 2nd-line, placebo-controlled, MET-

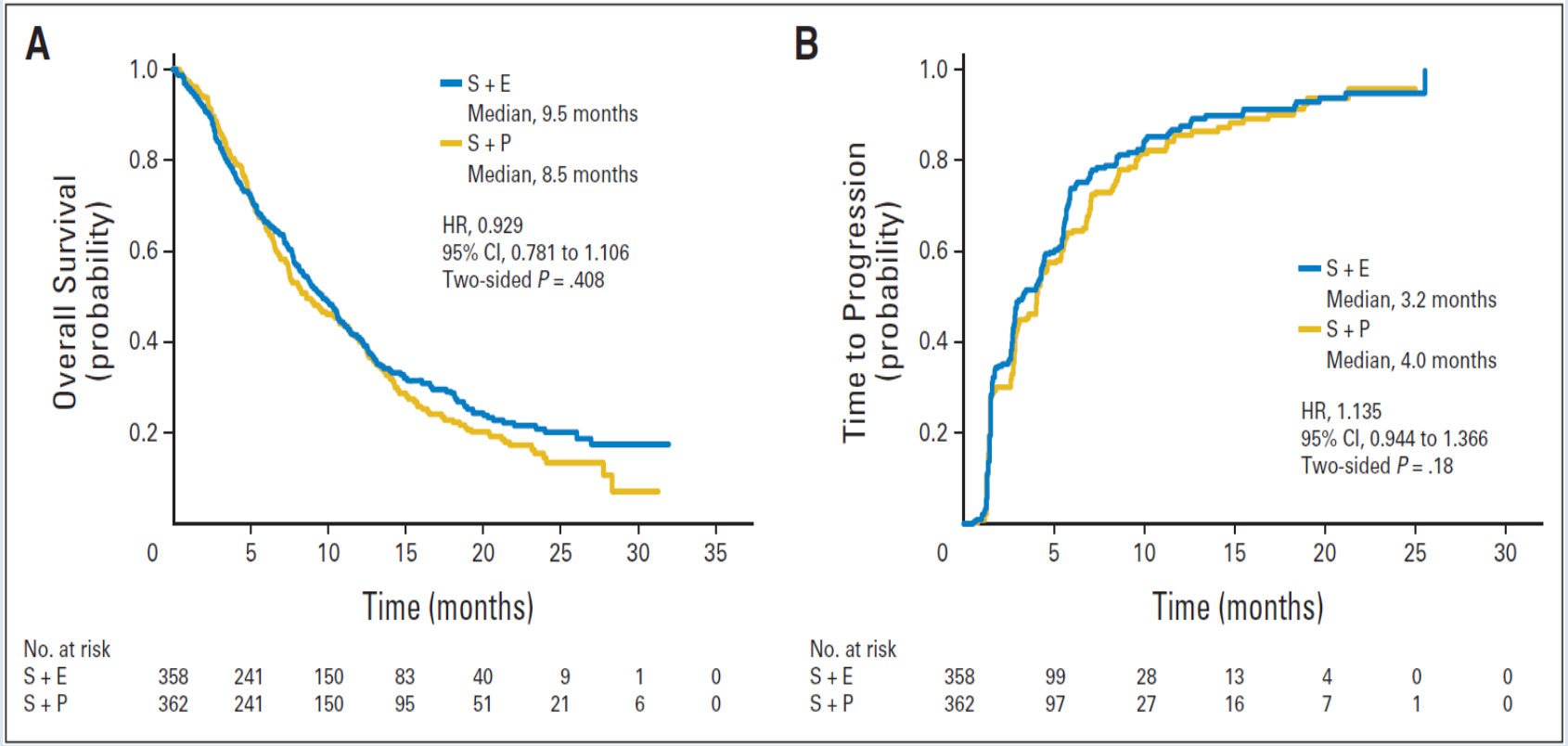
Phase III, 2nd-line,

C-MET inhibitors

- ≦1 systemic Tx (51% sorafenib)
- Cabozantinib 100 mg/day x12 wks, lead-in.
- 2/36 PR (RR=5%, DCR=68%) at lead-in.
- One more PR after randomization.

Verslype C et al Proc. ASCO 2012;#4007

SEARCH: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Sorafenib Plus Erlotinib in Patients With Advanced HCC



Zhu A X. et al J Clin Oncol 2015;33:559-566

Why MTT fails in HCC ?

- New drugs for HCC have not shown significant activity. Phase II results were not solid enough to support Phase III trials.

- Failed to enrich biomarker subgroups for drug testing.

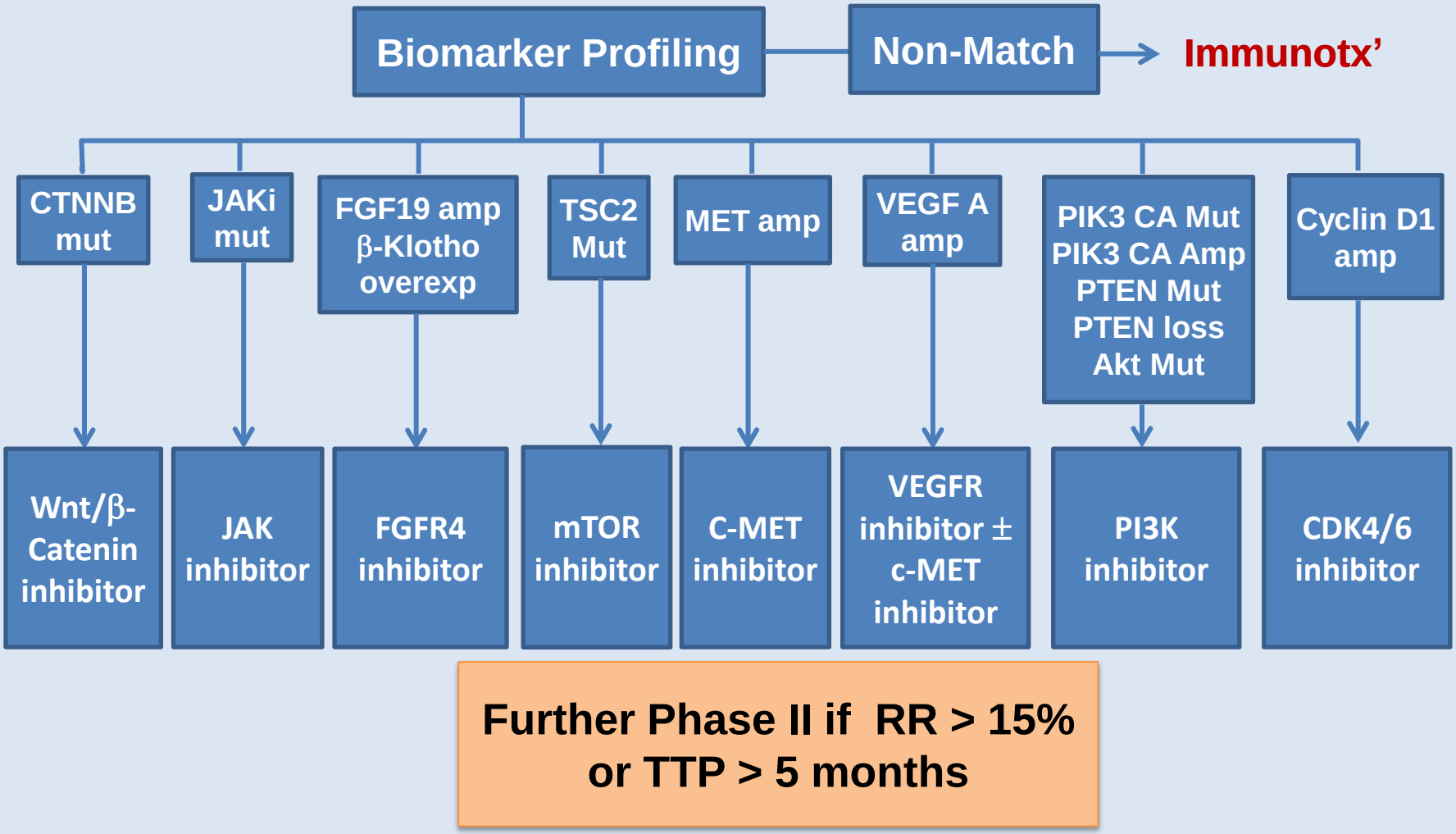
Basic Problems of Biomarker-Driven Clinical Trials in HCC

- Diagnosis of HCC does not routinely require histopathology. Biopsy is not without any risk.

Testing one drug for one biomarker at one time is painstaking, costly, and frustrating to patients and investigators.

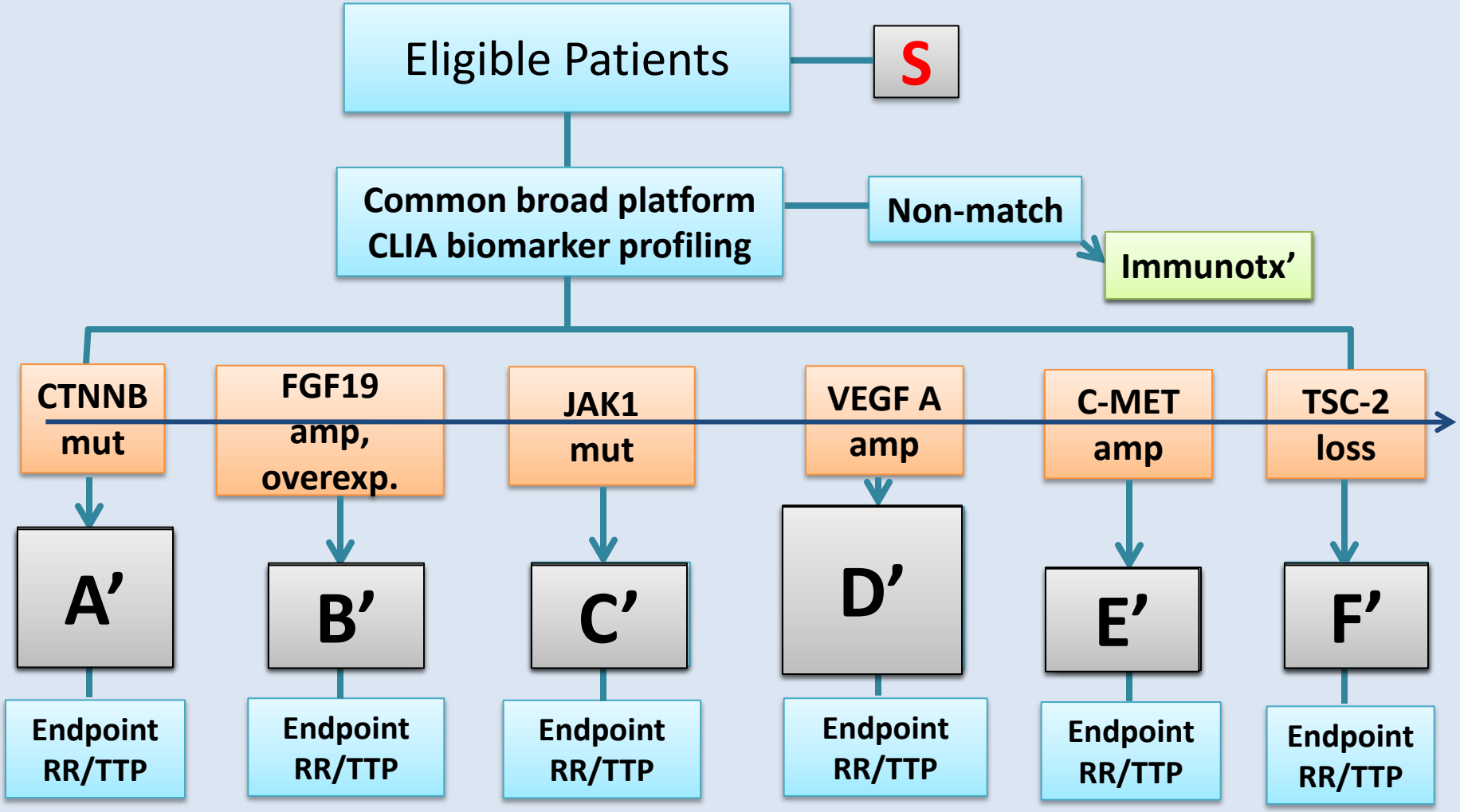
Master Protocol for 2nd-line HCC

- Exploratory, single-arm



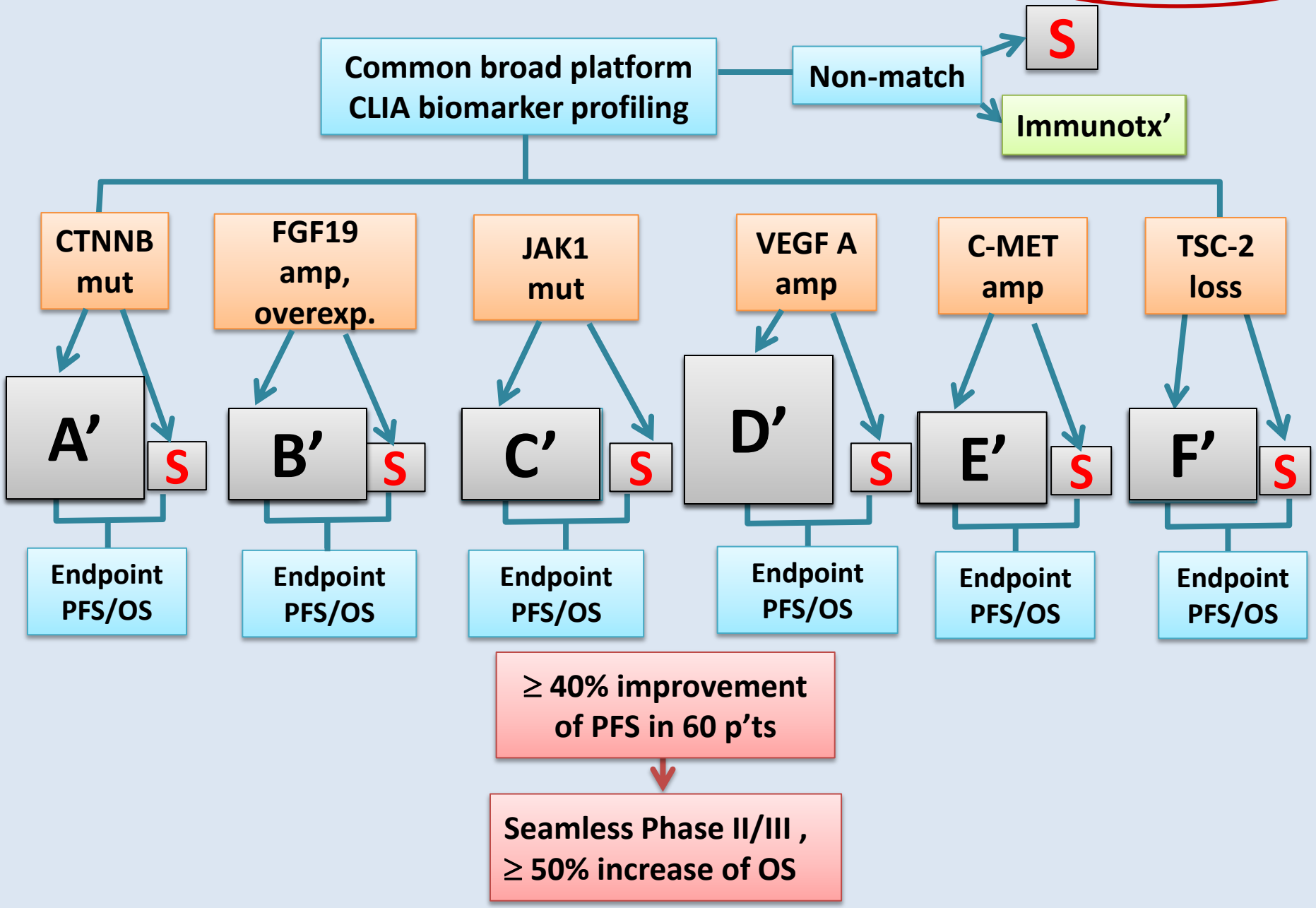
Further Phase II if RR > 15% or TTP > 5 months

Master Protocol for 1st-line HCC – Adaptive, Exploratory



Randomized phase II (vs sorafenib), if RR ≥ 25% or TTP ≥ 6 months.

Master Protocol for 1st-line HCC – Adaptive, confirmatory



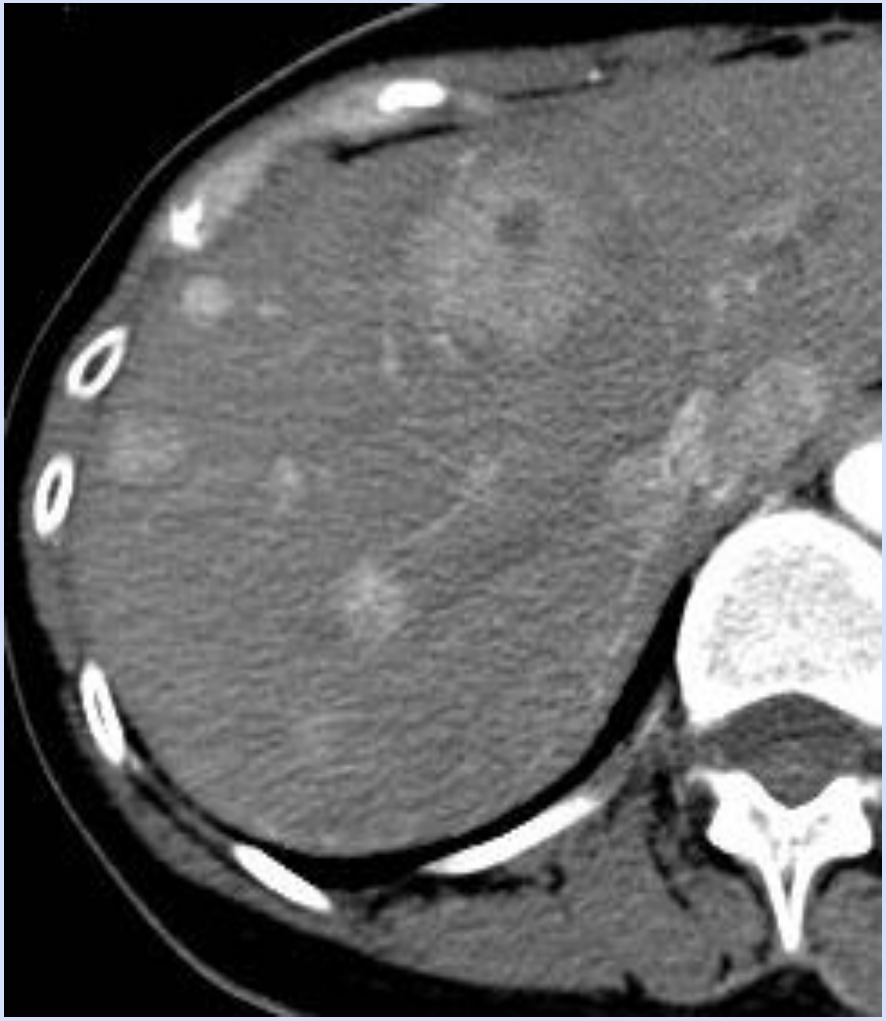
Determine Molecular Subtypes for HCC – a daunting task

Clonality of Primary and Recurrent HCC

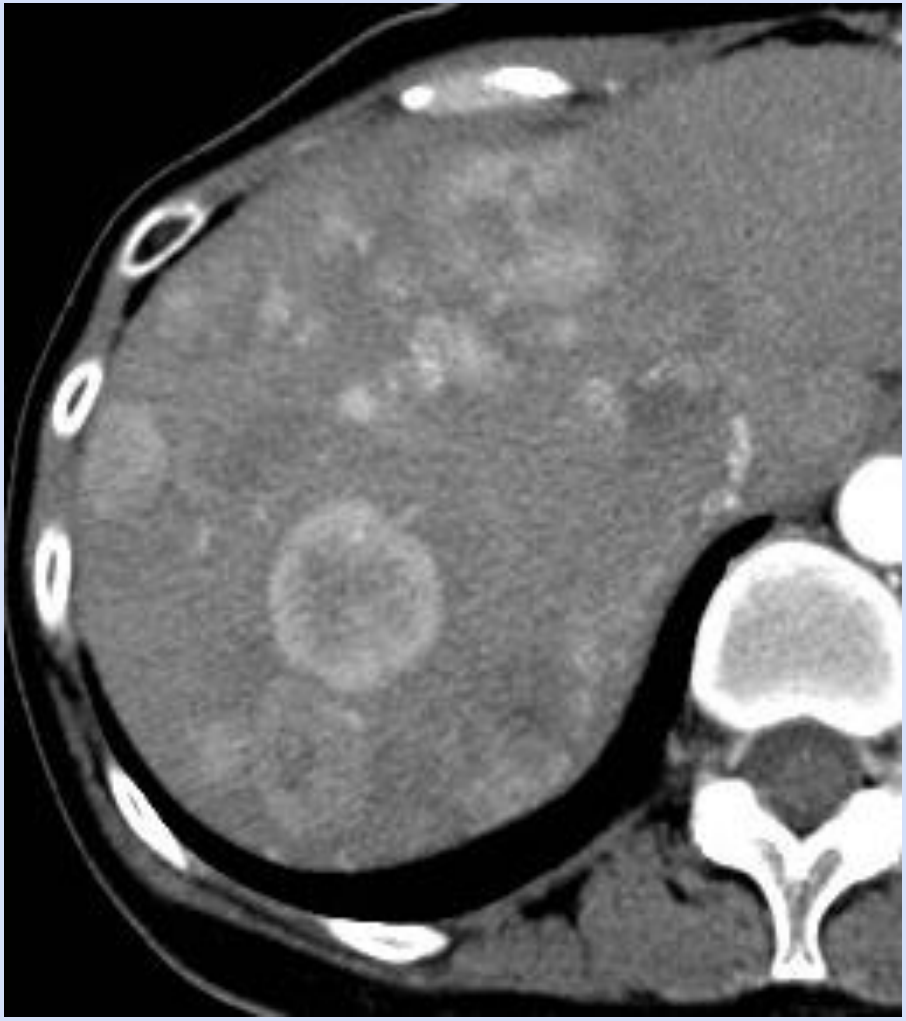
Year/Country/Journal	Methods	Different Clonality	Etiology
1989 / Taiwan/ Gastroenterology[2]	Integrated HBV DNA (Southern blot analysis)	3/5 (60%)	HBV
1992 / Japan/ Clin Exp Metastasis[10]	DNA ploidy (microspectrophotometry)	11/25 (44%); Lung mets	unknown
2000/ Taiwan/ Gastroenterology[11]	CGH + Integrated HBV DNA	13/31 (42%)	HBV in 19
2003/ Japan/ J Hepatol[7]	LOH of 15 MSI (>30%)	10/19 (53%)	unknown
2008/ China/ J Gastrointest Surg[12]	LOH + MSI	48/160 (30%)	HBV

Lu LC et al, 2014

Clonality of Co-existing Multifocal Hepatic Tumors ?



Baseline



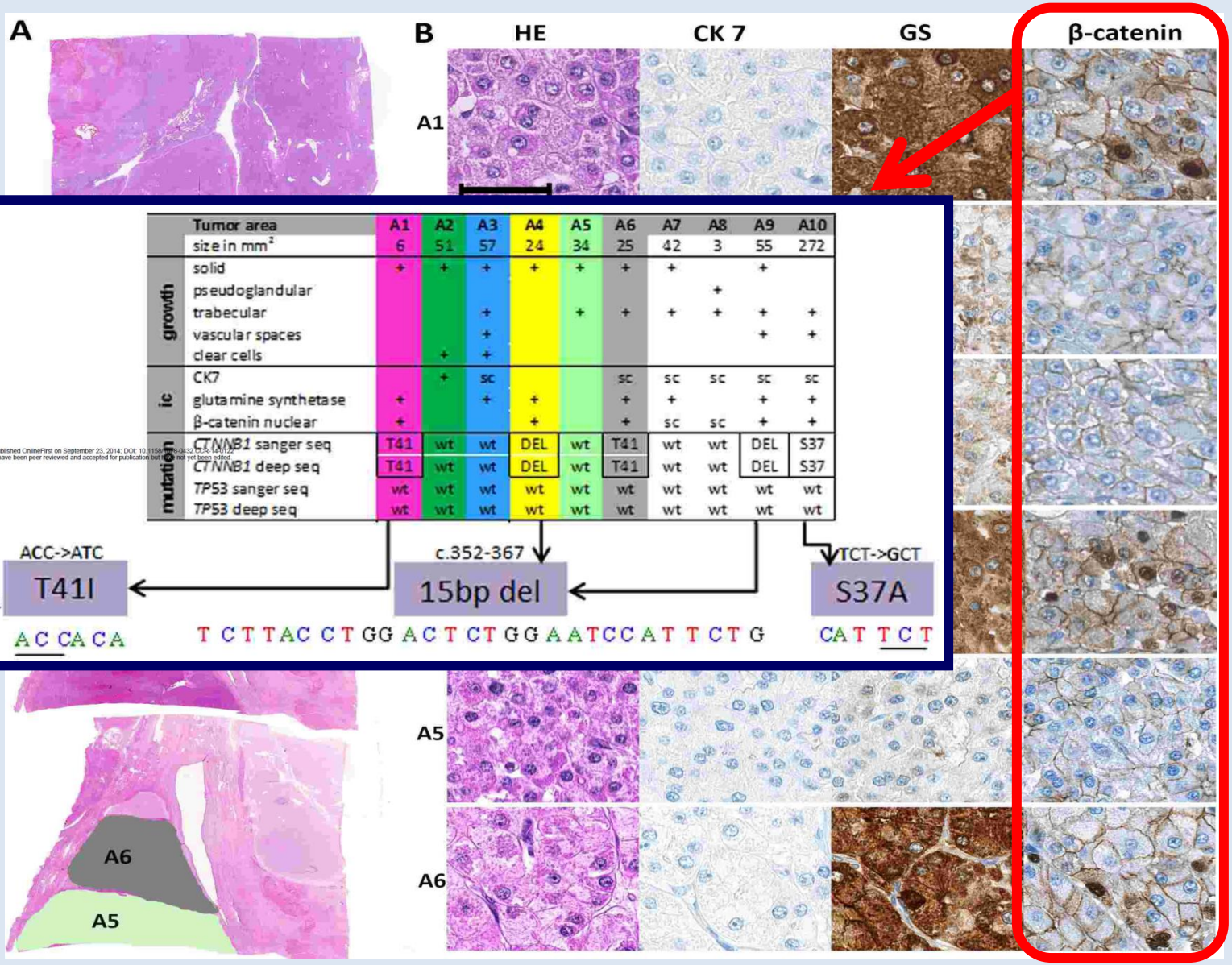
After 3 months

Clonality of Multifocal HCC

Year/Country/Journal	Methods	Different Clonality	Etiology
1987 / Taiwan/ Liver[1]	DNA ploidy (Feulgen analysis)	4/14 (29%)	HBV predominant
1989 / Taiwan/ Gastroenterology[2]	DNA fingerprint/ Integrated HBV DNA	11/18 (61%)	HBV in 9
1991 / Taiwan/ Hepatol[3]	Integrated HBV DNA (Southern blot analysis)	16/28 (57%)	HBV
1999/ UK/ Gut[4]	DNA fingerprint/AP-PCR	13/13 (100%)	unknown
2002/ Hong Kong/ Cancer Res[5]	cDNA array + p53 + HBV integration	2/6 (33%)	HBV
2003/ Hong Kong/ J Pathol[6]	DNA fingerprint/ LOH +CGH + HBV integration	4/11 (36%)	HBV in 10
2003/ Japan/ J Hepatol[7]	LOH of 15 MSI (>30%)	2/9 (22%)	unknown
2005/ Taiwan/ J Gastroenterol Hepatol[8]	LOH	8/16 (50%)	HBV in 11
2007/ Japan/ Br J Cancer[9]	Promoter hypermethylation	15/19 (79%)	HCV in 13

Lu LC et al, 2014

Intratumor Heterogeneity in HCC



Author Manuscript Published OnlineFirst on September 23, 2014; DOI: 10.1158/1078-0432.CCR-14-1122
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Friemel J, et al. Clin Cancer Res. 2014 Sep 23.[Epub ahead of print]

Intratumor Heterogeneity of HCC

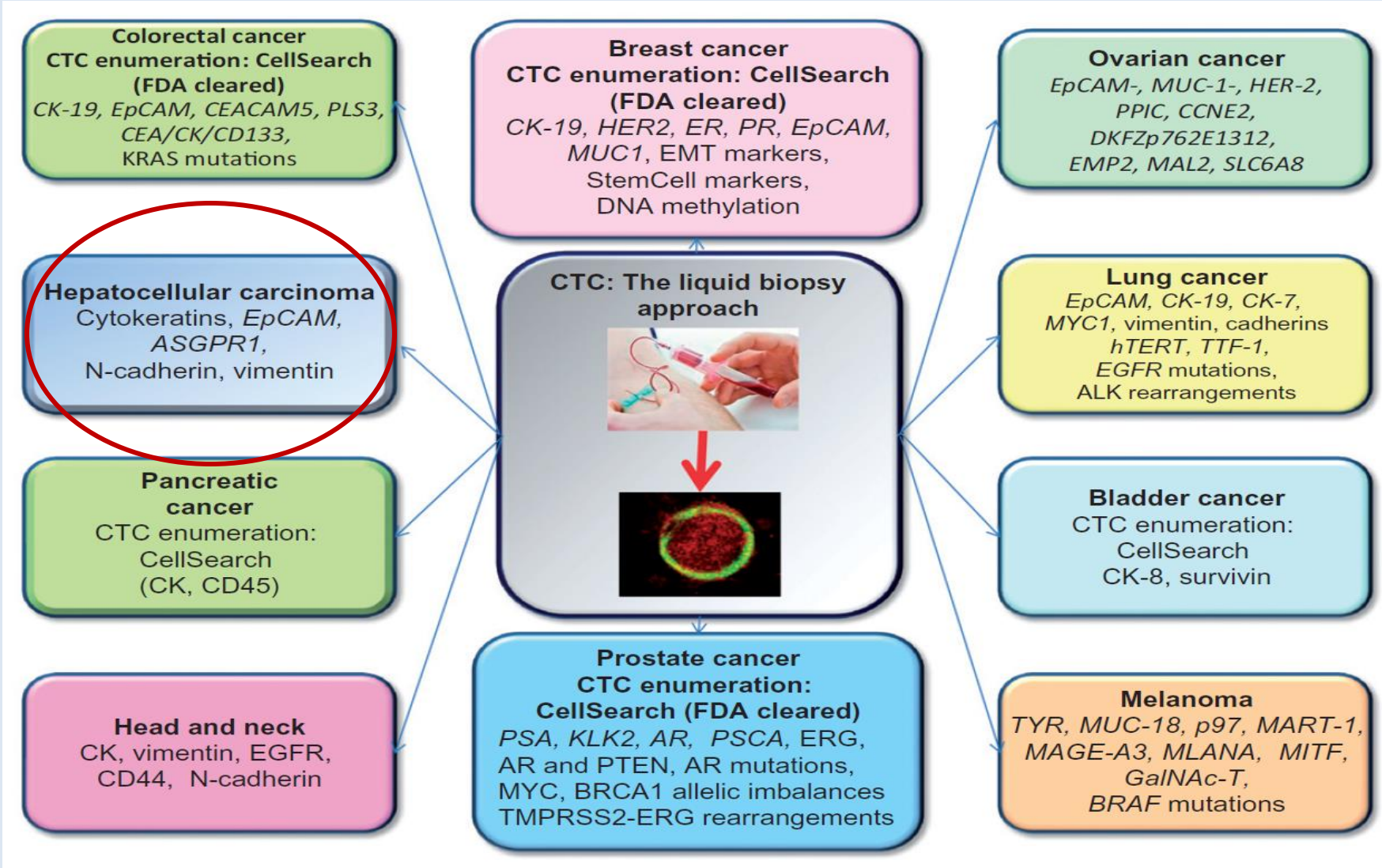
Year/Country/Journal	Methods	Different Clonality	Etiology
1987 / Taiwan/ Liver[1]	DNA ploidy (Feulgen analysis)	2/17 (12 %)	HBV predominant
2003/ Japan/ J Hepatol[7]	LOH of 15 MSI (>30%)	1/7 (14%)	unknown
1995/ Japan/ Cancer[13]	DNA ploidy/ flow cytometry	7/28 (25%)	Alcohol in 9
1998/ Japan/ J Hepatol[14]	DNA ploidy/ flow cytometry	9/20 (45%)	HCV in 12 HBV in 10
2000/ Japan/ J Hepatol[15]	Restriction Landmark Genomic Scanning	4/6 (66%)	HCV in 5
2001/ Japan/ Int J Cancer[16]	Histology	14/41 (34%)	HCV predominant
2014/ Switzerland/ Clin Cancer Res[17]	Histology + IHC + p53/ β-catenin mutations	5/23 (22%)	mixed

Lu LC et al, 2014

Determining Molecular Subtypes for a Tumor with Extreme Tumor Heterogeneity

– Are their solutions ?

CTC analysis and molecular characterization in various types of solid cancers

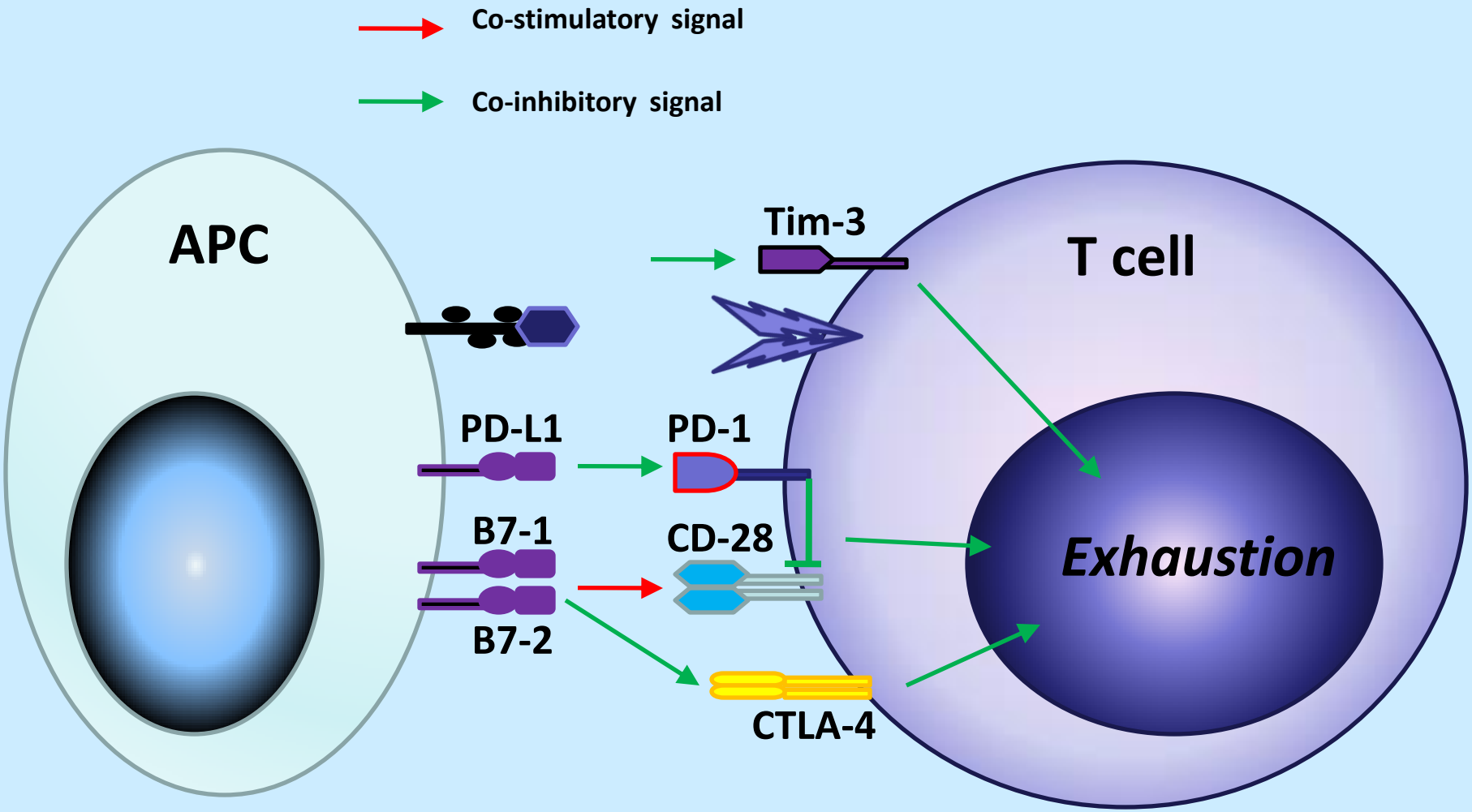


Lianidou E.S., et al. Crit Rev Clin Lab Sci, 2014;51(3): 160-17

Determining Molecular Subtypes for a Tumor with Extreme Tumor Heterogeneity

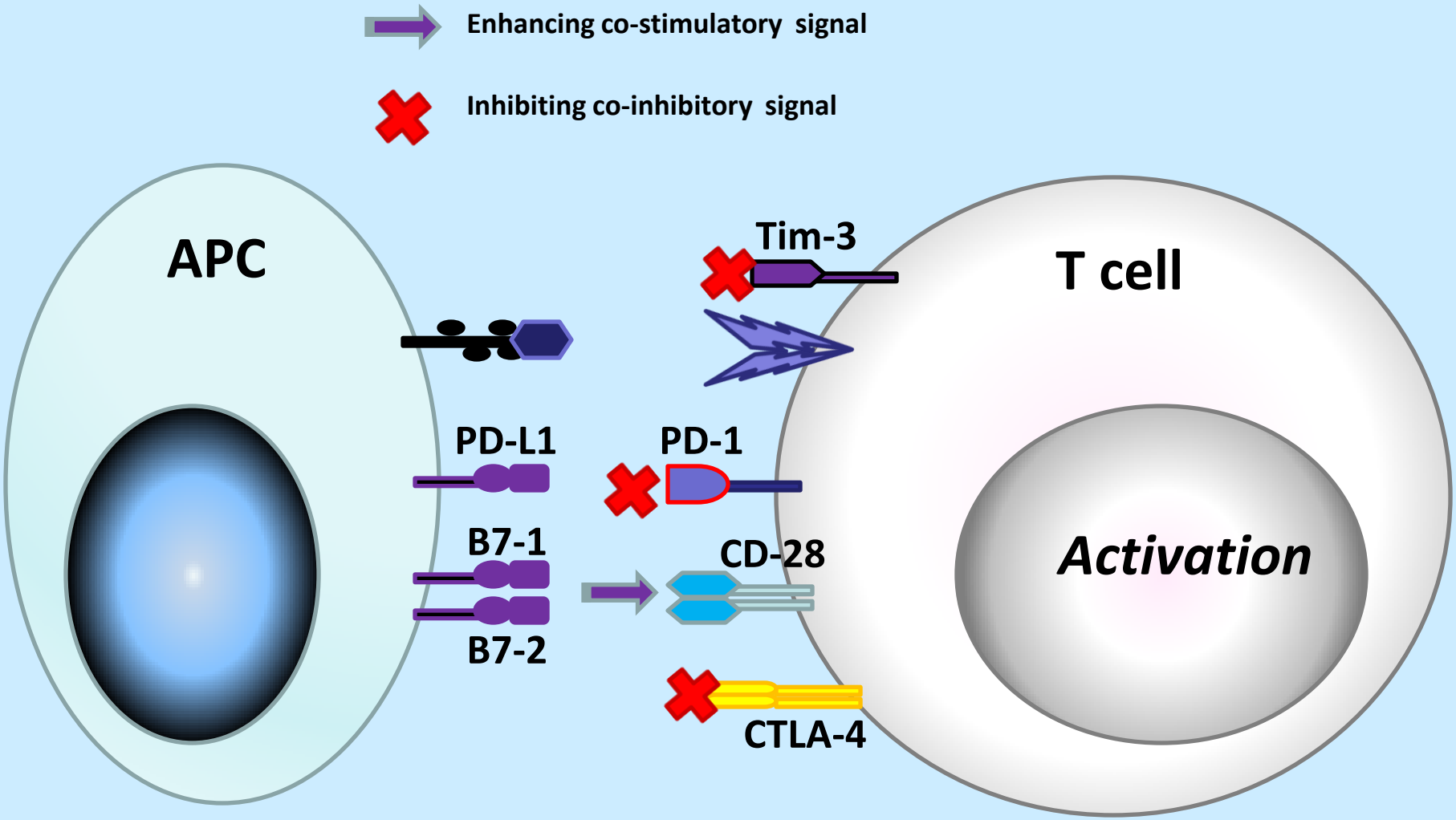
– Are their solutions ?

T cell dysfunction in cancers



Modified from Watanabe T, et al. *J Viral Hepat* 2010

Restoring T cell function in cancers



Modified from Watanabe T, et al. *J Viral Hepat* 2010

Nivolumab (anti-PD1) plus Ipilimumab (anti-CTLA4) in Advanced Melanoma

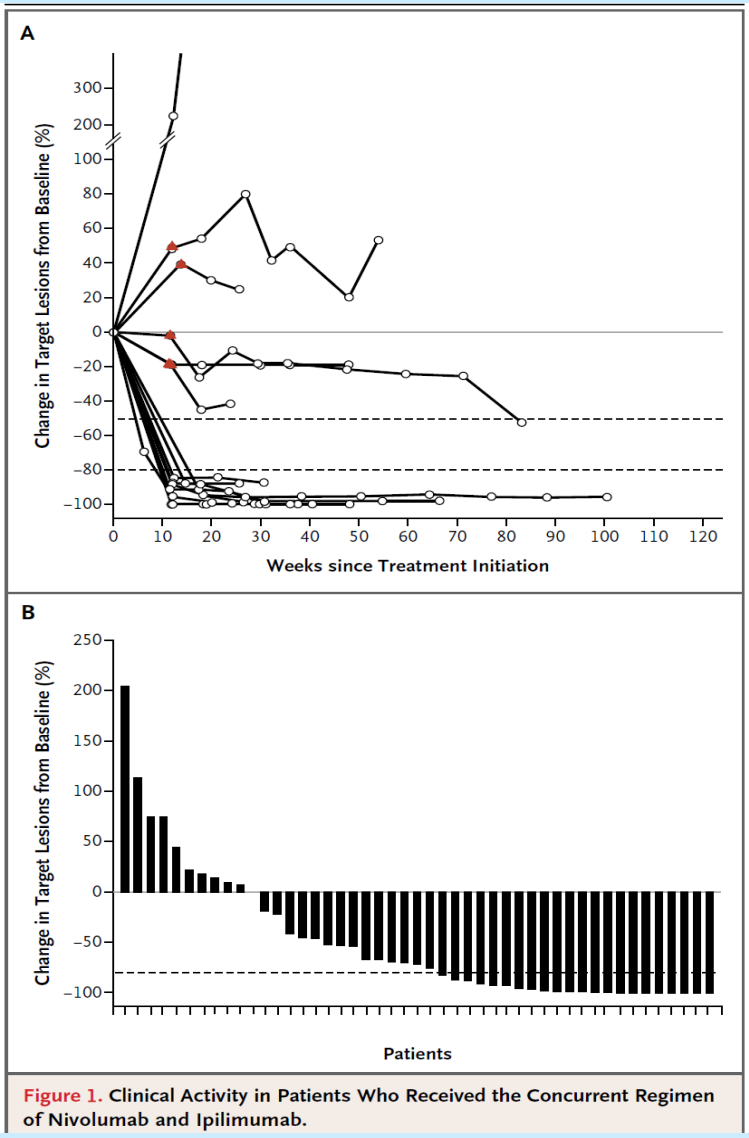


Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

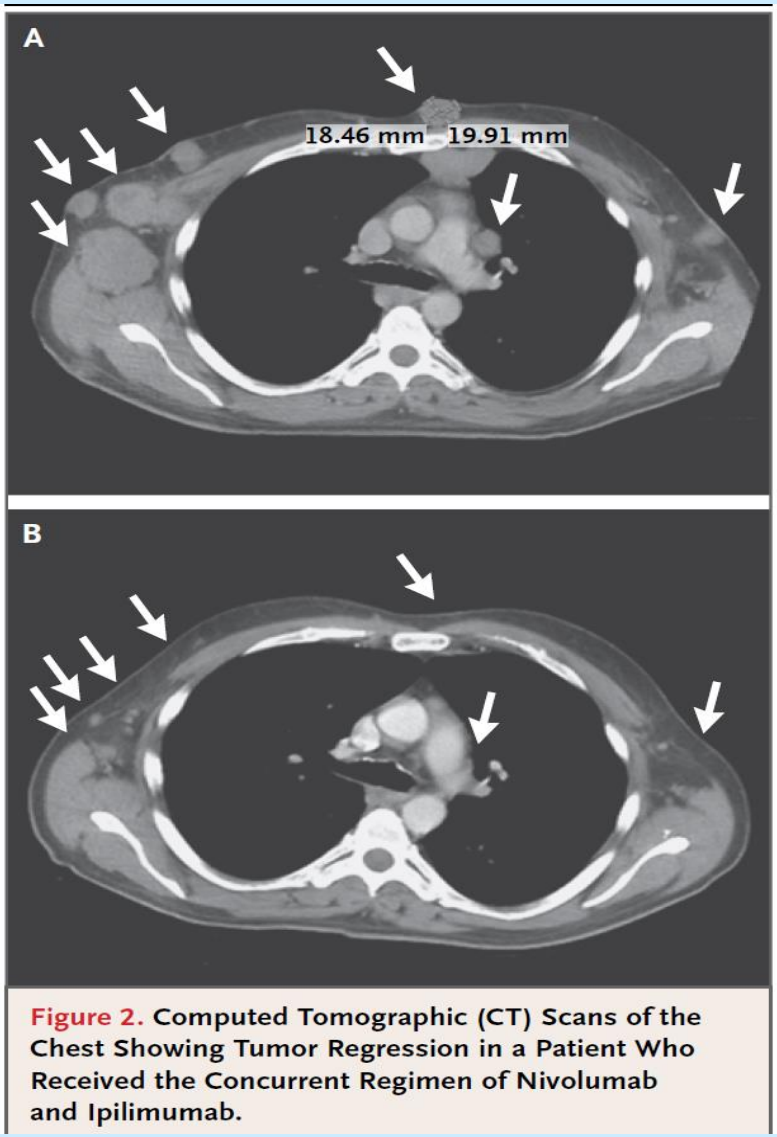


Figure 2. Computed Tomographic (CT) Scans of the Chest Showing Tumor Regression in a Patient Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Jedd D et al. NEJM Jun 2, 2013

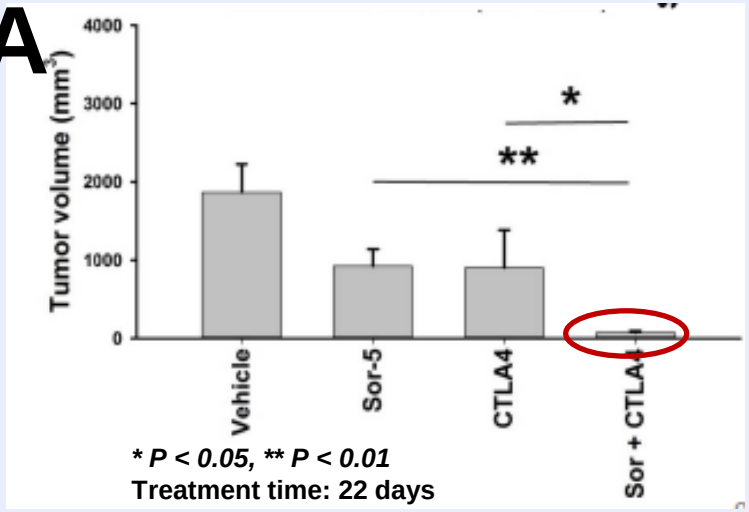
Clinical Trials of Immune Checkpoint Inhibitors in HCC

Target	Drug	Trial ID	HBV/HCV eligibility	Phase	Treatment	Results
CTLA-4	Tremelimumab	NCT 01008358	HCV + only	I	Monotherapy (n = 20)	PR 17.6% DCR 76.4%
	Tremelimumab	NCT 01853618	Not specified	I	With RFA or TACE	Pending
PD-1	Nivolumab	NCT 01658878	Non-infected/ HBV/ HCV 3 arms	I	Monotherapy	Pending
PD-L1	MEDI4736	NCT 01693562 (n= 20)	HBV+ / HCV+ allowed in HCC cohort	I/II	Monotherapy (n = 20)	12wk DCR 21%

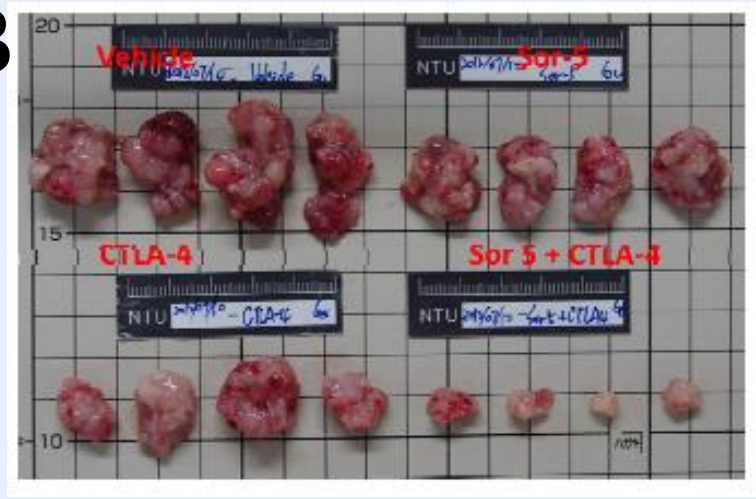
Modified from Hato T et al. Hepatology 2014; 60: 1776
ESMO 2014 # 1058PD

Potential Anti-tumor Synergy Between Sorafenib and Anti-CTLA4

A

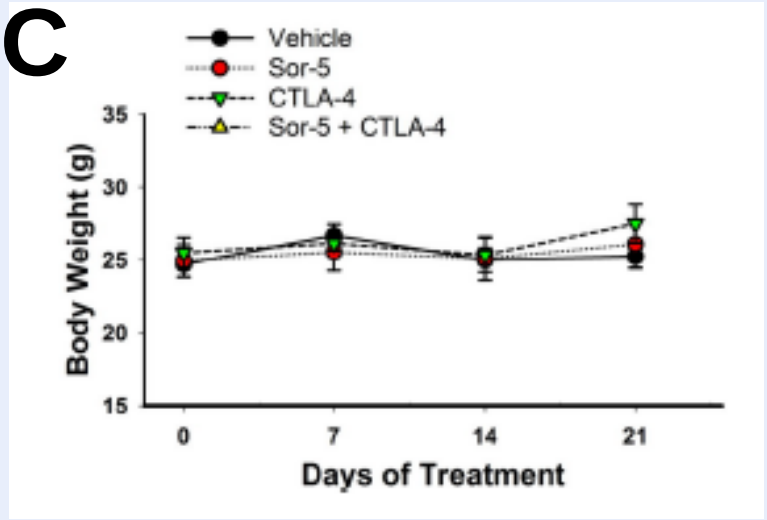


B



➢ anti-CTLA4: 100 μg/ i.p. × 5 doses (days 5, 7, 9, 14, 21)

C



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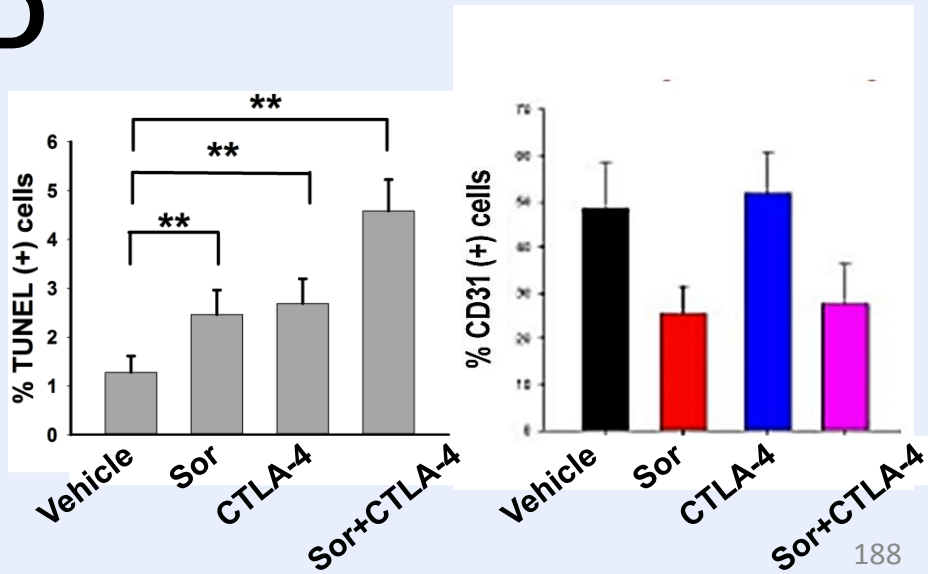
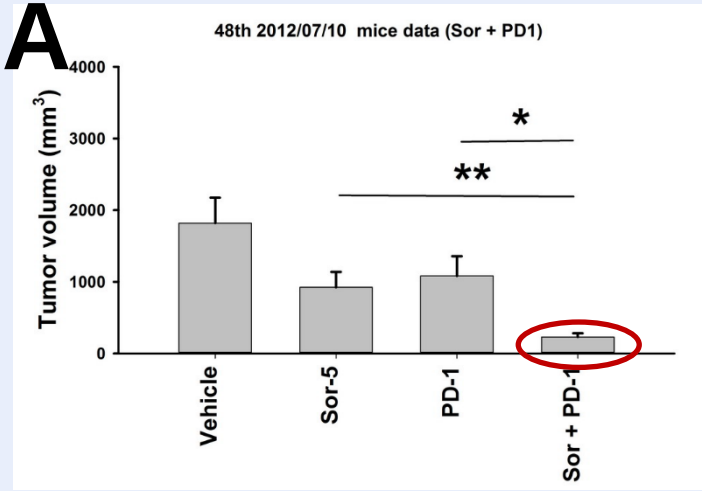


Potential Anti-tumor Synergy Between Sorafenib and Anti-PD-1

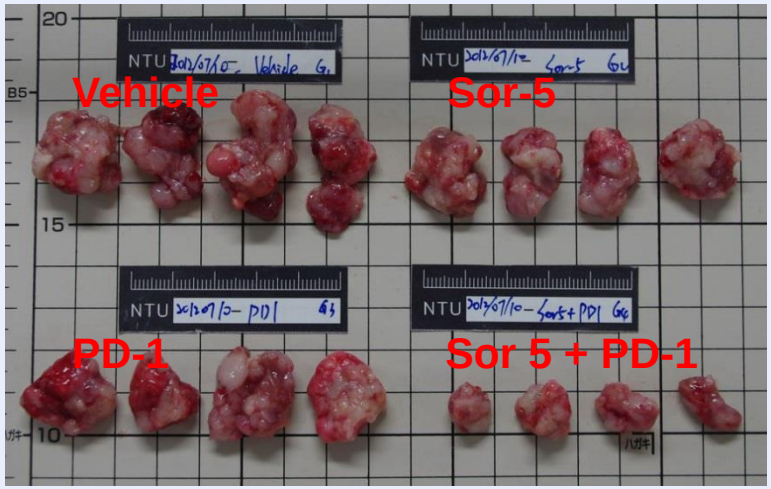
A



P < 0.05, ** P < 0.01

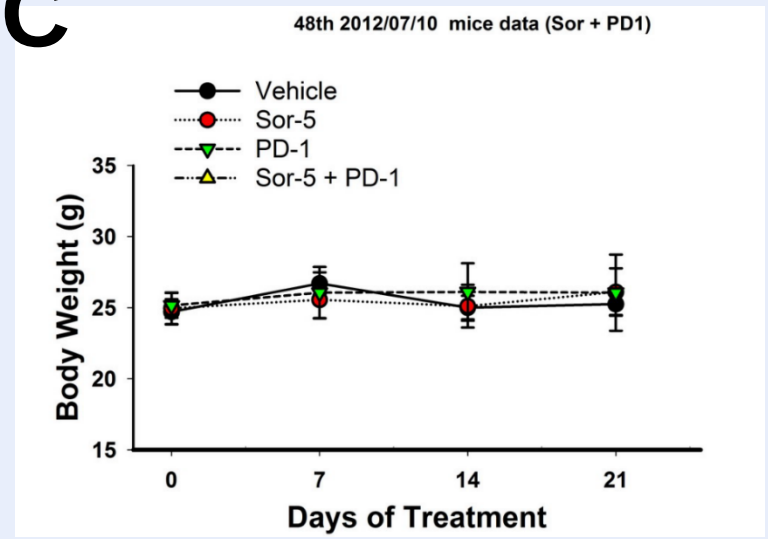
Treatment time: 22 days

B



- anti-PD1: 200 μg/ i.p. × 5 doses (days 5, 7, 9, 14, 21)

C



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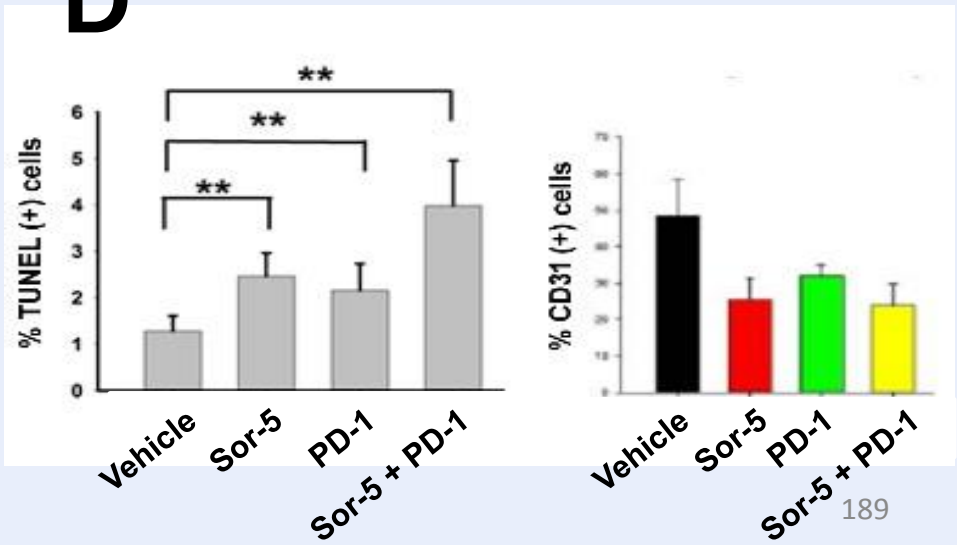


Combination of Immune Checkpoint Inhibitors and Cancer Antigen – Specific Immunotherapy

e.g. Anti-glypican 3 plus Anti-PDL1

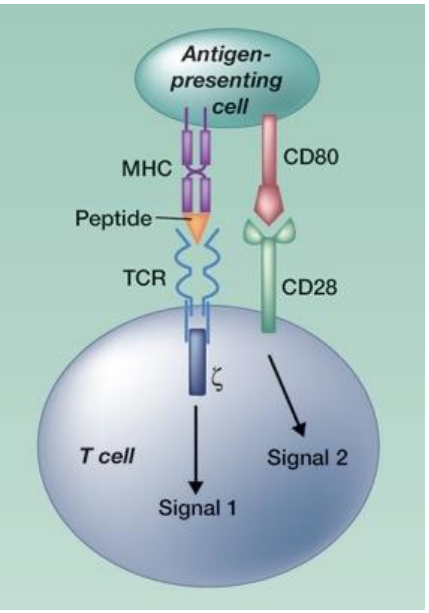
SUMMARY

- HCC is the third leading cause of cancer death in the world. Global harmonization of etiology and epidemiology is expected to happen.
- NTUH has been leading drug development for HCC in the past 10 years.
- Many newly-discovered targets need to be tested, and biomarker-driven adaptive trials are under discussion.
- HCC is extremely heterogeneous, a fact that may jeopardize the determination of molecular subtypes. Liquid biopsy should be pursued.
- Immunotherapy for HCC has just begun, and looks promising.

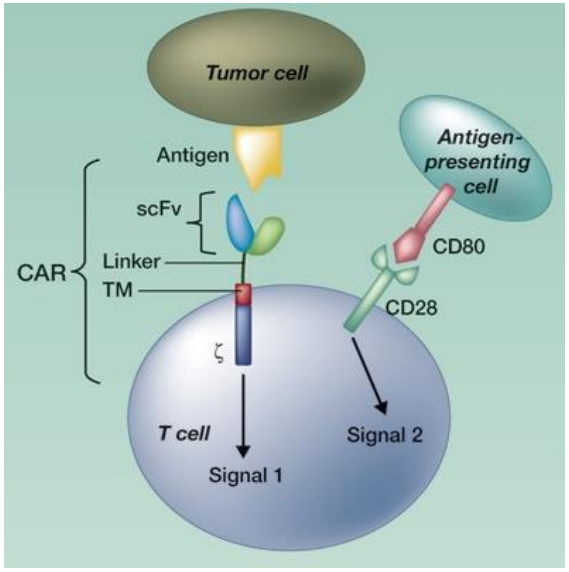
Recent Progress in Drug Development for Hepatocellular Carcinoma

T cells and Chimeric Antigen Receptors (CARs)

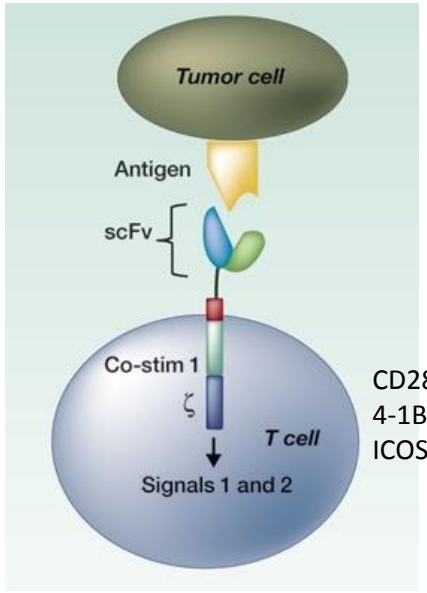
T cell receptor signaling



1st CAR signaling

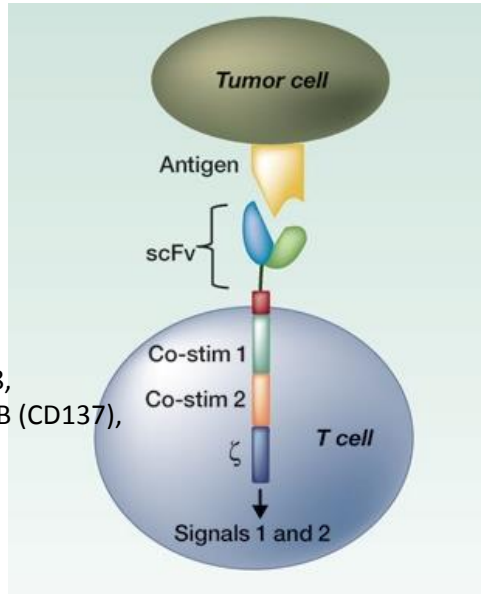


2nd CAR signaling



CD28,
4-1BB (CD137),
ICOS

3rd CAR signaling



"Living drugs"
Not HLA-restricted.
More cytotoxic , potent and persistent

scFv: single-chain variable fragment

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

Jeff Swensen for The New York Times

Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia. More Photos »

By DENISE GRADY

Published: December 9, 2012 | 381 Comments

PHILIPSBURG, Pa. — Emma Whitehead has been bounding around the house lately, practicing somersaults and rugby-style tumbles that

Well Tara Parker-Pope on Health

Culprits in a Child's Headaches
July 8, 2013

How Pregnancy Changes a Runner's Body
July 10, 2013, 12:01 AM

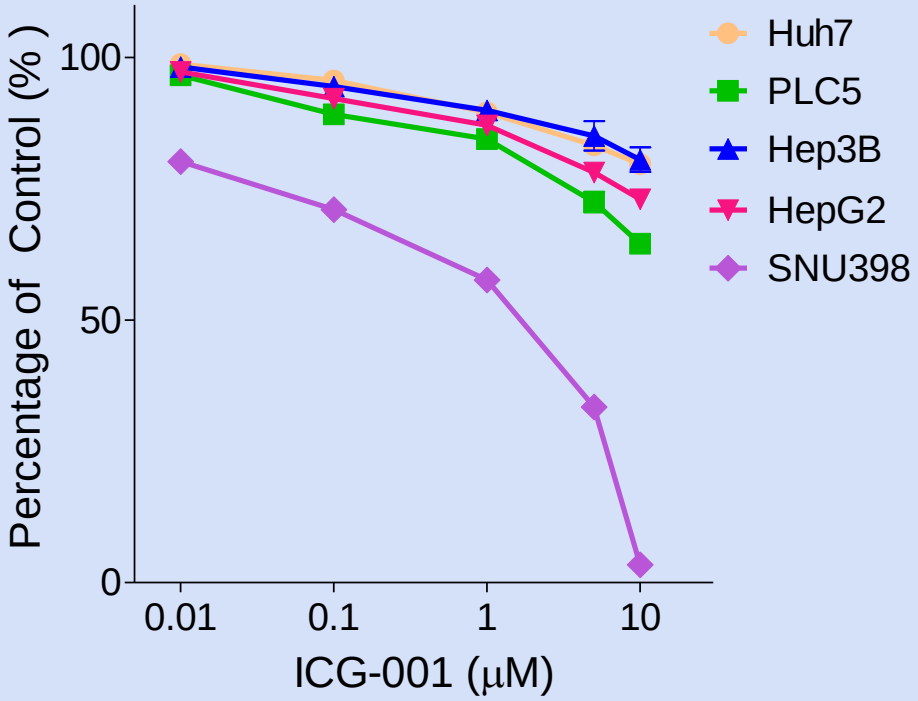
Using a Robot to Ease a Child's Pain
July 9, 2013

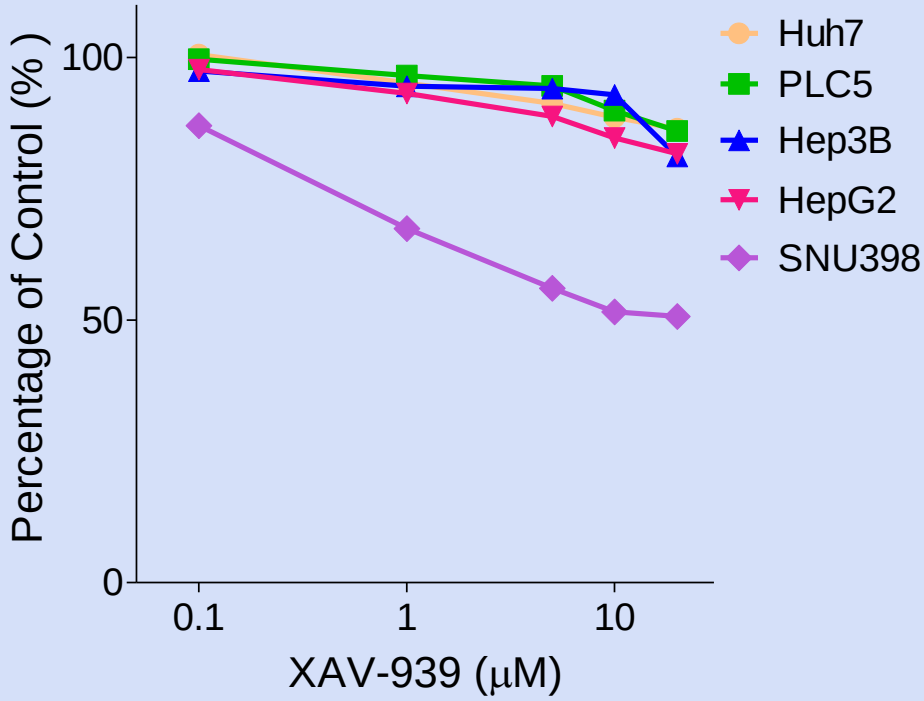
Playing, and Losing, as a Medical Team
July 8, 2013

What Does Birth Cost? Hard to Tell
July 8, 2013

HCC cell lines	*FZR1*	*CTNNB1*	*APC*	*AXIN1*	*AXIN2*	*STK11 (LKB1)*	*RNF43*
SNU398	Nil	Missense mutation (pS37C)	Nil	Nil	Nil		
HepG2	Nil	Nil	Nil	Nil	Nil		
Huh7	Nil	Nil	Nil	Nil	Nil	(Nil)	
PLC5	Nil	Nil	Nil	Nil	Nil	Misense mutation (pD194N)	
SK-hep1	Nil	Nil	Nil	Nil	Nil	(Nil)	
HLE		(Nil) (by Sanger)	(Nil) (by Sanger)	?		(Nil)	
Hep-3B		?	?	?			
SNU-387	Nil	Nil	Nil	Nil	Nil	(Nil)	
SNU-449	Nil	Nil	Nil	Nonsense mutation p.R712*	Nil	(Nil)	
SNU-423	Nil	IntronSNP No aa change	Nl	Nil	Nil	(Nil)	
SNU-475	Nil	Nil	Nil	Nil	Nil	(Nil)	

Wnt/β-Catenin Inhibitors in HCC Cells





Hsu CH et al, manuscript in preparation

Small-molecules Targeting Wnt Signaling

IWP (Inhibitors of Wnt production)

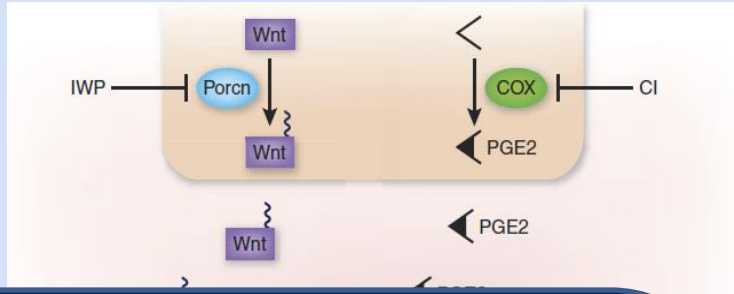
- LGK974

IWR (Inhibitor…

- XA…
- Otl…

β-ID

- ICG…
- PR…



1. **Inactivating mutation of RNF43 (a negative regulator of Wnt/β-catenin signaling) predicts LGK974 sensitivity of pancreatic cancer cells.**
   (Jiang X et al PNAS 2013;110:12649-54)
2. **Loss-of-function mutation of Notch signaling predicts LGK974 sensivity of HNSCC cells.**
   (Liu J et al PNAS 2013;110:20224-9)

~ Chen B et al: Nature Chem Biol 2009;5:100-.

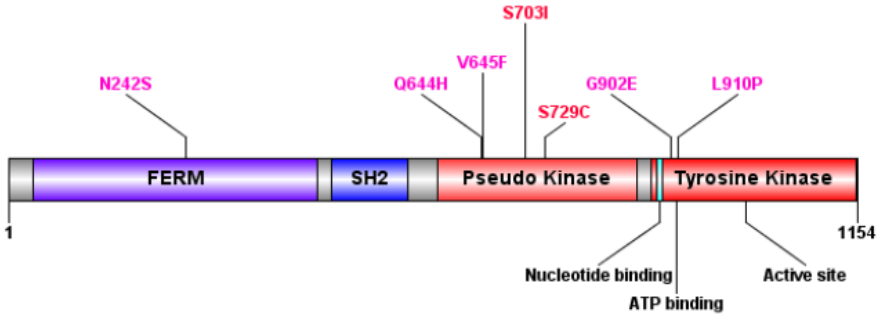
Whole Genome Sequencing Identifies Recurrent Mutations in HCC – 88 cases from HBV-endemic area

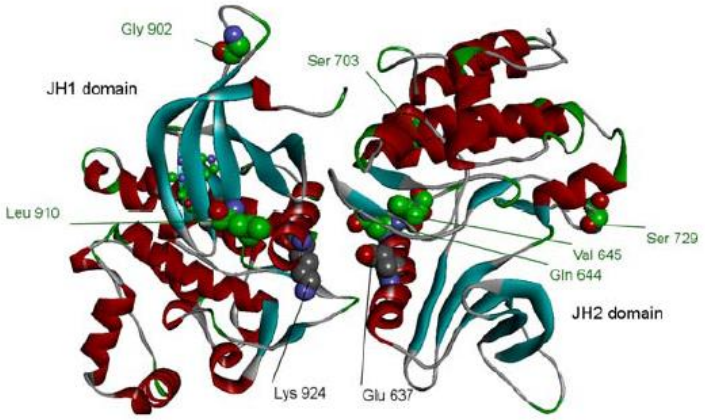
Table 1 Significantly mutated genes in primary HCC

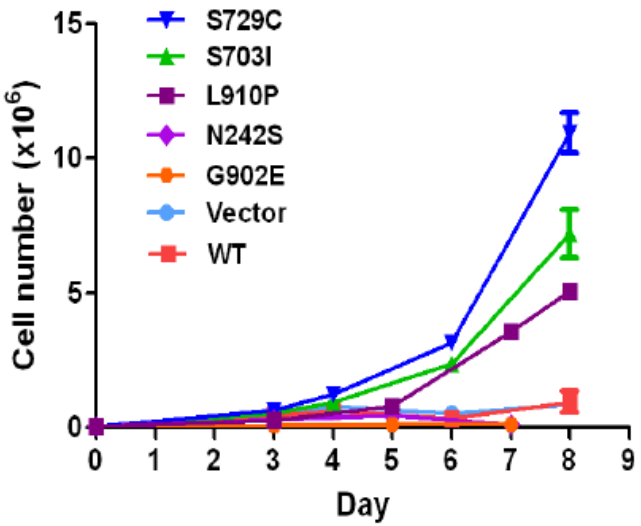
Gene	Description	Mutation Frequency	Confidence Interval (95%)	# COSMIC Matched	# Recurrence	FDR
TP53	tumor protein p53	35.2% (31)	±10.0%	29	1	0
CTNNB1	catenin (cadherin-associated protein), beta 1, 88kDa	15.9% (14)	±7.6%	12	1	0
JAK1	Janus kinase 1	9.1% (8)	±6.0%	2	2	0.001
AXIN1	axin 1	4.5% (4)	±4.4%	0	0	0.043
EPS15	epidermal growth factor receptor pathway substrate 15	4.5% (4)	±4.4%	0	0	0.043
SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	3.4% (3)	±3.6%	0	0	0.047
CACNA2D4	calcium channel, voltage-dependent, alpha 2/delta subunit 4	5.7% (5)	±4.8%	0	0	0.066
ADCY2	adenylate cyclase 2 (brain)	5.7% (5)	±4.8%	0	0	0.067
LRP1B	low density lipoprotein receptor-related protein 1B	11.4% (10)	±6.6%	0	0	0.073
FAM5C	family with sequence similarity 5, member C	5.7% (5)	±4.8%	0	0	0.077
COL11A1	collagen, type XI, alpha 1	6.8% (6)	±5.3%	0	0	0.093

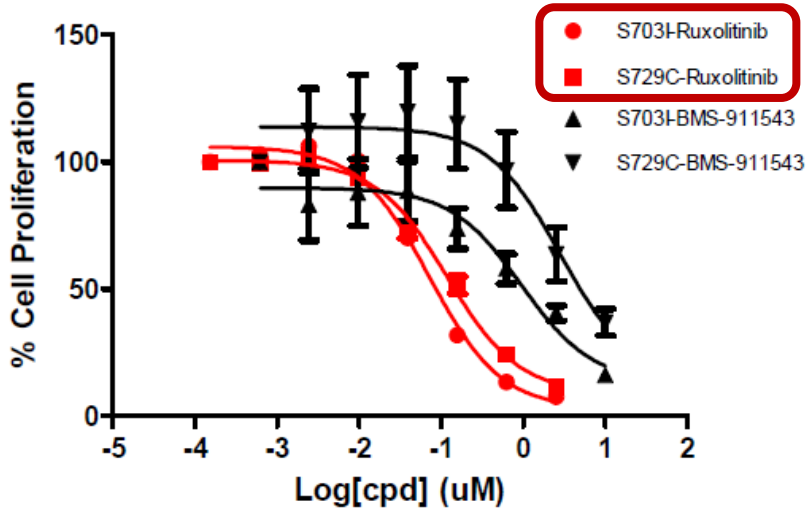
Kan Z, et al. Genome Res. 2013 Jun 20. [Epub ahead of print]

Activating mutations in JAK1









Kan Z, et al. Genome Res. 2013 Jun 20. [Epub ahead of print]

Activating JAK1-S703I Mutation May Predict the Sensitivity of JAK-STAT Inhibition in HCC Patient-derived Xenograft Tumor Model

- 4/60 PDX harbor JAK1 mutations.
- JAK1-S703I activates JAK-STAT pathway and drive cell proliferation.
- JAK1/2 inhibitor is modestly active in growth suppression.

Yang S et al Proc AACR 2015, Abs #688

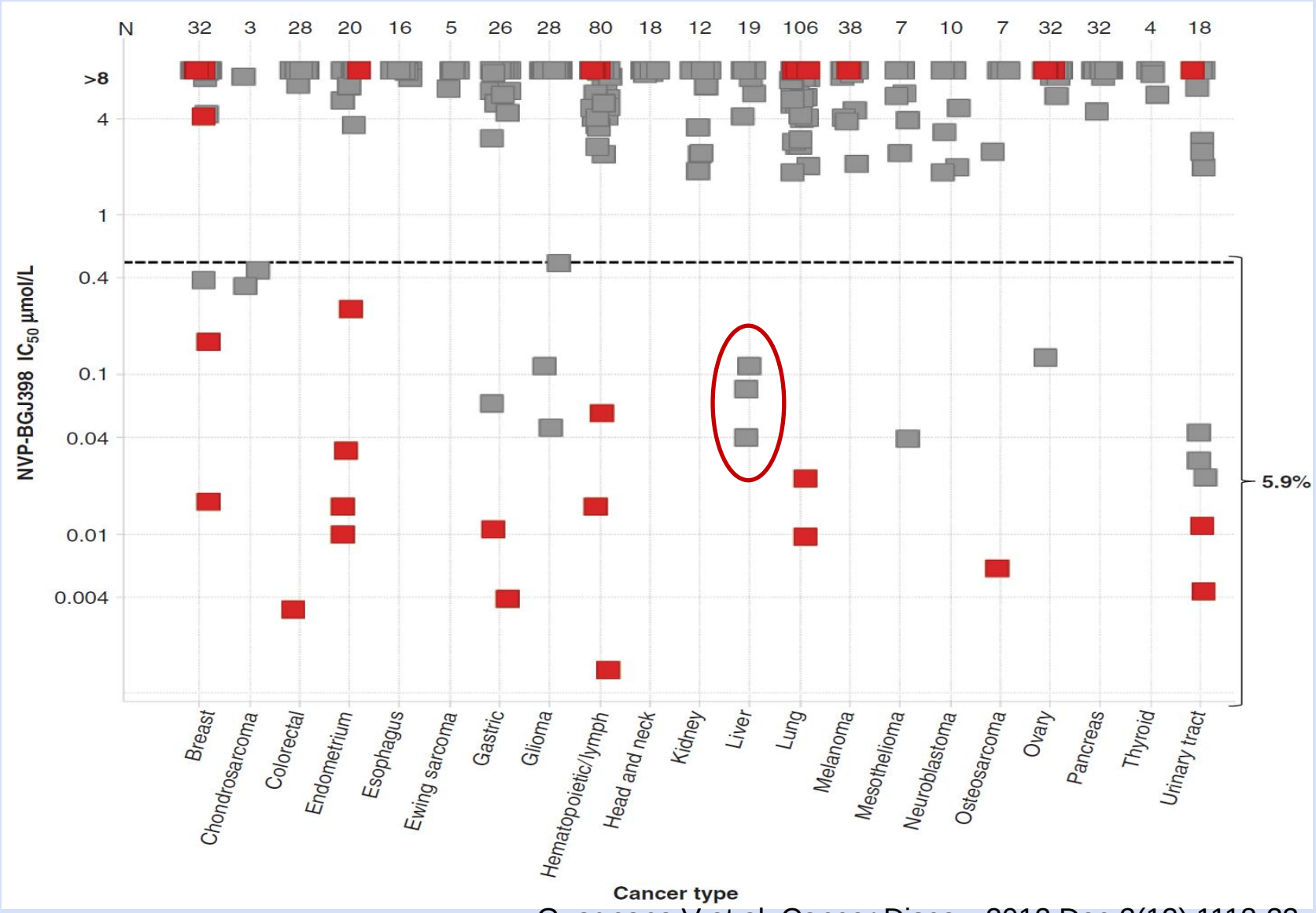
Whole Genome Sequencing Identifies Recurrent Mutations in HCC – 88 cases from HBV-endemic area

Table 2 Potentially actionable mutations and matched clinical stage inhibitors

Genes	Mutation	Amplification	Deletion	Combined Frequency	Inhibitor
JAK1	*JAK1* (9.1%)	-	-	9.1%	JAKi (ruxolitinib)
FAK	-	*FAK* (26.1%)	-	26.1%	FAKi (PF-04554878, PF-562271)
CCND1, *CDKN2A*	-	*CCND1* (4.5%)	*CDKN2A* (10.2%)	14.7%	CDK4/6i (PD-0332991, LY2835219, LEE011)
FGF19	-	*FGF19* (4.5%)	-	4.5%	FGFRi (brivanib, BGJ398, LY2874455)
BRCA1/2, *PARP1*	*BRCA1* (1.1%), *BRCA2* (5.7%)	*PARP1* (18.2%)	-	25.0%	PARPi (AG-14699, olaparib)

Kan Z, et al. Genome Res. 2013 Jun 20. [Epub ahead of print]

FGFR Genetic Alterations Predict for Sensitivity to NVP-BGJ398, a Selective Pan-FGFR Inhibitor



Guagnano V et al. Cancer Discov. 2012 Dec;2(12):1118-33

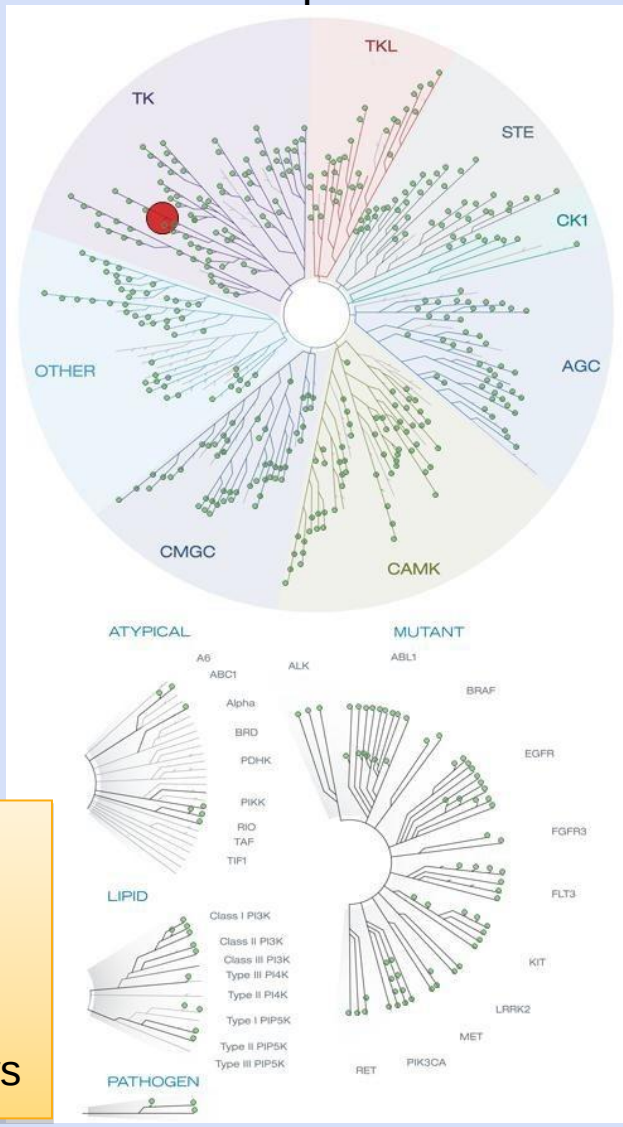
Novartis has a Highly Selective FGFR4 Inhibitor

Activity in FGF19/FGFR4/KLB cancer cell lines only

Biochemical assay	
Kinase	**IC50 µM**
FGFR1	>10
FGFR2	>10
FGFR3	>10
FGFR4	**0.0024**
auroraA	5.6
MK2	9.4
Others (59 kinases)	>10

Cellular assay	
BaF3 model	**IC50 µM**
BAF3/Tel-FGFR1	>10
BAF3/Tel-FGFR2	>10
BAF3/Tel-FGFR3	>10
BAF3/Tel-FGFR4	**0.0011**
Others (42 kinases)	>10

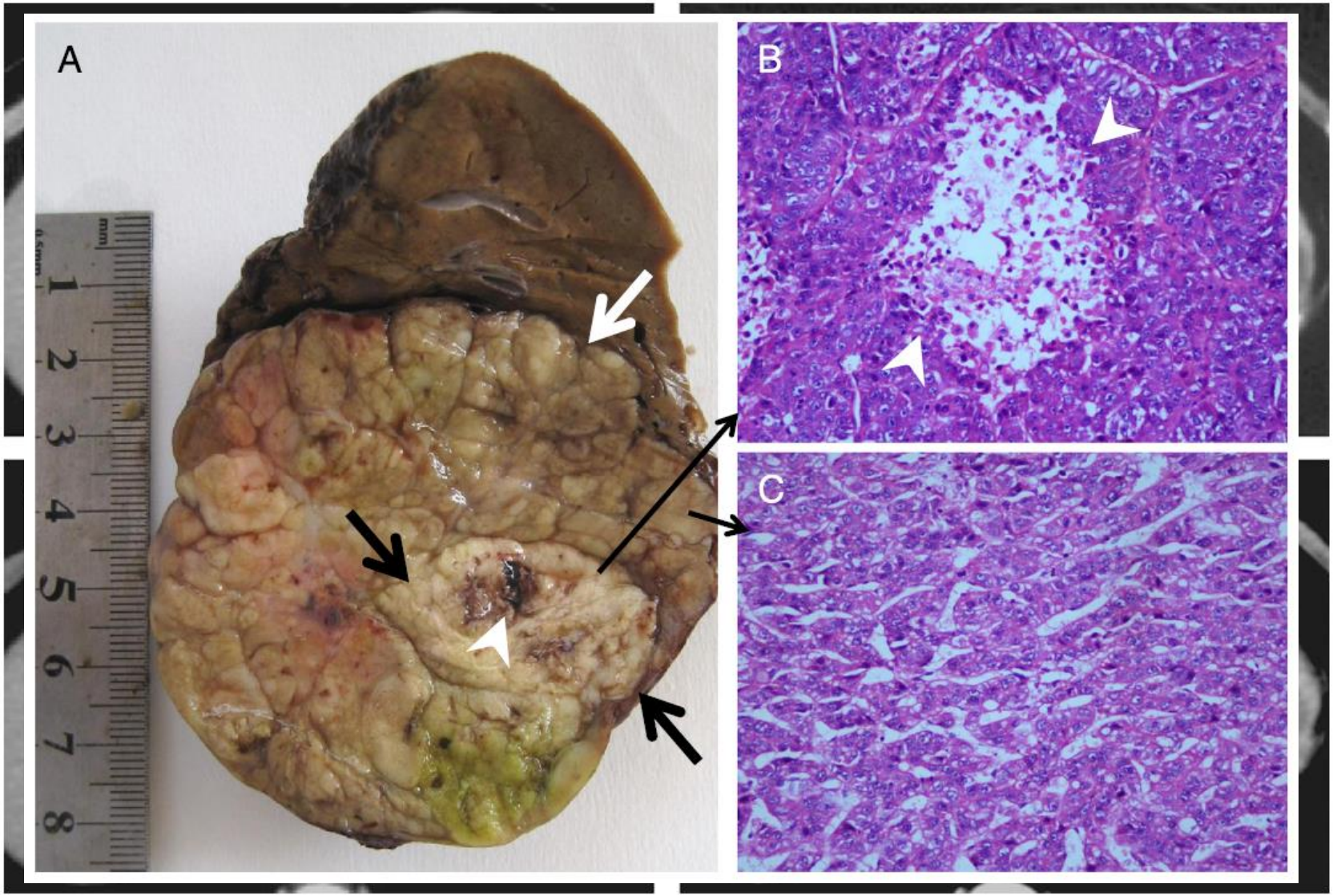
KINOMEscan: 456 kinases
FGFR4 inhibitor at 3 µM



Conclusions:

- FGFR4 inhibitor selectively binds the ATP site of FGFR4 in a kinome wide scan
- > 1,000-fold selectivity vs. panel of 65 kinases in biochemical assays
- > 1,000-fold selectivity vs. panel of 46 kinases in cellular assays

FDG PET/CT and Enhanced CT Imaging of Tumor Heterogeneity in Hepatocellular Carcinoma -- Imaging-Pathologic Correlation

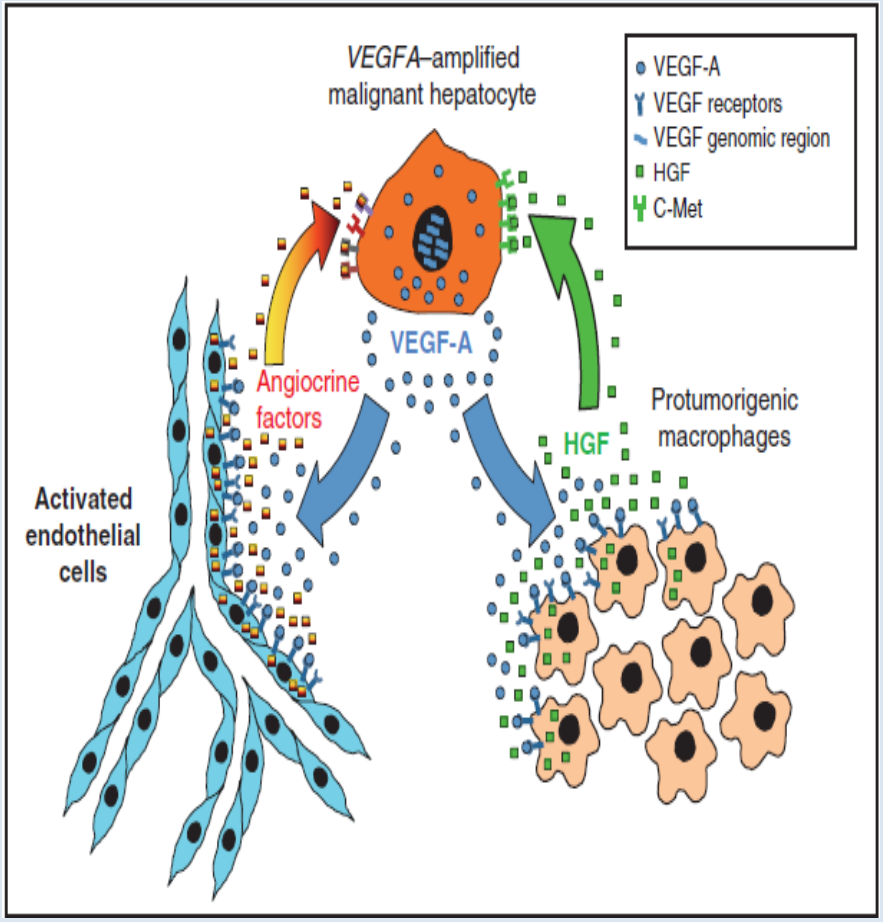


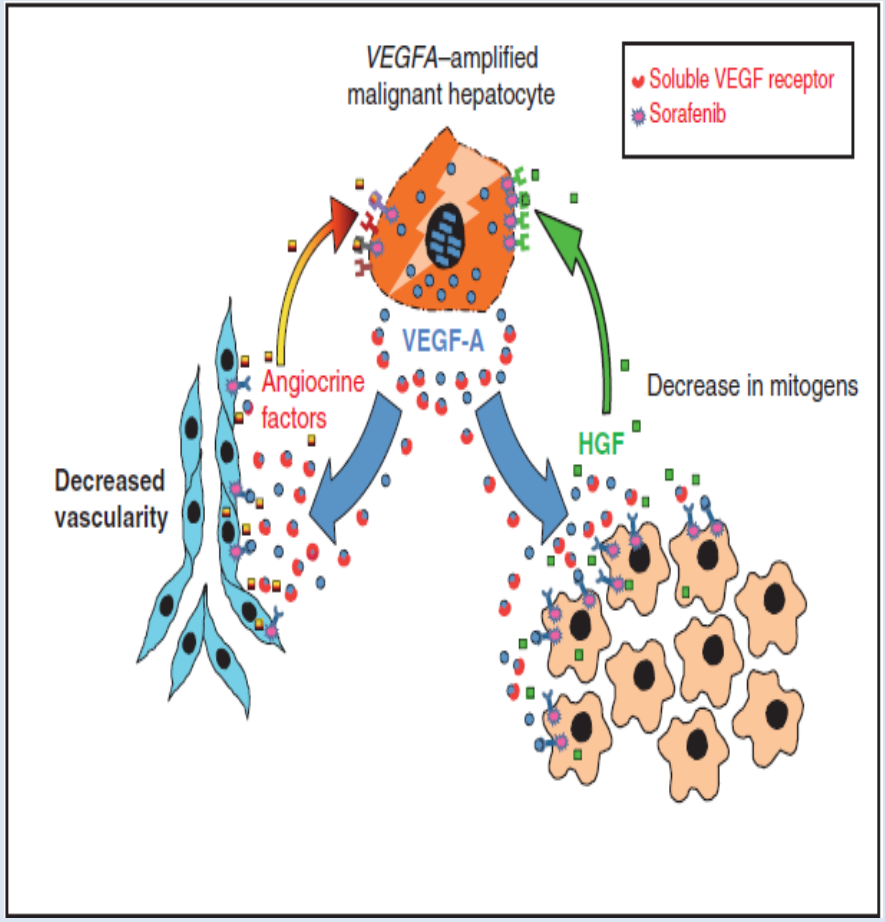
Dong A, et al. Clin Nucl Med 2014;39: 808-810

New Targets for HCC

- Wnt/β-Catenin
- JAK/STAT
- FGF19/FGFR4
- VEGF-A
- c-MET
- TSC-2

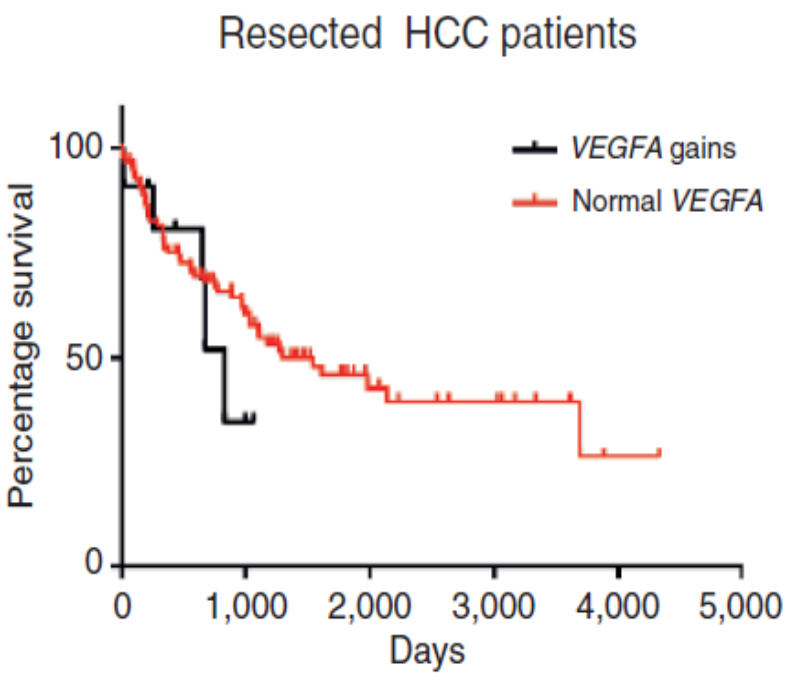
Human and Mouse VEGFA –Amplified HCC Are Highly Sensitive to Sorafenib Treatment

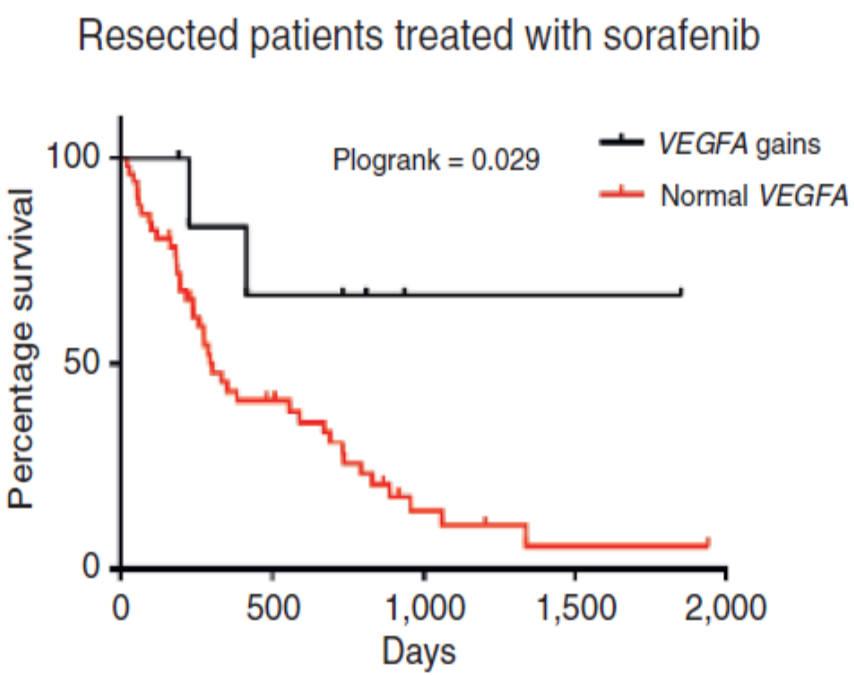




Horwitz E et al. Cancer Discovery 2014;4:730-743

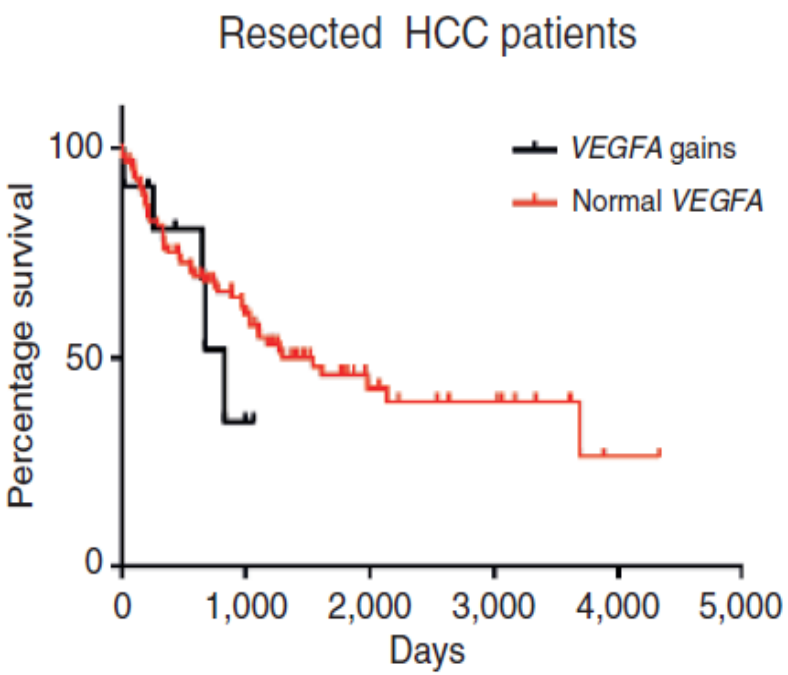
Human and Mouse VEGFA –Amplified HCC Are Highly Sensitive to Sorafenib Treatment

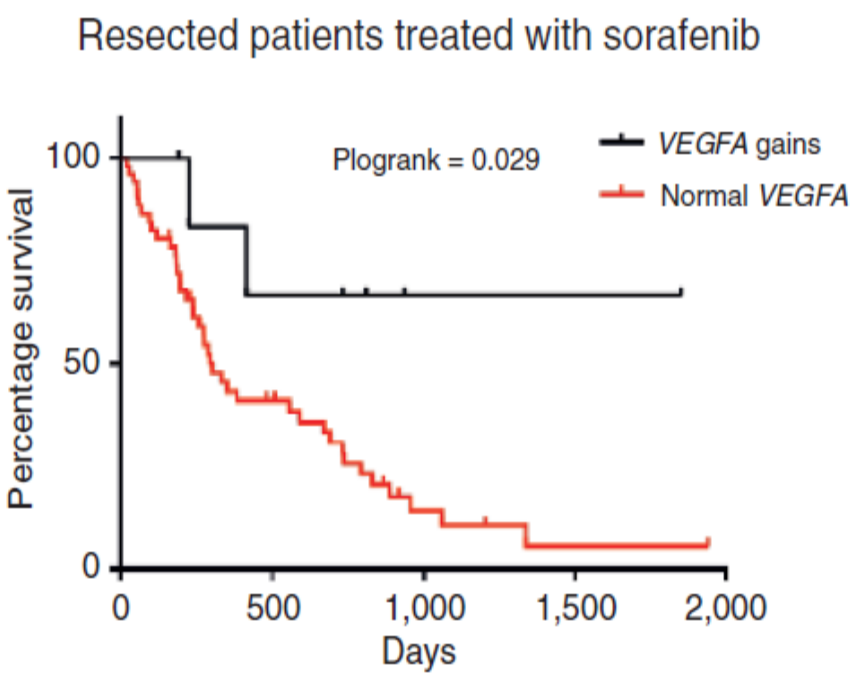




Horwitz E et al. Cancer Discovery 2014;4:730-743

Human and Mouse VEGFA –Amplified HCC Are Highly Sensitive to Sorafenib Treatment





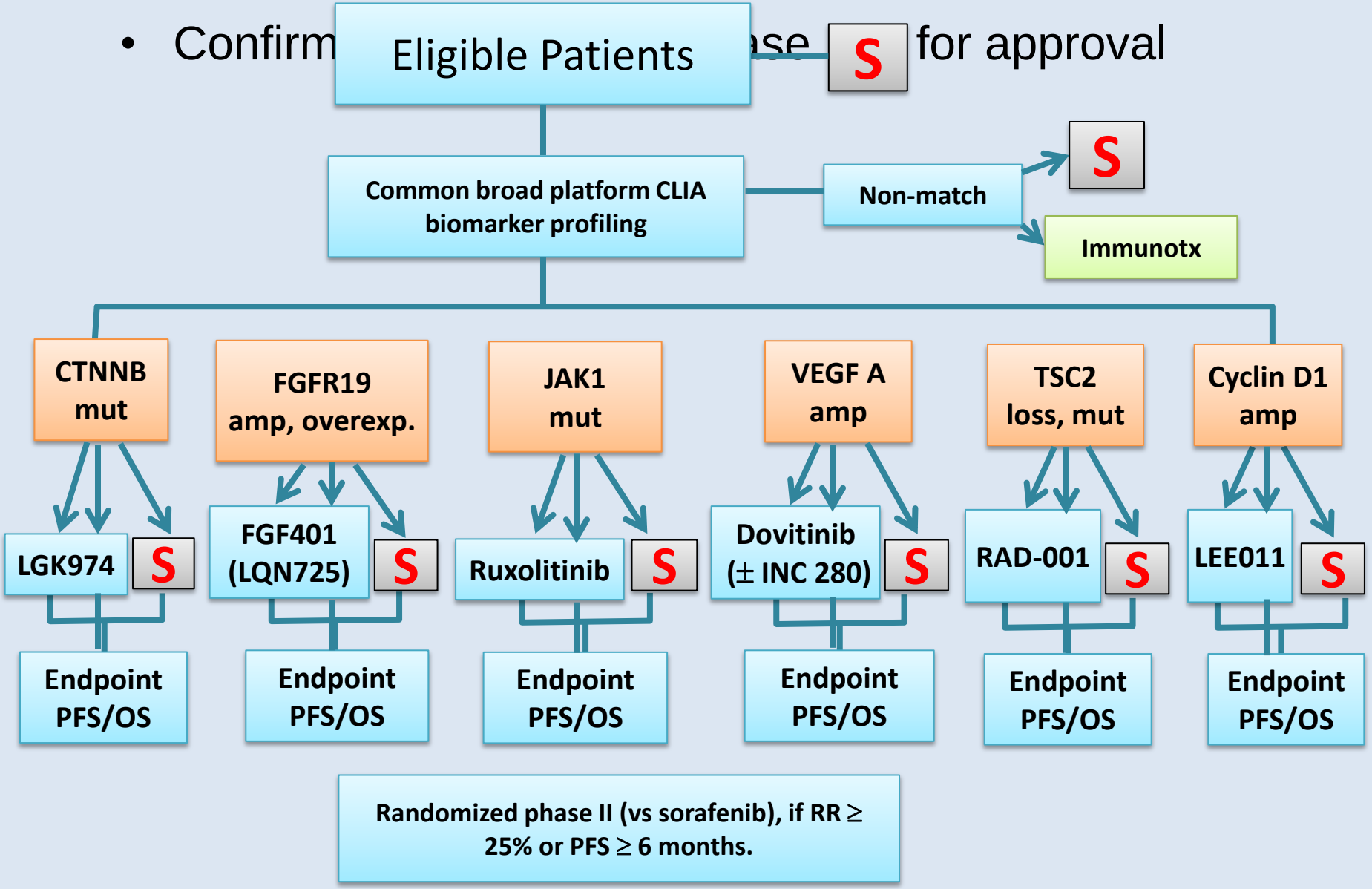
Horwitz E et al. Cancer Discovery 2014;4:730-743

New Targets for HCC

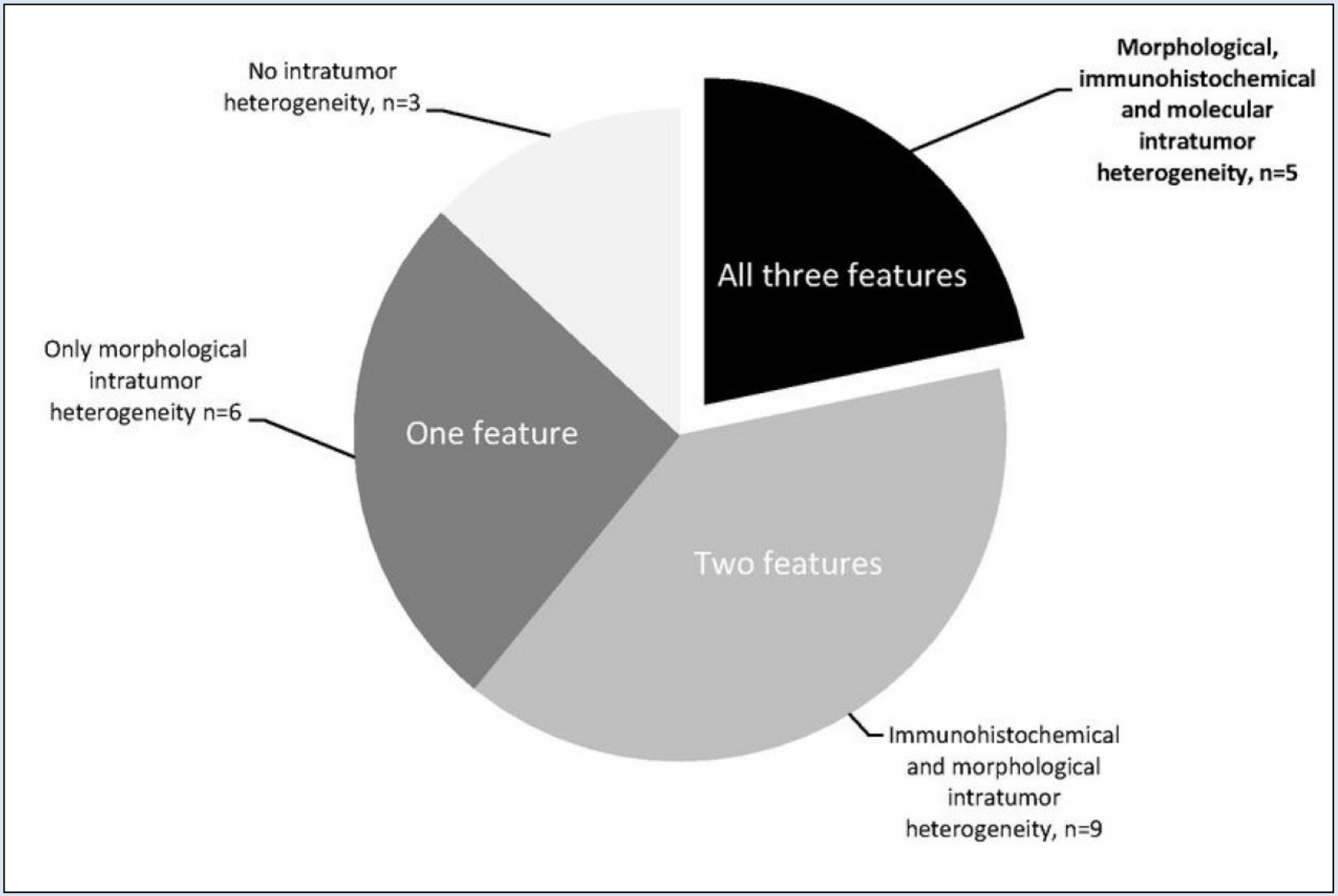
- Wnt/β-Catenin
- JAK/STAT
- FGF19/FGFR4
- VEGF-A
- c-MET
- TSC-2

Master Protocol for Novartis 1st-line HCC

- Confirm … ase S for approval



Intratumor Heterogeneity in Hepatocellular Carcinoma



Friemel J, et al. Clin Cancer Res. 2014 Sep 23.[Epub ahead of print]

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Predictive Biomarkers of Antiangiogenic Therapy for Advanced HCC

Table 2. Studies of predictive and prognostic markers, other than serum or plasma markers, for advanced HCC

	Authors	Treatment	Results		
			Predictive markers	Prognostic markers	Others
Tumor characteristics					
Phospho-ERK expression	Abou-Alfa et al. [71]	Sorafenib	High p-ERK → longer TTP	—	
	Ozenne et al. [72]	Sorafenib	No predictive value	—	
Phospho-c-Jun expression	Hagiwara et al. [73]	Sorafenib	Phospho-c-Jun expression → poor response, TTP	Phospho-c-Jun expression → poor OS	

Shao YY, et al. Liver Cancer 2013;2:93–107

Predictive Biomarkers of Antiangiogenic Therapy for Advanced HCC

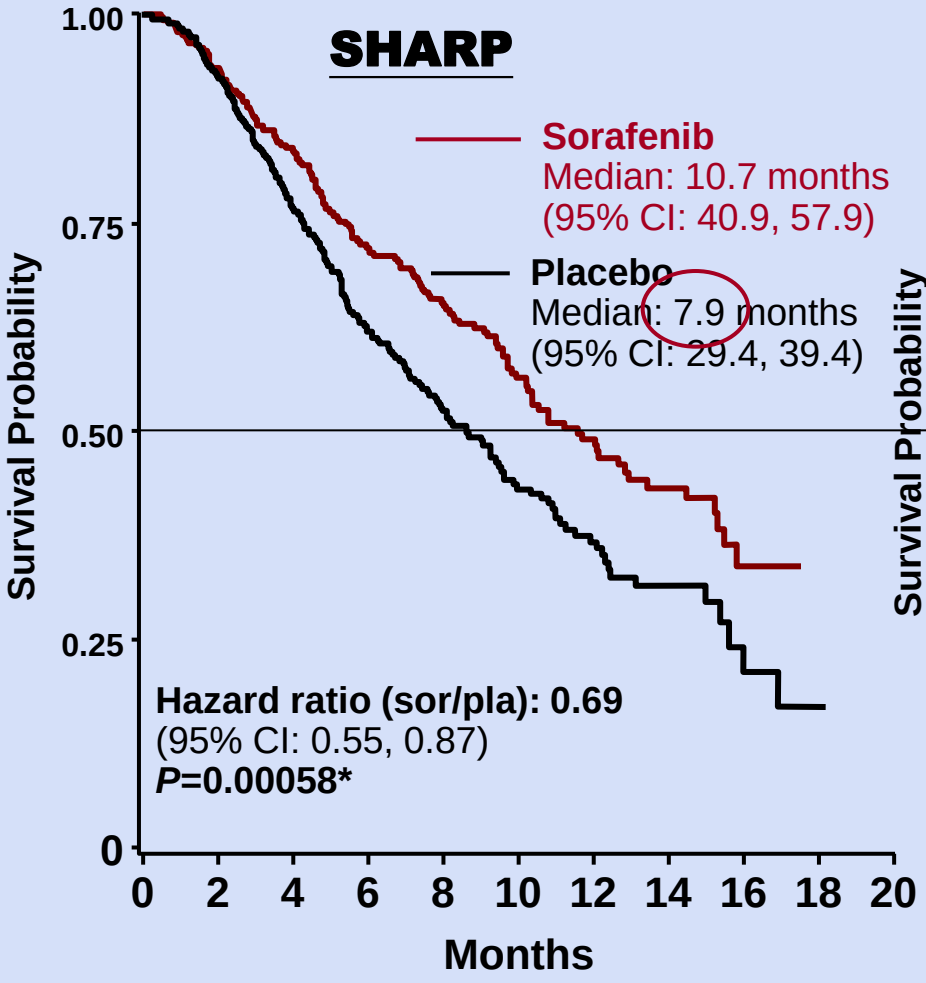
Functional imaging					
DCE-MRI	Hsu et al. [75]	Sorafenib plus UFT	High baseline K^{trans} or decreased K^{trans} after treatment→ DCR	Vascular response[a] → better OS	Vascular response[a] → better PFS
Positron emission tomography	Lee et al. [83]	Sorafenib	—	Low SUV → better OS	Low SUV → better PFS
Treatment side effects					
Hypertension	Estfan et al. [87]	Sorafenib	Hypertension → better TTP (?)[b]	Hypertension → better OS	
	Otsuka et al. [88]	Sorafenib	No predictive value	No prognostic value	
Skin toxicity	Otsuka et al. [88]	Sorafenib	No predictive value	Skin toxicity → better OS	
	Vincenzi et al. [89]	Sorafenib	Early[c] skin toxicitiy → better DCR and TTP	Early skin toxicity → better OS[d]	

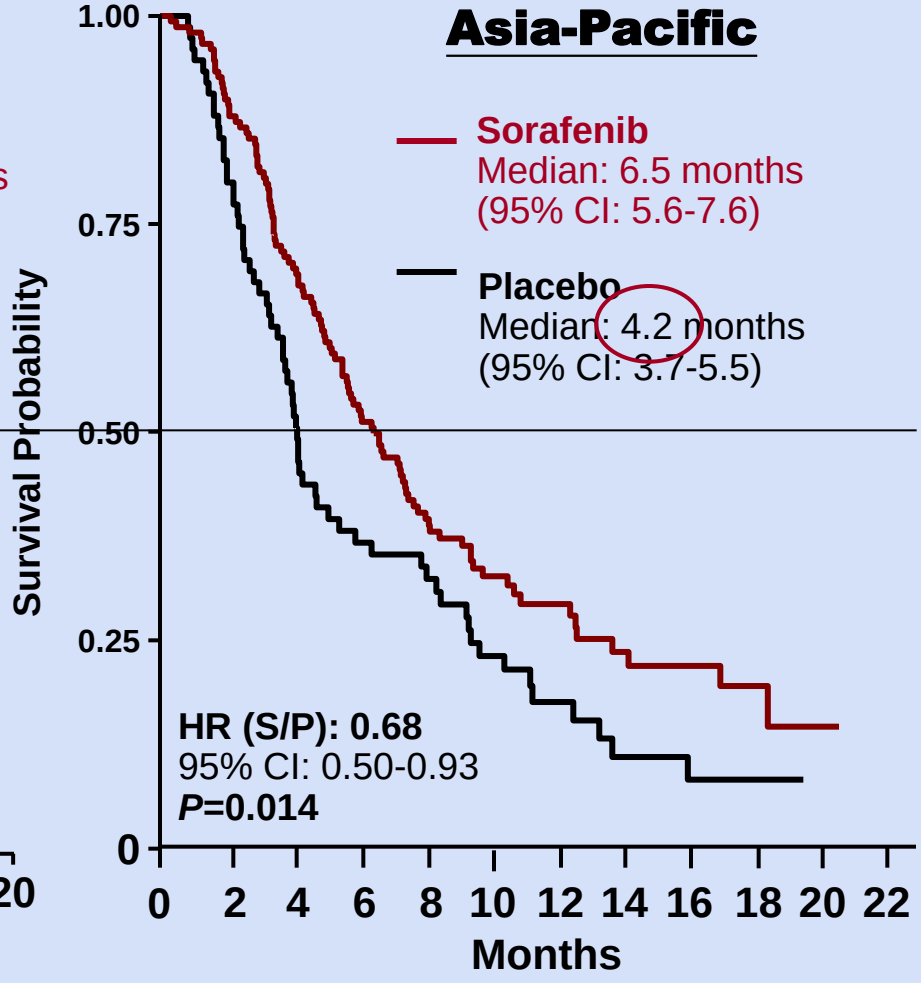
a=defined as ≥ 40% decrease in K^{trans} after treatment; b=statistical values of the comparison not reported; c=within the first month of treatment; d=borderline statistical significance.

Shao YY, et al. Liver Cancer 2013;2:93–107

Phase III SHARP and Asia-Pacific

Overall Survival

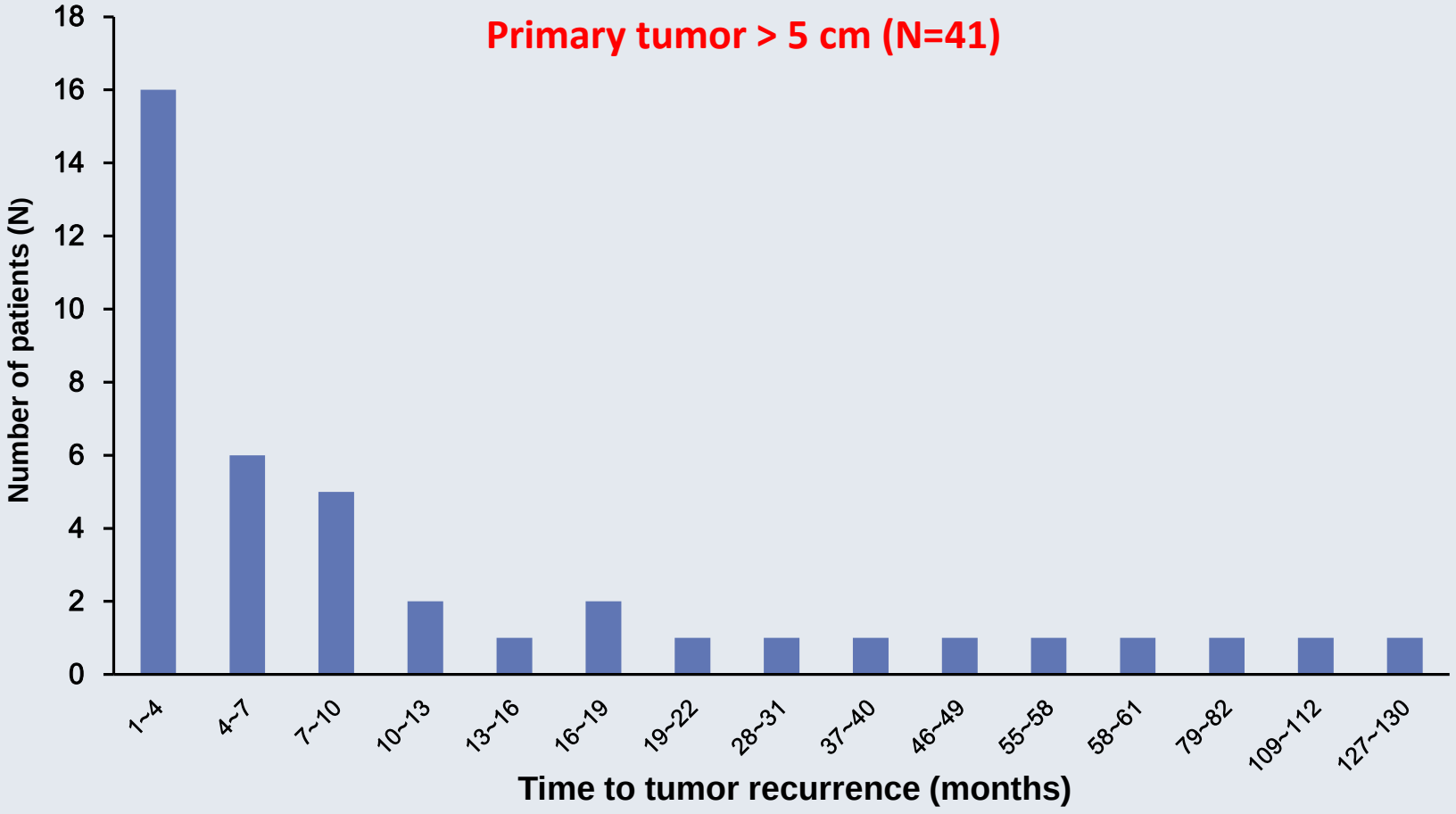




Llovet JM, et al. N Engl J Med 2008:359:378-90

Cheng AL, et al. Lancet Oncol 2009;10:25-34.

Recurrence of HBV-related HCC after Curative Resection (TCOG, T1297 study)



Cheng LT et al (unpublished data)

Study Methods

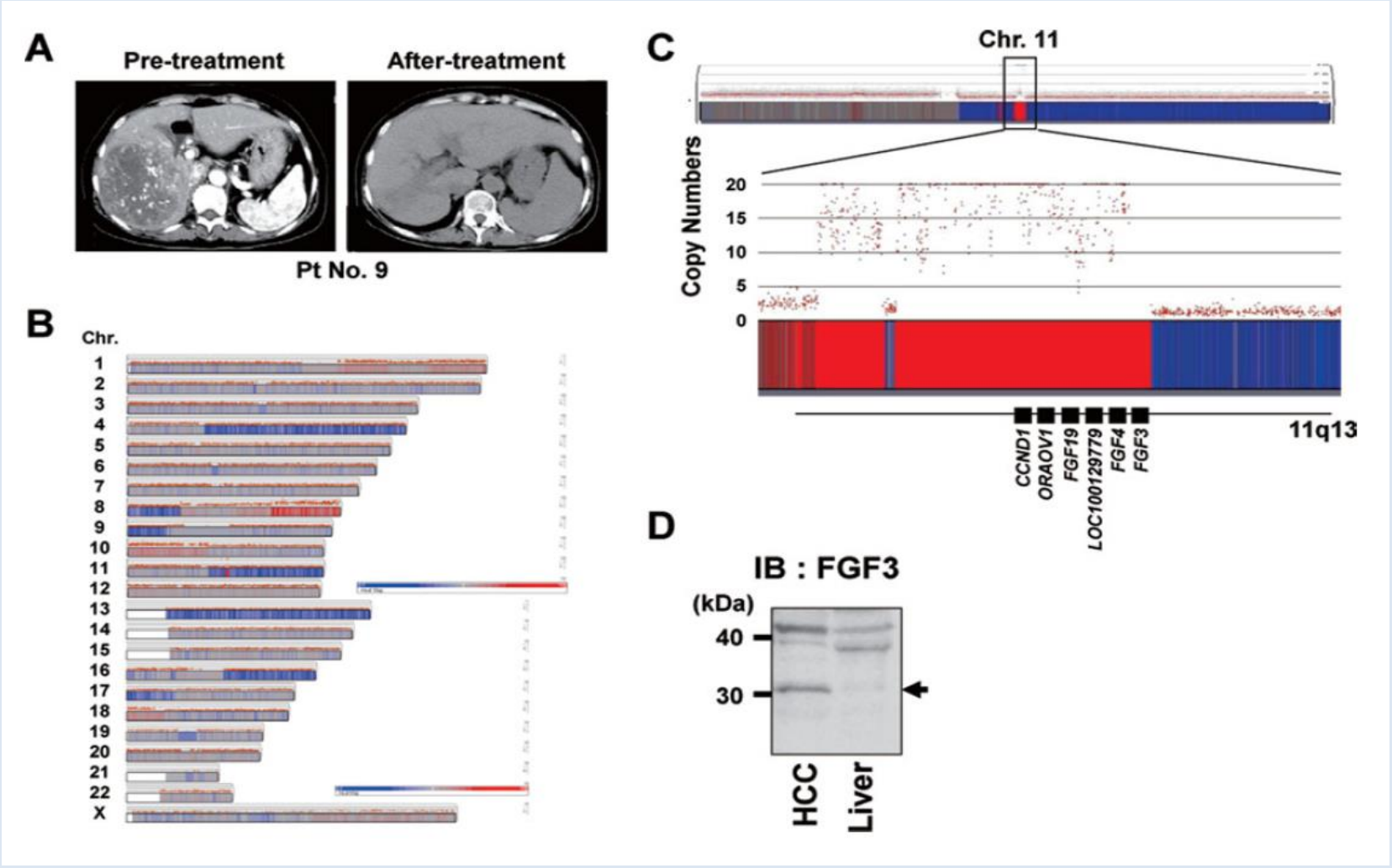
Clinico-pathologic analysis of patients with long survival/good tumor response.

Retrospective biomarker analyses.

Molecular studies of extreme responders.

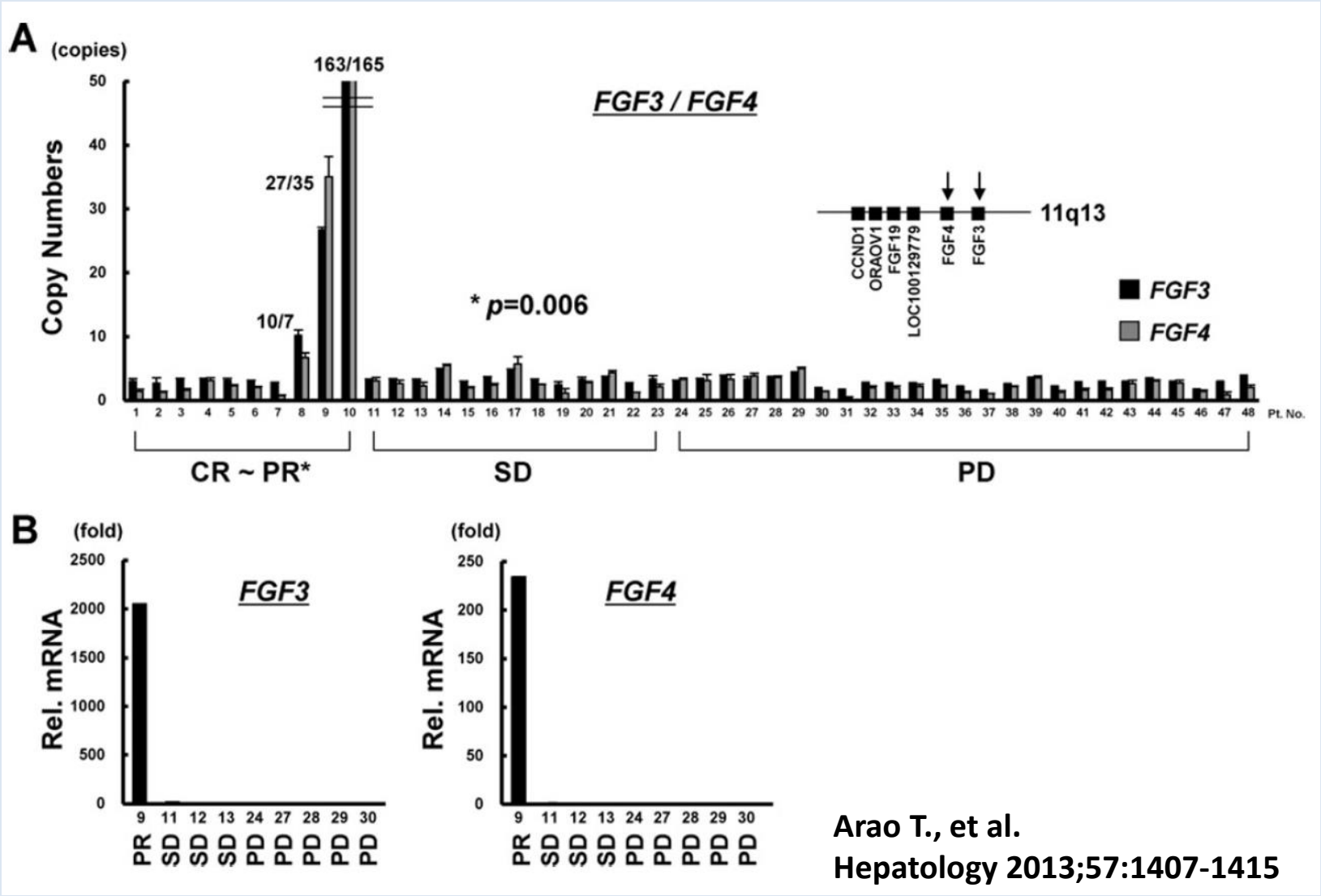
Inventory biomarkers and validation studies.

FGF3/FGF4 Amplification and Multiple Lung Metastases in Responders to Sorafenib in HCC



Arao T., et al. Hepatol 2013;57:1407-1415

FGF3/FGF4 Amplification and Multiple Lung Metastases in Responders to Sorafenib in HCC

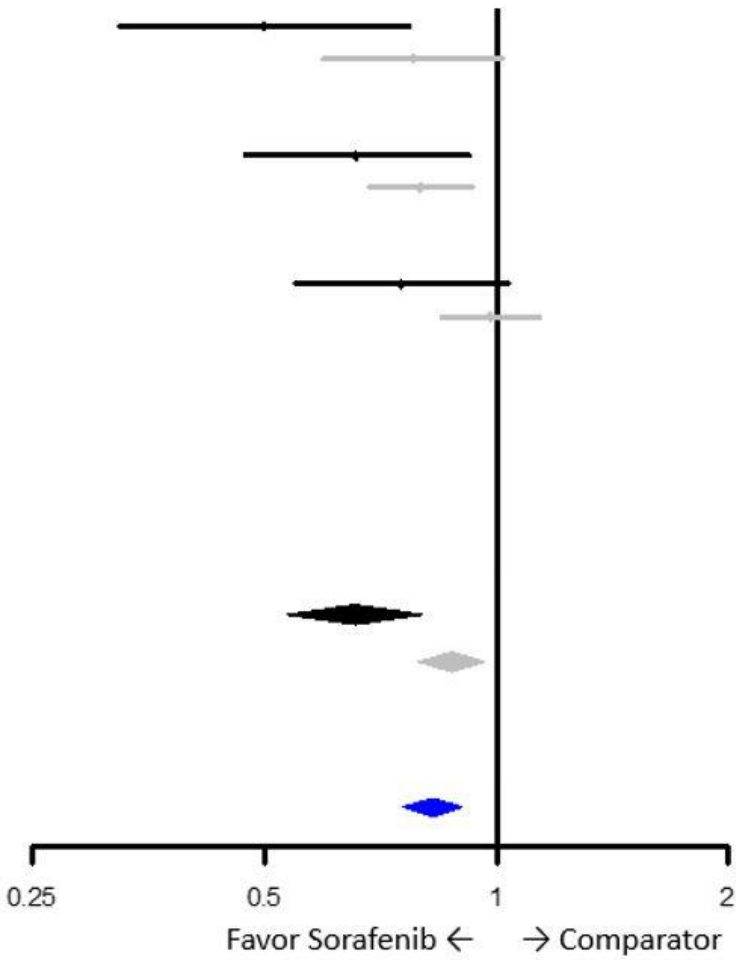


Arao T., et al.
Hepatology 2013;57:1407-1415

HCV (+) vs HCV (-) Patients

Study	Subgroup	HR	95% CI	
SHARP	HCV	0.50	(0.32,	0.77)
	Non-HCV	0.78	(0.60,	1.02)
Sorafenib vs. sunitinib	HCV	0.66	(0.47,	0.92)
	Non-HCV	0.80	(0.68,	0.93)
Sorafenib vs. brivanib	HCV	0.75	(0.55,	1.03)
	Non-HCV	0.98	(0.84,	1.14)
AP	HCV	NA		
	Non-HCV	NA		
Synthesized	**HCV**	**0.65**	**(0.53,**	**0.80)**
	Non-HCV	**0.87**	**(0.79,**	**0.96)**
Overall		**0.82**	**(0.75,**	**0.90)**

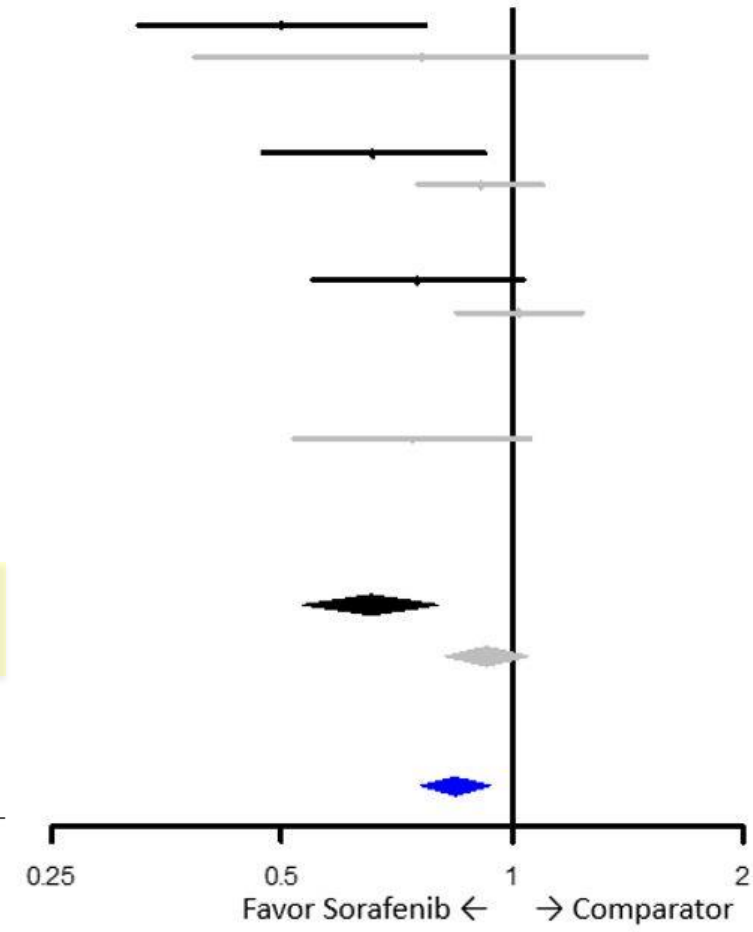
***p* = 0.013**



HCV (+) vs. HBV (+) Patients

Study	Subgroup	HR	95% CI
SHARP	HCV	0.50	(0.32, 0.77)
	HBV	0.76	(0.39, 1.50)
Sorafenib vs. sunitinib	HCV	0.66	(0.47, 0.92)
	HBV	0.91	(0.75, 1.10)
Sorafenib vs. brivanib	HCV	0.75	(0.55, 1.03)
	HBV	1.02	(0.84, 1.24)
AP	HCV	NA	
	HBV	0.74	(0.52, 1.06)
Synthesized	**HCV**	**0.65**	**(0.53, 0.80)**
	HBV	**0.92**	**(0.82, 1.05)**
Overall		**0.84**	**(0.76, 0.94)**

***p* = 0.004**



Drug development for Squamous NSCLC

- Many possible biomarkers and many potentially active drugs.

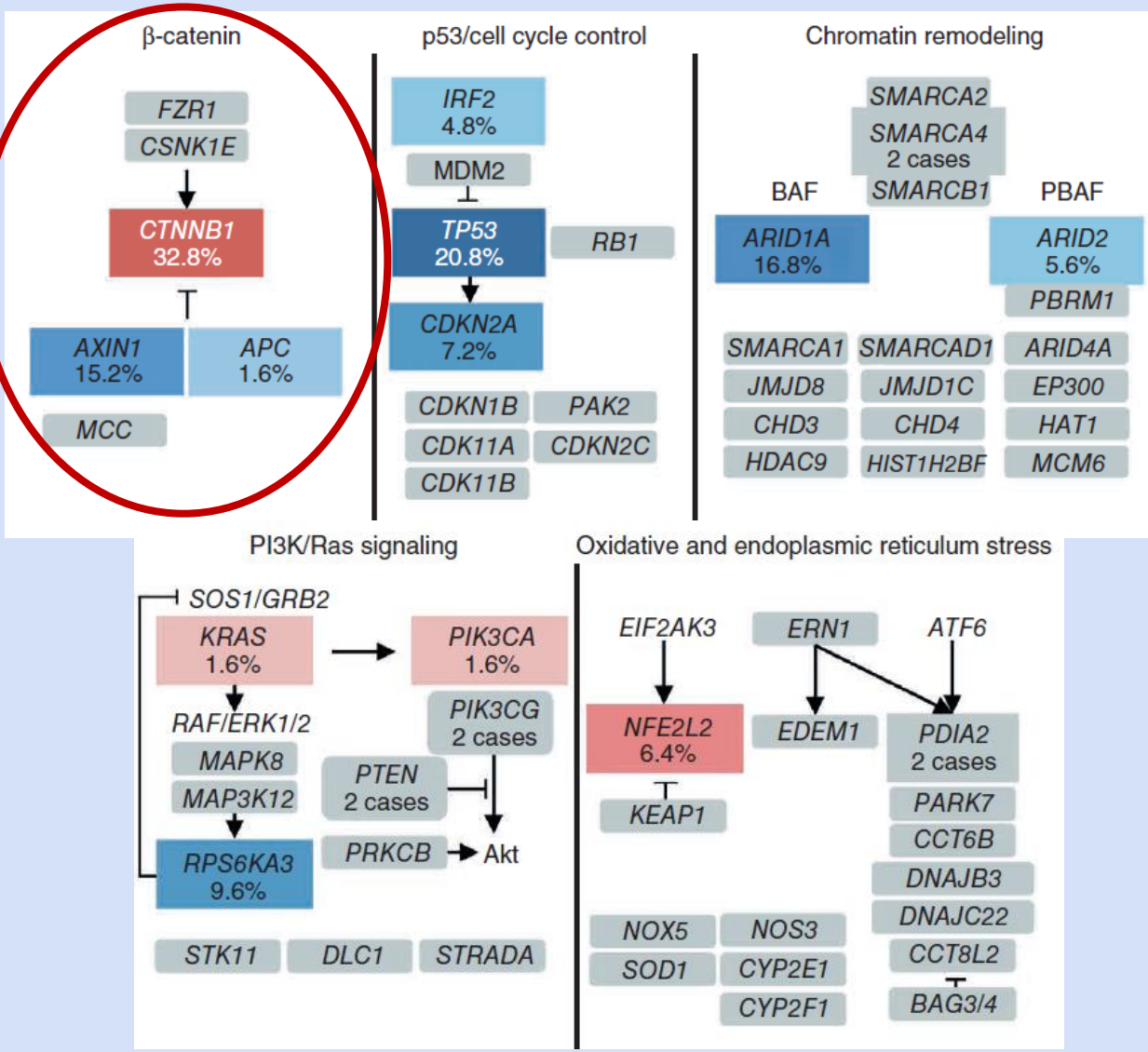
However, testing one drug for one biomarker at one time is painstaking, costly, and frustrating to patients and investigators.

Landscape of the Most Prevalent Mutations and High-Level Gene Amplifications in Human HCC

Gene	Pathways/Gene Functions Involved	Estimated Frequency Based on Deep-Sequencing Studies (%)
Driver Genes Frequently Mutated in HCC		
TERT promoter	telomere stability	60
TP53	genome integrity	20–30
CTNNB1	WNT signaling	15–25
ARID1A	chromatin remodeling	10–16
TTN	chromosome segregation	4–10
NFE2L2	oxidative stress	6–10
JAK1	JAK/STAT signaling	0–9
Oncogenes/Tumor Suppressors Rarely Mutated in HCC		
IDH1, IDH2	NAPDH metabolism	<5
EGFR	growth factor signaling	<5
BRAF	RAS/MAPK signaling	<5
KRAS, NRAS	RAS/MAPK signaling	<5
PIK3CA	AKT signaling	<5
PTEN	AKT signaling	<5
Oncogenes Contained in High-Level Amplifications in HCC		
FGF19	FGF signaling	5–10
CCND1	cell cycle	5–10
VEGFA	HGF signaling/angiogenesis	7–10

Josep M. Llovet. Cancer Cell 2014;25:560-2

Integrated Analysis of Somatic Mutations and Focal Copy-number Changes Identifies Key Genes and Pathways in HCC



Guichard C et al: Nature Genetics 2012:44: 694.

Time Has Come to Raise the Bar in Oncology Trials

Oncology clinical trials are at crossroads,…..

There is a need to completely re-envision what a clinical trial looks like, including the mandatory use of “- omics”, and “adaptive design” enabled by high-functioing systems and processes.

Dilts DM, J Clin Oncol 2014;32:1186

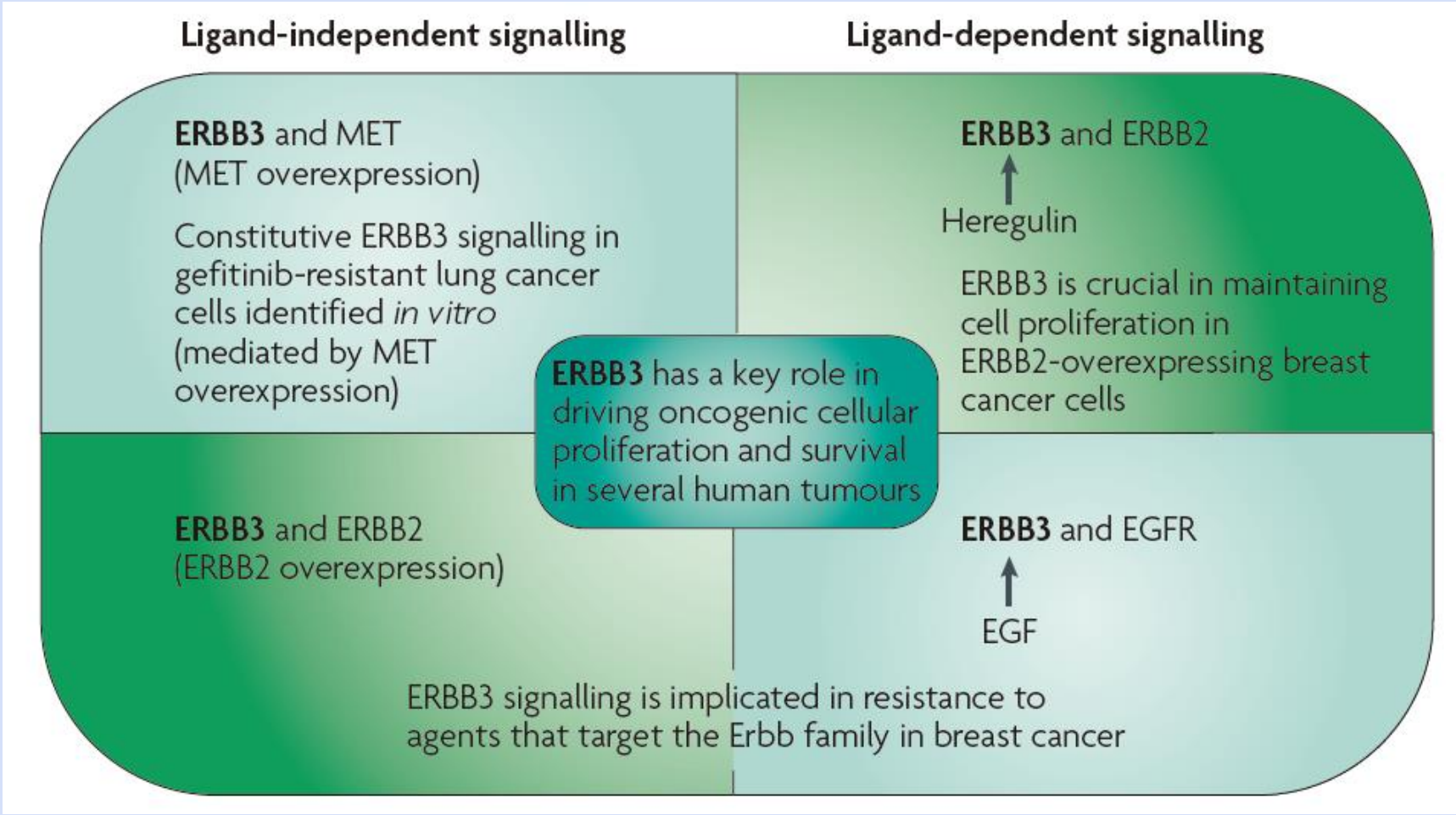
New Targets for HCC

- Wnt/β-Catenin
- JAK/STAT
- FGF19/FGFR4
- VEGF-A
- c-MET
- TSC-2

CONCLUSIONS

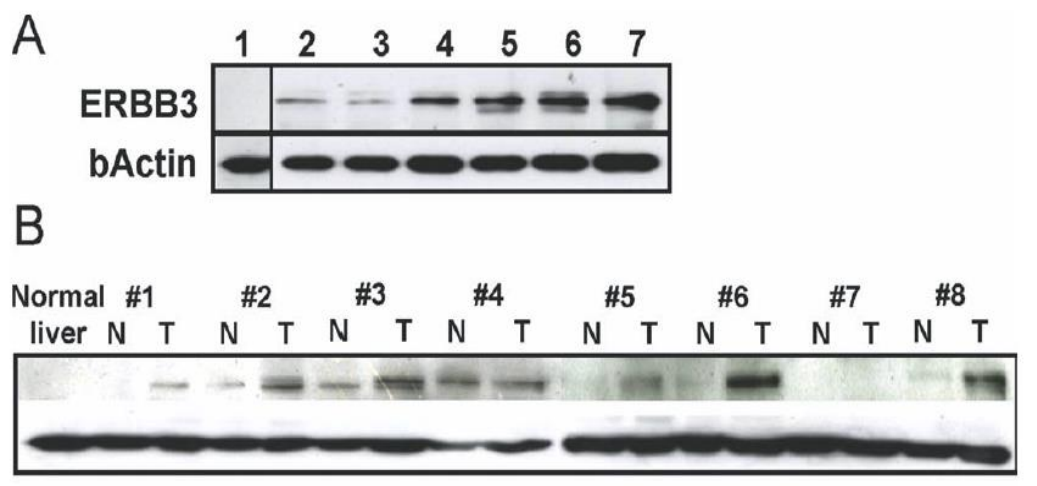
1. **Biomarker-driven adaptive trials, testing multi-drugs in multi-arms are possible in HCC.**
2. **“Super-adaptive” design of trials may help expedite drug development in HCC.**
3. **A disinterested organization that works with multiple companies, and provides the logistic support for a big data-managing operation is mandatory – These problems can be solved by a single- or oligo-company study.**
4. **Regulatory approval may be a problem, but can be solved by conducting the study in a single/oligo, well-experienced countries.**

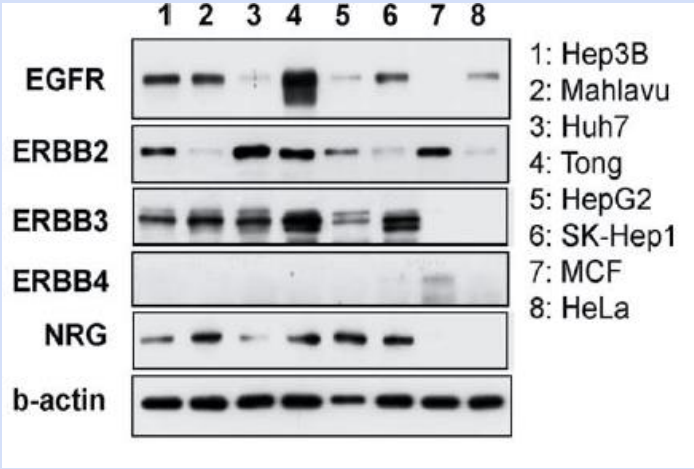
The Central Role of HER-3



~ Baselga J & Swain SM: Nature Rev Cancer 2009; 9 463.

Neuregulin/HER3 Autocrine Loop Contributes to Invasion and Early Recurrence of Human HCC





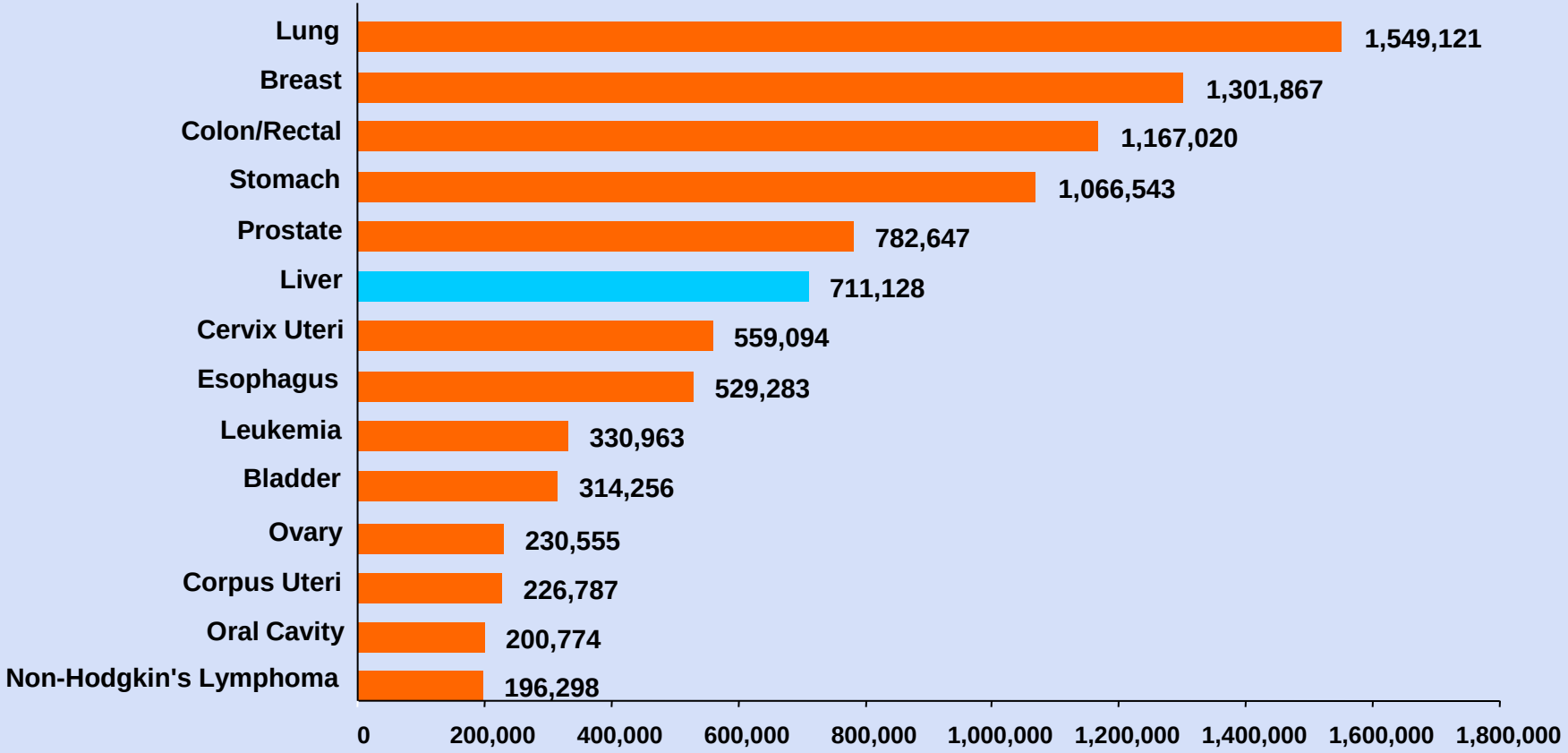
- HER-3 overexpression associated with intra-hepatic metastasis, recurrence, and poor prognosis

~ Hsieh SY et al: Hepatol 2011; 53: 504.

(A) Immunoblotting of HER-3: Lane 1, normal liver tissue; 2, Huh7; 3, HepG2; 4, Mahlavu; 5, SK-Hep1; 6, Tong; 7, and Hep3B. By real-time qRT-PCR, the overexpression of HER-3 in HCC compared to non-tumor part (2 fold-elevation) was seen in 50/71 HCC patients (~ 70%).

Liver Cancer:

- **Sixth most common cancer worldwide[1]**
- **Third most common cause of cancer-related death[2]**



1. Garcia M, et al. American Cancer Society, 2007. www.cancer.org. Accessed March 20, 2008.
2. http://www.who.int/mediacentre/factsheets/fs297/en/index.html. Accessed June, 2008.

Whole-genome Sequencing of Liver Cancers Identifies Etiological Influences on Mutation Patterns and Recurrent Mutations in Chromatin Regulators

Table 1 Significantly mutated genes and their mutation frequency in the validation set

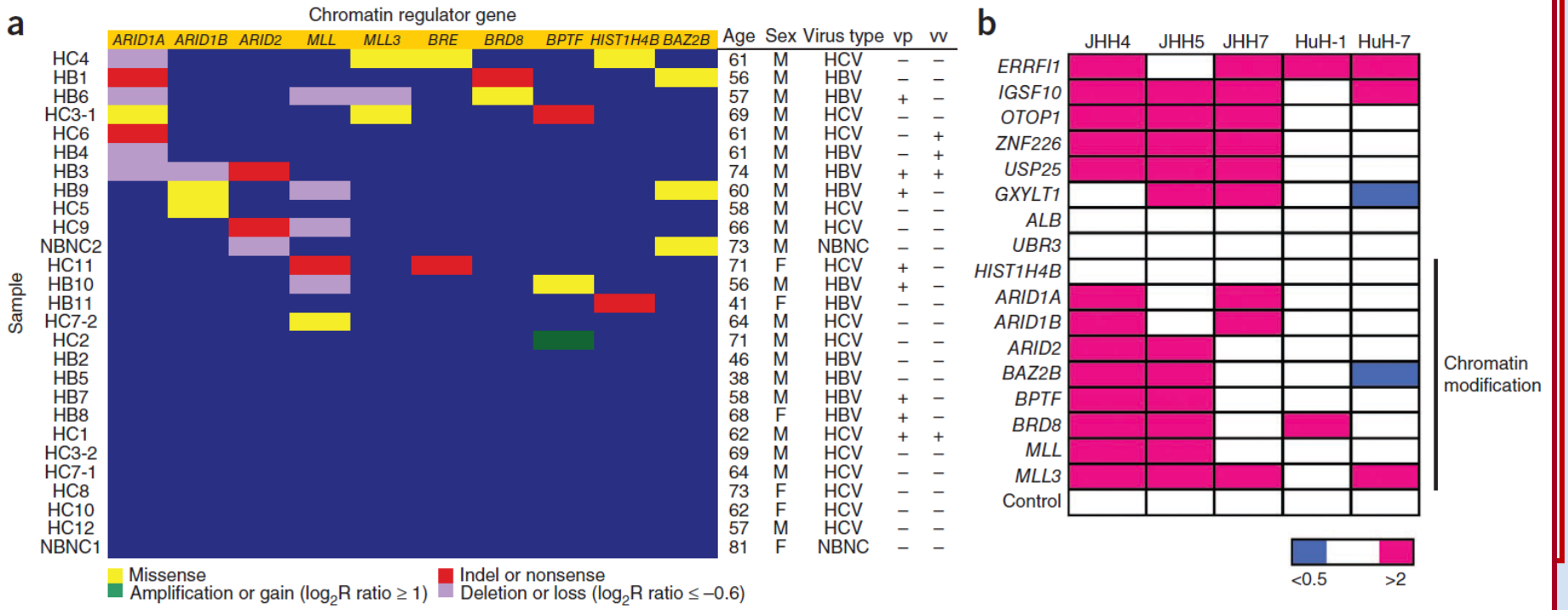
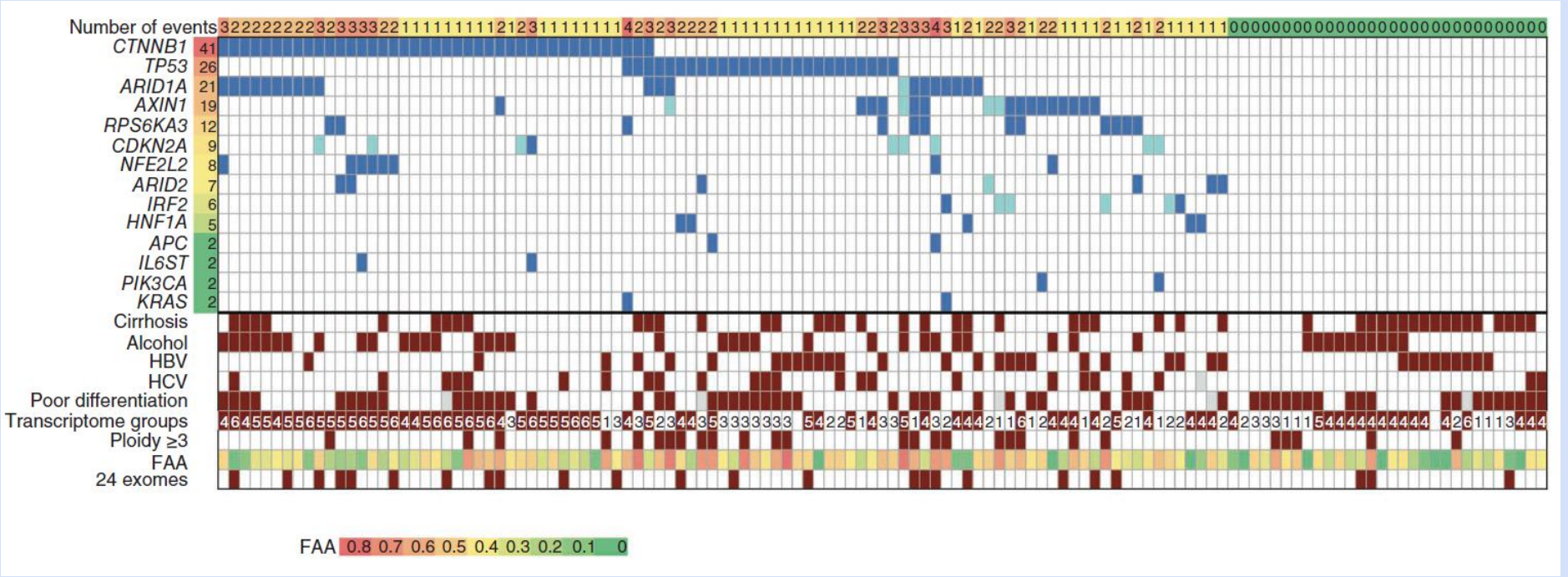


Figure 4 Mutations in chromatin regulators and functional analysis of potential driver genes. (**a**) Mutations in chromatin regulators in 27 HCC genomes. Mutations in chromatin-regulator genes are summarized. In addition to point mutations, 55.6-kb genomic deletion of *ARID2* in NBNC2, which was identified by the read-pair method, and several copy-number alternations of chromatin-regulator genes are included. HC6 had both 1-bp deletion and low-level loss in *ARID1A*. (**b**) Functional assays of potential driver genes in HCC cell lines. Changes in cell proliferation in five HCCs compared to proliferation with control siRNA treatment are presented. Magenta and blue boxes represent more than 2-fold and less than 0.5-fold changes in the cell number, respectively. Genes involved in chromatin modification are indicated by the line.

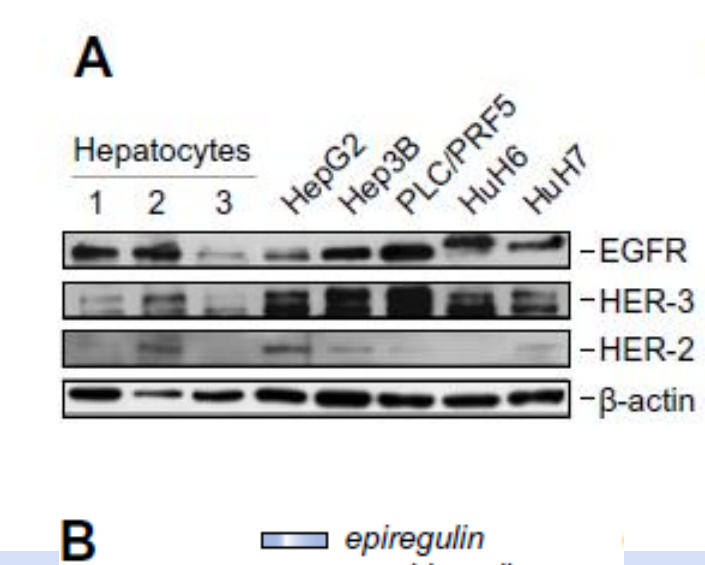
Fujimoto A, et al. Nat Genet. 2012 May 27 (Epub).

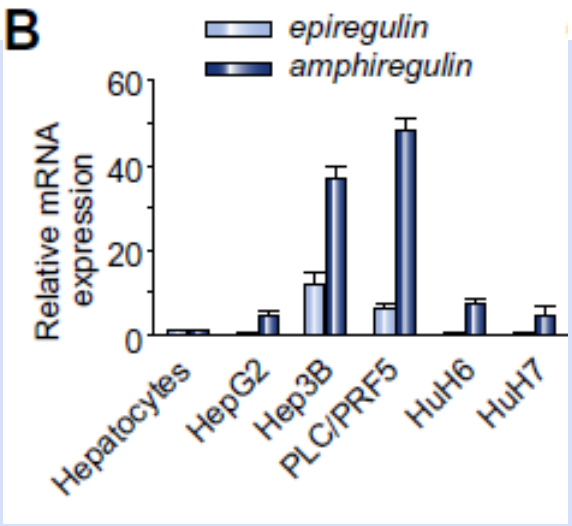
Integrated Analysis of Somatic Mutations and Focal Copy-number Changes Identifies Key Genes and Pathways in Hepatocellular Carcinoma

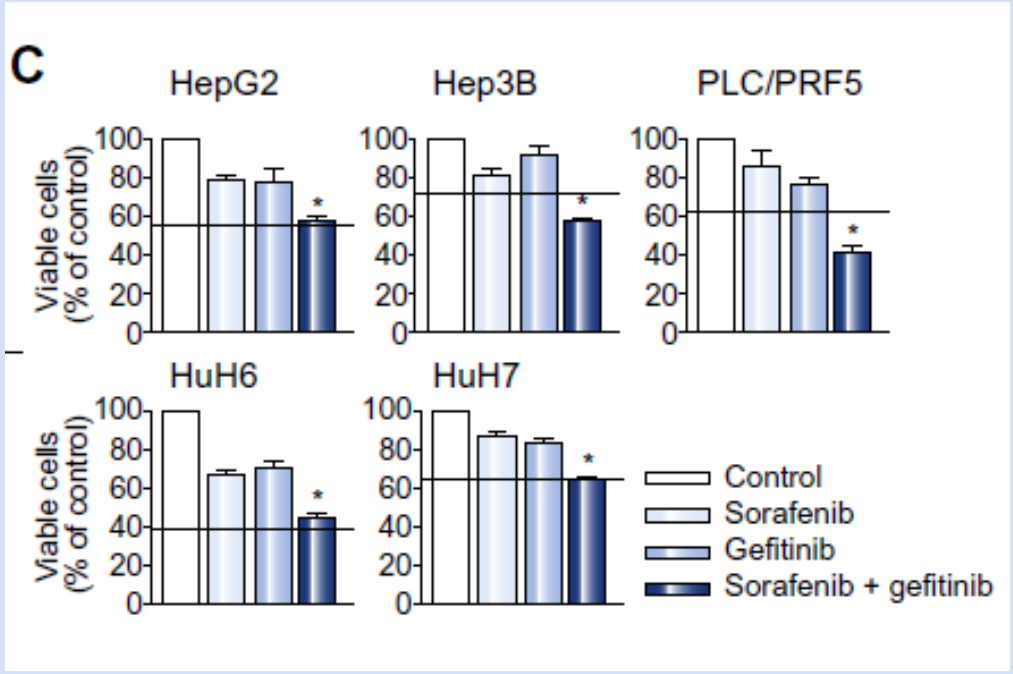


Guichard C et al: Nature Genetics 2012:44: 694.

Increased HER-3 and EGF-like Ligands in HCC Cells



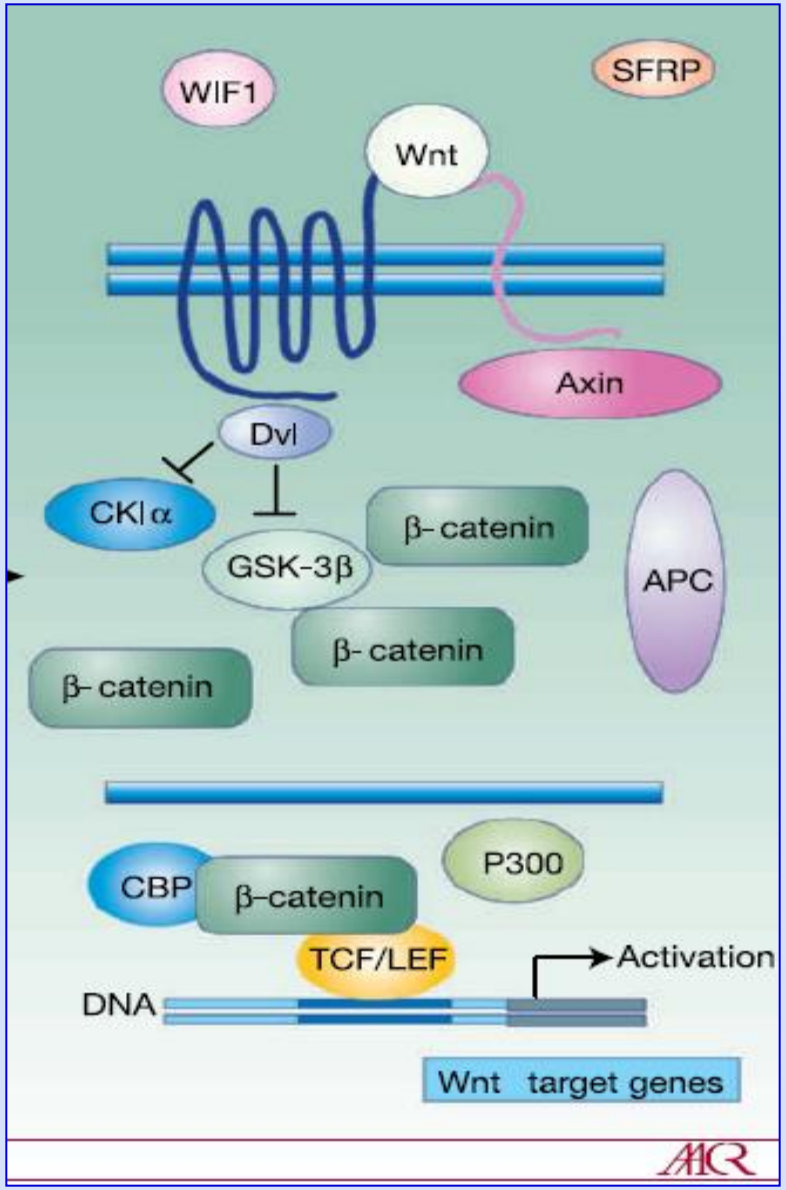




~ Blivet-Van Eggelpoël MJ, et al: J Hepatol 2012; 57(1):108-15.

Targeting WNT/β-catenin Pathway

- Biologics:
  - Restoration of inhibitors
  - Targeting Wnt ligand-Fz receptor
- siRNA
- Small molecules:
  - Novel compounds
  - Existing drugs



Small-molecules Targeting Wnt Signaling

IWP (Inhibitors of Wnt production)

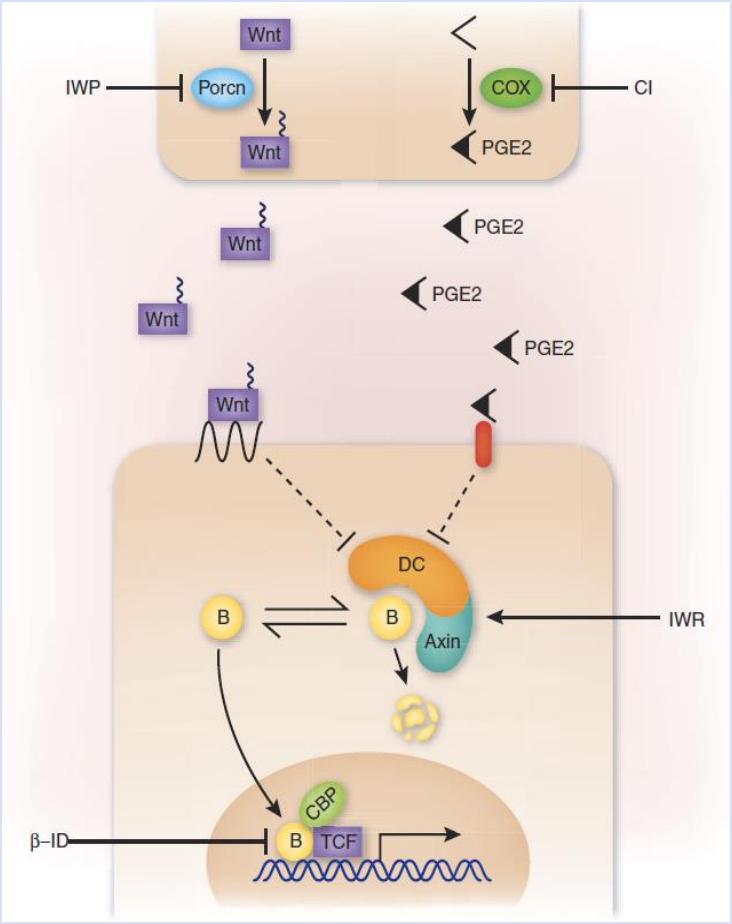
- LGK974

IWR (Inhibitors of Wnt response)

- XAV939
- Other Tankyrase inhibitors

β-ID (β-catenin interaction disruptors)

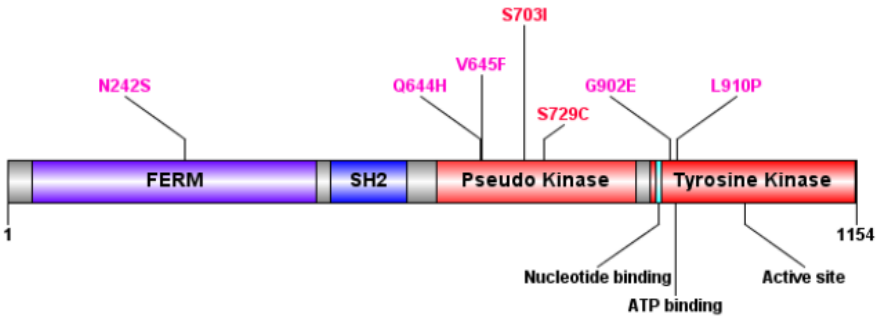
- ICG-001
- PRI-724

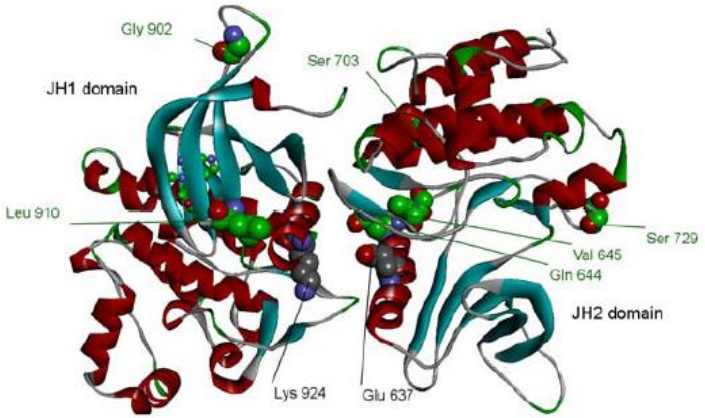


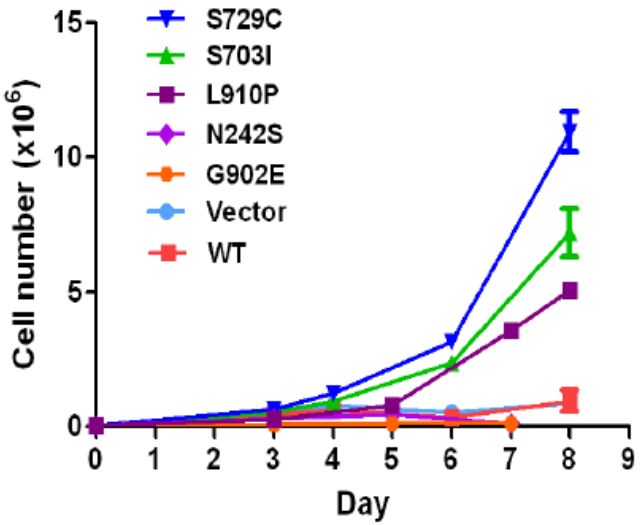
~ Yeh JY & Peterson RT: Nature Chem Biol 2009;5:74 (News) &
~ Chen B et al: Nature Chem Biol 2009;5:100-.

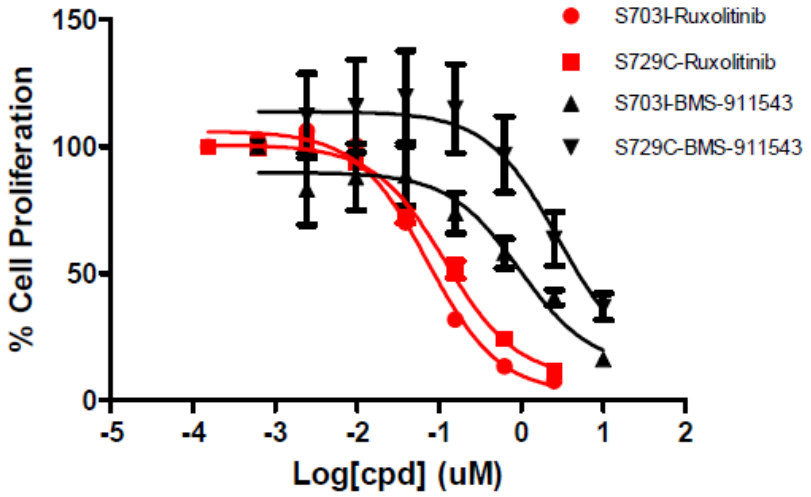
Whole Genome Sequencing Identifies Recurrent Mutations in HCC – 88 cases from HBV-endemic area

Activating mutations in JAK1



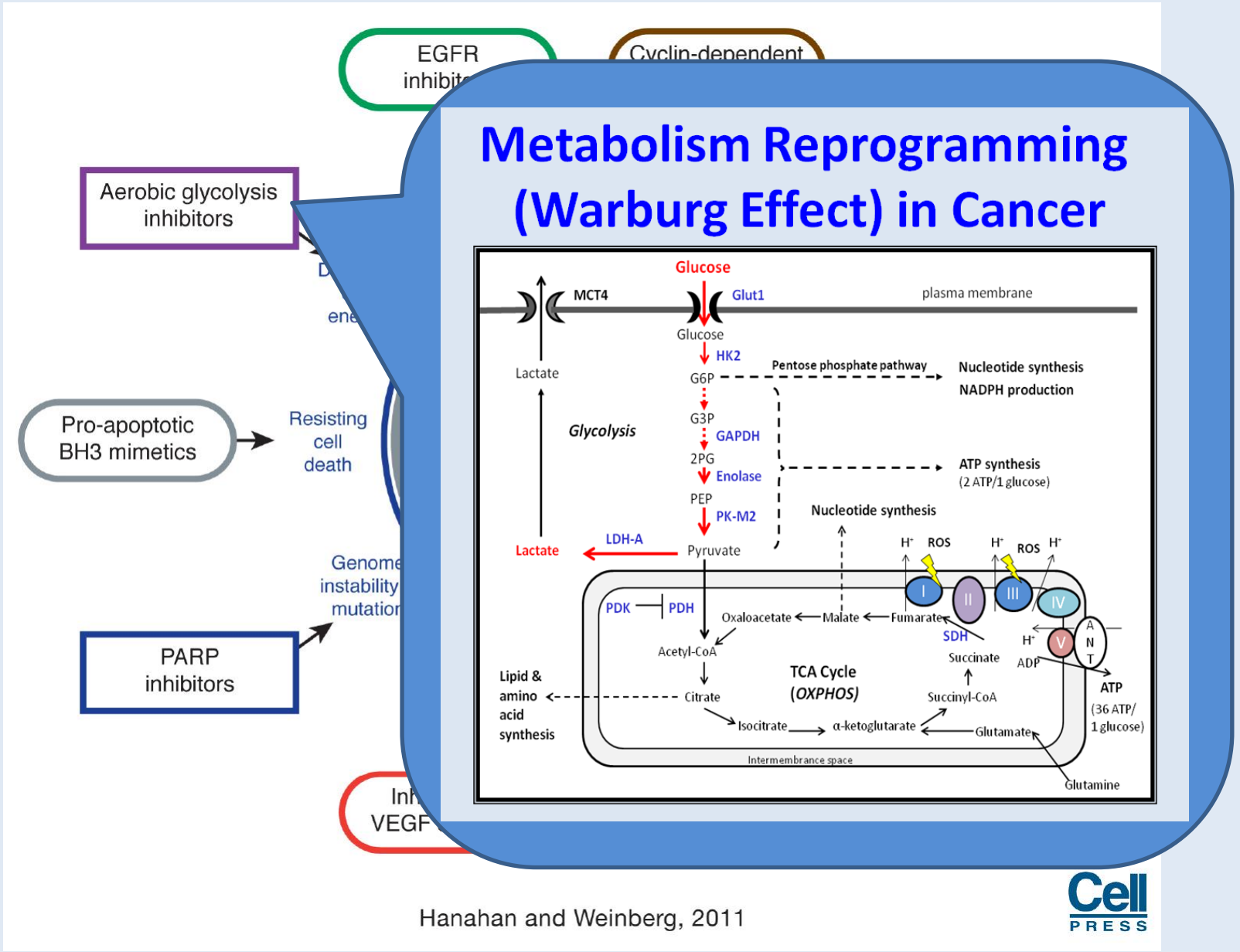






Kan Z, et al. Genome Res. 2013 Jun 20. [Epub ahead of print]

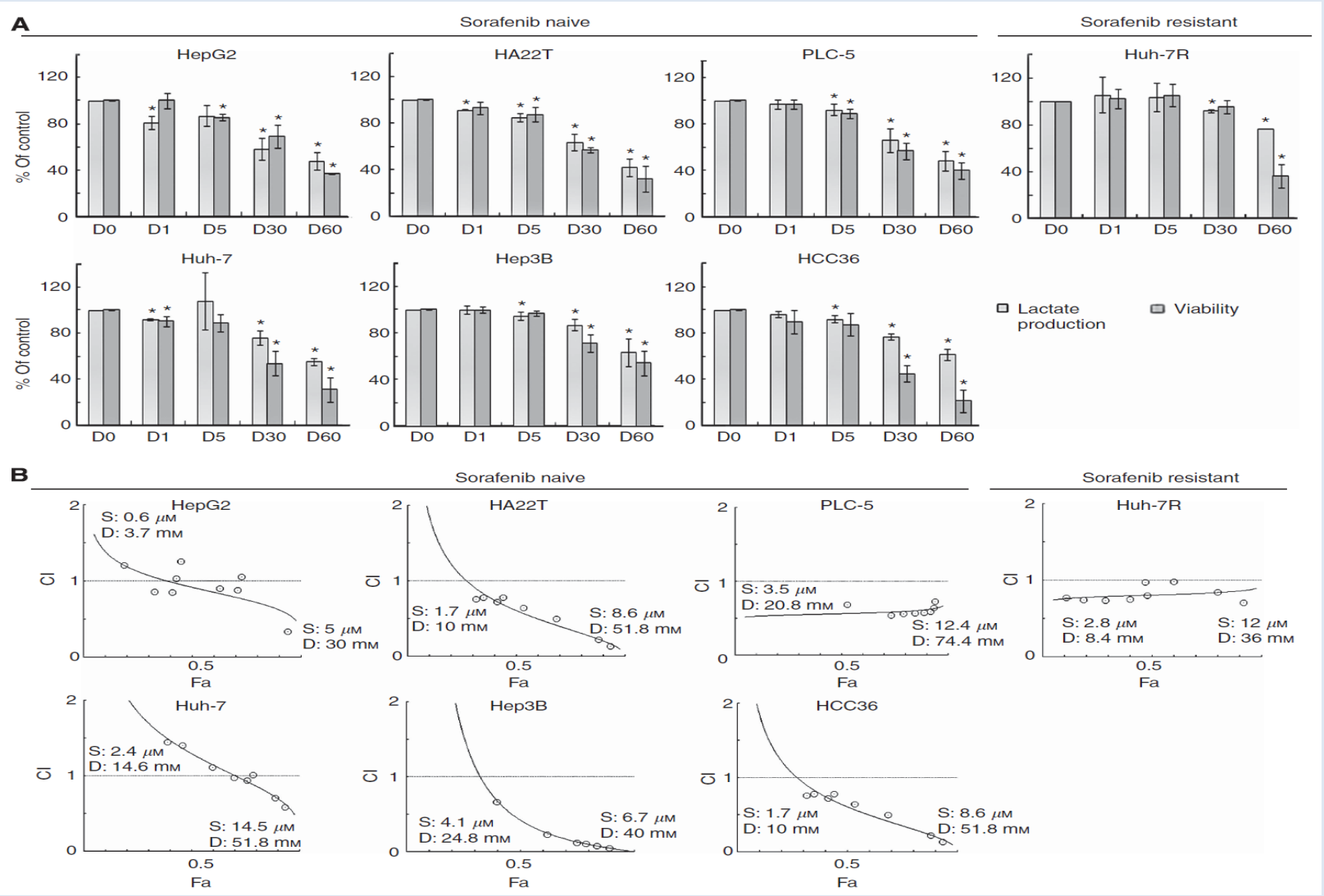
Therapeutic Targeting of the Hallmarks of Cancer



Hanahan and Weinberg, 2011

Cell PRESS

Activating Oxidative Phosphorylation by a PDK inhibitor Overcomes Sorafenib Resistance of HCC



Shen YC et al. Br J Cancer (2013) 108, 72–81

7 Years On - - -

- **Results of SHARP was presented in June 2007. Sorafenib was approved by FDA (Dec. 2007) and EMEA (Oct. 2007).**
- **Notable ongoings:**

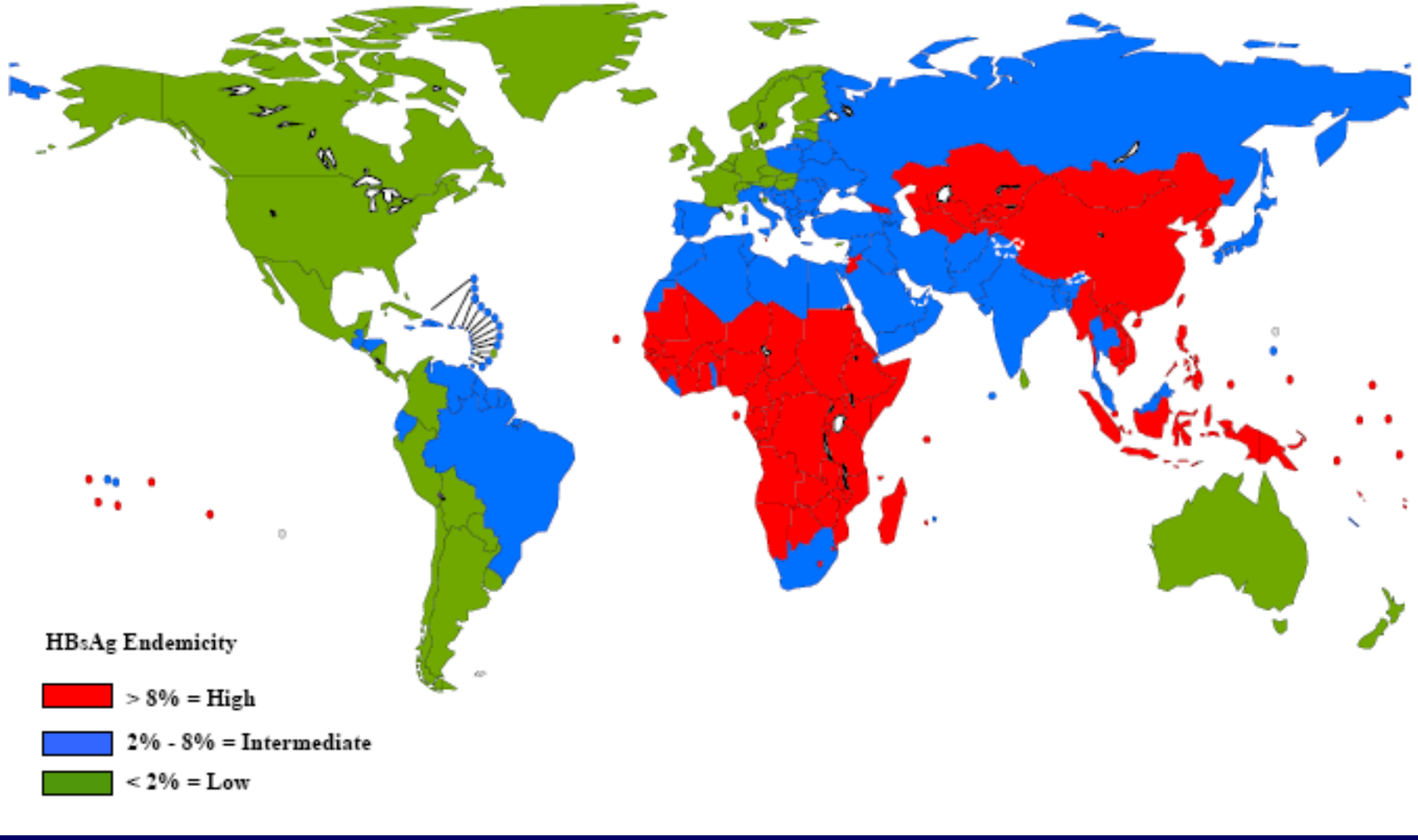
  Lenvatinib – phase III, 1st-line (vs sorafenib)

  Tivantinib – phase III, 2nd-line (c-met enriched)

  Cabozantinib – phase III, 2nd-line

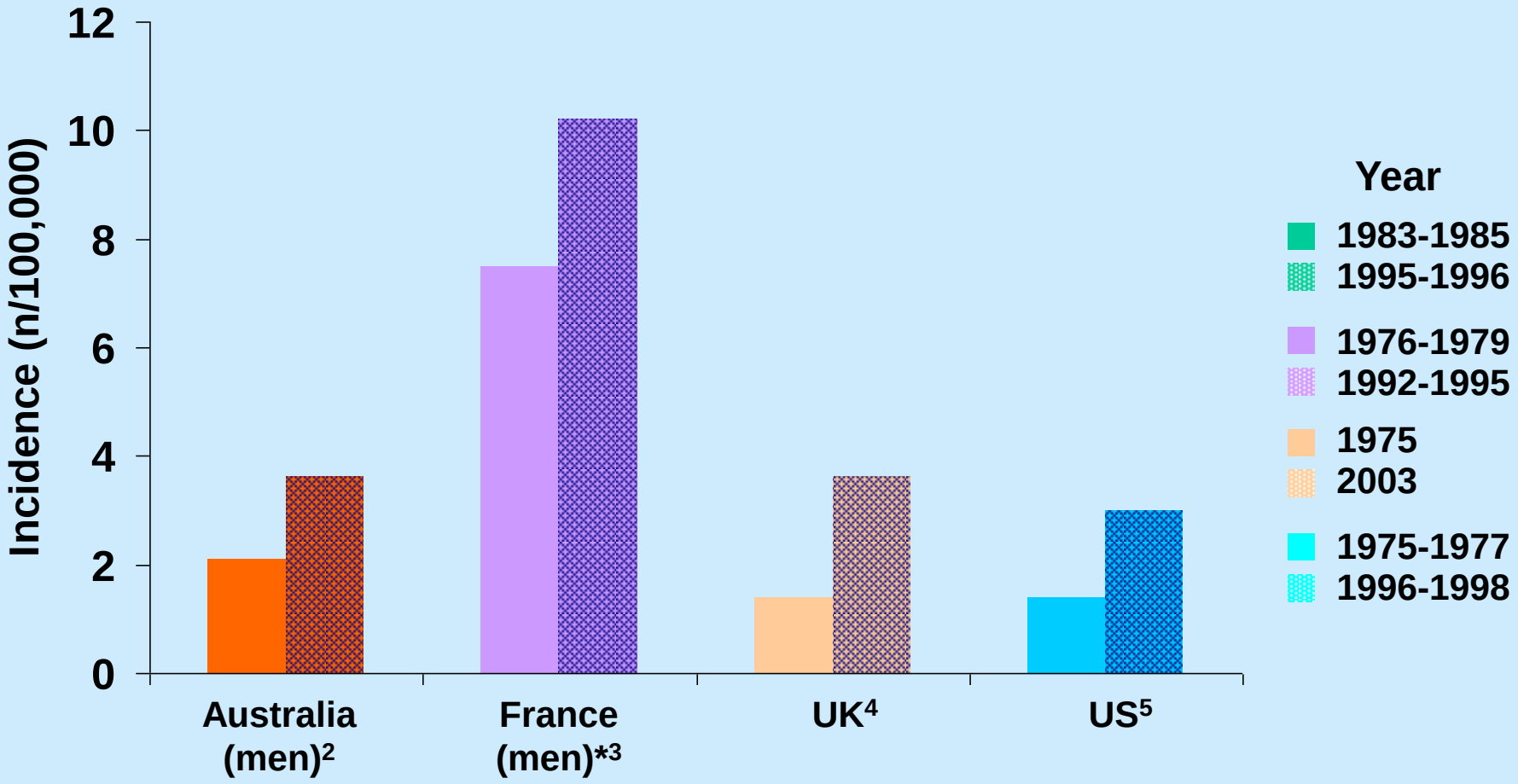
  Regorafenib – phase III, 2nd-line

Geographic Variations of HBV infection



WHO

Incidence of HCC – Increasing in Western Countries



*Primary liver cancer.

1. El-Serag HB et al. *Gastroenterology*. 2007;132:2557–2576; 2. Law MG, et al. *Med J Aus.* 2000;173:403-405;
3. Benhamiche A-M, et al. *J Hepatol*. 1998;29:802-806;
4. http://info.cancerresearchuk.org/cancerstats/types/liver/incidence/?a=5441. Accessed January 2008;
5. El-Serag HB, et al. *Ann Intern Med*. 2003;139:817-823.

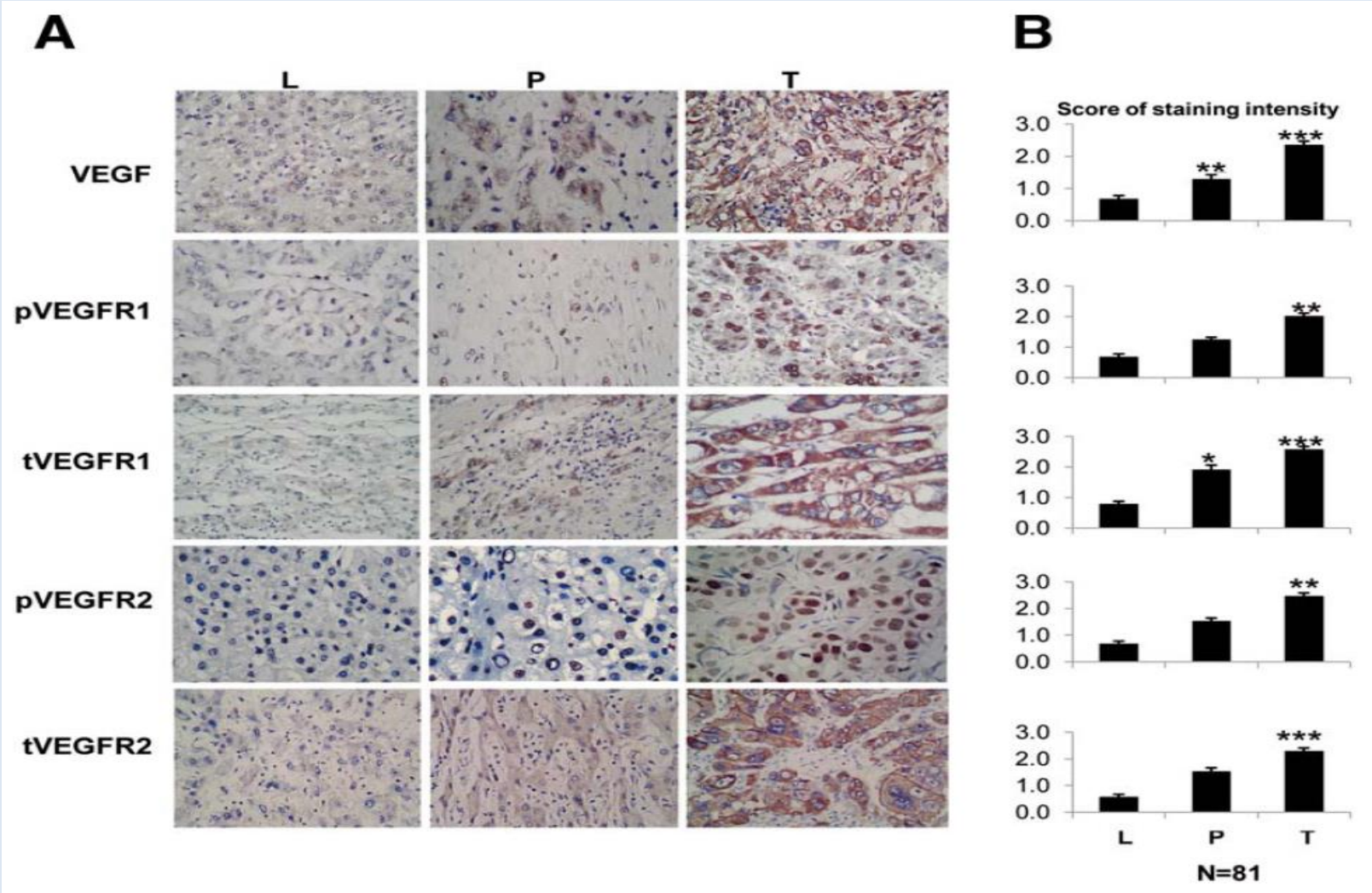
ASCO 2011

Phase 3 Trial of Sunitinib versus Sorafenib in Advanced Hepatocellular Carcinoma

A-L Cheng,[1] Y-K Kang,[2] D-Y Lin,[3] J-W Park,[4] M Kudo,[5] S Qin,[6] M Omata,[7] S Pitman Lowenthal,[8] S Lanzalone,[9] L Yang,[8] MJ Lechuga,[9] E Raymond[10] for the SUN1170 HCC Study Group

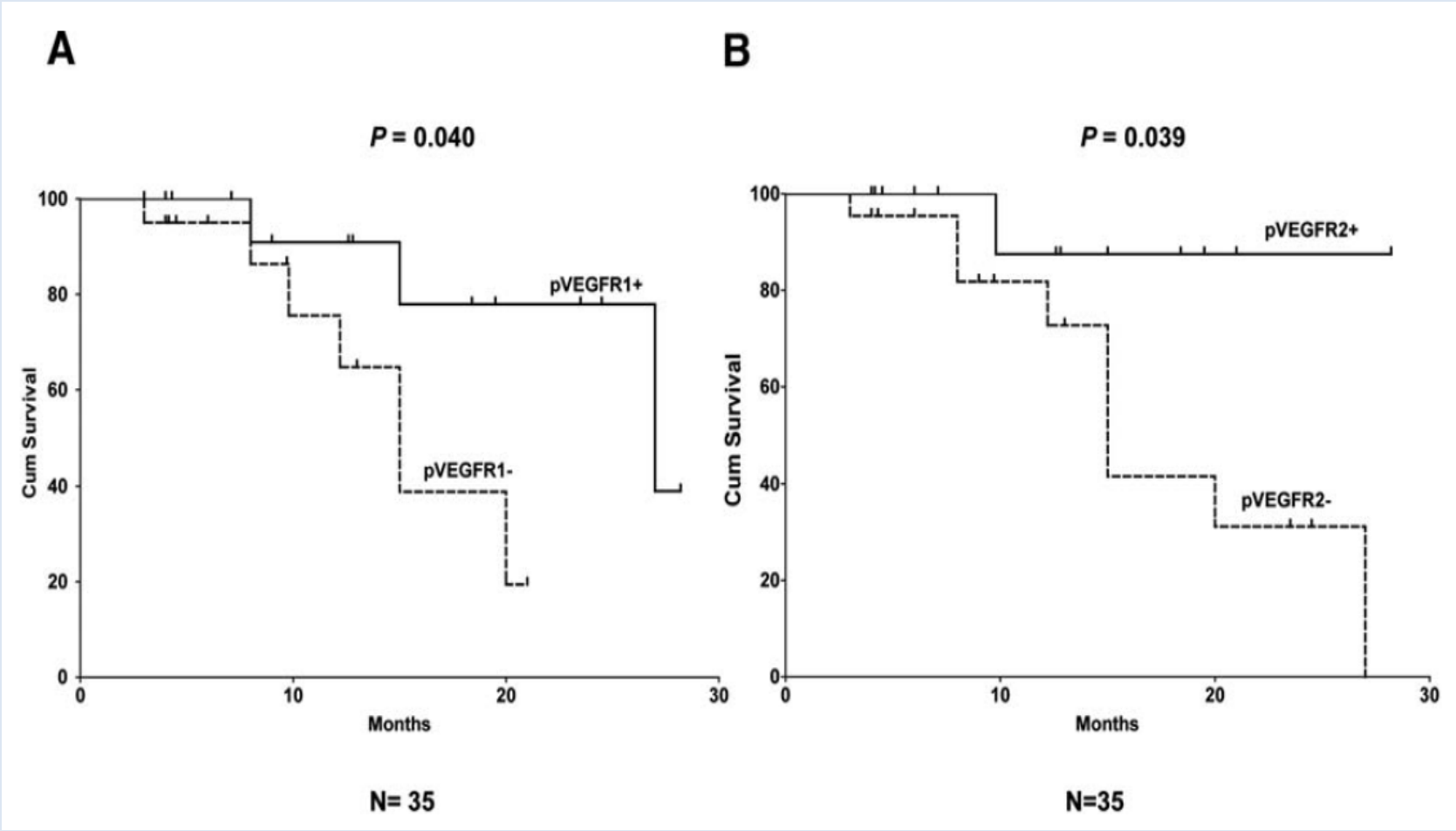
[1]National Taiwan University Hospital, Taipei, Taiwan; [2]Asan Medical Center, Seoul, Republic of Korea; [3]Chang Gung Memorial Hospital, Chang Gung University, Taiwan; [4]Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea; [5]Kinki University Hospital, Osaka, Japan; [6]Nanjing Bayi Hospital, Nanjing, Jiangsu, China; [7]Yamanashi Prefecture Central Hospital, Kofu, Yamanashi, Japan; [8]Pfizer Oncology, La Jolla, California, USA; [9]Pfizer Italia Srl, Milan, Italy; [10]Service Inter Hospitalier de Cancerologie Bichat-Beaujon, Clichy, France

Autocrine VEGF Signaling Promotes Cell Proliferation and Modulates Sorafenib Treatment Efficacy in HCC



Peng S, et al. Hepatol 2014;60:1264-1277

Autocrine VEGF Signaling Promotes Cell Proliferation and Modulates Sorafenib Treatment Efficacy in HCC



Peng S, et al. Hepatol 2014;60:1264-1277

Expression of FGF19 is Associated with Recurrence and Poor Prognosis of HCC

- FGF19 expression in 48% of 281 HCC

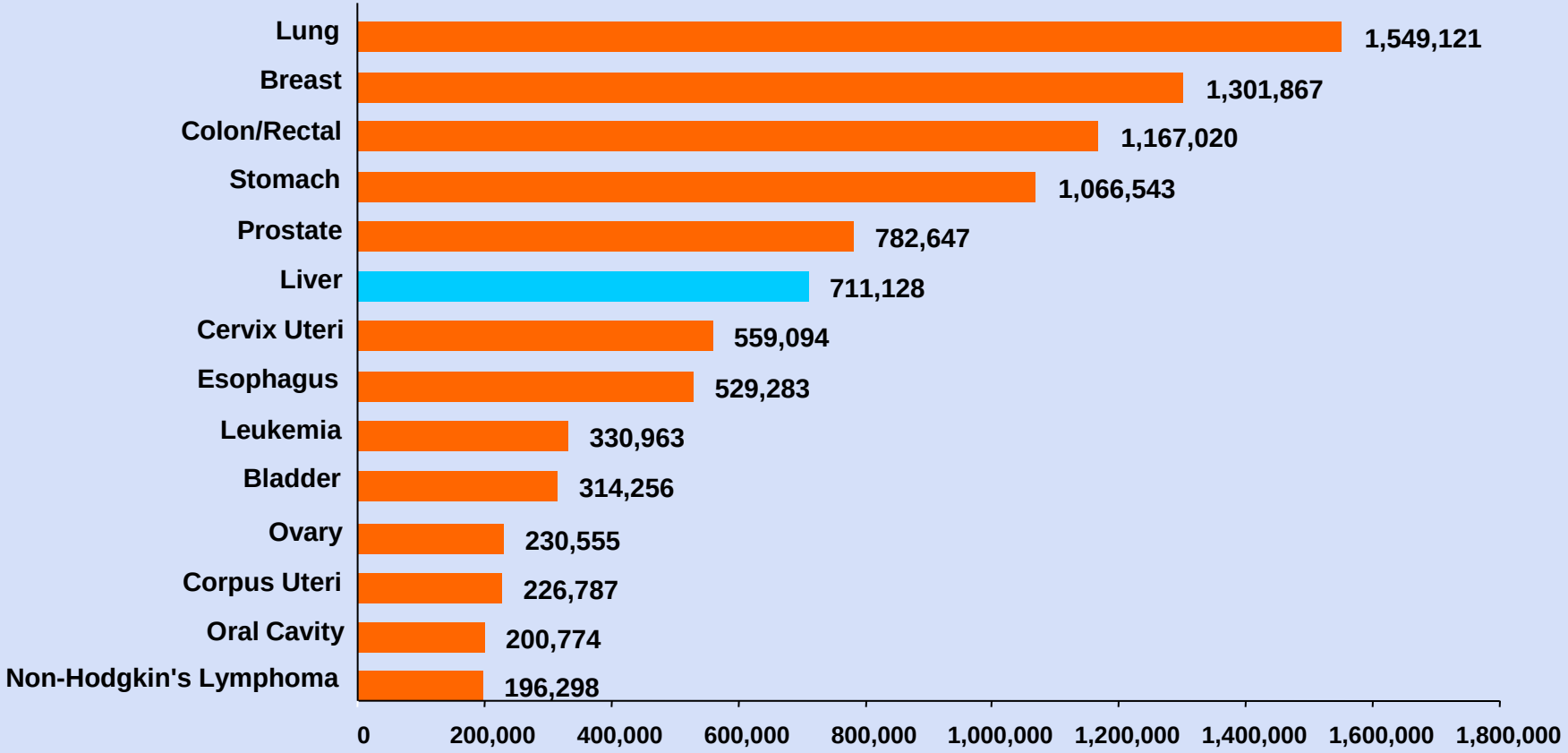
  (> 5% tumor cells showed IHC memb. staining)

- FGF19 expression is associated with large tumor, higher BCLC stages, early recurrence, and shorter DFS.

Hyeon J et al Dig Dis Sci 2013;58:1916-22

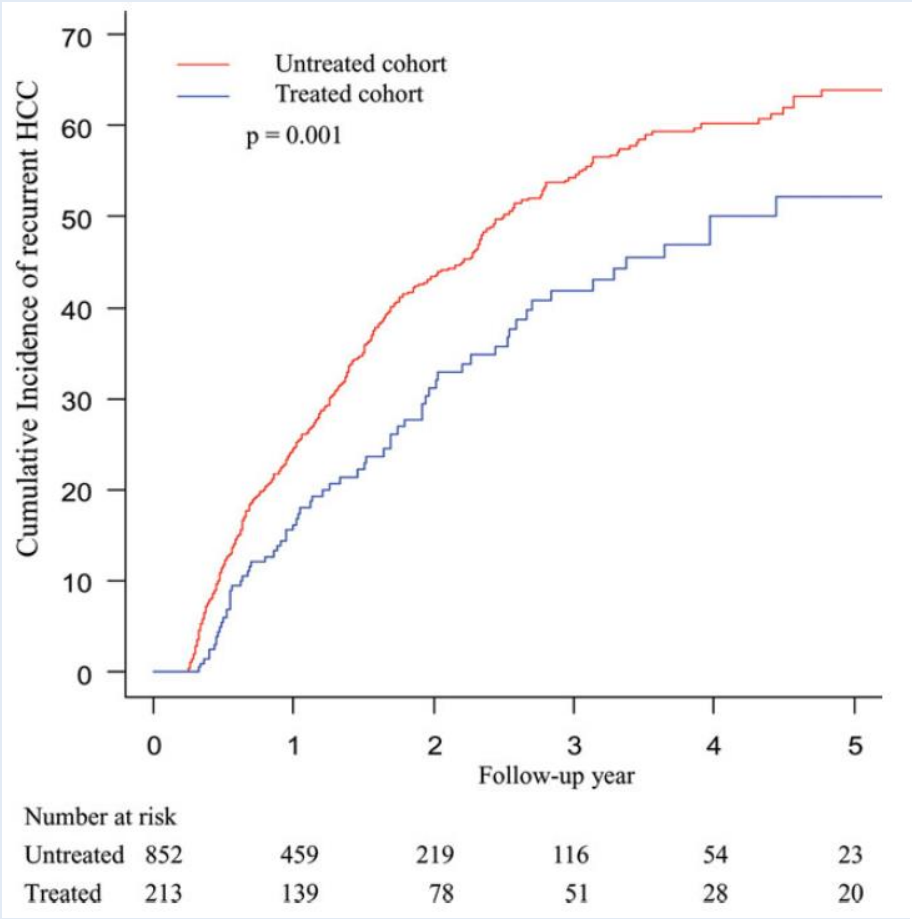
Liver Cancer:

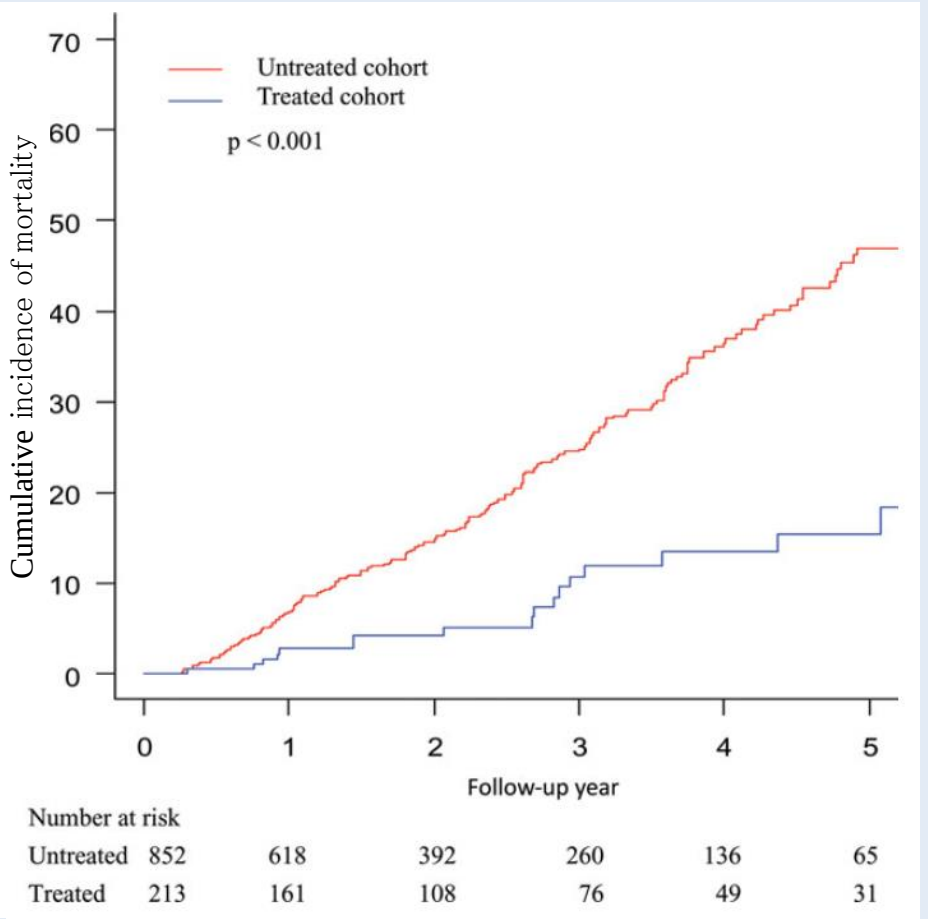
- **Sixth most common cancer worldwide[1]**
- **Third most common cause of cancer-related death[2]**



1. Garcia M, et al. American Cancer Society, 2007. www.cancer.org. Accessed March 20, 2008.
2. http://www.who.int/mediacentre/factsheets/fs297/en/index.html. Accessed June, 2008.

Postoperative Peg-Interferon Plus Ribavirin Is Associated with Reduced Recurrence of HCV-Related HCC





Hsu YC et al Hepatol 2013;58:150-157

Effect of Antiviral Treatment With Nucleotide/Nucleoside Analogs on Postoperative Prognosis of HBV–Related HCC:

A Two-Stage Longitudinal Clinical Study

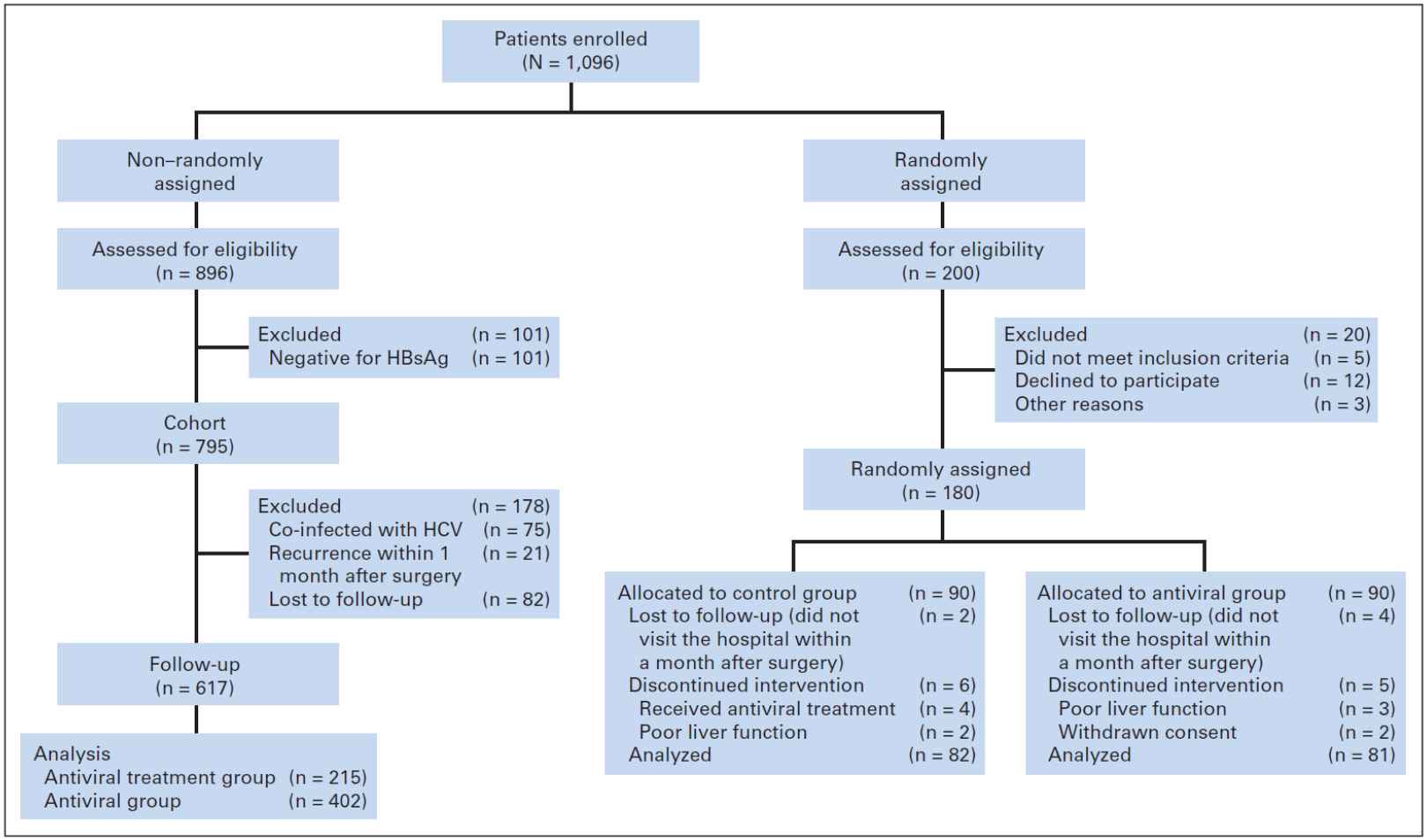
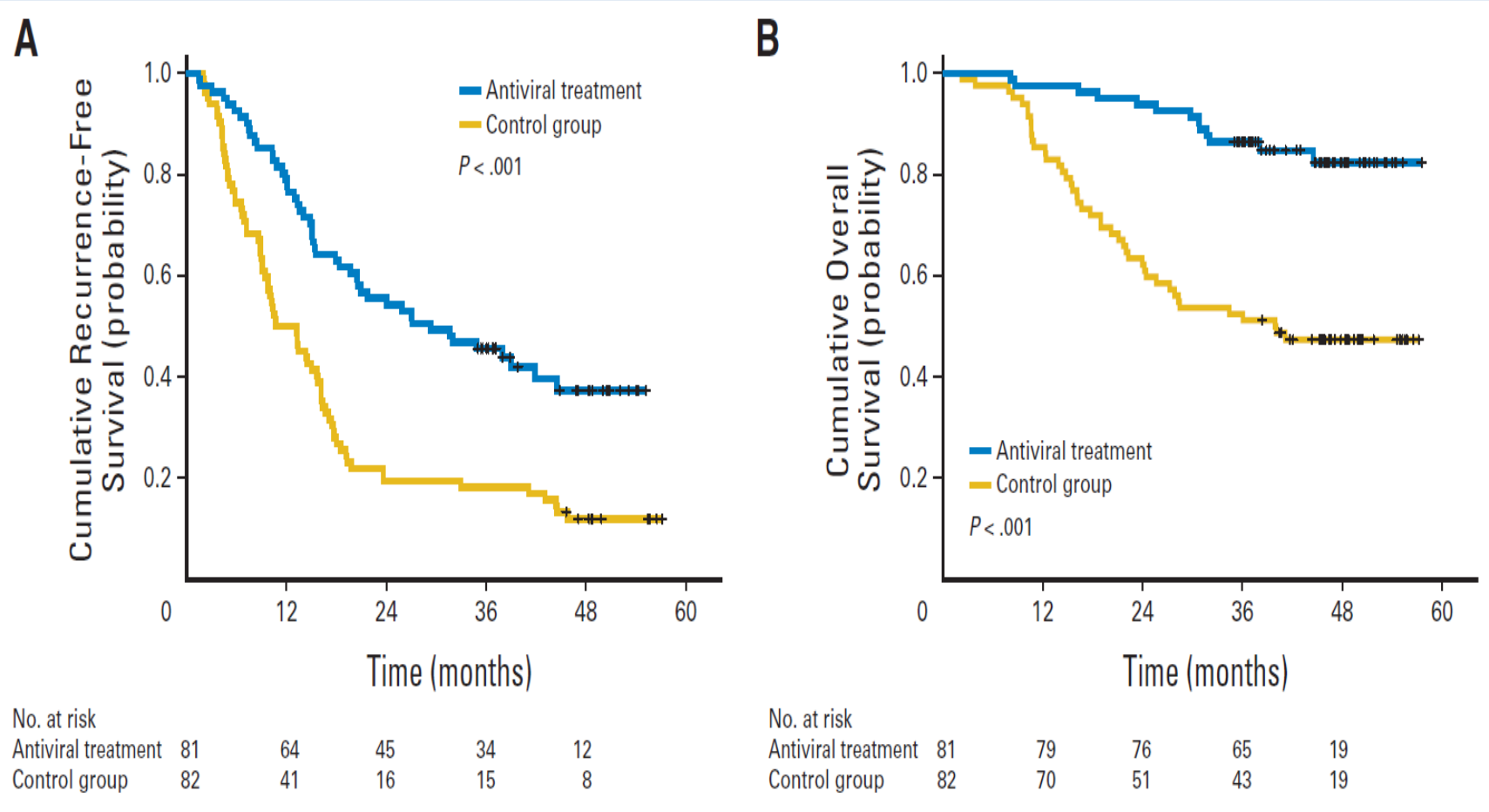


Fig 1. CONSORT diagram of the patients enrolled onto the nonrandomized cohort and the randomized clinical trial. HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Yin J et al J Clin Oncol 31:3647-3655

Effect of Antiviral Treatment With Nucleotide/Nucleoside Analogs on Postoperative Prognosis of HBV–Related HCC:

A Two-Stage Longitudinal Clinical Study



Yin J et al J Clin Oncol 31:3647-55

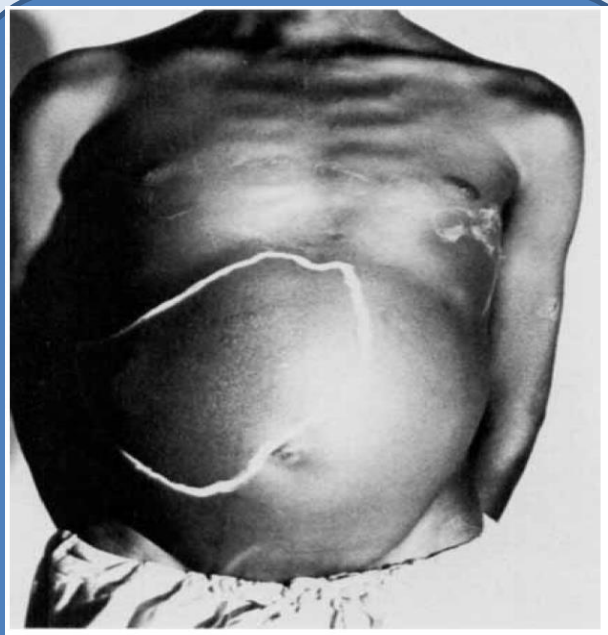


FIG. 1. Patient A.B. on admission. Note the wasting, liver size, and abdominal distention d[illegible]ites.

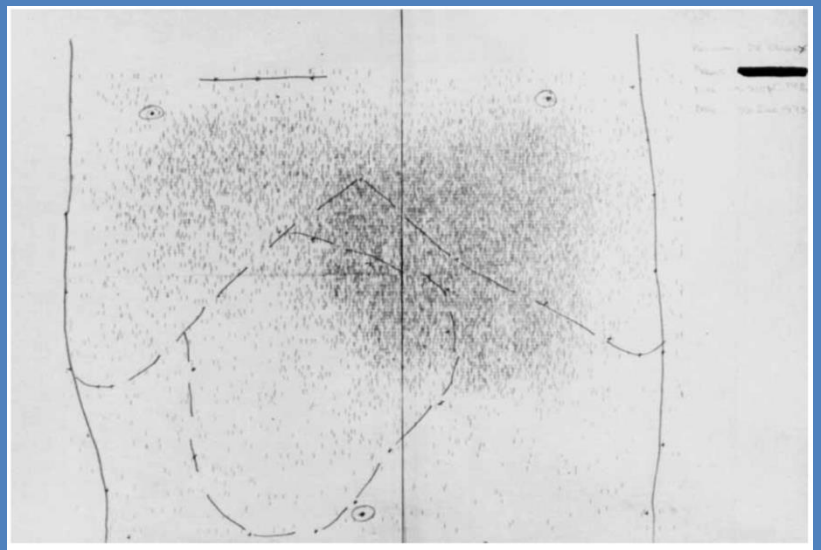
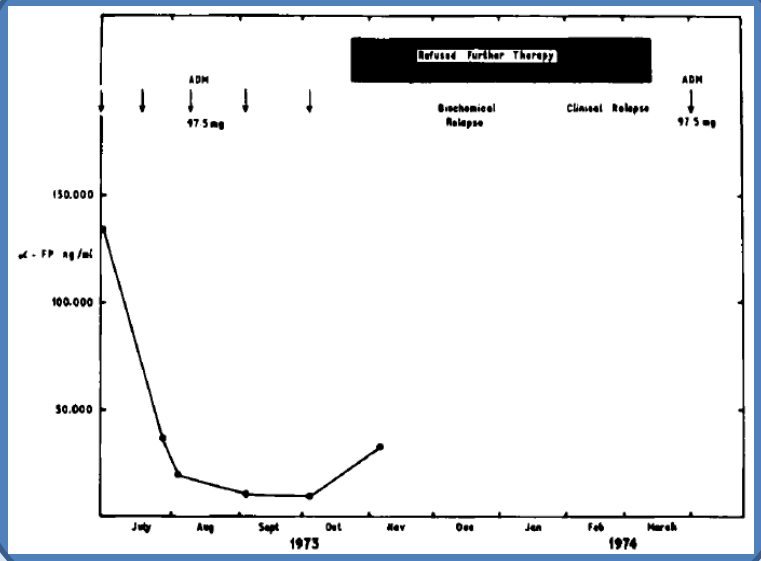
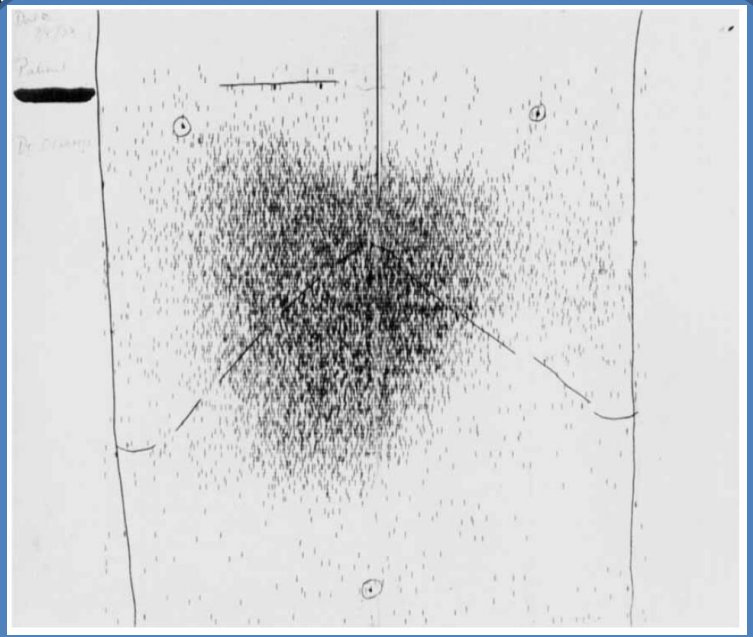


FIG. 2. Liver scan of patient A.B. done on admission, June, 1973. Note the mass outlined.





A Randomized Phase III Study of Doxorubicin Versus Cisplatin/Interferon α -2b/Doxorubicin/Fluorouracil (PIAF) Combination Chemotherapy for Unresectable HCC

Parameter	Doxorubicin arm	PIAF arm	*P* value†
Median no. of cycles	4	3	
Responses			
Complete response	0	0	
Partial response	9	19	
Stable disease	37	35	
Progressive disease	40	37	
Overall responses	10.5% (95% CI = 3.9 to 16.9%)	20.9% (95% CI = 12.5 to 29.2%)	.058
Median overall survival (mo.) based on intent-to-treat	6.83 (95% CI = 4.80 to 9.56)	8.67 (95% CI = 6.36 to 12.00)	.830

Yeo W, et al. J Natl Cancer Inst 2005;97:1532 – 8

Table 3. Toxicity profiles by treatment arm*

Toxicities	Doxorubicin arm		PIAF arm		*P* value†
	N	%	N	%	
Neutropenia	59	63	77	82	.003
Thrombocytopenia	23	24	54	57	<.001
Anemia	26	28	26	28	1.000
Febrile neutropenia	16	17	12	12	.412
Raised hepatic transaminase	12	13	16	17	.413
Hyperbilirubinaemia	15	16	12	13	.533
Diarrhea	7	7	11	12	.322
Vomiting	4	4	11	12	.059
Stomatitis	7	7	3	3	.193
Anorexia	3	3	7	7	.193
Abdominal pain	6	6	3	3	.305
Alkaline phosphatase	7	7	5	5	.550
Malena/gastrointestinal bleeding	5	5	5	5	1.000
Hypokalemia	0	0	7	7	.007
Hyponatremia	1	1	6	6	.054
Nausea	4	4	2	2	.406
Treatment-related mortality	3	3	8	9	.194

Yeo W, et al. J Natl Cancer Inst 2005;97:1532 – 8

APASL Guideline : Chemotherapy/New drugs

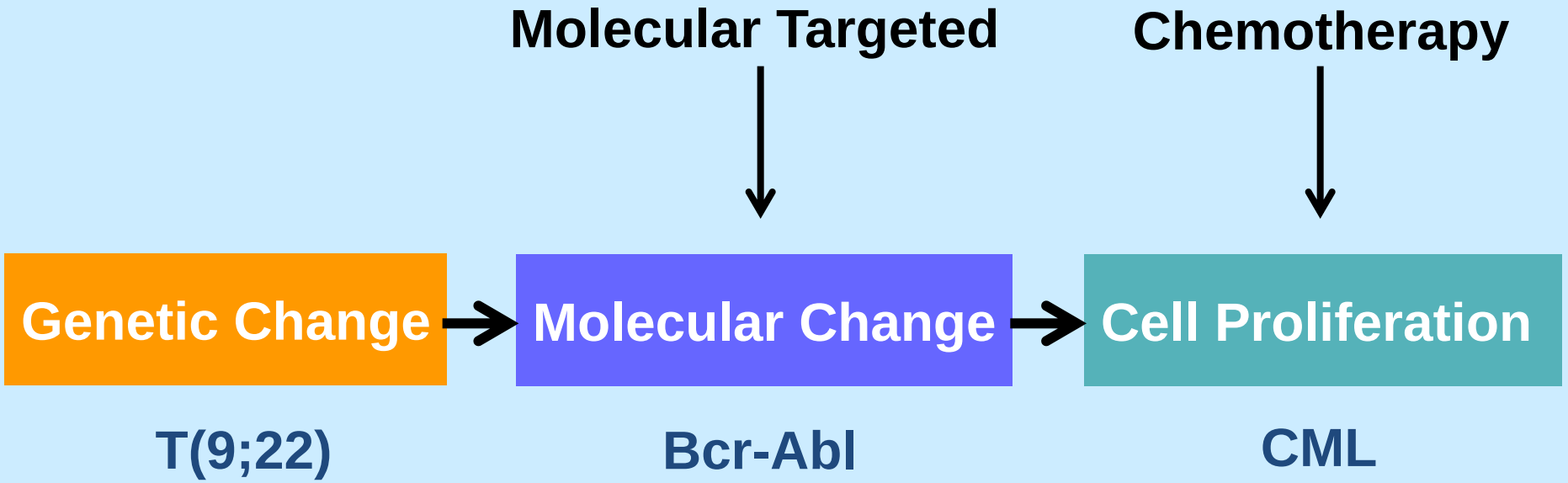
Recommendation (3)

- Cytotoxic therapy, such as anthracyclines, platinums, fluoropyrimidines, and gemcitabine, are not routinely recommended, but can possibly be considered in highly selected patients whose general and hepatic conditions are adequate, so as to minimize treatment-related toxicity. (Grade C)

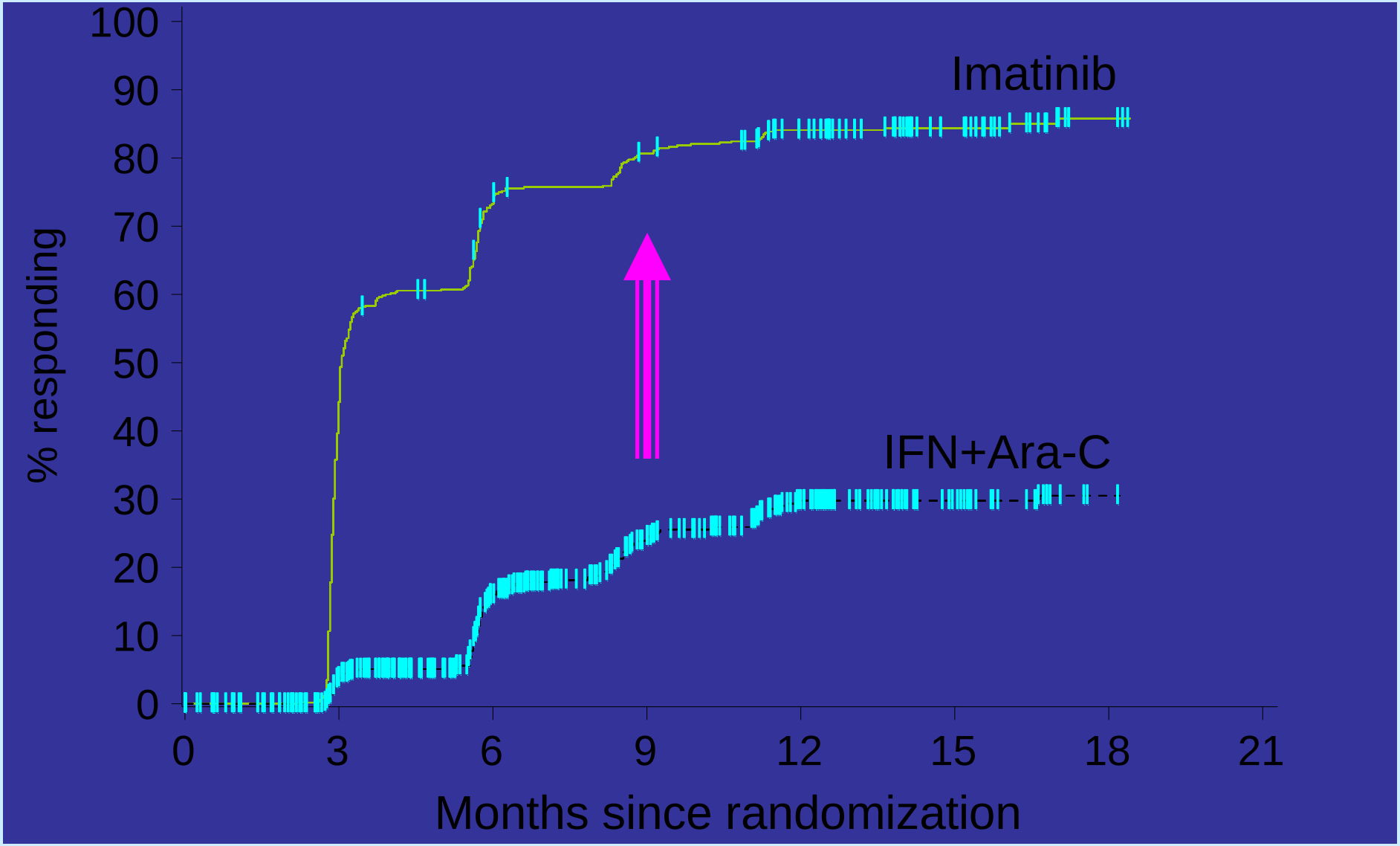
Imatinib for Chronic Myeloid Leukemia

– An ideal example of molecular targeted therapy

- T (9;22) → Bcr-Abl → CML
- Bcr-Abl, a protein absent in normal cells
- Imatinib binds to Bcr-Abl and abolish its kinase activity


Molecular Targeted
Chemotherapy
Genetic Change
Molecular Change
Cell Proliferation
T(9;22)
Bcr-Abl
CML

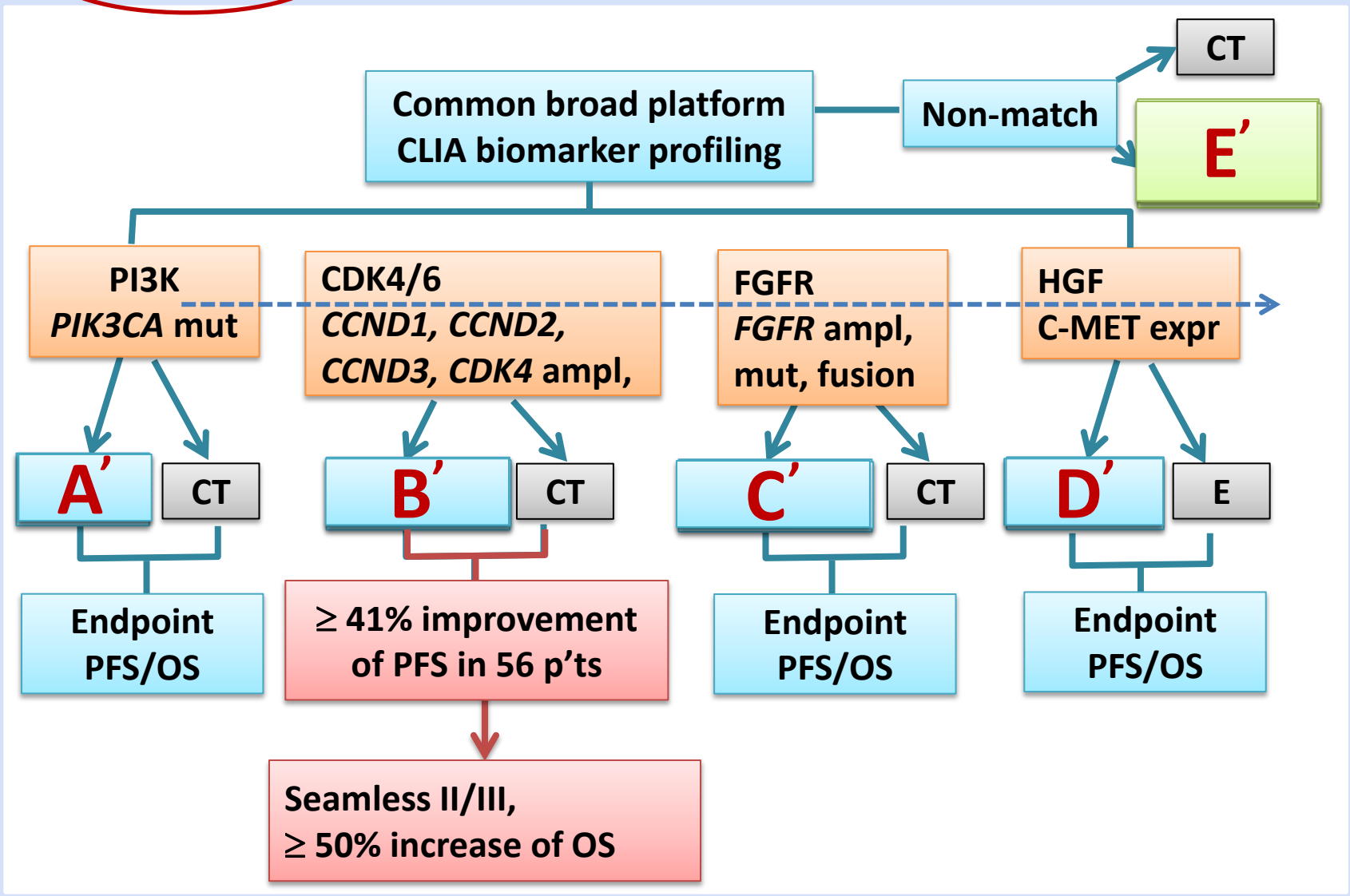
Major Cytogenetic Responses



Druker et al. NEJM 2006; 355 (23): 2408

US Master Protocol for 2nd-line Squamous NSCLC

- Confirmatory, seamless phase II/III for approval



Cancer Discovery March 2014

"Super-adaptive" Master Protocol

- Biomarker-driven, multi-arm, multi-drug.
- Drop the losers, add newcomers, and push forward winners.
- A trial that is "living" and "growing".

Synergism of Anti-CTLA4 and Anti-PD1

- Simultaneous activity on effector T cells.

- Anti-PD1 restores the function of exhausted T cells (high PD-1 expression after chronic immune activation) and Anti-CTLA4 suppresses Treg.

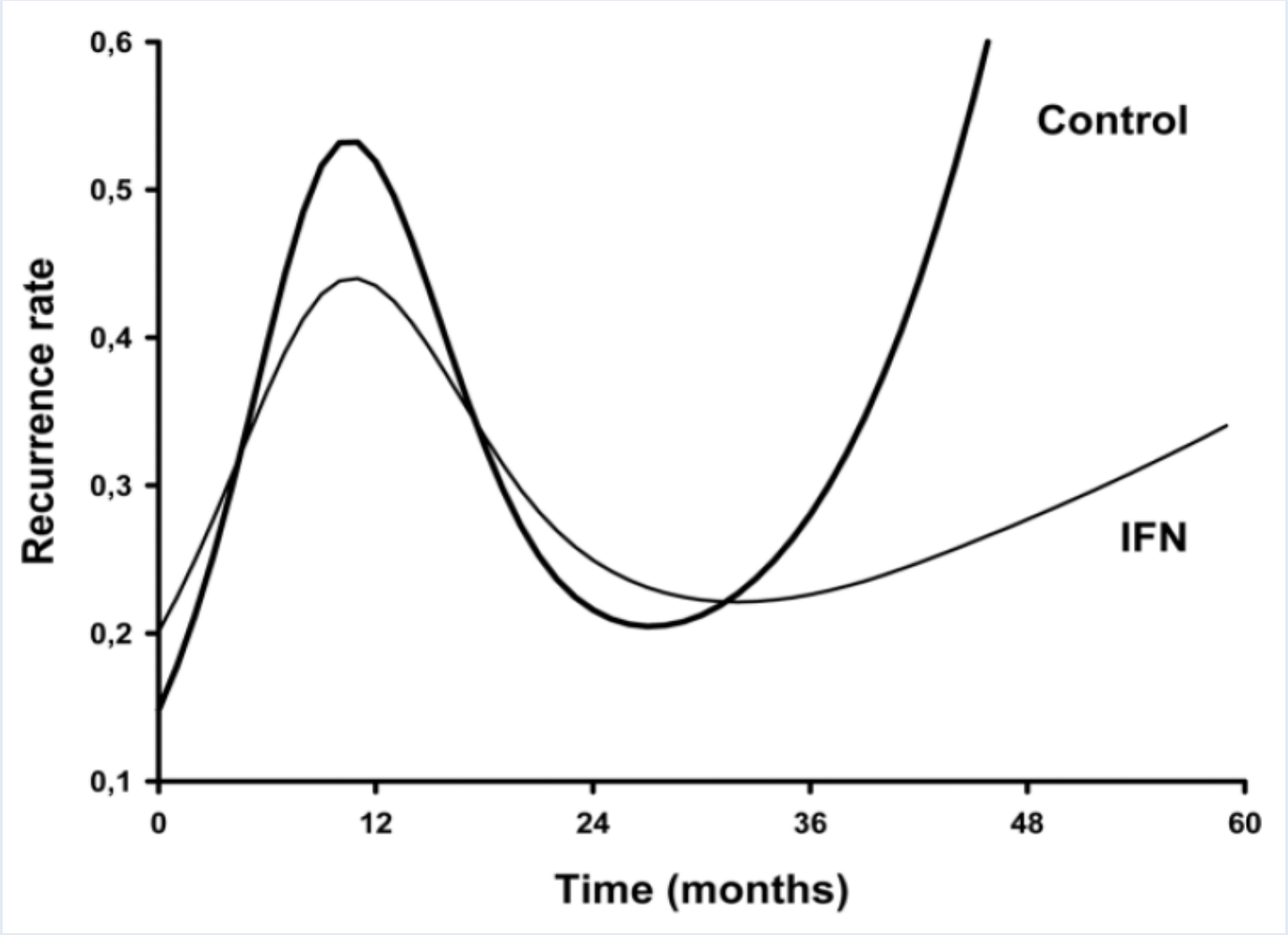
Notable ongoings:

Lenvatinib – phase III, 1st-line (vs sorafenib)
Tivantinib – phase III, 2nd-line (c-met enriched)
Cabozantinib – phase III, 2nd-line
Regorafenib – phase III, 2nd-line

Half of recurrent HCC are second primary tumor. Therefore, archived tissues of the primary tumors may not be adequate enough to determine molecular subtypes of recurrent tumors which are under treatment.

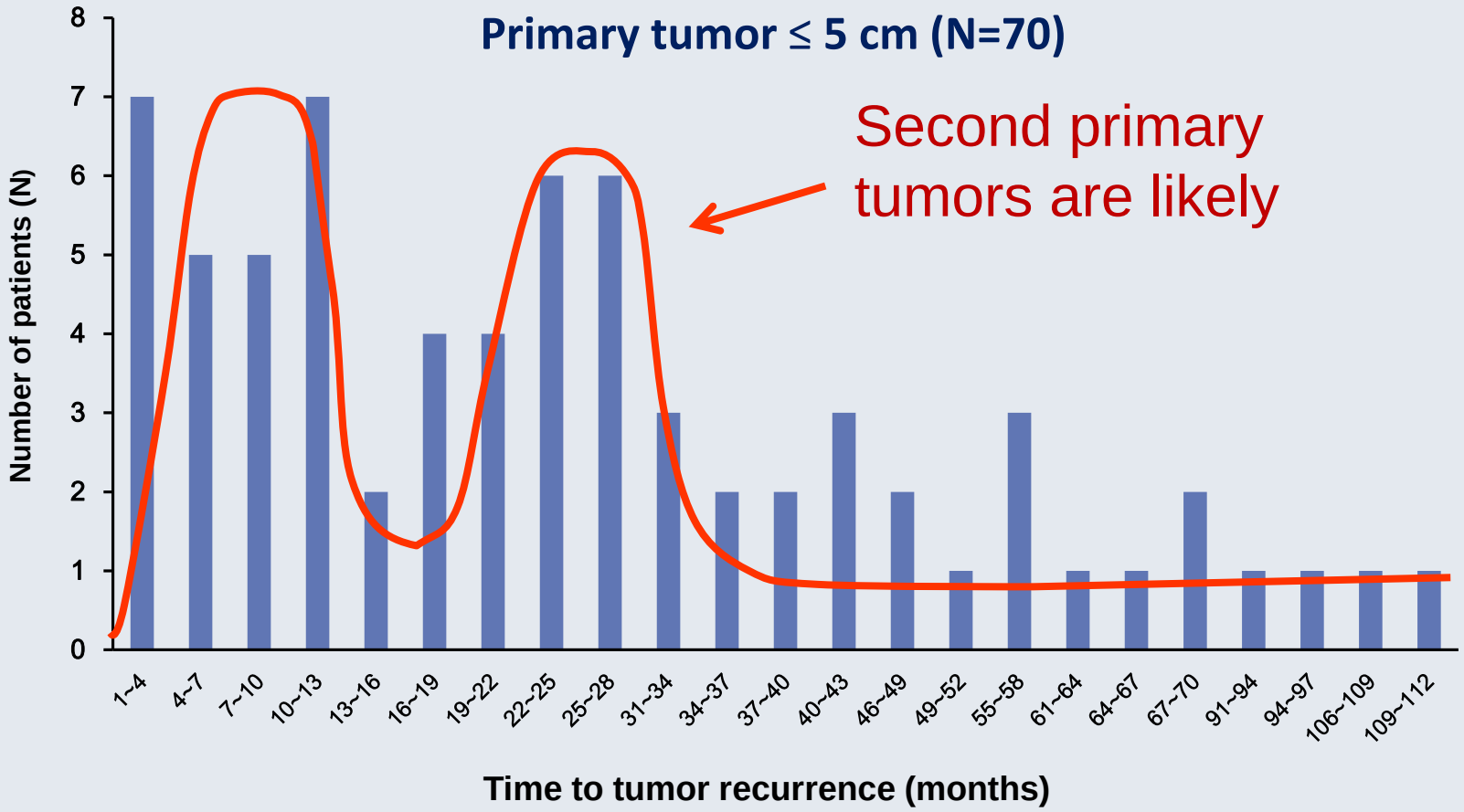
Fresh biopsy is always preferred, but HCC is unique in that tissue diagnosis is not routinely required.

Prevention of HCC Recurrence with Alpha-Interferon after Liver Resection in HCV Cirrhosis



Mazzaferro V et al Hepatol 2006;44:1543-54

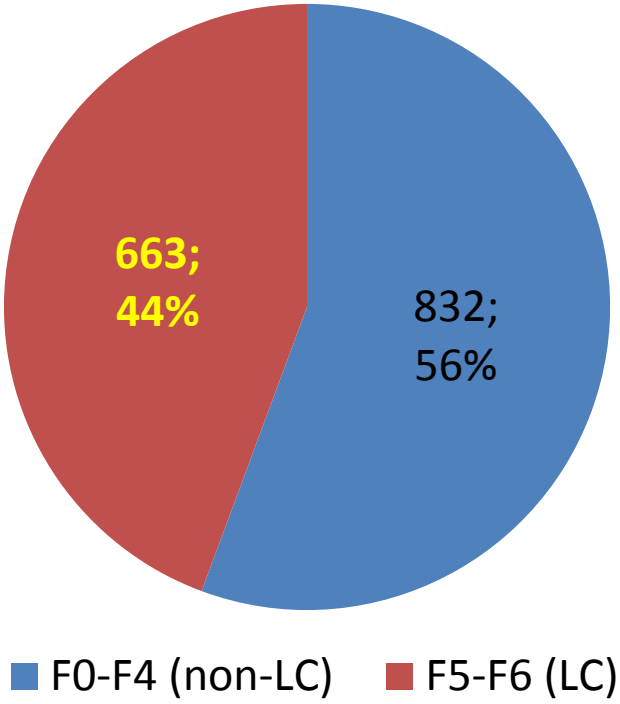
Recurrence of HBV-related HCC after Curative Resection (TCOG, T1297 study)



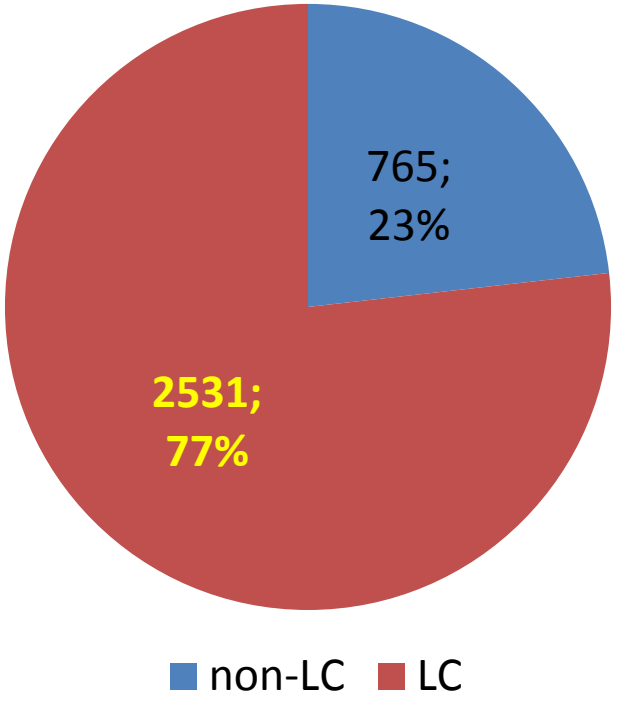
Chen LT et al (unpublished data)

Prevalence of LC in HCC patients (I)

By pathology, surgical patients (surgical treatment)



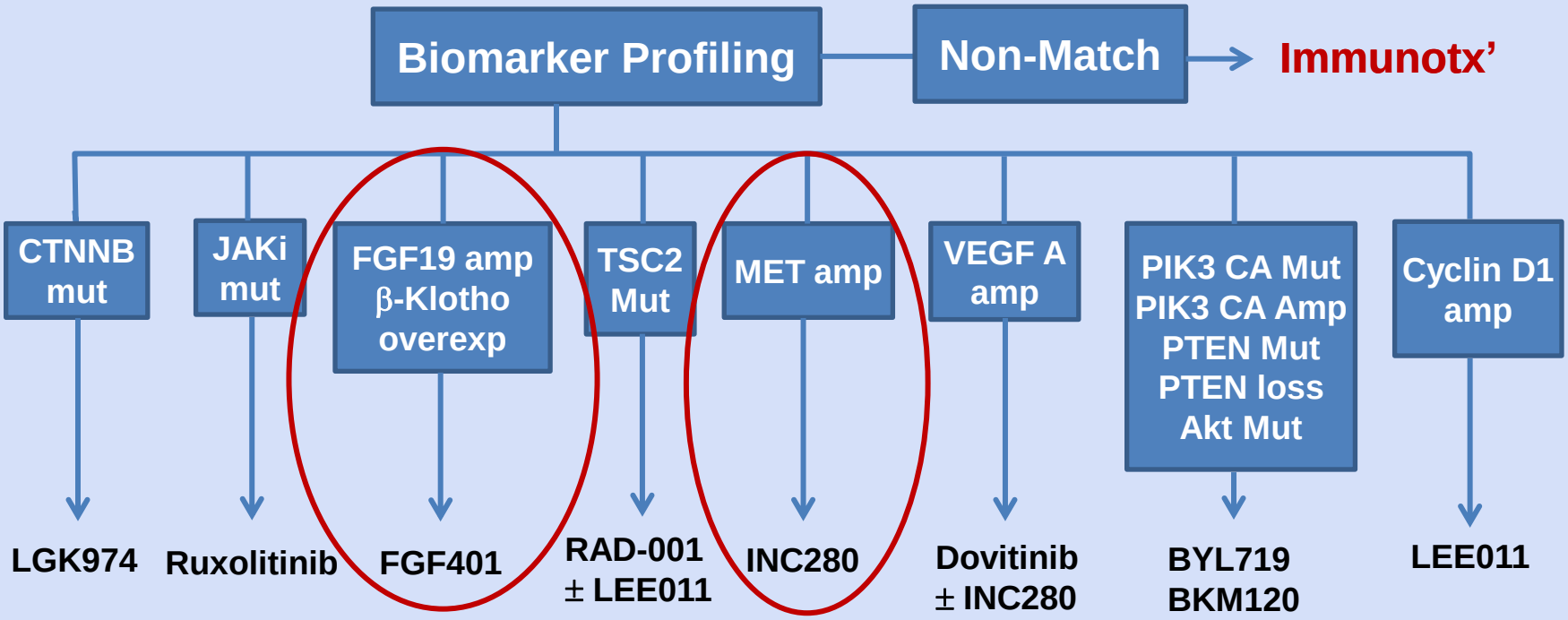
By image, non-surgical patients (non-surgical treatment)



Lu SN et al, unpublished data

Master Protocol for Novartis 2nd-line HCC

- Exploratory, single-arm



Further Phase II if RR > 15% or PFS > 5 months

Linifanib Versus Sorafenib in Patients With Advanced HCC: Results of a Randomized Phase III Trial

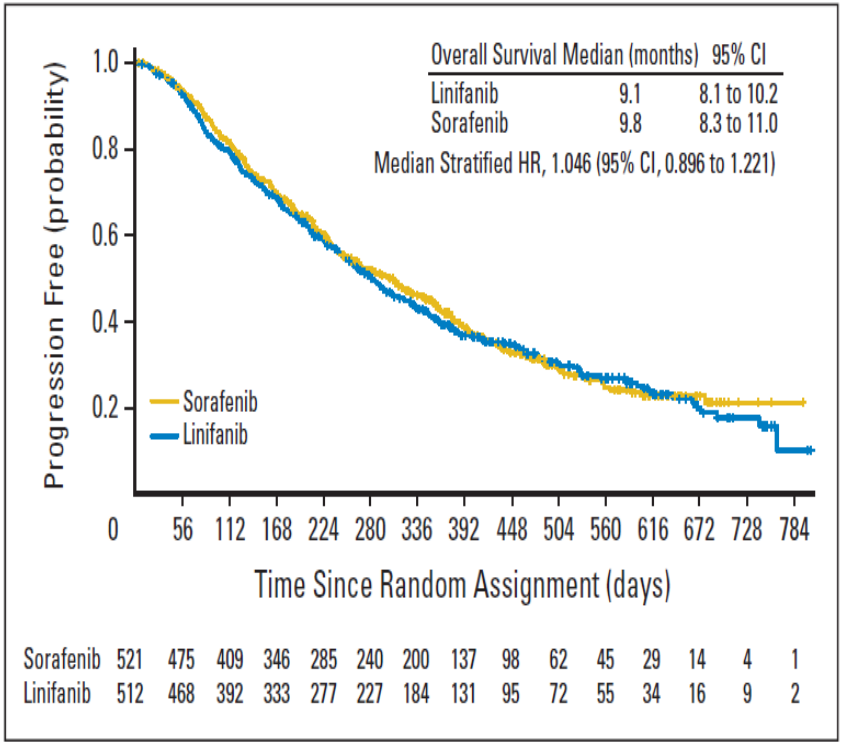


Fig 2. Kaplan-Meier analysis of overall survival with a cutoff point at the 667th patient death. HR, hazard ratio.

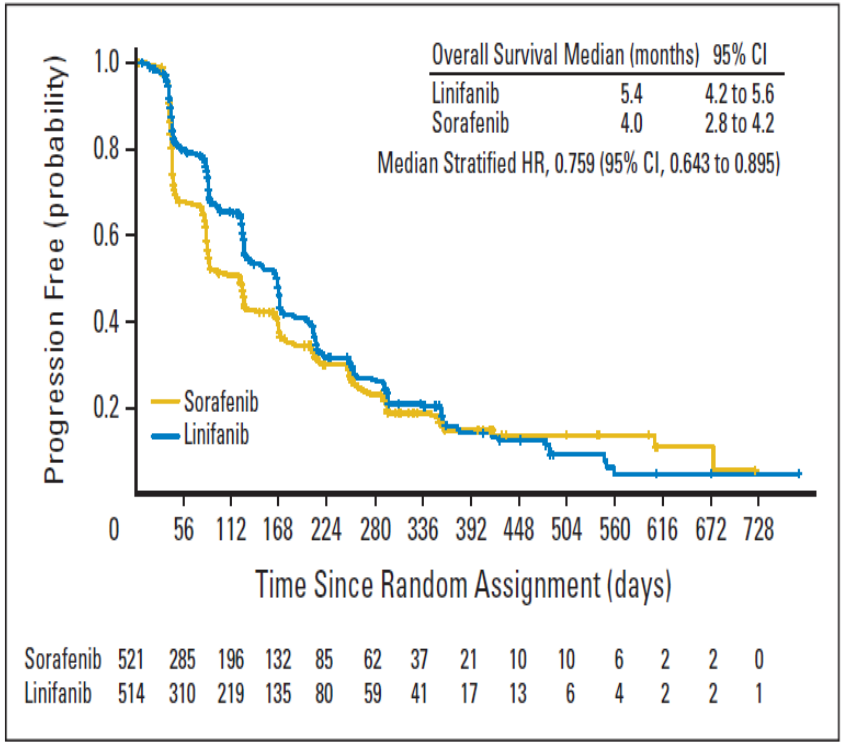
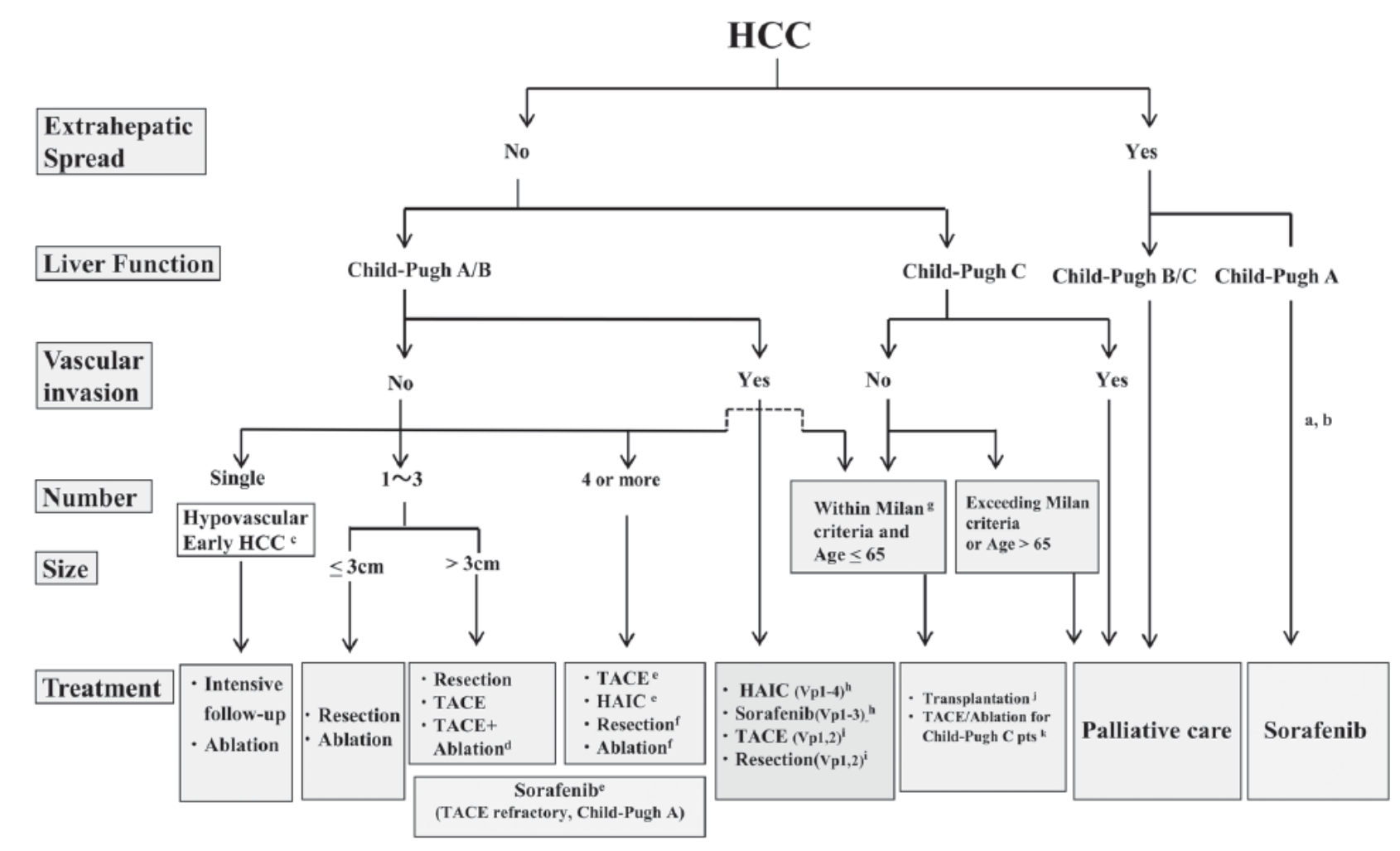


Fig 4. Kaplan-Meier analysis of time to progression. HR, hazard ratio.

Cainap C, et al. J Clin Oncol 2015; 33:172-179

JSH-LCSGJ Consensus-based Treatment Algorithm for HCC revised in 2014



Kudo M et al. Liver Cancer 2014;3:458–468

Combination Trials of c-MET inhibitors for HCC

Drugs/ (Identifier)	Design	Patients	Primary outcome	Site	Start date/ Status
Sorafenib+ Onartuzumab (NCT01897038)	I, open-label	Advanced HCC	DLT	International	2013-Sep Completed
Sorafenib +/- Golvatinib (NCT01271504)	I/II, randomized	First-line (phase II)	I: MTD II: TTP, OS	International	2011 April Not recruiting

#32