New Pharmacological Agents to Treat Hepatocellular Carcinoma

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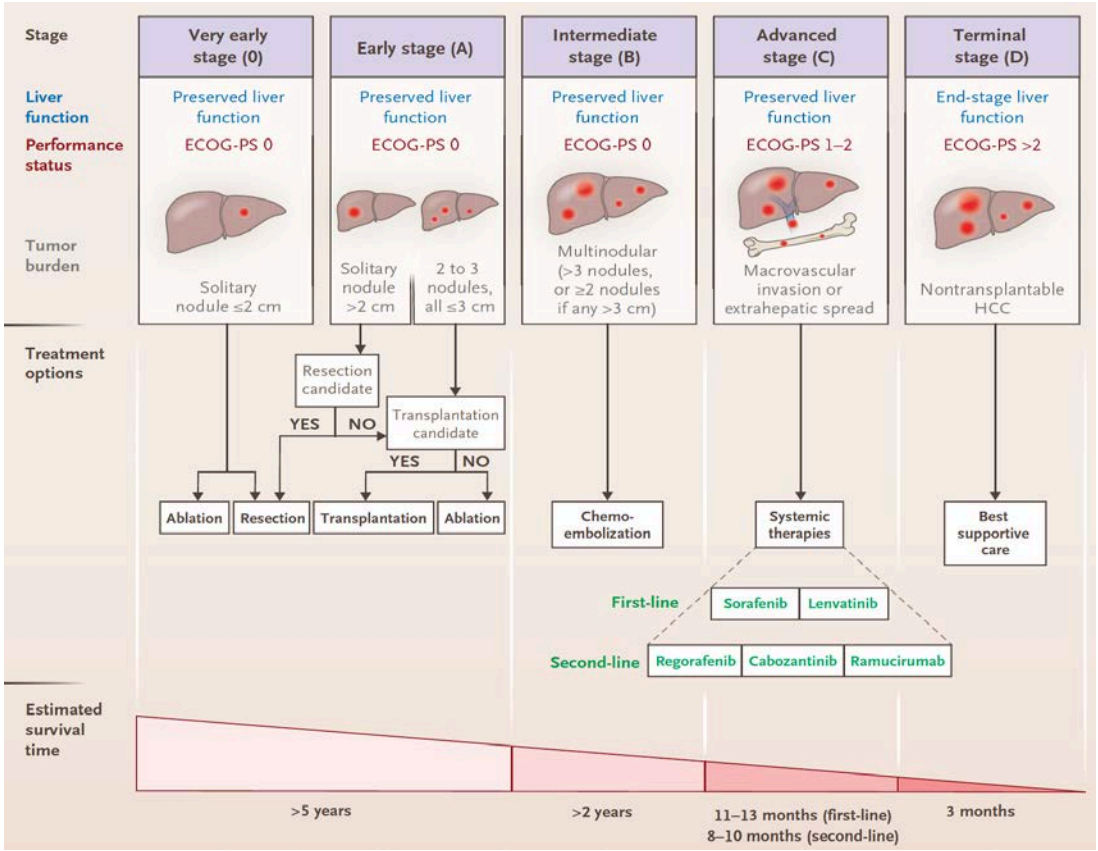
Outline

- Systemic therapies for HCC
  - Targeted therapies
  - Immune-based therapies
  - Combinations

- Biomarkers for patient selection

HCC staging

Barcelona Clinic Liver Cancer Algorithm (EASL, AASLD)

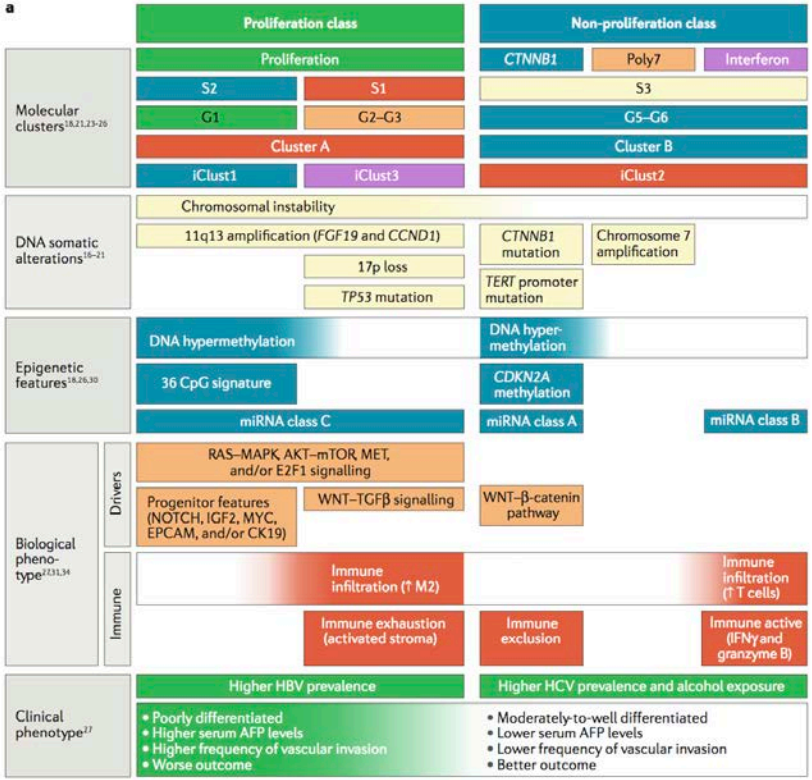


Villanueva A. *N Engl J Med* 2019

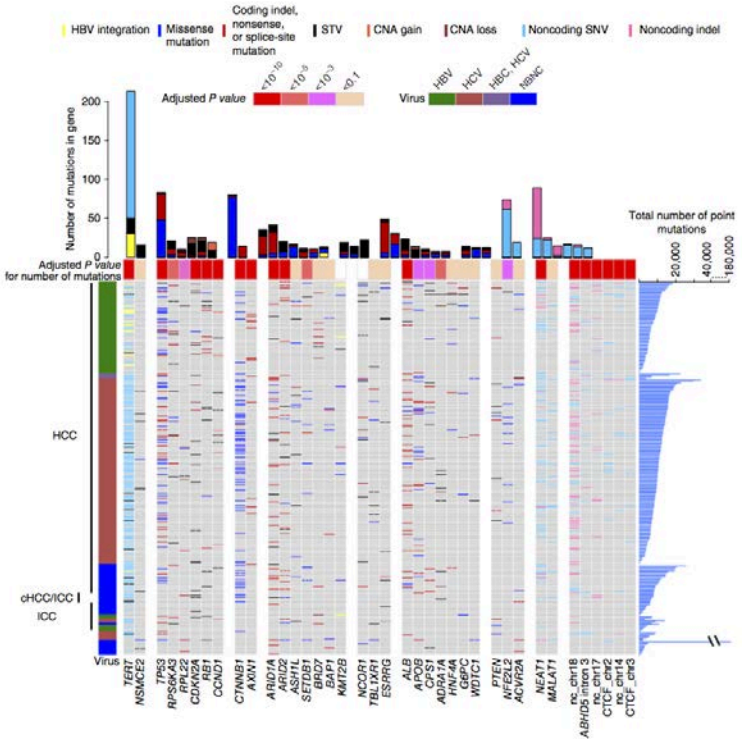
Molecular alterations in HCC

Contribution to targeted therapies?

Molecular classification



Mutation profiling

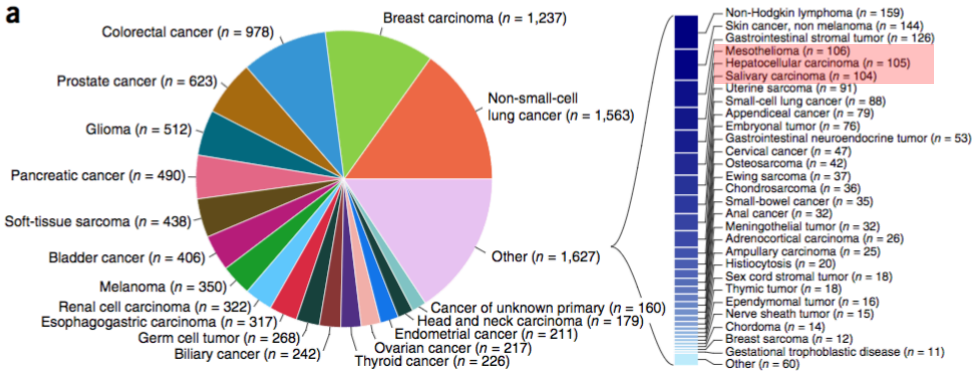


Llovet et al. Nat Rev Clin Oncol 2018; Fujimoto et al. Nat Genet 2016

‘Druggable’ genome

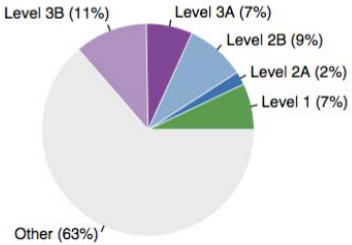
Hepatocellular Carcinoma (MSK-IMPACT)

Tumor samples (n ~10,000)

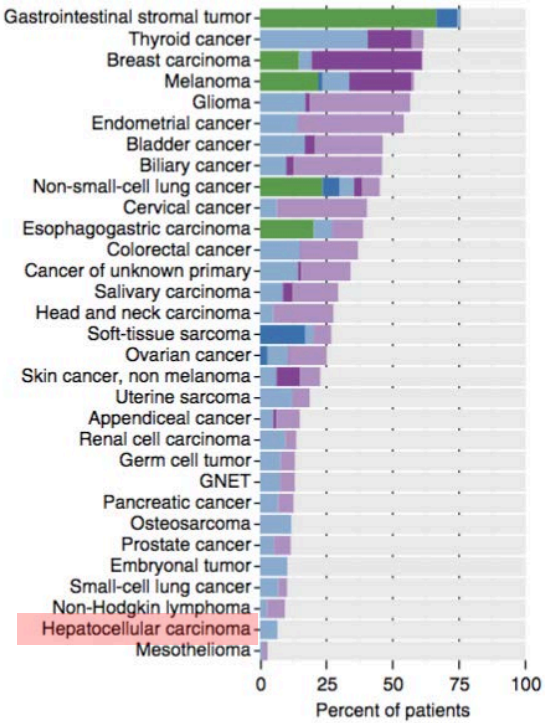


Levels of ‘druggability’

Level 1	FDA-recognized biomarker for an FDA-approved drug in the same indication
Level 2A	Standard of care biomarker for an FDA-approved drug in the same indication
Level 2B	Standard of care biomarker for an FDA-approved drug in another indication
Level 3A	Compelling clinical evidence supporting the biomarker as being predictive of drug response in the same indication
Level 3B	Compelling clinical evidence supporting the biomarker as being predictive of drug response in another indication



‘Druggable’ genome in cancer

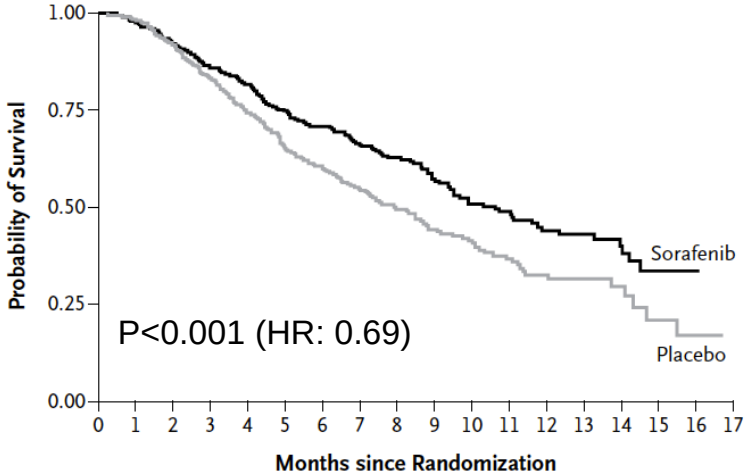


Zehir A et al Nat Med 2017

Hepatocellular carcinoma

Advanced stage (BCLC-C) – First line

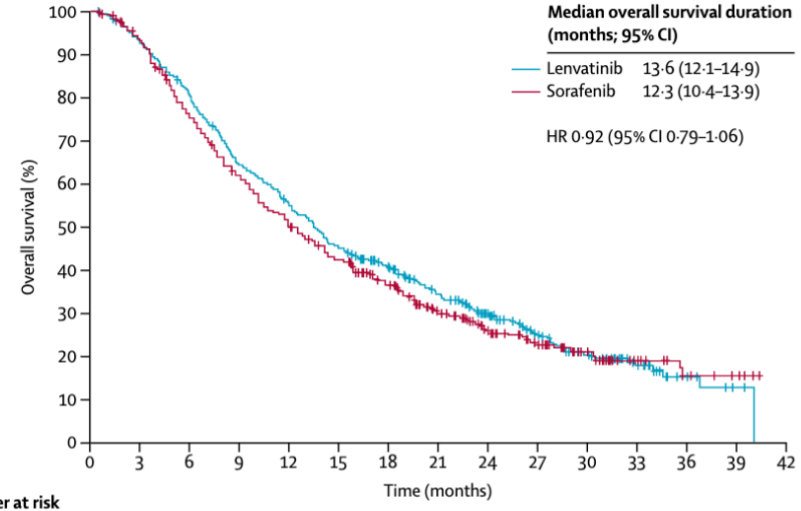
Sorafenib
(RAS/MAPK)



No. at Risk

Sorafenib	299	290	270	249	234	213	200	172	140	111	89	68	48	37	24	7	1	0
Placebo	303	295	272	243	217	189	174	143	108	83	69	47	31	23	14	6	3	0

Lenvatinib - Non-inferior to sorafenib
(FGFR)



Number at risk

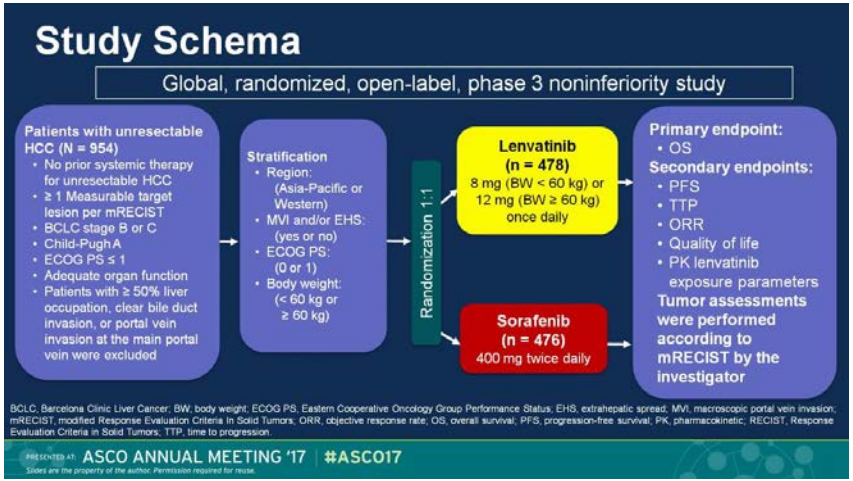
Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

Llovet et al. *N Engl J Med* 2008; Kudo et al. *Lancet* 2018

Hepatocellular carcinoma

Advanced stage (BCLC-C) – Lenvatinib (FGFR)

Summary



Adverse events

	Lenvatinib (n=476)	Sorafenib (n=475)
Total treatment-emergent adverse events	470 (99%)	472 (99%)
Total treatment-related treatment-emergent adverse events	447 (94%)	452 (95%)
Treatment-emergent adverse events of grade ≥3	357 (75%)	316 (67%)
Treatment-related treatment-emergent adverse events of grade ≥3	270 (57%)	231 (49%)
Serious treatment-emergent adverse events	205 (43%)	144 (30%)
Serious treatment-related treatment-emergent adverse events	84 (18%)	48 (10%)

	Lenvatinib (n=476)	Sorafenib (n=475)
Palmar-plantar erythrodysaesthesia		
Any grade	128 (27%)	249 (52%)
Grade ≥3	14 (3%)	54 (11%)
Diarrhoea		
Any grade	184 (39%)	220 (46%)
Grade ≥3	20 (4%)	20 (4%)
Hypertension		
Any grade	201 (42%)	144 (30%)
Grade ≥3	111 (23%)	68 (14%)
Decreased appetite		
Any grade	162 (34%)	127 (27%)
Grade ≥3	22 (5%)	6 (1%)
Decreased weight		
Any grade	147 (31%)	106 (22%)
Grade ≥3	36 (8%)	14 (3%)
Fatigue		
Any grade	141 (30%)	119 (25%)
Grade ≥3	18 (4%)	17 (4%)

(Table 3 continues in next column)

Response rate

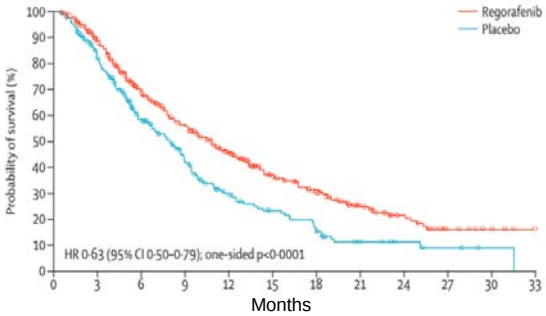
	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Investigator review according to mRECIST				
Overall survival (months)	13·6 (12·1–14·9)	12·3 (10·4–13·9)	HR 0·92 (0·79–1·06)	–
Progression-free survival (months)	7·4 (6·9–8·8)	3·7 (3·6–4·6)	HR 0·66 (0·57–0·77)	<0·0001
Time to progression (months)	8·9 (7·4–9·2)	3·7 (3·6–5·4)	HR 0·63 (0·53–0·73)	<0·0001
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)	<0·0001
Complete response	6 (1%)	2 (<1%)	–	–
Partial response	109 (23%)	42 (9%)	–	–
Stable disease	246 (51%)	244 (51%)	–	–
Durable stable disease lasting ≥23 weeks	167 (35%)	139 (29%)	–	–
Progressive disease	71 (15%)	147 (31%)	–	–
Unknown or not evaluable	46 (10%)	41 (9%)	–	–
Disease control rate (%, 95% CI)	361 (75·5%, 71·7–79·4)	288 (60·5%, 56·1–64·9)	–	–

Kudo et al. *Lancet* 2018

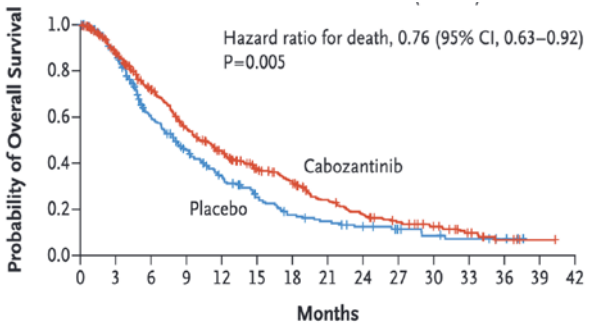
Hepatocellular carcinoma

Advanced stage (BCLC-C) – Second line

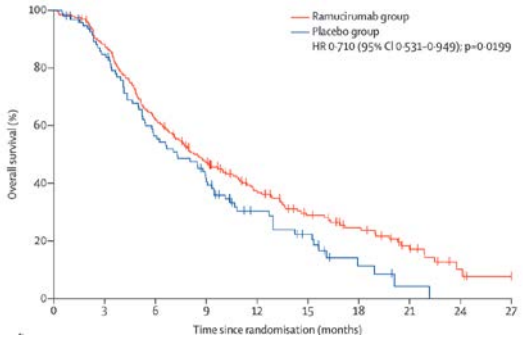
Regorafenib
(RAS/MAPK)



Cabozantinib
(MET)



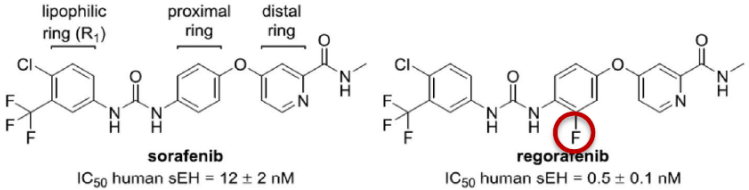
Ramucirumab - AFP > 400 ng/dL
(VEGFR2)



Bruix et al. *Lancet* 2017; Kudo et al. Abou-Alfa et al. *NEJM* 2018; Zhu et al. *Lancet Oncol* 2019

Hepatocellular carcinoma

Advanced stage (BCLC-C) – Regorafenib



Summary

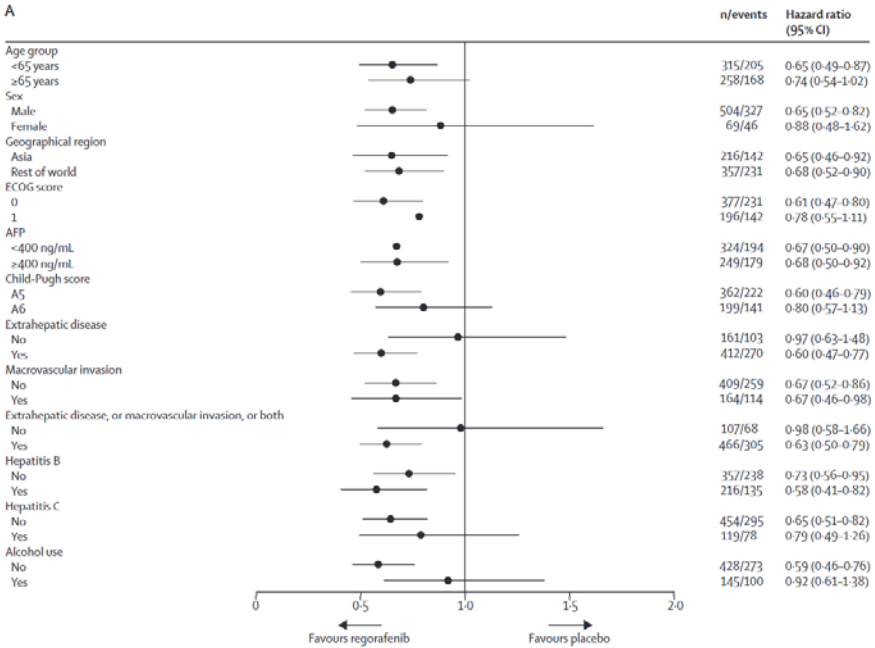
- HCC patients with documented radiological progression during sorafenib treatment
- Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)

R 2:1

Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

Placebo
(n=194)

Sub-group analyses

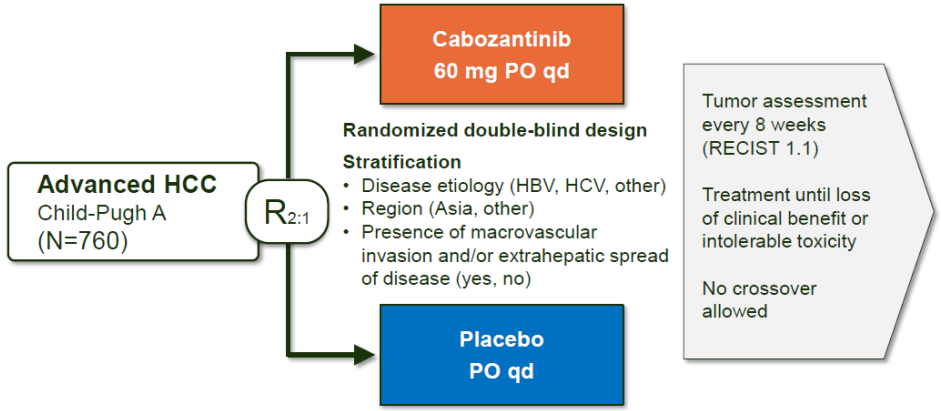


Bruix et al. *Lancet* 2017

Hepatocellular carcinoma

Advanced stage (BCLC-C) – Cabozantinib (MET)

CELESTIAL Study Design



Adverse events

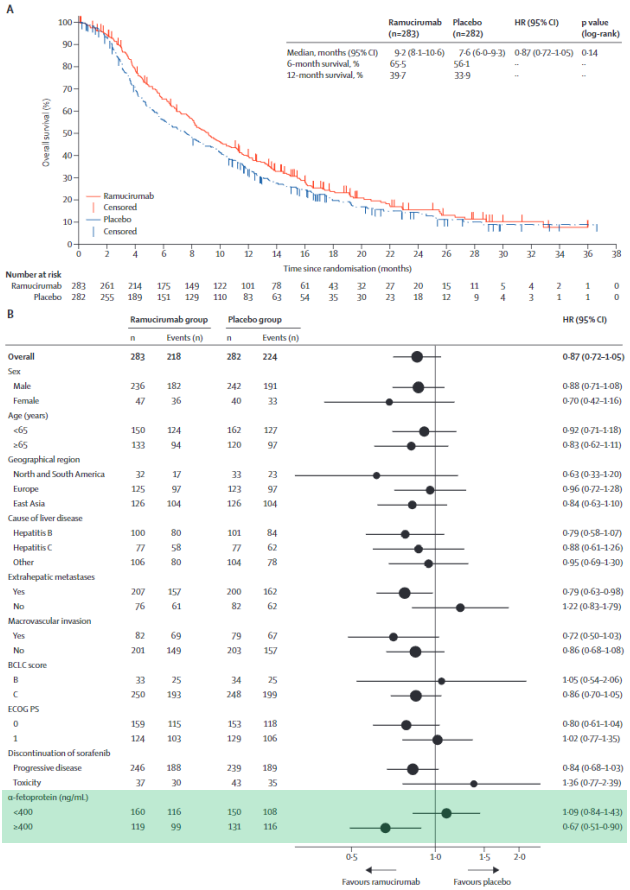
Table 2. Adverse Events.*

Event	Cabozantinib (N=467)			Placebo (N=237)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	460 (99)	270 (58)	46 (10)	219 (92)	80 (34)	6 (3)
Diarrhea	251 (54)	45 (10)	1 (<1)	44 (19)	4 (2)	0
Decreased appetite	225 (48)	27 (6)	0	43 (18)	1 (<1)	0
Palmar–plantar erythrodysesthesia	217 (46)	79 (17)	0	12 (5)	0	0
Fatigue	212 (45)	49 (10)	0	70 (30)	10 (4)	0
Nausea	147 (31)	10 (2)	0	42 (18)	4 (2)	0
Hypertension	137 (29)	73 (16)	1 (<1)	14 (6)	4 (2)	0
Vomiting	121 (26)	2 (<1)	0	28 (12)	6 (3)	0
Increase in aspartate aminotransferase level	105 (22)	51 (11)	4 (1)	27 (11)	15 (6)	1 (<1)
Asthenia	102 (22)	31 (7)	1 (<1)	18 (8)	4 (2)	0
Dysphonia	90 (19)	3 (1)	0	5 (2)	0	0
Constipation	87 (19)	2 (<1)	0	45 (19)	0	0
Abdominal pain	83 (18)	7 (1)	1 (<1)	60 (25)	10 (4)	0
Weight loss	81 (17)	5 (1)	0	14 (6)	0	0
Increase in alanine aminotransferase level	80 (17)	23 (5)	0	13 (5)	5 (2)	0
Mucosal inflammation	65 (14)	8 (2)	0	5 (2)	1 (<1)	0
Pyrexia	64 (14)	0	0	24 (10)	1 (<1)	0
Upper abdominal pain	63 (13)	3 (1)	0	31 (13)	0	0
Cough	63 (13)	1 (<1)	0	26 (11)	0	0
Peripheral edema	63 (13)	4 (1)	0	32 (14)	2 (1)	0

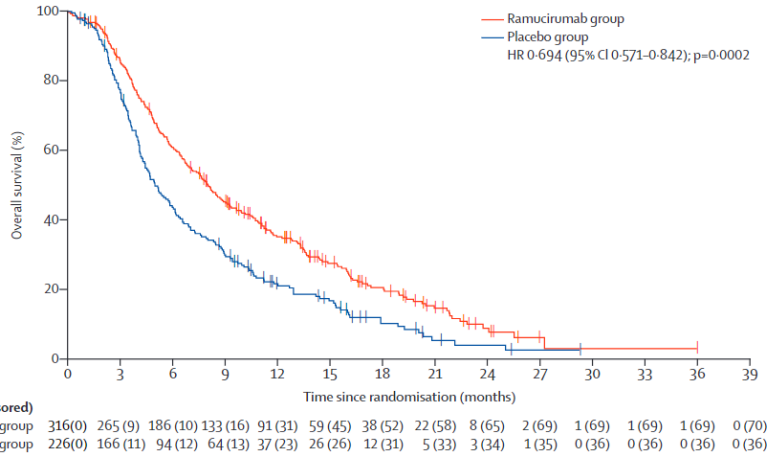
Abou-Alfa et al. *NEJM* 2018

Hepatocellular carcinoma

Advanced stage (BCLC-C) – Ramucirumab (VEGFR2)



Meta-analysis



Zhu et al. *Lancet Oncol* 2015; Zhu et al. *Lancet Oncol* 2019

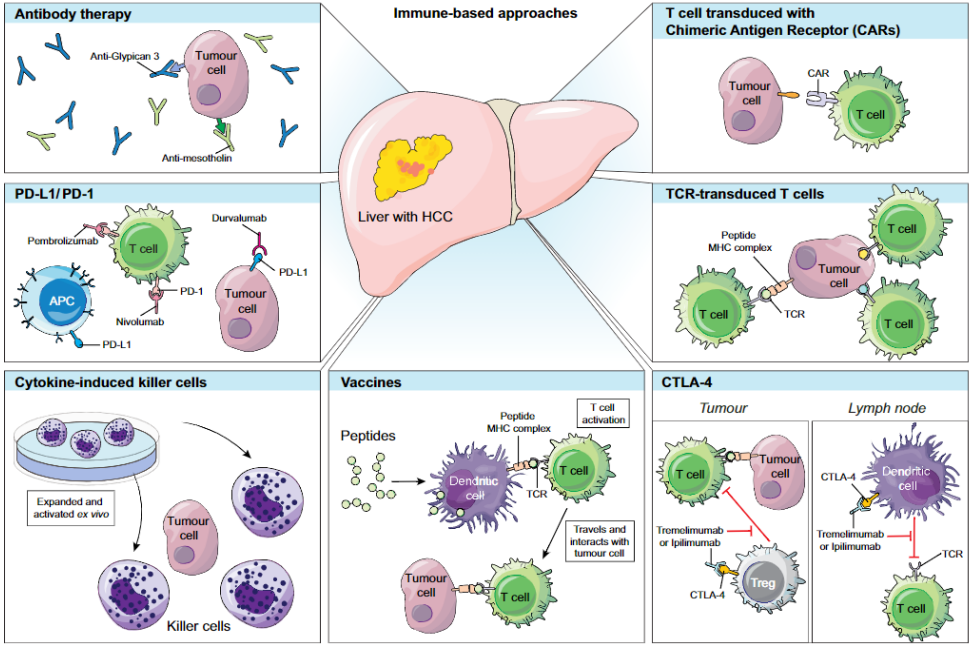
Outline

- Systemic therapies for HCC
  - Targeted therapies
  - Immune-based therapies
  - Combinations

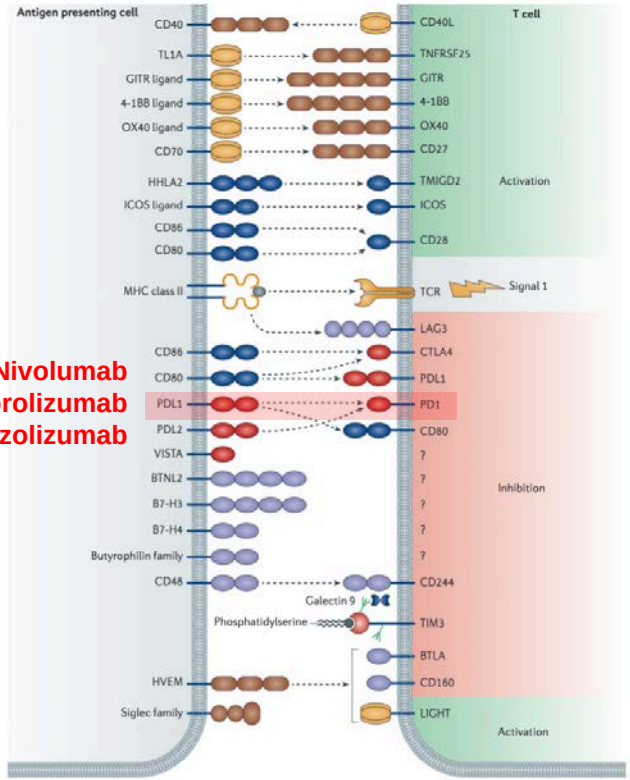
- Biomarkers for patient selection

Immunotherapy in cancer

Strategies



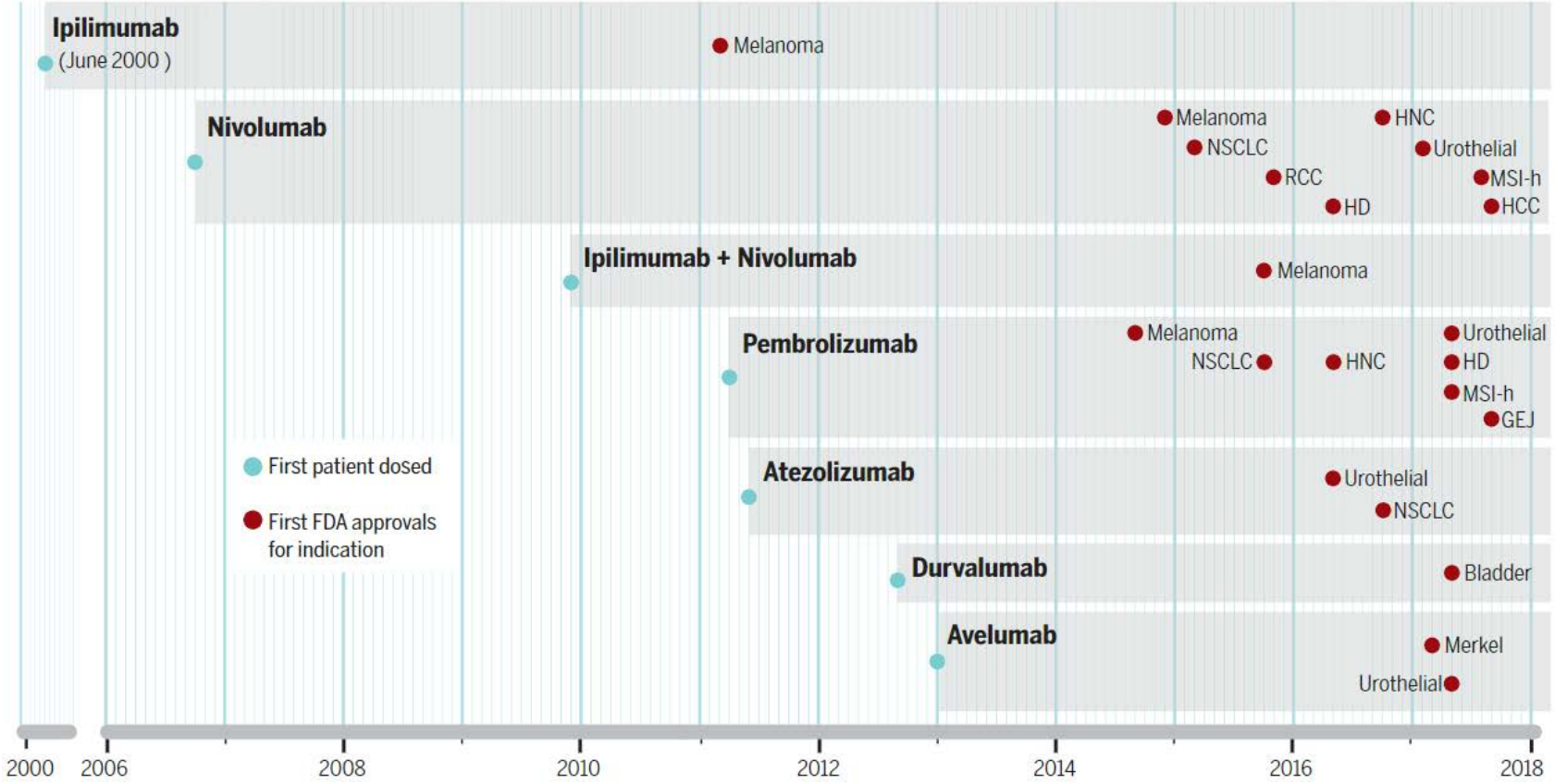
Immune checkpoints



Greten T et al. *J Hepatol* 2018; Mahoney KM et al. *Nat Rev Drug Disc* 2015

Immunotherapy in cancer

Regulatory timeline



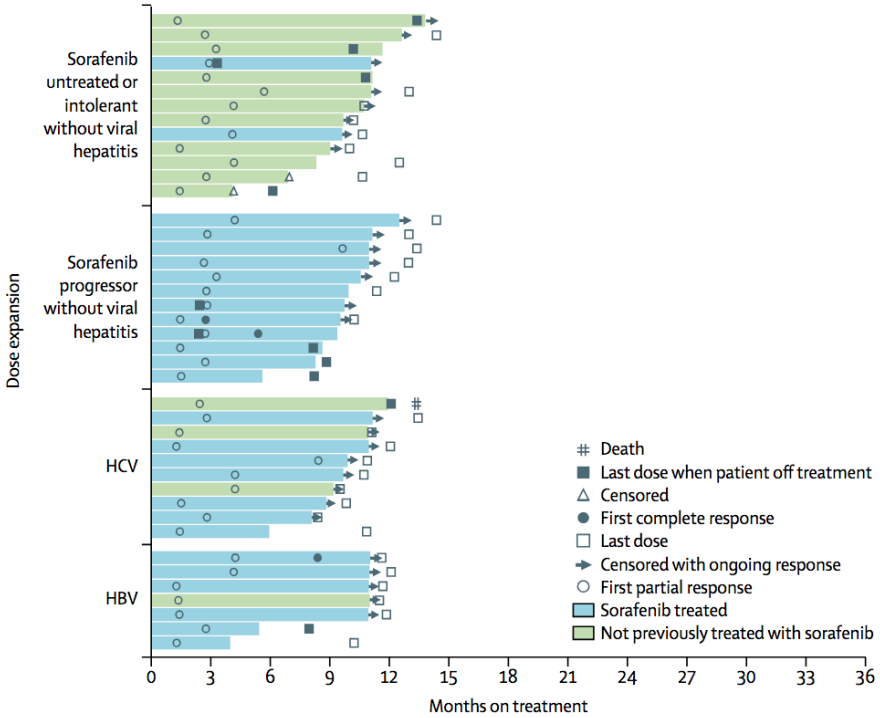
Ribas et al. Science 2018

Hepatocellular carcinoma

Advanced stage (BCLC-C) – Immune checkpoint inhibitors

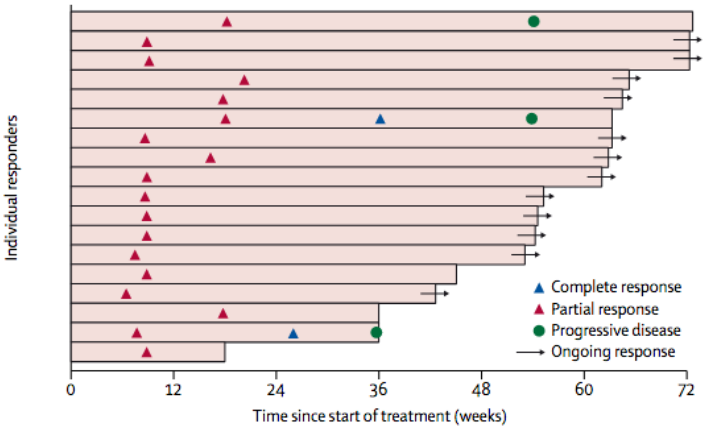
Nivolumab (n=214)

Objective response rate 18% (duration >12 months – 55%)



Pembrolizumab (n=104)

Objective response rate 17% (duration >9 months – 77%)

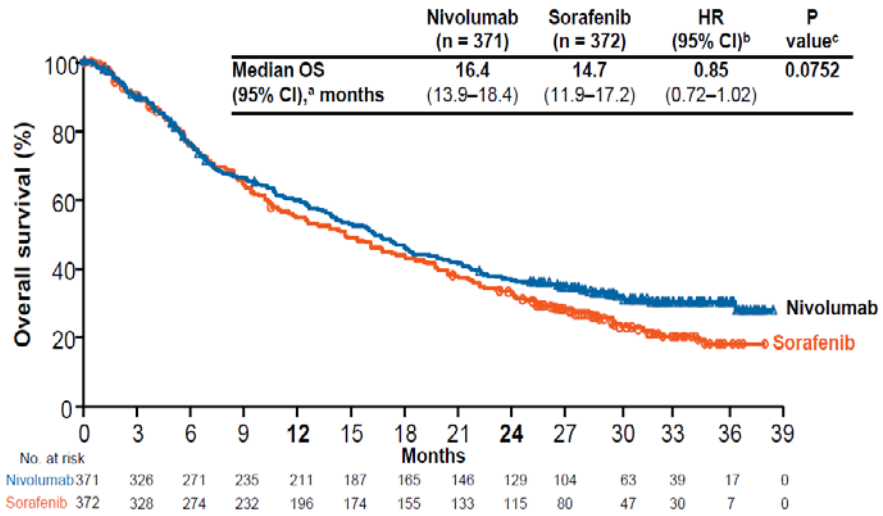


El-Khoueiry et al *Lancet* 2017; Zhu AX et al. *Lancet Oncol* 2018

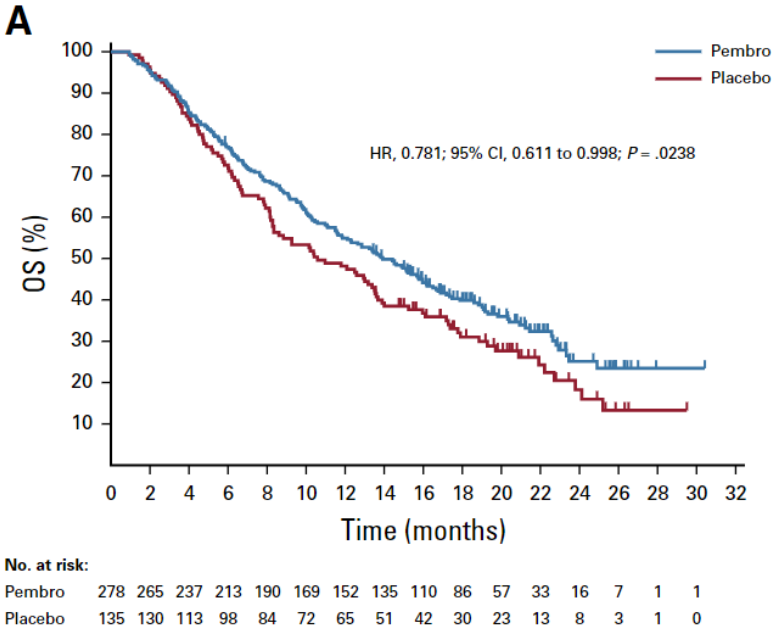
Hepatocellular carcinoma

Advanced stage (BCLC-C) – Immune checkpoint inhibitors (Phase III)

Nivolumab vs sorafenib (1L)



Pembrolizumab vs placebo (2L)

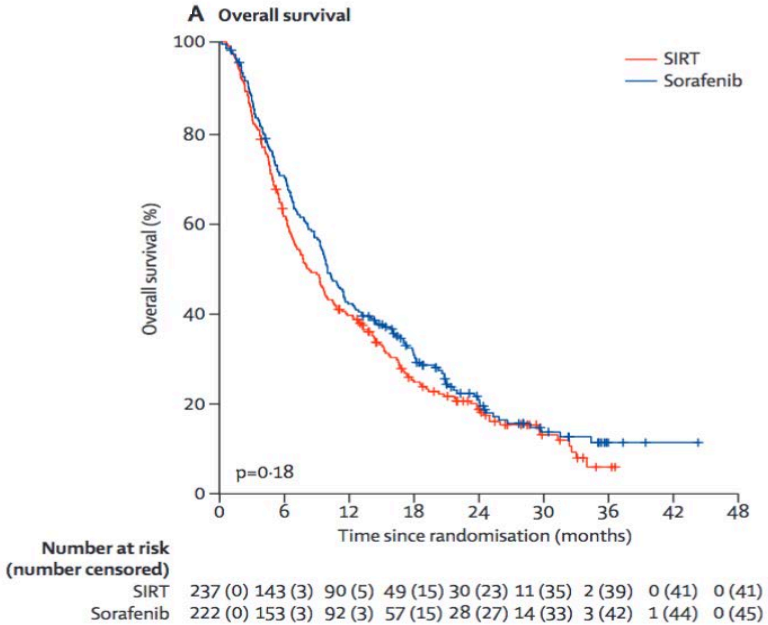


Yau T et al. ESMO 2019; Finn RS et al. JCO 2019

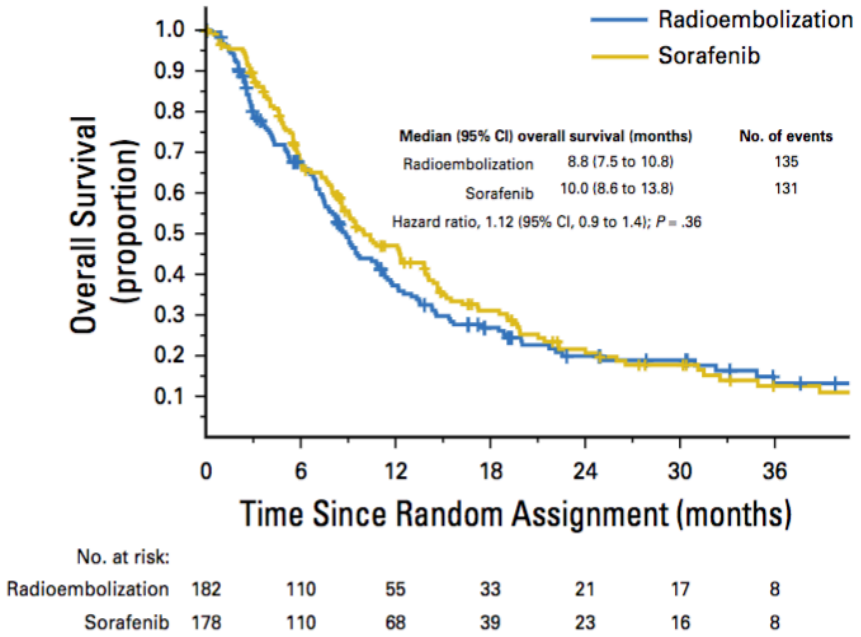
Hepatocellular carcinoma

Advanced stage (BCLC-C) – TARE with Y-90

SARAH



SIRveNIB

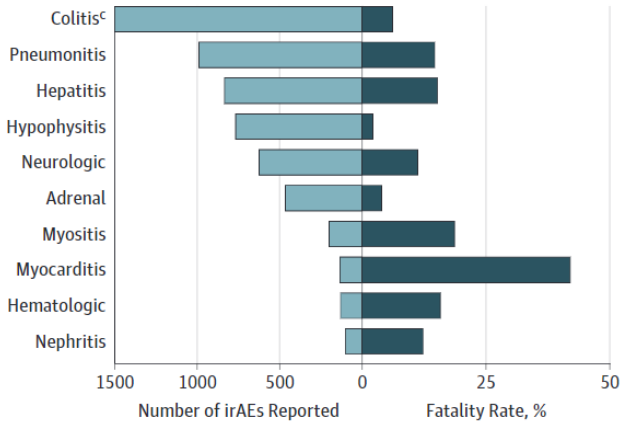


Chow PKH et al *JCO* 2018; Vilgrain V et al. *Lancet Oncol* 2017

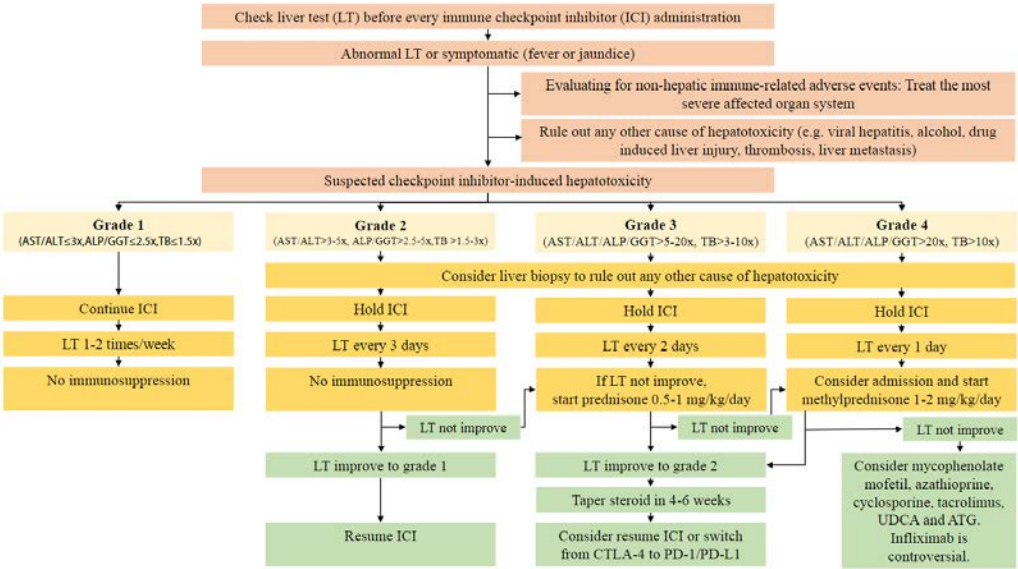
Immune checkpoint inhibitors

Adverse events

Systematic review
(31,059 reports – 613 fatal (1.9%))



Hepatotoxicity

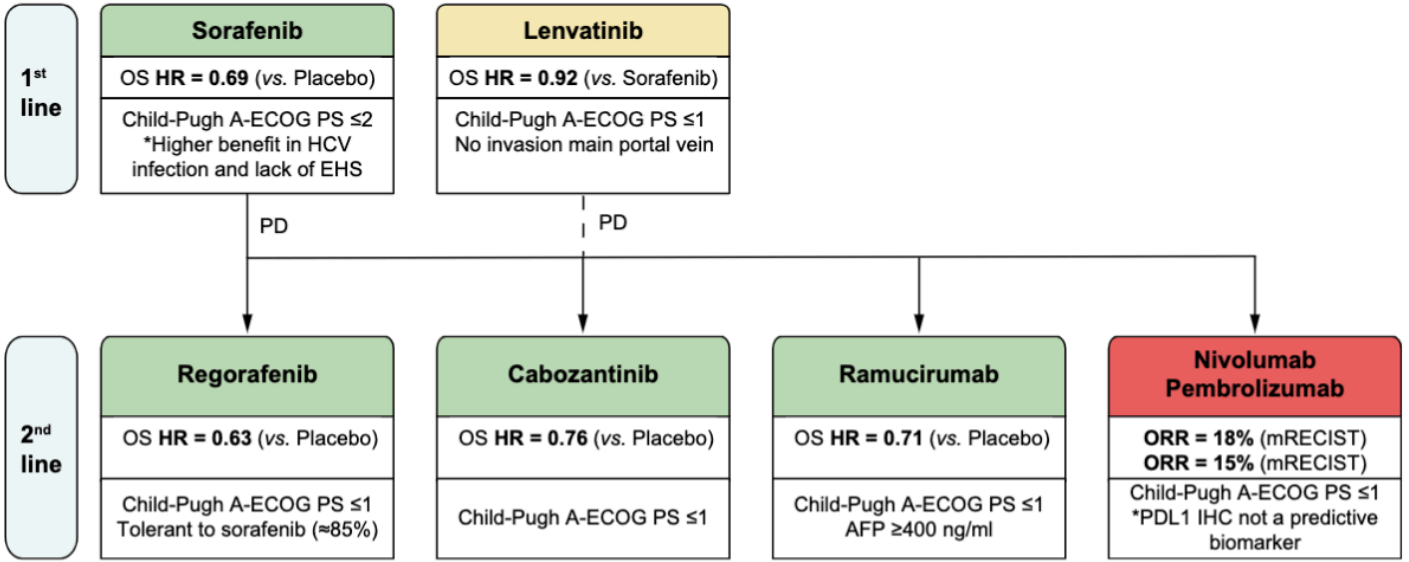


Wang et al *JAMA Oncol* 2017; Peeraphatdit et al. *Hepatology* 2020

Advanced HCC (BCLC-C)

Effective therapies

Advanced stage (BCLC C: *Portal invasion* and/or *extrahepatic spread)*
Intermediate stage (BCLC B: *Multinodular*) **progressing upon loco-regional therapies**



Adapted from Llovet et al. *J Hepatol* 2019

Outline

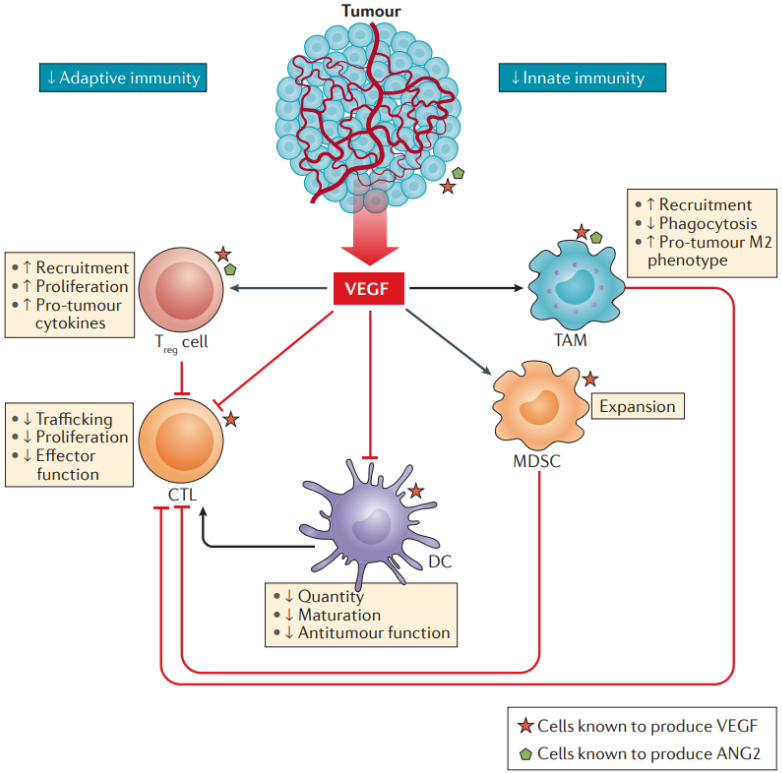
- Systemic therapies for HCC
  - Targeted therapies
  - Immune-based therapies
  - Combinations

- Biomarkers for patient selection

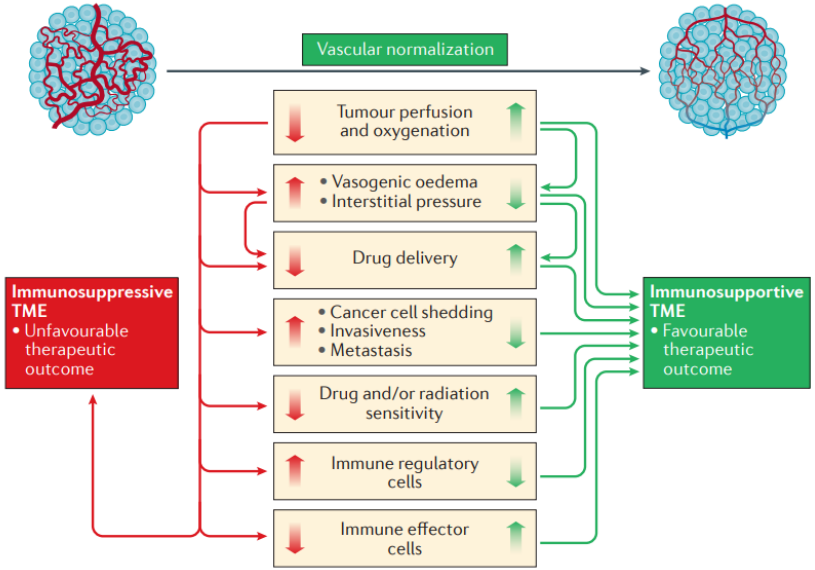
Combination therapies

Anti-angiogenics – Immune checkpoint inhibitors

Effects on immune system



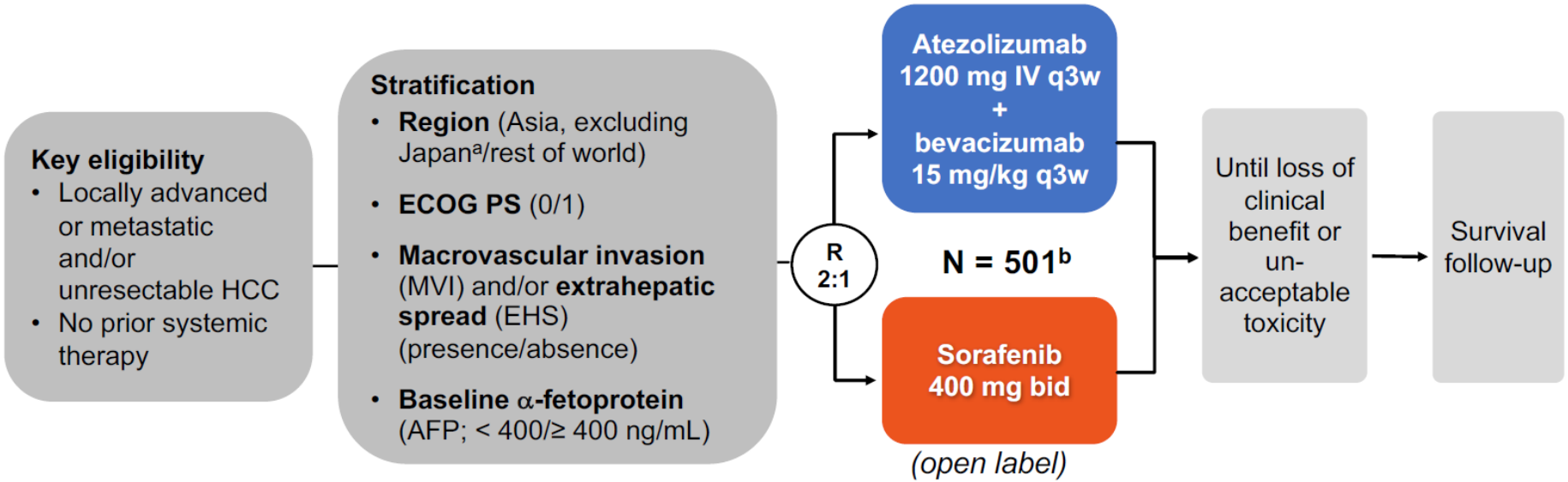
Immune reprogramming



Fukumura D et al. *Nat Rev Clin Oncol* 2018

Hepatocellular carcinoma

Advanced stage (BCLC-C) – Immune checkpoint inhibitors



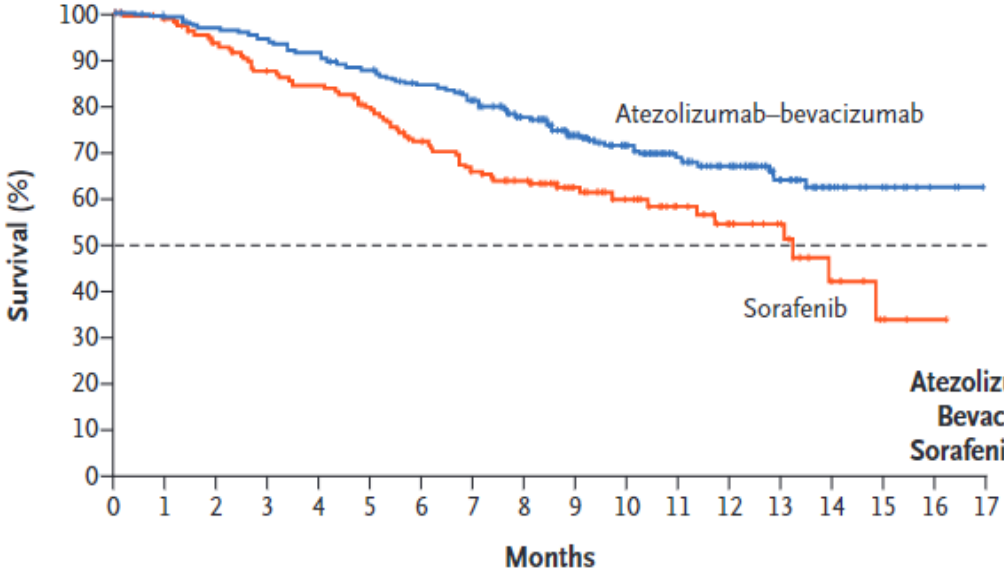
Co-primary endpoints[c]
- OS
- IRF-assessed PFS per RECIST 1.1

Secondary endpoints included[c]:
- IRF-assessed ORR per RECIST 1.1, HCC mRECIST
- Patient-reported outcomes per EORTC QLQ-C30

Finn RS et al. *N Engl J Med* 2020

Hepatocellular carcinoma

Advanced stage (BCLC-C) – Immune checkpoint inhibitors



	No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI)	Overall Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)
P<0.001

No. at Risk

Atezolizumab–bevacizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

Finn RS et al. *N Engl J Med* 2020

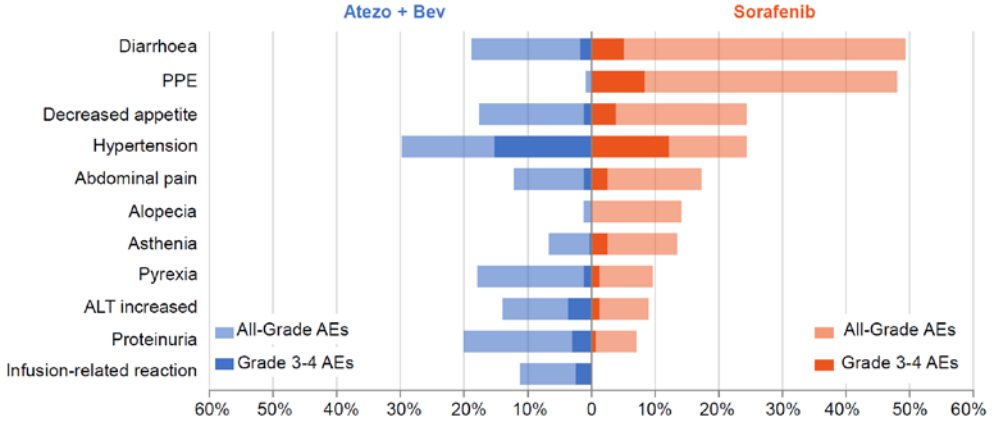
Hepatocellular carcinoma

Advanced stage (BCLC-C) – Immune checkpoint inhibitors

Radiological response

	IRF RECIST 1.1[a]		IRF HCC mRECIST[b]	
	Atezo + Bev (n = 130)	Sorafenib (n = 60)	Atezo + Bev (n = 128)	Sorafenib (n = 59)
Confirmed ORR, n (%) (95% CI)	32 **(25)** (18, 33)	4 **(7)** (2, 16)	38 **(30)** (22, 38)	5 **(8)** (3, 19)
CR, n (%)	5 (4)	0	16 (13)	0
PR, n (%)	27 (21)	4 (7)	22 (17)	5 (8)
Difference in ORR (95% CI), %	18 (7, 29)		21 (9, 33)	
SD, n (%)	59 (45)	25 (42)	52 (41)	24 (41)
PD, n (%)	29 (22)	19 (32)	28 (22)	18 (31)
DCR, n (%)[c]	91 (70)	29 (48)	90 (70)	29 (49)
Ongoing response at data cutoff, n (%)[d]	29 (91)	3 (75)	33 (87)	3 (60)

Adverse events



Finn RS et al. *N Engl J Med* 2020

Hepatocellular carcinoma

Combination clinical trials

Table 2. Ongoing trials of novel combinations of molecular therapies for HCC.

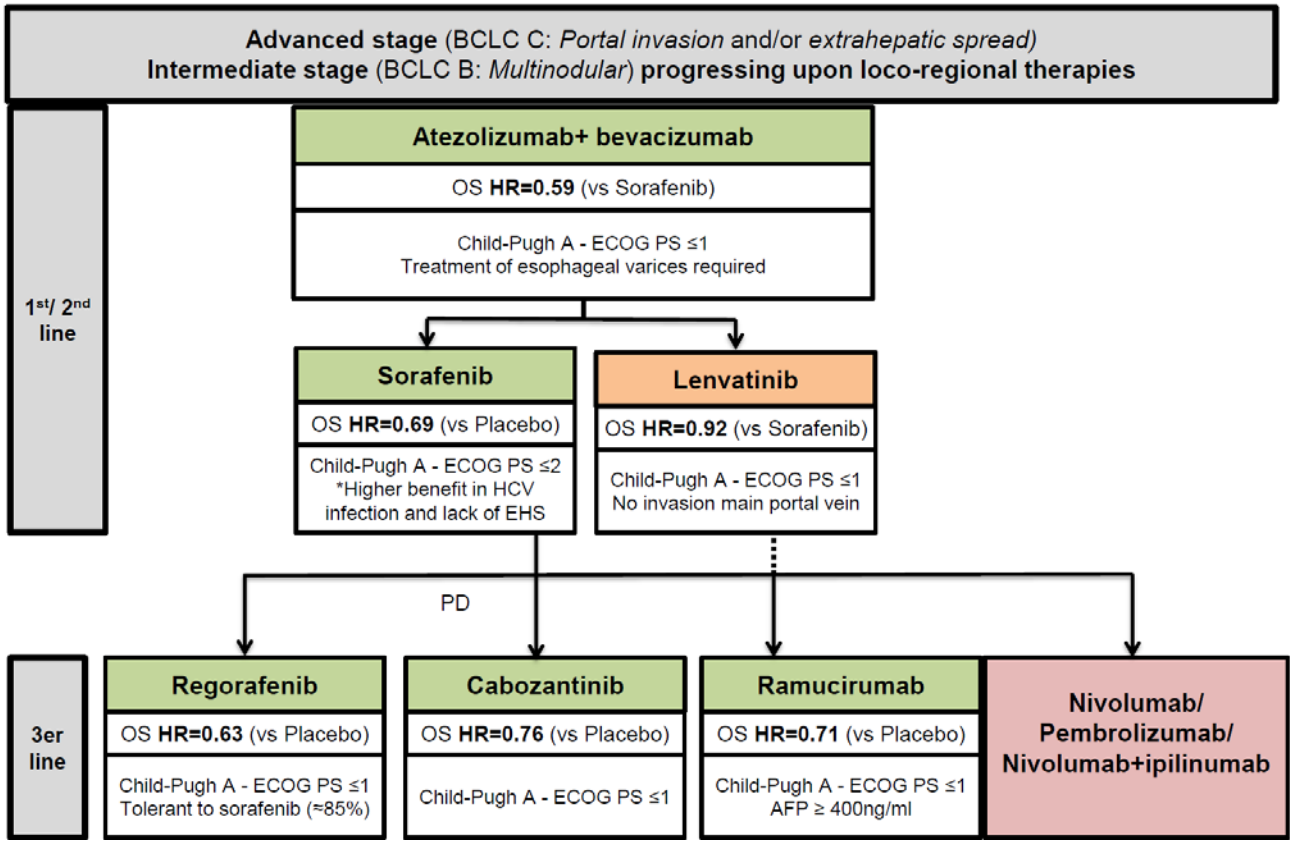
Trial name/ identifier	Setting	Treatment	Primary endpoints	Study type	Planned enrollment, n
Phase I/II trials					
GO30140/ NCT02715531*	Advanced HCC/first-line	Bevacizumab + atezolizumab	Safety, ORR, PFS	Phase Ib	430 (across all cohorts)
NCT03006926	Advanced HCC/first-line	Lenvatinib + pembrolizumab	Dose escalation: Safety, DLTs Dose expansion: ORR, DOR	Phase Ib (dose-escalation and dose-expansion)	97
NCT03418922	Advanced HCC/first-line	Lenvatinib + nivolumab	Part 1: DLTs, safety Part 2: Safety	Phase Ib (part 1 and part 2)	26
NCT03895970	Advanced hepatobiliary tumors/second-line	Lenvatinib + pembrolizumab	ORR, DCR, PFS	Phase IIb	50
CheckMate 040/ NCT01658878*	Advanced HCC/first- or second-line	Cabozantinib + nivolumab +/– ipilimumab	Safety, ORR	Phase I/II (dose-escalation, dose-expansion)	620 (across all cohorts)
COSMIC-021/ NCT03170960	Advanced solid tumors, HCC/first-line	Cabozantinib + atezolizumab	Dose escalation: MTD, Recommended dose Dose expansion: ORR	Phase Ib (dose-escalation and dose-expansion)	1000 (across all cohorts)
CaboNivo/ NCT03299946	Locally advanced HCC/neoadjuvant	Cabozantinib + nivolumab	Safety, number of patients who complete preoperative treatment and proceed to surgery	Phase Ib	15
CAMILLA/ NCT03539822	Advanced GI tumors, HCC/second-line	Cabozantinib + durvalumab	MTD	Phase Ib	30
NCT03347292	Advanced HCC/first-line	Regorafenib + pembrolizumab	Safety, DLTs	Phase Ib (dose-escalation and dose-expansion	40
REGOMUNE/ NCT03475953	Advanced GI tumors, HCC/second-line	Regorafenib + avelumab	Part 1: Recommended phase II dose of regorafenib art 2: ORR	Phase I/II (part 1 and part 2)	212
NCT02572687	Advanced solid tumors, HCC/second-line and AFP ≥1.5x upper limit of normal	Ramucirumab + durvalumab	DLTs	Phase I	114
NCT02082210	Advanced solid tumors, HCC/second-line	Ramucirumab + emibetuzumab	Part A: DLTs Part B: ORR	Phase I/II	97
NCT02423343	Advanced solid tumors, HCC/second-line and AFP ≥200 ng/mL	Galunisertib + nivolumab	Phase Ib: MTD	Phase Ib/II (dose escalation and cohort expansion)	75
Phase III trials					
IMbrave150/ NCT03434379	Advanced HCC/first-line	Atezolizumab + bevacizumab *vs.* sorafenib	OS, PFS	Phase III, randomised, open-label	480
LEAP-002/ NCT03713593	Advanced HCC/first-line	Lenvatinib + pembrolizumab *vs.* lenvatinib + placebo	PFS, OS	Phase III, randomised, double-blinded	750
COSMIC-312/ NCT03755791	Advanced HCC/first-line	Cabozantinib + atezolizumab *vs.* sorafenib *vs.* cabozantinib	PFS, OS	Phase III randomised, open-label	740

AFP, alpha-fetoprotein; DCR, disease control rate; DLTs, dose-limiting toxicities; DOR, duration of response; GI, gastrointestinal; HCC, hepatocellular carcinoma; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. *Trials include other cohorts.

Faivre S et al. *J Hepatol* 2020

Advanced HCC (BCLC-C)

Effective therapies



Adapted from JM Llovet et al. J Hepatol 2019

Outline

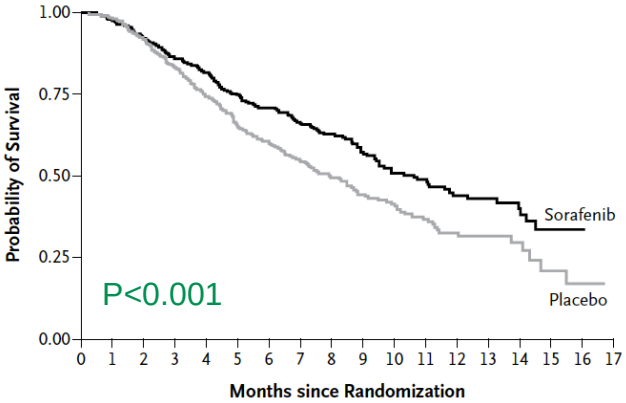
- Systemic therapies for HCC
  - Targeted therapies
  - Immune-based therapies
  - Combinations

- Biomarkers for patient selection

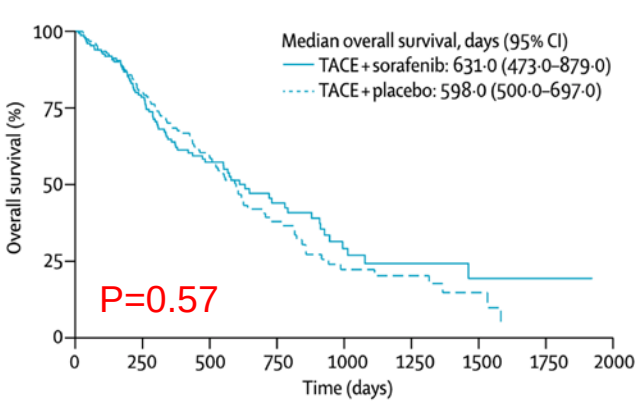
Systemic therapies in HCC

Expanding indications to early stages - Sorafenib

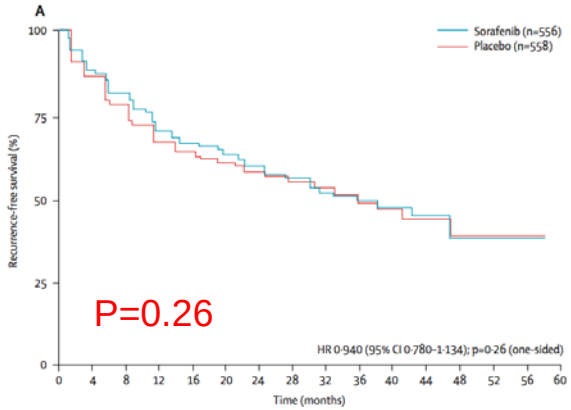
Sorafenib improves survival
(Advanced stage / BCLC-B)



Sorafenib does not improve survival
(Intermediate stage / BCLC-B)



Sorafenib does not improve survival
(Early stage / BCLC-0A)

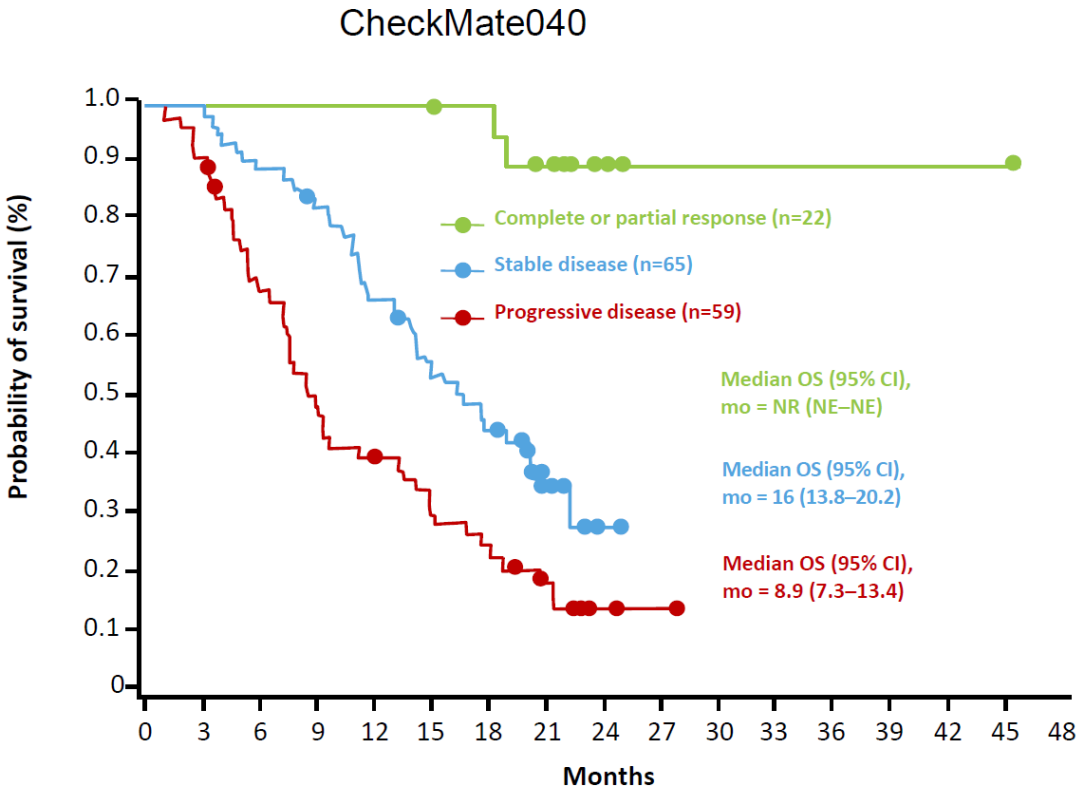


Disease stage does matter... the disease evolves over time

Bruix J et al *Lancet Oncol* 2015; Meyer et al. *Lancet Gastro Hepatol* 2018; Llovet et al. *NEJM* 2008

Checkpoint inhibitors in HCC

Who responds?



	Escalation phase (n=44)*	Expansion phase (n=174)*
PD-L1 ≥1%†	11 (25%)	34 (20%)
Objective response	3/11 (27%; 6–61)	9/34 (26%; 13–44)
Complete response	1 (9%)	1 (3%)
Partial response	2 (18%)	8 (24%)
Stable disease	0	16 (47%)
Progressive disease	7 (64%)	9 (26%)
Not determined	1 (9%)	0
PD-L1 <1%†	33 (75%)	140 (80%)
Objective response	4/33 (12%; 3–28)	26/140 (19%; 13–26)
Complete response	2 (6%)	2 (1%)
Partial response	2 (6%)	24 (17%)
Stable disease	19 (58%)	62 (44%)
Progressive disease	8 (24%)	46 (33%)
Not determined	2 (6%)	6 (4%)

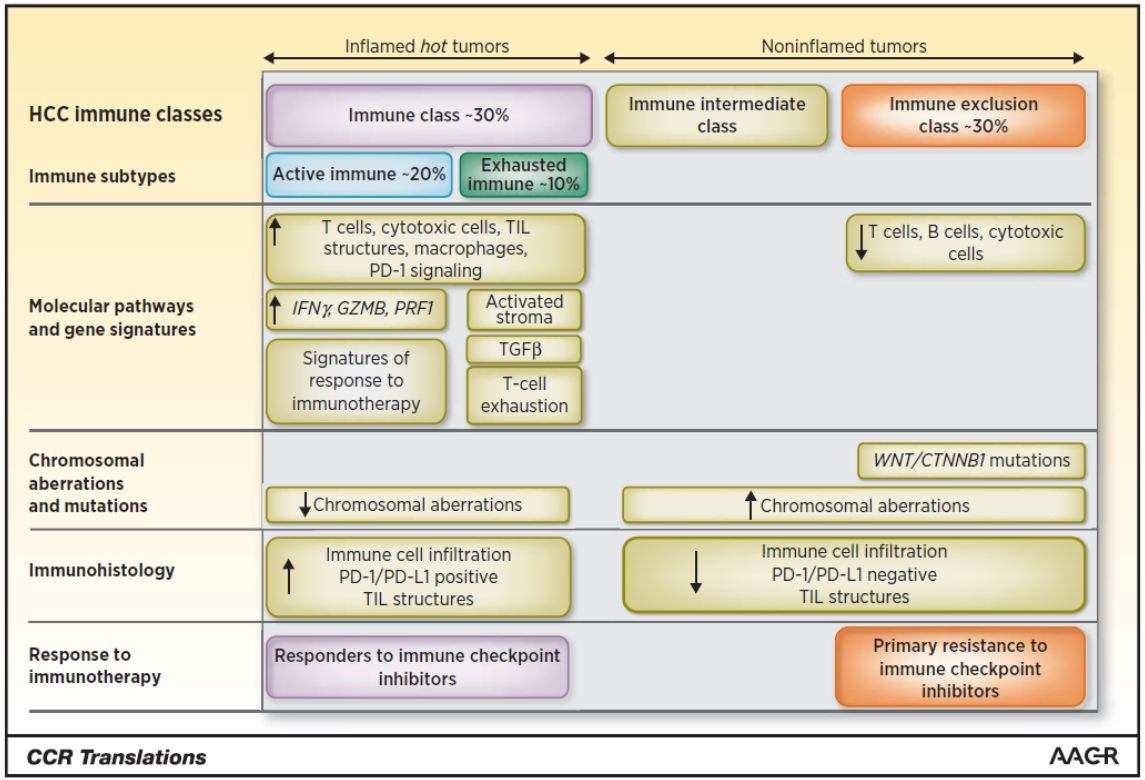
Data are n (%); n/N (%; 95% CI). PD-L1=programmed death-ligand 1.
*Four patients in the dose-escalation phase and 40 patients in the dose-expansion phase did not have tumour PD-L1 expression data available.
†PD-L1 membrane expression on tumour cells.

Table 5: PD-L1 expression on tumour cells and response

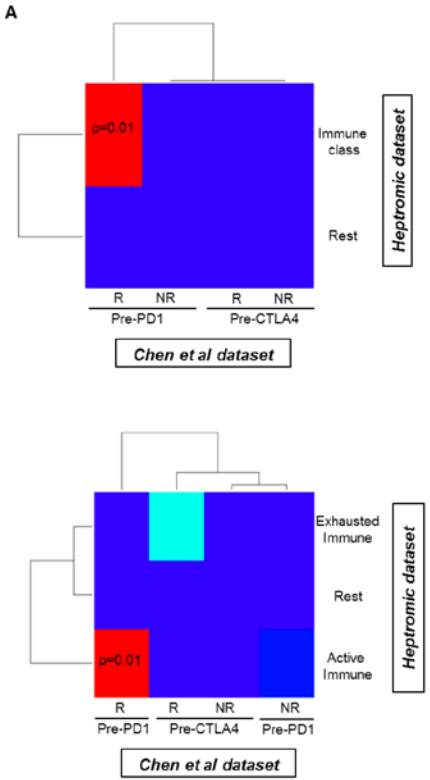
El-Khoueiry et al *Lancet* 2017

Hepatocellular carcinoma

Advanced stage (BCLC-C) – Immune checkpoint inhibitors (predictors of response)



Response to CPI

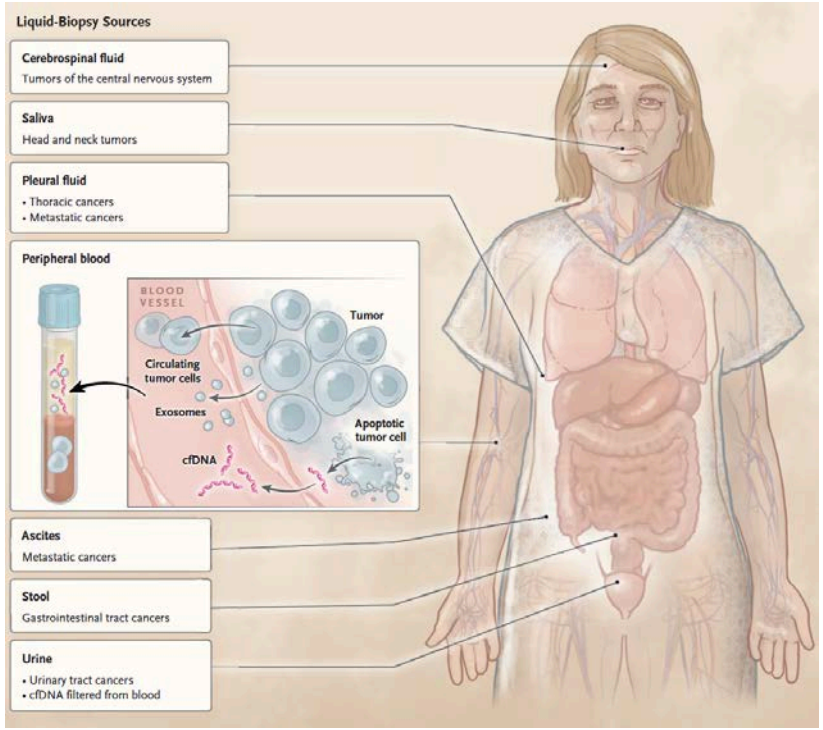


Sia D et al *Gastroenterology* 2017; Pinyol et al. *CCR* 2019

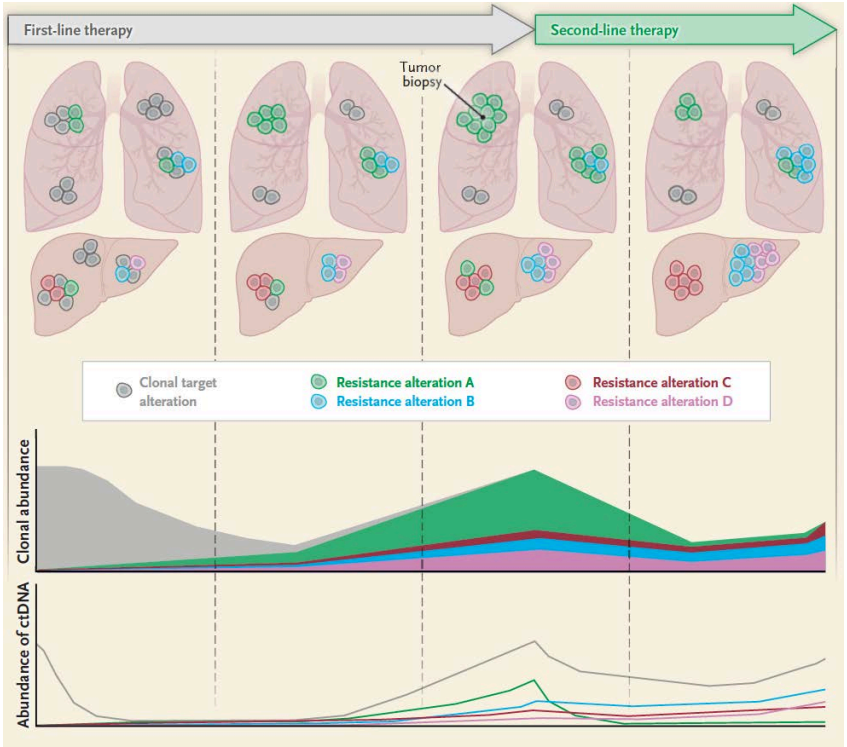
Liquid biopsy (ctDNA)

Clinical applications

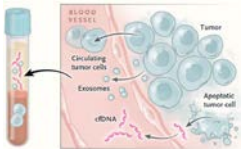
Tumor components released to fluids



Monitor tumor clonal composition



Corcoran RB et al. *N Engl J Med* 2018



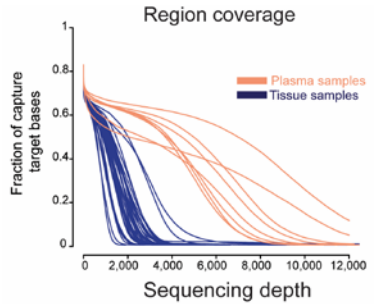
Liquid biopsy

ctDNA in early stage HCC

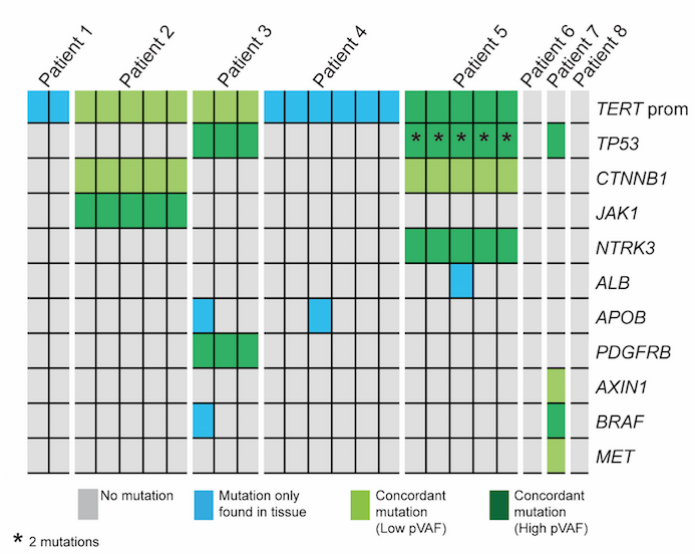
Circulating tumor DNA: 8 patients (paired tissue-blood)

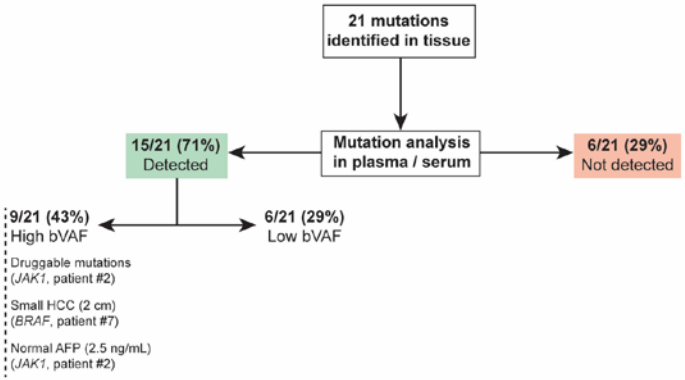
- Ultra-deep targeted DNA sequencing --- all exons
- Capture methods: SureSelect (Agilent®) – n=**58** genes

Ultra-deep NGS

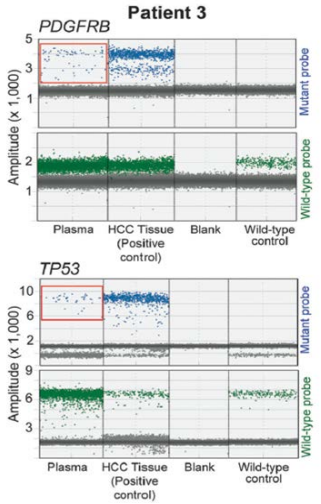


Performance (Mutation detection)





Validation (ddPCR)

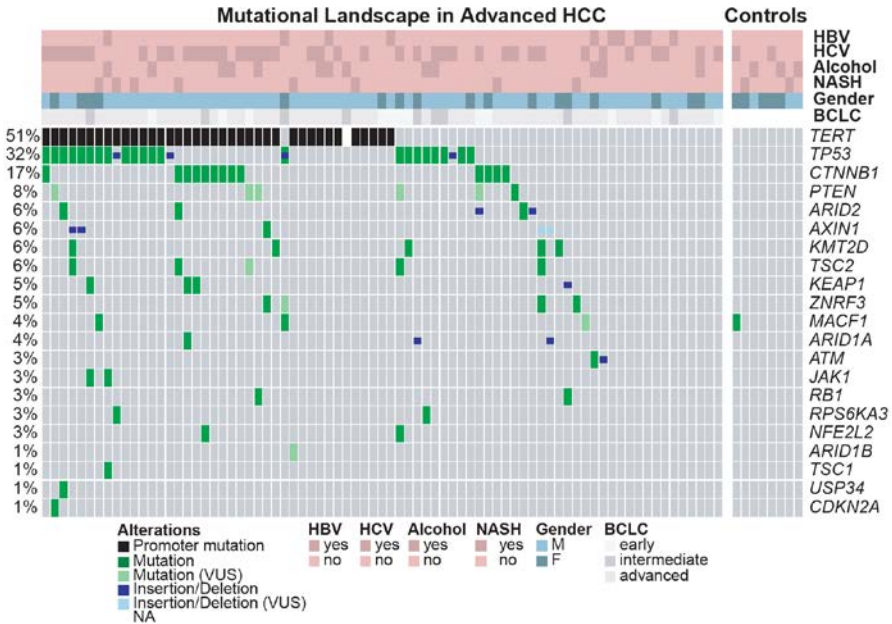


Labgaa I et al. *Oncogene* 2018

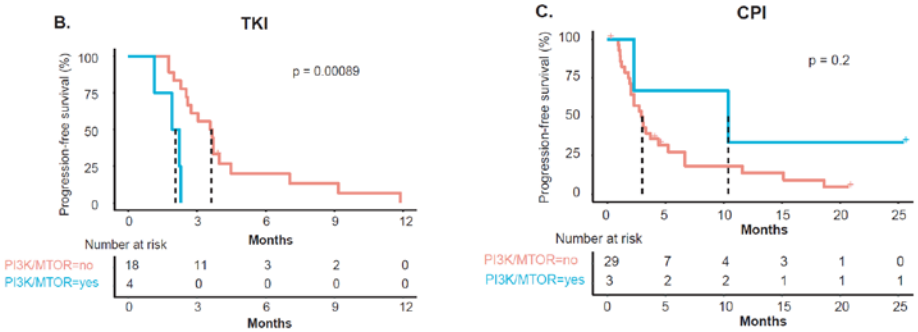
Liquid biopsy

ctDNA in advanced stage HCC

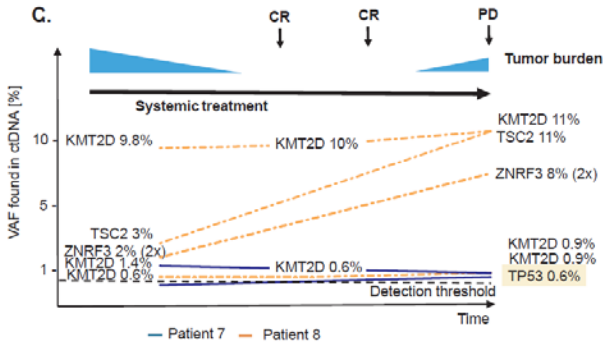
HCC patients (n=88)



Predictors of response to sorafenib



Molecular monitoring

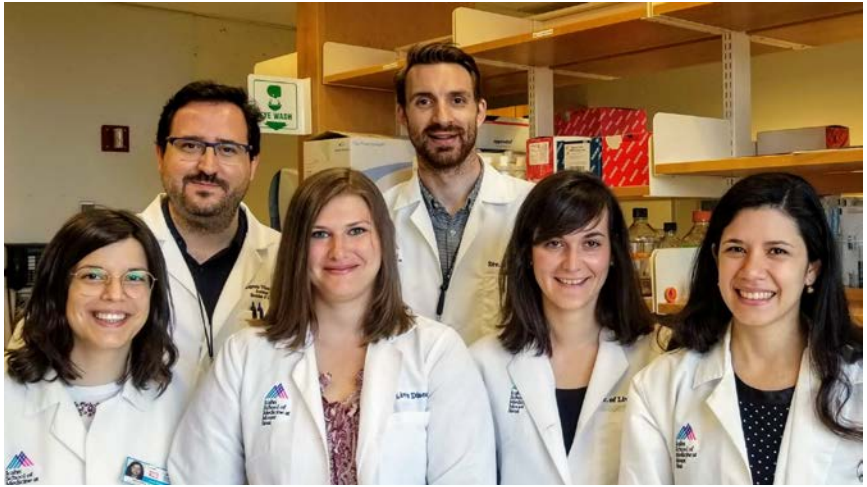


Von Felden I et al. *Oncogene* 2020

Conclusions

- There has been major changes in the management of HCC with systemic therapies
- There are 10 drugs approved by the FDA (atezo+bev, sorafenib, lenvatinib, regorafenib, cabozantinib, ramucirumab, nivolumab, pembrolizumab, nivo+ipi) for HCC. Still unclear best way to sequence therapies.
- Short-term future includes combination therapies and application of these therapies at earlier stages (neoadjuvant, combination with loco-regional, etc…)

Acknowledgements



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