Selection and Sequencing of Treatment for Patients with Relapsed HCC

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Timeline of the US FDA approval for HCC treatments

Lai et al. (1988) Cancer 62:479

Llovet et al. (2008) NEJM 359:2508

Bruix et al. (2017) Lancet 389:56

Courtesy of Tim Greten, MD

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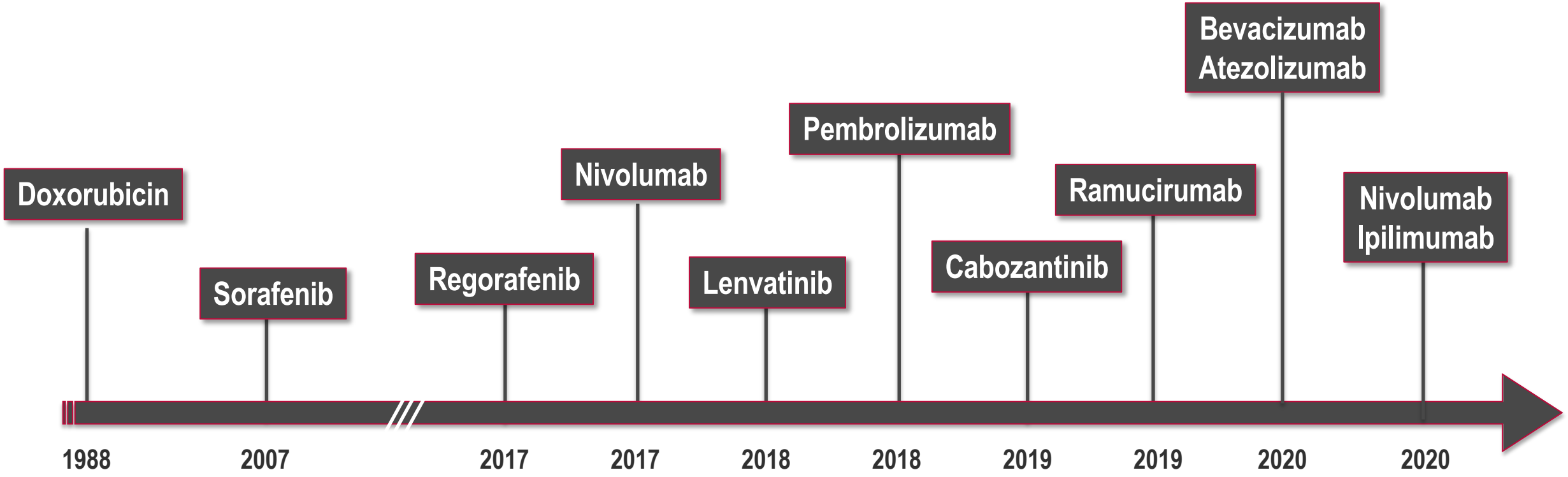

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El-Khoueiry et al. (2017) Lancet 389:2492

Kudo et al. (2018) Lancet 391:1163

Zhu et al. (2018) Lancet Onc. 19:940

Abou-Alfa et al. (2019) NEJM 379:54

Zhu et al. (2019) Lancet Onc. 16:859

Finn et al. (2020) NEJM 382:1849

Yau et al. (2020) JAMA Oncol. e204564

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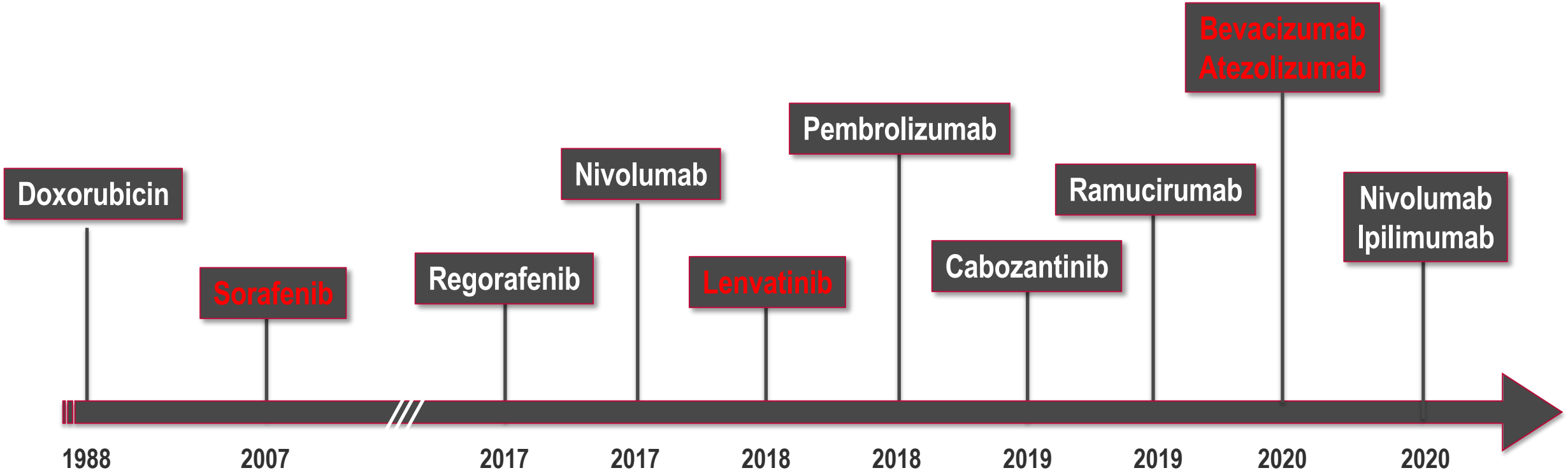

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Kudo et al. (2018) Lancet :3911163

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Courtesy of Tim Greten, MD

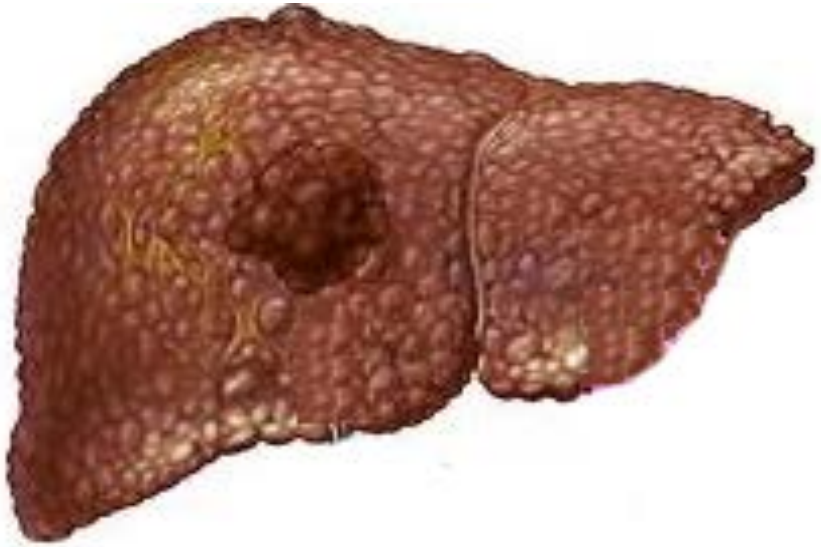
FDA approved first and second line therapies

- Sorafenib
- Lenvatinib
- Atezo + bev
- Regorafenib
- Cabozantinib
- Ramucirumab
- Nivolumab*
- Pembrolizumab*
- Nivo + ipi*

*Accelerated approval

Courtesy of Tim Greten, MD

Key factors influencing the selection and sequence of approved regimens



- Performance status
- Tumor size & location
- AFP

- Comorbidities
- Tolerability

- Liver function

- Prior treatment (mechanism of action)

- Data from RCT

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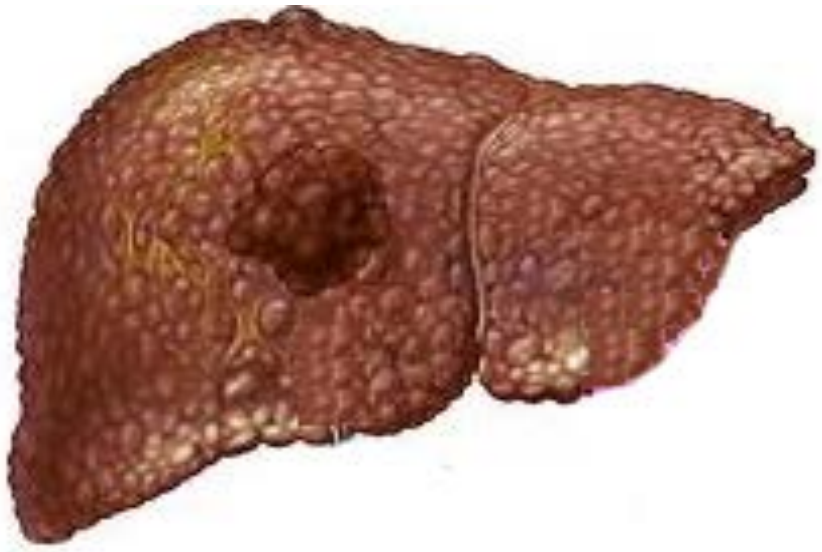

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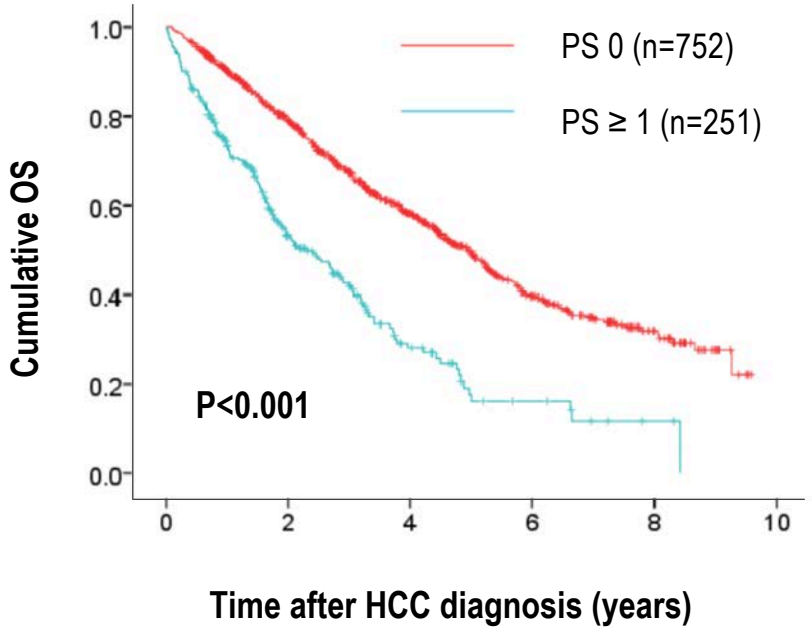
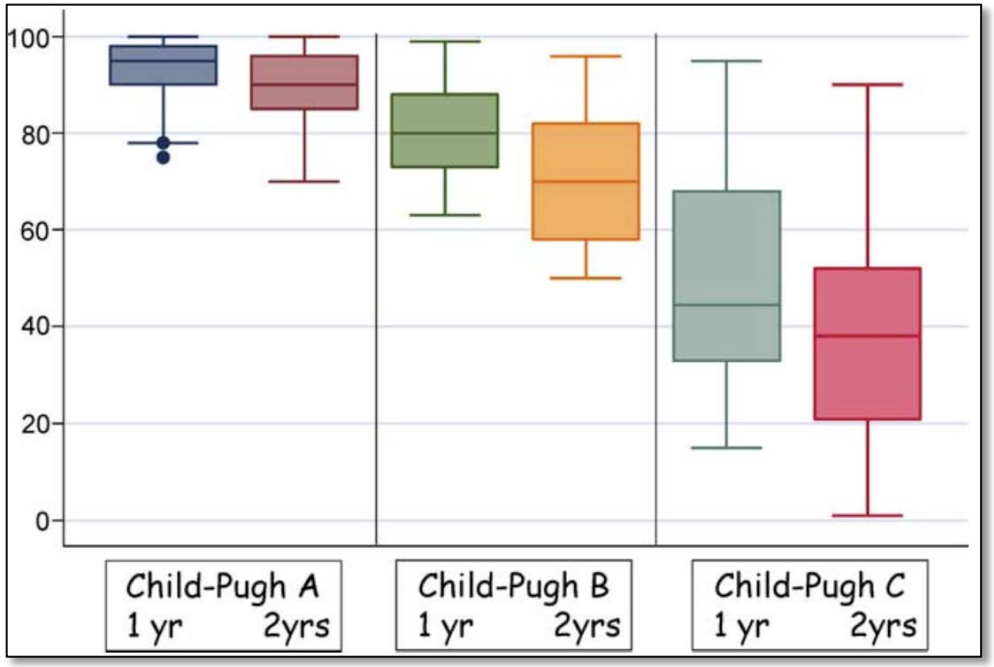


Nishikawa et al. (2015) Journal of Cancer 6:394

Courtesy of Tim Greten, MD

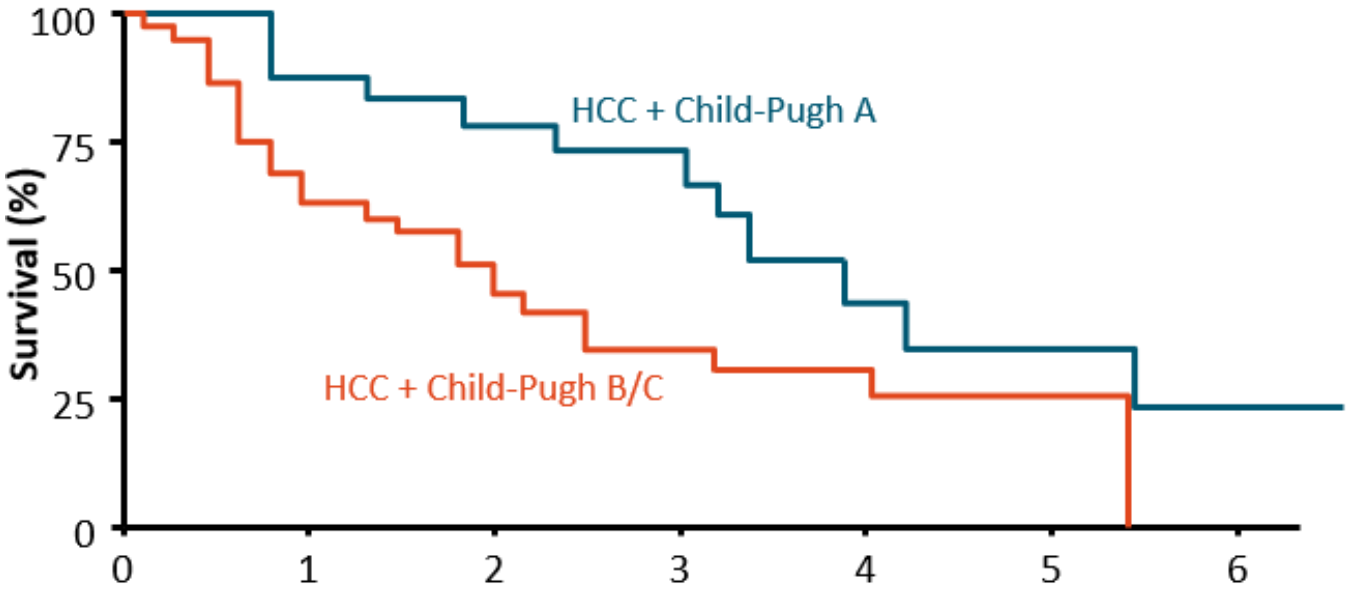
The impact of liver cirrhosis in patients with HCC

Natural history and prognostic indicators for survival in cirrhosis



D'Amico et al. J Hepatol. (2006)44:217

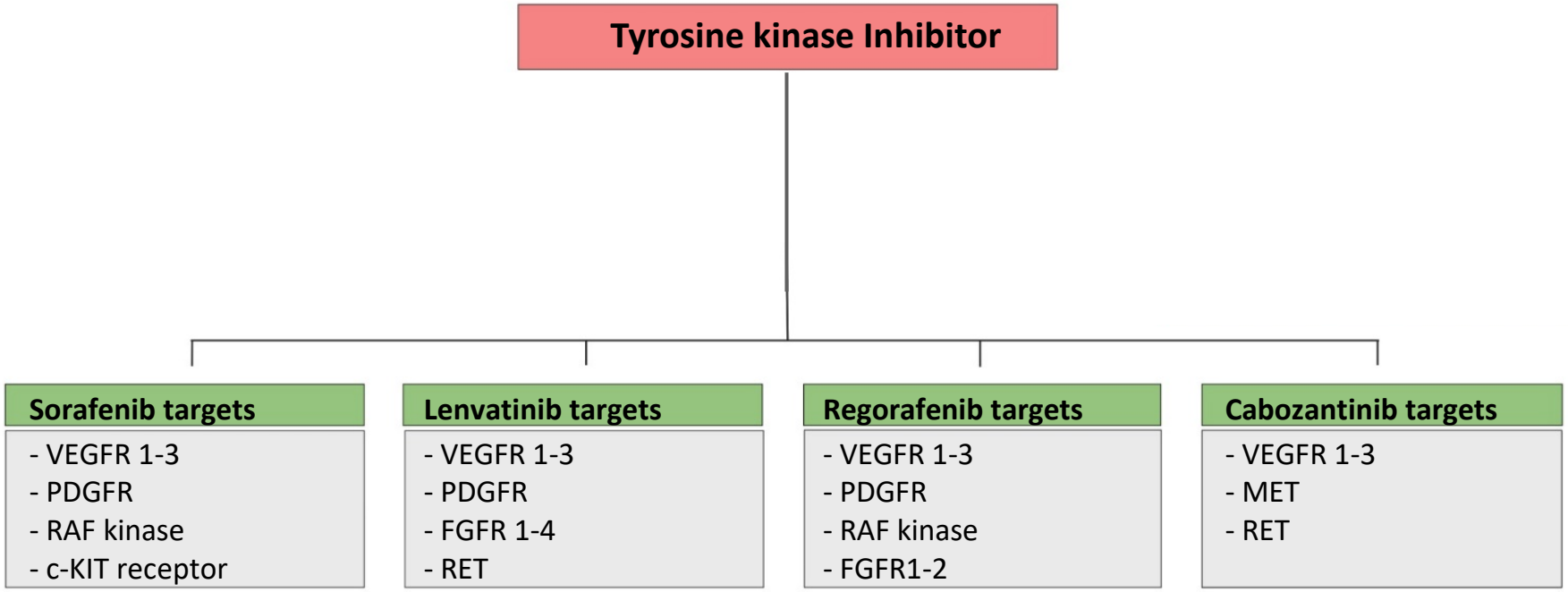
The effect of liver cirrhosis on OS in HCC



Bolondi et al. Gut (2001) 48:251-59

Courtesy of Tim Greten, MD

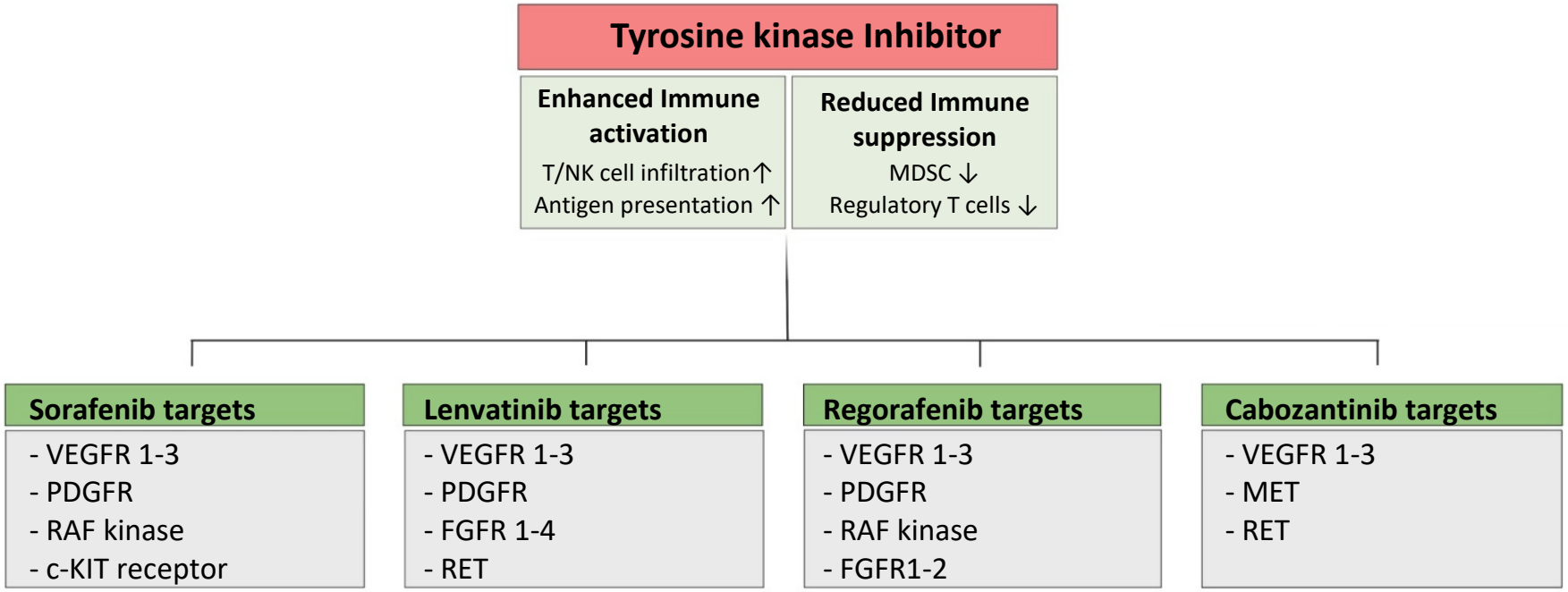
Tyrosine kinase inhibitors



Courtesy of Tim Greten, MD

Llovet, …, Greten, …, Lencioni Nat Rev Gastro in press

Tyrosine kinase inhibitors



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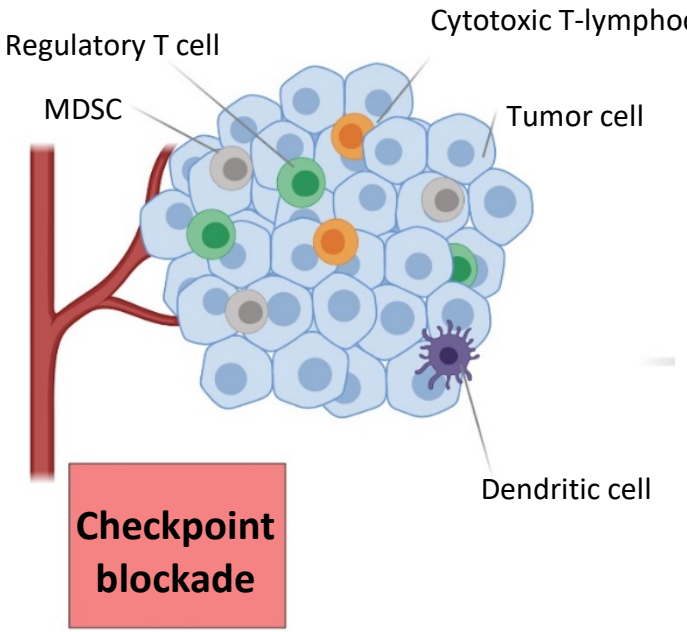
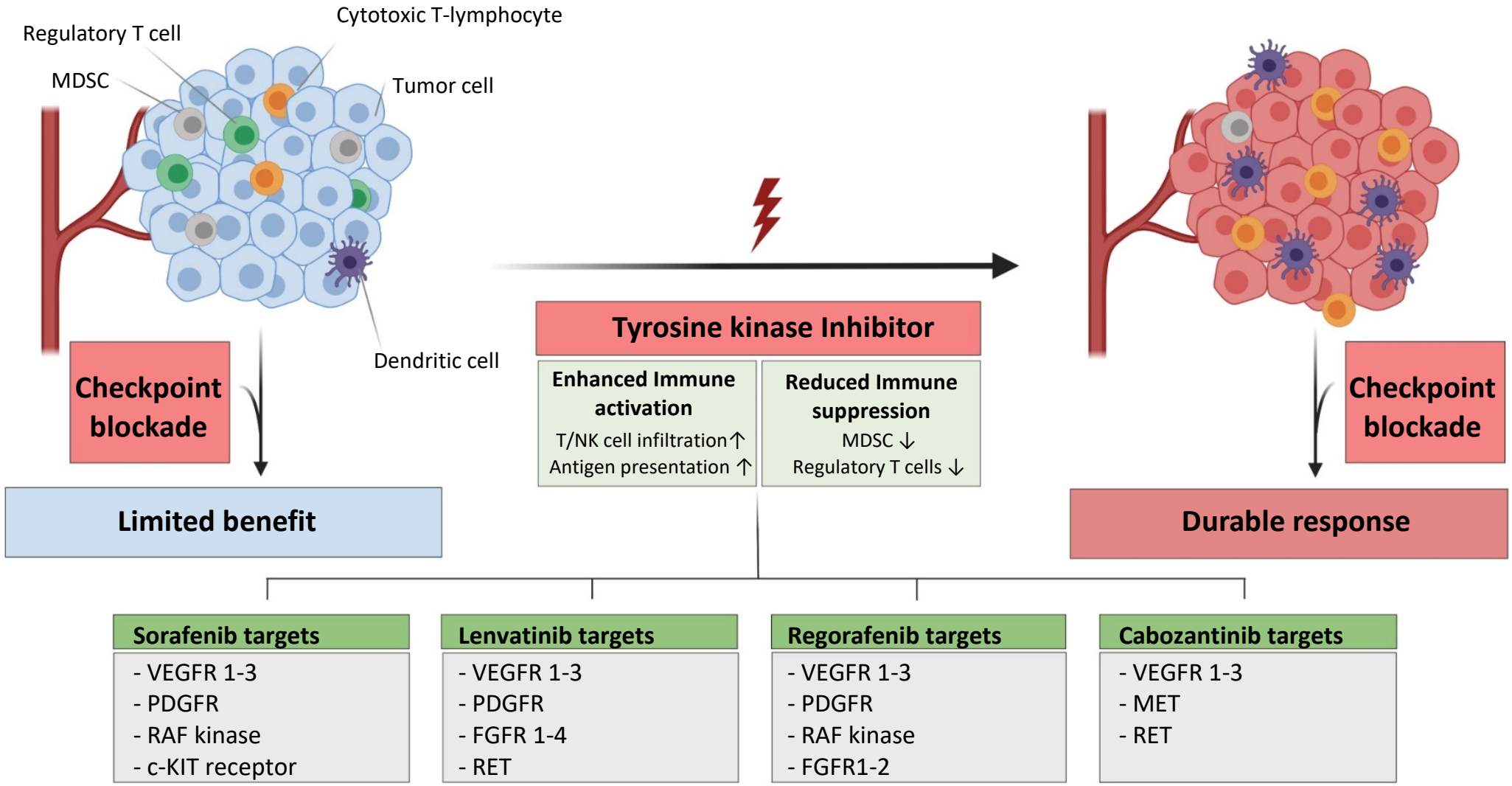
Immune checkpoint inhibitors



Courtesy of Tim Greten, MD

Llovet, …, Greten, …, Lencioni Nat Rev Gastro in press

Tyrosine kinase inhibitors plus immunotherapy



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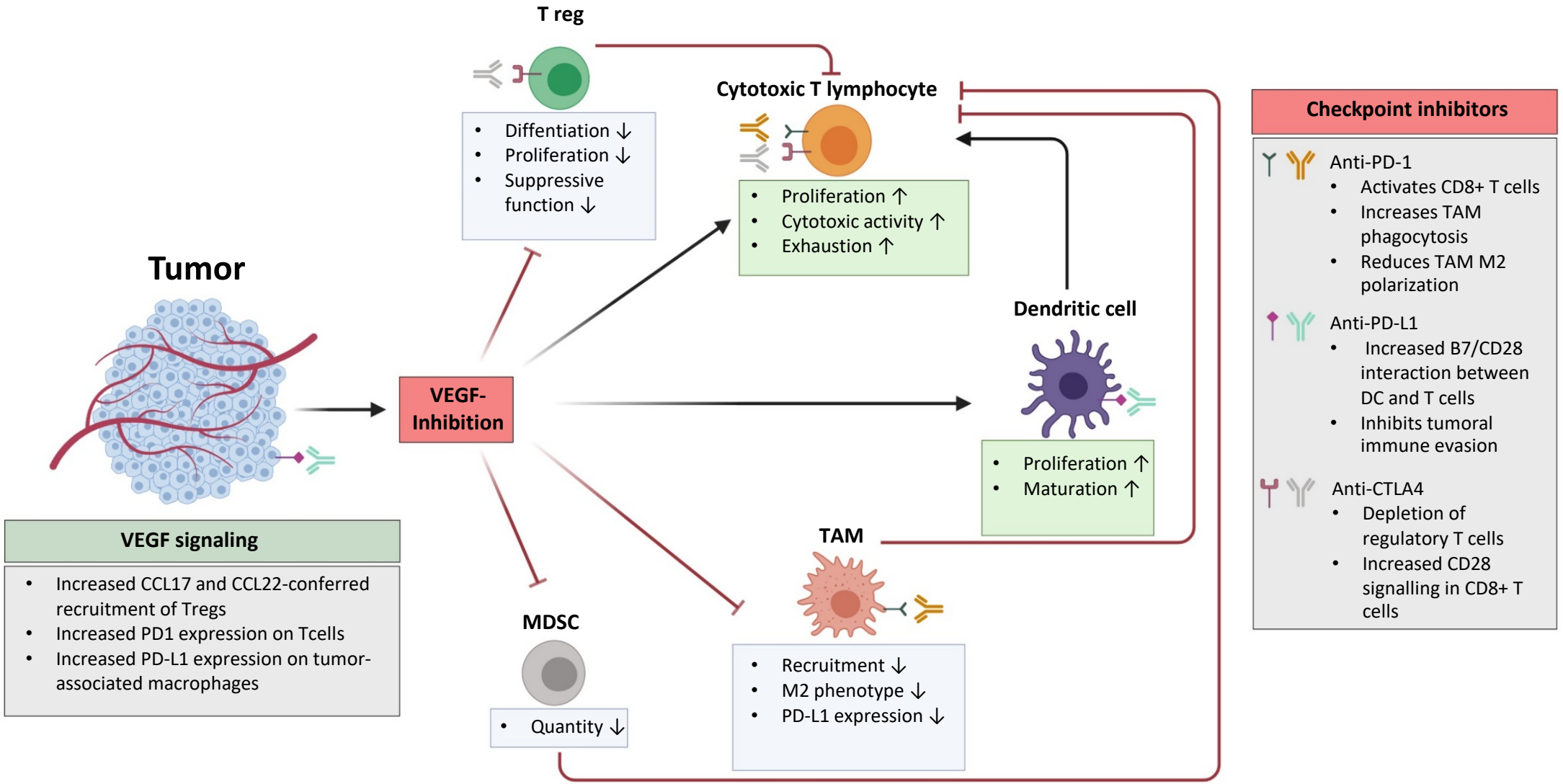
Targeting VEGF plus immunotherapy



Courtesy of Tim Greten, MD

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FDA approved first line therapies

SHARP	REFLECT	IMbrave150
Sorafenib vs placebo	Lenva vs sorafenib	Atezo + bev vs placebo
TKI	TKI	IO + anti-VEGF
Advanced HCC	unresectable HCC Excluded: 50% or higher liver occupation, obvious invasion of the bile duct, or invasion at the main portal vein	locally advanced metastatic or unresectable HCC
Median OS: 10.7 vs 7.9 months	noninferior OS	6 months OS: 84.8% (95% CI, 80.9 to 88.7) 72.2% (95% CI, 65.1 to 79.4)
Treatment until the occurrence of both radiologic progression, **and** symptomatic progression.		Patients received treatment until loss of **clinical benefit**. Treatment beyond disease progression optionable

Llovet et al.N Engl J Med (2008) 359:378-90.

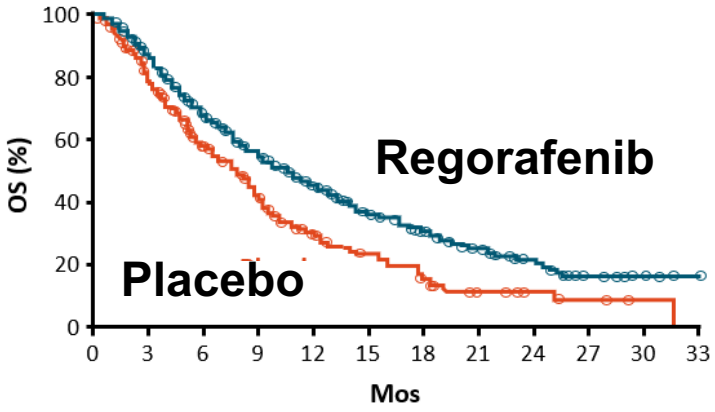
Kudo et al. (2018) Lancet :3911163

Finn et al. (2020) NEJM 382:1849

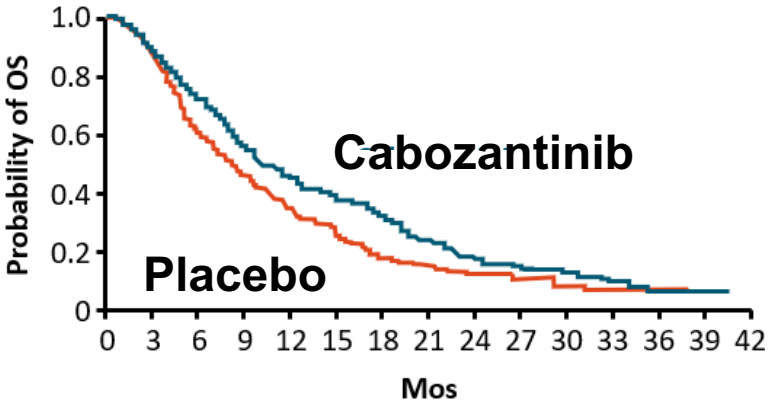
Courtesy of Tim Greten, MD

TKIs as second line treatment for HCC

RESORCE	CELESTIAL	REACH-2
Regorafenib vs placebo	Cabozantinib vs placebo (N = 707)	Ramucirumab vs placebo
2L, sorafenib-tolerating pts only (N = 573)	2L or 3L (N = 707)	2L, AFP ≥ 400 ng/mL (N = 292)
Median OS: 10.6 vs 8.0 mos	Median OS: 10.2 vs 8.0 mos	Median OS: 8.5 vs 7.3 mos
HR: 0.63 (P < .0001)	HR: 0.76 (P = .005)	HR: 0.71 (P = .0199)



Bruix. Lancet. 2017;389:56



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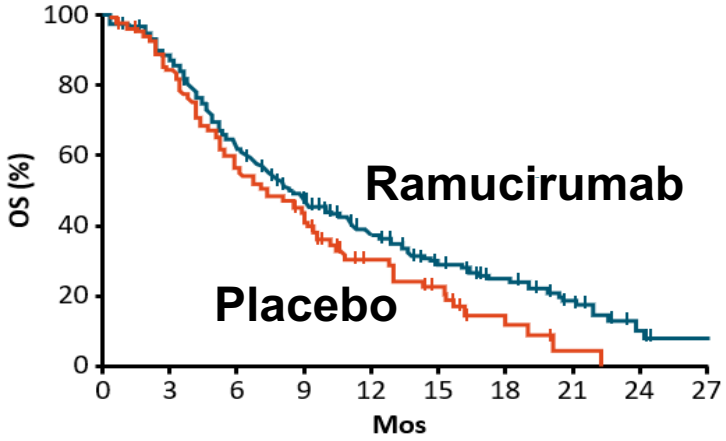
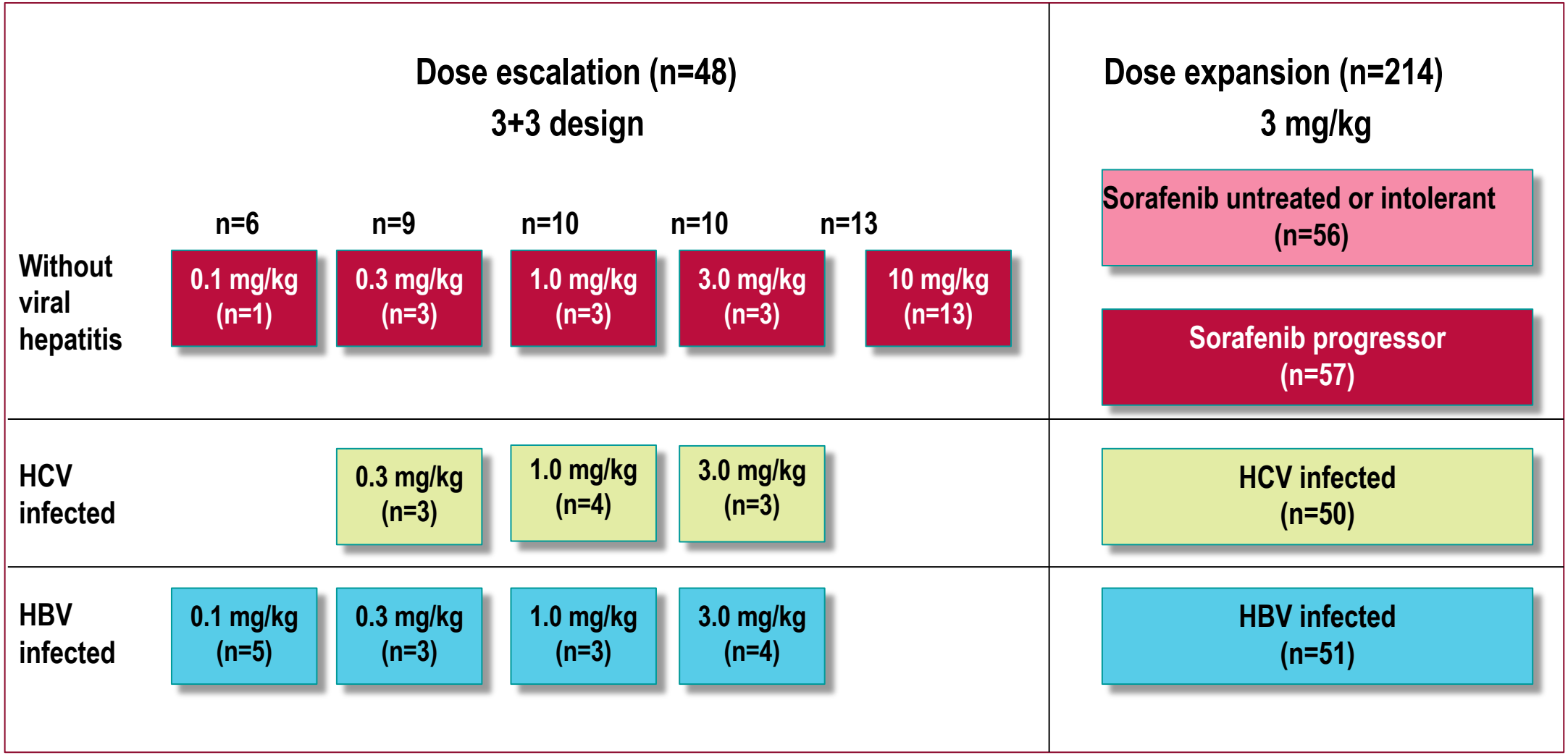


Zhu. Lancet Oncol. 2019;20:282.

Apatinib (AHELP), VEGFR2 inhibitor, OS: 8.7 vs 6.8 months, HR: 0.785 (0.617-0.998); Li. ASCO 2020. Abstr 4507

Courtesy of Tim Greten, MD

Nivolumab in patients with advanced HCC (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

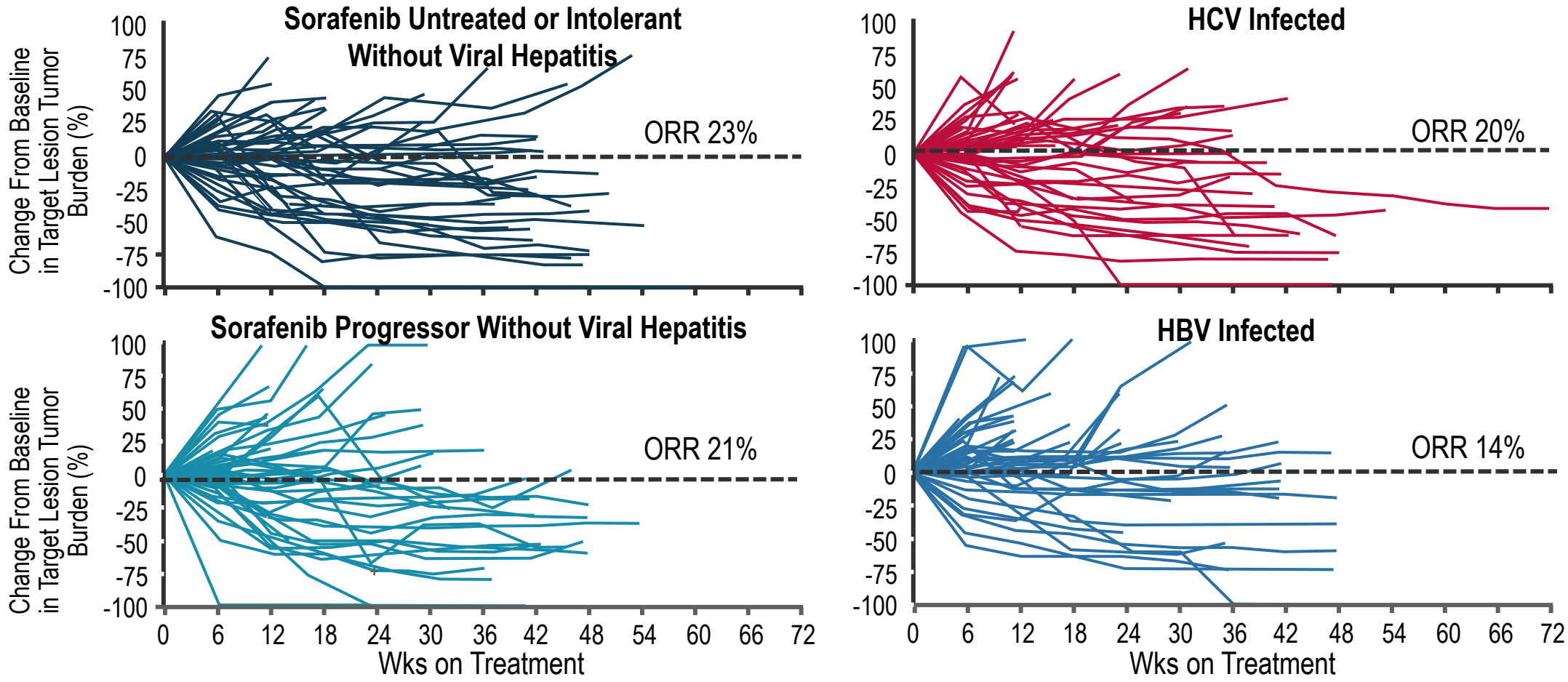


El-Khoueiry et al. (2017) Lancet 389:2492-507

Courtesy of Tim Greten, MD

Nivolumab in patients with advanced HCC (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

Open-label phase I/II trial of nivolumab in patients with advanced HCC with Child-Pugh class A/B7 (escalation phase), class A (expansion phase), ECOG PS < 1; previous sorafenib treatment allowed



Overall ORR: 20%/15% (dose exp vs esc)

Courtesy of Tim Greten, MD

El-Khoueiry et al. (2017) Lancet 389:2492-507

KEYNOTE-240: Pembrolizumab for Patients With Previously Treated HCC

Randomized, double-blind phase III trial of **pembrolizumab** vs **placebo** (both with BSC) for pts with advanced HCC with intolerance to or PD on or after sorafenib; Child-Pugh A (N = 413)

- Patients with advanced HCC intolerance to or PD on or after sorafenib
- Child-Pugh A; BCLC stage B/C
- ECOG PS ≤ 1
- no invasion of main portal vein

(N = 413)

Pembrolizumab 200 mg Q3W + **BSC**
(n = 278)

Placebo + BSC
(n = 135)

Coprimary endpoints: PFS,* OS

– Efficacy boundaries: PFS at first interim cutoff, *P* = .0020 (primary analysis for PFS); OS at final analysis cutoff, *P* = .0174

Secondary endpoints: ORR,* DoR, DCR, TTP, safety

*PFS, secondary response outcomes centrally reviewed.

Courtesy of Tim Greten, MD

Finn et al. JCO (2020) 38:193

KEYNOTE-240: Pembrolizumab for Patients With Previously Treated HCC

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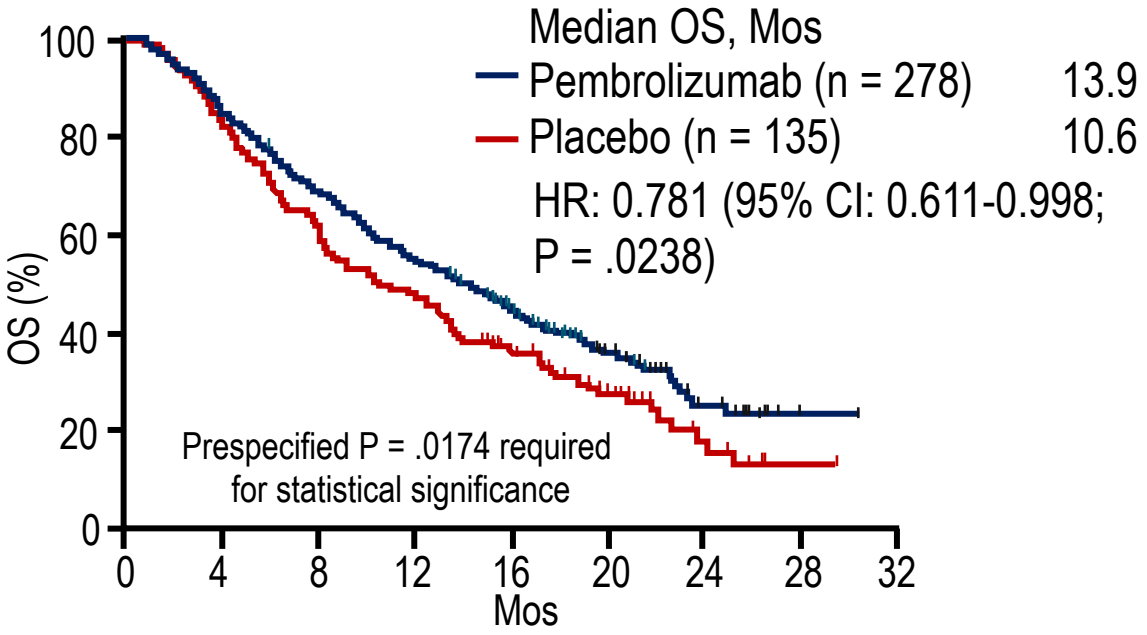
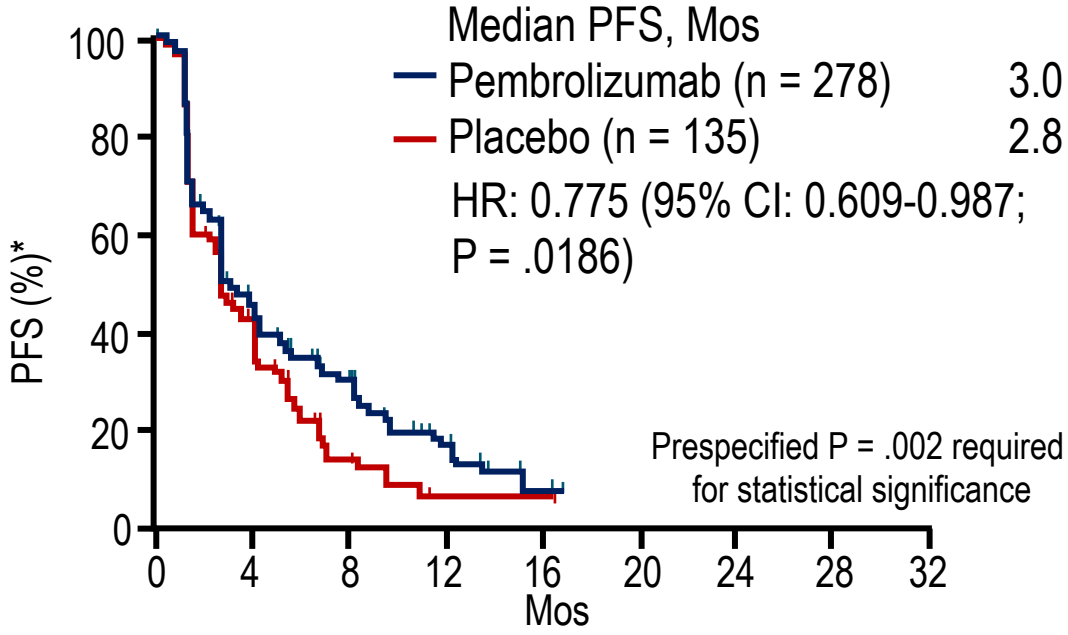




- Failed to reach prespecified level of statistical significance for OS, PFS
- ORR: pembrolizumab, 18.3%; sorafenib, 4.4% (*P* = .00007)

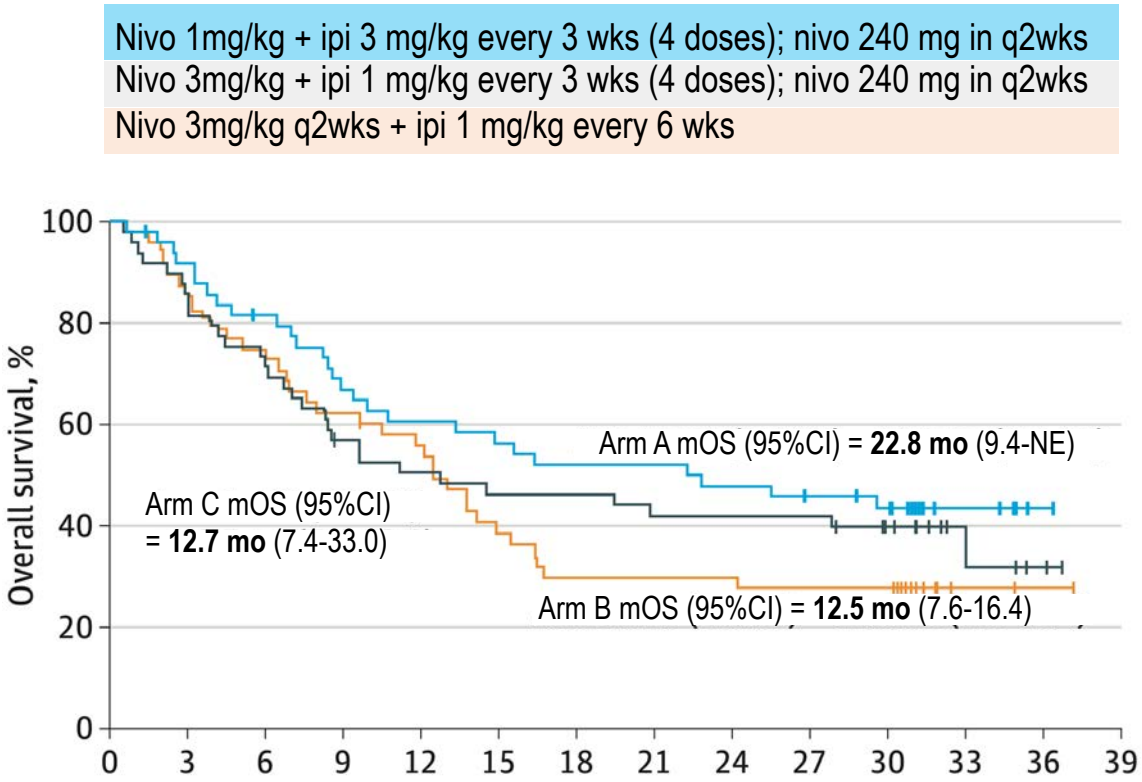
Courtesy of Tim Greten, MD

Finn et al. JCO (2020) 38:193

CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC

Open-label phase I/II trial of 3 different dosing schemes of **nivolumab + ipilimumab** for patients with advanced HCC and prior sorafenib treatment; uninfected or infected with HBV or HCV; CP score A5-A6; ECOG PS 0/1

Response	Arm A NIVO1/IPI3 Q3W (n = 50)	Arm B NIVO3/IPI1 Q3W (n = 49)	Arm C NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR, n (%)	16 (32)	13 (27)	14 (29)
BOR, n (%)			
▪ CR	4 (8)	3 (6)	0
▪ PR	12 (24)	12 (24)	15 (31)
▪ SD	9 (18)	5 (10)	9 (18)
▪ PD	20 (40)	24 (49)	21 (43)
▪ Undetermined	3 (6)	4 (8)	4 (8)
DCR, n (%)	27 (54)	21 (43)	24 (49)
Median TTR, mos (range)	2.0 (1.3-2.7)	2.6 (1.3-4.0)	2.7 (1.3-2.7)
Median DoR, mos (range)	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)



Courtesy of Tim Greten, MD

Yau et al. JAMA Oncol Published online October 1, 2020

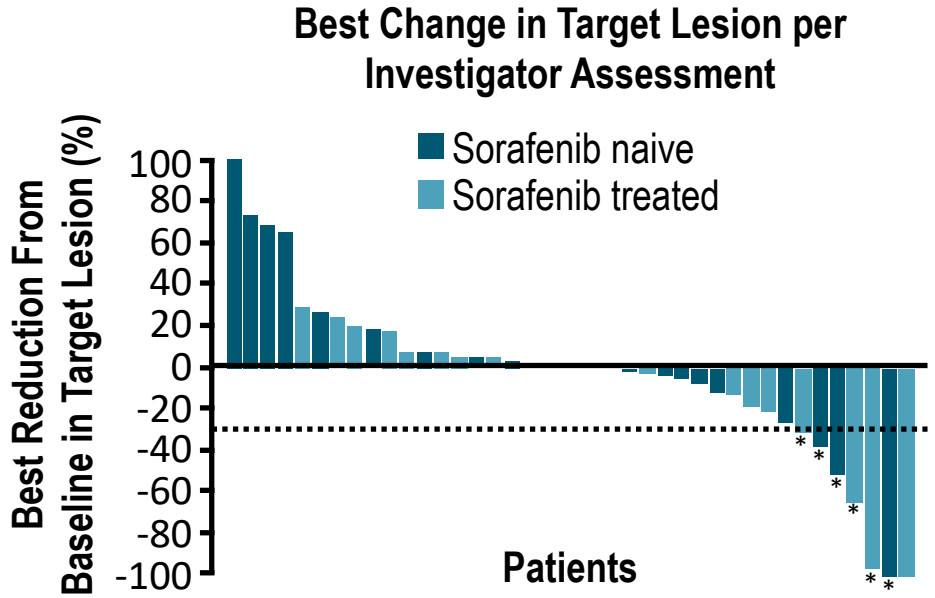
CheckMate 040: Nivolumab + Ipilimumab Safety

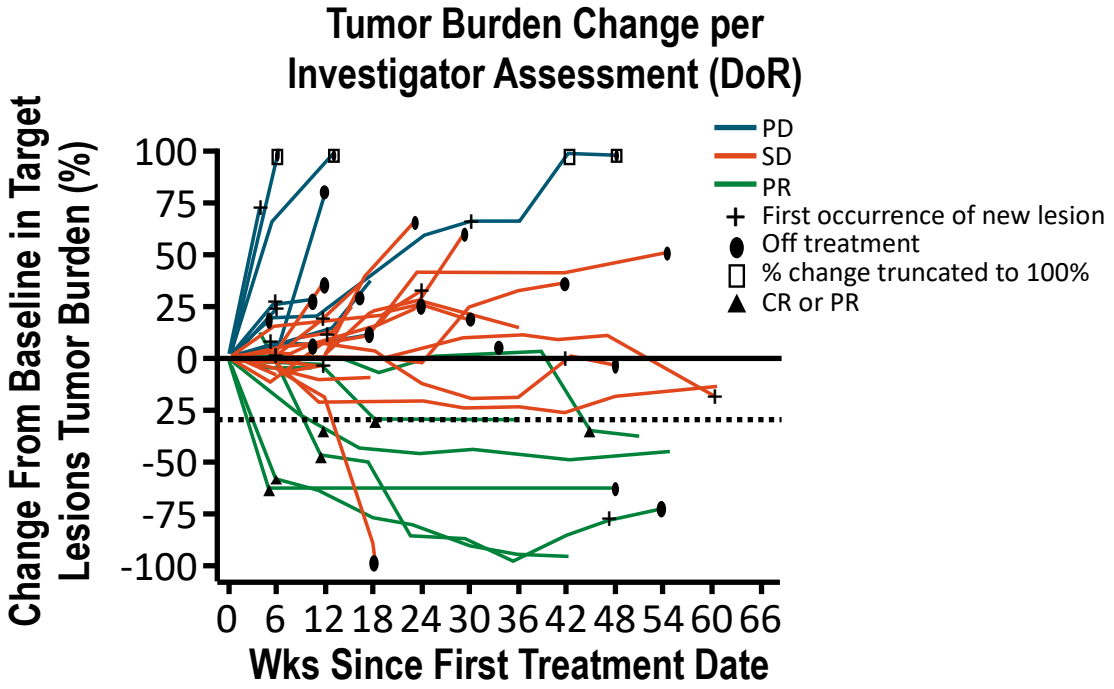
TRAEs, n (%)	NIVO1/IPI3 Q3W (n = 49)		NIVO3/IPI1 Q3W (n = 49)		Q2W/IPI1 Q6W (n = 48)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAE	46 (94)	26 (53)	35 (71)	14 (29)	38 (79)	15 (31)
Skin and subcutaneous tissue	30 (61)	4 (8)	24 (49)	2 (4)	23 (48)	1 (2)
Investigations (including liver laboratory abnormalities	24 (49)	16 (33)	21 (43)	11 (22)	15 (31)	7 (15)
General and administration site	19 (39)	2 (4)	15 (31)	0	16 (33)	0
Gastrointestinal	18 (37)	3 (6)	18 (37)	1 (2)	17 (35)	2 (4)
Endocrine	16 (33)	1 (2)	9 (18)	1 (2)	9 (19)	1 (2)
Metabolism and nutrition	14 (29)	7 (14)	6 (12)	2 (4)	6 (13)	1 (2)
Respiratory, thoracic, and mediastinal	7 (14)	1 (2)	2 (4)	0	3 (6)	0
Nervous system	7 (14)	0	6 (12)	0	2 (4)	0
Musculoskeletal and connective tissue	6 (12)	0	3 (6)	0	6 (13)	0
Hepatobiliary	3 (6)	3 (6)	1 (2)	0	1 (2)	0

Courtesy of Tim Greten, MD

Child Pugh B

BCLC stage:	B, 16%; C, 74%; D, 6%
Child-Pugh classification:	B7, 76%; B8, 22%



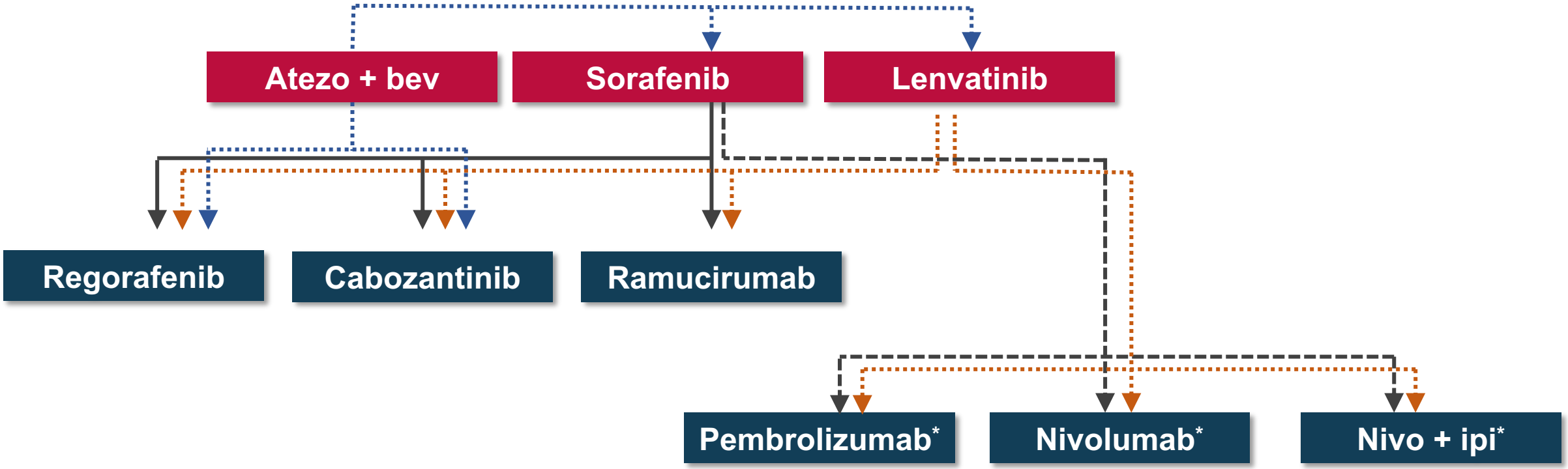


- TRAEs manageable; rates of discontinuation due to TRAEs not higher than Child-Pugh A cohort
- Hepatic TRAEs not higher in Child-Pugh B cohort vs Child-Pugh A cohort
- ORR 10.2%; median OS (overall) 7.6 mos; median OS (sorafenib naive/previously treated) 9.8/7.4 mos

Courtesy of Tim Greten, MD

Kudo. ASCO GI 2019. Abstr 327. Kudo. AASLD 2018. Abstr LB-2.

How do I sequence first and second line therapy?



Courtesy of Tim Greten, MD

Case #1

69 y/o male

Diagnosed with hepatitis C 1990.

Hepatocellular carcinoma diagnosed on screening ultrasound in August 2012, consisting of a single lesion in segment 7 of the liver -> RFA

2015: multifocal recurrence TACE therapy x3

2017 Sorafenib. He developed epistaxis and PD after 2 cycles and was taken off study.

2017: development of bone mets in the spine and shoulder – radiation therapy

2018: developed a lump on right buttock – radiation

2018: started on nivolumab -> PR and continues to have a PR

Skin rash, itching, trace of edema

Courtesy of Tim Greten, MD

Case #2

55 y/o male

Approximately 7 years ago he was evaluated for a life insurance policy and at that time was diagnosed with HCV.

Previous tobacco use (1/2 ppd x 37 years); Former EtOH use - 07/2018 last alcoholic drink

In 2018, he was hospitalized for pneumonia and during his hospitalization was diagnosed as a new Type II diabetic and also incidentally found to have abnormal hepatic panel. Further workup with ultrasound and MRI scan revealed cirrhosis, lesion in segment 8 measuring 5.5 x 8.2 x 5.7 cm. He was also noted to have anterior branch right portal vein thrombus. He was diagnosed with hepatocellular carcinoma at that time.

He underwent EGD and was found to have 3 non-bleeding esophageal varices with the largest a grade II. He was also noted to have hypertensive portal gastropathy. Biopsy of stomach revealed H. pylori active gastritis.

He was seen by surgery and was determined to not be a transplant candidate.

Courtesy of Tim Greten, MD

Case #2 (continued)

2018 – TACE x3

2019 – splenic embolization

2019 – TACE

2019 – pembrolizumab for 12 months

2020 – lenvatinib 12 mg PO daily due to disease progression

Developed HTN with SBP 160s. Started amlodipine 5 mg PO daily

2020 – admission in local hospital for altered mental status that was attributed to decompensated liver disease (hepatic encephalopathy ammonia 87). On CNS imaging he was also found to have hemorrhage of the left cerebral hemisphere: 0.5 cm left temporal intracerebral hemorrhage.

Courtesy of Tim Greten, MD