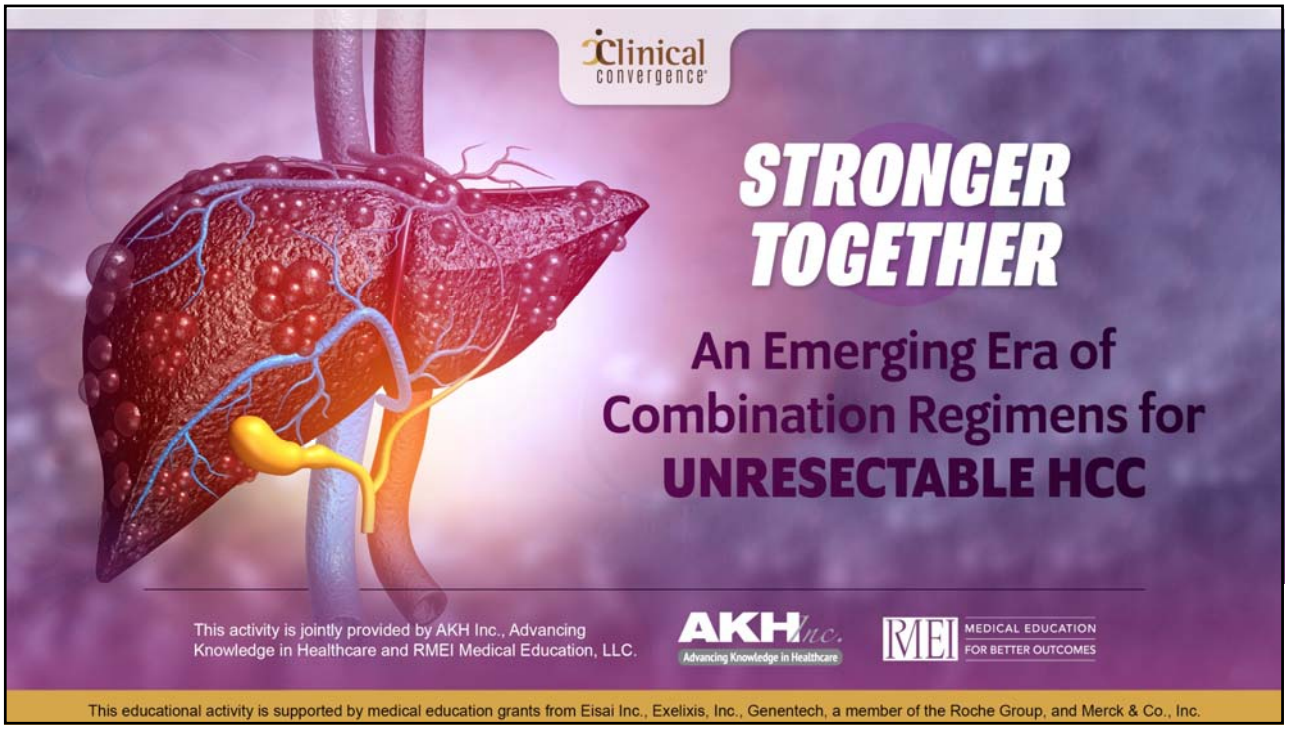

1

Faculty

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Medical Oncology Director, Liver Cancer Multidisciplinary Clinic
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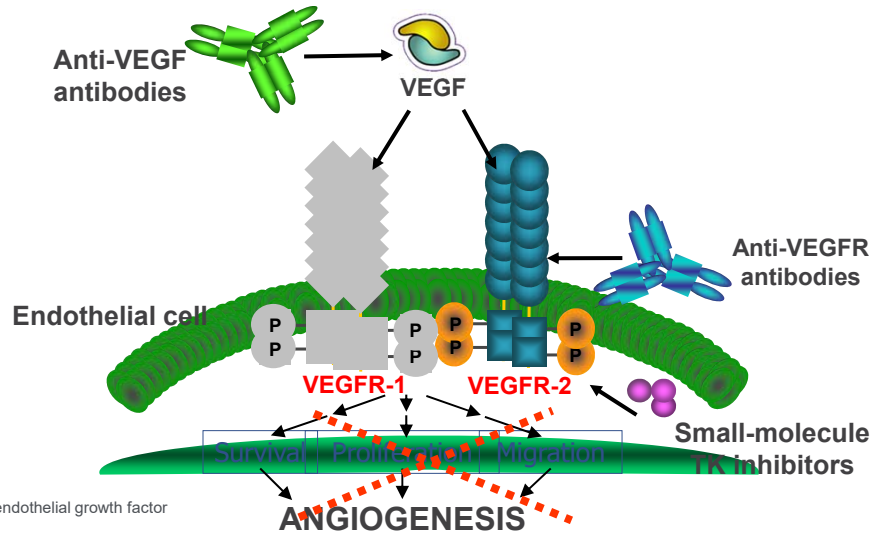
Clinical convergence

2

Agents Targeting the VEGF Pathway



VEGF, Vascular endothelial growth factor

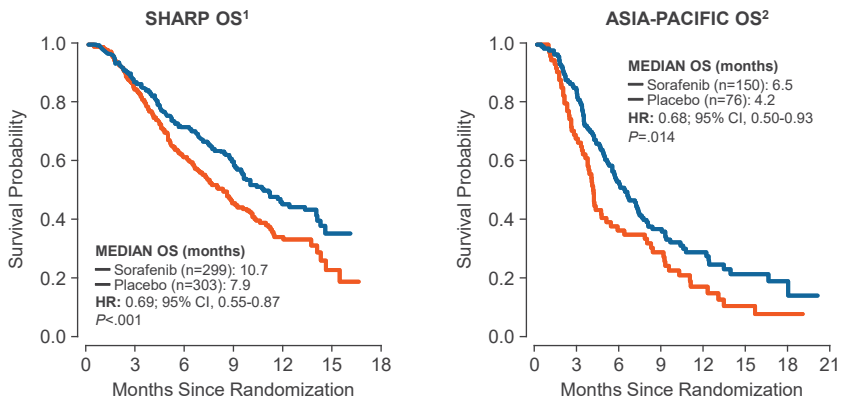
Podar K, et al. *Blood*. 2005;105(4):1383-1395.

Clinical convergence

3

Pivotal Trials Demonstrated OS Benefit with Sorafenib in HCC

Sorafenib consistently increased OS in different patient populations across geographic regions and etiologies



HR, hazard ratio; SHARP, Sorafenib HCC Assessment Randomized Protocol Trial; OS, overall survival

1. Llovet JM, et al. *N Engl J Med*. 2008;359:378-390. 2. Cheng A-L, et al. *Lancet Oncol*. 2009;10(1):25-34.

Clinical convergence

4

Lenvatinib: REFLECT Study

- Lenvatinib is an oral multi-kinase inhibitor that targets VEGFR(1-3), FGFR(1-4), PDGFRα, RET, and KIT[1-4]
- There have been 4 failed Phase 3 trials in front-line HCC in the past 10 years[5-8]
- In a global, randomized, open-label Phase 3 noninferiority study, lenvatinib was noninferior to sorafenib for OS, and significantly improved PFS, TTP, and ORR in patients with untreated advanced HCC[9]

In vitro kinase inhibitory profiles[3]

IC_{50} (nmol/L)	Lenvatinib	Sorafenib
VEGFR1	4.7	21
VEGFR2	3.0	21
VEGFR3	2.3	16
FGFR1	61	340
FGFR2	27	150
FGFR3	52	340
FGFR4	43	3400
RET	6.4	15
KIT	85	140
PDGFRα	29	1.6
PDGFRβ	160	27
BRAF	8700	310
RAF1	1600	46

HCC, hepatocellular carcinoma; FGFR, fibroblast growth factor receptor; ORR, overall response rate; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; TTP, time to progression; VEGFR, vascular endothelial growth factor receptor;

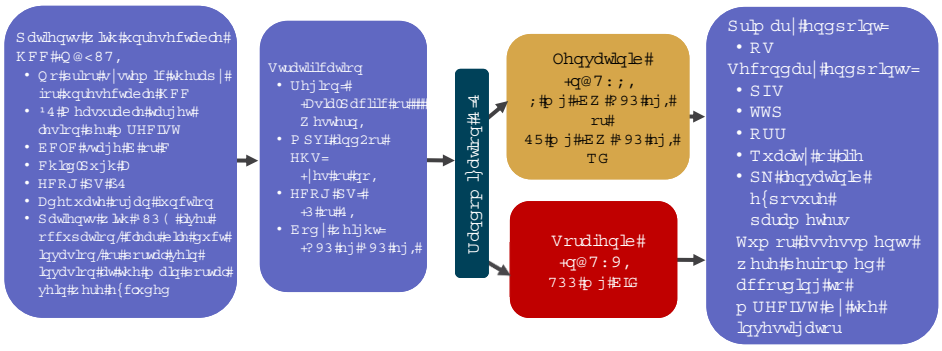
1. Matsui et al. *Int J Cancer* 2008;122:664-71; 2. Matsui et al. *Clin Cancer Res* 2008;14:5459-65; 3. Tohyama et al. *J Thyroid Res* 2014;2014:638747; 4. Yamamoto et al. *Vasc Cell* 2014;6:18; 5. Cheng et al. *J Clin Oncol* 2013; 31: 4067-75; 6. Johnson et al. *J Clin Oncol* 2013; 31: 3517-24; 7. Cainap et al. *J Clin Oncol* 2015; 33: 172-9; 8. Zhu et al. J Clin Oncol 2015; 33: 559-66; 5. Cheng A.-L., ASCO 2017.

Clinical convergence

5

REFLECT: Frontline Lenvatinib versus Sorafenib

Global, randomized, open-label, Phase 3 noninferiority study



BCLC, Barcelona Clinic Liver Cancer; BW; body weight; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHS, extrahepatic spread; MPVI, macroscopic portal vein invasion; mRECIST, modified Response Evaluation Criteria In Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

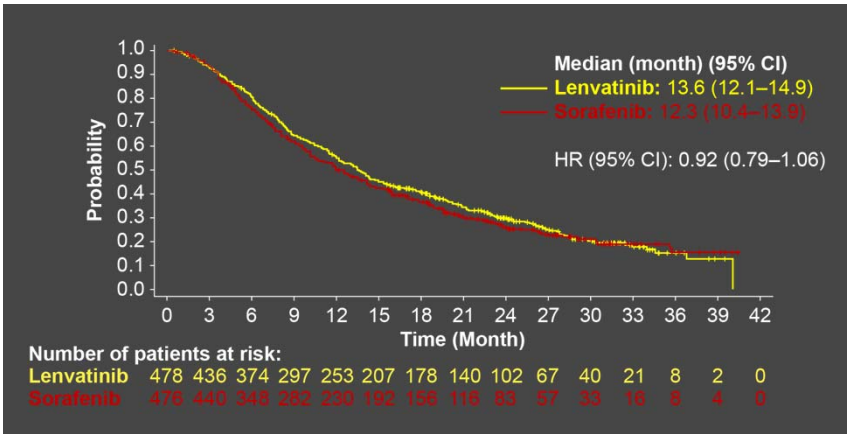
Kudo M, et al. *Lancet*. 2018;391(10126):1163-1173.

Clinical convergence

6

REFLECT: Primary Endpoint

Kaplan-Meier Estimate of OS

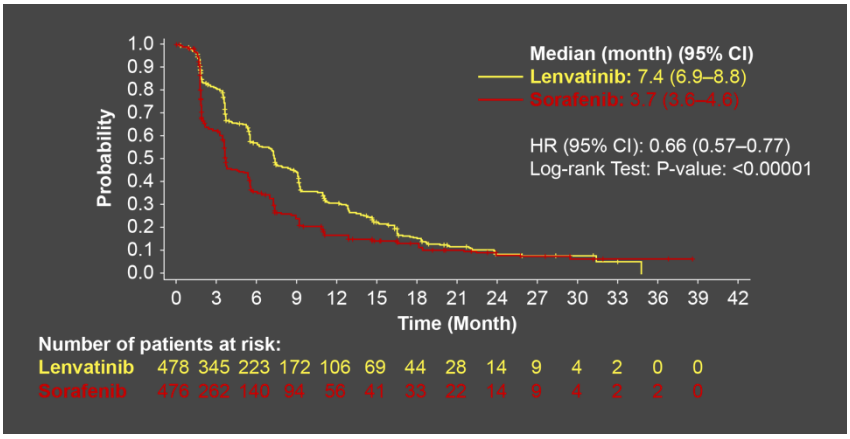


Kudo M, et al. *Lancet*. 2018;391(10126):1163-1173.

7

REFLECT: Secondary Endpoint

Kaplan-Meier Estimate of PFS by mRECIST



Kudo M, et al. *Lancet*. 2018;391(10126):1163-1173.

8

REFLECT: Tumor Assessments

Lenvatinib

Parameter	mRECIST by investigator	mRECIST by independent review	RECIST v1.1 by independent review
Lenvatinib (n = 478)			
ORR, n (%)	115 (24.1)	194 (40.6)	90 (18.8)
95% CI	20.2–27.9	36.2–45.0	15.3–22.3
Odds ratio (95%CI)[a]	3.13 (2.15–4.56)	5.01 (3.59–7.01)	3.34 (2.17–5.14)
BOR, n (%)			
Complete response	6 (1)	10 (2)	2 (<1)
Partial response	109 (23)	184 (38)	88 (18)
Stable disease	246 (51)	159 (33)	258 (54)
Durable stable disease[b]	167 (35)	84 (18)	163 (34)
Progressive disease	71 (15)	79 (17)	84 (18)
Not evaluable/unknown	46 (10)	46 (10)	46 (10)

Sorafenib

Parameter	mRECIST by investigator	mRECIST by independent review	RECIST v1.1 by independent review
Sorafenib (n = 476)			
ORR, n (%)	44 (9.2)	59 (12.4)	31 (6.5)
95% CI	6.6–11.8	9.4–15.4	4.3–8.7
BOR, n (%)			
Complete response	2 (<1)	4 (1)	1 (<1)
Partial response	42 (9)	55 (12)	30 (6)
Stable disease	244 (51)	219 (46)	250 (53)
Durable stable disease[b]	139 (29)	90 (19)	118 (25)
Progressive disease	147 (31)	152 (32)	152 (32)
Not evaluable/unknown	41 (9)	46 (10)	43 (9)

[a] Lenvatinib versus sorafenib.
[b] Stable disease lasting ≥23 weeks.

BOR, best overall response; CI, confidence interval; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate

Kudo M, et al. *Lancet*. 2018;391(10126):1163-1173.

9

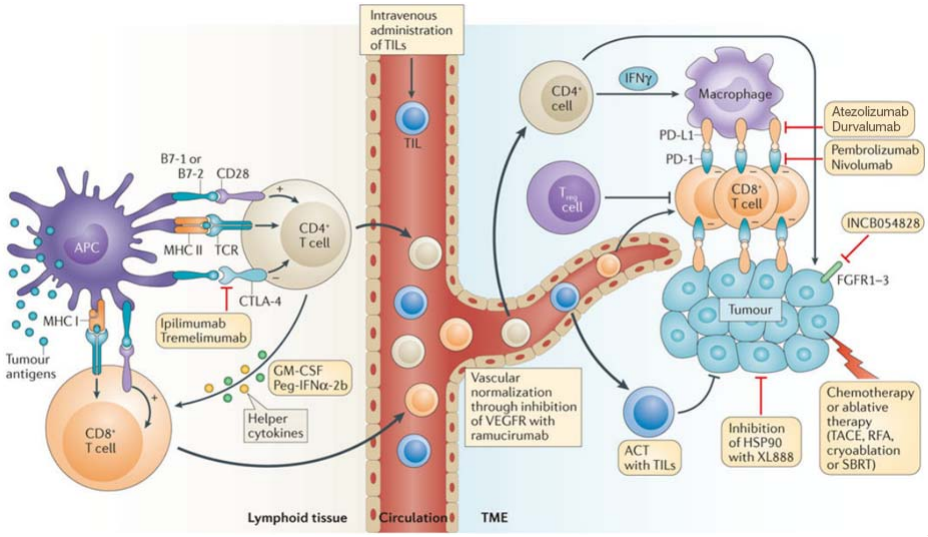
REFLECT: Treatment-Related Adverse Events (≥15%)

Adverse event, n (%)	Lenvatinib (n=476)		Sorafenib (n=475)	
	Dq|#Judgh	Judgh#627	Dq|#Judgh	Judgh#627
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
Palmar-plantar erythrodysesthesia	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (0)	57 (12)	0 (0)
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (6)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0 (0)	8 (2)	0 (0)
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0 (0)
Elevated aspartate aminotransferase	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0 (0)	76 (16)	2 (0)
Alopecia	14 (3)	0 (N/A)	119 (25)	0 (N/A)

Kudo M, et al. *Lancet*. 2018;391(10126):1163-1173.

10

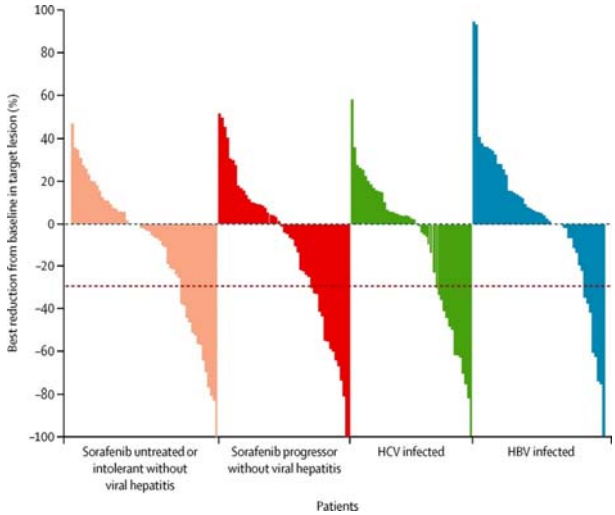
Targeting the Immune System in Cancer



Rizvi S, et al. *Nat Rev Clin Oncol*. 2018;15(2):95-111.

11

Nivolumab in Advanced HCC



RR (dose esc, n=48): 15%
RR (dose exp, n=214): 20%

mOS (dose esc, n=48): 15 months
mOS (dose exp, n=214): NR

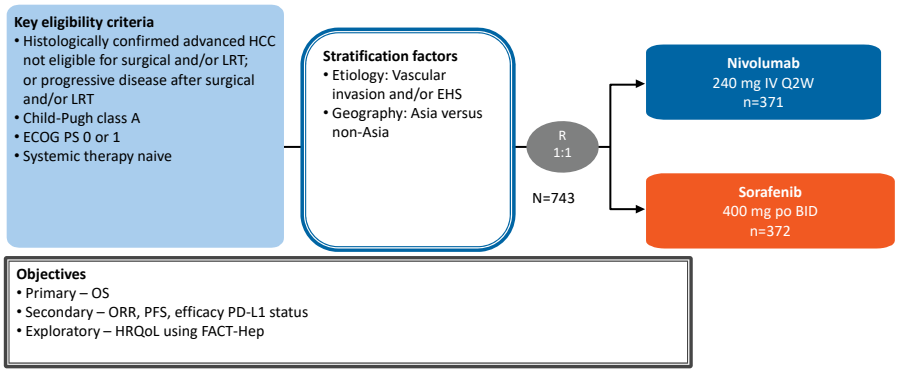
FDA Label: 14.8% RR BICR (n=154)

Median DoR: 16.6 months

El-Kouheiry AB, et al. *Lancet*. 2017;389(10088):2492-2502.

12

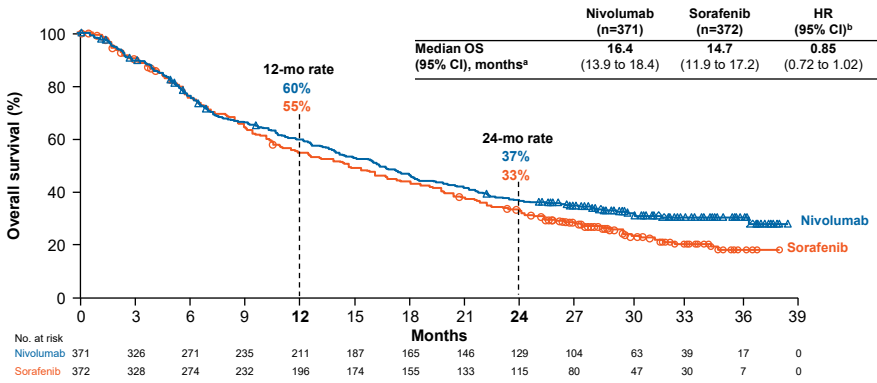
CheckMate 459: Frontline Nivolumab versus Sorafenib



Yau T, et al. *Ann Oncol*. 2019;30(suppl_5):v851-v934.

13

CheckMate 459: Overall Survival



	Nivolumab (n=371)	Sorafenib (n=372)	HR (95% CI)[b]	*P* value[c]
Median OS (95% CI), months[a]	16.4 (13.9 to 18.4)	14.7 (11.9 to 17.2)	0.85 (0.72 to 1.02)	.0752

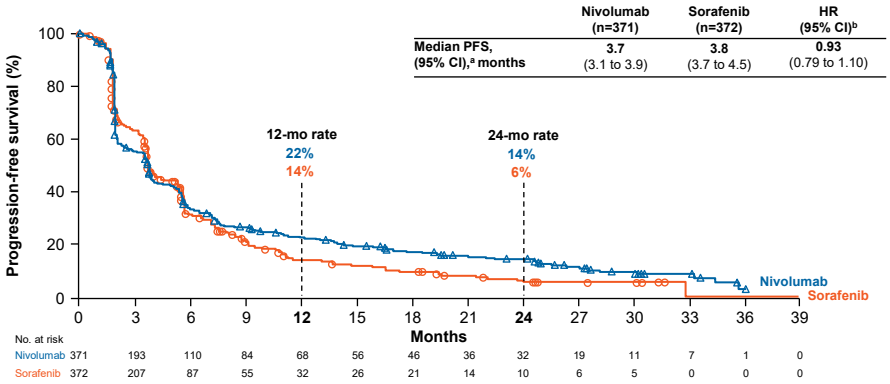
[a] Based on Kaplan–Meier estimates; [b] Stratified Cox proportional hazards model. HR is nivolumab over sorafenib; [c] *P* value from log-rank test; final OS boundary: 0.0419 for a 2-sided nominal *P* value. HR, hazard ratio.

- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit

Yau T, et al. *Ann Oncol*. 2019;30(suppl_5):v851-v934.

14

CheckMate 459: Progression-Free Survival



	Nivolumab (n=371)	Sorafenib (n=372)	HR (95% CI)[b]
Median PFS, (95% CI),[a] months	3.7 (3.1 to 3.9)	3.8 (3.7 to 4.5)	0.93 (0.79 to 1.10)

[a] Based on Kaplan–Meier estimates; [b] Stratified Cox proportional hazards model. HR is nivolumab over sorafenib.

Yau T, et al. *Ann Oncol.* 2019;30(suppl_5):v851-v934.

15

CheckMate 459: Response, Disease Control, and Durability

	Nivolumab (n=371)	Sorafenib (n=372)
ORR,[a] n (%)	57 (15)	26 (7)
Best overall response, n (%)		
CR	14 (4)	5 (1)
PR	43 (12)	21 (6)
SD	130 (35)	180 (48)
Non-CR/non-PD	16 (4)	9 (2)
PD	136 (37)	105 (28)
Not evaluable	32 (9)	52 (14)
DCR,[b] n (%)	203 (55)	215 (58)
Median duration of disease control (95% CI), months	7.5 (6.5 to 10.7)	5.7 (5.6 to 7.4)
Median time to response (range), months	3.3 (1.6 to 19.4)	3.7 (1.5 to 11.1)
Median duration of response (range), months	23.3 (3.1 to 34.5+)	23.4 (1.9+ to 28.7+)

[a] Per blinded independent central review using RECIST v1.1. Defined as CR + PR. [b] Defined as CR + PR + SD + non-CR/non-PD.
CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

- Improvement in ORR was observed with nivolumab compared with sorafenib (odds ratio, 2.41 [95% CI, 1.48 to 3.92])
  - Higher CR rate was observed with nivolumab compared with sorafenib

Yau T, et al. *Ann Oncol.* 2019;30(suppl_5):v851-v934.

16

CheckMate 459: Subsequent Therapy

	Nivolumab (n=371)	Sorafenib (n=372)
Any subsequent therapy,[a] n (%)	181 (49)	196 (53)
Systemic therapy, n (%)	140 (38)	170 (46)
Tyrosine kinase inhibitor	132 (36)	86 (23)
Chemotherapy	15 (4)	25 (7)
Investigational agent[b]	10 (3)	40 (11)
I-O	7 (2)	76 (20)
Other	2 (1)	4 (1)
Local therapy, n (%)	63 (17)	61 (16)
Radiotherapy, n (%)	52 (14)	38 (10)
Surgery, n (%)	10 (3)	14 (4)

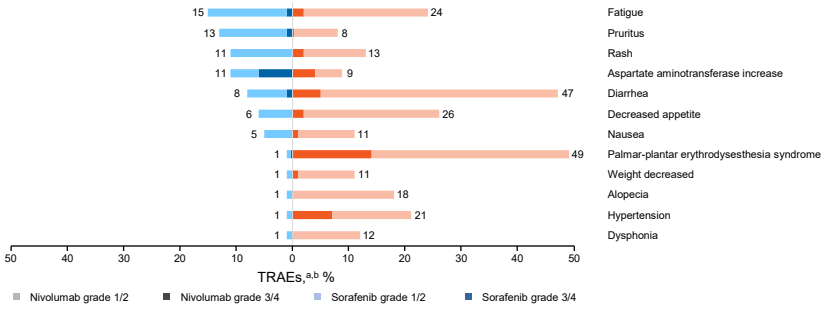
[a] Patient may have received more than 1 type of subsequent therapy; [b] Includes indeterminate therapies received in subsequent clinical trials, including I-O.
I-O, immuno-oncology.

- 140 patients (38%) in the nivolumab arm and 170 patients (46%) in the sorafenib arm received subsequent systemic therapy
  - 20% of patients in the sorafenib arm received subsequent I-O therapy

Yau T, et al. *Ann Oncol.* 2019;30(suppl_5):v851-v934.

17

CheckMate 459: Treatment-Related Adverse Events



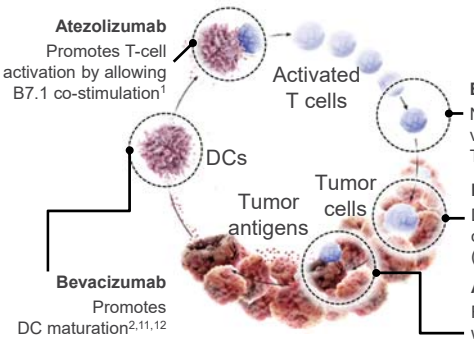
[a] Events occurring in >10% of patients in either treatment arm. Includes events reported between first dose and 30 days after last dose of study therapy; data labels represent rates of any-grade events; [b] One grade 5 event was reported in the nivolumab arm (cerebrovascular event), and 1 was reported in the sorafenib arm (hepatic failure).
AE, adverse event; TRAE, treatment-related adverse event.

- Nivolumab demonstrated an improved safety profile compared with sorafenib, with fewer grade 3/4 TRAEs and TRAEs leading to discontinuation versus sorafenib
  - Grade 3/4 TRAEs were reported in 81 patients (22%) in the nivolumab arm and 179 patients (49%) in the sorafenib arm

Yau T, et al. *Ann Oncol.* 2019;30(suppl_5):v851-v934.

18

Combining VEGF Inhibition and PD-1/PD-L1 Inhibition



- Bevacizumab (anti-VEGF) is an anti-angiogenic agent with additional immunomodulatory effects
- In combination, bevacizumab may further enhance atezolizumab's efficacy by reversing VEGF-mediated immunosuppression to promote T-cell infiltration into the tumor

1. Chen DS, et al. *Immunity*. 2013;39(1):1-10. 2. Hegde PS, et al. *Semin Cancer Biol*. 2018;52(Pt 2):117-124. 3. Wallin JJ, et al. *Nat Commun*. 2016;7:12624. 4. Goel S, et al. *Physiol Rev*. 2011;91(3):1071-1121. 5. Motz GT, et al. *Nat Med*. 2014;20(6):607-615. 6. Hodi FS, et al. *Cancer Immunol Res*. 2014;2(7):632-642. 7. Gabrilovich DI, et al. *Nat Rev Immunol*. 2009;9(3):162-174. 8. Roland CL, et al. *PLoS One*. 2009;4(11):e7669. 9. Facciabene A, et al. *Nature*. 2011;475(7355):226-230. 10. Voron T, et al. *J Exp Med*. 2015;212(2):139-148. 11. Gabrilovich DI. *Nat Med*. 1996;2(10):1096-1103. 12. Oyama T, et al. *J Immunol*. 1998;160(3):1224-1232.

Clinical convergence

19

20

IMbrave150: Atezolizumab/Bevacizumab versus Sorafenib

Key eligibility

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy
- ECOG PS 0-1
- Child-Pugh class A liver function

Stratification

- **Region** (Asia excluding Japan[a]/Rest of world)
- **ECOG** (0/1)
- **Macrovascular invasion** and/or **extrahepatic spread** (Presence/Absence)
- **Baseline AFP** (<400/≥400 ng/mL)

R 2:1

Atezolizumab 1200 mg IV Q3W + Bevacizumab 15 mg/kg Q3W

N=501

Sorafenib 400 mg BID

(open-label)

Until loss of clinical benefit or unacceptable toxicity[b]

Survival follow-up

Co-primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

Secondary endpoints included:

- IRF-assessed ORR, DOR per RECIST 1.1 and HCC mRECIST[b]
- PROs: TTD[c] of QOL, physical and role functioning (EORTC QLQ-C30)
- Safety and tolerability assessed based on the nature, frequency, and severity of AEs per NCI CTCAE version 4.0

[a] Japan is included in rest of world. [b] Tumor assessment by computed tomography or magnetic resonance imaging was done at baseline and every 6 weeks until 54 weeks, then every 9 weeks thereafter. [c] Time from randomization to first decrease from baseline of ≥10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.

AFP, α-fetoprotein; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer; IRF, independent review facility; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; QOL, quality of life; TTD, time to deterioration.

Finn RS, et al. *N Engl J Med*. 2020;382(20):1894-1905.

Clinical convergence

IMbrave150: Baseline Patient Characteristics (ITT)[a]

n (%)	Atezolizumab/Bevacizumab (n=336)	Sorafenib (n=165)
Median age (range), years	64 (26 to 88)	66 (33 to 87)
Male	277 (82)	137 (83)
Asia excluding Japan | rest of world[b]	133 (40) | 203 (60)	68 (41) | 97 (59)
ECOG PS 0 | 1	209 (62) | 127 (38)	103 (62) | 62 (38)
Child-Pugh score A5 | A6	239 (72) | 94 (28)	121 (73) | 44 (27)
Barcelona Clinic Liver Cancer stage B | C	52 (15) | 276 (82)	26 (16) | 133 (81)
AFP at baseline ≥400 ng/mL	126 (38)	61 (37)
MVI present	129 (38)	71 (43)
EHS present	212 (63)	93 (56)
MVI and/or EHS present	258 (77)	120 (73)
Varices at baseline	88 (26)	43 (26)
Varices treated at baseline	36 (11)	23 (14)
HCC etiology		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Non-viral[c]	100 (30)	53 (32)

EHS, extrahepatic spread; ITT, intention to treat, MVI, macrovascular invasion. [a] All randomized patients. [b] Includes United States, Australia, New Zealand, and Japan. [c] Includes alcohol, other and unknown non–hepatitis B and C causes.

Finn RS, et al. *N Engl J Med.* 2020;382(20):1894-1905.

Clinical convergence

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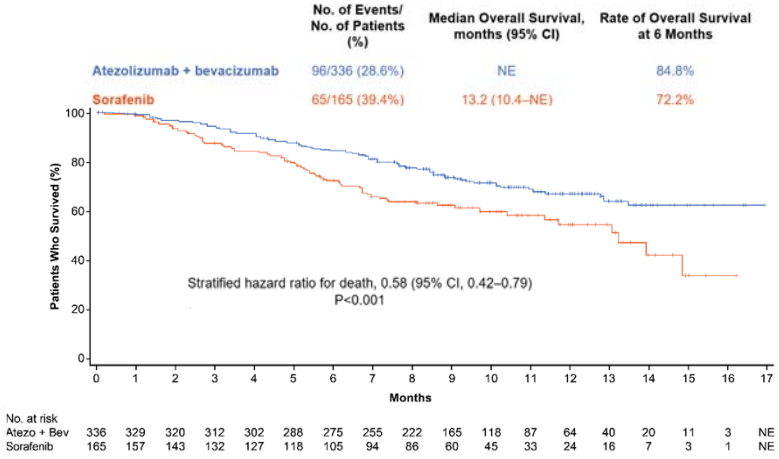
IMbrave150 Co-primary Endpoint: OS (ITT Population)

- OS was statistically significantly longer with atezolizumab + bevacizumab than sorafenib
- Estimated 6-month survival rates were:
  - 84.8% (95% CI, 80.9 to 88.7) in the atezolizumab + bevacizumab group
  - 72.2% (95% CI, 65.1 to 79.4) in the sorafenib group
- Estimated 12-month survival rates were:
  - 67.2% (95% CI, 61.3 to 73.1) in the atezolizumab + bevacizumab group
  - 54.6% (95% CI, 45.2 to 64.0) in the sorafenib group



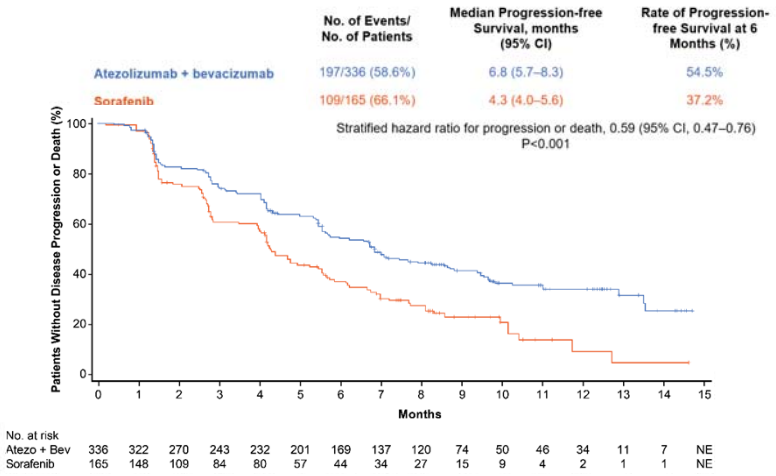
Factors included in the stratified *P* value and Cox model were geographic region (Asia [excluding Japan] versus the rest of the world), AFP level at baseline (<400 ng per milliliter vs ≥400 ng per milliliter), and macrovascular invasion, extrahepatic spread, or both (yes versus. no). Tick marks indicate censored data. NE, could not be evaluated.

Finn RS, et al. *N Engl J Med.* 2020;382(20):1894-1905.

Clinical convergence

22

IMbrave150 Co-primary Endpoint: PFS (ITT Population)



PFS was statistically significantly longer with atezolizumab + bevacizumab than sorafenib

PFS assessed at an independent review facility according to RECIST 1.1. Factors included in the stratified *P* value and Cox model were geographic region (Asia [excluding Japan] versus the rest of the world), AFP level at baseline (<400 ng per milliliter vs ≥400 ng per milliliter), and macrovascular invasion, extrahepatic spread, or both (yes versus no). Tick marks indicate censored data.

Finn RS, et al. *N Engl J Med*. 2020;382(20):1894-1905.

23

IMbrave150: Secondary Efficacy Outcomes

Variable	IRF RECIST 1.1[a]			IRF HCC-specific mRECIST[b]		
	Atezolizumab + bevacizumab (n=326)	Sorafenib (n=159)	Difference (*P* value)[c]	Atezolizumab + bevacizumab (n=325)	Sorafenib (n=158)	Difference (*P* value)[c]
Confirmed[d] objective response, n ([95% CI]%)	89 (27.3 [22.5 to 32.5])	19 (11.9 [7.4 to 18.0])	15.4 (<.001)	108 (33.2 [28.1 to 38.6])	21 (13.3 [8.4 to 19.6])	19.9 (<.001)
Complete response, n (%)	18 (5.5)	0		33 (10.2)	3 (1.9)	
Partial response, n (%)	71 (21.8)	19 (11.9)		75 (23.1%)	18 (11.4)	
Stable disease, n (%)	151 (46.3)	69 (43.4)		127 (39.1%)	66 (41.8)	
Disease control rate[e], n (%)	240 (73.6)	88 (55.3)		235 (72.3)	87 (55.1)	
Progressive disease, n (%)	64 (19.6)	39 (24.5)		66 (20.3)	40 (25.3)	
Could not be evaluated	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response at data cutoff, n/total n (%)	77/89 (86.5)	13/19 (68.4)		84/108 (77.8)	13/21 (61.9)	

[a] Based on patients who presented at baseline with measurable disease per IRF RECIST criteria. [b] Based on patients who presented at baseline with measurable disease per HCC mRECIST criteria. [c] Between-group difference (atezolizumab + bevacizumab minus sorafenib) in the percentage of patients with confirmed response, expressed in percentage points. The *P* value was derived from a Cochran–Mantel–Haenszel test. Randomization, which was performed through an interactive voice-response or Web-response system, included as stratification factors geographic region (Asia excluding Japan versus the rest of the world), alpha-fetoprotein level (<400 ng per milliliter vs. ≥400 ng per milliliter) at baseline, and macrovascular invasion, extrahepatic spread, or both (yes versus no). [d] Defined as a response (complete response or partial response) seen at two consecutive tumor assessments at least 28 days apart. [e] Calculated from the sum of complete response, partial response and stable disease.

Finn RS, et al. *N Engl J Med*. 2020;382(20):1894-1905.

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IMbrave150: Adverse Events From Any Cause

- Median duration of treatment:
  - 7.4 months with atezolizumab
  - 6.9 months with bevacizumab
  - 2.8 months with sorafenib
- Mean (±SD) dose intensity and median (range) dose intensities:
  - 95±7% and 98% (54% to 104%) for atezolizumab
  - 93±10% and 97% (44% to 104%) for bevacizumab
  - 84±20% and 96% (27% to 100%) for sorafenib
- No specific events were responsible for the increased SAE rate in the atezolizumab + bevacizumab group
- There were no SAEs with a ≥2% difference between treatment groups

	Atezolizumab + bevacizumab (n=329)[a]	Sorafenib (n=156)[a]
Patients with an adverse event from any cause, n (%)	323 (98.2)	154 (98.7)
Grade 3 or 4 events[b]	186 (56.5)	86 (55.1)
Grade 5 events[c]	15 (4.6)	9 (5.8)
Serious adverse events	125 (38.0)	48 (30.8)
Adverse events leading to withdrawal from any study drug	51 (15.5)	16 (10.3)
Withdrawal from atezolizumab + bevacizumab	23 (7.0)	–
Adverse events leading to dose modification or interruption of any study drug	163 (49.5)	95 (60.9)
Dose interruption of any study treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib[d]	–	58 (37.2)

[a] Received one dose of study treatment and included in safety population. [b] Represents the highest grades assigned. [c] Gastrointestinal hemorrhage (in 3 patients), pneumonia (in 2 patients), empyema, gastric ulcer perforation, abnormal hepatic function, liver injury, multiple-organ dysfunction syndrome, esophageal varices hemorrhage, subarachnoid hemorrhage, respiratory distress, sepsis, and cardiac arrest (in 1 patient each) in the atezolizumab + bevacizumab group; and death (in 2 patients), hepatic cirrhosis (in 2 patients), cardiac arrest, cardiac failure, general physical health deterioration, hepatitis E, and peritoneal hemorrhage (in 1 patient each) in the sorafenib group. [d] Dose modification of atezolizumab or bevacizumab was not permitted

Finn RS, et al. *N Engl J Med*. 2020;382(20):1894-1905.

Clinical convergence

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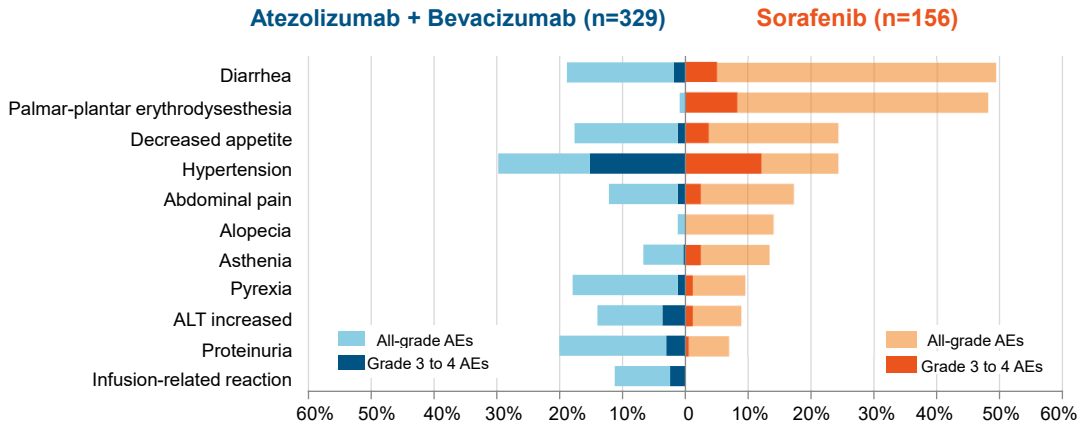
IMbrave150: Adverse Events from Any Cause with ≥10% Frequency in Either Arm and >5% Difference Between Arms



- Other than hypertension, most high-grade AEs were infrequent

ALT, alanine aminotransferase.

Finn RS et al. *N Engl J Med* 2020; 382:1894-1905

Clinical convergence

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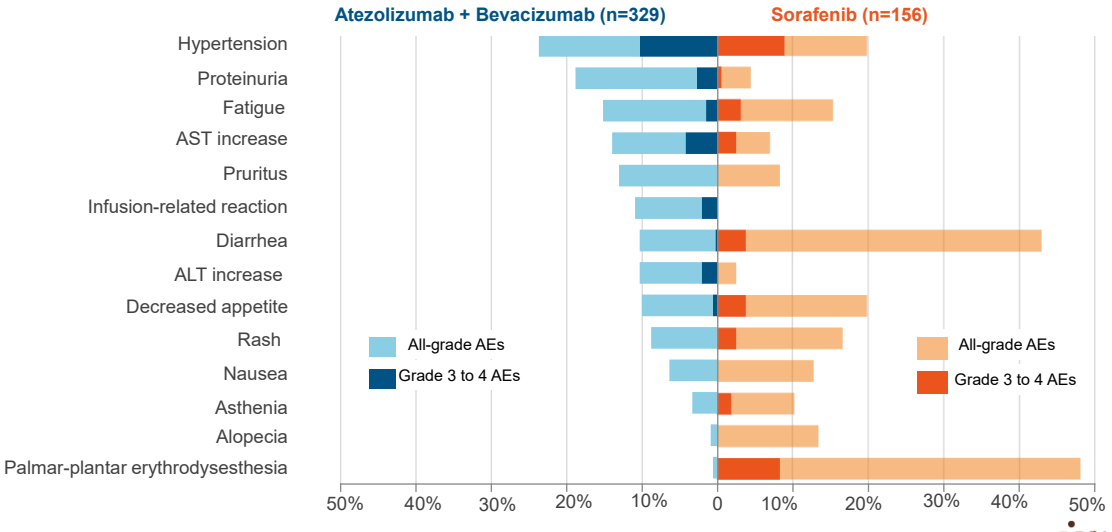
IMbrave150: Any-Grade Treatment-Related Adverse Events with ≥10% Frequency in Either Arm



Finn RS, et al. *N Engl J Med.* 2020;382(20):1894-1905.

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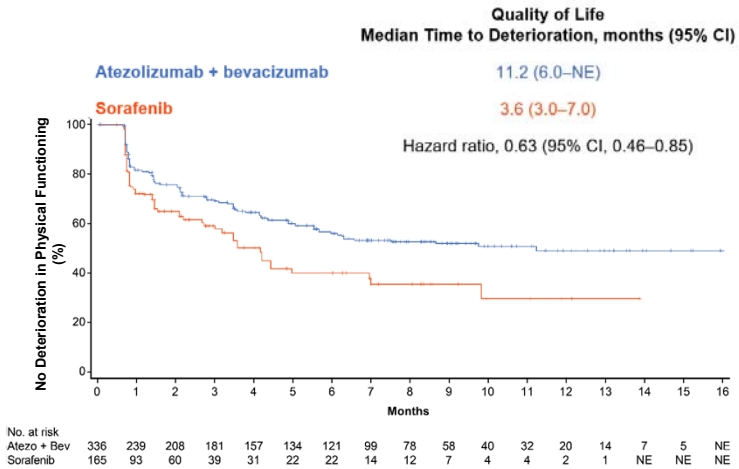
IMbrave150: Patient-Reported TTD of QOL (ITT Population)



Atezolizumab + bevacizumab delayed deterioration of patient-reported QOL

Finn RS, et al. *N Engl J Med.* 2020;382(20):1894-1905.

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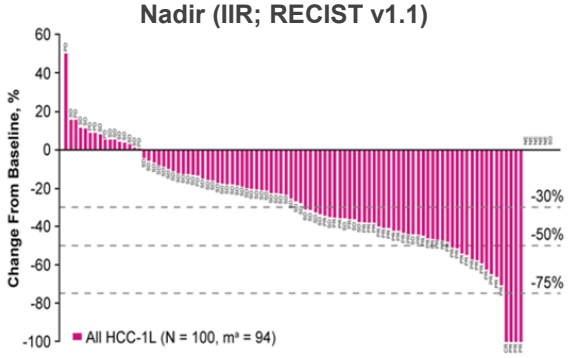
KEYNOTE-524: Frontline Lenvatinib + Pembrolizumab

Parameter	Lenvatinib + Pembrolizumab (N=100)
	RECIST v1.1 per IIR
ORR (confirmed responses), n (%) (95% CI)[a]	36 (36) (26.6 to 46.2)
Best overall response, n (%)	
Complete response	1 (1)
Partial response	35 (35)
Stable disease[b]	52 (52)
Progressive disease	7 (7)
Unknown/not evaluable	5 (5)
Median DOR[c] for confirmed responders, months (95% CI)[d]	12.6 (6.9–NE)
Median TTR for confirmed responders, months (range)	2.8 (1.2 to 7.7)
Disease control rate, n (%) (95% CI)[a]	88 (88) (80.0 to 93.6)

[a]The 95% CIs are calculated using an exact method of binomial distribution (Clopper–Pearson method); [b]includes unconfirmed partial response, noncomplete response/ nonprogressive disease, and durable stable disease; [c]the Kaplan–Meier method was used for estimating DOR; [d]the 95% CIs are based on a generalized Brookmeyer and Crowley method.

Percentage Change From Baseline in Sum of Diameters of Target Lesions at Post-baseline Nadir (IIR; RECIST v1.1)



[a]m = number of patients with both baseline and postbaseline values for the sum of diameters of target lesions.

Finn RS, et al. *N Engl J Med.* 2020;382(20):1894-1905.

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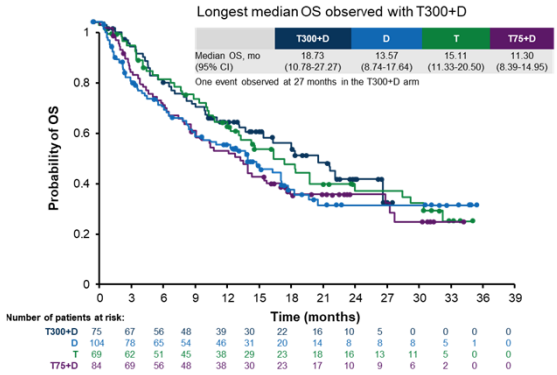
Phase 2 Study 22: Tremelimumab + Durvalumab

EFFICACY



SAFETY

	T300+D (n=75)	T75+D (n=84)	D (n=104)	T (n=69)
Grade 3/4 TRAEs, %	35.1	24.4	17.8	42.0
Serious TRAEs, %	13.5	11.0	10.9	21.7
Grade 5 trAEs, n	0	1[a]	3[b]	0
Discontinuation due to TRAEs, %	10.8	6.1	7.9	11.6
ORR, % (95% CI)	24.0 (14.9 to 35.3)	9.5 (4.2 to 17.9)	10.6 (5.4 to 18.1)	7.2 (2.4 to 16.1)
Median DoR, mo	NR	13.2	11.2	24.0

Kelley RK, et al. *J Clin Oncol.* 2020;38(15):abstr 4508.

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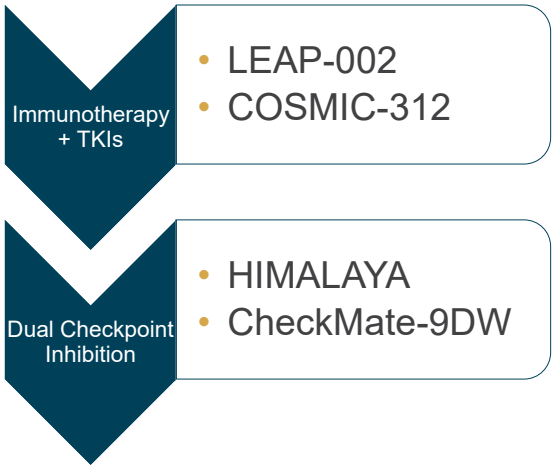
Phase 3 Trials of Immunotherapy Combinations



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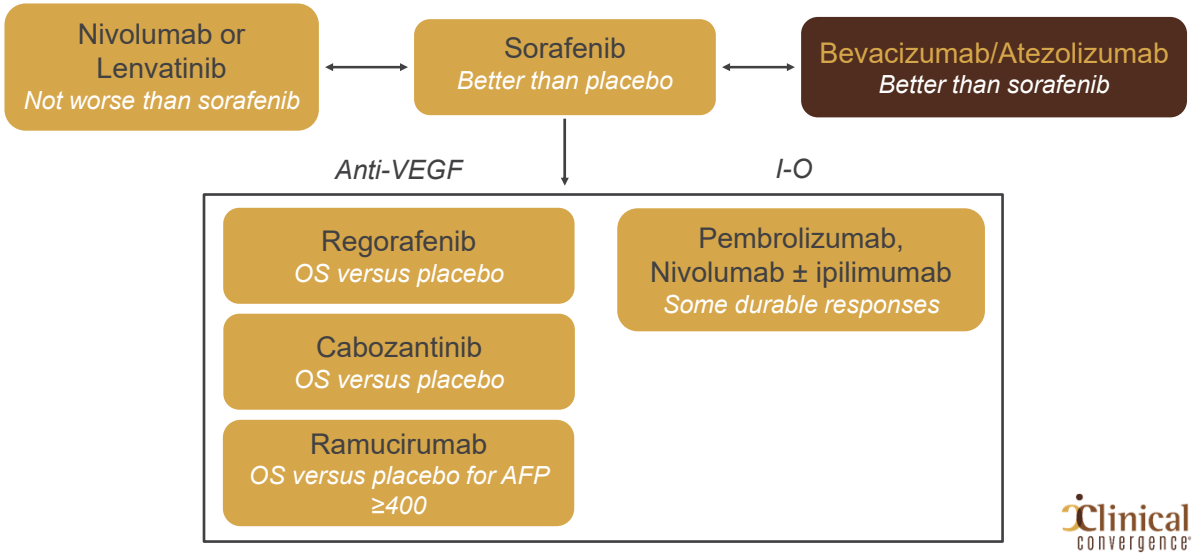
Evolving Landscape of HCC



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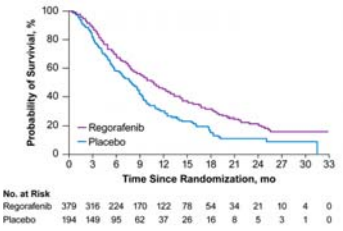
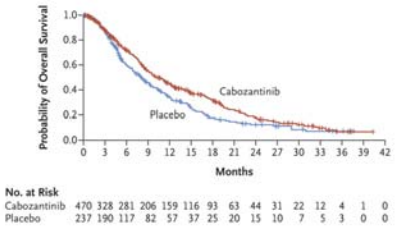
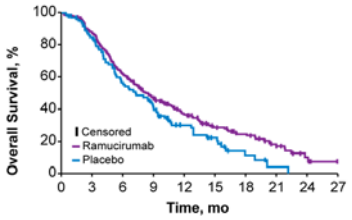
Multiple Anti-VEGF Targeted Therapies Have Activity After Sorafenib

RESOURCE: Regorafenib versus Placebo [1] 2nd Line, Sorafenib-Tolerating Only	CELESTIAL: Cabozantinib versus Placebo [2] 2nd or 3rd Line	REACH 2: Ramucirumab versus Placebo [3] 2nd Line, AFP ≥400 ng/mL
Median OS: 10.6 months vs 7.8 months	Median OS: 10.2 months vs 8.0 months	Median OS: 8.5 months vs 7.3 months
HR = 0.63 (*P*<.001)	HR = 0.76 (*P*=.005)	HR = 0.71 (*P*=.02)







1. Bruix J, et al. *Lancet*. 2017;389(10064):56-66.
2. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63.
3. Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296.

Clinical convergence

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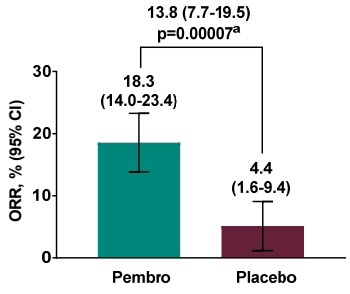
KEYNOTE 240: 2L Pembrolizumab versus Placebo

Objective Response Rate at Final Analysis (RECIST 1.1, BICR)



Response n (%)	Pembrolizumab N=278	Placebo N=135
Best Overall Response		
CR	6 (2.2)	0 (0.0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
SD ≥23 weeks	37 (18.3)	20 (14.8)
Progressive Disease	90 (32.4)	57 (42.2)
Disease Control Rate (CR+PR+SD)	173 (62.2)	72 (53.3)

Duration of response, median (range)[b,c]:
- Pembrolizumab: 13.8 months (1.5+ to 23.6+ months)
- Placebo: Not reached (2.8 months to 20.4+ months)

[a] Nominal one-sided *P*-value based on the Miettinen and Nurminen method stratified by randomization factors. [b] From product-limit (Kaplan-Meier) method for censored data. [c] "+" indicates no PD by the time of last disease assessment. Data cutoff: Jan 2, 2019.

Finn RS, et al. *J Clin Oncol*. 2020;38(3):193-202.

Clinical convergence

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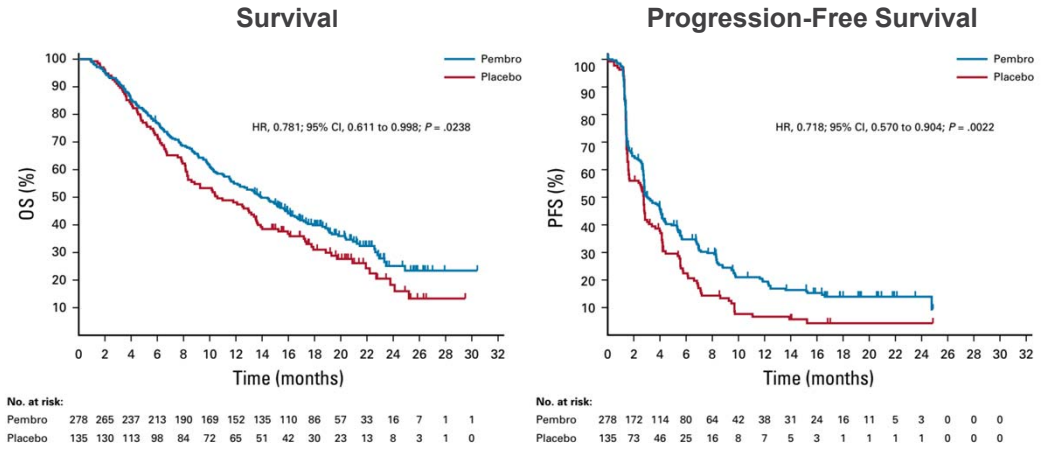
Keynote-240: 2L Pembrolizumab versus Placebo



OS and PFS did not reach statistical significance per specified criteria

Finn RS, et al. *J Clin Oncol.* 2020;38(3):193-202.

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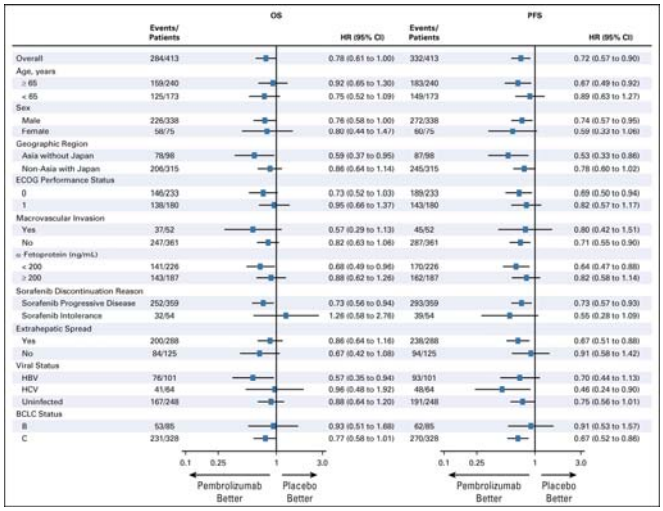
Keynote-240: Subpopulation Analysis



Finn RS, et al. *J Clin Oncol.* 2020;38(3):193-202.

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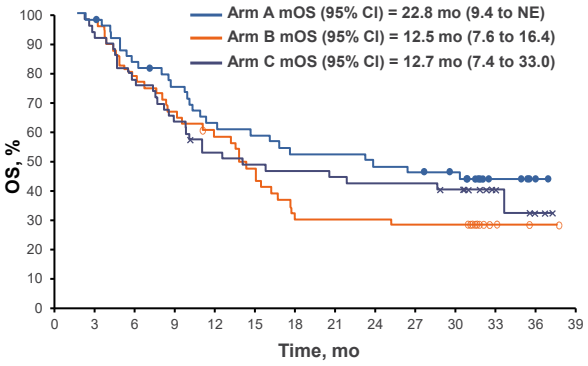
CheckMate 040: 2L Nivolumab + Ipilimumab

Response by Treatment Arm

	Arm A NIVO1/IPI3 Q3W (n=50)	Arm B NIVO3/IPI1 Q3W (n=49)	Arm C NIVO3 Q2W/ IPI1 Q6W (n=49)
ORR by BICR using RECIST v1.1, n (%)	16 (32)	15 (31)	15 (31)
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)
Unable to determine	3 (6)	4 (8)	4 (8)
DCR, n (%)	27 (54)	21 (43)	24 (49)
Median TTR (range), months	2.0 (1.1 to 12.8)	2.6 (1.2 to 5.5)	2.7 (1.2 to 8.7)
Median DOR (range), months	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)

Kaplan-Meier Median Overall Survival



- Similar ORR, DCR, and DOR were observed across treatment arms
  - Consistently high ORR (>30%) was achieved in all treatment arms
  - In total, 7 patients had complete response (4 in arm A and 3 in arm B)
- Arm A: NIVO1/ IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose
- Arm B: NIVO3/ IPI1 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose
- ORR is defined as CR + PR
- SD does not include 2 patients in arm A and 1 patient in arm B who were reported as non-CR/non-PD
- DCR is defined as CR + PR + SD + non-CR/non-PD

Yau T, et al. *JAMA Oncol*. 2020:6(11):e204564. Online ahead of print.

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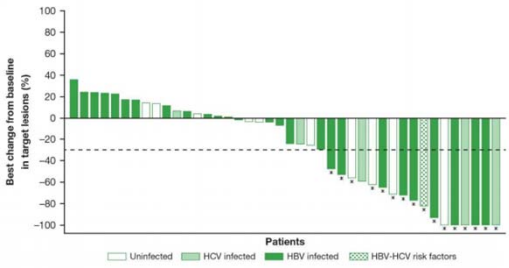
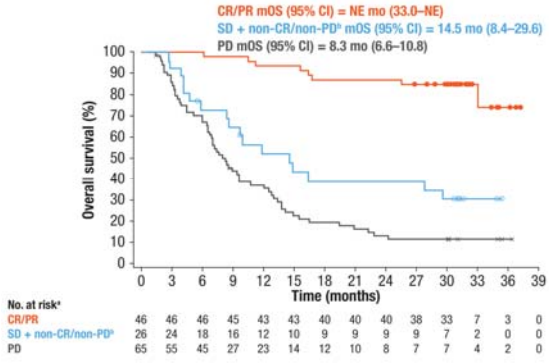
CheckMate 040: Tumor Response and Survival

Nivo1/Ipi3: Reduction in Tumor Burden



Stratified Median Overall Survival



Yau T, et al. *JAMA Oncol*. 2020:e204564. Online ahead of print.

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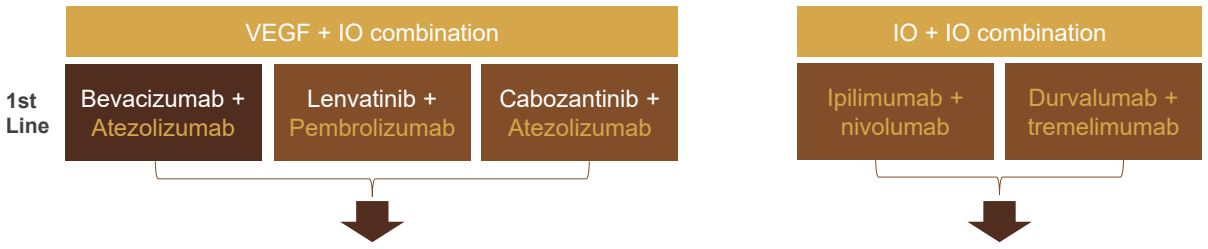

None studied after bevacizumab/atezolizumab

	Targeted therapies	Immunotherapies
Historical 1st-line options	Sorafenib Lenvatinib	
Historical 2nd-line options	Regorafenib Cabozantinib Ramucirumab (AFP ≥400)	Nivolumab Pembrolizumab Nivolumab + Ipilimumab

Clinical convergence

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Summary of NCCN Recommendations

First-Line Therapy	Subsequent-Line Therapy
Preferred Regimens • Atezolizumab + bevacizumab • Sorafenib • Lenvatinib	• Regorafenib • Cabozantinib • Ramucirumab • Lenvatinib • Nivolumab • Nivolumab + ipilimumab • Sorafenib • Pembrolizumab
Useful in Certain Circumstances • Nivolumab	

NCCN Guidelines. Hepatobiliary Cancers. V5.2020. Issued August 4, 2020.

Clinical convergence

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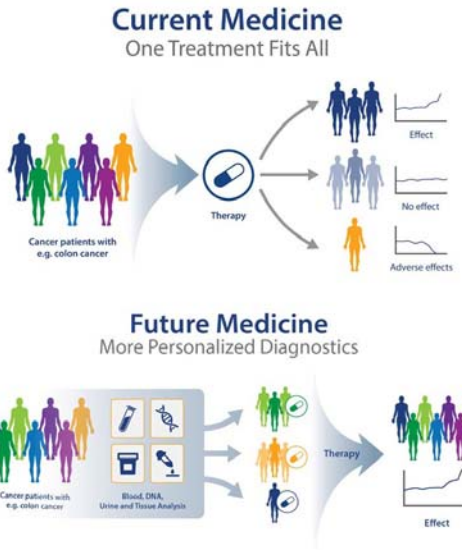
Appeal of Precision Medicine



THE PRECISION MEDICINE INITIATIVE

Clinical convergence

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Targeted Therapies Summary

TKI	Therapy Line	VEGF A	VEGF R1	VEGFR 2	VEGF R3	PDGF B	Other
Bevacizumab	1st Line	X					
Sorafenib	1st Line		26	90	20	57	BRAF (22), FLT3(58), c-Kit (68), FGFR1 (580)
Lenvatinib	1st Line		22	4	5.2	39	FGFR1 (46), Kit (100)
Regorafenib	2nd Line		13	4.2	46	22	BRAF (28), Ret (1.5), Kit (50.7)
Cabozantinib	2nd Line			0.035		234	c-Met (1.3), Ret (4), Kit (4.6), Flt-1/3/4 (12/11.3/6), Tie2 (14.3), and AXL (7)
Ramucirumab	2nd Line			X			

Clinical convergence

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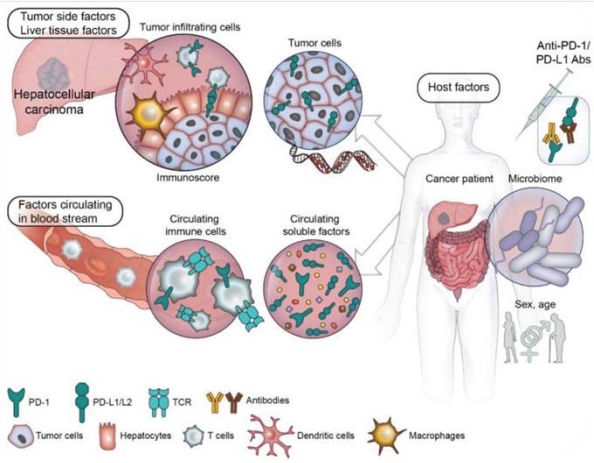
Several Treatment Response Biomarkers of Interest



Tumor and immunologic factors
- PD-L1 expression by tumor and immune infiltrate
- Features of intra-tumoral lymphoid infiltrates

Tumor mutations and microsatellite instability
- Tumor mutation burden
- MSI-high status

Circulating factors
- Circulating immune cells
- Circulating soluble factors, eg, TGF-*B*
- Extracellular vesicles, such as exosomes

Host factors
- Male sex and older age
- Gut microbiome

Jilkova ZM, et al. *Cancers* (Basel). 2019;11(10):1554.

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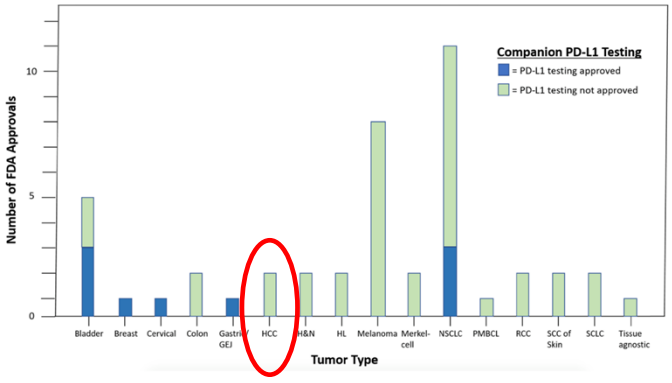
PD-L1: Role as a Treatment Response Biomarker



Among 45 approvals thru April 2019:
- PD-L1 predictive in 28.9%
- PD-L1 not predictive in 53.3%
- PD-L1 not tested in 17.8%

Heterogeneity in threshold, types of cells expressing PD-L1 (tumor infiltrating cells, tumor cells, or composite score) and companion diagnostics

MSI has also been approved, albeit rare in HCC

Davis AA, et al. *J Immunotherapy of Cancer.* 2019;7(1):278.

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Clinical Factors Have Historically Helped Select Between Sorafenib and Lenvatinib

	SORAFENIB	LENVATINIB
Level of Evidence	Phase 3	Phase 3
Inclusion Criteria	Child A cirrhosis, ECOG 0-1	Child A cirrhosis, ECOG 0-1 Excluded patients with >50% liver involvement, main portal vein or bile duct invasion
Efficacy	Improved survival versus placebo	Non-inferior survival versus sorafenib Improved objective responses and time to progression compared to sorafenib
AE Profile	Increased hand-foot skin reaction	Increased hypertension, proteinuria, anorexia
Logistics	Oral, twice daily Taken 1 to 2 hours removed from food	Oral, once daily Can be taken with or without food
Miscellaneous	Real-world effectiveness data in populations including Child B cirrhosis	

Clinical convergence

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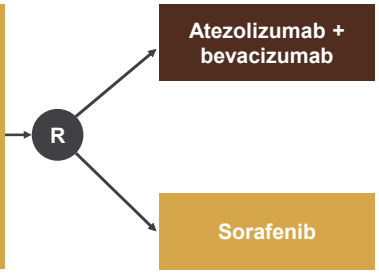
Several Clinical Factors are Also Important When Considering Atezolizumab/Bevacizumab

Key Eligibility Criteria
- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy for HCC
- ≥1 measurable untreated lesion
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function
- Child–Pugh class A



Exclusion Criteria:
- Autoimmune disease or transplant
- Incompletely treated high-risk varices
- Prior bleeding varices within 6 months
- Moderate-severe ascites
- History of hepatic encephalopathy
- Chronic daily treatment with NSAIDs
- Platelet count <75,000

Finn RS, et al. *N Engl J Med.* 2020;382(20):1894-1905.

Clinical convergence

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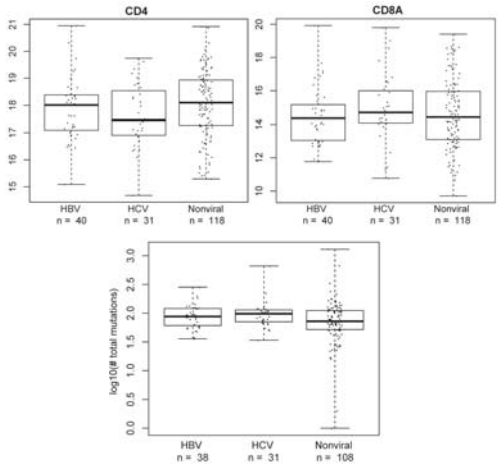
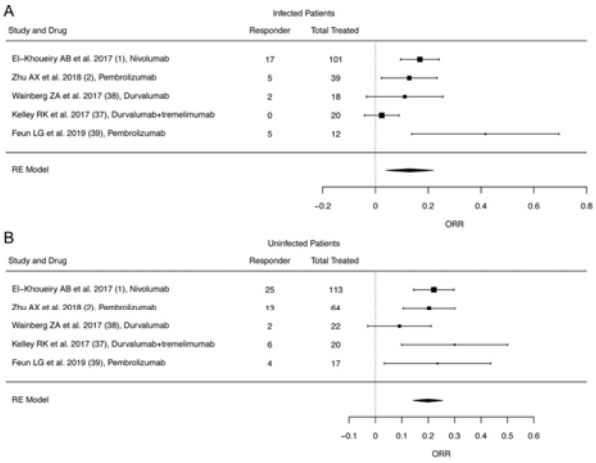
Viral Status Does Not Predict ICI Response





Ho WJ, et al. *J Immunotherapy Cancer.* 2020;8:e000394.

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Patient Case

- 56-year-old male with HCV-related cirrhosis, treated with sustained viral response
- Lost to follow-up and presents 2 years later with abdominal pain
- Otherwise healthy, actively working, ECOG 0
- Labs: Child A – bilirubin 0.7 mg/dL, albumin 3.5 g/dL, INR 1.0; platelets 74; AFP 2,417 ng/mL Imaging: Multifocal bilobar HCC, largest lesion 9.7 cm with branch vascular invasion
- Referred for systemic therapy

WHAT IS THE NEXT STEP?

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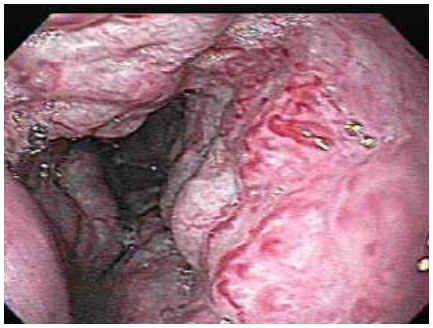
Patient Case

- 56-year-old male with HCV-related cirrhosis, treated with sustained viral response
- Lost to follow-up and presents 2 years later with abdominal pain
- Otherwise healthy, actively working, ECOG 0
- Labs: Child A – Bilirubin 0.7 mg/dL, Albumin 3.5 g/dL, INR 1.0; platelets 74; AFP 2,417 ng/mL
- Imaging: Multifocal bilobar HCC, largest lesion 9.7 cm with branch vascular invasion
- Referred for systemic therapy



On EGD, found to have large varices with red wale signs, suggesting high risk of bleeding

Clinical convergence

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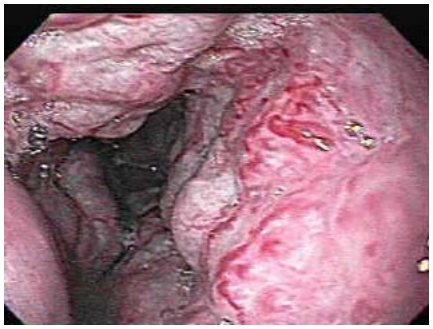

We would not use atezolizumab/bevacizumab until varices are treated

Clinical convergence

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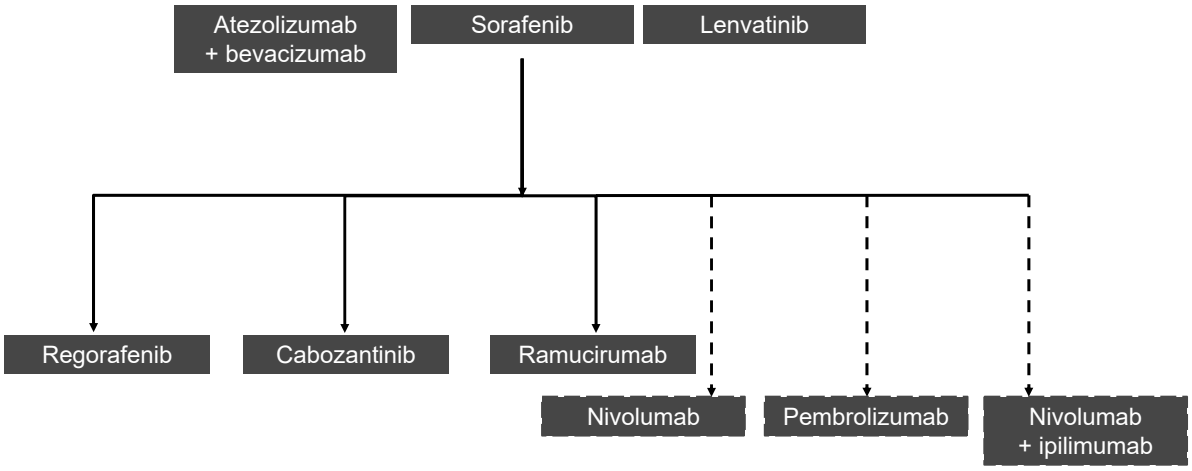
Multiple Second-Line Treatment Options After Sorafenib



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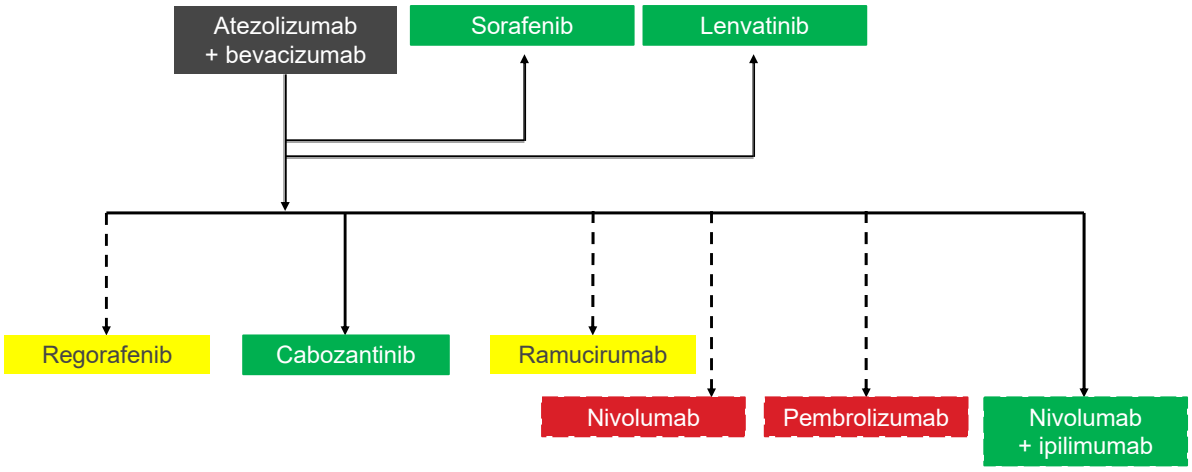
Can They be Applied After Atezolizumab and Bevacizumab?



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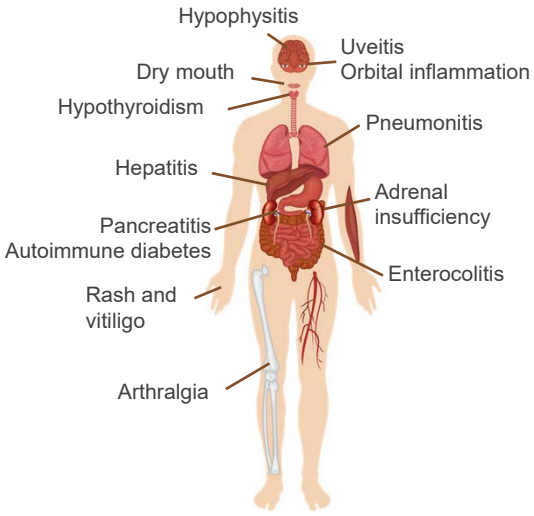
Potential Immune-Mediated Adverse Events



Grade 1: ICI often continued with close monitoring

Grade 2: ICI often held until improved

Grade 3: ICI held and steroids (1 to 2 mg/kg/d) initiated

Grade 4: ICI often permanently discontinued

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-1768.

Clinical convergence

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Summary

- There is strong desire for biomarkers to help with patient selection, although none currently exist
  - We are forced to rely on clinical characteristics and differences in clinical trial inclusion/exclusion criteria in the interim
- Atezolizumab/bevacizumab has shown superior survival compared to TKI-based therapy, but careful patient selection is critical
- Continue to monitor patients on checkpoint inhibitor therapy for rare, albeit potentially serious, adverse events

Clinical convergence

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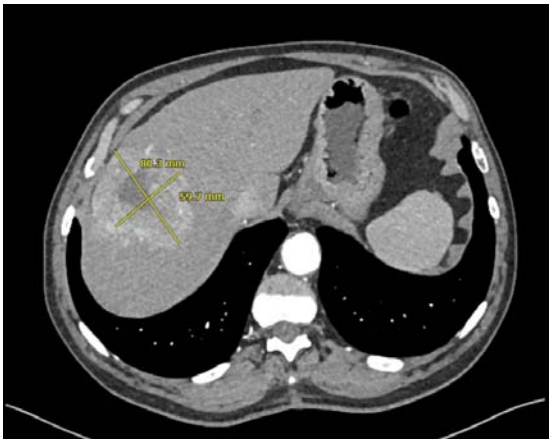
Clinical Convergence: Patient Case

- 70-year-old retired college professor with no history of liver cirrhosis is found to have abnormal LFTs on routine lab work.
- Imaging reveals an 8 x 6 cm T2 hyperintense mass
- Labs: AFP 4.6 ng/mL, HBV negative, HCV negative, ALP 150 U/L, bilirubin 0.9 mg/dL, albumin 4.7 g/dL



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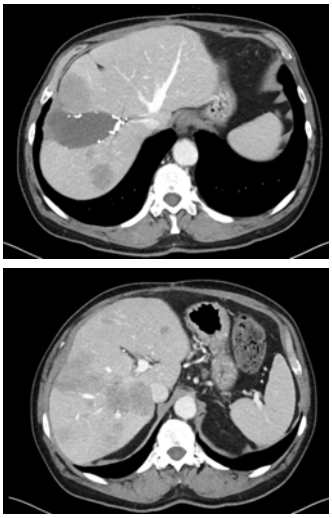
Case Presentation

- Pathology: Moderately differentiated HCC, margins negative
- 5 months later (November 2018), recurrence of disease
- Enrolled on HIMALAYA study (sorafenib versus durvalumab versus durvalumab + tremelimumab)
  - Randomized to standard of care arm (sorafenib)
- Started on sorafenib
  - Some hand-foot syndrome (moderate) and diarrhea, and some hair changes
- Progression of disease on first restaging scan with new rib metastasis
- Started single agent nivolumab (January 2019)
  - Complete response to therapy



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