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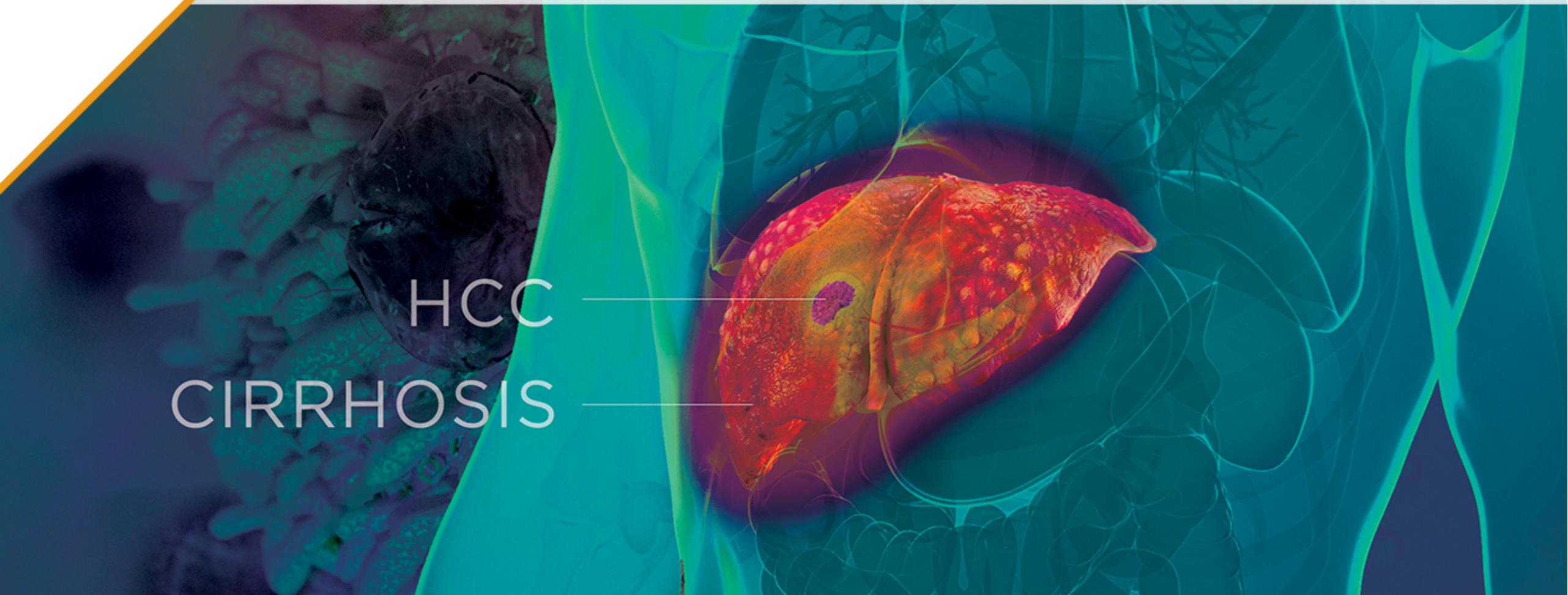
Multidisciplinary Perspectives in Advanced HCC:

A Focus on Immune Checkpoint Inhibitors



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Disclosure of Conflicts of Interest

- Richard Finn, MD, reported a financial interest/relationship or affiliation in the form of *Consultant*: AstraZeneca Pharmaceuticals LP; Bayer HeatlhCare, Inc; Bristol-Myers Squibb Co; Eisai Inc; CStone Pharmaceuticals; Eli Lilly and Co; Pfizer, Inc; Merck & Co, Inc; Exelixis, Inc; Roche; and Genentech, Inc.

Activity Agenda

- Current Treatment Landscape and Rationale for Immunotherapy in HCC
- Emerging Approaches with Immunotherapy
- Safety of Immune Checkpoint Inhibitors in Advanced HCC
- Multidisciplinary Care and Interprofessional Collaboration in HCC

Learning Objectives

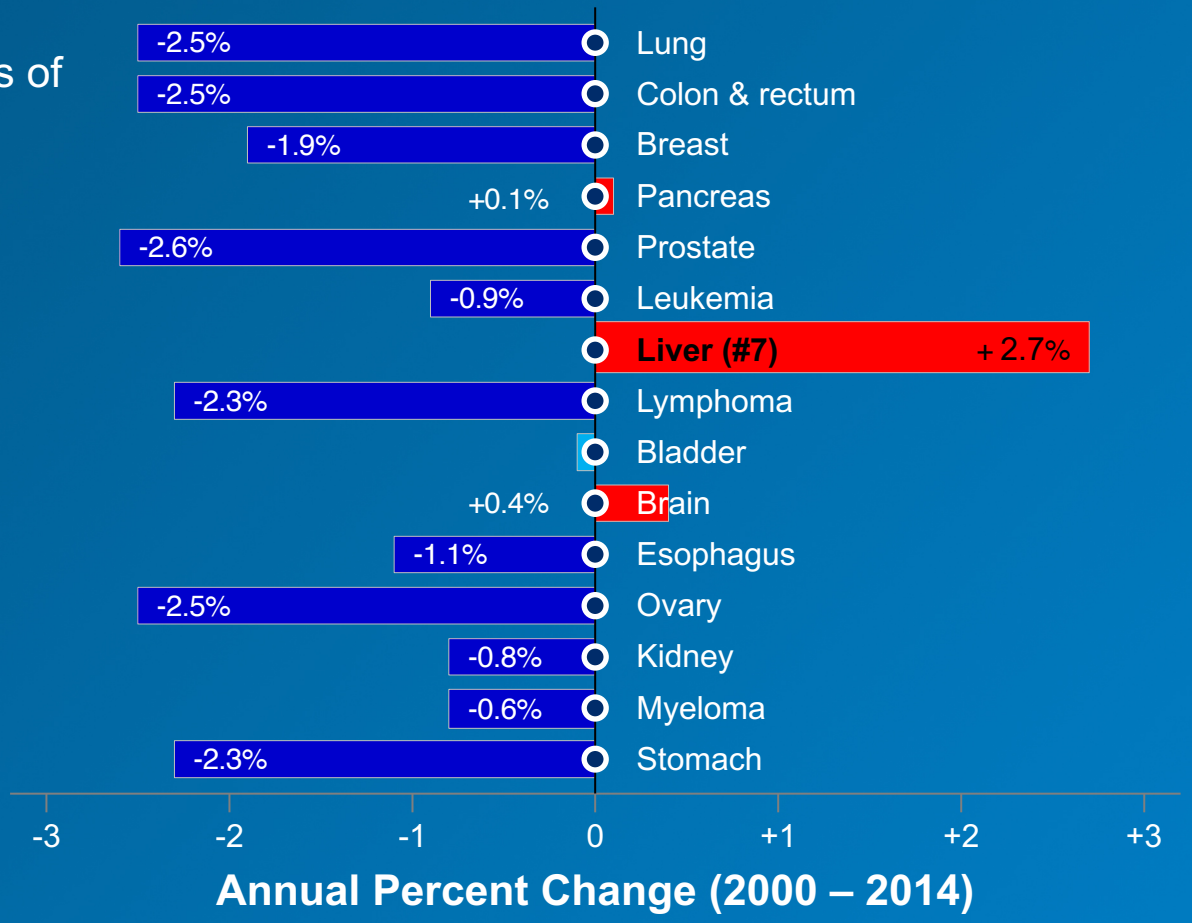
Upon completion of this activity, participants should be better able to:

- Assess the efficacy and safety of immune checkpoint inhibitors for the treatment of advanced HCC
- Develop evidence-based treatment strategies with immune checkpoint inhibitors for patients with advanced HCC based on guideline recommendations
- Integrate emerging immune checkpoint inhibitor treatment strategies being investigated in clinical trials into treatment strategies for the treatment of advanced HCC
- Develop approaches to identify and manage immune-related adverse events that can occur with immune checkpoint inhibitors to improve patient outcomes
- Implement a multidisciplinary team approach to optimize care coordination and the management of patients with HCC and cirrhosis

Current Treatment Landscape and Rationale for Immunotherapy in HCC

HCC Mortality in the United States Is Increasing

Top 15 causes of cancer death United States 2010-2014



HCC, hepatocellular carcinoma.
Courtesy of Amit Singal UT Southwestern
Data from http://seer.cancer.gov

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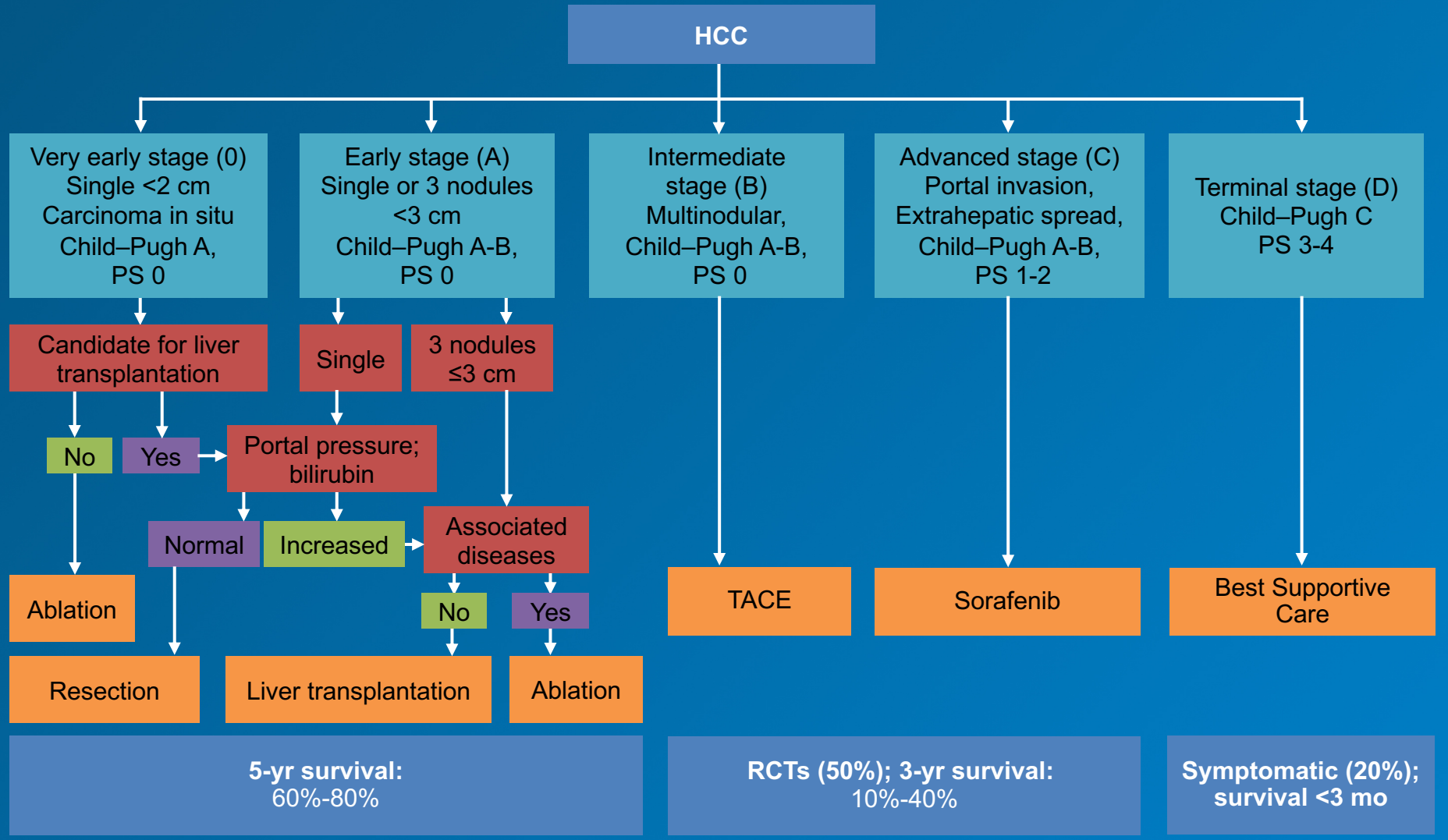
Early 2017: Barcelona Clinic Liver Cancer Staging and Treatment Strategy



HCC, hepatocellular carcinoma, TACE, transarterial chemoembolization; RCTs, randomized controlled trials.
Bruix et al. *Gastroenterology* 2016;150:835-853; Llovet et al. *N Engl J Med*. 2008;359:378-390.

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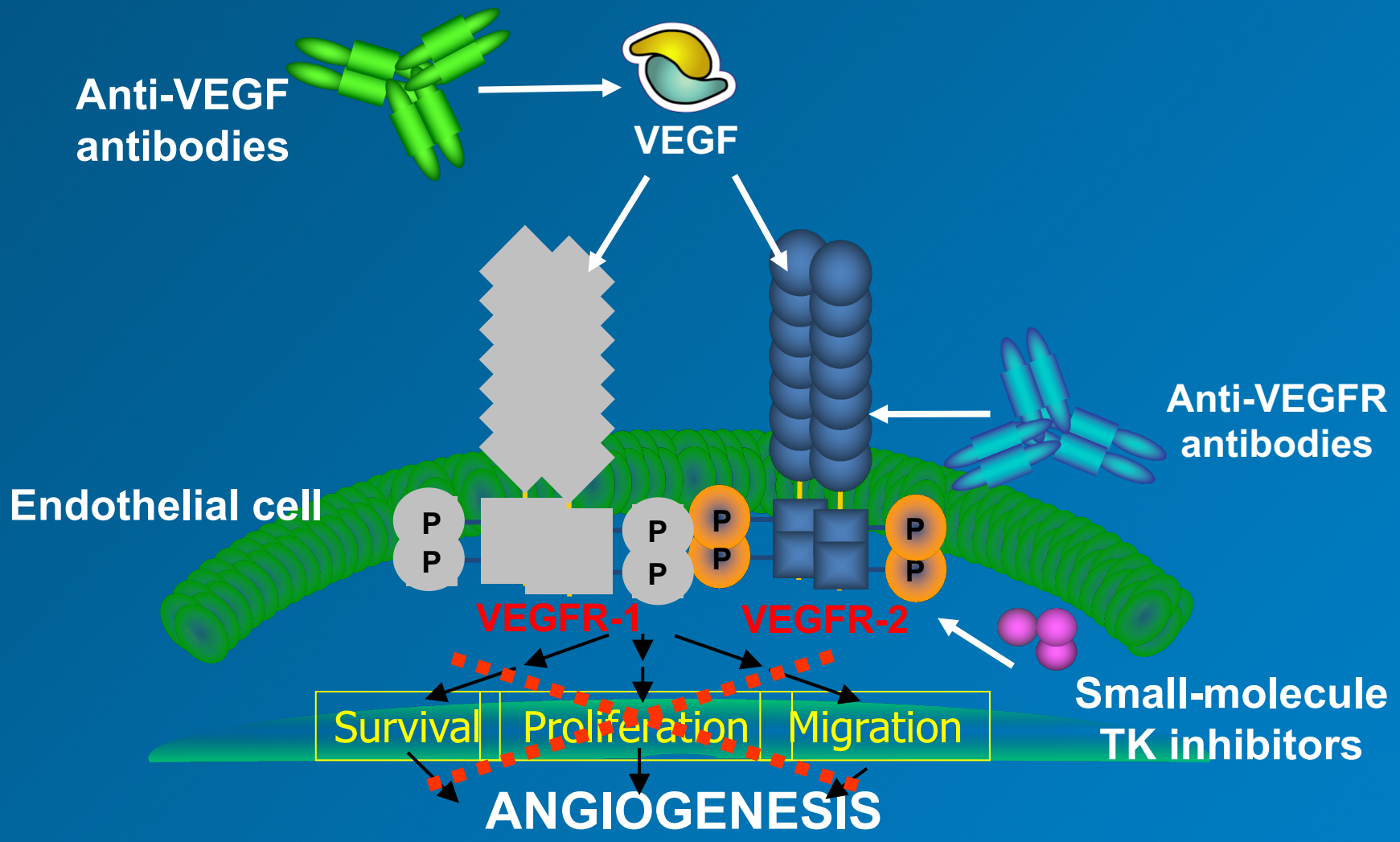
HCC Treatment Landscape: Agents Targeting the VEGF Pathway



HCC, hepatocellular carcinoma; TK, tyrosine kinase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.
Podar et al. *Blood* 2005;105:1383-1395.

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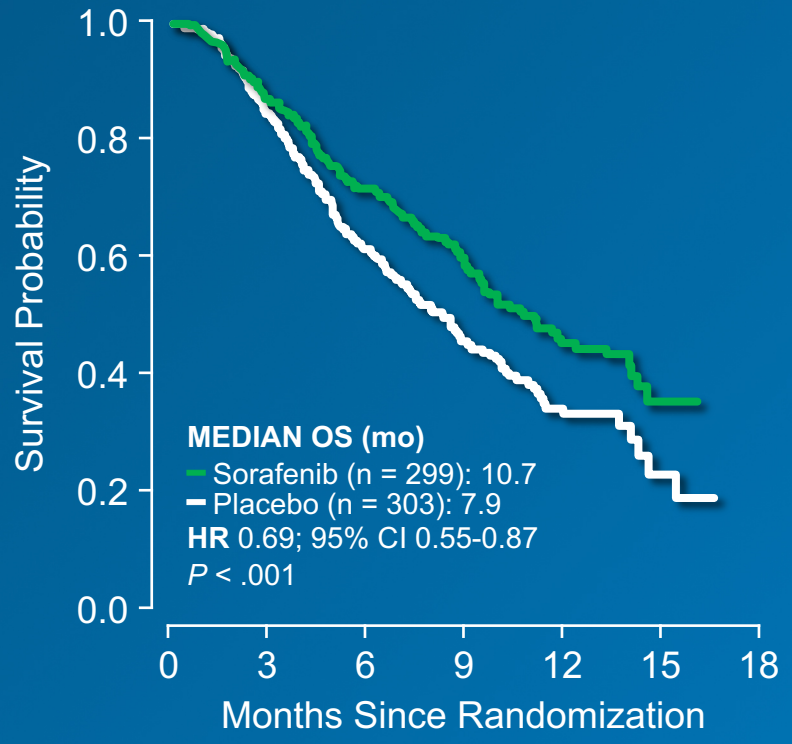
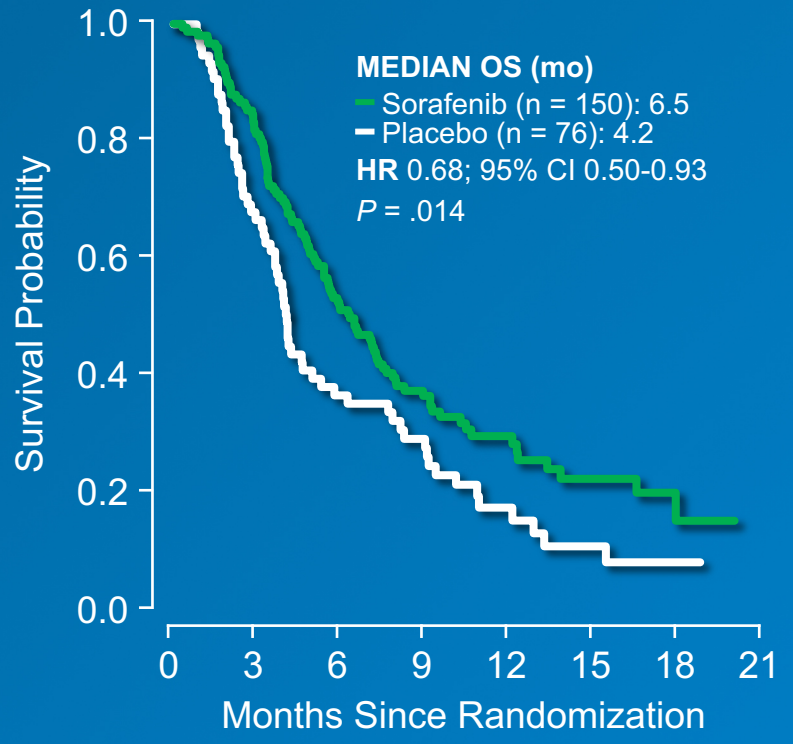
Pivotal Trials Demonstrated OS Benefit With Sorafenib in Advanced HCC

Sorafenib consistently increased OS in different patient populations across geographic regions and regardless of cause

SHARP OS[1]



ASIA-PACIFIC OS[2]



HCC, hepatocellular carcinoma; OS, overall survival; SHARP, Sorafenib HCC Assessment Randomized Protocol Trial.

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

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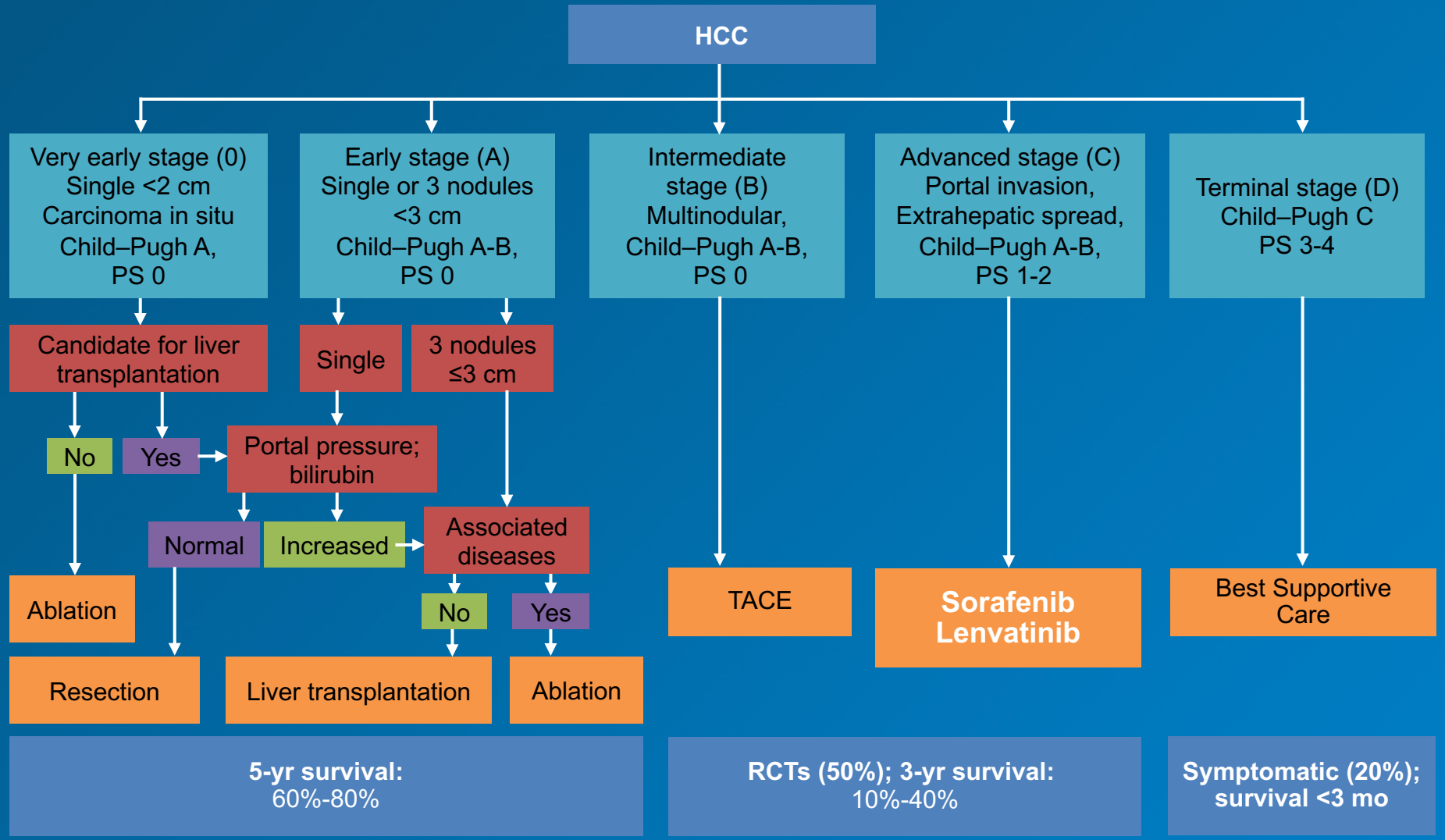
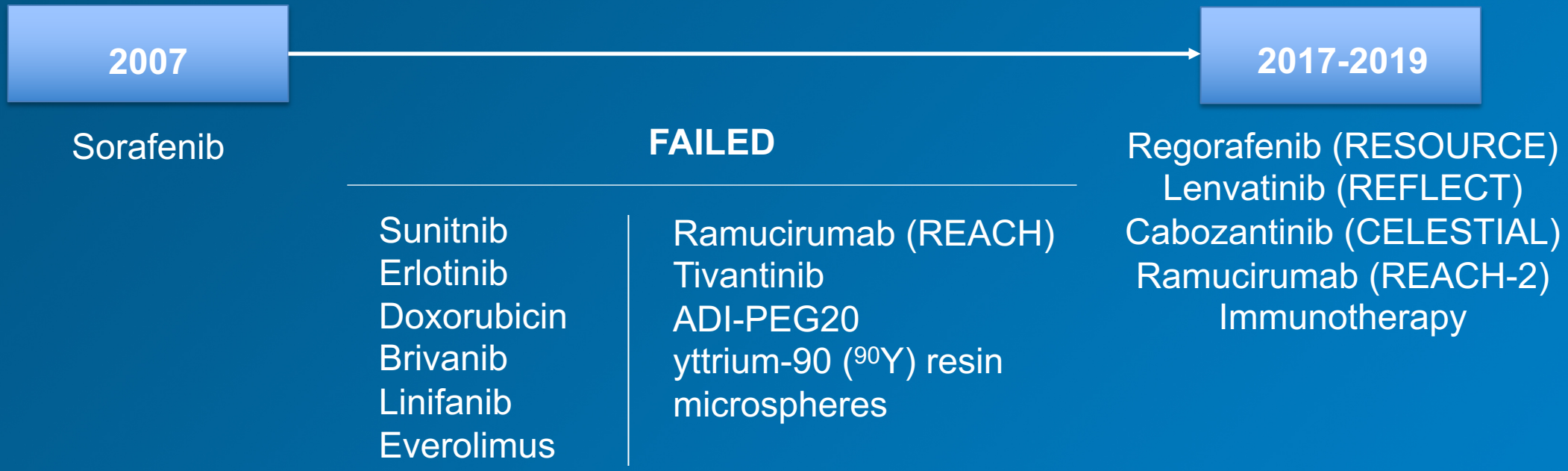
2019: Barcelona Clinic Liver Cancer Staging and Treatment Strategy



HCC, hepatocellular carcinoma, TACE, transarterial chemoembolization; RCTs, randomized controlled trials.

Bruix J et al. *Gastroenterology* 2016;150:835-853; Llovet JM et al. *N Engl J Med*. 2008;359:378-390.

Advanced HCC: A Long Drought



HCC, hepatocellular carcinoma.
Courtesy of Richard Finn.

NCCN Guidelines®: Systemic Therapy

Version 5.2020 – August 4, 2020

First-Line Therapy	Subsequent-Line Therapy if Disease Progression
Preferred Regimens • Sorafenib (Child-Pugh Class A or B7) • Lenvatinib (Child-Pugh Class A only) • Atezolizumab + bevacizumab (Child-Pugh Class A only)	• Regorafenib (Child-Pugh Class A only; category 1) • Cabozantinib (Child-Pugh Class A only; category 1) • Ramucirumab (AFP ≥400 ng/mL only; category 1) • Lenvatinib (Child-Pugh Class A only) • Nivolumab (Child-Pugh Class A or B) • Nivolumab + ipilimumab (Child-Pugh Class A only) • Sorafenib (Child-Pugh Class A or B7) • Pembrolizumab (Child-Pugh Class A only)
Useful in Certain Circumstances • Nivolumab (ineligible for TKI or other anti-angiogenic agents) • FOLFOX	

AFP, alpha fetoprotein; FOLFOX, fluorouracil, leucovorin, oxaliplatin; TKI, tyrosine kinase inhibitor.

Benson et al. NCCN Guidelines Hepatobiliary Cancers. Version 5.2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

Immunotherapy FDA Approvals in HCC

Immunotherapy	Trial	FDA Approval
First-Line		
Atezolizumab + bevacizumab	IMbrave150[1,2]	May 2020: FDA approved for patients with unresectable or metastatic HCC who have not received prior systemic therapy
Second-line		
Nivolumab	CheckMate-040[3]	Sept 2017: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib
Pembrolizumab	KEYNOTE-224[4]	Nov 2018: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib
Nivolumab + ipilimumab	CheckMate-040[5,6]	March 2020: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib

1. Cheng et al. *Ann Oncol*. 2019;30:ix186-ix187. 2. Finn et al. *N Engl J Med*. 2020;382:1894-1905. 3. El-Khoueiry et al. *Lancet* 2017;389:2492-2502.
4. Zhu et al. *Lancet Oncol*. 2018;19:940-952. 5. Yau et al. *J Clin Oncol*. 2019; 37:4012-4012 6. He et al. *J Clin Oncol*. 2020;38:512.
FDA, US Food & Drug Administration; HCC, hepatocellular carcinoma.

First Line

Phase 3 Nivolumab vs Sorafenib First Line CheckMate 459

Key eligibility criteria

- Histologically confirmed advanced HCC not eligible for surgical and/or LRT; or progressive disease after surgical and/or LRT
- Child-Pugh class A
- ECOG PS 0 or 1
- Systemic therapy naive

Stratification factors

- Etiology Vascular invasion and/or EHS
- Geography (Asia vs non-Asia)

R 1:1

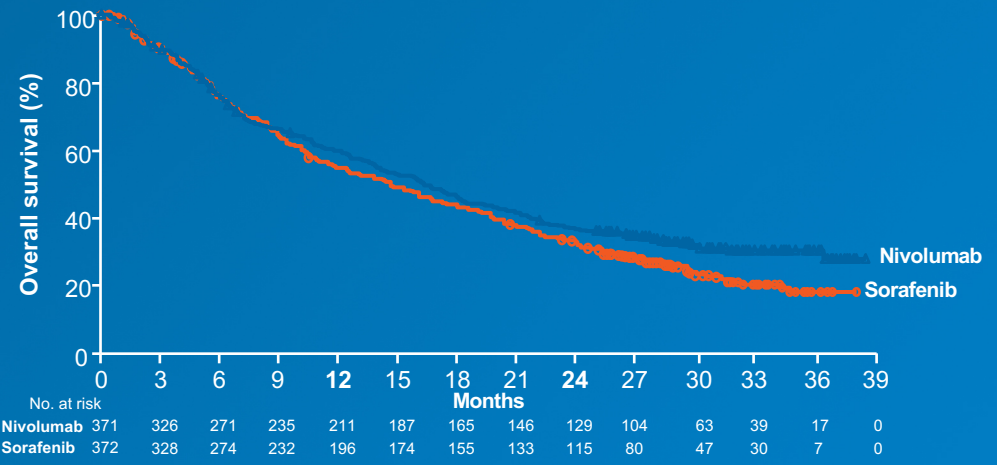
N = 743

Nivolumab
240 mg IV Q2W
n = 371

Sorafenib
400 mg po BID
n = 372

Objectives
- Primary – OS
- Secondary – ORR, PFS, efficacy PD-L1 status
- Exploratory – HRQoL using FACT-Hep

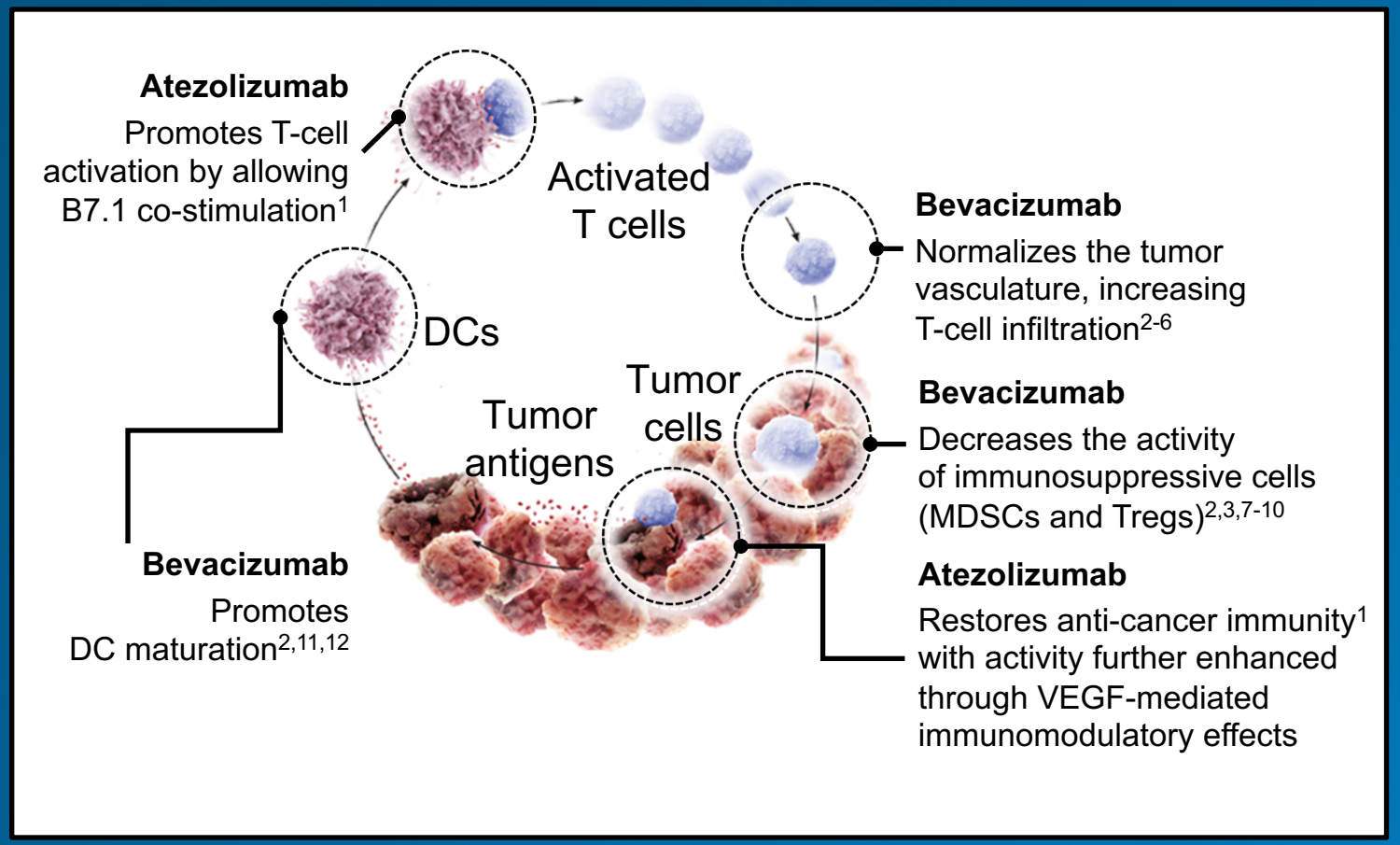
	Nivolumab (n = 371)	Sorafenib (n = 372)	HR (95% CI)	*P*
Median OS 95% CI, mo	16.4 (13.9-18.4)	14.7 (11.9-17.2)	0.85 (0.72-1.02)	.0752



BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; FACT-Hep, Functional Assessment of Cancer Therapy-. Hepatobiliary; LRT, locoregional radiation therapy; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; R, randomized.

Yau et al. Ann Oncol. 2019;30:v851-v934. https://www.annalsofoncology.org/article/S0923-7534(19)60389-3/pdf

Combining VEGF Inhibition and PD-1/PD-L1

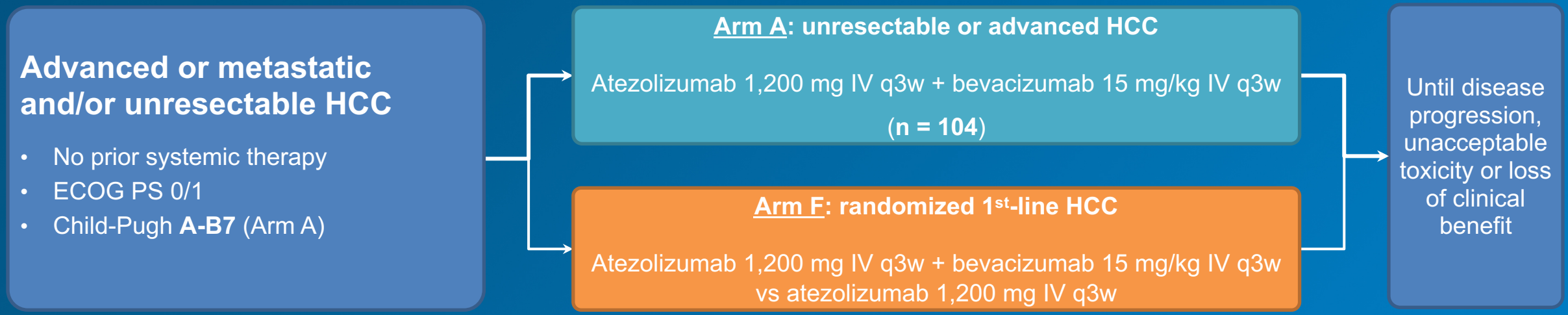


- Bevacizumab (anti-VEGF) is an antiangiogenic agent with additional immunomodulatory effects
- In combination, bevacizumab may further enhance atezolizumab's efficacy by reversing VEGF-mediated immunosuppression to promote T-cell infiltration into the tumor

DC, dentritic cell; MDSCs, myeloid-derived suppressor cell; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

1. Chen and Mellman. *Immunity* 2013;39:1-10. 2. Hegde et al. *Semin Cancer Biol.* 2018;52:117-124. 3. Wallin et al. *Nat Commun*. 2016;7:12624.
4. Goel et al. *Physiol Rev*. 2011;91:1071-1121. 5. Motz et al. *Nat Med*. 2014;20:607-615. 6. Hodi et al. *Cancer Immunol Res*. 2014;2:632-642.
7. Gabrilovich and Nagaraj. *Nat Rev Immunol*. 2009;9:162-174. 8. Roland et al. *PLoS One*. 2009;4:e7669. 9. Facciabene et al. *Nature* 2011;475:226-230.
10. Voron et al. *J Exp Med*. 2015;21:139-148. 11. Gabrilovich. *Nat Med*. 1996;2:1096-1103. 12. Oyama et al. *J Immunol*. 1998;160:1224-1232.
From Hsu et al. APASL 2019 Manila.

GO30140: Arm A Design
Atezolizumab + Bevacizumab

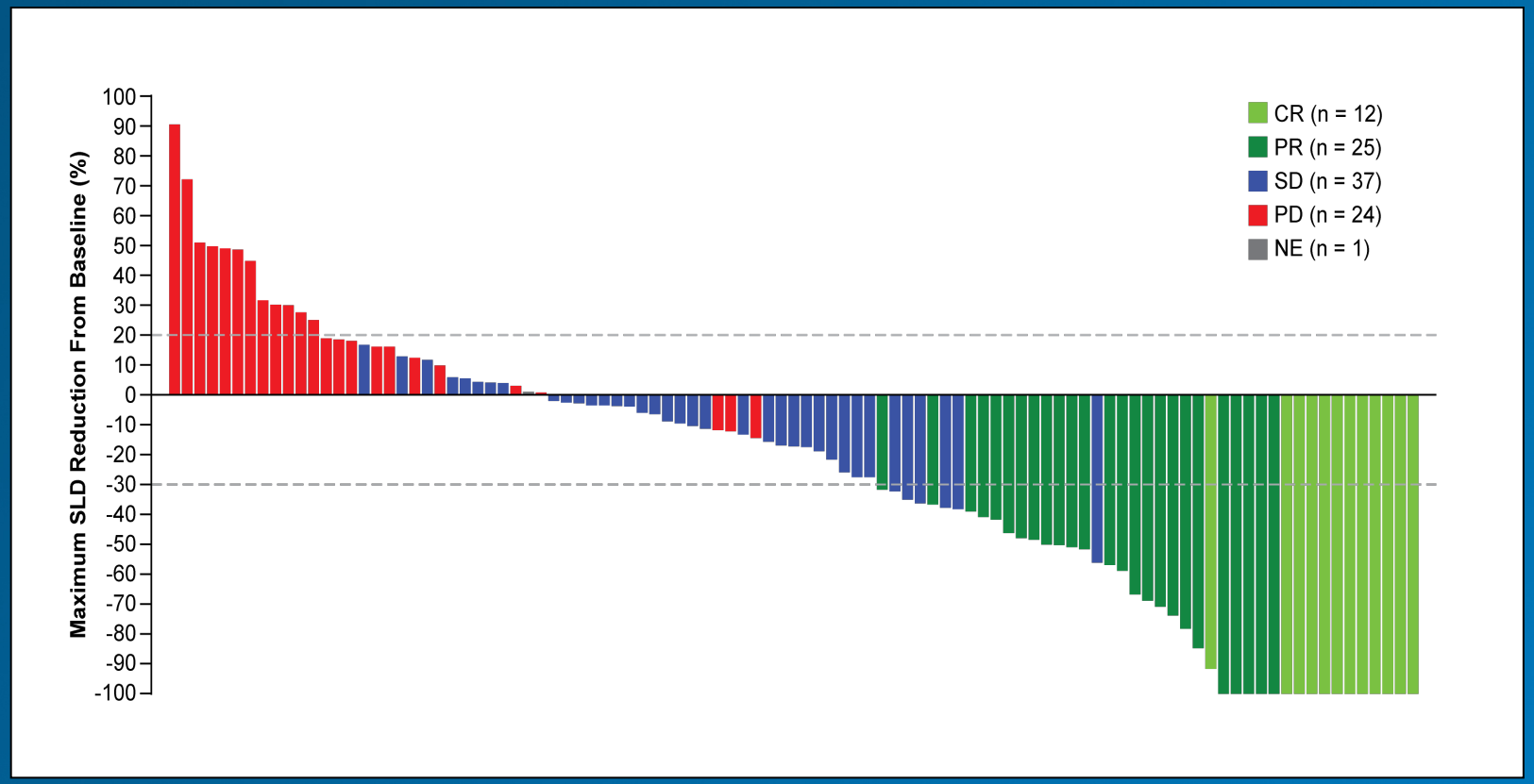


Primary endpoints	IRF-assessed ORR per RECIST v1.1 and safety
Key secondary endpoints	IRF-assessed ORR, DoR, PFS and TTRP per RECIST v1.1 (excl ORR) & HCC mRECIST
	INV-assessed ORR, DoR, PFS and TTRP per RECIST v1.1
	OS

Arm A: at clinical data cut-off (14 June 2019), 104 patients were evaluable with a **median follow-up of 12.4 months**

DoR, duration of response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; INV, investigator; IRF, independent review facility; mRECIST, modified Response Evaluation Criteria in Solid Tumours; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; TTRP, time to radiographic progression.
NCT02715531; Hsu et al. APASL 2019 Manila.

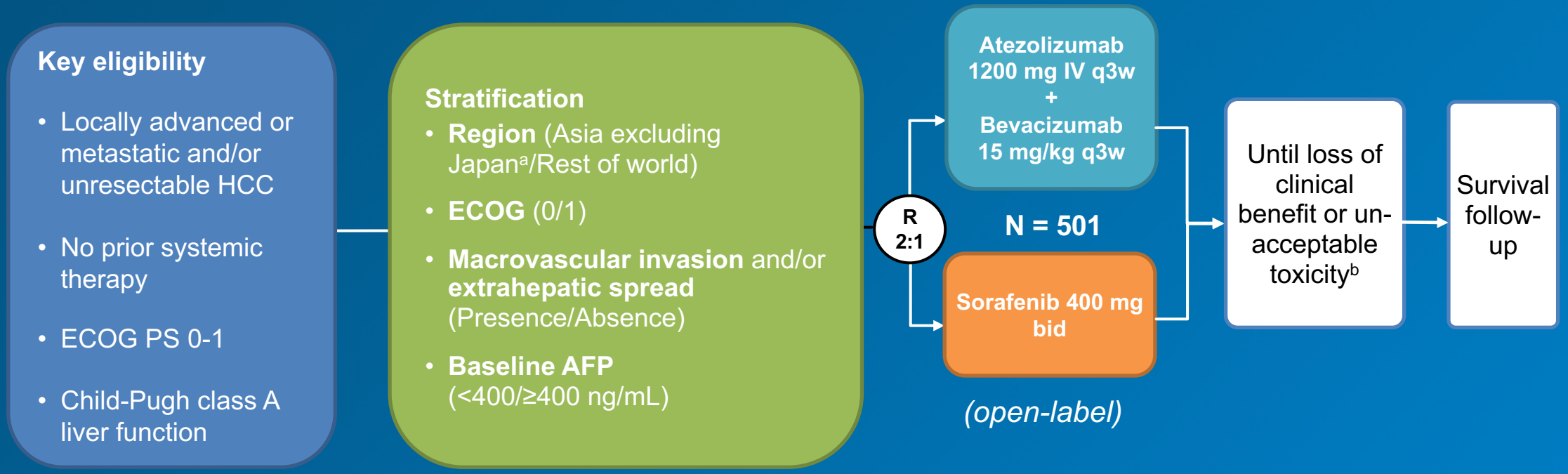
GO30140: Arm A
Primary Efficacy Endpoint: ORR (IRF, R1.1)



Confirmed responses per IRF, R1.1, n (%)	(N = 104)
ORR 95% CI	37 (36) (26-46)
CR	12 (12)
PR	25 (24)
SD	37 (36)
DCR	74 (71)
PD	25 (24)

All CRs reached with systemic therapy only. Missing/unevaluable: 5 patients (5%), 99 patients showed on the plot Data cut-off: 14 June 2019
CR, complete response; DCR, disease control rate; IRF, independent review facility; ORR, objective response rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of the longest diameter.
NCT02715531; Hsu et al. APASL 2019 Manila.

IMbrave150: Study Design
Atezolizumab + Bevacizumab



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.
AEs, adverse events; AFP, alpha-fetoprotein; bid, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; 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; HCC, hepatocellular carcinoma; IRF, independent review facility; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; QOL, quality of life; R, randomized; TTD, time to deterioration.
Finn et al. *New Engl J Med.* 2020;382:1894-1905.

IMbrave150: Patient Characteristics at Baseline

Characteristic	Atezolizumab + Bevacizumab (n = 336)	Sorafenib (n = 165)
Median age (IQR), y	64 (56-71)	66 (59-71)
Male, n (%)	277 (82)	137 (83)
Geographic region, n (%)		
Asia excluding Japan	133 (40)	68 (41)
Rest of the world[a]	203 (60)	97 (59)
ECOG performance status score, n (%)		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child-Pugh score, n (%)		
A5	239 (72)	121 (73)
A6	94 (28)	44 (27)
Barcelona Clinic Liver Cancer stage, n (%)		
A	8 (2)	6 (4)
B	52 (15)	26 (16)
C	276 (82)	133 (81)

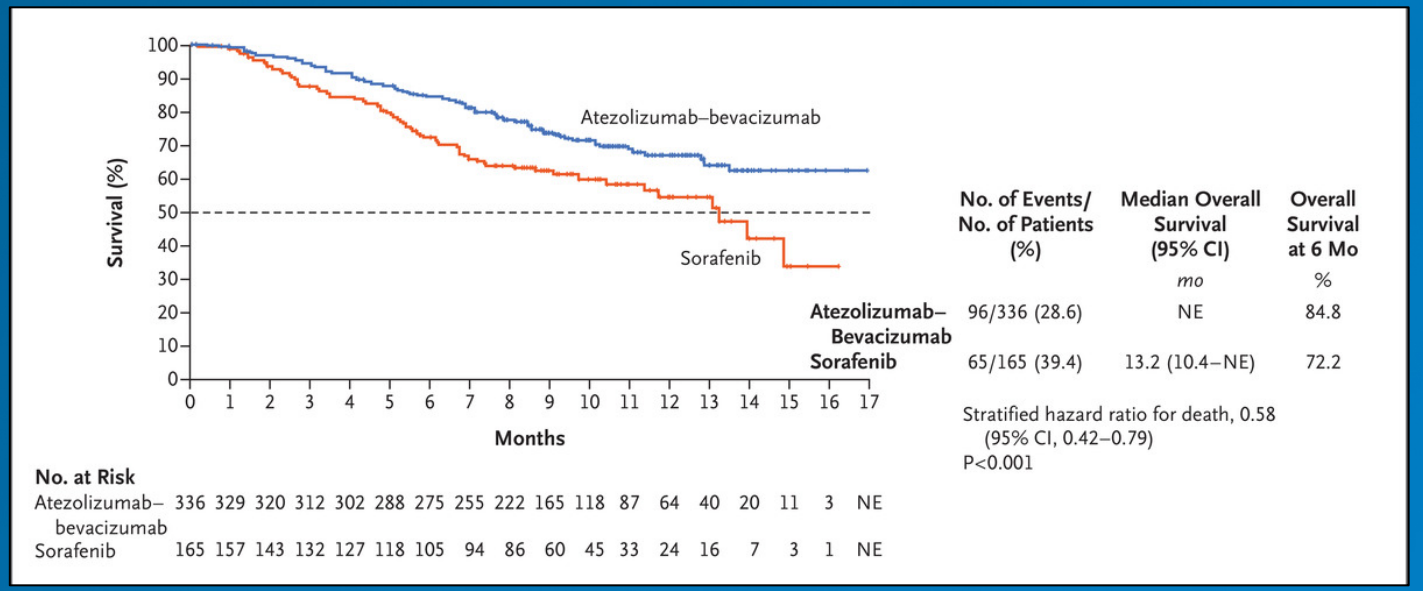
Characteristic	Atezolizumab + Bevacizumab (n = 336)	Sorafenib (n = 165)
AFP at baseline ≥ 400 ng/mL	126 (38)	61 (37)
Macrovascular invasion and/or extrahepatic spread present, n (%)	258 (77)	120 (73)
Macrovascular invasion present, n (%)	129 (38)	71 (43)
Extrahepatic spread present, n (%)	212 (63)	93 (56)
Varices at baseline	88 (26)	43 (26)
Varices treated at baseline	36 (11)	23 (14)
Cause of hepatocellular carcinoma, n (%)		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Nonviral[b]	100 (30)	53 (32)
Prior local therapy for hepatocellular carcinoma, n (%)	161 (48)	85 (52)

[a] The rest of the world includes the United States, Australia, New Zealand, and Japan.
[b] Includes alcohol, other and unknown non-hepatitis B and C causes.
Clinical data cut-off: August 29, 2019.
AFP, alpha fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

- 501 patients enrolled from 111 sites in 17 countries between March 15, 2018 and January 30, 2019
- Median duration of follow-up was 8.6 mo
  - 8.9 mo in atezolizumab + bevacizumab group
  - 8.1 mo in sorafenib group

IMbrave 150
Co-Primary Endpoint: OS (ITT Population)

- OS longer with atezolizumab + bevacizumab vs sorafenib (*P* < .001)
- Estimated 6-month survival rates:
  - Atezolizumab + bevacizumab: 84.8% (95% CI 80.9-88.7)
  - Sorafenib: 72.2% (95% CI 65.1-79.4)
- Estimated 12-month survival rates:
  - Atezolizumab + bevacizumab: 67.2% (95% CI 61.3-73.1)
  - Sorafenib: 54.6% (95% CI 45.2-64.0)



Factors included in the stratified *P* value and Cox model were geographic region (Asia [excluding Japan] vs the rest of the world), AFP level at baseline (<400 ng/mL vs ≥400 ng/mL), and macrovascular invasion, extrahepatic spread, or both (yes vs no).
Tick marks indicate censored data.
ITT, intention to treat; OS, overall survival; NE, could not be evaluated.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

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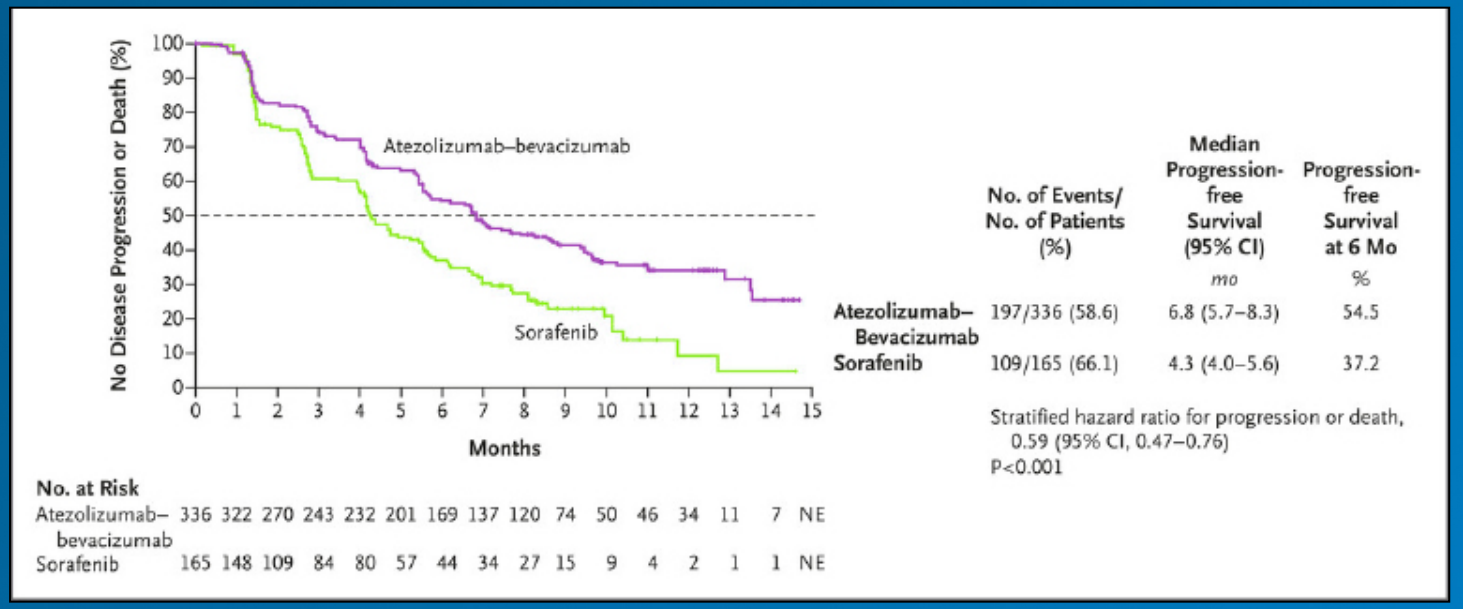
IMbrave 150
Co-Primary Endpoint: PFS[a] (ITT Population)

PFS longer with atezolizumab + bevacizumab vs sorafenib ($P < .001$)



	No. of Events/ No. of Patients (%)	Median Progression-free Survival (95% CI)	Progression-free Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	197/336 (58.6)	6.8 (5.7–8.3)	54.5
Sorafenib	109/165 (66.1)	4.3 (4.0–5.6)	37.2

Stratified hazard ratio for progression or death, 0.59 (95% CI, 0.47–0.76)
P<0.001

[a] As 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] vs the rest of the world), AFP level at baseline (<400 ng/mL vs ≥400 ng/mL), and macrovascular invasion, extrahepatic spread, or both (yes vs no).
Tick marks indicate censored data.
ITT, intention to treat; NE, not evaluated; PFS, progression-free survival.
Adapted from Finn et al. *N Engl J Med*. 2020;382:1894-1905.

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IMbrave 150: Secondary Efficacy Outcomes

Variable	IRF RECIST 1.1[a]			IRF HCC-specific mRECIST[b]		
	Atezolizumab + Bevacizumab (n = 326)	Sorafenib (n = 159)	Difference (P)[c]	Atezolizumab + Bevacizumab (n = 325)	Sorafenib (n = 158)	Difference (*P*)[c]
Confirmed[d] objective response, n (% [95% CI])	89 (27.3 [22.5-32.5])	19 (11.9 [7.4-18.0])	15.4 (<.001)	108 (33.2 [28.1-38.6])	21 (13.3 [8.4-19.6])	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, n (%)	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing, n (%)	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response at data cutoff, n/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 vs. 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 vs. 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.
IRF, independent review facility.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

KEYNOTE-524/Study 116
Lenvatinib + Pembrolizumab

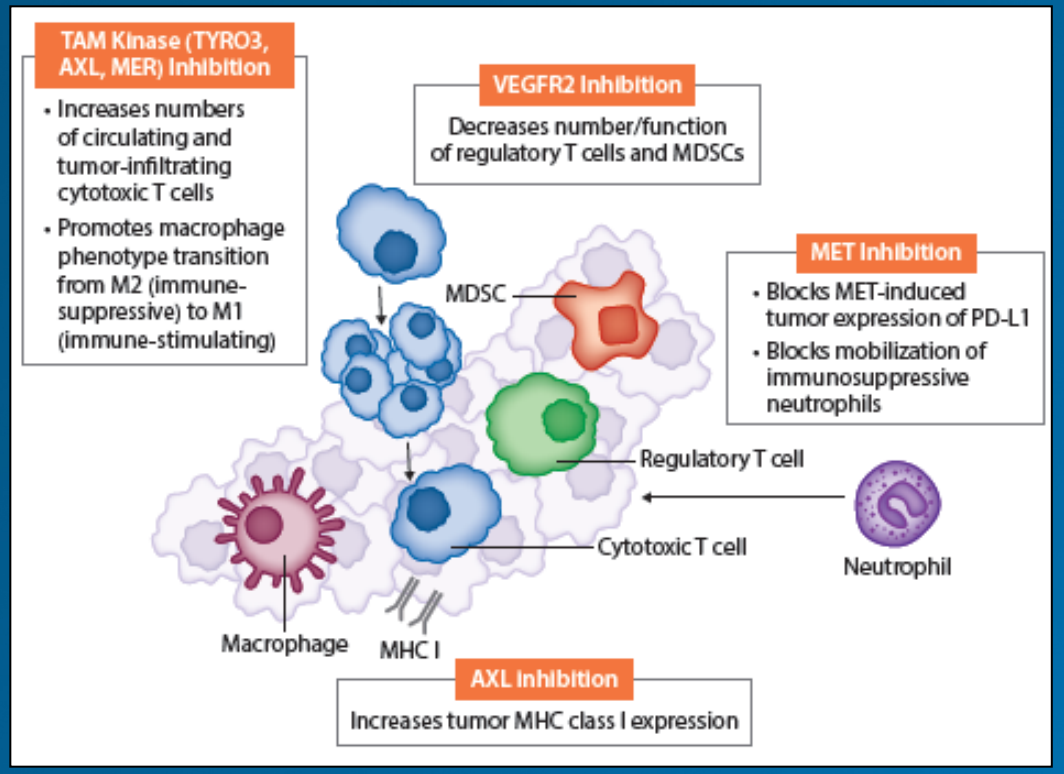
Summary of Efficacy Outcomes			
Parameter	**Lenvatinib + Pembrolizumab (N = 100)**		
	mRECIST per IIR	**RECIST Version 1.1 per IIR**	**mRECIST per IR**
ORR (confirmed responses), n (%) (95% CI)	46 (46) (36.0–56.3)	36 (36) (26.6–46.2)	41 (41) (31.3–51.3)
Best overall response, n (%)			
Complete response	11 (11)	1 (1)	5 (5)
Partial response	35 (35)	35 (35)	36 (36)
Stable disease	42 (42)	52 (52)	45 (45)
Progressive disease	7 (7)	7 (7)	7 (7)
Unknown/not evaluable	5 (5)	5 (5)	7 (7)
Median DOR for confirmed responders, months (95% CI)	8.6 (6.9-NE)	12.6 (6.9-NE)	12.6 (6.2-18.7)
Median TTR for confirmed responders, months (range)	1.9 (1.2-5.5)	2.8 (1.2-7.7)	2.7 (1.2-11.8)
Disease control rate, n (%) (95% CI)	88 (88) (80.0-93.6)	88 (88) (80.0–93.6)	86 (86) (77.6-92.1)

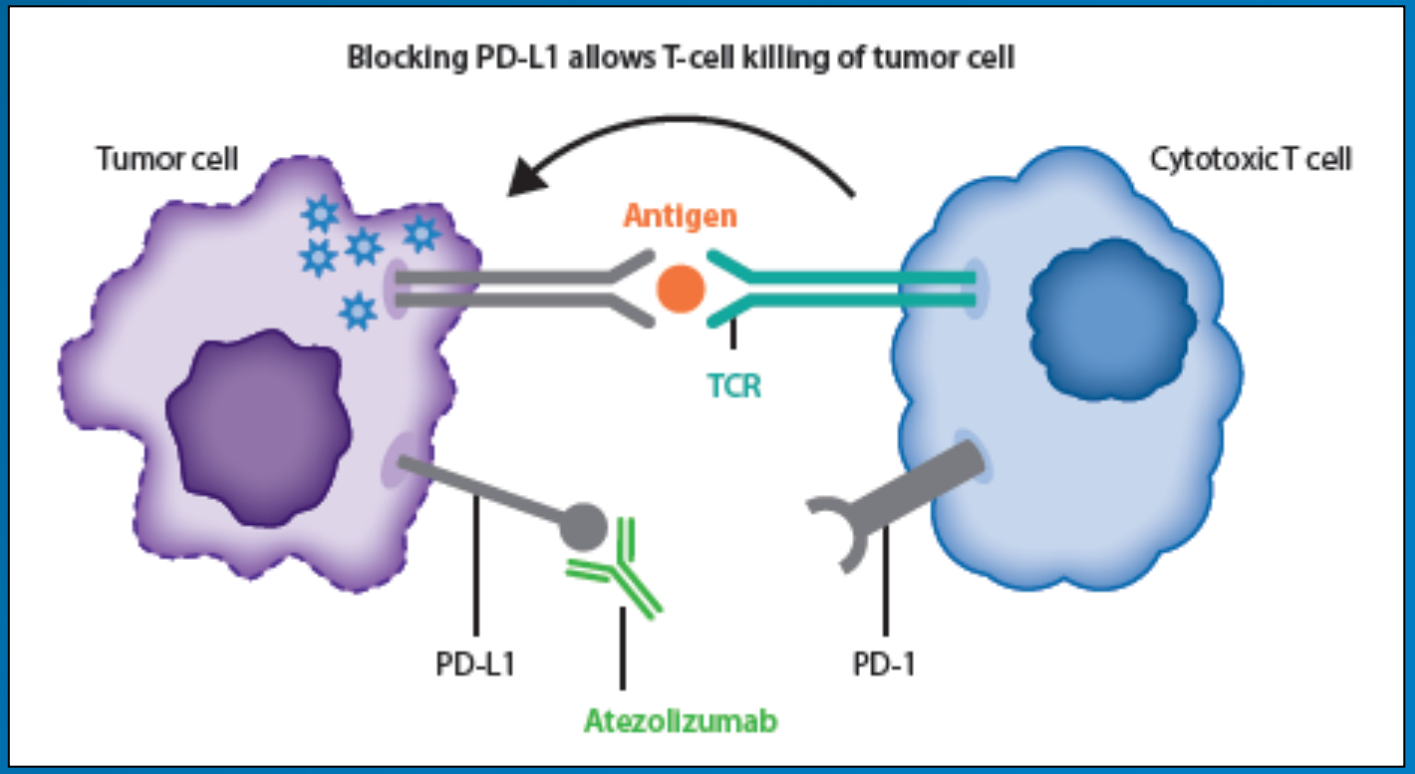
- Phase 1b, open-label, single-arm trial
- 100 patients with unresectable HCC with no prior systemic therapy
- July 2019: FDA Breakthrough Therapy Designation
- Phase 3 LEAP-002 trial ongoing (NCT03713593)
  - Lenvatinib in combination with pembrolizumab versus lenvatinib as first-line therapy in patients with advanced HCC

FDA, US Food & Drug Administration; DOR, duration of response; HCC, hepatocellular carcinoma; IIR, independent imaging review; IR, investigator review; NE, not evaluable; ORR, objective response rate; TTR, time to response.

Finn et al. *J Clin Oncol*. 2020;38: abstract 4519.

COSMIC-312 Trial
ICI + TKI: Atezolizumab + Cabozantinib





ICI, immune checkpoint inhibitor; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TKI, tyrosine kinase inhibitor.

Kelley et al. *J Clin Oncol.* 2019;37(15_suppl): abstract TPS4157.

CheckMate 9DW Trial
PD-1 + CTLA-4: Nivolumab + Ipilimumab

- Phase 3 CheckMate 9DW study recruiting (NCT04039607)
- Nivolumab + ipilimumab versus sorafenib or lenvatinib as first-line treatment in patients with advanced hepatocellular carcinoma

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD1, programmed cell death protein 1.

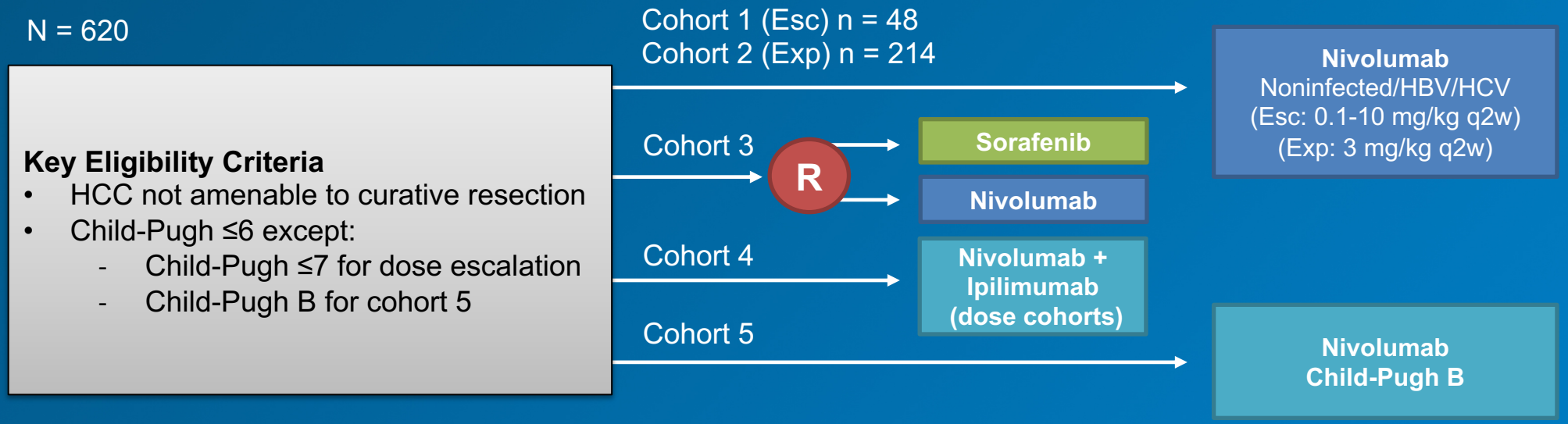
HIMALAYA Trial
PD-L1 + CTLA-4: Durvalumab +/- Tremelimumab

- Phase 3 HIMALAYA study ongoing (NCT03298451)
- Durvalumab + tremelimumab vs. durvalumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma
- January 2020: Orphan Drug Designation

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD1, programmed cell death protein 1.

Second Line

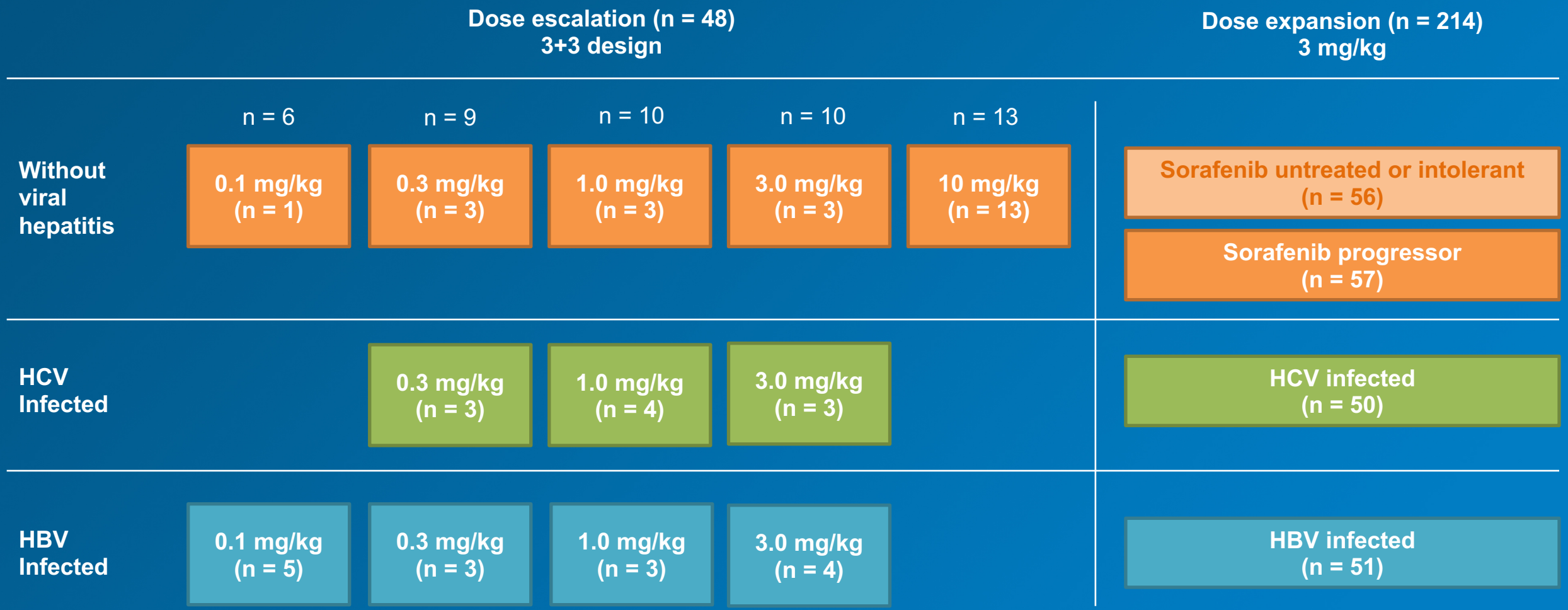
CheckMate-040: Study Design Nivolumab



Primary Endpoints (Cohorts 1&2): Safety and tolerability, ORR
Location: Multinational
Status: Ongoing

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, overall response rate.
El-Khoueiy et al. *Lancet* 2017;389:2492-2502.

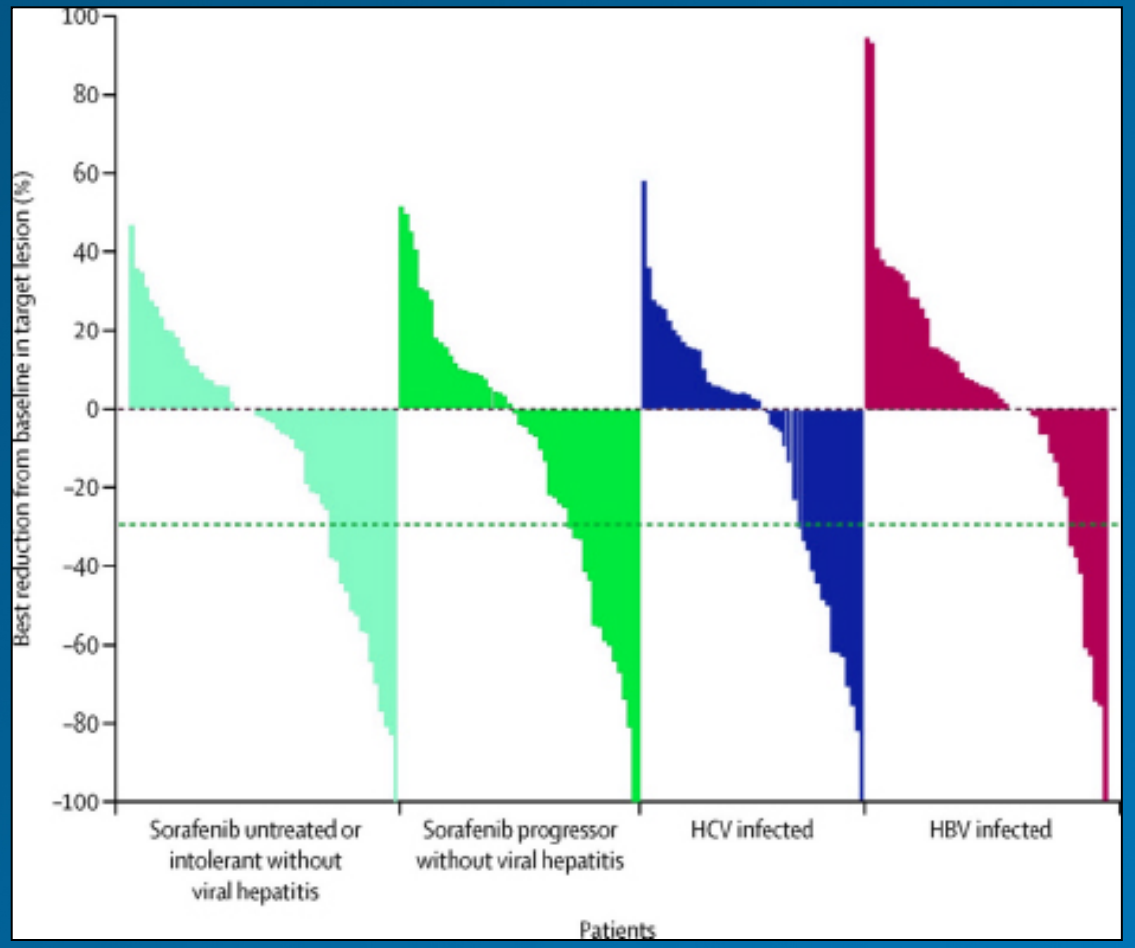
CheckMate-040: Study Design
Nivolumab



HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, overall response rate.

El-Khoueiy et al. *Lancet* 2017;389:2492-2502.

CheckMate-040: Nivolumab



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

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

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

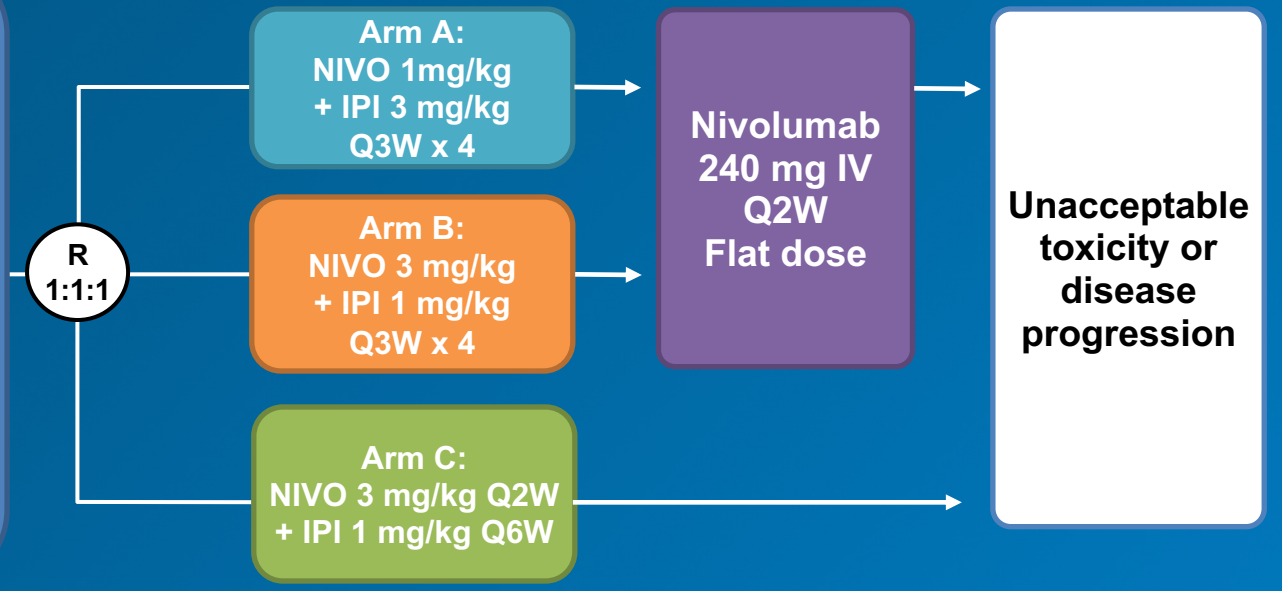
Median DoR: 16.6 mo

BICR, blinded independent central review; DoR, duration of response; FDA, US Food & Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; mOS, median overall survival; NR, not reached; RR, response rate.
Adapted from El-Khoueiy et al. *Lancet* 2017;389:2492-2502.

CheckMate-040: Study Design
Nivolumab + Ipilimumab

Key eligibility

- Advanced HCC sorafenib-treated intolerant or progressors
- Uninfected, HCV-infected, or HBV-infected



Study endpoints

Primary
- Safety and tolerability using NCI CTCAE v4.0
- ORR and DOR based on investigator assessment[a]

Secondary
- DCR
- PFS
- OS
- TTP
- TTR

Other
- BOR and ORR based on BICR-assessed tumor response[a]

[a]Using RECIST v1.1.
BICR, blinded independent central review; BOR, best overall response; DCR, disease control rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPI, ipilimumab; NIVO, nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, randomized; Q2W, every 2 weeks; TTP, time to progression; TTR, time to response.
Yau et al. *J Clin Oncol*. 2019; 37:4012-4012.

CheckMate-040: Nivolumab + Ipilimumab

Result	Arm A Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W (4 doses) followed by Nivolumab 240 mg Q2W n = 50	Arm B Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W (4 doses) followed by Nivolumab 240 mg Q2W n = 49	Arm C Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W n = 49
ORR by BICR, 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)	6 (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, mo	2.0	2.6	2.7
Median DOR, mo	17.5	22.2	16.6
ORR by investigator assessment, n (%)	16 (32)	13 (27)	14 (29)
Median OS, mo	22.8	12.5	12.7

BICR, blinded independent control review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; Q, every; W, weeks; SD, stable disease; TTR, time to response.

Yau et al. *J Clin Oncol*. 2019; 37:4012-4012. He et al. *J Clin Oncol*. 2020;38:512.

KEYNOTE-224: Study Design Pembrolizumab

Key eligibility criteria

- ≥18 y
- Pathologically confirmed HCC
- Progression on or intolerance to sorafenib treatment
- Child Pugh class A
- ECOG PS 0-1
- BCLC Stage C or B disease
- Predicted life expectancy >3 mo

Pembrolizumab 200 mg Q3W for 2y or until PD, intolerable toxicity, withdrawal of consent or investigator decision

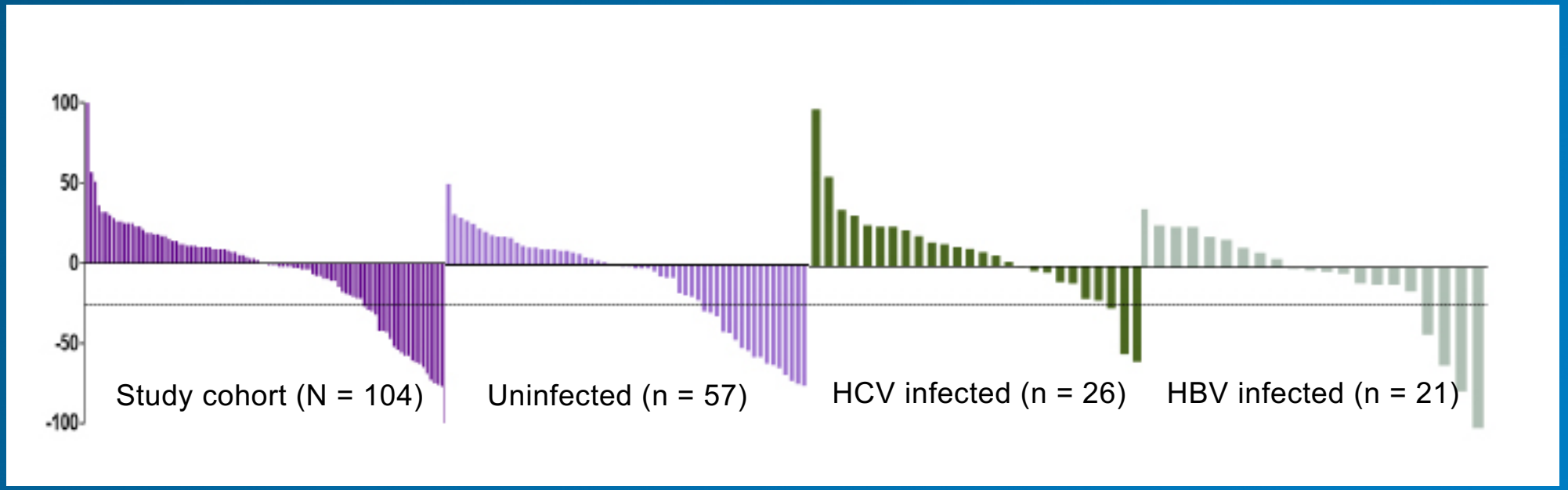
Survival follow-up

- Response assessed Q9W
- Primary endpoint: OR (Recist v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS and safety and tolerability

BCLC, Barcelona-Clinic Liver Cancer; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; Q9W, every 9 weeks.

KEYNOTE-224: Pembrolizumab

Maximum Percentage Changes From Baseline in Target Lesions



Based on RESIST v1.1 by central radiology review in patients who had both pre- and post-treatment image measurements. Dotted line is threshold for response.
Data cutoff date: Aug 24, 2017.
Adapted from Zhu et al. *Lancet Oncol.* 2018;19:940-952.

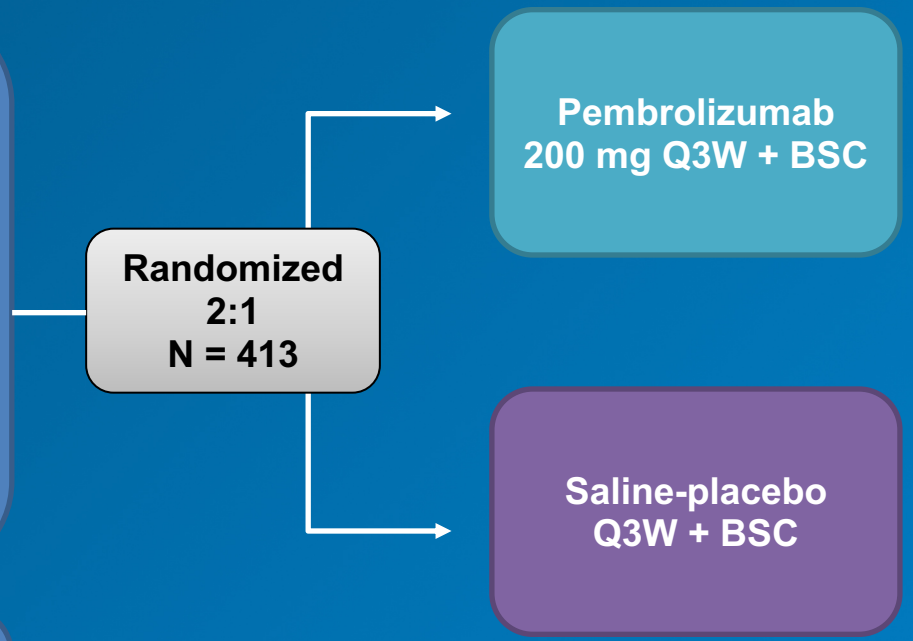
KEYNOTE-240: Study Design Pembrolizumab

Key Eligibility Criteria

- Pathologically/radiographically confirmed HCC
- Progression on/intolerance to sorafenib
- Child Pugh class A
- BCLC stage B/C
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Main portal vein invasion was excluded

Stratification Factors

- Geographic region (Asia w/o Japan vs non-Asia w/Japan)
- Macrovascular invasion (Y vs N)
- AFP level (≥200 vs <200 ng/mL)

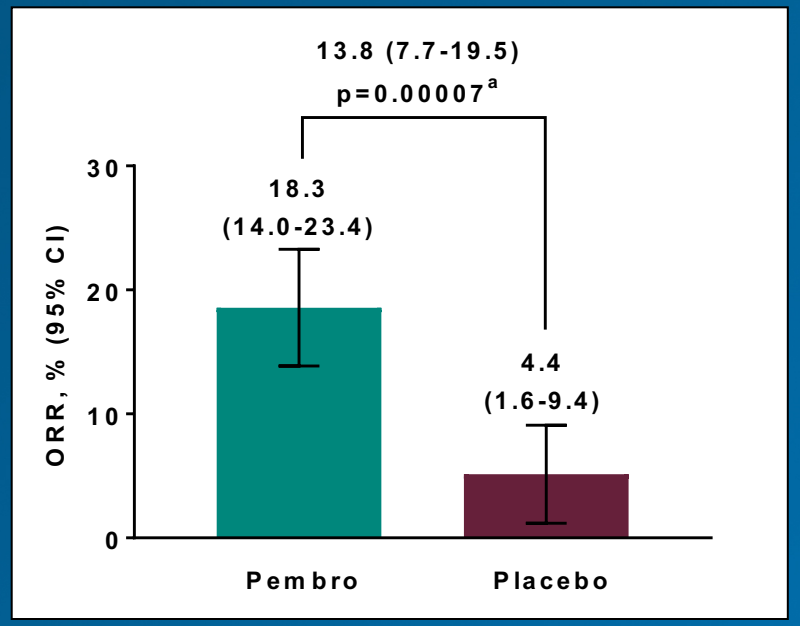


Enrollment May 31, 2016 – November 23, 2017

AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; Q3W, every 3 weeks.

Finn et al. *J Clin Oncol*. 2019;37:4004.

KEYNOTE-240: Objective Response Rate at Final Analysis (RECIST 1.1, BICR)



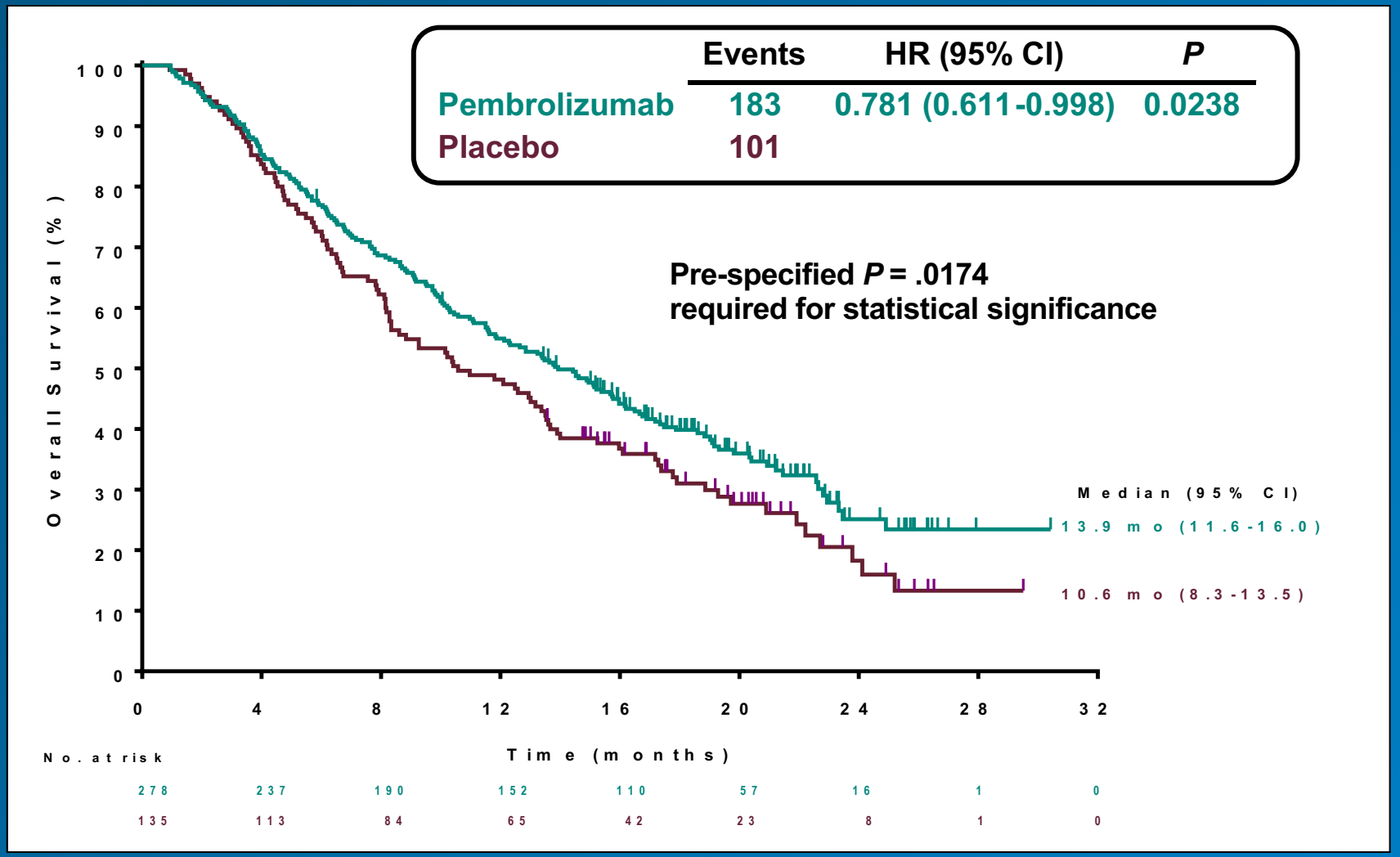
Response n (%)	Pembrolizumab N = 278	Placebo N = 135
Best overall response, n (%)		
CR	6 (2.2)	0 (0.0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
SD ≥23 wk	37 (18.3)	20 (14.8)
Progressive disease, n (%)	90 (32.4)	57 (42.2)
Disease control rate (CR+PR+SD), n (%)	173 (62.2)	72 (53.3)

Duration of response, median (range)[b,c]:

- Pembrolizumab: 13.8 mo (1.5+ to 23.6+ mo)
- Placebo: not reached (2.8 to 20.4+ mo)

[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.
BICR, blinded independent central review; CR, complete response; ORR, overall response rate; Pembro, pembrolizumab; PR, partial response; SD, stable disease.
Finn et al. *J Clin Oncol*. 2019;37:4004.

KEYNOTE-240: Overall Survival

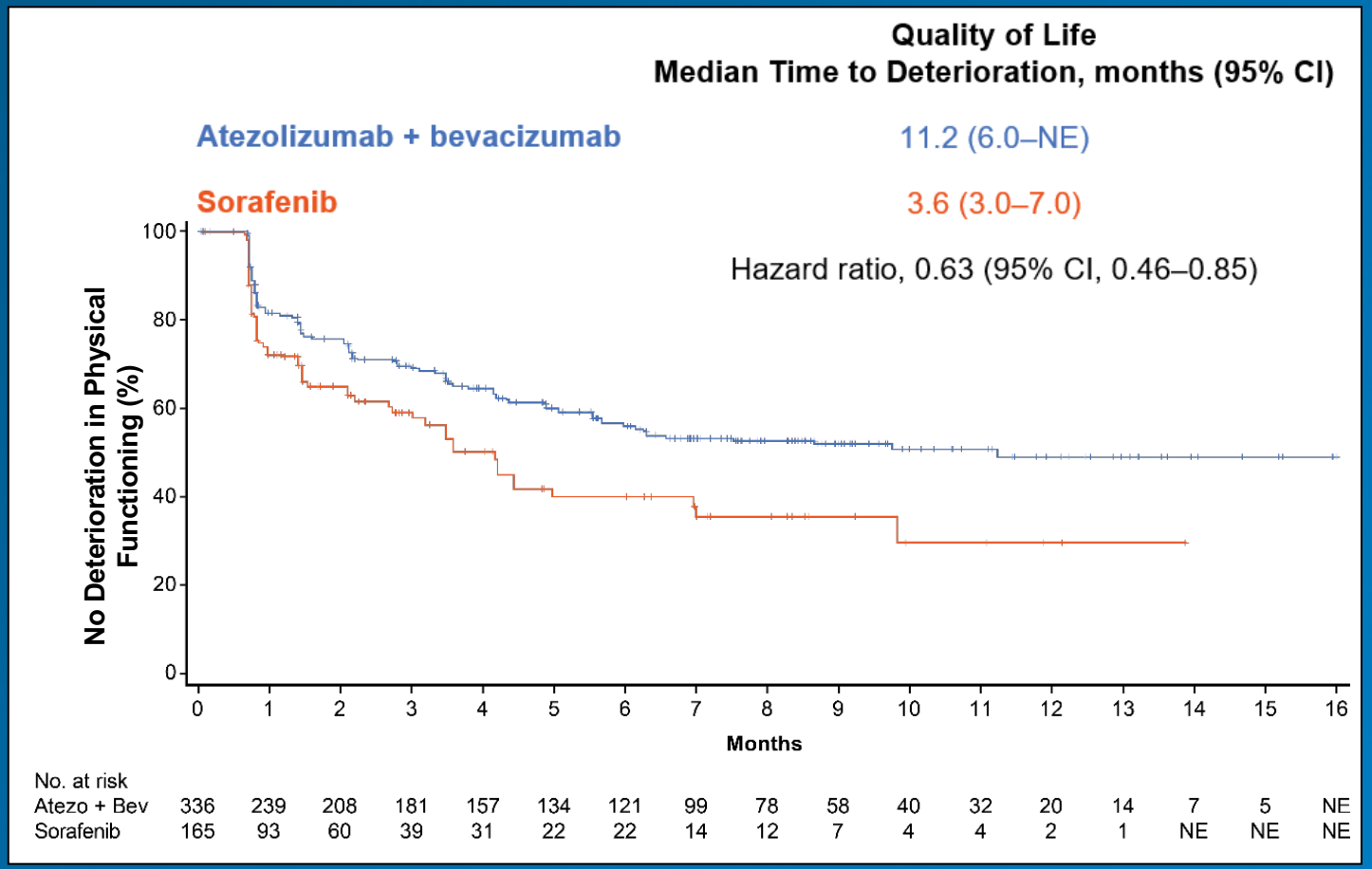


Data Cutoff: Jan 2, 2019.

Finn et al. *J Clin Oncol*. 2019;37:4004.

Safety of Immune Checkpoint Inhibitors in Advanced HCC

IMbrave 150: Atezolizuamb + Bevacizumab Patient-reported Outcomes: TTD of QOL (ITT Population)



Atezolizumab + bevacizumab delayed deterioration of patient-reported QOL

ITT, intention to treat; QOL, quality of life; TTD, time to deterioration.

Finn et al. *N Engl J Med*. 2020;382:1894-1905; Galle et al. *J Clin Oncol*. 2020;38(suppl 4):476-476.

IMbrave 150: Atezolizuamb + Bevacizumab 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%-104%) for atezolizumab
  - 93±10% and 97% (44%-104%) for bevacizumab
  - 84±20% and 96% (27%-100%) for sorafenib
- No specific events were responsible for increased serious adverse event rate in atezolizumab + bevacizumab group
- No serious adverse events with a ≥2% difference between treatment groups

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

IMbrave 150: Atezolizuamb + Bevacizumab Adverse Events With an Incidence of ≥10% in Either Group

Adverse Event	Atezolizumab + bevacizumab (n = 329)[a]		Sorafenib (n = 156)[a]	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Fatigue	67 (20.4)	8 (2.4)	29 (18.6)	5 (3.2)
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Aspartate aminotransferase increase	64 (19.5)	23 (7.0)	26 (16.7)	8 (5.1)
Pruritus	64 (19.5)	0	15 (9.6)	0
Diarrhea	62 (18.8)	6 (1.8)	77 (49.4)	8 (5.1)
Decreased appetite	58 (17.6)	4 (1.2)	38 (24.4)	6 (3.8)
Pyrexia	59 (17.9)	4 (1.2)	15 (9.6)	2 (1.3)
Alanine aminotransferase increase	46 (14.0)	12 (3.6)	14 (9.0)	2 (1.3)
Constipation	44 (13.4)	0	22 (14.1)	0
Blood bilirubin increase	43 (13.1)	8 (2.4)	22 (14.1)	10 (6.4)
Rash	41 (12.5)	0	27 (17.3)	4 (2.6)
Abdominal pain	40 (12.2)	4 (1.2)	27 (17.3)	4 (2.6)
Nausea	40 (12.2)	1 (0.3)	25 (16.0)	1 (0.6)
Cough	39 (11.9)	0	15 (9.6)	1 (0.6)
Infusion related reaction	37 (11.2)	8 (2.4)	0	0
Weight decrease	37 (11.2)	0	15 (9.6)	1 (0.6)
Platelet count decrease	35 (10.6)	11 (3.3)	18 (11.5)	2 (1.3)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Asthenia	22 (6.7)	1 (0.3)	21 (13.5)	4 (2.6)
Alopecia	4 (1.2)	0	22 (14.1)	0
Palmar-plantar erythrodysesthesia syndrome	3 (0.9)	0	75 (48.1)	13 (8.3)

[a] Received one dose of study treatment and included in safety population.

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

AXIS Medical Education

CheckMate-040: Nivolumab Treatment-related Adverse Events

	Uninfected (n = 112)		HCV (n = 51)		HBV (n = 51)		Total (N = 214)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Patients with any TRAE, n(%)	72 (64)	21 (19)	37 (73)	15 (29)	30 (59)	3 (6)	139 (65)	39 (18)
Symptomatic TRAEs reported in > 4% of all patients								
Fatigue	31 (28)	2 (2)	7 (14)	0	7 (14)	0	45 (21)	2 (1)
Pruritus	11 (10)	0	11 (22)	0	11 (22)	0	33 (15)	0
Rash	12 (11)	1 (1)	8 (16)	0	6 (12)	0	26 (12)	1 (0.5)
Diarrhea	16 (14)	2 (2)	3 (6)	0	1 (2)	1 (2)	20 (9)	3 (1)
Nausea	8 (7)	0	6 (12)	0	0	0	14 (7)	0
Decreased appetite	5 (5)	0	2 (4)	0	3 (6)	0	10 (5)	0
Dry mouth	5 (4)	0	1 (2)	0	2 (4)	0	8 (4)	0
Laboratory-value TRAEs reported in > 4% of all patients								
ALT increased	6 (5)	2 (2)	7 (14)	4 (8)	2 (4)	0	15 (7)	6 (3)
AST increased	7 (6)	3 (3)	6 (12)	6 (12)	0	0	13 (6)	9 (4)
Platelet count decreased	4 (4)	1 (1)	3 (6)	2 (4)	5 (10)	1 (2)	8 (4)	3 (1)
Anemia	2 (2)	0	3 (6)	1 (2)	3 (6)	0	8 (4)	1 (0.5)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B Virus; HCV, hepatitis C virus; TRAEs, treatment-related adverse events.
Adapted from El Kouheiry et al. *Lancet* 2017;389:2492-2502.

CheckMate-040: Nivolumab + Ipilimumab Treatment-related Adverse Events

Summary of TRAEs	Arm A NIVO1/IPI3 Q3W* N = 49		Arm B NIVO3/IPI1 Q3W** N = 49		Arm C NIVO3 Q2W/IPI1 Q6W N = 48	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any TRAE, n(%)	46 (94)	26 (53)	35 (71)	14 (29)	38 (79)	15 (31)
Pruritus	22 (45)	2 (4)	16 (33)	0	14 (29)	0
Rash	14 (29)	2 (4)	11 (22)	2 (4)	8 (17)	0
Diarrhea	12 (24)	2 (4)	6 (12)	1 (2)	8 (17)	1 (2)
AST increased	10 (20)	8 (16)	10 (20)	4 (8)	6 (13)	2 (4)
Upase Increased	7 (14)	6 (12)	6 (12)	3 (6)	8 (17)	4 (8)
Fatigue	9 (18)	1 (2)	6 (12)	0	5 (10)	0
ALT increased	8 (16)	4 (8)	7 (14)	3 (6)	4 (8)	0
Hypothyroidism	10 (20)	0	4 (8)	0	4 (8)	0
Rash maculo-papular	7 (14)	2 (4)	4 (8)	0	3 (6)	0
Decreased appetite	6 (12)	0	4 (8)	0	3 (6)	0
Malaise	6 (12)	1 (2)	3 (6)	0	3 (6)	0
Adrenal insufficiency	7 (14)	1 (2)	3 (6)	0	2 (4)	0
Nausea	5 (10)	0	4 (8)	0	1 (2)	0
Pyrexia	2 (4)	0	4 (8)	0	5 (10)	0

- Rates of any grade TRAEs:
  - 94% Arm A
  - 71% Arm B
  - 79% Arm C
- Types of TRAEs similar across all treatment arms

*NIVO1/IPI3 Q3W x 4 followed by nivolumab 240 mg IV Q2W flat dose; **NIVO3/IPI1 Q3W x 4 followed by nivolumab 240 mg IV Q2W flat dose.
Listed are adverse events that occurred in at least 10% of patients in either arm. Includes events reported between first dose and 30 days after last dose of study therapy.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IPI, ipilimumab; NIVO, nivolumab; TRAEs, treatment-related adverse events.
Adapted from Yau et al. *J Clin Oncol*. 2019; 37:4012-4012.

CheckMate-040: Nivolumab + Ipilimumab Immune-mediated Adverse Events

Summary of IMAEs	Arm A NIVO1/IPI3 Q3W* N = 49		Arm B NIVO3/IPI1 Q3W** N = 49		Arm C NIVO3 Q2W/IPI1 Q6W N = 48	
n(%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Rash	17 (35)	3 (6)	14 (29)	2 (4)	8 (17)	0
Hepatitis	10 (20)	10 (20)	6 (12)	5 (10)	3 (6)	3 (6)
Adrenal Insufficiency	9 (18)	2 (4)	3 (6)	0	3 (6)	0
Diarrhea/colitis	5 (10)	3 (6)	1 (2)	1 (2)	1 (2)	1 (2)
Pneumonitis†	5 (10)	3 (6)	0	0	0	0
Nephritis/renal dysfunction	0	0	1 (2)	0	1 (2)	1 (2)
Hypersensitivity	0	0	1 (2)	1 (2)	1 (2)	0
Hypophysitis	1 (2)	0	0	0	1 (2)	1 (2)
Hyperthyroidism	0	0	1 (2)	0	1 (2)	0
Hypothyroidism/ thryroiditis	0	0	0	0	1 (2)	0
Diabetes mellitus	0	0	0	0	0	0

- Most common IMAEs in all arms: rash, hepatitis, and adrenal insufficiency
- Arm A had higher rates of IMAEs compared with Arms B and C

*NIVO1/IPI3 Q3W x 4 followed by nivolumab 240 mg IV Q2W flat dose; **NIVO3/IPI1 Q3W x 4 followed by nivolumab 240 mg IV Q2W flat dose;
†Within 100 days after the final dose of study drug, 1 patient from Arm A died of a serious TRAE (grade 5 pneumonitis).
IMAEs are specific events considered as potential immune-mediated events by investigator occurring within 100 days of last dose, regardless of causality treated with immune-modulating medication.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IPI, ipilimumab; NIVO, nivolumab; TRAEs, treatment-related adverse events; IMAEs, immune-related adverse events.
Adapted from Yau et al. *J Clin Oncol*. 2019; 37:4012-4012.

KEYNOTE-224: Pembrolizumab Treatment-related Adverse Events

Treatment-related Adverse Events	Pembrolizumab (N = 104)
Any, n (%)	76 (73)
Serious TRAEs	16 (15)
Grade 3 TRAEs	25 (24)
Increased AST	7 (7)
Increased ALT	4 (4)
Fatigue	4 (4)
Grade 4 TRAEs	
Hyperbilirubinemia	1 (1)
Death	
Ulcerative esophagitis	1
Immune-mediated	
Hepatitis	3 (3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAEs, treatment-related adverse events.
Zhu et al. *Lancet Oncol*. 2018;19:940-952.

Immune Checkpoint Inhibitor–related Toxicities

Dermatologic	Maculopapular rash Pruritus Blistering disorder
Gastrointestinal	Diarrhea/colitis Hepatic toxicity Elevation in amylase/lipase Acute pancreatitis
Endocrine	Hyperglycemia/diabetes mellitus Thyroid Hypophysitis Adrenal insufficiency
Pulmonary	Pneumonitis
Renal	Elevated serum creatinine/acute renal failure
Ocular	Vision changes

Nervous System	Myasthenia gravis Guillain-Barre syndrome Peripheral neuropathy Aseptic meningitis Encephalitis Transverse myelitis
Cardiovascular	Myocarditis Pericarditis Arrhythmias Impaired ventricular function Conduction abnormalities
Musculoskeletal	Inflammatory arthritis Myalgias/myositis Polymyalgia rheumatica/giant cell arteritis

Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

Immune-related Adverse Events Guideline Recommendations

Guidelines for the management of immune-related adverse events have been developed:

- ASCO[1]
- ESMO[2]
- NCCN[3]
- SITC[4,5]

Grade	American Society of Clinical Oncology Clinical Practice Guideline (2018) Immune Checkpoint Inhibitor Therapy General Recommendations[1]
1	• Continued with close monitoring • Exception: some neurologic, hematologic, and cardiac toxicities
2	• Suspended for most, with consideration of resuming when symptoms revert to grade 1 or less • Corticosteroids may be administered
3	• Suspended • Initiation of high-dose corticosteroids - prednisone 1-2 mg/kg/d - methylprednisolone 1-2 mg/kg/d • Corticosteroids should be tapered over the course of at least 4-6 weeks • Some refractory cases may require infliximab or other immunosuppressive therapy
4	• Permanent discontinuation • Exception: endocrinopathies that have been controlled by hormone replacement

1. Brahmer et al. *J Clin Oncol*. 2018;36(17):1714-1768; 2. Haanen et al, 2017; 3. Thompson et al, 2019; 4. Puzanov et al, 2017; 5. Ernstoff et al, 2019.

NCCN Guidelines®
Routine Monitoring for Immune-Checkpoint Inhibitors

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Comprehensive pt history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening as indicated	Clinical exam at each visit with adverse event symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain magnetic resonance imaging if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork • CBC with differential • Comprehensive metabolic panel	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6-12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation Skin biopsy if indicated
Pancreatic • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis

BSA, body surface area; CBC, complete blood cell count; CT, computed tomography; TSH, thyroid-stimulating hormone; MRCP, magnetic resonance cholangiopancreatography; PFTs, pulmonary function tests.
[a]Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs).
[b]Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.
[c]After first four doses of immunotherapy, only as clinically indicated.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

NCCN Guidelines®
Routine Monitoring for Immune-Checkpoint Inhibitors (cont.)

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Thyroid • TSH, free thyroxine (T4)[c]	Every 4-6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 and free T4 if abnormal thyroid function suspected.
Adrenal/Pituitary • Adrenal: Serum cortisol (morning preferred)[c] • Pituitary: TSH, free thyroxine (T4)[c]	Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6-12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FISH), testosterone (males), estradiol (females), adrenocorticotropic hormone (ACTH)
Pulmonary • Oxygen saturation (resting and with ambulation) • PFTs for high-risk pts	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy if needed to exclude other causes.
Cardiovascular • Consider baseline electrocardiograph • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal • Joint examination/functional assessment as needed for pts with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine phosphokinase (CPK)

CT, computed tomography; PFTs, pulmonary function tests; TSH, thyroid-stimulating hormone.
[a]Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B).
[b]Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.
[c]After first four doses of immunotherapy, only as clinically indicated.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

NCCN Guidelines®
Immunotherapy: Healthcare Provider Information

Prior to Starting ICI Therapy
Assess patient's understanding of disease and recommendations for treatment
Educate patients about MOA and rationale for use of ICIs
Document any underlying medical conditions affecting any organ system (eg, pulmonary, cardiac, neurologic, musculoskeletal)
Take a history of any autoimmune diseases
Record all medications, including OTC medications and herbal supplements
Patients of reproductive age should be advised to use effective birth control during and for at least 5 months after final dose of ICI • Effect of ICI on human reproductive function is unknown • Consider fertility preservation and reproductive endocrinology referral
Breast feeding is contraindicated during and for at least 5 months after the final dose of ICI
Provide patient with and instruct them to carry a **wallet card** that outlines: • Type of ICI they are receiving • Potential irAEs • Contact numbers for their oncology health care team
Assess patient's ability to monitor and report potential irAEs. Engagement of caregiver may be necessary
Assess patient for potential for home care support service needs during therapy
Educate patient about potential toxicity profile of ICI therapy, including presenting symptoms and timing
Inform patient of existing educational resources (see following slide)

ICI, immune checkpoint inhibitor; MOA, mechanism of action; OTC, over the counter; irAE, immune-related adverse events.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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NCCN Guidelines®
Immunotherapy: Healthcare Provider Information

Instruct Patients to Notify Oncology Health Care Team If:
Any new signs or symptoms develop, including: • Severe fatigue • Headache • Rash • Cough • Shortness of breath • Chest pain • Abdominal bloating • Change in bowel pattern • Weight loss • Vision changes or eye pain • Severe muscle weakness • Severe muscle or joint pains • Mood changes Patients should monitor symptoms for at least 2 years following conclusion of ICI therapy
Patient is evaluated by other HCPs or admitted to hospital
Any new medications are prescribed
Prior to receiving any immunization or vaccinations

Inform Patient of Existing Educational Resources:	
Understanding Immunotherapy Side Effects	https://www.nccn.org/images/pdf/Immunotherapy_Infographic.pdf
Oncology Nursing Society Immunotherapy Wallet Cards	https://www.ons.org/sites/default/files/2019-01
Society for Immunotherapy of Cancer Understanding Cancer Immunotherapy	https://www.sitcancer.org/HigherLogic/System/DownloadDocumentFile.ashx?DocumentFileKey=567abb47-c7f1-2fa3-b008-053953020940&forceDialog=0#page=1&zoom=auto,-91,783
AIM with Immunotherapy	https://aimwithimmunotherapy.org

HCPs, healthcare providers; ICI, immune checkpoint inhibitor.

Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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NCCN Guidelines®
Immunotherapy: Healthcare Provider Information

Review patient medications for potential drug interactions (eg, QT prolongation) when administering agents to manage ICI-related toxicity

Toxicity Management	
Mild to moderate AEs	• Provide symptomatic management • Delay in ICI may be recommended if unclear if irAE is developing or until AEs resolve to grade 1 or pre-treatment baseline • Corticosteroids may be required if AE does not improve • If hormone replacement required: usually for lifetime & may continue beyond completion of ICI
Severe AEs	• Discontinue ICI • Initiate corticosteroid therapy immediately • IV methylprednisolone should be considered until evidence of improvement in toxicity • Additional immunosuppressant therapy may be required for steroid-refractory AEs • Inpatient care and additional supportive care may be required
Supportive care during immunosuppressant therapy may include:	• Monitoring of blood glucose levels • PPIs or H2 blockers to prevent gastritis • Antimicrobial and antifungal prophylaxis to prevent opportunistic infections • Vitamin D and calcium supplementation to prevent osteoporosis

AEs, adverse events; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; PPIs, proton pump inhibitors.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

NCCN Guidelines®: Immunotherapy Patient Education

Immunotherapy Background	• One of the functions of the immune system is to distinguish healthy cells from abnormal cells • Tumor cells have proteins on their surface that bind to immune cells, blocking ability of immune cells to recognize them as foreign • ICIs are a class of medications that prevent tumors from “hiding” or “evading” the body’s natural immune system • ICIs block these proteins, “releasing the brakes” on the immune system’s WBCs • ICI therapy may be given in combination with other ICIs, chemotherapy, or targeted therapy
Side Effects	• AEs from ICI differ from those of other types of cancer treatment • Can affect one or several different organ systems • Amplifying immune system can cause T cells to attack healthy cells in the body, causing inflammatory conditions that mimic a range of autoimmune conditions, some can be serious. Known as irAEs • irAEs can occur at any time during treatment or after treatment is completed • irAE rebound during steroid taper can also occur, which may impact steroid taper • Severity of AEs can range from asymptomatic to severe or life-threatening; may be cumulative over the course of therapy • Combination therapy may increase severity of AEs

Educational efforts must consider patient’s primary language and literacy level

Education should be provided at start of therapy and at regular intervals as the trajectory of irAEs is variable

Reinforcement of educational concepts is essential

AEs, adverse events; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; WBC, white blood cells.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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NCCN Guidelines®: Immunotherapy Patient Education

Monitoring and Treatment Response

• Therapy with ICI requires close communication between patient/family and treating center
• Symptoms that patients may think are unrelated are often signs of ICI toxicity
  ○ Diarrhea or nausea
• Educate patients to notify all HCPs (esp. PCPs) that they are receiving/have received immunotherapy
• Regular monitoring will be conducted to detect any potential irAEs and to assess treatment response
• Laboratory tests should be obtained prior to each treatment and at regular intervals after completion of immune checkpoint blockade to assess for organ function
  ○ Complete metabolic panel; kidney, liver, thyroid, pancreas
• Physical exams will include monitoring of organ function
  ○ Cardiac, pulmonary, neurologic, skin
• Assess for significant shifts in weight, as they may be indicative of fluid balance disorders
• Treatment response time differs from standard cancer therapy; may take longer to see a response
• Most irAEs can be managed effectively if detected and treated early

HCPs healthcare professionals; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; PCPs, primary care providers.

Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Discussion Topics

- Common immune-related adverse events and patterns generally associated with checkpoint blockade
- Early identification, monitoring, and management of immune-related adverse events so that patients can remain on therapy and derive optimal benefit
- Managing adverse events with combination approaches—What are the nuances?
- Specific issues relevant to the hepatocellular carcinoma population: cirrhosis, hepatitis, ethnic disparities, etc

Multidisciplinary Care and Interprofessional Collaboration in Hepatocellular Carcinoma

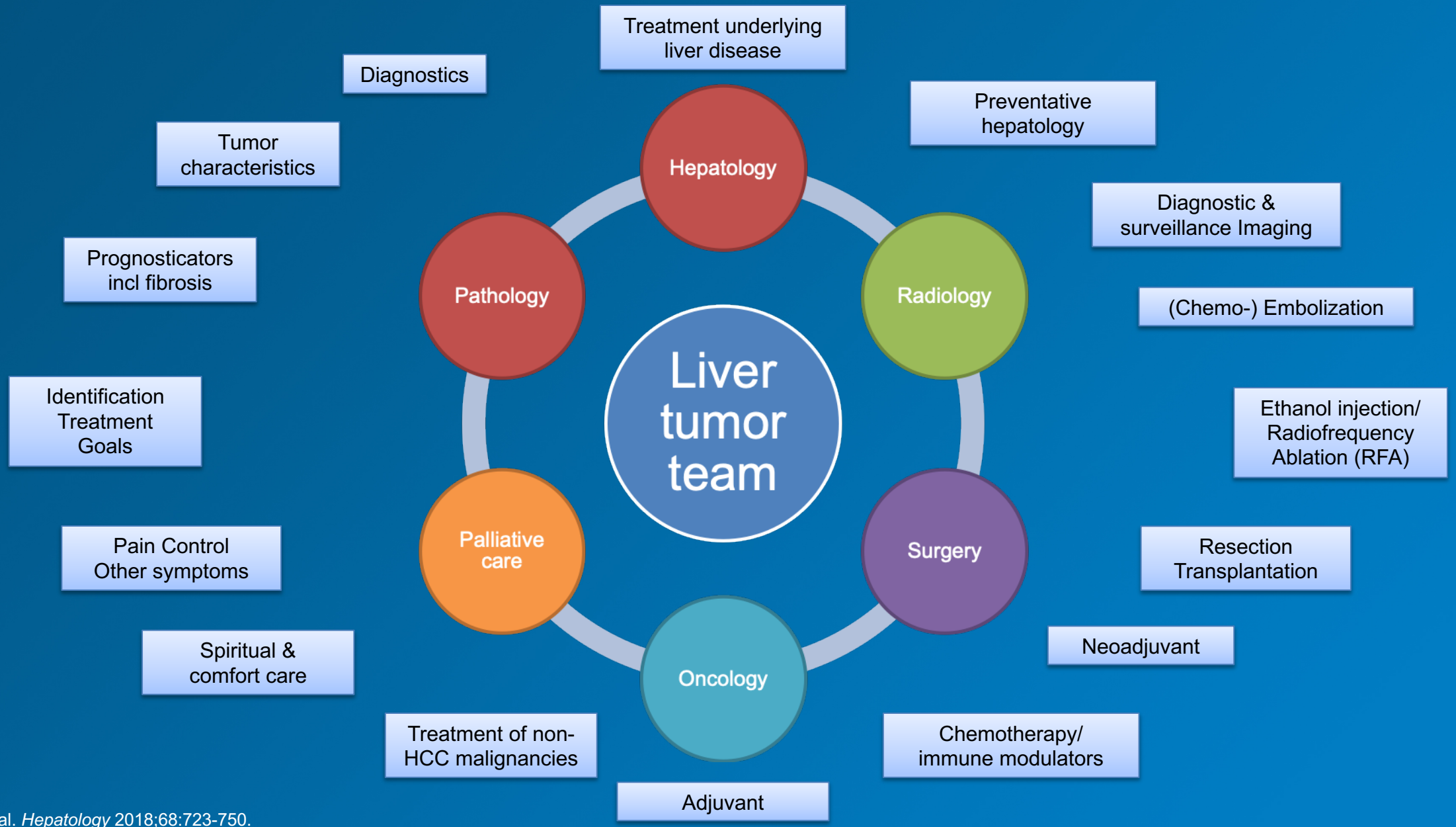
Multidisciplinary Approach

- Multidisciplinary management of HCC:
  - Can ensure accurate and timely screening, early detection, diagnosis, staging, treatment referral/consultation
  - Can ensure that treatment plans are evidence-based and personalized for individual patients
  - Can be effective in improving patient survival
- Includes specialists with varying roles who are essential to maximizing patient outcomes, improving care coordination, and effectively managing the complexities of HCC
- Communication and collaboration through a multidisciplinary approach is vital to the treatment and management of hepatocellular carcinoma, underlying liver disease, and adverse events
- Multidisciplinary tumor boards assist in:
  - Guiding treatment planning
  - Improving coordination of care across disciplines
  - Contribute to better patient outcomes
- A multidisciplinary approach to the treatment and management of HCC should be standard of care

HCC, hepatocellular carcinoma.

Agarwal et al. *J Clin Gastroenterol*. 2017;51:845-849. Yopp et al. *Ann Surg Oncol*. 2013;21:1287-1295. 2013; Siddique et al. *J Multidiscip Healthcare* 2017;10:95-100.

Management of HCC: Multidisciplinary Team



Marrero et al. *Hepatology* 2018;68:723-750.

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Multidisciplinary Care Can Be Achieved In Multiple Formats

- Goal is facilitating input from different provider types to promote efficient communication and transitions of care
- Different potential formats
  - Same-day, single-visit format: Patients seen by multiple providers from different specialties
  - Multidisciplinary conference: Patients discussed in conference and then referred to appropriate provider
  - Virtual: Patients discussed via teleconference, particularly areas with limited subspecialty availability

Multidisciplinary Care Improves HCC Outcomes

Study	No. of Patients	Description	Outcomes
Sinn 2019	6,619	Single day MDT conference	Improves survival
Serper 2017	3,988	Multi-specialty evaluation or tumor board	Increases HCC treatment receipt and improves survival
Yopp 2014	355	Single day MDT clinic and conference	Improves early detection, curative treatment, time to treatment, and survival
Zhang 2013	343	Single day MDT clinic	Changes imaging/pathology interpretation and therapy plan
Chang 2008	183	Fluid referrals and joint conference	Improves early detection, curative treatment, and survival

MDT, multidisciplinary team.

Serper et al. *Gastroenterology* 2017;152:1954-1964; Yopp et al *Ann Surg Oncol*. 2014;21:1287-1295; Chang et al *HPB (Oxford)* 2008;10:405-411; Zhang et al *Curr Oncol* 2013;20:e123-e131.

Multidisciplinary Care Associated With Improved Survival

Variable (N = 3,988)	HR (95% CI)
BCLC stage (vs BCLC 0)	
A	1.13 (0.94-1.36)
B	1.63 (1.36-1.96)
C	2.50 (2.05-3.05)
Child Pugh B	1.5 (1.37-1.64)
Type of HCC therapy	
Liver transplant	0.22 (0.16-0.31)
Resection	0.38 (0.28-0.52)
Ablation	0.63 (0.52-0.76)
Transarterial therapies	0.83 (0.74-0.92)
Systemic therapies	1.99 (1.80-2.20)
MDC tumor board	0.83 (0.77-0.90)
Specialist within 1 month	
Hepatology	0.70 (0.63-0.78)
Medical oncology	0.82 (0.74-0.91)
surgery	0.79 (0.71-0.89)

- Cohort study of national VA from Jan 2008 to Dec 2014
- Multi-specialty evaluation was associated with HCC therapy (HR 1.60, 95% CI 1.15-2.21)
- Review by MDC tumor board was associated with reduced mortality (HR 0.83, 95% CI 0.77-0.90)

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; MDC, multidisciplinary committee.
Serper et al. *Gastroenterology* 2017;152:1954-1964

HCC and Cirrhosis

- Approximately 80% of patients diagnosed with HCC have preexisting cirrhosis
  - Caused by hepatitis B virus, hepatitis C virus, alcohol, and nonalcoholic fatty liver disease
- Added complication of underlying chronic liver disease and cirrhosis underscores the importance of coordinated care for optimal HCC management
- Spotlight: hepatologists in HCC care
  - Diagnosis and referral
  - Management of underlying cirrhotic disease

"It is important to reiterate that the management of patients with HCC is complicated by the presence of underlying liver disease. Furthermore, differences in the etiologies of HCC and their effects on the host liver may impact treatment response and outcome. These complexities make treatment decisions in patients with HCC challenging and are the reason for multidisciplinary care with the involvement of hepatologists, cross-sectional radiologists, interventional radiologists, transplant surgeons, pathologists, medical oncologists, and surgical oncologists, thereby requiring careful coordination of care" (Benson et al, 2020).

HCC, hepatocellular carcinoma.

Marrero et al. *Hepatology* 2018;68:723-750.
Benson et al. NCCN Guidelines Hepatobiliary Cancers. Version 5.2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

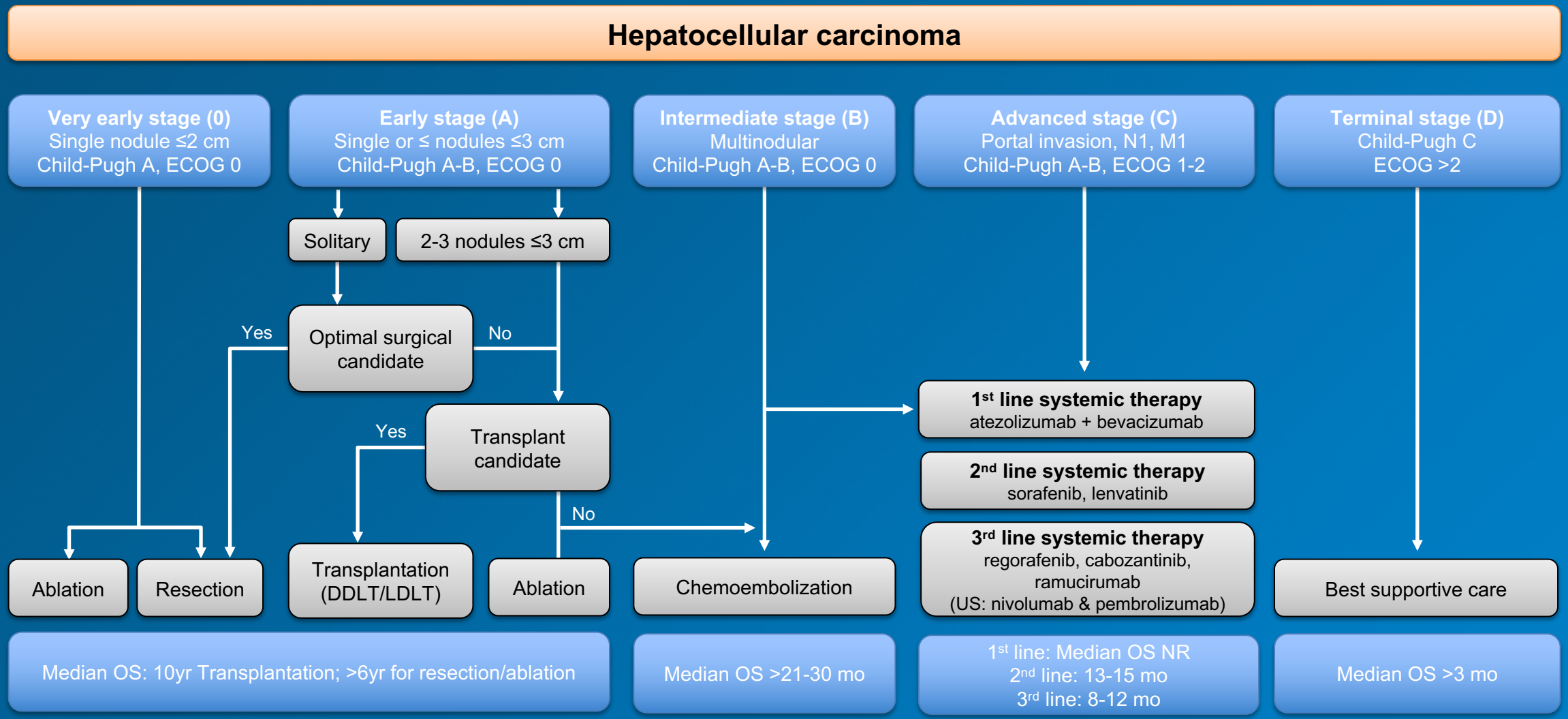
Key Takeaways

- After nearly a decade, 4 positive phase 3 studies have resulted in FDA approval of 4 new drugs in HCC that improve survival
  - Lenvatinib non-inferior to sorafenib, HR 0.92
  - Regorafenib vs placebo, second line, HR 0.62
  - Cabozantinib vs placebo, second and third line (HR 0.70 prior sorafenib)
  - Ramucirumab vs placebo, second line, high AFP
- For the first-time, there is a highly active regimen that is superior to sorafenib first-line (practice changing)
- Level 1 Evidence for single agent checkpoint inhibitors?
  - Nivolumab vs sorafenib first-line: did not meet endpoint
  - Pembrolizumab vs placebo second-line: did not meet stats
- Ongoing studies looking at novel combinations
  - Checkpoint inhibitors and TKIs
  - PD-1+ CTLA-4

Immunotherapy	Trial	FDA Approval
First-Line		
Atezolizumab + bevacizumab	IMbrave150	May 2020: FDA approved for patients with unresectable or metastatic HCC who have not received prior systemic therapy
Second-line		
Nivolumab	CheckMate-040	Sept 2017: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib
Pembrolizumab	KEYNOTE-224	Nov 2018: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib
Nivolumab + ipilimumab	CheckMate-040	March 2020: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib

AFP, alpha fetoprotein; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; FDA, US Food & Drug Administration; HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; TKIs, tyrosine kinase inhibitors.

Treatment Strategy in the Management of HCC 2020



ECOG, Eastern Cooperative Oncology Group; OS, overall survival.

Adapted from Llovet et al. *Hepatology* 2020 May 20. doi: 10.1002/hep.31327. Online ahead of print.

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Multidisciplinary Perspectives in Advanced HCC:

A Focus on Immune Checkpoint Inhibitors