Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Hepatocellular Carcinoma

Wednesday, January 27, 2021
5:00 PM – 6:30 PM ET

Faculty

Richard S Finn, MD
Tim Greten, MD
James J Harding, MD
Ahmed Omar Kaseb, MD, CMQ

Moderator

Neil Love, MD

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Faculty

Richard S Finn, MD
Professor, Department of Medicine
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David Geffen School of Medicine at UCLA
Director
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Jonsson Comprehensive Cancer Center at UCLA
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Tim Greten, MD
Bethesda, Maryland

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Professor and Director
Hepatocellular Carcinoma Program
Co-Director, MD Anderson HCC SPORE
Editor-in-Chief, *Journal of Hepatocellular Carcinoma*
Department of Gastrointestinal Medical Oncology
The University of Texas
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Houston, Texas

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, and Merck.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seagen Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

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Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Finn — Disclosures

Consulting Agreements	Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, CStone Pharmaceuticals, Genentech, a member of the Roche Group, Lilly, Merck, Pfizer Inc
Contracted Research	Bristol-Myers Squibb Company, Eisai Inc, Genentech, a member of the Roche Group, Lilly, Merck, Pfizer Inc
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

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Dr Greten — Disclosures

No relevant conflicts of interest to disclose

Dr Harding — Disclosures

Consulting Agreements	Bristol-Myers Squibb Company, CytomX Therapeutics, Eisai Inc, Exelixis Inc, Imvax, Lilly, Merck
Contracted Research	Bristol-Myers Squibb Company
Data and Safety Monitoring Board/Committee	Merck

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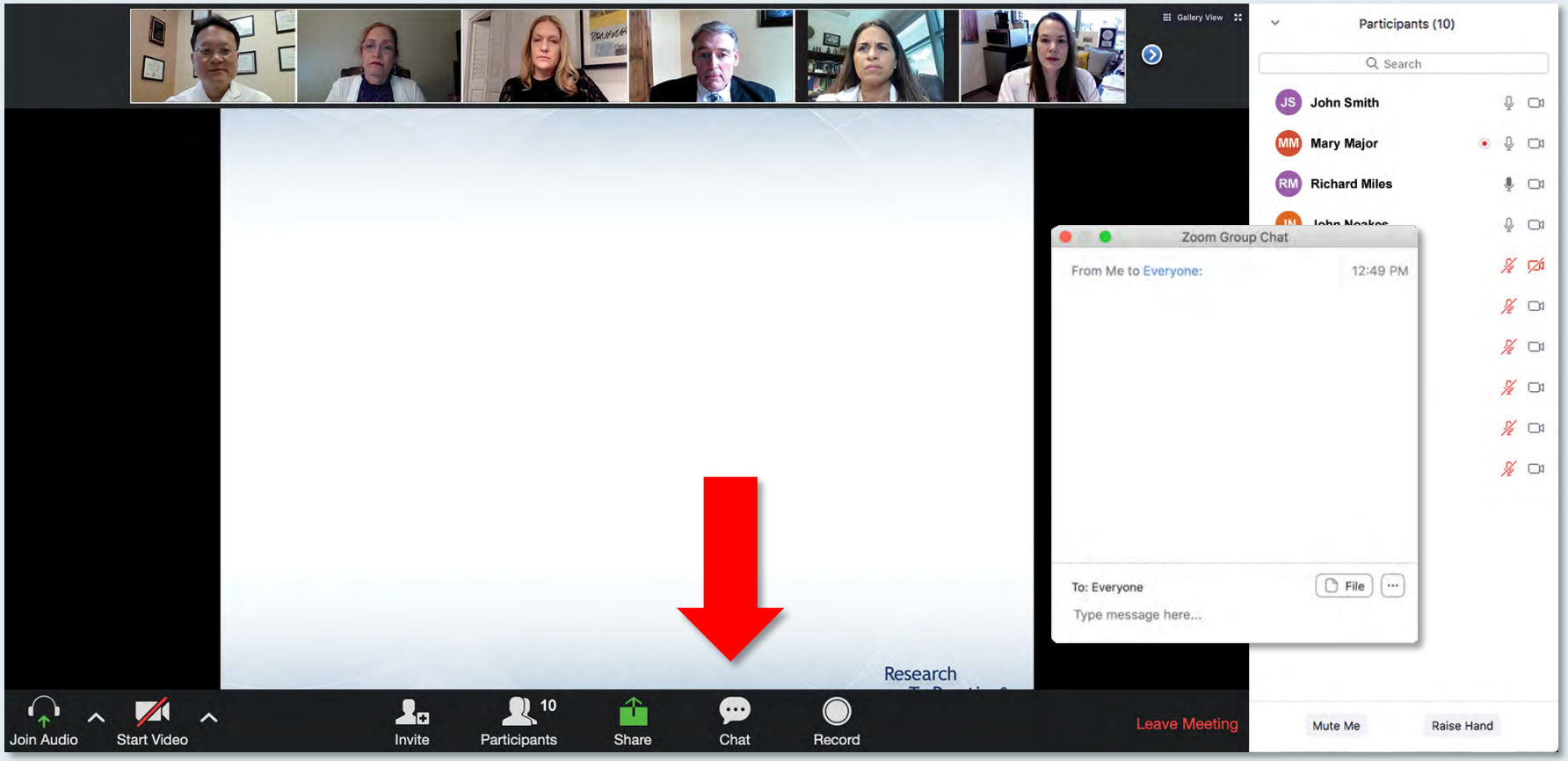
Dr Kaseb — Disclosures

Advisory Committee and Consulting Agreements	Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group
Contracted Research	Adaptimmune, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Hengrui Therapeutics Inc

We Encourage Clinicians in Practice to Submit Questions



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Familiarizing Yourself with the Zoom Interface

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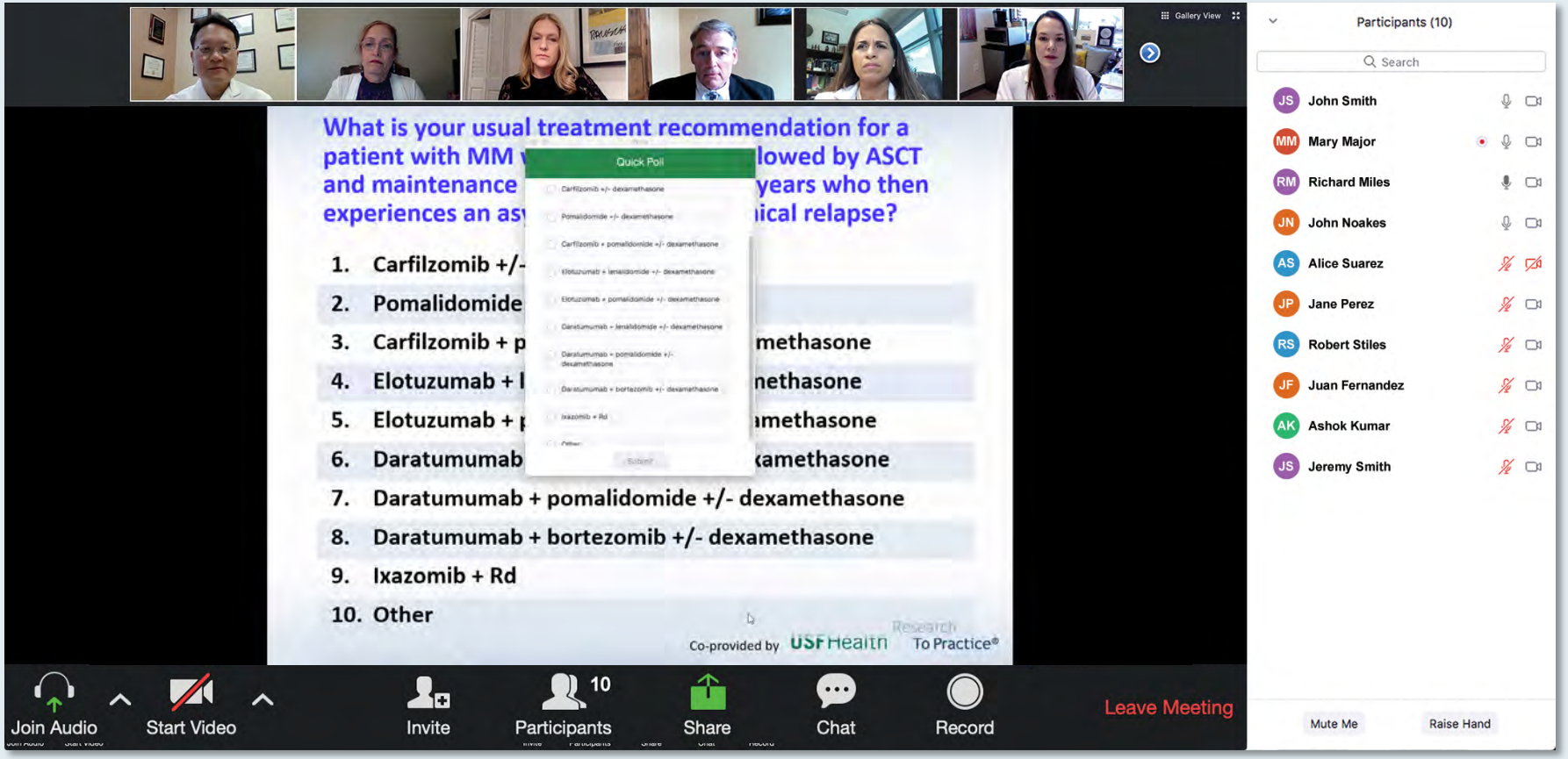

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WITH DR NEIL LOVE

Key Recent Data Sets in Gastrointestinal Cancers

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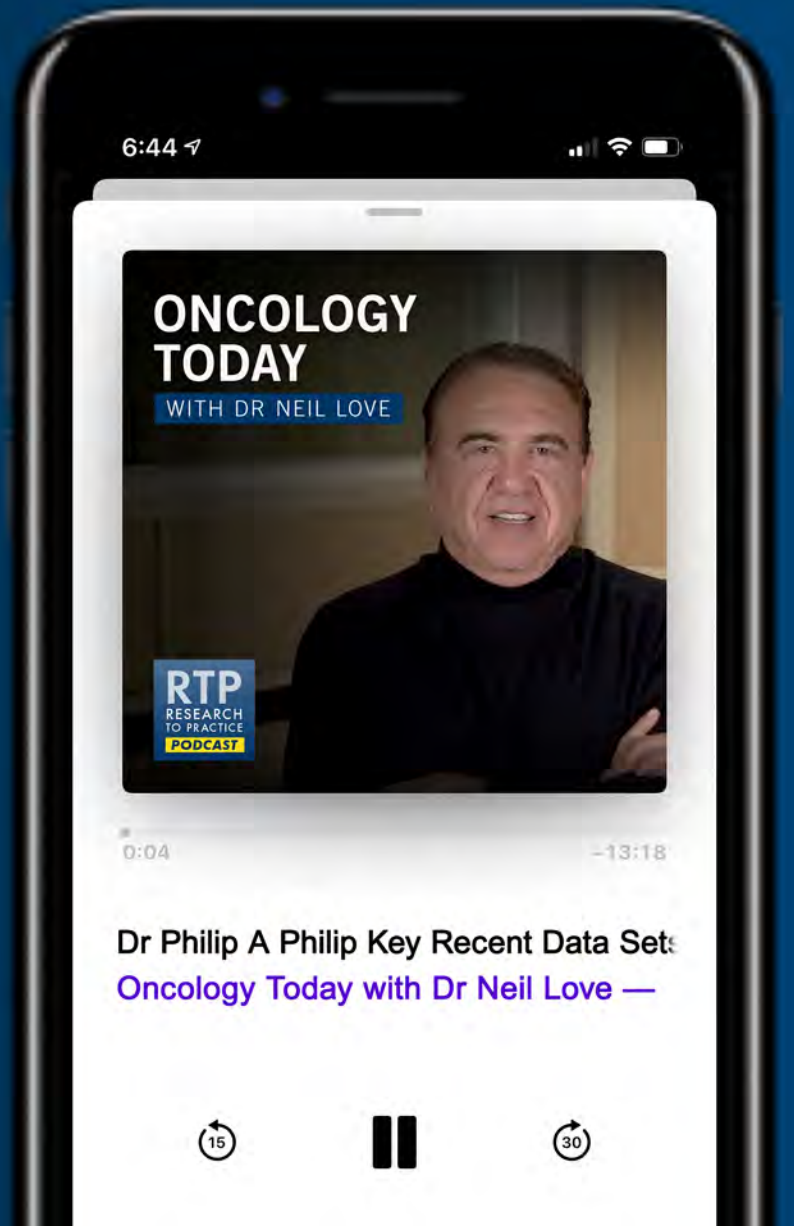

Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Multiple Myeloma

Thursday, January 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Rafael Fonseca, MD
Jonathan L Kaufman, MD

Moderator

Neil Love, MD

RTP Year in Review 2020

Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Bladder Cancer and Renal Cell Carcinoma

Tuesday, February 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Sumanta K Pal, MD
David I Quinn, MBBS, PhD

Moderator

Neil Love, MD

RTP Year in Review 2020

Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62nd ASH Annual Meeting

Part 2 — Hodgkin and Non-Hodgkin Lymphoma

Wednesday, February 3, 2021
5:00 PM – 6:00 PM ET

Faculty

John Kuruvilla, MD
John P Leonard, MD
Michael E Williams, MD, ScM

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Gastroesophageal Cancers (Part 2 of a 3-Part Series)

Thursday, February 4, 2021
5:00 PM – 6:30 PM ET

Faculty

Daniel Catenacci, MD
Yelena Y Janjigian, MD
Rutika Mehta, MD, MPH
Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

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Meet The Professor
Management of Lung Cancer

Friday, February 5, 2021
12:00 PM – 1:00 PM ET

Faculty

Joshua Bauml, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.


6 5 0
15 2 0
18 8 3
22 4 0
20 10 2
16 6 0
11 5 1
2 2 0


A woman in her early 70s with Child-Pugh B multifocal HCC
Child-Pugh B multifocal HCC (largest tumor 7 cm)
AFP = 2,500
Localized interventional radiation treatment for dominant mass
Sorafenib x 5 months → disease progression
Hand-foot syndrome, dose reduction
Dr Park


CELESTIAL: Overall Survival
CELESTIAL: Overall Survival


Coke
Nutrition Facts
Calories 0

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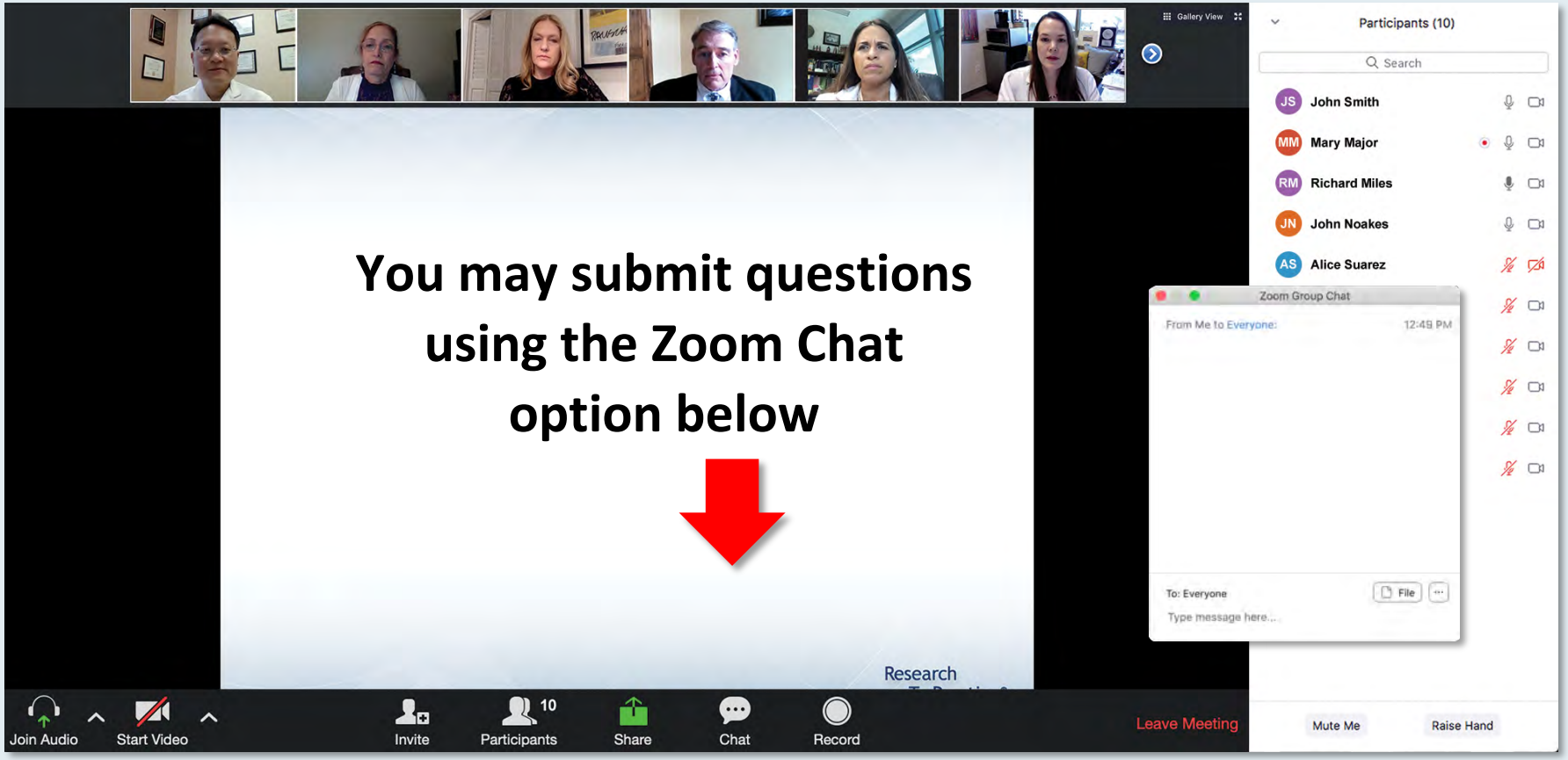

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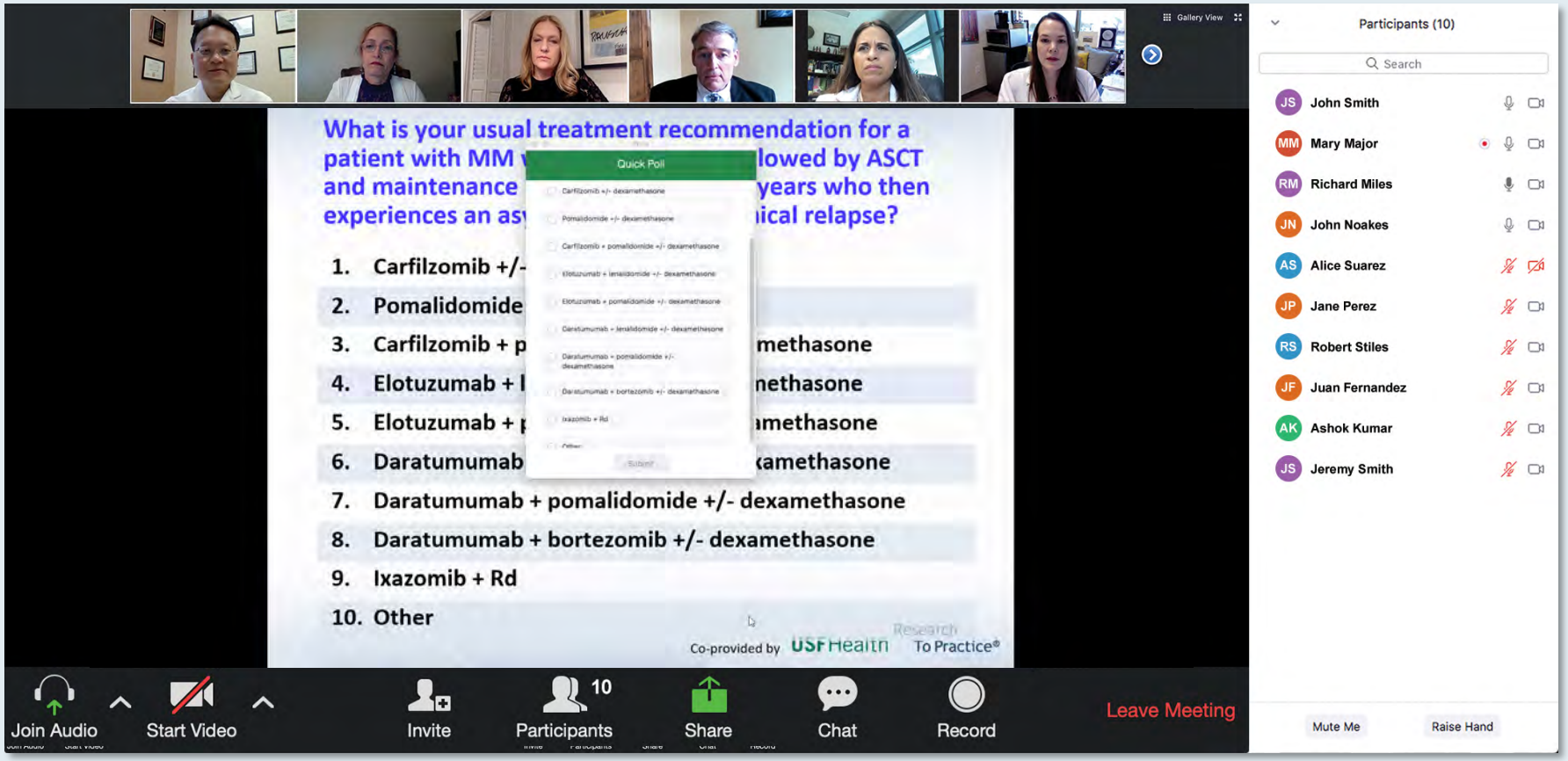

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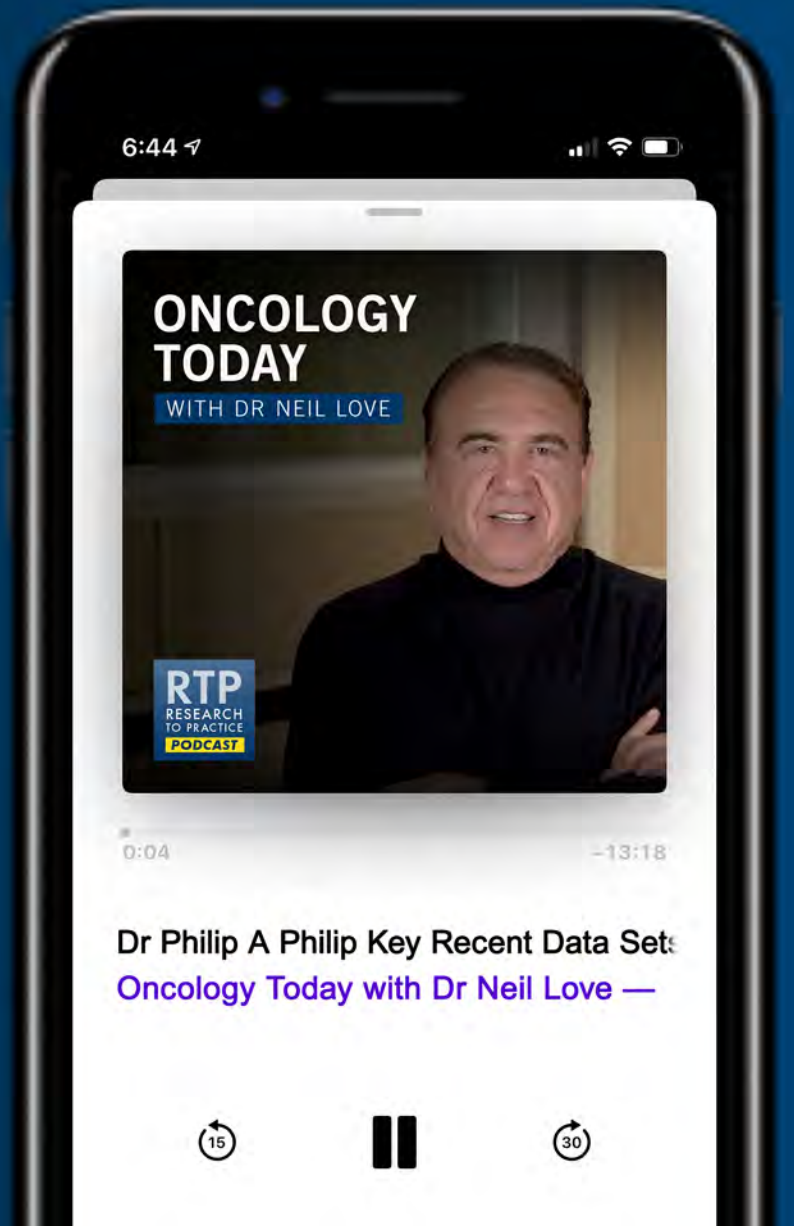

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Medical Director, Oncology Clinical Research
Chairman, Cancer Committee
Memorial Healthcare System
Clinical Associate Professor
Florida International University Herbert Wertheim College of Medicine
Hollywood, Florida

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Vikas Malhotra, MD
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Cleveland Clinic Akron General Medical Center
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Syed F Zafar, MD
Hematologist and Medical Oncologist
Florida Cancer Specialists and Research Institute
Chief, Division of Hematology and Oncology
Lee Health
Fort Myers, Florida

Nasfat Shehadeh, MD
Medical Oncologist
Oncology Specialists of Charlotte, PA
Charlotte, North Carolina

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Agenda

Module 1: Front-Line Management Options for Advanced Hepatocellular Carcinoma (HCC) – Dr Kaseb

Module 2: Selection and Sequencing of Treatment for Patients with Relapsed HCC – Dr Greten

Module 3: Considerations for the Treatment of HCC in Special Patient Populations – Dr Harding

Module 4: New Directions in the Management of HCC – Dr Finn

Case Presentation – Dr Brenner: An 84-year-old man with advanced Child-Pugh A5 HCC

Warren Brenner, MD

- 10/2019: Diagnosed with Child-Pugh A5 HCC, with cirrhotic liver most likely due to steatohepatitis
  - PMH: Hypertension treated with medication
- 11/2019: Radiofrequency ablation
- 9/2020: Recurrent disease treated with cryoablation
- 12/2020: Progressive disease
- Atezolizumab/bevacizumab
  - Currently receiving 4 medications to control hypertension (Systolic ~150 mm Hg)

Case Presentation – Dr Brenner: An 84-year-old man with advanced Child-Pugh A5 HCC (cont)

Warren Brenner, MD

Questions

- Is atezolizumab/bevacizumab now considered the standard up-front therapy for patients with advanced HCC who have maintained liver functioning? Is there any concern for giving bevacizumab in patients who have baseline low platelets (ie, 50-70)?
- Is there still a role for doing any genetic testing of HCC?
- Is there any data regarding PD-L1 staining and response to immunotherapy?

ASCO special articles

Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline

John D. Gordan, MD, PhD[1]; Erin B. Kennedy, MHSc[2]; Ghassan K. Abou-Alfa, MD, MBA[3]; Muhammad Shaalan Beg, MD, MS[4]; Steven T. Brower, MD[5]; Terence P. Gade, MD, PhD[6]; Laura Goff, MD[7]; Shilpi Gupta, MD[8]; Jennifer Guy, MD[9]; William P. Harris, MD[10]; Renuka Iyer, MD[11]; Ishmael Jaiyesimi, DO, MS[12]; Minaxi Jhawer, MD[13]; Asha Karippot, MD[14]; Ahmed O. Kaseb, MD[15]; R. Kate Kelley, MD[1]; Jennifer J. Knox, MD, MS[16]; Jeremy Kortmansky, MD[17]; Andrea Leaf, MD[18]; William M. Remak, MT[19]; Rachna T. Shroff, MD, MS[20]; Davendra P.S. Sohal, MD, MPH[21]; Tamar H. Taddei, MD[22]; Neeta K. Venepalli, MD, MBA[23]; Andrea Wilson, MFA[24]; Andrew X. Zhu, MD, PhD[25]; and Michal G. Rose, MD[26]

J Clin Oncol 2020;38:4317-45.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Summary of Recommendations – ASCO Guidelines, 2020

First-Line Therapy

Recommendation 1.1

Atezolizumab-bevacizumab may be offered as first-line treatment for most patients with advanced HCC, Child-Pugh class A, ECOG PS 0-1 and following management of esophageal varices, when present, according to institutional guidelines.

Recommendation 1.2

Where there are contraindications to atezolizumab and/or bevacizumab, tyrosine kinase inhibitors **sorafenib or lenvatinib** may be offered as first-line treatment for patients with advanced HCC, Child-Pugh class A, and ECOG PS 0-1.

ASCO Guidelines

Courtesy of Ahmed Omar Kaseb, MD, CMQ

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investigators*

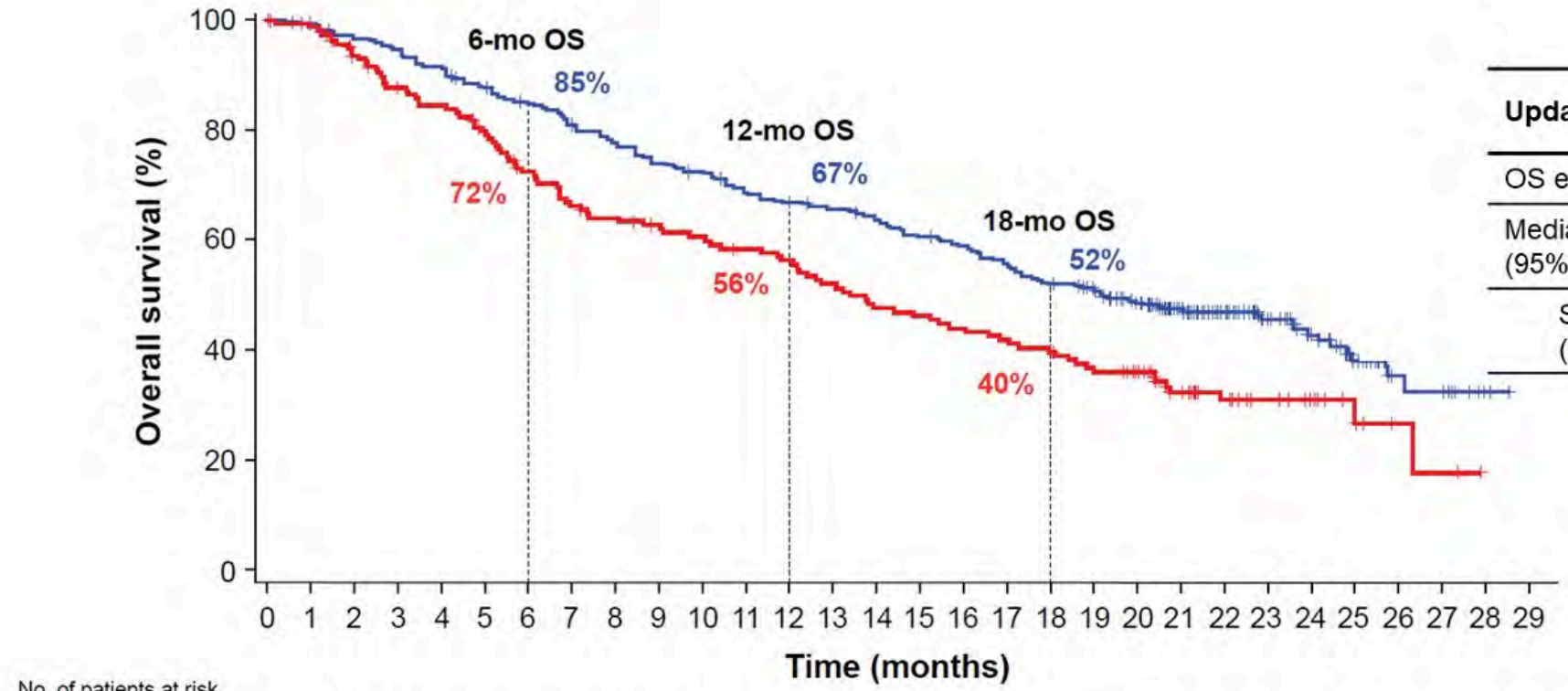
Courtesy of Richard S Finn, MD

IMbrave150: Updated Overall Survival (OS) Data from a Global, Randomized, Open-Label Phase III Study of Atezolizumab (atezo) + Bevacizumab (bev) versus Sorafenib (sor) in Patients (pts) with Unresectable Hepatocellular Carcinoma (HCC)

Finn RS et al.

Gastrointestinal Cancers Symposium 2021;Abstract 267.

IMbrave150: Updated Overall Survival



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Finn RS et al. Gastrointestinal Cancers Symposium 2021;Abstract 267.

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Future ONCOLOGY

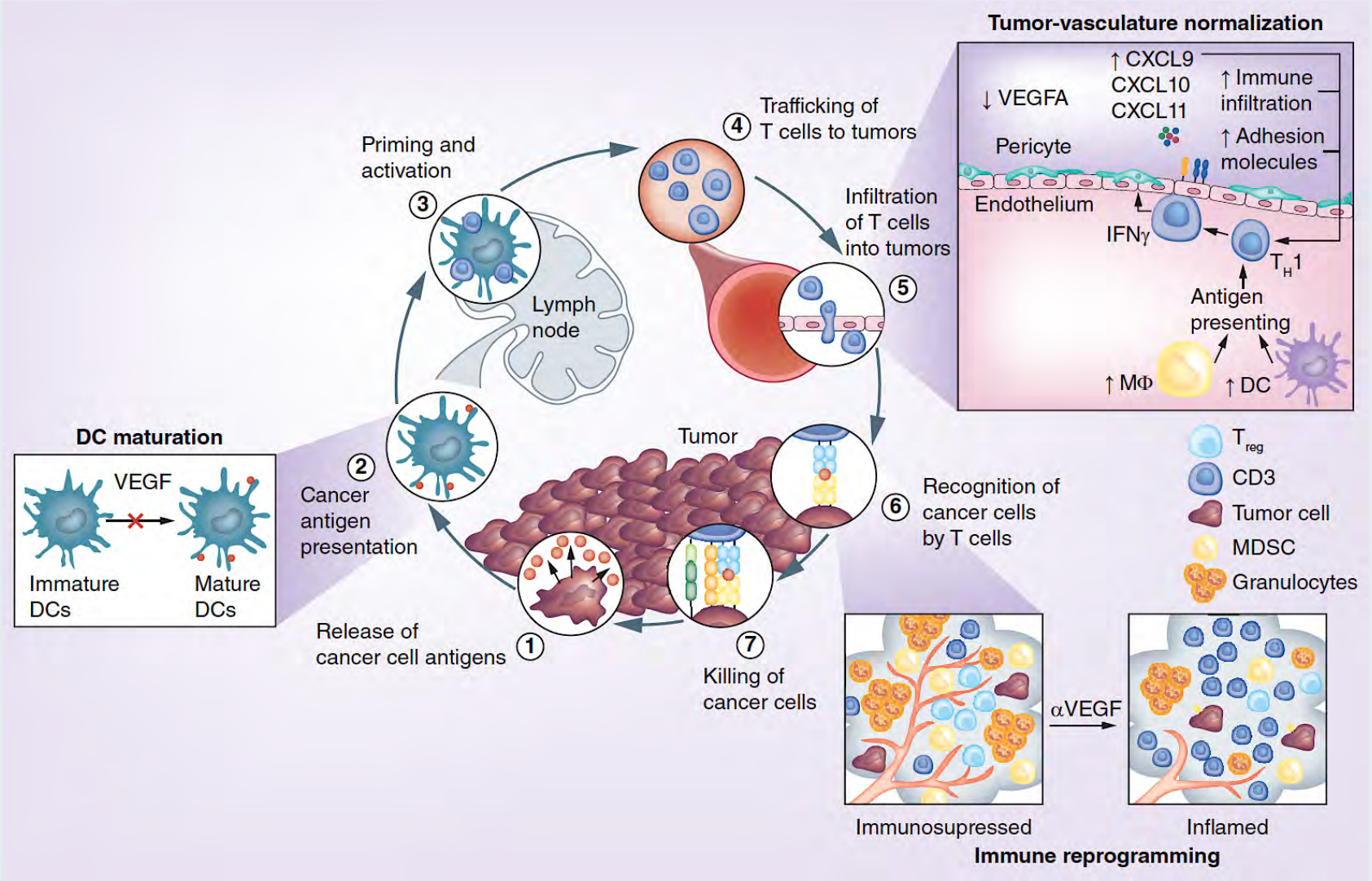
Clinical Trial Protocol

IMbrave 050: a Phase III trial of atezolizumab plus bevacizumab in high-risk hepatocellular carcinoma after curative resection or ablation

Stephen P Hack*,[1], Jessica Spahn[1], Minshan Chen[2], Ann-Lii Cheng[3], Ahmed Kaseb[4], Masatoshi Kudo[5], Han Chu Lee[6], Adam Yopp[7], Pierce Chow[8] & Shukui Qin[9]

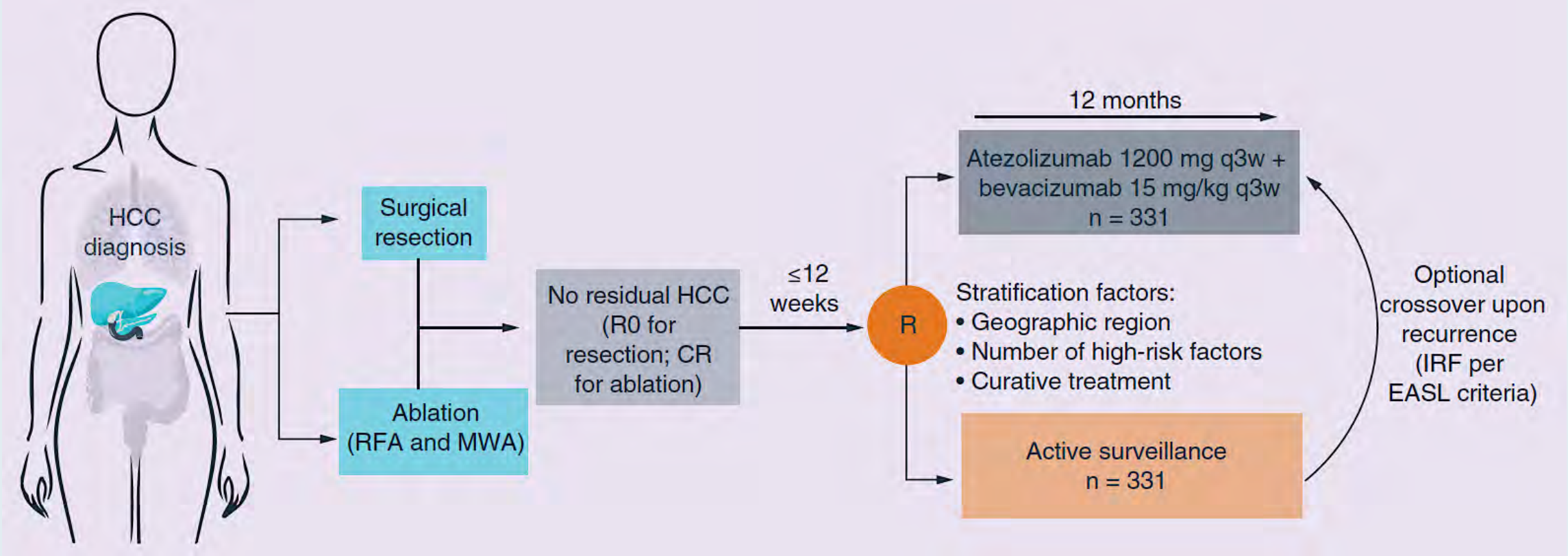
Future Oncol 2020;16(15):975-89.

Interaction Between VEGF and the Cancer Immunity Cycle



Hack SP et al. *Future Oncol* 2020;16(15):975-89.

IMbrave 050 Study Design

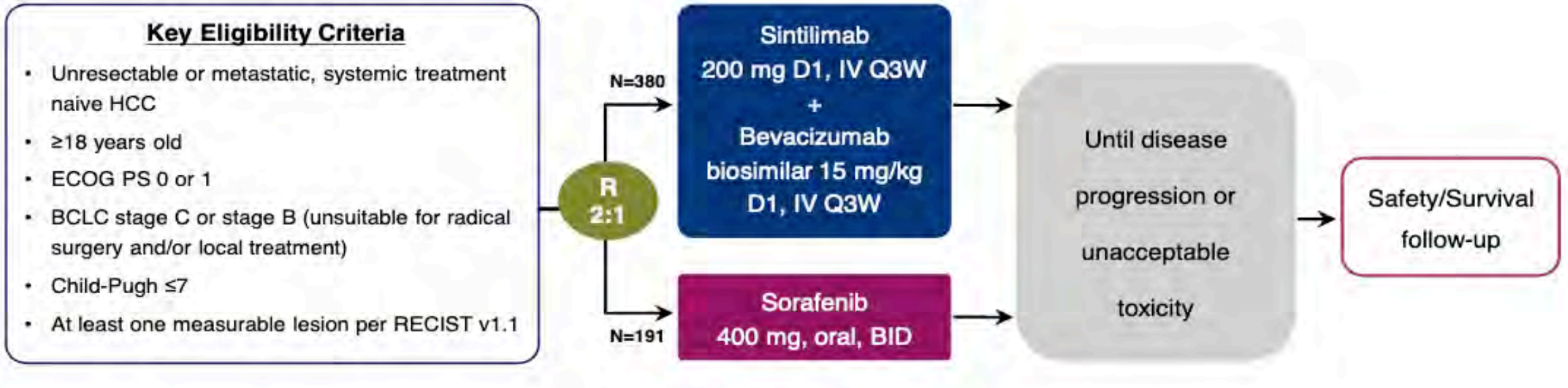


Hack SP et al. *Future Oncol* 2020;16(15):975-89.

Sintilimab plus Bevacizumab Biosimilar vs Sorafenib as First-Line Treatment for Advanced Hepatocellular Carcinoma (ORIENT-32)

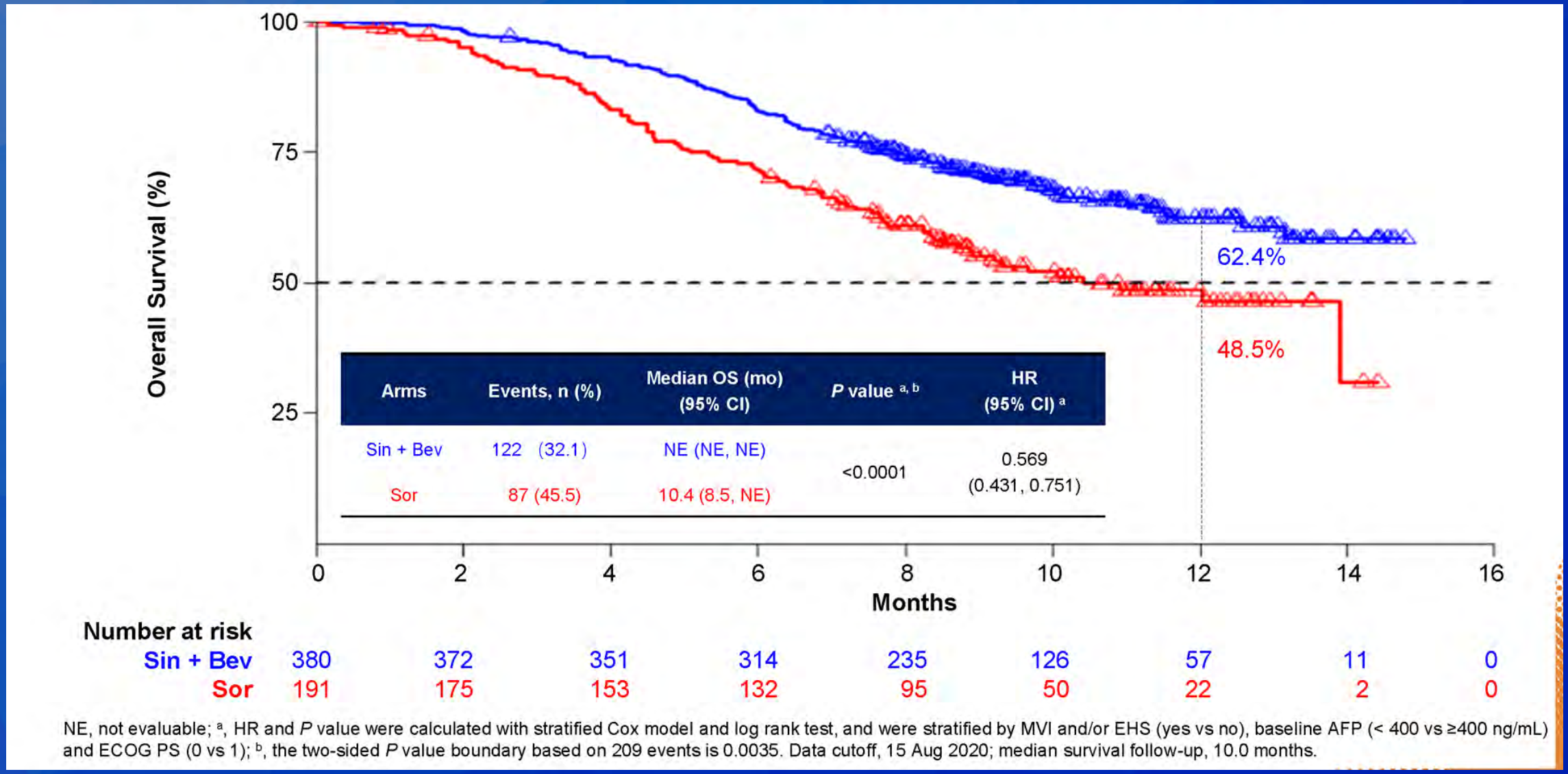
Ren Z et al. ESMO Asia 2020;Abstract LBA2.

Phase III ORIENT-32 Trial of Sintilimab plus Bevacizumab Biosimilar vs Sorafenib as First-Line Therapy for Advanced HCC



Ren Z et al. ESMO Asia 2020;Abstract LBA2.

ORIENT-32 Coprimary Endpoint: Overall Survival



Arms	Events, n (%)	Median OS (mo) (95% CI)	*P* value [a, b]	HR (95% CI) [a]
Sin + Bev	122 (32.1)	NE (NE, NE)	<0.0001	0.569 (0.431, 0.751)
Sor	87 (45.5)	10.4 (8.5, NE)		

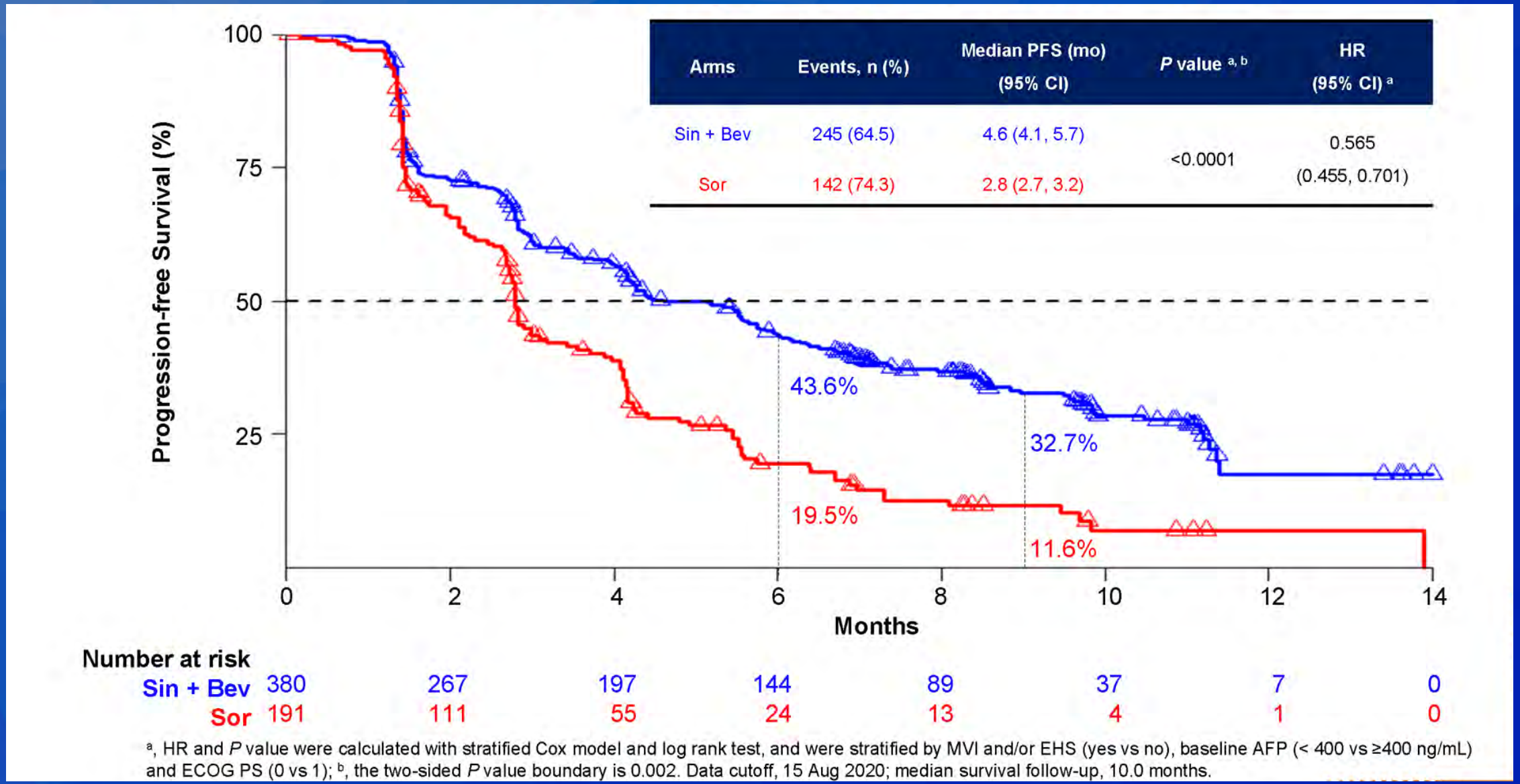
Number at risk									
Sin + Bev	380	372	351	314	235	126	57	11	0
Sor	191	175	153	132	95	50	22	2	0

NE, not evaluable; [a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary based on 209 events is 0.0035. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior OS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

ORIENT-32 Coprimary Endpoint: Progression-Free Survival

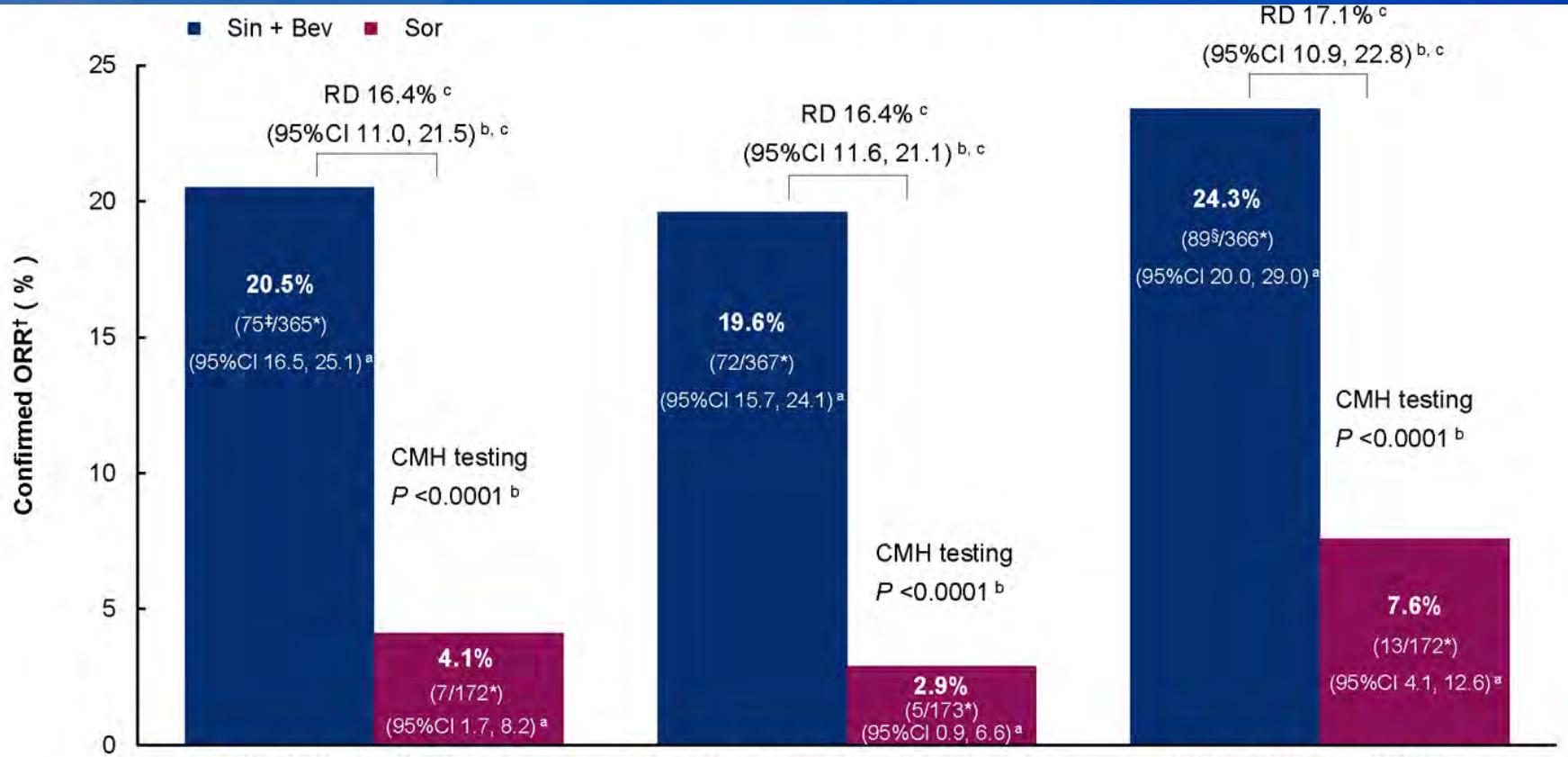


[a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary is 0.002. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior PFS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

ORIENT-32: Response Rate and Duration of Response



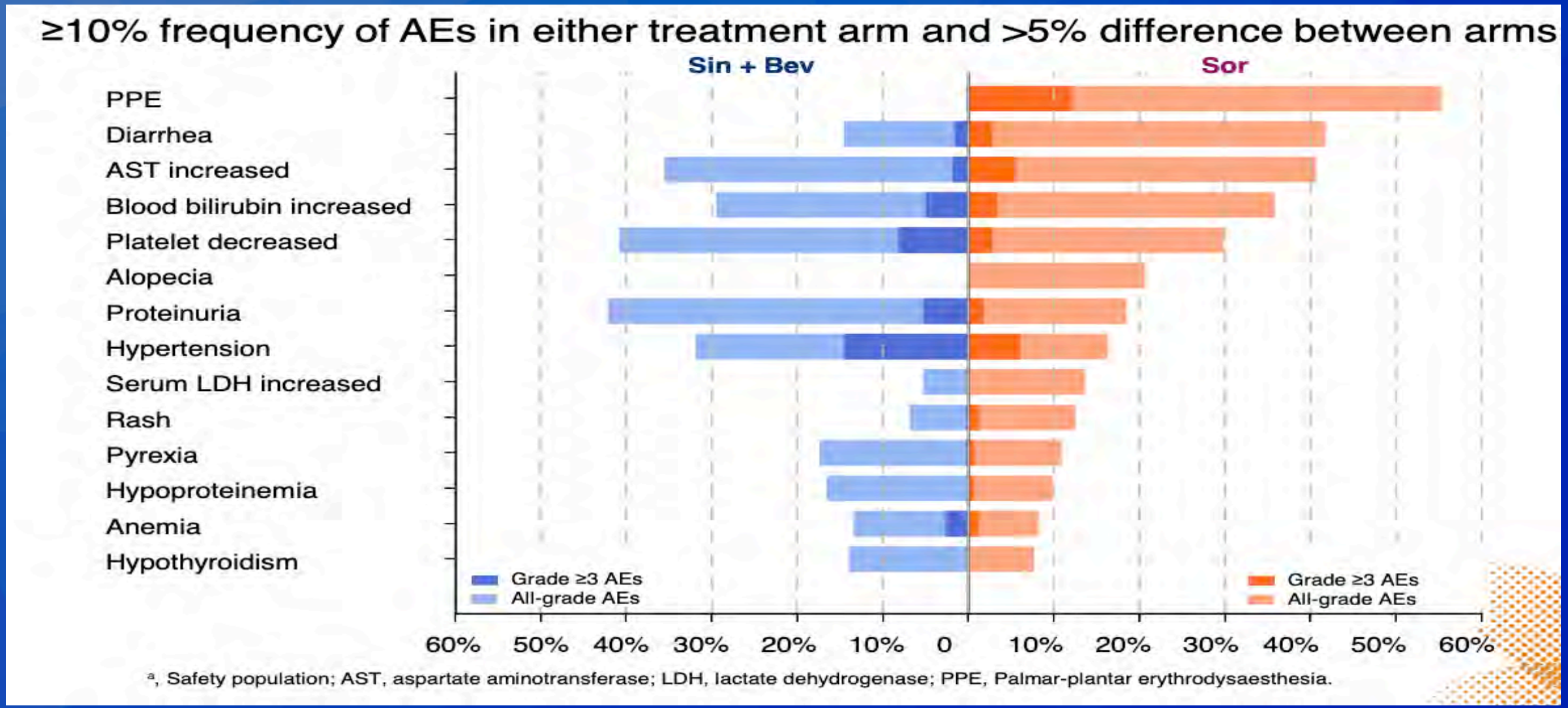
Median DOR, months	**NE**	**9.8**	**NE**	**NE**	**NE**	**6.6**
(95% CI)	(NE, NE)	(2.8, NE)	(NE, NE)	(2.5, NE)	(8.2, NE)	(2.6, NE)

*, response-evaluable population
†, defined as a response (complete or partial) confirmed by two consecutive tumor assessments with at least 28-day interval
‡, 3 subjects who had 2 consecutive partial responses (PRs) cross cutoff date were included
§, 2 patients who had 2 consecutive PRs cross cutoff date were included

a, 95% CI was calculated using Clopper-Pearson method
b, the stratification factors included MVI and/or EHS (yes vs. no), AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1)
c, RD, rate difference = $ORR_{Sin+Bev} - ORR_{Sor}$, and was calculated using stratified M-N method
NE, not evaluable.

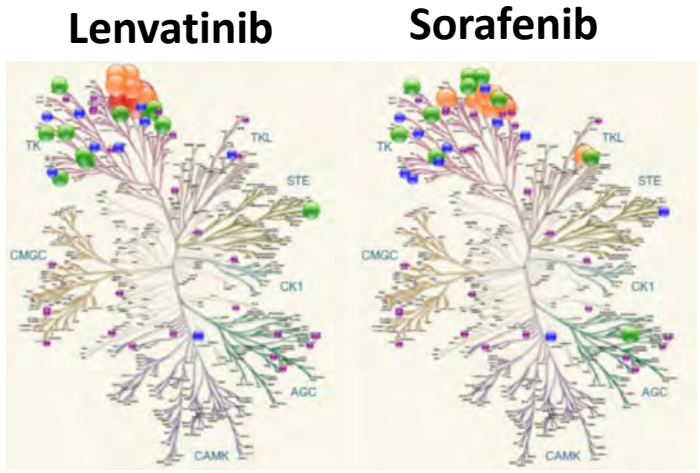
Ren Z et al. ESMO Asia 2020;Abstract LBA2.

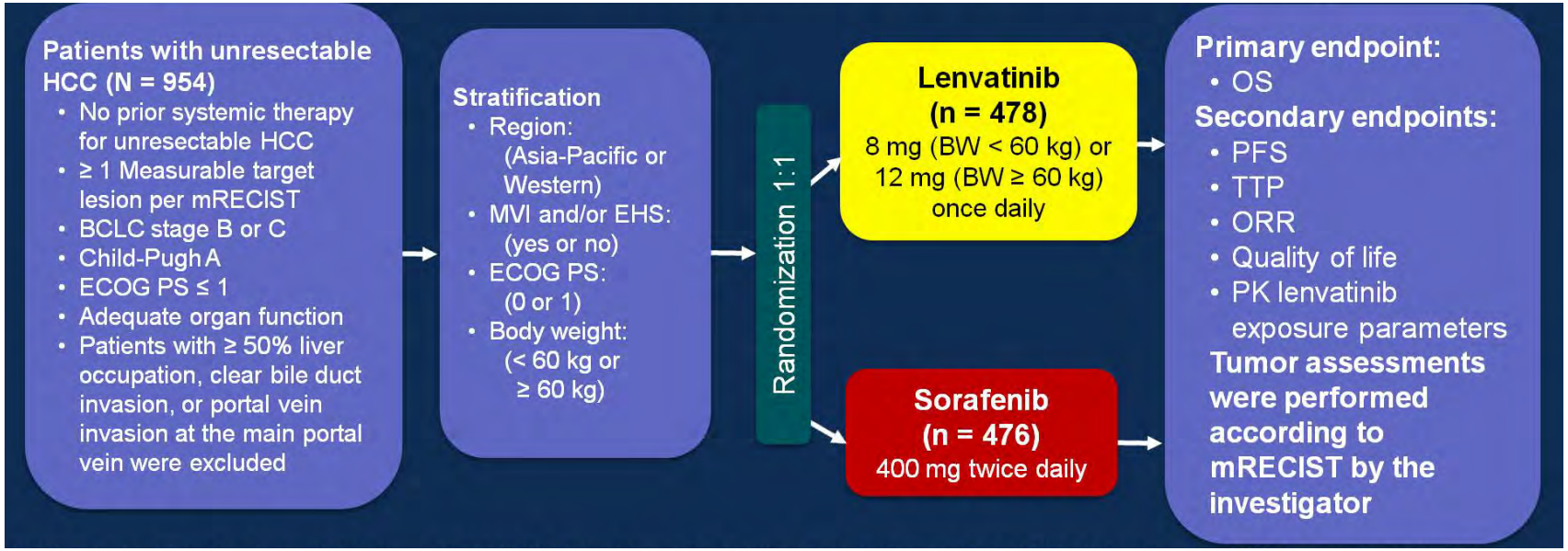
ORIENT-32: Safety



Ren Z et al. ESMO Asia 2020;Abstract LBA2.

REFLECT: Lenvatinib vs. Sorafenib





Kudo et al. Lancet 2018

Courtesy of James J Harding, MD

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Lenvatinib Vs Sorafenib in HCC
First-line randomized Phase III study

Outcomes	LENVATINIB	SORAFENIB	HR
Median OS, mos (95% CI)	13.6 (12.1–14.9)	12.3 (10.4–13.9)	0.92 (0.79–1.06)
Median PFS, mos (95% CI)*	7.4 (6.9–8.8)	3.7 (3.6–4.6)	0.66 (0.57–0.77)
Median TTP, mos (95% CI)*	8.9 (7.4–9.2)	3.7 (3.6–5.4)	
ORR, n (%)*	115 (24)	44 (9)	

Kudo M et al. Lancet 2018;391(10126):1163-73.

Courtesy of Ahmed Omar Kaseb, MD, CMQ

Exposure-Response (E-R) Efficacy and Safety (E-S) Analyses of Tremelimumab as Monotherapy or in Combination with Durvalumab in Patients (pts) with Unresectable Hepatocellular Carcinoma (uHCC)

Song X et al.

Gastrointestinal Cancers Symposium 2021;Abstract 313.

Efficacy Outcomes for the Overall Study Population by Tremelimumab Treatment Arm

	T300+D	T mono	T75+D
Safety endpoints,[a] n (%)	**n=74**	**n=69**	**n=82**
Grade 3/4 treatment-related AEs[b]	26 (35.1)	30 (43.5)	19 (23.2)
Grade 3/4 treatment-related AESI[b]	20 (27.0)	22 (31.9)	16 (19.5)
Treatment-related AEs leading to discontinuation of study treatment	8 (10.8)	9 (13.0)	5 (6.1)
Efficacy endpoints[c]	**n=75**	**n=69**	**n=84**
Confirmed ORR, % (95% CI)	24.0 (14.9, 35.3)	7.2 (2.4, 16.1)	9.5 (4.2, 17.9)
PFS, median (95% CI), months	2.17 (1.91, 5.42)	2.69 (1.87, 5.29)	1.87 (1.77, 2.53)
OS, median (95% CI), months	18.7 (10.8, 27.3)	15.1 (11.3, 20.5)	11.3 (8.4, 15.0)

[a]Reported for the safety analysis set—all patients who received at least 1 dose of study treatment.
[b]Only included patients with treatment-related maximum grade 3 or 4 AEs.
[c]Reported for the full analysis set—all randomized patients.

Song X et al. Gastrointestinal Cancers Symposium 2021;Abstract 313.

FDA approved first and second line therapies

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

*Accelerated approval

Courtesy of Tim Greten, MD

What would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC, a Child-Pugh B7 score and PS 1?

1. Sorafenib
2. Lenvatinib
3. Atezolizumab/bevacizumab
4. Chemotherapy
5. Other

Do you believe that patients with unresectable HCC limited to the liver who in the past underwent liver-directed therapy such as TACE should now instead receive initial systemic treatment (eg, atezolizumab/bevacizumab)?

1. Yes
2. No

What is your usual first-line systemic therapy for HCC in a 70-year-old patient with a Child-Pugh A score and Grade 1 esophageal varices being managed with a beta blocker?

1. Sorafenib
2. Lenvatinib
3. Sorafenib or lenvatinib — coin flip
4. Atezolizumab/bevacizumab
5. Chemotherapy
6. Other

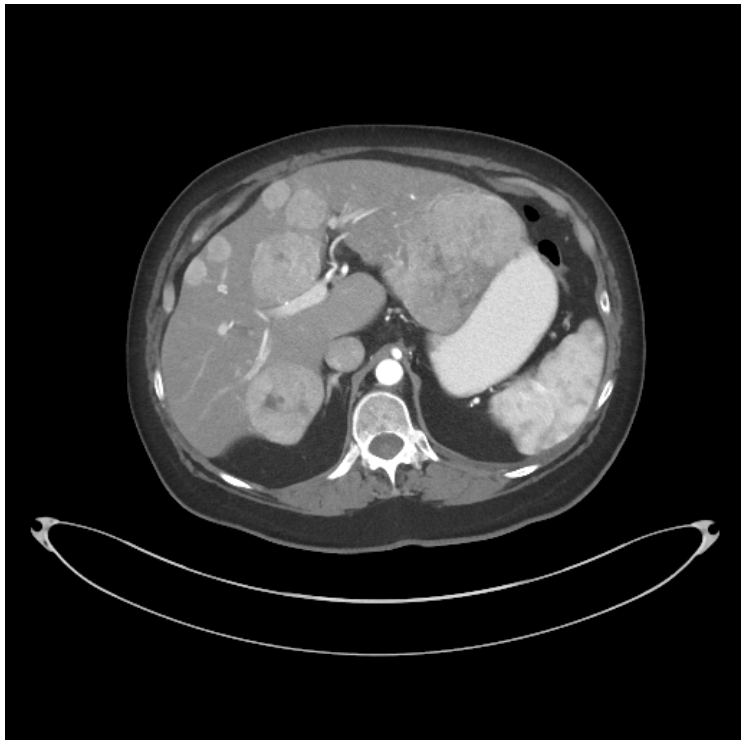
Case Presentation – Dr Kaseb: A 65-Year-Old Woman with Child-Pugh A HCC

- 65 y.o. female with h/o metabolic syndrome, DM-type 2, dyslipidemia, hypothyroidism
- Patient was in her usual state of health until 9/2018 when she developed a persistent cough prompting CXR evaluation which showed left lower lobe pneumonia. Follow-up CT Chest on 9/21/18 confirmed left lower lobe pneumonia with surrounding pleural effusion, but also incidentally showed numerous centrally necrotic masses throughout the liver.
- The patient underwent CT Abdomen on 9/26/18 which showed multiple bilobar liver masses, largest measuring 9.8 cm in right liver, as well as an 8.5 cm soft tissue mass in the left liver, in addition to left portal vein tumor thrombus.
- On 9/27/18, she underwent CT-guided liver biopsy with pathology confirming hepatocellular carcinoma.
- Baseline Child-Pugh score was A, HCC staging: BCLS stage C, and AFP=528
- Patient started on atezolizumab + bevacizumab in 10/2018 after EGD that showed no varices. Treatment was tolerated very well, except for non-significant proteinuria, and occasional fatigue
- Baseline scans in 10/2018 as well as follow up scans in 2/2020 are shown, indicating major tumor response. AFP normalized as well.

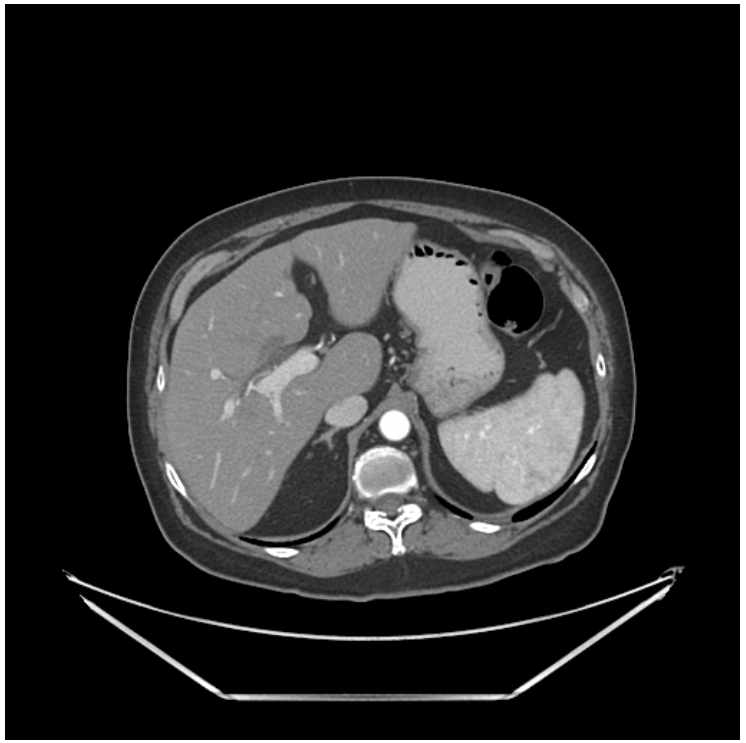
Courtesy of Ahmed Omar Kaseb, MD, CMQ

Case Presentation – Dr Kaseb: A 65-Year-Old Woman with Child-Pugh A HCC (cont)

Baseline and last follow up imaging: bilobar tumors



10/2018

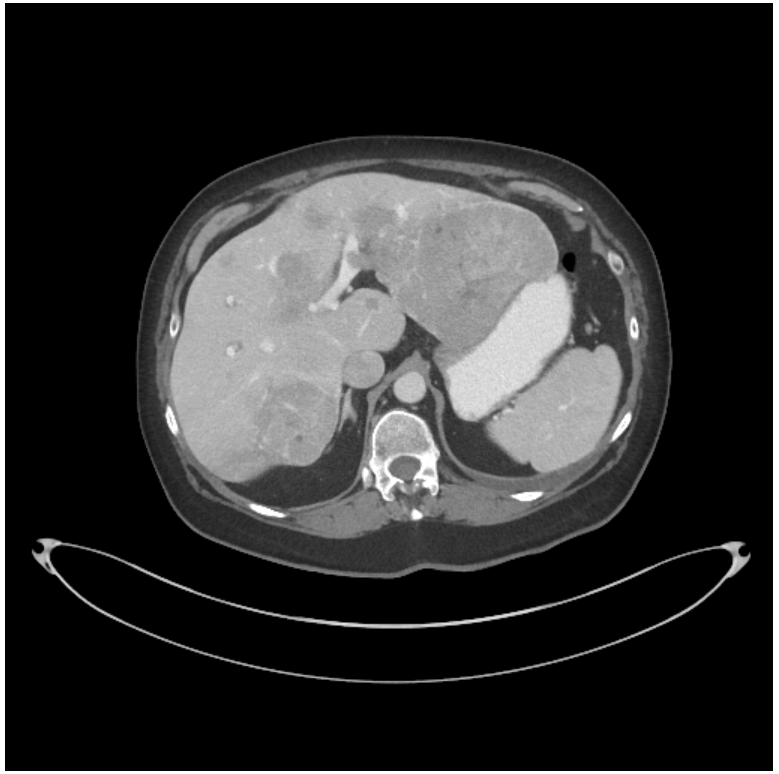


02/2020

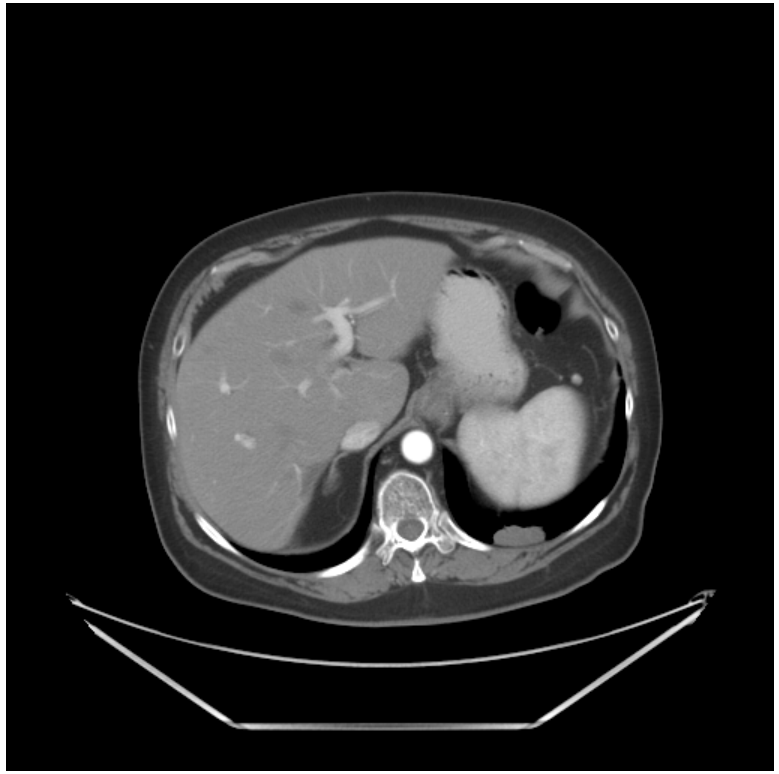
Courtesy of Ahmed Omar Kaseb, MD, CMQ

Case Presentation – Dr Kaseb: A 65-Year-Old Woman with Child-Pugh A HCC (cont)

Baseline and last follow up imaging: left PV tumor thrombus



10/2018

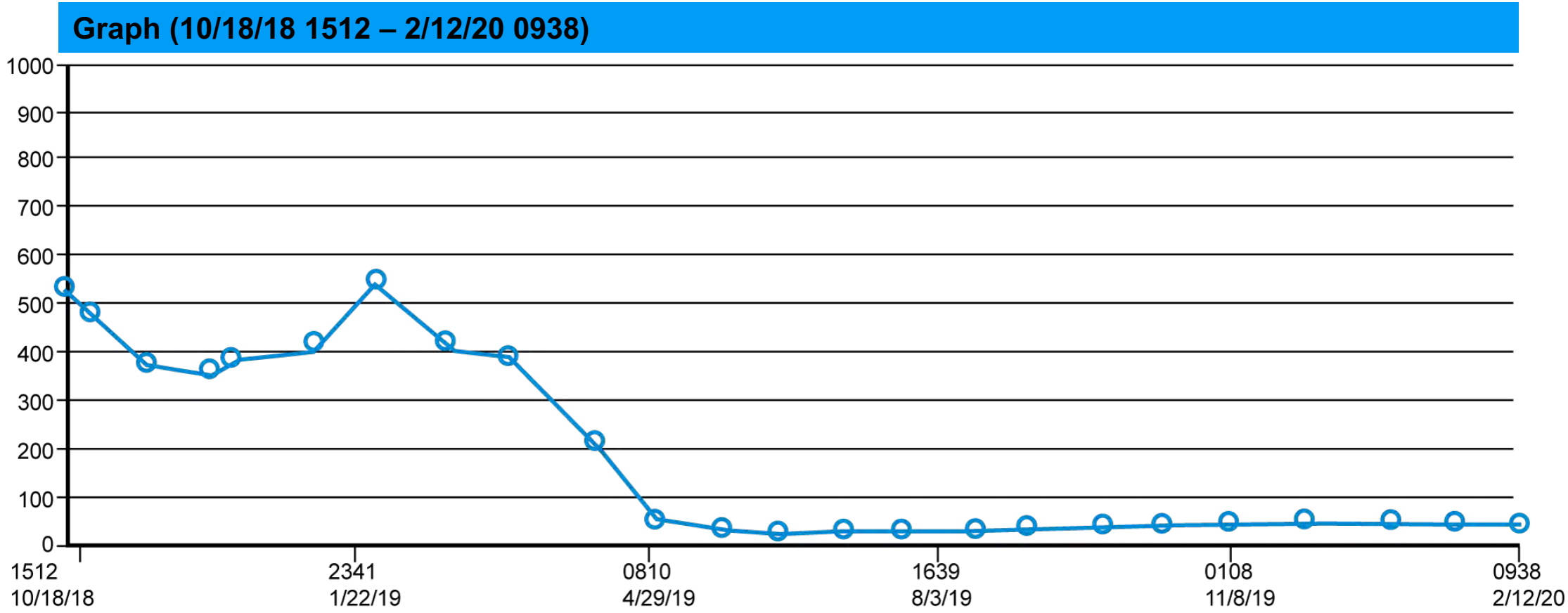


02/2020

Courtesy of Ahmed Omar Kaseb, MD, CMQ

Case Presentation – Dr Kaseb: A 65-Year-Old Woman with Child-Pugh A HCC (cont)

Baseline and last follow up AFP levels



Courtesy of Ahmed Omar Kaseb, MD, CMQ

Case Presentation – Dr Deutsch: A 68-year-old man with advanced HCC

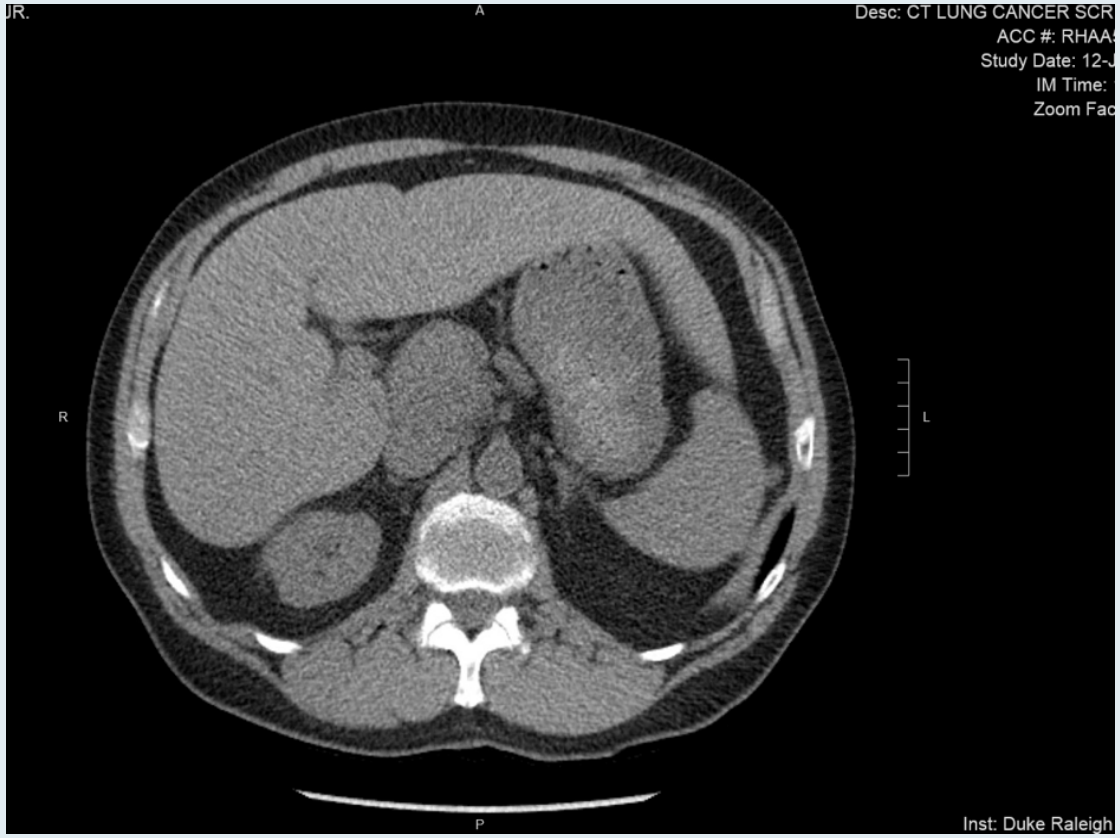
Margaret Deutsch, MD

- PMH: Cirrhosis secondary to viral hepatitis C, COPD
- 6/2018: During CT screening for lung cancer (smoker): Incidental finding of a large 6-cm portacaval mass
- Biopsy: High-grade adenocarcinoma consistent with HXCC
- Sorafenib, without response
- Nivolumab, with decrease in portocaval mass, reduced abdominal pain
  - Hypothyroidism (TSH: 50) after 1 year, treated with levothyroxine sodium
- 10/2020: Increase in liver lesion → microwave ablation
- 12/2020: Increase in portocaval mass → palliative RT, continue nivolumab

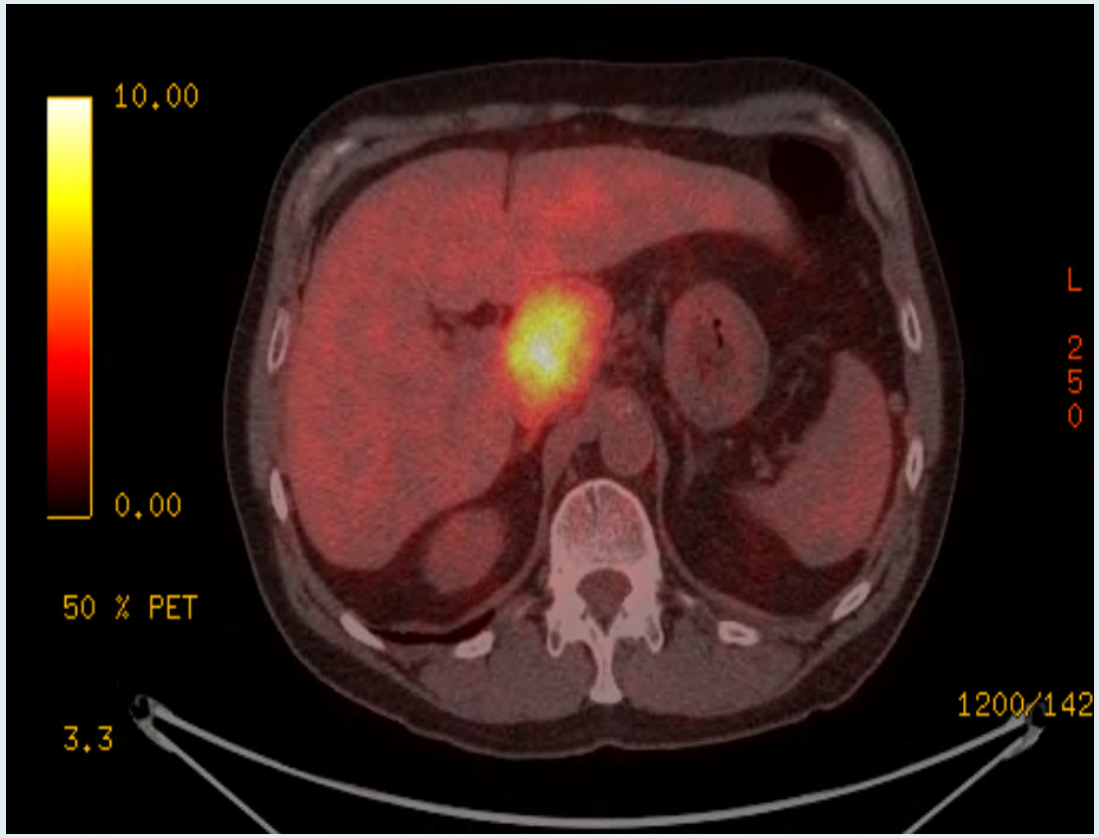
Case Presentation – Dr Deutsch: A 68-year-old man with advanced HCC

Margaret Deutsch, MD

Portocaval mass: 6/2018



Portocaval mass: 7/2019



Agenda

Module 1: Front-Line Management Options for Advanced Hepatocellular Carcinoma (HCC) – Dr Kaseb

Module 2: Selection and Sequencing of Treatment for Patients with Relapsed HCC – Dr Greten

Module 3: Considerations for the Treatment of HCC in Special Patient Populations – Dr Harding

Module 4: New Directions in the Management of HCC – Dr Finn

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Case Presentation – Dr Malhotra: A 65-year-old man with advanced HCC

Vikas Malhotra, MD

- S/p resection of early-stage HCC, with progressive disease 2 years ago
- Sorafenib, dose-reduced to 600 mg x 9 months → progressive disease
- Patient desires treatment holiday, goes off treatment
- Cabozantinib x 6 months → progressive disease
- Atezolizumab/bevacizumab – compassionate use

Questions

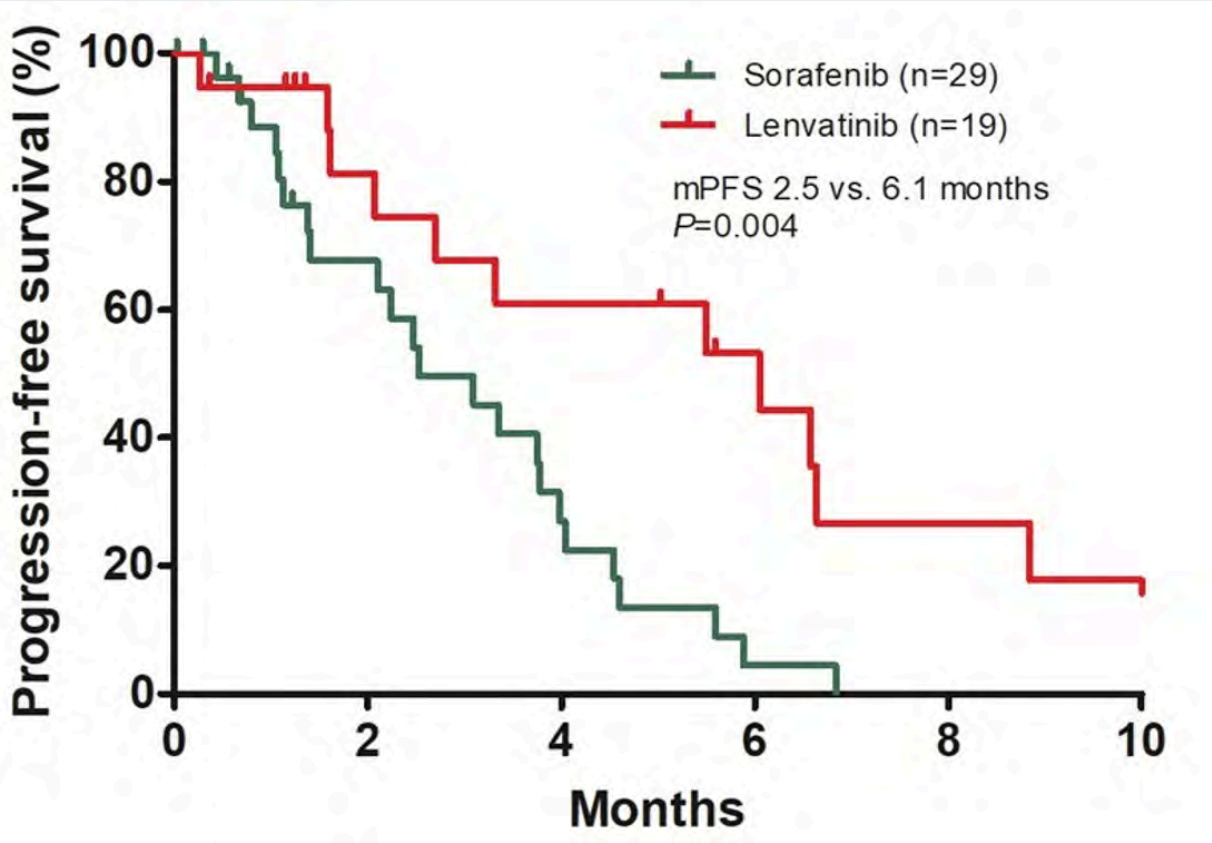
- How are the faculty using atezolizumab/bevacizumab in subsequent lines of therapy for patients who received other TKIs – sorafenib or cabozantinib? Are they getting paid for using the combination?
- What other treatment options are on the horizon?

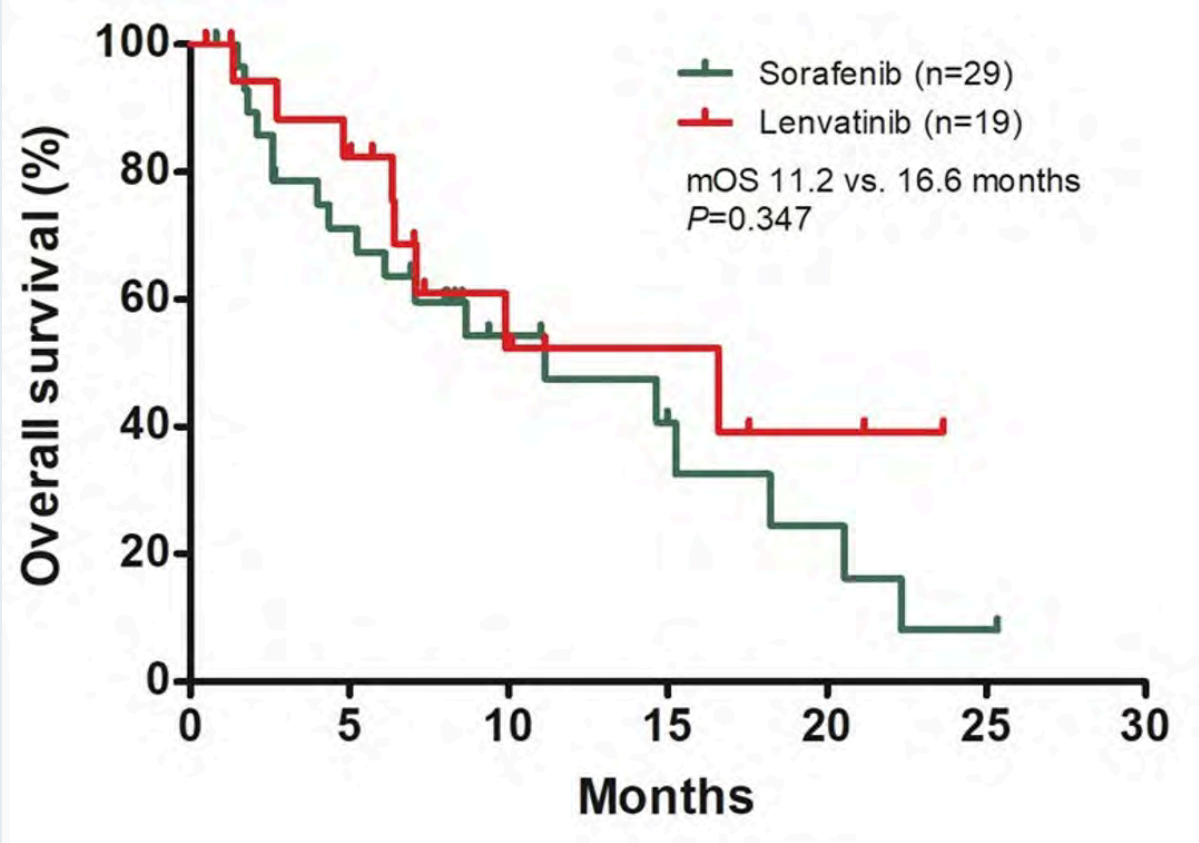
Clinical Outcomes with Multikinase Inhibitors After Progression on First-Line Atezolizumab plus Bevacizumab in Patients with Advanced Hepatocellular Carcinoma: A Multinational, Multicenter Retrospective Study

Yoo C et al.

Gastrointestinal Cancers Symposium 2021;Abstract 272.

Survival Outcomes with the Most Commonly Used* Second-Line Multikinase Inhibitors After First-Line Atezolizumab/Bevacizumab



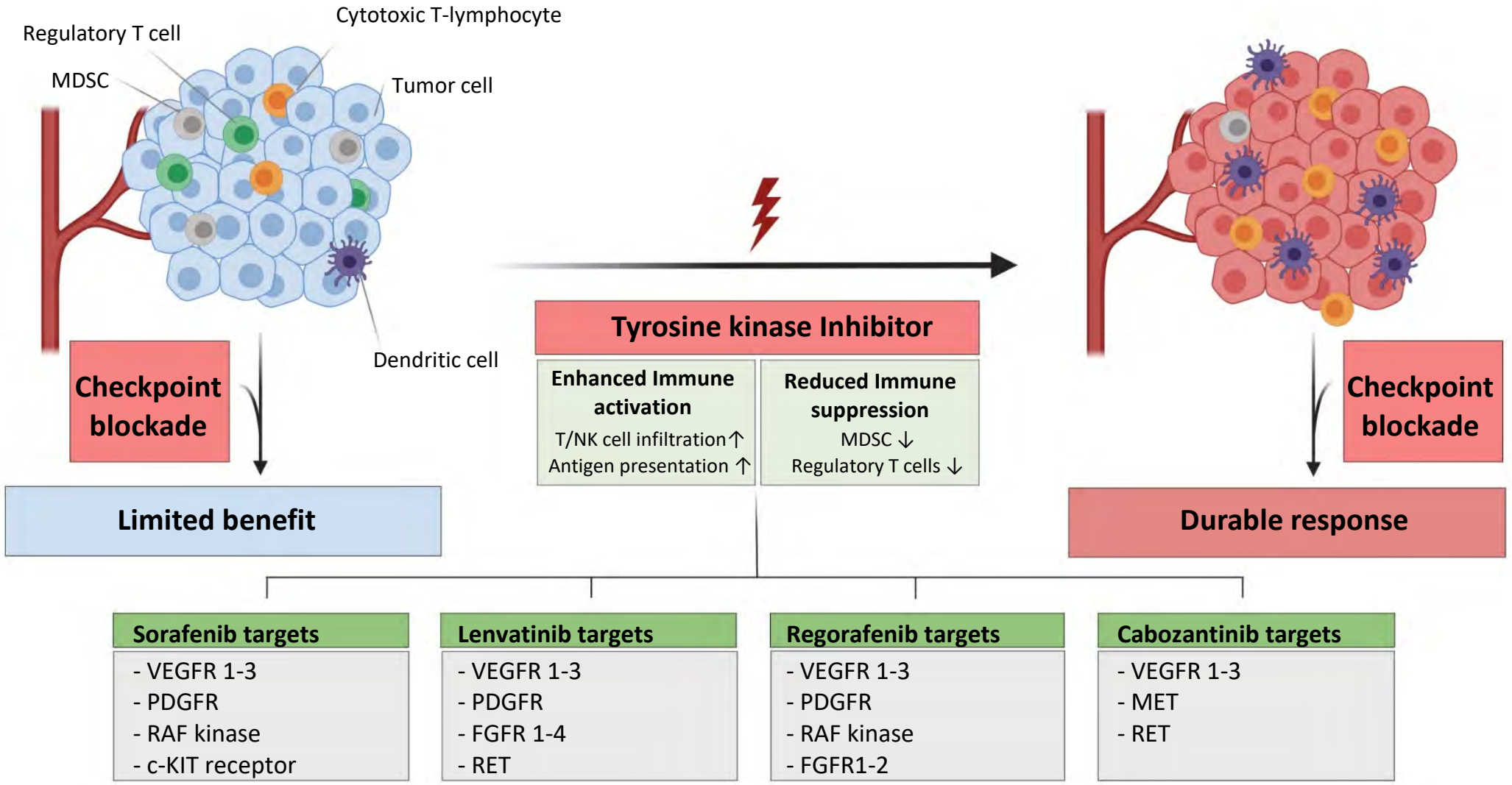


*In a multinational, multicenter retrospective analysis

Yoo C et al. Gastrointestinal Cancers Symposium 2021;Abstract 272.

RTP RESEARCH TO PRACTICE

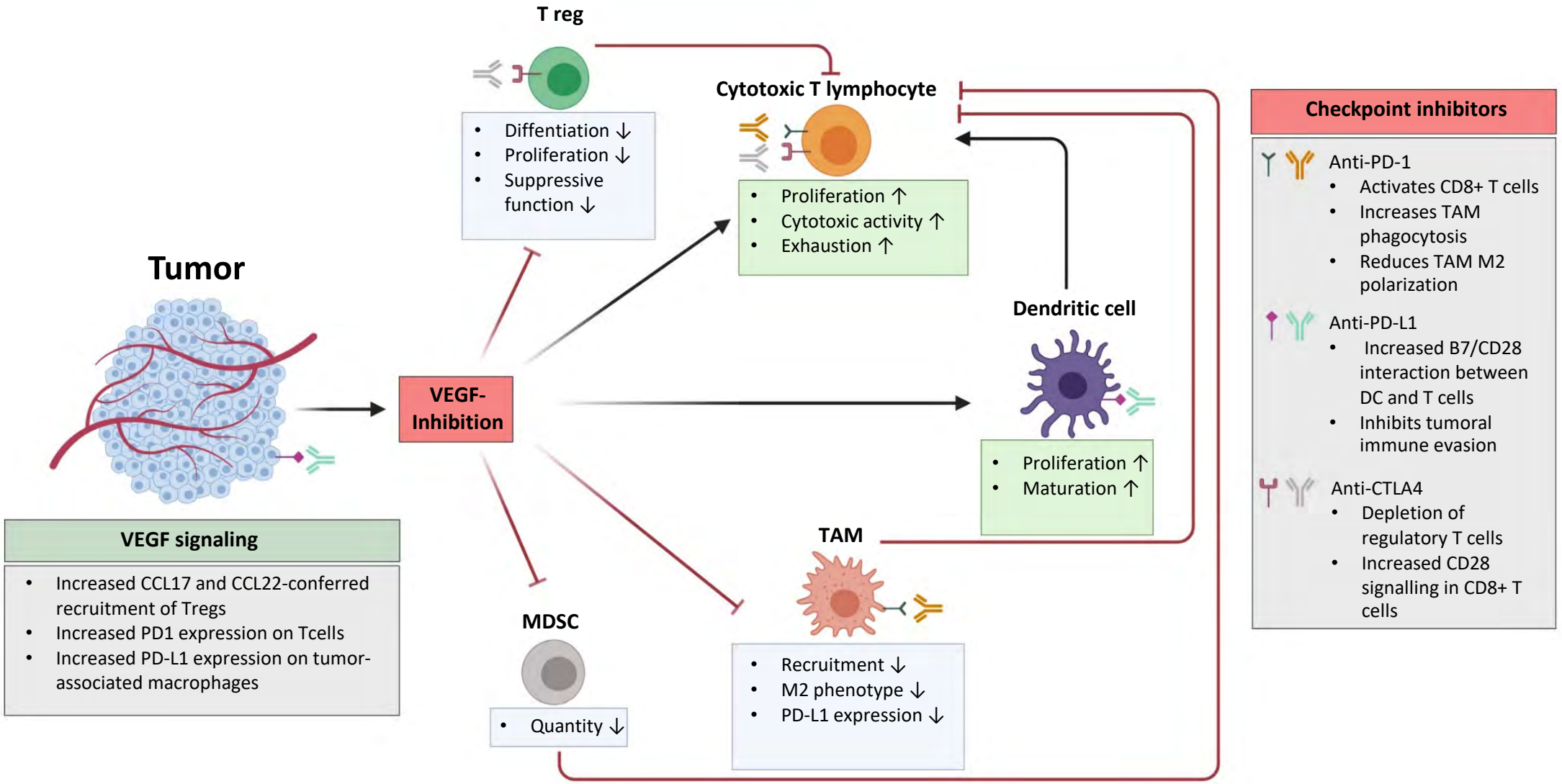
Tyrosine kinase inhibitors plus immunotherapy



Courtesy of Tim Greten, MD

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

Targeting VEGF plus immunotherapy

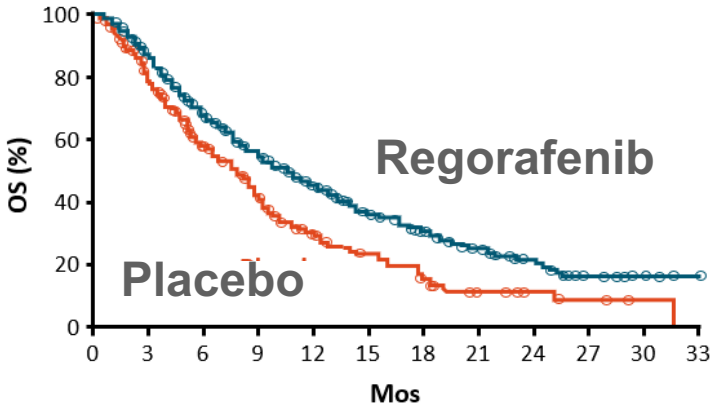


Courtesy of Tim Greten, MD

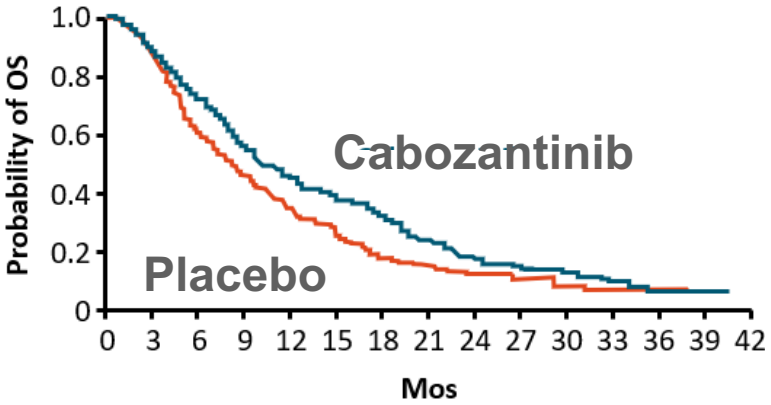
Llovet, …, Greten, …, Lencioni Nat Rev Gastro in press

TKIs as second line treatment for HCC

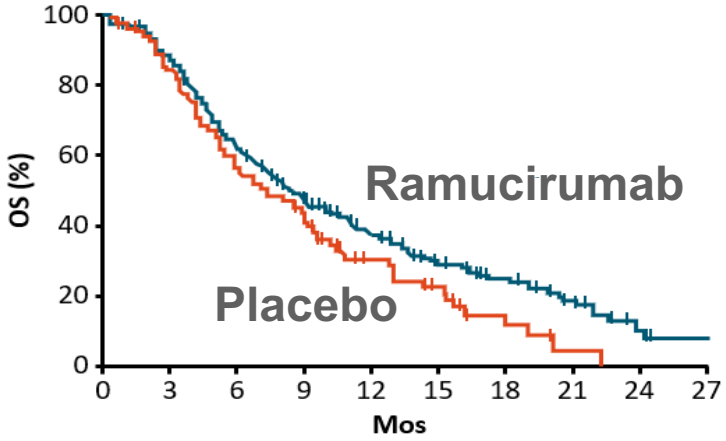
RESORCE	CELESTIAL	REACH-2
Regorafenib vs placebo	Cabozantinib vs placebo (N = 707)	Ramucirumab vs placebo
2L, sorafenib-tolerating pts only (N = 573)	2L or 3L (N = 707)	2L, AFP ≥ 400 ng/mL (N = 292)
Median OS: 10.6 vs 8.0 mos	Median OS: 10.2 vs 8.0 mos	Median OS: 8.5 vs 7.3 mos
HR: 0.63 (P < .0001)	HR: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



Bruix. Lancet. 2017;389:56



Abou-Alfa. NEJM. 2018;379:54.



Zhu. Lancet Oncol. 2019;20:282.

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

Courtesy of Tim Greten, MD

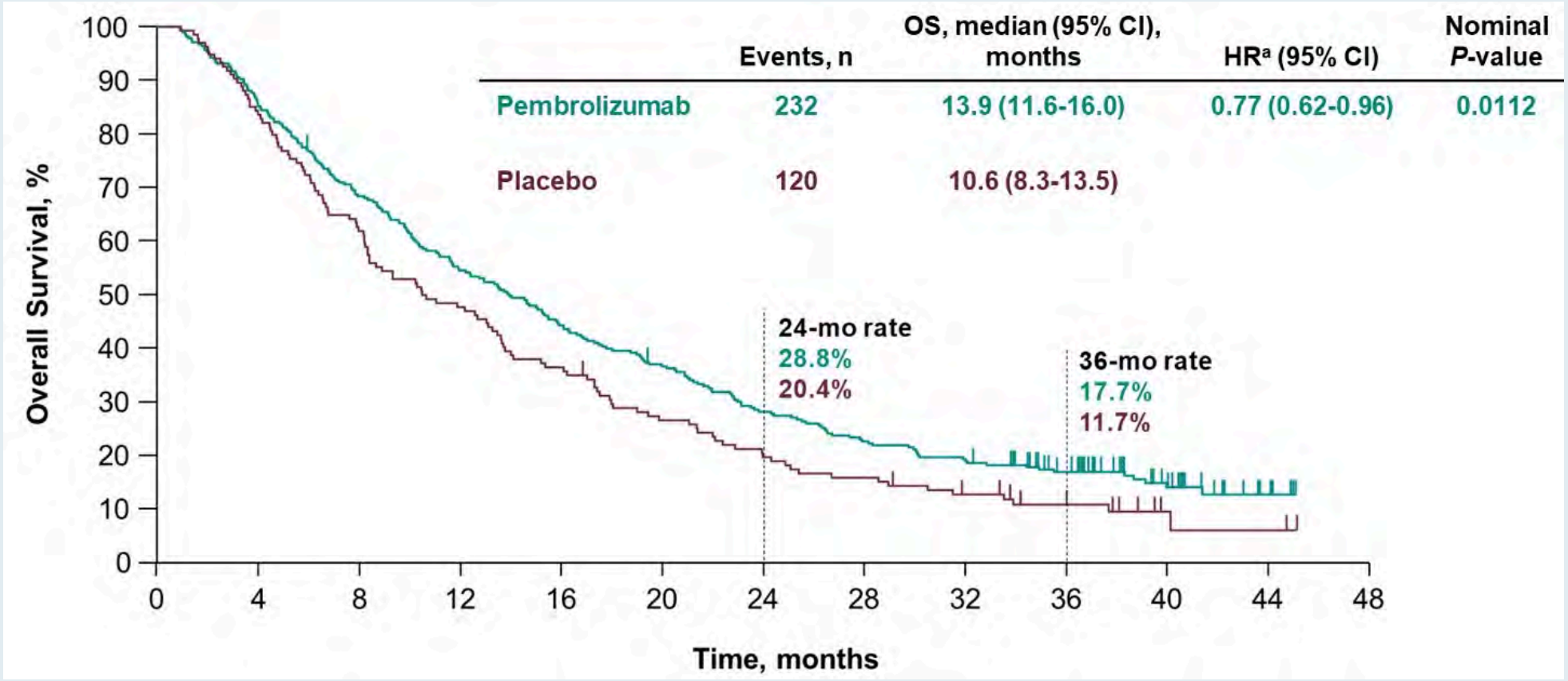
Pembrolizumab (pembro) vs Placebo (pbo) in Patients (pts) with Advanced Hepatocellular Carcinoma (aHCC) Previously Treated with Sorafenib: Updated Data from the Randomized, Phase III KEYNOTE-240 Study

Merle P et al.

Gastrointestinal Cancers Symposium 2021;Abstract 268.

KEYNOTE-240: Updated OS and PFS
Hazard Ratios Maintained with Longer Follow-Up

Overall Survival

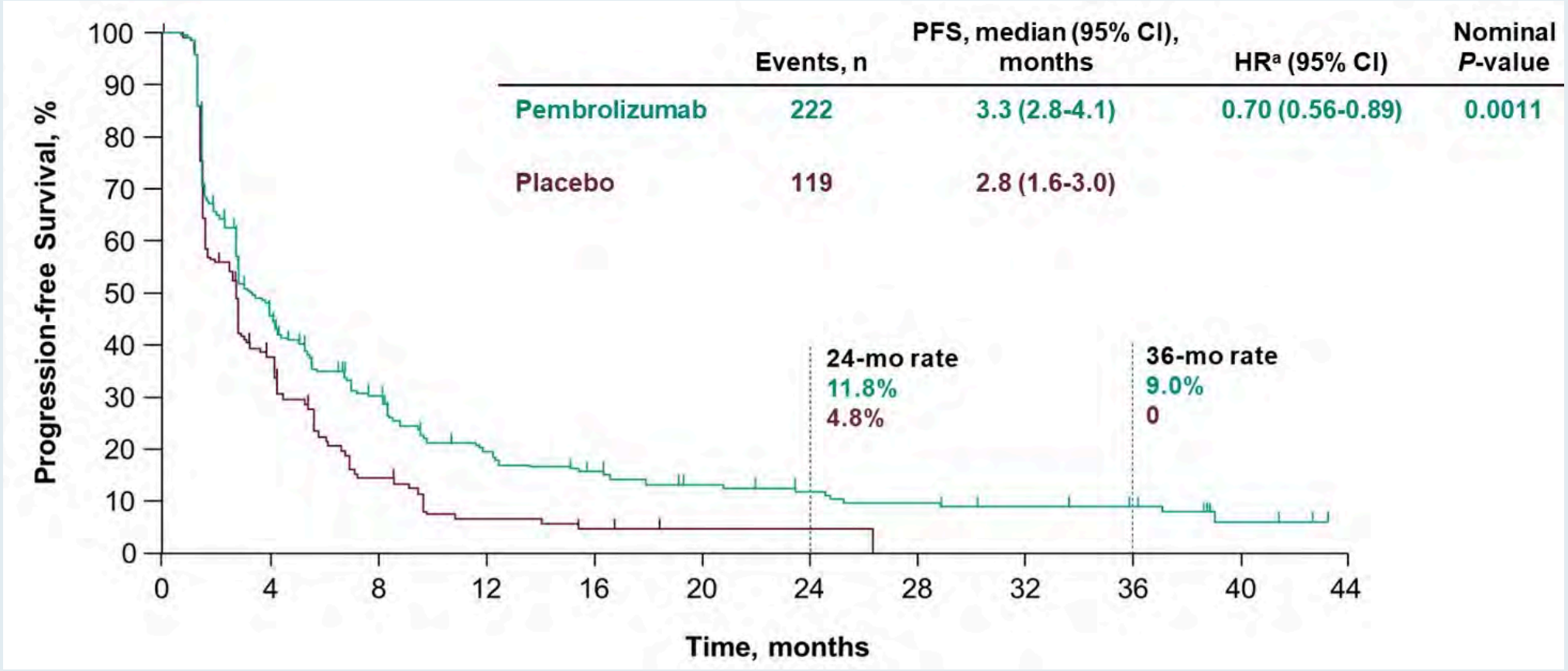


Merle P et al. Gastrointestinal Cancers Symposium 2021;Abstract 268.

RTP RESEARCH TO PRACTICE

KEYNOTE-240: Updated OS and PFS
Hazard Ratios Maintained with Longer Follow-Up

Progression-Free Survival



	Events, n	PFS, median (95% CI), months	HR[a] (95% CI)	Nominal *P*-value
Pembrolizumab	222	3.3 (2.8-4.1)	0.70 (0.56-0.89)	0.0011
Placebo	119	2.8 (1.6-3.0)		

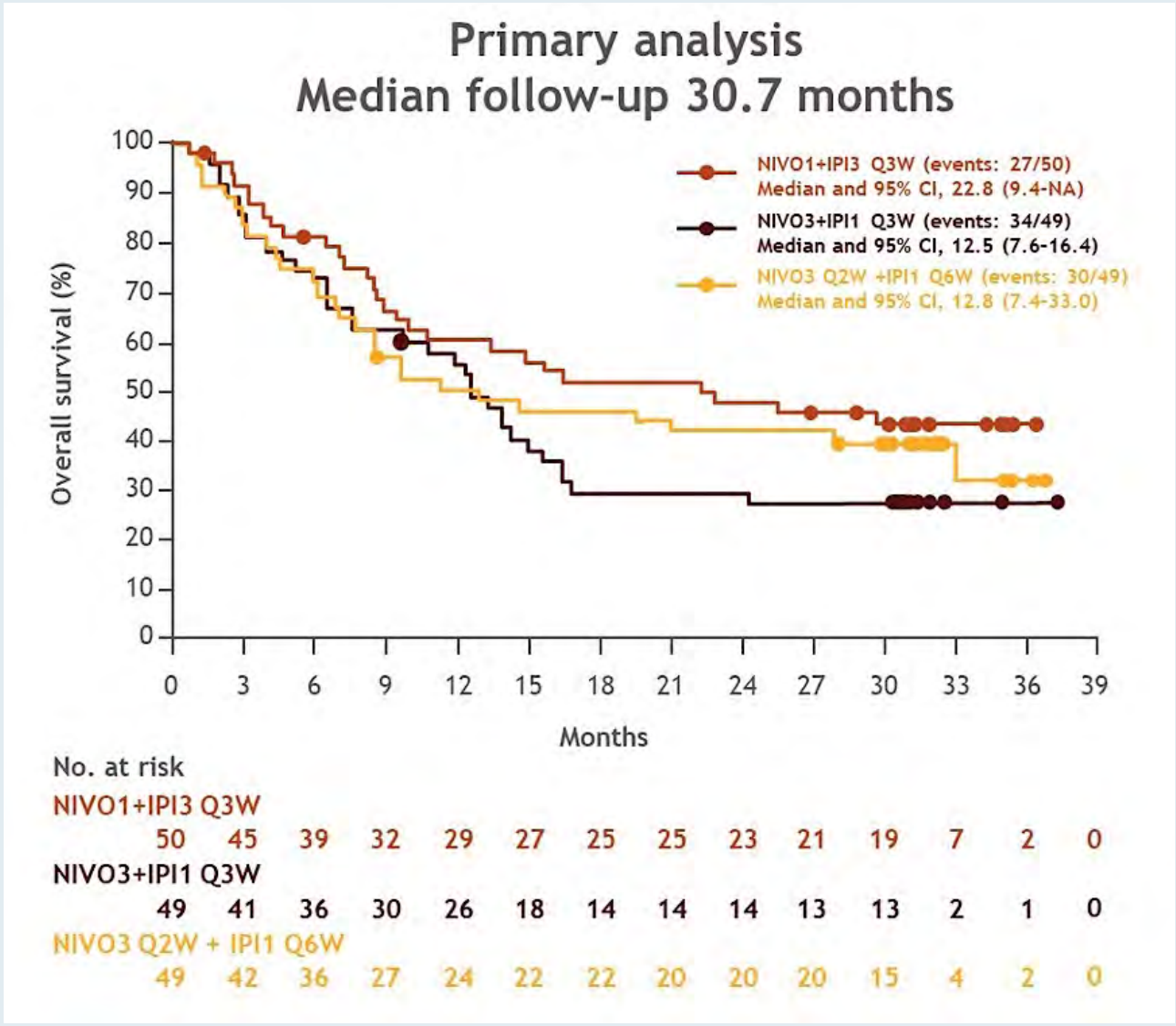
Merle P et al. Gastrointestinal Cancers Symposium 2021;Abstract 268.

Nivolumab (NIVO) plus Ipilimumab (IPI) Combination Therapy in Patients (Pts) with Advanced Hepatocellular Carcinoma (aHCC): Long-Term Results from CheckMate 040

El-Khoueiry AB et al.

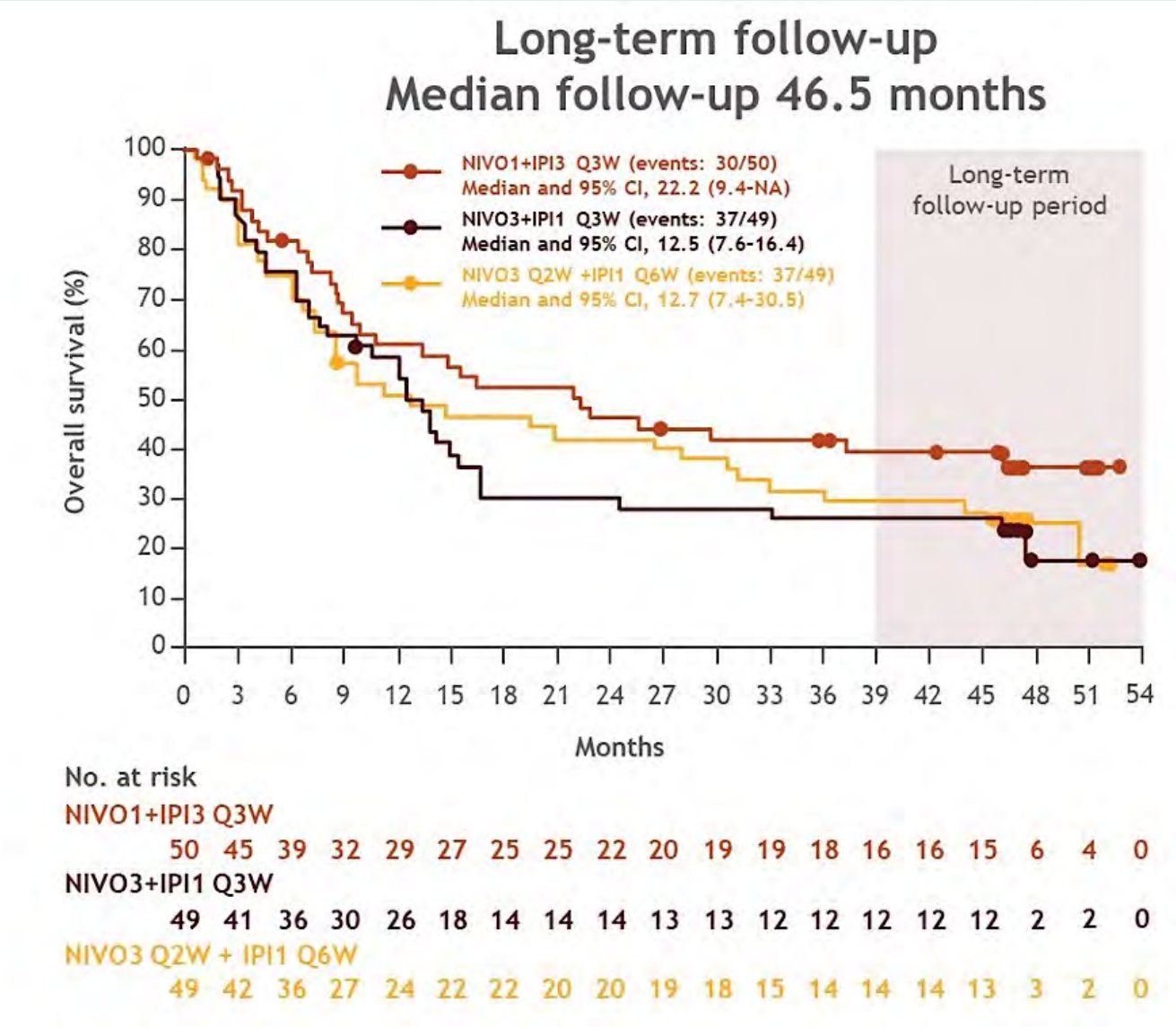
Gastrointestinal Cancers Symposium 2021;Abstract 269.

CheckMate 040: Updated Overall Survival with Ipilimumab/Nivolumab



El-Khoueiry AB et al. Gastrointestinal Cancers Symposium 2021;Abstract 269.

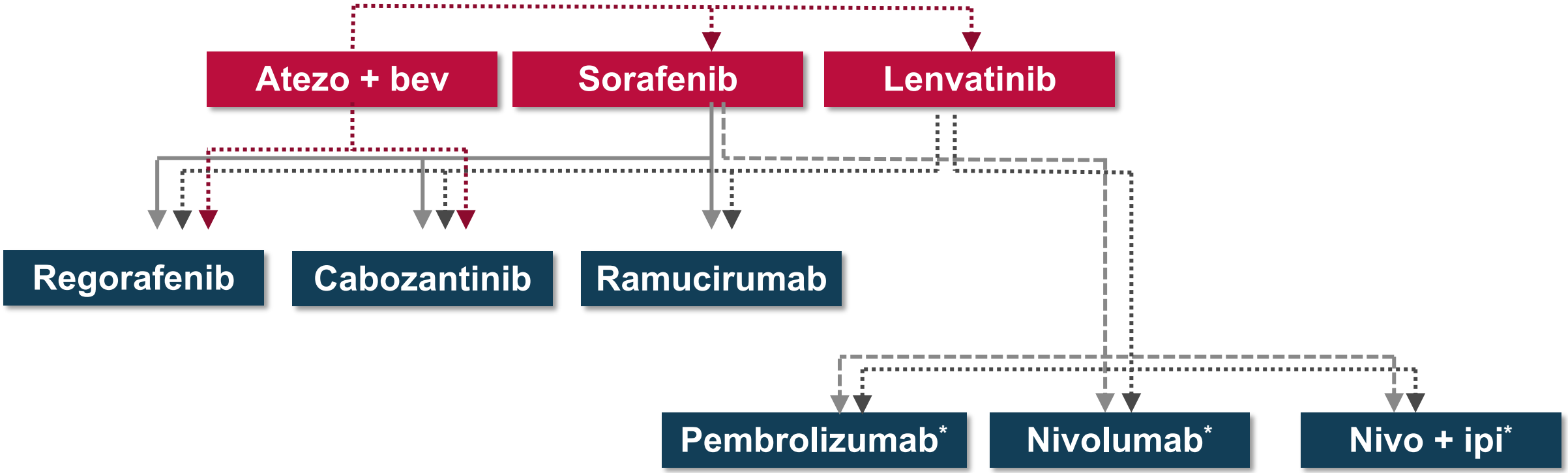
CheckMate 040: Updated Overall Survival with Ipilimumab/Nivolumab



El-Khoueiry AB et al. Gastrointestinal Cancers Symposium 2021;Abstract 269.

RTP RESEARCH TO PRACTICE

How do I sequence first and second line therapy?



Courtesy of Tim Greten, MD

Regulatory and reimbursement issues aside, what would be your second therapy for a 65-year-old patient with HCC, a Child-Pugh A score and PS 0 who received first-line sorafenib with minimal toxicity, had stable disease for 14 months and then experienced disease progression (AFP 250 ng/mL)?

1. Lenvatinib
2. Regorafenib
3. Cabozantinib
4. Anti-PD-1 antibody
5. Atezolizumab/bevacizumab
6. Pembrolizumab/lenvatinib
7. Nivolumab/ipilimumab
8. Other

What would be your second-line therapy for a 65-year-old patient with HCC, a Child-Pugh A score and PS 0 who received first-line atezolizumab/bevacizumab and experienced disease progression after 18 months (AFP 2,500 ng/mL)?

1. Cabozantinib
2. Lenvatinib
3. Anti-PD-1 antibody
4. Nivolumab/ipilimumab
5. Ramucirumab
6. Regorafenib
7. Sorafenib
8. Other

What would be your most likely third-line systemic therapy recommendation for an otherwise healthy 65-year-old patient with HCC who experienced disease progression on first-line atezolizumab/bevacizumab and second-line lenvatinib (AFP 2,500 ng/mL)?

1. Sorafenib
2. Regorafenib
3. Cabozantinib
4. Ramucirumab
5. Anti-PD-1 antibody
6. Nivolumab/ipilimumab
7. Chemotherapy
8. Other

Case Presentation – Dr Greten: A 69-Year-Old Man with Relapsed HCC

69 y/o male

Diagnosed with hepatitis C 1990.

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

2015: multifocal recurrence TACE therapy x3

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

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

2018: developed a lump on right buttock – radiation

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

Skin rash, itching, trace of edema

Courtesy of Tim Greten, MD

Questions and Comments: Incorporation of local therapies during an era of effective systemic therapies

Vikas Malhotra, MD

RTP RESEARCH TO PRACTICE

Agenda

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Module 3: Considerations for the Treatment of HCC in Special Patient Populations – Dr Harding

Module 4: New Directions in the Management of HCC – Dr Finn

Case Presentation – Dr Matt-Amaral: A 68-year-old man with de novo metastatic HCC

Laurie Matt-Amaral, MD, MPH

- 7/2020: Stage IV HCC with metastases to the lung
- 8/10 – 8/21/2020: Sorafenib (discontinued due to recognition of emerging atezolizumab/bevacizumab data)
- 9/2020: Atezolizumab/bevacizumab, with great response
  - Pre-existing psoriasis now has a “terrible” flare up, treated with apremilast

Questions

- Do you have any suggestions for management of his autoimmune disease to keep the psoriasis under control?

RTP RESEARCH TO PRACTICE

Generalizability of IMbrave150 and REFLECT?

- **Stringent selection criteria**
  - Limited the extent of liver disease
  - Exclusion of main portal vein involvement
  - Restricted to CP-A
  - Minimization of bleeding risk
- **Application to selected special population**
  - Decompensated liver function
  - Recent GI bleeding
  - Autoimmune conditions
  - Liver transplant recipient

Courtesy of James J Harding, MD

Child-Pugh score restricts access to pivotal clinical trials

Pivotal Study Randomized Study	CHILD-PUGH B or worse
SHARP	Yes
REFLECT	NO
IMbrave150	NO
RESORCE	NO
CELESTIAL	NO
REACH-2	NO
CheckMate 459	NO
KEYNOTE-240	NO

Data with Sorafenib and decompensated liver function

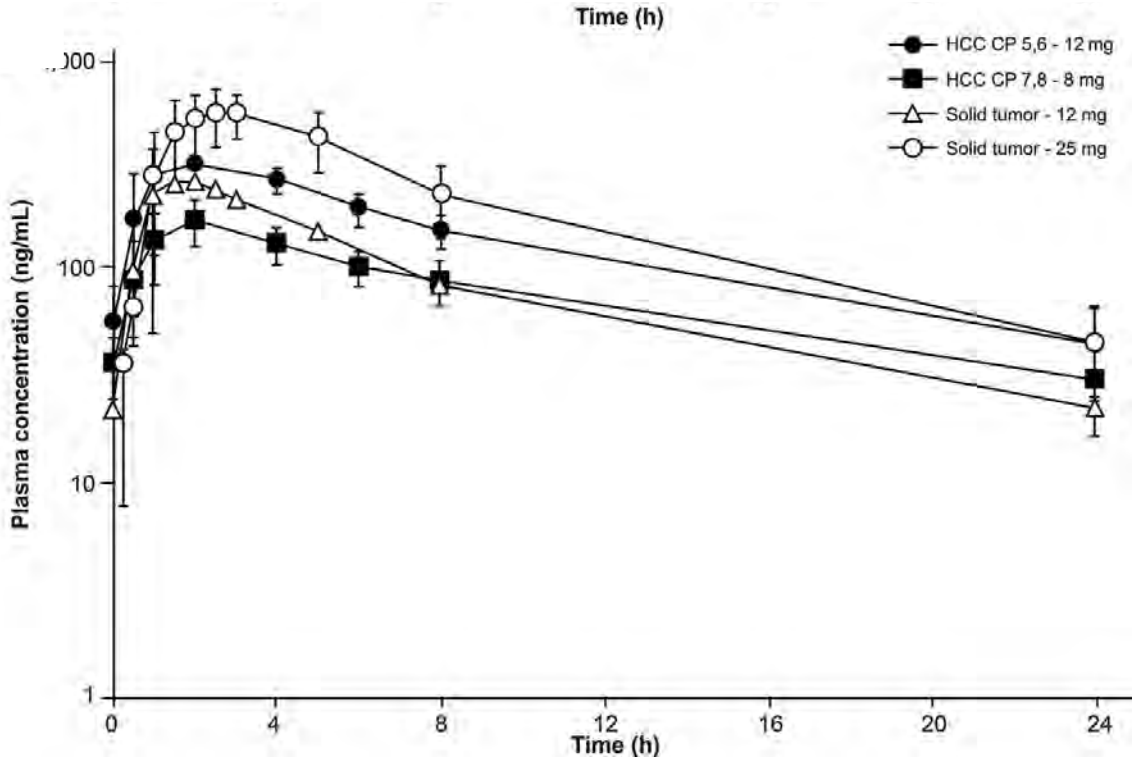
- CP-B and CP-C HCC patients are known to have worse OS on sorafenib (OS: CP-A 13.6 vs CP-B 5.2 months vs CP-C 2.6 months)
- CP-C is typically a contraindication to treatment
- A phase 1 study for sorafenib in patients with organ dysfunction indicates sorafenib dose modifications are required for CP-B or worse
- Newer TKIs and IO agents will require careful evaluation and this is ongoing

Marrero et al. J Hepatology 2016; Miler et al. JCO 2009

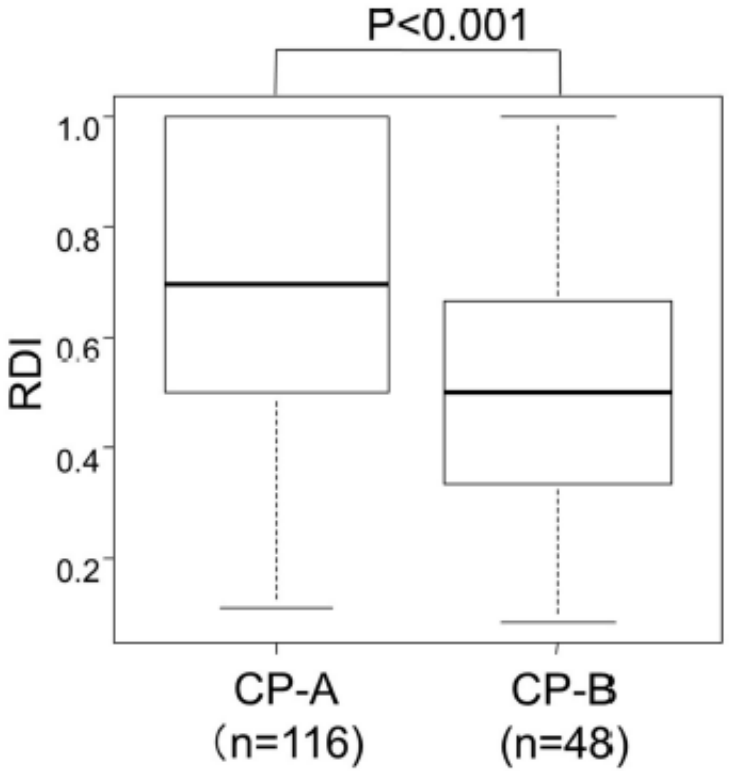
Courtesy of James J Harding, MD

Lenvatinib and CP-B liver function

Limited PK data but dose may matter relative to Liver function



Retrospective studies indicate a similar rate of AEs despite lower relative dose intensity (PDI)



Ikeda et al. CCR 2017; Ogushi et al. Clinical and Experimental Gastroenterology

Courtesy of James J Harding, MD

Immuno-oncology agents and decompensated liver function

CheckMate 040 CP-B N= 49	
ORR	10.2%
DCR	55.1%
mDOR	9.9 months
mOS	7.2 months
TEAEs	51%
AEs leading to discontinuation	4.1%

Nivolumab in Patients With Advanced Hepatocellular Carcinoma and Child-Pugh Class B Cirrhosis: Safety and Clinical Outcomes in a Retrospective Case Series

Swetha Kambhampati, MD [1,2]; Kelly E. Bauer, AB, MSc[2]; Paige M. Bracci, PhD, MPH[3]; Bridget P. Keenan, MD, PhD[1,2]; Spencer C. Behr, MD[4]; John D. Gordan, MD, PhD[1,2,5]; and Robin K. Kelley, MD [1,2]

Post-registration experience of nivolumab in advanced hepatocellular carcinoma: an international study

Petros Fessas [1], Ahmed Kaseb,[2] Yinghong Wang [3], Anwaar Saeed,[4] David Szafron,[5] Tomi Jun,[6] Sirish Dharmapuri,[6] Abdul Rafeh Naqash,[7] Mahvish Muzaffar,[7] Musharraf Navaid,[7] Uqba Khan,[8] ChiehJu Lee,[9] Anushi Bulumulle,[7] Bo Yu,[10] Sonal Paul,[10] Neil Nimkar,[10] Dominik Bettinger,[11] Francesca Benevento,[12] Hannah Hildebrand,[4] Tiziana Pressiani,[13] Yehia I Abugabal,[2] Nicola Personeni,[13,14] Yi-Hsiang Huang [9], Lorenza Rimassa [13,14] Celina Ang,[6] Thomas Marron,[6] David J Pinato[1]

Single agent IO appears safe data are limited for new combinations

Kudo et al. JCO supplement 2019

Courtesy of James J Harding, MD

Bleeding risk with Atezolizumab + Bevacizumab and other agents?

Table 2. Major Toxicities/Adverse Effects Possibly Attributed to Bevacizumab

Toxicity	All Grades		Grades 3 and 4	
	No. of Patients	%	No. of Patients	%
Hypertension	15	33	7	15
Proteinuria	19	41	2	4
Epistaxis	5	11	0	0
Hemorrhage	12	26	5	11
Arterial thrombosis	2	4	2	4
Venous thrombosis	1	2	1	2
Rash	6	13	0	0
Thrombocytopenia	6	13	0	0
Increased AST	10	22	1	2
Increased ALT	9	20	1	2
Increased alkaline phosphatase	5	11	1	2
Increased bilirubin	12	26	5	11
Ascites	5	11	2	4
Fatigue	15	33	0	0
Vomiting	5	11	0	0
Anorexia	5	11	1	2
Nausea	5	11	0	0

Bevacizumab 5mg/kg
26% hemorrhage
11% Grade 3 or higher

IMbrave150*		
	Sorafenib	A + B
Any Grade Hemorrhage	17.3%	25.2%
Grade 3-4	5.8%	6.4%
Grade 5	<1%	1.8%

*EGD and primary prophylaxis were required for patient entry,
? Ablity to extrapolate to patients with portal HTN and impaired liver function

Siegel et al. JCO 2008; Finn et al NEJM 2020

Courtesy of James J Harding, MD

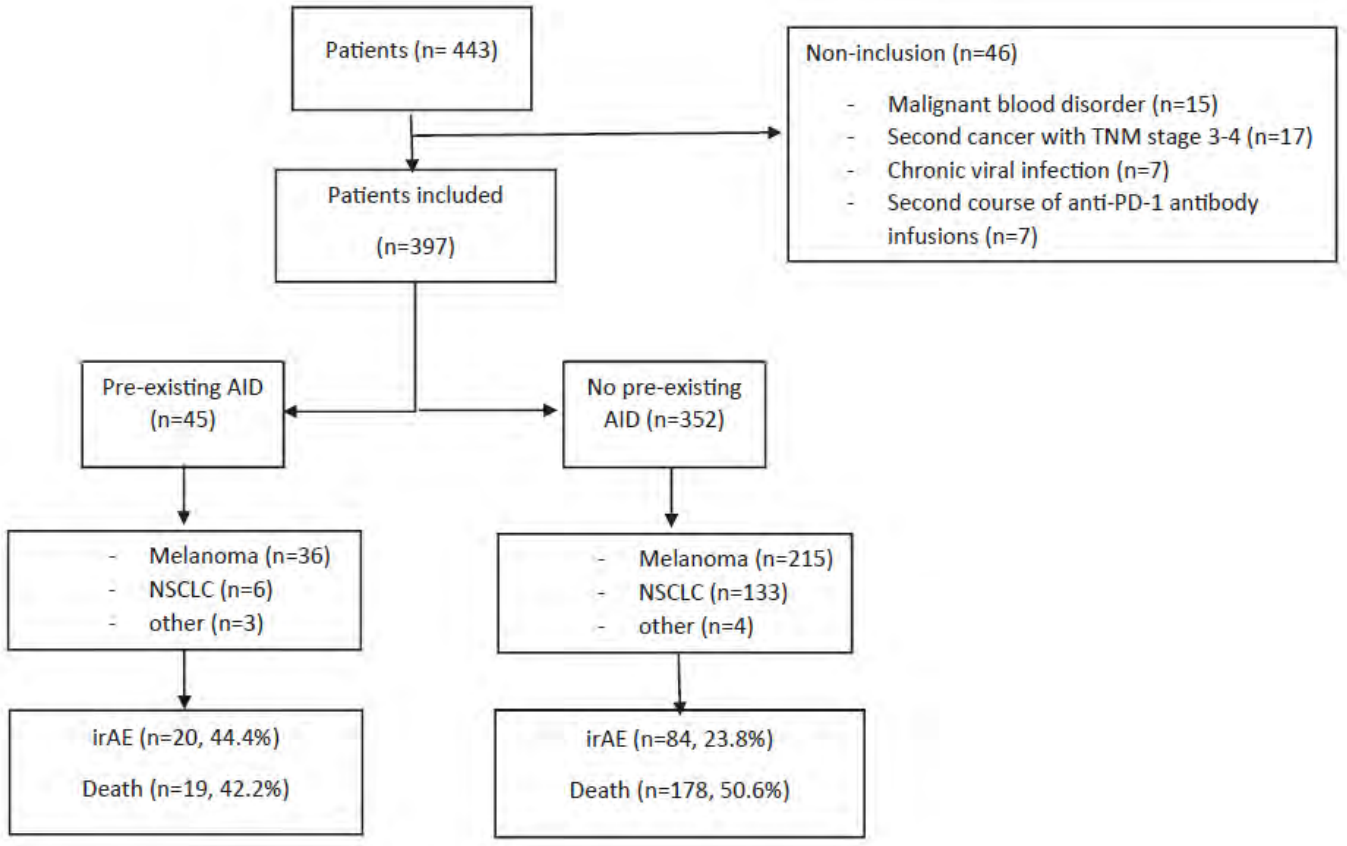
Immunotherapy in patients with autoimmune diseases must be used with caution

HCC in the context of autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC)
Incidence 3-18 cases per 1000 patient year

Co-occurring autoimmune disease (AID)
Incidence unknown

All Prospective Studies in HCC and IO have excluded, thus limitation in data

REISAMIC Registry for Patient Autoimmune Disease (AID)



irAE 44% for those with AID vs 23.8% for those without AID

Danlos et al. European Journal of Cancer 2018

Courtesy of James J Harding, MD

Immunotherapy following liver transplant is contraindicated in routine practice

Change in liver function in 7 patients following IO treatment in prior liver transplant recipient

ID	Change in Child Pugh	Change in MELD	Change in AFP (ng/mL)	Change in albumin (g/dL)	Change in Tbili (mg/dL)	Change in AST (U/L)	Change in ALT (U/L)	Change in INR
1	0	+5	+1,000	–0.3	0	+162	+84	+0.08
2	0	0	N/A	+0.3	+0.1	–4	–7	–0.2
3	+1	0	+214,082	–0.1	0	+3	+26	+0.08
4	+1	+1	+8,480	–0.3	+0.1	+7	0	+0.08
5	0	+1	+206.1	+1.5	–0.1	+11	+1	+0.45
6	+2	+5	+64.6	–1.1	+0.2	+900	+846	0.18
7	+2	+6	+44,767	–0.1	+0.8	169	+151	+0.1
Median	+1	+1	+1,000	–0.3	+0.1	+11	+26	+0.08

ID, patient identification; MELD, model for end stage liver disease; AFP, alpha-fetoprotein; Tbili, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; ng/Ml, nanograms per milliliter; g/dL, grams per deciliter; mg/dL, milligrams per deciliter; U/L, units per liter.

7 patients with advanced solid tumors and prior liver transplant- 5 with HCC

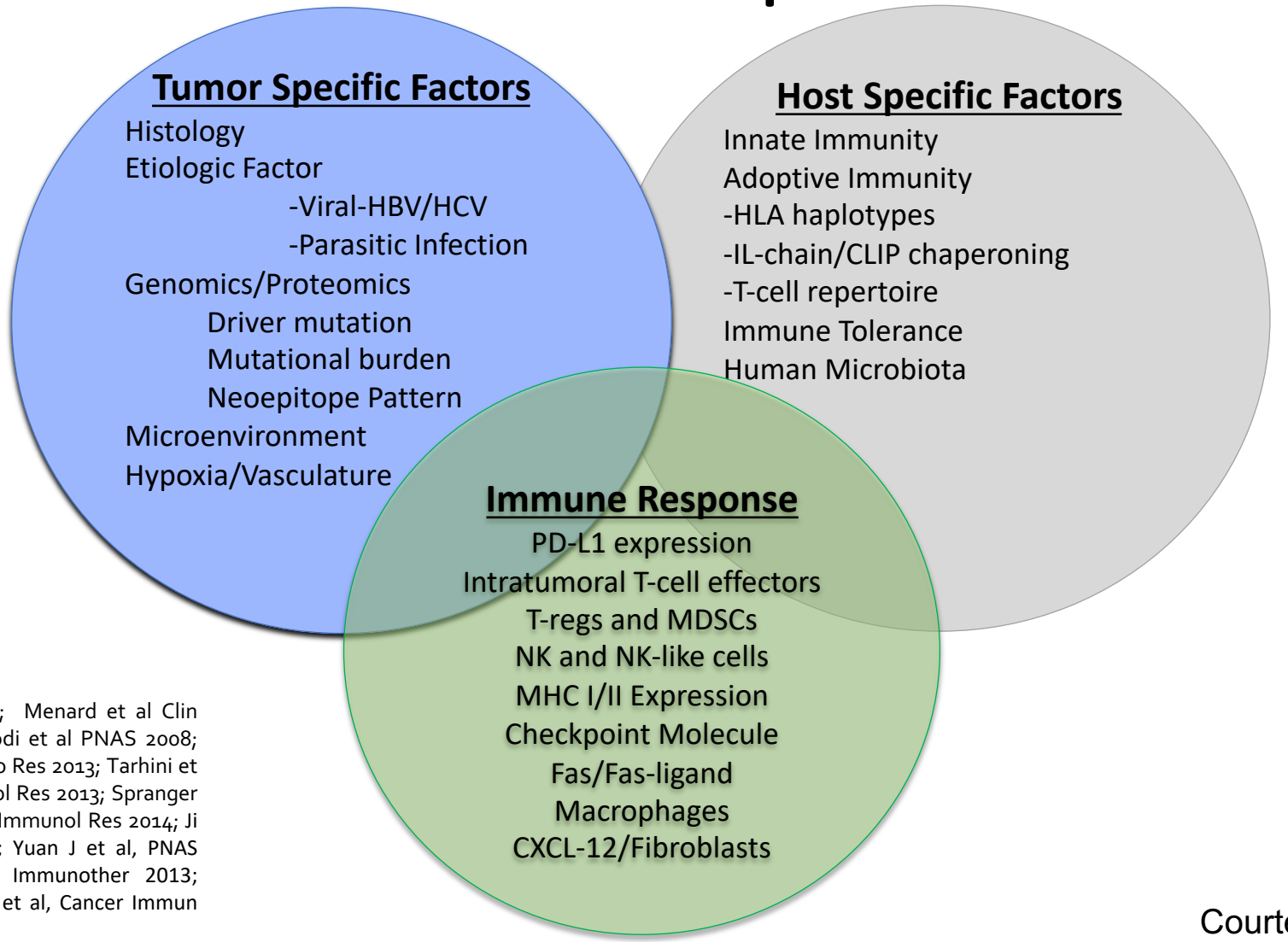
2 of 7 (29%) patients with prior liver transplant treated with IO developed acute rejection

0 of 5 HCC patients had clinical benefit

DeLeon et al. JGO 2018

Courtesy of James J Harding, MD

Why do subsets of patients and tumors respond to immune checkpoint blockade?

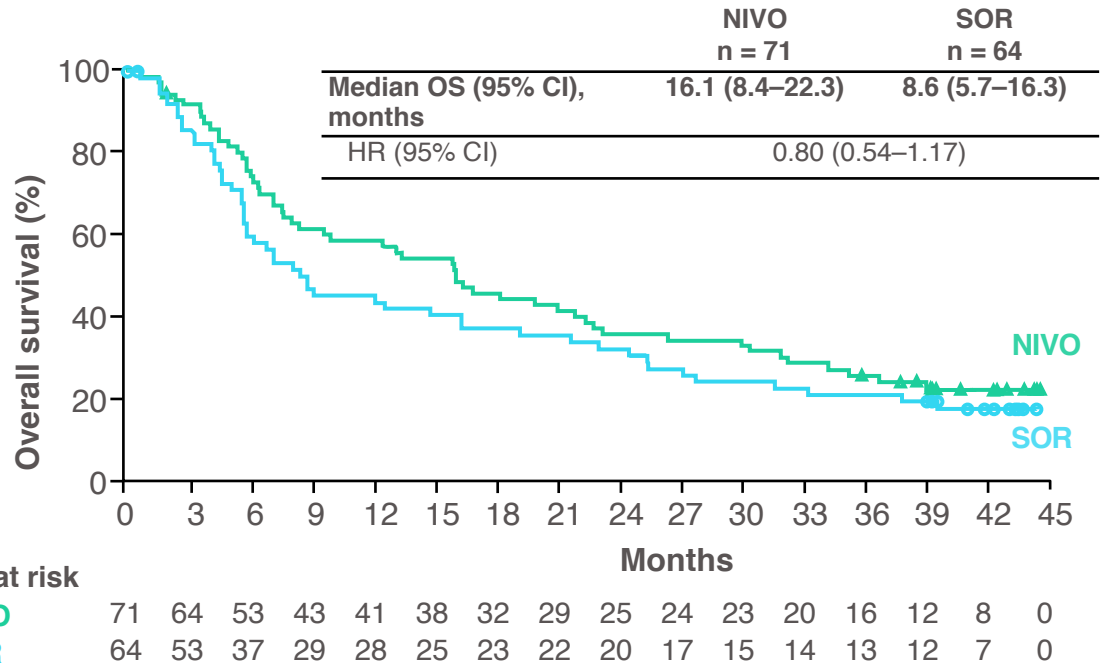


Feig et al PNAS 2013; Ku et al Cancer 2010; Menard et al Clin Cancer Res 2008; Weber et al JCO 2009; Hodi et al PNAS 2008; Hamid et al JCO 2009; Ng et al Cancer Immuno Res 2013; Tarhini et al PLoS One 2014; Kitano et al Cancer Immunol Res 2013; Spranger et al Sci Transl Med 2013; Kitano et al Cancer Immunol Res 2014; Ji RR et al, Cancer Immunol Immunother 2012; Yuan J et al, PNAS 2011; DiGiacoa\m lo etal Cancer Immunol Immunother 2013; Queirolog et al, Cancer Invest 2013; Wolchok et al, Cancer Immun 2010.

Courtesy of James J Harding, MD

CheckMate 459: Overall survival by PD-L1 expression

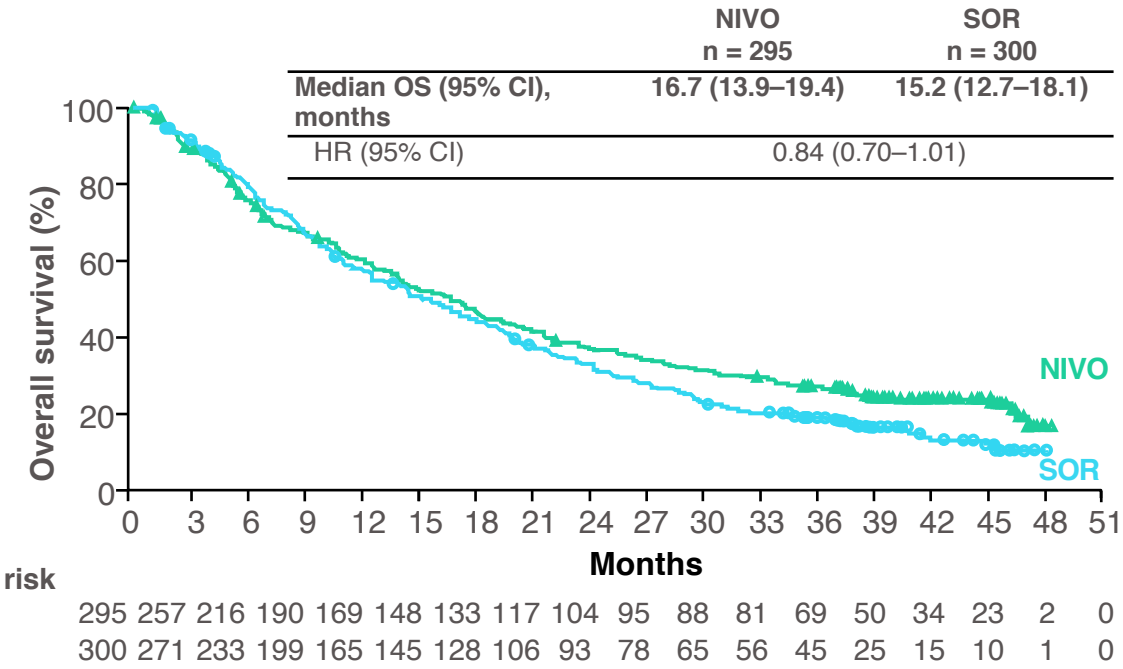
Tumor cell PD-L1 expression ≥ 1%



No. at risk

NIVO	71	64	53	43	41	38	32	29	25	24	23	20	16	12	8	0
SOR	64	53	37	29	28	25	23	22	20	17	15	14	13	12	7	0

Tumor cell PD-L1 expression < 1%



No. at risk

NIVO	295	257	216	190	169	148	133	117	104	95	88	81	69	50	34	23	2	0
SOR	300	271	233	199	165	145	128	106	93	78	65	56	45	25	15	10	1	0

- OS in the PD-L1 ≥ 1% group was longer in the NIVO arm compared with the SOR arm

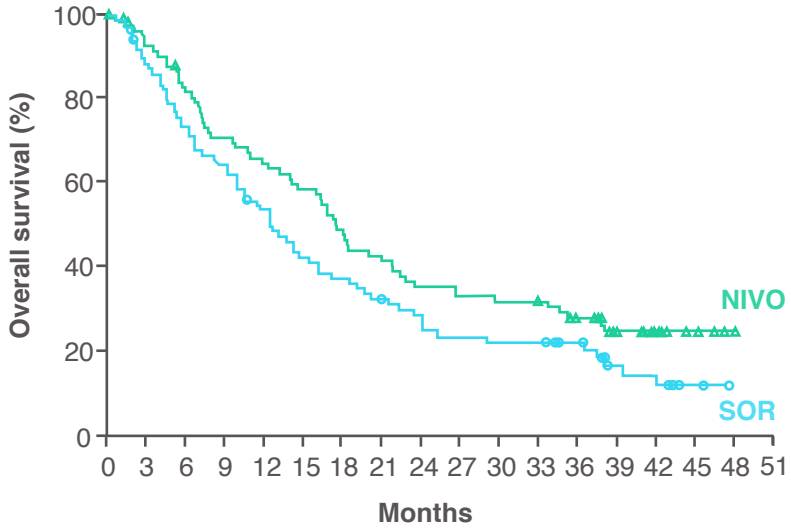
[a]IHC 28-8 pharmDx assay.
IHC, immunohistochemistry; PD-L1, programmed death ligand 1.

Courtesy of James J Harding, MD

CheckMate 459: Overall survival by etiology

HCV

	NIVO n = 87	SOR n = 86
Median OS (95% CI), months	17.5 (13.9–21.9)	12.7 (9.9–16.2)
HR (95% CI)	0.72 (0.51–1.02)	

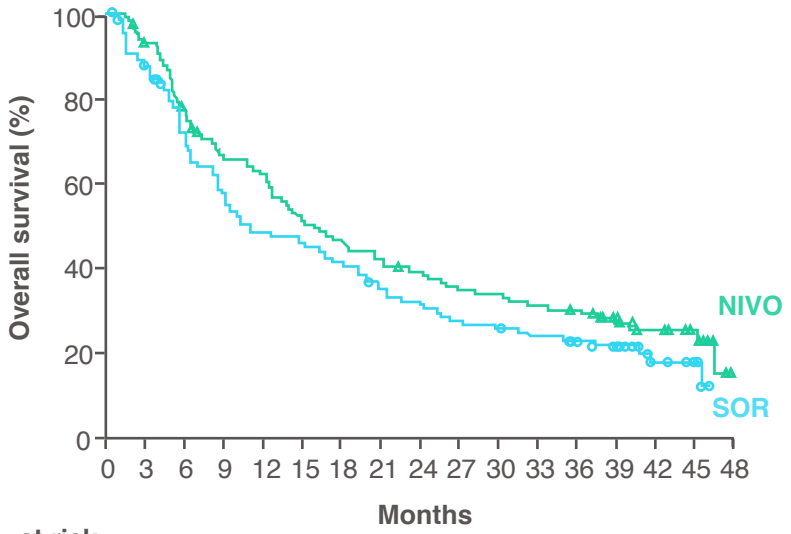


No. at risk

NIVO	87	77	67	58	53	48	40	34	29	27	26	25	20	13	8	4	1	0
SOR	86	74	61	54	43	34	30	25	22	18	17	17	14	7	5	2	0	0

HBV

	NIVO n = 116	SOR n = 117
Median OS (95% CI), months	16.1 (12.5–21.3)	10.4 (8.5–17.3)
HR (95% CI)	0.79 (0.59–1.07)	

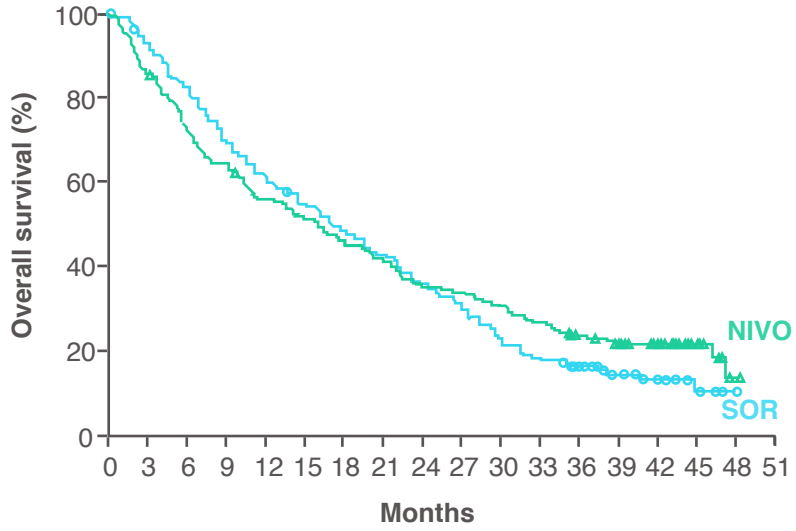


No. at risk

NIVO	116	106	86	72	68	56	51	46	42	37	36	33	31	21	14	9	0	
SOR	117	101	77	63	53	50	45	37	33	29	27	24	21	17	8	4	0	

Uninfected

	NIVO n = 168	SOR n = 168
Median OS (95% CI), months	16.0 (10.8–20.2)	17.4 (13.7–21.3)
HR (95% CI)	0.91 (0.72–1.16)	



No. at risk

NIVO	168	143	120	107	92	85	76	68	59	56	50	44	35	29	20	10	1	0	
SOR	168	154	137	116	101	90	80	70	60	50	37	30	23	13	9	4	1	0	

- In the HCV and HBV groups, median OS was numerically longer with NIVO versus SOR

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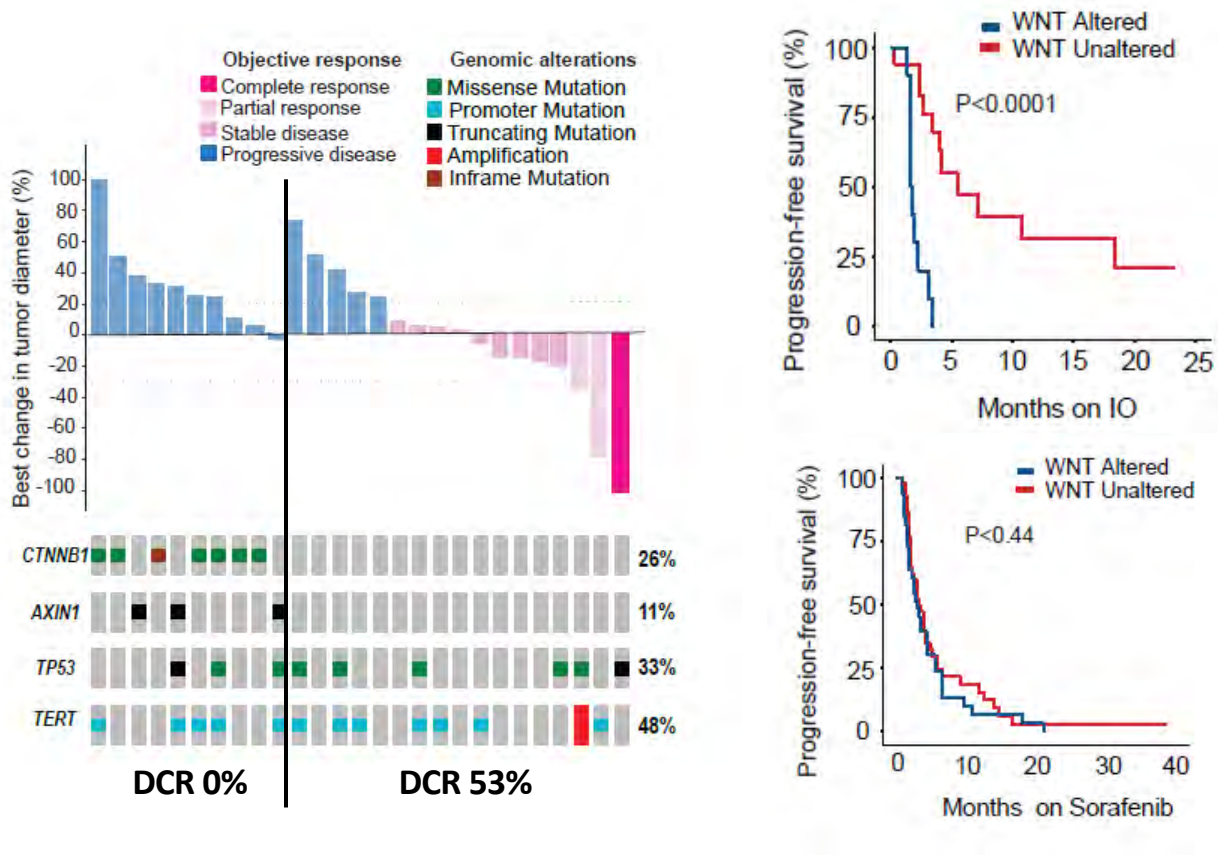
[a]Patients could have had active or resolved HBV or HCV infection as a risk factor for HCC as assessed by the investigator.

Courtesy of James J Harding, MD

WNT genomic alterations as a determinant of response to immune checkpoint inhibitors

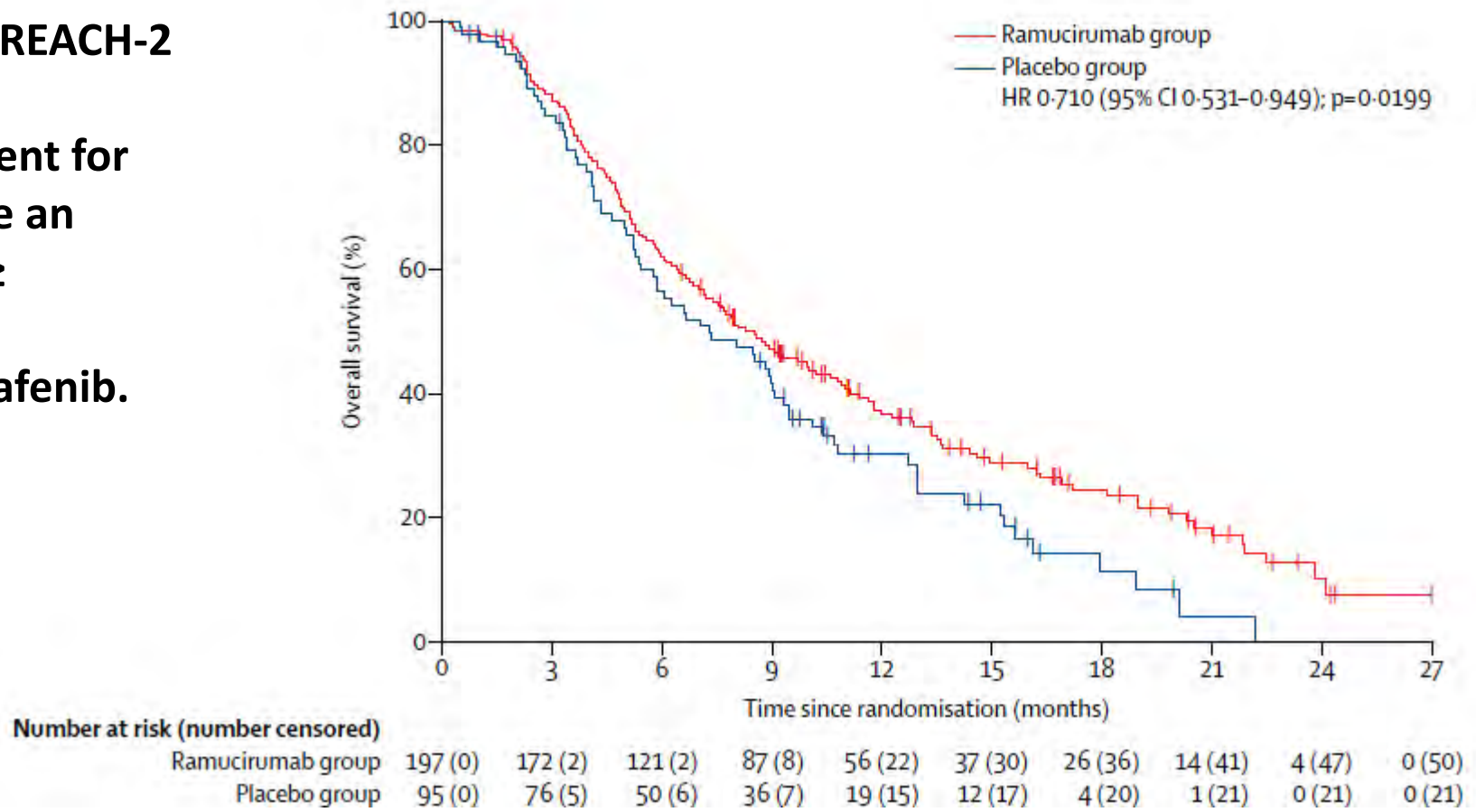


Harding et al. *Clinical Cancer Research* 2018

Courtesy of James J Harding, MD

REACH-2 trial and the value of AFP

Based on the results of the REACH-2 trial, the FDA approved ramucirumab as a single agent for patients with HCC who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL and have been previously treated with sorafenib.



Zhu et al. Lancet 2019

Courtesy of James J Harding, MD

What is your usual first-line systemic therapy for HCC in a 70-year-old patient with a Child-Pugh A score and cirrhosis but with a history of extensive psoriasis controlled with local therapy?

1. Sorafenib
2. Lenvatinib
3. Sorafenib or lenvatinib — coin flip
4. Cabozantinib
5. Atezolizumab/bevacizumab
6. Chemotherapy
7. Other

What is your usual first-line systemic therapy for HCC in a 70-year-old patient with a Child-Pugh A score and cirrhosis but with a history of liver transplant currently off therapy?

1. Sorafenib
2. Lenvatinib
3. Sorafenib or lenvatinib — coin flip
4. Cabozantinib
5. Atezolizumab/bevacizumab
6. Chemotherapy
7. Other

What is your usual first-line systemic therapy for HCC in a 70-year-old patient with a Child-Pugh A score and cirrhosis but with a history of renal transplant currently off therapy?

1. Sorafenib
2. Lenvatinib
3. Sorafenib or lenvatinib — coin flip
4. Cabozantinib
5. Atezolizumab/bevacizumab
6. Chemotherapy
7. Other

Case Presentation – Dr Harding: A 43-Year-Old Female with Stage IV HCC

- A 43-year-old female with controlled lupus and autoimmune hepatitis with AJCC Stage IV HCC
- She received lenvatinib with a partial response for 8 months and then cabozantinib with stable disease for 6 months.
- After a discussion regarding the risks and benefits of immunotherapy, the patient went on to receive a single agent anti-PD-1 therapy.
- The patient had normalization of AFP and a partial response on imaging.
- Subsequently the patient developed hypoalbuminemia, proteinuria, anasarca and hyperlipidemia and worsening liver function.
- Restaging showed continued disease control and a renal biopsy showed evidence of lupus glomerulonephritis.
- Immunotherapy was halted and the patient had improvement in her symptoms with high-dose steroids and mycophenolate.
- Restaging after 6 months showed growth of her malignancy and she has entered into a clinical trial for treatment

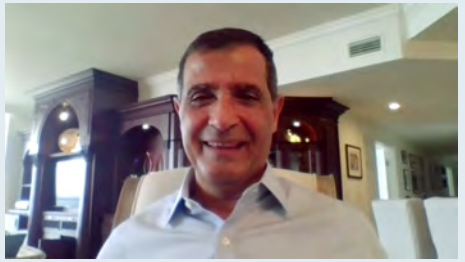
Courtesy of James J Harding, MD

Case Presentation – Dr Harding : A 76-Year-Old Male with HBV-Associated HCC

- A 76-year-old male with HBV associated HCC to the LNs and adrenal gland with CP-A liver function
- Patient underwent a screening EGD that was normal, and received atezolizumab and bevacizumab
- After 9 weeks, he attained a partial response.
- The patient developed Grade 3 HTN and was treated with antihypertensives.
- After 6 months of treatment, the patient continued to have a sustained PR with well controlled blood pressure.
- The patient incidentally developed a painful inguinal hernia that required surgery.
- Bevacuzimab was held for 9 weeks while atezolizumab was continued in preparation for surgery.
- Surgery was uncomplicated and bevacizumab was resumed 9 weeks later

Courtesy of James J Harding, MD

Case Presentation – Dr Hussein: A 66-year-old woman with a 7-cm right hepatic mass with portal vein thrombosis



Atif Hussein, MD, MMM

- Alcoholic cirrhosis, with a 7-cm right hepatic lobe mass and portal vein thrombosis
- Child-Pugh score = 2, Serum alpha fetoprotein: 2,350 ng/mL, serum PT: 12.2 seconds, INR: 1.6, serum albumin: 3.1 g/dL, total bilirubin: 1.9 mg/dL, no ascites or hepatic encephalopathy
- Sorafenib → PD
- Nivolumab x 9 months, with decrease in serum alpha fetoprotein

Questions

- In the pivotal study of atezolizumab/bevacizumab, all the patients underwent upper GI endoscopy, even if they were asymptomatic. Do you still do that in all your patients, or do you select those at high risk?
- What do you generally use as second-line therapy after atezolizumab/bevacizumab?

Agenda

Module 1: Front-Line Management Options for Advanced Hepatocellular Carcinoma (HCC) – Dr Kaseb

Module 2: Selection and Sequencing of Treatment for Patients with Relapsed HCC – Dr Greten

Module 3: Considerations for the Treatment of HCC in Special Patient Populations – Dr Harding

Module 4: New Directions in the Management of HCC – Dr Finn

Case Presentation – Dr Zafar: A 77-year-old man with advanced HCC and good performance status

Syed Zafar, MD

- PMH: Hepatitis C, prostate cancer (1999), radiation cystitis with occasional hematuria
- Chronic peri-anal fistula
  - Vesicle artery embolization. Post-procedure CT revealed low-density left liver lesion
- MRI: Infiltrative left hepatic mass, tumor thrombus in the intrahepatic portal system, 13 x 9 cm, consistent with HCC, multiple lung nodules
  - AFP >40,000 ng/mL
- Nivolumab x 6 mos → progressive disease

Questions

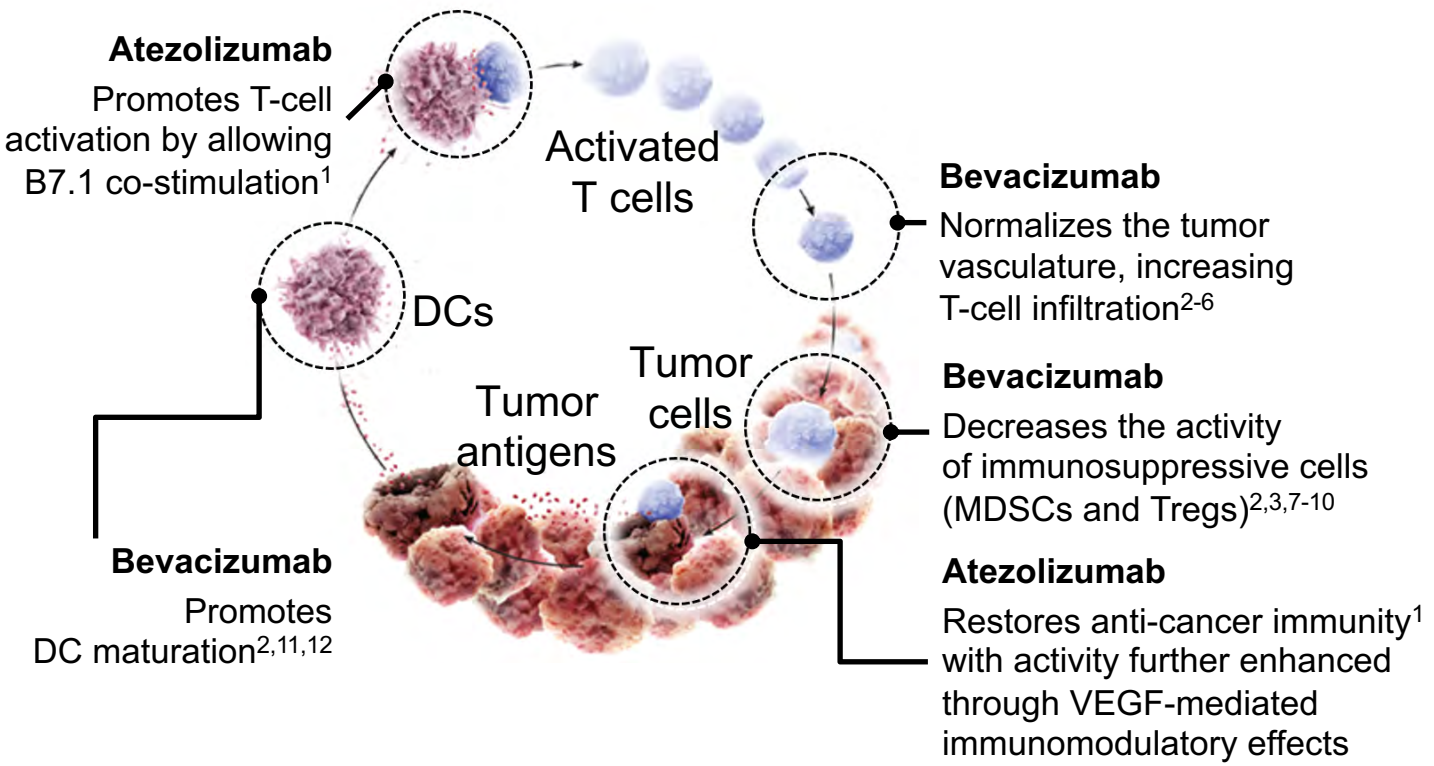
- In light of his occasional hematuria and the ongoing fistula, I am concerned about using anti-VEGF therapy, so what would you recommend now that his disease is progressing on nivolumab – add ipilimumab? Try a TKI?

The Challenge

- Progress in systemic therapy has been slow
- Incremental improvements with sequential VEGFR TKIs
- Immune checkpoint inhibitors have demonstrated single-agent activity in advanced HCC but phase 3 studies did not meet their endpoints
- How do we improve outcomes with IO in HCC?
  - Biomarker select those patients that are most likely to benefit
  - Novel combinations that increase efficacy

Courtesy of Richard S Finn, MD

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



- 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

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

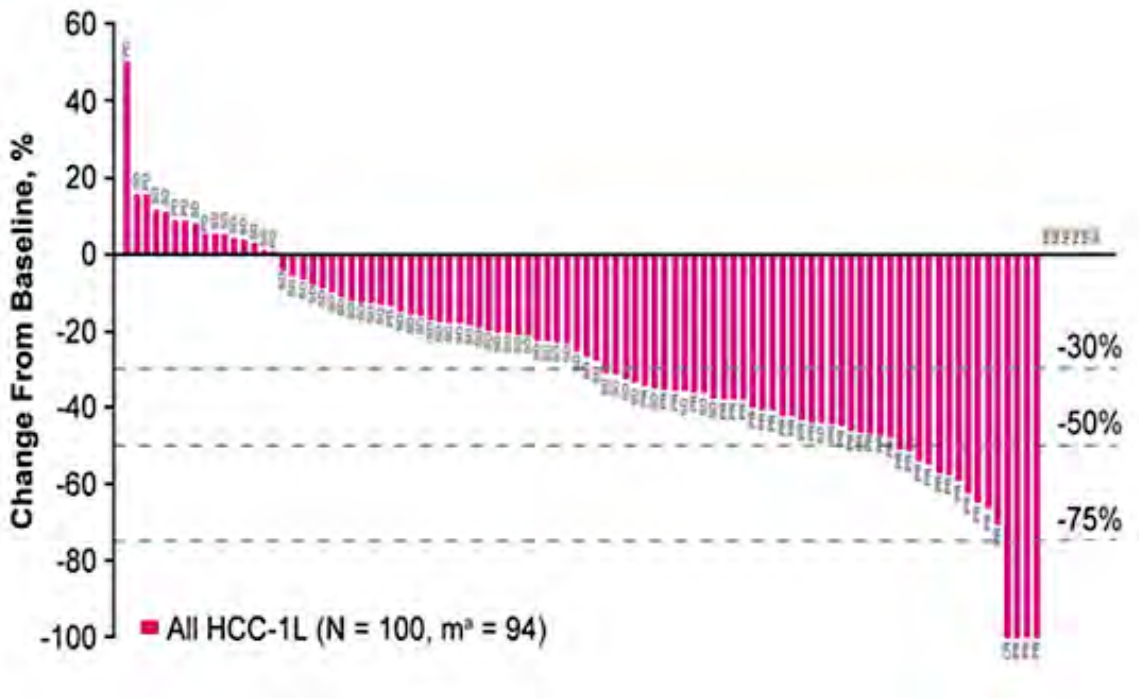
Courtesy of Richard S Finn, MD

KEYNOTE-524: Lenvatinib+Pembrolizumab Efficacy Outcomes

Parameter	Lenvatinib + Pembrolizumab (N = 100)
	RECIST v1.1 per IIR
ORR (confirmed responses), n (%) (95% CI)[a]	36 (36) (26.6–46.2)
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 (1.2–7.7)
Disease control rate, n (%) (95% CI)[a]	88 (88) (80.0–93.6)

[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 Postbaseline Nadir (IIR; RECIST v1.1)

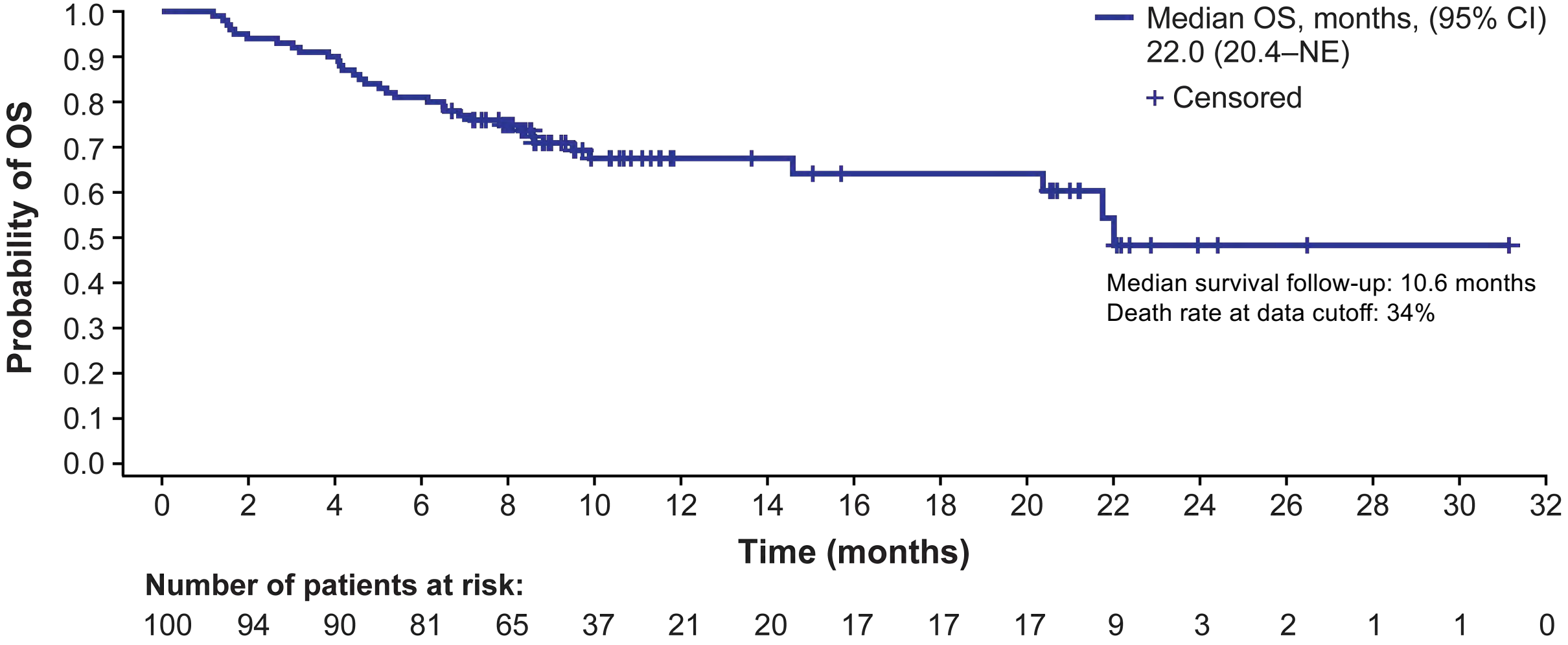


[a]m = number of patients with both baseline and postbaseline values for the sum of diameters of target lesions.

- Finn et al JCO 2020.

Courtesy of Richard S Finn, MD

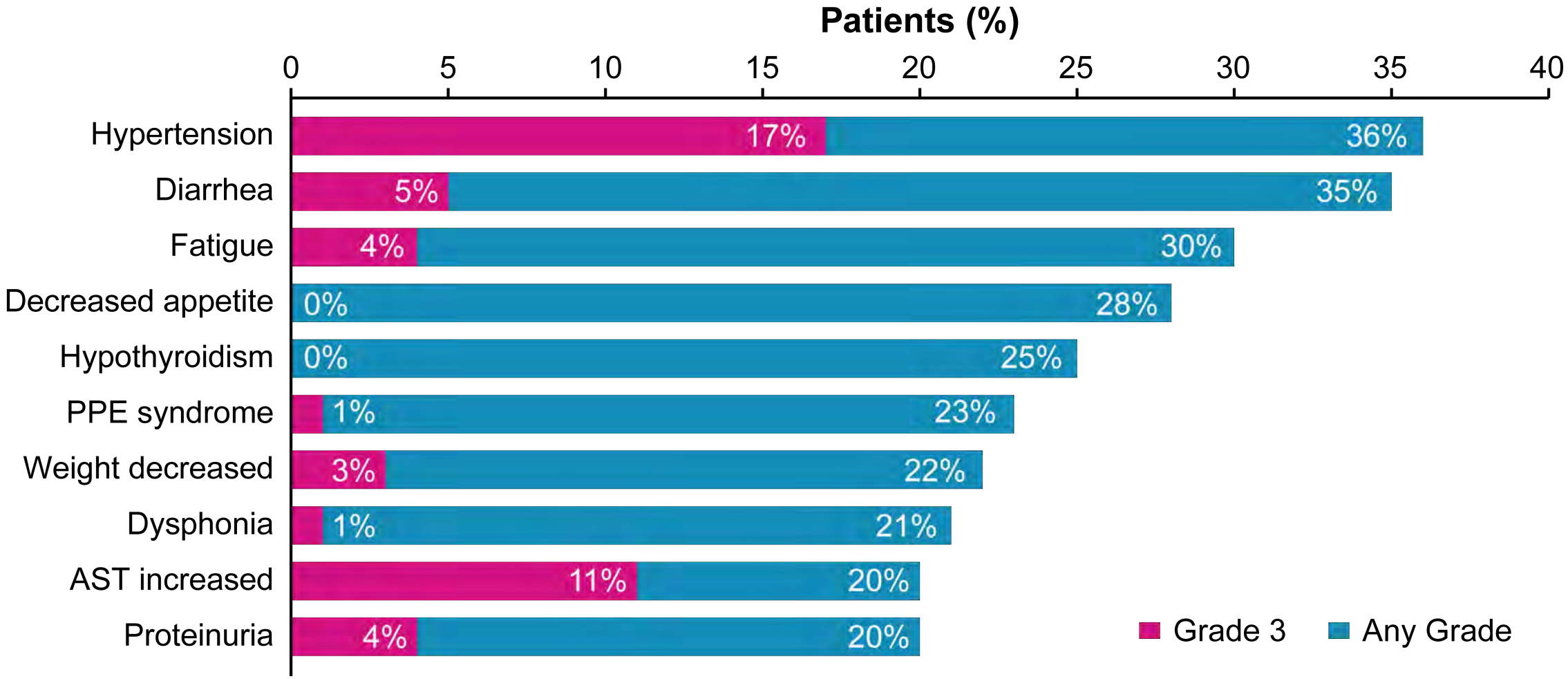
KEYNOTE-524 Kaplan-Meier Estimates of OS



- Finn et al JCO 2020.

Courtesy of Richard S Finn, MD

KEYNOTE-524 Most Common TRAEs[a] (≥ 20% of Patients)

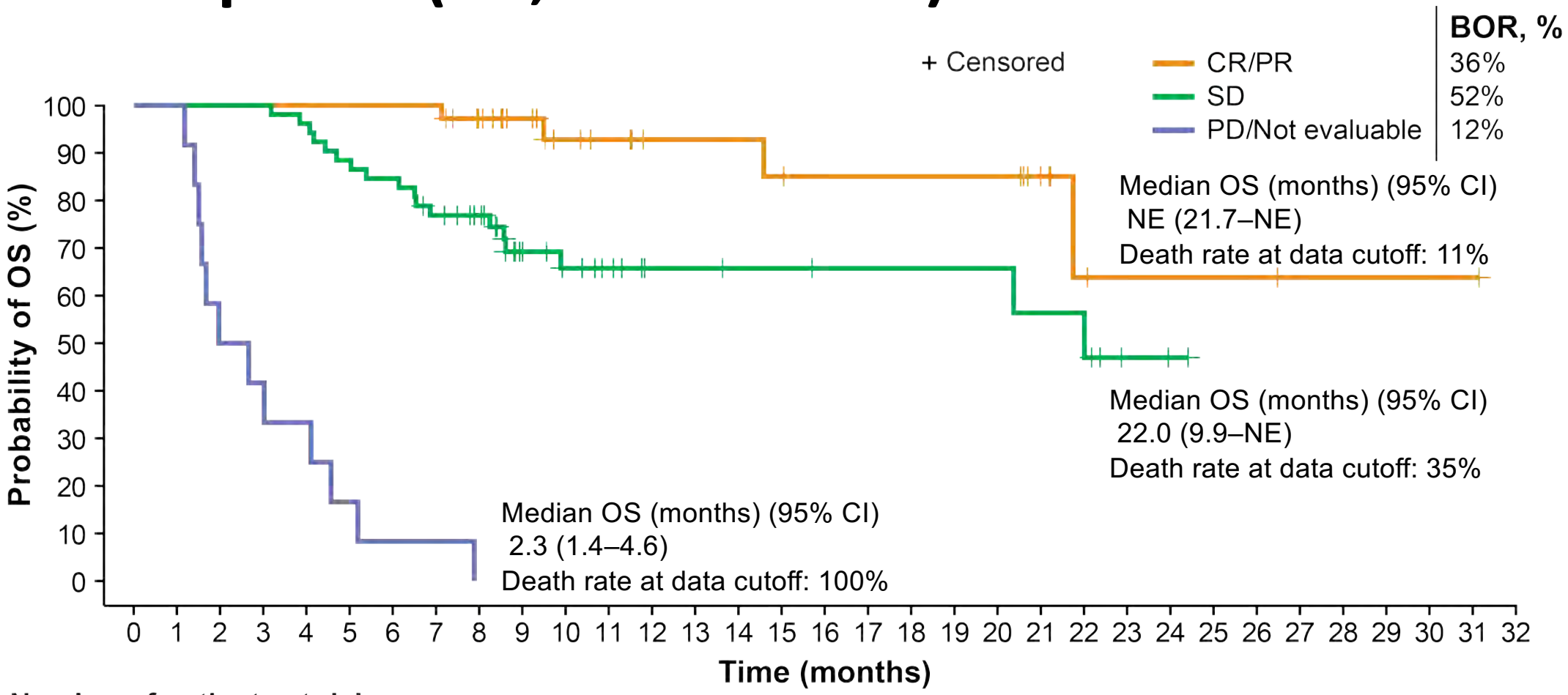


[a]There was 1 grade 4 treatment-related AE (leukopenia/neutropenia).

- Finn et al JCO 2020.

Courtesy of Richard S Finn, MD

KEYNOTE-524 Kaplan–Meier Estimates of OS by Best Overall Response (IIR; RECIST v1.1)



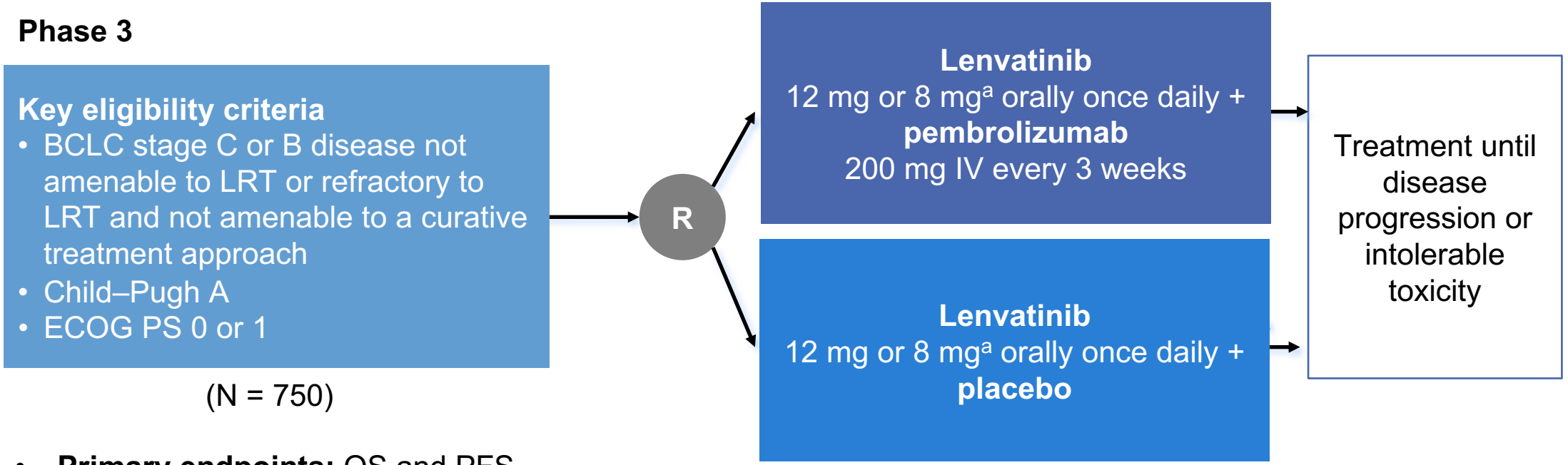
Number of patients at risk:

CR/PR	36	36	36	36	36	36	36	36	31	24	19	17	12	12	12	11	10	10	10	10	10	6	3	2	2	2	2	1	1	1	1	1	0
SD	52	52	52	52	50	46	44	39	34	22	18	13	9	9	8	8	7	7	7	7	7	6	6	2	1	0	0	0	0	0	0	0	0
PD/Not evaluable	12	12	6	5	4	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- Finn et al EASL 2020.

Courtesy of Richard S Finn, MD

LEAP-002: First-Line Lenvatinib Plus Pembrolizumab Versus Lenvatinib Plus Placebo in Advanced HCC[1]



- **Primary endpoints:** OS and PFS
- **Secondary endpoints:** ORR, DOR, DCR, and safety

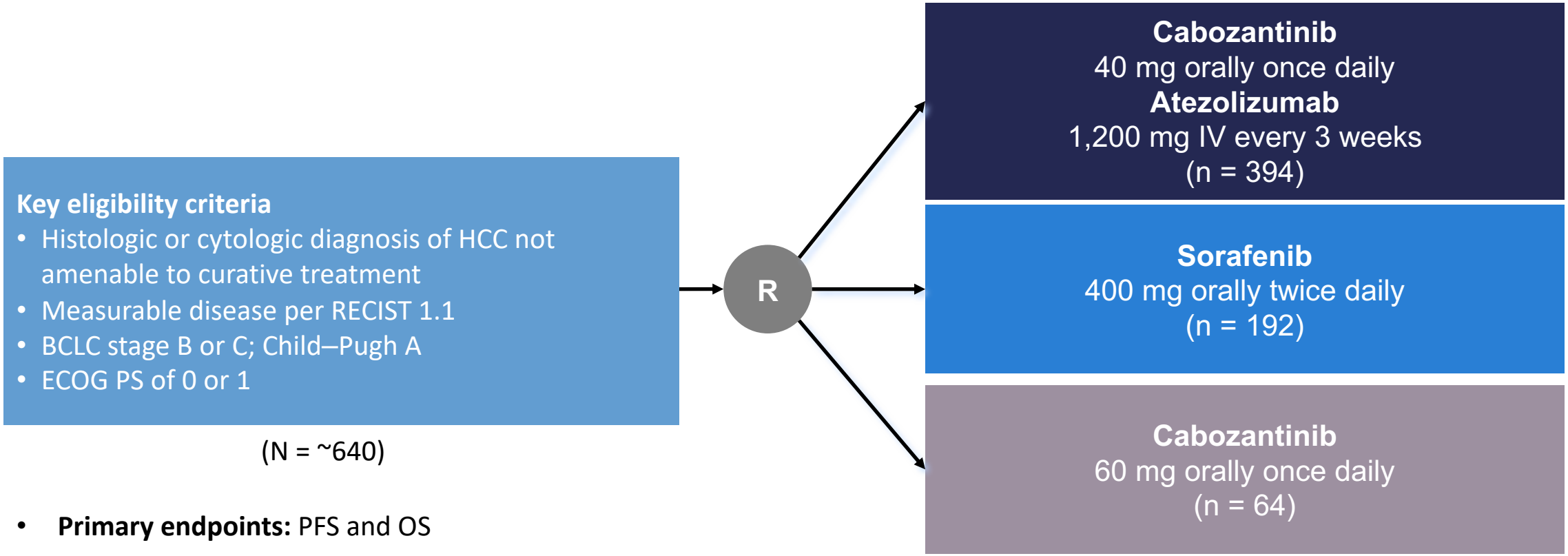
[a] 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg).

1. https://clinicaltrials.gov/ct2/show/NCT03713593. Accessed May 13, 2019.

Courtesy of Richard S Finn, MD

Phase 3 COSMIC-312 Study: Cabozantinib ± Atezolizumab Versus Sorafenib in Advanced HCC[1]

Study in Adults With Advanced HCC Who Have Not Received Prior Systemic Anticancer Therapy in the Advanced Setting



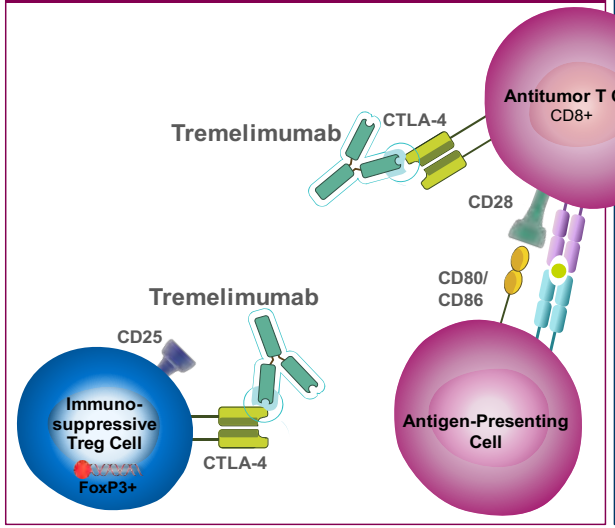
- **Primary endpoints:** PFS and OS

1. https://clinicaltrials.gov/ct2/show/NCT03755791. Accessed May 13, 2019.

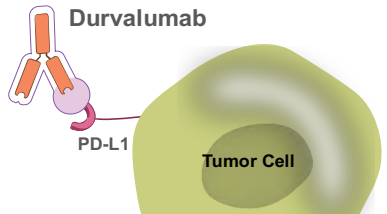
Courtesy of Richard S Finn, MD

Revisiting anti-CTLA-4 and anti-PD-(L)1 Combination Strategy

Tremelimumab Blocks Suppressive T-Cell Signaling in the Lymph Node



Durvalumab Inhibits Suppressive PD-1/ PD-L1 Interactions in the TME

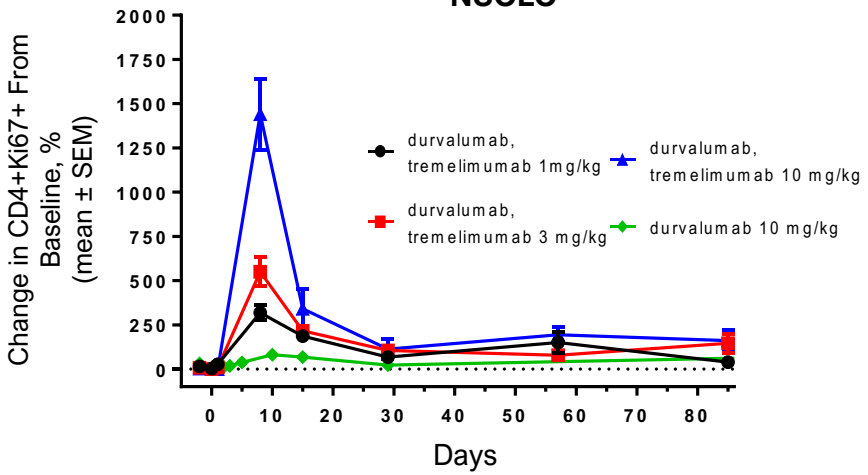


Durvalumab continues to maintain immune activity through inhibition of interactions between PD-1 induced on activated T cells and IFN-γ-driven PD-L1 expression in the TME.[1-3]

In solid tumors, ICI regimens incorporating higher doses of anti-CTLA-4 combined with anti-PD-(L)1 are often associated with improved OS compared to those with lower doses of anti-CTLA-4 but with increased toxicity.[4-9]

- High-dose T combined with D results in an initial burst of peripheral T-cells in patients with NSCLC.[10]
- Similarly in melanoma, the initial dose of ipilimumab + nivolumab causes a proliferative burst of peripheral Tcells, which is not repeated at subsequent doses.[11]

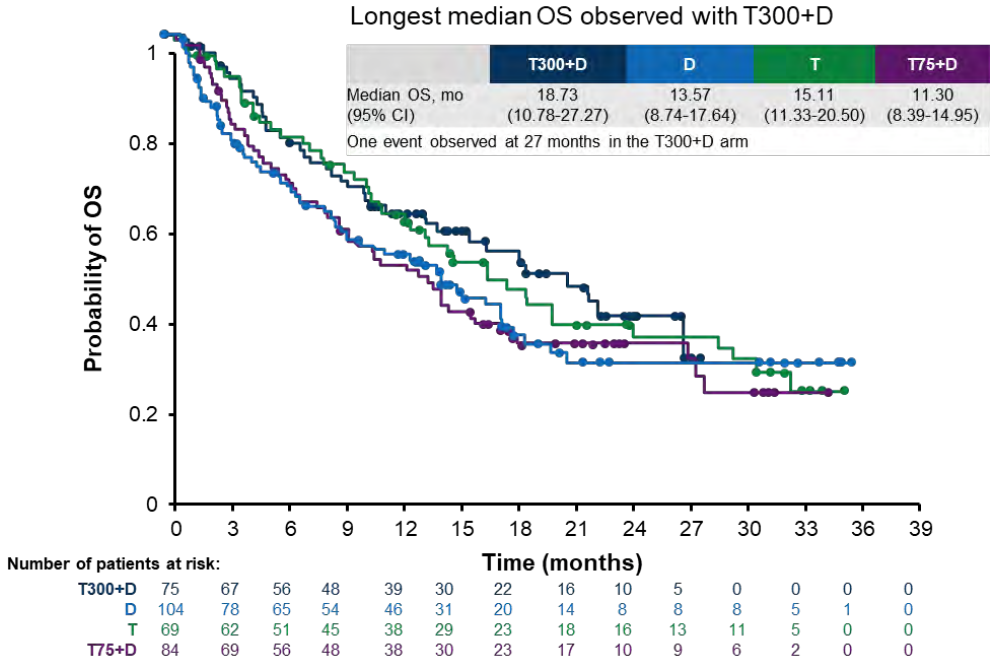
NSCLC[10]



Could a single priming dose of tremelimumab with durvalumab improve immune-mediated clinical activity in HCC patients while minimizing toxicity?

1. Huang, et al. *Nature,* 2017. 60-65; 2. Kamphorts, et al. *PNAS,* 2017. 4993-4998; 3. Butte, et al. *Immunity,* 2007. 111-122; 4.Yau, et al. *J Clin Oncol,* 2019. abstr 4012; 5. Naumann, et al. *Ann Oncol,* 2019. v851-v934; 6. Hellmann, et al. *J Cin Oncol,* 2017. abstr 8503; 7. Sharma, et al. *J Clin Oncol,* 2019. 1608-1616; 8. Janjigian, et al. *J Clin Oncol,* 2018. 2836-2844; 9. Weber, et al. *J Clin Oncol,* 2012. 2691-2697; 10. Antonia, et al. Lancet Oncol, 2016. 299-308. 11. Souza, et al. *Cancer Res*, 2018. abstr CT 104.

Phase 2 Trial: Tremelimumab and Durvalumab[1]

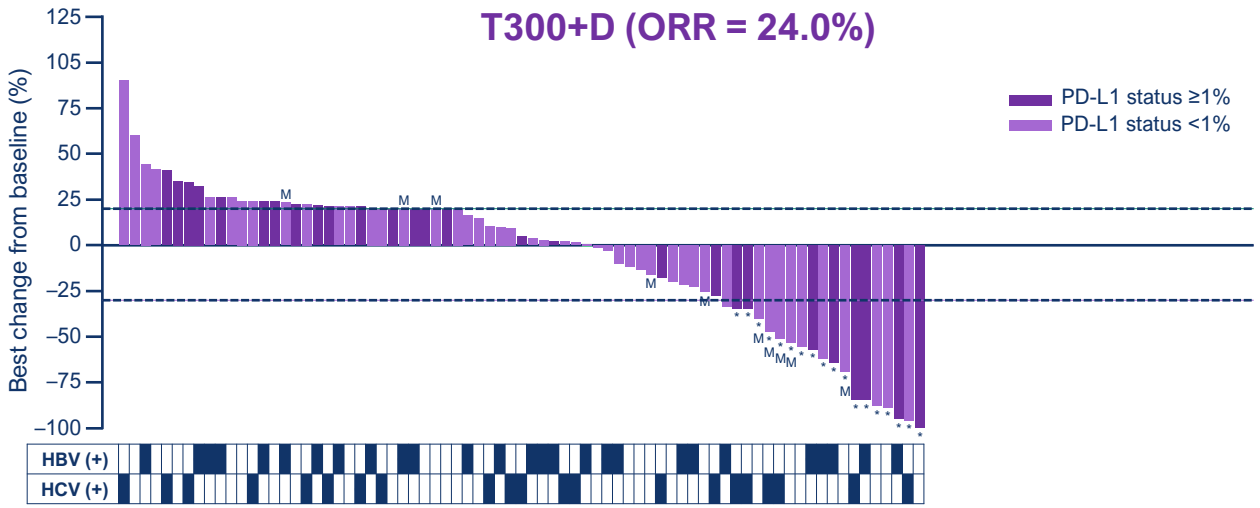


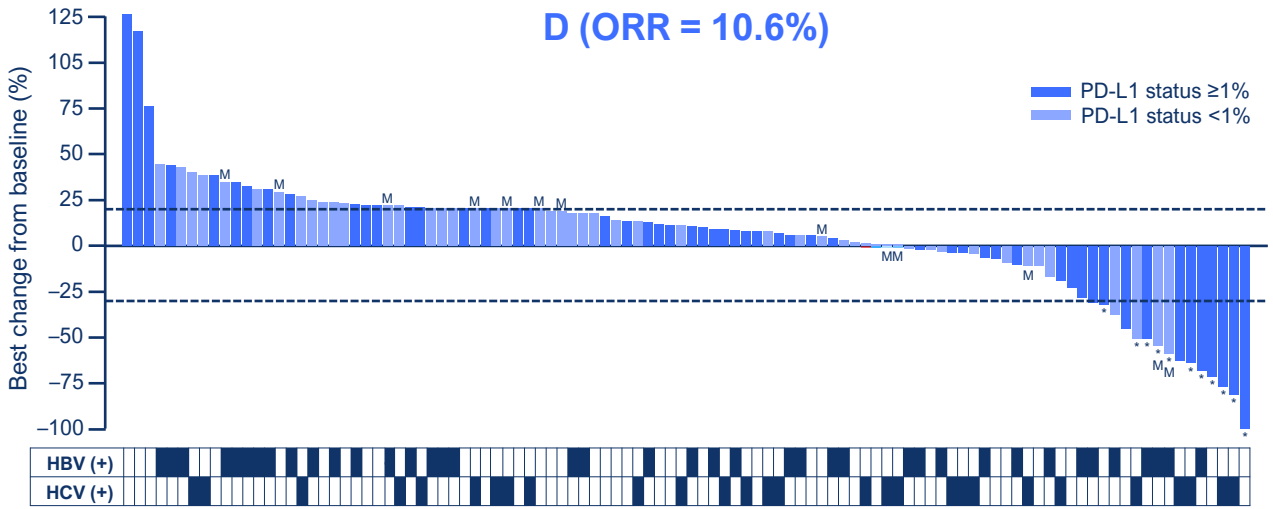
	T300+D (n = 75)	T75+D (n = 84)	D (n = 104)	T (n = 69)
Grade 3/4 TRAEs, %	35.1	24.4	17.8	42.0
Serious TRAEs, %	13.5	11.0	10.9	21.7
Grade 5 TRAEs, n	0	1[a]	3[b]	0
Discontinuation due to TRAEs, %	10.8	6.1	7.9	11.6
ORR, % (95% CI)	24.0 (14.9-35.3)	9.5 (4.2-17.9)	10.6 (5.4-18.1)	7.2 (2.4-16.1)
Median DoR,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

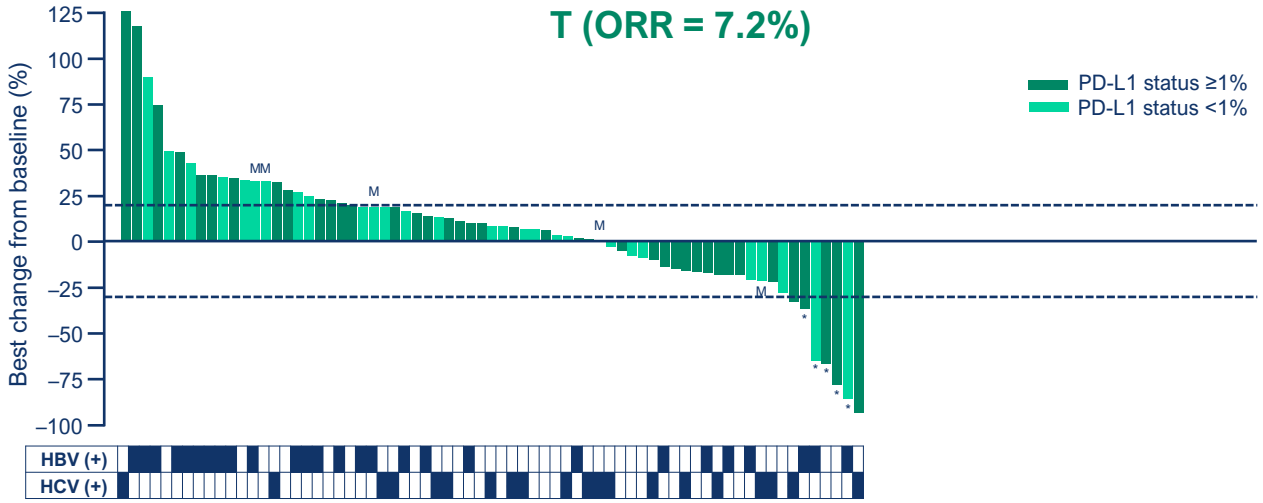
1. Kelley RK et al. ASCO 2020. Abstract 4508.

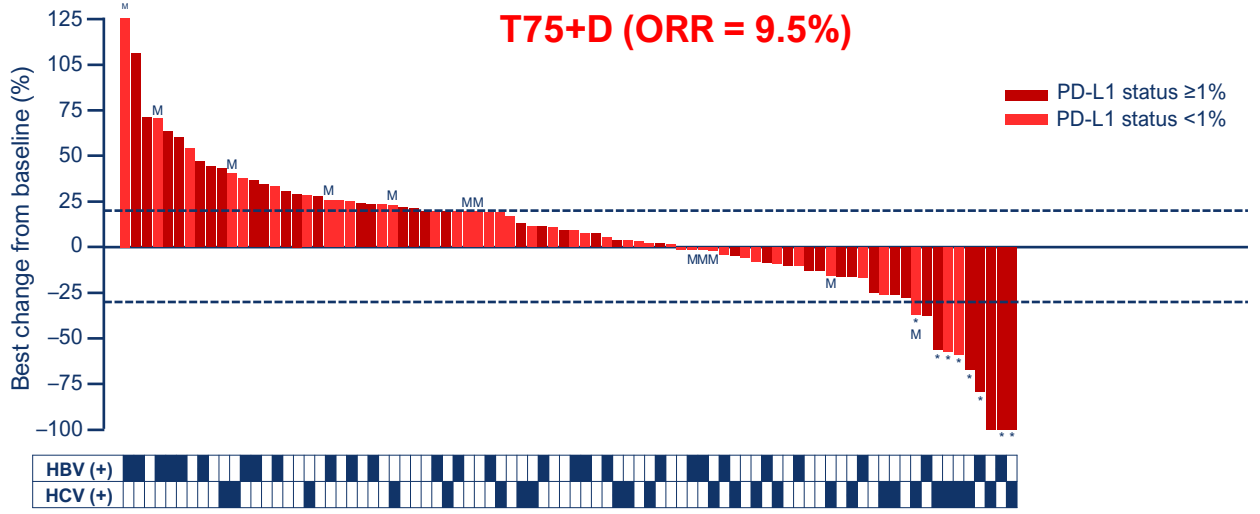
Courtesy of Richard S Finn, MD

Responses Observed Regardless of PD-L1 or Viral Status





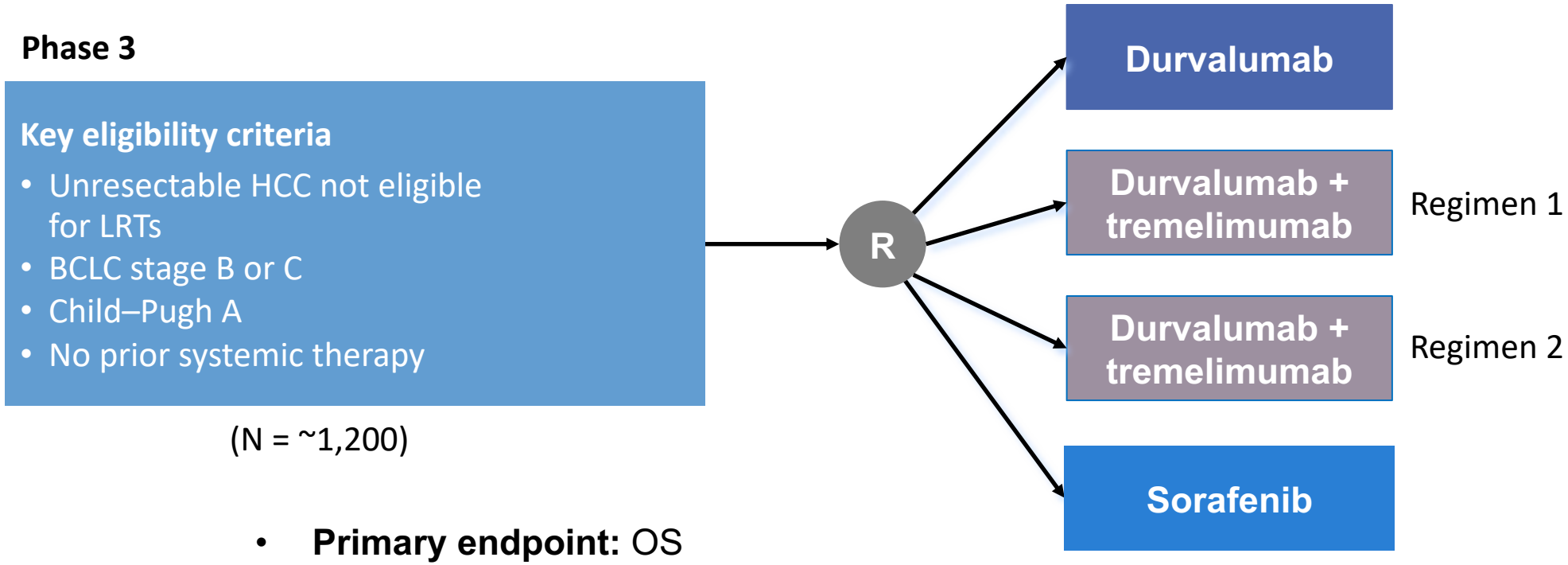




Courtesy of Richard S Finn, MD

*Responders; M, PD-L1 status missing
PD-L1 status is calculated as total number of tumor cells and tumor-associated immune cells positive for PD-L1 divided by tumor area

Phase III HIMALAYA Trial: Durvalumab Plus Tremelimumab Versus Sorafenib[1]

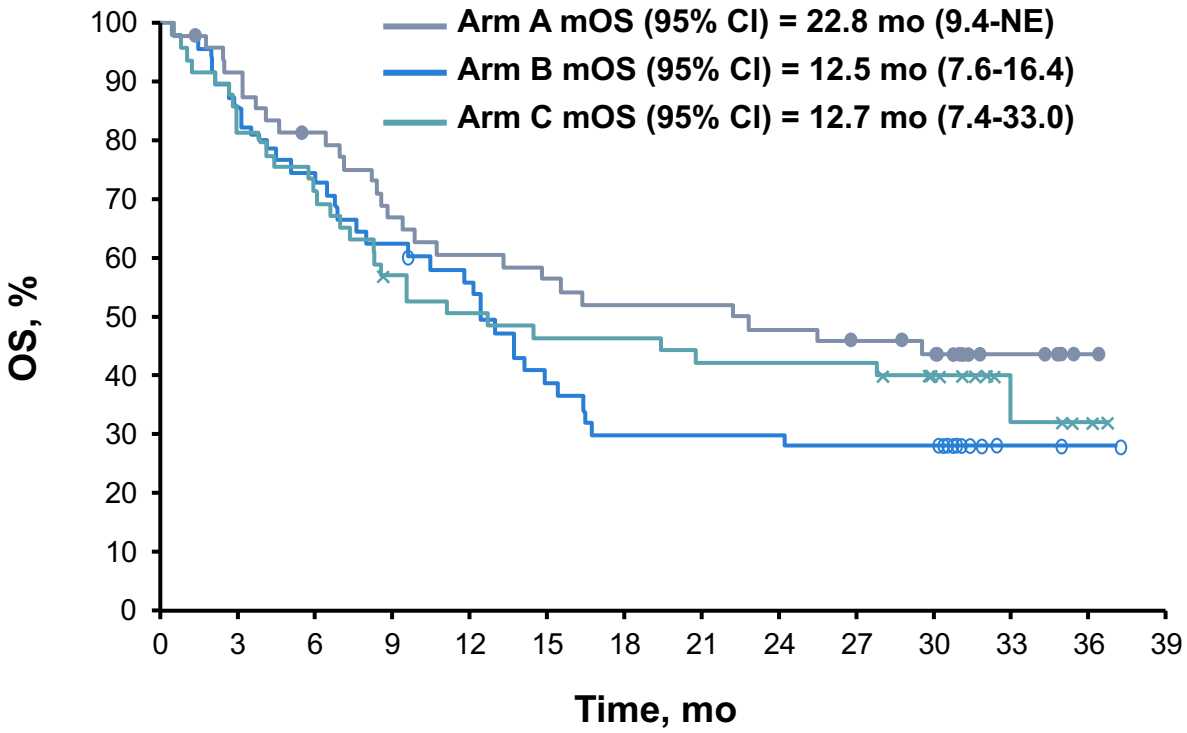


- **Primary endpoint:** OS
- **Other endpoints:** TTP, PFS, ORR, DCR, DOR, and QOL

Courtesy of Richard S Finn, MD

CheckMate-040: Nivolumab + Ipilimumab Efficacy Results[1,2]

	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 (1.1–12.8)	2.6 (1.2–5.5)	2.7 (1.2–8.7)
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+)



- 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

1. El-Khoueiry AB et al. ILCA 2019. Abstract O-13. 2. Yau T et al JAMA Onc 2020

Courtesy of Richard S Finn, MD

CheckMate 9DW

- ***A Randomized, Multi-center, Phase 3 Study of Nivolumab in Combination With Ipilimumab Compared to Sorafenib or Lenvatinib as First-Line Treatment in Participants With Advanced Hepatocellular Carcinoma***
  - Primary Outcome Measure:
    - Overall Survival (OS)
  - Secondary Outcome Measures:
    - Objective Response Rate (ORR)
    - Duration of Response (DOR)
    - Time to Symptom Deterioration (TTSD)
- Start 9/19
- Primary Completion 9/23

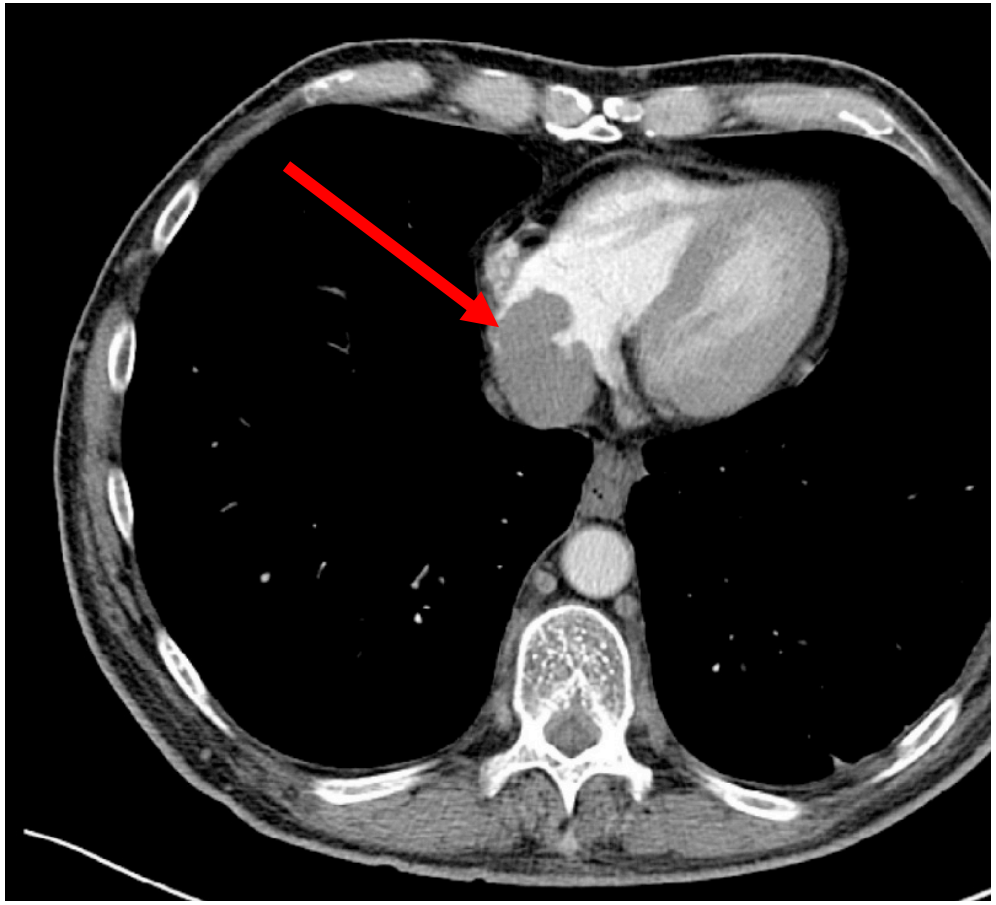
Courtesy of Richard S Finn, MD

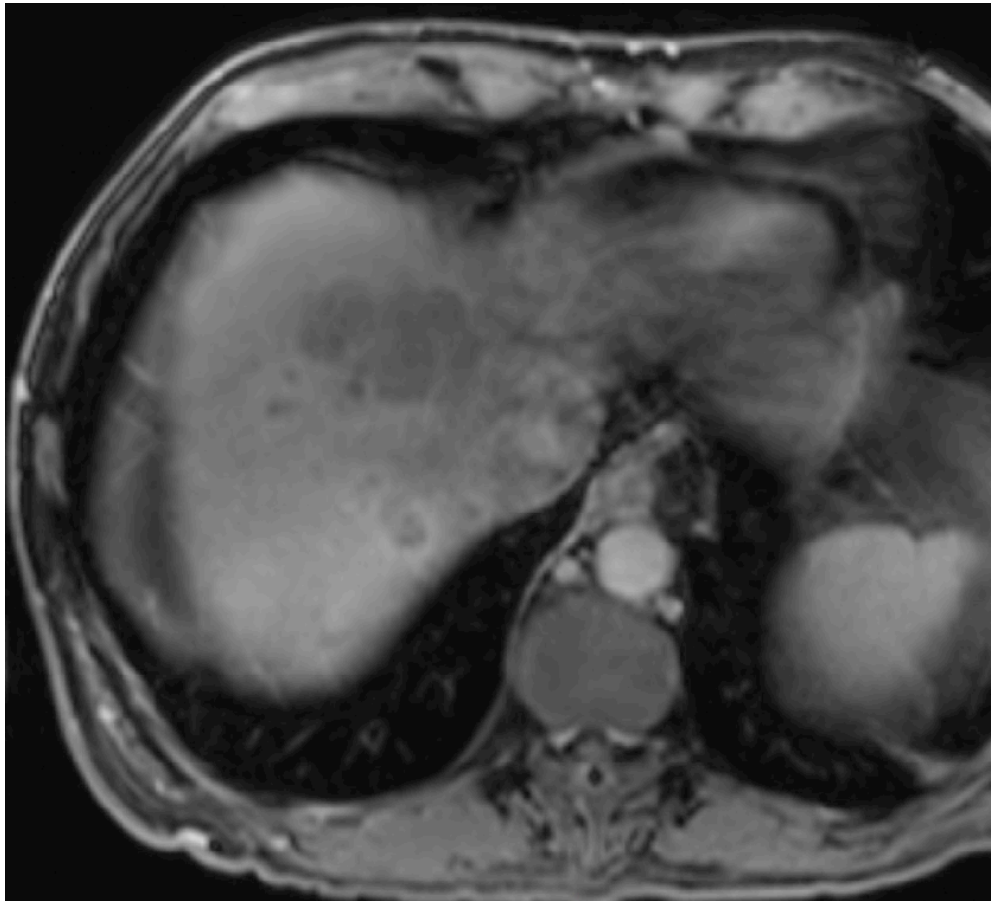
Case Presentation – Dr Finn: A 65-Year-Old Man with Newly Diagnosed mHCC and Elevated AFP

- 65 y.o. male who presented in late November of 2019, with progressive ascites, and muscle wasting. Ultimately, a CT scan was done on 12/20/19, which showed cirrhotic liver, with multiple enhancing liver lesions, largest 5.5cm compressing and invading his IVC.
- Labs done on 1/2/20 showed AFP of 1357, and positive for Hep C. Previous to this, he states he was not aware of being Hep C positive, but did use IV drugs in his teen years.
- WBC 7.0, Hgb 15.7, plts 89, Cr 0.5, T bili 1.4, Alb 3.8, AST 96, ALT 38.
- ECOG PS 2.

Courtesy of Richard S Finn, MD

Case Presentation – Dr Finn: A 65-Year-Old Man with Newly Diagnosed mHCC and Elevated AFP (cont)





Courtesy of Richard S Finn, MD

Case Presentation – Dr Finn: A 65-Year-Old Man with Newly Diagnosed mHCC and Elevated AFP (cont)

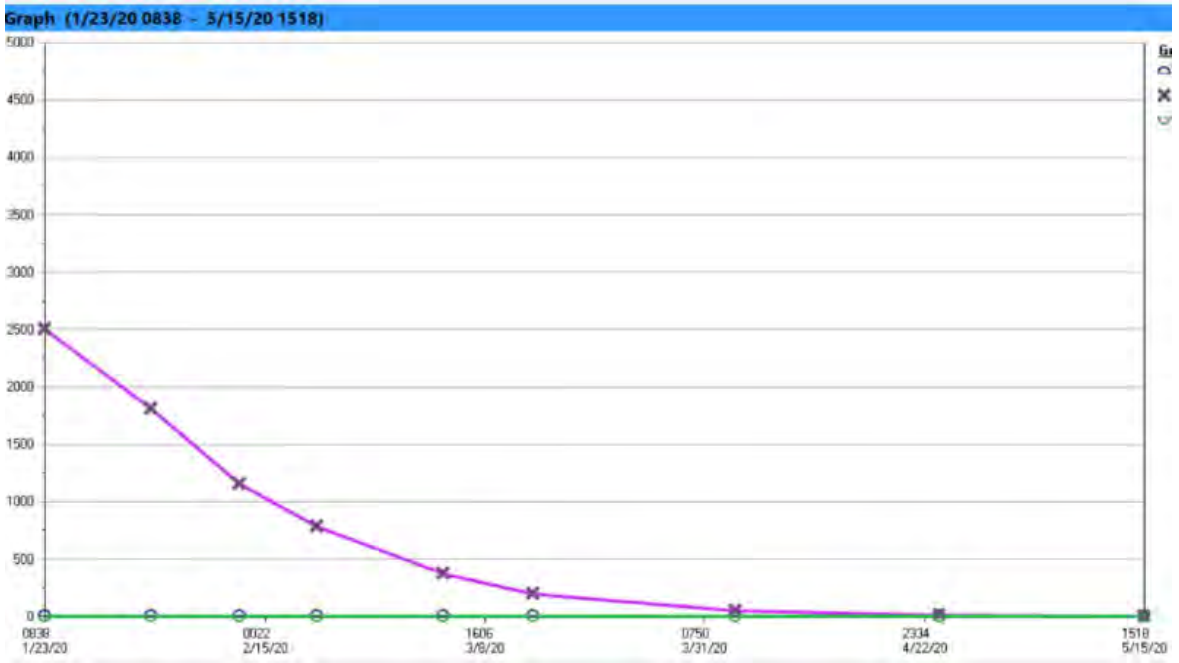
- Have discussion, pt with very advanced HCC with invasion into the RA
- CP A6/ B7 (from ascites)
- Needs a response and quickly
- Start len 12 mg + pembro Feb 2020
- T bili slowly rises, peaking at 4.6 in March

and len held, wt loss

- AFP rapidly declines
- T bili starts falling and len resumed at

4 mg then titrated to 8 mg

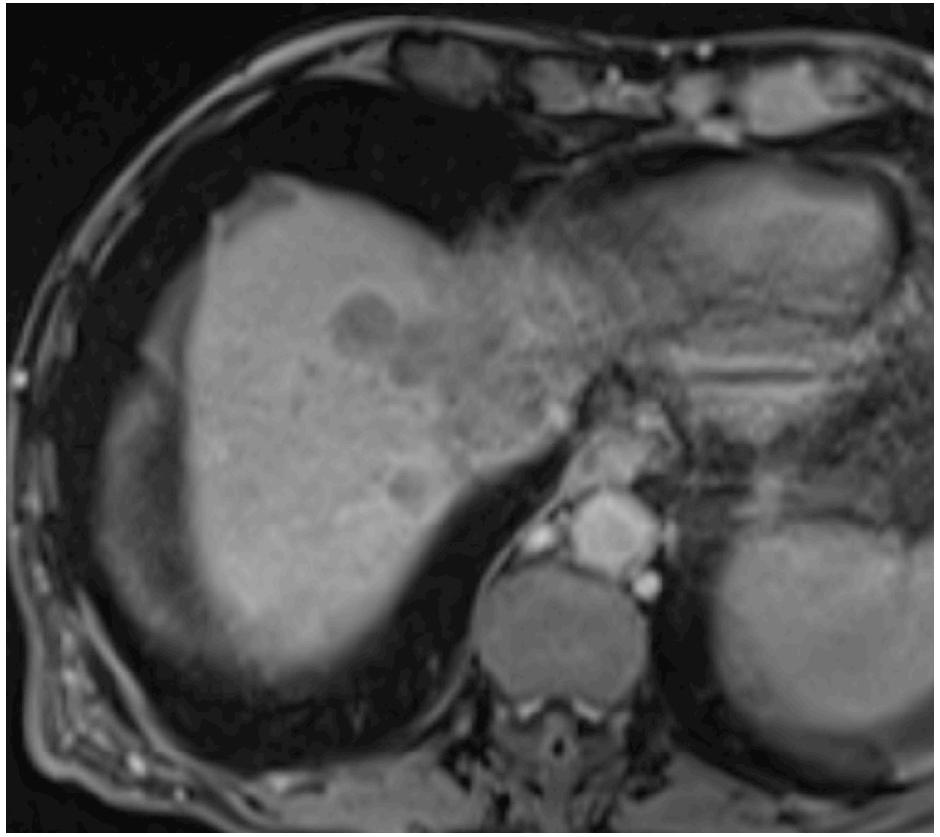
AFP over time



Courtesy of Richard S Finn, MD

Case Presentation – Dr Finn: A 65-Year-Old Man with Newly Diagnosed mHCC and Elevated AFP (cont)

- Overall improving energy, decreased ascites, stopped using walker
- Reimaged May 2020 after C5 pembro
  - Significant response
- Ongoing response, 2021



Courtesy of Richard S Finn, MD

Case Presentation – Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC

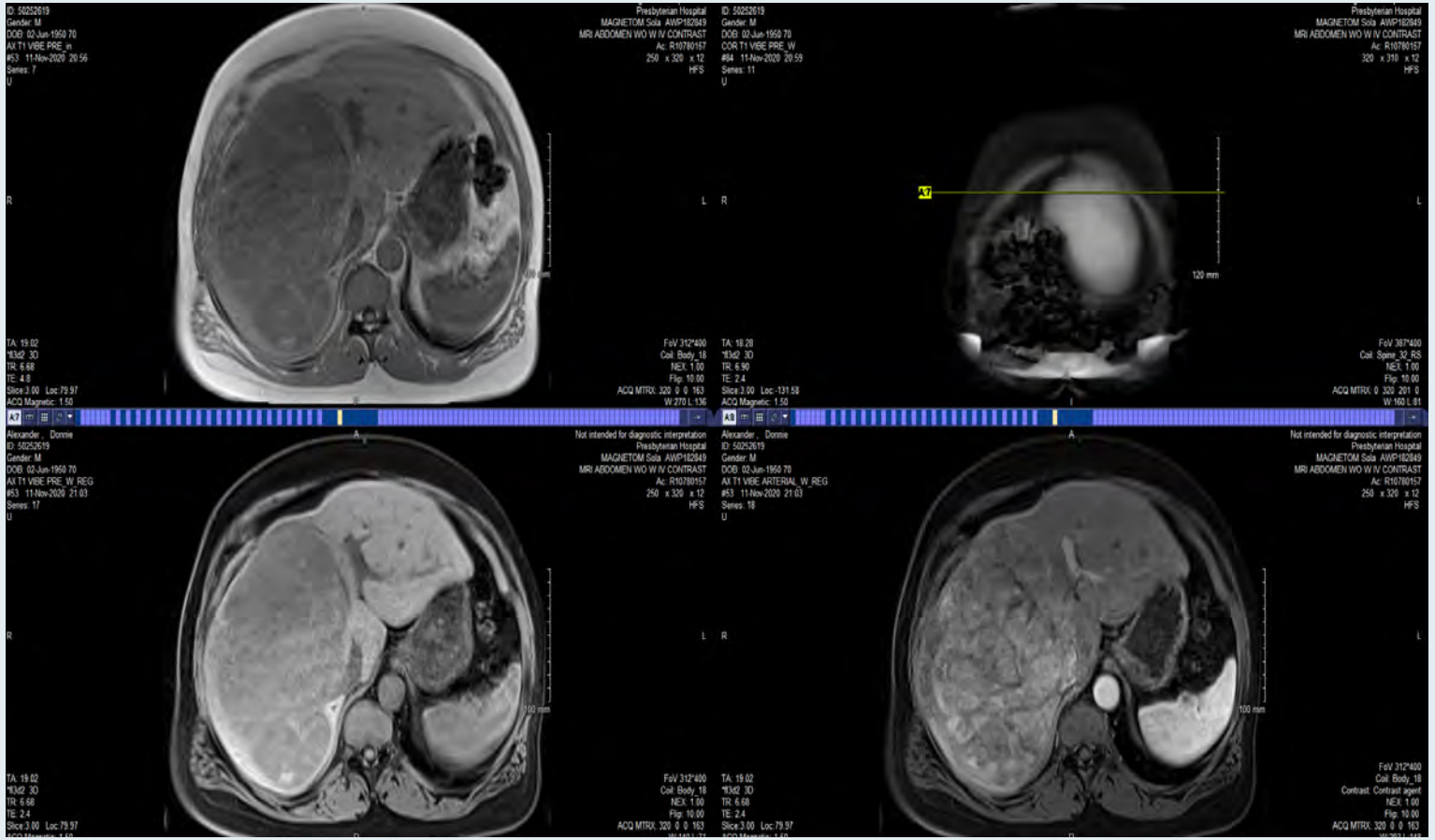
Nasfat Shehadeh, MD

- PMH: Treated hepatitis C, alcohol abuse
- 11/2020: Child-Pugh A HCC (MELD: 7) heavily involving the right lobe (see images), with no extrahepatic disease
  - AFP: 63,000 ng/mL
- Referred for liver-directed therapy (delayed due to social issues)
- 1/2021: Admitted with SOB, wide complex tachycardia, probably alcohol-induced cardiomyopathy
  - Currently stable on medications, EF: 35%, PS 1
- Interventional radiology/radiation oncology plan: yttrium-90 radioembolization

Case Presentation – Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC

Nasfat Shehadeh, MD

MRI Abdomen (11/11/2020)



Case Presentation – Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC (cont)

Nasfat Shehadeh, MD

Questions

- How to decide between radioembolization vs chemoembolization for patients like him? Since his right lobe is almost totally occupied by HCC, do you consider multi-stage embolization, and how often?
- What about future TKI and IO in the context of his significant cardiomyopathy?

Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Multiple Myeloma

Thursday, January 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Rafael Fonseca, MD
Jonathan L Kaufman, MD

Moderator

Neil Love, MD

RTP Year in Review 2020

Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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RESEARCH TO PRACTICE