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

Hepatobiliary and Pancreatic Cancers

Tuesday, December 15, 2020
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
Lipika Goyal, MD, MPhil

Moderator

Neil Love, MD

Year in Review 2020

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Eisai Inc, Exelixis Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Merck and Taiho Oncology Inc.

Year in Review 2020

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, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Genomic Health Inc, 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, 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.

Year in Review 2020

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

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Dr Bekaii-Saab — Disclosures

Advisory Committee	Immuneering Corporation, Imugene, Sun BioPharma Inc
Consulting Agreements	Array BioPharma Inc, a subsidiary of Pfizer Inc, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celularity Inc, Daiichi Sankyo Inc, Eisai Inc, Exact Sciences, Genentech, a member of the Roche Group, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Natera Inc, Seagen Inc, Sobi, Treos Bio
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Data and Safety Monitoring Board/Committee	1Globe Health Institute, AstraZeneca Pharmaceuticals LP, Exelixis Inc, Lilly, Merck, Pancreatic Cancer Action Network

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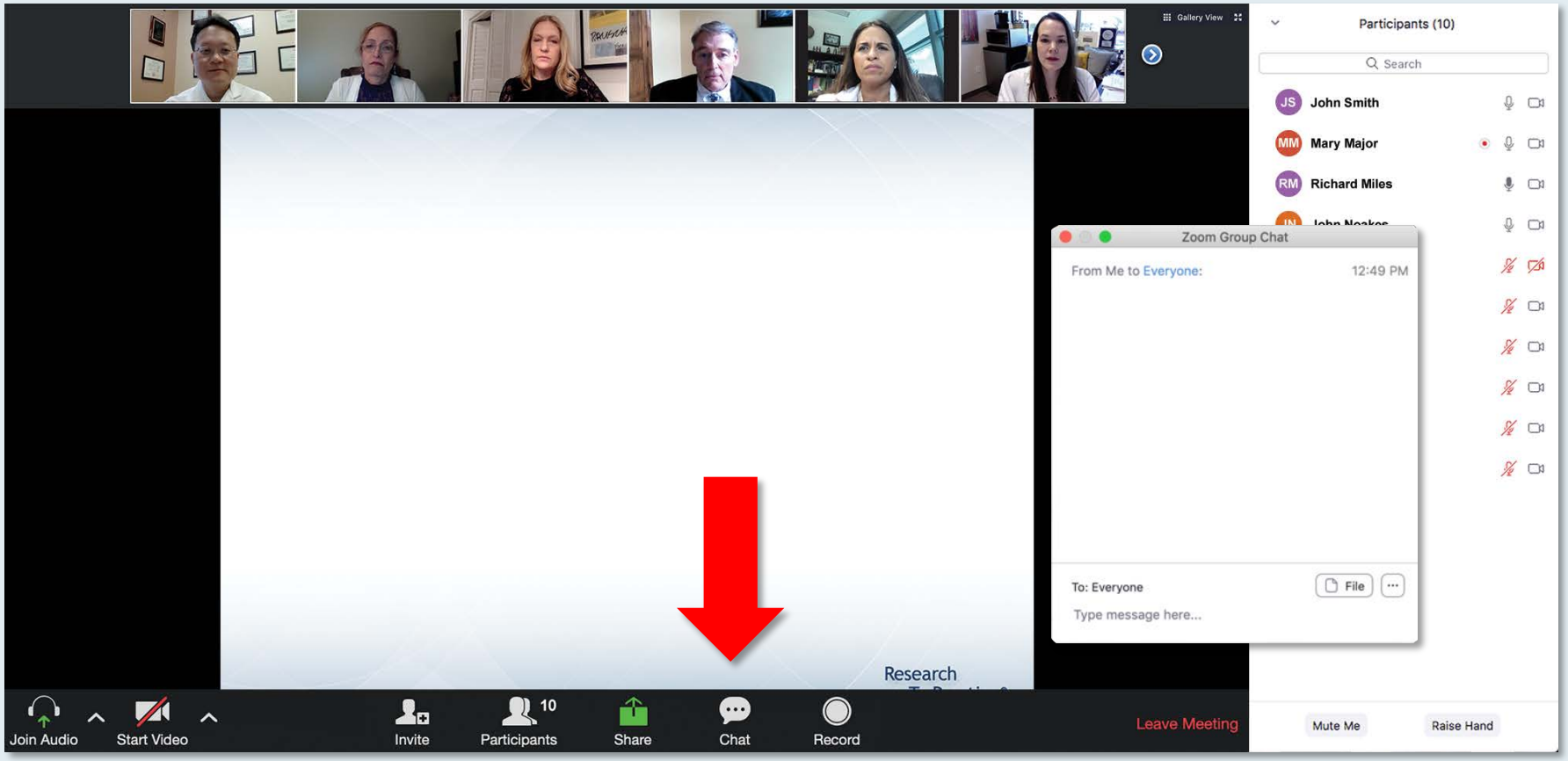
Dr Goyal — Disclosures

Advisory Committee	Agios Pharmaceuticals Inc, Alentis Therapeutics AG, Debiopharm Group, H3 Biomedicine, Incyte Corporation, QED Therapeutics, Sirtex Medical Ltd, Taiho Oncology Inc
Consulting Agreements	Agios Pharmaceuticals Inc, Alentis Therapeutics AG, Incyte Corporation, QED Therapeutics, Sirtex Medical Ltd, Taiho Oncology Inc
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

Year in Review 2020

We Encourage Clinicians in Practice to Submit Questions



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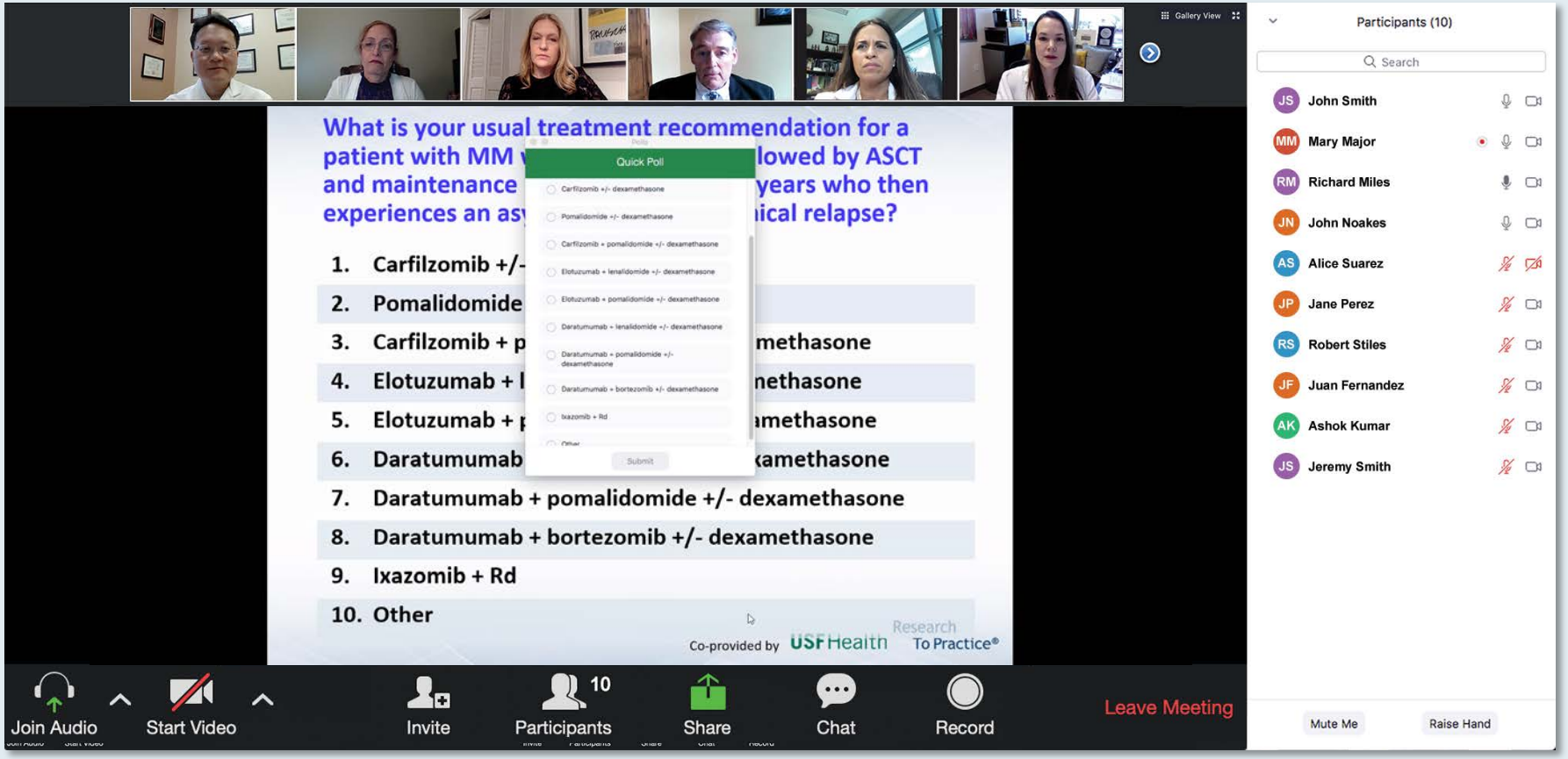
Year in Review 2020

Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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Year in Review 2020

Meet The Professor
Management of Multiple Myeloma

Wednesday, December 16, 2020
12:00 PM – 1:00 PM ET

Faculty

Peter Voorhees, MD

Moderator

Neil Love, MD

RTP
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TO PRACTICE

Meet The Professor

Management of Chronic Lymphocytic Leukemia

Wednesday, December 16, 2020
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Acute Myeloid Leukemia and Myelodysplastic Syndromes

Tuesday, January 5, 2020
5:00 PM – 6:00 PM ET

Faculty

Mikkael A Sekeres, MD, MS
Richard M Stone, MD

Moderator

Neil Love, MD

Year in Review 2020

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

Year in Review 2020

ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of Pancreatic Cancer

DR ANDREW KO
UNIVERSITY OF CALIFORNIA,
SAN FRANCISCO

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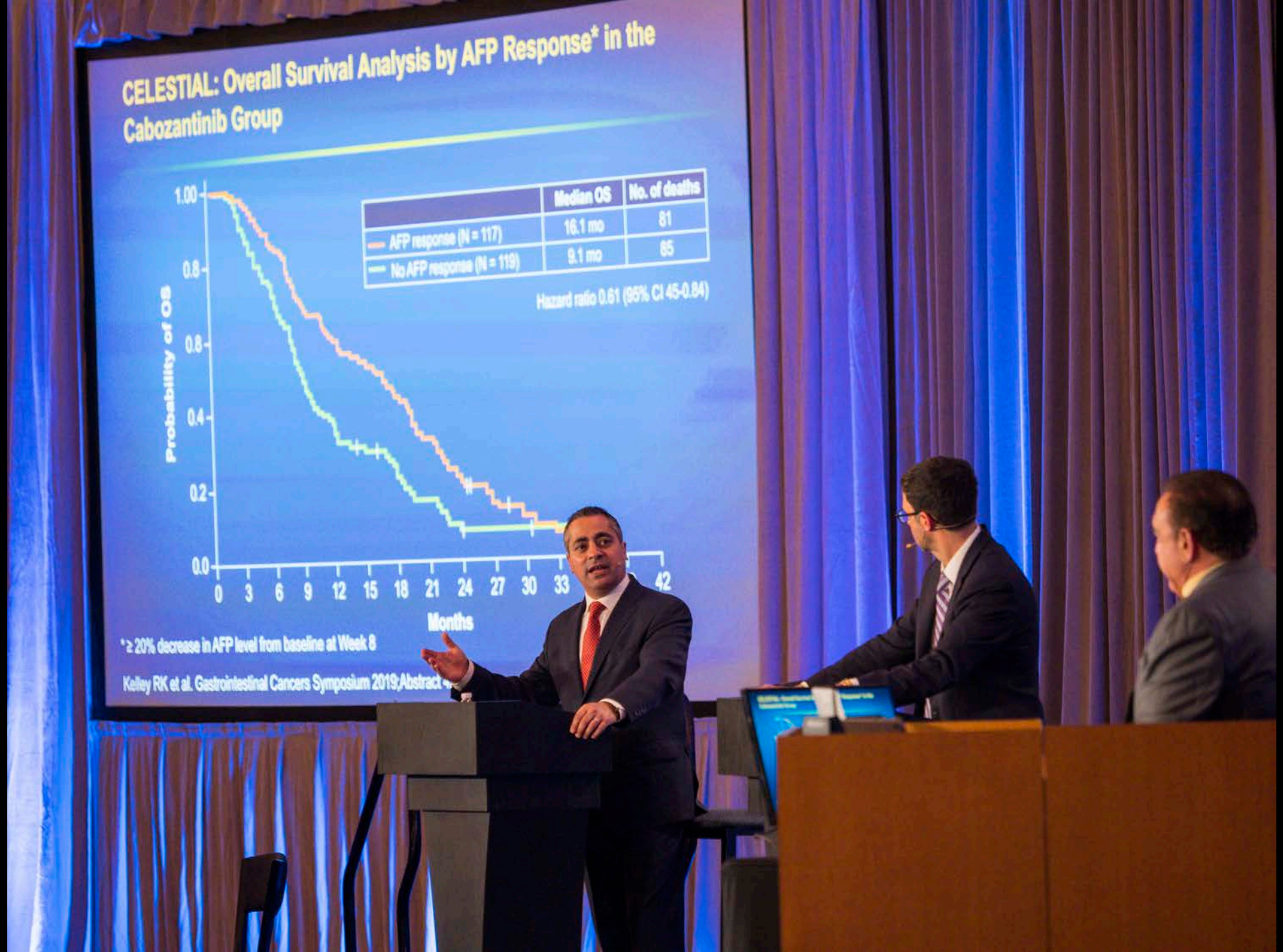
ABDULRAHEEM QASEM
SHAWNEE MISSION, KS


What is your likely adjuvant systemic therapy recommendation for an otherwise healthy 75-year-old patient who is s/p surgical resection of pancreatic adenocarcinoma?
Gemcitabine
10%
Gemcitabine/capecitabine
37%
Gemcitabine/nab paclitaxel
15%
5-FU/LV
2%
Modified FOLFIRINOX
33%
Other


CELESTIAL: Overall Survival Analysis by AFP Response* in the Cabozantinib Group
Median OS
No. of deaths
AFP response (N = 117)
16.1 mo
81
No AFP response (N = 119)
9.1 mo
85
Hazard ratio 0.61 (95% CI 45-0.84)
Probability of OS
1.00
0.8
0.8
0.4
0.2
0.0
0 3 6 9 12 15 18 21 24 27 30 33 42
Months
* ≥ 20% decrease in AFP level from baseline at Week 8
Kelley RK et al. Gastrointestinal Cancers Symposium 2019;Abstract


What would be your most likely t
an otherwise healthy 65-year-old
progression on first-line sorafeni

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Year in Review 2020

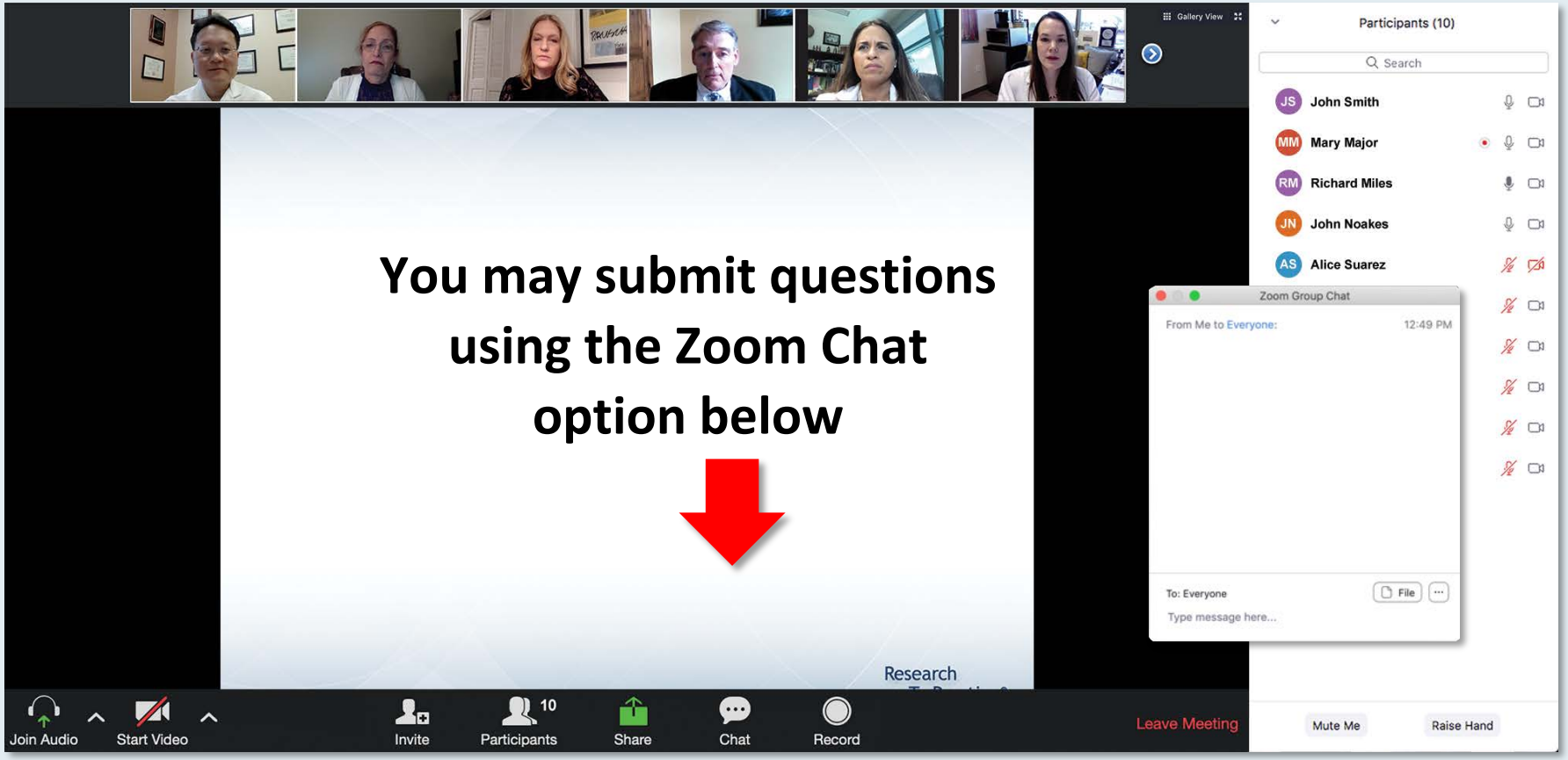
YiR Hepatobiliary and Pancreatic Cancers Faculty

Tanios Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, Gastrointestinal Cancer
Mayo Clinic Cancer Center
Consultant, Mayo Clinic in Arizona
Phoenix, Arizona

Lipika Goyal, MD, MPhil
Lead of the Liver Cancer Research Program
Massachusetts General Hospital Cancer Center
Assistant Professor
Harvard Medical School
Boston, Massachusetts

Year in Review 2020

We Encourage Clinicians in Practice to Submit Questions



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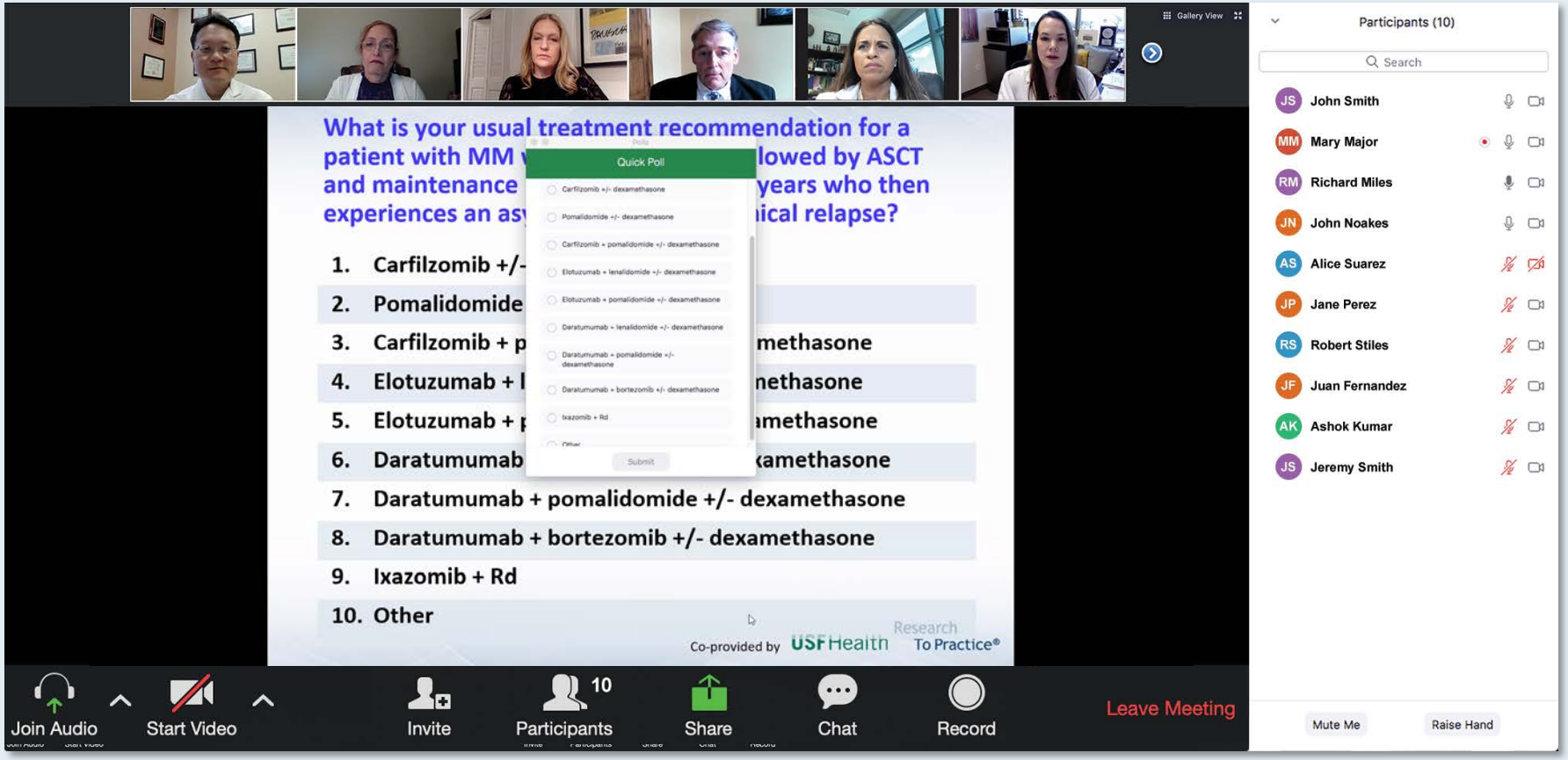

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Year in Review 2020

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Year in Review 2020

Agenda

MODULE 1: Hepatocellular Carcinoma

MODULE 2: Cholangiocarcinoma

MODULE 3: Pancreatic Cancer

Year in Review 2020

Which of the following statements is true?

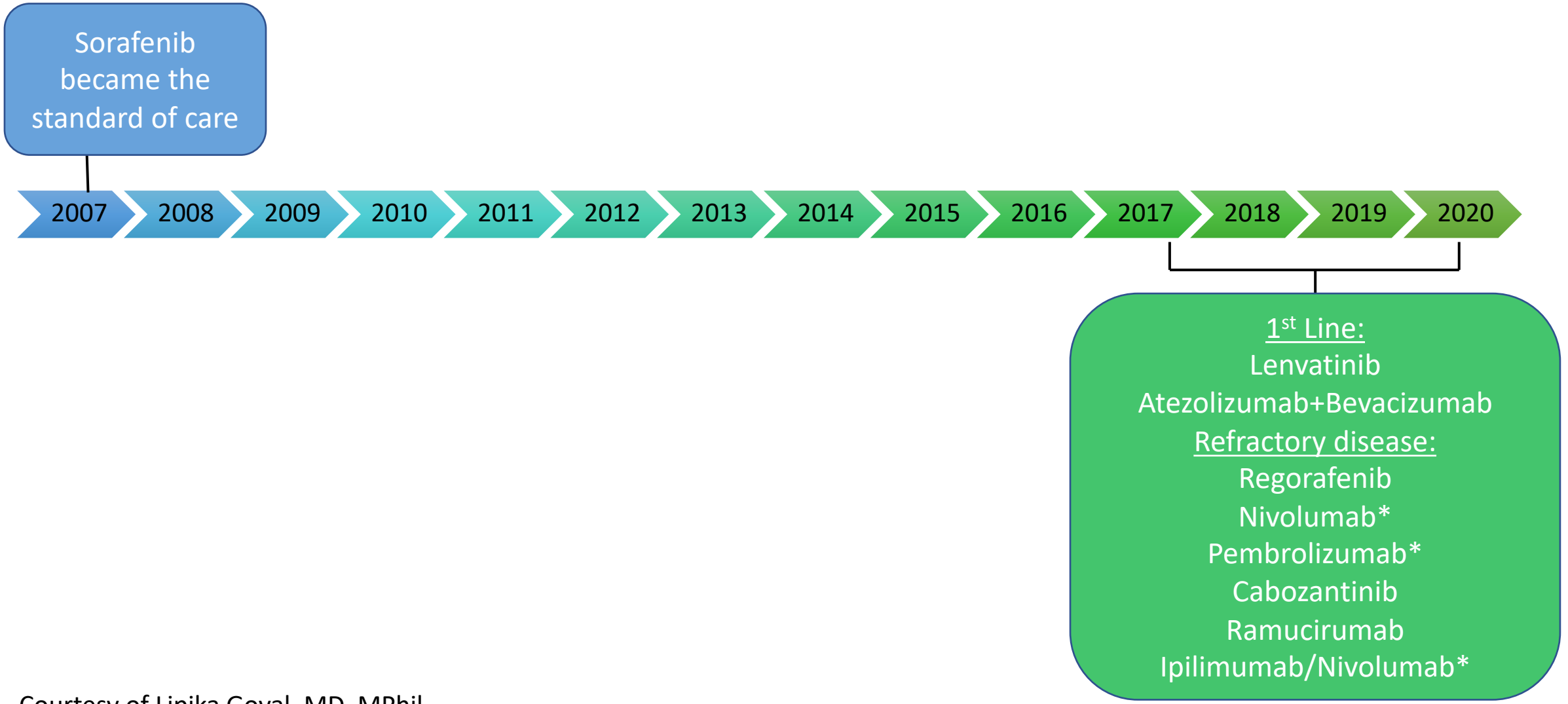
a. HCC is the new RCC
b. Cholangiocarcinoma is the new non-small cell lung cancer
c. Both a and b
d. Neither

Year in Review 2020

MODULE 1: Treatment of HCC — First Line

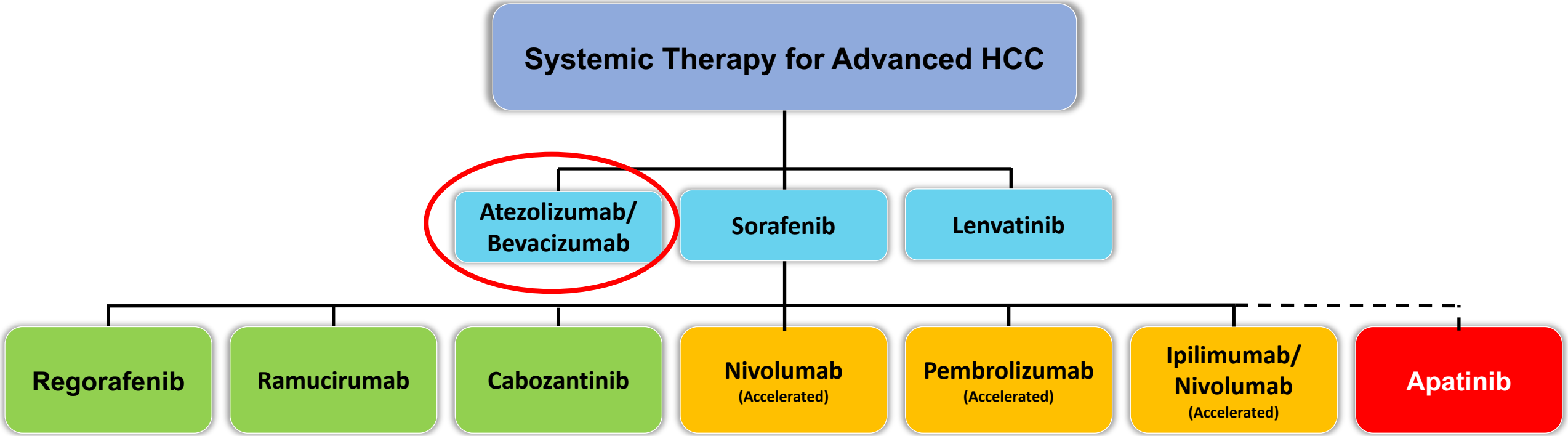
- **Key Relevant Data Sets**
  - IMbrave150: Atezolizumab + bevacizumab vs sorafenib in unresectable HCC
  - ORIENT-32: Sintilimab + bevacizumab biosimilar vs sorafenib as first-line treatment for HCC
  - Lenvatinib + pembrolizumab in unresectable HCC
  - Study 117: Lenvatinib + nivolumab in unresectable HCC
  - COSMIC-312: Cabozantinib + atezolizumab vs sorafenib in advanced HCC
  - Donafenib vs sorafenib in advanced HCC

FDA-Approved Systemic Therapy for Advanced HCC



Courtesy of Lipika Goyal, MD, MPhil

*Accelerated Approval



Courtesy of Lipika Goyal, MD, MPhil

The NEW ENGLAND JOURNAL of MEDICINE

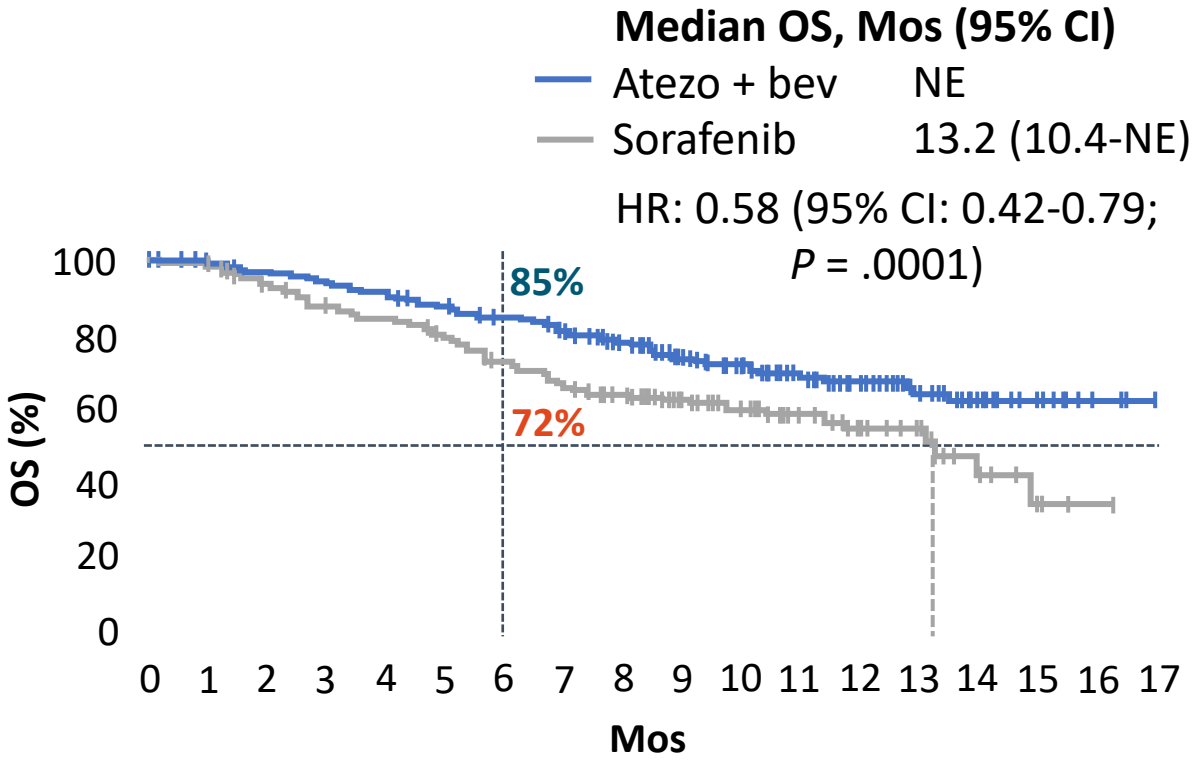
ORIGINAL ARTICLE

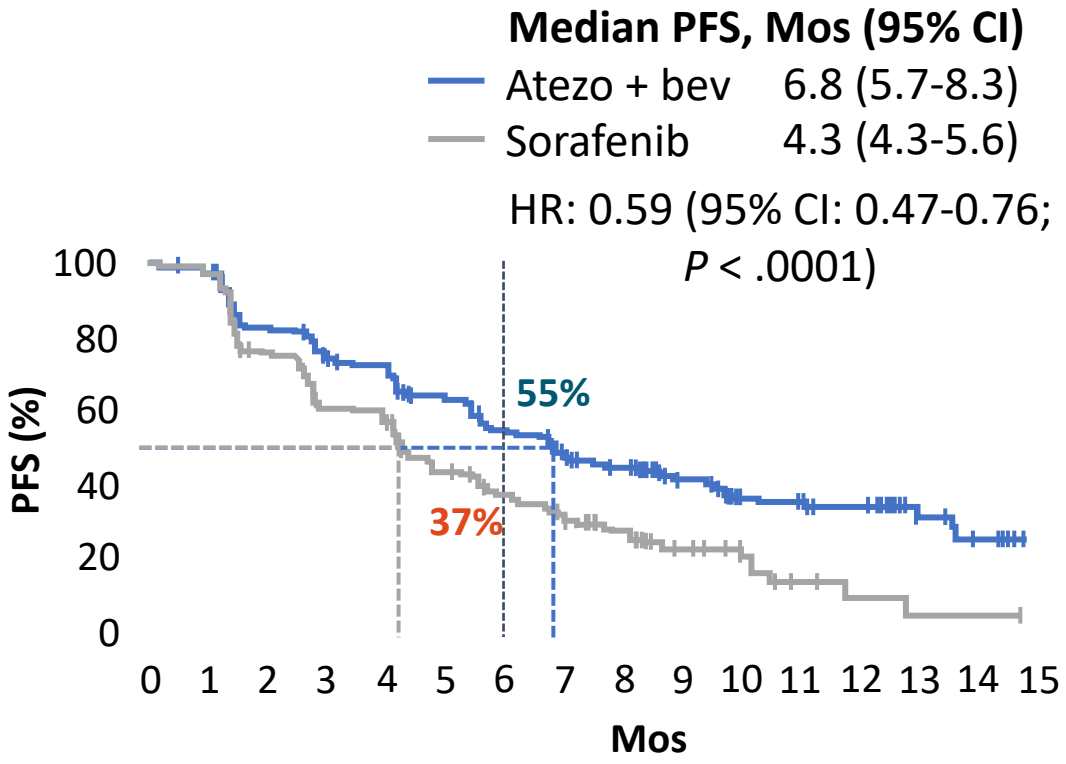
Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

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*

NEJM 2020;382(20):1894-1905.

IMbrave150: Atezo/Bevacizumab vs Sorafenib in Unresectable or Metastatic HCC





- ORR by modified RECIST with atezo + bev vs sorafenib: 33.2% vs 13.3%; CR rate, 10.2% vs 1.9%

Median follow-up: 8.6 mos.

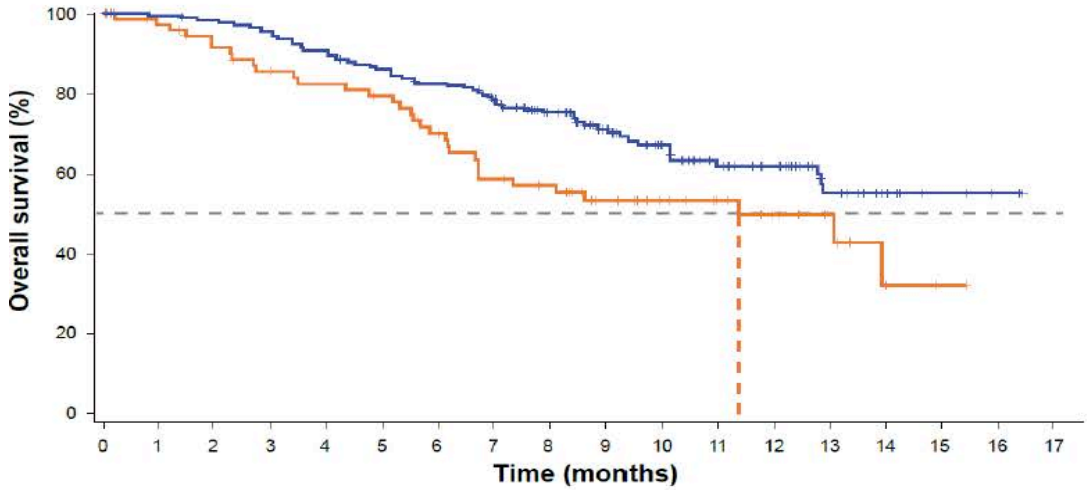
Courtesy of Lipika Goyal, MD, MPhil

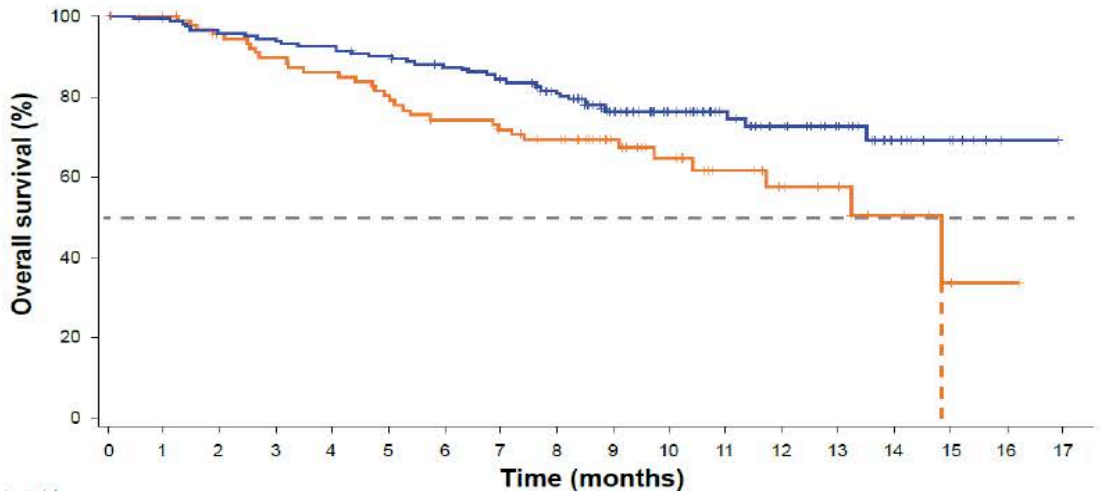
Finn, et al *NEJM* 2020;382:1894.

IMbrave150: Atezo/Bevacizumab vs Sorafenib in Younger vs Older Patients Overall Survival Curves

	< 65 years	
	Atezo + bev (n = 175)	Sorafenib (n = 74)
Median OS, mo	NE	11.4
HR (95% CI)[a]	0.59 (0.38, 0.91)	

	≥ 65 years	
	Atezo + bev (n = 161)	Sorafenib (n = 91)
Median OS, mo	NE	14.9
HR (95% CI)[a]	0.58 (0.36, 0.92)	





Characteristic	< 65 years		≥ 65 years	
	Atezo + bev (n = 175)	Sorafenib (n = 74)	Atezo + bev (n = 161)	Sorafenib (n = 91)
Response-evaluable population, n[b]	171	70	155	89
ORR, n (%)	49 (29)	7 (10)	40 (26)	12 (13)
CR, n (%)	11 (6)	0	7 (5)	0

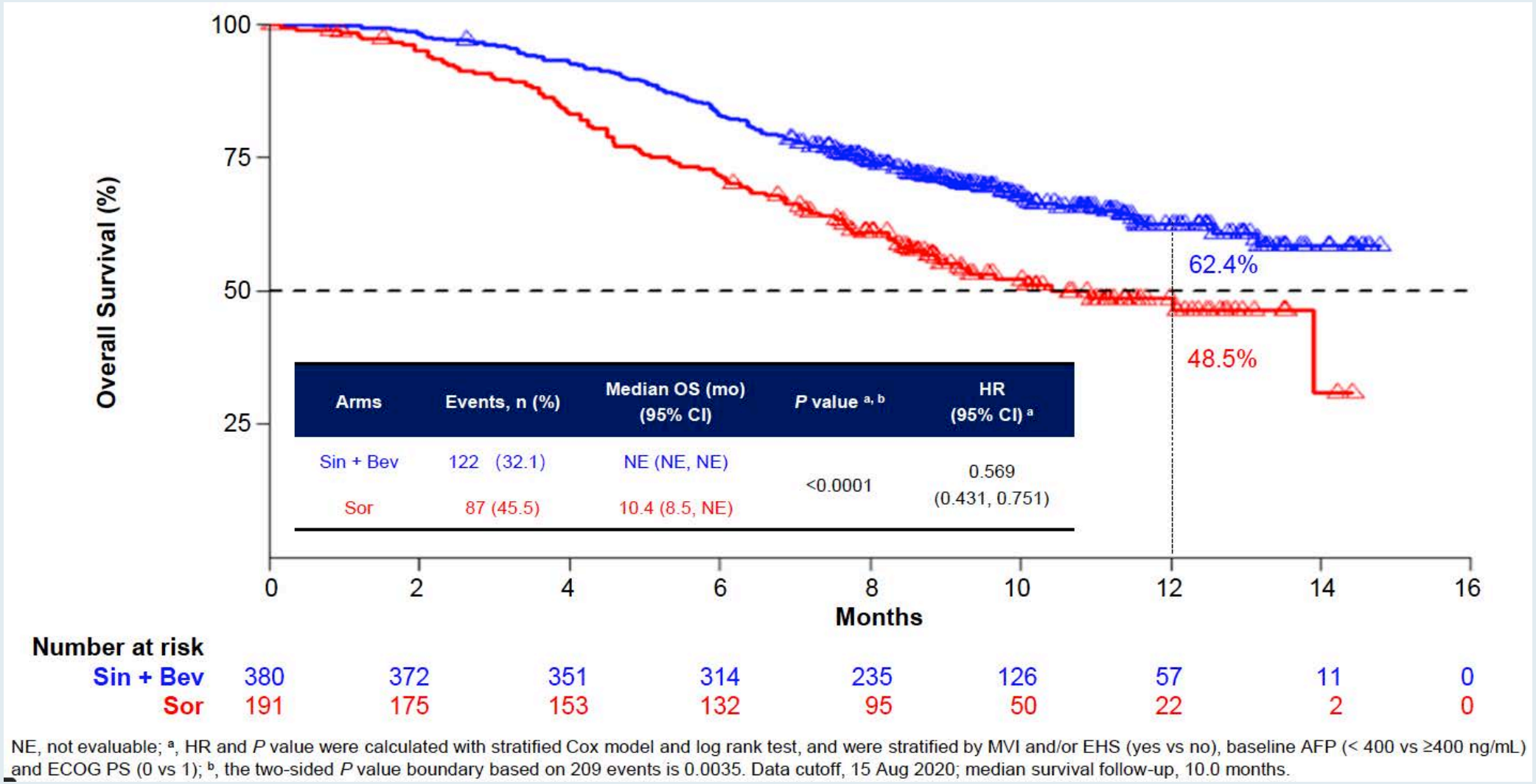
Courtesy of Lipika Goyal, MD, MPhil

Li et al, *GI ESMO*, 2020

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.

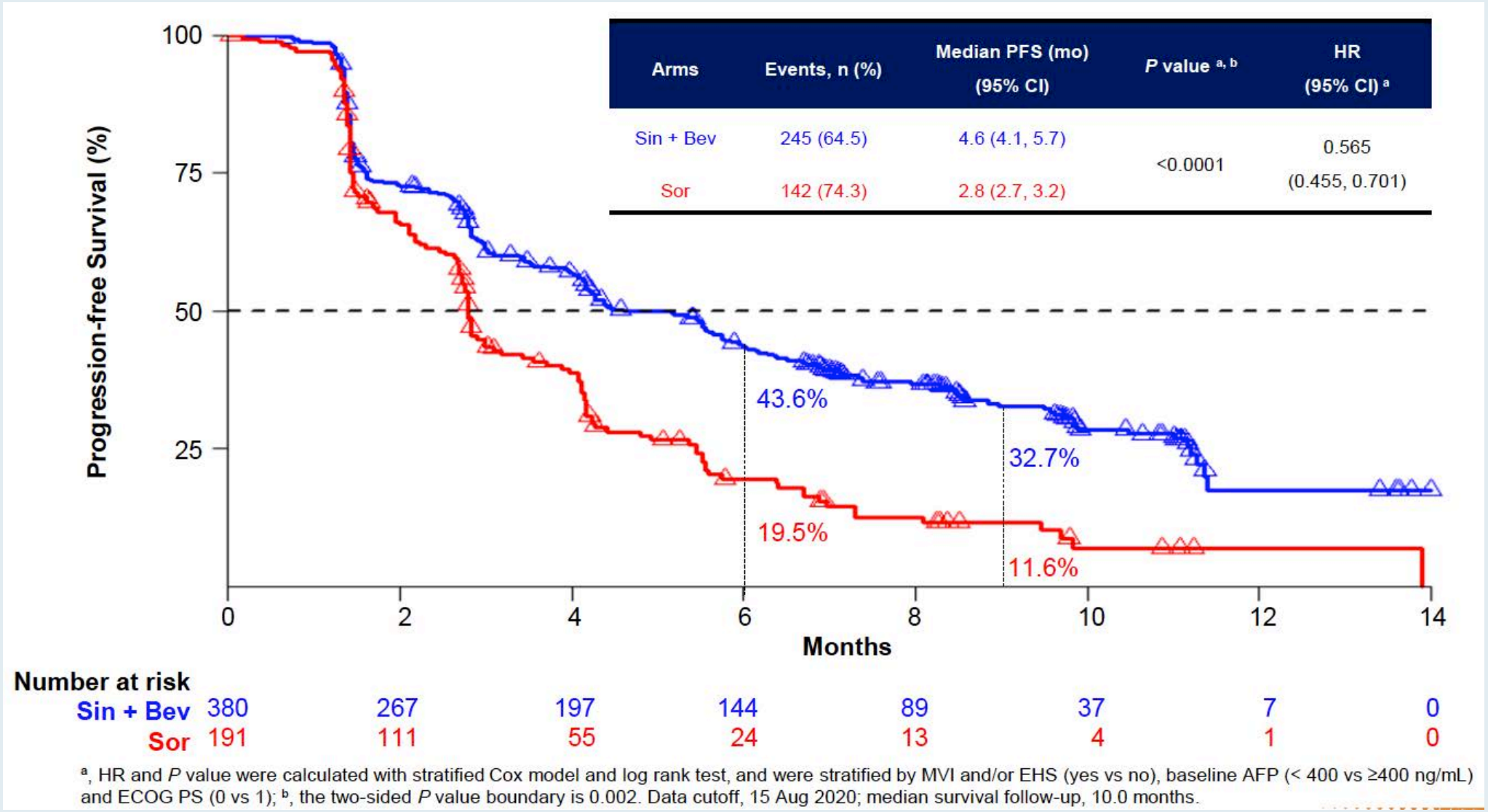
ORIENT-32: Overall Survival (Coprimary Endpoint)



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.

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

ORIENT-32: IRRC-PFS (Coprimary Endpoint)

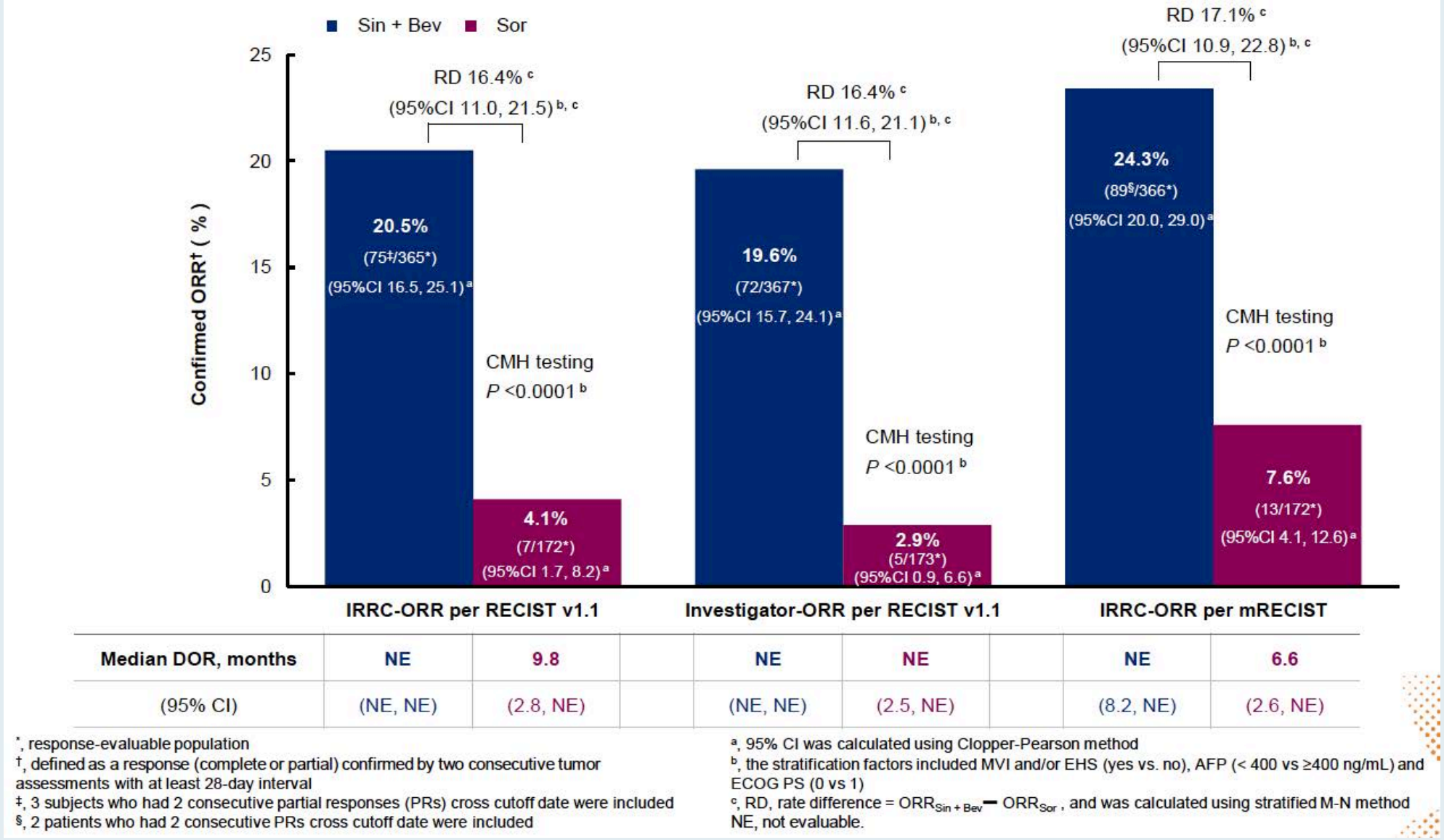


Arms	Events, n (%)	Median PFS (mo) (95% CI)	*P* value [a, b]	HR (95% CI) [a]
Sin + Bev	245 (64.5)	4.6 (4.1, 5.7)	<0.0001	0.565 (0.455, 0.701)
Sor	142 (74.3)	2.8 (2.7, 3.2)		

[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.

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

ORIENT-32: Response Rate and Duration of Response



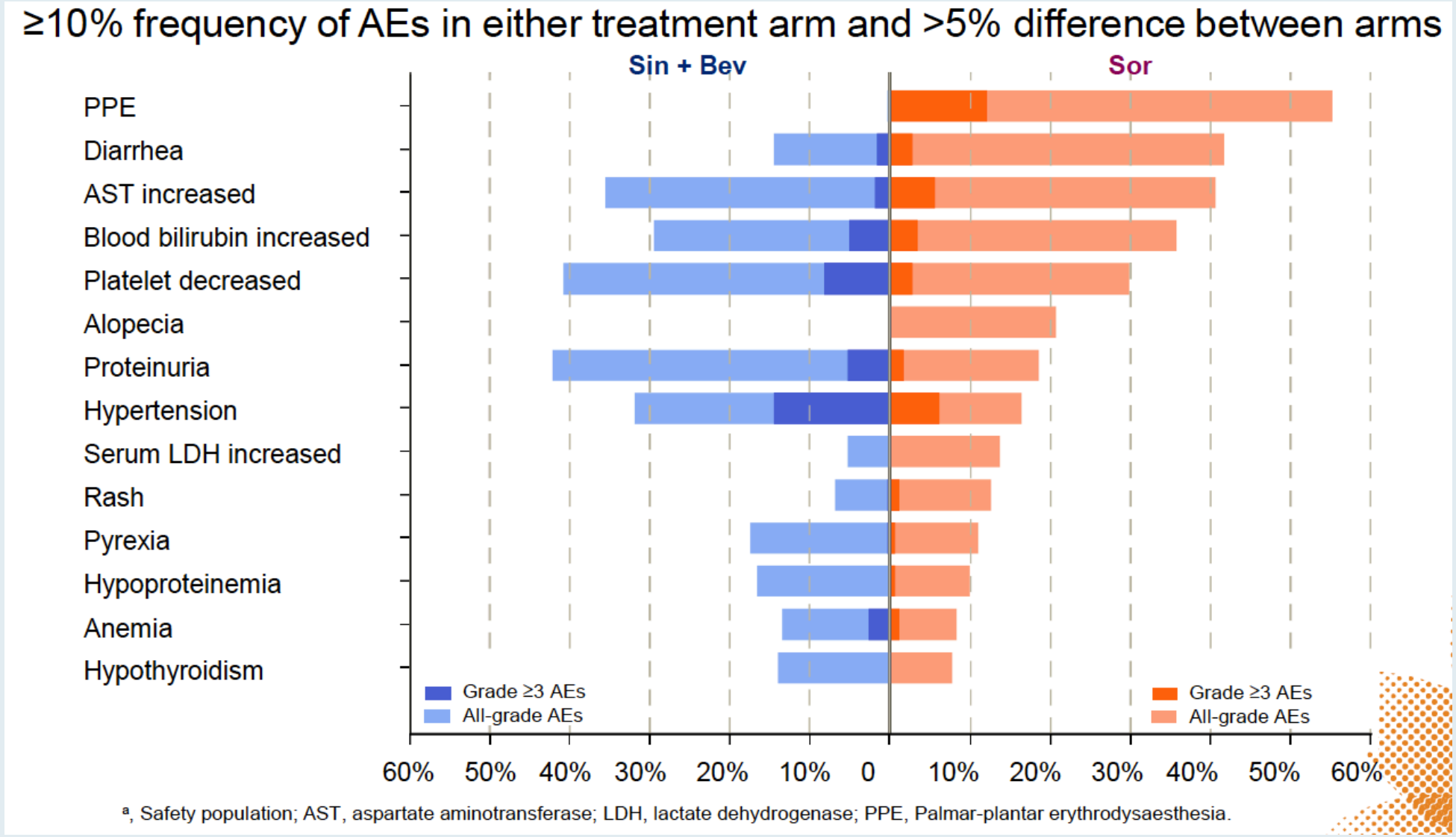
Median DOR, months	**NE**	**9.8**	**NE**	**NE**	**NE**	**6.6**
(95% CI)	(NE, NE)	(2.8, NE)	(NE, NE)	(2.5, NE)	(8.2, NE)	(2.6, NE)

*, 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: Adverse Events



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

Year in Review 2020

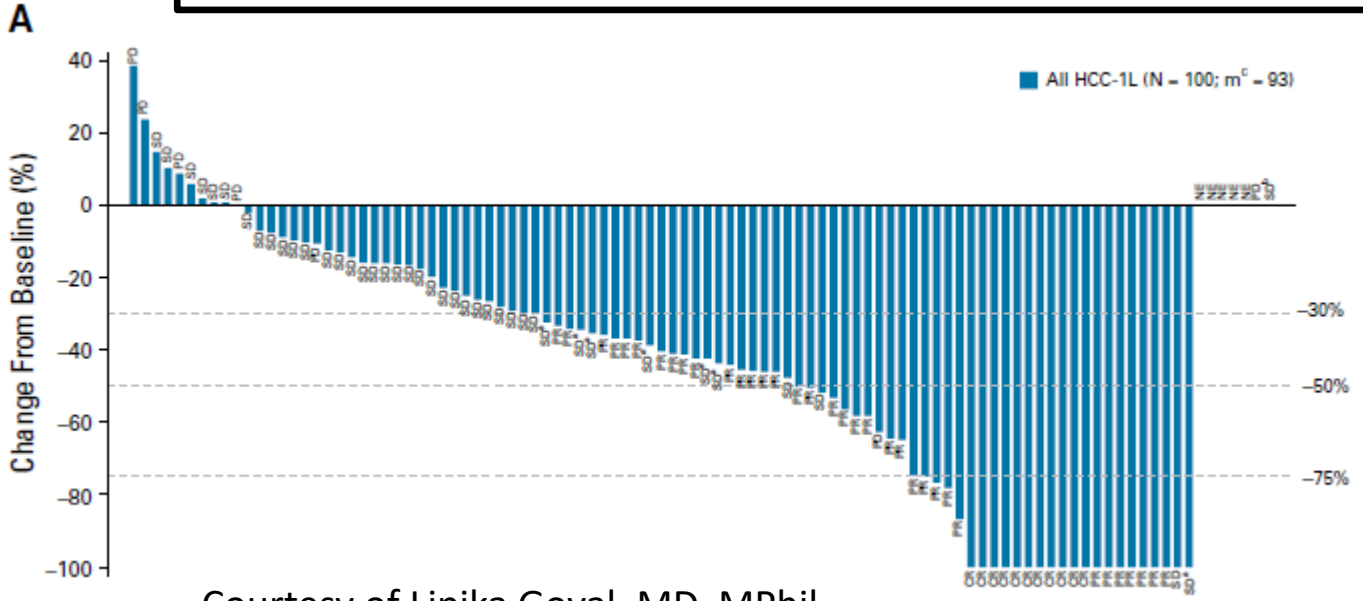
Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma

N=104 patients
No DLTs in DLT phase
Expansion phase in 1st line unresectable HCC
BCLC B (n=29), BCLC C (n=71)
Median follow-up: 10.6 months

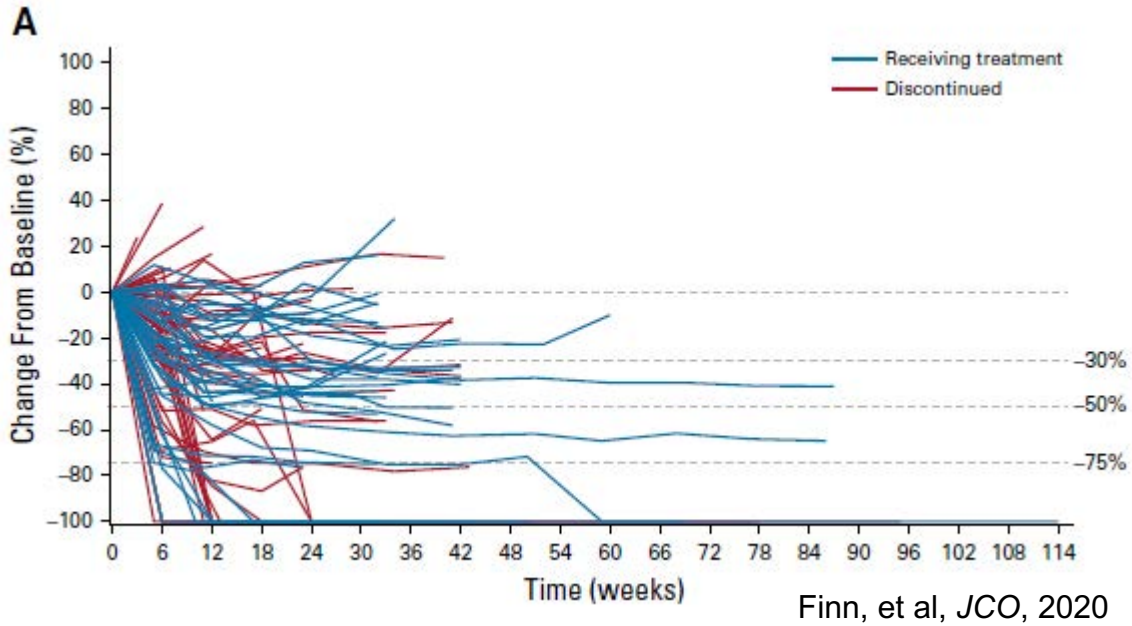
Efficacy Parameter	RECIST v1.1	modified RECIST
ORR	36.0%	46.0%
Median Duration of Response	12.6 months	8.6 months
Median PFS	8.6 months	9.3 months

Median OS: 22 months

% change from Baseline in Sum of Target Lesions by **modified RECIST** (mRECIST) per independent imaging review



Courtesy of Lipika Goyal, MD, MPhil



Finn, et al, *JCO*, 2020

Study 117: Phase Ib study of lenvatinib plus nivolumab in patients with unresectable HCC

Figure 1. Design of Phase 1b Study of Lenvatinib Plus Nivolumab in uHCC

Lenvatinib 12 or 8 mg/day (based on body weight) orally once daily + nivolumab 240 mg IV every 2 weeks

Part 1: DLT Evaluation
- n = 6
- Patients for whom no other appropriate therapy was available

Part 2: Expansion
- n = 24
- Patients with no prior systemic therapy for uHCC

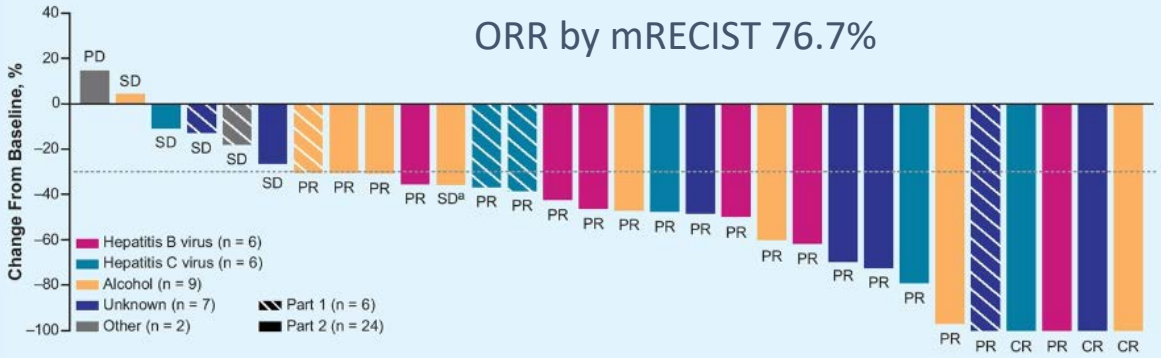
Key Eligibility Criteria
- uHCC
- ≥ 1 Measurable target lesion
- BCLC stage B (not applicable for TACE) or C
- Child-Pugh class A
- ECOG performance status 0–1

Primary end points
- Tolerability
- Safety of combination

Secondary end points
- ORR (mRECIST by investigator)
- Pharmacokinetic profiles of lenvatinib and nivolumab

BCLC, Barcelona Clinic Liver Cancer; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; mRECIST, modified Response Evaluation Criteria In Solid Tumors; ORR, objective response rate; TACE, transarterial chemoembolization; uHCC, unresectable hepatocellular carcinoma.

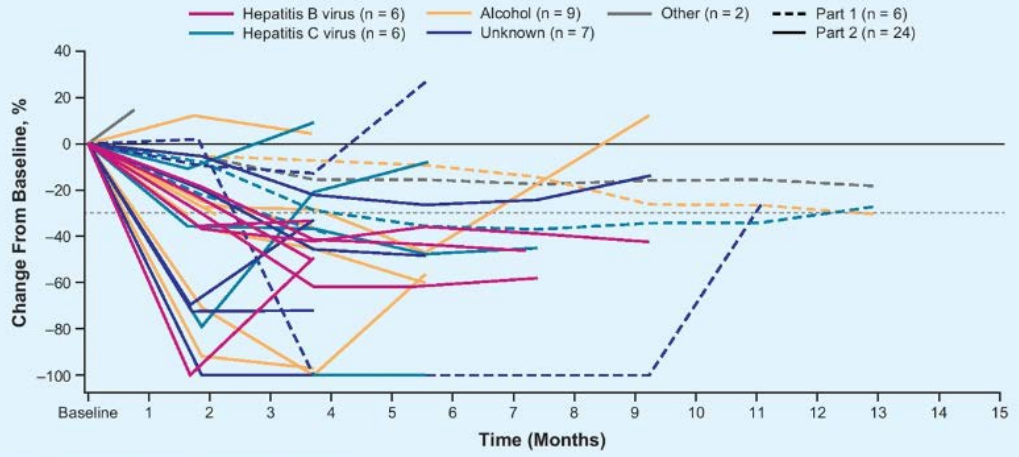
Figure 2. Percentage Changes From Baseline in Sums of Tumor Diameters by Investigator Assessment (mRECIST) Following Treatment With Lenvatinib Plus Nivolumab



[a]Patient experienced a 35% tumor shrinkage at the target lesion, but a nontarget lesion progressed at the same time.
CR, complete response; mRECIST, modified Response Evaluation Criteria In Solid Tumors; PD, progressive disease; PR, partial response; SD, stable disease.

- Tumor reductions appeared durable for most patients (**Figure 3** and **Figure 4**).

Figure 3. Percentage Change From Baseline in Sums of Diameters of Target Lesions Over Time by Investigator Assessment (mRECIST) Following Treatment With Lenvatinib Plus Nivolumab

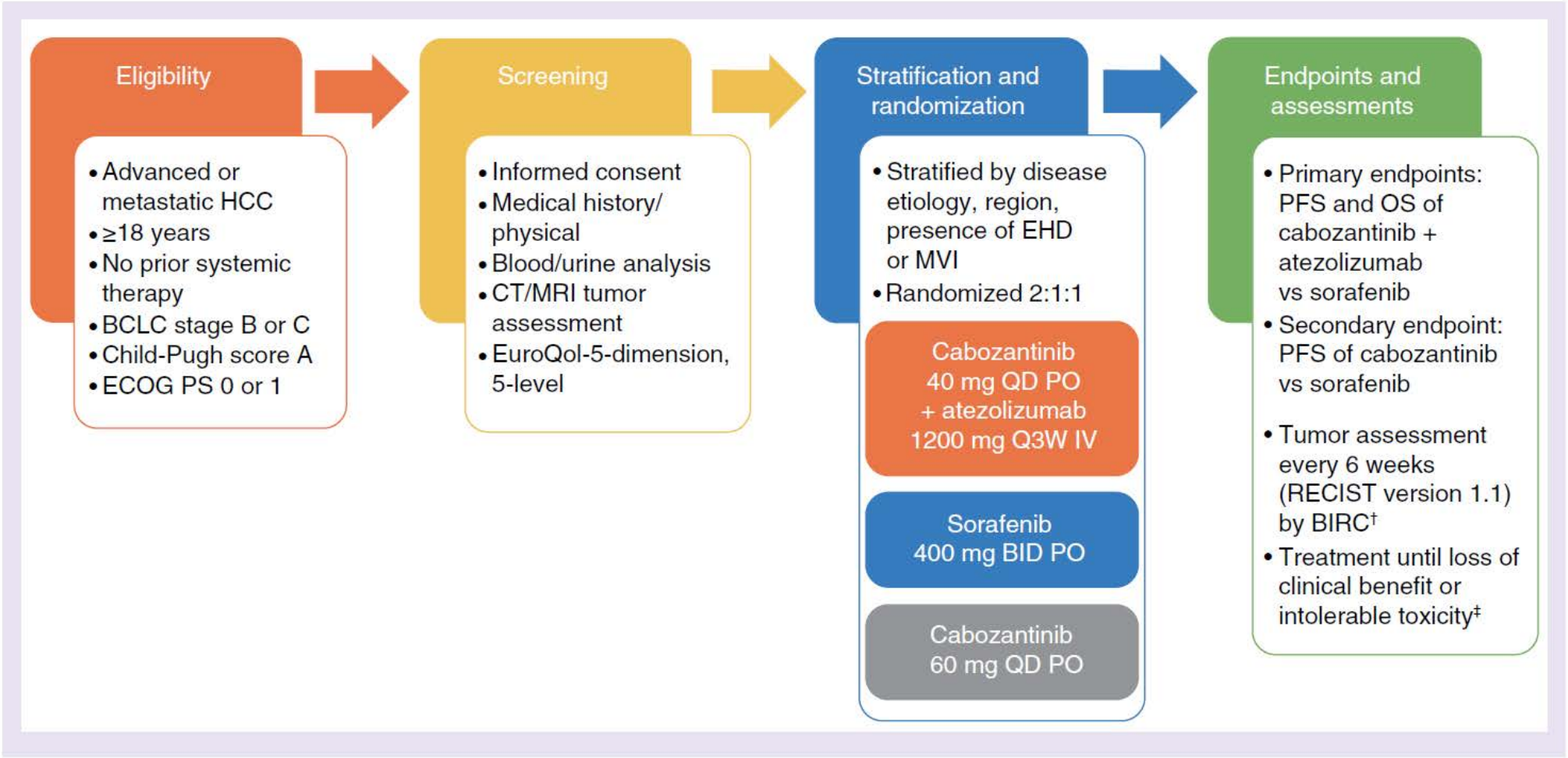


mRECIST, modified Response Evaluation Criteria In Solid Tumors.

Courtesy of Lipika Goyal, MD, MPhil

Kudo, et al, *GI ASCO* 2020

COSMIC-312: Cabozantinib/Atezolizumab vs sorafenib in treatment-naive advanced HCC



Courtesy of Lipika Goyal, MD, MPhil

Kelley, et al, *Future Oncology,* 2020

Donafenib versus Sorafenib as First-Line Therapy in Advanced Hepatocellular Carcinoma: An Open-Label, Randomized, Multicentre Phase II/III Trial

Feng Bi et al. ASCO 2020;Abstract 4506.

Conclusions

- Donafenib demonstrated superiority versus sorafenib in overall survival in patients with HCC (12.1 months *vs* 10.3 months, HR 0.831, 95% CI 0.699–0.988, $p = 0.0363$)
- Donafenib showed improved trends versus sorafenib in PFS, ORR, and DCR, though differences were not significant
- Donafenib exhibited favourable safety and tolerability compared with sorafenib
- Donafenib should be considered an optimal first-line therapy for advanced HCC

Feng Bi et al. ASCO 2020;Abstract 4506.

Research

JAMA Oncology | Original Investigation

Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma

A Systematic Review and Network Meta-analysis

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Sonbol MB et al. *JAMA Oncol* 2020;[Online ahead of print].

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?

a. Sorafenib
b. Lenvatinib
c. Sorafenib or lenvatinib — coin flip
d. Atezolizumab/bevacizumab
e. Chemotherapy
f. 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 extensive psoriasis controlled with local therapy?

a. Sorafenib
b. Lenvatinib
c. Sorafenib or lenvatinib — coin flip
d. Cabozantinib
e. Atezolizumab/bevacizumab
f. Chemotherapy
g. Other

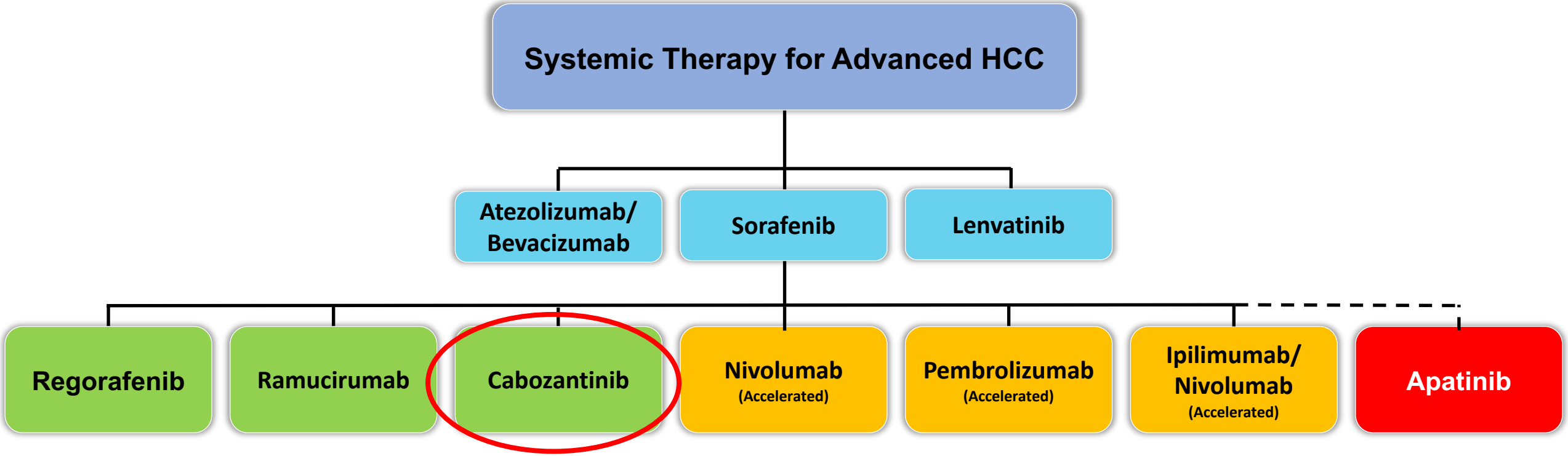
What is your usual first-line systemic therapy for HCC in a 70-year-old patient with a Child-Pugh A score and cirrhosis but with a history of moderately symptomatic multiple sclerosis currently off therapy?

a. Sorafenib
b. Lenvatinib
c. Sorafenib or lenvatinib — coin flip
d. Cabozantinib
e. Atezolizumab/bevacizumab
f. Chemotherapy
g. Other

MODULE 1: Treatment of HCC — Second and Third Line

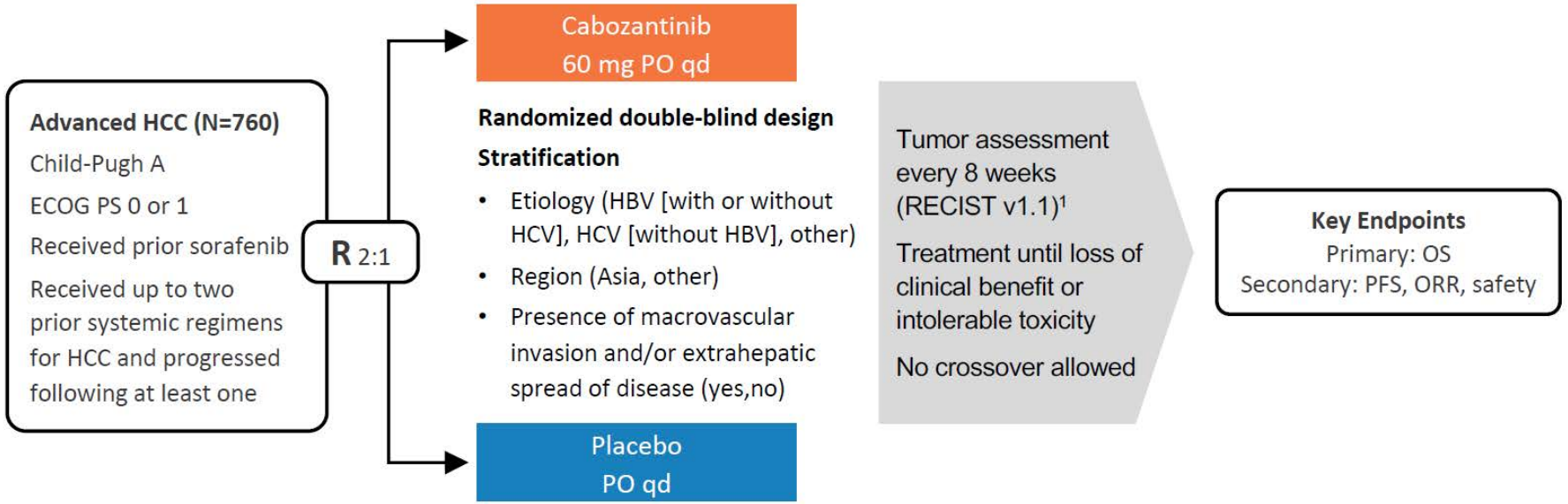
Key Relevant Data Sets

- CELESTIAL: Cabozantinib vs placebo in advanced HCC
- CheckMate 040: Cabozantinib cohort
- KEYNOTE-224: Updated analysis of pembrolizumab in advanced HCC
- KEYNOTE-240: Second-line pembrolizumab in advanced HCC
- CheckMate 040: Nivolumab with ipilimumab in advanced HCC after sorafenib
- Study 22: Tremelimumab + durvalumab in advanced HCC



Courtesy of Lipika Goyal, MD, MPhil

CELESTIAL: Cabozantinib in Advanced HCC Subgroup analysis in Child Pugh B population



- **Outcomes were analyzed from randomization for the subgroup of patients who were Child-Pugh B on study by Week 8 (time of first Child-Pugh assessment post randomization)**
- **Child-Pugh class was assessed by the investigator**

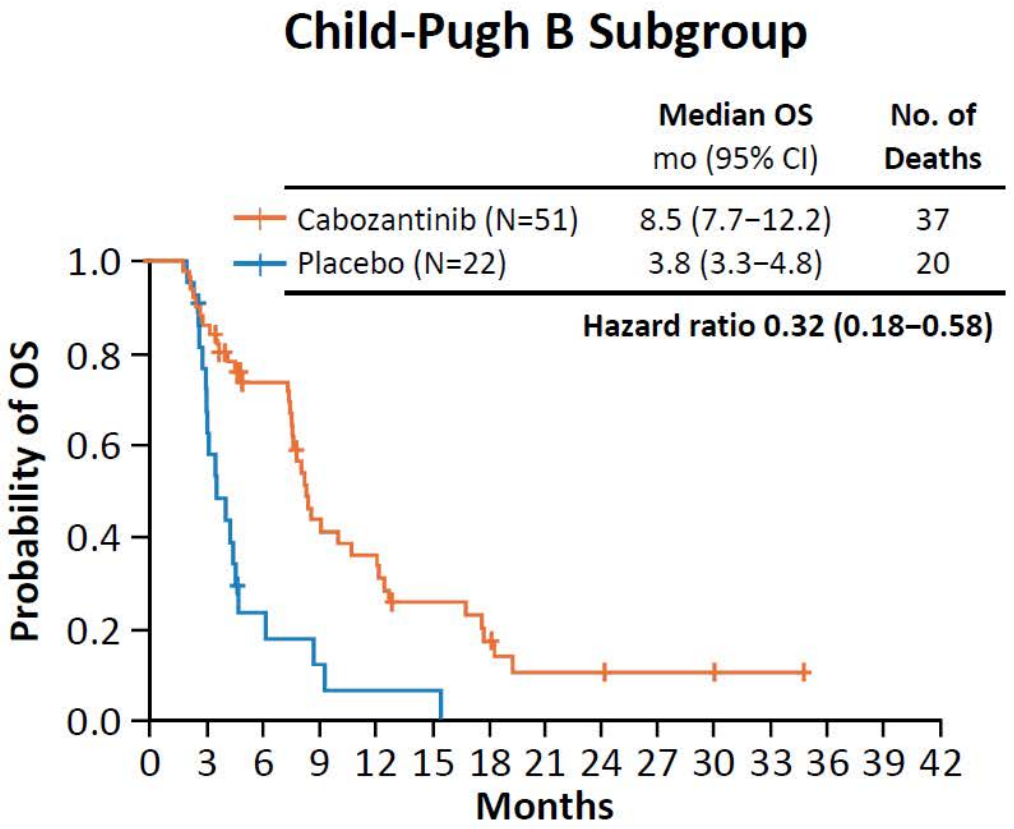
Child Pugh B population:
11% of cabozantinib group
9% of placebo group

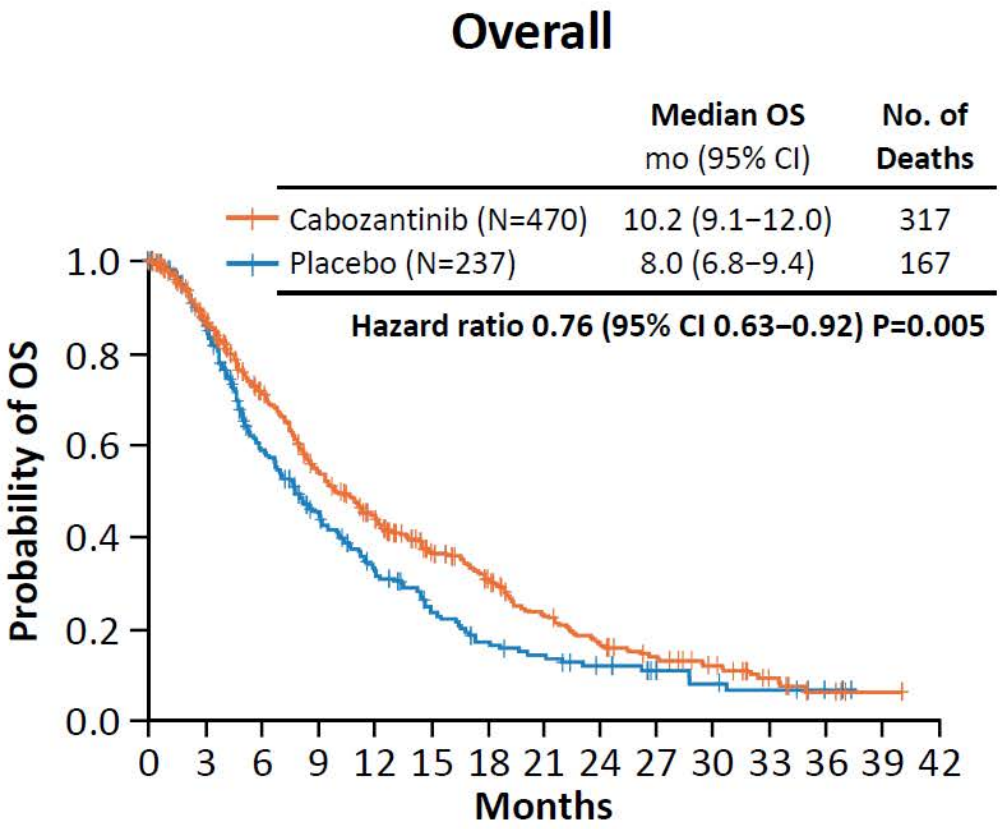
Higher rates of:
- macrovascular invasion
- extrahepatic spread
- elevated AFP
- HBV and HCV

Courtesy of Lipika Goyal, MD, MPhil

El-Khoueiry, et al, GI ESMO 2020

CELESTIAL: Cabozantinib in Advanced HCC Subgroup analysis in Child Pugh B population

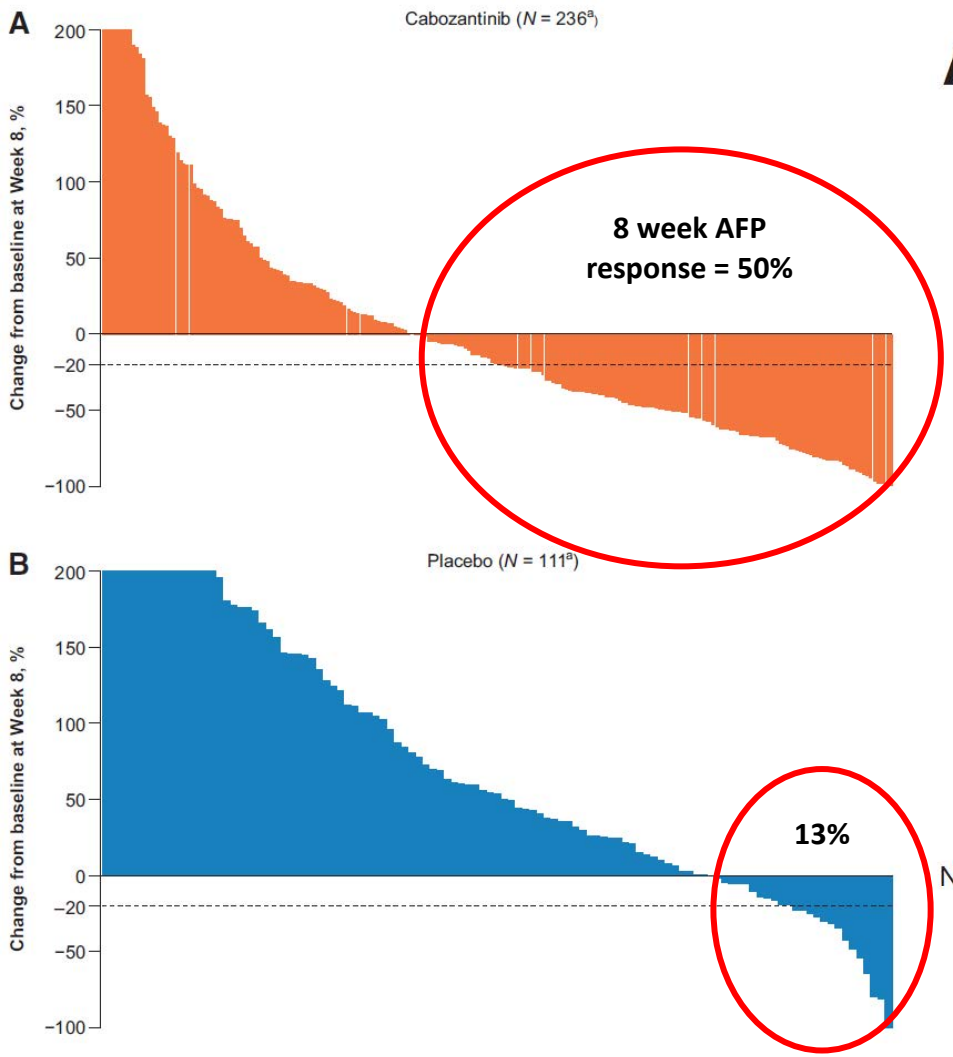


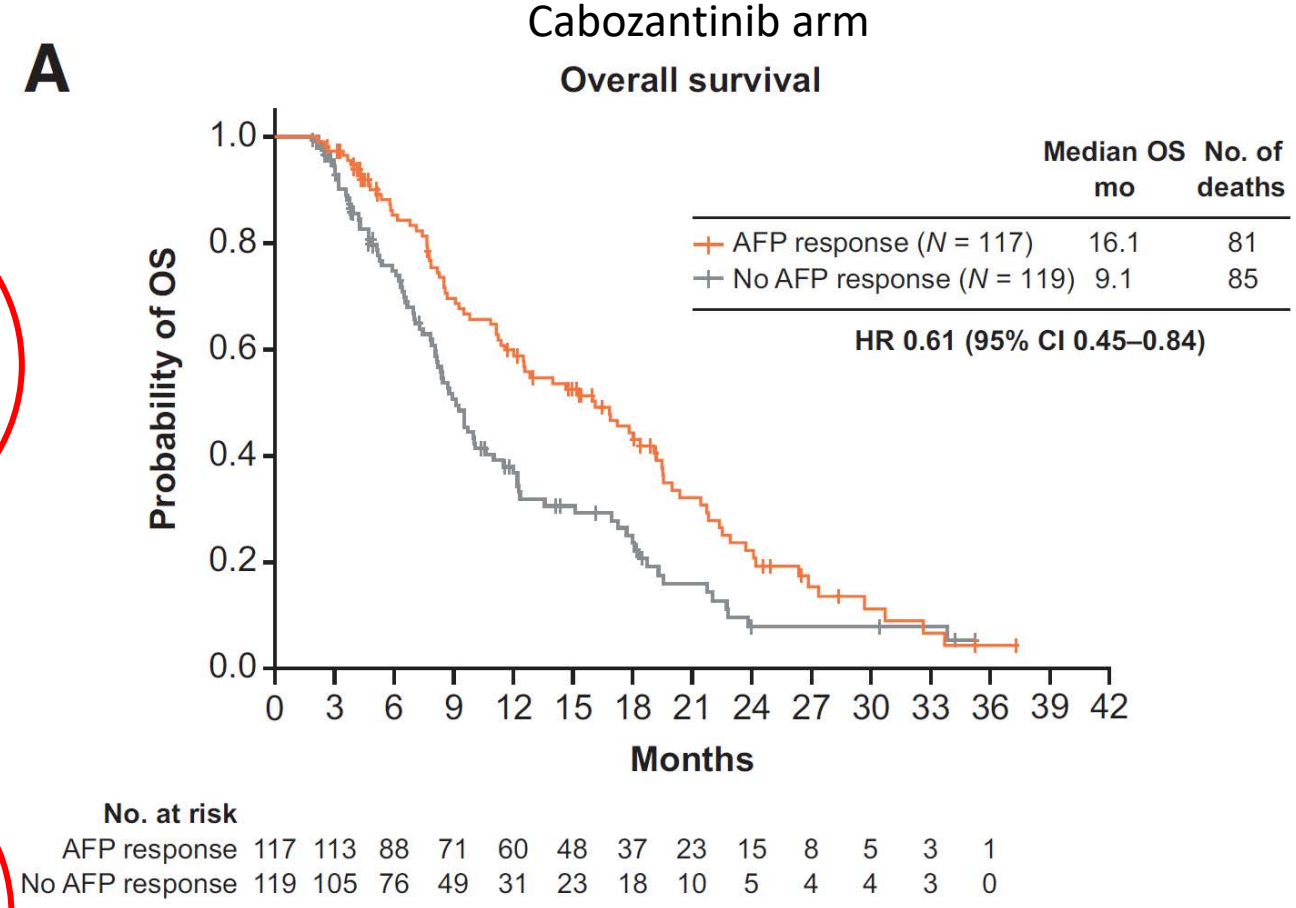


Courtesy of Lipika Goyal, MD, MPhil

El-Khoueiry, et al, GI ESMO 2020

CELESTIAL: Cabozantinib in Advanced HCC
Subgroup analysis by baseline AFP and AFP response



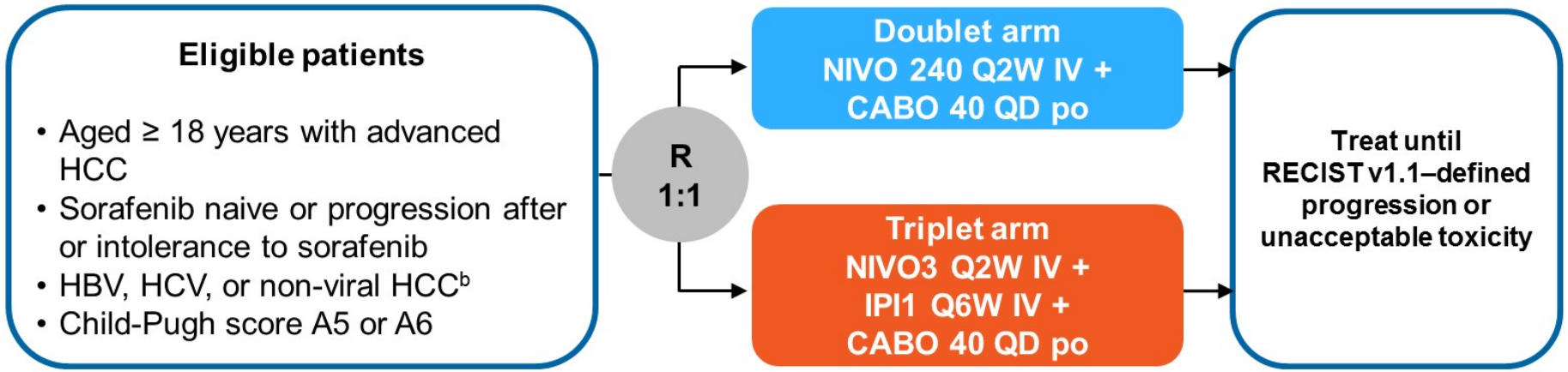


Kelley, et al, *CCR* 2020

Courtesy of Lipika Goyal, MD, MPhil

CheckMate 040 Study Design[a]

Cabozantinib Cohort



Primary endpoints
Safety and tolerability
ORR by investigator assessment

Secondary endpoints[c]
DCR, DOR, TTR, TTP, PFS, OS

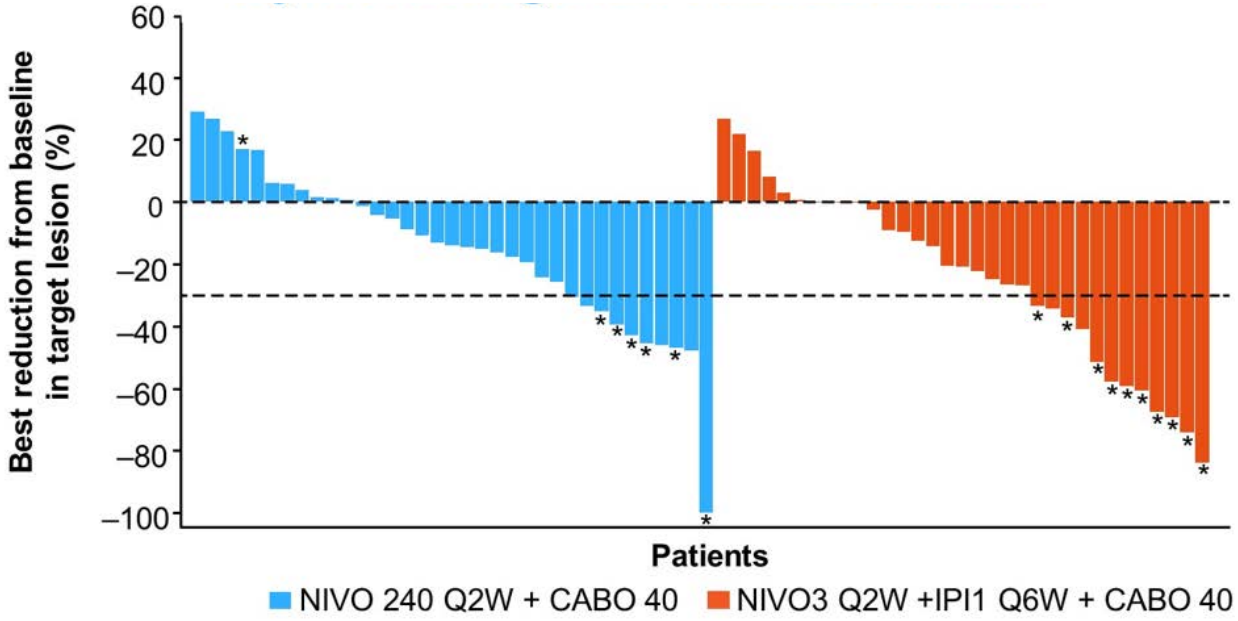
Database lock: September 2019

[a]ClinicalTrials.gov, NCT01658878; [b]Co-infection with HBV and HCV was an exclusion criterion; [c]Efficacy outcomes were evaluated by both investigator assessment and BICR.
BICR, blinded independent central review; CABO 40, cabozantinib 40 mg; DCR, disease control rate; DOR, duration of response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPI1, ipilimumb 1 mg/kg; IV, intravenous; NIVO 240, nivolumab 240 mg; NIVO3, nivolumab 3 mg/kg; PFS, progression-free survival; po, oral administration; Q2W, every 2 weeks; Q6W, every 6 weeks; QD, once daily; TTP, time to progression; TTR, time to response.

Courtesy of Lipika Goyal, MD, MPhil

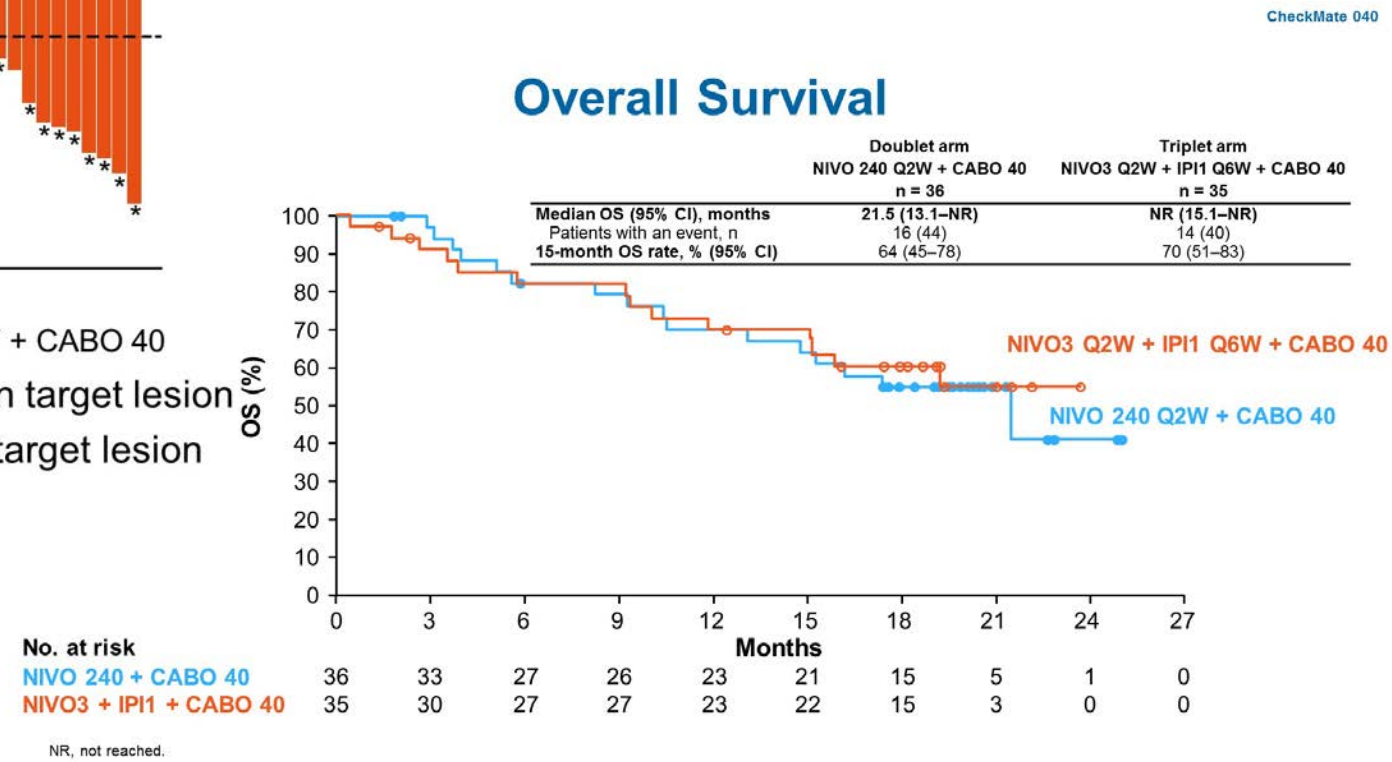
Yau, et al, GI ASCO 2020

CheckMate 040: Nivo/Cabo vs Nivo/Ipi/Cabo



In the doublet arm, 24 of 35 patients (68.6%) had a decrease in target lesion

In the triplet arm, 23 of 33 patients (69.7%) had a decrease in target lesion



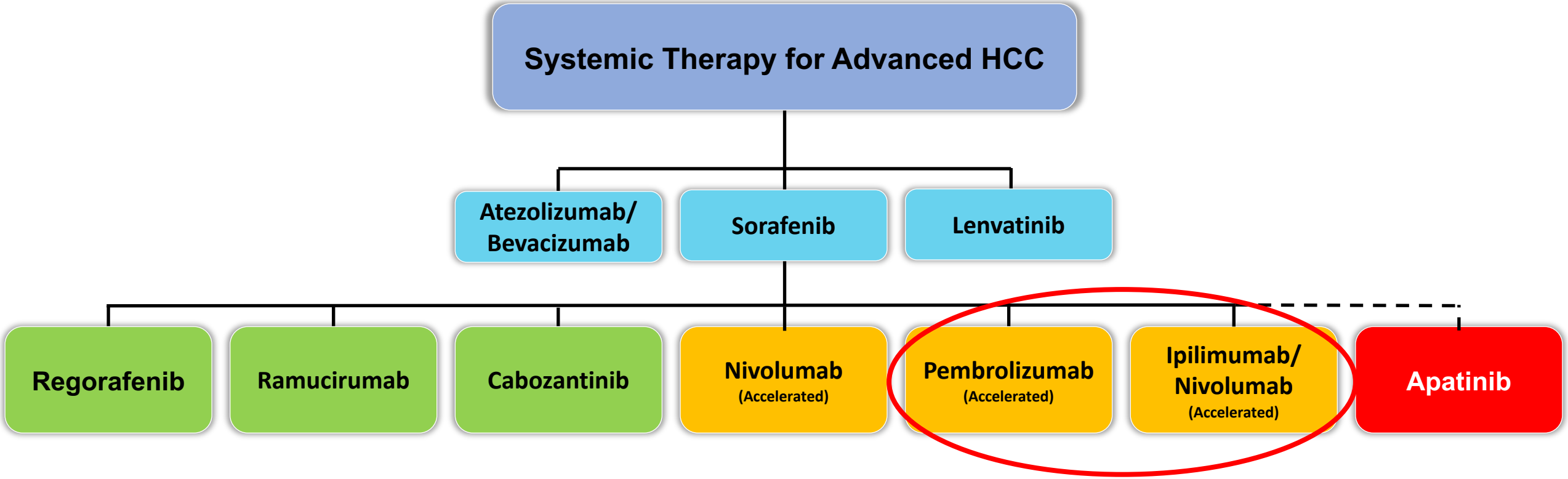
Courtesy of Lipika Goyal, MD, MPhil

Yau, et al, GI ASCO 2020

Apatinib as Second-Line Therapy in Chinese Patients with Advanced Hepatocellular Carcinoma: A Randomized, Placebo-Controlled, Double-Blind, Phase III Study

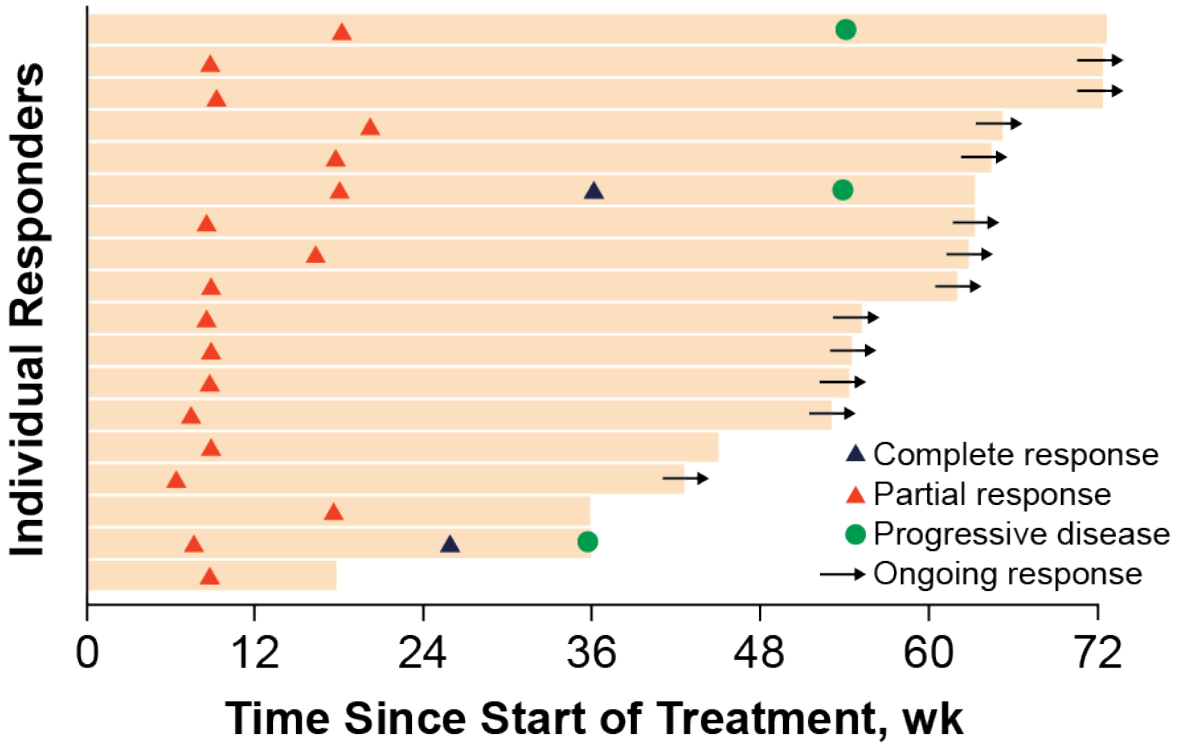
Qui L et al. ASCO 2020;Abstract 4507.

Year in Review 2020



Courtesy of Lipika Goyal, MD, MPhil

KEYNOTE-224: Pembrolizumab in advanced HCC



Median DOR not reached
Objective response: 17%

Zhu AX et al. *Lancet Oncol*. 2018;19:940-952.

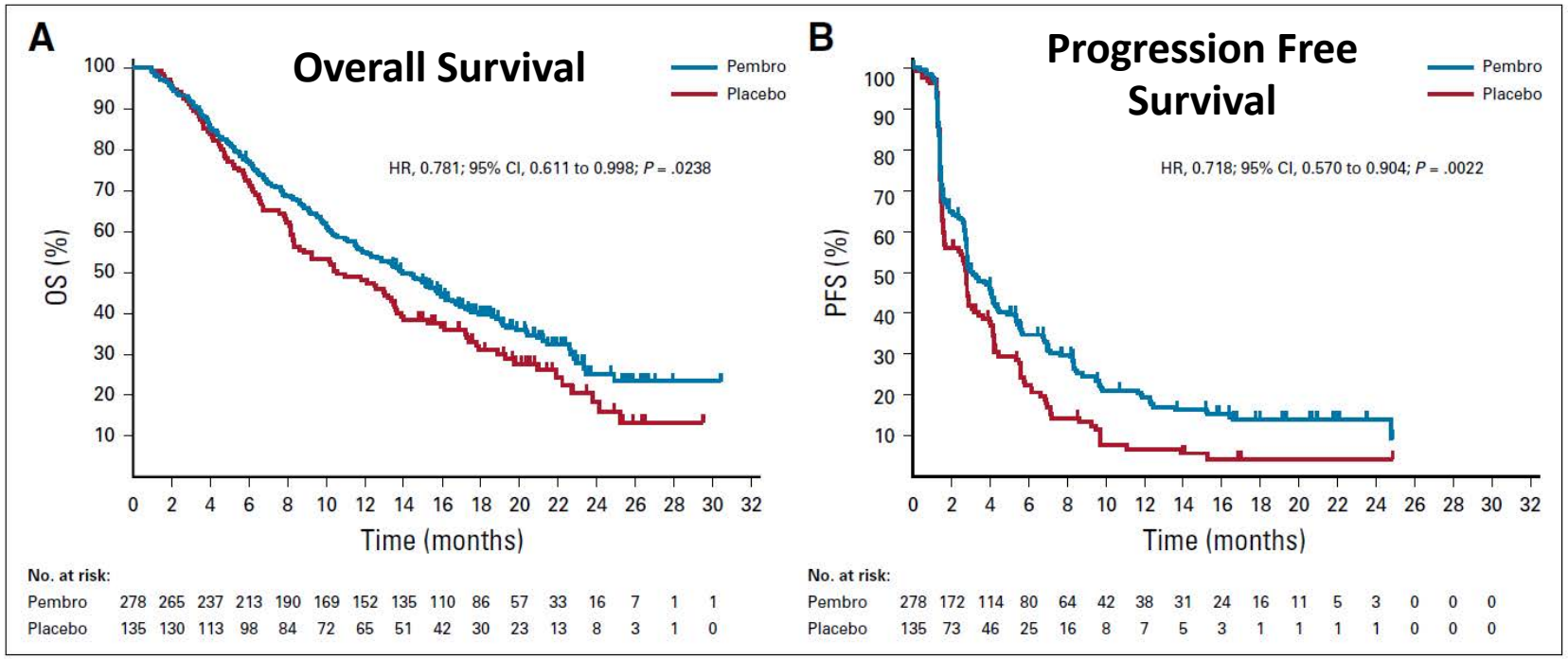
Updated data for KEYNOTE-224:

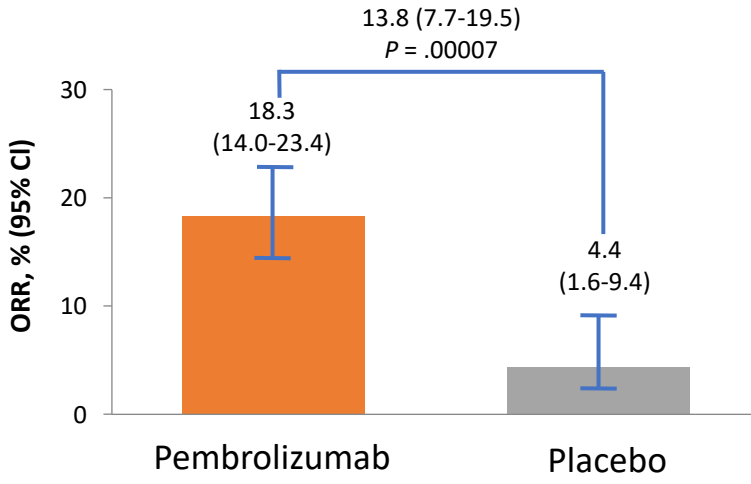
1. ORR improved from 17.3% to 18.3%
2. Duration of response ≥ 12 months improved from 61.4% to 77.0%
3. Complete response rate improved from 1.0% to 3.8%
4. Safety profile of pembrolizumab not significantly changed

Kudo, et al, *GI ASCO* 2020

Courtesy of Lipika Goyal, MD, MPhil

KEYNOTE-240: Pembrolizumab vs Placebo in Advanced HCC





Pembrolizumab reduced the risk of death by 22% and improved PFS over placebo

"These differences did not meet significance per the prespecified statistical plan"

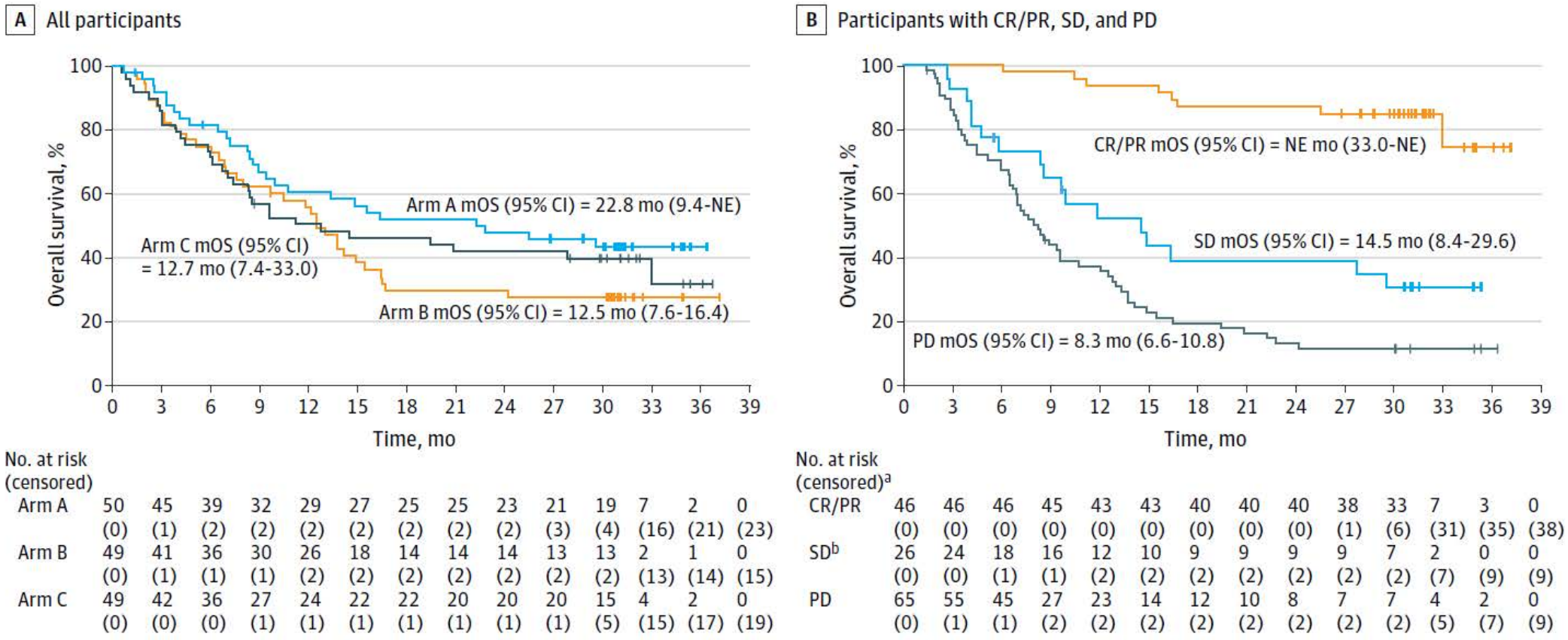
Favorable risk-to-benefit ratio for pembrolizumab

Courtesy of Lipika Goyal, MD, MPhil

Finn, et al *JCO* 2020

CheckMate 040: Ipilimumab and Nivolumab in advanced HCC after sorafenib

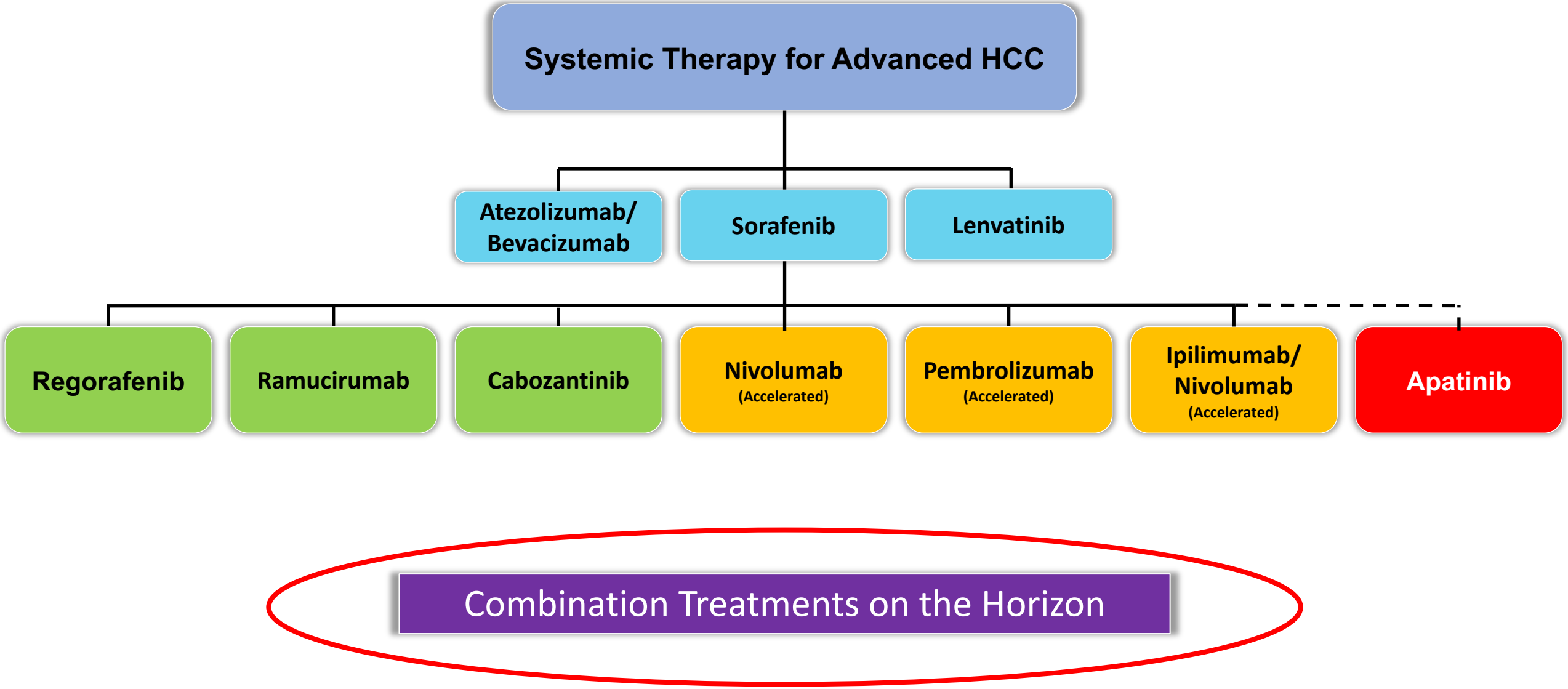
Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for four doses, followed by nivolumab 240 mg alone every 2 weeks



Objective Response Rate 32%

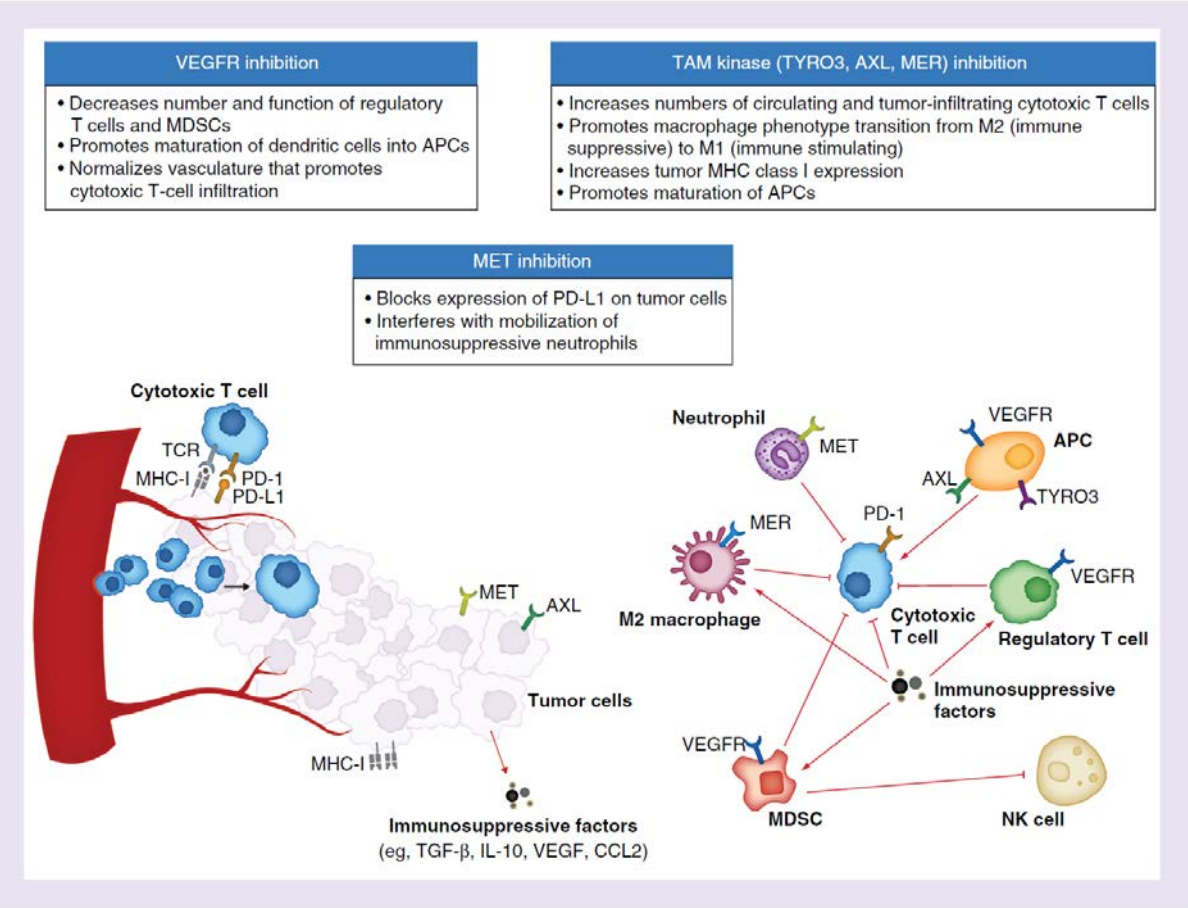
Yao, et al, *JAMA Onc*, 2020

Courtesy of Lipika Goyal, MD, MPhil



Courtesy of Lipika Goyal, MD, MPhil

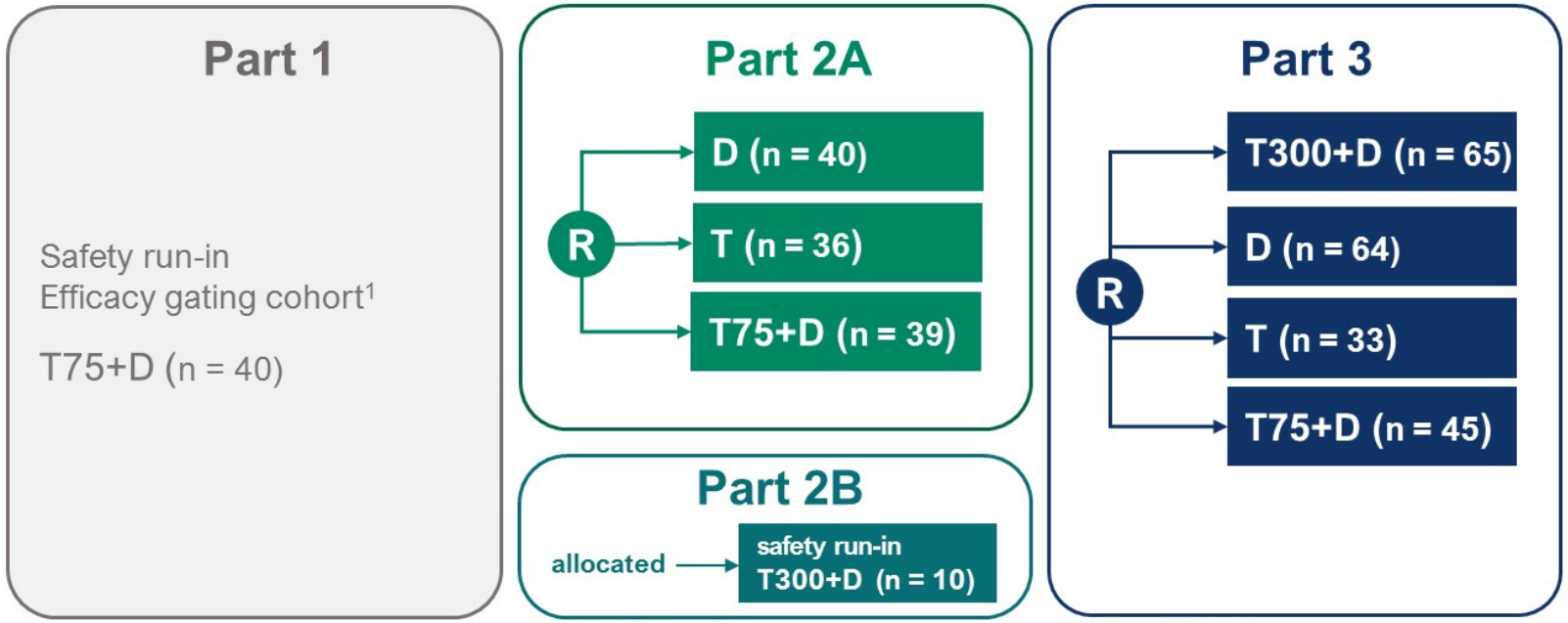
Rationale for Immunotherapy/TKI combinations



Kelley, et al, *Future Oncology,* 2020

Courtesy of Lipika Goyal, MD, MPhil

Study 22: Tremelimumab (T) in Combination with Durvalumab (D) for Advanced HCC



Key Milestones

FSI Part 2A	February 2017
FSI Part 2B	October 2017

Key Milestones

FSI Part 3	February 2018
LSI Part 3	April 2019

Treatments and Regimens

T300+D	tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W
D	durvalumab 1500 mg Q4W
T	tremelimumab monotherapy 750 mg Q4W × 7 doses, Q12W thereafter
T75+D	tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W

Key Eligibility

- Unresectable HCC with fresh or archival tumor biopsy sample available
- Progressed on, intolerant to, or refused prior sorafenib
- Child Pugh A liver function

Objectives and Assessments

Primary Endpoint: Safety

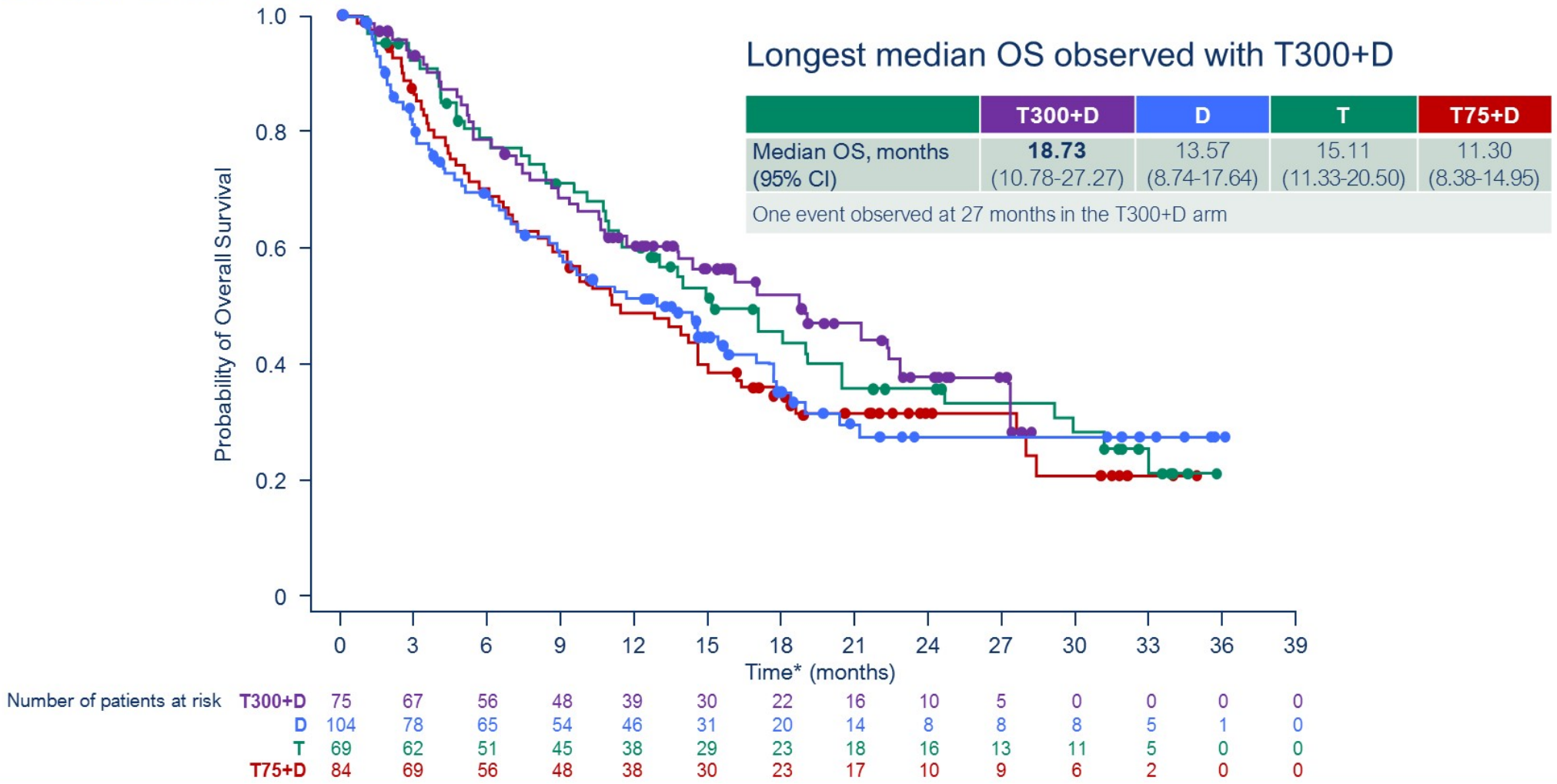
Key Secondary Endpoints
- Overall survival
- Objective response rate
- Duration of response

Key Assessments
- Multiphase imaging Q8 weeks
- Circulating immune cells
- PD-L1 status (Ventana SP263)

Courtesy of Lipika Goyal, MD, MPhil

Sangro, et al, GI ESMO 2020; Kelley, et al, ASCO 2020

Study 22: Overall Survival



Courtesy of Lipika Goyal, MD, MPhil

Sangro, et al, GI ESMO 2020; Kelley, et al, ASCO 2020

What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh A score and a PS of 0 who received first-line standard-dose sorafenib with minimal toxicity, had stable disease for 14 months and then experienced disease progression (AFP 2,500 ng/mL)?

a. Lenvatinib
b. Regorafenib
c. Cabozantinib
d. Ramucirumab
e. Anti-PD-1 antibody
f. Atezolizumab/bevacizumab
g. Nivolumab/ipilimumab
h. Other

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

a. Cabozantinib
b. Lenvatinib
c. Anti-PD-1 antibody
d. Nivolumab/ipilimumab
e. Ramucirumab
f. Regorafenib
g. Sorafenib
h. 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)?

a. Sorafenib
b. Regorafenib
c. Cabozantinib
d. Ramucirumab
e. Anti-PD-1 antibody
f. Nivolumab/ipilimumab
g. Chemotherapy
h. Other

MODULE 2: Targeted Treatment of Cholangiocarcinoma

Key Relevant Data Sets

- FIGHT-202: FDA approval of pemigatinib for cholangiocarcinoma with FGFR2 fusion
- FOENIX-CCA2: Phase II study of futibatinib for cholangiocarcinoma harboring FGFR2 gene fusions
- Phase II study of infigratinib for cholangiocarcinoma harboring FGFR2 gene fusions
- FIGHT-302: First-line pemigatinib vs gemcitabine with cisplatin for advanced cholangiocarcinoma with FGFR2 rearrangements
- ClarIDHy: Ivosidenib in chemotherapy-refractory cholangiocarcinoma with IDH1 mutation

Year in Review 2020

Biliary Tract Cancers (BTC): A Complex Landscape

Anatomic and Genetic Diversity → Targets Galore

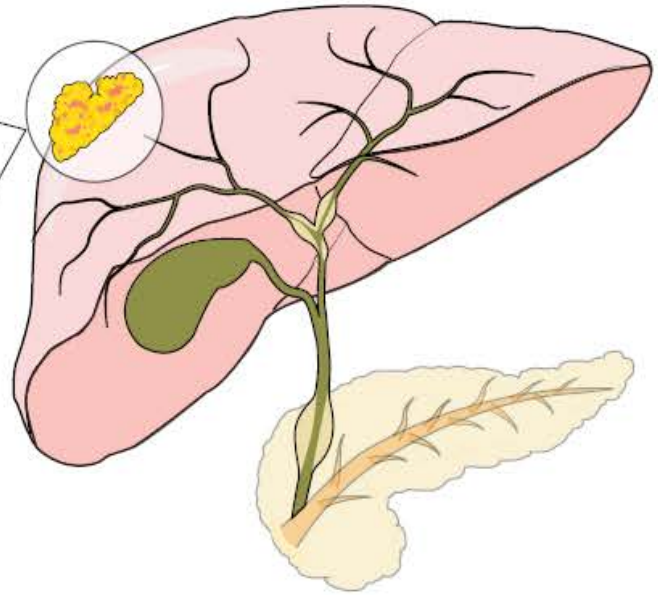
Intrahepatic Cholangiocarcinoma (IHCC)

Targeted therapies

FGFR small molecule kinase inhibitors
Mutant IDH inhibitors
HDAC inhibitors
MET kinase inhibitors
Mcl-1 selective inhibitor
MEK inhibitors
AKT inhibitors, mTOR inhibitors

Molecular aberrations

FGFR2 fusion (7–14%)
IDH 1/2 (23–28%)
BAP1 (9-12%), ARID1A (15–36%)
MET-HGF (7%)
Mcl-1 (16–21%)
KRAS (11–25%)
PI3K-AKT-mTOR (4–8%)



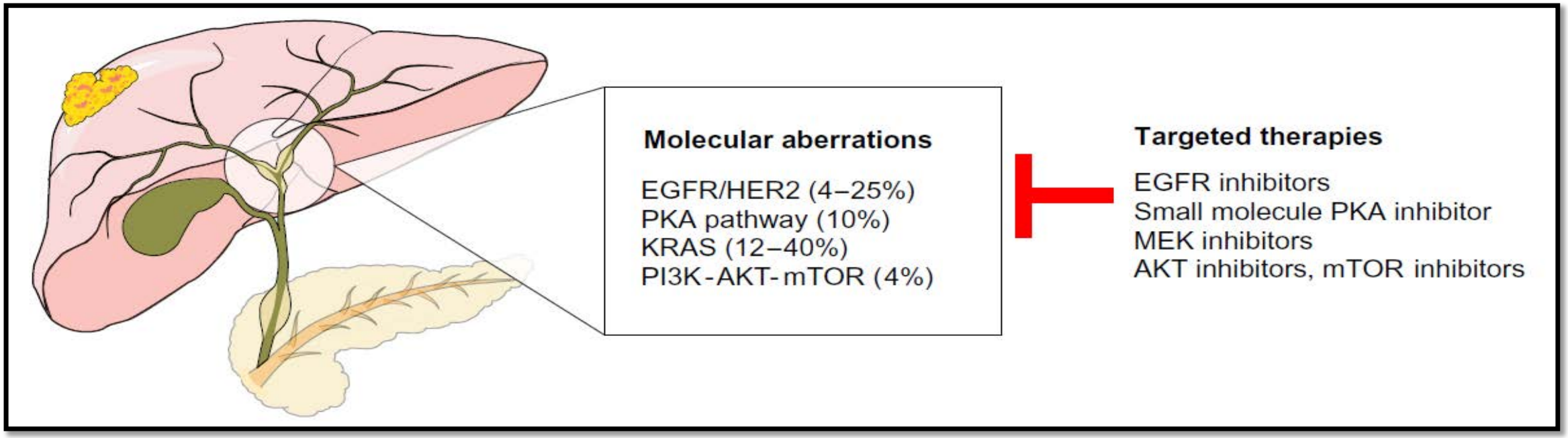
Valle J et al. Cancer Discov 2017;7:943-962

Courtesy of Tanios Bekaii-Saab, MD

Biliary Tract Cancers (BTC): A Complex Landscape

Anatomic and Genetic Diversity → Targets Galore

Perihilar Cholangiocarcinoma



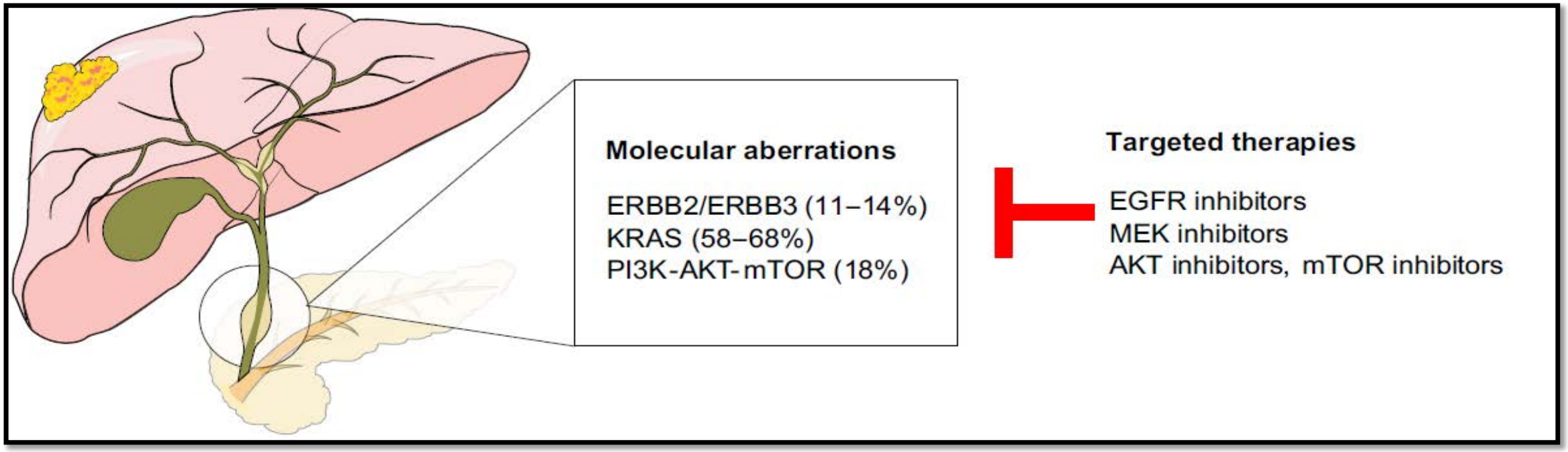
Valle J et al. Cancer Discov 2017;7:943-962

Courtesy of Tanios Bekaii-Saab, MD

Biliary Tract Cancers (BTC): A Complex Landscape

Anatomic and Genetic Diversity → Targets Galore

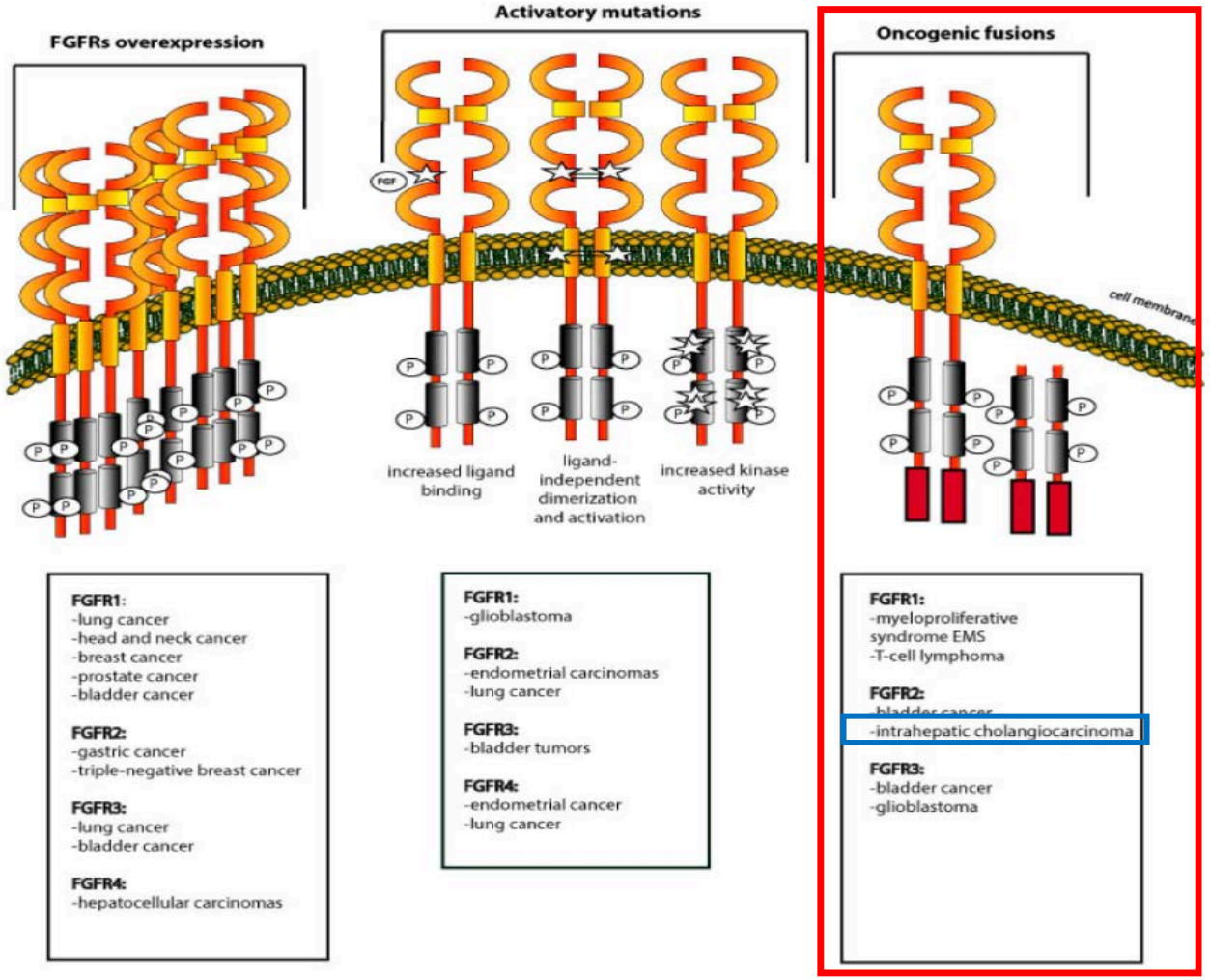
Distal Cholangiocarcinoma + Gallbladder Cancer



Valle J et al. Cancer Discov 2017;7:943-962

Courtesy of Tanios Bekaii-Saab, MD

Targeting Dysregulation of FGFR in BTC



Agents in Development:

- Pemigatinib
- Infigratinib
- Futibatinib
- Derazantinib
- And others

Borad M et al. Current Opinion in Gastroenterology. May 2015

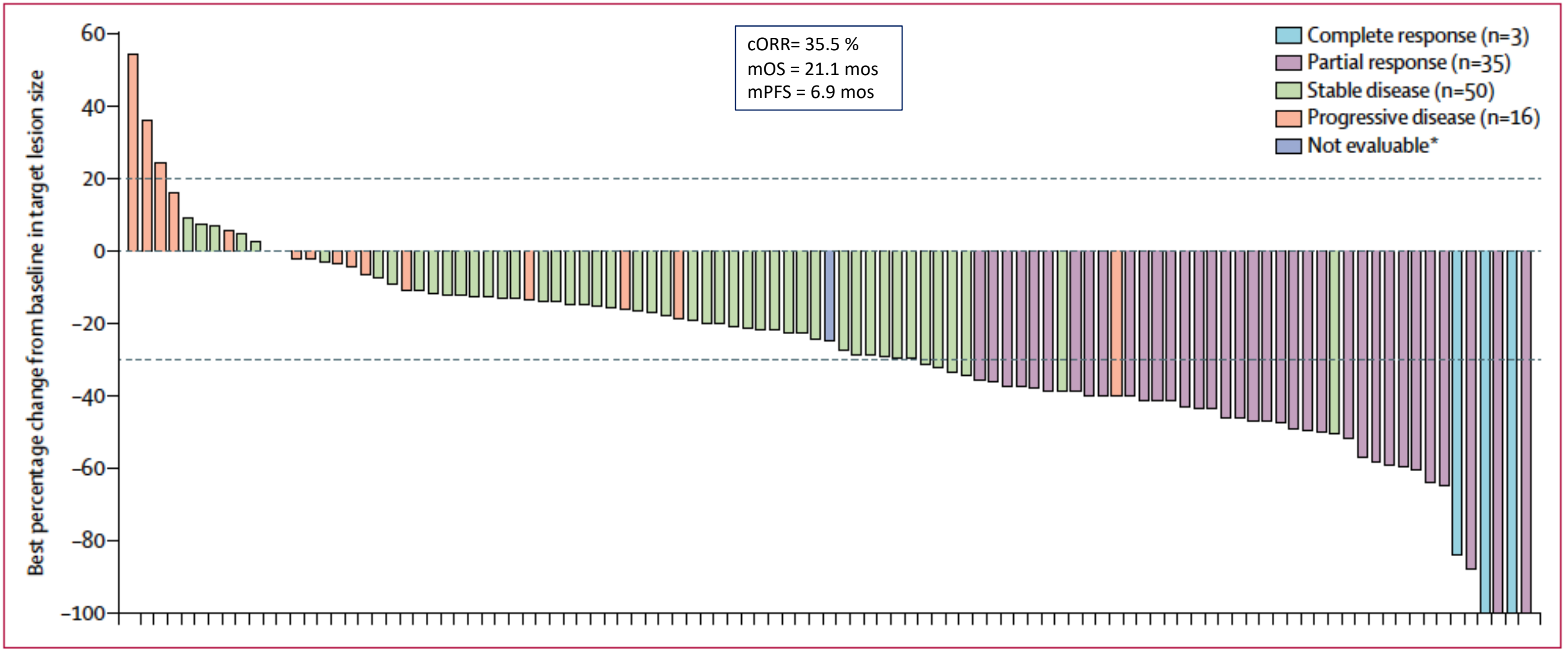
Courtesy of Tanios Bekaii-Saab, MD

Patients with advanced cholangiocarcinoma should have…

a. NGS or panel somatic testing
b. Germline panel testing
c. Both
d. Neither

Year in Review 2020

FIGHT-202 (Pemigatinib)
Waterfall Plot results for individual patients with *FGFR2* fusions or rearrangements



Abou-Alfa G et al. Lancet Oncology . March 20 , 2020

Courtesy of Tanios Bekaii-Saab, MD

Pemigatinib: Common AEs

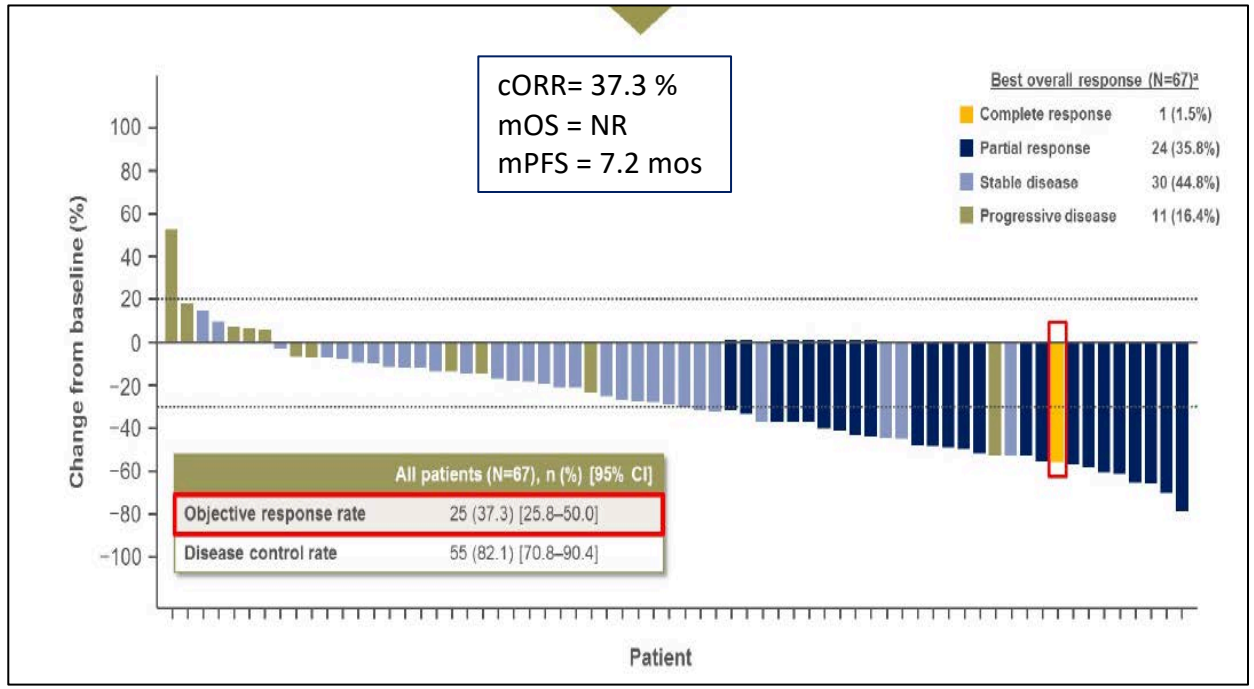
	Grade 1–2	Grade 3	Grade 4
Paronychia	81 (55%)	0	0
Alopecia	67 (46%)	0	0
Dysgeusia	55 (38%)	0	0
Diarrhoea	49 (34%)	4 (3%)	0
Fatigue	45 (31%)	2 (1%)	0
Stomatitis	39 (27%)	8 (5%)	0
Dry mouth	42 (29%)	0	0
Nausea	34 (23%)	2 (1%)	0
Decreased appetite	34 (23%)	1 (1%)	0
Dry eye	30 (21%)	1 (1%)	0
Dry skin	22 (15%)	1 (1%)	0
Arthralgia	16 (11%)	6 (4%)	0
Palmar-plantar erythrodysaesthesia	16 (11%)	6 (4%)	0
Constipation	20 (14%)	0	0
Hypophosphataemia*	8 (5%)	10 (7%)	0
Pain in extremity	15 (10%)	0	0
Vomiting	13 (9%)	1 (1%)	0
Weight decreased	13 (9%)	1 (1%)	0
Myalgia	10 (7%)	1 (1%)	0
Nail discolouration	10 (7%)	1 (1%)	0
Abdominal pain	8 (5%)	1 (1%)	0
Anaemia	8 (5%)	1 (1%)	0
Onychoclasis	8 (5%)	1 (1%)	0
Paronychia	8 (5%)	1 (1%)	0

Courtesy of Tanios Bekaii-Saab, MD

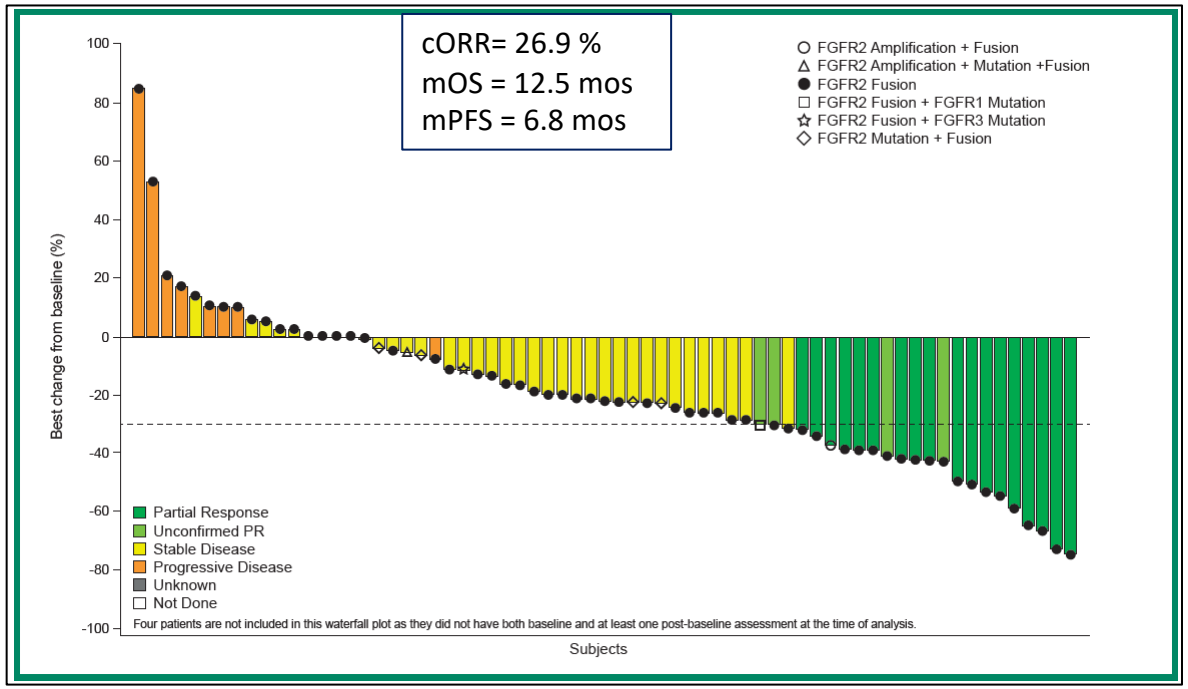
Abou-Alfa G et al. Lancet Oncology . March 20 , 2020

Other FGFR inhibitors in patients with FGFR2 fusions and IHCC

FUTIBATINIB (FOENIX-CCA2 Phase II Trial)[1]



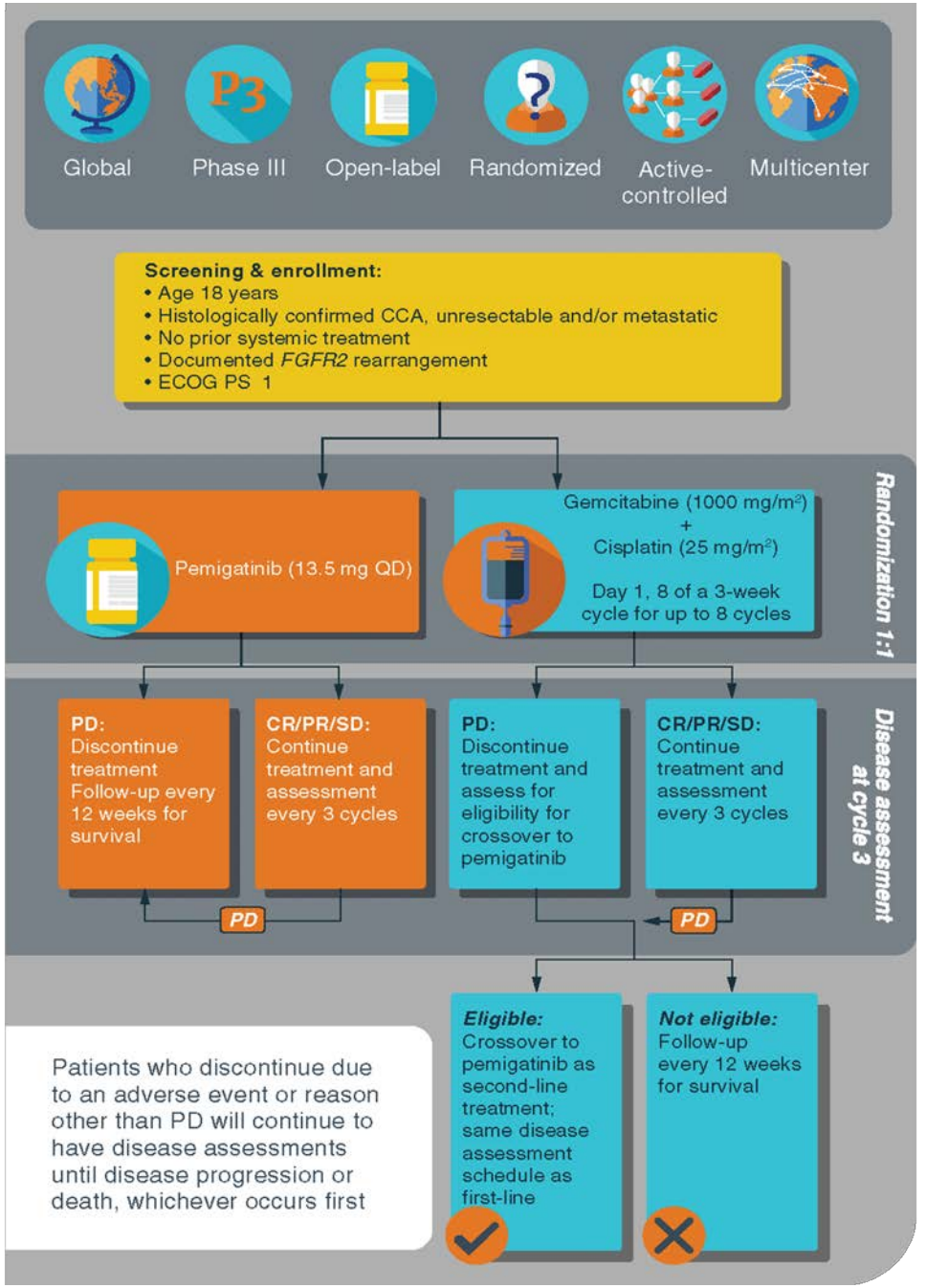
INFIGRATINIB (Phase II Trial)[2]



1-Goyal L et al ASCO 2020; 2- Javle M et al ESMO 2018

Courtesy of Tanios Bekaii-Saab, MD

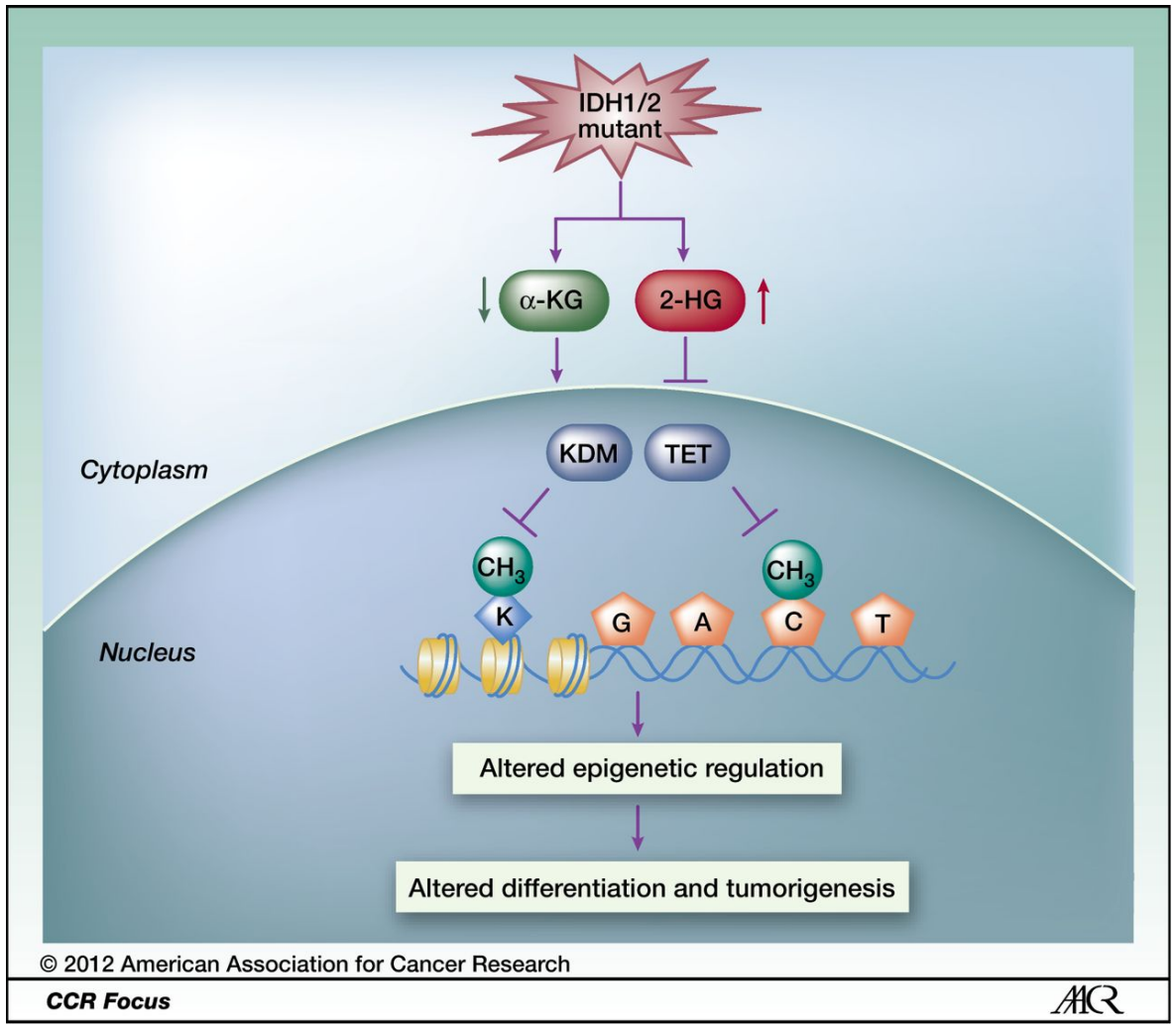
FIGHT-302: 1L Pemigatinib vs gemcitabine plus cisplatin for advanced IHCA with *FGFR2* rearrangements



Bekaii-Saab T et al. *Future Oncology* 2020.

Courtesy of Tanios Bekaii-Saab, MD

IDH1/2 mutations inhibit both histone and DNA demethylation and alter epigenetic regulation.



Hui Yang et al. *Clin Cancer Res* 2012;18:5562-5571

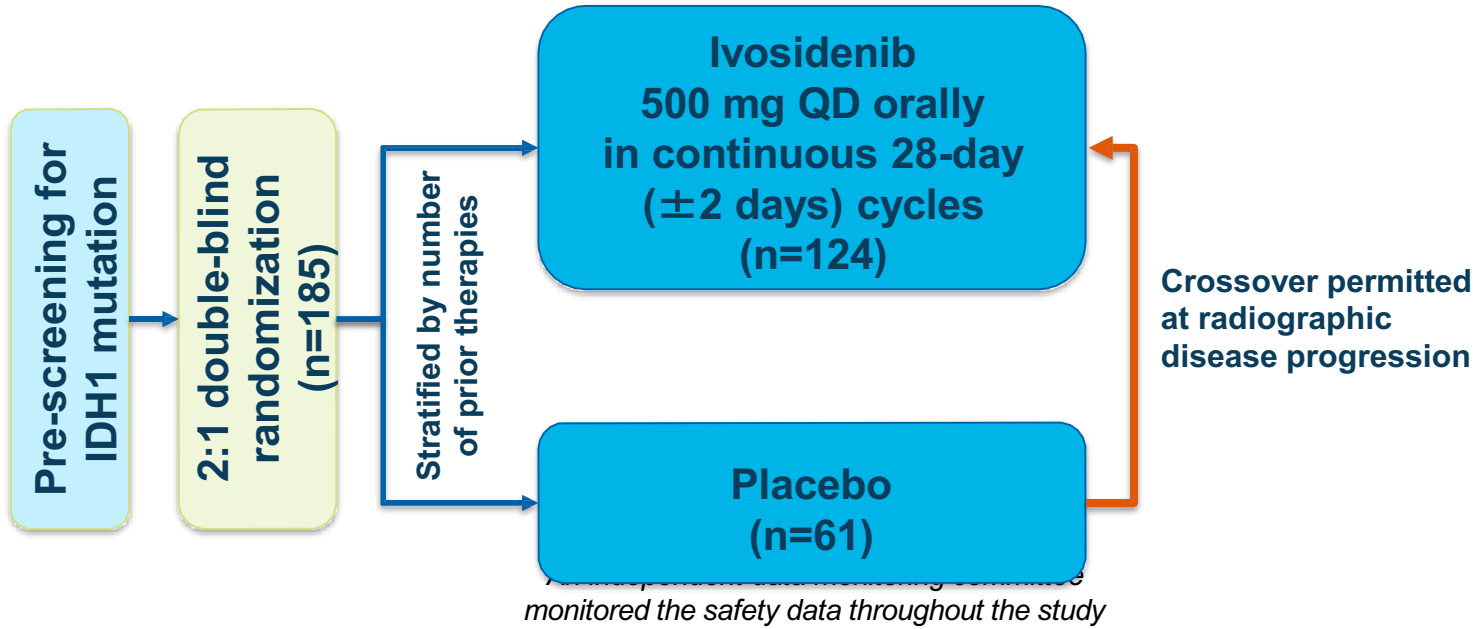
Courtesy of Tanios Bekaii-Saab, MD

ClarIDHy

Key eligibility criteria

- ≥18 years of age
- Histologically confirmed diagnosis of cholangiocarcinoma
- Centrally confirmed mIDH1* status by NGS
- ECOG PS score 0 or 1
- 1-2 prior therapies (at least 1 gemcitabine- or 5-FU-containing regimen)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function

NCT02989857



- **Primary endpoint:** PFS by blinded independent radiology center (IRC)
- **Secondary endpoints included:** safety and tolerability; PFS by local review; OS; objective response rate; quality of life (QoL)†; pharmacokinetics/pharmacodynamics
- Sample size of ~186 patients based on hazard ratio (HR)=0.5, 96% power, 1-sided alpha=0.025
- 780 patients were screened for IDH1 mutations across 49 sites and 6 countries

*IDH1 mutation status prospectively confirmed by NGS-based Assay on formalin-fixed, paraffin-embedded tumor tissue in a Clinical Laboratory Improvement Amendments-certified laboratory.

†Assessed using EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BIL21, and PGI questions.

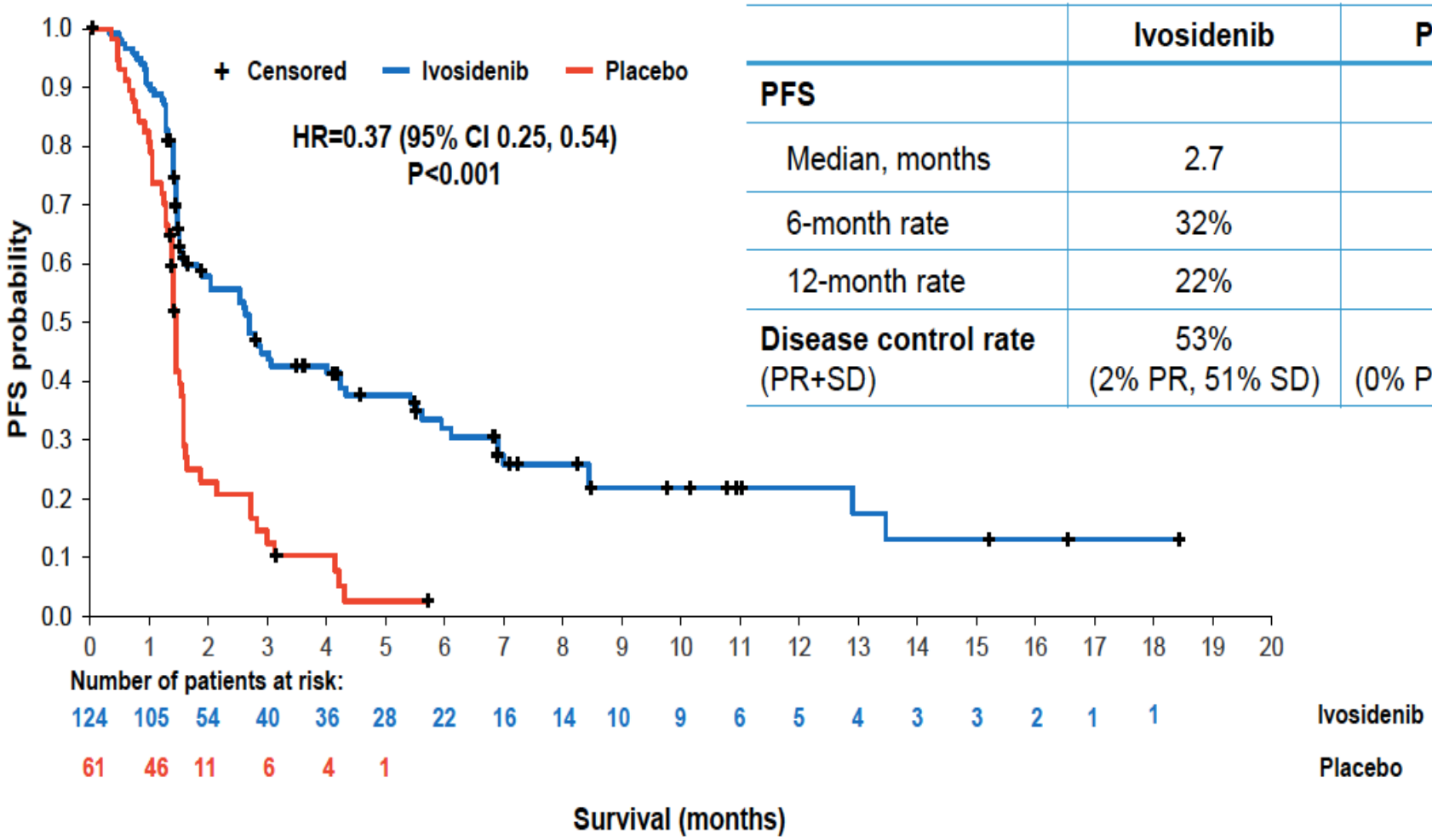
ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=5-level EuroQoL-5 Dimension questionnaire; FU=fluorouracil; NGS=next-generation sequencing; PGI=Patient Global Impression; QD=once daily; QLQ-BIL21=Cholangiocarcinoma and Gallbladder Cancer module; QLQ-C30=Quality of Life Questionnaire Core 30;

RECIST=Response Evaluation Criteria in Solid Tumors.

Courtesy of Tanios Bekaii-Saab, MD

Abou Alfa et al ESMO 2019

Targeting IDH1 in IHCC: Ivosidenib vs. Placebo



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

Abou-Alfa GK et al. *Lancet Oncol* 2020;32(6):796-807; Abou-Alfa G et al. ESMO 2019

Courtesy of Tanios Bekaii-Saab, MD

MODULE 3: Pancreatic Cancer

Key Relevant Data Sets

- Liposomal irinotecan
- POLO: Maintenance olaparib
- Maintenance rucaparib for pancreatic cancer with BRCA or PALB2 mutation
- Platinum-based therapy +/- veliparib for patients with germline BRCA/PALB2 mutations

Year in Review 2020

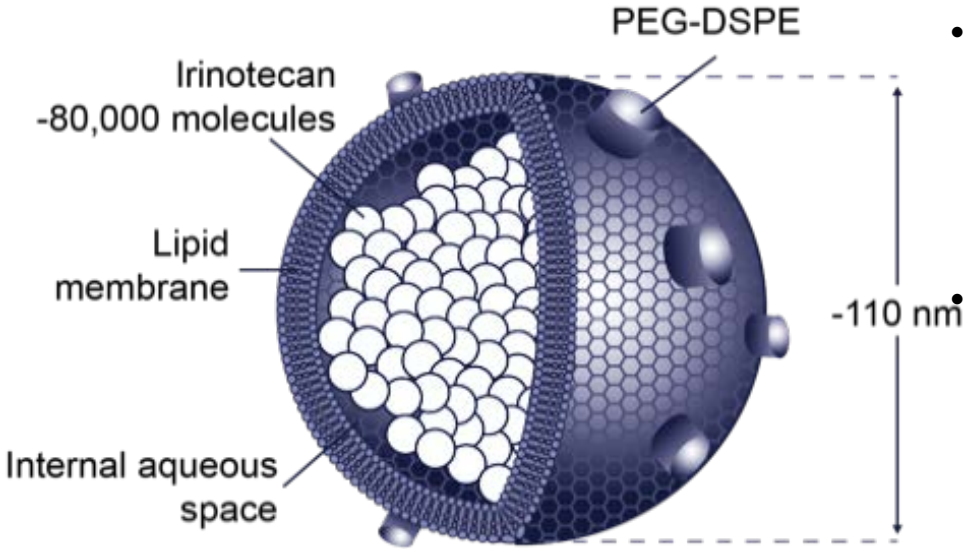
Do you generally offer neoadjuvant chemotherapy to your patients with resectable pancreatic cancer?

a. Almost always
b. Frequently
c. Occasionally
d. Rarely

Year in Review 2020

Liposomal Irinotecan (nal-IRI): Drug Characteristics

nal-IRI is a stable nanoliposomal therapy



- The half-life (t½) of total irinotecan following administration of nal-IRI 70 mg/m^2 is 25.8 hours, >4 x longer than irinotecan (5.8 hours)[1,2]
- 95% of irinotecan remains liposome-encapsulated, and the ratios between total and encapsulated forms did not change with time from 0 to 169.5 hours post-dose[1]

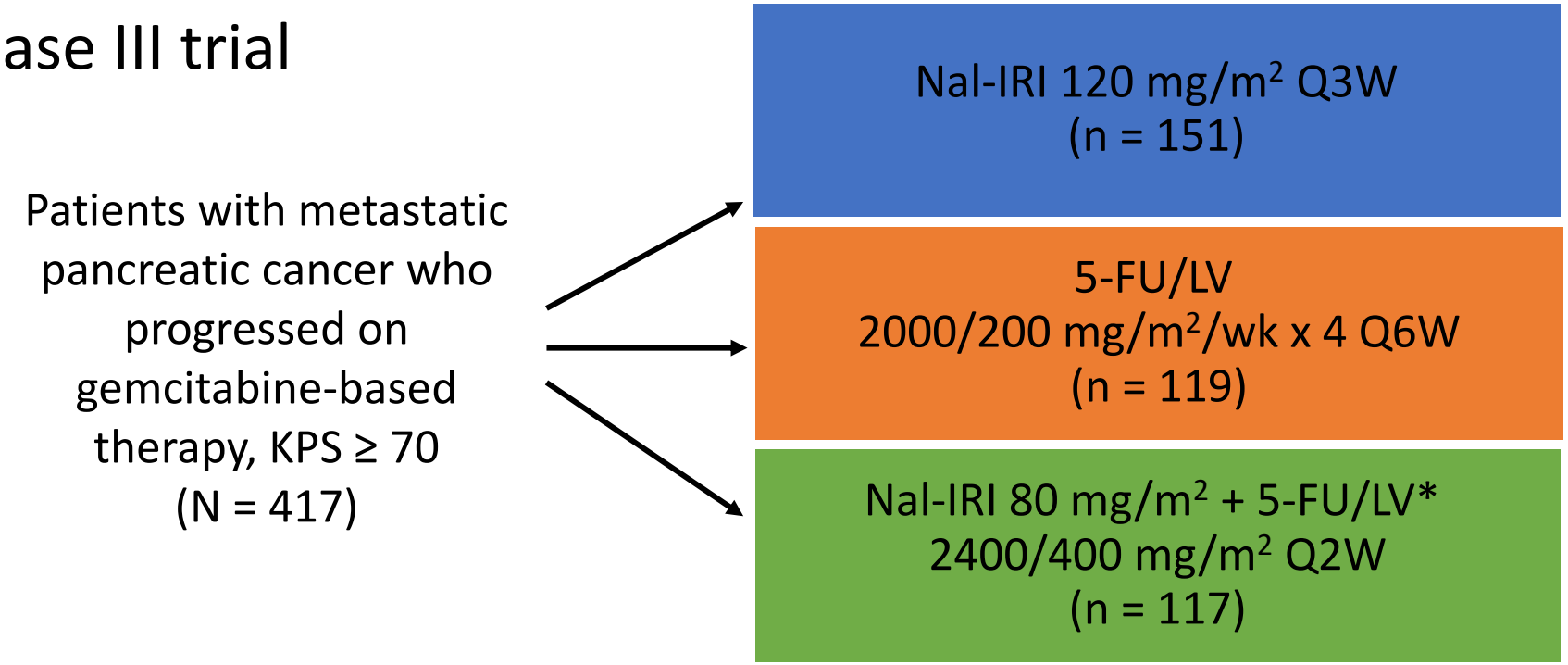
- In humans, nal-IRI results in 46-fold greater exposure of irinotecan in the blood than free irinotecan[3]
- In human tumor biopsies, SN-38 levels were substantially higher in tumor than plasma[4]
- nal-IRI resulted in SN-38 duration of exposure at site of tumor >3x longer than standard irinotecan in mouse model[5]
- nal-IRI had greater tumor volume reduction than free irinotecan in mouse models[5,6]

1. Irinotecan liposome Prescribing Information. https://www.onivyde.com/_assets/pdf/ONIVYDE_USPI.pdf. Accessed January 10, 2020.
2. Irinotecan Prescribing Information. https://www.pfizermedicalinformation.com/en-us/camptosar. Accessed January 10, 2020. 3. Adiwijaya BS et al. *Clin Pharmacol Ther*. 2017;102:997-1005. 4. Ramanathan RK et al. American Association for Cancer Research Annual Meeting 2014 (AACR 2014). Poster CT224. 5. Kalra AV et al. *Cancer Res*. 2014;74:7003-7013. 6. Goldwasser F et al. *Cancer Res*. 1995;55:2116-2121.

Courtesy of Tanios Bekaii-Saab, MD

NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV in PDAC

- Phase III trial



*Combination arm added after safety data were available.
Patients in 5-FU/LV arm used as controls for combination arm.

Wang-Gillam A, et al. Lancet. 2016;387:545-557.

Courtesy of Tanios Bekaii-Saab, MD

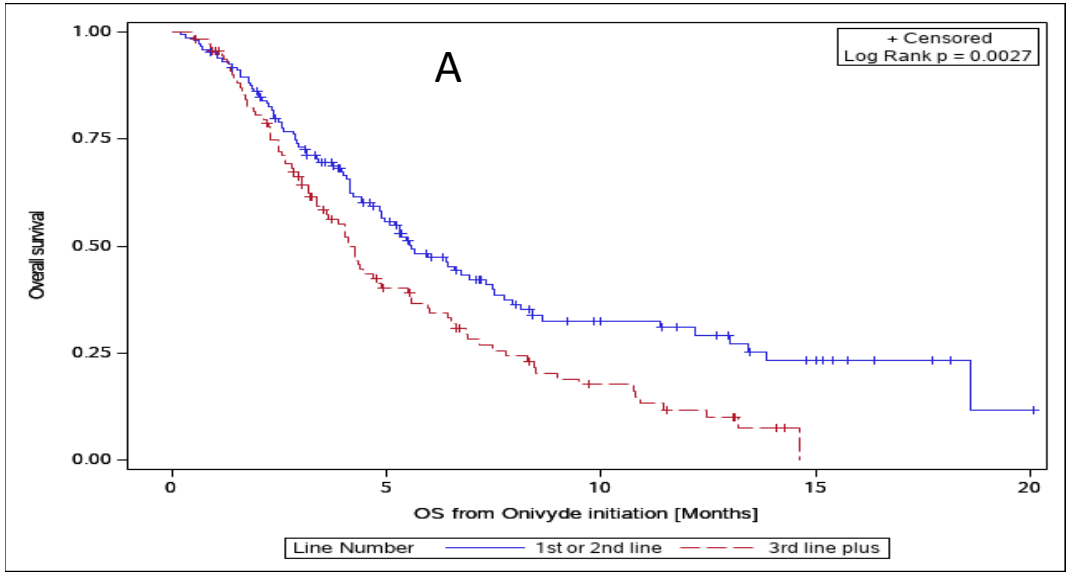
NAPOLI-1: Results

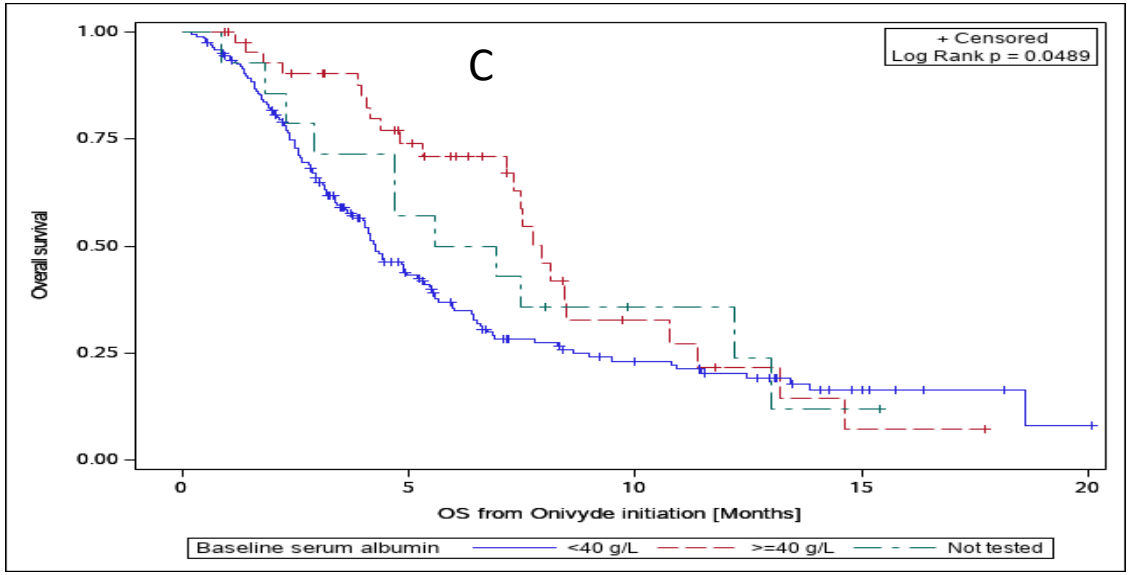
Tumor Response and Control	Nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 119)
Median OS, mos	6.1	4.2
	P = .0009	
Median PFS, mos	3.1	1.5
	P = .0001	
ORR, %	16	1
	P < .001	
CA19-9 reduction, %	36	12
	P = .0009	

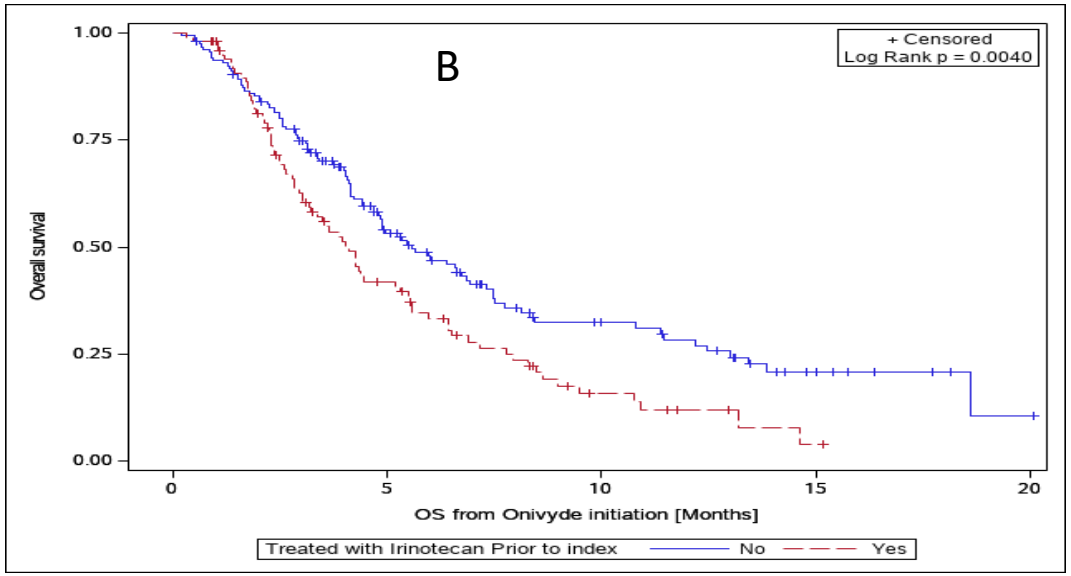
Wang-Gillam A, et al. Lancet. 2016;387:545-557.

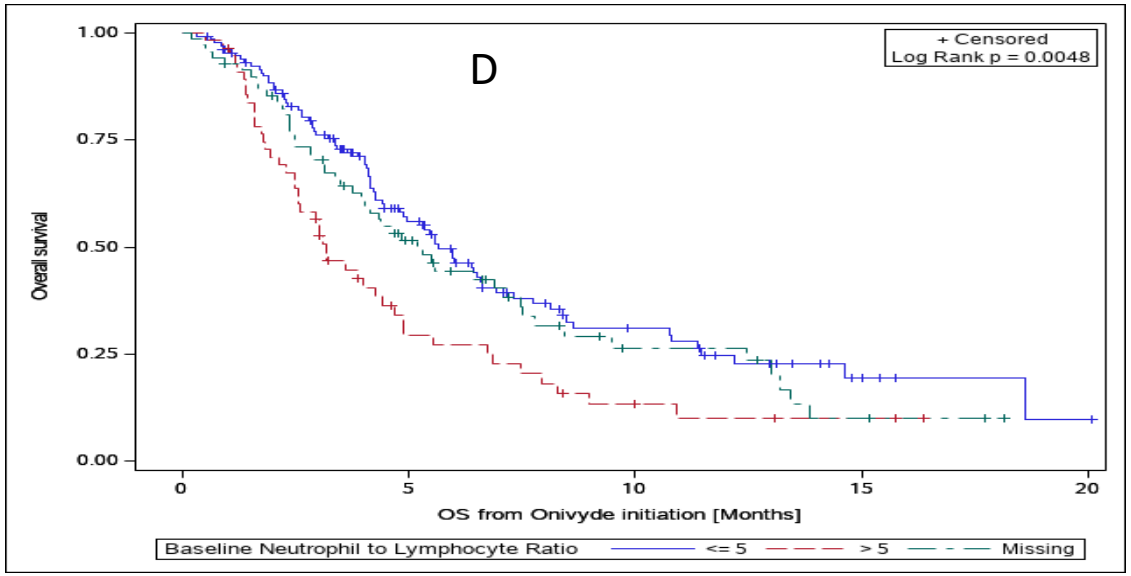
Courtesy of Tanios Bekaii-Saab, MD

RW Outcomes: Overall survival curves among patients by: (A) nal-IRI as first-/second-line therapy compared with third-line-or-later therapy, (B) prior treatment with irinotecan, (C) baseline serum albumin level, and (D) baseline neutrophil to lymphocyte ratio







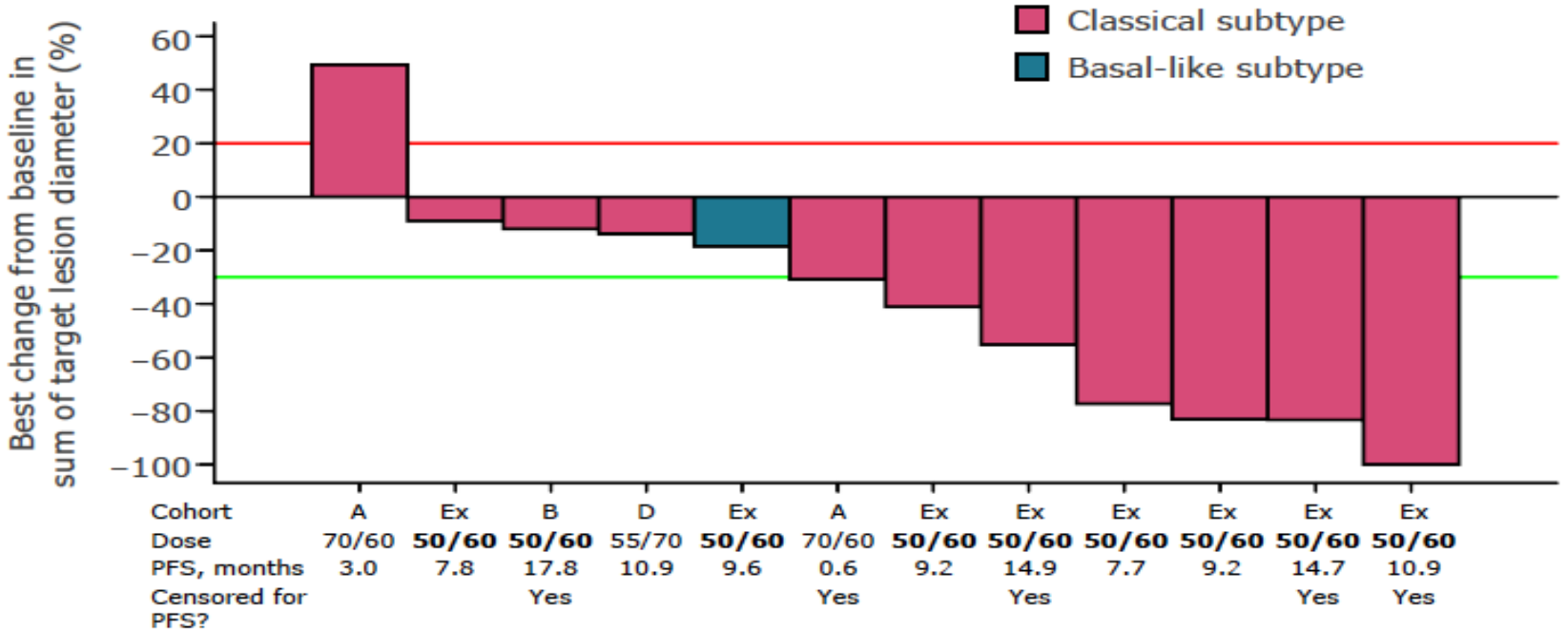


Barzi A et al . *Pancreas* • Volume 49, Number 2, February 2020

Courtesy of Tanios Bekaii-Saab, MD

NALIRIFOX: Biomarkers – Genomic Profiling

Tumour response data were available for 12 patients



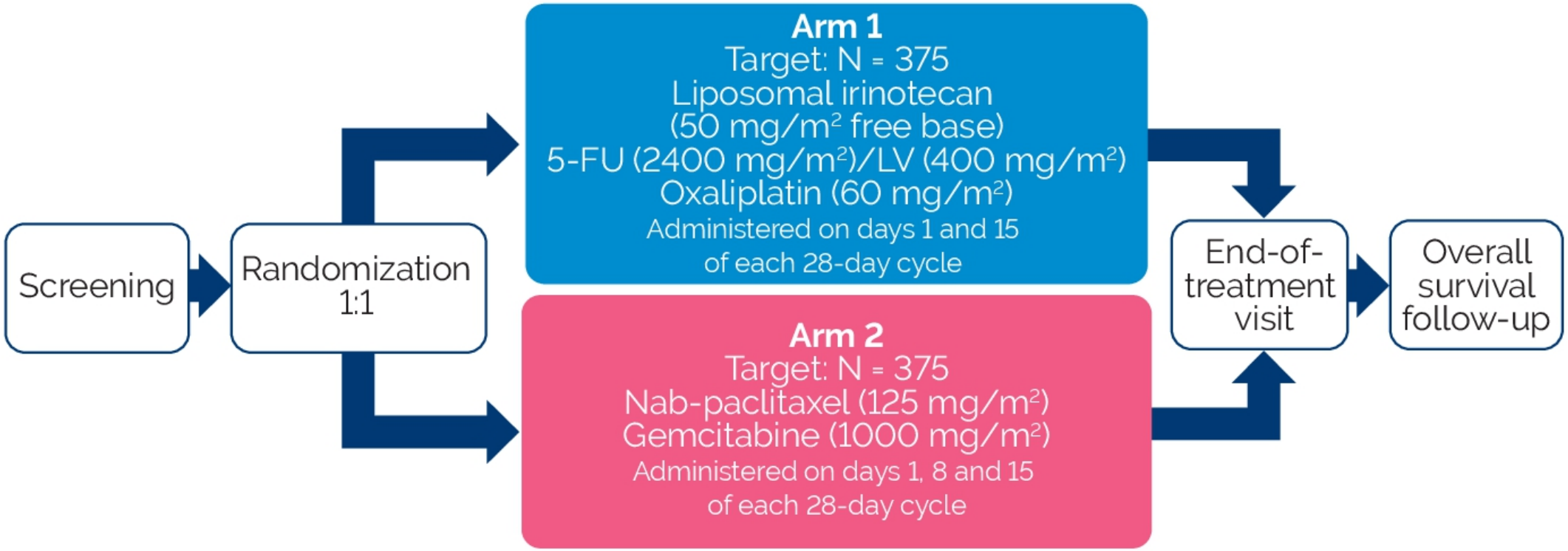
PFS in the pooled population 50/60

- Classical subtype: range 7.7–17.8 months (n = 8)
- Basal-like subtype: 9.6 months (n = 1)

Courtesy of Tanios Bekaii-Saab, MD

- Wainberg, Z.A., et al. Presented at the ESMO World Congress on Gastrointestinal Cancer (WCGI 2020, abstract #LBA-1)

NAPOLI-3: An open-label, randomized, phase III study of first-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin versus nab-paclitaxel + gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma

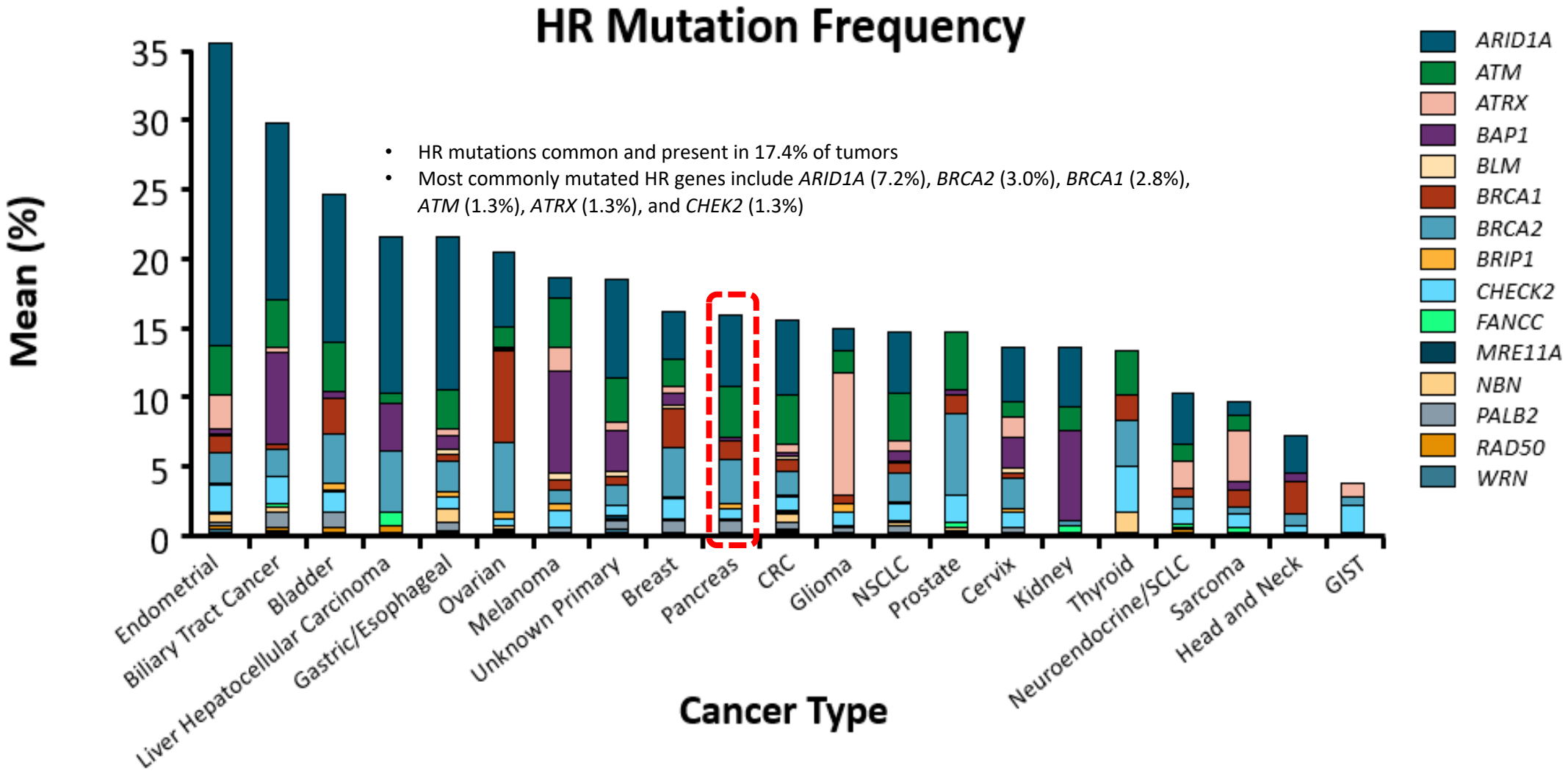


Wainberg, Z.A., et al. J Clin Oncol 38: 2020 (suppl; abstr TPS4661)

Courtesy of Tanios Bekaii-Saab, MD

Which approach would you take to genomic evaluation for a 75-year-old patient with metastatic pancreatic cancer?

a. NGS or panel somatic testing
b. Germline panel testing
c. Both
d. Neither



- HR mutations common and present in 17.4% of tumors
- Most commonly mutated HR genes include *ARID1A* (7.2%), *BRCA2* (3.0%), *BRCA1* (2.8%), *ATM* (1.3%), *ATRX* (1.3%), and *CHEK2* (1.3%)

Heeke. *JCO Precis Oncol*. 2018

Courtesy of Tanios Bekaii-Saab, MD

What is your usual second-line treatment for an 80-year-old patient without a somatic or germline mutation who received first-line gemcitabine/*nab* paclitaxel?

a. Nal-IRI + 5-FU/LV
b. OFF (oxaliplatin/5-FU/LV)
c. FOLFOX
d. FOLFIRI or other irinotecan-based regimen
e. Capecitabine/oxaliplatin
f. Capecitabine
g. Palliative care
h. Other

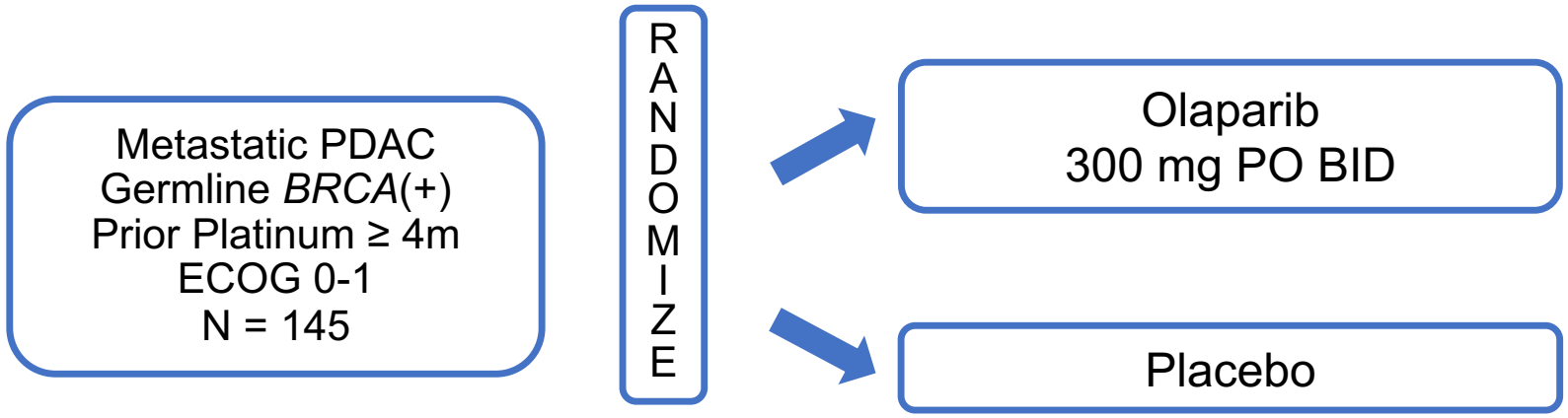
Single-Agent PARPi Trials in PDAC

	Olaparib	Veliparib	Talazoparib	Rucaparib
N	23	16	10	19
BRCA Type	Germline	Germline	Germline (including PALB2)	Germline (15)/ Somatic (4)
Lines of Therapy	Mean = 2	Mean = 2	1-2	1-2
Prior platinum	15/23 (65%)	14/16 (88%)	-	-
Response Rate	5/23 (22%)	**0%**	2/10 20%	3/19 (15%)
Stable Disease	8/22 (35%)	4/16 (25%) 4, 4, 10, 11 m	1/10 10%	4/19 (21%) 1 CR: 14 m+

Kaufmann, B. *J Clin Oncol*, 2014. Lowery, MA. Eur J Cancer, 2017. Domchek, S. *J Clin Oncol*, 2016 (34):4110

Courtesy of Tanios Bekaii-Saab, MD

POLO: Phase III Maintenance (Switch) in g*BRCA+* PDAC: Platinum Therapy → Olaparib/Placebo



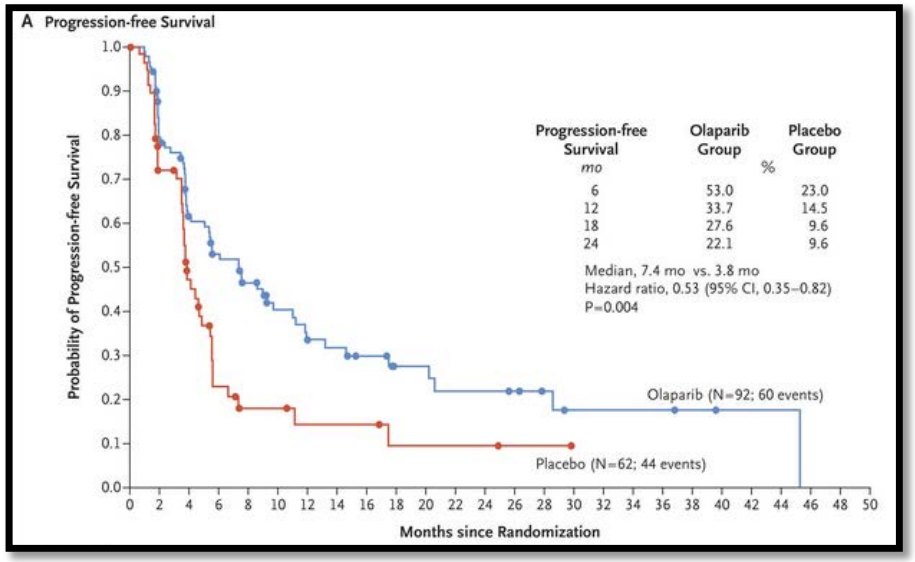
Randomization 3:2
Primary Endpoint: PFS (blinded independent central review mRECIST 1.1)
N ~ 3,500 screened

Golan T et al. *N Engl J Med.* 2019;381:317-327.

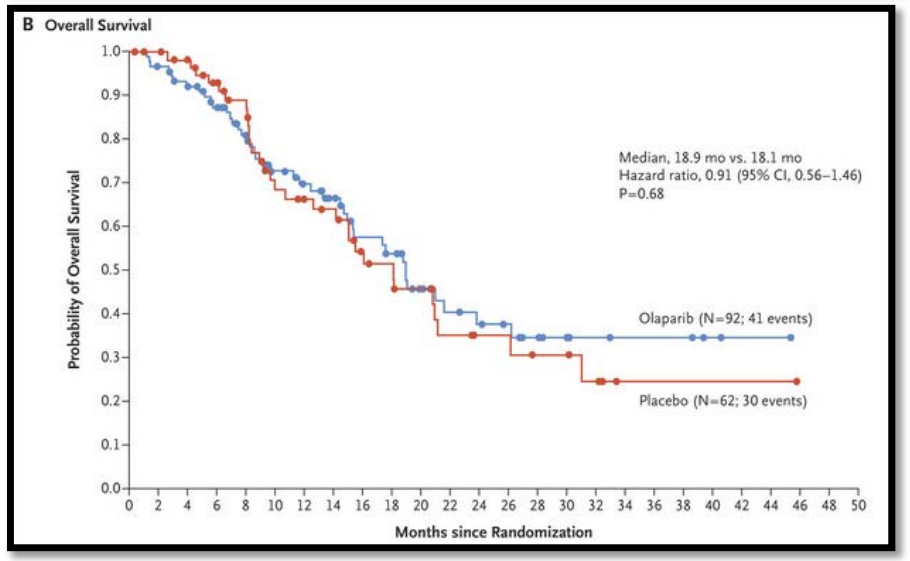
Courtesy of Tanios Bekaii-Saab, MD

POLO Trial Results

- 3315 patients screened to identify 154 eligible patients



Median PFS: 7.4 vs 3.8 mos
HR: 0.53 (*P* = .004)



No difference in OS on interim analysis
(Median OS, 18.9 vs 18.1 mos)
HR: 0.91 (*P* = 0.68)

Golan et al. N Engl J Med 2019;381(4):317-327;
Hochhauser et al. ESMO 2020;Abstract 1527P.

Courtesy of Tanios Bekaii-Saab, MD

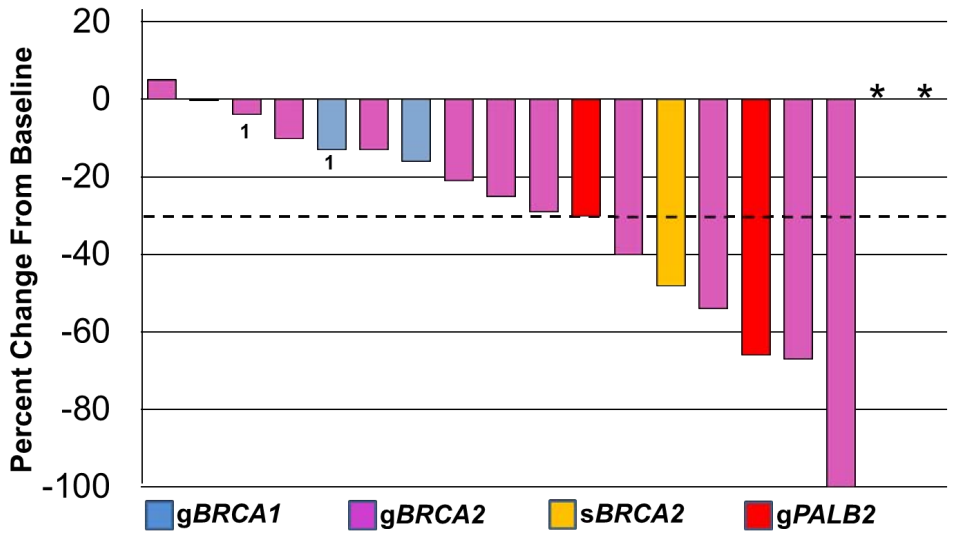
Maintenance olaparib in patients aged ≥ 65 years with a germline *BRCA* mutation and metastatic pancreatic cancer: POLO trial

	Olaparib		Placebo	
	Age < 65 years (n = 63)	Age ≥ 65 years (n = 28)	Age < 65 years (n = 48)	Age ≥ 65 years (n = 12)
Any grade	59 (93.7)	28 (100)	44 (91.7)	12 (100)
CTCAE grade ≥ 3	24 (38.1)	12 (42.9)	10 (20.8)	4 (33.3)
AEs leading to death	0	0	0	0
SAEs	16 (25.4)	6 (21.4)	7 (14.6)	2 (16.7)
AEs leading to dose interruption	22 (34.9)	10 (35.7)	2 (4.2)	1 (8.3)
AEs leading to dose reduction	13 (20.6)	2 (7.1)	1 (2.1)	1 (8.3)
AEs leading to treatment discontinuation	3 (4.8)	2 (7.1)	1 (2.1)	0

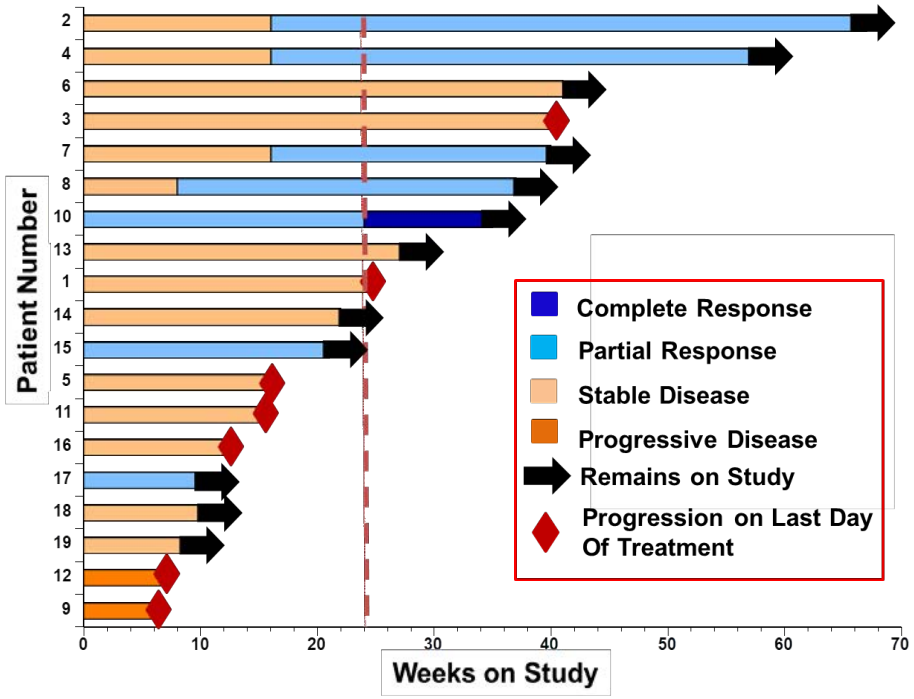
Kindler HL et al. ESMO GI 2020

Courtesy of Tanios Bekaii-Saab, MD

Maintenance Rucaparib Treatment in BRCA- or PALB2-Mutated PDAC (including Somatic Alterations)



ORR all patients	37.8%
ORR evaluable patients	41.1%
DCR at 8 weeks	89.5%



Binder KAR et al. *Cancer Res.* 2019;79(13_suppl): Abstract CT234.

Courtesy of Tanios Bekaii-Saab, MD

Randomized Phase II Trial of Gemcitabine and Cisplatin +/- Veliparib in Patients With PDAC and Germline *BRCA/PALB2* Mutation

TABLE 2. Best Response to Treatment

	Arm A (gemcitabine, cisplatin, veliparib) (n = 27)				Arm B (gemcitabine, cisplatin) (n = 23)				
Response	**No.**	**%**	**Median (months)**	**95% CI**	**No.**	**%**	**Median (months)**	**95% CI**	***P***
Response rate	20	74.1			15	65.2			.55
Disease control rate (CR + PR + SD)	27	100			18	78.3			.02
PFS			10.1	6.7 to 11.5			9.7	4.2 to 13.6	.73
OS			15.5	12.2 to 24.3			16.4	11.7 to 23.4	.6

Abbreviations: CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Eileen M. O'Reilly et al *Journal of Clinical Oncology* 2020 381378-1388.

Courtesy of Tanios Bekaii-Saab, MD

Regulatory and reimbursement issues aside, have you attempted or would you attempt to access a PARP inhibitor for a patient with metastatic pancreatic cancer and a somatic BRCA mutation?

a. I have not and would not
b. I have not, but I would for the right patient
c. I have

Meet The Professor
Management of Multiple Myeloma

Wednesday, December 16, 2020
12:00 PM – 1:00 PM ET

Faculty

Peter Voorhees, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

Year in Review 2020