Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hepatobiliary Cancers (Part 3 of a 3-Part Series)

Friday, January 21, 2022
6:15 PM – 7:45 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD
Robin K Kelley, MD

Moderator

Tanios Bekaii-Saab, MD

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Faculty

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Director, Signal Transduction and
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Moderator

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
Chair, ACCRU Research Consortium
Phoenix, Arizona

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Clinicians in the Meeting Room

Networked iPads are available for you to

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Virtual Zoom Clinicians

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Agenda

Module 1 – Advances in First-Line Treatment for Unresectable or Metastatic Hepatocellular Carcinoma (HCC) — Prof Abou-Alfa

Module 2 – Selection and Sequencing of Therapy for Patients with Relapsed/ Refractory HCC — Dr Finn

Module 3 – Current Treatment Strategies for Advanced Biliary Tract Cancers — Dr Kelley

Module 4 – Future Directions in the Management of Biliary Tract Cancers — Dr Bekaii-Saab

Hepatobiliary Cancers Survey Respondents

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Dirk Arnold, MD, PhD

Tanios Bekaii-Saab, MD

Al B Benson, MD

Kristen K Ciombor, MD, MSCI

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Robin K Kelley, MD

Christopher Lieu, MD

Jeffrey A Meyerhardt, MD, MPH

Katrina S Pedersen, MD, MS

Stacey M Stein, MD

Eric Van Cutsem, MD, PhD

Alan P Venook, MD

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MODULE 1: Advances in First-Line Treatment for Unresectable or Metastatic Hepatocellular Carcinoma — Prof Abou-Alfa

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Advances in First-Line Treatment for Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

Ghassan Abou-Alfa, M.D., M.B.A.
Memorial Sloan Kettering Cancer Center

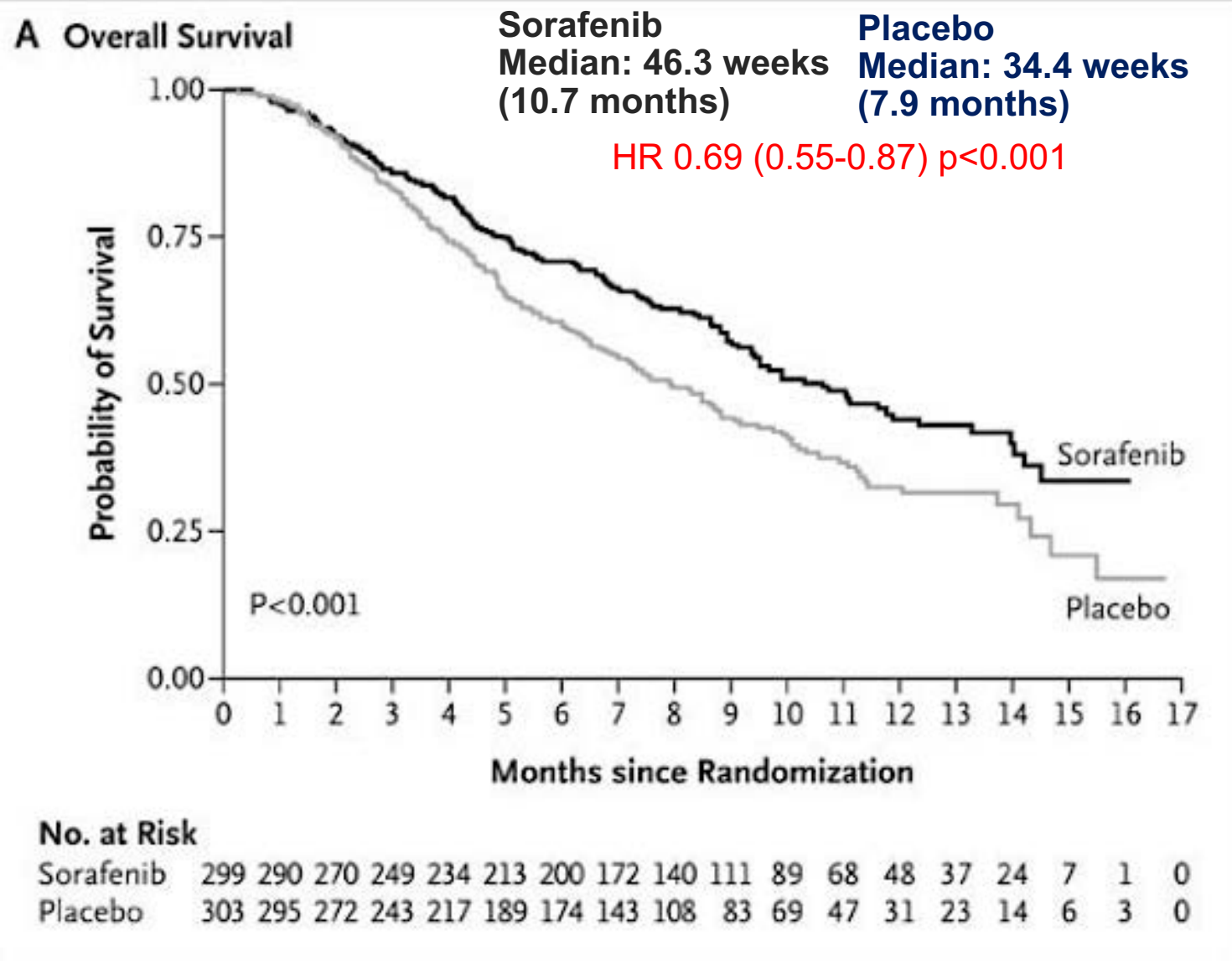
Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hepatobiliary Cancers

January 21, 2022

Ghassan Abou-Alfa, MD, MBA — Disclosures
Faculty

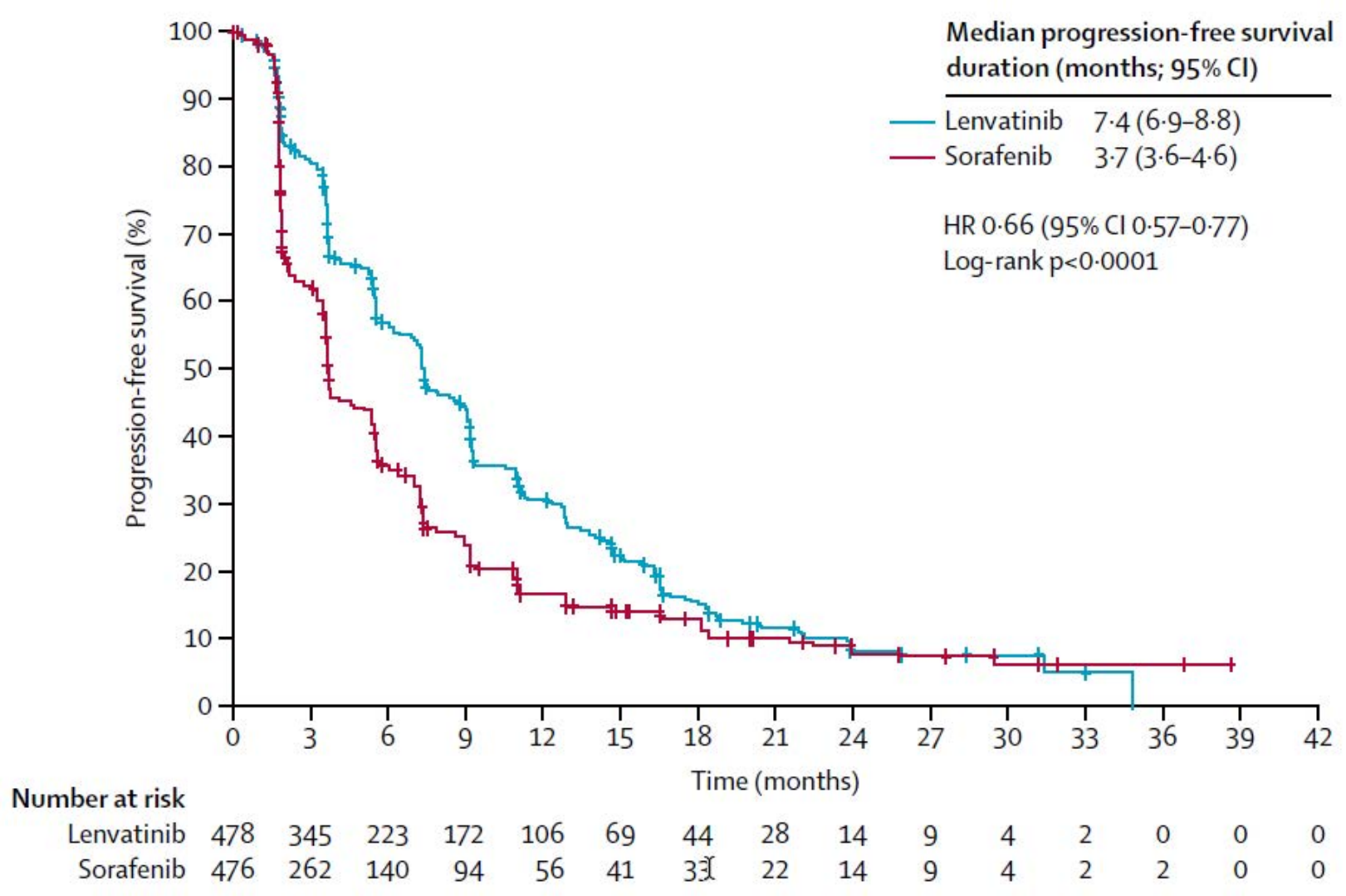
Consulting Agreements	Adicet Bio, Alnylam Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Autem Medical, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Berry Genomics, Celgene Corporation, Cend Therapeutics Inc, CytomX Therapeutics, Eisai Inc, Exelixis Inc, Flatiron Health, Genentech, a member of the Roche Group, Genoscience Pharma, Helio Health, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Legend Biotech, Lilly, Merck, Nerviano Medical Sciences Srl, QED Therapeutics, Rafael Pharmaceuticals Inc, RedHill Biopharma Ltd, Servier Pharmaceuticals LLC, Silenseed Ltd, Sobi, Surface Oncology, TheraBionic, Vector Pharma, Yiviva
Contracted Research	Agios Pharmaceuticals Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, BioNTech, Bristol-Myers Squibb Company, Celgene Corporation, Flatiron Health, Genentech, a member of the Roche Group, Genoscience Pharma, Incyte Corporation, Polaris Pharmaceuticals, Puma Biotechnology Inc, QED Therapeutics, Silenseed Ltd, Yiviva

SHARP Overall Survival (ITT)



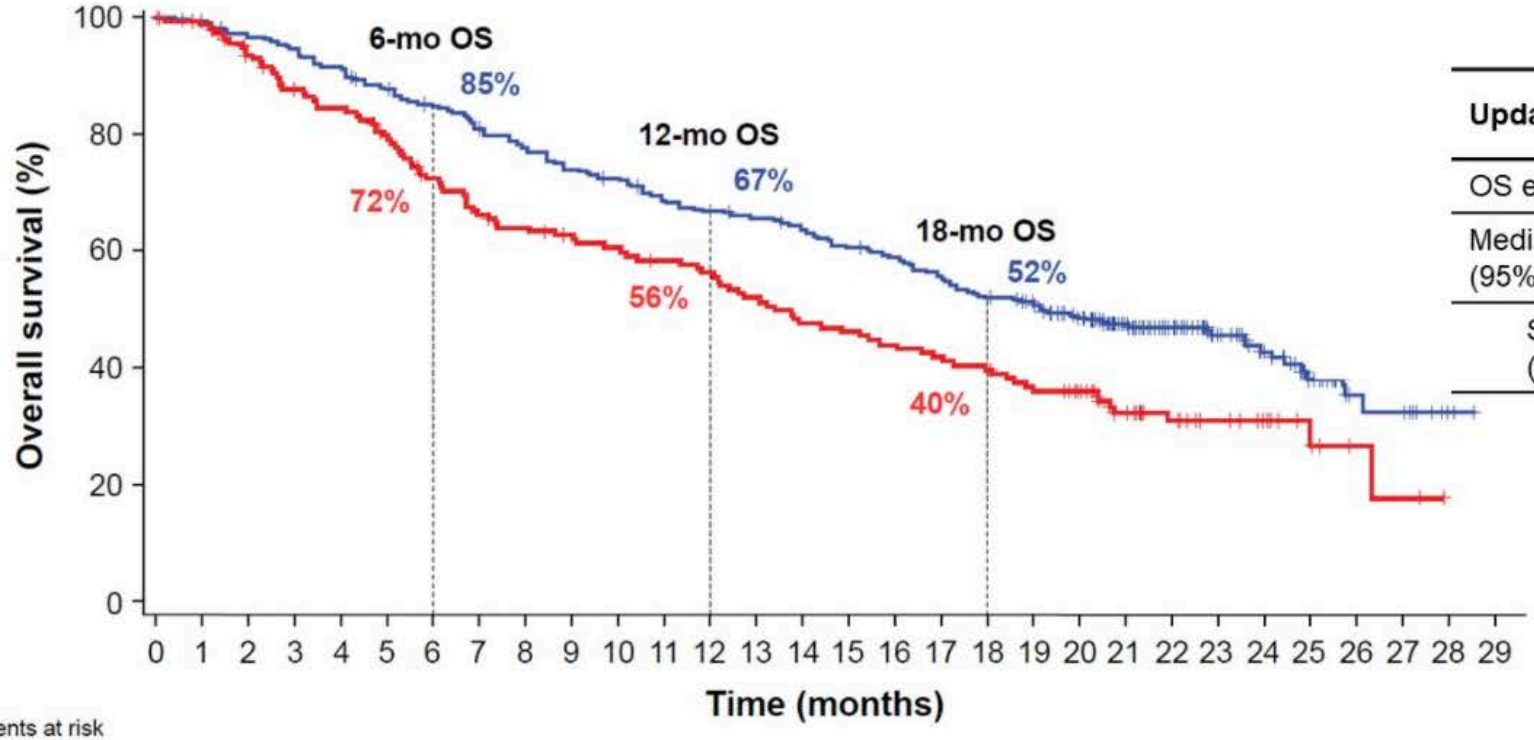
Llovet JM, et al. *N Engl J Med.* 2008;359: 378-390

Lenvatinib vs Sorafenib Progression-Free Survival



Kudo,M, et al. The Lancet 2018 391, 1163-1173DOI: (10.1016/S0140-6736(18)30207-1)

IMbrave150 OS: co-Primary Endpoint



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]	

No. of patients at risk

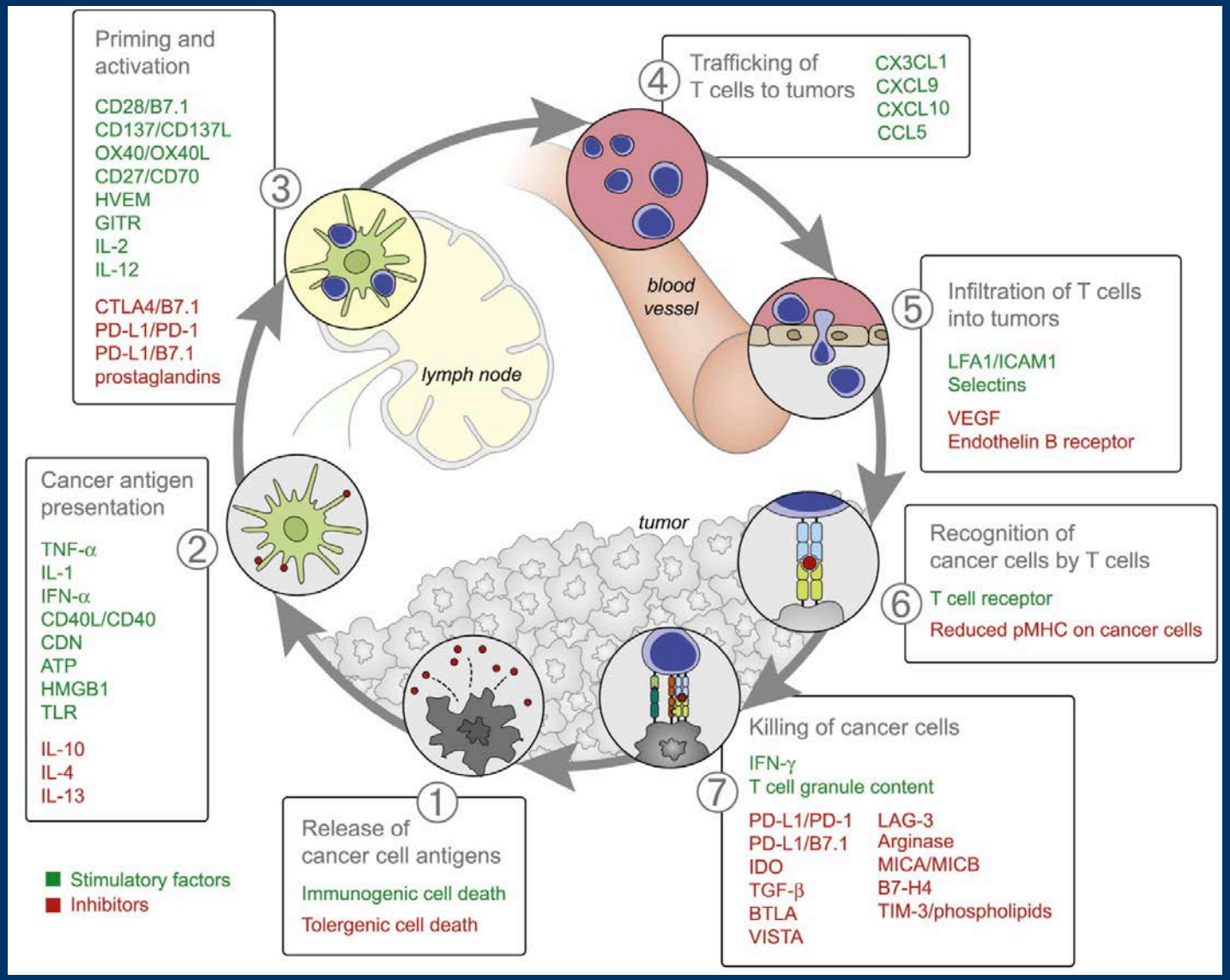
Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

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.

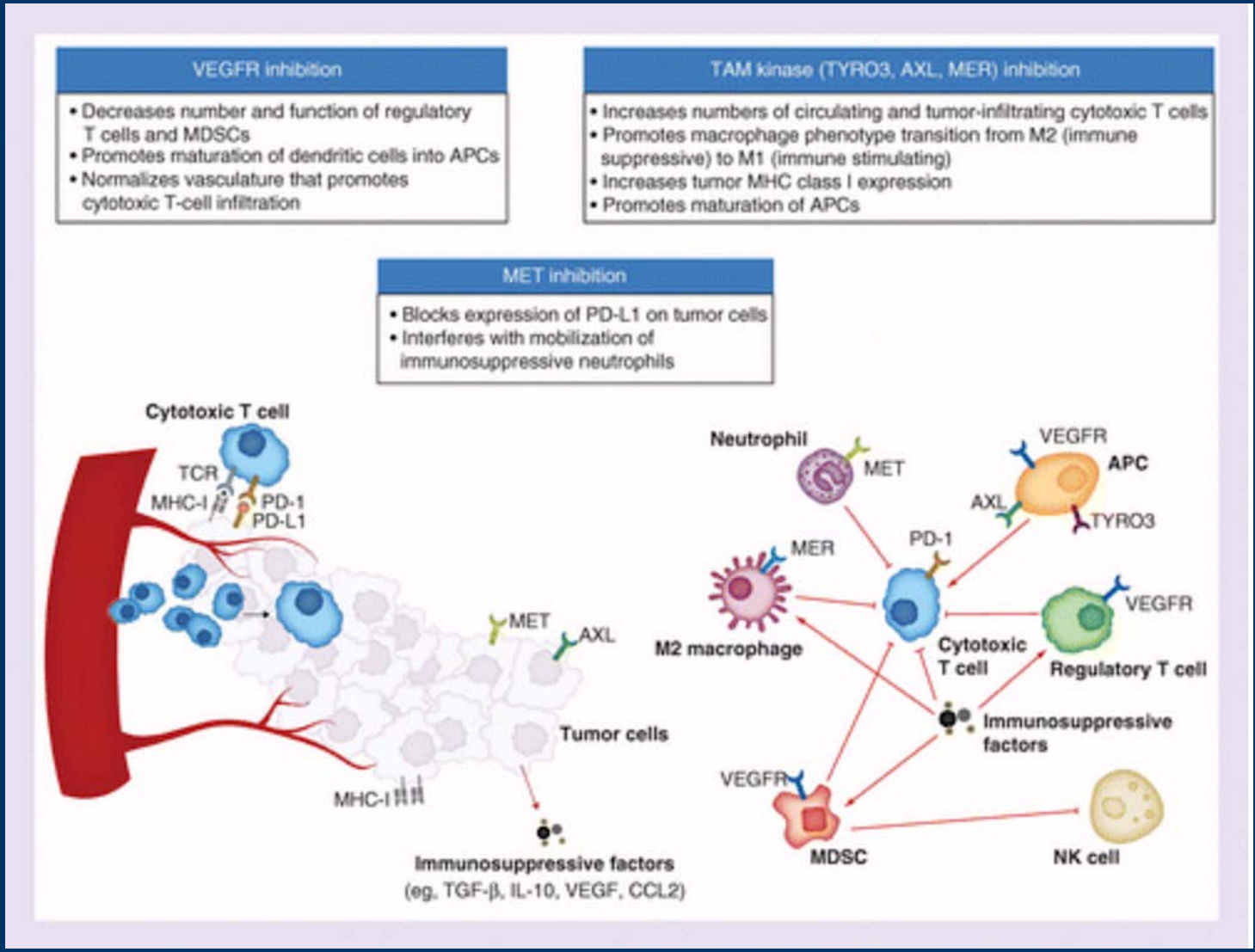
Finn, RS, et al. J Clin Oncol 39, 2021 (suppl 3; abstr 267)

Inhibitory Factors in the Cancer-Immunity Cycle



Chen, DS, Mellman I. Immunity. 2013 Jul 25;39(1):1-10

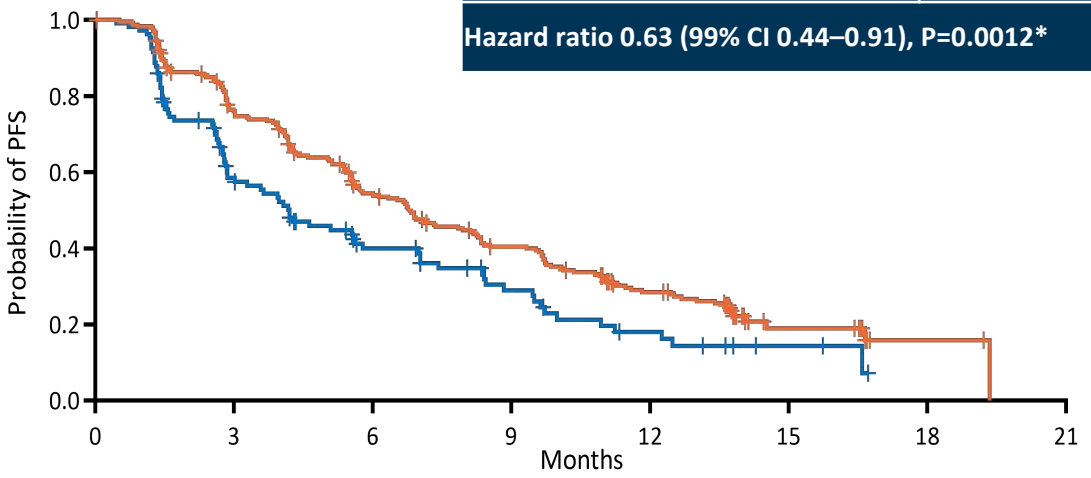
AXL, MET, and more



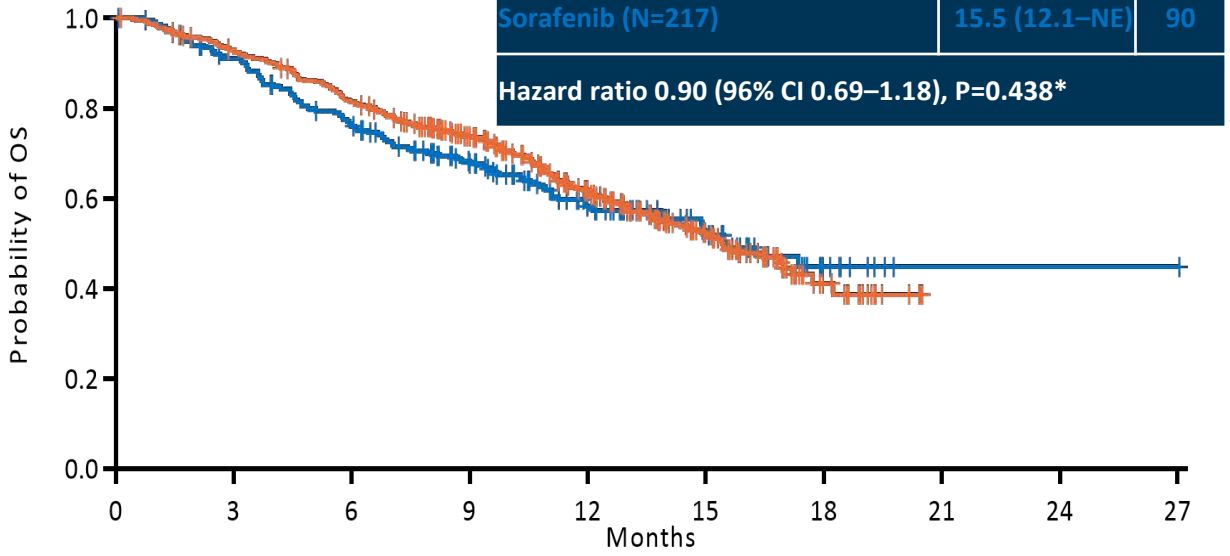
Kelley, KK et al. Future Oncol. 2020 Jul;16(21):1525-1536

COSMIC-312 PFS and OS

PITT Population	Median PFS mo (99% CI)	No. of Events
Cabozantinib + Atezolizumab (N=250)	6.8 (5.6–8.3)	174
Sorafenib (N=122)	4.2 (2.8–7.0)	78
Hazard ratio 0.63 (99% CI 0.44–0.91), P=0.0012*		

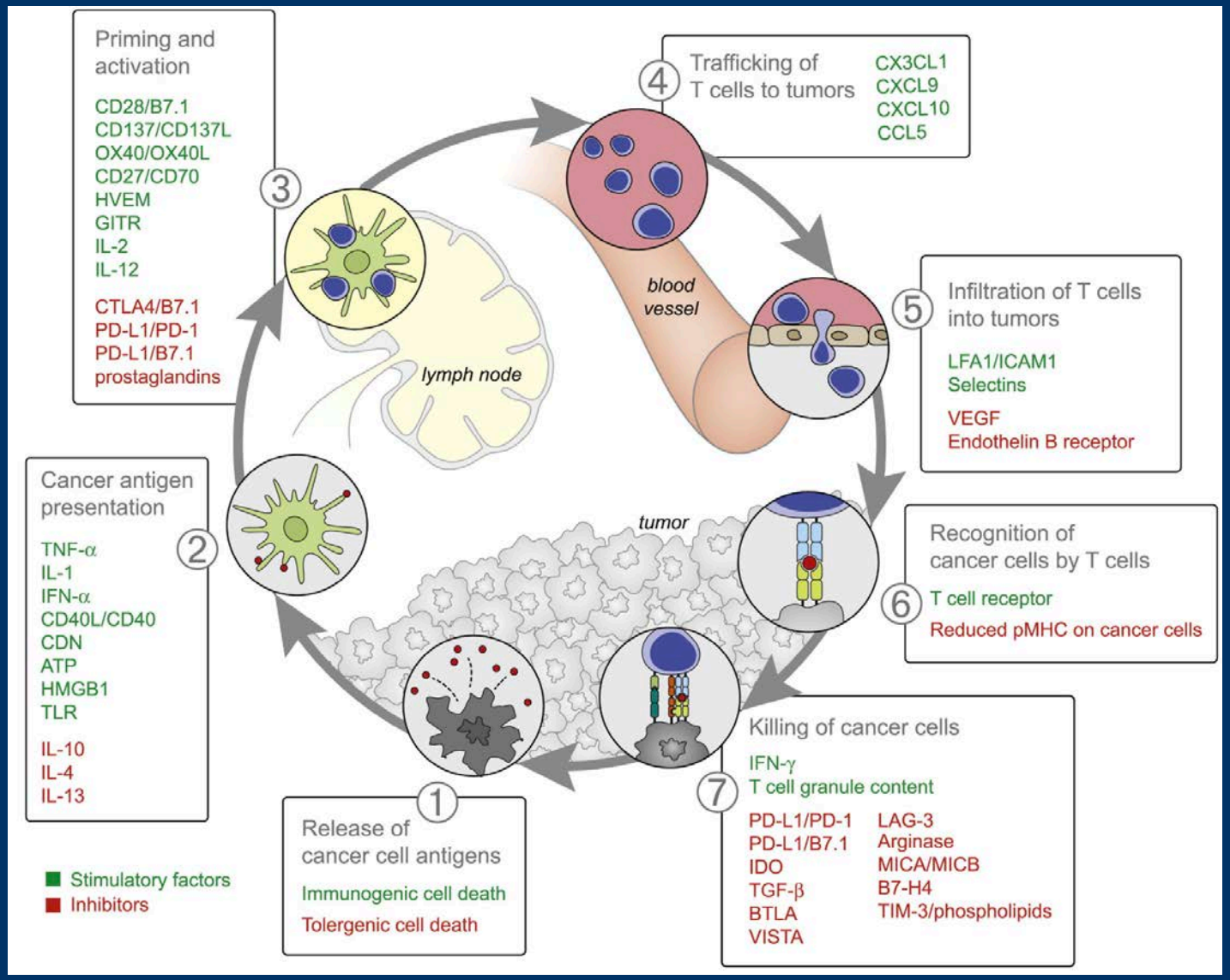


ITT Population	Median OS mo (96% CI)	No. of Events
Cabozantinib + Atezolizumab (N=432)	15.4 (13.7–17.7)	183
Sorafenib (N=217)	15.5 (12.1–NE)	90
Hazard ratio 0.90 (96% CI 0.69–1.18), P=0.438*		



Kelley, KK et al. ESMO Asia Virtual Oncology Week 2021, VP10-2021

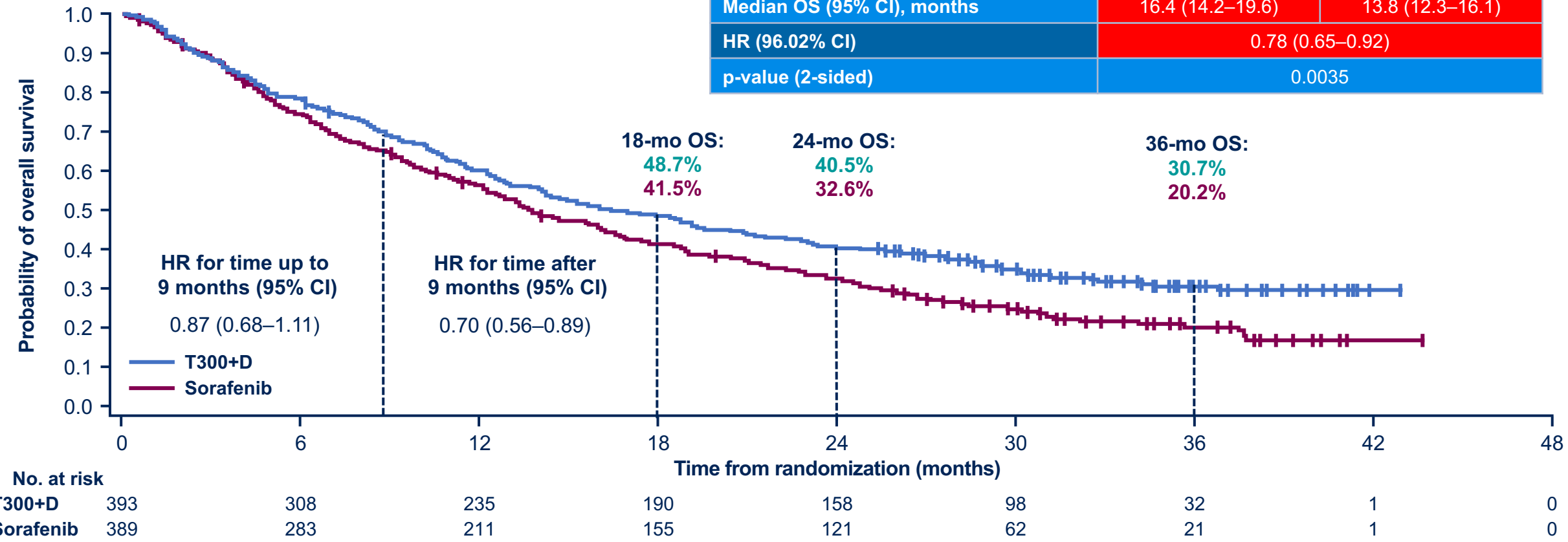
Anti-CTLA4



Chen, DS, Mellman I. Immunity. 2013 Jul 25;39(1):1-10

HIMALAYA T300+D vs Sorafenib OS

	T300+D (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	



No. at risk								
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

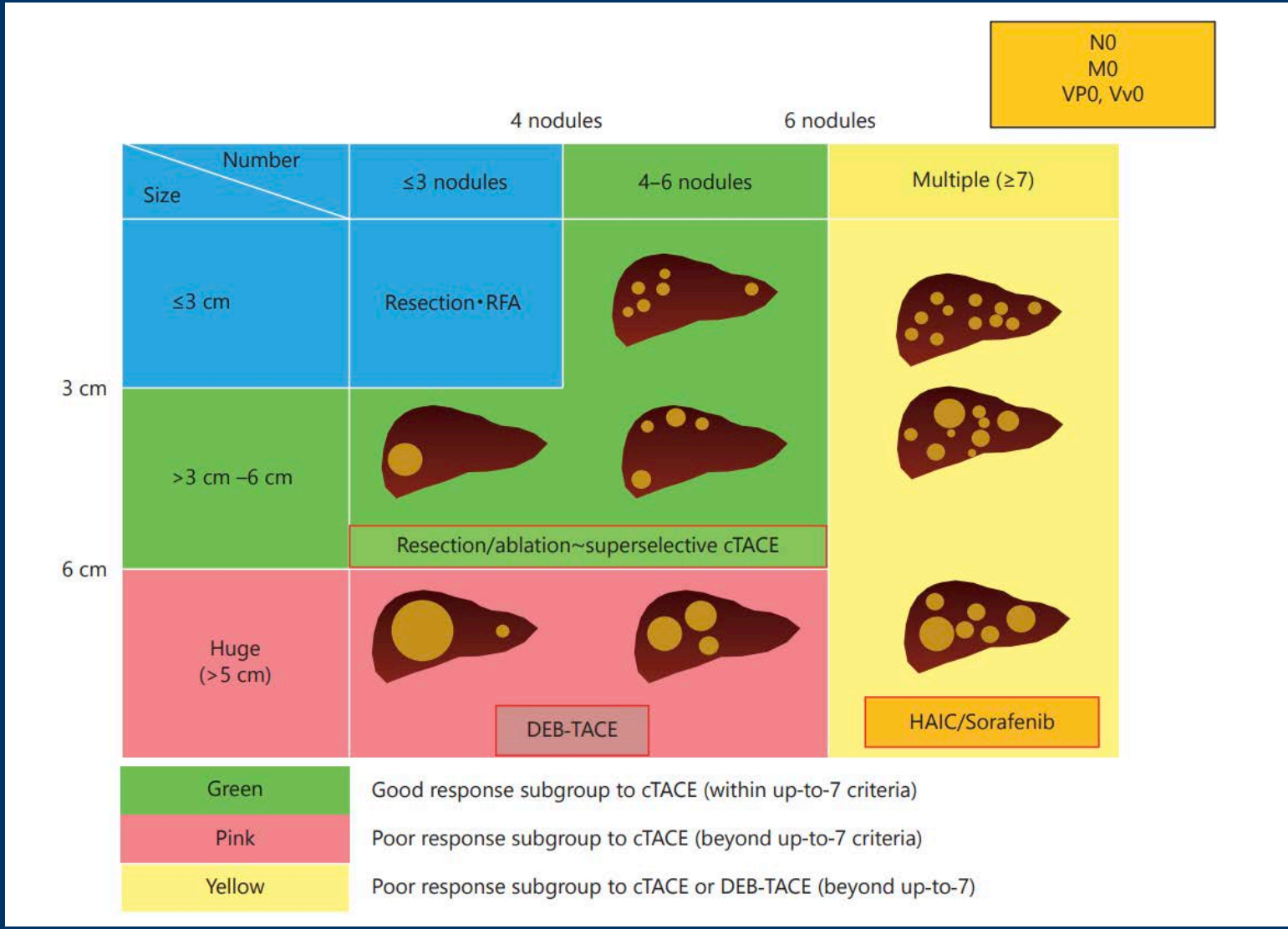
CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Systemic and Local Therapy Dilemmas

Enhanced Systemic “adjuvant” therapy	TKI[1,2]
	Checkpoint inhibitors[2]
	Combination therapies
Local plus systemic for systemic	TKI plus HAI[4]
Are all BCLC-B Equal?[4]	

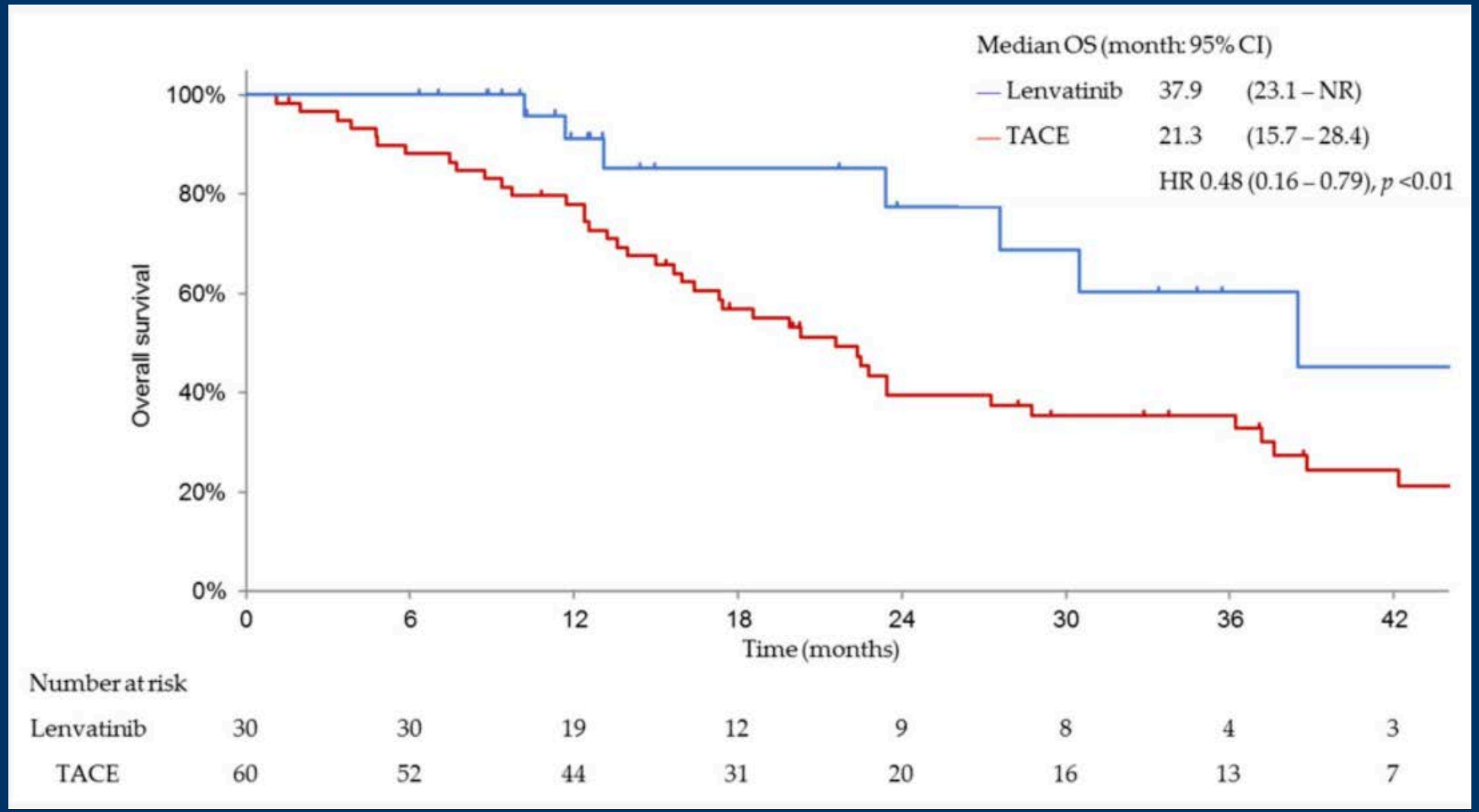
(1) Lencioni, R, et al. J Hepatol. 2016 May;64(5):1090-1098. (2) Meyer T, et al. Lancet Gastroenterol Hepatol. 2017 Aug;2(8):565-575. (3) Harding, JH, et al GI ASCO 2022. (4) He M, et al. *JAMA Oncol.* 2019;5(7):953-960, (4) Kudo M, et al. Dig Dis 2015;33:751–758

BCLC-B is Not a One Size Fits All



Kudo M, et al. Dig Dis 2015;33:751–758

Lenvatinib as Initial Treatment For Intermediate-Stage HCC Beyond Up-To-Seven Criteria and Child–Pugh A



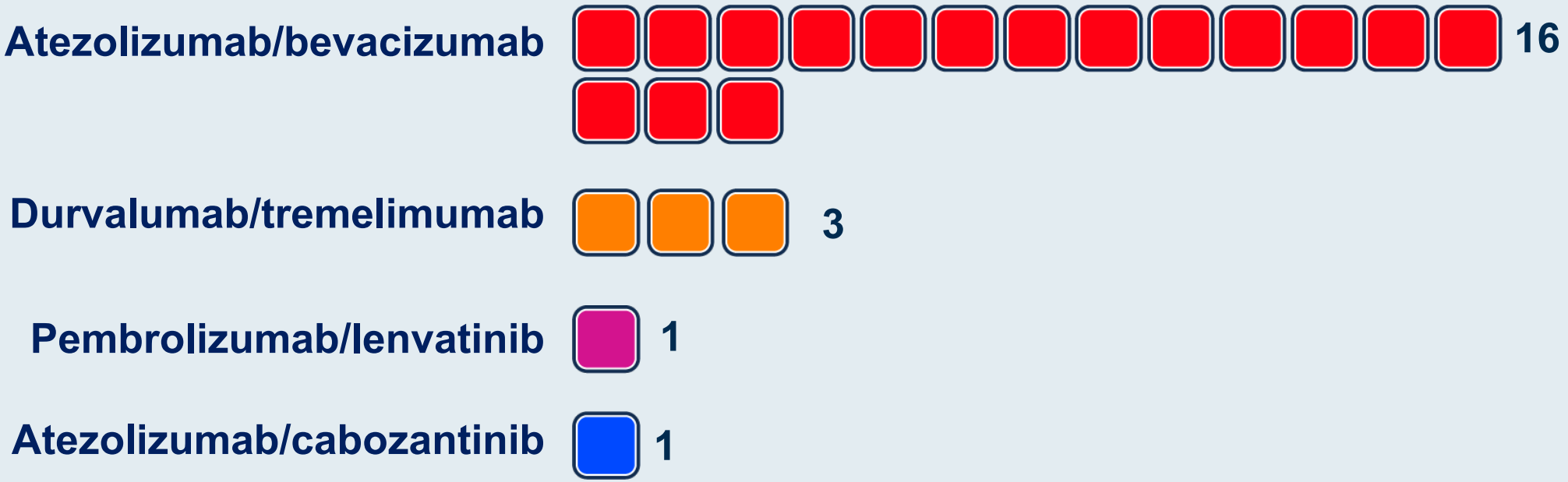
Kudo M, et al. Cancers (Basel). 2019 Jul 31;11(8):1084.

Conclusions

- Combination therapies have a positive impact the outcome of patient receiving first line therapy for HCC
- Combination therapies differ mechanistically, which translates into different outcomes
- A global perspective the HCC locally advanced disease is needed

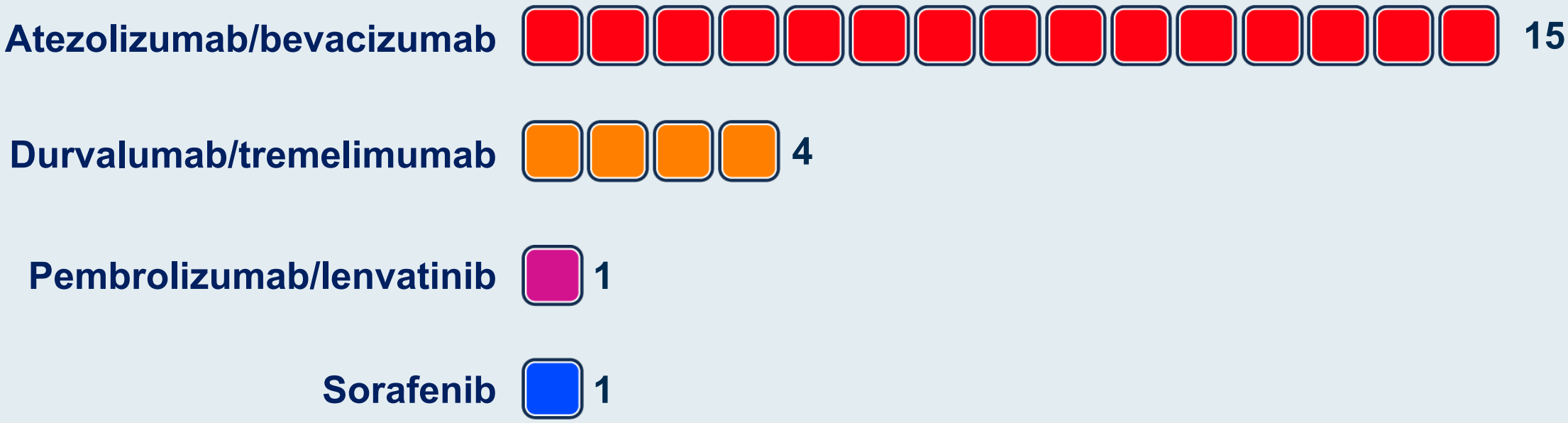
Clinical Investigator Survey Results

Regulatory and reimbursement issues aside and assuming all of these regimens were available, what would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC, a Child-Pugh A score and a PS of 0?



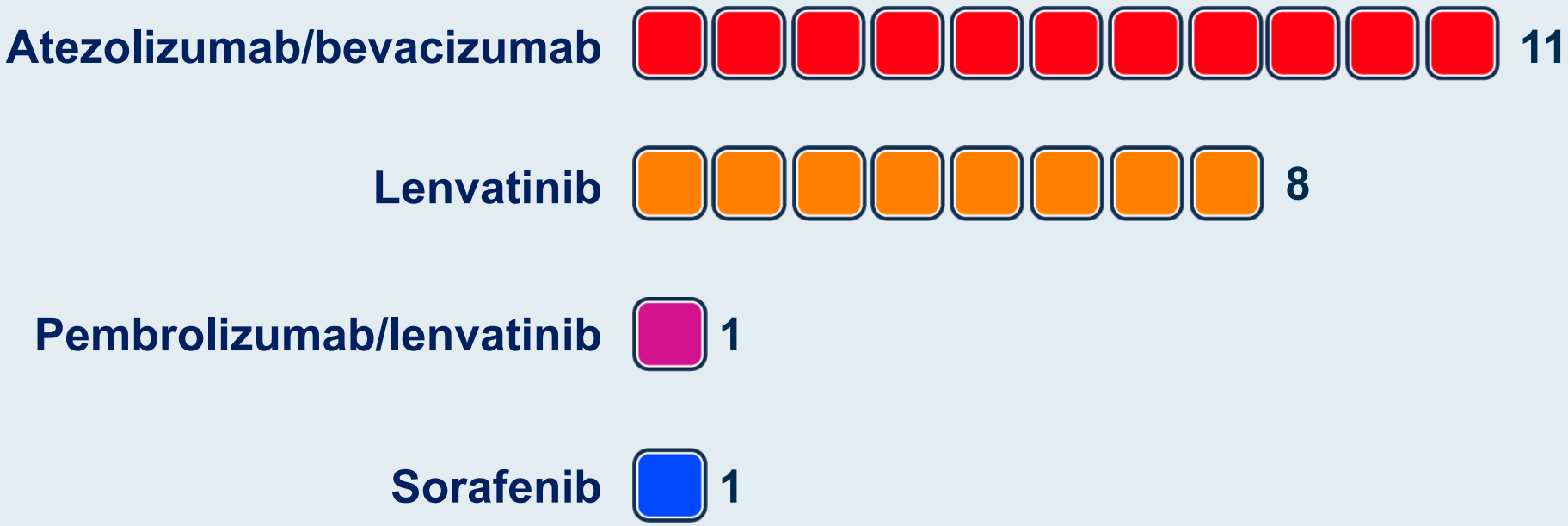
Survey of Gastrointestinal Cancers Clinical Investigators

Regulatory and reimbursement issues aside and assuming all of these regimens were available, what would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC, a Child-Pugh A score and Grade 1 esophageal varices being managed with a beta blocker?



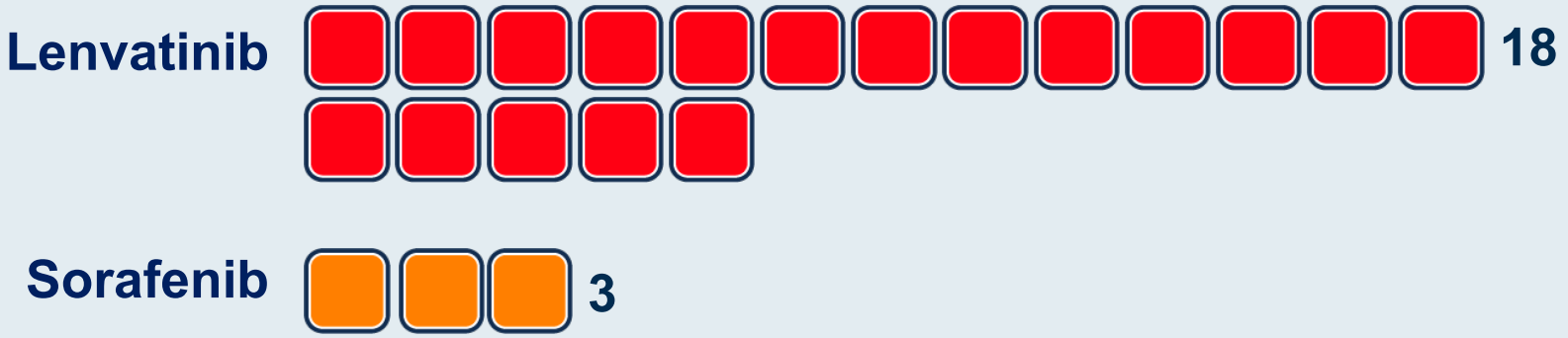
Survey of Gastrointestinal Cancers Clinical Investigators

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?



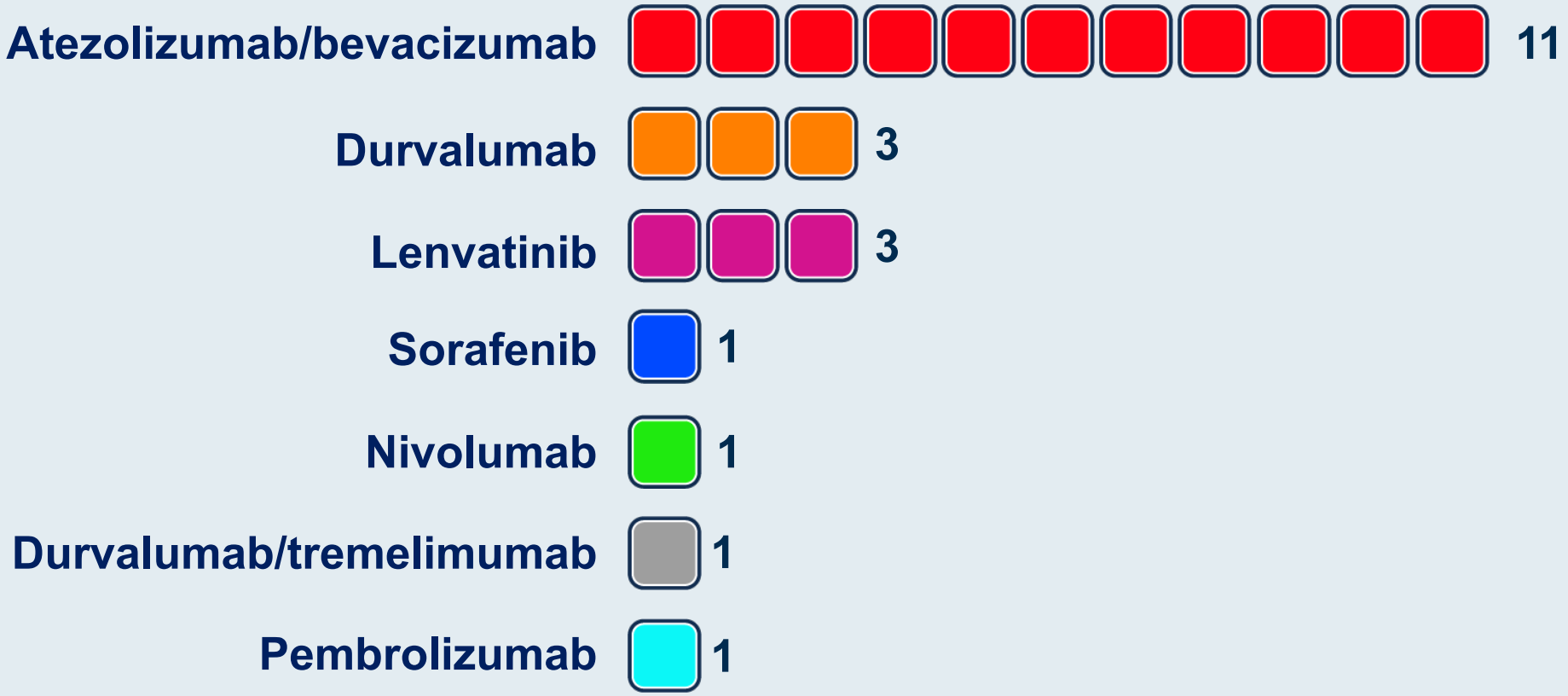
Survey of Gastrointestinal Cancers Clinical Investigators

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?



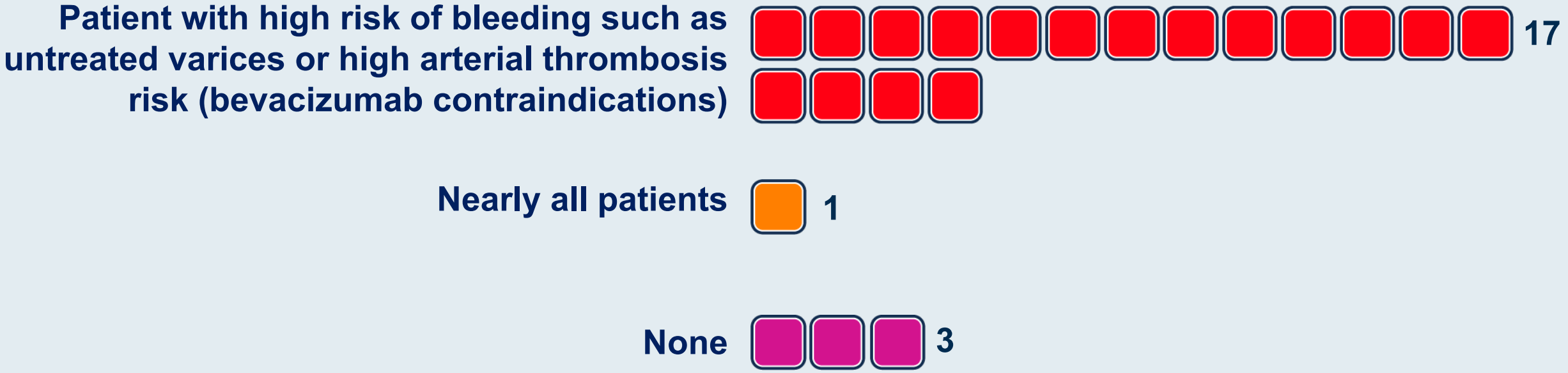
Survey of Gastrointestinal Cancers Clinical Investigators

Regulatory and reimbursement issues aside and assuming all of these regimens were available, what would be your current preferred first-line systemic treatment for a 78-year-old patient with HCC, a Child-Pugh B7 score and a PS of 1?



Survey of Gastrointestinal Cancers Clinical Investigators

If durvalumab/tremelimumab were available today, for which patients with advanced HCC, if any, would you be inclined to prioritize its use as first-line therapy?



Survey of Gastrointestinal Cancers Clinical Investigators

MODULE 2: Selection and Sequencing of Therapy for Patients with Relapsed/Refractory HCC — Dr Finn

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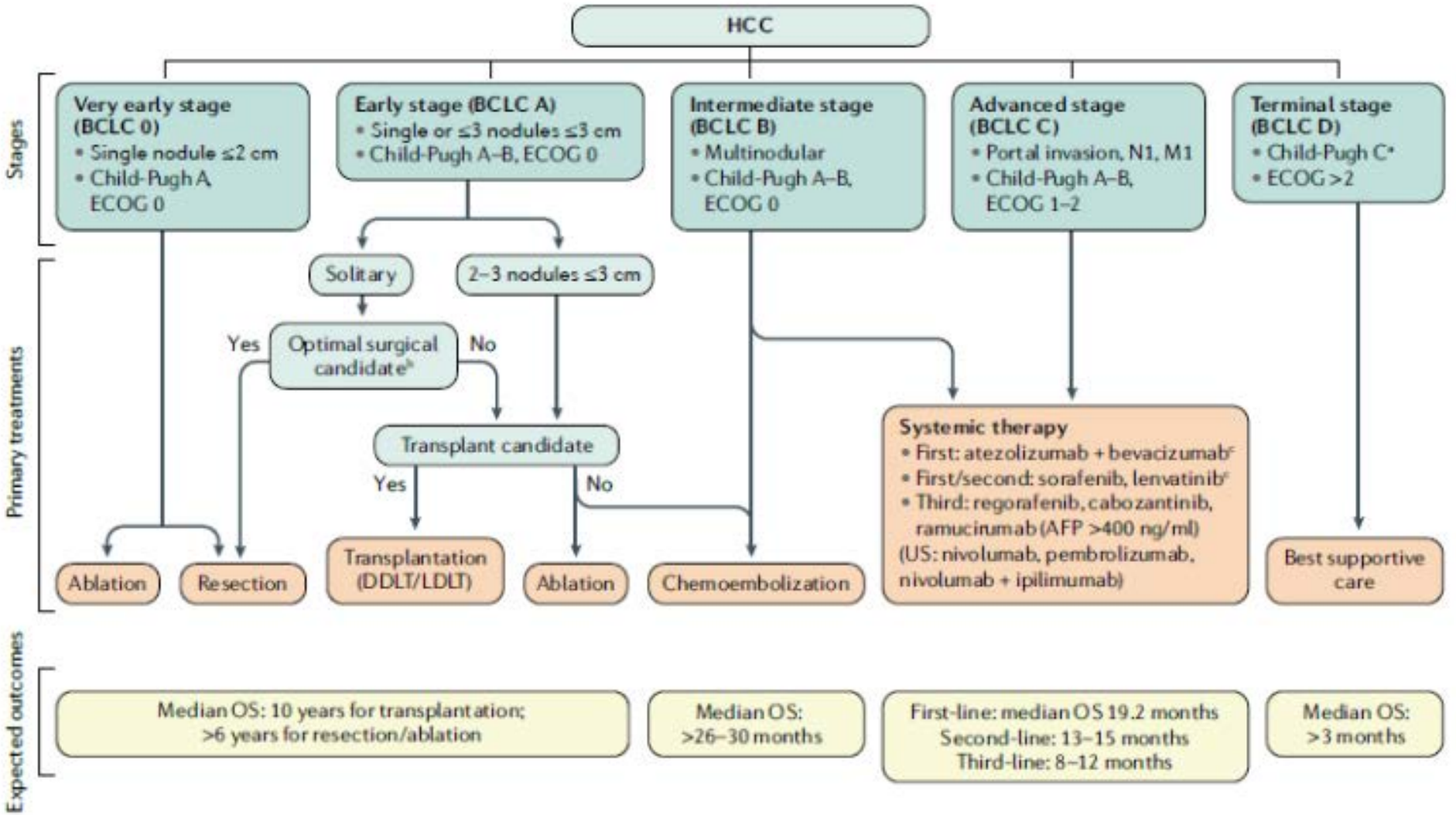
Selection and Sequencing of Therapy for Patients with Relapsed/Refractory (R/R) HCC

Richard S. Finn, MD
Professor of Clinical Medicine
Division of Hematology/Oncology
Director, Signal Transduction and Therapeutics Program
Jonsson Comprehensive Cancer Center
Geffen School of Medicine at UCLA

Richard S Finn, MD — Disclosures
Faculty

Advisory Committee	CStone Pharmaceuticals
Consulting Agreements	Adaptimmune, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, CStone Pharmaceuticals, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Lilly, Merck, Pfizer Inc
Contracted Research (to UCLA)	Adaptimmune, Bayer HealthCare Pharmaceuticals, Eisai Inc, Genentech, a member of the Roche Group, Lilly, Merck, Pfizer Inc
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP, Hengrui Therapeutics Inc



Llovet et al Nat Rev Primers 2021

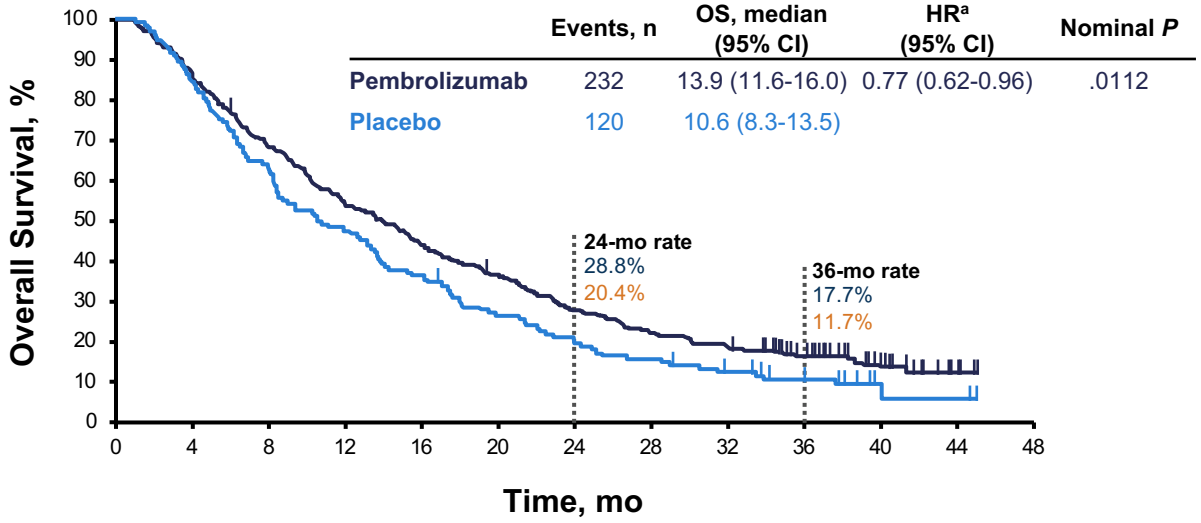
FDA Approved Second Line Systemic Therapies

Study Name	Treatment	Median OS (mos)	Median PFS (mos)	ORR mRECIST; RECIST	Grade 3/4 TRAEs	Most common G3/4	D/C rate
RESORCE	reografenib	10.6	3.1	11%/ 7%	50%	HTN 13% HFSR 13% Fatigue 13%	10%
CELESTIAL	cabozantinib	10.2	5.2	NR/ 7%	68% (all cause)	HFSR 17% HTN 16% Increased ALT 12%	16%
REACH-2 (AFP≥400)	ramucirumab	8.5	2.8	NR/ 5%	NR	HTN 8% Liver injury 4% Proteinuria 2%	11%
KEYNOTE 240/224 (accelerated approval)	pembrolizumab	13.9	3.0	NR/ 18.3%	18.3	Increased AST 13% Increased Bili 7.5% Fatigue 2.5%	6.5%
CheckMate 040, arm A (accelerated approval)	ipilimumab+ nivolumab	22.8	3.9	34%/ 32%	53%	Pruritis 45% Rash 29% Diarrhea 24%	22%

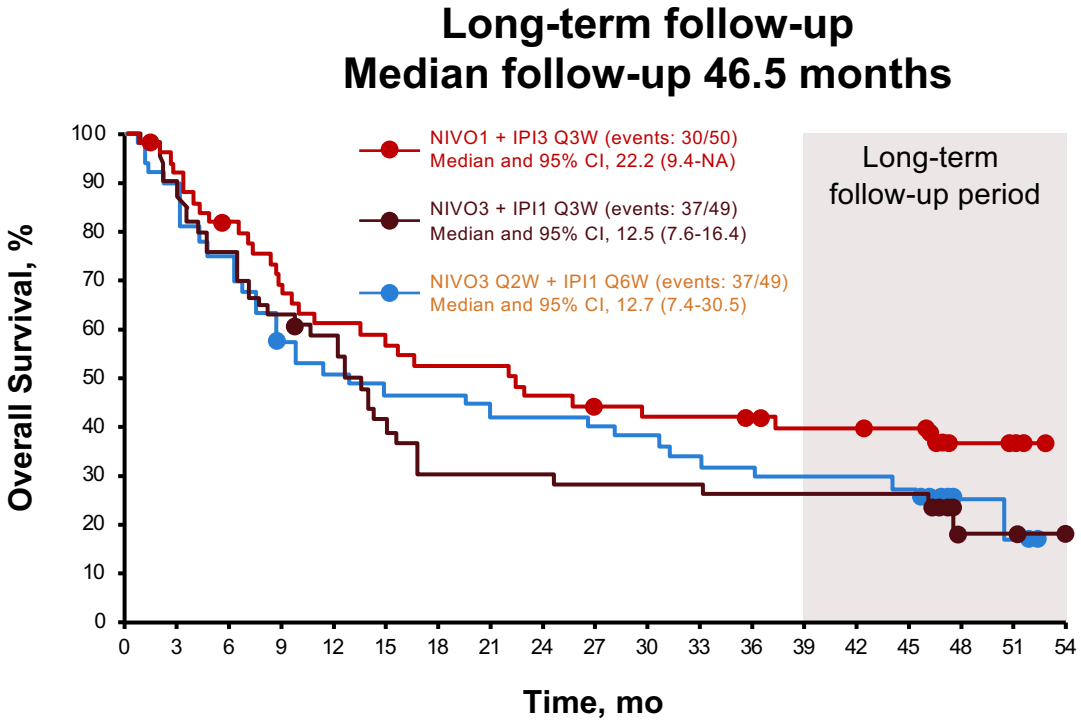
Bruix 2017, Abou-Alfa 2018, Zhu 2019, Finn 2020, Zhu 2018, Yau 2020
NR- not reported

Long-Term Follow-up of Second-Line Immunotherapy Studies

Phase 3 KEYNOTE-240 Trial: Pembrolizumab Monotherapy[1]



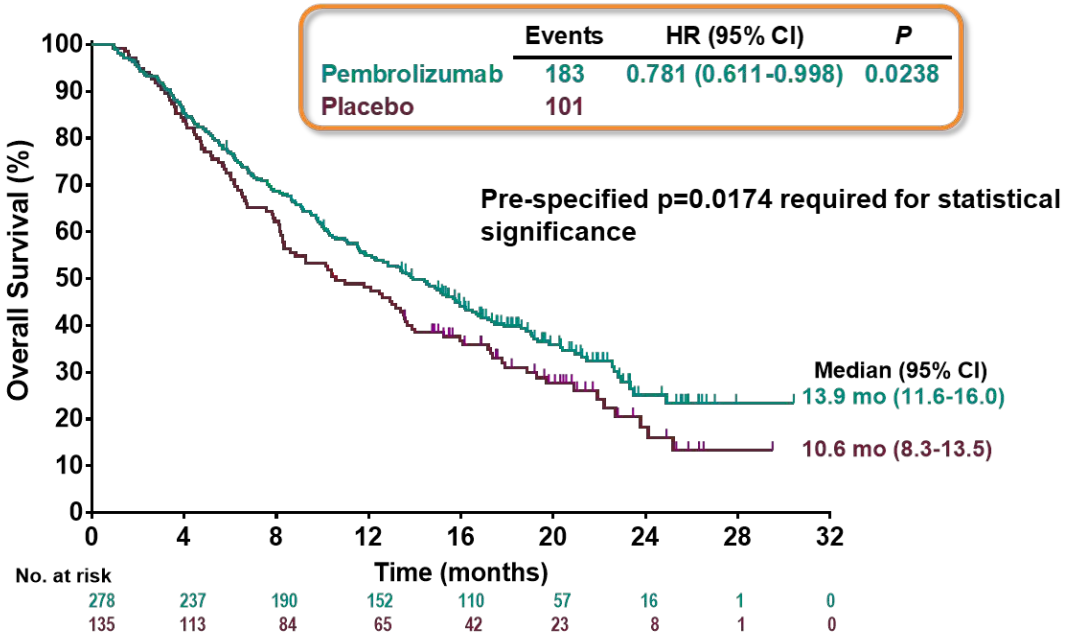
Phase 2 CheckMate -040: Nivolumab + Ipilimumab Cohort[2]



1. Merle P et al. ASCO GI 2021. Abstract 268. 2. El-Khoueiry AB et al. ASCO-GI 2021. Abstract 269.

Have We Confirmed Pembrolizumab's Activity in Second-Line HCC?

KEYNOTE 240



Finn et al JCO 2020

KEYNOTE 394

Randomized Phase 3 Pembro vs BSC

N=453 pts, 2:1

mOS 14.6 mos (12.6-18.0) vs 13.0 mos (10.5-15.1)
HR 0.79; 95% CI, 0.63-0.99; P=0.018

mPFS 2.6 mos (1.5-2.8) vs 2.3 mos (1.4-2.8)
HR 0.74; 95% CI, 0.60-0.92; P=0.0032

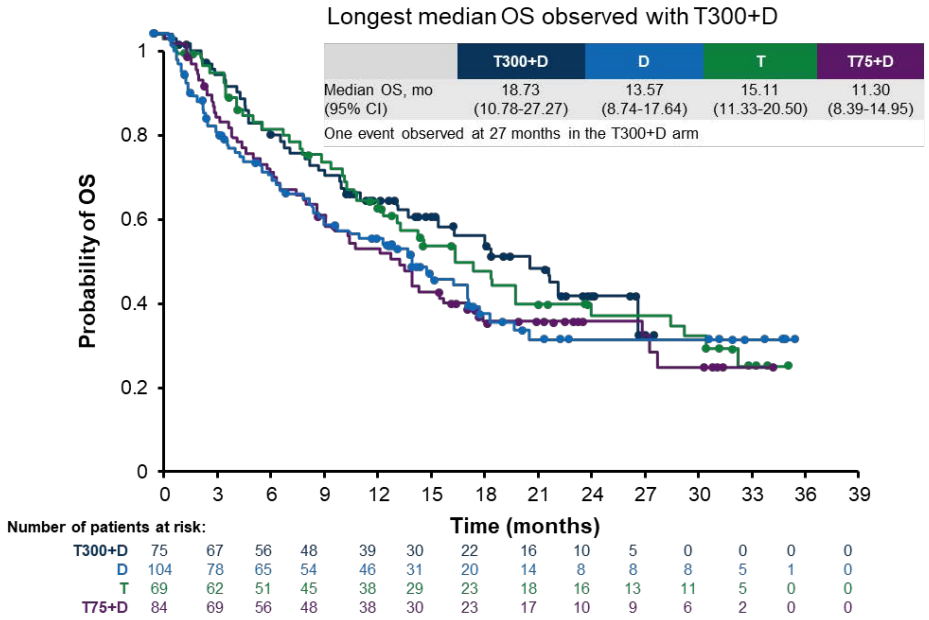
ORR 13.7% vs 1.3%

Qin et al ASCO GI 2022

Paradigms for Sequencing in Advanced HCC

Front-line	**IO Doublet** **Atezo-bev (FDA approved)** **Atezo-cabo (not approved)** **Durva-treme (not approved)**	**TKI** **Sorafenib** **Lenvatinib**
Second-line	**1st Line TKI** **Sorafenib** **Lenvatinib**	**2nd Line (+) TKI/ mAb** **Regorafenib** **Cabozantinib** **Ramucirumab** **Pembrolizumab** **Nivo/ ipi**
Third-line and beyond	**2nd Line (+) TKI/ mAb** **Regorafenib** **Cabozantinib** **Ramucirumab**	**2nd Line (+) TKI/ mAb** **Regorafenib** **Cabozantinib** **Ramucirumab** **Pembrolizumab** **Nivo/ ipi**

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.

Phase 2 Trial: Tremelimumab and Durvalumab[1]

	T300 + D (n = 74), No. (%)		Durvalumab (n = 101), No. (%)		Tremelimumab (n = 69), No. (%)		T75 + D (n = 82), No. (%)	
AE	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Patients with any trAE	61 (82.4)	28 (37.8)	61 (60.4)	21 (20.8)	58 (84.1)	30 (43.5)	58 (70.7)	20 (24.4)
Pruritus	24 (32.4)	0	11 (10.9)	0	19 (27.5)	1 (1.4)	13 (15.9)	0
Rash	24 (32.4)	2 (2.7)	7 (6.9)	0	15 (21.7)	2 (2.9)	11 (13.4)	0
AST increased	12 (16.2)	9 (12.2)	8 (7.9)	3 (3.0)	10 (14.5)	6 (8.7)	12 (14.6)	7 (8.5)
ALT increased	11 (14.9)	3 (4.1)	5 (5.0)	0	7 (10.1)	3 (4.3)	8 (9.8)	2 (2.4)
Amylase increased	11 (14.9)	5 (6.8)	2 (2.0)	1 (1.0)	3 (4.3)	0	6 (7.3)	1 (1.2)
Lipase increased	9 (12.2)	5 (6.8)	1 (1.0)	0	9 (13.0)	4 (5.8)	4 (4.9)	4 (4.9)
Fatigue	8 (10.8)	0	9 (8.9)	1 (1.0)	11 (15.9)	0	8 (9.8)	0
Diarrhea	7 (9.5)	1 (1.4)	9 (8.9)	1 (1.0)	14 (20.3)	6 (8.7)	10 (12.2)	1 (1.2)
Alkaline phosphatase increased	6 (8.1)	3 (4.1)	7 (6.9)	1 (1.0)	1 (1.4)	0	1 (1.2)	0
Hyperthyroidism	6 (8.1)	0	2 (2.0)	0	0	0	4 (4.9)	1 (1.2)
Hypothyroidism	6 (8.1)	0	10 (9.9)	0	2 (2.9)	0	7 (8.5)	0
Bilirubin increased	4 (5.4)	1 (1.4)	3 (3.0)	0	2 (2.9)	0	5 (6.1)	0
Abdominal pain	2 (2.7)	0	0	0	5 (7.2)	0	4 (4.9)	0
Rash maculopapular	2 (2.7)	1 (1.4)	2 (2.0)	0	7 (10.1)	0	5 (6.1)	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks; trAE, treatment-related adverse event.

[a]Listed by frequency in T300 + D arm.

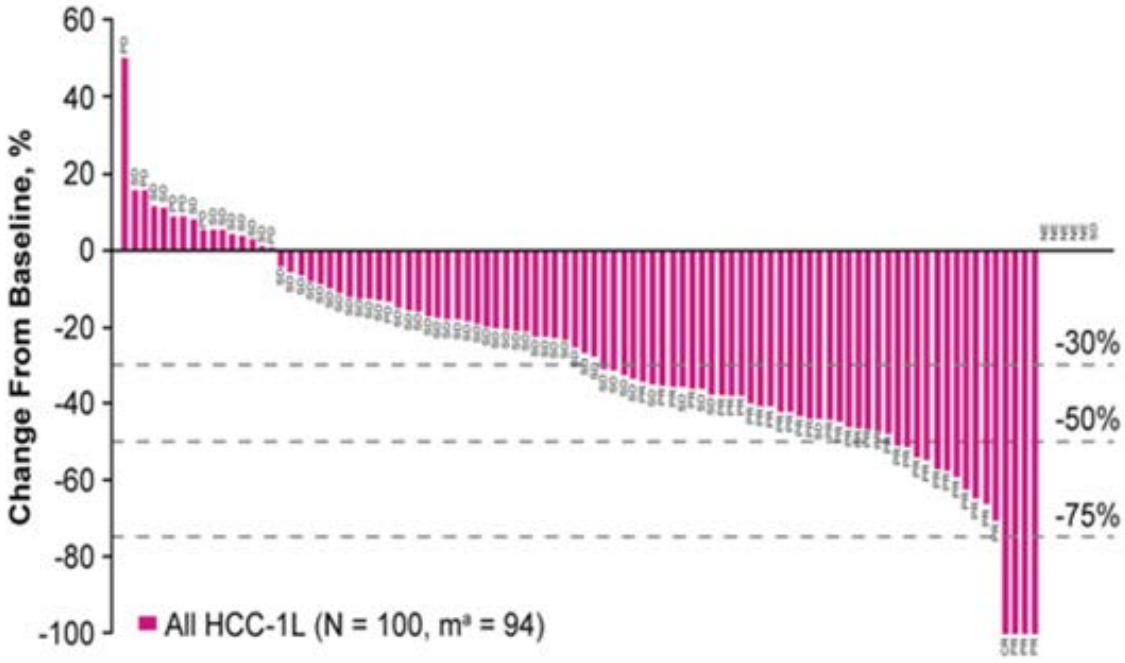
1. Kelley RK et al. JCO 2021.

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.

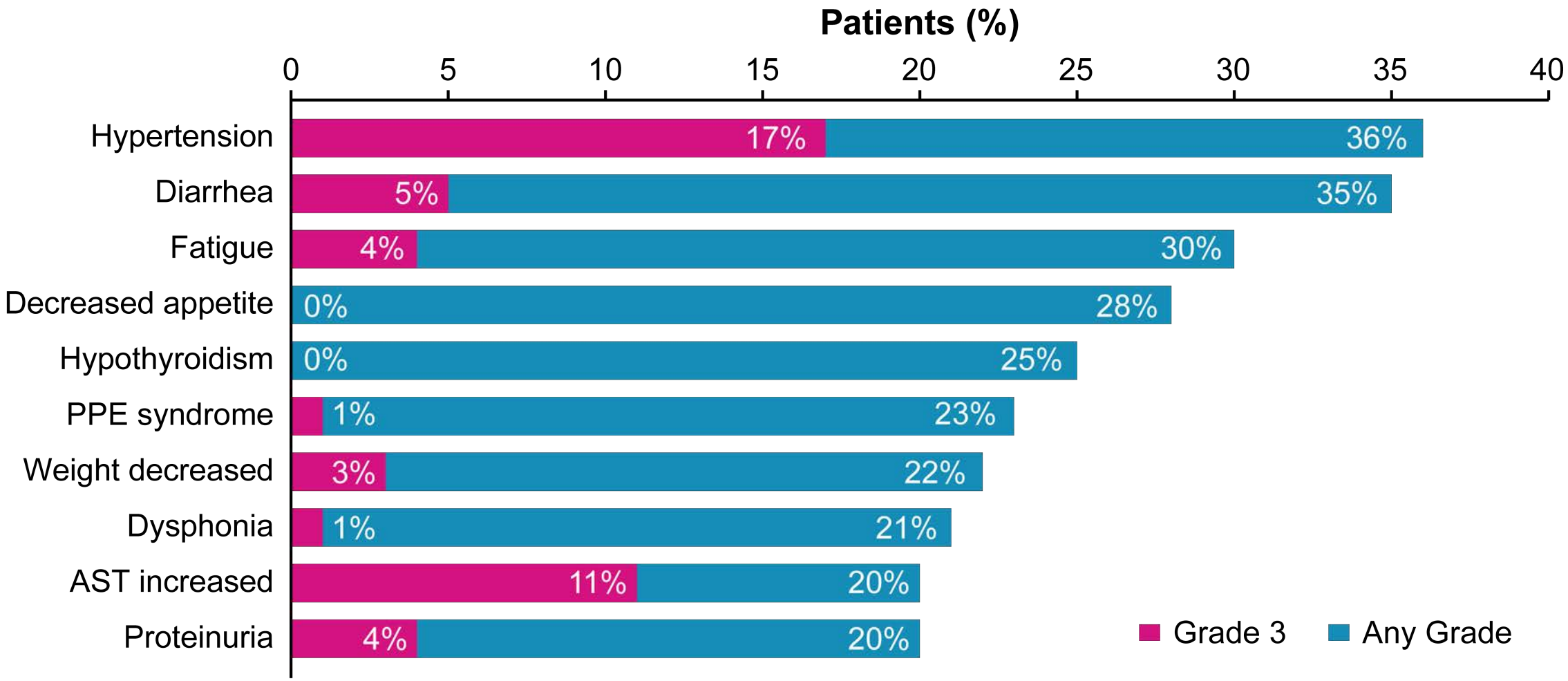
Percentage Change From Baseline in Sum of Diameters of Target Lesions at Postbaseline Nadir (IIR; RECIST v1.1)



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

- Finn et al JCO 2020.

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

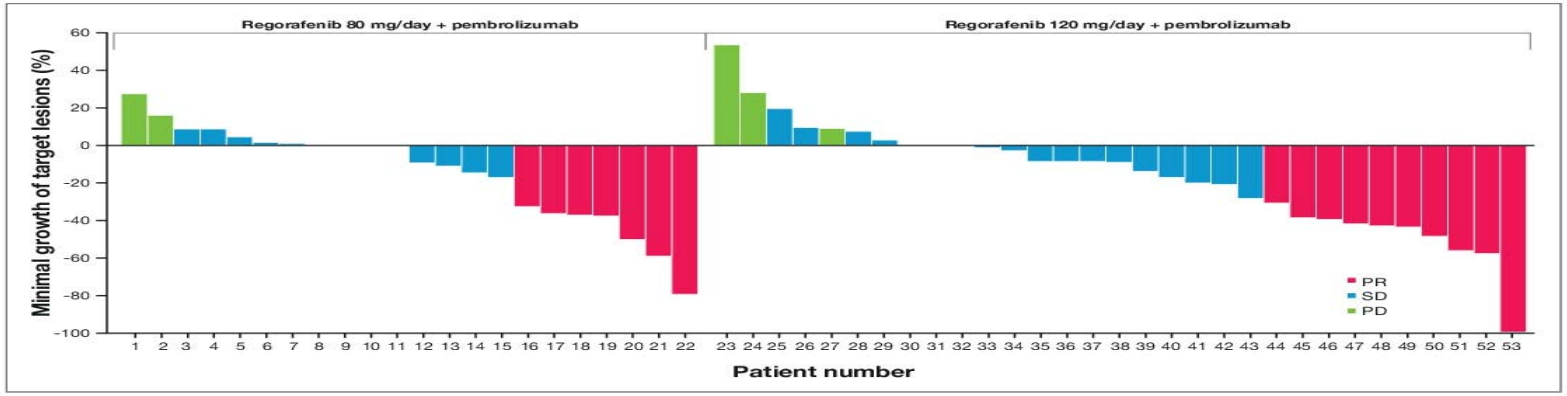


[a]There was 1 grade 4 treatment-related AE (leukopenia/neutropenia).

- Finn et al JCO 2020.

Phase 1b study: Pembrolizumab plus Regorafenib in First-Line Advanced HCC[1]

Percentage change in tumor size (target lesions)



Best Objective Tumor Response[a]

Responses, n (%)	Regorafenib 120 mg + pembrolizumab (n=32)[b]	Regorafenib 80 mg + pembrolizumab (n=22)	All patients (N=54)
Complete response	0	0	0
Partial response	10 (31)	7 (32)[a]	17 (31)
Stable disease	18 (56)	13 (59)[a]	31 (5.7)
Progressive disease	3 (9)	2 (9)	5 (9)
Objective response rate	10 (31)	7 (32)	17 (31)
Disease control rate	28 (88)	20 (91)	48 (89)

[a] Tumor response according to RECIST v1.1 Response data are derived from the updated efficacy analysis. Three partial responses occurred after thee primarycompletion cut-off date.
[b] One patient was excluded from this table owing to their radiological tumor assessment being conducted on W2D1, which was substantially earlier than the first planned assessment at W6D1.

1. El-Khoueiry A et al. ASCO 2021. Abstract 4078.

Salvage Ipilimumab and Nivolumab in Patients With Metastatic Renal Cell Carcinoma After Prior Immune Checkpoint Inhibitors

Anita Gul, MD[1]; Tyler F. Stewart, MD[2,3]; Charlene M. Mantia, MD[4]; Neil J. Shah, MD[5]; Emily Stern Gatof, MD[4]; Ying Long, PharmD[2]; Kimberly D. Allman, MSN, CNP[1]; Moshe C. Ornstein, MD, MA[1]; Hans J. Hammers, MD, PhD[6]; David F. McDermott, MD[4]; Michael B. Atkins, MD[5]; Michael Hurwitz, MD, PhD[2]; and Brian I. Rini, MD[1]

N=45
All had prior IO
76% prior PD-1
24% prior PD-L1

Variable	No. (%)
Best response to prior ICI	
PR	24 (53)
SD	12 (27)
PD	9 (20)

Median PFS 4 mos

BOR to Prior ICI	No. (%)	BOR to Salvage Ipilimumab and Nivolumab	No. (%)
PR	24 (53)	PR	4 (17)
		SD	2 (8)
		PD	17 (71)
		NE	1 (4)
SD	12 (27)	PR	3 (25)
		SD	5 (42)
		PD	4 (33)
PD	9 (20)	PR	2 (22)
		PD	7 (78)

JCO 2020

Journal for ImmunoTherapy of Cancer

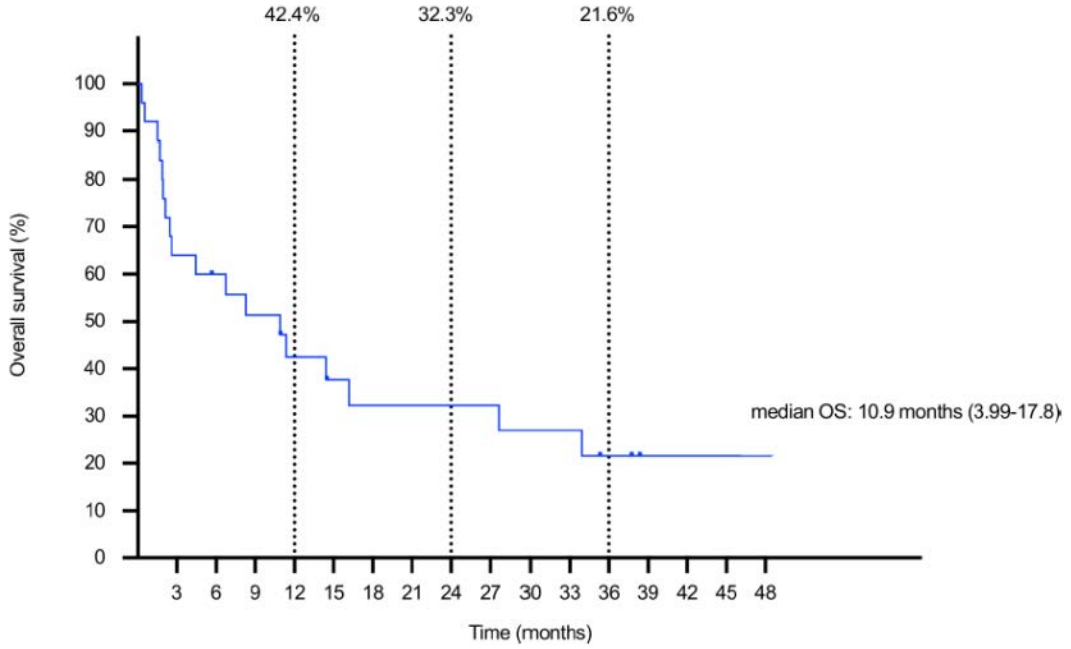
Ipilimumab and nivolumab/ pembrolizumab in advanced hepatocellular carcinoma refractory to prior immune checkpoint inhibitors

Jeffrey Sum Lung Wong ,[1] Gerry Gin Wai Kwok,[1] Vikki Tang,[1] Bryan Cho Wing Li,[1] Roland Leung,[1] Joanne Chiu,[1] Ka Wing Ma,[2] Wong Hoi She,[2] Josephine Tsang,[1] Chung Mau Lo,[2] Tan To Cheung,[2] Thomas Yau[1]

N=25
All had prior IO
19 pts nivo
5 pts pembro
1 pt Arez-bev

Table 2 Best objective response

Activity	n (%)
CR	3 (12)
PR	1 (4)
SD	6 (24)
PD	12 (48)
Non-evaluable	3 (12)
ORR (%)	4 (16)



median OS acquired resistance to prior IO 11.4 mos (n=13)
median OS primary resistance to prior IO 4.4 mos (n=12)

Liver Cancer

Original Paper

Liver Cancer 2021;10:107–114
DOI: 10.1159/000512781

Received: September 1, 2020
Accepted: October 31, 2020
Published online: March 3, 2021

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

Changhoon Yoo[a] Jwa Hoon Kim[a] Min-Hee Ryu[a] Sook Ryun Park[a]
Danbi Lee[b] Kang Mo Kim[b] Ju Hyun Shim[b] Young-Suk Lim[b] Han Chu Lee[b]
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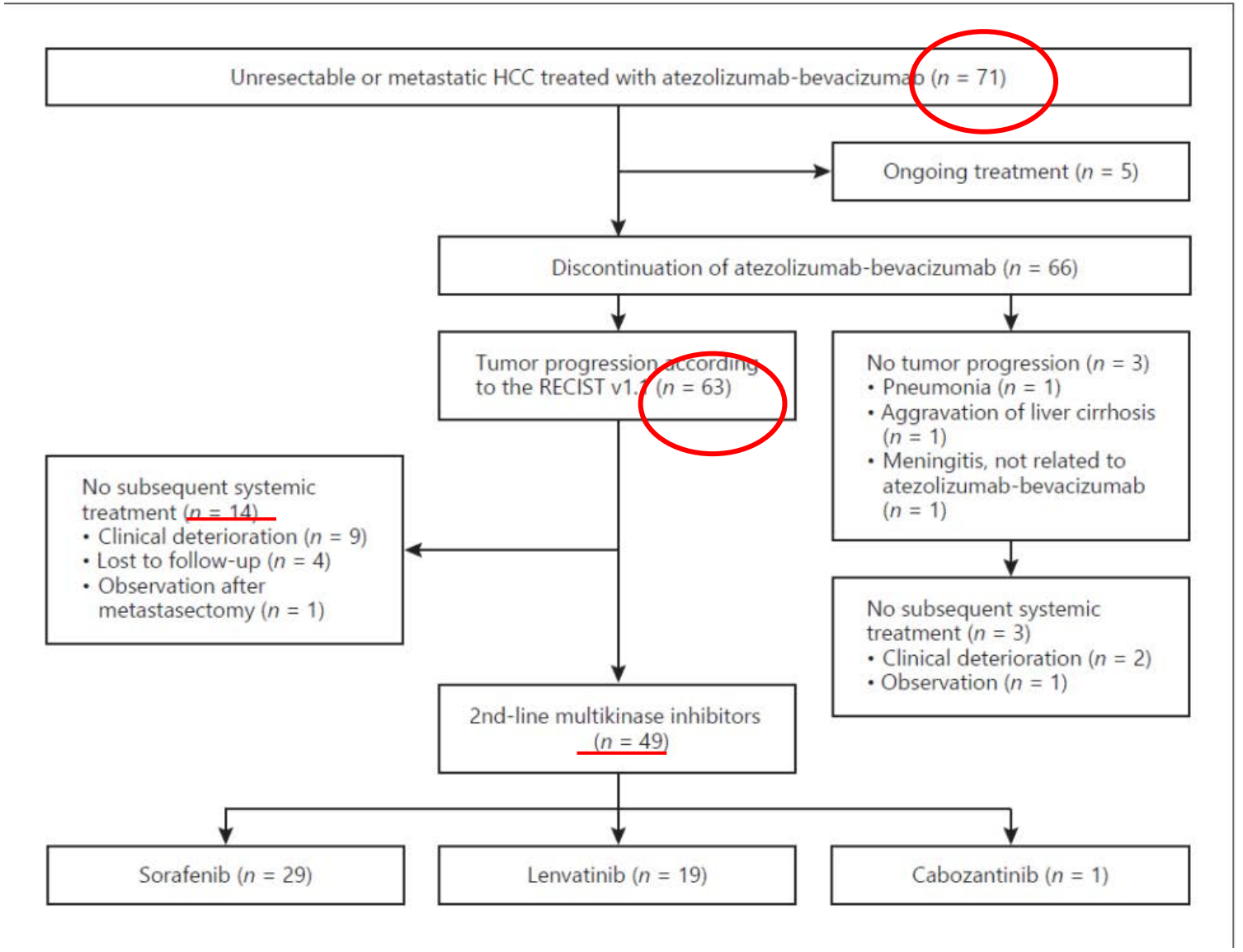

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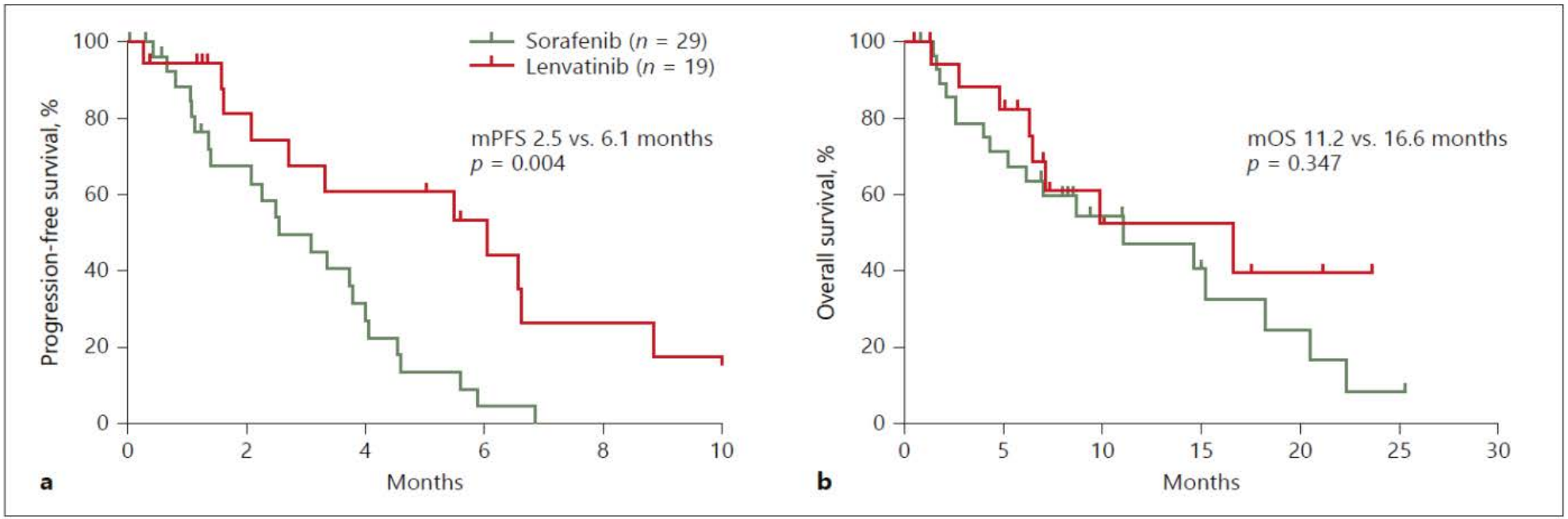
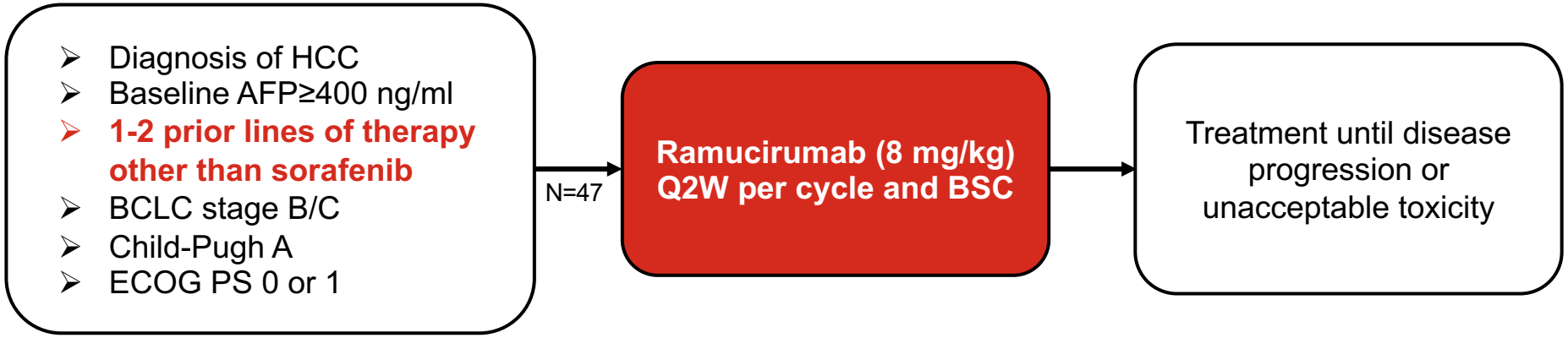
Joycelyn Lee[c] David Tai[c] Stephen Lam Chan[d] Baek-Yeol Ryoo[a]

	Total (n = 49)[a]	Sorafenib (n = 29)	Lenvatinib (n = 19)	p value
PR	3 (6.1)	0 (0)	3 (15.8)	
SD	28 (57.1)	18 (62.1)	9 (47.4)	
PD	14 (28.6)	8 (27.6)	6 (31.6)	
NE[b]	4 (8.2)	3 (10.3)	1 (5.3)	
ORR	3 (6.1)	0 (0)	3 (15.8)	0.062
DCR	31 (63.3)	18 (62.1)	12 (63.2)	1.000



REACH-2 Open Label Expansion



ClinicalTrials.gov: NCT02435433

- **Primary endpoint:** Safety
- **Secondary endpoints:** OS, PFS (RECIST v1.1), TTP, ORR, PK, patient-reported outcomes, immunogenicity
- **Pooled analysis:** open-label cohort was indirectly compared to patients from REACH (AFP ≥400 ng/mL) and REACH-2 who received prior sorafenib using individual patient data meta-analysis

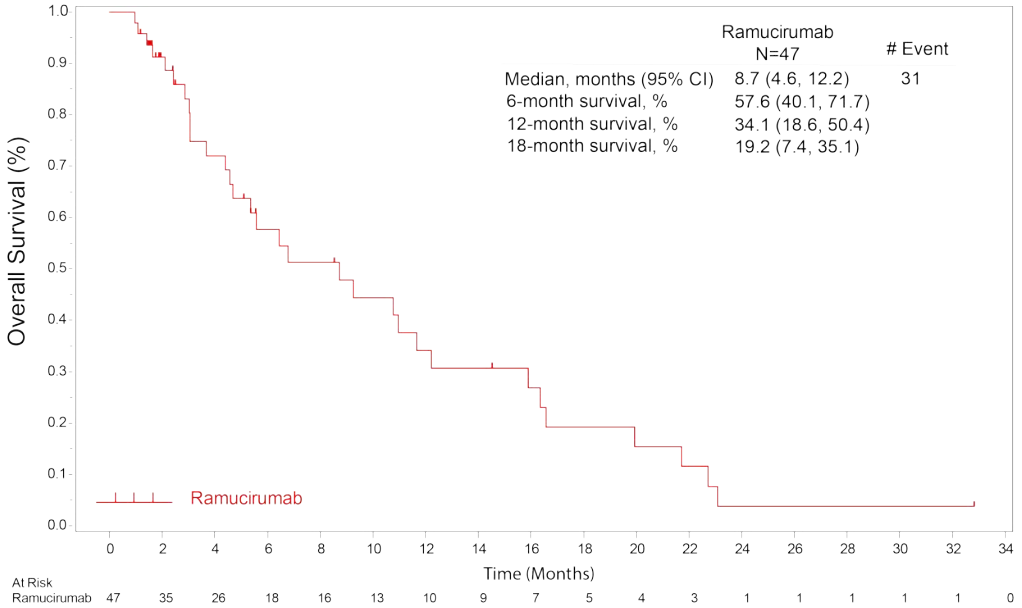
Analysis of single arm Open-Label Expansion Cohort will be independent of Main Cohort. The final analysis of the primary and secondary endpoints will occur after all patients enrolled in the OLE cohort have completed at least 3 cycles of ramucirumab or discontinued for any reason.

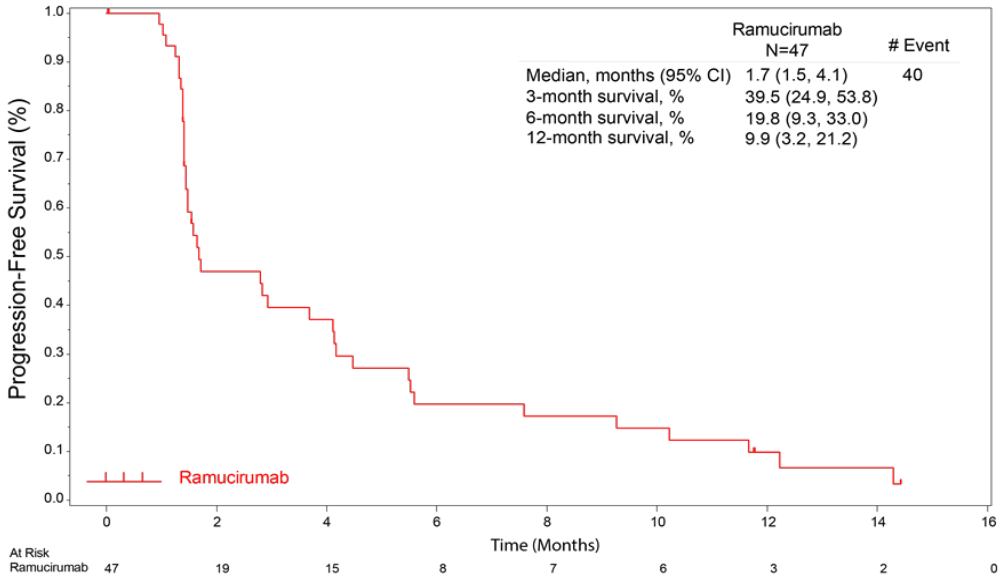
Abbreviations: AFP= alpha-fetoprotein; BCLC= Barcelona Clinic Liver Cancer; BSC= best supportive care; ECOG PS= Eastern Cooperative Oncology Group Performance Status; ORR= objective response rate; OS= overall survival; PFS= progression-free survival; PK= pharmacokinetics; Q2W= every 2 weeks; TTP= time-to-progression

Data cut-off date was May 11, 2021

REACH-2 Open Label Expansion

n (%)	Ramucirumab N=47
TKI monotherapy	
Lenvatinib	20 (43)
Cabozantinib	2 (4)
Tepotinib	1 (2)
CPI monotherapy	
Nivolumab	6 (13)
Durvalumab	2 (4)
Tislelizumab	1 (2)
Pembrolizumab	1 (2)
Toripalimab	1 (2)
CPI + antiangiogenic	
Atezolizumab + bevacizumab	4 (9)
Pembrolizumab + lenvatinib	3 (6)
Sintilimab + bev Biosimilar	1 (2)
Nivolumab + lenvatinib	1 (2)
Atezolizumab + cabozantinib	1 (2)
Pembro (or placebo) + lenvatinib	1 (2)
Camrelizumab + apatinib	1 (2)
Serplulimab + bev Biosimilar	1 (2)
CS1003 (or placebo) + lenvatinib	1 (2)
CPI + CPI	
Nivolumab + ipilimumab	2 (7)
Durvalumab + tremelimumab	2 (7)
Ezabenlimab + anti-Lag3	1 (2)
Other	
DKK1 mAb (DKN-01)	1 (2)





Finn et al ASCO GI 2022

Conclusions:

- IO combinations are now the standard of care for advanced HCC in the front-lien setting
  - If contraindication to IO, then lenvatinib or sorafenib
  - Contraindication to bevacizumab then potential atezo-cabo or durva-treme (when they are approved)

- Since all Phase 3 studies in second-line were done only after sorafenib optimal sequencing is not yet established
  - Very reasonable to offer patients known active drugs if medically fit
  - Likely sequential single agents as in other diseases

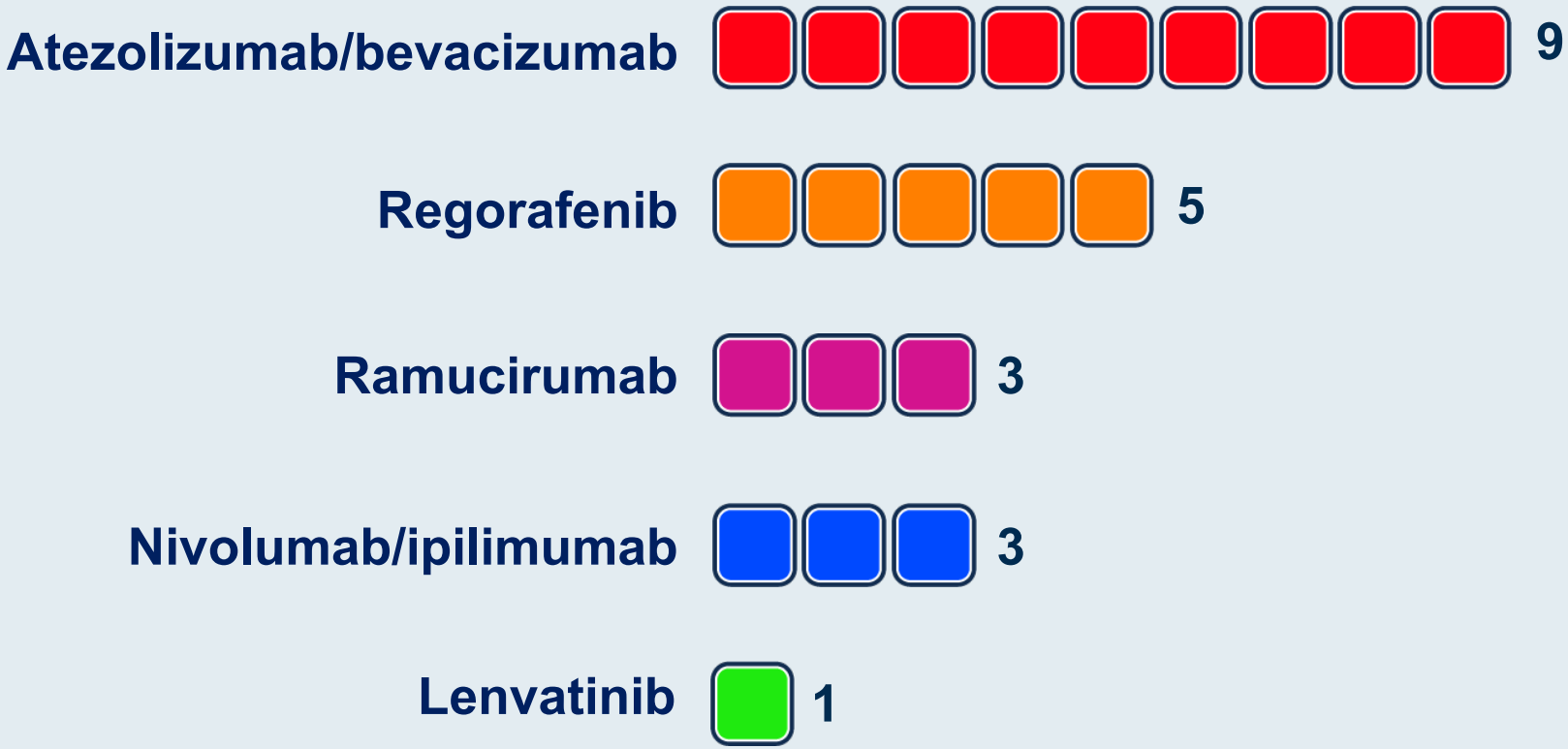
- Potential for IO combinations after front-line IO is of interest but larger datasets are needed
  - PD (L)1+ CTLA4
  - PD (L)1+TKI

Clinical Investigator Survey Results

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, had stable disease for 14 months and then experienced disease progression (AFP = 2,500 ng/mL)?

Survey of Gastrointestinal Cancers Clinical Investigators

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 4 months and then experienced disease progression (AFP = 2,500 ng/mL)?

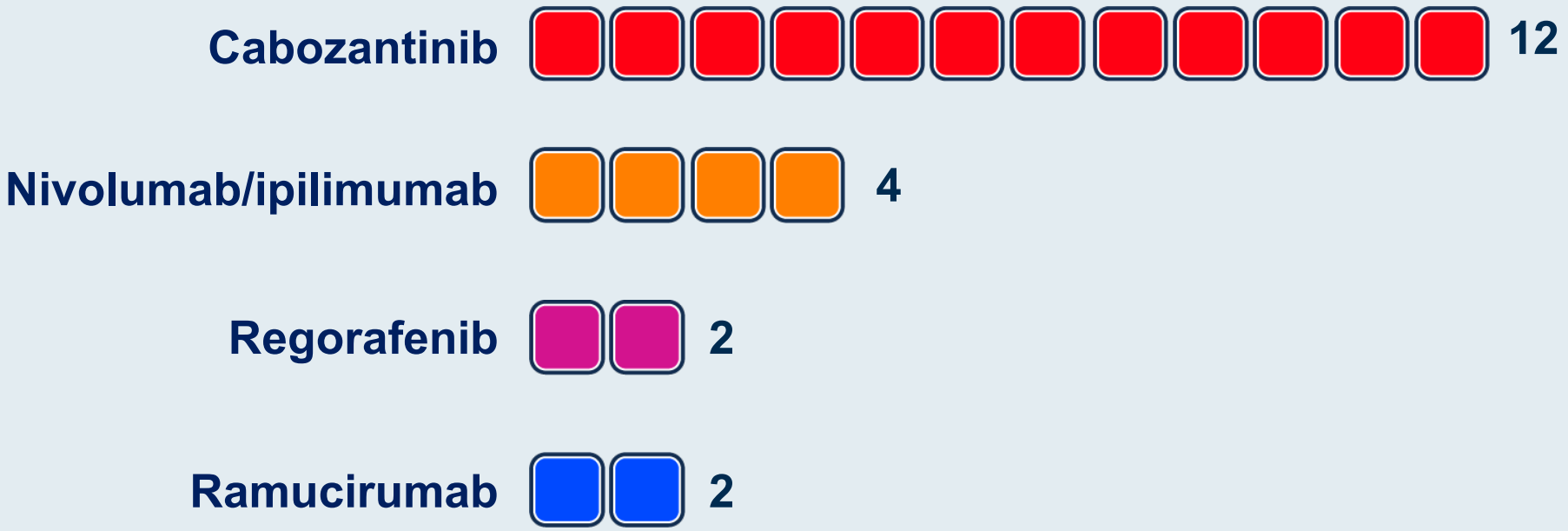


Survey of Gastrointestinal Cancers Clinical Investigators

What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh B7 score and a PS of 1 who received first-line atezolizumab/bevacizumab with minimal toxicity, had stable disease for 14 months and then experienced disease progression (AFP = 2,500 ng/mL)?

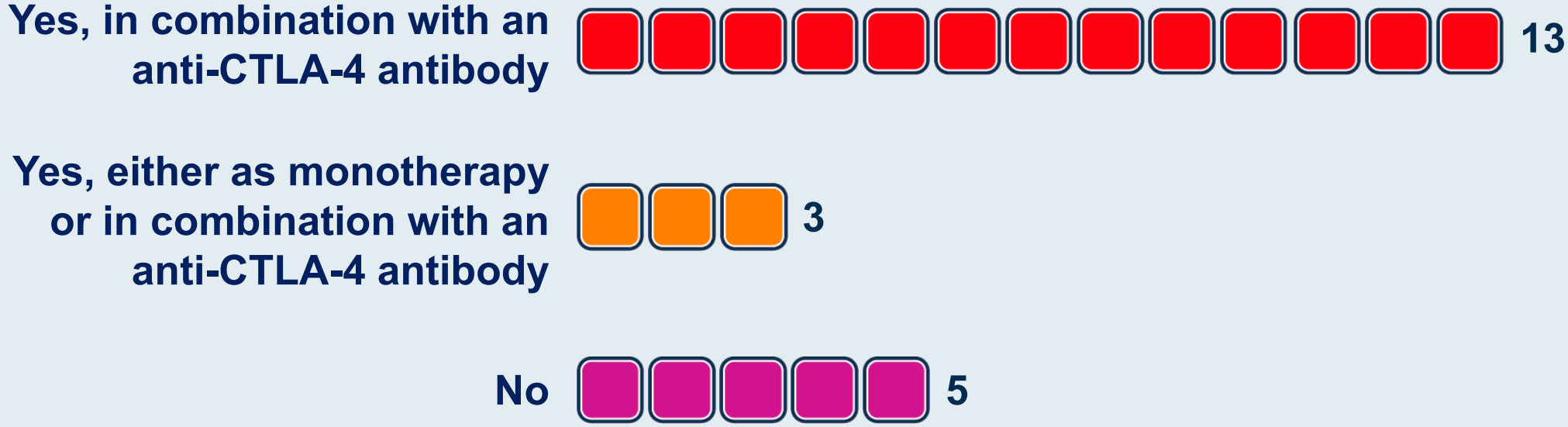
Survey of Gastrointestinal Cancers Clinical Investigators

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)?



Survey of Gastrointestinal Cancers Clinical Investigators

For a patient who has received atezolizumab/bevacizumab in the up-front setting and experienced disease progression, are there any circumstances in which you will recommend an anti-PD-1/PD-L1 antibody later in the treatment course?



Survey of Gastrointestinal Cancers Clinical Investigators

MODULE 3: Current Treatment Strategies for Advanced Biliary Tract Cancers — Dr Kelley

RTP
RESEARCH
TO PRACTICE

UCSF Helen Diller Family Comprehensive Cancer Center

Current Treatment Strategies for Advanced Biliary Tract Cancers (BTC)

Integrating Molecularly-Targeted Therapies

Katie Kelley, MD
Professor of Clinical Medicine
University of California, San Francisco

1/21/22

Robin K Kelley, MD — Disclosures
Faculty

Advisory Committee	Agios Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Ipsen Biopharmaceuticals Inc, Merck
Consulting Agreement	Exact Sciences Inc
Contracted Research	Agios Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, EMD Serono Inc, Exelixis Inc, Genentech, a member of the Roche Group, Lilly, Merck, Novartis, Partner Therapeutics, QED Therapeutics, Surface Oncology, Taiho Oncology Inc
Data and Safety Monitoring Board/Committee	Genentech, a member of the Roche Group, Merck

RTP RESEARCH TO PRACTICE

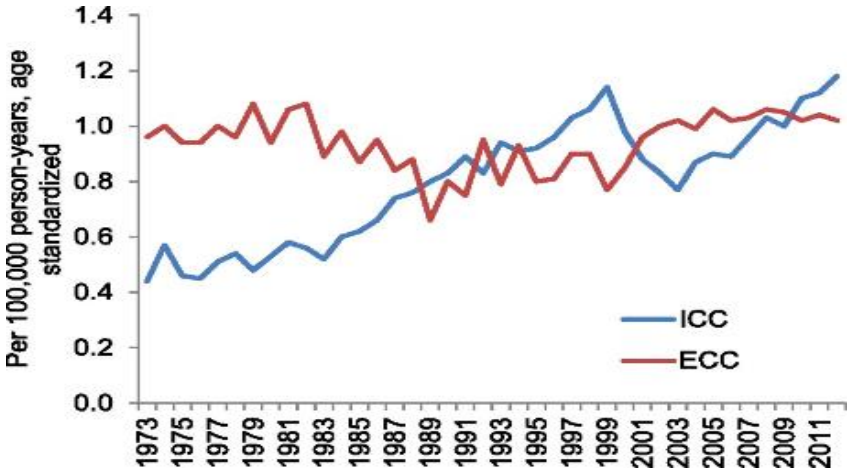
Outline

- Background on advanced BTC and current treatment standards
- Spectrum of molecular alterations in cholangiocarcinoma and other biliary tract cancers
- Emerging role for FGFR2-targeted therapy in intrahepatic cholangiocarcinoma (iCCA) with *FGFR2* fusions or other rearrangements
  - Pemigatinib
  - Infigratinib
  - Next-generation inhibitors and ongoing trials (e.g. FIGHT-302, PROOF, FOENIX-CCA3)
- IDH1-targeted therapy in iCCA with *IDH1* mutation
  - Ivosidenib
  - Ongoing trials
- Conclusions and future directions

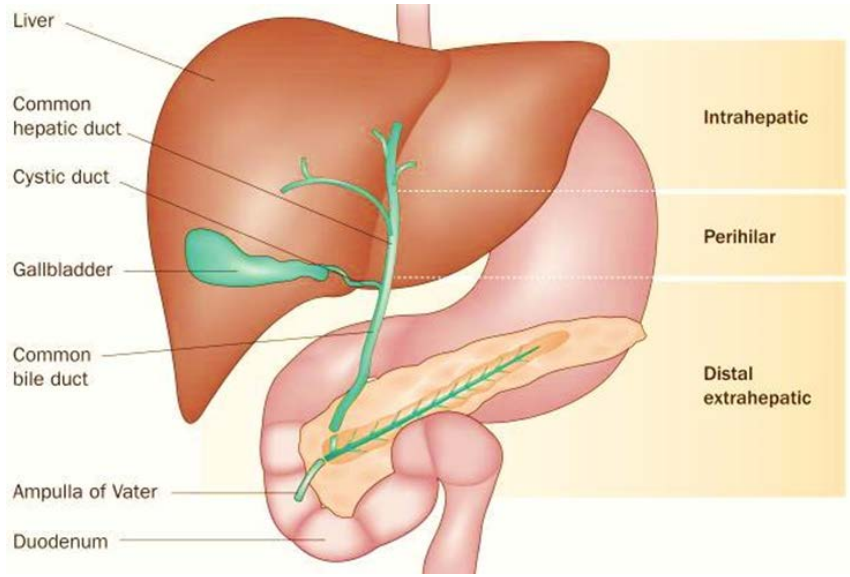
Biliary Tract Cancers (BTC)

- Uncommon tumors with rising incidence
  - ~15,000 cases/year in US for all BTC combined
- Clinically heterogeneous
  - Varied etiologies: Underlying liver inflammation/injury (NAFLD, HBV, HCV, ETOH, PSC); fluke infection; hereditary; idiopathic
  - Multiple anatomic subsites
    - Gallbladder (GBC)
    - Cholangiocarcinoma (CCA)
      - Intrahepatic (iCCA)
      - Extrahepatic (eCCA)
        - Perihilar ("Klatskin", pCCA)
        - Distal (dCCA)
- Heterogeneous tumor biology and microenvironment

Age-adjusted incidence of ICC and ECC 1973–2012



Saha et al. The Oncologist 2016;21:594-99

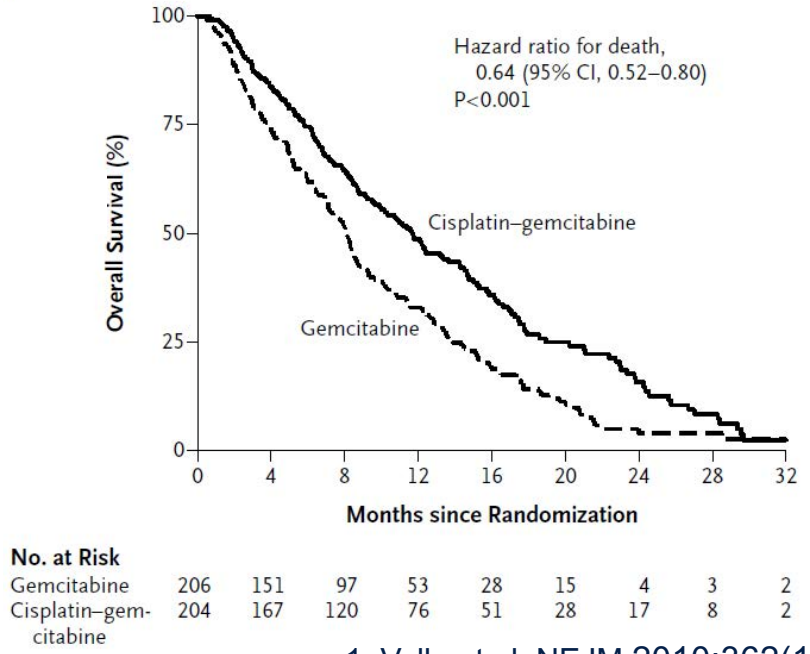


Cancer.org; seer.cancer.gov

UCSF

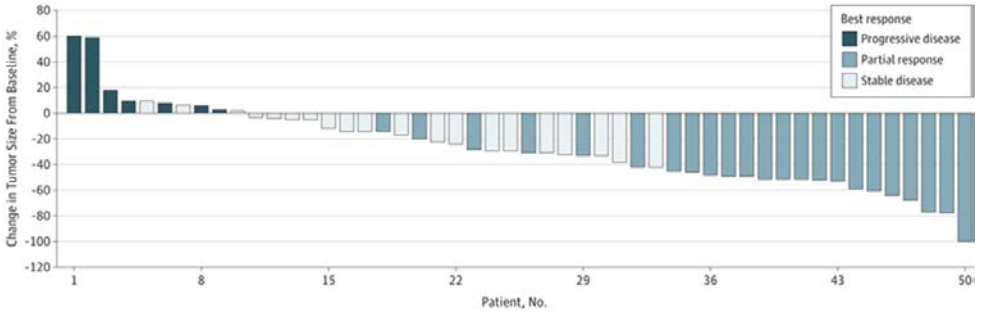
1st Line Chemotherapy for Advanced BTC

- Gemcitabine plus cisplatin (GEMCIS) is global standard per ABC-02 trial[1]
  - Median overall survival (mOS) 11.7 vs. 8.1 mos. (p<0.001)
  - Objective response rate (ORR) 25.5% vs. 14.8%
- New chemotherapy combinations being studied in 1st line phase 3 trials:
  - SWOG 1815 GEMCIS ± nab-paclitaxel (NCT03768414)[2]
  - NUC-1031 (protide analog of gemcitabine) + cisplatin (NCT04163900)
  - FOLFIRINOX vs. GEMCIS (NCT02591030)
  - GEMCIS + immunotherapy (TOPAZ-1, KEYNOTE-966)



1. Valle et al, NEJM 2010;362(14)

Phase 2 Trial of GEMCIS+nab-paclitaxel



2. Shroff et al, JAMA Oncol 2019;5(6)

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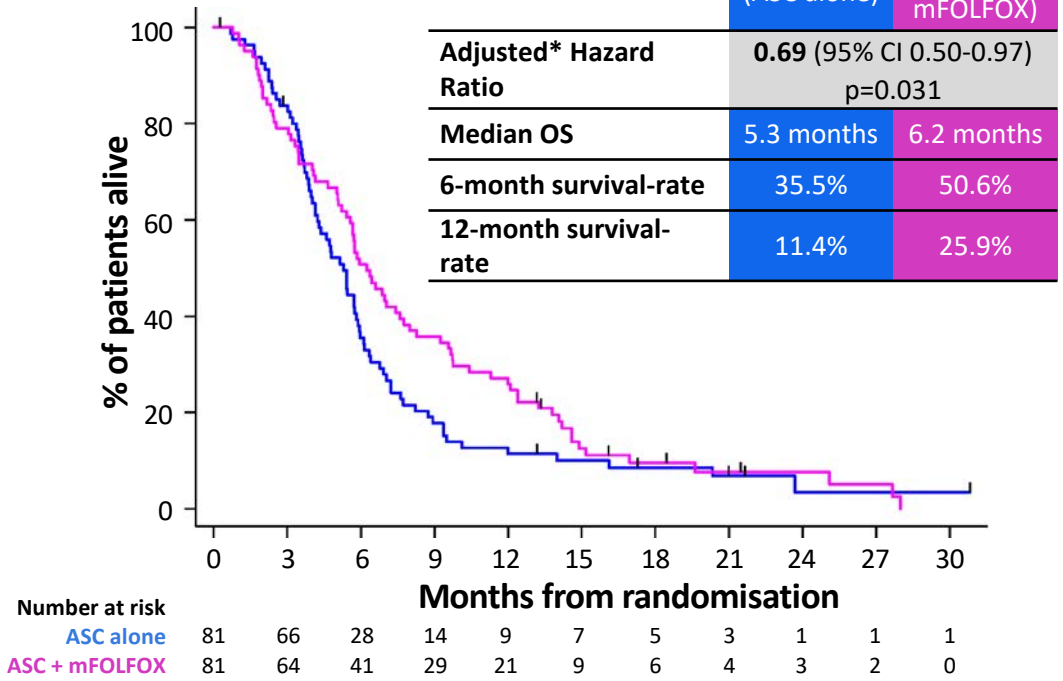
2nd+ Line Chemotherapy Options for Advanced BTC

- Before 2019: No established 2L therapy after GEMCIS
- 2019: Phase 3 ABC-06 trial of active supportive care (ASC) vs. FOLFOX+ASC showed improved PFS and OS for FOLFOX+ASC
  - mOS 6.2 vs. 5.3 mos.
  - mPFS 4.0 months for FOLFOX+ASC
  - ORR 5% for FOLFOX+ASC arm
- Other regimens such as FOLFIRI, capecitabine, GEM/nab-paclitaxel are commonly used based upon phase 2 data

ABC-06:
Overall survival by trial arm



	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

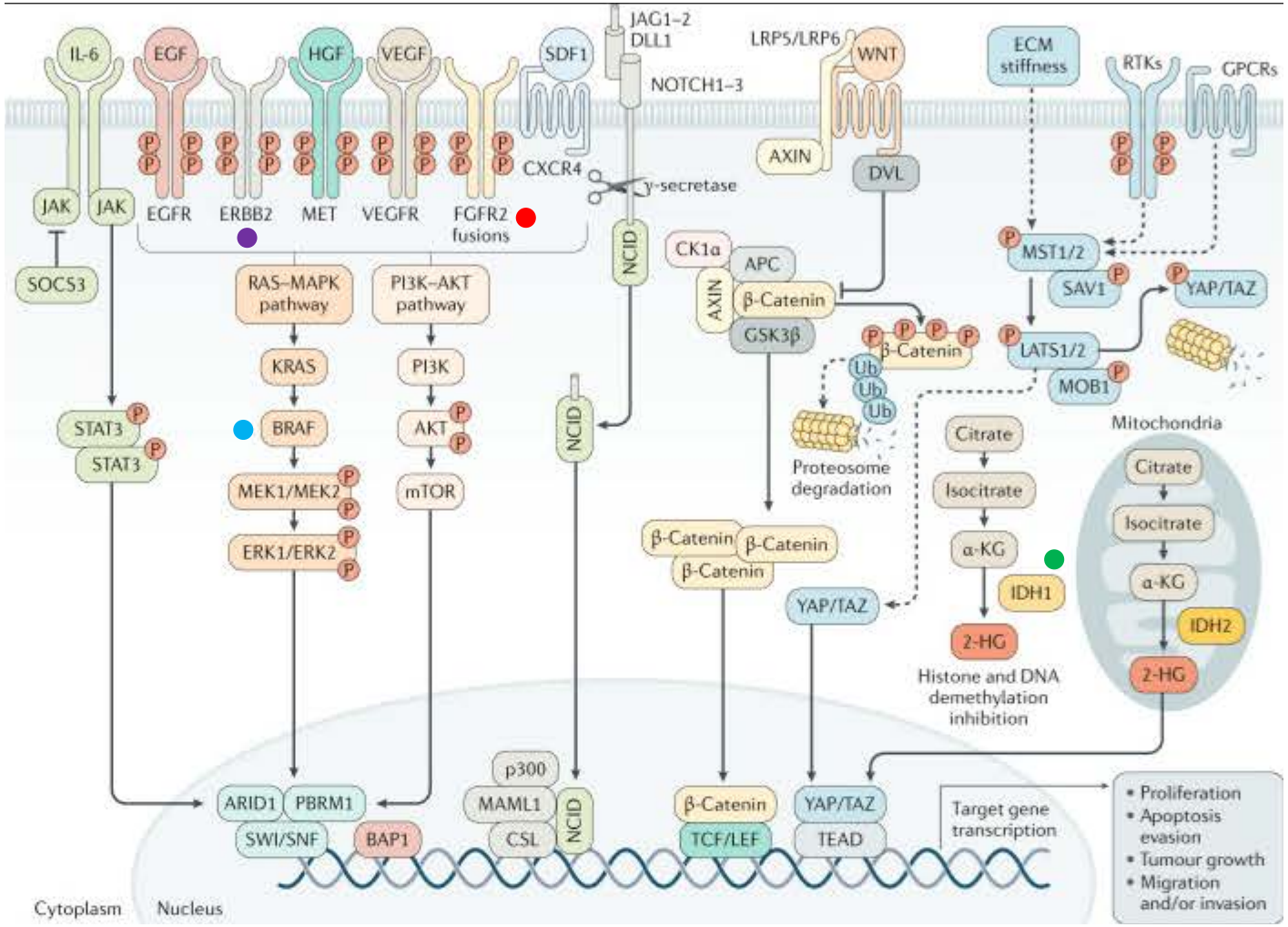
Lamarca et al, Lancet Oncol 2021;22(5)

UCSF

Beyond Standard Chemotherapy: Emerging Molecular Targets in CCA

- Emerging therapeutic targets:
  - Receptor tyrosine kinases (RTK)
    - *FGFR2* fusion/rearrangement (10-15%)
    - *NTRK* fusion (rare)
    - *ERBB2/EGFR* mut./amp.(7-19%)
  - Cellular metabolism
    - *IDH1* mutation (~15%)
  - Intracellular kinases
    - *BRAF V600E* (5-7%)

Targetable aberrations are present in ≥30% of iCCA patients, with evolving levels of evidence.

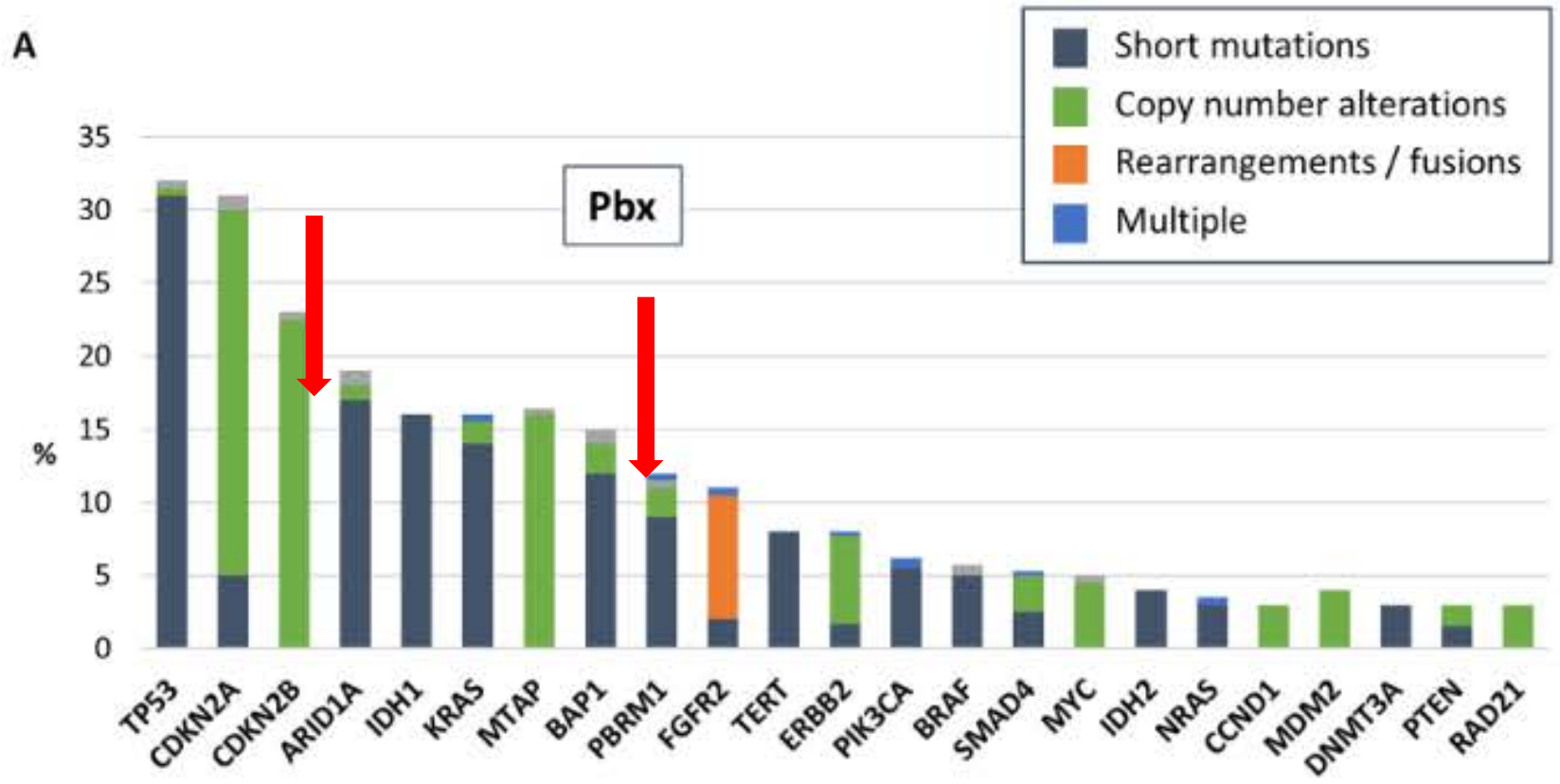


Banales et al. Nat Rev Gastroenterol Hepatol 2020: 17(9); Zehir et al Nature Med 2017;23(6)

UCSF

Emerging Targets in iCCA: Focus on FGFR2 and IDH1

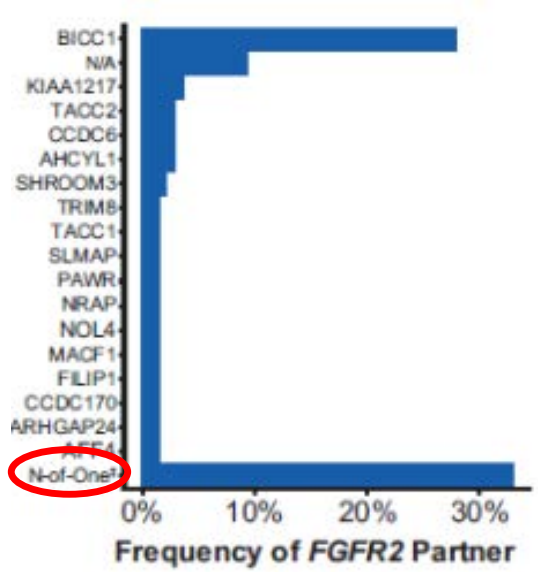
- Mutation profiling of N=1632 iCCA using Foundation Medicine panel
  - n=1048 with primary tumor biopsy (Pbx)
  - *FGFR2* fusion or rearrangement: 9%
  - *IDH1* mutation: 16%

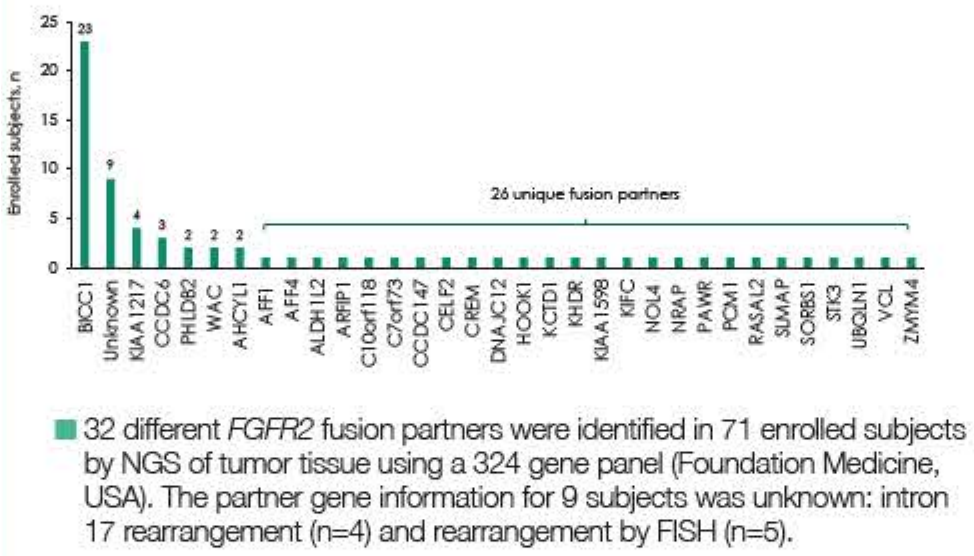


Israel et al. Oncologist 2021;26(9)

FGFR2 Fusions and Rearrangements in ICC

- Present in ~10-15% of iCCA, very rare in other subsites
  - Kinase domain of *FGFR2* fused in-frame to a 3' partner (fusions) or to unidentified partner (other rearrangements)
    - Breakpoint hotspots: intron 17, exon 18
  - Many different/unique intronic fusion partners, "n-of-one"
    - Most not detectable by cfDNA assays; requires tumor next generation sequencing (NGS) for diagnosis of most intronic fusions
- Produce chimeric constitutively active FGFR2 independent of ligand





32 different *FGFR2* fusion partners were identified in 71 enrolled subjects by NGS of tumor tissue using a 324 gene panel (Foundation Medicine, USA). The partner gene information for 9 subjects was unknown: intron 17 rearrangement (n=4) and rearrangement by FISH (n=5).

Makawita et al. GI ASCO 2020, Poster 579; Silverman et al Cancer Discov 2021;11(2):326-339

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Approaches to FGFR2 Inhibition

- Early generation multikinase inhibitors with varying degrees of FGFR inhibition (e.g. ponatinib, pazopanib)
  - Insufficient specificity and potency
- Multiple selective pan-FGFR (1-3>4) inhibitors approved or in later stage trials
  - ATP-competitive, reversible
    - Pemigatinib, infigratinib (BGJ398), erdafitinib, Debio 1347, derazantinib, others
  - Non-ATP competitive, covalent/irreversible
    - Futibatinib (TAS-120)
- Selective FGFR2 covalent inhibitor
  - RLY-4008

Pemigatinib

- Selective oral inhibitor FGFR1-3
- Phase 2 trial FIGHT-202 (NCT02924376)
  - N=146
    - *FGFR2* fusions/rearrangements: n=107
    - Other *FGFR2* alterations: n=20
    - No *FGFR2* alterations: n=18
  - Stage IV: 86%
  - 2/3/4th line: 61%/26%/13%
  - ECOG 0/1/2: 40%/52%/8%

- Treatment: Pemigatinib 13.5 mg daily days 1-14 Q21 days
- Primary endpoint: Objective response by RECIST 1.1 in patients with FGFR2 fusion/rearrangement

Key treatment-related safety results
- Hyperphosphatemia: 60% (all cause)
- Nail toxicity: 42%
- Stomatitis: 32%
- Subretinal fluid: 4%
- Grade ≥ 3 AE: 64% (all cause)
- Discontinuation for AE: 9%

Abou-Alfa et al. Lancet Oncol 2020:21

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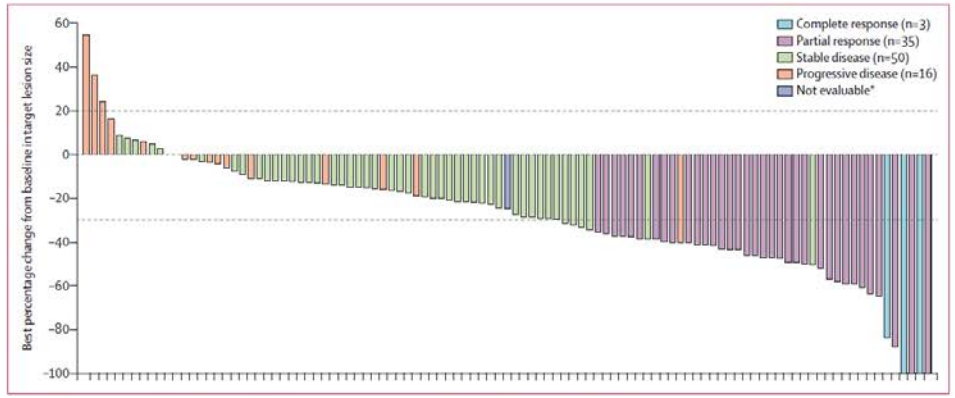
Pemigatinib: FIGHT-202 Outcomes

	FGFR2 fusions or rearrangements (n=107)	Other *FGF/FGFR* alterations (n=20)	No *FGF/FGFR* alterations (n=18)
Proportion of patients with an objective response	35·5% (26·5 to 45·4)	0	0
Best overall response*			
Complete response	3 (2·8%)	0	0
Partial response	35 (32·7%)	0	0
Stable disease	50 (46·7%)	8 (40·0%)	4 (22·2%)
Progressive disease	16 (14·9%)	7 (35·0%)	11 (61·1%)
Not evaluable	3 (2·8%)	5 (25·0%)	3 (16·7%)
Duration of response			
Patients with events	21/38 (55%)	0	0
Patients censored	17/38 (45%)	0	0
Median duration of response, months	7·5 (5·7 to 14·5)	..	..



	FGFR2 fusions or rearrangements (n=107)	Other *FGF/FGFR* alterations (n=20)	No *FGF/FGFR* alterations (n=18)
Progression-free survival			
Patients with events	71 (66%)	17 (85%)	16 (89%)
Patients censored	36 (34%)	3 (15%)	2 (11%)
Median, months	6·9 (6·2 to 9·6)	2·1 (1·2 to 4·9)	1·7 (1·3 to 1·8)
Kaplan-Meier estimates of progression-free survival			
At 6 months	62% (52 to 70)	25% (8 to 47)	6% (<1 to 25)
At 12 months	29% (19 to 40)	0	0
Overall survival†			
Patients with events	40 (37%)	16 (80%)	14 (78%)
Patients censored	67 (63%)	4 (20%)	4 (22%)
Median overall survival, months	21·1 (14·8 to not estimable)	6·7 (2·1 to 10·6)	4·0 (2·3 to 6·5)
Kaplan-Meier estimates of overall survival			
At 6 months	89% (81 to 93)	51% (26 to 71)	31% (11 to 54)
At 12 months	68% (56 to 76)	23% (7 to 43)	13% (2 to 33)

Abou-Alfa et al. Lancet Oncol 2020:21

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Infigratinib

- Selective oral inhibitor FGFR1-3
- Phase 2 trial (NCT02150967)
  - N=122
    - *FGFR2* fusions/rearrangements: n=108
    - Other *FGFR2* alterations: n=14
  - Stage IV: 99%
  - 2/3/4th line: 46%/30%/13%
  - ECOG 0/1/2: 42%/57%/1%

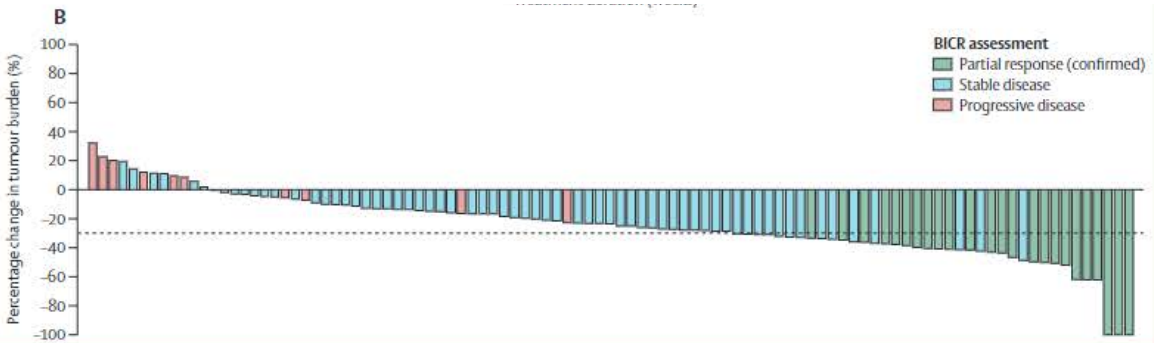
- Treatment: Infigratinib 125 mg daily D1-21 Q28 days
- Primary endpoint: Objective response rate by RECIST 1.1, central review

Key all-cause safety results

- Hyperphosphatemia: 77%
- Onycholysis: 12%
- Stomatitis: 55%
- Subretinal fluid: 17%
- Grade ≥3 AE: 64%
- Discontinuation for AE: 14%

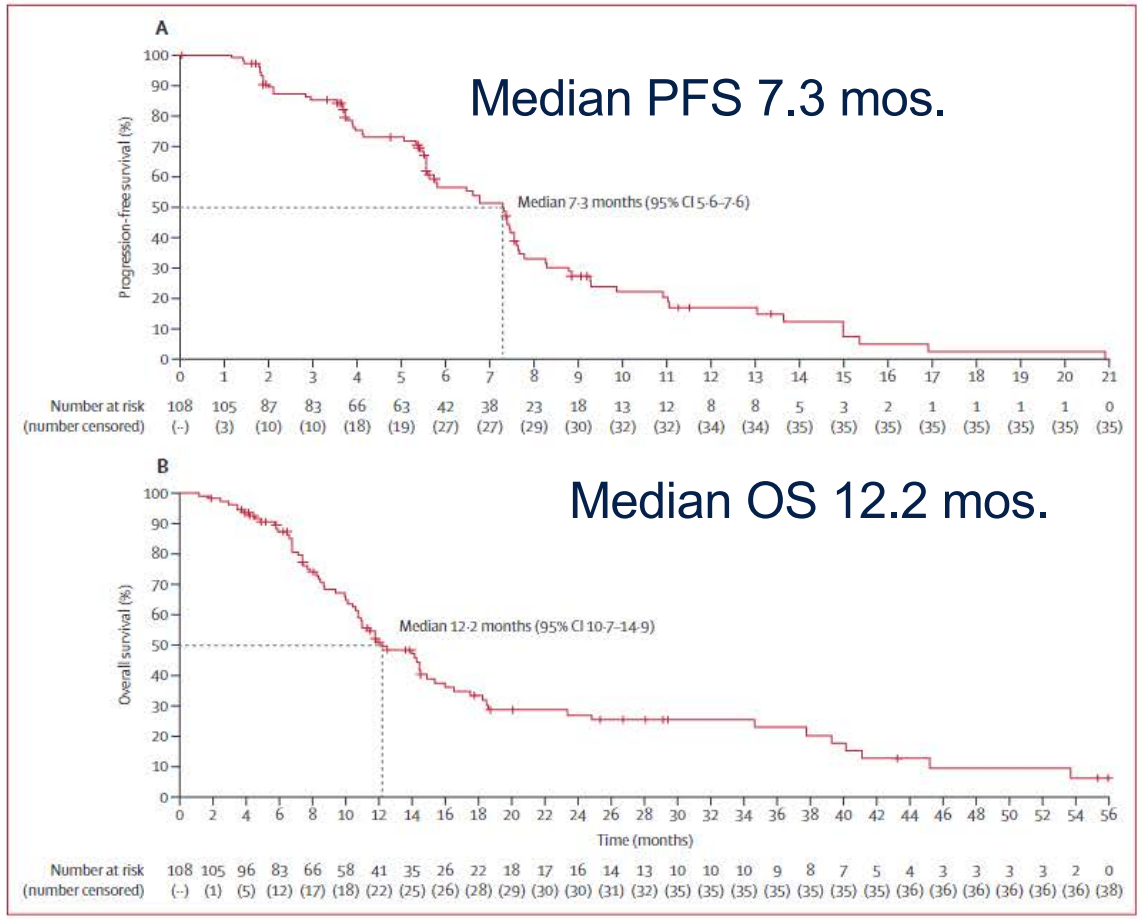
*Does not include other "nail disorder" categories

Infigratinib: Phase 2 Outcomes



- ORR: 23.1% in overall population
  - 34% in 2nd line subgroup (n=50)
  - Median duration of response 7.3 mos.

	Overall (n=108)	Previous lines of therapy			
		1 (n=50)	2 (n=32)	3 (n=14)	≥4 (n=12)
BICR-assessed objective response rate	25 (23·1%, 15·6–32·2)	17 (34·0%, 21·2–48·8)	5 (15·6%, 5·3–32·8)	2 (14·3%, 1·8–42·8)	1 (8·3%, 0·2–38·5)
BICR-assessed best overall response					
Complete response	1 (1%)	0	0	1 (7%)	0
Partial response	24 (22%)	17 (34%)	5 (16%)	1 (7%)	1 (8%)
Stable disease	66 (61%)	27 (54%)	22 (69%)	10 (71%)	7 (58%)
Unconfirmed complete response or partial response	12 (11%)	4 (8%)	7 (22%)	0	1 (8%)
Progressive disease	11 (10%)	4 (8%)	3 (9%)	1 (7%)	3 (25%)
Unknown	6 (6%)	2 (4%)	2 (6%)	1 (7%)	1 (8%)
BICR-assessed confirmed or unconfirmed response	37 (34·3%, 25·4–44·0)	21 (42·0%, 28·2–56·8)	12 (37·5%, 21·1–56·3)	2 (14·3%, 1·8–42·8)	2 (16·7%, 2·1–48·4)
BICR-assessed disease control rate	91 (84·3%, 76·0–90·6)	44 (88·0%, 75·7–95·5)	27 (84·4%, 67·2–94·7)	12 (85·7%, 57·2–98·2)	8 (66·7%, 34·9–90·1)



Median PFS 7.3 mos.

Median OS 12.2 mos.

Javle et al. Lancet Gastroenterol Hepatol 2021;6

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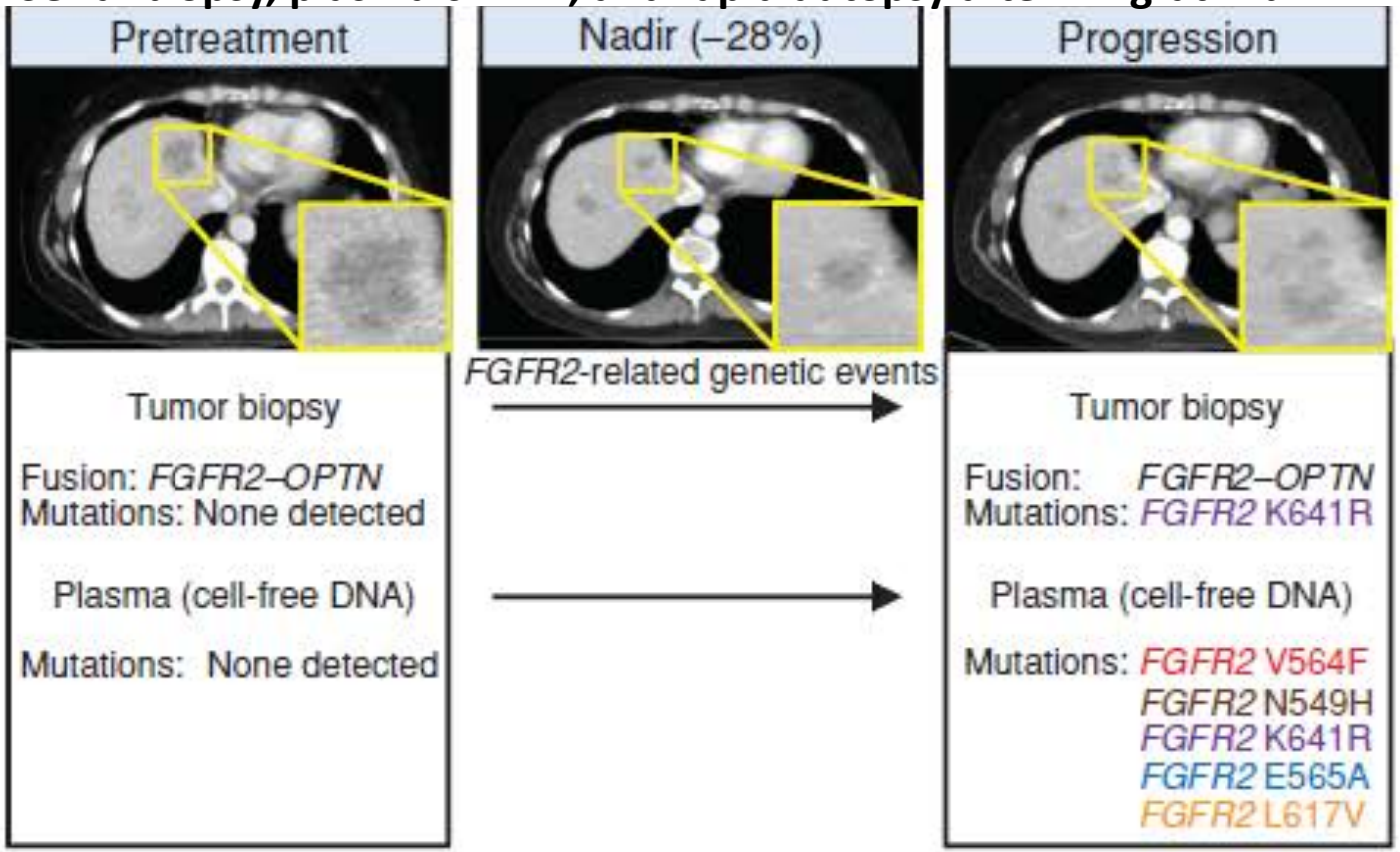
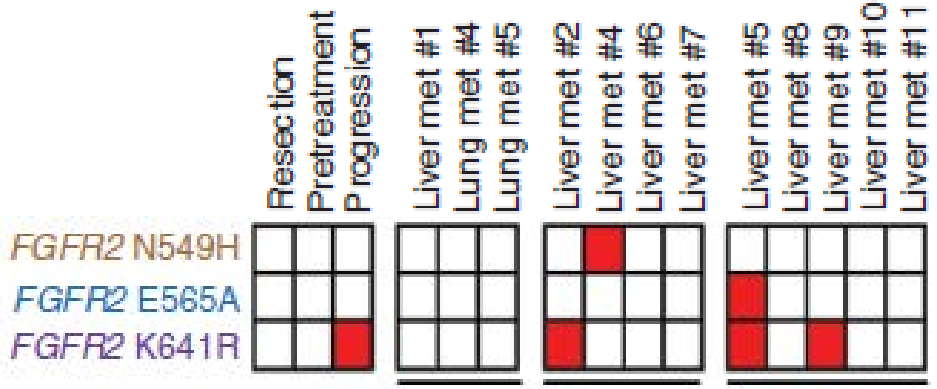
Mechanisms of Acquired Resistance to ATP-Competitive FGFR Inhibition

Serial biopsy, plasma cfDNA, and rapid autopsy after infigratinib:

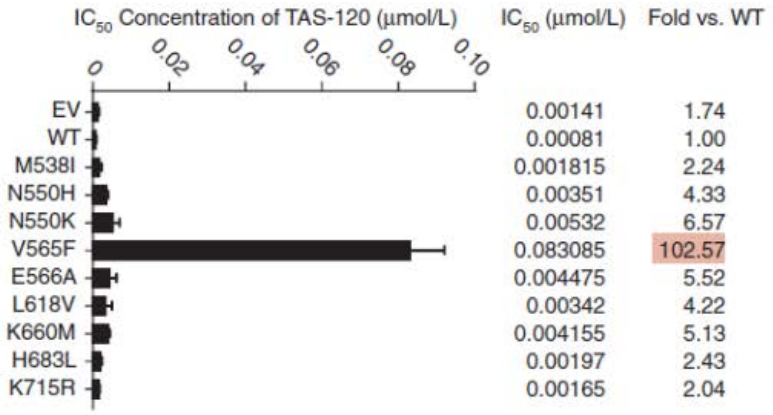


Goyal et al Cancer Discov 2017;7(3):252-63

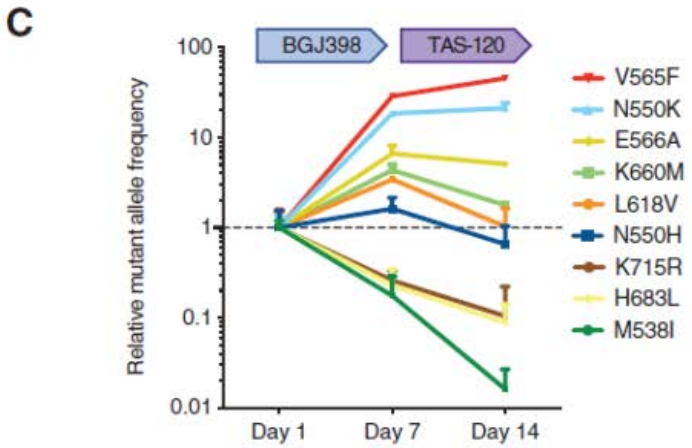
- Acquired, polyclonal secondary *FGFR2* kinase domain point mutations cause resistance to infigratinib
  - Gatekeeper (ATP-binding pocket)
  - Molecular brake (disrupts normal inhibitory residues)
  - Hydrophobic spine
- Other FGFR2 inhibitors have activity against certain kinase domain resistance mutations
  - Role for sequential molecular profiling to guide subsequent therapy?



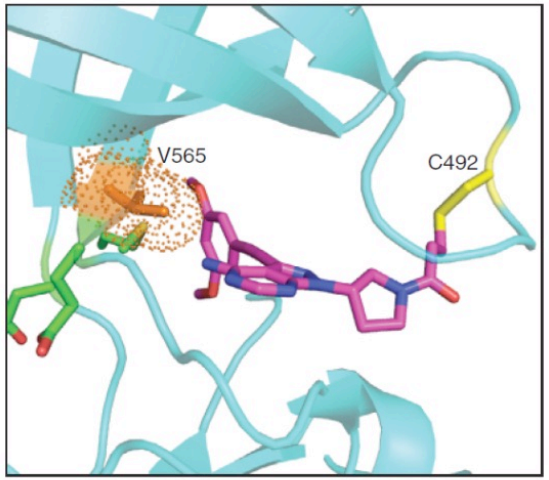
Futibatinib (TAS-120) has Activity Against Multiple KD Resistance Mutations in Preclinical and Early Phase Studies



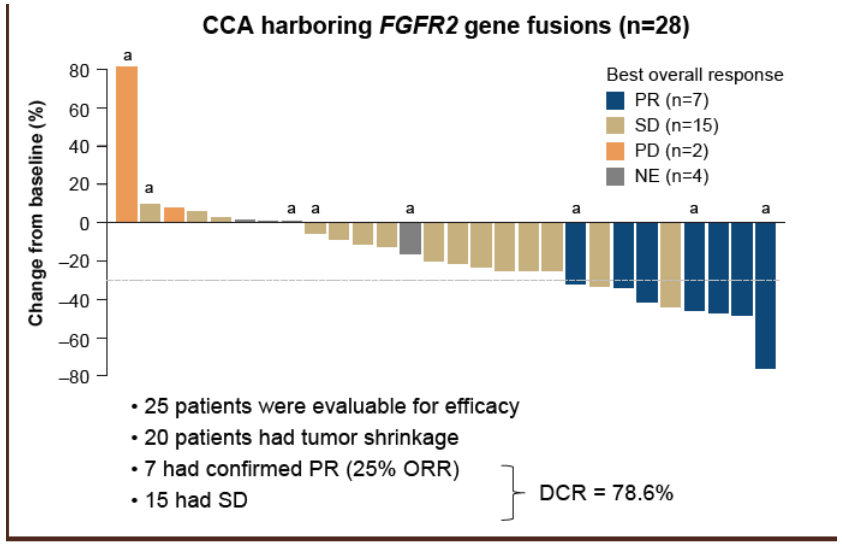
	IC_{50} (µmol/L)	Fold vs. WT
EV	0.00141	1.74
WT	0.00081	1.00
M538I	0.001815	2.24
N550H	0.00351	4.33
N550K	0.00532	6.57
V565F	0.083085	102.57
E566A	0.004475	5.52
L618V	0.00342	4.22
K660M	0.004155	5.13
H683L	0.00197	2.43
K715R	0.00165	2.04



- Studied BGJ398, Debio 1347, and TAS-120 (futibatinib) in cell lines with 9 KD resistance mutations
- IC50 and pooled cell clone studies show futibatinib had activity in all resistance clones except V565F
  - Steric hindrance



Goyal et al Cancer Discov 2019



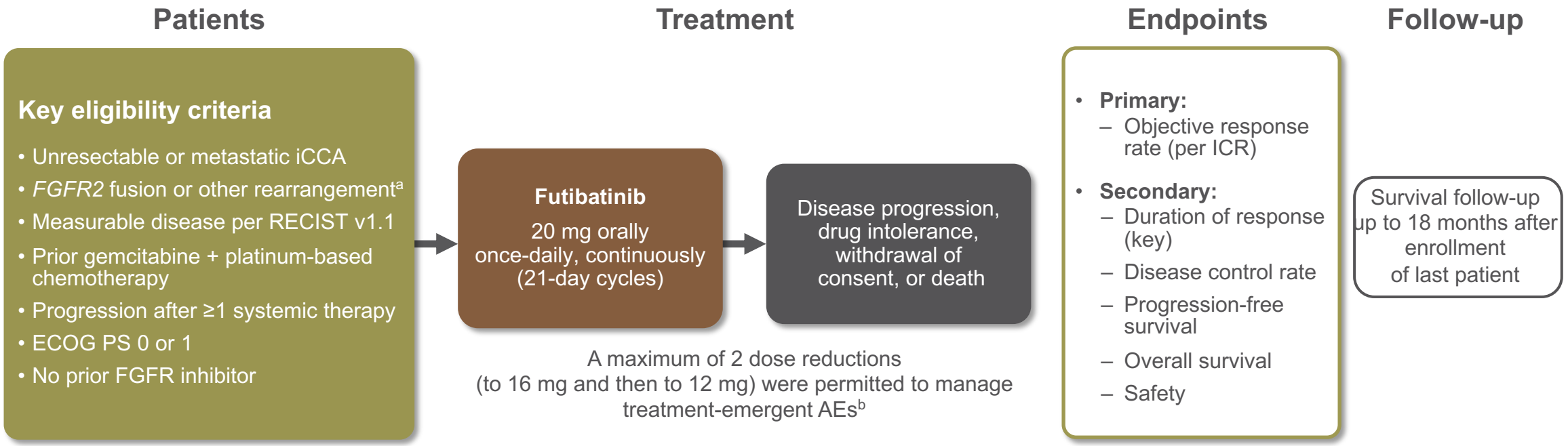
Data shown represent patients who had at least one dose of TAS-120; data cutoff date: Feb 2, 2018
NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease
[a]Received prior FGFR inhibitor; [b]*FGFR2* rearrangement; [c]*FGFR2* amplification

NCT02052778

Meric-Bernstam et al. CCF Annual Conference 2019

FOENIX CCA2

FOENIX-CCA2: Phase 2 Global Study of Futibatinib in *FGFR2* Fusion or Rearrangement-Positive Intrahepatic CCA



- 103 patients enrolled across 36 international sites[c]
- At data cutoff (October 1, 2020), all patients had ≥6 months follow-up; median follow-up was 17.1 months

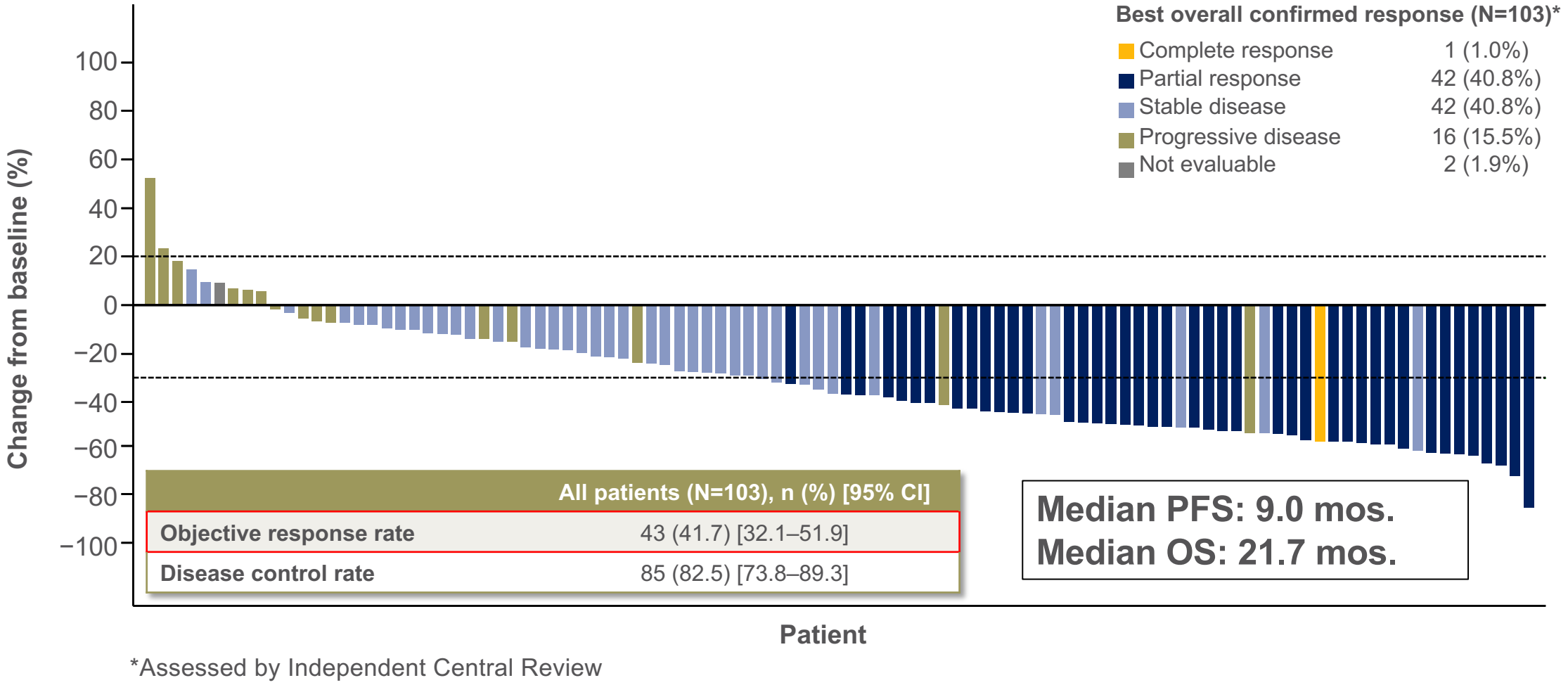
AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; iCCA, intrahepatic cholangiocarcinoma; ICR, independent central radiology review; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1.
[a]Identified centrally in tumor tissue by Foundation Medicine (FMI) or by local laboratory testing of tumor tissue or circulating tumor DNA; [b]Treatment was discontinued if treatment-emergent AEs did not resolve after 2 dose modifications or if the next cycle of treatment was delayed >21 days; [c]Between April 2018 and November 2019.

ClinicalTrials.gov Identifier: NCT02052778

Goyal et al. AACR 2021

FOENIX CCA2

Futibatinib in iCCA: Best Percent Change in Target Lesion Size

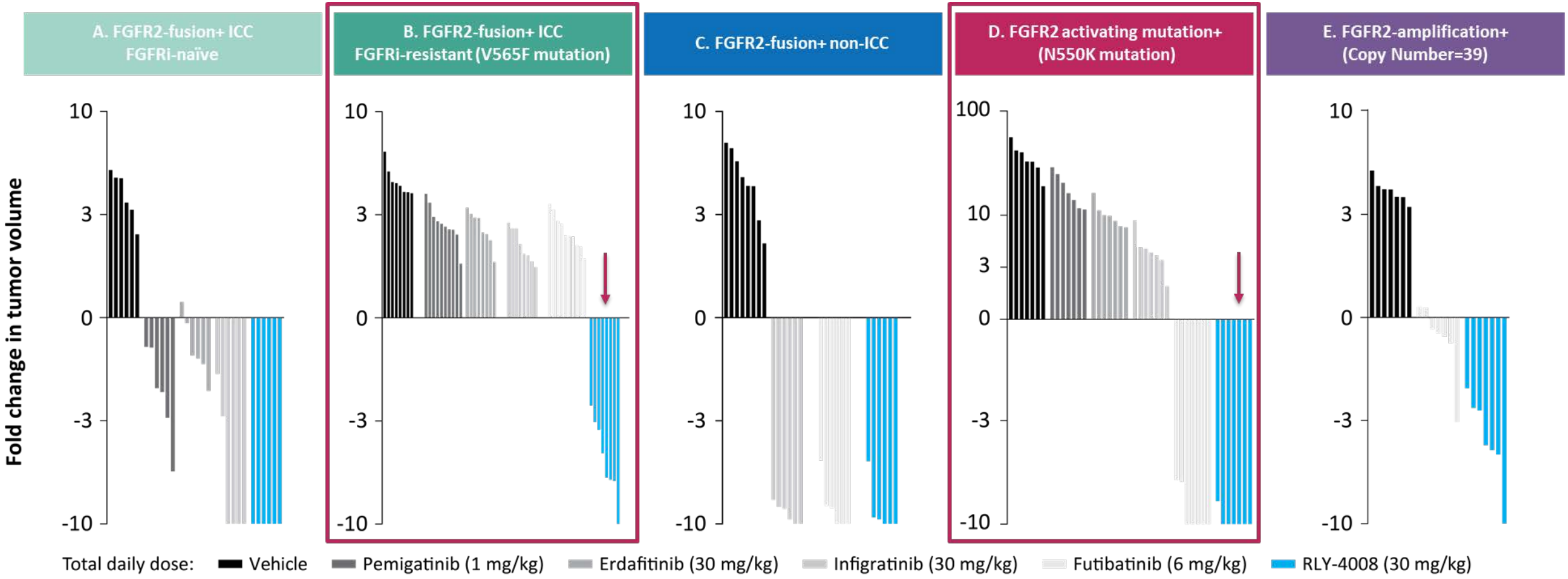


*Assessed by Independent Central Review

Data cutoff: October 1, 2020. Dotted horizontal lines represent partial response (≥30% reduction in lesion size) and progressive disease (≥20% increase) per RECIST v1.1.
CI, confidence interval; iCCA, intrahepatic cholangiocarcinoma; ICR, independent central review; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Goyal et al. AACR 2021

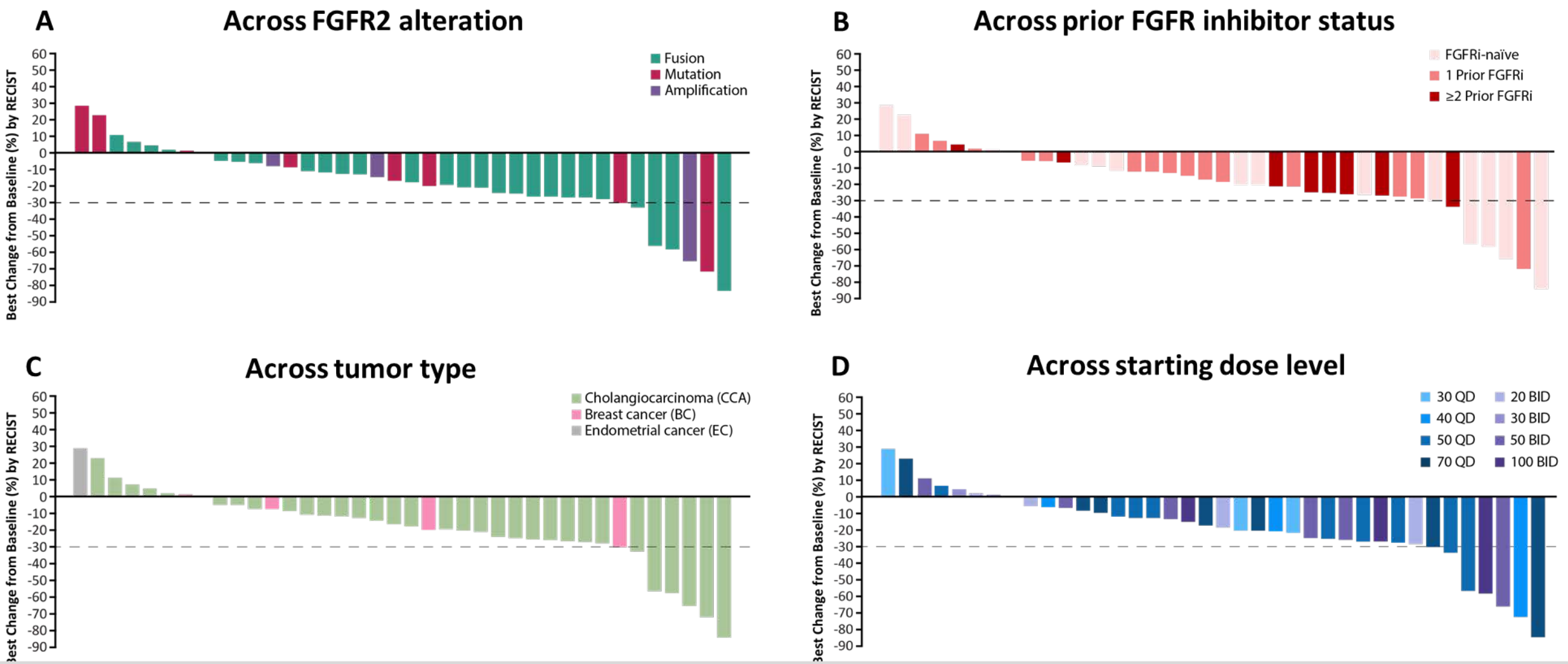
RLY-4008 is highly selective irreversible FGFR2 inhibitor with potent *in vivo* antitumor activity against primary FGFR2 alterations and common resistance mutations



Note: End-of-treatment waterfall plots (change in tumor volume) for tumor models treated with 30 mg/kg RLY-4008 or the indicated pan-FGFRi used at doses equivalent to their recommended human doses.
CC6702 cholangiocarcinoma xenograft with FGFR2-TTC28 fusion **(Figure A)**; ICC13-7 cholangiocarcinoma xenograft harboring FGFR2-OPTN fusion with an V565F gatekeeper resistance mutation introduced by CRISPR **(Figure B)**; Gastric adenocarcinoma PDX, FGFR2-WDR11 fusion **(Figure C)**; AN3 CA endometrial adenocarcinoma xenograft, with FGFR2 N550K activating mutation **(Figure D)**; and SNU-16 gastric carcinoma xenograft with FGFR2 amplification (FGFR2 copy number=39) **(Figure E)**.
ICC: Intrahepatic cholangiocarcinoma.

Goyal et al. AACR-NCI-EORTC 2021

RLY-4008 induces radiographic tumor regression across FGFR2 alterations, FGFR inhibitor status, tumor types and dose levels



Most common AE: Stomatitis, PPE, retinopathy (9%) in daily dosing regimen; minimal hyperphosphatemia

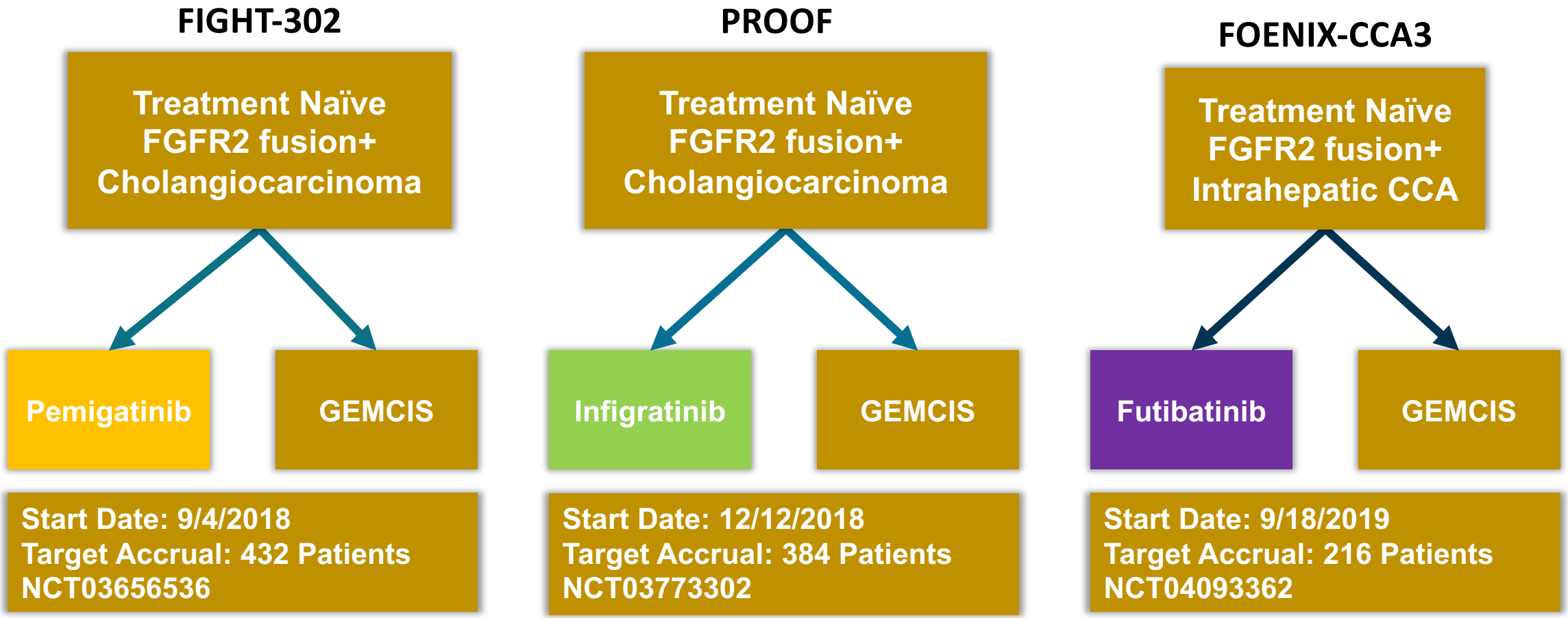
FGFRi, fibroblast growth factor receptor inhibitor.

Goyal et al. AACR-NCI-EORTC 2021

Preliminary data as of 09-Sept-2021

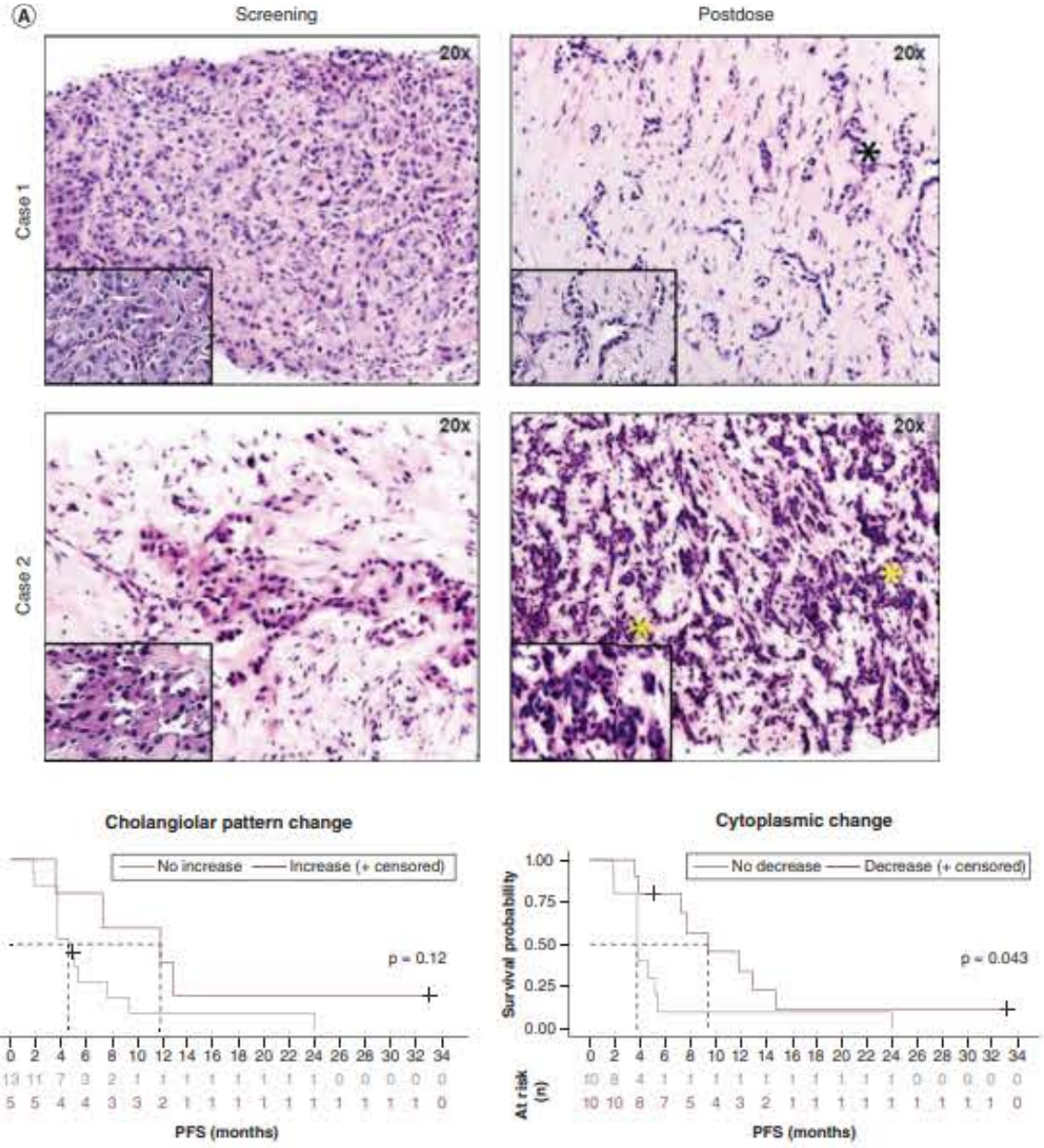
Phase III Trials of FGFR inhibitors vs Gemcitabine/Cisplatin for *FGFR2* fusion or rearrangement+ cholangiocarcinoma

Frequency of FGFR2 fusions in Intrahepatic Cholangiocarcinoma: 10-15%



IDH1 Mutation as a Therapeutic Target in ICC

- Isocitrate dehydrogenase-1 (*IDH1*) mutations occur in ~15% of ICC, very rare in other subsites
  - Result in accumulation of oncometabolite 2-hydroxyglutarate (2-HG) which blocks cell differentiation
- Inhibition of mIDH1 leads to cell differentiation and maturation, reduced proliferation
  - Tumor morphologic changes (e.g. cholangiolar pattern, decreased cytoplasm) and upregulation of hepatocyte differentiation genes were associated with clinical benefit in a phase 1 trial of mIDH1 inhibitor, ivosidenib (AG-120)
    - n=21 patients with paired samples



Boscoe et al J Gastrointest Oncol 20(4) 2019; Aguado-Fraile et al. Future Oncol (epub 3/12/21)

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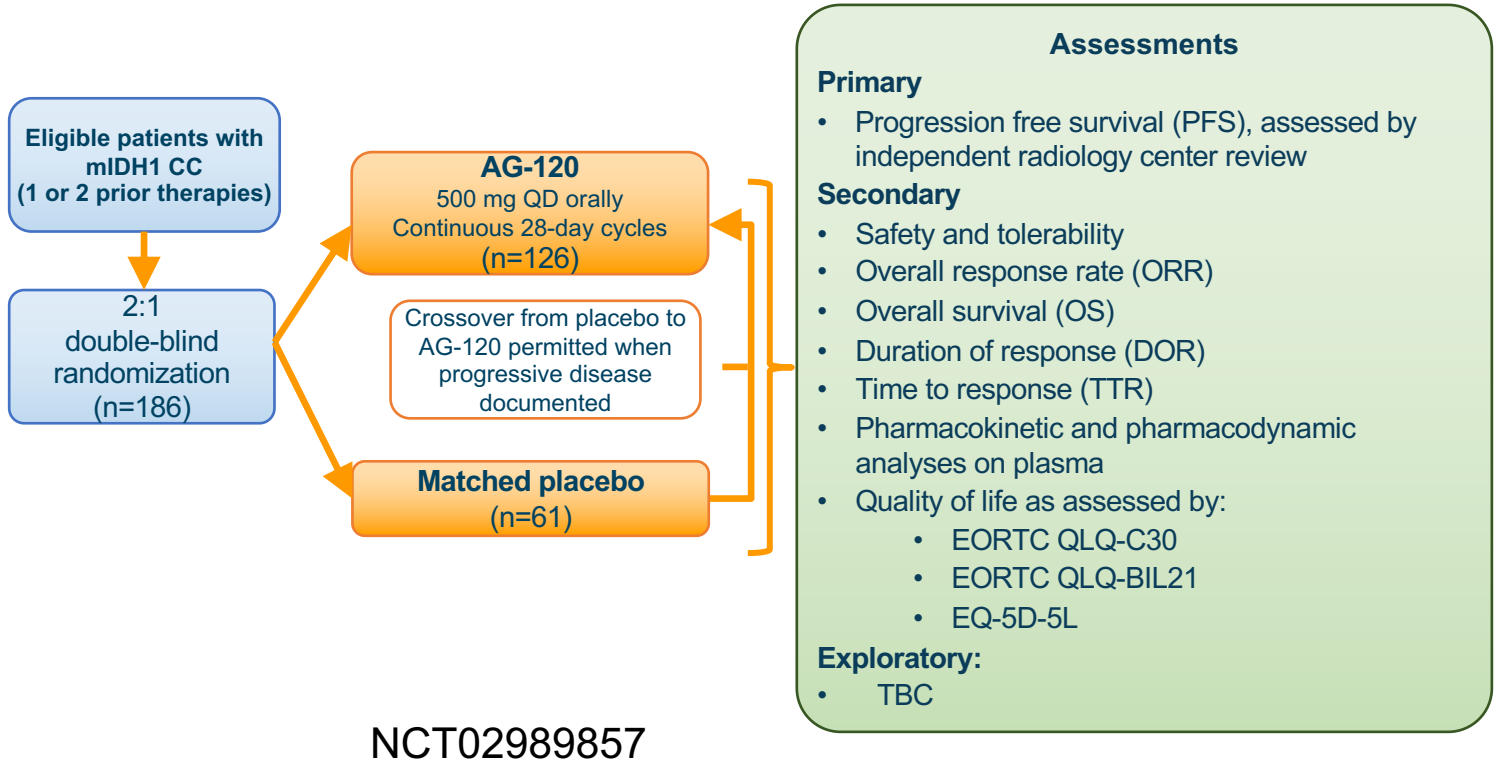
Ivosidenib (AG-120) for *mIDH1* iCCA

- Ivosidenib (AG-120) is a selective oral inhibitor of mutant IDH1
- Showed safety and median PFS of 3.8 months in phase 1 trial
- ClarIDHy was a randomized, phase 3 trial of ivosidenib vs. placebo:
  - N=187 patients with CCA
  - *IDH1* mutation centrally confirmed (Oncomine assay)
  - Documented progression after 1-2 prior therapies including gemcitabine or 5-FU-based

Phase 3 ClarIDHy Trial



NCT02989857

Abou-Alfa et al. Lancet Oncol 21(6) 2020; Zhu et al. 2021;7(11)

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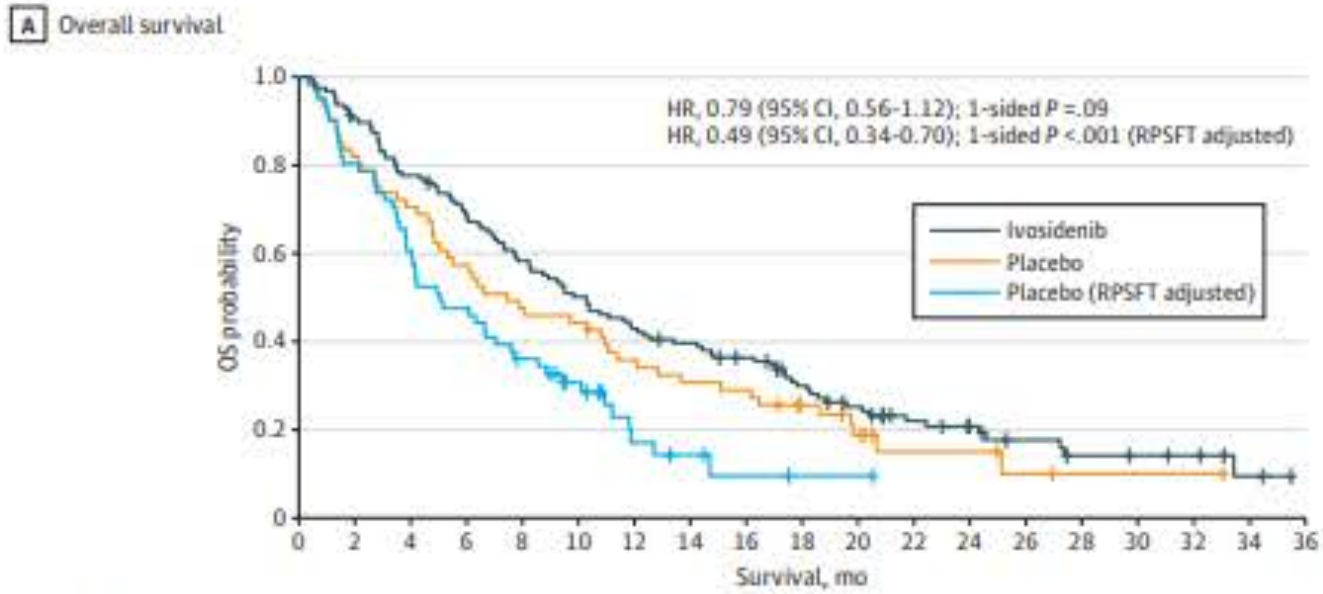
ClarIDHy Outcomes

- Outcomes for ivosidenib vs. placebo:
  - Median PFS 2.7 vs. 1.4 months (HR 0.37)
  - Median OS 10.3 vs. 7.5 months (HR 0.79)
  - ORR 2% vs. 0
- Most common TEAEs for ivosidenib:
  - Ascites (7%), anemia (7%), increased bilirubin (6%), hyponatremia (10%)
- Discontinuation for AE in 6% for ivosidenib, 8% for placebo
- EORTC QLQ-C30 physical functioning scores favored ivosidenib arm
- Ivosidenib approved by USFDA 8/25/21



Treatment group	Events/patients, No.	OS, median (95% CI), mo
Ivosidenib	100/126	10.3 (7.8-12.4)
Placebo	50/61	7.5 (4.8-11.1)
Placebo adjusted by RPSFT	49/61	5.1 (3.8-7.6)

RPSFT: Rank-preserving structural failure time

Abou-Alfa et al. Lancet Oncol 21(6) 2020; Zhu et al. 2021;7(11)

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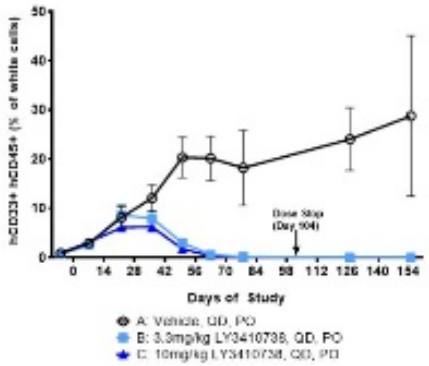
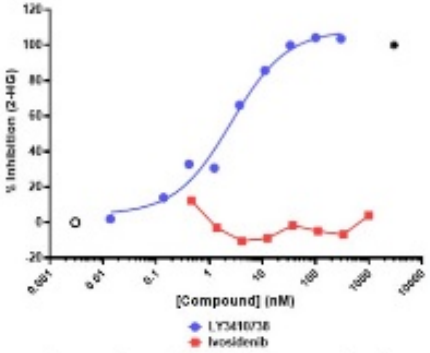
First-in-Class Covalent mIDH1/2 Inhibitor: LY3410738

- Potent, selective, covalent mIDH1 and mIDH2 inhibitor
- Binds outside dimer interface enabling activity in setting of 2nd site *IDH1* mutations
- Phase 1 trials ongoing in patients with AML and advanced solid tumors with mIDH1 R132X and mIDH2 R140X or R172X

Efficacy in mIDH1 AML Model[13]



2-HG inhibition in mIDH1 R132H_S280F Cells[13]



* Represents results using cell-free controls

Dose Escalation Cohort

LY3410738 monotherapy (oral) in patients with mIDH1 R132 solid tumors

- Dose level 5
- Dose level 4
- Dose level 3
- Dose level 2
- Dose level 1

RP2D

Dose Expansion Cohorts

All patients in the dose expansion cohorts will have mIDH1 R132

Cohort 1
- LY3410738 (monotherapy RP2D)
- Patients with cholangiocarcinoma with measurable disease
- Patients who have received a prior therapy

Cohort 2
- LY3410738 (monotherapy RP2D)
- Patients with non-cholangiocarcinoma and measurable disease
- Patients who have received standard therapy

Cohort 3
- LY3410738 (monotherapy RP2D)
- Patients with solid tumor and non-measurable disease
- Patients who have received standard therapy

Cohort 4
- Combination of LY3410738 (RP2D) with cisplatin (i.v. 25 mg/m^2) plus gemcitabine (i.v. 1000 mg/m^2) on D1, D8 of 21-day cycles
- Patients with cholangiocarcinoma and measurable disease
- Patients who have not received prior therapy

NCT04521686

Salama et al. AACR Annual Meeting 2020, Abstract 6417; Pauff et al. GI ASCO 2021, TPS Abstract 350; Clinicaltrials.gov

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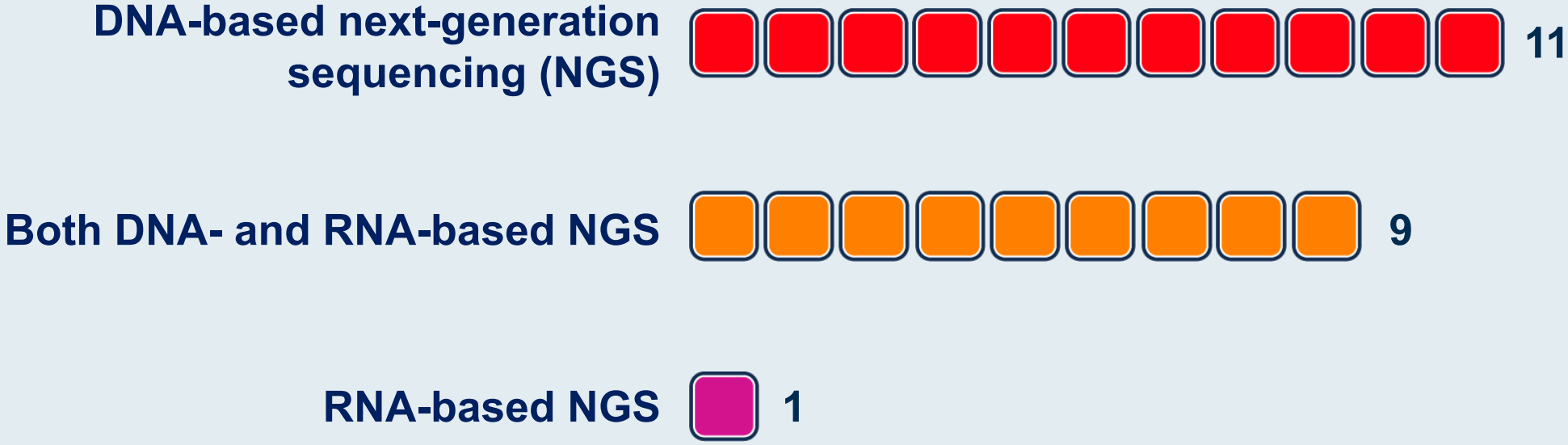
Conclusions and Future Directions

- *FGFR2* fusions or rearrangements are present in ~10-15% of iCCA
  - 2 ATP-competitive FGFR1-3 inhibitors are now approved by USFDA after progression on prior chemotherapy: pemigatinib, infigratinib
  - Polyclonal kinase domain mutations are common mechanism of resistance
- Next-generation inhibitors include covalent pan-FGFR inhibitor futibatinib and selective FGFR2 inhibitor RLY-4008
- *IDH1* mutations are present in ~15% of iCCA
  - mIDH1 inhibitor ivosidenib improved PFS in phase 3 ClarIDHy trial after 1-2 prior lines of therapy leading to FDA approval
  - Covalent inhibitors of both mutant IDH1 and IDH2 in development
- Activity in earlier stages of treatment and combination strategies are being studied

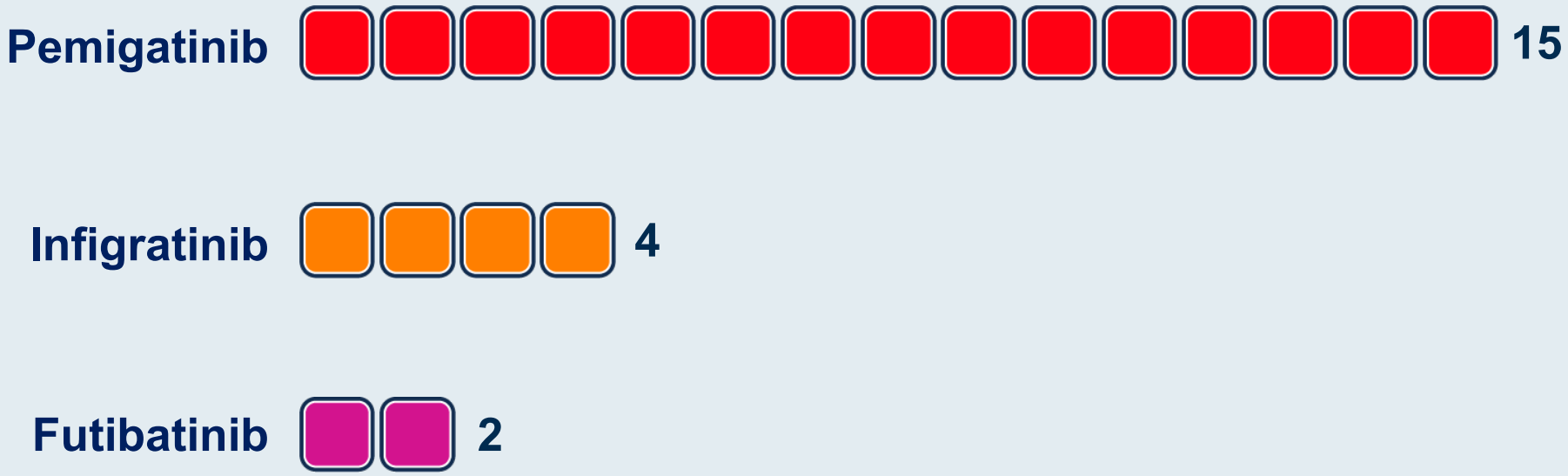
Clinical Investigator Survey Results

Which assay(s) do you generally use to test for targetable mutations in your patients with advanced biliary tract cancers?



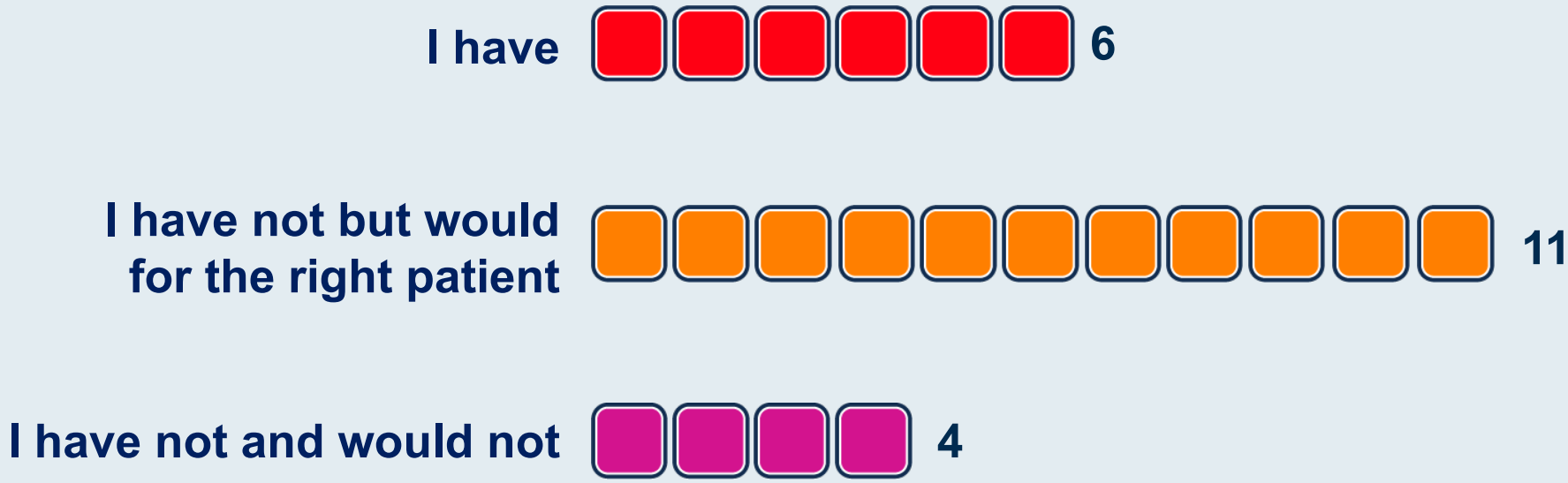
Survey of Gastrointestinal Cancers Clinical Investigators

Regulatory and reimbursement issues aside and assuming all of these agents were available, what would be your preferred second-line systemic treatment for a 65-year-old patient with metastatic cholangiocarcinoma with an FGFR2 fusion who experienced disease progression on first-line cisplatin/gemcitabine?



Survey of Gastrointestinal Cancers Clinical Investigators

Have you administered or would you administer an alternative FGFR inhibitor to a patient with metastatic cholangiocarcinoma with an FGFR2 fusion who had experienced disease progression on another FGFR inhibitor?

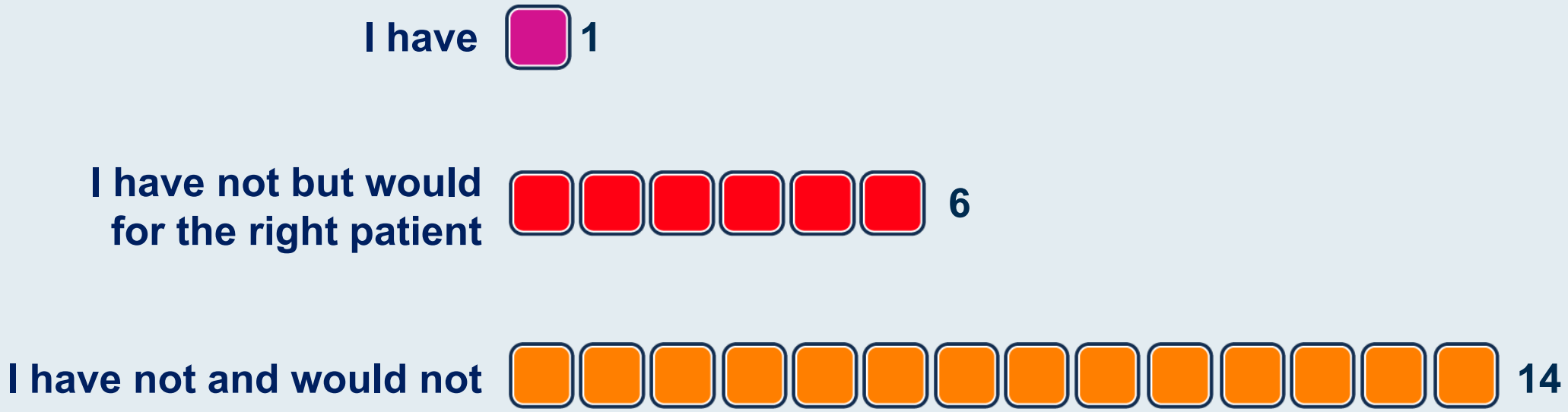


Survey of Gastrointestinal Cancers Clinical Investigators

What would be your preferred second-line systemic treatment for a 65-year-old patient with metastatic cholangiocarcinoma with an IDH1 mutation who experienced disease progression on first-line cisplatin/gemcitabine?

Survey of Gastrointestinal Cancers Clinical Investigators

Have you administered or would you administer ivosidenib in combination with cytotoxic therapy to a patient with metastatic cholangiocarcinoma with an IDH1 mutation outside of a protocol setting?



Survey of Gastrointestinal Cancers Clinical Investigators

MODULE 4: Future Directions in the Management of Biliary Tract Cancers — Dr Bekaii-Saab

RTP
RESEARCH
TO PRACTICE

Future Directions in the Management of Biliary Tract Cancers (BTC)

Tanios Bekaii-Saab, MD ,FACP
Program Leader, GI Cancer, Mayo Clinic Cancer Center
Professor , Mayo Clinic College of Medicine and Science
Consultant, Mayo Clinic AZ
Chair , ACCRU Consortium

Tanios Bekaii-Saab, MD — Disclosures
Moderator

Advisory Committee	Immuneering Corporation, Imugene, Sun Biopharma
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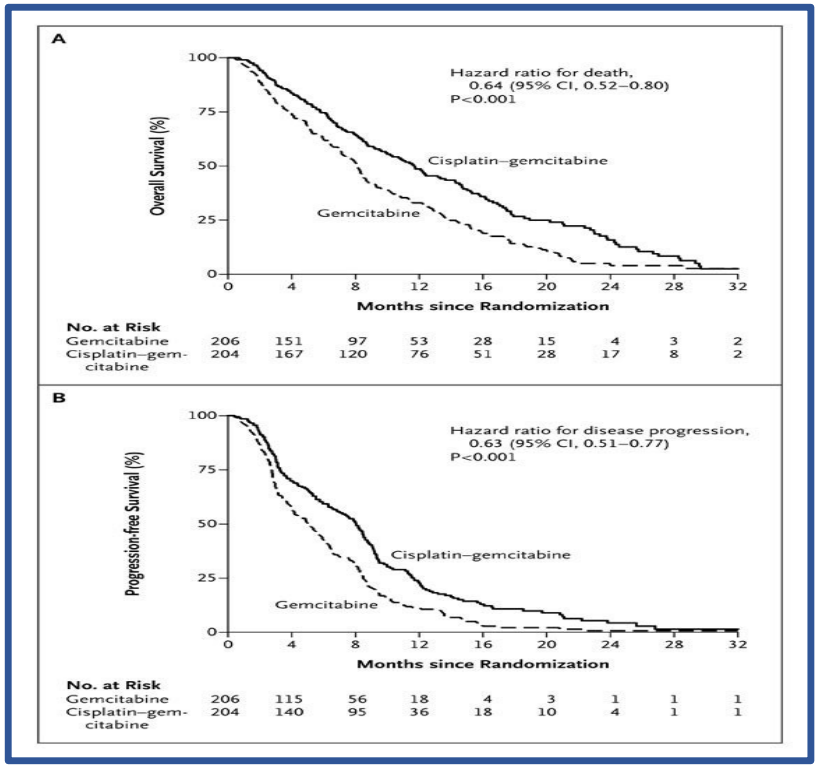
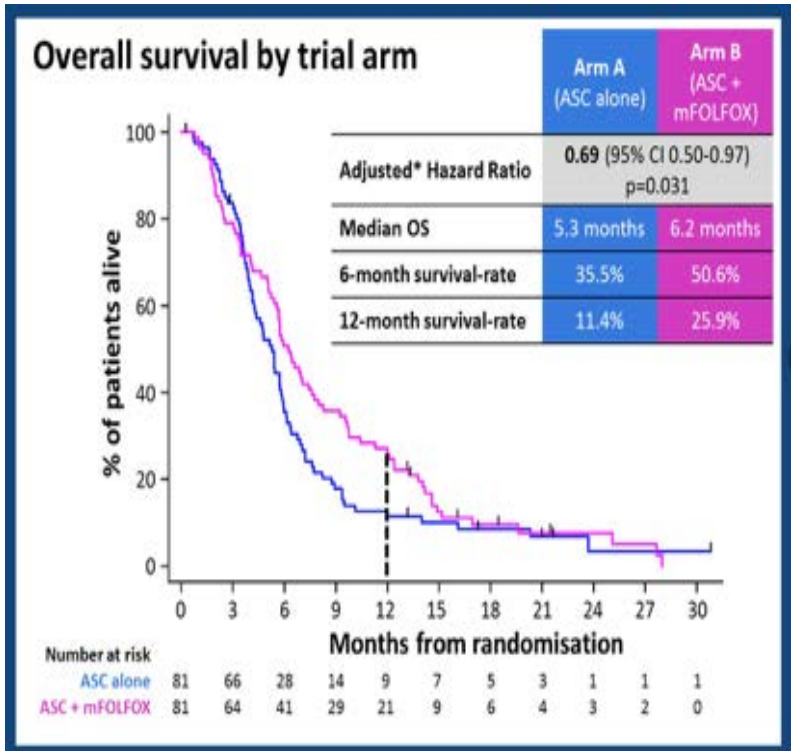
Data and Safety Monitoring Board/Committee	1Globe Health Institute, AstraZeneca Pharmaceuticals LP, Exelixis Inc, FibroGen, Kintor, Lilly, Pancreatic Cancer Action Network
Inventions/Patents	WO/2018/183488, WO/2019/055687

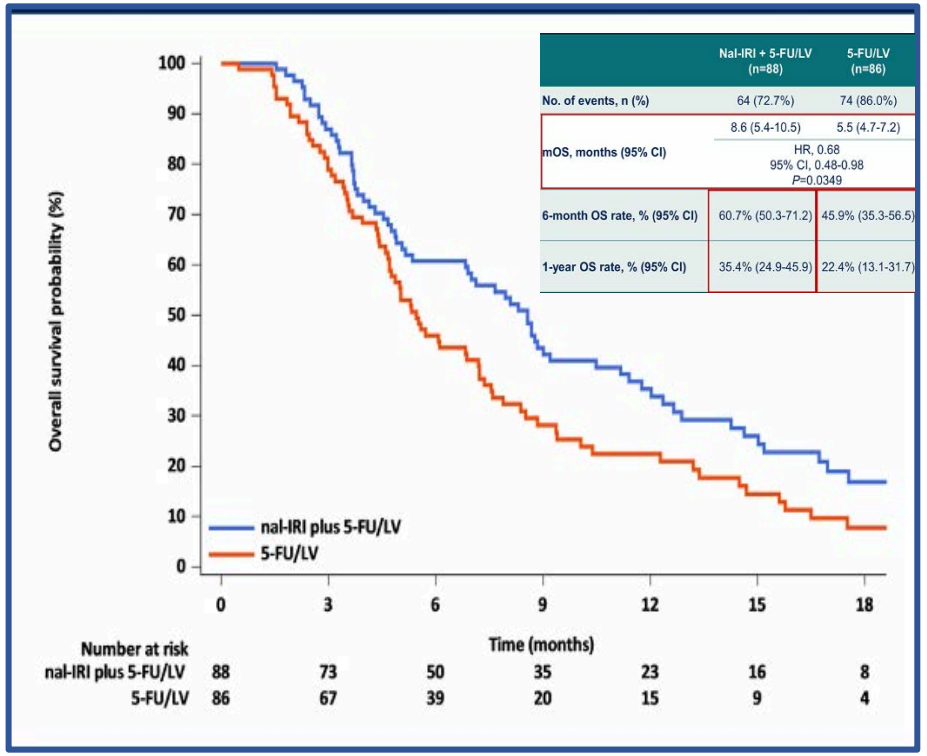
Chemotherapy is Marginally Effective in Unselected CCA



Valle J et al. N Engl J Med 2010;362:1273-1281.



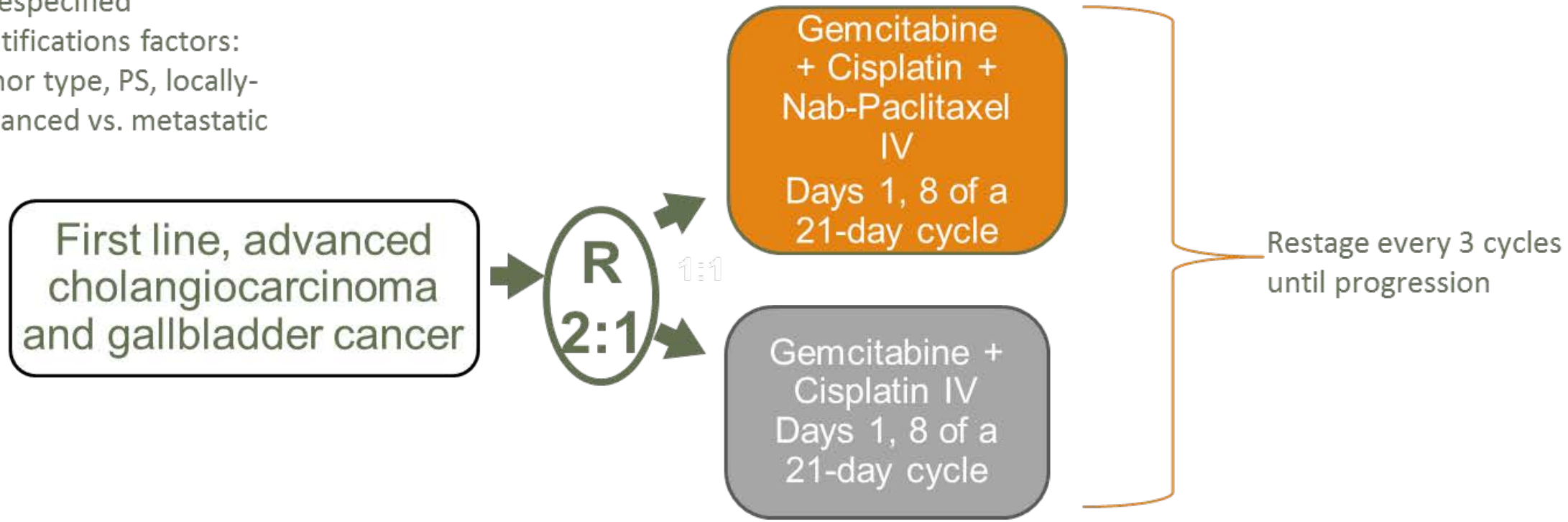
Lamarca A et al . ASCO 2019



Yoo C et al . ASCO 2021

S1815: study design

*Prespecified stratifications factors: tumor type, PS, locally-advanced vs. metastatic

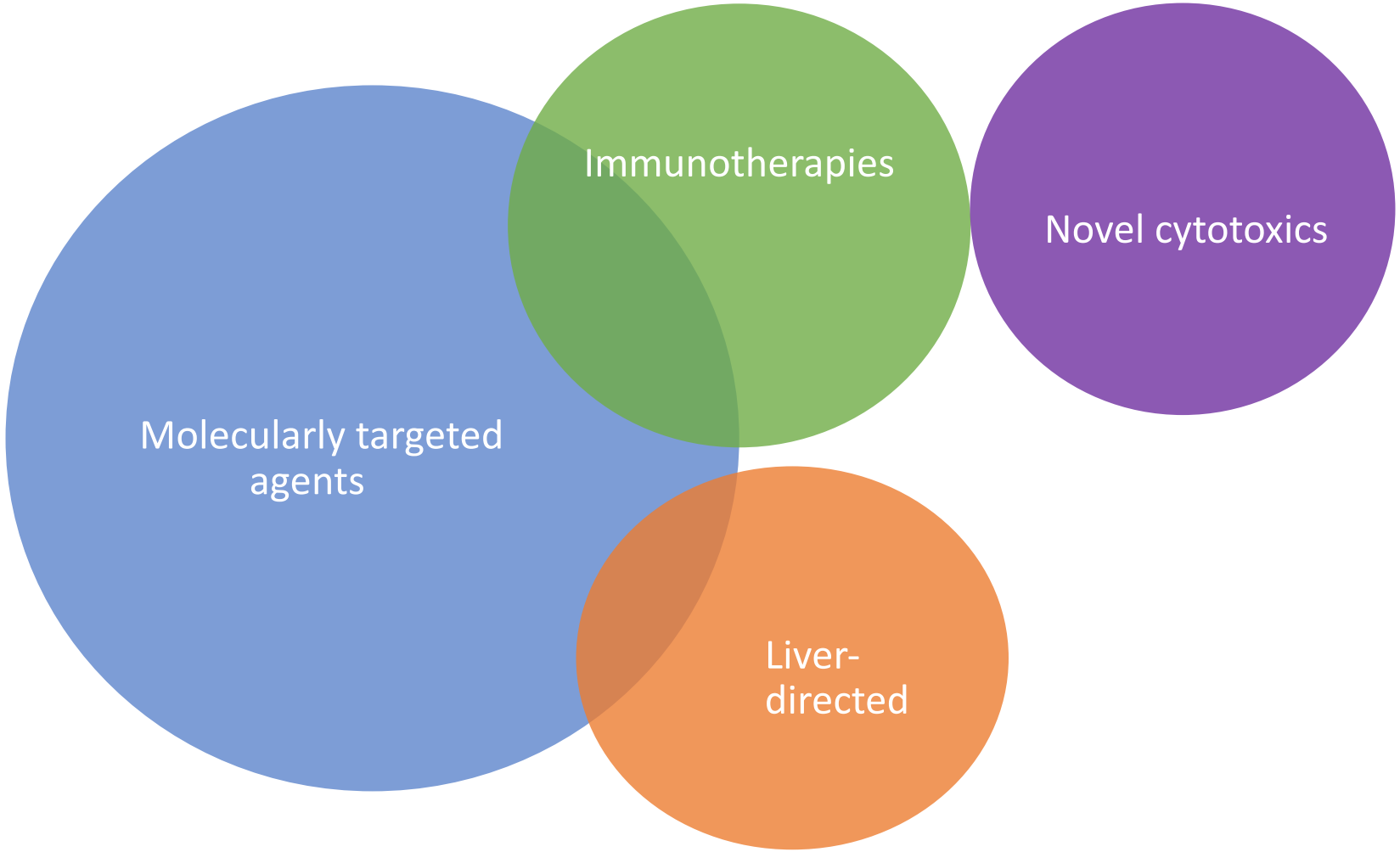


Primary EP: OS
Secondary: ORR, PFS, DCR, safety, CA 19-9 changes

Archival blood and tissue specimens to be banked

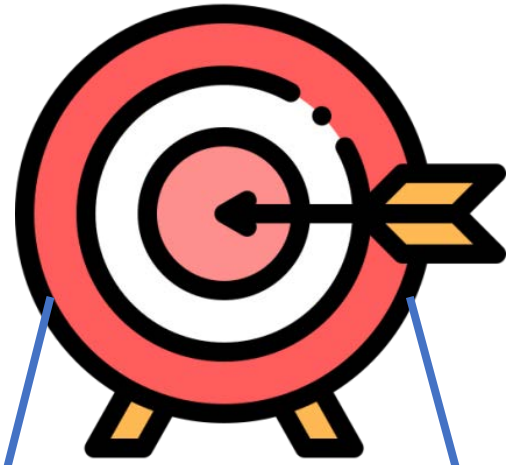
NIH 2020. NCT03768414. https://clinicaltrials.gov/ct2/show/NCT03768414. Accessed 7 January 2021

Classes of novel therapeutics under investigation for BTC



Approaches to evaluating targeted therapy in an uncommon cancer

Target-specific cholangiocarcinoma trial



IDH1

FGFR2

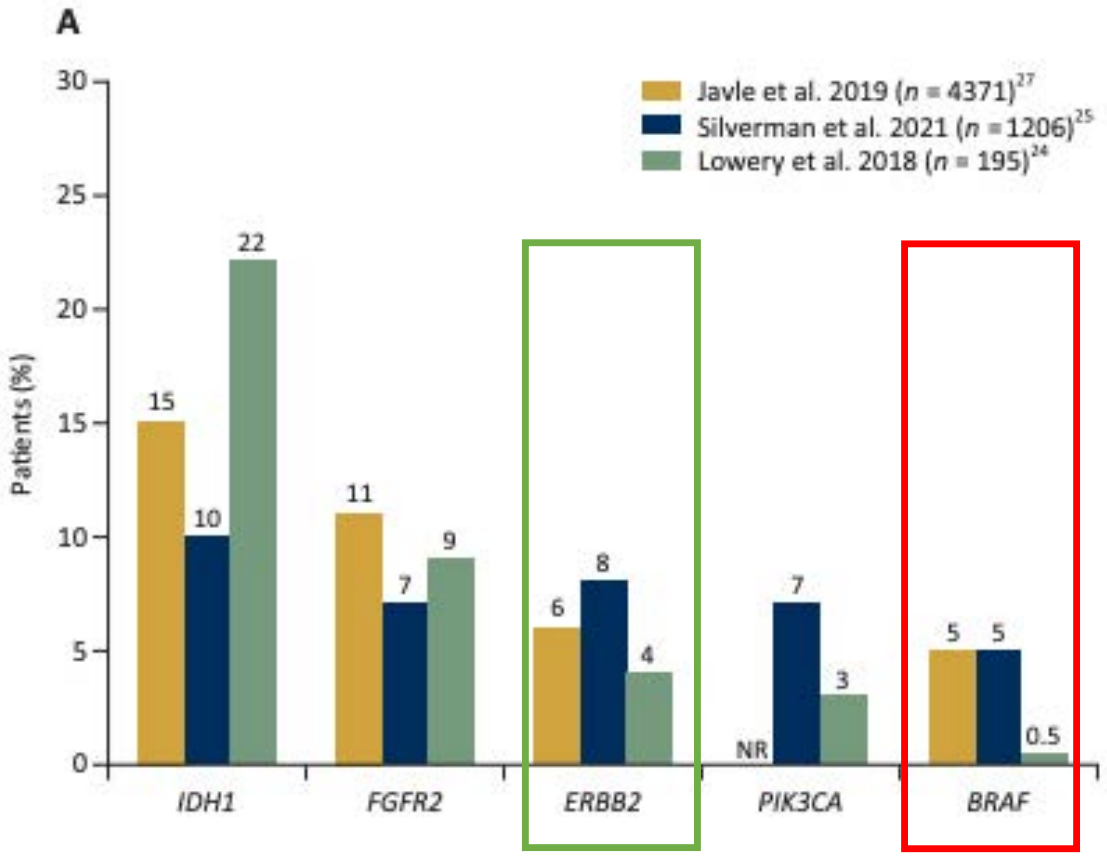
Target-specific all-comer basket trial with biliary cohort

BRAF, NTRK, and MSI

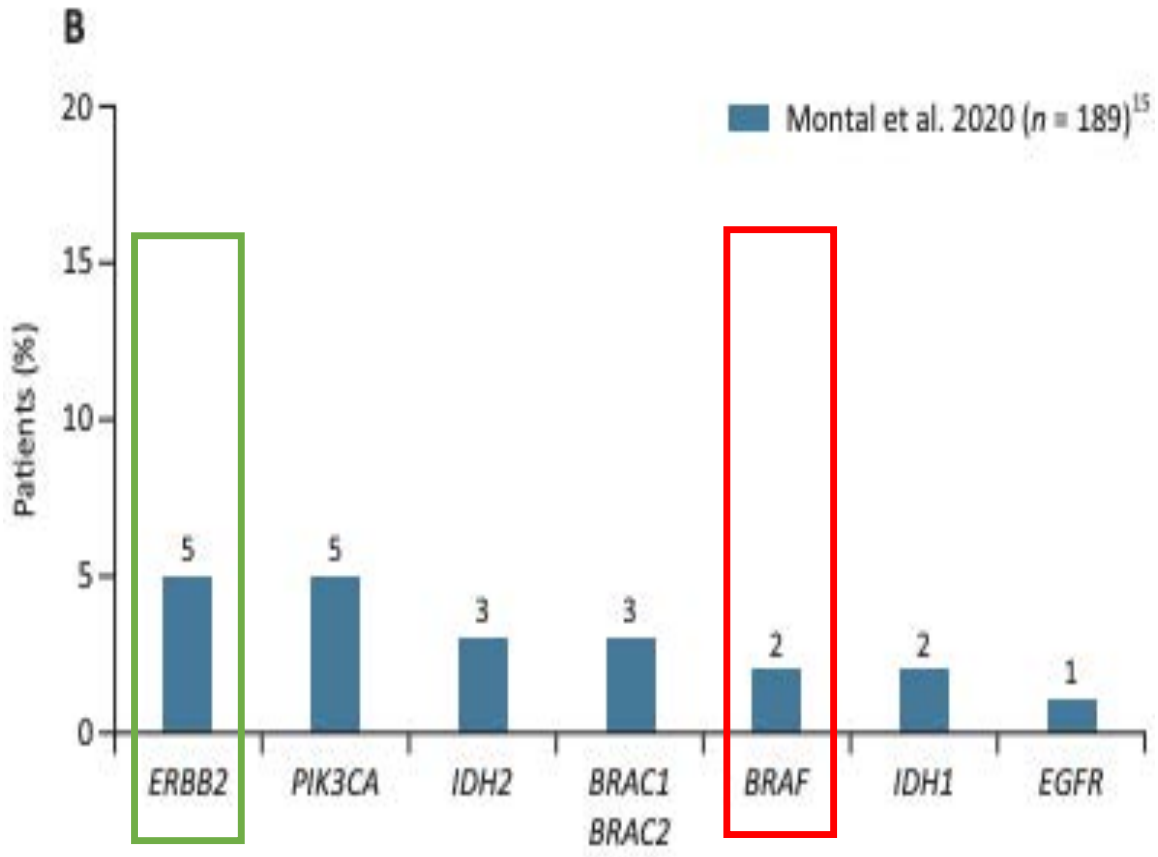
Biliary Umbrella/Basket trial with target-specific arms

ABC10/SAFIR*

Commonly altered genes with actionable alterations in cholangiocarcinoma (CCA)



Intrahepatic CCA (iCCA)



Extrahepatic CCA (eCCA)

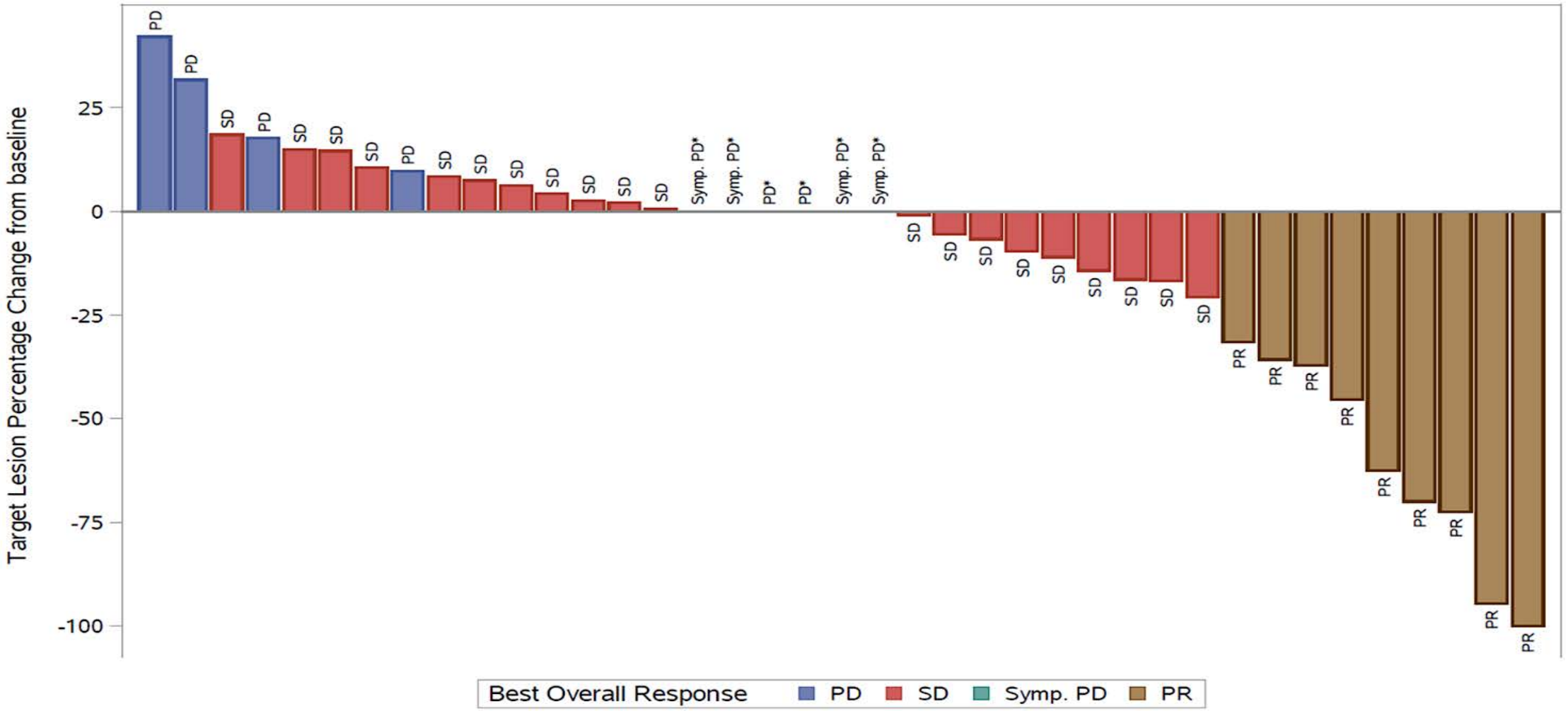
Bekaii-Saab T , et al. *Annals of Oncology* ; 2021

Molecular heterogeneity: Western vs Asian CCA patients

Modulator genes of dysregulation pathways or gene subgroups with statistically significant levels between the two patient cohorts

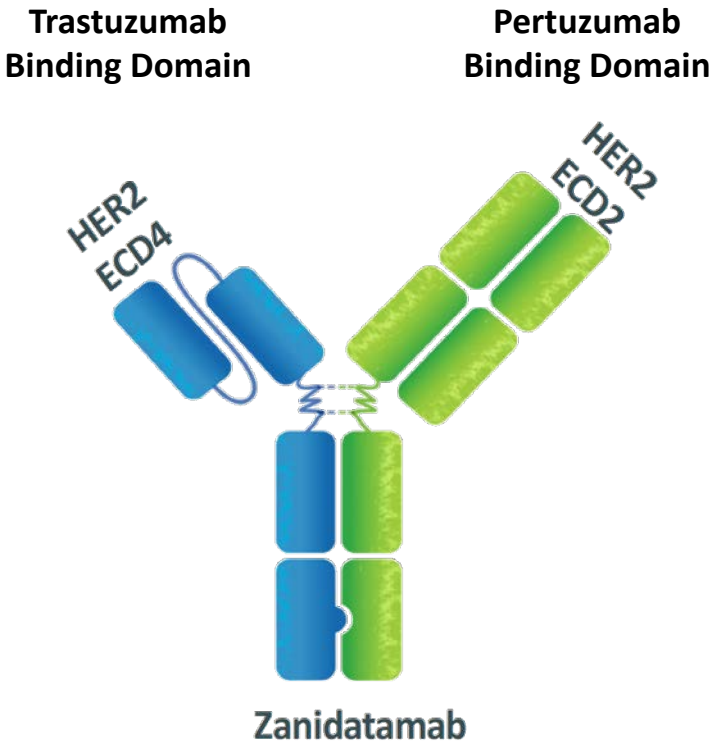
Cao J, et al. *JCO Precis Oncol* 2020;4:557–569

Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway)



Javle M, et al. *Lancet Oncol* 2021

Zanidatamab, a Bispecific HER2-Targeted Antibody for HER2-expressing BTC



- Zanidatamab (also known as ZW25) is a humanized, bispecific, immunoglobulin G isotype 1 (IgG1)-like antibody directed against the juxtamembrane domain (ECD4) and the dimerization domain (ECD2) of HER2

- Zanidatamab's unique binding properties result in:
  - Receptor clustering, internalization, and downregulation
  - Inhibition of growth factor-dependent and –
  - Independent tumor cell proliferation – Antibody-dependent cellular cytotoxicity and phagocytosis, and complement-dependent cytotoxicity

Meric-Bernstam et al, *J Clin Oncol* 2021

Zanidatamab, a Bispecific HER2-Targeted Antibody for HER2-expressing BTC

Phase I Study: BTC Patients

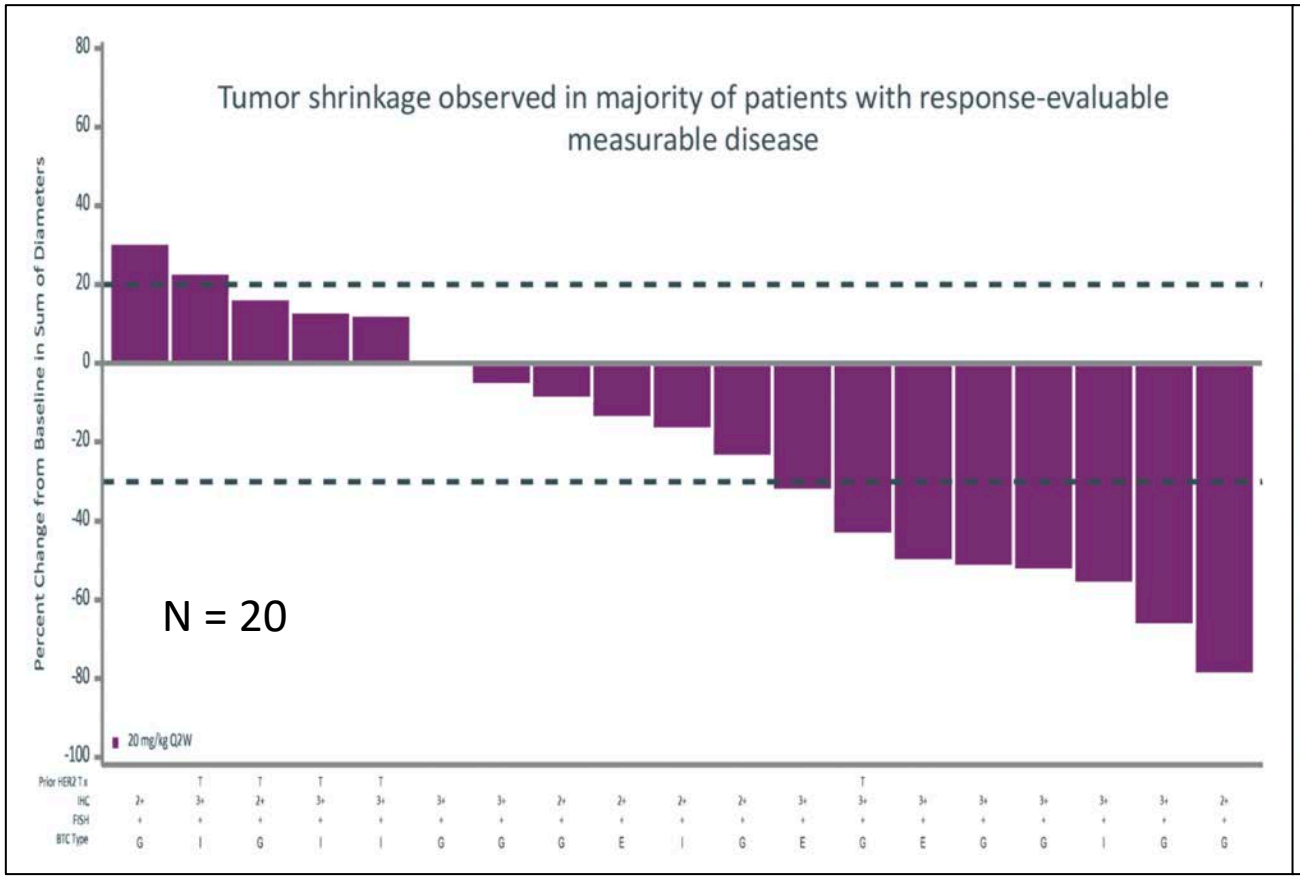


Table 3: Disease Response Endpoints[a] and DOR	(N = 20)
Confirmed objective response, n (%) (95% CI)	8 (40) (19.1, 63.9)
Partial response	8 (40)
Stable disease	5 (25)
Progressive disease	7 (35)
Disease control rate, n (%)	13 (65)

Duration of response,[b] months	(N=8)
Median (95% CI)	7.4 (3.2, NE)

DOR=duration of response; NE= not estimable.
a, per Investigator Assessment using RECIST 1.1 in response-evaluable patients; b, in response-evaluable patients who had a complete or partial response followed by at least one more response assessment.

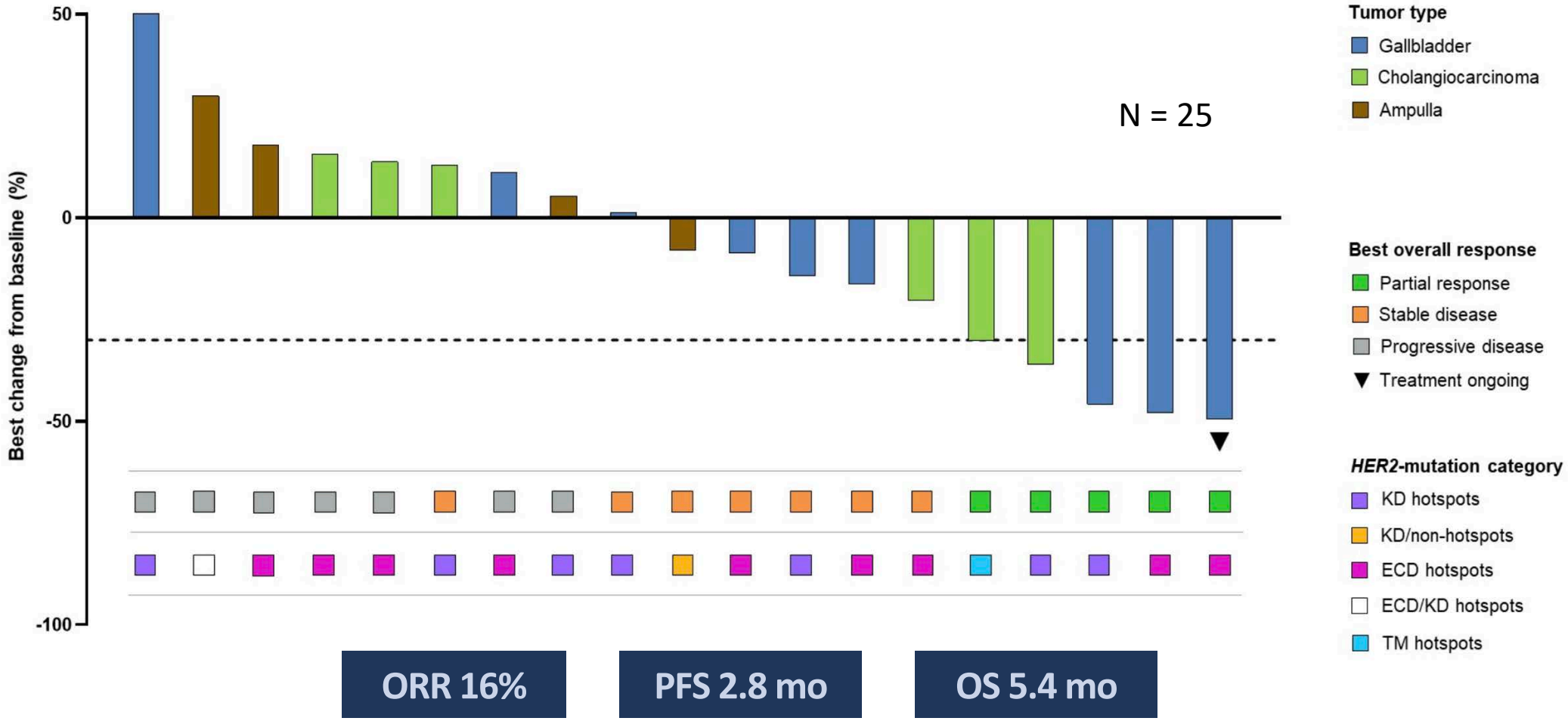
Meric-Bernstam et al, *J Clin Oncol* 2021

Table 2: Zanidatamab-related AEs

	(N = 21)
Patients with treatment-emergent AEs, n (%)	21 (100)
Patients with zanidatamab-related AEs (occurring in ≥ 15% of BTC patients)	
Any, n (%)	15 (71)
Diarrhea	9 (43)
Infusion-related reaction	7 (33)

Neratinib, a TKI for Activating HER2 Mutations

Phase II SUMMIT Study: BTC Patients

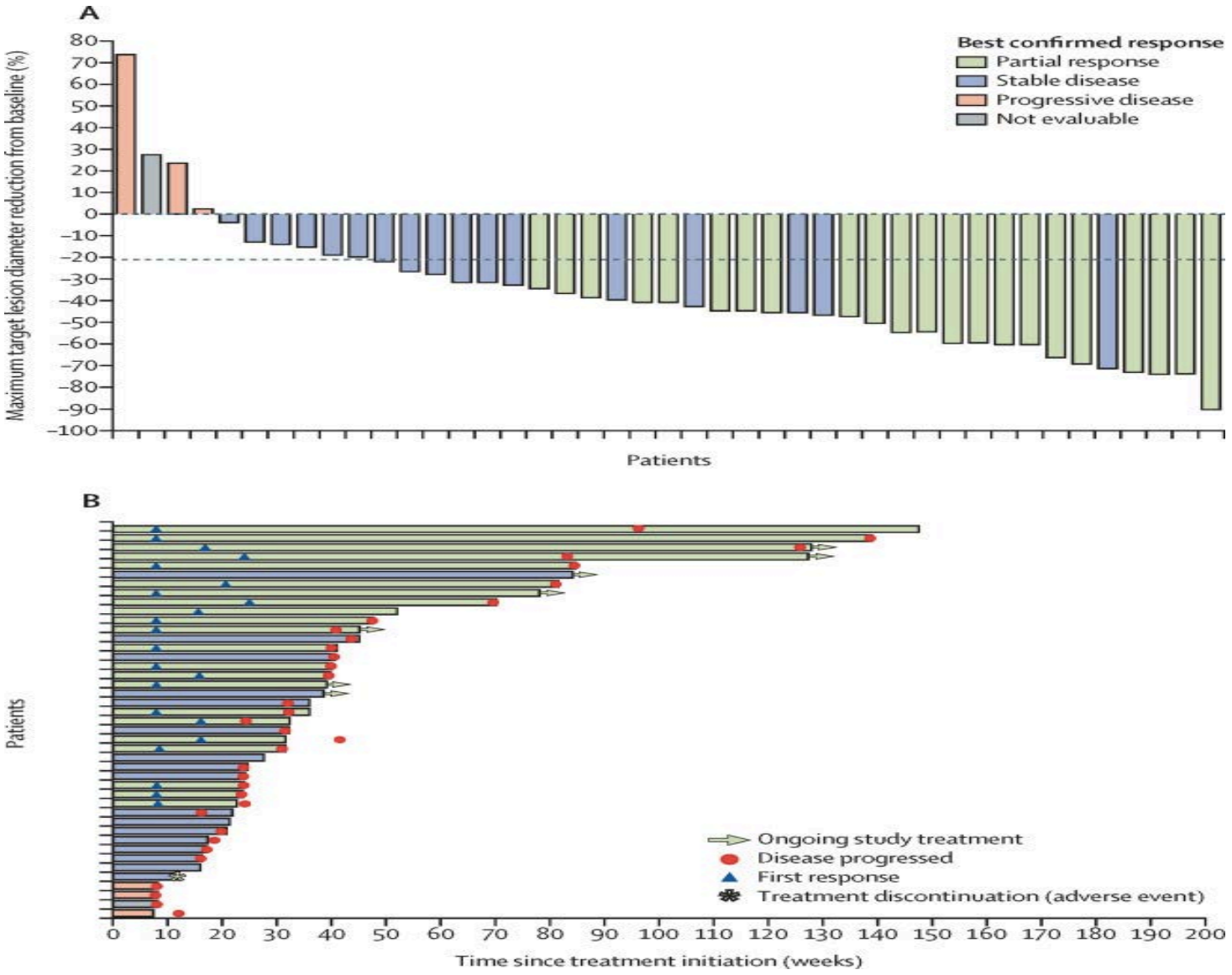


ORR 16% | **PFS 2.8 mo** | **OS 5.4 mo**

Harding, *ASCO GI 2021*

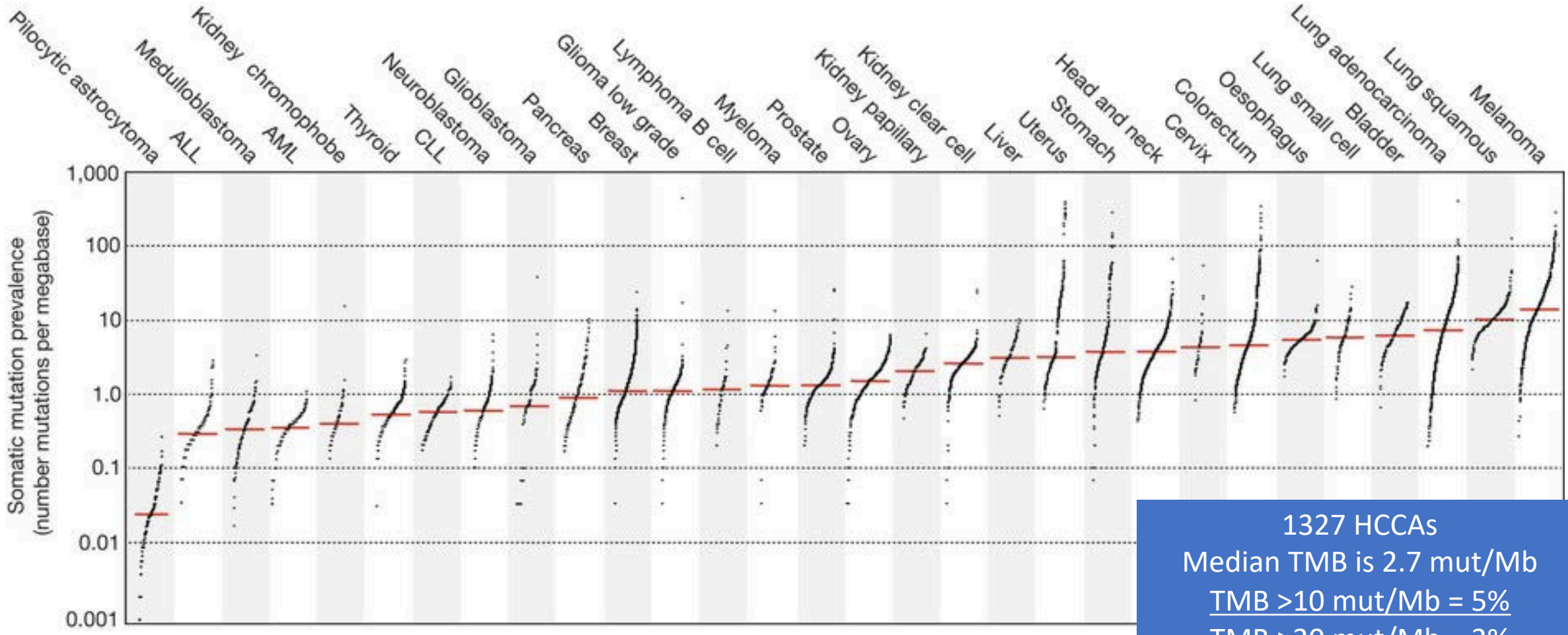
BRAF V600E mutated cholangiocarcinoma : The ROAR Basket Trial

Efficacy of
Dabrafenib + Trametinib



Subbiah V, et al. *Lancet Oncol* 2020;21:1234–1243

Immunotherapy: mutation load



1327 HCCAs
Median TMB is 2.7 mut/Mb
TMB >10 mut/Mb = 5%
TMB >20 mut/Mb = 2%
MSI high = 1%

Alexandrov LB, et al. *Nature* 2013;500:415–421

Summary of efficacy results from immunotherapy studies in BTC

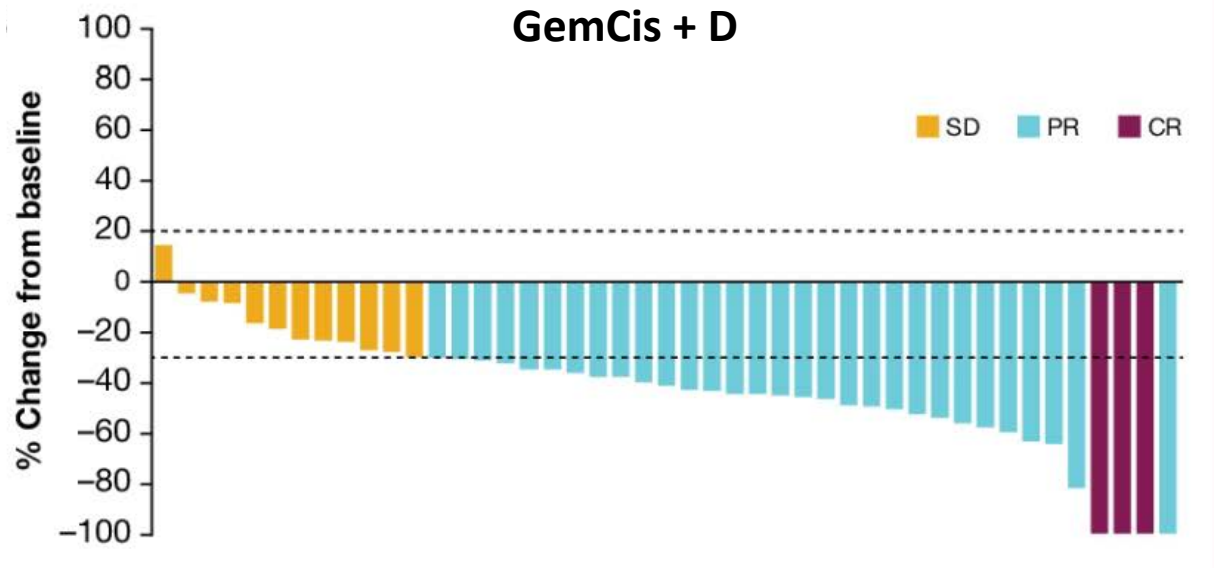
Study	Agent(s)	Line of therapy	Patients (n)	ORR	DCR	PFS	OS
KEYNOTE-158[1]	**Pembrolizumab**	**≥2L**	**104 (BTC cohort)**	**6% (95% CI, 2.1–12.1)**	**22%**	**2.0 months (95% CI, 1.9–2.1)**	**9.1 months (95% CI, 5.6–10.4)**
Kim R, et al[2]	Nivolumab	≥2L	54 (46 evaluable for response)	IR: 22% ICR: 11%	IR: 59% ICR: 50%	ITT: 3.7 months (95% CI, 2.3–5.7)	ITT: 14.2 months (95% CI, 6.0–NR)
Kelley RK, et al[3]	**Pembrolizumab + GM-CSF**	**≥2L**	**27**	**19% (95% CI, 3–34)**	**33%**	**6-month PFS: 35% (95% CI, 15–54)**	**NR**
Klein O, et al[4]	Nivolumab + ipilimumab	≥1L	39	23%	44%	2.9 months (95% CI, 2.2–4.6)	5.7 months (95% CI, 2.7–11.9)
Ueno M, et al[5]	**Nivolumab**	**≥2L**	**30**	**3% (90% CI, 0.7–13.6)**	**23% (90% CI, 13.2–37.9)**	**1.4 months (90% CI, 1.4–1.4)**	**5.2 months (90% CI, 4.5–8.7)**
	Nivolumab + GemCis	**1L**	**30**	**37% (90% CI, 23.9–51.7)**	**63% (90% CI, 48.3–76.1)**	**4.2 months (90% CI, 2.8–5.6)**	**15.4 months (90% CI, 11.8–NE)**
Ioka T, et al[6]	Durvalumab	≥2L	42	5% (95% CI, 0.6–16.2)	17%	1.5 months (95% CI, 1.4–2.6)	8.1 months (95% CI, 5.6–10.1)
	Tremelimumab + durvalumab		65	11% (95% CI, 4.4–20.9)	32%	1.6 months (95% CI, 1.4–2.8)	10.1 months (95% CI, 6.2–11.4)

1. Ueno M et al. Presented at: ESMO Congress 2018; 19–23 October 2018; Munich, Germany. Abs 4525; 2. Kim R et al. *JAMA Oncol* 2020;6:888–894; 3. Kelley RK, et al. Presented at: ASCO Annual Meeting 2018; 1–5 June 2018; Chicago, IL. Abs 4087; 4. Klein O, et al. Poster presented at: ASCO Annual Meeting 2020; 29–31 May, 2020. Pos 196; 5. Ueno M, et al. *Lancet Gastroenterol Hepatol* 2019;4:611–621; 6. Ioka T, et al. Poster presented at: ASCO GI; 17–19 January 2019; San Francisco, CA. Poster 387

ICR, independent central review; IR, investigator review; ITT, intent-to-treat; NE, not estimable; NR, not reached

First-line GemCis + durvalumab in BTC

Characteristic	Biomarker cohort n=30	GemCis plus D cohort n=45
ORR, % (95% CI)	50.0 (32.1–67.9)	**73.4 (60.5–86.3)**
Complete response	6.7 (0–15.6)	6.7 (0–14.0)
Partial response	43.3 (25.6–61.0)	66.7 (52.9–80.5)
Stable disease	46.7 (28.8–64.6)	26.7 (13.8–39.6)
Disease progression	3.3 (0–9.7)	0
DCR, % (95% CI)	96.7 (90.3–100)	**100.0 (100.0–100.0)**
Median DoR, months (95% CI)	11.0 (3.9–18.1)	**9.8 (8.1–11.4)**



Oh D-Y, et al. Poster presented at: 2020 ASCO Annual Meeting; 29–31 May, 2020. Poster 128

CI, confidence interval; D, durvalumab; DCR, disease control rate; DoR, duration of response; GemCis, gemcitabine plus cisplatin; ORR, objective response rate

Durvalumab or Placebo in Combination With Gemcitabine/Cisplatin in Patients With 1st Line Advanced Biliary Tract Cancer (TOPAZ-1); N=757

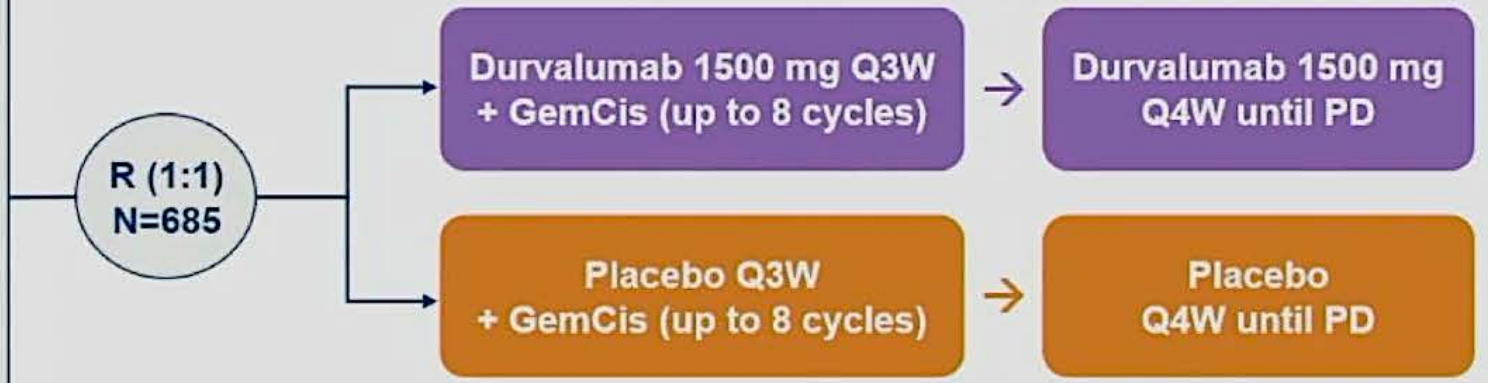
The combination of durvalumab (Imfinzi) and chemotherapy resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) compared with chemotherapy alone when used in the first-line treatment of patients with advanced biliary tract cancer, meeting the primary end point of the phase 3 TOPAZ-1 trial (NCT03875235). At the time of the predefined interim analysis, the regimen also resulted in improved progression-free survival (PFS) and overall response rate (ORR), which served as important secondary end points.

TOPAZ-1 study design

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)



Primary objective
- Overall survival

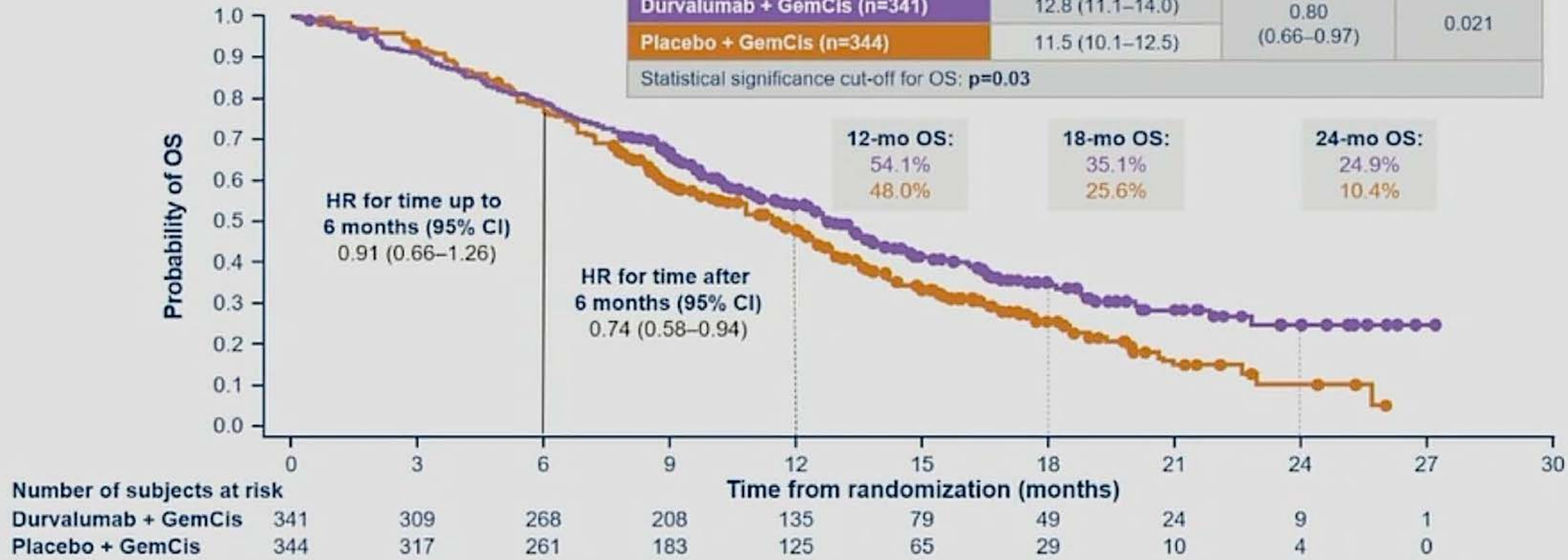
Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			

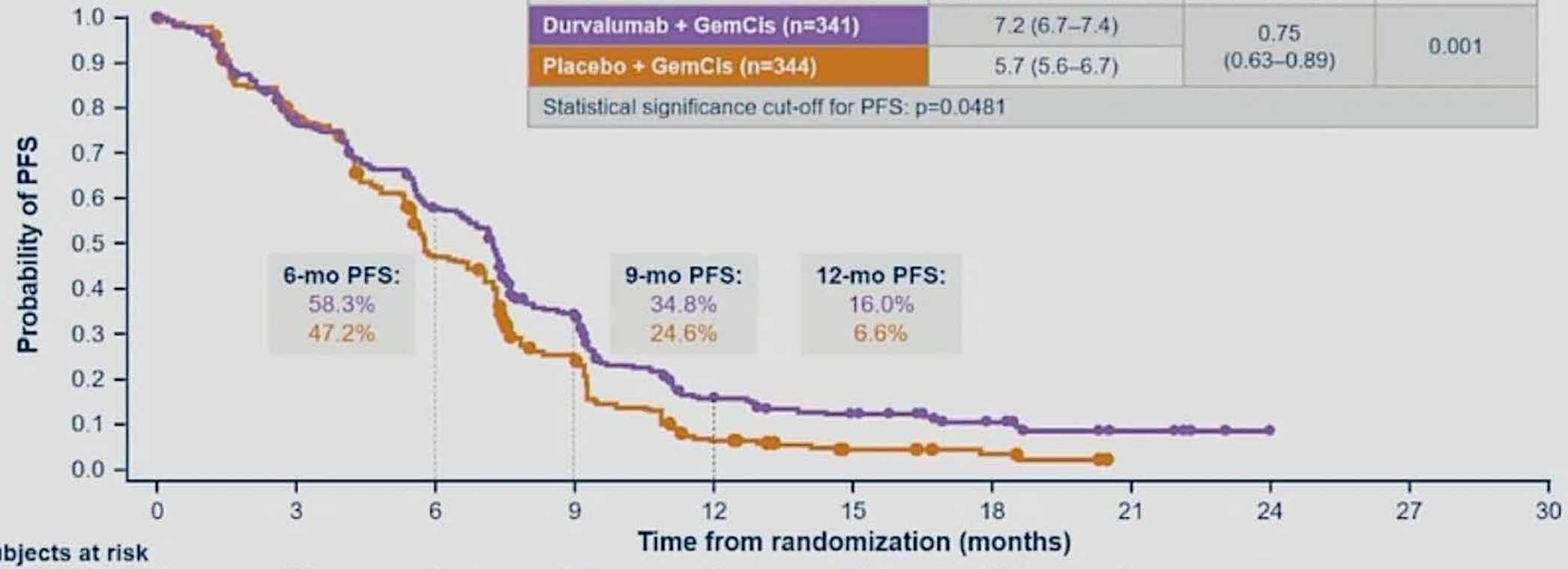


Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

Secondary endpoint: PFS

	Median PFS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	7.2 (6.7–7.4)	0.75 (0.63–0.89)	0.001
Placebo + GemCis (n=344)	5.7 (5.6–6.7)		
Statistical significance cut-off for PFS: p=0.0481			



Number of subjects at risk									
Durvalumab + GemCis	341	258	189	100	38	25	15	5	0
Placebo + GemCis	344	255	149	71	17	7	4	0	0

Median duration of follow-up (95% CI) was 9.2 (0.0–24.0) months with durvalumab + GemCis and 6.9 (0.0–20.4) months with placebo + GemCis.
CI, confidence interval; GemCis, gemcitabine and cisplatin; PFS, progression-free survival.

Summary of AEs and treatment exposure

	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Median duration of exposure (range), months		
Durvalumab/placebo	7.33 (0.1–24.5)	5.77 (0.2–21.5)
Gemcitabine	5.19 (0.1–8.3)	5.03 (0.2–8.6)
Cisplatin	5.13 (0.1–8.3)	4.88 (0.2–8.5)
Adverse event, n (%)		
Any AE	336 (99.4)	338 (98.8)
Any TRAE	314 (92.9)	308 (90.1)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any grade 3/4 TRAE	212 (62.7)	222 (64.9)
Any serious AE	160 (47.3)	149 (43.6)
Any serious TRAE	53 (15.7)	59 (17.3)
Any AE leading to discontinuation	44 (13.0)	52 (15.2)
Any TRAE leading to discontinuation	30 (8.9)	39 (11.4)
Any AE leading to death	12 (3.6)	14 (4.1)
Any TRAE leading to death	2 (0.6)	1 (0.3)
Any immune-mediated AE	43 (12.7)	16 (4.7)

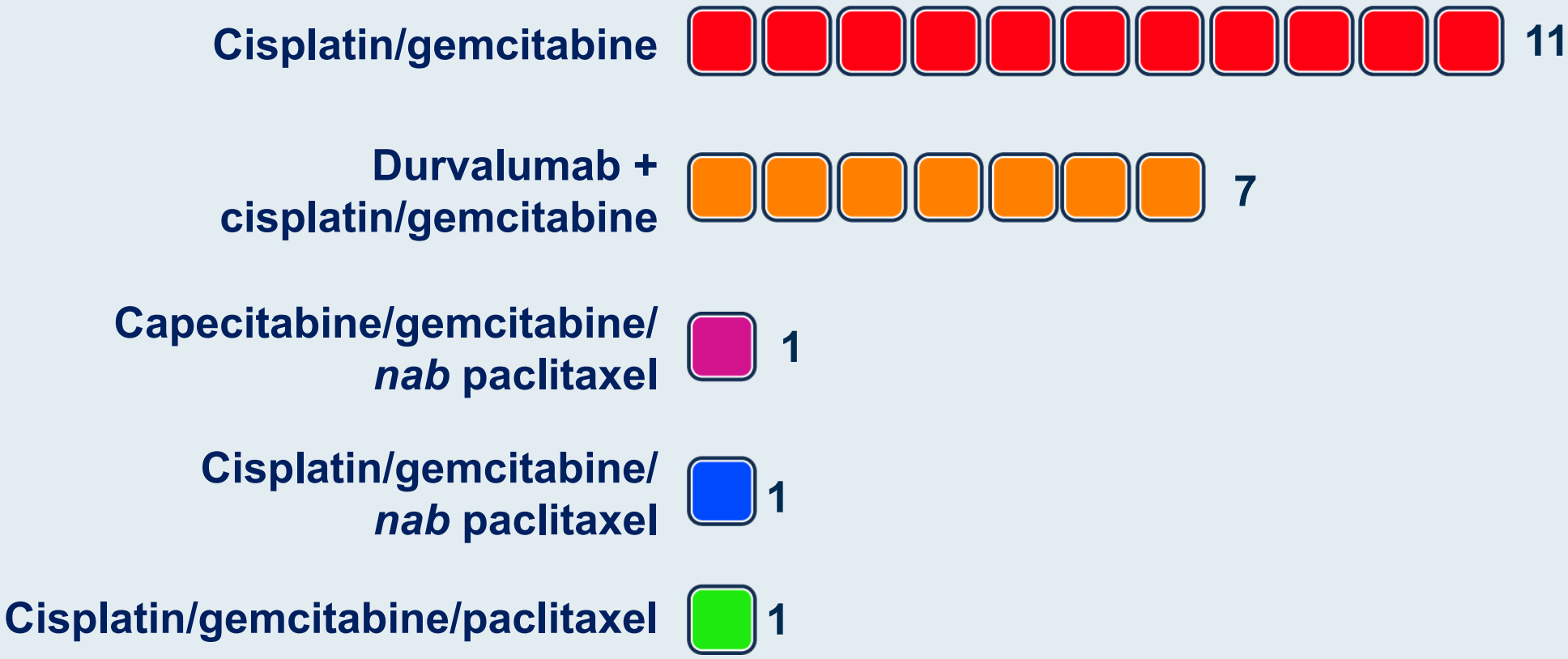
Includes AEs with onset date on or after the date of the first dose or AEs that worsened after the first dose. Includes AEs occurring up to 90 days following the date of the last dose or up to the first subsequent therapy.
AE, adverse event; GemCis, gemcitabine and cisplatin; TRAE, treatment-related adverse event.

Conclusions/Take-Away

- NGS (+ emerging liquid platforms) testing is central to future applications of novel therapies in Biliary Cancer
  - Applying genomic technology and molecular classification critically and timely in cholangiocarcinoma is changing the therapeutic landscape.
  - Ongoing efforts to expand the role of targeted therapies to IDH2, BRAF V600E, Her2 amplifications and others.
  - Drug resistance mechanisms and novel strategies to overcome drug resistance
- The role of immunotherapy in cholangiocarcinoma is being defined;
  - TOPAZ-1 with Gem/Cis +/- Durvalumab positive
  - KEYNOTE 966 (G/C +/- P) ongoing

Clinical Investigator Survey Results

Regulatory and reimbursement issues aside, what would be your preferred first-line systemic treatment for a 65-year-old patient with metastatic cholangiocarcinoma and a PS of 0?



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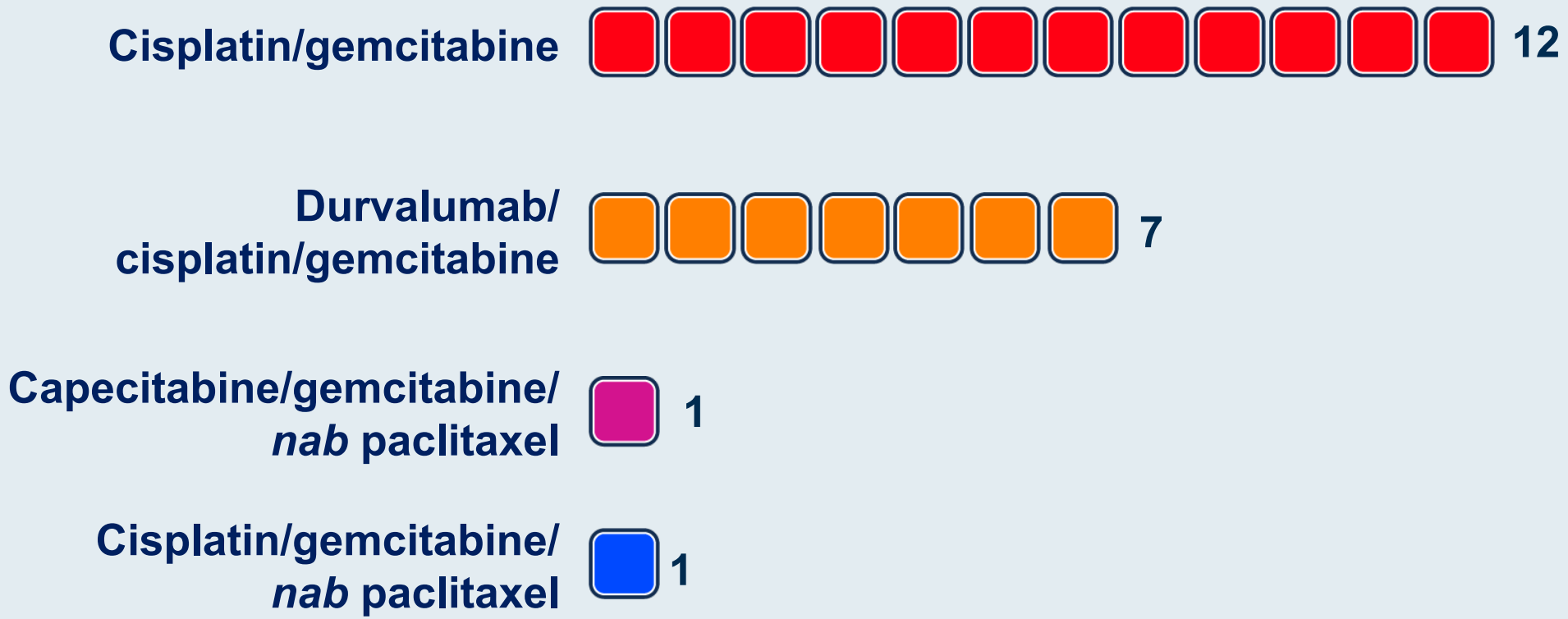
Regulatory and reimbursement issues aside, what would be your preferred first-line systemic treatment for a 65-year-old patient with metastatic gallbladder cancer and a PS of 0?



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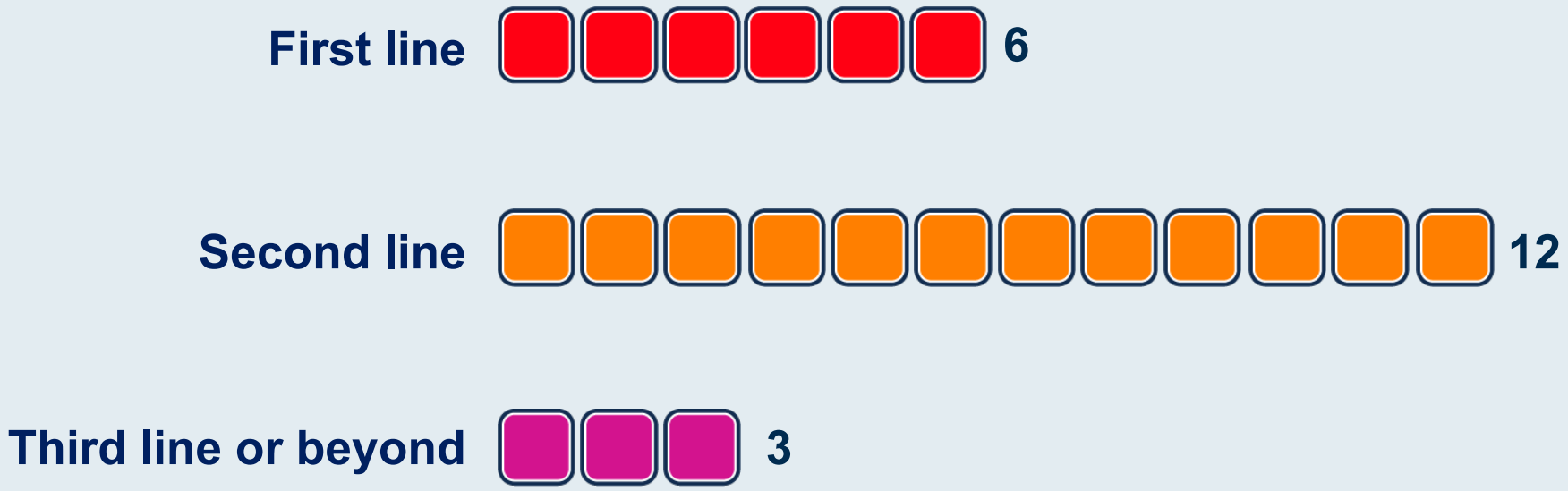
Reimbursement and regulatory issues aside, for a patient with advanced biliary tract cancer and HER2 amplification, in which line of therapy would you generally administer anti-HER2 therapy?



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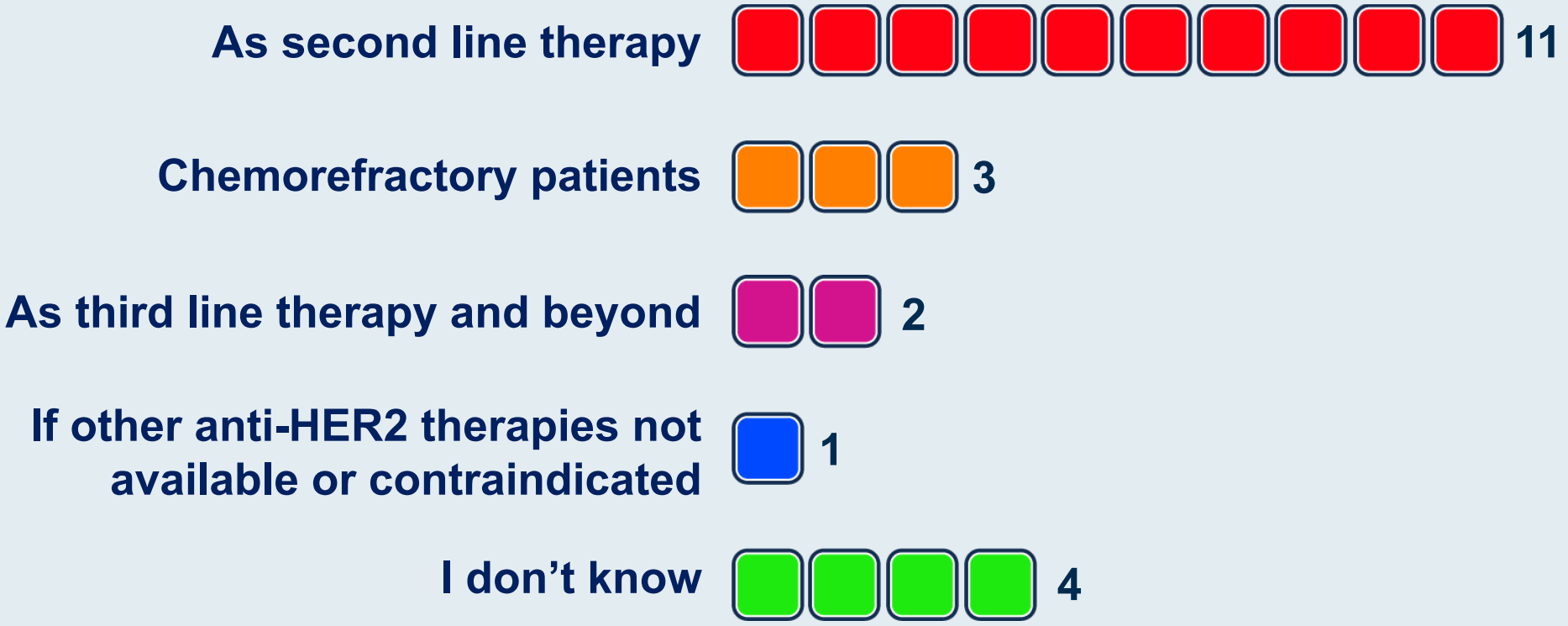
For a patient with advanced biliary tract cancer and HER2 amplification to whom you would administer anti-HER2 therapy, which would you generally recommend?

Survey of Gastrointestinal Cancers Clinical Investigators

If zanidatamab were available today, under what cirumstances, if any, would you administer it to your patients with HER2-amplified advanced biliary tract cancer?



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Thank you for attending!

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For those participating in person today, please remit your CME credit form as you exit the meeting room.

For all others, a CME credit link will be provided in the chat room at the conclusion of the program.

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