Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Hepatobiliary Cancers

Part 3 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Friday, January 20, 2023

6:00 PM – 7:30 PM PT

Faculty

Richard S Finn, MD

Professor Arndt Vogel, MD

Lipika Goyal, MD, MPhil

Moderator

Robin K (Katie) Kelley, MD

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Faculty

Richard S Finn, MD
Professor, Department of Medicine
Division of Hematology/Oncology
David Geffen School of Medicine at UCLA
Director, Signal Transduction and Therapeutics Program
Jonsson Comprehensive Cancer Center at UCLA
Los Angeles, California

Professor Arndt Vogel, MD
Managing Senior Consultant
Department of Gastroenterology, Hepatology and Endocrinology
Hannover Medical School
Hannover, Germany

Lipika Goyal, MD, MPhil
Director of Gastrointestinal Oncology
Stanford Cancer Center
Associate Professor
Stanford University School of Medicine
Palo Alto, California

Moderator
Robin K (Katie) Kelley, MD
Professor of Clinical Medicine
Division of Hematology/Oncology
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco (UCSF)
San Francisco, California

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Commercial Support

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Richard S Finn, MD — Disclosures
Faculty

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Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP, Hengrui Therapeutics Inc
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Lipika Goyal, MD, MPhil — Disclosures
Faculty

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Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

Professor Arndt Vogel, MD — Disclosures
Faculty

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Moderator

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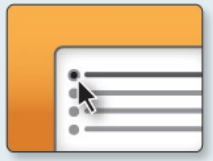
Networked iPads are available.

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



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Clinicians Attending via Zoom

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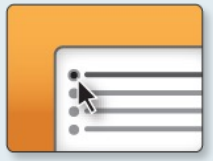

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- The live meeting is being video and audio recorded.
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Agenda

Module 1: First-Line Treatment for Advanced Hepatocellular Carcinoma (HCC) — Dr Finn

Module 2: Selection and Sequencing of Therapies for Relapsed/Refractory HCC — Dr Kelley

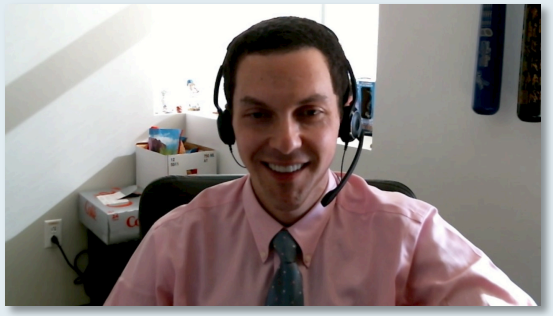
Module 3: Current and Future Role of Immunotherapy in the Treatment of Advanced Biliary Tract Cancers (BTCs) — Prof Vogel

Module 4: Integration of Targeted Therapy into the Management of Advanced BTCs — Dr Goyal

Susmitha Apuri, MD
Florida Cancer Specialists
Lutz, Florida

Lionel A Kankeu Fonkoua, MD
Mayo Clinic
Rochester, Minnesota

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida



Jeremy Lorber, MD
Cedars-Sinai Medical Center
Beverly Hills, California

Farshid Dayyani, MD, PhD
Stern Center for Cancer Clinical Trials and Research
Orange, California

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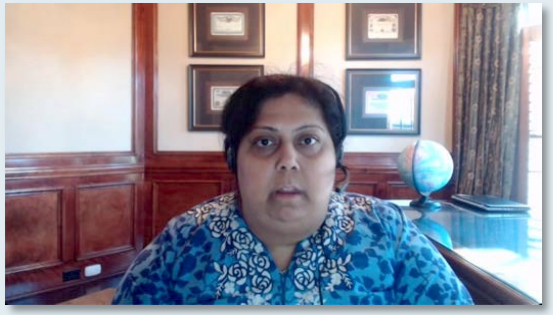
Joseph Martins, MD
UT Health Science Center
Tyler, Texas

Priya Rudolph, MD
Georgia Cancer Specialists
Athens, Georgia



Niyati A Nathwani, MD
Carolina Blood and Cancer Care Associates
Charlotte, North Carolina

Liudmila N Schafer, MD
Saint Luke's Cancer Institute
Kansas City, Missouri

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MODULE 1: First-Line Treatment for Advanced Hepatocellular Carcinoma (HCC) — Dr Finn

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Case Presentation: 70-year-old man with newly diagnosed metastatic HCC receives atezolizumab/bevacizumab

Dr Warren Brenner (Boca Raton, Florida)

QUESTIONS FOR THE FACULTY

Warren S Brenner, MD

"My questions for the investigators are…

Is there a role for genetic profiling in patients with HCC? Is a biopsy really necessary in patients with clinical HCC and high alpha-fetoprotein (greater than 400)?

How are the investigators choosing between atezolizumab and bevacizumab and dual checkpoint inhibitor therapy based on the HIMALAYA trial?

Are there any clinical parameters to decide between the two regimens? Are patients with hepatitis-associated HCC more likely to respond to one regimen versus another?

Do all patients with HCC receiving bevacizumab require upper endoscopy prior to initiating therapy?"

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Case Presentation: 59-year-old woman with a history of hepatitis C and chronic kidney disease on dialysis with localized HCC s/p surgical resection — the patient developed metastatic disease 10 months later

Dr Liudmila Schafer (Kansas City, Missouri)

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QUESTIONS FOR THE FACULTY

Liudmila N Schafer, MD

"For most of the patients we see after primary surgery we follow up with surveillance, but is there a role for adjuvant systemic therapy, including immunotherapy?

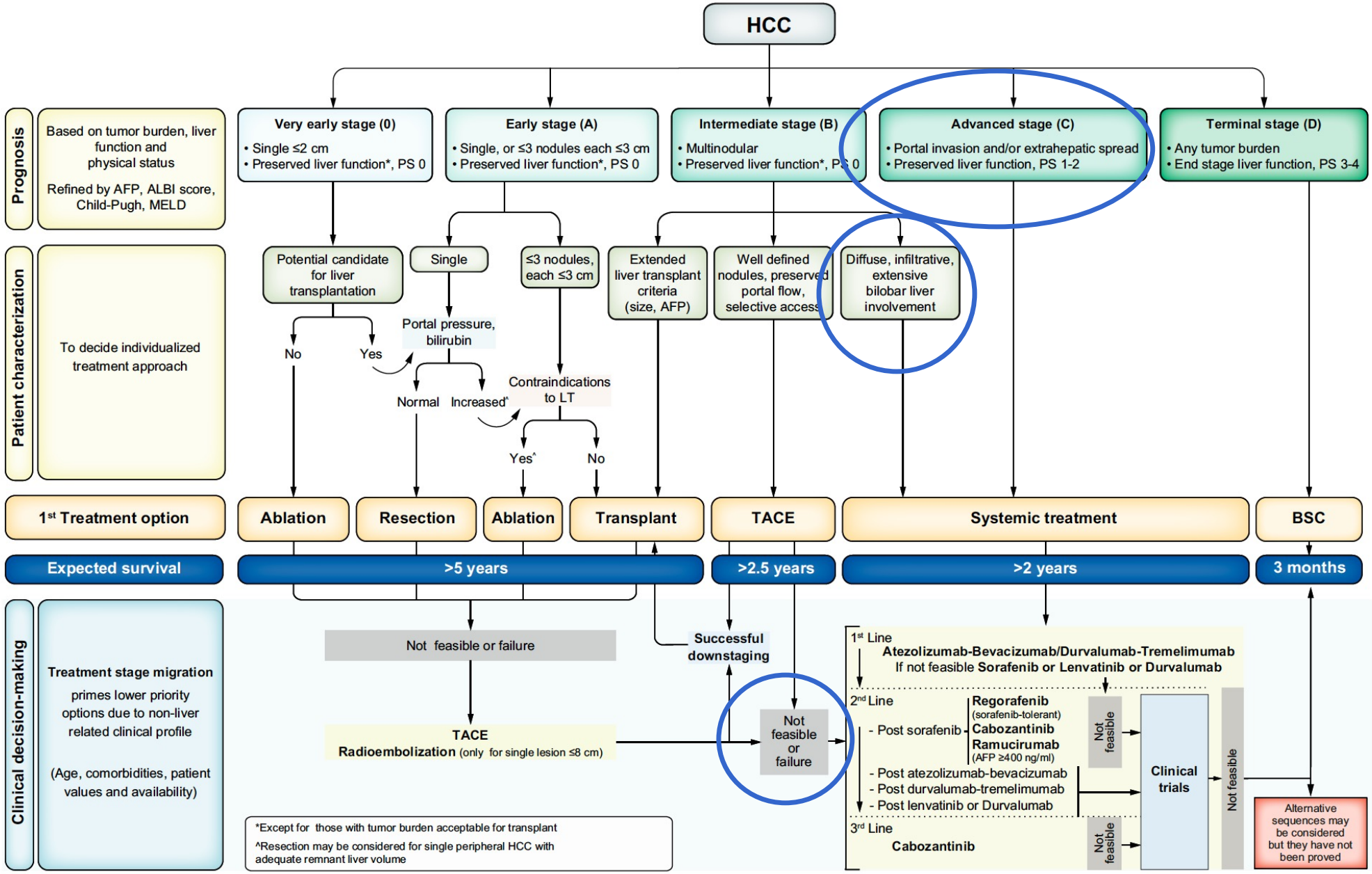
This patient developed metastatic disease to the liver and nodes within 10 months of surgery but otherwise has a good performance status, although she is on dialysis. What treatment would you recommend?"

Current Role of Systemic Therapy in Front-line 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

Front-line

BCLC management of HCC-2022: Where to use Systemic Therapy



- Reig M et al J Hep 2022

Finn et al. *New Engl J Med.* 2020

IMbrave150 Study Design

Key eligibility

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

Stratification

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

R 2:1

Atezolizumab 1200 mg IV q3w + Bevacizumab 15 mg/kg q3w

N = 501

Sorafenib 400 mg bid

(open-label)

Until loss of clinical benefit or un-acceptable toxicity[b]

Survival follow-up

Co-primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

No exclusion for main PVT

Secondary endpoints included:

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

[a] Japan is included in rest of world. [b] Tumor assessment by computed tomography or magnetic resonance imaging was done at baseline and every 6 weeks until 54 weeks, then every 9 weeks thereafter.
[c] Time from randomization to first decrease from baseline of ≥ 10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
AFP, α-fetoprotein; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer; IRF, independent review facility; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; QOL, quality of life; TTD, time to deterioration.

Baseline patient characteristics (ITT)[a]

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

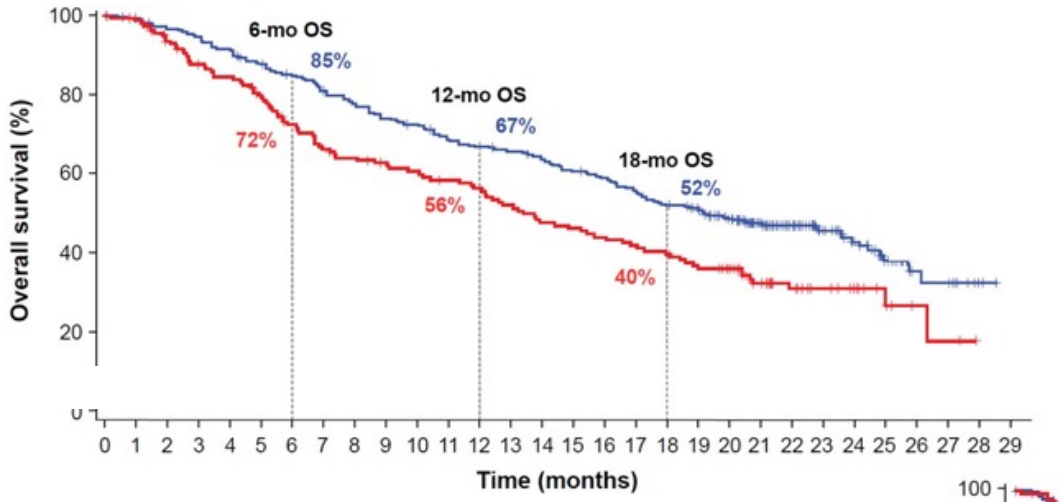
EHS, extrahepatic spread; ITT, intention to treat, MVI, macrovascular invasion. [a] All randomised patients. [b] Includes United States, Australia, New Zealand, and Japan. [c] Includes alcohol, other and unknown non–hepatitis B and C causes.

Finn, *N Engl J Med* 2020.

IMbrave150 Trial

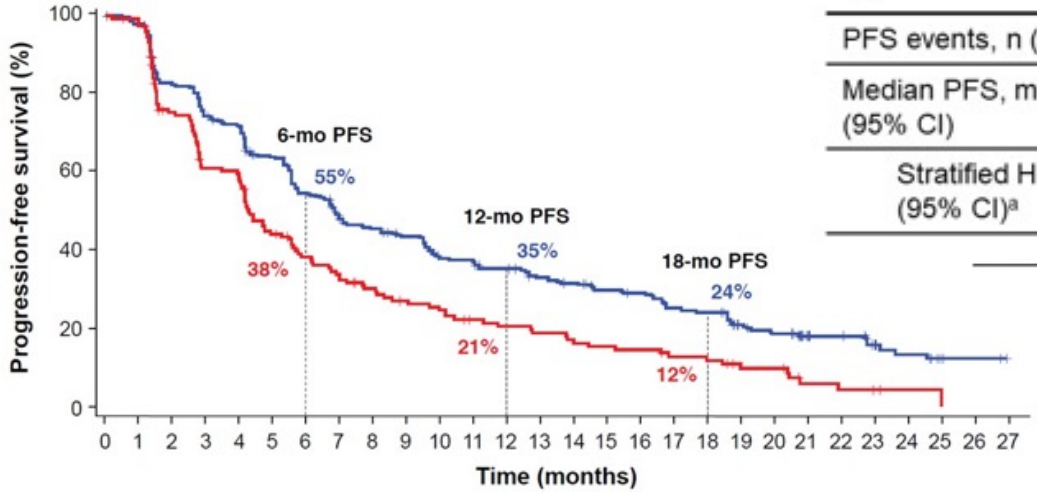
Key Efficacy Data: Updated OS and PFS

– Primary analysis OS/PFS HR: 0.58/0.59 (median follow-up: 8.6 mo)



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]	

– Median follow-up: 15.6 mo



Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	

- Finn RS et al NEJM 2020, Finn RS et al ASCO GI 2021, Cheng AL J Hep 2022

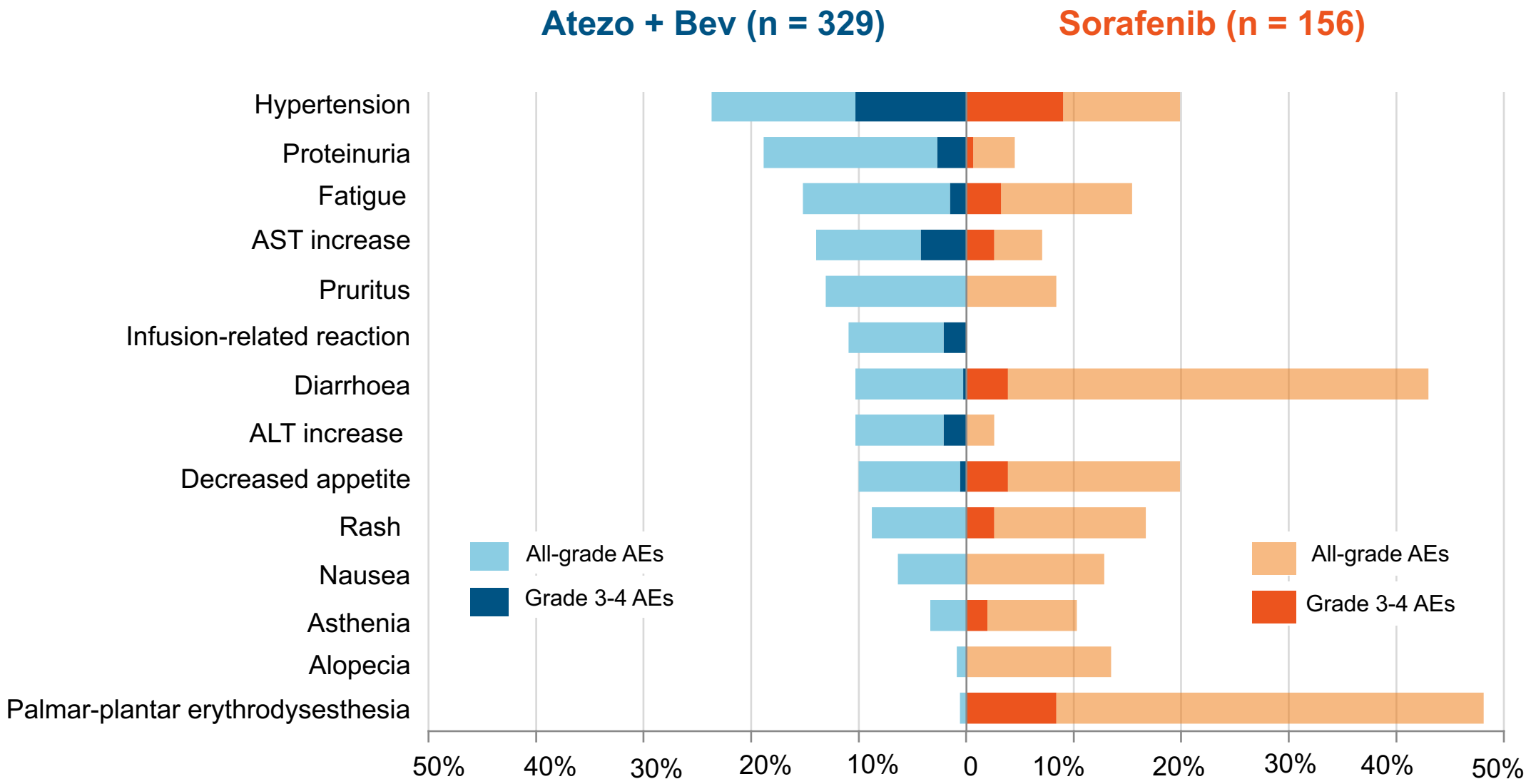
Updated response and duration of response

	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. DCR, disease control rate.
[a] Only patients with measurable disease at baseline were included in the analysis of ORR.
[b] Only confirmed responders were included in the analysis of ORR and DOR.

Cheng AL J Hep 2022

TRAEs: ≥ 10% any grade in either arm



Finn et al , *N Engl J Med* 2020.

HIMALAYA study design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial

Study population
- Patients with confirmed uHCC
- BCLC B (not eligible for locoregional therapy) and C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

Stratification factors
- Macrovascular invasion: Y / N
- Etiology of liver disease: HBV / HCV / others
- Performance status: ECOG 0 / 1

R
N=1324

T300+D (n=393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

Durvalumab (n=389):
Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389):
Sorafenib 400 mg BID*

T75+D (n=153): *arm closed* †
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Primary objective
- OS for T300+D vs sorafenib

Key secondary objective
- OS for durvalumab vs sorafenib

Additional secondary objectives
- PFS, ORR, and DoR as assessed by investigator per RECIST v1.1
- Safety

Multiple testing procedure

OS *superiority* for T300+D vs sorafenib

OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

OS *superiority* for durvalumab vs sorafenib

*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.

Baseline characteristics

Characteristic	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Male sex, n (%)	327 (83.2)	323 (83.0)	337 (86.6)
Median age (range), years	65.0 (22–86)	64.0 (20–86)	64.0 (18–88)
Region, n (%) Asia (excluding Japan) Rest of world (including Japan)	 156 (39.7) 237 (60.3)	 167 (42.9) 222 (57.1)	 156 (40.1) 233 (59.9)
Viral etiology,*,† n (%) HBV HCV Nonviral	 122 (31.0) 110 (28.0) 161 (41.0)	 119 (30.6) 107 (27.5) 163 (41.9)	 119 (30.6) 104 (26.7) 166 (42.7)
ECOG PS, n (%) 0 1	 244 (62.1) 148 (37.7)	 237 (60.9) 150 (38.6)	 241 (62.0) 147 (37.8)
BCLC,† n (%) B C	 77 (19.6) 316 (80.4)	 80 (20.6) 309 (79.4)	 66 (17.0) 323 (83.0)

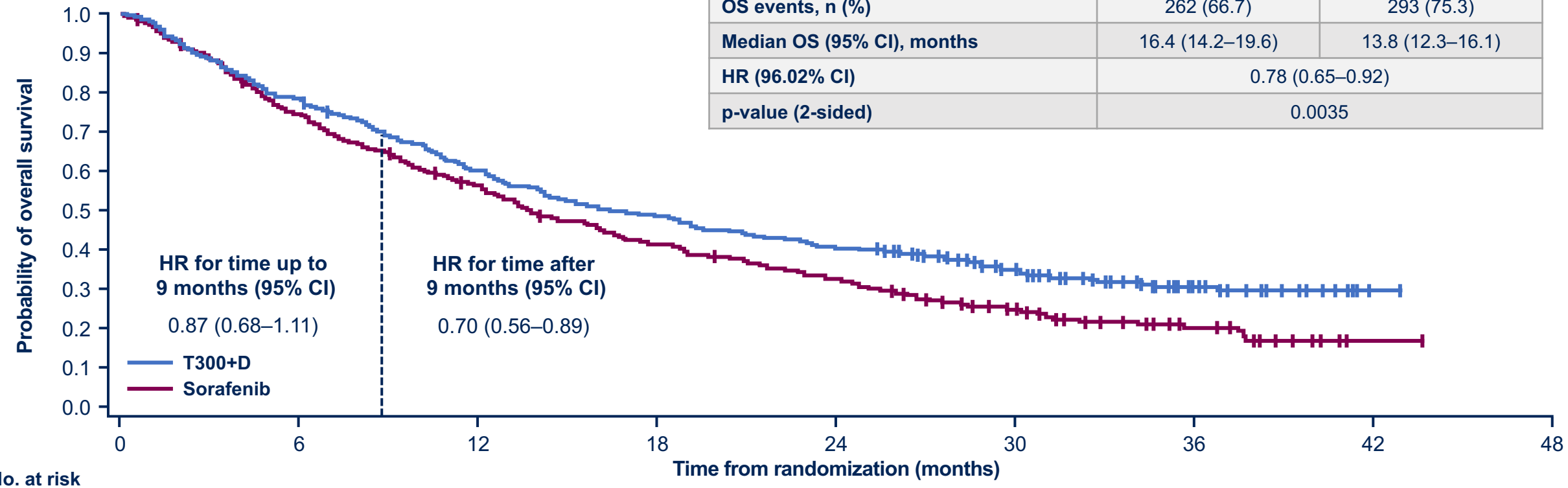
Characteristic	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Child-Pugh classification,† n (%) A B Missing	 392 (99.7) 0 1 (0.3)	 388 (99.7) 1 (0.3) 0	 386 (99.2) 3 (0.8) 0
ALBI grade, n (%) 1 2 3	 217 (55.2) 174 (44.3) 1 (0.3)	 198 (50.9) 189 (48.6) 2 (0.5)	 203 (52.2) 185 (47.6) 1 (0.3)
MVI,† n (%)	103 (26.2)	94 (24.2)	100 (25.7)
EHS,† n (%)	209 (53.2)	212 (54.5)	203 (52.2)
PD-L1 positive,‡ n (%)	148 (37.7)	154 (39.6)	148 (38.0)
AFP ≥400 ng/ml,† n (%)	145 (36.9)	137 (35.2)	124 (31.9)

*HBV: patients who tested positive for HBsAg or anti-HBc with detectable HBV DNA; HCV: patients who tested positive for HCV or had history of HCV infection; Nonviral: no active viral hepatitis identified. †Determined at screening. ‡Defined as tumor area positivity score ≥1%.

T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Primary objective: overall survival for T300+D vs sorafenib

	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

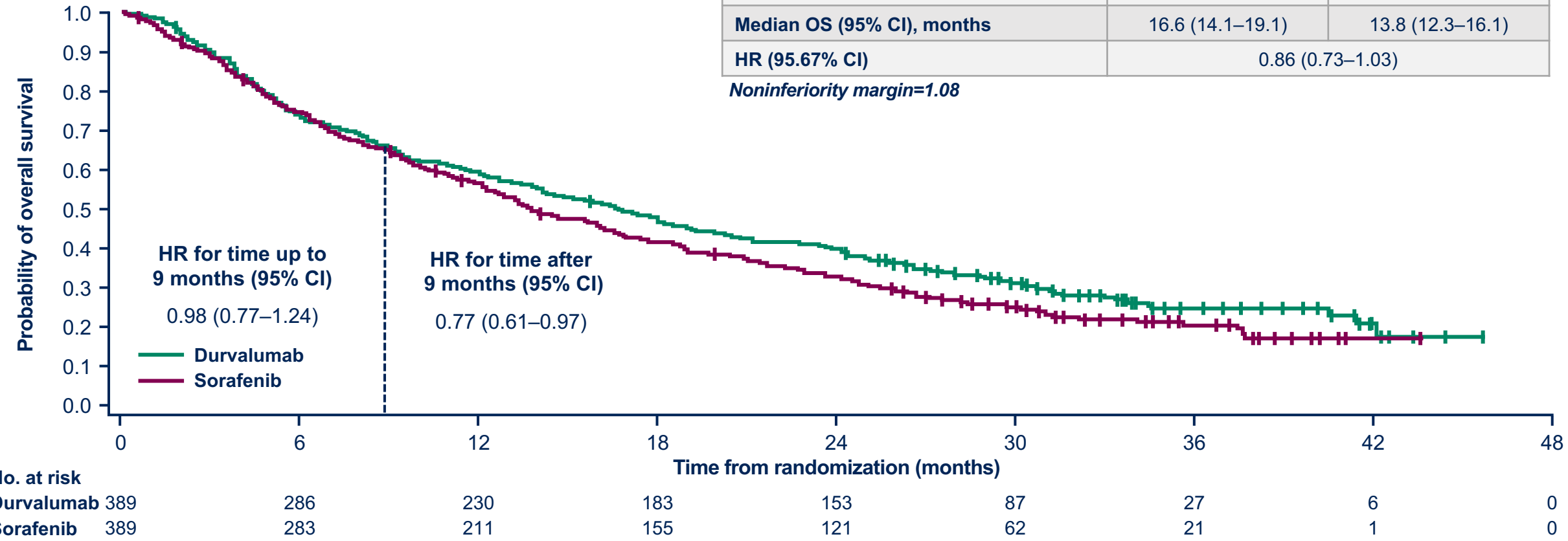
Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

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

Secondary objective: overall survival for durvalumab vs sorafenib

	Durvalumab (n=389)	Sorafenib (n=389)
OS events, n (%)	280 (72.0)	293 (75.3)
Median OS (95% CI), months	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95.67% CI)	0.86 (0.73–1.03)	

Noninferiority margin=1.08

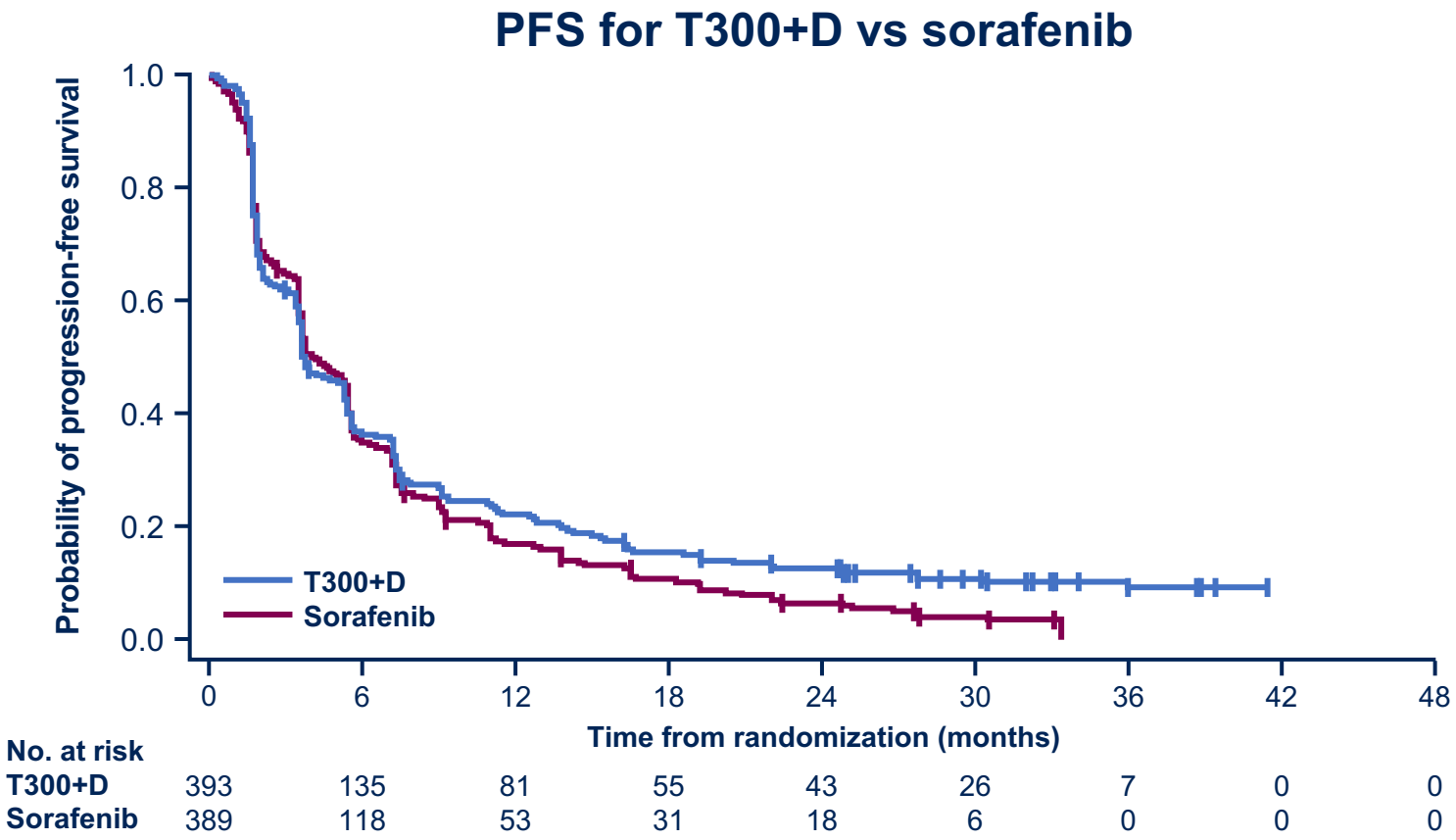


No. at risk								
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 32.56 (95% CI, 31.57–33.71) months for durvalumab and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI, confidence interval; HR, hazard ratio; NI, noninferiority; OS, overall survival.

Progression-free survival



	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68–5.32)	3.65 (3.19–3.75)	4.07 (3.75–5.49)
PFS HR* (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	–
Progression-free at DCO, n (%)	49 (12.5)	32 (8.2)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
Treated ≥1 cycle beyond progression, n (%)†	182 (46.9)	188 (48.5)	134 (34.4)

*Versus sorafenib. †Percent calculated from total patients in the safety analysis set: T300+D, N=388; durvalumab, N=388, sorafenib, n=374.

CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTP, time to progression.

Tumor response

	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* n (%)	**79 (20.1)**	**66 (17.0)**	**20 (5.1)**
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months 25th percentile 75th percentile	22.34 8.54 NR	16.82 7.43 NR	18.43 6.51 25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ % 6 months 12 months	 82.3 65.8	 81.8 57.8	 78.9 63.2

*By investigator assessment according to RECIST v1.1. Responses are confirmed. †Defined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD. ‡Calculated using Kaplan-Meier technique.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTR, time to response.

Safety and tolerability

Event, n (%)	T300+D (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)†	0	3 (0.8)‡
Any TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy.

*Treatment-related was as assessed by investigator. †Nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1). ‡Hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1).

AE, adverse event; SMQ, Standardized MedDRA Query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TRAE, treatment-related adverse event.

Immune-mediated adverse events

Event, n (%)	T300+D (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0

Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm.

T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Tislelizumab

Cancer Immunology, Immunotherapy (2018) 67:1079–1090
https://doi.org/10.1007/s00262-018-2160-x

ORIGINAL ARTICLE

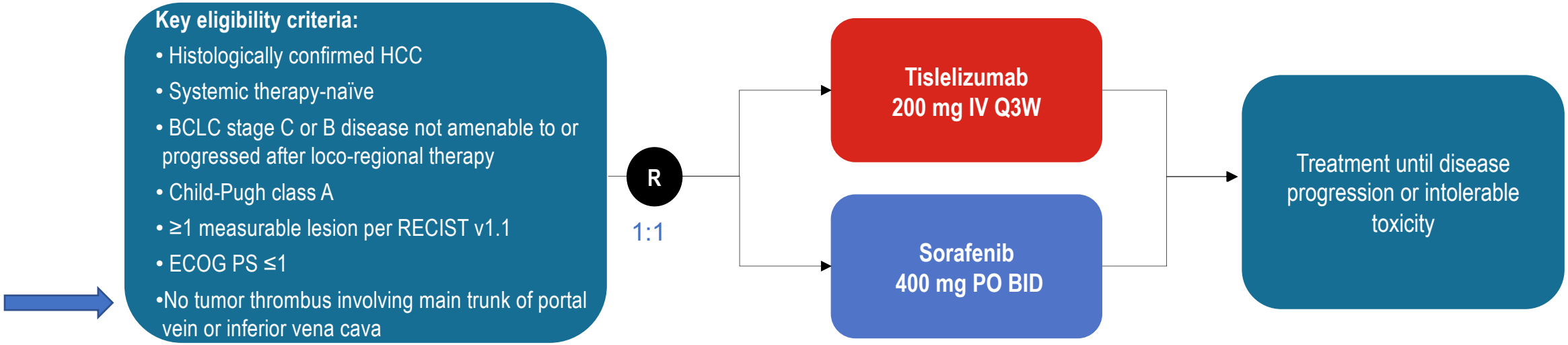
The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions

Tong Zhang[1] · Xiaomin Song[1] · Lanlan Xu[1] · Jie Ma[1] · Yanjuan Zhang[1] · Wenfeng Gong[1] · Yilu Zhang[1] · Xiaosui Zhou[1] · Zuobai Wang[1] · Yali Wang[1] · Yingdi Shi[1] · Huichen Bai[1] · Ning Liu[1] · Xiaolong Yang[1] · Xinxin Cui[1] · Yanping Cao[1] · Qi Liu[1] · Jing Song[1] · Yucheng Li[1] · Zhiyu Tang[1] · Mingming Guo[1] · Lai Wang[1] · Kang Li[1]

- Tislelizumab, a monoclonal antibody with high binding affinity for PD-1, was specifically engineered to minimize Fcγ receptor binding on macrophages

RATIONALE-301: Study Design

Randomized, open-label, multicenter, multiregional phase 3 study

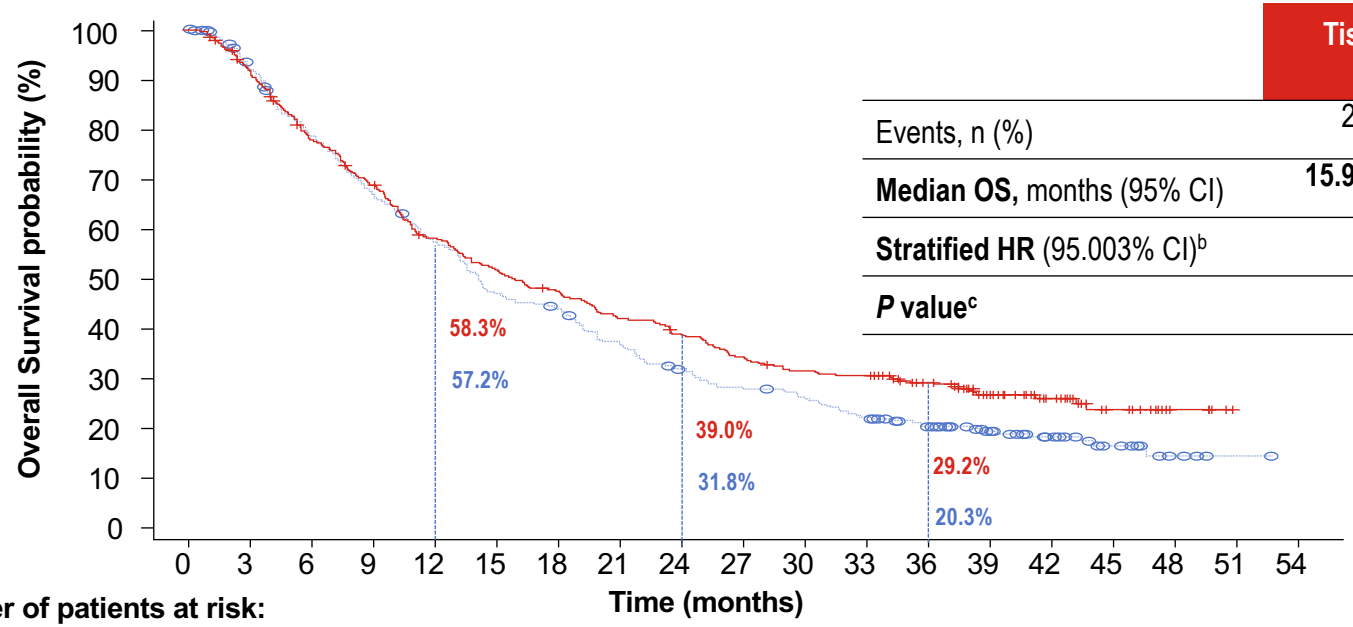


Primary endpoint: OS in the ITT population
Key secondary endpoints: ORR, PFS, and DoR by BIRC per RECIST v1.1, and safety
Stratification factors: Macrovascular invasion (present vs absent), extrahepatic spread (present vs absent), ECOG PS (0 vs 1), etiology (HCV vs other[a]), geography (Asia [excluding Japan], vs Japan vs rest of world)

[a]Includes HBV. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; BIRC, blinded independent review committee; DoR, duration of response; ECOG PS, European Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

RATIONALE-301: Overall Survival

Tislelizumab demonstrated OS noninferiority[a] vs sorafenib; OS superiority vs sorafenib was not met



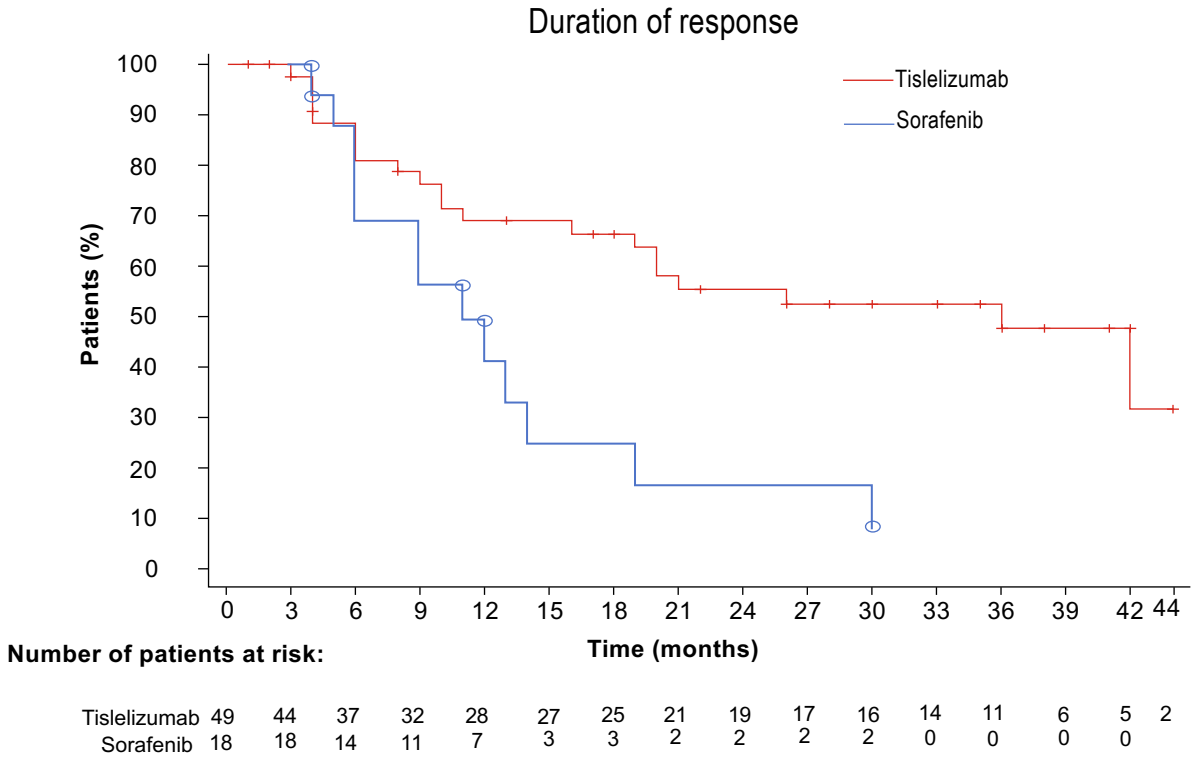
	Tislelizumab (n=342)	Sorafenib (n=332)
Events, n (%)	242 (70.8)	255 (76.8)
Median OS, months (95% CI)	**15.9** (13.2, 19.7)	**14.1** (12.6, 17.4)
Stratified HR (95.003% CI)[b]	**0.85** (0.712, 1.019)	
***P* value**[c]	**0.0398**	

Data cutoff: July 11, 2022. OS was assessed in the ITT population. [a]Prespecified boundary of NI: upper bound of 95.003% CI of stratified HR <1.08; pre-specified boundary of superiority: one-sided *P* value <0.0223 (approximate HR <0.8352). [b]HR was based on a Cox proportional hazard model including treatment as a covariate, geography (Asia [including Japan] vs rest of world [EU/US]), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other), and ECOG PS (0 vs 1) as stratification factors. [c]One-sided stratified log-rank test. Abbreviations: CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; HCV, hepatitis C virus; HR, hazard ratio; ITT, intent-to-treat; NI, non-inferiority; OS, overall survival.

RATIONALE-301: Overall Response Rate by IRC

Tislelizumab was associated with a higher ORR and more durable responses vs sorafenib

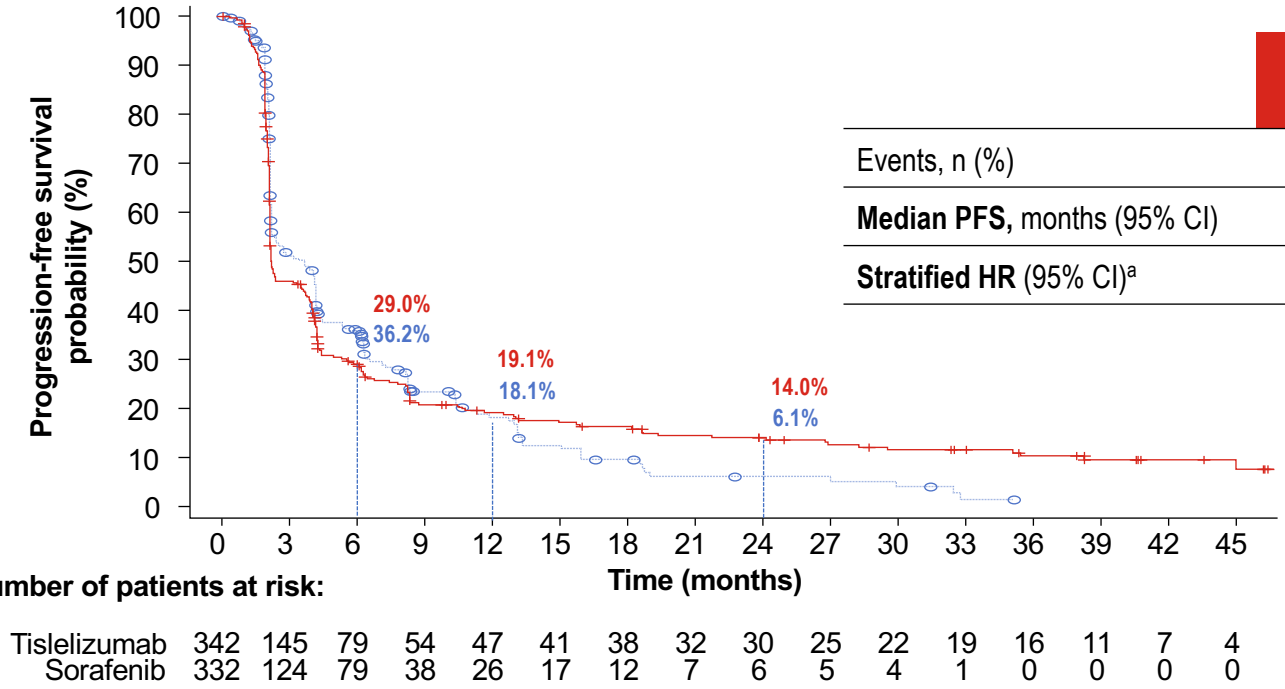
	Tislelizumab (n=342)	Sorafenib (n=332)
ORR, n (%) [95% CI][a]	49 (14.3) [10.8, 18.5]	18 (5.4) [3.2, 8.4]
Best overall response, n (%)[a]		
CR	10 (2.9)	1 (0.3)
PR	39 (11.4)	17 (5.1)
SD	94 (27.5)	137 (41.3)
PD	166 (48.5)	117 (35.2)
Undetermined[b]	26 (7.6)	50 (15.1)
Non-CR/non-PD[c]	7 (2.0)	10 (3.0)
Responders	**Tislelizumab (n=49)**	**Sorafenib (n=18)**
Median DoR, months (95% CI)	36.1 (16.8, NE)	11.0 (6.2, 14.7)
Patients with ongoing response, n (%)[d]	20/28 (71.4)	2/5 (40.0)



Data cutoff: July 11, 2022. ORR was assessed in the ITT population. [a]Confirmed responses; [b]Patients with no postbaseline tumor assessment (not assessable) or a nonevaluable tumor assessment. [c]Patients were assessed as non-CR/non-PD if the IRC was not able to identify the target lesions at screening. Patients with no target lesions were evaluated based on the assessment of nontarget lesions or the presence of new lesions. [d]Patients who had PD or died were excluded from this analysis. Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; IRC, independent review committee; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

RATIONALE-301: Progression-Free Survival by IRC

The median PFS was longer with sorafenib versus tislelizumab



	Tislelizumab (n=342)	Sorafenib (n=332)
Events, n (%)	273 (79.8)	220 (66.3)
Median PFS, months (95% CI)	**2.2** (2.1, 3.5)	**3.6** (2.2, 4.1)
Stratified HR (95% CI)[a]	**1.10** (0.92, 1.33)	

Data cutoff: July 11, 2022. PFS was assessed in the ITT population. [a]HR was based on a Cox proportional hazard model including treatment as a covariate, geography (Asia [including Japan] vs rest of world [EU/US]), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other), and ECOG PS (0 vs 1) as stratification factors. Abbreviations: CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; HCV, hepatitis C virus; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival.

RATIONALE-301: Safety Summary

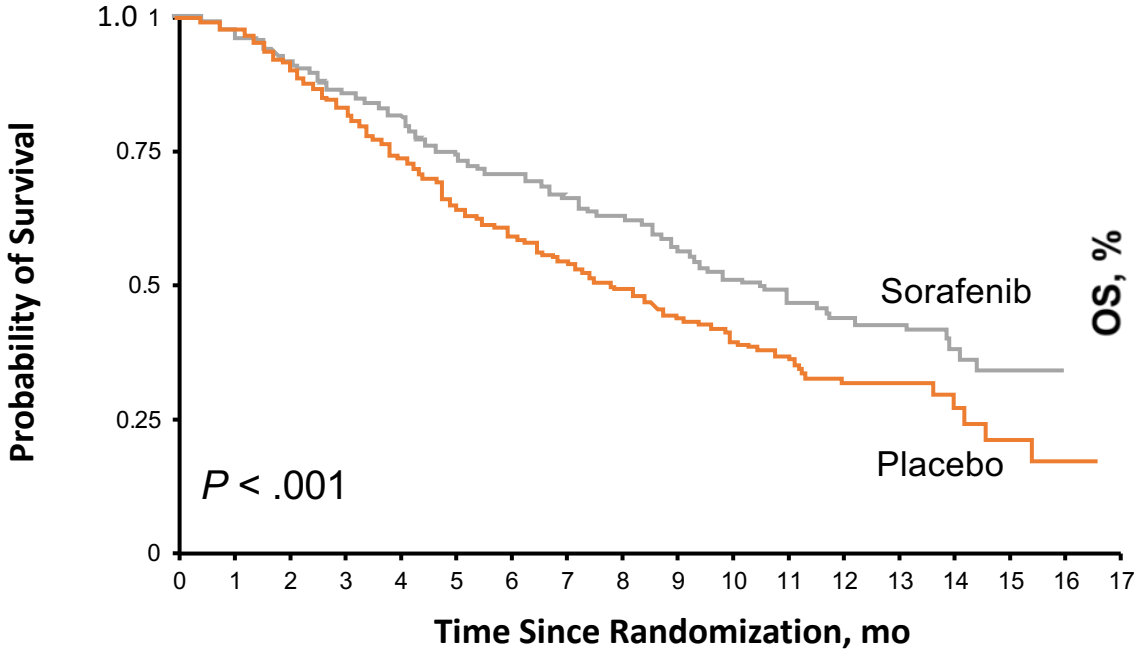
TEAEs and treatment-related TEAEs at grade ≥3 were less frequent with tislelizumab and treatment with tislelizumab led to fewer discontinuations/dose modifications vs sorafenib

Patients	Tislelizumab (n=338)	Sorafenib (n=324)
Safety, n (%)		
Any TEAE	325 (96.2)	324 (100.0)
Treatment-related	259 (76.6)	311 (96.0)
TEAE at ≥grade 3	163 (48.2)	212 (65.4)
Treatment-related	75 (22.2)	173 (53.4)
Serious TEAE	101 (29.9)	91 (28.1)
Treatment-related	40 (11.8)	33 (10.2)
TEAE leading to discontinuation	37 (10.9)	60 (18.5)
Treatment-related	21 (6.2)	33 (10.2)
TEAE leading to drug modification[a]	105 (31.1)	210 (64.8)
Treatment-related	68 (20.1)	187 (57.7)
TEAE leading to death	15 (4.4)	17 (5.2)
Treatment-related	3 (0.9)	2 (0.6)
Immune-mediated AEs	58 (17.2)	10 (3.1)
Immune-mediated AEs treated with systemic corticosteroids	43 (12.7)	10 (3.1)
Immune-mediated AEs in ≥5% of patients		
Hepatitis	18 (5.3)	1 (0.3)
Hypothyroidism	18 (5.3)	0 (0)
Treatment		
Median duration of treatment, months	4.1	2.7

Safety was assessed in the safety population. Data cutoff: July 11, 2022. [a]Drug modification included an interrupted/held or reduced dose. Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

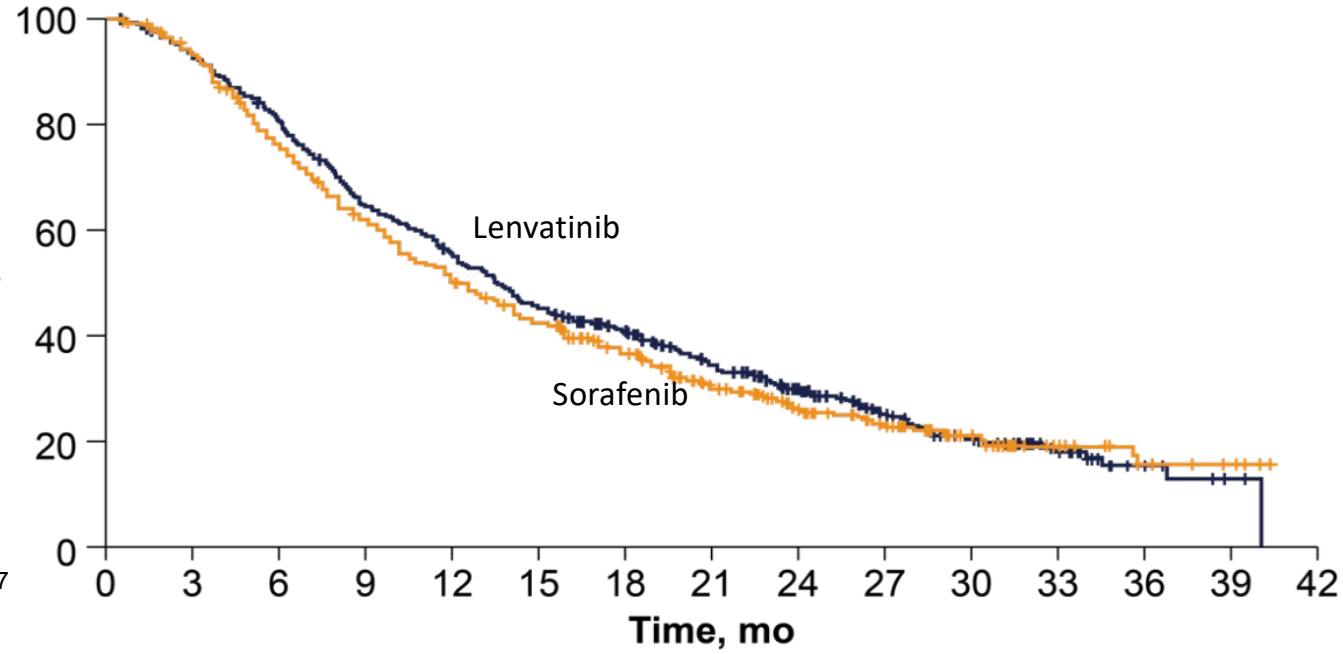
Alternative First-Line TKI Options

Phase 3 SHARP Trial[1]



Sorafenib OS: 10.7 months
Placebo OS: 7.9 months

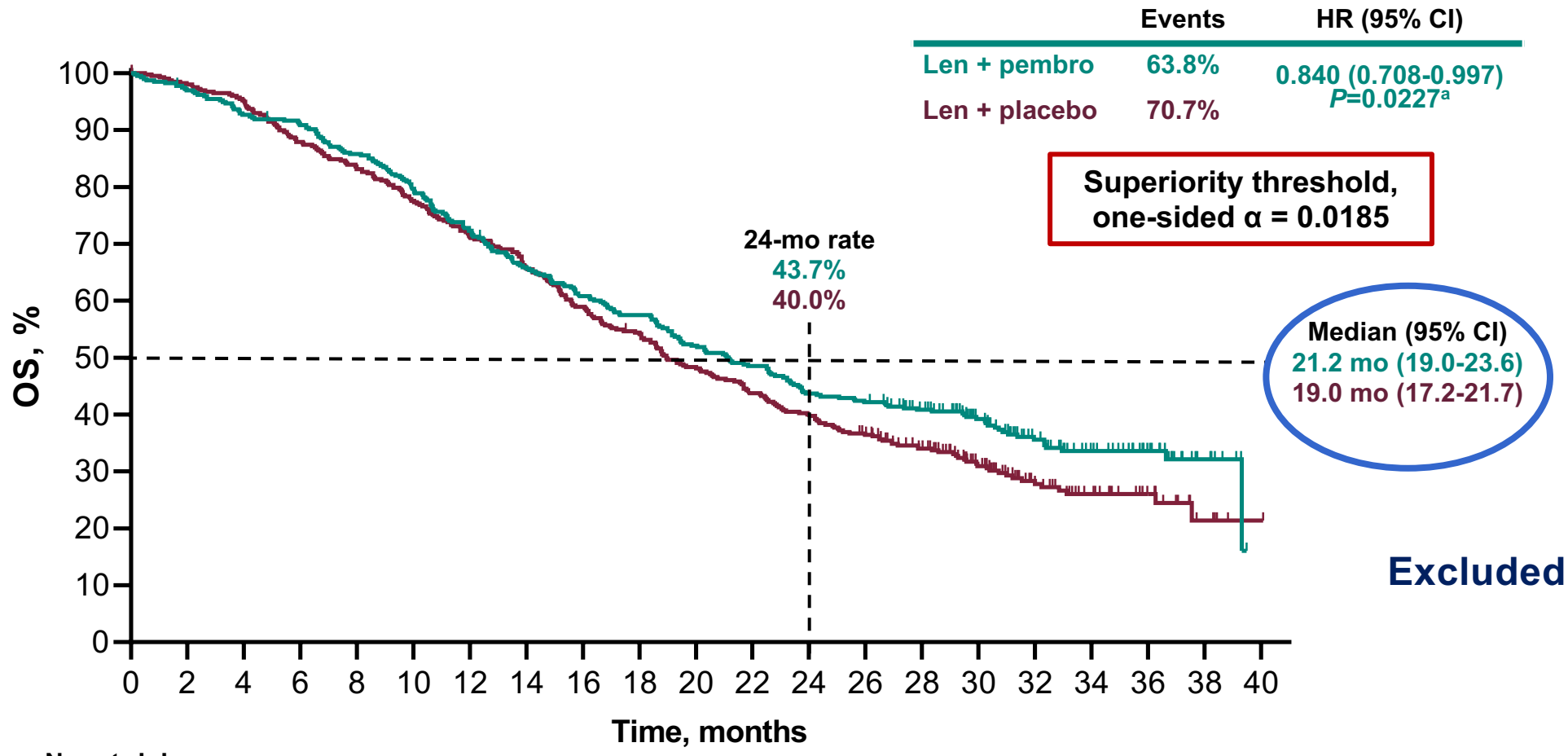
Phase 3 REFLECT Trial[2]



Lenvatinib OS: 13.6 months
Sorafenib OS: 12.3 months

1. Llovet JM et al. *N Engl J Med*. 2008;359:378-390. 2. Kudo M et al. *Lancet*. 2018;391:1163-1173.

LEAP-002: Overall Survival, ITT, FA



Excluded main PVT

[a]Did not reach superiority threshold, one-sided α=0.0185.
Data cutoff date for FA: 21 June 2022.

Finn RS et al ESMO 2022; Abstract LBA34

Conclusions:

- We have made tremendous progress in improving the survival of patients with advanced HCC
- The introduction of IO in the front-line setting is practice changing
  - No clear biomarker or patient population to serve as predictive markers of benefit
- Not every patient will be a candidate for IO combinations
  - Consider TKIs or single agent IO
- Studies evaluating the role of IO in earlier stage disease are ongoing

Atezolizumab Plus Bevacizumab is the First Treatment Combination to Reduce the Risk of Liver Cancer Returning in Early-Stage HCC

Press Release: January 18, 2023

The Phase III IMbrave050 study met its primary endpoint of recurrence-free survival (RFS) at the prespecified interim analysis. The study is evaluating atezolizumab in combination with bevacizumab as adjuvant treatment following surgery for people with early-stage hepatocellular carcinoma (HCC) at high risk of disease recurrence. The atezolizumab combination showed a statistically significant improvement in RFS in the intention-to-treat population of HCC patients who have an increased risk of recurrence following resection or ablation with curative intent, compared with active surveillance.

Overall survival data were immature at the time of interim analysis and follow-up will continue to the next analysis. Safety for atezolizumab and bevacizumab was consistent with the known safety profile of each therapeutic agent and with the underlying disease.

https://www.gene.com/media/press-releases/14981/2023-01-18/genentechs-tecentriq-plus-avastin-is-the

RTP RESEARCH TO PRACTICE

MODULE 2: Selection and Sequencing of Therapies for Relapsed/Refractory HCC — Dr Kelley

RTP
RESEARCH
TO PRACTICE

Case Presentation: 65-year-old man with metastatic HCC and a past medical history of hepatitis C develops ILD on atezolizumab/bevacizumab

Dr Priya Rudolph (Athens, Georgia)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Priya Rudolph, MD, PhD

"The patient developed dyspnea on exertion. CT scan showed ground-glass opacities. He was COVID-negative, but he had been cleaning his boat and possibly inhaled some strong chemicals. We held treatment and put him on a steroid taper. Are there any data to suggest that continuing single-agent bevacizumab has any efficacy, and can we just continue that for a while? What would you recommend as his next systemic therapy?"

- **What is your usual next systemic therapy after atezolizumab/bevacizumab, and what factors do you consider in this decision?**
- **What is your usual first-line systemic therapy for a patient with a contraindication to immunotherapy such as a major autoimmune disorder?**

RTP
RESEARCH
TO PRACTICE

Dr Lionel Kankeu Fonkoua
(Rochester, Minnesota)

68-year-old man with post-transplant recurrence develops metastatic HCC and receives lenvatinib followed by cabozantinib followed by regorafenib

Dr Susmitha Apuri
(Lutz, Florida)

79-year-old man with metastatic HCC who is s/p treatment with atezolizumab/bevacizumab, lenvatinib and currently cabozantinib

QUESTIONS FOR THE FACULTY

Lionel A Kankeu Fonkoua, MD

"The patient had a transplant years ago for multifocal HCC in the background of alcoholic cirrhosis and was doing fine on immunosuppressive therapy but had a post-transplant recurrence. He started on lenvatinib and then eventually progressed, switched to cabozantinib and then progressed and was placed on regorafenib. In a patient like this, would you consider atezolizumab/bevacizumab?

The patient wanted to remain aggressive, but I just didn't feel comfortable knowing the graft failure rate is about 30% to 40% in this patient population.

The second question is, there have been some data suggesting that activating mutations in β-catenin actually confer resistance to immune checkpoint inhibition. Would that be a factor in this setting — in a patient who you already have reservations?"

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RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Susmitha Apuri, MD

"He's on cabozantinib right now with an ECOG PS of 0. He's back to his woodworking. He has a PIK3CA somatic mutation. Would an agent like alpelisib be helpful? Would he be a candidate for ipilimumab/nivolumab."

Selection and Sequencing of Therapies for Advanced HCC: *Second-Line and Beyond*

Katie Kelley, MD

Helen Diller Family Comprehensive Cancer Center

University of California, San Francisco

Outline

- Increasing utilization of subsequent lines of therapies in HCC
- Currently available 2nd line therapies
  - Agents with FDA approval after progression on sorafenib
  - Role for sorafenib, lenvatinib, or other multikinase tyrosine kinase inhibitors (TKI) after 1st line immune checkpoint inhibitor (ICI)-based combinations?
  - Role for anti-PD-(L)1 and anti-CTLA-4 combination regimens after prior ICI-based combinations?
- Factors in selection and sequencing of ≥ 2nd line treatment options
- Other promising agents and strategies under investigation as subsequent lines of therapy

Increasing Uptake of Subsequent Lines of Therapy

- A meaningful number of patients receive ≥ 2nd line therapies
- Increase may be due to:
  - More efficacious 1st line options?
  - Better supportive care?
  - Stage migration?

Incidence of ≥2nd line therapy in IMbrave150:

Table S1. Follow-up systemic treatment for hepatocellular carcinoma

	Atezolizumab plus bevacizumab (n=336)	Sorafenib (n=165)
≥1 systemic treatment*	120 (36)	86 (52)
Second-line therapy	102 (30)	81 (49)
Third-line therapy	33 (10)	39 (24)

Cheng et al. J Hepatol 2022;76:862-73

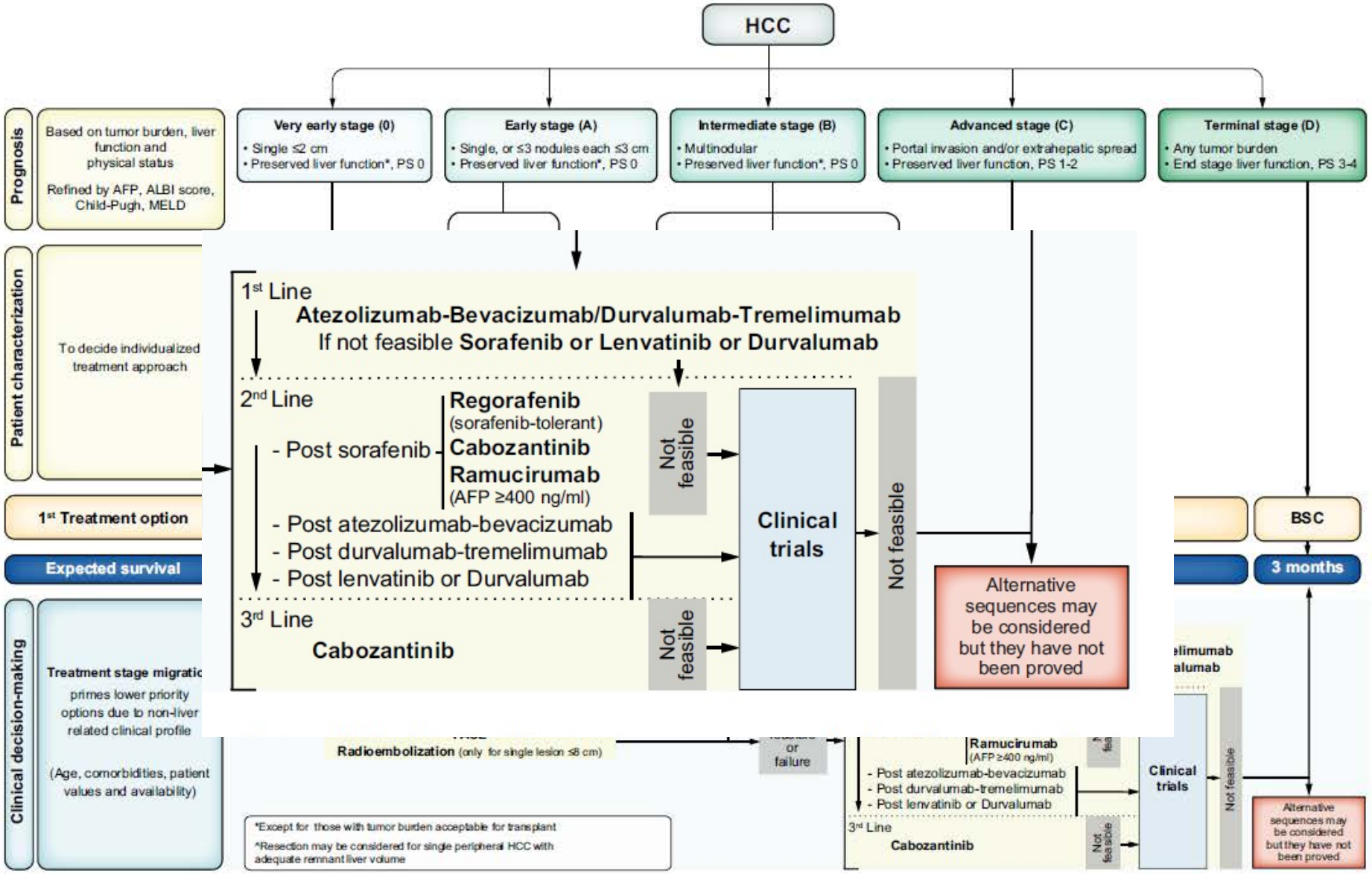
Incidence of subsequent therapies post 2nd line durva/treme in Study 22:

SUPPLEMENTAL TABLE 9 (online only). Subsequent Cancer Therapy[a]

	T300+D (n=75)	Durvalumab (n=104)	Tremelimumab (n=69)	T75+D (n=84)
Number of patients receiving post progression cancer therapy, n (%)[b]	32 (42.7)	37 (35.6)	22 (31.9)	32 (38.1)
Systemic therapy	27 (36.0)	31 (29.8)	19 (27.5)	27 (32.1)

Kelley et al. J Clin Oncol 2021; epub 22Jul21

Updated BCLC Algorithm 2022



Reig et al. J Hepatol. 2022

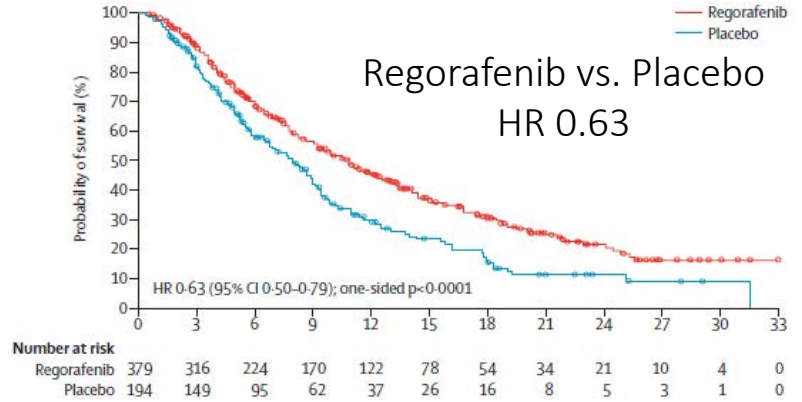
Beyond 1st Line: Currently Approved 2nd Line Therapies for HCC

- Antiangiogenic therapies with USFDA approval and level 1 evidence:
  - Regorafenib: Multikinase inhibitor, similar to sorafenib including VEGFR1-3, BRAF, PDGFR, RET
  - Cabozantinib: Multikinase inhibitor with targets including VEGFR1-3, MET, AXL
  - Ramucirumab (serum AFP ≥400 ng/mL): Monoclonal antibody targeting VEGFR2
- ICI with USFDA accelerated approval based upon phase 1/2 studies:
  - Pembrolizumab: Anti-PD-1 ICI
  - Nivolumab + ipilimumab: Anti-PD-1 plus anti-CTLA-4 ICI combinations

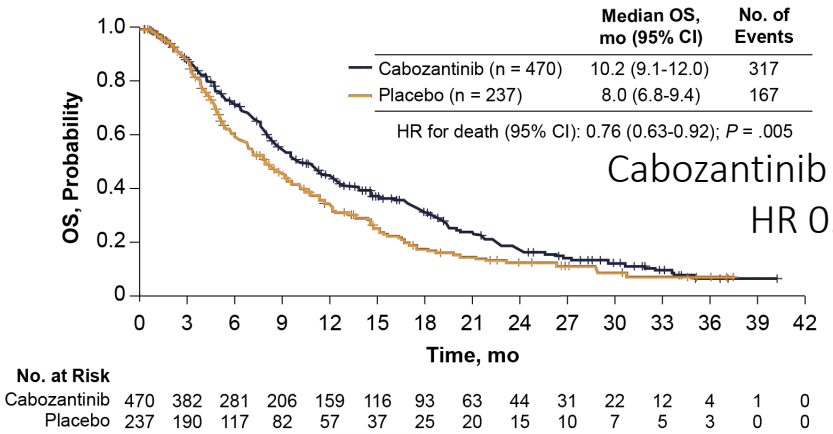
All of these 2nd line treatments have been studied after sorafenib as 1st line treatment.

2nd Line Systemic Therapies With Level 1 Evidence

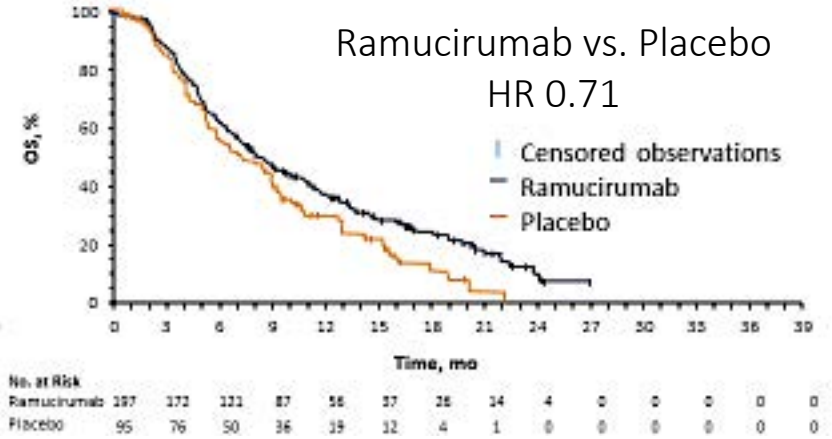
- Regorafenib improved OS as 2nd line therapy after progression on sorafenib in patients who tolerated sorafenib[1]
- Cabozantinib improved OS as 2nd or 3rd line of therapy after sorafenib[2]
- Ramucirumab improved OS as 2nd line therapy after sorafenib in patients with AFP ≥ 400 ng/mL[3]
  - First biomarker-selected therapy in HCC



Regorafenib vs. Placebo
HR 0.63



Cabozantinib vs. Placebo
HR 0.76



Ramucirumab vs. Placebo
HR 0.71

1. Bruix J, et al. *Lancet*. 2017;389(10064):56-66
2. Abou-Alfa G, et al. *N Engl J Med*. 2018;379(1):54-63
3. Zhu AX et al. *Lancet Oncol.* 2019;20(2):282-96

Role for Multikinase Inhibitors After 1st Line ICI-Based Therapy

- There is limited prospective data for treatment selection after 1st line ICI-based therapies; multikinase inhibition has biologic rationale
- Retrospective analysis of 71 patients treated with 2nd line TKI (sorafenib or lenvatinib) after 1st line atezo+beva reported median PFS 3.4 months, median OS 14.7 months[1]
  - Median PFS was longest for lenvatinib-treated patients: 6.1 vs 2.5 months (p=0.004)
- A systematic literature review of cabozantinib treatment after prior ICI therapies showed benefit across range of tumor types including HCC[2]

1. Yoo et al. Liver Cancer 2021;10:107-14; 2. Graham et al. Cancer Treatment Rev 2022;110:102453

Beyond 1st Line: Currently Approved 2nd Line Therapies for HCC

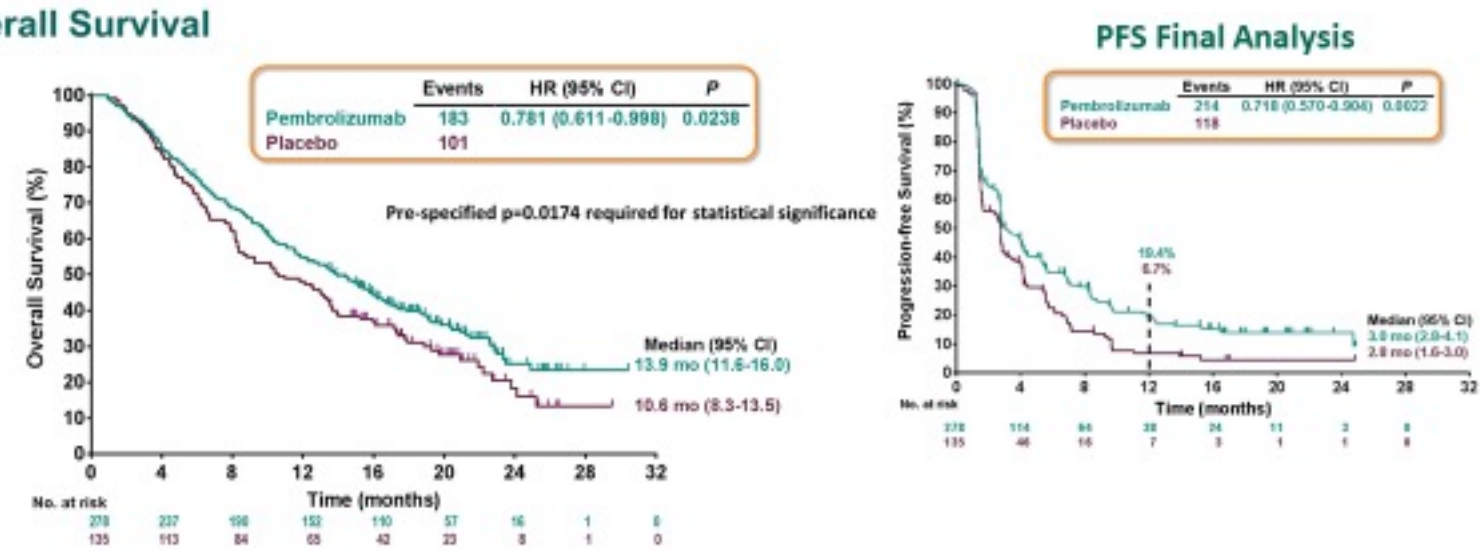
- Antiangiogenic therapies with USFDA approval and level 1 evidence:
  - Regorafenib: Multikinase inhibitor, similar to sorafenib including VEGFR1-3, BRAF, PDGFR, RET
  - Cabozantinib: Multikinase inhibitor with targets including VEGFR1-3, MET, AXL
  - Ramucirumab (serum AFP ≥400 ng/mL): Monoclonal antibody targeting VEGFR2
- ICI with USFDA accelerated approval based upon phase 1/2 studies:
  - Pembrolizumab: Anti-PD-1 ICI
  - Nivolumab + ipilimumab: Anti-PD-1 plus anti-CTLA-4 ICI combinations

All of these 2nd line treatments have been studied after sorafenib as 1st line treatment.

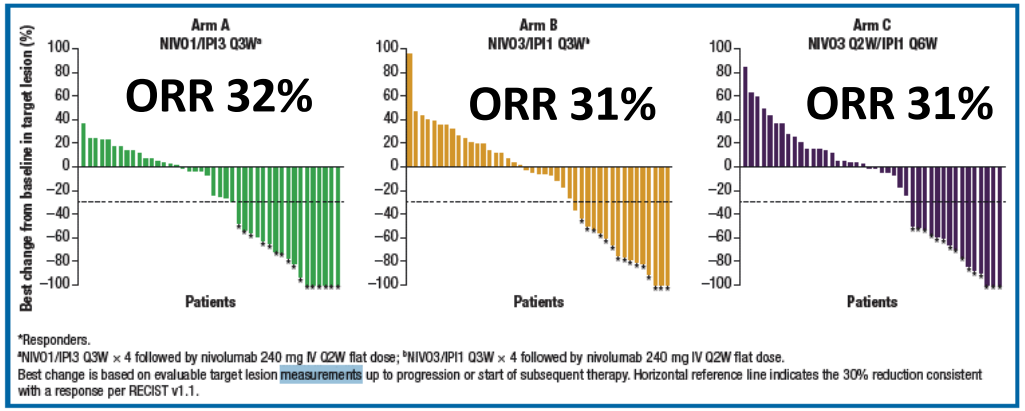
2nd Line ICI Therapies with Accelerated Approvals

- Pembrolizumab
  - KEYNOTE 240[1] did not improve OS but showed durable ORR 18.3%; KEYNOTE-394[2] improved OS, PFS, and ORR compared to placebo
- Nivolumab + Ipilimumab[3]
  - Deep and durable responses in ~30% by RECIST 1.1
  - Median DOR > ~17 months
  - Steroids required ~25-50%

KEYNOTE 240: Pembrolizumab vs. Placebo[1]



CheckMate-040: Nivolumab + Ipilimumab Cohort[3]



1. Finn RS, et al. *J Clin Oncol.* 2020;38(3):193-202
2. Clinicaltrials.gov, NCT03062358; Qin et al. GI ASCO 2022
3. Yau T, et al. *JAMA Oncol.* 2020;6(11):e204564

KEYNOTE-394 Study Design (NCT03062358) and Statistical Considerations

Key Eligibility Criteria

- Confirmed HCC[a]
- Measurable disease per RECIST v1.1[b]
- Progression during or after or intolerance to sorafenib or oxaliplatin-based chemotherapy
- Child-Pugh class A
- BCLC stage C or B not amenable or refractory to locoregional therapy, and not amenable to curative treatment
- ECOG PS 0 or 1

Stratification Factors

- Prior treatment (sorafenib vs. chemotherapy)
- Macrovascular invasion (yes vs. no)
- HCC etiology (HBV vs. other [HCV or non-infection])

R (2:1)
N = 453

n = 300 → Pembrolizumab 200 mg Q3W + BSC for up to 35 cycles

n = 153 → Placebo Q3W + BSC for up to 35 cycles

End Points

- Primary: OS
- Secondary: PFS, ORR, DOR, DCR, TTP (all assessed by BICR per RECIST v1.1), and safety/tolerability

- Overall Type I error = 0.025 controlled across testing of OS, PFS, and ORR[1]
  - Initial allocation PFS = 0.002; OS = 0.023
  - Re-allocated per multiplicity strategy specified in the protocol among 3 endpoints above
- Per protocol, there were 2 interim and 1 final analysis for OS and 1 interim and 1 final analysis for PFS and ORR
  - Interim analysis for PFS and ORR at the time of OS 1st interim analysis
  - Final analysis at the time of OS 2nd interim analysis
- Efficacy boundaries
  - $P = 0.0193$ for OS (final analysis cutoff, June 30, 2021, based on 350 observed events)
  - $P = 0.0134$ for PFS and $P = 0.0091$ for ORR (at 2nd interim cutoff, June 30, 2020; only if OS criteria met)

[a]Histologically, cytologically, or radiographically confirmed HCC. [b]Based on investigator assessment.

1. Maurer W, Bretz F. *Stat Biopharm Res*. 2013; 5(4): 311-20. 2. Finn RS et al. *J Clin Oncol*. 2020;38:193-202

Median time from randomization to data cutoff for the final analysis was 33.8 months (range 18.7-49.0) and 21.8 months (range 6.7-37.0) for the 2nd interim analysis.

Baseline Demographics and Clinical Characteristics

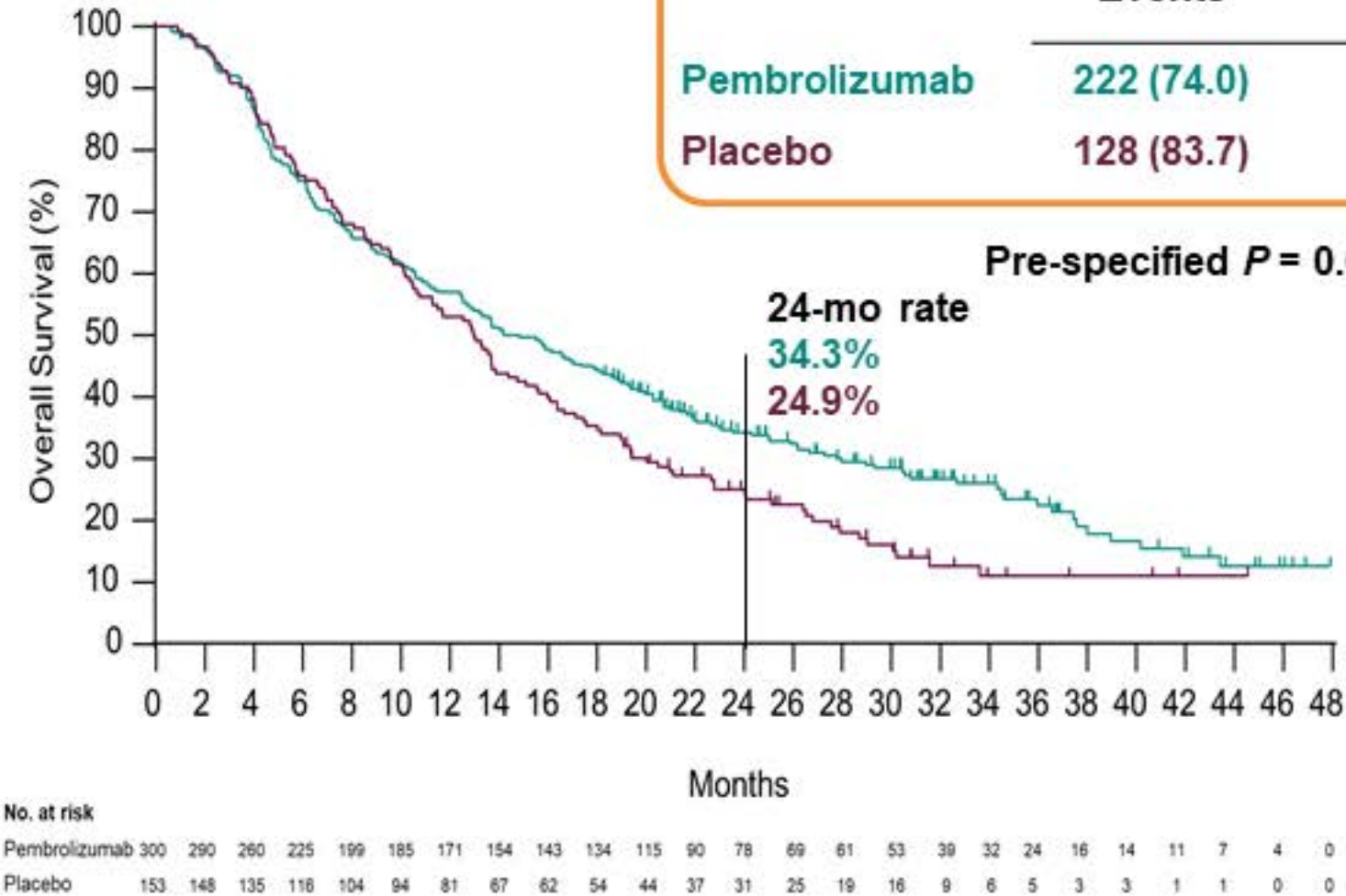
	Pembrolizumab n = 300	Placebo n = 153
Age, median (range), years	54 (22-82)	54 (22-78)
≥65 years, n (%)	69 (23.0)	29 (19.0)
Male	257 (85.7)	126 (82.4)
Region[a]		
China	255 (85.0)	132 (86.3)
Ex-China	45 (15.0)	21 (13.7)
ECOG PS 1	176 (58.7)	93 (60.8)
Child-Pugh Class A	300 (100.0)	153 (100.0)
α-fetoprotein ≥200 ng/mL	169 (56.3)	78 (51.0)
Extrahepatic spread	232 (77.3)	120 (78.4)
Macrovascular invasion	33 (11.0)	17 (11.1)
BCLC stage C	277 (92.3)	146 (95.4)

	Pembrolizumab n = 300	Placebo n = 153
Hepatitis B status		
Positive[b]	236 (78.7)	124 (81.0)
Hepatitis C status		
Positive[c]	5 (1.7)	1 (0.7)
Prior first-line treatment		
Sorafenib	272 (90.7)	139 (90.8)
Oxaliplatin-based chemotherapy	28 (9.3)	14 (9.2)

n (%) unless otherwise specified. Percentages may not equal 100 because of rounding. [a]Region for China includes China Mainland, Hong Kong, and Taiwan; region for ex-China includes Republic of Korea and Malaysia. [b]Hepatitis B status was collected from the electronic case report form and positive was defined as hepatitis B surface antigen positive and/or detectable HBV DNA based on investigator assessment. [c]Hepatitis C was collected from the electronic case report form and positive was defined as anti–hepatitis C antibody positive and detectable HCV RNA based on investigator assessment.

Overall Survival

	Events	OS, median (95% CI), mo	HR (95% CI)	*P*[a]
Pembrolizumab	222 (74.0)	14.6 (12.6-18.0)	0.79 (0.63-0.99)	*0.0180*
Placebo	128 (83.7)	13.0 (10.5-15.1)		



Pre-specified *P* = 0.0193 required for statistical significance

Post-Study Systemic Anticancer Therapy

	Pembrolizumab n = 300	Placebo n = 153
Any post-study systemic anticancer therapy	152 (50.7)	102 (66.7)
PD-1 inhibitor or PD-L1 inhibitor[b]	62 (20.7)	43 (28.1)

[a]One-sided *P* for testing difference. Data cutoff: June 30, 2021 (final analysis). [b]Includes both with/without prior exposure to other post-study systemic anticancer therapies.

Objective Response

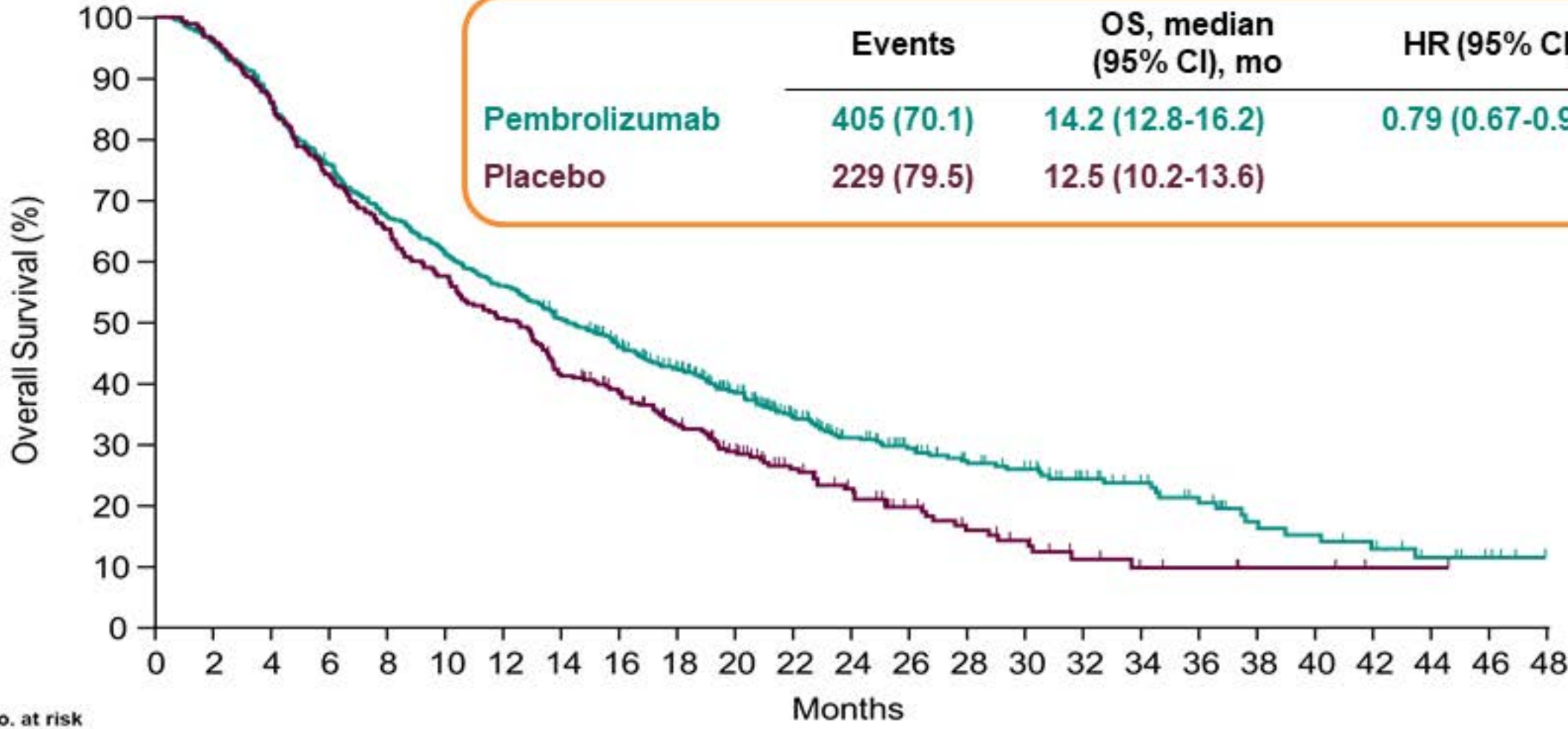
	Pembrolizumab n = 300	Placebo n = 153
ORR (CR + PR), % (95% CI)	12.7 (9.1-17.0)	1.3 (0.2-4.6)
Estimated treatment difference, (95% CI; *P*[a])	11.4 (6.7-16.0); *<0.0001*	
Best overall response, n (%)		
CR	6 (2.0)	1 (0.7)
PR	32 (10.7)	1 (0.7)
SD	115 (38.3)	70 (45.8)
Sustained SD[b]	26 (8.7)	8 (5.2)
PD	129 (43.0)	72 (47.1)
Not evaluable	10 (3.3)	1 (0.7)
Not assessable[c]	8 (2.7)	8 (5.2)
DOR,[d] median (range), mo	23.9 (2.8 to 32.0+)	5.6 (3.0+ to 5.6)

Pre-specified *P* = 0.0091 required for statistical significance

[a]One-sided *P* for testing difference. [b]Duration of stable disease ≥23 weeks (stable disease within 24-week scan window or later).[c]Includes patients with a baseline assessment (by investigator or blinded independent central review) but no postbaseline assessment on the data cutoff date, including discontinuation or death before the first postbaseline scan. [d]Assessed in the 38 patients in the pembrolizumab group and 2 patients in the placebo group who had a confirmed complete response or partial response. Data cutoff: June 30, 2020 (second-interim analysis).

Overall Survival Based on Meta-Analysis of KEYNOTE-394 and KEYNOTE-240

	Events	OS, median (95% CI), mo	HR (95% CI)
Pembrolizumab	405 (70.1)	14.2 (12.8-16.2)	0.79 (0.67-0.93)
Placebo	229 (79.5)	12.5 (10.2-13.6)	



No. at risk

Pembrolizumab	578	555	497	438	389	354	323	289	253	220	172	123	94	76	62	54	39	32	24	16	14	11	7	4	0
Placebo	288	278	248	214	188	166	146	118	104	84	67	50	39	28	20	16	9	6	5	3	3	1	1	0	0

Meta-analysis of pooled OS data from KEYNOTE-240[2] and KEYNOTE-394 was performed using all patients receiving pembrolizumab or placebo in the intent-to-treat populations of each study. Data cutoff: KEYNOTE-240: January 2, 2019 (final analysis; Finn RS et al. *J Clin Oncol* 2020;38:193-202); KEYNOTE-394: June 30, 2021 (final analysis).

Role of Anti-PD-(L)1 and Anti-CTLA-4 Therapies After Prior ICI-based Combinations

- There is no established role for ICI monotherapy after receipt of prior ICI monotherapy or in combination
- Combination of anti-PD-(L)1 + anti-CTLA-4 has shown potential for eliciting responses after progression on anti-PD-(L)1 monotherapy in multiple tumor types[1,2]
- A retrospective analysis of patients treated with nivolumab plus ipilimumab after 1st line atezo+beva reported objective responses in 3 of 10 (30%) patients treated[3]

1. Pires da Silva et al. Lancet Oncol. 2021;22(6):836-47; 2. Choueiri et al. J Immunother Cancer 2022; e005780; 3. Roessler et al. J Cancer Res and Clin Oncol 2022;doi:10.1007/s00432-022-04206-8

Selection and Sequencing of ≥ 2nd Line Treatments

Factors to consider:

- Which 1st line therapy was received?
  - What was response and duration?
  - What was AE profile?
- Contraindication to ICI?
  - E.g. transplant, prior high-grade immune-related toxicity, significant autoimmune disease
- Contraindication to anti-angiogenic therapies?
  - E.g. significant vascular disease, severe proteinuria, non-healing wounds, high risk for bleeding
- AFP
- Liver function

Current consensus strategies:

- Progressed on 1st line ICI-based combination → 2nd line TKI
- Progressed on 1st line TKI → 2nd line ICI or ICI combination
- Contraindication to ICI → TKI or ramucirumab if AFP ≥ 400 ng/mL
- Contraindication to anti-angiogenic therapy → pembrolizumab, nivolumab + ipilimumab
- Discontinued 1st line therapy for reasons other than progression → individualized treatment decision
- Child Pugh B liver function → limited data; ICI monotherapy has shown acceptable safety in small studies in Child Pugh B HCC; consider empiric TKI dose reduction
- Clinical trials are needed!

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Hepatocellular Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1] • Tremelimumab-actl + durvalumab (category 1)[b,2]	• Sorafenib (Child-Pugh Class A) ([category 1] or B7)[d,e,3,4] • Lenvatinib (Child-Pugh Class A only)[5,6] (category 1) • Durvalumab[b,7] • Pembrolizumab[b,8] (category 2B)	• Nivolumab[b,9] (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B)

Subsequent-Line Therapy[f] if Disease Progression[g]

Options	Other Recommended Regimens	Useful in Certain Circumstances
• Regorafenib (Child-Pugh Class A only) (category 1)[h,10] • Cabozantinib (Child-Pugh Class A only) (category 1)[i,11] • Ramucirumab (AFP ≥400 ng/mL and Child-Pugh Class A only) (category 1)[i,12] • Lenvatinib (Child-Pugh Class A only) • Sorafenib (Child-Pugh Class A or B7)[d,e]	• Nivolumab + ipilimumab (Child-Pugh Class A only)[b,i,13] • Pembrolizumab (Child-Pugh Class A only) (category 2B)[b,j,k,14-16]	• Nivolumab (Child-Pugh Class B only)[b,j,17-20] (category 2B) • Dostarlimab-gxly[b,j,l,21,22] for MSI-H/dMMR tumors (category 2B) • For *RET* gene fusion-positive tumors: ▸ Selpercatinib (category 2B)[23]

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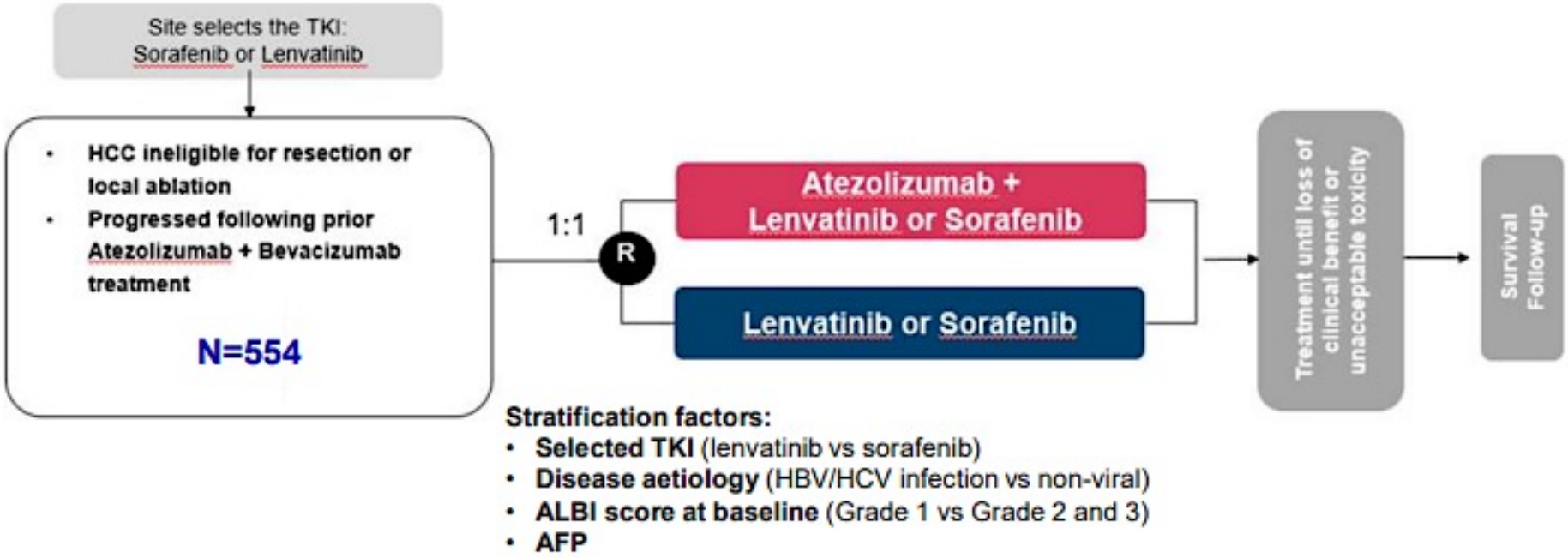
Current Summary of ≥ 2nd Line HCC Therapy

- 2nd line treatment options:
  - Anti-angiogenic: Regorafenib, cabozantinib, ramucirumab (if AFP ≥ 400 ng/mL)
    - Lenvatinib, sorafenib also reasonable options
  - Immunotherapy: Pembrolizumab, nivolumab + ipilimumab
- All current FDA-approved treatments have been studied after 1st line sorafenib (or as 1st line)
- Current selection of 2nd line treatment is based upon 1st line therapy received plus comorbidity profile
- Need ≥ 2nd line clinical trials to inform choice of treatment after ICI-based 1st line therapy
  - Phase 3 IMbrave251 trial ongoing of 2nd line sorafenib or lenvatinib ± atezolizumab (NCT04770896)
- New immuno-oncology strategies and combinations are being studied in early-phase trials

IMbrave251 Study Design



Efficacy objectives
- **Primary:** OS
- **Secondary:** PFS,* ORR,* DoR,* TTP,* TTD in PROs

Safety objective
- Incidence and severity of AEs

Exploratory objectives
- Biomarkers
- Pharmacokinetics

NCT04770896

New Agents and Strategies Under Investigation for Subsequent HCC Therapy

- ICI combinations with targeted therapies
- ICI combinations with complementary immune checkpoint pathways
  - LAG-3, TIGIT, others
- Inhibition of immunosuppressive myeloid pathways
- Promoting/boosting tumor immunogenicity
  - Locoregional therapy combinations, oncolytic viruses, cellular therapies targeting tumor antigens
- Many others!

clinicaltrials.gov; Llovet et al. Nature Cancer 2022;3:386-401

MODULE 3: Current and Future Role of Immunotherapy in the Treatment of Advanced Biliary Tract Cancers (BTCs) — Prof Vogel

RTP
RESEARCH
TO PRACTICE

Case Presentation: 75-year-old woman with metastatic cholangiocarcinoma who received first-line gemcitabine/ cisplatin with durvalumab

Dr Warren Brenner (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Warren S Brenner, MD

"My questions for the investigators are…

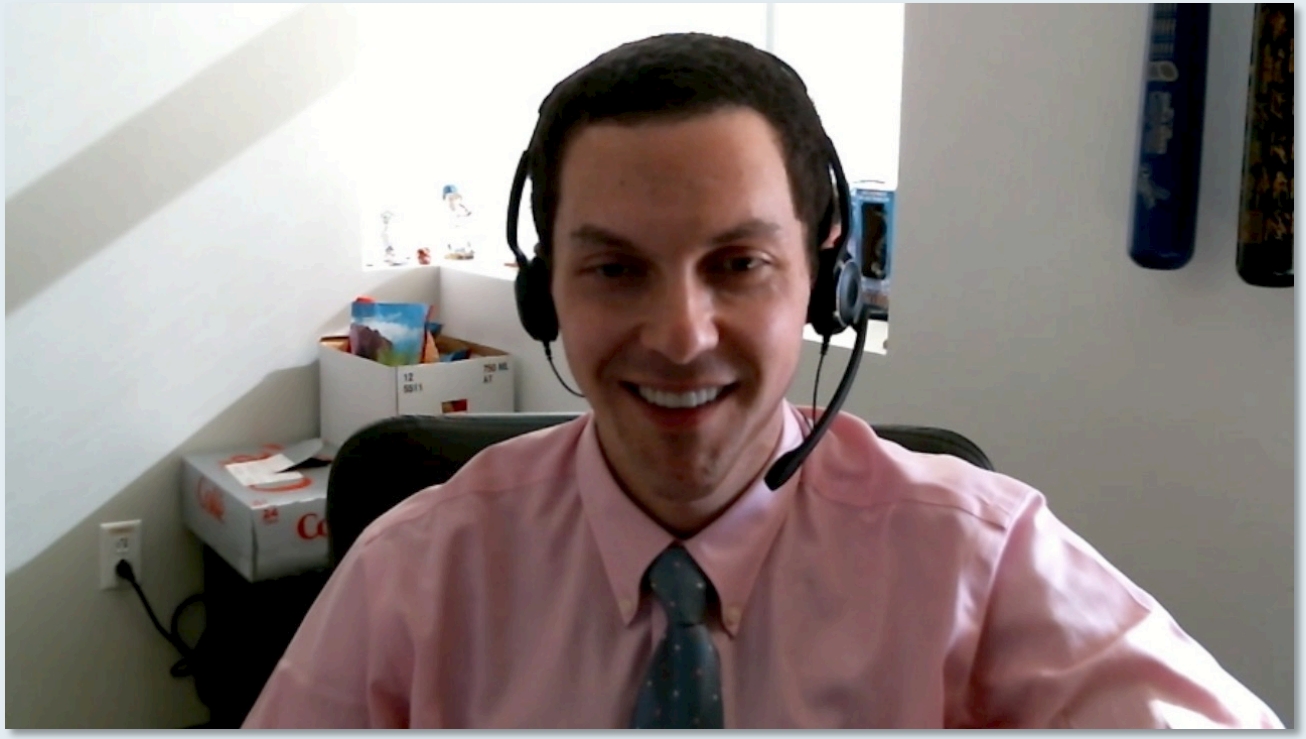
Are there subtypes, such as gallbladder cancer versus intrahepatic versus extrahepatic cholangiocarcinoma, that may respond differently to these agents, particularly checkpoint inhibitors?

Is there any differential effect based on PD-L1 and tumor mutational burden? And what are the management options for patients with progressive disease who have no targetable mutations?

Another question for the investigators is, there are a lot of liquid biopsies with high tumor mutational burden readings. I think the original pembrolizumab pan-tumor approval was based on the Foundation TMB. Do they use tumor mutational burden reported on liquid biopsies?"

RTP
RESEARCH
TO PRACTICE

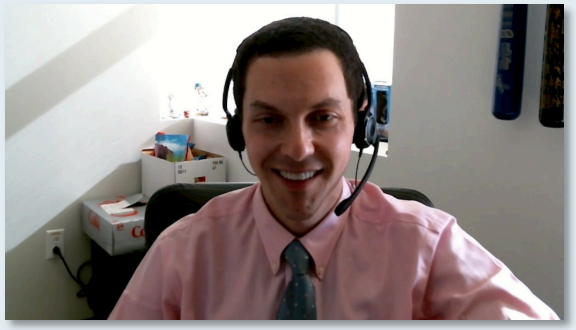
Case Presentation: 72-year-old man with localized cholangiocarcinoma deemed potentially resectable with tumor response



Dr Jeremy Lorber (Beverly Hills, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY



Jeremy Lorber, MD

"The surgeon deemed him not a surgical candidate for the time being but potentially in the future. He's thus far had a partial response to durvalumab, gemcitabine and cisplatin. He's tolerated it very well. He's still not a perfect surgical candidate, and the surgeon ideally would like further response before considering resection. Any suggestions? Would you consider radiation therapy?"

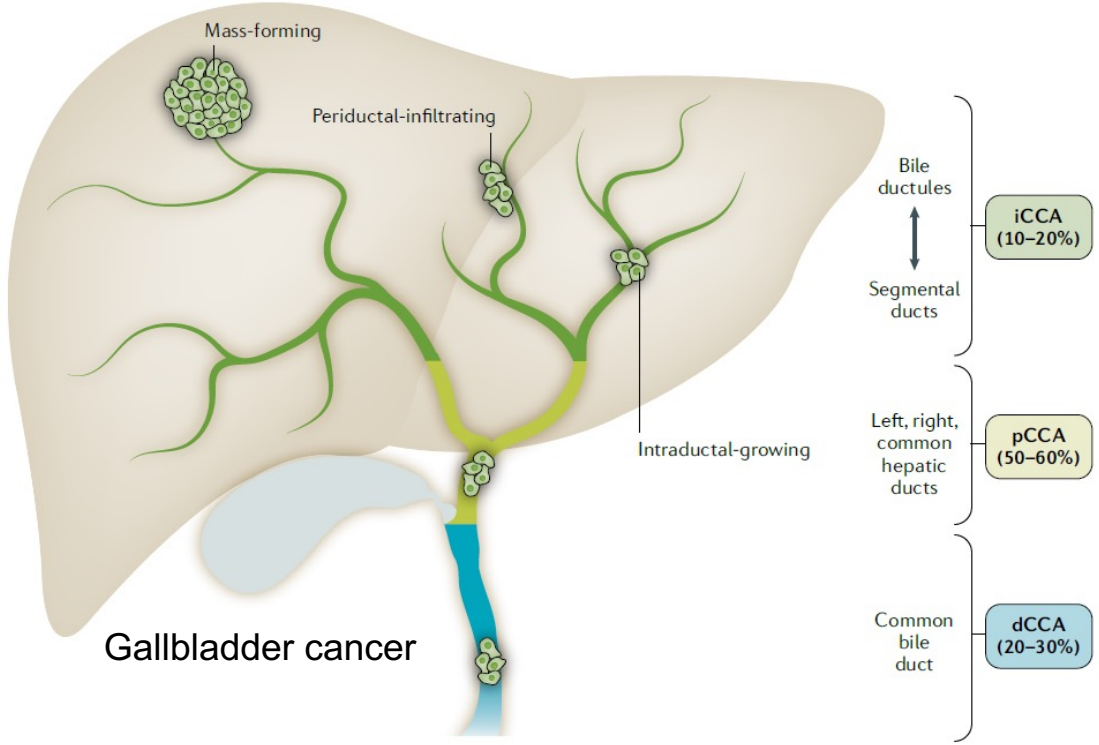
RTP
RESEARCH
TO PRACTICE

Current and Future Role of Immunotherapy in the Treatment of Advanced Biliary Tract Cancers (BTCs)

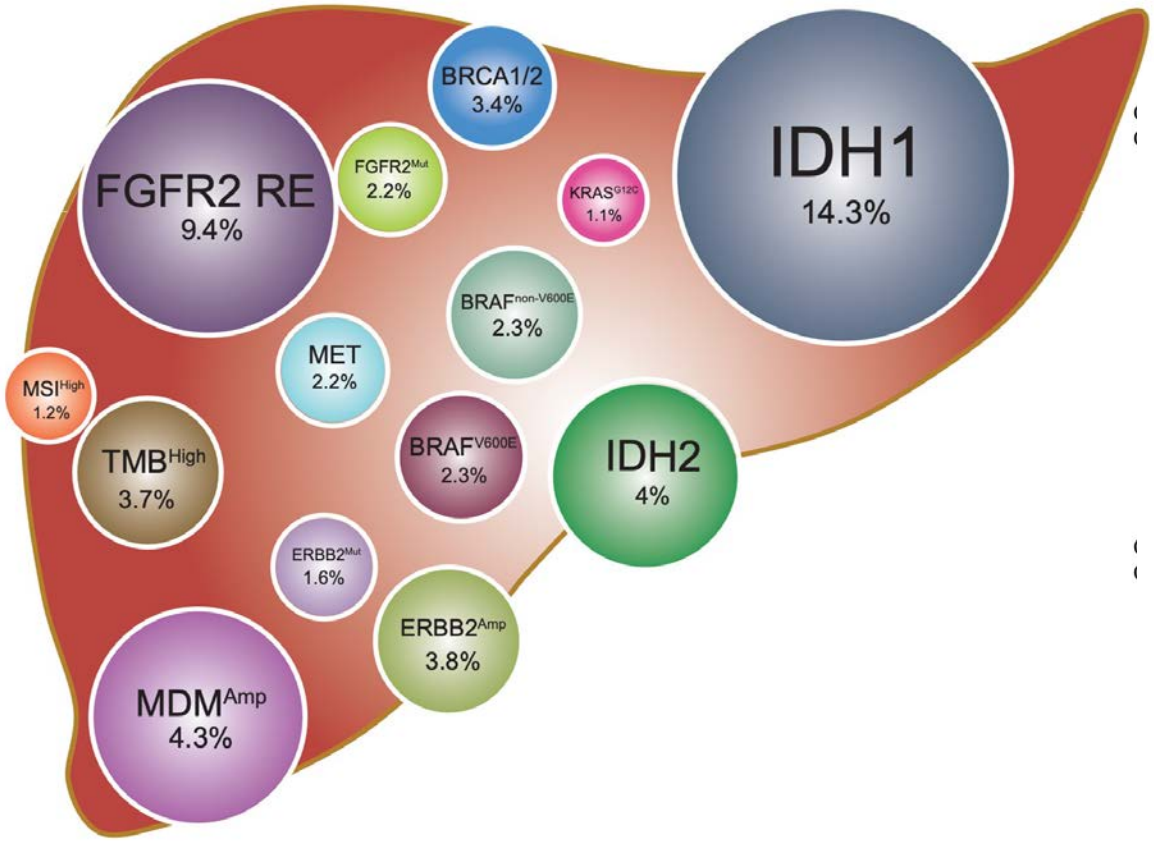
Arndt Vogel

Biliary Tract Cancers: a heterogeneous disease entity

Anatomic heterogeneity



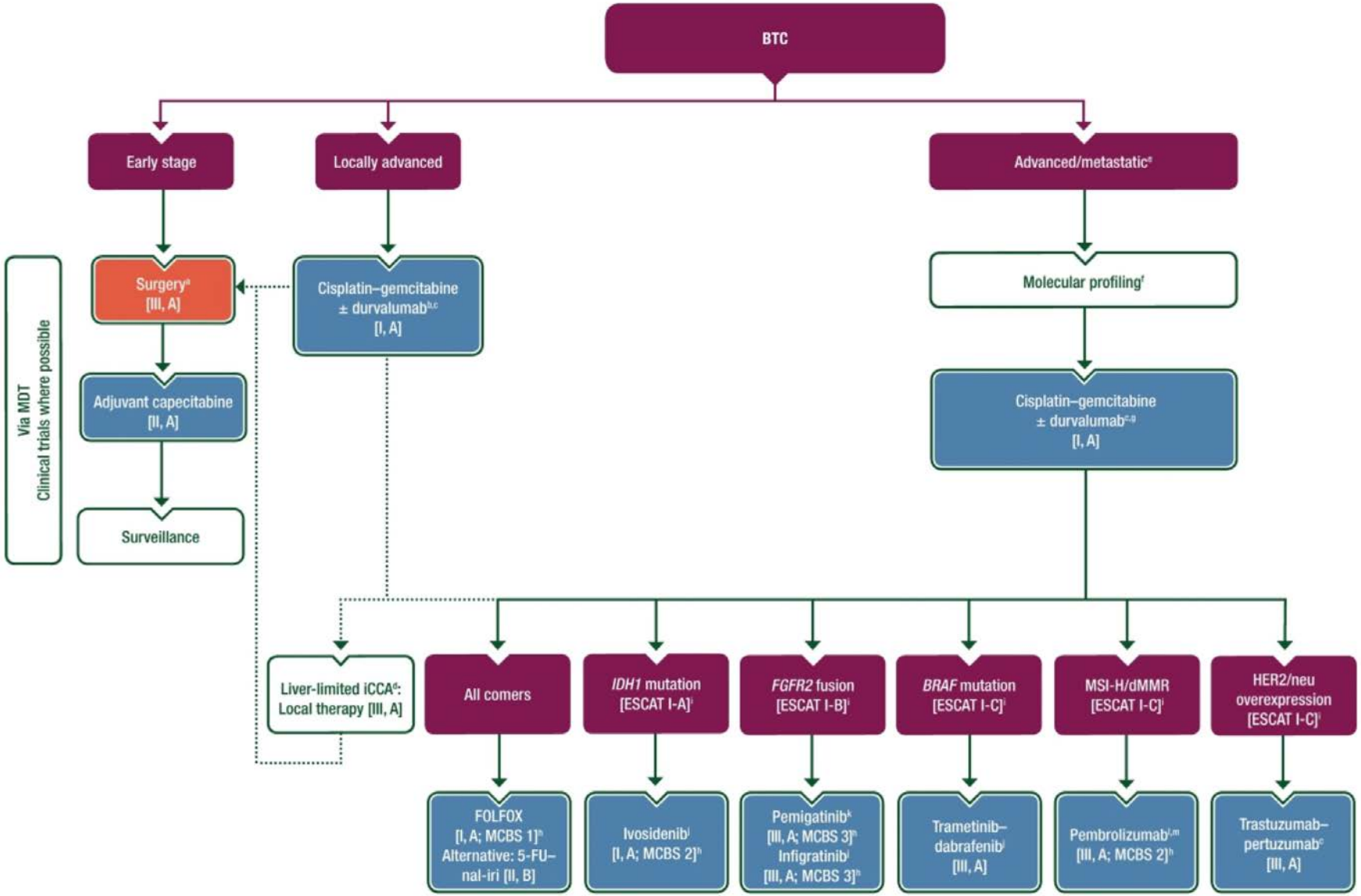
Genetic heterogeneity



Banales et al. Nat Rev Gastroent Hepatol 2020

Vogel/Saborowski Journal of Hepatology, 2022

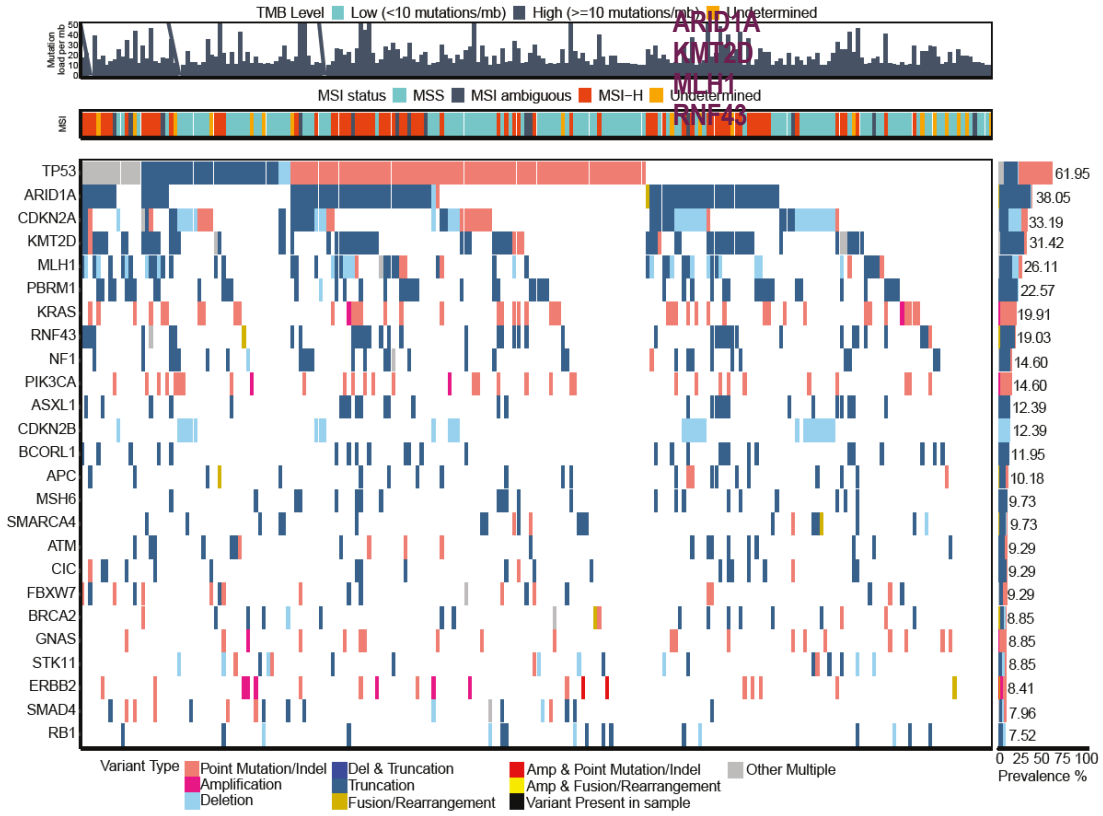
Diagnosis and Management of Biliary Tract Cancer



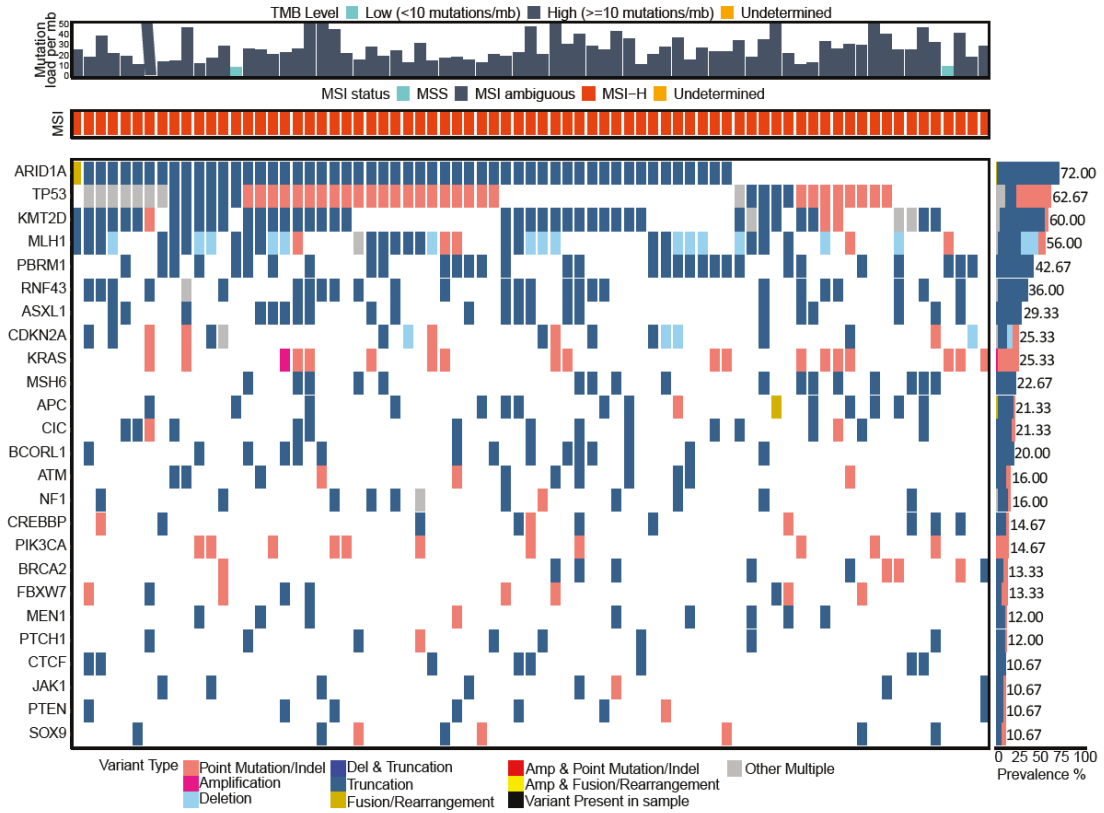
Vogel A et al. Annals of Oncology 2022

BTC: low prevalence of established IO biomarkers

TMB^{high} 226/6130 iCCAs (3.7%)



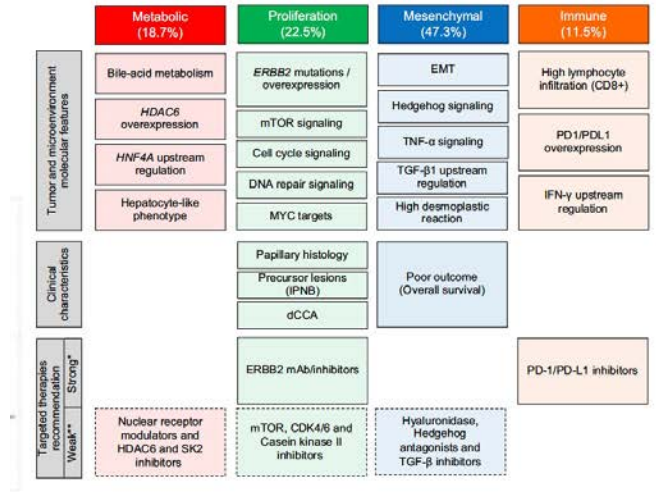
MSI^{high} 75/6130 iCCAs (1.2%)



Vogel/Saborowski Journal of Hepatology 2002

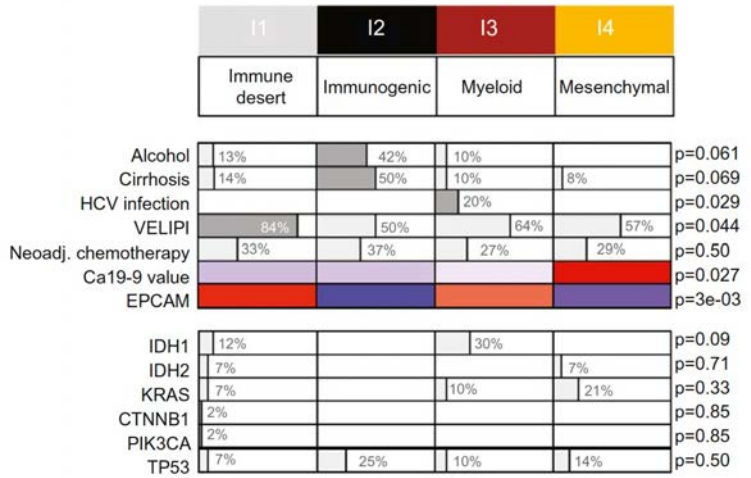
Biliary Tract Cancers: 10-30% with “immunogenic” phenotype according to “multi-omic” classification

Extrahepatic CCA, n=189; → 11% immune subclass



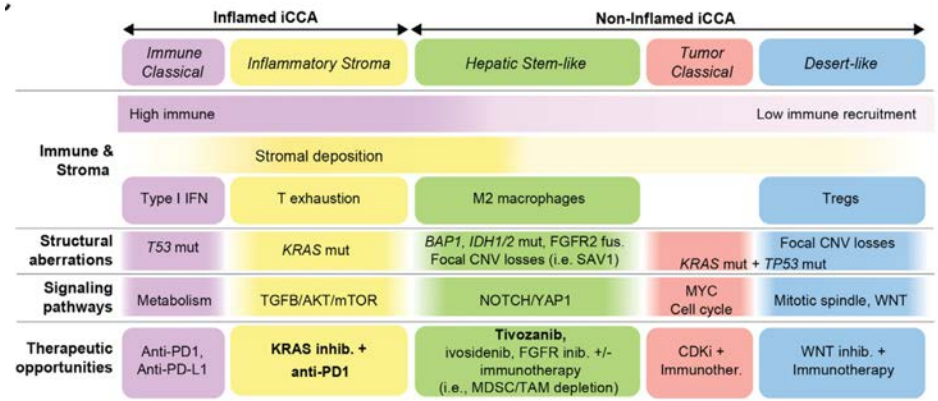
Montal et al, J. Hepatol 2020

Intrahepatic, n=566 → 13% immunogenic



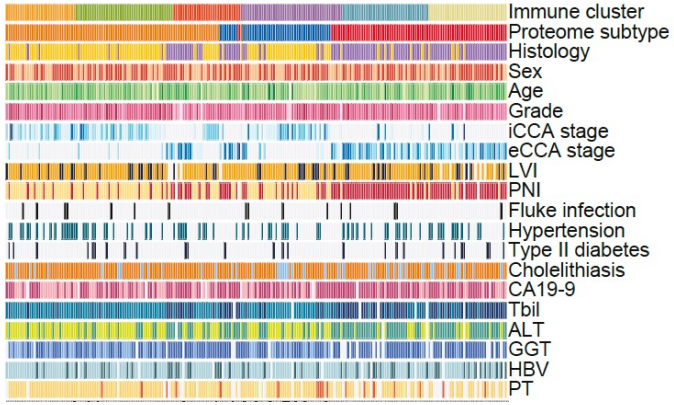
Job et al. Hepatology 2020

Intrahepatic CCA, n=900 → 10% immune classical



Martin-Serrano et al, GUT 2022

Intra- and extrahepatic, n=217 → 30% „immun-responsive“



Deng et al, Hepatology 2022

Pembrolizumab in Advanced BTC with Proficient MMR/MSS: KEYNOTE-158

N=104, multicenter basket trial biliary tract cancer (BTC) cohort with planned biomarker analyses

≥1 prior line of therapy, median 2

ICC, ECC, GBC % not reported

PD-L1+ (CPS ≥1, 22C3) 59%

99 with proficient mismatch repair (pMMR), 5 unknown

Treatment-related AE Grade 3-5 in 13.5%

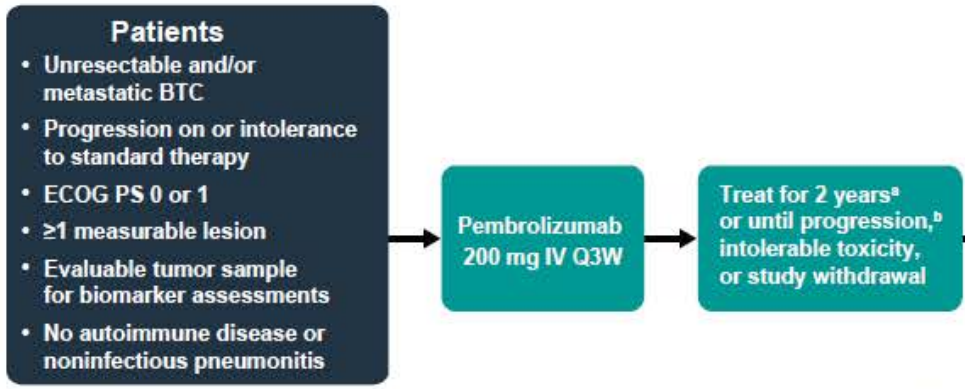
Confirmed PR (central) in 5.8% overall

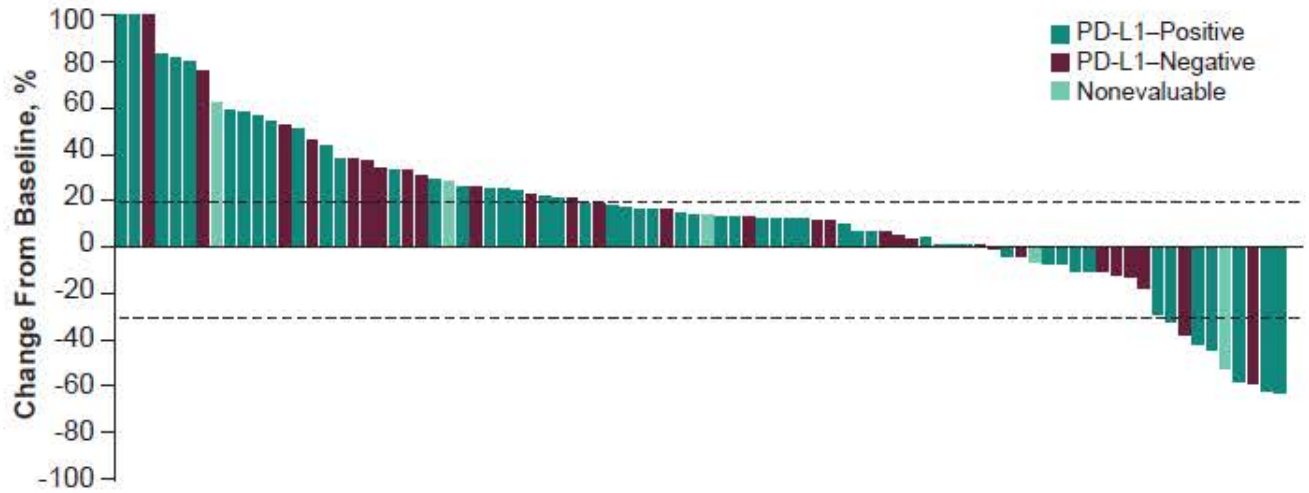
6.6% for PD-L1+

2.9% PD-L1-

mPFS 2.0 months

mOS 7.4 months

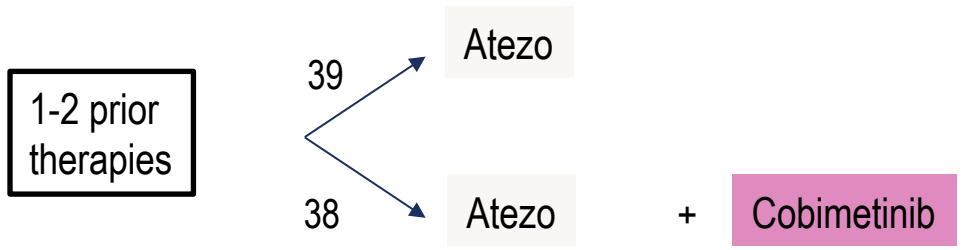


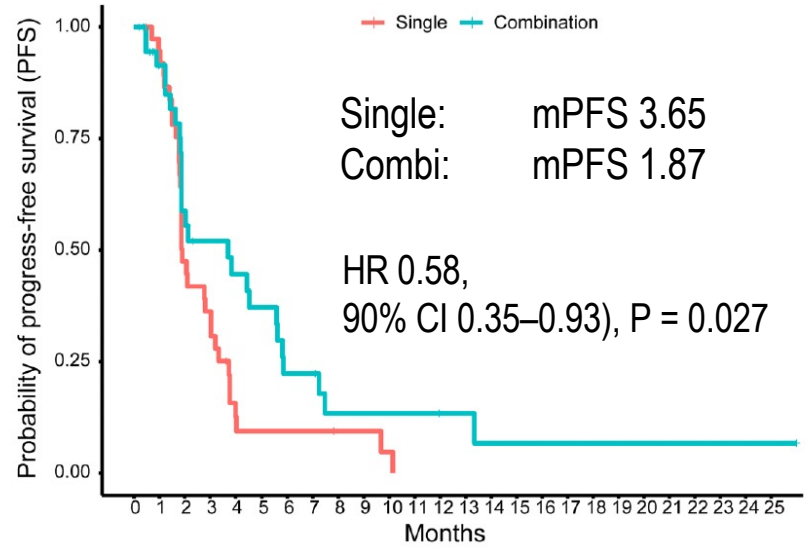


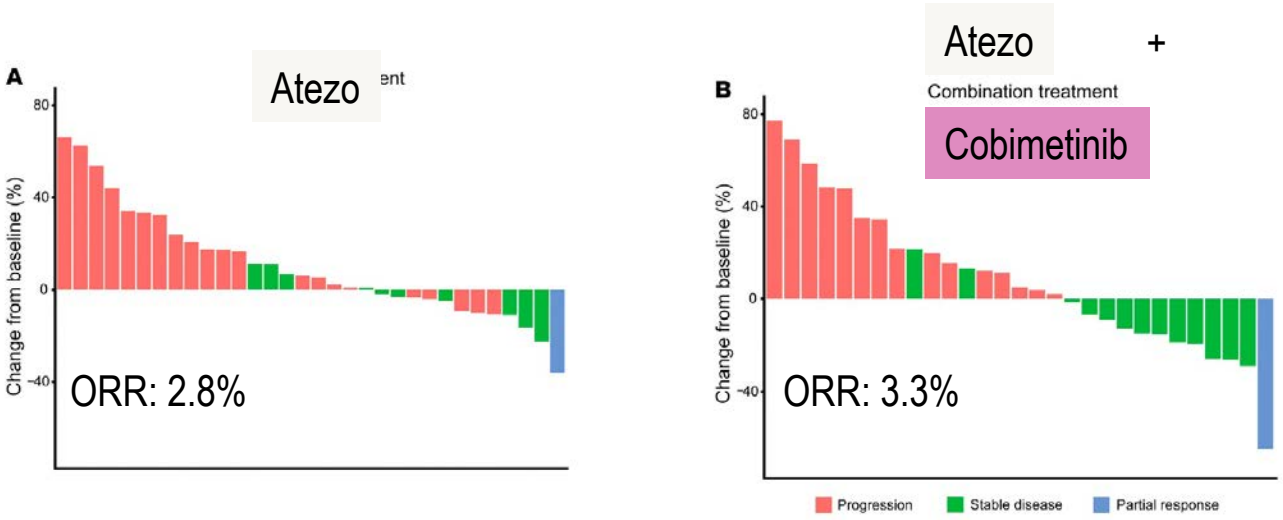
Piha-Paul et al. Int J Cancer 2020;147(8):2190-8

Chemo-free approaches: IO +/- MEK in BTC: Atezolizumab (PD-L1) + Cobimetinib (MEK)

Rationale:
MEK inhibition enhances MHC1 expression, PD-L1 expression, and CD8+ T cell infiltration







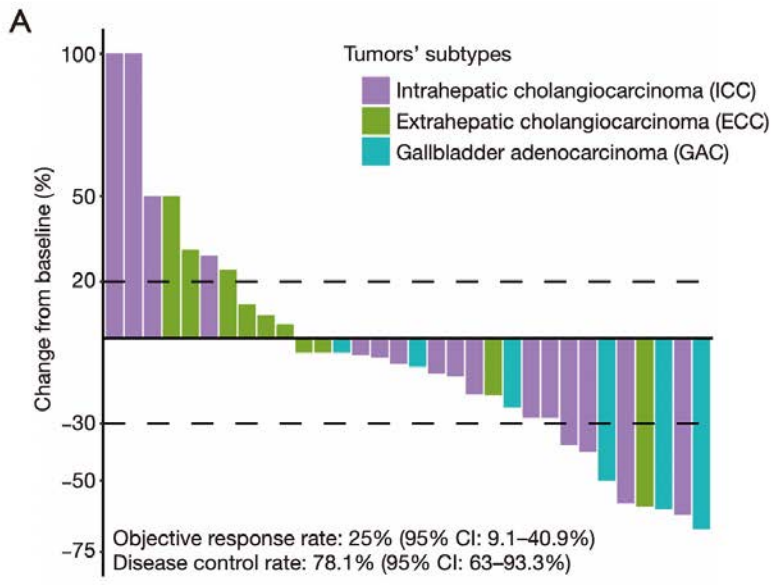
Formally positive (primary EP PFS)
Low ORR

Yarchoan et al, JCI 2021

IO + anti-angiogenic Pembrolizumab/Lenvatinib

N= 32
PFS 4.9 mo
OS: 11.0 mo
ORR: 25%

AE 3/4: 62%



Lin J, et al. Hepatobiliary Surg Nutr. 2020

IO + IO (BTC subgroup CA209-538) Nivolumab/Ipilimumab

N= 39
PFS: 2.9 mo
OS: 5.7 mo
ORR: 23%

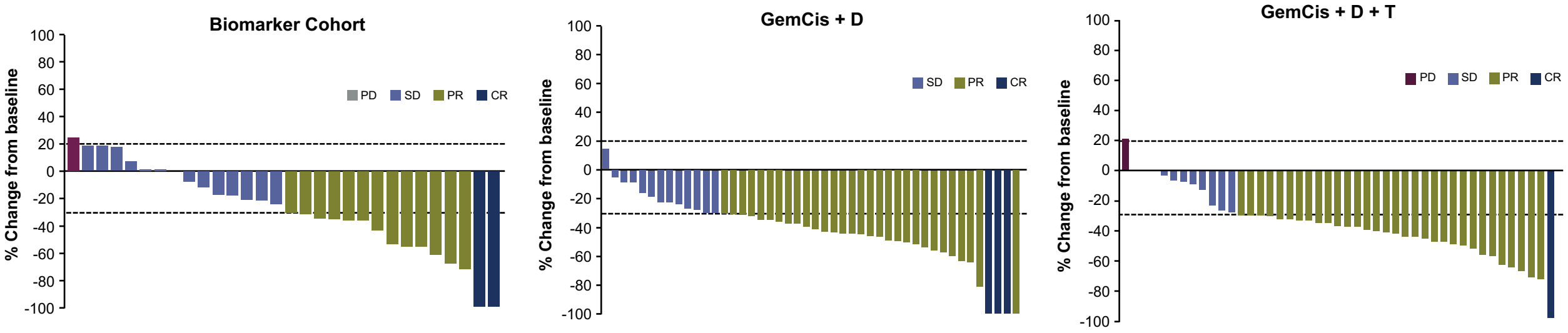
IR-AE: 49% (15% >= 3˚)

Table 2. Antitumor Activity of Ipilimumab and Nivolumab

	No. (%)			
			Cholangiocarcinoma	
Best overall response	Total cohort (n = 39)	Gallbladder (n = 13)	Intrahepatic (n = 16)	Extrahepatic (n = 10)
Objective response rate (CR or PR)	9 (23)	4 (31)	5 (31)	0
Disease control rate (CR, PR, or SD)	17 (44)	9 (70)	7 (44)	1 (10)
CR	0	0	0	0
PR	9 (23)	4 (31)	5 (31)	0
SD	8 (21)	5 (39)	2 (13)	1 (10)
No assessment[a]	9 (23)	2 (15)	3 (19)	4 (40)
Progressive disease	13 (33)	2 (15)	6 (37)	5 (50)
Duration of response, median (range), mo[b]	Not reached (2.5-23+)	2.5+, 5.7, 11.8+, and 23+ mo	3, 4.2, 9, 10.8, and 14.8 mo	NA

Klein et al, JAMA Oncol 2020

MediTreme Study: Best Objective Response



- Objective response rates were similar in the GemCis + D cohort and GemCis + D + T cohort, and were higher compared with the BMC.
- Complete response rates were lower in GemCis + D + T cohort, whereas BMC and GemCis + D cohorts exhibited similar CR rates.
- GemCis + D + T cohort had the highest partial response rate among the three cohorts.
- The Biomarker cohort had the highest rate of stable disease among the three cohorts.
- Disease progression was not observed in the GemCis + D cohort.

CR = complete response; D = durvalumab; GemCis = gemcitabine/cisplatin; OS = median overall survival; RR = response rates; PD = progressive disease; PR = partial response; SD = stable disease; T = tremelimumab.

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

IO-Phase-III studies in BTC: TOPAZ-1 & KEYNOTE-966

TOPAZ-1[1,2]

Study popula
- Adults wi
  metastati
- Recurren
  curative s
  completic
- Measural
- ECOG PS

ab 1500 mg Q4W until
eptable toxicity or study
withdrawal

ebo Q4W until PD,
table toxicity or study
withdrawal

KEYNOTE-966[3–6]

Study popula
- Adults wi
  unresecta
- Measural
- ECOG PS
- No prior s
  BTC

t to continue until:
acceptable toxicity or
withdrawal [for
olizumab and
abine]
5 cycles [for
olizumab]
cycles [for cisplatin]

NEJM Evidence

Published June 1, 2022

DOI: 10.1056/EVIDoa2200015

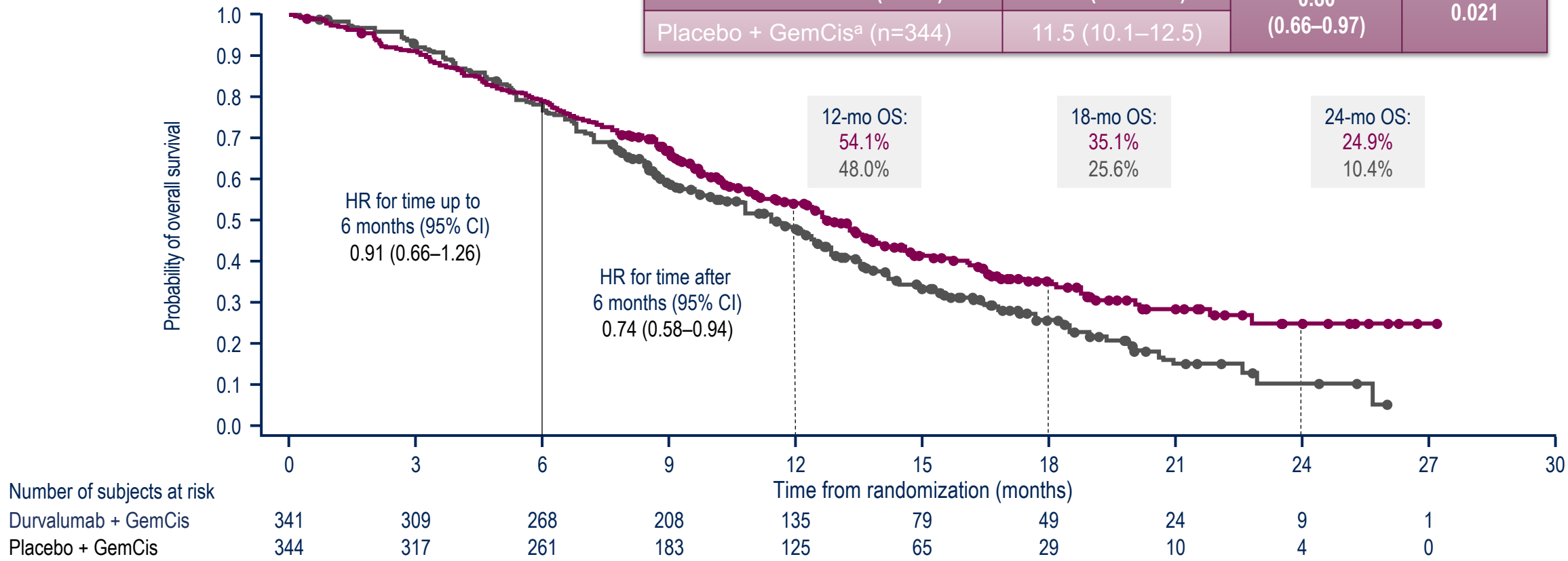
ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

Do-Youn Oh, M.D., Ph.D.,[1] Aiwu Ruth He, M.D., Ph.D.,[2] Shukui Qin, M.D.,[3] Li-Tzong Chen, M.D., Ph.D.,[4,5,6] Takuji Okusaka, M.D., Ph.D.,[7] Arndt Vogel, M.D.,[8] Jin Won Kim, M.D., Ph.D.,[9] Thatthan Suksomboon charoen, M.D.,[10] Myung Ah Lee, M.D., Ph.D.,[11] Masayuki Kitano, M.D., Ph.D.,[12] Howard Burris, M.D.,[13] Mohamed Bouattour, M.D.,[14] Suebpong Tanasanvimon, M.D.,[15] Mairéad G. McNamara, M.B., Ph.D.,[16] Renata Zaucha, M.D., Ph.D.,[17] Antonio Avallone, M.D.,[18] Benjamin Tan, M.D.,[19] Juan Cundom, M.D.,[20] Choong-kun Lee, M.D., Ph.D.,[21] Hidenori Takahashi, M.D., Ph.D.,[22] Masafumi Ikeda, M.D., Ph.D.,[23] Jen-Shi Chen, M.D.,[24] Julie Wang, Ph.D.,[25] Mallory Makowsky, Pharm.D.,[25] Nana Rokutanda, M.D., Ph.D.,[25] Philip He, Ph.D.,[25,26] John F. Kurland, Ph.D.,[25] Gordon Cohen, M.D., M.P.H.,[25] and Juan W. Valle, M.D.[16]

TOPAZ-1: Durvalumab + GemCis Improved OS vs. GemCis

	Median OS, months (95% CI)	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis[a] (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis[a] (n=344)	11.5 (10.1–12.5)		



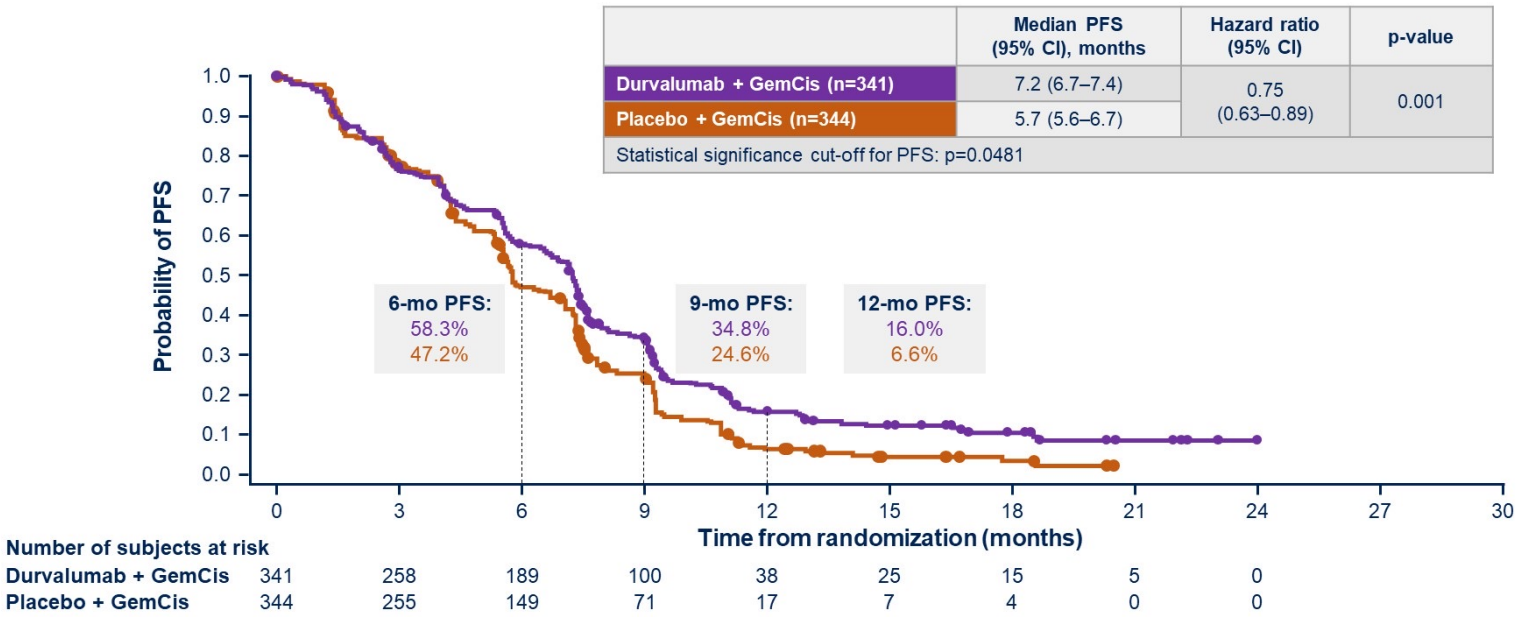
Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

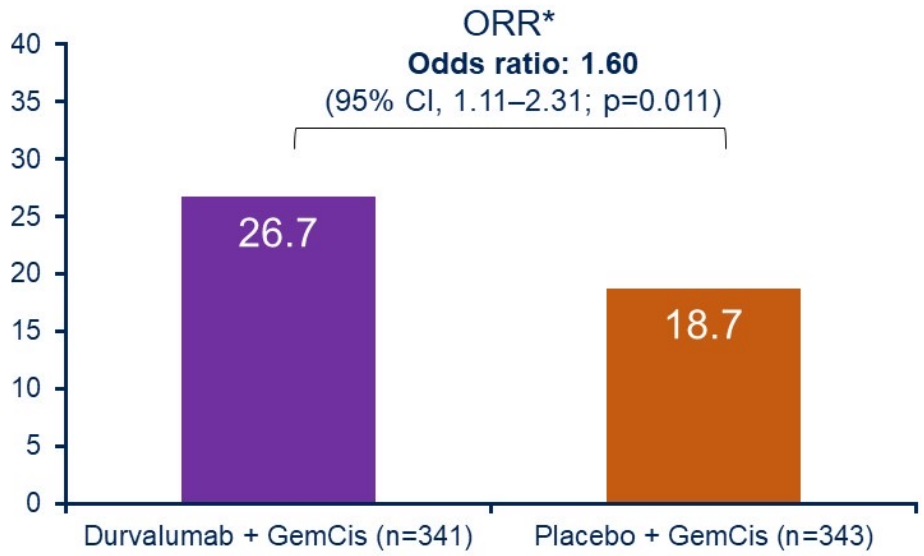
Oh D-Y, et al. @ ASCO GI

Arndt Vogel

IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

Efficacy data 2ndary objectives: PFS and ORR





Oh D-Y et al. Gastrointestinal Cancers Symposium 2022.

IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

Relevant Subgroups: "RACE"

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of the world	163 (47.8)	148 (43.0)

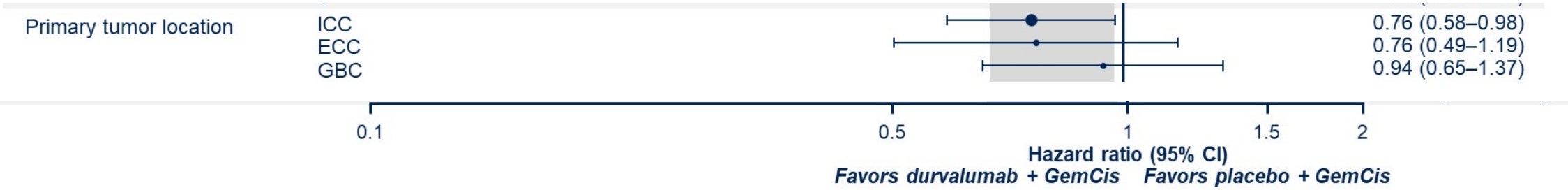
Oh D-Y et al. Gastrointestinal Cancers Symposium 2022.

ORR MEDITREME (Chemo + Durva, all Asian): 73%
ORR Topaz: 26%

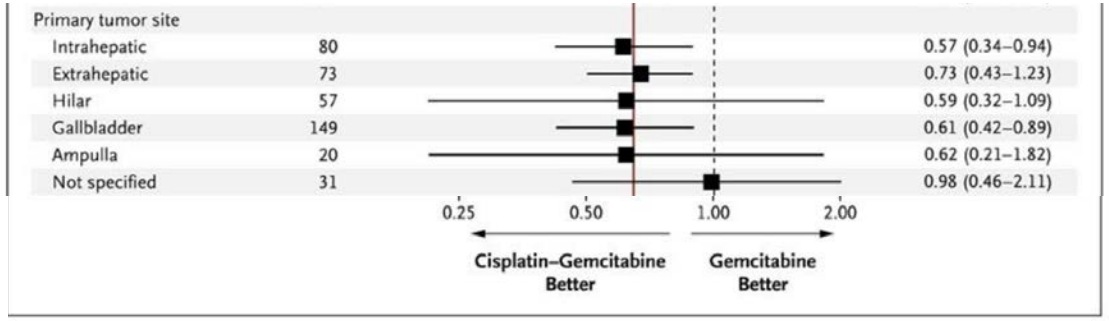
IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

Relevant Subgroups: "anatomic location"

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Primary tumor location at diagnosis, n (%)		
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)



Oh D-Y et al. Gastrointestinal Cancers Symposium 2022.



Valle et al, NEJM 2010

IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

Adverse events profile

	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any grade 3/4 TRAE	212 (62.7)	222 (64.9)

No added Durvalumab-associated toxicity

Immune-mediated AEs

Event, n (%)	Durvalumab + GemCis (n=338)		Placebo + GemCis (n=342)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any immune-mediated AE*	43 (12.7)	8 (2.4)	16 (4.7)	5 (1.5)
Hypothyroid events	20 (5.9)	0	5 (1.5)	0
Dermatitis/rash	12 (3.6)	3 (0.9)	1 (0.3)	0
Pneumonitis	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.3)
Hepatic events	4 (1.2)	2 (0.6)	2 (0.6)	1 (0.3)
Adrenal insufficiency	4 (1.2)	0	1 (0.3)	0
Diarrhea/colitis	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)
Hyperthyroid events	2 (0.6)	0	0	0
Type 1 diabetes mellitus	1 (0.3)	1 (0.3)	0	0
Pancreatic events	1 (0.3)	0	2 (0.6)	1 (0.3)
Hypophysitis	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	0	0
Renal events	0	0	2 (0.6)	0
Myositis	0	0	1 (0.3)	1 (0.3)
Other rare/miscellaneous†	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)

irAE: 12.7%

9.5% Hypothyroid events or Dermatitis

Oh D-Y et al. Gastrointestinal Cancers Symposium 2022.

TOPAZ update @ ESMO 2022

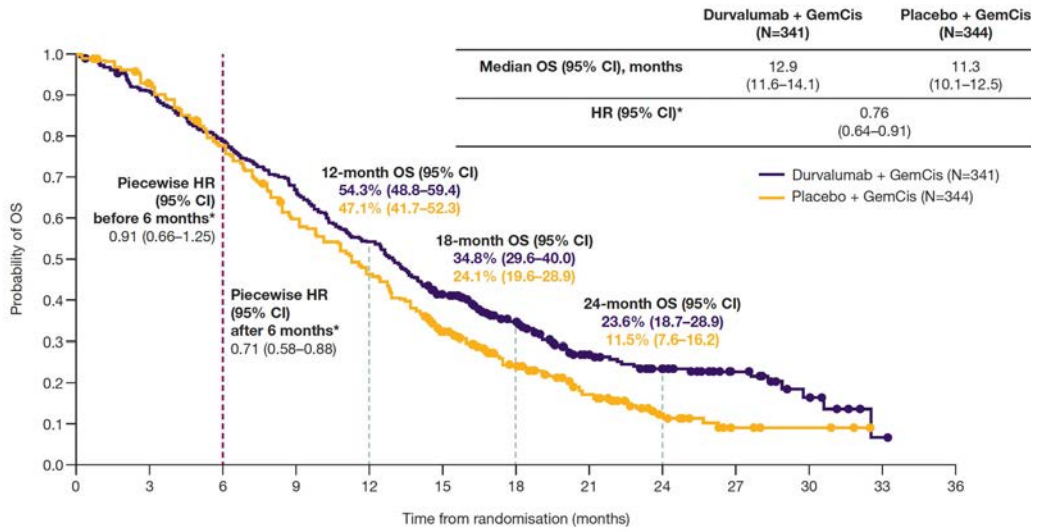


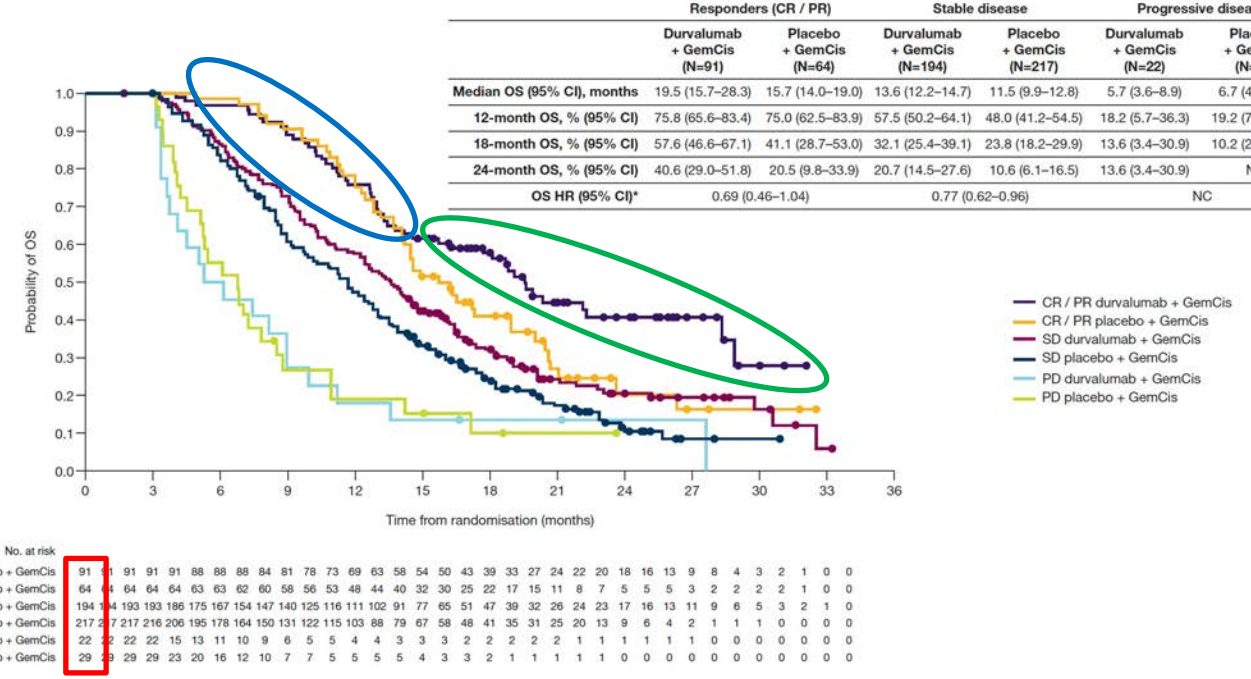
Table 1. Best objective response

	Durvalumab + GemCis (N=341)	Placebo + GemCis (N=343)
Responders,[1,*] n (%)	91 (26.7)	64 (18.7)
Complete response,[†] n (%)	7 (2.1)	2 (0.6)
Partial response,[†] n (%)	84 (24.6)	62 (18.1)
Non-responders, n (%)	250 (73.3)	279 (81.3)
Stable disease, n (%)	200 (58.7)	220 (64.1)
Progressive disease,[†] n (%)	47 (13.8)	51 (14.9)
Not evaluable	3 (0.9)	8 (2.3)

*Confirmed response; †Death recorded within 13 weeks after randomisation is considered progression
GemCis, gemcitabine and cisplatin

Do-Youn Oh et al, ESMO 2022 poster 56P

Figure 4. Kaplan-Meier curve of overall survival by best objective response



Responders: late separation, but strong long-term effect

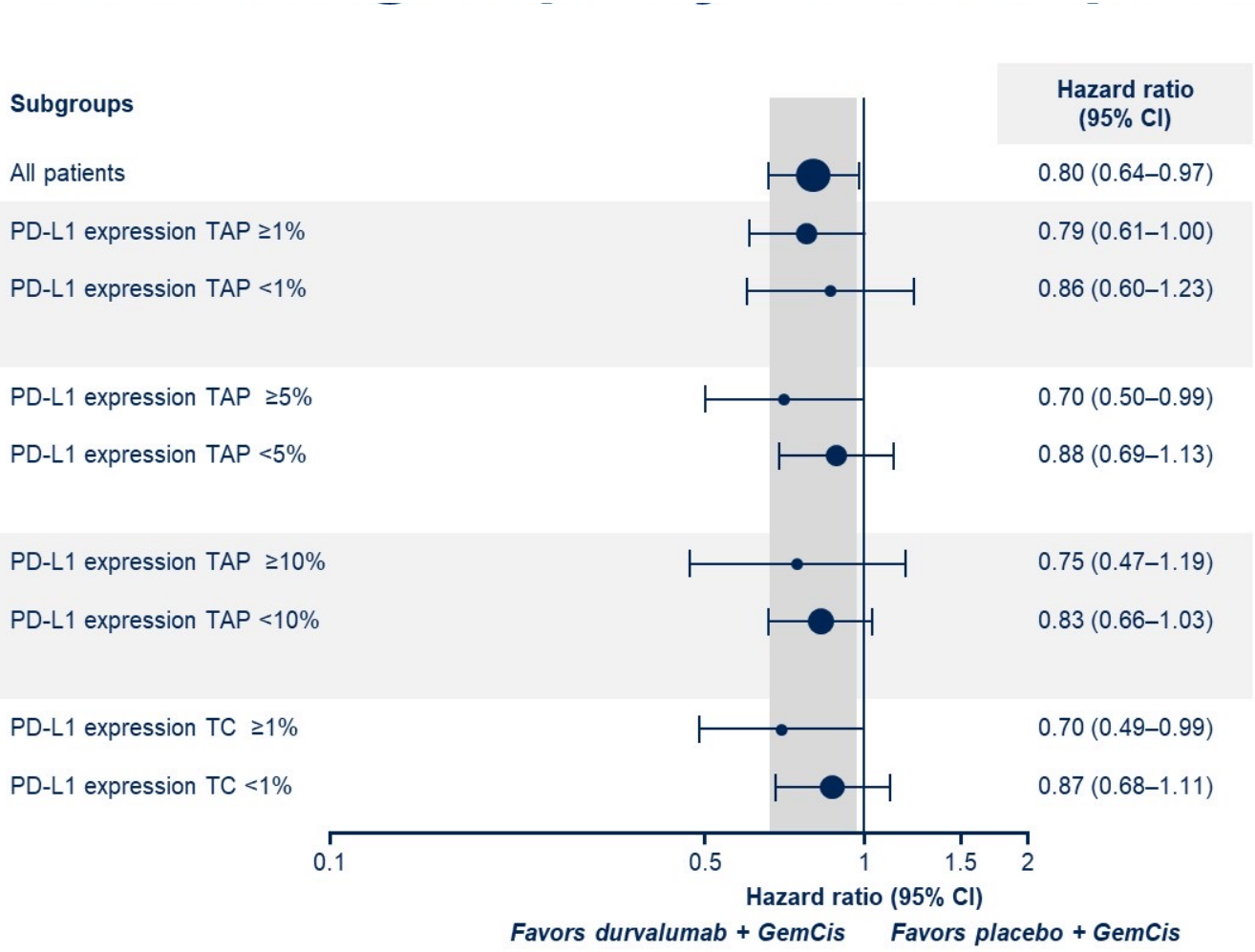
SD: early & continuous separation

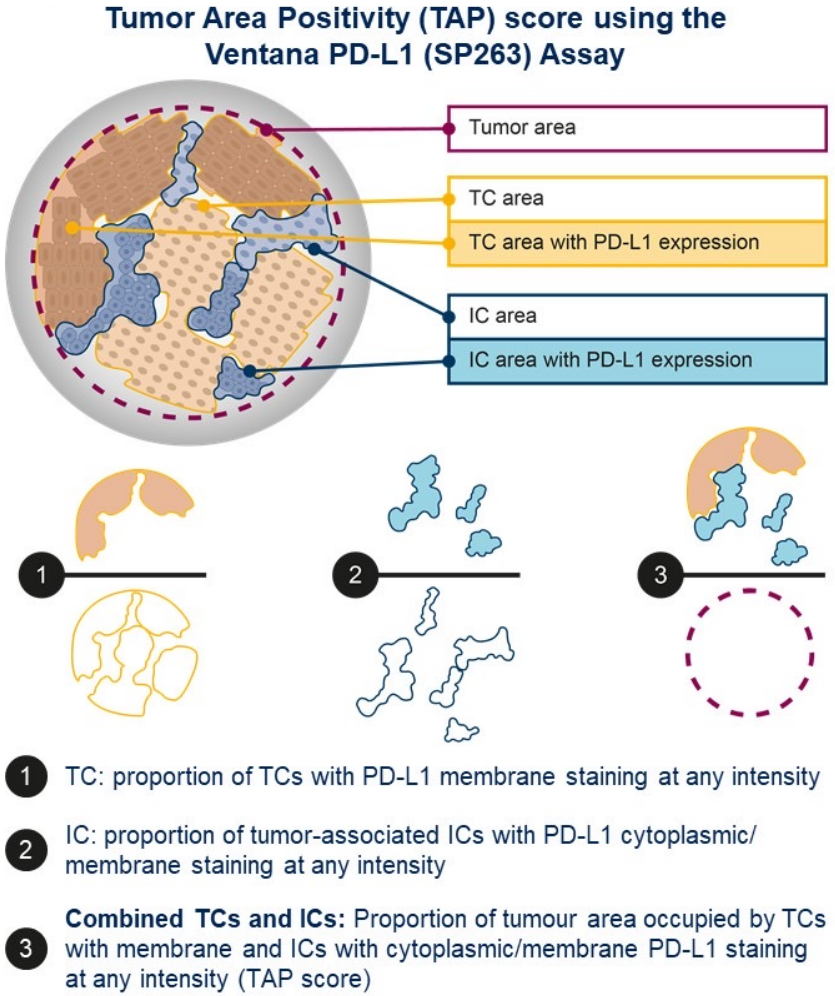
PD: no separation

Speculation: „initial 6 mo“ of responses influenced by „lifting“ of selected SD pts

IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

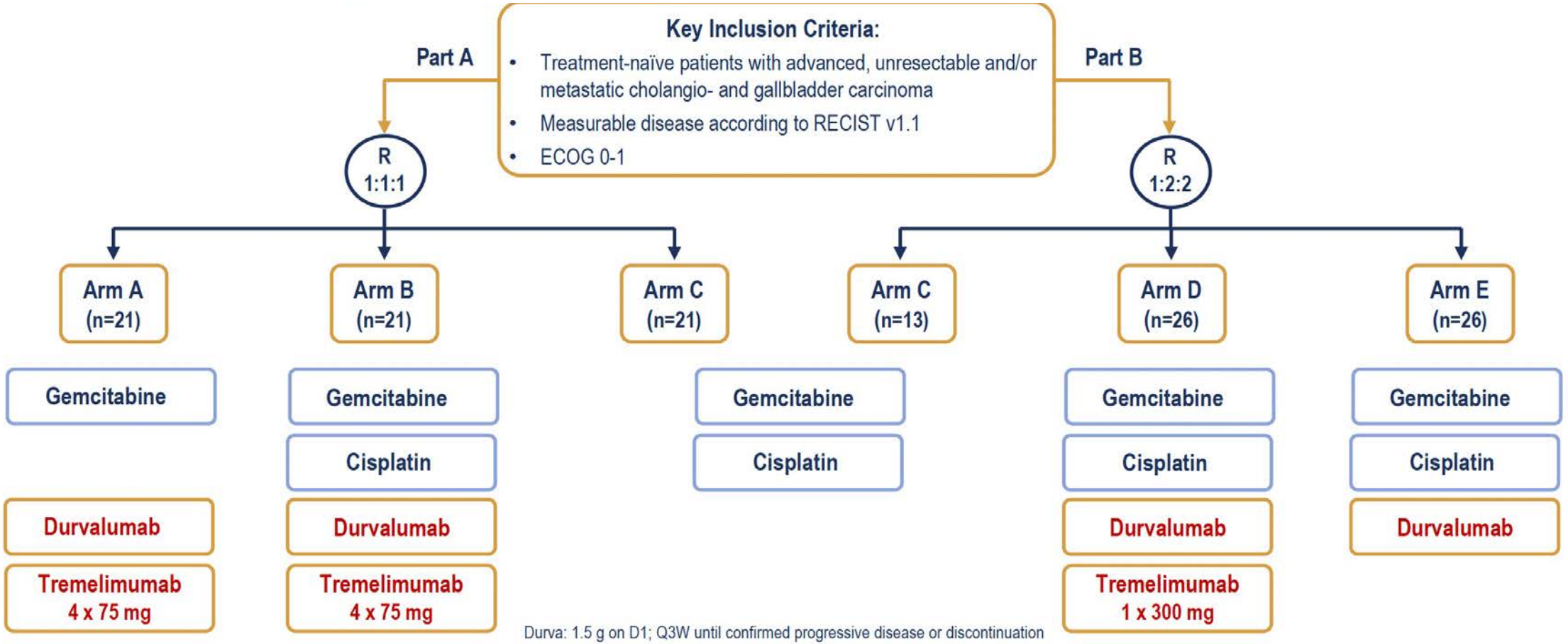
OS in subgroups by PD-L1 expression





IMMUCHEC: an exploratory IO trial in BTC

Aim: identify early „signal of activity“ for different IO combinations



Durva: 1.5 g on D1; Q3W until confirmed progressive disease or discontinuation

Treme: 75 mg on D1; Q3W; max 4 cycles in Arm A + B; 300 mg one-time bolus on C1D1 in Arm D

Gem: 1000 mg/m² on D1 + D8; Q3W; max. 8 cycles in Arm A + B + D + E & max. number of cycles at investigator's discretion in Arm C

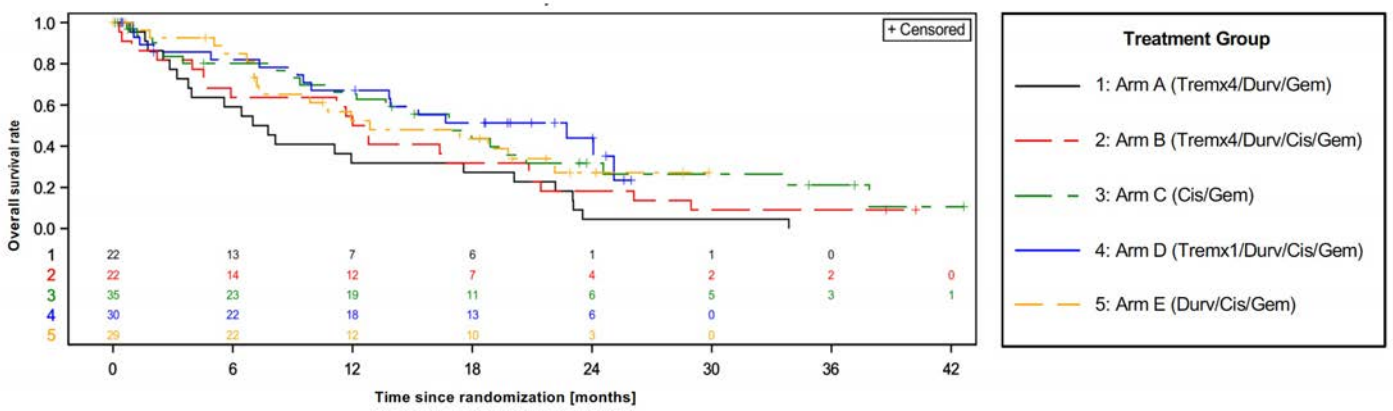
Cis: 25 mg/m² on D1 + D8; Q3W; max. 8 cycles in Arm B + D + E & max. number of cycles at investigator's discretion in Arm C

IMMUCHEC: an exploratory IO trial in BTC

Objective Response Rate (ORR) as per investigators' assessment according to RECIST v1.1

ITT		Arm A Tremx4+Durva+Gem N=22	Arm B Tremx4+Durva+Gem+Cis N=22	Arm C Gem+Cis N=35	Arm D Tremx1+Durva+Gem+Cis N=30	Arm E Durva+Gem+Cis N=29
ORR (95% PC*)		4.6% (0.0012-0.284)	18.2% (0.05-0.040)	28.6% (0.15-0.46)	26.7% (0.12-0.46)	20.7% (0.08-0.40)

Overall Survival (OS)



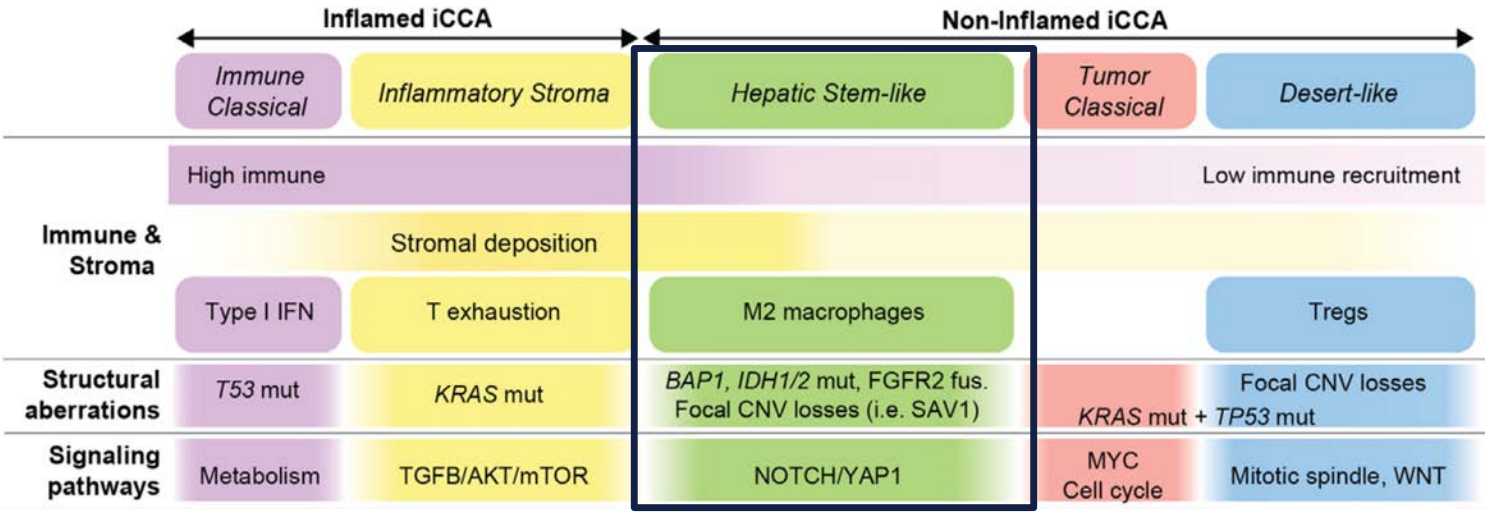
ITT		Arm A Tremx4+Durva+Gem N=22	Arm B Tremx4+Durva+Gem+Cis N=22	Arm C Gem+Cis N=35	Arm D Tremx1+Durva+Gem+Cis N=30	Arm E Durva+Gem+Cis N=29
OS	Median time to event [months]; (95% CI)	7.38 (3.2 – 17.57)	12.32 (4.53 – 20.83)	16.93 (9.37 – 20.7)	22.73 (9.53 – 25.1)	12.87 (7.2 – 22.13)

What did we learn?

1. Addition of IO to chemo did not improve ORR (negative trial)
    1. compared to TOPAZ: small cohort?
    2. compared to TOPAZ: non-Asian cohort
2. mOS in control arm longer than in previous phase 2 and 3 trials
    1. small cohort
    2. overall improved post progression care in participating institutions?
3. Omitting Platinum cannot be compensated for by IO
4. Trend for improved OS in ArmD (Gem/Cis + Durva + single dose Tremelimumab)

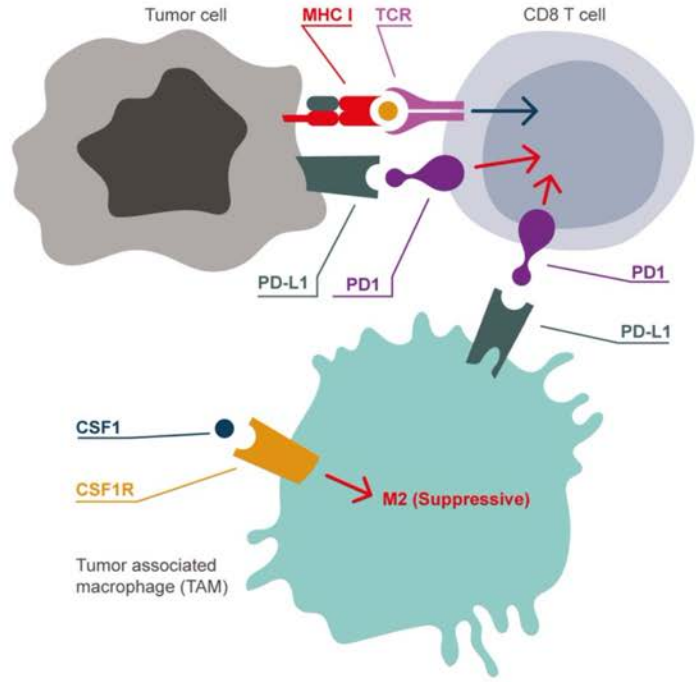
Rationale ADVANCE:

Molecular Subclasses of iCCA



Martin-Serrano et al, GUT 2022

Derazantinib „sensitizes“ to IO



Derazantinib targets:

- FGFR1
- FGFR2
- FGFR3
- CSF1-R
- VEGF-R2

Atezolizumab:

- PD-L1

- Reprogram suppressive M2 macrophages
- Restore T-cell activity
- Improve susceptibility to IO

Ongoing Trials IO + Chemo 1st line

	Arm A	Arm B	Primary EP	Population
KEYNOTE-966 * Phase 3 NCT04003636	Gem/Cis	Gem/Cis/**Pembro**	OS	1st line N = 1048
IMbrave151 Phase 2 * NCT04677504	Gem/Cis/**Atezo**	Gem/Cis/**Atezo**/**Bev**	PFS	1st line N = 150

* RESULTS EXPECTED EARLY 2023

Ongoing IO + Locoregional Therapy (LRT) Combinations in Advanced BTC

Combination Targets	Agents	Trial Design: Phase, Population	Sample Size	NCT
ICI + LRT	Durvalumab ± tremelimumab + ablation	Phase 2, advanced HCC or BTC	90	NCT02821754
	Durvalumab + tremelimumab + RT	Phase 2, advanced >1L HCC or BTC	70	NCT03482102
	Durvalumab ± tremelimumab + Y90 SIRT	Phase 2, locally-advanced ICC	50	NCT04238637
	Nivolumab + RT ± ipilimumab	RP2, advanced BTC or pancreas cancer	160	NCT02866383

Key: 1L=1st line; 2L=2nd line; RP2, RP3=randomized phase 2 or 3 trial; LRT=locoregional therapy; RT=radiation therapy; SIRT=selective internal radiation therapy

TAKE HOME: Immunotherapy in BTC

TOPAZ-1: Positive Phase III data and FDA approval for Gem/Cis + Durvalumab (vs Gem/Cis)
→FDA & EMA approved
→subgroup analysis:
→ no significant difference depending on region/ethnicity and tumor location (trends?)

No established biomarker to select for patients who benefit from IO
→ personal opinion: there will not be a “single” marker

Data expected in the near future:
KN-966 (Gem/Cis +- Pembro)
Combination of IO+ locoregional therapies
Combination of IO+ targeted therapies

MODULE 4: Integration of Targeted Therapy into the Management of Advanced BTCs — Dr Goyal

RTP
RESEARCH
TO PRACTICE

Dr Lionel Kankeu Fonkoua
(Rochester, Minnesota)

77-year-old woman with intrahepatic cholangiocarcinoma considered unresectable — an FGFR2-KIAA1598 fusion was detected on NGS

Dr Joseph Martins
(Tyler, Texas)

60-year-old man with metastatic cholangiocarcinoma with severe muscle pain on pemigatinib

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Lionel A Kankeu Fonkoua, MD

"She wanted to preserve her quality of life and was very reluctant to try chemotherapy, so we started pemigatinib. She has mild hyperphosphatemia, which we managed with dietary changes. Otherwise, she tolerated it well. Her 6-month PET restaging demonstrated that the avidity had resolved, so very impressive response with just pemigatinib.

We had her evaluated by a surgeon, and she was taken for a left hepatectomy and now is under surveillance. Is there any role for using cfDNA as part of the surveillance strategy but also to pick up potential clonal mutations that may evolve?"

QUESTIONS FOR THE FACULTY

Joseph Martins, MD

"We were thinking of hospice for him, but the next-generation sequencing showed an FGFR fusion, so we started pemigatinib.

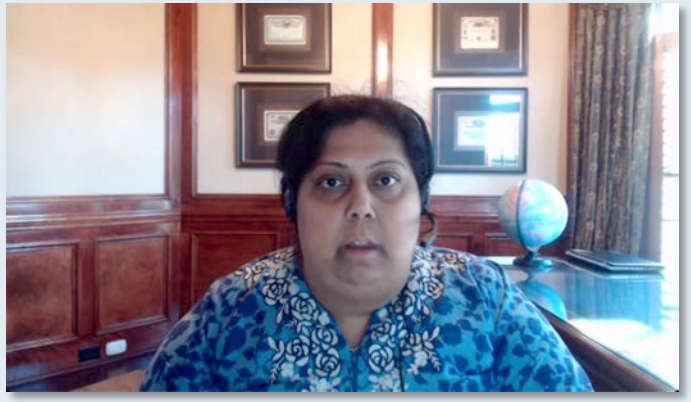
Immediately, his tumor markers started coming down, his liver pain got better and now he's doing great. However, he's having a lot of bone and muscle pain, which is a listed side effect of that drug.

Have they seen muscle aches and muscle pain bad enough to cause a need for hydrocodone? What other side effects are seen? How do they deal with hyperphosphatemia?"

RTP RESEARCH TO PRACTICE

Dr Farshid Dayyani
(Orange, California)

53-year-old man with recurrent metastatic cholangiocarcinoma with a BRAF V600E mutation treated with dabrafenib/trametinib



Dr Niyati Nathwani
(Charlotte, North Carolina)

64-year-old woman with cholangiocarcinoma with an IDH1 mutation is treated with ivosidenib

RTP
RESEARCH
TO PRACTICE

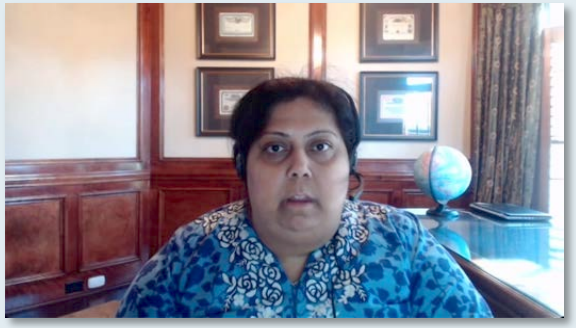
QUESTIONS FOR THE FACULTY

Farshid Dayyani, MD, PhD

"He had a great quick response. Within 4 weeks, his CA19-9 normalized, and the MRD assay turned negative. He trucked along for about a year, but more recently his Signatera has slowly gone up. I repeated his liquid biopsy, and the BRAF clone is gone and his original p53-mutant clone is taking over. The question is, do you continue dabrafenib/trametinib or switch to another regimen?"

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY



Niyati A Nathwani, MD

"She's currently getting concurrent treatment with radiation and capecitabine. We also did biomarker testing, which did show an IDH1 mutation. Should we use ivosidenib after completing concurrent chemoradiation? I'm guessing there's no differentiation syndrome with this agent in cholangiocarcinoma, but what is their experience with this?"

Integration of Targeted Therapy into the Management of Advanced BTCs

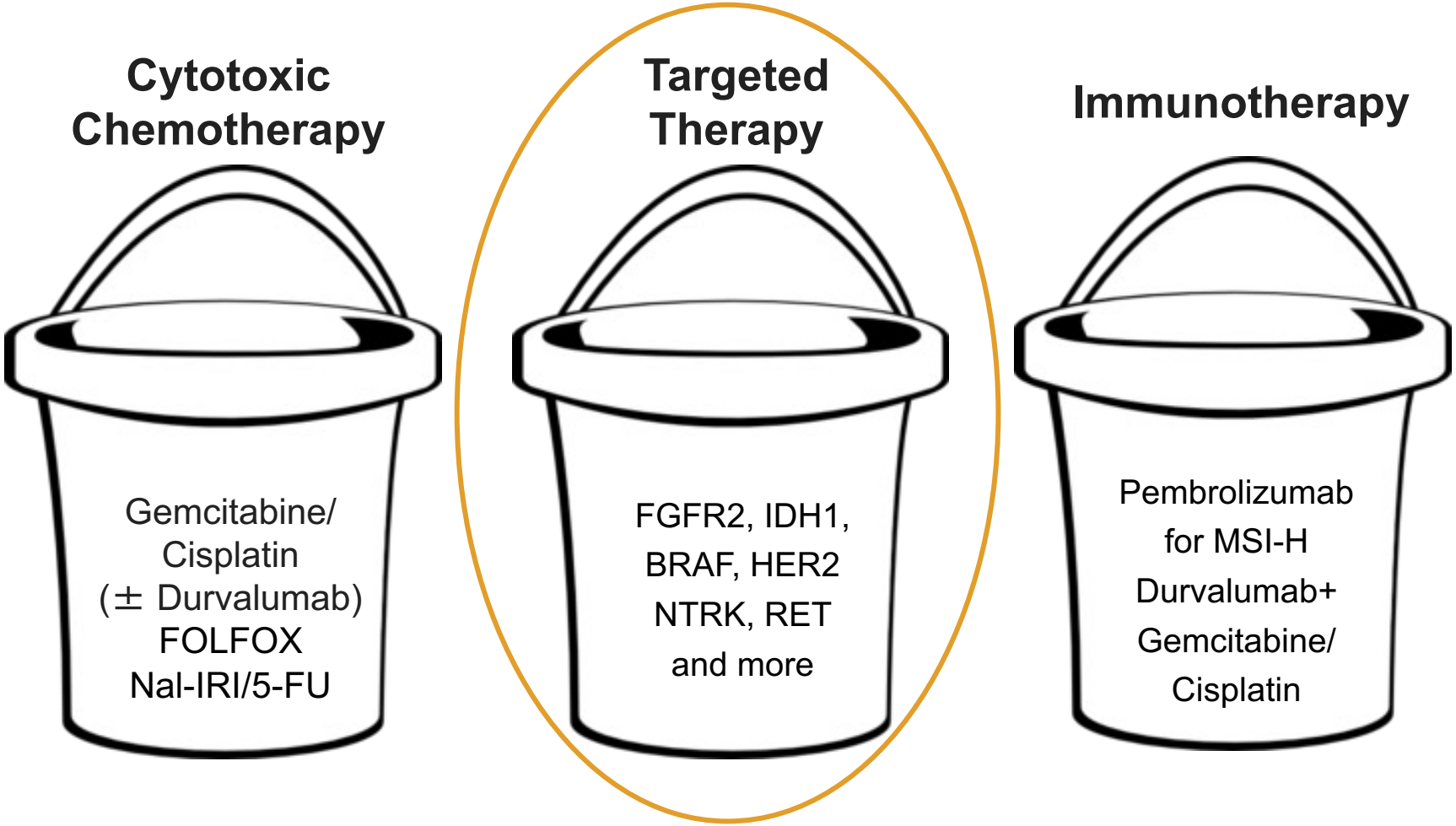
Lipika Goyal, MD, Mphil
Associate Professor
Director of Gastrointestinal Oncology
Stanford School of Medicine

Research to Practice CME

2023 ASCO Gastrointestinal Cancers Symposium

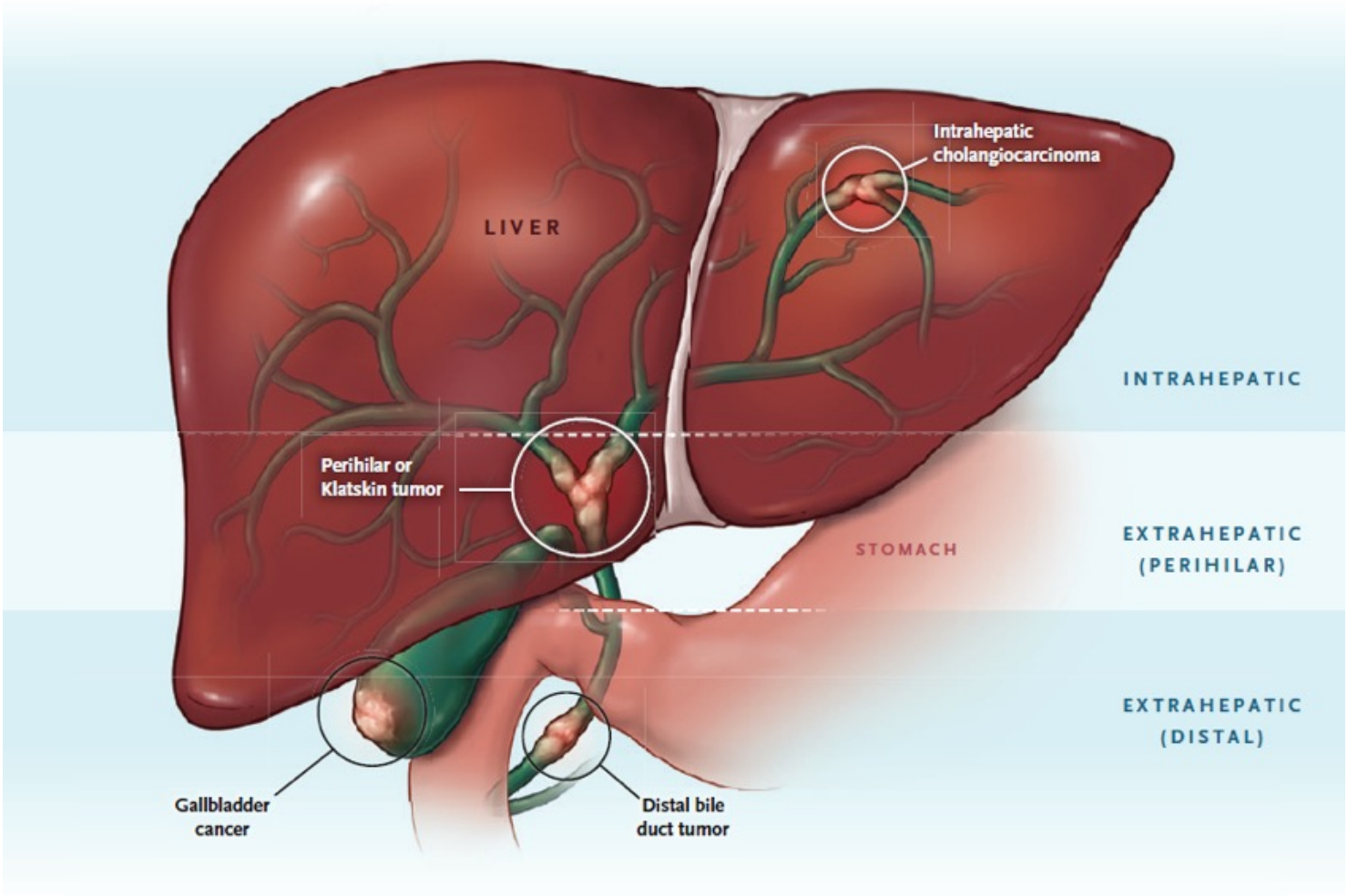
January 20, 2023

Systemic Therapy for Cholangiocarcinoma



BRAF, v-raf murine sarcoma viral oncogene homolog B; CAR, chimeric antigen receptor; FGFR2, fibroblast growth factor receptor 2; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HER2, human epidermal growth factor receptor; IDH, isocitrate dehydrogenase; MAPK, mitogen-activated protein kinase; NTRK, neurotrophic tyrosine kinase; PI3K, phosphatidylinositol-3-kinase; RET, rearranged during transfection.
Image credit: Clipart Panda.

Anatomic Classification of Biliary Tract Cancer



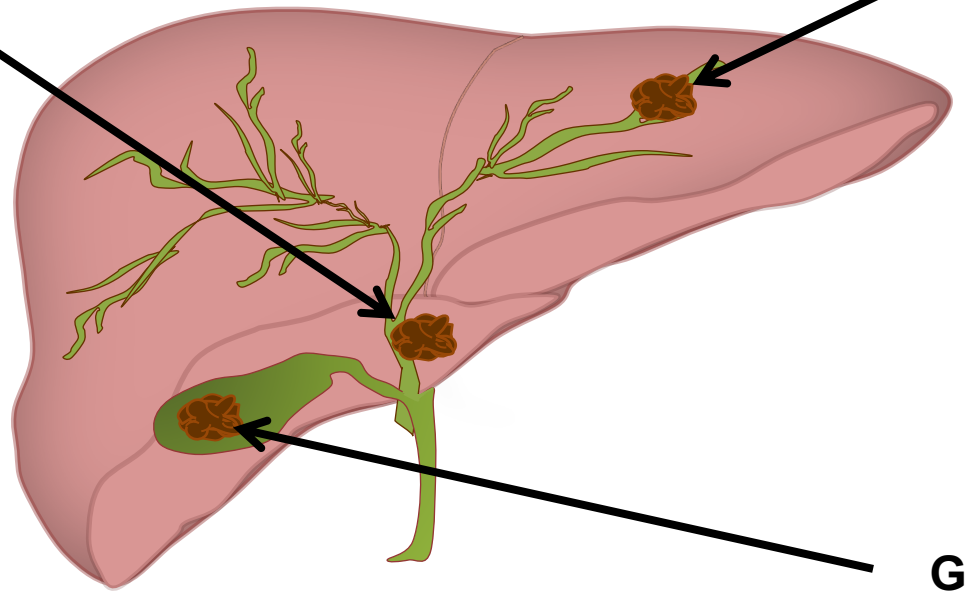
Goyal L, et al. *N Engl J Med,* 2022

Biliary Tract Cancer: Frequent Actionable Alterations

ECC

PIK3CA mutation (7%)
HER2 amplification/mutation (5%–10%)

IDH1/2 mutation (0%–7%)
MET mutation (4%)
BRAF mutations (3%)
MET amplification (1%)



ICC

FGFR1-3 alterations (11%–17%)
IDH1/2 mutation (5%–36%)

RNF43 mutation (9%)
PIK3CA mutations (3%–9%)

BRAF mutations (3%–7%)
HER2 amplification/mutation (7%)

MET amplification (2%–7%)
MET mutation (5%)
EGFR mutation (1%–2%)
RET-fusion (<1%)

GBCA

HER2 amplification/mutation (10%–19%)
PIK3CA mutation (6%–13%)
BRAF mutation (1–6%)

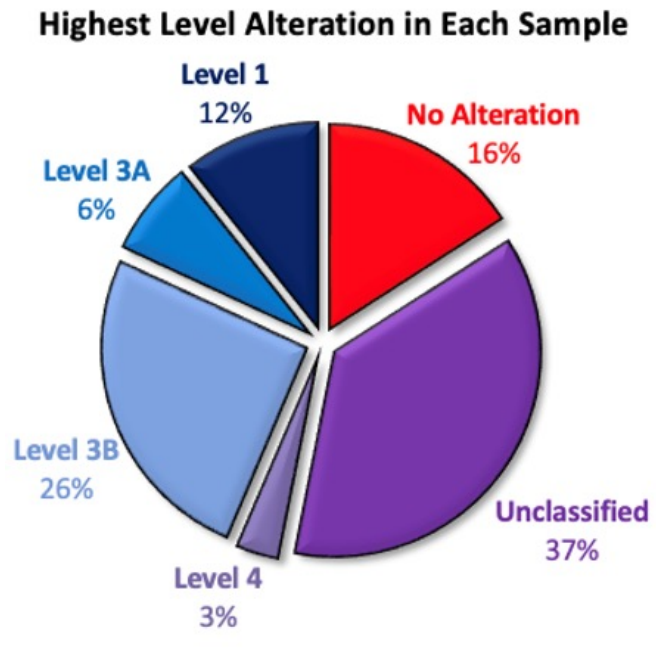
RNF43 mutation (4%)
MAP2K4 mutation (4%)
EGFR mutation (4%)
FGFR1-3 fusions, mutations, and amplifications (3%)
IDH1/2 mutation (2%)

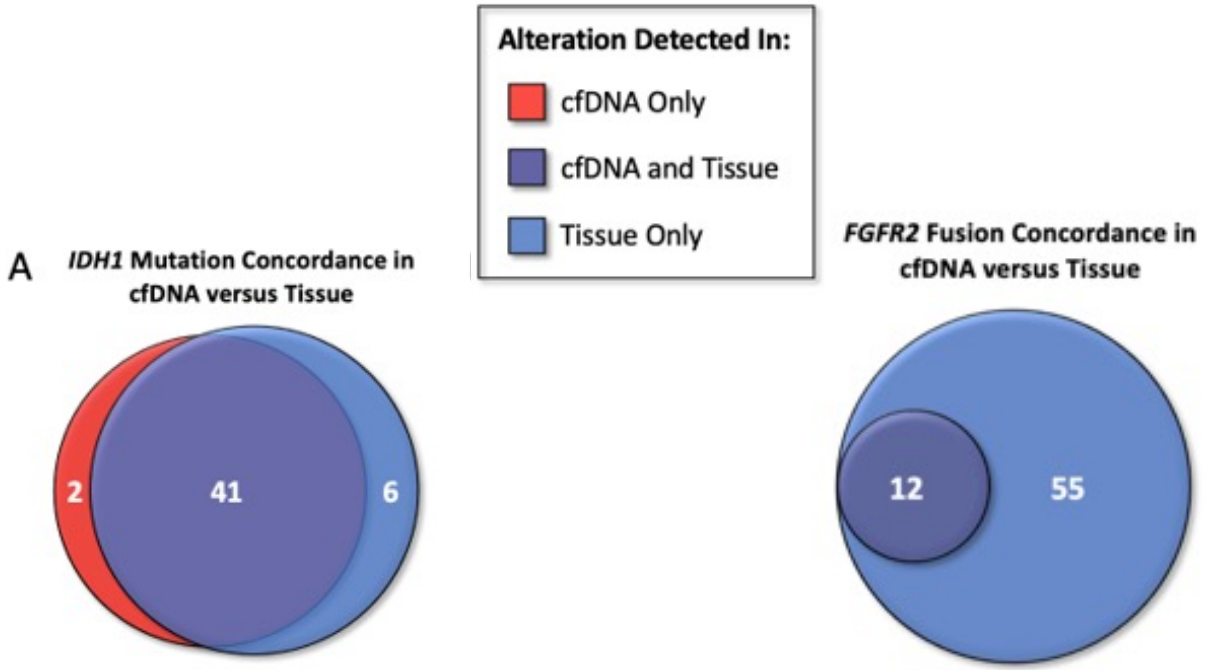
Biomarkers Matter

cholangiocarcinoma FOUNDATION®

BRAF, v-raf murine sarcoma viral oncogene homolog B; ECC, extrahepatic cholangiocarcinoma; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GBCA, gallbladder carcinoma; HER2, human epidermal growth factor receptor 2; ICC, intrahepatic cholangiocarcinoma; IDH, isocitrate dehydrogenase; MAP, mitogen-activated protein kinase; MET, mesenchymal to epithelial transition; PIK3CA, phosphatidylinositol 3-kinase catalytic alpha polypeptide; RET, rearranged during transfection; RNF43, ring finger protein 43.
Adapted from Valle JW, et al. Cancer Discov 2017;7(9):943–962.

Role for Liquid Biopsy in Biliary Tract Cancer?





44% of patients with actionable alteration

87% detection for *IDH1* mutations

18% detection for *FGFR2* fusions

Berchuck, etal, *Annals of Onc*, 2022

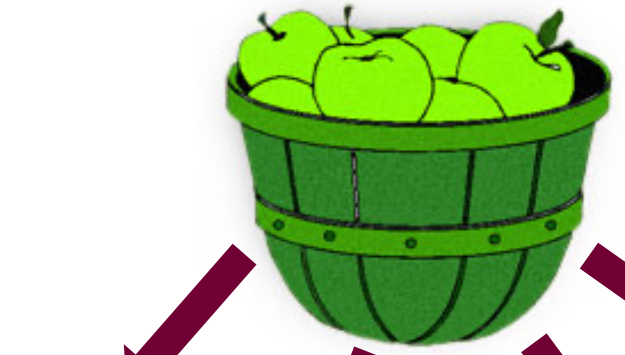
Evaluating Targeted Therapy in an Uncommon Cancer: Approaches

Target-Specific Cholangiocarcinoma Trial

FGFR2 fusions 10%–15%

IDH1 mutations 15%–20%

Target-Specific All Comer Basket Trial



BRAF V600E mutations 4%–5%

HER2 amplification 5-15%

MSI-high 1%–2%

NTRK-fusion <1%

RET-fusion <1%

Biliary Umbrella Trial With Target-Specific Arms

ABC10

ABC10, ABC transporter 10; BRAF, v-raf murine sarcoma viral oncogene homolog B; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor 2; IDH, isocitrate dehydrogenase; MSI, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection.

Valle JW, et al. Cancer Discov 2017;7(9):943–962.

Selective FGFR Inhibitors for FGFR2 Fusions or Rearrangement Positive Cholangiocarcinoma[1–4]

Pemigatinib
ATP-competitive FGFR1–3 inhibitor

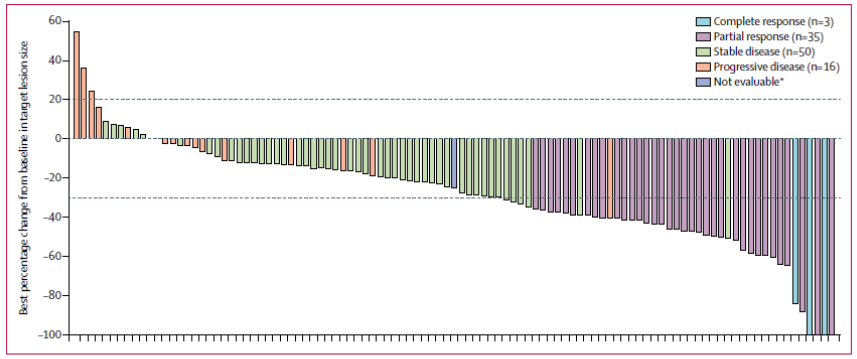
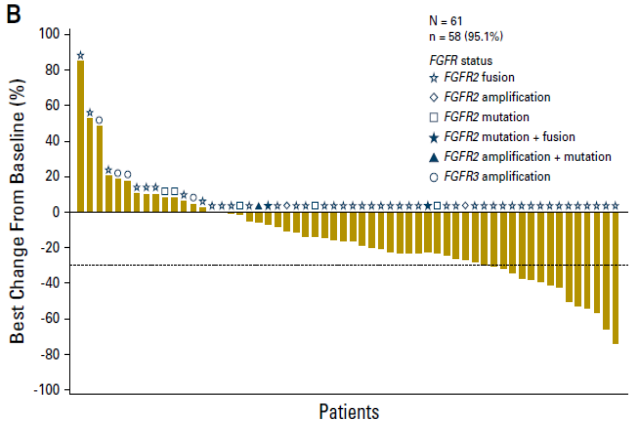


Figure 2: **Best percentage change from baseline in target lesion size for individual patients with *FGFR2* fusions or rearrangements**
Coloured bars indicate confirmed responses assessed by RECIST 1·1. FGFR=fibroblast growth factor receptor. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. *Patient had a decrease in target lesion size but was not evaluable for response using RECIST.

ORR: 35.5% (updated: 37.0%)
DCR: 82.2% (updated 82.4%)
PFS (updated): 7.0 months

Infigratinib
ATP-competitive FGFR1–3 inhibitor

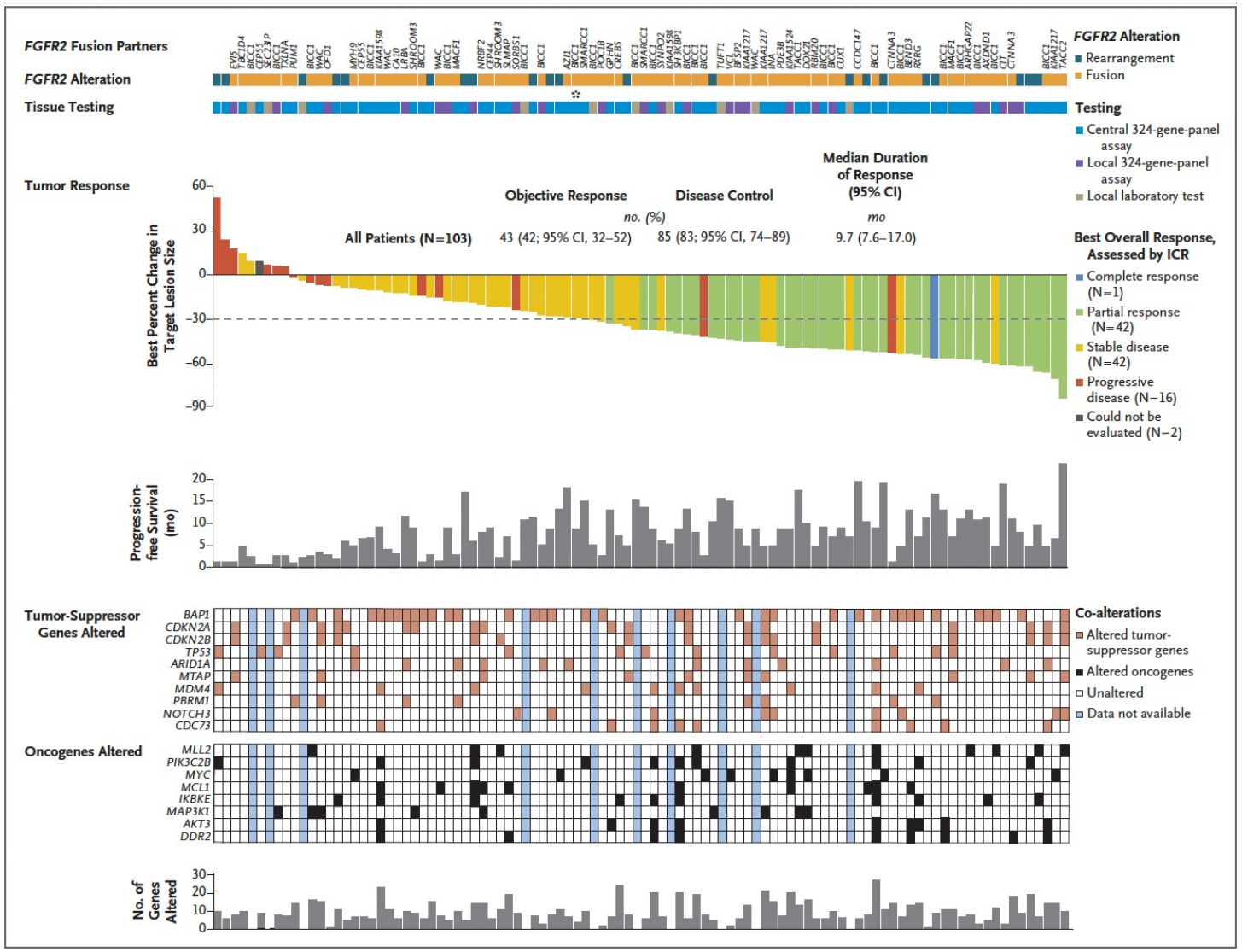


ORR: 18.8% (updated: 23.1%)
DCR: 83.3% (updated: 84.3%)
PFS (updated): 7.3 months

ATP, adenosine triphosphate; DCR, disease control rate; FGFR, fibroblast growth factor receptor; ORR, overall response rate; PFS, progression-free survival.

1. Javle M, et al. J Clin Oncol 2018;36(3):276–282; 2. Javle M, et al. ASCO Gastrointestinal (GI) Cancers Symposium, 2021;
3. Abou-Alfa GK, et al. Lancet Oncol 2020;21(5):671–684; 4. Abou-Alfa GK et al. ASCO 2021;Abstract 4086.

FOENIX-CCA2 Study of Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma

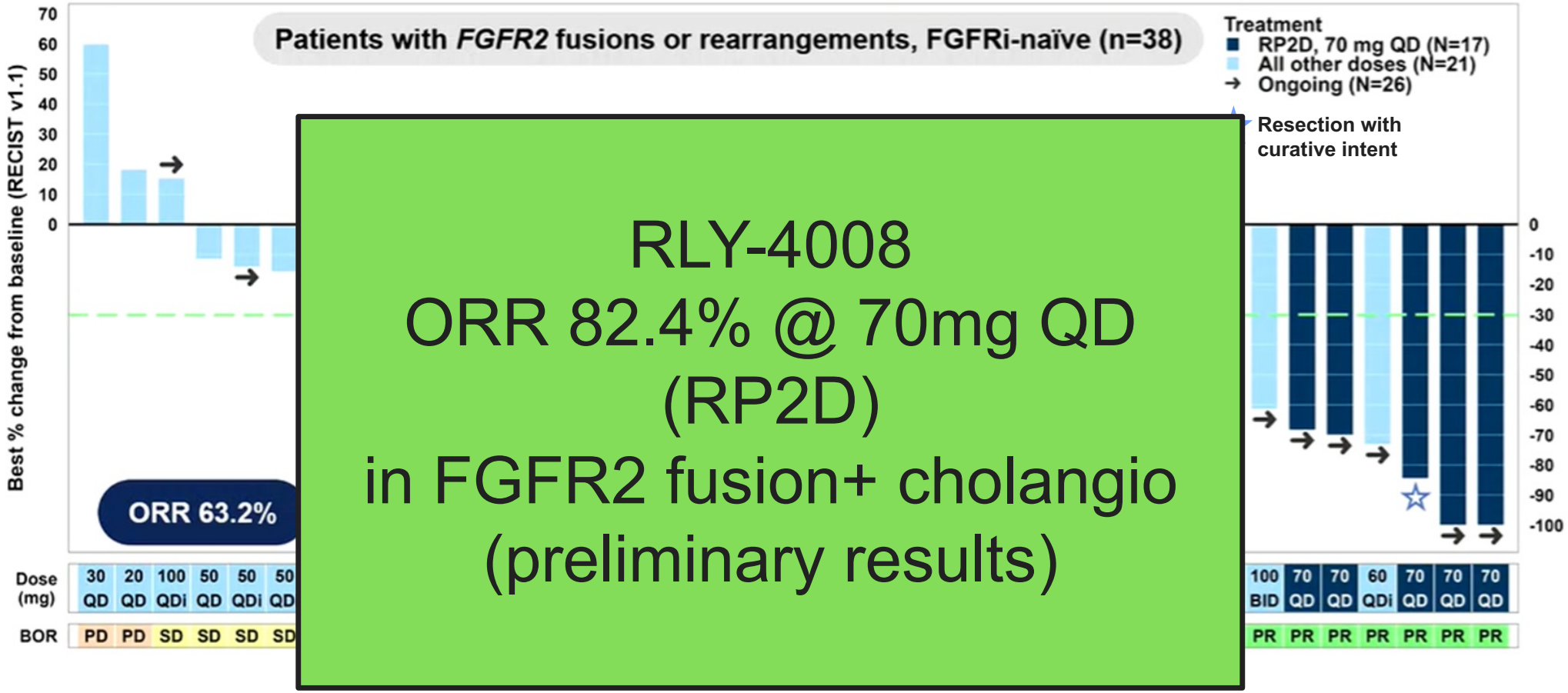


ORR: 42%
Median duration of response: 9.7 months
PFS: 9.0 months

Goyal L et al. *N Engl J Med* 2023;388(3):228-39.

RLY-4008, FGFR2-specific inhibitor, in FGFR2-fusion or Rearrangement+ Cholangiocarcinoma

Radiographic tumor regression and response per RECIST 1.1 across all doses



BID, twice daily; BOR, best overall response; CCA, cholangiocarcinoma; DoR, duration of response; FGFR, fibroblast growth factor receptors; FGFRi, fibroblast growth factor receptor inhibitor; ORR, objective response rate; PD, progressive disease; PR, partial response; QD, once daily; QDi once daily on an intermittent schedule; RP2D, recommended phase 2 dose; SD, stable disease; uPR, unconfirmed partial response.

Hollebecque A, et al. Ann Onc 2022;33(suppl_7):S808-S869.

A Phase II Study Of FGFR1-3 Inhibitor Tinengotinib As Monotherapy In Patients With Advanced Or Metastatic Cholangiocarcinoma :Interim Analysis

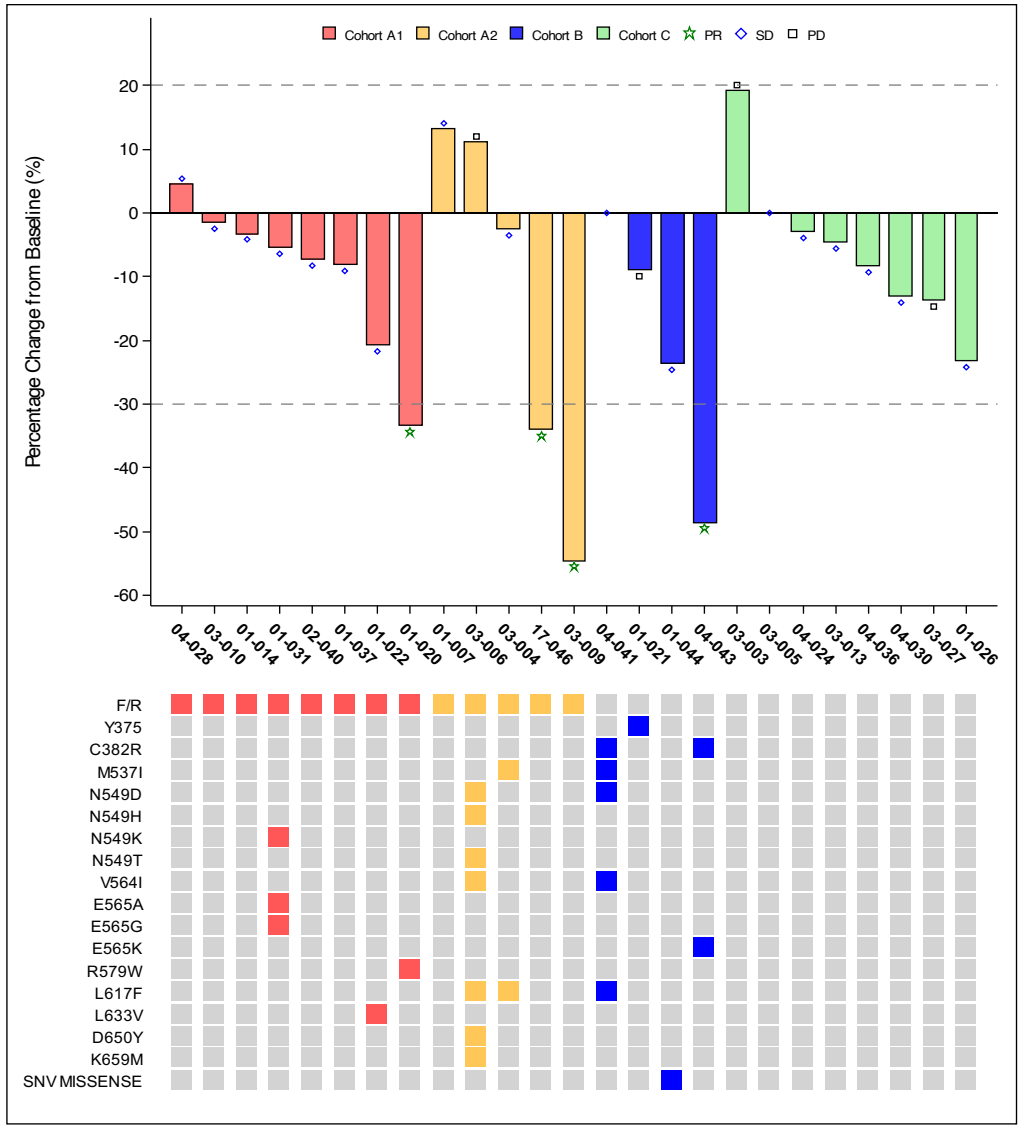
Figure 2. Study Design

Patients

- ≥18 years, advanced/metastatic CCA with/without FGFR alterations;
- At least one line of prior systemic chemotherapy;
- ECOG ≤ 1;
- measurable lesion as defined by RECIST V1.1 criteria
- Adequate organ function

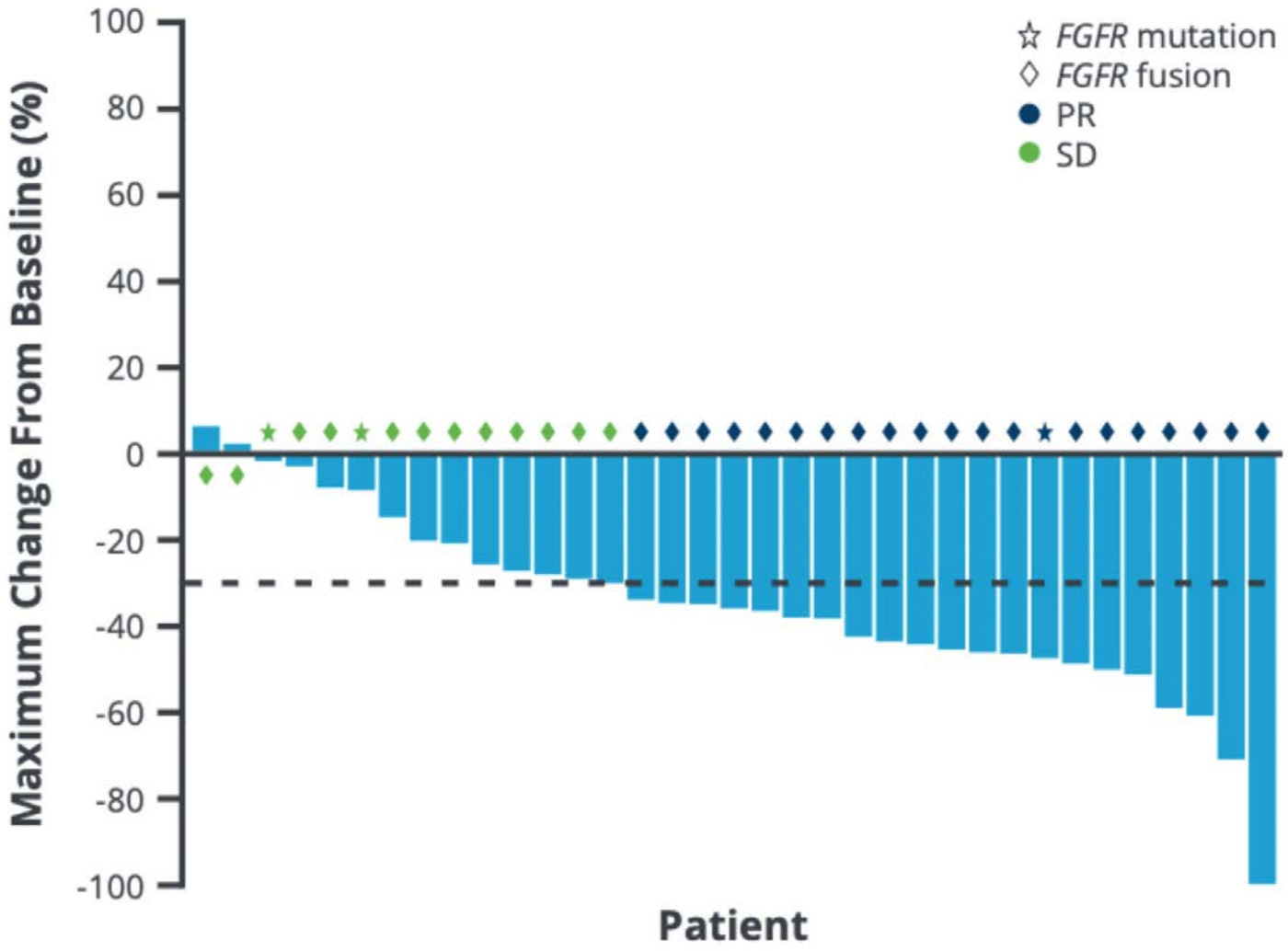
- Cohort A1: FGFR2 fusions who have progressed on prior treatment with FGFR inhibitor (FGFRi)
- Cohort A2: FGFR2 fusions who had a response on prior treatment with FGFRi and discontinued due to PD
- Cohort B: Other FGFR alterations
- Cohort C: FGFR wild-type

Oral tinengotinib
10 mg once daily
28-day cycles
Until progression or toxicity



F/R: FGFR2 fusion or rearrangement.
Subject 02-040, 01-037, 01-044 no baseline cfDNA NGS data was detected, only historical FGFR data available.

RAGNAR Trial of Erdafitinib for Cholangiocarcinoma with Prespecified FGFR Alterations: Expansion Cohort Results

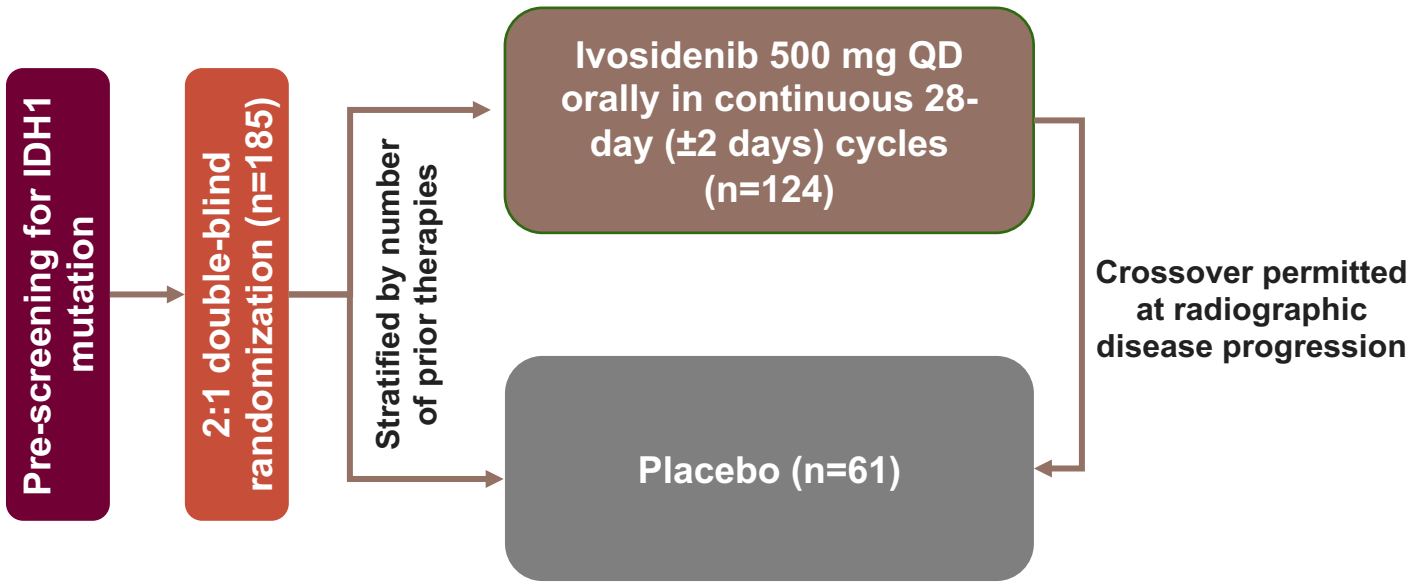


Pant S et al. Gastrointestinal Cancers Symposium 2023;Abstract 610.

Ivosidenib in IDH-Mutant Cholangiocarcinoma

Randomized, double-blind, placebo-controlled, multicenter phase 3 trial

Key eligibility criteria
- ≥18 years of age
- Histologically confirmed diagnosis of cholangiocarcinoma
- Centrally confirmed IDH1 mutation status by next-generation sequencing
- ECOG performance status score 0 or 1
- 1–2 prior therapies (at least 1 gemcitabine- or 5-fluorouracil-containing regimen)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic and renal function

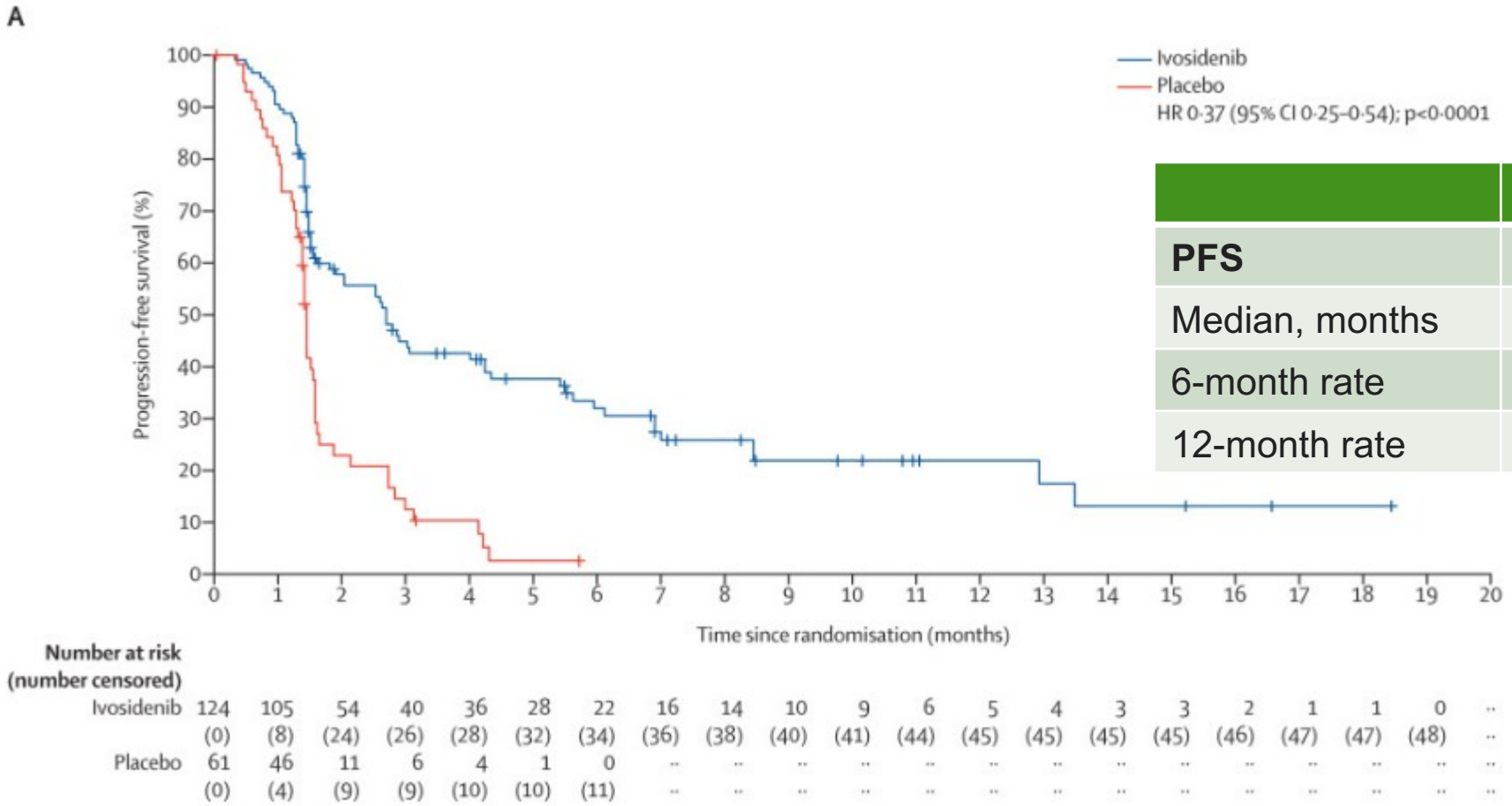


An independent data monitoring committee monitored the safety data throughout the study

Primary end point: PFS
Secondary end points: OS, ORR, safety, QOL

ECOG, Eastern Cooperative Oncology Group; IDH, isocitrate dehydrogenase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.
Abou-Alfa GK, et al. Lancet Oncol 2020;21:796–807; NCT02989857.

Ivosidenib in IDH-Mutant Cholangiocarcinoma (Contd.)



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE

Primary end point: PFS
Secondary end points:
OS, ORR, safety, QOL

CI, confidence interval; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1; PFS, progression-free survival.
Abou-Alfa GK, et al. Lancet Oncol 2020;21:796–807.

Evaluating Targeted Therapy in an Uncommon Cancer: Approaches

Target-Specific Cholangiocarcinoma Trial

FGFR2 fusions
10%–15%

IDH1 mutations
15%–20%

Target-Specific All Comer Basket Trial

BRAF V600E mutations
4%–5%

HER2 amplification
5-15%

MSI-high
1%–2%

NTRK-fusion
<1%

RET-fusion
<1%

Biliary Umbrella Trial With Target-Specific Arms

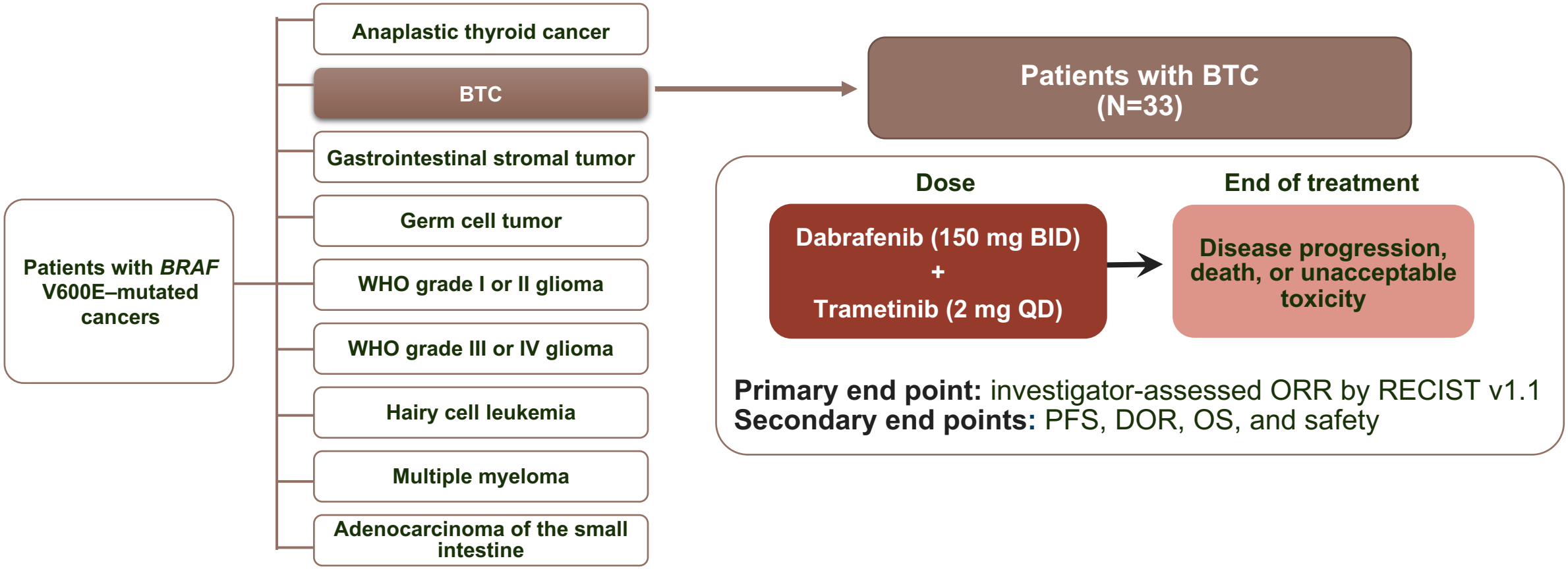
ABC10

ABC10, ABC transporter 10; BRAF, v-raf murine sarcoma viral oncogene homolog B; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor 2; IDH, isocitrate dehydrogenase; MSI, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection.

Valle JW, et al. Cancer Discov 2017;7(9):943–962.

Dabrafenib/Trametinib: ROAR

Phase 2 Study: BRAF V600E–Mutant Advanced Solid Tumors

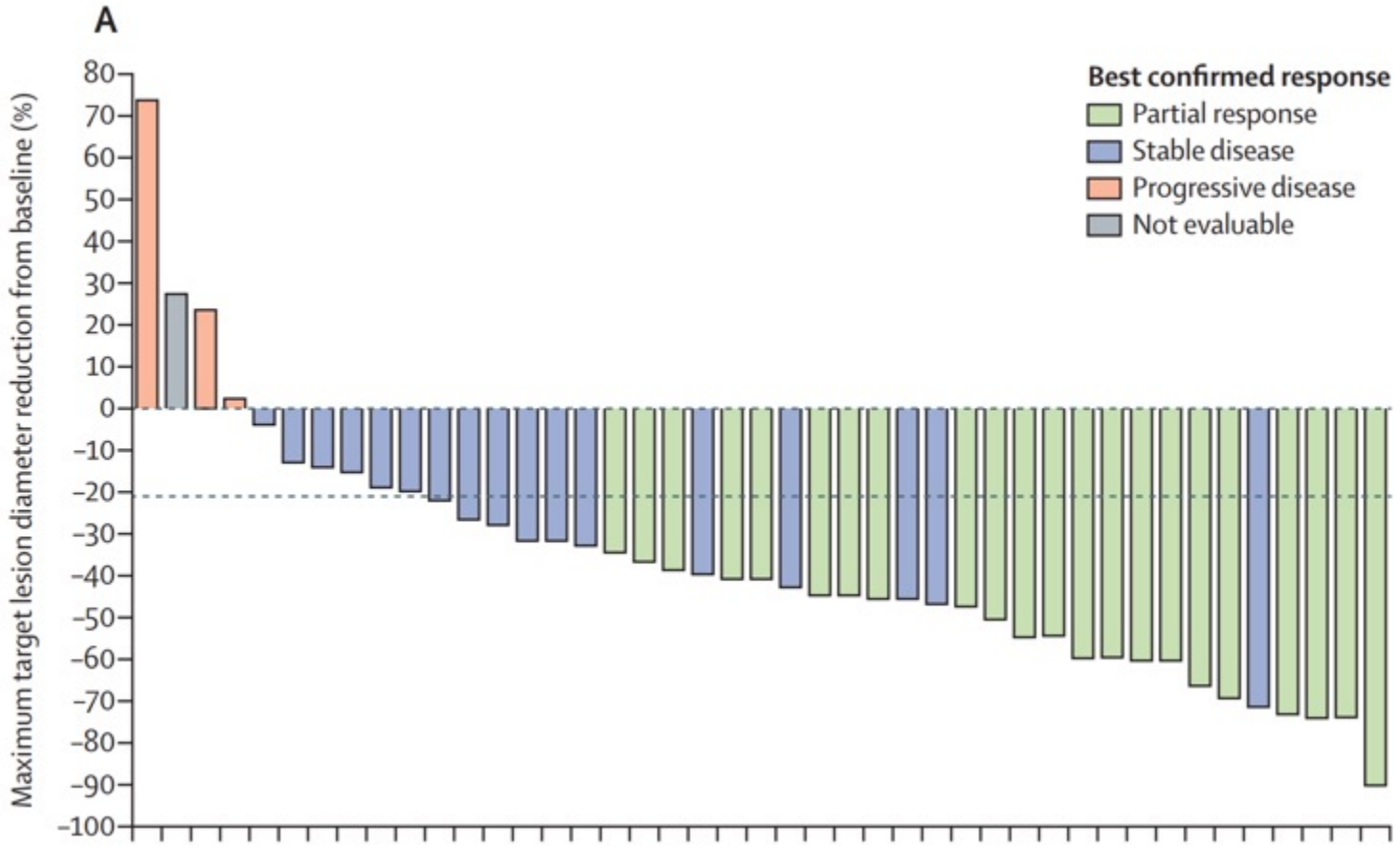


BID, twice daily; BRAF, v-raf murine sarcoma viral oncogene homolog B; BTC, biliary tract cancer; BID, twice daily; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

Wainberg ZA, et al,. J Clin Onc 2019 37:4(Suppl):187–187.

Dabrafenib/Trametinib: ROAR

Biliary Tract Cancer Cohort (n=43)



Primary end point:
ORR: 51% (95% CI: 36–67)
by investigator assessment

ORR: 47% (95% CI: 31–62)
by independent review

Secondary end points:
Median DOR:
9 months (95% CI: 6–14)
by investigator assessment

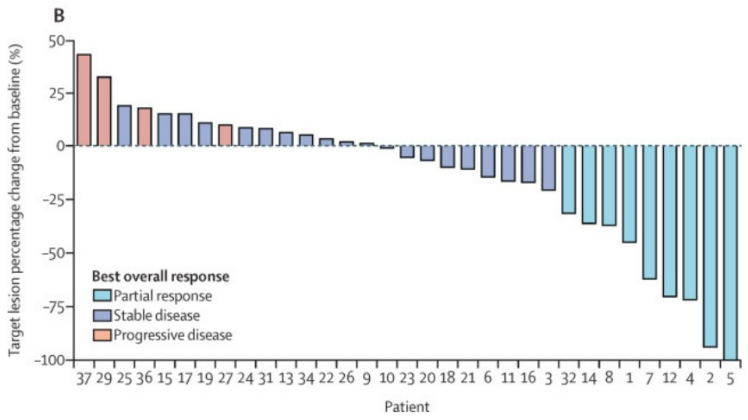
Median PFS: 9 months
(95% CI: 5–10)
by investigator assessment

Median OS: 14 months
(95% CI: 10–33)

CI, confidence interval; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
Subbiah V, et al. Lancet Oncol 2020; 21:1234–43.

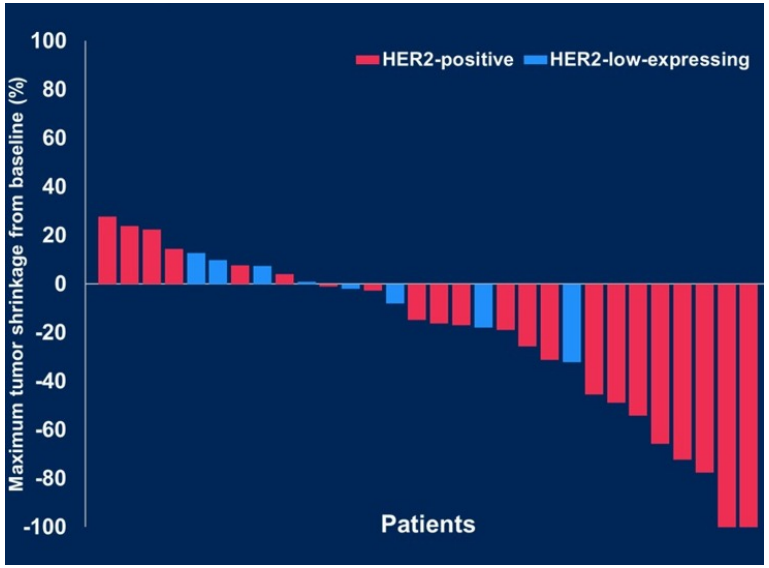
Targeting HER2 overexpression/amplification

Trastuzumab/Pertuzumab MyPathway



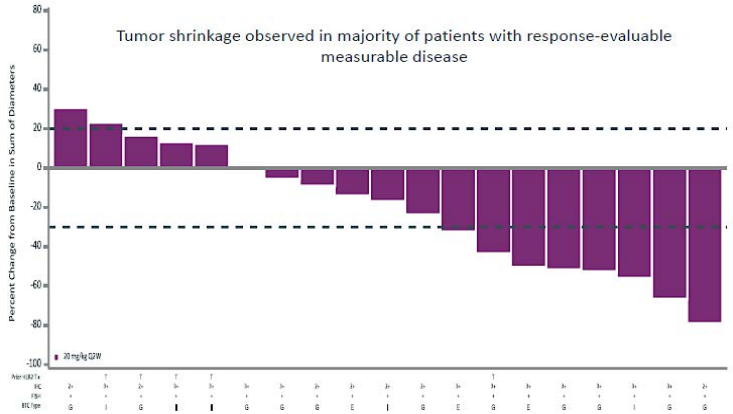
ORR 23%
Median DOR 10.8 months
(0.7-25.4)
N=39 patients

Trastuzumab deruxtecan



ORR 36.4%
Median DOR 7.4 months
(n=22)

Zanidatamab



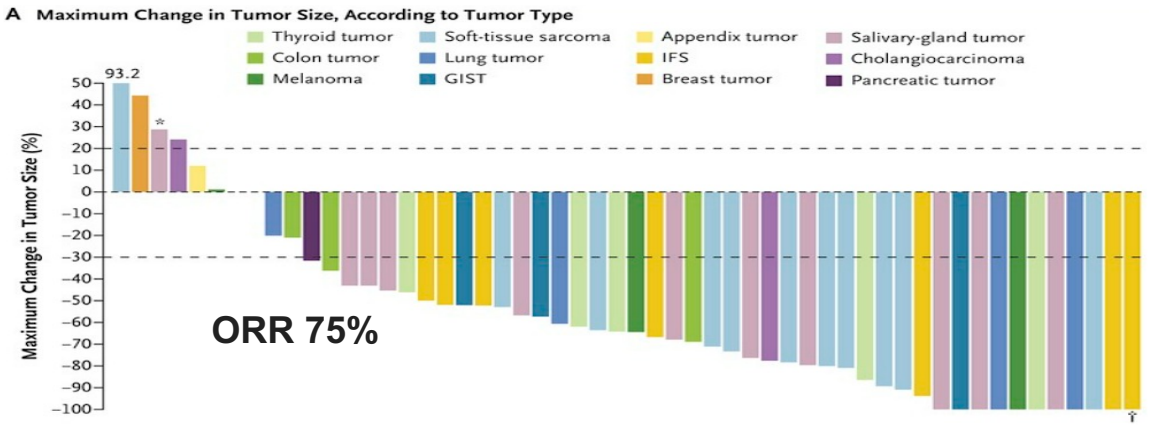
ORR 40%
Median DOR 7.4 months
(3.2-NE)
(n=20)

DOR, duration of response; HER2, human epidermal growth factor receptor 2; ORR, objective response rate

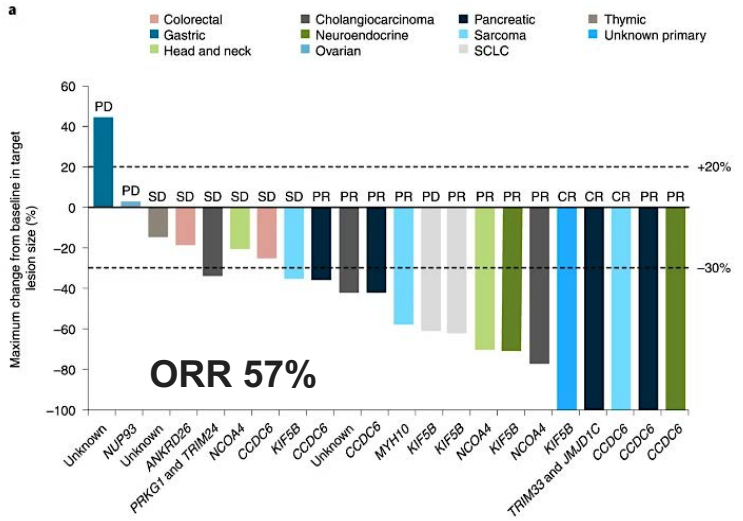
Javle M et al. Lancet Oncol 2021;22(9):1290-1300; Ohba A et al. ASCO 2022;Abstract 4006; Meric-Bernstam F et al. Gastrointestinal Cancers Symposium 2021;Abstract 299.

Targeting NTRK and RET Fusions

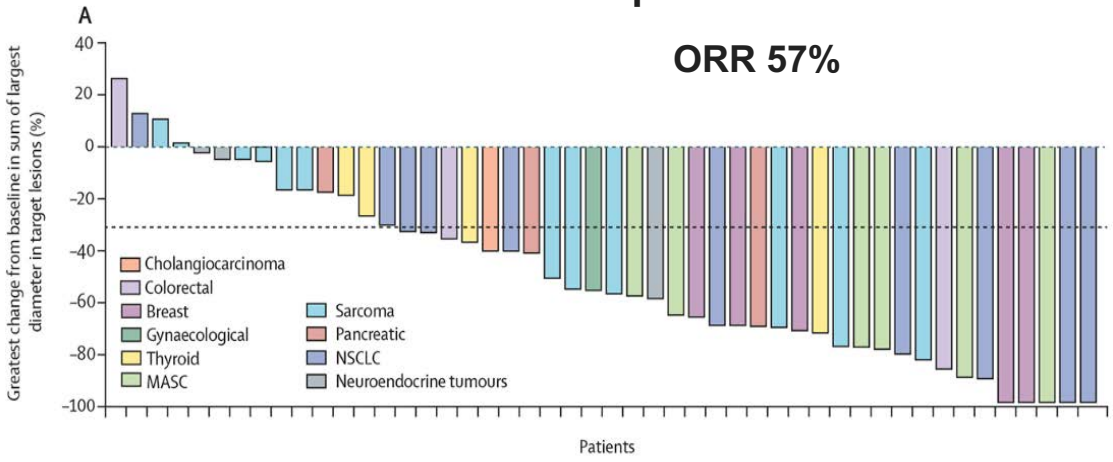
Larotrectinib in TRK Fusion–Positive Cancers



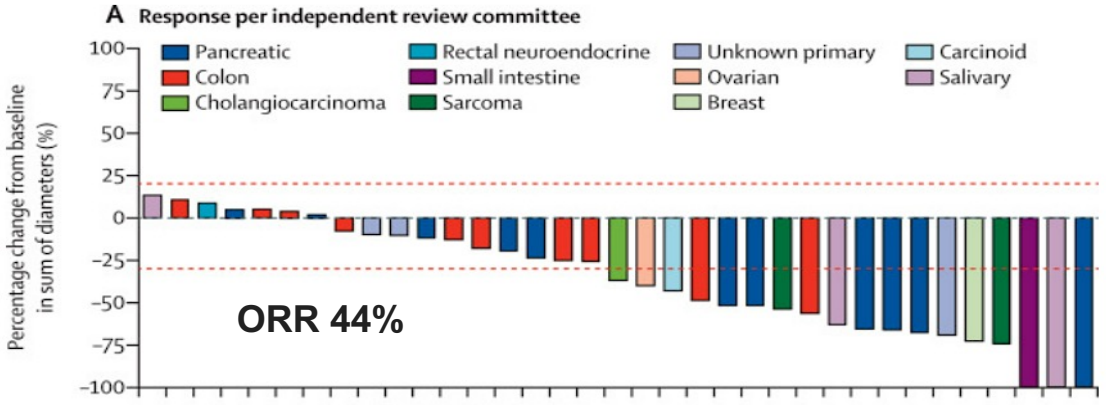
Pralsetinib in RET Fusion–positive Solid Tumors



Entrectinib in NTRK Fusion-positive Solid Tumors



Selpercatinib in RET Fusion–positive Solid Tumors



Drilon A, et al, N Engl J Med 2018;378:731–9; Doebele RC, et al. Lancet Oncol. 2020;21(2):271–282; Subbiah V, et al, 2022 Nat Med 2022;28:1640–1645; Subbiah V, et al. Lancet Oncol 2022;12:S1470-2045(22)00541–1

Other Actionable Signatures in Cholangiocarcinoma[1,2]

BRCA, breast cancer gene; DNA, deoxyribonucleic acid; KRAS, Kirsten rat sarcoma viral oncogene homolog; PIK3CA, phosphatidylinositol-4,5-biphosphate 3-kinase catalyic alpha polypeptide; RNF43, ring finger protein 43; RSPO, recurrent R-spondin.

1. Valle JW, et al. Cancer Discov 2017;7(9):943–962; 2. Le DT, et al. Science 2017;357(6349):409–413.

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin[4] (category 1)
- Durvalumab + gemcitabine + cisplatin (category 1)[d,e,5]

Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- 5-fluorouracil + cisplatin (category 2B)
- Capecitabine + cisplatin (category 2B)
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B)
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,10,11]
- For *RET* gene fusion-positive tumors:
  - Pralsetinib (category 2B)[12]
  - Selpercatinib for CCA (category 2B)[13]

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[g]

Preferred Regimens

- FOLFOX[14]

Other Recommended Regimens

- FOLFIRI[15] (category 2B)
- Regorafenib[16] (category 2B)
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[17]
- Durvalumab + gemcitabine + cisplatin (category 2B)[e,h,5]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

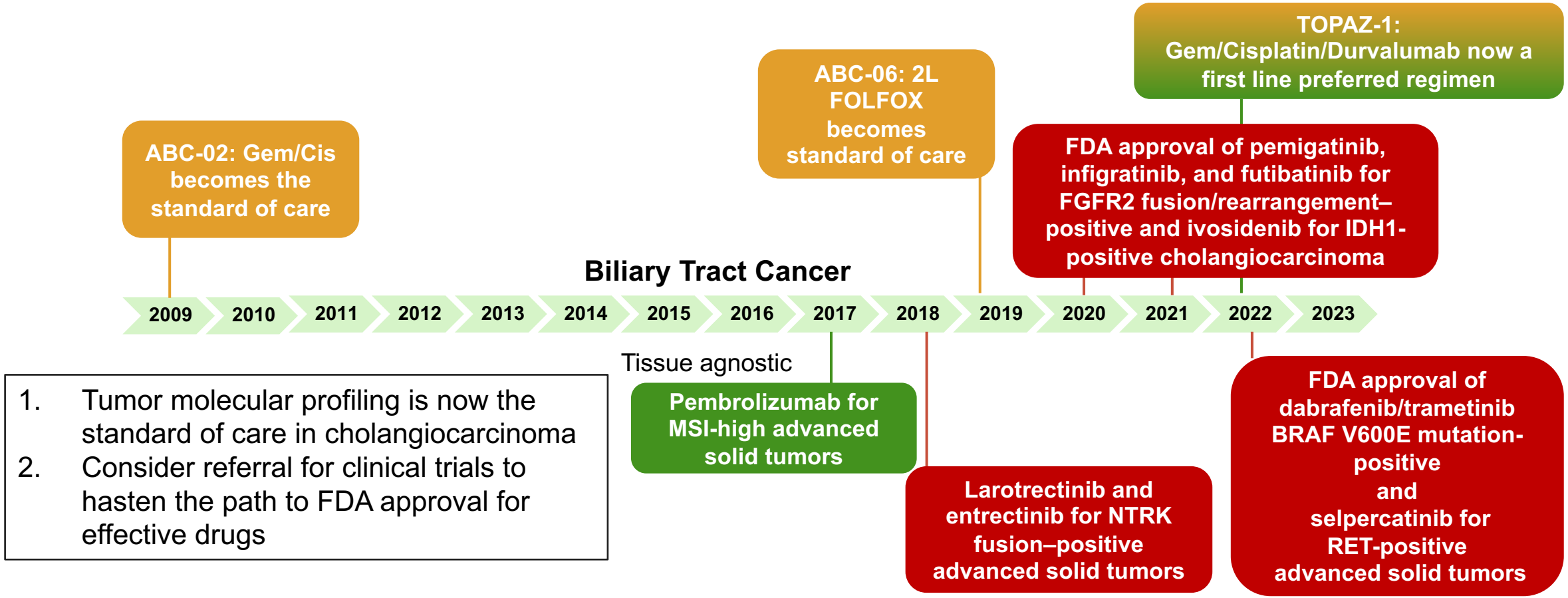
Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,h,10,11]
  - Dostarlimab-gxly[e,h,i,18,19] (category 2B)
- For TMB-H tumors:
  - Pembrolizumab[e,f,h,20]
- For *BRAF*-V600E mutated tumors
  - Dabrafenib + trametinib[21,22]
- For CCA with *FGFR2* fusions or rearrangements:
  - Pemigatinib[23]
  - Infigratinib[24]
  - Futibatinib[25]
- For CCA with *IDH1* mutations
  - Ivosidenib[26,27]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib for CCA[13]
  - Pralsetinib (category 2B)[12]
- For HER2-positive tumors:
  - Trastuzumab[j] + pertuzumab[28]
- Nivolumab[e,h,29] (category 2B)
- Lenvatinib + pembrolizumab[e,h,30] (category 2B)

[d] Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] There are limited clinical trial data to support pembrolizumab in this setting. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744-750.
[g] Treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction.
[h] For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[i] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
[j] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Conclusions

Precision Oncology is Key for Management of Advanced Cholangiocarcinoma



1. Tumor molecular profiling is now the standard of care in cholangiocarcinoma
2. Consider referral for clinical trials to hasten the path to FDA approval for effective drugs

2L, second line; BRAF, v-raf murine sarcoma viral oncogene homolog B; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; FOLFOX, folinic acid, fluorouracil and oxaliplatin; Gem/Cis, gemcitabine/ cisplatin; IDH, isocitrate dehydrogenase; MEK, mitogen-activated protein kinase kinase; MSI, microsatellite instability; NTRK, neurotrophic tyrosine kinase.

Valle JW, et al. Cancer Discov 2017;7(9):943–962; Goyal L, et al. Cancer Treat Rev 2021;95:102170; National Comprehensive Cancer Network (2021). Hepatobiliary cancers: NCCN evidence blocks. Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary_blocks.pdf; Abou-Alfa GK, et al (2019). Ann Oncol (ESMO Congress Abstracts), 30(suppl_5). Abstract 1867; Subbiah V, et al. Lancet 2020;21(9):1234–1243.

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Hepatobiliary Cancers

Part 3 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Friday, January 20, 2023

6:00 PM – 7:30 PM PT

Faculty

Richard S Finn, MD

Professor Arndt Vogel, MD

Lipika Goyal, MD, MPhil

Moderator

Robin K (Katie) Kelley, MD

RTP RESEARCH TO PRACTICE

Thank you for attending!

CME Credit Information

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.

RTP
RESEARCH
TO PRACTICE