Systemic Therapy Updates in HCC and Cholangiocarcinoma

Amit Mahipal MBBS, MPH

Professor, Case western Reserve University

Director, GI Oncology Program, Seidman Cancer Center

MLS Cleveland | Precision Medicine and Immunotherapy

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University Hospitals
Seidman Cancer Center
Cleveland | Ohio

Case Western Reserve University
Case Comprehensive Cancer Center

Role of adjuvant systemic therapy in HCC

- There is no standard of care adjuvant therapy after potentially curative therapy for BCLC B patients
  - Ablation
  - Surgery
  - Embolization (TACE or TARE)
- Systemic therapy with TKIs had limited utility
- Immunotherapy may change how we treat patients
- Rates of recurrences/progression is >50% after locoregional modalities

Hepatocellular Cancer: Adjuvant trials

IMbrave050 Trial

Emerald-1 Trial

IMbrave050

Efficacy, safety and patient-reported outcomes from the Phase III IMbrave050 trial of adjuvant atezolizumab + bevacizumab vs active surveillance in patients with hepatocellular carcinoma at high risk of disease recurrence following resection or ablation

Masatoshi Kudo,[1] Minshan Chen,[2] Pierce Chow,[3] Ahmed Kaseb,[4] Han Chu Lee,[5] Adam Yopp,[6] Lars Becker,[7] Sairy Hernandez,[8] Bruno Kovic,[9] Qinshu Lian,[8] Ning Ma,[8] Chun Wu,[10] Shukui Qin,[11] Ann-Lii Cheng[12]

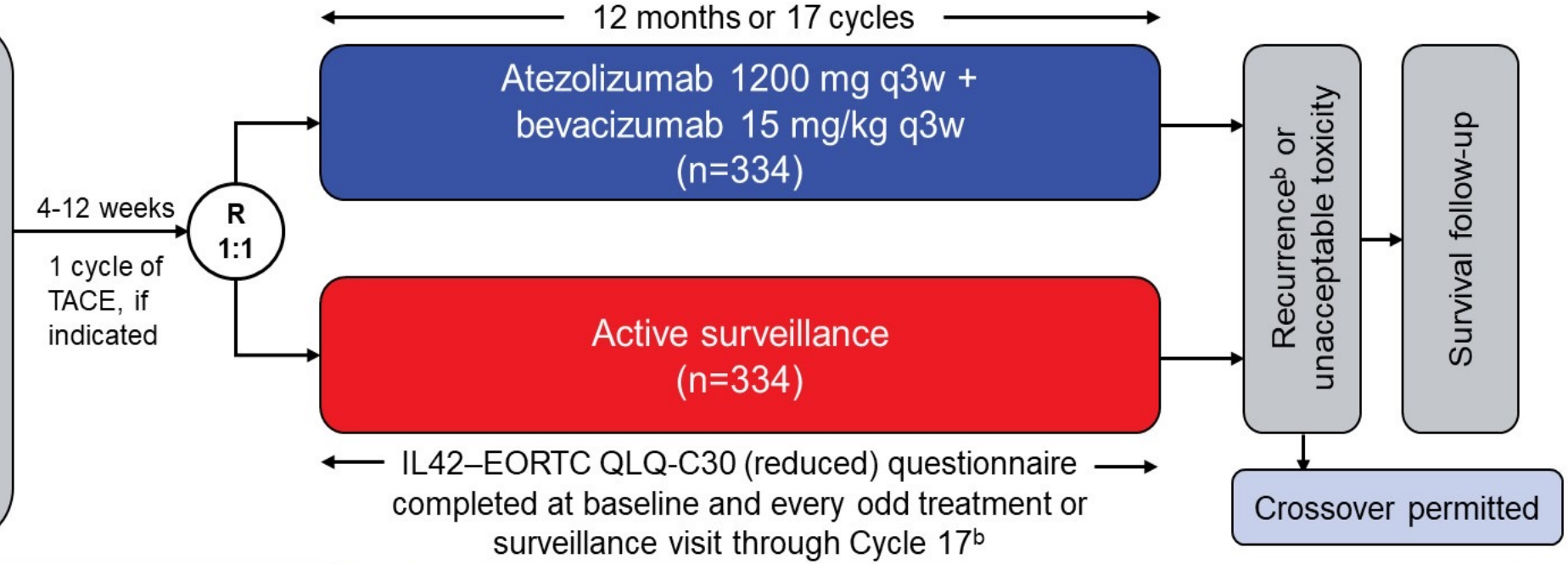
IMbrave050: High Risk Features

- Tumor size > 5 cm
- > 3 tumors
- Microvascular invasion
- Grade 3/4 pathology

IMbrave050: Study Design

Patient Population

- Confirmed first diagnosis of HCC and had undergone curative resection or ablation
- Disease free
- Child-Pugh Class A
- High risk of recurrence[a]
- No extrahepatic disease or macrovascular invasion (except Vp1/Vp2)
- ECOG PS 0 or 1



Stratification

- Region (APAC excluding Japan vs rest of world)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, ≥2 risk features, adjuvant TACE (yes vs no)

Primary endpoint

- Recurrence-free survival assessed by the independent review facility[c]

Prespecified exploratory PRO endpoints

- Change from baseline in GHS/QoL, and physical, role, emotional and social functioning
  - Clinically meaningful deterioration was defined as a ≥10-point decrease[2]

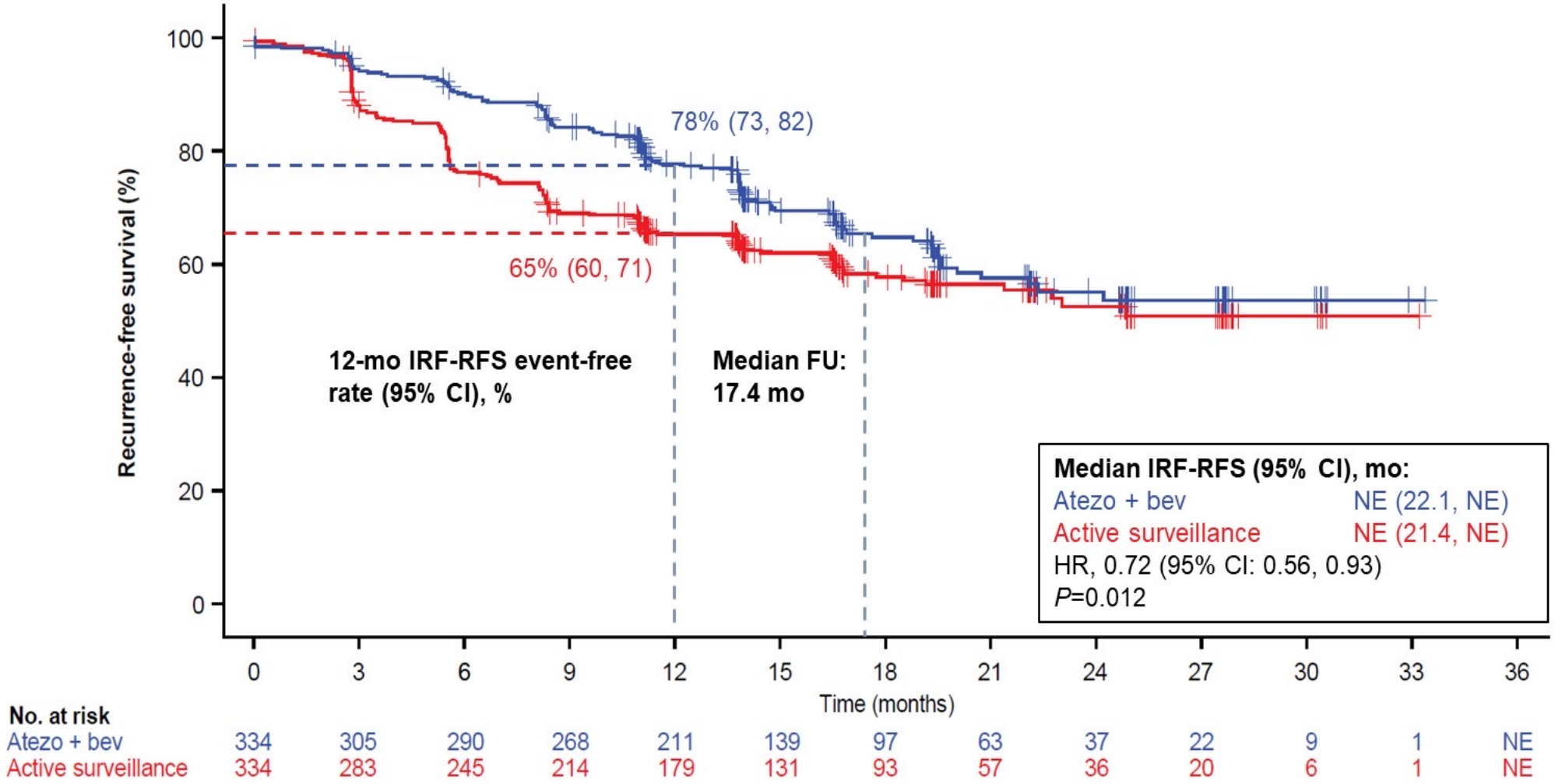
IMbrave050: Baseline Characteristics

Characteristic	Atezo + Bev (n=334)	Active surveillance (n=334)
Median age (range), years	60 (19-89)	59 (23-85)
Male sex, n (%)	277 (82.9)	278 (83.2)
Ethnicity, n (%)		
Asian	276 (82.6)	269 (80.5)
White	35 (10.5)	41 (12.3)
Other	23 (6.9)	24 (7.2)
Geographic region, n (%)		
Asia-Pacific excluding Japan | rest of world	237 (71.0) | 97 (29.0)	238 (71.3) | 96 (28.7)
ECOG PS score, n (%)		
0 | 1	258 (77.2) | 76 (22.8)	269 (80.5) | 65 (19.5)
PD-L1 status, n (%)[a,b]		
≥1% | <1%	154 (54.0) | 131 (46.0)	140 (50.2) | 139 (49.8)
Etiology, n (%)		
Hepatitis B	209 (62.6)	207 (62.0)
Hepatitis C	34 (10.2)	38 (11.4)
Non-viral | unknown	45 (13.5) | 46 (13.8)	38 (11.4) | 51 (15.3)
BCLC stage at initial diagnosis, n (%)		
0	2 (0.6)	3 (0.9)
A	287 (85.9)	277 (82.9)
B	25 (7.5)	32 (9.6)
C	20 (6.0)	22 (6.6)

IMbrave050: Baseline Characteristics

Characteristic	Atezo + Bev (n=334)	Active surveillance (n=334)
Resection, n (%)	293 (87.7)	292 (87.4)
Longest diameter of the largest tumor at diagnosis, median (range), cm[a]	5.3 (1.0-18.0)	5.9 (1.1-25.0)
Tumors, n (%)		
1	266 (90.8)	260 (89.0)
2	20 (6.8)	29 (9.9)
3	4 (1.4)	2 (0.7)
4+	3 (1.0)	1 (0.3)
Adjuvant TACE following resection, n (%)	32 (10.9)	34 (11.6)
Any tumors >5 cm, n (%)	152 (51.9)	175 (59.9)
Microvascular invasion present, n (%)	178 (60.8)	176 (60.3)
Minor macrovascular invasion (Vp1/Vp2) present, n (%)	22 (7.5)	17 (5.8)
Poor tumor differentiation (Grade 3 or 4), n (%)	124 (42.3)	121 (41.4)
Ablation, n (%)	41 (12.3)	42 (12.6)
Longest diameter of the largest tumor at diagnosis, median (range), cm	2.5 (1.2-4.6)	2.6 (1.5-4.6)
Tumors, n (%)		
1	29 (70.7)	31 (73.8)
2	11 (26.8)	8 (19.0)
3	1 (2.4)	3 (7.1)

IMbrave050: RFS



EMERALD-1

EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization

EMERALD-1: Study Design

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)

R 1:1:1
N=616

Arm A: **Durvalumab‡** (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ placebo** for bevacizumab (Q3W)

Arm B: **Durvalumab†** (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ bevacizumab** (15 mg/kg Q3W)

Arm C: **Placebo** for durvalumab (Q4W) **+ TACE§** → **Placebo** for durvalumab (Q3W) **+ placebo** for bevacizumab (Q3W)

Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

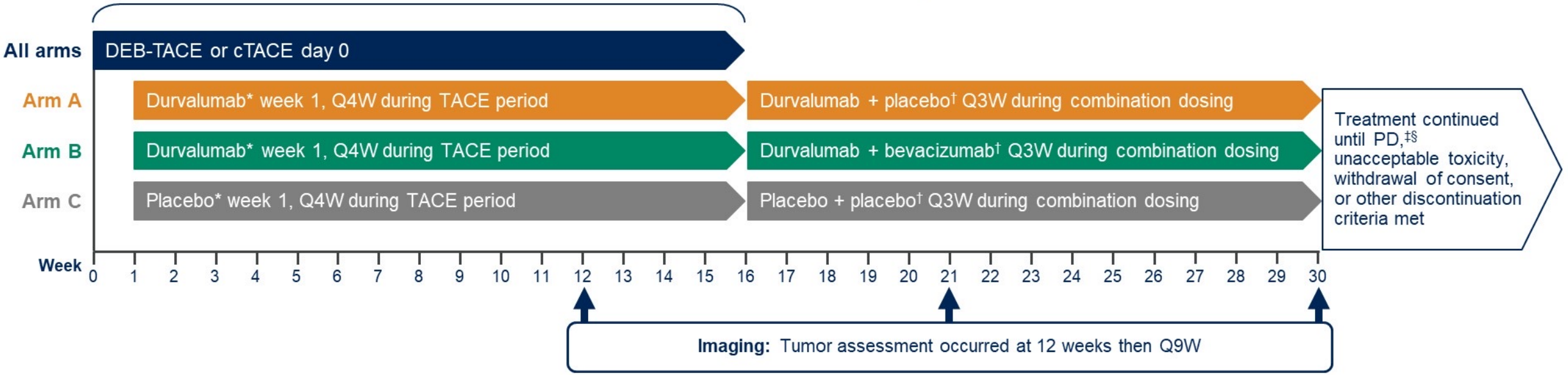
EMERALD-1: Study Treatment

Number and timings of TACE at the investigator's discretion:

- 1–4 TACE procedures within 16 weeks

Combination therapy begins after the final TACE procedure

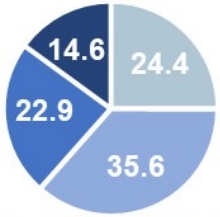
- Median (range) start of combination systemic therapy: 14 (2–113) weeks post first dose of TACE at Day 0



EMERALD-1

Participant disposition

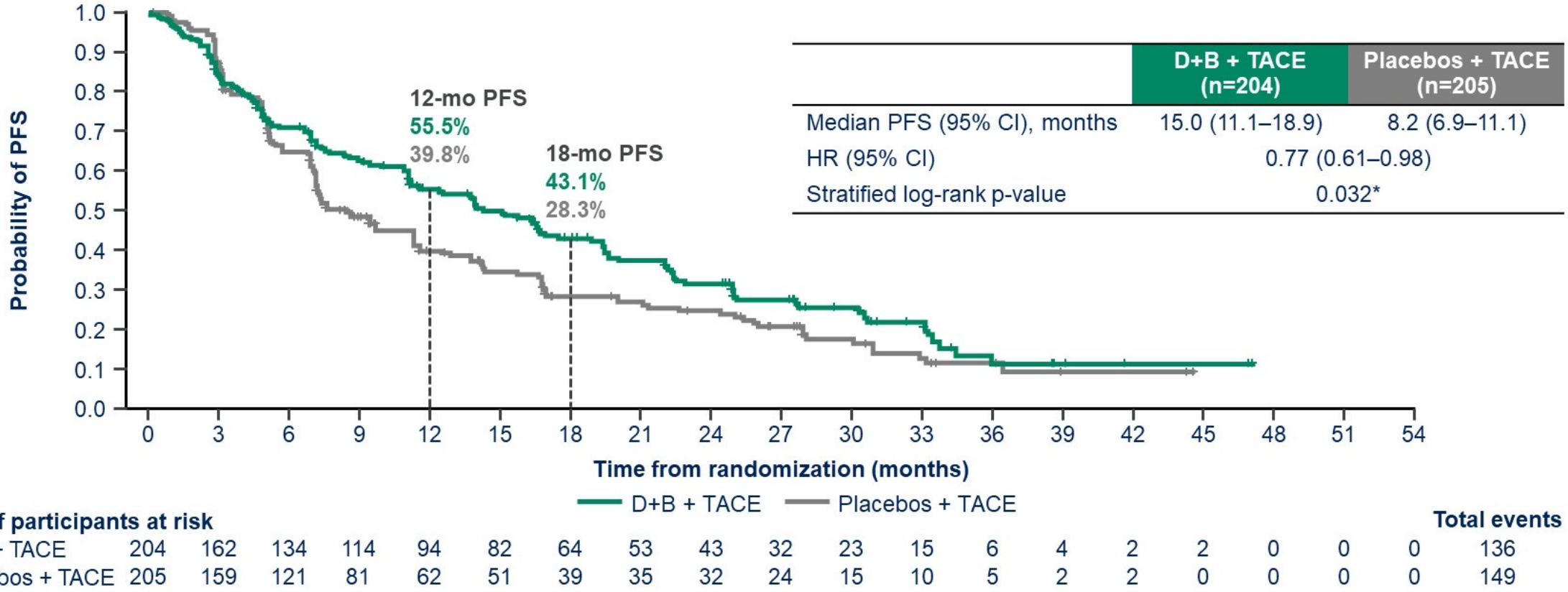
The majority of participants had 1 or 2 TACE procedures with or without durvalumab

	D + TACE	D+B + TACE	Placebos + TACE
	616 participants randomized		
Randomized	**207**	**204**	**205**
No. of TACE procedures,* %				
Dosed with durvalumab,† n / N (%)	193 / 207 (93.2%)	193 / 204 (94.6%)	200 / 205 (97.6%)
Dosed with combination n / N (%)	162 / 207 (78.3%)	154 / 204 (75.5%)	155 / 205 (75.6%)
Ongoing study, n / N (%)	**88 / 207 (42.5%)‡**	**89 / 204 (43.6%)§**	**82 / 205 (40.0%)‖**
On durvalumab treatment†	25 / 193 (13.0%)	27 / 193 (14.0%)	27 / 200 (13.5%)
Discontinued study treatment, n / N (%)¶	**168 / 193 (87.0%)****	**166 / 193 (86.0%)††**	**173 / 200 (86.5%)‡‡**
Condition under investigation worsened§§	122 / 193 (63.2%)	85 / 193 (44.0%)	119 / 200 (59.5%)

EMERALD-1: Baseline Characteristics

		D + TACE (n=207)*	D+B + TACE (n=204)*	Placebos + TACE (n=205)*
Age (years)	Median	65.0	64.5	66.0
Sex, n (%)	Male	156 (75.4)	162 (79.4)	163 (79.5)
Geographical region, n (%)	Japan	15 (7.2)	15 (7.4)	15 (7.3)
	Asia (non-Japan)	108 (52.1)	107 (52.4)	107 (52.1)
	Others	84 (40.5)	82 (40.1)	83 (40.4)
TACE modality, n (%)	DEB-TACE	81 (39.1)	84 (41.2)	84 (41.0)
	cTACE	123 (59.4)	119 (58.3)	120 (58.5)
Etiology of liver disease, n (%)	HBV	70 (33.8)	75 (36.8)	74 (36.1)
	HCV	48 (23.2)	42 (20.6)	54 (26.3)
	Non-viral	88 (42.5)	86 (42.2)	76 (37.1)
BCLC stage, n (%)	A	59 (28.5)	51 (25.0)	49 (23.9)
	B	114 (55.1)	117 (57.4)	122 (59.5)
	C	33 (15.9)	35 (17.2)	31 (15.1)
Portal vein invasion, n (%)	No	194 (93.7)	188 (92.2)	192 (93.7)
	Yes	13 (6.3)	16 (7.8)	13 (6.3)
Screening ECOG PS, n (%)	0	173 (83.6)	167 (81.9)	175 (85.4)
	1	34 (16.4)	37 (18.1)	30 (14.6)
Baseline PD-L1†, n (%)	High (≥1%)	63 (30.4)	61 (29.9)	64 (31.2)
	Low (<1%)	97 (46.9)	93 (45.6)	88 (42.9)
	Unknown	47 (22.7)	50 (24.5)	53 (25.9)
Child-Pugh score, n (%)	A	201 (97.1)	200 (98.0)	201 (98.0)
	B	6 (2.9)	4 (2.0)	4 (2.0)
ALBI at baseline, n (%)	Grade 1	107 (51.7)	117 (57.4)	126 (61.5)
	Grade ≥2	100 (48.3)	87 (42.6)	79 (38.5)
Tumor burden at baseline, n (%)	Within up-to 7 criteria (≤7)	97 (46.9)	97 (47.5)	102 (49.8)
	Beyond up-to-7 criteria (>7)	110 (53.1)	106 (52.0)	103 (50.2)
HAP score, n (%)	A	63 (30.4)	66 (32.4)	64 (31.2)
	B	72 (34.8)	74 (36.3)	75 (36.6)
	C	52 (25.1)	41 (20.1)	48 (23.4)
	D	20 (9.7)	20 (9.8)	18 (8.8)
	Missing	0	3 (1.5)	0

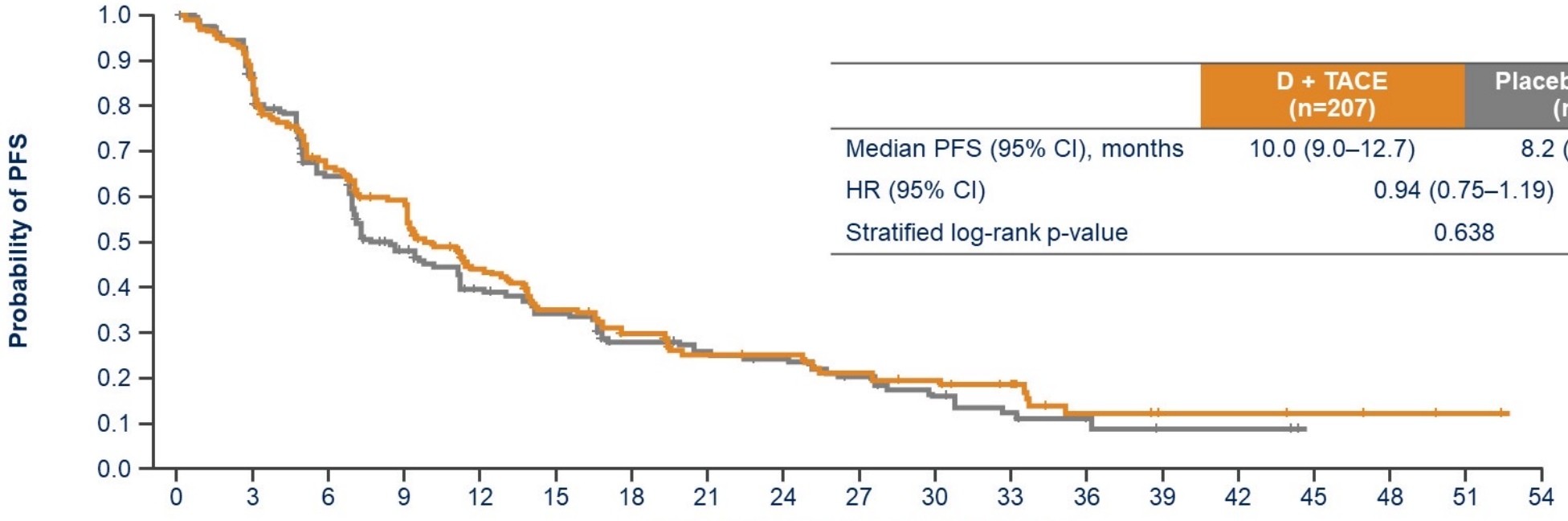
Emerald-1: PFS (D + B + TACE)



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

No. of participants at risk																				Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

EMERALD-1: PFS (D + TACE)



	D + TACE (n=207)	Placebos + TACE (n=205)
Median PFS (95% CI), months	10.0 (9.0–12.7)	8.2 (6.9–11.1)
HR (95% CI)	0.94 (0.75–1.19)	
Stratified log-rank p-value	0.638	

No. of participants at risk																			Total events
D + TACE	207	160	124	103	71	53	42	33	32	27	22	14	7	5	5	4	2	1	0	144
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

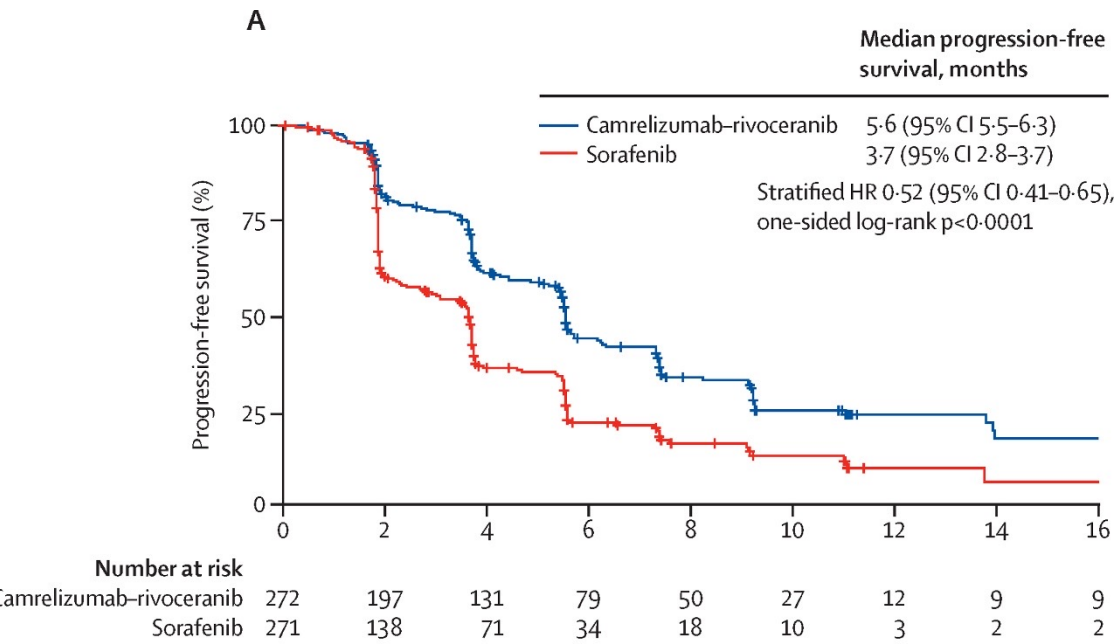
Key Takeaways

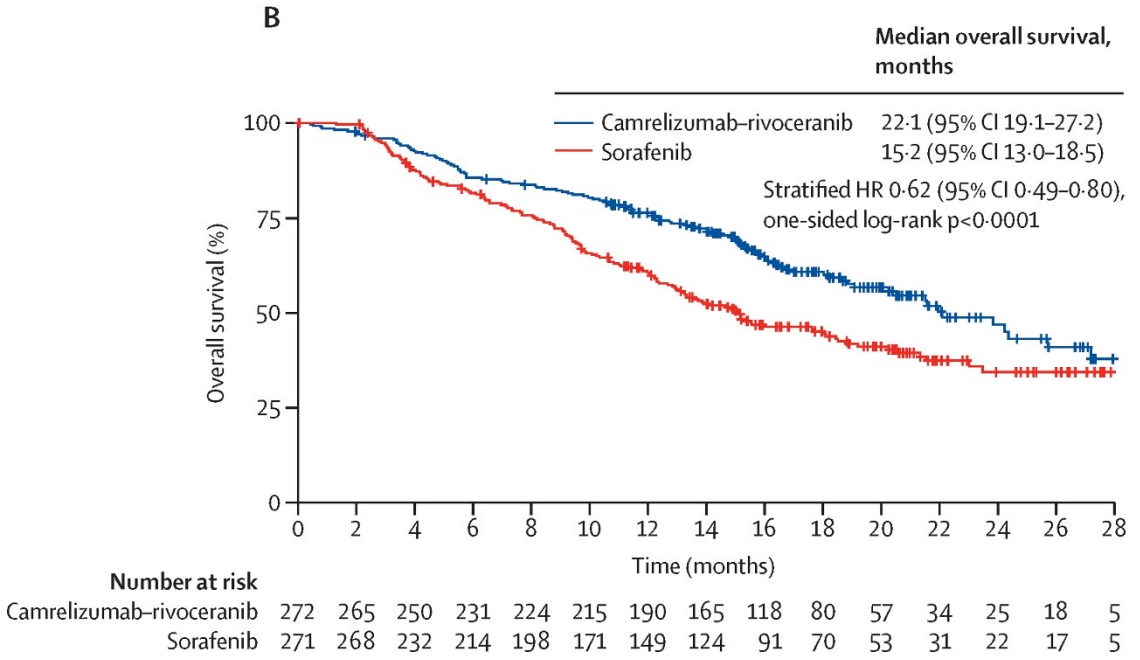
- First time we have positive adjuvant trials in HCC
  - Atezolizumab + bevacizumab post ablation/resection
  - Durvalumab + bevacizumab post TACE
- OS data is immature for both trials
- Relevant for patients with high risk disease
- TACE vs TARE
- Is adjuvant therapy delaying recurrences vs increasing cure rates
- Increasing role of systemic therapy in HCC
- Eagerly awaiting mature OS data
- Is there role of radiation therapy in adjuvant setting

CARES-310: Camrelizumab + Rovoceranib

Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study

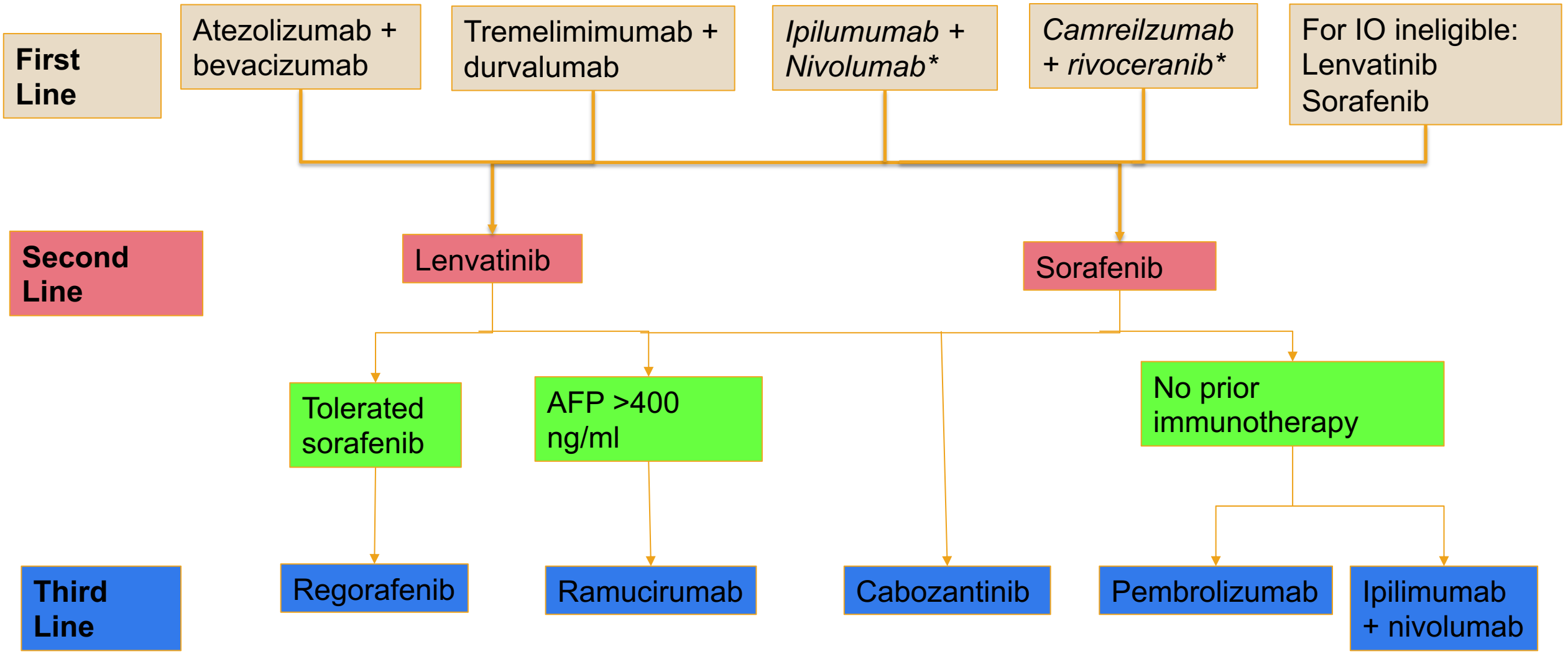
CARES-310: Camrelizumab + Rivoceranib





Qin et al. Lancet 2023

Systemic therapy for HCC: How to treat



*Not FDA approved

Bile Duct Cancers: Targeted Therapy

- FGFR2 fusions
  - Futibatinib
  - Pemigatinib
  - Infigratinib (withdrawn from the market)
- IDH1 mutation
  - Ivosidenib
- MSI-high
  - Pembrolizumab
  - Ipilimumab + nivolumab
- Her-2 overexpression/amplification

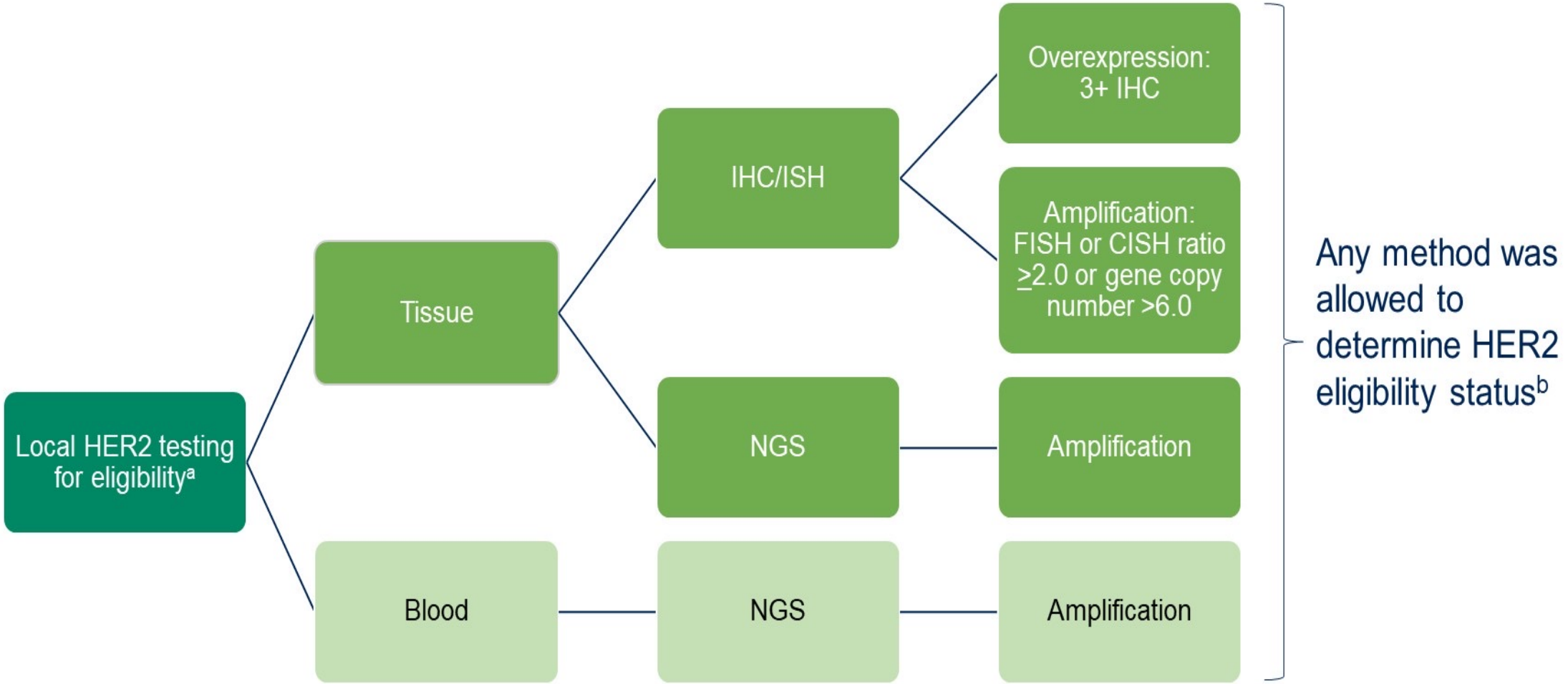
Tucatinib and Trastuzumab for Previously Treated HER2-Positive Metastatic Biliary Tract Cancer (SGNTUC-019): A Phase 2 Basket Study

Yoshiaki Nakamura

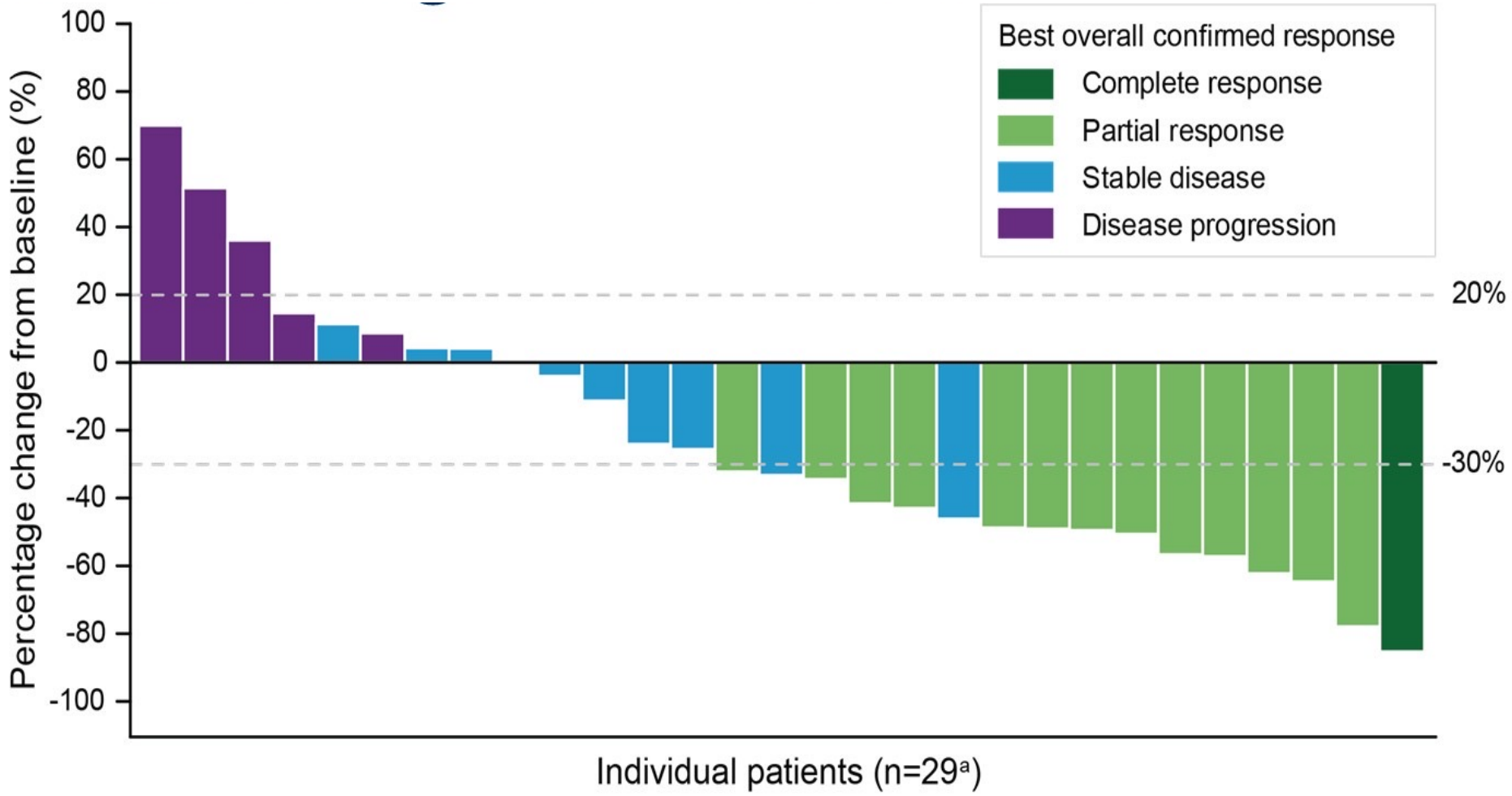
National Cancer Center Hospital East, Kashiwa, Japan

Nobumasa Mizuno, Yu Sunakawa, Erika P. Hamilton, Hidetoshi Hayashi, Seung Tae Kim, Keun-Wook Lee, Bradley J. Monk, Danny Nguyen, Alicia Okines, David M. O'Malley, Paula R. Pohlmann, Martin Reck, Evan Y. Yu, Roman Groisberg, Jorge Ramos, Sherry Tan, Thomas E. Stinchcombe, Tanios S. Bekaii-Saab

SGNTUC-019: Her-2 eligibility



SGNTUC-019: Waterfall Plot



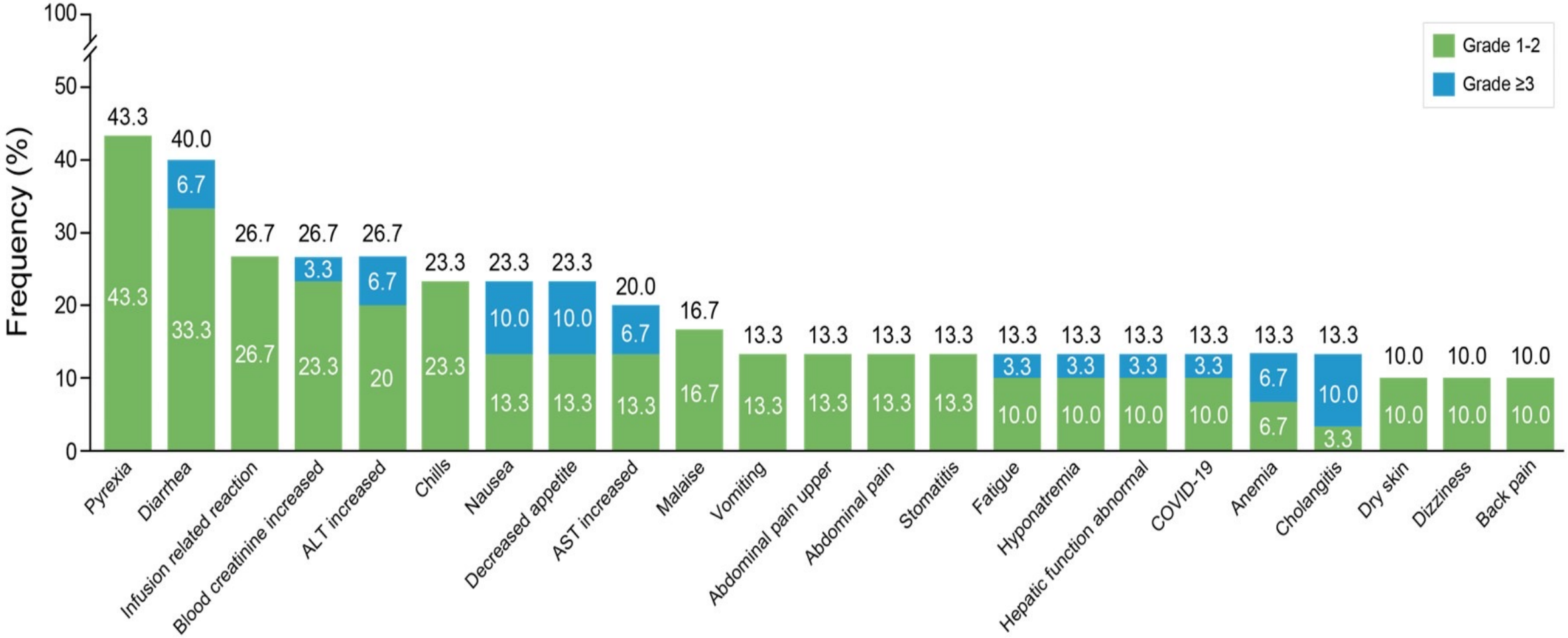
CR: 3.3%
PR: 43.3%
SD: 30%
PD: 20%

mPFS: 5.5 months

mOS: 15.5 months

Twenty-one patients (70.0%[b]) had a reduction in tumor size
Median time to first response was 2.1 months (range, 1.2-4.3)

SGNTUC-019: Adverse Events



Most common grade ≥3 TEAEs were nausea, decreased appetite, and cholangitis (each in 3 patients [10.0%])

SGNTUC-019: Central vs Local Her-2 testing

	Centrally HER2+		Centrally HER2–	
	Responder/Total	ORR (90% CI)	Responder/Total	ORR (90% CI)
IHC/FISH[a]	12/21	57.1% (37.2-75.5)	0/3	0% (0-63.2)
FISH[b]	12/21	57.1% (37.2-75.5)	0/3	0% (0-63.2)
Blood-based NGS[c]	14/22	63.6% (43.9-80.4)	0/7	0% (0-34.8)

Regardless of testing method, all central HER2– patients were nonresponders

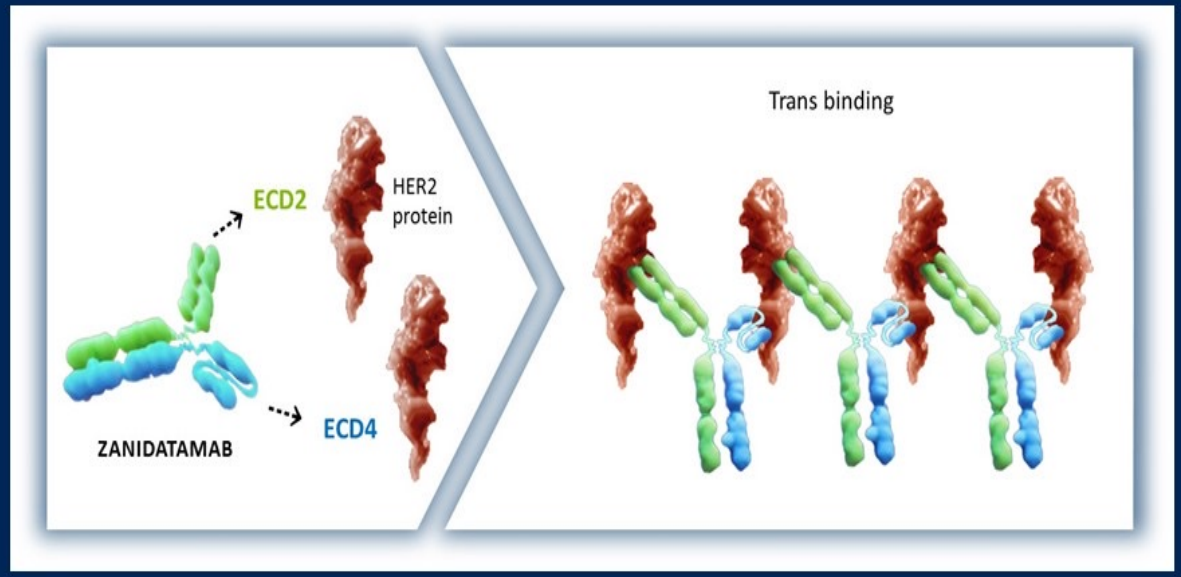
Zanidatamab

Results from the Pivotal Phase 2b HERIZON-BTC-01 Study: Zanidatamab in Previously-treated HER2-amplified Biliary Tract Cancer (BTC)

Shubham Pant, MD[1]; Jia Fan, MD, PhD[2]; Do-Youn Oh, MD, PhD[3]; Hye Jin Choi, MD, PhD[4]; Jin Won Kim, MD, PhD[5]; Heung-Moon Chang, MD, PhD[6]; Lequn Bao, MD[7]; Sun Huichuan, MD, PhD[2]; Teresa Macarulla, MD, PhD[8]; Feng Xie, MD[9]; Jean-Philippe Metges, MD[10]; Jie'er Ying, MD[11]; John A Bridgewater, MD, PhD[12]; Myung-Ah Lee, MD, PhD[13]; Mohamedtaki A Tejani, MD[14]; Emerson Y Chen, MD, MCR[15]; Dong Uk Kim, MD[16]; Harpreet Wasan, MD, FRCP[17]; Michel Ducreux, MD, PhD[18]; Yuanyuan Bao, MS[19]; Lin Yang, PhD[20]; JiaFang Ma, MD[19]; Phillip M Garfin, MD[20]; James J Harding, MD[21]

Zanidatamab: Her-2 targeted bispecific antibody

- Zanidatamab simultaneously binds 2 separate HER2 molecules in *trans*[1]
- Unique binding properties of zanidatamab to HER2 result in multiple MOAs[1]
- Preclinical studies demonstrate greater activity than trastuzumab ± pertuzumab[1]
- Zanidatamab has shown a manageable safety profile and encouraging antitumor activity in patients with HER2-expressing BTC in a Phase 1 trial[2]



ECD = extracellular domain

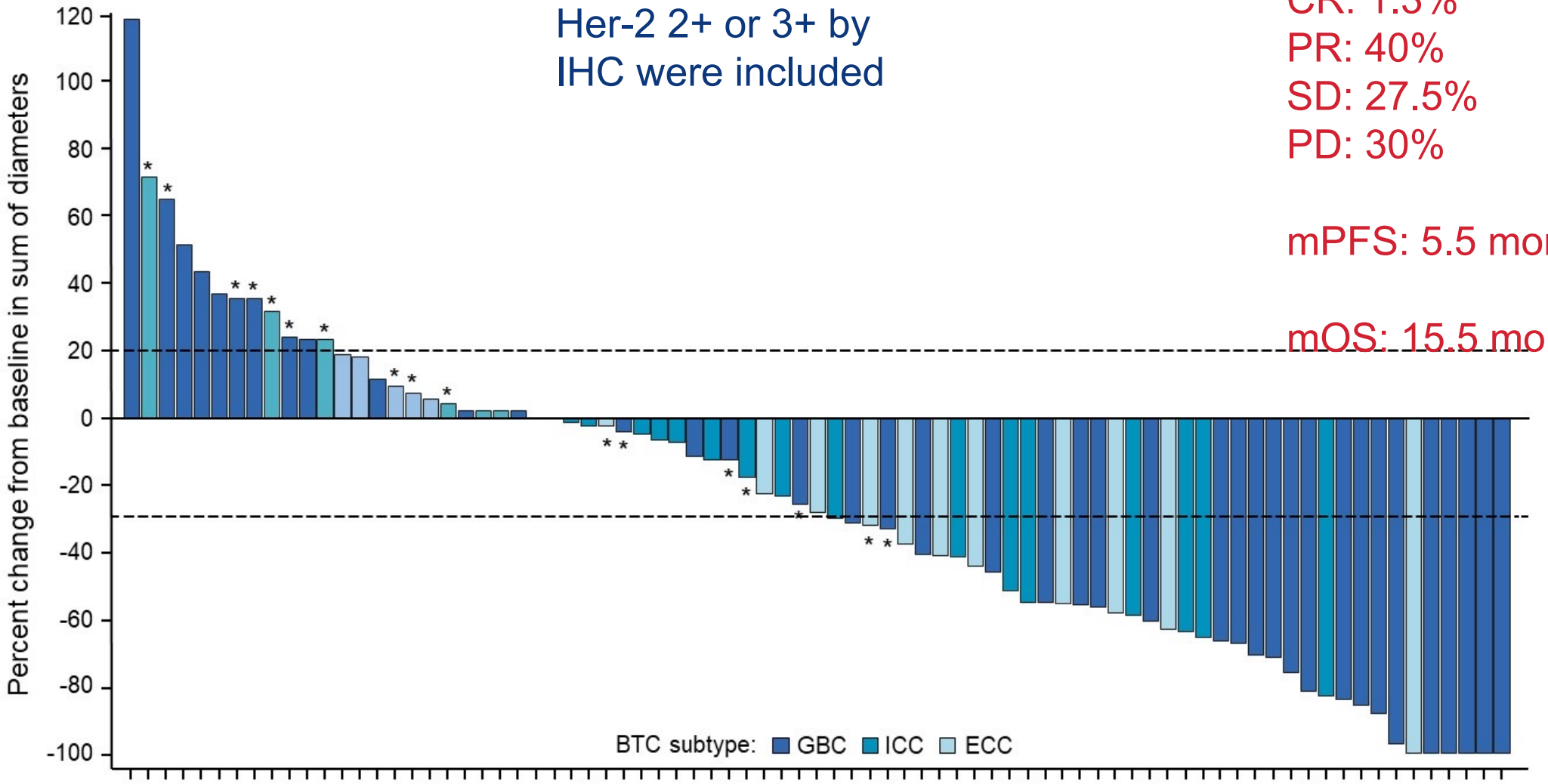
Zanidatamab: Waterfall Plot

Her-2 2+ or 3+ by IHC were included

CR: 1.3%
PR: 40%
SD: 27.5%
PD: 30%

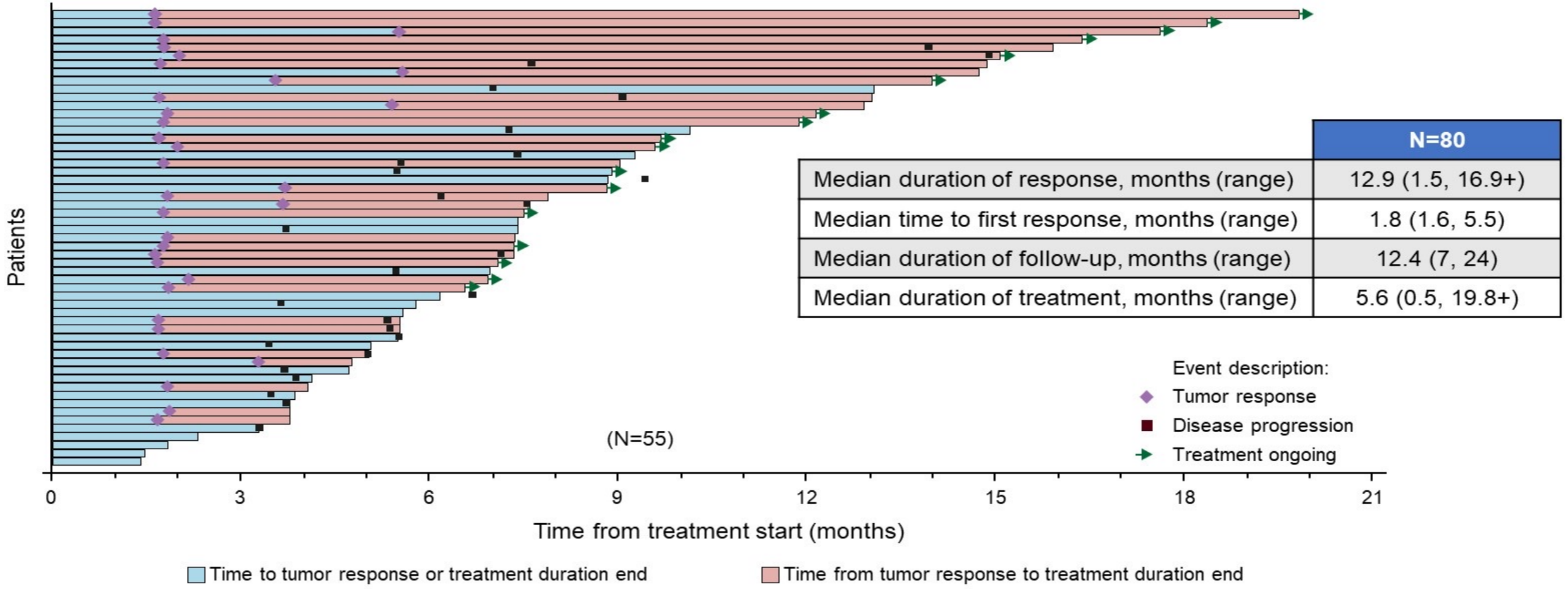
mPFS: 5.5 months

mOS: 15.5 months



N=80

Zandatamab: Duration of Response



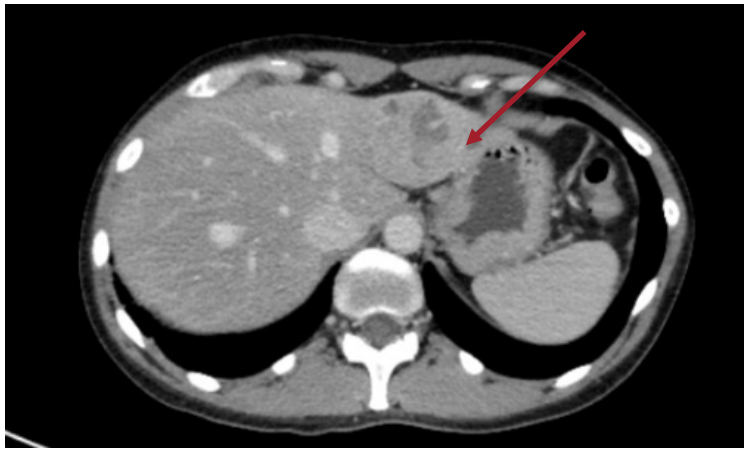
	N=80
Median duration of response, months (range)	12.9 (1.5, 16.9+)
Median time to first response, months (range)	1.8 (1.6, 5.5)
Median duration of follow-up, months (range)	12.4 (7, 24)
Median duration of treatment, months (range)	5.6 (0.5, 19.8+)

Key takeaways

- Tucatinib + trastuzumab had ORR of 46.7% and DCR of 76.7% in Her-2 amplified BTCs
  - The benefit was seen regardless of methodology: IHC, FISH, tissue or blood based NGS
- Zanidatamab had ORR of 41.3% and DCR of 68.8%
  - Her-2 2+ and 3+ were included
- Relatively well tolerated regimens
- Her-2 is becoming a viable target with multiple therapies being tested
- Due to rarity of disease, it may not be feasible to do a randomized trial
- Possibly consider Her-2 targeted therapies as second line treatment in advanced BTCs

Case Presentation

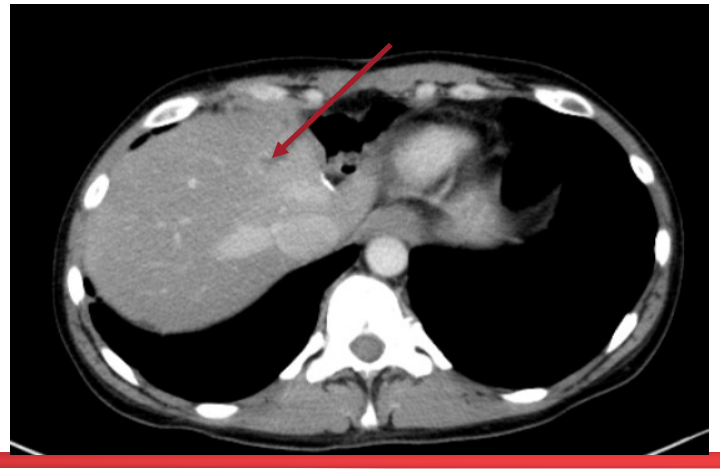
44 year old female presented with right upper quadrant pain

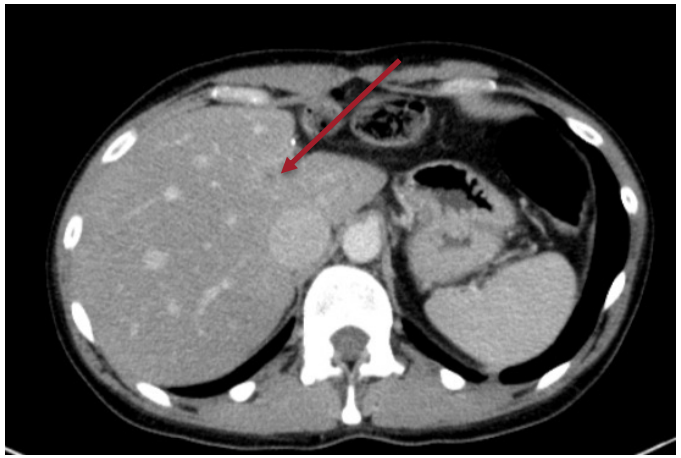


3/2021: Left hepatectomy, T2N0

4/2021-12/2021: Adjuvant capecitabine

1/2022: Recurrence





Biopsy consistent with recurrence

Case Presentation

1/2023: Solid tumor NGS showed mutation in *IDH1, KRAS G12C, BAP1, PBRM1, ERBB3*

2/2023-6/2023: Gemcitabine + cisplatin + durvalumab. Progressive disease

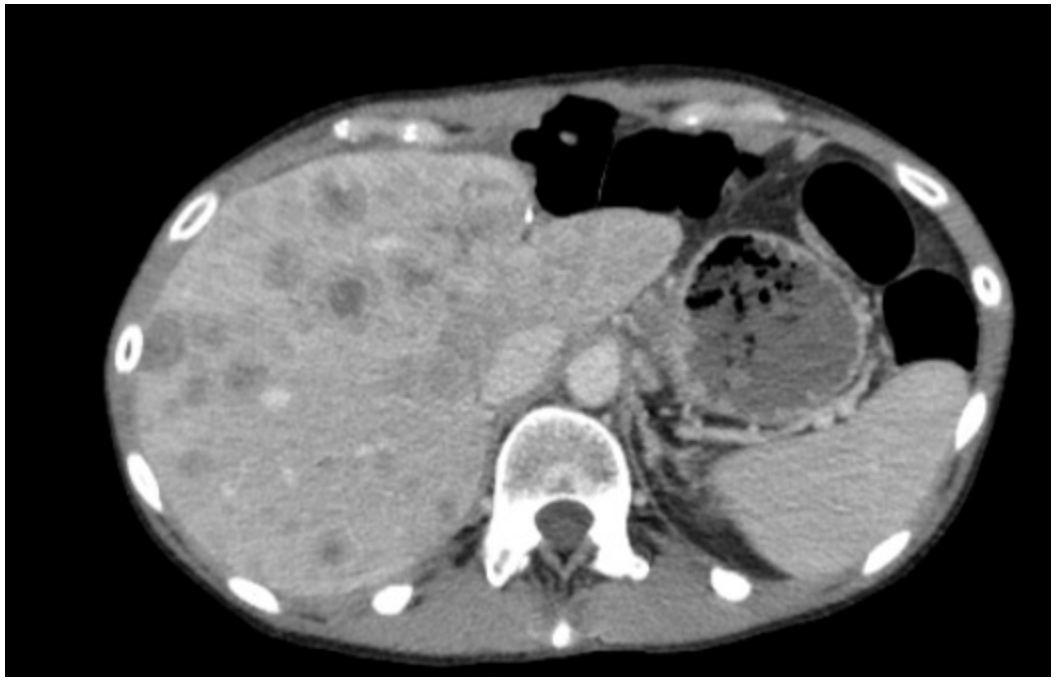
7/2023-9/2023: Sotorasib targeting *KRAS G12C*. Progressive disease

9/2023-10/2023: FOLFOX. Progressive disease

11/2023-1/2024: Ivosidenib targeting *IDH1*. Progressive disease

Case Presentation

2/2024



2/2024: Repeat NGS showed mutation in *CHEK2, TERT, TP53, ERBB2, IDH1*

What would be next steps*:*

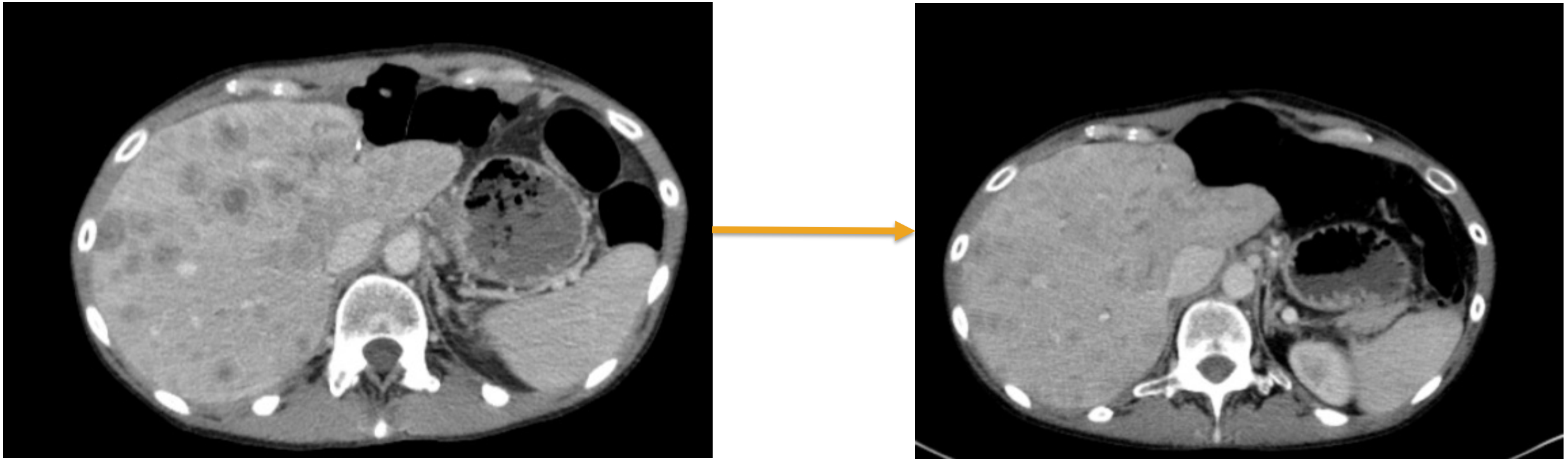
Hospice?

Phase 1 Clinical trial?

Others?

Case Presentation

2/2024: Fam-trastuzumab deruxtecan (6.4 mg/kg), 21 Day Cycles



Keep in mind that this patient had *ERBB2* mutation and not ERBB2 overexpression or amplification

Questions