2025 Johns Hopkins Updates: Cholangiocarcinoma

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THE UNIVERSITY OF ARIZONA
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2nd line and beyond: Targeted Therapy

ABC-06 study design

Phase III, randomised, open-label

Inclusion criteria

- Histo/cytologically verified **advanced BTC**

  ECOG performance score 0-1

  Progression after 1st-line CisGem
- Max **6 weeks progression to randomisation**
- Adequate haematological, renal & hepatic function

R

Arm A

Active Symptom Control (ASC)

- May include: biliary drainage, antibiotics, analgesia, steroids, anti-emetics etc
- 4-weekly clinical review

Arm B

Active Symptom Control + mFOLFOX

- Chemotherapy every 14 days for up to 12 cycles
- Day 1: Oxaliplatin 85mg/m^2, L-folinic acid 175 mg (or folinic acid 350 mg), 5 FU 400 mg/m^2 (bolus), 5 FU 2400 mg/m^2 46 hours continuous infusion
- 4-weekly clinical review after chemotherapy
- 3-monthly radiological assessment

Follow up

- **Overall survival** = primary end-point
- Until death or until completion of 12 months after enrolment of the final patient (whichever happened first)

Platinum sensitivity (yes vs. no; determined from first-line CisGem*)
Serum albumin (<35 vs. ≥35 g/L)
Stage (locally advanced vs. metastatic disease)

*determined from first-line CisGem: sensitive (progression after three months (90 days) of day 1 of the last cycle of 1st-line CisGem), refractory (progression during 1st line CisGem), resistant (progression within the first three months (90 days) after completion of day 1 of the last cycle of 1st line CisGem). CisGem: cisplatin and gemcitabine; BTC: biliary tract cancer; ECOG: Eastern Cooperative Oncology Group

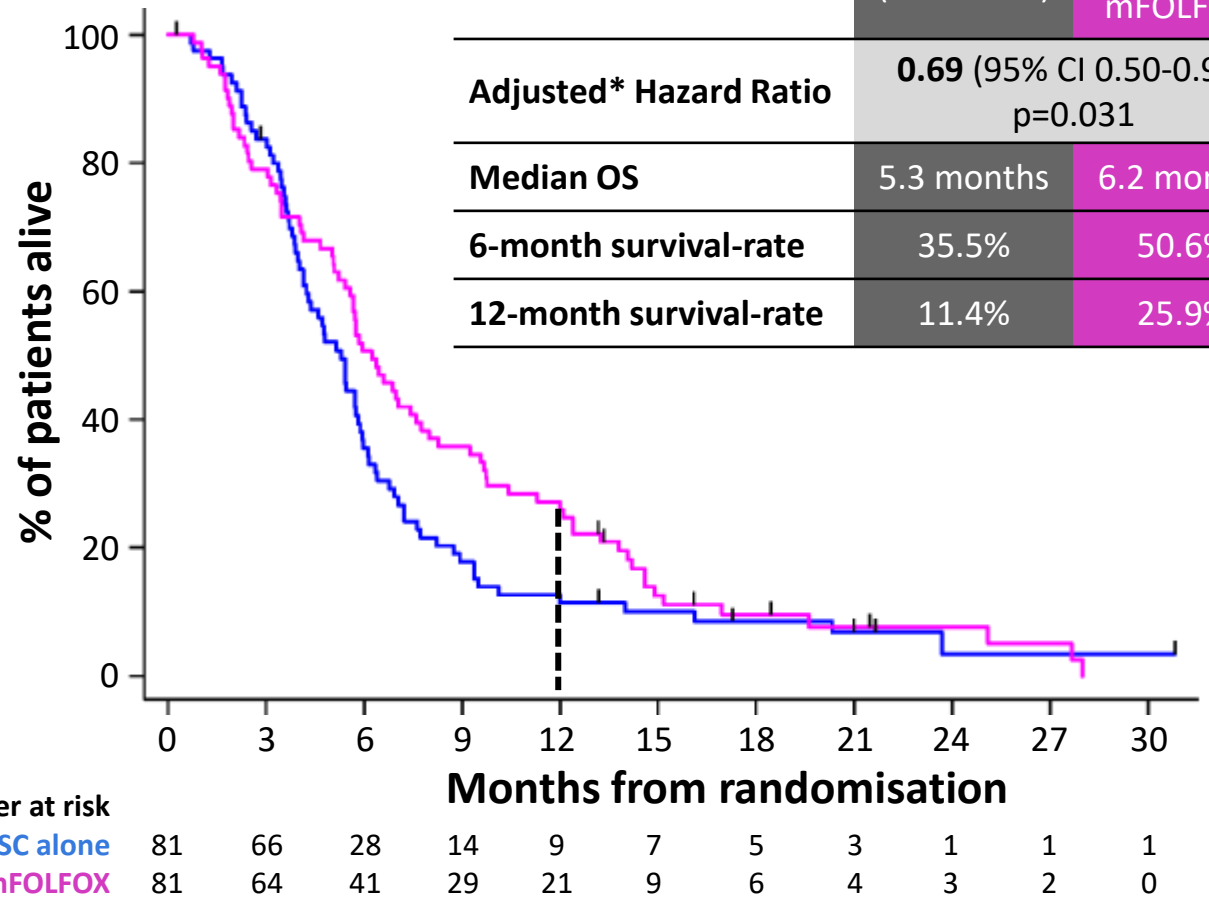
Lamarca A, et al, ASCO 2019

Primary end-point: Overall Survival (ITT)

- The **primary end-point was met**: adjusted* HR was 0.69 (95% CI 0.50-0.97; p=0.031) for OS in favour of ASC + mFOLFOX arm (vs ASC)

- No marked evidence was identified against the key proportional hazards assumption**; which confirmed the validity of using the Cox Regression analysis

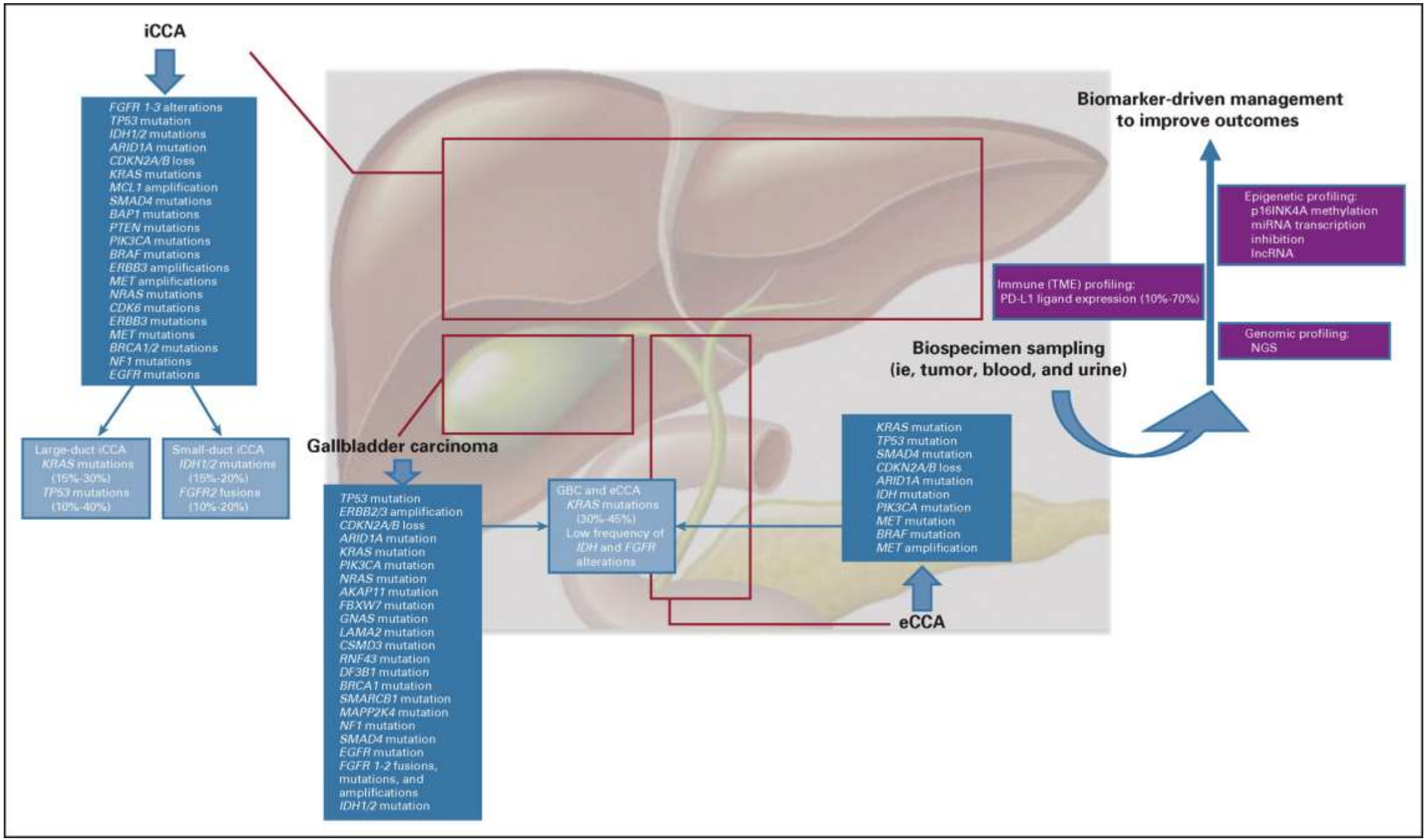
Overall survival by trial arm



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

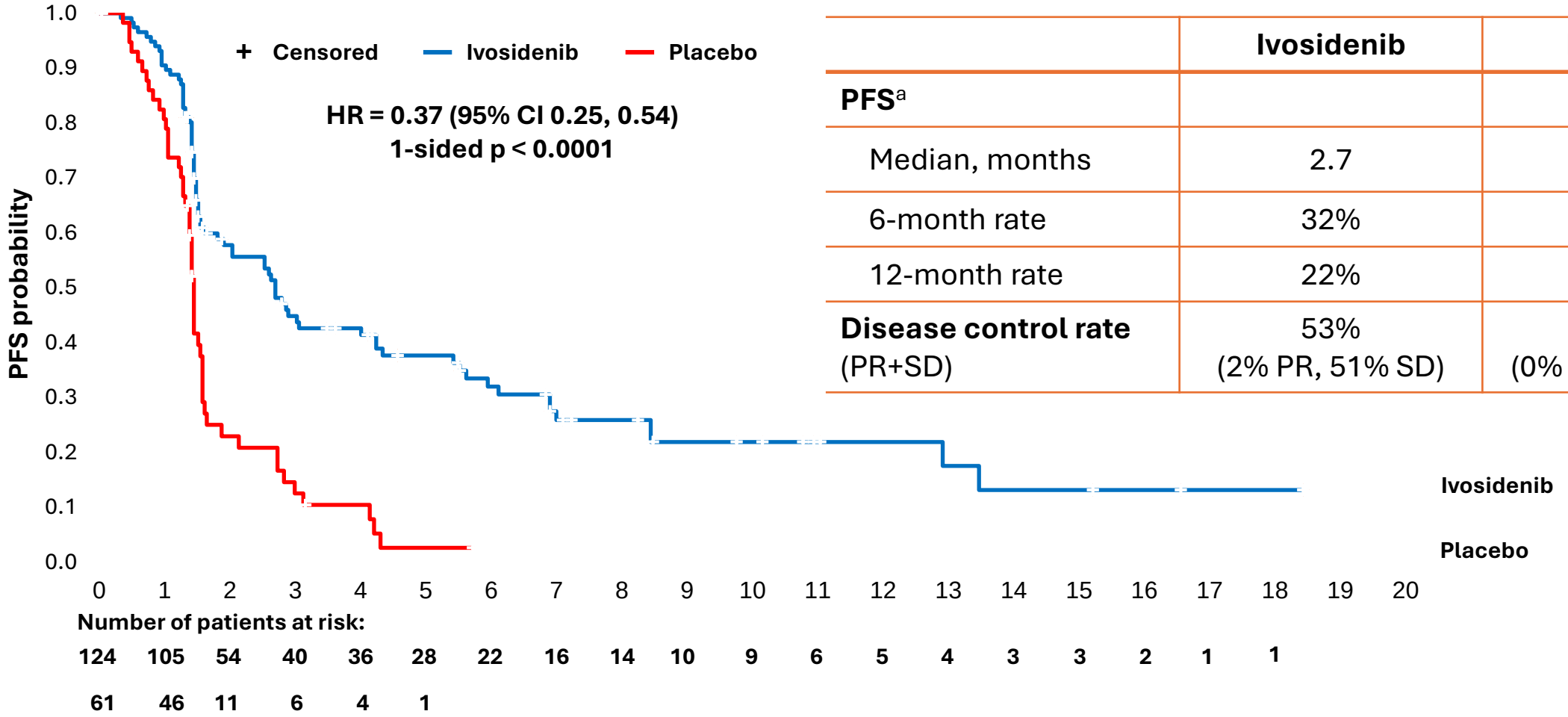
*adjusted for platinum sensitivity, albumin and stage
**proportional hazards assumption test p-value 0.6521
ITT: intention-to-treat analysis; ASC: active symptom control

Lamarca A, et al, ASCO 2019



Scott AJ et al, J Clin Oncol 2022

IDH - ClarIDHy



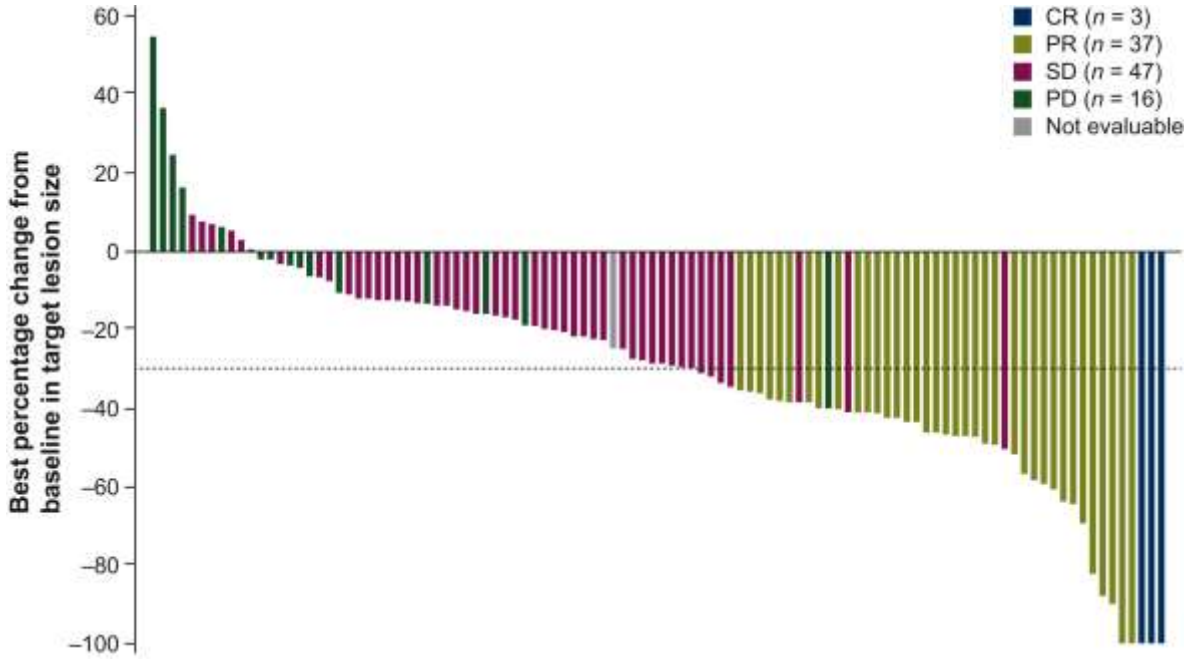
	Ivosidenib	Placebo
PFS[a]		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

[a]All randomized patients as of 31Jan2019
NE = not estimable; PR = partial response; SD = stable disease
Abou-Alfa GK et al. Lancet Oncol. 2020;21:796-807.

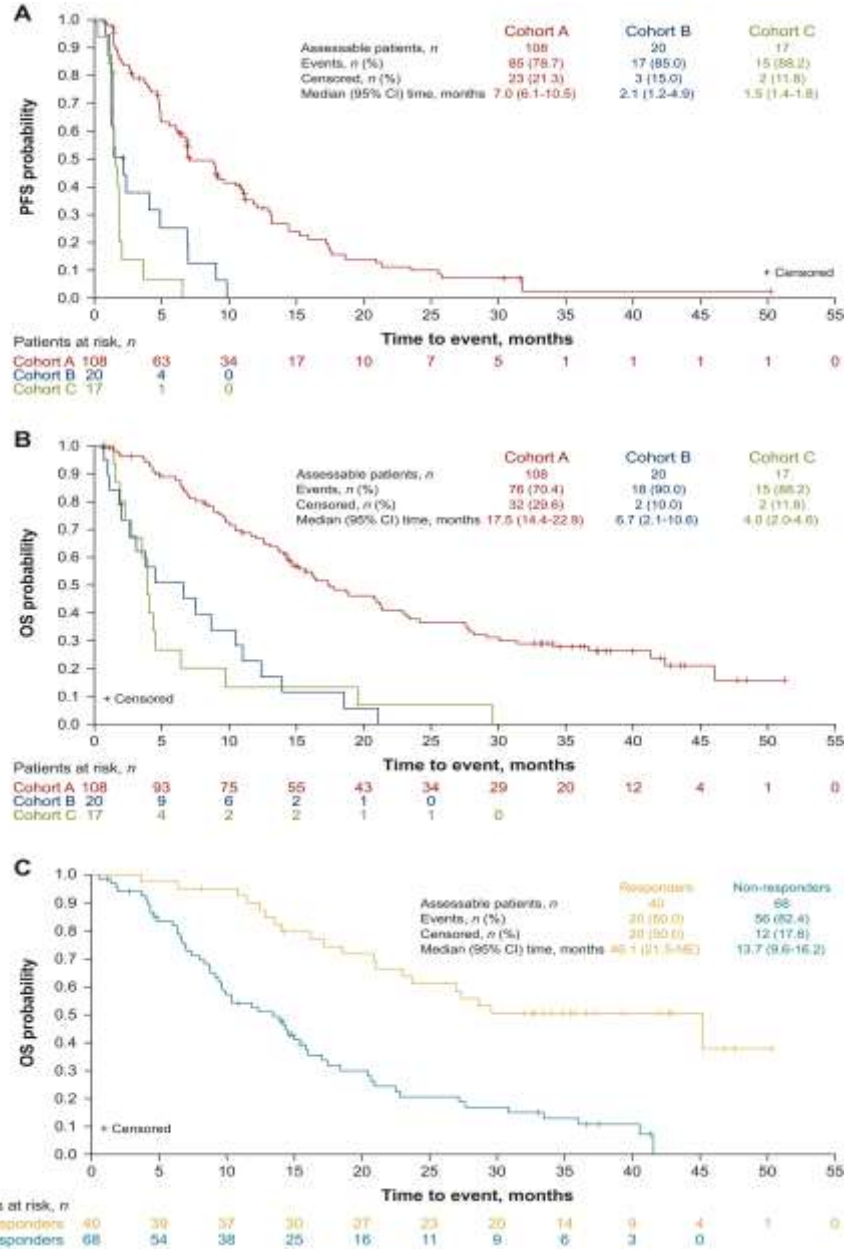
Zhu A, et al. GI ASCO 2021

FGFR2 as a target: Pemigatinib

- Updated Results from FIGHT-202

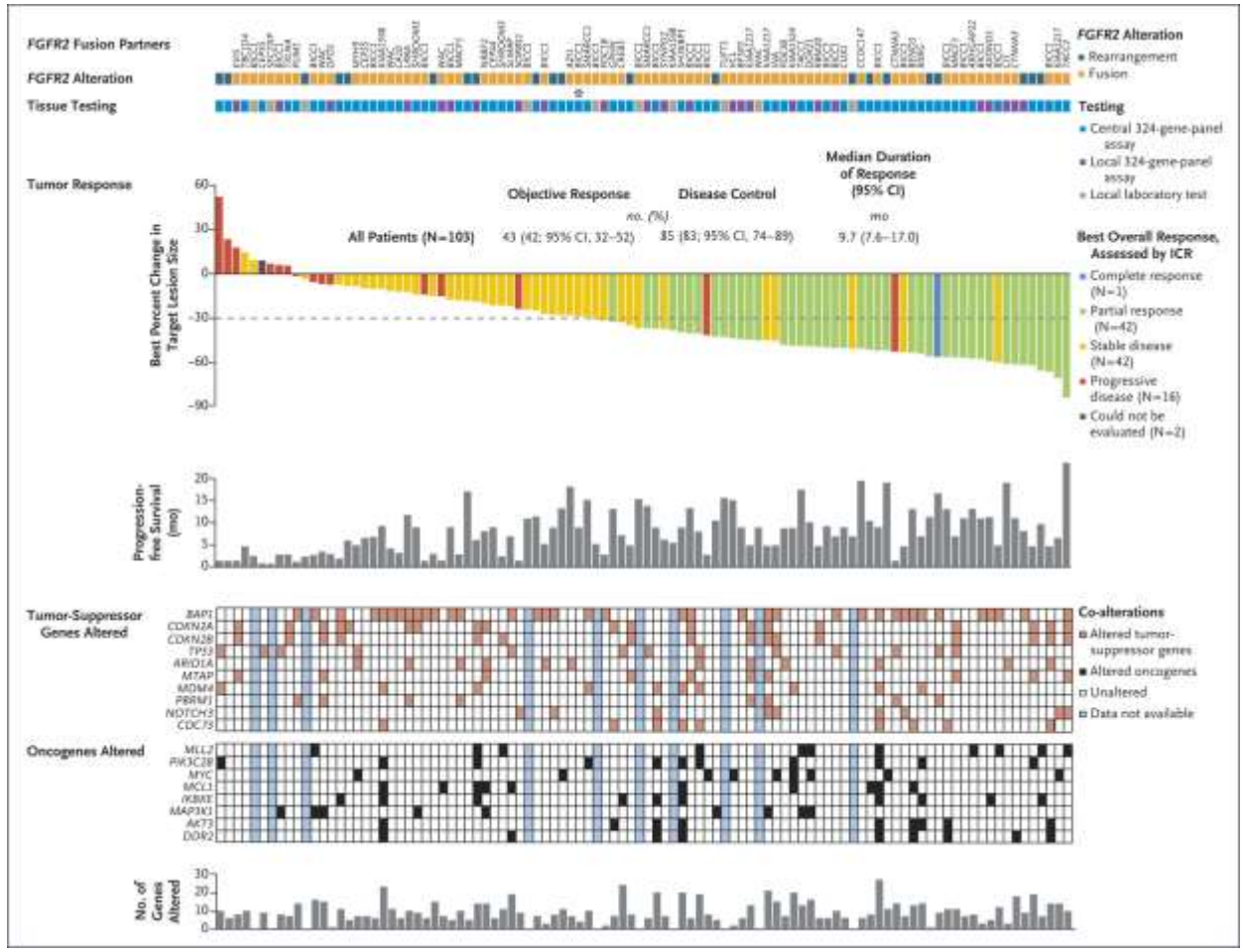


- Median follow-up was 45.4 months
- ORR of 37%, median DOR of 9.1 months
- Median PFS was 7.0
- Median OS was 17.5 months



Vogel A, et al. ESMO Open 2024

FGFR2 as a target: futibatinib



- 103 patients with FGFR2 fusions
- Median follow-up was 17.1 months
- ORR of 43%, median DOR of 9.7 months
- Median time to response was 2.5 months
- Median PFS was 9.0
- Median OS was 21.7 months

Goyal L, et al NEJM 2023

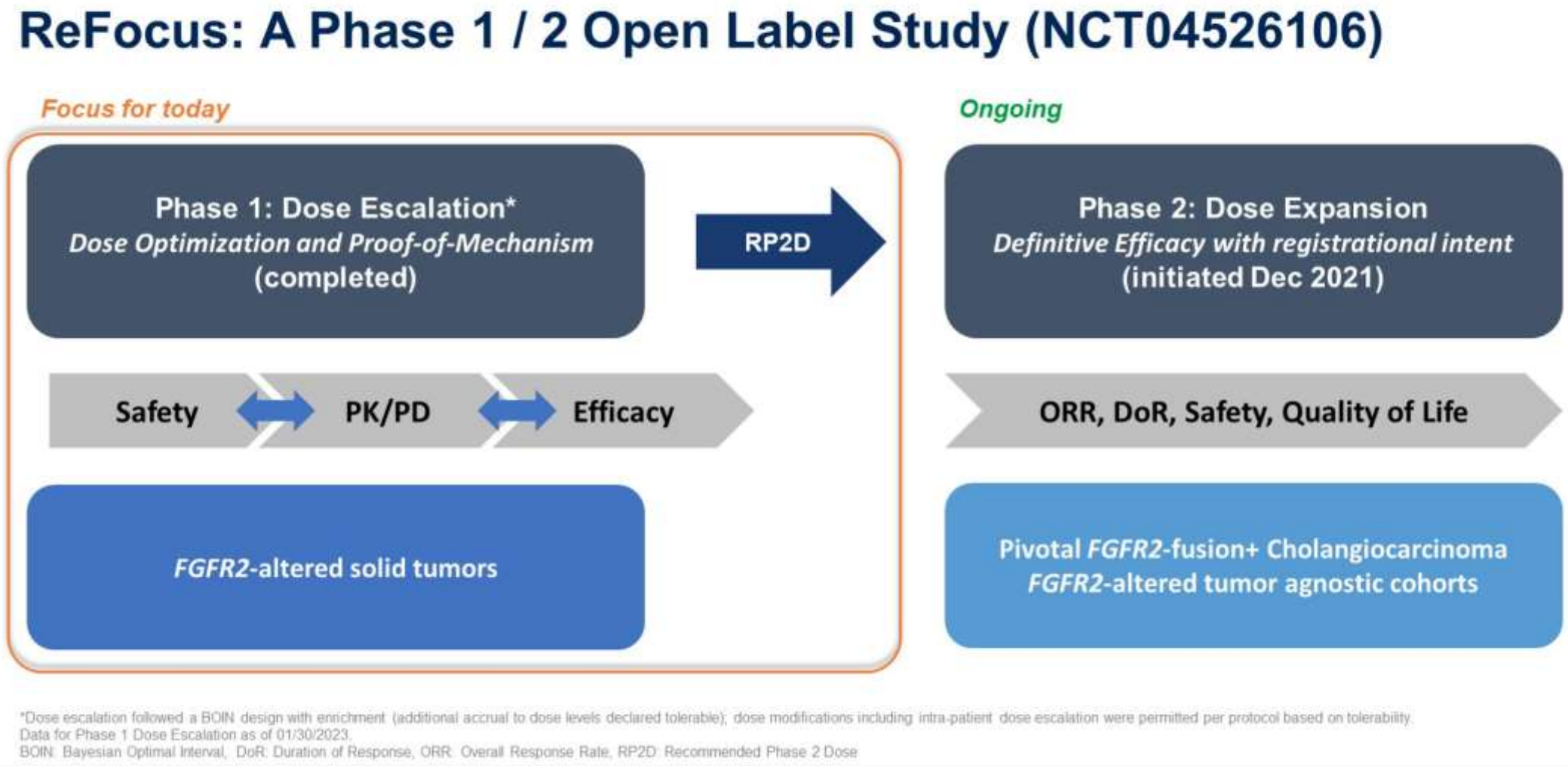
Key Toxicities of FGFR Inhibitors

Hyperphosphatemia, cutaneous toxicity (dry skin, painful/discolored nails, dry eyes [corneal abrasions], dry mouth), retinal toxicity (central serous retinopathy)

AE, %	Pemigatinib (N = 146)[1]		Futibatinib (N = 103)[2]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Hyperphosphatemia	**55**	**0**	**85**	**30**
Alopecia	49	0	34	0
Diarrhea	47	3	39	1
Nail toxicity	43	2	47	2
Fatigue	42	5	37	8
Stomatitis	35	5	30	6
Dry eye	35	1	25	1
Constipation	35	1	39	0

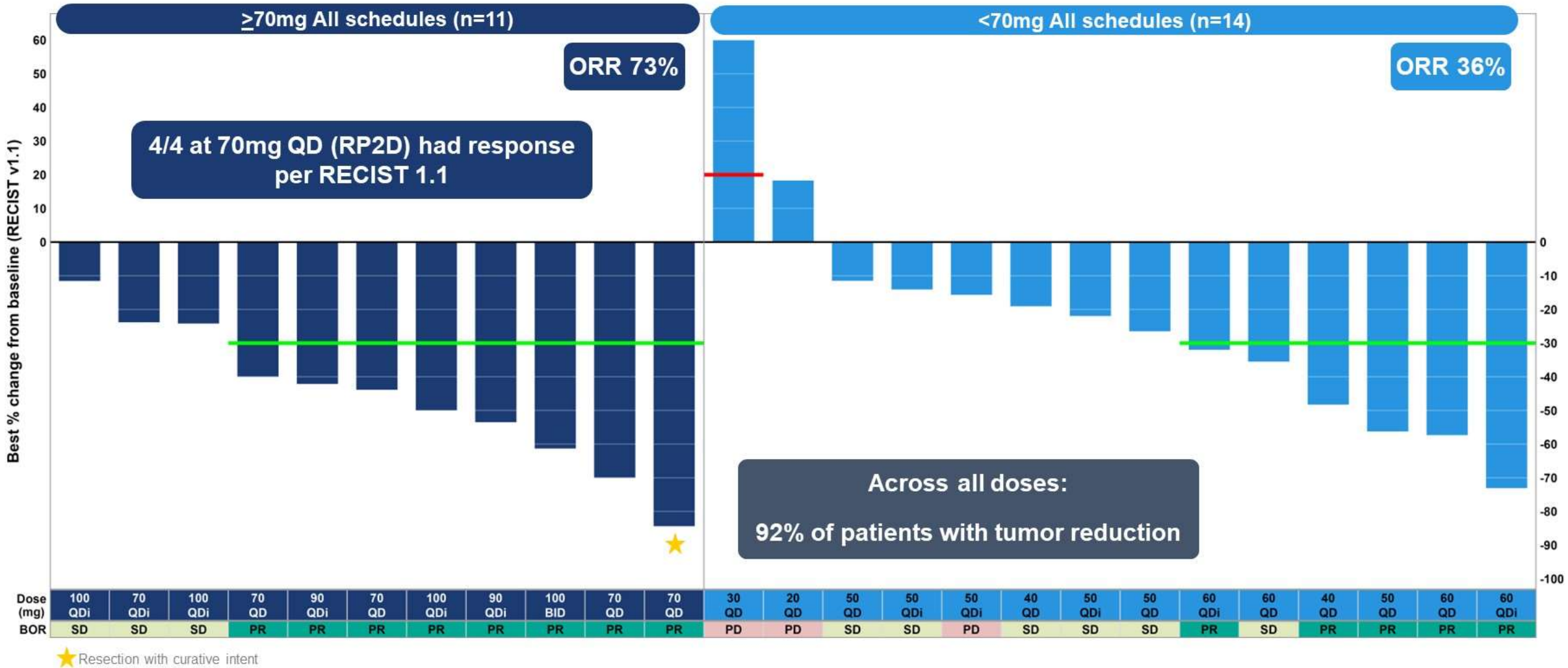
Abou-Alfa. Lancet Oncol. 2020;21:671. Goyal. NEJM. 2023;388:228.
Slide courtesy of Dr. Pishvaian

FGFR2 as a target: lirafugratinib



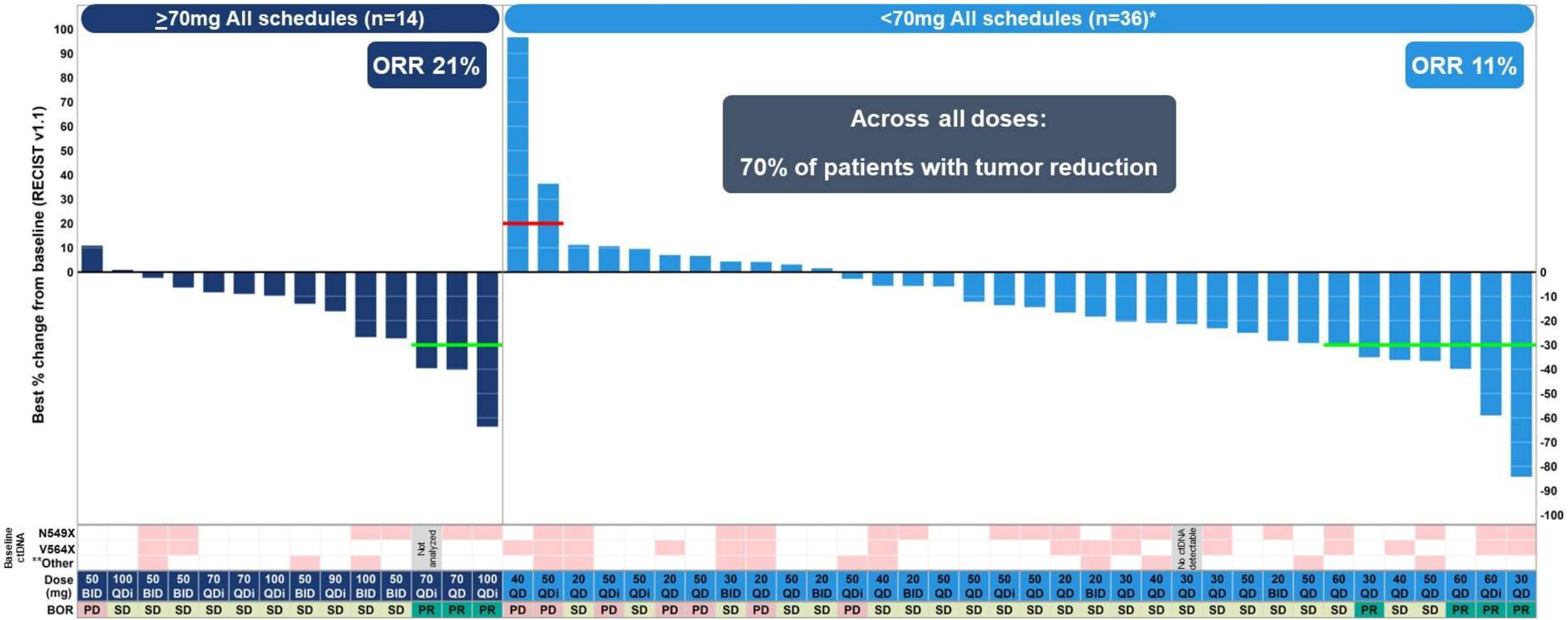
Borad M, et al ASCO 2023

ReFocus Phase 1 Efficacy - FGFRi-Naïve *FGFR2* Fusion+ Cholangiocarcinoma



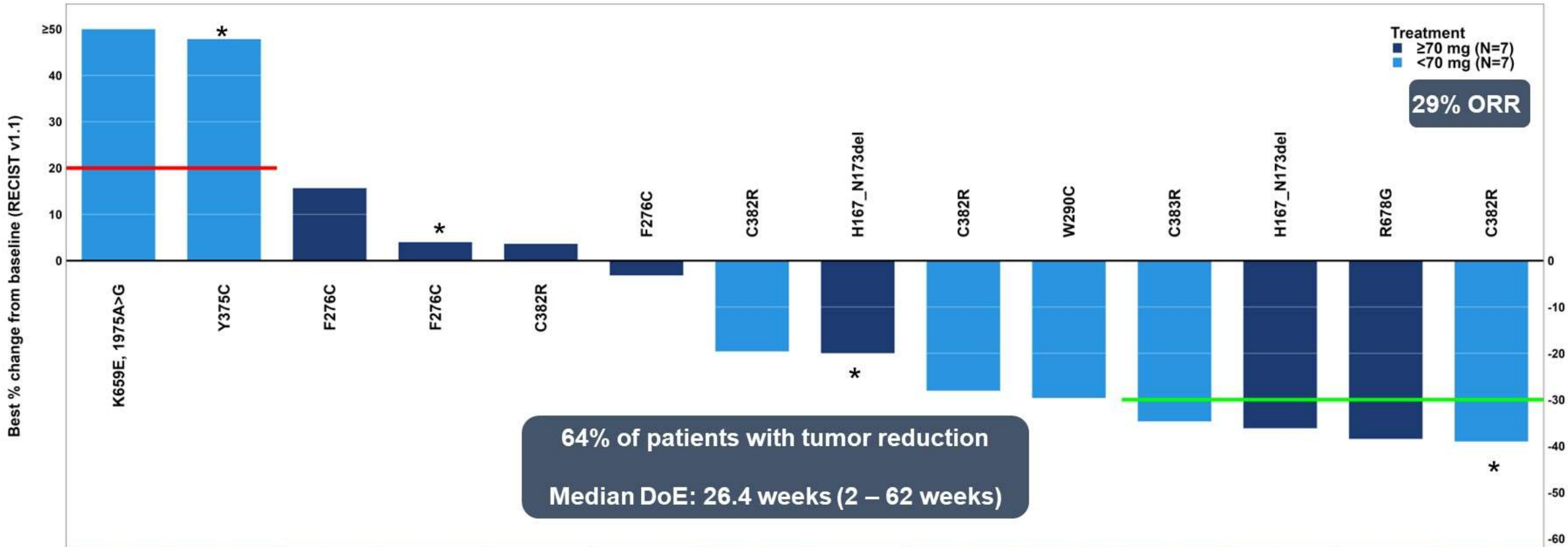
Data for Phase 1 Dose Escalation as of 01/30/2023.
ORR: Overall Response Rate; RP2D: Recommended Phase 2 Dose

ReFocus Phase 1 Efficacy - FGFRi-Refractory, *FGFR2* Fusion+ Cholangiocarcinoma



*Waterfall excludes 2 FGFRi-Refractory patients with clinical progressive disease without post baseline tumor assessment.
N549X and V564X correspond to FGFR2 IIIc isoform; X denotes any amino acid substitution
** Other includes FGFR2 mutations other than N549X and V564X (pink), no detectable FGFR2 mutation (white)
Data for Phase 1 Dose Escalation as of 01/30/2023.

ReFocus Phase 1 Efficacy - *FGFR2*-Mutated Cholangiocarcinoma



Dose (mg)	50 QDi	60 QDi	70 QD	90 QDi	90 QDi	70 QD	20 QD	70 QD	30 QD	40 QD	20 QD	70 QDi	70 QDi	40 QD
BOR	PD	PD	PD	SD	SD	PD	SD	PD	SD	SD	PR	PR	PR	PR
DoE (weeks)	7	16	2	16	24	8	40	16	48	29	38	62	40	54

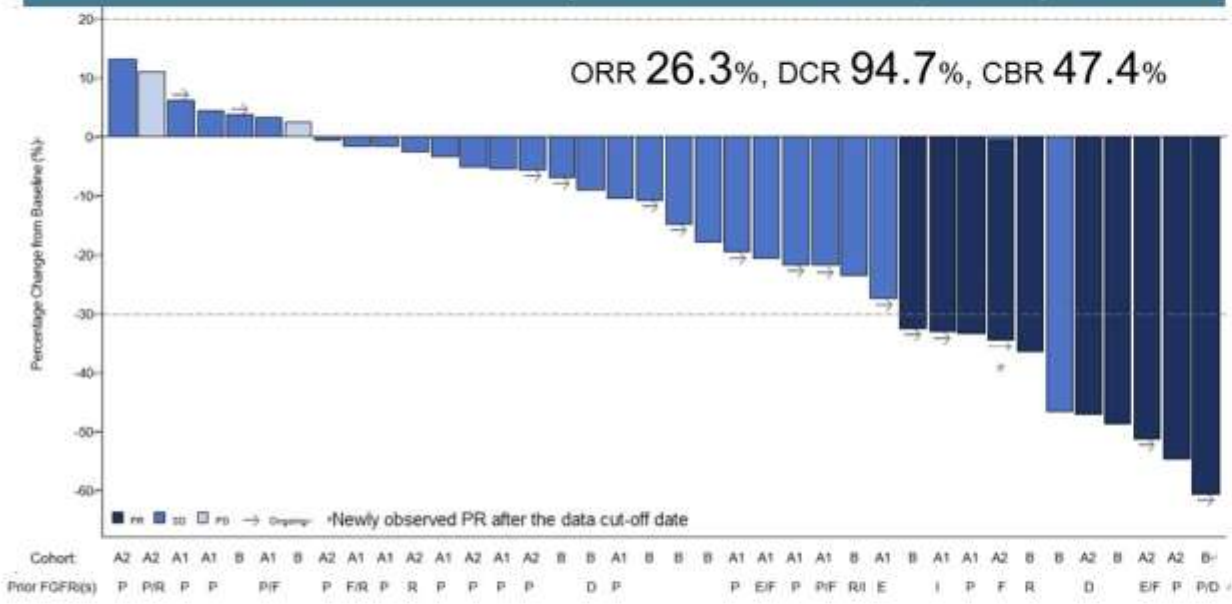
* FGFRi-pretreated patients

Mutation based on local/central assessment; Data for Phase 1 Dose Escalation as of 01/30/2023. DoE: Duration of Exposure, ORR: Overall Response Rate

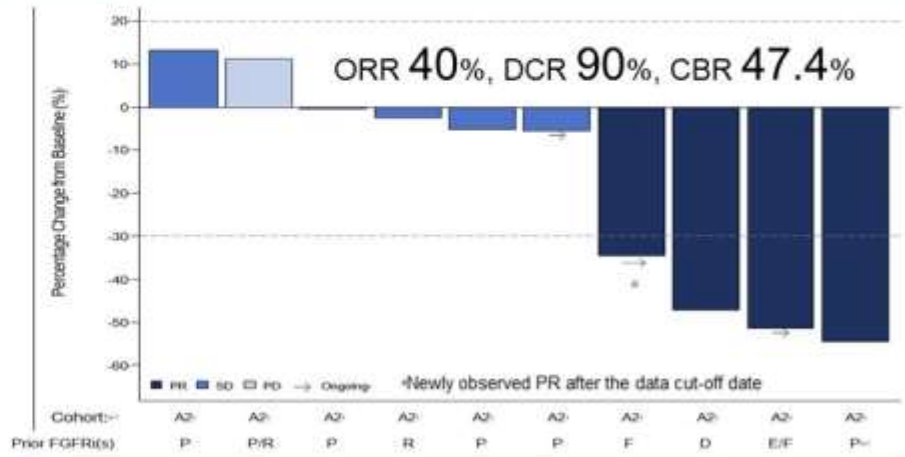
PRESENTED BY: Mitesh J. Borad, M.D.

Tinengotinib- Best Overall Response
(CCA with FGFR alteration)

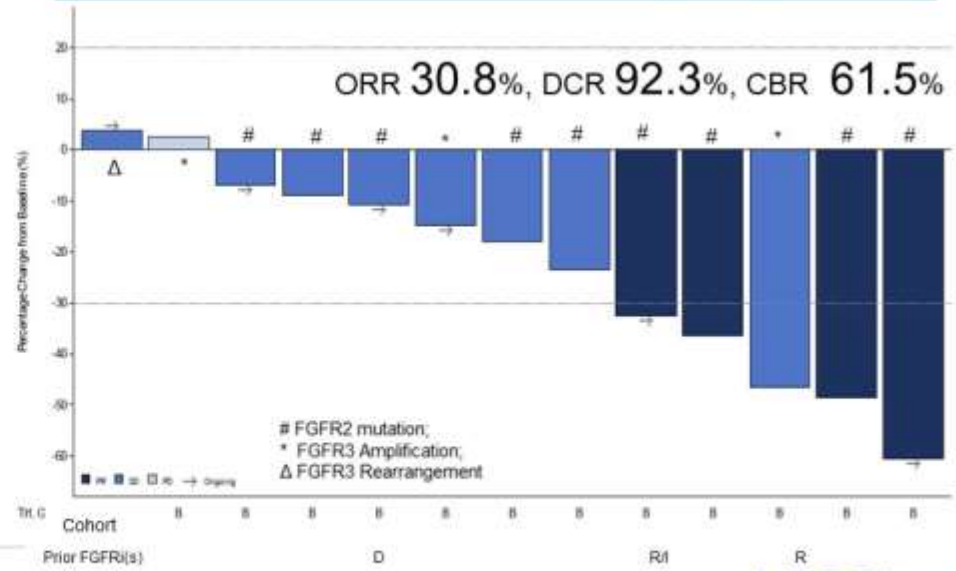
FGFR Altered CCA (Cohorts A1+A2+B, N=38)



Acquired Resistance to Prior-FGFRi in CCA (N=10)



Other FGFR-Altered CCA (N=13)



ORR: overall response rate, DCR: disease control response, CBR: clinical benefit rate, CR + PR + **SD >= 24 weeks**.

P- Pemigatinib; R- RLY-4008; F- Futibatinib; D-Derazantinib; I- Infigratinib; E- Erdafinitib;

Her2 as a target: Zanidatamab

- HERIZON-BTC-01

- Phase 2b study of zanidatamab monotherapy in patients with HER2-amplified BTC

Key Eligibility Criteria

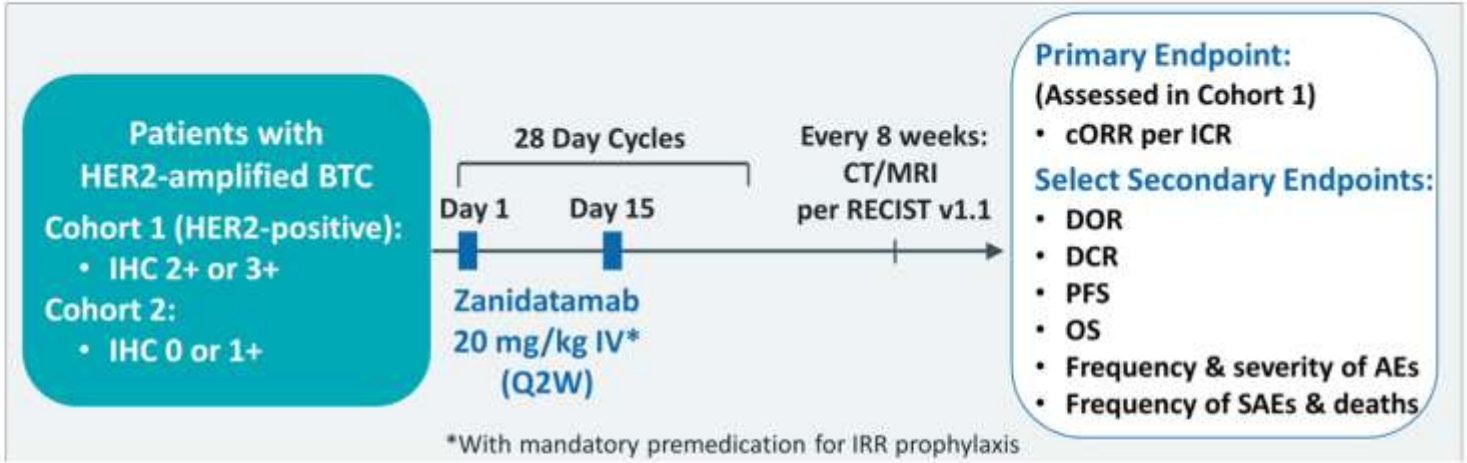
Locally advanced or metastatic BTC[1]

Tissue required to confirm HER2 status by central lab

Progressed after treatment with a gemcitabine-containing regimen

No prior HER2-targeted therapies

ECOG PS of 0 or 1



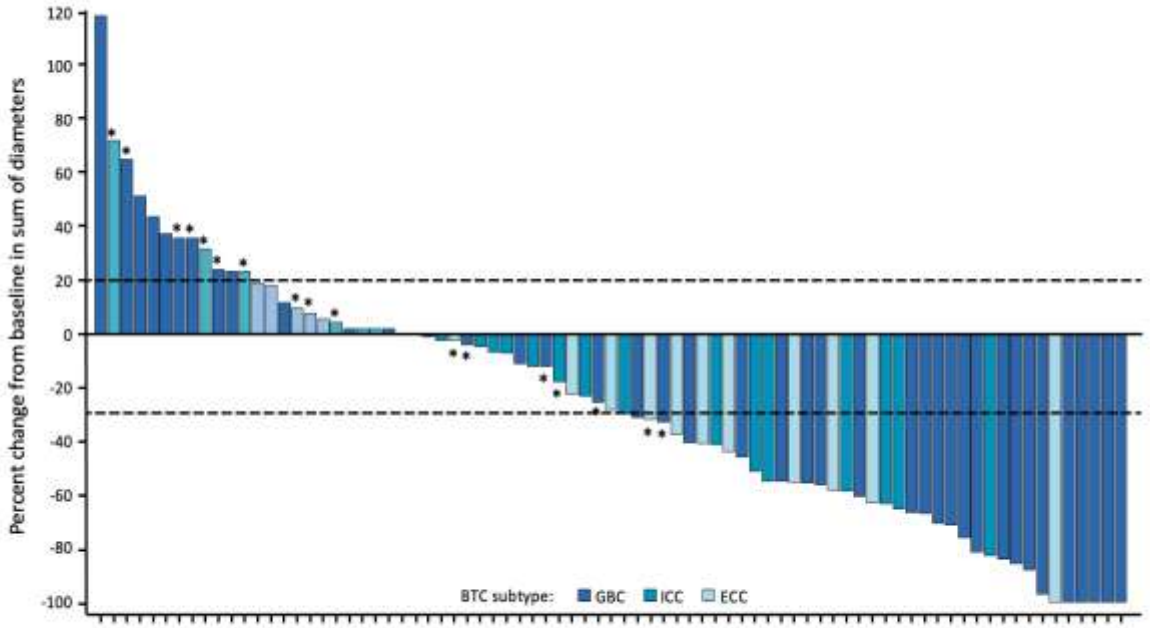
[1] Excludes ampullary

AE = adverse event; cORR = confirmed objective response rate; CT = computed tomography scan; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ICR = independent central review; IHC = immunohistochemistry; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; OS = overall survival; Q2W = every two weeks; RECIST= Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Pant S, et al ASCO 2024

Her2 as a target: Zanidatamab

- Data from HERIZON-BTC-01



*Indicates patients with IHC 2+ status; all other patients had IHC status of 3+.
Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors.

- 80 patients with HER2 amplified BTC, median f/u 21.9 mths
- ORR of 41.3% by IRC, median DOR was 14.9 months
- Median OS was 15.5 months
- FDA approval in November 2024

Pant S, et al ASCO 2024

Study Design

- SGNTUC-019 (NCT04579380) is an open-label phase 2 basket study evaluating antitumor activity and safety of tucatinib and trastuzumab[a] in patients with HER2-altered solid tumors

Key eligibility criteria

- HER2 overexpression, amplification, or mutation per IHC/ISH or NGS testing determined locally
- Unresectable locally advanced or metastatic cancer
- Baseline measurable disease
- Previously treated with ≥1 prior systemic treatment for locally advanced or metastatic disease
- No prior HER2-directed therapy[b]

→

- Cohort 1: Cervical (overexpression or amplification)
- Cohort 2: Uterine (overexpression or amplification)
- **Cohort 3: Biliary Tract (overexpression or amplification)[c]**
- Cohort 4: Urothelial (overexpression or amplification)
- Cohort 5: Nonsquamous NSCLC (overexpression or amplification)
- Cohort 6: Other solid tumors (overexpression or amplification)
- Cohort 7: Nonsquamous NSCLC (mutation)
- Cohort 8: Breast (mutation)
- Cohort 9: Other solid tumors (mutation)

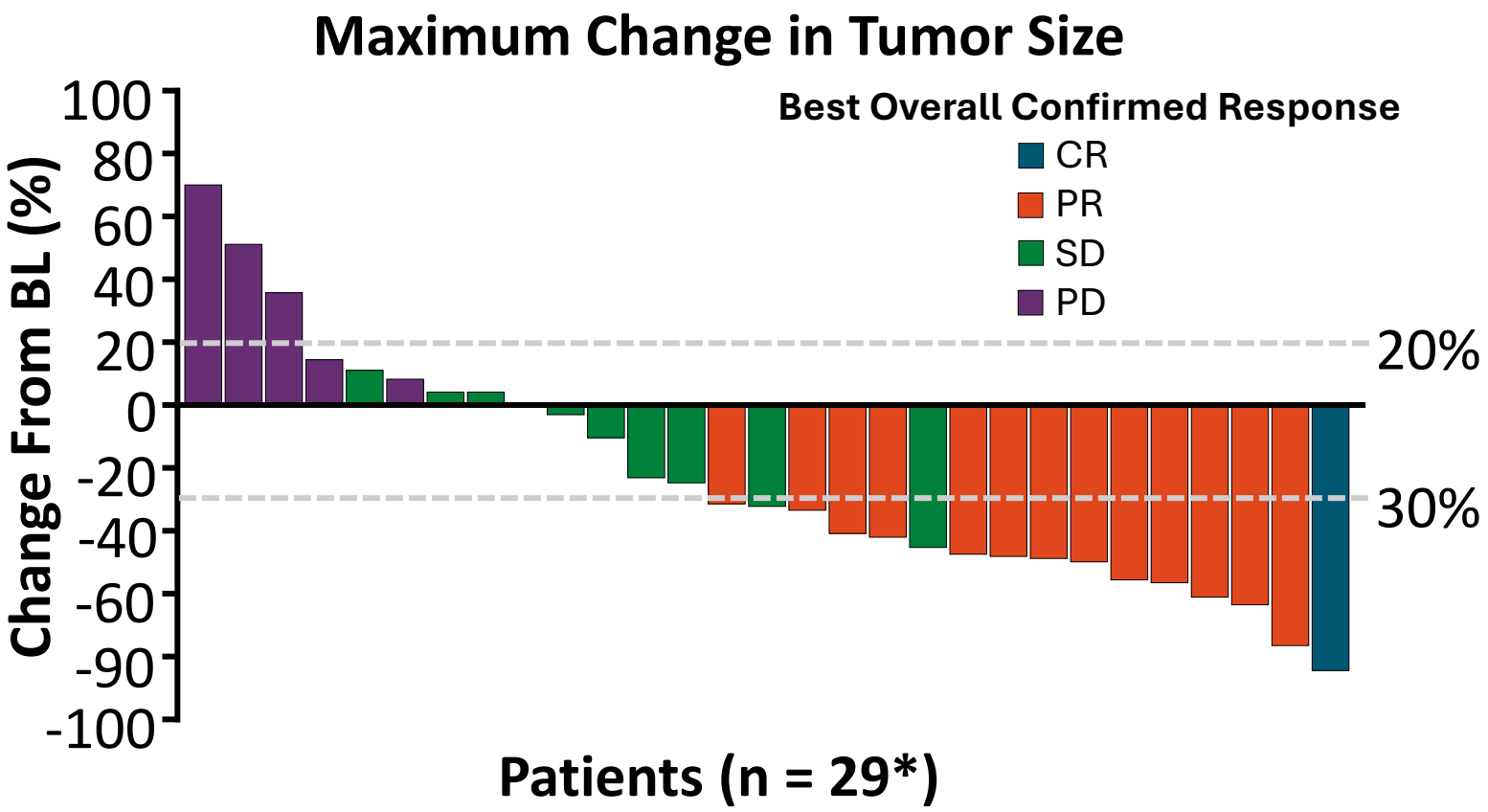
Outcomes

Primary endpoint:
Confirmed ORR per RECIST 1.1 by investigator

Secondary endpoints:
Safety, DCR, DOR, PFS, and OS

a Tucatinib dose: 300 mg PO BID; trastuzumab dose: 6 mg/kg IV Q3W (loading dose of 8 mg/kg C1D1); each treatment cycle is 21 days. b Except for patients with uterine serous carcinoma or HER2-mutated gastroesophageal cancer without HER2-overexpression or amplification. c The cohort aimed to enroll up to 30 patients, a number calculated per the 90% exact CI given a range of expected confirmed ORR of 10% to 30%.
BID, twice daily; C1D1, Day 1 of Cycle 1; DCR, disease control rate; DOR, duration of response; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Tucatinib + Trastuzumab for HER2 Amplified CCA



- Reduction in tumor size observed in 70.0% of patients

*Excludes n = 1 lacking postbaseline response assessment.

Outcome	Patients (N = 30)
Best overall response, n (%)	
▪ CR	1 (3.3)
▪ PR	13 (43.3)
▪ SD	9 (30.0)
▪ PD	6 (20.0)
▪ Not available	1 (3.3)*
Confirmed ORR, % (90% CI) (primary endpoint)	**46.7 (30.8-63.0)**
Median DoR, mo (90% CI)	6.0 (5.5-6.9)
DCR, n (%)	23 (76.7)
Median time to first response, mo (range)	2.1 (1.2-4.3)

Nakamura, et al, ASCO 2023

Study Design[1,2,3]

Recruiting (Part 2)

A Phase 2, multicenter, non-randomized, open-label study to evaluate the efficacy and safety of T-DXd for the treatment of selected HER2–expressing solid tumors (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population[a]
- HER2 expression (by ASCO/CAP gastric cancer guidelines)
  - Part 1: IHC 3+ or IHC 2+ Local test or central test[4,b]
  - Part 2: IHC and ISH (cohort B only) results by central assessment as pre-defined for each cohort
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

HER2-expressing solid tumors[c]

T-DXd 5.4 mg/kg Q3w

(N ≈ 468)

n≈40 per cohort planned[d]

Part 1[1]

- **Cohort 1** Biliary tract cancer
- **Cohort 2** Bladder cancer
- **Cohort 3** Cervical cancer[e]
- **Cohort 4** Endometrial cancer
- **Cohort 5** Ovarian cancer
- **Cohort 6** Pancreatic cancer
- **Cohort 7** Other tumors[f]

Part 2[3,g]

- **Cohort A** HER2 IHC 3+ Metastatic Solid Tumors[h]
- **Cohort B** HER2 IHC 2+/ISH+ Metastatic Solid Tumors[h]
- **Cohort C** HER2 IHC 2+ or 1+ Endometrial cancer
- **Cohort D** HER2 IHC 2+ or 1+ Ovarian cancer
- **Cohort E** HER2 IHC 2+ or 1+ Cervical cancer

Primary endpoint

- Confirmed ORR (investigator)[i]

Secondary endpoints

- DoR[2,i]
- DCR[2,i]
- PFS[2,i]
- OS
- Safety

Exploratory endpoint

- Subgroup analyses by HER2 status[5,j]
- Subgroup analyses by biomarkers[5,j]

[a]Patients with no satisfactory treatment options were also included; [b]Patients were eligible for either test. All patients were centrally confirmed; [c]Excluding breast, gastric, colorectal cancer; [d]Cohorts with no objective responses in the first 15 patients were to be closed; [e]Cervical cohort was expanded to include five IHC1+ patients; [f]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer; [g]Enrollment started in 2024; [h]Excluding breast, gastric cancer, and colorectal cancer. Patients with non-small cell lung cancer can be included; [i]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1; [j]Subgroup analyses were based on central HER2 testing

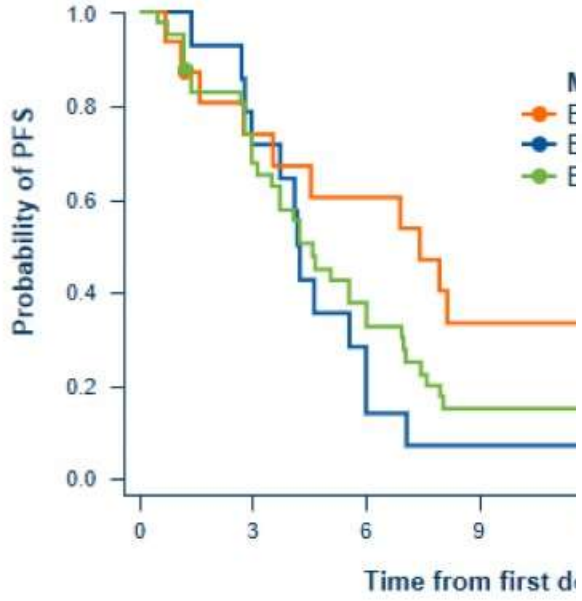
1. Meric-Bernstam F et al. Presented at: ESMO Congress; October 20-24, 2023; Madrid, Spain. LBA34. 2. Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47–58. 3. Study NCT04482309. ClinicalTrials.gov website. 4. Hofmann M et al. *Histopathology 2008*;52(7):797–805. 5. Makker V, et al. Presented at: SGO 2024 Annual Meeting; March 16-18, 2024; San Diego, California.

Biliary Tract Cancer Cohort: Secondary Efficacy Endpoints (Central Testing)

Characteristic	All patients (n=41)	All patients (ICR) (n=41)	HER2 IHC 3+ (n=16)	HER IHC 2+ (n=14)	HER2 IHC 1+[a] (n=3)	HER2 IHC 0[a] (n=7)
Median DoR, months (95% CI)	8.6 (2.1–NE)	10.9 (5.5–NE)	8.6 (2.1–NE)	–	–	–
Median PFS, months (95% CI)	4.6 (3.1–6.0)	4.1 (2.8–5.3)	7.4 (2.8–12.5)	4.2 (2.8–6.0)	5.1 (1.2–NE)	3.1 (1.2–5.6)
Median OS, months (95% CI)	7.0 (4.6–10.2)	7.0 (4.6–10.2)	12.4 (2.8–NE)	6.0 (3.7–11.7)	5.1 (1.6–NE)	7.6 (3.0–10.2)
DCR at 12 weeks, % (95% CI)	65.9 (49.4–79.9)	51.2 (35.1–67.1)	68.8 (41.3–89.0)	71.4 (41.9–91.6)	66.7 (9.4–99.2)	57.1 (18.4–90.1)

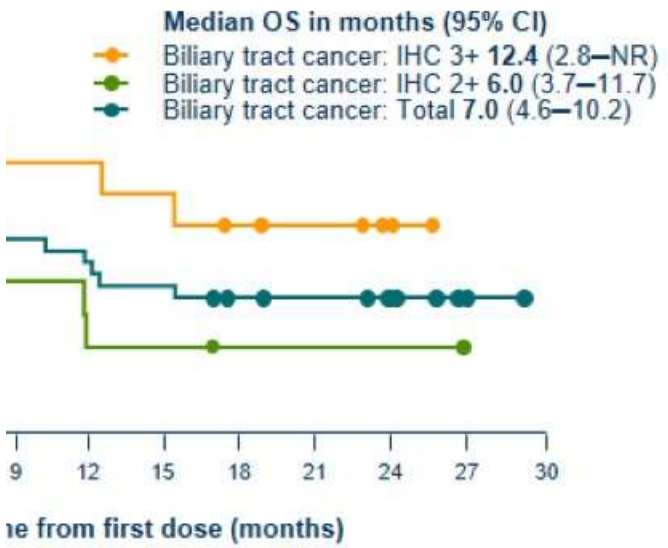
CIs omitted where 0%.
[a]Patients with a central HER IHC status of 1+/0/unknown were enrolled as HER2 IHC 3+/2+ by local testing.
Oh DY, et al. Poster presented at: ASCO 2024 Annual Meeting; May 31- June 4, 2024; Chicago, IL. Poster #4090.

Biliary Tract Cancer Cohort: Kaplan-Meier Estimates of PFS and OS by HER2 Status (Central Testing)



The most common (>5%) Grade ≥3 drug-related TEAEs in the biliary tract cohort:

- **Neutropenia (9.8%)[a]**
- **Neutrophil count decrease (9.8%)[a]**
- **Nausea (7.3%)**
- **Fatigue (7.3%)**



Number of patients at risk, month

Biliary tract cancer: IHC 3+	16	11	9	5					
Biliary tract cancer: IHC 2+	14	10	3	1	1	1	1	1	0
Biliary tract cancer: Total	41	27	14	6	6	4	3	3	0

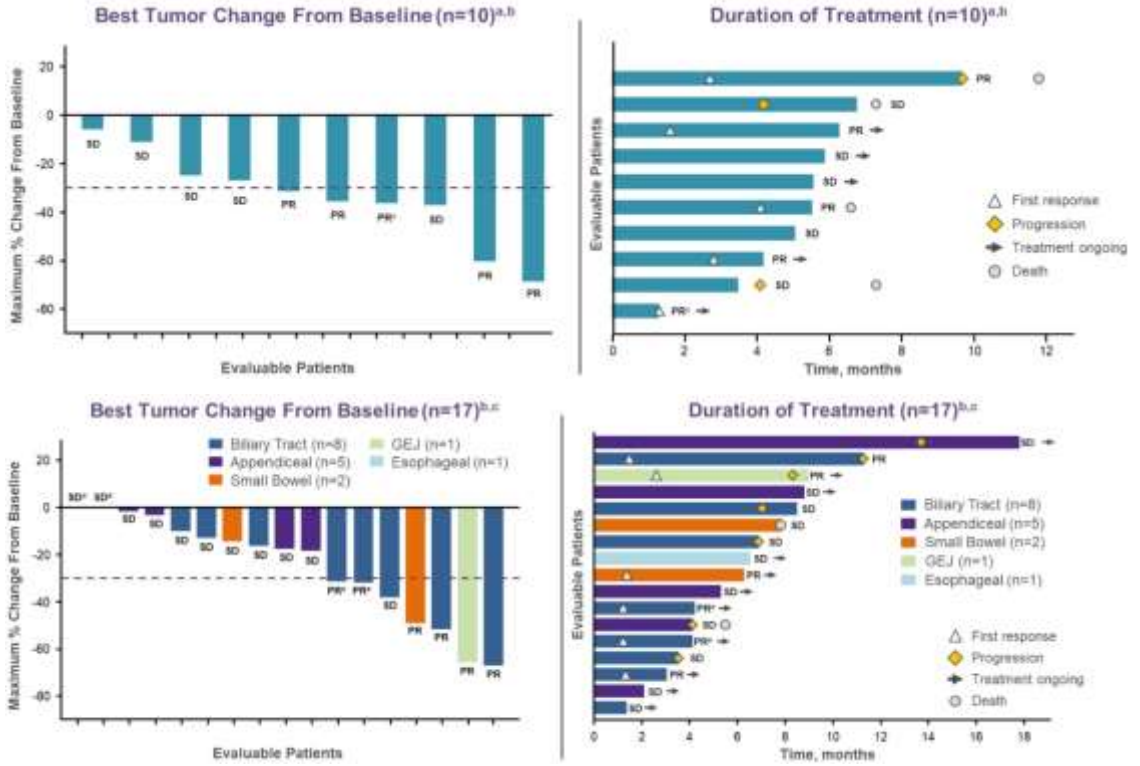
	8	8	7	5	4	1	0				
IHC 2+	14	12	7	4	2	2	1	1	1	0	0
Biliary tract cancer: Total	41	32	21	15	12	11	8	7	4	1	0

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47–58.

KRYSTAL-1: Adagrasib in KRAS^{G12C} Mutated GI Cancers

- Adagrasib demonstrated efficacy
  - ORR was 41% overall
  - 50% in biliary cancers
  - 50% in pancreatic cancer
  - Disease control rate (including SD through at least 1st scan) = 100%
- All GI cancers
  - mDOR = 8 months
  - mPFS = 8 months

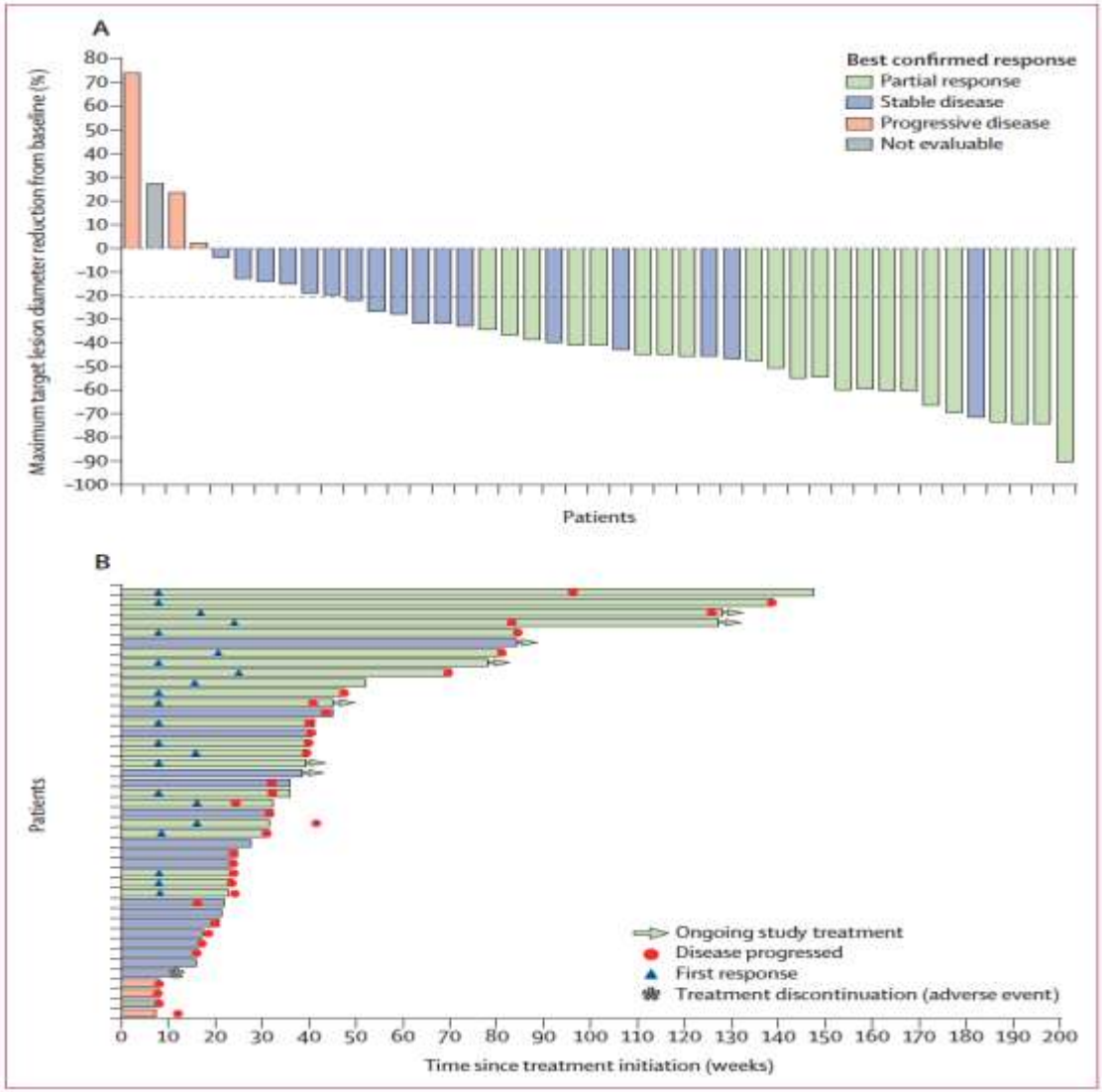
Efficacy outcome[b], n (%)	PDAC (n=10)[c]	Other GI cancers (n=17)[d]	Overall GI cancers[a] (n=27)[c,d]
Objective response rate	5 (50)[e]	6 (35)[f]	11 (41)[g]
Best overall response			
Complete response (CR)	0 (0)	0 (0)	0 (0)
Partial response (PR)	5 (50)[e]	6 (35)[f]	11 (41)[g]
Stable disease (SD)	5 (50)	11 (65)	16 (59)
Disease control rate	10 (100)	17 (100)	27 (100)

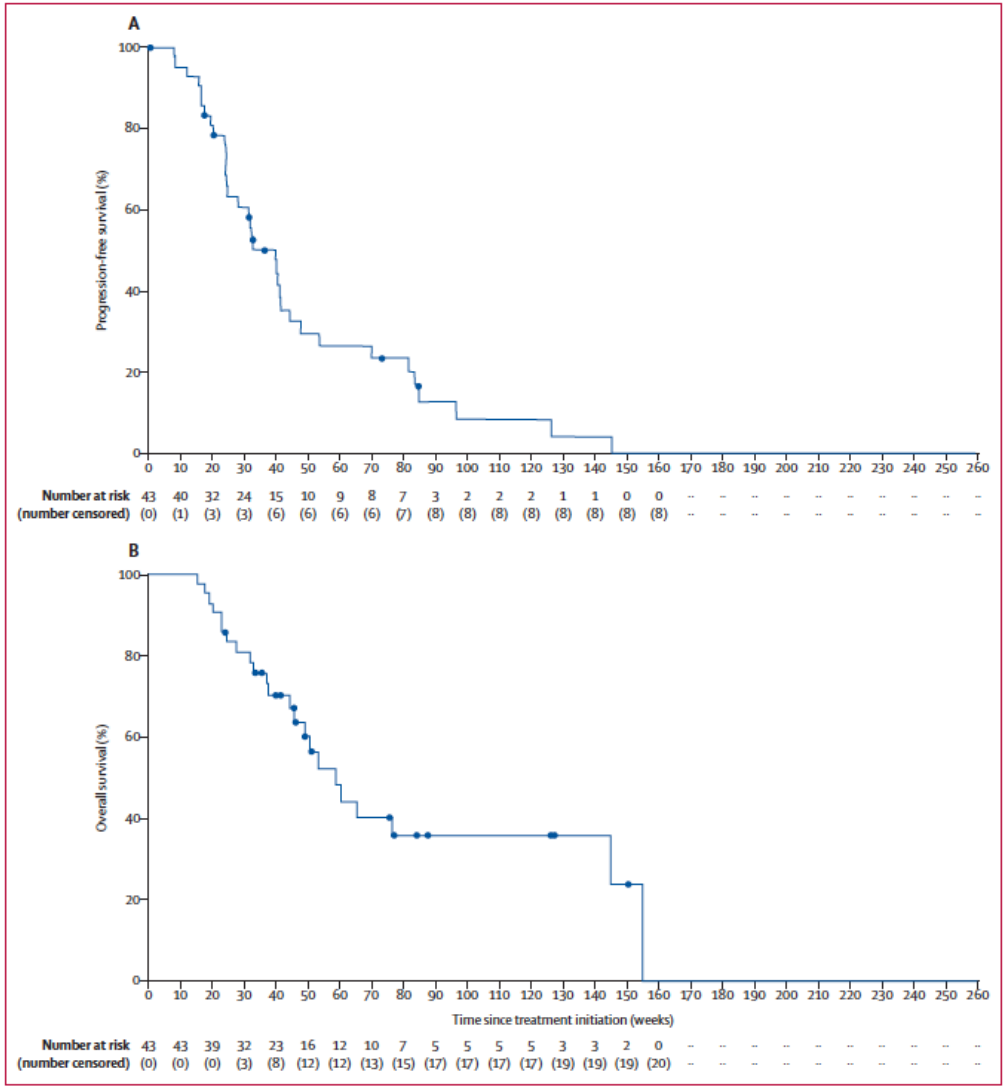


Saab T, et al, GI ASCO 2022

BRAF V600E: ROAR trial

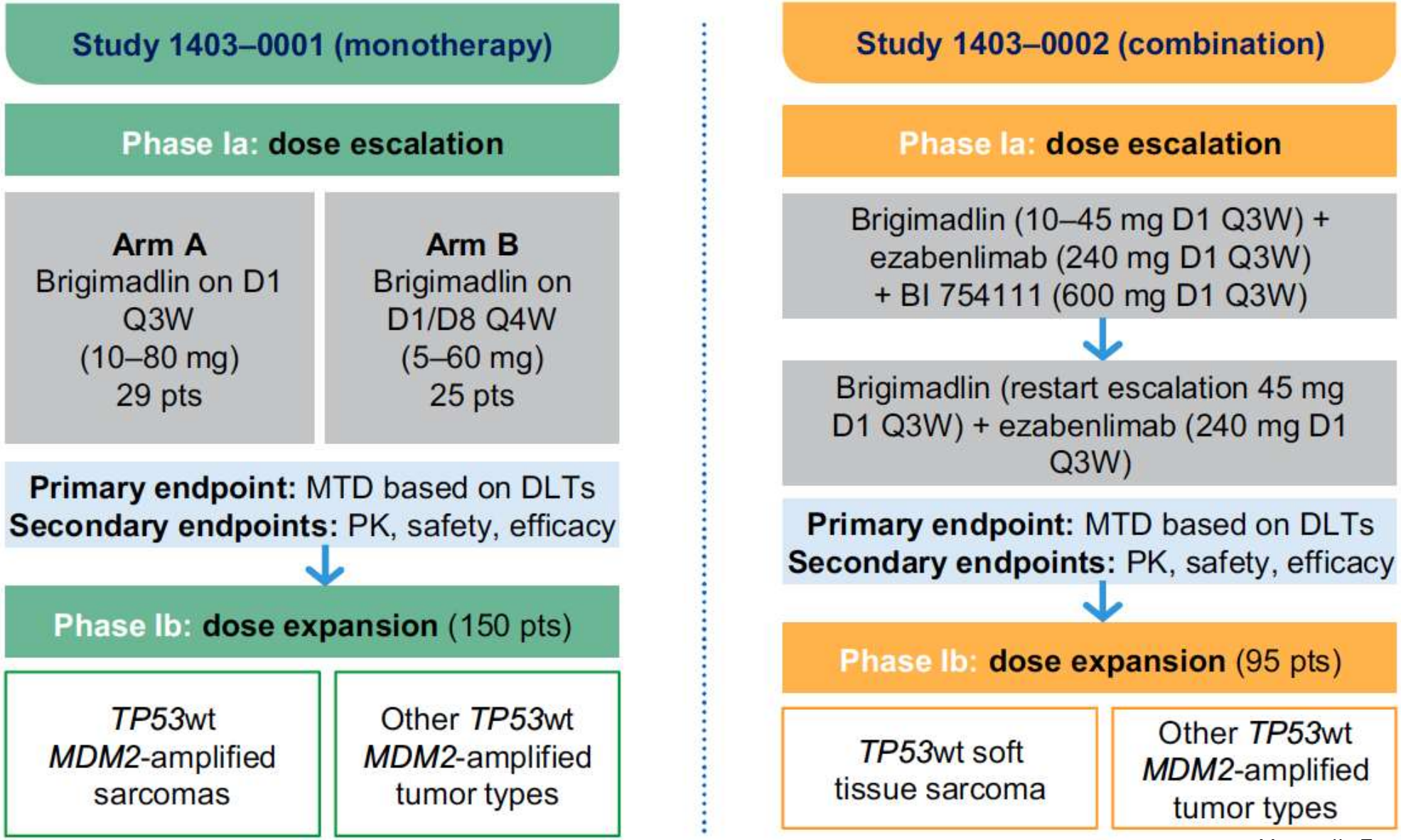
ORR (per IRC): 47%





Subbiah V, et al Lancet Oncol 2020

MDM2 as a target: Brigmadlin

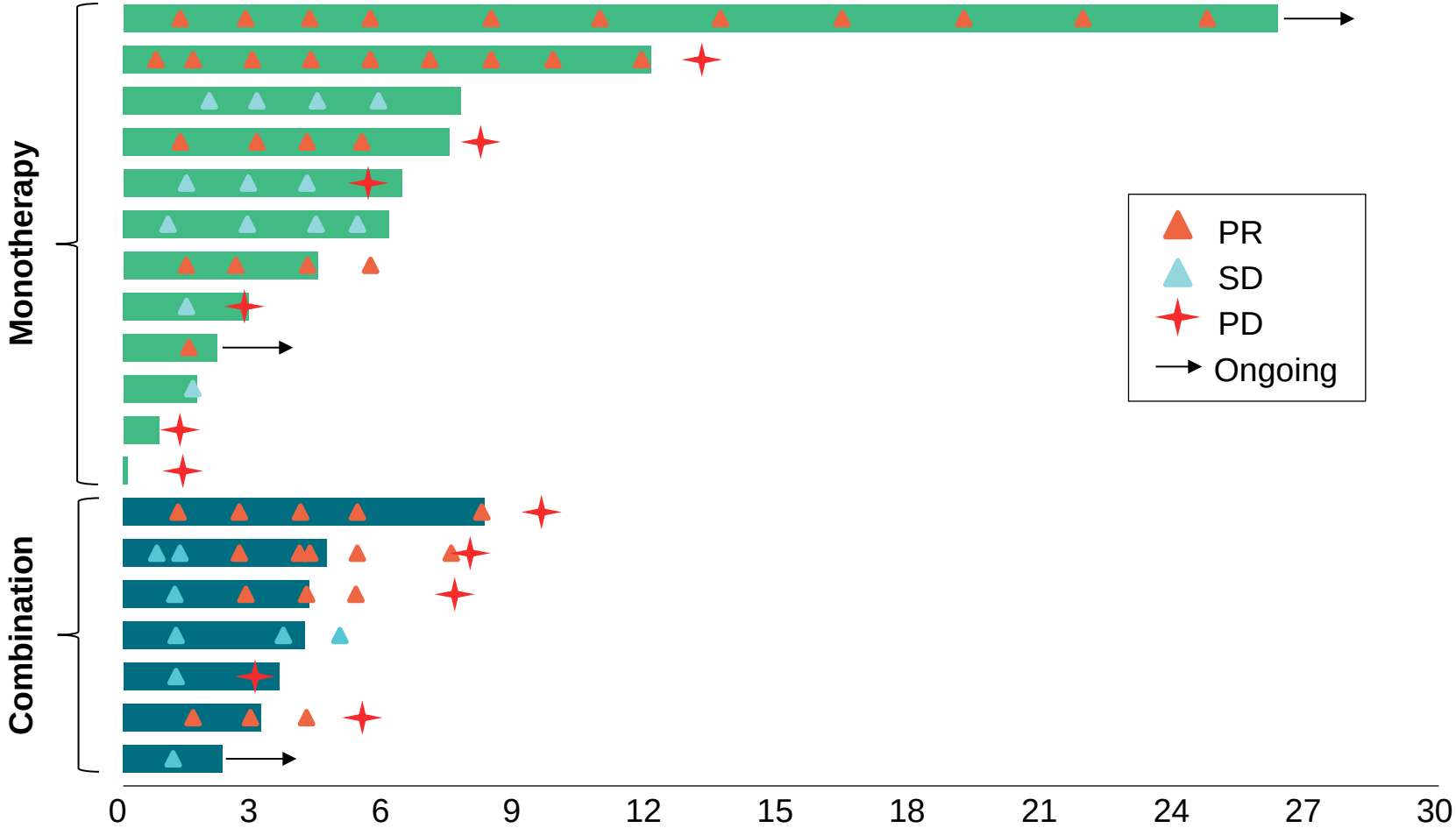


Macarulla T, et al GI ASCO 2024

MDM2 AS A TARGET: BRIGMADLIN

- As of October 2023, 23 patients with BTC have been enrolled across both trials,16 in the monotherapy trial and 7 in the combination trial
- 12 of 16 patients with BTC in the monotherapy trial were response-evaluable:
  - 4 patients have achieved confirmed PR and 6 have achieved SD
- All 7 patients with BTC in the combination trial were response-evaluable:
  - 4 patients have achieved confirmed PR and 3 have achieved SD

Time on treatment in patients with BTC treated with brigimadlin monotherapy and in combination with ezabenlimab (n=19)



BTC, biliary tract cancer; PD, progressive disease; PR, partial response; SD, stable disease; ToT, time on treatment

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Summary

- The standard of care is rapidly changing in cholangiocarcinoma

  - Immunotherapy and targeted therapy are at the forefront of managing CCA
  - Multiple drugs are approved in the refractory setting, but it remains Gem/Cis + Immunotherapy for all in the frontline setting
  - IDH and FGFR2 alterations are established targets with drugs available to patients NOW
  - Newer generation FGFR inhibitors show promise, even in the acquired resistance population
  - HER2 is a target with multiple drugs with varying mechanisms of action → Abs, TKIs, ADCs
  - KRAS inhibitors are here → G12C has shown proof of principle
  - Tumor agnostic approvals/basket trials have given biliary cancer patients with “rarer” targets access to important therapies → BRAF, HER2, NTRK, etc
  - Other targets are emerging, which opens doors to novel drugs → MDM2
  - This disease remains the model for precision medicine
    - **It is a testament to the investigators that so many drugs have moved forward so quickly!**

Thank you!