Upper GI/Hepatobiliary Cancers

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Disclosure of Conflicts of Interest

Chandrikha Chandrasekharan, MD has the following financial relationship to disclose:

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ASCO 2022 updates in GEJ/Gastric cancers and Hepatobiliary cancers

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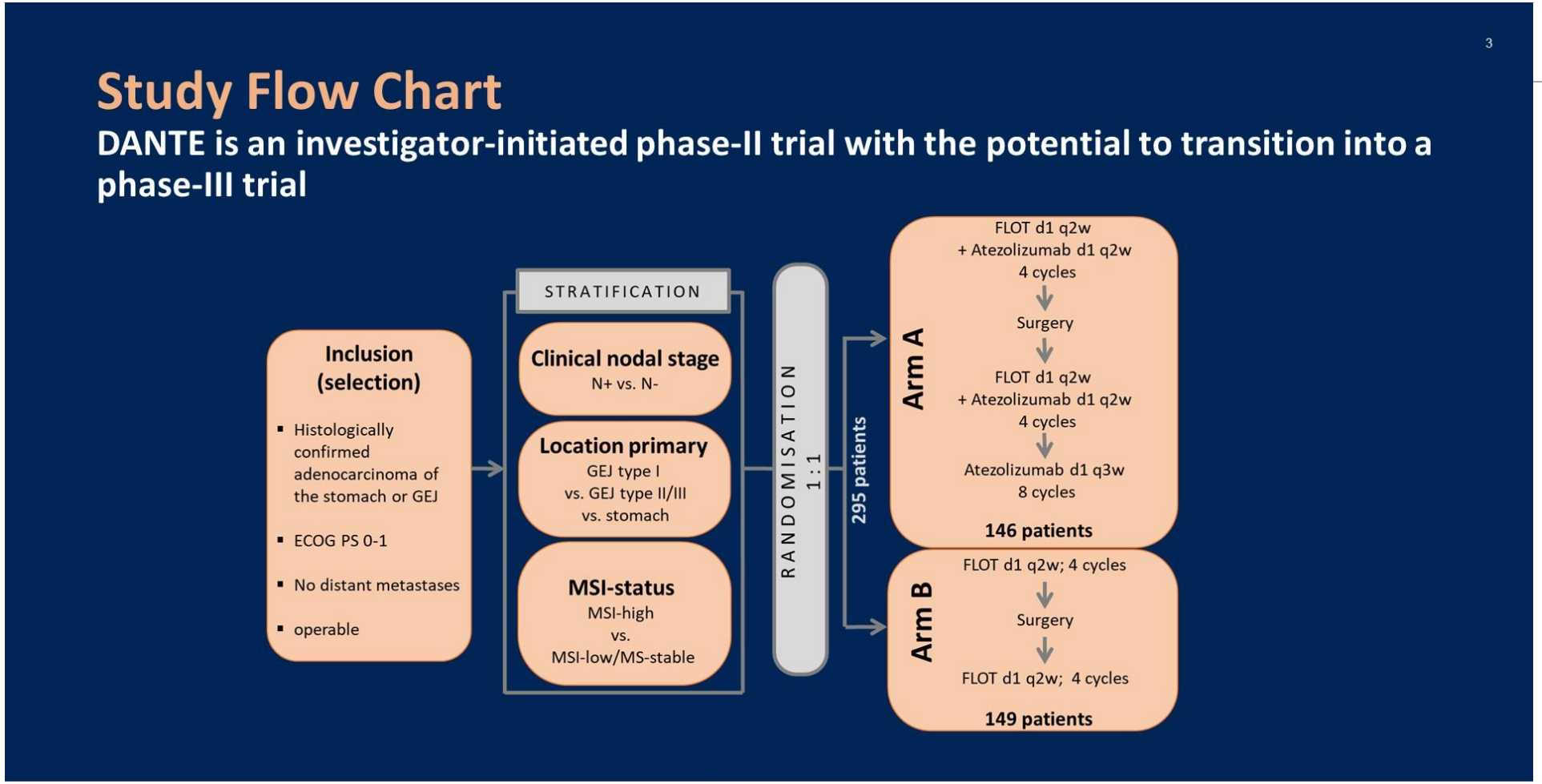
DANTE trial- Al-Batran et al



Primary endpoint
- PFS/DFS

Secondary endpoints
- Path CR
- R0 resection rates, pTNM
- Overall survival

Safety endpoints-
- chemo/IO side effects
- Surgical mortality

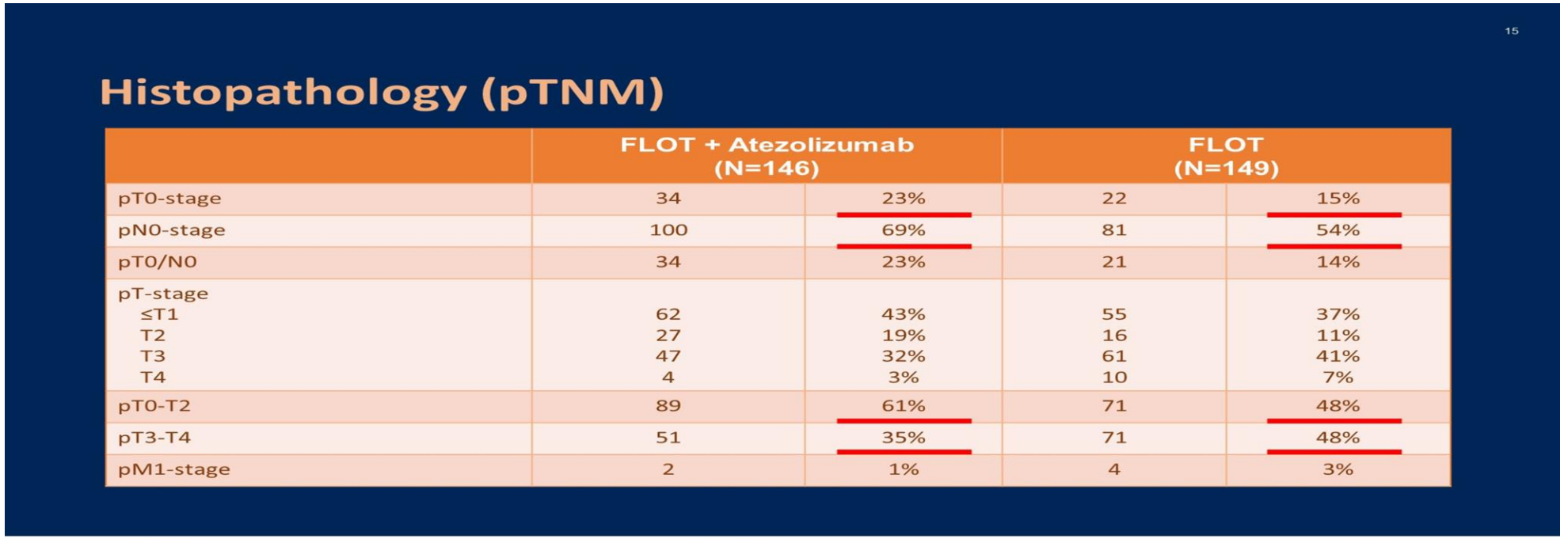
295 patients randomized between Sept 2018- Oct 2020

Medial follow up 24 months Arm A and 22 months Arm B

Approx imately 30% each GEJ Siewert type 1 and 2 and 3. Rest stomach

93% completed allocated pre op chemo(or chemo /IO)

While 68% started post op therapy, 43% completed all post op therapy



Pathological regression (local assessment)

Pathological Regression **FLOT + Atezolizumab (arm A) vs. FLOT (arm B)**	**Becker Classification**			
	TRG1a[1]		**TRG1a/b[2]**	
	A	**B**	**A**	**B**
All patients (N= 295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	22 (55%)	18 (44%)
PD-L1 CPS ≥10 (N=53; 27|26)	9 (33%)	3 (12%)	18 (67%)	10 (39%)
MSI high (N=23; 8|15)	5 (63%)	4 (27%)	6 (75%)	7 (47%)

[1]pathological complete regression acc. to Becker
[2]pathological subtotal regression acc. to Becker

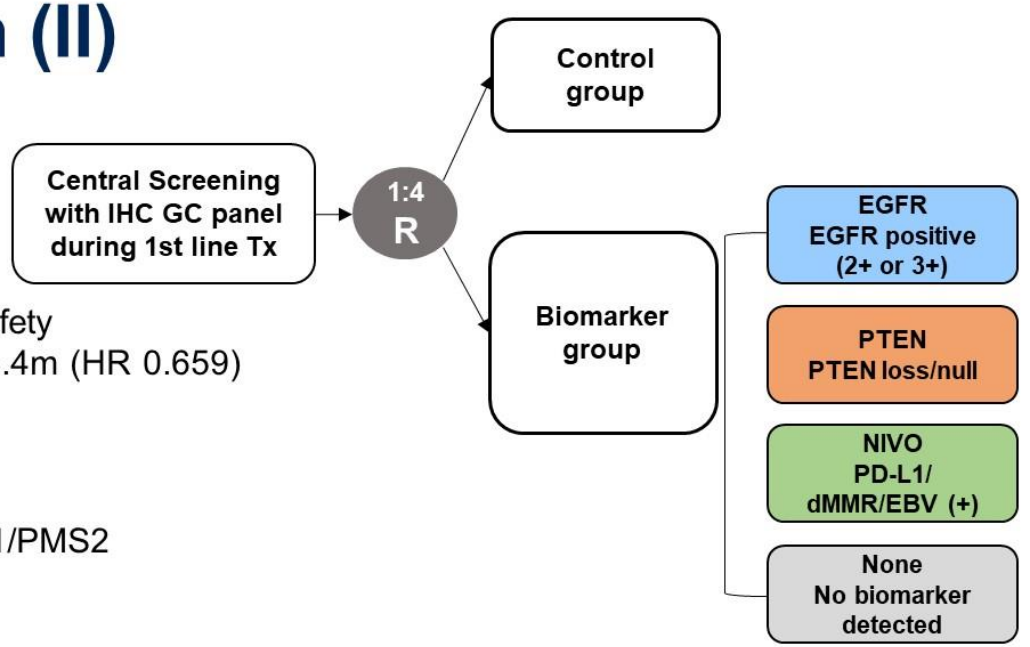
Key conclusions

- Perioperative FLOT+ Atezolizumab is feasible and safe
- Did not increase AE rates significantly (66% vs 69%)
- Surgical complications/ mortality not different between arms
- Combination may improve down staging and increased pathological regression(however limited more to MSI high and higher PDL1 expression)
- PFS/DFS data is awaited
- Will be proceeding to phase 3 clinical trial

K-Umbrella Gastric Cancer study

- Focus on biomarker driven second line therapy
- Current SOC is ramucirumab or Ramucirumab + TaXol
- Multiple second line therapies targeting Her2neu protein expression. However only benefits 15% at best
- Prior non biomarker driven studies not successful(anti EGF therapies e.g.,)
- Novel design- standard of care is same control group. Biomarker driven investigational grouwp.
- 1:4 randomization.

K-Umbrella GC: Study Design (II)

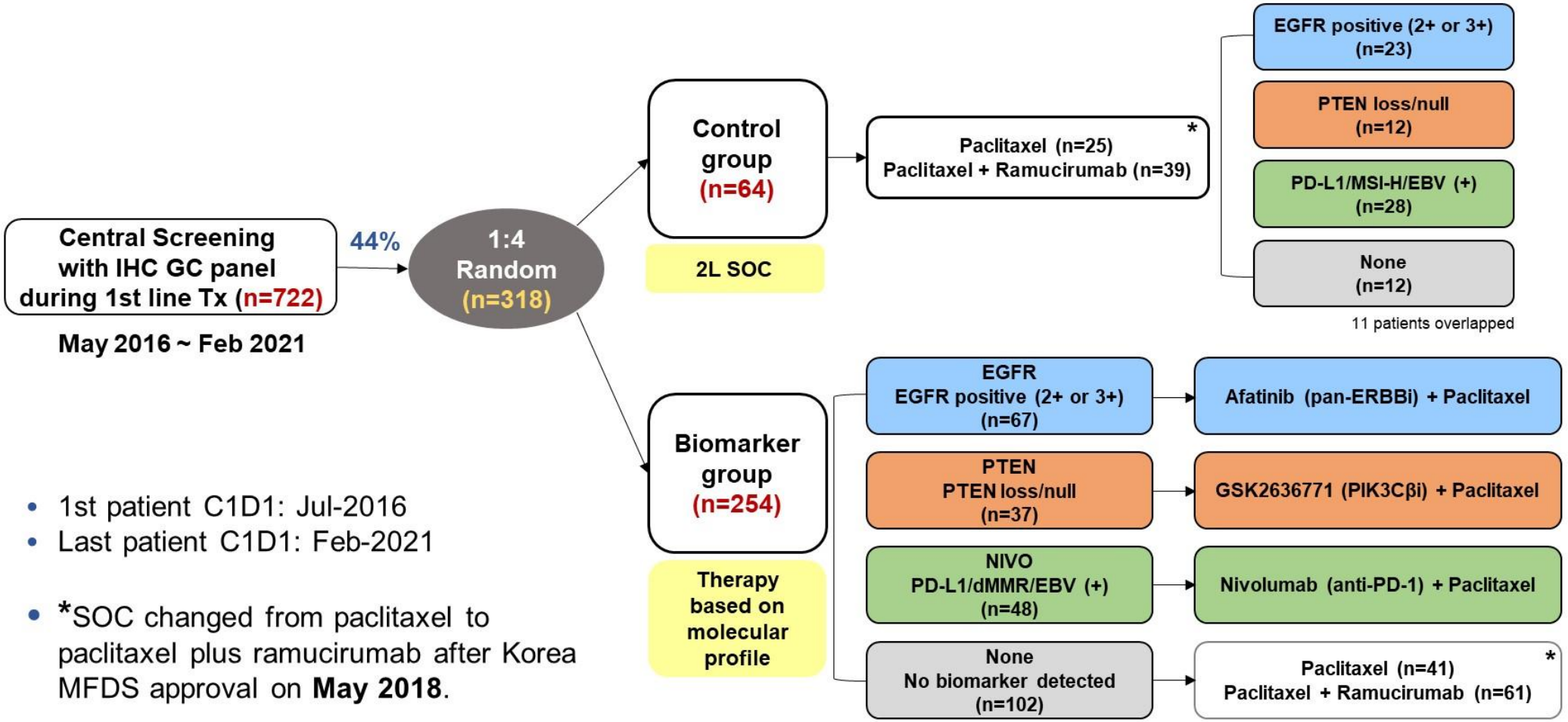


- ◆ Endpoints and statistical consideration
  - ✓ Primary end point: PFS between biomarker *vs* control group
  - ✓ Secondary end points: OS, ORR, DCR, PFS of each arm and safety
  - ✓ Statistical consideration: Control PFS 2.9m *vs.* Biomarker PFS 4.4m (HR 0.659)
- ◆ Biomarker screening strategies
  - ✓ Central screening at YCC using GC panel (IHC & ISH): HER2, EGFR, c-MET, PTEN, EBV, PD-L1(22C3), hMLH1/PMS2
  - ✓ Priority of patient allocation: PTEN>NIVO>EGFR
- ◆ Biomarker group Tx: Combination with targeted agent + Paclitaxel **
  - ✓ EGFR 2+/3+: Afatinib# (pan-ERBB inhibitor)[1]
  - ✓ PTEN loss/null: GSK2636771 # (PIK3Cβ inhibitor)[2]
  - ✓ PD-L1+, dMMR/MSI-high, and/or EBV+: Nivolumab # [3]
  - ✓ No biomarker detected: none arm with SOC treatment
  - ✓ PTEN and NIVO cohorts had phase Ib part to determine RP2D

* EGFR+:IHC 2+/3+; PTEN loss/null: H-score <100; PD-L1+: 22C3 CPS≥1
** paclitaxel 80mg/m2 D1,8,15 q4w
# Afatinib 40mg QD, GSK2636771 200mg QD, Nivolumab 3mg/kg q2weeks

1. Schuler et al. Ann Oncol 2016; 2. Mateo et al. Clinical Cancer Res. 2017; 3. Kang et al. Lancet 2017

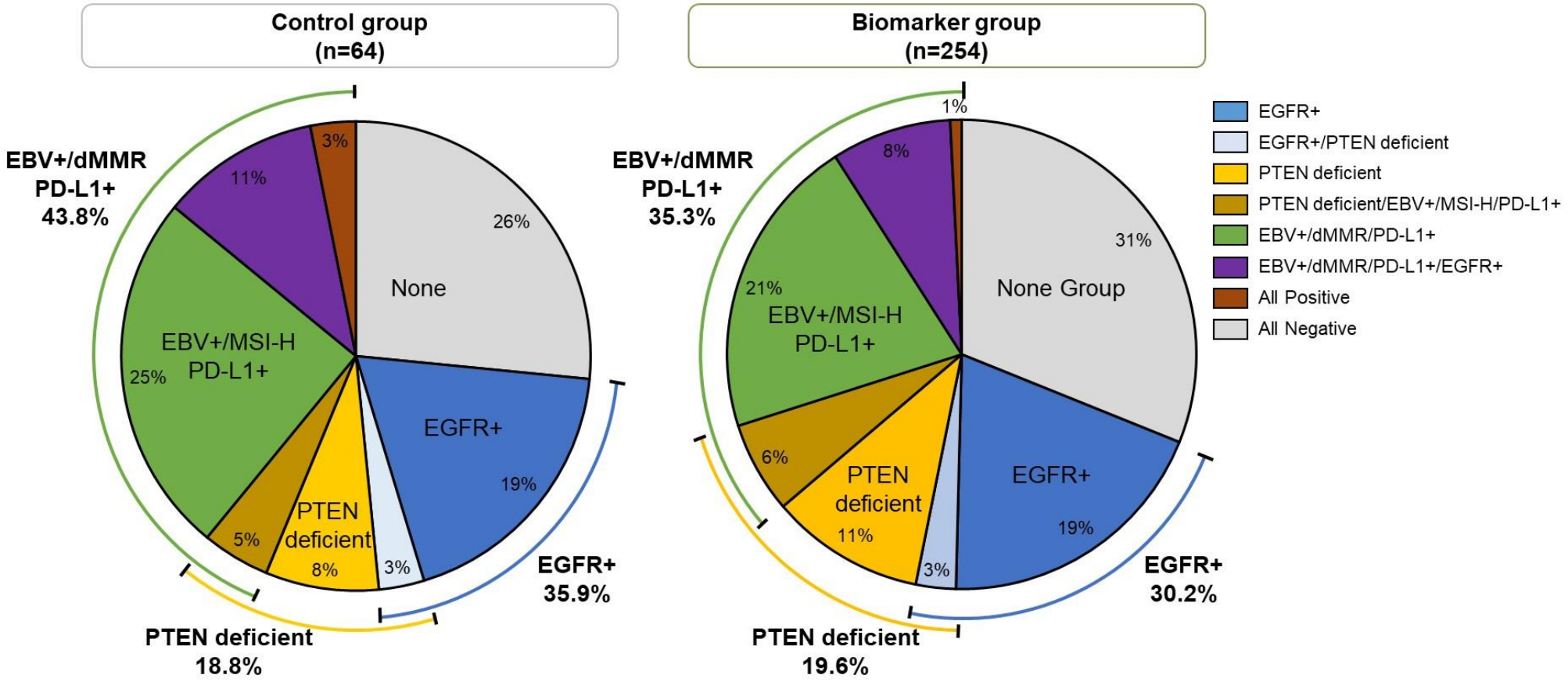
K-Umbrella GC: Patient allocation



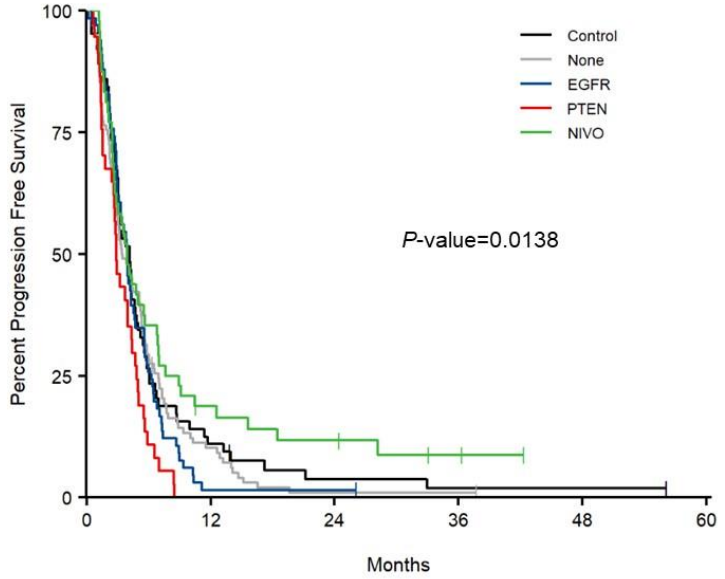
- 1st patient C1D1: Jul-2016
- Last patient C1D1: Feb-2021

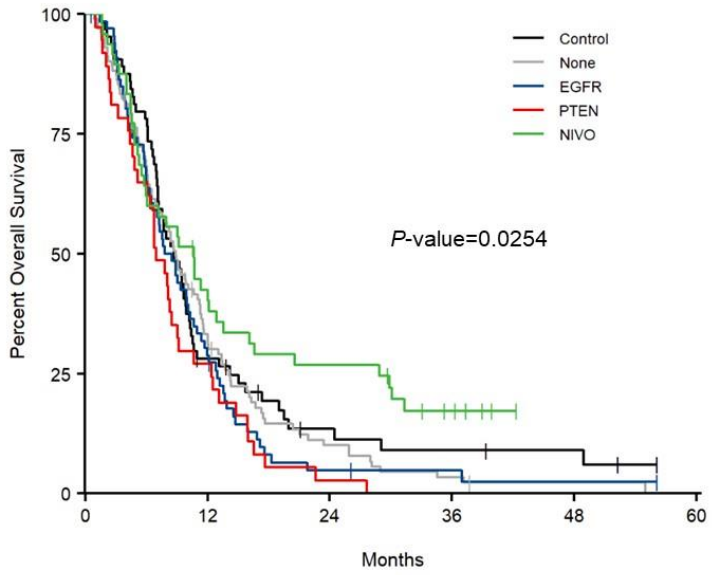
- *SOC changed from paclitaxel to paclitaxel plus ramucirumab after Korea MFDS approval on **May 2018**.

Distribution of biomarkers



Comparison of survival between control group and each biomarker cohort





	Group	n	# of events	Median PFS (95% CI)
	Control	64	62	4.13 (3.03 – 4.70)
Biomarker	None	102	100	3.45 (2.80 – 5.10)
	EGFR	67	65	3.97 (3.00 – 4.53)
	PTEN	37	37	2.83 (2.40 – 4.37)
	NIVO	48	43	3.92 (2.67 – 5.63)

	Group	n	# of events	Median OS (95% CI)
	Control	64	57	8.72 (7.13 – 9.90)
Biomarker	None	102	96	8.87 (7.10 – 11.03)
	EGFR	67	63	8.13 (6.30 – 10.10)
	PTEN	37	37	6.97 (5.17 – 9.07)
	NIVO	48	38	10.67 (5.77 – 12.90)

Data cut-off: ARP-18-2022, Median follow up: 35 months (95%CI 26.1-55.3)

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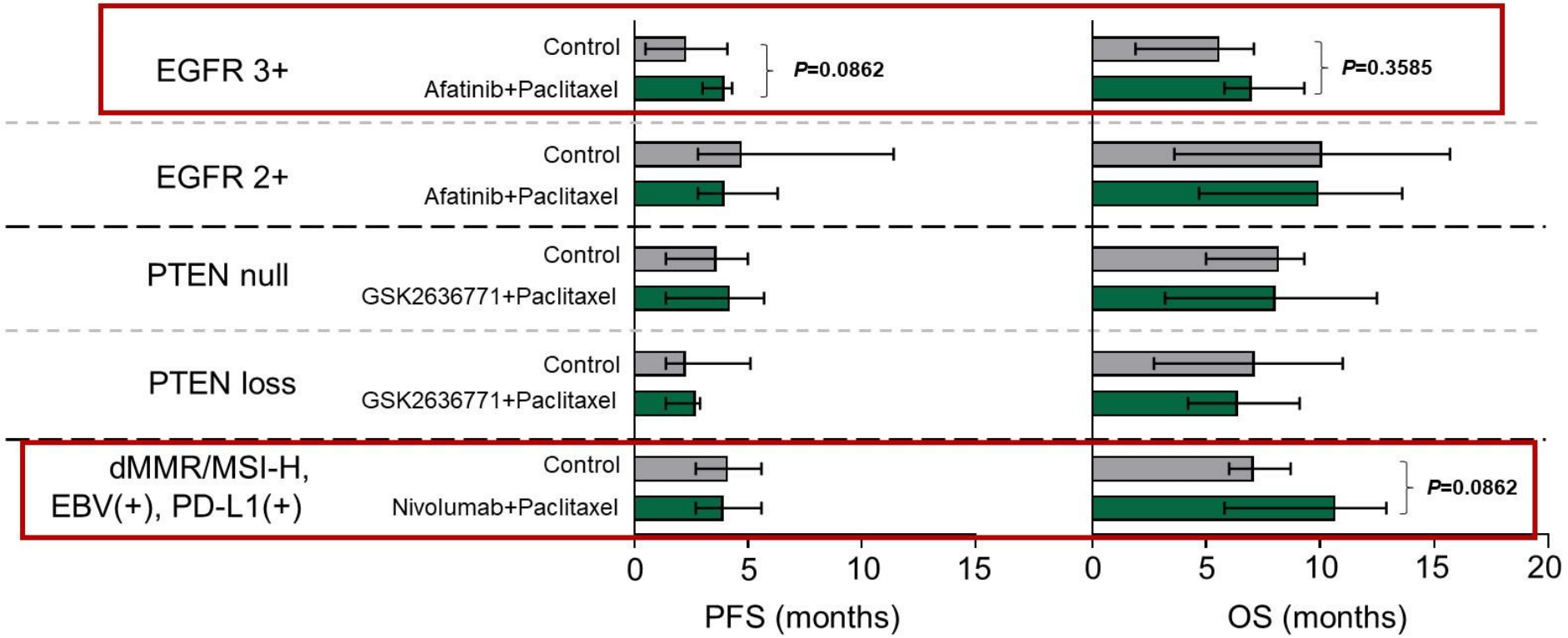
Efficacy of biomarker group with targeted Tx compared to control SOC group



Data cut-off: ARP-18-2022
Median follow up: 35 months (95%CI 26.1-55.3)

Key Conclusions

Biomarker driven study with smaller subsets is feasible

EGFR 3+, PTEN loss poor prognostic markers.

Targeting EGFR3+ with afatinib + paclitaxel modestly enhanced PFS in this group.

However PI3Kinase targeting in PTEN loss subgroup no benefit

Nivolumab and paclitaxel in immune biomarker enriched subset improved OS

Biomarker driven therapy not better than SOC??

KC Umbrella GC 2 with NGS testing underway

HERB trial

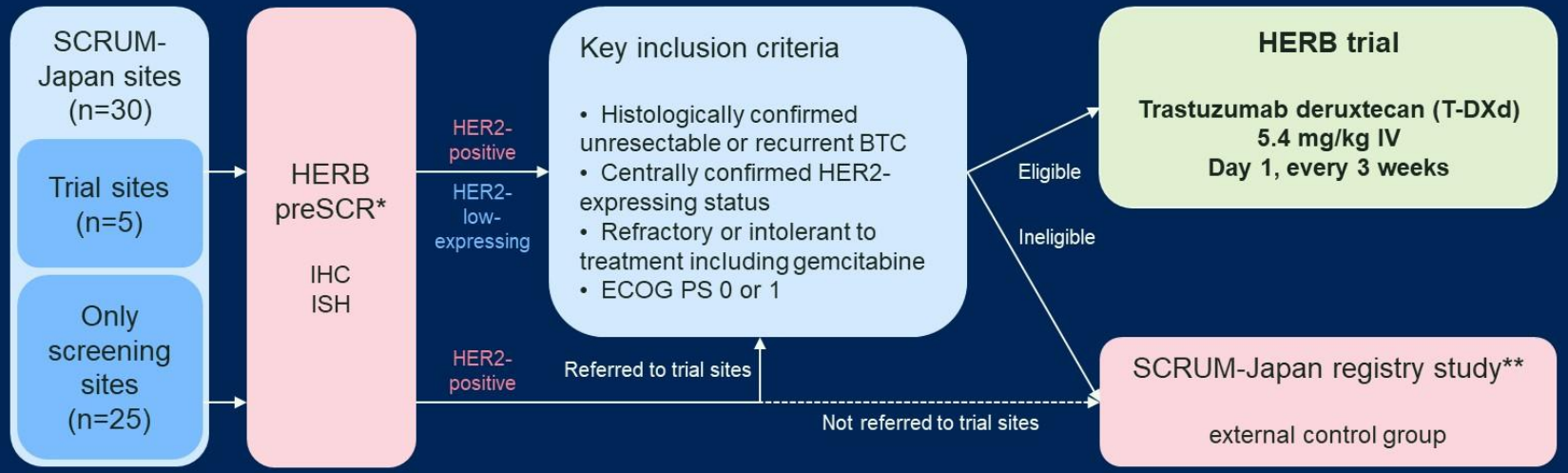
Transtuzumab Derixtecan in patients with Her2 expressing unresectable or recurrent biliary tract cancer- investigator initiated multicenter phase 2 study

Ohba A et al

- Her2 overexpressions, gene ampligicantion or both reported in GBC(30%), ECC(10-20%) and ICC (5%) roughly
- BTC Her2 expression pattern more similar to gastric cancer than breast cancer, heterogeneous

Studies Overview

IHC, immunohistochemistry; ISH, in situ hybridization;
ECOG PS, Eastern Cooperative Oncology Group performance status;
IV, intravenous; pts, patients.



The HERB trial (NCCH1805, JMA-IIA00423) is an investigator-initiated, multicenter, single-arm, phase 2 trial of T-DXd in pts with HER2-expressing BTCs.

*: UMIN000036697. **: UMIN000028058.

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Akihiro Ohba, MD

- Central Her2 screening
- Her2 positive- 2+ IHC/ISH +ve or 3+ by IHC
- 300 screened, 296 with IHC /ISH
- 61 patients positive, 120 low expression

Primary endpoint: Confirmed ORR (BICR)

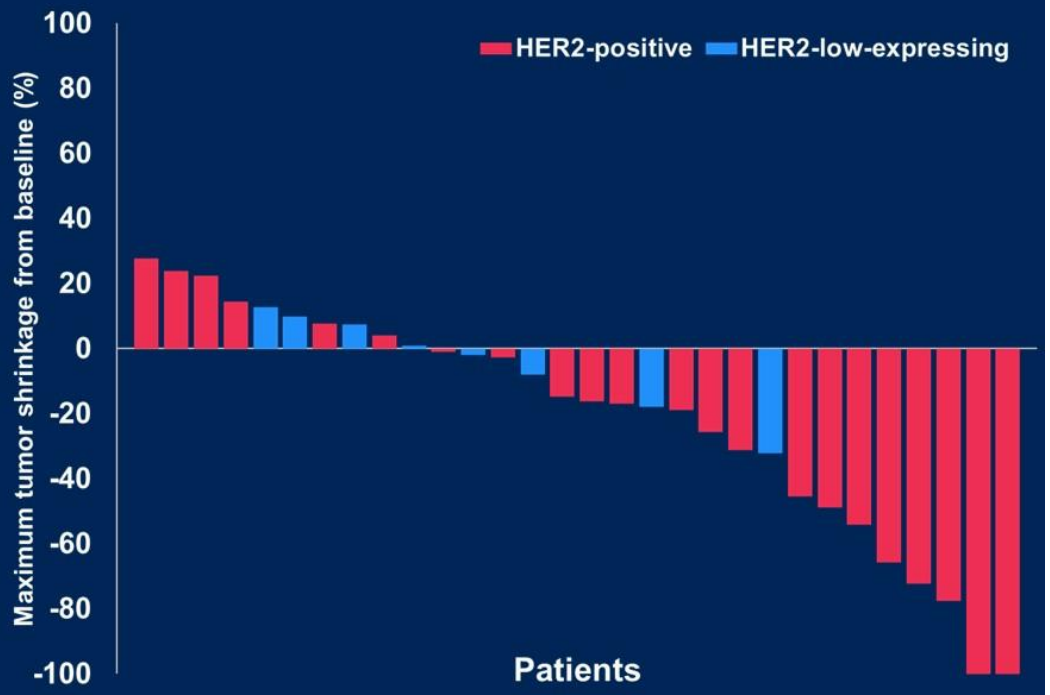
BICR, blinded independent central review;
DCR, disease control rate;
CR, complete response; PR, partial response;
SD, stable disease; PD, progressive disease;
NE, not evaluable.

- Tumor response

*: P =0.01

	HER2-positive (n=22)	HER2-low-expressing (n=8)	All pts (n=30)
Confirmed ORR (90% CI) (95% CI)	**36.4% (19.6-56.1)*** (17.2–59.3)	12.5% – (0.3–52.7)	30.0% – (14.7–49.4)
Confirmed DCR (95% CI)	81.8% (59.7–94.8)	75.0% (34.9–96.8)	80.0% (61.4–92.3)
Confirmed best response, n (%)			
CR	2 (9.1)	0 (0)	2 (6.7)
PR	6 (27.3)	1 (12.5)	7 (23.3)
SD	10 (45.5)	5 (62.5)	15 (50.0)
PD	3 (13.6)	1 (12.5)	4 (13.3)
NE	1 (4.5)	1 (12.5)	2 (6.7)

- Best percentage change



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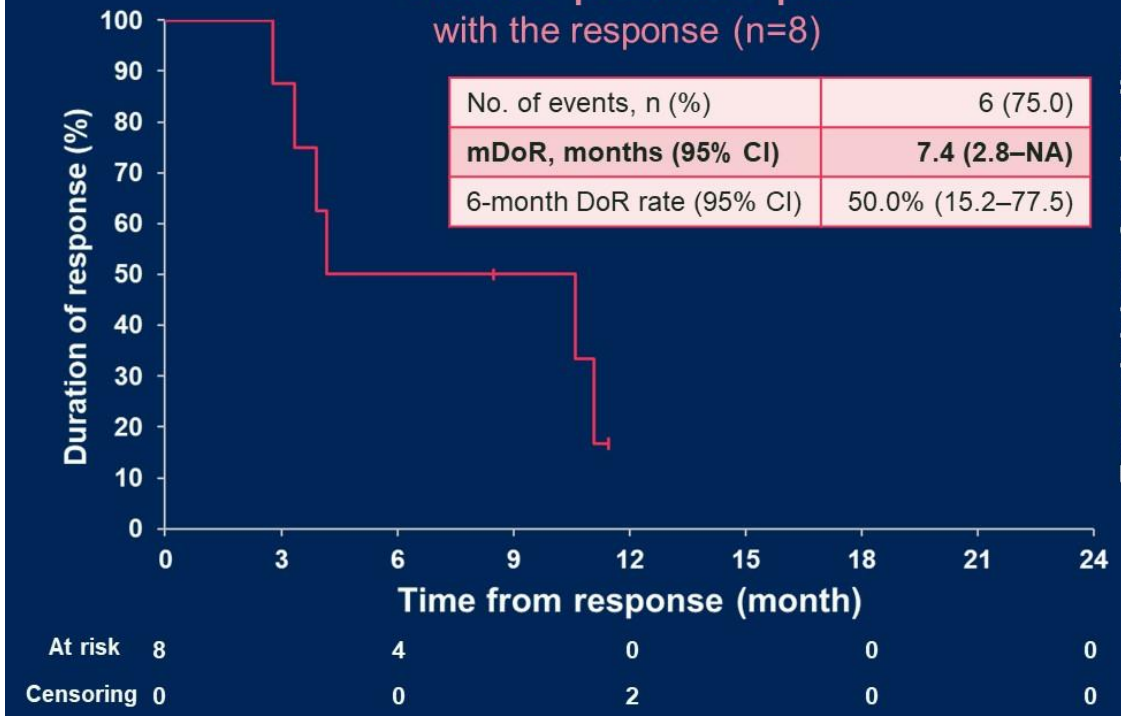
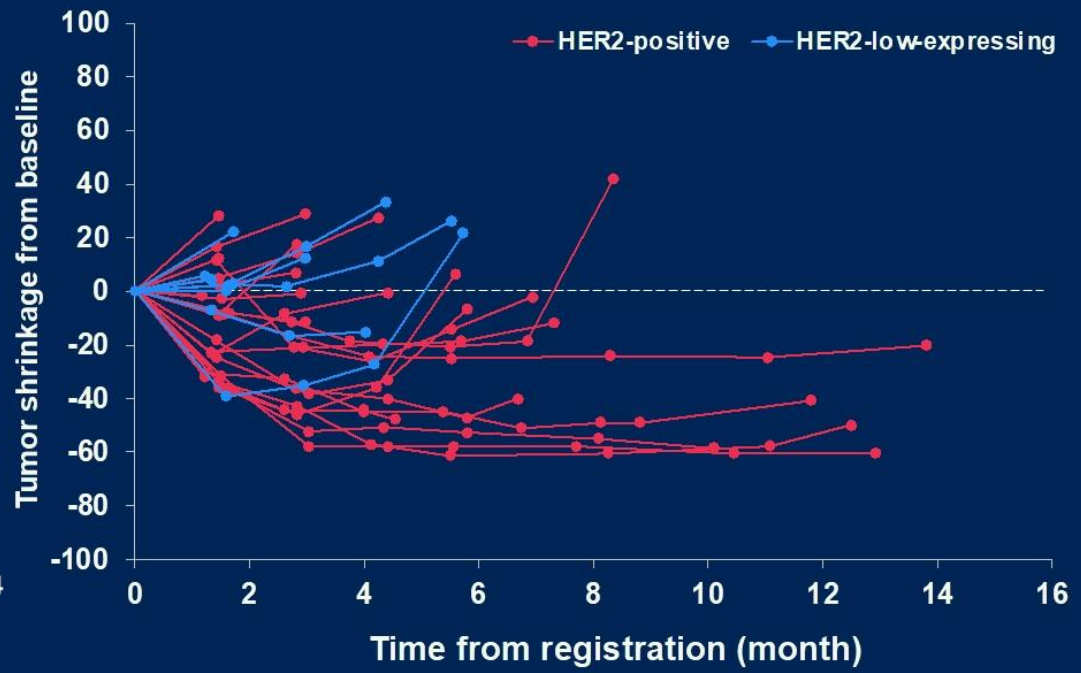
DoR, duration of response; NA, not available.

Post hoc: Duration of Response (LIR)

HER2-positive pts
with the response (n=8)

No. of events, n (%)	6 (75.0)
mDoR, months (95% CI)	**7.4 (2.8–NA)**
6-month DoR rate (95% CI)	50.0% (15.2–77.5)





Key Conclusions

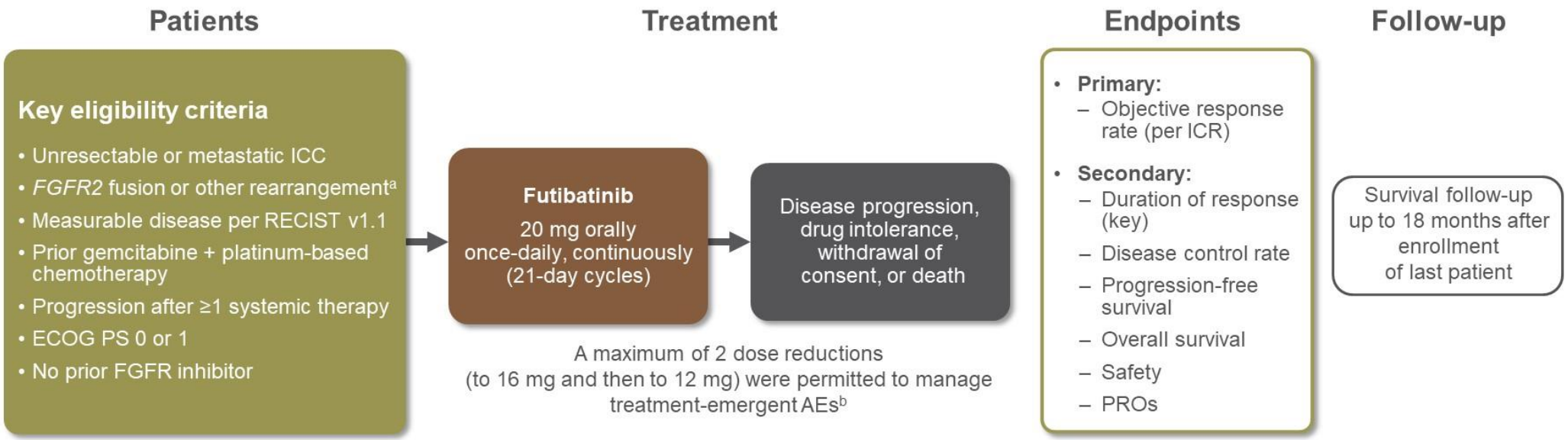
- T-Dxd showed confirmed ORR of 36.4%, mDOR of 7.4 months, median PDA of 5.1 months and median OS of 7.1 months in Her2 positive BTC
- Activity noted in Her2 low expressing tumors as well
- Interstitial lung disease- 6 patients grade 5 included in 2 patients. Median time to onset 124 days

FOENIX-CCA1 TRIAL updated results- Goyal L et al

- Futibatinib – highly selective irreversible FGFR1-4 inhibitor
- Covalent binding to the conserved cysteine in FGFR kinase domain P-loop, robust inhibition resistant to reversible ATP-competitive inhibitors
- Shows activity against tumors of any origin harboring various FGFR aberrations
- 9-14% of intrahepatic cholangiocarcinomas harbor FGFR2 fusions/rearrangements

- SEQUENCE YOUR BILIARY TRACT CANCER- TARGET RICH!

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



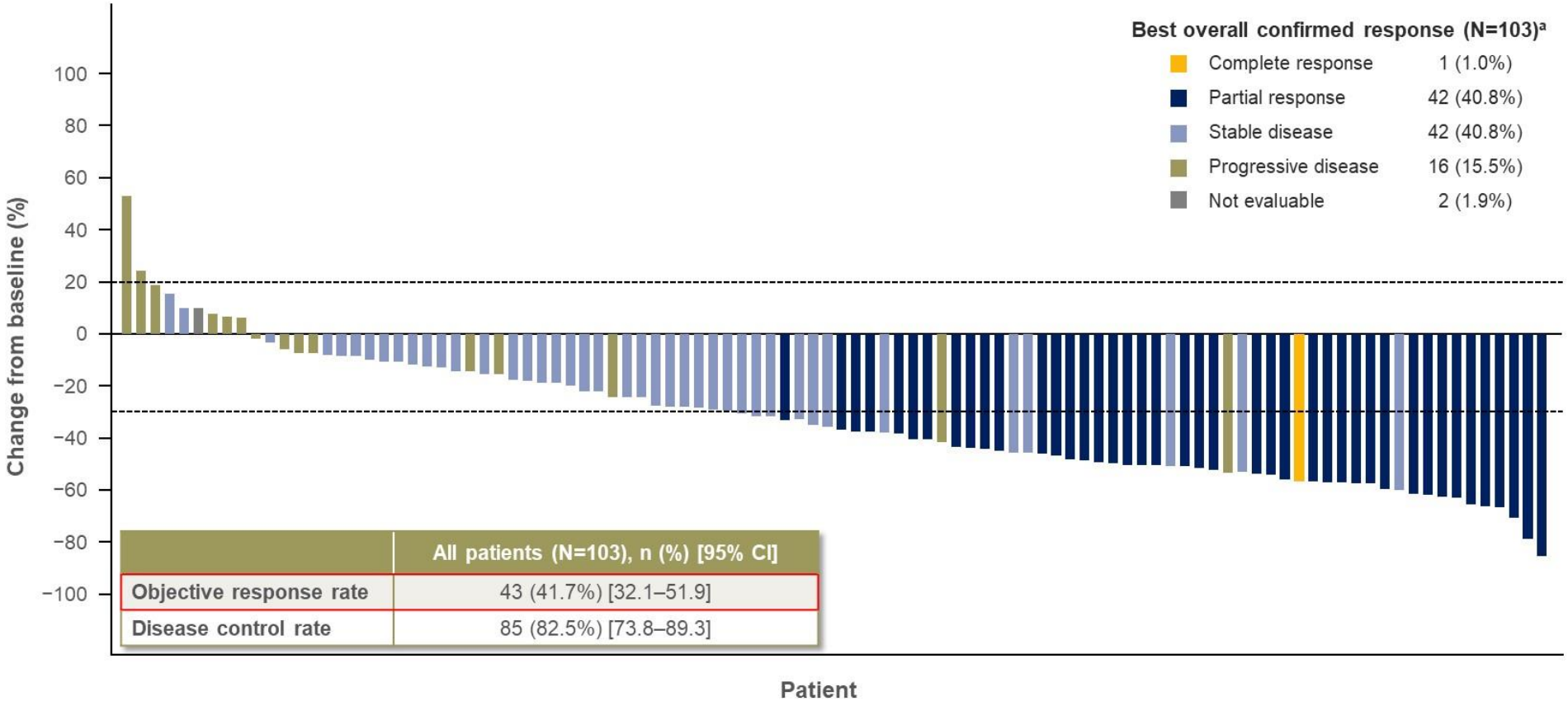
- At the time of the final data cutoff (May 29, 2021), median follow-up was 25.0 months, and 96/103 patients (93%) had discontinued treatment
- The median number of treatment cycles was 13.0, for a median treatment duration of 9.1 months

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

ClinicalTrials.gov Identifier: NCT02052778

FOENIX CCA2

Futibatinib in Intrahepatic Cholangiocarcinoma: Best Percent Change in Target Lesion Size



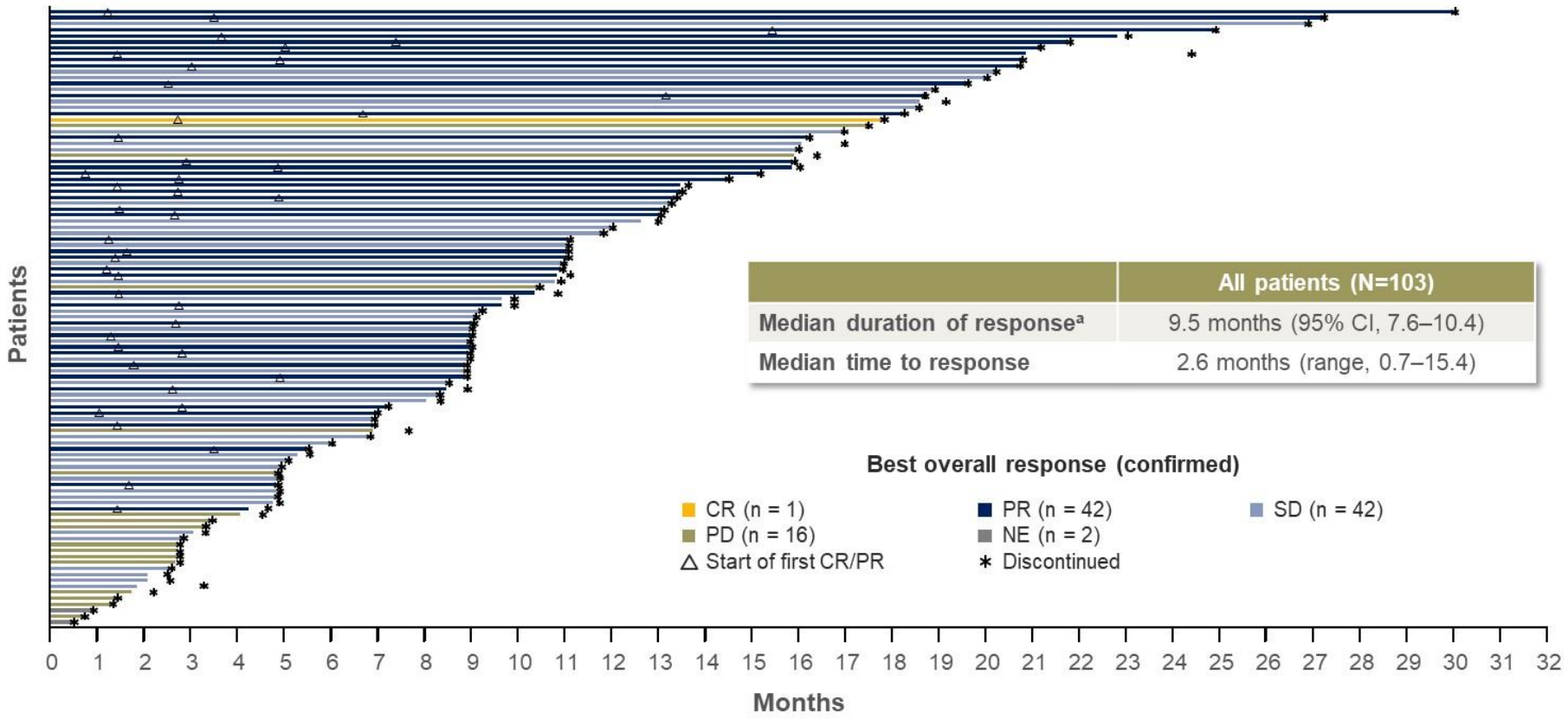
	All patients (N=103), n (%) [95% CI]
Objective response rate	43 (41.7%) [32.1–51.9]
Disease control rate	85 (82.5%) [73.8–89.3]

[a]Assessed by independent central review

Data cutoff: May 29, 2021. Dotted horizontal lines represent partial response (≥30% reduction in lesion size) and progressive disease (≥20% increase) per RECIST v1.1.
RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

FOENIX CCA2

Duration of Futibatinib Response in Intrahepatic Cholangiocarcinoma



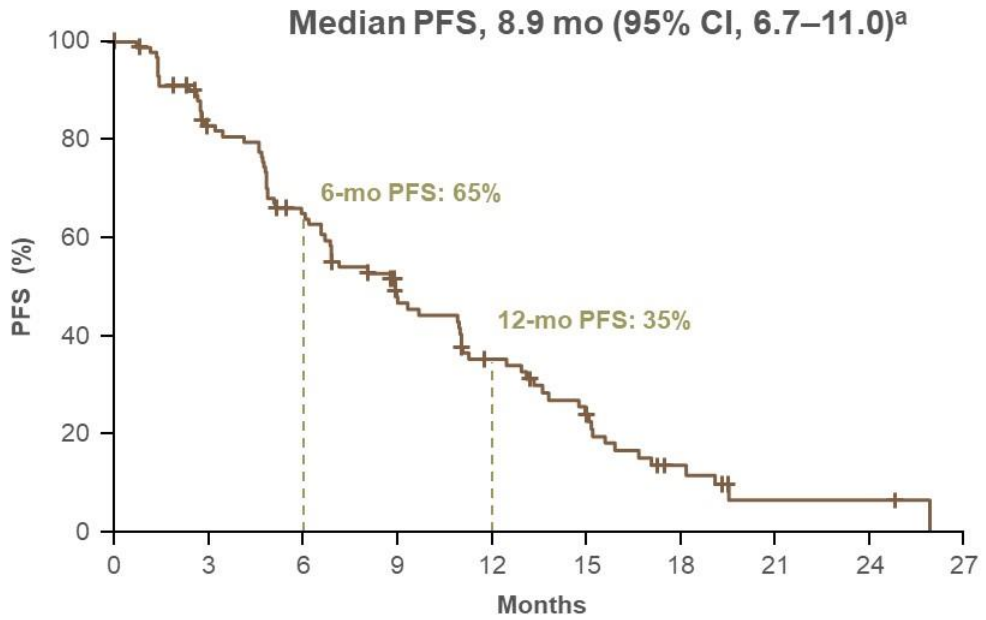
	All patients (N=103)
Median duration of response[a]	9.5 months (95% CI, 7.6–10.4)
Median time to response	2.6 months (range, 0.7–15.4)

- At data cutoff, 74% of responses had continued for ≥6 months and 18.6% had continued for ≥12 months

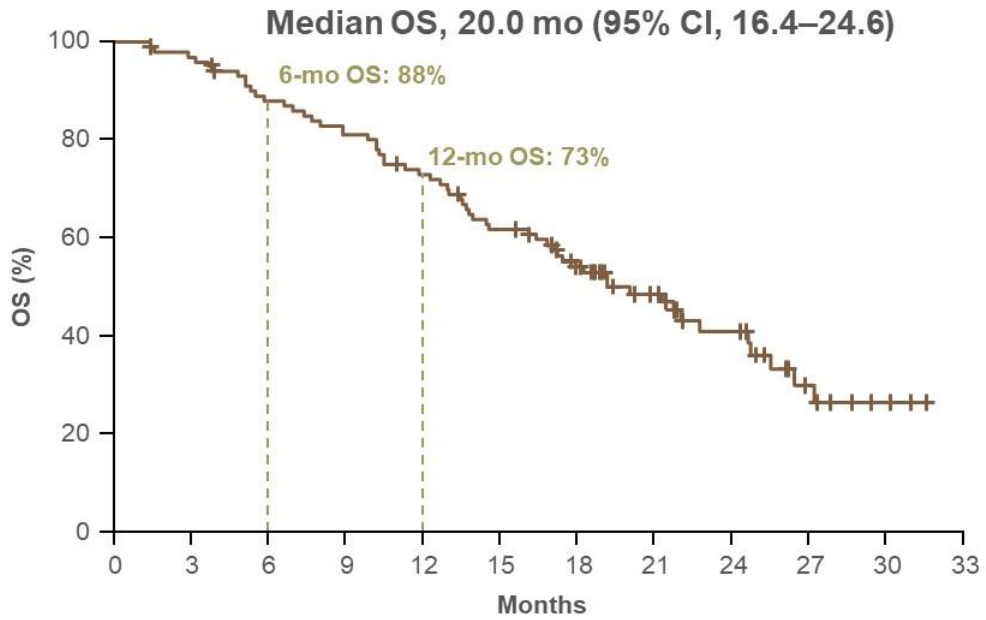
Data cutoff: May 29, 2021. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.
[a]Calculated using the Kaplan–Meier method; responses were based on independent central review per RECIST v1.1.

FOENIX CCA2

PFS and OS With Futibatinib in Intrahepatic Cholangiocarcinoma



At risk	103	79	60	38	26	17	7	2	2	0
Censored	–	7	2	7	2	1	3	2	0	1



At risk	103	99	88	81	72	60	46	30	19	8	3	0
Censored	–	1	2	0	1	1	7	12	7	7	4	3

Data cutoff: May 29, 2021.
OS, overall survival; PFS, progression-free survival.
[a]Assessed by independent central review.

Key Conclusions

- 41.7% ORR in previously treated patients with ICC harboring FGFR2 fusions/rearrangements
- Durable ORR, 9.1 months median treatment duration
- Median OS 20 months, 12 month OS rate 73%
- Hyperphosphatemia, nail toxicities, Palmar plantar erythrodysesthesia, rash, retinal disorders, increased ALT/AST- no new safety signals noted
- Of 103 patients, 95 had ct DNA and 83 samples positive for FGFR2 fusion/rearrangements