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Efficacy, Safety, and Quality of Life With Futibatinib in Patients With Intrahepatic Cholangiocarcinoma Harboring *FGFR2* Fusions or Rearrangements: Interim Analysis of FOENIX-CCA2

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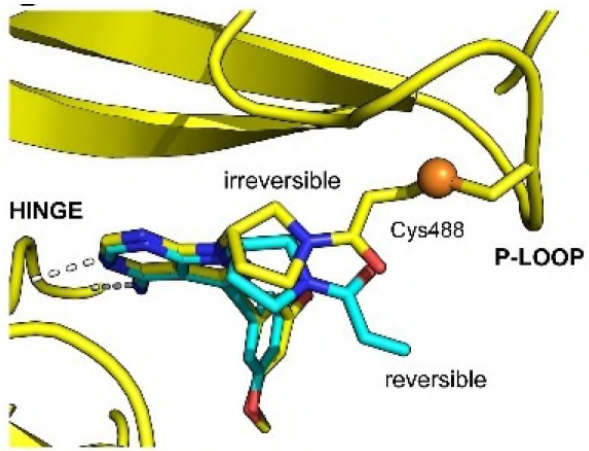
Introduction

- Survival outcomes are poor in advanced iCCA
  - 1st line median OS is ~1 year on standard gemcitabine/cisplatin[1,2]
  - 2nd line median OS is 6.2 months on FOLFOX[3]
- *FGFR2* fusions occur in 13%–14% of iCCA tumors[4–6]
  - Pemigatinib, a reversible FGFR inhibitor, was recently approved for advanced/metastatic CCA with *FGFR2* fusions/rearrangements[7]
- Futibatinib, a novel, highly selective, potent, irreversible FGFR1–4 inhibitor:[8]
  - Binds covalently to a conserved cysteine in the P-loop of the kinase domain
  - Showed robust activity against FGFR2 kinase domain mutations resistant to reversible ATP-competitive inhibitors[8,10]
  - Demonstrated tolerability and antitumor activity in a phase 1 study in various tumor types, including CCA[11,12]

Futibatinib binding to the FGFR kinase domain[9]



Activity of futibatinib against wild-type FGFR isoforms[8]		Activity of futibatinib against FGFR2 kinase domain mutants[8]	
FGFR isoform	IC_{50} (nmol/L)	FGFR2	IC_{50} (nmol/L)
FGFR1	1.8	Wild type	0.9
FGFR2	1.4	N550H	3.6
FGFR3	1.6	E566G	2.4
FGFR4	3.7	K660M	5.2
		V565I	1.3

ATP, adenosine triphosphate; FGFR, fibroblast growth factor receptor; $IC_{50,}$ half-maximal inhibitory concentration; iCCA, intrahepatic cholangiocarcinoma; FOLFOX, folfinic acid, fluorouracil, and oxaliplatin; OS, overall survival

Figure adapted from *Cancer Research*, 2020, DOI: 10.1158/0008-5472. Sootome H, et al. "Futibatinib is a novel irreversible FGFR 1-4 inhibitor that shows selective antitumor activity against FGFR-deregulated tumors" with permission from AACR.

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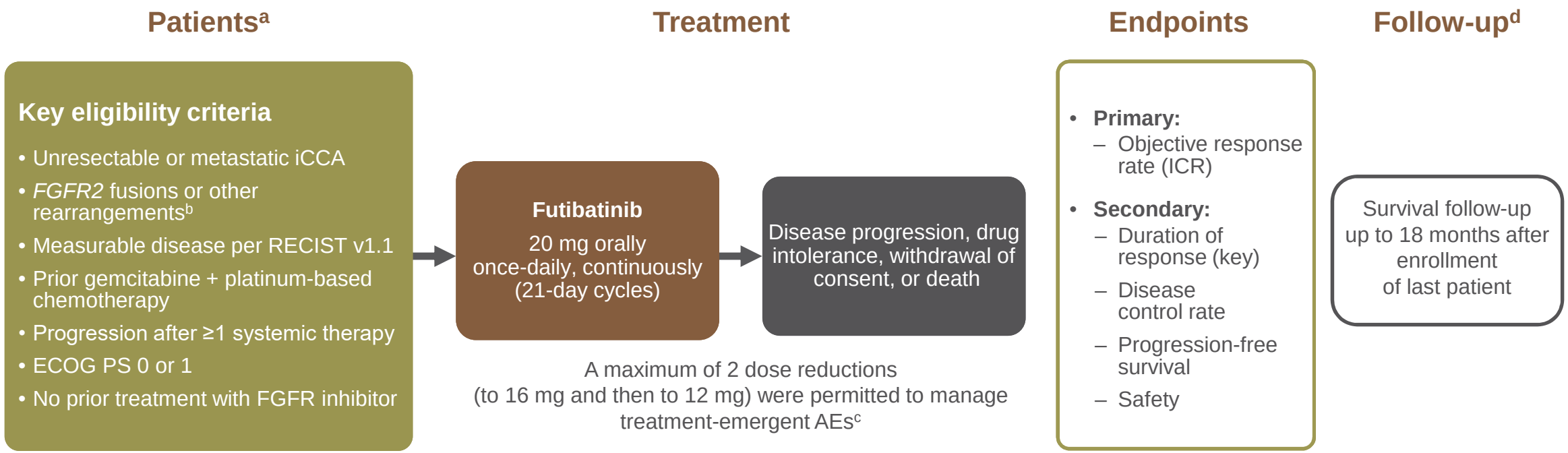
FOENIX-CCA2: Phase II Global Study of Futibatinib



- 103 patients enrolled across 36 international sites
- Planned interim analysis on 67 patients with ≥6 mo follow-up (median follow-up 11.4 mo)

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; iCCA, intrahepatic cholangiocarcinoma; ICR, independent central radiology review; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1. Database lock: March 30, 2020. [a]Across 36 international sites, 703 patients were prescreened and assessed for eligibility.[b]Identified centrally in tumor tissue by Foundation Medicine (FMI) or by local laboratory testing of tumor tissue or circulating tumor DNA (ctDNA); [c]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. [d]A planned interim analysis was performed when ≈70% of all treated patients had ≥6 months' follow-up.

ClinicalTrials.gov Identifier: NCT02052778

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FOENIX-CCA2 Patient Baseline Demographics

		All patients (N=67)
Age (range), years	Median	57.0 (22–79)
Sex, n (%)	Female	39 (58)
ECOG PS, n (%)	0	29 (43)
	1	38 (57)
Region, n (%)	North America	37 (55)
	Europe	15 (22)
	Japan	8 (12)
	Asia Pacific	7 (10)
Number of prior regimens, n (%)	1	30 (45)
	2	19 (28)
	≥3	18 (27)
***FGFR2* aberration[a,b], n (%)**	Translocation/fusion	55 (82)
	Rearrangement	12 (18)

- Treatment ongoing for 25 patients (37%) at datalock, most discontinuations due to disease progression

ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor.[a]Rearrangements were categorized as fusions by central review only if the fusion gene partner was known or was predicted to be in-frame with *FGFR*. [b]Of 37 unique fusion partners identified, those occurring in >1 patient were *BICC1* (n=15); *KIAA1217* and *WAC* (each n=3); and *SHROOM3* and *SMARCC1* (each n=2).

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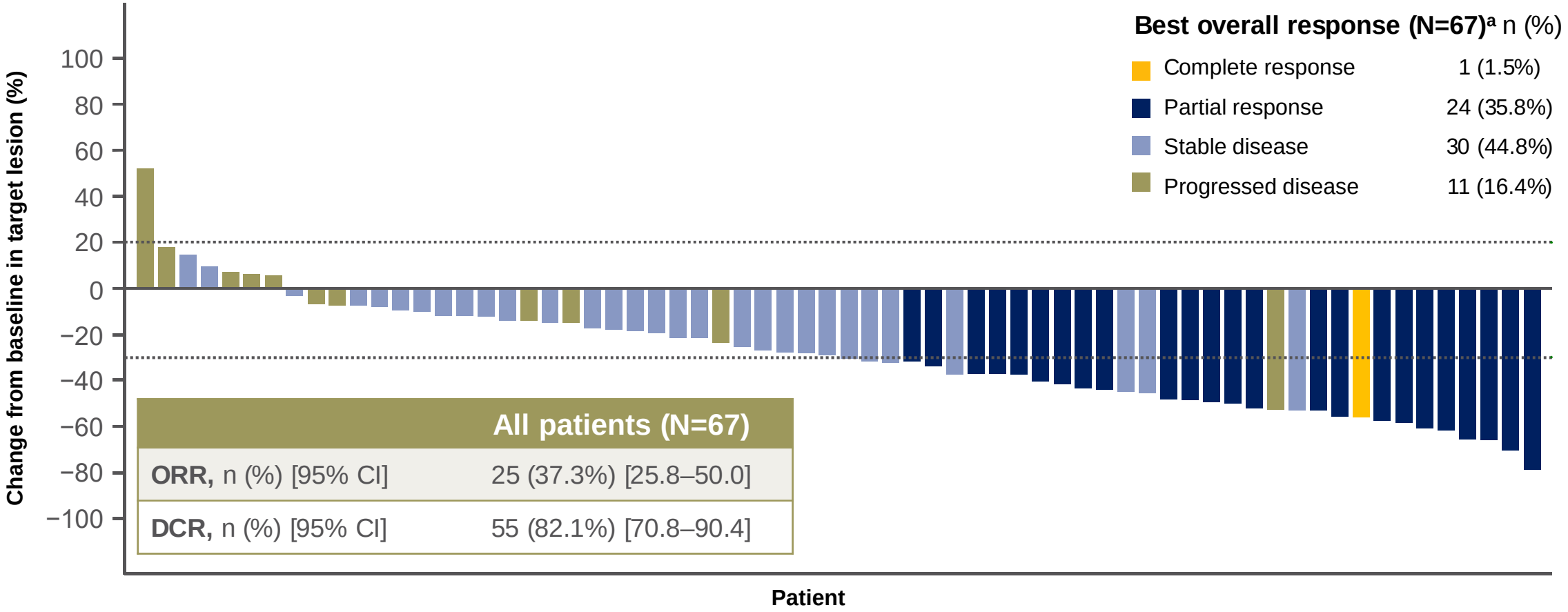
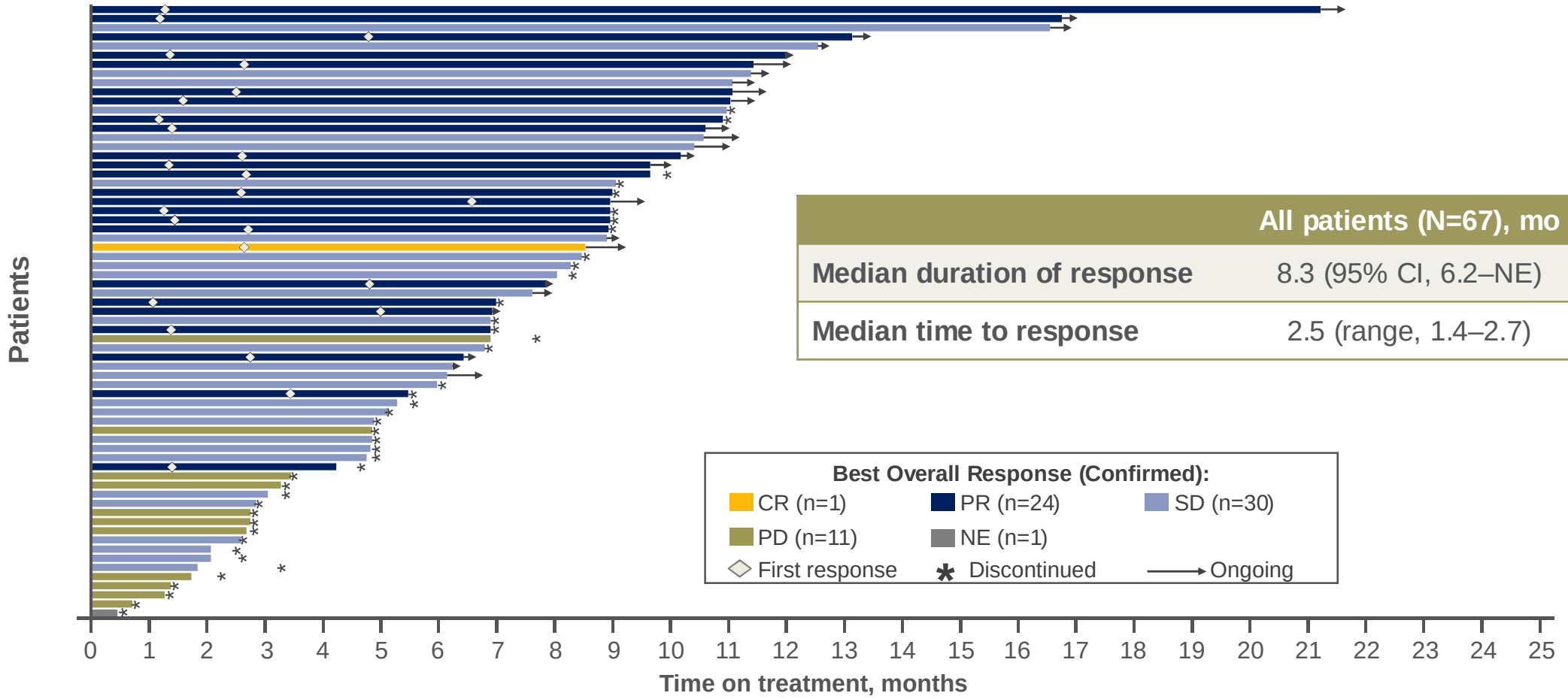
Futibatinib in iCCA: Tumor Response



CI, confidence interval; NE, not evaluable; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1. Dashed horizontal lines represent the ≥30% reduction in lesion size defined as a partial response and the ≥20% increase in lesion size defined as progressive disease per RECIST v1.1. [a]One patient was not evaluable.

Futibatinib in iCCA: Duration of Response



	All patients (N=67), mo
Median duration of response	8.3 (95% CI, 6.2–NE)
Median time to response	2.5 (range, 1.4–2.7)

CI, confidence interval; NE, not evaluable.
Shrinkage of target lesions from baseline occurred in 28 of 30 patients who had a best response of stable disease.
Duration of response was ≥6 months in 14 patients (21%); 9 patients (13%) had an ongoing response of ≥6 months at data cutoff.

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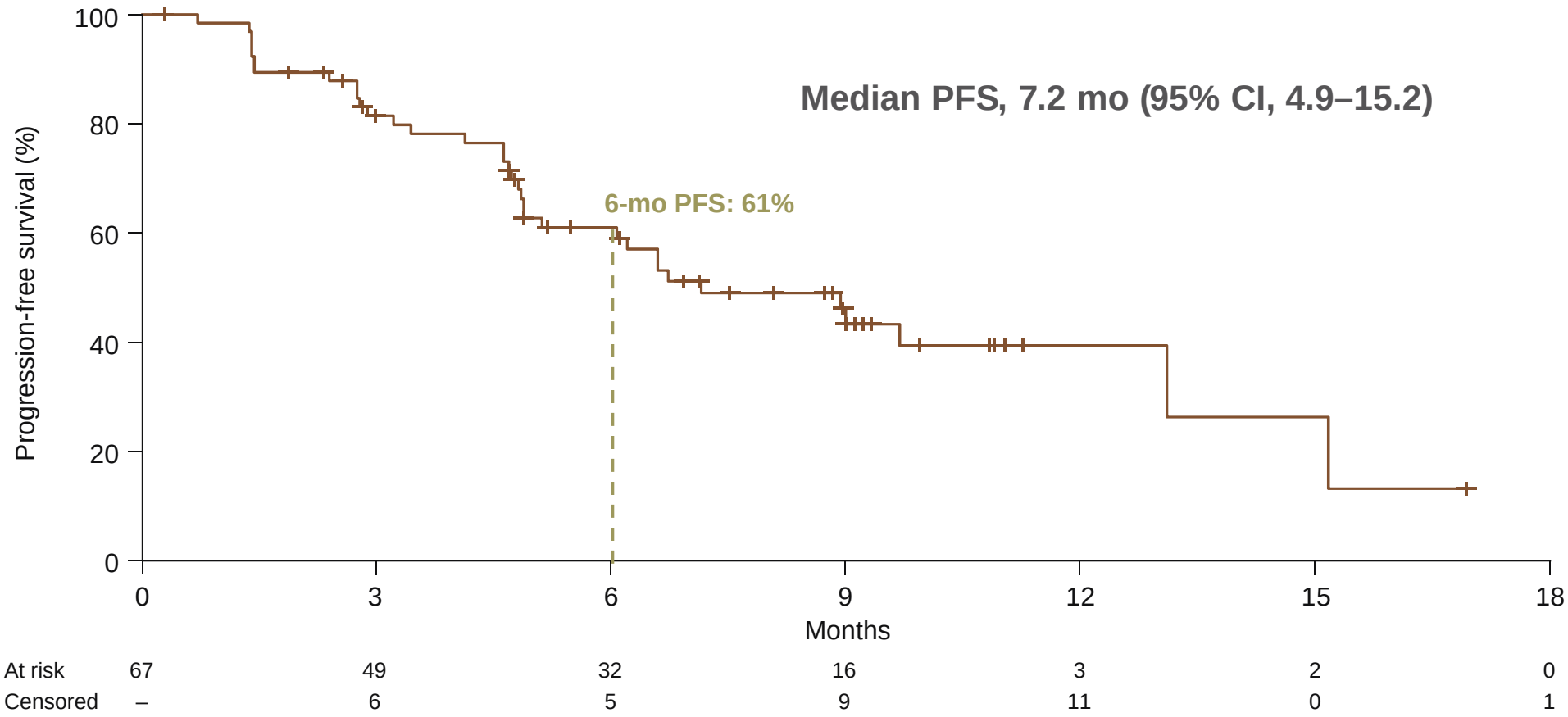
Futibatinib in iCCA: Progression-Free Survival[a]



- Median OS was not reached, and the 6-month OS rate was 86% (95% CI, 74.7–92.4)[b]

CI, confidence interval; OS, overall survival; PFS, progression-free survival. [a]PFS was calculated from the date of the first dose of the study drug to the date of first objective evidence of disease progression or date of death due to any cause, whichever occurs first; patients who did not have disease progression, die, or begin a subsequent therapy without progression were censored on the date of their last tumor assessment. [b]OS was immature, and median OS was not reached.

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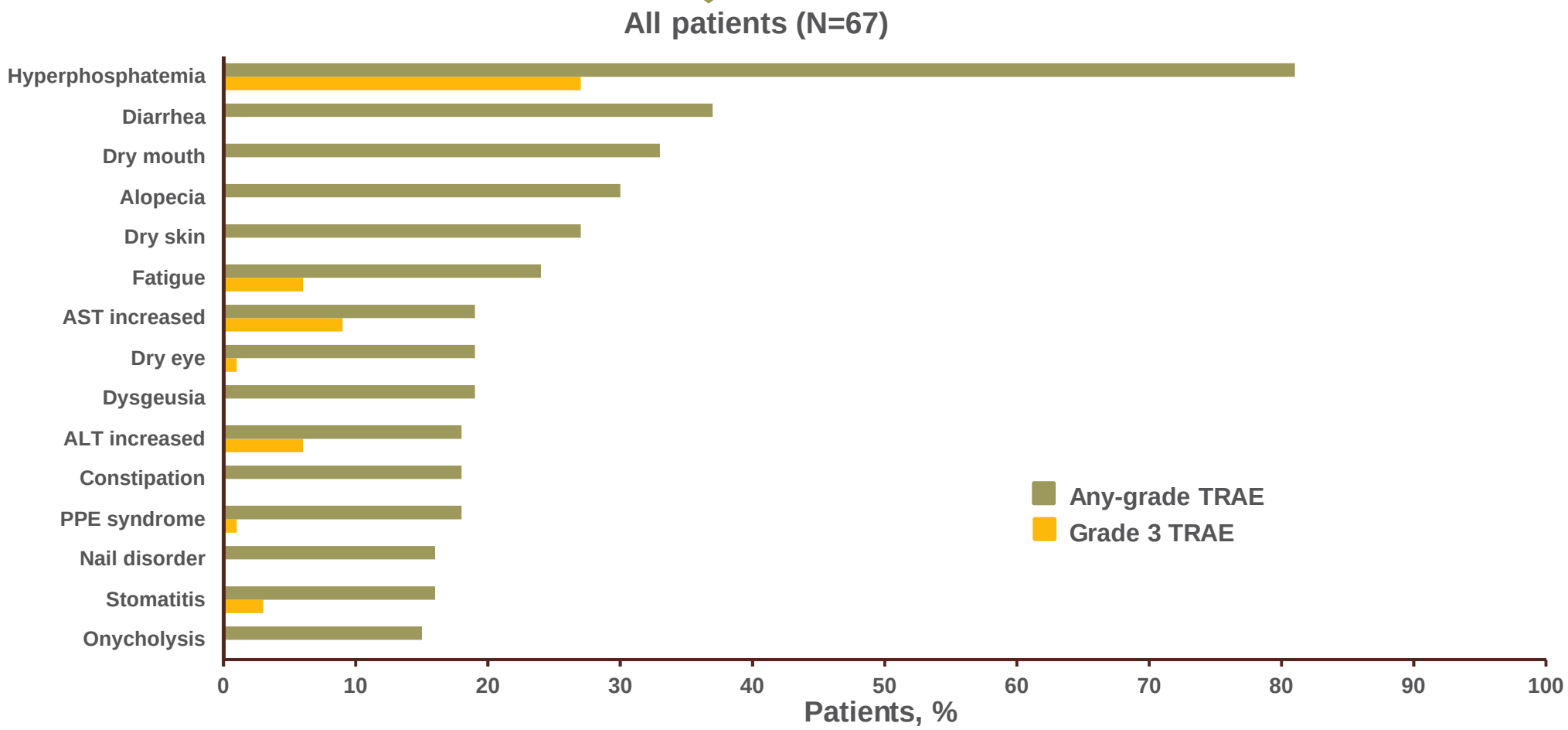
Futibatinib in iCCA: Response in Patient Subgroups

Patient characteristic/molecular alteration	Subgroup	Patients with response, n/N	ORR	95% CI, %
Age, years	<65	17/53	32.1%	19.9–46.3
	≥65	8/14	57.1%	28.9–82.3
Baseline ECOG PS	0	11/29	37.9%	20.7–57.7
	1	14/38	36.8%	21.8–54.0
***FGFR2* aberration**	Fusion[a]	21/58	36.2%	24.0–49.9
	Rearrangement	4/9	44.4%	13.7–78.8
Number of prior therapy regimens	1	8/30	26.7%	12.3–45.9
	2	8/19	42.1%	20.3–66.5
	≥3	9/18	50.0%	26.0–74.0
Prior primary tumor resection	Yes	3/10	30.0%	6.7–65.2
	No	22/57	38.6%	26.0–52.4
Sex	Female	17/39	43.6%	27.8–60.4
	Male	8/28	28.6%	13.2–48.7
Race	White	11/36	30.6%	16.3–48.1
	Asian	6/16	37.5%	15.2–64.6
	Black	3/7	42.9%	9.9–81.6
	Other	5/8	62.5%	24.5–91.5
Region	North America	13/37	35.1%	20.2–52.5
	Europe	8/15	53.3%	26.6–78.7
	Asia Pacific	2/7	28.6%	3.7–71.0
	Japan	2/8	25.0%	3.2–65.1

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; ORR, objective response rate. Objective response and ORR by subgroup are based on patient baseline demographics.[a]ORRs were 33.3% in patients with a *BICC1* fusion and 38.1% in patients with all other fusions.

Futibatinib in iCCA: Common Treatment-related AEs



- Overall, 57% of patients experienced grade 3 TRAEs
- One patient discontinued because of TRAEs (stomatitis, oral dysesthesia, and pharyngeal inflammation)

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; PPE, palmar-plantar erythrodysesthesia; TRAE, treatment-related adverse event.

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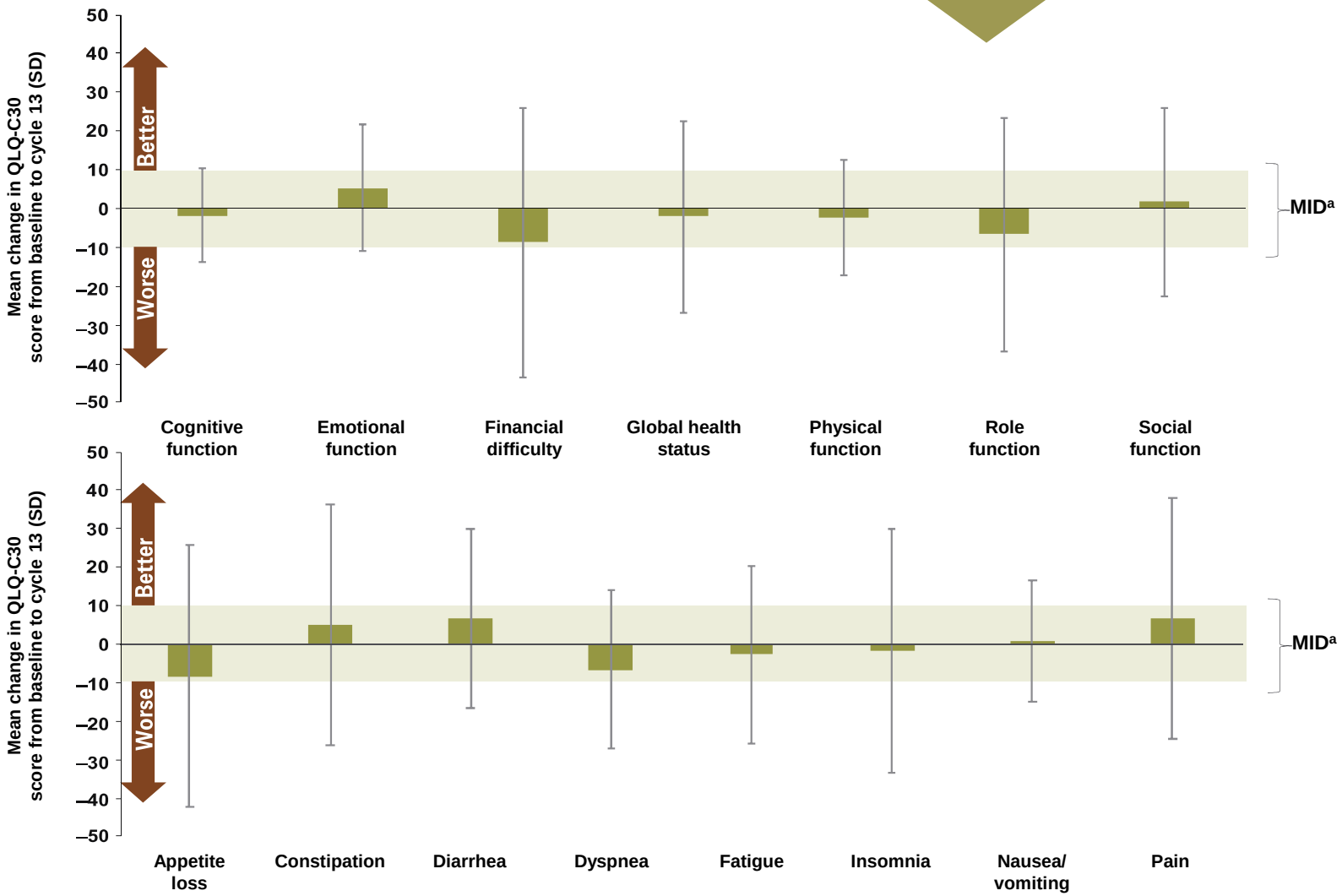
Futibatinib in iCCA: AEs of Special Interest

	Safety population (N=67), n (%)	
	Any grade	Grade 3
Any AE of special interest[a]	**64 (96)**	**20 (30)**
Hyperphosphatemia (including increased blood phosphorus)	59 (88)	19 (28)
Nail toxicities[b]	28 (42)	1 (1)
Palmar-plantar erythrodysesthesia syndrome	12 (18)	1 (1)
Rash	7 (10)	0
Central serous retinopathy	6 (9)	0
Other eye disorders[c]	34 (51)	1 (1)
Other skin toxicities[d]	33 (49)	0

- All AEs of special interest were managed with dosing modifications or medications
  - Hyperphosphatemia was managed with phosphate binders (88%), dose reductions/interruptions (12%/19%)
  - No treatment discontinuations occurred due to hyperphosphatemia

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Event; TRAE, treatment-related adverse event. [a]No grade 4 or 5 TRAEs were reported. [b]The most common TRAEs in ≥20% of patients are listed below. [c]Hyperphosphatemia was graded according to protocol-defined serum phosphate levels. [d]Group terms of AEs of special interest are listed below. [e]Nail toxicities occurring in >1 patient were nail disorder (n=11), onycholysis (n=10), nail discoloration (n=7), paronychia (n=5), and onychalgia (n=2). [f]Other eye disorders reported in >1 patient were dry eye (n=16), blurred vision (n=6), increased lacrimation (n=5), trichomegaly (n=4), blepharitis (n=3), cataract (n=2), eye pain (n=2), impaired vision (n=2), and trichiasis (n=2). [g]Other skin toxicities reported in >1 patient were alopecia (n=20), dry skin (n=18), pruritus (n=7), and skin fissure (n=2).

Futibatinib in iCCA: Patient Quality of Life



- Functional status measures were stable from baseline through cycle 13 (~9 mo)
- Individual symptom measures were largely stable from baseline through cycle 13 (~9 mo)

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; MID, minimally important difference; PRO, patient-reported outcome; SD, standard deviation. Error bars represent SD, and the shaded box indicates scores with no clinically meaningful change from baseline. The PRO-evaluable population comprised 57 patients at baseline, except for financial difficulty (n=56), and data from 20 patients were available for the cycle 13 assessment for all measures other than financial difficulty (n=19). [a]A ≥10-point change from baseline for QLQ-C30 scores was predefined as the MID to designate a change as clinically meaningful.

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Conclusions

In this interim analysis of FOENIX-CCA2:

1. Futibatinib resulted in frequent and durable responses (ORR, 37.3%; median DOR, 8.3 mo; PFS, 7.2 mo)
2. Objective responses were observed across patient subgroups, regardless of baseline characteristics or prior lines of therapy
3. Futibatinib had a manageable safety profile and treatment-related discontinuations were rare
4. Futibatinib treatment did not adversely impact patient quality of life; symptoms remained stable

Together, these data indicate that futibatinib is effective and tolerable in previously treated patients with iCCA harboring *FGFR2* fusions/rearrangements

Updated results to be presented at AACR 2021:

Title: Primary results of phase 2 FOENIX-CCA2: the irreversible FGFR1-4 inhibitor futibatinib in intrahepatic cholangiocarcinoma (iCCA) with *FGFR2* fusions/rearrangements

Session: Clinical Trials Plenary Session (Targeted Therapy and Ovarian Cancer Trials)

Date/time: April 11, 2021; 2.00 pm EST

AE, adverse event; DOR, duration of response; FGFR, fibroblast growth factor receptor; iCCA, intrahepatic cholangiocarcinoma; ORR, objective response rate; PFS, progression-free survival

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