E-poster: 1383P

Phase 1 Study of the Irreversible FGFR Inhibitor Futibatinib in Japanese Patients With Advanced Solid Tumors: Updated Dose Expansion Results and Activity in Gastric Cancer

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Background

FGFR aberrations in cancer

• Dysregulation of the fibroblast growth factor receptor (FGFR) pathway is known to drive oncogenesis in various cancers harboring *FGFR* aberrations¹

Gastric cancer

- Patients with advanced unresectable gastric cancer have poor survival outcomes and few treatment options after failure of standard second-line chemotherapy^{2,3}
- Objective response rates (ORRs) with second-line chemotherapy range from 7% (with docetaxel)⁴ to 28% (with paclitaxel plus ramucirumab),⁵ and they are even lower with third-line systemic therapy (≈4–11%)^{6,7}
- FGFR2 amplifications are associated with poor prognosis in gastric cancer, suggesting that FGFR2-amplified gastric cancer may be sensitive to FGFR inhibitor—based therapy^{8–10}

Futibatinib

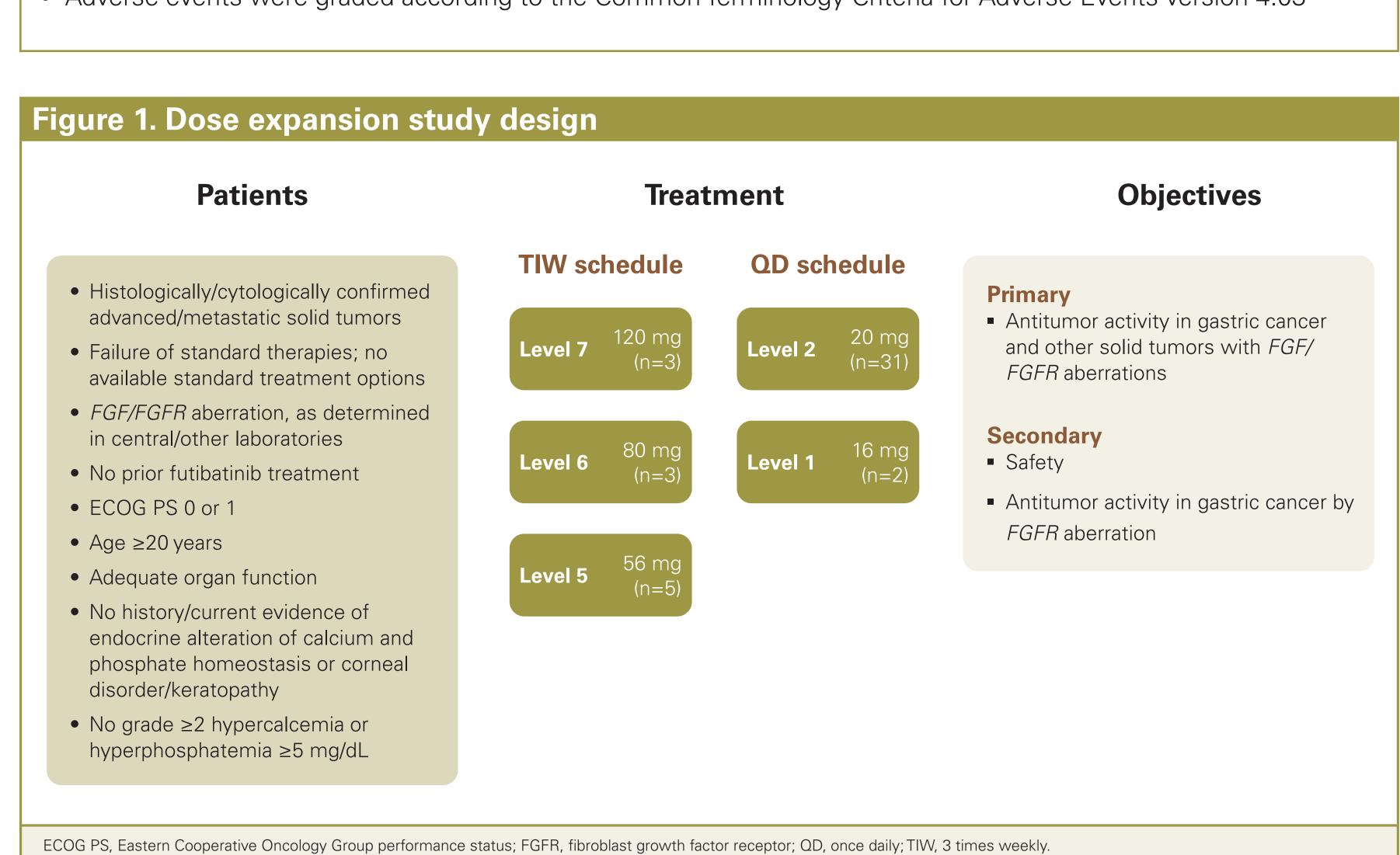
- Futibatinib is an oral, highly selective, potent, irreversible FGFR1-4 inhibitor¹¹
- In preclinical studies, futibatinib demonstrated potent antitumor activity in various tumor cell lines and xenograft models harboring a spectrum of *FGFR* aberrations¹¹
- Robust activity was noted against *FGFR2*-amplified gastric cancer cell lines and xenograft models
- In a global phase 1 dose escalation/expansion study (NCT02052778), futibatinib showed manageable safety and antitumor activity in patients with advanced solid tumors^{12–14}
- Futibatinib 20 mg once daily (QD) was established as the recommended phase 2 dose
- Preliminary activity was observed in cholangiocarcinoma (CCA), urothelial carcinoma, gastric cancer, and breast cancer harboring various FGFR aberrations
- The phase 2 FOENIX-CCA2 study further demonstrated the efficacy (ORR, 41.7%) and safety of futibatinib in FGFR2 fusion/rearrangement-positive intrahepatic CCA¹⁵

Phase 1 dose escalation/expansion study in Japanese patients (JapicCTI-142552)

- A phase 1 dose escalation/expansion trial was conducted to evaluate the safety and efficacy of futibatinib (dosed at 8–160 mg 3 times weekly [TIW] or 16–20 mg QD) in Japanese patients with advanced solid tumors 16,17
- The safety and pharmacokinetic profiles of futibatinib in the Japanese dose escalation study were consistent with data from the global phase 1 study
- Here, we present updated results from the dose expansion portion of this Japanese phase 1 study, including activity in patients with gastric cancer
- The primary objective was to assess antitumor activity in FGFR-aberrant gastric cancer and other FGF/FGFR-aberrant tumors
- Secondary objectives were to evaluate safety (with the recommended phase 2 dose) and antitumor activity in gastric cancer, based on FGFR aberration

Methods

- Patients enrolled in the dose expansion study had advanced FGF/FGFR-aberrant tumors and no alternative treatment options (**Figure 1**)
- FGF/FGFR aberrations were determined at screening in central or other laboratories
- Patients received futibatinib 56, 80, or 120 mg TIW or 16 or 20 mg QD until disease progression, unacceptable toxicity, investigator decision, or withdrawal of consent
- Tumor response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors
- In patients with gastric cancer, antitumor activity was assessed by FGFR2 amplification levels:
- FGFR2 amplification was assessed using FGFR2 copy number value (CNV), and patients were grouped into categories of *FGFR2* CNV <4 or ≥4 and CNV <10 or ≥10
- Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.03



Results

Patient population

- As of November 26, 2020, 44 patients were enrolled into 3TIW (n=11) and 2 QD (n=33) dose expansion cohorts • Most patients were male (82%); median age was 61 years in the combined TIW cohorts and 65 years in the combined
- All patients had previously received systemic chemotherapy for advanced disease

Table 1. Baseline demographics and disease characteristics

- Gastric cancer was the most common tumor type (n=20 [TIW: n=1; QD: n=19]; **Table 1**), followed by biliary tract tumors (n=5 [TIW: n=3; QD: n=2]) and esophageal cancer (n=4 [QD: n=4])
- A total of 19 patients with gastric cancer received futibatinib 20 mg QD, 11 of whom had tumors harboring FGFR2 amplifications

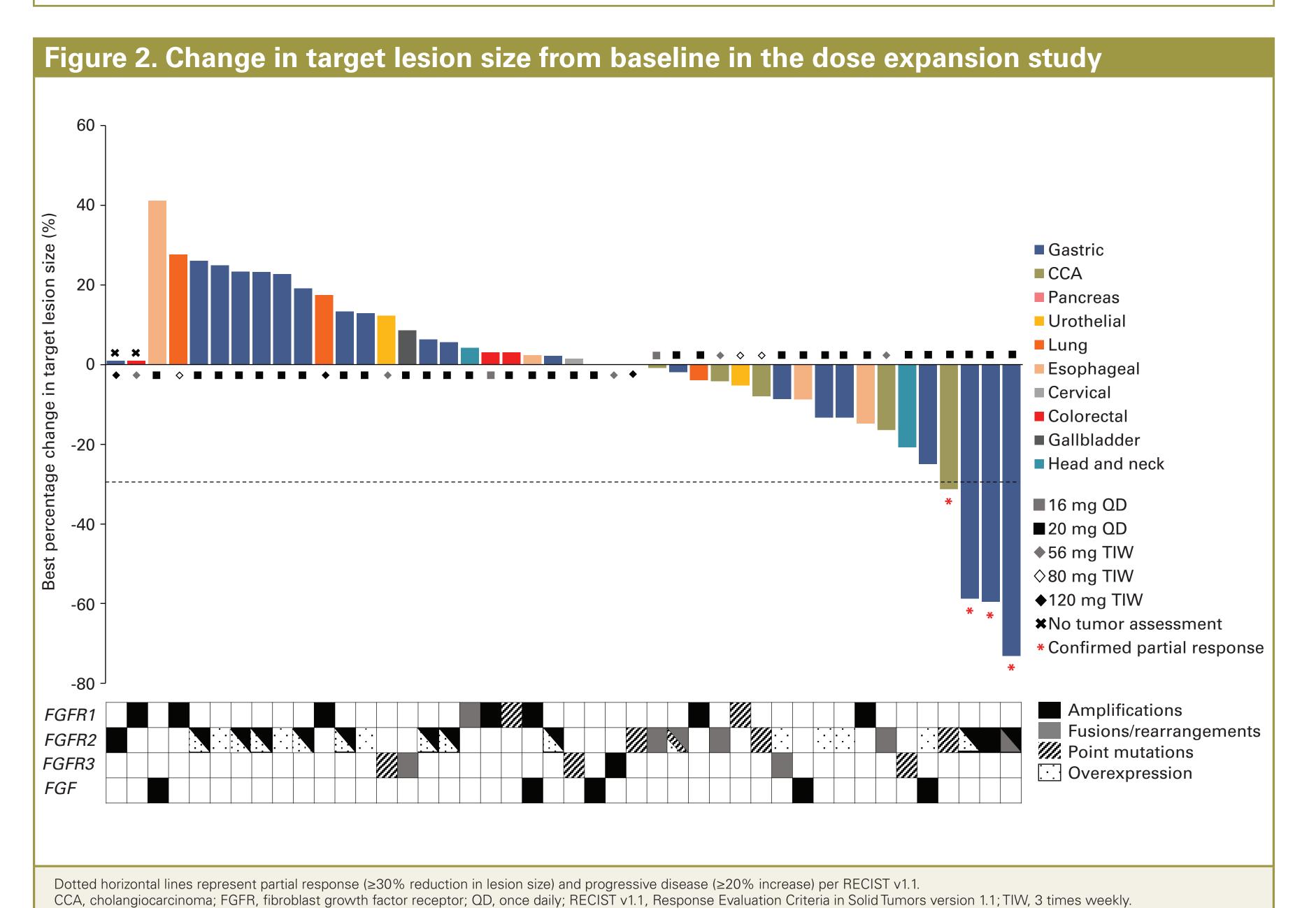
Combined QD cohorts

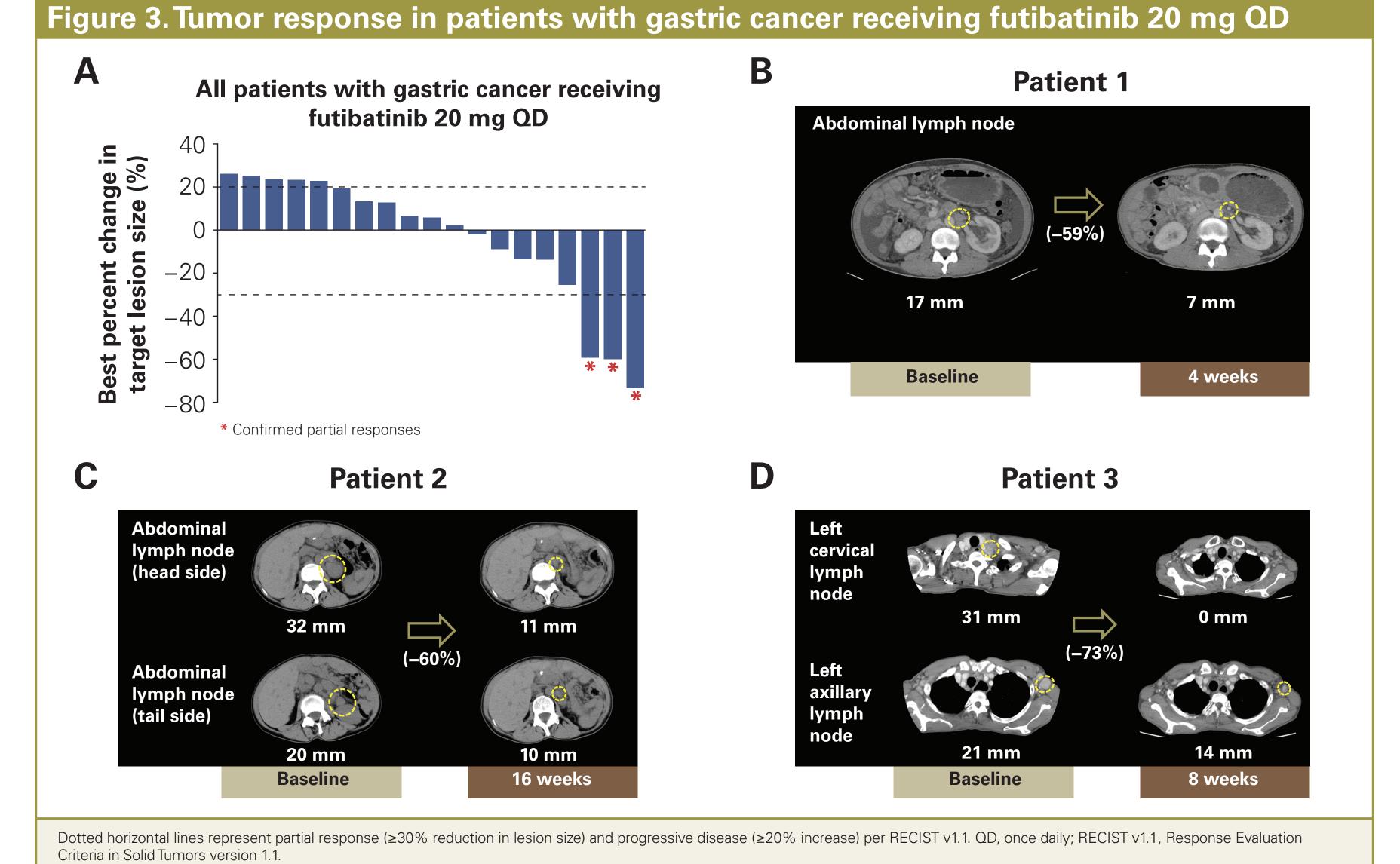
	(11=11)	(11=33)
Median (range), years <65 years, n (%) ≥65 years, n (%)	61 (30–76) 7 (64) 4 (36)	65 (32–77) 16 (48) 17 (52)
Male Female	9 (82) 2 (18)	27 (82) 6 (18)
0 1	7 (64) 4 (36)	25 (76) 8 (24)
Chemotherapy Adjuvant chemotherapy Neoadjuvant chemotherapy	11 (100) 3 (27) 2 (18)	33 (100) 6 (18) 4 (12)
Gastric Biliary tract Esophageal Colorectal Lung Bladder Pancreatic	1 (9) 3 (27) 0 (0) 1 (9) 2 (18) 2 (18) 2 (18)	19 (58) 2 (6) 4 (12) 2 (6) 1 (3) 0 (0) 0 (0) 5 (15)
	<65 years, n (%) ≥65 years, n (%) Male Female 0 1 Chemotherapy Adjuvant chemotherapy Neoadjuvant chemotherapy Gastric Biliary tract Esophageal Colorectal Lung Bladder Pancreatic	Median (range), years 61 (30–76) <65 years, n (%)

ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily; TIW, 3 times weekly.

Antitumor activity in the dose expansion cohorts

- ORR in the QD dosing cohort was 12% (4/33), and the disease control rate (DCR) was 33% (**Figure 2**)
- Partial responses (PRs) were observed in 3 patients with gastric cancer (FGFR2 amplifications) and 1 patient with CCA
- All PRs were observed in patients receiving futibatinib 20 mg QD
- No responses were observed in patients receiving futibatinib TIW
- Among patients with gastric cancer harboring *FGFR2* amplifications who received futibatinib 20 mg QD, the ORR was 16% (3/19) and the DCR was 26% (**Figure 3A**)
- All 3 patients with PRs had received 2 or more previous treatment regimens; they experienced tumor shrinkage ranging from 59% to 73% (Table 2; Figure 3B–D)

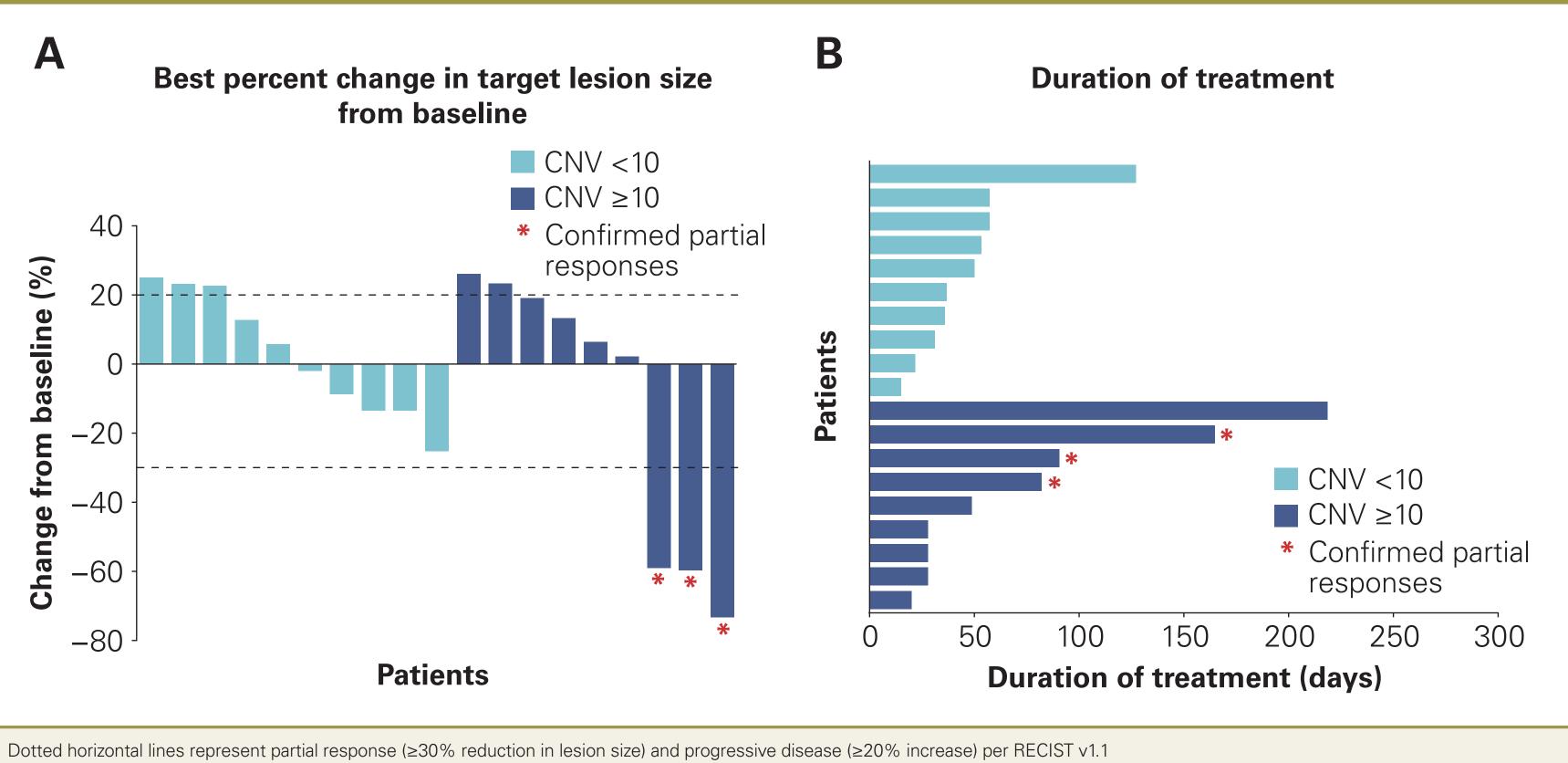




Antitumor activity in gastric cancer by *FGFR2* aberration

- When patients with gastric cancer receiving futibatinib 20 mg QD (n=19) were grouped by FGFR2 amplification levels (CNV <4 or \geq 4 and CNV <10 or \geq 10; **Figure 4**; **Table 3**):
 - Futibatinib activity was most pronounced in patients with advanced gastric cancer harboring FGFR2 CNV ≥10 ■ The ORR was 33% (3/9) in patients with FGFR2 CNV \geq 10 and 0% (0/10) in patients with FGFR2 CNV <10
 - Patients with FGFR2 CNV ≥10 stayed longer on treatment (49 days) than those with FGFR2 CNV <10 (34 days)</p>
 - Similarly, futibatinib activity was greater in patients with tumors harboring *FGFR2* CNV ≥4 than in those with tumors harboring *FGFR2* CNV <4 (**Table 3**)

Figure 4. Tumor response by FGFR2 CNV in patients with gastric cancer receiving futibatinib 20 mg QD



CNV, copy number value; FGFR, fibroblast growth factor receptor; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

- In Japanese patients with advanced solid tumors, futibatinib showed antitumor activity and a safety profile consistent with those of previous futibatinib studies No new safety concerns were noted
- Promising preliminary antitumor activity was observed in patients with advanced gastric cancer harboring *FGFR2* amplifications with CNV ≥10
- Data from this phase 1 trial and the global phase 1 trial form the basis for an ongoing global phase 2 study evaluating futibatinib in patients with gastric cancer harboring FGFR2 amplifications (NCT04189445)

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Conclusions

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Taiho Pharmaceutical.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; QD, once daily; TRAE, treatment-related adverse event.

Table 2. Characteristics of responders with gastric cancer

CNV, copy number value; DCR, disease control rate; FGFR, fibroblast growth factor receptor; ORR, objective response rate

Overall, 31 patients received futibatinib 20 mg QD in the dose expansion study

Safety in patients receiving futibatinib 20 mg QD

≥5.5 mg/dL to <5.5 mg/dL was 4 days (range, 2–21 days)

No patient discontinued treatment because of hyperphosphatemia

Table 4.TRAEs in patients receiving futibatinib 20 mg QD

Median treatment duration, days

(13%; 6%)

Any TRAE, n (%)

Dose interruption

Dose reduction

Discontinuation

Hyperphosphatemia

Decreased appetite

Increased AST

Increased ALT

Subretinal fluid

Hyponatremia

Increased blood creatinine

Diarrhea

Vomiting

Malaise

Action taken because of TRAEs, n (%)

TRAEs in ≥10% of patients, n (%)

patients receiving futibatinib 20 mg QD

FGFR aberration

CNV, copy number value (for FGFR2 amplification); ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; QD, once daily.

• Hyperphosphatemia was the most common treatment-related adverse event (TRAE; **Table 4**), occurring in all

- Hyperphosphatemia resolved with dose modifications and concomitant medications; median time to resolution

• Paronychia was reported in 3 patients receiving futibatinib 20 mg QD (10%); all events were grade 1–2 in severity

• TRAEs were managed with dosing interruptions and reductions; no patient discontinued treatment because of

decreased appetite (interruptions: 26%; reductions: 10%), hyperphosphatemia (19%; 10%), and malaise

Any grade

31 (100)

31 (100)

13 (42)

4 (13)

– The following TRAEs led to dose interruptions/reductions in ≥3 patients receiving futibatinib 20 mg QD:

from a value >7 mg/dL to ≤5.5 mg/dL was 4 days (range, 2–6 days), and median time to resolution from a value

Table 3. Antitumor activity in gastric cancer by FGFR2 amplification levels

60%

- **Acknowledgments** This study is sponsored by Taiho Pharmaceutical Co., Ltd.
- **Contact information** Taiho Pharmaceutical Co., Ltd. tpc.publications@taiho.co.jp Japic Clinical Trials Information JapicCTI-142552

Presented at the European Society for Medical Oncology (ESMO) Congress, September 16–21, 2021.

20-mg QD cohort (n=31)

Grade ≥3

6 (19)

Disclosures Astellas Pharma, AstraZeneca, Boehringer Ingelheim,

Y. Kuboki reports institutional research funding from Amgen Chugai Pharma, Daiichi Sankyo, Genmab, GlaxoSmithKline Incyte, Janssen Oncology, Ono Pharmaceutical, Taiho Pharmaceutical, and Takeda; a consulting or advisory role with Amgen, Boehringer Ingelheim, and Takeda; and honoraria from Baver, Bristol-Myers Squibb Japan, Lilly

Japan, Merck Serono, Ono Pharmaceutical, Sanofi, and

 Professional medical writing and editorial assistance was provided by Vasupradha Vethantham, PhD, Meredith Kalish, PhD, and Jennifer Robertson, PhD, at Ashfield MedComms, an Ashfield Health company

(NJ, USA), funded by Taiho Oncology, Inc.