388P Early tumor shrinkage and depth of response analyses in metastatic colorectal cancer treated with first-line mFOLFOX6 plus panitumumab or bevacizumab: Results from the phase 3 PARADIGM trial

Kei Muro,¹ Jun Watanabe,² Kohei Shitara,³ Kentaro Yamazaki,⁴ Hisatsugu Ohori,⁵ Manabu Shiozawa,⁶ Hirofumi Yasui,⁴ Eiji Oki,⁷ Takeo Sato,⁸ Takeshi Kato,¹¹ Masamitsu Hihara,¹² Junpei Soeda,¹² Kouji Yamamoto,¹³ Kiwamu Akagi,¹⁴ Atsushi Ochiai,¹⁵ Hiroyuki Uetake,¹⁶ Katsuya Tsuchihara,¹⁷ Takayuki Yoshino¹⁸ Department of Clinical Oncology, Aichi Cancer Center, Shizuoka, Japan; ⁵Division of Gastrointestinal Oncology, National Cancer Center, Yokohama City University Medical Center, Shizuoka, Japan; ⁵Division of Gastrointestinal Oncology, Shizuoka, Japan; ⁵Division of Medical Oncology, Japanese Red Cross Ishinomaki Hospital, Miyagi, Japan; ⁵Division of Gastrointestinal Oncology, National Cancer Center, Kanagawa, Japan; ⁴Division of Gastrointestinal Oncology, National Cancer Center, Yokohama, Japan; ⁵Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁵Division of Gastrointestinal Oncology, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Kanagawa, Japan; ⁶Division of Gastrointestinal Oncology, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Kanagawa, Japan; ⁶Division of Gastrointestinal Oncology, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Kanagawa, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, Japan; ⁶Division of Gastrointestinal Oncology, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Kanagawa, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁶Division of Gastrointestinal Oncology, National Cancer Center, Shizuoka, Japan; ⁶Division of Gastrointest Department of Surgery, Kitasato University, School of Medicine, Sagamihara, Japan; ¹⁰Division of Cancer Center, Sapporo, Japan; ¹¹Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; ¹⁶National Hospital, Osaka, Japan; ¹⁵Pathology Business Unit, Takeda Pharmaceutical Company Ltd., Tokyo, Japan; ¹⁴Division of Medical Affairs, Japan; ¹⁴Division of Molecular Diagnosis and Cancer Center, Saitama, Japan; ¹⁴Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, National Cancer Center, Chiba, Japan; ¹⁴Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, National Cancer Center, Saitama, Japan; ¹⁵Pathology Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; ¹⁶National Hospital Organization, Disaster Medical Center, Tokyo, Japan; ¹⁷Division of Molecular Diagnosis and Cancer Center, Saitama, Japan; ¹⁸Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Saitama, Japan; ¹⁹Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Saitama, Japan; ¹⁹Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Saitama, Japan; ¹⁹Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Saitama, Japan; ¹⁹Division, Exploratory Oncology Research & Clinical Trial Center, National Hospital Organ; ¹⁰Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Saitama, Japan; ¹⁰Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Saitama, Japan; ¹⁰Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Saitama, Japan; ¹⁰Division, Exploratory Oncology Research & Clinical Trial Center, Saitama, Japan; ¹⁰Division, Exploratory Oncology Research & Clinical Trial Center, Saitama, Japan; ¹⁰Division, Exploratory Oncology Research & Clinical Trial Center, Saitama, Japan; ¹⁰Division, Exploratory Oncology Research & Clinical Trial Center, Saitama, Japan; ¹⁰Division, Exploratory Oncology Research & Clinical Trial C Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; 18 Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan;

Introduction

• The primary analysis of the PARADIGM trial (NCT02394795) demonstrated that panitumumab plus modified FOLFOX6 (mFOLFOX6) significantly improved overall survival (OS) compared with bevacizumab plus mFOLFOX6 in patients with RAS wild-type (WT) and left-sided metastatic colorectal cancer (mCRC) (Table 1)¹

Table 1: Primary efficacy outcomes from the phase 3 PARADIGM trial							
Parameter	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6	HR (95% CI)				
Left-sided mCRC	n=312	n=292					
Median OS, mo (95% CI)	37.9 (34.1–42.6)	34.3 (30.9–40.3)	0.82 (0.68–0.99); <i>P</i> =0.031				
Median PFS, mo (95% CI)	13.7 (12.7–15.3)	13.2 (11.4–14.5)	0.98 (0.82–1.17)				
Response rate, % (95% CI)	80.2 (75.3–84.5)	68.6 (62.9–74.0)	ΝΑ				
Right-sided mCRC	n=84	n=103					
Median OS, mo (95% CI)	20.2 (15.2–32.0)	23.2 (18.5–29.1)	1.09 (0.79–1.51); <i>P</i> =0.605				
Median PFS, mo (95% CI)	7.7 (6.3–10.6)	10.6 (7.6–13.0)	1.23 (0.91–1.67)				
Response rate, % (95% CI)	54.9 (43.5–65.9)	63.1 (53.0–72.4)	ΝΑ				
Overall population	n=400	n=402					
Median OS, mo (95% CI)	36.2 (32.0–39.0)	31.3 (29.3–34.1)	0.84 (0.72–0.98); <i>P</i> =0.030				
Median PFS, mo (95% CI)	12.9 (11.3–13.6)	12.0 (11.3–13.5)	1.01 (0.87–1.18)				
Response rate, % (95% CI)	74.9 (70.3–79.1)	67.3 (62.4–71.9)	NA				

• Early tumor shrinkage (ETS) and depth of response (DpR) are on-treatment prognostic factors for favorable OS and progression-free survival (PFS) outcomes associated with chemotherapy for mCRC^{2,3} • Here, we report ETS and DpR from the PARADIGM trial and the correlation of these prognostic factors

- with OS and PFS
- The objective was to examine the correlation of ETS with OS and PFS



^a Adjuvant fluoropyrimidine monotherapy allowed if completed >6 months before enrollment. ^b Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgment or curative intent resection. ° Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum. Data cutoff: January 14, 2022

• The relative change in the sum of the longest diameters of target lesions was analyzed between

baseline and 8 weeks of treatment

- ETS was defined as ≥30% decrease in the sum of the longest diameters of target lesions at week 8; OS and PFS were compared in patients with or without ETS with stratification by treatment arm and primary tumor location (left-sided vs right-sided vs overall)
- DpR was defined as the maximum post-baseline percent decrease in the sum diameter of target lesions • No formal hypothesis testing was performed
- Descriptive *P* values were determined based on a two-sided stratified log-rank test

Results

- In patients with left-sided mCRC, the rate of ETS was higher with panitumumab than with bevacizumab (Table 2)
- A similar trend was observed in the overall population

Table 2: Early tumor shrinkage at week 8										
	Left-sided population		Right-sided population		Overall population					
Parameter	Panitumumab + mFOLFOX6 (n=312)	Bevacizumab + mFOLFOX6 (n=292)	Panitumumab + mFOLFOX6 (n=84)	Bevacizumab + mFOLFOX6 (n=103)	Panitumumab + mFOLFOX6 (n=400)	Bevacizumab + mFOLFOX6 (n=402)				
Patients with ETS, n	201	111	30	42	234	156				
Rate of ETS, % (95% CI)	64 (59–70)	38 (32–44)	36 (26–47)	41 (31–51)	59 (54–63)	39 (34–44)				

Acknowledgments

References

- 1. Yoshino T, et al. J Clin Oncol. 2022;40(17 suppl):LBA1. 2. Giessen C, et al. Cancer Sci. 2013;104:718-724.
- 3. Cremolini C, et al. Ann Oncol. 2015;26:1188-1194.

The authors would like to thank the patients, their families, and their caregivers; the PARADIGM investigators and their team members at each study site; and colleagues from Takeda. Professional medical writing assistance was provided by Kalpana Vijayan, PhD, and Lauren Gallagher, RPh, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ,

Abbreviations CI, confidence interval; DpR, depth of response; ECOG, Eastern Cooperative Oncology Group; ETS, Early tumor shrinkage; HR, harzard ratio; mCRC, metastatic colorectal cancer; mFOLFOX6, modified FOLFOX6; NA, not applicable; OS, overall survival;

Presented at the 2022 Annual Meeting of the European Society of Medical Oncology (ESMO), 9–13 September, Paris, France

USA, and funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned

subsidiary of Takeda Pharmaceutical Company Limited. The study was sponsored by Takeda.

		Table 3: Demographic and baseline cha								
		Left-sided population				Right-s				
racteristic	Panitumumab	+ mFOLFOX6	Bevacizumab + mFOLFOX6		Panitumumab + mFOLFOX6					
	ETS n=201	No ETS n=111	ETS n=111	No ETS n=181	ETS n=30	No ETS n=54				
e category, n (%) –64 years –79 years	89 (44.3) 112 (55.7)	49 (44.1) 62 (55.9)	41 (36.9) 70 (63.1)	86 (47.5) 95 (52.5)	11 (36.7) 19 (63.3)	15 (27.8) 39 (72.2)				
nale, n (%)	57 (28.4)	47 (42.3)	35 (31.5)	56 (30.9)	13 (43.3)	30 (55.6)				
DG performance status, n (%)	169 (84.1) 32 (15.9)	92 (82.9) 19 (17.1)	91 (82.0) 20 (18.0)	140 (77.3) 41 (22.7)	28 (93.3) 2 (6.7)	37 (68.5) 16 (29.6)				
nary tumor location, n (%) ft-sided ght-sided	202 (100.0) 0	111 (100.0) 0	111 (100.0) 0	181 (100.0) 0	0 30 (100.0)	0 54 (100.0)				
nber of metastatic organs, n (%)	98 (48.8) 103 (51.2)	57 (51.4) 54 (48.6)	58 (52.3) 53 (47.7)	89 (49.2) 92 (50.8)	14 (46.7) 16 (53.3)	26 (48.1) 28 (51.9)				
astatic site, n (%) ver ver as the only metastatic site	164 (81.6) 71 (35.3)	61 (55.0) 19 (17.1)	86 (77.5) 43 (38.7)	120 (66.3) 46 (25.4)	20 (66.7) 7 (23.3)	29 (53.7) 7 (13.0)				
or treatment, n (%) imary tumor resection idiotherapy ljuvant chemotherapy	127 (63.2) 1 (0.5) 10 (5.0)	58 (52.3) 1 (0.9) 7 (6.3)	71 (64.0) 1 (0.9) 6 (5.4)	122 (67.4) 2 (1.1) 10 (5.5)	19 (63.3) 0 2 (6.7)	32 (59.3) 0 3 (5.6)				

• In the left-sided population, patients with ETS had longer PFS and OS than those without ETS, regardless of treatment with panitumumab or bevacizumab (Figure 2) Figure 2: Survival outcomes by ETS in patients in the left-sided population



• In the right-sided population, patients in the panitumumab arm who had ETS had longer OS than patients without ETS (Figure 3)



• In the overall population, patients with ETS had longer PFS and OS than those without ETS, regardless of treatment with panitumumab or bevacizumab (Figure 4)



Disclosures

KM: Consulting/advisory role (Chugai Pharma, Astra Zeneca, Ono Pharmaceutical, Amgen); honoraria (Chugai Pharma, Ono Pharmaceutical, Takeda, Lilly, Bayer, Sanofi, Bristol Myers Squibb, Taiho Pharmaceutical); research grant (Taiho Pharmaceutical, Astellas Pharma, Amgen Astellas Biopharma, [rest to institution:] MSD, Daiichi Sankyo, Shionogi, Kyowa Kirin, Gilead Sciences, Merck Serono, Pfizer, Sanofi, PAREXEL, Mediscience Planning, Sumitomo Dainippon Pharma, Solasia Pharma); JW: Speakers bureau (Covidien Japan, Johnson & Johnson/Janssen, Lilly Japan); research funding (to institution: Medtronic, TERUMO); KS: Honoraria (Bristol Myers Squibb, Takeda); consulting/advisory role (Lilly, Bristol Myers Squibb, Takeda, Pfizer, Ono Pharmaceutical, MSD, Taiho, Novartis, Abbvie, GSK, Daiichi Sankyo, Boehringer Ingelheim, Janssen); research funding (all to institution: MSD,

PFS, progression-free survival; WT, wild type

racteristics **Overall population** Panitumumab + mFOLFOX6 Bevacizumab + mFOLFOX6 Bevacizumab + mFOLFOX6 No ETS ETS No ETS ETS No ETS ETS n=234 n=156 n=246 n=42 n=61 n=166 16 (38.1) 23 (37.7) 100 (42.7) 64 (38.6) 58 (37.2) 110 (44.7) 26 (61.9) 38 (62.3) 134 (57.3) 102 (61.4) 98 (62.8) 136 (55.3) 77 (46.4) 54 (34.6) 80 (32.5) 18 (42.9) 24 (39.3) 71 (30.3) 47 (77.0) 129 (77.7) 191 (77.6) 35 (83.3) 199 (85.0) 128 (82.1) 7 (16.7) 14 (23.0) 35 (15.0) 36 (21.7) 28 (17.9) 55 (22.4) 201 (85.9) 111 (66.9) 111 (71.2) 181 (73.6) 42 (100.0) 61 (100.0) 30 (12.8) 54 (32.5) 42 (26.9) 61 (24.8) 20 (47.6) 24 (39.3) 113 (48.3) 83 (50.0) 79 (50.6) 115 (46.7) 121 (51.7) 83 (50.0) 77 (49.4) 22 (52.4) 37 (60.7) 131 (53.3) 115 (73.7) 26 (61.9) 185 (79.1) 90 (54.2) 163 (66.3) 40 (65.6) 26 (15.7) 7 (16.7) 14 (23.0) 79 (33.8) 51 (32.7) 62 (25.2) 104 (66.7) 30 (71.4) 43 (70.5) 148 (63.2) 91 (54.8) 168 (68.3) 1 (0.4) 1 (0.6) 1 (0.6) 2 (0.8) 3 (4.9) 12 (5.1) 10 (6.0) 7 (4.5) 13 (5.3)





Daiichi Sankyo, Taiho, Chugai Pharma, Ono Pharmaceutical, Astellas Pharma, Medi Science, Eisai, Amgen); KY: Honoraria (Chugai Pharma, Daiichi Sankyo, Yakult Honsha, Takeda, Bayer, Merck Serono, Taiho Pharmaceutical, Lilly, Sanofi, Ono Pharmaceutical, MSD, Bristol Myers Squibb); research funding (to institution: Taiho Pharmaceutical); **HO:** The author has no relationships to disclose; **MS:** The author has no relationships to disclose; HY: The author has no relationships to disclose; EO: Speakers bureau (Chugai Pharma, Lilly Japan, Takeda, Ono Pharmaceutical, Bayer Yakuhin, Bristol Myers Squibb Japan); **TS:** Consulting/advisory role (Takeda); speakers bureau (Chugai Pharma, Lilly Japan, Taiho Oncology, Takeda, Bayer Yakuhin, Ono Yakuhin, Daiichi Sankyo/UCB Japan); TN: Honoraria (Chugai Pharma, Taiho Pharmaceutical, Kaken, Daiichi Sankyo, Eli Lilly Japan, Takeda, Merck, Bayer, Boehringer Ingelheim); research funding (to institution: Chugai, Taiho, Kaken, Daiichi-Sankyo, Eli Lilly Japan); **YK:** Speakers

bureau (Ono, Taiho, Chugai, Eli Lilly, Bayer Yakuhin); research funding (Ono, Taiho, Daiichi Sankyo, Chugai, IQVIA); TK: Honoraria (Chugai, Yakult Honsha, Ono Pharmaceutical, Takeda, Lilly Japan, Taiho Pharmaceutical, Asahi Kasei); research funding (Chugai); MH: Employment (Takeda); JS: Employment (Takeda); KY: Honoraria (Chugai, J-Pharma, Johokiko, Triceps, CMIC Holdings); research funding (Taiho, Boehringer Ingelheim, Takeda, Daiichi Sankyo, Astellas); KA: The author has no relationships to disclose; AO: The author has no relationships to disclose; HU: Speakers bureau (Takeda, Chigai, Taiho); KT: Honoraria (Chugai Pharma, Novartis, Takeda, Miyarisan Pharmaceutical, Bristol Myers Squibb Japan, AstraZeneca); TY: Honoraria (Chugai Pharma, Merck, Bayer Yakuhin, Ono Pharmaceutical, MSD); research funding (to institution: MSD, Daiichi

(Figure 5)





Horizontal dotted line at 30% indicates response per RECIST v1.1 Depth of response was assessed in patients with measurable lesions at baseline

Conclusions

- but not with bevacizumab

Future Directions: Biomarker Multi-omics Analysis

- Pre-treatment
- ribonucleic acid; TMB, tumor mutational burden; WT, wild type

• In left-sided and overall populations, DpR was greater with panitumumab compared with bevacizumab

• Regardless of treatment with panitumumab or bevacizumab, patients with ETS had favorable survival outcomes compared with those without ETS • Patients with left-sided mCRC treated with panitumumab had a higher rate of ETS and a greater DpR

compared with patients treated with bevacizumab • In patients with right-sided mCRC, ETS appeared to predict better survival outcomes with panitumumab

– This finding highlights the need for additional analyses to identify biomarkers that may predict a benefit with panitumumab in this population

• A large-scale biomarker analysis is currently underway using plasma and tumor tissue samples collected pre- and post-treatments (NCT02394834)

Potential biomarkers on outcomes will be reported in upcoming meetings

• Biomarkers that may predict a benefit with panitumumab in patients with mCRC will be identified



deoxyribonucleic acid; IF, immunofluorescence; IFN, interferon gene signature; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; RNA,

Sankyo, Ono Pharmaceutical, Taiho Pharmaceutical, Amgen, Sanofi, Pfizer, Genomedia Inc., Sysmex, Nippon Boehringer Ingelheim, Chugai Pharma)

For an e-Print, scan this QR code. Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from the authors of this poster.

