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

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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)				

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		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

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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)





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(Figure 5)



Conclusions

- but not with bevacizumab

Future Directions: Biomarker Multi-omics Analysis

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

Depth of response was assessed in patients with measurable lesions at baseline

• 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)

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