Negative hyperselection of patients with *RAS* wild-type metastatic colorectal cancer for panitumumab: A biomarker study of the phase III PARADIGM trial

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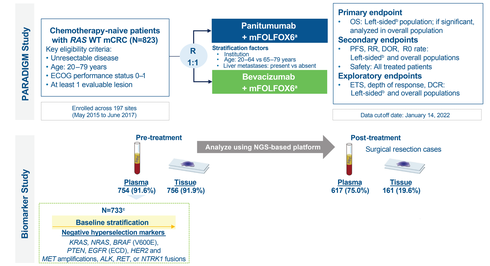
Introduction

- The phase 3 PARADIGM trial (NCT02394795) met the primary endpoint, demonstrating the superiority of first-line panitumumab in combination with modified FOLFOX6 (mFOLFOX6) vs bevacizumab in combination with mFOLFOX6 in the left-sided and overall *RAS* wild-type (WT) metastatic colorectal cancer (mCRC) populations[1]
  - Left-sided population: median overall survival (mOS), 37.9 vs 34.3 months; hazard ratio (HR), 0.82 (95.798% CI: 0.68–0.99); *P*=0.031
  - Overall population: mOS, 36.2 vs 31.3 months; HR, 0.84 (95% CI: 0.72–0.98); *P*=0.030
  - Right-sided population (exploratory endpoint): mOS, 20.2 vs 23.2 months; HR, 1.09 (95% CI: 0.79–1.51)
- The PARADIGM biomarker study (NCT02394834) was designed to investigate potential biomarkers related to primary and secondary resistance of each therapy by using tumor tissue and circulating tumor DNA (ctDNA)
- In this analysis, we evaluated the usefulness of negative hyperselection by gene alterations in ctDNA related to primary resistance to anti-epidermal growth factor receptor (EGFR) therapy in patients enrolled in the PARADIGM biomarker study

Methods

Figure 1: Study design



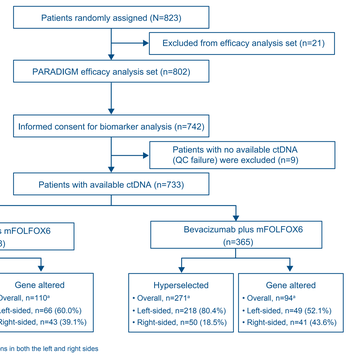
[a]Until disease progression, unacceptable toxicity, withdrawal of consent, investigator's judgement, or curative intent resection; [b]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum; [c]Patients with available ctDNA among those included in efficacy analysis set in the PARADIGM study
ALK, anaplastic lymphoma kinase; Amp, amplification; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; DCR, disease control rate; DOR, duration of response; ECD, extracellular domain; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; *HER2*, human epidermal growth factor receptor 2; *MET*, mesenchymal epithelial transition factor receptor; NGS, next-generation sequencing; *NTRK1*, neurotrophic tyrosine receptor kinase 1; PFS, progression-free survival; *PTEN*, phosphatase and tensin homolog; R, randomization; R0, margin-negative resection; *RET*, rearranged during transfection; RR, response rate; WT, wild-type

- Baseline plasma ctDNA (>10 ng/mL and >10 nM DNA) from patients enrolled in the biomarker study was assessed using a custom panel (PlasmaSELECT-R 91, PGDx)
- The panel was designed to detect mutations, amplifications, and rearrangements in 90, 26, and 3 mCRC-related genes, respectively, as well as microsatellite instability
  - Targeted genomic regions spanned 250 kb
- Prespecified gene alterations for hyperselection that have been reported to confer resistance to anti-EGFR antibody therapy included *KRAS*, *NRAS*, *BRAF* (V600E), *PTEN*, and extracellular domain *EGFR* mutations, *HER2* and *MET* amplifications, and *ALK*, *RET*, or *NTRK1* fusions[2-5]
- Hyperselection status (all negative vs gene altered [any positive biomarker]) was correlated with OS, PFS, and RR in the PARADIGM study population

Results

- ctDNA status was evaluable in 91% (733/802) of patients (**Figure 2**; **Figure 3**)
  - 28% of patients had at least 1 gene alteration
  - 72% of patients had no gene alterations and were classified as hyperselected patients
- When stratified by primary tumor sidedness, any gene alteration was detected in 21% of patients with left-sided mCRC and 50% of patients with right-sided mCRC

Figure 2: Disposition

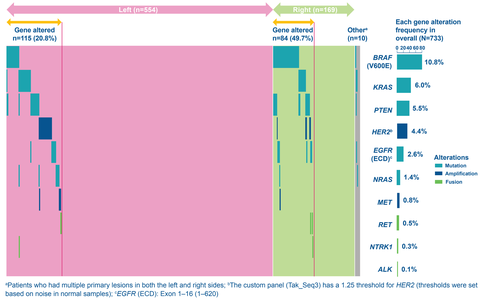


[a]Some patients had multiple primary lesions in both the left and right sides
QC, quality control

- Baseline characteristics of patients who were hyperselected or had gene alteration within each treatment arm and across left- and right-sided mCRC populations are shown in **Table 1**
- The OncoPrint profile of mutational frequencies and types of alterations of the 10 genes sequenced are shown in **Figure 3**

Figure 3: Co-occurring gene alterations in left- and right-sided tumors

	Left-sided (n=554)	Right-sided (n=169)	Other (n=10)	Overall (N=733)
Gene altered n (%)	115 (20.8)	84 (49.7)	5 (50)	204 (27.8)
Hyperselected n (%)	439 (79.2)	85 (50.3)	5 (50)	529 (72.2)



[a]Patients who had multiple primary lesions in both the left and right sides; [b]The custom panel (Tak_Seq3) has a 1.25 threshold for *HER2* (thresholds were set based on noise in normal samples); [c]*EGFR* (ECD): Exon 1–16 (1–620)

Table 2: Number of genetic alterations in ctDNA

Gene alteration, n (%)	Overall population (N=733)		Left-sided population (n=554)		Right-sided population (n=169)	
	Panitumumab (n=368)	Bevacizumab (n=365)	Panitumumab (n=287)	Bevacizumab (n=267)	Panitumumab (n=78)	Bevacizumab (n=91)
BRAF (V600E)	43 (11.7)	36 (9.9)	17 (5.9)	8 (3.0)	26 (33.3)	27 (29.7)
KRAS	22 (6.0)	23 (6.3)	11 (3.8)	15 (5.6)	9 (11.5)	6 (6.6)
PTEN	23 (6.3)	17 (4.7)	12 (4.2)	8 (3.0)	10 (12.8)	9 (9.9)
HER2 amplification	19 (5.2)	14 (3.8)	16 (5.6)	11 (4.1)	3 (3.8)	2 (2.2)
EGFR (ECD)	12 (3.3)	7 (1.9)	7 (2.4)	3 (1.1)	5 (6.4)	3 (3.3)
NRAS	10 (2.7)	3 (0.8)	6 (2.1)	2 (0.7)	1 (1.3)	0
MET amplification	3 (0.8)	2 (0.5)	3 (1.0)	2 (0.7)	0	0
RET fusion	2 (0.5)	2 (0.5)	0	2 (0.7)	2 (2.6)	0
NTRK1 fusion	1 (0.3)	1 (0.3)	0	1 (0.4)	1 (1.3)	0
ALK fusion	0	1 (0.3)	0	0	0	1 (1.1)

Table 1: Baseline patient characteristics

Characteristic	Overall population (N=733)				Left-sided population (N=554)				Right-sided population (N=169)			
	Hyperselected		Gene Altered		Hyperselected		Gene Altered		Hyperselected		Gene Altered	
	Panitumumab +mFOLFOX6 n=258	Bevacizumab +mFOLFOX6 n=271	Panitumumab +mFOLFOX6 n=110	Bevacizumab +mFOLFOX6 n=94	Panitumumab +mFOLFOX6 n=221	Bevacizumab +mFOLFOX6 n=218	Panitumumab +mFOLFOX6 n=66	Bevacizumab +mFOLFOX6 n=49	Panitumumab +mFOLFOX6 n=35	Bevacizumab +mFOLFOX6 n=50	Panitumumab +mFOLFOX6 n=43	Bevacizumab +mFOLFOX6 n=41
Age category, n (%)												
20–64 years	104 (40.3)	116 (42.8)	45 (40.9)	36 (38.3)	94 (42.5)	91 (41.7)	30 (45.5)	23 (46.9)	10 (28.6)	24 (48.0)	15 (34.9)	12 (29.3)
65–79 years	154 (59.7)	155 (57.2)	65 (59.1)	58 (61.7)	127 (57.5)	127 (58.3)	36 (54.5)	26 (53.1)	25 (71.4)	26 (52.0)	28 (65.1)	29 (70.7)
Sex, female, n (%)	97 (33.7)	83 (30.6)	47 (42.7)	37 (39.4)	71 (32.1)	66 (30.3)	23 (34.8)	15 (30.6)	16 (45.7)	17 (34.0)	23 (53.5)	21 (51.2)
ECOG performance status, n (%)												
0	219 (84.9)	213 (78.6)	85 (77.3)	75 (80.0)	187 (84.6)	171 (78.4)	54 (81.8)	39 (79.6)	31 (88.6)	39 (78.0)	31 (72.1)	33 (80.5)
1	39 (15.1)	58 (21.4)	24 (21.8)	19 (20.2)	34 (15.4)	47 (21.6)	12 (18.2)	10 (20.4)	4 (11.4)	11 (22.0)	11 (25.6)	8 (19.5)
Primary tumor location, n (%)												
Left-sided	221 (85.7)	218 (80.4)	66 (60.0)	49 (52.1)	221 (100)	218 (100)	66 (100)	49 (100)	0	0	0	0
Right-sided	35 (13.6)	50 (18.5)	43 (39.1)	41 (43.6)	0	0	0	0	35 (100)	50 (100)	43 (100)	41 (100)
Number of metastatic organs, n (%)												
1	141 (54.7)	139 (51.3)	40 (36.4)	39 (41.5)	120 (54.3)	115 (52.8)	21 (31.8)	20 (40.8)	20 (57.1)	22 (44.0)	19 (44.2)	18 (43.9)
≥2	117 (45.3)	132 (48.7)	70 (63.6)	55 (58.5)	101 (45.7)	103 (47.2)	45 (68.2)	29 (59.2)	15 (42.9)	28 (56.0)	24 (55.8)	23 (56.1)
Metastatic site, n (%)												
Liver	172 (66.7)	182 (67.2)	82 (74.5)	66 (70.2)	153 (69.2)	147 (67.4)	55 (83.3)	38 (77.6)	18 (51.4)	32 (64.0)	27 (62.8)	25 (61.0)
Liver as only site of metastasis	73 (28.3)	78 (28.8)	23 (20.9)	24 (25.5)	66 (29.9)	64 (29.4)	16 (24.2)	16 (32.7)	6 (17.1)	12 (24.0)	7 (16.3)	7 (17.1)
Prior treatment, n (%)												
Primary tumor resection	165 (64.0)	184 (67.9)	57 (51.8)	60 (63.8)	136 (61.5)	145 (66.5)	35 (53.0)	30 (61.2)	27 (77.1)	36 (72.0)	22 (51.2)	27 (65.9)

Figure 4: Survival outcomes in the overall population analyzed for ctDNA

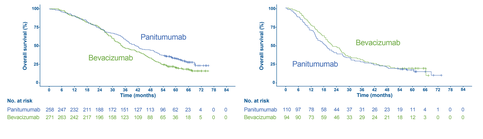


Figure 5: Survival outcomes in the left-sided mCRC population analyzed for ctDNA

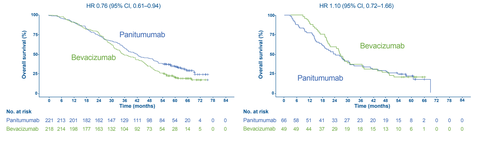


Figure 6: Survival outcomes in the right-sided mCRC population analyzed for ctDNA

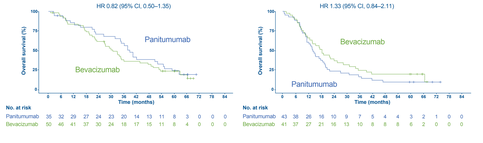


Figure 7: Overall survival in ctDNA-analyzed population

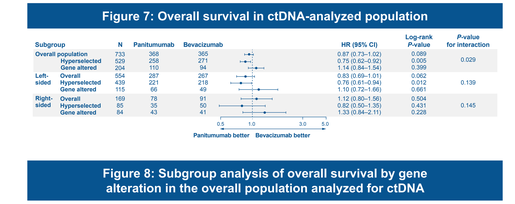
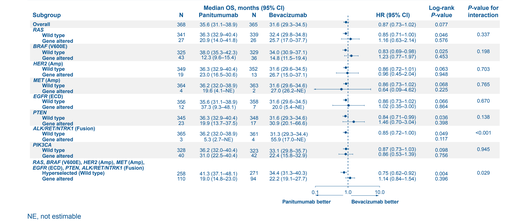


Figure 8: Subgroup analysis of overall survival by gene alteration in the overall population analyzed for ctDNA



NE, not estimable

Figure 9: Progression-free survival in ctDNA-analyzed population

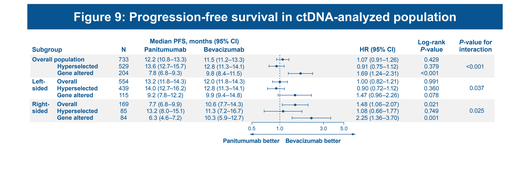
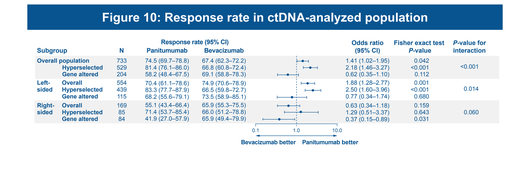


Figure 10: Response rate in ctDNA-analyzed population



Conclusions

- In hyperselected patients with no gene alterations, OS tended to be longer with panitumumab than with bevacizumab regardless of primary tumor sidedness
  - Overall: mOS, 41.3 vs 34.4 months; HR, 0.75 (95% CI: 0.62–0.92)
  - Left-sided: mOS, 42.1 vs 35.5 months; HR, 0.76 (95% CI: 0.61–0.94)
  - Right-sided: mOS, 38.9 vs 30.9 months; HR, 0.82 (95% CI: 0.50–1.35)
- OS was similar or inferior with panitumumab vs bevacizumab regardless of the primary tumor sidedness in patients with any of these gene alterations
- Negative hyperselection using ctDNA analysis rather than tumor sidedness may identify appropriate patients for first-line panitumumab over bevacizumab
- These results warrant further validation in additional cohorts

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