Abstract 160

First-Line Treatment with Modified FOLFOX6 (mFOLFOX6) + Panitumumab or Bevacizumab in Patients with *RAS/BRAF* Wild-Type Metastatic Colorectal Carcinoma

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BACKGROUND

- Panitumumab is an epidermal growth factor receptor (EGFR) inhibitor that is indicated in the EU in combination with FOLFOX or FOLFIRI for the treatment of patients with metastatic colorectal cancer (mCRC)[1]
- In the phase II PEAK study, first-line panitumumab + mFOLFOX6 was associated with longer median overall survival than bevacizumab + mFOLFOX6 in patients with *RAS* wild-type (WT) mCRC (41.3 vs 28.9 months, respectively, hazard ratio [HR]: 0.63 [95% confidence intervals {CI}: 0.39–1.02]; p=0.058)[2]
  - RECIST overall response rates (ORR) were similar between treatments[2]
  - RECIST does not fully take into account the timing, depth and duration of response (DoR) – all of which may influence long-term outcomes in mCRC[3,4]
- While the presence of *RAS* mutations appear to be a predictive rather than prognostic biomarker in mCRC,[5] *BRAF* mutations appear to be linked with poor prognosis, irrespective of first-line treatment received[5,6]
- Here, we report exploratory analyses of tumour assessments beyond RECIST in the *RAS/BRAF* WT population of PEAK

METHODS

Study Design

- PEAK (NCT00819780) was a 1:1 randomised phase II study of first-line panitumumab (6 mg/kg Q2W) + mFOLFOX6 vs bevacizumab (5 mg/kg Q2W) + mFOLFOX6 in patients with previously untreated *KRAS* exon 2 WT mCRC

Key Inclusion Criteria

- Aged ≥18 years with an Eastern Cooperative Oncology Group performance score of 0 or 1
- Histologically or cytologically confirmed mCRC with unresectable metastatic disease
- WT *KRAS* exon 2 (codons 12 and 13) tumour status (confirmed by a validated testing method)
- ≥1 unidimensionally measurable lesion of ≥20 mm (per modified RECIST guidelines)
- No prior chemotherapy, anti-EGFR therapy or bevacizumab therapy for mCRC

Analyses

- Banked tumour samples for patients with *KRAS* exon 2 WT tumours were tested for prespecified mutations in *NRAS* exon 2 (codons 12 and 13) and *KRAS* and *NRAS* exons 3 (codons 59 and 61) and 4 (codons 117 and 146) using bidirectional Sanger sequencing and WAVE-based SURVEYOR® scan kits (Transgenomic)
  - Mutations were also assessed in exon 15 of *BRAF* (codon 600: exploratory analysis)
- ORR (investigator assessed [secondary endpoint]), median DoR (from first confirmed response to disease progression or death [secondary endpoint]), time to response (TTR: from randomisation to first confirmed response) and depth of response (DpR; the percentage of tumour shrinkage at nadir or progression) were calculated in *RAS/BRAF* WT patients by treatment
- DpR has a positive value for tumour reduction and a negative value for tumour growth and is defined for each patient in the following way:
  - If a patient experiences any tumour reduction while on treatment then the DpR is the greatest percentage of tumour shrinkage observed vs baseline
  - If a patient does not experience tumour reduction (i.e. only tumour growth or no change), then the DpR is the percentage of tumour shrinkage (vs baseline) at the time of progression, if the patient experiences disease progression (not death). The value will be either 0 or negative by definition
  - Data for any patients experiencing neither tumour reduction nor progression were excluded from the analysis of DpR
- Mean percentage change in tumour load and carcinoembryonic antigen (CEA) levels vs baseline (over time) were assessed
- An exploratory analysis of early tumour shrinkage (ETS) was also performed by treatment; ETS was defined as the proportion of patients with ≥30% or ≥20% tumour shrinkage at week 8
- Median progression-free survival (PFS; primary endpoint) was calculated for patients with/without ≥30% tumour shrinkage at week 8, overall and by treatment
- Overall resection rates and 6-month PFS rates by resection status were calculated by treatment
- All analyses and p-values are descriptive

RESULTS

Patients

- Overall, 156 patients in PEAK had *RAS/BRAF* WT tumours; baseline demographics and disease characteristics were similar between treatment groups (Table 1)
  - *BRAF* mutations were found in tumours from 14 patients (panitumumab + mFOLFOX6 n=11; bevacizumab + mFOLFOX6 n=3)

Table 1. Baseline Demographics and Disease Characteristics (RAS/BRAF Wild-Type Patients)

	Panitumumab + mFOLFOX6 (n=77)	Bevacizumab + mFOLFOX6 (n=79)
Male sex, n (%)	50 (65)	55 (70)
Age, years – median (range)	62 (23–82)	60 (39–82)
ECOG PS, n (%)		
0 or 1	77 (100)	78 (99)
Missing	0 (0)	1 (1)
Primary tumour diagnosis, n (%)		
Colon	53 (69)	54 (68)
Rectum	24 (31)	25 (32)
Sites of metastases, n (%)		
Liver only	21 (27)	22 (28)
Liver + other	37 (48)	33 (42)
Other only	19 (25)	24 (30)
Number of metastatic organs, median (range)	2.0 (1.0–5.0)	2.0 (0.0–4.0)
Sum of longest diameters of all target lesions, mm – mean (SD)	131.6 (123.5)	109.6 (85.3)
CEA levels, µg/L – median (range)	12.6 (0.5–8453.0)	15.2 (0.7–4888.7)

CEA = carcinoembryonic antigen; ECOG PS = Eastern Cooperative Oncology Group performance status; SD = standard deviation

Efficacy

- Overall, 155 patients with *RAS/BRAF* WT mCRC were included in the ORR analysis and 143 had tumour shrinkage data available at baseline and week 8
- ORRs were similar for the panitumumab + mFOLFOX6 and bevacizumab + mFOLFOX6 arms (p=0.80; Table 2)

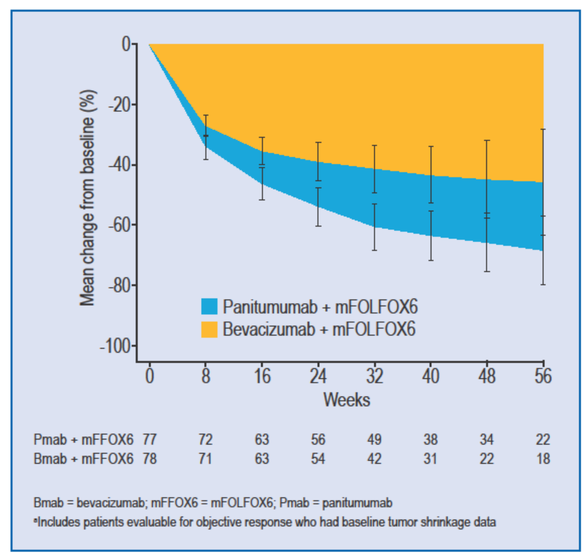
Table 2. Response Outcomes (RAS/BRAF Wild-Type Patients)

	Panitumumab + mFOLFOX6 (n=77)[a]	Bevacizumab + mFOLFOX6 (n=78)[a]
Best response over study, n (%)		
Complete response	3 (3.9)	1 (1.3)
Partial response	47 (61.0)	48 (61.5)
Stable disease	22 (28.6)	21 (26.9)
Disease progression	1 (1.3)	4 (5.1)
Unevaluable/not done	4 (5.2)	4 (5.1)
Objective response, n (%) [95% CI])	50 (64.9) [53.2–75.5]	49 (62.8) [51.1–73.5]

CI = confidence intervals; [a]Local tumour response analysis set

- TTR was numerically shorter in the panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6 arm (median: 2.1 [95% CI: 1.9–3.7] vs 3.8 [95% CI: 2.1–5.4] months, respectively; HR: 0.86 [95% CI: 0.58–1.27]; p=0.44)
- Longer DoR was observed with panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6 (median: 13.0 [95% CI: 10.1–14.4] vs 8.4 [95% CI: 5.9–9.3] months, respectively; HR: 0.49 [95% CI: 0.29–0.81]; p=0.0052)
- DpR was also greater in the panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6 group (median: 74% [Q1, Q3: 50, 91] vs 49% [Q1, Q3: 39, 69]; p=0.0009)
- More *RAS/BRAF* WT patients in the panitumumab + mFOLFOX6 arm had ≥30% ETS at week 8 compared with the bevacizumab + mFOLFOX6 arm (p=0.019; Table 3)
  - Similar results were seen in the analysis using the ≥20% ETS criterion
- For those achieving ≥30% ETS, numerically longer median PFS was seen in the panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6 group (Table 3 and Figure 3)
  - Intra-treatment comparisons are shown in Table 4
- When treatment arms were combined, median PFS was longer in patients with ETS ≥30% than in those with ETS <30% (12.9 vs 10.6 months; HR: 0.55 [95% CI: 0.37–0.83]; p=0.004)
  - Similar results were seen in the analysis using the ≥20% ETS criterion
- The mean percentage change from baseline in tumour load (sum of the longest diameters of all target lesions) appeared to favour panitumumab at all measured time points (Figure 1)
  - Figure 1 shows tumour load data at each scheduled visit; following progression, patients were only followed-up for survival and no further CT scans were taken

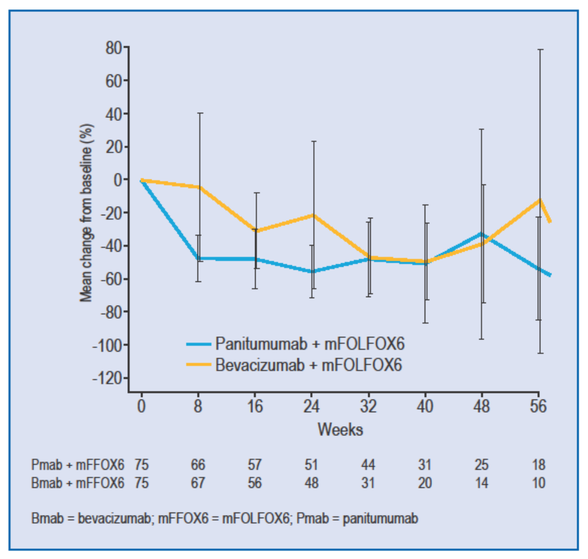
Figure 1. Mean (95% Confidence Intervals) Percentage Change from Baseline in Tumour Load (Sum of All Target Lesions) Over Time (RAS/BRAF Wild-Type Patients)[a]



Bmab = bevacizumab; mFFOX6 = mFOLFOX6; Pmab = panitumumab
[a]Includes patients evaluable for objective response who had baseline tumor shrinkage data

- Although CIs were wide, mean percentage decrease in CEA levels appeared to be more rapid in the panitumumab arm, with both arms associated with an approximate 50% decrease in CEA by week 32 (Figure 2)

Figure 2. Mean (95% Confidence Intervals) Percentage Change from Baseline in Carcinoembryonic Antigen Over Time (RAS/BRAF Wild-Type Patients)



Bmab = bevacizumab; mFFOX6 = mFOLFOX6; Pmab = panitumumab

- The proportion of patients with a ≥75% reduction in CEA levels was 57% vs 47% for the panitumumab vs bevacizumab arms, respectively (odds ratio: 0.67 [95% CI: 0.33–1.38]; p=0.32)

Table 3. Impact of Early Tumour Shrinkage on Progression-Free Survival – Between Treatment Comparisons (RAS/BRAF Wild-Type Patients)

	Tumour shrinkage at week 8			
	<30%		≥30%	
	Pmab + mFOLFOX6	Bmab + mFOLFOX6	Pmab + mFOLFOX6	Bmab + mFOLFOX6
n (%)	25 (35)	39 (55)	47 (65)	32 (45)
PFS, months – median (95% CI)	11.6 (6.1–15.4)	10.6 (7.4–12.9)	14.6 (10.9–18.2)	10.1 (7.5–17.2)
HR (95% CI); p-value[a]	0.80 (0.44–1.45); 0.46		0.66 (0.37–1.17); 0.15	

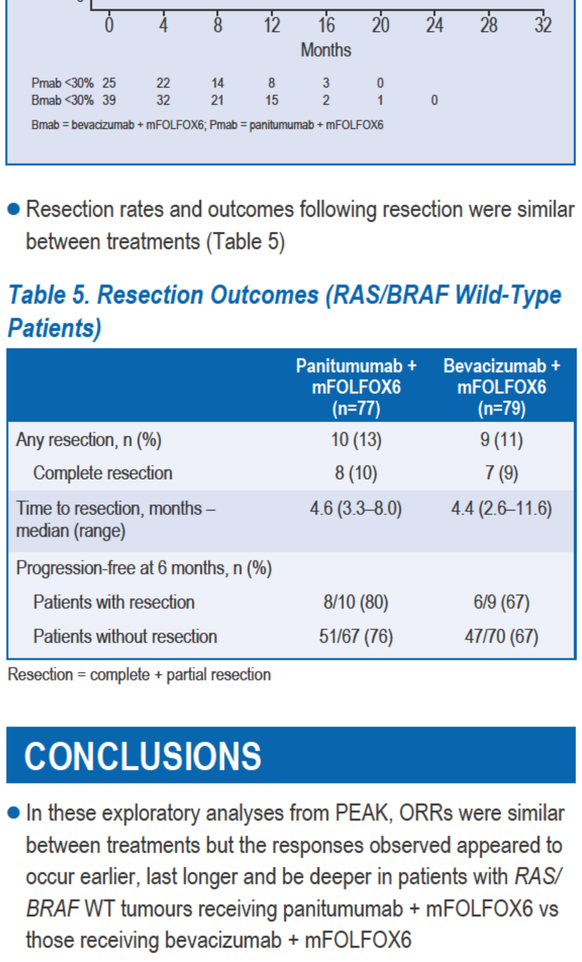
Bmab = bevacizumab; CI = confidence intervals; HR = hazard ratio; PFS = progression-free survival; Pmab = panitumumab
[a]Statistics shown are for between-treatment comparisons

Table 4. Impact of Early Tumour Shrinkage on Progression-Free Survival – Intra-Treatment Comparisons (RAS/BRAF Wild-Type Patients)

	Tumour shrinkage at week 8			
	Panitumumab + mFOLFOX6		Bevacizumab + mFOLFOX6	
	<30%	≥30%	<30%	≥30%
n (%)	25 (35)	47 (65)	39 (65)	32 (45)
PFS, months – median (95% CI)	11.6 (6.1–15.4)	14.6 (10.9–18.2)	10.6 (7.4–12.9)	10.1 (7.5–17.2)
HR (95% CI); p-value[a]	0.52 (0.28–0.97); 0.039		0.69 (0.40–1.21); 0.12	

CI = confidence intervals; HR = hazard ratio; PFS = progression-free survival
[a]Statistics shown are for intra-treatment comparisons

Figure 3. Progression-Free Survival by Tumour Shrinkage of A) ≥30%, B) <30% at Week 8 (RAS/BRAF Wild-Type Patients)



Bmab = bevacizumab + mFOLFOX6; Pmab = panitumumab + mFOLFOX6

- Resection rates and outcomes following resection were similar between treatments (Table 5)

Table 5. Resection Outcomes (RAS/BRAF Wild-Type Patients)

	Panitumumab + mFOLFOX6 (n=77)	Bevacizumab + mFOLFOX6 (n=79)
Any resection, n (%)	10 (13)	9 (11)
Complete resection	8 (10)	7 (9)
Time to resection, months – median (range)	4.6 (3.3–8.0)	4.4 (2.6–11.6)
Progression-free at 6 months, n (%)		
Patients with resection	8/10 (80)	6/9 (67)
Patients without resection	51/67 (76)	47/70 (67)

Resection = complete + partial resection

CONCLUSIONS

- In these exploratory analyses from PEAK, ORRs were similar between treatments but the responses observed appeared to occur earlier, last longer and be deeper in patients with *RAS/BRAF* WT tumours receiving panitumumab + mFOLFOX6 vs those receiving bevacizumab + mFOLFOX6
- More patients treated with panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6 had ETS ≥30% at week 8
- Early, deep and sustained tumour responses may offer clinical benefit to patients with mCRC and the long-term impact of such responses warrants further investigation

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