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Tumour Shrinkage and Response Outcomes During Second-Line Panitumumab + FOLFIRI vs FOLFIRI Treatment

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BACKGROUND

- In the first-line metastatic colorectal cancer (mCRC) setting, early tumour shrinkage and objective response appear to be associated with higher chance of surgical resection
  - Panitumumab + FOLFOX4 has been reported to achieve higher rates of early tumour shrinkage, objective response and resection compared with FOLFOX4 alone in patients with *RAS* wild-type [WT]) tumours (those without mutations in *KRAS* and *NRAS* exons 2, 3 and 4)[1, 2]
- In the second-line setting, early tumour shrinkage and objective response may offer benefit in terms of symptomatic relief and delayed progression
- Here we report exploratory tumour shrinkage and response outcomes for patients with *RAS* WT mCRC treated with panitumumab + FOLFIRI vs FOLFIRI alone in the second-line 181 study

METHODS

Study Design

- 181 was a phase III randomised study of second-line panitumumab (6.0 mg/kg Q2W) + FOLFIRI vs FOLFIRI alone in patients who had progressed while receiving or within 6 months of one prior fluoropyrimidine-based mCRC therapy[3]
  - Randomisation was stratified by Eastern Cooperative Oncology Group performance status (ECOG PS 0/1 vs 2), prior oxaliplatin exposure (yes/no) and prior bevacizumab exposure (yes/no)
  - Progression-free (PFS) and overall survival (OS) were the co-primary endpoints

Key Inclusion Criteria

- Documented, measurable disease progression on or within 6 months of only one prior fluoropyrimidine-based therapy for mCRC
  - No prior epidermal growth factor receptor-targeted monoclonal antibody (EGFR mAb) and/or irinotecan therapy
- Paraffin-embedded tumour tissue available for central biomarker testing
- ECOG PS of 0-2 and adequate haematological, renal and hepatic function

Analyses

- Banked tumour samples for patients with *KRAS* exon 2 WT tumours were tested for mutations in *KRAS* exons 3 and 4, *NRAS* exons 2, 3 and 4 and *BRAF* exon 15, via bidirectional Sanger sequencing and WAVE-based SURVEYOR® scan kits (Transgenomic) to identify patients with *RAS* WT tumours
- Objective response rates (ORRs), median duration of response (DoR), median deepness of response (DpR) and mean percentage change in tumour load over time were calculated by treatment
- DpR is a percentage of tumour shrinkage, which is positive for tumour reduction and negative for tumour growth. It 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 experiences no 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
  - If a patient experiences neither tumour reduction nor progression then DpR was set to missing
- Only patients that fell into the first two categories were included in the analysis of DpR
- Median PFS was calculated for patients with/without ≥30% tumour shrinkage at week 8, by treatment

RESULTS

Patients

- Of the 1186 patients randomised in this study, tumour *RAS* status was available for 1014 patients (85%)[4]
- Overall, 107 of the 597 patients (18%) with *KRAS* exon 2 WT tumours had *RAS* mutations elsewhere in the *KRAS* or *NRAS* genes
- In the 421 patients with *RAS* WT tumours, baseline demographics and disease characteristics were generally well balanced between treatment groups (Table 1)
  - Primary rectal cancer was more common in the panitumumab + FOLFIRI group; primary colon cancer was more common in the FOLFIRI group
  - More patients in the FOLFIRI group received subsequent therapy with an EGFR-targeted mAb

Table 1. Baseline Demographics, Patient Characteristics and Subsequent Therapies (RAS Wild-Type Patients)

	Panitumumab + FOLFIRI (n=208)	FOLFIRI alone (n=213)
Male sex, n (%)	136 (65)	140 (66)
Age, years – median (range)	60 (28, 81)	60 (33, 85)
White race, n (%)	203 (98)	202 (95)
ECOG PS 0/1, n (%)	196 (94)	198 (93)
Primary diagnosis, n (%)		
Colon cancer	119 (57)	148 (69)
Rectal cancer	89 (43)	65 (31)
Sites of metastases, n (%)		
Liver only	37 (18)	49 (23)
Liver + other sites	140 (67)	134 (63)
Subsequent therapies, n (%		
Bevacizumab	21 (10)	25 (12)
EGFR mAb	21 (10)	68 (32)
Oxaliplatin, irinotecan or fluorouracil	93 (45)	107 (50)

ECOG PS = Eastern Cooperative Oncology Group performance status;
EGFR mAb = epidermal growth factor receptor-targeted monoclonal antibody

Efficacy

- Overall, 411 patients were included in the ORR analysis and 361 had data available at baseline and week 8 and so were included in the tumour shrinkage analysis
- ORRs were higher for panitumumab + FOLFIRI vs FOLFIRI (41% [n=83] vs 10% [n=21]; difference 31% [95% confidence intervals {CI}: 23, 38%]) [Table 2]

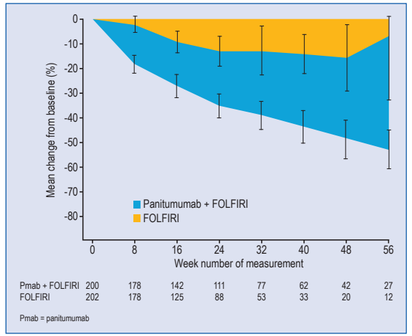
Table 2. Best Response and Objective Response Rates (RAS Wild-Type Patients)

	Panitumumab + FOLFIRI (n=204)	FOLFIRI alone (n=207)
Best response, n (%)		
Complete response	0 (0)	0 (0)
Partial response	83 (41)	21 (10)
Stable disease	78 (38)	117 (57)
Disease progression	29 (14)	48 (23)
Unevaluable/not done	14 (7)	21 (10)
Objective response, n (%) [95% CI]	83 (41) [34, 48]	21 (10) [6, 15]

CI = confidence intervals

- Median DoR was 7.7 (95% CI: 6.7, 9.9) vs 9.3 (95% CI: 6.1, 12.8) months for panitumumab + FOLFIRI vs FOLFIRI and median (Q1, Q3) DpR was 37% (n=50; 13, 56%) vs 10% (n=12; -5, 26%) for these treatments, respectively (p<0.0001)
- Over the first 56 weeks of treatment, panitumumab + FOLFIRI offered a consistent benefit over FOLFIRI alone in terms of mean percentage change from baseline in tumour load (sum of the longest diameters of all target lesions) [Figure 1]
  - Figure 1 shows tumour 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 Interval) Percentage Change from Baseline in Tumour Load (Sum of All Target Lesions) Over Time (RAS Wild-Type Patients[a])



[a]Includes those patients evaluable for objective response who had baseline tumour shrinkage data

- More patients in the panitumumab + FOLFIRI vs FOLFIRI group also had ≥30% tumour shrinkage at week 8 (37% vs 7%; difference: 30% [95% CI: 22, 38%]) [Table 3]

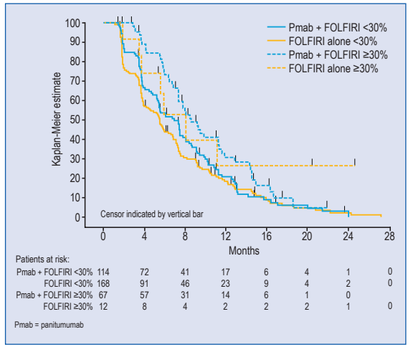
Table 3. Progression-Free Survival by Tumour Shrinkage at Week 8 (RAS Wild-Type Patients)

	Panitumumab + FOLFIRI		FOLFIRI alone	
	Week 8 tumour shrinkage, %			
	<30	≥30	<30	≥30
N (%)	114 (63)	67 (37)	168 (93)	12 (7)
Median PFS, months (95% CI)	6.9 (5.4, 8.0)	8.6 (7.3, 11.3)	5.5 (3.9, 6.7)	8.0 (3.5, NE)
HR (95% CI); p-value	0.66 (0.47, 0.93); 0.0182		0.51 (0.24, 1.08); 0.0797	

CI = confidence interval; HR = hazard ratio; NE = non-evaluable;
PFS = progression-free survival

- ≥30% tumour shrinkage at week 8 appeared to be associated with longer median PFS in both treatment groups vs <30% shrinkage (Table 3)
- Similar PFS results were seen when patients with missing baseline or week 8 measurements were assumed to have not achieved ≥30% tumour shrinkage at week 8 (data not shown)
- Numerically longer median PFS was seen in the panitumumab + FOLFIRI vs FOLFIRI group, irrespective of tumour shrinkage status at week 8 (Figure 2 and Table 3)

Figure 2. Progression-Free Survival by Tumour Shrinkage Status at Week 8 (RAS Wild-Type Patients)



- Numerically more patients in the panitumumab + FOLFIRI vs FOLFIRI group underwent surgical resection following treatment (Table 4)

Table 4. Resection Outcomes (RAS Wild-Type Patients)

	Panitumumab + FOLFIRI (n=204)	FOLFIRI alone (n=207)
Any resection, n (%)	7 (3)	2 (1)
Complete resection, n (%)	2 (1)	2 (1)
Time to resection,[a] months – median (range)	5.3 (3.5, 17.7)	4.1 (3.5, 4.6)
Progression free at 6 months, n (%)		
Patients with resection	3 (60)	1 (50)
Patients without resection	101 (51)	78 (37)

[a]Time to complete or partial resection (n=5 for panitumumab + FOLFIRI; n=2 for FOLFIRI)

CONCLUSIONS

- Combination of panitumumab with FOLFIRI achieved a 30% improvement in ORR vs FOLFIRI alone in patients with *RAS* WT mCRC
  - More patients also achieved ≥30% tumour shrinkage at week 8 with panitumumab + FOLFIRI vs FOLFIRI alone
  - Tumour response data beyond that obtained using RECIST (e.g. the timing and magnitude of response), supports the beneficial anti-tumour activity of adding panitumumab to FOLFIRI
- Early tumour shrinkage appears to be associated with improved PFS in patients receiving second-line treatment for mCRC
- In these exploratory analyses, panitumumab + FOLFIRI appears to be associated with earlier and deeper responses than FOLFIRI alone in patients with *RAS* WT tumours

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