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Original Research

First-line panitumumab plus FOLFOX4 or FOLFIRI in colorectal cancer with multiple or unresectable liver metastases: A randomised, phase II trial (PLANET-TTD)

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On behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumours (TTD)

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FOLFOX;
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Resection

Abstract ***Background:*** In first-line wild-type (WT)-Kirsten rat sarcoma viral oncogene homologue (*KRAS*) metastatic colorectal cancer (mCRC), panitumumab (Pmab) improves outcomes when added to FOLFOX [folinic acid, 5-fluorouracil, and oxaliplatin] or FOLFIRI [folinic acid, 5-fluorouracil, and irinotecan]. However no trial has directly compared these combinations.

Methods: Multicentre, open-label study in untreated patients ≥ 18 years with (WT)-*KRAS* mCRC and multiple or unresectable liver-limited disease (LLD) randomised to either Pmab-FOLFOX4 or Pmab-FOLFIRI. The primary end-point was objective response rate (ORR). Secondary end-points included liver metastases resection rate (R0 + R1), progression-free survival (PFS), overall survival (OS), adverse events and perioperative safety. Exploratory end-points were: response by *RAS* status, early tumour shrinkage (ETS) and depth of response (DpR) in WT-*RAS* patients.

Results: Data on 77 patients were analysed (38 Pmab-FOLFOX4; 39 Pmab-FOLFIRI; WT-*RAS*: 27/26, respectively). ORR was 74% with Pmab-FOLFOX4 and 67% with Pmab-FOLFIRI (WT-*RAS*: 78%/73%). Out of the above, 45% and 59% underwent surgical resection, respectively (WT-*RAS*: 37%/69%). The R0-R1 resection rate was 34%/46% (WT-*RAS*:26%/54%). Median PFS was 13/14 months (hazard ratio [HR] Pmab-FOLFIRI versus Pmab-FOLFOX4: 0.9; 95% confidence interval: [0.6−1.5]; WT-*RAS*:13/15; HR: 0.7 [0.4 −1.3]). Median OS was 37/41 months (HR:1.0 [0.6−1.8]; WT-*RAS*: 39/49; HR:0.9 [0.4 −1.9]). In WT-*RAS* patients with confirmed response, median DpR was 71%/66%, and 65%/77% of patients showed ETS ≥ 30%/ ≥ 20% at week 8, without significant differences between arms; these patients had longer median PFS and OS and higher resectability rates. Surgery was associated with longer survival. Perioperative and overall safety were similar, except for higher grade 3/4 neutropenia (40%/10%; p = 0.003) and neuropathy (13%/0%; p = 0.025) in the Pmab-FOLFOX4 arm.

Conclusions: In patients with WT-*KRAS* mCRC and LLD, both first-line Pmab-FOLFOX4 and Pmab-FOLFIRI resulted in high ORR and ETS, allowing potentially curative resection. No significant differences in efficacy were observed between the two regimens.

(clinicaltrials.gov:NCT00885885).

1. Introduction

The addition of epidermal growth factor receptor (EGFR)-targeted therapies to chemotherapy for the first-line treatment of wild-type (WT) *RAS* metastatic colorectal cancer (mCRC) has improved patient's objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) [1–4]. For this reason, current guidelines recommend their use in combination with the most common backbone chemotherapeutic regimens such as FOLFOX [folinic acid, 5-fluorouracil, and oxaliplatin] or FOLFIRI [folinic acid, 5-fluorouracil, and irinotecan] [5,6].

In mCRC patients with liver-limited disease (LLD), resection of liver metastasis is the main objective. An OS rate of up to 45% at 5 years, and a median OS of 52 months has been reported [7]. However, 80–90% of liver metastases are unresectable due to size, location, extent of disease or remnant liver.

Conversion chemotherapy can increase the resectability rate [8]. After oxaliplatin-based chemotherapy, 14–51% of unresectable patients were subjected to surgery, with 5-year OS rates (34–50%) similar to those from initially resectable patients [9,10]. The addition of anti-EGFR agents increases the ORR to 45% and the resection rate to 28–30% [11–15].

Panitumumab (Pmab) has demonstrated efficacy and a manageable safety profile in WT-*KRAS* (exon 2) mCRC patients, either as a monotherapy [16–19] or in combination with first-line FOLFOX4 [19] or FOLFIRI [4] or second-line FOLFIRI [20].

Mutant *KRAS* (exon 2) predicts a lack of response to anti-EGFR agents, and may also be a factor for chemotherapy resistance [21], better established for irinotecan than for oxaliplatin. Recently, other activating mutations for the members of the *RAS* oncogene family, *KRAS* and *NRAS*, were confirmed to predict a lack of response to Pmab, leading to a label variation [1]. Nevertheless, there are still one quarter of WT-*RAS* patients that are non-responders as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) [22]. Several assessments beyond RECIST may help in predicting OS, such as timing, depth, and duration of response (DoR). Early tumour shrinkage

(ETS) of ≥20% or ≥30% at weeks 6–8 predicts improved PFS and OS [23–26]. Other clinical benefits of early and deep responses may include symptomatic relief and improved resectability [25].

Our aim was to evaluate the efficacy and safety of the addition of Pmab to FOLFOX4 (Pmab-FOLFOX4) or FOLFIRI (Pmab-FOLFIRI) as a first-line treatment for WT-*KRAS* (exon 2) mCRC patients with LLD. We also explored differences in outcomes according to *RAS* status (exons 2, 3, 4 of *KRAS*/*NRAS*) and investigated tumour assessments beyond RECIST in the WT-*RAS* population, including ETS and DpR.

2. Patients and methods (see extended version in Appendix)

2.1. Study design

This phase II, open-label, randomised (1:1), multicentre, two-arm parallel study was conducted in 15 Spanish centres. Patients were included between May 2009 and November 2012. All patients provided written informed consent.

2.2. Patients

Inclusion criteria were: (1) age ≥ 18 years; (2) histologically confirmed WT-*KRAS* (exon 2) mCRC untreated patients; (3) multiple (>4 liver metastasis or any liver metastasis longer than 10 cm) or unresectable LLD considered by the local hepatic surgeons' criteria; (4) at least one unidimensionally measurable lesion according to the modified response evaluation criteria in solid tumours (mRECIST); (5) recurrence after adjuvant treatment with 5-fluorouracil/folinic acid or capecitabine with or without radiotherapy with a disease-free interval (DFI) > 6 months, or with an oxaliplatin-based regimen with a DFI > 12 months, or recurrence after surgical treatment and/or radiotherapy without adjuvant systemic treatment or *de novo* diagnosis; (6) Karnofsky performance status ≥ 70%; and (7) adequate bone marrow, hepatic and renal function and magnesium levels.

Main exclusion criteria were: hormonal-, chemo-, immunotherapy, experimental or approved proteins/antibodies (e.g. bevacizumab) received for mCRC; surgery and/or radiotherapy in the previous 4 weeks.

2.3. Study treatment

Patients were randomised to either Pmab-FOLFOX4 or Pmab-FOLFIRI. Pmab (6 mg/kg) was administered with FOLFOX4 or FOLFIRI every 14 ds for 4–8 cycles. When surgery became an option, it was performed 4–6 weeks after the last chemotherapy dose. Patients with stable disease or who did not achieve resectability received additional cycles until progressive disease (PD), unacceptable toxicity or patient withdrawal. In the event of successful resection, six cycles of adjuvant treatment (similar to presurgery) were administered starting 4–8 weeks after surgery.

2.4. Study procedures

Tumour response was determined by mRECIST criteria every 8 ± 1 weeks until PD or patient withdrawal. Resectability was assessed every 2 months.

2.5. Statistical analysis

Primary end-point: ORR (complete response + partial response). Secondary end-points: resection rate (R0 + R1) of liver metastases, time to resection, PFS, OS, adverse events (AEs) and perioperative safety. Exploratory end-points: response according to *RAS* status, ETS and DpR in the WT-*RAS* population, and their relationship with PFS, OS and surgical resection.

Considering a minimum ORR of 30%, a sample of 40 subjects per arm was required for correctly selecting better treatment when the superior arm was 10% higher, with at least 80% probability (Simon-Wittes-Ellenberg design).

The analysis set included all patients who received at least one dose of Pmab or chemotherapy and were followed up to 31st March 2015. Efficacy end-points were reported using descriptive statistics, 95% confidence intervals (CI), and Kaplan–Meier plots. Results of unconfirmed response are reported because liver metastases resection was performed in some patients before radiological response confirmation.

Data analysis was performed using the SAS® statistical package for Windows (v9.4, SAS Institute Inc., Cary, U.S.).

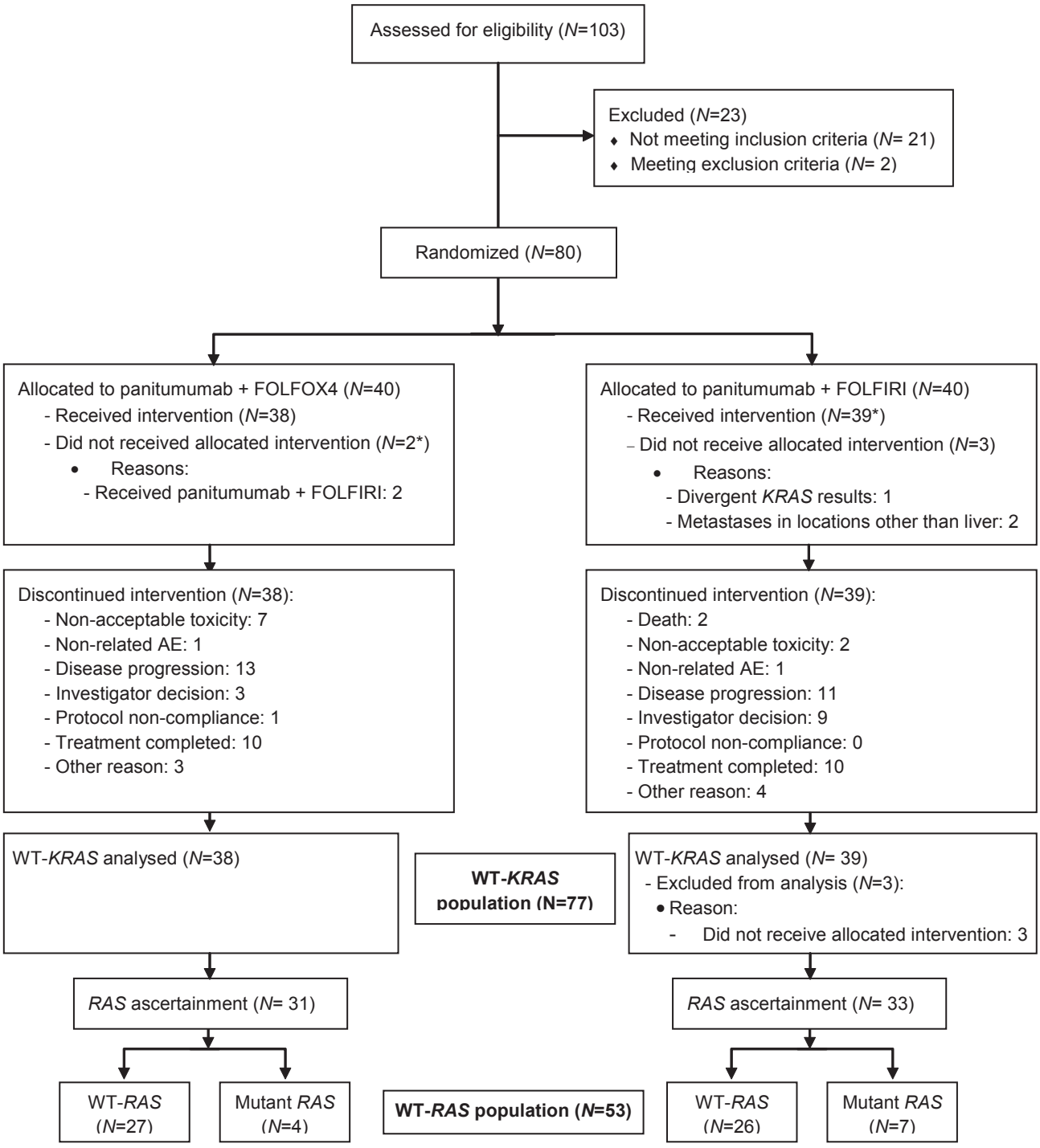
3. Results

3.1. Patients' characteristics

The study included 77 patients (38 received Pmab-FOLFOX4 and 39 received Pmab-FOLFIRI) with WT-*KRAS* mCRC (Fig. 1). The *RAS* status was determined in 83% of the WT-*KRAS* patients, of which 83% were WT-*RAS* (exons 2, 3, 4 [*KRAS*]; exons 2, 3, 4 [*NRAS*]). No double mutations were observed. Baseline characteristics were similar between arms except for a numerically higher proportion of WT-*RAS* patients with technically resectable metastases in the Pmab-FOLFIRI arm (Table 1).

3.2. Treatment

In both arms, patients received a median of eight infusions of Pmab (range: 1–80) (Table 2) and achieved a median presurgery absolute intensity dose of 5.2 mg/kg/week (range: 2.6–6.1). Some 64% of patients received



*Two patients allocated to panitumumab + FOLFOX4 arm received panitumumab + FOLFIRI by error.

WT: wild type; AE: adverse event

Fig. 1. Study flow-chart.

≥ 80% of the planned dose of Pmab (32% received ≥ 90%).

Dose reductions and delays were slightly higher in the Pmab-FOLFOX4 arm, leading to a lower median relative dose-intensity (Table 2).

3.3. Efficacy in the WT-KRAS population

Unconfirmed ORR was noted in 70% of the patients (74% (95% CI: 60–88) with Pmab-FOLFOX4 and in 67% (52–82) with Pmab-FOLFIRI) (Table 3, Supplemental

Table 1
Patient characteristics at baseline in the WT-*KRAS* population and in the WT-*RAS* population.

	WT-*KRAS* Population		WT-*RAS* Population	
	Pmab-FOLFOX4	Pmab-FOLFIRI	Pmab-FOLFOX4	Pmab-FOLFIRI
	(N = 38)	*(N = 39)*	*(N = 27)*	*(N = 26)*
Male, n (%)	31 (82)	28 (72)	23 (85)	18 (69)
Median age, years (min, max)	65 (32, 79)	63 (37, 83)	65 (32, 79)	60 (37, 78)
Median time since CRC diagnosis, months (Q1, Q3)	3.4 (1.3, 22.7)	1.6 (0.6, 11.5)	3.1 (1.5, 21.0)	1.6 (0.5, 27.0)
Technically resectable liver metastases, n (%)	12 (32)	12 (31)	5 (19)	9 (35)
Primary tumour diagnosis, n (%)				
Colon	28 (74)	27 (69)	19 (70)	16 (62)
Rectum	9 (24)	11 (28)	7 (26)	9 (35)
Colon and rectum	1 (3)	1 (3)	1 (4)	1 (4)
TNM stage at diagnosis				
I	1 (3)	2 (5)	0	1 (4)
II	0	1 (3)	0	1 (4)
III	5 (13)	3 (8)	4 (15)	2 (8)
IV	32 (84)	32 (82)	23 (85)	22 (85)
Prior surgery for primary tumour, n (%)	26 (68)	22 (56)	19 (70)	15 (58)
Prior adjuvant/neoadjuvant CT and/or radiotherapy, n (%)	6 (16)	4 (10)	4 (15)	3 (12)
Prior FOLFOX, n (%)	3 (8)	3 (8)	2 (7)	3 (12)

CRC = colorectal cancer; CT = chemotherapy; Pmab = panitumumab; WT = wild-type.

Fig. S1 (online only)). Median time to response was 5.9 months (95% CI: 4.2–6.9) and 4.2 months (95% CI: 3.9–6.7), respectively, without differences between arms (HR Pmab-FOLFIRI versus Pmab-FOLFOX4: 1.1; 95% CI: 0.5–2.3; $p = 0.853$).

After preoperative treatment, some 52% of the patients underwent surgical resection of liver metastases (45% of the Pmab-FOLFOX4 treatment arm and 59% of the Pmab-FOLFIRI) (Table 3). In the subgroup with unresectable metastases, resection was possible in 27% and 50% of patients, respectively. The (R0 + R1) resection rate was 34% and 46%. Median time to resection was 7.8 months and 6.2 months, without significant differences between arms (HR: 1.4; 95% CI: 0.8–2.6; $p = 0.284$). Median time to recurrence in patients with R0 or R1 was 11 months and 9 months, respectively.

After a median follow-up of 33 months (range: 1.4–64.0), median PFS was 13 months with Pmab-FOLFOX4 and 14 months with Pmab-FOLFIRI ($p = 0.730$) (Fig. 2). Median OS was 37 months and 41 months, respectively ($p = 0.966$) (Fig. 2).

Table 2
Treatment exposure in the WT-*KRAS* population.

	Pmab-FOLFOX4	Pmab-FOLFIRI
	(N = 38)	*(N = 39)*
Pre-surgery		
Median Pmab doses per patient (min, max)	8 (2, 80)	8 (1, 30)
Median CT doses per patient (min, max)	8.5 (2, 81)	8 (1, 31)
Median relative dose-intensity for Pmab, % (Q1, Q3)	80 (73, 93)	88 (81, 96)
Median relative dose-intensity for CT, % (Q1, Q3)	83 (64, 92)	89 (78, 94)
Post-surgery		
Median Pmab doses per patient (min, max)	6 (1, 22)	6 (1, 8)
Median CT doses per patient (min, max)	6 (1, 16)	6 (1, 9)
Median relative dose-intensity for Pmab, % (Q1, Q3)	91 (78, 96)	89 (78, 98)
Median relative dose-intensity for CT, % (Q1, Q3)	78 (69, 89)	94 (84, 100)

CT = chemotherapy; Pmab = panitumumab.

3.4. Efficacy according to RAS status

In patients with WT-*RAS*, the unconfirmed ORR increased to 76%, without differences between arms (Table 3, Supplemental Fig. S1 (online only)).

After preoperative treatment, some 53% of WT-*RAS* subgroup of patients underwent surgical resection. In the subgroup with unresectable metastases (n = 39), surgical resection was possible in 54% of patients.

The (R0 + R1) resection rate in the WT-*RAS* subgroup was 40% (32% R0; 8% R1).

Median PFS in WT-*RAS* patients was 13 months with Pmab-FOLFOX4 and 15 months with Pmab-FOLFIRI (Fig. 2). Median OS was 39 and 49 months, respectively (Fig. 2).

3.5. Depth of response in the WT-RAS population

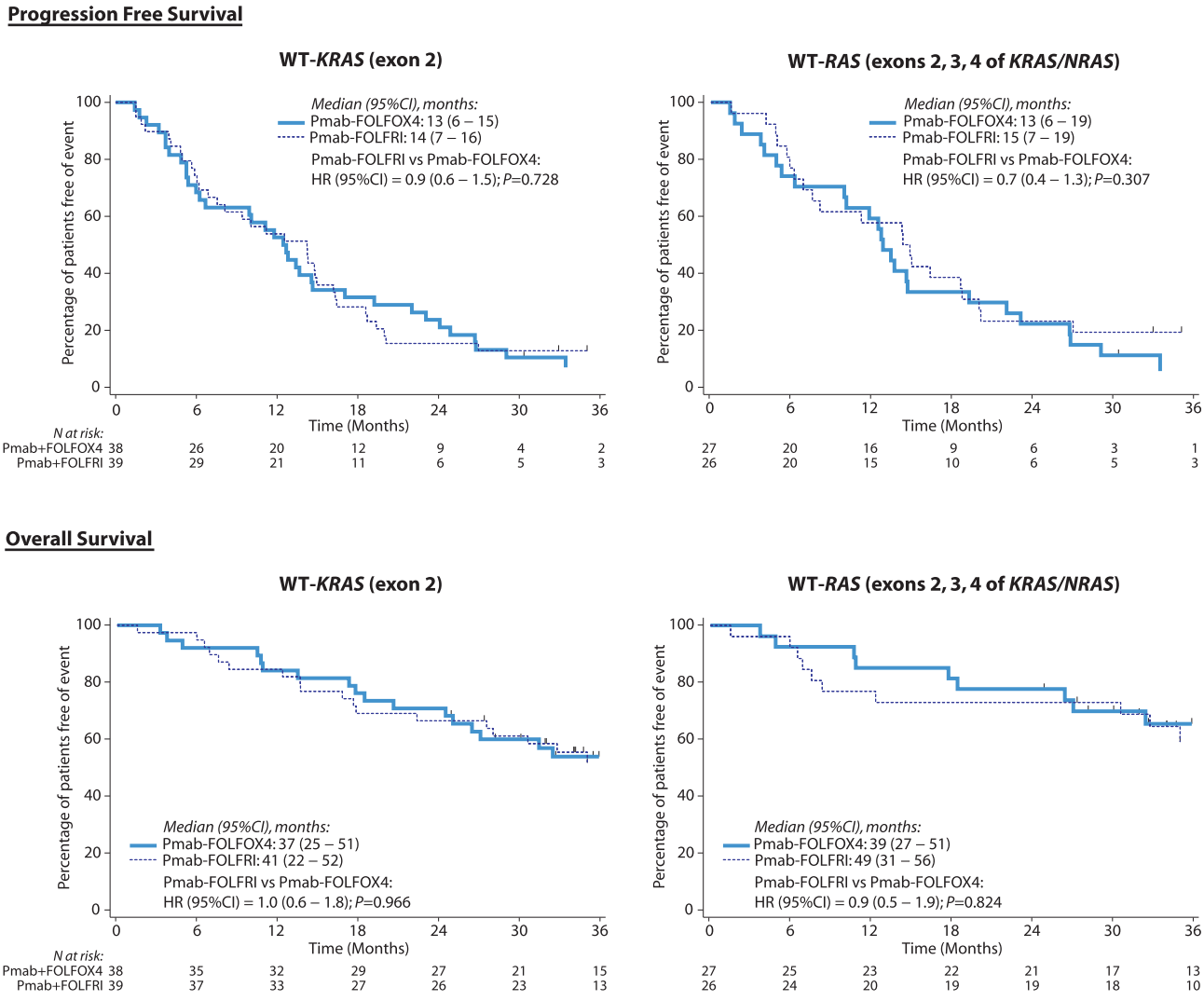
Median DpR was 48% (Q1-Q3: 32–67%), without differences between arms. In patients with radiologically confirmed response (n = 23), median DpR was 67% (Q1-Q3: 56–82%) (Table 4).

DpR correlated with PFS (Spearman Coefficient: 0.53, $p < 0.0001$) and OS (Spearman Coefficient: 0.51; $p = 0.0002$).

Table 3
Main efficacy results in the WT-*KRAS* population and according to *RAS* status.

	Pmab-FOLFOX4	Pmab-FOLFIRI	*P* value*	Total
	% or median (95% CI)	*% or median (95% CI)*	Pmab-FOLFOX4 versus Pmab-FOLFIRI	
WT-*KRAS*, *N*	38	39		77
ORR (not confirmed)	74 (60–88)	67 (52–82)	0.501	70 (60–80)
Surgical resection	45 (29–61)	59 (44–74)	0.211	52 (41–63)
Resection rate (R0 + R1)	34 (19–49)	46 (31–62)	0.285	40 (29–51)
PFS, months	13 (6–15)	14 (7–16)	0.728	13 (9–15)
OS, months	37 (25–51)	41 (22–52)	0.966	37 (28–49)
WT-*RAS*, *N*	27	26		53
ORR (not confirmed)	78 (62–94)	73 (56–90)	0.691	76 (64–87)
Surgical resection	37 (19–55)	69 (52–87)	0.019	53 (39–66)
Resection rate (R0 + R1)	26 (9–42)	54 (35–73)	0.038	40 (26–53)
PFS, months	13 (6–19)	15 (7–19)	0.307	14 (10–16)
OS, months	39 (27–51)	49 (31–56)	0.824	46 (35–52)

NA = not achieved; CI = confidence interval; ORR = objective response rate (complete response + partial response); OS = overall survival; PFS = progression-free survival.



CI: confidence interval; HR: hazard ratio; Pmab: panitumumab; WT: wild type.

Fig. 2. Progression-free survival (top) and overall survival (bottom) in the WT-*KRAS* population and in the WT-*RAS* population.

Table 4
Depth of response and relationship between early tumour shrinkage and progression-free survival and overall survival in the WT-*RAS* population.

WT-*RAS* population	Pmab-FOLFOX4 (N = 27)	Pmab-FOLFIRI (N = 26)	Total (N = 53)
Depth of response			
All patients, *N*	27	24	51
median (Q1, Q3)	47 (32, 71)	48 (42, 64)	48 (32, 67)
Patients with confirmed response, *N*	13	10	23
median (Q1, Q3)	71 (56, 92)	66 (60, 80)	67 (56, 82)
ETS, *N*	26	22	48
≥30%, *N* (%)	16 (62)	15 (68)[†]	31 (65)
PFS, months, median (95% CI)	14 (12–27)	19 (6–27)	15 (13–23)
OS, months, median (95% CI)	51 (33 – NE)	NE (35 – NE)	60 (45 – NE)
<30%, *N* (%)	10 (39)	7 (32)	17 (35)
PFS, months, median (95% CI)	5 (1–13)	11 (4–19)	8 (4–14)
OS, months, median (95% CI)	22 (4–37)	31 (6–56)	26 (8–37)
HR-PFS (95% CI) ≥30% versus <30% (p value)	0.4 (0.2–1.0) (0.050)	0.6 (0.2–1.5) (0.253)	0.5 (0.2–0.9) (0.013)
HR-OS (95% CI) ≥30% versus <30% (p value)	0.2 (0.1–0.5), (0.002)	0.2 (0.1–0.9), (0.030)	0.2 (0.1–0.5), (0.001)
≥20%, *N* (%)	20 (77)	17 (77)[‡]	37 (77)
PFS, months, median (95% CI)	14 (10–27)	15 (6–27)	15 (13–20)
OS, months, median (95% CI)	51 (27 – NE)	52 (35 – NE)	51 (45 – NE)
<20%, *N* (%)	6 (23)	5 (23)	11 (23)
PFS, months, median (95% CI)	3 (1–13)	8 (4 – NE)	6 (2–13)
OS, months, median (95% CI)	31 (11–39)	8 (6–56)	26 (7–39)
HR-PFS (95% CI) ≥20% versus <20% (p value)	0.2 (0.1–0.5) (0.001)	0.7 (0.2–2.2) (0.548)	0.4 (0.2–0.8) (0.016)
HR-OS (95% CI) ≥20% versus <20% (p value)	0.3 (0.1–0.8), (0.021)	0.3 (0.1–1.0), (0.055)	0.3 (0.1–0.6) (0.002)

[†]p versus Pmab-FOLFOX4 = 0.632; [‡]p versus Pmab-FOLFOX4 = 0.977; CI = confidence interval; DpR = depth of response; ETS = early tumour shrinkage; NE = non-estimable; PFS = progression-free survival.

3.6. Impact of ETS and resection on PFS and OS in the WT-RAS population

Forty-eight WT-*RAS* patients had tumour shrinkage data at week 8. Of them, 65% and 77% had ≥30% and ≥20% shrinkage at week 8, respectively, without differences between arms (Table 4).

PFS and OS were longer in patients who achieved ETS ≥ 30% and ≥20% (Table 4 and Fig. 3), although differences were only significant for most comparisons in the Pmab-FOLFOX4 arm and all comparisons in the overall study group.

Resectability rates were numerically higher in patients achieving ETS ≥ 30% (65% versus 35%; $p = 0.052$) and in patients achieving ≥ 20% (59% versus 36%; $p = 0.177$).

In the WT-*RAS* population, surgery (n = 28) was associated with a longer OS (52 versus 36 months in patients without surgery [n = 25]), HR: 0.4 (95% CI: 0.2–0.8; $p = 0.014$) (Fig. 3). A comparison between patients with and without surgery showed that 85% and 77% of patients with surgery had ETS ≥ 30% or ≥20%, respectively, compared to only 68% and 50% in patients without surgery.

3.7. Safety

Adverse events in the WT-*KRAS* population are reported in Table 5. Perioperative safety, induced liver toxicity and skin toxicity (Supplemental Table S1 (online only)) were similar between arms. The incidence of diarrhoea (any grade) was similar between arms (76% Pmab-FOLFOX4; 69% Pmab-FOLFIRI). Most cases of diarrhoea were grade 1–2. Alopecia was more frequent with Pmab-FOLFIRI (26% versus 5%). There were only two infusion reactions in the Pmab-FOLFOX4 arm (5%). Neutropenia and neuropathy were the only grade 3/4 AEs that differed significantly between arms (more frequent with Pmab-FOLFOX4).

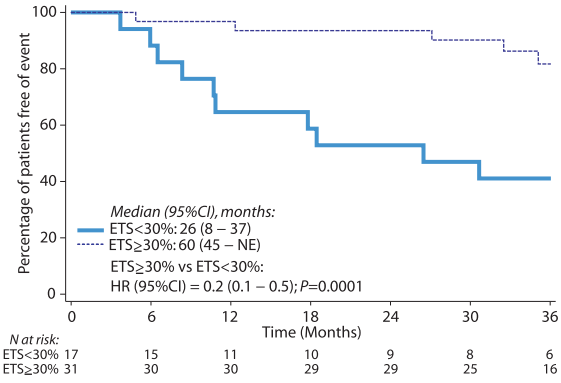
Twenty-four (63%) patients treated with Pmab-FOLFOX4 and 24 (62%) treated with Pmab-FOLFIRI died. One patient in the Pmab-FOLFOX4 arm (3%) died due to a treatment-related serious AE (SAE) necrotising fasciitis.

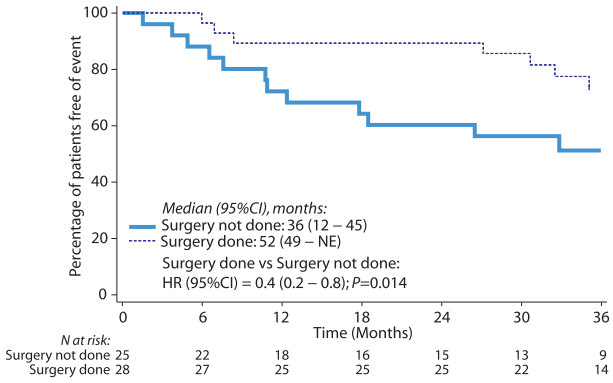
There were eight more SAEs related to chemotherapy (five in the Pmab-FOLFOX4 arm in four patients [two neutropenia events, one diarrhoea, one gastrointestinal inflammation and one ischaemic stroke] and three in the Pmab-FOLFIRI arm in two patients [one febrile neutropenia and two diarrhoeas]).

Safety results in the WT-*RAS* population were similar, except that no differences in neutropenia and neuropathy were observed between arms, and that no deaths related to Pmab and/or chemotherapy were observed (Supplemental Table S2 (online only)).

4. Discussion

This is the first trial reporting a head-to-head comparison between Pmab-FOLFOX4 and Pmab-FOLFIRI in a first-line mCRC setting. Both chemotherapy regimens have similar activity when used without biologicals [27].





CI: confidence interval; ETS: early tumour shrinkage; HR: hazard ratio; NE: non estimable.

Fig. 3. Overall survival according to early tumour shrinkage ≥30% or <30% at week 8 (left) and according to surgical resection of liver metastases (right) in the WT-*RAS* population.

Pmab improves outcomes when added to either FOLFOX [19] or FOLFIRI [4,20], without compromising quality of life [28]. In our population of WT-*KRAS* patients with LLD, no significant differences were observed between the two regimens for any of the efficacy outcomes, in line with previous studies with another anti-EGFR agent. In the CELIM study (cetuximab-FOLFOX versus cetuximab-FOLFIRI in patients with LLD [30% unresectable] [29]), the OS and PFS in the WT-*KRAS* population were similar (OS: 36–42 months compared with 37–41 months in our study; PFS: 12–12 months versus 13–14 months) [15]. In the CECOG trial (cetuximab-FOLFOX6 versus cetuximab-FOLFIRI in WT-*KRAS* patients with unresectable LLD), the PFS (9–8 months) and OS (23-20) were shorter, however >80% of patients had received prior adjuvant treatments, compared to only 13% in our study [30].

The extended *RAS* testing corroborated that this determination was crucial for identifying patients suitable for receiving anti-EGFR antibodies [1,14].

The high response rate observed in the WT-*RAS* population allowed a potentially curative resection in 53% of subjects (R0 + R1 resection was finally achieved in 40%), of whom 75% had initially unresectable metastases. The resection rate was higher in the Pmab-FOLFIRI arm, but this difference may be related to the higher proportion of patients with baseline potentially resectable metastases. In the Pmab-FOLFOX4 arm, the resection rate was similar to that observed in the PRIME study (31% in the subpopulation with LLD treated with Pmab-FOLFOX) [25]. As in prior studies [11,15], surgery was associated with an improved survival.

In the PRIME and PEAK studies [25,26], ETS at week 8 was also an early surrogate marker of improved

Table 5
Summary of adverse events in the WT-*KRAS* population.

WT-*KRAS* population	Pmab-FOLFOX4 *N = 38*	Pmab-FOLFIRI *N = 39*	P value
Grade 3–4, *N* (%)	32 (84)	30 (77)	0.419
Treatment-related Grade 3–4, *N* (%)	28 (74)	23 (59)	0.172
Fatal AEs, *N* (%)	2 (5)	3 (8)	0.975
Treatment-related fatal AEs, *N* (%)	1 (3)	0 (0)	–
Serious AE, *N* (%)	13 (34)	15 (39)	0.698
Pmab and/or CT-related serious AE, *N* (%)	4 (11)	2 (5)	0.431
Perioperative AEs, *N* (%) (in patients with surgery)	4 (24)	5 (22)	0.803
Selected grade 3/4[a] treatment-related adverse events			
Neutropenia, *N* (%)	15 (40)	4 (10)	**0.003**
Conjunctivitis, *N* (%)	2 (5)	2 (5)	1.000
Diarrhoea, *N* (%)	5 (13)	4 (10)	0.481
Asthenia, *N* (%)	4 (11)	2 (5)	0.431
Neuropathy, *N* (%)	5 (13)	0 (0)	**0.025**
Decreased appetite, *N* (%)	2 (5)	0 (0)	0.240
Induced liver toxicity in patients with surgical resection	17	23	
Any liver complication, *N* (%)	3 (18)	6 (26)	0.803
Sinusoidal dilatation, *N* (%)	0 (0)	0 (0)	–
Steatohepatitis, *N* (%)	1 (6)	6 (26)	0.214
Fibrotic changes, *N* (%)	1 (6)	0 (0)	–
Hepatocyte necrosis, *N* (%)	1 (6)	0 (0)	–

[a] There was only one grade 5 AE related to Pmab in the Pmab-FOLFOX4 arm (necrotising fasciitis).

PFS and OS, and was associated to an increased resectability rate. Relatively speaking, our results are also consistent with the exploratory analyses of the FIRE-3 study of first-line cetuximab versus bevacizumab therapy [31], and of other studies of cetuximab plus chemotherapy [32]. It is still not clear if the association between ETS $\geq$ 30% or $\geq$20% and increased PFS or OS is predominantly due to the increased resectability rate rather than an independent effect. In a multivariate analysis of the PRIME study, after adjusting by resection status, the benefit of ETS $\geq$ 30%/$\geq$20% was not only observed in resected patients but also in non-resected patients, suggesting that there could be an independent effect in this subgroup [25]. In our study, the median OS in WT-*RAS* patients with ETS $\geq$ 30%/$\geq$20% (60/51 months), despite including more than one-third of subjects without resection, was similar to that of resected patients (52 months), which supports the aforementioned hypothesis.

Depth of response values were consistent with prior studies (65% in the Pmab-FOLFOX6 of the PEAK study [26], 54% in the Pmab-FOLFOX4 arm of the PRIME study [25], 48% for first-line cetuximab-FOLFIRI [31]) and higher than the 33% observed with bevacizumab-FOLFIRI [31]. The differences in assessments beyond RECIST favouring Pmab versus bevacizumab, also found in the PEAK study, suggest that these variables could be more informative than ORR, which appeared to be similar [26].

Our results indicate a manageable toxicity profile, consistent with prior studies of Pmab-FOLFOX or Pmab-FOLFIRI, or with any of these treatments alone [2,27,33]. It is well known that FOLFIRI is associated with a higher frequency of alopecia and severe diarrhoea whereas FOLFOX is associated with a higher frequency of polyneuropathy [27]. Our results are consistent with this pattern, except for a similar frequency of diarrhoea, probably due to a higher incidence in the FOLFOX arm compared with previous studies [27].

The main limitation was the unblinded surgical review of computed tomography or magnetic resonance imaging scans, which does not ensure homogeneity in resectability assessments across centres. However, the protocol requested the fulfilment of TTD guidelines [34], which may have reduced subjective evaluations. The fact that only 11 tumours had *RAS* mutations in exons 3,4 of *KRAS* or exons 2,3,4 of *NRAS*, prevents us from drawing any conclusions about this subgroup, although prior Pmab studies clearly show a negative effect on outcome [1].

In conclusion, similar efficacy and safety results were obtained in WT-*KRAS* patients with either first-line Pmab-FOLFOX4 or Pmab-FOLFIRI, leading both to high resectability rates. Better outcomes were observed in the WT-*RAS* subgroup, without notable differences between the two regimens. ETS at week 8 was an early surrogate marker of improved PFS and OS and allowed more surgeries for hepatic metastases. DpR values were consistent with prior studies and correlated with PFS and OS. In patients with WT-*RAS* mCRC and LLD, Pmab plus standard first-line treatment chemotherapy doublet offers the possibility of a rapid and high overall response rate and a potentially curative hepatic resection. This strategy in LLD mCRC is also associated with a favourable long-term survival.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.04.024.

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M[a] J. Safont has received honoraria from Roche, A. Carrato and E. Aranda has received honoraria for

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Appendix

Extended methods

Study design

This phase II, open-label, randomised (1:1), multicentre, two-arm parallel study was conducted in 15 Spanish centres (PLANET Study [TTD-08-04], clinicaltrials.gov identifier NCT00885885, EudraCT Number: 2008-006766-28). The ethic committee at each participating centre approved the study protocol and its amendments. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patients were included between May 2009 and November 2012. All patients provided written informed consent.

Patients

Inclusion criteria were: age $\geq$18 years; histologically confirmed WT-*KRAS* (exon 2) mCRC untreated patients; LLD (including those patients who had undergone complete resection [R0] of the primary tumour at least 4 weeks before randomisation) fulfilling one of the following criteria: $\geq$ 4 metastases, at least 1 metastasis >10 cm in diameter, and metastases technically unresectable, considered by the local hepatic surgeons' criteria, due to vascular compromise and/or location in which complete resection was impossible and/or 25–30% of healthy liver would not remain functional after resection; no major contra-indication to liver surgery; at least one unidimensionally measurable lesion according to the modified RECIST (mRECIST) criteria (Version 1.1); recurrence after adjuvant treatment with 5-fluorouracil/folinic acid or capecitabine with or without radiotherapy with a disease-free interval (DFI) > 6 months, or after adjuvant treatment with an oxaliplatin-based regimen with a DFI > than 12 months, or recurrence after surgical treatment and/or radiotherapy without adjuvant systemic treatment, or *de novo* diagnosis; Karnofsky performance status $\geq$ 70%; adequate bone marrow, hepatic and renal function and magnesium levels.

Main exclusion criteria were: prior malignant tumour in the last 5 years, except for a history of basal cell carcinoma of the skin or preinvasive carcinoma of the skin; hormonal therapy, chemotherapy, immunotherapy or experimental or approved proteins/antibodies (e.g. bevacizumab) received for mCRC treatment; significant cardiovascular disease including unstable angina or myocardial infarction within previous 12 months or a history of ventricular arrhythmia; prior anti-EGFR therapy or treatment with small molecule EGFR tyrosine kinase inhibitors; known positive test for human immunodeficiency virus infection, hepatitis C virus, chronic active hepatitis B infection; surgery (not including diagnostic biopsy or central venous catheter placement) and/or radiotherapy in the previous 4 weeks.

Study treatment

Patients were randomised to Pmab plus FOLFOX4 or Pmab plus FOLFIRI. Random assignment was stratified by prior adjuvant FOLFOX therapy and technically resectable/ unresectable metastases. Preoperative Pmab (Vectibix®, Amgen Europe B.V.) was administered with FOLFOX4 or FOLFIRI every 14 ds for 4–8 cycles at a dose of 6 mg/kg, over a 30–90 $\pm$ 15 min intravenous infusion. When surgery became an option, it was performed 4–6 weeks after the last chemotherapy dose. Patients with stable disease (SD) or who did not achieve resectability received additional cycles until progressive disease (PD), unacceptable toxicity or patient withdrawal. In the event of successful resection (R0 or R1), 6 cycles of adjuvant treatment was administered starting 4–8 weeks after surgery.

If during or after Pmab infusion a reaction occurred, premedication with acetaminophen/paracetamol and/or histamine H1 blockers such as diphenhydramine was administered for subsequent cycles.

Study procedures

Pre-study evaluations included complete medical history, physical examination (including weight and height), haematology and biochemistry tests, serum carcinoembryonic antigen (CEA), electrocardiogram and radiological imaging of the chest, abdomen, pelvis and all other sites of disease by computed tomography, or magnetic resonance imaging if clinically indicated. *KRAS* mutation status (exon 2, codons 12 and 13) was evaluated at each centre while extended *RAS* mutation status was analysed at a central laboratory. Mutations in *KRAS* exon 3 (at codons 59 and 61) and exon 4 (at codons 117 and 146); *NRAS* exon 2 (at codons 12 and 13), exon 3 (at codons 59 and 61) and exon 4 (at codons 117 and 146) were detected by Pyrosequencing using 'Ras Extension Pyro Kit' and 'Therascreen *NRAS* Pyro Kit' (Qiagen, Hilden, Alemania) according to the manufacturer's recommended protocol.

Tumour response was determined by the mRECIST criteria (RECIST criteria version 1.1) every 8 $\pm$ 1 weeks until PD or patient withdrawal. Resectability was assessed every 2 weeks. AEs were collected throughout the study until 30 $\pm$ 3 ds after the last dose of Pmab. Long-term follow-up visits were performed every 3 $\pm$ 1 months after the last safety visit and up to 36 months.

Statistical analysis

The primary end-point was the ORR (complete response [CR]+partial response [PR]) over the entire treatment period. Secondary end-points were: resection rate (R0 + R1) of liver metastases, time to resection, progression-free survival (PFS), overall survival (OS), adverse events (AEs) and perioperative safety. Exploratory end-points were: response according to *RAS* status, ETS and DpR in the WT-*RAS* population and their relationship with PSF, OS and surgical resection.

Considering a minimum of ORR of 30% (according to prior results of CRC patients with LLD, treated with FOLFOX4 or FOLFIRI monotherapy), a sample of 40 subjects per arm were required for correctly selecting the better treatment when the superior arm was 10% higher, with at least 80% probability (Simon-Wittes-Ellenberg design).

The analysis set included all patients who received at least one dose of Pmab or chemotherapy and followed up to March 31st, 2015. Efficacy end-points were reported using descriptive statistics, 95% confidence intervals (CI), and Kaplan–Meier (KM) plots. Results of unconfirmed response are reported because liver metastases resection was performed in some patients before radiological response confirmation. PFS and OS were calculated as the time from the start of the treatment to first evidence of clinical progression or death by any cause. Surgical resection between subgroups defined by ETS $\geq$ or $<$20% or 30% was compared using Chi-square tests. The effect of ETS, DpR and resection rate on PFS and OS was assessed with the log-rank test.

AEs were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE) version 3.0, with the exception of Pmab-related skin toxicities, which were graded on CTC version 3.0 with modifications.

DpR was defined as the maximum percentage change form baseline in the sum of the longest diameter during the treatment period prior to surgery. The value was positive in patients with tumour reduction and negative in patients with tumour growth. ETS was defined as at least 20% or 30% tumour decrease in the sum of the longest diameter compared with baseline at week 8 ($\pm$2) post-treatment initiation.

Data analysis was performed using the SAS® statistical package for Windows (version 9.4, SAS Institute Inc., Cary, North Carolina, U.S.).

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