Phase II trial of panitumumab (Pmab) plus FOLFOX4 or FOLFIRI in subjects with KRAS wild-type colorectal cancer (CRC) and liver-limited disease LLD): The PLANET study

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

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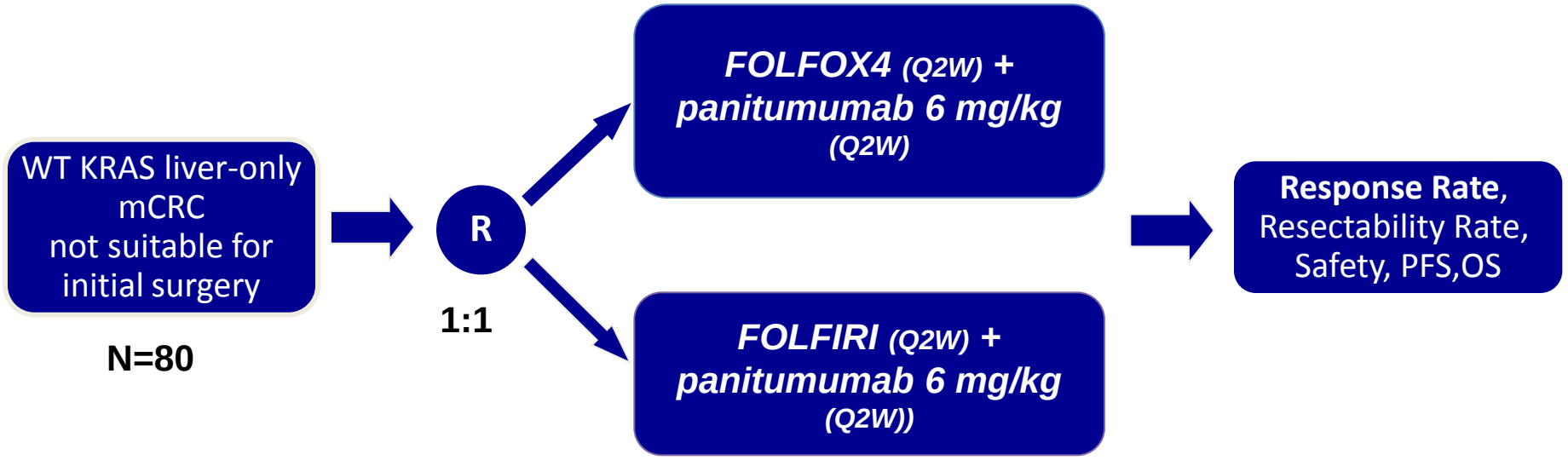
PLANET randomized phase II trial
Objectives

- **Primary Endpoint:**
  - Objective response rate (ORR) over the entire Pmab + CT treatment period
- **Secondary Endpoints:**
  - Resection rate (R0+R1) of liver metastases
  - Time to resection
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Adverse Events (AEs) and peri-operative safety
- **Exploratory Endpoints:**
  - Response according to molecular biomarkers (RAS status)

PLANET trial
Study design



- **Sponsor:** Spanish Cooperative Group for Digestive Tumour Therapy (TTD)
- **Principal investigators**: Dr. Albert Abad & Dr. Alfredo Carrato

- ClinicalTrials.gov identifier: NCT00885885

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PLANET study
Eligibility criteria: main inclusion criteria (I)

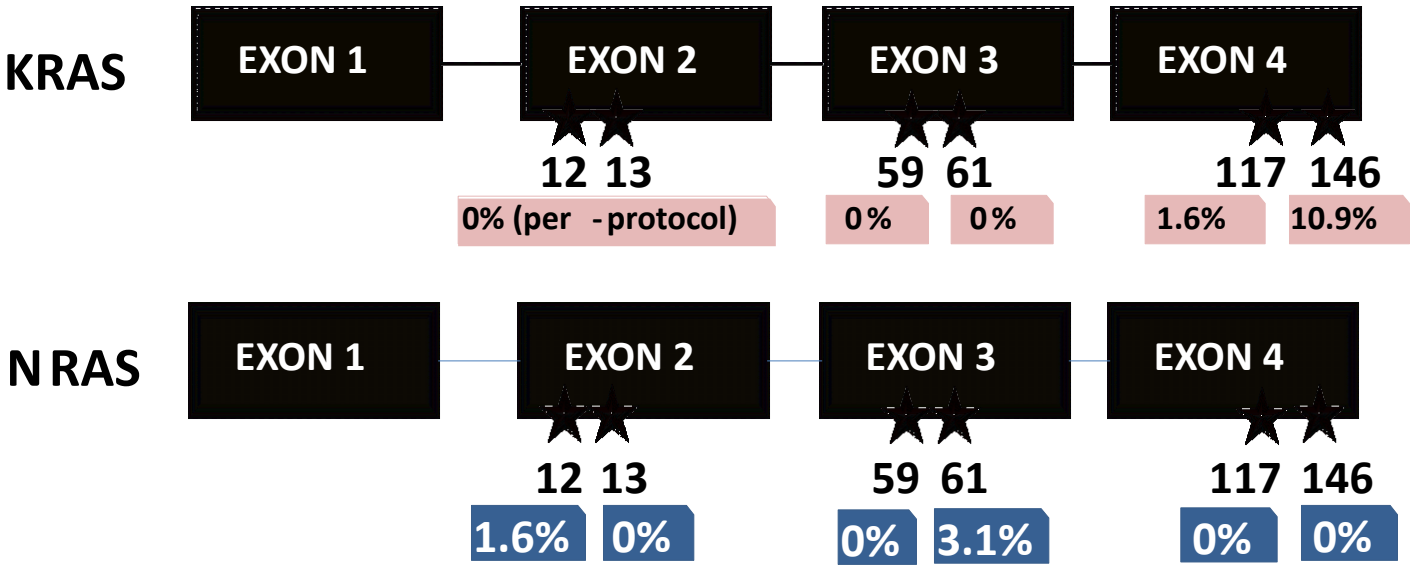
- >18 years of age
- WT KRAS CRC with at least one unidimensionally measurable lesion ≥20 mm with the conventional techniques (computed tomography (CT), magnetic resonance imaging) or >10 mm with spiral CT, according to the modified RECIST criteria (Version 1.1).
- Synchronous or metachronous liver-only metastases deemed resectable or unresectable, including those patients who had undergone complete resection (R0) of the primary tumor at least 4 weeks before randomization, fulfilling one of the following criteria:
  - ≥4 liver metastases
  - at least 1 metastasis >10 cm in diameter
  - Liver metastases technically not resectable (vascular compromise and/or location in which complete resection is impossible and/or 25-30% of healthy liver would not remain functional after resection)

PLANET study
Patient characteristics (WT KRAS population)

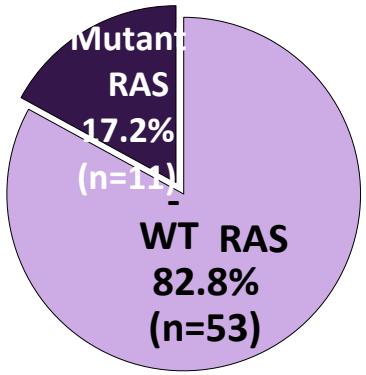
	Pmab-FOLFOX4 (N = 38)	Pmab-FOLFIRI (N = 39)	TOTAL (N = 77)
Male, n (%)	31 (81.6)	28 (71.8)	59 (76.6)
Median age, years (min, max)	65 (32, 79)	63 (37, 83)	64 (32, 83)
Mean body mass index, kg/m^2 (SD)	27.4 (4.4)	25.9 (3.6)	26.7 (4.0)
Median time since CCR diagnosis, months (Q1, Q3)	3.4 (1.3, 22.7)	1.6 (0.6, 11,5)	1.9 (0.6, 22.2)
Technically resectable liver metastases, n (%)	12 (31.6)	12 (30.8)	24 (31.2)
Prior surgery for primary tumor, n (%)	26 (68.4)	22 (56.4)	48 (62.3)
Prior adjuvant/neoadjuvant CT and/or radiotherapy, n (%)	6 (15.8)	4 (10.3)	10 (13.0)
Prior FOLFOX, n (%)	3 (7.9)	3 (7.7)	6 (7.8)

PLANET study
Prevalence of RAS mutations (other than KRAS exon 2)

Individual RAS mutations (n=64)



Any RAS mutation (n=64 patients, 83.1% ascertainment*)



*Ascertainment defined as percentage of patients with a known codon sequence result at all positions

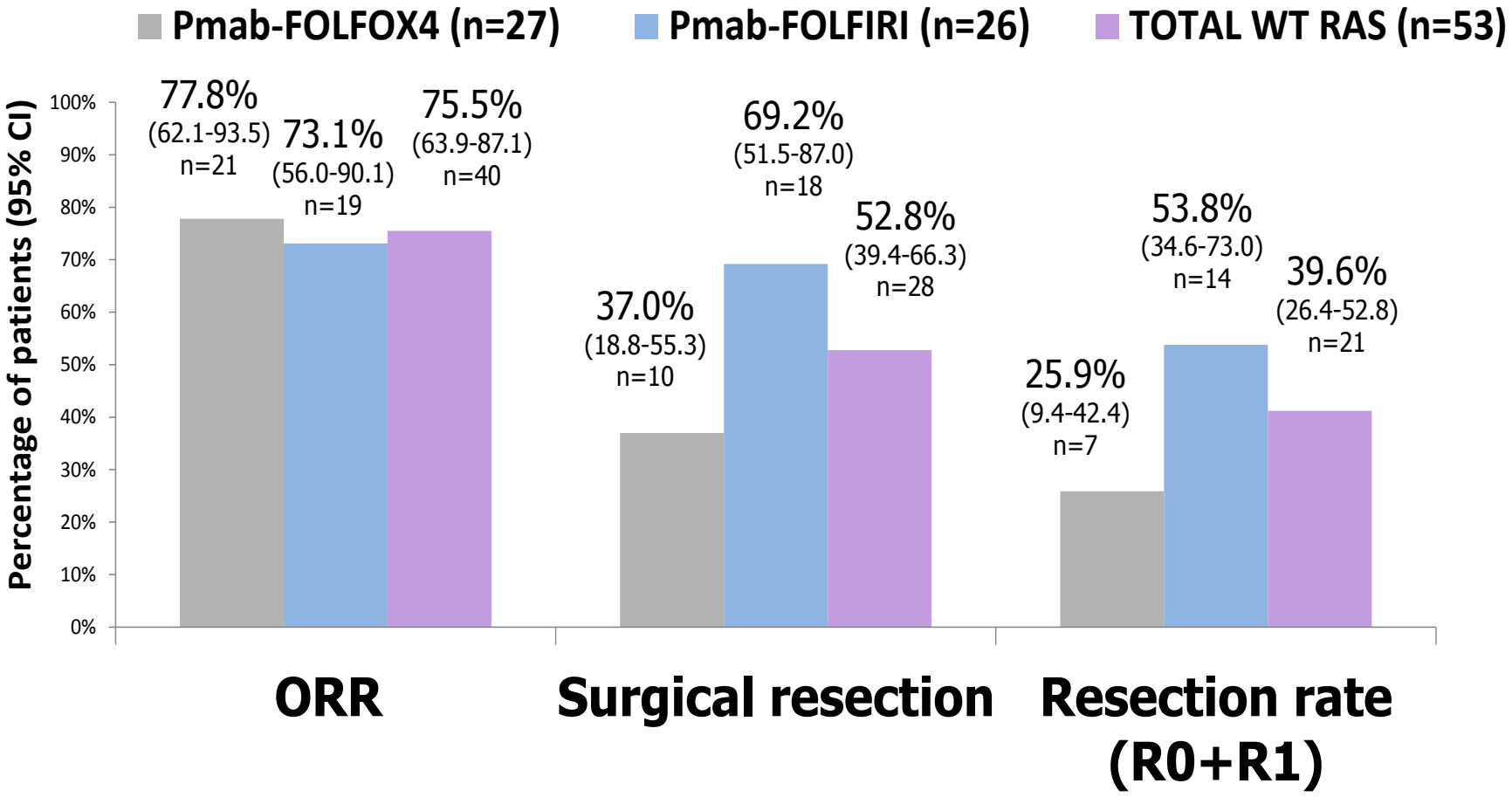
PLANET study
Patient characteristics (WT RAS population)

	Pmab-FOLFOX4 (N = 27)	**Pmab-FOLFIRI** (N = 26)
Male, n (%)	23 (85.2)	18 (69.2)
Median age, years (min, max)	65 (32, 79)	60 (37, 78)
Median time since CCR diagnosis, months (Q1, Q3)	3.1 (1.5, 21.0)	1.6 (0.5, 27.0)
Technically resectable liver metastases	5 (18.5)	9 (34.6)
Prior surgery for primary tumor, n (%)	19 (70.4)	15 (57.7)
Prior adjuvant/neoadjuvant CT and/or radiotherapy, n (%)	4 (14.8)	3 (11.5)
Prior FOLFOX, n (%)	2 (7.4)	3 (11.5)

PLANET study
Efficacy according to RAS status

- In the RAS ascertainment subgroup, the **ORR was 75.5% in WT-RAS patients and 54.6% (25.1-84.0) in the Mutant (Mt)-RAS stratum**.
- After preop tt, 52.8% of WT-RAS underwent surgical resection of liver mets. In the WT-RAS with non-resectable metastases group (n=39), surgical resection was possible in 53.8% of patients.
- The R0+R1 resection rate in the WT-RAS subgroup was 39.6% (25.9% with P-FOLFOX4 and 53.8% with P-FOLFIRI). % of patients with R0 and R1 were 32.1% and 7.5%, respectively.
- Longer PFS and OS were observed in WT-RAS versus Mutant-RAS patients in the overall population, although differences were not significant, probably due to small sample sizes.

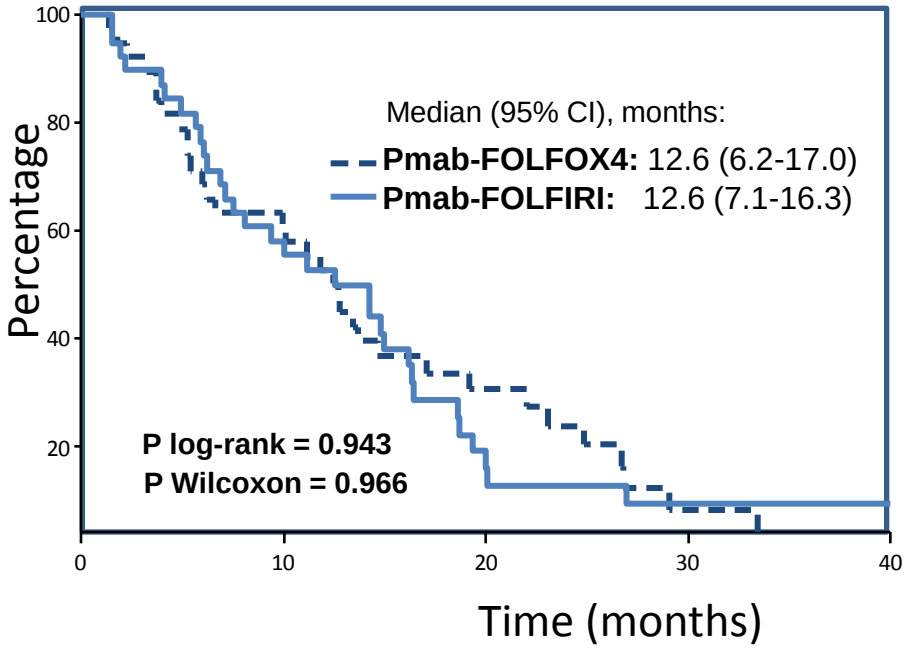
PLANET study
Response rate and resectability (WT RAS population)



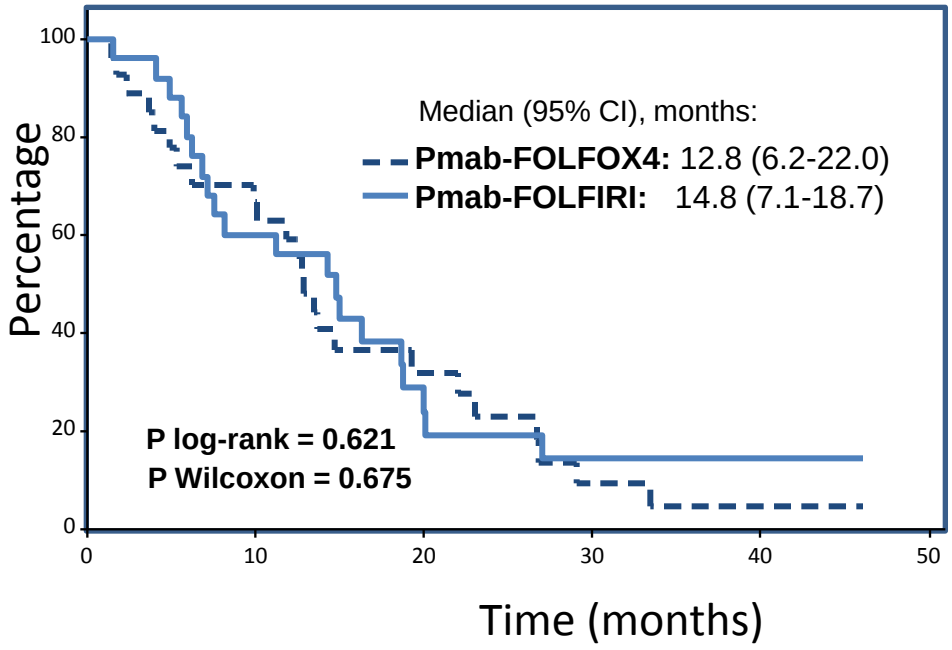
ORR: Objective response rate (not confirmed*); *patients resected before response confirmation

PLANET study
Progression-free survival according to treatment
(WT KRAS & WT RAS populations)

WT-KRAS (exon 2)



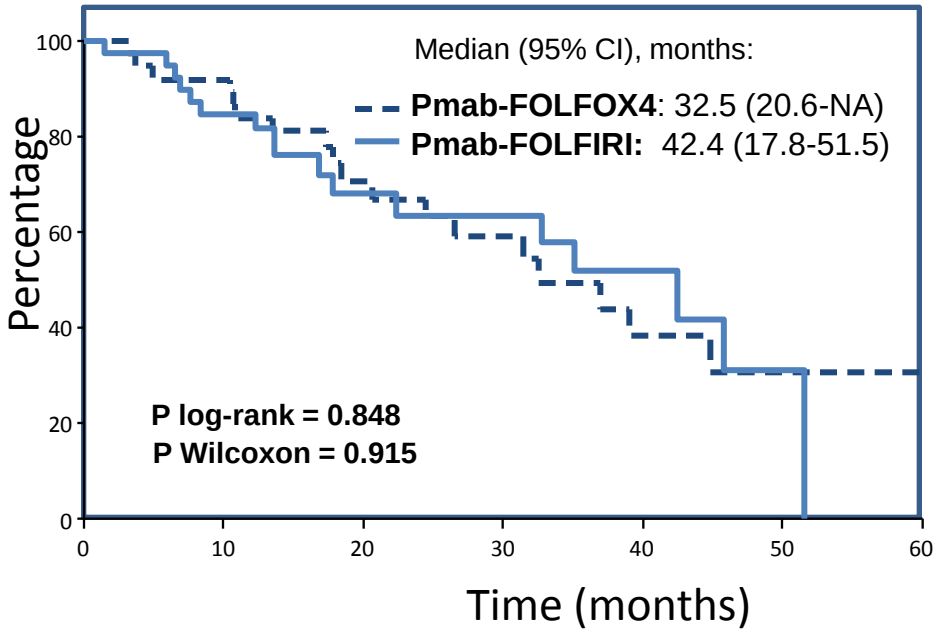
WT-RAS (exons 2, 3, 4 of KRAS/NRAS)



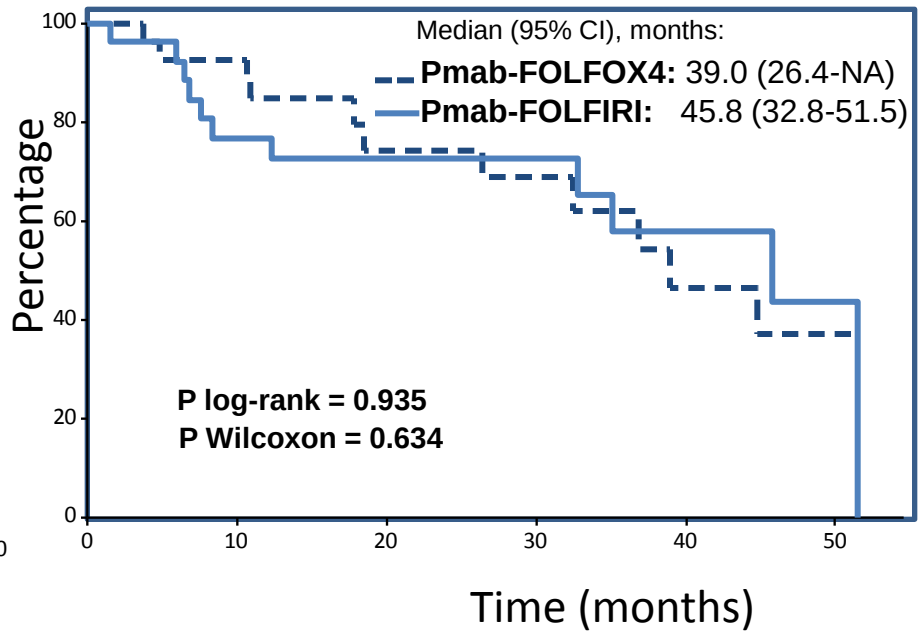
CI: confidence interval

PLANET study
Overall survival according to treatment
(WT KRAS & WT RAS populations)

WT-KRAS (exon 2)

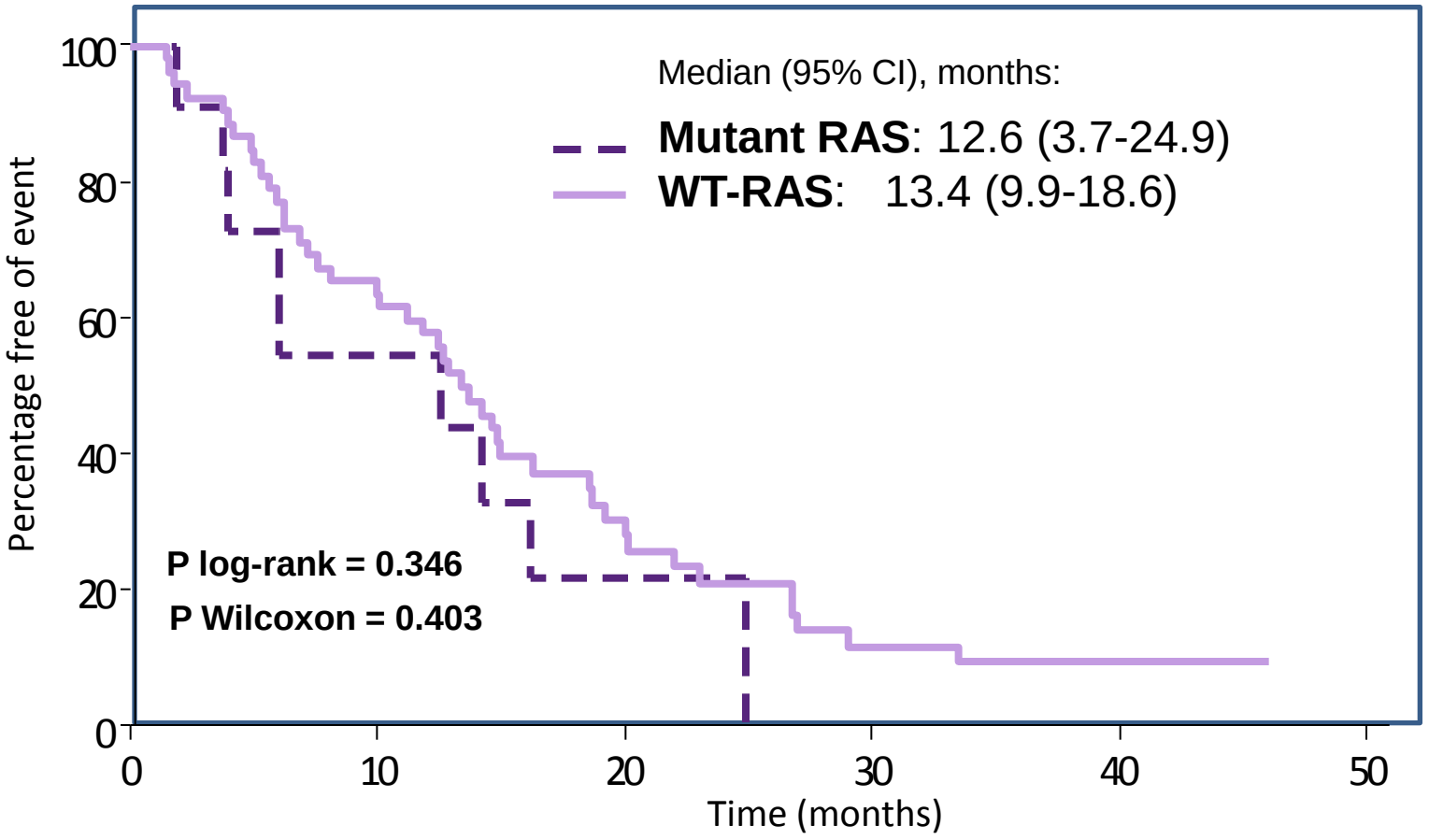


WT-RAS (exons 2, 3, 4 of KRAS/NRAS)

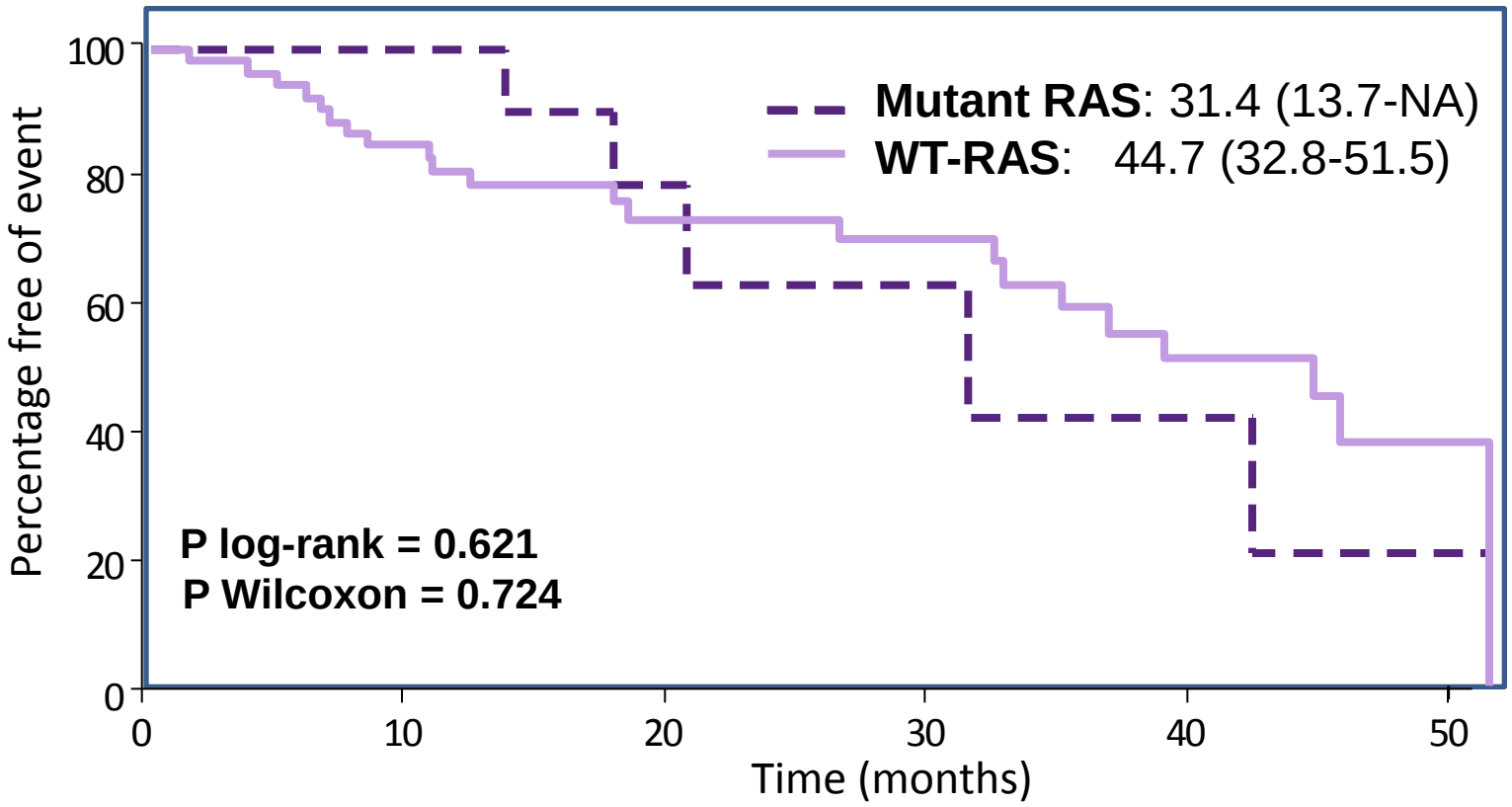


CI: confidence interval; NA: not achieved

PLANET study
Progression-free survival
(WT RAS vs Mutant RAS)



PLANET study
Overall survival
(WT RAS vs Mutant RAS)



CI: confidence interval; NA: not achieved

PLANET study
Summary of adverse events
(WT RAS population)

	Pmab-FOLFOX4 (N = 27)	Pmab-FOLFIRI (N = 26)
Grade 3-4, n (%)	22 (81.5)	20 (76.9)
Treatment-related Grade 3-4, n (%)	18 (66.7)	16 (61.5)
Fatal AEs, n (%)	1 (3.7)	3 (11.5)
Treatment-related fatal AEs, n (%)	0	0
Serious AE, n (%)	6 (22.2)	7 (26.9)
Pmab and/or CT-related serious AE, n (%)	0	0
Peri-operative AEs, n (%) (in patients with surgery)	1 (10.0)	5 (27.8)

PLANET study
Conclusions

- In this selected population with WT KRAS CRC and LLD, panitumumab plus CT offers the possibility of a high overall response and a potentially curative hepatic resection.
- Similar efficacy and safety results were obtained with either Pmab-FOLFOX4 or Pmab-FOLFIRI.
- Patients with RAS mutations (KRAS, NRAS) other than KRAS exon 2 showed a non-significant clear trend to worse efficacy outcomes than WT-RAS patients, without differences between Pmab-FOLFOX4 and Pmab-FOLFIRI