13as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2018

Anti-EFGR humano: 10 años de logros en el cáncer colorrectal metastásico

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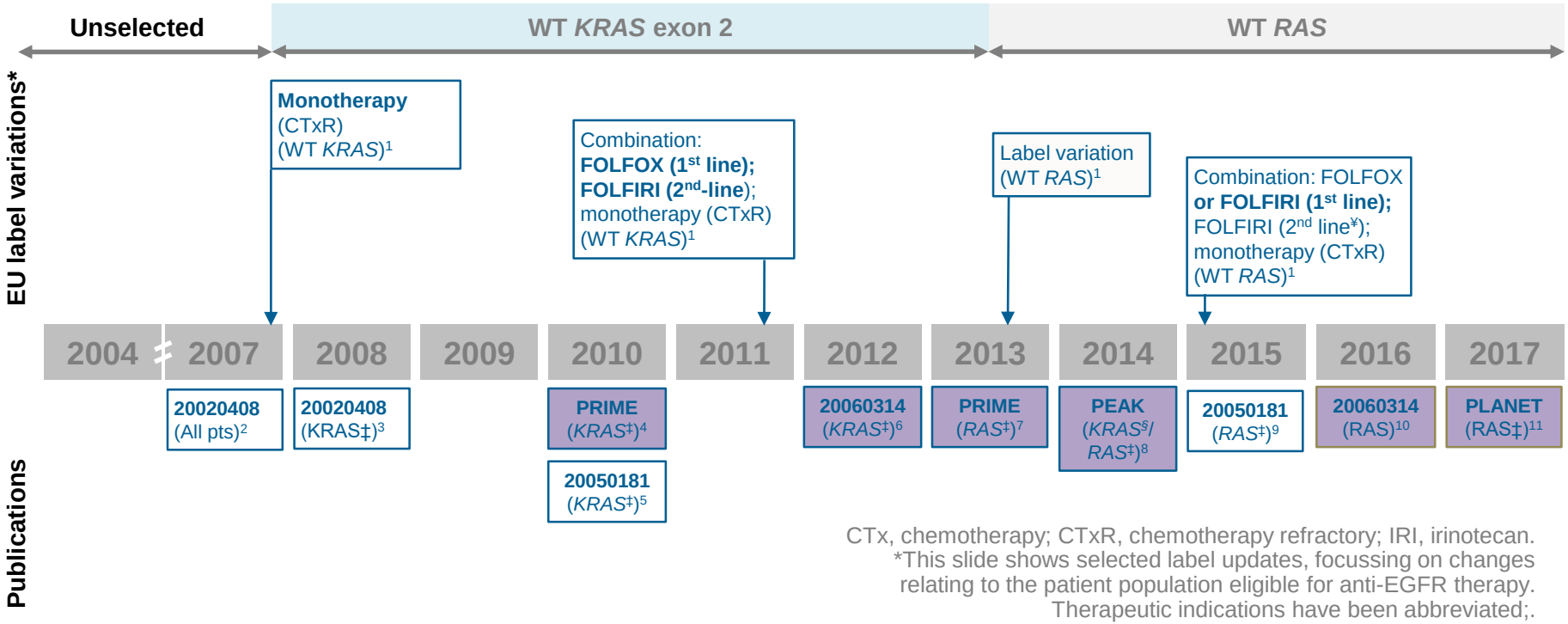
Panitumumab key studies in mCRC: 1st line evidence



CTx, chemotherapy; CTxR, chemotherapy refractory; IRI, irinotecan.
*This slide shows selected label updates, focussing on changes relating to the patient population eligible for anti-EGFR therapy. Therapeutic indications have been abbreviated;.

‡subgroup analysis by (*K*)*RAS* mutation status; §WT *KRAS* status required for study eligibility; ¥for patients who have received 1st-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

1. http://ec.europa.eu/health/documents/community-register/html/h423.htm (accessed 15-12-15); 2. Van Cutsem E, et al. J Clin Oncol 2007;25:1658–64; 3. Amado RG, et al. J Clin Oncol 2008;26:1626–34 4. Douillard JY, et al. J Clin Oncol 2010;28:4697–705; 5. Peeters M, et al. J Clin Oncol 2010;28:4706–13; 6. Kohne CH, et al. J Cancer Res Clin Oncol 2012;138:65–72; 7. Douillard JY, et al. N Engl J Med 2013;369:1023–34; 8. Schwartzberg LS, et al. J Clin Oncol; 9. Peeters M, et al. Clin Cancer Res 2015;21:5469–79; 10. Karthaus M. et al. Br. J Cancer 2016; 115:1215-22; 11. Carrato A, et al. Eur J Cancer 2017; 81:191–202.

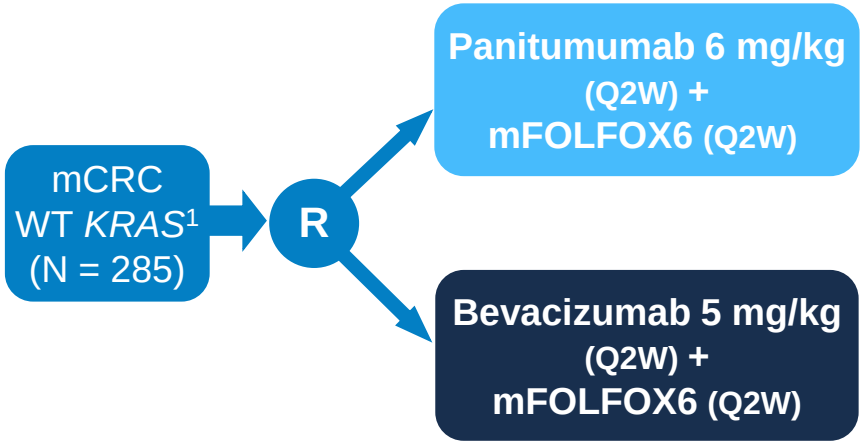
PRIME trial: FOLFOX4 ± panitumumab in 1st-line tt of mCRC

PRIME is the only phase 3 trial of a mAb + FOLFOX performed in 1st-Line mCRC, designed to compare efficacy against FOLFOX, that statistically demonstrated significant benefit in the three main efficacy endpoints in a pre-specified RAS analysis[1,2,3]

WT *RAS*[2,3]	Panitumumab + FOLFOX4 (n = 259)	FOLFOX4 (n = 253)
Median PFS, mo*	10.1	7.9
HR (95% CI) P-value	0.72 (0.58–0.90) P = 0.004	
Median OS, mo*	26.0	20.2
HR (95% CI) P-value	0.78 (0.62–0.99) P = 0.04	
ORR, %*‡ (95% CI)	59 (52–65)	46 (40–53)
Odds ratio P-value	1.63§ P = 0.009	

Phase 2 PEAK study

mFOLFOX6 + panitumumab or bevacizumab in 1st-L treatment of mCRC



- Primary endpoint: PFS[1]
  - No planned formal hypothesis testing
- Prespecified extended *RAS* analysis[1,2]
  - *RAS* ascertainment rate: 82%

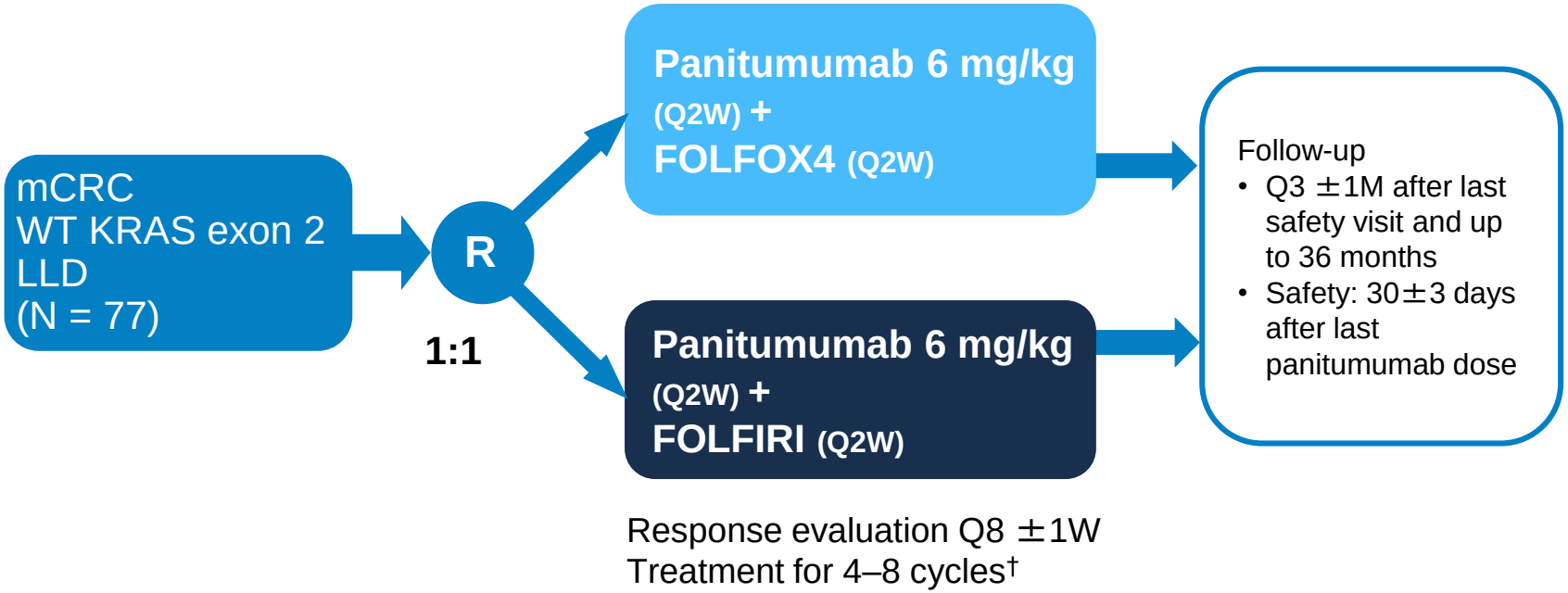
WT *RAS*	Panitumumab + mFOLFOX6 (n = 88)	Bevacizumab + mFOLFOX6 (n = 82)
Median PFS, mo†[2]	12.8	10.1
HR (95% CI) P-value	0.68 (0.48–0.96) P = 0.029	
Median OS, mo†[2]	36.9	28.9
HR (95% CI) P-value	0.76 (0.53–1.11) P = 0.15	
ORR, %†[2]	(n = 88) 65	(n = 81) 60
OR (95% CI) P-value	1.12 (0.56–2.22) P = 0.86	

†Final analysis.
WT *RAS* = WT *KRAS* and *NRAS* exons 2, 3, 4.

1. Schwartzberg LS, et al. J Clin Oncol 2014;32:2240−7;
2. Rivera F, et al. Int J Colorectal Dis 2017; 32:1179–90

Phase 2 PLANET study

Panitumumab + FOLFOX4 or FOLFIRI in untreated mCRC with multiple or unresectable liver-limited metastases



†If surgery became possible, it was performed 4–6 weeks after the last chemotherapy dose and followed by adjuvant treatment. Patients with SD or who remained unresectable received additional cycles until PD, unacceptable toxicity, or patient withdrawal.

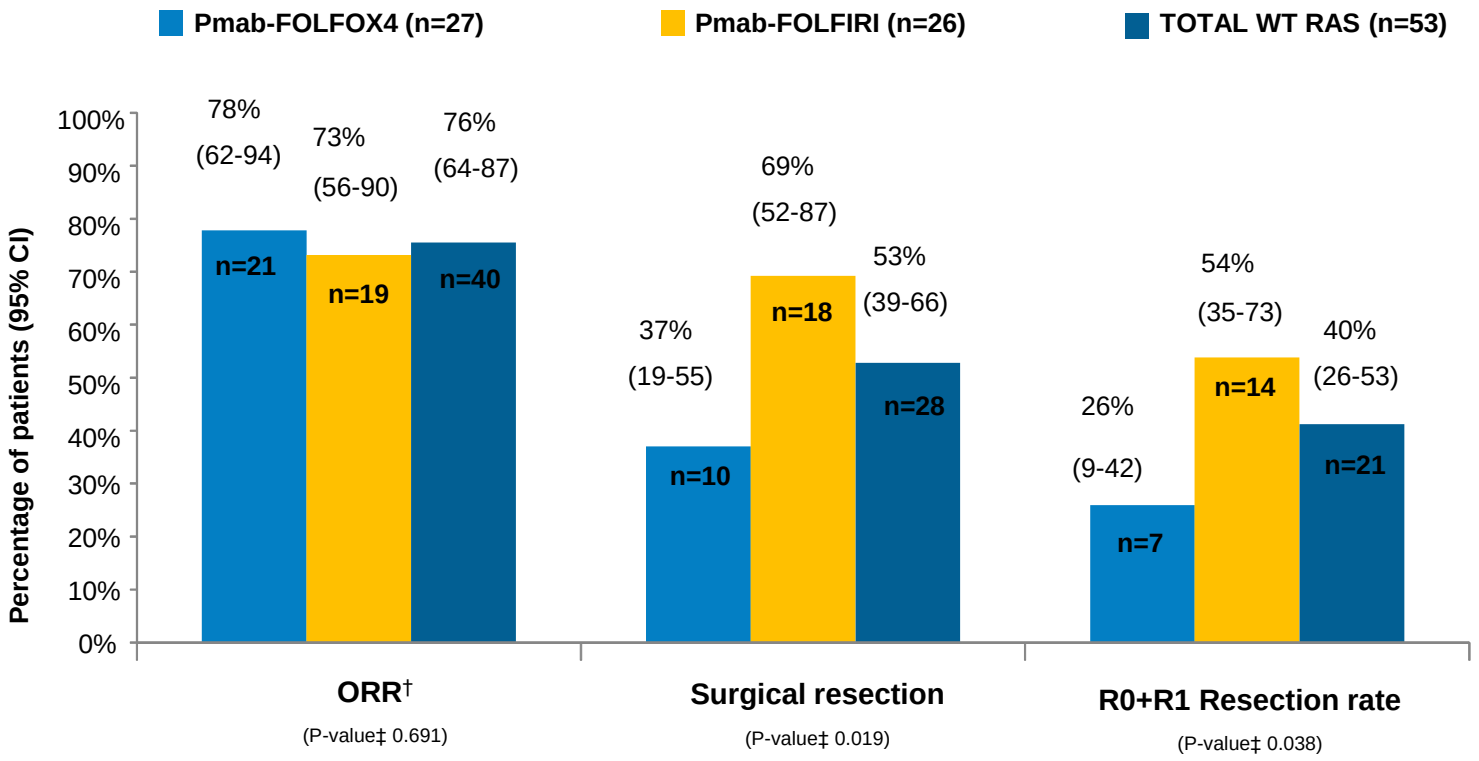
Carrato A, et al. Eur J Cancer 2017;81:191–202.
ClinicalTrials.gov identifier: NCT00885885.

LLD, liver-limited disease; PD, disease progression; SD, stable disease. *RAS* ascertainment rate: 83%. WT *RAS* = WT *KRAS/NRAS* exons 2/3/4.

Phase 2 PLANET study

Panitumumab + FOLFOX4 or FOLFIRI in untreated mCRC with multiple or unresectable liver-limited metastases

Response rate and resectability (WT RAS population)



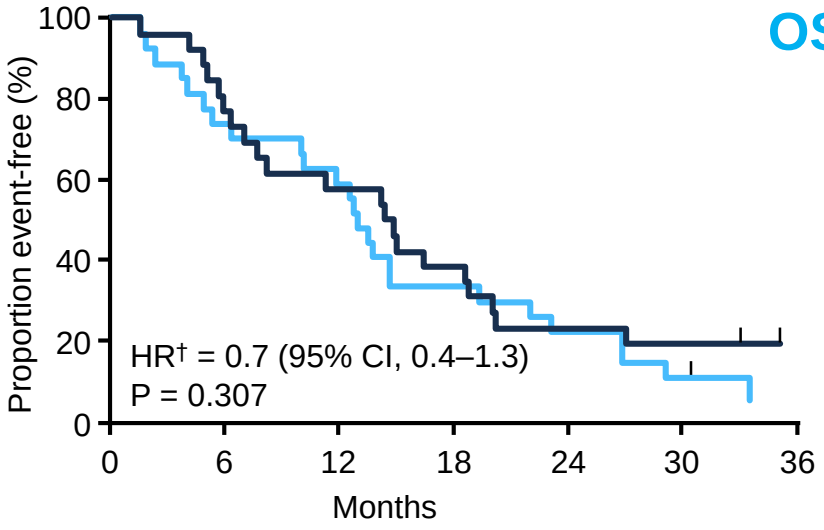
Carrato A, et al. Eur J Cancer 2017;81:191–202

†Not confirmed; patients resected before response confirmation
‡Panitumumab + FOLFOX4 vs Panitumumabb +FOLFIRI

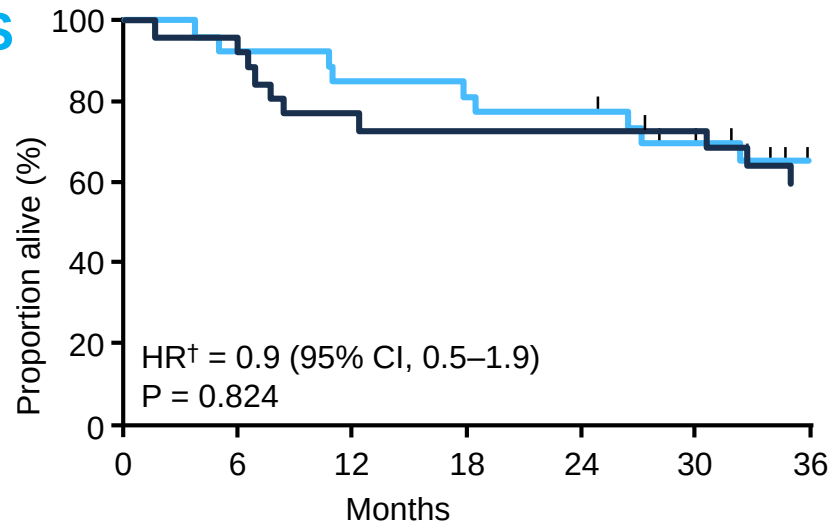
Phase 2 PLANET study

Panitumumab + FOLFOX4 or FOLFIRI in untreated mCRC with multiple or unresectable liver-limited metastases

PFS



OS



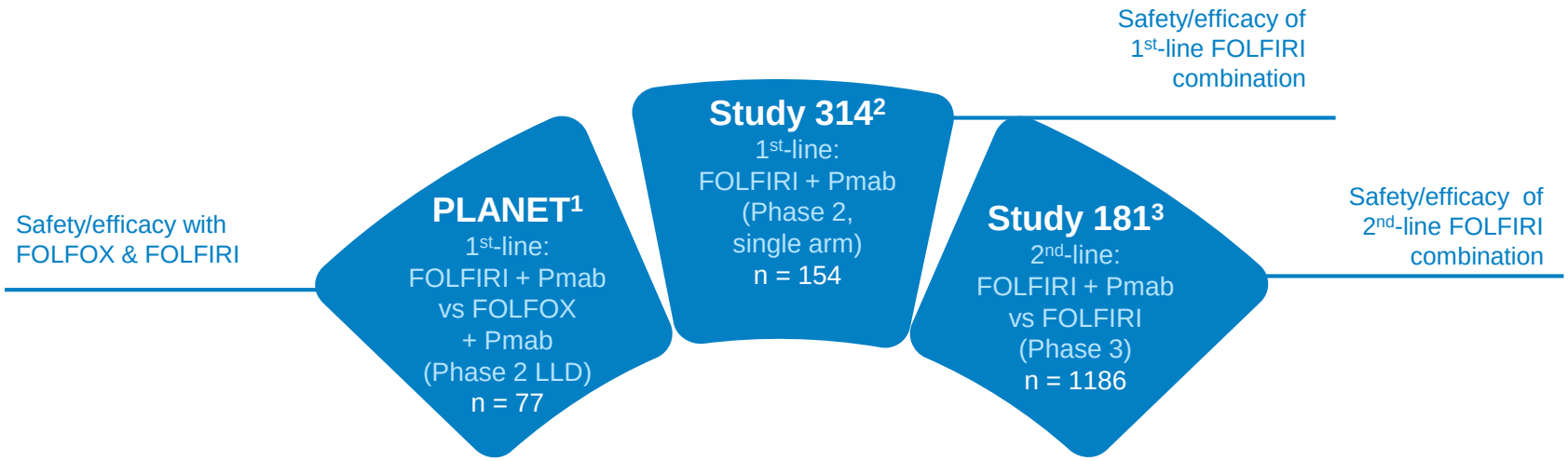
	Median, months (95% CI)
Panitumumab + FOLFOX4 (n = 27)	13 (6–19)
Panitumumab + FOLFIRI (n = 26)	15 (7–19)

	Median, months (95% CI)
Panitumumab + FOLFOX4 (n = 27)	39 (27–51)
Panitumumab + FOLFIRI (n = 26)	49 (31–56)

Carrato A, et al. Eur J Cancer 2017;81:191–202.

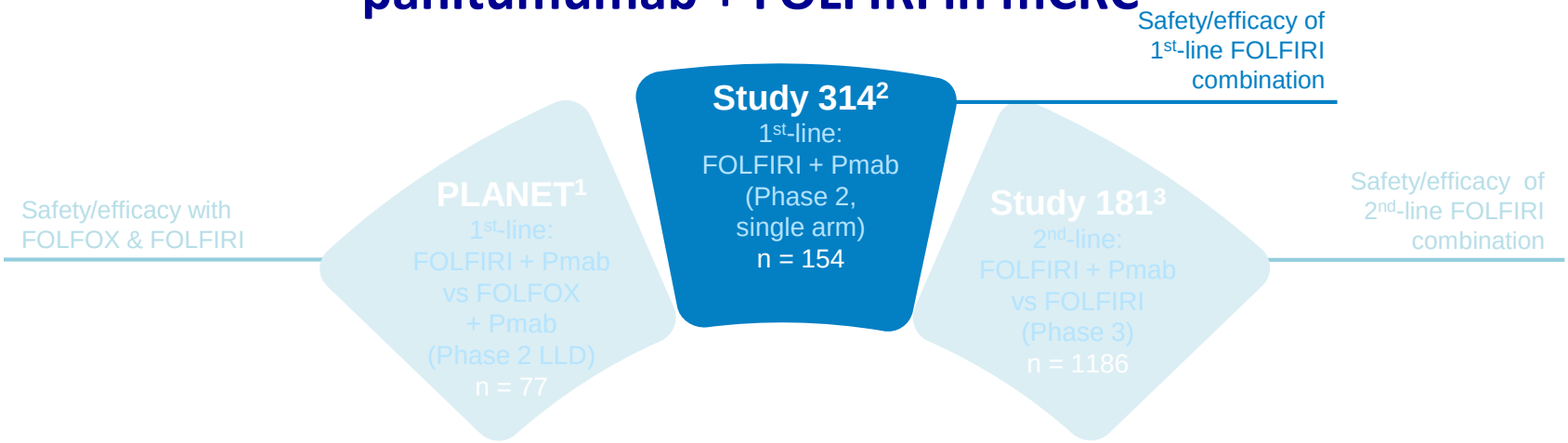
†Panitumumab + FOLFIRI vs panitumumab + FOLFOX4.

Studies of interest in relation to potential utility of 1st-line panitumumab + FOLFIRI in mCRC



1. Carrato A, et al. Eur J Cancer 2017;81:191–202; 2 Karthaus M, et al. Br J Cancer 2016;115:1215–22;
4. Peeters M, et al. J Clin Oncol 2010; 28:4706-13

Studies of interest in relation to potential utility of 1st-line panitumumab + FOLFIRI in mCRC



Study endpoints included: ORR (1º), DoR, PFS, TTP, safety[2,3]
Resection rates evaluated post hoc
Retrospective, descriptive *RAS* analysis[2]

Phase 2 20060314 study

Panitumumab + FOLFIRI in 1st-line treatment of mCRC[2]

Treatment until PD, unacceptable toxicity or consent withdrawal

Response evaluation Q8W until Week 48 then Q3M until PD

mCRC (n = 154) → **Panitumumab 6 mg/kg (Q2W) + FOLFIRI (Q2W)** → Follow-up

1. Carrato A, et al. Eur J Cancer 2017;81:191–202;
2. Karthaus M, et al. Br J Cancer 2016;115:1215–22;
3.. Peeters M, et al. J Clin Oncol 2010; 28:4706-13

RAS ascertainment rate: 93%.
WT RAS = WT KRAS/NRAS exons 2/3/4. DoR, duration of response; TTP, time to progression.

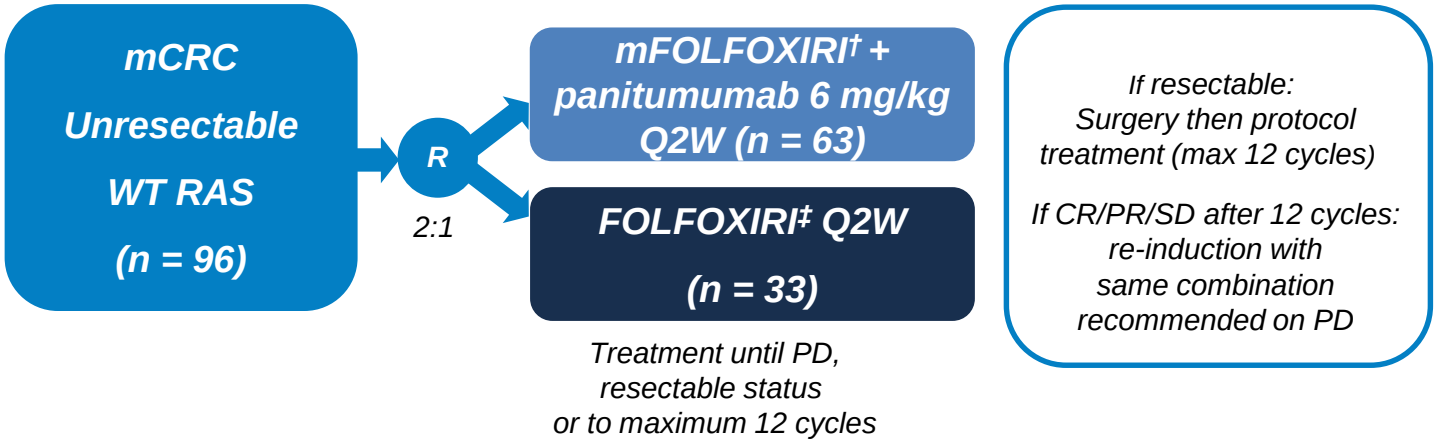
Key first-line studies: efficacy results (*RAS* WT)

	2006314	PLANET		20050203
	Pmab+FOLFIRI	Pmab+FOLFIRI	Pmab+FOLFOX	Pmab+FOLFOX
Total number of subjects enrolled per treatment arm	154	39	38	593
Overall *RAS* ascertainment rate	93%	83%		90%
Number of subjects with wild-type RAS status	69	26	27	259
ORR, %	58.8	73.1	77.8	58.7
PFS				
Median months (95% CI)	11.2 (7.6, 14.8)	14.8 (7.1, 18.7)	12.8 (6.2, 22.0)	10.1 (9.3, 12.0)
Hazard ratio vs. control arm (95% CI)	NA	0.86 (0.47, 1.56)		0.72 (0.58, 0.90)
OS				
Median OS, months (95% CI)	NE	45.8 (32.8, 51.5)	39.0 (26.5, NE)	26.0 (21.7, 30.4)
Hazard ratio vs. control arm (95% CI)	NA	0.97 (0.41, 2.28)		0.78 (0.62, 0.99)

EPAR Vectibix http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000741/WC500187313.pdf (accessed 23-

CI: confidence Interval; NA: Not applicable; NE: Not estimable; ORR: Overall response rate; PFS: progression-free survival; OS: Overall survival

Phase 2 VOLFI study



- Cohort 1: histologically confirmed and definitively inoperable or unresectable
- Cohort 2: chance of secondary resection with curative intent
- Primary endpoint: ORR

†Irinotecan 150 mg/m^2, oxaliplatin 85 mg/m^2, LV 200 mg/m^2, 5-FU 3000 mg/m^2 CIV;
‡irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, LV 200 mg/m^2, 5-FU 3200 mg/m^2 CIV.
Trial started with irinotecan 165 mg/m^2 (n = 2); irinotecan dose reduced to 130 mg/m^2 (n = 9) in 1st amendment and to 150 mg/m^2 (n = 52) in final amendment.

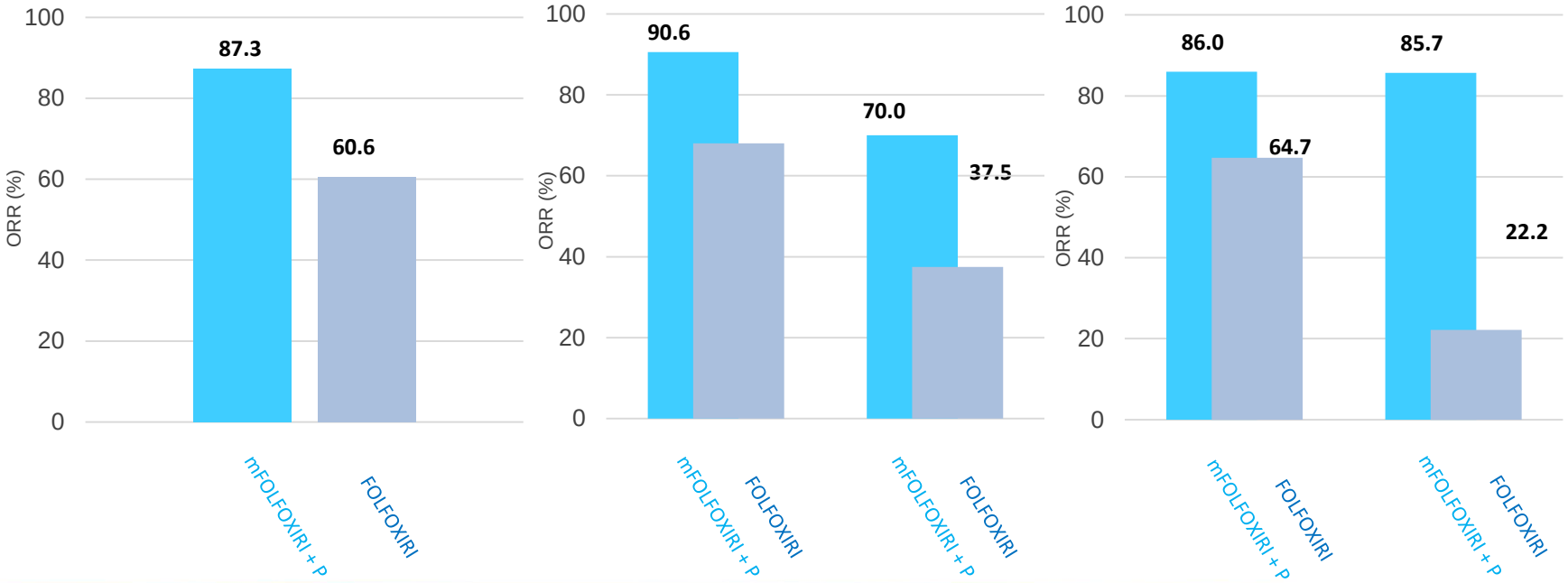
Study sponsor: AIO-Studien-gGmbH.
ClinicalTrials.gov identifier: NCT01328171 (accessed 18-09-17);
Geissler et al. ASCO congress 2018. Abstract 3509
Geissler et al. WCGIC 2018. Abstract O-024

CR, complete response; LV, leucovorin; PR, partial response; SD, stable disease.

Phase 2 VOLFI study

Objective Response Rate

Full Analysis Set	by Tumor Sidedness		by Genotype	
N = 96	Left N = 78	Right N = 18	RAS/BRAF wt N = 60	BRAF mut N = 16
P = 0.004	*P* = 0.021	*P* = 0.345	*P* = 0.081	*P* = 0.041
OR = 4.47	OR = 4.52	OR = 3.89	OR = 3.36	OR = 21.0
95%CI 1.61 – 12.38	1.30 – 15.72	0.54 – 27.89	0.90 – 12.55	1.50 – 293.25



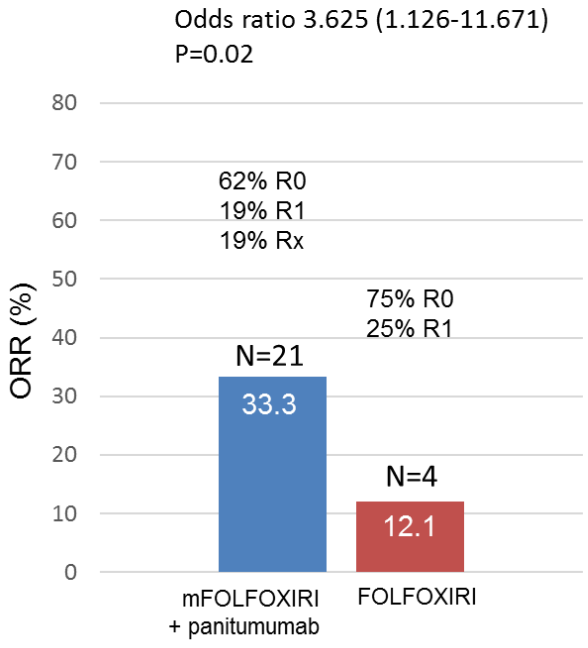
Phase 2 VOLFI study

Secondary Resection of Metastasis

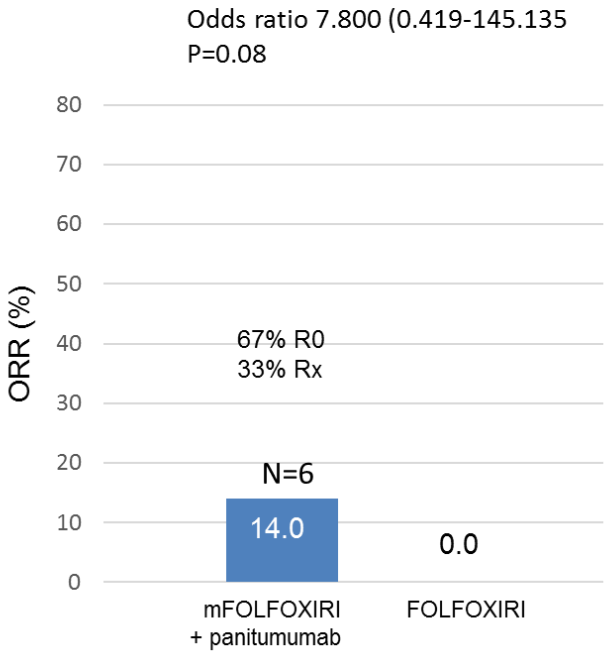
Relapse-free survival after first resection was 7.9 months in arm A and 4.0 months in arm B in full analysis set (*P* = 0.56)

Cohort	A		B	
	N	%	N	%
1: definitive non-resectable	43	68.3	22	66.7
2: potentially resectable	20	31.7	11	33.3

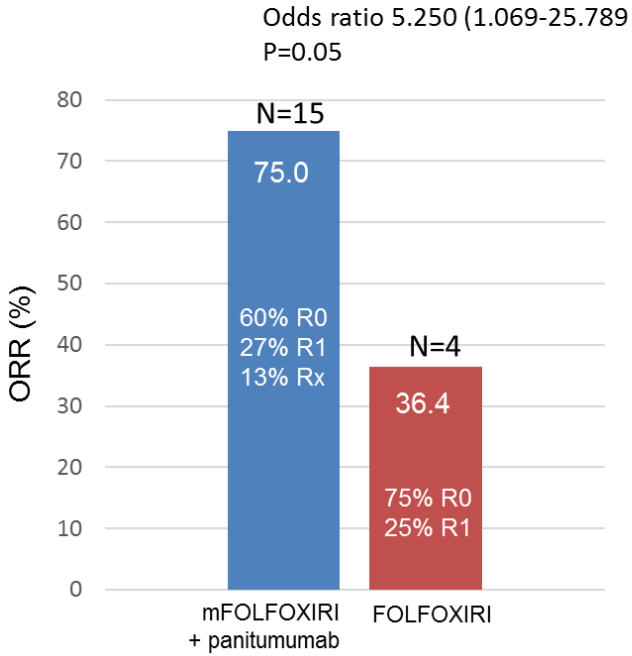
Full Analysis Set



Cohort 1



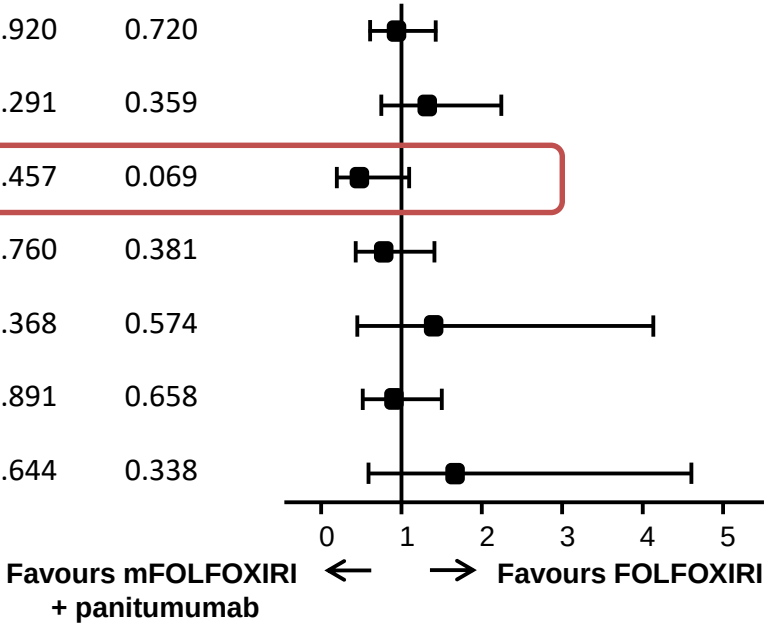
Cohort 2



Phase 2 VOLFI study

Progression Free Survival

WT *RAS*	Median PFS, months (95% CI)		HR	P-value
	mFOLFOXIRI + panitumumab	**FOLFOXIRI**		
Full analysis set	9.7 (9.0–11.5)	10.1 (7.8–12.1)	0.920	0.720
Cohort 1	9.0 (7.4–9.6)	10.7 (7.8–13.1)	1.291	0.359
Cohort 2	13.0 (10.8–28.3)	9.0 (4.4–22.1)	0.457	0.069
WT *RAS/BRAF*	12.0 (9.6–13.3)	10.8 (9.2–12.2)	0.760	0.381
MT *BRAF*	6.5 (3.5–7.2)	6.1 (2.4–10.5)	1.368	0.574
Left-sided primary	10.8 (9.2–12.4)	10.5 (7.7–12.2)	0.891	0.658
Right-sided primary	6.3 (4.0–9.3)	8.5 (6.2–13.1)	1.644	0.338



Geissler et al. WCGIC 2018. Abstract O-024

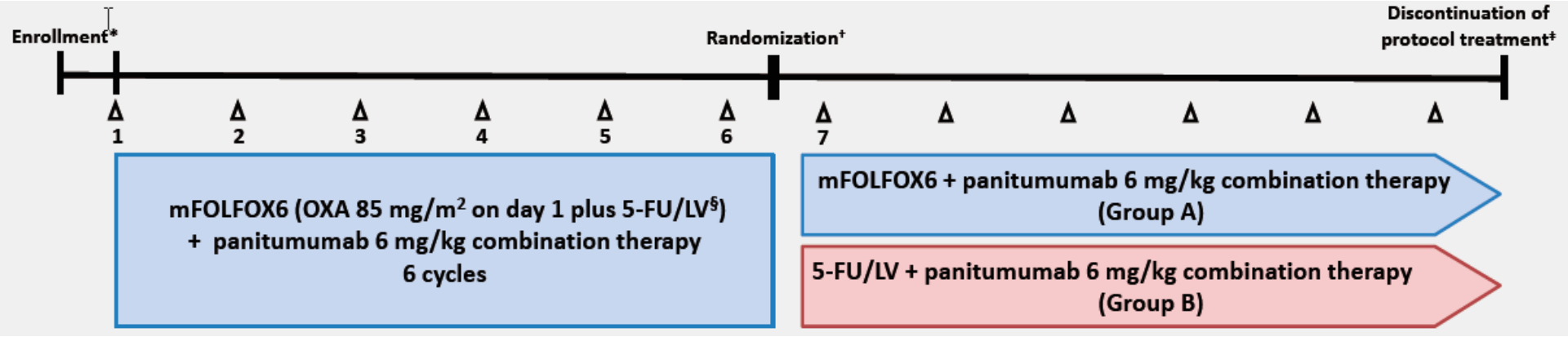
FOLFOXIRI + mAb
Efficacy results: ORR

VOLFI study	Overall response rate
RAS wild-type subgroup	
FOLFOXIRI + panitumumab	87.3%
RAS and BRAF wild-type subgroup	
FOLFOXIRI + panitumumab	86%
BRAF-mutation-positive group	
FOLFOXIRI + panitumumab	85.7%

TRIBE study	Overall response rate
RAS wild-type subgroup	
FOLFOXIRI + bevacizumab	63%
RAS and BRAF wild-type subgroup	
FOLFOXIRI + bevacizumab	65%
BRAF-mutation-positive group	
FOLFOXIRI + bevacizumab	56%

Phase 2 SAPPHIRE study

- Phase 2, multi-center, randomized, open-label, non-comparative, parallel-group study.[1]
- Patients received 6 treatment cycles (one cycle every 2 weeks) until randomization, and then for a further 9 months or until PD.



- Primary endpoint: PFS rate at 9 months after randomization.
- Secondary endpoints: PFS, OS, RR, TTF, and safety

Nakamura M et al. WGICC 2018. Abstract PD-011
1. Buyse, M. Drug Inf J. 2000;34:387–96.

OXA = oxaliplatin; PD = disease progression

Phase 2 SAPPHIRE study

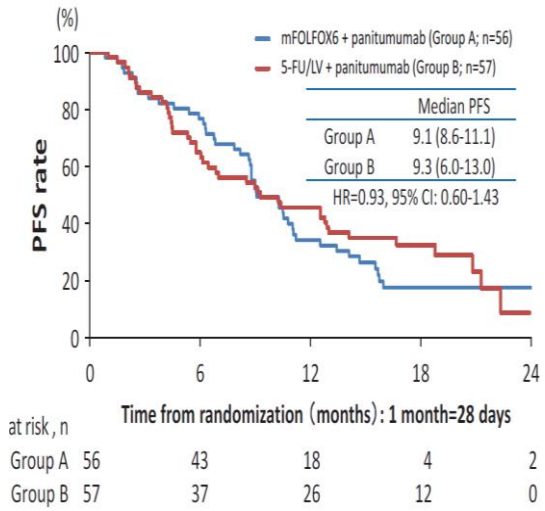
PFS rate after 9 months of randomization

	Group A (N=56)	Group B (N=57)
PFS rate (80% CI), %	46.4 (38.1–54.9)	47.4 (39.1–55.8)
H0: PFS rate ≤30%	p=0.0037	p=0.0021

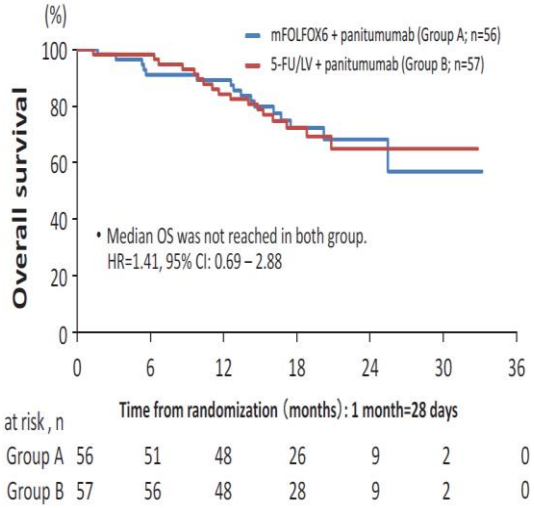
PN-related AEs* after enrollement

Group A and Group B both met the primary endpoint with a PFS rate 9 months significantly above the 30% threshold.

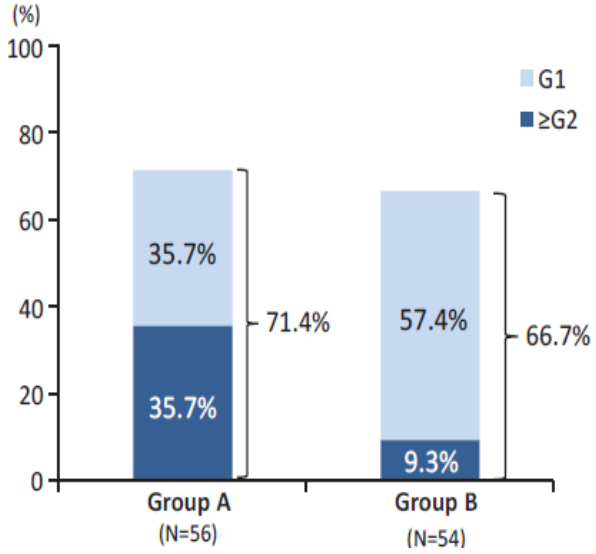
PFS after radomization



OS after radomization



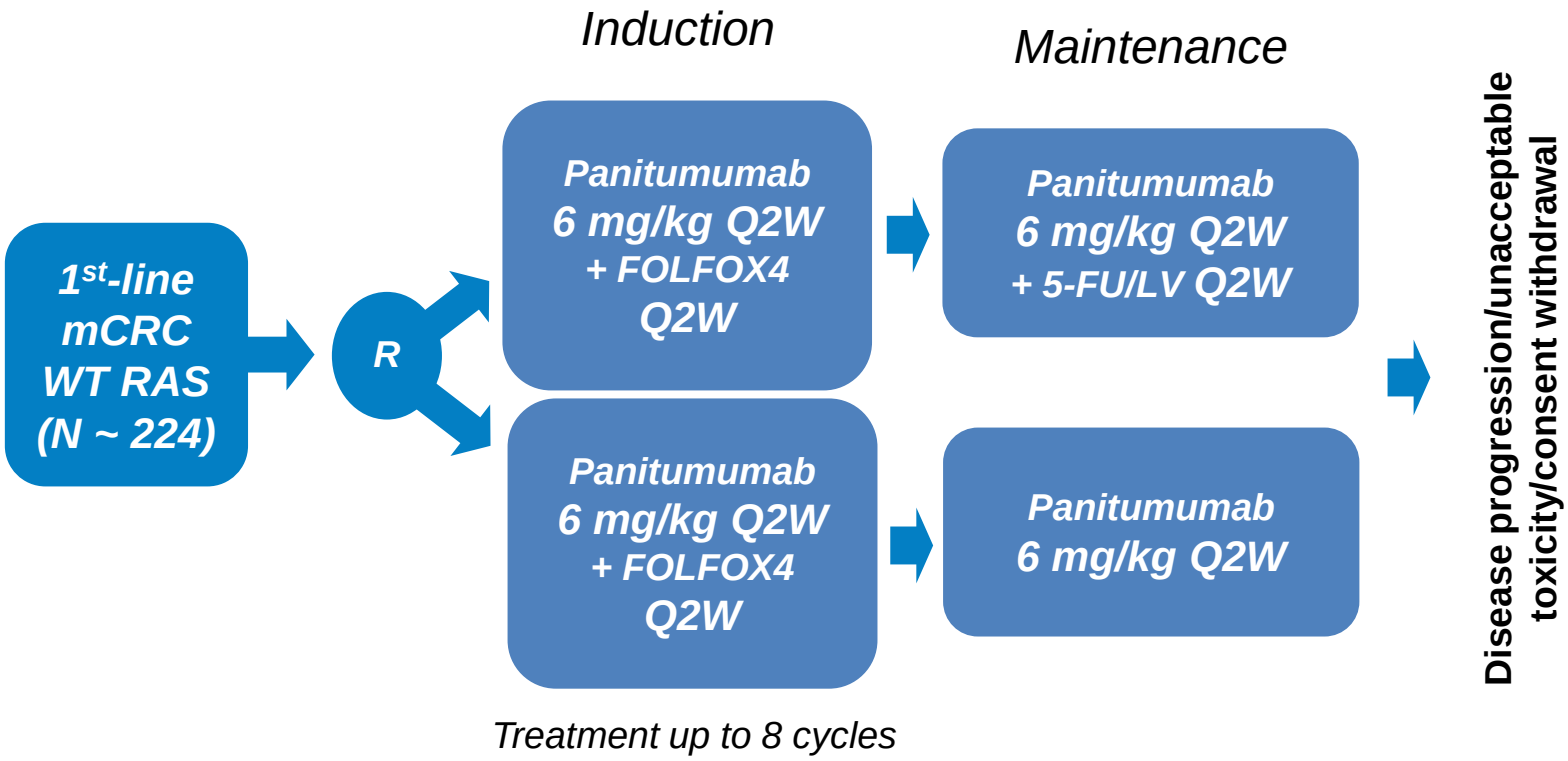
PN-related AEs* after enrollment



*PN related AEs; Peripheral motor neuropathy and Peripheral sensory neuropathy

Nakamura M et al. WGICC 2018. Abstract PD-011

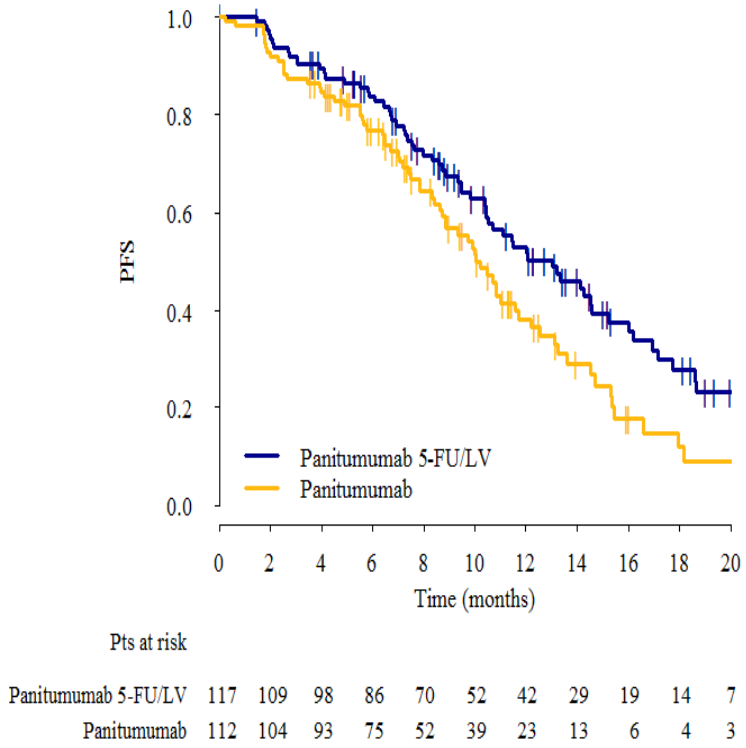
VALENTINO study



Pietrantonio F et al. ASCO 2018. Abstract 3505
Pietrantonio F et al. WCGIC 2018. Abstract O-016

VALENTINO study

Progression Free Survival



Median Follow Up, months (IQR): 13.8 (8.6-18.3)

HR =1.55; 95% CI: 1.09-2.20; p=0.011

	10-months PFS		Median PFS	
	Rate	95% CI	Months	95% CI
Arm A (5-FU/LV + pani)	62.8%	54.0-73.1	13.0	10.5-16.0
Arm B (pani)	52.8%	43.4-64.3	10.2	8.9-12.2

Pietrantonio F et al. ASCO 2018. Abstract 3505
Pietrantonio F et al. WCGIC 2018. Abstract O-016

CONCLUSIONS

- Panitumumab + chemotherapy achieved consistent efficacy results in several 1st line studies in RAS WT population: PRIME, PEAK, 314
- PLANET study showed very good results in terms of ORR, resection rates, PFS and OS for Panitumumab + FOLFOX/FOLFIRI in LLD patients
- The addition of Panitumumab to FOLFOXIRI resulted in a high ORR independently of the primary tumor location or RAS/BRAF status. Moreover, high secondary resection rates were achieved with this combination
- 5-FU/LV plus Panitumumab should be the preferred maintenance option for patients stopping oxaliplatin and continuing an active treatment.

¡¡¡Muchas gracias!!!