Phase II study of first-line mFOLFOX plus cetuximab (C) for 8 cycles followed by mFOLFOX plus C or single agent (s/a) C as maintenance therapy in patients (p) with KRAS wild type metastatic colorectal cancer (mCRC): the MACRO-2 trial

P. García Alfonso, M. Benavides, A. Sánchez Ruiz, C. Guillén-Ponce, M.J. Safont, J. Alcaide, A. Gómez, R. López, J.L. Manzano, M. Méndez Ureña, F. Rivera, J. Sastre, C. Grávalos, T. García García, J.I. Martin-Valadés, E. Falcó, E. González Flores, M. Navalón, E. Díaz Rubio, E. Aranda

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

MADRID 2014 ESMO congress

TTD
GRUPO DE TRATAMIENTO DE LOS TUMORES DIGESTIVOS

DISCLOSURE SLIDE

- Advisory role: Amgen, Bayer, Merk, Roche, Sanofi

MACRO-2 trial

Background

- Metastatic colorectal cancer (mCRC) is treated with a combination of cytotoxic drugs and targeted treatments. However, most of these treatments are palliative and need to be administered over prolonged periods of time.
- There is no clear evidence that continuing treatment with chemotherapy to progression or unacceptable toxicity is necessary for adequate control of the disease.
- MACRO-2 trial is one of a series of trials that seeks to optimize treatment with oxaliplatin-based regimens trying to prevent premature discontinuations for reasons other than disease progression, and thus improving the quality of life of these patients while maintaining treatment efficacy.
- Although different studies have evaluated single agent bevacizumab after induction chemotherapy plus bevacizumab, but there are no data regarding the use of cetuximab in new treatment strategies for mCRC using shorter chemotherapy schemes.

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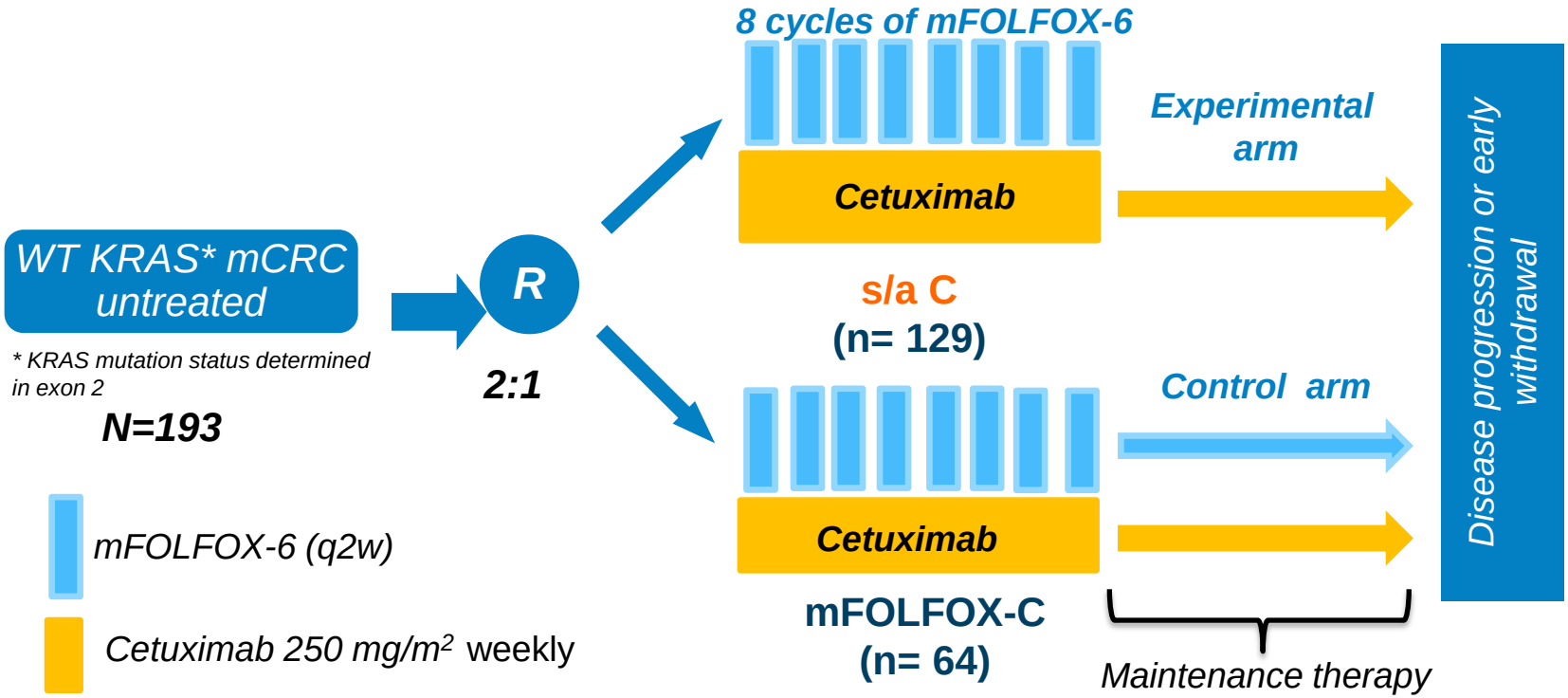
Design



- ***Sponsor:*** *Spanish Cooperative Group for Digestive Tumour Therapy (TTD)*
- ***Study:*** TTD-09-04
- ***Principal investigators****: Dr. Eduardo Díaz Rubio & Dr. Enrique Aranda Aguilar*
- ***ClinicalTrials.gov identifier:*** NCT01161316

GRUPO DE TRATAMIENTO DE LOS TUMORES DIGESTIVOS

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Statistical Design

Sample Size:

- Non-inferiority hypothesis in terms of the proportion of patients free of progression at 9 months
- 47% of patients in the standard arm would be progression-free at 9 months and a maximum difference of 15% was expected in the experimental arm.
- Sample size of 192 patients, 128 in the experimental arm + 64 in the control arm (sample ratio 2:1), α=0.1 and power of 80%

Populations:

- ITT population: all randomized patients
- Safety population: all patients with, at least, one dose of treatment

Statistical Analysis:

- Descriptive statistics, 95% CI, and Kaplan-Meier plots

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Study Objectives

- **Primary Endpoint**
  - Progression free survival (PFS) at 9 months
- **Secondary Endpoints:**
  - PFS
  - Overall survival (OS)
  - Objective response rate (ORR)
  - Resectability of the disease (R0)
  - To assess hypomagnesaemia as a predictor of treatment efficacy
  - CTC enumeration
  - Safety profile of the two treatment groups

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Eligibility criteria: main selection criteria

- Age ≥ 18 years and < 71
- ECOG performance status ≤ 2
- Measurable disease (RECIST)
- Wild-type KRAS CRC
- Not amenable to radical surgery of metastases.
- Life expectancy >12 weeks
- First evidence of chemotherapy-naïve metastatic disease
- No adjuvant chemotherapy within 6 months before randomization
- No major surgery or radiotherapy during the 4 weeks prior to inclusion in the study
- No previous administration of monoclonal antibodies, agents inhibiting EGFR signal transduction or EGFR-targeted treatment.
- No clinically relevant peripheral neuropathy.

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Treatment

- **mFOLFOX-6-C (control arm)**
  - Oxaliplatin 85 mg/m^2, IV, d1, q2w
  - Folinic acid 400 mg/m^2, IV, d1, q2w
  - 5-FU 400 mg/m^2 IV bolus, d1, q2w
  - 5-FU 2400 m g/m^2 continuous infusion over 46 hours, d1, q2w
  - Cetuximab 250 mg/m^2 , IV, weekly
  - Administered until disease progression or early withdrawal
- **s/a C (experimental arm)**
  - 8 cycles of mFOLFOX-6-C q2w
  - Cetuximab 250 mg/m^2 , IV, weekly until disease progression or early withdrawal

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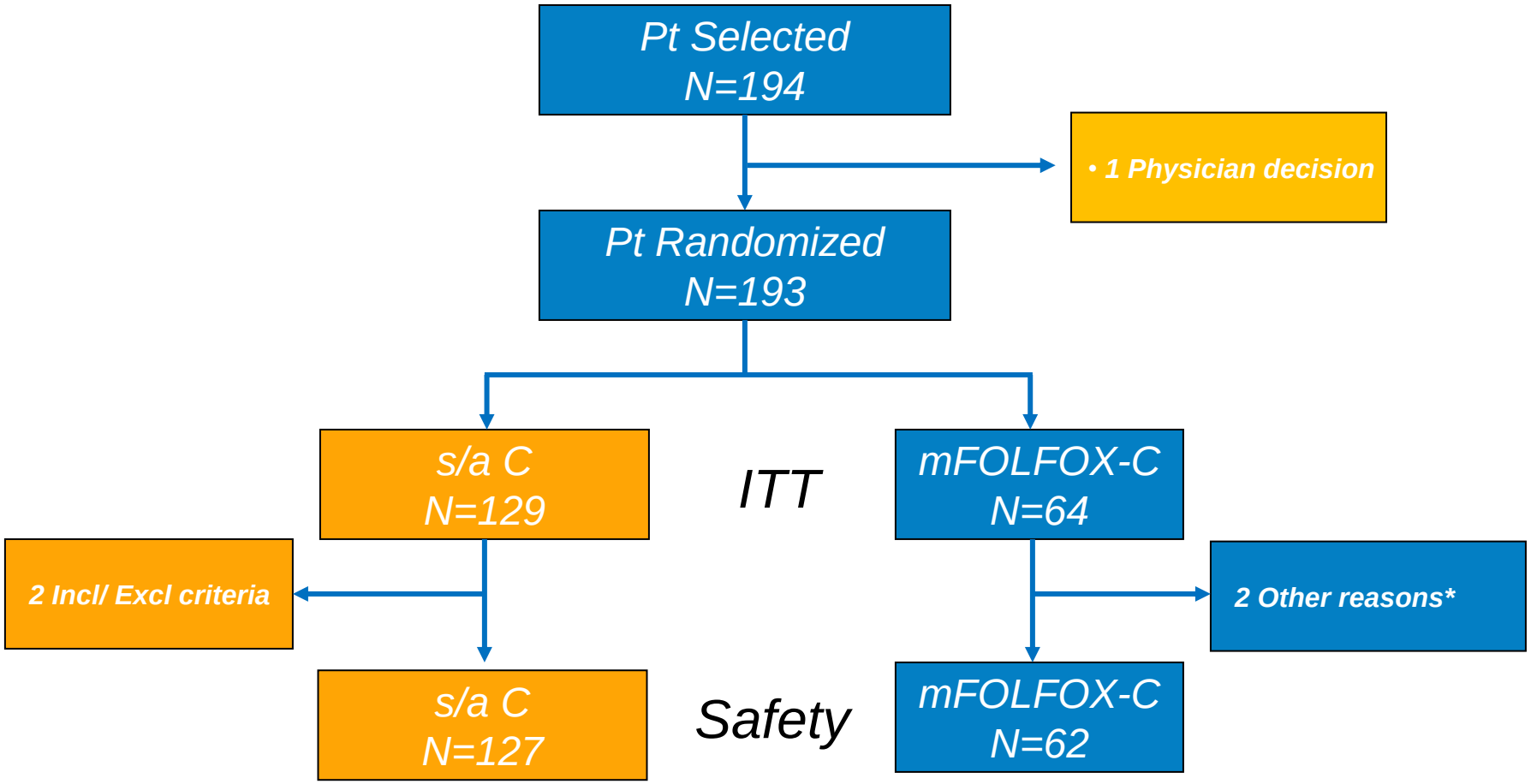
CONSORT



** One patient presented anatomical problems for the use of catheter so the physician decided to change the treatment and the other patient presented a protocol violation (more than 14 days between the patient inclusion and treatment start)*

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Demographic and clinical data at baseline

	s/a C N = 129	mFOLFOX-C N = 64
Age median (range), years	61 (33 - 74)	60 (34 - 73)
Sex: Male/Female, %	64/36	67/33
ECOG PS 0/1/2, %	50/46/3	47/45/8
Primary tumour site colon/rectum/both, %	61/22/15	66/23/11
Metastatic site liver, %	80	88
Previous adjuvant CT/RDT, %	8/7	8/6
Nº of organs affected	2 (1-6)	2 (1-3)
Surgical of primary tumour, %	53	61

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Results: primary endpoint

Progression free-survival at 9 months

	s/a C N = 129	FOLFOX-C N = 64
Patients free of progression at 9 months, n (%)	82 (63.6)	46 (71.9)
OR (95%CI)	0.6827 (0.3556 to 1.3108)	
P-value	0.25	

Median duration of follow-up was 13.9 months (range, 0-38)

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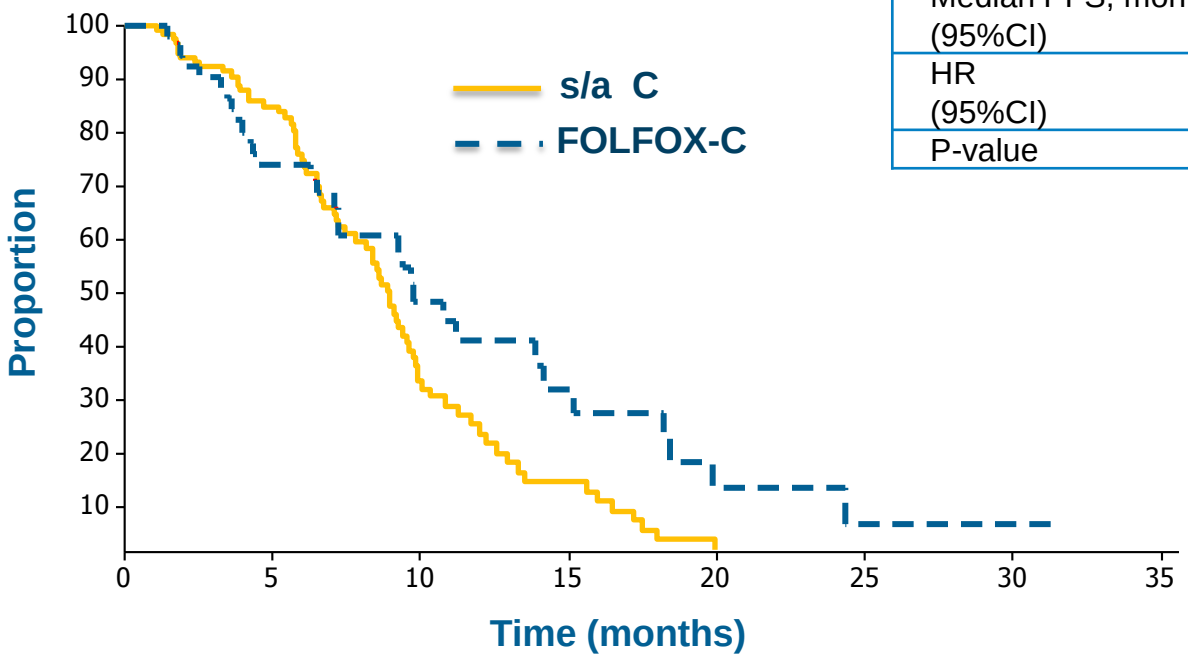
Results: secondary endpoint

Progression free-survival



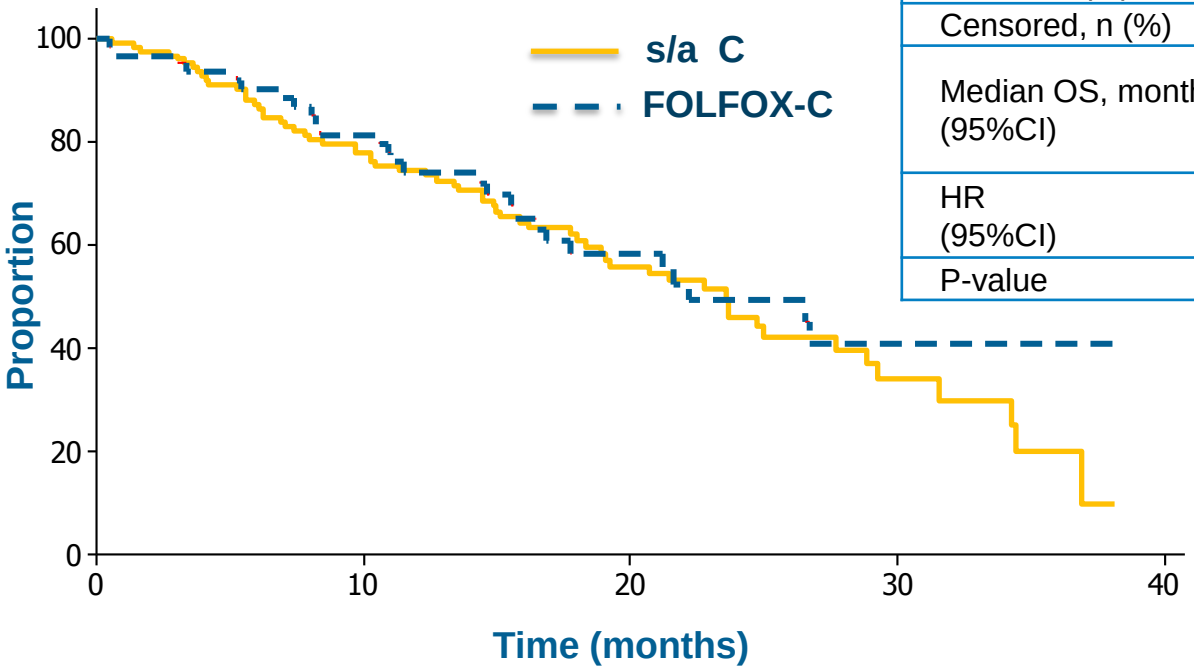
	s/a C N = 129	FOLFOX-C N = 64
Events, n (%)	75 (58.1)	31 (48.4)
Censored, n (%)	54 (41.9)	33 (51.6)
Median PFS, months (95%CI)	**8.9** (7.8 to 9.6)	**9.8** (7.2 to14.2)
HR (95%CI)	0.690 (0.4498 to 1.0580)	
P-value	0.09	

Median duration of follow-up was 13.9 months (range, 0-38)

MACRO-2 trial

Results: secondary endpoint

Overall survival



	s/a C N = 129	FOLFOX-C N = 64
Events, n (%)	63 (48.8)	27 (42.1)
Censored, n (%)	66 (51.2)	37 (57.8)
Median OS, months (95%CI)	**23.6** (18.3 to 28.9)	**22.2** (16.4 –not estimable)
HR (95%CI)	1.151 (0.7330 to 1.8070)	
P-value	0.54	

Median duration of follow-up was 13.9 months (range, 0-38)

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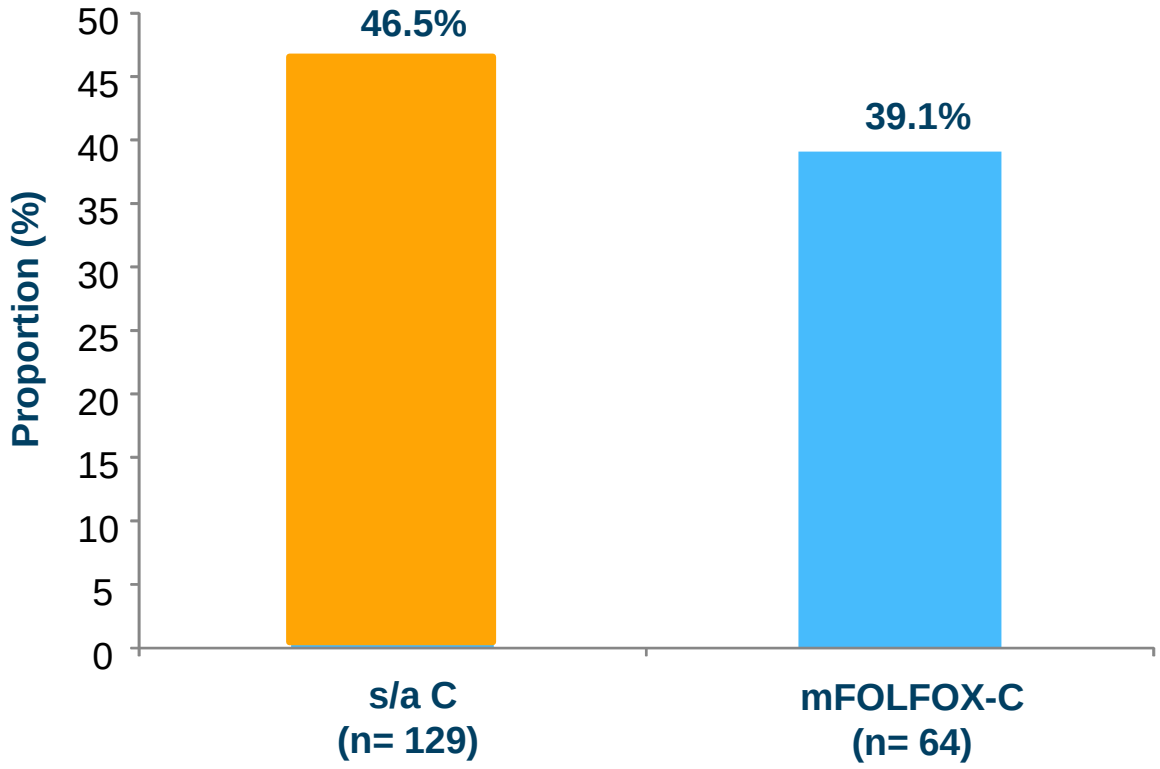
Results : secondary endpoint

Objective response rate (confirmed responses)

Odds ratio (95% CI) = 1.3565 (0.7372-2.4961)
P-value= 0.33



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Safety

Treatment-related AEs

N (%)	s/a C N = 127	mFOLFOX-C N = 62
G 3-4 AEs	78 (61.4)	37 (59.7)
SAEs	11 (8.7)	6 (9.7)
AEs leading to death*	2 (1.6)	1 (1.6)

** s/a C group: Femoral pseudoaneurysm in one patient and acute prerenal failure.in the other patient*

mFOLFOX-C group: bronchopneumonia

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Safety

Grade 3/4 selected treatment-related adverse events

	s/a C N = 127	mFOLFOX-C N = 62	P-value
Neutropenia, n (%)	32 (25.2)	16 (26.0)	0.928
Rash acneiform, n (%)	17 (13.4)	14 (22.6)	0.109
Neuropathy, n (%)	2 (1.6)	9 (14.5)	<0.001
Asthenia, n (%)	10 (7.9)	3 (4.8)	0.551
Diarrhoea, n (%)	9 (7.1)	4 (6.5)	1.000
Mucositis, n (%)	9 (7.1)	4 (6.5)	1.000

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Treatment compliance

	s/a C N = 127	mFOLFOX-C N = 62
Induction phase cycles, median (range)	8 (1-8)	8 (1-8)
Maintenance phase cycles, median (range)*	7 (1-69)	5 (1-20)

**57.5% patients in the s/a C group and 48.4% patients in the mFOLFOX-C group continued with the maintenance treatment*

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Treatment discontinuation reasons

N (%)	s/a C N = 129	mFOLFOX-C N = 64
Disease progression	60 (48.8)	18 (30.0)
Adverse events/toxicity	29 (23.6)	16 (26.7)
Surgery	20 (16.3)	15 (25.0)
Physician decision	5 (4.1)	0 (0.0)
Patient decision	1 (0.8)	7 (11.7)
Other reasons	8 (6.5)	4 (6.6)

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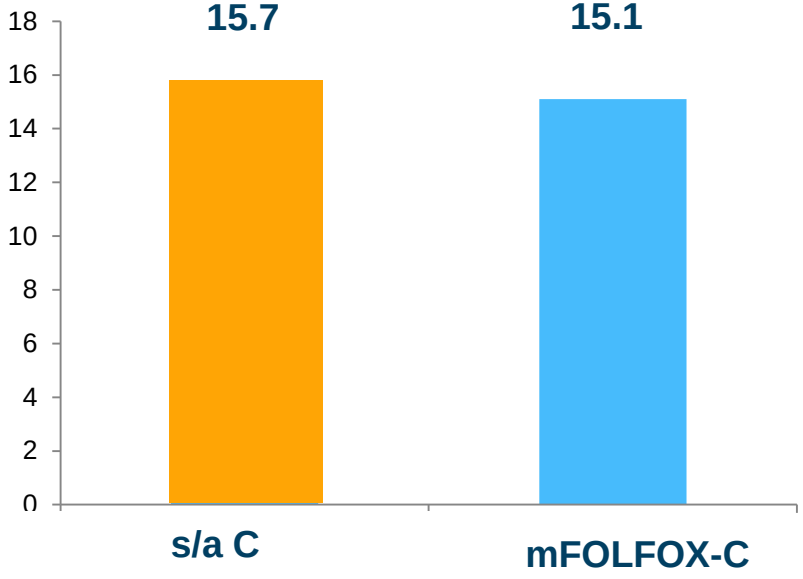
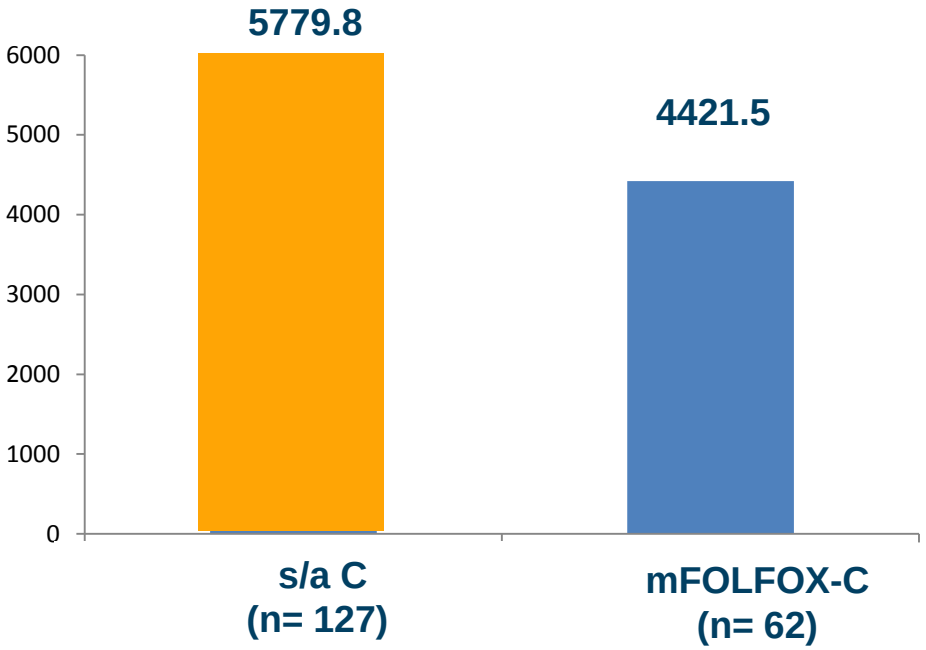
Treatment compliance

Cetuximab exposure

% Cycles Reduced or Suspended



Mean Cumulative Dose (mg/m²)



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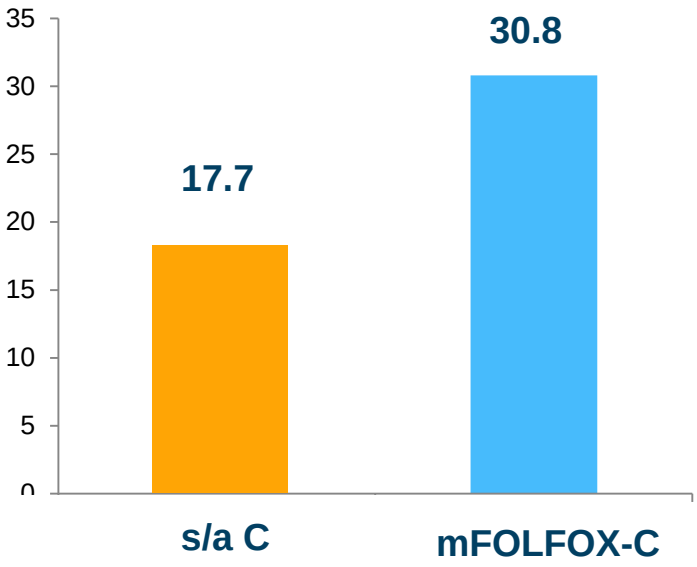
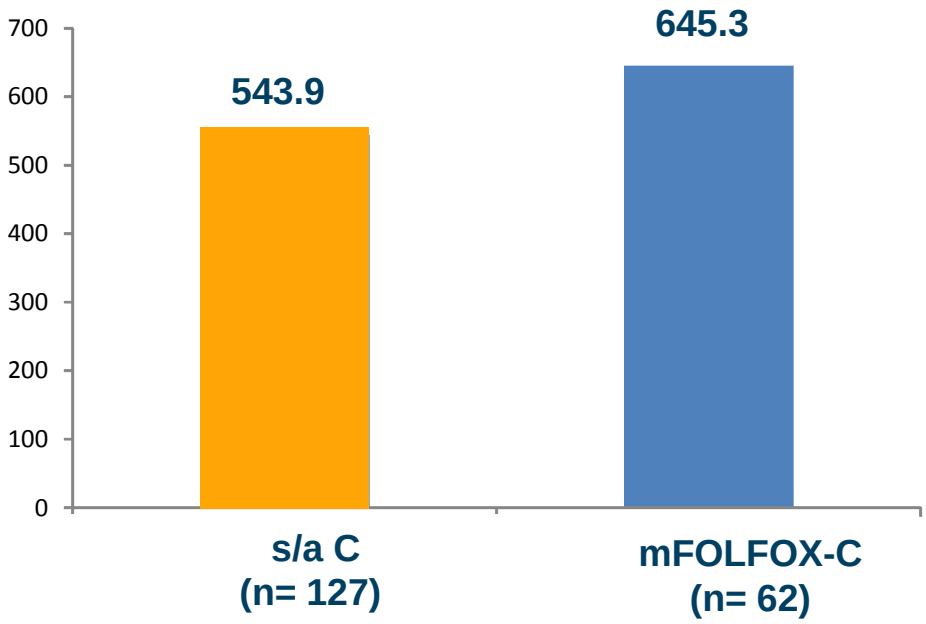
Treatment compliance

Oxaliplatin exposure

% Cycles Reduced or Suspended



Mean Cumulative Dose (mg/m^2)



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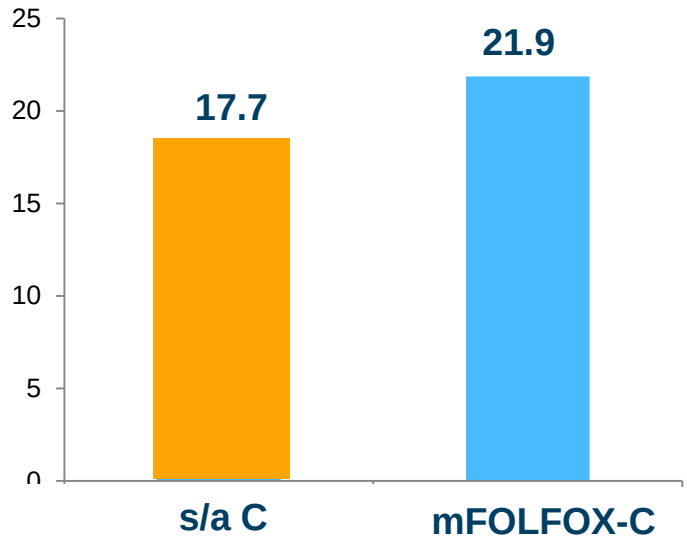
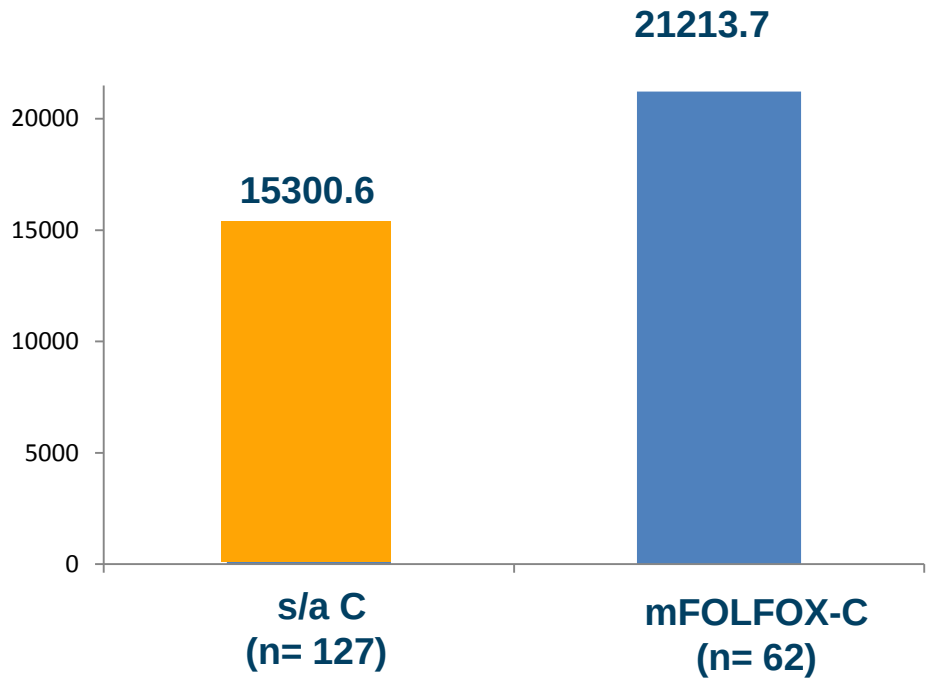
Treatment compliance

5-FU exposure

% Cycles Reduced or Suspended



Mean Cumulative Dose (mg/m²)



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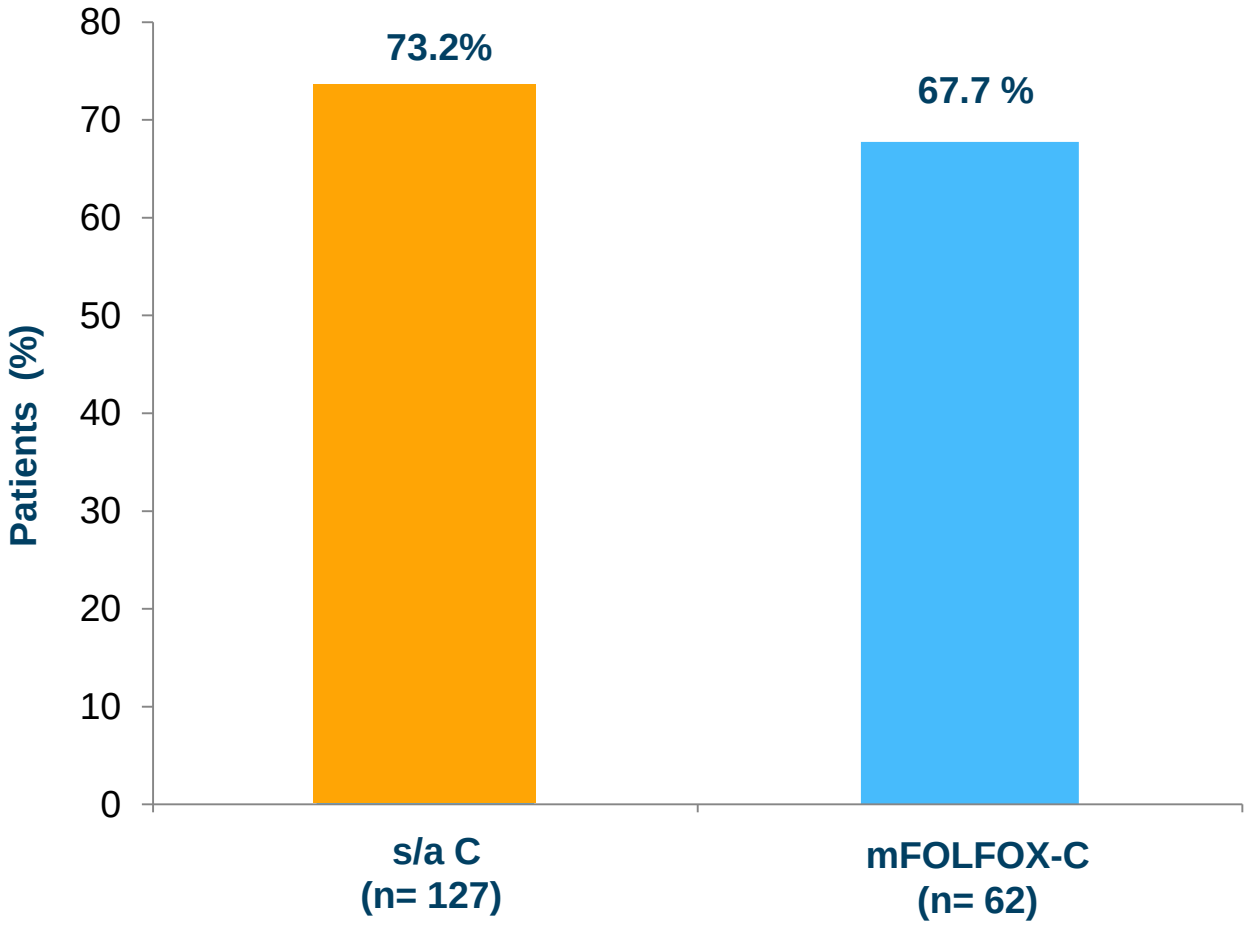
Treatment upon progression

2nd lines



MACRO-2 trial

Conclusions

- The results of the present hypothesis-generating phase II exploratory trial with a non-inferiority design suggest that maintenance therapy with single agent cetuximab following mFOLFOX plus cetuximab induction is not inferior to continuing treatment with mFOLFOX plus cetuximab with respect to PFS at 9 months.
- Analysis of *RAS* status (KRAS and NRAS exon 2,3,4) and its predictive role in efficacy variables is ongoing.
- Analysis of resectability of the disease (R0), hypomagnesaemia as predictor efficacy factor and CTC enumeration is ongoing.
- Phase III studies are needed to confirm the benefit of cetuximab as maintenance therapy following induction chemotherapy

MACRO-2 trial

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