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

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

DISCLOSURE SLIDE

Advisory role: Amgen, Bayer, Merck, Roche, Sanofi

MACRO-2 trial

Background

- Metastatic colorectal cancer (mCRC) is frequently treated over prolonged periods of time but there is no clear evidence that continuing the whole treatment until progression or unacceptable toxicity is necessary for adequate control of the disease.

- Many different studies have evaluated the role of maintenance therapy after induction, but only the MACRO-2 trial, another exploratory phase II (COIN B) and a phase III (NORDIC-VII) have evaluated the role of cetuximab as maintenance therapy.

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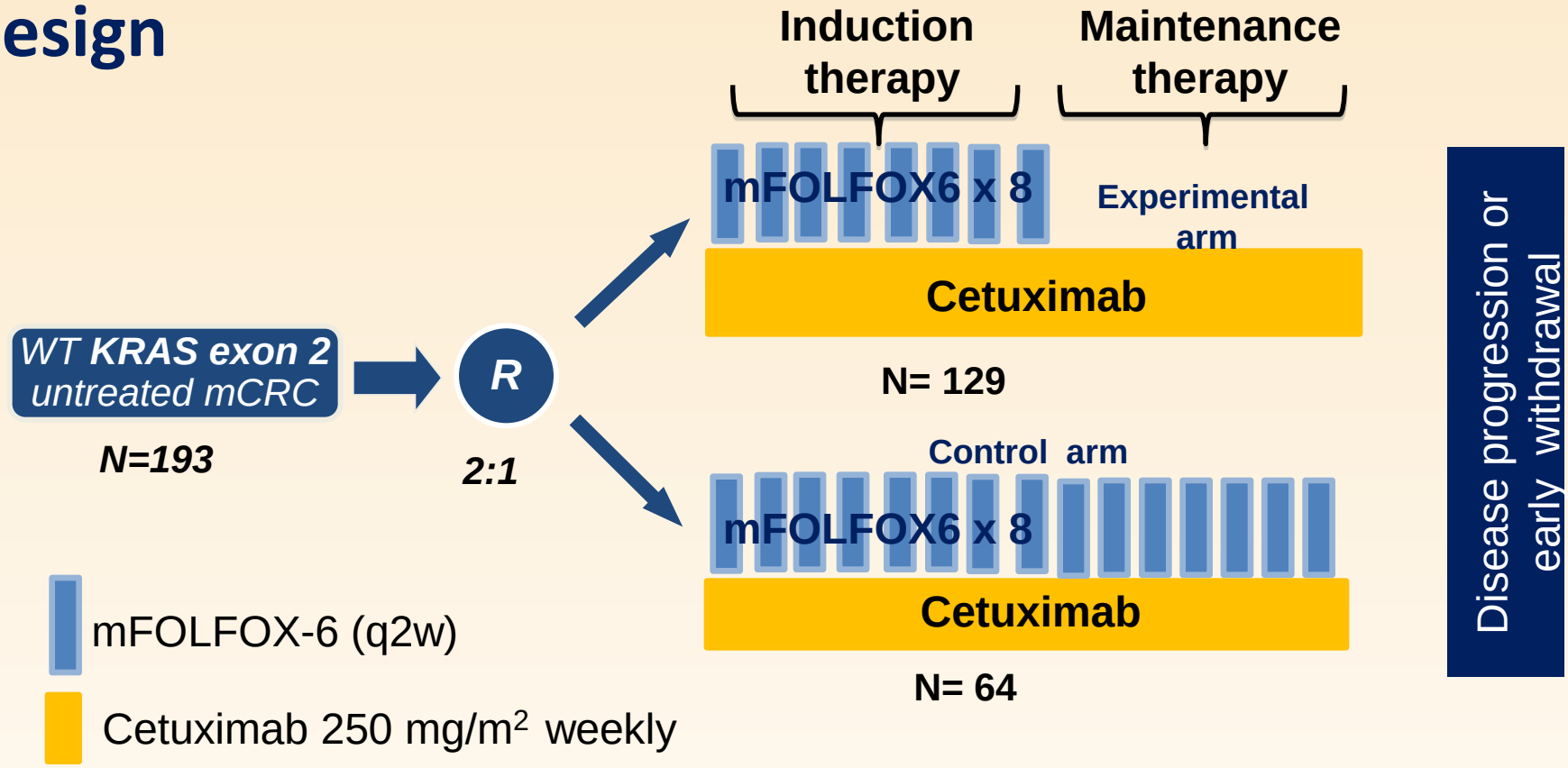
Design



- ***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

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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**
  - **Proportion of patients free of progression 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 exon 2 mCRC**
- Not amenable to radical surgery of metastases.
- Life expectancy >12 weeks
- 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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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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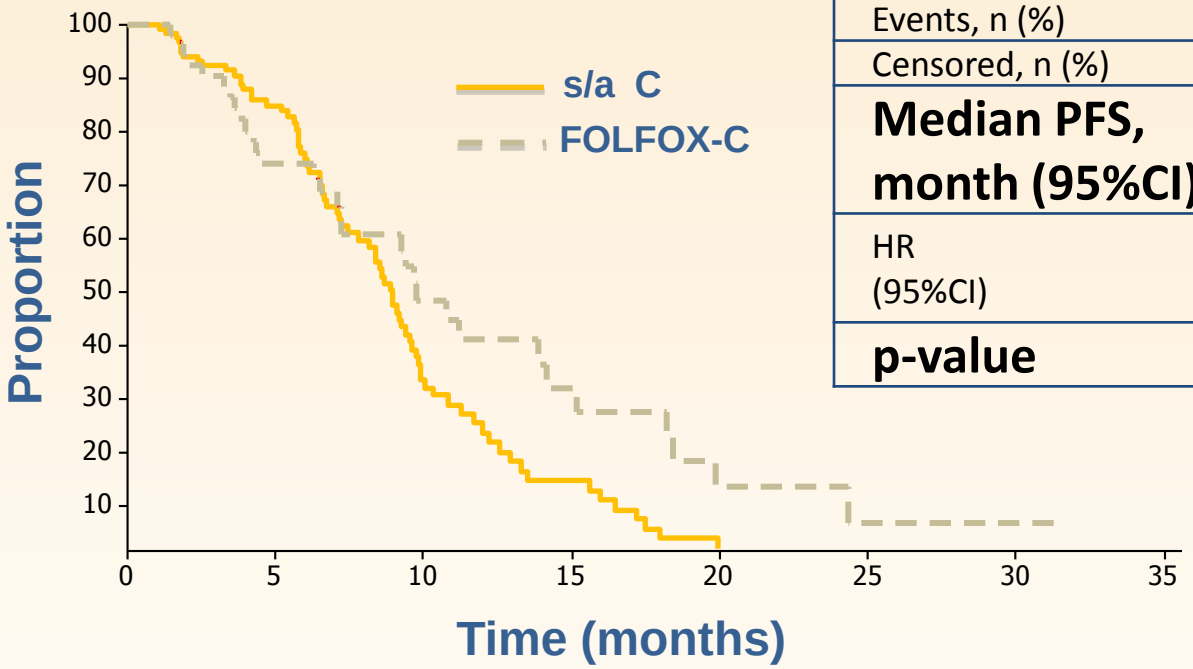
Results: secondary endpoint

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, month (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)

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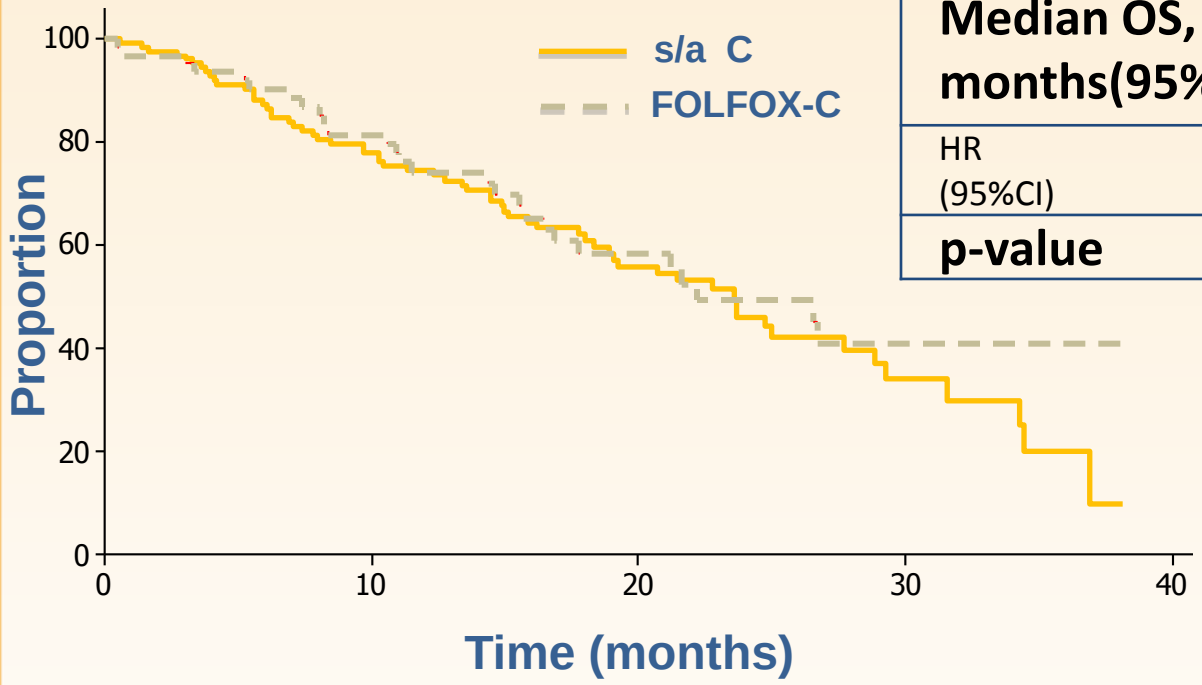
Results: secondary endpoint

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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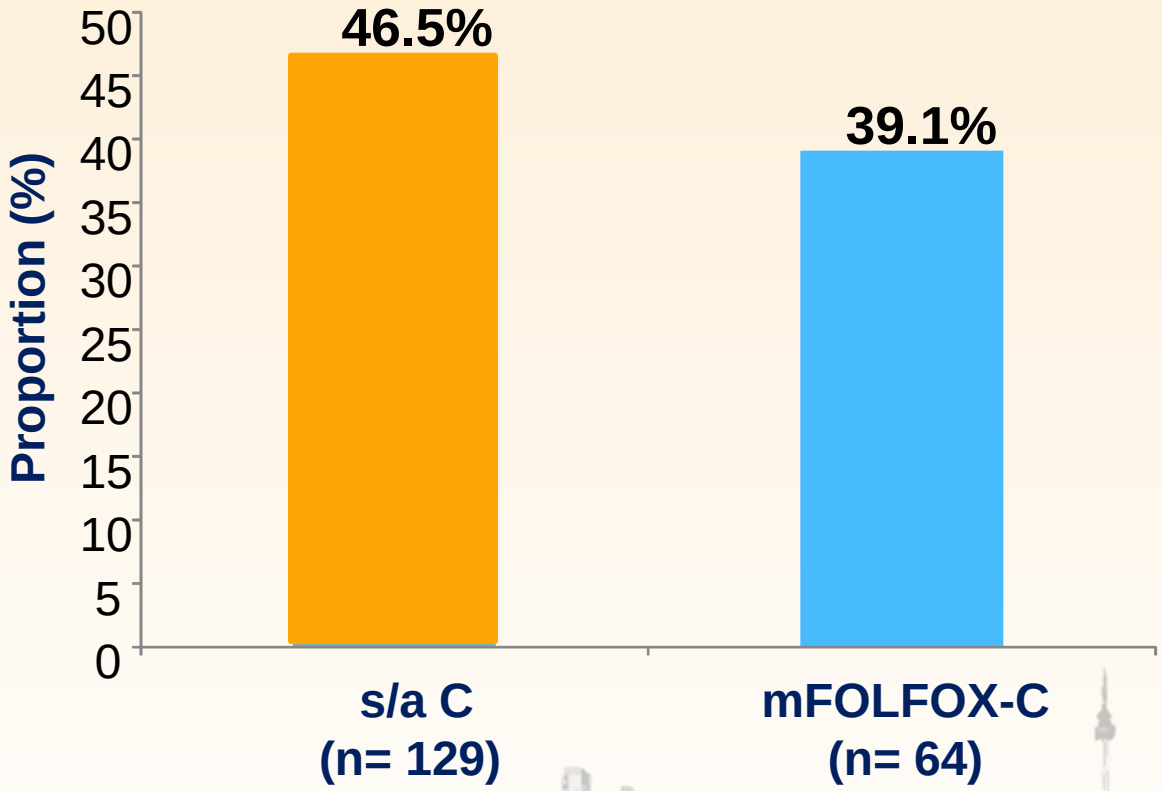
Results : secondary endpoint

Objective response rate (confirmed responses)

OR (95%CI):1.3565 (0.7372-2.4961) ; p-value= 0.33



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Safety

Treatment-related AEs	s/a C N=127	mFOLFOX-C N=62
G 3-4 AEs: N (%)	78 (61.4)	37 (59.7)
AEs leading to death: N%	2 (1.6)	1 (1.6)

Grade 3/4 selected treatment-related AE	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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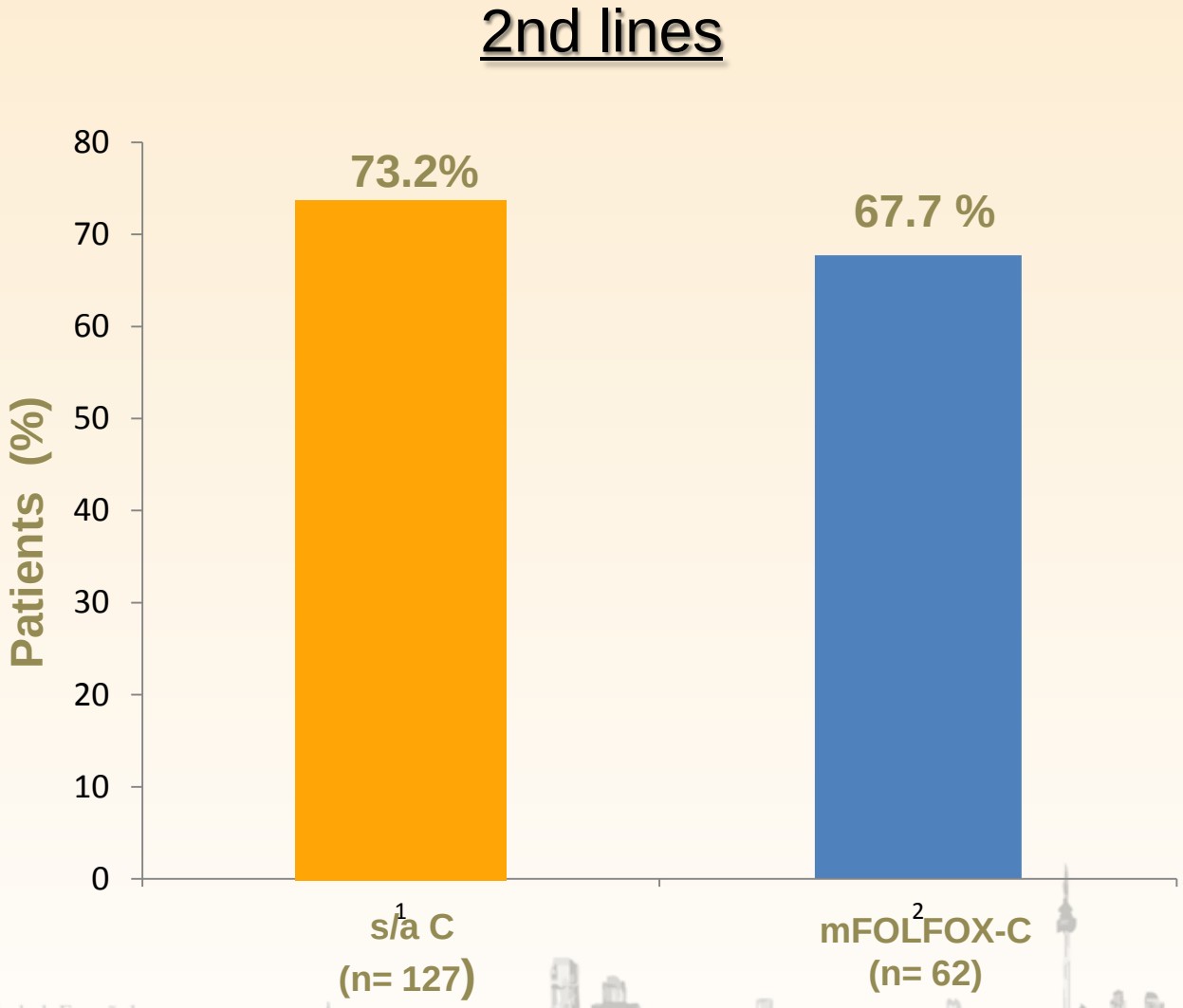
Treatment upon progression



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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), resectability, hypomagnesemia and CTC is ongoing

- This is a phase II exploratory study so Phase III studies are needed to confirm the benefit of cetuximab as maintenance therapy following induction chemotherapy

MACRO-2 trial

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