
# Update on Chemotherapy for Metastatic Colorectal Cancer

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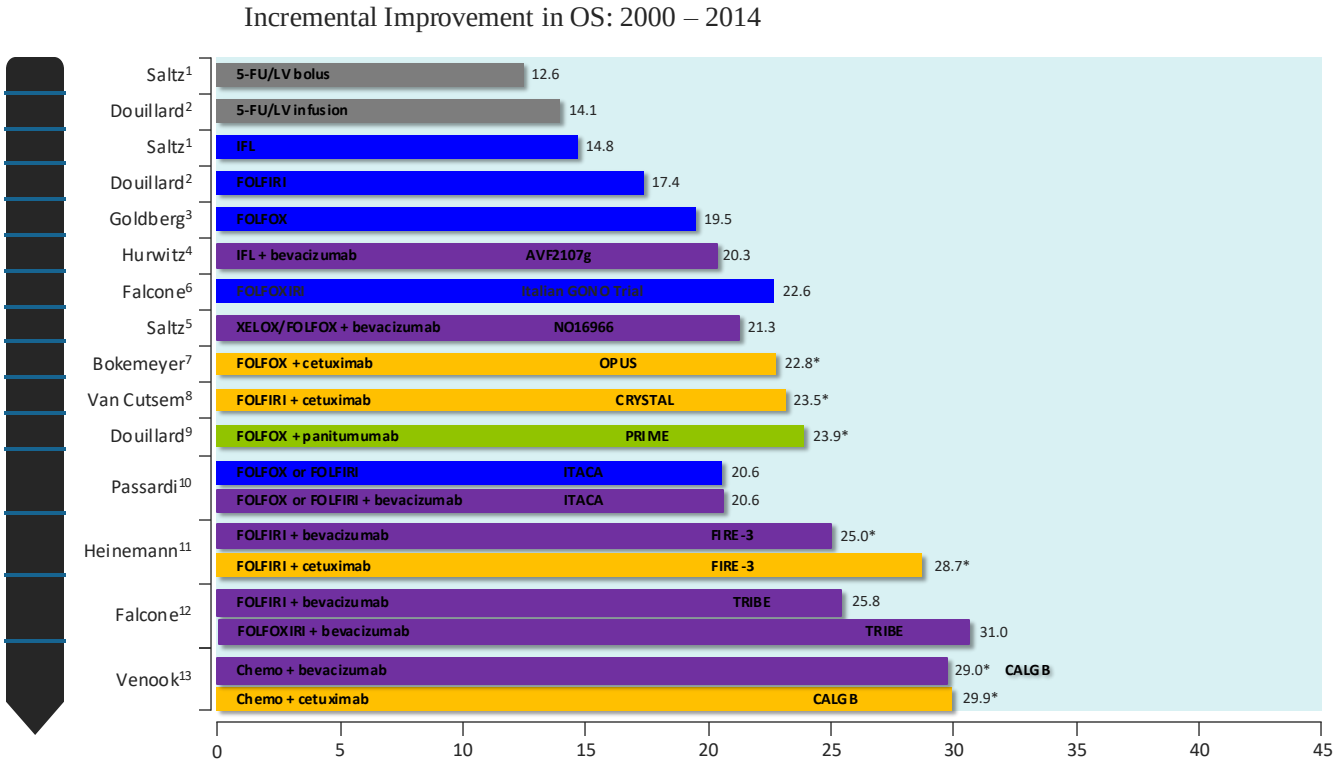
# Update on Chemotherapy for Metastatic Colorectal Cancer

# Historical OS for mCRC




**KRAS* WT tumors.

NOTE: Informal comparison as these are not head-to-head clinical trials.

5-FU, 5-fluorouracil; FOLFIRI, 5-FU + LV + irinotecan; FOLFOX, 5-FU + LV + oxaliplatin; IFL, irinotecan/bolus 5-FU/LV; LV, leucovorin; XELOX, capecitabine + oxaliplatin.

1. Saltz. 2000; 2. Douillard. 2000; 3. Goldberg. 2004; 4. Hurwitz. 2004; 5. Saltz. 2008; 6. Falcone. 2007; 7. Bokemeyer. 2011; 8. Van Cutsem. 2011; 9. Douillard. 2011; 10. Passardi. 2013; 11. Heinemann. 2013; 12. Venook. 2014; 13. Falcone. 2013.





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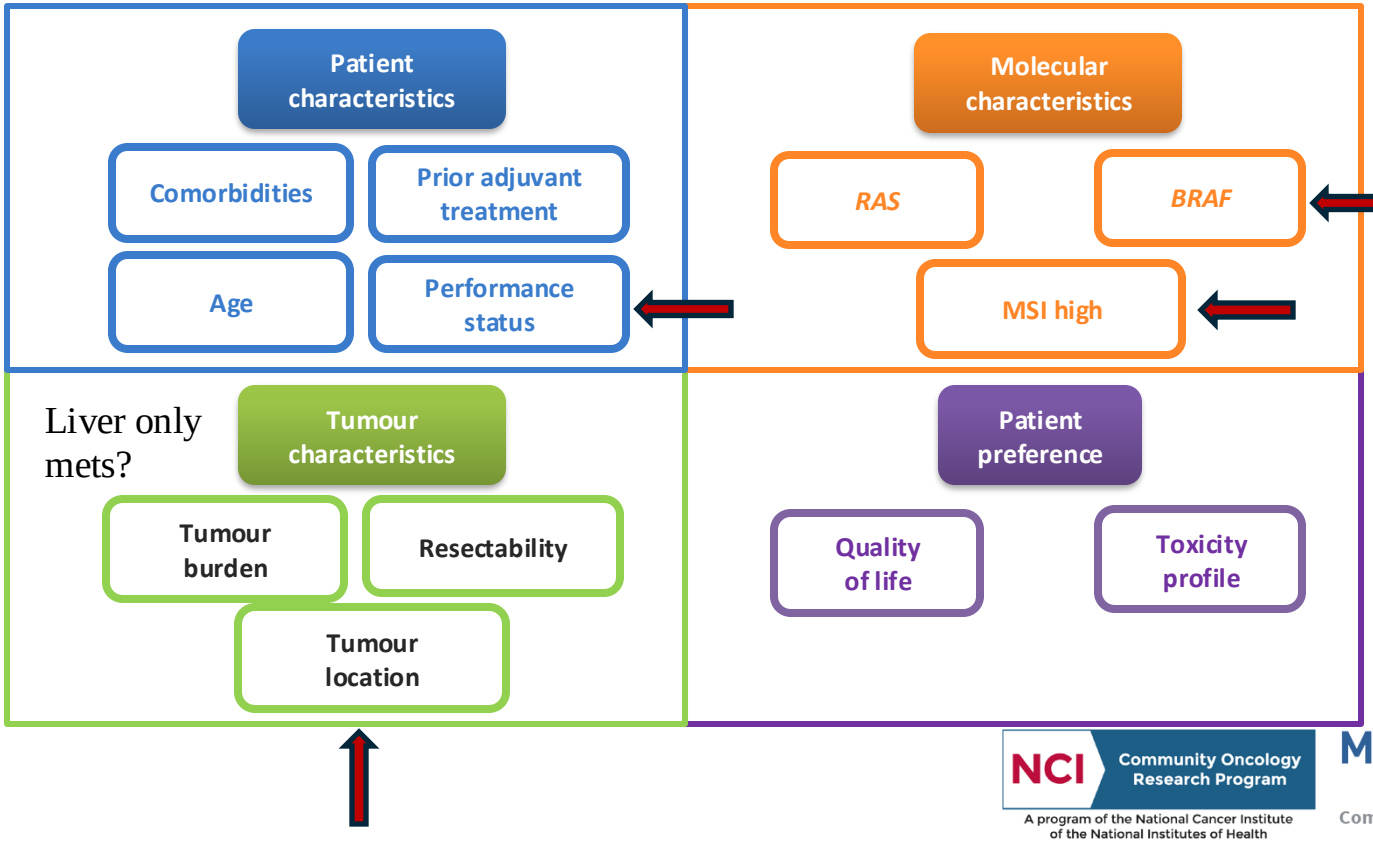
# Paradigm shift in chemotherapy choice

FOLFOXIRI vs FOLFOX upfront?




Novel Therapies vs Triple Therapy?

Maintenance vs Treatment Holiday?

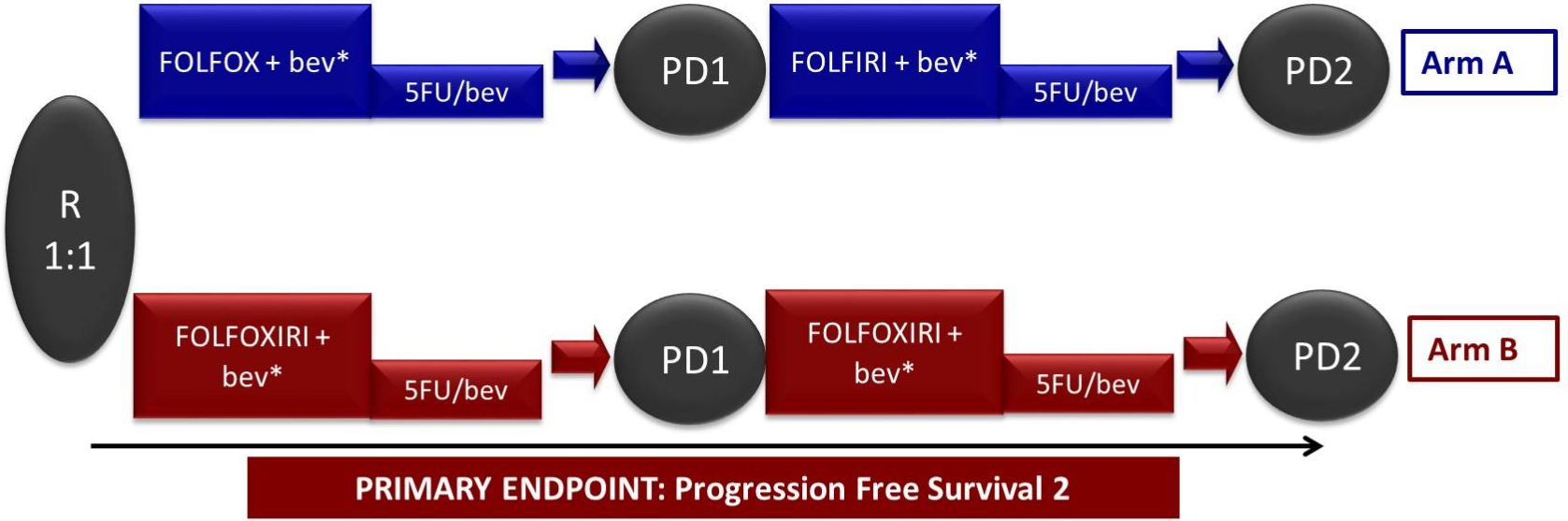
NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

Mount Sinai MEDICAL CENTER
Comprehensive Cancer Center

# Updates on 1st Line Chemotherapy for Metastatic CRC

# Triplet vs Doublet chemotherapy
# Updated data

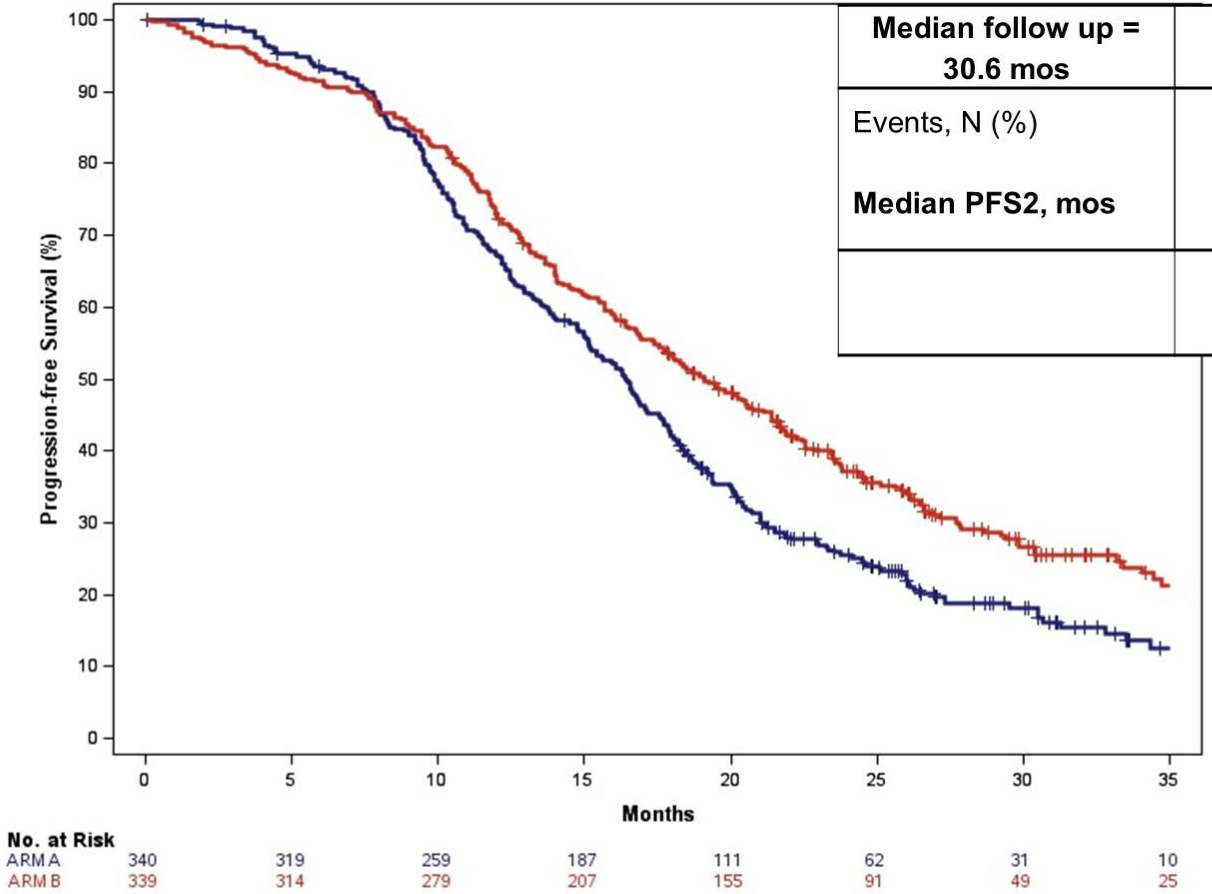
# TRIBE2: Study design




Cremolini, C et al (2020). Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2). *Lancet Oncology*, *21*(4), 497–507.

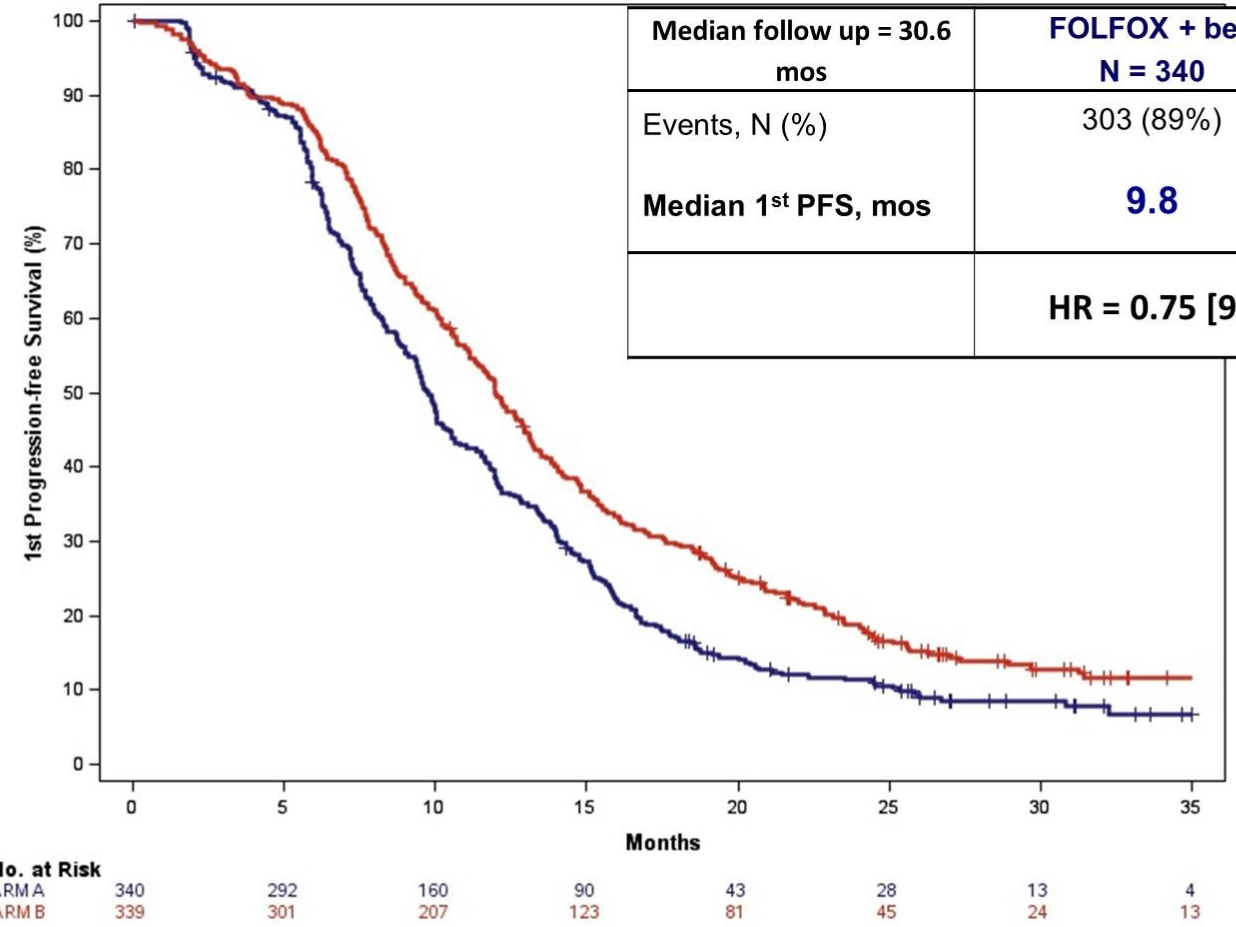
*** Up to 8 cycles**

# Primary endpoint: Progression Free Survival 2




| Median follow up = 30.6 mos | Arm A N = 340 | Arm B N = 339 |
|---|---|---|
| Events, N (%) | 272 (80%) | 242 (71%) |
| **Median PFS2, mos** | **17.5** | **19.1** |
| | **HR = 0.74 [95% CI: 0.62-0.88] p<0.001** | |

# 1st line - Progression Free Survival




| Median follow up = 30.6 mos | FOLFOX + bev N = 340 | FOLFOXIRI + bev N = 339 |
|---|---|---|
| Events, N (%) | 303 (89%) | 291 (86%) |
| **Median 1st PFS, mos** | **9.8** | **12.0** |
| | **HR = 0.75 [95% CI: 0.63-0.88] p<0.001** | |

# 1st line – Response and Resection Rate

| | FOLFOX + bev N = 340 | FOLFOXIRI + bev N = 339 | OR [95%CI], p |
|---|---|---|---|
| **Complete Response** | 4% | 3% | |
| **Partial Response** | 46% | 59% | |
| **Response Rate** | **50%** | **62%** | **1.61 [1.19-2.18], p=0.002** |
| **Stable disease** | 40% | 29% | |
| **Progressive Disease** | 7% | 4% | |
| **Not Assessed** | 3% | 5% | |

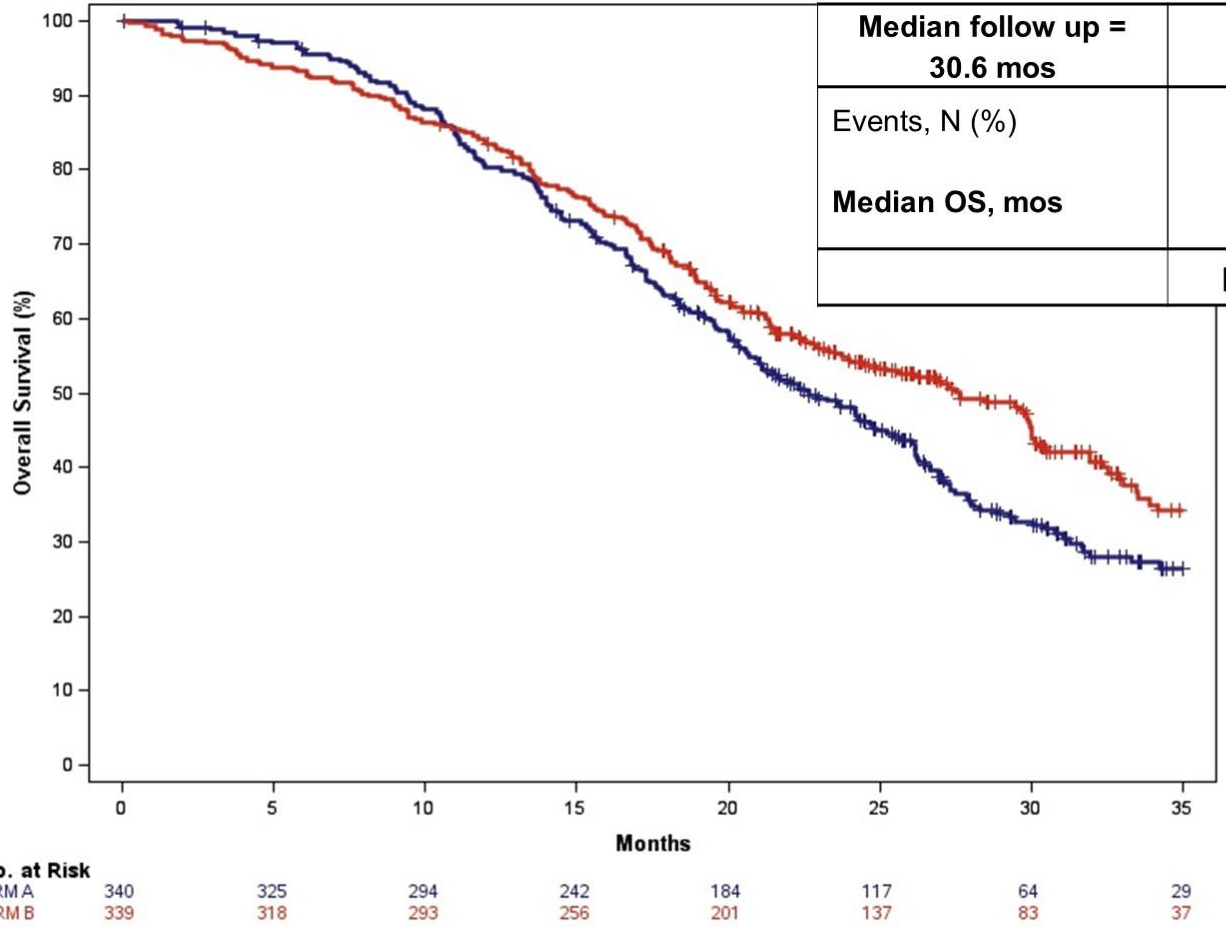
Cremolini, C et al (2020). Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2). *Lancet Oncology*, *21*(4), 497–507.

# 2nd line therapy

| | Arm A<br>N = 340 | Arm B<br>N = 339 |
|---|---|---|
| **PD events** | 291 (86%) | 272 (80%) |
| **Death before PD** | 12 (4%) | 19 (6%) |
| **Any 2nd-line therapy** | **86%**<br>(251/291) | **81%**<br>(219/272) |

Cremolini, C et al (2020). Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2). *Lancet Oncology*, *21*(4), 497–507.

# Overall Survival – preliminary results




| Median follow up = 30.6 mos | Arm A N = 340 | Arm B N = 339 |
|---|---|---|
| Events, N (%) | 217 (64%) | 191 (56%) |
| **Median OS, mos** | 22.6 | 27.6 |
| | **HR = 0.81 [95%CI: 0.67-0.98] p=0.033** | |

# Summary

- ✓ The **primary endpoint was met**: the upfront treatment with FOLFOXIRI/bev followed by the reintroduction of the same agents after PD increased PFS2 when compared with a pre-planned sequential strategy of FOLFOX/bev followed by FOLFIRI/bev.

- ✓ At the preliminary **OS** analysis (60% of events), a consistent OS advantage was observed

- ✓ As compared with FOLFOX/bev, **1st-line FOLFOXIRI/bev** was associated with:
  - higher response rate
  - higher R0 resection rate
  - longer PFS
  - higher incidence of diarrhea (17%), neutropenia (50%) and febrile neutropenia (7%)

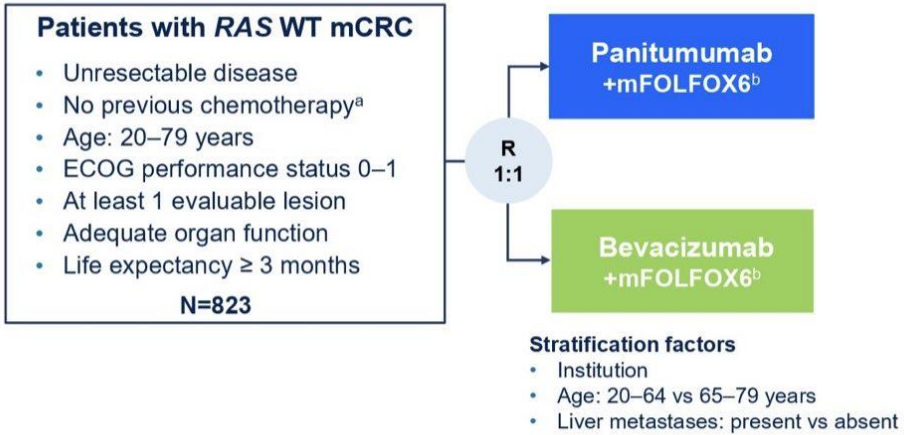
- ✓ No significant difference was observed in 2nd PFS, but among pts able to receive the planned 2nd-line therapy, as compared with FOLFIRI/bev, **2nd-line FOLFOXIRI/bev** was associated with:
  - higher disease control rate
  - longer PFS
  - higher incidence of neurotoxicity (5%)

# Updates on Left-sided Tumors
# RAS WT

# PARADIGM for Left-Sided RAS WT

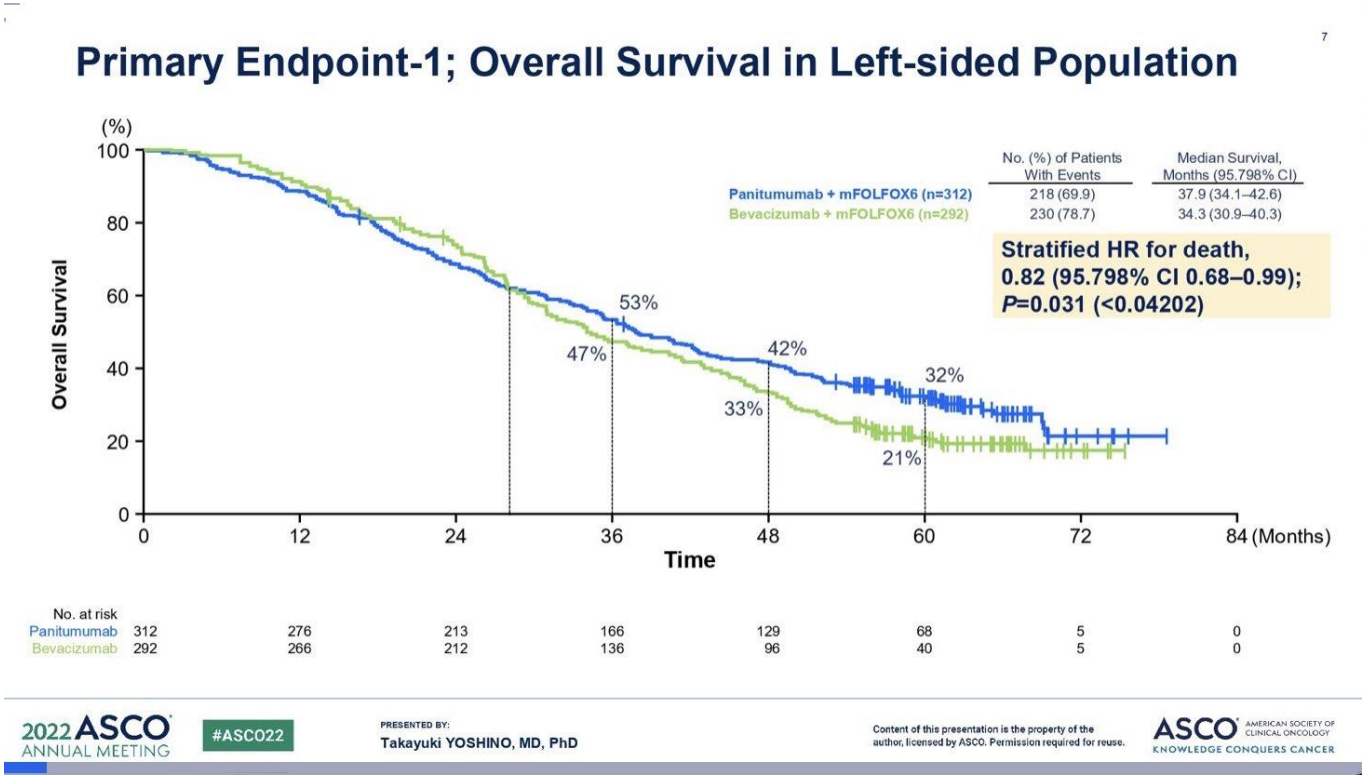
## PARADIGM Trial Design

Phase 3, randomized, open-label, multicenter study (NCT02394795)






Yoshino, T., et al . (2022). Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial.. *Journal of Clinical Oncology, 40*(17_suppl), LBA1–LBA1. https://doi.org/10.1200/jco.2022.40.17_suppl.lba1




Yoshino, T., et al . (2022). Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial.. *Journal of Clinical Oncology*, *40*(17_suppl), LBA1–LBA1. https://doi.org/10.1200/jco.2022.40.17_suppl.lba1

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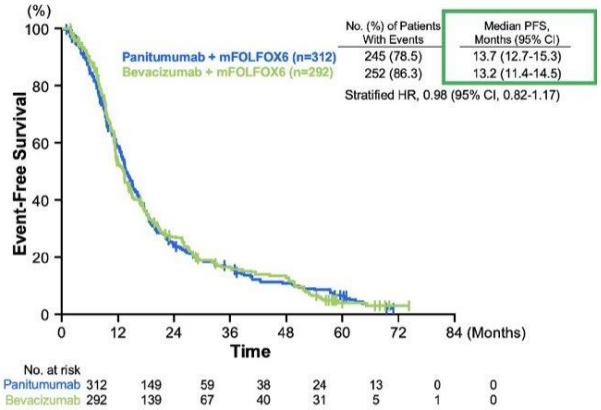
## Secondary endpoints: RR and PFS in the left-sided subgroup

| Parameter | Left-sided Population | |
|---|---|---|
| | Panitumumab + mFOLFOX6 (n=308) | Bevacizumab + mFOLFOX6 (n=287) |
| Response rate, % (95% CI) | 80.2 (75.3–84.5) | 68.6 (62.9–74.0) |
| Difference (95% CI) | 11.2 (4.4–17.9) | |
| Disease control rate, % (95% CI) | 97.4 (94.9–98.9) | 96.5 (93.7–98.3) |
| Median duration of response,* months (95%CI) | 13.1 (11.1–14.8) | 11.2 (9.6–13.1) |
| Curative resection rate,† % (95% CI) | 18.3 (14.1–23.0) | 11.6 (8.2–15.9] |




2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY: Chiara Cremolini, MD PhD



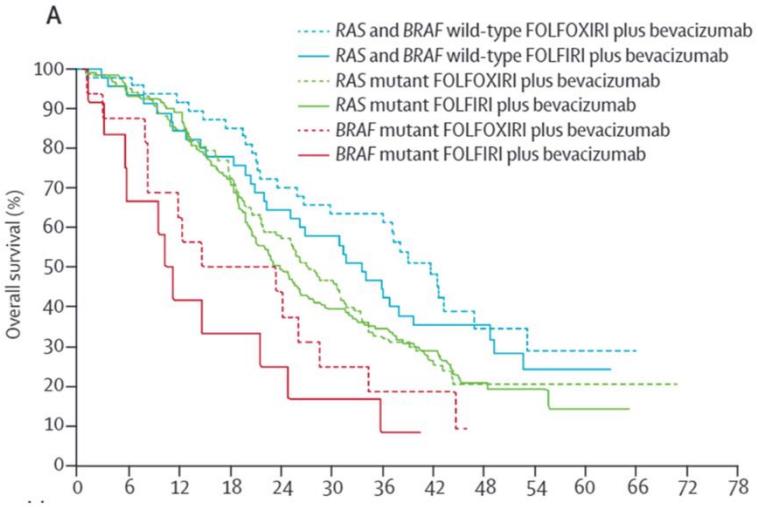
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Yoshino, T., et al . (2022). Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial.. *Journal of Clinical Oncology*, *40*(17_suppl), LBA1–LBA1. https://doi.org/10.1200/jco.2022.40.17_suppl.lba1

Pre-BREAKWATER Era

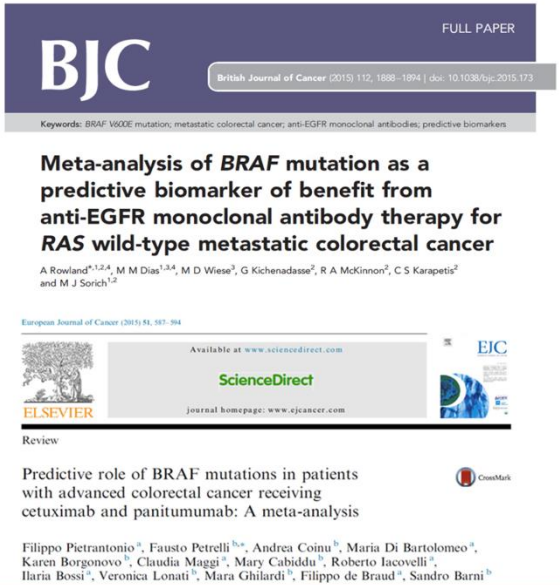
# Rationale of the study design

➔ **Prospective** randomized **data** on BRAF V600E mutant in first-line mCRC **are missing**.




Cremolini C, et al. Lancet Oncol 2015;16:1306–1315.

➔ The use of **EGFR antibodies** in BRAF V600E mutant mCRC **is controversial**.



FULL PAPER

BJC

British Journal of Cancer (2015) 112, 1888–1894 | doi: 10.1038/bjc.2015.173

Keywords: *BRAF* V600E mutation; metastatic colorectal cancer; anti-EGFR monoclonal antibodies; predictive biomarkers

**Meta-analysis of *BRAF* mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for *RAS* wild-type metastatic colorectal cancer**

A Rowland[a,1,2,4], M M Dias[1,3,4], M D Wiese[3], G Kichenadasse[2], R A McKinnon[2], C S Karapetis[2] and M J Sorich[1,2]

European Journal of Cancer (2015) 51, 587–594

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC

Review

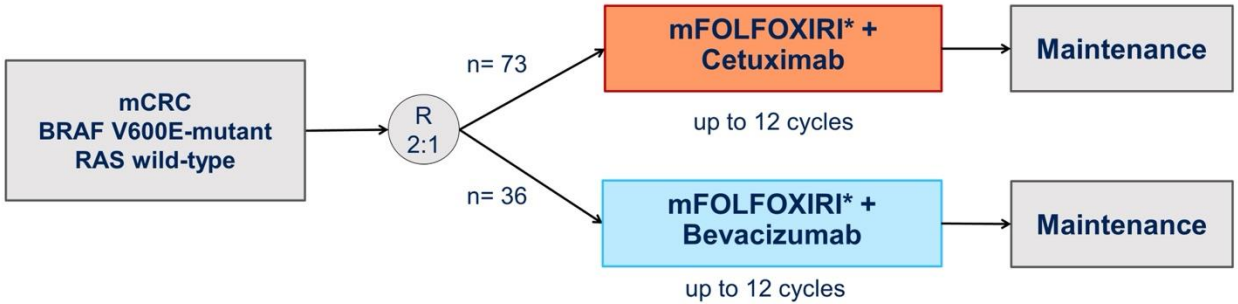
**Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: A meta-analysis**

Filippo Pietrantonio[a], Fausto Petrelli[b,*], Andrea Coinu[b], Maria Di Bartolomeo[a], Karen Borgonovo[b], Claudia Maggi[a], Mary Cabiddu[b], Roberto Iacovelli[a], Ilaria Bossi[a], Veronica Lonati[b], Mara Ghilardi[b], Filippo de Braud[a], Sandro Barni[b]



Presented By: Prof. Sebastian Stintzing. MD
Charité – Universitaetsmedizin Berlin

# FIRE-4.5 Study Design
## AIO KRK-0116




**Primary endpoint:**
Objective response rate (ORR) according to RECIST 1.1

**Secondary endpoints:** PFS, OS, toxicity

***mFOLFOXIRI:** irinotecan 150 mg/m², oxaliplatin 85 mg/m², folinic acid 400 mg/m² 5-FU 3,000 mg/m² within 48hrs
**Cetuximab:** cetuximab 400mg/m² loading dose followed by 250mg/m² weekly
**Bevacizumab:** bevacizumab 7.5mg/kg body weight biweekly

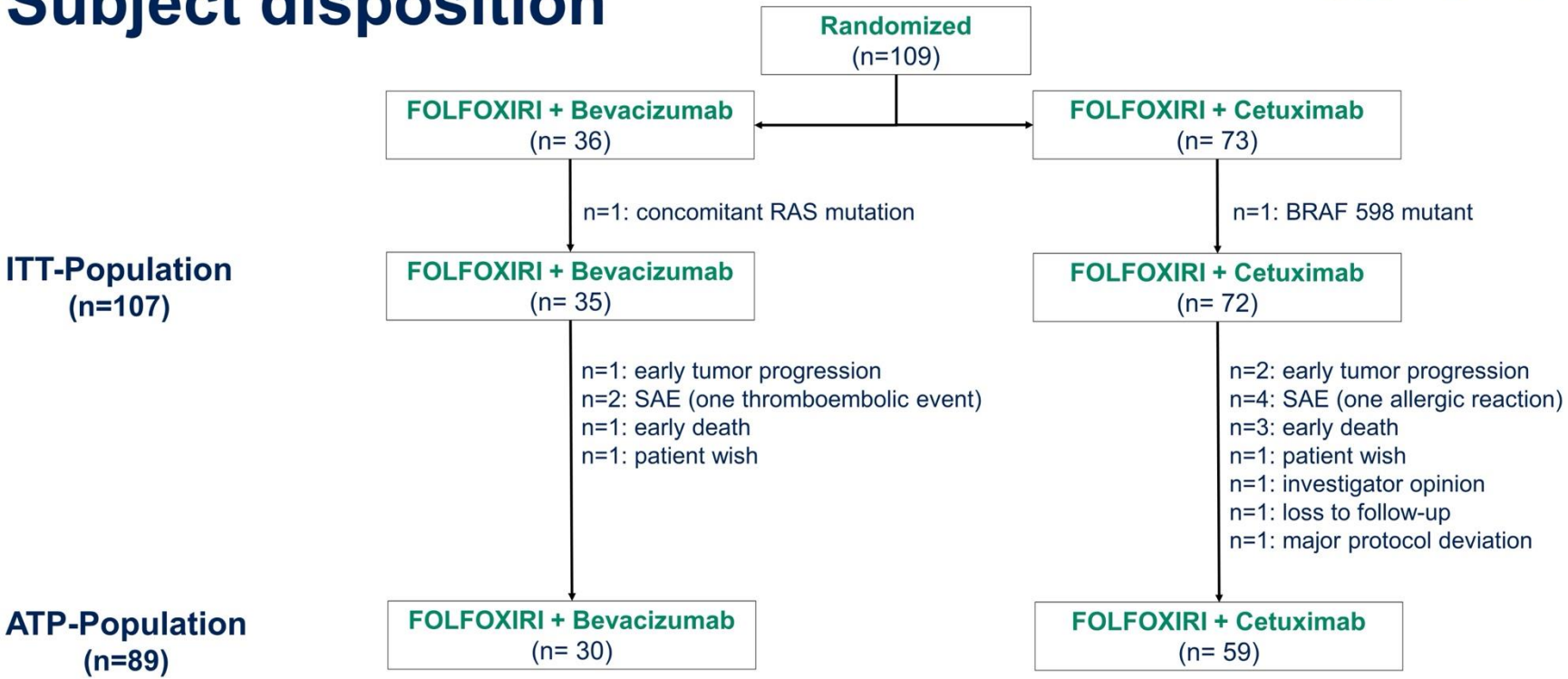
**Stratification factors:** - ECOG PS: 0 vs. 1
- location of the primary: right vs. left

# Statistics

- **Primary Endpoint: Objective Response Rate (ORR)** according to RECIST 1.1
- Assumption: **relative improvement by 37.5%**
  - ORR for FOLFOXIRI plus Bevacizumab: 60%
  - ORR for FOLFOXIRI plus Cetuximab: ≥ 82.5%
- Power **80%**, one-sided alpha error rate **10%**
- **81 Patients** with an ORR event (≥3 cycles of treatment; 1 follow up assessment) needed for an 2:1 randomization (n= 54 and 27)
- With a **25% drop-out rate** due to the poor prognostic group a total of **108 patients need** to be randomized.

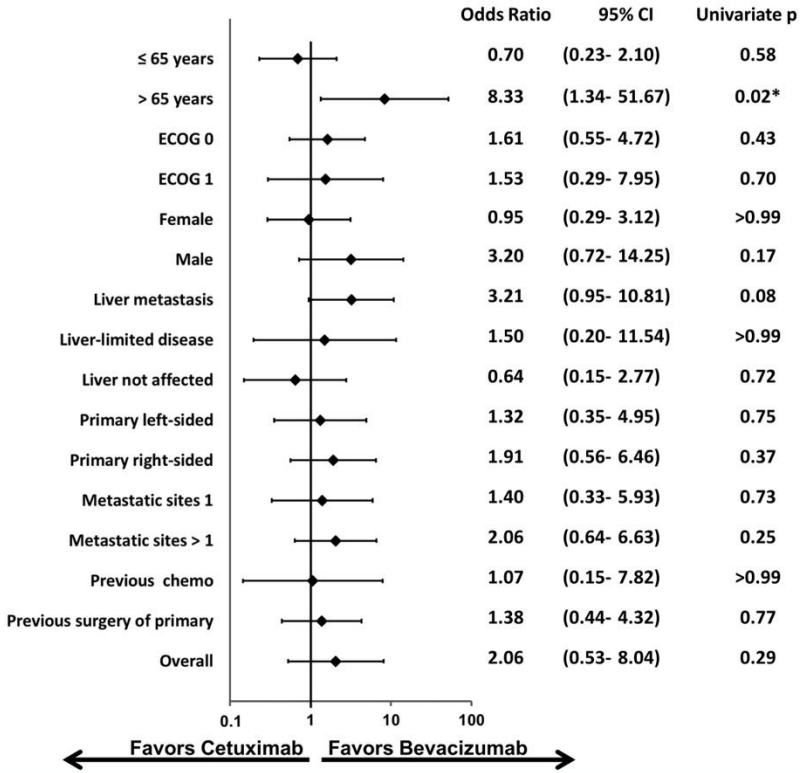
# Subject disposition




IIT: (intent-to-treat population): at least one cycle of treatment within the FIRE-4.5 study
ATP: (according to protocol population): at least 3 cycles of treatment and at least one follow up scan; evaluable for response

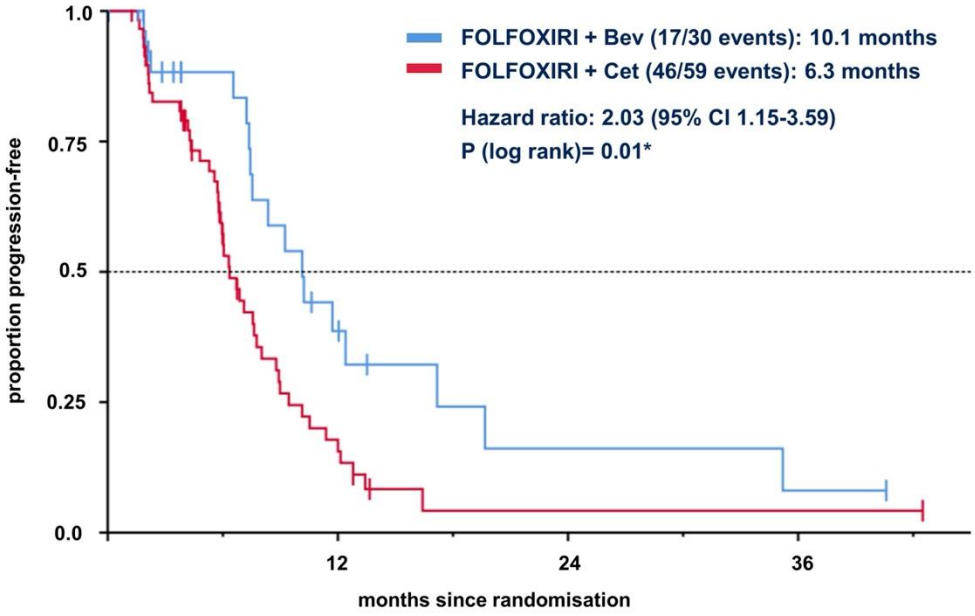
# Evaluation of primary endpoint
## ORR in the according to protocol population

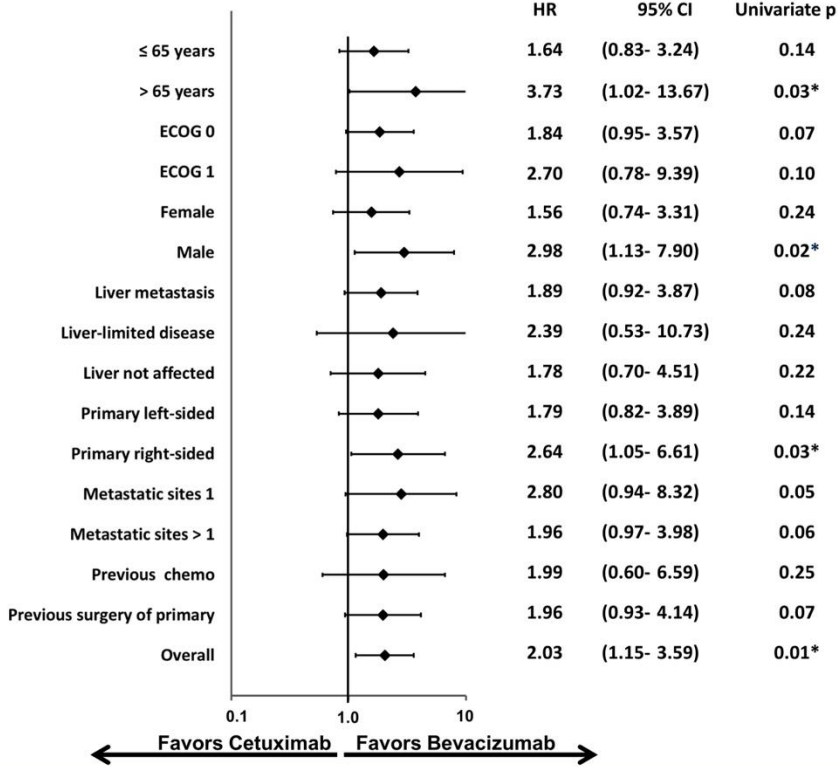
| RECIST, % (n) | FOLFOXIRI Cetuximab (n=59) | FOLFOXIRI Bevacizumab (n=30) |
|---|---|---|
| Complete Response | 3.4% (2) | 6.7% (2) |
| Partial Response | 45.8% (27) | 53.3% (16) |
| Stable Disease | 32.2% (19) | 30.0% (9) |
| Progressive Disease | 18.6% (11) | 10.0% (3) |
| **Objective Response Rate#** | **49.2% (29)** | **60.0% (18)** |
| | **p= 0.33** | |
| | **OR= 1.55 (80%CI: 0.87-2.78)** | |
| Disease Control Rate | 81.4% (48) | 90.0% (27) |
| | p=0.29 | |
| | OR = 2.06 (95% CI: 0.53-8.04) | |




#Primary endpoint, OR: odds ratio; P = Chi-square test p, CI= confidence interval;
*significant univariate value

# Progression-Free-Survival (PFS)
## ATP (n=89)

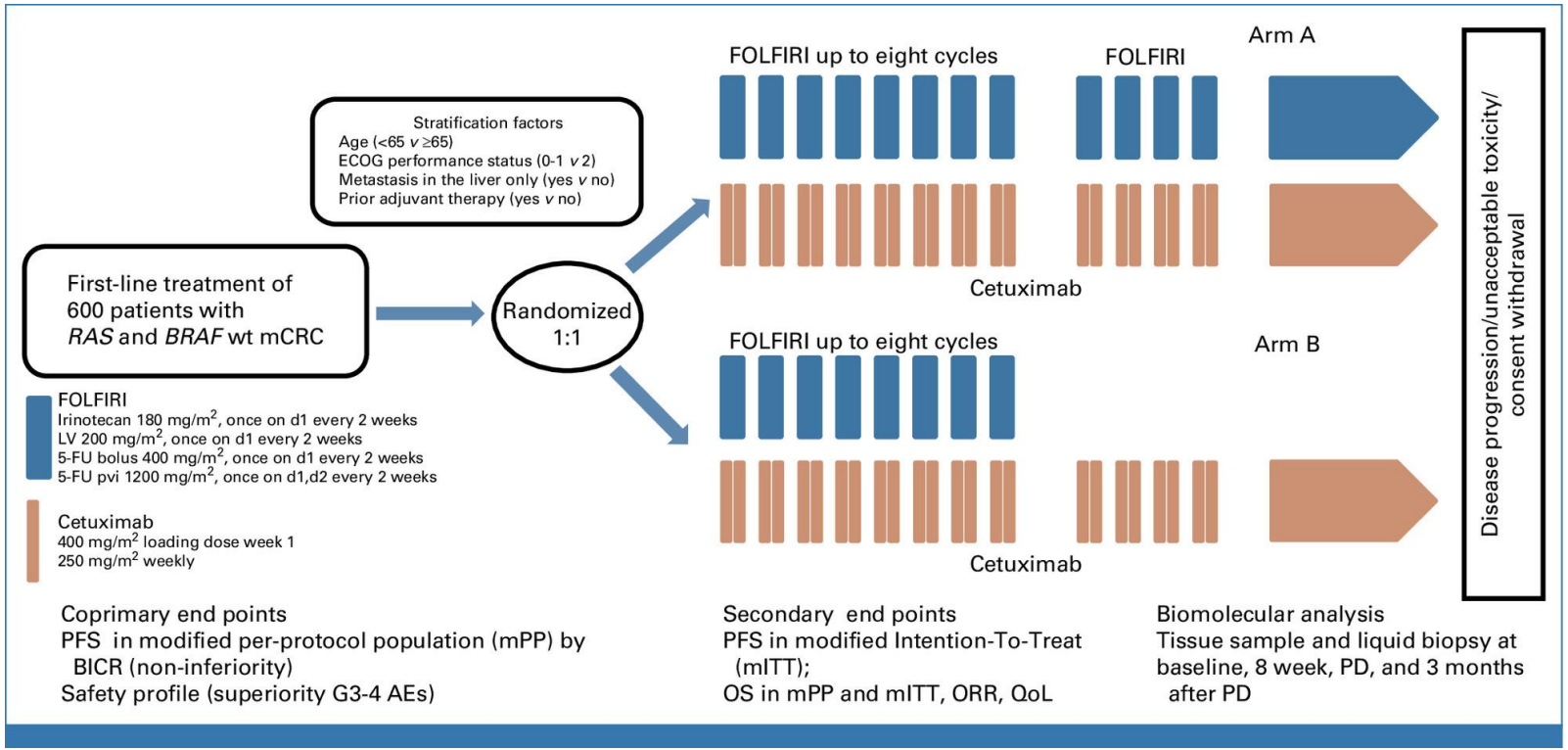


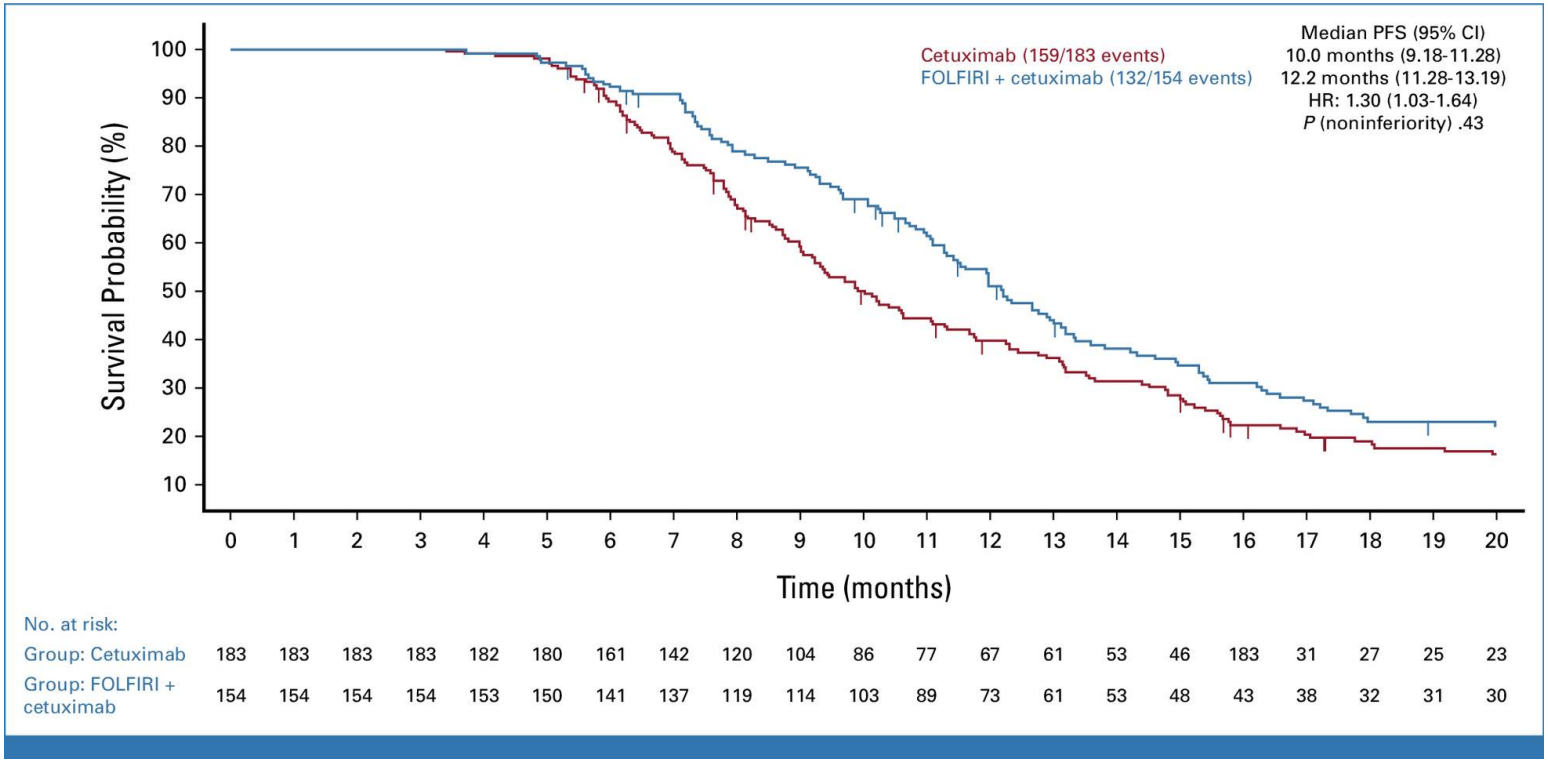

*significant univariate value

# Maintenance Therapy for Metastatic CRC

# ERMES study

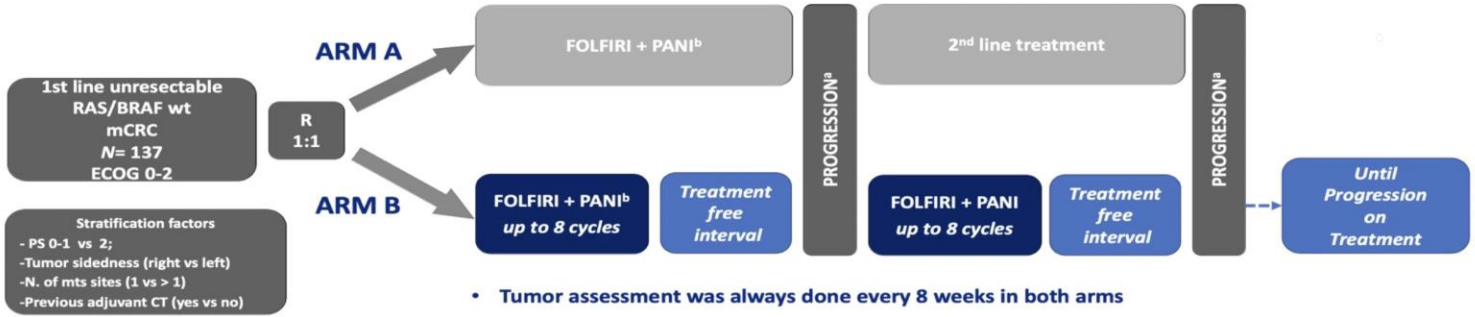

Stratification factors
Age (<65 v ≥65)
ECOG performance status (0-1 v 2)
Metastasis in the liver only (yes v no)
Prior adjuvant therapy (yes v no)
First-line treatment of 600 patients with RAS and BRAF wt mCRC
Randomized 1:1
FOLFIRI up to eight cycles
FOLFIRI
Arm A
Cetuximab
FOLFIRI up to eight cycles
Arm B
Cetuximab
Disease progression/unacceptable toxicity/ consent withdrawal
FOLFIRI
Irinotecan 180 mg/m2, once on d1 every 2 weeks
LV 200 mg/m2, once on d1 every 2 weeks
5-FU bolus 400 mg/m2, once on d1 every 2 weeks
5-FU pvi 1200 mg/m2, once on d1,d2 every 2 weeks
Cetuximab
400 mg/m2 loading dose week 1
250 mg/m2 weekly
Coprimary end points
PFS in modified per-protocol population (mPP) by BICR (non-inferiority)
Safety profile (superiority G3-4 AEs)
Secondary end points
PFS in modified Intention-To-Treat (mITT);
OS in mPP and mITT, ORR, QoL
Biomolecular analysis
Tissue sample and liquid biopsy at baseline, 8 week, PD, and 3 months after PD

# ERMES study



# IMPROVE: study design

IMPROVE is a randomized, non-comparative, multicenter, phase 2 study



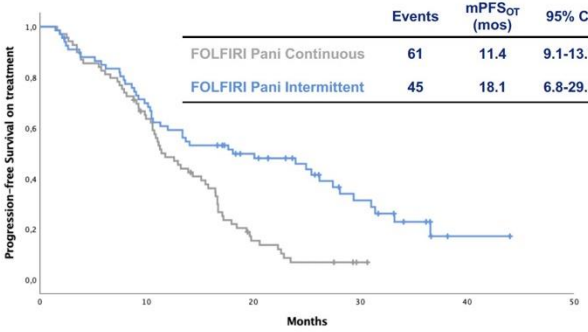

ClinicalTrials.gov.NCT04425239; [a]or until unacceptable toxicity or withdrawal consent; [b]Irinotecan 180 mg/m$^2$, folinic acid 200 mg/m$^2$, fluorouracil bolus 400 mg/m$^2$ followed by 2400 mg/m$^2$ continuous infusion over 46 hours plus panitumumab 6 mg/kg on day 1 every 2 weeks

**Primary endpoint:** Progression-Free Survival on treatment ($PFS_{OT}$) at 1 year

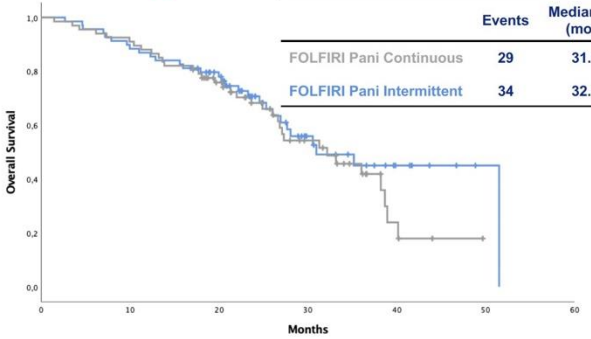
**Secondary endpoints:** Safety profile, Overall Response Rate (ORR), Deepness of Response, Overall Survival (OS), Quality of Life, Translational studies on tissue and blood samples (i.e. ctDNA)

# Survival analysis

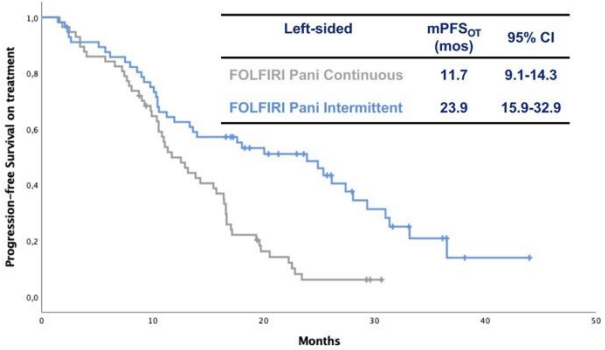
| | Events | mPFS$_{OT}$ (mos) | 95% CI |
|---|---|---|---|
| FOLFIRI Pani Continuous | 61 | 11.4 | 9.1-13.7 |
| FOLFIRI Pani Intermittent | 45 | 18.1 | 6.8-29.3 |



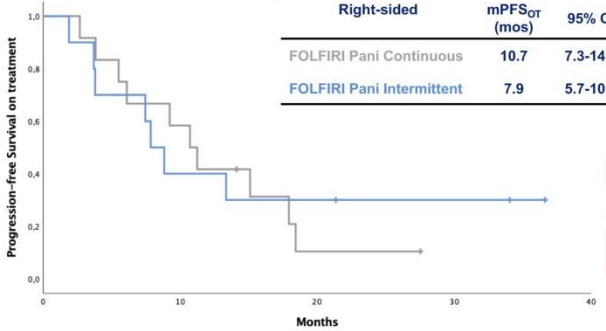

| | Events | Median OS (mos) | 95% CI |
|---|---|---|---|
| FOLFIRI Pani Continuous | 29 | 31.0 | 24.7-37.2 |
| FOLFIRI Pani Intermittent | 34 | 32.2 | 23.6-40.8 |




| Left-sided | mPFS$_{OT}$ (mos) | 95% CI |
|---|---|---|
| FOLFIRI Pani Continuous | 11.7 | 9.1-14.3 |
| FOLFIRI Pani Intermittent | 23.9 | 15.9-32.9 |




| Right-sided | mPFS$_{OT}$ (mos) | 95% CI |
|---|---|---|
| FOLFIRI Pani Continuous | 10.7 | 7.3-14.1 |
| FOLFIRI Pani Intermittent | 7.9 | 5.7-10.1 |



# Thank you for your attention