



# GI connect

---

POWERED BY COR2ED

Supported by an Independent Educational Grant from



# MEETING SUMMARY

ASCO GI, SATURDAY JANUARY 17<sup>TH</sup> 2015

BY DR. GUILLEM ARGILES, BARCELONA, SPAIN

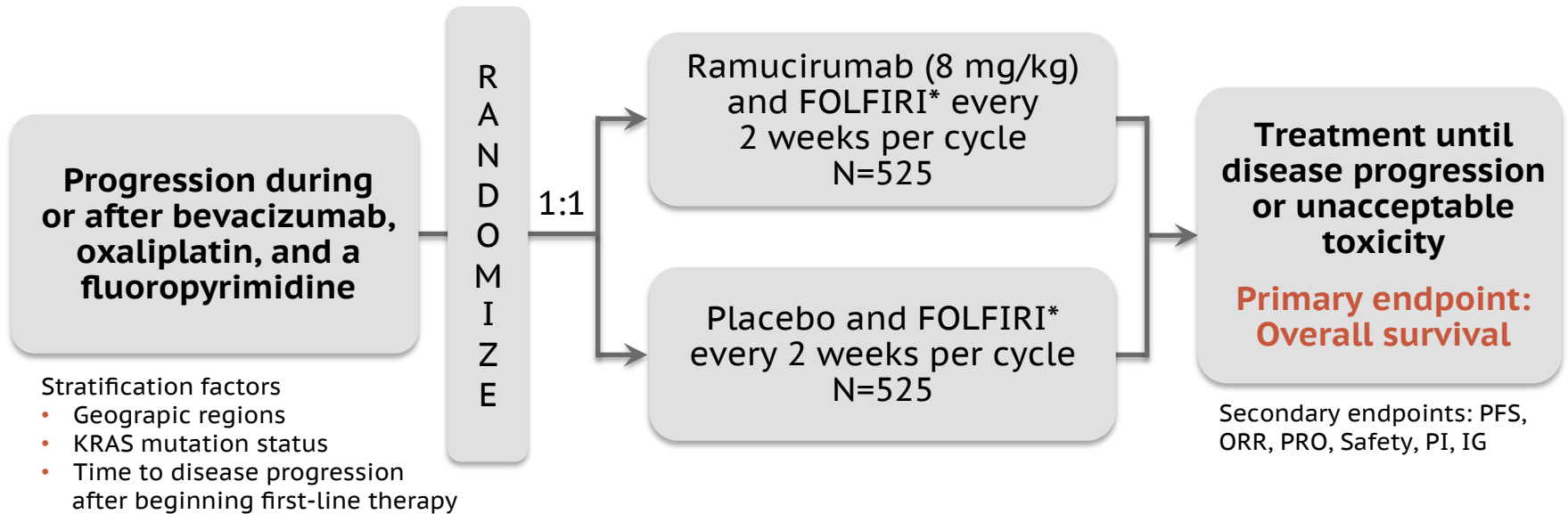
## Cancers of the Lower GI Tract

**RAISE: A RANDOMIZED, DOUBLE-BLIND,  
MULTICENTER PHASE III STUDY OF  
IRINOTECAN, FOLINIC ACID, AND 5-  
FLUOROURACIL (FOLFIRI) PLUS RAMUCIRUMAB  
OR PLACEBO IN PATIENTS WITH METASTATIC  
COLORECTAL CARCINOMA PROGRESSION  
DURING FOR FOLLOWING FIRST-LINE  
COMBINATION THERAPY WITH BEVACIZUMAB,  
OXALIPLATIN, AND A FLUOROPYRIMIDINE**

Josep Tabernero\*, Allen Lee Cohn, Radka Obermannova,  
Gyorgy Bodoky, Rocio Garcia-Carbonero, Tudor-Eliade Ciuleanu,  
David C. Portnoy, Eric Van Cutsem, Axel Grothey, Jana Prausová,  
Pilart Garcia-Alfonso, Kentaro Yamazaki, Philip R. Clingan,  
Vittorina Zagonel, Tae Won Kim, Lorrinda Simms, Shao-Chun  
Chang, Federico Nasroulah, Takayuki Yoshino

\*On behalf of the RAISE Investigators

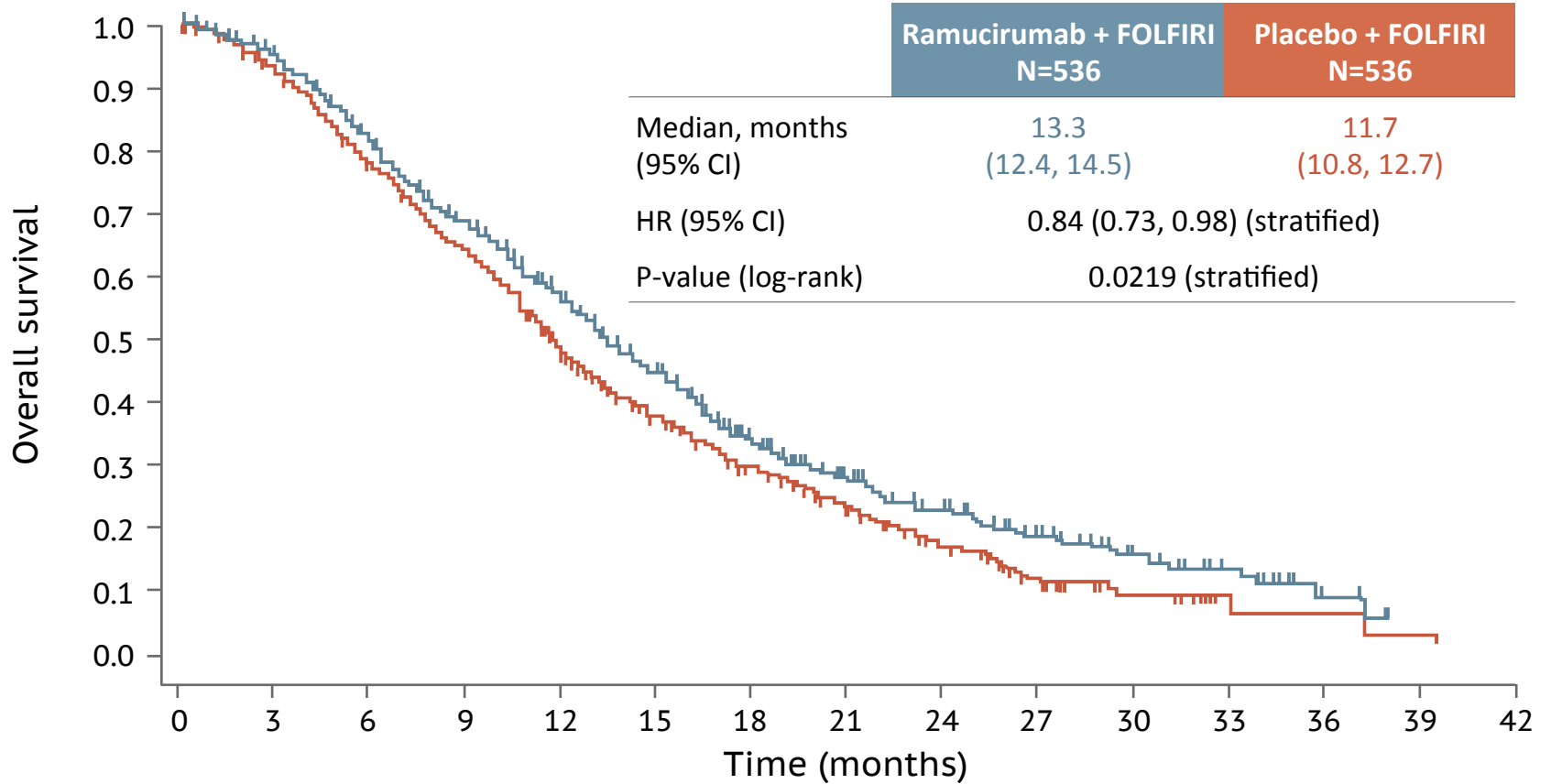
# RAISE: STUDY DESIGN



## Sample size assumptions

- Hazard ratio of 0.8
- Median overall survival of 10 months in the control arm vs 12.5 months with ramucirumab with a 2-sided  $\alpha$  level of 0.05
- Enrollment of 1050 patients with 756 events for 85% power
- Gatekeeping from OS to PFS to ORR

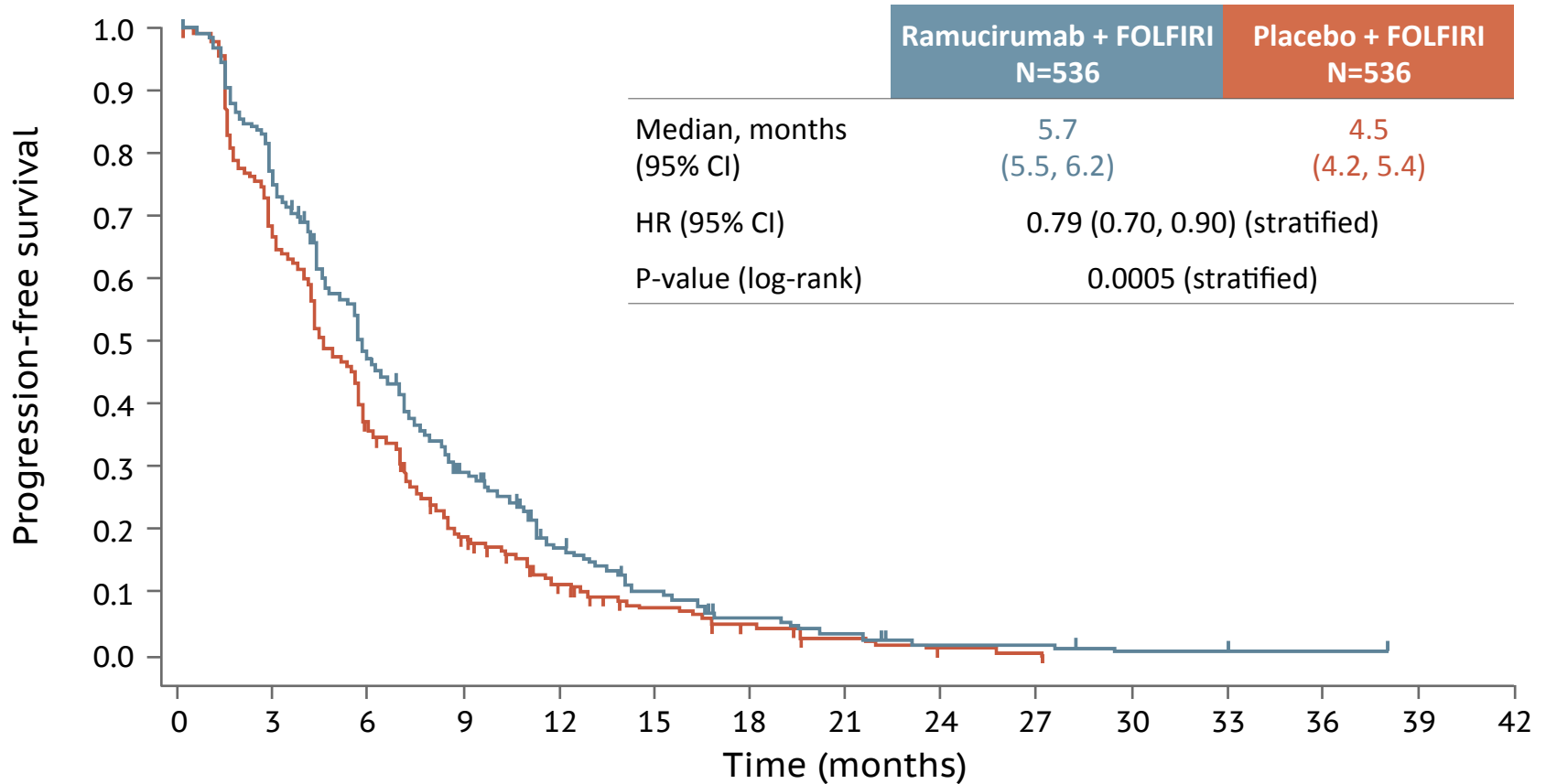
# RAISE: STUDY DESIGN



## Patients at risk

|                   | 0   | 3   | 6   | 9   | 12  | 15  | 18  | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 |
|-------------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|
| Ram + FOLFIRI     | 536 | 497 | 421 | 345 | 269 | 195 | 114 | 78 | 53 | 34 | 22 | 12 | 4  | 0  | 0  |
| Placebo + FOLFIRI | 536 | 486 | 400 | 329 | 228 | 166 | 108 | 66 | 44 | 22 | 10 | 2  | 2  | 1  | 0  |

# RAISE: PROGRESSION-FREE SURVIVAL



## Patients at risk

|                   | 0   | 3   | 6   | 9   | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 |
|-------------------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|
| Ram + FOLFIRI     | 536 | 381 | 234 | 142 | 77 | 38 | 20 | 11 | 6  | 5  | 22 | 2  | 1  | 0  | 0  |
| Placebo + FOLFIRI | 536 | 345 | 182 | 92  | 52 | 31 | 17 | 10 | 3  | 1  | 10 | 0  | 0  | 0  | 0  |

# TREATMENT-EMERGENT ADVERSE EVENTS (ALL GRADES 20% OR HIGHER, OR GRADE 3-5 5% OR HIGHER IN EITHER TREATMENT ARM)

| Preferred Term          | Any Grade                      |             |                            |             | Grade ≥3                       |             |                            |             |
|-------------------------|--------------------------------|-------------|----------------------------|-------------|--------------------------------|-------------|----------------------------|-------------|
|                         | Ramucirumab + FOLFIRI<br>N=529 |             | Placebo + FOLFIRI<br>N=528 |             | Ramucirumab + FOLFIRI<br>N=529 |             | Placebo + FOLFIRI<br>N=528 |             |
|                         | n                              | %           | n                          | %           | n                              | %           | n                          | %           |
| Any TEAE                | 522                            | 98.7        | 519                        | 98.3        | 418                            | 79.0        | 329                        | 62.3        |
| <i>Neutropenia</i>      | <i>311</i>                     | <i>58.8</i> | <i>241</i>                 | <i>45.6</i> | <i>203</i>                     | <i>38.4</i> | <i>123</i>                 | <i>23.3</i> |
| <i>Fatigue</i>          | <i>305</i>                     | <i>57.7</i> | <i>275</i>                 | <i>52.1</i> | <i>61</i>                      | <i>11.5</i> | <i>41</i>                  | <i>7.8</i>  |
| Diarrhea                | 316                            | 59.7        | 271                        | 51.3        | 57                             | 10.8        | 51                         | 9.7         |
| <i>Hypertension</i>     | <i>136</i>                     | <i>25.7</i> | <i>45</i>                  | <i>8.5</i>  | <i>57</i>                      | <i>10.8</i> | <i>15</i>                  | <i>2.8</i>  |
| Stomatitis              | 163                            | 30.8        | 110                        | 20.8        | 20                             | 3.8         | 12                         | 2.3         |
| <i>Abdominal pain</i>   | <i>140</i>                     | <i>26.5</i> | <i>139</i>                 | <i>26.3</i> | <i>18</i>                      | <i>3.4</i>  | <i>19</i>                  | <i>3.6</i>  |
| <i>Thrombocytopenia</i> | <i>150</i>                     | <i>28.4</i> | <i>72</i>                  | <i>13.6</i> | <i>16</i>                      | <i>3.0</i>  | <i>4</i>                   | <i>0.8</i>  |
| Vomiting                | 154                            | 29.1        | 144                        | 27.3        | 15                             | 2.8         | 13                         | 2.5         |
| Nausea                  | 262                            | 49.5        | 271                        | 51.3        | 13                             | 2.5         | 14                         | 2.7         |
| Decreased appetite      | 198                            | 37.4        | 144                        | 27.3        | 13                             | 2.5         | 10                         | 1.9         |
| <i>Anemia</i>           | <i>86</i>                      | <i>16.3</i> | <i>110</i>                 | <i>20.8</i> | <i>8</i>                       | <i>1.5</i>  | <i>19</i>                  | <i>3.6</i>  |
| Constipation            | 151                            | 28.5        | 120                        | 22.7        | 5                              | 0.9         | 8                          | 1.5         |
| Peripheral edema        | 108                            | 20.4        | 48                         | 9.1         | 1                              | 0.2         | 0                          |             |
| Epistaxis               | 177                            | 33.5        | 79                         | 15.0        | 0                              |             | 0                          |             |
| Alopecia                | 155                            | 29.3        | 165                        | 31.3        | 0                              |             | 0                          |             |

- The febrile neutropenia rate (any grade) was 3.6% in ramucirumab patients and 2.7% in placebo patients

# RAISE: ADVERSE EVENTS OF SPECIAL INTEREST

|                               | Any Grade                      |      |                            |      | Grade ≥3                       |      |                            |     |
|-------------------------------|--------------------------------|------|----------------------------|------|--------------------------------|------|----------------------------|-----|
|                               | Ramucirumab + FOLFIRI<br>N=529 |      | Placebo + FOLFIRI<br>N=528 |      | Ramucirumab + FOLFIRI<br>N=529 |      | Placebo + FOLFIRI<br>N=528 |     |
|                               | n                              | %    | n                          | %    | n                              | %    | n                          | %   |
| Bleeding/hemorrhage event     | 232                            | 43.9 | 120                        | 22.7 | 13                             | 2.5  | 9                          | 1.7 |
| Hypertension                  | 138                            | 26.1 | 45                         | 8.5  | 59                             | 11.2 | 15                         | 2.8 |
| Proteinuria                   | 90                             | 17.0 | 24                         | 4.5  | 16                             | 3.0  | 1                          | 0.2 |
| GI hemorrhage                 | 65                             | 12.3 | 36                         | 6.8  | 10                             | 1.9  | 6                          | 1.1 |
| Venous thromboembolic events  | 44                             | 8.3  | 34                         | 6.4  | 22                             | 4.2  | 11                         | 2.1 |
| Infusion-related reaction     | 31                             | 5.9  | 16                         | 3.0  | 4                              | 0.8  | 2                          | 0.4 |
| Renal failure                 | 18                             | 3.4  | 18                         | 3.4  | 7                              | 1.3  | 5                          | 0.9 |
| GI perforation                | 9                              | 1.7  | 3                          | 0.6  | 9                              | 1.7  | 3                          | 0.6 |
| Arterial thromboembolic event | 8                              | 1.5  | 13                         | 2.5  | 4                              | 0.8  | 6                          | 1.1 |
| Pulmonary hemorrhage events   | 7                              | 1.3  | 3                          | 0.6  | 0                              |      | 0                          |     |
| Healing complication          | 6                              | 1.1  | 1                          | 0.2  | 1                              | 0.2  | 0                          |     |
| Congestive heart failure      | 4                              | 0.8  | 3                          | 0.6  | 4                              | 0.8  | 3                          | 0.6 |
| Fistula                       | 4                              | 0.8  | 2                          | 0.4  | 0                              |      | 0                          |     |
| RPLS                          | 1                              | 0.2  | 1                          | 0.2  | 0                              |      | 0                          |     |
| Thrombotic microangiopathy    | 1                              | 0.2  | 0                          |      | 1                              | 0.2  | 0                          |     |
| Hepatic hemorrhage event      | 0                              |      | 1                          | 0.2  | 0                              |      | 1                          |     |

GI, gastrointestinal; RPLS, reversible posterior leukoencephalopathy syndrome.



# CONCLUSIONS

- RAISE met its primary endpoint
  - Demonstrated a statistically significant improvement in overall survival for ramucirumab and FOLFIRI vs placebo and FOLFIRI
  - In second-line metastatic CRC patients who progressed after first-line treatment with bevacizumab, oxaliplatin, and a fluoropyrimidine
- Consistent survival benefits were observed across subgroups
- Ramucirumab in combination with FOLFIRI was well tolerated in patients with mCRC. Overall, the adverse events were considered manageable

**PREOPERATIVE HEPATIC AND REGIONAL  
ARTERIAL CHEMOTHERAPY (PHRAC)  
REDUCES THE OCCURRENCE OF  
METACHRONOUS LIVER METASTASIS AFTER  
CURATIVE COLORECTAL CANCER RESECTION**

**A PROSPECTIVE, MULTI-CENTER, RANDOMIZED CONTROLLED TRIAL**

Jianmin Xu

*Zhongshan Hospital, Fudan University  
Shanghai, China*

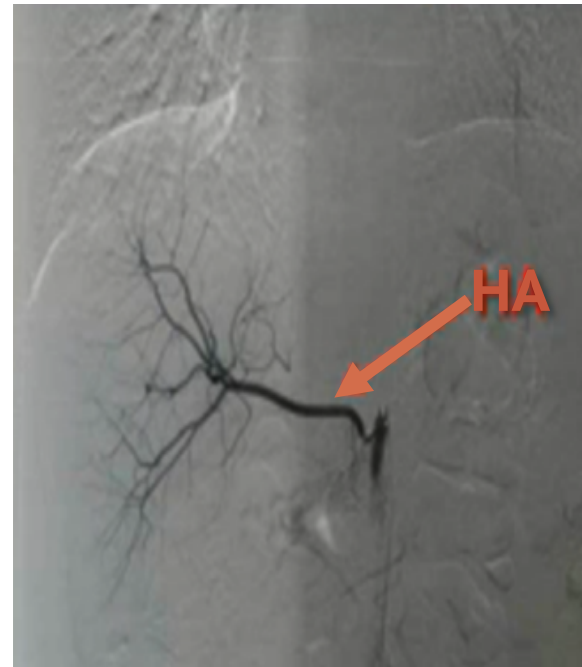
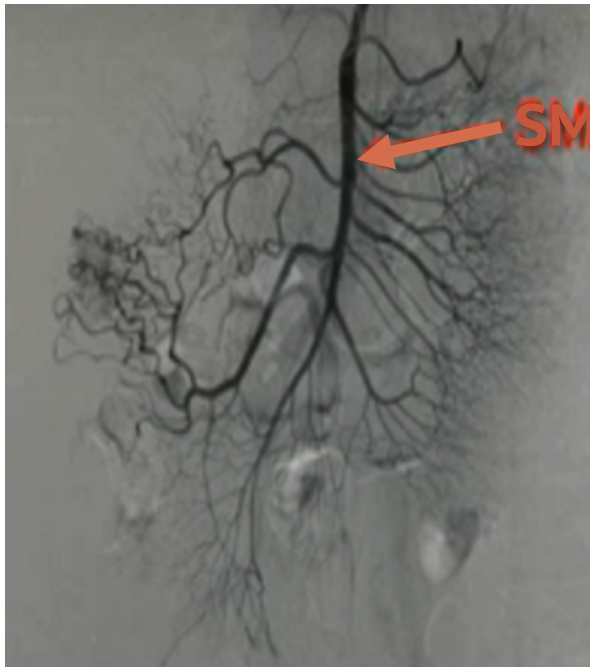
# PHRAC

## Right colon cancer

Brain tumor supplying  
artery chemotherapy

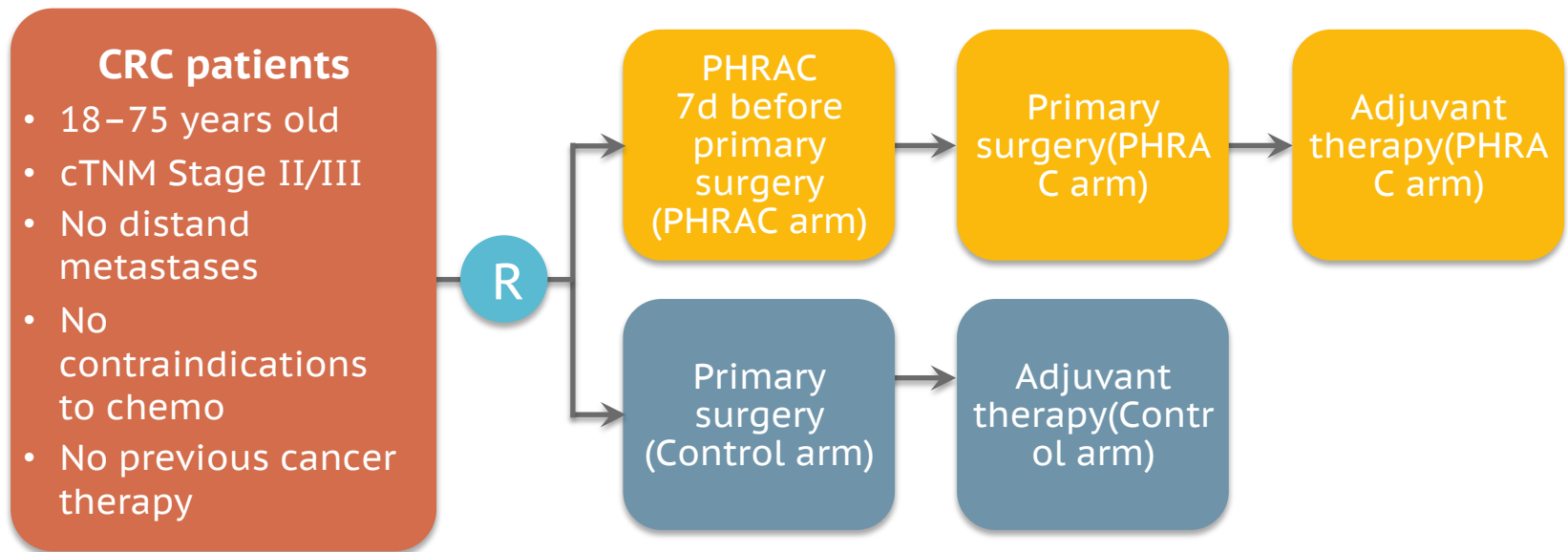


Common hepatic artery  
chemotherapy



FUDR 650 mg/m<sup>2</sup>, Oxaliplatin 75 mg/m<sup>2</sup>, MMC 8 mg/m<sup>2</sup>  
Half in each artery

# STUDY DESIGN



# OUTCOMES

## Primary outcome

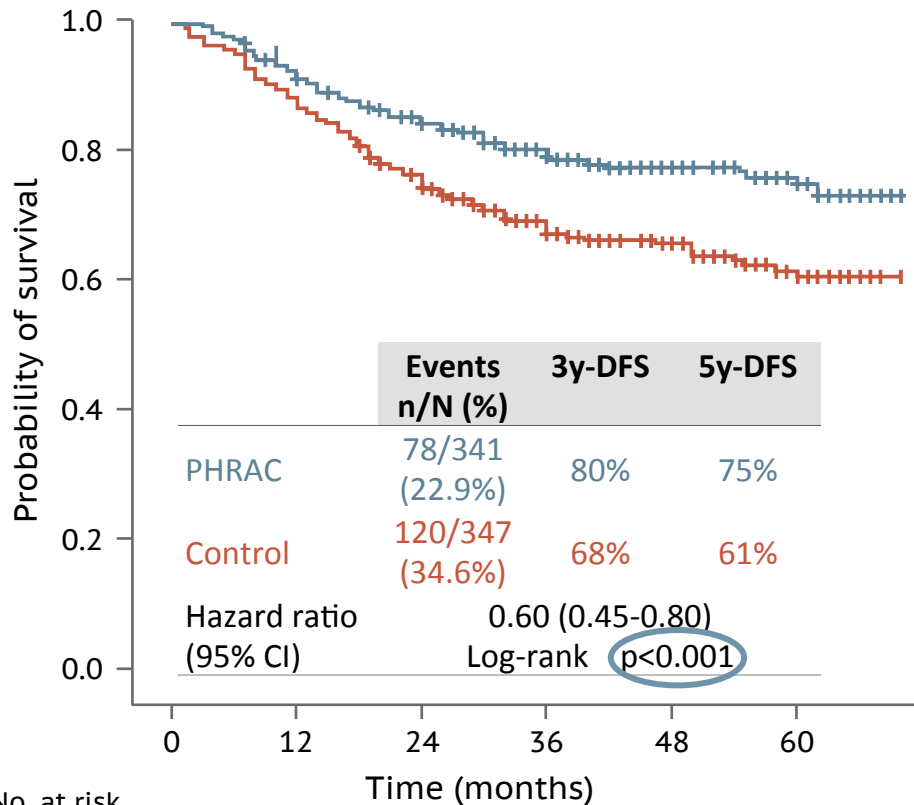
- DFS

## Secondary outcome

- Cumulative incidence of liver metastasis
- OS
- Safety

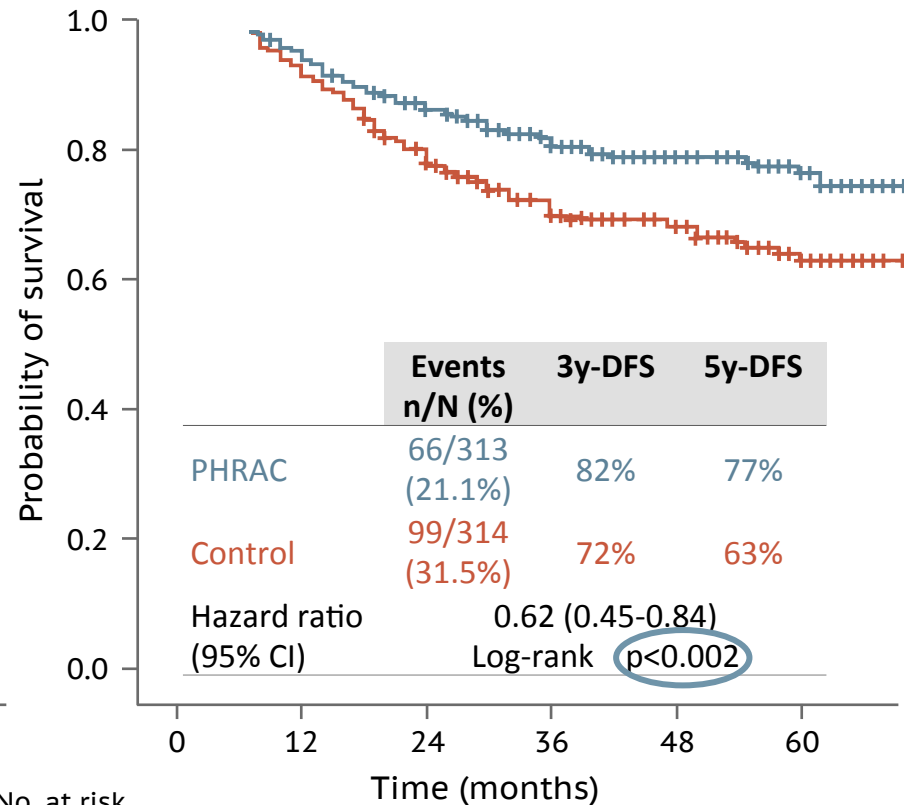
# PRIMARY OUTCOME-DFS

## ITT population



| No. at risk | 0   | 12  | 24  | 36  | 48  | 60 |
|-------------|-----|-----|-----|-----|-----|----|
| PHRAC       | 341 | 313 | 282 | 213 | 147 | 82 |
| Control     | 347 | 305 | 257 | 169 | 120 | 63 |

## Eligible population

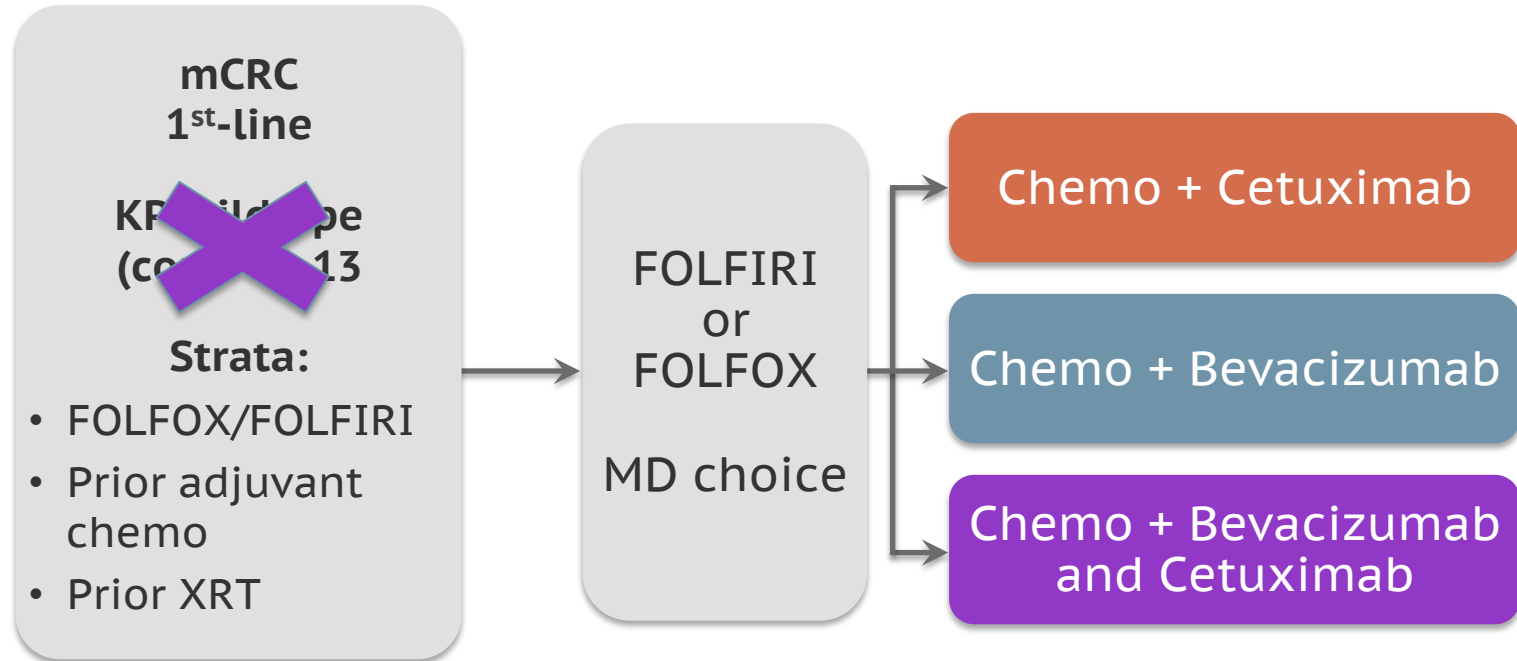


| No. at risk | 0   | 12  | 24  | 36  | 48  | 60 |
|-------------|-----|-----|-----|-----|-----|----|
| PHRAC       | 313 | 297 | 266 | 202 | 140 | 78 |
| Control     | 314 | 292 | 245 | 161 | 117 | 62 |

# VITAMIN D STATUS AND SURVIVAL OF METASTATIC COLORECTAL CANCER PATIENTS: RESULTS FROM CALGB/SWOG 80405 (ALLIANCE)

Kimie Ng, Alan P. Venook, Kaori Sato, Bruce W. Hollis,  
Donna Niedzwiecki, Cynthia Ye, I-Wen Chang, Bert H. O'Neil,  
Federico Innocenti, Heinz-Josef Lenz, Charles D. Blanke,  
Robert J. Mayer, Charles S. Fuchs, Jeffrey A. Meyerhardt

# CALGB/SWOG 80405: ~~FINAL~~ DESIGN ORIGINAL



N = ~~1140~~ 2334

Endpoint: Overall Survival



# STATISTICAL METHODS

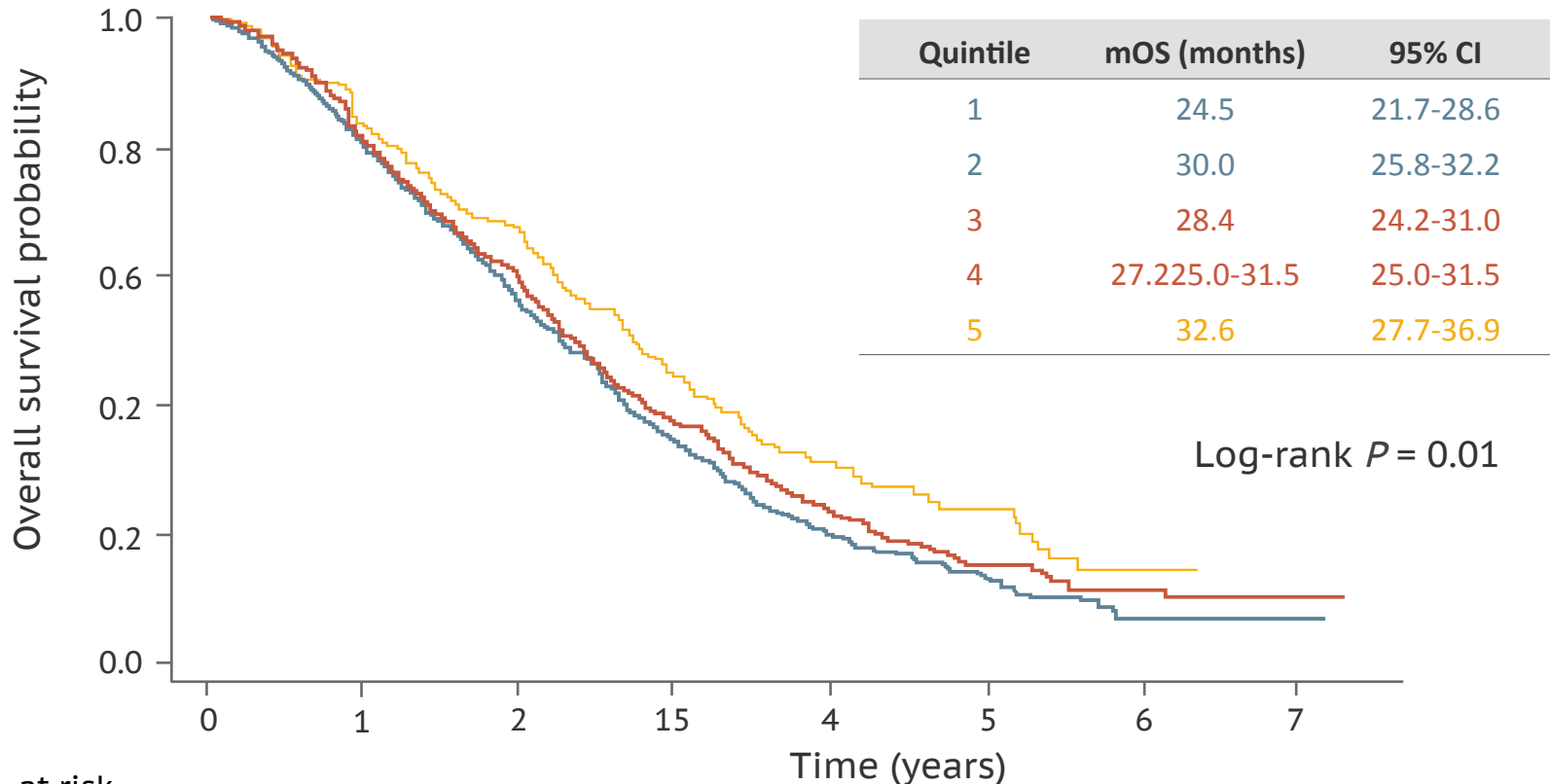
- Pre-planned, prospective, observational cohort study
- Primary endpoint: Overall survival
  - Kaplan-Meier method
  - Log rank test
- Plasma 25(OH)D measured by radioimmunoassay prior to treatment
- Validated diet and lifestyle questionnaires prior to treatment
- Multivariable analyses using Cox proportional hazards models
- All  $P$  values two-sided and considered significant at the 0.05 level

# BASELINE CHARACTERISTICS

Median 25(OH)D = 17.2 ng/mL

|                               | Q1<br>(n=208)    | Q2<br>(n=209)       | Q3<br>(n=208)       | Q4<br>(n=210)       | Q5<br>(n=208)       | P       |
|-------------------------------|------------------|---------------------|---------------------|---------------------|---------------------|---------|
| Median 25(OH)D, ng/mL (range) | 8.0<br>2.2-10.8) | 13.6<br>(10.9-15.4) | 17.2<br>(15.4-19.2) | 21.4<br>(19.3-24.0) | 27.5<br>(24.1-72.7) | -       |
| Median age, years             | 59               | 60                  | 60                  | 61                  | 61                  | 0.07    |
| Male, %                       | 48               | 64                  | 58                  | 64                  | 55                  | 0.004   |
| Black, %                      | 25               | 12                  | 6                   | 7                   | 2                   | <0.0001 |
| ECOG 0 / 1, %                 | 49 / 50          | 64 / 36             | 58 / 42             | 63 / 37             | 70 / 30             | 0.002   |
| RAS WT / mut / unknown, %     | 33 / 30 / 37     | 31 / 30 / 39        | 26 / 39 / 35        | 38 / 29 / 33        | 37 / 21 / 42        | 0.02    |

# HIGHER VITAMIN D LEVELS ASSOCIATED WITH BETTER SURVIVAL



| No. at risk     | 0   | 1   | 2   | 15  | 4  | 5  | 6  | 7 |
|-----------------|-----|-----|-----|-----|----|----|----|---|
| Quintiles 1 & 2 | 417 | 328 | 227 | 117 | 56 | 27 | 5  | 1 |
| Quintiles 3 & 4 | 418 | 332 | 237 | 125 | 64 | 34 | 11 | 2 |
| Quintile 5      | 208 | 171 | 137 | 76  | 41 | 22 | 1  | 0 |