## 2014 European Oncology Congress in Madrid

# *Clinical Spotlight in Colorectal Cancer*

**Reference Slide Deck**

**Abstract 501O**
**Abstract 497O**

# CALGB/SWOG 80405: Phase III Trial of Irinotecan/5-FU/Leucovorin (FOLFIRI) or Oxaliplatin/5-FU/Leucovorin (mFOLFOX6) With Bevacizumab (BV) or Cetuximab (CET) for Patients (Pts) With Untreated Metastatic Adenocarcinoma of the Colon or Rectum (MCRC): Expanded RAS Analyses

## Abstract 501O

**Lenz H-J, Niedzwiecki D, Innocenti F, Blanke CD, Mahoney MR, O'Neil B, Shaw JE, Polite BN, Franklin W, Frankel W, Hochster H, Atkins N, Goldberg RM, Mayer RJ, Schilsky RL, Bertagnolli MM, Venook A; for ALLIANCE and SWOG**

# Background (1)

- **In first-line treatment of *KRAS* codon 12/13 wildtype mCRC, CALGB/SWOG 80405 showed no difference in OS or PFS between the addition of bevacizumab (BV) or cetuximab (CET) to chemotherapy with FOLFOX or FOLFIRI[1]**
- **Activating mutations at other codons within *KRAS* or *NRAS* have been associated with resistance to EGFR inhibitors[2,3]**
- **Current exploratory analysis investigated treatment effects in *RAS* wildtype patients as determined by expanded *RAS* testing using BEAMing†**

*As assessed using a high-sensitivity locked nucleic acid–mediated PCR clamping and melting curve technique
†Beads, emulsion, amplification, magnetics

1. Venook A, et al. *J Clin Oncol.* 2014;32(Suppl): Abstract LBA3; 2. Stintzing S, et al. Presented at: 2014 World Congress on Gastrointestinal Cancer; 25-28 June 2014; Barcelona, Spain; 3. Douillard J-Y, et al. *N Engl J Med.* 2013;369(11):1023-1034.

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# *RAS* Mutation Analysis: BEAMing

- **Tumor *RAS* mutation status was assessed by BEAMing[1]**
  - **PCR amplification of single-target DNA molecules on magnetic beads in the aqueous compartments of a water-in-oil microemulsion**
  - **Fluorescently tagged wildtype and mutant oligonucleotide probe pairs hybridized to bead-associated PCR products and beads typed by flow cytometry**
  - **Highly sensitive quantitative technology with the capacity to detect and enumerate mutant sequences down to a 1:10,000 ratio (mutant fraction 0.01%)[2]**

1. Dressman D, et al. *Proc Natl Acad Sci USA.* 2003;100(15):8817-8822; 2. Diehl F, et al. *Gastroenterology.* 2008;135(2):489-498.

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# *RAS* Mutation Analysis: BEAMing

- ***KRAS*** **and** ***NRAS*** **genes were screened for particular missense mutations:**
  - ***KRAS*** **exon 2: codons 12, 13**
    **exon 3: codons 59, 61**
    **exon 4: codons 117, 146**
  - ***NRAS*** **exon 2: codons 12, 13**
    **exon 3: codons 59, 61**
    **exon 4: codons 117, 146**
- **In line with other techniques that may be used clinically to determine** ***RAS*** **mutation status, a cutoff of ≥1% mutant to wildtype alleles was used to discriminate between patients**
  - **Tumors were scored as** ***RAS*** **mutant if mutant alleles were detected at a prevalence of ≥1% of total amplified sequences, regardless of whether all loci were evaluable**
  - **Tumors were scored as** ***RAS*** **wildtype only if all 26 mutation assays were evaluable and prevalence of mutant alleles was <1%**

1. Dressman D, et al. *Proc Natl Acad Sci USA.* 2003;100(15):8817-8822; 2. Diehl F, et al. *Gastroenterology.* 2008;135(2):489-498.

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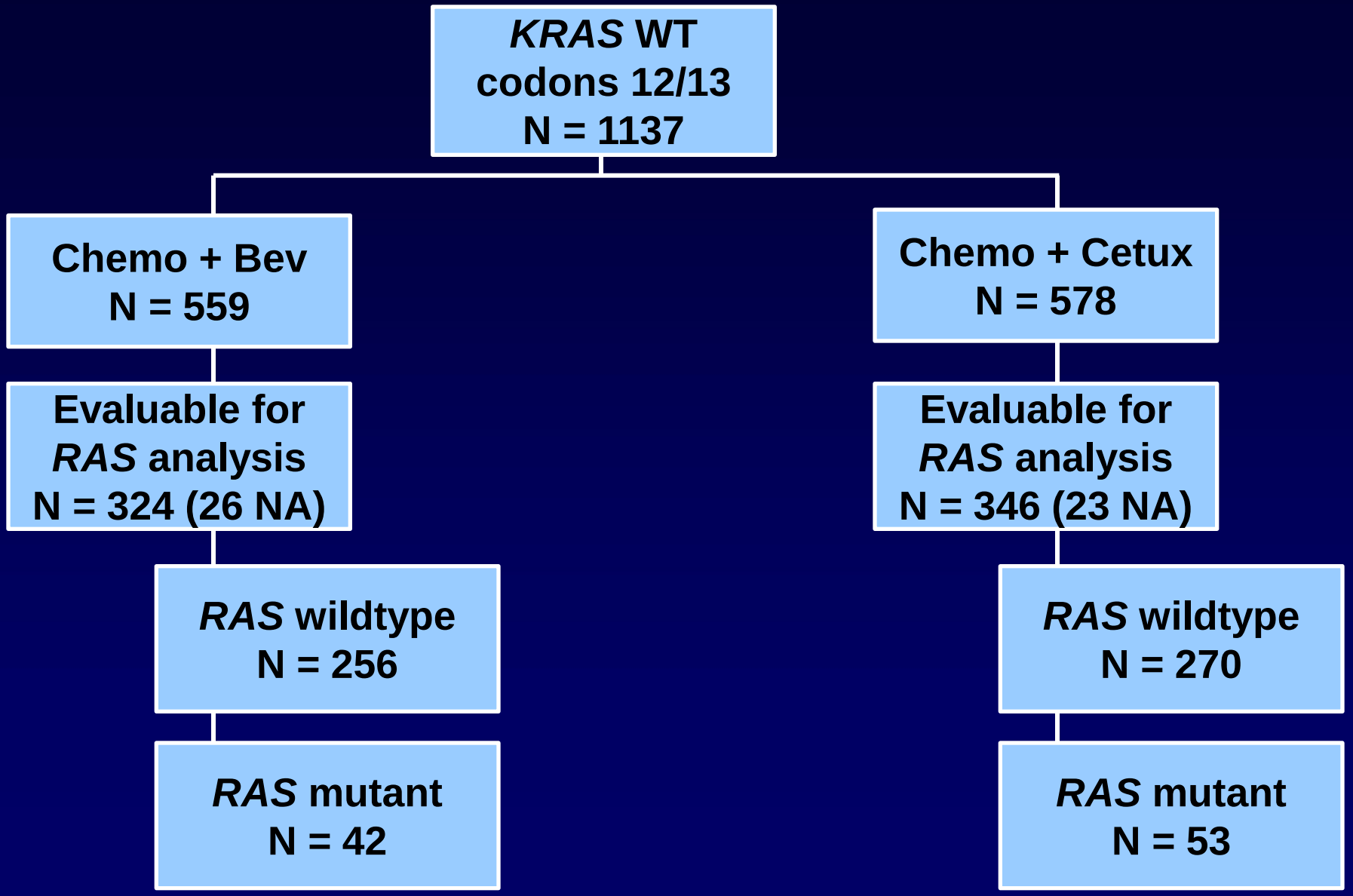
# Study Profile

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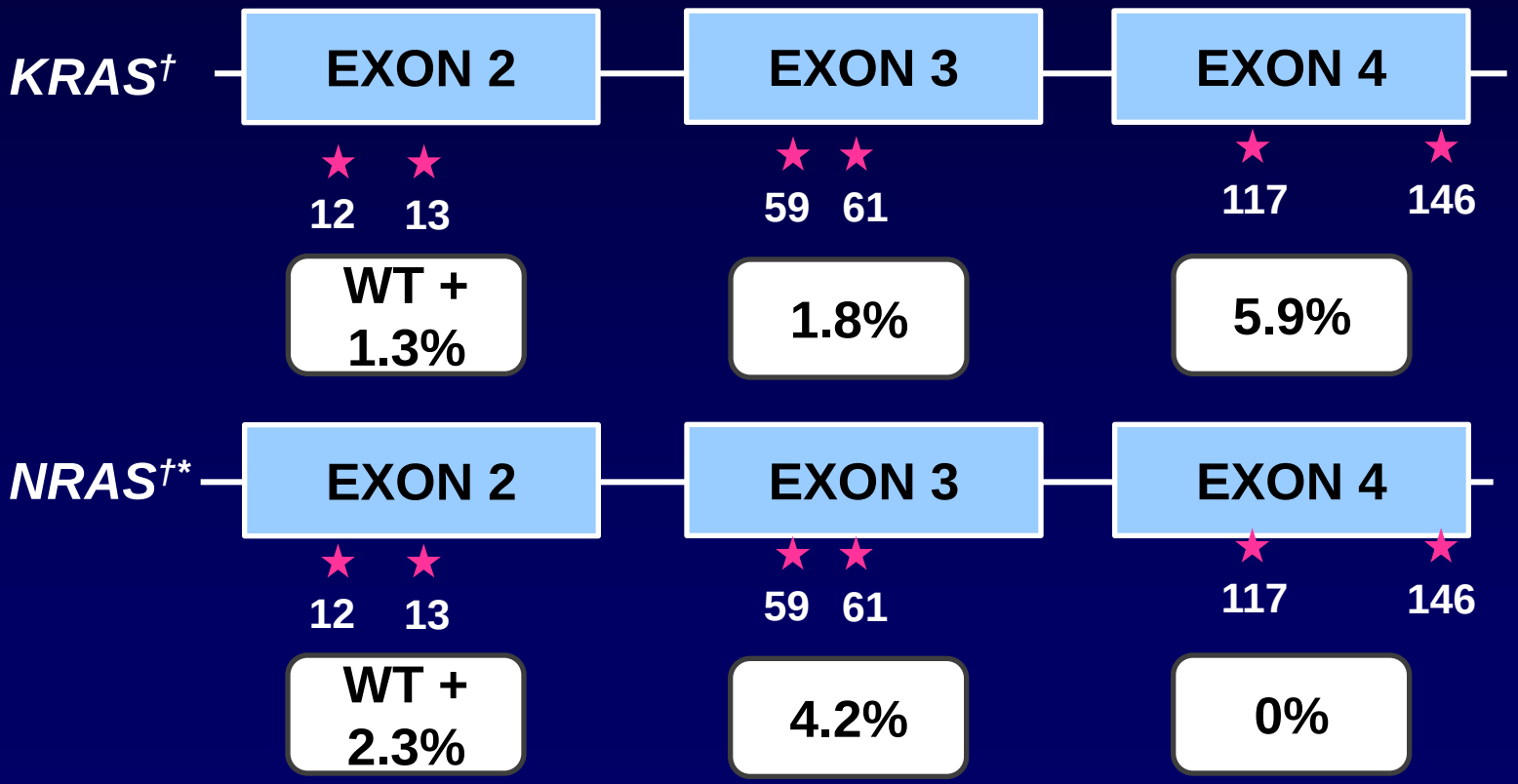
# *RAS* Mutations: CALGB/SWOG 80405

670/1137 patients (59%) with *KRAS* codon 12/13 WT tumors evaluable
621/1137 analyzed (55%)
95/621 (15.3%) patients new *RAS* mutation identified




†Percentages relate to fraction of *RAS* evaluable patients with mutations in particular exons
*One patient had a mutation at both *NRAS* exon 1 codon 12 and exon 3 codon 61

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# *RAS* Mutation Rates: First-Line Studies

## Patients With *KRAS* Codon 12/13 Wildtype Tumors

| Study | Evaluable Patients* | Method | Other *RAS* Mutations, % |
|---|---|---|---|
| **CALGB/SWOG 80405** | **670** | **BEAMing††** | **15.3** |
| OPUS | 118 | BEAMing† | 26.3 |
| CRYSTAL | 430 | BEAMing† | 14.7 |
| FIRE-3‡ | 407 | Pyrosequencing | 16.0 |
| PRIME§ | 620 | Dideoxy sequencing/WAVE | 17.4 |
| PEAK | 221 | Dideoxy sequencing/WAVE | 23.1 |

*For other tumor *RAS* mutations
†5% mutant/wildtype alleles diagnostic cutoff
††1% mutant/wildtype alleles diagnostic cut off
‡*KRAS* codons 59 and 117 not considered
§*KRAS* and *NRAS* codon 59 not considered

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# Baseline Characteristics

| Characteristic | *KRAS* Codon 12/13 Wildtype | | | |
|---|---|---|---|---|
| | Overall n = 1137 | | *RAS* Evaluable n = 670 | |
| | Chemo + BV n = 559 | Chemo + CET n = 578 | Chemo + BV n = 324 | Chemo + CET N = 346 |
| Age, years Median (range) | 59 (21-85) | 59 (20-89) | 60 (23-84) | 59 (21-90) |
| Male, % | 62.3 | 60.4 | 64.0 | 62.1 |
| Non-Caucasian, % | 14.6 | 16.5 | 12.4 | 13.9 |
| FOLFOX, % | 73 | 74 | 75 | 74 |
| Prior radiation, % | 8.9 | 9.0 | 9.0 | 9.0 |
| Prior adjuvant chemotherapy, % | 14.5 | 13.7 | 15.4 | 14.2 |
| Palliative intent, % | 86.4 | 82.5 | 83.0 | 79.5 |
| Primary in place, % | 28 | 27 | 22 | 17 |
| Liver metastases only, % | 29.3 | 31.8 | 32.7 | 35.8 |

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# Comparability of *RAS* Subgroups: Efficacy

| Subgroup | Chemo + BV<br>N | Chemo + CET<br>N | Response Rate , %*<br>BV vs CET | PFS time<br>Hazard ratio<br>95% CI | OS time<br>Hazard ratio<br>95% CI |
|---|---|---|---|---|---|
| ***KRAS* codon 12/13 wild-type** | **559** | **578** | **57.2 vs 65.6**<br>***P* = .02** | **10.8 vs 10.4†**<br>**1.04**<br>**0.91-1.17**<br>***P* =.55** | **29.0 vs 29.9†**<br>**0.92**<br>**0.78-1.09**<br>***P* = .34** |
| ***RAS* evaluable‡** | **324** | **346** | **56.0 vs 68.8**<br>***P*<.01** | **11.4 vs 10.9†**<br>**1.10**<br>**0.90-1.30**<br>***P* = .31** | **30.3 vs 30.8†**<br>**0.90**<br>**0.70-1.10**<br>***P* = .40** |

*733 *KRAS* codon 12/13 WT and 406 *RAS* evaluable patients are evaluable for response
†Median, months
‡Patients with *KRAS* codon 12/13 wild-type tumors for which tumor DNA samples were evaluable for other *RAS* mutations

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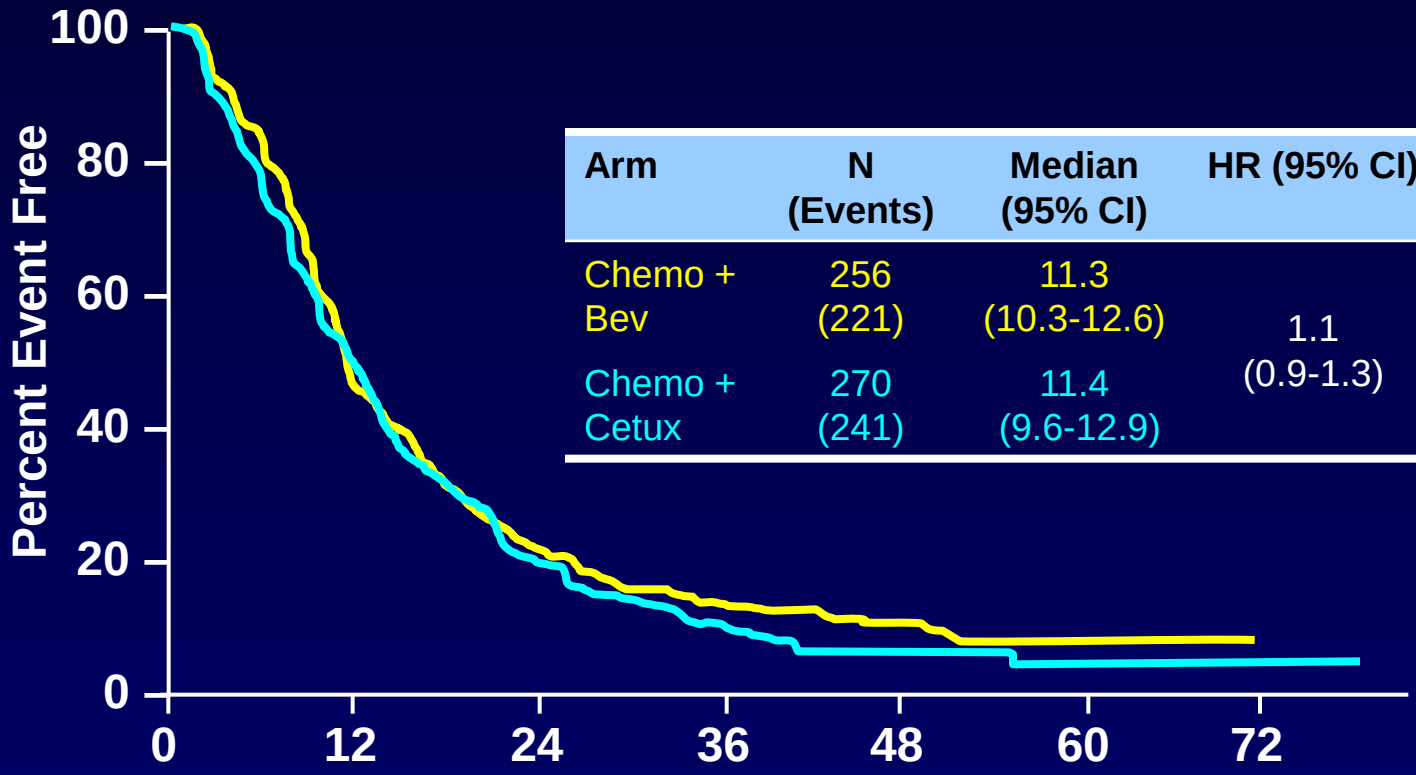
# Progression-Free Survival By Arm (All *RAS* Wildtype Patients)




| Arm | N (Events) | Median (95% CI) | HR (95% CI) | *P* |
|---|---|---|---|---|
| Chemo + Bev | 256 (221) | 11.3 (10.3-12.6) | 1.1 (0.9-1.3) | .31 |
| Chemo + Cetux | 270 (241) | 11.4 (9.6-12.9) | | |

No at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| 256 | 112 | 49 | 23 | 13 | 6 | |
| 270 | 126 | 49 | 18 | 5 | 2 | 1 |

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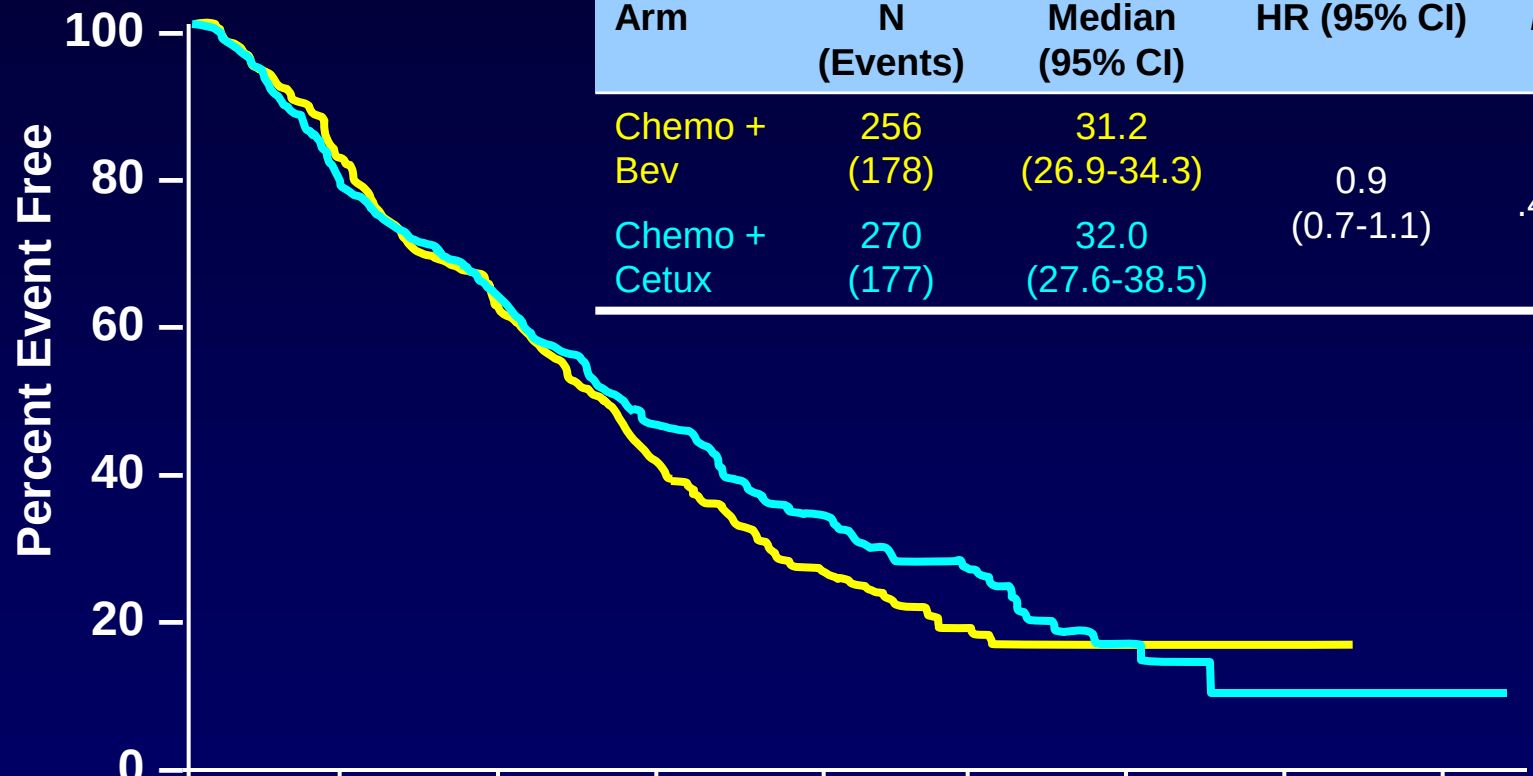
# Overall Survival By Arm (All *RAS* Wildtype Patients)

| Arm | N (Events) | Median (95% CI) | HR (95% CI) | *P* |
|---|---|---|---|---|
| Chemo + Bev | 256 (178) | 31.2 (26.9-34.3) | 0.9 (0.7-1.1) | .40 |
| Chemo + Cetux | 270 (177) | 32.0 (27.6-38.5) | | |




No at Risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 256 | 199 | 147 | 77 | 35 | 16 | 5 | 2 | |
| 270 | 205 | 164 | 88 | 41 | 24 | 7 | 1 | 1 |

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# Overall Survival
# *RAS* WT vs *KRAS* WT / All *RAS* Mutant*

| | RAS WT | | | *KRAS* WT Exon 2 / all *RAS* Mut | | |
|---|---|---|---|---|---|---|
| ARM | N (Events) | Median, Months (95% CI) | HR (95% CI) *P* | N (Events) | Median, Months (95% CI) | HR (95% CI) |
| Chemo + Bev | 256 (178) | 31.2 (26.9-34.3) | 0.9 (0.7, 1.1) *P* = *.40* | 42 (33) | 22.3 (15.3, 29.0) | 0.74 (0.4, 1.1) *P* = 0.21 |
| Chemo + Cetux | 270 (177) | 32.0 (27.6-38.5) | | 53 (41) | 28.7 (20.2, 34.7) | |

*These findings may not apply to *KRAS* mutations codons 12 and 13

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# Outcomes by Chemotherapy Backbone

## All *RAS* Wildtype FOLFOX Patients

| | Progression-Free Survival | | | | Overall Survival | | | |
|---|---|---|---|---|---|---|---|---|
| | N (Events) | Median (95% CI) | HR (95% CI) | *P* | N (Events) | Median (95% CI) | HR (95% CI) | *P* |
| Chemo + Bev | 192 (163) | 11.0 (9.5-13.1) | 1.1 (0.9-1.4) | .3 | 192 (137) | 29.0 (24.0-32.8) | 0.86 (0.6-1.1) | .2 |
| Chemo + Cetux | 198 (177) | 11.3 (9.4-13.1) | | | 198 (129) | 32.5 (26.1-40.4) | | |

## All *RAS* Wildtype FOLFIRI Patients

| | Progression-Free Survival | | | | Overall Survival | | | |
|---|---|---|---|---|---|---|---|---|
| | N (Events) | Median (95% CI) | HR (95% CI) | *P* | N (Events) | Median (95% CI) | HR (95% CI) | *P* |
| Chemo + Bev | 64 (58) | 11.9 (10.3-14.8) | 1.1 (0.7-1.5) | .7 | 64 (41) | 35.2 (28.3-41.3) | 1.1 (0.7-1.6) | .7 |
| Chemo + Cetux | 72 (64) | 12.7 (8.9-14.1) | | | 72 (48) | 32.0 (25.6-42.9) | | |

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# 80405: Work in Progress

- Identifying and collecting additional tumor blocks from patients enrolled in 80405
- Confirmed response rate / depth of response
- Duration of therapy / dose intensity
- Analysis of special subsets:
  - Patients rendered “no evidence of disease”
  - Disease recurs after adjuvant therapy
- Further details 2nd and later treatments

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# Conclusions

- All patients with newly diagnosed mCRC should be tested for *RAS*
- Overall survival >30 months in both arms sets a new benchmark for patients with mCRC that was achieved across a broad clinical trials network and suggests that the results apply in a variety of practice settings.
- First-line therapy should reflect treatment goal and concern for potential side effects.
- With additional data such as dose intensity, treatment duration, location, tumor shrinkage, second-line therapies and additional biomarker for anti-EGFR and anti-VEGF therapies we might understand better the differences between FIRE3 and 80405

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# Bevacizumab-Erlotinib As Maintenance Therapy in Metastatic Colorectal Cancer: Final Results of the GERCOR DREAM Study

**Abstract 497O**

**Chibaudel B, Tournigand C, Samson B, Scheithauer W, Mésange P, Lledo G, Viret F, Ramée J-F, Tubianna-Mathieu N, Dauba J, Dupuis O, Rinaldi Y, Mabro M, Aucoin N, Latreille J, Bonnetain F, Louvet C, Larsen AK, André T, de Gramont A**

# Rationale

- VEGF inhibition (bevacizumab or aflibercept) increases survival in combination with oxaliplatin- or irinotecan-based chemotherapy in first- or second-line[1-4]
- EGFR inhibition (panitumumab or cetuximab) increases survival in patients with *RAS* wildtype tumors[5-9]
- OPTIMOX 1 & 2 studies validated oxaliplatin stop-and-go strategy[10-11]
- Crosstalk between EGFR pathway and VEGF is involved in tumor growth and survival
- Combination of monoclonal antibodies targeting EGFR and VEGF provided no benefit in mCRC phase III studies[12-13]
- The combination of bevacizumab and erlotinib is active in mouse xenograft models

1. Saltz LB, et al. *J Clin Oncol.* 2008;26(12):2013-2019; 2. Hurwitz H, et al. *N Engl J Med.* 2004;350(23):2335-2342; 3. Giantonio BJ, et al. *J Clin Oncol*. 2007;25(12):1539-1544; 4. Van Cutsem E, et al. *J Clin Oncol.* 2012;30(28):3499-3506; 5. Van Cutsem E, et al. *J Clin Oncol.* 2011;29(15):2011-2019; 6. Douillard JY et al, *J Clin Oncol.* 28(31):4697-4705; 7. Peeters M, et al. *J Clin Oncol.* 2010;28(31):4706-4713; 8. Karapetis CS, et al. *N Engl J Med*. 2008;359(17):1757-1765; 9. Amado RG, et al. *J Clin Oncol.* 2008;26(10):1626-1634; 10. Tournigand C, et al. *J Clin Oncol.* 2006;24(3):394-400; 11. Chibaudel B, et al. *J Clin Oncol.* 2009;27(34):5727-5733; 12. Hecht JR, et al. *J Clin Oncol.* 2009;27(5):672-680; 13. Tol J, et al. *N Engl J Med.* 2009;360(6):563-572.

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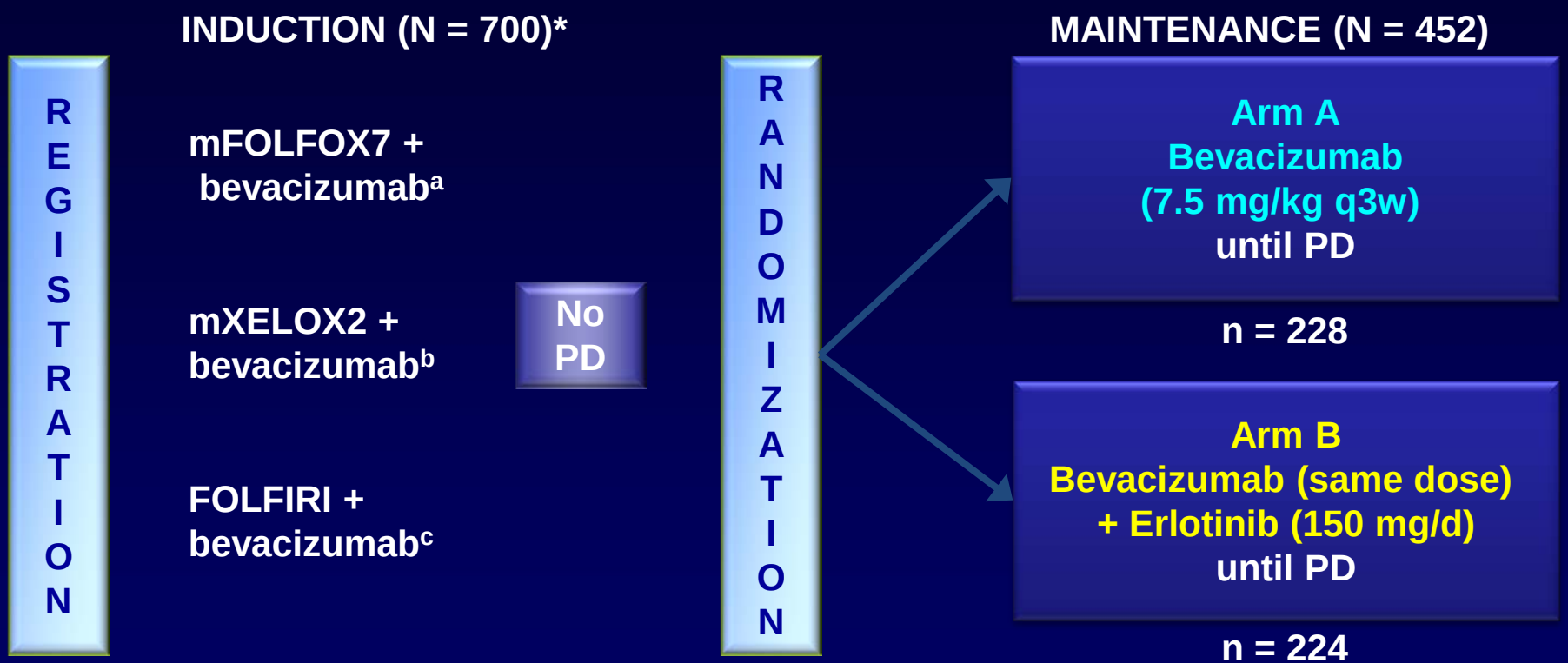
# DREAM Design




***4 Jan 2007 – 13 Oct 2011**

Design #1 (4 Jan 2007-23 Jan 2009): randomization between induction a and b (6 cycles), 310 patients

Design #2 (26 Jan 2009-13 Oct 2011): no randomization between induction a, b (6 cycles with and 6 cycles without oxaliplatin or c (12 cycles), 390 patients

[a]Oxaliplatin 100 mg/m² d1 (6 cycles), 5-FU 2.4 g/m² d1-2, FA 400 mg/m² d1, bev 5 mg/kg d1, q2w, 6-12 cycles

[b]Oxaliplatin 100 mg/m² d1 (6 cycles), capecitabine 1.25-1.5 g/m² bid d1-d8, bev 5 mg/kg d1 q2w, 6-12 cycles

[c] Irinotecan 180 mg/m² d1, 5-FU 2.4 g/m² d1-2, FA 400 mg/m² d1, bev 5 mg/kg d1, q2w, 12 cycles

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# Main Eligibility Criteria

- Histologically proven colorectal adenocarcinoma
- Measurable or evaluable metastasis
- Not suitable for complete surgical resection
- No prior chemotherapy or targeted agent for metastatic disease
- Age 18-80 years
- WHO performance status 0-2
- Alkaline phosphatase <3-5 × ULN
- Bilirubin <1.5 × ULN
- Adjuvant chemotherapy >6 months before diagnosis of metastasis (2 years if oxaliplatin)

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# Endpoints

- **Primary endpoint: Progression-free survival (PFS) on maintenance therapy**
- **Secondary endpoints**
  - Overall survival and survival from maintenance
  - PFS from registration
  - Duration without chemotherapy
  - Response rate (RECIST)
  - Survival according to *KRAS* mutational status
  - Toxicity, QoL, and pharmacoeconomic evaluation
- **Sample size**
  - Superiority study, power of 80%, 2-sided test $\alpha = .05$
  - Δ median maintenance PFS: from 4.5 months (bevacizumab) to 6.5 months (bevacizumab + erlotinib)
  - Anticipated dropout rate 40% (withdrawn consent, premature discontinuation, metastasis surgery, or progression/death)
  - 700 patients to be enrolled / 418 evaluable patients/ 231 events

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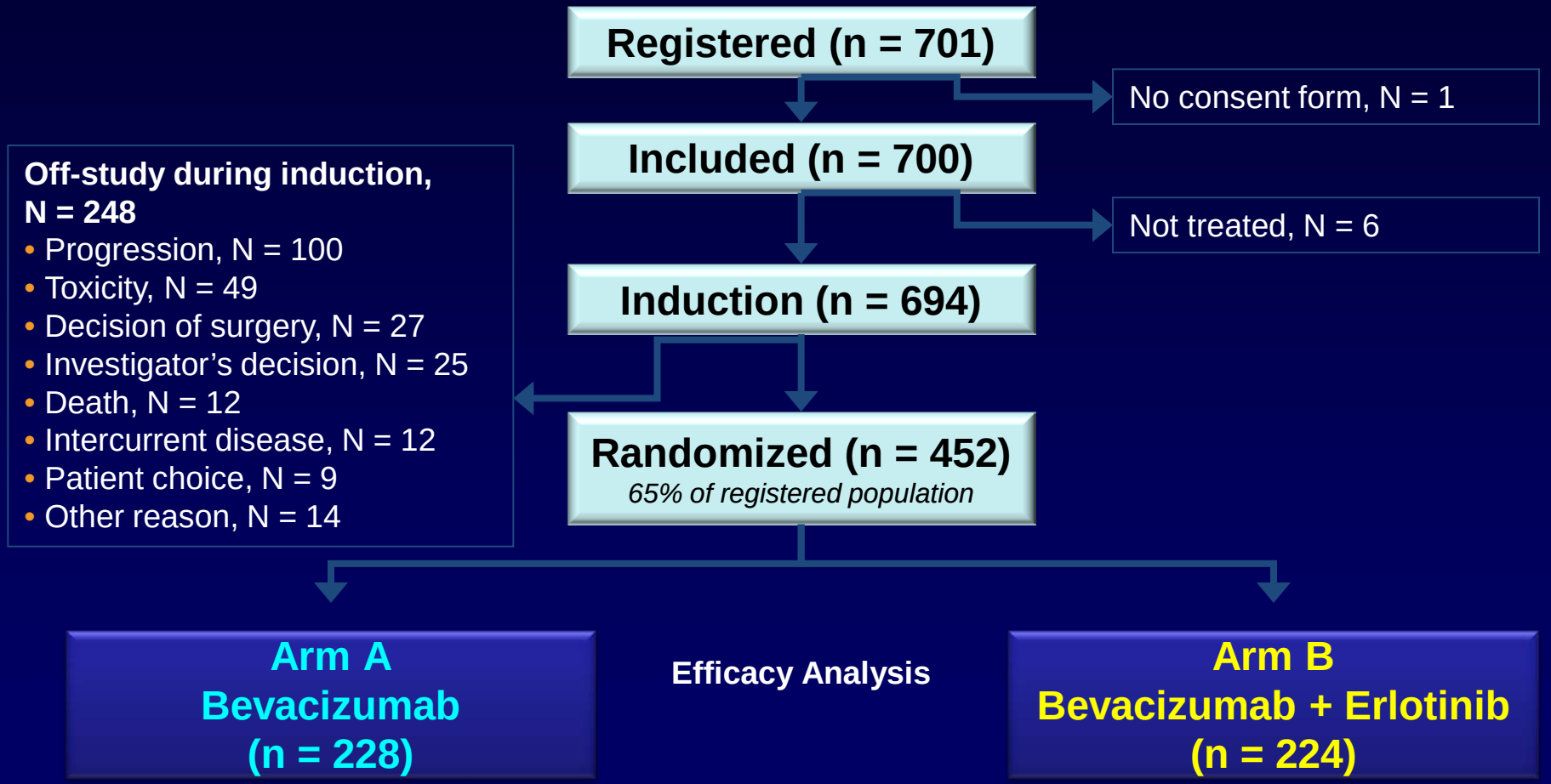
# CONSORT Diagram

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# Patient Characteristics

| | Bevacizumab (N = 228) | Bevacizumab + Erlotinib (N = 224) |
|---|---|---|
| **Registration Variables (before induction)** | **%** | **%** |
| Age, ≥70 years | 27 | 26 |
| *KRAS* wildtype | 49 | 58 |
| Metachronous | 15 | 16 |
| Single metastatic site | 45 | 48 |
| **Randomization Variables (before maintenance)** | | |
| ECOG performance status, 0 / ≥1 | 54 / 46 | 57 /43 |
| Platelet count, <400,000/mm$^3$ | 97 | 99 |
| LDH, normal value | 69 | 66 |
| Alkaline phosphatase, normal value | 71 | 72 |
| CEA, normal value | 30 | 34 |
| Induction response rate | | |
| *Complete or Partial Response* | 55 | 58 |
| *Stable Disease* | 46 | 42 |

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# Treatment Delivery

| | Bevacizumab (N = 228) | Bevacizumab + Erlotinib (N = 224) | |
|---|---|---|---|
| | | Bevacizumab | Erlotinib |
| No. of cycles | 3017 | 3370 | 3279 |
| Mean no. of cycles/patient | 7.1 | 8.1 | 7.2 |
| No. of cycles postponed (%) | 279 (9) | 286 (8) | - |
| No. of cycles at full dose (%) | 2879 (95) | 3196 (94) | 2377 (70) |

**Median duration of erlotinib therapy: 110 days (3.6 months)**

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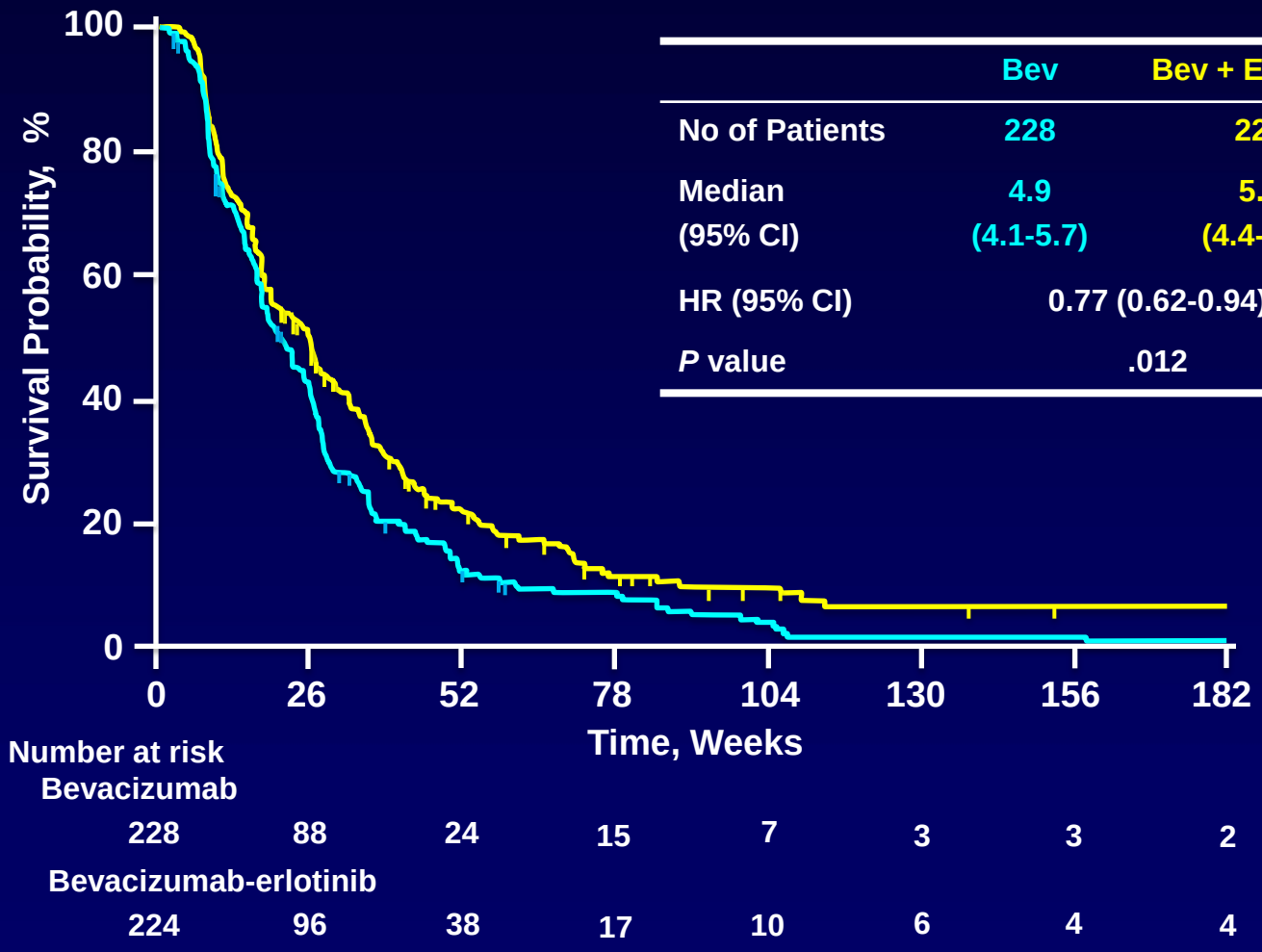
# Maintenance Progression-Free Survival




| | Bev | Bev + Erlotinib |
|---|---|---|
| No of Patients | 228 | 224 |
| Median (95% CI) | 4.9 (4.1-5.7) | 5.9 (4.4-6.6) |
| HR (95% CI) | 0.77 (0.62-0.94) | |
| *P* value | .012 | |

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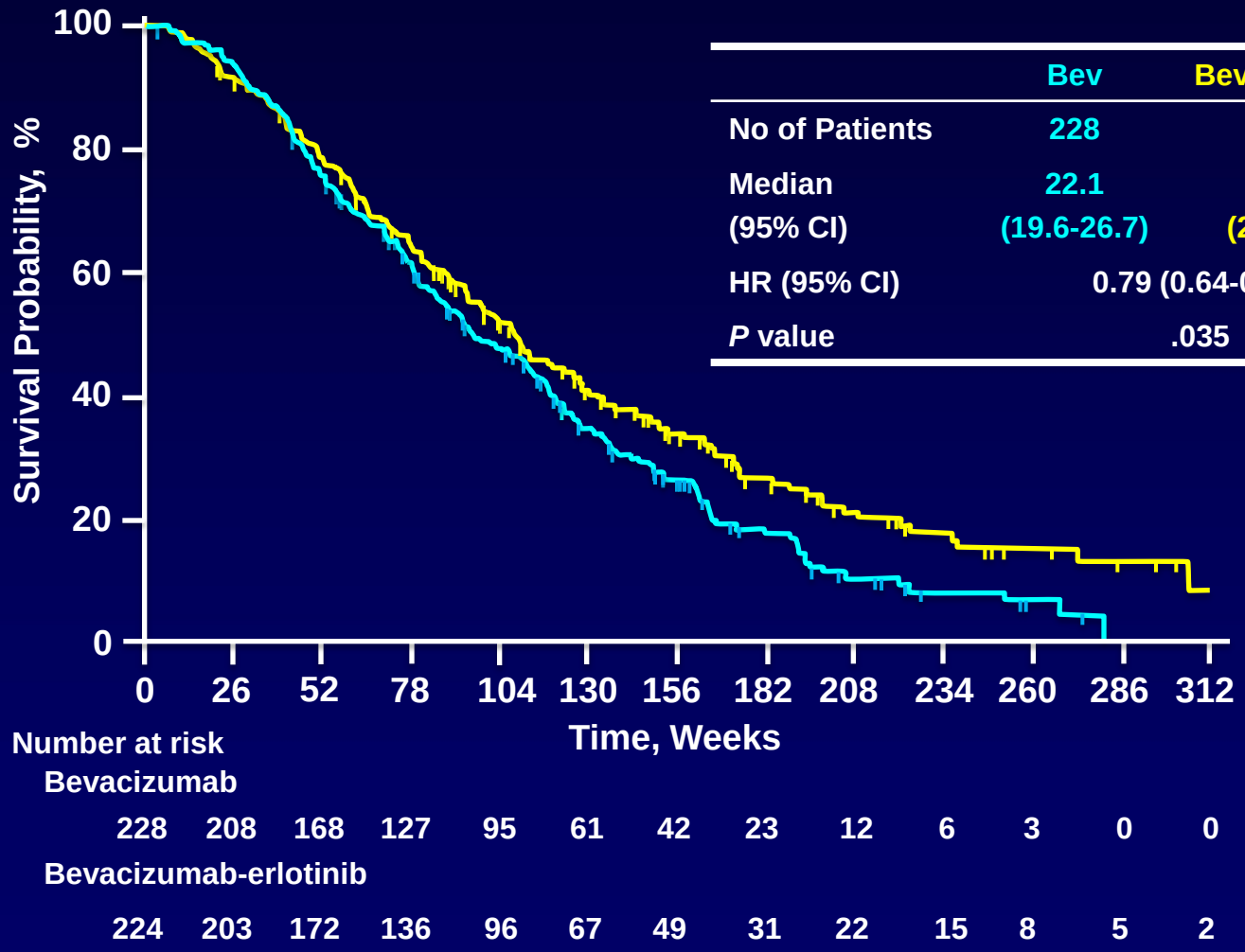
# Maintenance Overall Survival




| | Bev | Bev + Erlotinib |
|---|---|---|
| No of Patients | 228 | 224 |
| Median (95% CI) | 22.1 (19.6-26.7) | 24.9 (21.6-28.9) |
| HR (95% CI) | 0.79 (0.64-0.98) | |
| *P* value | .035 | |

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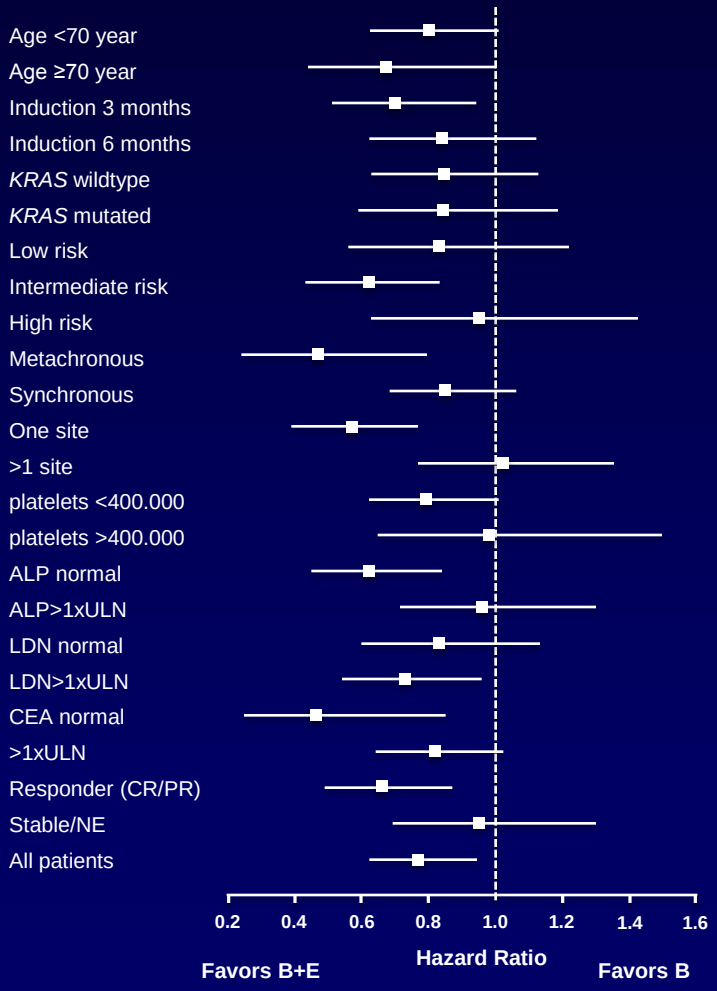
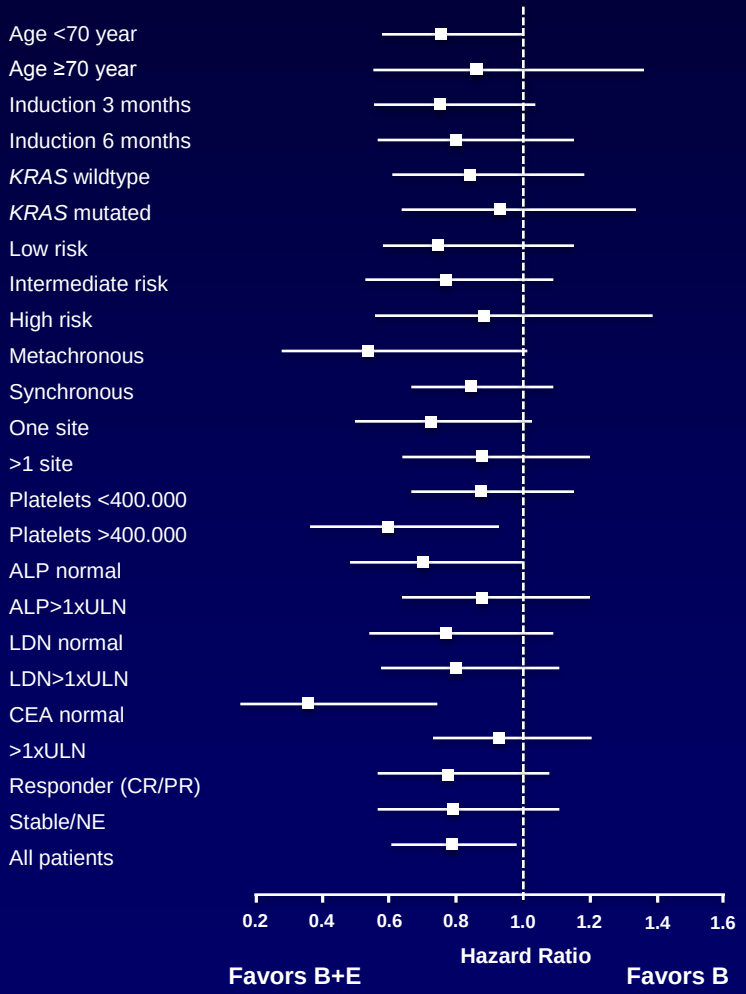
# Subgroup Analysis

## Maintenance PFS




## Maintenance OS

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# Maintenance Response Rate (%)

| | All Patients | | *KRAS* Wildtype | | *KRAS* Mutant | |
|---|---|---|---|---|---|---|
| | Bev N = 208 | Bev + Erlot N = 213 | Bev N = 104 | Bev + Erlot N = 121 | Bev N = 84 | Bev + Erlot N = 76 |
| **CR** | **1.9** | **4.2** | **2.9** | **5.8** | **1.2** | **1.3** |
| **PR** | **9.5** | **18.3** | **12.5** | **18.2** | **7.1** | **18.4** |
| **SD** | **60.6** | **57.7** | **60.6** | **56.2** | **61.9** | **59.2** |
| **PD** | **20.2** | **13.1** | **19.2** | **13.2** | **17.9** | **14.5** |
| **NE** | **7.7** | **6.6** | **4.8** | **6.6** | **11.9** | **6.6** |
| **ORR** | **11.5** | **22.5** | **15.4** | **24.0** | **8.3** | **19.7** |
| ***P* value** | **.003** | | **.133** | | **.041** | |

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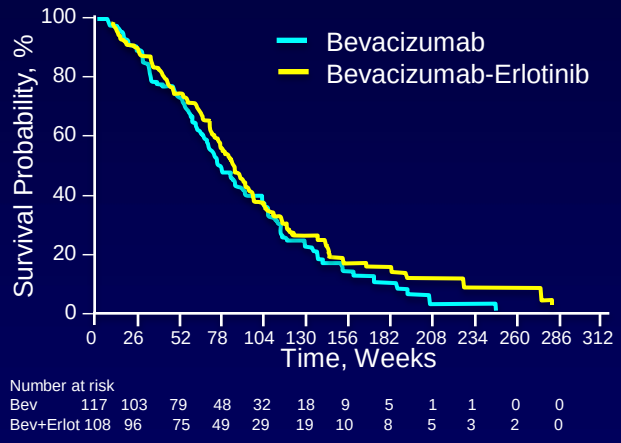
# Toxicity – Any Grade

| CTCAE Term, % patients | Bevacizumab (N = 228) | Bevacizumab + Erlotinib (N = 224) | *P* Value |
|---|---|---|---|
| Neutrophils | 10 | 13 | .211 |
| Platelets | 20 | 16 | .556 |
| Hemoglobin | 30 | 31 | .613 |
| Febrile neutropenia | 0 | 0 | 1.00 |
| Nausea | 8 | 17 | .025 |
| Vomiting | 6 | 10 | .355 |
| Mucositis | 4 | 13 | .012 |
| Diarrhea | 14 | 59 | <.001 |
| Hand-Foot Syndrome | 3 | 8 | .126 |
| Skin rash | 9 | 89 | <.001 |
| Thromboembolism | 1 | 0 | .471 |
| Proteinuria | 24 | 35 | .026 |
| Hypertension | 30 | 35 | .430 |
| Conjunctivitis | 1 | 5 | .123 |

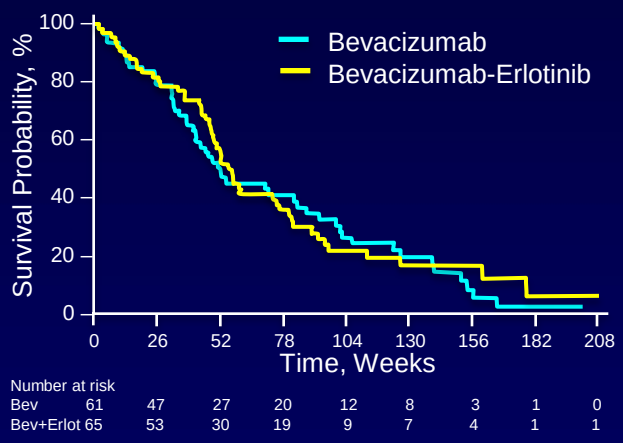
Chibaudel B, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 497O.

# Post-Progression Therapy

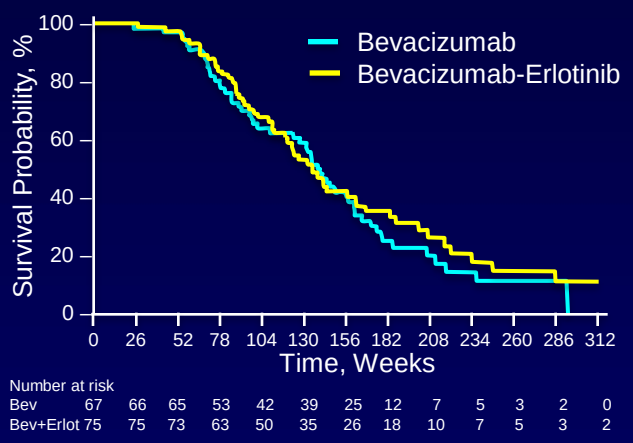
### Oxaliplatin-Reintroduction




### Irinotecan-Based Second-Line




### EGFRI mAb All lines




**The same proportion of patients received the same post-progression therapy in both arms.**

**Survival in patients who received post-progression therapy and in those who received EGFRI mAb, is similar in both arms.**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# Conclusions (1)

- **Unlike monoclonal antibodies combination, there is a strong preclinical rationale to combine bevacizumab with erlotinib, a small-molecule EGFR-TKI.**
- **In patients with metastatic colorectal cancer, induction therapy followed by bevacizumab and erlotinib significantly improves survival compared to the same induction followed by bevacizumab alone: maintenance PFS, PFS from registration, OS from maintenance, OS from registration.**
- **This effect is observed whatever the *KRAS* status. Furthermore, a significant difference in response rate is observed during the chemotherapy-free maintenance therapy in *KRAS*-mutated tumors.**
- **Safety is acceptable despite an increased incidence of severe skin rash and diarrhea.**

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# Conclusions (2)

- **The survival benefit is observed whatever the subsequent therapy used: oxaliplatin-reintroduction, irinotecan-based second-line, EGFR mAb administration.**
- **EGFR mAb remains active in patients who received erlotinib before.**
- **A prolonged follow-up was needed to observe the survival benefit.**
- **Maintenance therapy with fluoropyrimidines and bevacizumab prolongs PFS and delays second-line therapy over a complete stop in chemotherapy. However, there is no evidence of survival prolongation nor of superiority over bevacizumab alone.**

**Bevacizumab and a short period of erlotinib therapy is a new treatment option in first-line therapy following induction chemotherapy with bevacizumab.**

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