MADRID 2014 ESMO congress

Bevacizumab-erlotinib as maintenance therapy in metastatic colorectal cancer.

Final results of the GERCOR DREAM study

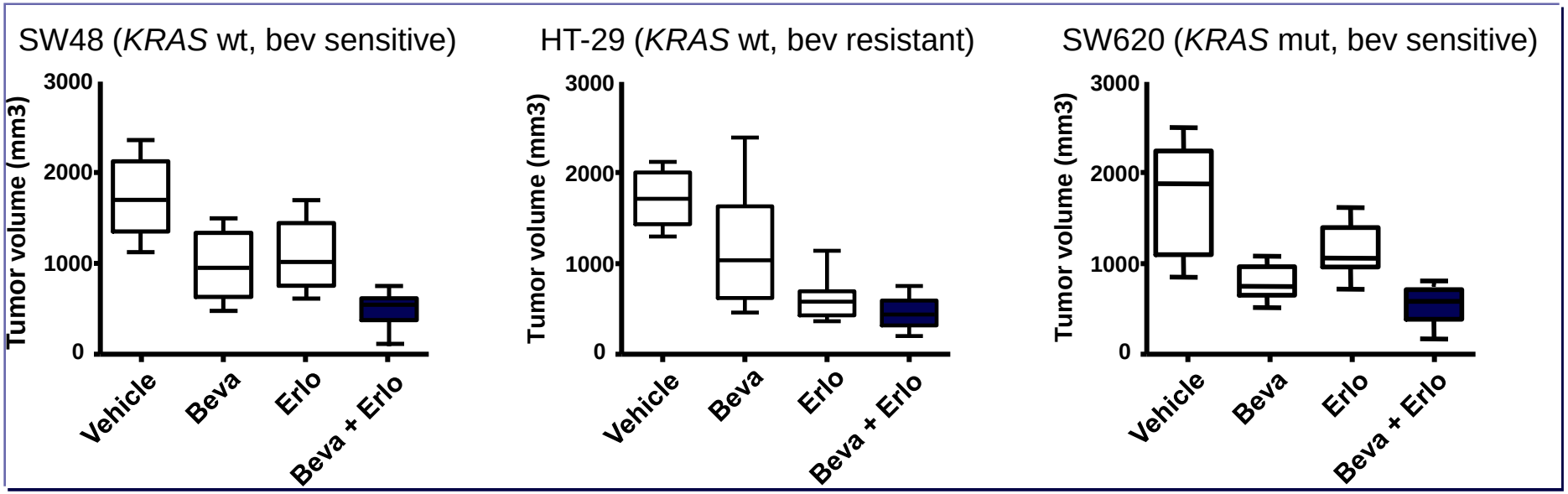
Benoist Chibaudel, Christophe Tournigand, Benoit Samson, Werner Scheithauer, Paul Mésange, Gérard Lledo, Frédéric Viret, Jean-François Ramée, Nicole Tubianna-Mathieu, Jérôme Dauba, Olivier Dupuis, Yves Rinaldi, May Mabro, Nathalie Aucoin, Jean Latreille, Franck Bonnetain, Christophe Louvet, Annette K Larsen, Thierry André, Aimery de Gramont

Rationale (1)

- **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 wild-type tumors [5–9]**
- **OPTIMOX 1 & 2 studies validated oxaliplatin stop-and-go strategy [10-11]**
- **Crosstalk between EGFR pathway and VEGF is involved in tumour growth and survival**
- **Combination of monoclonal antibodies targeting EGFR and VEGF provided no benefit in mCRC phase III studies [12-13]**

1. Saltz LB et al. J Clin Oncol 2008;26:2013–9
2. Hurwitz H et al. N Engl J Med 2004;350:2335–42
3. Giantonio BJ, J Clin Oncol 2007;25:1539–44
4. Van Cutsem E et al, J Clin Oncol;2012;30:3499-506
5. Van Cutsem E, et al. J Clin Oncol 2011;29:2011–9
6. Douillard JY et al, J Clin Oncol 28:4697-4705.
7. Peeters M, et al. J Clin Oncol 2010;28: 4706–13
8. Karapetis CS, et al. N Engl J Med.2008;359:1757–65
9. Amado RG, et al. J Clin Oncol 2008;26:1626–34
10. Tournigand C, et al. J Clin Oncol 2006;24:394–400
11. Chibaudel B, et al. J Clin Oncol 2009;27:5727–33
12. Hecht JR, et al. J Clin Oncol 2009;27:672–80
13. Tol J, et al. N Engl J Med 2010;360:563–72

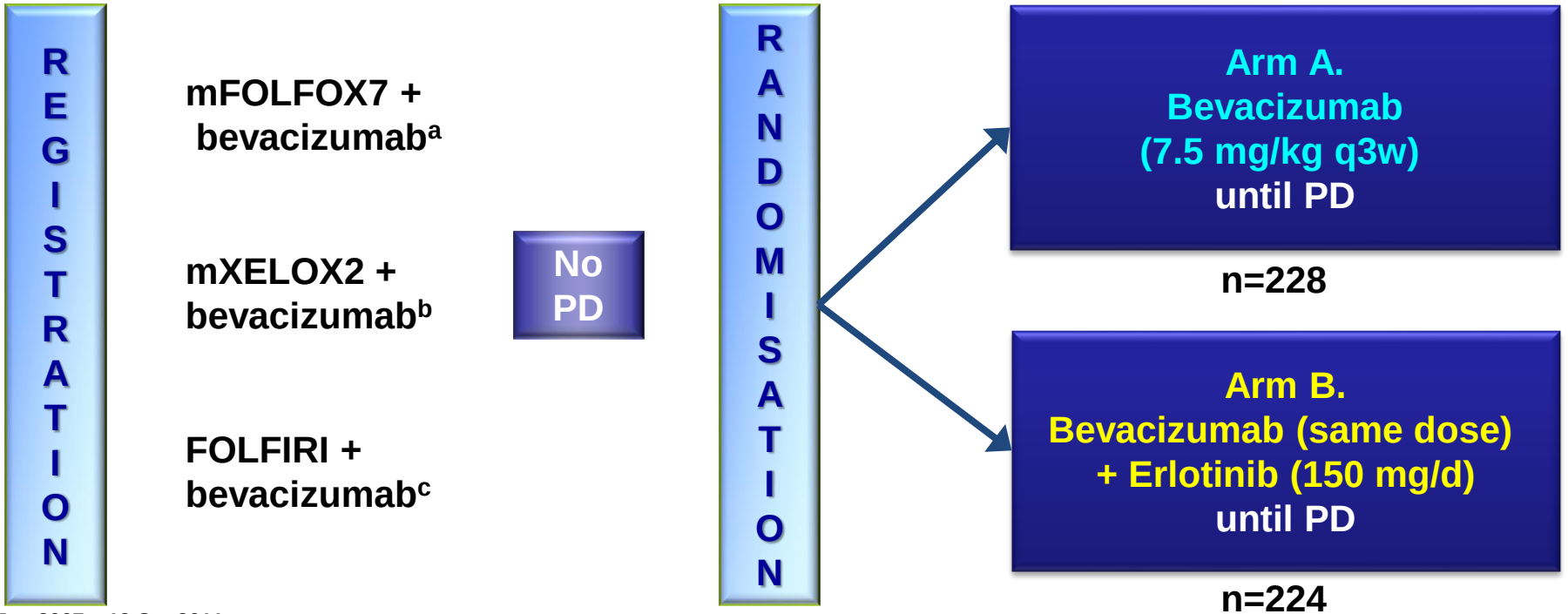
Rationale (2) : Mouse DREAM



- Bevacizumab and erlotinib are more active than bevacizumab alone for all three xenograft models.
- Quantitative IHC analysis showed that bevacizumab activated EGFR in the tumor cells and in the tumor-associated endothelial cells which was attenuated by erlotinib.

Mésange P et al. ESMO 2013

DREAM Design



***4 Jan 2007 – 13 Oct 2011**

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

Design #2 (26 Jan 2009-13 Oct 2011): no randomisation 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

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)**

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**

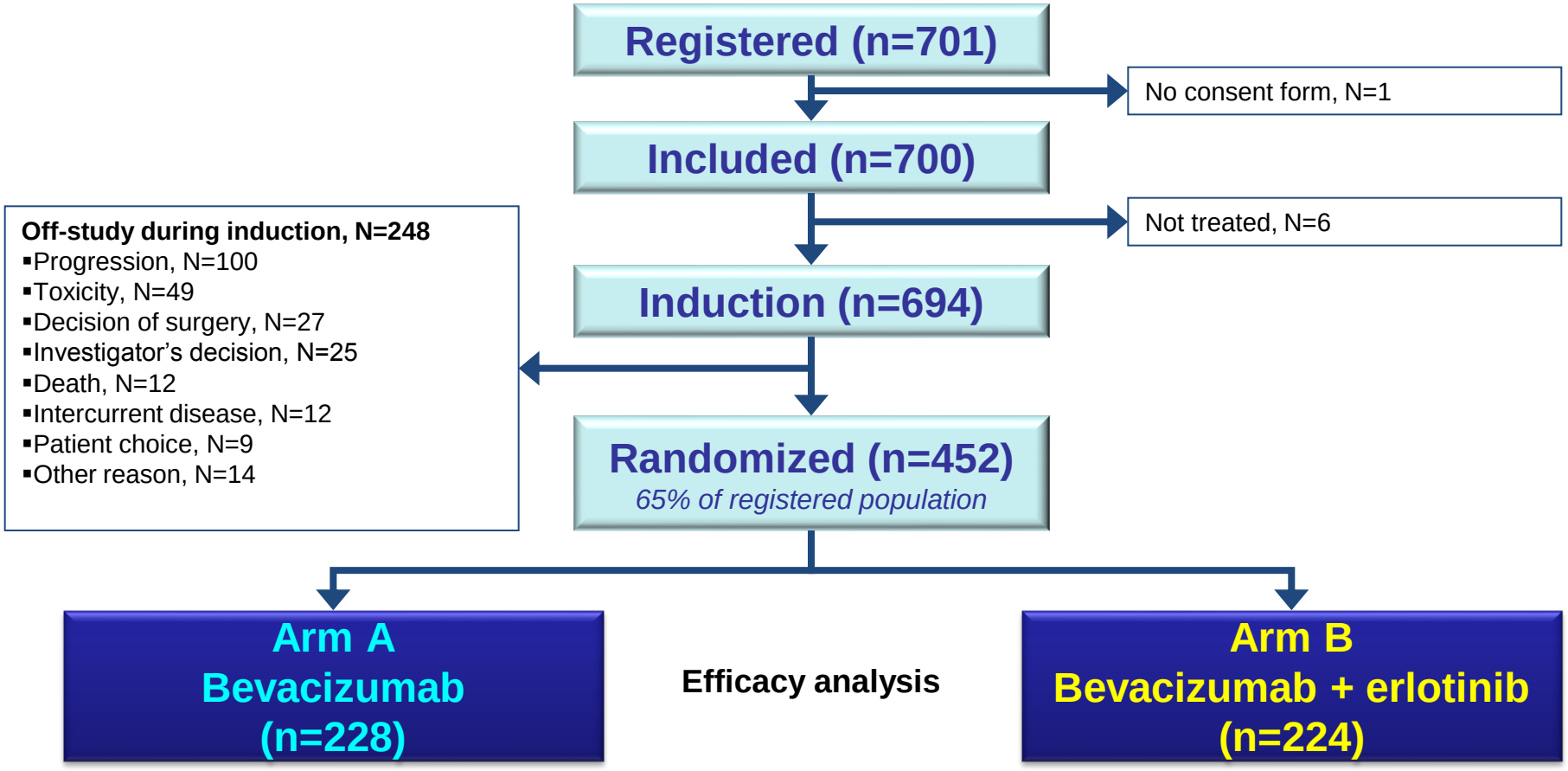
  Superiority study, power of 80%, 2-sided test α=0.05

  Δ median maintenance PFS: from 4.5 months (bevacizumab) to 6.5 months (bevacizumab + erlotinib)

  Anticipated drop-out rate 40% (withdrawn consent, premature discontinuation, metastasis surgery or progression/death)

  700 patients to be enrolled / 418 evaluable patients/ 231 events

CONSORT Diagram



Patient Characteristics

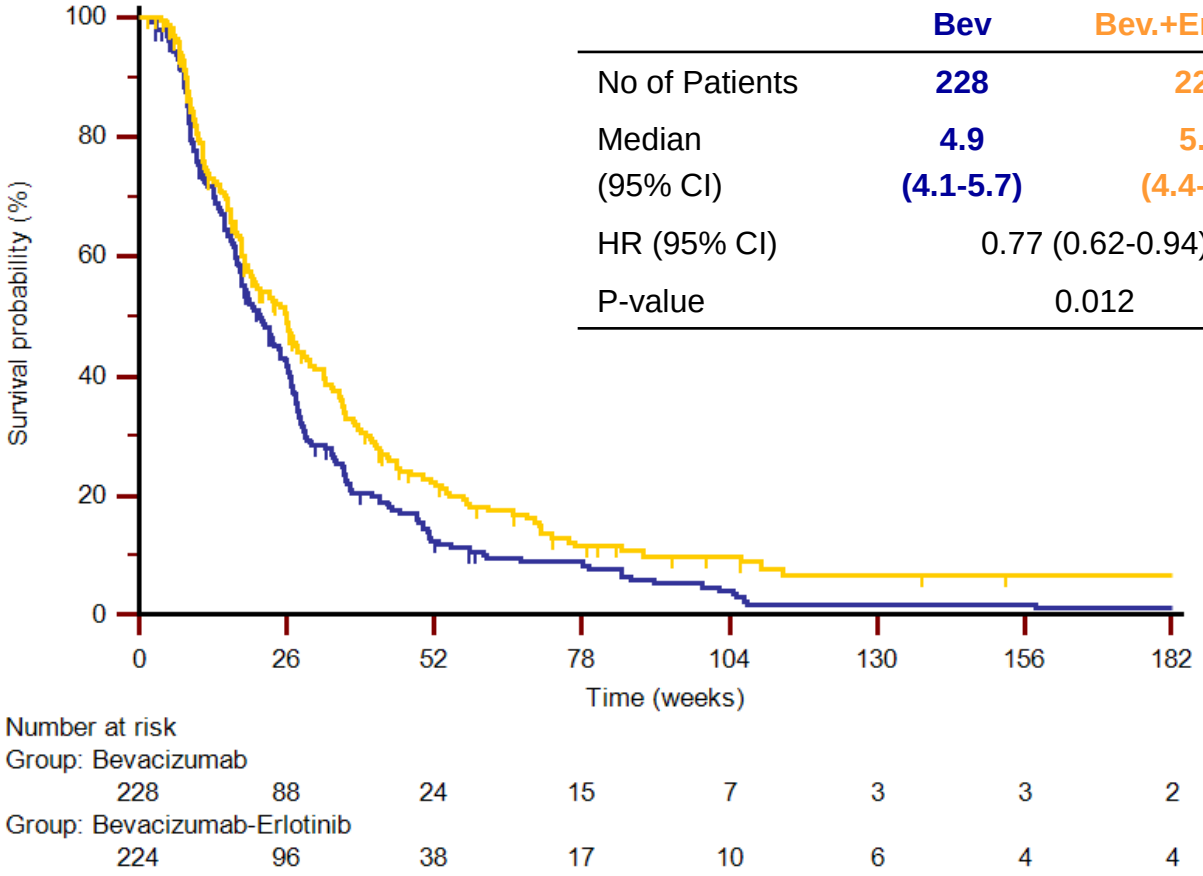
	Bevacizumab (N=228)	Bevacizumab + erlotinib (N=224)
Registration variables (before induction)	**%**	**%**
Age, ≥70 years	27	26
KRAS wild-type	49	58
Metachronous	15	16
Single met. site	45	48
Randomisation variables (before maintenance)		
ECOG performance status, 0 / ≥1	54 / 46	57 /43
Platelet count, <400,000/mm3	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

Treatment delivery

	Bevacizumab (N=228)	**Bevacizumab + erlotinib (N=224)**	
	Bevacizumab	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)

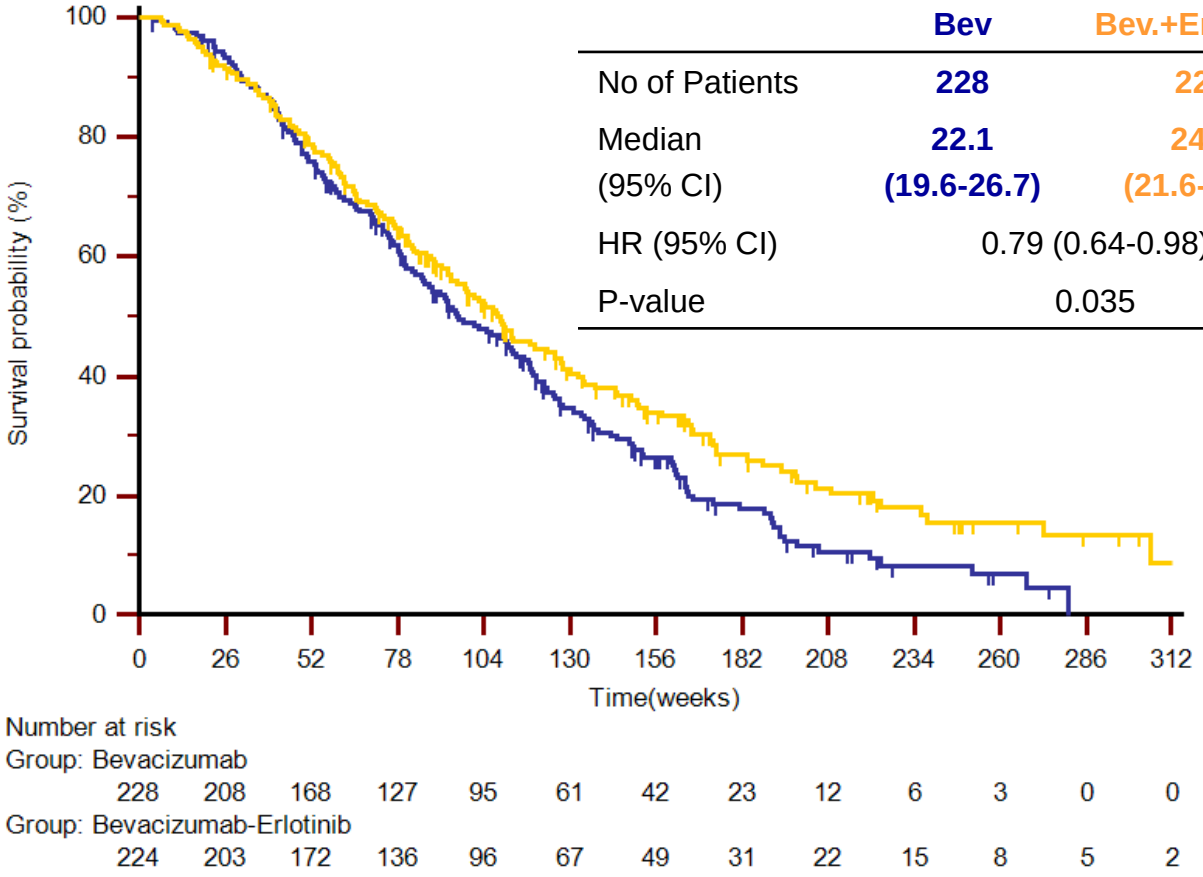
Median duration of erlotinib therapy: 110 days (3.6 months)

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	0.012	

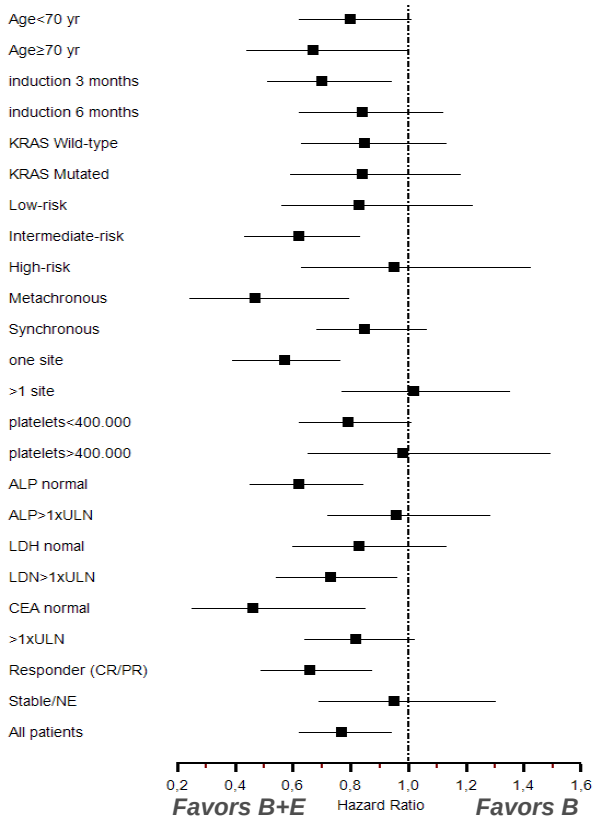
Maintenance Overall Survival



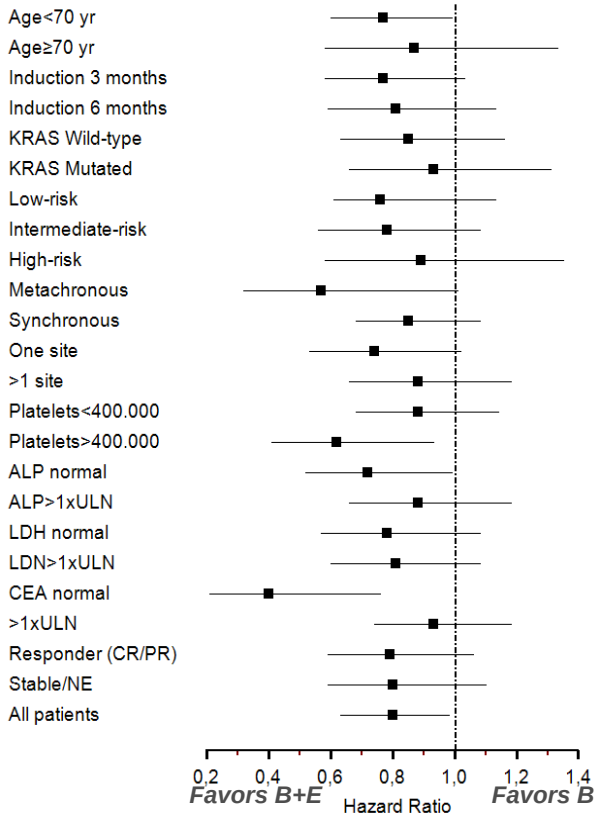
	Bev	Bev.+Erlotinib
No of Patients	228	224
Median (95% CI)	22.1 (19.6-26.7)	24.9 (21.6-28.9)
HR (95% CI)	0.79 (0.64-0.98)	
P-value	0.035	

Subgroup Analysis

Maintenance PFS



Maintenance OS



Maintenance Response Rate (%)

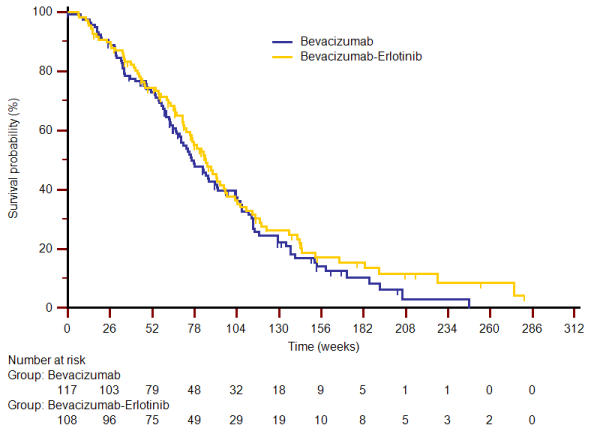
	All Patients		Wild-type KRAS		Mutant KRAS	
	Bev N=208	Bev+erlo N=213	Bev N=104	Bev+erlo N=121	Bev N=84	Bev+erlo N=76
CR	1.9	4.2	2.9	5.8	1.2	1.3
PR	9.5	18.3	12.5	18.2	7.1	18.4
SD	60.6	57.7	60.6	56.2	61.9	59.2
PD	20.2	13.1	19.2	13.2	17.9	14.5
NE	7.7	6.6	4.8	6.6	11.9	6.6
ORR	**11.5**	**22.5**	**15.4**	**24.0**	**8.3**	**19.7**
P-value	**0.003**		**0.133**		**0.041**	

Toxicity – Any grade

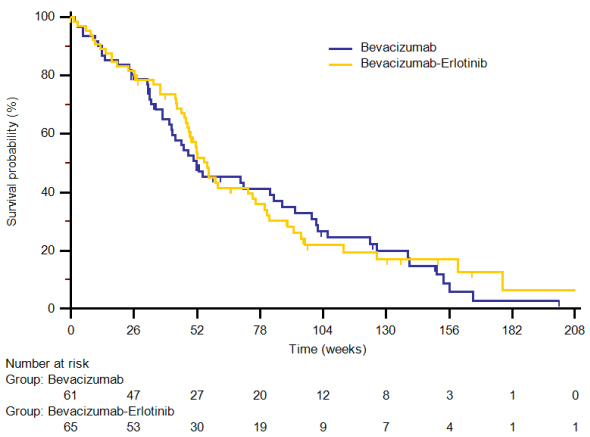
CTCAE Term, % patients	Bevacizumab (N=228)	Bevacizumab + erlotinib (N=224)	P-value
Neutrophils	10	13	0.211
Platelets	20	16	0.556
Hemoglobin	30	31	0.613
Febrile neutropenia	0	0	1.00
Nausea	8	17	0.025
Vomiting	6	10	0.355
Mucositis	4	13	0.012
Diarrhea	14	59	<0.001
Hand Foot Syndrom	3	8	0.126
Skin rash	9	89	<0.001
Thromboembolism	1	0	0.471
Proteinuria	24	35	0.026
Hypertension	30	35	0.430
Conjuntivitis	1	5	0.123

Post-progression Therapy

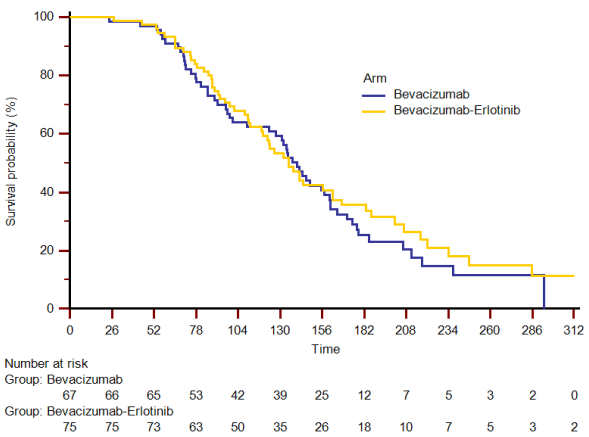
Oxaliplatin-Reintroduction



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

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 RAS mutated tumors.**
- **Safety is acceptable despite an increased incidence of severe skin rash and diarrhea.**

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.