Adjuvant FOLFOX4 plus or minus cetuximab (Cmab) in patients (pts) with *KRAS* mutant (m*KRAS*) resected stage III colon cancer (CC). Results from the PETACC8 intergroup trial

Ramon Salazar,* Enrico Mini, Gunnar Folprecht, Fabien Subtil, Jean-Luc Van Laethem, Josef Thaler, John Bridgewater, Eric Van Cutsem, Come Lepage, Julien Taïeb

[*]Catalan Institute of Oncology (IDIBELL), Barcelona, Spain

Disclosures

- Grants to support the trial were received from:
  - Merck Serono
  - Sanofi-Aventis

- Professor/Dr Ramon Salazar declares:
  - Consultancy/advisory role
    - Merck KGaA
  - Speaker´s bureau honoraria
    - Merck KGaA

Background: standard adjuvant therapy

- 5-FU, oxaliplatin, and LV is standard adjuvant therapy for resected stage III colon cancer
  - MOSAIC FOLFOX4 vs LV5FU2[1,2]
  - NSABP C-07 FLOX vs 5-FU/LV[3,4]
- Monoclonal antibodies against EGFR and VEGF failed to improve 3-year DFS in the adjuvant setting:
  - For anti-VEGF in 2 trials (AVANT, NSABP-C08)[5,6]
  - For anti-EGFR in one (NCCTG N0147, PETACC8)[7,8]

[1]André T, et al., NEJM 2004; [2]André T, et al., JCO 2009; [3]Kuebler JP, et al., JCO 2007; [4]Yothers G, et al., JCO 2011; [5]De Gramont A, et al., ASCO GI 2011; [6]Allegra C, et al., JCO 2011; [7]Alberts SR, et al., JAMA 2012; [8]Taieb J et al., ESMO 2012

Background: FOLFOX + anti-EGFR in m*KRAS* mCRC

- Adding anti-EGFR mAbs to FOLFOX might harm patients with *KRAS* mutant tumors[1,2]

- OPUS trial (FOLFOX4 +/- cetuximab): m*KRAS* pts PFS, HR 1.72, 95% CI 1.10-2.68, p=0.015

- PRIME trial (FOLFOX4 +/- panitumumab): m*KRAS* pts PFS, HR 1.29, 95% CI 1.04-1.62, p=0.02

[1]Bokemeyer C, et al., Ann Oncol 2011;
[2]Douillard JY, et al., JCO 2010

Original 2-arm design for PETACC8

Fully resected stage III colon cancer (N = 2000)

R

FOLFOX4 (12 cycles)

Every 2 weeks:

- **Oxaliplatin 85 mg/m^2 on d1 and**
- **LV 200 mg/m^2, 5-FU bolus 400 mg/m^2 followed by 5-FU 600mg/m^2 22-hour IV on d1 and d2**

FOLFOX4 + cetuximab (12 cycles)

- **FOLFOX4**
  Cetuximab d1 and d8
  - **400 mg/m^2 initial dose**
  - **250 mg/m^2 weekly**

Stratification factors:
- N-status (N1 vs N2)
- T-status (T1-3 vs T4)
- Obstruction/perforation status

Enrolment was restricted to wild-type *KRAS* and sample size increased in 2008

Main inclusion criteria

- Completely resected, pathologically confirmed, stage III colon adenocarcinoma regardless of EGFR status
- ≥1 pathologically confirmed LN identified
- Age ≥18 and <75 years
- WHO PS 0 or 1
- Acceptable liver and kidney function
- Standard hematologic parameters
- Life expectancy ≥5 years

LN, lymph node

Main exclusion criteria

- Evidence of metastatic disease
  - En bloc resection for locally advanced disease allowed
- Rectal cancer
- Prior chemo- or radiation therapy for colon cancer
- Prior or concurrent malignancies within 5 years
- Clinically significant peripheral neuropathy

KRAS mutation status

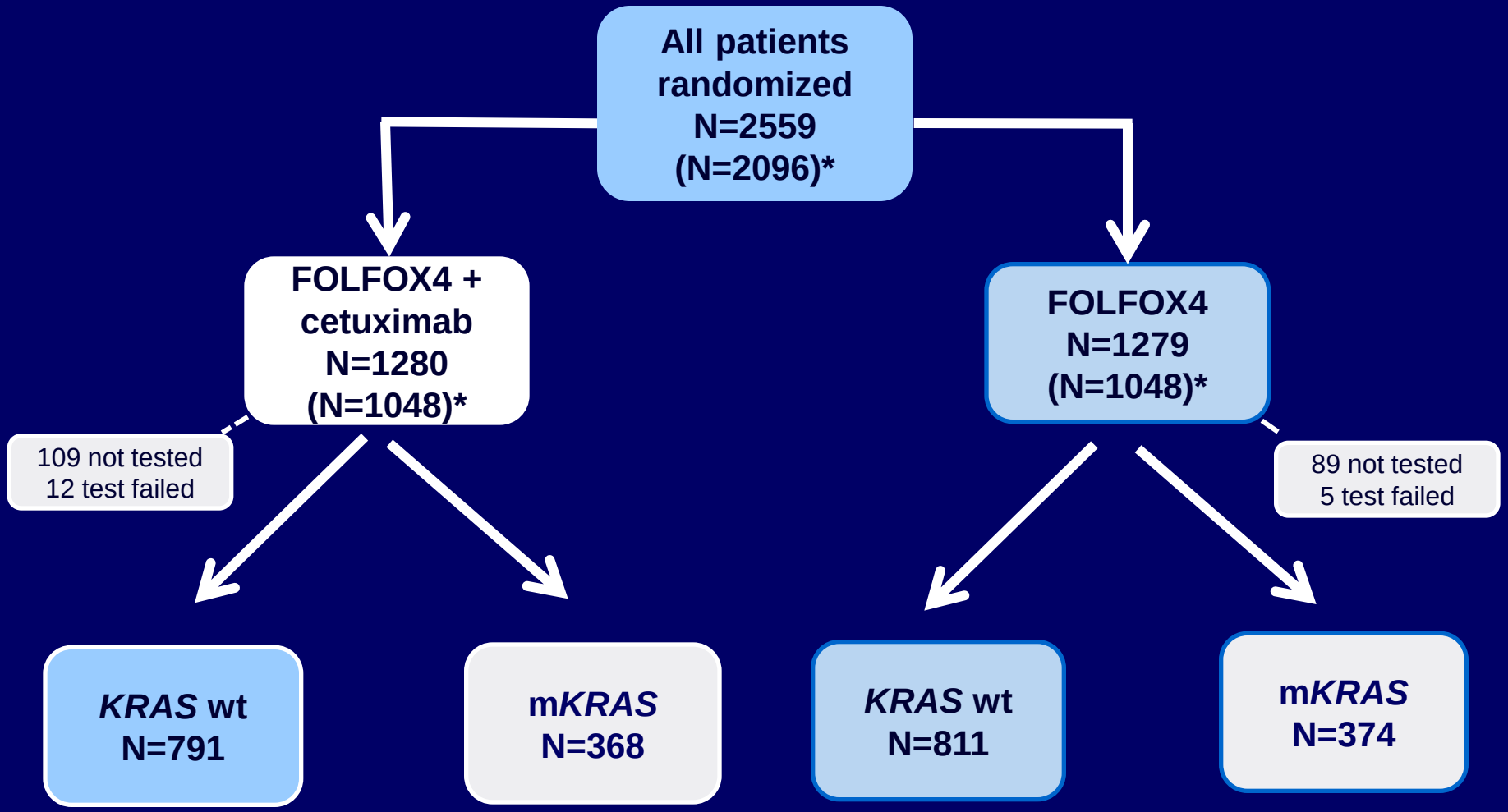
- The trial protocol was amended mid-2008 for the primary objective to be determined in *KRAS* wt patients only

- The present analysis will focus on those patients with m*KRAS* colon cancer recruited prior to the amendment only

Objectives

- To assess disease-free survival (DFS) according to treatment in patients with resected stage III m*KRAS* tumors
  - DFS = until recurrence, 2nd CRC or death
- Treatment compliance and toxicity
- Overall survival (OS)

Patient disposition: all patients



* Randomized prior to protocol amendment irrespective of *KRAS* status

Baseline characteristics: m*KRAS* patients

Patient characteristics	FOLFOX4 + cetuximab N=368	FOLFOX4 N=374
Male Female	56.5% 43.5%	52.4% 47.6%
Age, years: Mean (SD) Median (range)	 60.1 (9.21) 61.0 (23.0-74.0)	 60.1 (9.39) 61.0 (26.0-75.0)
Age ≤70 years	88.0%	87.4%
WHO performance status: 0 1 2	 79.3% 16.6% 0.3%	 79.7% 16.0% 0.3%

Baseline tumor characteristics: m*KRAS*

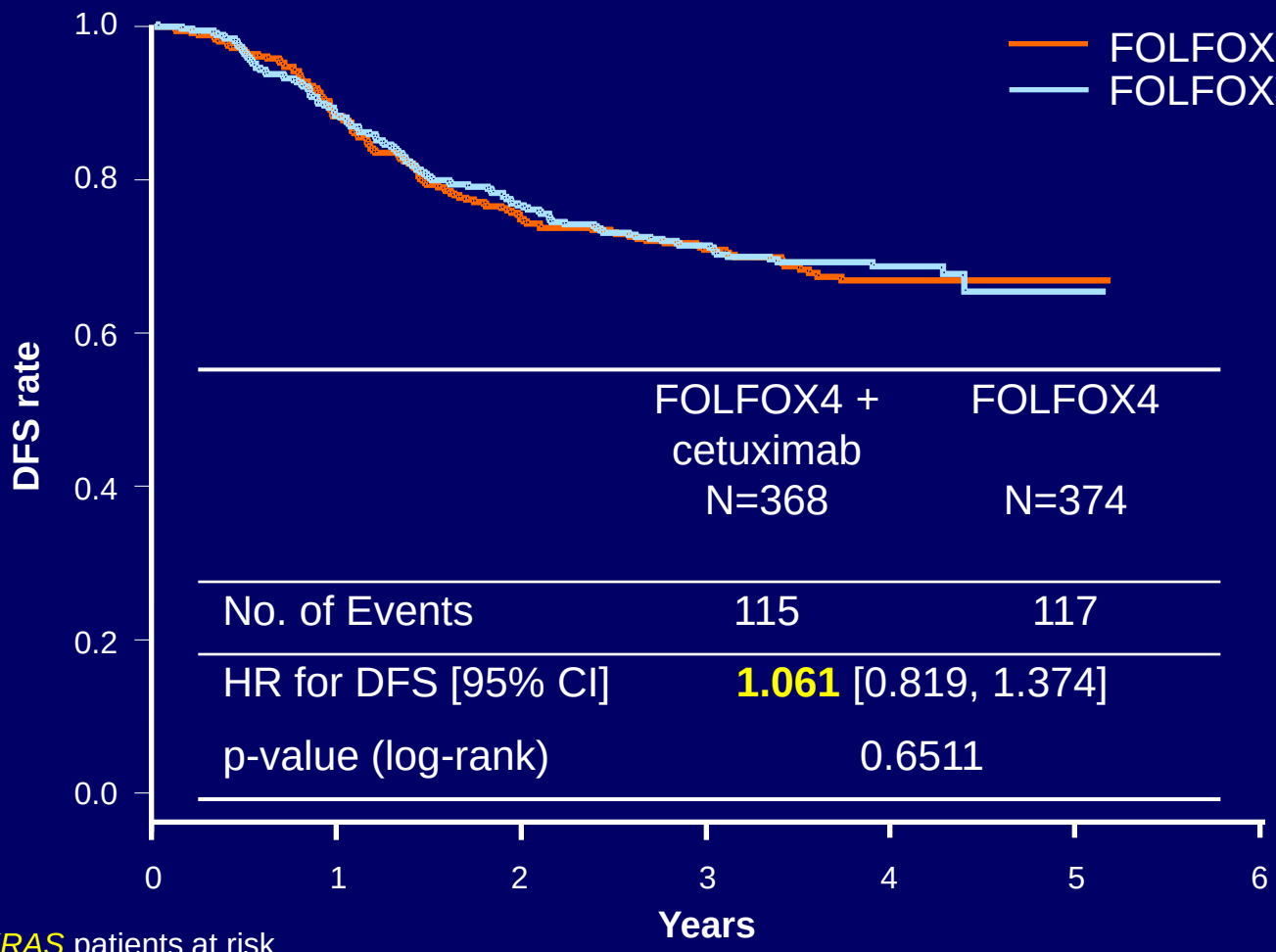
Tumor characteristics		FOLFOX4 + cetuximab N=368	FOLFOX4 N=374
Pathological staging:			
	pT4	**20.1%**	**25.1%**
	pN2	35.6%	36.1%
Bowel obstruction and/or perforation		17.7%	20.3%
Vascular or lymphatic invasion		50.5%	52.7%
Type of surgery:	Open	73.1%	74.6%
	Laparoscopic	26.9%	24.6%
	Other	0	0.8%
Tumor localization:	Left	54.3%	54.3%
	Right	43.2%	43.0%
	Both	2.4%	1.6%
Histopathology grade:	G1-2	82.9%	80.5%
	G3-4	16.0%	17.9%

Outcomes

for m*KRAS* patients

Median follow-up for DFS: 45.4 months

Disease-free survival (N=742)



Number of *mKRAS* patients at risk

FOLFOX4 + cetuximab	368	315	265	228	80	3	0
FOLFOX4	374	324	280	237	93	2	0

DFS: *KRAS* wt and m*KRAS*

***KRAS* populations**	***KRAS* wt**		m*KRAS*	
	FOLFOX4 + cetuximab N=791	**FOLFOX4 N=811**	**FOLFOX4 + cetuximab N=368**	**FOLFOX4 N=374**
No. of events	190	179	115	117
HR for DFS [95% CI]	**1.047** [0.853, 1.286]		**1.061** [0.819, 1.374]	
p-value (log-rank)	0.6562		0.6511	

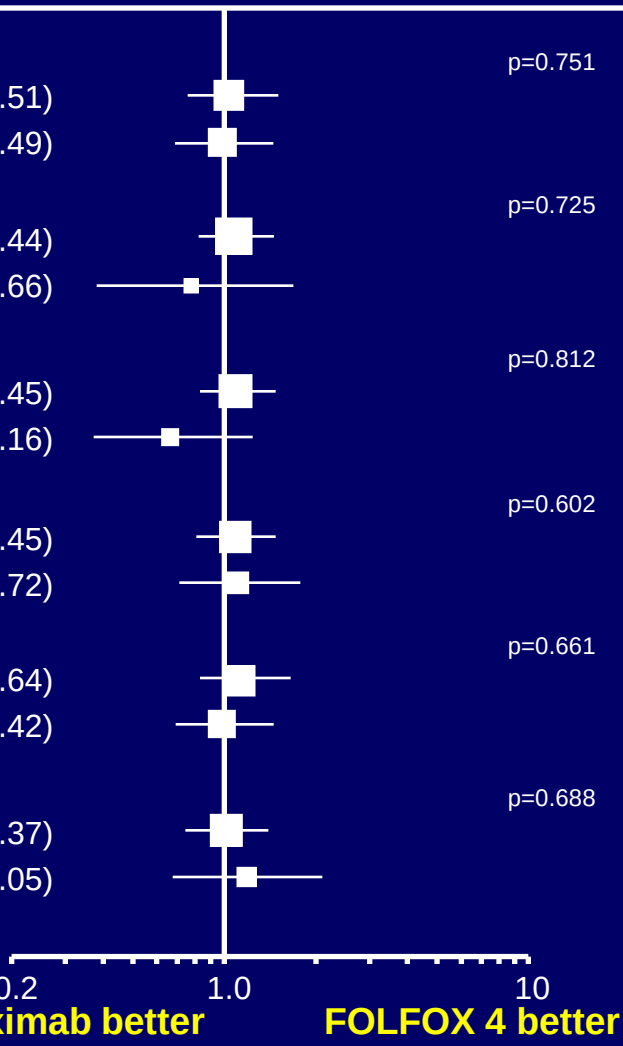
DFS time: m*KRAS* vs *KRAS* wt

	FOLFOX4 + cetuximab		FOLFOX4	
***KRAS* populations**	***KRAS* wt* N=791**	**m*KRAS*** N=368**	***KRAS* wt* N=811**	**m*KRAS*** N=374**
Number of events, (%)	190 (24.0)	115 (31.3)	179 (22.1)	117 (31.3)
DFS -Year 1 [95% CI], %	90.4 [88.1,92.2]	88.1 [84.3, 91.0]	92.0 [89.9, 93.7]	87.9 [84.1, 90.8]
DFS-Year 2 [95% CI], %	79.7 [76.6, 82.4]	74.4 [69.5, 78.6]	81.5 [78.6, 84.1]	76.2 [71.5, 80.2]
DFS-Year 3 [95% CI], %	**75.1 [71.7, 78.1]**	**70.7 [65.6, 75.1]**	**78.0 [74.8, 80.8]**	**71.0 [66.0, 75.3]**
DFS- Year 4 [95% CI], %	72.4 [68.6, 75.8]	66.7 [61.3, 71.5]	75.5 [71.9, 78.6]	68.5 [63.3, 73.0]

Median follow up time: * ~ 40 months, **45.4 months

Forest plot for DFS: m*KRAS*

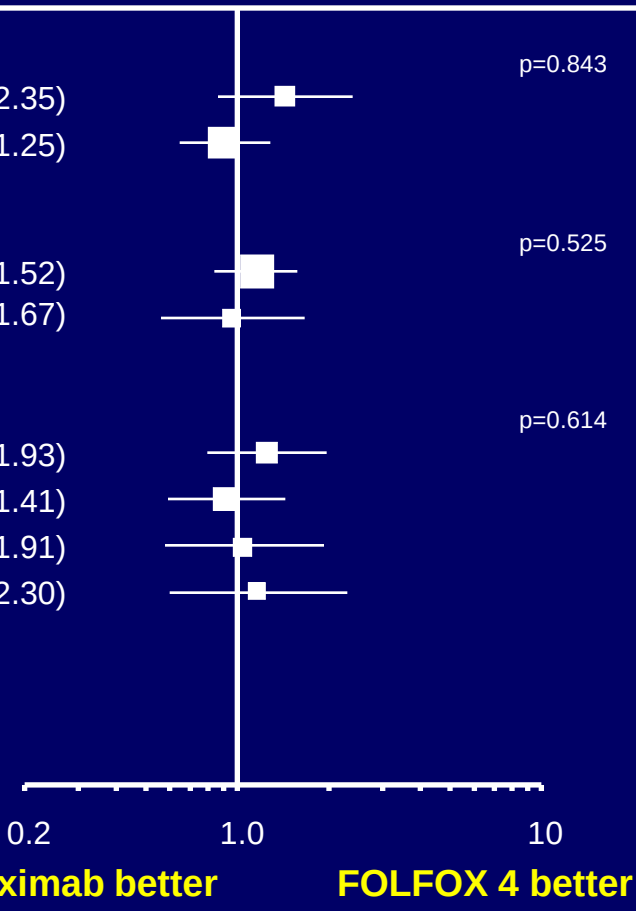
Strata	Control O/N	Treatment O/N	Adjusted HR* (CI)	Test of treatment effect	Test of heterogeneity
Sex				p=0.751	p=0.833
Male	62 / 196	68 / 208	1.06 (0.75, 1.51)		
Female	55 / 178	47 / 160	1.00 (0.68, 1.49)		
Age category				p=0.725	p=0.414
Age <= 70	100 / 327	102 / 324	1.09 (0.83, 1.44)		
Age > 70	17 / 47	13 / 44	0.78 (0.37, 1.66)		
WHO performance status				p=0.812	p=0.123
WHO PS = 0	87 / 298	88 / 292	1.08 (0.80, 1.45)		
WHO PS >= 1	27 / 61	21 / 62	0.63 (0.35, 1.16)		
Pathological staging pT				p=0.602	p=0.924
pT1-2-3	75 / 280	81 / 294	1.06 (0.78, 1.45)		
pT4	42 / 94	34 / 74	1.09 (0.69, 1.72)		
Pathological staging pN				p=0.661	p=0.540
pN1	59 / 239	62 / 237	1.14 (0.80, 1.64)		
pN2	58 / 135	53 / 131	0.97 (0.67, 1.42)		
Bowel obstr. or perfor.				p=0.688	p=0.641
None of both	92 / 294	88 / 294	1.02 (0.76, 1.37)		
Obstr. or perfor.	25 / 80	27 / 74	1.18 (0.68, 2.05)		



* Stratified HR for CT + cetuximab vs CT

Forest plot for DFS: m*KRAS*

Strata	Control O/N	Treatment O/N	Adjusted HR (CI)	Test of Treatment effect	Test of Heterogeneity
VELI				p=0.843	p=0.120
None of both	30 / 115	35 / 117	1.42 (0.86, 2.35)		
Invasion or Infiltration	72 / 197	60 / 186	0.88 (0.63, 1.25)		
Histopathological grading				p=0.525	p=0.598
Histopat: G1-2	86 / 301	91 / 305	1.13 (0.84, 1.52)		
Histopat: G3-4	28 / 67	23 / 59	0.95 (0.54, 1.67)		
Combinations of pT and pN				p=0.614	p=0.794
pT1-2-3 & pN1	35 / 182	44 / 193	1.24 (0.79, 1.93)		
pT1-2-3 & pN2	40 / 98	37 / 101	0.90 (0.58, 1.41)		
pT4 & pN1	24 / 57	18 / 44	1.04 (0.56, 1.91)		
pT4 & pN2	18 / 37	16 / 30	0.16 (0.59, 2.30)		



* Stratified HR for CT + cetuximab vs CT

Safety m*KRAS* : Grade 3-4 AEs (N=738)

MedDRA preferred terms/ composite categories	FOLFOX4 + cetuximab N=364	FOLFOX4 N=374
Neutropenia	39.6%	40.4%
Febrile neutropenia	**2.7%**	**0.8%**
Hypersensitivity reactions	3.3%	2.4%
Acne like rash	**29.1%**	**0.0%**
Nausea	2.7%	2.4%
Diarrhea	**15.1%**	**9.4%**
Asthenia	9.3%	4.5%
Neurotoxicity	15.7%	18.4%
Mucositis	**9.8%**	**0.8%**
On-treatment deaths	<1%	<1%
Pts with at least one Gr 3-4 AE	81.0%	68.4%

Treatment exposure and discontinuation

m*KRAS* populations	FOLFOX4 + cetuximab N=368	FOLFOX4 N=374
12 cycles of FOLFOX4, %	71.7	78.9
≥ 80% cetuximab, %	79.1	NA
Treatment discontinuation, %	28.3	20.3
Reason:		
-Toxicity	10.1	11.5
-Refusal	10.1	2.9
-Other	8.1	6.0

Conclusions (I)

- Outcome was the same for both treatment groups showing:
  - Neither a beneficial **NOR** a deleterious effect

    of FOLFOX4 + cetuximab in terms of DFS in m*KRAS* patients

Conclusions (II)

- Subgroup analysis within the m*KRAS* patients showed no differential effect of the addition of cetuximab on any of the subgroups analysed

- In this large trial m*KRAS* patients seemed to be associated with a poorer outcome than those with *KRAS* wt tumors suggesting a prognostic impact of *KRAS* mutation status in stage III colon cancer

Acknowledgments

- Special thanks to all of the participating patients
- Collaborative European effort
- Study team

Acknowledgments

- PETACC - Pr. Bernard Nordlinger and Pr. Eric Van Cutsem
- ABCSG - Austrian Breast and Colorectal cancer Study Group, Pr. Josef Thaler
- AIO - Arbeitsgemeinschaft Internistische Onkologie, Dr. Gunnar Folprecht
- BGDO - Belgian Group of Digestive Oncology, Pr. Jean-Luc Van Laethem
- Denmark - Pr. Lone Nørgård Petersen
- EORTC GI - Pr. Eric Van Cutsem
- GISCAD, GOCCI, GONO, GOIRC, GOIM, IOR - Italian groups, Pr. Enrico Mini
- GICD - Gruppo Portugues de Investigação doCancro Digestivo, Dr.Evaristo Sanches
- TTD - Grupo Esp para Tratamiento de los Tumores Digestivos, Pr. Josep Tabernero
- United Kingdom - Pr. John Bridgewater
- FFCD/France - Prs Philippe Rougier and Laurent Bedenne

Thanks to the top recruiting sites...

- Austria: 13 pts - site 704, **R. Greil**
  13 pts - site 713, **J. Thaler**
- Belgium: 19 pts - site 806, **G. D'Haens**
- Denmark: 12 pts - site 953, **M. Yilmaz**
- France: 38 pts - site 079, **M.A. Zawadi**
- Germany: 19 pts - site 331, **A. Matzdorff**
- Italy: 20 pts - site 547, **E. Maiello**
- Portugal: 12 pts - site 600, **E. Sanches**
- Spain: 38 pts - site 457, **R. Salazar**
- UK: 22 pts - site 900, **J. Bridgewater**

…and all other participating investigators!