Phase III clinical trial of FOLFOX with or without cetuximab in resected *KRAS* wild type stage III colon cancer:

The PETACC8 Cooperative Group Trial

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Disclosures

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

- Professor Julien Taïeb declares:
  - Consultancy/advisory role
    - Merck KGaA
  - Honoraria
    - Merck KGaA

Background: standard adjuvant therapy

- Combination of 5-FU, oxaliplatin, and LV has been the standard adjuvant therapy for resected stage III colon cancer since 2004 with the communication of:
  - MOSAIC FOLFOX4 versus LV5FU2[1,2]
- And confirmed by:
  - NSABP C-07 FLOX versus 5-FU/LV[3,4]

3-year disease-free survival (DFS): ~70%

[1]AndréT, et al., NEJM 2004; [2]André T, et al., JCO 2009;
[3]Kuebler JP, et al., JCO 2007; [4] Yothers G, et al., JCO 2001

Potential ‘added benefit’ of targeted therapy

- Limited ability of new chemotherapy drugs to improve outcomes
- Monoclonal antibodies against EGFR and VEGF demonstrate improved outcome in mCRC when combined with chemotherapy
- But failed to improve 3-year DFS in the adjuvant setting:
  - For anti VEGF in 2 trials (AVANT, NSABP-C08),[1,2]
  - For anti-EGFR in one (NCCTG N0147)[3]

[1]De Gramont A, et al., ASCO GI 2011; [2]Allegra C, et al., JCO 2011;
[3]Alberts SR, et al., JAMA 2012

Original 2-arm design for PETACC8

Fully resected stage III colon cancer (N = 2000)

R

FOLFOX4 (12 cycles)
- Oxaliplatin 85 mg/m^2
- LV 400 mg/m^2 & 5FU bolus 200 mg/m^2
- 5-FU 2,400 mg/m^2 over 46 hrs every 2 weeks

FOLFOX4 + cetuximab (12 cycles)
- FOLFOX4
- Cetuximab days 1,8
  - 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

Role of *KRAS* mutation analysis

- Ability to select patients based on *KRAS* mutation status established in early 2008
  - Mutated *KRAS* (*KRAS* mut) predicts for a lack of response to cetuximab[1,2]
  - Patients with wild type *KRAS* (*KRAS* wt) tumors maintain ability to respond to cetuximab [1,2]

- Protocol was amended mid 2008 for the primary objective to be determined in *KRAS* wt patients and the sample size increased

[1]Bokemeyer C, et al., Annals Oncol 2009; 2011;
[2]Van Cutsem E, et al., NEJM 2009; JCO 2011

KRAS mutation analysis

- *KRAS* analyses were possible for 92.3% of all randomized patients
- Centralized *KRAS* testing was performed in an approved lab at the Georges Pompidou European Hospital in Paris
  - An allelic discrimination technique was used
  - 99.3% of samples provided an interpretable result

Study objectives

- Primary
  - To assess disease free survival (DFS) according to treatment in patients with resected stage III *KRAS* wt tumors
  - DFS = until recurrence, 2nd CRC or death

- Secondary
  - Overall survival (OS)
  - Treatment compliance and toxicity

PETACC8 statistical analysis plan

- Planned accrual of 1,407 *KRAS* wt pts provides a 90% power to detect a hazard ratio (HR) of 0.75 with 2-sided α=0.05
- An interim analysis was planned after 65% of planned events
- Intent-to-treat analysis
- Planned subgroup analyses for main criteria

Main inclusion criteria

- Completely resected pathologically confirmed stage III colon adenocarcinoma regardless of EGFR status
- KRAS wt (after amendment mid 2008)
- ≥ 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

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

Study population at the interim analysis

- 2559 patients from 340 sites in Europe
  - 62.5% known to have *KRAS* wt tumors
- 1602 *KRAS* wt patients randomized to FOLFOX or FOLFOX + cetuximab
- Median follow-up for DFS:
  - FOLFOX 3.30 years
  - FOLFOX + cetuximab 3.33 years

Baseline characteristics

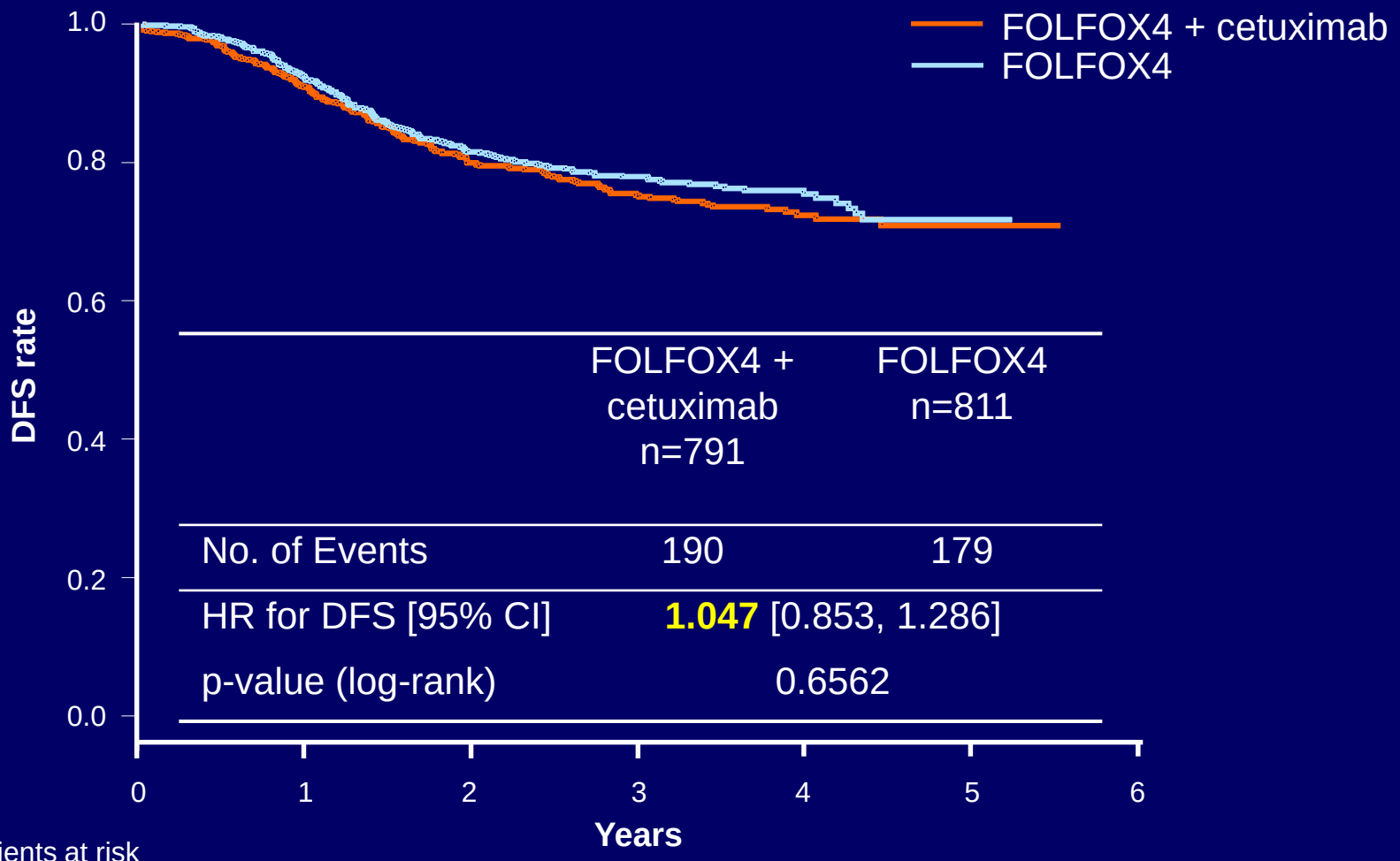
Patient characteristics	FOLFOX + cetuximab (N=791)	FOLFOX (N=811)
Male Female	59.2% 40.8%	57.7% 42.3%
Age, years: Mean (SD) Median (range)	 58.5 (9.91) 60.0 (19–75)	 58.9 (9.56) 60.0 (21–75)
Age ≤70 years	90.4%	91.0%
WHO performance status: 0 1 2	 78.5% 17.6% 0.1%	 78.5% 16.8% 0.2%

Baseline tumor characteristics

Tumor characteristics	FOLFOX + cetuximab (N=791)	FOLFOX (N=811)
pT4	20.4%	17.5%
pN2	38.6%	37.1%
Bowel obstruction and/or perforation	18.6%	18.0%
Vascular or Lymphatic invasion	58.5%	60.2%
Type of surgery: Open Laparoscopic Other	68.3% 31.7% 0	68.7% 31.1% 0.2%
Tumor Localization: Left Right Both	63.1% 36.2% 0.6%	63.7% 35.0% 0.5%
Histopathology grading: G1-2 G3-4	79.9% 18.7%	79.0% 19.7%

Outcomes of pre-planned interim analysis for *KRAS* wt patients

Disease-free survival (DFS)(N=1602)



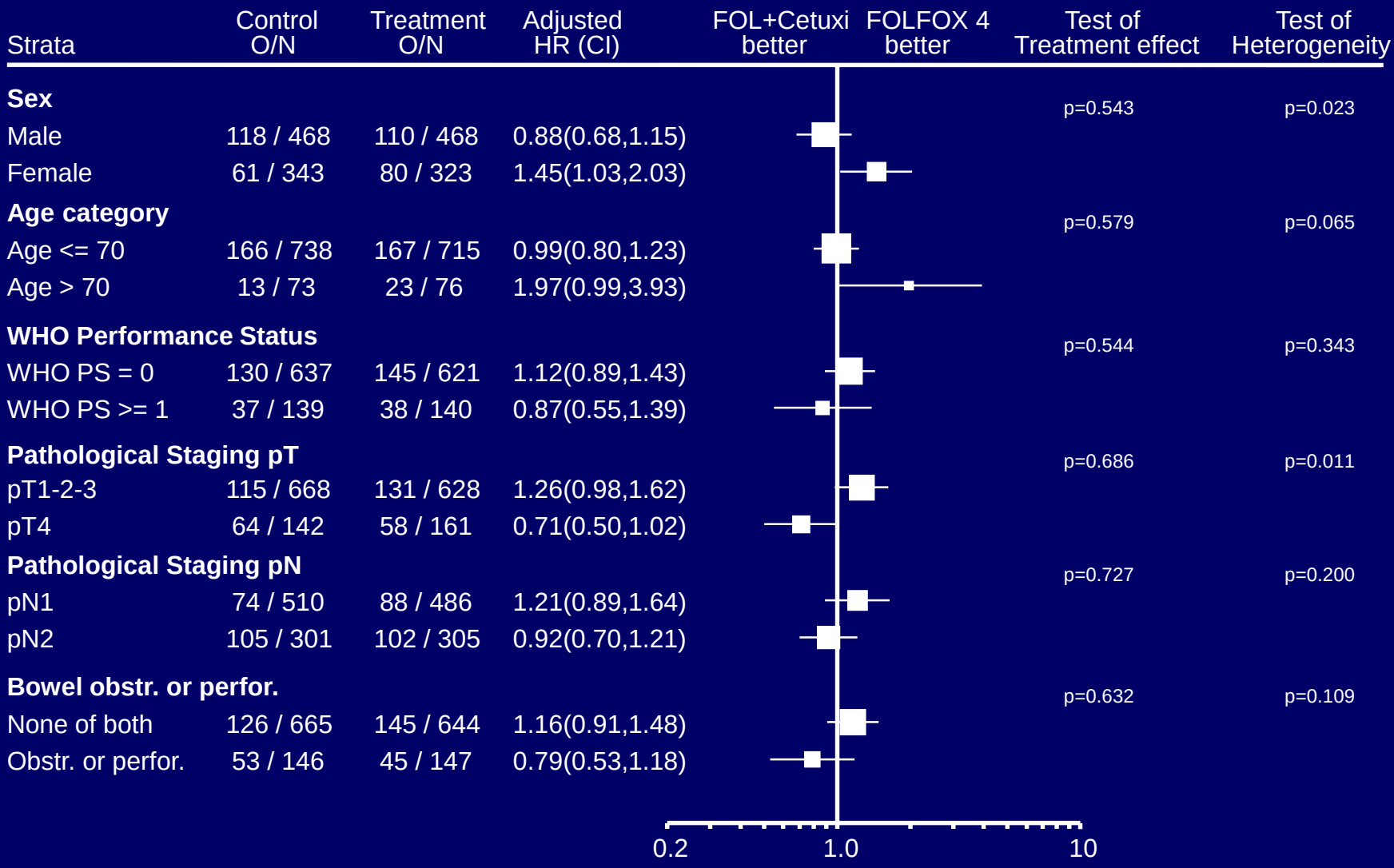
Number of patients at risk

FOLFOX4 + cetuximab	791	699	505	356	132	2	0
FOLFOX4	811	732	527	381	131	4	0

Efficacy – DFS time

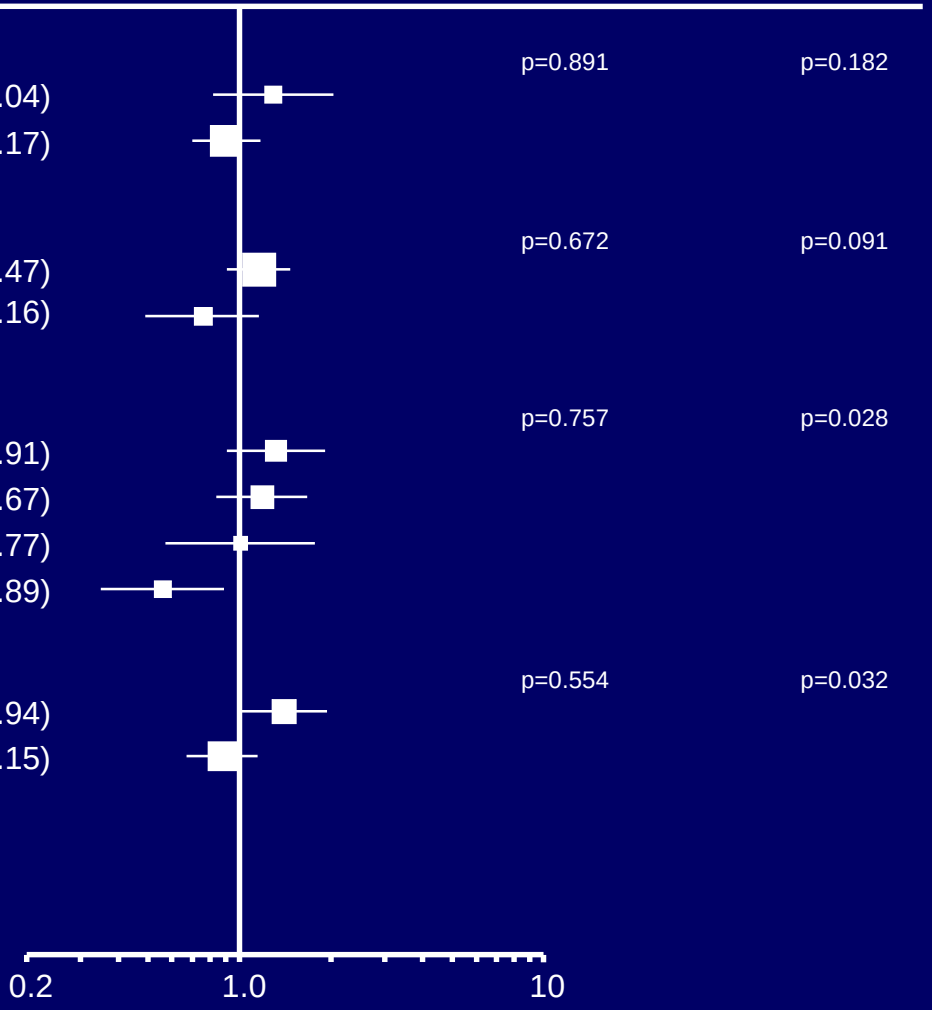
ITT *KRAS* wt population	**FOLFOX + cetuximab (N=791)**	**FOLFOX (N=811)**
Number of events, %	190 (24.0)	179 (22.1)
DFS -Year 1 [95% CI], %	90.4 [88.1-1.186]	92.0 [89.9-93.7]
DFS-Year2 [95% CI], %	79.7 [76.6-82.4]	81.5 [78.6-84.1]
DFS-Year 3 [95% CI], %	**75.1 [71.7-78.1]**	**78.0 [74.8-80.8]**
DFS- Year 4 [95% CI], %	72.4 [68.6-75.8]	75.5 [71.9-78.6]

Forest plot for DFS



Forest plot for DFS

Strata	Control O/N	Treatment O/N	Adjusted HR (CI)	Test of Treatment effect	Test of Heterogeneity
VELI				p=0.891	p=0.182
None of both	34 / 223	45 / 209	1.29(0.82,2.04)		
Invasion or Infiltration	125 / 488	115 / 463	0.90(0.70,1.17)		
Histopathological grading				p=0.672	p=0.091
Histopat: G1-2	128 / 641	148 / 632	1.16(0.91,1.47)		
Histopat: G3-4	48 / 160	39 / 148	0.76(0.49,1.16)		
Combinations of pT and pN				p=0.757	p=0.028
pT1-2-3 & pN1	51 / 435	62 / 403	1.32(0.91,1.91)		
pT1-2-3 & pN2	64 / 233	69 / 225	1.19(0.84,1.67)		
pT4 & pN1	23 / 75	26 / 82	1.01(0.57,1.77)		
pT4 & pN2	41 / 67	32 / 79	0.56(0.35,0.89)		
Tumor Localization				p=0.554	p=0.032
Right localization	66 / 284	85 / 286	1.40(1.01,1.94)		
Left localization	111 / 517	104 / 499	0.88(0.67,1.15)		



Scenarios for future observations

Scenarios for future observation	HR (interim analysis)	Conditional probability
HR=0.75 (optimistic one)	1.047	0.0078
HR=1.00	1.047	0.0007
HR=1.047 (realistic one)	1.047	0.0021

Safety *KRAS* wt: Grade 3-4 AEs

Defined as special AE (MedRA)	FOLFOX + cetuximab (N=785)	FOLFOX (N=805)
Neutropenia	35.8%	36.8%
Febrile neutropenia	2.8%	2.0%
Hypersensitivity reactions	3.9%	1.7%
Acne like rash	26.6%	0.5%
Nausea	1.7%	2.2%
Diarrhea	15.4%	9.1%
Neurotoxicity	16.2%	18.9%
Mucositis	8.0%	1.2%
On-treatment deaths	<1%	<1%
Pts with at least one Gr 3-4 AE	80.9%	66.2%

Treatment exposure and discontinuation

	FOLFOX + cetuximab (N=785)	FOLFOX (N=805)
≥10 cycles of FOLFOX, %	81.5	86.8
≥ 80% cetuximab, %	77.7	NA
Treatment discontinuation, %:	28.3	21.7
Reason:		
-Toxicity	12.1	11.8
-Refusal	7.8	4.1
-Other	8.4	5.8

Conclusions

- No benefit of adding cetuximab to patients with resected stage III *KRAS* wt colon cancer is observed in this interim analysis

- Probability for a positive result in the final analysis is <1% (futility analysis)

Potential explanations and next steps

- Decreased tolerability with cetuximab leading to differences in dose intensity
- Interaction with age, gender and tumor stage
- Cetuximab may have a different form of activity on micrometastatic disease compared to that observed in stage IV disease

Currently the focus of correlative studies and collaborative works with N0147 trial team

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