2012 GASCO Highlights
GI Oncology

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Conflict of interest disclosure

- **Advisory board member and lectures for:**
  - **Roche/Genentech**
  - **Sanofi-Aventis**
  - **Pfizer**
  - **Amgen**
  - **Bayer**
  - **Onyx**
  - **Genomic Health**

Role of maintenance therapy in CRC

- **OPTIMOX1-2 studies validated oxaliplatin stop-and-go strategy[1-2]**

- MACRO trial showed bevacizumab was not inferior to XELOX + bevacizumab as maintenance therapy after XELOX-BEV primary therapy[3]

1. **Tournigand C, et al. J Clin Oncol 2006;24:394–400**
2. **Chibaudel B, et al. J Clin Oncol 2009;27:5727–33**
3. **ASCO2010; Abstr 3501**

Bevacizumab with or without erlotinib as maintenance therapy, following induction first-line chemotherapy plus bevacizumab, in patients with metastatic colorectal cancer:

Efficacy and safety results of the international GERCOR DREAM phase III trial

C. Tournigand, B. Samson, W. Scheithauer, G. Lledo, F. Viret,
T. Andre, J.F. Ramée, N. Tubiana-Mathieu, J. Dauba, O. Dupuis,
Y. Rinaldi, M. Mabro, N. Aucoin, A. Khalil, J. Latreille, C. Louvet,
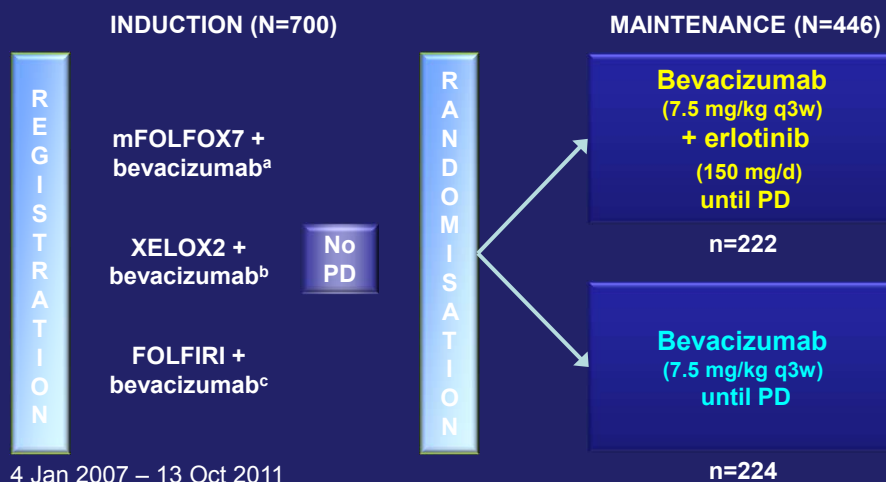D. Brusquant, F. Bonnetain, B. Chibaudel, A. de Gramont

Rationale

- **Crosstalk between EGFR pathway and VEGF is involved in tumour growth and survival**

- **Phase III studies in mCRC: combination of monoclonal antibodies targeting EGFR and VEGF provided no benefit[1,2]**

- **In colorectal cancer xenografts, combining TKIs targeting VEGFR and EGFR shows synergistic antitumor activity, even in KRAS mutant model[3]**

- **Combination of bevacizumab and erlotinib has been tested in preclinical models[4]**

1. Hecht JR, et al. J Clin Oncol 2009;27:672–80
2. Tol J, et al. N Engl J Med 2010;360:563–72
3. Poindessous V, et al. Clin Cancer Res 2011;17:6522–30
4. Naumov GN, et al. Clin Cancer Res 2009;15:3484–94

OPTIMOX3 – DREAM protocol

INDUCTION (N=700)

REGISTRATION

mFOLFOX7 + bevacizumab[a]

XELOX2 + bevacizumab[b]

No PD

FOLFIRI + bevacizumab[c]

RANDOMISATION

MAINTENANCE (N=446)

Bevacizumab
(7.5 mg/kg q3w)
+ erlotinib
(150 mg/d)
until PD

n=222

Bevacizumab
(7.5 mg/kg q3w)
until PD

n=224

4 Jan 2007 – 13 Oct 2011

[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 d1–8, bev 5 mg/kg d1 q2w, 6–12 cycles
[c]Irinotecan 180 mg/m² d1, 5-FU 2.4 mg/m² d1–2, FA 400 mg/m² d1, bev 5 mg/kg d1, q2w, 12 cycles

Inclusion 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**

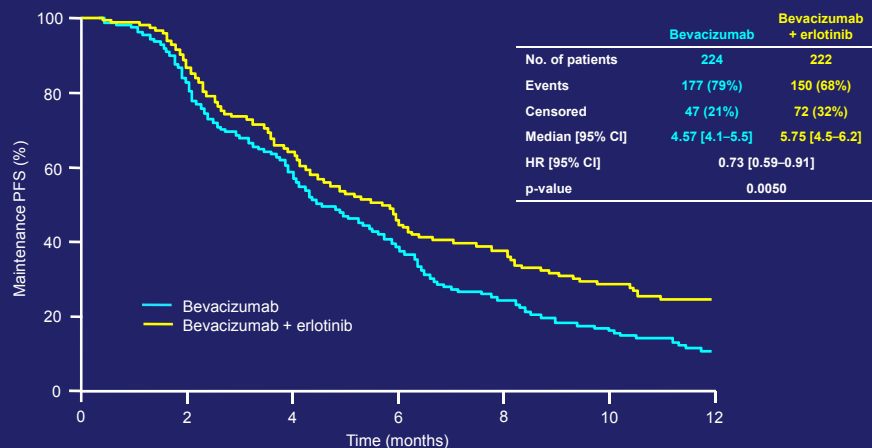- **Adjuvant chemotherapy >6 months before diagnosis of metastasis (2 years if oxaliplatin)**

Endpoints

- **Primary endpoint**
  - Progression-free survival (PFS) on maintenance therapy

- **Secondary endpoints**
  - Overall survival
  - Overall survival from maintenance
  - Duration without chemotherapy
  - Response rate (RECIST)
  - Survival according to KRAS mutational status

- **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
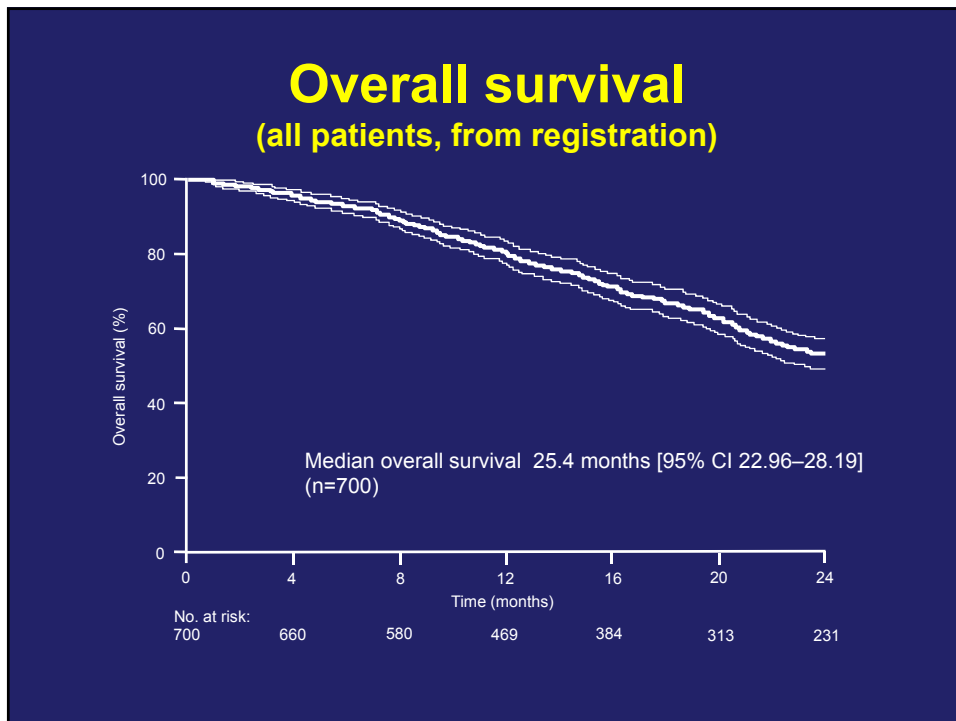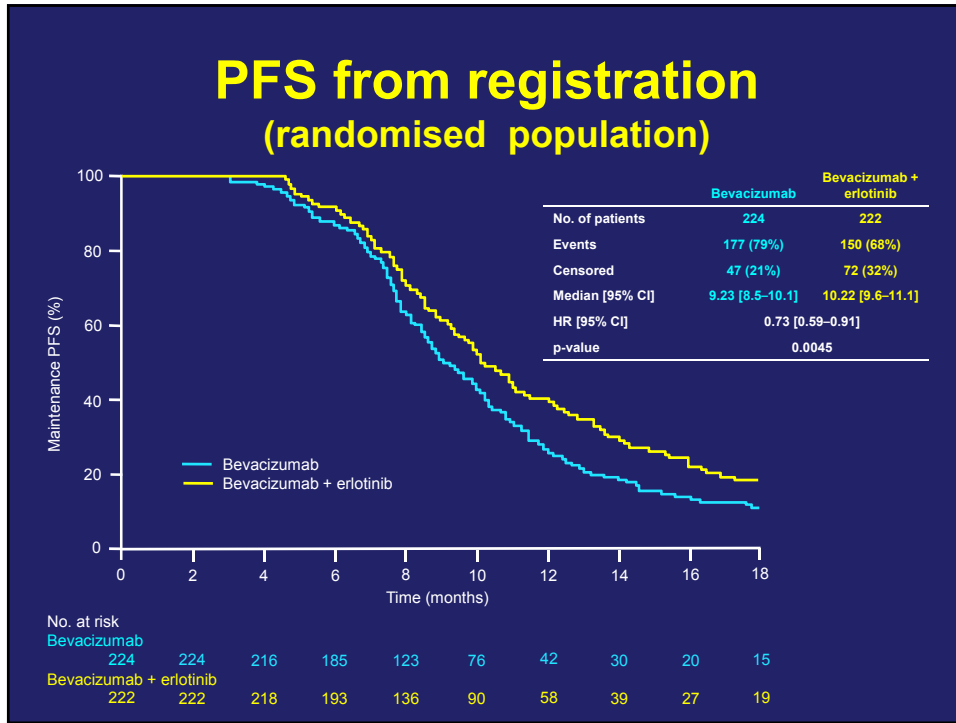   - 231 events required

Patient characteristics

Characteristic, % patients	Bevacizumab (N=224)	Bevacizumab + erlotinib (N=222)
Age, <70 / ≥70	73 / 27	74 / 26
Sex, male / female	56 / 44	66 / 34
Colon / rectum / both	73 / 25 / 2	74 / 23 / 3
Prior adjuvant chemotherapy	9	11
Metachronous / synchronous disease	17 / 83	18 / 82
PS, 0 / 1 / 2	60 / 37 / 4	60 / 36 / 4
Chemotherapy regimen		
FOLFOX-bev	59	59
XELOX-bev	30	30
FOLFIRI-bev	10	10
Platelet count, <400 / >400	71 / 29	74 / 26
LDH, N / >ULN	47 / 53	49 / 51
Alkaline phosphatase, N / >ULN	48 / 52	50 / 50
CEA, N / >ULN	15 / 81	15 / 83

Maintenance PFS
(from randomization)

	Bevacizumab	Bevacizumab + erlotinib
No. of patients	224	222
Events	177 (79%)	150 (68%)
Censored	47 (21%)	72 (32%)
Median [95% CI]	4.57 [4.1–5.5]	5.75 [4.5–6.2]
HR [95% CI]	0.73 [0.59–0.91]	
p-value	0.0050	

No. at risk:

Bevacizumab						
224	172	110	67	40	26	15
Bevacizumab + erlotinib						
222	176	116	73	53	37	28

PFS from registration
(randomised population)

	Bevacizumab	Bevacizumab + erlotinib
No. of patients	224	222
Events	177 (79%)	150 (68%)
Censored	47 (21%)	72 (32%)
Median [95% CI]	9.23 [8.5–10.1]	10.22 [9.6–11.1]
HR [95% CI]	0.73 [0.59–0.91]	
p-value	0.0045	

Overall survival
(all patients, from registration)

Median overall survival 25.4 months [95% CI 22.96–28.19] (n=700)

Toxicity (1)

Selected grade 3/4 AEs[a], %	Bevacizumab (n=219)	Bevacizumab + erlotinib (n=218)
Neutropenia	0	0
Anaemia	0.5	0.9
Thrombocytopenia	0	0.5
Febrile neutropenia	0	0
Nausea	0.5	0
Vomiting	0	1.4
Mucositis	0	0.5
Hand–foot syndrome	0.5	0
Venous thrombosis	0	0
Proteinuria	0.5	0.9
Hypertension	2.7	2.8

[a]NCI-CTC version 3.0

Toxicity (2)

Grade, %	Bevacizumab (n=219)				Bevacizumab + erlotinib (n=218)			
	1	2	3	4	1	2	3	4
Diarrhoea	11	1	1	0	29	20	9	0
Skin	8	0	0	0	28	37	19	1

Conclusions

- **The addition of erlotinib to bevacizumab following induction therapy with bevacizumab-based chemotherapy significantly increases maintenance PFS**

- **The combination of bevacizumab and erlotinib is well tolerated, but with a substantial increase in diarrhoea and skin toxicity**

- **These results suggest that erlotinib may be active in patients with mCRC and provide a clinical rationale for double inhibition of VEGF and EGFR**

- **Overall survival and KRAS analyses are ongoing**

Second line therapy: Where we were

- E3200 showed longer survival in the second line when BEV was added to FOLFOX in patients treated with 5FU/irinotecan and no BEV in first line[1]

- BRITE/ARIES registry demonstrated longer survival in patients receiving BEV beyond progression[2,3]

- Cetuximab added to irinotecan significantly improved PFS in patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine and oxaliplatin[4]

- Panitumumab lengthens progression free survival when added to FOLFIRI in second line therapy[5]

1. JCO 2007;25:1539
2. Grothey et al. J Clin Oncol 2008;26:5326–34
3. Cohn et al. J Clin Oncol 2010;28(15s):Abstr 3596
EPIC trial, JCO 2008;26:2311
5. ASCO2010; 3565

Bevacizumab (BEV) plus chemotherapy (CT)
continued beyond first progression in patients with
metastatic colorectal cancer (mCRC) previously
treated with BEV + CT: Results of a randomised phase
III intergroup study – TML (ML18147)

D Arnold[1], T Andre[2], J Bennouna[3], J Sastre[4], P Österlund[5], R Greil[6]
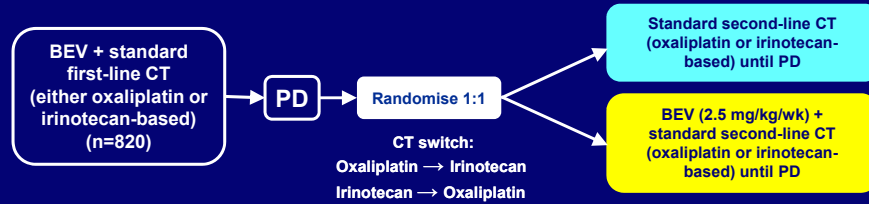E Van Cutsem[7], R von Moos[8], I Reyes-Rivera[9], B Bendahmane[10], S Kubicka[11]

on behalf of the AIO, GERCOR, FFCD, UNICANCER GI, TTD, BGDO, GEMCAD and AGMT groups

[1]Hamburg, Germany; [2]Paris, France; [3]Nantes, France; [4]Madrid, Spain
[5]Helsinki, Finland; [6]Salzburg, Austria; [7]Leuven, Belgium; [8]Chur, Switzerland [9]South
San Francisco, USA; [10]Basel, Switzerland; [11]Reutlingen, Germany

ML18147 study design (phase III)

BEV + standard first-line CT (either oxaliplatin or irinotecan-based) (n=820) → **PD** → **Randomise 1:1**

CT switch:
Oxaliplatin → Irinotecan
Irinotecan → Oxaliplatin

→ **Standard second-line CT (oxaliplatin or irinotecan-based) until PD**

→ **BEV (2.5 mg/kg/wk) + standard second-line CT (oxaliplatin or irinotecan-based) until PD**

Primary endpoint
- Overall survival (OS) from randomisation

Secondary endpoints included
- Progression-free survival (PFS)
- Best overall response rate
- Safety

Stratification factors
- First-line CT (oxaliplatin-based, irinotecan-based)
- First-line PFS (≤9 months, >9 months)
- Time from last BEV dose (≤42 days, >42 days)
- ECOG PS at baseline (0/1, 2)

Study conducted in 220 centres in Europe and Saudi Arabia

Main eligibility criteria

Inclusion

- **Patients ≥18 years with histologically confirmed diagnosis of mCRC**

- **Eastern Cooperative Oncology Group (ECOG) PS 0–2**

- **PD (≥1 measurable lesion according to RECIST v1 assessed by investigator, documented by CT or MRI), ≤4 weeks prior to start of study treatment**

- **Previously treated with BEV plus standard first-line CT, not candidates for primary metastasectomy**

Exclusion

- **Diagnosis of PD >3 months after last BEV administration**

- **First-line patients with PFS in first-line of <3 months**

- **Patients receiving <3 consecutive months of BEV in first-line**

Demographic and baseline characteristics: Randomised patients

Characteristic	CT (n=411)	BEV + CT (n=409)
Male, %	63	65
Age, median years	63	63
ECOG performance status, %		
0	43	44
1	52	51
2	5	5
First-line PFS, %		
≤9 months	56	54
>9 months	44	46
First-line CT, %		
Irinotecan-based	58	59
Oxaliplatin-based	42	41

Patients were accrued between February 2006 and June 2010

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Demographic and baseline characteristics: Randomised patients (cont'd)

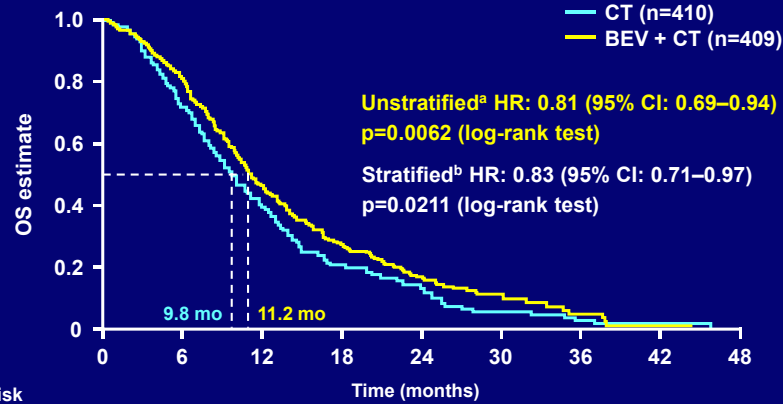| Characteristic	CT (n=411)	BEV + CT (n=409)
Duration from last BEV dose to randomisation, %		
≤42 days	77	77
>42 days	23	23
Patient population[a], %		
AIO	32	32
ML18147	68	68
Liver metastasis only, %		
No	71	73
Yes	29	27
No. of organs with metastasis, %		
1	39	36
>1	61	64

[a]Patient population refers to sequential enrolment of patients in original AIO study and subsequent enrolment in ML18147 when study was transferred to Roche

Second-line chemotherapy during study: Randomised patients

Second-line CT regimen, %	CT (n=407)	BEV + CT (n=407)
Irinotecan-based CT	**43**	**42**
FOLFIRI	14	16
LV5FU2 + CPT11 (Douillard regimen[1])	7	7
Capecitabine / irinotecan	12	12
Other regimens	10	7
Oxaliplatin-based CT	**57**	**58**
FOLFOX4 / mFOLFOX4	18	19
FOLFOX6	13	16
FUFOX	9	6
Capecitabine / oxaliplatin	11	14
Other regimens	6	4

1. Douillard et al. Lancet 2000;355:1041–7

OS: ITT population

CT (n=410)
BEV + CT (n=409)

Unstratified[a] HR: 0.81 (95% CI: 0.69–0.94)
p=0.0062 (log-rank test)

Stratified[b] HR: 0.83 (95% CI: 0.71–0.97)
p=0.0211 (log-rank test)

9.8 mo   11.2 mo

OS estimate

Time (months)

No. at risk								
CT	410	293	162	51	24	7	3	2	0
BEV + CT	409	328	188	64	29	13	4	1	0

Median follow-up: CT, 9.6 months (range 0–45.5); BEV + CT, 11.1 months (range 0.3–44.0)

[a]Primary analysis method; [b]Stratified by first-line CT (oxaliplatin-based, irinotecan-based), first-line PFS (≤9 months, >9 months), time from last dose of BEV (≤42 days, >42 days), ECOG performance status at baseline (0, ≥1)

Subsequent anti-cancer therapies: Safety population

Subsequent therapy, %	CT (n=409)	BEV + CT (n=401)
Patients who received ≥1 subsequent anti-cancer therapy	67.7	68.6
Subsequent anti-cancer therapies		
BEV	12.2	11.5
Anti-EGFR	41.3	39.2
Other	50.4	54.9

EGFR: epidermal growth factor receptor

Subgroup analysis of OS: ITT population

Category	Subgroup	n		HR	(95% CI)
All	All	819		0.81	(0.69–0.94)
Patient population[a]	AIO	260		0.86	(0.67–1.11)
	ML18147	559		0.78	(0.64–0.94)
Gender	Female	294		0.99	(0.77–1.28)
	Male	525		0.73	(0.60–0.88)
Age	<65 years	458		0.79	(0.65–0.98)
	≥65 years	361		0.83	(0.66–1.04)
ECOG performance status	0	357		0.74	(0.59–0.94)
	≥1	458		0.87	(0.71–1.06)
First-line PFS	≤9 months	449		0.89	(0.73–1.09)
	>9 months	369		0.73	(0.58–0.92)
First-line CT	Oxaliplatin-based	343		0.79	(0.62–1.00)
	Irinotecan-based	476		0.82	(0.67–1.00)
Time from last BEV	≤42 days	630		0.82	(0.69–0.97)
	>42 days	189		0.76	(0.55–1.06)
Liver metastasis only	No	592		0.81	(0.67–0.97)
	Yes	226		0.79	(0.59–1.05)
No. of organs with metastasis	1	307		0.83	(0.64–1.08)
	>1	511		0.77	(0.64–0.94)

HR   0   1   2

[a]Patient population refers to sequential enrolment of patients in original AIO and subsequent enrolment in ML18147 when study was transferred to Roche. All patients listed under AIO were included in primary analysis

PFS: ITT population

CT (n=410)
BEV + CT (n=409)

Unstratified[a] HR: 0.68 (95% CI: 0.59–0.78)
p<0.0001 (log-rank test)

Stratified[b] HR: 0.67 (95% CI: 0.58–0.78)
p<0.0001 (log-rank test)

4.1 mo   5.7 mo
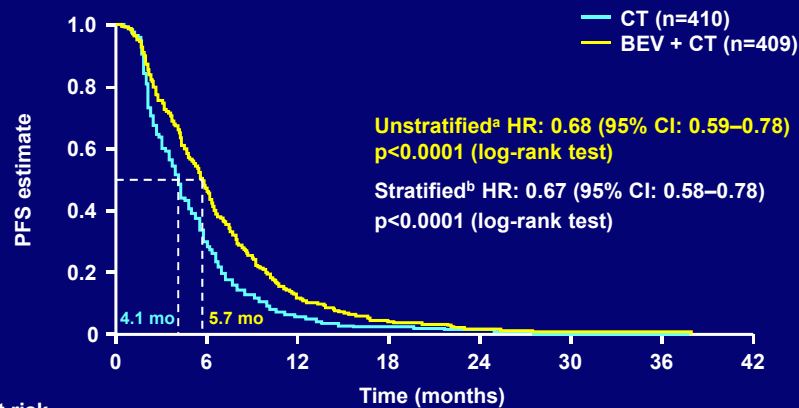
No. at risk								
CT	410	119	20	6	4	0	0	0
BEV + CT	409	189	45	12	5	2	2	0

[a]Primary analysis method; [b]Stratified by first-line CT (oxaliplatin-based, irinotecan-based), first-line PFS (≤9 months, >9 months), time from last dose of BEV (≤42 days, >42 days), ECOG performance status at baseline (0, ≥1)

Best overall response: Measurable disease population

Outcome	CT (n=406)	BEV + CT (n=404)
Responders[a], n (%)	16 (3.9)	22 (5.4)
p-value (unstratified)	0.3113	
p-value (stratified)	0.4315	
Complete response, n (%)	2 (<1)	1 (<1)
Partial response, n (%)	14 (3)	21 (5)
Stable disease, n (%)	204 (50)	253 (63)
Disease control rate, n (%)	220 (54)	275 (68)
p-value[b]	<0.0001	
PD, n (%)	142 (35)	87 (22)
Missing[c], n (%)	44 (11)	42 (10)

[a]Patients with a best overall response of confirmed complete or partial response
[b]This analysis was not prespecified
[c]Includes 'not-evaluable' or 'no tumour assessment' following baseline visit

Grade 3–5 adverse events (incidence ≥2%) in any arm: Safety population

Adverse event, %	CT (n=409)	BEV + CT (n=401)
Neutropenia	13	16
Leukopenia	3	4
Diarrhoea	8	10
Vomiting	3	4
Nausea	3	3
Abdominal pain	3	4
Subileus	<1	2
Asthenia	4	6
Fatigue	2	4
Mucosal inflammation	1	3
Dyspnoea	3	2
Pulmonary embolism	2	3
Polyneuropathy	2	3
Neuropathy peripheral	2	1
Hypokalaemia	2	2
Decreased appetite	2	1

Adverse events of special interest to BEV: Safety population

Patients, %	CT (n=409)		BEV + CT (n=401)	
	All grades	Grade 3–5	All grades	Grade 3–5
AEs of special interest to BEV	21	6	41	12
Hypertension	7	1	12	2
Proteinuria	1	–	5	<1
Bleeding/haemorrhage	9	<1	26	2
Abscesses and fistulae	–	–	1	<1
GI perforation	<1	<1	3	2
Congestive heart failure	<1	<1	<1	–
VTE	4	3	6	5
ATE	1	<1	<1	<1
Wound-healing complications	<1	<1	1	<1
RPLS	–	–	–	–

ATE: arterial thromboembolic events; GI: gastrointestinal; RPLS: reverse posterior leukoencephalopathy syndrome; VTE: venous thromboembolic events

Summary

- **BEV + standard second-line CT, crossed over from BEV + standard first-line CT, significantly prolongs OS and PFS**
  - OS
    - **Median: BEV + CT 11.2 months, CT 9.8 months**
    - **HR: 0.81 (95% CI: 0.69–0.94), p=0.0062[a]**
  - PFS
    - **Median: BEV + CT 5.7 months, CT 4.1 months**
    - **HR: 0.68 (95% CI: 0.59–0.78), p≤0.0001[a]**
- **Findings from subgroup analyses for OS generally consistent with overall population**
  - **Treatment effect according to gender appeared to be different; treatment-gender interaction test was not statistically significant**
- **Differences in best overall response rate not statistically significant; low response rate in both treatment groups**
- **AEs not increased when continuing BEV beyond PD; AE profile consistent with previous findings**

[a]Unstratified log-rank test

Effects of Prior Bevacizumab Use on Outcomes From the VELOUR Study: A Phase 3 Study of Aflibercept and FOLFIRI in Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Regimen
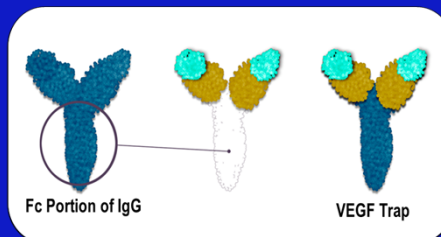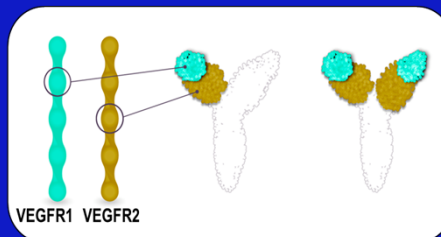
Carmen Allegra,*
Josep Tabernero, Radek Lakomy, Jana Prausova, Paul Ruff, Guy Van Hazel,
Vladimir M. Moiseyenko, David R. Ferry, Joe McKendrick, Eric Van Cutsem

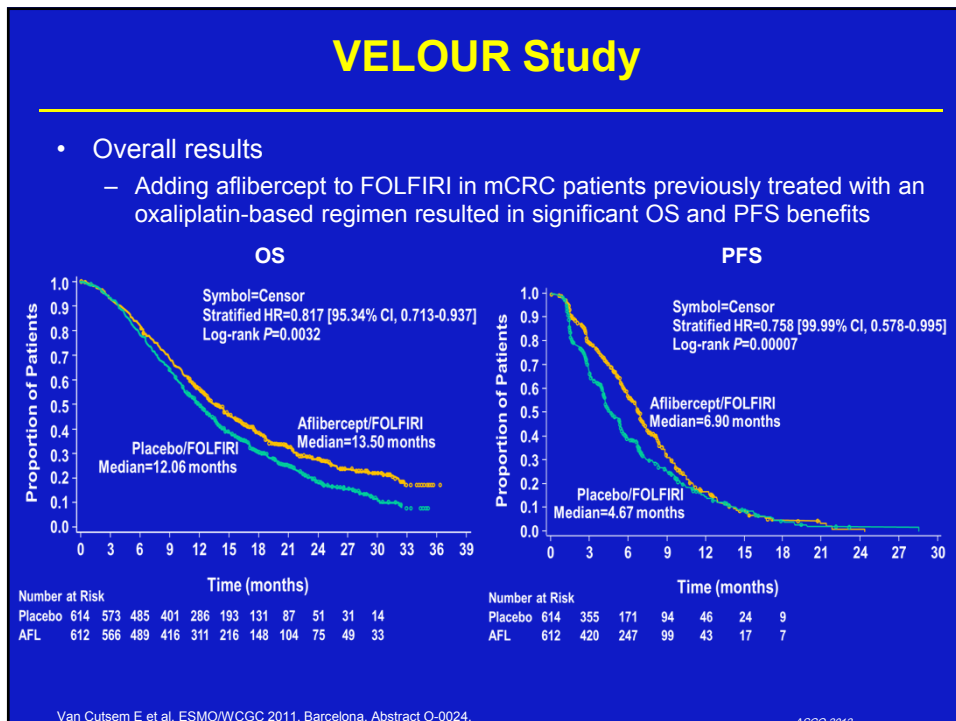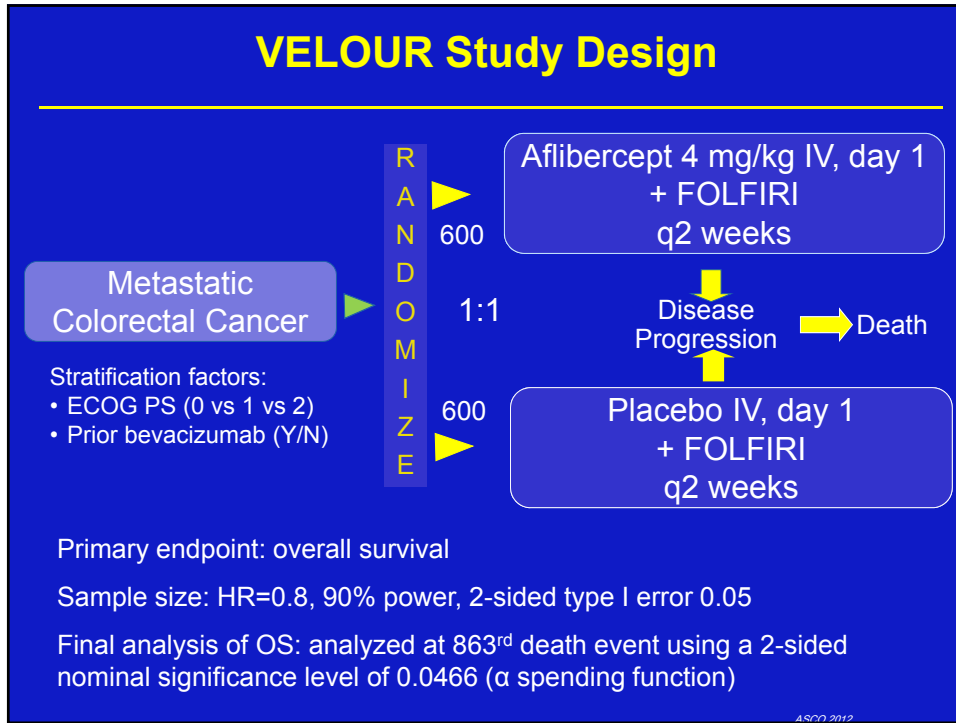*University of Florida, Gainesville, FL

ASCO 2012

Aflibercept

- Fusion protein of key domains from human VEGF receptors 1 and 2 with human IgG Fc[1]

- Blocks all human VEGF-A isoforms, VEGF-B, and placental growth factor (PlGF)[2]

- High affinity – binds VEGF-A more tightly than native receptors

1. Holash J et al. *Proc Natl Acad Sci USA.* 2002;99:11393-11398.
2. Tew WP et al. *Clin Cancer Res.* 2010;16:358-366.

ASCO 2012

VELOUR Study Design

Metastatic Colorectal Cancer

Stratification factors:
• ECOG PS (0 vs 1 vs 2)
• Prior bevacizumab (Y/N)

RANDOMIZE

1:1

600 → Aflibercept 4 mg/kg IV, day 1 + FOLFIRI q2 weeks

600 → Placebo IV, day 1 + FOLFIRI q2 weeks

Disease Progression → Death

Primary endpoint: overall survival

Sample size: HR=0.8, 90% power, 2-sided type I error 0.05

Final analysis of OS: analyzed at 863rd death event using a 2-sided nominal significance level of 0.0466 (α spending function)

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VELOUR Study

• Overall results
  – Adding aflibercept to FOLFIRI in mCRC patients previously treated with an oxaliplatin-based regimen resulted in significant OS and PFS benefits

OS

Proportion of Patients

Symbol=Censor
Stratified HR=0.817 [95.34% CI, 0.713-0.937]
Log-rank *P*=0.0032

Aflibercept/FOLFIRI
Median=13.50 months

Placebo/FOLFIRI
Median=12.06 months

Time (months)

Number at Risk
Placebo 614 573 485 401 286 193 131 87 51 31 14
AFL   612 566 489 416 311 216 148 104 75 49 33

PFS

Proportion of Patients

Symbol=Censor
Stratified HR=0.758 [99.99% CI, 0.578-0.995]
Log-rank *P*=0.00007

Aflibercept/FOLFIRI
Median=6.90 months

Placebo/FOLFIRI
Median=4.67 months

Time (months)

Number at Risk
Placebo 614 355 171 94 46 24 9
AFL   612 420 247 99 43 17 7

Van Cutsem E et al. ESMO/WCGC 2011, Barcelona, Abstract O-0024.

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Introduction

- The pivotal Phase 3 trial of 2L bevacizumab plus FOLFOX4 for previously treated mCRC showed a significant survival benefit compared with FOLFOX4 alone[1]
  - Median OS: 12.9 vs 10.8 months, HR=0.75, *P*=0.0011
  - Median PFS: 7.3 vs 4.7 months, HR=0.61, *P*<0.0001
- The goal of the current analysis is to assess consistency of the effect of aflibercept on OS and PFS by prior bevacizumab use in a pre-specified analysis

1. Giantonio BJ et al. *J Clin Oncol.* 2007;25:1539-1544.

ASCO 2012

Patient Demographics: Prior Bevacizumab

Parameter	Prior Bevacizumab		No Prior Bevacizumab	
	Placebo/ FOLFIRI (n=187)	Aflibercept/ FOLFIRI (n=186)	Placebo/ FOLFIRI (n=427)	Aflibercept/ FOLFIRI (n=426)
ECOG PS, %				
0	57	58	57	57
1	40	40	41	41
Male, %	56	59	58	60
Age, y, median (range)	60 (27-86)	59 (32-81)	61 (19-84)	61 (21-82)
Region, %				
Europe	56	54	58	63
North America	28	26	5	3
Other countries	16	19	37	34
>1 metastatic organ, %	54	57	56	59
Duration of bevacizumab use, months, median (range)	6 (0-28)	6 (0-29)	–	–
Antiangiogenic-free period, months, median (range)	2 (1-21)	2 (1-33)	–	–

ASCO 2012

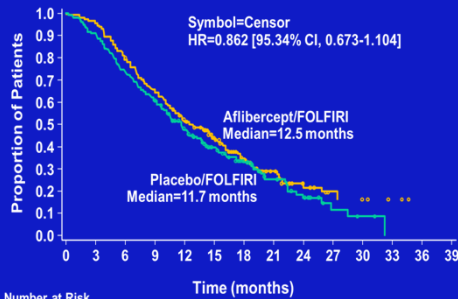## Consistency of OS and PFS With and Without Prior Bevacizumab

	Prior Bevacizumab			No Prior Bevacizumab		
	Placebo/ FOLFIRI (n=187)	Aflibercept/ FOLFIRI (n=186)	Δ	Placebo/ FOLFIRI (n=427)	Aflibercept/ FOLFIRI (n=426)	Δ
OS (months) (95.34% CI)	11.7 (9.8-13.8)	12.5 (10.8-15.5)	0.8	12.4 (11.2-13.5)	13.9 (12.7-15.6)	1.5
PFS (months) (99.99% CI)	3.9 (2.9-5.4)	6.7 (4.8-8.7)	2.8	5.4 (4.2-6.7)	6.9 (5.8-8.2)	1.5

- Interaction between "treatment arm" and "prior bevacizumab" factor was not significant at the 2-sided 10% level (P=0.57 for OS; P=0.2 for PFS)

ASCO 2012　37

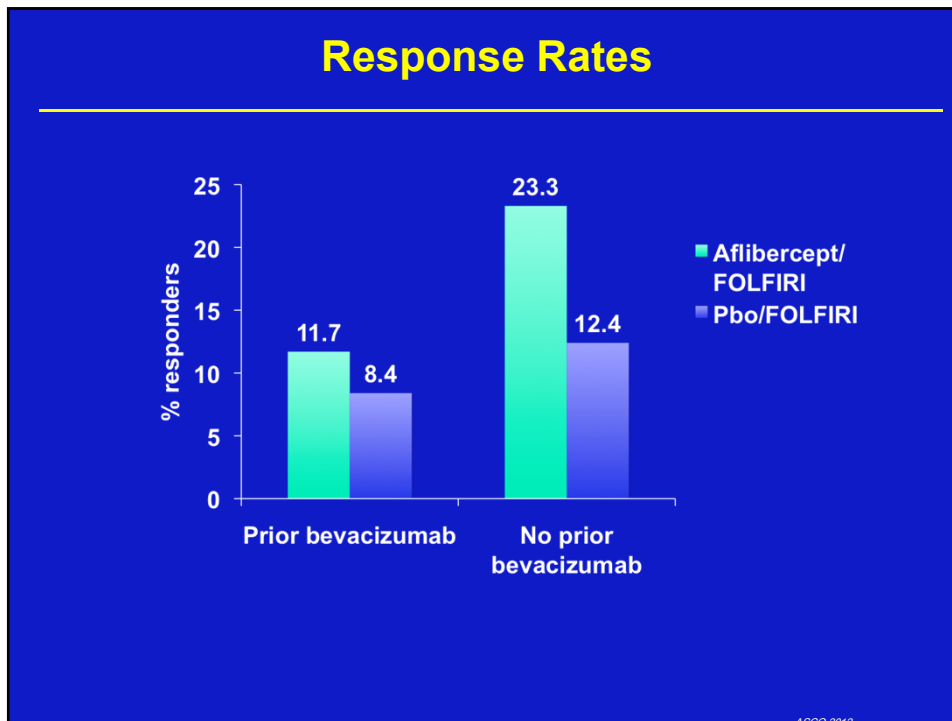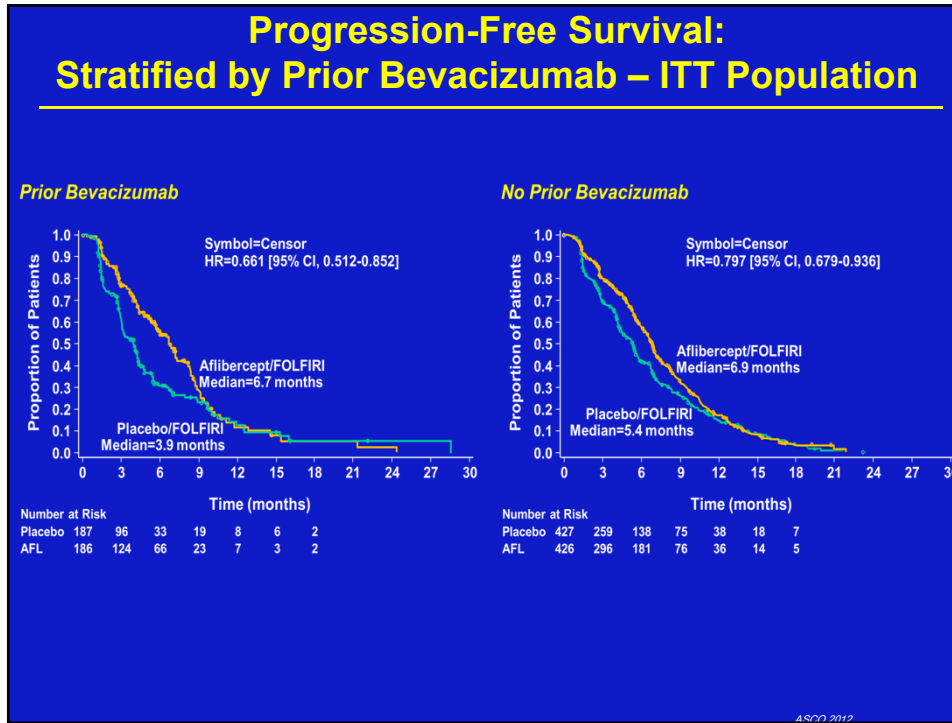## Overall Survival: Stratified by Prior Bevacizumab – ITT Population

Prior Bevacizumab

Symbol=Censor
HR=0.862 [95.34% CI, 0.673-1.104]

Aflibercept/FOLFIRI
Median=12.5 months

Placebo/FOLFIRI
Median=11.7 months

Time (months)

Number at Risk
Placebo 187 170 138 115 81 54 37 22 13
AFL   186 178 150 121 89 59 36 22 13

No Prior Bevacizumab

Symbol=Censor
HR=0.788 [95.34% CI, 0.699-0.927]

Aflibercept/FOLFIRI
Median=13.9 months

Placebo/FOLFIRI
Median=12.4 months

Time (months)

Number at Risk
Placebo 427 403 347 286 205 139 94 65 38
AFL   426 388 348 295 222 157 112 82 62

ASCO 2012

**Progression-Free Survival:
Stratified by Prior Bevacizumab – ITT Population**

Response Rates

Safety:
Anti-VEGF Associated Events

Safety Population % of Patients	Prior Bevacizumab		No Prior Bevacizumab	
	Placebo/ FOLFIRI (n=172)	Aflibercept/ FOLFIRI (n=171)	Placebo/ FOLFIRI (n=433)	Aflibercept/ FOLFIRI (n=440)
Grouped Term, PT	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Proteinuria	0.6	9.4	1.4	7.3
Hypertension	0.6	16.4	1.8	20.5
Hemorrhage	1.2	3.5	1.8	2.7
GI origin	0.6	3.5	1.2	1.4
Headache (PT)	0	0.6	0.5	2.0
Venous thromboembolic event	5.8	7.0	6.5	8.2
Pulmonary embolism	2.9	2.3	3.7	5.5
Arterial thromboembolic event	0.6	1.8	0.5	1.8
GI perforation	0	0	0.5	0.7

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Safety:
Adverse Events

Safety Population, % of Patients	Prior Bevacizumab		No Prior Bevacizumab	
	Placebo/ FOLFIRI (n=172)	Aflibercept/ FOLFIRI (n=171)	Placebo/ FOLFIRI (n=433)	Aflibercept/ FOLFIRI (n=440)
Serious AEs	32	52	33	47
Any AE leading to death	6	6	4	6
Grade 3/4 AEs in >10% of patients in any treatment group				
Neutropenia	13	20	25	27
Diarrhea	9	19	7	20
Asthenic conditions	9	16	11	17
Infections and infestations	8	14	7	12
Stomatitis	4	11	5	14

ASCO 2012

Conclusions

- This preplanned subgroup analysis demonstrates consistent trends of increased OS and PFS with aflibercept regardless of prior treatment with bevacizumab

- Prior treatment with bevacizumab does not appear to impact the safety profile of aflibercept

- Although analysis of a pre-specified subgroup, this study was not powered to show a treatment difference between arms, therefore no definitive conclusions may be drawn concerning the benefit of aflibercept in the prior bevacizumab-treated subgroup

ASCO 2012

Refractory Metastatic CRC: a major problem

- Need for new therapies after failure of fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab

- No standard salvage therapy available, although many patients retain good performance status[1]

1. NCCN Guidelines. Colon cancer. v.2.2012.

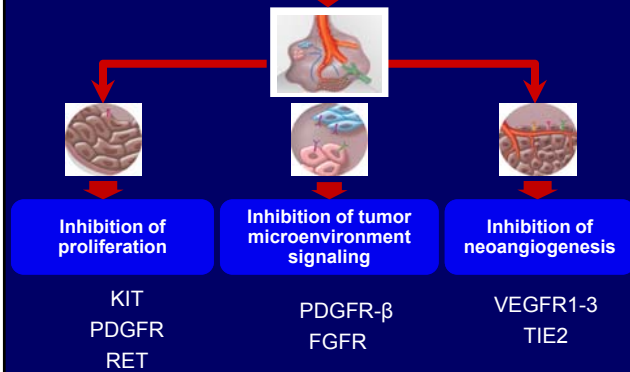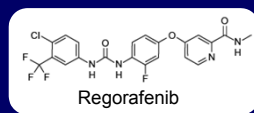## Phase III CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC)

Eric Van Cutsem, MD, PhD
University Hospitals Gasthuisberg/Leuven,
Leuven, Belgium

On behalf of:

Alberto Sobrero, Salvatore Siena, Alfredo Falcone, Marc Ychou, Yves Humblet,
Olivier Bouché, Laurent Mineur, Carlo Barone, Antoine Adenis,
Josep Tabernero, Takayuki Yoshino, Heinz-Josef Lenz, Richard Goldberg,
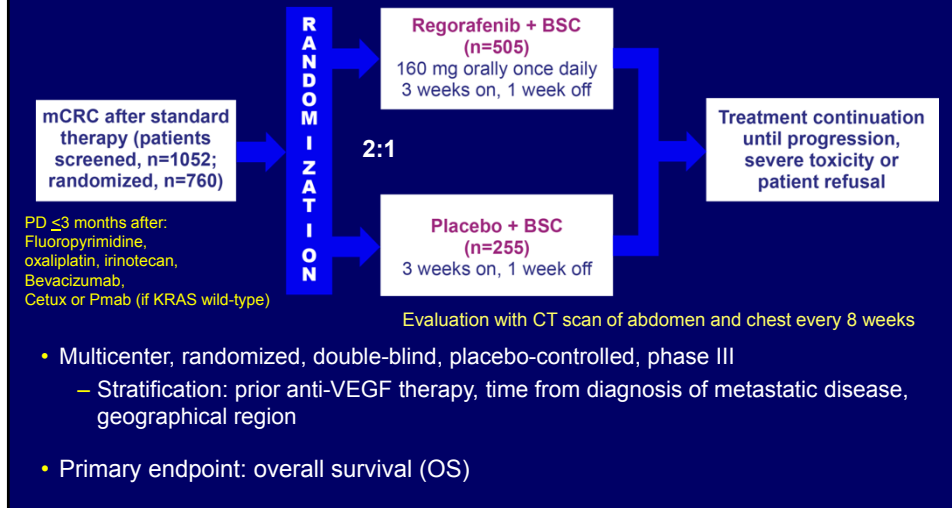Daniel J. Sargent, Frank Cihon, Andrea Wagner, Dirk Laurent, Axel Grothey

Regorafenib (BAY 73-4506), an oral multikinase inhibitor targeting multiple tumor pathways[1-3]

Regorafenib

Inhibition of proliferation
KIT
PDGFR
RET

Inhibition of tumor microenvironment signaling
PDGFR-β
FGFR

Inhibition of neoangiogenesis
VEGFR1-3
TIE2

Biochemical activity	Regorafenib IC$_{50}$ mean ± SD nmol/l (n)	
VEGFR1	13 ± 0.4	(2)
Murine VEGFR2	4.2 ± 1.6	(10)
Murine VEGFR3	46 ± 10	(4)
TIE2	311 ± 46	(4)
PDGFR-β	22 ± 3	(2)
FGFR1	202 ± 18	(6)
KIT	7 ± 2	(4)
RET	1.5 ± 0.7	(2)
RAF-1	2.5 ± 0.6	(4)
B-RAF	28 ± 10	(6)
B-RAF^{V600E}	19 ± 6	(6)

1. Wilhelm SM *et al. Int J Cancer* 2011.
2. Mross K *et al. Clin Cancer Research* 2012.
3. Strumberg D *et al. Expert Opin Invest Drugs* 2012.

CORRECT: Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy

mCRC after standard therapy (patients screened, n=1052; randomized, n=760)

PD ≤3 months after:
Fluoropyrimidine,
oxaliplatin, irinotecan,
Bevacizumab,
Cetux or Pmab (if KRAS wild-type)

RANDOMIZATION 2:1

Regorafenib + BSC (n=505)
160 mg orally once daily
3 weeks on, 1 week off

Placebo + BSC (n=255)
3 weeks on, 1 week off

Treatment continuation until progression, severe toxicity or patient refusal

Evaluation with CT scan of abdomen and chest every 8 weeks

- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: prior anti-VEGF therapy, time from diagnosis of metastatic disease, geographical region

- Primary endpoint: overall survival (OS)

Baseline disease characteristics

		Regorafenib N=505	Placebo N=255
Primary site of disease, %	Colon	64.0	67.5
	Rectum	29.9	27.1
	Colon and rectum	5.9	5.5
KRAS mutation, %*	No	40.6	36.9
	Yes	54.1	61.6
	Unknown	5.3	1.6
Histology, %	Adenocarcinoma	98.0	97.3
	Other (adenosquamous or unspecified carcinoma)	2.0	2.8
Number of prior lines of therapy for metastatic disease, %	1-2	26.7	24.7
	3	24.8	28.2
	≥4	48.5	47.1
Prior bevacizumab, %		100	100

*KRAS status based on historical patient record
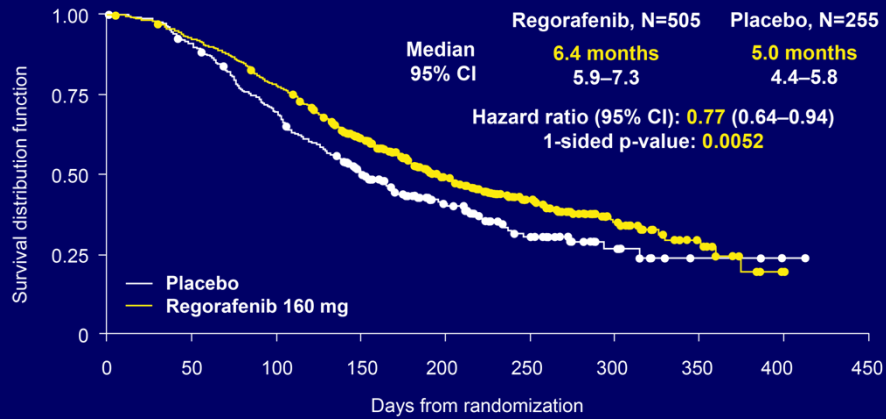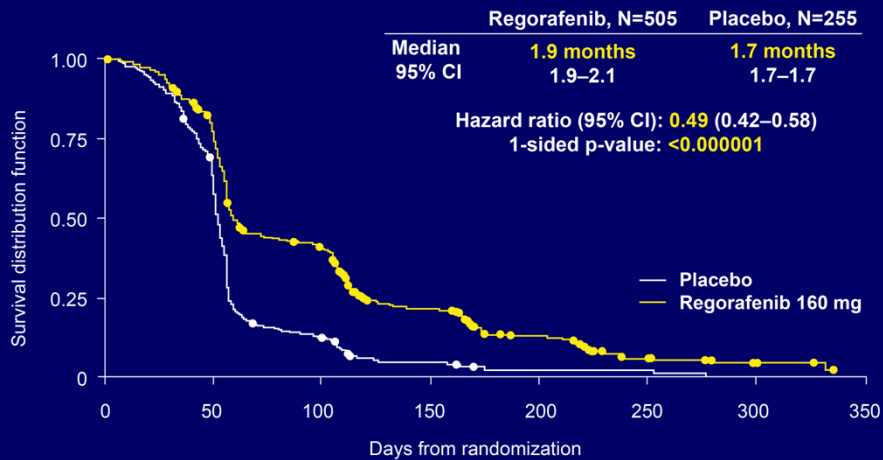
Overall response and disease control rates (secondary endpoints)

Regorafenib significantly improves DCR compared to placebo

Best response, %	Regorafenib N=505	Placebo N=255
Complete response	0	0
PR	1.0	0.4
SD	42.8	14.5
Progressive disease	49.5	80.0
DCR*	**41.0**	**14.9**

*DCR = PR + SD (≥6 weeks after randomization); p<0.000001

Subgroup analysis of overall survival

Regorafenib benefit *vs* placebo is achieved across subgroups

		N		HR (95% CI)
All patients		760		0.774 (0.636, 0.942)
Sex	Male	464		0.773 (0.599, 0.998)
	Female	296		0.751 (0.552, 1.022)
Age	<65 years	475		0.716 (0.561, 0.914)
	≥65 years	285		0.856 (0.614, 1.193)
Region	NA, WE, IS, AU	632		0.768 (0.622, 0.948)
	Asia	104		0.790 (0.429, 1.456)
	EE	24		0.694 (0.195, 2.466)
Baseline ECOG	0	411		0.702 (0.530, 0.929)
	1	349		0.773 (0.586, 1.020)
Primary site of disease	Colon	495		0.703 (0.557, 0.887)
	Rectum	220		0.953 (0.633, 1.436)
	Colon and rectum	44		1.091 (0.441, 2.697)

NA (North America), WE (Western Europe), IS (Israel), AU (Australia), EE (Eastern Europe)

0.0 0.5 1.0 1.5 2.0 2.5 3.0

← Favors regorafenib   Favors placebo →

Subgroup analysis of overall survival

Regorafenib benefit *vs* placebo is achieved across subgroups

		N		HR (95% CI)
All patients		760		0.774 (0.636, 0.942)
Time from first diagnosis of metastatic disease to randomization	<18 months	140		0.816 (0.532, 1.251)
	≥18 months	620		0.760 (0.609, 0.948)
Prior anticancer treatment	F, Ox, Iri, Bev	375		0.825 (0.625, 1.089)
	F, Ox, Iri, Bev, anti-EGFR	385		0.710 (0.538, 0.938)
Prior treatment lines for metastatic disease	≤3	301		0.709 (0521, 0.967)
	>3	459		0.804 (0.624, 1.038)
KRAS mutation status (historical)	N	299		0.653 (0.476, 0.895)
	Y	430		0.867 (0.670, 1.123)

F (fluoropyrimidine), Ox (oxaliplatin), Iri (irinotecan), Bev (bevacizumab)

0.0 0.5 1.0 1.5 2.0 2.5 3.0

← Favors regorafenib   Favors placebo

Subgroup analysis of PFS

Regorafenib benefit *vs* placebo is achieved across subgroups

Subgroup	N	Hazard ratio (regorafenib/placebo)	
		Estimate	95% CI
All patients	760	0.494	0.419-0.582
Age			
< 65 years	475	0.418	0.340-0.514
≥ 65 years	285	0.651	0.496-0.855
Region			
NA, WE, IS, AU	632	0.500	0.418-0.599
Asia	104	0.433	0.277-0.679
Eastern Europe	24	0.576	0.199-1.664
Primary site of disease			
Colon	495	0.550	0.450-0.671
Rectum	220	0.454	0.332-0.620
Colon and rectum	44	0.348	0.163-0.745
Prior line of Tx			
≤ 3	301	0.523	0.404-0.676
>3	459	0.478	0.387-0.592
KRAS mutation			
N	299	0.475	0.362-0.623
Y	430	0.525	0.425-0.649

NA (North America), WE (Western Europe), IS (Israel), AU (Australia)

KRAS subgroup analysis

		Regorafenib N=505	Placebo N=255	HR (95% CI)
KRAS mutation, %	No	40.6	36.9	NA
	Yes	54.1	61.6	NA
Median OS, months	KRAS wild-type	7.3	5.0	0.653 (0.476-0.895)
	KRAS mutant	6.2	5.1	0.867 (0.670-1.123)
Median PFS, months	KRAS wild-type	2.0	1.8	0.475 (0.362-0.623)
	KRAS mutant	1.9	1.7	0.525 (0.425-0.649)

- Regorafenib shows OS and PFS benefit in both KRAS-wild-type and KRAS-mutant subgroups

- KRAS mutational status was not prognostic nor predictive in the study population

Drug-related treatment-emergent adverse events occurring in ≥10% of patients

Adverse event, %	Regorafenib N=500				Placebo N=253			
	All grades	Grade 3	Grade 4	Grade 5*	All grades	Grade 3	Grade 4	Grade 5*
Hand-foot skin reaction	46.6	16.6	0	0	7.5	0.4	0	0
Fatigue	47.4	9.2	0.4	0	28.1	4.7	0.4	0
Hypertension	27.8	7.2	0	0	5.9	0.8	0	0
Diarrhea	33.8	7.0	0.2	0	8.3	0.8	0	0
Rash / desquamation	26.0	5.8	0	0	4.0	0	0	0
Anorexia	30.4	3.2	0	0	15.4	2.8	0	0
Mucositis, oral	27.2	3.0	0	0	3.6	0	0	0
Thrombocytopenia	12.6	2.6	0.2	0	2.0	0.4	0	0
Fever	10.4	0.8	0	0	2.8	0	0	0
Nausea	14.4	0.4	0	0	11.1	0	0	0
Bleeding	11.4	0.4	0	0.4	2.8	0	0	0
Voice changes	29.4	0.2	0	0	5.5	0	0	0
Weight loss	13.8	0	0	0	2.4	0	0	0

* Grade 5 drug-related AEs: 1.0% in regorafenib arm vs 0% in placebo arm

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Health-related QoL analyses:
time-adjusted area under the curve

No significant difference in health-related QoL with regorafenib *vs* placebo

	Treatment group	Least-squares mean	(95% CI)
EORTC QLQ-C30	Placebo	58.13	(55.72, 60.53)
	Regorafenib	56.93	(54.79, 59.08)
EQ-5D index	Placebo	0.67	(0.64, 0.70)
	Regorafenib	0.67	(0.64, 0.70)
EQ-5D VAS	Placebo	61.84	(59.59, 64.09)
	Regorafenib	60.62	(58.62, 62.63)

VAS, visual analog scale

Summary of CORRECT results

- The study met its primary endpoint at the preplanned interim analysis

- Regorafenib *vs* placebo:
  - **OS: 6.4 *vs* 5.0 months, HR=0.77, p=0.0052**
    - Crossed prespecified boundary (1-sided p<0.009279)
  - PFS: 1.9 *vs* 1.7 months, HR=0.49, p<0.000001
  - DCR (PR + SD): 41.0% *vs* 14.9%, p<0.000001

- Subgroup analyses:
  - Regorafenib showed OS and PFS benefit across prespecified subgroups
  - Efficacy of regorafenib was independent of KRAS mutation status

- No new or unexpected safety findings:
  - Most frequent grade 3 events related to regorafenib were hand–foot skin reaction, fatigue, diarrhea, hypertension and rash

Results of the X-PECT Study: A phase III randomized double-blind placebo-controlled study of perifosine plus capecitabine (P-CAP) vs. placebo plus capecitabine (CAP) in patients (pts) with refractory metastatic colorectal cancer (mCRC)
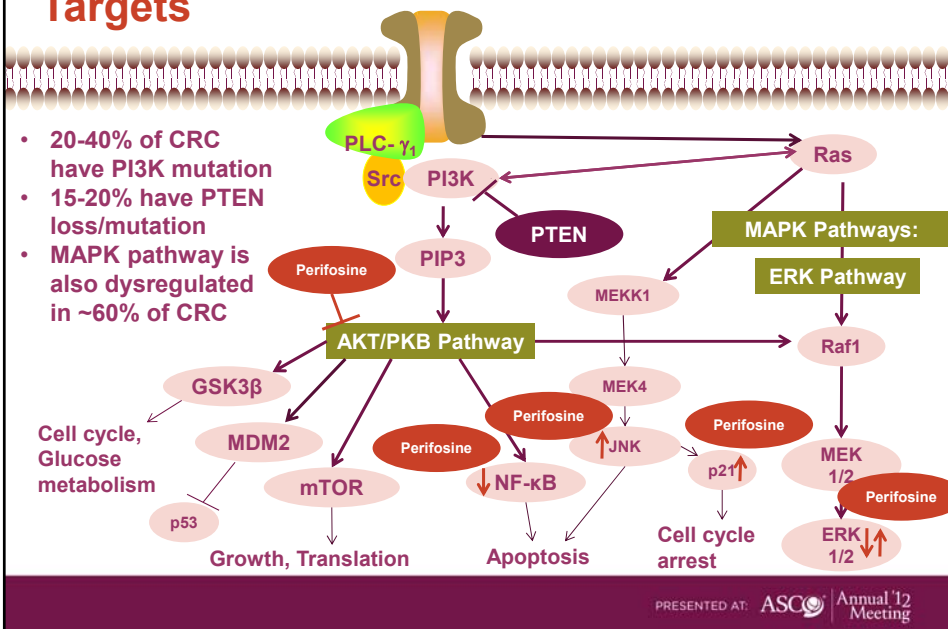
Bendell JC, Ervin T, Senzer N, Richards D, Firdaus I, Lockhart C, Cohn A, Saleh M, Sportelli P, Gardner L, Eng C.

Presented at the 2012 ASCO Annual Meeting. Presented data is the property of the author.   ASCO Annual '12 Meeting

PI3K/ AKT Pathway and Its Downstream Targets

- 20-40% of CRC have PI3K mutation
- 15-20% have PTEN loss/mutation
- MAPK pathway is also dysregulated in ~60% of CRC

PLC-γ_1 Src   PI3K   PTEN   Ras

PIP3   Perifosine

MAPK Pathways:
ERK Pathway

MEKK1

AKT/PKB Pathway   Raf1

GSK3β   MEK4

Perifosine

Cell cycle, Glucose metabolism   MDM2   Perifosine   ↑JNK   Perifosine   MEK 1/2

p53   mTOR   ↓NF-κB   p21↑   Perifosine

Growth, Translation   Apoptosis   Cell cycle arrest   ERK 1/2 ↓↑

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Randomized Phase II

- Patients with 2nd or 3rd line mCRC
- No prior Rx with CAP in metastatic setting
- Prior Rx with 5-FU or 5-FU based regimen

R

Perifosine 50 mg PO QD
Capecitabine 825 mg/m² BID d 1 – 14
N = 20

Cycle = 21 Days
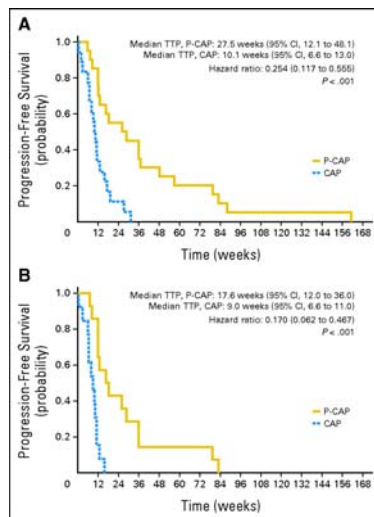
Placebo PO QD
Capecitabine 825 mg/m² BID d 1 – 14
N = 18

- Primary Objective:
  - To compare time to progression (TTP) of P-CAP vs. CAP as 2nd or 3rd line Rx
- Secondary Objective:
  - To compare overall response rate (CR + PR) and overall survival (OS)
  - To evaluate the safety of P-CAP vs. CAP

Bendell JCO 2011

Presented at the 2012 ASCO Annual Meeting. Presented data is the property of the author.   ASCO | Annual '12 Meeting

Randomized Phase II PFS and OS Results

A
Median TTP, P-CAP: 27.5 weeks (95% CI, 12.1 to 48.1)
Median TTP, CAP: 10.1 weeks (95% CI, 6.6 to 13.0)
Hazard ratio: 0.254 (0.117 to 0.555)
P < .001

B
Median TTP, P-CAP: 17.6 weeks (95% CI, 12.0 to 36.0)
Median TTP, CAP: 9.0 weeks (95% CI, 6.6 to 11.0)
Hazard ratio: 0.170 (0.062 to 0.467)
P < .001

A
Median OS, P-CAP: 17.7 months (95% CI, 8.5 to 24.6)
Median OS, CAP: 7.6 months (95% CI, 5.0 to 16.3)
Hazard ratio: 0.370 (0.180 to 0.763)
P = .0052

B
Median OS, P-CAP: 15.1 months (95% CI, 7.2 to 22.3)
Median OS, CAP: 6.5 months (95% CI, 4.6 to 10.9)
Hazard ratio: 0.295 (0.118 to 0.739)
P = .0061

Kaplan-Meier plot of time to progression (TTP) in (A) all evaluable patients and (B) evaluable fluorouracil-refractory patients.
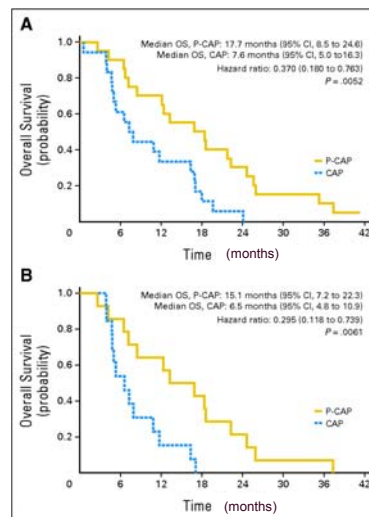
Kaplan-Meier plot of overall survival (OS) in (A) all evaluable patients and (B) evaluable fluorouracil-refractory patients.

Bendell, et al. JCO 2011;29:4394-4400
©2011 by American Society of Clinical Oncology

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X-PECT Treatment / Schema

Patients with refractory mCRC

No prior Rx with CAP in metastatic setting unless rad-sensitizing

R

Perifosine 50 mg PO QD

Capecitabine 1000 mg/m² BID d 1 - 14

Cycle = 21 Days

Placebo PO QD

Capecitabine 1000 mg/m² BID d 1 - 14

- Randomized 1:1, Double-blind, placebo-controlled phase III
- N = ~430 patients
- Primary endpoint: OS
  - Log-rank test with two-sided Type 1 error rate of 0.05. 90% power to detect a treatment difference at the two-sided 0.05 significance level
  - mOS for P-CAP group assumed 7.75 mo and 5.5 mo for CAP group
  - Stratification factors: K-ras mutation status, oxaliplatin discontinuation secondary to toxicity vs. progression
- Secondary endpoints – RR, PFS, toxicity, biomarkers
- US trial – 66 sites, enrollment 3/30/2010-8/10/2011, 468 randomized

Presented at the 2012 ASCO Annual Meeting. Presented data is the property of the author. ASCO Annual '12 Meeting

Key eligibility criteria

- Histologically (or cytologically) confirmed adenocarcinoma of the colon or rectum that is recurrent or metastatic
- Patients must have failed available therapy for the treatment of advanced colorectal cancer.
  - Progressive disease during or within 6 months after fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab, and for K-ras wild-type (WT) patients, anti-EGFR antibody (cetuximab/panitumumab) containing therapies, with most recent progression by RECIST criteria.
  - For oxaliplatin-based therapy, failure of therapy will also include patients who progressed within 12 months of adjuvant therapy and patients who had oxaliplatin stopped secondary to toxicity
- No previous capecitabine in the metastatic setting (except radiosensitizing)
- ECOG 0-1, age ≥ 18 years, adequate bone marrow, renal, and hepatic function

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Baseline Disease Characteristics

	Placebo (N=234)		Perifosine (N=234)	
	n	%	n	%
K-Ras Mutation Status				
Mutant	118	50.4	120	51.3
Wild Type	116	49.6	114	48.7
Diagnosis				
Colon Cancer	184	78.6	178	76.1
Rectal Cancer	50	21.4	56	23.9
Median Prior Therapy Regimens				
2	2	0.9	2	0.9
3	60	25.6	64	27.4
≥4	172	73.5	168	71.7
Prior Adjuvant Therapy				
Yes	40	17.1	43	18.4
No	194	82.9	191	81.6
Strata				
Oxaliplatin discontinuation secondary to progression	155	66.2	141	60.3
Oxaliplatin discontinuation secondary to toxicity	79	33.8	93	39.7

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OS Analysis in ITT Population

	Placebo (N=234)	Perifosine (N=234)
Overall		
No. of Patients	234	234
No. of Events	178 (76.07%)	187 (79.91%)
Median OS (95% CI) (mos)	**6.9 (5.9 , 7.4)**	**6.4 (5.1 , 6.9)**
HR (95% CI) (Relative to Placebo)		**1.111 (0.905 , 1.365)**
P-value (Log-rank)		0.315
K-Ras Wild Type		
No. of Patients	116	114
Median OS (95% CI) (mos)	**6.8 (5.1 , 7.7)**	**6.6 (5.1 , 7.9)**
HR (95% CI) (Relative to Placebo)		**1.020 (0.763 , 1.365)**
P-value (Log-rank)		0.894
K-Ras Mutant		
No. of Patients	118	120
Median OS (95% CI) (mos)	**6.9 (5.6 , 8.0)**	**5.4 (4.7 , 6.8)**
HR (95% CI) (Relative to Placebo)		**1.192 (0.890 , 1.596)**
P-value (Log-rank)		0.238

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PFS Analysis in ITT Population

	Placebo (N=234)	Perifosine (N=234)
Overall		
No. of Patients	234	234
No. of Events	215 (91.88%)	223 (95.30%)
Median PFS Time (95% CI) (wks)	**11.4 (7.7 , 12.1)**	**10.9 (8 , 12)**
HR (95% CI) (Relative to Placebo)		**1.031 (0.854 , 1.244)**
P-value (Log-rank)		0.752
K-Ras Wild Type		
No. of Patients	116	114
Median PFS Time (95% CI) (wks)	**9.4 (6.4 , 12)**	**11.1 (7.3 , 12.3)**
HR (95% CI) (Relative to Placebo)		**0.883 (0.677 , 1.153)**
P-value (Log-rank)		0.362
K-Ras Mutant		
No. of Patients	118	120
Median PFS Time (95% CI) (wks)	**11.8 (7.7 , 12.4)**	**10.6 (6.6 , 12.7)**
HR (95% CI) (Relative to Placebo)		**1.167 (0.895 , 1.523)**
P-value (Log-rank)		0.254

RR 3 vs 2.6%

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Most frequent treatment-related adverse events

Non-Hematologic	Grade 1/2				Grade 3/4			
	Placebo		Perifosine		Placebo		Perifosine	
	n	%	n	%	n	%	n	%
Anemia	30	12.9	49	21.0	7	3.0	5	2.1
Neutropenia	4	1.7	3	1.3	2	0.9	1	0.4
Thrombocytopenia	3	1.3	5	2.1	0	0.0	1	0.4
Fatigue	95	40.6	125	53.4	1	0.4	3	1.3
Nausea	72	30.8	91	38.9	5	2.1	10	4.3
Diarrhea	71	30.3	94	40.2	14	6.0	14	6.0
Decreased Appetite	49	20.9	63	26.9	1	0.4	6	2.6
Vomiting	45	19.2	62	26.5	7	3.0	8	3.4
Palmar-plantar	42	17.9	49	20.9	15	6.4	10	4.3
Stomatitis	18	7.7	14	6.0	2	0.9	2	0.9
Hyperglycemia	12	5.1	7	3.0	4	1.7	1	0.4

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Subgroup – Kras WT and oxaliplatin discontinuation secondary to toxicity

	Placebo	Perifosine
Progression Free Survival		
No. of Patients	40	46
Median PFS Time (95% CI) (wks)	**6.6 (6.1 , 12.4)**	**18.1 (11.6 , 22.1)**
HR (95% CI) (Relative to Placebo)		0.514 (0.329 , 0.801)
P-value (Log-rank)		0.003
Overall Survival		
No. of Patients	40	46
Median OS Time (95% CI) (mos)	**6.2 (4.1 , 7.9)**	**8 (6.4 , 10.6)**
HR (95% CI) (Relative to Placebo)		0.769 (0.477 , 1.239)
P-value (Log-rank)		0.280

When oxaliplatin is stopped secondary to toxicity rather than resistance, are these cells different? How does this interact with Kras?
Biomarker studies pending

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Conclusions

- Despite promising data from a small randomized phase II study, the addition of perifosine to capecitabine for patients with refractory colorectal cancer did not show a benefit
  - Differences between the treatment groups between the phase II and III - ? less pretreatment
  - There was no significant difference in toxicity profiles between the two arms
- Biomarker studies are pending to evaluate if any subgroups may have received benefit
  - Is there a real signal in the patients who stopped oxaliplatin secondary to toxicity and who are also Kras WT?
  - Refractory colorectal cancer cells are different
- As we continue to search for new agents in the treatment of colorectal cancer, biomarker analyses are a necessity to help us understand what we are doing

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Perioperative chemotherapy for resected hepatic metastases

Peri-operative adjuvant therapy for resected mets: Where we were

- Pooled analysis of 2 studies of post-op 5FU/LV: marginally significant benefit in PFS and OS (JCO 2008;26:4906)

- Post-op CAPOX + Bev vs CAPOX closed for slow accrual (ASCO2011;3565): 2Y DFS: 52 vs 70% (p=0.074).

- HAI with FUDR: MS: 68 vs 59 mo (P=NS); DFS: 31 vs 17 mo (p<0.03); (NEJM 1999;341:2039; ASCO GI 2005;#184)

- EORTC 40983 [EPOC]: FOLFOX pre- and post resection vs surgery (Lancet 2008;371:1007): 3Y PFS 35 vs 28%

Peri-operative FOLFOX4 chemotherapy and surgery for resectable liver metastases from colorectal cancer

Long-term survival results of the EORTC Intergroup phase III study 40983.

B. Nordlinger, H. Sorbye, B. Glimelius, G.J. Poston, P.M. Schlag, P. Rougier, W.O. Bechstein, J. Primrose, E.T. Walpole, M.E. Mauer, T. Gruenberger

For the EORTC GI Group, CR UK, ALMCAO, AGITG and FFCD

Aim and design

Demonstrate that chemotherapy combined with surgery is a better treatment than surgery alone

1° endpoint: PFS

Randomize → FOLFOX4 → Surgery → FOLFOX4

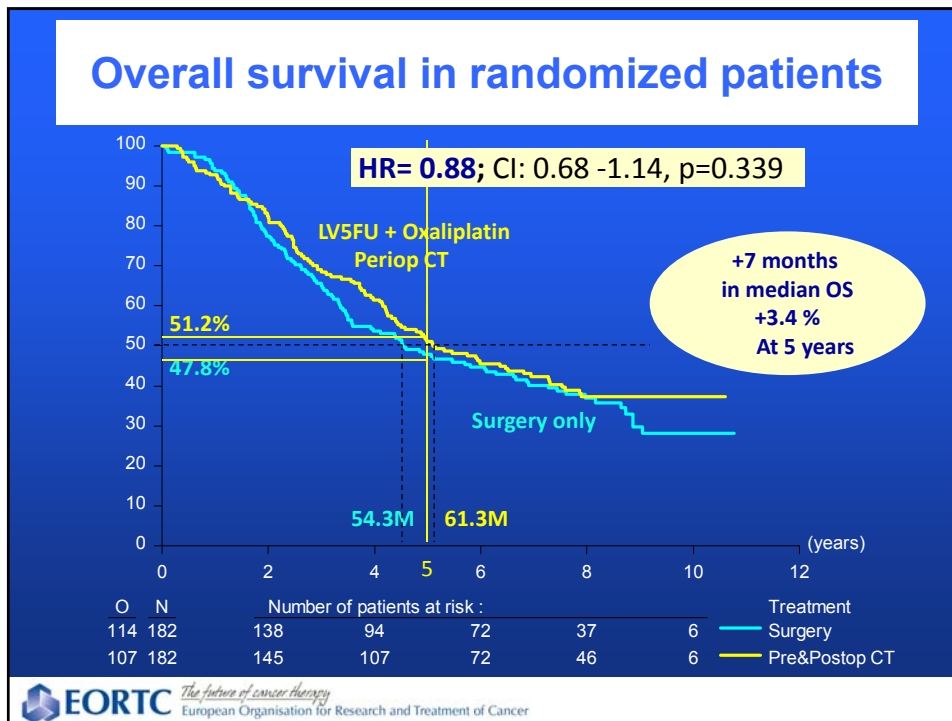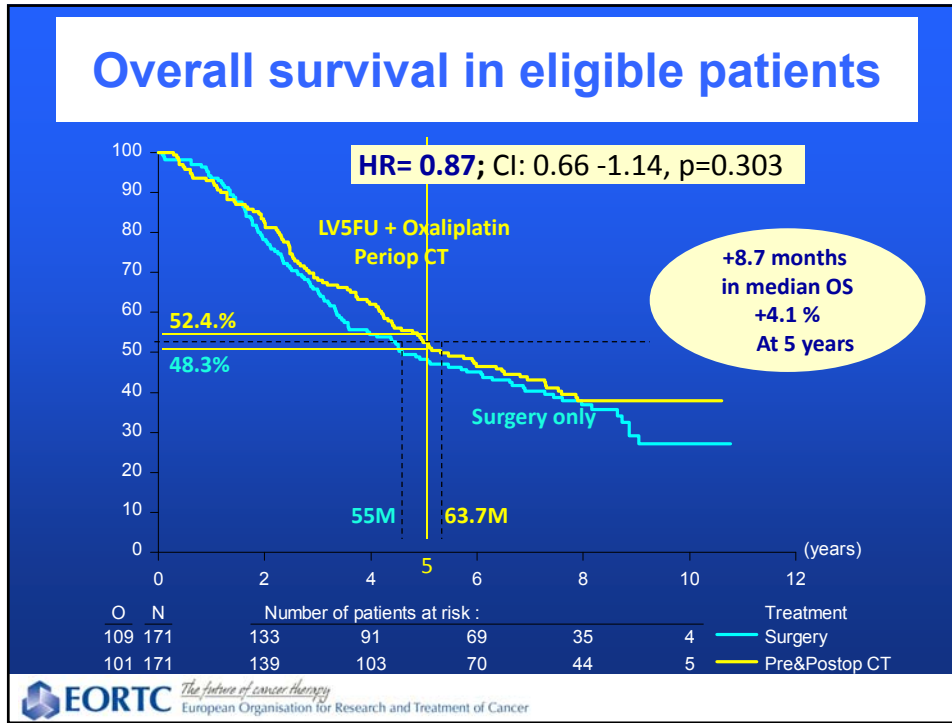6 cycles (3months)   6 cycles (3 months)
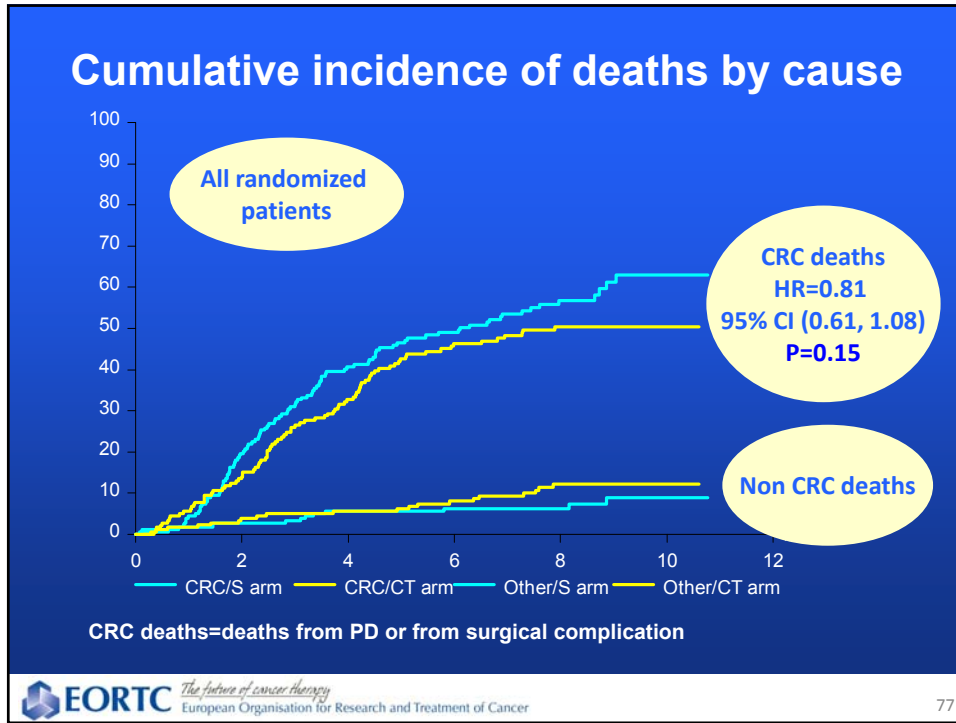
Randomize → Surgery

N=364 patients

Main Eligibility criteria
- Potentially resectable liver metastases of colorectal cancer
- Up to 4 deposits (on CT-scan, at randomization)

Overall survival in eligible patients

HR= **0.87**; CI: 0.66 -1.14, p=0.303

LV5FU + Oxaliplatin Periop CT

+8.7 months in median OS +4.1 % At 5 years

52.4.%
48.3%

Surgery only

55M   63.7M

(years)

O	N	Number of patients at risk :					Treatment
109	171	133	91	69	35	4	Surgery
101	171	139	103	70	44	5	Pre&Postop CT

EORTC — European Organisation for Research and Treatment of Cancer

Overall survival in randomized patients

HR= **0.88**; CI: 0.68 -1.14, p=0.339

LV5FU + Oxaliplatin Periop CT

+7 months in median OS +3.4 % At 5 years

51.2%
47.8%

Surgery only

54.3M   61.3M

(years)

O	N	Number of patients at risk :					Treatment
114	182	138	94	72	37	6	Surgery
107	182	145	107	72	46	6	Pre&Postop CT

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Cumulative incidence of deaths by cause

All randomized patients

**CRC deaths
HR=0.81
95% CI (0.61, 1.08)
P=0.15**

Non CRC deaths

Legend: CRC/S arm — CRC/CT arm — Other/S arm — Other/CT arm

CRC deaths=deaths from PD or from surgical complication

EORTC — *The future of cancer therapy* — European Organisation for Research and Treatment of Cancer

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Second line treatments

1) All patients

	Pre+Postop CT (N=182)	Surgery alone (N=182)
	N (%)	N (%)
Surgery	66 (36.3)	65 (35.7)
Chemotherapy	93 (51.1)	117 (64.3)

2) Patients with cancer relapse

	Pre+Postop CT (N=123)	Surgery alone (N=130)
	N (%)	N (%)
Surgery	66 (53.7)	65 (50.0)
Chemotherapy	93 (75.6)	117 (90.0)

EORTC — *The future of cancer therapy* — European Organisation for Research and Treatment of Cancer

Conclusion

No sufficient evidence to be standard treatment

Peri-operative chemotherapy with FOLFOX4 improves PFS which was the primary endpoint

This trial failed to demonstrate an improvement in OS, for which it was not powered

- **Observed HR is quite similar for PFS and for CRC deaths (HR=0.8). More deaths not related to cancer in CT arm**

- **Observed absolute increase in OS of 4% is similar to positive trials in CRC (ex.: Mosaic: + 4.2% OS at 6 years)**

- Higher than anticipated survival rates in the control arm ,

EORTC *The future of cancer therapy*
European Organisation for Research and Treatment of Cancer

Validation of the 12-gene colon cancer Recurrence Score® result in NSABP C-07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5FU/LV (5FU) and 5FU/LV + oxaliplatin (5FU+Ox)

O'Connell MJ,[1] Lee M,[2] Lopatin M,[2] Yothers G,[1] Clark-Langone K,[2] Millward C,[2] Paik S,[1] Sharif S,[1] Shak S,[2] Wolmark N[1]

[1]National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA;
[2]Genomic Health, Inc., Redwood City, CA

Study Objectives

Prospectively-designed study using archived tissue with pre-specified endpoints, analytical methods and analysis plan (a "Prospective-Retrospective" study[1])

- Primary Objective:
  - Determine whether there is a significant relationship between the continuous 12-gene Recurrence Score® value and recurrence risk in stage II/III patients treated with 5FU or 5FU+oxaliplatin
- Secondary Objectives
  - Determine whether the Recurrence Score result provides significant information beyond number of nodes examined, pathologic T-stage, tumor grade and MMR status
  - Compare recurrence risk between high and low Recurrence Score groups defined using pre-specified cut-points

1. Simon et al. J Natl Cancer Inst. 2009.

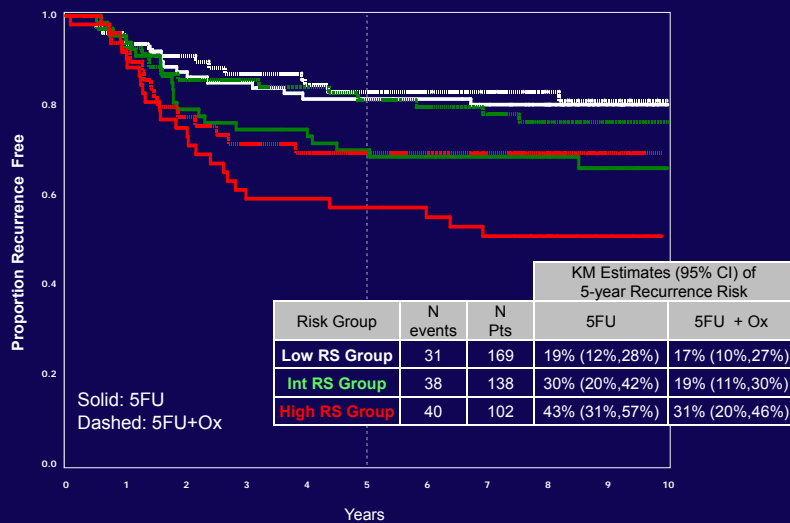**Quantitative Gene Expression Analysis**

- Standardized Onco*type* DX® Colon Cancer Assay performed using RT-PCR from 25 μm of manually microdissected, fixed, paraffin embedded primary colon cancer tissue
  - Expression of seven cancer-related genes and five reference genes analyzed by TaqMan assays
  - RT-PCR performed in triplicate qPCR wells (2 ng RNA input per 10 μL-reaction)
- The 12-gene Recurrence Score® result was calculated using the same pre-specified gene list and algorithm as previously validated in QUASAR and CALGB 9581.
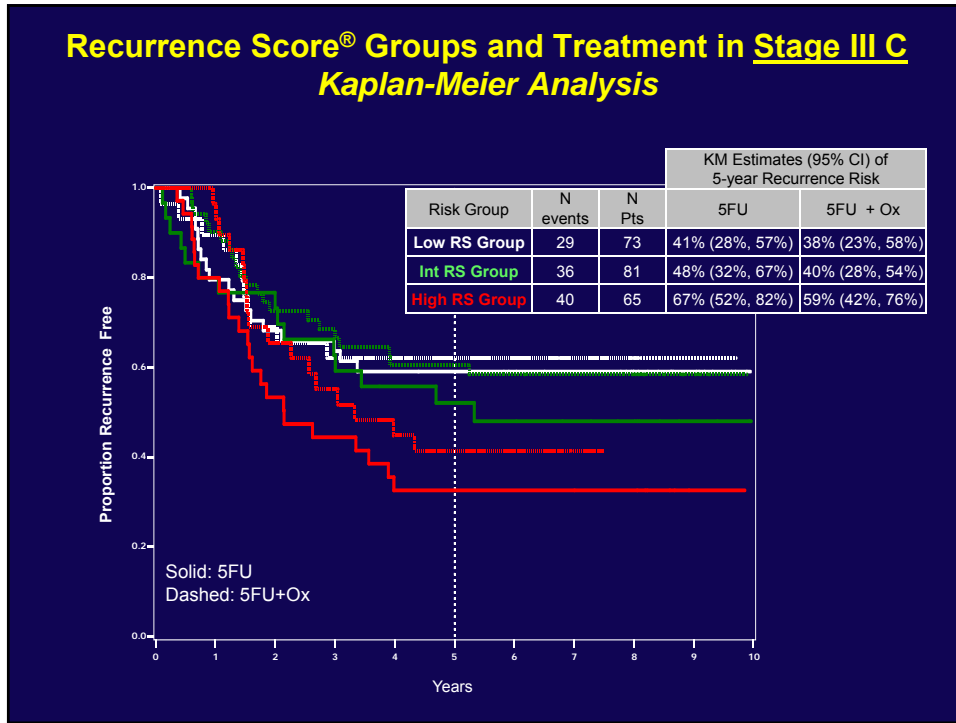
Primary Analysis: Recurrence Score® Result Predicts Recurrence Risk in Stage II & III Colon Cancer Patients in NSABP C-07 (n=892)
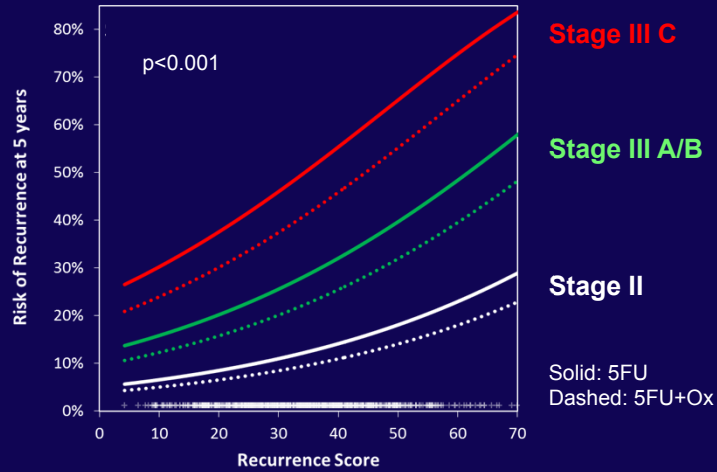
- With similar relative benefit of oxaliplatin added to adjuvant 5FU across the range of Recurrence Score results, absolute benefit of oxaliplatin increases with increasing Recurrence Score result, most apparently in stage II and stage IIIA/B patients

Recurrence Score® Groups and Treatment in Stage III A/B
Kaplan-Meier Analysis

Risk Group	N events	N Pts	KM Estimates (95% CI) of 5-year Recurrence Risk	
			5FU	5FU + Ox
Low RS Group	31	169	19% (12%,28%)	17% (10%,27%)
Int RS Group	38	138	30% (20%,42%)	19% (11%,30%)
High RS Group	40	102	43% (31%,57%)	31% (20%,46%)

Recurrence Score® Groups and Treatment in <u>Stage III C</u>
Kaplan-Meier Analysis

		KM Estimates (95% CI) of 5-year Recurrence Risk	
Risk Group	N events	N Pts	5FU	5FU + Ox
Low RS Group	29	73	41% (28%, 57%)	38% (23%, 58%)
Int RS Group	36	81	48% (32%, 67%)	40% (28%, 54%)
High RS Group	40	65	67% (52%, 82%)	59% (42%, 76%)

Solid: 5FU
Dashed: 5FU+Ox

Contribution of Recurrence Score® Result Beyond Clinical and Pathologic Covariates
Pre-specified Multivariate Analysis (n=892)

Variable	Value	HR	HR 95% CI	P value
Stage (by nodal status)				<0.001
	Stage III A/B vs II	0.97	(0.55,1.71)	
	Stage III C vs II	2.07	(1.16,3.68)	
Treatment	5FU+Ox vs 5FU	0.82	(0.64,1.06)	0.12
MMR	MMR-D vs MMR-P	0.27	(0.12,0.62)	<0.001
T-stage	T4 st II & T3-T4 st III vs T3 st II & T1-T2 st III	3.04	(1.84,5.02)	<0.001
Nodes examined	<12 vs ≥12	1.51	(1.17,1.95)	0.002
Tumor grade	High vs Low	1.36	(1.02,1.82)	0.041
RS	**per 25 units**	**1.57**	**(1.19,2.08)**	**0.001**

- The Recurrence Score value is significantly associated with risk of recurrence after controlling for effects of T and N stage, MMR status, number of nodes examined, grade and treatment.

Summary

- The Recurrence Score result predicts recurrence risk in stage II and III colon Ca patients treated with 5FU or 5FU+oxaliplatin.
  - RS performs similarly in stage II and stage III colon cancer.
  - RS predicts recurrence risk beyond T and N stage, MMR status, number of nodes examined, grade and treatment.

- With similar relative risk reduction observed for oxaliplatin across the range of Recurrence Score values, the Recurrence Score result enables better discrimination of absolute oxaliplatin benefit as a function of risk.
  - Absolute benefits of oxaliplatin increases with increasing Recurrence Score values, most apparently in stage II and stage IIIA/B patients.

- The Recurrence Score result also predicts DFS and OS.

Metastatic Esophago-Gastric Cancer: Where we were

- REAL2 trial2: EOC vs ECF (median OS 11.2mo vs 9.9mo, p=0.020; HR 0.80, 95% CI 0.66-0.97)[1]

- For gastric cancer patients, overall survival was longer with DCF versus CF (23% risk reduction; log-rank P = .02)[2]

1. Cunningham et al, NEJM 2008
2. J Clin Oncol. 2006 Nov 1;24(31):4991-7.

Key Eligibility Criteria

- Inoperable locally advanced / metastatic adenocarcinoma or undifferentiated carcinoma oesophagus, GOJ, stomach
- RECIST-measurable disease
- No prior chemotherapy / radiotherapy including previous adjuvant therapy
- PS 0, 1 or 2
- Archival tissue available for biomarker analyses

- Locally advanced tumours suitable for chemo-radiotherapy excluded
- EGFR positivity / HER-2 status / KRAS mutation status not required for study entry

Survival was worse for EOC + Panitumumab

Primary Endpoint – OS

	Median OS (95% CI)	% alive at 1 year (95% CI)
	11.3m (9.6 – 13.0)	46% (38% - 54%)
	8.8m (7.7 – 9.8)	33% (26% - 41%)
	HR 1.37, p = 0.013	

HR 1.37 (95% CI: 1.07 – 1.76)

Number at risk

EOC	275	49	3
EOC-P	278	38	2
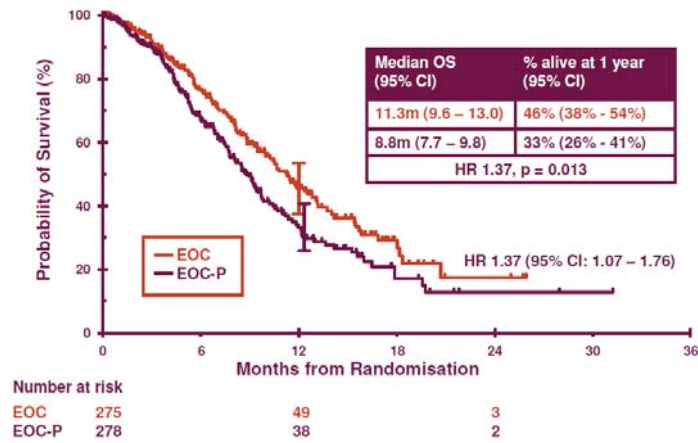
Based on 251 OS events
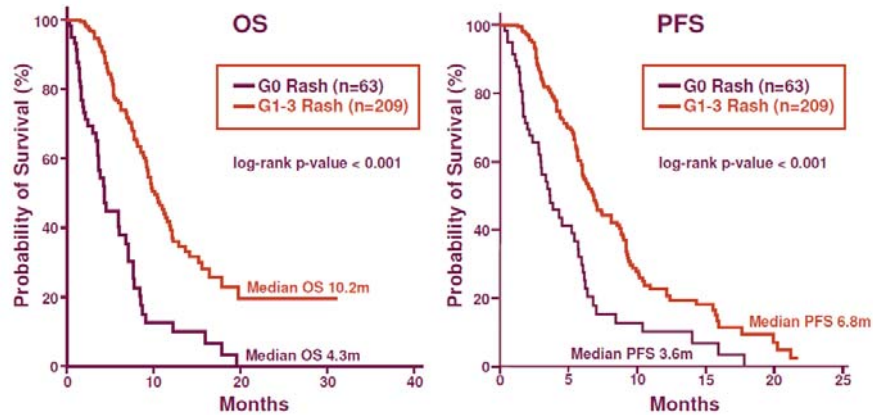
Poorer OS outcome possibly due to reduced chemotherapy delivery in mEOC-P arm
– lower doses of oxaliplatin and capecitabine
– lower median number of cycles

		EOC	mEOC-P
Median no. of cycles (n)		6	5
Dose intensity for cycles given (% of expected dose in each arm)	Epirubicin	89.9%	89.1%
	Oxaliplatin	89.9%	89.6%*
	Capecitabine	91.0%	86.9%*
	Panitumumab	-	88.1%
Dose reductions due to toxicity		36%	39%
Treatment cessation due to toxicity		18%	18%

* Not including protocol-specified baseline dose reductions

Biomarkers: Rash on mEOC-P

OS — G0 Rash (n=63), G1-3 Rash (n=209), log-rank p-value < 0.001, Median OS 10.2m, Median OS 4.3m

PFS — G0 Rash (n=63), G1-3 Rash (n=209), log-rank p-value < 0.001, Median PFS 6.8m, Median PFS 3.6m

• Similar correlation between rash and response rate (p<0.001)

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Anal Cancer (ACT II study): ASCO2012 (abstr 4004): Best time to assess response

29% of pts not in CR at 11 weeks achieved CR at 26 weeks.
Early surgical salvage would not have been appropriate for these pts.
We recommend assessment at 26 weeks in future trials.

Pts with CR		CR rate %	MMC	Absolute risk difference (95% CI) CisP	HR (95% CI) (CR vs not-CR) PFS	OS
Week 11	429	65.6	57.9	7.7% (0.52, 14.9) p=0.04	0.74 (0.56, 0.97) p=0.03	0.68 (0.48, 0.97) p=0.03
Week 18	527	75.4	76.2	0.8% (-7.2, +5.6) p=0.81	0.54 (0.40, 0.73) p<0.001	0.44 (0.31, 0.64) p<0.001
Week 26	582	83.5	84.0	0.5% (-5.9, +5.1) p=0.88	0.26 (0.19, 0.35) p<0.001	0.23 (0.16, 0.33) p<0.001

Gastrointestinal Stromal Tumor

- Imatinib and sunitinib are currently the only two drugs approved for the treatment of advanced GIST

Randomized Phase III Trial of Regorafenib in Patients (pts) with Metastatic and/or Unresectable Gastrointestinal Stromal Tumor (GIST) Progressing Despite Prior Treatment with at least Imatinib (IM) and Sunitinib (SU): The GRID Trial

GD Demetri, P Reichardt, Y-K Kang, J-Y Blay, H Joensuu, RG Maki,
P Rutkowski, P Hohenberger, H Gelderblom, MG Leahy, M von Mehren,
P Schöffski, ME Blackstein, A Le Cesne, G Badalamenti, J-M Xu, T Nishida,
D Laurent, I Kuss, and PG Casali, on behalf of GRID Investigators

Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA;
HELIOS Klinikum,Bad Saarow, Germany; Asan Medical Center, Seoul, South Korea;
Centre Léon Bérard, Lyon, France; Helsinki University Central Hospital, Helsinki, Finland;
Mount Sinai School of Medicine,New York, NY, USA; Maria Sklodowska-Curie Memorial Cancer Center,
Warsaw, Poland; Mannheim University Medical Center, Mannheim, Germany;
Leiden University Medical Center, Leiden, Netherlands;Christie NHS Foundation Trust, Manchester, UK; Fox
Chase Cancer Center, Philadelphia,PA, USA; Universitaire Ziekenhuis Gasthuisberg, Leuven, Belgium;
Mount Sinai Hospital, Toronto, Canada; Institut Gustave Roussy, Villejuif, France; University of Palermo,
Italy; Affiliated Hospital of Academy Military Medical Sciences, Beijing, China;
Department of Surgery, Osaka Police Hospital, Osaka, Japan;
Bayer HealthCare Pharmaceuticals, Berlin, Germany; Istituto Nazionale dei Tumori, Milan, Italy

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Regorafenib (BAY 73-4506) is a Structurally Distinct Oral Inhibitor of Multiple Kinases Relevant to GIST and Other Cancers

Regorafenib

Percent control
- 0%
- 0.1%
- 0.1-1%
- 1-5%
- 5-10%
- 10-35%
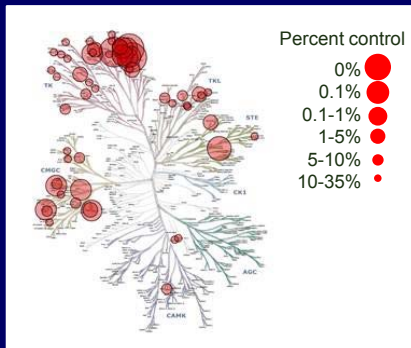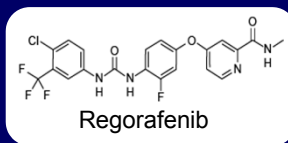
Biochemical activity

	IC_{50} (nmol/l)
KIT	7
VEGFR-1	13
Murine VEGFR-2	4
PDGFR-β	22
RET	1.5
B-RAF	28
FGFR1	202

Wilhelm SM *et al. Int J Cancer* 2011; **129**: 245-255.

GIST – Regorafenib In Progressive Disease (GRID): Study Design

Metastatic/ unresectable GIST pts progressing despite at least prior imatinib and sunitinib (n=236 screened; n=199 randomized)

RANDOMIZATION 2 : 1

Regorafenib + best supportive care (BSC) 160 mg once daily 3 weeks on, 1 week off (n=133)

Placebo + BSC 3 weeks on, 1 week off (n=66)

Disease progression per independent blinded central review

Unblinding Crossover offered for placebo arm or continued regorafenib for treatment arm

Regorafenib (unblinded) until next progression

OFF TREATMENT

- Multicenter, randomized, double-blind, placebo-controlled phase III study
  - Global trial: 17 countries across Europe, North America, and Asia-Pacific
  - Stratification: treatment line (2 vs >2 prior lines), geographical location (Asia vs "Rest of World")
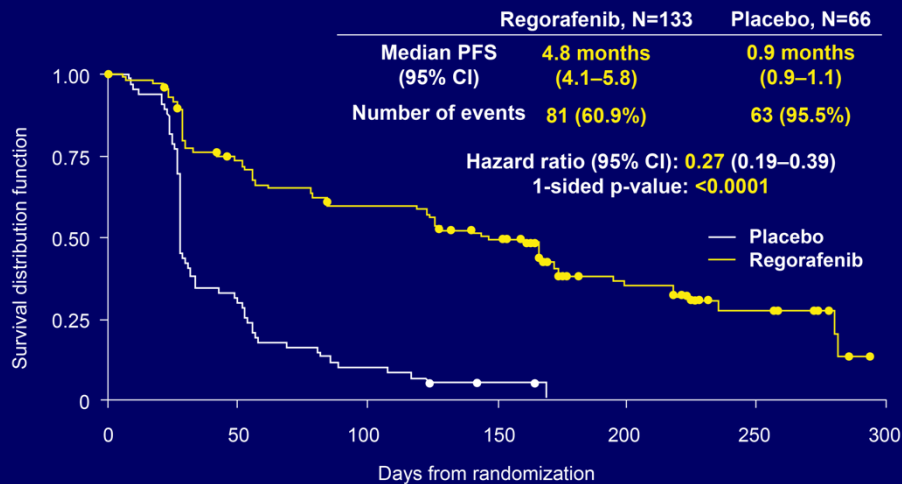
GRID Study: Patient Eligibility

Key inclusion criteria	Key exclusion criteria
Histologically confirmed metastatic or unresectable GIST	Prior treatment with any VEGFR inhibitors other than sunitinib
Progression of GIST on imatinib (or medically severe intolerance to imatinib), AND progression of GIST on sunitinib	Other cancer (different histology) within 5 years prior to randomization
Age ≥18 years	Major surgical procedure, open biopsy, or significant trauma <28 days before study
ECOG performance status 0–1	Pregnancy or breastfeeding
Measurable disease according to modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1	Cardiovascular dysfunction: • Congestive heart failure • Myocardial infarction <6 months before study • Cardiac arrhythmias requiring therapy • Uncontrolled hypertension • Unstable or new-onset angina

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GRID Study: Prior GIST Therapies at Entry

	Regorafenib (N=133) n (%)	Placebo (N=66) n (%)
Imatinib	133 (100.0)	66 (100.0)
Sunitinib	133 (100.0)	66 (100.0)
Nilotinib	29 (21.8)	20 (30.3)
Other tyrosine kinase inhibitors	2 (1.5)	1 (1.5)
mTOR inhibitor	3 (2.3)	1 (1.5)
Cytotoxic chemotherapy	13 (9.8)	2 (3.0)
Other	5 (3.8)	1 (1.5)

GRID Study: Progression-Free Survival (primary endpoint per blinded central review)

	Regorafenib, N=133	Placebo, N=66
Median PFS (95% CI)	4.8 months (4.1–5.8)	0.9 months (0.9–1.1)
Number of events	81 (60.9%)	63 (95.5%)

Hazard ratio (95% CI): 0.27 (0.19–0.39)
1-sided p-value: <0.0001

Regorafenib significantly improved PFS *vs* placebo (p<0.0001); primary endpoint met

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**Prespecified Subgroup Analysis:
PFS per central review**

Subgroup		N	Favors regorafenib ← → Favors placebo	Hazard Ratio	95% (CI)
All patients		199		0.27	(0.19, 0.39)
Anticancer line	Third	113		0.23	(0.14, 0.37)
	Fourth or more	86		0.31	(0.18, 0.54)
Region	Asia	47		0.30	(0.15, 0.62)
	Rest of World	152		0.24	(0.16, 0.37)
	North America	36		0.42	(0.19, 0.92)
	Not North America	163		0.22	(0.15, 0.34)
Sex	Male	127		0.31	(0.20, 0.48)
	Female	72		0.18	(0.09, 0.34)
Age	<65 years	136		0.30	(0.19, 0.46)
	≥65 years	63		0.15	(0.08, 0.30)
BMI	<25 kg/m²	112		0.29	(0.18, 0.46)
	25 to <30 kg/m²	56		0.24	(0.12, 0.48)
	≥30 kg/m²	22		0.19	(0.06, 0.61)
ECOG score	0	110		0.22	(0.14, 0.37)
	1	89		0.30	(0.18, 0.51)
Duration of imatinib treatment	<6 months	22		0.50	(0.17, 1.73)
	≥6 to <18 months	33		0.19	(0.07, 0.55)
	≥18 months	144		0.24	(0.15, 0.36)

Hazard ratio (95%CI)

**GRID Study: Overall Survival
(following 85% cross-over of patients on placebo arm)**

	Regorafenib, N=133	Placebo, N=66
Median OS	Not reached	Not reached
Number of events	29 (21.8%)	17 (25.6%)

Hazard ratio (95% CI): 0.77 (0.42–1.41)
1-sided p-value: 0.199

Because of the crossover design, lack of statistical significance between regorafenib and placebo was not unexpected

Progression-Free Survival Following Crossover (per Investigator Assessment)
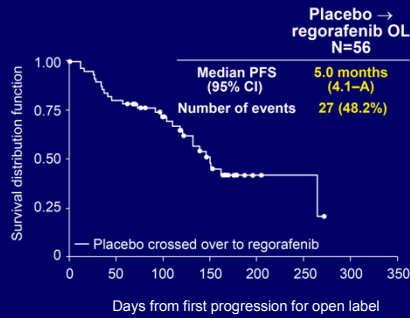
Substantial PFS benefit in patients initially randomized to placebo and subsequently crossed over to open-label regorafenib
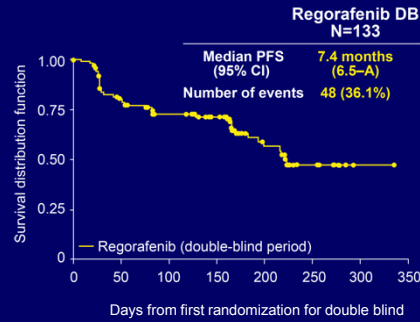
PFS benefit in placebo arm after crossover to regorafenib is comparable to PFS benefit in patients initially randomized to regorafenib

Disease Control and Overall Response Rates

	Regorafenib (N=133) n (%)	Placebo (N=66) n (%)
Disease control rate CR + PR + durable SD (≥12wks)	**70 (52.6)**	**6 (9.1)**
Objective response rate	**6 (4.5)**	**1 (1.5)**
Complete response	0 (0.0)	0 (0.0)
Partial response	6 (4.5)	1 (1.5)
Stable disease (at any time)	95 (71.4)	22 (33.3)
Progressive disease	28 (21.1)	42 (63.6)

Responses based on modified RECIST v1.1

Regorafenib improved rates of disease control *vs* placebo

Drug-Related Treatment-Emergent Adverse Events in ≥10% of Patients During Double-Blind Treatment

Grade	Regorafenib (N=132), % Median 23 wks exposure				Placebo (N=66), % Median 7 wks exposure			
	All	3	4	5	All	3	4	5
Hand-foot skin reaction	56.1	**19.7**	0	0	15.2	**1.5**	0	0
Hypertension	48.5	**22.7**	0.8	0	16.7	**3.0**	0	0
Diarrhea	40.9	5.3	0	0	7.6	0	0	0
Fatigue	38.6	2.3	0	0	27.3	1.5	0	1.5
Mucositis, oral	37.9	1.5	0	0	9.1	1.5	0	0
Alopecia	23.5	1.5	0	0	3.0	0	0	0
Hoarseness	22.0	0	0	0	4.5	0	0	0

Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment

Regorafenib	Placebo
8 (6.1%)	5 (7.6%)

Baseline GIST Genotype per Site Reports: Exploratory Analysis of Outcomes

Tumor genotype, n (%)	Placebo	Regorafenib	Total
Prior GIST genotype available and reported at study entry (% total study population)	36 (54.5%)	60 (45.1%)	96 (48.2%)
KIT exon 11 mutation	17 (47.2%)	34 (56.7%)	51 (53.1%)
KIT exon 9 mutation	6 (16.7%)	9 (15.0%)	15 (15.6%)
Wild type KIT and PDGFRA	2 (5.6%)	6 (10.0%)	8 (8.3%)
Unspecified or other exon mutant	11 (30.5%)	11 (18.3%)	22 (22.9%)

Mutation biomarker	Progression-free survival					
	N	Events	HR	95% CI	Placebo, median months	Regorafenib, median months
KIT exon 11 mutation	51	40	0.212	0.098, 0.458	1.1	5.6
KIT exon 9 mutation	15	11	0.239	0.065, 0.876	0.9	5.4

Conclusions

- Regorafenib significantly increases PFS compared with placebo in patients with metastatic or unresectable GIST progressing despite prior therapy with at least imatinib and sunitinib
  - **PFS: median 4.8 *vs* 0.9 months, HR 0.27, p<0.0001**

- No new or unexpected safety findings with regorafenib
  - Most common grade ≥3 adverse events related to regorafenib were hand-foot skin reaction, hypertension, and diarrhea

- Regorafenib has the potential to fulfill an unmet need for advanced GIST patients progressing after imatinib and sunitinib
  - Potential new standard of care for this patient population

Advanced HCC treated with SOR prophylactic urea-based cream or best supportive care after HSFR

	Urea Cream	Placebo
All grade HFSR	56%	74% (P<0.0001)
> Grade II HFSR	22%	29% (p=0.1638)
Time to 1st HFSR	84d	34d (P<0.001)

Ren, ASCO2012 (abstr 4008)

Pancreatic cancer: Not a big year at ASCO

- FIRGEM : FOLFIRI for 2 mo alternating with GEM vs GEM in metastatic pancreatic cancer: PFS at 6 months of 48% vs 30% (ASCO2012: Abst 4018)

- cixutumumab (IGF-1R inhibitor) did not improve the PFS or OS of patients with metastatic PAC treated with erlotinib and G in a molecularly unselected population (ASCO2012 4019)

- Gem/Vismodegib (HH inhibitor): Median OS: 6.3/5.4 mo; 1Y survival (%): 24/24. (**ASCO 2012;4022**)

- **Maintenance sunitinib: 6 mo PFS better for maintenance sutent 23 vs 3% (P=0.01);** 2y OS: 25 vs 4% (P=.09). (ASCO2012;Abstr 4017)

Questions?