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Colorectal cancer proffered papers discussion:

1/ LBA 17: BEBYP/GONO trial
Bevacizumab post progression (Gianluca Mosi)

2/ Abst 518 O: IMPACT trial
MGN 1703 maintenance trial (Dirk Arnold)

3/ LBA 18: CORRECT trial update
Regorafenib in late lines

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ICO R Gauducheau nantes France

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Related Disclosures:

- Consultant, Advisor, speaker in symposia:
  - Roche, Sanofiaventis,

- Consultant, Advisor, DSMB Chair
  - Bayer

A randomized study evaluating the continuation of bevacizumab beyond progression in metastatic colorectal cancer patients who received bevacizumab as part of first-line treatment: results of the BEBYP trial by the Gruppo Oncologico Nord Ovest (GONO).

LBA 17

G. MASI
Pisa Italy

On behalf of F. Loupakis[1], L. Salvatore[1], L. Fornaro[1], C. Cremolini[1], M. Schirripa[1], E. Fea[2], C. Granetto[2], L. Antonuzzo[3], E. Giommoni[3], G. Allegrini[4], S. Cupini[5], C. Boni[6], M. Banzi[6], S. Chiara[7], C. Sonaglio[7], C. Valsuani[8], A. Bonetti[9], L. Boni[10], A. Falcone[1,11]

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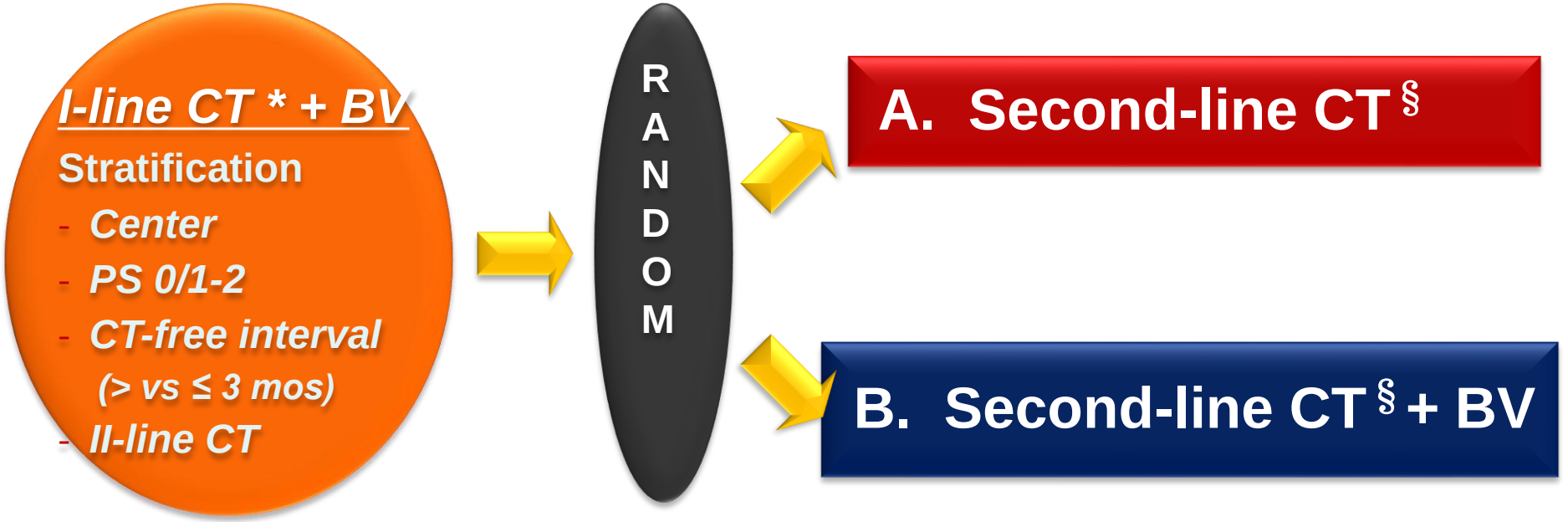
BEPYP

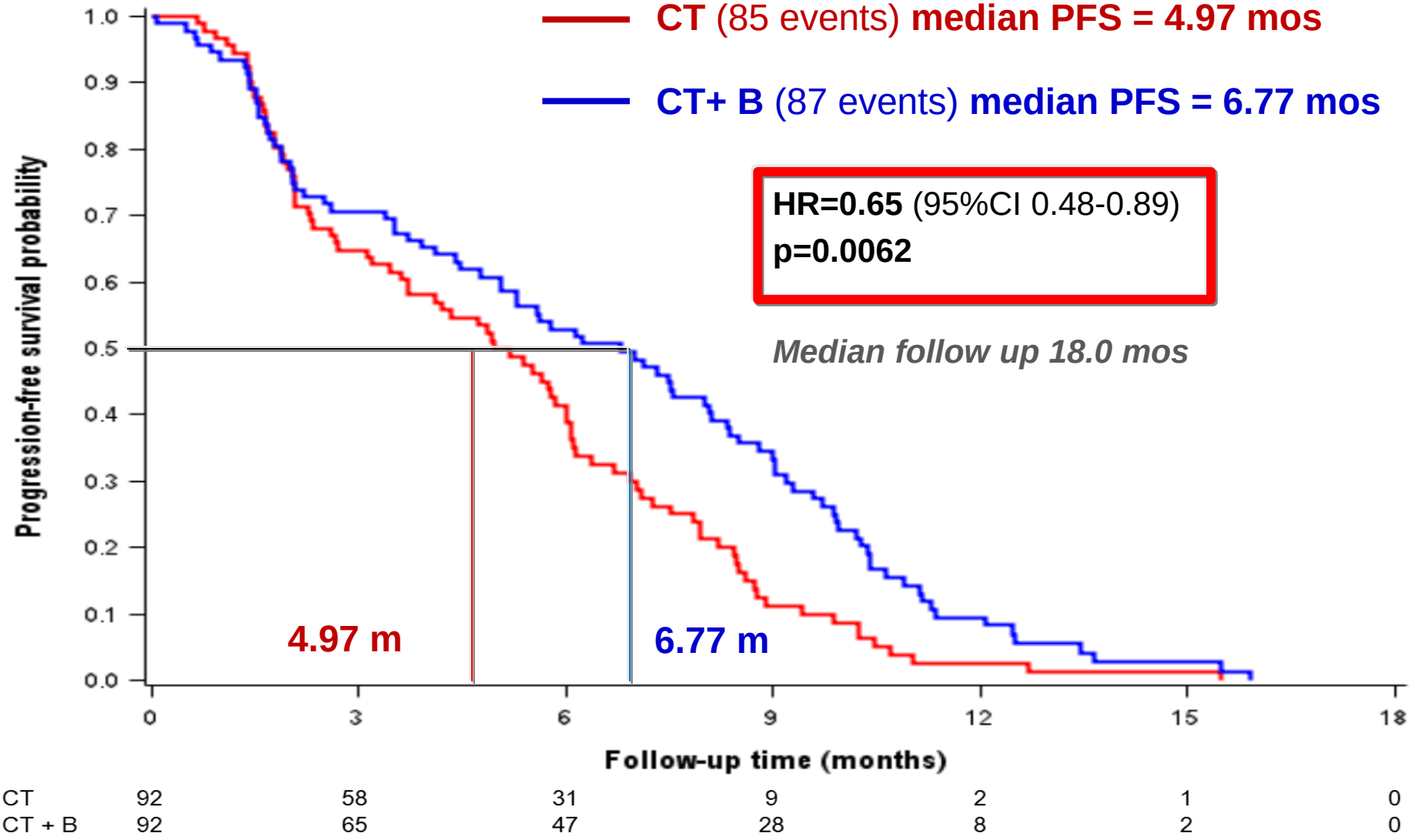


*
- FOLFIRI
- FOLFOX
- FOLFOXIRI
- Fluoropyrimidine mono-tx

§
- FOLFIRI
- mFOLFOX-6

- **Original Hypothesis: HR for PFS of 0.70 in favor of CT+BV**
- **262 pts terminated early with 184 ITT pts**

BEBYP PFS (Primary end-point)



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How does BEBY compare with TML?

TML

- Randomized phase III
- N= 820
- Complete accrual
- All Bev. Pre-treated 1st line
- 2nd line w/wo Bev

- 1st EP: OS since rando
- 2nd EP:
  - PFS
  - ORR
  - Safety

BEBYP

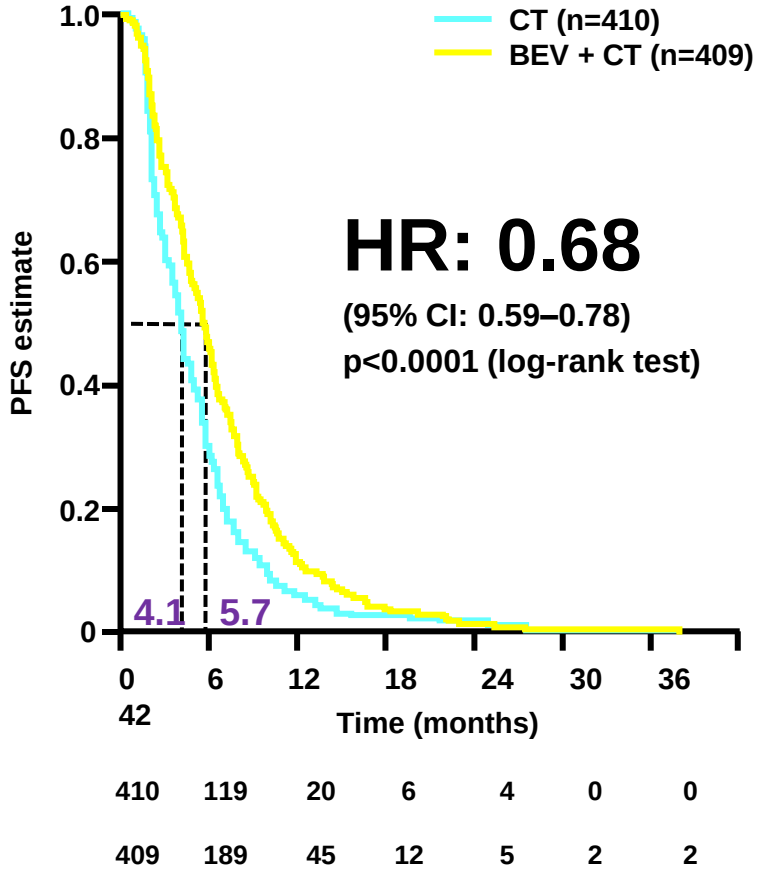
- Randomized phase II
- N=262 planned
- Terminated early at 184 pt
- All Bev. Pre-treated 1st line
- 2nd line w/wo Bev

- 1st EP: PFS since rando
- 2nd EP:
  - OS (immature)
  - ORR
  - Safety

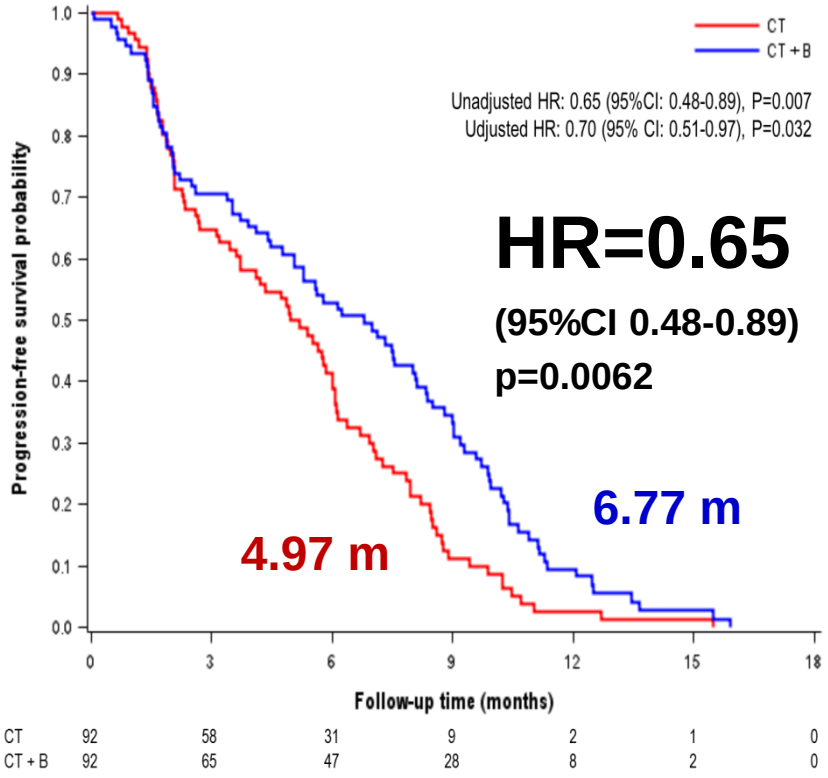
Both studies evaluated the use of Bevacizumab beyond progression

How does BEBY compare with TML? PFS analysis

TML (2nd EP)



BEBYP (1st EP)



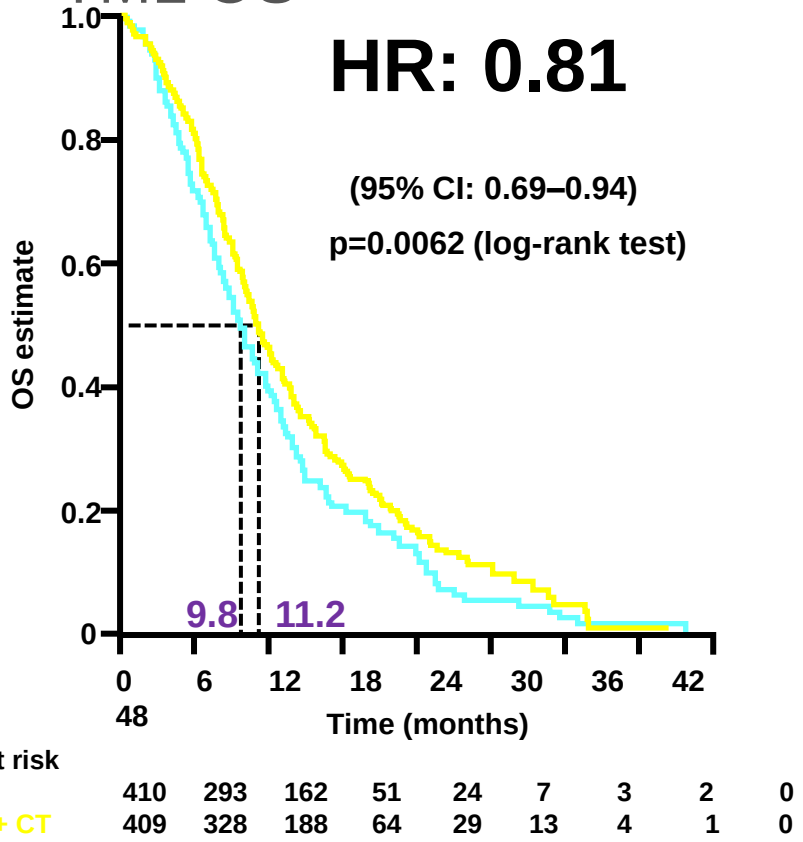
How does BEBY compare with TML? ORR analysis

	TML				BEBYP		
	CT	p	CT+BEV		CT	p	CT+BEV
ORR	16	ns	22		18	ns	21
DCR	54	0.0001	68		62	ns	71

How does BEBY compare with TML? OS analysis

TML

- TML OS



BEBYP

- OS not available yet

?

How does BEBY compare with TML? Patient populations

TML

- Inclusion criteria
- Exclusion criteria
  - PD>3m after last Bev
  - 1st line PFS < 3 m
  - 1st line Bev< 3 consecutive m
- 1st line PFS
  - ≤ 9m: 55%
  - > 9m: 45%
- Post-study treatment
  - Bev: 12/12%
  - Anti EGFR 41/39%

BEBYP

- Inclusion criteria
  - PD after 3m or during 1st line CT+Bev
  - Or 3m after Folfoxiri Bev
- 1st line PFS
  - 10.3 m
- Post-study treatment
  - Bev 1/3%
  - Anti EGFR 46/32%

How does BEBY compare with TML? Sub-group analysis

- All sub groups studied in both TML and BEBYP benefitted from Bevacizumab continuation on PFS
- No data on OS for BEBYP

- Partial population analysis for Kras:
  - In TML the benefit of Bev was independant of Kras for PFS but not on OS for Kras mutant as opposed to wild-type
  - In BEBYP the benefit on PFS was seen in both mutant and kras wild-type as well. No data so far on OS

Bevacizumab beyond progression

- 2 randomized studies showed similar benefit on PFS in term of HR
- Data are still pending for OS in BEBYP
- No additional benefit on RR from Bev added to 2nd line
- These studies validate the use of Bevacizumab beyond progression
  - With all chemo combination
  - In selected patients initially responding to Bevacizumab (TML)
  - No data on maintenance Bev reported in the studies
  - With a benefit on median PFS of 1.6 to 1.8 m in 2nd line
  - Associated to an increased cost.

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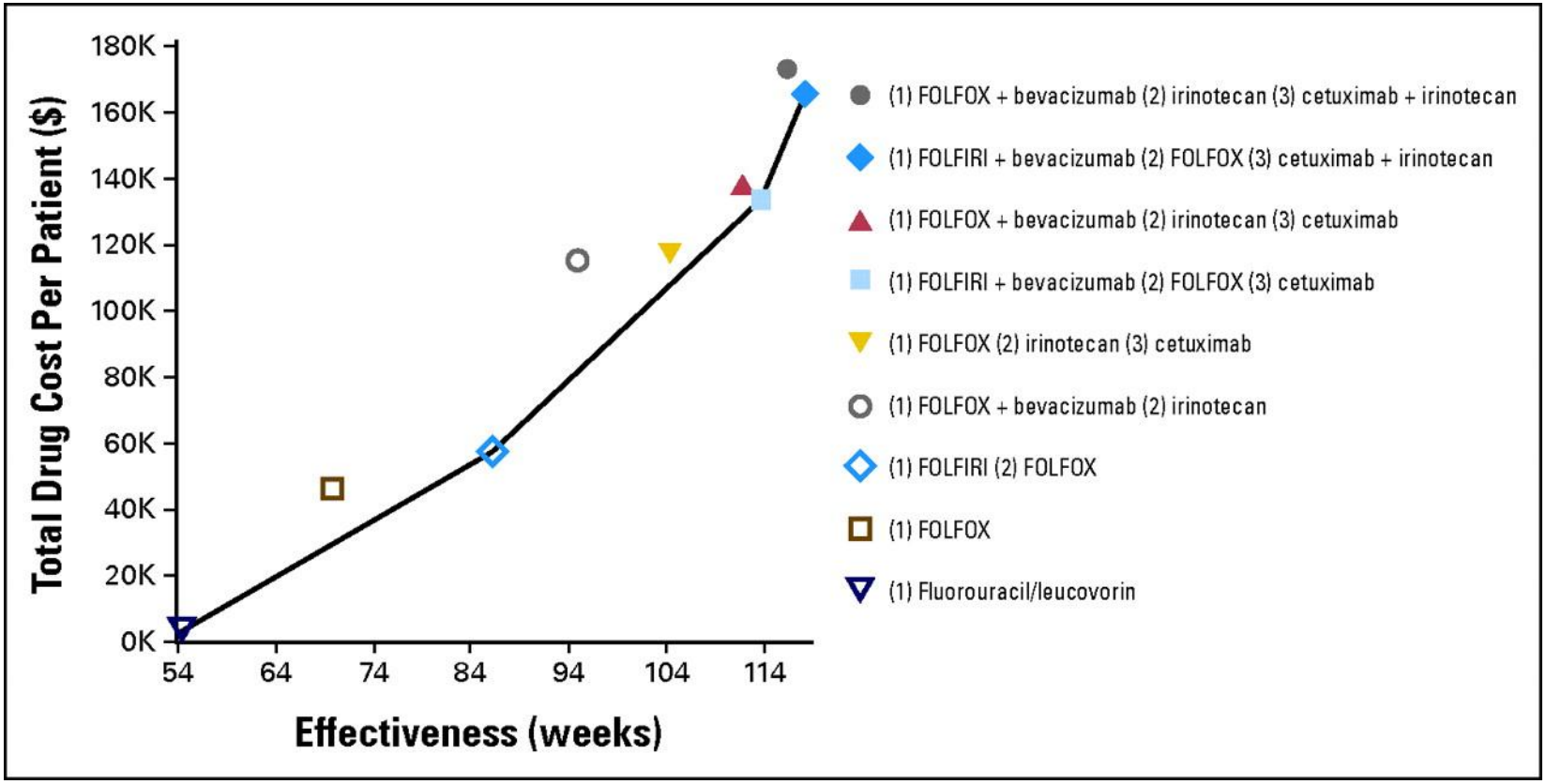
Cost effectiveness of colon cancer treatment.



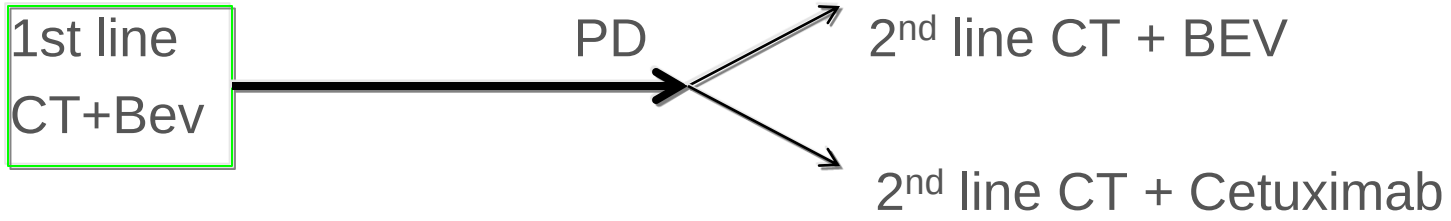
Meropol N J , Schulman K A JCO 2007;25:180-186

JOURNAL OF CLINICAL ONCOLOGY

Integration of other targeted therapy

- In Kras wild-type mCRC anti EGFR are approved in 1st and 2nd lines
- Other sequences are also feasible
  - Anti EGFR 1st line followed by Bev 2nd line
  - Bev 1st line followed by anti EGFR 2nd line
  - Head to head comparison of Bev vs. anti EGFR in 1st line

- ACCORD 22/PRODIGE 18 Trial:
  - Randomized phase II Kras wt mCRC



- Earlier use of other targeted agents (eg. Regorafenib) in combination with CT

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Abstract 518O

Maintenance treatment with immunomodulator MGN1703 following induction with standard 1st line therapy prolongs progression-free survival in patients with metastatic colorectal carcinoma (mCRC): results of the phase II/III IMPACT trial.

D. ARNOLD
Hamburg Germany

On behalf of Schmoll H.J.[2], Riera-Knorrenschild J.[3], Mayer F.[4], Kroening H.[5], Scheithauer W.[6], Ziebermayr R.[7], Nitsche D.[8], Andel J.[9], Taupitz M.[10], Frericks B.[11], Tschaika M.[12], Schmidt M.[12], Wittig B.[13] for the IMPACT Study Team

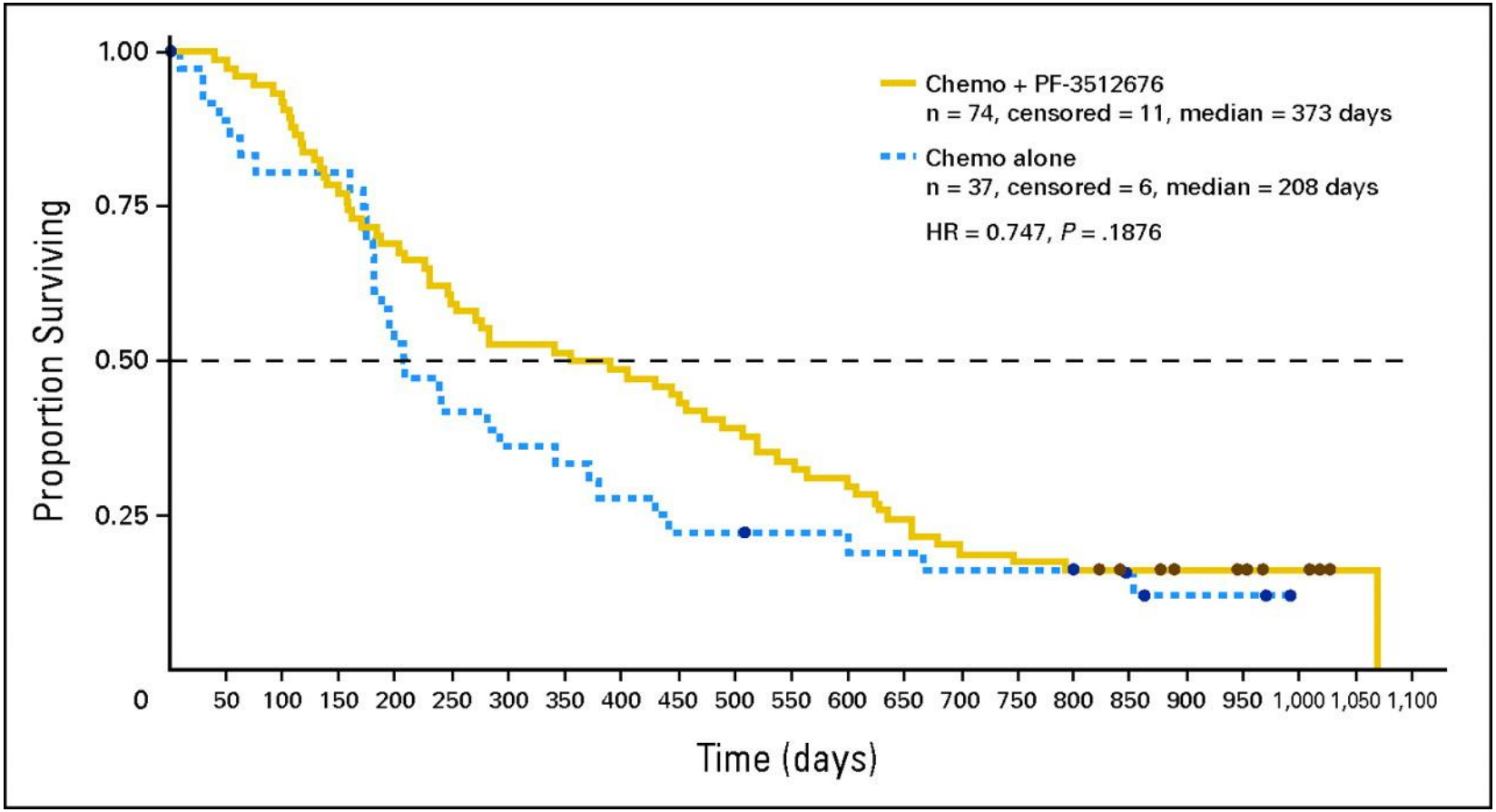
IMPACT Trial

- A new approach for mCRC of immunostimulation after disease control by conventional CT/Targeted therapy
  - Boosting the innate and adaptive immune reaction
    - Proof of principle established in other solid tumor types
  - Goal: prolong disease control after tumor burden reduction by induction CT/Targeted therapy

MGN 1703

- A Toll-Like Receptor 9 agonist
- TLR9 play an important role in defense against pathogens thru activation on innate immunity (Dentritic cells, monocytes, NK…) and may induce cytokine production and immune reaction.
- TLR9 agonist have shown activity in clinical trials in renal cell cancer, Cutaneous T cell lymphoma, non-Hodgkin lymphoma and NSCLC

Kaplan-Meier analysis of overall survival of patients treated with PF-3512676 plus chemotherapy and patients treated with chemotherapy alone.



Manegold C et al. JCO 2008;26:3979-3986

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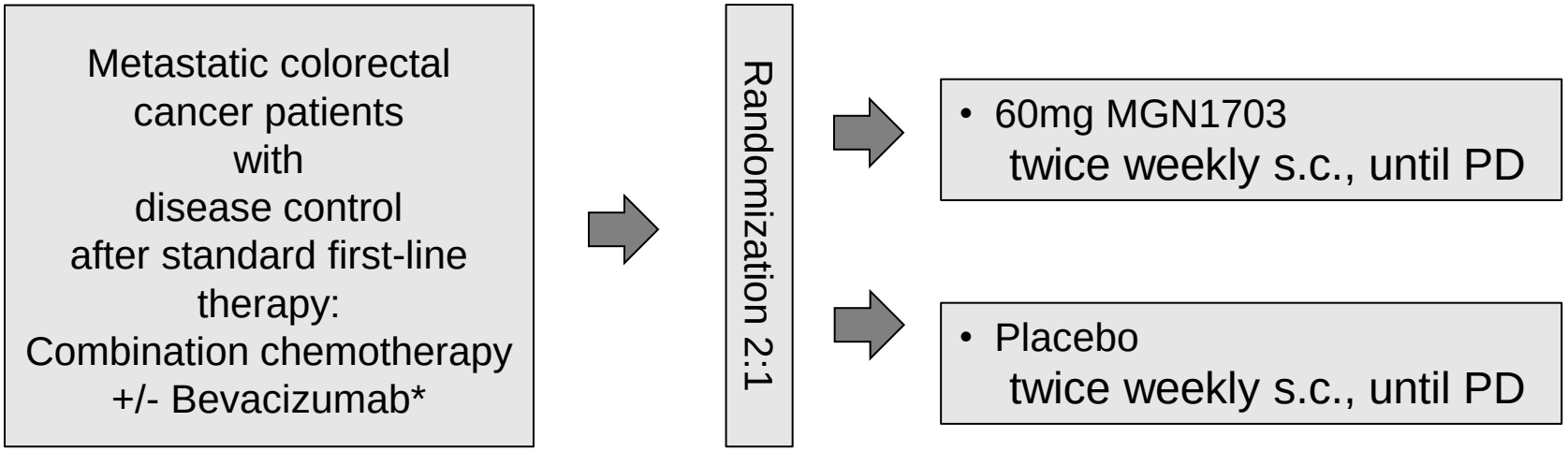
IMPACT design



* at investigators discretion

Primary endpoint:

- PFS from randomization

Secondary endpoints:

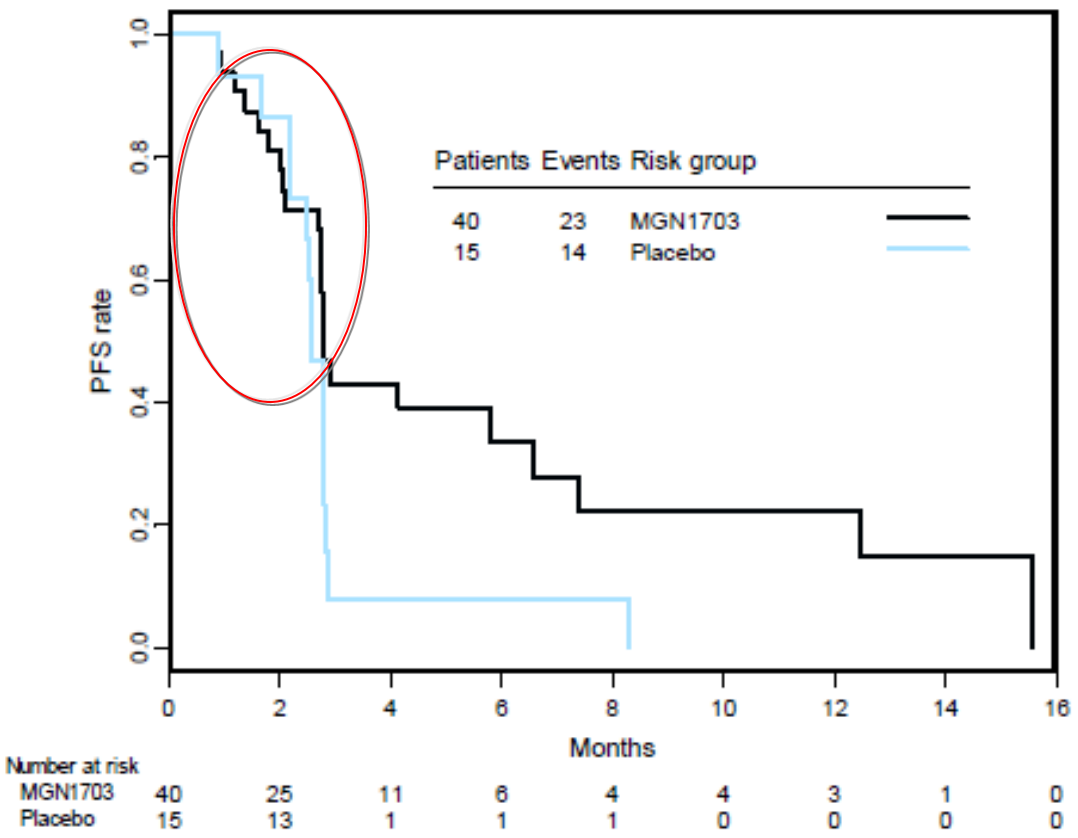
- PFS from induction therapy
- Overall survival, Overall response rates
- Safety (CTCAE v4.0)
- Pharmacodynamics
- Biomarker (incl. immunologic response)
- QoL (QLQ-C30 and -CR29)

PRETREATMENT CHARACTERISTICS

Characteristics [% patients]		MGN1703 N=40	Placebo N=15
Induction therapy duration	mean [months]	5.2	5.5
	median [months]	5.4	5.3
Regimen (in %):			
FOLFOX / XELOX + bevacizumab		37.5	46.7
FOLFIRI / XELIRI + bevacizumab		47.5	46.7
FOLFOX / XELOX alone		15.0	6.7
Best response (according to investigator)			
CR / PR		**72%**	**93%**
SD		28%	7%
Max. tumor size reduction 1st line [median]		-40,5%	-42.6%

PRIMARY ENDPOINT: PFS OF MAINTENANCE

Intent-to-treat (ITT) population



	Months [95% CI]	
PFS	**MGN1703**	**Placebo**
Median PFS	**2.8** [2.8; 6.6]	**2.6** [2.5; 2.8]
25% quartile	2.1 [1.6; 2.8]	2.2 [1.7; 2.6]
75% quartile	7.4 [2.9;15.6]	2.8 [2.6; 2.9]

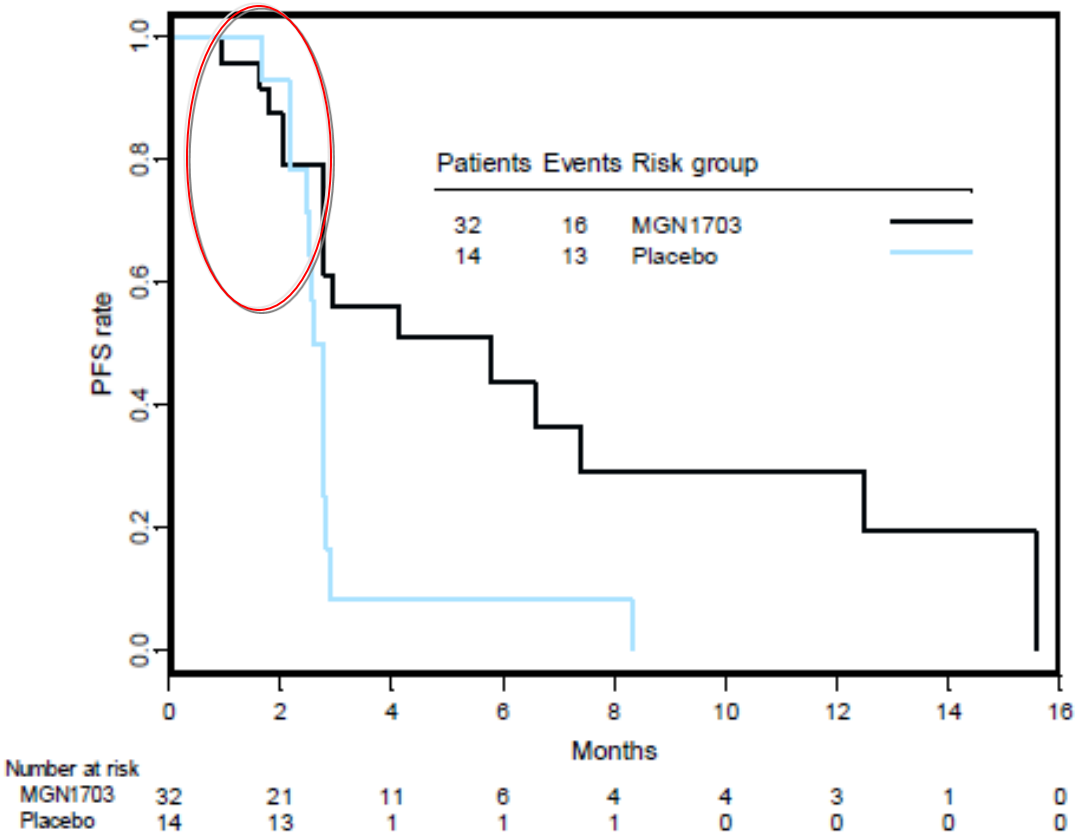
Log-rank test: p-value 0.0617

Hazard ratio = 0.53

95% Confidence Interval [0.27; 1.06]

PFS OF MAINTENANCE: GOOD RISK SUBGROUP

Population: Sub-group Population



	Months [95% CI]	
PFS	**MGN1703**	**Placebo**
Median PFS	**5.8** [2.8; 12.5]	**2.7** [2.5; 2.8]
25% quartile	2.8 [1.8; 4.1]	2.5 [2.2; 2.8]
75% quartile	12.5 [5.8;15.6]	2.8 [2.6; 2.9]

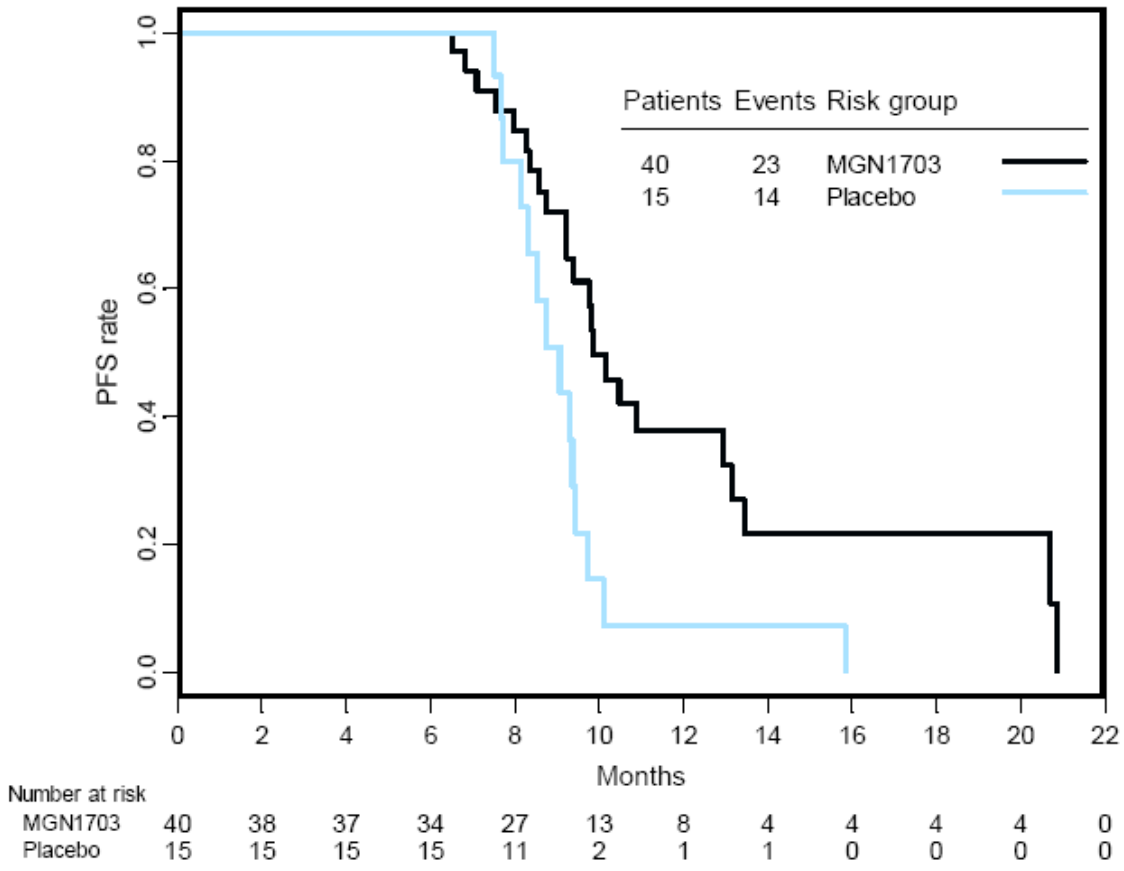
Log-rank test: p-value 0.0133

Hazard ratio = 0.39

95% Confidence Interval [0.18; 0.85]

PFS FROM INDUCTION START

Intent-to-treat (ITT) population



	Months [95% CI]	
PFS	**MGN1703**	**Placebo**
Median PFS	**9.0** [9.2; 13.1]	**8.6** [8.1; 9.4]
25% quartile	8.3 [7.1; 8.7]	7.9 [7.0; 8.6]
75% quartile	13.0 [9.5; 20.9]	9.1 [8.5; 9.3]

Log-rank test: p-value 0.0478

Hazard ratio = 0.50

95% Confidence Interval [0.25; 1.01]

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IMPACT Trial

- Additional set of data showing activity with TLR9 agonist
- First time in metastatic colorectal cancer
- Excellent tolerance profile
- Deserves further evaluation with a larger sample to convince.

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Phase 3 CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC): overall survival update
LBA 18

Eric Van Cutsem, MD, PhD

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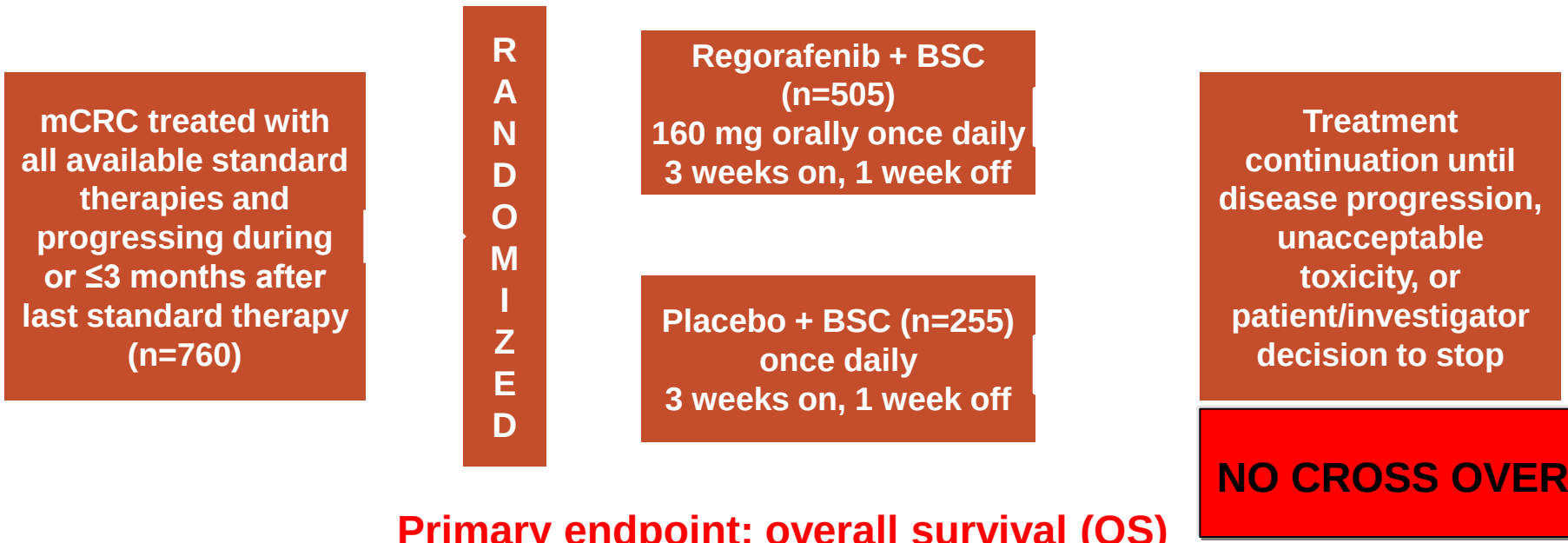
On behalf of Alberto Sobrero, Salvatore Siena, Alfredo Falcone, Marc Ychou, Yves Humblet, Olivier Bouché, Laurent Mineur, Carlo Barone, Antoine Adenis, Josep Tabernero, Takayuki Yoshino, Heinz-Josef Lenz, Richard M. Goldberg, Daniel J. Sargent, Frank Cihon, Lisa Cupit, Andrea Wagner, Dirk Laurent,Axel Grothey and the CORRECT Investigator Group

CORRECT: Trial design

- Multicenter, randomized, double-blind, placebo-controlled, phase III trial
  - 16 countries, 114 centers
  - Recruitment: May 2010 to March 2011
- Stratification: prior anti-VEGF therapy, time from diagnosis of metastasis,

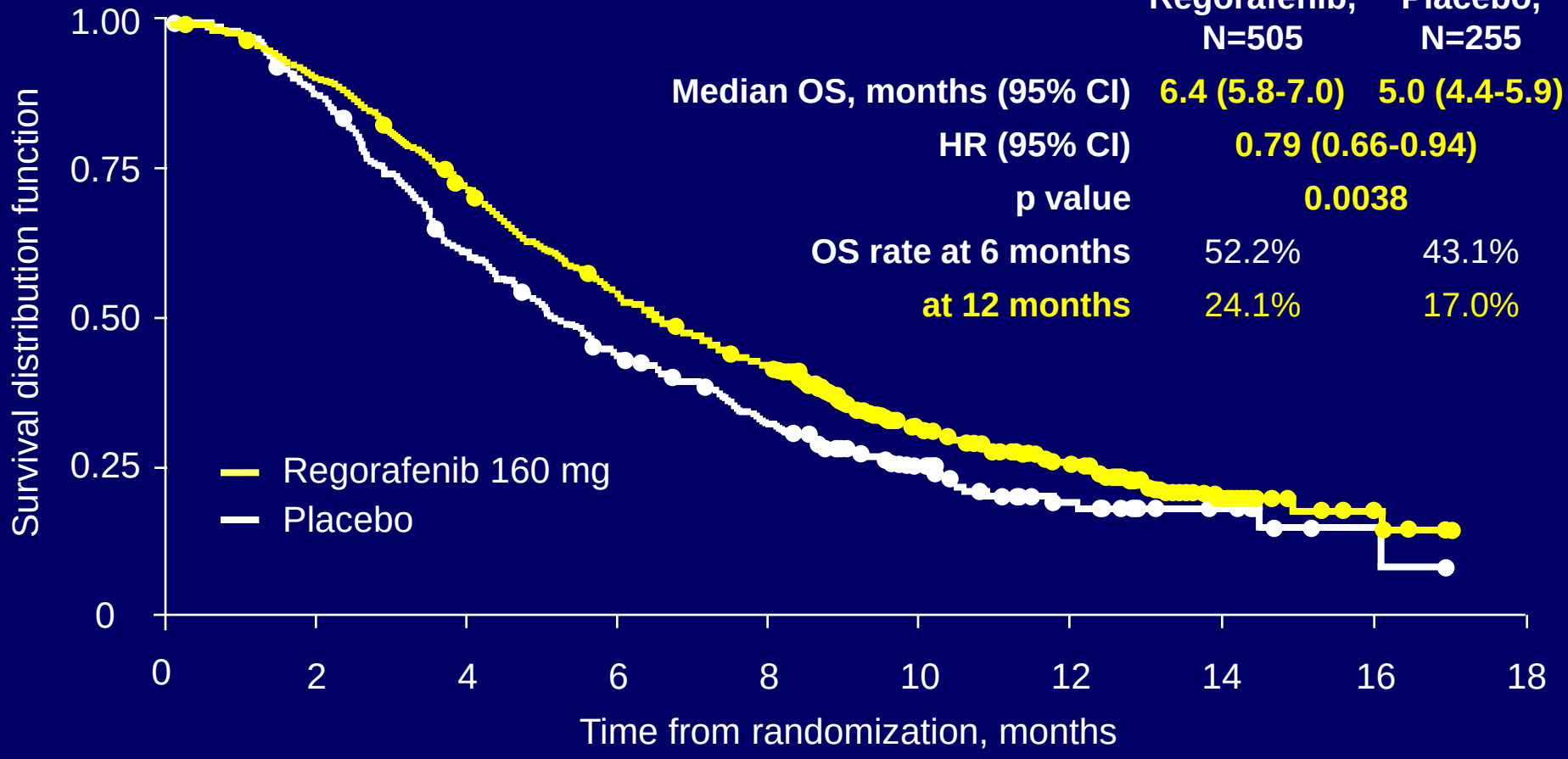


Primary endpoint: overall survival (OS)

90% power to detect 33.3% increase (HR=0.75), 1-sided overall α=0.025

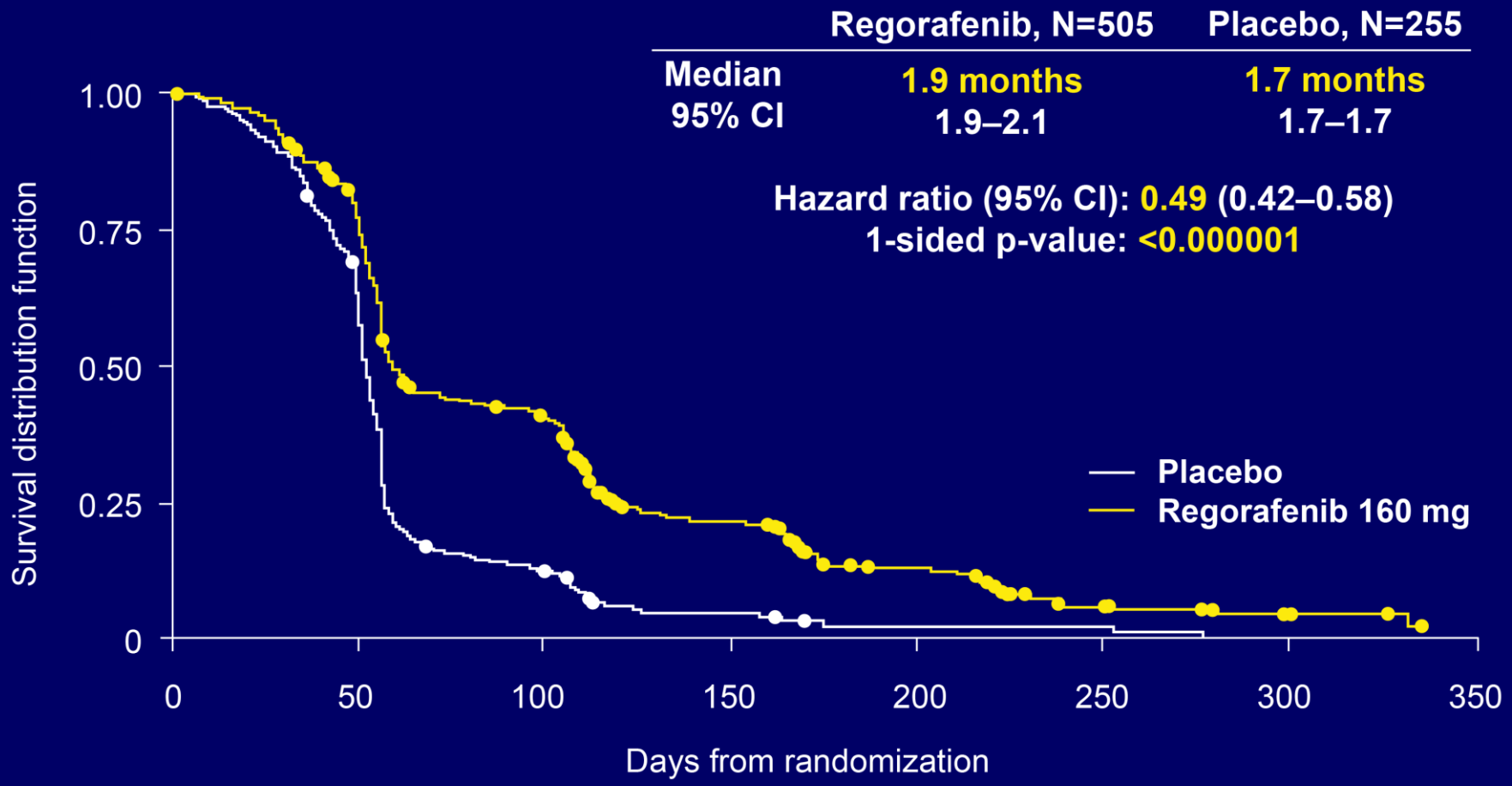
Overall survival (updated analysis)

566 events (97% of planned total)



ASCO 2012
Progression-free survival (secondary endpoint)

Regorafenib significantly improves PFS compared to placebo



Patient demographics

		Regorafenib N=505	Placebo N=255
Age, median years (range)		61 (22-82)	61 (25-85)
Race, %	White	77.6	78.8
	Asian	15.0	13.7
ECOG PS, %	0	52.5	57.3
	1	47.5	42.7
Region, %	North America, Western Europe, Israel, Australia	83.2	83.1
***KRAS* mutation, %**	Yes	54.1	61.6

Baseline disease characteristics

		Regorafenib N=505	Placebo N=255
lines of therapy %	2-3	26.7	24.7
	4	24.8	28.2
	5 and more	48.5	47.1
Prior bevacizumab, %		100	100

- **Patients population reflecting the European practice**
- **All with advanced disease, heavily pre-treated**
- **With no other options**

- **Previous exposure to anti-EGFR?**

CORRECT trial

- What about predictive markers?
  - The PFS curves indicate that a sub group is deriving benefit

***KRAS* mutation**	**No**	**299**	**0.653 (0.476-0.895)**
	Yes	**430**	**0.867 (0.670-1.123)**

  - Other biomarkers based on the mechanism of action?
    - Nras?
    - Braf?
    - cKit?
    - VEGF pathway
    - Ret?

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Regorafenib in M+ colorectal cancer

- A new alternative for patients in late lines of treatment
- Toxicity profile has to be taken under consideration:
  - Most are mild Grade 1 or 2 but may cumulate
    - Rash+Hand-Foot Syndrom
    - Diarrhea+nausea+mucositis+anorexia
    - Fatigue+ Hypertension
  - Added toxicity does not impair Quality of Life
- As for other targeted agents, a fraction of the population benefit and predictive biomarkers should be looked for.
- Regorafenib was just approved a few days ago by FDA
- Development in combination with CT in earlier lines