GI SLIDE DECK 2016

Selected abstracts on **Colorectal Cancer** from:

esdo european society of digestive oncology

Supported by Eli Lilly and Company.
Eli Lilly and Company has not influenced the content of this publication

Lilly

Letter from ESDO

DEAR COLLEAGUES

It is my pleasure to present this ESDO slide set which has been designed to highlight and summarise key findings in digestive cancers from the major congresses in 2016. This slide set specifically focuses on the **European Society of Medical Oncology 2016 Congress** and is available in English, French and Japanese.

The area of clinical research in oncology is a challenging and ever changing environment. Within this environment, we all value access to scientific data and research which helps to educate and inspire further advancements in our roles as scientists, clinicians and educators. I hope you find this review of the latest developments in digestive cancers of benefit to you in your practice. If you would like to share your thoughts with us we would welcome your comments. Please send any correspondence to info@esdo.eu.

And finally, we are also very grateful to Lilly Oncology for their financial, administerial and logistical support in the realisation of this activity.

Yours sincerely,

Eric Van Cutsem
Wolff Schmiegel
Phillippe Rougier
Thomas Seufferlein

(ESDO Governing Board)

esdo

european society of digestive oncology

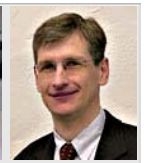
ESDO Medical Oncology Slide Deck
Editors 2016

COLORECTAL CANCERS



Prof Eric Van Cutsem	Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium
Prof Wolff Schmiegel	Department of Medicine, Ruhr University, Bochum, Germany
Prof Thomas Gruenberger	Department of Surgery I, Rudolf Foundation Clinic, Vienna, Austria

PANCREATIC CANCER AND HEPATOBILIARY TUMOURS

Prof Jean-Luc Van Laetham	Department of Gastroenterology-GI Cancer Unit, Erasme University Hospital, Brussels, Belgium
Prof Thomas Seufferlein	Clinic of Internal Medicine I, University of Ulm, Ulm, Germany

GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS


Prof Philippe Rougier	Digestive Oncology Department, European Hospital Georges Pompidou, Paris, France
Prof Côme Lepage	University Hospital & INSERM, Dijon, France

BIOMARKERS


Prof Eric Van Cutsem	Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium
Prof Thomas Seufferlein	Clinic of Internal Medicine I, University of Ulm, Ulm, Germany

esdo

Glossary

1L	first line
2L	second line
5FU	5-fluorouracil
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Bev	bevacizumab
BSC	best supportive care
Cape	capecitabine
CEA	carcinoembryonic antigen
Cetux	cetuximab
cfDNA	cell-free DNA
CI	confidence interval
(p)CR	(pathologic) complete response
(m)CRC	(metastatic) colorectal cancer
CRT	chemoradiotherapy
CT	chemotherapy
CTC	circulating tumour cells
ctDNA	circulating DNA
DCR	disease control rate
ddPCR	droplet digital polymerase chain reaction
DFS	disease-free survival
(m)DoR	median duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	endothelial growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
ETS	early tumour shrinkage
FISH	fluorescence in situ hybridisation
FIT	fecal immune test
FOLFIRI	leucovorin, fluorouracil, irinotecan
FOLFOXIRI	leucovorin, fluorouracil, irinotecan, oxaliplatin
FOLFOX	leucovorin, fluorouracil, oxaliplatin
FP	fluoropyrimidine
GGT	gamma-glutamyl transpeptidase
HR	hazard ratio
IHC	immunohistochemistry
(m)ITT	(modified) intent-to-treat
iv	intravenous
LV	leucovorin
LDA	Linear Discriminant Analysis
LDH	lactate dehydrogenase
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
mrTRG	MRI tumour regression grade
MSI-H	microsatellite instability high
MSS	microsatellite stable
mut	mutant
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NEXIRI	irinotecan, sorafenib
NGS	next generation sequencing
NS	non-significant
OR	odds ratio
(O)RR	(objective) response rate
(m)OS	(median) overall survival
Oxali	oxaliplatin
(qRT)PCR	(quantitative real-time) polymerase chain reaction
PD	progressive disease
(m)PFS	(median) progression-free survival
PD	pharmacodynamic
PK	pharmacokinetic
PR	partial response
PS	performance status
QoL	quality of life
R	randomised
RCTx	radiochemotherapy
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	relapse-free survival
RT	radiotherapy
SD	stable disease
TTF	time to treatment failure
TTR	time to recurrence
VEGF(R)	vascular endothelial growth factor (receptor)
WHO	World Health Organization
wt	wild type

Contents

Note: To jump to a section, right click on the number and ‘Open Hyperlink’

METASTATIC COLORECTAL CANCER

Metastatic Colorectal Cancer

FIRST-LINE THERAPY

455O: Efficacy and circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E–mutated (BRAFm) metastatic colorectal cancer (mCRC) – Corcoran et al

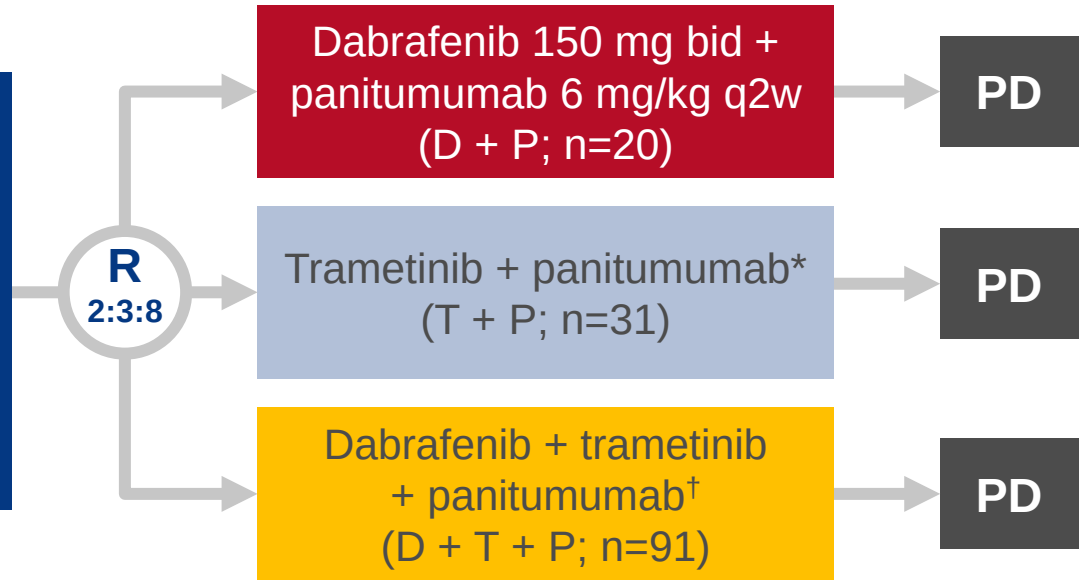
Study objective

- To assess the efficacy and safety of panitumumab with dabrafenib and/or trametinib in BRAF-mutant mCRC with integrated biomarker analyses

Key patient inclusion criteria

- BRAF-mutant CRC
- ECOG PS 0 or 1
- Adequate organ system function

(n=142)



PRIMARY ENDPOINT(S)

- Safety

SECONDARY ENDPOINTS

- Efficacy: CR, PR, SD, PFS
- ctDNA

*T 2 mg/d + P 6 mg/kg q2w (n=11); T 1.5 mg/d + P 6 mg/kg q2w (n=10); T 2 mg/d + P 4.8 mg/kg q2w (n=10). †D 150 mg bid + T 2 mg/d + P 6 mg/kg q2w (n=48); D 150 mg bid + T 2 mg/d + P 4.8 mg/kg q2w (n=36); D 150 mg bid + T 1.5 mg/d + P 6 mg/kg q2w (n=4); D 150 mg bid + T 1.5 mg/d + P 4.8 mg/kg q2w (n=3).

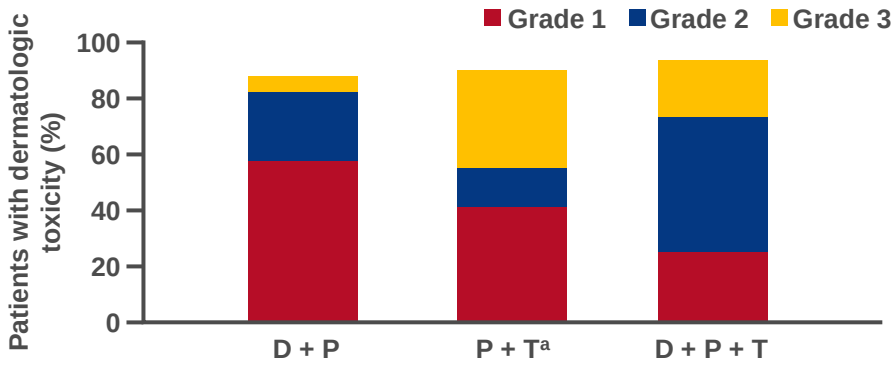
Corcoran RB et al. Ann Oncol 2016; 27 (suppl 6): abstr 455O

455O: Efficacy and circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E–mutated (BRAFm) metastatic colorectal cancer (mCRC) – Corcoran et al

Key results

Adverse event, n (%)	D + P (n=20)		T + P (n=51[a])		D + T + P (n=91)	
	Total	Grade 3/4	Total	Grade 3/4	Total	Grade 3/4
Diarrhoea	9 (45)	0	37 (73)	1 (2)	59 (65)	6 (7)
Dermatitis acneiform	12 (60)	0	27 (53)	9 (18)	54 (59)	9 (10)
Nausea	10 (50)	0	18 (35)	1 (2)	51 (56)	2 (2)
Dry skin	7 (35)	1 (5)	17 (33)	3 (6)	49 (54)	2 (2)
Fatigue	10 (50)	0	13 (25)	0	45 (49)	6 (7)
Pyrexia	7 (35)	0	20 (39)	0	44 (48)	4 (4)
Vomiting	6 (30)	0	15 (29)	1 (2)	39 (43)	2 (2)
Decreased appetite	5 (25)	0	13 (25)	0	36 (40)	2 (2)
Rash	3 (15)	0	16 (31)	0	28 (31)	10 (11)

Dermatologic toxicity	D+P (n=20)	T + P (n=13)	D + T + P (n=35)
Patients, n (%)	18 (90)	12/13 (92)	33 (94)



[a]T + P safety data were derived from a total of 51 patients (BRAF-mutant cohort [n=31] and anti-EGFR-therapy-resistant cohort [n=20]).

Corcoran RB et al. Ann Oncol 2016; 27 (suppl 6): abstr 455O

455O: Efficacy and circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E–mutated (BRAFm) metastatic colorectal cancer (mCRC) – Corcoran et al

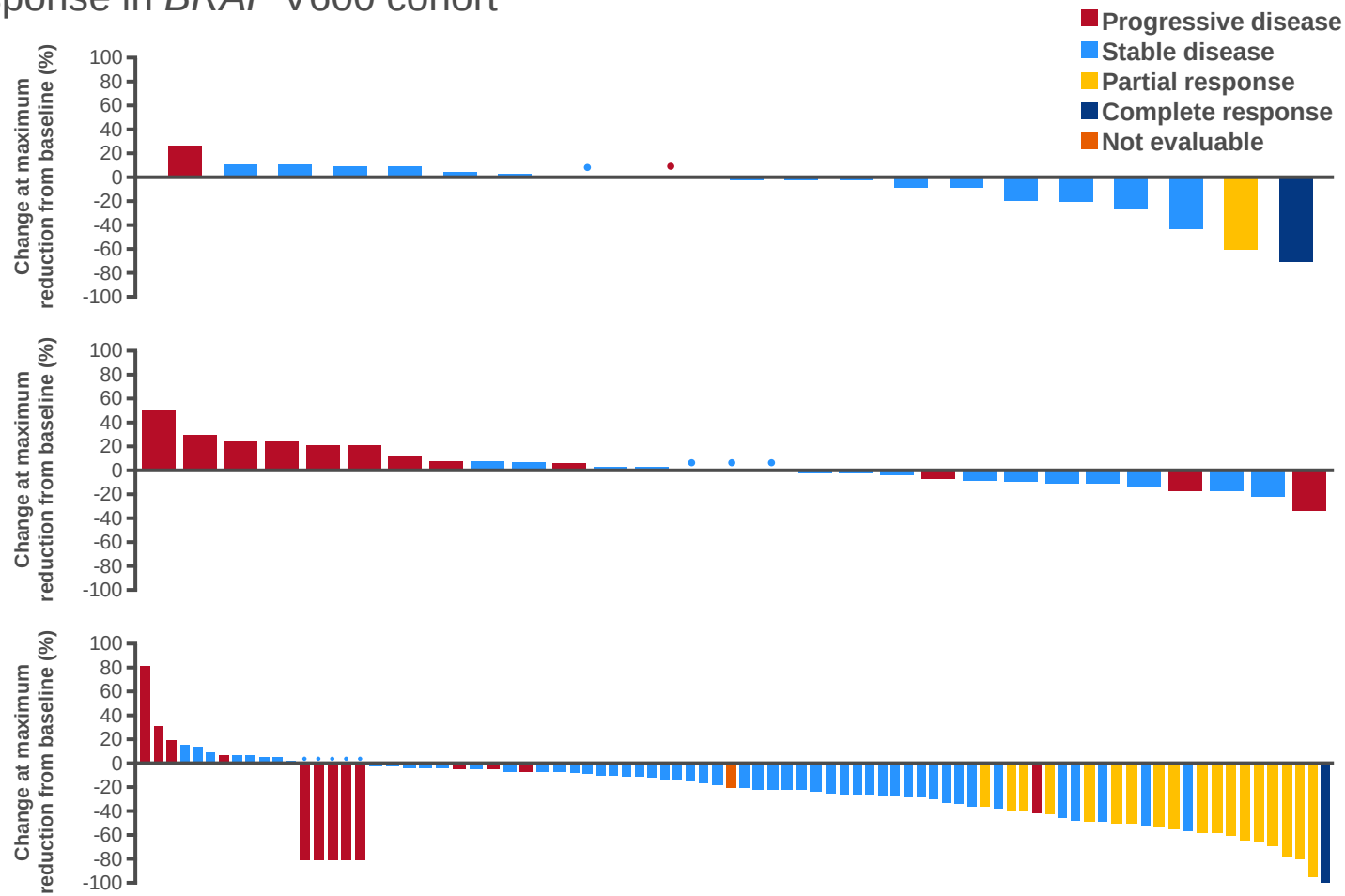
Key results (continued)

Confirmed best response in *BRAF* V600 cohort

D + P (n=20), (%)
Confirmed CR/PR: 2 (10)
Stable disease: 16 (80)
Disease control: 18 (90)

T + P (mutant *BRAF*; n=31), n (%)
Confirmed CR/PR: 0 (0)
Stable disease: 17 (55)
Disease control: 17 (55)

D + T + P (n=91), n (%)
Confirmed CR/PR: 19 (21)
Stable disease: 59 (65)
Disease control: 78 (86)

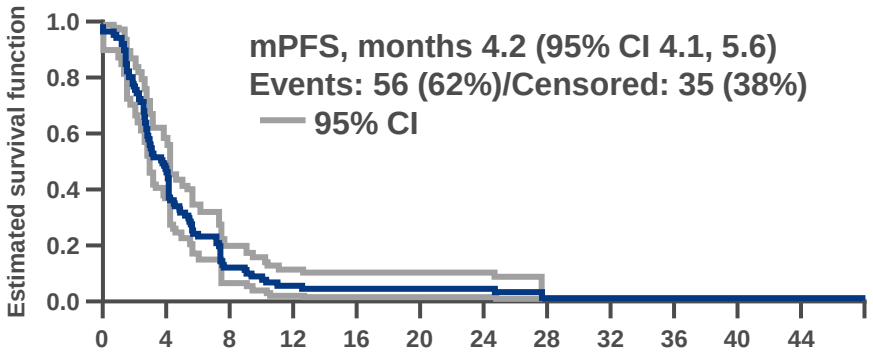


Corcoran RB et al. Ann Oncol 2016; 27 (suppl 6): abstr 455O

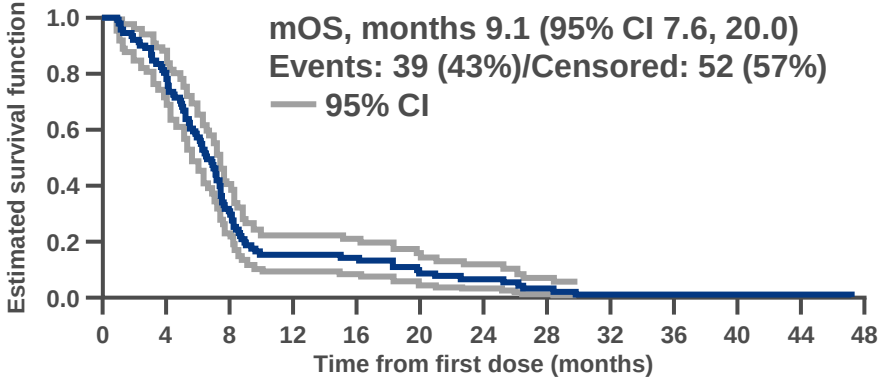
455O: Efficacy and circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E–mutated (BRAFm) metastatic colorectal cancer (mCRC) – Corcoran et al

Key results (continued)

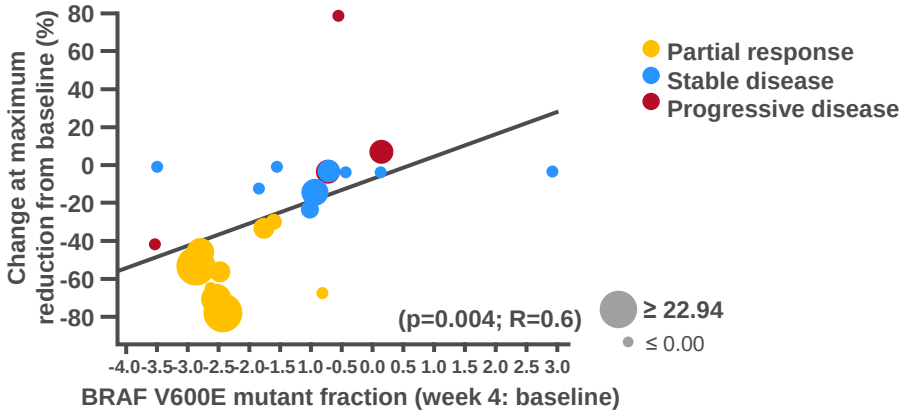
Kaplan-Meier PFS for D + T + P Arm

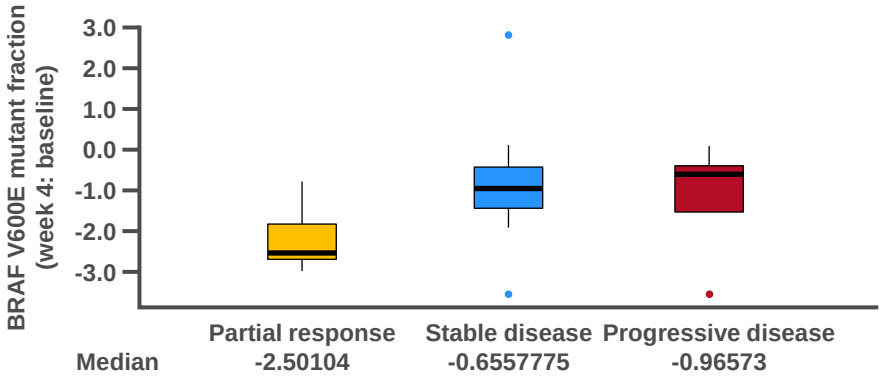


Kaplan-Meier OS for D + T + P Arm



ctDNA tracking response: BRAF V600 mutant fraction burden





Corcoran RB et al. Ann Oncol 2016; 27 (suppl 6): abstr 455O

455O: Efficacy and circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E–mutated (BRAFm) metastatic colorectal cancer (mCRC) – Corcoran et al

Key results (continued)

- ctDNA analysis showed emergence of RAS mutations at disease progression in 9 of 22 (41%) patients
  - In 3 of these patients, multiple RAS mutations were detectable in ctDNA at progression

Conclusions

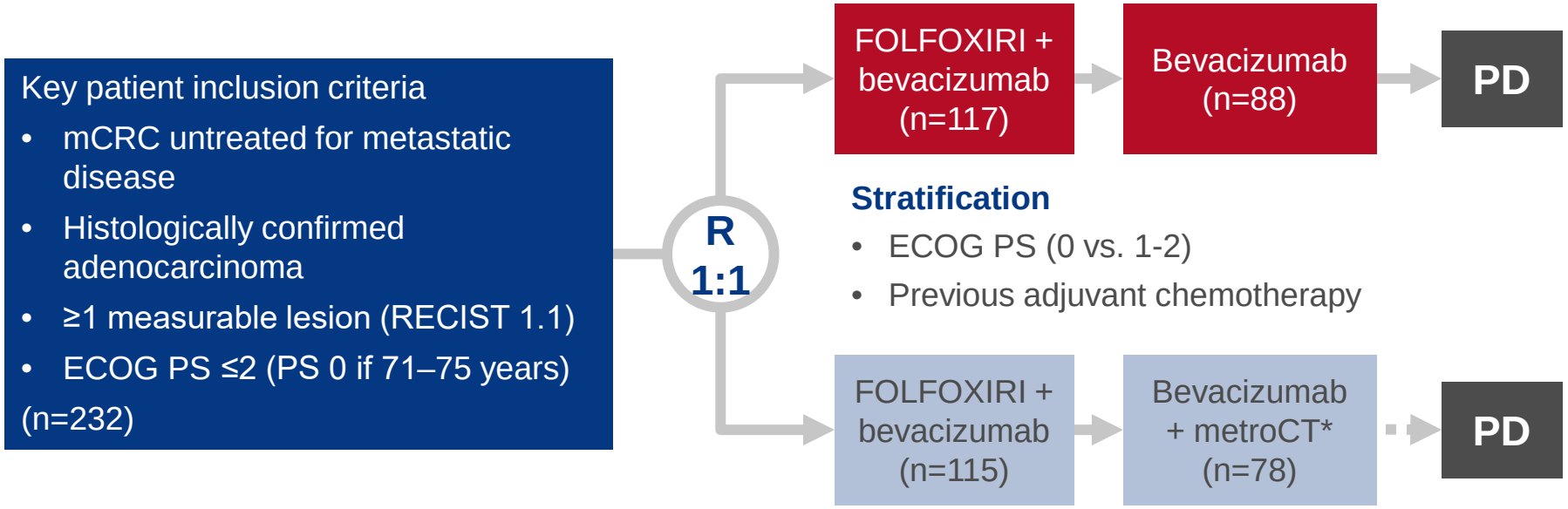
- **D + T + P appeared to be more active than D + T, D + P or T + P in mBRAF mCRC**
- **D + P and D + T + P were tolerable at full dose, but full dose T + P was not tolerable due to dermatologic toxicity**
- **More effective inhibition of MAPK signalling may contribute to increased efficacy of D + P +T**
- **Monitoring mBRAF in ctDNA is feasible and can effectively predict response**

Corcoran RB et al. Ann Oncol 2016; 27 (suppl 6): abstr 455O

LBA21: FOLFOXIRI plus bevacizumab (bev) followed by maintenance with bev alone or bev plus metronomic chemotherapy (metroCT) in metastatic colorectal cancer (mCRC): The phase II randomized MOMA trial – Falcone et al

Study objective

- To evaluate the efficacy of metronomic chemotherapy added to bevacizumab as maintenance therapy after 4 months induction with FOLFOXIRI + bevacizumab



PRIMARY ENDPOINT

- PFS

SECONDARY ENDPOINTS

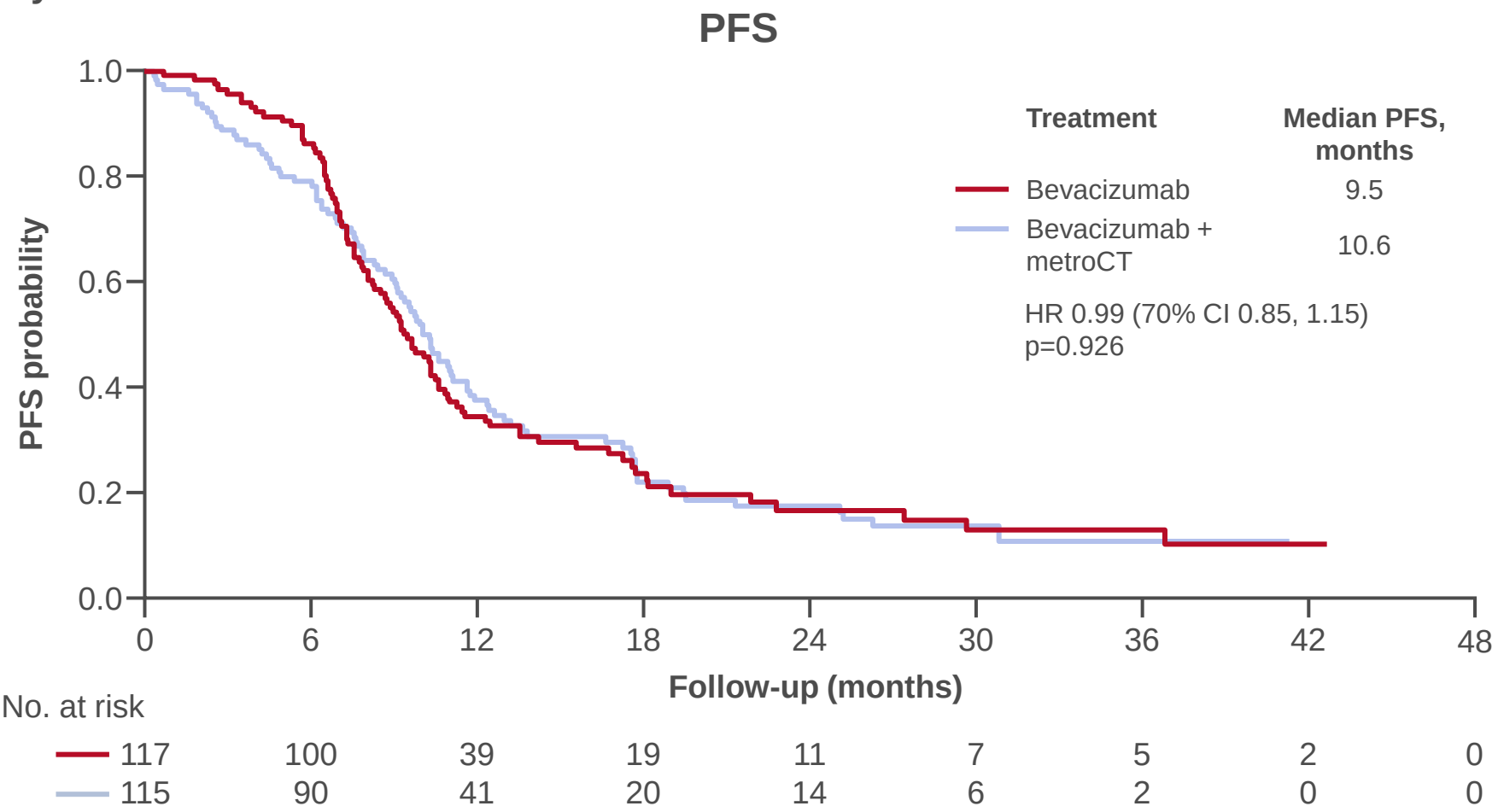
- RR

*Bevacizumab 7.5 mg/kg iv + capecitabine 500 mg tid + cyclophosphamide 50 mg/d; every 21 days

Falcone A et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA21

LBA21: FOLFOXIRI plus bevacizumab (bev) followed by maintenance with bev alone or bev plus metronomic chemotherapy (metroCT) in metastatic colorectal cancer (mCRC): The phase II randomized MOMA trial – Falcone et al

Key results



Falcone A et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA21

LBA21: FOLFOXIRI plus bevacizumab (bev) followed by maintenance with bev alone or bev plus metronomic chemotherapy (metroCT) in metastatic colorectal cancer (mCRC): The phase II randomized MOMA trial – Falcone et al

Key results (continued)

Best response, %	Bevacizumab (n=117)	Bevacizumab + metroCT (n=115)	All (n=232)
CR	4	2	3
PR	64	56	60
RR	68	58	63
SD	26	30	28
DCR	94	88	91
PD	2	5	3
Not assessed	4	7	6

Falcone A et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA21

LBA21: FOLFOXIRI plus bevacizumab (bev) followed by maintenance with bev alone or bev plus metronomic chemotherapy (metroCT) in metastatic colorectal cancer (mCRC): The phase II randomized MOMA trial – Falcone et al

Key results (continued)

Grade 3/4 AEs during induction, %	Bevacizumab (n=116)	Bevacizumab + metroCT (n=115)	All (n=231)
Nausea	2.6	3.5	3.0
Vomiting	0.86	6.1	3.5
Diarrhoea	11.2	15.7	13.4
Stomatitis	3.5	4.4	3.9
Neutropenia	55.0	47.8	51.9
Febrile neutropenia	13.7	8.7	11.2
Hypertension	5.2	1.7	3.5

Grade 3/4 AEs during maintenance, %	Bevacizumab (n=88)	Bevacizumab + metroCT (n=78)
Hand & foot skin reaction	0	7.9
Diarrhoea	0	1.3
Neutropenia	0	4
Hypertension	4.6	2.6
Venous thrombosis	2.3	2.6

Falcone A et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA21

LBA21: FOLFOXIRI plus bevacizumab (bev) followed by maintenance with bev alone or bev plus metronomic chemotherapy (metroCT) in metastatic colorectal cancer (mCRC): The phase II randomized MOMA trial – Falcone et al

Conclusions

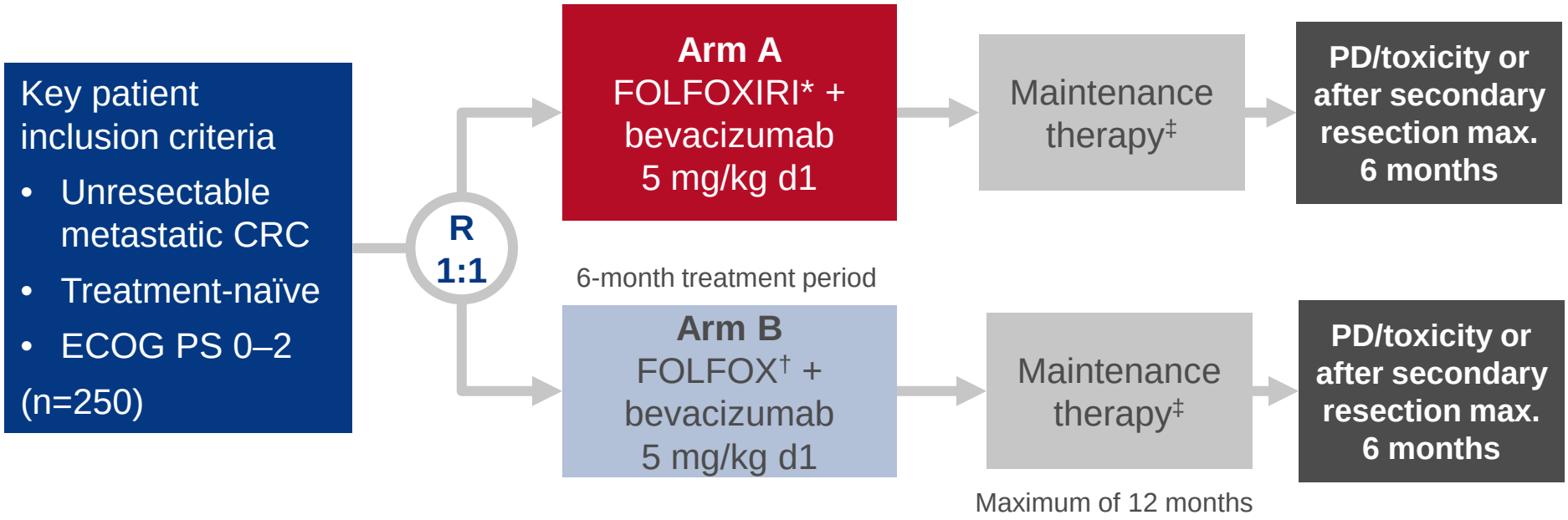
- There was no significant improvement in PFS with the addition of metronomic chemotherapy to maintenance therapy with bevacizumab
- A standard dose of fluoropyrimidine + bevacizumab remains the preferred maintenance after CT + bevacizumab

Falcone A et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA21

LBA22: FOLFOX / Bevacizumab (Beva) +/- Irinotecan in advanced Colorectal Cancer (CRC): A randomized Phase II trial (AIO KRK 0209, CHARTA) – Schmoll et al

Study objective

- To assess the efficacy and safety of FOLFOXIRI + bevacizumab compared with FOLFOX + bevacizumab in patients with advanced colorectal cancer



PRIMARY ENDPOINT

- PFS at 9 months

SECONDARY ENDPOINT

- RR, PFS, OS, secondary resection rate, tolerability, QoL

*Oxaliplatin 85 mg/m^2 + LV 200 mg/m^2 + 5FU 3200 mg/m^2 + irinotecan 165 mg/m^2; †oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + 5-FU 3200 mg/m^2; ‡bevacizumab 5 mg/kg d1 + LV/5FU or bevacizumab 7.5 mg/kg d1 + capecitabine 1600 mg/m^2 d1–14.

Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA22

LBA22: FOLFOX / Bevacizumab (Beva) +/- Irinotecan in advanced Colorectal Cancer (CRC): A randomized Phase II trial (AIO KRK 0209, CHARTA) – Schmoll et al

Key results

	FOLFOXIRI + bevacizumab (n=121)	FOLFOX + bevacizumab (n=121)	p-value
PFS at 9 months, % (95% CI)	68 (48, 66)	56 (60, 7 7)	0.086
CR + PR, % (n + n)	70 (5 + 65)	60 (5 + 55)	0.16
Secondary metastasis resection, %	23	21	
Subgroup analysis (median PFS), months			**HR**
BRAF mutation	10.1	7.8	0.72
RAS mutation	12.3	10.4	0.82
RAS wild-type	13.1	9.6	0.67

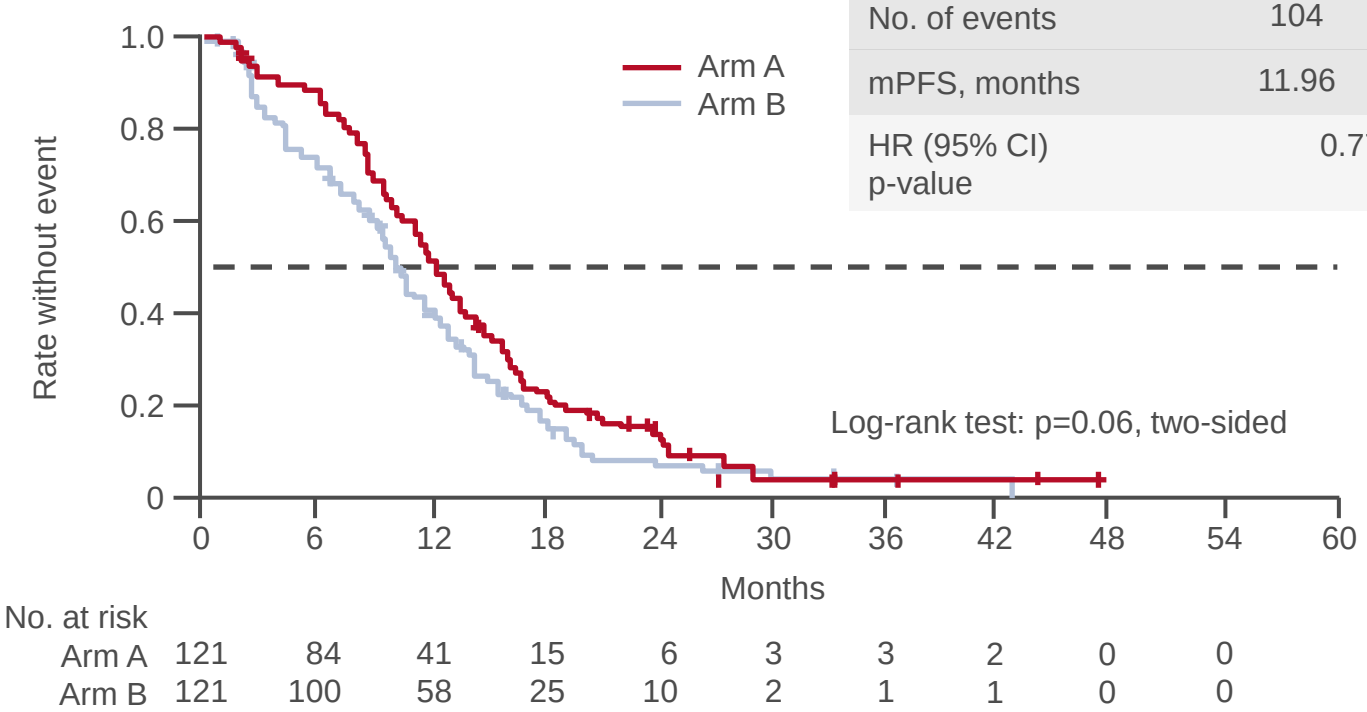
No significant difference was observed in clinical subgroups (Koehne-score & ESMO-groups)

Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA22

LBA22: FOLFOX / Bevacizumab (Beva) +/- Irinotecan in advanced Colorectal Cancer (CRC): A randomized Phase II trial (AIO KRK 0209, CHARTA) – Schmoll et al

Key results (continued)

	FOLFOXIRI + bevacizumab (n=121)	FOLFOX + bevacizumab (n=121)
No. of events	104	107
mPFS, months	11.96	9.76
HR (95% CI) p-value	0.77 (0.59, 1.01) 0.06	



Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA22

LBA22: FOLFOX / Bevacizumab (Beva) +/- Irinotecan in advanced Colorectal Cancer (CRC): A randomized Phase II trial (AIO KRK 0209, CHARTA) – Schmoll et al

Key results (continued)

Grade 3–5 AEs, %	FOLFOXIRI + bevacizumab (n=121)	FOLFOX + bevacizumab (n=121)
Diarrhoea	16	12
Nausea	8	3
Vomiting	3	3
Mucositis	3	3
Neutropenia	20	14
Febrile neutropenia	1	1
Infection	10	12
Hypertension	9	7
Neuropathy	3	4
Pulmonary embolism	2	3
Fatigue/Asthenia	9	3

Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA22

LBA22: FOLFOX / Bevacizumab (Beva) +/- Irinotecan in advanced Colorectal Cancer (CRC): A randomized Phase II trial (AIO KRK 0209, CHARTA) – Schmoll et al

Conclusions

- **The study met its primary endpoint, with significant improvements in PFS noted with FOLFOXIRI + bevacizumab vs. FOLFOX + bevacizumab (statistical consideration alpha 0.1, beta of 0.2) at 9 months**
  - **Improvements, although statistically non-significant, in response rate and PFS with the 4 drug-combination are quite similar to TRIBE/STEAM6**
- **Improvement in RR/PFS is comparable in all clinical and molecular subgroups**
- **The combination is well-tolerated, even in frail and elderly patients**
- **Such findings support the value of 4-drug-regimen for 1L treatment for almost all patients**

Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA22

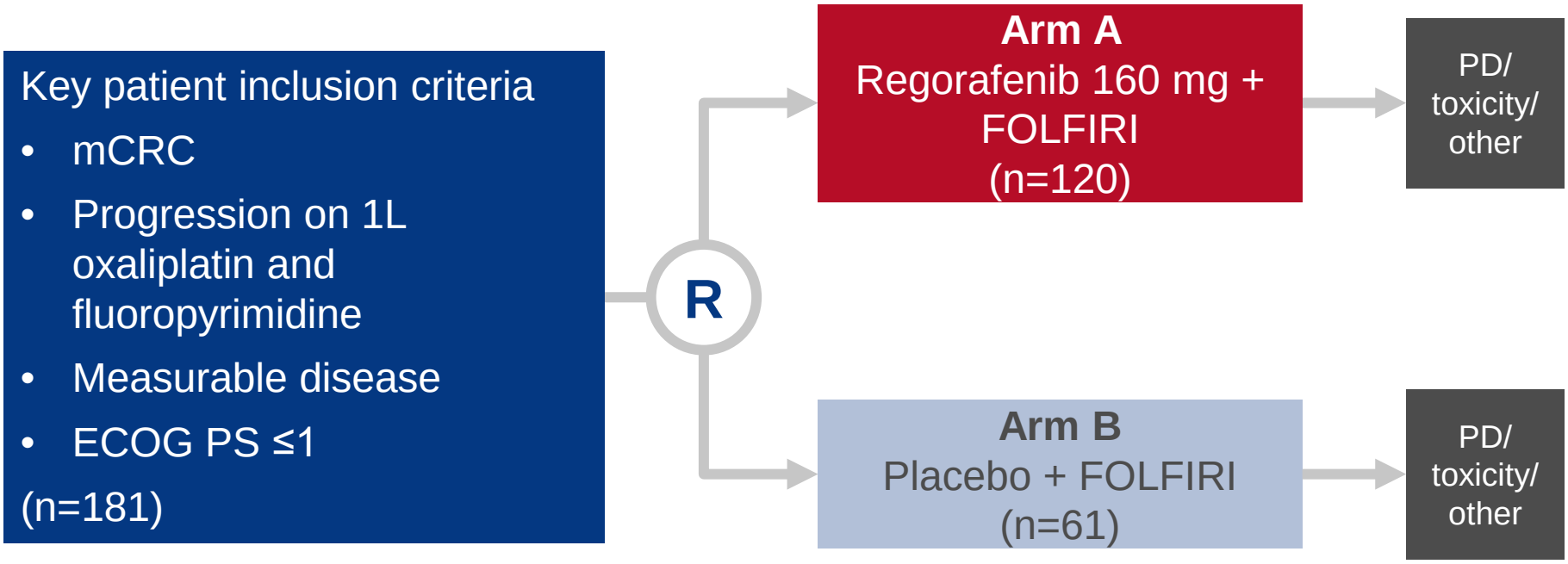
Metastatic Colorectal Cancer

SECOND-LINE THERAPY

464PD: A multi-center, randomized, double-blind phase II trial of FOLFIRI + regorafenib or placebo for patients with metastatic colorectal cancer who failed one prior line of oxaliplatin-containing therapy – O'Neil et al

Study objective

- To assess the efficacy of 2L FOLFIRI ± regorafenib administered on an intermittent dosing strategy (week on, week off) in patients with mCRC



PRIMARY ENDPOINT(S)

- PFS

SECONDARY ENDPOINTS

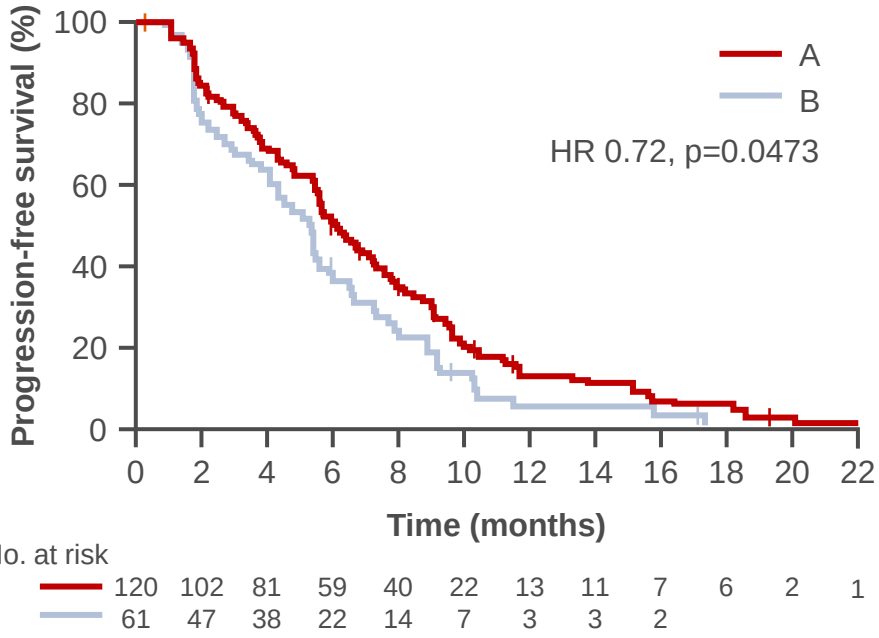
- RR (CR + PR), OS

O'Neil B et al. Ann Oncol 2016; 27 (suppl 6): abstr 464PD

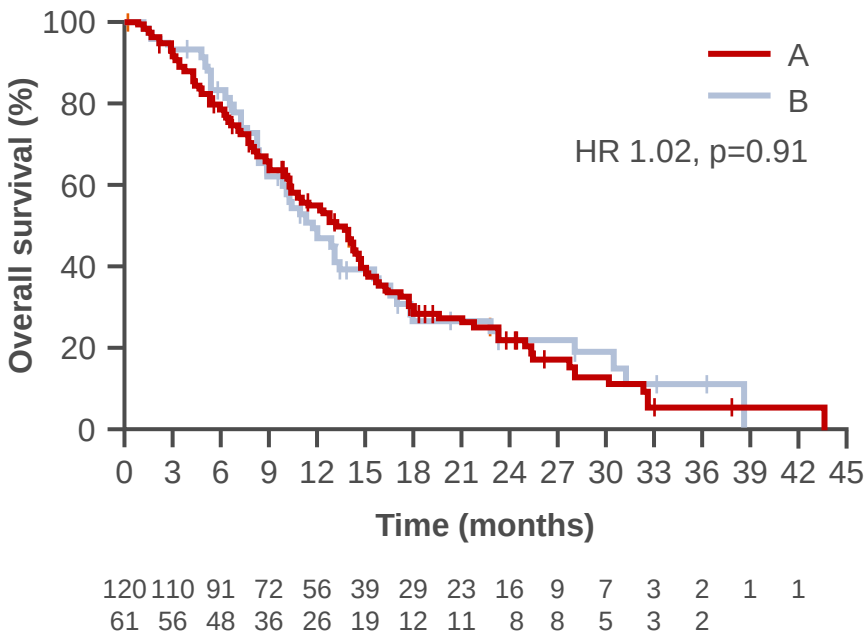
464PD: A multi-center, randomized, double-blind phase II trial of FOLFIRI + regorafenib or placebo for patients with metastatic colorectal cancer who failed one prior line of oxaliplatin-containing therapy – O'Neil et al

Key results

Progression-free survival



Overall survival



- mPFS was 6.5 and 5.3 months for regorafenib + FOLFIRI and placebo + FOLFIRI, respectively
- mOS was 13.8 vs. 11.7 months, respectively (p=NS)

O'Neil B et al. Ann Oncol 2016; 27 (suppl 6): abstr 464PD

464PD: A multi-center, randomized, double-blind phase II trial of FOLFIRI + regorafenib or placebo for patients with metastatic colorectal cancer who failed one prior line of oxaliplatin-containing therapy – O'Neil et al

Key results (continued)

Grade ≥3 AE, n (%)	Regorafenib	Placebo
Neutropenia	49 (41)	18 (30)
Diarrhoea	18 (15)	3 (5)
Hypophosphatemia	17 (14)	0 (0)
Fatigue	13 (11)	4 (7)
Febrile neutropenia	11 (9)	2 (3)
Mucositis oral	11 (9)	6 (10)
White blood cell decreased	11 (9)	7 (11)
Hypertension	10 (8)	1 (2)
Lipase increased	10 (8)	3 (5)
Dehydration	7 (6)	2 (3)
Hypokalaemia	7 (6)	1 (2)
Anorexia	6 (5)	0 (0)

O'Neil B et al. Ann Oncol 2016; 27 (suppl 6): abstr 464PD

464PD: A multi-center, randomized, double-blind phase II trial of FOLFIRI + regorafenib or placebo for patients with metastatic colorectal cancer who failed one prior line of oxaliplatin-containing therapy – O'Neil et al

Conclusions

- **Compared with FOLFIRI alone, combination therapy of regorafenib with FOLFIRI prolonged PFS (HR 0.72)**
  - **Similar results have been observed with other inhibitors of the VEGF/VEGFR axis in larger studies**
- **Regorafenib + FOLFIRI did not prolong OS**
  - **This could be due to a variety of reasons, including subsequent therapies or crossover (currently under investigation)**
- **Regorafenib + FOLFIRI combination was well tolerated**
- **In a sub-population of this study, PK interaction between regorafenib and irinotecan will be explored**
- **An extensive biomarker programme including pharmacogenetic markers of toxicity has now been initiated. In addition, the programme will also investigate potential markers of response**

O'Neil B et al. Ann Oncol 2016; 27 (suppl 6): abstr 464PD

Metastatic Colorectal Cancer

SALVAGE THERAPY

LBA20_PR: Nintedanib plus best supportive care (BSC) versus placebo plus BSC for the treatment of patients (pts) with colorectal cancer (CRC) refractory to standard therapies: Results of the phase III LUME-colon 1 study – Van Cutsem et al

Study objective

- To evaluate the efficacy and safety of nintedanib (an oral angiokinase inhibitor) in patients with mCRC after failure of standard therapies

Key patient inclusion criteria

- Metastatic or locally advanced CRC not amenable to surgery/radiotherapy
- Progression or toxicity to standard treatments*
- ECOG PS ≤1
- Age ≥18 years

(n=764)

Nintedanib 200 mg bid + BSC (n=386) → PD/ toxicity/ other

Placebo + BSC (n=382) → PD/ toxicity/ other

Stratification

- Previous treatment with regorafenib
- Time from onset of metastatic disease until randomisation
- Region

PRIMARY ENDPOINTS

- OS and PFS (central review)

SECONDARY ENDPOINTS

- ORR and DCR (central review)

*Oxaliplatin, irinotecan, fluoropyrimidines, anti-VEGF (bevacizumab or aflibercept) and anti-EGFR (cetuximab or panitumumab) in RAS wt

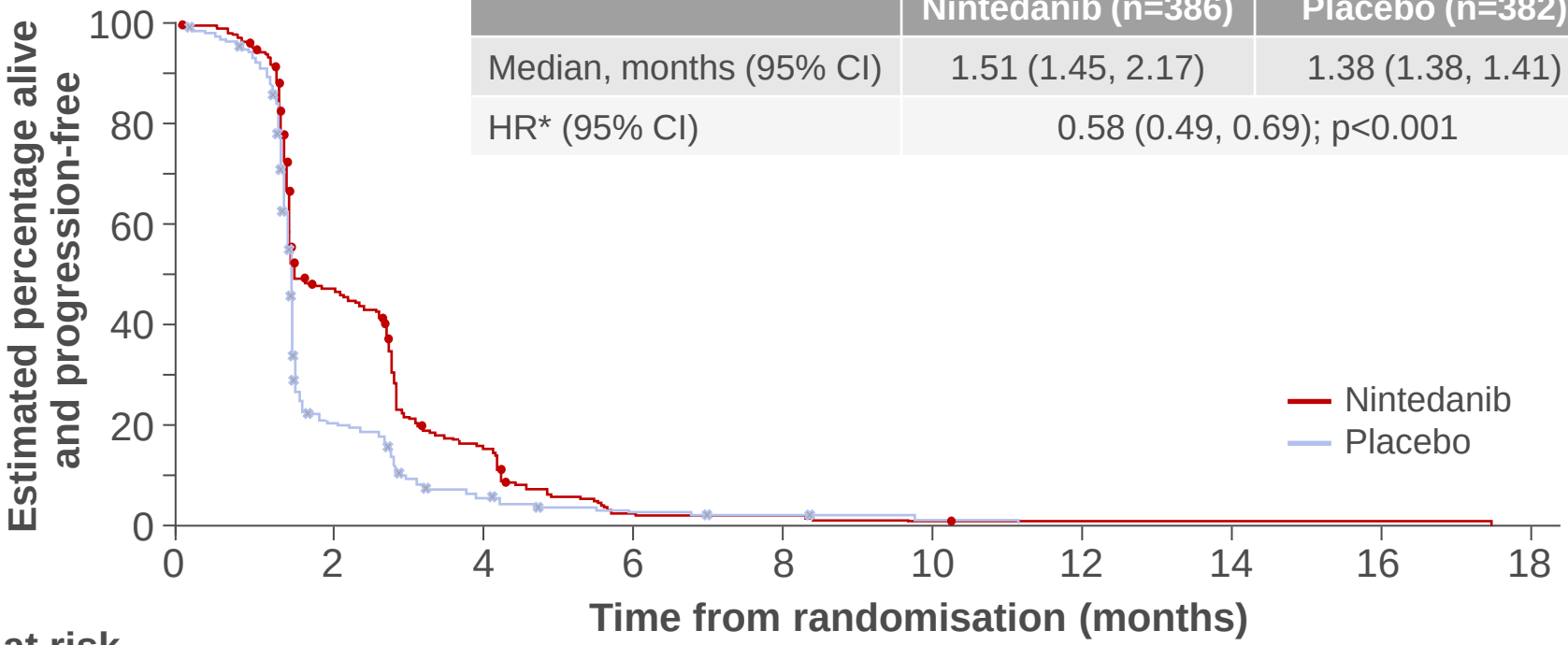
Van Cutsem E et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA20_PR

LBA20_PR: Nintedanib plus best supportive care (BSC) versus placebo plus BSC for the treatment of patients (pts) with colorectal cancer (CRC) refractory to standard therapies: Results of the phase III LUME-colon 1 study – Van Cutsem et al

Key results

Co-primary endpoint: PFS by central review

	Nintedanib (n=386)	Placebo (n=382)
Median, months (95% CI)	1.51 (1.45, 2.17)	1.38 (1.38, 1.41)
HR* (95% CI)	0.58 (0.49, 0.69); p<0.001	



No. at risk

Nintedanib	386	162	51	6	5	2	1	1	1	0
Placebo	382	63	15	6	3	1	0			

*Stratified by previous treatment with regorafenib, time from onset of metastatic disease until randomisation, and region

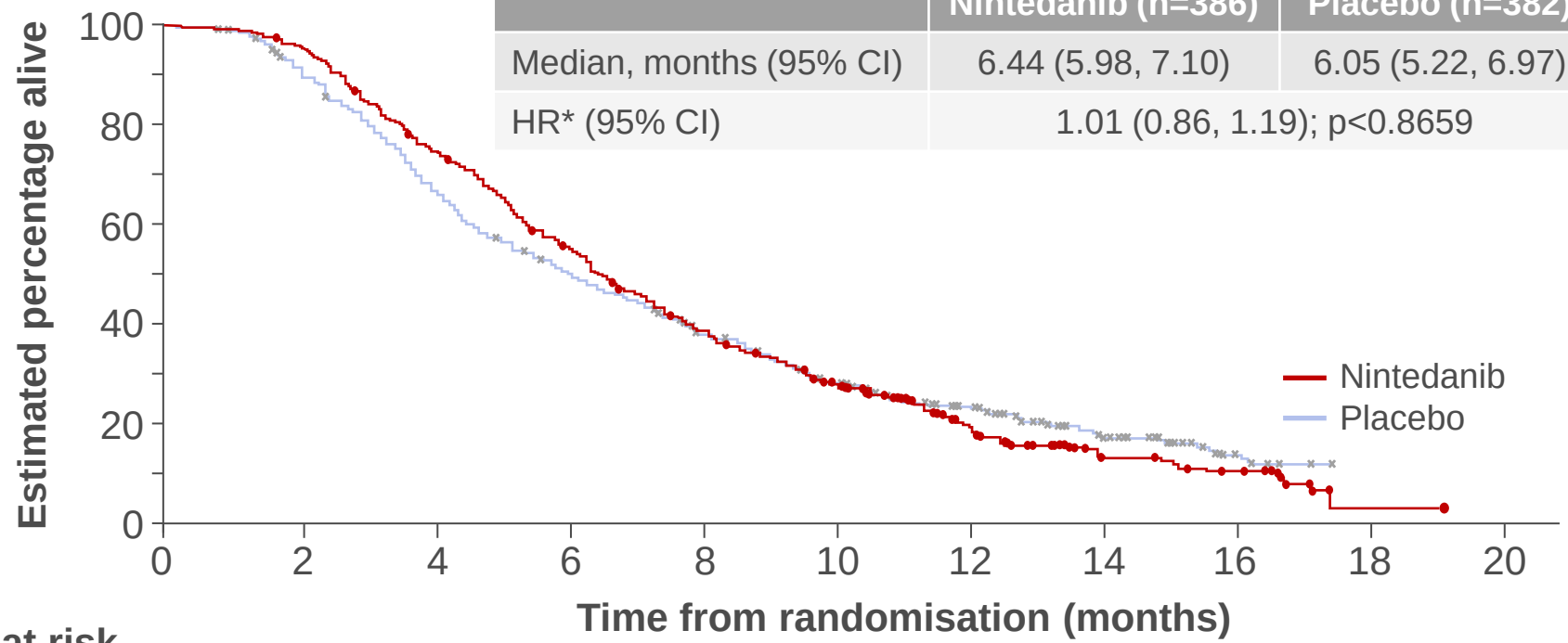
Van Cutsem E et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA20_PR

LBA20_PR: Nintedanib plus best supportive care (BSC) versus placebo plus BSC for the treatment of patients (pts) with colorectal cancer (CRC) refractory to standard therapies: Results of the phase III LUME-colon 1 study – Van Cutsem et al

Key results (continued)

Co-primary endpoint: OS

	Nintedanib (n=386)	Placebo (n=382)
Median, months (95% CI)	6.44 (5.98, 7.10)	6.05 (5.22, 6.97)
HR* (95% CI)	1.01 (0.86, 1.19); p<0.8659	



No. at risk

Nintedanib	386	365	283	207	143	95	49	24	13	1	0
Placebo	382	337	247	184	135	96	58	29	7	0	

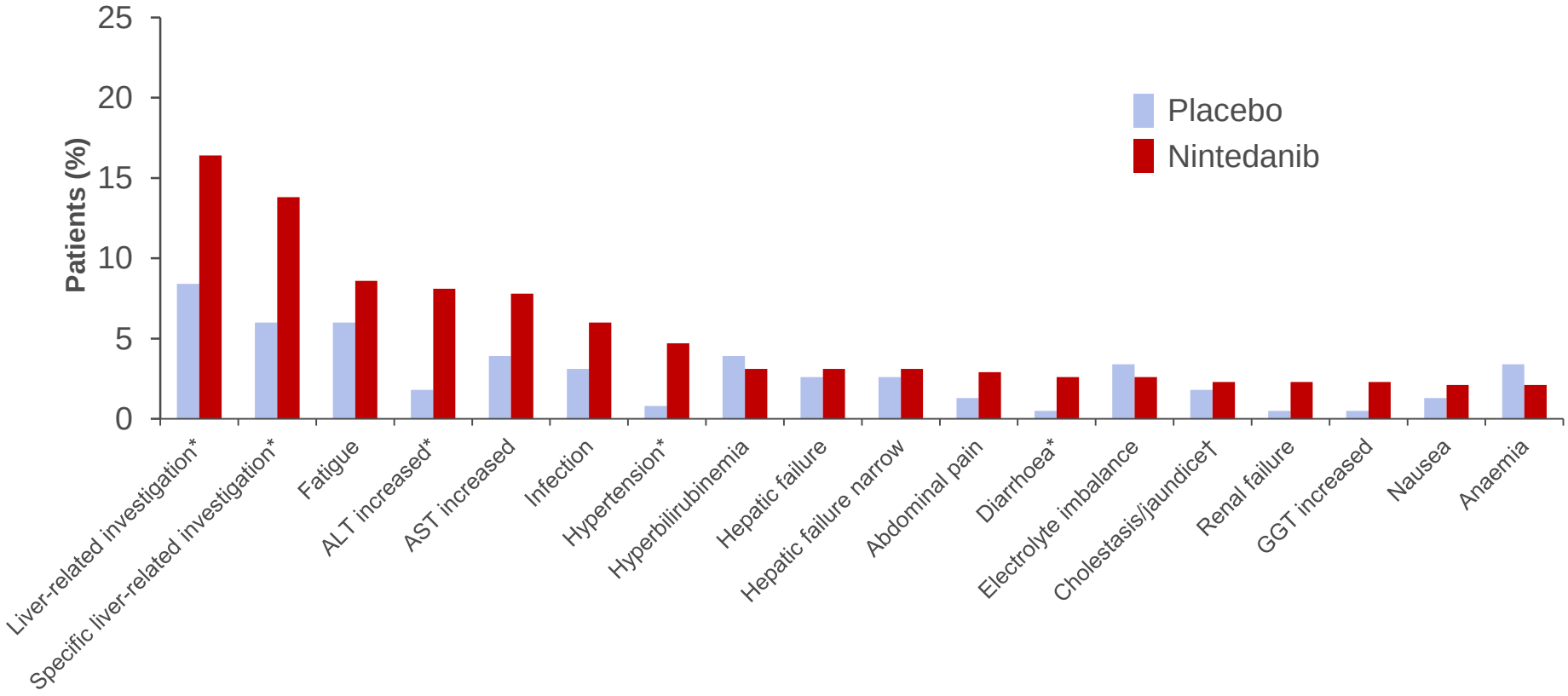
*Stratified by previous treatment with regorafenib, time from onset of metastatic disease until randomisation, and region

Van Cutsem E et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA20_PR

LBA20_PR: Nintedanib plus best supportive care (BSC) versus placebo plus BSC for the treatment of patients (pts) with colorectal cancer (CRC) refractory to standard therapies: Results of the phase III LUME-colon 1 study – Van Cutsem et al

Key results (continued)

Grade ≥3 AEs (incidence ≥2% in nintedanib arm)



AEs by user-defined category using US National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
*Relevant difference based on the 95% CI for the incidence rate ratios and incidence rate difference; †Hepatic origin

Van Cutsem E et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA20_PR

LBA20_PR: Nintedanib plus best supportive care (BSC) versus placebo plus BSC for the treatment of patients (pts) with colorectal cancer (CRC) refractory to standard therapies: Results of the phase III LUME-colon 1 study – Van Cutsem et al

Conclusions

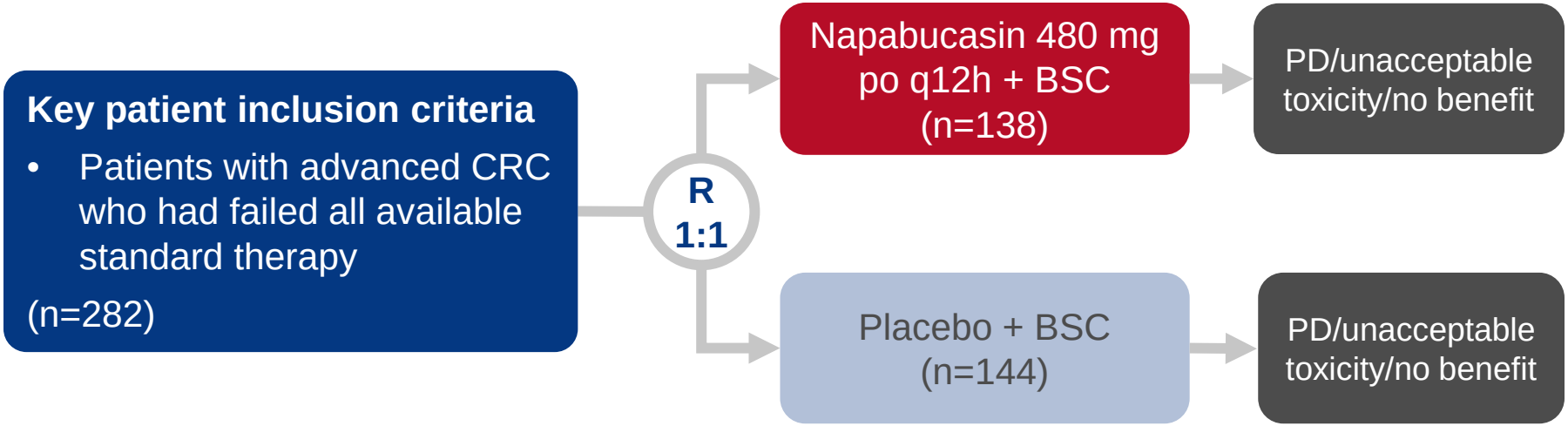
- Nintedanib demonstrated clinical activity in patients with refractory mCRC
  - The co-primary endpoint of PFS was met (HR 0.58 [0.49, 0.69]; p<0.0001); however, that of OS was unmet (HR 1.01 [0.86, 1.19]; p=0.8659)
  - A significant improvement in disease control was observed following treatment with nintedanib (OR 3.0 [2.0, 4.5]; p<0.0001)
- Further study is being carried out to investigate the effect of nintedanib on OS; lack of improved OS as a result of nintedanib therapy may be associated with post-study therapies
- Nintedanib was well tolerated
- Results of patient QoL and biomarker analyses will be presented separately

Van Cutsem E et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA20_PR

454O: A randomized phase III study of napabucasin [BBI608] (NAPA) vs placebo (PBO) in patients (pts) with pretreated advanced colorectal cancer (ACRC): The CCTG/AGITG CO.23 trial – Jonker et al

Study objective

- To assess the efficacy of napabucasin (BBI608; a cancer stemness inhibitor that targets STAT3) vs. placebo in patients with pre-treated advanced CRC in a randomised phase 2 trial



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- Pre-specified biomarker analyses

Note: Based on data from abstract only

Jonker DJ et al. Ann Oncol 2016; 27 (suppl 6): abstr 454O

454O: A randomized phase III study of napabucasin [BBI608] (NAPA) vs placebo (PBO) in patients (pts) with pretreated advanced colorectal cancer (ACRC): The CCTG/AGITG CO.23 trial – Jonker et al

Key results

- No significant differences were observed between napabucasin and placebo for OS, PFS or DCR
- pSTAT3 positivity was a poor prognostic factor in patients receiving placebo
  - mOS 3.0 vs. 4.9 months (HR 2.3 [95% CI 1.5, 3.6]; p=0.0002)
- Napabucasin improved OS in patients who were pSTAT3 positive (HR 0.24)

mOS, months (95% CI)	Napabucasin	Placebo	HR (95% CI); p-value
ITT			
All patients (n=282)	4.4	4.8	1.13 (0.88, 1.46); 0.34
pSTAT3+ (n=55)	5.1	3.0	0.24 (0.12, 0.51); 0.0002
pSTAT3 − (n=196)	4.0	4.9	1.44 (1.06, 1.95); 0.02
Adjusted interaction			0.28 (0.14, 0.55); <0.0001
Pre-defined minimum effective treatment			
All patients (n=128)	6.6	5.8	0.88 (0.61, 1.28); 0.50
pSTAT3+ (n=25)	9.0	4.0	0.28 (0.11, 0.69); 0.0057
pSTAT3 − (n=88)	6.4	6.4	1.27 (0.80, 2.01); 0.32
Adjusted interaction			0.22 (0.08, 0.61); 0.0038

Note: Based on data from abstract only

Jonker DJ et al. Ann Oncol 2016; 27 (suppl 6): abstr 454O

454O: A randomized phase III study of napabucasin [BBI608] (NAPA) vs placebo (PBO) in patients (pts) with pretreated advanced colorectal cancer (ACRC): The CCTG/AGITG CO.23 trial – Jonker et al

Key results (continued)

AE more frequent with napabucasin, %	Napabucasin	Placebo	p-value
Any grade AEs			
Diarrhoea	88	32	<0.05
Nausea	63	47	<0.05
Anorexia	56	46	<0.05
Grade ≥3 AEs			
Any	57	40	<0.01
Diarrhoea	17	1	<0.01

Note: Based on data from abstract only

Jonker DJ et al. Ann Oncol 2016; 27 (suppl 6): abstr 454O

454O: A randomized phase III study of napabucasin [BBI608] (NAPA) vs placebo (PBO) in patients (pts) with pretreated advanced colorectal cancer (ACRC): The CCTG/AGITG CO.23 trial – Jonker et al

Conclusions

- Napabucasin monotherapy did not improve OS or PFS in unselected patients with advanced CRC
- pSTAT3 positivity could be a marker of poor prognosis in patients receiving placebo + BSC
- Significant improvement in OS was observed in pSTAT3-positive patients receiving napabucasin

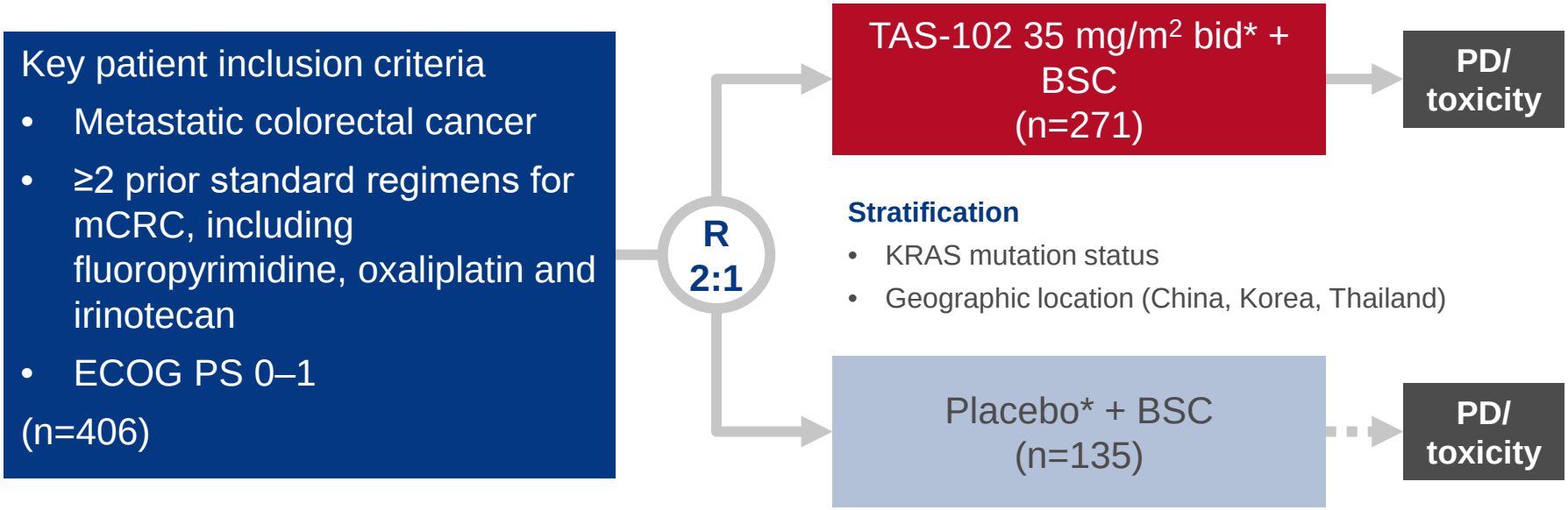
Note: Based on data from abstract only

Jonker DJ et al. Ann Oncol 2016; 27 (suppl 6): abstr 454O

465PD: TERRA: A randomized, double-blind, placebo-controlled phase 3 study of TAS-102 in Asian patients with metastatic colorectal cancer – Kim et al

Study objective

- To evaluate the efficacy and safety trifluridine/tipiracil (TAS-102) in Asian patients with mCRC who had failed conventional cytotoxic therapies



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

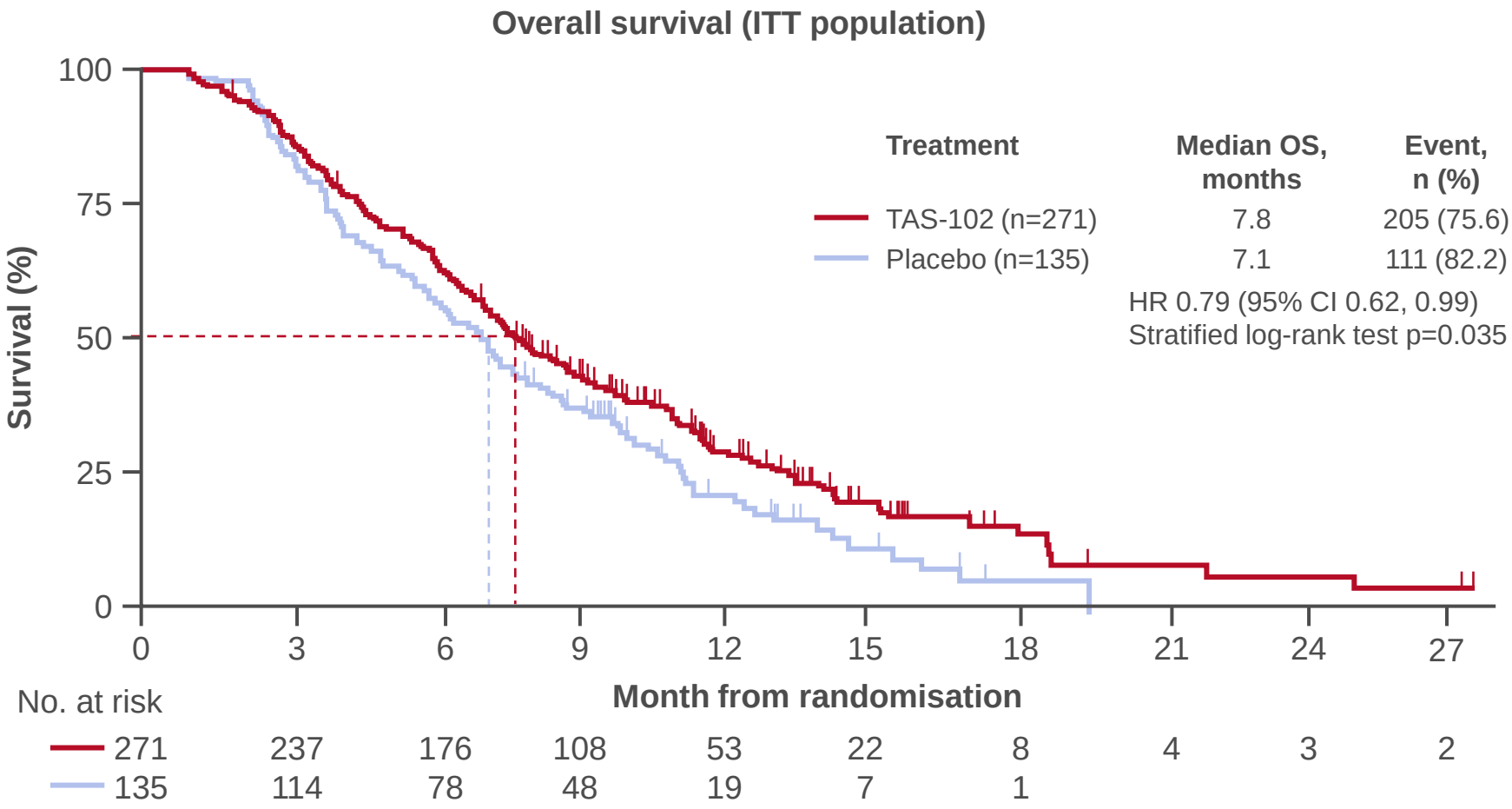
- PFS, safety, ORR, DCR, DoR, TTF

*Administered po on d1–5 and 8–12 q4w.

Kim T et al. Ann Oncol 2016; 27 (suppl 6): abstr 465PD

465PD: TERRA: A randomized, double-blind, placebo-controlled phase 3 study of TAS-102 in Asian patients with metastatic colorectal cancer – Kim et al

Key results



Kim T et al. Ann Oncol 2016; 27 (suppl 6): abstr 465PD

465PD: TERRA: A randomized, double-blind, placebo-controlled phase 3 study of TAS-102 in Asian patients with metastatic colorectal cancer – Kim et al

Conclusions

- In East-Asian patients with mCRC who were refractory or intolerant to previous treatments TAS-102 statistically significantly prolonged OS and PFS
- No new safety concerns were reported for TAS-102
- These results indicate that TAS-102 may be an alternative treatment option for East-Asian patients with mCRC who were refractory or intolerant to previous treatments

Kim T et al. Ann Oncol 2016; 27 (suppl 6): abstr 465PD

466PD: Sorafenib (Soraf) and irinotecan (Iri) combination for pretreated RAS-mutated metastatic colorectal cancer (mCRC) patients: A multicentre randomized phase II trial (NEXIRI 2-PRODIGE 27) – Samalin et al

Study objective

- To determine the 2-month PFS rate (2-PFS) of NEXIRI vs. irinotecan or sorafenib monotherapy in RAS-mutant mCRC patients after the failure of all approved active drugs

Key patient inclusion criteria

- CRC/mCRC with unresectable measurable lesions
- PD after failure of all approved active drugs
- KRAS mutated status
- WHO PS ≤1
- Bilirubin ≤1.5 ULN

(n=173)

R 1:1

NEXIRI
Irinotecan 120 mg/m^2 cycle 1, 150 mg/m^2 cycle 2, 180 mg/m^2 cycle 3 if diarrhoea grade <1, iv 90 min d1=15 + **Sorafenib** 400 mg x 2/d d1=d28

Irinotecan 180 mg/m^2 iv 90 min d1=d15

Sorafenib 400 mg x 2/d d1=d28

Progression/ toxicity

NEXIRI

PRIMARY ENDPOINT

- 2-PFS (RECIST v1.1)

SECONDARY ENDPOINTS

- DCR, RR, toxicity (NCI-CTC v4.0), PFS, OS, QoL

Samalin E et al. Ann Oncol 2016; 27 (suppl 6): abstr 466PD

466PD: Sorafenib (Soraf) and irinotecan (Iri) combination for pretreated RAS-mutated metastatic colorectal cancer (mCRC) patients: A multicentre randomized phase II trial (NEXIRI 2-PRODIGE 27) – Samalin et al

Key results

	NEXIRI (n=51)*	Irinotecan (n=52)*	Sorafenib (n=49)*	Crossover† (n=57)*
2-PFS rate, % (95% CI)	59 (39, 66)	23 (10, 33)	22 (8, 30)	51 (30, 54)
PR, n (%)	2 (4)	1 (2)	0 (0)	1 (2)
SD, n (%)	28 (55)	12 (23)	11 (22)	28 (49)
Disease control, n (%)	30 (59)	13 (25)	11 (22)	29 (51)
	NEXIRI (n=59)	**Irinotecan (n=57)**	**Sorafenib (n=57)**	**Crossover (n=69)**
Median PFS (range)	3.7 (2.2–4.9)	1.9 (1.7–2.1)	2.1 (1.9–2.5)	3.5 (2.1–3.7)

*Non-evaluable patients: NEXIRI: 6; irinotecan: 4; sorafenib: 8; crossover: 12

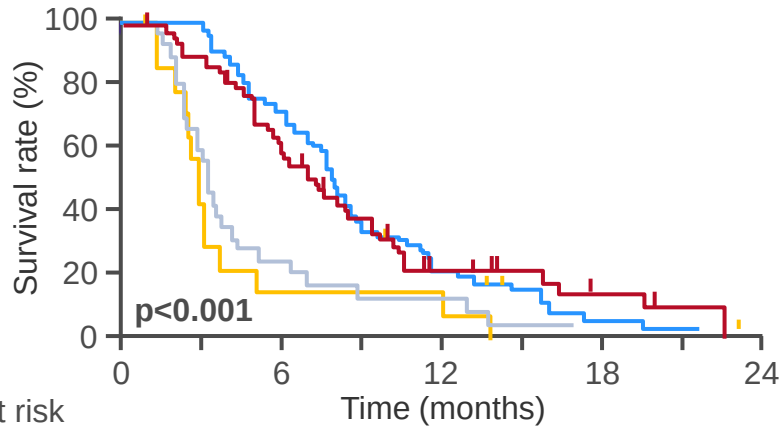
†Crossover patients – who crossed over to NEXIRI therapy due to PD on monotherapy

Samalin E et al. Ann Oncol 2016; 27 (suppl 6): abstr 466PD

466PD: Sorafenib (Soraf) and irinotecan (Iri) combination for pretreated RAS-mutated metastatic colorectal cancer (mCRC) patients: A multicentre randomized phase II trial (NEXIRI 2-PRODIGE 27) – Samalin et al

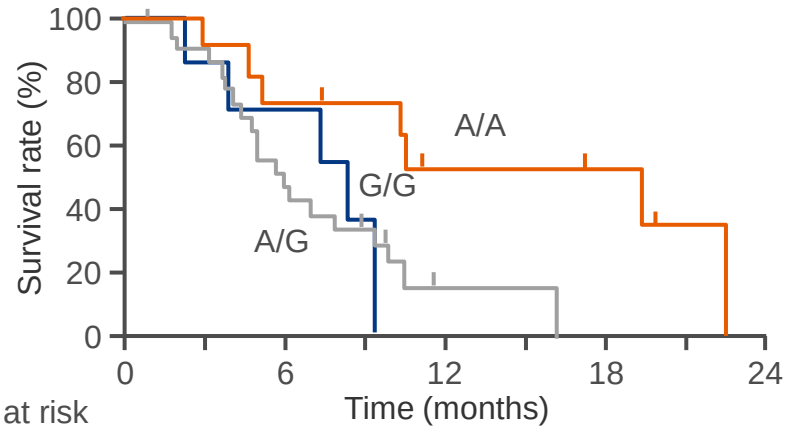
Key results (continued)

Overall survival according to treatment



No. at risk				
A	56	32	6	3
B	14	2	2	0
C	30	7	3	0
D	68	49	12	2

Overall survival according to CCND1* genotype



No. at risk					
CCND1 = A/A	12	8	4	3	0
CCND1 = A/G	25	12	1	0	0
CCND1 = G/G	7	5	0	0	0

A (NEXIRI)	B (Irinotecan)	C (Sorafenib)	D (Crossover)
7.2 (5.8, 9.4)	3 (2.1, 3.8)	3.3 (2.5, 4.2)	7.9 (7.1, 8.7)

Months (95% CI)	A/A	A/G + G/G
NEXIRI	19.6 (4.8, N/A)	6.2 (4.9, 9.4)
Sorafenib	3.0 (2.3, N/A)	3.3 (1.5, 4.4)

*CCND1 is the gene for cyclin-D1.

Samalin E et al. Ann Oncol 2016; 27 (suppl 6): abstr 466PD

466PD: Sorafenib (Soraf) and irinotecan (Iri) combination for pretreated RAS-mutated metastatic colorectal cancer (mCRC) patients: A multicentre randomized phase II trial (NEXIRI 2-PRODIGE 27) – Samalin et al

Key results (continued)

- All listed AEs are grade 3, unless otherwise indicated

	NEXIRI (n=57)	Irinotecan (n=56)	Sorafenib (n=57)	Crossover (n=69)
Diarrhoea	15 (26.3)	4 (7.1)	4 (7)	15 (21.7)
Hand-foot syndrome	11 (19.3)	0 (0)	9 (15.8)	6 (8.7)
Haematological AEs				
Neutropenia (grade 3)	9 (15.8)	3 (5.5)	0 (0)	1 (1.4)
Neutropenia (grade 4)	1 (1.8)	0 (0)	0 (0)	0 (0)
Febrile neutropenia	3 (5.3)	0 (0)	0 (0)	0 (0)
Anaemia	1 (1.8)	2 (3.6)	0 (0)	3 (4.3)
Thrombocytopenia	1 (1.8)	1 (1.8)	0 (0)	1 (1.4)

Samalin E et al. Ann Oncol 2016; 27 (suppl 6): abstr 466PD

466PD: Sorafenib (Soraf) and irinotecan (Iri) combination for pretreated RAS-mutated metastatic colorectal cancer (mCRC) patients: A multicentre randomized phase II trial (NEXIRI 2-PRODIGE 27) – Samalin et al

Conclusions

- **NEXIRI therapy was shown to be effective for refractory RAS-mutant mCRC patients**
- **CCND1 rs9344 status may be of use as a predictive factor for treatment response in patients on NEXIRI**
- **These results justify comparing NEXIRI to regorafenib monotherapy in a CCND1 rs9344 A/A patient subgroup**

Samalin E et al. Ann Oncol 2016; 27 (suppl 6): abstr 466PD

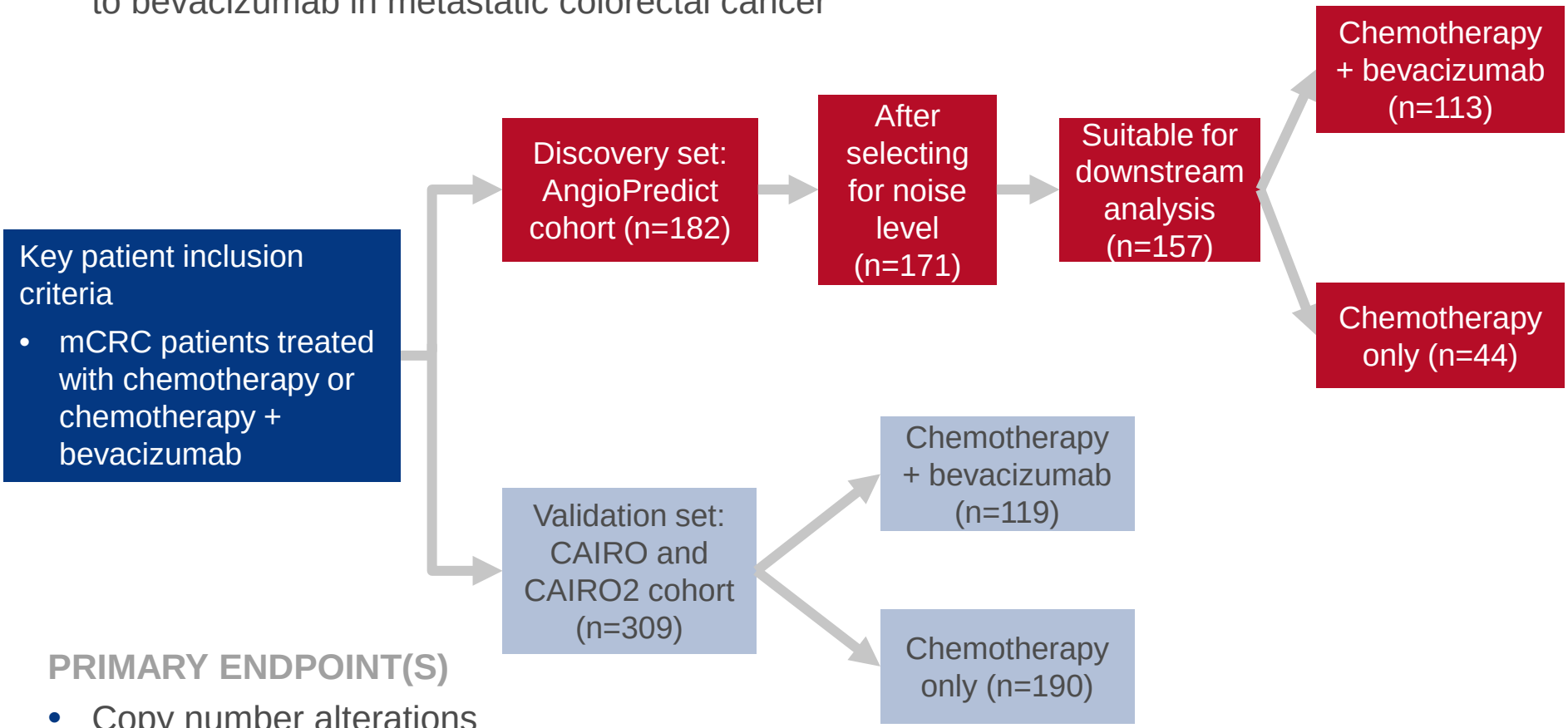
Metastatic Colorectal Cancer

SCREENING, BIOMARKERS, PROGNOSTIC MARKERS AND SURVEILLANCE

53PD: Copy number alterations as predictive biomarkers for response to bevacizumab in metastatic colorectal cancer – Van Grieken et al

Study objective

- To identify copy number alterations that could serve as predictive biomarkers of response to bevacizumab in metastatic colorectal cancer



PRIMARY ENDPOINT(S)

- Copy number alterations

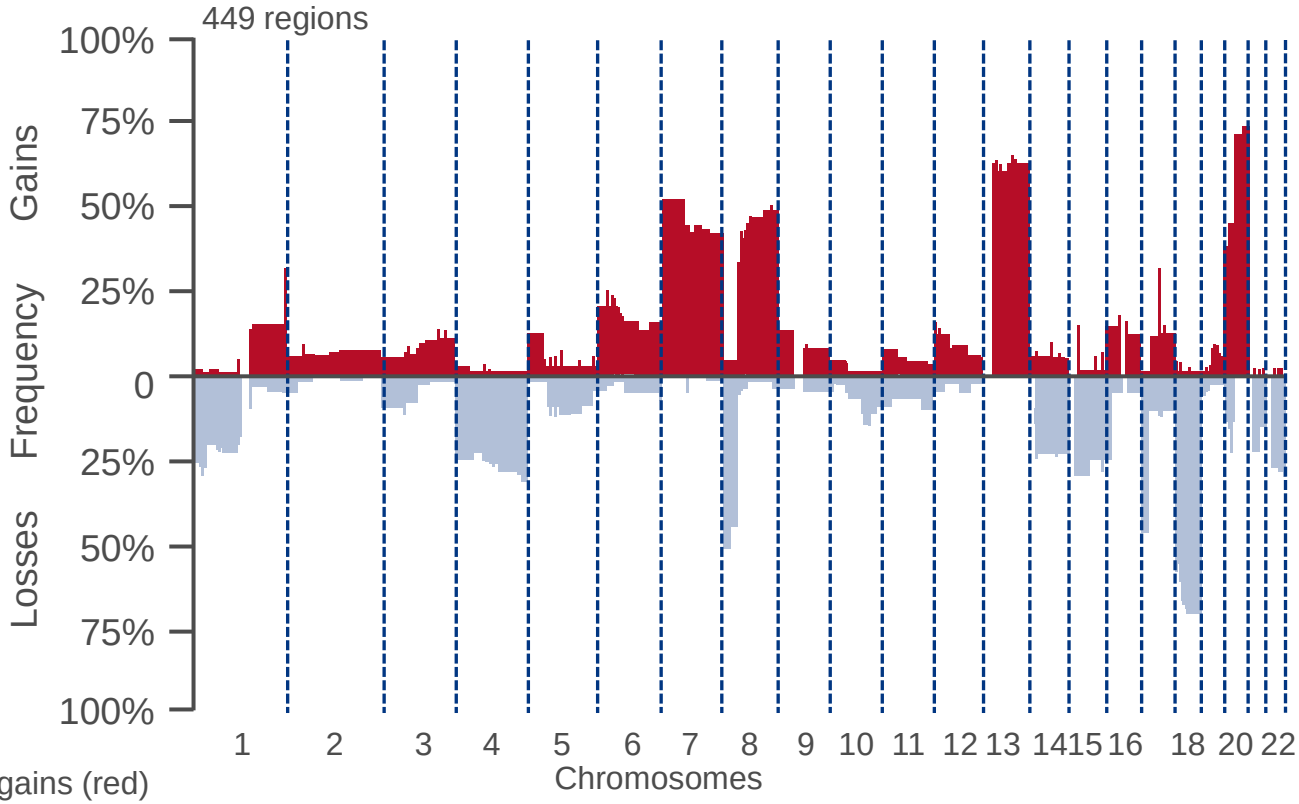
Van Grieken NC et al. Ann Oncol 2016; 27 (suppl 6): abstr 53PD

53PD: Copy number alterations as predictive biomarkers for response to bevacizumab in metastatic colorectal cancer – Van Grieken et al

Key results

- **Discovery set**
  - Median PFS: 217 days. The frequency of copy number alterations observed in this cohort was similar to that reported in the literature

All AngioPredict cohort patients (n=157)



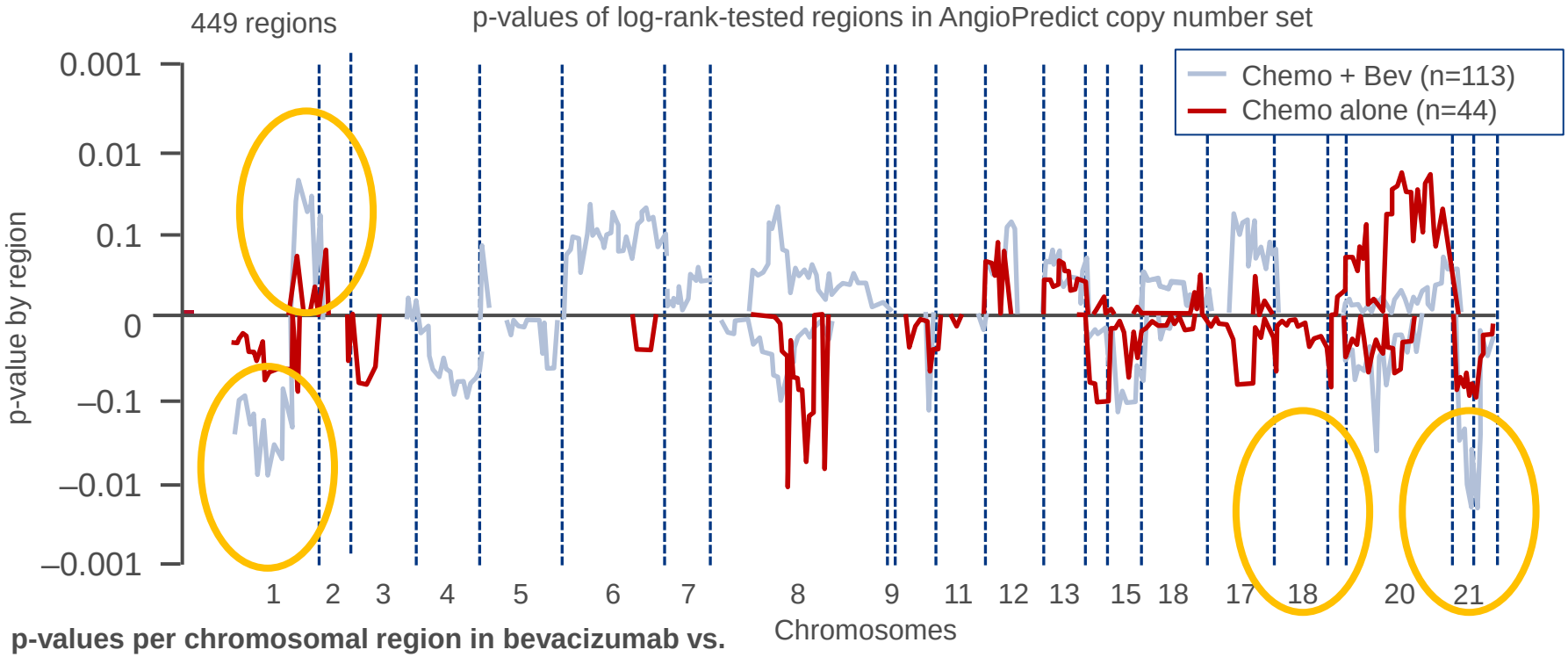
Copy number gains (red) and losses (blue)

Van Grieken NC et al. Ann Oncol 2016; 27 (suppl 6): abstr 53PD

53PD: Copy number alterations as predictive biomarkers for response to bevacizumab in metastatic colorectal cancer – Van Grieken et al

Key results (continued)

- **Discovery set**
  - Significant associations were observed between copy number alterations and PFS in patients receiving bevacizumab + chemotherapy (p=0.002)
  - No association was observed in patients receiving chemotherapy only



p-values per chromosomal region in bevacizumab vs. non-bevacizumab groups show several regions with significant differences in PFS

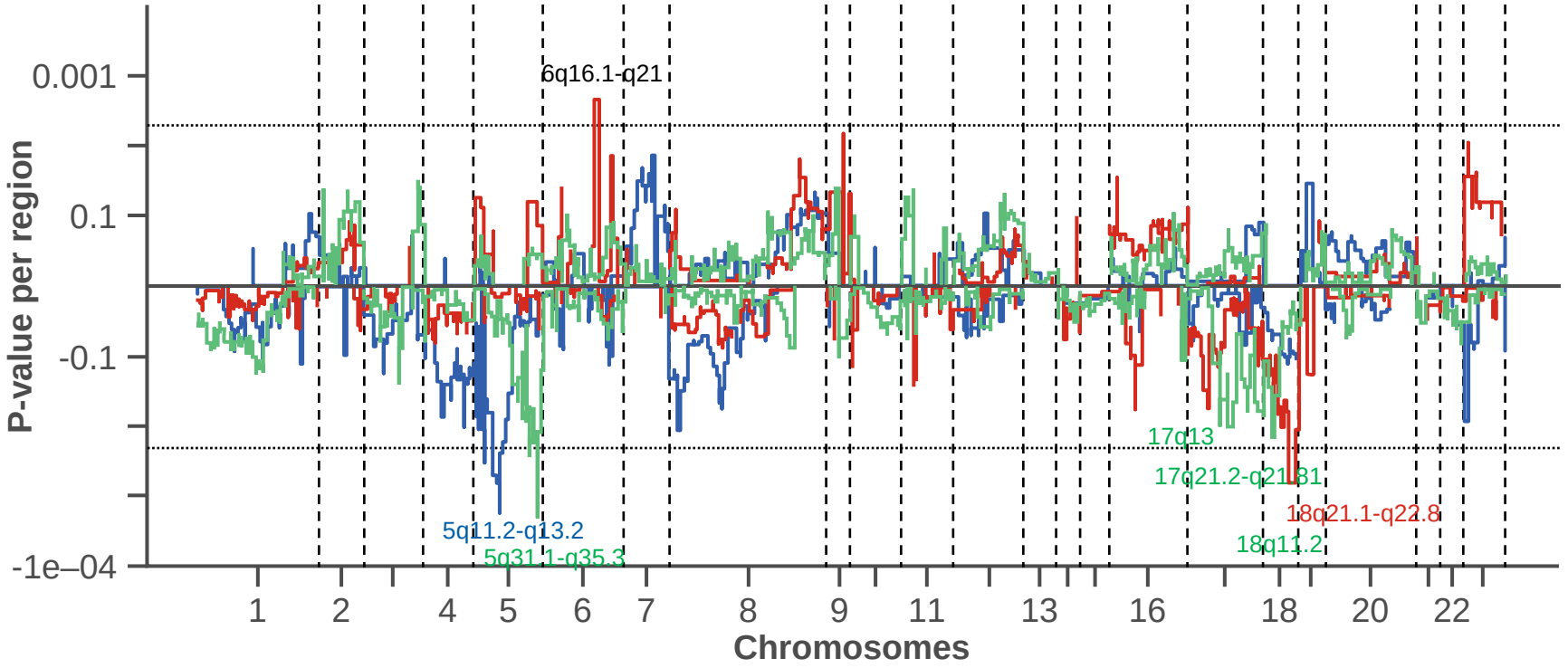
Van Grieken NC et al. Ann Oncol 2016; 27 (suppl 6): abstr 53PD

53PD: Copy number alterations as predictive biomarkers for response to bevacizumab in metastatic colorectal cancer – Van Grieken et al

Key results (continued)

- **Validation in CAIRO2**
  - The predictive value of loss at chromosome 18q12.1-18q21.32 was assessed in the AngioPredict cohort and confirmed using data from the CAIRO/CAIRO2 trials

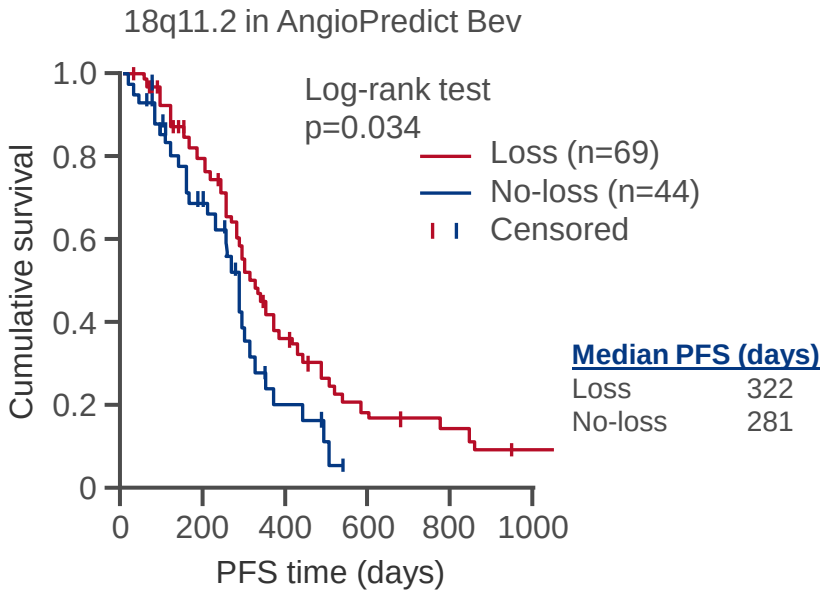
p-values of log-rank tested regions in CAIRO/CAIRO2 copy number set.
The green line represents tumours treated with bevacizumab

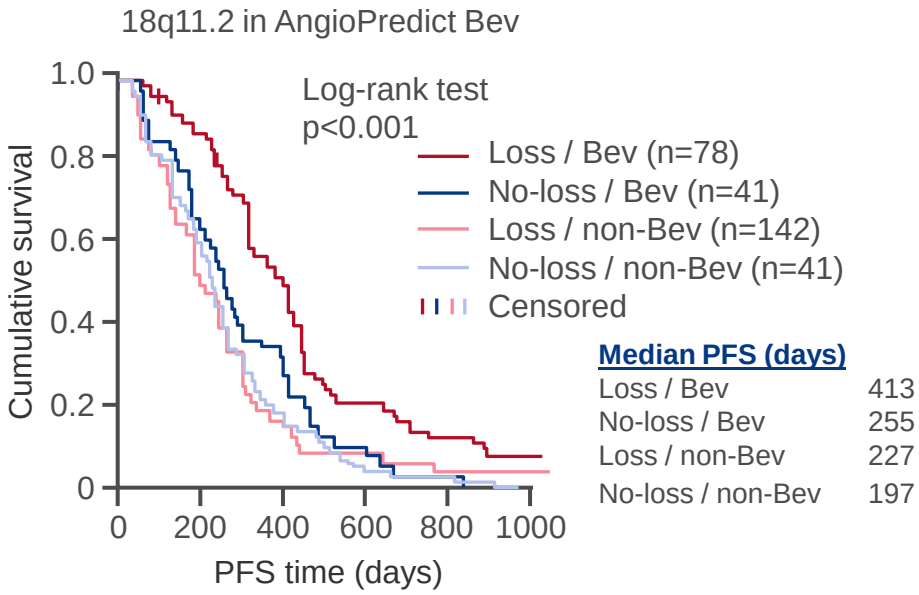


Van Grieken NC et al. Ann Oncol 2016; 27 (suppl 6): abstr 53PD

53PD: Copy number alterations as predictive biomarkers for response to bevacizumab in metastatic colorectal cancer – Van Grieken et al

Key results (continued)





Conclusions

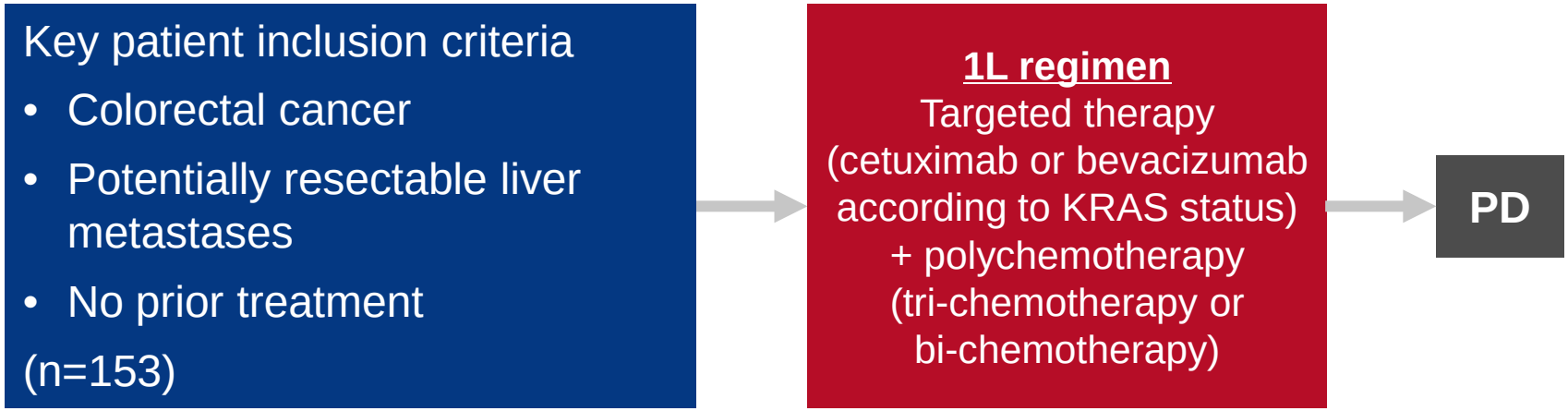
- **Loss of chromosome 18q12.1-18q21.32 may be predictive of response to bevacizumab regimens in two independent cohorts of patients with mCRC**
- **Identification of this mutation may be used as a candidate biomarker for response to bevacizumab**
- **Expansion of the AngioPredict non-bevacizumab group and further validation in other series is currently underway**

Van Grieken NC et al. Ann Oncol 2016; 27 (suppl 6): abstr 53PD

456O: Circulating tumor DNA and circulating tumor cells as predictor of outcome in the PRODIGE14-ACCORD21-METHEP2 phase II trial – Bidard et al

Study objective

- To report the detection rate and prognostic impact of circulating tumour DNA (ctDNA) and circulating tumour cell (CTC) levels in patients from three randomised phase 2 clinical trials



Patients were scheduled for liver surgery if adequate response was observed

PRIMARY ENDPOINT(S)

- Resection rate (R0/R1)
- ctDNA and CTC levels

SECONDARY ENDPOINTS

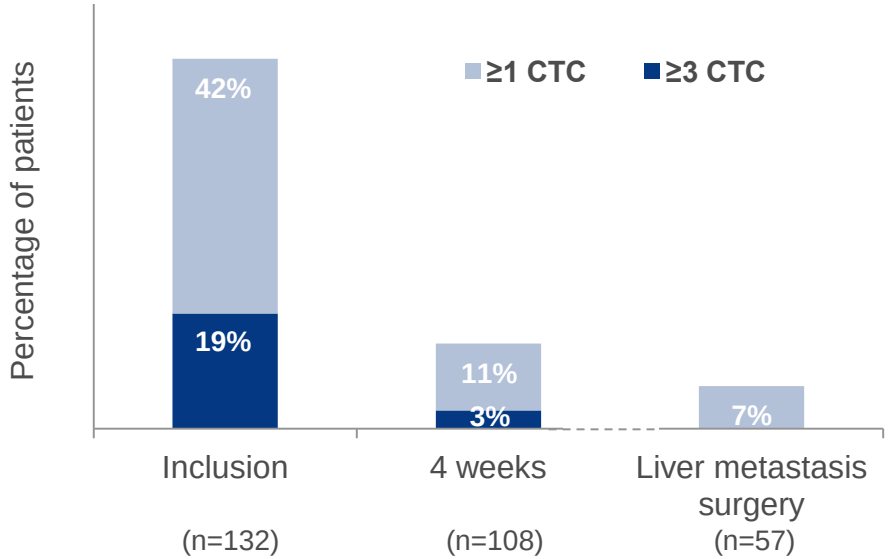
- OS

Bidard F et al. Ann Oncol 2016; 27 (suppl 6): abstr 456O

456O: Circulating tumor DNA and circulating tumor cells as predictor of outcome in the PRODIGE14-ACCORD21-METHEP2 phase II trial – Bidard et al

Key results

- All patients had non-resectable liver metastases (>25% in 55% of patients), with unresected primary tumours in 67% and unresected lung metastases in 11% of patients
- The presence of ≥1 CTC at baseline and at 4 weeks was linked to baseline extent (%) of liver involvement (p=0.004 and 0.05, respectively)
- CTC levels decreased during therapy (p<0.0001), with only 3 of 108 patients (3%) showing high levels after 4 weeks
  - The decrease did not differ according to chemotherapy type (i.e. bi- vs. tri-chemotherapy)



Bidard F et al. Ann Oncol 2016; 27 (suppl 6): abstr 456O

456O: Circulating tumor DNA and circulating tumor cells as predictor of outcome in the PRODIGE14-ACCORD21-METHEP2 phase II trial – Bidard et al

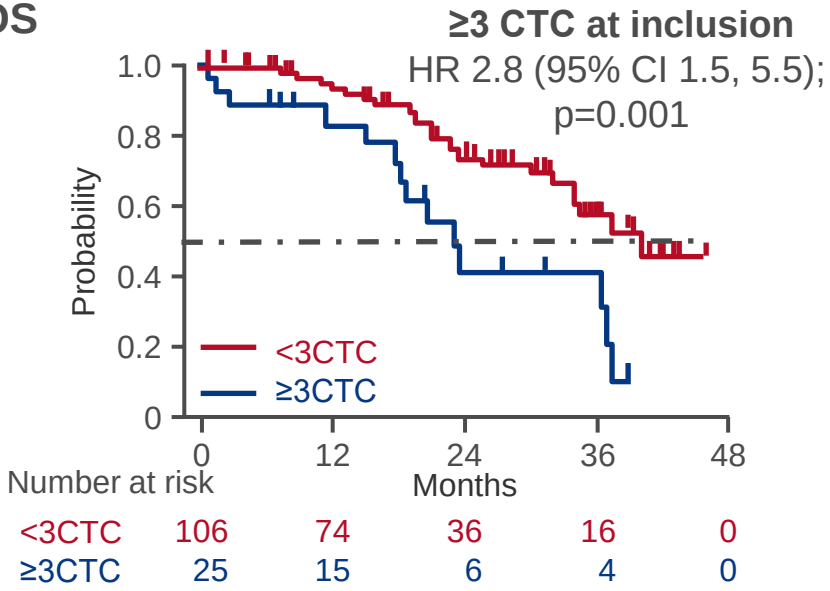
Key results (continued)

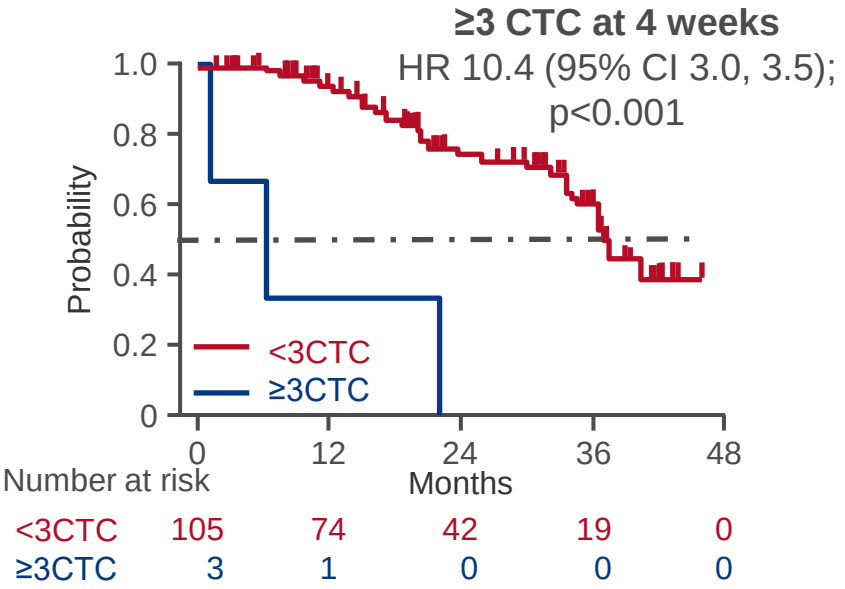
- Persistently high CTC count was associated with a lower R0/R1 liver metastasis resection rate (p=0.06)

At 4 weeks	R0/R1 resection of liver metastasis NOT ACHIEVED, n (%)	R0/R1 resection of liver metastasis ACHIEVED, n (%)
<2 CTC	41 (39)	64 (61)
≥3 CTC	3 (100)	0

- Elevated CTC levels were associated with reduced OS, both at inclusion and at 4 weeks

OS



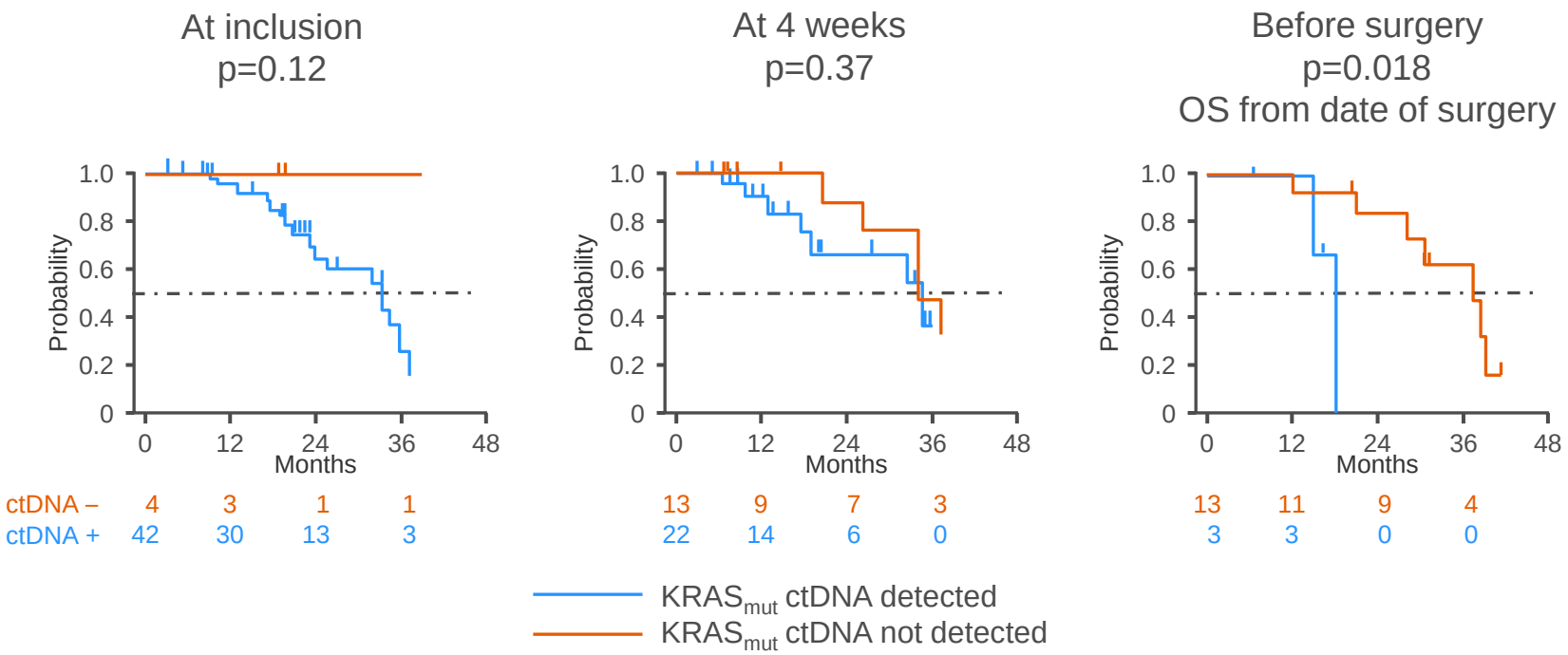


Bidard F et al. Ann Oncol 2016; 27 (suppl 6): abstr 456O

456O: Circulating tumor DNA and circulating tumor cells as predictor of outcome in the PRODIGE14-ACCORD21-METHEP2 phase II trial – Bidard et al

Key results (continued)

- *KRAS*-mutated ctDNA was significantly associated with a lower rate of R0/R1 liver metastases resection (p=0.004) after 4 weeks of therapy



Bidard F et al. Ann Oncol 2016; 27 (suppl 6): abstr 456O

456O: Circulating tumor DNA and circulating tumor cells as predictor of outcome in the PRODIGE14-ACCORD21-METHEP2 phase II trial – Bidard et al

Key results (continued)

Correlation between liquid and solid biopsy

Plasma DNA (ddPCR)

		Baseline (n=125)		4 weeks (n=54)		Surgery (n=50)	
		KRAS$_{mut}$	*KRAS*$_{wt}$	*KRAS*$_{mut}$	*KRAS*$_{wt}$	*KRAS*$_{mut}$	*KRAS*$_{wt}$
Tumour tissue (standard techniques), n (%)	*KRAS*$_{mut}$	42 (91)	4 (9)	22 (63)	13 (37)	4 (19)	17 (81)
	KRAS$_{wt}$	6 (8)	73 (92)	1 (5)	18 (95)	1 (3)	28 (97)
Sensitivity, %		91		63		15	
Specificity, %		92		95		97	
Global accuracy, %		92		74		64	

Decrease of *KRAS*$_{mut}$ ctDNA/cfDNA during therapy: p=0.0001

Conclusions

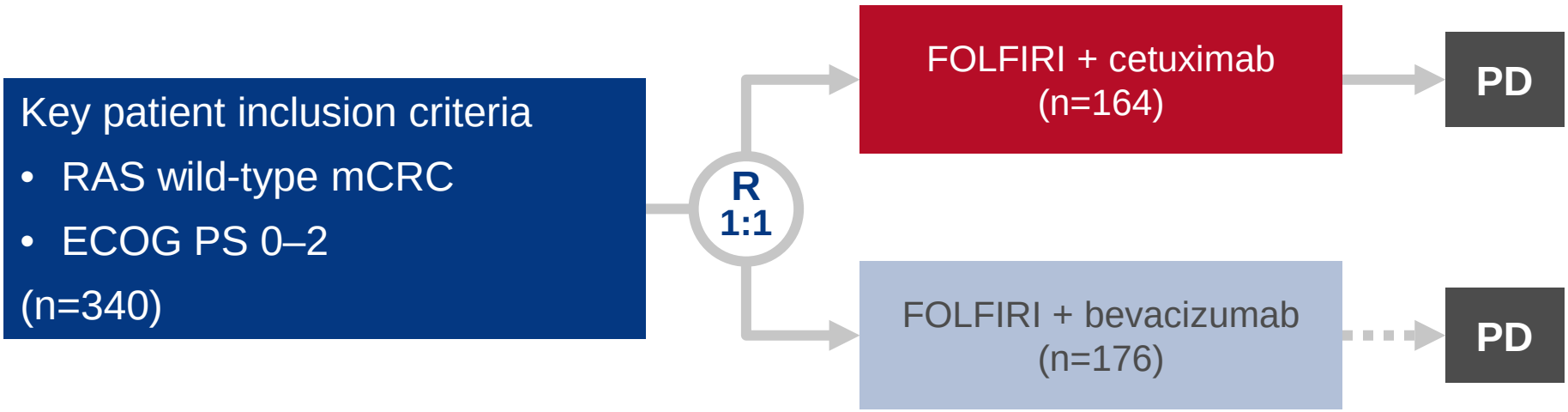
- **Although CTC count is a prognostic factor for outcomes in patients with colorectal cancer, it is rare at baseline or during therapy**
- **There is an excellent concordance between liquid (ctDNA) and solid biopsies**
- **Change of ctDNA levels during therapy is a very promising biomarker**
  - **Persistently detectable ctDNA levels during therapy may be:**
    - **Predictive of later R0/R1 resection of liver metastases (after 4 weeks of chemotherapy)**
    - **Prognostic for OS (prior to liver metastases surgery)**

Bidard F et al. Ann Oncol 2016; 27 (suppl 6): abstr 456O

457O: MiR-31-3p is a predictive biomarker of cetuximab response in FIRE3 clinical trial – Laurent-Puig et al

Study objective

- To assess whether MiR-31-3p expression can predict cetuximab efficacy on survival in RAS wild-type mCRC patients



PRIMARY ENDPOINT(S)

- PFS, OS

SECONDARY ENDPOINTS

- OR, DoR, ETS, prediction of response by miR-31-3p expression

miR-31-3p expression

- MiR-31-3p expression was measured by qRT-PCR after extraction from 370 RAS wt paraffin embedded tumour samples
  - Patients were divided into “low” or “high” miR-31-3p expressors based on pre-defined cut-off threshold

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 457O

457O: MiR-31-3p is a predictive biomarker of cetuximab response in FIRE3 clinical trial – Laurent-Puig et al

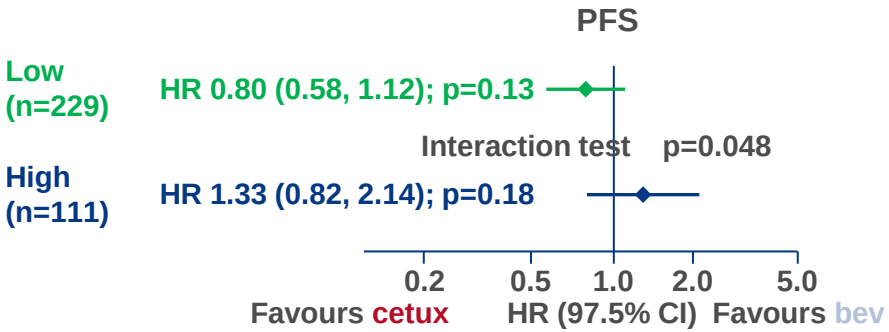
Key results

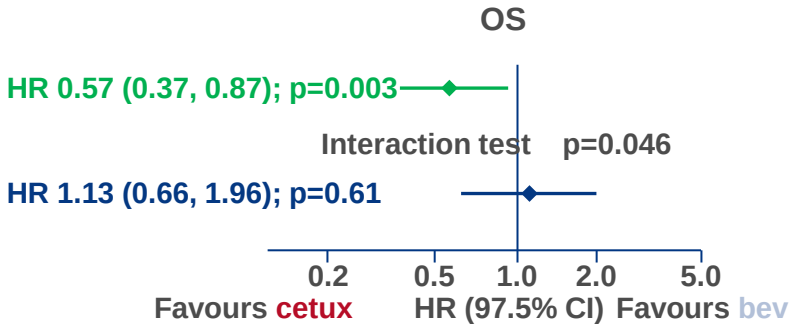
Treatment effect on PFS and OS

- Overall HR (95% CI) not adjusted

	PFS	OS
ITT RAS wt	HR 0.93 (0.74, 1.17); p=0.54	HR 0.70 (0.53, 0.92); p=0.011
mITT	HR 0.92 (0.73, 1.16); p=0.46	HR 0.71 (0.53, 0.93); p=0.014

- In miR-31-3p subgroups: HR (97.5% CI) adjusted on age, number of organs and BRAF status





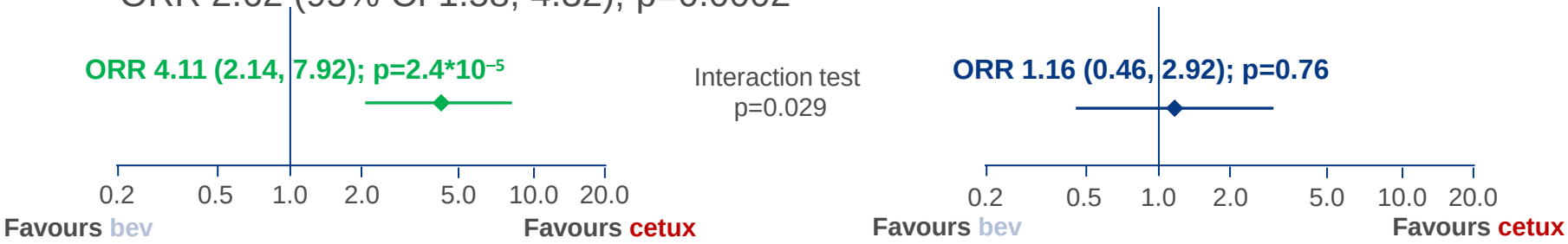
- miR-31-3p levels were predictive of treatment effects on PFS and OS; a benefit of cetuximab therapy was seen only in low miR-31-3p expressors vs. high-expression peers
  - Similar results were observed for ORR

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 457O

457O: MiR-31-3p is a predictive biomarker of cetuximab response in FIRE3 clinical trial – Laurent-Puig et al

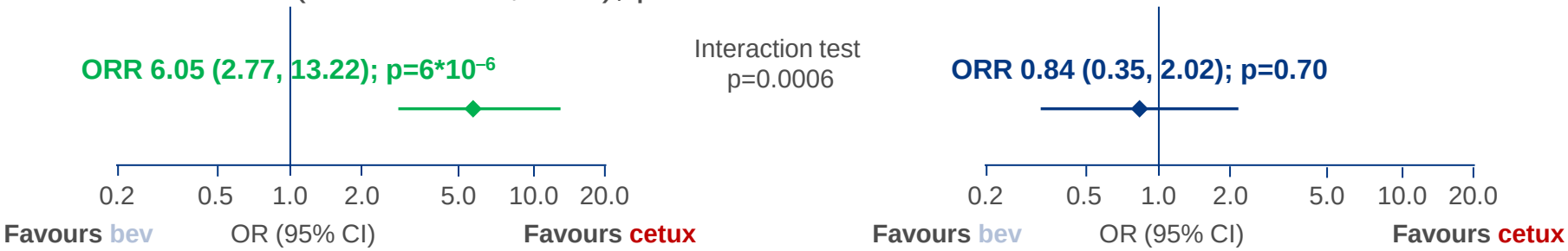
Key results (continued)

- **ETS**
  - ORR 2.62 (95% CI 1.58, 4.32); p=0.0002



Low miR-31-3p expression | **High miR-31-3p expression**

- **DoR**
  - ORR 2.36 (95% CI 1.43, 3.90); p=0.0008

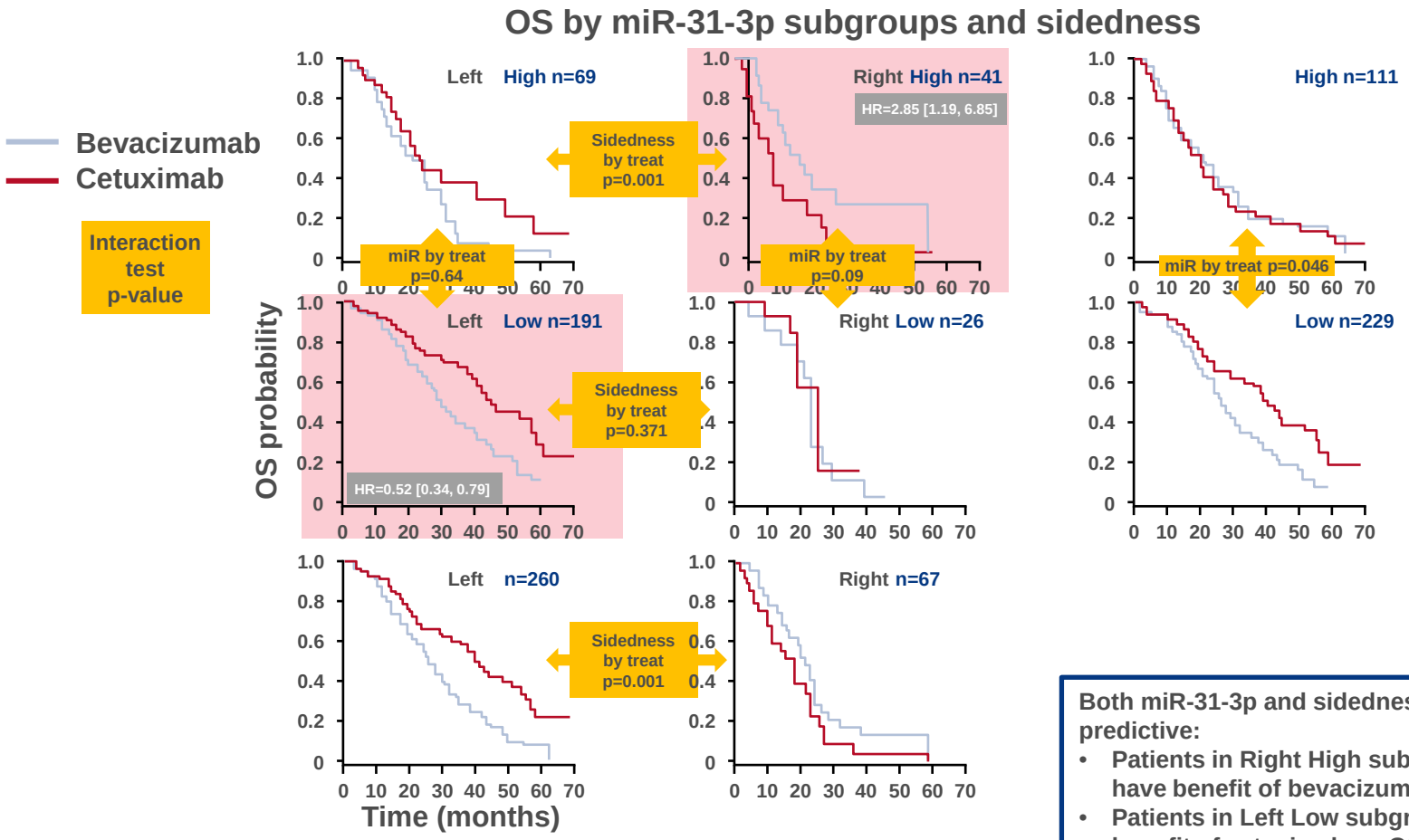


Low miR-31-3p expression | **High miR-31-3p expression**

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 457O

457O: MiR-31-3p is a predictive biomarker of cetuximab response in FIRE3 clinical trial – Laurent-Puig et al

Key results (continued)



Both miR-31-3p and sidedness are predictive:

- **Patients in Right High subgroup have benefit of bevacizumab on OS**
- **Patients in Left Low subgroup have benefit of cetuximab on OS**

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 457O

457O: MiR-31-3p is a predictive biomarker of cetuximab response in FIRE3 clinical trial – Laurent-Puig et al

Conclusions

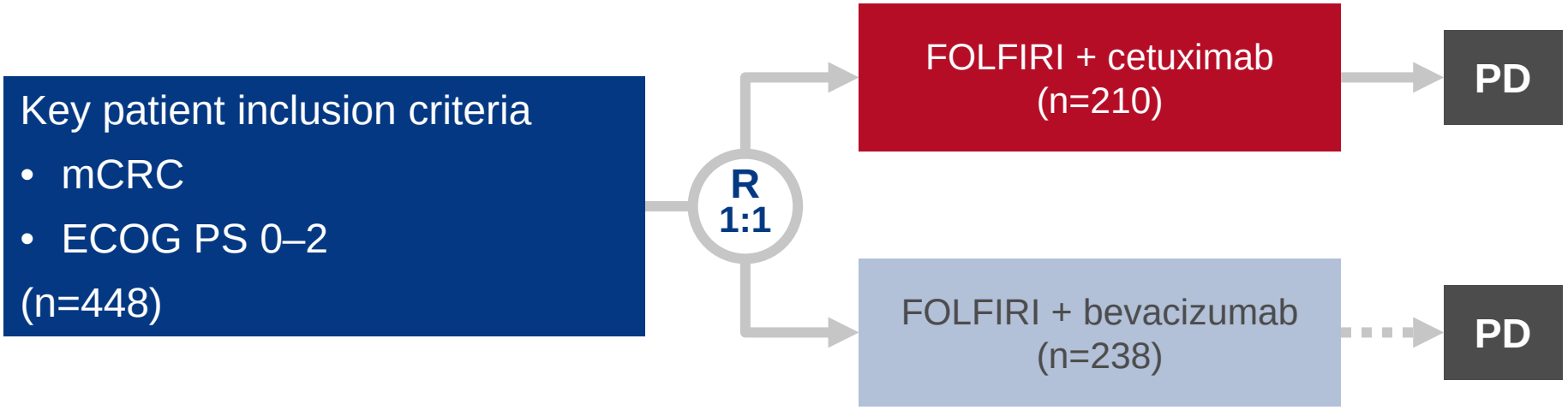
- **miR-31-3p predicted cetuximab effect on OS, PFS and ORR in patients with mCRC**
- **The beneficial effect of cetuximab seen in the FIRE-3 study was restricted to patients with low miR-31-3p levels**
- **miR-31-3p may be clinically useful to select patients for 1L anti-EGFR therapy, and to identify those with low miR-31-3p who will have a better DoR leading to more frequent resection**

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 457O

468PD: Evaluation for surgical treatment options in metastatic colorectal cancer (mCRC) – a retrospective, central evaluation of FIRE-3 – Neumann et al

Study objective

- A retrospective central radiographic review of tumours lesions with regard to surgical treatment options (± local thermic ablation, body radiation, etc.) in addition to systemic treatment in FIRE-3 trial conducted by 8 visceral surgeons and 3 medical oncologists



PRIMARY ENDPOINT(S)

- PFS, OS

SECONDARY ENDPOINTS

- OR, DoR, ETS

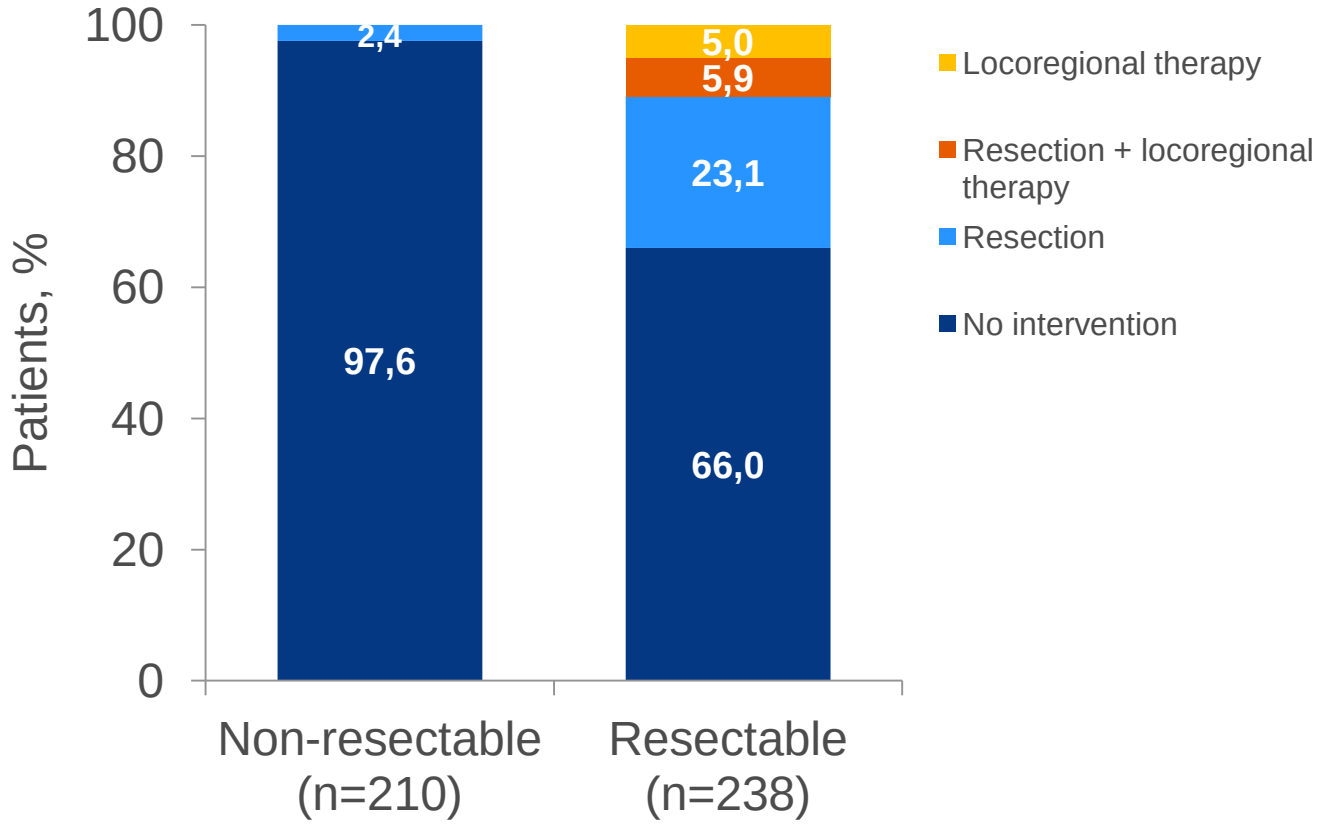
- Evaluation of resectability based on archived scans (computed tomography/MRI) was performed at baseline (before study treatment) and at “best response”

Neumann U et al. Ann Oncol 2016; 27 (suppl 6): abstr 468PD

468PD: Evaluation for surgical treatment options in metastatic colorectal cancer (mCRC) – a retrospective, central evaluation of FIRE-3 – Neumann et al

Key results

Comparison of resectable patients between the review data and reality



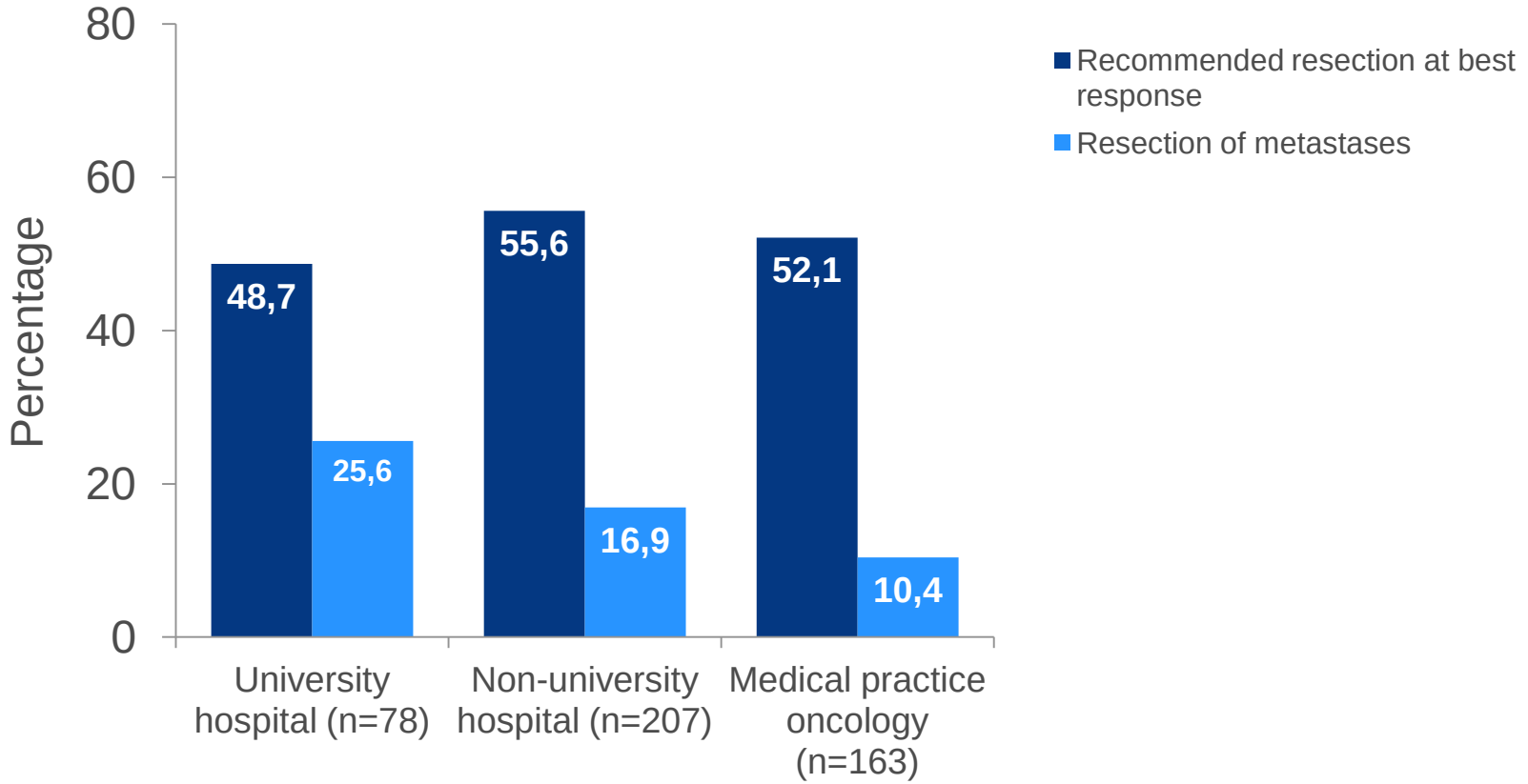
Neumann U et al. Ann Oncol 2016; 27 (suppl 6): abstr 468PD

468PD: Evaluation for surgical treatment options in metastatic colorectal cancer (mCRC) – a retrospective, central evaluation of FIRE-3 – Neumann et al

Key results (continued)

- More patients were scheduled for resection of metastases in university hospitals than patients in other hospitals or medical practices (p=0.02)

Influence of treatment context on resection of metastases

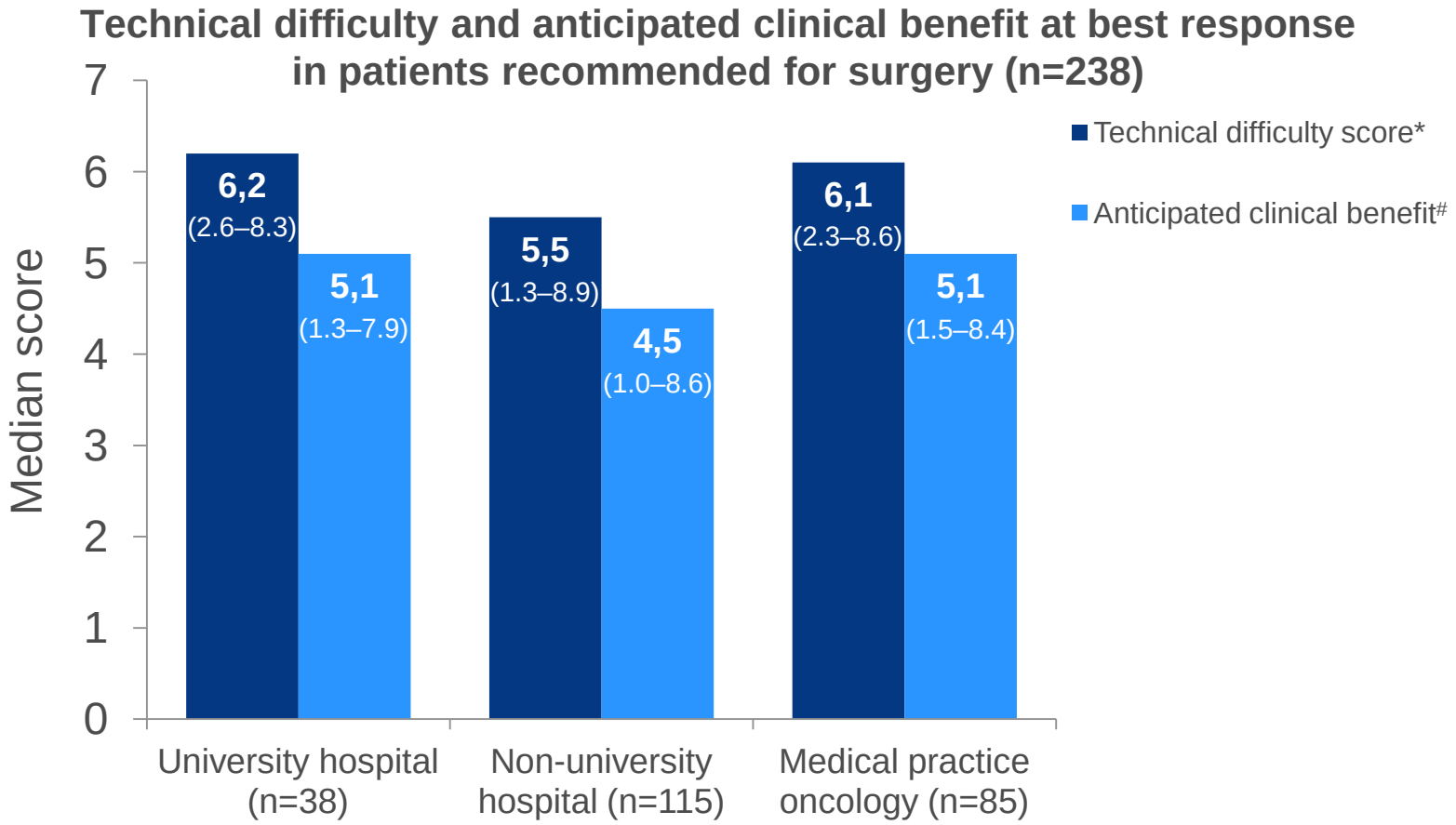


Neumann U et al. Ann Oncol 2016; 27 (suppl 6): abstr 468PD

468PD: Evaluation for surgical treatment options in metastatic colorectal cancer (mCRC) – a retrospective, central evaluation of FIRE-3 – Neumann et al

Key results (continued)

- Potential interventions and anticipated clinical in patients treated in the different clinical settings were similar



*1=easy to 10=impossible; #1=great benefit to 10=no benefit.

Neumann U et al. Ann Oncol 2016; 27 (suppl 6): abstr 468PD

468PD: Evaluation for surgical treatment options in metastatic colorectal cancer (mCRC) – a retrospective, central evaluation of FIRE-3 – Neumann et al

Conclusions

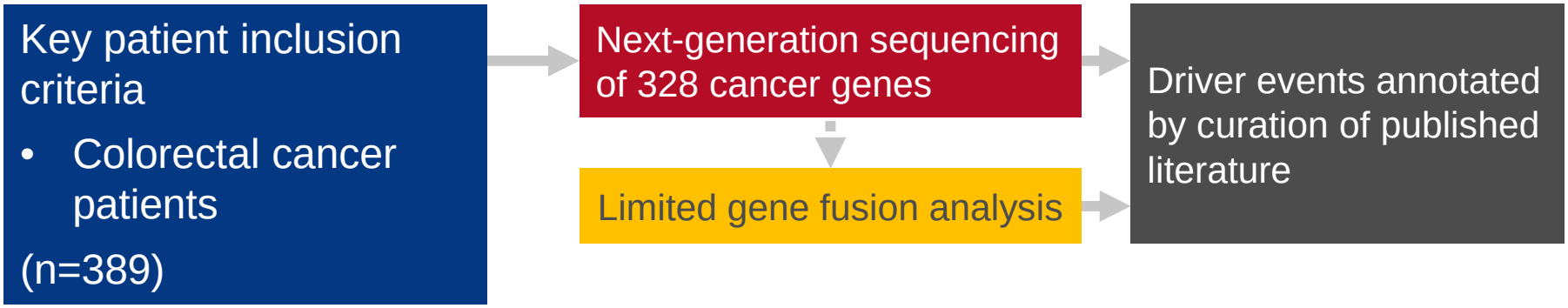
- **In FIRE-3, there were more patients who were candidates for surgery than those who actually underwent resection**
  - **Missing clinical information and patient preferences can lead to overestimation of resectability**
- **It is recommended that during the course of treatment regular and pre-planned evaluation of resectability is undertaken at specialised centres**

Neumann U et al. Ann Oncol 2016; 27 (suppl 6): abstr 468PD

458O: Frequency of potentially actionable genetic alterations in EORTC SPECTAcolor – Folprecht et al

Study objective

- To assess whether new potential therapeutic targets can be identified through the EORTC Screening Platform for Efficient Clinical Trial Access (SPECTAcolor)



PRIMARY ENDPOINT(S)

- Identification of rare genomic targets

Folprecht G et al. Ann Oncol 2016; 27 (suppl 6): abstr 458O

458O: Frequency of potentially actionable genetic alterations in EORTC SPECTAcolor – Folprecht et al

Key results

Most frequently-observed mutations

Mutation,%	MSS (n=370)			MSI-H (n=19)	
	Total	Left	Right	Total	p-value (location)
APC	77.8	80.8	73.6	21.1	0.20
TP53	72.2	76.5	62.3	52.6	0.017
KRAS	47.8	45.5	53.8	42.1	0.35
PIK3CA	17.6	14.1	25.5	47.4	0.029
FBXW7	11.1	12.2	8.5	36.8	0.53
BRAF	10.5	5.1	22.6	36.8	<0.0001
SOX9	8.1	6.2	13.2	21.1	0.075
SMAD4	7.6	7.1	9.4	0	0.64
ARD1A	5.1	5.5	3.8	0	0.33
NRAS	5.1	4.3	7.5	0	0.39

- MSS and MSI-H tumours harboured a median of 3 (range 0–16) and 8 (range 3–16) potential “driver” mutations, respectively

Folprecht G et al. Ann Oncol 2016; 27 (suppl 6): abstr 458O

458O: Frequency of potentially actionable genetic alterations in EORTC SPECTAcolor – Folprecht et al

Key results (continued)

Genetic alterations of interest

Mutations, %	MSS (n=370)			MSI-H (n=19)
	Total	Left	Right	Total
BRAF	10.5	5.1	22.6	37
BRCA2	1.6	0.8	3.8	5
HER2	1.9	2.0	1.0	
TSC1				16
Amplifications				
HER2	2.5			
FGFR 1/2/3	3.5			
Fusions				
AML4/ALK	Validations ongoing			
Immunochemistry				
MSI-H	4.0			

Folprecht G et al. Ann Oncol 2016; 27 (suppl 6): abstr 458O

458O: Frequency of potentially actionable genetic alterations in EORTC SPECTAcolor – Folprecht et al

Conclusions

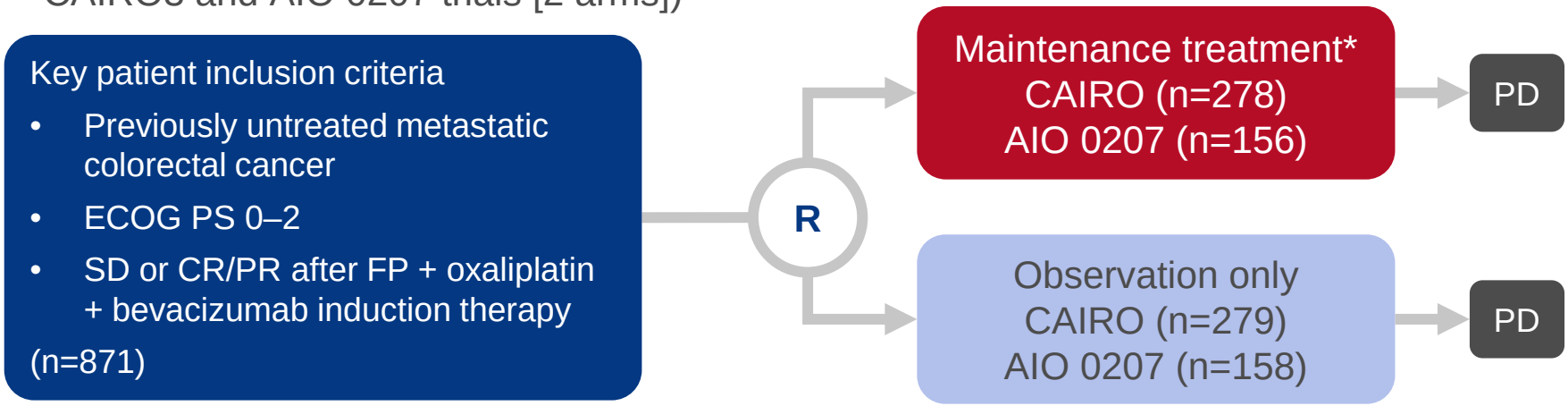
- **Over 20% of patients with CRC have targetable genetic alterations**
- **The SPECTA programme provides an effective platform for identifying rare, potentially actionable genomic targets**

Folprecht G et al. Ann Oncol 2016; 27 (suppl 6): abstr 458O

463PD: Clinical factors influencing outcome in metastatic colorectal cancer (mCRC) patients treated with fluoropyrimidine and bevacizumab (FP+Bev) maintenance treatment (Tx) vs observation: A pooled analysis of the phase 3 CAIRO3 and AIO 0207 trials – Goey et al

Study objective

- To identify subgroups with clinical characteristics that maximally benefit from maintenance treatment with fluoropyrimidine (FP) + bevacizumab (pooled analysis of the phase 3 CAIRO3 and AIO 0207 trials [2 arms])



Methods

- Analysis of the effect of variables (sex, age, performance status, response to induction treatment, disease stage; primary tumour site and resection status, number of metastatic sites, synchronous vs. metachronous mCRC, LDH at randomisation, platelet count and CEA at start of induction treatment) on treatment
- Analysis of PFS1†, PFS2‡ and OS

*Maintenance therapy for CAIRO3 and AIO studies, FP + bevacizumab and capecitabine + bevacizumab, respectively;
†time to 1st progression; ‡time to 2nd progression after FP + oxaliplatin + bevacizumab reintroduction

Goey K et al. Ann Oncol 2016; 27 (suppl 6): abstr 463PD

463PD: Clinical factors influencing outcome in metastatic colorectal cancer (mCRC) patients treated with fluoropyrimidine and bevacizumab (FP+Bev) maintenance treatment (Tx) vs observation: A pooled analysis of the phase 3 CAIRO3 and AIO 0207 trials – Goey et al

Key results

- Maintenance treatment vs. observation resulted in a highly significant benefit in
  - PFS1 (HR 0.40 [95% CI 0.34, 0.47])
  - PFS2 (HR 0.68 [95% CI 0.59, 0.80])
- Benefit of maintenance treatment was observed in all investigated subgroups
- Results for OS showed a marked heterogeneity between the two studies (HR 0.90 [95% CI 0.76, 1.05])
- Patients with elevated platelet count (>400*10^9/L) at start of induction treatment had significantly more benefit from maintenance treatment vs. observation in PFS1 and PFS2
  - Tests for interaction were $p<0.05$

Goey K et al. Ann Oncol 2016; 27 (suppl 6): abstr 463PD

463PD: Clinical factors influencing outcome in metastatic colorectal cancer (mCRC) patients treated with fluoropyrimidine and bevacizumab (FP+Bev) maintenance treatment (Tx) vs observation: A pooled analysis of the phase 3 CAIRO3 and AIO 0207 trials – Goey et al

Conclusions

- These results indicate that in the 1L treatment of mCRC, fluoropyrimidine + bevacizumab maintenance treatment is associated with significant benefit compared with observation alone
- All subgroups included in this study showed treatment benefit with maintenance treatment vs. observation alone
- Patient response to fluoropyrimidine + bevacizumab maintenance treatment could be predicted from platelet count at start of induction treatment; this was a significant predictive factor for effect size

Goey K et al. Ann Oncol 2016; 27 (suppl 6): abstr 463PD

LBA23: A novel epigenetic immunoassay approach to profiling circulating nucleosomes for CRC detection – Herzog et al

Study objective

- To evaluate combined Nu.Q™ blood score and numeric FIT score as a triage approach for positive FIT in an average risk population

Key patient inclusion criteria

- FIT+ colonoscopic confirmation of diagnosis*

(n=1907)

Patients were classified into 3 groups by colonoscopy results: CRC, adenoma and clean bowel

Analysis of 10 µL serum samples (Nu.Q™ ELISA blood tests)

LDA developed algorithm to identify individuals with no evidence of cancer

PRIMARY ENDPOINT(S)

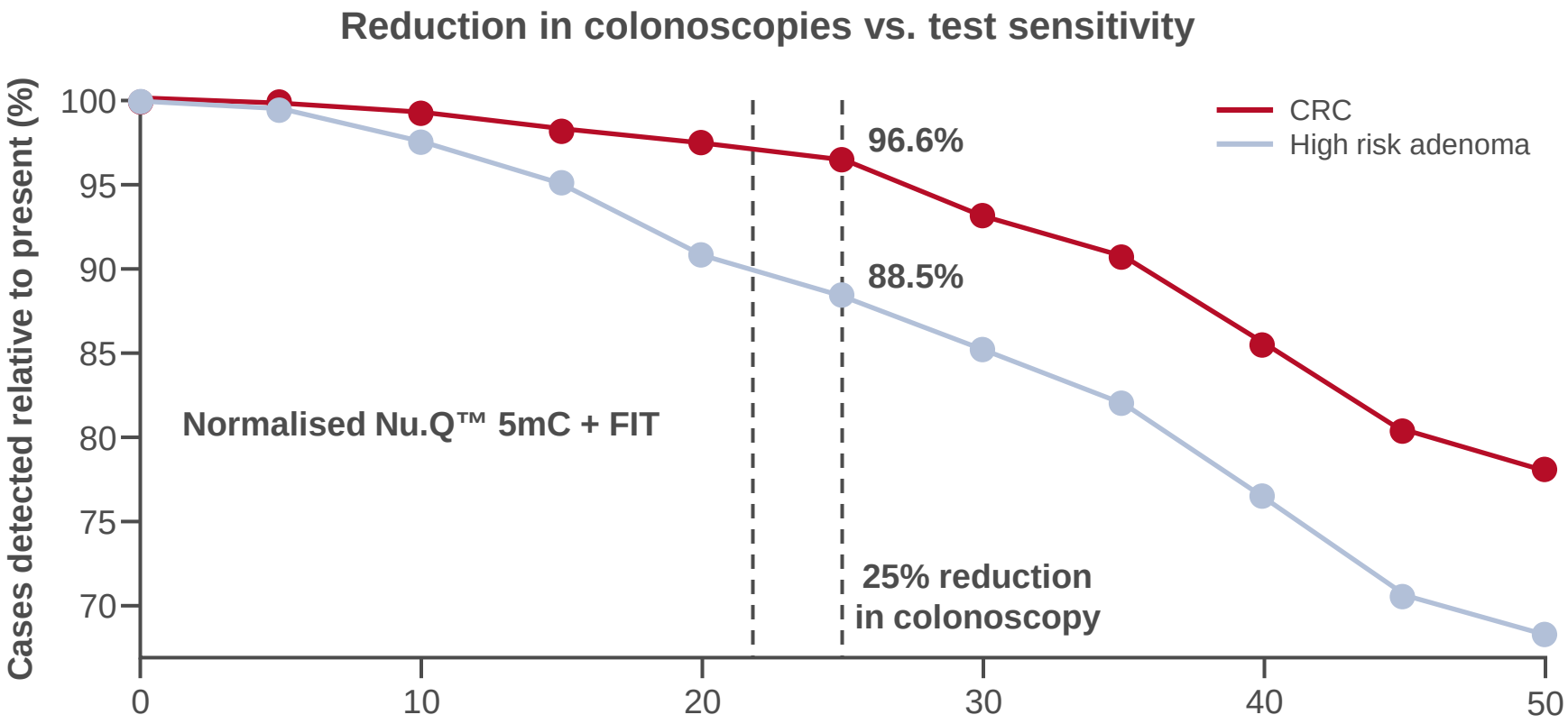
- To identify individuals with low risk adenomas or no findings on colonoscopy

LDA, Linear Discriminant Analysis; FIT, Fecal Immune Test, ELISA, enzyme-linked immunosorbent assay

Herzog M et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA23

LBA23: A novel epigenetic immunoassay approach to profiling circulating nucleosomes for CRC detection – Herzog et al

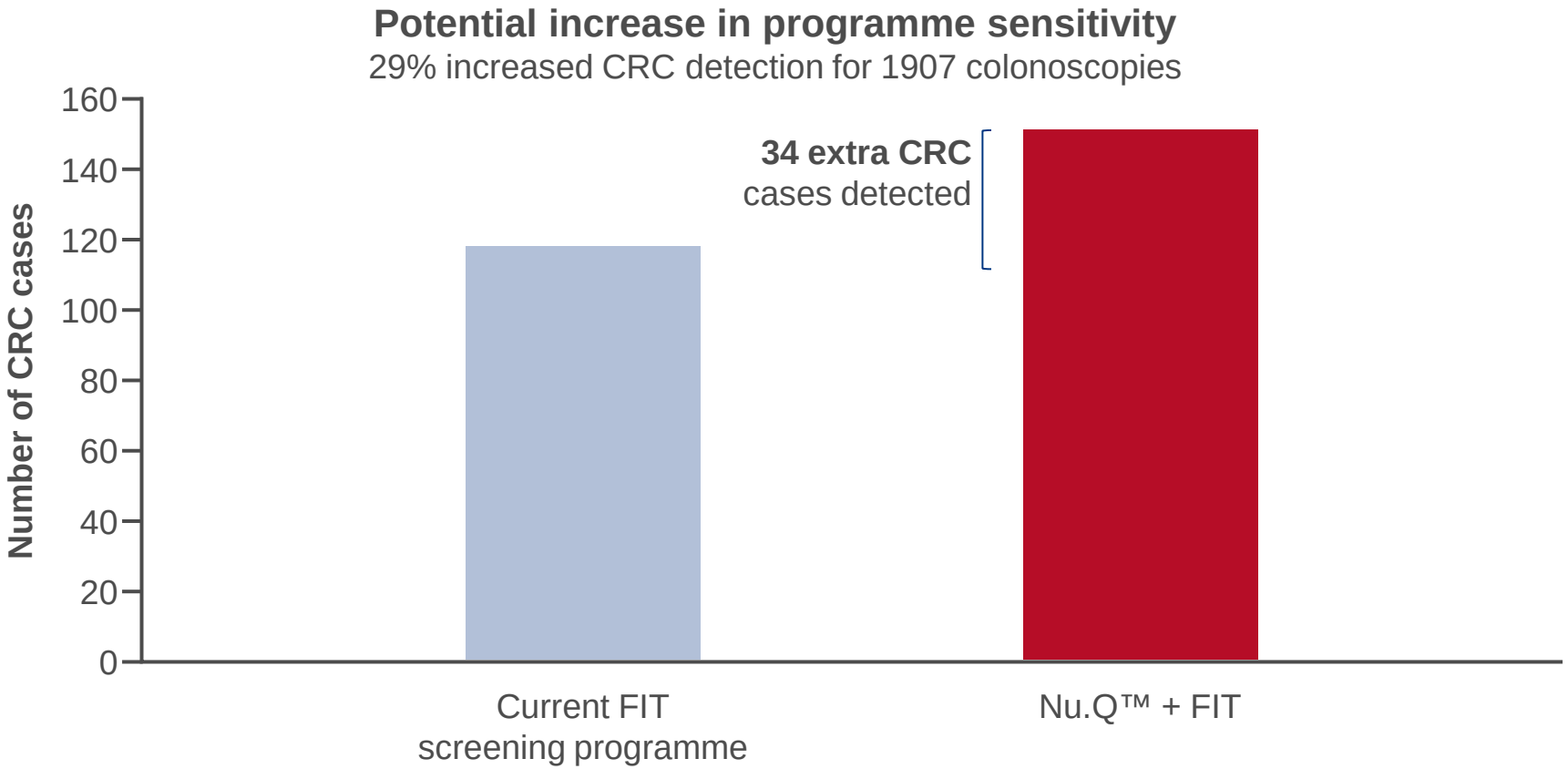
Key results



Herzog M et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA23

LBA23: A novel epigenetic immunoassay approach to profiling circulating nucleosomes for CRC detection – Herzog et al

Key results



Herzog M et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA23

LBA23: A novel epigenetic immunoassay approach to profiling circulating nucleosomes for CRC detection – Herzog et al

Conclusions

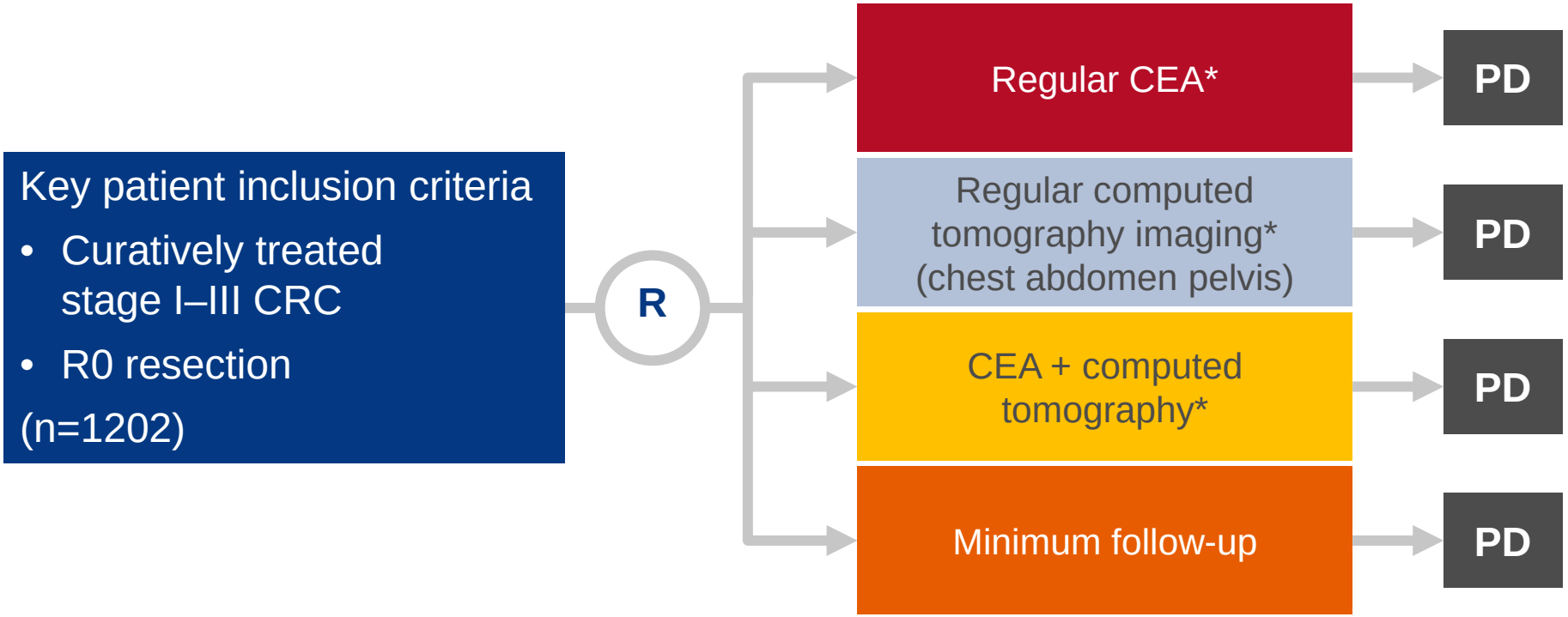
- **Nu.QTM blood tests (age-adjusted) along with the FIT score can be used to decrease non screen-relevant colonoscopies in FIT+ individuals with minimal reduction in cancer detection**
- **These results imply that the test could reduce the number of unnecessary colonoscopies and ease pressure on colonoscopy capacity or alternatively, identify more cancers by increasing the flow of screened subjects**

Herzog M et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA23

453O: Scheduled use of CEA and CT follow-up to detect recurrence of colorectal cancer: 6-12 year results from the FACS randomised controlled trial – Pugh et al

Study objective

- To assess the efficacy and safety of panitumumab with dabrafenib and/or trametinib in BRAF-mutant mCRC with integrated biomarker analyses



PRIMARY ENDPOINT(S)

- Surgical treatment of recurrence with curative intent

*Grouped as intensive follow-up

SECONDARY ENDPOINTS

- OS

Note: Based on data from abstract only

Pugh SA et al. Ann Oncol 2016; 27 (suppl 6): abstr 453O

453O: Scheduled use of CEA and CT follow-up to detect recurrence of colorectal cancer: 6-12 year results from the FACS randomised controlled trial – Pugh et al

Key results

	Intensive follow-up	Minimum follow-up	p-value
Identification of recurrences treatable with curative intent, n/N (%)	68/901 (7.5)	8/301 (2.7)	0.003
OS in all patients			0.45
Patients still alive, n/N (%)	43/901 (4.8)	7/301 (2.3)	0.07
Identification of recurrences treatable with curative intent by primary tumour location, n/N (%)			
Rectal Left colon Right colon	27/275 (9.8) 24/327 (7.3) 14/282 (5.0)	6/87 (6.9) 1/108 (0.9) 0/104 (0)	0.41 0.01 0.02
OS in colon with left-sided tumours, years	4.4	3.1	0.03

Note: Based on data from abstract only

Pugh SA et al. Ann Oncol 2016; 27 (suppl 6): abstr 453O

453O: Scheduled use of CEA and CT follow-up to detect recurrence of colorectal cancer: 6-12 year results from the FACS randomised controlled trial – Pugh et al

Conclusions

- **The detection of treatable recurrence was increased using intensive follow-up, however, this was only in those with colonic tumours**
- **Patients with recurrence from a left-sided tumour seemed to derive a survival advantage**

Note: Based on data from abstract only

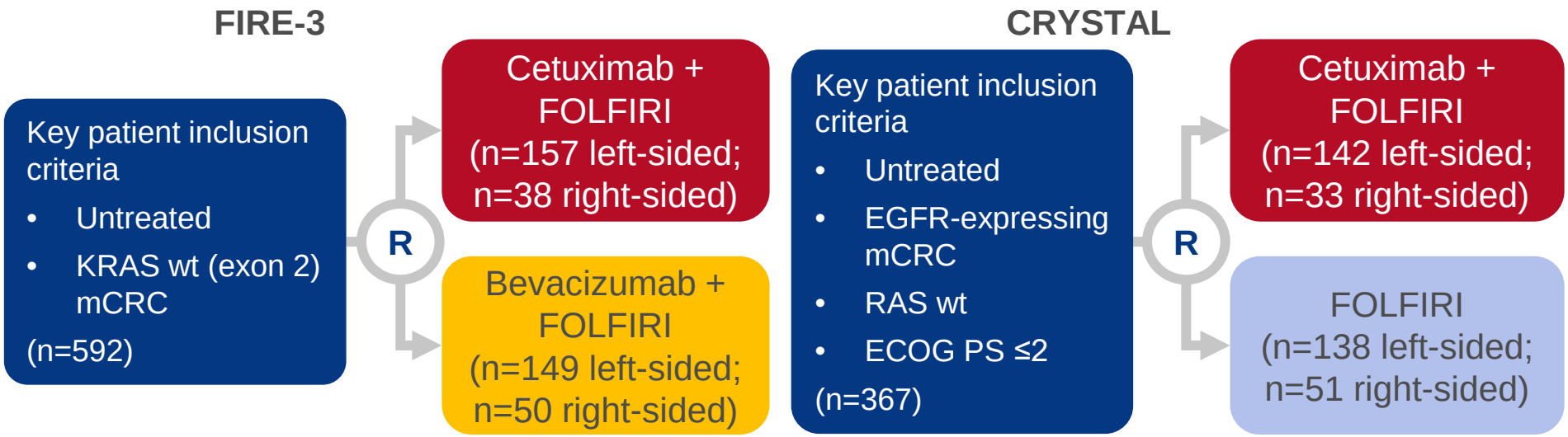
Pugh SA et al. Ann Oncol 2016; 27 (suppl 6): abstr 453O

Right or left metastatic colon cancer: Will the side change your treatment?

Objective

- To discuss using data from the FIRE-3 and CRYSTAL trials whether primary tumour location (left vs. right)* has prognostic and predictive relevance in patients with mCRC and if this will change treatment options

Study designs



Left-sided defined as tumours originating in the splenic flexure, descending colon, sigmoid colon or rectum; right-sided defined as tumours originating in the appendix, cecum, ascending colon, hepatic flexure or transverse colon

ENDPOINT(S)

- PFS, OS, ORR

Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

Right or left metastatic colon cancer: Will the side change your treatment?

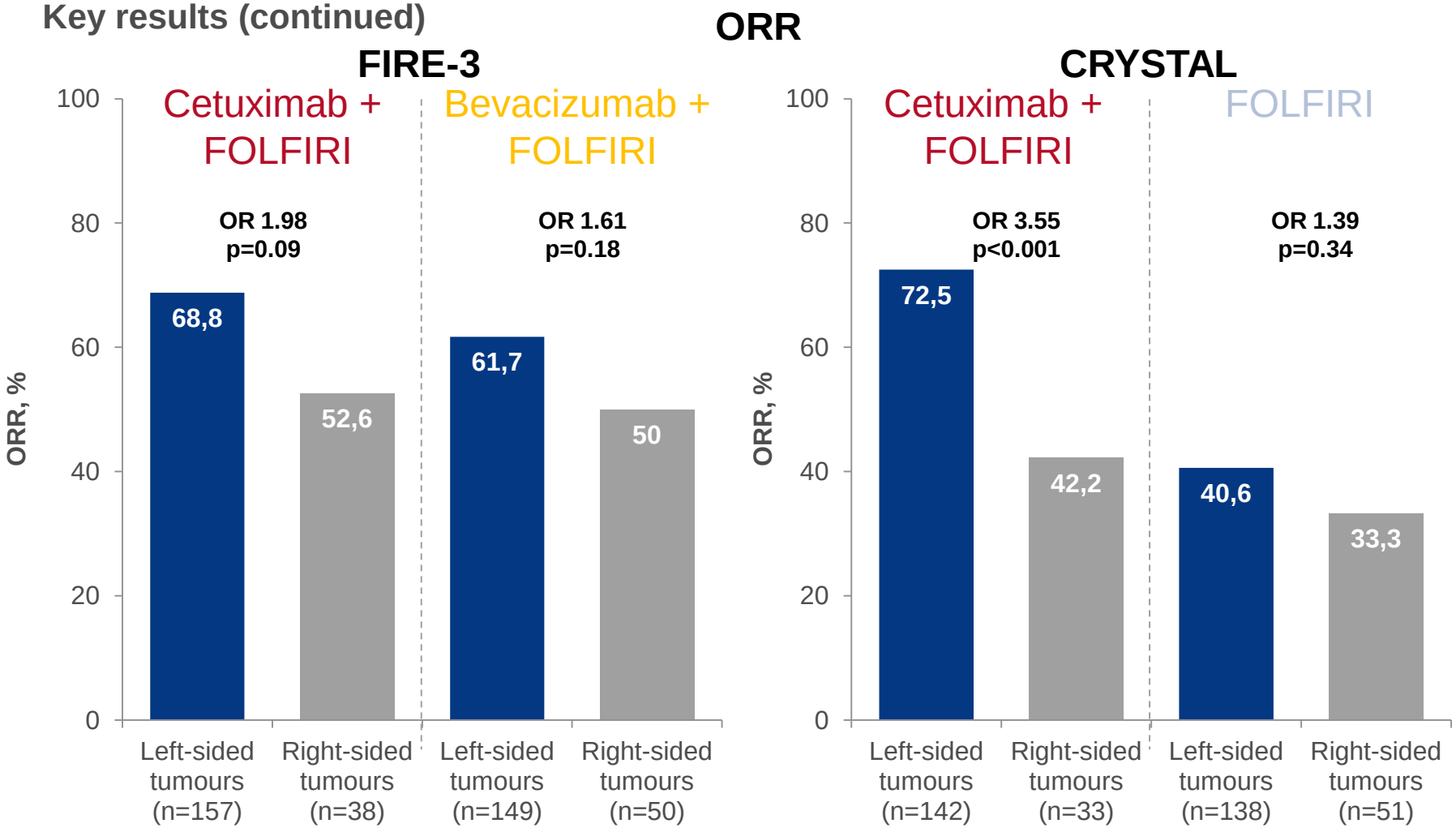
Key results

Parameter	FIRE-3				CRYSTAL			
	Cetuximab + FOLFIRI		Bevacizumab + FOLFIRI		Cetuximab + FOLFIRI		FOLFIRI	
	Left-sided (n=157)	Right-sided (n=38)	Left-sided (n=149)	Right-sided (n=50)	Left-sided (n=142)	Right-sided (n=33)	Left-sided (n=138)	Right-sided (n=51)
mPFS								
Months	10.7	7.6	10.7	9.0	12.0	8.1	8.9	7.1
HR (95% CI)	2.00 (1.36, 2.93)		1.38 (0.99, 1.94)		1.77 (1.08, 2.91)		1.54 (0.96, 2.46)	
p-value	<0.001		0.06		0.02		0.07	
mOS								
Months	38.3	18.3	28.0	23.0	28.7	18.5	21.7	15.0
HR (95% CI)	2.84 (1.86, 4.33)		1.48 (1.02, 2.16)		1.93 (1.24, 2.99)		1.35 (0.93, 1.97)	
p-value	<0.0001		0.04		0.003		0.11	

Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

Right or left metastatic colon cancer: Will the side change your treatment?

Key results (continued)

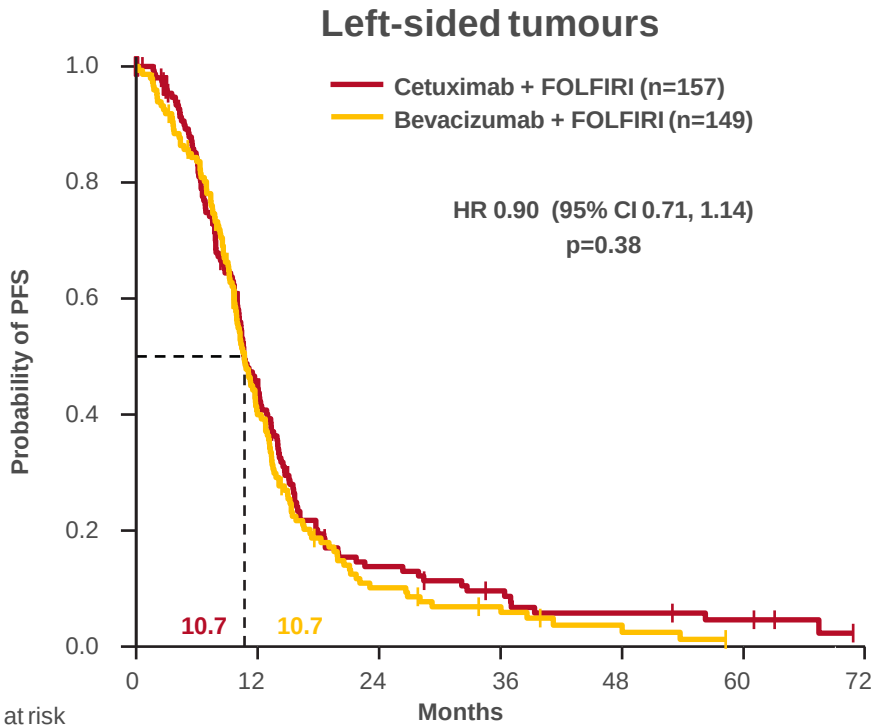


Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

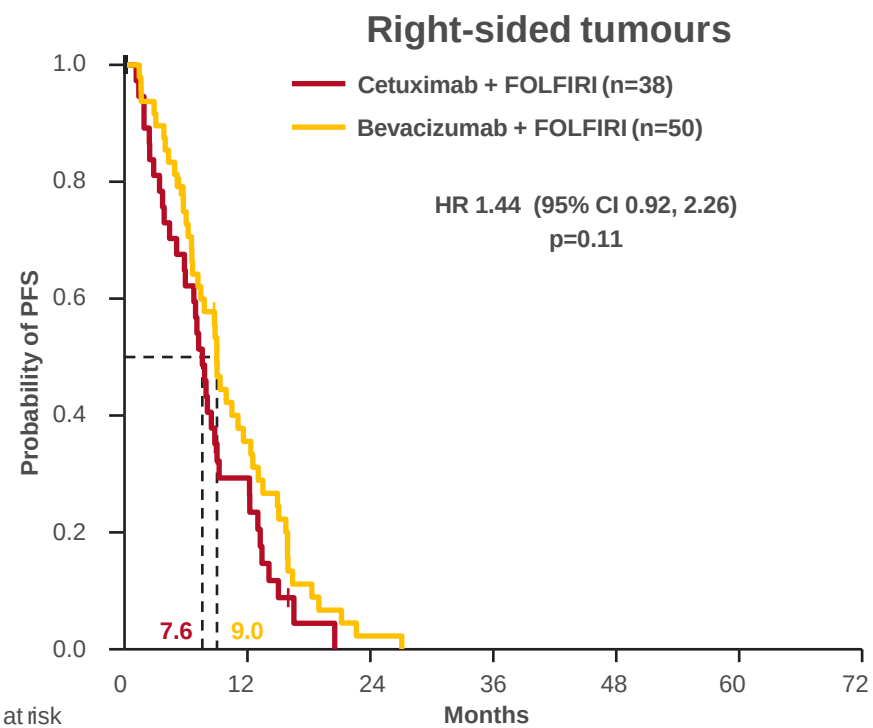
Right or left metastatic colon cancer: Will the side change your treatment?

Key results (continued)

FIRE-3: PFS



No. at risk							
Cet + FOLFIRI	157	60	17	10	6	4	0
Bev + FOLFIRI	149	56	13	7	2	0	0



No. at risk							
Cet + FOLFIRI	38	10	0	0	0	0	0
Bev + FOLFIRI	50	16	1	0	0	0	0

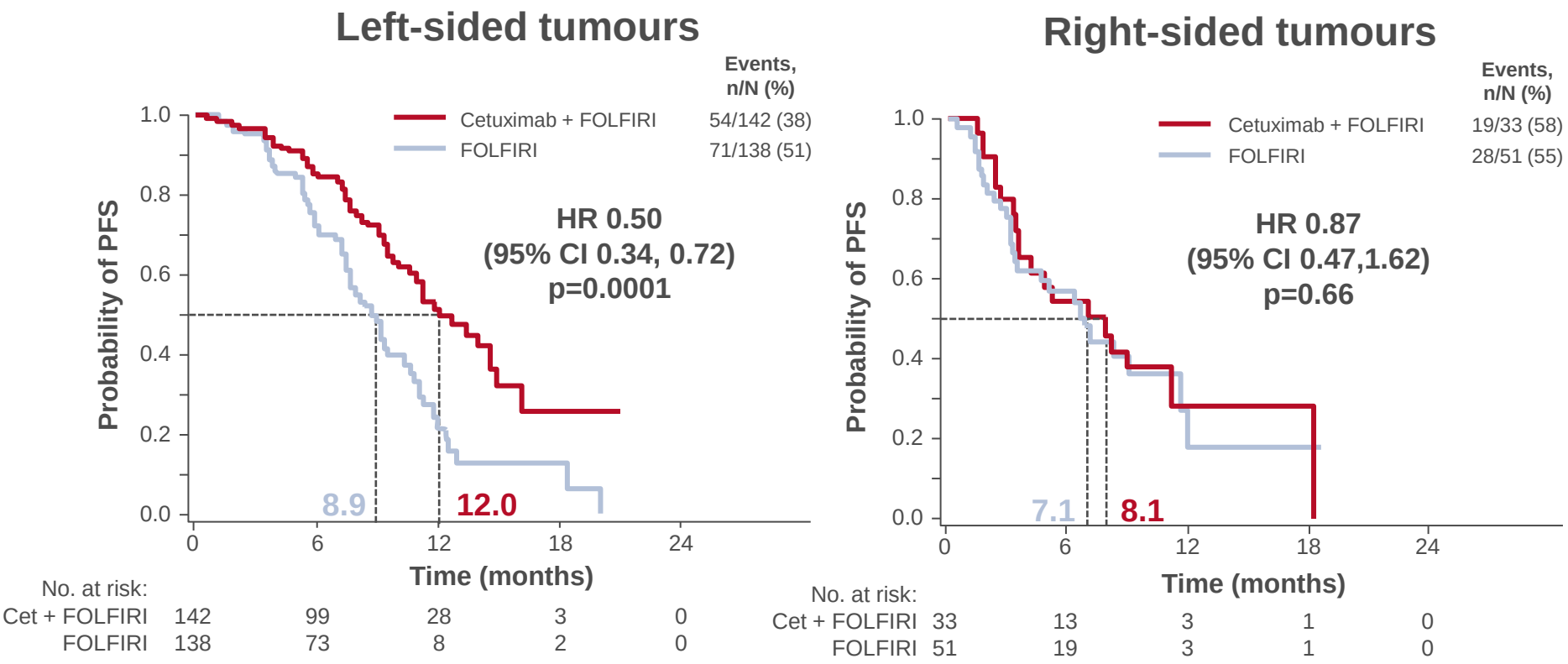
Interaction p-value: 0.09

Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

Right or left metastatic colon cancer: Will the side change your treatment?

Key results (continued)

CRYSTAL: PFS



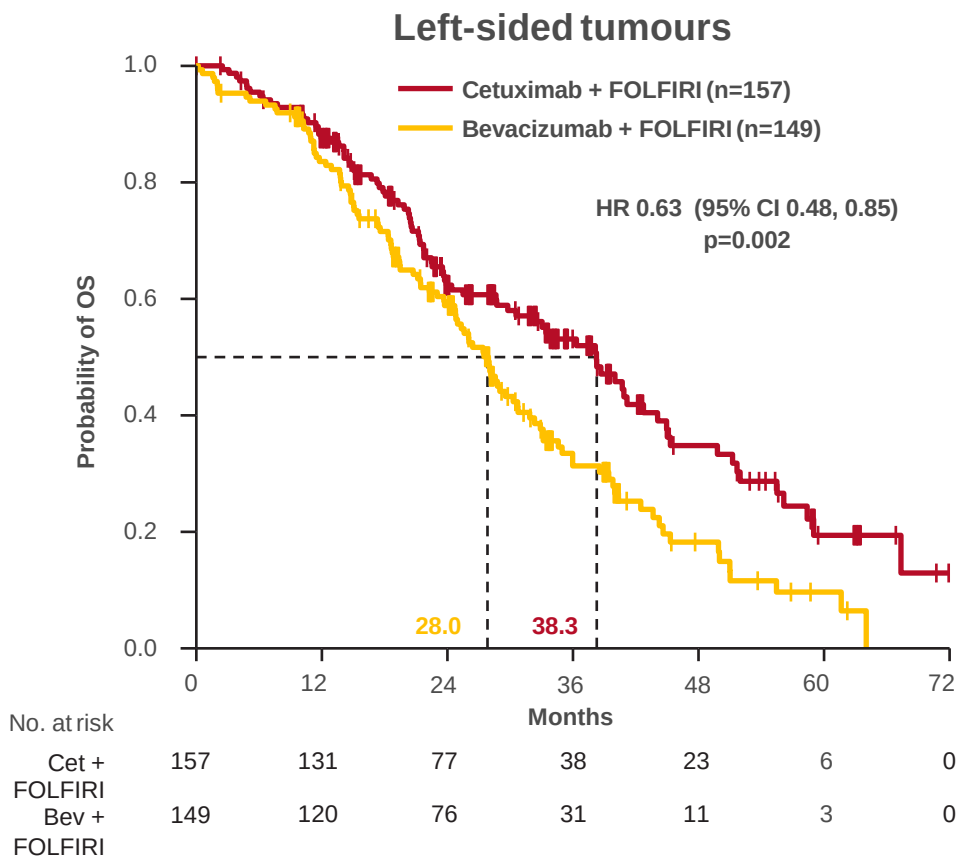
Interaction p-value: 0.11

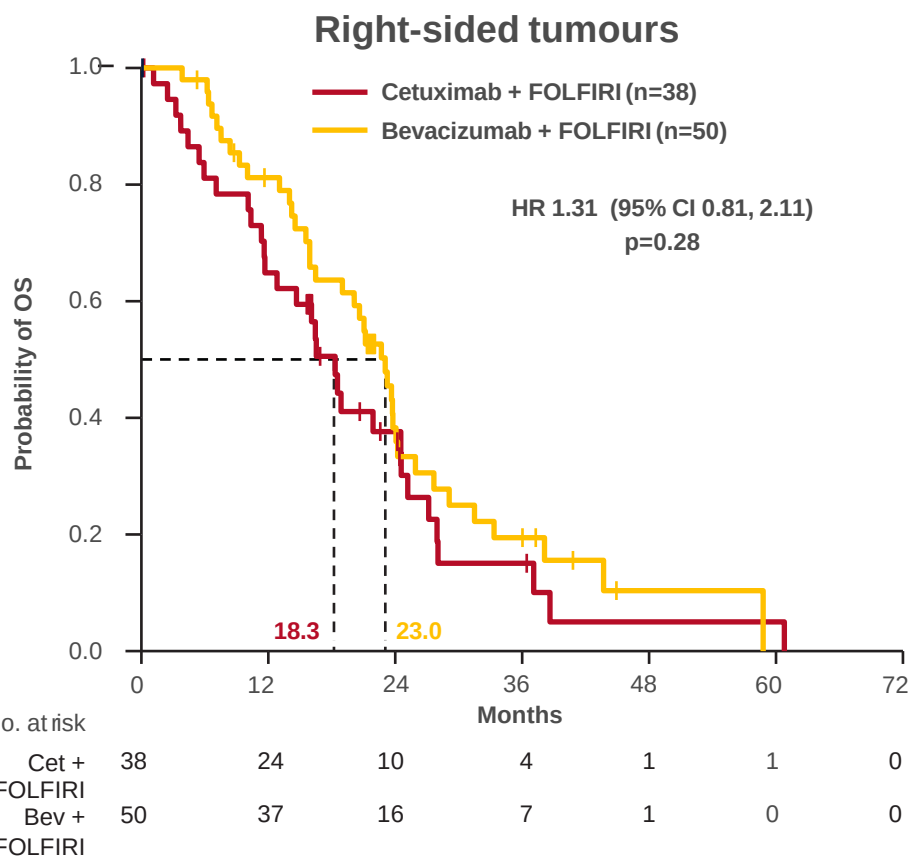
Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

Right or left metastatic colon cancer: Will the side change your treatment?

Key results (continued)

FIRE-3: OS





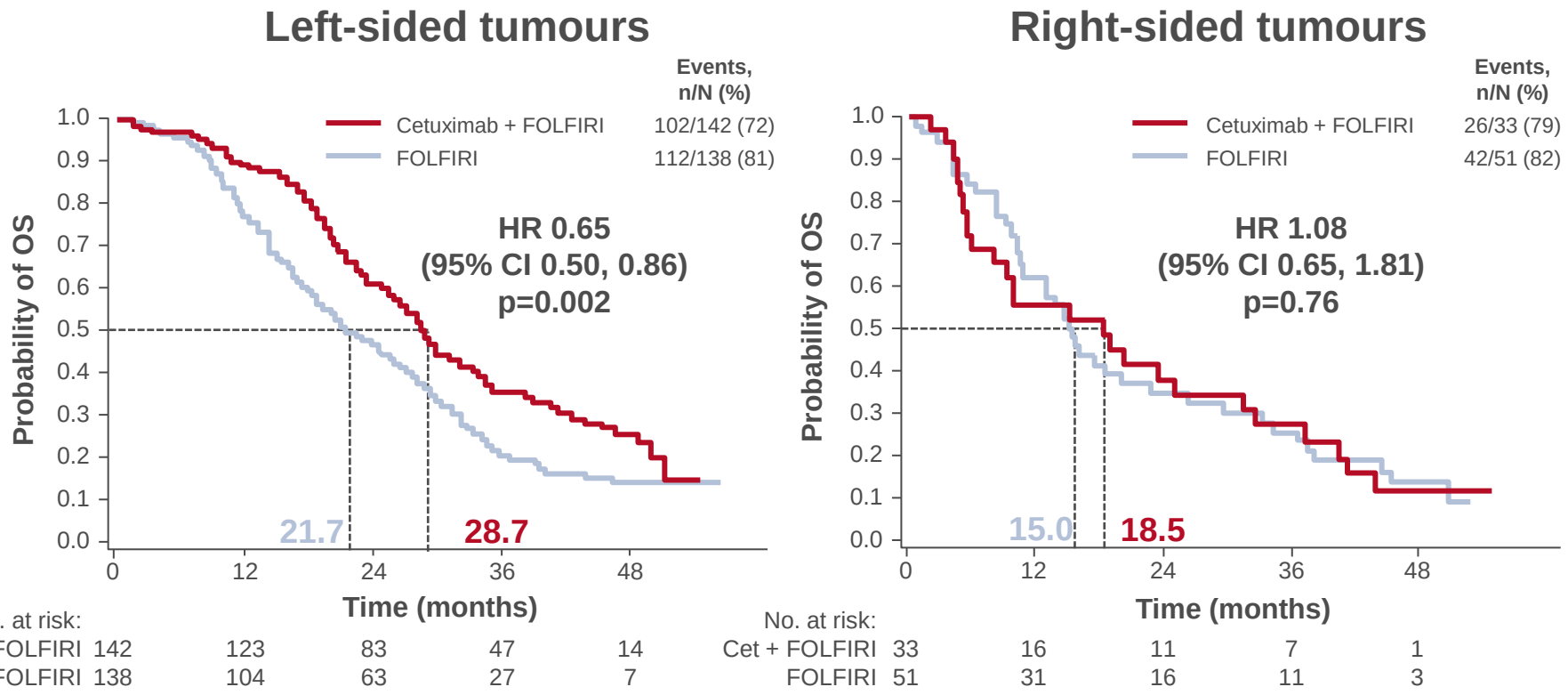
Interaction p-value: 0.009

Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

Right or left metastatic colon cancer: Will the side change your treatment?

Key results (continued)

CRYSTAL: OS

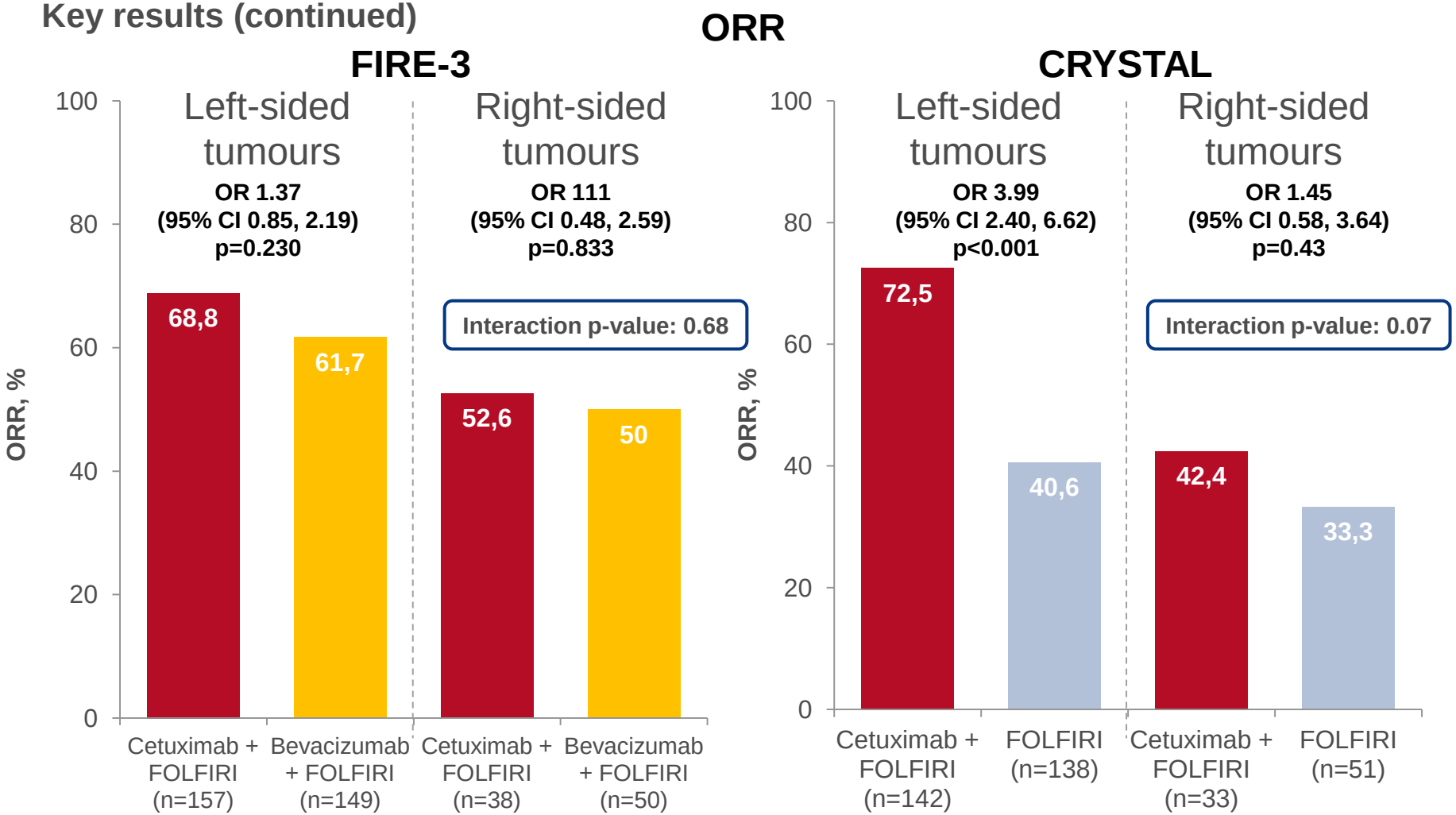


Interaction p-value: 0.17

Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

Right or left metastatic colon cancer: Will the side change your treatment?

Key results (continued)



Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

Right or left metastatic colon cancer: Will the side change your treatment?

Conclusions

- **Patients with left-sided tumours have a better prognosis than those with right-sided tumours**
- **Patients with left-sided tumours gained more benefit from cetuximab + FOLFIRI than from bevacizumab + FOLFIRI in the FIRE-3 trial**
  - **Patients with right-sided tumours may benefit from bevacizumab + FOLFIRI although the results were only numerically greater**
- **Patients with left-sided tumours gained more benefit from the addition of cetuximab to 1L FOLFIRI than those with right-sided tumours in the CRYSTAL trial**
- **Any new trials should stratify by location (right vs. left)**
- **Results and recommendations are quite robust if it is only the first-line treatment that matters**
- **However, more prospective sequentially designed clinical trials based on clinical/location and molecular characteristics are required if all the treatment sequences matter**

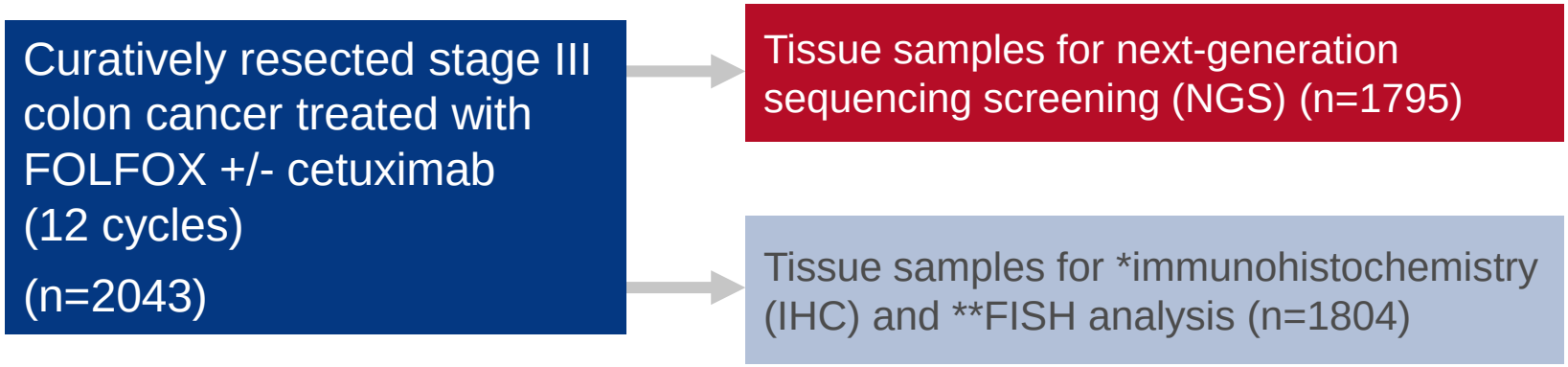
Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

ADJUVANT COLON CANCER

459O: ERBB2 alterations a new prognostic biomarker in stage III colon cancer from a FOLFOX based adjuvant trial (PETACC8) – Laurent-Puig et al

Study objective

- To evaluate the occurrence and the prognostic impact of ERBB2 alterations in patients with stage III colon cancer



PRIMARY ENDPOINT(S)

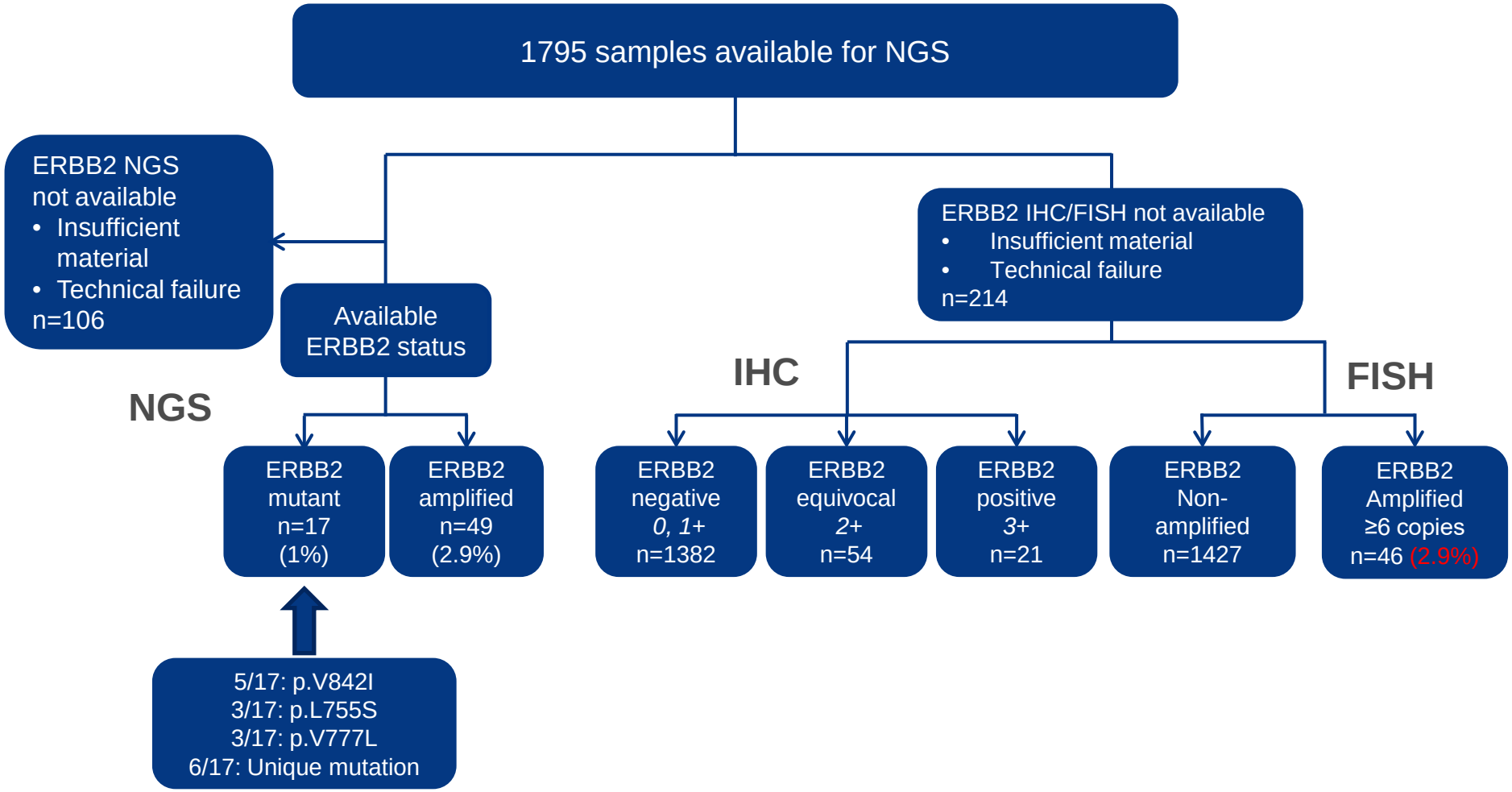
- Identification of ERBB2 alterations (i.e. mutation in exon 19–21/amplification)

*Polyclonal antibody HER2 clone 4B5, Ventana Roche

**Kit zytolight SPEC ERBB2/CEN17 dual colour.

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 459O

459O: ERBB2 alterations a new prognostic biomarker in stage III colon cancer from a FOLFOX based adjuvant trial (PETACC8) – Laurent-Puig et al

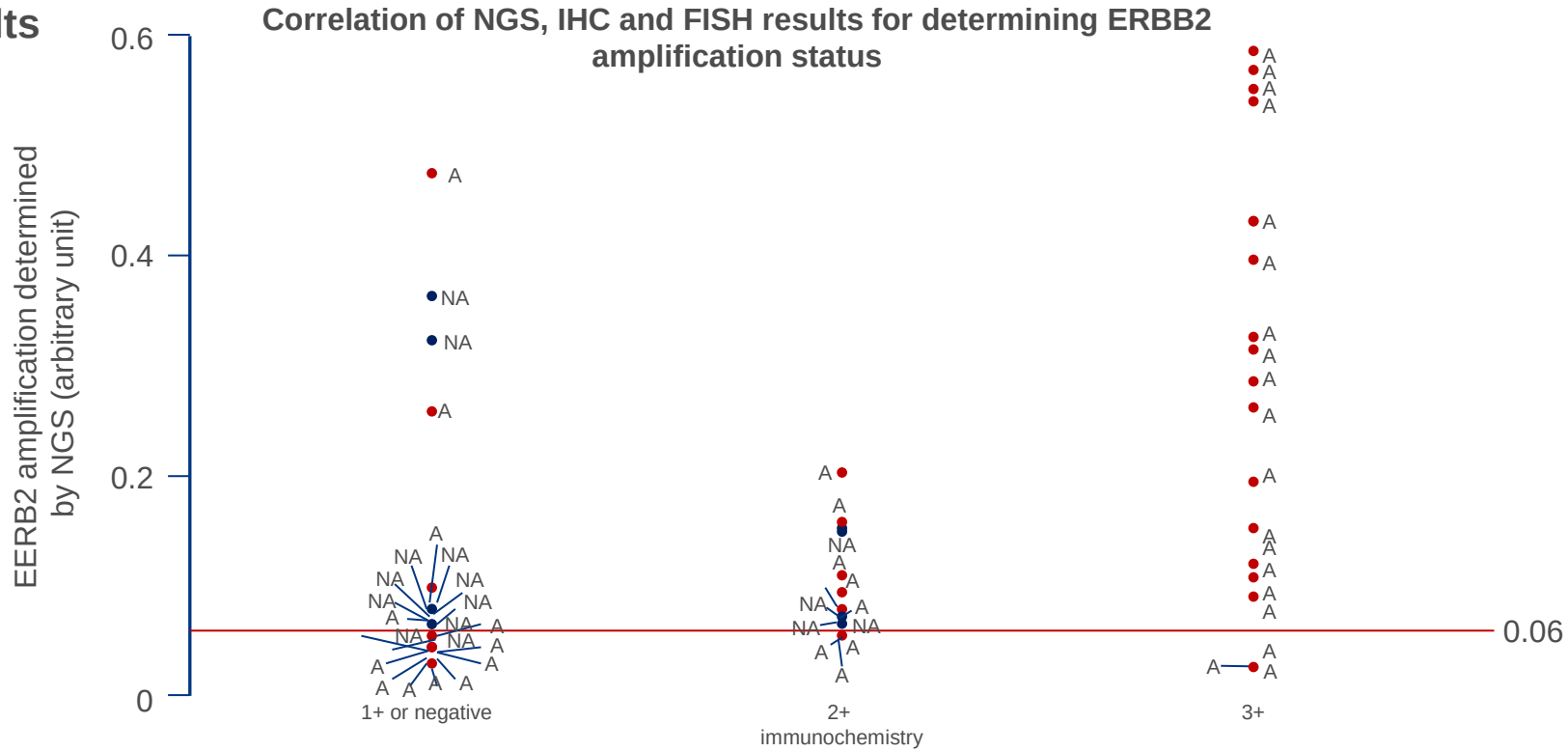


A mutation and an amplification were observed in 2 cases, with ERBB2 alteration in 64 (3.8%) cases . In the *KRAS* wild-type group, 42 (5.6%) ERBB2 alterations were reported.

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 459O

459O: ERBB2 alterations a new prognostic biomarker in stage III colon cancer from a FOLFOX based adjuvant trial (PETACC8) – Laurent-Puig et al

Key results



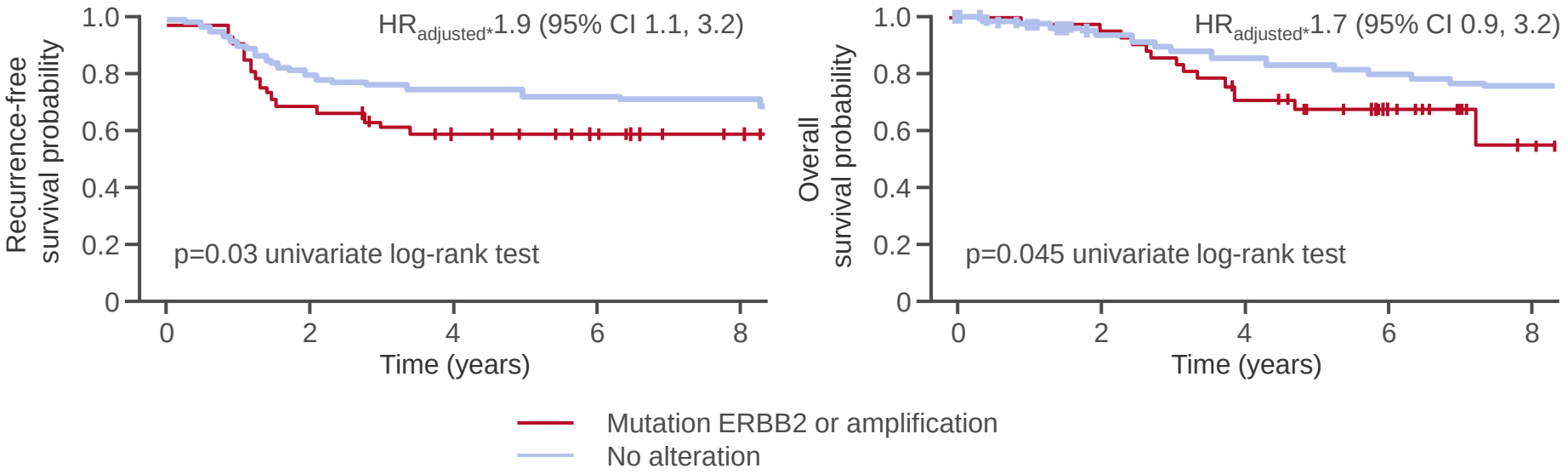
- No significant differences were observed between patient groups on the basis of age, gender, tumour location, perforation/occlusion status, histological grading, N staging or vascular and lymphatic infiltration
- However, significant differences in ERBB2 alteration status were observed when patients were divided by T staging (pT1-2 vs. pT3-4; p=0.04) and RAS status
  - A total of 42 (5.6%) patients in the KRAS wild-type group displayed ERBB2 alterations vs. 22 (2.4%) patients with RAS mutation (p<0.001)

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 459O

459O: ERBB2 alterations a new prognostic biomarker in stage III colon cancer from a FOLFOX based adjuvant trial (PETACC8) – Laurent-Puig et al

Key results (continued)

- Recurrence-free survival and OS were assessed according to ERBB2 status, utilising amplification data derived from both NGS and FISH (where concordant) and mutation data derived from NGS



*Results adjusted according to RAS status, histological grading, perforation or occlusion pN and pT, age, tumour location, vascular and lymphatic invasion, treatment arm

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 459O

459O: ERBB2 alterations a new prognostic biomarker in stage III colon cancer from a FOLFOX based adjuvant trial (PETACC8) – Laurent-Puig et al

Conclusions

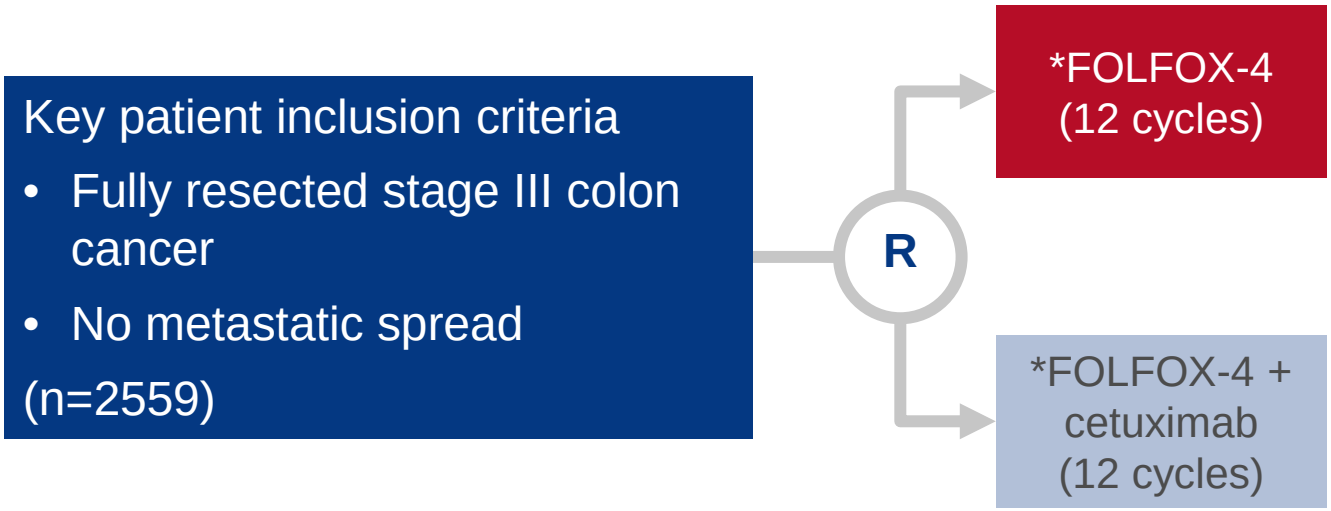
- **In this analysis, ERBB2 alterations occurred in 3.9% of patients with stage III colon cancer**
  - **Alterations in ERBB2 were found to be more common in the patients with a wild-type KRAS genotype vs. patients with a mutant KRAS genotype**
- **NGS and FISH results showed good correlation when detecting ≥6 copies of ERBB2**
- **Based on these findings, ERBB2 is considered to be a poor prognostic indicator for colorectal cancer**

Laurent-Puig P et al. Ann Oncol 2016; 27 (suppl 6): abstr 459O

461O: Adjuvant FOLFOX+ cetuximab vs FOLFOX in full RAS and BRAF wild type stage III colon cancer patients: Results from the PETACC8 trial – Taieb et al

Study objective

- To assess whether mutations in NRAS and BRAF have a prognostic impact on patients with stage III colon cancer treated with FOLFOX with or without cetuximab



PRIMARY ENDPOINT(S)

- DFS

SECONDARY ENDPOINTS

- TTR, OS, prognostic value of KRAS, NRAS and BRAF mutations

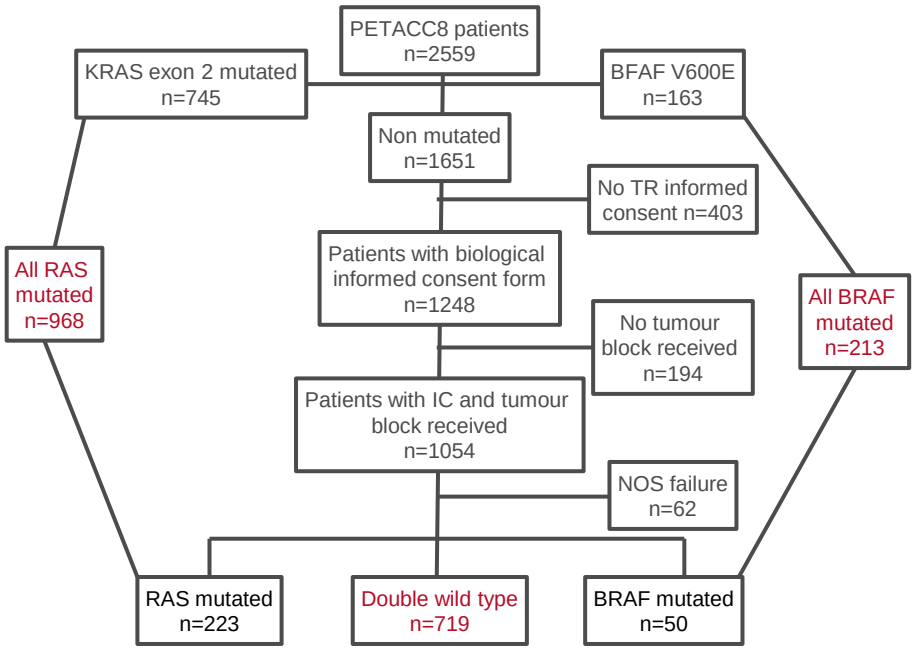
*FOLFOX-4: oxaliplatin iv over 2 h on d1 and leucovorin calcium iv over 2 h and fluorouracil iv continuously over 22 h on d1 and 2, on a 14-day cycle for up to 12 cycles

Taieb J et al. Ann Oncol 2016; 27 (suppl 6): abstr 461O

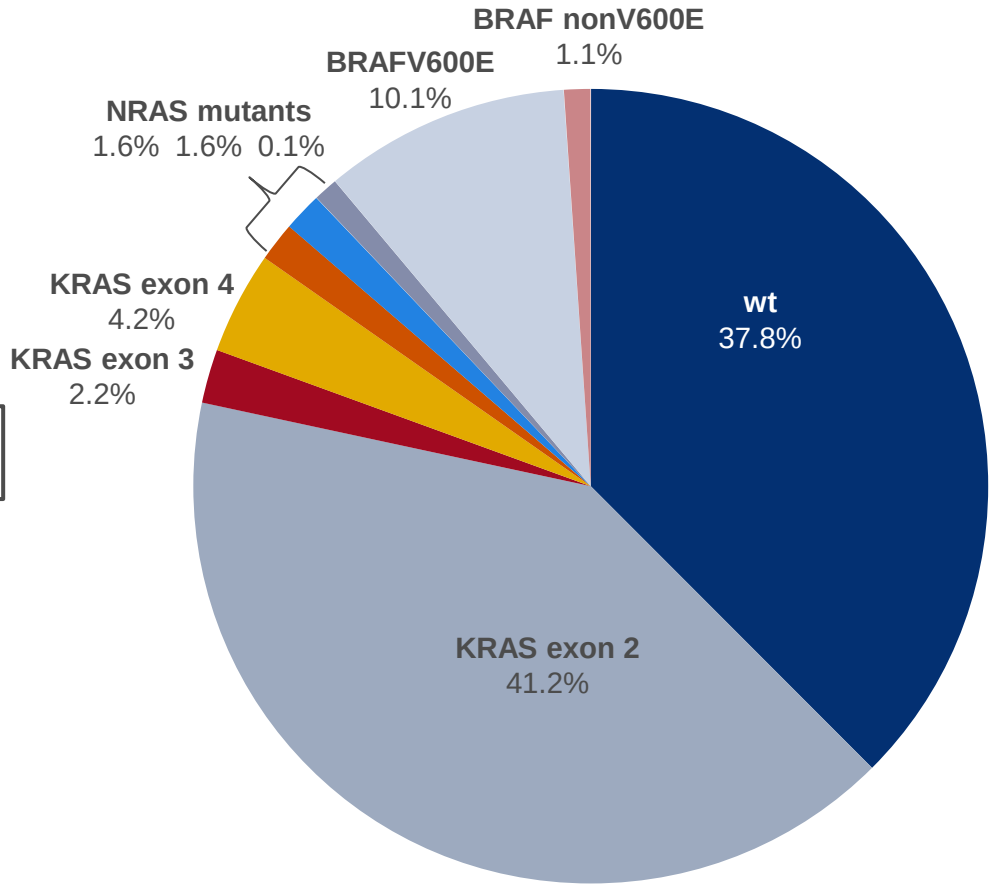
461O: Adjuvant FOLFOX+ cetuximab vs FOLFOX in full RAS and BRAF wild type stage III colon cancer patients: Results from the PETACC8 trial – Taieb et al

Key results

Flow chart



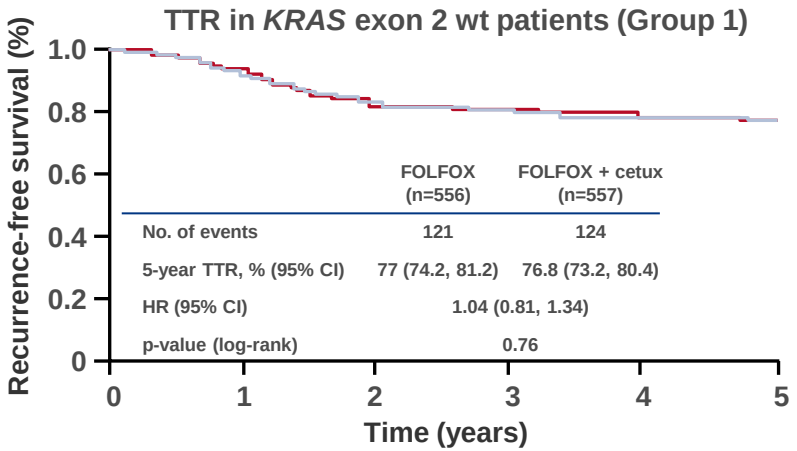
RAS and BRAF mutations in patients with NGS assessed tumours (n=1900)

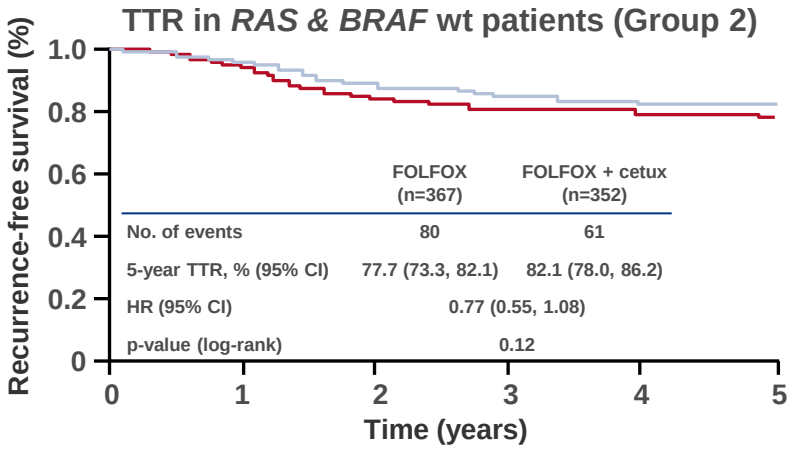


Taieb J et al. Ann Oncol 2016; 27 (suppl 6): abstr 461O

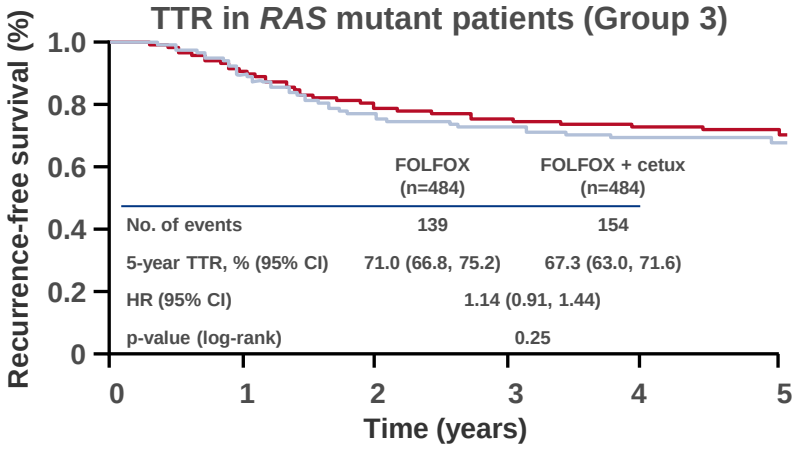
461O: Adjuvant FOLFOX+ cetuximab vs FOLFOX in full RAS and BRAF wild type stage III colon cancer patients: Results from the PETACC8 trial – Taieb et al

Key results





FOLFOX
FOLFOX + cetux

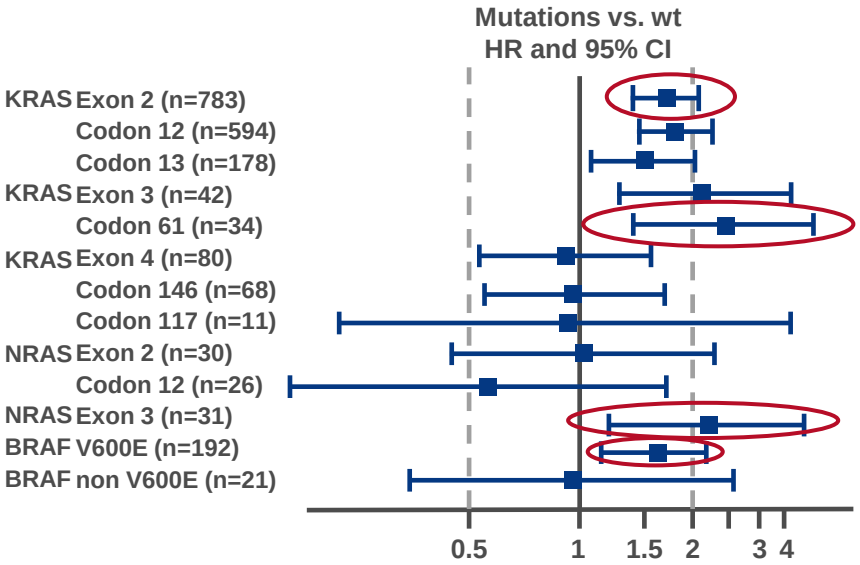


Taieb J et al. Ann Oncol 2016; 27 (suppl 6): abstr 461O

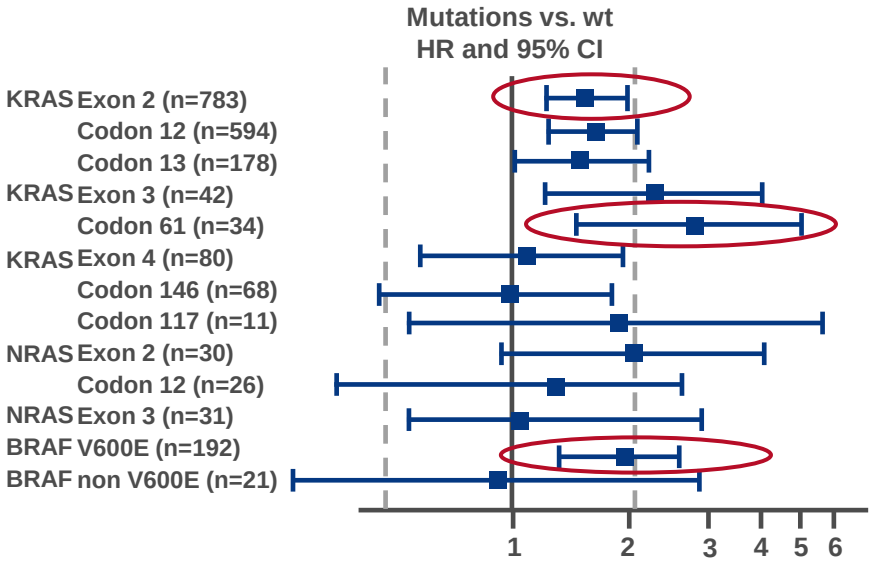
461O: Adjuvant FOLFOX+ cetuximab vs FOLFOX in full RAS and BRAF wild type stage III colon cancer patients: Results from the PETACC8 trial – Taieb et al

Key results (continued)

Impact of rare individual mutations on TTR



Impact of rare individual mutations on OS



Taieb J et al. Ann Oncol 2016; 27 (suppl 6): abstr 461O

461O: Adjuvant FOLFOX+ cetuximab vs FOLFOX in full RAS and BRAF wild type stage III colon cancer patients: Results from the PETACC8 trial – Taieb et al

Conclusions

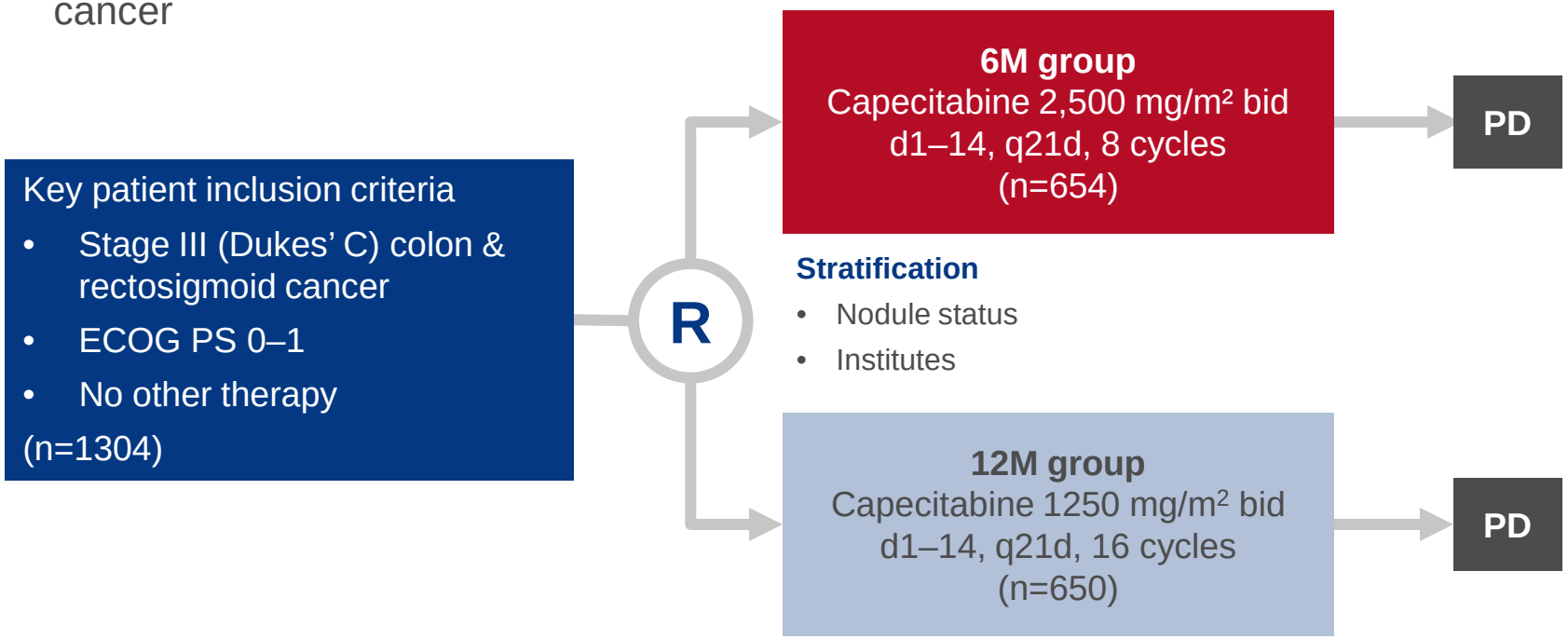
- A trend for improved TTR, DFS and OS was seen by adding cetuximab to FOLFOX in patients with RAS and BRAF wt tumours
  - Alternatively, a trend for a worse TTR, DFS and OS was seen when adding cetuximab to FOLFOX in patients with RAS mutant tumours
- None of the results reached statistical significance
- NRAS and KRAS codon 61 mutations appear to have the same prognostic value as KRAS exon 2 or BRAF V600E

Taieb J et al. Ann Oncol 2016; 27 (suppl 6): abstr 461O

469PD: Phase III trial of 24 weeks vs. 48 weeks capecitabine adjuvant chemotherapy for patients with stage III colon cancer: Final results of JFMC37-0801 – Yamaguchi et al

Study objective

- To test the superiority of 48-week treatment of capecitabine-adjuvant CT to 24-week conventional treatment with regard to DFS in patients with stage III colon and rectosigmoid cancer



PRIMARY ENDPOINT(S)

- DFS

SECONDARY ENDPOINTS

- OS, RFS, 2-year DFS, AEs

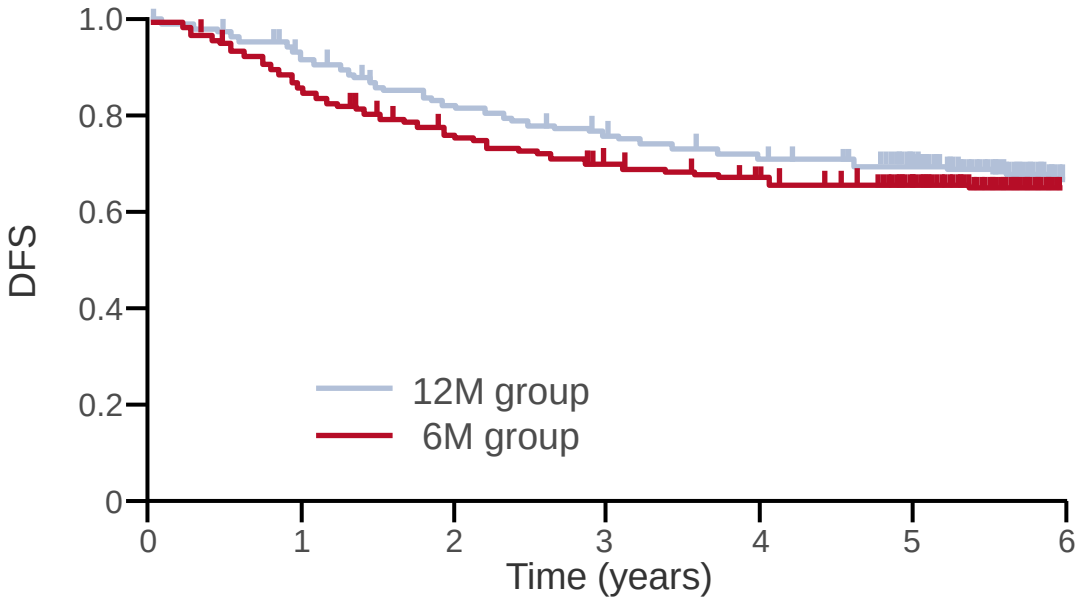
*Duration: 5 weeks; †duration: 6 weeks.

Yamaguchi S et al. Ann Oncol 2016; 27 (suppl 6): abstr 469PD

469PD: Phase III trial of 24 weeks vs. 48 weeks capecitabine adjuvant chemotherapy for patients with stage III colon cancer: Final results of JFMC37-0801 – Yamaguchi et al

Key results

DFS



HR 0.866 (95% CI 0.717, 1.046)
p=0.068

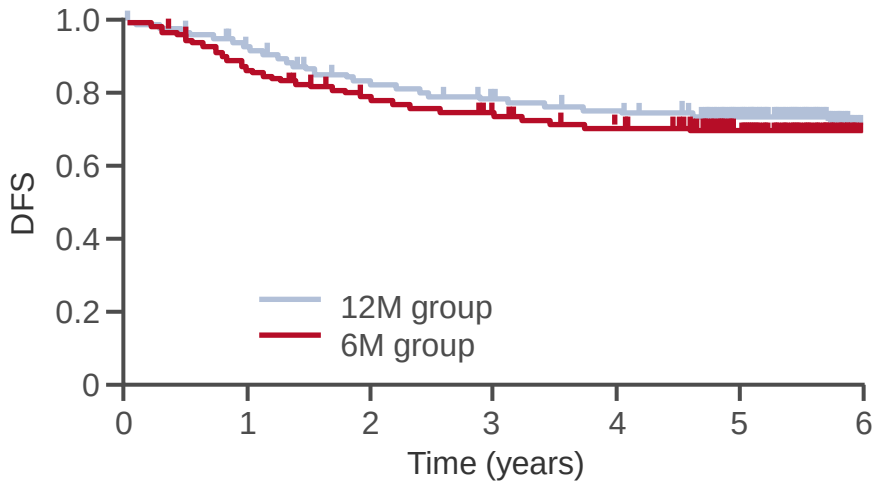
	12M group	6M group
3-year DFS, % (95% CI)	75.3 (71.77, 78.45)	70.0 (66.32, 73.37)
5-year DFS, % (95% CI)	68.7 (64.92, 72.10)	65.3 (61.45, 68.79)

Yamaguchi S et al. Ann Oncol 2016; 27 (suppl 6): abstr 469PD

469PD: Phase III trial of 24 weeks vs. 48 weeks capecitabine adjuvant chemotherapy for patients with stage III colon cancer: Final results of JFMC37-0801 – Yamaguchi et al

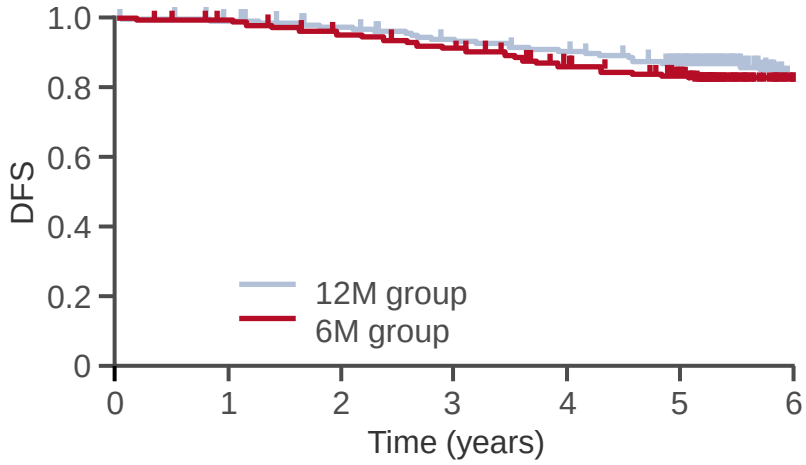
Key results (continued)

RFS



HR 0.808 (95% CI 0.658, 0.992)
p=0.0207

OS



HR 0.737 (95% CI 0.557, 0.975)
p=0.0159

	12M group	6M group
5-year RFS, % (95% CI)	74.1 (70.53, 77.32)	69.3 (65.57, 72.69)
5-year OS, % (95% CI)	87.6 (84.73, 89.89)	83.2 (80.07, 85.87)

Yamaguchi S et al. Ann Oncol 2016; 27 (suppl 6): abstr 469PD

469PD: Phase III trial of 24 weeks vs. 48 weeks capecitabine adjuvant chemotherapy for patients with stage III colon cancer: Final results of JFMC37-0801 – Yamaguchi et al

Key results (continued)

Completion rate of protocol treatment

All treated patients	12M group (n=636), n (%)	6M group (n=642), n (%)
Complete	293 (46.1)	459 (71.5)
Incomplete	343 (53.9)	183 (28.5)
8 courses completion	456 (71.7)	459 (71.5)

Dose reduction and delay/interruption rates

All treated patients	12M group (n=636), n (%)	6M group (n=642), n (%)
Dose reduction (+)	306 (48.1)	241 (37.5)
Delay/interruption (+)	437 (68.7)	379 (59.0)

Yamaguchi S et al. Ann Oncol 2016; 27 (suppl 6): abstr 469PD

469PD: Phase III trial of 24 weeks vs. 48 weeks capecitabine adjuvant chemotherapy for patients with stage III colon cancer: Final results of JFMC37-0801 – Yamaguchi et al

Key results (continued)

- Overall, grade 3–4 adverse events were comparable in both groups
  - However, incidence of hand-foot disease syndrome was increased in the 12-month treatment group

Conclusions

- **Compared with conventional therapy, the 48-week (12-month) treatment of capecitabine adjuvant chemotherapy did not demonstrate DFS superiority in patients with stage III colon cancer**
- **However, p-values associated with OS and RFS comparing the 48-week (12-month) treatment with conventional 24-week (6-month) treatment were $p<0.025$**
- **With regard to the optimal duration of adjuvant chemotherapy for stage III colon cancer, further investigation should be considered**

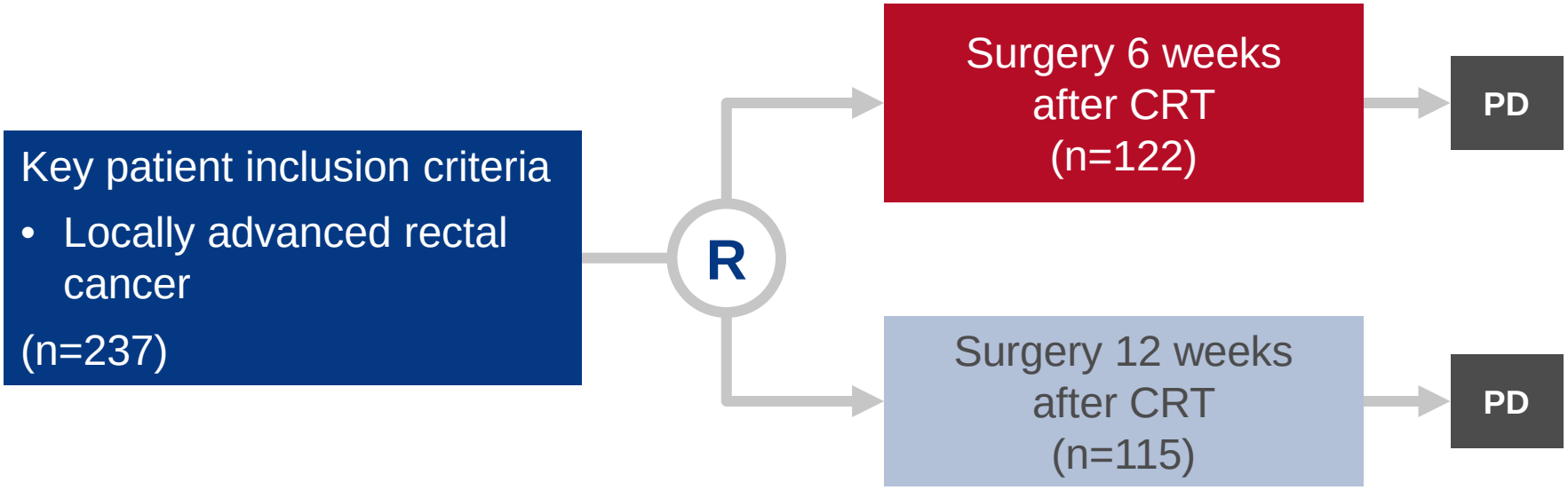
Yamaguchi S et al. Ann Oncol 2016; 27 (suppl 6): abstr 469PD

PERIOPERATIVE RECTAL CANCER

452O: Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy? – Evans et al

Study objective

- To investigate whether delay in surgery to 12 weeks vs. 6 weeks after CRT leads to greater rectal cancer downstaging and regression



PRIMARY ENDPOINT(S)

- Difference in proportion of patients in each arm downstaged according to MRI T-stage*

SECONDARY ENDPOINTS

- pCR rate
- mrTRG 1–2 rate

*Defined as any reduction in T-stage/sub-stage.

mrTRG, MRI-assessed tumour regression grade

Evans J et al. Ann Oncol 2016; 27 (suppl 6): abstr 452O

452O: Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy? – Evans et al

Key results

	12-week arm (n=115)	6-week arm (n=122)	p-value
mrTRG downstaging, n (%)	67 (58)	52 (43)	0.019
mrTRG, n (%)	21 (22)	7 (6)	<0.05
ypT0, n	23	9	<0.05
pCR, %	20	9	<0.05

Surgical morbidity

- The following were assessed in this study
  - ASA grade
  - stoma formation/type of operation performed
  - operative difficulty
  - blood loss
  - length of hospital stay
  - post-operative complications

Evans J et al. Ann Oncol 2016; 27 (suppl 6): abstr 452O

452O: Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy? – Evans et al

Conclusions

- Surgery scheduled 12 weeks after CRT leads to a significant increase in mrT downstaging, pCR and improves mrTRG
- Since mrTRG is a confirmed predictor of DFS, performing surgery before maximal regression may not be clinically beneficial to patients

Evans J et al. Ann Oncol 2016; 27 (suppl 6): abstr 452O

467PD: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: Final analyses – Schmoll et al

Study objective

- To assess whether the addition of oxaliplatin to preoperative fluoropyrimidine-based CRT followed by postoperative adjuvant fluoropyrimidine-based CT improves DFS in locally advanced rectal cancer

Key patient inclusion criteria

- Rectal adenocarcinoma ≤12 cm from anal verge
- T3/4 and/or N+
- R0/1-resectable +/- preop RCTx
- WHO/ECOG PS 0–2

(n=1094)

R 1:1

Capecitabine* + oxaliplatin† RT 45 Gy: 1.8 Gy** Optional: RT 5.4 Gy‡

Capecitabine* RT 45 Gy: 1.8 Gy** Optional: RT 5.4 Gy‡

Surgery

Capecitabine# + oxaliplatin## q3w 6 cycles

Capecitabine q3w 6 cycles

*825 mg/m^2 po bid on d1–33 w/o weekends; †50 mg/m^2 iv on d1, 8, 15, 22, 29; **d1–33 w/o weekends; ‡d36–38 with capecitabine 825 mg/m^2 po bid; #1000/m^2 po bid (evening of d1– morning of d15); ##130 mg/m^2 iv d1

PRIMARY ENDPOINT

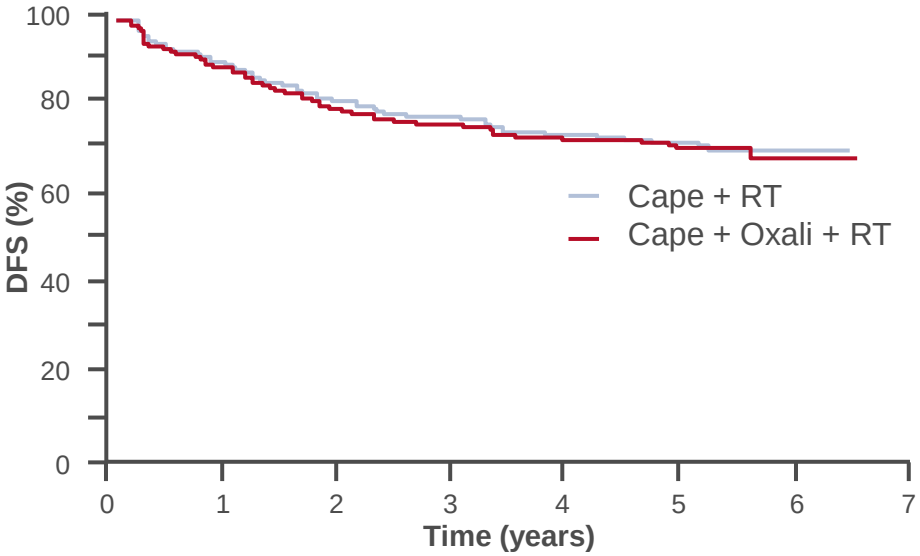
- 3-year DFS (65% → 72%; HR 0.763)

Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr 467PD

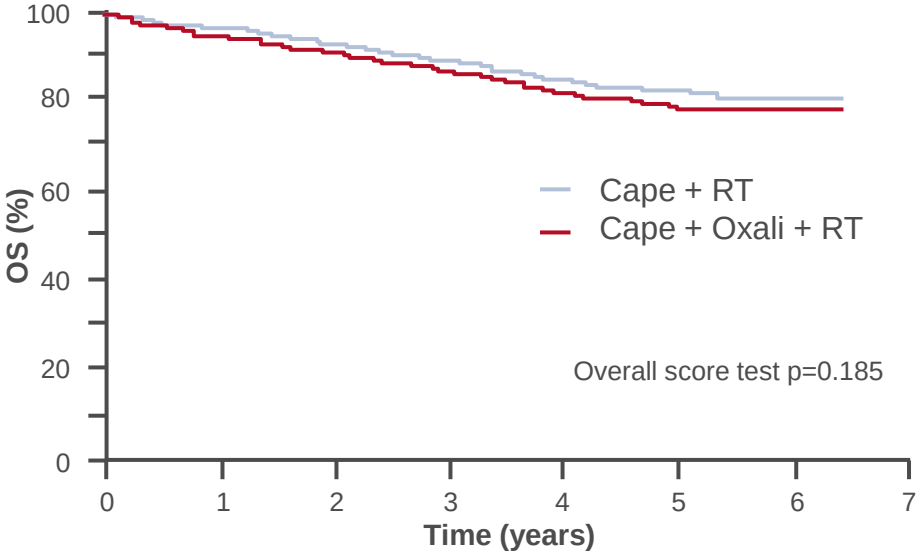
467PD: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: Final analyses – Schmoll et al

Key results

DFS



OS



	Capecitabine + oxaliplatin	Capecitabine
3-year DFS, %	75.4	76.5
HR (95% CI) p-value	1.04 (0.82, 1.31) 0.768	

	Capecitabine + oxaliplatin	Capecitabine
3-year OS, %	87.6	90.1
HR (95% CI) p-value	1.22 (0.91, 1.65) 0.185	

Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr 467PD

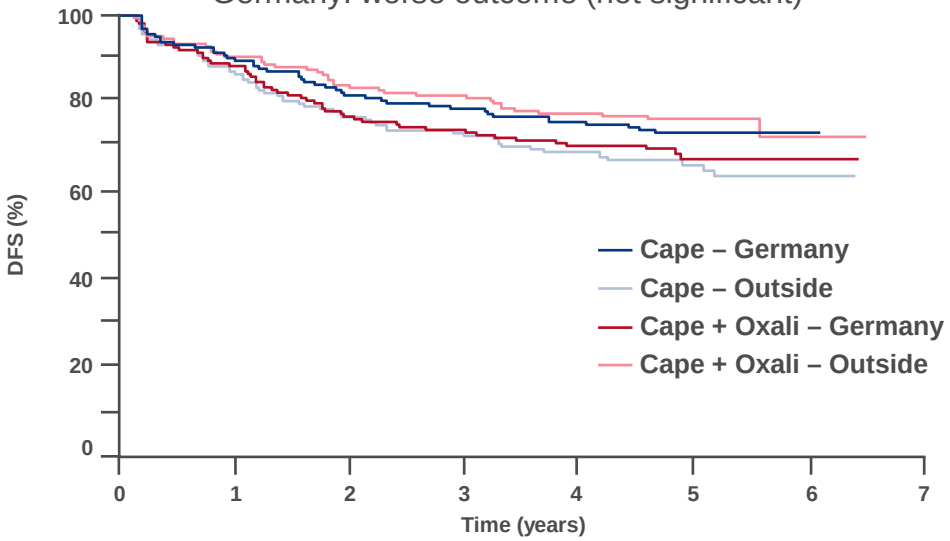
467PD: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: Final analyses – Schmoll et al

Key results (continued)

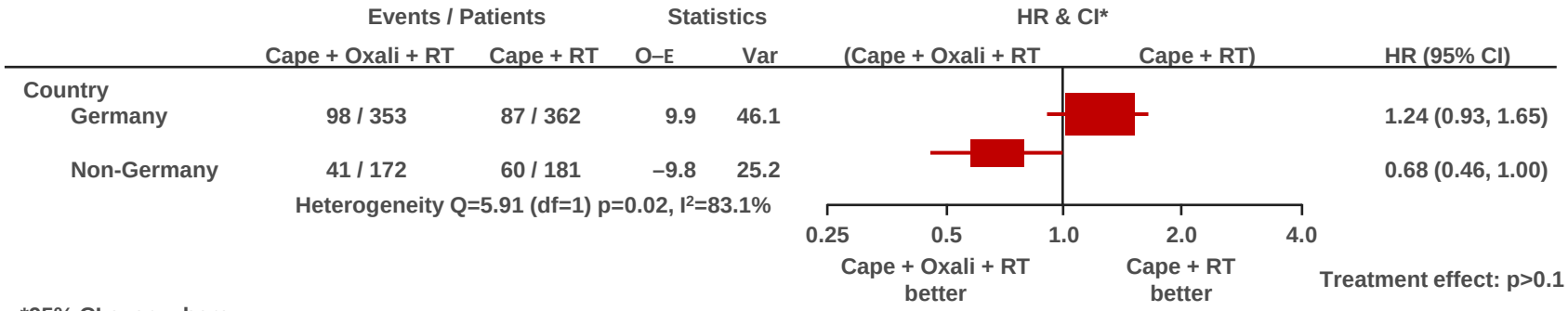
DFS Germany vs. non-Germany

Non--Germany: borderline significant improvement

Germany: worse outcome (not significant)



	Capecitabine + oxaliplatin	Capecitabine
Germany		
3-year DFS, %	73.6	78.2
HR (95% CI) p-value	1.24 (0.93, 1.65) 0.145	
Non-Germany		
3-year DFS, %	73.2	81.1
HR (95% CI) p-value	0.68 (0.45, 1.10) 0.052	

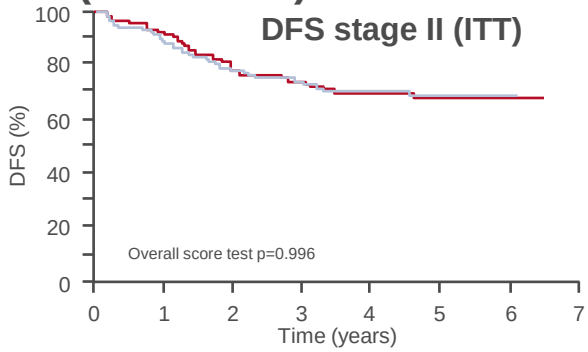


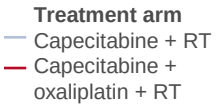
*95% CI everywhere

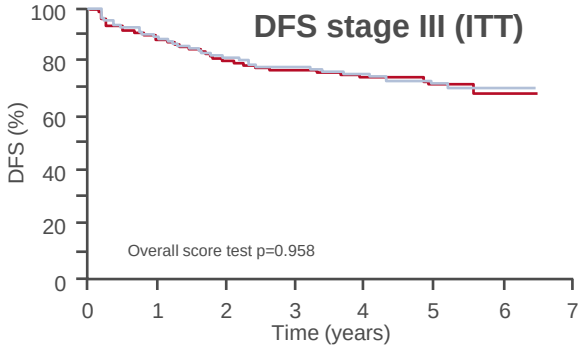
Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr 467PD

467PD: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: Final analyses – Schmoll et al

Key results (continued)

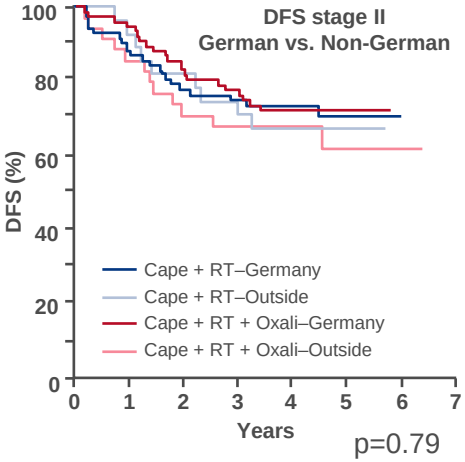




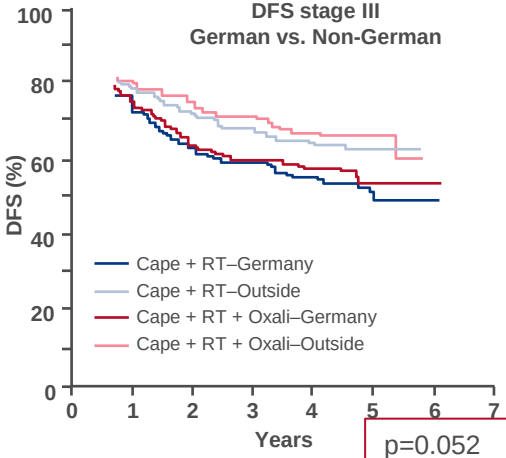


	Capecitabine + oxaliplatin	Capecitabine
3-year DFS, %	74.5	74.6
HR (95% CI); p-value	1.0 (0.61, 1.63); 0.996	

	Capecitabine + oxaliplatin	Capecitabine
3-year DFS, %	77.5	78.0
HR (95% CI); p-value	1.0 (0.75, 1.31); 0.958	



	Cape + oxaliplatin	Cape
Germany, n	83	88
3-year DFS, %	77.6	74.8
HR	0.92	1.0
Non-Germany, n	35	28
3-year DFS, %	67.4	74.1
HR	1.31	1.13



	Cape + oxaliplatin	Cape
Germany, n	238	242
3-year DFS , %	73.1	80.9
HR	1.41	1.0
Non-Germany, n	133	149
3-year DFS, %	84.8	73.0
HR	0.89	1.57

Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr 467PD

467PD: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: Final analyses – Schmoll et al

Conclusions

- **The addition of oxaliplatin to capecitabine therapy was not associated with improvement in DFS vs. capecitabine alone**
- **Strong differences were observed between German and non-German patients**
  - **Non-German patients with stage III disease had significantly improved outcomes on capecitabine + oxaliplatin vs. capecitabine**
  - **In contrast, German patients had non-significant trend for superior outcomes with capecitabine vs. capecitabine + oxaliplatin**
- **Multivariate analysis by baseline factors could not detect the factors responsible for the difference between German and non-German groups**
- **These results contradict those of the CAO/ARO/AIO-4 and PETACC 6 trials, therefore, the role of adjuvant oxaliplatin in addition to capecitabine/5FU remains unclear**

Schmoll H et al. Ann Oncol 2016; 27 (suppl 6): abstr 467PD