

GI SLIDE DECK 2013

Selected abstracts from:



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 gastrointestinal cancers from the major congresses in 2013: American Society of Clinical Oncology, ECCO-ESMO and WCGIC.

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 gastrointestinal 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, administrative and logistical support in the realisation of this activity.

Yours sincerely,

Eric Van Cutsem (President)
Philippe Rougier (Treasurer)
Thomas Seufferlein (Secretary General)
Executive Officers – ESDO Governing Board



ESDO Medical Oncology Slide Deck Editors 2013



Colorectal cancers

Prof Eric Van Cutsem, *Digestive Oncology, Leuven Cancer Institute, Belgium*



Prof Wolff Schmiegell, *Department of Medicine, Ruhr-University, Germany*



Prof Thomas Grünberger, *Department of General Surgery, Medical University of Vienna, Austria*



Pancreatic cancer and hepatobiliary tumours

Prof Jean-Luc Van Laetham, *Hôpital Erasme, Clinique Universitaire de Bruxelles, Belgium*



Prof Thomas Seufferlein, *Department of Internal Medicine, University of Ulm, Germany*



Gastro-oesophageal and neuroendocrine tumours

Prof Philippe Rougier, *Hôpital Européen Georges Pompidou, Paris, France*



Prof Côme Lepage, *Department of Hepatogastroenterology, University of Burgundy, France*



Biomarkers

Prof Eric Van Cutsem, *Digestive Oncology, Leuven Cancer Institute, Belgium*



Prof Thomas Seufferlein, *Department of Internal Medicine, University of Ulm, Germany*

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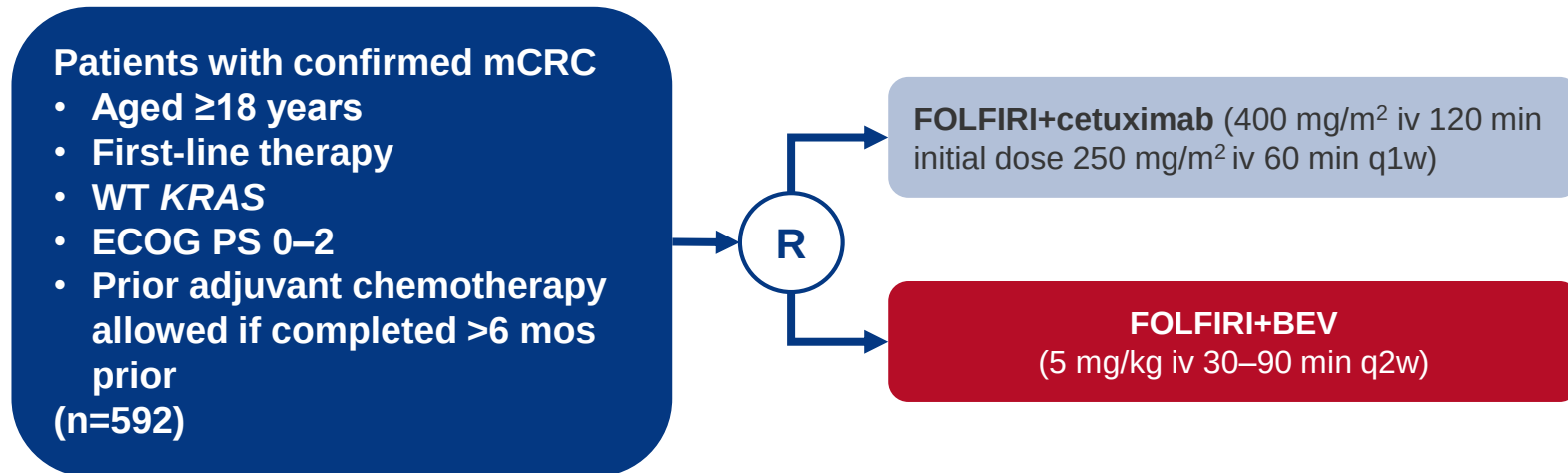
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ADJUVANT THERAPY

LBA3506: Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3) – Stintzing S et al

- Study objective
 - To compare FOLFIRI+cetuximab with FOLFIRI+BEV in first-line treatment of WT *KRAS* mCRC
- Study type / design



Primary endpoint

- ORR

Secondary endpoints

- PFS, OS, time to failure of strategy, safety

FOLFIRI: 5-FU: 400 mg/m² (iv bolus; folinic acid: 400 mg/m²
Irinotecan: 180 mg/m²
5-FU: 2400 mg/m² (iv 46 h)

LBA3506: Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3) – Stintzing S et al

- Key results

Patient characteristics	FOLFIRI+cetuximab (n=297)	FOLFIRI+BEV (n=295)
Male, %	72.1	66.4
Median age, years	64.0	65.0
Age <65, %	53.2	54.2
Age ≥65, %	46.8	45.8
Age >70, %	30.3	23.4
ECOG PS, %		
0	51.9	53.6
1	45.8	45.1
2	2.4	1.4
Site of primary tumour, %		
Colon	56.6	60.0
Rectum	38.7	35.9
Colon+rectum	3.0	4.1
Liver metastasis, %		
Yes	31.3	31.9

LBA3506: Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3) – Stintzing S et al

- Key results (continued)

Evaluation of ORR

ORR	FOLFIRI+cetuximab		FOLFIRI+BEV		Odds ratio	
	%	95% CI	%	95% CI	95% CI	p-value
ITT population (n=592)	62.0	56.2, 67.5	58.0	52.1, 63.7	1.18 (0.85, 1.64)	0.183
Assessable for response (n=526)	72.2	66.2, 77.6	63.1	57.1, 68.9	1.52 (1.05, 2.19)	0.017

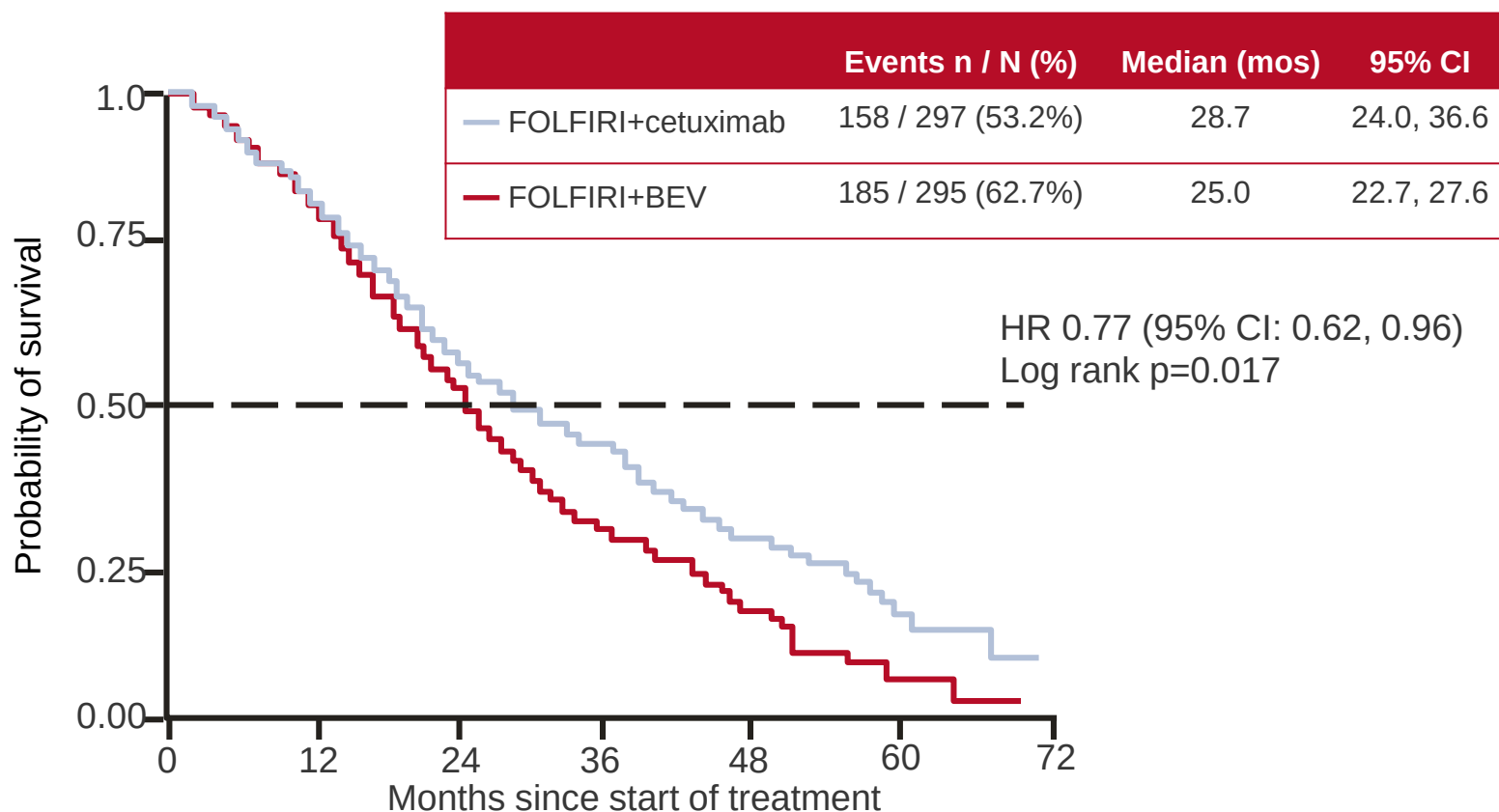
Evaluation of response

RECIST, n (%)	FOLFIRI+cetuximab (n=297)	FOLFIRI+BEV (n=295)
Complete response	13 (4.4)*	4 (1.4)*
Partial response	171 (57.6)	167 (56.6)
Stable disease	53 (17.5)*	85 (28.8)*
Progressive disease	21 (7.1)	16 (5.4)
Not evaluable	39 (13.1)	23 (7.8)

*Significant response differences; p = two-sided Fisher's exact test

LBA3506: Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3) – Stintzing S et al

- Key results (continued)
 - There was no difference in PFS between treatment arms
 - OS was significantly longer with FOLFIRI+cetuximab vs. FOLFIRI+BEV (figure)



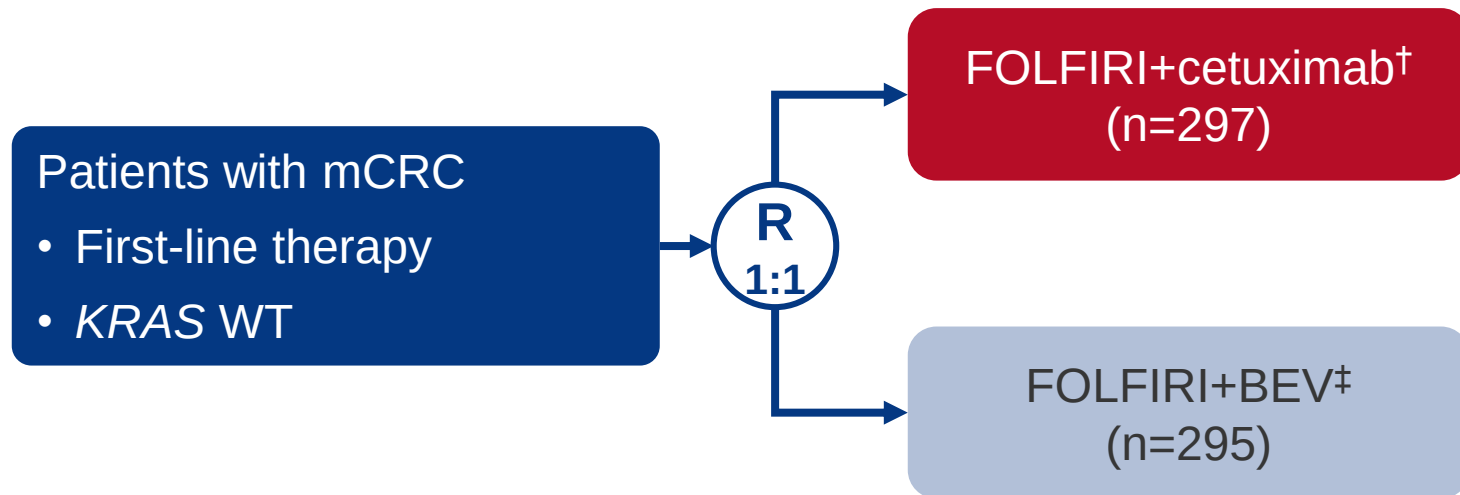
LBA3506: Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3) – *Stintzing S et al*

- **Conclusions**

- FIRE-3 is the first head-to-head comparison of FOLFIRI+cetuximab vs. FOLFIRI+BEV in WT *KRAS* mCRC patients
- ORR favoured FOLFIRI+cetuximab (62% vs. 58%, $p=0.183$), but did not reach significance in the ITT population
- ORR was significantly higher in patients receiving FOLFIRI+cetuximab (72.2% vs. 63.1%, $p=0.017$) in patients assessable for response
- FOLFIRI+cetuximab produced a clinically meaningful difference in median OS of 3.7 mos (HR 0.77) compared with FOLFIRI+BEV
- No difference in PFS between treatment arms was observed
- Toxicity profiles were manageable and as expected

17: Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients – Heinemann V et al

- Study objective
 - To examine the effects of *RAS** and *BRAF* mutations on ORR, PFS and OS in patients with mCRC
 - To compare FOLFIRI+cetuximab with FOLFIRI+BEV as first-line treatments



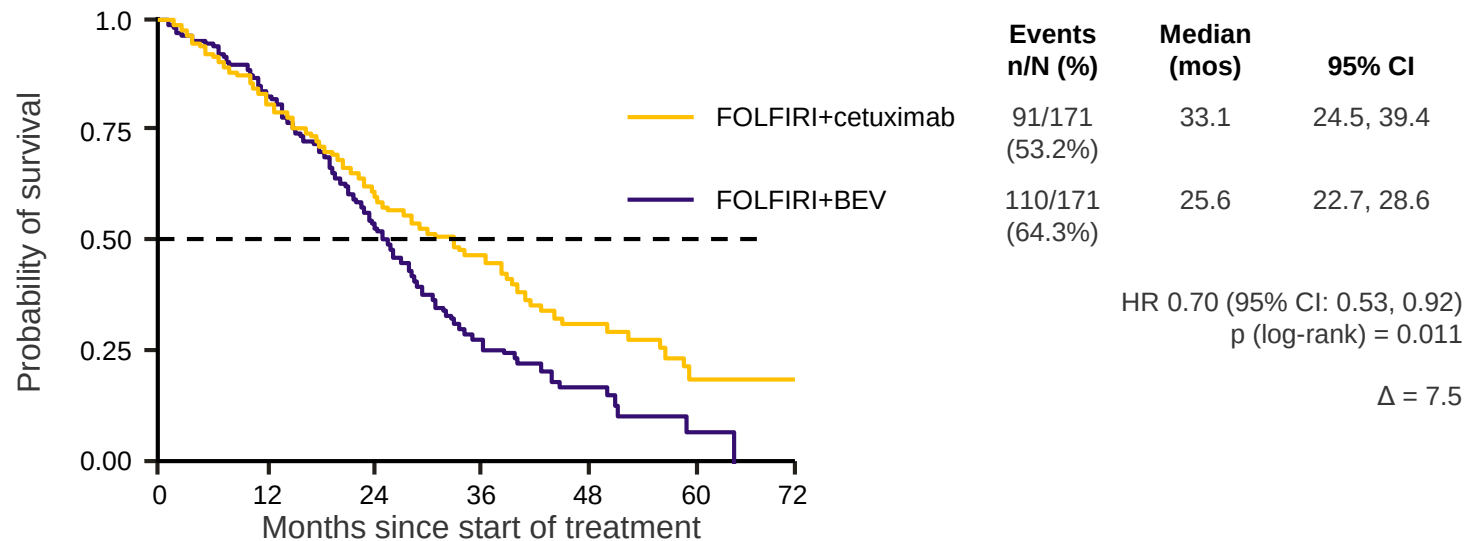
Primary endpoint

- ORR

*KRAS and NRAS exon 2, 3 and 4; †400 mg/m² iv 120-min initial dose, 250 mg/m² iv 60 min q1w; ‡5 mg iv 30–90 min q2w

17: Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients – Heinemann V et al

- Key results
 - The FIRE-3 study did not meet its primary endpoint
 - ORR 62% with FOLFIRI+cetuximab vs. 58% with FOLFIRI+BEV (p=0.183)
 - ORR and PFS were not significantly different between treatment arms in *RAS** WT tumours
 - OS significantly improved with FOLFIRI+cetuximab vs. FOLFIRI+BEV in *RAS** WT tumours (figure)



- First-line treatment with cetuximab did not provide any benefit vs. BEV in *RAS** mutant tumours

17: Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients – *Heinemann V et al*

- **Conclusions**
 - Patients without *RAS* mutations are more likely to benefit from first-line treatment with FOLFIRI+cetuximab
 - FOLFIRI+cetuximab-treated patients showed a clinically relevant survival benefit compared with patients receiving FOLFIRI+BEV therapy
 - Patients with mCRC may therefore benefit from being tested upfront for *RAS* (*KRAS* and *NRAS*) mutation status

3620: Overall survival (OS) analysis from PRIME: Randomized phase III study of panitumumab (pmab) with FOLFOX4 for first-line metastatic colorectal cancer (mCRC) – *Douillard J-V et al*

- Study objective
 - To estimate treatment effect of panitumumab+FOLFOX4 vs. FOLFOX4 alone on OS by *KRAS* exon 2 status
- Study type / design
 - Randomised Phase III study (PRIME) of panitumumab with FOLFOX4 for first-line mCRC
 - Patients were randomly allocated (1:1) to panitumumab 6.0 mg/kg q2w or FOLFOX4 alone and had no prior chemotherapy for mCRC, ECOG PS ≤ 2 and tumour tissue for biomarker testing
 - Exploratory updated OS analysis (the most mature estimate of OS in PRIME)

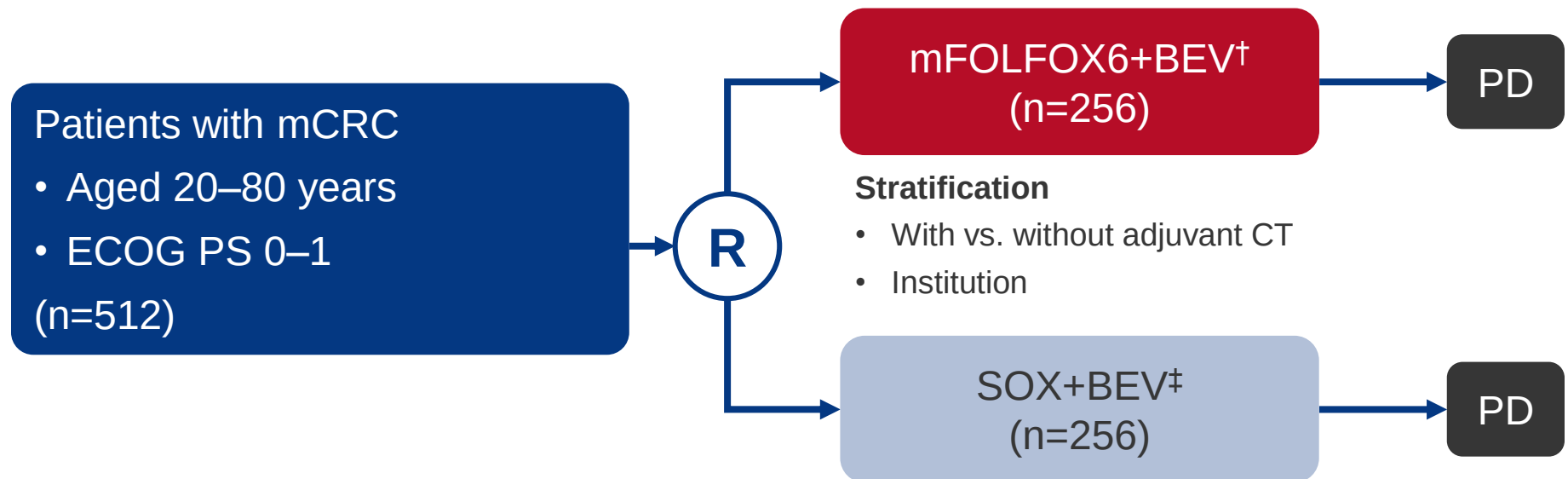
3620: Overall survival (OS) analysis from PRIME: Randomized phase III study of panitumumab (pmab) with FOLFOX4 for first-line metastatic colorectal cancer (mCRC) – *Douillard J-V et al*

- Key results
 - Median OS in patients with WT *KRAS* exon 2 mCRC: 4.4 mos improvement with panitumumab+FOLFOX4 vs. FOLFOX4 alone (HR 0.83; 95% CI: 0.70, 0.98; p=0.027)
 - Median OS in patients with mutant *KRAS* exon 2 mCRC: numerically worse in the panitumumab+FOLFOX4 vs. FOLFOX4 alone (15.5 vs. 19.2 mos, HR 1.16; 95% CI: 0.94, 1.41; p=0.162)
 - Subsequent anti-EGFR monoclonal antibody therapy and subsequent chemotherapy were less frequent in the panitumumab+FOLFOX4 arm vs. FOLFOX4 alone arm in both WT and mutant *KRAS* exon 2 subgroups
- Conclusion
 - ***KRAS* testing is critical to select appropriate patients with mCRC for treatment with panitumumab+FOLFOX4**

2167: The SOFT study: A randomized phase III trial of S-1/oxaliplatin (SOX) plus bevacizumab versus 5-FU/I-LV/oxaliplatin (mFOLFOX6) plus bevacizumab in patients with metastatic colorectal cancer [SOFT Study Group]

– *Matsumoto H et al*

- Study objective
 - To evaluate non-inferiority* of SOX+BEV vs. mFOLFOX6+BEV as first-line treatment in patients with mCRC



Primary endpoint

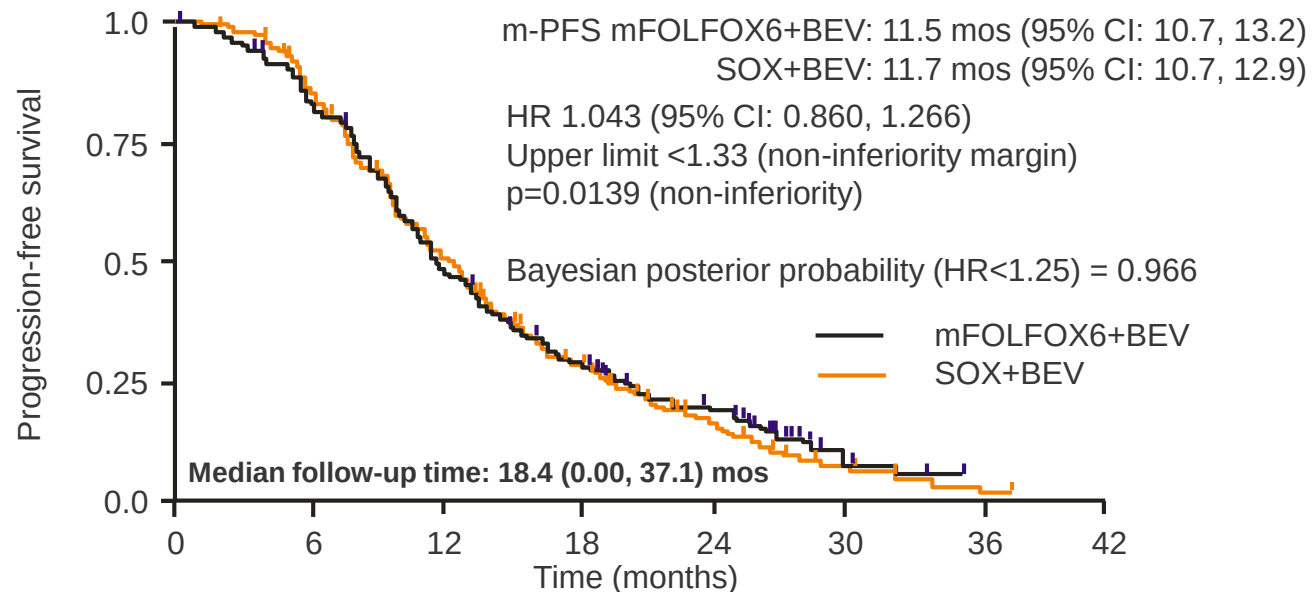
- PFS

*Non-inferiority margin of HR: 1.33; †L-OHP: 85 mg/m² d1 + Bev: 5 mg/kg d1 + I-LV: 200mg/m² d1 + 5-FU: 400mg/m² bolus d1 + 5-FU: 2,400mg/m² 46 hr civ d1-2 q2w; ‡L-OHP: 130 mg/m² d1 + Bev: 7.5 mg/kg d1 + S-1: 80, 100, 120 mg/body d1-14 q3w

2167: The SOFT study: A randomized phase III trial of S-1/oxaliplatin (SOX) plus bevacizumab versus 5-FU/I-LV/oxaliplatin (mFOLFOX6) plus bevacizumab in patients with metastatic colorectal cancer [SOFT Study Group]

– *Matsumoto H et al*

- Key results



mFOLFOX6	255	206	112	60	28	5	0	0
SOX	256	214	121	59	23	6	1	0

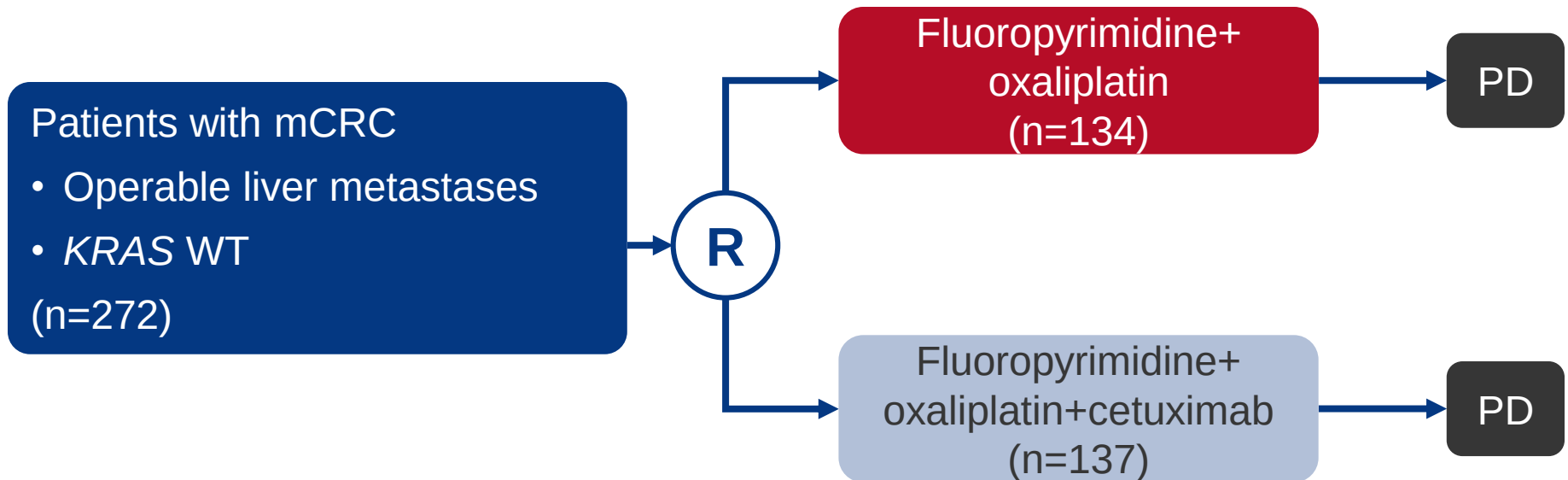
- Key outcomes with mFOLFOX6+BEV vs. SOX+BEV: time to treatment failure: 6.2 vs. 6.2 mos (HR 1.05 [95% CI: 0.88, 1.26]); mean survival time: 30.9 vs. 29.6 mos (HR 1.05 [95% CI: 0.81, 1.38]); response rate: 62.7 vs. 61.5; p=0.8026

- Conclusion

- SOX+BEV was shown to be non-inferior to mFOLFOX6+BEV in terms of PFS

2438: A randomised clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild type patients with operable metastases from colorectal cancer: The new EPOC study – *Bridgewater J et al*

- Study objective
 - To investigate the benefit of cetuximab in addition to standard CT in patients with operable liver metastases from colorectal cancer



2438: A randomised clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild type patients with operable metastases from colorectal cancer: The new EPOC study – *Bridgewater J et al*

- Key results

- The new EPOC study was stopped when the study met a protocol pre-defined futility analysis, as recommended by the Independent Data Monitoring Committee
 - As a result, only 45.3% (96/212) of the expected events were observed
- PFS was significantly worse in the CT+cetuximab group vs. the CT alone group
 - 14.8 vs. 24.2 mos, HR 1.50; 95% CI: 1.00, 2.25; p<0.048

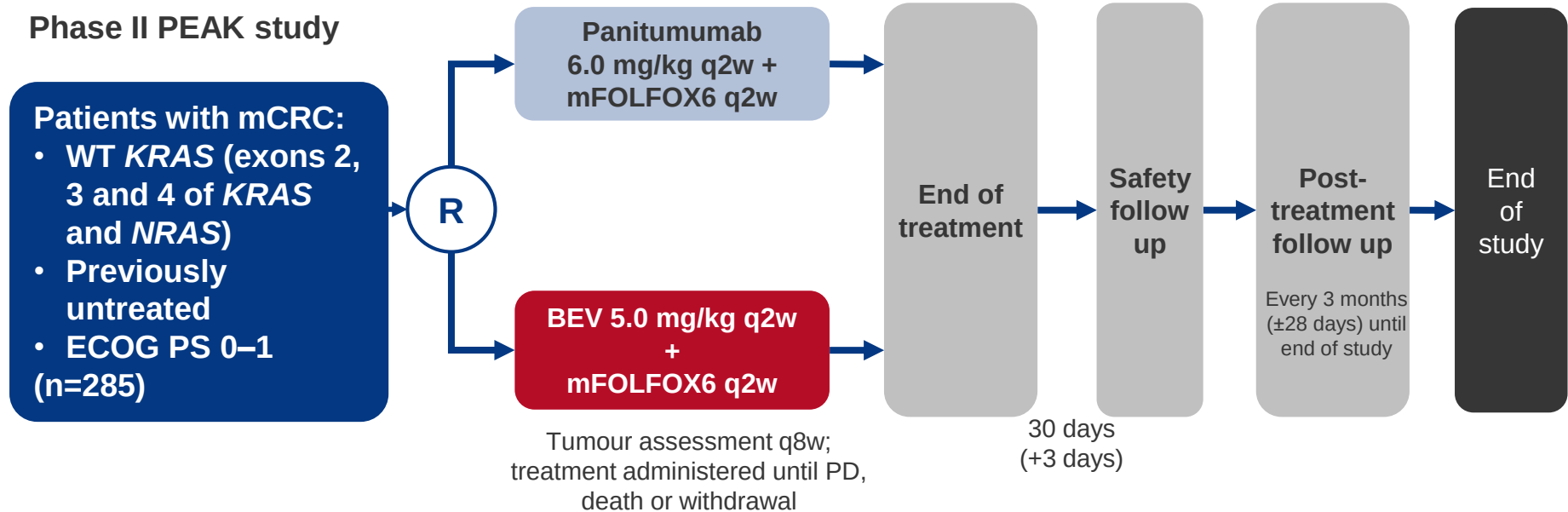
n, %	CT alone (n=134)	CT+cetuximab (n=137)
Complete response	7 (5.2)	7 (5.1)
Partial response	65 (48.5)	73 (53.3)
Stable disease	26 (19.4)	27 (17.5)
Progressive disease	11 (8.2)	10 (7.3)
Not assessable	3 (2.2)	2 (1.5)
Median RR (IQR)	42 (22.9–57.7)	50 (20.9–60.5)

- Conclusion

- Although it is currently accepted clinical practice, the addition of cetuximab to standard CT may not be beneficial to patients with *KRAS* WT mCRC

O-0013: KRAS/NRAS mutations in PEAK: a randomized phase 2 study of 1st-line treatment with FOLFOX6 + panitumumab or bevacizumab for wild-type KRAS MCRC – Rivera F et al

- Study objective
 - To compare the effect of FOLFOX6+panitumumab or FOLFOX6+BEV in patients with WT RAS mCRC



Primary endpoint

- PFS

Secondary endpoints

- OS, ORR, resection rate, safety

O-0013: KRAS/NRAS mutations in PEAK: a randomized phase 2 study of 1st-line treatment with FOLFOX6 + panitumumab or bevacizumab for wild-type KRAS MCRC – Rivera F et al

- Key results

	WT RAS exons 2 (ITT set)				WT RAS (exons 2, 3, 4 of KRAS/NRAS)			
	Events n/N (%)	Median mos (95% CI)	HR* (95% CI)	p-value	Events n/N (%)	Median mos (95% CI)	HR* (95% CI)	p-value
PFS								
Pmab+ mFOLFOX6	100/142 (70)	10.9 (9.7, 12.8)	0.84 (0.64, 1.11)	0.22	57/88 (65)	13.0 (10.9, 15.1)	0.66 (0.46, 0.95)	0.03
BEV+ mFOLFOX6	108/143 (76)	10.1 (9.0, 12.0)			66/82 (80)	10.1 (9.0, 12.7)		
OS								
Pmab+ mFOLFOX6	52/142 (37)	34.2 (26.6, NR)	0.62 (0.44, 0.89)	0.009	30/88 (34)	41.3 (28.8, 41.3)	0.63 (0.39, 1.02)	0.058
BEV+ mFOLFOX6	78/143 (55)	24.3 (21.0, 29.2)			40/82 (49)	28.9 (23.9, 31.3)		

*Stratified Cox proportional hazards model

O-0013: KRAS/NRAS mutations in PEAK: a randomized phase 2 study of 1st-line treatment with FOLFOX6 + panitumumab or bevacizumab for wild-type KRAS MCRC – Rivera F et al

- Key results (continued)

	WT RAS exons 2 (ITT set)		WT RAS (exons 2, 3, 4 of KRAS/NRAS)	
	Pmab+ mFOLFOX6 (n=86)	BEV+ mFOLFOX6 (n=80)	Pmab+ mFOLFOX6 (n=24)	BEV+ mFOLFOX6 (n=27)
Patients with any adverse event, n (%)	24 (100)	27 (100)	86 (100)	80 (100)
Worst grade of 3, n (%)	13 (54)	16 (59)	60 (70)	43 (54)
Worst grade of 4, n (%)	7 (29)	8 (30)	17 (20)	15 (19)
Worst grade of 5, n (%)	1 (4)	1 (4)	4 (5)	7 (9)
Serious adverse event, n (%)	9 (38)	13 (48)	37 (43)	32 (40)
Leading to permanent discontinuation of any study drug, n (%)	9 (38)	7 (26)	25 (29)	24 (30)

- Conclusions
 - PFS and OS outcomes favoured panitumumab+mFOLFOX6 compared with BEV+mFOLFOX6
 - Activating RAS mutations appear to be predictive for panitumumab treatment effect
 - The adverse event profile was not influenced by RAS mutations

3619: Randomized, phase II study of bevacizumab with mFOLFOX6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: Resectability and safety in OLIVIA – Gruenberger T et al

- Study objective
 - To gain a better understanding of the optimal combination of biological and chemotherapy for improving resectability
- Study type / design
 - Open-label multinational study
 - Patients with unresectable colorectal cancer liver-only metastases were randomised to mFOLFOX6+BEV or FOLFOXIRI q2w
 - Unresectability was defined as ≥ 1 of the following:
 - No possibility of upfront R0 / R1 resection of all hepatic lesions
 - $< 30\%$ estimated residual liver after resection
 - Disease in contact with major vessels of the remnant liver
 - The primary endpoint was overall resection rate (R0 / R1 / R2)

3619: Randomized, phase II study of bevacizumab with mFOLFOX6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: Resectability and safety in OLIVIA – Gruenberger T et al

- Key results

Outcome	mFOLFOX6+ BEV (n=39)	FOLFOXIRI+ BEV (n=41)	Difference	p-value
Resection rate (R0 / 1 / 2)	48.7 (32.4, 65.2)	61.0 (44.5, 75.8)	12.3 (–11.0, 35.5)	0.271
Resection rate (R0 / 1)	33.3 (19.1, 50.2)	51.2 (35.1, 67.1)	17.9 (–5.0, 40.7)	0.106
Resection rate (R0)	23.1 (11.1, 39.3)	48.8 (32.9, 64.9)	25.7 (3.9, 47.5)	0.017
ORR	61.5 (44.6, 76.6)	80.5 (65.1, 91.2)	18.9 (–2.1, 40.0)	0.061
Median PFS (immature), mos (95% CI)	11.6 (8.1, 14.2)	21.0 (18.6, 31.8)	–	–
Grade ≥3 adverse events, %	84	95	–	–
Neutropenia	35	48	–	–
Diarrhoea	14	28	–	–

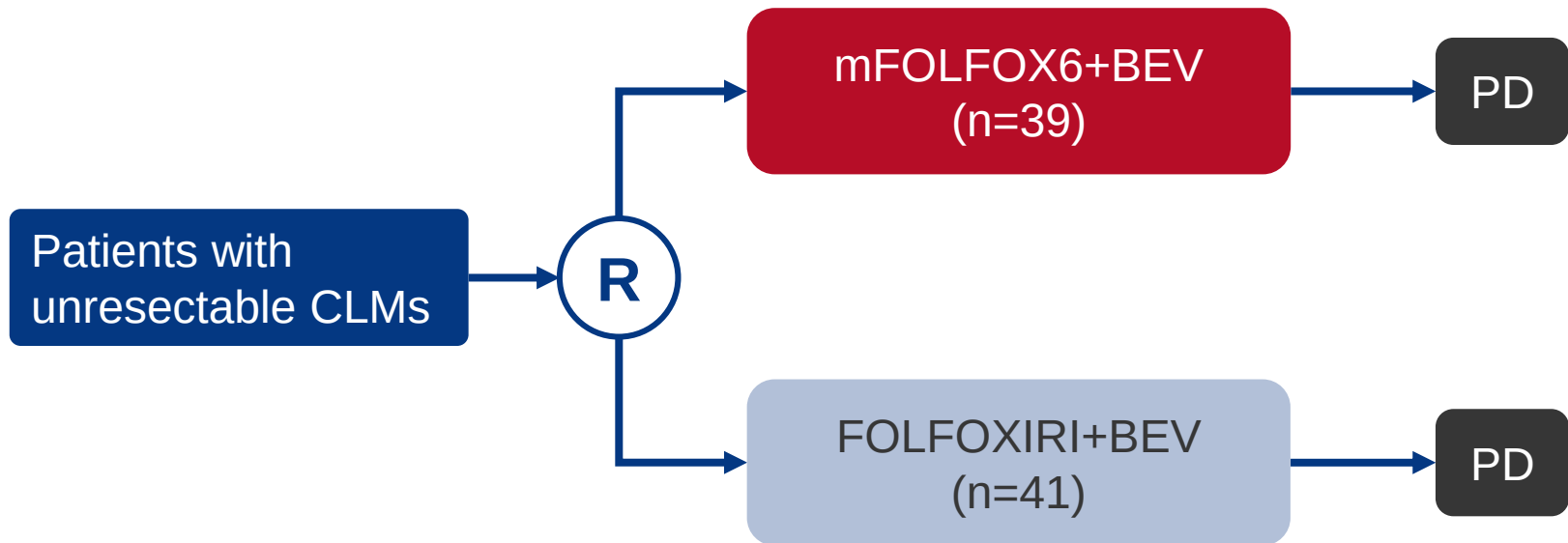
- Conclusions

- In patients with initially unresectable colorectal cancer liver-only metastases the combination of FOLFOXIRI+BEV improves resection rates, ORR and long-term outcomes compared with mFOLFOX6+BEV
- Adverse events were consistent with these treatments and were considered manageable

2159: Updated efficacy/safety findings from a randomized, phase 2 study of bevacizumab plus mFOLFOX6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer (OLIVIA study)

– *Bridgewater J et al*

- Study objective
 - To investigate whether adding irinotecan to FOLFOX in combination with BEV improved resection rates in patients with unresectable colorectal cancer liver-only metastases



Primary endpoint

- Overall resection rate (R0 / R1 / R2)

2159: Updated efficacy/safety findings from a randomized, phase 2 study of bevacizumab plus mFOLFOX6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer (OLIVIA study)

– *Bridgewater J et al*

- Key results

- FOLFOXIRI+BEV was associated with higher resection rates, increased response rates and prolonged PFS

Endpoint	mFOLFOX6+ BEV (n=39)	FOLFOXIRI+ BEV (n=41)	Difference	p-value
Resection R0 / 1 / 2 rate, % (95% CI)	48.7 (32.4, 65.2)	61.0 (44.5, 75.8)	12.3 (–11.0, 35.5)	0.271
Histopathological response rate, n (%)	7/14 (50)	10/20 (50)	0	1.0
Radiological response rate, % (95% CI)	61.5 (44.6, 76.6)	80.5 (65.1, 91.2)	18.9 (–2.1, 40.0)	0.061
Median PFS, mos (95% CI)	12.0 (9.5, 14.1)	18.8 (12.4, 21.0)	–	0.0009
R0 / R1	13.6 (9.8, 15.9)	21.0 (16.0, 31.8)	–	–
R2 /other outcome	10.3 (7.4, 12.4)	12.4 (8.5, 19.6)	–	–

- No new safety concerns were identified

- The incidence of grade ≥ 3 adverse events was 84% with mFOLFOX6+BEV vs. 95% with FOLFOXIRI+BEV

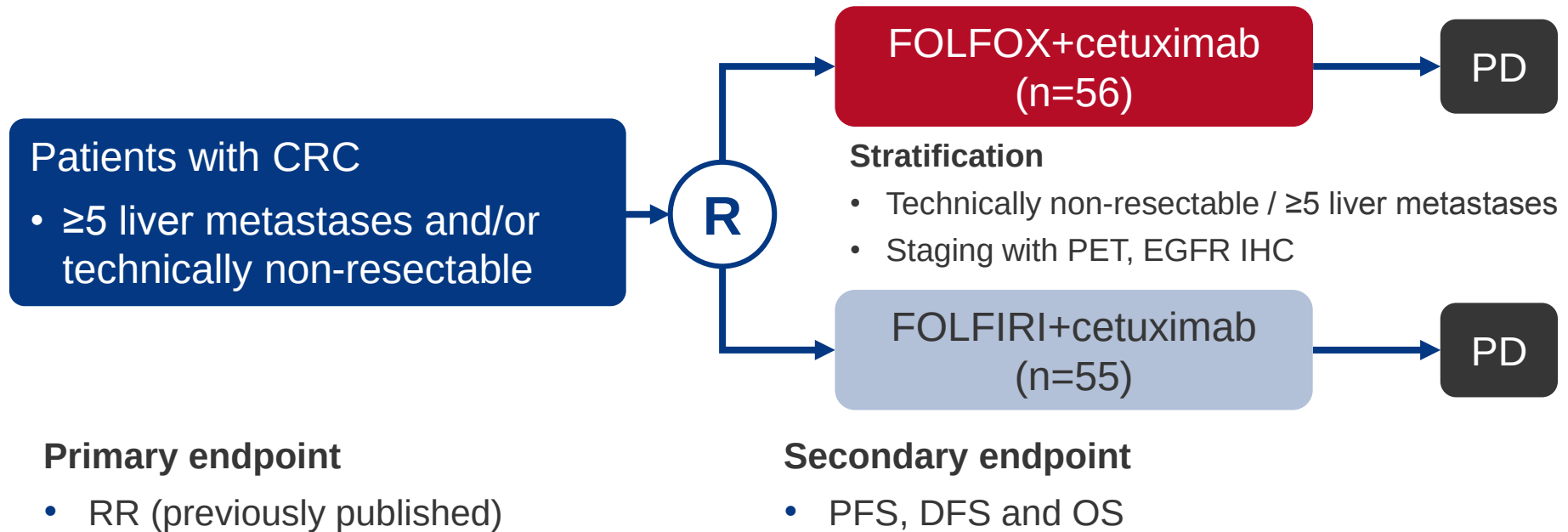
- Conclusion

- FOLFOXIRI+BEV provided higher resection and response rates plus longer PFS than mFOLFOX6+BEV in patients with initially unresectable colorectal cancer liver-only metastases

2216: Overall survival, resection of liver metastases and response to treatment in patients with initially unresectable colorectal liver metastases and following treatment with FOLFOX/cetuximab or FOLFIRI/cetuximab (CELIM-study)

– Köhne C et al

- Study objective
 - To assess the effectiveness of FOLFOX+cetuximab vs. FOLFIRI+cetuximab in enabling resectability in patients with initially unresectable CRC

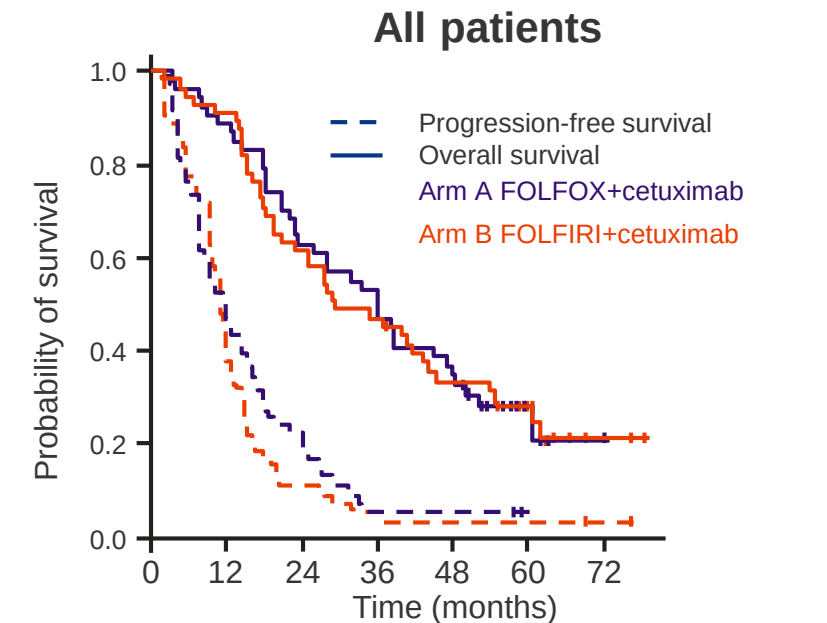


2216: Overall survival, resection of liver metastases and response to treatment in patients with initially unresectable colorectal liver metastases and following treatment with FOLFOX/cetuximab or FOLFIRI/cetuximab (CELIM-study)

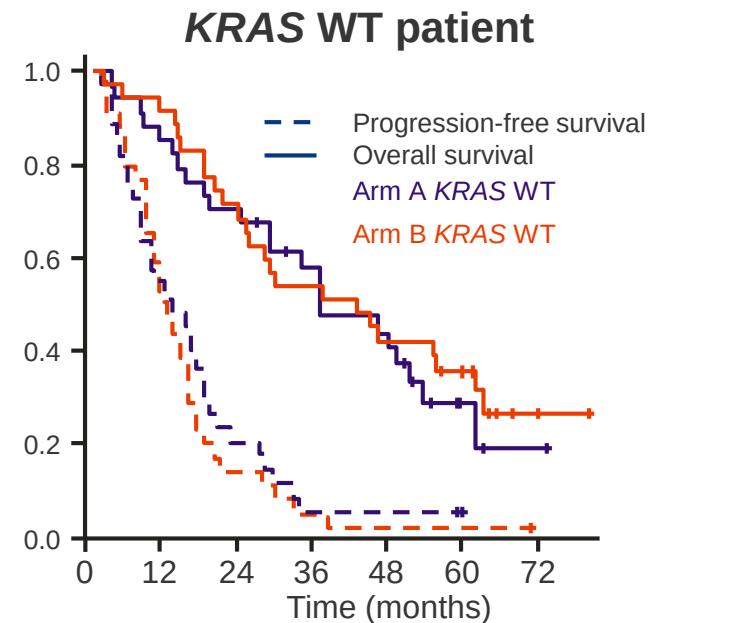
– Köhne C et al

- Key results

- CR / RR: 68% with FOLFOX+cetuximab vs. 57% with FOLFIRI+cetuximab
 - 70% with *KRAS* WT vs. 41% with *KRAS* mutant
- There was no significant difference in PFS and OS between treatment arms



OS	Arm A	35.8 mos (95% CI: 28.1, –43.6); HR 1.03 (0.66, 1.61)
	Arm B	29.0 mos (95% CI: 16.0, 41.9); p=0.9
PFS	Arm A	11.2 mos (95% CI: 7.2, –15.3); HR 1.18 (0.79, 1.74)
	Arm B	10.5 mos (95% CI: 8.9, 12.2); p=0.4



OS	Arm A	36.1 mos (95% CI: 21.1, 51.1); HR 0.86 (0.48,1.53)
	Arm B	41.6 mos (95% CI: 22.6, 60.6); NS
PFS	Arm A	12.1 mos (95% CI: 5.2, 19.1); HR 1.13 (0.69, 1.85)
	Arm B	11.5 mos (95% CI: 8.8, 14.1); NS

2216: Overall survival, resection of liver metastases and response to treatment in patients with initially unresectable colorectal liver metastases and following treatment with FOLFOX/cetuximab or FOLFIRI/cetuximab (CELIM-study)

– *Köhne C et al*

- Key results (continued)
 - R0 resections: 38% with FOLFOX+cetuximab vs. 30% with FOLFIRI+cetuximab
 - Patients with R0 resection had improved PFS and OS compared with patients without R0 resection

	R0 resected	Not resected	HR	p-value
OS mos (95% CI)	53.9 (35.9, 71.9)	21.9 (17.1, 26.7)	0.29	<0.001
PFS mos (95% CI)	15.4 (11.4, 19.5)	6.9 (5.9, 8.0)	0.31	<0.001

- Five-year survival in R0 resected patients was 46.2% (95% CI: 29.5, 62.9)
- **Conclusions**
 - Resection significantly improved PFS and OS
 - There was no significant difference in outcomes between the FOLFOX+cetuximab group vs. the FOLFIRI+cetuximab group

COLORECTAL CANCER

NEOADJUVANT THERAPY

3502: Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG) – *Koopman M et al*

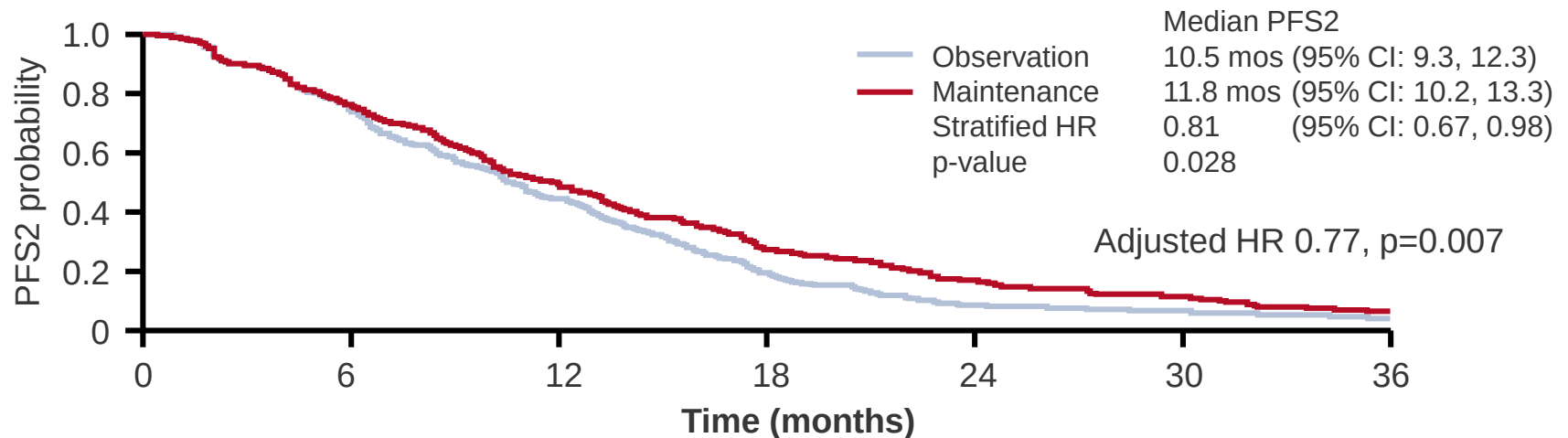
- Study objective
 - To investigate the efficacy of maintenance treatment with capecitabine+BEV vs. observation in patients with mCRC not progressing during induction treatment with capecitabine, oxaliplatin and BEV (CAPOX-B)
- Study type / design
 - Phase III CAIRO3 study
 - Previously untreated mCRC patients, PS 0–1, with stable disease or better after 6 cycles of CAPOX-B*, not eligible for metastasectomy and eligible for future treatment with oxaliplatin, were randomised between observation or maintenance treatment with capecitabine 625 mg/m² bid continuously and BEV 7.5 mg/kg iv q3w
 - After first progression (PFS1), patients in both arms were then treated with CAPOX-B until second progression (PFS2)
 - For patients not able to receive CAPOX-B after PFS1, PFS2 was considered equal to PFS1
 - Primary endpoint: PFS2

*Pre-study induction treatment with 6 cycles of 3-weekly CAPOX-B:
capecitabine 1000 mg/m² bid d1–14, oxaliplatin 130 mg/m² d1, BEV 7.5 mg/kg d1

3502: Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG) – *Koopman M et al*

- Key results

- Total of 558 patients randomised (279 patients in each treatment arm)
- Median PFS1 in those who received observation vs. those who maintenance with capecitabine+BEV was 4.1 vs 8.5 mos (stratified HR 0.44, 95% CI: 0.36, 0.53, $p < 0.0001$)
- After PFS1, 76% of patients received CAPOX-B in the observation arm and 47% in the maintenance arm

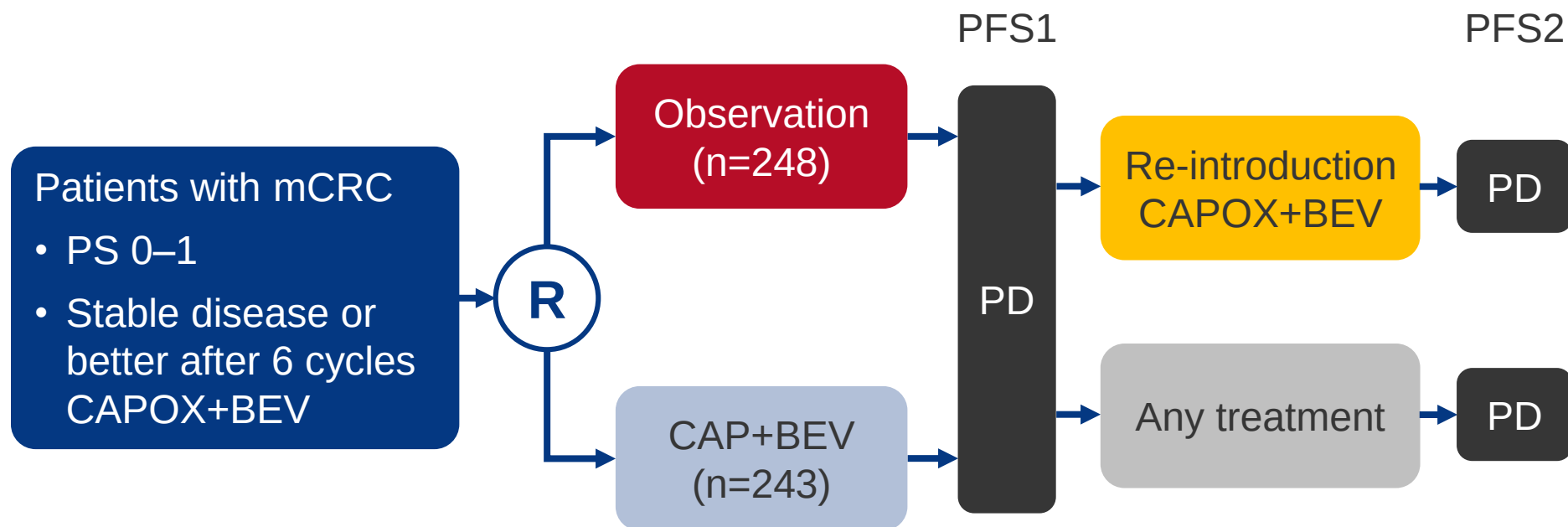


- Conclusions

- Maintenance treatment with capecitabine+BEV after 6 cycles of CAPOX-B significantly prolonged PFS1 and PFS2
- The number of patients eligible for re-introduction of CAPOX-B was lower than expected

2166: Updated results including quality of life of the phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG): Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC) – Punt CJA et al

- Study objective
 - To investigate the efficacy of maintenance treatment with capecitabine+BEV vs. observation in patients with mCRC not progressing during induction treatment with capecitabine, oxaliplatin and BEV (CAPOX-B)



Primary endpoint

- PFS2

2166: Updated results including quality of life of the phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG): Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC) – *Punt CJA et al*

- Key results

Outcome, mos	Observation	CAP+BEV	HR	p-value
PFS1	4.1	8.5	0.44	<0.00001
PFS2	10.5	11.8	0.81	0.028
Time to second progression	15.0	19.8	0.67	<0.00001
OS	18.2	21.7	0.80	0.035

- QoL (between group treatment differences):

- Overall QoL score: 3.9 (95% CI: 1.2, 6.5); p=0.004 (not clinically relevant)
- Fatigue score: –4.2 (95% CI: –7.0, –1.3), p=0.004

- Conclusions

- CAP+BEV significantly prolonged PFS1, PFS2, time to second progression and OS vs. the observation group
- QoL and fatigues scores were better in the observation group vs. the CAP+BEV, although the differences were not clinically relevant

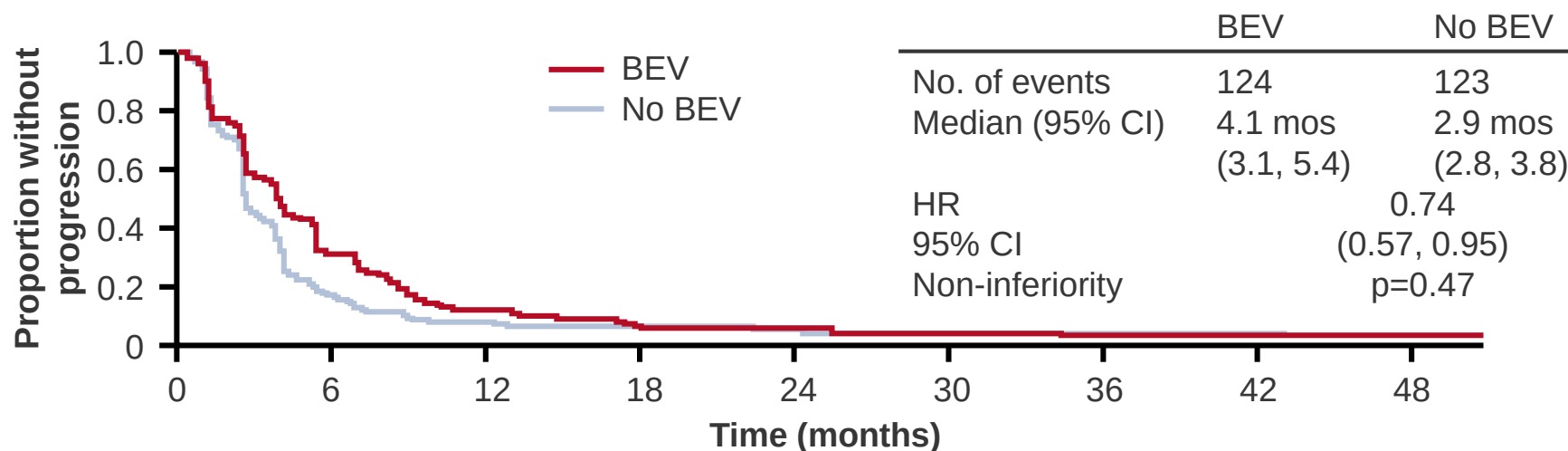
3503: Bevacizumab continuation versus no continuation after first-line chemo-bevacizumab therapy in patients with metastatic colorectal cancer: A randomized phase III noninferiority trial (SAKK 41/06) – Koeberle D et al

- Study objective
 - To assess whether no continuation is non-inferior to continuation of BEV after cessation of first-line chemotherapy
- Study type / design
 - Open-label, Phase III multicentre study
 - Patients with unresectable mCRC having non-progressive disease after 4–6 mos of standard first-line chemotherapy+BEV were randomly assigned (1:1) to continuing BEV (7.5 mg/kg q3w) or no treatment
 - Computed tomography scans were performed every 6 weeks between randomisation and disease progression
 - Primary endpoint: time to progression (TTP)

3503: Bevacizumab continuation versus no continuation after first-line chemo-bevacizumab therapy in patients with metastatic colorectal cancer: A randomized phase III noninferiority trial (SAKK 41/06) – Koeberle D et al

- Key results

- Per-protocol population: 262 patients (131 in each treatment arm)
- Median (range) follow-up: 30.1 (2.7–54.9) mos



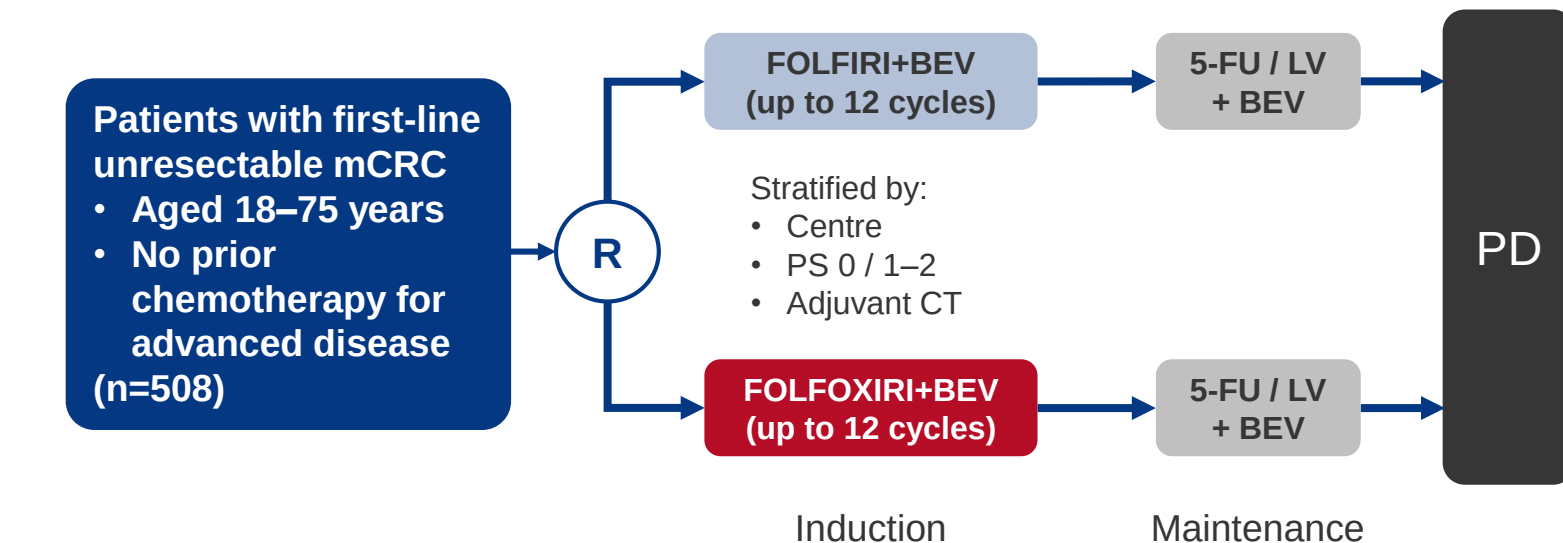
- Grade 3–4 adverse events in the BEV continuation arm were rare

- Conclusions

- Non-inferiority could not be demonstrated
- The difference in median TTP between BEV continuation vs. no treatment after randomisation was 5 weeks

3505: FOLFOXIRI/bevacizumab (BEV) versus FOLFIRI/BEV as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group – *Falcone A et al*

- Study objective
 - To confirm the superiority of FOLFOXIRI vs. FOLFIRI when BEV is added to chemotherapy
- Study type / design
 - Phase III TRIBE study



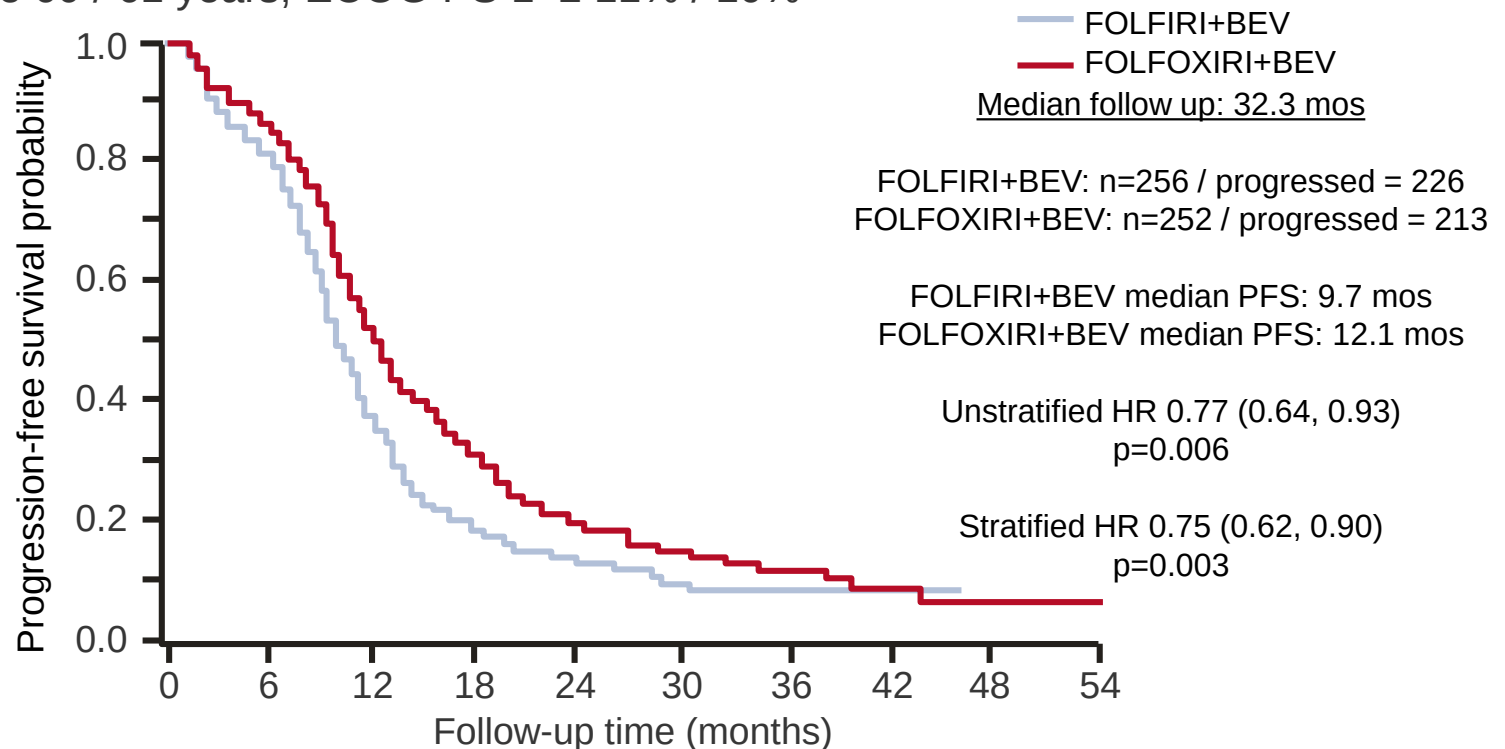
Primary endpoint

- PFS

3505: FOLFOXIRI/bevacizumab (BEV) versus FOLFIRI/BEV as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group – *Falcone A et al*

- Key results

- Patients characteristics were (FOLFIRI+BEV / FOLFOXIRI+BEV):
median age 60 / 61 years; ECOG PS 1–2 11% / 10%



- For FOLFIRI+BEV vs. FOLFOXIRI+BEV, there was significantly less neutropenia (20 vs. 50%; p<0.001), diarrhoea (11 vs. 19%; p=0.012), stomatitis (4 vs. 9%; p=0.048) and neurotoxicity (0 vs. 5%; p<0.001)

3505: FOLFOXIRI/bevacizumab (BEV) versus FOLFIRI/BEV as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group – *Falcone A et al*

- **Conclusions**
 - FOLFOXIRI+BEV significantly reduced the risk of disease progression compared with FOLFIRI+BEV
 - There were increases in specific adverse effects with FOLFOXIRI+BEV compared with FOLFIRI+BEV, although the overall safety profile was considered acceptable
 - The findings support the use of FOLFOXIRI+BEV as a new standard treatment option for patients with mCRC selected according to the eligibility criteria of this study

3604: Bevacizumab plus chemotherapy continued beyond first disease progression in patients with metastatic colorectal cancer previously treated with bevacizumab based therapy: Patterns of disease progression and outcomes based on extent of disease in the ML18147 study – Greil R et al

- Study objective
 - To explore patterns of disease progression and outcomes based on extent of disease in the ML18147 study
- Study type / design
 - Randomised Phase III intergroup study: ML18147
 - Patients with unresectable, histologically confirmed mCRC who progressed ≤ 3 mos after discontinuation of first-line BEV were randomised to second-line CT $\pm$ BEV
 - Primary outcome was OS from randomisation; secondary outcomes were PFS from randomisation, best ORR
 - This analysis examined patterns of PD according to the extent of disease (liver-limited or non-liver-limited)

3604: Bevacizumab plus chemotherapy continued beyond first disease progression in patients with metastatic colorectal cancer previously treated with bevacizumab based therapy: Patterns of disease progression and outcomes based on extent of disease in the ML18147 study – Greil R et al

- Key results
 - 820 patients entered the study
 - Median time from treatment discontinuation to PD due to adverse events for BEV+CT vs. CT alone (n=77): 2.2 vs. 1.4 mos; HR 0.73; 95% CI: 0.37, 1.43; p=0.3430
 - Median time from treatment discontinuation to PD due to any reason for BEV+CT vs. CT alone (n=674): 0.5 vs. 0.4 mos; HR 0.082; 95% CI: 0.69, 0.98; p=0.02
- Conclusions
 - No difference in time to PD or patterns of PD in patients treated with BEV+CT after progressing on BEV in first-line
 - Patients with liver-limited or extensive disease appeared to benefit equally from BEV+CT continued beyond PD

3615: Second-line chemotherapy (CT) with or without bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts) who progressed to a first-line treatment containing BV: Updated results of the phase III “BEBYP” trial by the Gruppo Oncologico Nord Ovest (GONO) – Masi G et al

- Study objective
 - To assess if continuation of BEV with second-line CT beyond progression in patients who received BEV in first-line can improve the outcome
- Study type / design
 - Phase III randomised in patients with measurable mCRC
 - Treatment: patients treated in first-line with CT (fluoropyrimidine, FOLFIRI, FOLFOX or FOLFOXIRI)+BEV, to receive second-line mFOLFOX6 or FOLFIRI (depending on first-line CT)±BEV
 - Primary endpoint: PFS

3615: Second-line chemotherapy (CT) with or without bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts) who progressed to a first-line treatment containing BV: Updated results of the phase III “BEBYP” trial by the Gruppo Oncologico Nord Ovest (GONO) – Masi G et al

- Key results
 - A total of 185 patients were randomised and 184 patients were included in the ITT analysis
 - Patient characteristics were well balanced across treatment arms (except more males in CT arm)
 - PFS for CT vs. CT+BEV: 5.0 vs. 6.7 mos (HR 0.66; 95% CI: 0.49, 0.89; p=0.0065)
 - Subgroup analyses showed a consistent benefit in all subgroups including gender and first-line PFS
 - OS for CT vs. CT+BEV: 15.9 vs. 14.3 mos (HR 0.75; 95% CI: 0.5, 1.06; p=0.11)
 - Response rates for CT vs. CT+BEV: 18 vs. 21% (p=0.71)
 - Toxicity profile was as expected
- Conclusion
 - **PFS can be improved by continuing BEV in second-line therapy in patients who had previously received CT+BEV as first-line therapy**

3515: Maintenance therapy with bevacizumab with or without erlotinib in metastatic colorectal cancer (mCRC) according to KRAS: Results of the GERCOR DREAM phase III trial – *Tournigand C et al*

- Study objective
 - To assess maintenance therapy with BEV with or without erlotinib in mCRC according to *KRAS*
- Study type / design
 - Phase III GERCOR DREAM study
 - After induction therapy with FOLFOX+BEV, XELOX+BEV or FOLFIRI+BEV, patients were randomly allocated to one of two maintenance therapy arms until PD:
 - Arm A – BEV alone (BEV 7.5 mg/kg q3w)
 - Arm B – BEV+erlotinib (BEV 7.5 mg/kg q3w, erlotinib 150 mg/d)
 - Primary endpoint: PFS on maintenance therapy
 - Secondary endpoints: OS, survival according to *KRAS*
- Key results
 - 452 patients were randomised (228 in arm A, 224 in arm B)

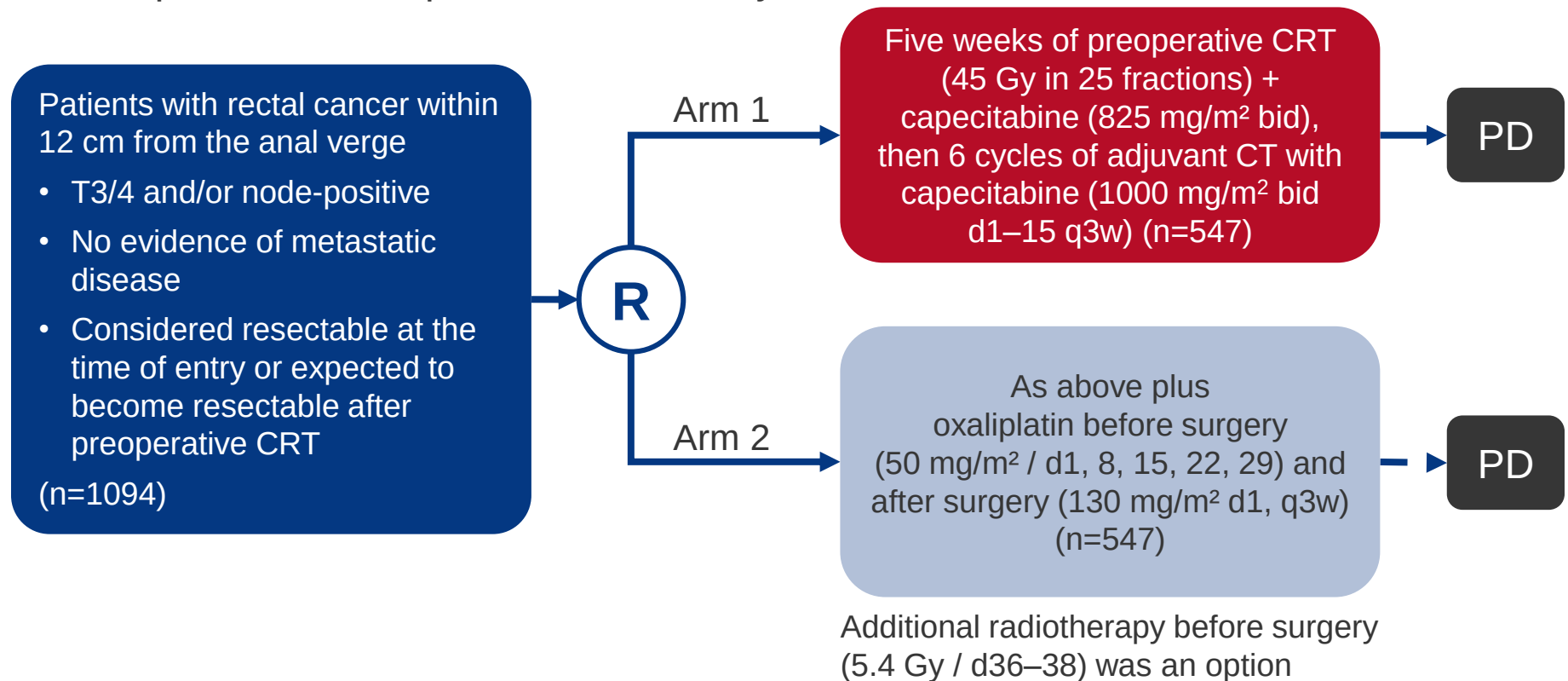
3515: Maintenance therapy with bevacizumab with or without erlotinib in metastatic colorectal cancer (mCRC) according to KRAS: Results of the GERCOR DREAM phase III trial – *Tournigand C et al*

- Key results (continued)
 - In the overall maintenance groups, PFS* in arm A vs. arm B: 4.8 vs. 5.9 mos (HR 0.76; 95% CI: 0.61, 0.94; p=0.010)
 - OS was 27.9 vs. 28.5 mos (HR 0.89; 95% CI: 0.70, 1.12; p=0.312)
 - In the WT *KRAS* subgroups, PFS* in arm A vs. arm B: 5.9 vs. 6.0 mos (HR 0.86; 95% CI: 0.64, 1.16; p=0.135)
 - OS was 31.5 vs. 31.8 mos (HR 0.92; 95% CI: 0.66, 1.30; p=0.644)
 - In the mutant *KRAS* subgroups, PFS* in arm A vs. arm B: 4.4 vs. 4.7 mos (HR 0.77; 95% CI: 0.54, 1.08; p=0.124)
 - OS was 26.9 vs. 26.3 mos (HR 1.06; 95% CI: 0.72, 1.55; p=0.767)
- Conclusion
 - Maintenance treatment with BEV+erlotinib increases PFS (but not OS) compared with BEV alone in patients with mCRC

3531: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: First results of the PETACC-6 randomized phase III trial

– *Schmoll H-J et al*

- Study objective
 - To determine if the addition of oxaliplatin to preoperative oral fluoropyrimidine-based CRT followed by postoperative adjuvant fluoropyrimidine-based CT improves DFS in patients with locally advanced rectal cancer



3531: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: First results of the PETACC-6 randomized phase III trial

– *Schmoll H-J et al*

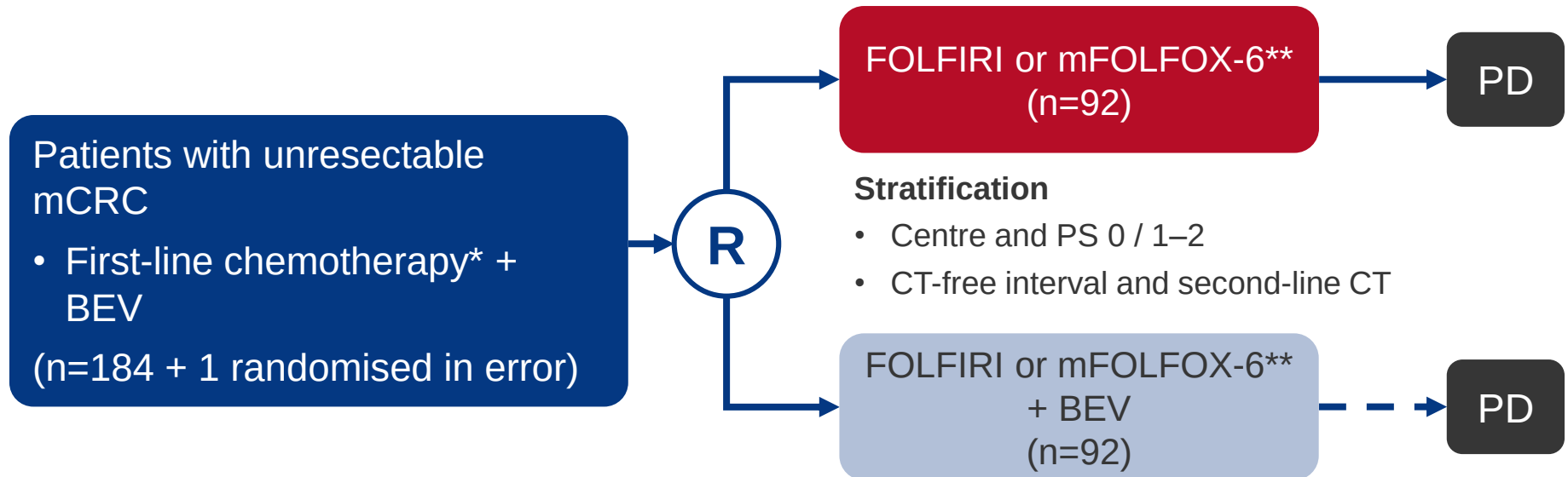
- Key results
 - Primary endpoint not met, longer follow-up required

Outcome	Arm 1	Arm 2	p-value
≥90% full dose concurrent CT delivered, %	91	63	–
Preoperative grade 3/4 toxicity, %	15.1	36.7	–
Deaths before surgery	1	3	–
R0 resection rate, %	92.0	86.3	–
Pathological complete remission rate (ypT0N0), %	11.3	13.3	0.31
Anal sphincter preserved, %	70	65	0.09
Postoperative complications, % (no. of deaths)	38 (5)	41 (4)	–

- Conclusion
 - Oxaliplatin added to preoperative fluoropyrimidine-based chemoradiation did not improve surgical outcomes and was associated with decreased treatment compliance and increased toxicity

O-0027: Bevacizumab beyond progression in metastatic colorectal cancer patients receiving a first-line treatment containing bevacizumab: update of the BEBYP trial by the GONO group – Salvatore L et al

- Study objective
 - To determine whether the addition of BEV to FOLFIRI or mFOLFOX-6 improves survival in patients with unresectable mCRC compared with chemotherapy alone



Primary endpoint

- PFS

Secondary endpoints

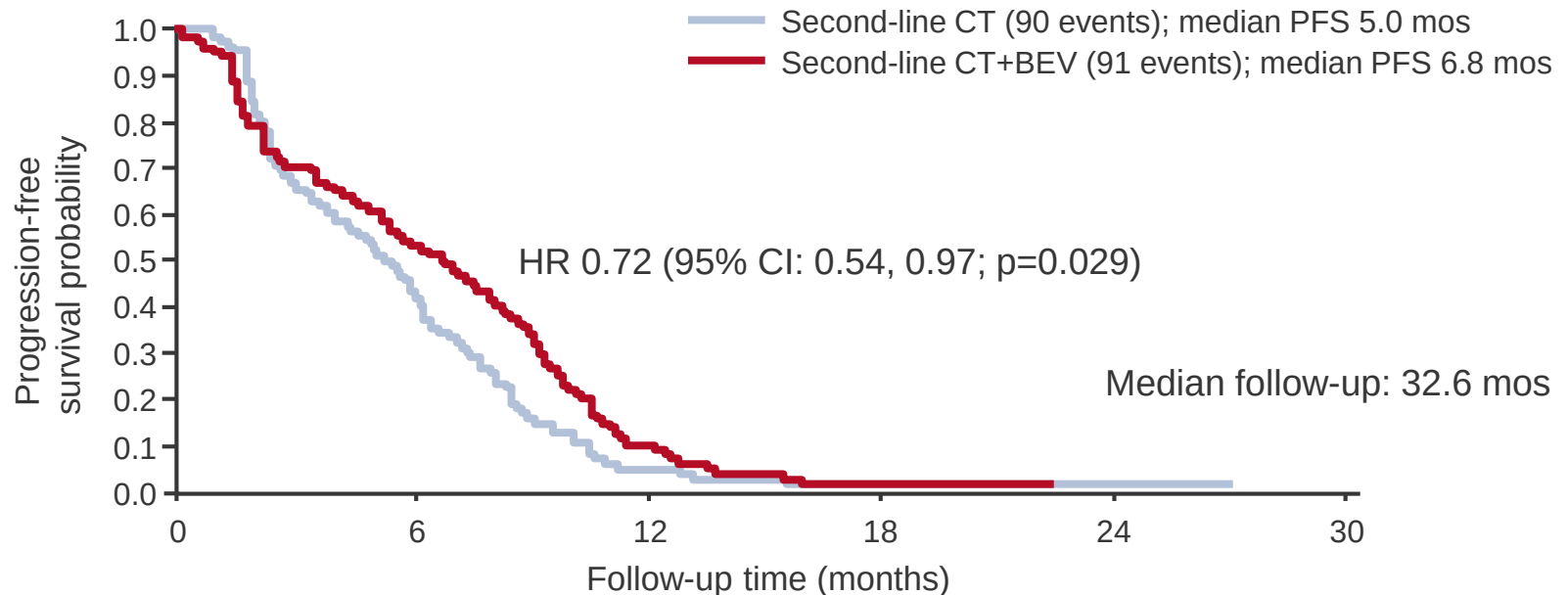
- RR, OS, safety and potential markers predictive of BEV activity

*First-line chemotherapy: FOLFIRI, FOLFOX, FOLFOXIRI, fluoropyrimidine monotherapy

**Second-line chemotherapy: FOLFIRI (34% in both arms); mFOLFOX-6 (66% in both arms)

O-0027: Bevacizumab beyond progression in metastatic colorectal cancer patients receiving a first-line treatment containing bevacizumab: update of the BEBYP trial by the GONO group – Salvatore L et al

- Key results



	Second-line CT, % (n=92)	Second-line CT+BEV, % (n=92)
Overall response rate	18	21
Stable disease	44	50

- Median OS was 15.5 mos for second-line CT (77 events) vs. 14.1 mos for second-line CT+BEV (73 events; HR 0.77; 95% CI: 0.56, 1.07; p=0.12)

O-0027: Bevacizumab beyond progression in metastatic colorectal cancer patients receiving a first-line treatment containing bevacizumab: update of the BEBYP trial by the GONO group – Salvatore L et al

- Key results (continued)

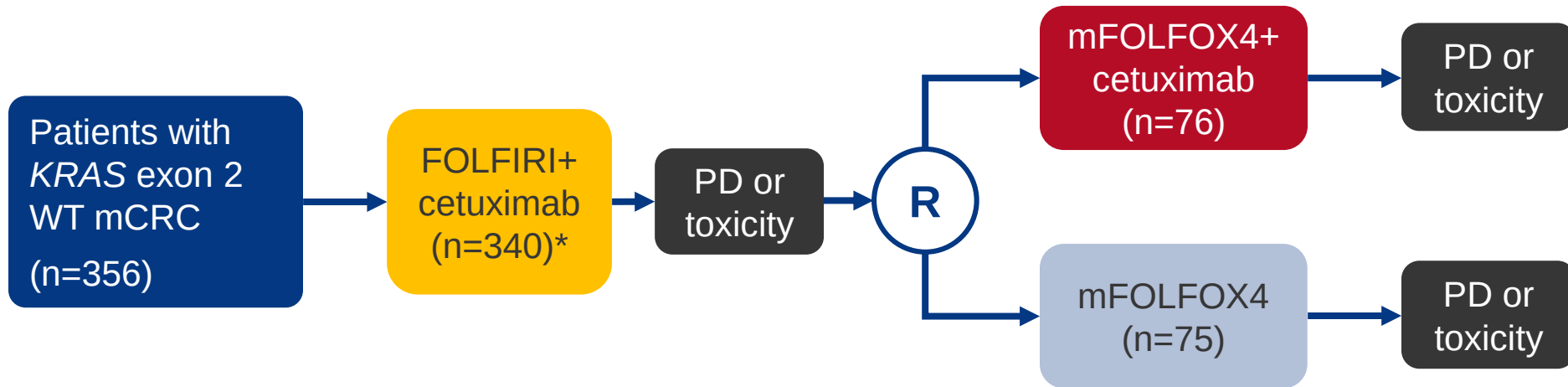
	Second-line CT, % (n=92)	Second-line CT + BEV, % (n=92)
Any grade adverse event	93	94
Grade 3–4 adverse events	43	44
Serious adverse events	7	7
Toxic deaths	0	1

- Conclusions

- This study fulfilled its primary endpoint and demonstrated an improvement in PFS by continuing BEV in second-line treatment for patients with unresectable mCRC who had received first-line CT+BEV
- The addition of BEV in combination with second-line CT represents a well-tolerated treatment option

31: Molecular profiling of the CAPRI GOIM trial in KRAS wild type (wt) metastatic colorectal cancer (mCRC) patients (pts): Cetuximab + FOLFIRI followed by FOLFOX4 $\pm$ cetuximab – *Ciardiello F et al*

- Study objective
 - To compare FOLFIRI+cetuximab with mFOLFOX4 alone as second-line treatment in mCRC patients with WT tumours for *KRAS* exon 2, following first-line treatment with FOLFIRI+cetuximab



First-line treatment primary endpoint

- PFS

Second-line treatment primary endpoint

- PFS

*A 22 gene mutation analysis was performed in tumour samples from 54% of patients

31: Molecular profiling of the CAPRI GOIM trial in KRAS wild type (wt) metastatic colorectal cancer (mCRC) patients (pts): Cetuximab + FOLFIRI followed by FOLFOX4 ± cetuximab – *Ciardiello F et al*

- Key results
 - Outcomes for first-line treatment
 - Median PFS: 9.9 (95% CI: 8.8, 11.3) mos
 - ORR: 56.4%
 - Next generation sequencing* demonstrated that the more frequently mutated genes were: *TP53*, *KRAS*, *PIK3CA*, *BRAF*, *NRAS*

Gene	Nº. of cases (>2%) with mutations, n (%) (N=182 analysed)	
<i>TP53</i>	72 (39.5)	
<i>KRAS</i>	45 (24.7)	30 at codon 12 or 13 (16.5%); 16 at other (8.8%)
<i>PIK3CA</i>	24 (13.2)	16 at exon 9 (8.8%); 10 at exon 20 (5.5%)
<i>BRAF</i>	15 (8.2)	10 at codon 600 (5.5%); 5 at other (2.7%)
<i>NRAS</i>	13 (7.1)	
<i>MET</i>	7 (3.8)	
<i>FBXW7</i>	9 (4.9)	

*Using a 22 gene mutation analysis

31: Molecular profiling of the CAPRI GOIM trial in KRAS wild type (wt) metastatic colorectal cancer (mCRC) patients (pts): Cetuximab + FOLFIRI followed by FOLFOX4 ± cetuximab – *Ciardiello F et al*

- Key results (continued)

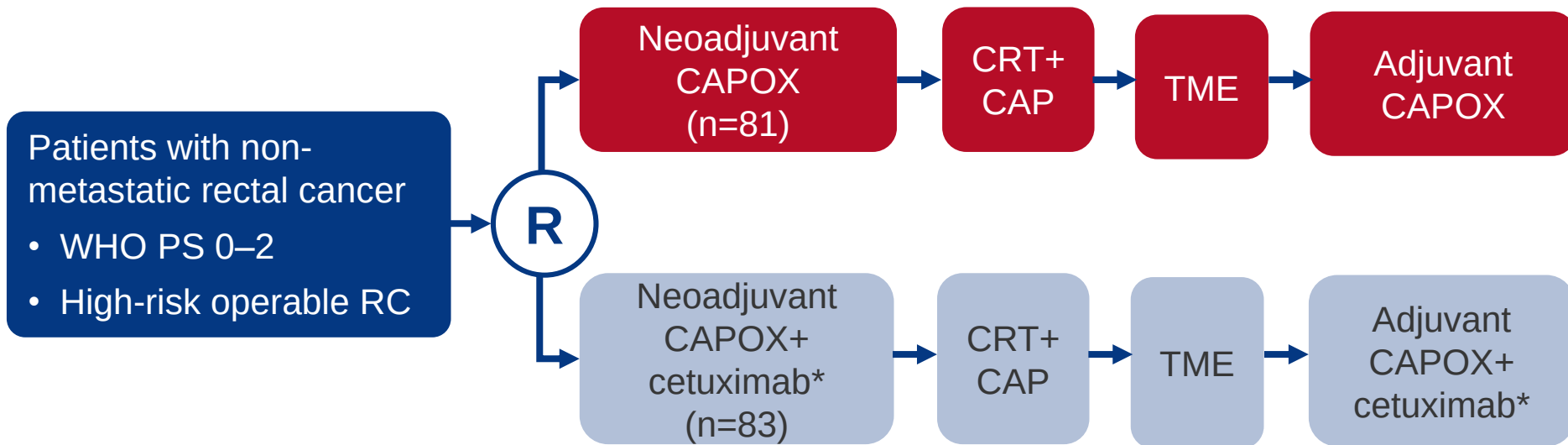
FOLFIRI+cetuximab	22 gene analysis (n=182)	KRAS / NRAS WT (n=124)	KRAS / NRAS MT (n=58)	KRAS / NRAS / BRAF / PIK3CA WT (n=104)	KRAS / NRAS / BRAF / PIK3CA mutant (n=78)
Complete response, %	6.6	6.4	6.9	7.7	5.1
Partial response, %	50.5	55.6	39.7	56.7	42.3
Stable disease, %	33.5	28.2	44.8	26.9	42.3
Progressive disease, %	9.3	9.7	8.6	8.6	10.3
ORR, %	57.1	62.1	46.6	64.4	47.4
Median PFS, mos (95% CI)	9.8 (8.7, 11.5)	11.1 (9.2, 12.8)	8.9 (7.4, 9.6)	11.3 (9.4, 13.2)	7.7 (5.4, 9.4)

Conclusions

- Results of first-line treatment with FOLFIRI+cetuximab are similar to those in the Phase III CRYSTAL study (*note: second-line treatment is currently ongoing*)
- Increased activity of FOLFIRI+cetuximab was observed in mCRC patients whose tumours were WT for *KRAS*, *NRAS*, *BRAF* and *PIK3CA* genes

2168: Updated survival analysis of EXPERT-C, a randomized phase II trial of neoadjuvant capecitabine and oxaliplatin (CAPOX) and chemoradiotherapy (CRT) with or without cetuximab in MRI-defined high risk rectal cancer patients – Sclafani F et al

- Study objective
 - To investigate the effect of adding cetuximab to neoadjuvant CT and CRT on survival outcomes in patients with MRI-defined high-risk rectal cancer



Primary endpoint

- CR in *KRAS/BRAF* WT patients

Secondary endpoints

- PFS and OS in *KRAS/BRAF* WT

*400 mg/m² initial dose, 250 mg/m² subsequent doses
TME, total mesorectal excision

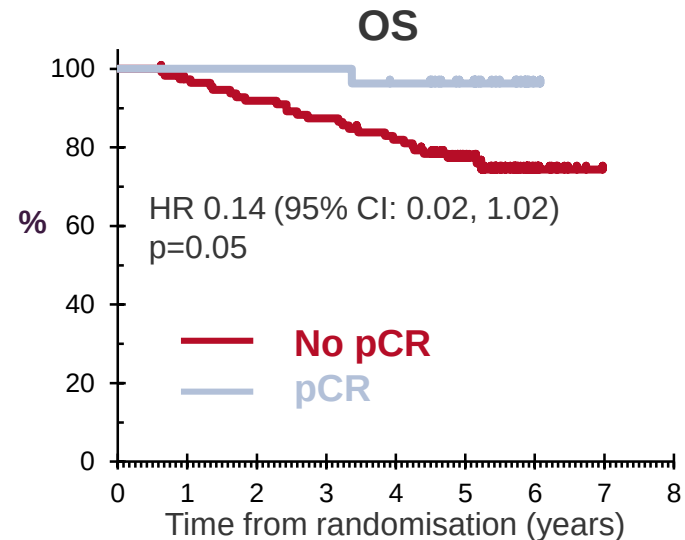
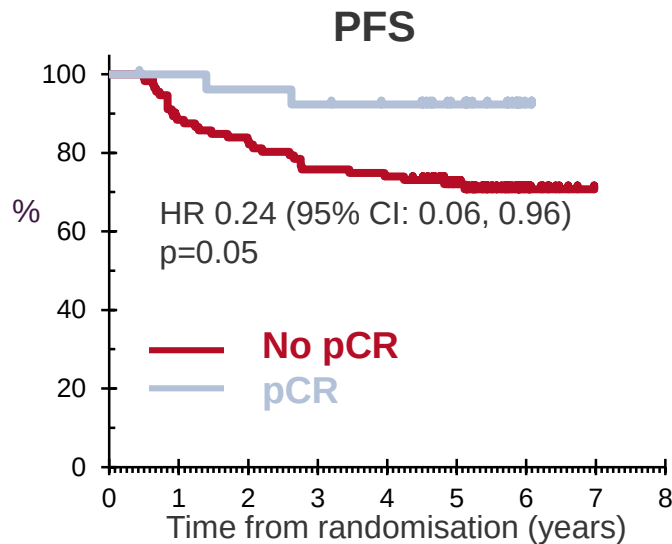
2168: Updated survival analysis of EXPERT-C, a randomized phase II trial of neoadjuvant capecitabine and oxaliplatin (CAPOX) and chemoradiotherapy (CRT) with or without cetuximab in MRI-defined high risk rectal cancer patients – Sclafani F et al

- Key results
 - Of the 149 (91%) patients tested for *KRAS/BRAF*, 90 (60%) were *KRAS/BRAF* WT, 44 in the CAPOX group and 46 in the CAPOX+cetuximab group
 - After a median follow-up of 63.8 mos, 29 events were observed in CAPOX and 25 in CAPOX+cetuximab groups

5-year survival (95% CI)				
	CAPOX	CAPOX+cetuximab	HR (95% CI)	p-value
<i>KRAS/BRAF</i> WT				
PFS	67.8 (53.9, 81.7)	75.4 (62.9, 87.9)	0.62 (0.29, 1.35)	0.23
OS	72.3 (59.0, 85.6)	84.3 (73.5, 95.1)	0.56 (0.23, 1.38)	0.20
ALL TREATED				
PFS	64.3 (53.7, 74.9)	69.4 (59.4, 79.4)	0.77 (0.45, 1.31)	0.34
OS	68.5 (58.3, 78.7)	77.8 (68.8, 86.8)	0.64 (0.35, 1.15)	0.13

2168: Updated survival analysis of EXPERT-C, a randomized phase II trial of neoadjuvant capecitabine and oxaliplatin (CAPOX) and chemoradiotherapy (CRT) with or without cetuximab in MRI-defined high risk rectal cancer patients – *Sclafani F et al*

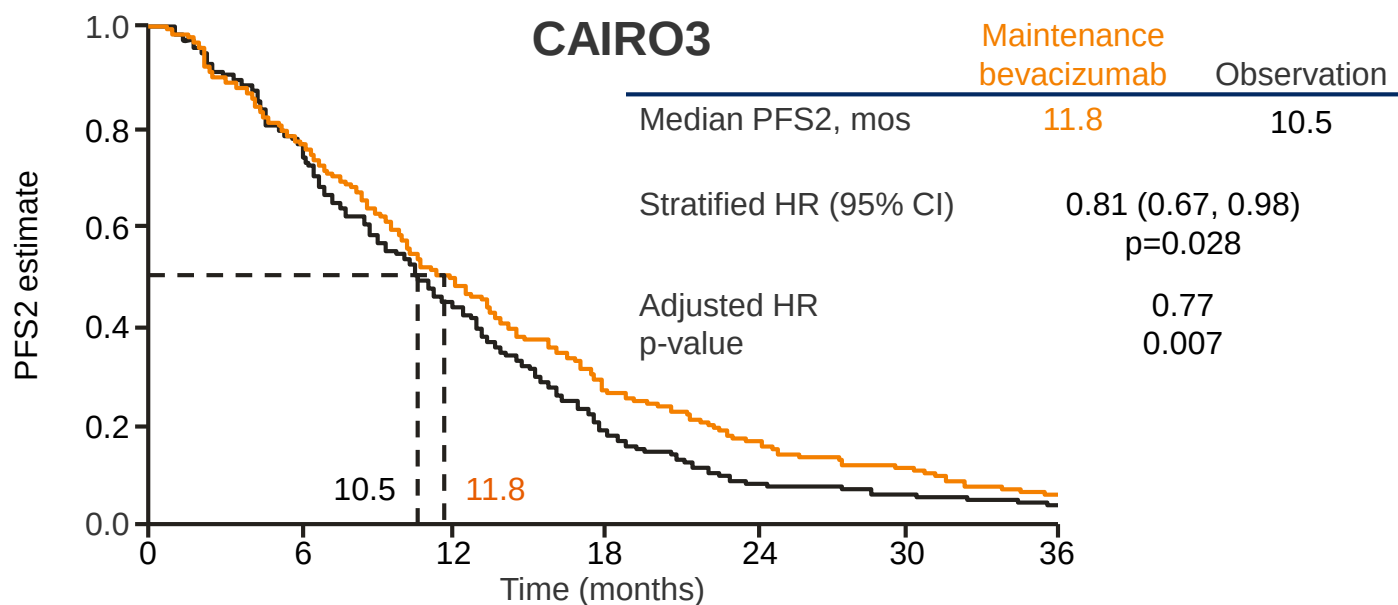
- Key results (continued)
 - Pathological complete response (pCR) was associated with a significant improvement in PFS and OS in patients who underwent RO surgery (n=140)



- **Conclusions**
 - Neoadjuvant CT was associated with promising long-term survival outcomes
 - The addition of cetuximab improved survival, but did not reach statistical significance
 - pCR was shown to be a valid surrogate endpoint

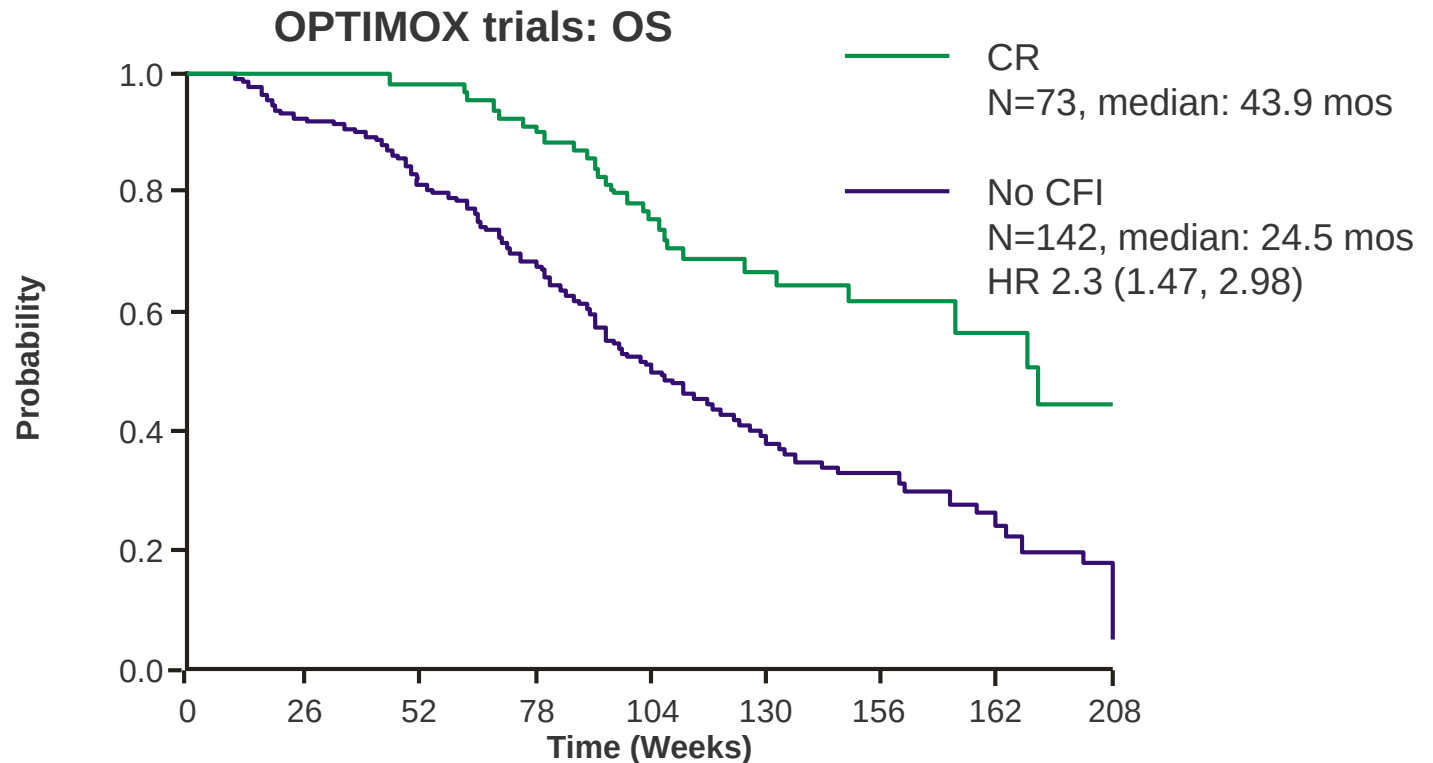
222: Selecting for maintenance or stop-and-go strategy in metastatic colorectal cancer – *De Gramont A et al*

- Study objective
 - To review alternative strategies in treating mCRC, including stop-and-go regimens as well as novel CT combinations
- Key results
 - Continuing long-term CT is associated with reduced QoL and neurotoxicity
 - Several studies have shown, however, that continuous CT is superior to stopping CT after 3–6 mos (COIN, OPTIMOX2, CAIRO3, SAKK studies)



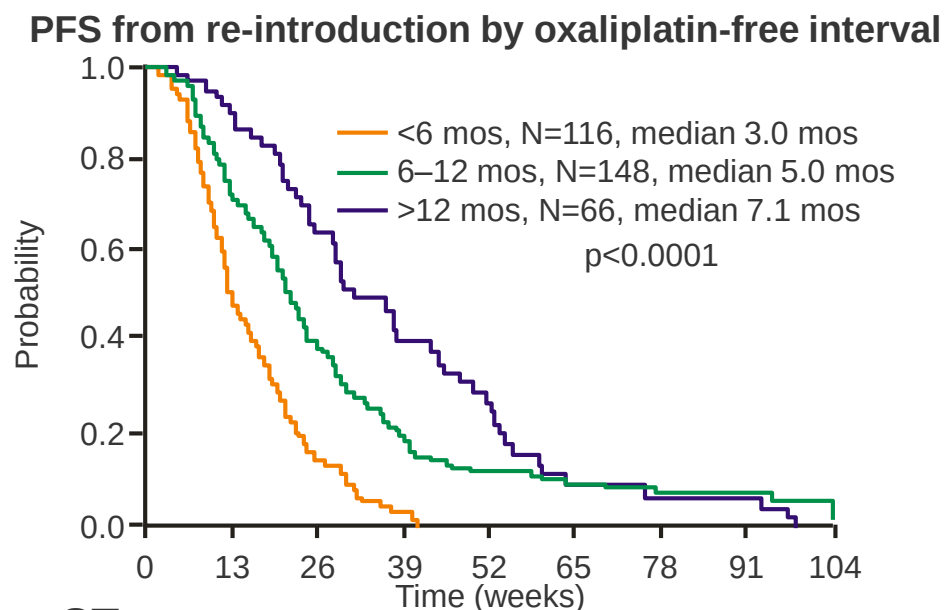
222: Selecting for maintenance or stop-and-go strategy in metastatic colorectal cancer – *De Gramont A et al*

- Key results (continued)
 - A subset of patients appear to benefit from stopping CT: those with normal platelet count at baseline or normal CEA levels at 3 mos
 - Optimal duration of CT prior to stopping is 6 mos



222: Selecting for maintenance or stop-and-go strategy in metastatic colorectal cancer – *De Gramont A et al*

- Key results (continued)
 - Oxaliplatin-based induction CT followed by maintenance is equivalent to continuous oxaliplatin-based CT
 - Optimal maintenance is fluoropyrimidine+bevacizumab or erlotinib+bevacizumab
 - Oxaliplatin stop-and-go has been shown to improve survival



- **Conclusions**
 - **Continuous CT is superior to stopping CT**
 - However, a subset of patients appear to benefit from stopping CT
 - **Oxaliplatin stop-and-go can improve survival in mCRC**

2276: Aflibercept in combination with FOLFIRI for the second-line treatment of patients with metastatic colorectal cancer: Interim safety data from the global Aflibercept Safety and Quality-of-Life Program (ASQoP and AFEQT studies)

– *Sobrero A et al*

- Study objective
 - To assess safety and health-related QoL of aflibercept in mCRC patients previously treated with an oxaliplatin-containing regimen

**Two single-arm, open-label studies
(interim safety analysis)**

Patients with mCRC

- Aged ≥ 18 years
- PS 0–1
- Previous oxaliplatin-based treatment

(n=1100)

Aflibercept+FOLFIRI
(n=116*)

PD

Primary endpoint

- Safety

Secondary endpoint

- QoL

Note: Similar study design to the VALOUR trial [Van Cutsem et al. J Clin Oncol 2012;30:3499]

2276: Aflibercept in combination with FOLFIRI for the second-line treatment of patients with metastatic colorectal cancer: Interim safety data from the global Aflibercept Safety and Quality-of-Life Program (ASQoP and AFEQT studies)

– *Sobrero A et al*

- Key results
 - There were 27 discontinuations due to adverse events: 15 (46.9%) with aflibercept vs. 12 (37.5%) with FOLFIRI
 - TEAEs were reported in 94.0% of patients

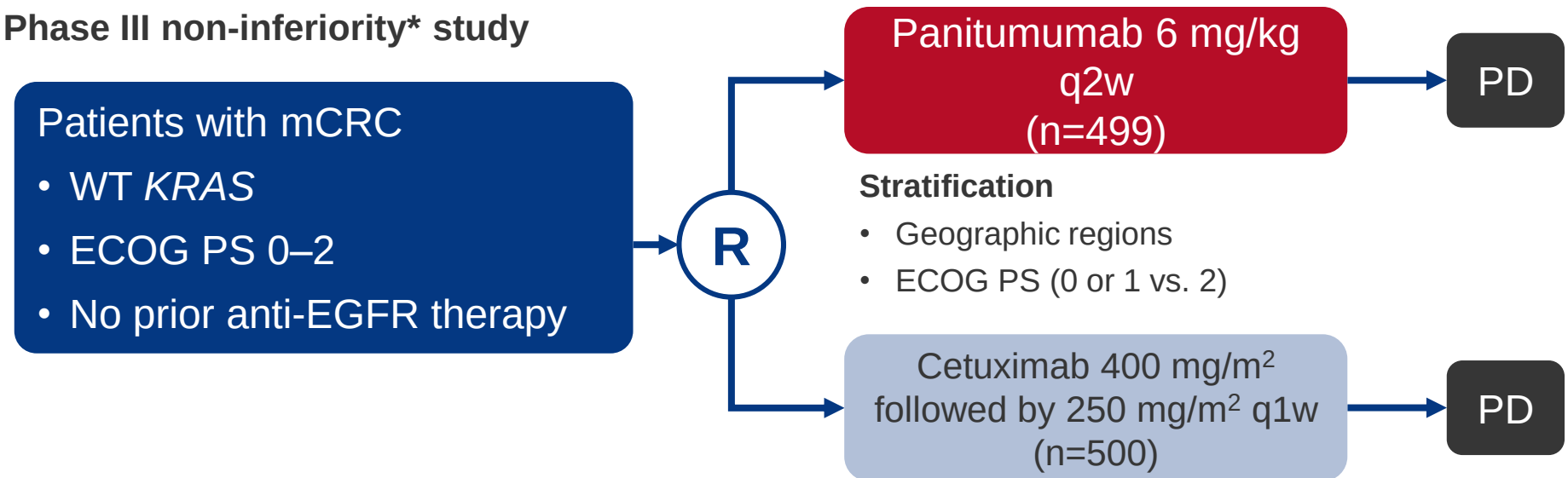
	ASQoP+AFEQT studies Aflibercept+FOLFIRI (n=116)	VALOUR study Aflibercept+FOLFIRI (n=611)
Any TEAE, %	94.0	99.2
Diarrhoea	50.9	69.2
Hypertension	34.5	41.2
Nausea	30.2	53.4
Fatigue	26.7	47.8
Neutropenia	25.0	39.0

- Conclusion
 - Baseline characteristics were similar to the VALOUR study, but this interim safety analysis suggests lower toxicity levels in the current study, with no new safety signals reported

18: ASPECCT: a randomized, multicenter, open-label, phase 3 study of panitumumab (pmab) vs cetuximab (cmab) for previously treated wild-type (WT) *KRAS* metastatic colorectal cancer (mCRC) – Price *T et al*

- Study objective
 - To compare the efficacy and safety of panitumumab with cetuximab in chemorefractory WT *KRAS* mCRC

Phase III non-inferiority* study



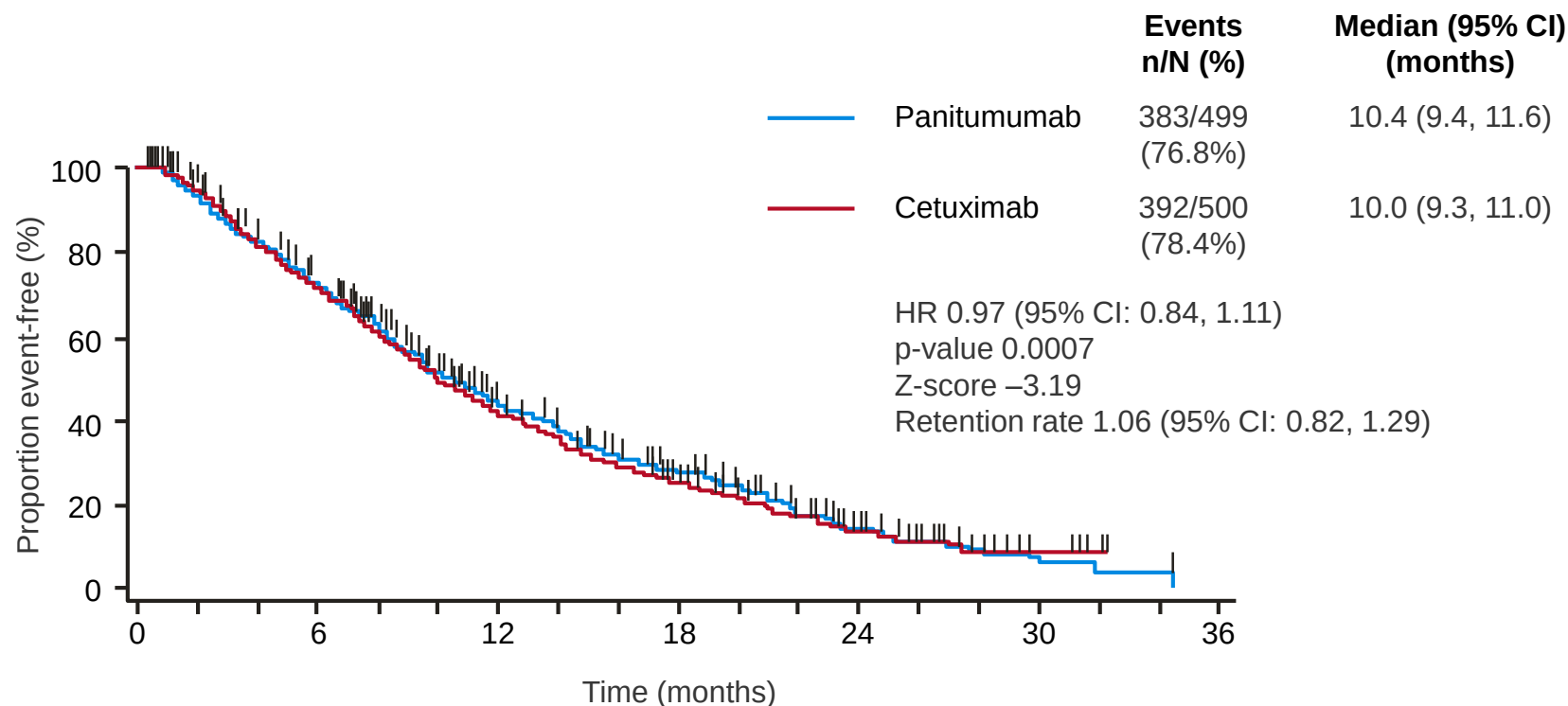
Primary endpoint:

- OS

*Non-inferiority: Reached if panitumumab achieves $\geq 50\%$ of the cetuximab OS effect vs. BSC, with a Z_{pc} score of less than -1.96

18: ASPECCT: a randomized, multicenter, open-label, phase 3 study of panitumumab (pmab) vs cetuximab (cmab) for previously treated wild-type (WT) KRAS metastatic colorectal cancer (mCRC) – Price *T et al*

- Key results
 - Non-inferiority of OS with panitumumab vs. cetuximab was met
 - Panitumumab retained 106% of the OS benefit of cetuximab over BSC



18: ASPECCT: a randomized, multicenter, open-label, phase 3 study of panitumumab (pmab) vs cetuximab (cmab) for previously treated wild-type (WT) KRAS metastatic colorectal cancer (mCRC) – Price T et al

- Key results (continued)

Objective response rates	Panitumumab (n=486)	Cetuximab (n=485)
Best tumour response over study, n (%)		
Complete response	2 (0.4)	0 (0)
Partial response	105 (21.6)	96 (19.8)
Stable disease or non-CR / non-PD	226 (46.5)	236 (48.7)
Patients with objective response*, n (%)	107 (22.0)	96 (19.8)
Rate (95% CI), %	22.0 (18.4, 26.0)	19.8 (16.3, 23.6)
Odds ratio (95% CI)	1.2 (0.8, 1.6)	

- The incidence of adverse events (97.8 vs. 98.2%) and serious adverse events (30.4 vs. 33.6%) were similar between panitumumab and cetuximab

- **Conclusions**

- **Panitumumab achieved non-inferiority to cetuximab for OS**
- **No new safety or tolerability issues were identified with panitumumab**

*Best tumour response or partial response

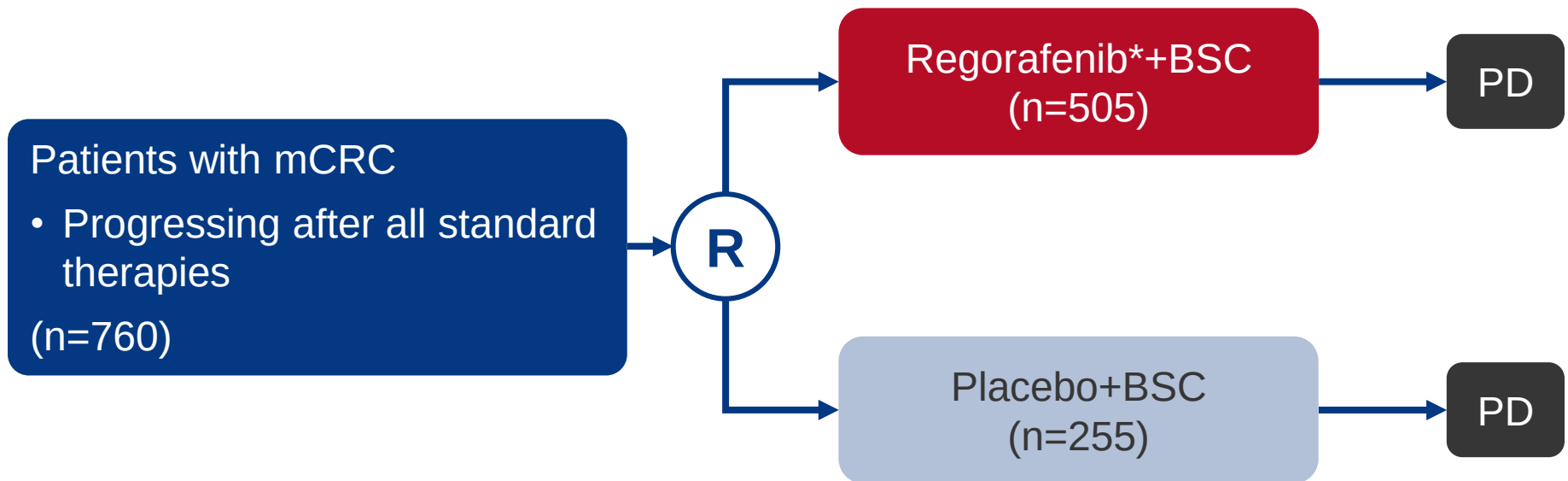
COLORECTAL CANCER

PALLIATIVE THERAPY

2156: Effects of regorafenib therapy on health-related quality of life in patients with metastatic colorectal cancer in the phase III CORRECT study

– *Siena S et al*

- Study objective
 - To investigate the impact of regorafenib efficacy and tolerability on QoL



Primary endpoint: OS

Secondary endpoint: QoL (assessed by EORTC QLQ-C30 and EQ-5D)

*160 mg od for 3 weeks of each 4-week cycle

2156: Effects of regorafenib therapy on health-related quality of life in patients with metastatic colorectal cancer in the phase III CORRECT study

– *Siena S et al*

- Key results
 - Regorafenib improved OS (HR 0.77 [95% CI: 0.64, 0.94]; p=0.005) and PFS (HR 0.94 [95% CI: 0.42, 0.58]; p<0.001) vs. placebo
 - Regorafenib was associated with higher rates of adverse events, including fatigue, hand–foot skin reaction, diarrhoea
 - Overall change in QoL was similar with regorafenib vs. placebo
 - Changes from baseline did not differ between regorafenib and placebo on most of the 15 domains assessed in the EORTC QLQ-C30

Difference vs. placebo	LS mean time-adjusted AUC	95% CI
EORTC QLQ-C30 (CMD: ≥10)	–1.19	–3.13, 0.75
EQ-5D health utility index (CMD: ≥0.08)	0.00	–0.03, 0.03
EQ-5D Visual analogue scale (CMD: ≥07)	–1.21	–3.04, 0.61

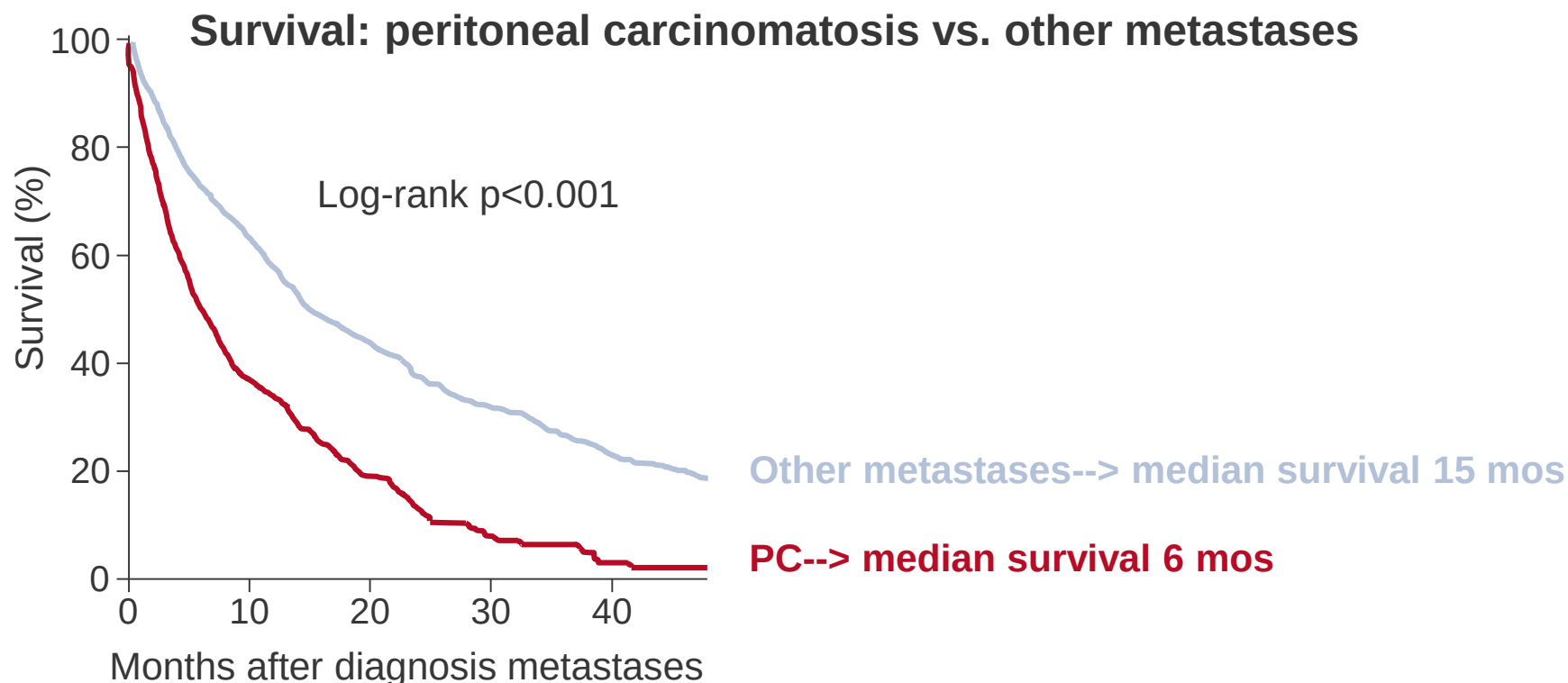
- Conclusion
 - There was no substantial difference in QoL with REG vs. placebo

2278: Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer – *Van Gestel YRBM et al*

- Study objective
 - To examine the incidence of and risk factors for developing metachronous peritoneal carcinomatosis from colorectal cancer
 - To investigate survival following diagnosis of peritoneal carcinomatosis
- Study design
 - Data on metachronous metastases were collected for 5671 patients diagnosed with M0 colorectal cancer (Dutch Eindhoven Cancer Registry)
 - Survival was defined as time from metastases diagnosis to death
 - Median follow-up was 5 years
- Key results
 - Of 1042 (18%) patients diagnosed with metastatic disease, 197 (19%) developed metachronous peritoneal carcinomatosis
 - Risk factors for developing metachronous peritoneal carcinomatosis included an advanced primary tumour stage (HR 2.0); positive lymph nodes at initial diagnosis (2.5); primary mucinous adenocarcinoma (1.9); positive resection margin (2.9); unknown differentiation grade (1.6) and primary colonic tumours (3.5)

2278: Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer – *Van Gestel YRBM et al*

- Key results (continued)



- **Conclusion**

- Identifying patients at high risk of developing metachronous peritoneal carcinomatosis may enable tailor-made follow-up and improve treatment outcomes

COLORECTAL CANCER

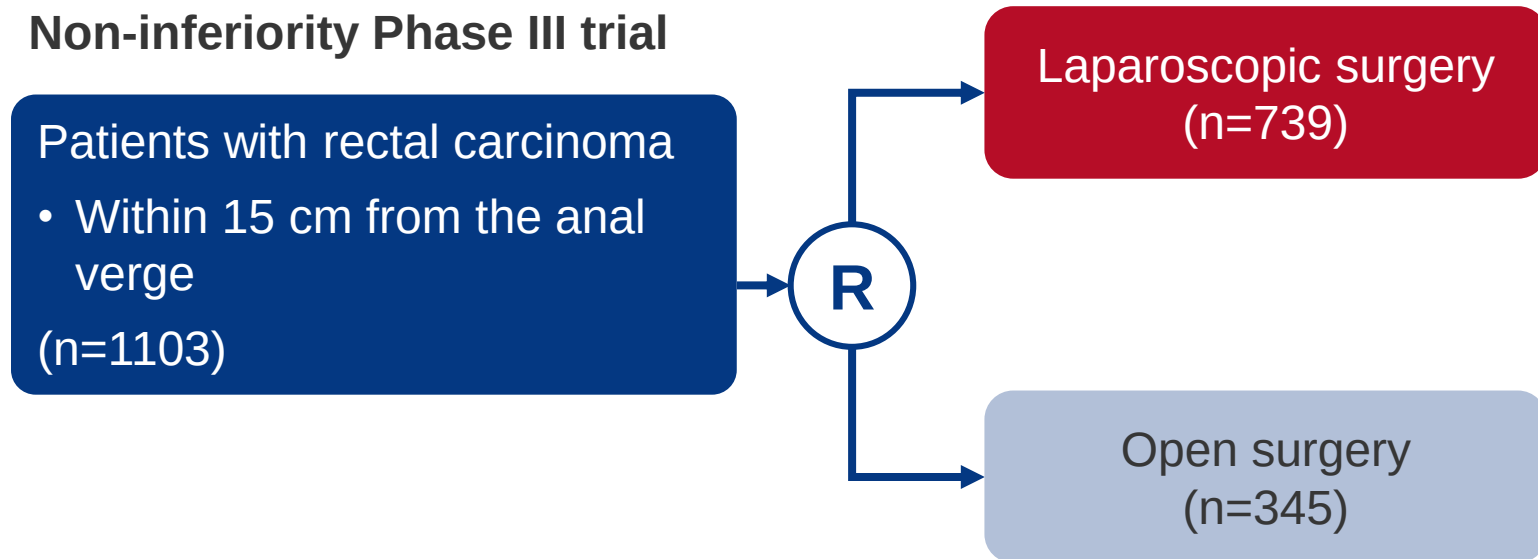
SURGERY

2150: Laparoscopic versus open surgery for rectal cancer: Short-term outcomes of a multicentre, open label, randomised controlled trial

– *Van der Pas M et al*

- Study objective
 - To determine the short-term outcomes of laparoscopic surgery vs. open surgery in patients with rectal cancer

Non-inferiority Phase III trial



2150: Laparoscopic versus open surgery for rectal cancer: Short-term outcomes of a multicentre, open label, randomised controlled trial

– *Van der Pas M et al*

- Key results

Outcome	Favours laparoscopic surgery	Favours open surgery	p-value
Blood loss	✓		<0.0001
Surgery duration		✓	<0.0001
Restoration of bowel function	✓		<0.0001
Hospital stay duration	✓		0.036
Macroscopically completeness	n/a	n/a	0.250
Positive circumferential margin	n/a	n/a	0.850
Complications	n/a	n/a	0.424
Mortality rates	n/a	n/a	0.409

- Conclusions

- Both treatments had similar short-terms outcomes in terms of safety and radicalness of surgery
- Laparoscopic surgery was associated with improved recovery compared with open surgery

PANCREATIC CANCER AND HEPATOBIILIARY TUMOURS

PANCREATIC CANCER

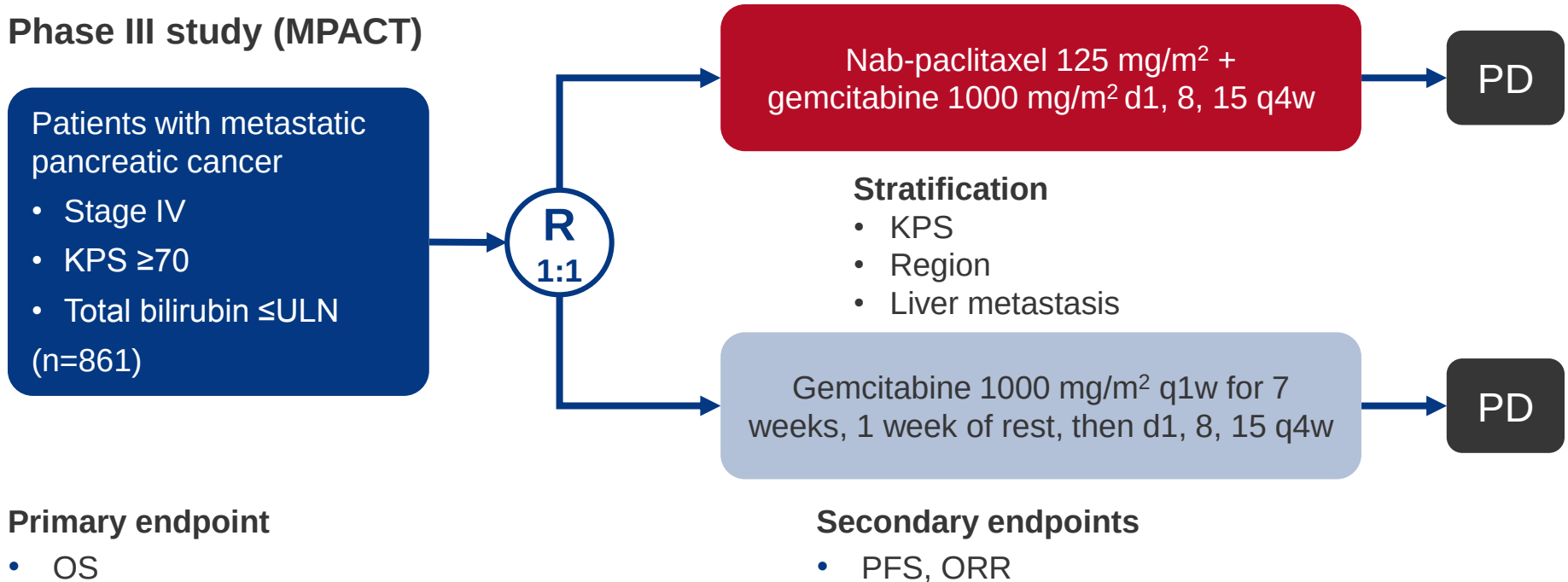
ADJUVANT THERAPY

4005: Results of a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates

– *Von Hoff DD et al*

- Study objective
 - To assess weekly nab-paclitaxel+gemcitabine vs. gemcitabine alone in patients with metastatic adenocarcinoma of pancreas with PET and CA19-9 correlates

Phase III study (MPACT)

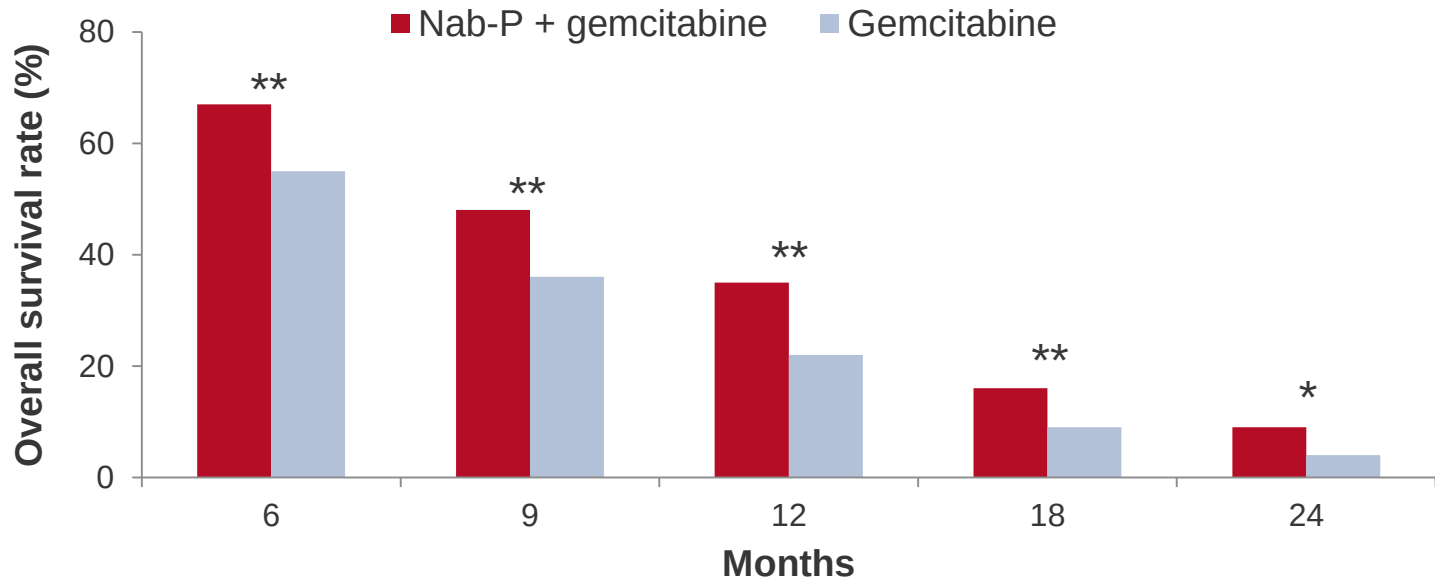


4005: Results of a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates

– *Von Hoff DD et al*

- Key results

- For all efficacy endpoints nab-paclitaxel+gemcitabine was superior to gemcitabine
 - Median OS: 8.5 vs. 6.7 mos (HR 0.72; 95% CI: 0.62, 0.84; p=0.000015)
 - Median PFS: 5.5 vs. 3.7 mos (HR 0.69; 95% CI: 0.58, 0.82; p=0.000024)



- Conclusion

- Nab-paclitaxel+gemcitabine was superior to gemcitabine across all efficacy endpoints and has an acceptable toxicity profile

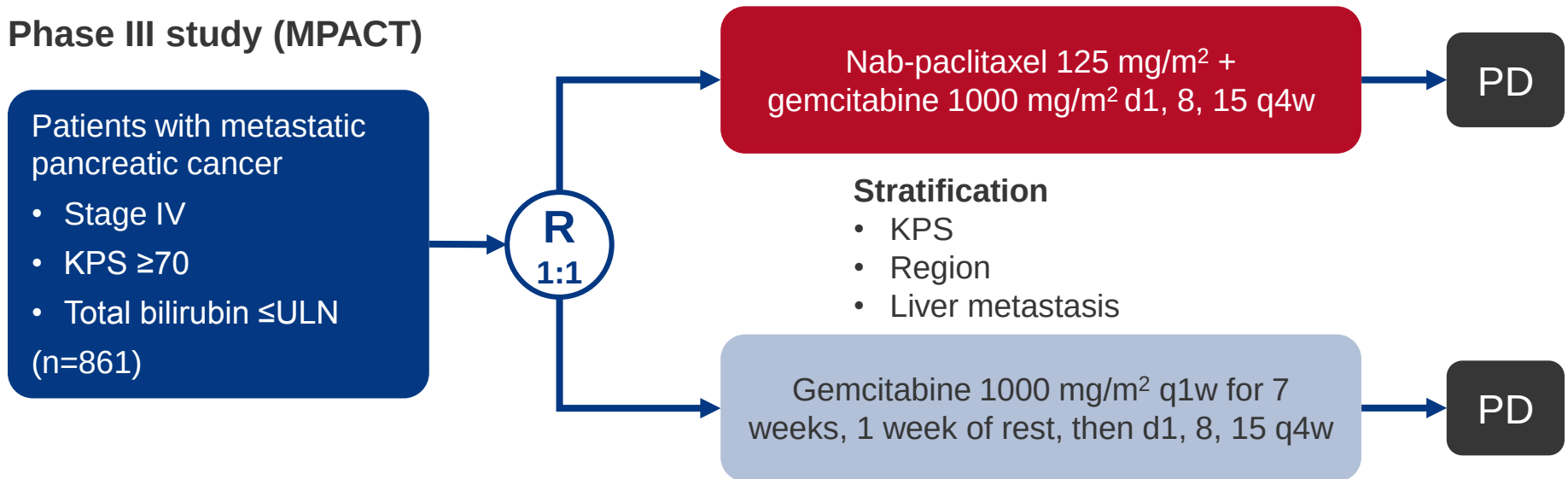
* p<0.05; **p<0.01

O-0001: Phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine in metastatic pancreatic cancer: influence of prognostic factors on survival

– *Tabernero J et al*

- Study objective
 - To evaluate the influence of prognostic factors on OS and PFS for nab-paclitaxel+gemcitabine vs. gemcitabine alone in patients with metastatic pancreatic cancer

Phase III study (MPACT)



Primary endpoint

- OS

Secondary endpoints

- PFS, ORR

O-0001: Phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine in metastatic pancreatic cancer: influence of prognostic factors on survival

– *Tabernero J et al*

- Key results

Factors predictive of OS	HR (95% CI)	p-value
Treatment (nab-paclitaxel+GEM vs. GEM)	0.72 (0.605, 0.849)	0.0001
KPS (70–80 vs. 90–100)	1.60 (1.346, 1.895)	<0.0001
Liver metastases (yes vs. no)	1.81 (1.404, 2.332)	<0.0001
Age (<65 vs. ≥65 years)	0.81 (0.686, 0.967)	0.0190
Region (Eastern Europe vs. North America)	1.22 (0.979, 1.516)	0.0765
Number of metastatic sites (1, 2, 3 vs. >3)	1.08 (0.988, 1.191)	0.0864

- Baseline CA19-9 level was found to be a predictor of OS by univariate analysis, but not in the stepwise procedure
- After adding known prognostic factors into the models, the effect of treatment on OS (HR 0.72; 95% CI: 0.61, 0.85; p<0.0001) and PFS (HR 0.66; 95% CI: 0.54, 0.80; p<0.0001) remained significant and favoured nab-paclitaxel treatment

O-0001: Phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine in metastatic pancreatic cancer: influence of prognostic factors on survival

– Tabernero J et al

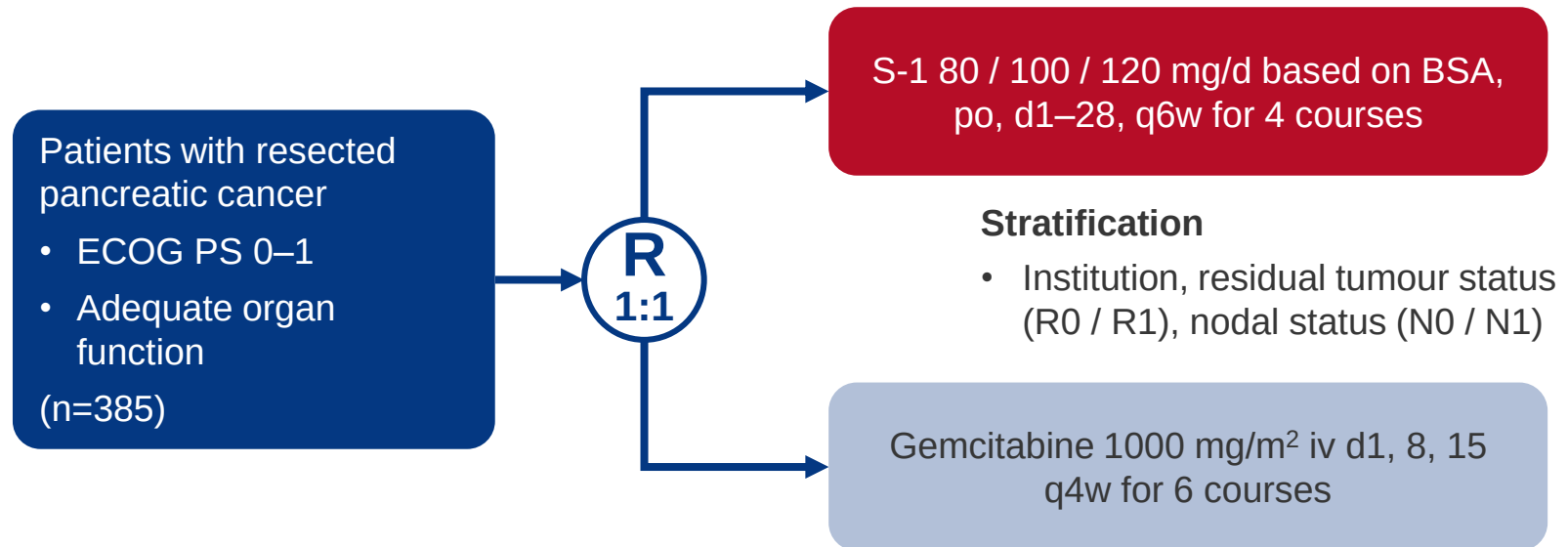
- **Conclusions**

- While baseline CA19-9 was not an independent predictor, the most important predictors of survival for patients with metastatic pancreatic cancer in the MPACT trial were KPS, presence of liver metastases, age, region and number of metastatic sites
 - KPS 70–80, presence of liver metastases, age ≥ 65 years and the region of Australia were significant predictors of worse PFS
- Treatment with nab-paclitaxel+gemcitabine remained an independent, highly significant predictor of improved survival and disease progression in metastatic pancreatic cancer even after correcting for known prognostic factors

4008: JASPAC 01: Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 for patients with resected pancreatic cancer

– *Fukutomi A et al*

- Study objective
 - To investigate non-inferiority of S-1 to gemcitabine on OS as adjuvant chemotherapy for resected pancreatic cancer in a Phase III study



Primary endpoint

- OS

Secondary endpoints

- RFS, adverse events, QoL (EQ-5D)

4008: JASPAC 01: Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 for patients with resected pancreatic cancer

– *Fukutomi A et al*

- Key results

- 378 patients (G/S: 191/187) included in full analysis set

Outcome	S-1 % (95% CI)	Gemcitabine % (95% CI)	HR (95% CI)	p-value
OS	70 (63, 76)	53 (46, 60)	0.54 (0.35, 0.83)*	<0.0001 for non-inferiority <0.0001 for superiority
RFS	49 (42, 56)	29 (23, 35)	0.57 (0.45, 0.72)	<0.0001 for superiority

- A greater proportion of patients in the gemcitabine group discontinued the study (42%) than the S-1 group (28%)
- Higher incidences of grade 3/4 leukopenia with gemcitabine (39%) vs. S-1 (9%)
- QoL (EQ-5D) scores were numerically greater with S-1 than gemcitabine

- Conclusions

- In patients with resected pancreatic cancer, S-1 adjuvant chemotherapy was well tolerated and superior to gemcitabine for OS and RFS
- S-1 is considered the new standard of treatment for resected pancreatic cancer in Asia

2454: Influence of time interval from histologic diagnosis to chemotherapy (CTx) on benefit of chemotherapy for advanced pancreatic adenocarcinoma – Teo M et al

- Study objective
 - To investigate whether the time interval between diagnosis and CT impacts on the benefit of CT
- Study design
 - Patients who received CT treatment were compared with untreated patients using data obtained from the National Cancer Registry of Ireland

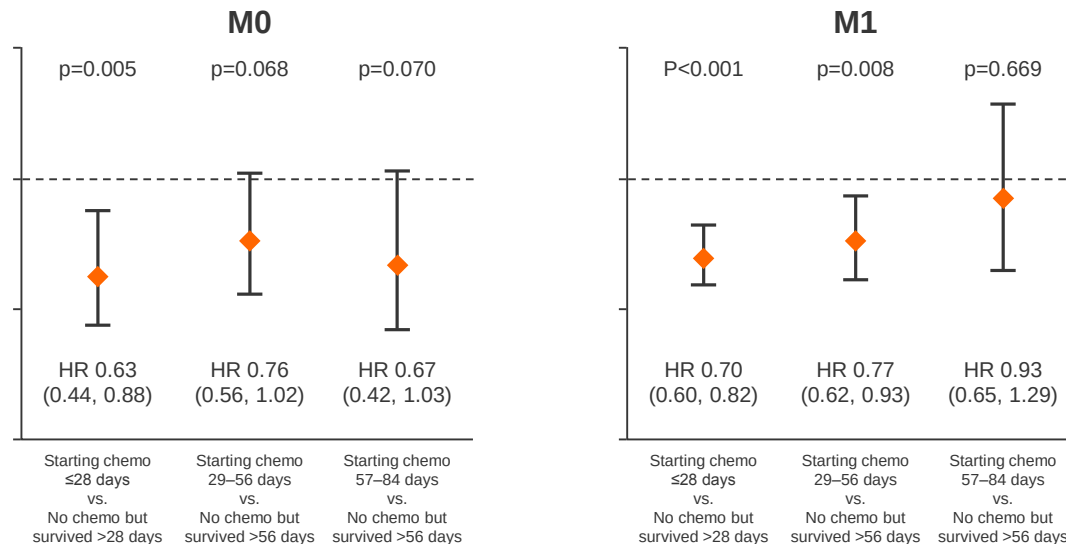
CT treatment (n=949)	No CT treatment (n=3560)
CT between ≤ 28 days	Survived > 28 days
CT between 29–56 days	Survived > 56 days
CT between 57–84 days	Survived > 84 days

- Subgroups:
 - Disease stage (M0 vs. M1 vs. Mx) – *Mx excluded*
 - Age (< 70 vs. ≥ 70 years old)

2454: Influence of time interval from histologic diagnosis to chemotherapy (CTx) on benefit of chemotherapy for advanced pancreatic adenocarcinoma – Teo M et al

- Key results

- 28.1% of treated patients and 73.3% of untreated patients were aged ≥ 70 years ($p < 0.001$)
- Amongst treated patients, 21.3% were M0 and 53.9% were M1, compared with 15.0% M0 and 38.6% M1 in untreated patients ($p < 0.001$)



- Conclusions

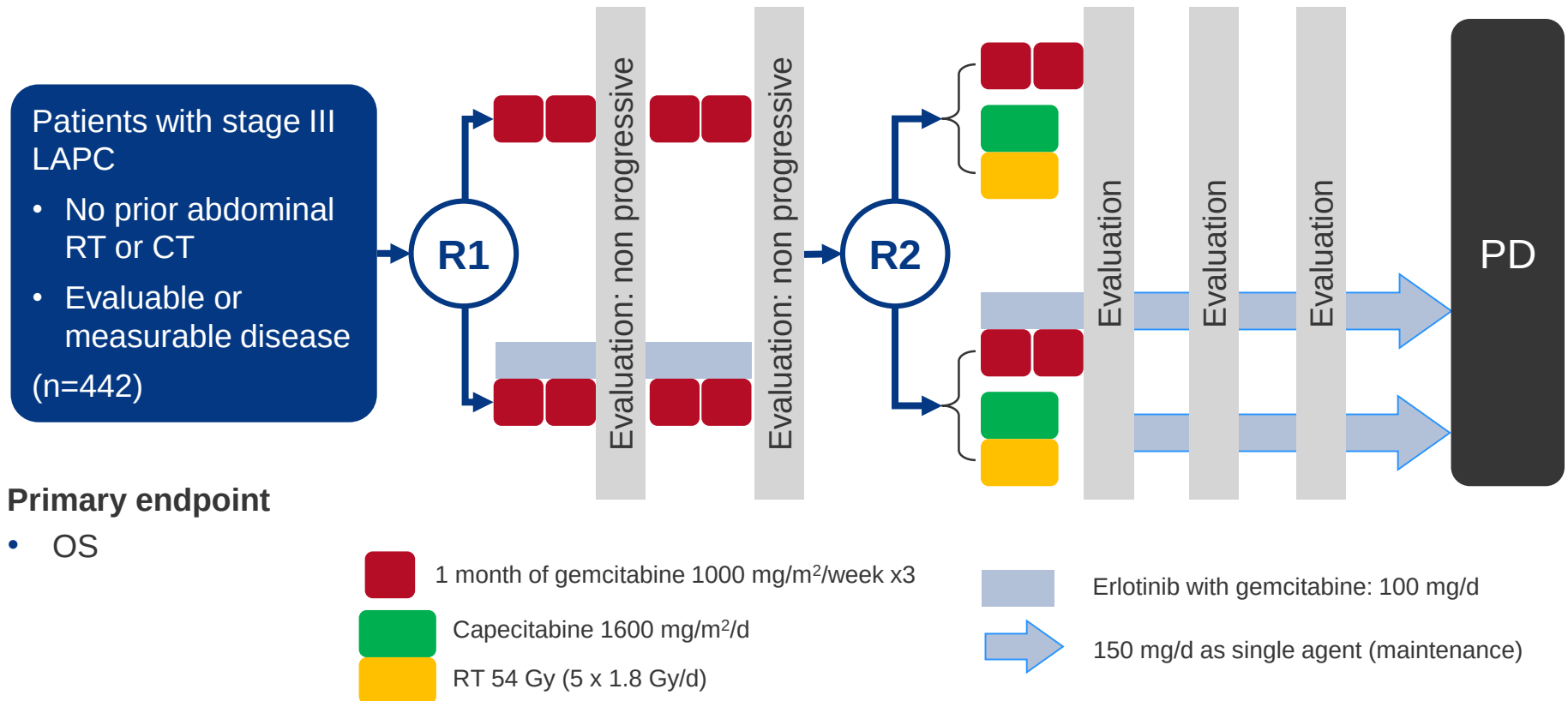
- CT benefit diminished as the time interval between diagnosis and CT increased
- This effect appears most pronounced in elderly or M1 patients

PANCREATIC CANCER

NEOADJUVANT THERAPY

LBA4003: Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study – *Hammel P et al*

- Study objective
 - To define the role of CRT in LAPC after disease control with 4 months of induction chemotherapy with gemcitabine and erlotinib



LBA4003: Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study – Hammel P et al

- Key results
 - From 442 patients included for R1, 269 patients reached R2 (arm 1: 136; arm 2: 133; mean age 63 / 62 years)
 - OS in R2 patients in arm 1 vs. arm 2: 16.4 vs. 15.2 mos (HR 1.03; 95% CI: 0.79, 1.34; p=0.83)
- Conclusions
 - Administering CRT is not superior to continuing CT in patients with controlled LAPC after 4 months of CT
 - The CRT regimen was associated with good tolerance
 - Erlotinib maintenance is not beneficial in LAPC, but increased toxicity
 - CT should still be considered standard of care in LAPC

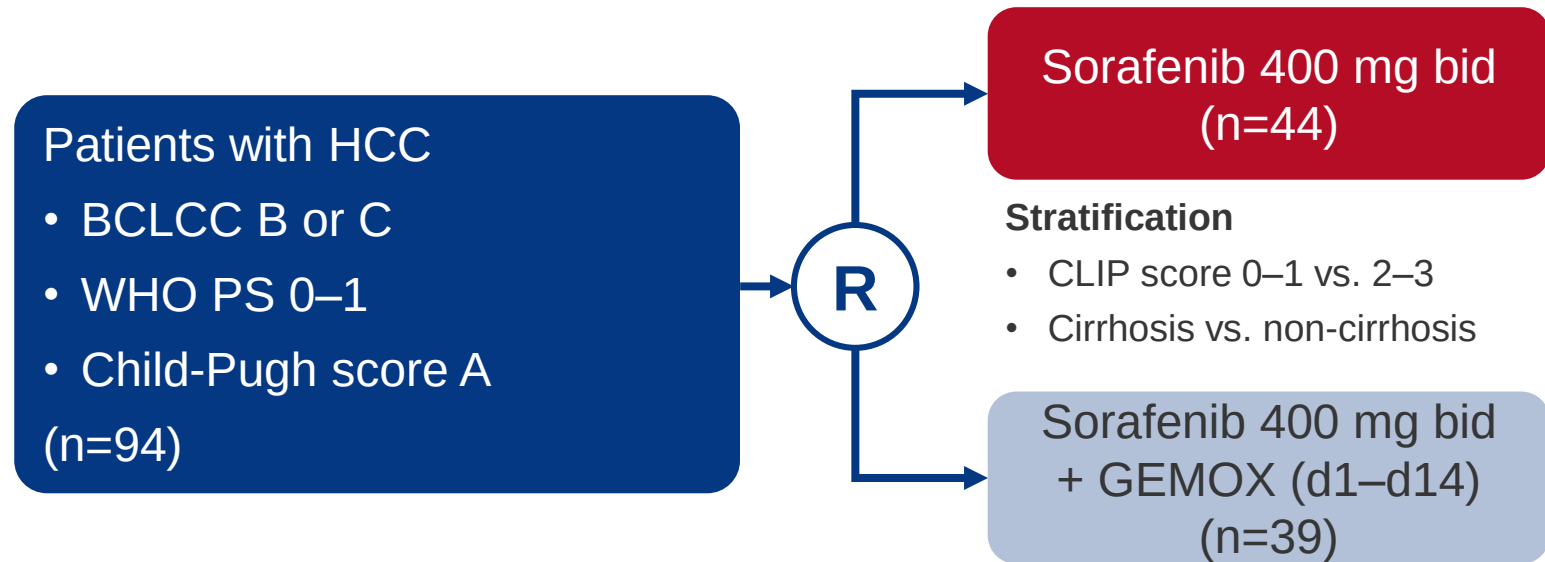
HEPATOCELLULAR CARCINOMA

ADJUVANT THERAPY

2467: Sorafenib alone versus Sorafenib combined with Gemcitabine and Oxaliplatin (GEMOX) in the first-line treatment of advanced hepatocellular carcinoma: final analysis of the randomized phase II GoNext trial

– *Assenat E et al*

- Study objective
 - To assess the efficacy and toxicity of sorafenib (400 mg bid) alone or in combination with GEMOX* every 2 weeks in patients with HCC



Primary endpoint

- PFS at 4 mos

*Gemcitabine, 1000 mg/m² d1; oxaliplatin, 100 mg/m² d2
BCLCC, Barcelona-Clinic Liver Cancer Classification

2467: Sorafenib alone versus Sorafenib combined with Gemcitabine and Oxaliplatin (GEMOX) in the first-line treatment of advanced hepatocellular carcinoma: final analysis of the randomized phase II GoNext trial

– *Assenat E et al*

- Key results
 - PFS at 4 mos: 54% with sorafenib vs. 64% with sorafenib+GEMOX
 - Median (95% CI) PFS: 4.6 (3.9, 6.2) vs. 6.2 (3.8, 6.8) mos (log-rank p=0.684)
 - Median (95% CI) OS: 13.0 (10.4, 22.2) mos with sorafenib vs. 13.5 (7.5, 19.1) mos with sorafenib+GEMOX
 - ORR: 9% with sorafenib vs. 16% with sorafenib+GEMOX
 - Sorafenib+GEMOX had acceptable tolerance
 - Main severe (grade 3–4) toxicity (sorafenib vs. sorafenib+GEMOX) consisted of neutropenia (grade 3–4: 0 vs. 7%), fatigue (18 vs. 24%), thrombocytopenia (0 vs. 9%) and diarrhoea (grade 2–4: 10 vs. 21%), respectively
 - More haematological, sensitive neuropathy were observed with sorafenib+GEMOX vs. more hand-foot syndrome with sorafenib alone
- Conclusions
 - The study met its primary endpoint (4-month PFS ≥ 50)
 - PFS, OS and ORR data were encouraging compared with published literature

GALLBLADDER CANCER

ADJUVANT THERAPY

264: Management of Stage 3 gallbladder cancer

– Gruenberger T et al

- Objective
 - To summarise the current understanding and treatment options for stage III gallbladder cancer
- Findings
 - Current gold standard in preoperative imaging is percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP)
 - Preoperative management varies between the UK and Japan:

	UK	Japan
Jaundice	Drainage (ERCP > PTC)	Drainage (PTC > ERCP)
Portal vein embolisation	No, unless extended hepatectomy	Patients with jaundice undergoing >50% liver resection
Modality for tumour evaluation	MRI, CT	Selective cholangiography, CT

264: Management of Stage 3 gallbladder cancer

– Gruenberger T et al

- Findings (continued)
 - Treatment options include [Hueman et al. Ann Surg Oncol 2009;16:2101]:
 - More radical hepatic resection
 - Vascular resection and reconstruction
 - Seldom curative
 - Lymphadenectomy
 - Five-year OS range: 0–44%
- **Conclusions**
 - **Recurrence remains a problem in gallbladder cancer**
 - **Adjuvant therapies may be beneficial, but data are currently limited**
 - **Awaiting results of BILCAP and ACTUCCA-1 trials**
 - **Advanced gallbladder cancer requires a multidisciplinary approach to overcome poor prognosis**

GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS

GASTRIC CANCER

ADJUVANT THERAPY

2457: Adjuvant chemoradiotherapy improves survival after a microscopically irradical (R1) gastric cancer resection – Stiekema J et al

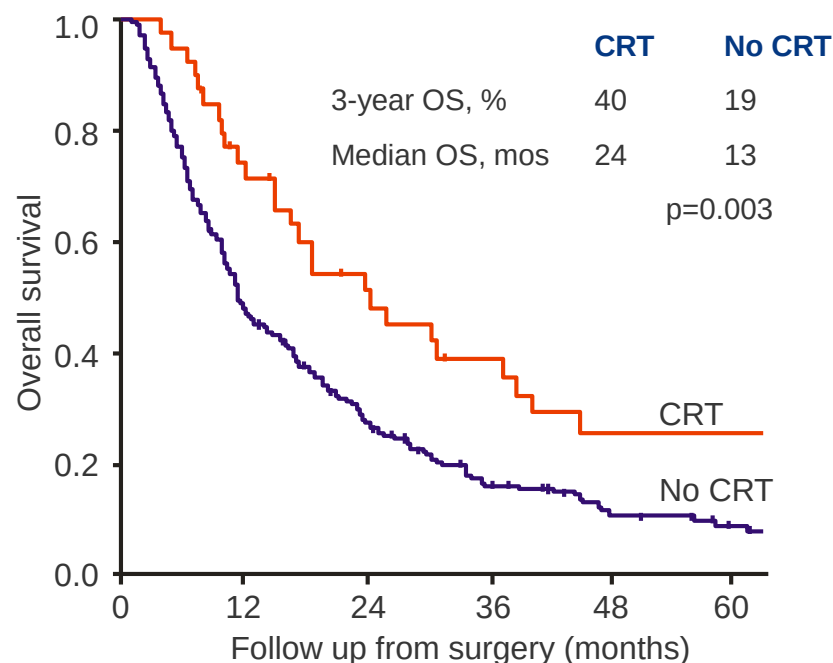
- Study objective
 - To evaluate the effect of adjuvant CRT on overall survival in patients with non-metastatic gastric cancer who had undergone an R1 resection
- Study design
 - Patients who had undergone an R1 resection for M0 gastric cancer were included in the study
 - Patients who had received CRT* (n=40) were compared with patients who did not receive CRT (n=369)
- Key results
 - There were significant differences in some baseline characteristics:
 - Median age (p<0.001)
 - Tumour location (p=0.005)
 - Extent of surgery (p=0.002)
 - Histological subtype (p<0.001)

*Radiotherapy (45 Gy / 25 fractions) + cisplatin and/or 5-FU

2457: Adjuvant chemoradiotherapy improves survival after a microscopically irradical (R1) gastric cancer resection – *Stiekema J et al*

- Key results (continued)

- Median overall survival was significantly improved in patients treated with adjuvant CRT (figure)
- Adjuvant CRT was an independent prognostic factor for improved overall survival (HR 0.556, $p=0.004$)
- Other prognostic factors were:
 - Tumour location ($p=0.047$)
 - Pathological T-stage ($p<0.001$)
 - Pathological N-stage ($p<0.001$)

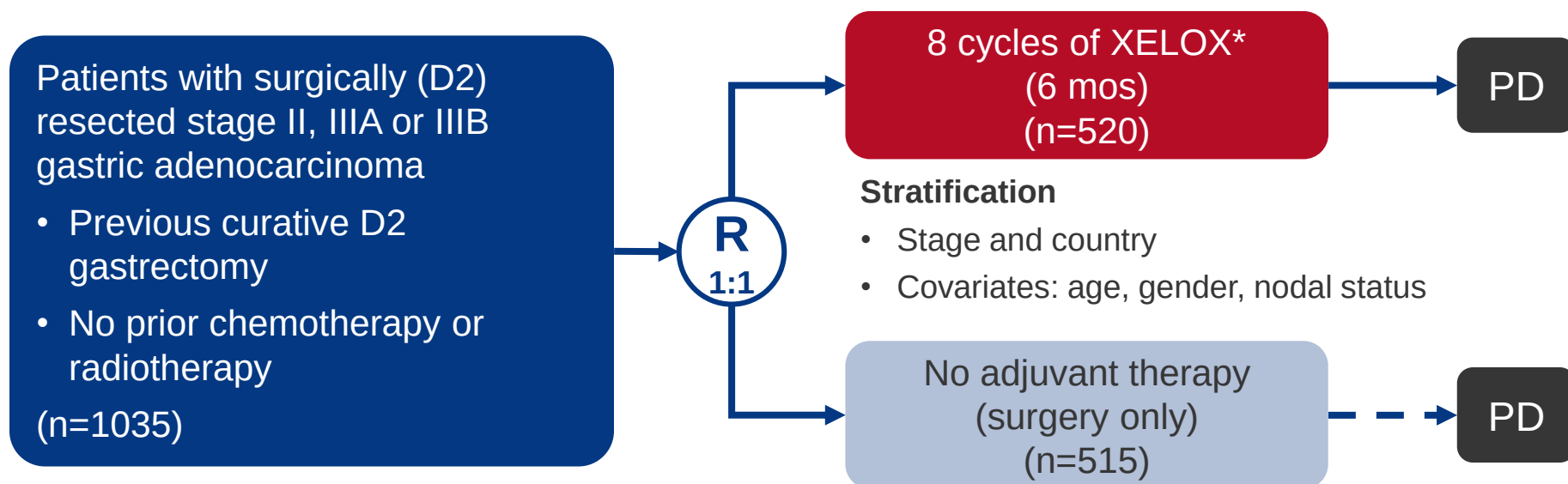


- Conclusion

- Adjuvant CRT after R1 resection in patients with non-metastatic gastric cancer was associated with a significant improvement in survival

O-0007: Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: final results from the CLASSIC trial – Noh SH et al

- Study objective
 - To prospectively examine adjuvant capecitabine+oxaliplatin vs. surgery alone in patients with gastric cancer included in the CLASSIC trial



Primary endpoint

- 3-year OS (previously reported)

Secondary endpoints

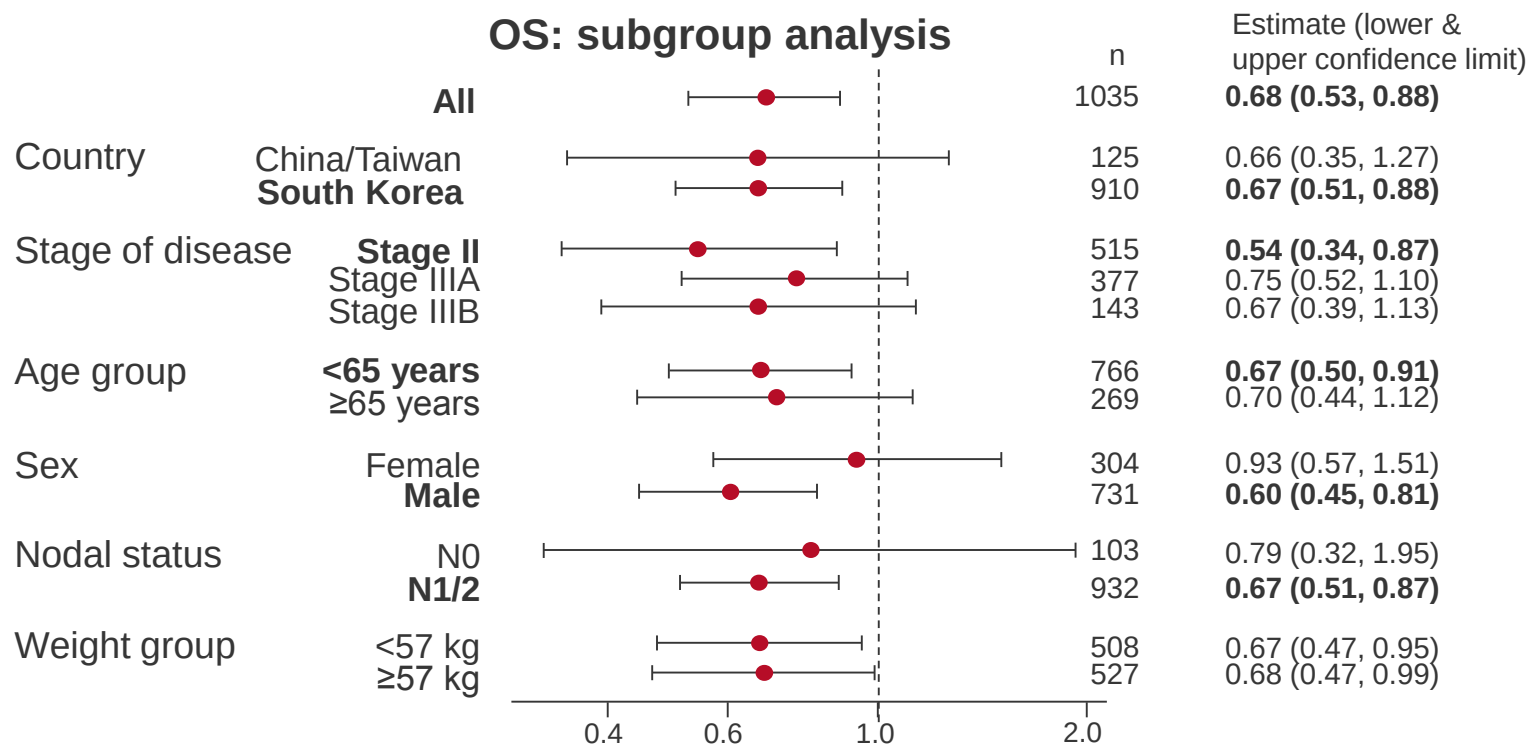
- 5-year OS, 5-year DFS, safety

*Capecitabine 1000 mg/m² bid d1–14 q3w plus oxaliplatin 130 mg/m² d1 q3w

O-0007: Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: final results from the CLASSIC trial – Noh SH et al

- Key results

- The 5-year OS rate for XELOX was significantly higher vs. surgery alone (78 vs. 69%, $p=0.0029$)
- There was a 34% reduction in risk of death with XELOX vs. surgery alone (stratified HR 0.66, 95% CI: 0.51, 0.85; $p=0.0015$)



O-0007: Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: final results from the CLASSIC trial – Noh SH et al

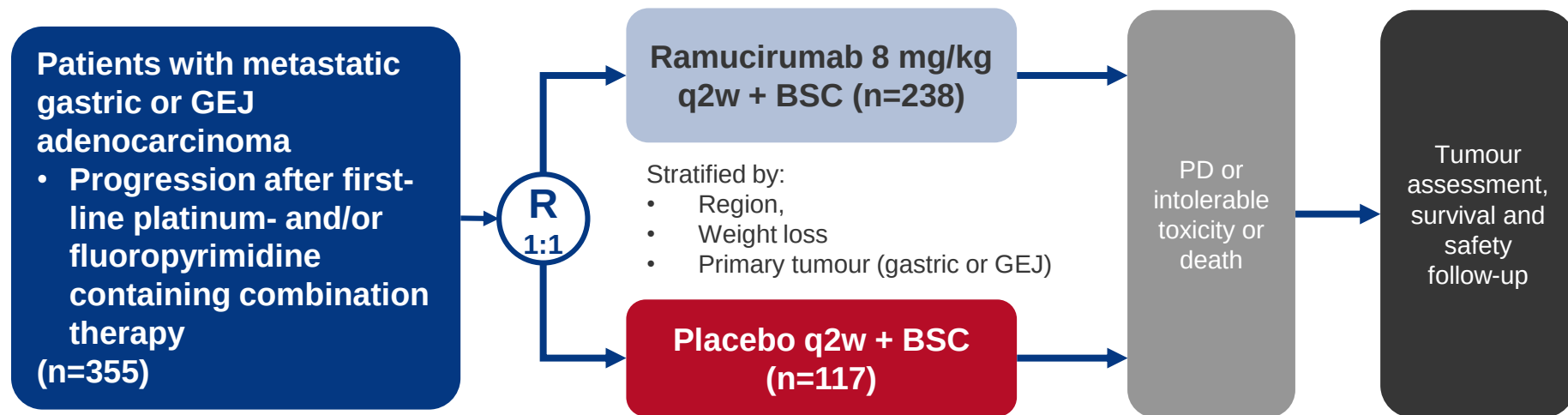
- Key results (continued)
 - The 5-year relapse rate was significantly higher with XELOX vs. surgery alone (68 vs. 53%; $p < 0.0001$)
 - There was a 42% reduction in risk of relapse with XELOX vs. surgery alone (stratified HR 0.58, 95% CI: 0.47, 0.72; $p < 0.0001$)
- **Conclusions**
 - Adjuvant XELOX provided a DFS benefit that translated to an OS benefit
 - The 34% (HR 0.66) reduction in risk of death at 5 years was greater than that previously reported at 3 years (28%, HR 0.72)
 - Postoperative adjuvant therapy with XELOX was an effective and well-tolerated option for patients with operable stage II / III gastric cancer following D2 gastrectomy
 - Adjuvant XELOX should be considered as a standard treatment for patients with operable gastric cancer

GASTRIC CANCER

NEOADJUVANT THERAPY

O-0008: REGARD Phase 3, randomized trial of ramucirumab in patients with metastatic gastric or GEJ adenocarcinoma following progression on first-line chemotherapy – *Tabernero J et al*

- Study objective
 - To evaluate ramucirumab in patients with metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma following progression on 1st-line platinum- and/or fluoropyrimidine-containing combination therapy



Primary endpoint

- OS

Secondary endpoints

- PFS, ORR, duration of response, QoL, safety

O-0008: REGARD Phase 3, randomized trial of ramucirumab in patients with metastatic gastric or GEJ adenocarcinoma following progression on first-line chemotherapy – *Tabernero J et al*

- Key results
 - Compared with placebo, ramucirumab reduced all-cause mortality by 22%

	Ramucirumab (n=238)	Placebo (n=117)	HR (95% CI)	p-value
OS			0.776 (0.603, 0.998)	0.0473
Median (95% CI), mos	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)		
6-mos, %	42	32		
12-mos, %	18	12		
PFS			0.483 (0.376, 0.620)	<0.0001
Median (95% CI), mos	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)		
At 12 weeks, %	40	16		
Tumour response				
Response rate, CR+PR, %	3.4	2.6		0.756
Disease control rate, CR+PR+SD, %	48.7	23.1		<0.0001

O-0008: REGARD Phase 3, randomized trial of ramucirumab in patients with metastatic gastric or GEJ adenocarcinoma following progression on first-line chemotherapy – *Tabernero J et al*

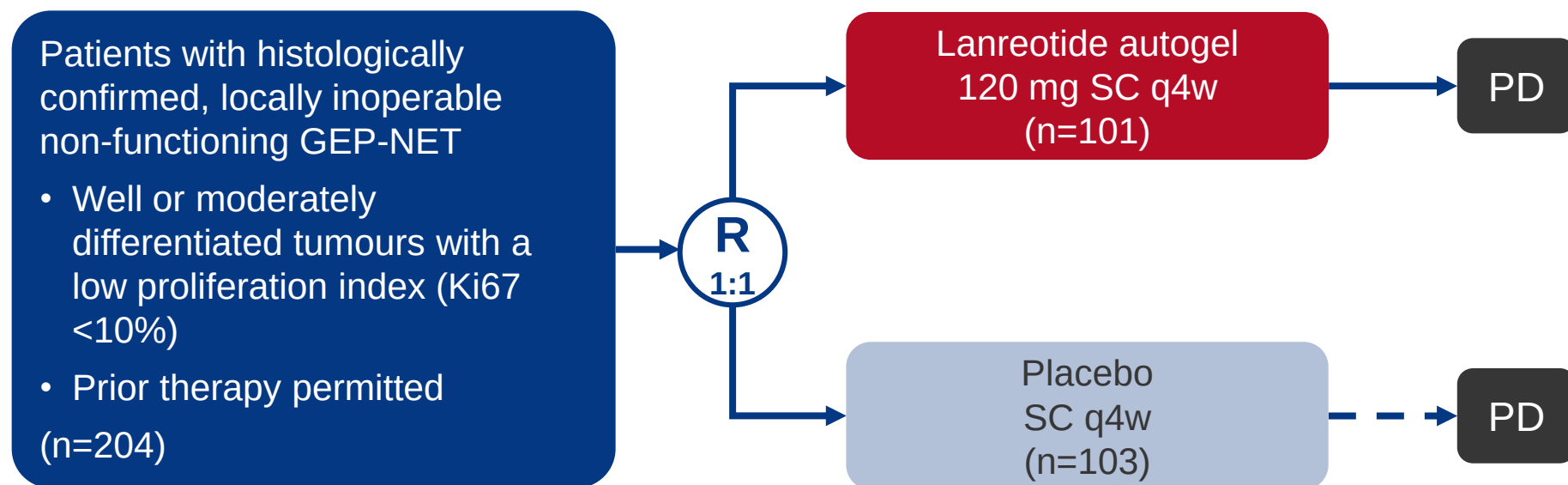
- Key results (continued)
 - The most frequent grade ≥ 3 adverse events (ramucirumab vs. placebo) were: hypertension (7.6 vs. 2.6%), fatigue (6.4 vs. 9.6%), anaemia (6.4 vs. 7.8%), abdominal pain (5.9 vs. 2.6%), ascites (4.2 vs. 4.3%), decreased appetite (3.4 vs. 3.5%), bleeding (3.4 vs. 2.6%) and hyponatraemia (3.4 vs. 0.9%)
- **Conclusions**
 - Among patients with metastatic gastric or GEJ cancer, ramucirumab+BSC was associated with significantly better OS and PFS than placebo+BSC
 - No grade ≥ 3 adverse events occurred in $>10\%$ of ramucirumab-treated patients
 - Ramucirumab is the first single-agent biological therapy to demonstrate an OS benefit in gastric cancer and could be a potential new standard of care for second-line therapy

NEUROENDOCRINE TUMOURS

ADJUVANT THERAPY

LBA3: A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET) – Caplin M *et al*

- Study objective
 - To prospectively evaluate the antiproliferative effects of lanreotide autogel (a somatostatin analogue) in patients with non-functioning gastroenteropancreatic neuroendocrine tumours (GEP-NET), including pancreatic and gastrointestinal tumours



Primary endpoint

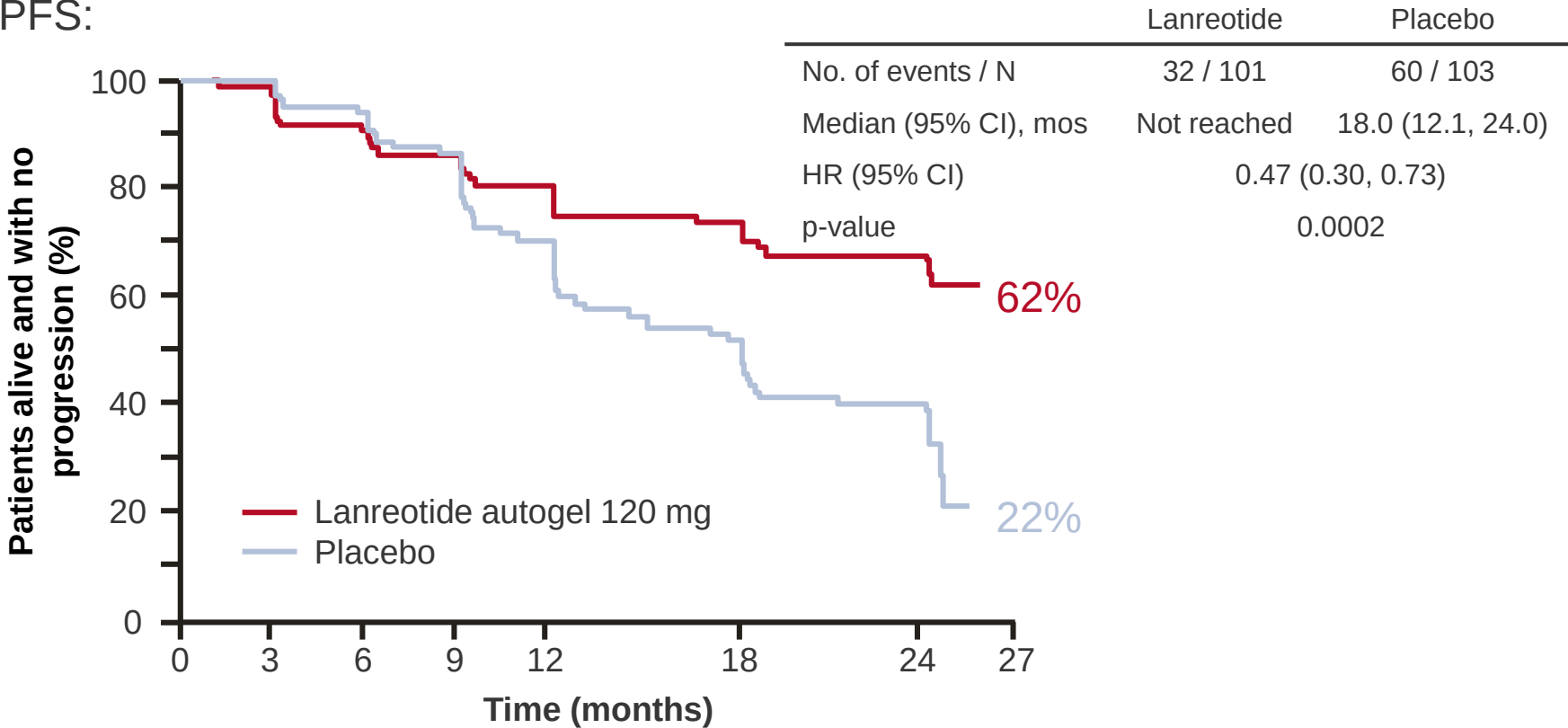
- PFS

Secondary endpoints

- PD, death, safety

LBA3: A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET) – Caplin M et al

- Key results
 - Primary tumour locations were: pancreas (45%), midgut (36%), hindgut (7%) and unknown (13%). Of the patients 96% had stable disease, 81% were treatment naïve, 33% had hepatic tumour load >25% and 22% had Ki67 3–10%
 - PFS:



LBA3: A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET) – Caplin M *et al*

- Key results (continued)
 - In a subgroup analysis, PFS in patients with midgut neuroendocrine tumours was significantly prolonged vs. placebo, HR 0.35 (95% CI: 0.16, 0.80); $p=0.0091$, but not in patients with pancreatic neuroendocrine tumours, HR 0.58 (95% CI: 0.32, 1.04); $p=0.0637$
 - There were no treatment-related deaths and few discontinuations due to AEs (3% in each group)
 - The most common treatment-emergent AEs occurring in $\geq 10\%$ of patients treated with lanreotide were diarrhoea, abdominal pain and cholelithiasis
- **Conclusions**
 - **Lanreotide prolonged PFS compared with placebo in patients with GEP-NET**
 - **It demonstrated antiproliferative activity in patients with midgut neuroendocrine tumours**

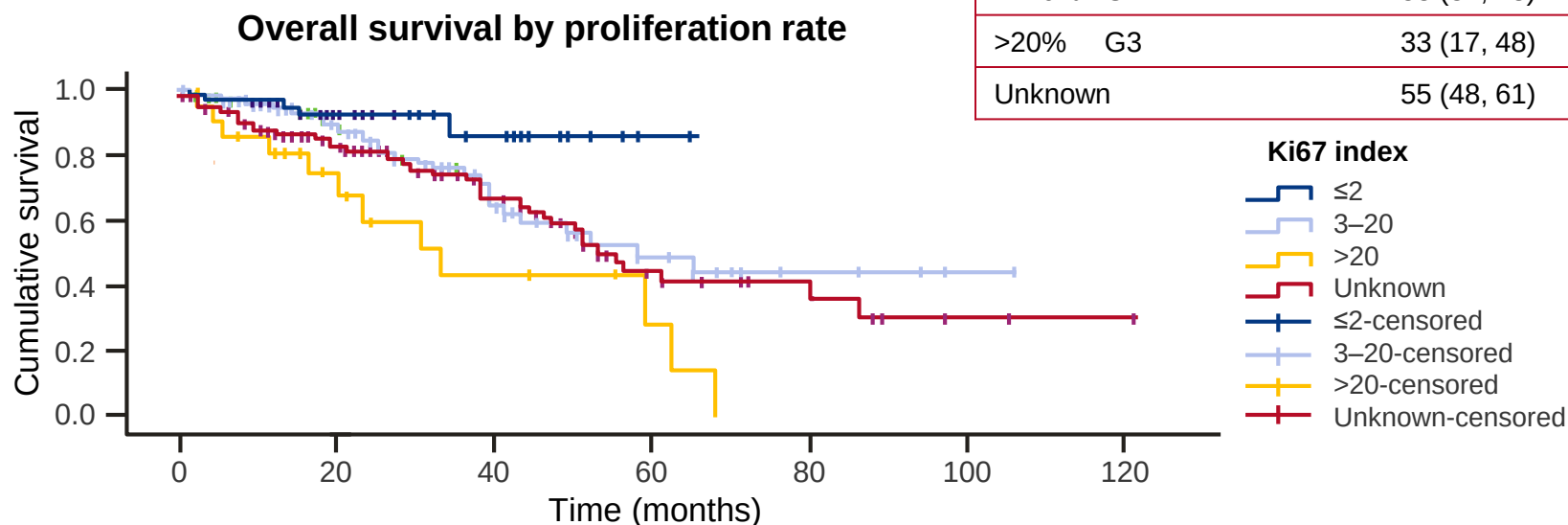
O-0005: Peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: A multi-institutional registry study with prospective follow up on 450 patients – *Ezziddin S et al*

- Study objective
 - To determine the efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine neoplasms (NENs)
- Study type / design
 - Multi-institutional, prospective German National Registry of 450 patients with inoperable metastatic NEN from 6 centres
 - Patients were treated with Lu-177-labelled (54%), Y-90-labelled (17%) or dual radionuclide PRRT (29%)
 - Primary NEN were derived from pancreas (38%), small bowel (30%), unknown primary (19%), lung (4%) and colorectum (3.5%)
- Key results
 - Mean (median) follow-up period was 24.8 (17.7) mos

O-0005: Peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: A multi-institutional registry study with prospective follow up on 450 patients – *Ezziddin S et al*

- Key results (continued)
 - Median (range) OS was 59 (49–68) mos and depended on the following factors, but not previous therapies:
 - Radionuclide used (Y-90: 38 mos; Lu-177: not reached; both: 58 mos),
 - Origin of primary tumours (pancreas: 53 mos; small bowel: not reached; unknown primary: 47 mos; lung: 38 mos)
 - Proliferation rate (see figure & table)

Ki-67 Grading		Median OS, mos (95% CI)
≤2%	G1	Not reached
2–20%	G2	58 (37, 78)
>20%	G3	33 (17, 48)
Unknown		55 (48, 61)



O-0005: Peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: A multi-institutional registry study with prospective follow up on 450 patients – *Ezziddin S et al*

- Key results (continued)
 - Overall median PFS was 41 mos (95% CI 35, 46)

Primary tumour	PFS median (95% CI), mos
Pancreas	39 (29, 48)
Small bowel	51 (35, 66)
Unknown primary cancer	38 (27, 48)

- Adverse events included grade 3–4 haematological dysfunction (2%) and grade 3–4 nephrotoxicity (0.2%)
- Conclusion
 - PRRT appears to be an effective therapy for patients with G1-G2 NENs, irrespective of previous therapy

BIOMARKERS

COLORECTAL CANCER

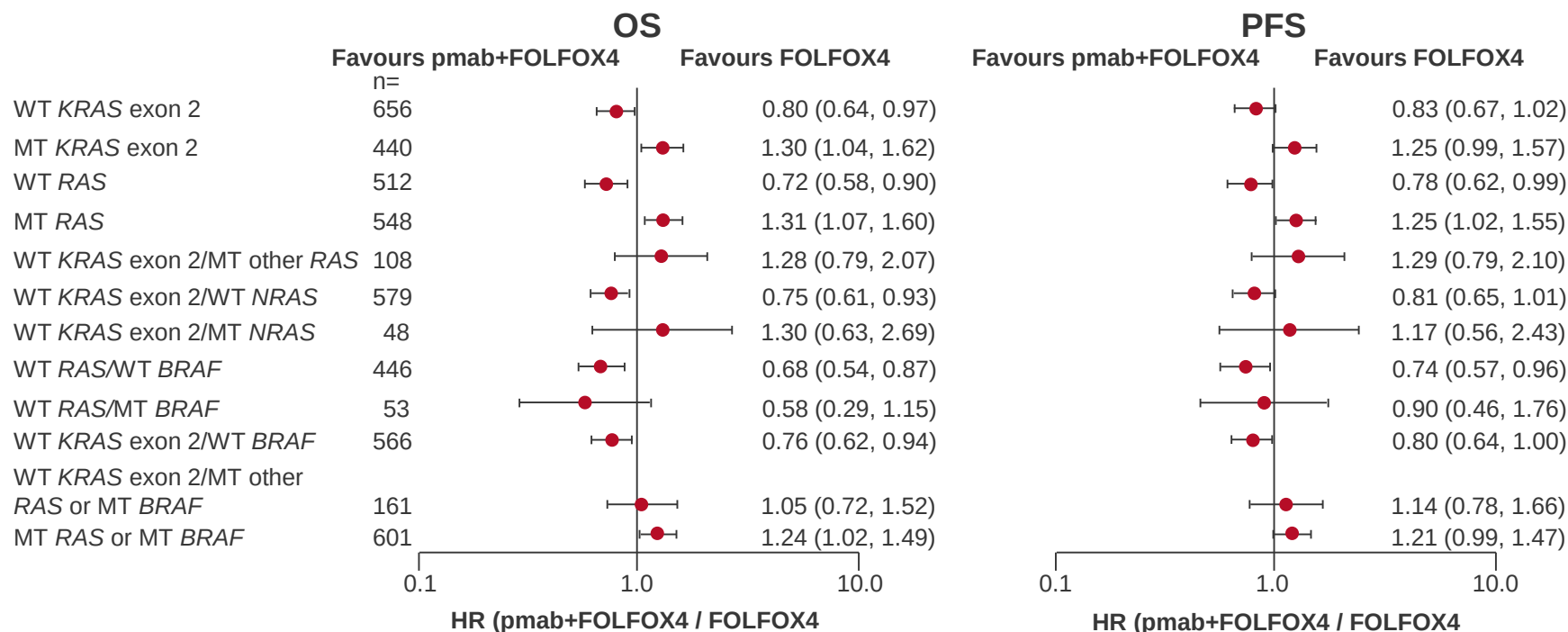
ADJUVANT THERAPY

3511: Analysis of *KRAS*/*NRAS* and *BRAF* mutations in the phase III PRIME study of panitumumab (pmab) plus FOLFOX versus FOLFOX as first-line treatment (tx) for metastatic colorectal cancer (mCRC) – Oliner KS et al

- Study objective
 - To compare the effect of panitumumab+FOLFOX4 with FOLFOX4 alone on PFS and OS in patients with mCRC that are:
 - WT for *RAS* (WT for *KRAS* and *NRAS* exons 2, 3 and 4) or
 - WT for *RAS* and *BRAF* (WT for *KRAS* and *NRAS* exons 2, 3, 4 and *BRAF* exon 15)
- Study type / design
 - Retrospective biomarker analyses were performed on the WT *KRAS* tumour specimens from patients included in the PRIME study
 - Treatment effects were compared using stratified log-rank tests; magnitude was estimated with Cox models
 - The predictive value of *RAS* was determined using interaction tests
 - The prognostic relevance of baseline covariates was examined with multivariate Cox models

3511: Analysis of *KRAS*/*NRAS* and *BRAF* mutations in the phase III PRIME study of panitumumab (pmab) plus FOLFOX versus FOLFOX as first-line treatment (tx) for metastatic colorectal cancer (mCRC) – Oliner KS et al

- Key results
 - Compared with FOLFOX4 alone, panitumumab+FOLFOX4 was associated with a significant improvement in OS for WT *RAS* patients (median gain 5.8 mos, HR 0.78; 95% CI, 0.62, 0.99; p=0.043). The HR for PFS was 0.72 (95% CI: 0.58, 0.90; p≤0.01)
 - Mutant *RAS* tumour status was associated with inferior OS and PFS outcomes in patients who received panitumumab+FOLFOX4 vs. FOLFOX4 alone



Oliner et al. J Clin Oncol 2013; 31 (suppl; abstr 3511)
 Oliner et al. Eur J Cancer 2013; 49 (suppl; abstr 2275)
 Oliner K et al. Ann Oncol 2013; 24 (suppl; abstr O-0031)

3511: Analysis of *KRAS*/*NRAS* and *BRAF* mutations in the phase III PRIME study of panitumumab (pmab) plus FOLFOX versus FOLFOX as first-line treatment (tx) for metastatic colorectal cancer (mCRC) – Oliner KS et al

- **Conclusions**
 - Compared with FOLFOX alone, panitumumab+FOLFOX is associated with significant OS benefit in patients with WT *RAS* mCRC
 - *BRAF* mutation was not associated with any predictive value with regards to treatment outcomes; *BRAF* V600E mutations appear to confer poor prognosis regardless of treatment
 - Panitumumab is unlikely to have benefit in patients with any *RAS* mutations; panitumumab+oxaliplatin-containing regimens should not be used in patients with mCRC tumours with *RAS* mutations
 - When excluding patients with mCRC tumours and *RAS* mutations, the risk profile of panitumumab is improved

3617: Comprehensive analysis of *KRAS* and *NRAS* mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408)

– *Patterson SD et al*

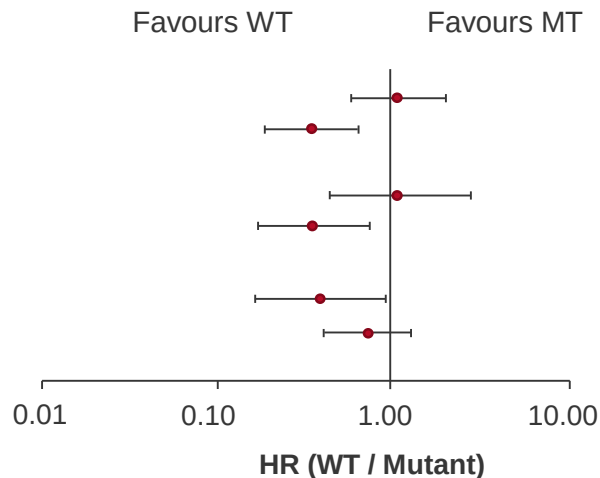
- Study objective
 - To determine whether mutations in exon 4 of the *KRAS* and *NRAS* are predictive for panitumumab treatment and to determine the treatment effect in the overall WT *KRAS* and *NRAS* population
- Study type / design
 - Biomarker analyses were conducted on archived patient tumours from a Phase III panitumumab study
 - Next-generation sequencing was used to detect mutations in *KRAS* and *NRAS* exon 4
- Key results
 - In one mCRC tumour sample, mutations in both *KRAS* and *NRAS* exon 4 were detected
 - Treatment HR for PFS in WT *RAS* group was 0.36 (95% CI: 0.25, 0.52) and in mutant *RAS* subgroup was 0.97 (95% CI: 0.73, 1.29)
 - Analysis of *KRAS* exon 3/4, *NRAS* exons 2/3/4 and *RAS* indicated they were predictive of panitumumab treatment effects but not prognostic

3617: Comprehensive analysis of *KRAS* and *NRAS* mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408)

– *Patterson SD et al*

- Key results (continued)

Prognostic analysis of PFS by genotype subgroup



Genotype	WT	Mutant	Total	HR	95% CI
RAS: BSC	63	14	77	1.05	0.57, 1.92
RAS: pmab+BSC	73	15	88	0.35	0.19, 0.65
KRAS exon 3/4 combined: BSC	72	6	78	1.10	0.44, 2.74
KRAS exon 3/4 combined: pmab+BSC	78	10	88	0.36	0.18, 0.75
NRAS exon 2/3/4 combined: BSC	69	8	77	1.00	0.48, 2.09
NRAS exon 2/3/4 combined: pmab+BSC	83	6	89	0.39	0.17, 0.92

- Patients with WT *RAS* tumour status had an ORR of 16% (12/73) whereas patients with mutant *RAS* tumour status had an ORR of 1% (1/99)
- Adverse events were similar to those previously reported for *KRAS* exon 2 subgroups

- Conclusions

- Mutant *KRAS* and *NRAS* occur in a small, but meaningful, proportion of patients with mCRC
- Patients with any activating mutant *KRAS* and/or mutant *NRAS* may not benefit from treatment with panitumumab

3514: Analysis of plasma protein biomarkers from the CORRECT phase III study of regorafenib for metastatic colorectal cancer – *Lenz H-J et al*

- Study objective
 - To identify plasma protein biomarkers with potential predictive or prognostic value from the CORRECT Phase III study (ClinicalTrials.gov NCT01103323)
- Study type / design
 - CORRECT Phase III study of regorafenib vs. placebo in patients with mCRC
 - Fifteen proteins of interest were quantified by multiplex luminex-based immunoassay or ELISA in baseline plasma samples collected at study entry from 80% (611/760) of patients
- Key results
 - High baseline sTie-1 subgroup showed a significant improvement in OS, but not PFS (best-fit and ROC curve cut-off methods)
 - Low baseline von Willebrand factor subgroup demonstrated a significant improvement in PFS, but not OS (median cut-off method)

3514: Analysis of plasma protein biomarkers from the CORRECT phase III study of regorafenib for metastatic colorectal cancer – *Lenz H-J et al*

- Key results (continued)
 - Following adjustment for multiple testing, neither baseline high sTie-1 nor low von Willebrand factor subgroups retained statistical significance
 - Baseline levels of IL-8 and placental growth factor were found to have prognostic value for OS
 - IL-8 was also prognostic for PFS
- **Conclusions**
 - **None of the baseline plasma proteins examined showed significant predictive value for regorafenib efficacy after multiple testing adjustment**
 - **Only IL-8 was prognostic for OS and PFS in patients with mCRC**

2161: Evaluation of PIK3CA mutation as a predictor of benefit from NSAID therapy in colorectal cancer – Church D et al

- Study objective
 - To assess the value of *PIK3CA* mutation in predicting benefit from COX-2 inhibition and aspirin
- Study design
 - Substudy of the VICTOR study, in which rofecoxib was compared with placebo following primary CRC resection
 - Molecular analysis was carried out on tumours to determine *PIK3CA* mutation status (n=896)
 - Relapse-free survival (RFS) and OS was compared between rofecoxib therapy vs. placebo, and between the use vs. non-use of low-dose aspirin, according to tumour *PIK3CA* status

2161: Evaluation of PIK3CA mutation as a predictor of benefit from NSAID therapy in colorectal cancer – Church D et al

- Key results

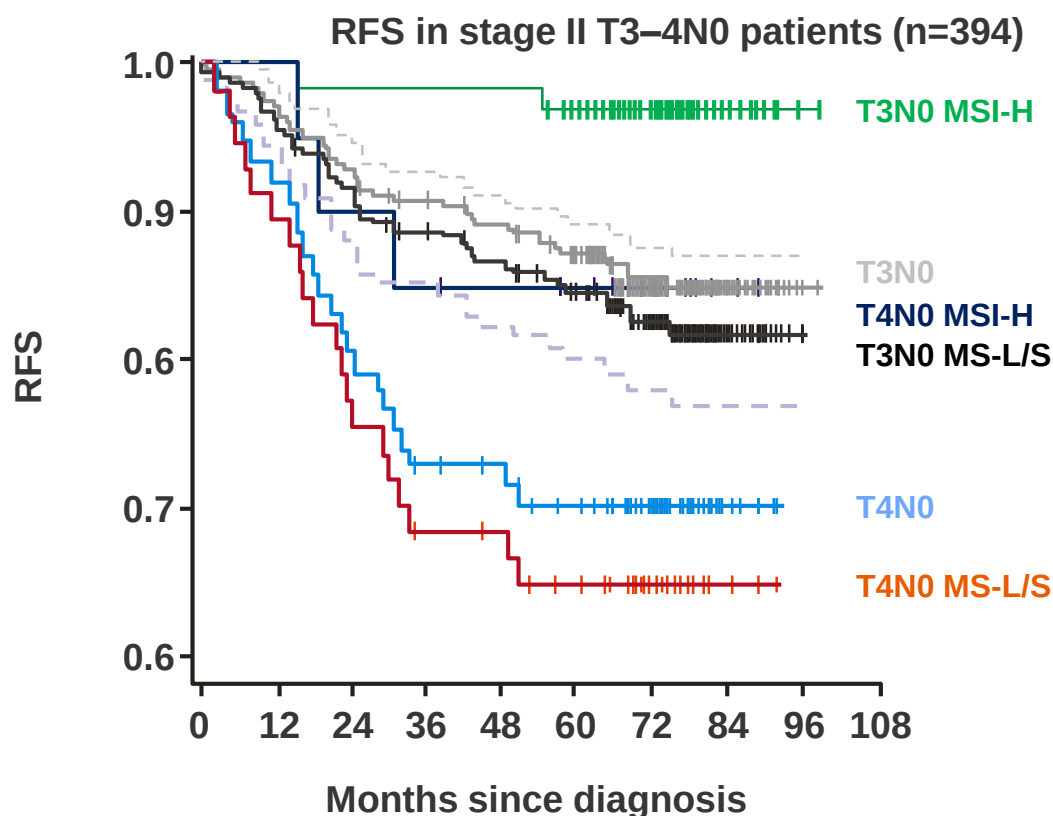
RFS	HR	95% CI	p-value
Rofecoxib vs. placebo			
<i>PIK3CA</i> mutation	1.2	0.53, 2.72	0.66
<i>PIK3CA</i> WT	0.87	0.64, 1.16	0.34
Aspirin vs. no aspirin			
<i>PIK3CA</i> mutation	0.11	0.00, 0.83	0.02
<i>PIK3CA</i> WT	0.92	0.60, 1.42	0.71

- Conclusions

- Tumour *PIK3CA* mutation did not predict benefit from rofecoxib treatment
- Aspirin use was associated with a reduced rate of CRC recurrence

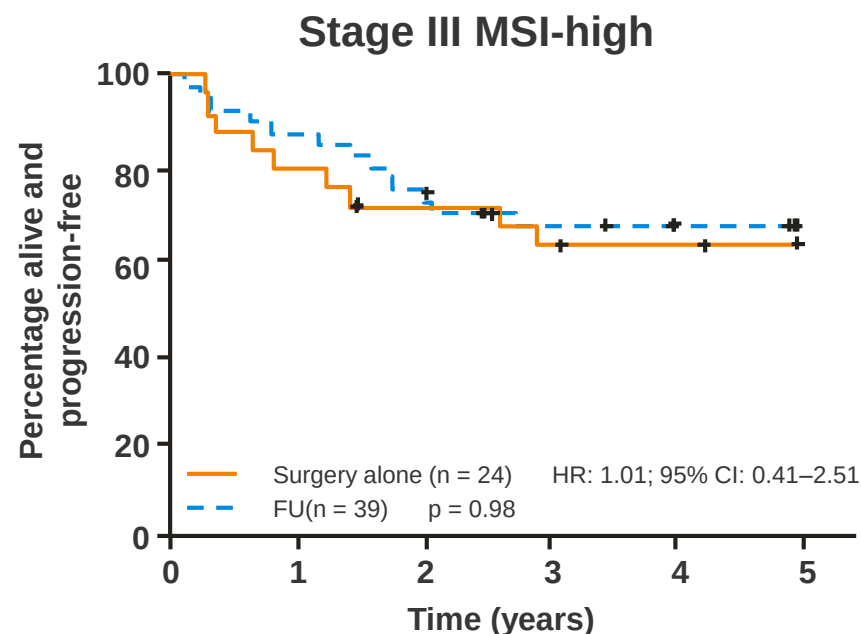
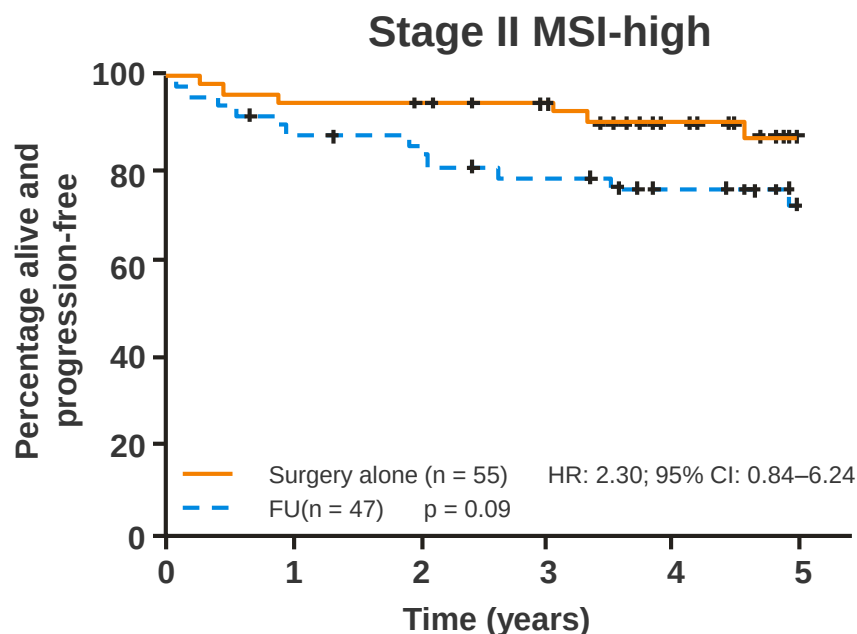
221: Are predictive/prognostic biomarkers/platforms ready to be used in adjuvant treatments? – Roth A

- Study objective
 - To explore the prognostic and predictive value of biomarkers in colon cancer
- Key results
 - Microsatellite instability (MSI) status and loss of SMAD4 expression are prognostic markers in colon cancer
 - Both seem to add value to TNM classification



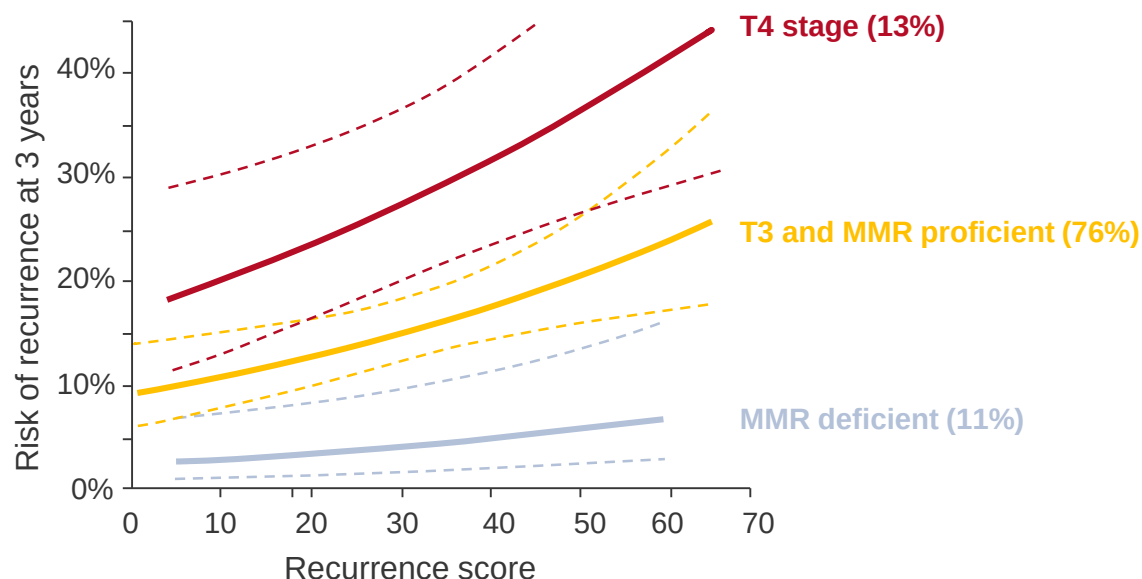
221: Are predictive/prognostic biomarkers/platforms ready to be used in adjuvant treatments? – Roth A

- Key results (continued)
 - MSI is not a negative predictor to 5-FU-based adjuvant CT in stage III colon cancer
 - Effect of MSI in stage II disease currently unclear



221: Are predictive/prognostic biomarkers/platforms ready to be used in adjuvant treatments? – Roth A

- Key results (continued)
 - Recurrence score, T stage and MMR deficiency are key predictors of recurrence in stage II colon cancer

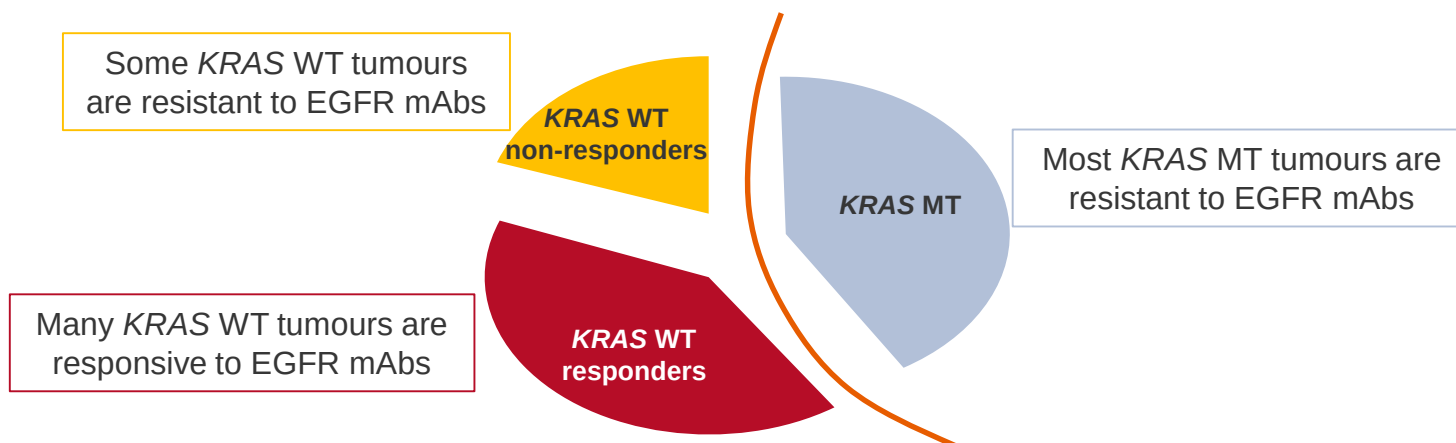


- Conclusions
 - MSI status and SMAD4 loss of expression may be useful add-on to TNM classification
 - Further studies are needed to assess the value of prognostic and predictive markers in colon cancer

223: Selecting for anti-EGFR inhibitors in CRC: KRAS and beyond?

– Van Cutsem E

- Study objective
 - To provide an overview of the prognostic and predictive markers in CRC other than *KRAS*
- Key results
 - *KRAS*
 - Demonstrated to predict treatment resistance in CRC patients, with higher response to treatment observed in *KRAS* WT patients
 - However, within the *KRAS* WT population there are responders and non-responders, suggesting other markers may be important



223: Selecting for anti-EGFR inhibitors in CRC: KRAS and beyond?

– Van Cutsem E

- Key results (continued)
 - *NRAS*, *BRAF*
 - Reduced survival in *BRAF* and *NRAS* MT tumours in *KRAS* WT CRC
 - *NRAS*, but not *BRAF*, was shown to predict treatment resistance
 - *RAS*
 - The PRIME study showed improved survival with panitumumab in *KRAS* WT tumours
 - Survival was further improved with panitumumab in all *RAS* WT tumours (Figure)
 - Furthermore, *RAS* mutant patients had substantially worse survival rates with panitumumab
 - As a result, panitumumab is only recommended in *RAS* WT patients

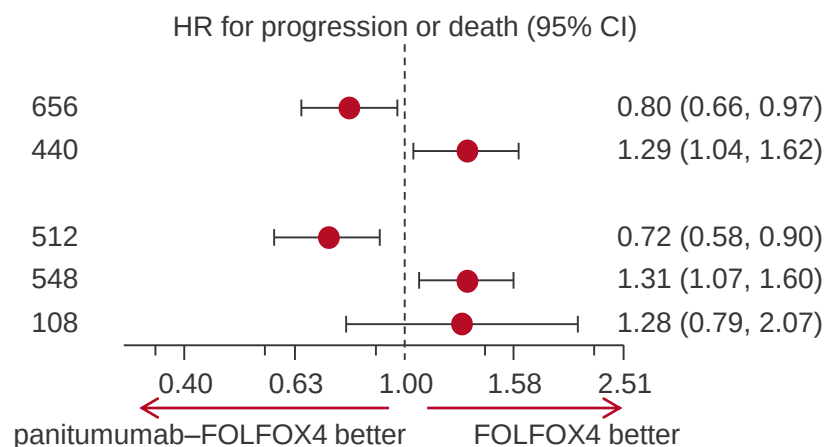
Progression-free survival

Primary analysis

Non-mutated <i>KRAS</i> exon 2	656		0.80 (0.66, 0.97)
Mutated <i>KRAS</i> exon 2	440		1.29 (1.04, 1.62)

Prospective-retrospective analysis

Non-mutated <i>RAS</i>	512		0.72 (0.58, 0.90)
Mutated <i>RAS</i>	548		1.31 (1.07, 1.60)
Non-mutated <i>KRAS</i> exon 2, mutated other <i>RAS</i>	108		1.28 (0.79, 2.07)



223: Selecting for anti-EGFR inhibitors in CRC: KRAS and beyond?

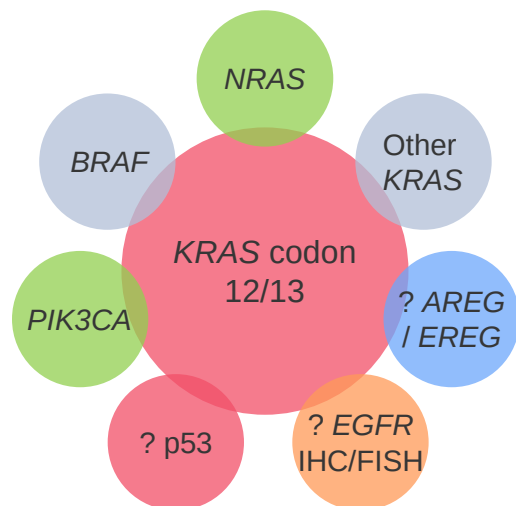
– Van Cutsem E

- Key results (continued)
 - There appear to be several important mutations in addition to *KRAS* exon 2:
 - *KRAS* exon 3 (codon 61), exon 4 (codon 117, 146)
 - *NRAS* exon 2 (codon 12, 13) exon 3 (codon 61), exon 4 (codon 117, 146)
 - *BRAF* exon 15
 - High EGFR expression is also associated with improved survival with cetuximab in *KRAS* WT patients
- **Conclusions**
 - **Several mutations beyond *KRAS* exon 2 appear to affect survival in CRC**
 - **Reduced survival in patients with WT *KRAS* but with other *RAS* mutations**
 - **Several studies suggest that genotyping should be expanded from *KRAS* to all *RAS* mutations**

Concluding remarks: Personalised treatment in colorectal cancer

– *Cunningham D*

- Personalised medicine is important in evaluating the risk–benefit to patients
 - There is currently poor selection of patients for adjuvant therapy, with many patients cured by surgery alone
 - Microsatellite instability testing recommended in Duke B patients, with insufficient evidence to support testing in Duke C patients
 - SMAD4 requires further validation
 - Emerging role for maintenance therapy in mCRC
- Biomarkers for CRC: validating the full RAS status of tumours is key



- Further information required for potential biomarkers such as p53 and *PIK3CA*

Concluding remarks: Personalised treatment in colorectal cancer

– *Cunningham D*

- Predictive biomarkers with angiogenesis
 - A validated biomarker for anti-angiogenic therapy is still needed
 - Reported biomarkers include:
 - Tissue markers, serum markers, genetic polymorphisms, dynamic imaging, hypertension
 - However, validation between studies is currently missing

284: Pitfalls of and opportunities for molecular characterisation in CRC

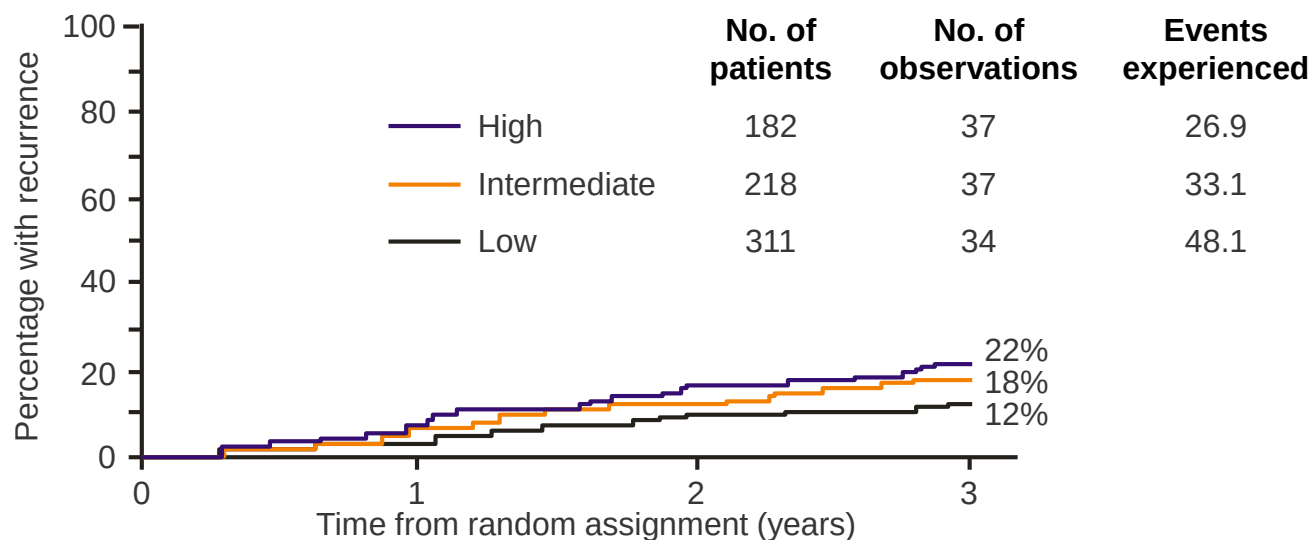
– Quirke P

- Study objective
 - To review our current understanding of molecular markers in CRC
- Key results
 - CRC can be classified by:
 - Pathology (staging, type, grading, loss of MMR expression, *BRAF* mutation)
 - Molecular – prognostic (mutations, gene expression)
 - Molecular – biology (genetic, immunological)
 - Molecular – treatment (mutations, amplifications, translocations, pathways)
 - Currently, most biomarkers are validated retrospectively
 - In contrast, the FOCUS 4 study has predefined selection criteria:
 - *BRAF* mutant; *PIK3CA* mutant and/or PTEN loss; *KRAS* or *NRAS* mutant; all WT; non-stratified

284: Pitfalls of and opportunities for molecular characterisation in CRC

– Quirke P

- Key results (continued)
 - The QUASAR study also had a pre-specified selection criteria
 - A recurrence score was calculated from tumour gene expression for stromal genes (FAP, INHBA, BGN), cell cycle genes (Ki-67, C-MYC, MYBL2) and GADD45B
 - Comparison of high and low recurrence risk was significant, but differences were small
 - There was no significant difference in benefit of CT at low vs. high recurrence risk



- Conclusion
 - Molecular characterisation is beneficial and can improve outcomes in CRC

2277: Survival after resection of colorectal liver metastases: Is the primary nodal status still a prognostic factor? – *Reitsma M et al*

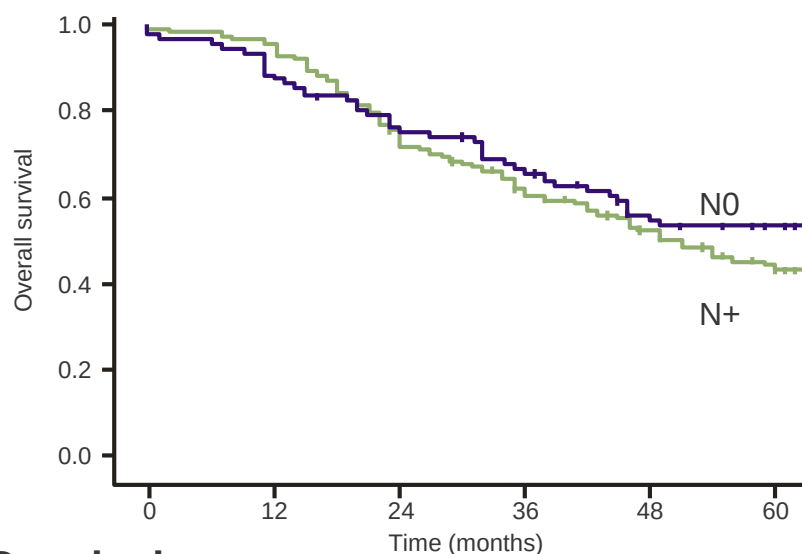
- Study objective
 - To evaluate the impact of nodal positivity of the primary tumour following liver resection for colorectal liver metastases
- Study design
 - Prospective study of 446 patients who had undergone curative liver resection for colorectal liver metastases (minimal follow-up 2 years)
 - Patients were excluded from the study if they had not received resection of the primary tumour, if therapy was without curative intent or if the nodal status of the primary tumour was unknown
 - 429 patients met the inclusion criteria

2277: Survival after resection of colorectal liver metastases: Is the primary nodal status still a prognostic factor? – *Reitsma M et al*

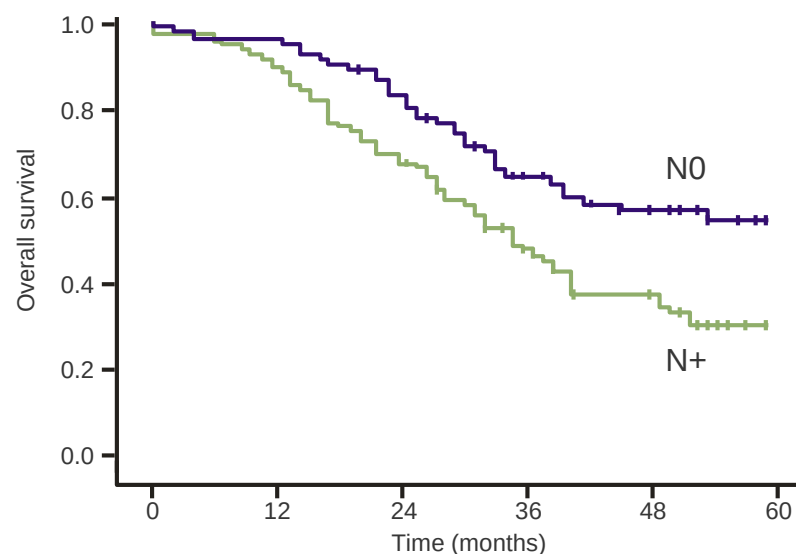
- Key results

Estimated 5-year survival	Node-positive	Node-negative	p-value
Primary colon cancer	50%	57%	0.33
Primary rectal cancer	37%	59%	0.003

OS: primary colon cancer



OS: primary rectal cancer



- Conclusion

- Nodal positivity has prognostic value in primary rectal cancer, but not in primary colon cancer, which may be related to the higher use of adjuvant CTx in colon cancer