GI SLIDE DECK 2015

Selected abstracts on **Colorectal Cancer** from:

EUROPEAN CANCER CONGRESS (ECC)

25–29 September 2015

Vienna, Austria

esdo european society of digestive oncology

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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 2015. This slide set specifically focuses on the European Cancer Congress 2015 Meeting and is available in English 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 that 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.

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
Wolff Schmiegel
Phillippe Rougier
Thomas Seufferlein

(ESDO Governing Board)

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european society of digestive oncology

ESDO Medical Oncology Slide Deck
Editors 2015

COLORECTAL CANCERS



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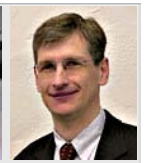
PANCREATIC CANCER AND HEPATOBILIARY TUMOURS

Prof Jean-Luc Van Laethem	Digestive Oncology, Erasme University Hospital, Brussels, Belgium
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GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS


Emeritus Prof Philippe Rougier	University Hospital of Nantes, Nantes, France
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BIOMARKERS


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esdo

Glossary

2L	second line
3L	third line
^{90}Y	Yttrium-90
5-FU	5-fluorouracil
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
BSC	best supportive care
CI	confidence interval
CEA	carcinoembryonic antigen
CR	complete response
CRC	colorectal cancer
CRT	chemoradiotherapy
CT	chemotherapy
CV	cardiovascular
DFS	disease-free survival
DNA	deoxyribonucleic acid
DOR	duration of response
DPR	depth of response
DSS	disease-specific survival
ECOG	Eastern Cooperative Oncology Group
EGFR	endothelial growth factor receptor
ELISA	enzyme-linked immunosorbent assay
ELSIPOT	enzyme-linked immunospot
FFPE	formalin-fixed paraffin embedded
FISH	fluorescence in situ hybridisation
FOLFIRI	leucovorin, 5-fluorouracil, irinotecan
FOLFOX	leucovorin, 5-fluorouracil, oxaliplatin
Gy	Gray
HR	hazard ratio
IHC	immunohistochemistry
ITT	intent-to-treat
IV	intravenous
LVI	lymphovascular invasion
mCRC	metastatic colorectal cancer
MHC	major histocompatibility complex
mFOLFOX6	modified FOLFOX6
MRI	magnetic resonance imaging
MSI-H	microsatellite instability high
MSS	microsatellite stable
NSCLC	non-small cell lung cancer
ORR	overall/objective response rate
(m)OS	(median) overall survival
pCR	pathological complete response
PCR	polymerase chain reaction
PD	progressive disease
PD-L1	programmed death-ligand 1
(m)PFS	(median) progression-free survival
PR	partial response
PS	performance status
q2w	every 2 weeks
QoL	quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	relapse-free survival
RNA	ribonucleic acid
RR	response rate
RT	radiotherapy
SD	stable disease
SNP	single nucleotide polymorphism
SoC	standard of care
Th1	T helper cell 1
TME	total mesorectal excision
Treg	regulatory T cell
TTR	time to response
VEGF	vascular endothelial growth factor
XELOX	oxaliplatin + capecitabine
WT	wild type

Contents

COLON CANCER

2005: EURECCA international comparison of treatment and survival in patients over the age of 80 years with stage III colon cancer – Bastiaannet E et al

Study objective

- To investigate survival outcomes according to treatment strategy in patients aged >80 years with stage III colon cancer receiving adjuvant CT

Study design

- Observational study: patients aged >80 years with stage III colon cancer were included in this analysis
- Data were from a five population cohort:

Country	Patients, n
Denmark	1,321
Sweden	1,075
Belgium	2,313
The Netherlands	3,071
Germany	1,674
Total	**9,454**

- Treatment (adjuvant CT) strategies were compared
- Survival status was determined using patient medical records
  - Expected survival was calculated as the ratio of observed survival in the study cohort to expected survival in the general population

Bastiaannet et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2005

2005: EURECCA international comparison of treatment and survival in patients over the age of 80 years with stage III colon cancer – Bastiaannet E et al

Key results

Neighbouring countries	Adjuvant CT usage, %	Differences in survival, RER* HR (95%CI); p-value
		Relative survival†
Denmark Sweden	10.7 0.9	0.8 (0.7, 1.0); p=0.1
The Netherlands Germany	5.4 6.0	1.1 (0.7, 2.3); p=0.4
The Netherlands Belgium	5.4 23.4	0.7 (0.4, 1.2); p=0.2
		Cancer specific survival
The Netherlands Belgium	1.2 23.4	1.1 (0.8, 1.6); p=0.6

*Relative excess risk (RER) of death due to colon cancer;
†Ratio of observed survival (study cohort) to expected survival (general population)

Bastiaannet et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2005

2005: EURECCA international comparison of treatment and survival in patients over the age of 80 years with stage III colon cancer – Bastiaannet E et al

Conclusions

- Greater use of CT was not associated with improvements in relative survival or cancer-specific survival in older patients with stage III colon cancer
- Cause of death is less reliable in older patients and may be underestimated
  - Relative survival* may provide a better estimate in older patients

*Ratio of observed survival (study cohort) to expected survival (general population)

Bastiaannet et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2005

2011: Multi-antigen vaccination for colon cancer treatment and prevention – Marquez-Manriquez JP et al

Study objective

- To investigate whether overexpressed proteins associated with poor prognosis in colon cancer were immunogenic, and whether vaccines targeting these antigens could prevent the development of colon cancer in murine models

Study design

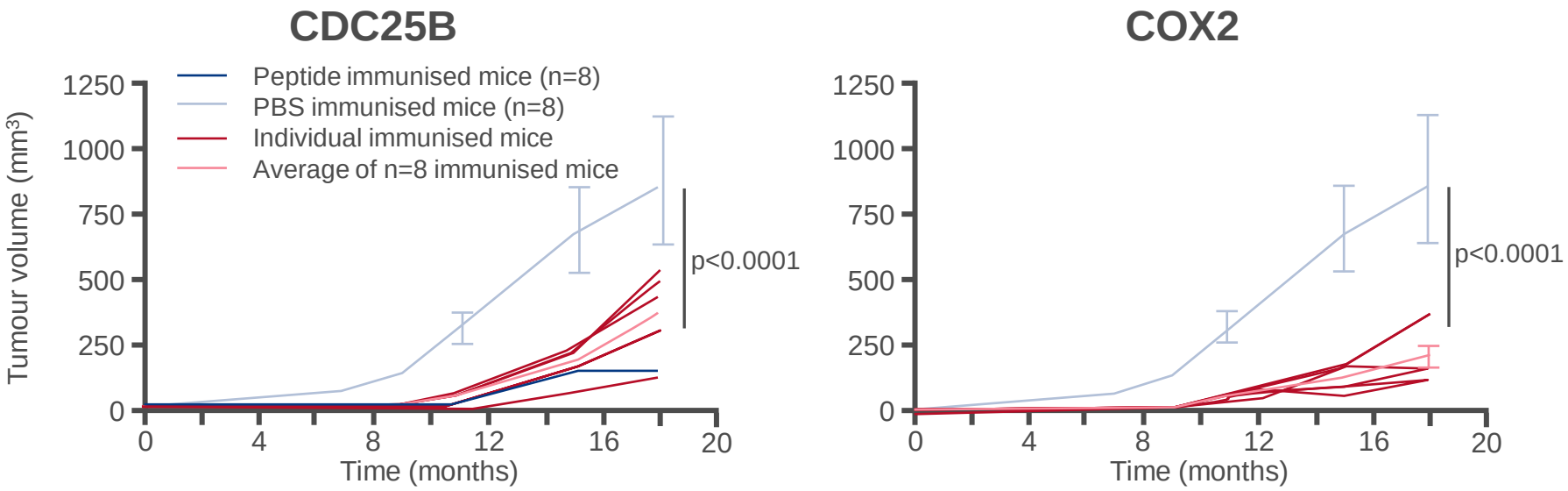
- A PubMed literature search identified four proteins associated with poor prognosis in colon cancer: CDC25B, COX2, Fascin1 and RCAS1
- Human subjects
  - Sera from patients with CRC (n=50) and healthy volunteers (n=50) were analysed
- Animals
  - Male and female mice testing positive for the Min mutation were included
- ELISA and ELISPOT assays were performed in human and murine samples
- Vaccination experiments
  - All mice were immunised three times subcutaneously, starting at 6 (±2) weeks
  - Tumour growth was monitored every 2–3 days and tumour volumes were calculated

Marquez-Manriquez et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2011

2011: Multi-antigen vaccination for colon cancer treatment and prevention – Marquez-Manriquez JP et al

Key results

- CDC25B, COX2, FASCIN1 and RCAS1 antibodies were significantly elevated in CRC patients vs. healthy volunteers
- MHC class II associated peptides derived from these antigens induced Th1 immunity in patients with CRC
- Immunisation against CDC25B and COX2 induced type I T-cells and significantly inhibited tumour growth (figures)
  - Inhibition of tumour growth by CDC25B and COX2 was mediated by CD8 T-cells



Marquez-Manriquez et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2011

2011: Multi-antigen vaccination for colon cancer treatment and prevention – Marquez-Manriquez JP et al

Key results (cont.)

- CDC25B- and COX2-specific vaccines inhibited the development of polyps and CRC in spontaneous tumour models

Conclusions

- **Vaccines targeting biologically relevant antigens in CRC can prevent the development of invasive cancer as well as polyp formation in mice**
- **Vaccination to induce type I immunity against 'biological drivers' associated with progression, recurrence and decreased survival may be a useful adjunct to adjuvant therapy in CRC**
- **Vaccination against multiple CRC antigens may be helpful in patients at high risk of CRC**

Marquez-Manriquez et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2011

RECTAL CANCER

2000: MRI including diffusion-weighted imaging to diagnose a local tumour re-growth after organ preserving treatment for rectal cancer – Lahaye M et al

Study objective

- To assess the value of MRI including diffusion-weighted imaging (DWI) for diagnosing local tumour re-growth during follow-up after organ-preserving treatment

Study design

- The study included 72 patients who underwent organ-preservation CRT + transanal endoscopic microsurgery (TEM) or watchful waiting
- Patients were followed with MRI including DWI every 3 months during the first year and every 6 months during the following years
- Local re-growth on each MRI was scored by two readers (R1 and R2) based on standard MRI followed by MRI + DWI
- Standard reference was histology and/or long-term clinical follow-up

Note: Based on data from abstract only.

Lahaye et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2000

2000: MRI including diffusion-weighted imaging to diagnose a local tumour re-growth after organ preserving treatment for rectal cancer – Lahaye M et al

Key results

- Of 72 patients, 17 underwent CRT + TEM and 55 underwent CRT + watchful waiting
  - 12 patients developed a local re-growth (5 from the TEM and 7 from the watchful waiting group)
- 440 MRI scans were assessed

	Standard MRI		MRI + DWI	
	R1	**R2**	**R1**	**R2**
No. equivocal scores	22	40	7	20
Sensitivity, %	58	58	75	75
Specificity, %	98	100	97	100
PPV, %	41	100	39	82
NPV, %	97	99	96	99

Conclusions

- **The addition of DWI to standard MRI decreased the number of equivocal scores**
- **Combined use of MRI + DWI improves sensitivity for diagnosing a local tumour re-growth and increases the chance of a conclusive imaging outcome**

Note: Based on data from abstract only.

Lahaye et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2000

2001: Anorectal function after watch and wait-policy in rectal cancer patients – Lambregts D et al

Study objective

- To evaluate the long-term dosimetric impact of chemoradiation on anorectal function in watch-and-wait policy (W&W) patients
- To evaluate the long-term anorectal function and its relation to radiation dosimetric data and symptom scores or QoL in W&W patients

Study design

- 21 patients with primary rectal cancer without distant metastases treated according to the W&W policy were included
- Patients were treated with 28x1.8 Gy combined with capecitabine 825 mg/m^2 x2
- Patients had a complete clinical response and a follow-up of at least 2 years
- Anorectal manometry was used to assess anorectal function and symptoms and quality-of-life were assessed using the Vaizey score and LARS score

Note: Based on data from abstract only.

Lambregts et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2001

2001: Anorectal function after watch and wait-policy in rectal cancer patients – Lambregts D et al

Key results

- Lower mean anal resting pressure was associated with higher LARS scores and higher Vaizey scores
- Most patients received full-dose radiotherapy to the anal sphincter complex
  - These patients had poor outcomes regarding symptom scores and manometry compared with patients irradiated with lower doses

Conclusions

- **Low mean anal resting pressure was associated with worse quality-of-life in W&W rectal cancer patients**
- **Higher doses of radiation were associated with poor sphincter function**
- **Options to reduce anal sphincter radiation dose should be explored**

Note: Based on data from abstract only.

Lambregts et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2001

2002: Impact of adjuvant chemotherapy following pre-operative short course radiotherapy in stage II rectal cancer – Loree J et al

Study objective

- To examine outcomes of patients with pathologic (p) stage II rectal cancer (RCa) treated with adjuvant chemotherapy (AC) following preoperative short-course radiotherapy (SCRT) and characterise patients in whom AC provides benefit

Study design

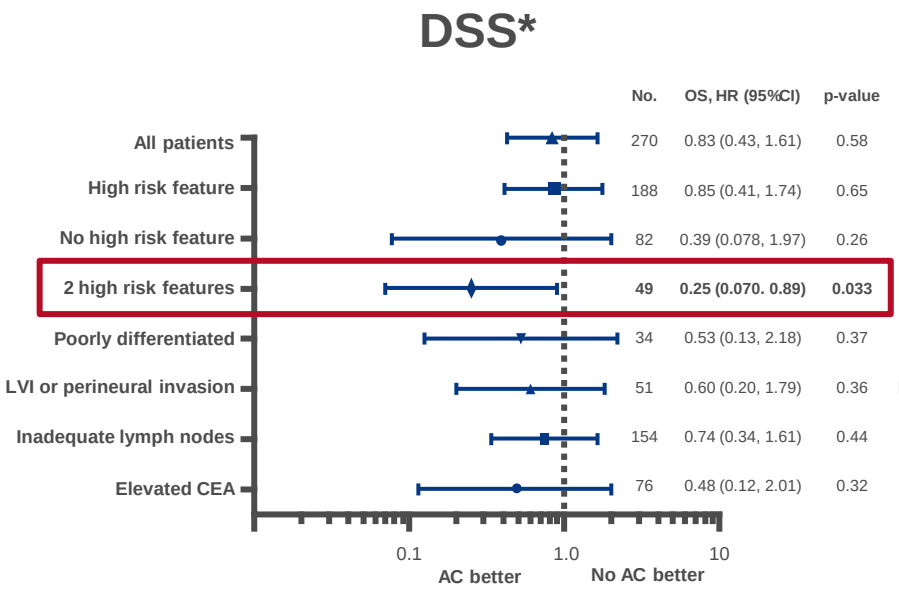
- Retrospective cohort study
- Outcomes Unit Database of the British Columbia Cancer Agency was searched between 1999−2009
- Patients with yp stage II rectal cancer and preoperative SCRT were included
  - Patients with a concurrent malignancy within 5 years were excluded
- 331 patients were identified of which 123 received AC
- Primary outcomes: DSS and RFS; secondary outcome: OS
- Subgroup analysis was performed for high risk features

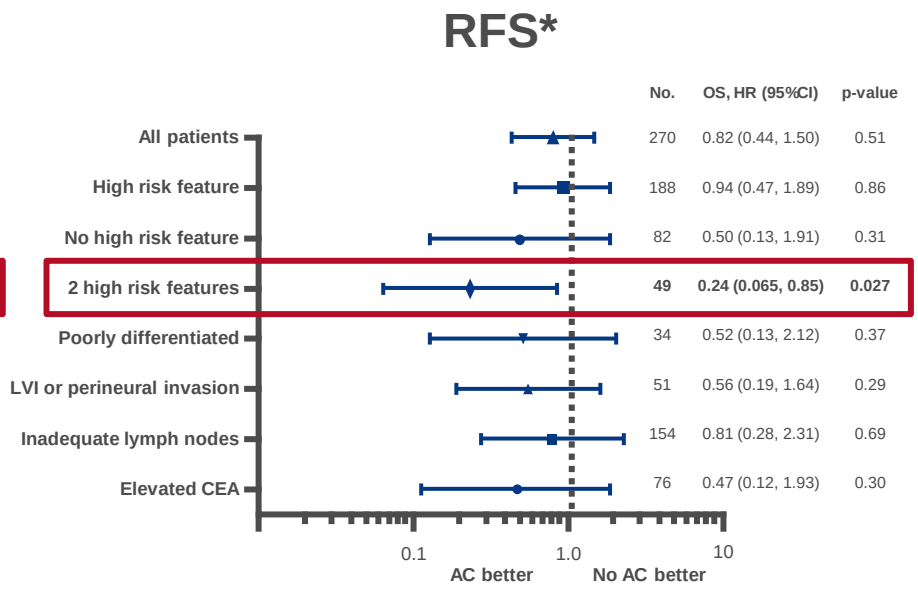
Loree et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2002

2002: Impact of adjuvant chemotherapy following pre-operative short course radiotherapy in stage II rectal cancer – Loree J et al

Key results

- Patients receiving AC were younger (median age 61 vs. 73 years [p<0.0001])
- Patients receiving AC had better ECOG PS (p<0.0001), but more high risk features (p<0.0001) than those not receiving AC
- Median follow up was 8.6 years in the AC arm and 7.9 years in the non-AC arm



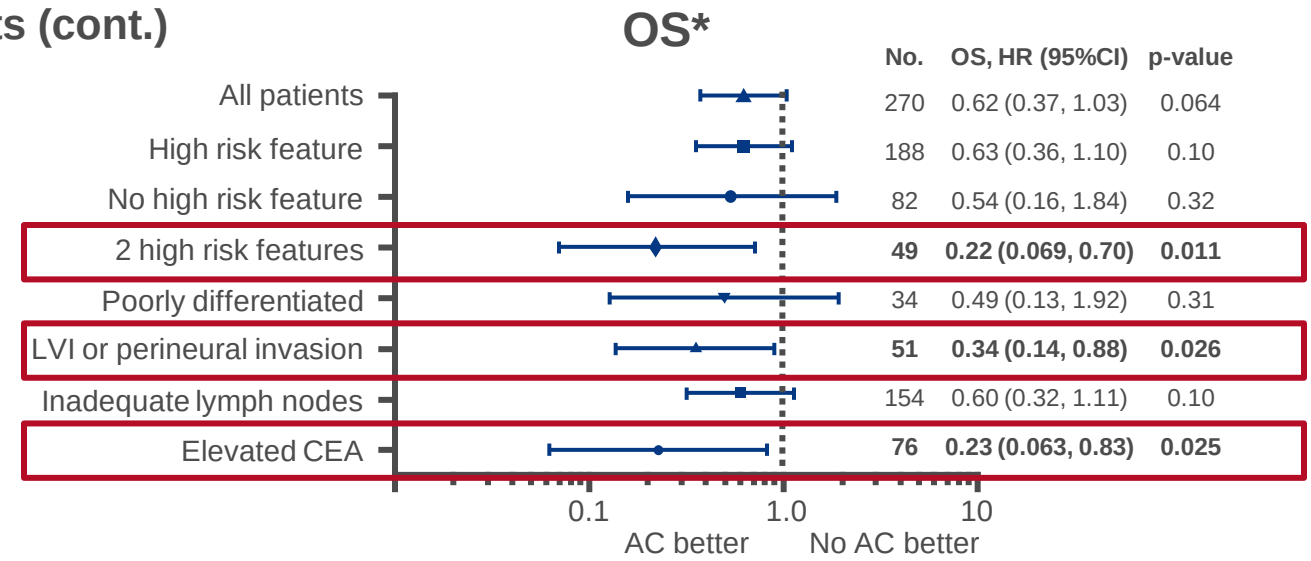


*All models controlled for age, gender, ECOG

Loree et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2002

2002: Impact of adjuvant chemotherapy following pre-operative short course radiotherapy in stage II rectal cancer – Loree J et al

Key results (cont.)



- There was a trend towards improved OS in all patients after AC, which was significant in three of the subgroups (shown above)

Conclusions

- **In this population-based cohort of patients with stage II RCa who received preoperative SCRT, AC did not improve outcomes after correcting for confounding factors**
- **The subgroup of patients with ≥2 risk factors may benefit from AC**
- **Biomarkers are needed to define risk stratification**

*All models controlled for age, gender, ECOG

Loree et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2002

2004: Factors, that may influence outcomes for stage II–III resectable rectal cancer patients treated with preoperative conventional chemoradiotherapy or short-term radiotherapy followed by delayed surgery. Data from the randomized single institution trial – Kairevice E et al

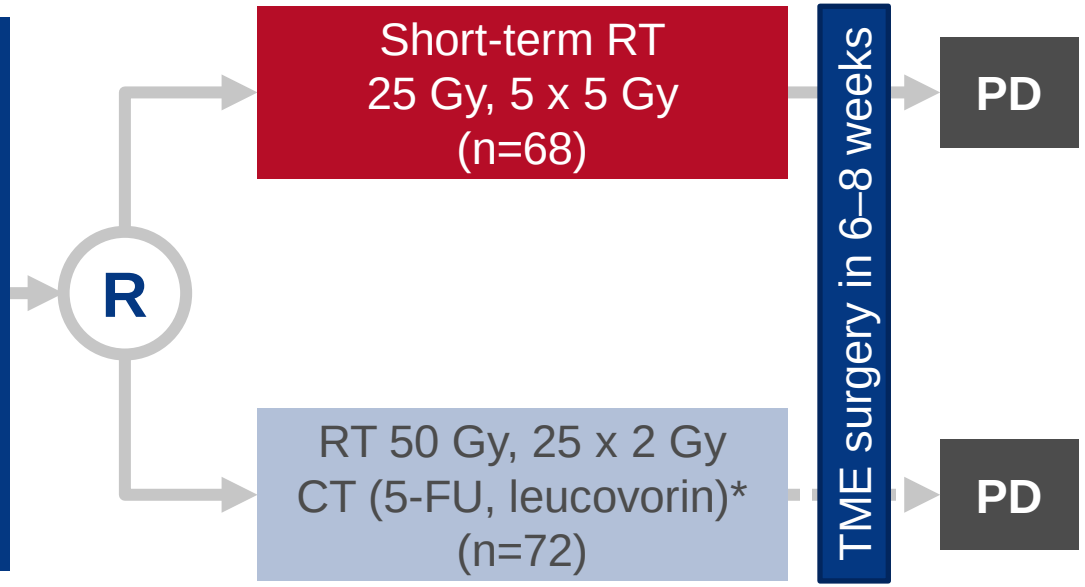
Study objective

- To investigate the efficacy of preoperative conventional CRT vs. short-term RT with delayed surgery in both arms, in patients with stage II–III resectable rectal cancer

Key patient inclusion criteria

- Stage II–III resectable rectal cancer <15 cm from anal verge
- No other cancer in 5 years
- Normal CV, pulmonary, hepatic and renal function

(n=140)



PRIMARY ENDPOINT(S)

- DFS

SECONDARY ENDPOINTS

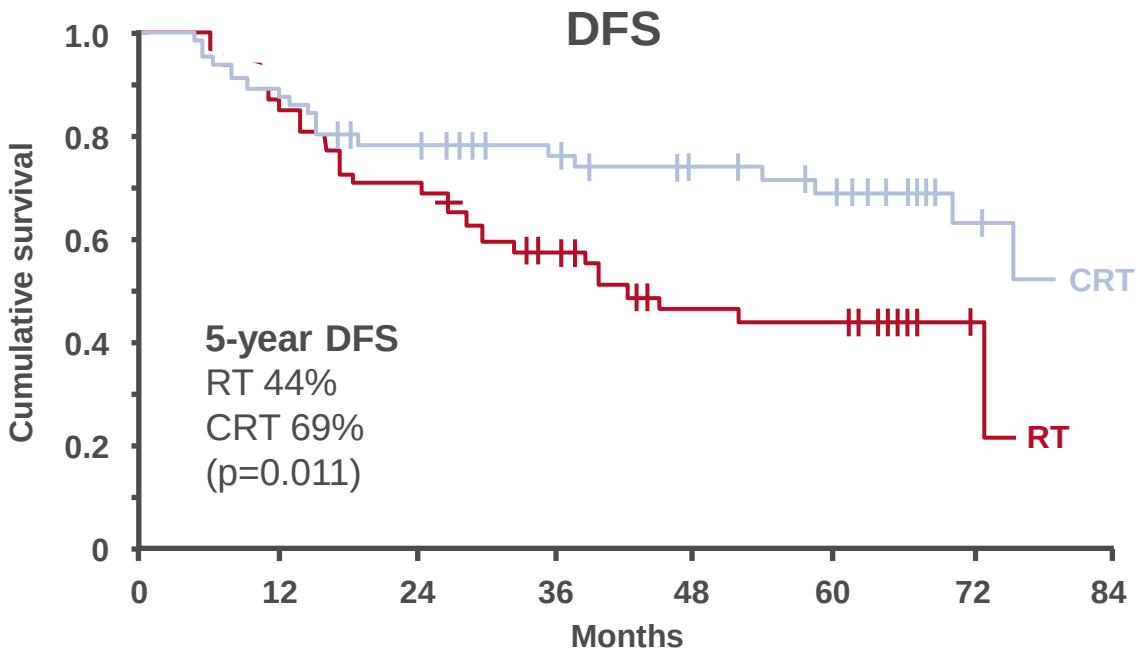
- OS
- Factors that may influence DFS/OS

*5-FU 400 mg/m^2/day d1–4, week 1, 5, leucovorin 20 mg/m^2/day d1–4, week 1, 5 (IV infusion), then 5-FU 425 mg/m^2/day d1–5, leucovorin 20 mg/m^2/day d1–5, 4 IV cycles

Kairevice et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2004

2004: Factors, that may influence outcomes for stage II–III resectable rectal cancer patients treated with preoperative conventional chemoradiotherapy or short-term radiotherapy followed by delayed surgery. Data from the randomized single institution trial – Kairevice E et al

Key results



	RT (n=69)	CRT (n=72)	p-value
Complete response, %	4.4	11.1	>0.05
Local recurrence rate, %	6	7	>0.05
Distant metastases rate, %	25	19	>0.05
5-year OS, %	64	76	0.055
5-year OS (ITT population), %	60	75	0.020

Kairevice et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2004

2004: Factors, that may influence outcomes for stage II–III resectable rectal cancer patients treated with preoperative conventional chemoradiotherapy or short-term radiotherapy followed by delayed surgery. Data from the randomized single institution trial – Kairevice L et al

Key results (cont.)

Factor affecting DFS	HR	95%CI	p-value
Age <65 years	1.000	-	-
Age ≥65 years	**2.079**	**1.185, 3.646**	**0.011**
Clinical N category cN0	1.000	-	-
Clinical N category cN1	1.361	0.622, 2.980	0.115
Clinical N category cN2	**2.538**	**1.039, 4.679**	**0.040**
Pathological N category ypN0	1.000	-	-
Pathological N category ypN1	1.227	0.647, 2.327	0.531
Pathological N category ypN2	**2.987**	**1.378, 6.477**	**0.006**
Neoadjuvant CRT	1.000	-	-
Neoadjuvant RT	**1.910**	**1.114, 3.276**	**0.019**

Conclusions

- **Conventional CRT was associated with significantly improved DFS vs. RT in patients with stage II–III resectable rectal cancer**
- **There was a trend towards improved OS with CRT vs. RT**
  - **OS was significantly better with CRT in the ITT population**
- **Age (≥65 years), cN2, ypN2 + use of RT regimen were associated with significantly worse DFS**

Kairevice et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2004

2009: Tumoral lymphocyte immune response to preoperative radiotherapy in locally advanced rectal cancer as a prognostic factor for survival: The LYMPHOREC study – Mirjolet C* et al

Study objective

- To assess the impact of CD8+ FoxP3+ tumour infiltrating lymphocytes (TILs) on PFS and OS after preoperative RT in patients with locally advanced rectal cancer undergoing total mesorectal excision (TME)

Study design

- Data were analysed from 237 patients with rectal cancer undergoing TME after neo-adjuvant treatment with preoperative RT ± CT
- Biopsy samples were collected in 133 patients to evaluate lymphocyte infiltration

*Presented by Crehange G.

Mirjolet et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2009

2009: Tumoral lymphocyte immune response to preoperative radiotherapy in locally advanced rectal cancer as a prognostic factor for survival: The LYMPHOREC study – Mirjolet C* et al

Key results

- There was no impact of baseline CD8+ TILs on PFS or OS
- High baseline FoxP3 was associated with significantly better PFS

FoxP3+ TILs after preoperative RT (n=232)	5-year PFS, %	HR (95%CI)	p-value
<6.5	36.7	1	0.059
6.5 to <15.5	53.5	0.884 (0.521, 1.502)	
15.5 to 36.5	56.0	0.671 (0.395, 1.140)	
≥36.5	73.2	0.481 (0.273, 0.849)	
Quantitative analysis	-	0.987 (0.978, 0.996)	0.007

- Low CD8+/FoxP3+ ratio (<−3.8) was associated with improved PFS (p=0.049)
- Low CD8+/FoxP3+ ratio (<−3.8) was associated with improved OS (p=0.024)

*Presented by Crehange G.

Mirjolet et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2009

2009: Tumoral lymphocyte immune response to preoperative radiotherapy in locally advanced rectal cancer as a prognostic factor for survival: The LYMPHOREC study – Mirjolet C* et al

Conclusions

- **FoxP3+ Treg density had a greater prognostic value than CD8+ lymphocytes in patients with locally advanced rectal cancer**
  - **High FoxP3+ Treg levels after RT positively correlated with survival**
- **A decreased CD8+/FoxP3+ ratio was associated with improved survival**

*Presented by Crehange G.

Mirjolet et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2009

2016: Early results of phase II trial of perioperative oxaliplatin and capecitabine (XELOX) without radiotherapy for high-risk rectal cancer (CORONA I) – Uehara K et al

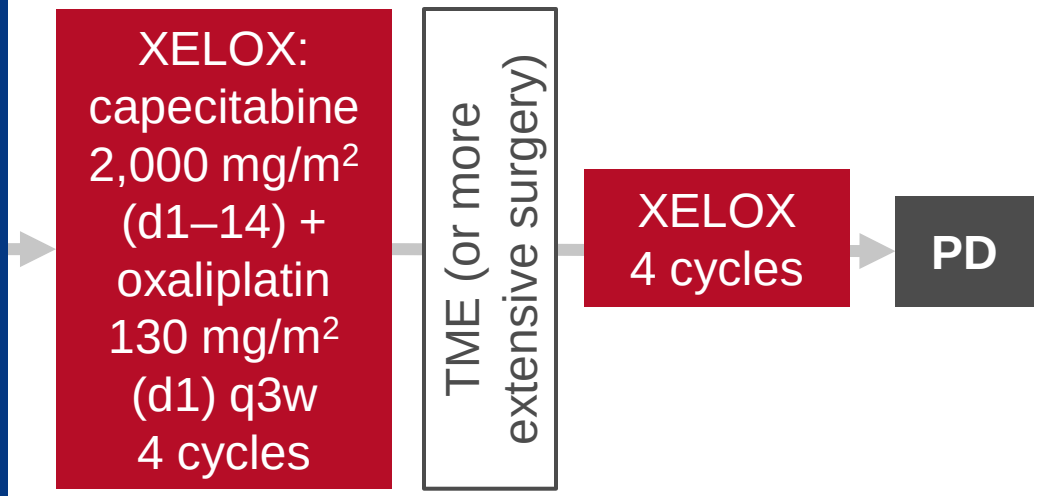
Study objective

- To investigate the efficacy and safety of perioperative capecitabine + oxaliplatin (XELOX) in patients with locally advanced rectal cancer (LARC). Early results are presented

Key patient inclusion criteria

- MRI-defined high-risk rectal cancer
- Tumour extending to within 1 mm of or beyond mesorectal fascia; tumour extending ≥5 mm into peripheral fat
- Tumour invading surrounding structures or peritoneum
- TN2 (stage IIIC)

(n=41)



PRIMARY ENDPOINT(S)

- 3-year DFS

SECONDARY ENDPOINTS

- OS, DFS, RFS, RR, R0 resection rate
- Pathological response, safety

Uehara et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2016

2016: Early results of phase II trial of perioperative oxaliplatin and capecitabine (XELOX) without radiotherapy for high-risk rectal cancer (CORONA I) – Uehara K et al

Key results

	XELOX (n=41)
Response by RECIST	
CR/PR/SD/PD, n	1/23/14/3
ORR, %	59
Post-operative complications, %	45.0
Residual tumour classification	
R0/R1/R2/Unavailable, n	37/2/1/1
R0 resection rate, %	90.2
pCR rate, %	12.2
Good responder, %	31.7
N down-staging rate, %	56.7
T down-staging rate, %	52.5

Uehara et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2016

2016: Early results of phase II trial of perioperative oxaliplatin and capecitabine (XELOX) without radiotherapy for high-risk rectal cancer (CORONA I) – Uehara K et al

Key results (cont.)

Grade 3+ AEs occurring in ≥3% of patients, %	Pre-XELOX (n=41)	Post-XELOX (n=29)
Leukopenia	0	3.4
Neutropenia	2.4	10.3
Thrombocytopenia	14.6	0
Febrile neutropenia	0	3.4
Increased AST	0	3.4
Increased ALT	2.4	3.4
Fatigue	2.4	3.4
Diarrhoea	2.4	3.4
Appetite loss	4.9	0
Peripheral neuropathy	3.1	3.4

Conclusions

- **Perioperative XELOX was feasible and safe in patients with LARC**
- **Postoperative treatment exposure was unsatisfactory and potency of preoperative XELOX alone may be underpowered for T4 tumours**
- **More aggressive CT and/or additional RT should be investigated**

Uehara et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2016

COLORECTAL CANCER

32LBA: The AGITG ICECREAM Study: The Irinotecan Cetuximab Evaluation and Cetuximab Response Evaluation Amongst Patients with a G13D Mutation - analysis of outcomes in patients with refractory metastatic colorectal cancer harbouring the KRAS G13D mutation – Segelov E et al

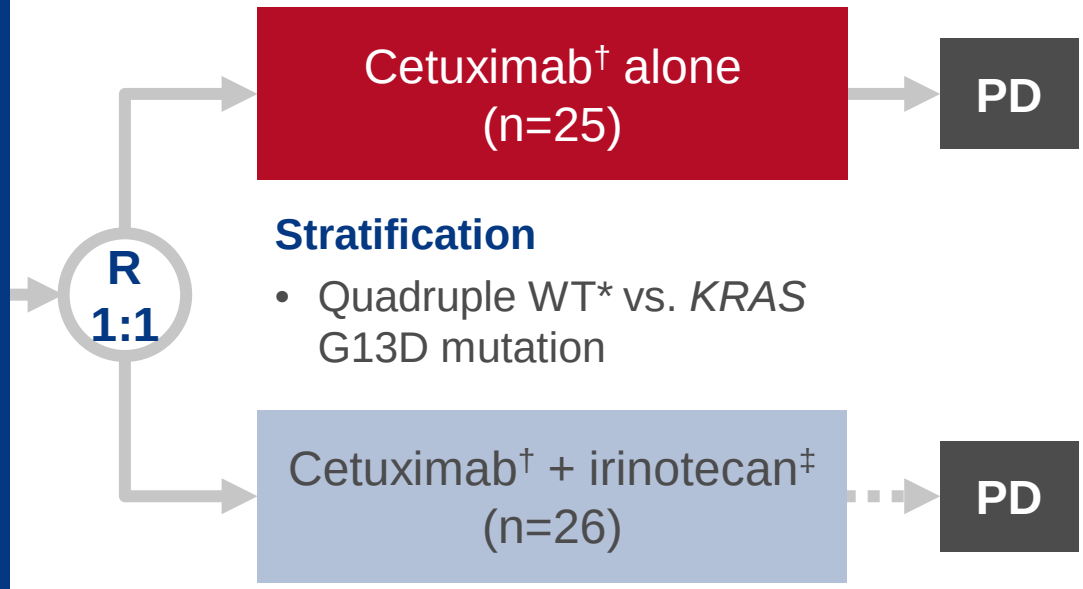
Study objective

- To evaluate the efficacy of cetuximab + irinotecan vs. cetuximab alone in patients with refractory mCRC harbouring a *KRAS* G13D mutation

Key patient inclusion criteria

- Refractory, unresectable mCRC
- Quadruple WT* or *KRAS* G13D mutation
- ECOG PS 0–2
- PD ≤6 months of irinotecan but still able to tolerate it

(n=100)



PRIMARY ENDPOINT(S)

- 6-month PFS

SECONDARY ENDPOINTS

- ORR, OS, QoL

*No mutations in *KRAS*, *BRAF*, *NRAF* or *PI3KCA* exon 20 (currently still recruiting patients); †400 mg/m^2 bolus then 250 mg/m^2 q1w; ‡180mg/m^2 q2w

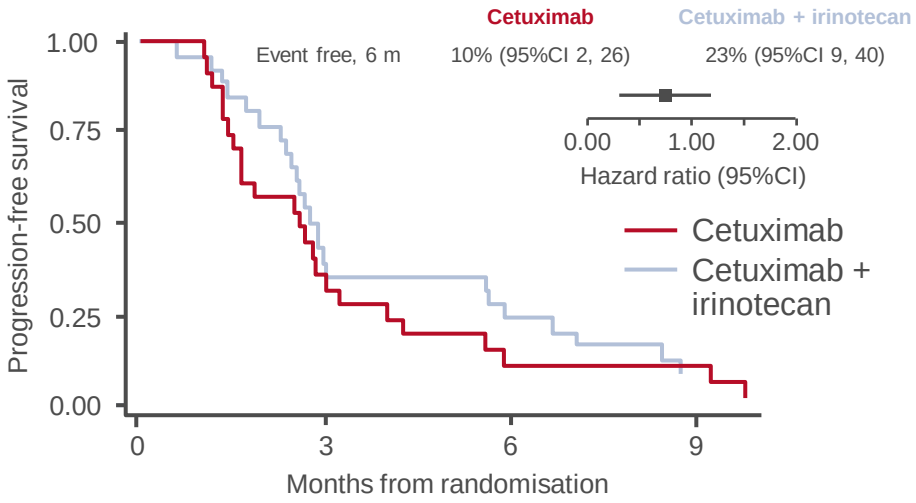
Segelov et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 32LBA

32LBA: The AGITG ICECREAM Study: The Irinotecan Cetuximab Evaluation and Cetuximab Response Evaluation Amongst Patients with a G13D Mutation - analysis of outcomes in patients with refractory metastatic colorectal cancer harbouring the KRAS G13D mutation – Segelov E et al

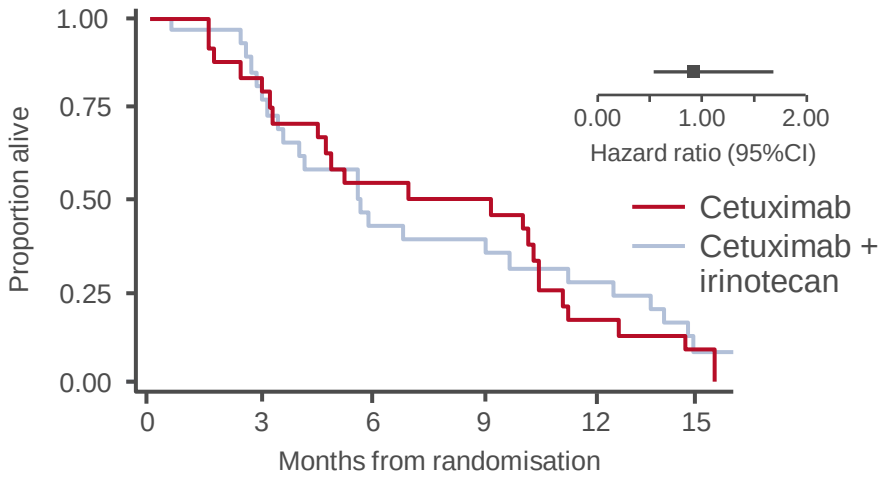
Key results

	Cetuximab alone (n=25*)	Cetuximab + irinotecan (n=26†)
CR, n (%)	0	0
PR, n (%)	0	2 (9)
SD, n (%)	14 (58)	16 (70)
PD, n (%)	10 (42)	5 (22)

G13D mutation: PFS



G13D mutation: OS



*n=24 evaluable patients; †n=23 evaluable patients

Segelov et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 32LBA

32LBA: The AGITG ICECREAM Study: The Irinotecan Cetuximab Evaluation and Cetuximab Response Evaluation Amongst Patients with a G13D Mutation - analysis of outcomes in patients with refractory metastatic colorectal cancer harbouring the KRAS G13D mutation – Segelov E et al

Key results (cont.)

n (%)	Cetuximab alone (n=25)	Cetuximab + irinotecan (n=25)
≥1 AEs ≥grade 3	11 (44)	16 (64)
≥1 Skin AEs ≥grade 3	3 (12)	3 (12)
≥1 SAEs	5 (20)	10 (40)

- There were no new or unexpected toxicities

Conclusions

- **Patients with refractory mCRC harbouring *KRAS* G13D mutations do not benefit from cetuximab monotherapy**
- **Cetuximab + irinotecan demonstrated some antitumour activity**
  - **The results of the quadruple WT* arm may help to ascertain if there was a true synergistic effect or the result of irinotecan rechallenge**

*No mutations in *KRAS*, *BRAF*, *NRAF* or *PI3KCA* exon 20 (currently still recruiting patients)

Segelov et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 32LBA

100: Understanding aggressive colorectal cancers by gene expression analysis of cancer stem cells – Manhas J et al

Study objective

- To elucidate the link between CSC, differentiation grade and metastasis to improve understanding and targeting of CSCs for anticancer therapy

Study design

- Samples of different histopathological grades of primary, untreated CRC and appropriate controls from 70 patients were analysed for the expression of four CSC markers: CD44, CD326, CD24 and CD166
- Marker-based isolation of CSC and non-CSC-bulk-tumour cells from fresh colorectal tissue and HT29 & HCT116 CRC cell lines was done
- Tumour sphere assay was performed with the sorted subsets
- Microarray analysis was done to study transcriptomic changes between CSC and non-CSC-bulk-tumour cells for both high grade and low grade CRC
- Validation was done using real-time PCR

Note: Based on data from abstract only.

CSC, cancer stem cells

Manhas et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 100

100: Understanding aggressive colorectal cancers by gene expression analysis of cancer stem cells – Manhas J et al

Key results

- There was a statistically significant difference ($p<0.05$) in the expression of CD44, CD326 and CD166 between cases and controls
- FACS showed higher prevalence of CSCs in primary high grade CRC vs. low grade CRC
- High throughput gene expression analysis of CSCs showed over expression of the classical stemness markers including Oct4, nanog, c-myc, klf4, MSH1 as well as EMT markers including MMPs, Snail, Twist and ZEB1
- Gene expression profile of CSCs from high grade tumours and low grade tumours were found to be different

Conclusions

- **CD44, CD166 and CD326 were identified as robust CRC-CSC markers by immunohistochemical studies**
- **The high metastatic potential of high grade CRC may be accredited to the differential expression profile of CSCs**
- **Novel genes such as AHSA1, CFH, ACSS1 and NUPR1 may contribute to high metastatic potential of high grade CRC**
- **Targeting these novel genes may be key to developing anti-CSC therapy for aggressive CRC**

Note: Based on data from abstract only.

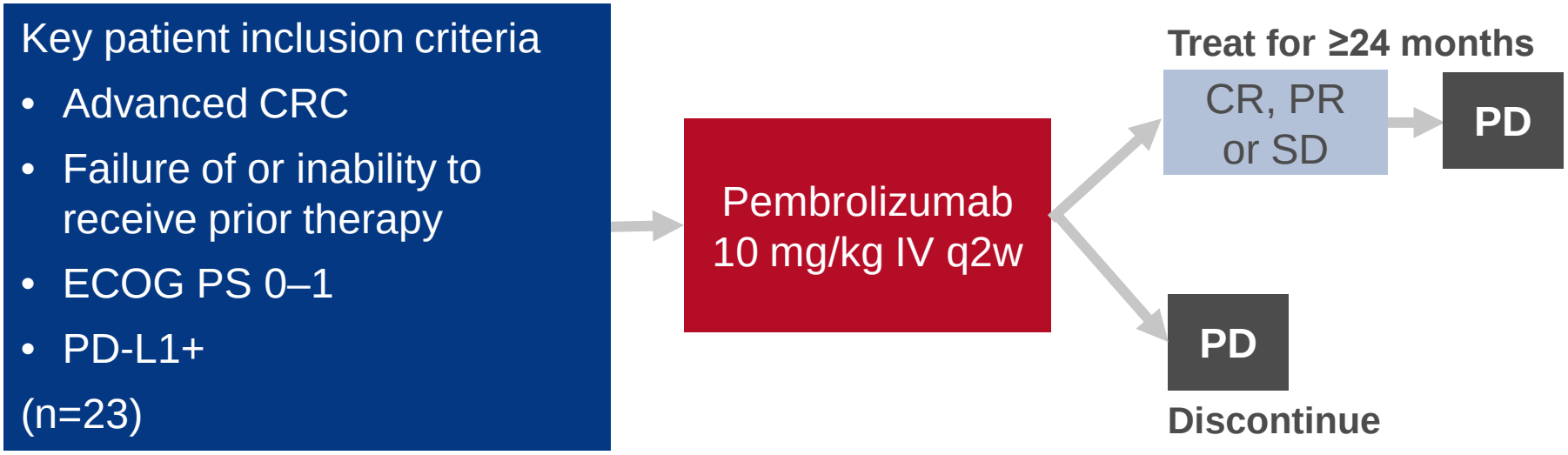
FACS, fluorescence-activated cell sorting

Manhas et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 100

502: Pembrolizumab (MK-3475) for patients (pts) with advanced colorectal carcinoma (CRC): Preliminary results from KEYNOTE-028 – O'Neil BH et al

Study objective

- To estimate response to pembrolizumab in patients with PD-L1+ advanced CRC



PRIMARY ENDPOINT(S)

- ORR (RECIST v1.1)

SECONDARY ENDPOINTS

- PFS, OS, duration of response
- Safety

O'Neil et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 502

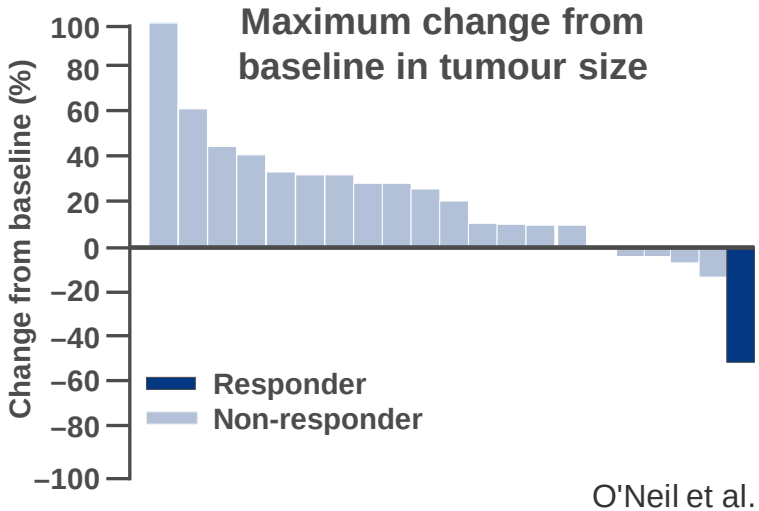
502: Pembrolizumab (MK-3475) for patients (pts) with advanced colorectal carcinoma (CRC): Preliminary results from KEYNOTE-028 – O'Neil BH et al

Key results

- TTR: 7.3 weeks; response duration: 12.4+ months; median SD duration: 5.1 months

Best response	n (%)	95%CI
ORR	1 (4.3)	0.1, 21.9
CR	0	0.0, 14.8
PR	1 (4.3)	0.1, 21.9
SD	4 (17.4)	5.0, 38.8
PD	16 (69.6)	47.1, 86.8
Not assessed	2 (8.7)	1.1, 28.0

- The one responder was the only patient with MSI-H CRC



O'Neil et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 502

502: Pembrolizumab (MK-3475) for patients (pts) with advanced colorectal carcinoma (CRC): Preliminary results from KEYNOTE-028 – O'Neil BH et al

Key results (cont.)

AEs, n (%)	n=23
Treatment related, any grade in ≥2 patients	
Fatigue	3 (13)
Stomatitis	2 (8.7)
Asthenia	2 (8.7)
Treatment related, grade ≥3	
Blood bilirubin increased (grade 4)	1 (4.3)

Conclusions

- **Pembrolizumab showed antitumour responses in MSI-H CRC, but not MSS CRC, despite selection for patients with PD-L1 expression**
- **The safety profile was manageable and consistence with previous studies**
- **The ongoing KEYNOTE-164 study will explore the efficacy and safety of pembrolizumab in patients with MSI-H CRC**

O'Neil et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 502

900: Transitional impact of short and long-term outcomes of a randomized controlled trial to evaluate laparoscopic versus open surgery for colorectal cancer from Japan Clinical Oncology Group Study JCOG0404 – Fujii S et al

Study objective

- To evaluate the short- and long-term outcomes of laparoscopic surgery (LAP) vs. open surgery (OP) over different registration periods in patients with CRC in Japan

Study design

- The study was conducted between October 2004 and March 2009 and was divided into three registration periods: 2004−2005, 2006−2007 and 2008−2009
- Patient eligibility criteria included:
  - Histologically proven CRC
  - Tumour located in the cecum, ascending, sigmoid or rectosigmoid colon
  - T3 or deeper lesion without involvement of other organs
  - N0−2 and M0
  - Tumour size <8 cm

Note: Based on data from abstract only.

Fujii et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 900

900: Transitional impact of short and long-term outcomes of a randomized controlled trial to evaluate laparoscopic versus open surgery for colorectal cancer from Japan Clinical Oncology Group Study JCOG0404 – Fujii S et al

Key results

- 1,057 randomised patients were included in the efficacy analysis and 1,045 patients who received assigned surgery were included in the safety analysis

	1st period (2004–2005)		2nd period (2006–2007)		3rd period (2008–2009)	
	OP (n=105)	**LAP (n=105)**	**OP (n=241)**	**LAP (n=243)**	**OP (n=174)**	**LAP (n=177)**
Median operation time, min	160	205	156	211	161	219
Median blood loss, mL	119	35	80	28	75	25
All grade of early complication, %	27.6	14.3	20.3	14.8	21.3	13.6
	OP (n=106)	**LAP (n=106)**	**OP (n=244)**	**LAP (n=246)**	**OP (n=178)**	**LAP (n=177)**
5-year OS, %	93.4	90.5	88.8	92.2	90.8	91.9
5-year RFS, %	83.0	80.1	78.4	80.9	79.6	76.7

Note: Based on data from abstract only.

Fujii et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 900

900: Transitional impact of short and long-term outcomes of a randomized controlled trial to evaluate laparoscopic versus open surgery for colorectal cancer from Japan Clinical Oncology Group Study JCOG0404 – Fujii S et al

Conclusions

- **Operating times were longer, but blood loss was less with LAP vs. OP**
- **There was no change in the operation time and survival rates in the later registration periods**
- **Both OP and LAP showed a decrease in blood loss in the later registration period; however, the incidence of early complications was reduced in the late period only in the OP group**

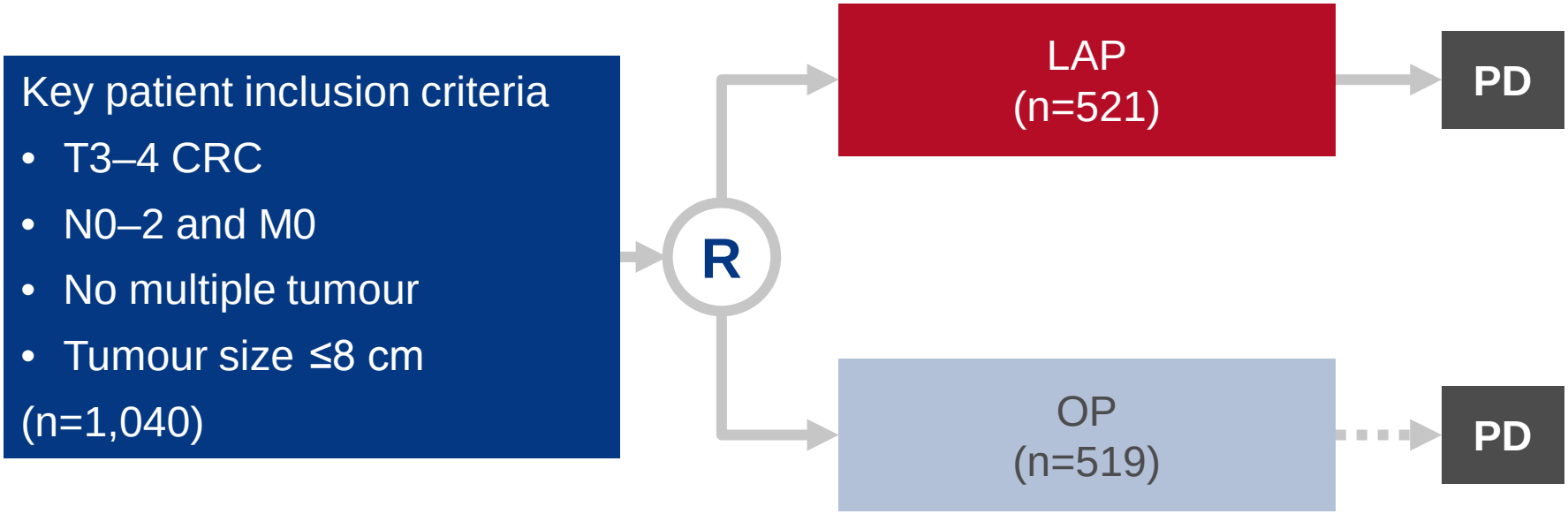
Note: Based on data from abstract only.

Fujii et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 900

2003: Institutional heterogeneity of survival and morbidity in laparoscopic surgery for colorectal cancer: From the data of a randomized controlled trial comparing open and laparoscopic surgery (JCOG0404) – Katayama H et al

Study objective

- To investigate hospital heterogeneity in survival and morbidity in patients undergoing laparoscopic surgery (LAP) vs. open surgery (OP) for CRC



PRIMARY ENDPOINT(S)

- OS

SECONDARY ENDPOINTS

- RFS, short-term clinical outcomes
- Safety

Katayama et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2003

2003: Institutional heterogeneity of survival and morbidity in laparoscopic surgery for colorectal cancer: From the data of a randomized controlled trial comparing open and laparoscopic surgery (JCOG0404) – Katayama H et al

Key results

	LAP (n=517)		OP (n=511)	
	%	Hospital heterogeneity?	%	Hospital heterogeneity?
Postoperative complications, grade 1–4	11.9	Yes	20.8	Yes
Postoperative complications, grade 2–4	8.8	Yes	12.7	No
Postoperative complications, grade 3–4	2.6	No	6.3	No
5-year OS	92.0	No	92.0	No
5-year RFS	80.8	Yes	81.9	No

- The following institutional factors did not influence outcomes:
  - Number of patients enrolled in study
  - Number of OP/LAP procedures performed
  - Number of qualified surgeons in 2009

Katayama et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2003

2003: Institutional heterogeneity of survival and morbidity in laparoscopic surgery for colorectal cancer: From the data of a randomized controlled trial comparing open and laparoscopic surgery (JCOG0404) – Katayama H et al

Conclusions

- **Hospital heterogeneity was observed with LAP and OP in patients with CRC**
- **LAP is considered an acceptable treatment option in this population as there was no heterogeneity in severe complications**

Katayama et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2003

2006: A phase III multicenter trial comparing two different sequences of second/third line therapy (cetuximab/irinotecan followed by FOLFOX versus FOLFOX followed by cetuximab/irinotecan) in metastatic K-RAS wt colorectal cancer (mCC) patients, refractory to FOLFIRI/Bevacizumab – Cascinu S et al

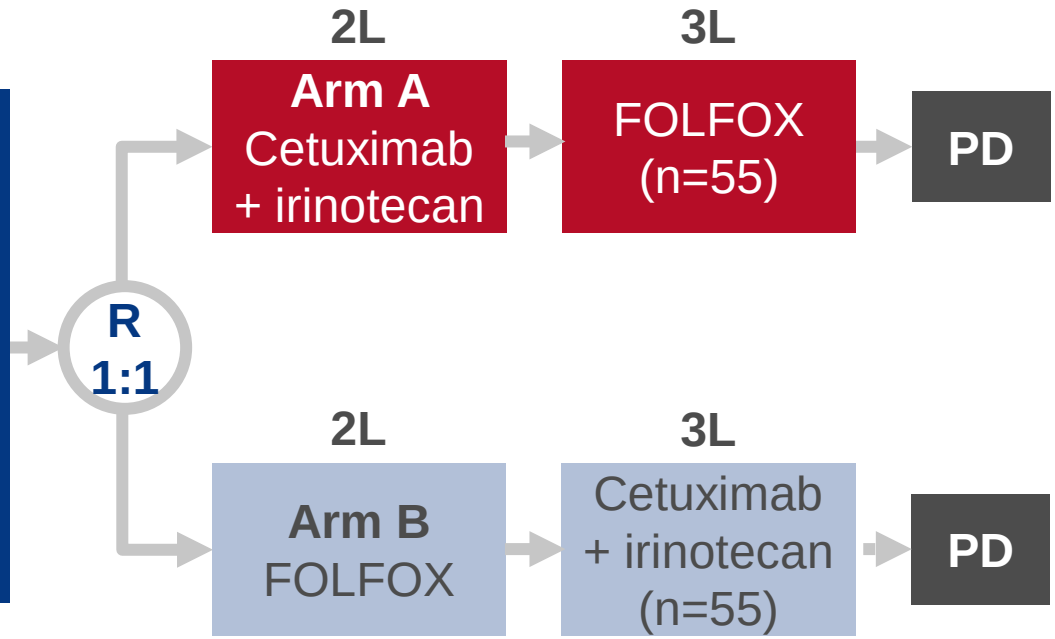
Study objective

- To evaluate the efficacy and safety of two different sequences of cetuximab/irinotecan and FOLFOX in patients with FOLFIRI/bevacizumab refractory mCRC

Key patient inclusion criteria

- *KRAS* WT mCRC
- ECOG PS 0–2
- Previous treatment with FOLFIRI/bevacizumab
- PD ≤4 weeks of study

(n=110)



PRIMARY ENDPOINT(S)

- PFS

SECONDARY ENDPOINTS

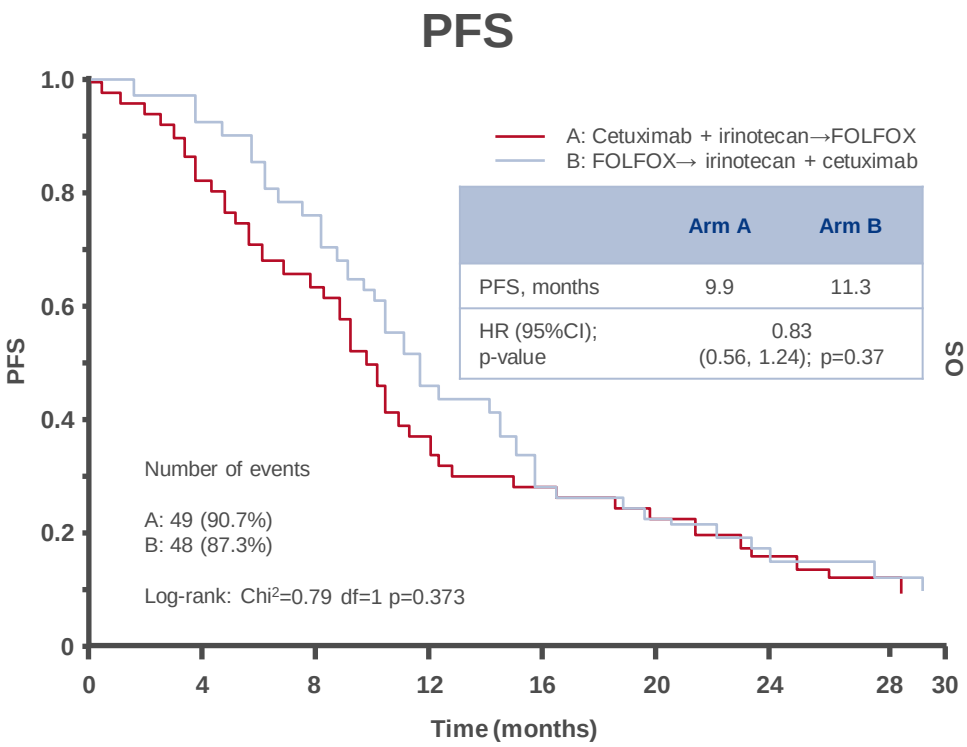
- OS, ORR, safety

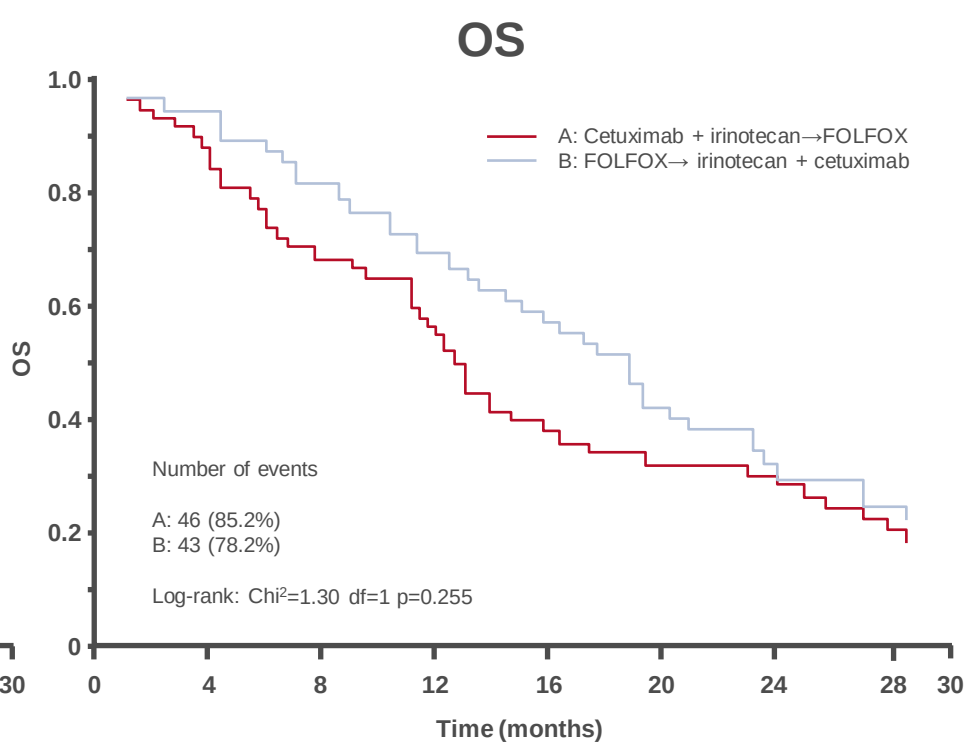
Cascinu et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2006

2006: A phase III multicenter trial comparing two different sequences of second/third line therapy (cetuximab/irinotecan followed by FOLFOX versus FOLFOX followed by cetuximab/irinotecan) in metastatic K-RAS wt colorectal cancer (mCC) patients, refractory to FOLFIRI/Bevacizumab – Cascinu S et al

Key results

- ORR: 37 vs. 57% with Arm A vs. Arm B (p=0.05)





Cascinu et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2006

2006: A phase III multicenter trial comparing two different sequences of second/third line therapy (cetuximab/irinotecan followed by FOLFOX versus FOLFOX followed by cetuximab/irinotecan) in metastatic K-RAS wt colorectal cancer (mCC) patients, refractory to FOLFIRI/Bevacizumab – Cascinu S et al

Key results (cont.)

Grade 3–4 AEs in ≥10% of patients, n (%)	Arm A (n=54)	Arm B (n=55)
Neutropenia	8 (15)	6 (11)
Diarrhoea	7 (13)	9 (16)
Asthenia	9 (16)	8 (15)
Skin toxicity	15 (27)	8 (15)

Conclusions

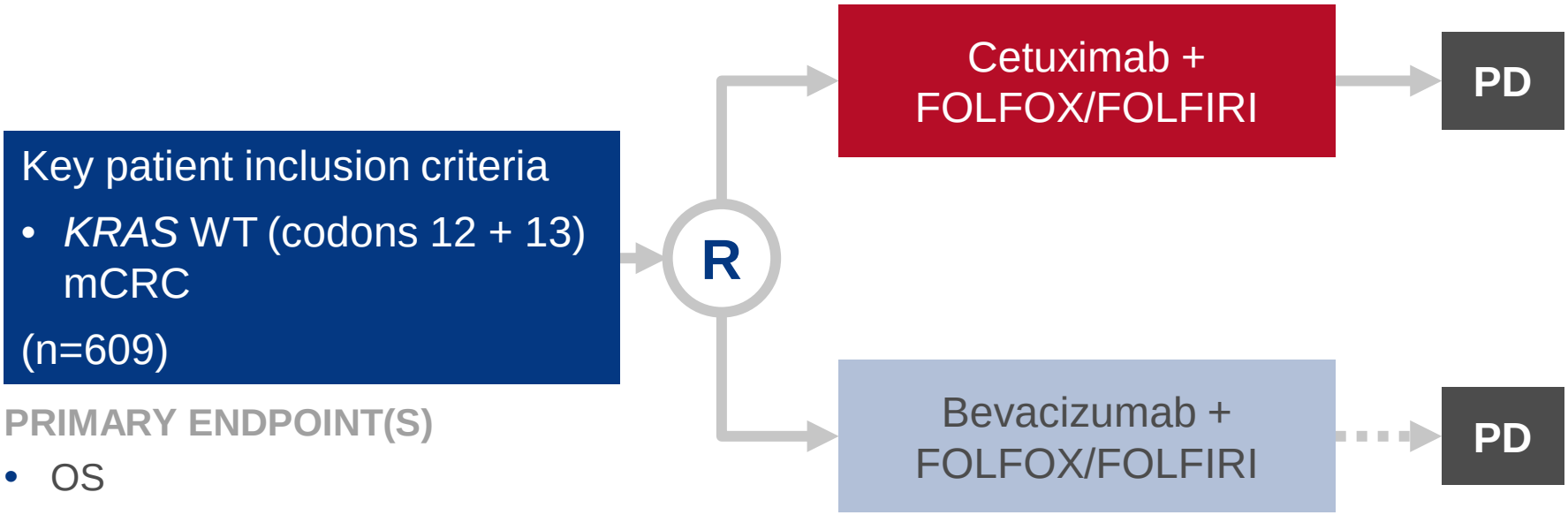
- **The study did not meet its primary endpoint, but FOLFOX followed by cetuximab showed improved ORR and OS vs. the reverse sequence in patients with FOLFIRI/bevacizumab refractory mCRC**
  - **These data suggest that in patients with *KRAS* WT tumours, cetuximab should not be given immediately after bevacizumab**
- **These results are consistent with previous studies suggesting that EGFR inhibition is not effective after VEGF blockade**
  - **These findings may help to explain data from the FIRE-3 study**
- **The toxicity profile was independent of treatment sequence**

Cascinu et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2006

2007: A genome-wide association study (GWAS) of overall survival (OS) in 609 metastatic colorectal cancer (mCRC) patients treated with chemotherapy and biologics in CALGB 80405 – Innocenti F et al

Study objective

- To identify germline variants associated with survival in patients with mCRC treated with FOLFOX or FOLFIRI in combination with either bevacizumab or cetuximab



PRIMARY ENDPOINT(S)

- OS

- DNA was extracted from peripheral blood and genotyped for ~700,000 SNPs
- The association between SNPs and OS was tested using a COX proportional hazards model

Note: Based on data from abstract only.

Innocenti et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2007

2007: A genome-wide association study (GWAS) of overall survival (OS) in 609 metastatic colorectal cancer (mCRC) patients treated with chemotherapy and biologics in CALGB 80405 – Innocenti F et al

Key results

- Median OS in genotyped patients was 29.6 months

SNPs associated with OS	HR	p-value
RDH14	1.63	$<1.12 \times 10^{-6}$
TMEM16J	1.52	$<2.03 \times 10^{-6}$
AXIN1	1.40	$<4.26 \times 10^{-6}$

- AXIN1 provides the most compelling evidence for a link to the biology of CRC
  - rs11644916 (G to A) in AXIN1 is a common germline intronic variant (30% allele frequency)
  - mOS for patients with the AA, AG or GG genotypes of rs11644916 was: 18.4 (95%CI 14.2, 27.6); 25.6 (23.6, 30.4); or 36.6 (32.9, 41.1) months, respectively

Conclusions

- **A common SNP in the AXIN1 gene confers worse OS**
- **This study selects AXIN1 as a new putative determinant of CRC progression**
- **Further studies in CRC experimental models are required**

Note: Based on data from abstract only.

Innocenti et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2007

2008: Non-Invasive testing of gene expressions using cell-free RNA increases the chemotherapy target information generated from cell-free DNA testing – Danenberg P et al

Study objective

- To investigate the value of non-invasive gene expression testing with cell-free (cf) RNA and cfDNA testing, in order to identify tumour-specific mutations in patients with CRC

Study design

- Blood samples were obtained from patients with CRC
  - All patients were refractory and undergoing CT or clinical trials
- Additionally, blood samples were obtained from healthy volunteers
- Gene expression and gene mutations were analysed for each patient
  - cfRNA was extracted from plasma and reverse-transcribed into cDNA, in order to determine the expression of *PD-L1*, *ERCC1*, *KRAS*, *AREG, EREG* and *EGFR*
  - cfDNA was analysed for *KRAS*, *BRAF* and *NRAS* mutations

Danenberg et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2008

2008: Non-Invasive testing of gene expressions using cell-free RNA increases the chemotherapy target information generated from cell-free DNA testing – Danenberg P et al

Key results

Expression levels in CRC	cfDNA	cfRNA
Median (range), ng/5 mL plasma	59.6 (5.9–2016.0)	608.5 (111.1–6312.0)

- DNA mutations were reflected in RNA samples
- PD-L1 expression could be measured in plasma using cfRNA
  - PD-L1+ patients responded to nivolumab, whereas PD-L1− did not*
  - In a responder patient*, there was a rapid decrease in PD-L1 levels following nivolumab treatment

PD-L1 expression	CRC (n=69)	Healthy volunteers (n=9)	NSCLC (n=30)
Frequency, %	17.4	0	50

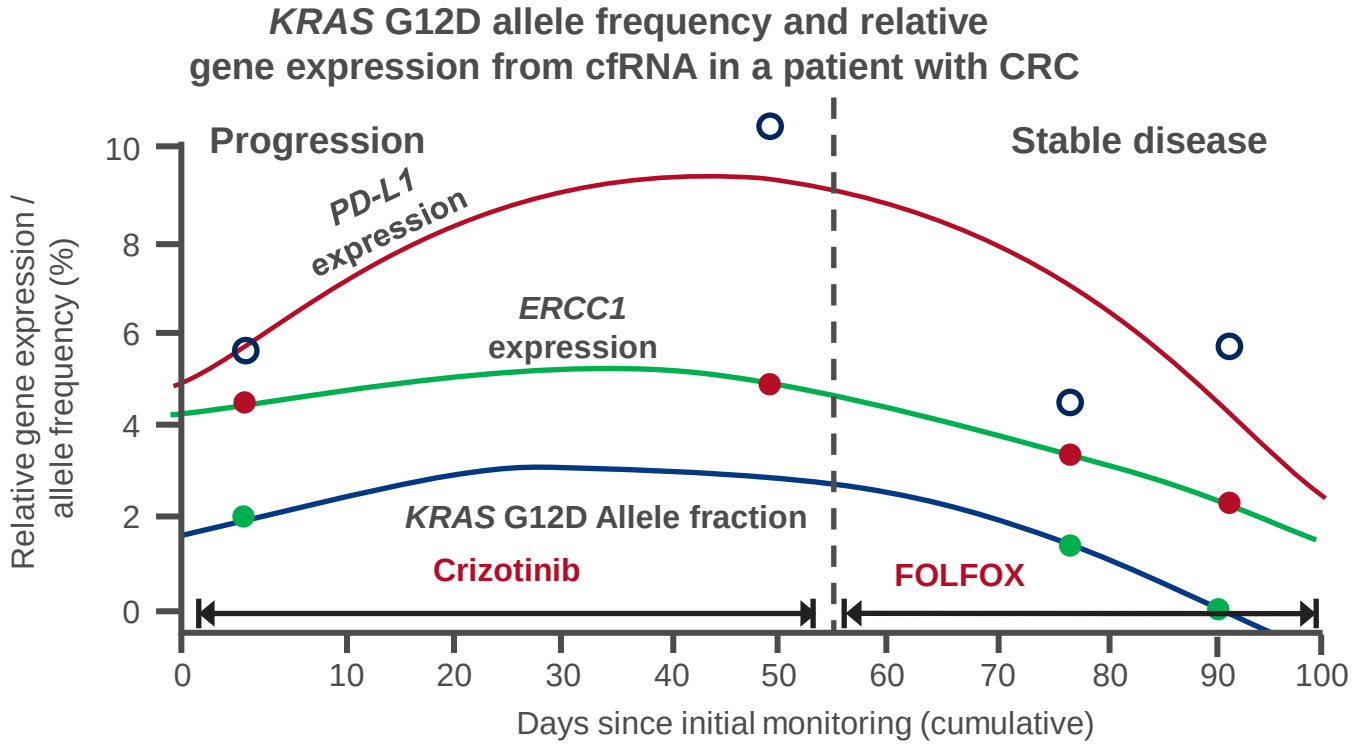
- Similar expression levels were observed in CRC vs. NSCLC in PD-L1+ patients
- In general, gene expression levels increased during progression and decreased during stable disease (see Figure on next slide)

*Example shown was in a patient with NSCLC

Danenberg et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2008

2008: Non-Invasive testing of gene expressions using cell-free RNA increases the chemotherapy target information generated from cell-free DNA testing – Danenberg P et al

Key results (cont.)



Conclusions

- The transition from tissue to non-invasive blood-based testing is critical
- Testing must comprise both DNA and RNA components
  - cfDNA mutation blood tests can replace tissue-based DNA tests
  - cfRNA mutation blood tests can replace tissue IHC and FISH tests

Danenberg et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2008

2010: A genetic variant in RASSF1A, a key regulator of HIPPO pathway, predicts survival in two independent cohorts of mCRC patients treated with cetuximab-based chemotherapy – Sebio A et al

Study objective

- To investigate whether polymorphisms within *RASSF1A* and the HIPPO pathway genes *TAZ* + *LATS* predict efficacy of cetuximab-based therapy in patients with mCRC

Study design

- Genomic DNA was isolated from FFPE tissue samples from two cohorts of patients
  - **Cohort 1 (FIRE-3)**: 297 *RAS* WT patients with mCRC receiving 1st-line FOLFIRI/cetuximab
  - **Cohort 2 (JACCRO CC-05/-06)**: 77 *KRAS* WT patients with mCRC receiving either 1st-line mFOLFOX6 + cetuximab (n=28) or S-1 + oxaliplatin + cetuximab (n=49)
- A total of 4 SNPs were evaluated:
  - 2 SNPs for *RASSF1A*; 1 SNP for *TAZ*; 1 SNP for *LATS*
    - *RASSF1* polymorphism rs2236947 was investigated
  - Genotyping was obtained using PCR-based direct Sanger sequencing

Sebio et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2010

2010: A genetic variant in RASSF1A, a key regulator of HIPPO pathway, predicts survival in two independent cohorts of mCRC patients treated with cetuximab-based chemotherapy – Sebio A et al

Key results

Effect of treatment according to RASF1A rs2236947 genotype

Cohort 1 (FIRE-3)	CC genotype	CA / AA genotype	HR (95%CI)	p-value
mOS, months	46.3	30.6	1.5 (0.94, 2.38)	0.08
mOS, left tumour, months	59.0	38.3	1.79 (1.01, 3.14)	0.044
mOS, right tumour, months	16.5	18.5	0.81 (0.04, 1.90)	0.61
mPFS, left tumour, months	10.4	11.5	0.92 (0.62, 1.38)	0.69

Cohort 2 (JACCRO CC-05/-06)	CC genotype	CA / AA genotype	HR (95%CI)	p-value
mOS, months	42.8	23.2	2.32 (1.08, 5.00)	0.032
mOS, left tumour, months	42.8	36.2	2.39 (1.01, 5.68)	0.048
mPFS, left tumour, months	15.2	11.1	1.88 (1.00, 3.53)	0.049

Sebio et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2010

2010: A genetic variant in RASSF1A, a key regulator of HIPPO pathway, predicts survival in two independent cohorts of mCRC patients treated with cetuximab-based chemotherapy – Sebio A et al

Conclusions

- **The HIPPO signalling pathway plays an important role in CRC**
- ***RASSF1A* rs2236947 polymorphism may be a promising predictive/prognostic marker in patients with mCRC treated with cetuximab + CT**
- **The prognostic value of *RASSF1A* is dependent of colon caner location**
- **Further studies are needed to establish the functional role of the *RASSF1A* rs2236947 polymorphism**

Sebio et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2010

2012: Concordance of RAS mutation status in metastatic CRC patients by comparison of results from circulating tumor DNA and tissue-based RAS testing – Jones F et al

Study objective

- To evaluate the accuracy of blood-based *RAS* testing for assessing eligibility of patients with mCRC for anti-EGFR antibody therapy vs. tissue-based *RAS* testing (current SoC)

Study design

- Pooled data were analysed from two independent *RAS* mutation concordance studies using samples from patients with mCRC to compare blood- vs. tissue-based *RAS* mutation testing
- Plasma *RAS* mutation status was determined using a BEAMing *RAS* 33 mutation panel and compared with SoC *RAS* DNA sequencing of FFPE tumour tissue samples
- Retrospective plasma and FFPE tumour tissue samples were tested from patients with stage IV CRC
- FFPE tissue originated from primary tumours of treatment-naïve patients (n=50) or metastatic sites in patients with PD during CT (n=26)

BEAMing, beads, emulsions, amplification, magnetics

Jones et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2012

2012: Concordance of RAS mutation status in metastatic CRC patients by comparison of results from circulating tumor DNA and tissue-based RAS testing – Jones F et al

Key results

		Tissue *RAS* result:		
		Positive	Negative	Total
Plasma *RAS* result:	Positive	39	2	**41**
	Negative	3	32	**35**
	Total	**42**	**34**	**76**

- Agreement between tissue and plasma-based *RAS* testing:
  - Overall agreement: 71/76 (93.4%)
  - Positive agreement: 39/42 (92.9%)
  - Negative agreement: 32/34 (94.1%)
- *RAS* mutation prevalence: plasma, 54%; tumour tissue, 55.3%

Conclusions

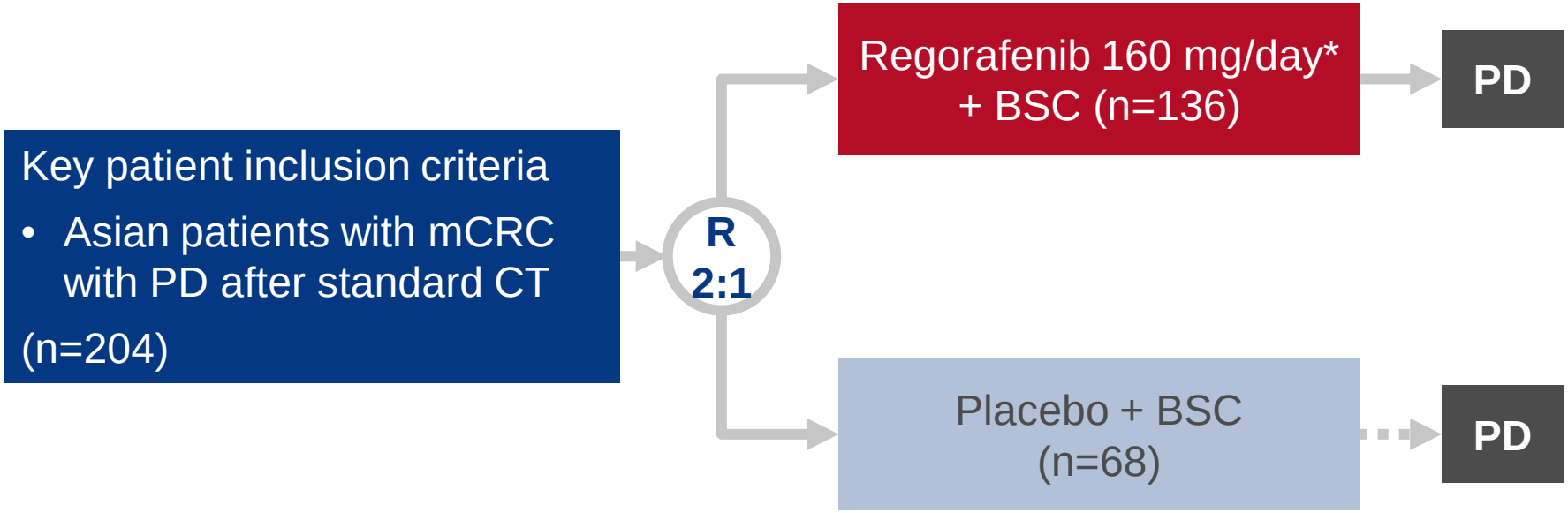
- **There was high concurrence between plasma- and tissue-based *RAS* testing**
- **Blood-based *RAS* mutation testing is a viable alternative to tissue-based testing for determining eligibility of CRC patients for anti-EGFR therapy**

Jones et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2012

2013: Analysis of biomarkers in circulating tumor DNA from the phase 3 CONCUR study of regorafenib in Asian patients with metastatic colorectal cancer (mCRC): Correlation with clinical outcome – Teufel M et al

Study objective

- To identify potential biomarkers associated with clinical outcomes in Asian patients with mCRC receiving the multikinase inhibitor regorafenib vs. placebo



- Circulating DNA was isolated from fresh plasma samples at baseline from 143 of 204 (70%) patients (n=98 regorafenib; n=45 placebo)
- Mutation analysis of circulating DNA in plasma was performed using BEAMing
- Historical *KRAS* mutation information was collected at study entry

*3 weeks on, 1 week off, 4-week cycle

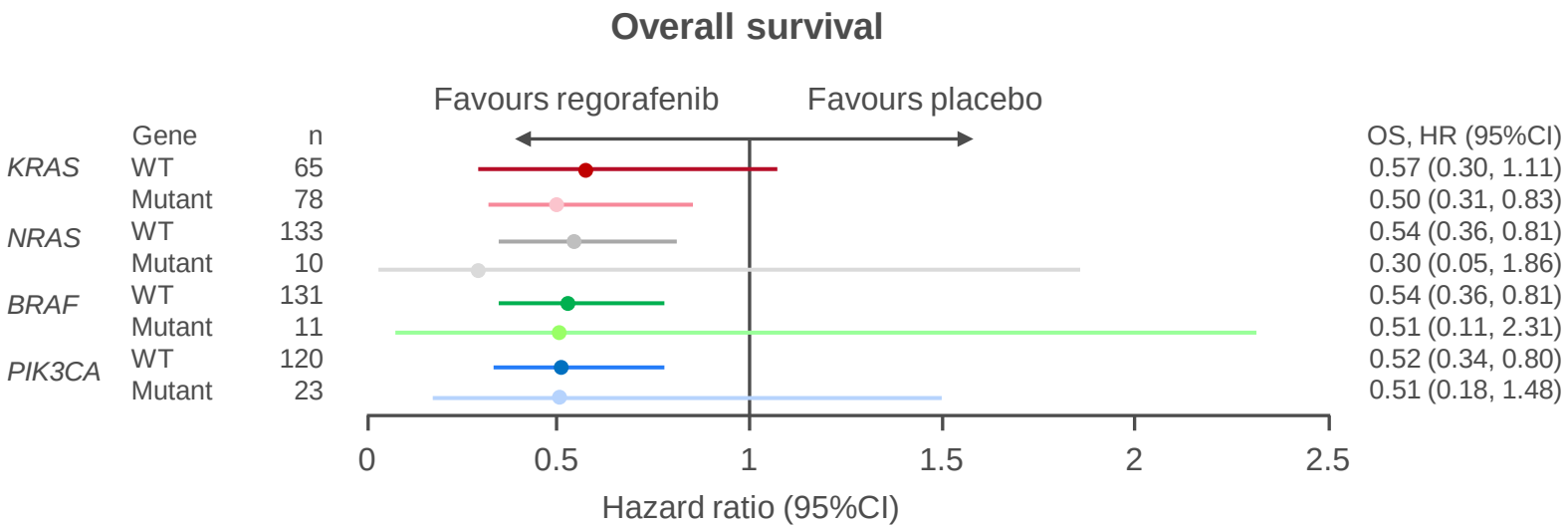
BEAMing, beads, emulsions, amplification, magnetics

Teufel et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2013

2013: Analysis of biomarkers in circulating tumor DNA from the phase 3 CONCUR study of regorafenib in Asian patients with metastatic colorectal cancer (mCRC): Correlation with clinical outcome – Teufel M et al

Key results

- *KRAS* mutations were detected in 55% of samples by BEAMing, while *NRAS* and *BRAF* mutations were each detected in 7–8% of samples
- Among 97 patients with matched plasma BEAMing and historical *KRAS* status from archival tumour testing, concordance was seen in n=63 (65%)
  - *KRAS* mutations: BEAMing n=53 vs. historical n=39



Teufel et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2013

2013: Analysis of biomarkers in circulating tumor DNA from the phase 3 CONCUR study of regorafenib in Asian patients with metastatic colorectal cancer (mCRC): Correlation with clinical outcome – Teufel M et al

Key results (cont.)

KRAS status	Prior targeted therapy	n	OS, HR (95%CI)
WT	No	21	0.46 (0.17, 1.19)
Mutant	No	40	0.41 (0.21, 0.78)
WT	Yes	44	0.68 (0.34, 1.34)
Mutant	Yes	38	0.60 (0.32, 1.15)

Conclusions

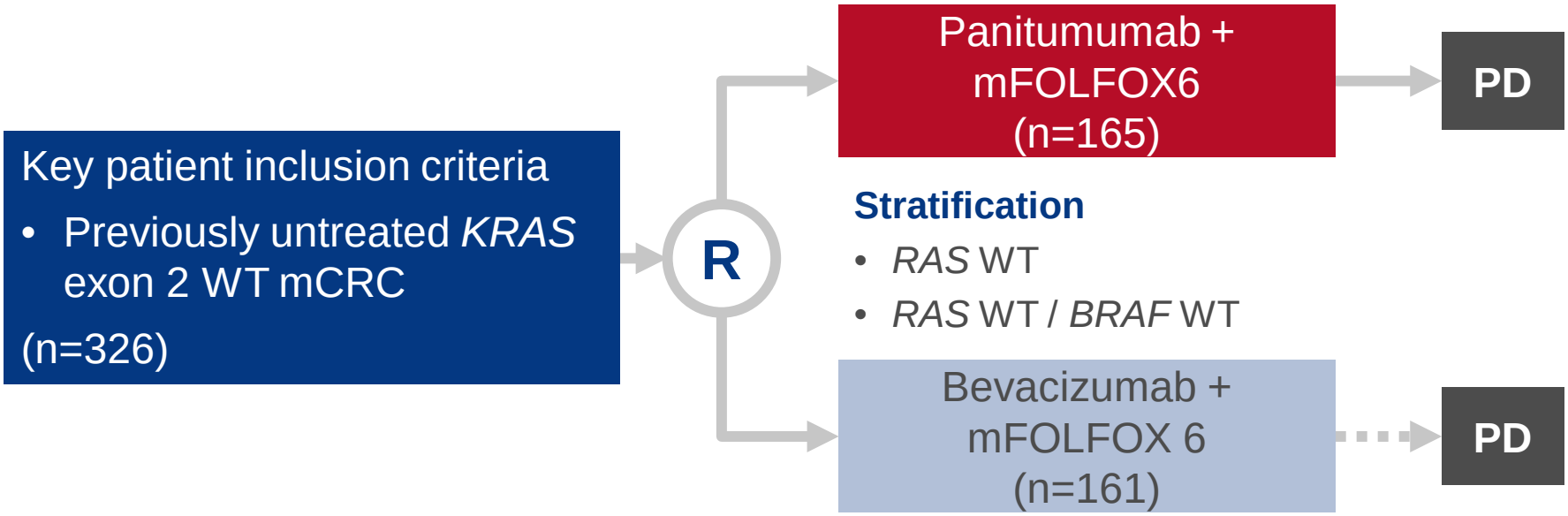
- **Mutational analysis of fresh plasma DNA is feasible and robust, and may better represent the current tumour mutational status than archival tumour tissue**
- **Regorafenib showed clinical beneficial vs. placebo across mutational subgroups**
  - ***KRAS*, *NRAS*, *PIK3CA* or *BRAF* mutations did not predict treatment benefit**
- **There was a trend toward improved clinical outcome across all mutational subgroups in patients who received no prior targeted therapy**

Teufel et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2013

2014: Final analysis of the PEAK trial: Overall survival (OS) and tumour responses during first-line treatment with mFOLFOX6 + either panitumumab (pmab) or bevacizumab (bev) in patients (pts) with metastatic colorectal carcinoma (mCRC) – Rivera F et al

Study objective

- To assess the efficacy of first-line panitumumab + mFOLFOX6 vs. bevacizumab mFOLFOX6 in patients with mCRC



PRIMARY ENDPOINT(S)

- PFS

SECONDARY ENDPOINTS

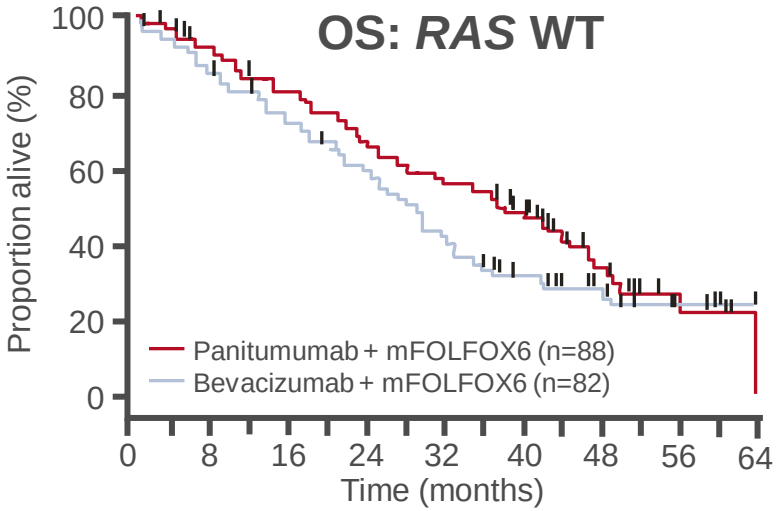
- OS
- ORR

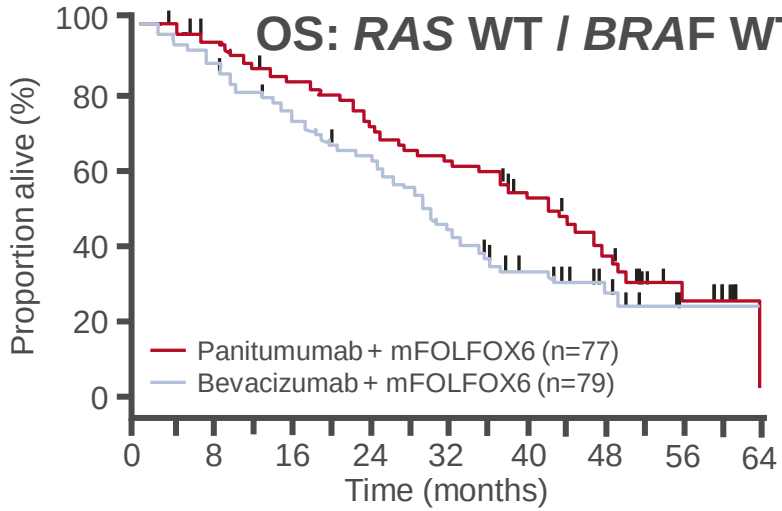
Rivera et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2014

2014: Final analysis of the PEAK trial: Overall survival (OS) and tumour responses during first-line treatment with mFOLFOX6 + either panitumumab (pmab) or bevacizumab (bev) in patients (pts) with metastatic colorectal carcinoma (mCRC) – Rivera F et al

Key results

	RAS WT		*RAS* WT / *BRAF* WT	
	PAN (n=88)	BEV (n=82)	PAN (n=77)	BEV (n=79)
mPFS, months (95%CI)	12.8 (10.7, 15.1)	10.1 (9.0, 12.7)	13.1 (11.6, 16.2)	10.1 (9.0, 12.7)
HR (95%CI); p-value	0.68 (0.48, 0.96); 0.029		0.61 (0.42, 0.88); 0.0075	
mOS, months (95%CI)	36.9 (27.9, 46.1)	28.9 (23.3, 32.0)	41.3 (31.6, 46.7)	28.9 (23.9, 33.1)
HR (95%CI); p-value	0.76 (0.53, 1.11); 0.15		0.70 (0.48, 1.04); 0.08	
ORR, n (%) [95%CI]	57 (65) [54, 75]	49 (60) [49, 71]	49 (64) [52, 74]	46 (59) [47, 70]
Odds ratio (95%CI); p-value	1.12 (0.56, 2.22); 0.86		1.17 (0.58, 2.38); 0.76	





PAN, panitumumab; BEV, bevacizumab

Rivera et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2014

2014: Final analysis of the PEAK trial: Overall survival (OS) and tumour responses during first-line treatment with mFOLFOX6 + either panitumumab (pmab) or bevacizumab (bev) in patients (pts) with metastatic colorectal carcinoma (mCRC) – Rivera F et al

Key results (cont.)

	PAN (n=88)	BEV (n=82)	HR (95%CI); p-value
Median DOR, months	11.4	9.0	0.59 (0.39, 0.88); 0.011
Median TTR, months	2.3	3.8	1.19 (0.81, 1.74); 0.37
Median DPR, %	65.0	46.3	n/a (n/a); 0.0018

Conclusions

- **PFS was significantly improved in patients with *RAS* WT mCRC receiving first-line panitumumab + mFOLFOX6 vs. bevacizumab + mFOLFOX6**
- **mOS was numerically longer with panitumumab vs. bevacizumab**
- **ORR was similar between the groups, but panitumumab was associated with earlier, longer and deeper tumour responses vs. bevacizumab**
- **Panitumumab + mFOLFOX6 is an effective first-line treatment for patients with *RAS* WT mCRC**

n/a, not available

Rivera et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2014

2015: Cavitation of lung metastases induced by regorafenib in patients with colorectal carcinoma: Data from the phase III CORRECT study – Ricotta R et al

Study objective

- To evaluate the occurrence and potential predictive value of cavitating pulmonary metastasis in patients with CRC receiving regorafenib vs. placebo

Study design

- Baseline and week 8 contrast enhanced computed tomography data were analysed in 108 patients with lung metastases randomised to regorafenib (n=75) or placebo (n=33) in a retrospective multicentre study
- The occurrence of cavitation was assessed in lung metastases of ≥10 mm at week 8 and compared with baseline
- Cavitation was defined as the onset of an air-filled cavity of ≥10% or an increase of a pre-existent cavitation, in ≥1 lung lesion

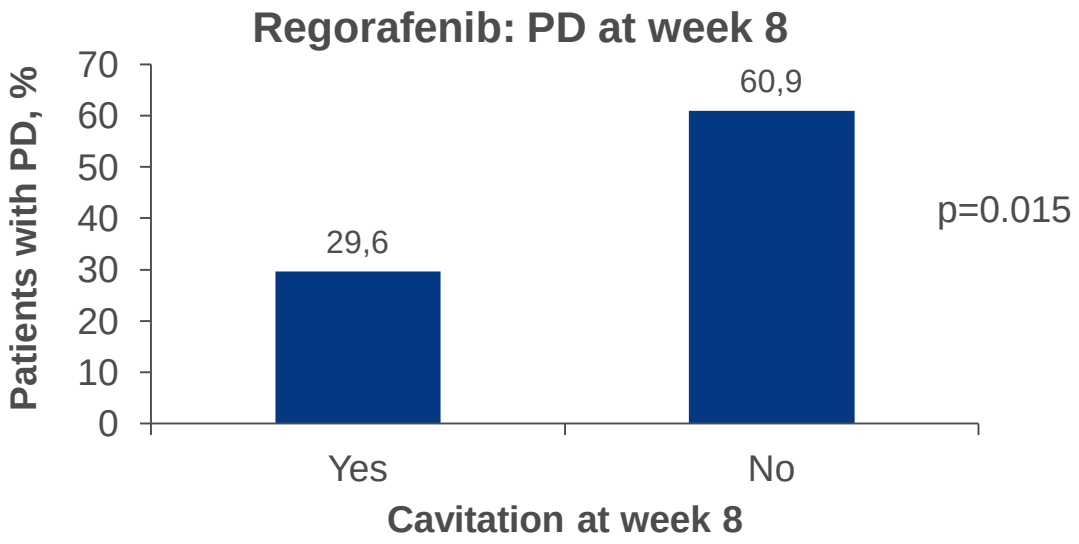
Ricotta et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2015

2015: Cavitation of lung metastases induced by regorafenib in patients with colorectal carcinoma: Data from the phase III CORRECT study – Ricotta R et al

Key results

RECIST response, n (%)	Regorafenib (n=75)	Placebo (n=33)
CR/PR	0	0
SD	37 (50.7)	4 (12.1)
PD	36 (49.3)	29 (87.9)

- Cavitation of lung metastases: baseline, n=18 (16.7%); regorafenib, n=15; placebo, n=3
  - Week 8: regorafenib, 29 (38.7%) patients; placebo, 0 patients (p<0.01)



Ricotta et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2015

2015: Cavitation of lung metastases induced by regorafenib in patients with colorectal carcinoma: Data from the phase III CORRECT study – Ricotta R et al

Conclusions

- **A higher frequency of cavitating lung metastasis was observed in patients with CRC receiving regorafenib vs. placebo**
- **This radiological change was associated with an absence of progression, making it an imaging marker to be prospectively validated as an early signal for PFS**

Ricotta et al. *Ann Oncol* 2015; 26 (suppl 6): abstr 2015