GI SLIDE DECK 2016

Selected abstracts on **Colorectal Cancer** from:

18th World Congress on Gastrointestinal Cancer

29 June–2 July 2016 | Barcelona, Spain

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 2016. This slide set specifically focuses on the **18th World Congress on Gastrointestinal Cancer 2016** 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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ESDO Medical Oncology Slide Deck
Editors 2016

COLORECTAL CANCERS



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Glossary

1L	first line
2L	second line
3L	third line
5FU	5-fluorouracil
AE	adverse event
ARCAD	Aide et Recherche en Cancérologie Digestive
BMI	body mass index
BSC	best supportive care
Cap	capecitabine
cfDNA	cell-free DNA
CI	confidence interval
CR	complete response
(m)CRC	(metastatic) colorectal cancer
CRM	circumferential resection margin
CRTx	conventional radiochemotherapy
CT	chemotherapy
ctDNA	circulating DNA
D	day
DCR	disease control rate
(m)DOR	median duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	endothelial growth factor receptor
EMS	extramural tumour spread
EORTC-QLQC30	European Organization for Research and Treatment of Cancer core quality of life questionnaire
FFPE	formalin-fixed, paraffin-embedded
FOLFIRI	leucovorin, fluorouracil, irinotecan
FOLFIRINOX/ FOLFOXIRI	leucovorin, fluorouracil, irinotecan, oxaliplatin
FOLFOX	leucovorin, fluorouracil, oxaliplatin
GemCap	gemcitabine, capecitabine
H&E	haematoxylin and eosin
HR	hazard ratio
IC	immune cells
IHC	immunohistochemistry
IL	interleukin
IQR	interquartile range
ITT	intent-to-treat
IV	intravenous
KRASmt	KRAS mutant
LARC	locally advanced rectal cancer
LDH	lactate dehydrogenase
LP-LA	left posterior-left anterior
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability high
MSS	microsatellite stable
MUT	mutant
NA	not available
NE	not estimable
NGS	next generation sequencing
NR	not reached
OR	odds ratio
ORR	overall response rate
(m)OS	(median) overall survival
OXA	oxaliplatin
(q)PCR	(quantitative) polymerase chain reaction
PD	progressive disease
PD-L1	programmed death-ligand 1
PFR	progression-free rate
(m)PFS	(median) progression-free survival
PD	pharmacodynamic
PK	pharmacokinetic
PO	by mouth
PR	partial response
PS	performance status
q2w	every 2 weeks
qw	every week
QoL	quality of life
R	randomised
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	recurrence-free survival
ROC	receiver operating characteristic
RT	radiotherapy
SAE	serious adverse event
SCCA	squamous cell carcinoma of the anus
SCRTx	short-course radiotherapy + consolidation chemotherapy
SD	stable disease
SIRT	selective internal radiation therapy
SLD	sum of longest diameter
SNP	single-nucleotide polymorphism
SoC	standard of care
TC	tumour cells
WHO	World Health Organization
WT	wild type
XELOX	oxaliplatin, capecitabine

Contents

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COLORECTAL CANCER

LBA-01: Safety and efficacy of cobimetinib (cobi) and atezolizumab (atezo) in a Phase 1b study of metastatic colorectal cancer (mCRC) – Bendell J, et al

Study objective

- To evaluate the efficacy and safety of cobimetinib (MEK inhibitor) combined with atezolizumab (anti-PD-L1) in patients with mCRC

Dose-escalation phase (3 + 3)

Key patient inclusion criteria
- Advanced solid tumour
- ECOG PS 0–1

(n=23)

→ Cobimetinib 20 mg/day PO + Atezolizumab 800 mg IV q2w (n=2 [1 KRASmt + 1 WT])

→ Cobimetinib 40 mg/day PO + Atezolizumab 800 mg IV q2w

→ Cobimetinib 60 mg/day PO + Atezolizumab 800 mg IV q2w (n=1 [KRASmt])

Dose-expansion stage phase

Cobimetinib 60 mg/day PO + Atezolizumab 800 IV q2w (n=20 [all KRASmt])

ENDPOINTS

- Safety
- ORR, mDOR, mPFS, mOS, 6 month OS

Bendell J, et al. Ann Oncol 2016; 27 (suppl 2): abstr LBA-01

LBA-01: Safety and efficacy of cobimetinib (cobi) and atezolizumab (atezo) in a Phase 1b study of metastatic colorectal cancer (mCRC) – Bendell J, et al

Key results

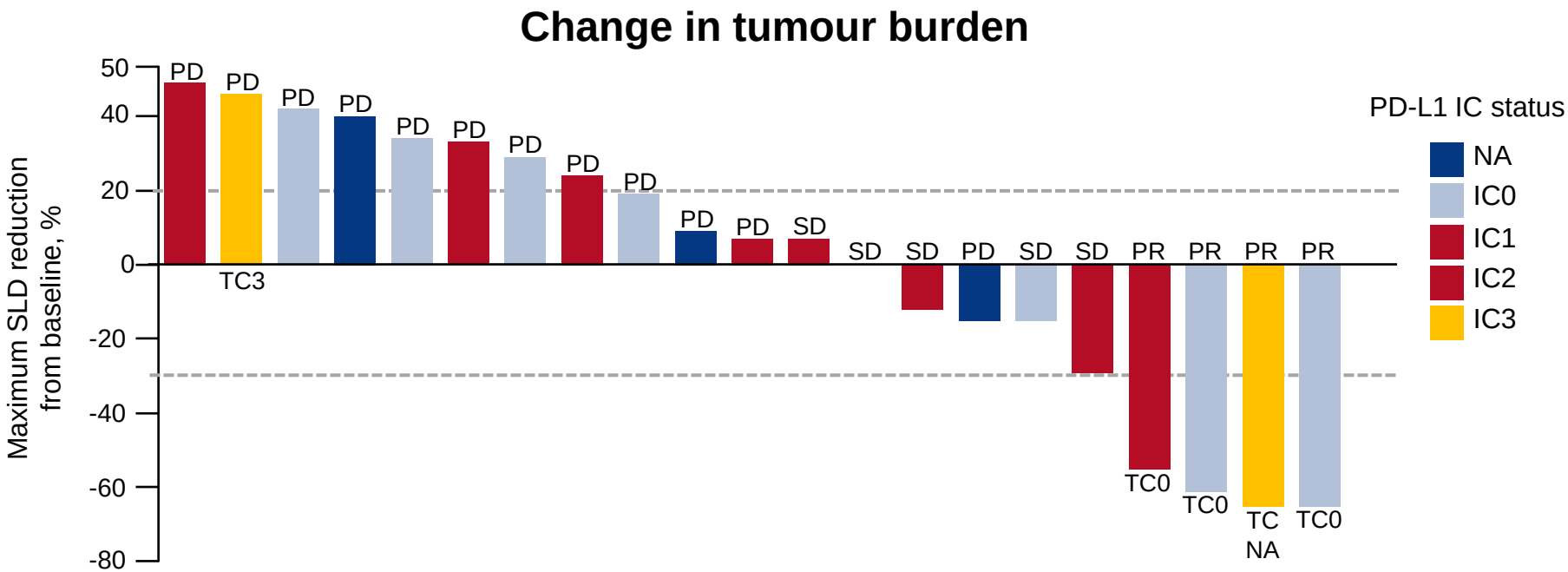
Patients with CRC (n=23)	Treatment-related, n (%)
Grade 3 AEs	8 (35)
Grade 4/5 AEs	0 (0)
Serious AEs	2 (9)
AEs leading to withdrawal from cobimetinib	4 (17)
AEs leading to withdrawal from atezolizumab	0 (0)
Grade 3 AEs occurring in >5% of patients	**%**
Diarrhoea	9

Efficacy endpoints	
ORR, % (95% CI)	17 (5.0, 38.8)
mDOR, months (range)	NR (5.4–11.1+)
mPFS, months (95% CI)	2.3 (1.8, 9.5)
mOS, months (95% CI)	NE (6.5, NE)
6-month OS, % (95% CI)	72 (0.52, 0.93)

Bendell J, et al. Ann Oncol 2016; 27 (suppl 2): abstr LBA-01

LBA-01: Safety and efficacy of cobimetinib (cobi) and atezolizumab (atezo) in a Phase 1b study of metastatic colorectal cancer (mCRC) – Bendell J, et al

Key results (cont.)



PD-L1 IHC status on tumour cells (TC) and tumour-infiltrating immune cells (IC) defined as: TC3 = TC ≥ 50% PD-L1+ cells; IC3 = IC ≥ 10% PD-L1+ cells; TC2 = TC ≥ 5% and < 50% PD-L1+ cells; IC2 = IC ≥ 5% and < 10% PD-L1+ cells; TC1 = TC ≥ 1% and < 5% PD-L1+ cells; IC1 = IC ≥ 1% and < 5% PD-L1+ cells; TC0 = TC < 1% PD-L1+ cells; IC0 = IC < 1% PD-L1+ cells. NA, not available; Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off, February 12, 2016.

Bendell J, et al. Ann Oncol 2016; 27 (suppl 2): abstr LBA-01

LBA-01: Safety and efficacy of cobimetinib (cobi) and atezolizumab (atezo) in a Phase 1b study of metastatic colorectal cancer (mCRC) – Bendell J, et al

Conclusions

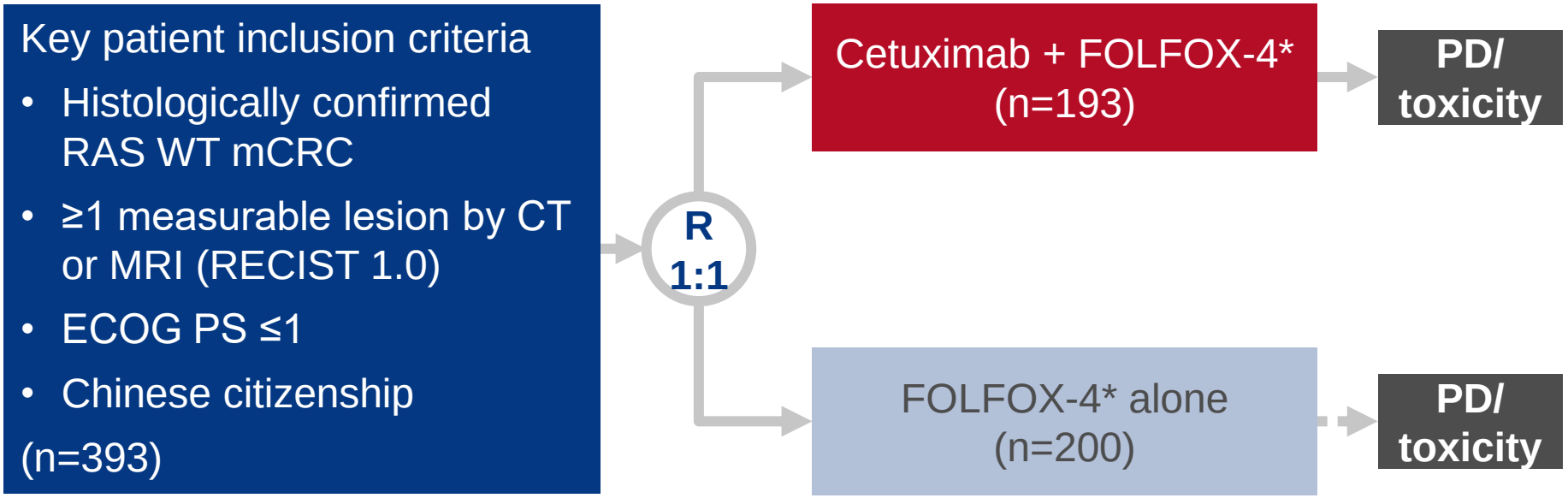
- **Cobimetinib + atezolizumab was well tolerated at a maximum administered doses in patients with chemorefractory KRAS mutant mCRC**
- **A higher clinical response rate in MSS patients was observed with the combination of cobimetinib + atezolizumab than would be expected from either cobimetinib or atezolizumab alone**
- **These results suggest that cobimetinib can sensitise tumours to atezolizumab by increasing MHC I expression on tumour cells and promoting intratumoral CD8 T cell accumulation**
- **Further analysis and a phase 3 study are ongoing**

Bendell J, et al. Ann Oncol 2016; 27 (suppl 2): abstr LBA-01

LBA-05: First-line FOLFOX-4 ± cetuximab in Chinese patients with RAS-wild-type (wt) metastatic colorectal cancer (mCRC): The open-label, randomized phase 3 TAILOR trial – Liu T, et al

Study objective

- To assess the efficacy and safety of 1L cetuximab + FOLFOX-4 vs FOLFOX-4 alone in patients with RAS WT mCRC



PRIMARY ENDPOINT

- PFS (RECIST 1.0)

SECONDARY ENDPOINTS

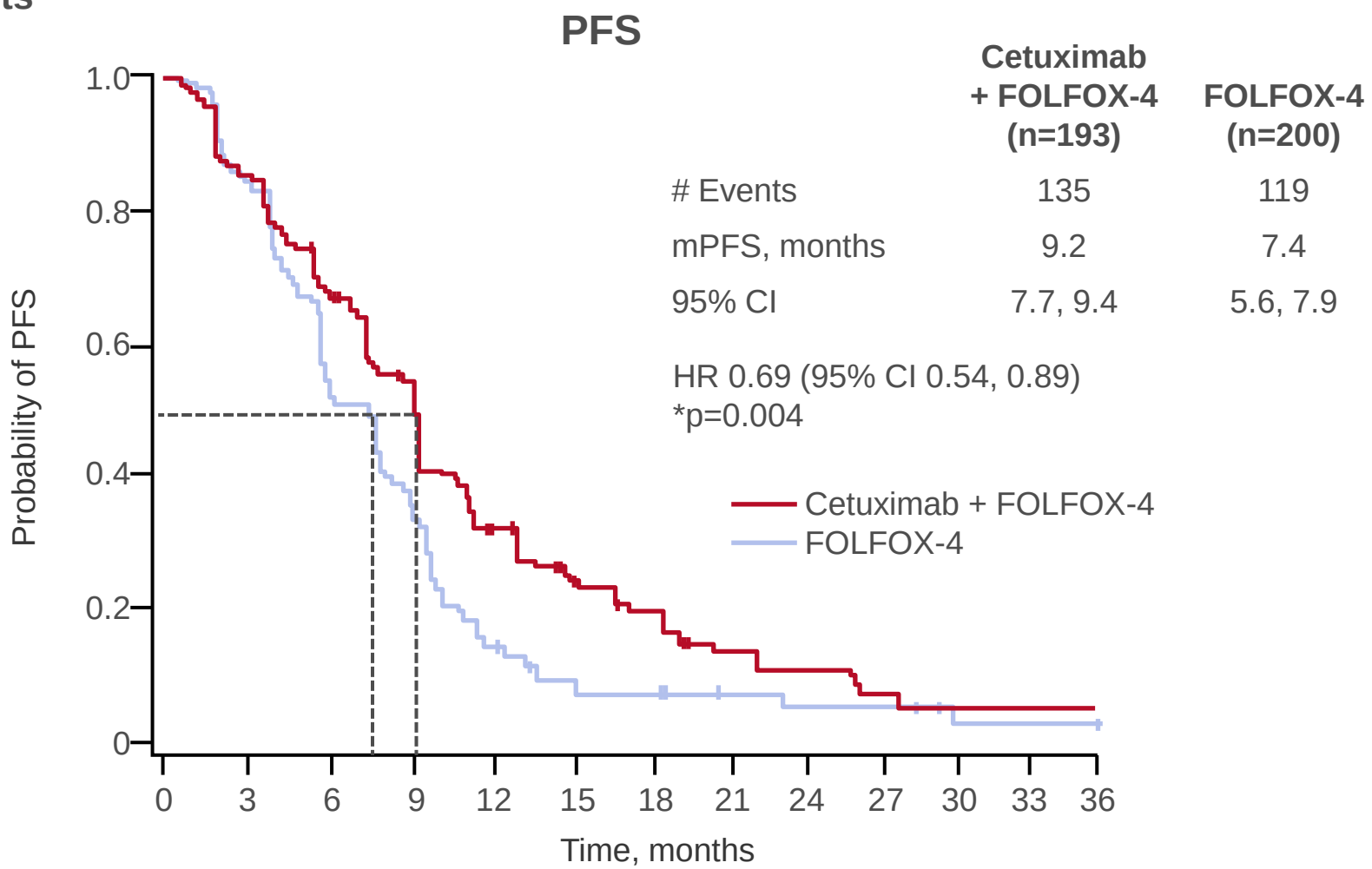
- OS, ORR
- Safety

*Cetuximab 400 mg/m^2 D1 then 250 mg/m^2/week; †oxaliplatin 85 mg/m^2 D1 q2w, 5FU 400 mg/m^2 bolus then 600 mg/m^2/day continuous infusion D1,2 q2w, leucovorin 200 mg/m^2 D1,2 q2w.

Liu et al. Ann Oncol 2016; 27 (suppl 2): abstr LBA-05

LBA-05: First-line FOLFOX-4 ± cetuximab in Chinese patients with RAS-wild-type (wt) metastatic colorectal cancer (mCRC): The open-label, randomized phase 3 TAILOR trial – Liu T, et al

Key results



	Cetuximab + FOLFOX-4 (n=193)	FOLFOX-4 (n=200)
# Events	135	119
mPFS, months	9.2	7.4
95% CI	7.7, 9.4	5.6, 7.9

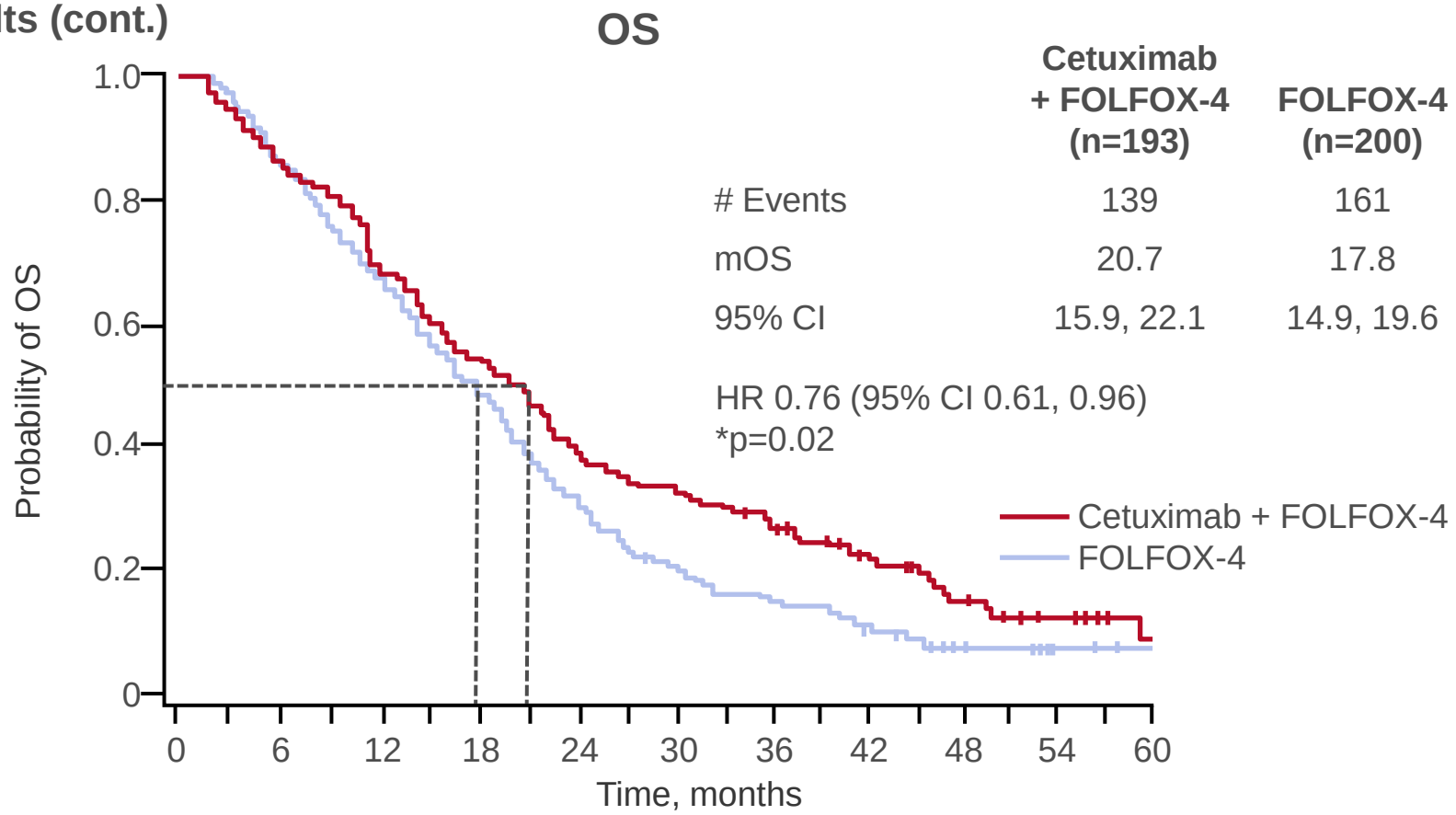
HR 0.69 (95% CI 0.54, 0.89)
*p=0.004

*Log-rank test.

Liu et al. Ann Oncol 2016; 27 (suppl 2): abstr LBA-05

LBA-05: First-line FOLFOX-4 ± cetuximab in Chinese patients with RAS-wild-type (wt) metastatic colorectal cancer (mCRC): The open-label, randomized phase 3 TAILOR trial – Liu T, et al

Key results (cont.)



	Cetuximab + FOLFOX-4	FOLFOX-4 alone	OR (95% CI); p-value†
ORR, %	61.1	39.5	2.41 (1.61, 3.61); <0.001

*Log-rank test; †Fisher exact test.

Liu et al. Ann Oncol 2016; 27 (suppl 2): abstr LBA-05

LBA-05: First-line FOLFOX-4 ± cetuximab in Chinese patients with RAS-wild-type (wt) metastatic colorectal cancer (mCRC): The open-label, randomized phase 3 TAILOR trial – Liu T, et al

Key results (cont.)

Grade ≥3 AEs in ≥10% of patients, n (%)	Cetuximab + FOLFOX-4 (n=194)	FOLFOX-4 alone (n=199)
Neutropenia	120 (61.9)	86 (43.2)
Leukopenia	52 (26.8)	42 (21.1)
Rash	27 (13.9)	0
Fatigue	25 (12.9)	19 (9.5)
Hypokalaemia	20 (10.3)	8 (4.0)
Thrombocytopenia	20 (10.3)	13 (6.5)

Conclusions

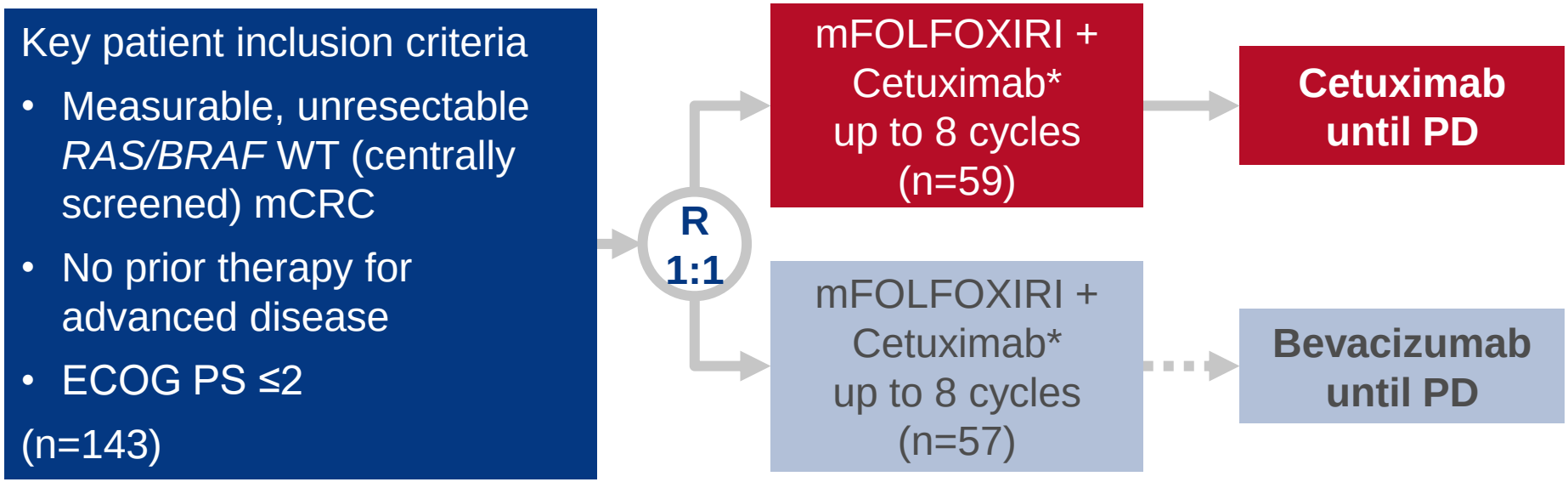
- **This study confirms cetuximab + FOLFOX-4 as a SoC 1L treatment for patients with RAS WT mCRC**
- **Cetuximab + FOLFOX-4 significantly improved PFS, OS + ORR vs FOLFOX-4 alone**
- **There were no new or unexpected safety findings**
- **Subgroup analyses are currently ongoing**

Liu et al. Ann Oncol 2016; 27 (suppl 2): abstr LBA-05

O-011: Modified FOLFOXIRI (mFOLFOXIRI) plus cetuximab (cet), followed by cet or bevacizumab (bev) maintenance, in RAS/BRAF wt metastatic colorectal cancer (mCRC): Results of the phase II randomized MACBETH trial by GONO – Antoniotti C, et al

Study objective

- To evaluate the activity and safety of 1L mFOLFOXIRI + cetuximab and the role of maintenance using cetuximab or bevacizumab in patients with unresectable mCRC (initially *KRAS* WT patients, but after an amendment in October 2013, only *RAS/BRAF* WT)



PRIMARY ENDPOINT

- 10-month progression-free rate (PFR)

SECONDARY ENDPOINTS

- Response, safety

*Cetuximab 500 mg/m^2 + irinotecan 130 mg/m^2 + oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + 5FU 2400 mg/m^{2}over 48h q2w

Antoniotti et al. Ann Oncol 2016; 27 (suppl 2): abstr O-011

O-011: Modified FOLFOXIRI (mFOLFOXIRI) plus cetuximab (cet), followed by cet or bevacizumab (bev) maintenance, in RAS/BRAF wt metastatic colorectal cancer (mCRC): Results of the phase II randomized MACBETH trial by GONO – Antoniotti C, et al

Key results

	Cetuximab (n=59)	Bevacizumab (n=57)
10-month progression free, n	26	23
Secondary resection rate, %		
R0/R1/R2	45.8	29.8
R0	32.2	22.8
Best response, %		
CR	5	4
PR	63	72
SD	24	14
PD	3	4
Not assessed	5	6
ORR	67.8	75.4
DCR	92	89

Antoniotti et al. Ann Oncol 2016; 27 (suppl 2): abstr O-011

O-011: Modified FOLFOXIRI (mFOLFOXIRI) plus cetuximab (cet), followed by cet or bevacizumab (bev) maintenance, in RAS/BRAF wt metastatic colorectal cancer (mCRC): Results of the phase II randomized MACBETH trial by GONO – Antoniotti C, et al

Key results (cont.)

Grade 3/4 AEs occurring in >5% of patients, %	Cetuximab (n=59)	Bevacizumab (n=57)
Neutropenia	28.8	33.3
Diarrhoea	20.3	15.8
Skin rash	18.6	12.3
Asthenia	10.1	8.8
Stomatitis	6.8	5.3
Neurotoxicity	6.7	0

Conclusions

- **The primary endpoint was not met in either of the two arms**
- **It is, however, feasible to use a 4-month induction with mFOLFOXIRI + cetuximab, with relevant activity, leading to high conversion rate which may positively affect OS results**

Antoniotti et al. Ann Oncol 2016; 27 (suppl 2): abstr O-011

O-023: Observational data outcomes of chemotherapy backbone for MSI-high metastatic colorectal cancer in molecular epidemiology of colorectal cancer study in Israel – Shulman K, et al

Study objective

- To evaluate the effectiveness of modern CT backbones and bevacizumab in the treatment of MSI mCRC

Study design

- Data on patients with MSI-high mCRC who were treated with a 1L CT with or without bevacizumab were extracted from the database of Israeli population-based CRC study*
- Patients were diagnosed in 1998–2010 and were followed up until December 2013
- MSI status was determined by comparing 10 molecular markers in tumour and normal tissue
- Date of metastases, death and treatment details were extracted from the oncological follow-up records supported by computerised pharmacy records

ENDPOINTS

- 5-year OS
- Disease-specific survival

*Molecular Epidemiology of Colorectal Cancer (MECC) study.

Shulman et al. Ann Oncol 2016; 27 (suppl 2): abstr O-023

O-023: Observational data outcomes of chemotherapy backbone for MSI-high metastatic colorectal cancer in molecular epidemiology of colorectal cancer study in Israel – Shulman K, et al

Key results

OS by treatment	All (n=87)		BRAF-WT (n=69)	
	mOS, months	60-month OS, %	mOS, months	60-month OS, %
5FU	18.5	10	24.2	13
Irinotecan + 5FU	17.2	11	20.0	14
Irinotecan + 5FU + bevacizumab	13.8	6	21.9	8
Oxaliplatin + 5FU + bevacizumab	24.2	31	20.2	33

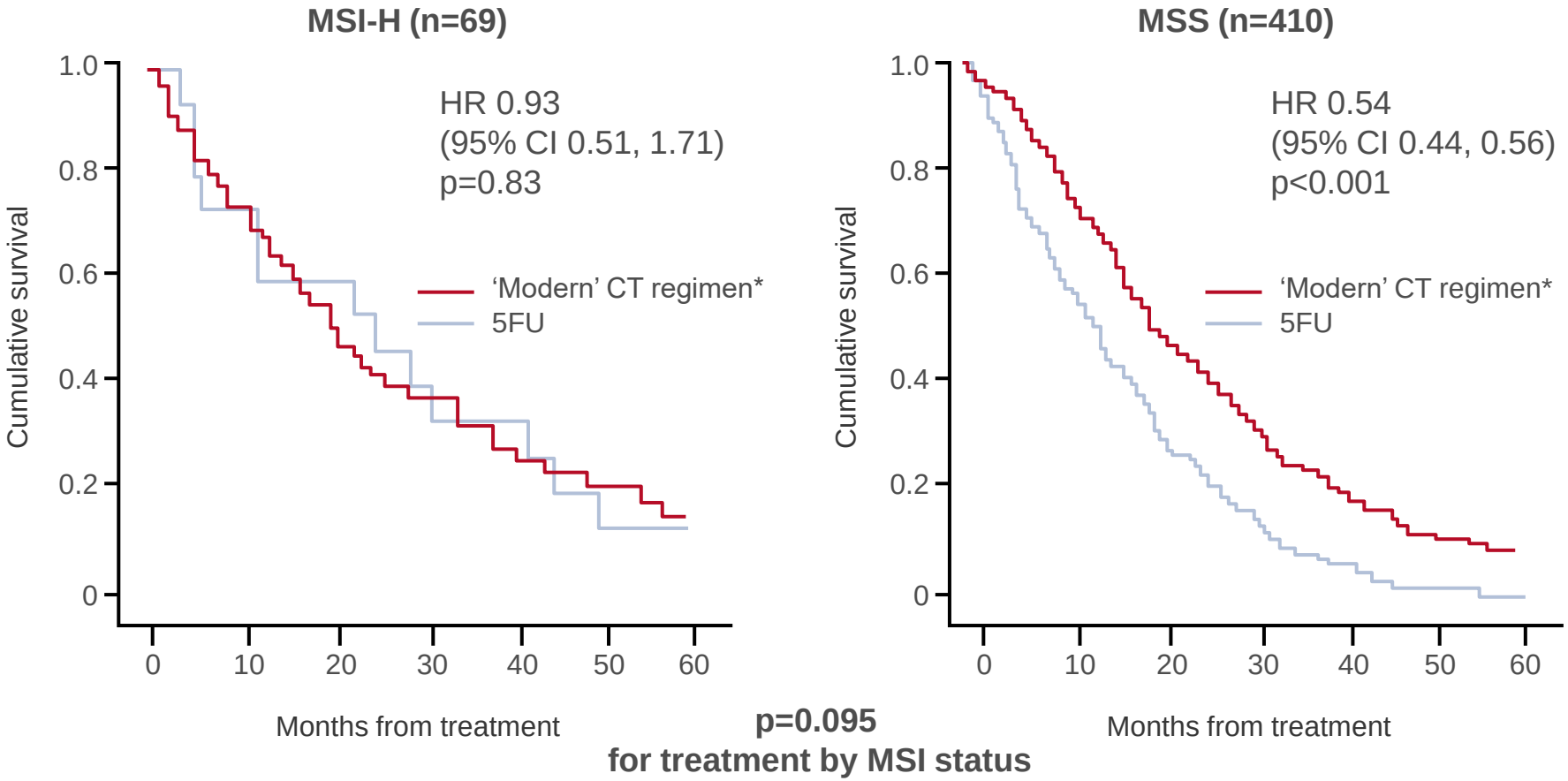
OS by BRAF status	n	# Events	HR (95% CI)	p-value
MUT	17	17	1.9 (1.1, 3.3)	0.02
WT	69	56	-	-

Shulman et al. Ann Oncol 2016; 27 (suppl 2): abstr O-023

O-023: Observational data outcomes of chemotherapy backbone for MSI-high metastatic colorectal cancer in molecular epidemiology of colorectal cancer study in Israel – Shulman K, et al

Key results (cont.)

OS by MSI status + treatment (BRAF-WT tumours)



p=0.095
for treatment by MSI status

*All combinations vs 5FU only.

Shulman et al. Ann Oncol 2016; 27 (suppl 2): abstr O-023

O-023: Observational data outcomes of chemotherapy backbone for MSI-high metastatic colorectal cancer in molecular epidemiology of colorectal cancer study in Israel – Shulman K, et al

Key results (cont.)

OS by MSI status (BRAF WT)	Patients, n	MSI-H vs MSS HR (95% CI)	p-value*
5FU treatment only	165	0.53 (0.30, 0.92)	0.025
Pooled treatments	479	0.77 (0.59, 1.01)	0.062

Conclusions

- **Patients with MSI-H mCRC represent a substantial and biologically distinct subset**
- **Patients with MSI-H tumours respond differently to 1L CT than patients with MSS tumours**
- **The treatment effect of modern CT protocols in MSI-H tumours is not statistically different from a simple 5FU effect**
- **It is possible that combination treatment with FOLFOX + bevacizumab has a more pronounced effect than other treatment regimens in MSI-H tumours**
- **MSS/BRAF-negative tumours have significant treatment benefit from 'modern' CT regimens compared with 5FU alone**

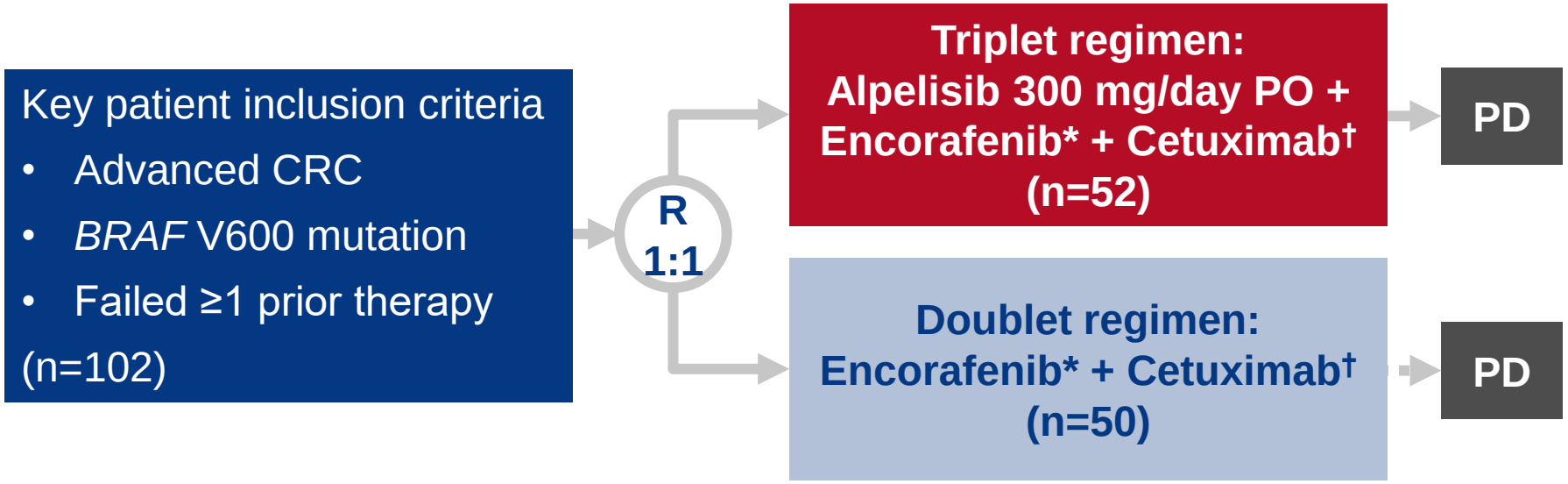
*Age adjusted.

Shulman et al. Ann Oncol 2016; 27 (suppl 2): abstr O-023

O-026: Combination of encorafenib and cetuximab with or without alpelisib in patients with advanced BRAF-mutant colorectal cancer (BRAFm CRC): Phase 2 results – Tabernero J, et al

Study objective

- To evaluate the efficacy and safety of encorafenib + cetuximab ± alpelisib (a PI3K inhibitor), in patients with advanced BRAF-mutant CRC



PRIMARY ENDPOINT(S)

- PFS

SECONDARY ENDPOINTS

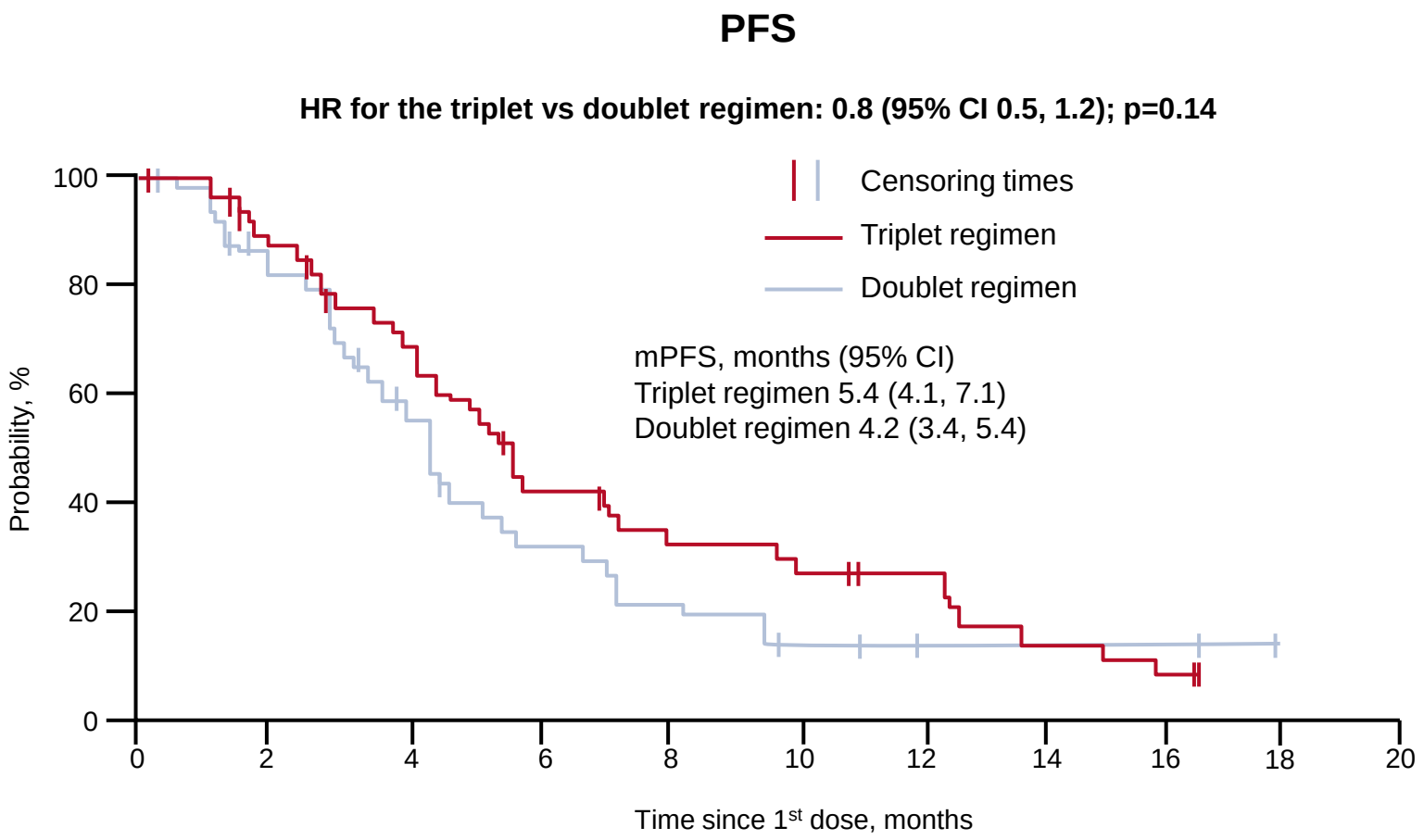
- ORR, DCR, OS
- Safety

*200 mg/day PO;
†400 mg/m^2 IV for first dose followed by 250 mg/m^2 weekly.

Tabernero et al. Ann Oncol 2016; 27 (suppl 2): abstr O-026

O-026: Combination of encorafenib and cetuximab with or without alpelisib in patients with advanced BRAF-mutant colorectal cancer (BRAFm CRC): Phase 2 results – Tabernero J, et al

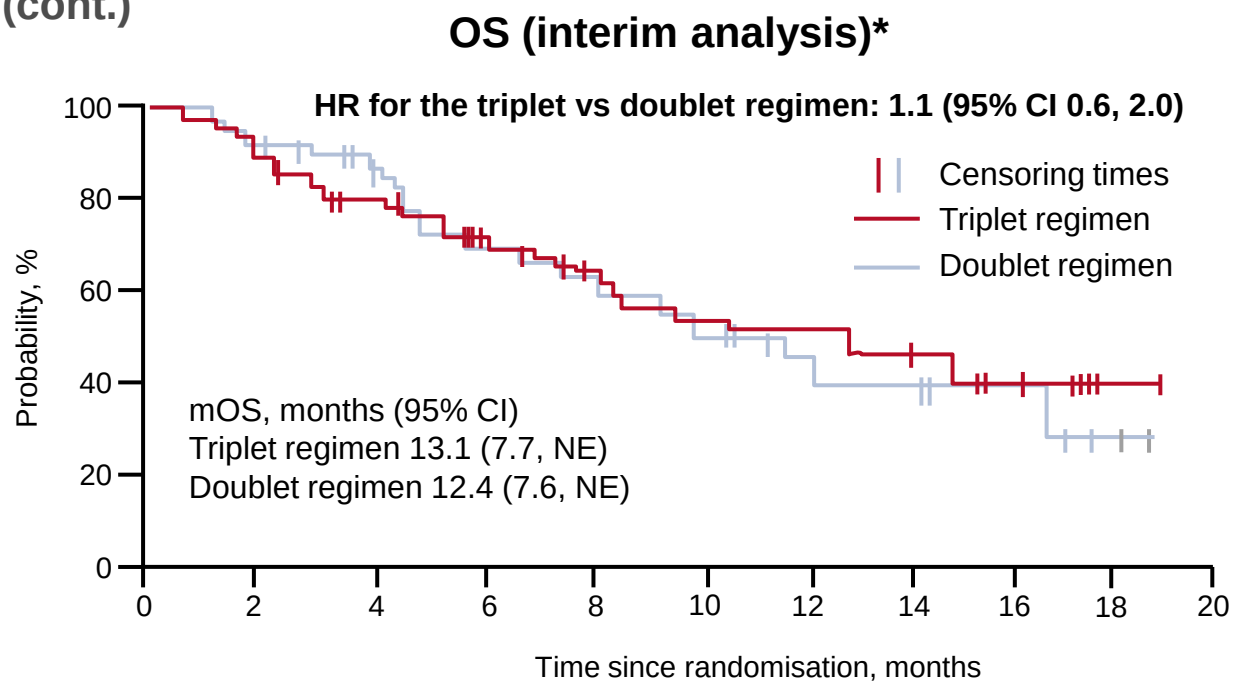
Key results



Tabernero et al. Ann Oncol 2016; 27 (suppl 2): abstr O-026

O-026: Combination of encorafenib and cetuximab with or without alpelisib in patients with advanced BRAF-mutant colorectal cancer (BRAFm CRC): Phase 2 results – Tabernero J, et al

Key results (cont.)



Response	Triplet regimen (n=52)	Doublet regimen (n=50)
ORR, % (95% CI)	27 (16, 41)	22 (12, 36)
DCR, % (95% CI)	85 (72, 93)	84 (71, 93)
mDOR, months (95% CI)	9.9 (2.8, 11.0)	4.6 (2.0, 6.7)

*With 44 events. NE, not estimable.

Tabernero et al. Ann Oncol 2016; 27 (suppl 2): abstr O-026

O-026: Combination of encorafenib and cetuximab with or without alpelisib in patients with advanced BRAF-mutant colorectal cancer (BRAFm CRC): Phase 2 results – Tabernero J, et al

Key results (cont.)

Grade 3–4 AEs in ≥10% of patients, %	Triplet regimen (n=52)	Doublet regimen (n=50)
Any	79	62
Abdominal pain	10	8
Hyperglycaemia	13	2
Anaemia	17	6
Increased lipase	8	22

Conclusions

- **Encorafenib + cetuximab ± alpelisib showed promising clinical activity in patients with advanced BRAF-mutant CRC, with improved survival vs historical data (not shown)**
- **Alpelisib added to encorafenib + cetuximab may improve PFS vs encorafenib + cetuximab alone**
- **Both regimens were generally well tolerated**
  - **AEs were more frequent with the triplet regimen**
- **Results of planned PK/PD and biomarker analyses may help interpret the efficacy and safety data**

Tabernero et al. Ann Oncol 2016; 27 (suppl 2): abstr O-026

O-027: A pivotal phase 3 Trial of MABp1 in advanced colorectal cancer – Hickish T, et al

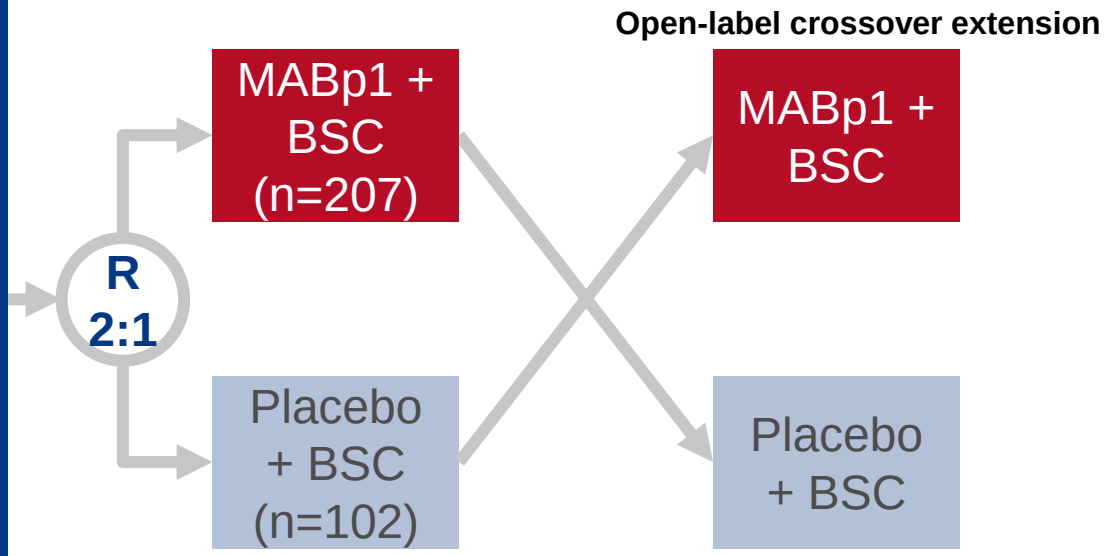
Study objective

- To evaluate a novel anti-IL-1 alpha antibody therapy in patients with advanced CRC and multiple symptoms known to inversely correlate with OS

Key patient inclusion criteria

- mRC
- Refractory to standard chemotherapy including Oxaliplatin and Irinotecan
- Other symptoms/functional impairment (pain, fatigue, anorexia, ECOG PS 1/2), weight loss or elevated systemic inflammation

(n=309)



PRIMARY ENDPOINT

- OR using dual-energy X-ray absorptiometry and EORTC-QLQC30

SECONDARY ENDPOINTS

- Pharmacodynamics measures known to co-relate with survival, safety, PD

Hickish et al. Ann Oncol 2016; 27 (suppl 2): abstr O-027

O-027: A pivotal phase 3 Trial of MABp1 in advanced colorectal cancer – Hickish T, et al

Key results

Primary endpoint	MABp1 (n=207)	Placebo (n=102)	p-value
Clinical response rate, %	33	19	0.0045

- Compared with placebo, relative risk SAEs reduced by 26% in MABp1-treated patients
- 5-fold improvement in platelet counts compared with placebo
- Higher incidence of SD of 53% in MABp1-treated patients

Objective measures	Non-responders	Responders	p-value
Lean body mass, kg	0.072	1.41	0.0007
Paraneoplastic thrombocytosis, 1000/mm^3	33.3	-2.0	0.0002
Systemic inflammation (serum IL-6), pg/mL	10.3	-3.38	0.0007

Hickish et al. Ann Oncol 2016; 27 (suppl 2): abstr O-027

O-027: A pivotal phase 3 Trial of MABp1 in advanced colorectal cancer – Hickish T, et al

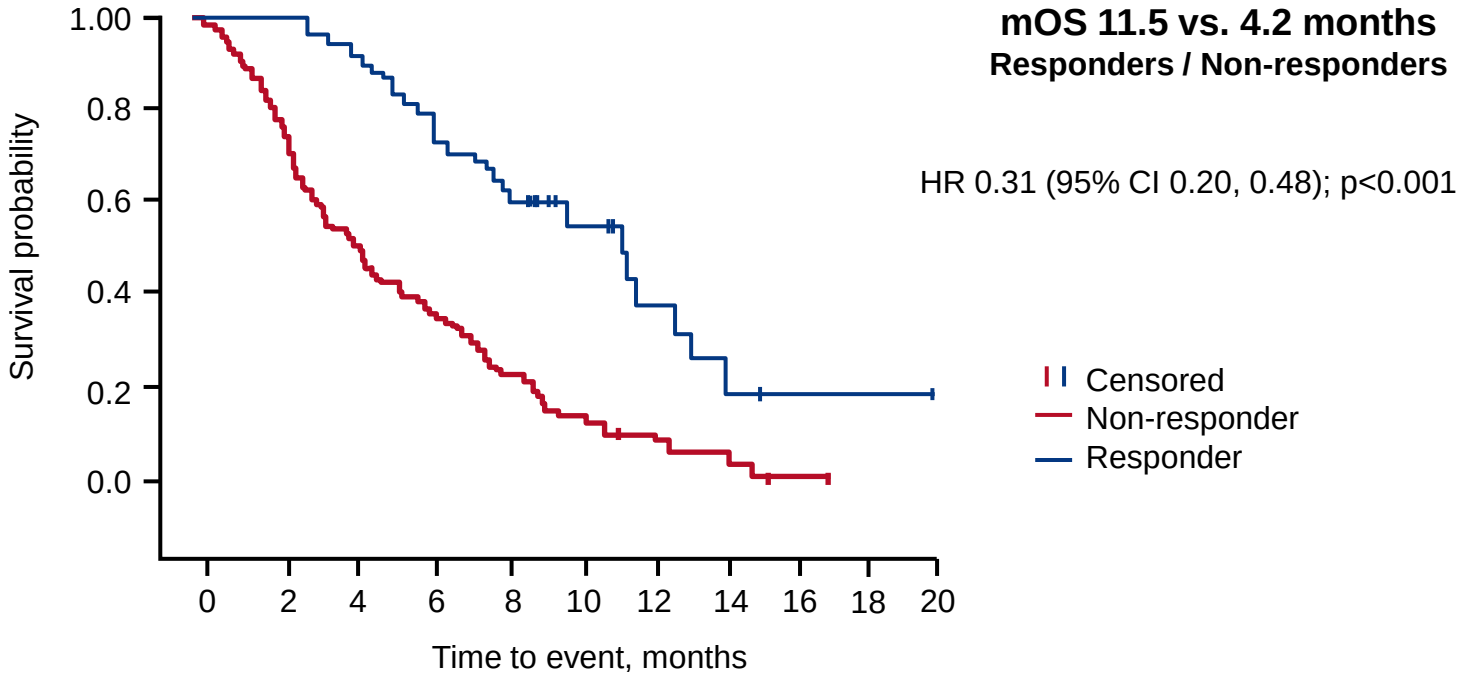
Key results (cont.)

Self-reported outcomes	Non-responders	Responders	p-value
Global QoL	-6.98	4.32	<0.001
Role function	-13.43	3.87	<0.001
Emotional function	-2.33	10.03	<0.001
Social function	-6.71	10.16	<0.001
Pain	16.19	-12.66	<0.001
Fatigue	13.08	-10.85	<0.001
Anorexia	17.34	-13.80	<0.001
SD (8 weeks), %	11.7	24.1	0.006
Incidence of SAEs (8 weeks), %	29.3	5.7	<0.01

Hickish et al. Ann Oncol 2016; 27 (suppl 2): abstr O-027

O-027: A pivotal phase 3 Trial of MABp1 in advanced colorectal cancer – Hickish T, et al

Key results (cont.)



Conclusion

- **Antibody therapy with MABp1 significantly improved clinical response rates, which translated into substantial benefit in OS**

Hickish et al. Ann Oncol 2016; 27 (suppl 2): abstr O-027

Colorectal Cancer

SCREENING, BIOMARKERS AND PROGNOSTIC MARKERS

O-012: Prognosis of lung metastases in patients with metastatic colorectal cancer: An ARCAD meta analysis – Henriques J, et al

Study objective

- To assess lung metastases prognostic for OS in patients with mCRC

Study design

- First-line treatment clinical trials involving lung metastases were selected from the ARCAD (Aide et Recherche en Cancérologie Digestive) database
- OS was evaluated based on date of randomisation and date of death due to any cause; association of OS with lung metastases was investigated in the general population, and in two subgroups – those with one metastatic site and those with at least two metastatic sites
- A propensity score approach was performed to assess heterogeneity in term of baseline characteristics between patients with and without lung metastases

Note: Based on data from abstract only

Henriques et al. Ann Oncol 2016; 27 (suppl 2): abstr O-012

O-012: Prognosis of lung metastases in patients with metastatic colorectal cancer: An ARCAD meta analysis – Henriques J, et al

Key results

	Patients, n	mOS, months	HR	95% CI	p-value
Overall population	17,102		0.85	0.82, 0.88	<0.0001
One metastatic site with lung metastases	955	24.9		22.7, 27.2	
			0.71	0.67, 0.75	<0.0001
One metastatic site without lung metastases	6399	20.0		18.7, 21.6	
Two or more metastatic sites with lung metastases	5564	15.3		14.8, 16.0	
			0.94	0.90. 0.97	0.001
Two or more metastatic sites without lung metastases	4184	14.4		13.8, 15.0	

Conclusions

- **In patients with mCRC, lung metastases were associated with a longer OS**
- **This protective effect appeared to be more important in patients who had one metastatic site only**

Note: Based on data from abstract only

Henriques et al. Ann Oncol 2016; 27 (suppl 2): abstr O-012

O-013: A new nomogram for estimating 12-weeks survival in patients (pts) with chemorefractory metastatic colorectal cancer (mCRC) – Pietrantonio F, et al

Study objective

- To develop a tool (a nomogram) to predict probability of death within 12 weeks from the date of an investigator's assessment of refractory metastatic colorectal cancer (mCRC)

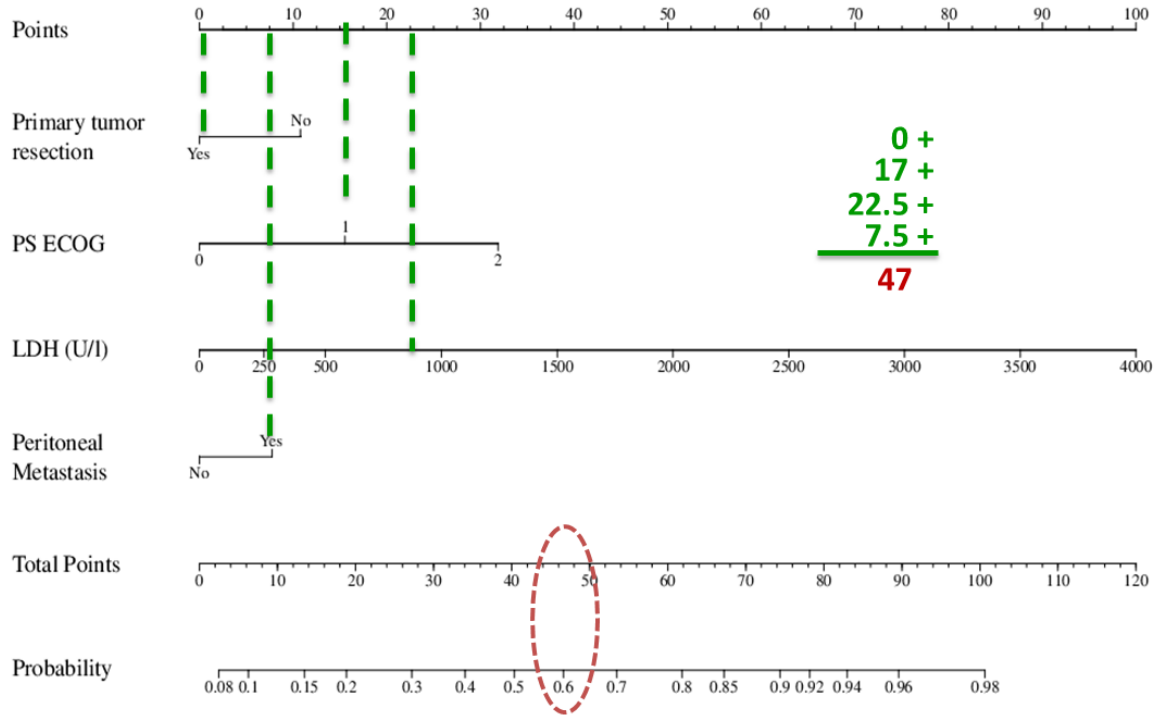
Study design

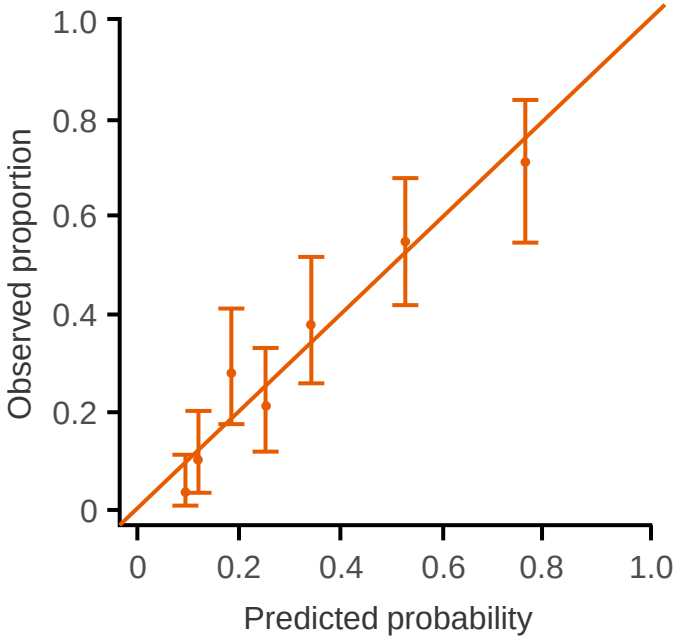
- Between 2001 and 2014, data from 515 patients with mCRC and ECOG PS ≤2 were collected at 8 Italian institutions
- Refractoriness was defined as progressive disease during or within 12 weeks following the last administration of approved standard therapies including fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab if (K)RAS wild type, or unacceptable toxicity
- A nomogram for predicting the probability of death within 12 weeks was built by processing the prognostic variables in a random Forest model
- The variables were selected based on the RI statistical significance, obtained by permuting the response variable and the final nomogram was built using a binary logistic model including only the significant variables
- The prognostic variables of interest were: sex, age, primary tumour site, tumour resection, synchronous metastases, number and sites of metastases, ECOG PS, carcinoembryonic antigen, platelets, leukocytes, haemoglobin, neutrophils/lymphocytes ratio, sodium, alkaline phosphatase, lactate dehydrogenase, time interval between metastatic diagnosis and refractoriness, number of previous treatment lines, and RAS and BRAF mutational status

Pietrantonio et al. Ann Oncol 2016; 27 (suppl 2): abstr O-013

O-013: A new nomogram for estimating 12-weeks survival in patients (pts) with chemorefractory metastatic colorectal cancer (mCRC) – Pietrantonio F, et al

Key results





- Internal calibration was optimal with a Hosmer-Lemeshow test (p=0.117)

Pietrantonio et al. Ann Oncol 2016; 27 (suppl 2): abstr O-013

O-013: A new nomogram for estimating 12-weeks survival in patients (pts) with chemorefractory metastatic colorectal cancer (mCRC) – Pietrantonio F, et al

Key results (cont.)

- Results obtained in the developing set (n=411) were reproduced in the validation set (n=359)

	Developing set (n=411)	Validation set (n=359)
Hosmer-Lemeshow test	p=0.117	p=0.0001
Harrell C index (95% CI)	0.778 (0.730, 0.824)	0.722 (0.717, 0.824)

Conclusions

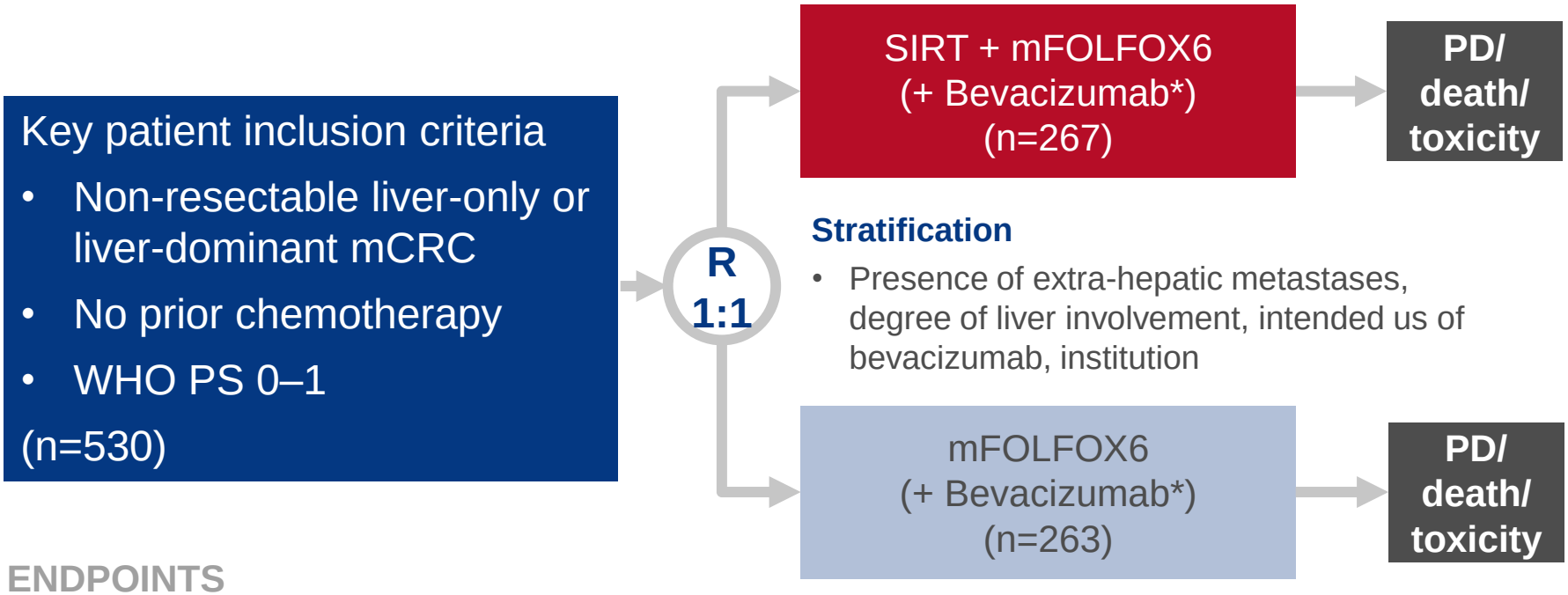
- **Four patient characteristics/clinical parameters (ECOG PS, resection, lactate dehydrogenase and peritoneal metastases) can be used to predict the probability of death within 12 weeks in patients with refractory mCRC**
- **The model developed is reliable and the results obtained in the developing set have been adequately reproduced in the validating set**
- **This nomogram may significantly improve the selection of later lines of therapy for patients with mCRC in the daily clinical practice**
  - **It may also assist researchers in determining life expectancy to ensure consistency of enrolment in early phase clinical trials**

Pietrantonio et al. Ann Oncol 2016; 27 (suppl 2): abstr O-013

O-014: Evaluation of depth of response within a volumetric model in patients with metastatic colorectal cancer: Results of the SIRFLOX study – Heinemann V, et al

Study objective

- To evaluate the depth of response with 1L mFOLFOX6 (+ bevacizumab at investigator's discretion) + SIRT using Y-90 resin microspheres compared with mFOLFOX6 (± bevacizumab) in patients with mCRC



ENDPOINTS

- Depth of response using novel volumetric model; association between tumour shrinkage with baseline tumour burden

SIRT, selective internal radiation therapy;
*investigator's discretion.

Heinemann et al. Ann Oncol 2016; 27 (suppl 2): abstr O-014

O-014: Evaluation of depth of response within a volumetric model in patients with metastatic colorectal cancer: Results of the SIRFLOX study – Heinemann V, et al

Key results

	SIRT + mFOLFOX6 (± bevacizumab) (n=251)	mFOLFOX6 (± bevacizumab) (n=235)	p-value
All patients			
Median baseline volume, cm^3 (IQR)	219.4 (451.7)	166.6 (427.7)	0.421
Mean depth of response, % (SD)	-75.0 (61.3)	-67.8 (82.9)	0.039
Median time to nadir, days (IQR)	266 (238)	206 (187)	<0.001
Tumour burden ≤12%			
Median baseline volume, cm^3 (IQR)	61.3	68.4 (87.6)	0.912
Mean depth of response, % (SD)	-72.5 (82.3)	-80.6 (34.0)	0.763
Median time to nadir, days (IQR)	243.5 (211)	220 (193)	0.152
Median hepatic PFS, months	15.1	12.2	0.112
Tumour burden >12%			
Median baseline volume, cm^3 (IQR)	512.0 (713.7)	439.9 (590.1)	0.188
Mean depth of response, % (SD)	-77.5 (29.2)	-57.2 (109.2)	0.003
Median time to nadir, days (IQR)	298 (246)	196 (176)	<0.001
Median hepatic PFS, months	27.2	13.1	0.003

IQR, interquartile range; SD, standard deviation.

Heinemann et al. Ann Oncol 2016; 27 (suppl 2): abstr O-014

O-014: Evaluation of depth of response within a volumetric model in patients with metastatic colorectal cancer: Results of the SIRFLOX study – Heinemann V, et al

Conclusions

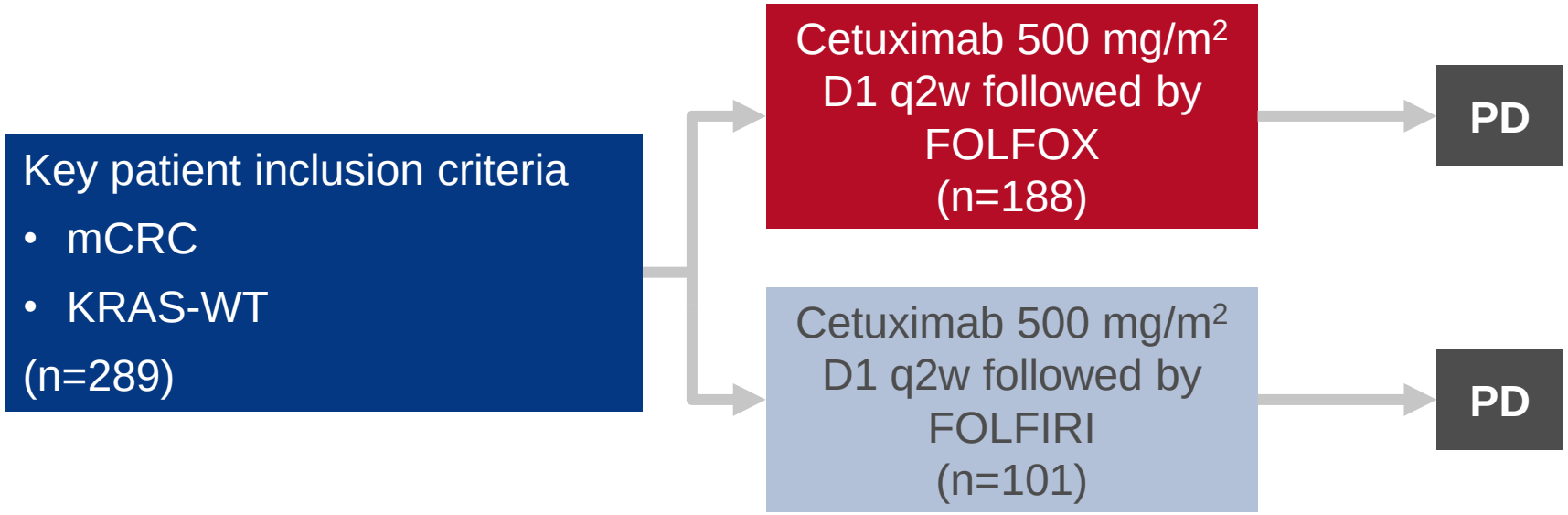
- **Hepatic depth of response was significantly greater in patients receiving SIRT using Y-90 microspheres compared with chemotherapy**
- **Patients with a baseline tumour burden of >12% had a significantly longer PFS in the liver as first event with SIRT, while those with tumour burden ≤12% had a greater impact on CR rate**
- **This may provide a useful predictor of PFS in the liver**

Heinemann et al. Ann Oncol 2016; 27 (suppl 2): abstr O-014

O-015: Association between depth of response (DpR) and survival outcomes in RAS-wild-type (wt) patients with metastatic colorectal cancer (mCRC) receiving first-line FOLFOX or FOLFIRI plus cetuximab once-every-2-weeks in the APEC study – Cheng A-L, et al

Study objective

- To evaluate the association between depth of response and PFS and OS in the *RAS*-WT population from the APEC study



PRIMARY ENDPOINT(S)

- Depth of response (defined as the extent of maximal tumour shrinkage)

SECONDARY ENDPOINTS

- PFS, OS, ORR, safety

Cheng et al. Ann Oncol 2016; 27 (suppl 2): abstr O-015

O-015: Association between depth of response (DpR) and survival outcomes in RAS-wild-type (wt) patients with metastatic colorectal cancer (mCRC) receiving first-line FOLFOX or FOLFIRI plus cetuximab once-every-2-weeks in the APEC study – Cheng A-L, et al

Key results

	Overall	Cetuximab + FOLFOX	Cetuximab + FOLFIRI
ORR, %	64.7	62.7	68.4
mPFS, months	13.0	13.3	12.8
mOS, months	28.4	27.8	28.7
Median depth of response, % (IQR)	62.2 (39.1–80.0)	62.2 (40.0–80.7)	62.5 (38.1–79.0)
Median time to tumour size nadir, months (95% CI)	5.9 (5.6, 7.6)	5.9 (5.6, 7.6)	7.4 (5.1, 9.2)

Cheng et al. Ann Oncol 2016; 27 (suppl 2): abstr O-015

O-015: Association between depth of response (DpR) and survival outcomes in RAS-wild-type (wt) patients with metastatic colorectal cancer (mCRC) receiving first-line FOLFOX or FOLFIRI plus cetuximab once-every-2-weeks in the APEC study – Cheng A-L, et al

Conclusions

- **These findings compare favourably to earlier subgroup analyses of analogous pivotal studies involving chemotherapy + weekly cetuximab**
- **Depth of response seems to be a sensitive indicator of response and is likely to be associated with PFS and OS**
- **The phase 2 APEC study suggests that patients with *RAS*-WT mCRC may benefit from continuation treatment with FOLFOX or FOLFIRI + cetuximab rather than having treatment breaks to achieve maximum tumour reduction**

Cheng et al. Ann Oncol 2016; 27 (suppl 2): abstr O-015

O-016: A prognostic marker for colorectal cancer: Combining analyses of ploidy and stroma – Fotheringham S, et al

Study objective

- To evaluate the prognostic value of DNA ploidy and tumour stroma in patients with early stage CRC

Study design

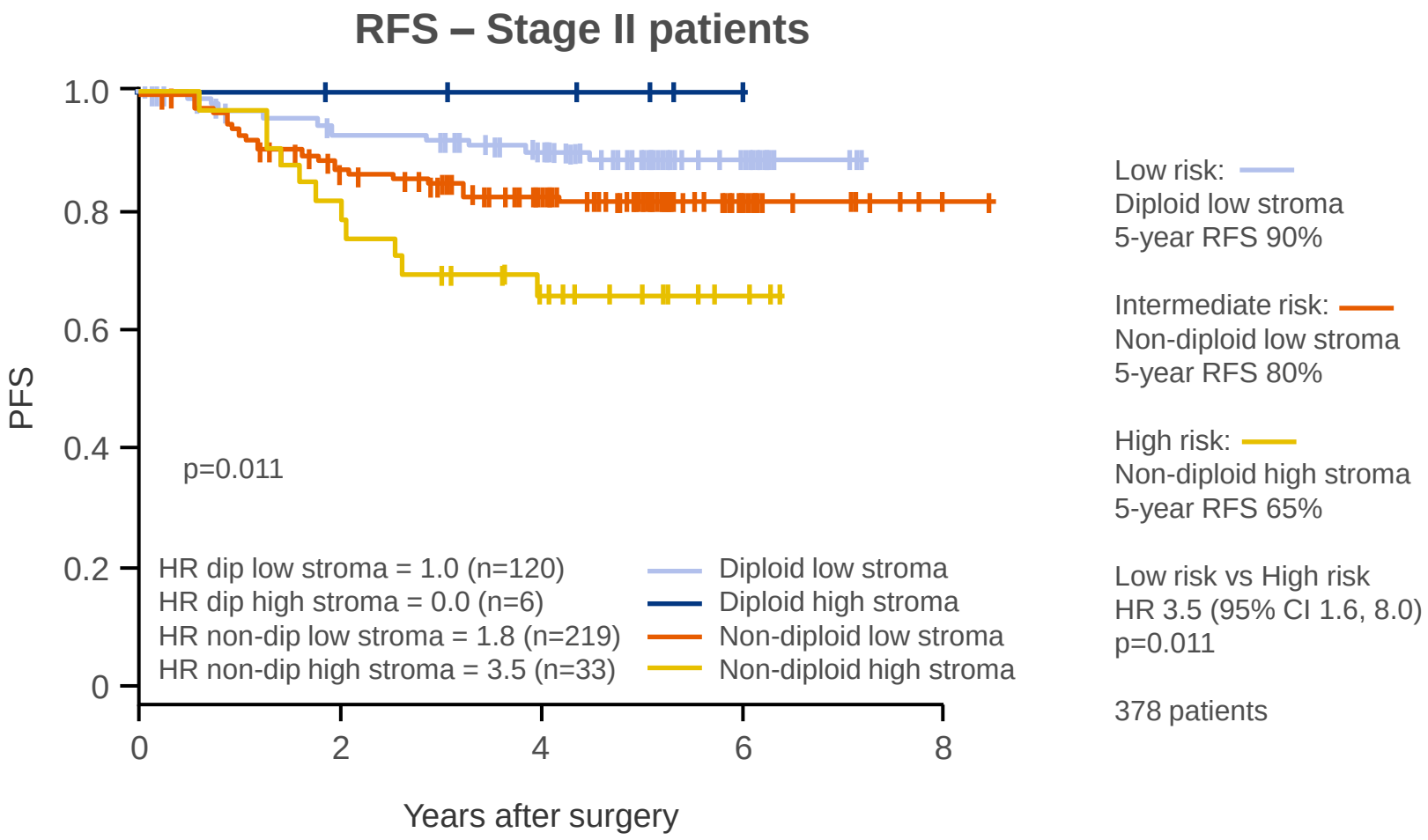
- Analysis of DNA content (ploidy) and stroma-tumour fraction was performed using automated digital imaging systems on FFPE tissue samples from 1074 patients enrolled in the QUASAR2 trial*
- Key inclusion criteria:
  - Stage III or high risk Stage II patients with CRC
  - Complete resection with no evidence of residual disease
- *Ploidy digital analyses*
  - Sample classified as diploid (low risk) when DNA content 2N
  - Sample classified as tetraploid (non-diploid; high risk) when DNA content 4N or higher
- *Stroma digital analyses*
  - The percentage of stroma tissue was determined by H&E staining
    - Stroma high: ≥50% (high risk)
    - Stroma low: <50% (low risk)

*Explored adjuvant capecitabine + bevacizumab.

Fotheringham et al. Ann Oncol 2016; 27 (suppl 2): abstr O-016

O-016: A prognostic marker for colorectal cancer: Combining analyses of ploidy and stroma – Fotheringham S, et al

Key results (cont.)



Fotheringham et al. Ann Oncol 2016; 27 (suppl 2): abstr O-016

O-016: A prognostic marker for colorectal cancer: Combining analyses of ploidy and stroma – Fotheringham S, et al

Conclusions

- **High risk Stage II patients with CRC can be divided into risk groups based on a combination of measurements of DNA ploidy and stroma**
- **Automated digital pathology could facilitate the adoption of biomarker analyses into patient treatment strategies**
- **Additional trial samples (n=2500) will confirm results in a larger patient population**
- **The ultimate aim is to develop a prognostic test that can be offered to patients to help inform the use of adjuvant treatment after surgery**

Fotheringham et al. Ann Oncol 2016; 27 (suppl 2): abstr O-016

O-017: Can single nucleotide variants in TGFBR1 and SMAD7 modify colorectal screening recommendations? – Mahon GAT, et al

Study objective

- To investigate the role of blood-based genetic markers in CRC pre-screening

Study design

- Blood samples were taken from 187 patients with CRC and 94 healthy controls from a European Caucasian population
- After gDNA extraction, selected sequences were amplified by PCR followed by melting curve analysis
- The SNP status for TGFBR1 (rs334348) and SMAD7 (rs4939827) was determined for each subject
- The association between allele frequency for the various SNPs and CRC status was evaluated by logistic regression

PRIMARY ENDPOINT(S)

- An index was developed to distinguish high-risk from low-risk subjects

SECONDARY ENDPOINTS

- Various thresholds of the index were investigated to optimise the economic performance of the test for various relative costs of false positives or false negatives

Note: Based on data from abstract only

Mahon et al. Ann Oncol 2016; 27 (suppl 2): abstr O-017

O-017: Can single nucleotide variants in TGFBR1 and SMAD7 modify colorectal screening recommendations? – Mahon GAT, et al

Key results

- A highly significant additive association between the G allele and colorectal cancer for TGFBR1 was observed
  - Both the AG (heterozygosity) and GG (homozygosity) genotypes were associated with progressively greater risk relative to the AA genotype (OR 3.43; p<0.00005)
  - There was no further significant effect for dominance (OR 0.70; p=0.216)
- Although there was no significant additive effect, i.e. the risks associated with the CC and TT genotypes were similar (OR 1.00; p=0.987) for SMAD7, there was a significant dominance effect and the CT heterozygote was associated with a lower risk (OR 0.50; p=0.014)
- Sensitivity was calculated as the ratio of test-positive cases to total cases, and specificity as the ratio of test-negative controls to total controls
- The trade-off between specificity and sensitivity was explored by ROC analysis
  - When sensitivity was 0.33, specificity was 0.96; when sensitivity was 0.65, specificity was also 0.65; and when sensitivity was 0.87, specificity was 0.33

Note: Based on data from abstract only

ROC, receiver operating characteristic.

Mahon et al. Ann Oncol 2016; 27 (suppl 2): abstr O-017

O-017: Can single nucleotide variants in TGFBR1 and SMAD7 modify colorectal screening recommendations? – Mahon GAT, et al

Conclusions

- **These results suggest that by being able to predict a clearly higher risk group, a repeat colonoscopy could be performed earlier than stated by guidelines for these individuals**
- **This inexpensive germline test, which only needs to be performed once, can be carried out at any age, including much earlier than is recommended by current guidelines**

Mahon et al. Ann Oncol 2016; 27 (suppl 2): abstr O-017

O-018: Clinical application of targeted next generation sequencing for colorectal cancer patients: A multicentric Belgian experience – Fontanges Q, et al

Study objective

- To examine 3 years of clinical experience of using NGS for assessing CRC-associated molecular alterations

Study design

- Mutations in 22 cancer-related genes can be detected using the Ion Torrent AmpliSeq colon/lung cancer panel; this was used prospectively in clinical practice via the BELAC ISO 15189 accredited method
- DNA from FFPE material of 741 colorectal tumours, including primary tumours and metastasis, was obtained from 14 different institutions, and subjected to targeted NGS using the Ion Torrent Personal Genome Machine

Fontanges et al. Ann Oncol 2016; 27 (suppl 2): abstr O-018

O-018: Clinical application of targeted next generation sequencing for colorectal cancer patients: A multicentric Belgian experience – Fontanges Q, et al

Key results

- Mean (range) number of mutations per tumour was 1.6 (0–5)
- At least one mutation was observed in 650 (89.4%) samples
  - The most frequent were TP53 (61.8%) and KRAS (46.1%)

Genes	Samples with mutations, %	
	This study	cBioPortal database
KRAS	46.1	42–55
NRAS	4.4	2.8–9
BRAF	10.7	4.3–9.9
PIK3CA	13.8	14.8–30.6
ERBB2 Mutation Amplification	 0.4 0.3	 2.8–4 3.1
AKT1	0.1	0.9–1.4

Fontanges et al. Ann Oncol 2016; 27 (suppl 2): abstr O-018

O-018: Clinical application of targeted next generation sequencing for colorectal cancer patients: A multicentric Belgian experience – Fontanges Q, et al

Conclusions

- **The results demonstrate that the AmpliSeq colon/lung cancer panel can be used routinely in clinical practice to provide reliable clinically relevant information for patients with colorectal cancer, which can used to facilitate therapeutic decisions in these patients**

Fontanges et al. Ann Oncol 2016; 27 (suppl 2): abstr O-018

O-024: Circulating tumor DNA extended RAS mutational analysis as a surrogate of mutational status of tumor samples in metastatic colorectal cancer and its impact on patient selection for anti-EGFR therapy – Grasselli J, et al

Study objective

- To assess the effectiveness of RAS status testing using ctDNA vs SoC to establish eligibility for anti-EGFR therapy in patients with mCRC

Study design

- RAS status was assessed using BEAMing assays on plasma and FFPE tumour tissue or SoC RAS testing using qPCR or pyrosequencing on FFPE tumour tissue, in 147 patients with mCRC

	SoC tumour	BEAMing tumour	BEAMing plasma
RAS testing sensitivity, %	1–5	1	0.02–0.04

PRIMARY ENDPOINT

- Concordance rate for RAS testing

SECONDARY ENDPOINT

- PFS, OS

Grasselli et al. Ann Oncol 2016; 27 (suppl 2): abstr O-024

O-024: Circulating tumor DNA extended RAS mutational analysis as a surrogate of mutational status of tumor samples in metastatic colorectal cancer and its impact on patient selection for anti-EGFR therapy – Grasselli J, et al

Key results

Concordance analysis		BEAMing plasma	
		RAS MUT	WT
SoC tumour	RAS MUT	49	5
	WT	10	83
	Total	59	88

- Overall concordance: 89.8%; Kappa index 0.81 (95% CI 0.71, 0.90)
  - RAS mutant: 40.1% with BEAMing plasma vs 36.7% with SoC tumour

Discordance analysis: mutations detected only in tumour					
SoC tumour	BEAMing plasma	BEAMing tumour	Codon	Prior CT lines	Possible explanation
MUT	WT	MUT	KRAS G12	0	Low tissue burden*
MUT	WT	MUT	KRAS G12	2	
MUT	WT	MUT	KRAS G12	0	ctDNA shedding
MUT	WT	MUT	NRAS G13	0	
MUT	WT	WT	KRAS Q61	0	Molecular heterogeneity

*Few hepatic metastases <1 cm, 3 small peritoneal implants.

Grasselli et al. Ann Oncol 2016; 27 (suppl 2): abstr O-024

O-024: Circulating tumor DNA extended RAS mutational analysis as a surrogate of mutational status of tumor samples in metastatic colorectal cancer and its impact on patient selection for anti-EGFR therapy – Grasselli J, et al

Key results (cont.)

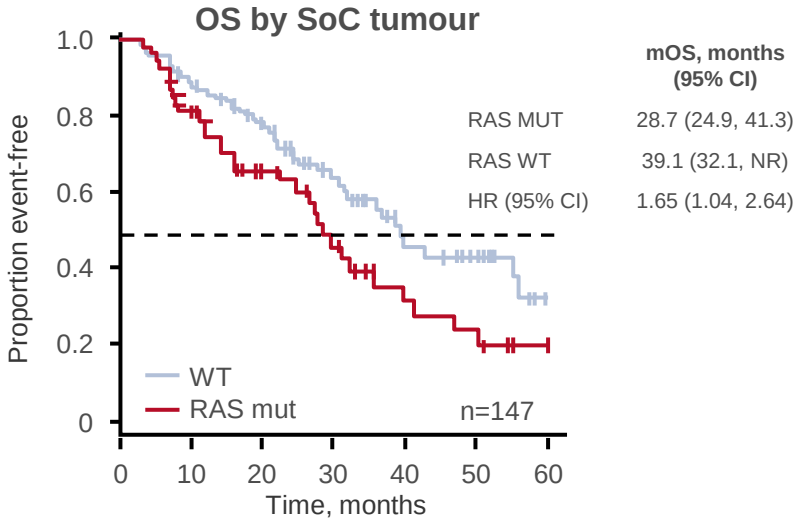
Discordance analysis: mutations detected only in plasma					
SoC tumour	BEAMing plasma	BEAMing tumour	Codon	Prior CT lines	Possible explanation
WT	MUT	MUT	KRAS G12	2	SoC sensitivity
WT	MUT	MUT	KRAS A146	0	
WT	MUT	MUT	KRAS A146	0	
WT	MUT	MUT	NRAS Q61	1	
WT	MUT	MUT	NRAS Q61	0	
WT	MUT	WT	KRAS G12	1	Molecular heterogeneity
WT	MUT	WT	KRAS G12	0	
WT	MUT	NA	KRAS Q61	2	
WT	MUT	WT	KRAS Q61	0	
WT	MUT	WT	NRAS Q61	1	

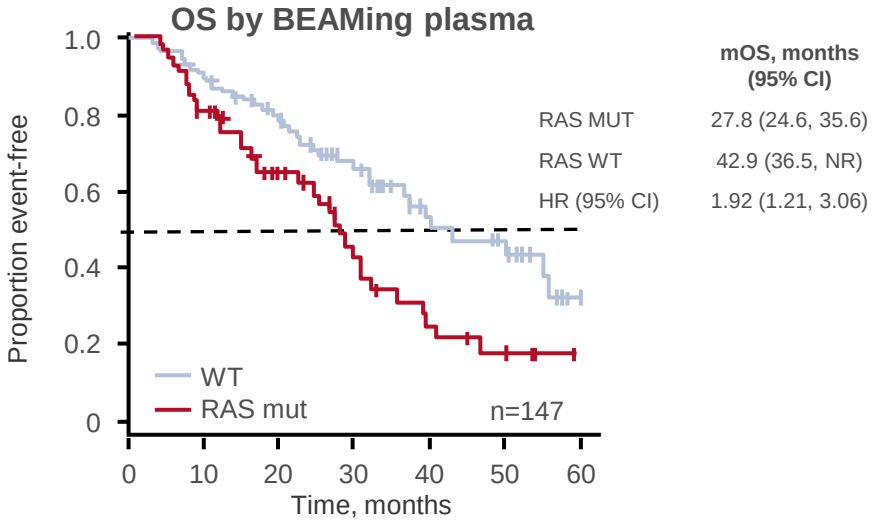
2L + 3L RAS WT	SoC tumour (n=51)	BEAMing plasma (n=47)
mPFS, months (95% CI)	8.7 (6.43, 10.23)	8.7 (6.77, 11.27)

Grasselli et al. Ann Oncol 2016; 27 (suppl 2): abstr O-024

O-024: Circulating tumor DNA extended RAS mutational analysis as a surrogate of mutational status of tumor samples in metastatic colorectal cancer and its impact on patient selection for anti-EGFR therapy – Grasselli J, et al

Key results (cont.)





Conclusions

- A concordance rate of 89.8% was achieved between ctDNA RAS testing and standard tissue testing in patients with mCRC eligible for anti-EGFR therapies
- Plasma RAS testing by BEAMing captures a population responding to anti-EGFR therapy with the same precision as that of SoC RAS testing in tumours
- Discordant samples could be explained by technical sensitivity, temporal or spatial heterogeneity and low tumour burden
- The feasibility and practicability of ctDNA analysis may significantly influence clinical practice for anti-EGFR treatment selection

NR, not reached.

Grasselli et al. Ann Oncol 2016; 27 (suppl 2): abstr O-024

Colorectal Cancer

COLON CANCER

O-010: An international phase III randomized, non-inferiority trial comparing 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: Compliance and safety of the phase III Japanese ACHIEVE trial – Eto T, et al

Study objective

- To evaluate the compliance and safety of the phase 3 ACHIEVE trial

Study design

- Patients with Stage III colon cancer (n=1313)
- Patients received 3 months (n=651) or 6 months (n=650) of oxaliplatin-based adjuvant treatment (mFOLFOX6 or XELOX)

Note: Based on data from abstract only

Eto et al. Ann Oncol 2016; 27 (suppl 2): abstr O-010

O-010: An international phase III randomized, non-inferiority trial comparing 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: Compliance and safety of the phase III Japanese ACHIEVE trial – Eto T, et al

Key results

	3 months		6 months	
	mFOLFOX6	XELOX	mFOLFOX6	XELOX
Compliance, %	87.6	69.6	85.9	58.7
Permanent discontinuation due to toxicity, %	11.5		28.7	
Grade 3/4 AEs, %	28.7		42.8	
Grade ≥2 neuropathy, %	13.6		36.5	

Grade 3/4 AEs, %	mFOLFOX6	XELOX
Neutropenia	30.4	12.4
Anorexia	1.9	5.1
Diarrhoea	1.3	5.5

Note: Based on data from abstract only

Eto et al. Ann Oncol 2016; 27 (suppl 2): abstr O-010

O-010: An international phase III randomized, non-inferiority trial comparing 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: Compliance and safety of the phase III Japanese ACHIEVE trial – Eto T, et al

Conclusions

- **mFOLFOX6 and XELOX were both safe and well tolerated**
- **There was, however, a difference in the grade 3–4 toxicities based on the 5FU backbone with patients in the 6-month arm having significantly higher rates than the 3-month arm**
- **In addition, compliance was better in the 3-month arm**

Note: Based on data from abstract only

Eto et al. Ann Oncol 2016; 27 (suppl 2): abstr O-010

Colorectal Cancer

RECTAL CANCER

O-019: Outcome results of STAR-01, a randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer – Lonardi S, et al

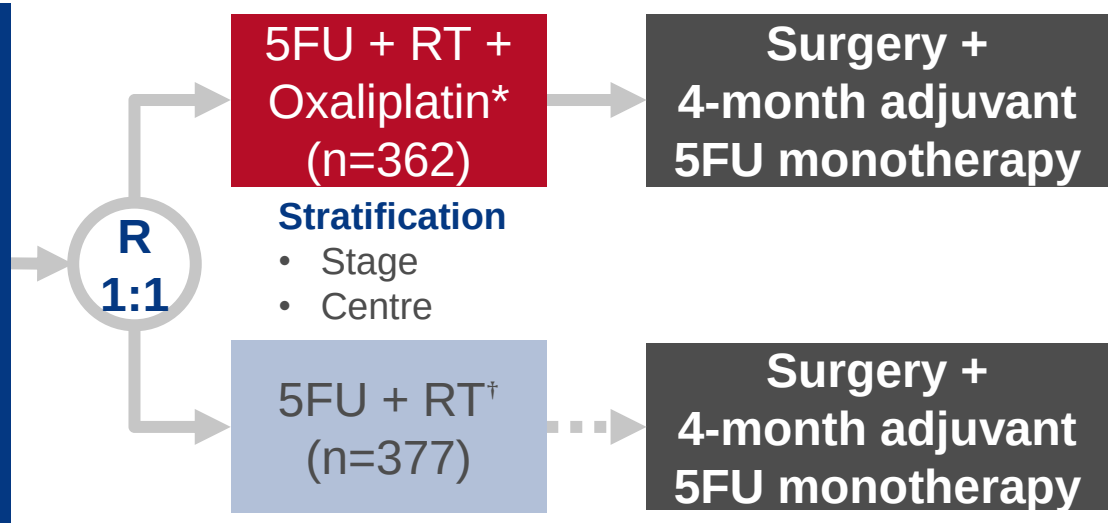
Study objective

- To investigate the effect of adding oxaliplatin to preoperative 5FU-based pelvic chemoradiation (RT) in patients with resectable locally advanced rectal cancer (LARC)

Key patient inclusion criteria

- Resectable, biopsy-proven rectal adenocarcinoma within 12 cm from the anal verge with radiological evidence of perirectal fat or nodal involvement

(n=747)



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- Cumulative incidence of distant metastasis

*Infused 5FU (225 mg/m^2/day) + external-beam pelvic radiation (50.4 Gy in 28 daily fractions) + weekly oxaliplatin (60 mg/m^2 x 6);

†Infused 5FU (225 mg/m^2/day) + external-beam pelvic radiation (50.4 Gy in 28 daily fractions).

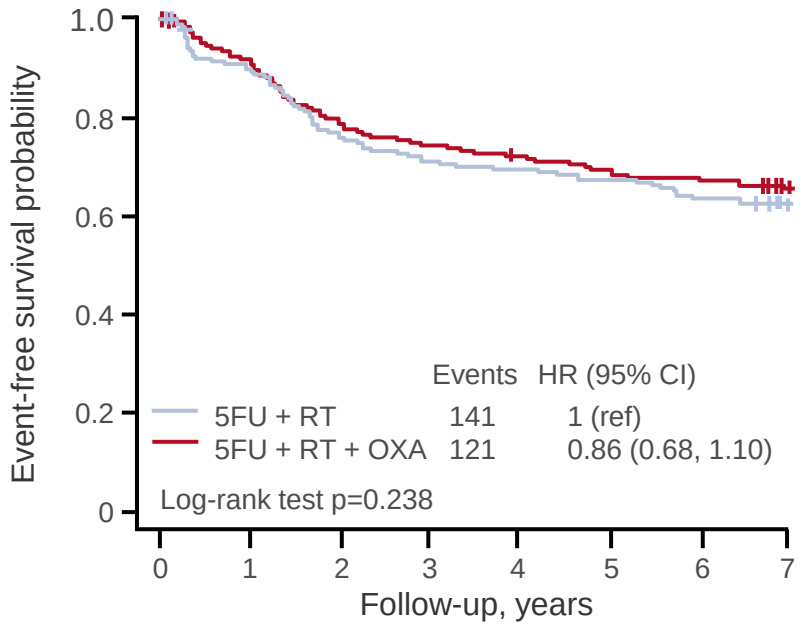
Lonardi et al. Ann Oncol 2016; 27 (suppl 2): abstr O-019

O-019: Outcome results of STAR-01, a randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer – Lonardi S, et al

Key results

- As of 31 December 2015, there were 248 deaths, median follow-up was 8.9 years (interquartile range 8.1–9.9) and 94.3% of patients had received ≥90% of expected follow-up

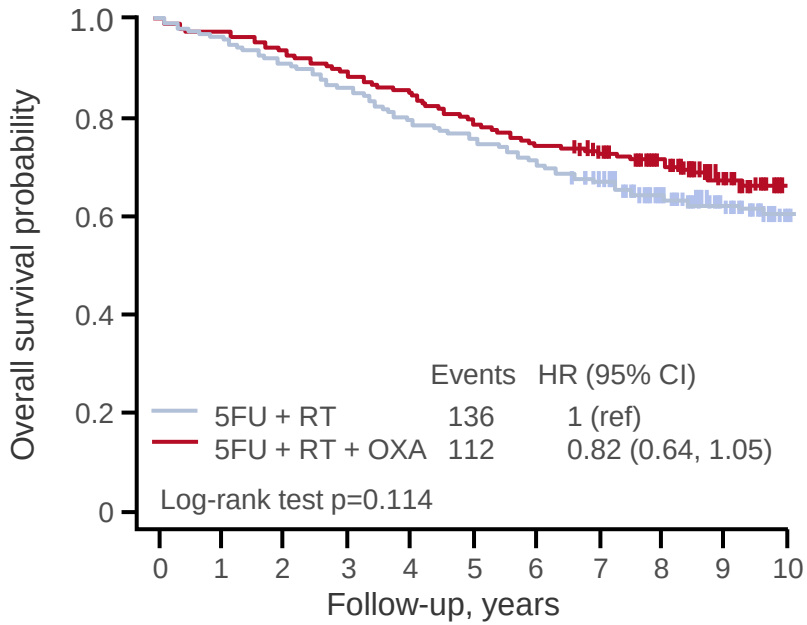
Event-free survival



No. at risk

5FU + RT	377	329	278	262	253	246	234	220
5FU + RT + OXA	362	325	280	266	257	247	238	230

OS



No. at risk

5FU + RT	377	364	345	326	302	290	271	248	184	114	50
5FU + RT + OXA	362	352	339	325	311	291	274	261	210	116	53

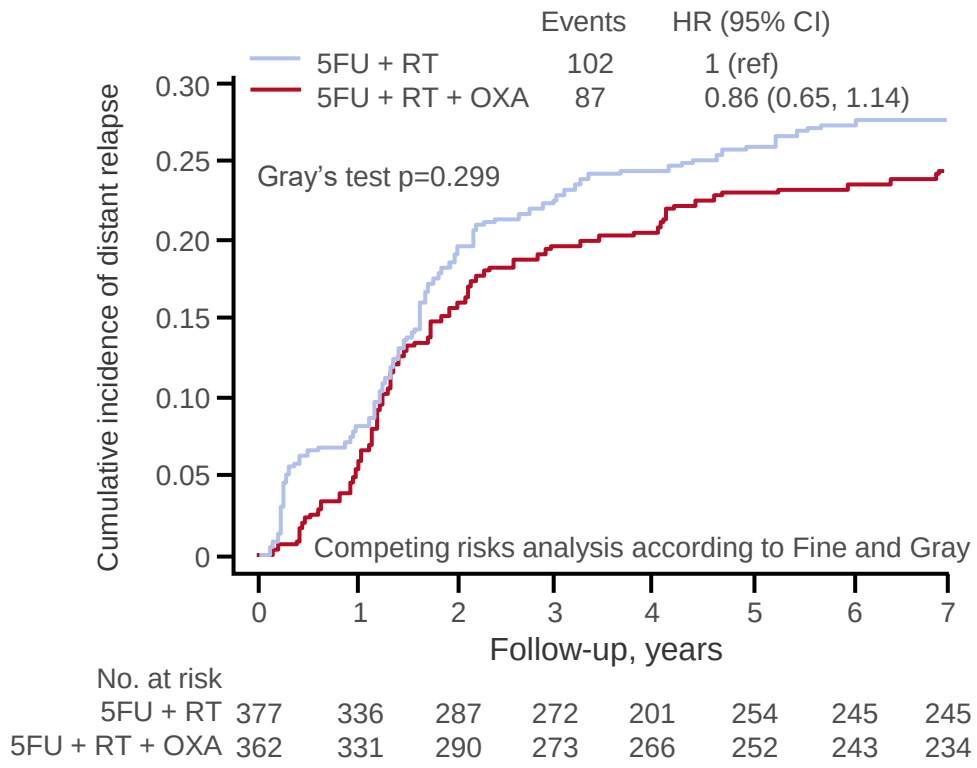
Lonardi et al. Ann Oncol 2016; 27 (suppl 2): abstr O-019

O-019: Outcome results of STAR-01, a randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer – Lonardi S, et al

Key results (cont.)

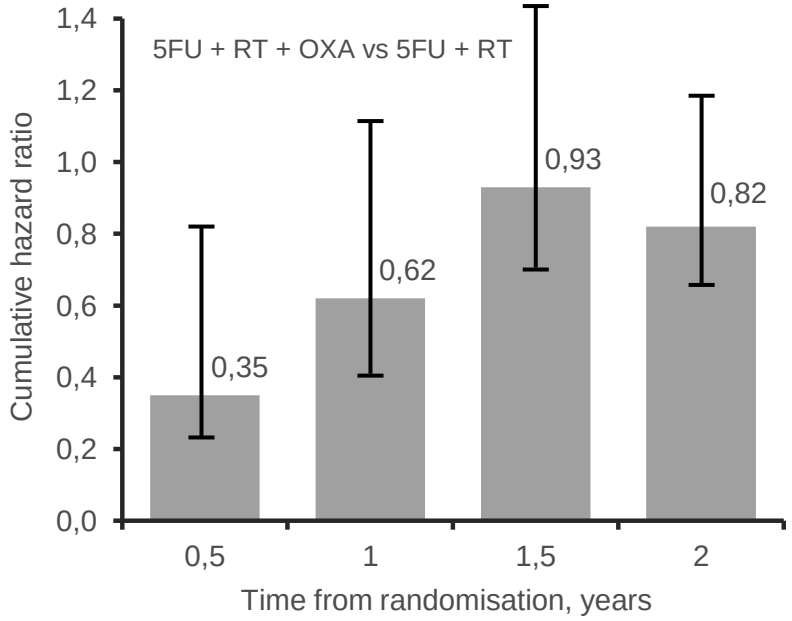
- Significantly more patients in the 5FU + RT group had metastases at time of surgery (n=16, 4.2%) than patients in the 5FU + RT + oxaliplatin group (n=2, 0.5%; p=0.001)

Distant metastases – cumulative incidence



Distant metastases – time course of HR

Proportional subdistribution hazards model for competing risks analysis according to Fine and Gray



Lonardi et al. Ann Oncol 2016; 27 (suppl 2): abstr O-019

O-019: Outcome results of STAR-01, a randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer – Lonardi S, et al

Key results (cont.)

Cause of death, n (%)	5FU + RT	5FU + RT + oxaliplatin
Disease	92 (24.4)	77 (21.3)
Toxicity	1 (0.2)	2 (0.5)
Other	29 (7.7)	24 (6.6)
Unknown	14 (3.7)	9 (2.5)
Overall	136 (36.1)	112 (30.9)

Conclusions

- **These results indicate a small and sustained impact on the development of distant metastases; although not statistically significant, these results support the study hypothesis of the systemic effect of weekly oxaliplatin concomitant to preoperative chemoradiation**
- **This difference is paralleled by a smaller than planned reduction in the relative risk of death with a long-term benefit of 3% (5-year) to 6% (8-year)**

Lonardi et al. Ann Oncol 2016; 27 (suppl 2): abstr O-019

O-020: Impact of surgical site experience on treatment outcomes of fixed-cT3 and cT4 rectal cancer patients in phase III study comparing preoperative radiochemotherapy and short-course radiotherapy with consolidation chemotherapy (Polish-II study) – Wyrwicz L, et al

Study objective

- To investigate if the experience of surgical centre has any influence on the outcomes of conventional radiotherapy in patients with locally advanced rectal cancer

Key patient inclusion criteria

- Locally advanced rectal cancer
- Responding/stable disease after 3 cycles GemCap*
- WHO PS 0–2
- Maximum tumour diameter 7 cm

(n=545)

R 1:1

SCRTx arm
Short-course radiotherapy (5 Gy/day for 5 days) + consolidation chemotherapy* (n=261)

PD

Stratification

- Number of surgeries (high [25–114] vs low [1–19]volume centres)

CRTx arm
Conventional radiochemotherapy + Oxaliplatin qw (n=254)

PD

ENDPOINTS

- RFS, OS (reported previously)

Note: Based on data from abstract only

*3 cycles of 5FU/leucovorin + oxaliplatin in FOLFOX4 regimen.

Wyrwicz et al. Ann Oncol 2016; 27 (suppl 2): abstr O-020

O-020: Impact of surgical site experience on treatment outcomes of fixed-cT3 and cT4 rectal cancer patients in phase III study comparing preoperative radiochemotherapy and short-course radiotherapy with consolidation chemotherapy (Polish-II study) – Wyrwicz L, et al

Key results

- R0 resection rate was improved in high volume vs low volume centres (80% vs 72%)
- After 3 years of follow-up, OS was significantly higher in those receiving SCRTx (78%) than those receiving CRTx (64%; $p<0.05$)
- Proportion of patients alive after 5 years was 75% and 60% in those receiving SCRTx and CRTx, respectively
- No differences in R0 resection rates ($p=0.54$) or OS ($p=0.718$) were observed in patients treated in low volume centres

Note: Based on data from abstract only

Wyrwicz et al. Ann Oncol 2016; 27 (suppl 2): abstr O-020

O-020: Impact of surgical site experience on treatment outcomes of fixed-cT3 and cT4 rectal cancer patients in phase III study comparing preoperative radiochemotherapy and short-course radiotherapy with consolidation chemotherapy (Polish-II study) – Wyrwicz L, et al

Conclusions

- **The combination of short-course radiotherapy + consolidation chemotherapy is an effective treatment in patients with locally advanced rectal cancer**
- **In experienced colorectal surgery centres, it improves survival compared with preoperative chemoradiation**
- **However, a longer follow-up is required to confirm the higher survival rates without significant improvement in the local control**

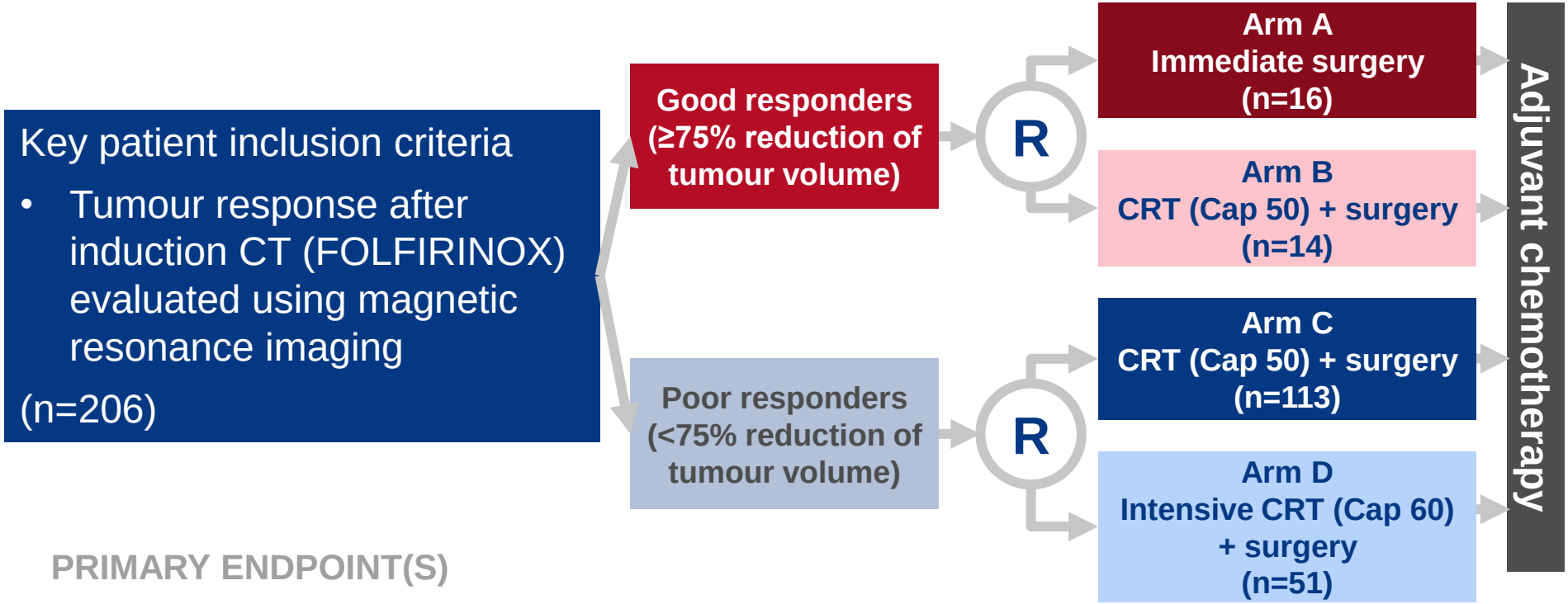
Note: Based on data from abstract only

Wyrwicz et al. Ann Oncol 2016; 27 (suppl 2): abstr O-020

O-021: Tailored strategy for locally-advanced rectal carcinoma: Preliminary results of a phase II multicenter trial (GRECCAR 4) – Rouanet P, et al

Study objective

- To evaluate the feasibility of a tailored management of locally advanced rectal carcinoma (LARC) according to the early tumour response to a short and intensive induction triplet chemotherapy, while respecting a minimal 90% R0 resection rate in all arms



PRIMARY ENDPOINT(S)

- Safety, efficacy

Cap, capecitabine.

Rouanet et al Ann Oncol 2016; 27 (suppl 2): abstr O-021

O-021: Tailored strategy for locally-advanced rectal carcinoma: Preliminary results of a phase II multicenter trial (GRECCAR 4) – Rouanet P, et al

Key results

- A comparison of baseline patient characteristics revealed differences between good responders and poor responders

	Good responders		Poor responders	
	Arm A n=11	Arm B: Cap 50 n=19	Arm C: Cap 50 n=52	Arm D: Cap 60 n=51
Female sex, n (%)	6 (54.5)	8 (42.1)	18 (34.6)	11 (21.6)
Median (range) age, years	66.0 (44–78)	63.0 (39–75)	61 (22–82)	62 (22–80)
Median (range) BMI, kg/m^2	25.3 (18.5–33.6)	24.6 (16.9–32.5)	25.4 (16.9–34.0)	25.5 (18.3–41.3)
Tumour topography LP-LA, cm Median (range)	1.5 (0–5.8)	0 (0–10)	3.3 (0–11)	2.2 (0–44)
Circumference ≥50%, n (%)	6 (66.7)	6 (50.0)	35 (94.6)	26 (74.3)
Tumour volume, cm^3 Median (range)	23.0 (3.0–148)	22.0 (10.0–57.4)	43.0 (8.3–387)	47.4 (3.3–312)
CRM, mm Median (range)	1.0 (0–3)	0 (0–5)	0 (0–20)	0 (0–5)
EMS, mm Median (range)	6.0 (3.0–11.0)	4.0 (1.0–16.0)	10.0 (1.5–40.0)	12.0 (0.5–50.0)

CRM, circumferential resection margin,
EMS, extramural tumour spread.

Rouanet et al Ann Oncol 2016; 27 (suppl 2): abstr O-021

O-021: Tailored strategy for locally-advanced rectal carcinoma: Preliminary results of a phase II multicenter trial (GRECCAR 4) – Rouanet P, et al

Key results (cont.)

- Toxicities to induction chemotherapy were observed in a greater proportion of good responders than poor responders; proportion of patients with grade 3–4 toxicities in groups A, B, C and D were 63.6%, 42.1%, 36.5% and 15.7%

	Good responders		Poor responders	
	Arm A (n=11)	Arm B: Cap 50 (n=19)	Arm C: Cap 50 (n=52)	Arm D: Cap 60 (n=51)
No surgery				
Progressive disease	0	0	0	3
Patient's withdrawal	1	0	0	1
Non-compliance	0	0	0	1
Resection R0				
n (%)	10 (100.0)	19 (100.0)	43 (82.7)	4 (87.8)
90% CI	(74, 100)	(85, 100)	(72, 91)	(77, 95)
R1	0	0	9 (17.3)	2 (4.1)
Peritoneal carcinomatosis	0	0	0	1 (2.0)
Progressive disease	0	0	0	3 (6.1)

CRM, circumferential resection margin.

Rouanet et al Ann Oncol 2016; 27 (suppl 2): abstr O-021

O-021: Tailored strategy for locally-advanced rectal carcinoma: Preliminary results of a phase II multicenter trial (GRECCAR 4) – Rouanet P, et al

Key results (cont.)

- Efficacy according to CRM
  - 111 predictive + CRM ≥ 103 CRM >1; efficacy: 93%
  - Arm C is the less effective group; 13% failure

CRM		Predictive CRM	CRM on pathology ≤1	CRM on pathology >1
Arm A	≤1	7	0	7
	>1	2	0	2
Arm B	≤1	18	0	18
	>1	1	0	1
Arm C	≤1	46	6	40
	>1	5	0	5
Arm D	≤1	40	2	38
	>1	4	0	4
Total	**≤1**	**111**	**8**	**103**
	>1	**12**	**0**	**12**

Conclusions

- **These preliminary results indicate that tailored management of rectal cancer based on early tumoral response to an inductive treatment is feasible**
- **By evaluating response early following neoadjuvant chemotherapy, good responders can be discriminated from poor responders without adverse effects on the curative resection rate**
- **Further long-term oncological and functional data is required to confirm this strategy**

CRM, circumferential resection margin.

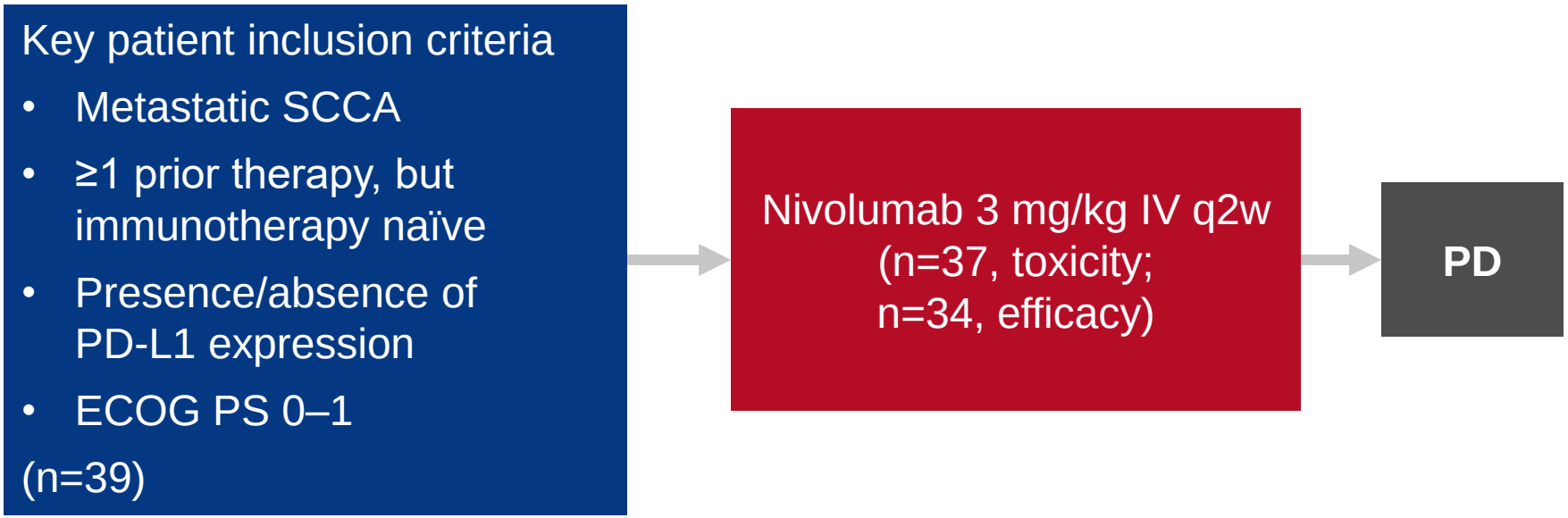
Rouanet et al Ann Oncol 2016; 27 (suppl 2): abstr O-021

ANAL CANCER

O-022: A multi-institutional phase 2 study of single agent nivolumab in previously treated metastatic squamous cell carcinoma of the anal canal (SCCA) – Eng C, et al

Study objective

- To assess the safety and toxicity of nivolumab in patients with previously treated metastatic SCCA



PRIMARY ENDPOINT

- ORR (RECIST 1.1)

SECONDARY ENDPOINTS

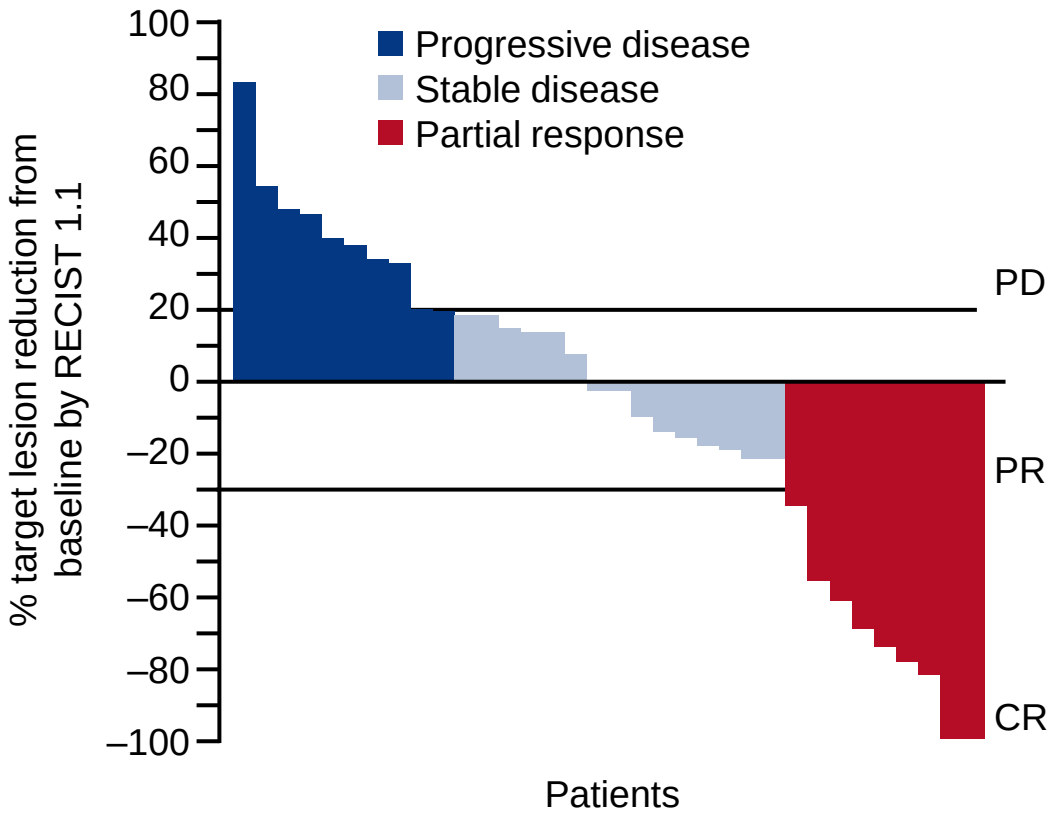
- PFS, safety

SCCA, squamous cell carcinoma of the anal canal.

Eng et al. Ann Oncol 2016; 27 (suppl 2):,abstr O-022

O-022: A multi-institutional phase 2 study of single agent nivolumab in previously treated metastatic squamous cell carcinoma of the anal canal (SCCA) – Eng C, et al

Key results

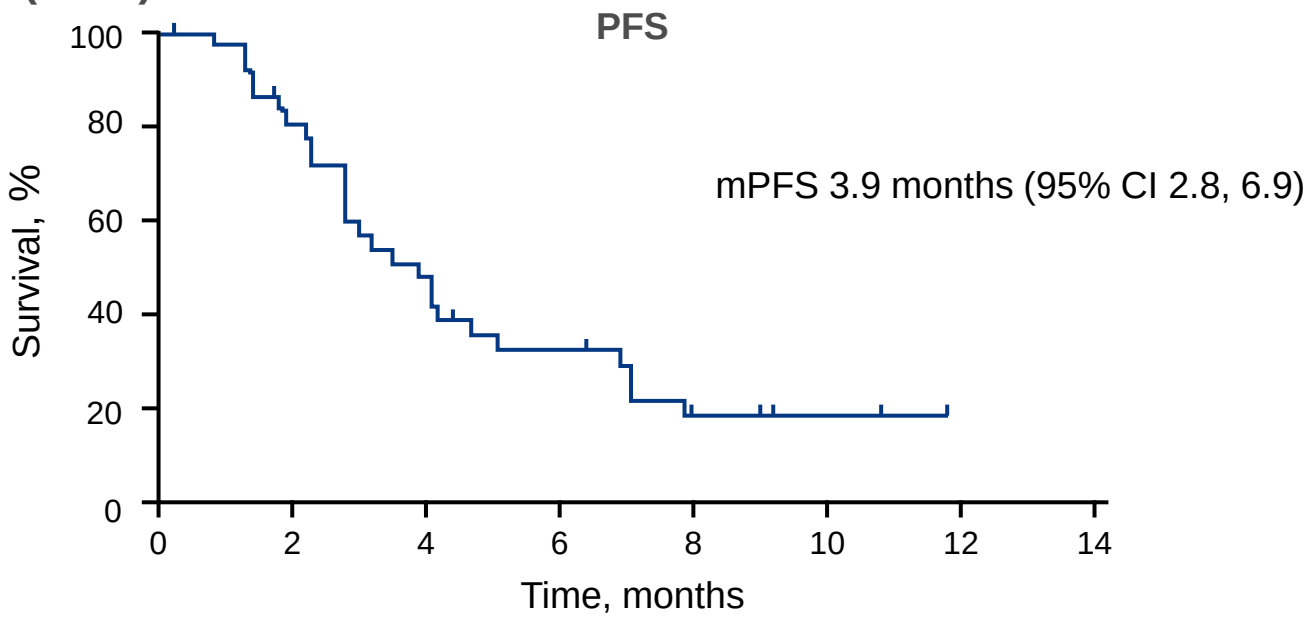


Response rate, n (%)	
CR	2 (5.4)
PR	7 (18.9)
SD	17 (45.9)
PD	8 (21.6)
Unevaluable	3 (8.1)
ORR (ITT, n=37)	**9 (24.3)**
ORR (evaluable, n=34)	**9 (26.4)**

Eng et al. Ann Oncol 2016; 27 (suppl 2):,abstr O-022

O-022: A multi-institutional phase 2 study of single agent nivolumab in previously treated metastatic squamous cell carcinoma of the anal canal (SCCA) – Eng C, et al

Key results (cont.)



Patients with metastatic SCCA (n=37)	Treatment-related grade 3 AEs, %
Anaemia	5
Fatigue	3
Hypothyroidism	3
Rash	3

Eng et al. Ann Oncol 2016; 27 (suppl 2):,abstr O-022

O-022: A multi-institutional phase 2 study of single agent nivolumab in previously treated metastatic squamous cell carcinoma of the anal canal (SCCA) – Eng C, et al

Key results (cont.)

Gene	Type	Incidence, n (%)
p53	Mutation	12 (46)
PIK3CA	Mutation	5 (19)
PIK3CA	Amplification	3 (12)

- No predictive correlation of cfDNA was observed for responders compared with non-responders and no prognostic correlation was identified

Conclusion

- **Nivolumab monotherapy was well tolerated and the primary endpoint (ORR) was met**

cfDNA, cell-free DNA.

Eng et al. Ann Oncol 2016; 27 (suppl 2):,abstr O-022