GI SLIDE DECK 2016

Selected abstracts on **Colorectal Cancer** from:

esdo european society of digestive oncology

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Letter from ESDO

DEAR COLLEAGUES

Yours sincerely, 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 **American Society of Clinical Oncology Annual Meeting 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.

Eric Van Cutsem
Wolff Schmiegel
Philippe Rougier
Thomas Seufferlein
(ESDO Governing Board)

esdo
european society of digestive oncology

ESDO Medical Oncology Slide Deck
Editors 2016

COLORECTAL CANCERS



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

PANCREATIC CANCER AND HEPATOBILIARY TUMOURS


Prof Jean-Luc Van Laethem	Digestive Oncology, Erasme University Hospital, Brussels, Belgium
Prof Thomas Seufferlein	Clinic of Internal Medicine I, University of Ulm, Ulm, Germany

GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS


Emeritus Prof Philippe Rougier	University Hospital of Nantes, Nantes, France
Prof Côme Lepage	University Hospital & INSERM, Dijon, France

BIOMARKERS


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

esdo

Glossary

1L	first line
2L	second line
3L	third line
5FU	5-fluorouracil
AE	adverse event
ADC	adenocarcinoma
CEA	carcinoembryonic antigen
CI	confidence interval
CIMP	CpG island methylator phenotype
CR	complete response
(m)CRC	(metastatic) colorectal cancer
CT	chemotherapy
DCR	disease control rate
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGFR	endothelial growth factor receptor
FLOX	fluorouracil, leucovorin, oxaliplatin
FOLFIRI	leucovorin, fluorouracil, irinotecan
FOLFIRINOX	leucovorin, fluorouracil, irinotecan, oxaliplatin
FOLFOX	leucovorin, fluorouracil, oxaliplatin
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
IHC	immunohistochemistry
ITT	intent-to-treat
IV	intravenous
KM	Kaplan–Meier
LRF	local regional failure
LRFS	local recurrence-free survival
Lu	lutetium
mAb	monoclonal antibody
miR	microRNA
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability high
MSS	microsatellite stable
OR	odds ratio
ORR	overall response rate
(m)OS	(median) overall survival
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
q3w	every 3 weeks
QoL	quality of life
qRT-PCR	quantitative reverse transcription polymerase chain reaction
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	recurrence-free survival
RT	radiotherapy
S-1	tegafur/CDHP/oteracil
SCCA	squamous cell carcinoma of the anus
SCCAC	squamous cell carcinoma of the anal canal
SD	stable disease
SEER	Surveillance Epidemiology and End Results
Treg	regulatory T cell
(m)TTR	(median) time to treatment response
WT	wild type

Contents

COLORECTAL CANCER

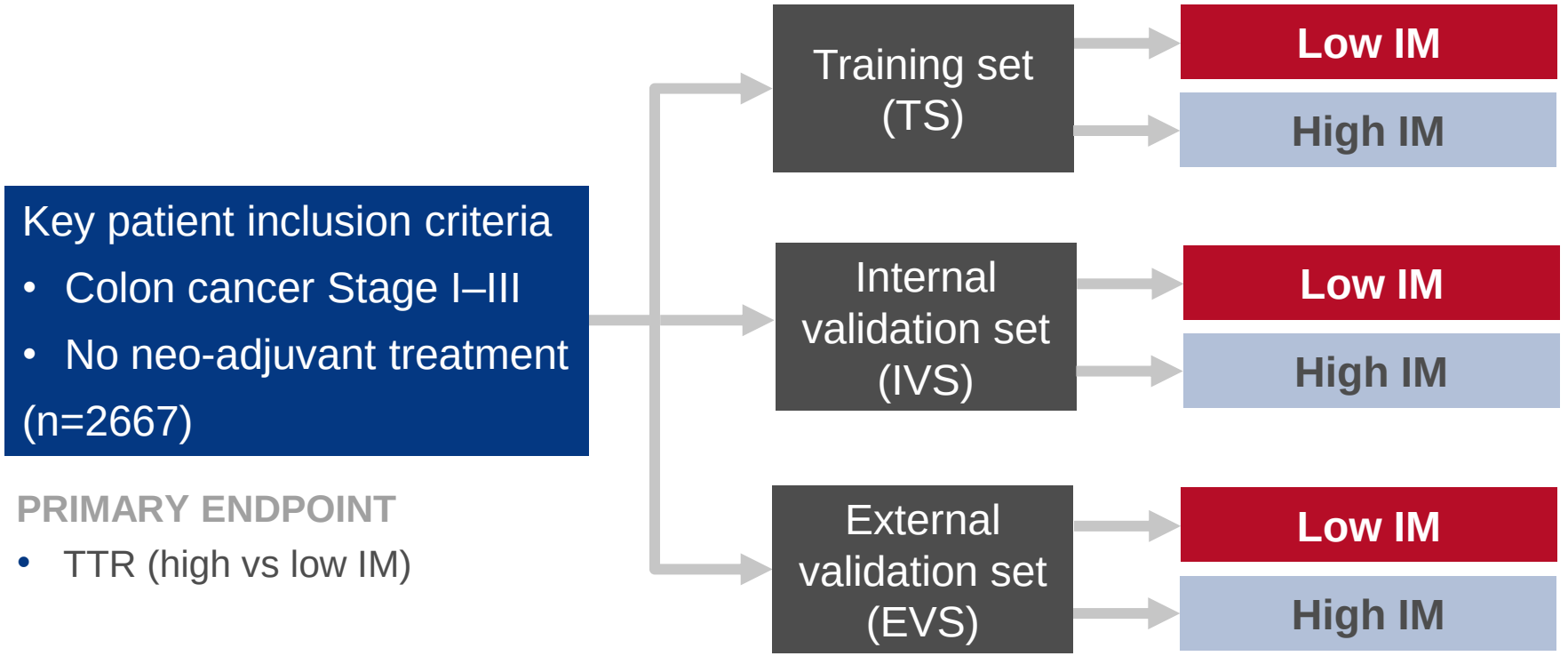
COLORECTAL CANCER

EARLY COLORECTAL CANCER – ADJUVANT STUDIES

3500: Validation of the Immunoscore (IM) as a prognostic marker in stage I/II/III colon cancer: Results of a worldwide consortium-based analysis of 1,336 patients – Galon J, et al

Study objective

- To investigate the prognostic value of the 'Immunoscore' biomarker in patients with Stage I–III colon cancer



IM analysis:

- Whole slide FFPE tissue samples were digitally analysed by IHC

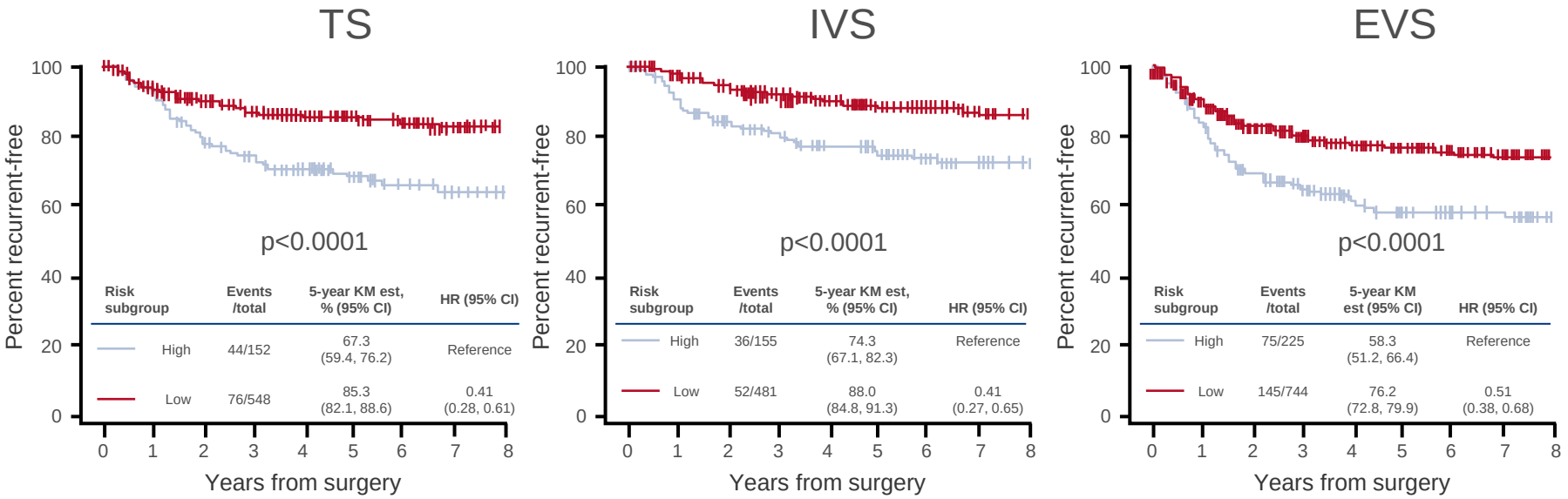
IM, immunoscore.

Galon et al. J Clin Oncol 2016; 34 (suppl): abstr 3500

3500: Validation of the Immunoscore (IM) as a prognostic marker in stage I/II/III colon cancer: Results of a worldwide consortium-based analysis of 1,336 patients – Galon J, et al

Key results

TTR: low vs high Immunoscore (n=2667)



TTR, HR (95% CI)	TS	IVS	EVS
High score	Reference	Reference	Reference
Medium score	0.51 (0.34, 0.77)	0.48 (0.30, 0.77)	0.62 (0.46, 0.84)
Low score	0.19 (0.10, 0.37)	0.27 (0.14, 0.53)	0.33 (0.22, 0.49)

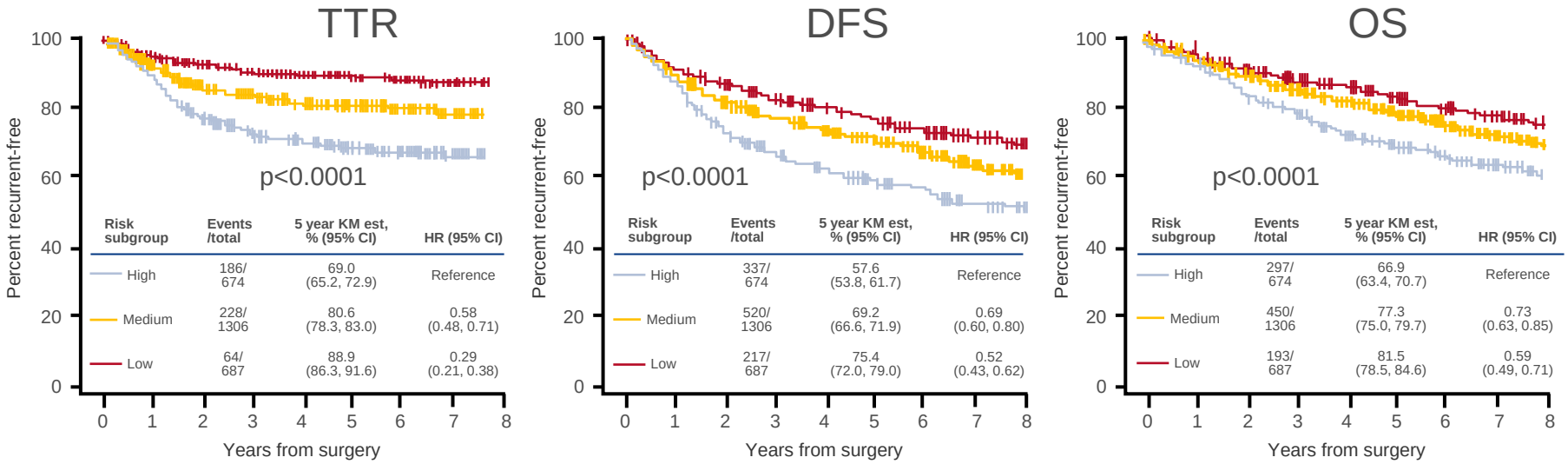
EVS, external validation set; IVS, internal validation set; TS, training set.

Galon et al. J Clin Oncol 2016; 34 (suppl): abstr 3500

3500: Validation of the Immunoscore (IM) as a prognostic marker in stage I/II/III colon cancer: Results of a worldwide consortium-based analysis of 1,336 patients – Galon J, et al

Key results (continued)

Overall population: low vs medium vs high Immunoscore (n=2667)



Conclusions

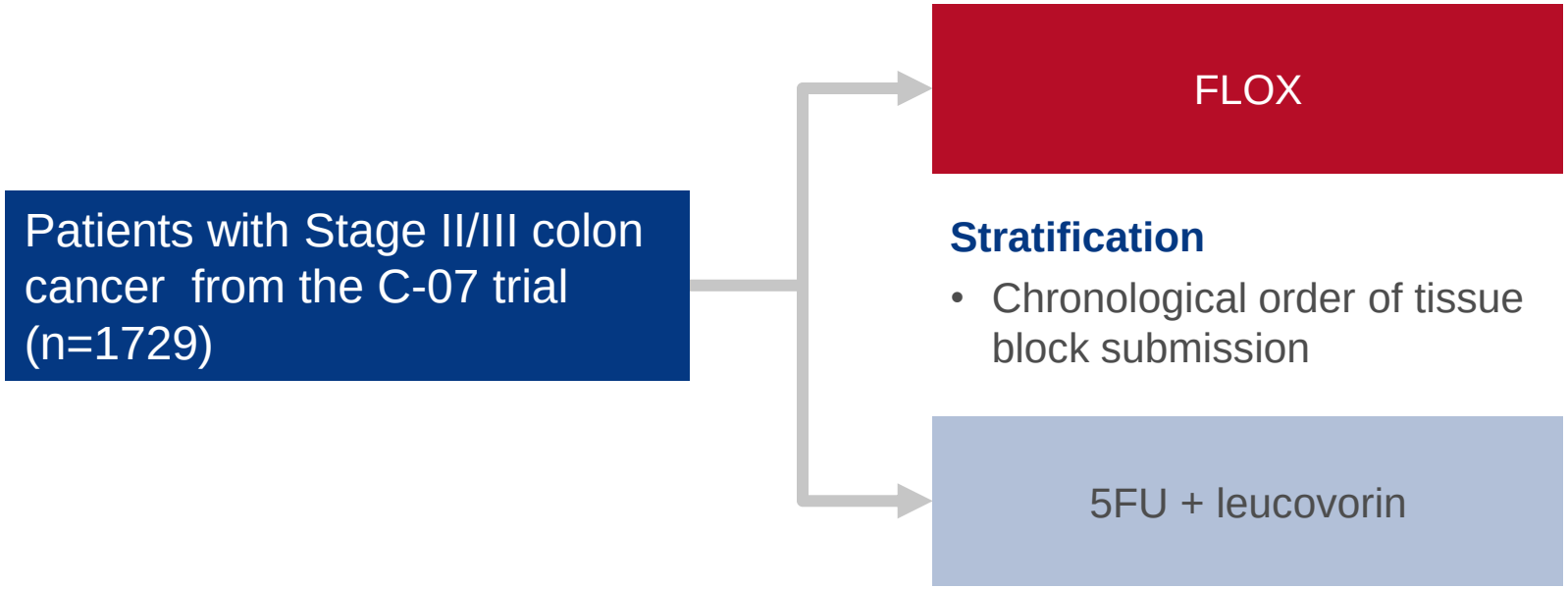
- TTR, DFS and OS were significantly longer in patients with Stage I–III colon cancer who had a high vs low Immunoscore
  - Low Immunoscore identified a subgroup of patients with high-risk disease
- The findings in this study may result in the implementation of the Immunoscore as a new component for the classification of cancer

Galon et al. J Clin Oncol 2016; 34 (suppl): abstr 3500

3510: Clinical outcome and benefit of oxaliplatin in colon cancer according to intrinsic subtypes: Results from NRG Oncology/NSABP C-07 – Pogue-Geile KL, et al

Study objective

- To examine if molecular subtypes of CRC were associated with differential prognosis and benefit for DFS with FLOX vs 5FU + leucovorin



- Two patients cohorts were analysed:
  - Discovery cohort (n=848): Patients subtyped with CRCA classifier
  - Validation cohort (n=881): Patients prospectively examined with a pre-specified statistical analysis plan

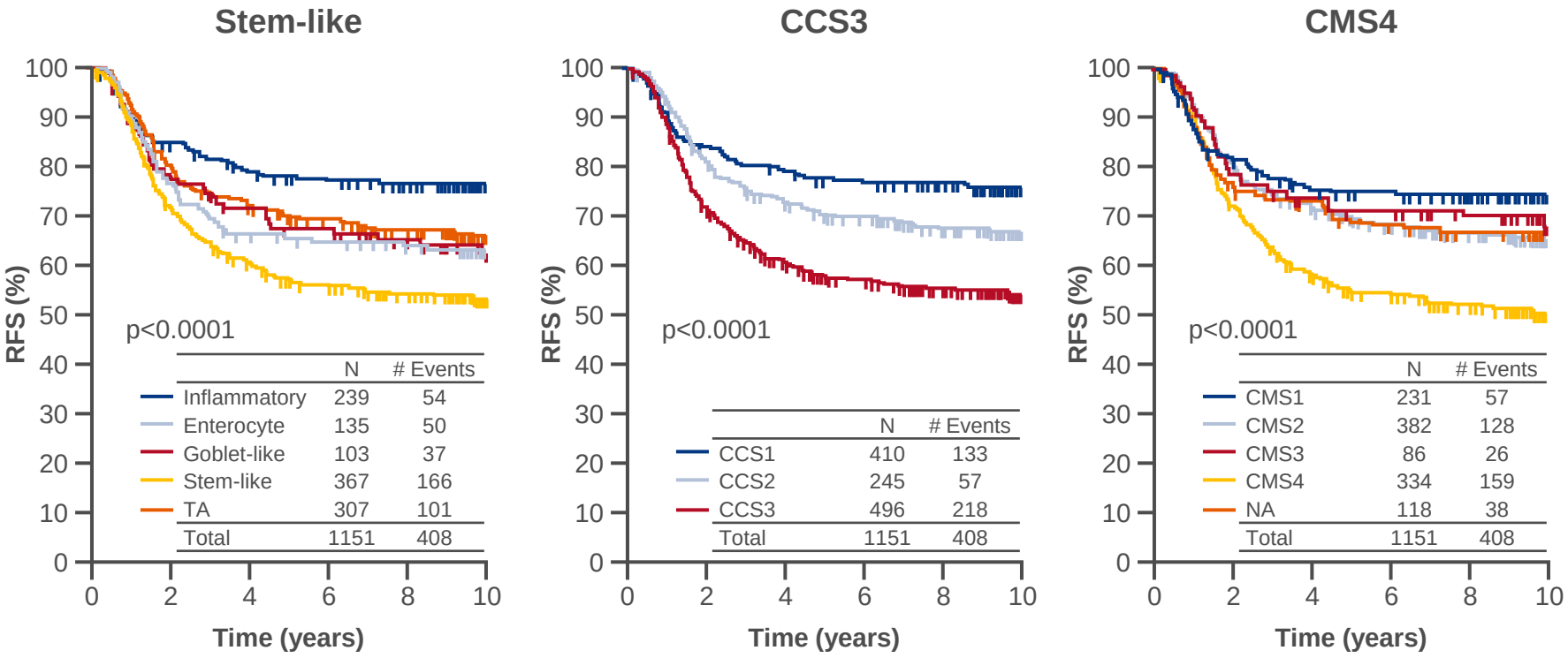
CRCA, Colorectal Cancer Assigner.

Pogue-Geile et al. J Clin Oncol 2016; 34 (suppl): abstr 3510

3510: Clinical outcome and benefit of oxaliplatin in colon cancer according to intrinsic subtypes: Results from NRG Oncology/NSABP C-07 – Pogue-Geile KL, et al

Key results

RFS (Stage III CRC)



NA, not available; TA, transit amplifying.

Kay et al. J Clin Oncol 2016; 34 (suppl): abstr 3510

3510: Clinical outcome and benefit of oxaliplatin in colon cancer according to intrinsic subtypes: Results from NRG Oncology/NSABP C-07 – Pogue-Geile KL, et al

Key results (continued)

RFS in Stage III patients: enterocyte subgroup	N	Events	HR (95% CI)	p-value
Discovery cohort				
5FU + leucovorin	34	21	0.223 (0.089, 0.556)	0.001
FLOX	31	6		
Validation cohort				
5FU + leucovorin	36	15	0.525 (0.222, 1.239)	0.141
FLOX	34	8		

Conclusions

- **Stem-like subtypes had the worst prognosis in patients with CRC, regardless of the stage or treatment type**
- **A trend towards oxaliplatin benefit with the enterocyte subtype was only seen in the validation cohort**

Kay et al. J Clin Oncol 2016; 34 (suppl): abstr 3510

3511: The potential of circulating tumor DNA (ctDNA) to reshape the design of clinical trials testing adjuvant therapy in patients with early stage cancers – Tie J, et al

Study objective

- To assess if minimal residual disease could be identified by the presence of ctDNA in patients with resected Stage II colon cancer

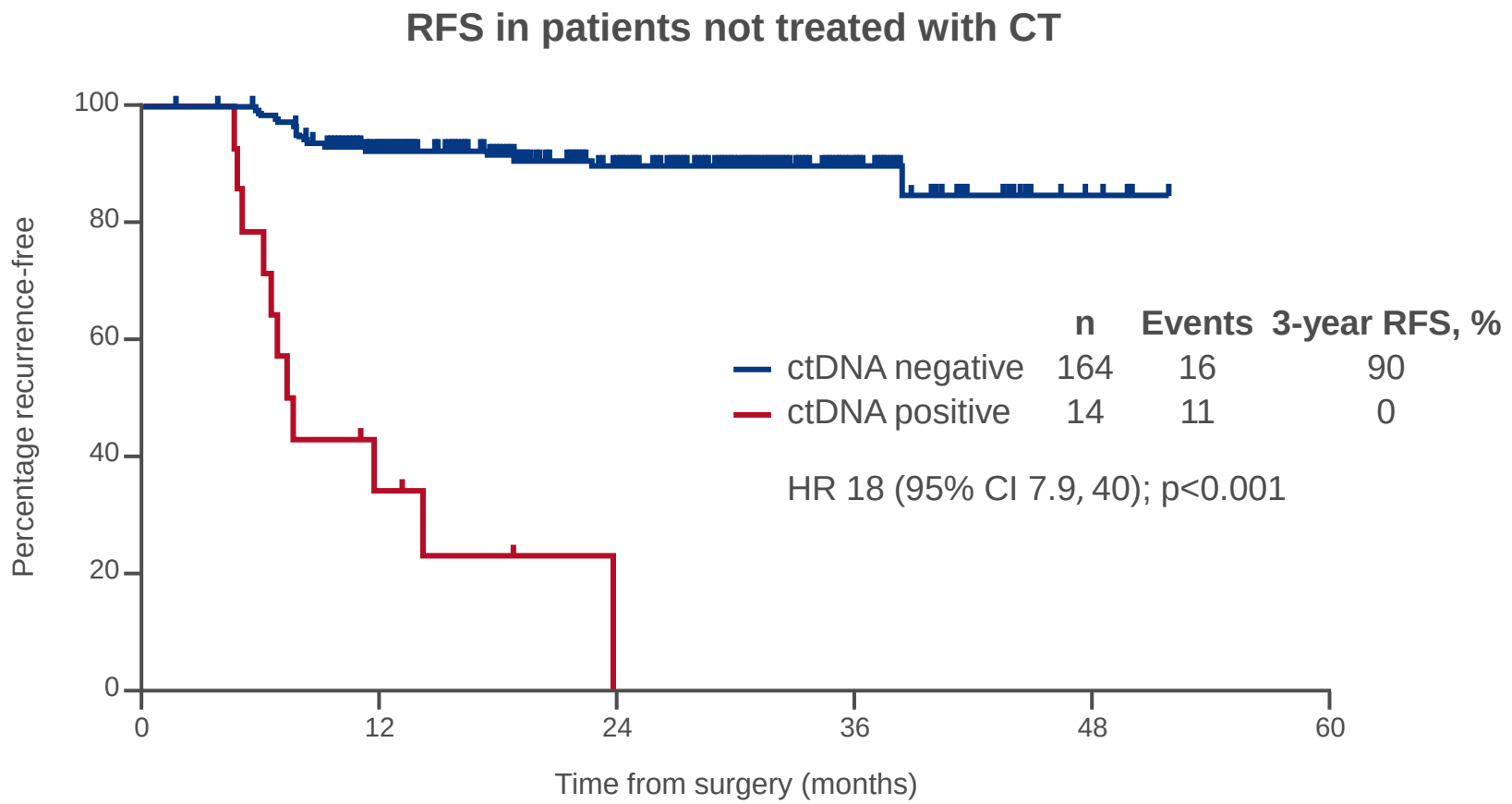
Study design

- A prospective trial in 231 patients with resected Stage II colon cancer
- Serial plasma samples were collected:
  - 4–10 weeks post-op (n=231)
  - 3-monthly follow-up blood collection (n=167)
- Somatic mutations were identified by gene sequencing (n=230)
  - Blood biomarker analyses were performed on ctDNA and serum CEA
- Adjuvant CT was administered at clinician discretion, blinded to ctDNA analysis
  - CT: n=52 (23%) vs no CT: n=178 (77%)
- Primary endpoint: RFS

Tie et al. J Clin Oncol 2016; 34 (suppl): abstr 3511

3511: The potential of circulating tumor DNA (ctDNA) to reshape the design of clinical trials testing adjuvant therapy in patients with early stage cancers – Tie J, et al

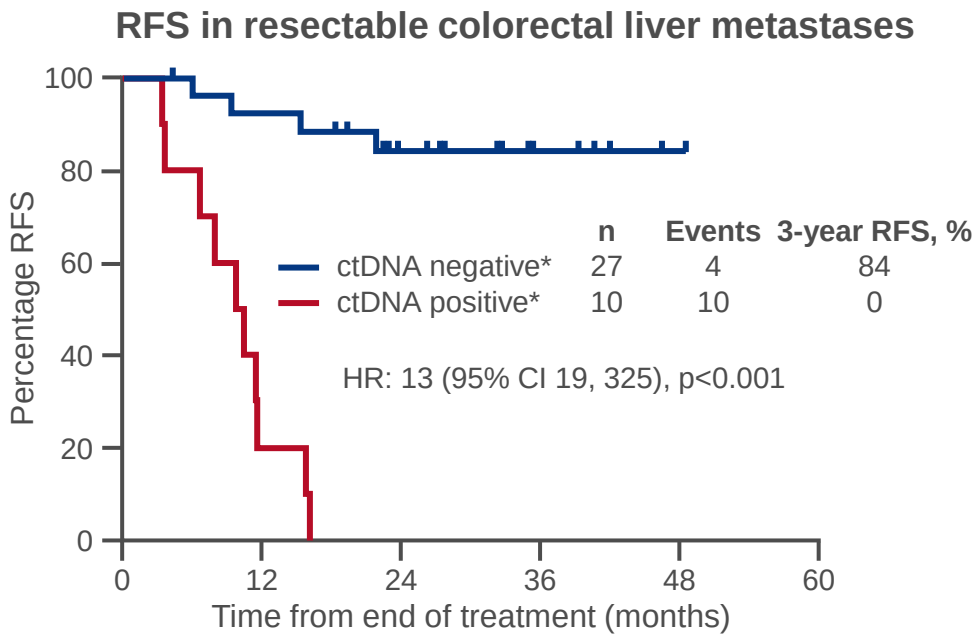
Key results



Tie et al. J Clin Oncol 2016; 34 (suppl): abstr 3511

3511: The potential of circulating tumor DNA (ctDNA) to reshape the design of clinical trials testing adjuvant therapy in patients with early stage cancers – Tie J, et al

Key results (continued)



Cohort	Stage 2	Resectable liver metastases
Serial 3-monthly ctDNA collected, n/N	27/34	13/14
ctDNA detectable up to time of recurrence, n/N (%)	23/27 (85)	12/13 (92)
Time (months) between ctDNA detection + radiologic recurrence, median (IQR)	5.5 (2.7–9.2)	3.0 (0.0–8.1)

Conclusions

- **Detection of ctDNA in patients with resected Stage II colon cancer provides direct evidence of residual disease**
- **In addition to defining patients at very high risk of radiologic-recurrence, serial ctDNA analysis may provide an early readout of adjuvant treatment benefit**

*ctDNA at the end of treatment (surgery ± CT).

Tie et al. J Clin Oncol 2016; 34 (suppl): abstr 3511

3518: Association of tumor infiltrating lymphocytes (TILs) with molecular subtype and prognosis in stage III colon cancers (CC) from a FOLFOX-based adjuvant chemotherapy trial – Sinicrope FA, et al

Study objective

- To determine if the density of TILs is associated with survival in patients with Stage III colon cancer

Study design

- The study population comprised patients with Stage III colon cancer (n=2293) from a randomised trial of adjuvant FOLFOX + cetuximab
- H&E stained tumour sections were analysed for TILs by light microscopy
  - TIL density was dichotomised as high (≥4 TILs per HPF) or low (<4 TILs per HPF)
- BRAF and KRAS status was analysed by PCR
- The association of TIL density with covariates and biomarkers was evaluated using Chi-square or Wilcoxon rank sum tests
- The prognostic association between TIL density and DFS/OS was determined by multivariate Cox regression analyses adjusting for various variables including:
  - Age, sex, ECOG PS, T-stage, number of possible nodes, treatment arm, BMI, histologic grade, tumour site, MMR, KRAS and BRAF

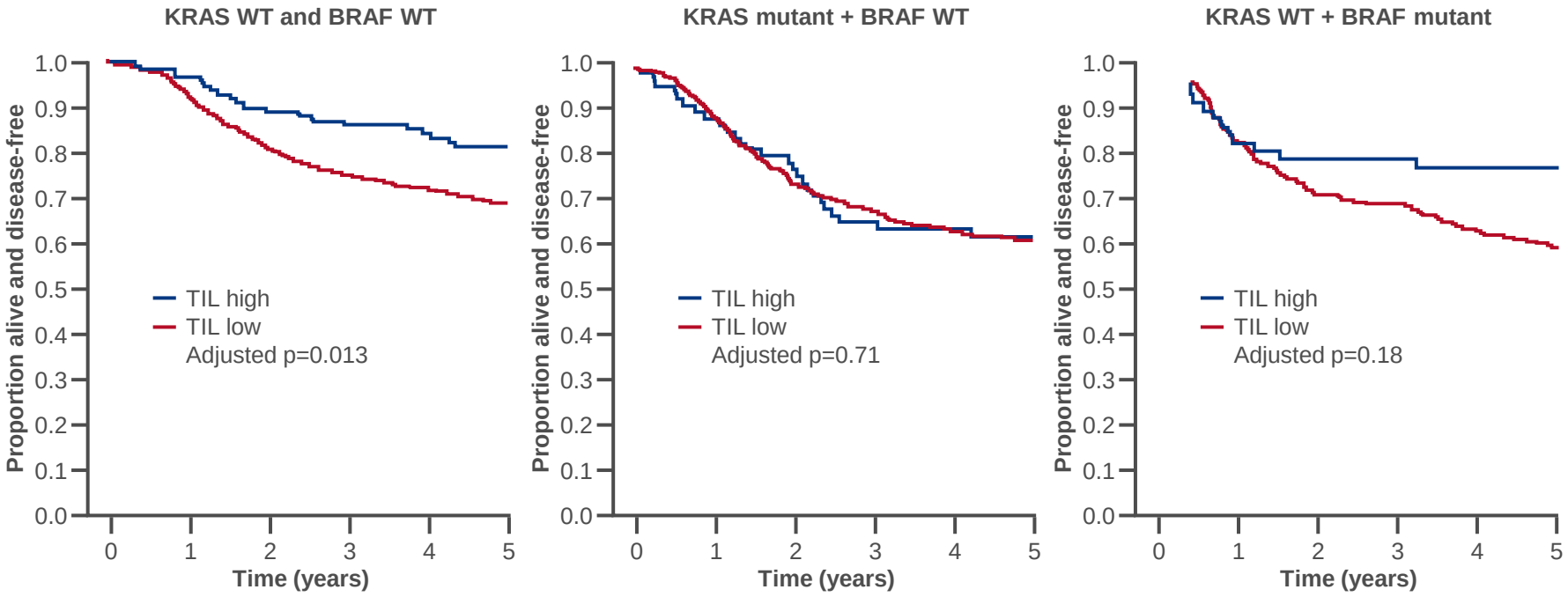
TIL, tumour infiltrating lymphocyte.

Sinicrope, et al. J Clin Oncol 2016; 34 (suppl): abstr 3518

3518: Association of tumor infiltrating lymphocytes (TILs) with molecular subtype and prognosis in stage III colon cancers (CC) from a FOLFOX-based adjuvant chemotherapy trial – Sinicrope FA, et al

Key results

DFS by TIL density + KRAS/BRAF status



TIL	n (events)	5-year rate	Adj. HR (95% CI)
High	113 (20)	0.81	0.56 (0.34, 0.92)
Low	983 (291)	0.69	Ref.

TIL	n (events)	5-year rate	Adj. HR (95% CI)
High	72 (26)	0.62	1.08 (0.71, 1.64)
Low	688 (259)	0.61	Ref.

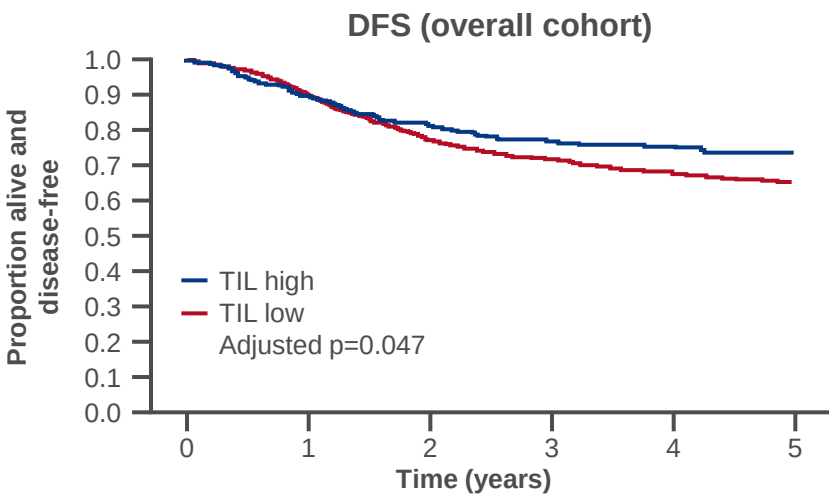
TIL	n (events)	5-year rate	Adj. HR (95% CI)
High	54 (13)	0.76	0.67 (0.37, 1.23)
Low	230 (95)	0.58	Ref.

Adj, adjusted; Ref, reference; TIL, tumour infiltrating lymphocyte.

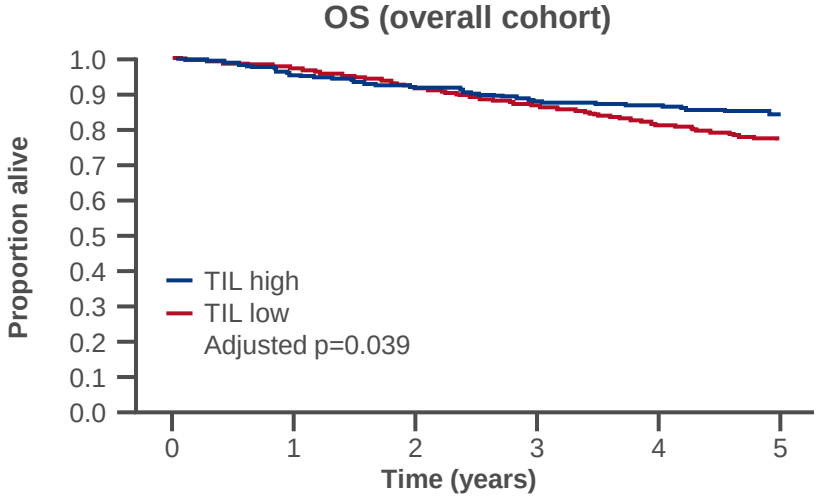
Sinicrope, et al. J Clin Oncol 2016; 34 (suppl): abstr 3518

3518: Association of tumor infiltrating lymphocytes (TILs) with molecular subtype and prognosis in stage III colon cancers (CC) from a FOLFOX-based adjuvant chemotherapy trial – Sinicrope FA, et al

Key results (continued)



TIL	n (events)	5-year rate	Adj. HR (95% CI)
High	262 (67)	0.73	0.76 (0.57, 1.01)
Low	2031 (680)	0.65	Ref.



TIL	n (events)	5-year rate	Adj. HR (95% CI)
High	262 (57)	0.84	0.73 (0.54, 1.00)
Low	2031 (559)	0.77	Ref.

Conclusions

- **High vs low TIL density indicates immune activation that was prognostic for DFS and OS in patients with Stage III colon cancer**
- **The association of TIL density with prognosis was lost in the presence of KRAS mutation and attenuated with BRAF mutations vs tumours lacking these mutations**

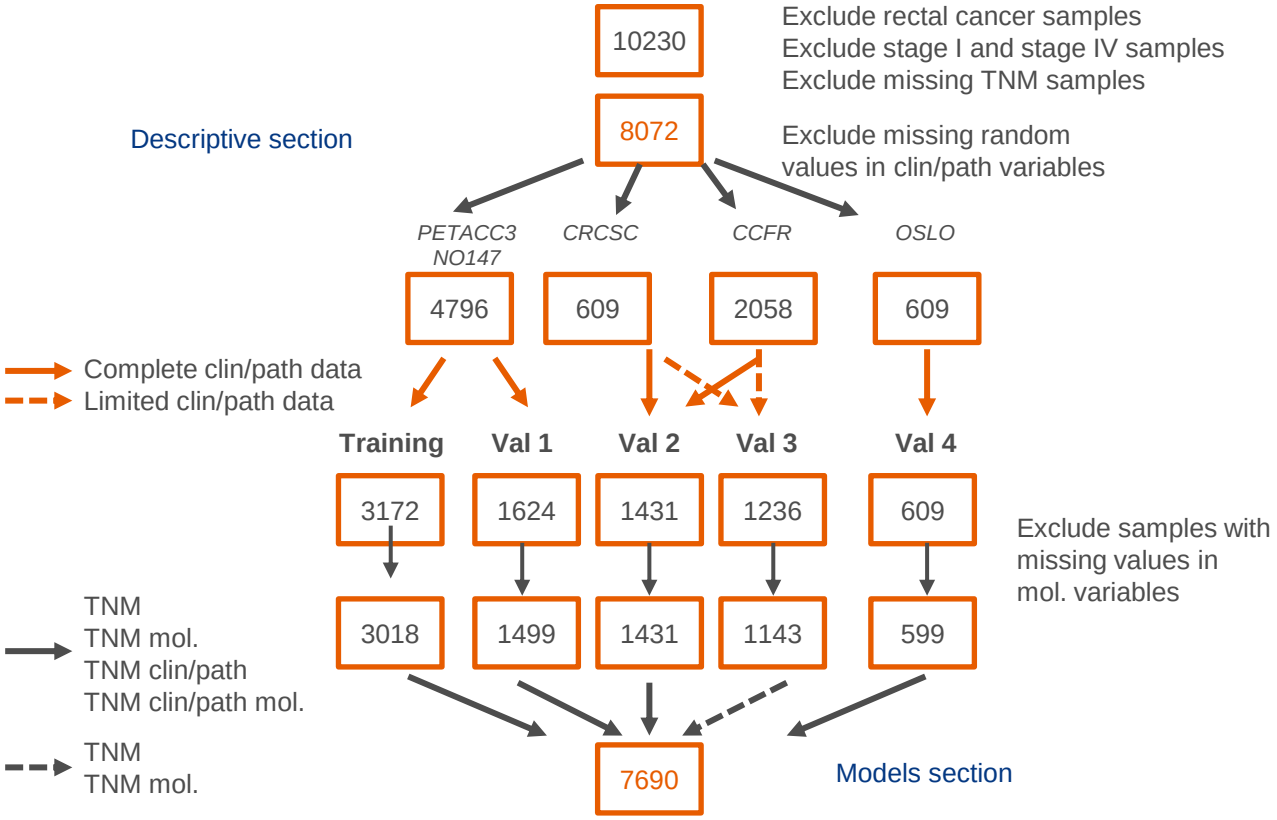
Adj, adjusted; Ref, reference; TIL, tumour infiltrating lymphocyte.

Sinicrope, et al. J Clin Oncol 2016; 34 (suppl): abstr 3518

3519: Improved prognostication using molecular markers and clinicopathological features in high-risk stage II/III colon cancer – Dienstmann R, et al

Study objective

- To evaluate the prognostic value of molecular markers (MSI and mutations in BRAF and KRAS) in patients with Stage II/III colon cancer receiving adjuvant CT



Clin/path, clinicopathological features; mol, molecular; val, validation.

Dienstmann et al. J Clin Oncol 2016; 34 (suppl): abstr 3519

3519: Improved prognostication using molecular markers and clinicopathological features in high-risk stage II/III colon cancer – Dienstmann R, et al

Key results: Multivariate model in training-validation cohort (PTACC3 and N0147)

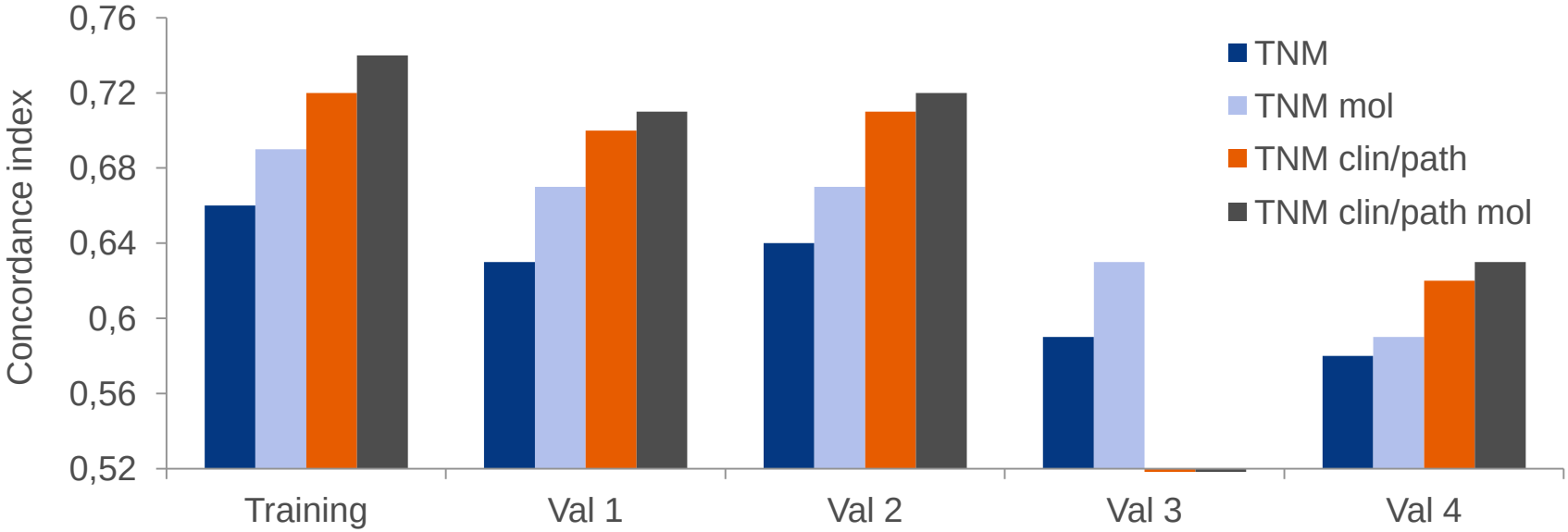
4353 patients, 829 events	HR	95% CI		p-value	p-value interaction
pT2 vs pT1	**1.06**	0.52	2.18	0.865457	
pT3 vs pT1	**2.23**	1.19	4.17	0.012612	
pT4 vs pT1	**4.23**	2.23	8.02	1.01E-05	
pN1 vs pN0	**1.76**	1.23	2.52	0.001963	
pN1 vs pN0	**2.88**	1.98	4.19	2.92E-08	
Age (continuous)	**1.01**	1.00	1.02	0.000924	
Male vs female	**1.36**	1.18	1.57	2.08E-05	
Lymph node assessed ≥12 vs <12	**0.70**	0.59	0.82	2.18E-05	
Lymph node positive (continuous)	**1.07**	1.05	1.09	<2e-16	
High grade vs low/medium	**1.29**	1.10	1.52	0.002295	
Right vs left	**1.53**	1.32	1.78	4.27E-08	
FOLFIRI vs 5FU/leucovorin	**1.00**	0.79	1.28	0.973726	
FOLFIRI/cetuximab vs 5FU/leucovorin	**0.47**	0.19	1.16	0.101751	
FOLFOX vs 5FU/leucovorin	**0.70**	0.56	0.88	0.002069	
FOLFOX/cetuximab vs 5FU/leucovorin	**0.90**	0.71	1.13	0.34398	
MSI vs MSS	**0.71**	0.56	0.90	0.003779	
MSI MSS Right (all)	**0.68**	0.53	0.88	0.003875	0.03852
MSI MSS Left (all)	**1.09**	0.66	1.81	0.729865	
MSI vs MSS Right*	**0.53**	0.38	0.76	0.00046	
MSI vs MSS Left*	**0.71**	0.36	1.41	0.326	0.151
BRAF mutant vs WT	**1.80**	1.45	2.23	8.73E-08	
KRAS mutant vs WT	**1.46**	1.25	1.70	1.90E-06	

*Excluding cetuximab-treated patients.

Dienstmann et al. J Clin Oncol 2016; 34 (suppl): abstr 3519

3519: Improved prognostication using molecular markers and clinicopathological features in high-risk stage II/III colon cancer – Dienstmann R, et al

Key results (continued)



- For Models 1–4, time-dependent AUCs (5-year summary) were:
  - 0.54, 0.66, 0.73, 0.74 (training set); 0.55, 0.68, 0.72, 0.73 (validation set)

Conclusions

- **Incorporation of molecular markers (MSI + mutations in BRAF + KRAS) improves prognostic estimation in patients with Stage II/III colon cancer receiving adjuvant CT**
- **The added value of molecular markers on top of TNM clinicopathological models is minor in both treated and untreated cohorts**

Clin/path, clinicopathological features;
mol, molecular; val, validation.

Dienstmann et al. J Clin Oncol 2016; 34 (suppl): abstr 3519

COLORECTAL CANCER

LIVER METASTASES

3512: FOLFIRINOX combined to targeted therapy according RAS status for colorectal cancer patients with liver metastases initially non-resectable: A phase II randomized Study—Prodige 14 – accord 21 (METHEP-2), a unicancer GI trial – Ychou M, et al

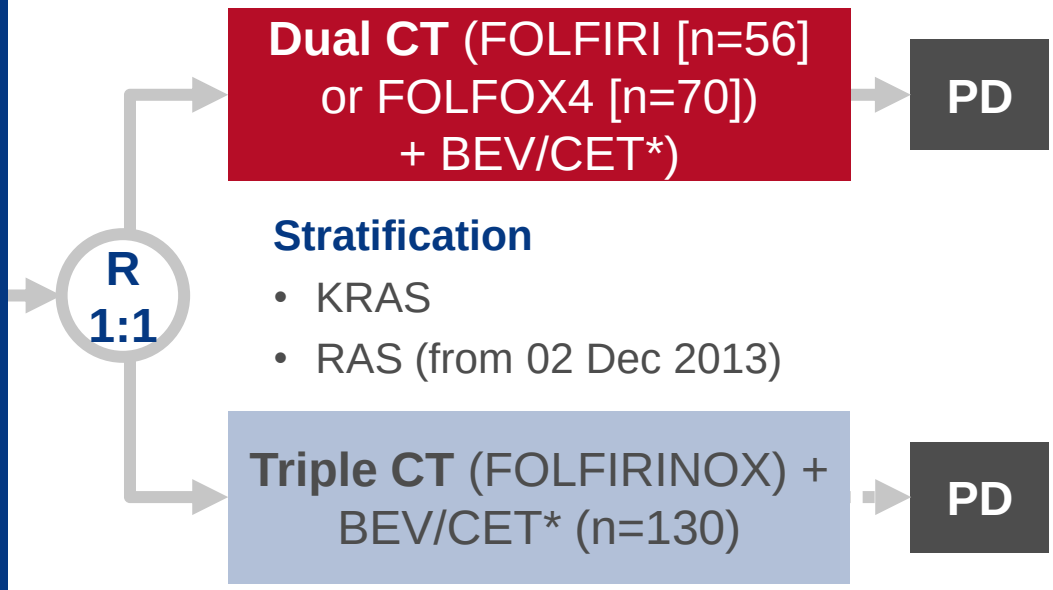
Study objective

- To assess the R0/R1 resection rate of liver metastases with dual (FOLFIRI/FOLFOX4) vs triple (FOLFIRINOX) CT in patients with CRC and initially unresectable liver metastases

Key patient inclusion criteria

- Histologically proven mCRC
- Resectable/resected 1° tumour
- Synchronous/metachronous liver metastases (LMs)
- Non-resectable, with curative intent, liver metastases
- 1–3 lung metastases ≤2 cm

(n=256)



PRIMARY ENDPOINT(S)

- Resection rate (R0 or R1)

SECONDARY ENDPOINTS

- OS; Safety

*(K)RAS WT: cetuximab; RAS mutant: bevacizumab.

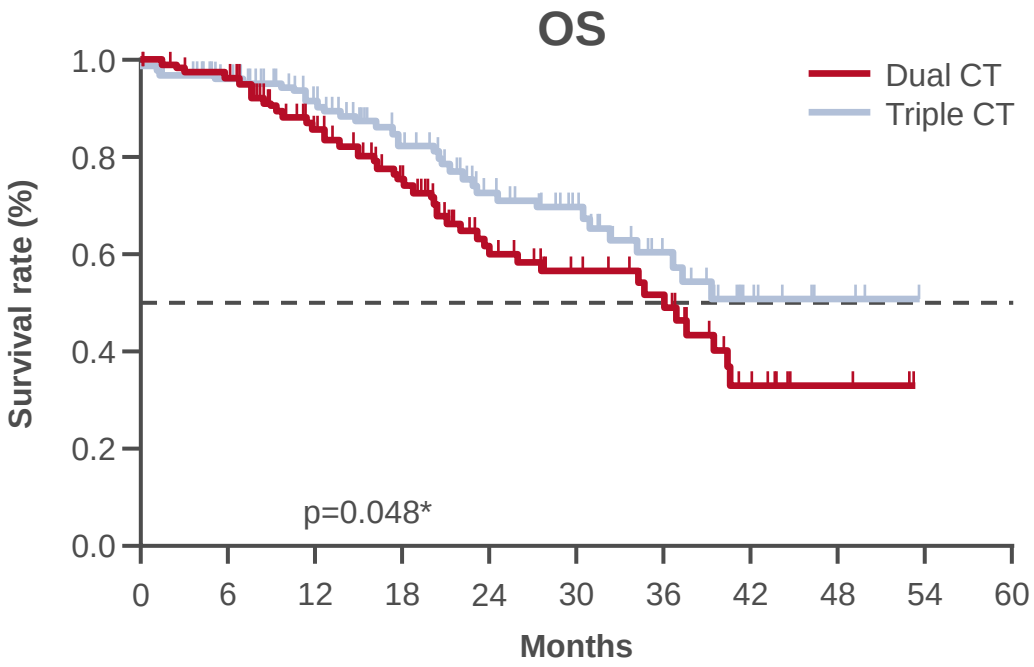
BEV, bevacizumab; CET, cetuximab.

Ychou et al. J Clin Oncol 2016; 34 (suppl): abstr 3512

3512: FOLFIRINOX combined to targeted therapy according RAS status for colorectal cancer patients with liver metastases initially non-resectable: A phase II randomized Study—Prodige 14 – accord 21 (METHEP-2), a unicancer GI trial – Ychou M, et al

Key results

	CT arm		Targeted therapy type	
	Dual CT	Triple CT	Bevacizumab	Cetuximab
LM R0/R1 resection rate, %	45.2	56.9	44.7	55.6
p-value	0.062		0.087	



	Dual CT	Triple CT
mOS, months (95% CI)	36 (23.5, 40.6)	NE
p-value	0.048	
1-year OS, %	86	92
2-year OS, %	60	73

*Log rank stratified. NE, not evaluable. LM, liver metastases.

Ychou et al. J Clin Oncol 2016; 34 (suppl): abstr 3512

3512: FOLFIRINOX combined to targeted therapy according RAS status for colorectal cancer patients with liver metastases initially non-resectable: A phase II randomized Study—Prodige 14 – accord 21 (METHEP-2), a unicancer GI trial – Ychou M, et al

Key results (continued)

AEs, n (%)	CT arm		Targeted therapy type	
	Dual CT	Triple CT	Bevacizumab	Cetuximab
Grade ≤2	78 (62.4)	74 (58.3)	73 (73.0)	79 (52.0)
Grade ≥3	47 (37.6)	53 (41.7)	27 (27.0)	73 (48.0)

Conclusion

- **Triple CT with FOLFIRINOX was associated with higher liver metastases resection rates and statistically longer OS vs dual CT in patients with mCRC**

Ychou et al. J Clin Oncol 2016; 34 (suppl): abstr 3512

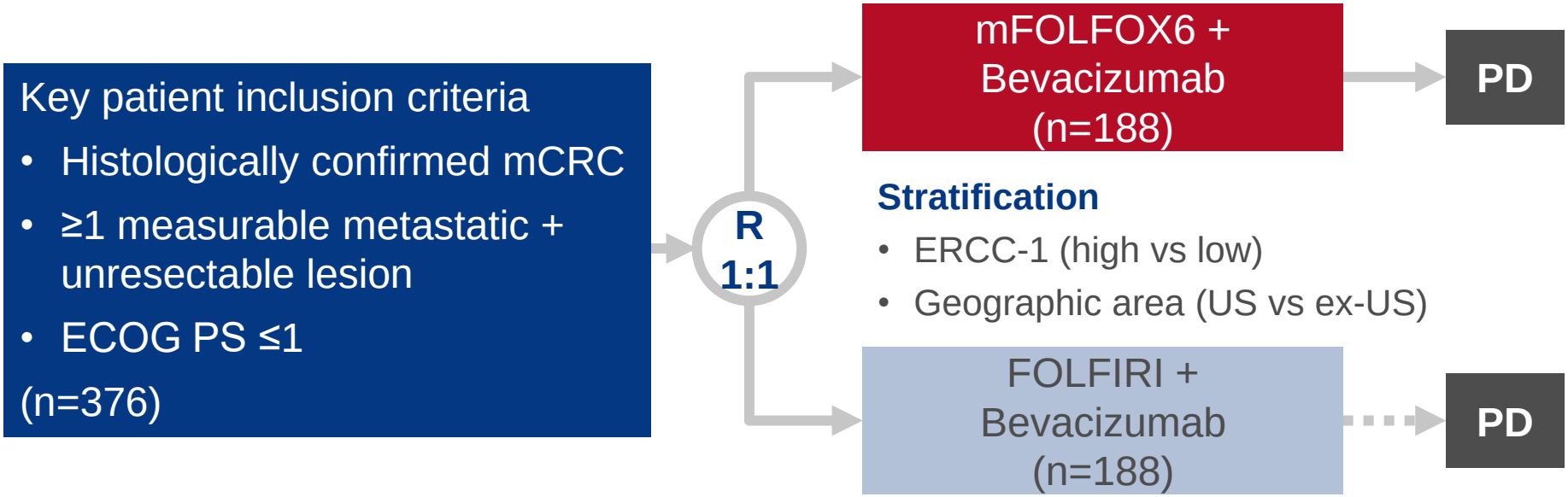
COLORECTAL CANCER

FIRST LINE

3515: MAVERICC, a phase II study of mFOLFOX6-bevacizumab (BV) vs FOLFIRI-BV as first-line (1L) chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC): Outcomes by tumor location and KRAS status – Lenz H-J, et al

Study objective

- To evaluate the prognostic impact of tumour location and KRAS status in patients with mCRC receiving 1L bevacizumab + either mFOLFOX6 or FOLFIRI*



ENDPOINTS

- PFS, OS
- Safety

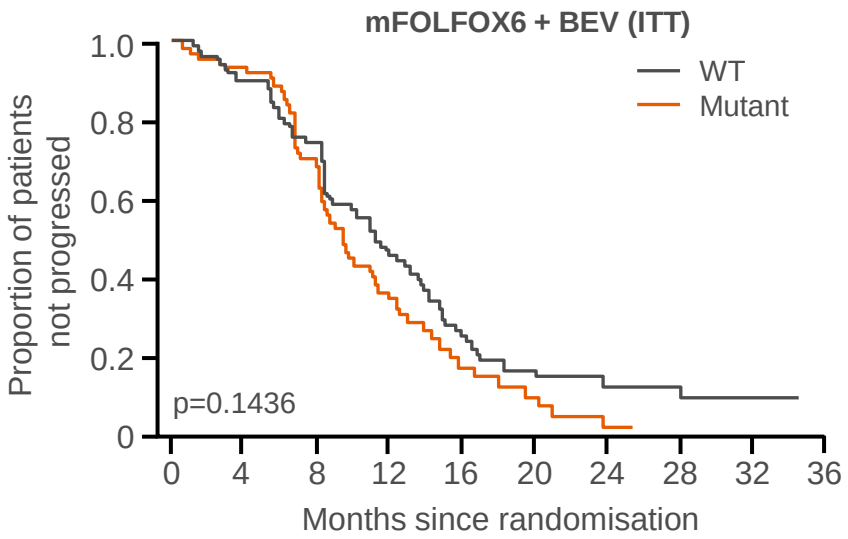
*Exploratory analysis of the MAVERICC trial.

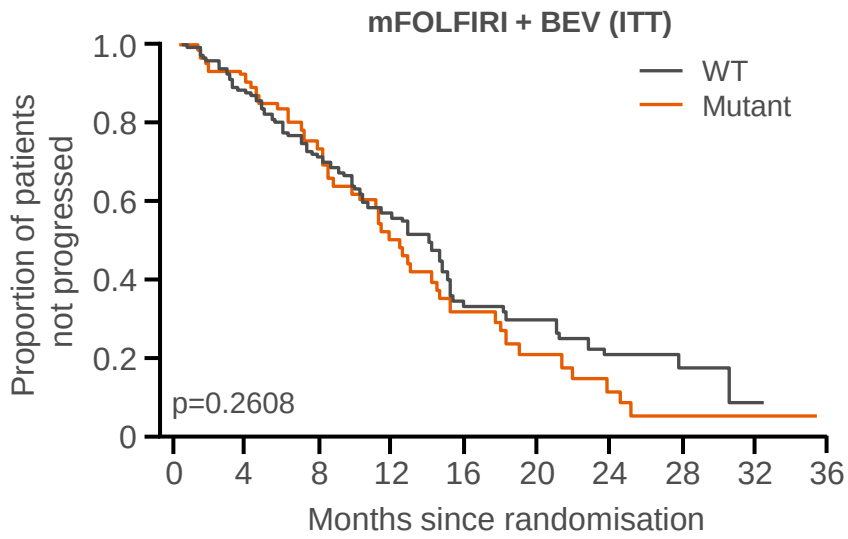
Lenz et al. J Clin Oncol 2016; 34 (suppl): abstr 3515

3515: MAVERICC, a phase II study of mFOLFOX6-bevacizumab (BV) vs FOLFIRI-BV as first-line (1L) chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC): Outcomes by tumor location and KRAS status – Lenz H-J, et al

Key results

PFS by KRAS exon 2 status





PFS	HR (95% CI)	p-value
Overall population	*0.79 (0.61, 1.01)	0.056
Right tumour location	*0.88 (0.60, 1.28)	0.494
Left tumour location	*0.71 (0.51, 0.98)	0.040
Tumour location, KRAS WT	†0.86 (0.61, 1.21)	0.383
Tumour location, KRAS mutant	†1.20 (0.77, 1.87)	0.431

*FOLFIRI vs FOLFOX; †Left vs right. BEV, bevacizumab.

Lenz et al. J Clin Oncol 2016; 34 (suppl): abstr 3515

3515: MAVERICC, a phase II study of mFOLFOX6-bevacizumab (BV) vs FOLFIRI-BV as first-line (1L) chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC): Outcomes by tumor location and KRAS status – Lenz H-J, et al

Key results (continued)

AEs of special interest in ≥6% of patients, n (%)	mFOLFOX6 + BEV (n=183)	FOLFIRI + BEV (n=183)
Any	56 (30.3)	57 (31.1)
Uncontrolled hypertension (grade ≥3)	27 (14.6)	23 (12.6)
Venous thromboembolic events (grade ≥3)	14 (7.6)	18 (9.8)
Gastrointestinal perforation	8 (4.3)	4 (2.2)
Bleeding other than pulmonary/CNS (grade ≥3)	6 (3.2)	4 (2.2)
Arterial thromboembolic events	4 (2.2)	9 (4.9)

Conclusions

- **PFS and OS were not significantly different between 1L mFOLFOX6 + bevacizumab vs FOLFIRI + bevacizumab in patients with mCRC**
- **There was a trend towards improved PFS + OS* in patients with WT vs mutant KRAS**
- **Tumour location did not impact PFS or OS in patients with WT or mutant KRAS**
  - **PFS and OS were numerically greater with left-sided tumours**
- **No new safety signals were observed**

*OS data not shown in these summary slides. BEV, bevacizumab.

Lenz et al. J Clin Oncol 2016; 34 (suppl): abstr 3515

COLORECTAL CANCER

SECOND LINE (including immunotherapy)

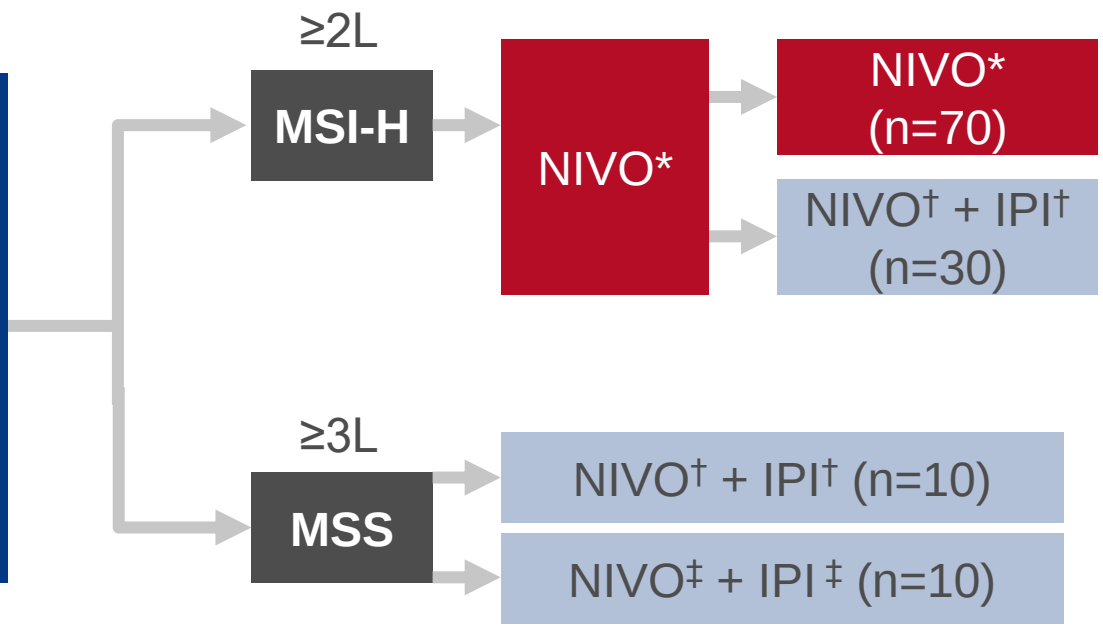
3501: Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results – Overman MJ, et al

Study objective

- To assess the efficacy and safety of nivolumab + ipilimumab vs nivolumab alone in patients with mCRC with or without MSI

Key patient inclusion criteria

- Histologically confirmed CRC
- Recurrent/metastatic disease
- ECOG PS ≤1
- PD on ≥1 therapy (MSI-H) or the latest treatment (all), or intolerance or refusal to take CT
- (n=120)



PRIMARY ENDPOINT(S)

- ORR (MSI-H; RECIST v1.1)

SECONDARY/EXPLORATORY ENDPOINTS

- Radiology review committee-assessed ORR (MSS)
- OS, PFS
- Safety

*3 mg/kg q2w; †NIVO 3 mg/kg + IPI 1 mg/kg q3w, then NIVO 3 mg/kg q2w; ‡NIVO 1 mg/kg + IPI 3 mg/kg q3w, then NIVO 3 mg/kg q2w. NIVO, nivolumab; IPI, ipilimumab.

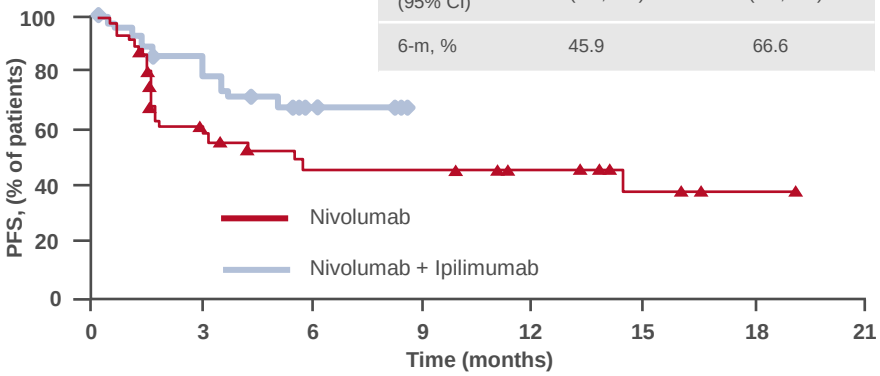
Overman et al. J Clin Oncol 2016; 34 (suppl): abstr 3501

3501: Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results – Overman MJ, et al

Key results

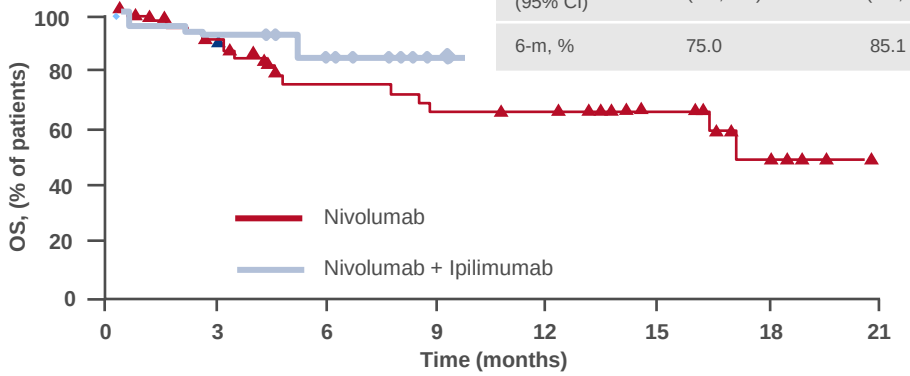
PFS in patients with MSI-H

	NIVO 3 mg/kg (n=70)	NIVO 3 mg/kg + IPI 1 mg/kg (n=30)
Median, m (95% CI)	17.1 (8.6, NE)	NE (3.4, NE)
6-m, %	45.9	66.6



OS in patients with MSI-H

	NIVO 3 mg/kg (n=70)	NIVO 3 mg/kg + IPI 1 mg/kg (n=30)
Median, m (95% CI)	17.1 (8.6, NE)	NE (NE, NE)
6-m, %	75.0	85.1



MSI-H	NIVO 3 mg/kg (n=47)	NIVO 3 mg/kg + IPI 1 mg/kg (n=27)
ORR, % (95% CI)	25.5 (15.4, 38.1)	33.3 (18.6, 50.9)

MSS	NIVO 1 mg/kg + IPI 3 mg/kg (n=10)	NIVO 3 mg/kg + IPI 1 mg/kg (n=10)
ORR, %	10 (n=1)	0
mPFS, m (95% CI)	2.28 (0.62, 4.40)	1.31 (0.89, 1.71)
mOS, m (95% CI)	11.53 (0.62, NE)	3.73 (1.22, 5.62)

IPI, ipilimumab; NE, not evaluable; NIVO, nivolumab.

Overman et al. J Clin Oncol 2016; 34 (suppl): abstr 3501

3501: Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results – Overman MJ, et al

Key results (continued)

MSI-H: AEs in ≥15% of patients, %	NIVO 3 mg/kg (n=47)		NIVO 3 mg/kg + IPI 1 mg/kg (n=27)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any AE	58.6	14.3	83.3	26.7
Fatigue	18.6	1.4	20.0	0
Diarrhoea	14.3	1.4	43.3	0
Pruritus	11.4	0	16.7	3.3
Nausea	7.1	0	20.0	0
Pyrexia	4.3	0	23.3	0
Any discontinuation due to AE	5.7	2.9	13.3	13.3

Conclusions

- Nivolumab alone had encouraging activity in patients with MSI-H mCRC
  - Nivolumab + ipilimumab also had promising preliminary activity in this population
- Responses to both treatments were durable in patients with MSI-H
- Both treatments had tolerable safety profiles, consistent with previous studies in other solid tumours

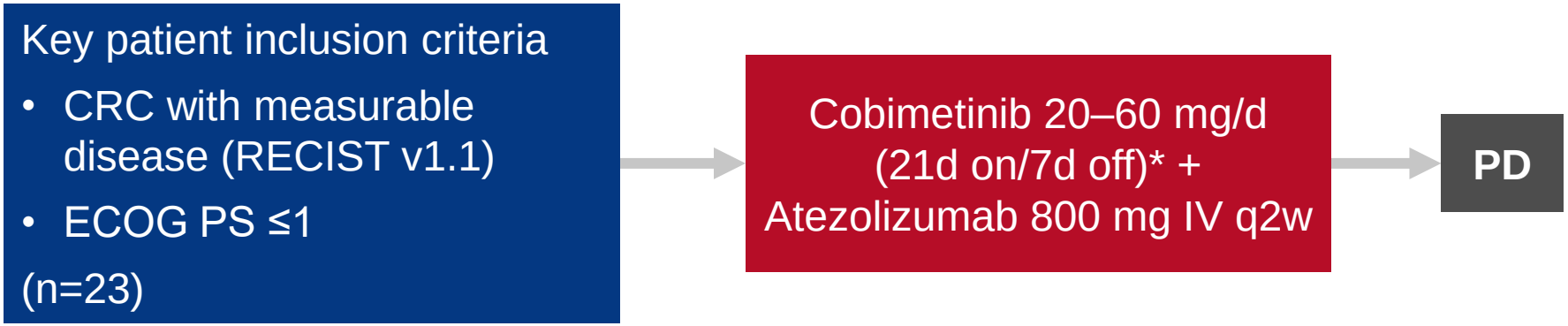
IPI, ipilimumab; NIVO, nivolumab.

Overman et al. J Clin Oncol 2016; 34 (suppl): abstr 3501

3502: Clinical activity and safety of cobimetinib (cobi) and atezolizumab in colorectal cancer (CRC) – Bendell JC, et al

Study objective

- To investigate the efficacy and safety of cobimetinib (MEK inhibitor) + atezolizumab (anti-PD-L1 mAb) in patients with CRC



PRIMARY ENDPOINT

- Safety

SECONDARY ENDPOINTS

- ORR
- PFS, OS

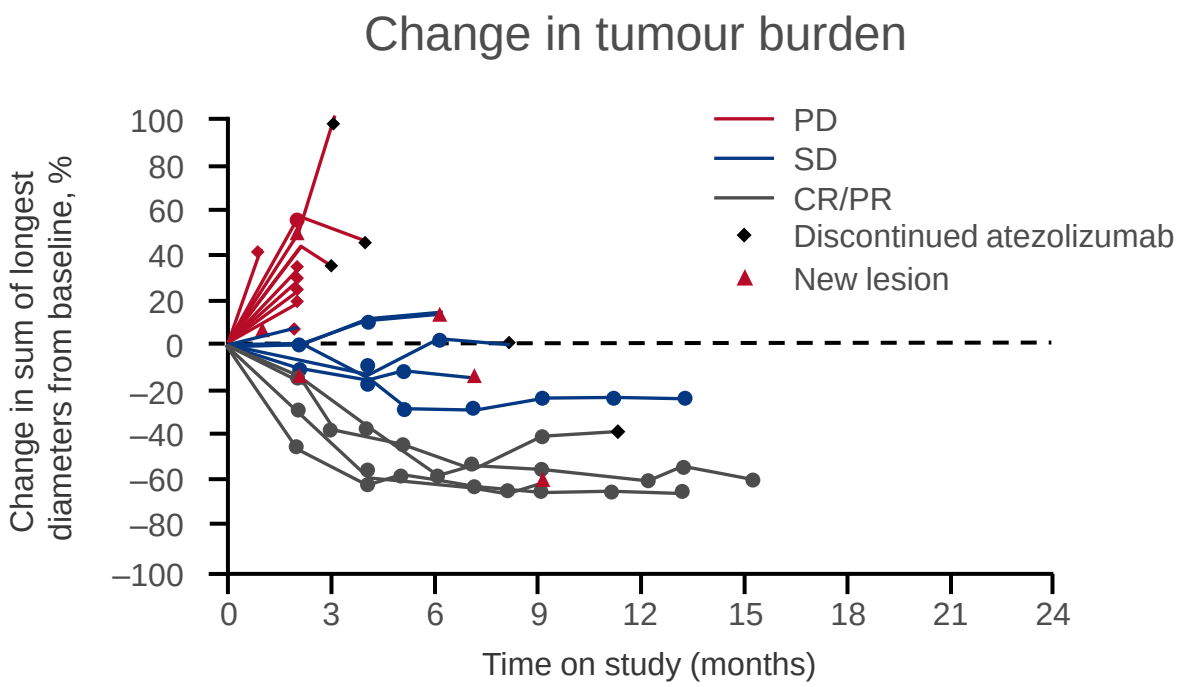
*Dose escalation.

Bendell et al. J Clin Oncol 2016; 34 (suppl): abstr 3502

3502: Clinical activity and safety of cobimetinib (cobi) and atezolizumab in colorectal cancer (CRC) – Bendell JC, et al

Key results

	6-month PFS, % (95% CI)	6-month OS, % (95% CI)	ORR, % (95% C)
KRAS mutant (n=20)	39 (0.16, 0.61)	77 (0.57, 0.97)	20 (5.7, 43.7)
All patients (n=23)	35 (0.14, 0.56)	72 (0.52, 0.93)	17 (5.0, 38.8)



Bendell et al. J Clin Oncol 2016; 34 (suppl): abstr 3502

3502: Clinical activity and safety of cobimetinib (cobi) and atezolizumab in colorectal cancer (CRC) – Bendell JC, et al

Key results (continued)

AEs, n (%)	n=23
Any	23 (100)
Grade 3	8 (35)
Grade 4	0
Grade 5	0
SAEs	2 (9)
AEs leading to cobimetinib withdrawal	4 (17)
AEs leading to atezolizumab withdrawal	0

Conclusions

- **Cobimetinib + atezolizumab was associated with superior clinical response than would be expected with either treatment alone in patients with MSS CRC**
- **These data suggest cobimetinib can sensitise tumours to atezolizumab by increasing MHC I expression on tumour cells + promoting CD8 T cell accumulation***
- **Cobimetinib + atezolizumab was well tolerated at the maximum administered dose**
- **Based on these results, the expansion of this study is currently ongoing**

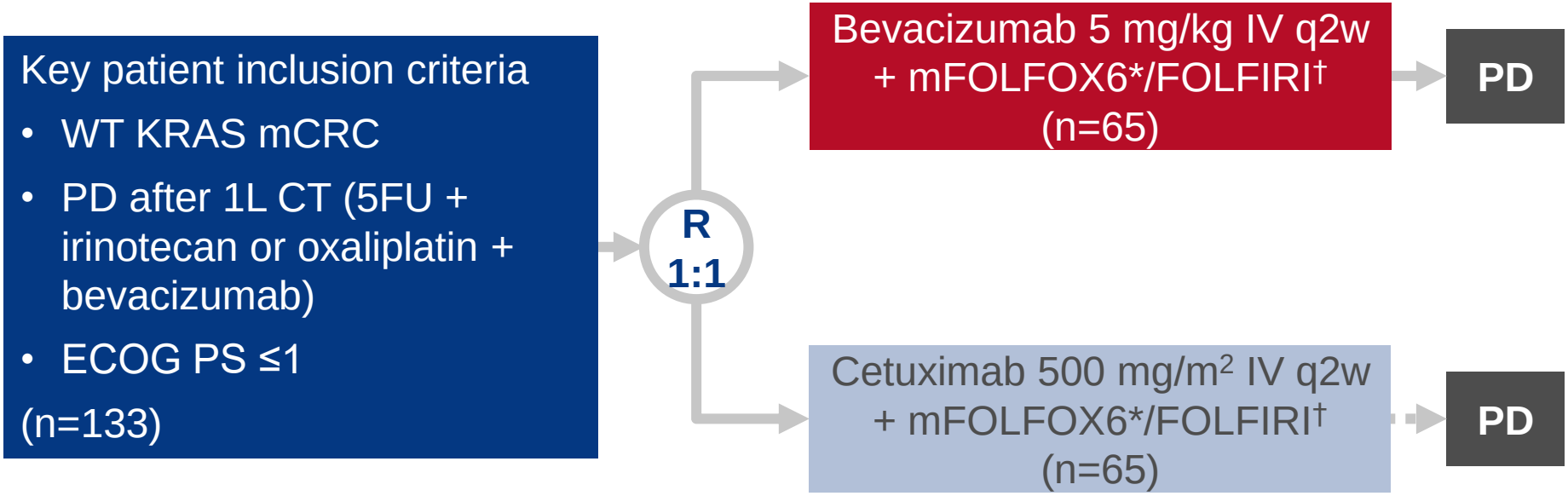
*Data not shown in these summary slides.

Bendell et al. J Clin Oncol 2016; 34 (suppl): abstr 3502

3514: Bevacizumab or cetuximab plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wtKRAS metastatic colorectal cancer: A randomized phase II study (Prodige 18 – Accord 22) – Hiret S, et al

Study objective

- To assess the efficacy and safety with crossover CT (FOLFIRI/mFOLFOX6) + bevacizumab or cetuximab, after progression with bevacizumab + CT in patients with WT KRAS mCRC



PRIMARY ENDPOINT(S)

- 4-month PFS

SECONDARY ENDPOINTS

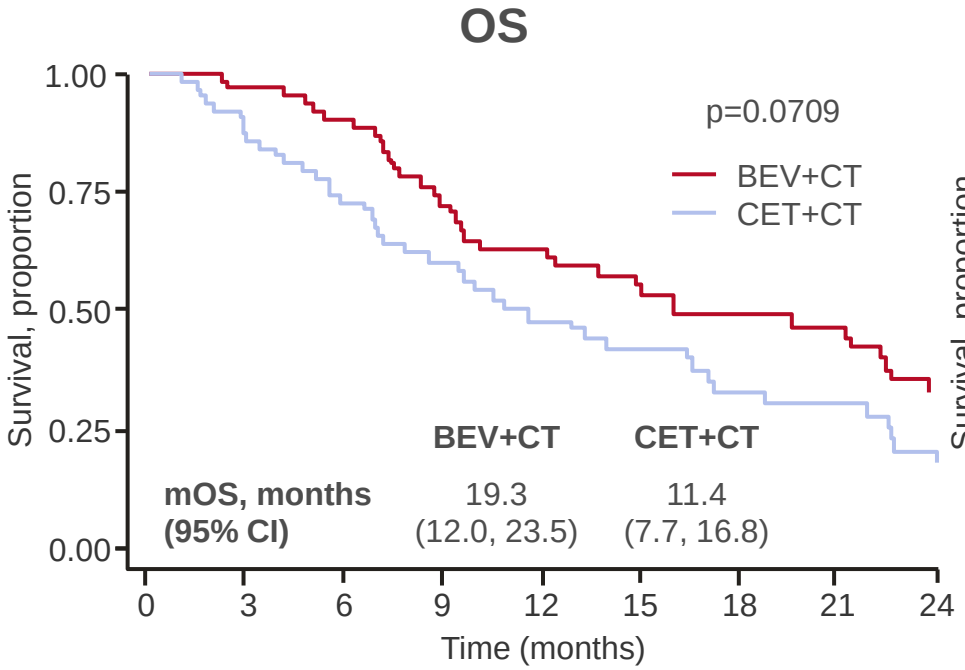
- ORR, mPFS, OS
- Safety, QoL

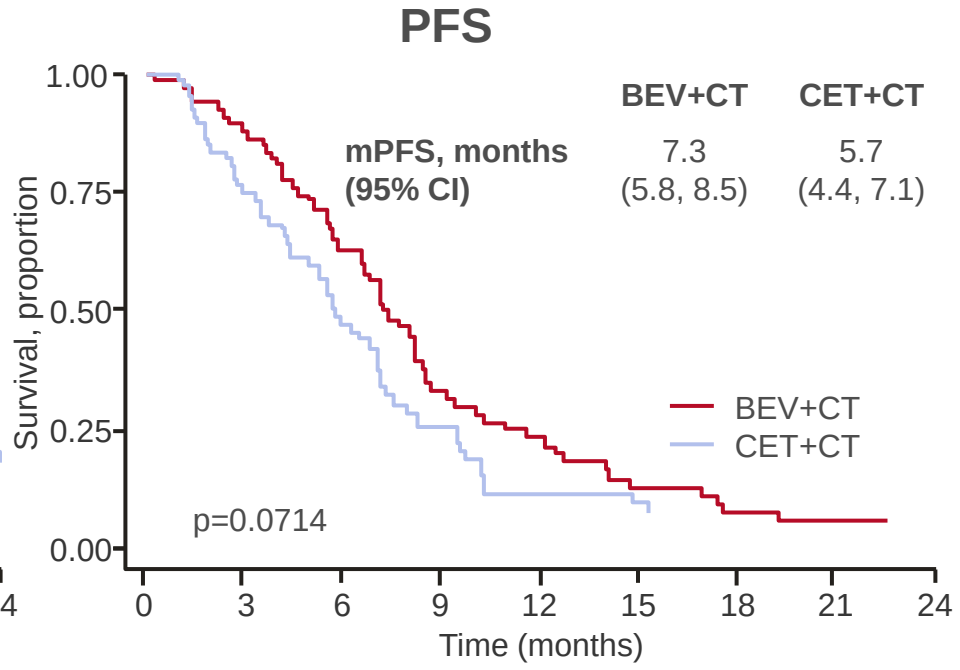
*Oxaliplatin 85 mg/m², leucovorin 400 mg/m² IV, 5FU 400 mg/m² bolus IV + 5FU 2400 mg/m² IV; †Irinotecan 180 mg/m², leucovorin 400 mg/m² IV, 5FU 400 mg/m² bolus IV + 5FU 2400 mg/m² IV.

Hiret et al. J Clin Oncol 2016; 34 (suppl): abstr 3514

3514: Bevacizumab or cetuximab plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wtKRAS metastatic colorectal cancer: A randomized phase II study (Prodige 18 – Accord 22) – Hiret S, et al

Key results





	Bevacizumab + CT (n=65)	Cetuximab + CT (n=65)
4-month PFS, % (95% CI)	81.5 (71.8, 91.2)	67.7 (56.0, 79.4)
ORR, % (95% CI)	24.6 (13.9, 35.4)	32.3 (20.2, 44.2)

BEV, bevacizumab; CET, cetuximab.

Hiret et al. J Clin Oncol 2016; 34 (suppl): abstr 3514

3514: Bevacizumab or cetuximab plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wtKRAS metastatic colorectal cancer: A randomized phase II study (Prodige 18 – Accord 22) – Hiret S, et al

Conclusions

- **In patients with WT KRAS mCRC who had progressed on bevacizumab + CT, continuation with bevacizumab + crossover CT was associated with a non-significant improvement in PFS and OS vs cetuximab + CT**
- **Multiple strategy in mCRC may help to chronicise disease and improve OS**
- **However, future strategies should focus on personalised therapies, with a better definition of resistance and sensitivity biomarkers**

Hiret et al. J Clin Oncol 2016; 34 (suppl): abstr 3514

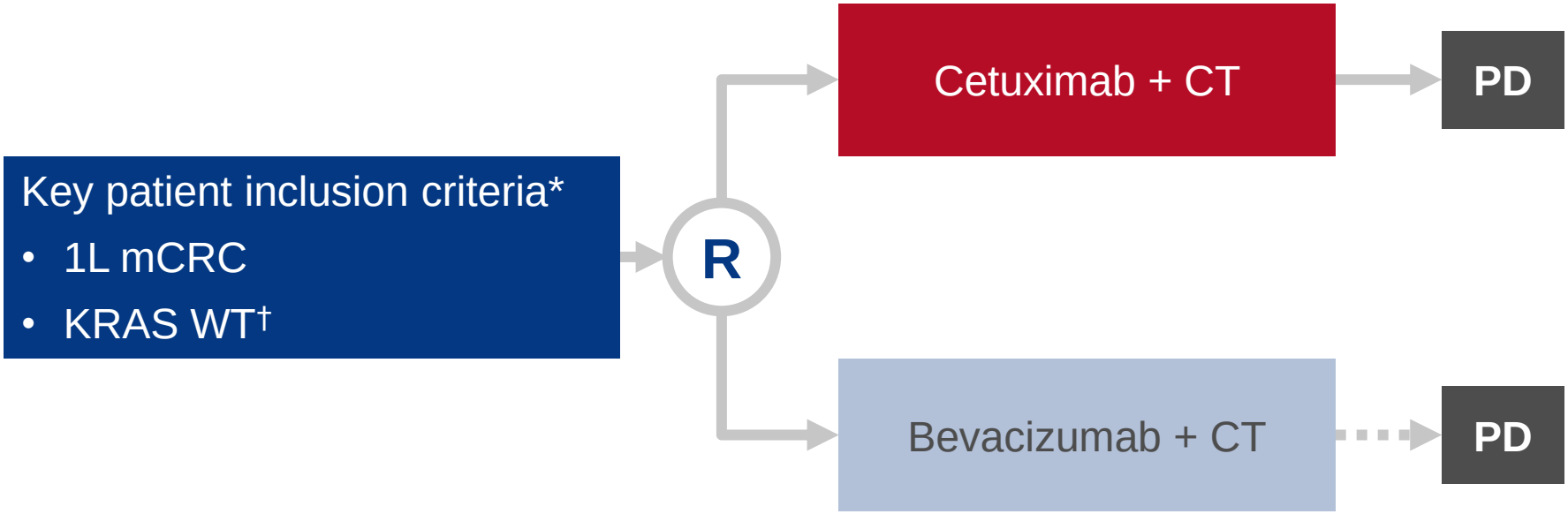
COLORECTAL CANCER

BIOMARKER

3504: Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance) – Venook AP, et al

Study objective

- To investigate the impact of primary tumour location (right vs left side) on survival in patients with mCRC*



ENDPOINTS

- OS and PFS by primary tumour location (left vs right)

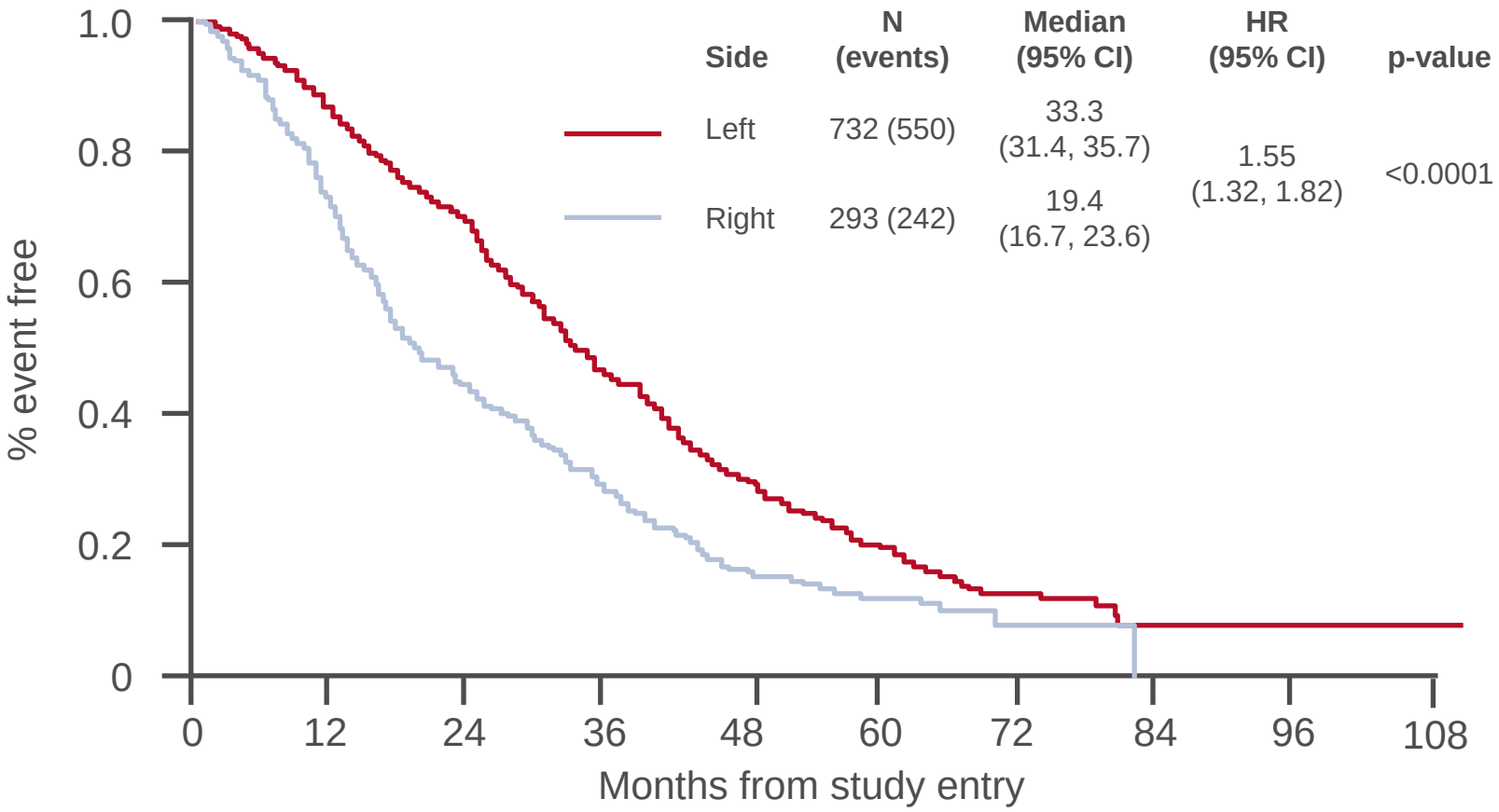
*Post-hoc analysis of the CALGB/SWOG 80405 study;
†Prior to amendment in June 2008.

Venook et al. J Clin Oncol 2016; 34 (suppl): abstr 3504

3504: Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance) – Venook AP, et al

Key results

OS by 1° tumour location (overall population)



Side	N (events)	Median (95% CI)	HR (95% CI)	p-value
Left	732 (550)	33.3 (31.4, 35.7)	1.55 (1.32, 1.82)	<0.0001
Right	293 (242)	19.4 (16.7, 23.6)		

Venook et al. J Clin Oncol 2016; 34 (suppl): abstr 3504

3504: Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance) – Venook AP, et al

Key results (continued)

KRAS WT	All patients (n=1025)	Cetuximab	Bevacizumab
mOS, HR (95% CI); p-value	1.55 (1.32, 1.82); <0.0001	*1.87 (1.48, 2.32); <0.0001	1.32 (1.05, 1.65); 0.01
mPFS, HR (95% CI); p-value	1.03 (1.11, 1.50); 0.0006	1.56 (1.26, 1.94); <0.0001	1.06 (0.86, 1.31); 0.55

Conclusions

- **OS and PFS were superior in patients with KRAS WT mCRC with left- vs right-sided 1° tumours**
- **Efficacy with 1L cetuximab vs bevacizumab differ according to 1° tumour location**
- **More precise biomarkers are needed to replace left- or right-sided tumour location in order to individualise patient care**
  - **However, for now mCRC studies should stratify patients by tumour sidedness**
- **These data support 1L bevacizumab in patients with mCRC and right-sided 1° tumours**

*Corresponds to a 19.3-month increase in mOS when the primary is on the left.

Venook et al. J Clin Oncol 2016; 34 (suppl): abstr 3504

Main discussion points
Kimmie Ng: Side matters

- Data on mOS by side has prognostic value, while data on biologic therapies divided by side interaction has predictive value

Strengths	Limitations
Large sample size	Retrospective post-hoc analysis
Clinical trial population • Uniform therapy • Standardised follow-up • Detailed information on prognostic factors • Prognostic vs predictive	No examination of individual colon subsites
	KRAS WT codon 12/13 only
	No molecular information
	Generalisability

Venook et al. J Clin Oncol 2016; 34 (suppl): abstr 3504

Main discussion points
Kimmie Ng: Side matters

- The study was thought to have confirmed prognostic associations, as well as investigating predictive implications
- Should EGFR antibodies be withheld in the first-line setting from patients with right-sided primaries? This remains to be determine
- Comprehensive molecular and genetic analysis of specimens from phase 2 and 3 clinical trial cohorts is encouraged, along with further detailed analysis of biological differences within subsites of the right and left colon
- These data are in agreement with previous results from the FIRE-3 study, which showed improved OS with left vs right sided tumours in patients receiving FOLFIRI + cetuximab
  - **FOLFIRI + cetuximab arm**: HR 0.26 (95% CI 0.16, 0.42); p<0.0001
  - **FOLFIRI + bevacizumab arm**: HR 0.63 (95% CI 0.41, 0.97); p=0.034

Venook et al. J Clin Oncol 2016; 34 (suppl): abstr 3504

3505: The relationship between primary tumor sidedness and prognosis in colorectal cancer – Schrag D, et al

Study objective

- To assess the impact of 1° tumour location (right vs left side) and OS in Stage-specific cohorts of patients with CRC

Study design

- Patients diagnosed between 2000 and 2012 with CRC in a SEER region were categorised by stage at diagnosis, and followed for deaths until the end of 2013

- The 1° tumour site was characterised as right-sided 1° (cecum to transverse colon), left-sided 1° (splenic flexure to sigmoid descending colon), 1° rectum (rectosigmoid) and rectal

- Primary endpoint: OS

- Covariates:
  - Age, gender, race, ethnicity, marital status, surgery, year of diagnosis and tumour substage

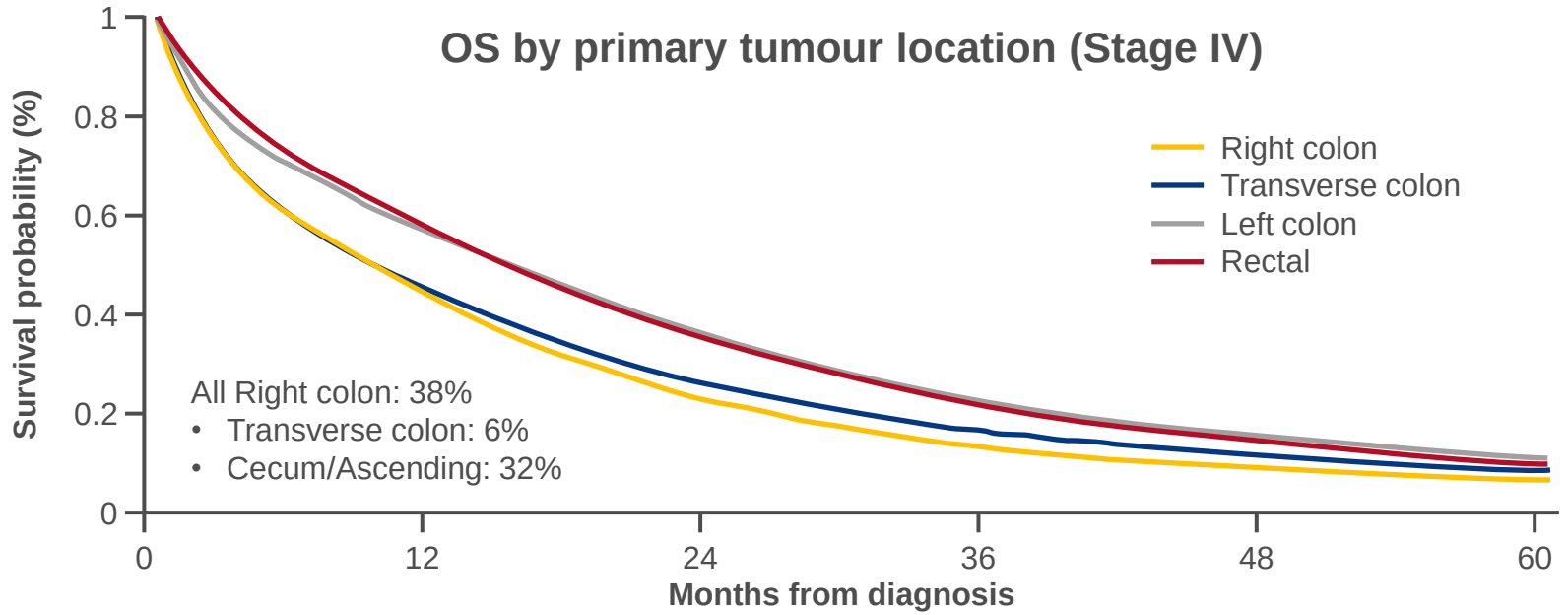
Schrag et al. J Clin Oncol 2016; 34 (suppl): abstr 3505

3505: The relationship between primary tumor sidedness and prognosis in colorectal cancer – Schrag D, et al

Key results

OS (Stage IV; n=64,770)	Adjusted HR	95% CI
Right vs left colon	1.25	1.22, 1.27
Rectal vs left colon	0.83	0.81, 0.85

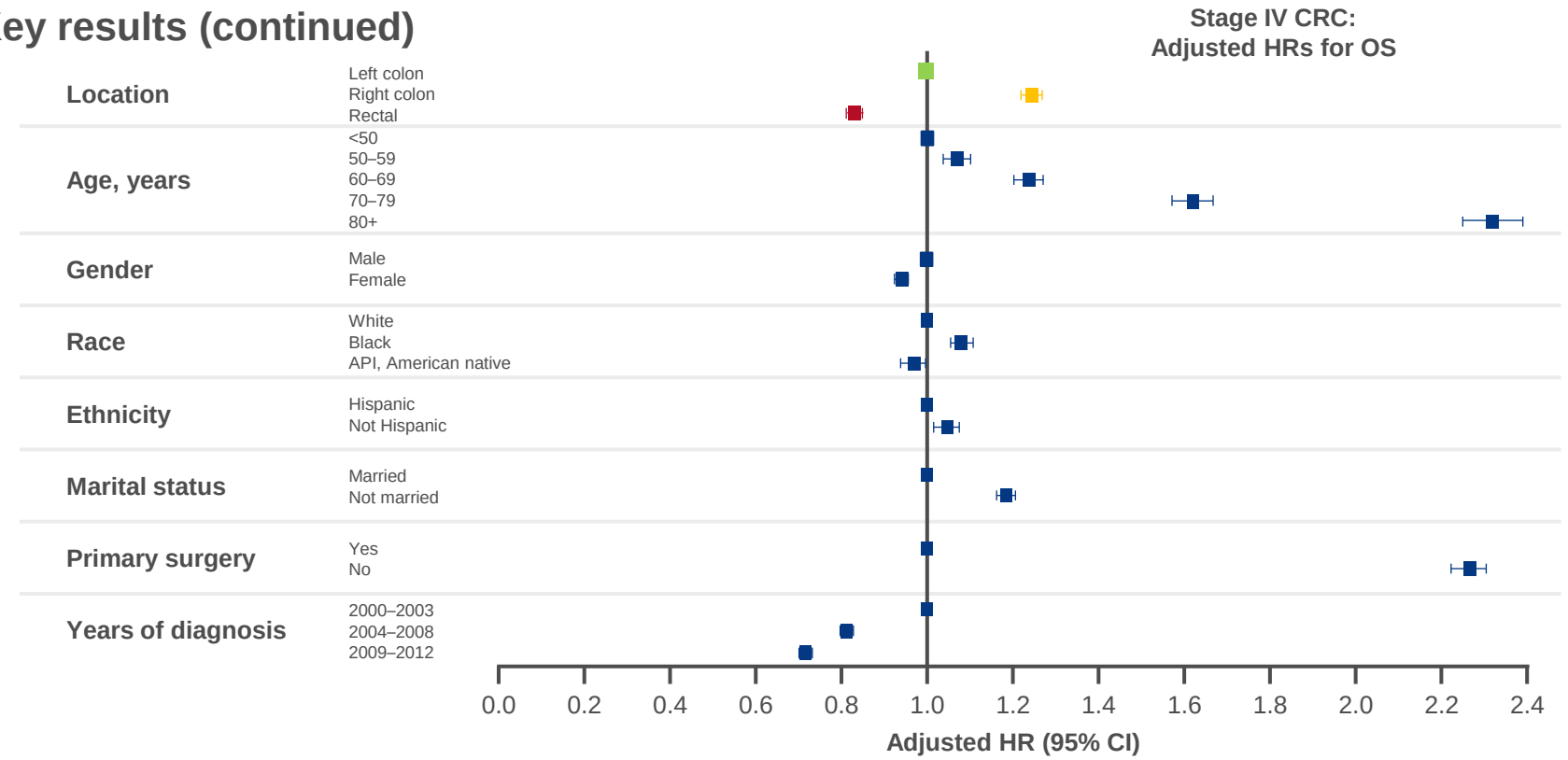
mOS, months	Right	Left	Rectal	Difference (right vs left)
Stage IV	9.5	15.5	15.5	6
Stage III	62.5	93.5	85.5	31



Schrag et al. J Clin Oncol 2016; 34 (suppl): abstr 3505

3505: The relationship between primary tumor sidedness and prognosis in colorectal cancer – Schrag D, et al

Key results (continued)



Conclusions

- **Right-sided 1° tumours have inferior prognosis in patients with CRC**
- **Prognosis is improving in both right- and left-sided tumours**
- **Tumour location may be beneficial, particularly when genomic data are unavailable**

API, Asian-Pacific Islander.

Schrag et al. J Clin Oncol 2016; 34 (suppl): abstr 3505

3506: Association of primary (1°) site and molecular features with progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (αEGFR) therapy – Lee MS, et al

Study objective

- To evaluate the effect of 1° tumour site (right vs left) on survival after anti-EGFR-based therapy in patients with mCRC, and to explore the association between molecular subtypes of CRC and 1° tumour site

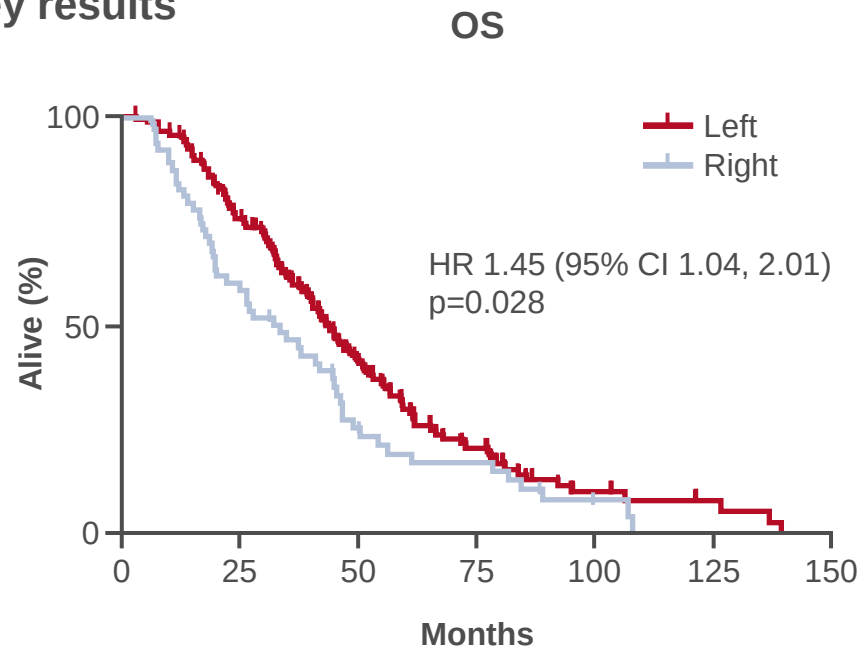
Study design

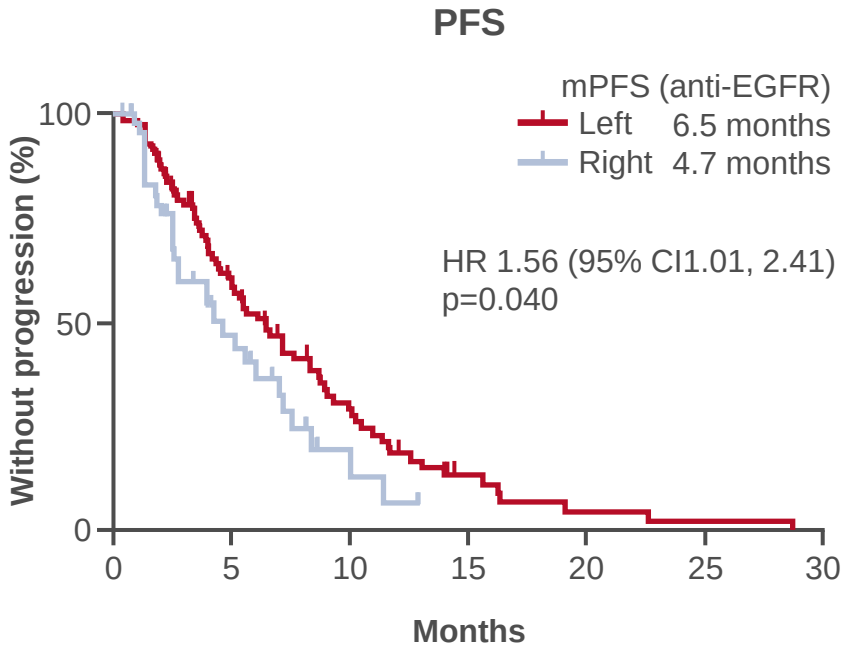
- Tumour tissue from 195 patients with 5FU refractory KRAS WT mCRC were tested for CIMP status (high vs low) for the following genes, using bisulfite pyrosequencing + PCR:
  - *MINT1, MINT2*, *MINT31*, *p14, p16, hMLH1*
- *NRAS*, *BRAF* + *PIK3CA* status was determined using next generation sequencing
- MSI was assessed by IHC or PCR
- Univariate and multivariate Cox regression analyses were conducted with multiple imputations

Lee et al. J Clin Oncol 2016; 34 (suppl): abstr 3506

3506: Association of primary (1°) site and molecular features with progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (αEGFR) therapy – Lee MS, et al

Key results





PFS, right-sided	HR (95% CI)	p-value
Overall population	1.32 (0.81, 2.16)	0.27
BRAF mutant	1.96 (1.04, 3.70)	0.04
NRAS mutant	1.97 (1.16, 3.33)	0.01
CIMP high	1.80 (1.02, 3.17)	0.04

Lee et al. J Clin Oncol 2016; 34 (suppl): abstr 3506

3506: Association of primary (1°) site and molecular features with progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (αEGFR) therapy – Lee MS, et al

Key results (conclusions)

CRC subtype, n (%)	Right (n=68)	Left (n=61)
CMS 1 (immune)	33 (49)	5 (8)
CMS 2 (canonical)	22 (32)	37 (61)
CMS 3 (metabolic)	6 (9)	2 (3)
CMS 4 (mesenchymal)	7 (10)	17 (28)

Conclusions

- **In patients with mCRC, right-sided 1° tumours are associated with inferior OS + PFS after anti-EGFR therapy**
- **Molecular analyses suggest that these tumours are impacted by BRAF, hypermethylation and distinct gene expression patterns**
- **The underlying biology may explain the effect of right-sided tumours on EGFR outcomes**

CMS, consensus molecular subtype.

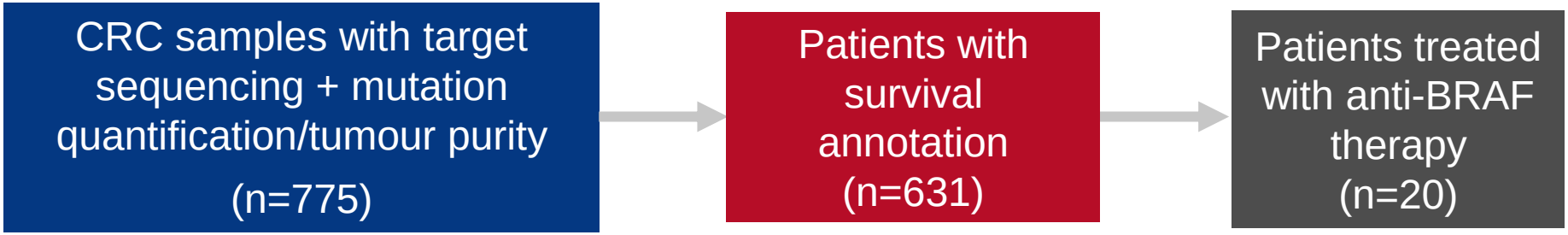
Lee et al. J Clin Oncol 2016; 34 (suppl): abstr 3506

3509: Clonality patterns of driver mutations (mut) to reveal spatial-temporal genomic heterogeneity in colorectal cancer (CRC) – Dienstmann R, et al

Study objective

- To examine the potential clinical implications of driver mutations in unpaired tumour samples from patients with primary vs metastatic CRC

Study design



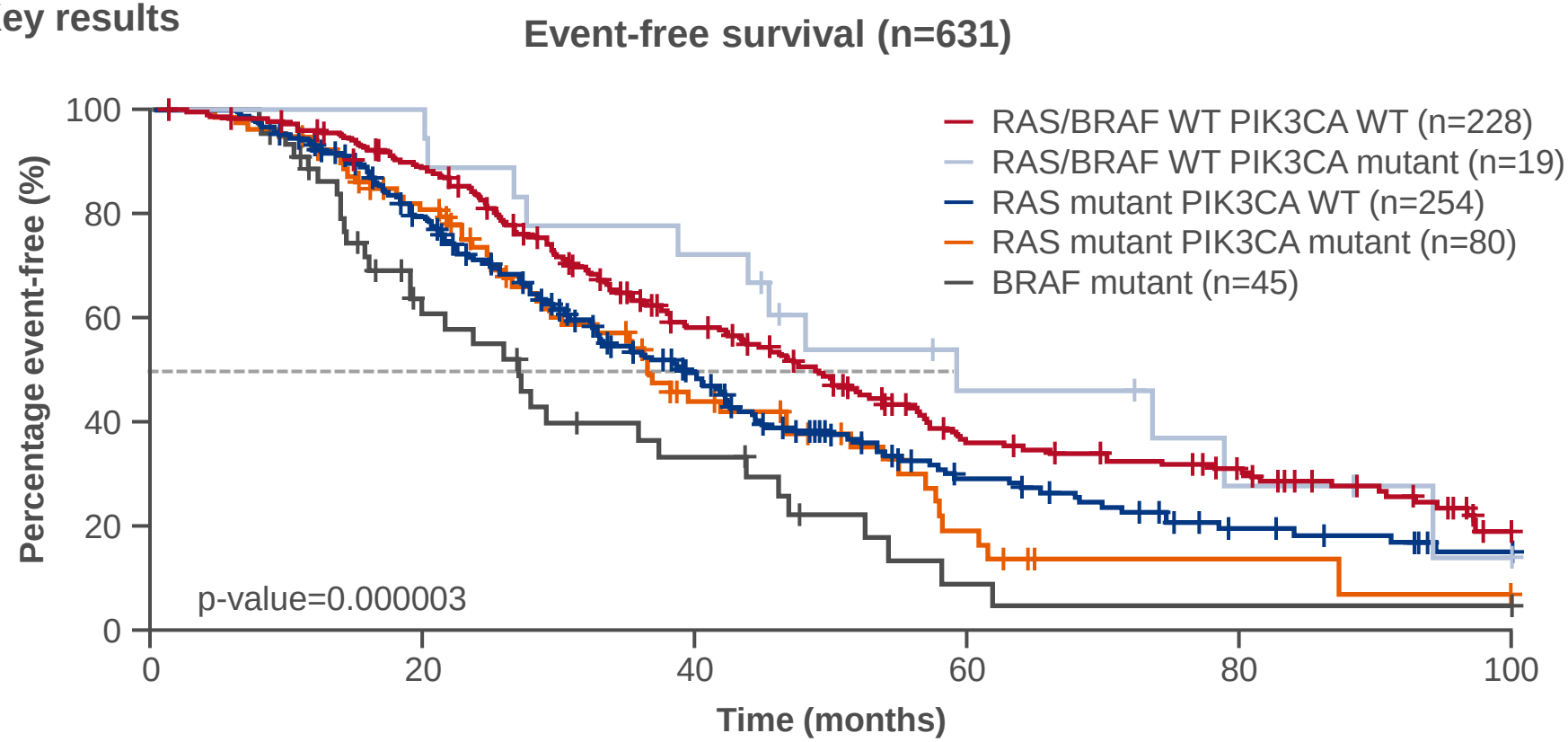
- The prognostic and predictive values of mutant allele fractions (MAFs)* was determined for unpaired primary vs metastatic CRC

*Defined as the number of mutant reads divided by the total number of read at the specific genomic position of interest.

Dienstmann et al. J Clin Oncol 2016; 34 (suppl): abstr 3509

3509: Clonality patterns of driver mutations (mut) to reveal spatial-temporal genomic heterogeneity in colorectal cancer (CRC) – Dienstmann R, et al

Key results



Median

46 months, control

55 months, HR 0.90 (95% CI 0.55, 1.45)

36 months, HR 1.39 (95% CI 1.14, 1.70)

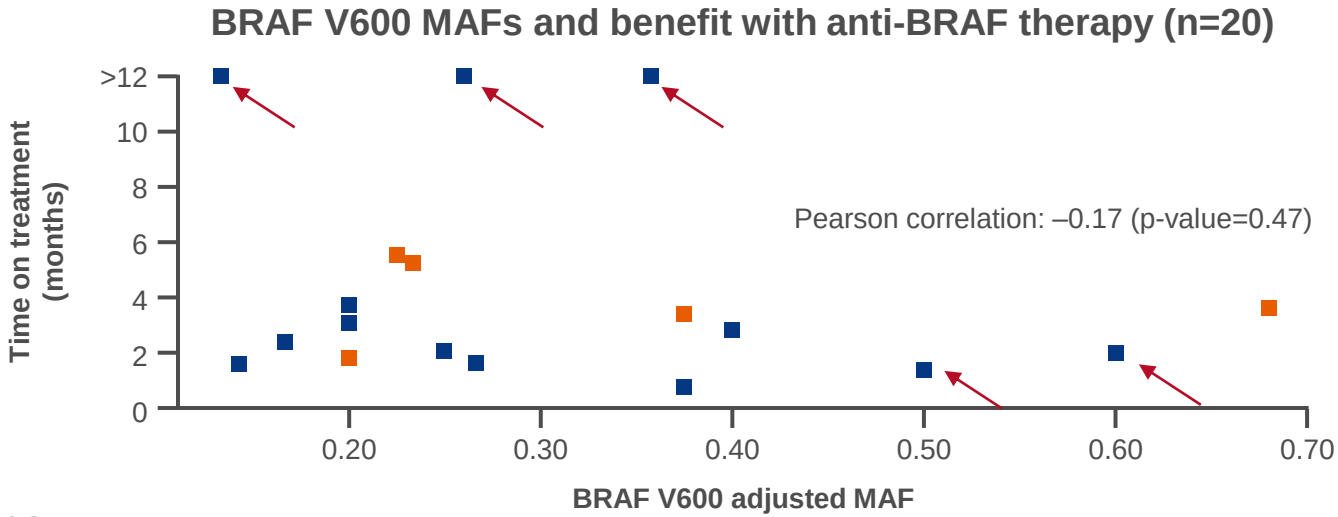
36 months, HR 1.40 (95% CI 1.06, 1.87)

27 months, HR 2.30 (95% CI 1.63, 3.27)

Dienstmann et al. J Clin Oncol 2016; 34 (suppl): abstr 3509

3509: Clonality patterns of driver mutations (mut) to reveal spatial-temporal genomic heterogeneity in colorectal cancer (CRC) – Dienstmann R, et al

Key results (continued)



Conclusions

- Clonality of RAS mutations and subclonality of BRAF V600 mutations and a subset of PIK3CA mutations were reported in patients CRC*
- Differences in primary vs metastatic sites for TP53 and BRAF V600 MAFs suggest acquired copy number events and clonal selection after therapy*
- RAS mutants and BRAF V600 have a negative impact on survival in the metastatic setting, irrespective of MAFs
- BRAF V600 MAFs in primary tissue did not predict benefit with targeted drugs in the metastatic setting

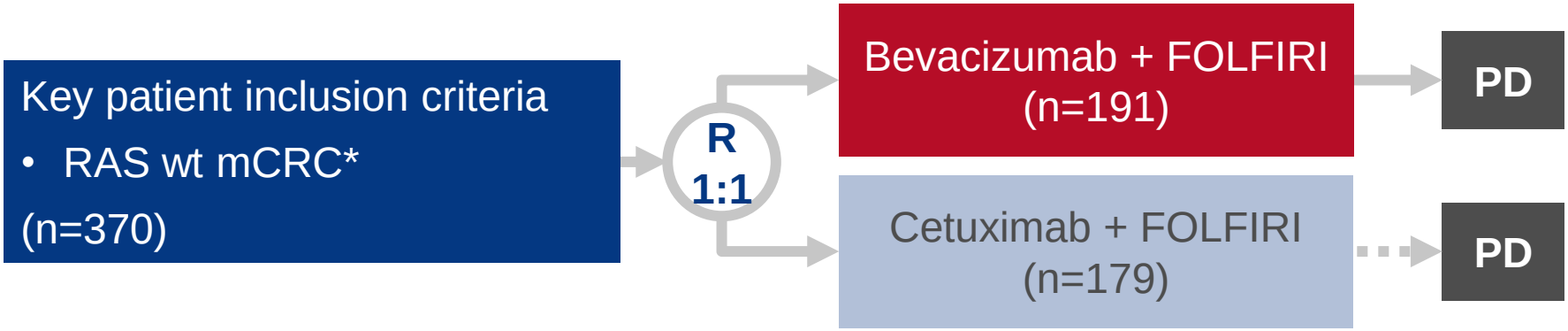
*Data not included in these summary slides.
MAF, mutant allele fraction.

Dienstmann et al. J Clin Oncol 2016; 34 (suppl): abstr 3509

3516: MiR 31 3p as a predictive biomarker of cetuximab efficacy effect in metastatic colorectal cancer (mCRC) patients enrolled in FIRE-3 study – Laurent-Puig P, et al

Study objective

- To determine the predictive value of miR-31-3p in patients with mCRC receiving 1L CT with FOLFIRI + cetuximab vs FOLFIRI + bevacizumab*



PRIMARY ENDPOINTS (original study)

- OS, PFS

EXPLORATORY ENDPOINTS (current analysis)

- OS, PFS and ORR according to miR-31-3p expression level

miR-31-3p expression

- RNA was extracted from FFPE tumour samples and miR-31-3p expression levels were measured by qRT-PCR
  - Patients were divided into “low” or “high” miR-31-3p expression level groups based on a pre-specified cut-off threshold

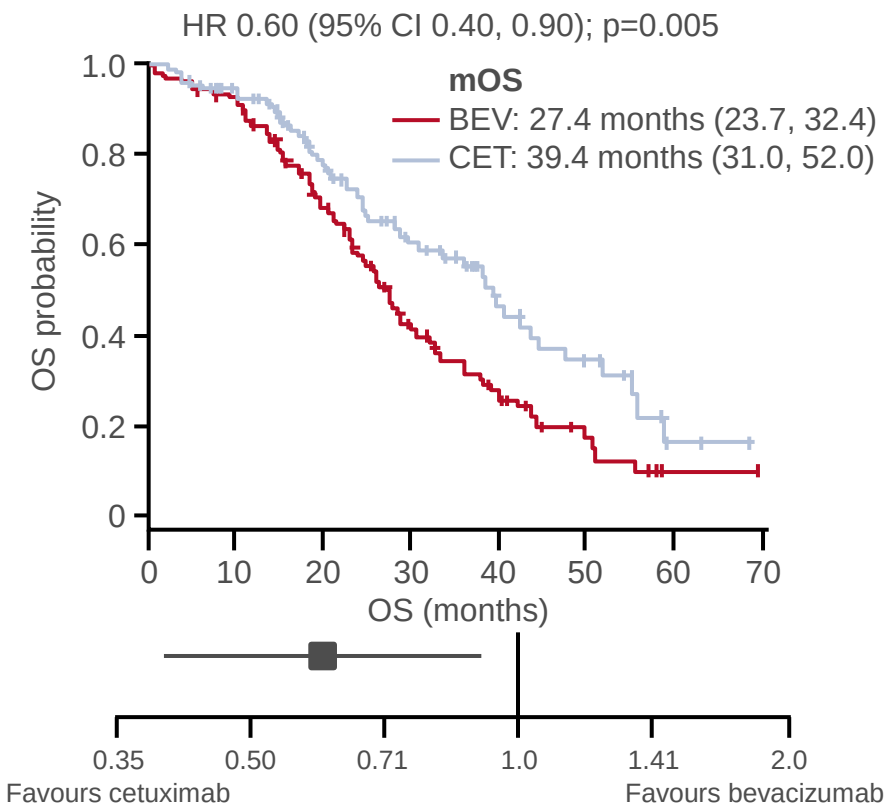
*Sub-analysis of the FIRE-3 study.

Laurent-Puig, et al. J Clin Oncol 2016; 34 (suppl): abstr 3516

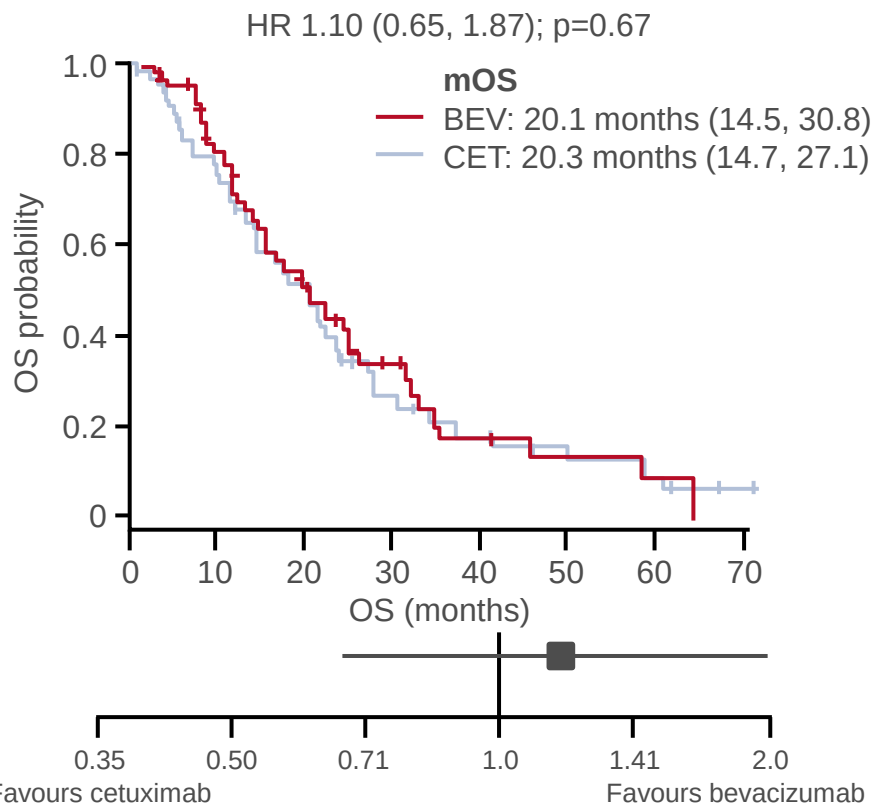
3516: MiR 31 3p as a predictive biomarker of cetuximab efficacy effect in metastatic colorectal cancer (mCRC) patients enrolled in FIRE-3 study – Laurent-Puig P, et al

Key results

OS: Low miR-31-3p



OS: High miR-31-3p



Treatment effect heterogeneity: p=0.07; p=0.004*

*Weighting by inverse of propensity score.

Laurent-Puig, et al. J Clin Oncol 2016; 34 (suppl): abstr 3516

3516: MiR 31 3p as a predictive biomarker of cetuximab efficacy effect in metastatic colorectal cancer (mCRC) patients enrolled in FIRE-3 study – Laurent-Puig P, et al

Key results (continued)

	Low miR-31-3p (n=245)		High miR-31-3p (n=125)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
PFS	0.82 (0.59, 1.13)	0.16	1.27 (0.81, 2.02)	0.24
ORR	3.37 (1.70, 6.67)	0.0005	1.25 (0.56, 2.77)	0.59

- ORR, miR-31-3p low: 63% with bevacizumab vs 85% with cetuximab
- ORR, miR-31-3p high: 55% with bevacizumab vs 64% with cetuximab

Conclusions

- **miR-31-3p predicted cetuximab effect on OS, PFS and ORR in patients with mCRC**
- **The beneficial effect of cetuximab seen in the FIRE-3 study was restricted to patients with low miR-31-3p levels**
- **miR-31-3p expression is clinically useful in selecting patients for 1L anti-EGFR therapy**

Laurent-Puig, et al. J Clin Oncol 2016; 34 (suppl): abstr 3516

3517: Validation of HER2 amplification as a negative predictive biomarker for anti-epidermal growth factor receptor antibody therapy in metastatic colorectal cancer – Raghav KP, et al

Study objective

- To assess the impact of HER2 amplification on survival in patients with mCRC treated with anti-EGFR-based therapy

Key patient inclusion criteria

- RAS + BRAF WT mCRC

(n=213)

→ **Cohort 1:** HER2 amplification tested (n=114)

→ **Cohort 2:** HER2 amplification validated (HER2$^+$ [n=37], HER2$^-$ [n=62]) (n=99)

PRIMARY ENDPOINT(S)

- PFS

SECONDARY ENDPOINTS

- OS

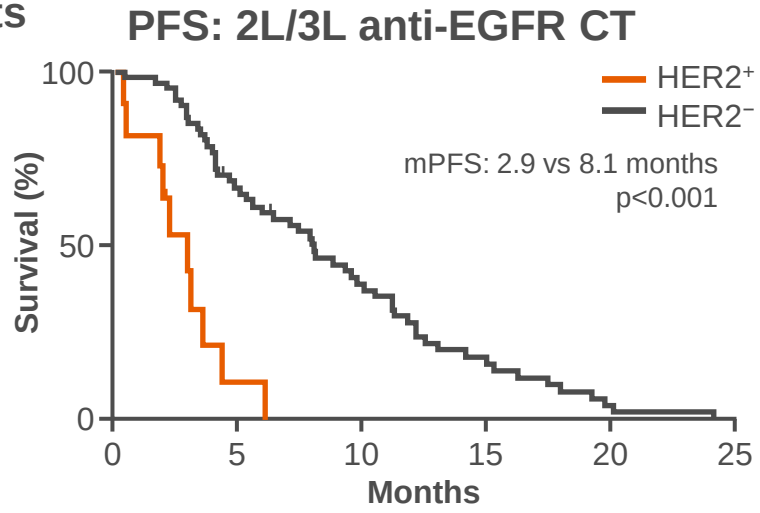
- **Cohort 1:** HER2 amplification was assessed by IHC and dual in-situ hybridization
  - HER2 amplification defined as HER2/CEP17 ≥2.2
- **Cohort 2:** HER2 amplification was previously identified by next-generation sequencing
  - HER2$^+$ defined as ≥4 copies

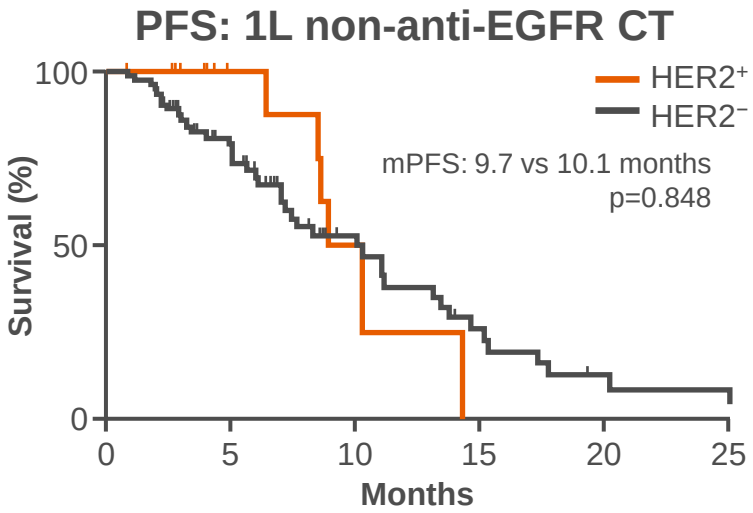
Raghav et al. J Clin Oncol 2016; 34 (suppl): abstr 3517

3517: Validation of HER2 amplification as a negative predictive biomarker for anti-epidermal growth factor receptor antibody therapy in metastatic colorectal cancer – Raghav KP, et al

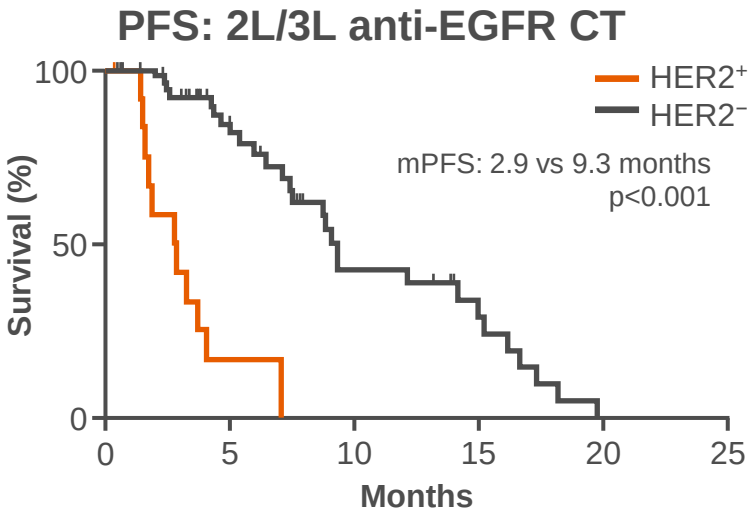
Key results

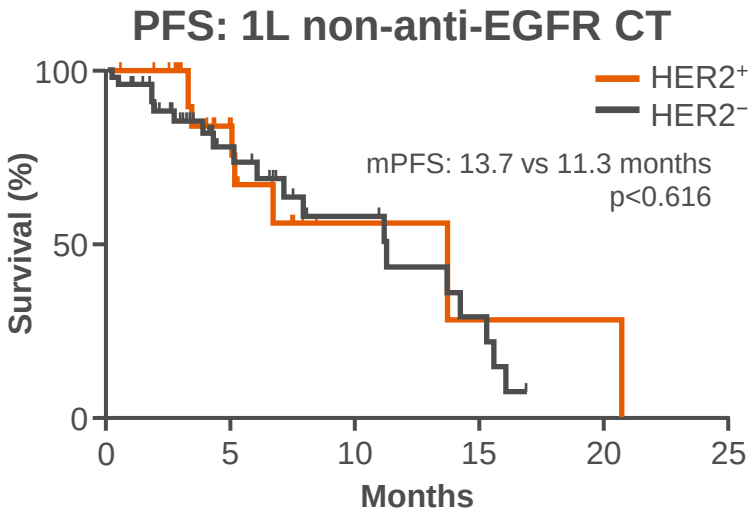
Cohort 1





Cohort 2



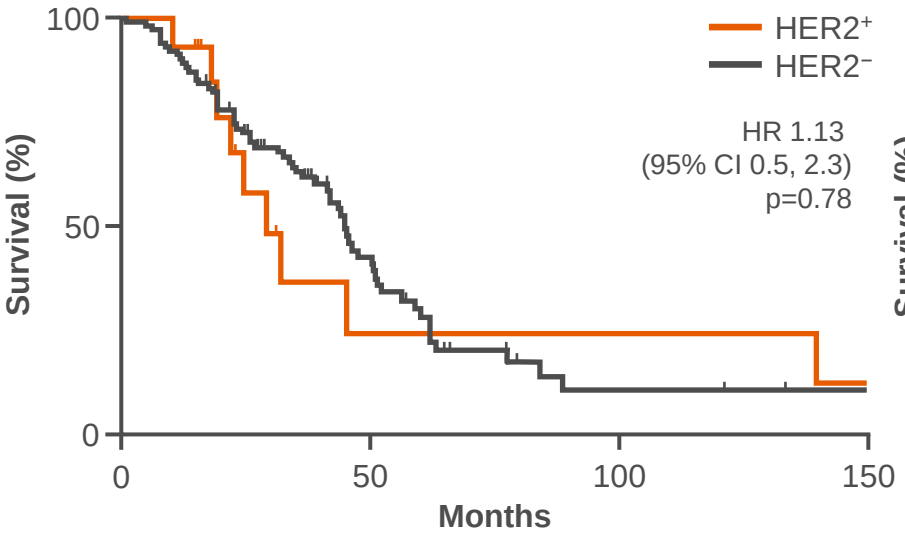


Raghav et al. J Clin Oncol 2016; 34 (suppl): abstr 3517

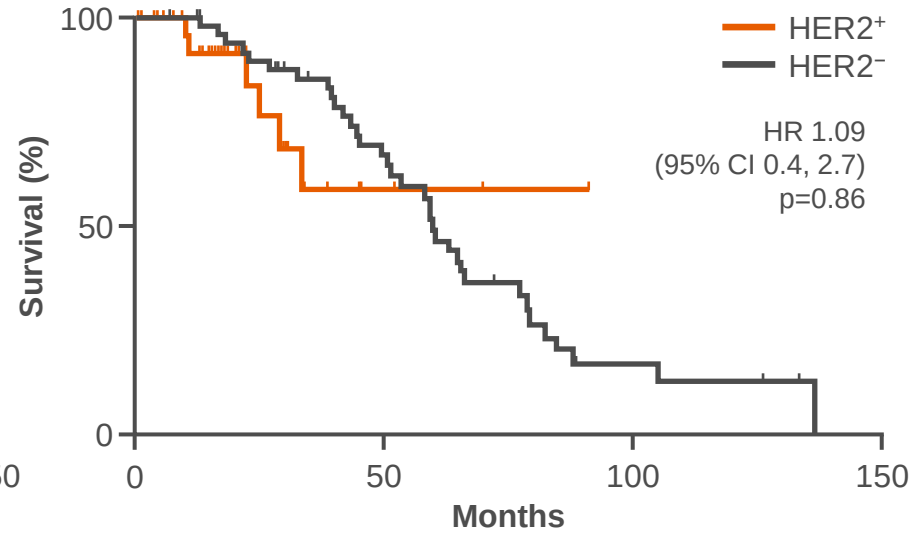
3517: Validation of HER2 amplification as a negative predictive biomarker for anti-epidermal growth factor receptor antibody therapy in metastatic colorectal cancer – Raghav KP, et al

Key results (continued)

OS: Cohort 1 (overall population)



OS: Cohort 2 (overall population)



Conclusions

- HER2 amplifications are seen in a distinct subset of patients with mCRC
  - They are largely independent of RAS and BRAF V600E mutations
- HER2 amplification is a robust negative predictor for efficacy of anti-EGFR therapy
  - The magnitude of its effect is comparable to RAS mutations

Raghav et al. J Clin Oncol 2016; 34 (suppl): abstr 3517

3520: Immunologic profiling of consensus molecular subtype (CMS) stratified colorectal cancer (CRC) primary and liver metastectomy specimens: Implications for immune targeting of proficient mismatch repair CRC – Reilley M, et al

Study objective

- To conduct immunologic profiling of primary tumours (MSI + MSS) and liver metastatectomy specimens in patients with CRC

Study design

- Archived tumour samples were analysed by IHC staining:
  - 23 primary MSI tumours
  - 45 primary MSS tumours
  - 34 untreated liver metastases
- Markers for T cell, B cell and myeloid cell lineages were used
- Immune regulatory surface markers and consensus molecular subtypes (CMS) of CRC were evaluated for possible correlations:
  - CMS1: MSI immune, 14%
  - CMS2: Canonical, 37%
  - CMS3: Metabolic, 13%
  - CMS4: Mesenchymal, 23%
- The average percent expression of surface markers was calculated for each group

Reilley et al. J Clin Oncol 2016; 34 (suppl): abstr 3520

3520: Immunologic profiling of consensus molecular subtype (CMS) stratified colorectal cancer (CRC) primary and liver metastectomy specimens: Implications for immune targeting of proficient mismatch repair CRC – Reilley M, et al

Key results

- **T-cell and macrophage infiltrates**
  - Liver metastases contained significantly more macrophages than primaries ($p<0.01$)
  - MSI primaries had higher levels of $CD8^+$ cells ($p<0.01$) and similar levels of $CD4^+$ cells
  - Primary tumours had high levels of infiltrating T cells than liver metastases ($p<0.01$)
- **PD-1/PD-L1 in MSI-H tumours and by CMS subtype**
  - PD-L1 expression was significantly higher in MSI-H infiltrates ($p<0.01$)
  - $CD8^+$ T cell infiltration was highest in CMS1 ($p<0.01$)
  - CMS1 tumours contained significantly higher levels of PD-L1 expression ($p<0.01$)
- **OX40 and ICOS by CMS subtype**
  - CMS3 had higher levels of OX40 in the tumour centre ($p=0.05$) and invasive margin ($p<0.01$) than other subtypes
  - CMS3 also had higher expression of ICOS in the tumour centre ($p<0.05$) compared with non-CMS3 subtypes

CMS, consensus molecular subtypes.

Reilley et al. J Clin Oncol 2016; 34 (suppl): abstr 3520

3520: Immunologic profiling of consensus molecular subtype (CMS) stratified colorectal cancer (CRC) primary and liver metastectomy specimens: Implications for immune targeting of proficient mismatch repair CRC – Reilley M, et al

Key results (continued)

- **Regulatory T cell infiltrate**
  - A greater proportion of Treg cells were present in primary tumours than liver metastases ($p<0.01$)

Conclusions

- **These data support PD-1/PD-L1 blockade in CMS1 and MSI tumours**
- **Liver metastases appear to have a myeloid cell predominant infiltrate that is distinct from primary tumours**
- **The CMS3 CRC subtype has increased expression of OX40 + ICOS**
  - **This pattern of immune surface marker expression suggests a potential benefit from novel immunotherapy combinations**
- **The greater proportion of Tregs in primary tumours vs liver metastases has therapeutic implications**

CMS, consensus molecular subtypes.

Reilley et al. J Clin Oncol 2016; 34 (suppl): abstr 3520

COLORECTAL CANCER

ENDOSCOPY AND SURGERY

3507: CREST: Randomised phase III study of stenting as a bridge to surgery in obstructing colorectal cancer—Results of the UK ColoRectal Endoscopic Stenting Trial (CREST) – Hill J, et al

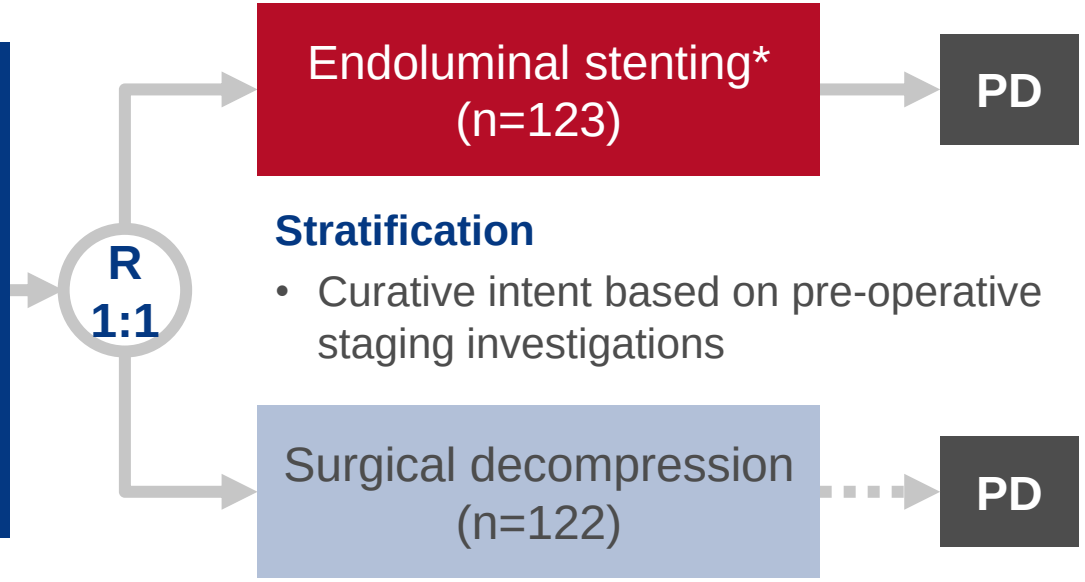
Study objective

- To investigate the effects of endoluminal stenting vs emergency surgery on outcomes and QoL in patients with potentially curable CRC

Key patient inclusion criteria

- Left-sided CRC
- Radiological evidence of obstruction
- No evidence of peritonitis or perforation

(n=245)



Stratification

- Curative intent based on pre-operative staging investigations

PRIMARY ENDPOINTS

- Length of hospital stay
- 30-day mortality

SECONDARY ENDPOINTS

- Stenting completion, complication rate
- Presence/duration of stoma/anastomosis rate
- 6-month OS; 3-year DFS
- QoL, perioperative morbidity

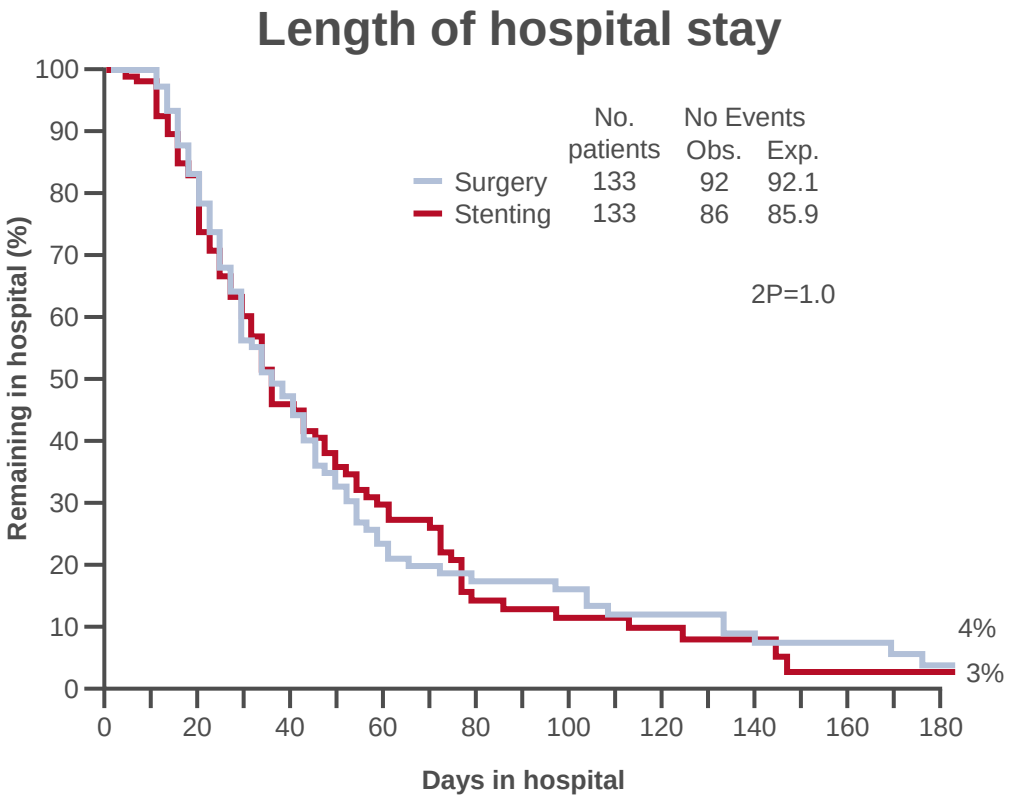
*Endoscopic/fluoroscopic technique with elective surgery performed 1–4 weeks later.

Hill et al. J Clin Oncol 2016; 34 (suppl): abstr 3507

3507: CREST: Randomised phase III study of stenting as a bridge to surgery in obstructing colorectal cancer—Results of the UK ColoRectal Endoscopic Stenting Trial (CREST) – Hill J, et al

Key results

	Stenting	Surgery
Hospital days (curative patients with complete 1 year data)		
N	86	92
Median (IQR)	14.5 (9–24)	13.5 (9.5–22.5)
Deaths within 30 days of randomisation		
N	5	6
Days from randomisation to death		
Median (IQR)	7 (6–15)	5 (3–9)



Hill et al. J Clin Oncol 2016; 34 (suppl): abstr 3507

3507: CREST: Randomised phase III study of stenting as a bridge to surgery in obstructing colorectal cancer—Results of the UK ColoRectal Endoscopic Stenting Trial (CREST) – Hill J, et al

Key results (continued)

	Stenting		Emergency surgery
Stoma formation, %	46		69
p-value		0.001	
All deaths, n/N	59/123		47/122
Deaths, cancer patients	58/120		47/109
Surgical complications*	48		45

- QoL and critical care utilisations at 3 and 12 months were not significantly different

Conclusions

- **In patients with potentially curable CRC, stenting as a bridge to surgery had an 80% clinical success rate and significantly reduced stoma formation**
- **Mortality, length of hospital stay and QoL were similar between stenting and emergency surgery**
- **Stenting appears to be a reasonable alternative to emergency surgery**

*Assessed by Clavien-Dindo classification.

Hill et al. J Clin Oncol 2016; 34 (suppl): abstr 3507

3508: A randomized trial comparing mesorectal excision with or without lateral lymph node dissection for clinical stage II, III lower rectal cancer: Primary endpoint analysis of Japan Clinical Oncology Group study JCOG0212 – Fujita S, et al

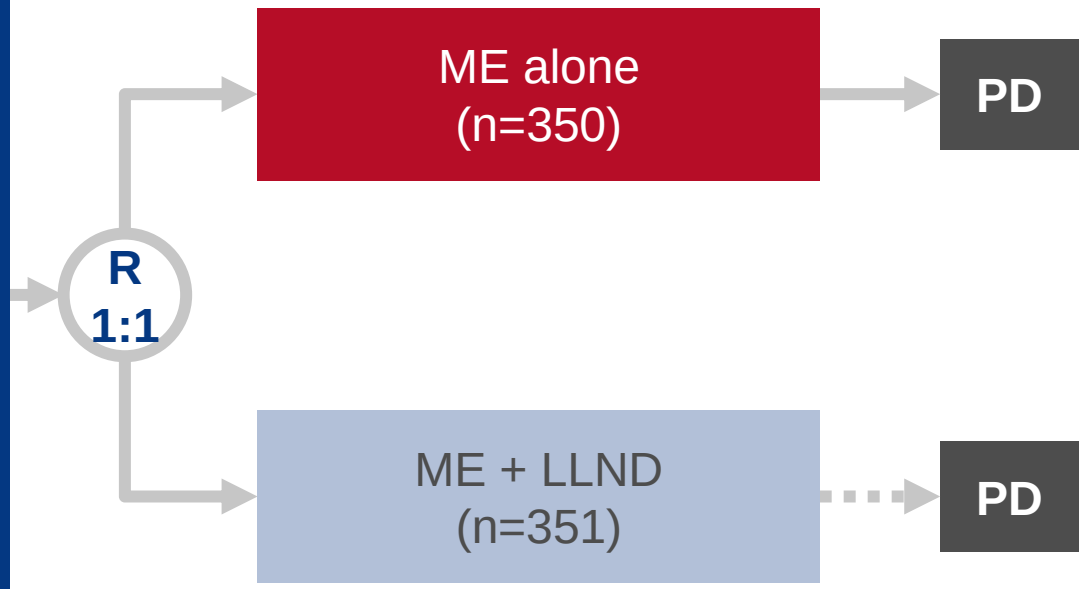
Study objective

- To evaluate whether the efficacy with mesorectal excision (ME) alone is non-inferior to ME + lateral lymph node dissection (LLND) in patients with Stage II/III lower rectal cancer

Key patient inclusion criteria

- Stage II/III rectal cancer
- Main lesion in rectum and lower margin below the peritoneal reflection
- No lateral pelvic lymph node enlargement
- PS ≤1

(n=701)



PRIMARY ENDPOINT(S)

- RFS*

SECONDARY ENDPOINTS

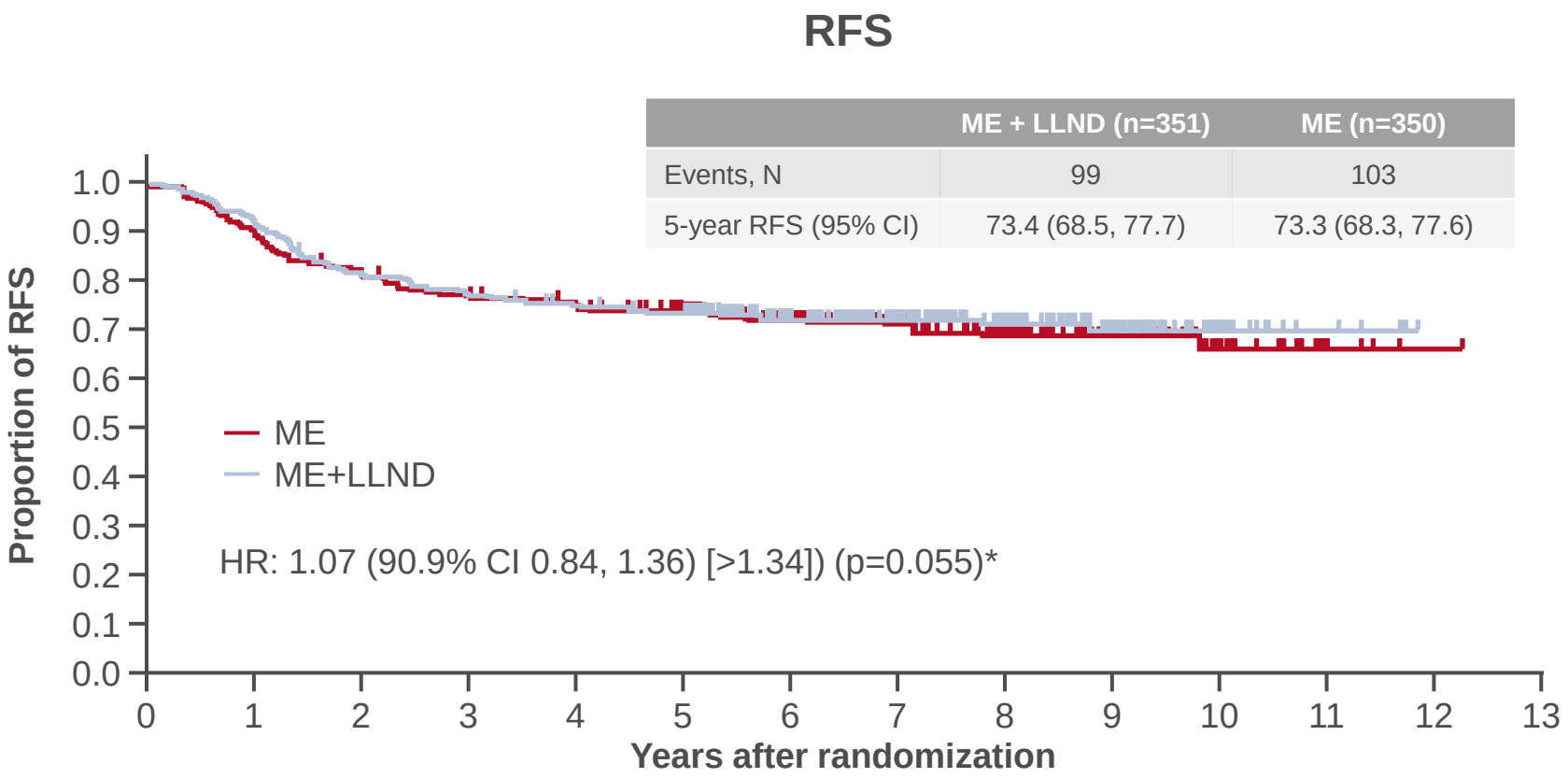
- OS, local RFS
- Operation time; blood loss
- Safety

*Non-inferiority margin of HR: 1.34.

Fujita et al. J Clin Oncol 2016; 34 (suppl): abstr 3508

3508: A randomized trial comparing mesorectal excision with or without lateral lymph node dissection for clinical stage II, III lower rectal cancer: Primary endpoint analysis of Japan Clinical Oncology Group study JCOG0212 – Fujita S, et al

Key results



*Cox proportional hazard model adjusted by sex + N stage (N0/N1–2). Fujita et al. J Clin Oncol 2016; 34 (suppl): abstr 3508

3508: A randomized trial comparing mesorectal excision with or without lateral lymph node dissection for clinical stage II, III lower rectal cancer: Primary endpoint analysis of Japan Clinical Oncology Group study JCOG0212 – Fujita S, et al

Key results (continued)

% (95% CI)	ME + LLND (n=351)	ME (n=350)	HR (95% CI)
5-year OS	92.6 (89.3, 94.9)	90.2 (86.5, 92.9)	1.25 (0.85, 1.84)
5-year LRFS	87.7 (83.8, 90.7)	82.4 (78.0, 86.1)	1.37 (0.97, 1.93)

- Local recurrence, n (%): 26 (7.4) with ME + LLND vs 44 (12.6) with ME alone (p=0.024)

Conclusions

- **Non-inferiority of ME alone vs ME + LLND remained unconfirmed**
- **ME + LLND significantly reduced local recurrence after surgery vs ME alone in patients with Stage II/III lower rectal cancer**
- **These data support ME + LLND as a viable procedure in this setting**

Fujita et al. J Clin Oncol 2016; 34 (suppl): abstr 3508

COLORECTAL CANCER

RECTAL CANCER

3513: FOLFIRINOX as induction treatment in rectal cancer patients with synchronous metastases (RCSM): Results of the FFCD 1102 phase II trial – Bachet JB, et al

Study objective

- To evaluate the efficacy and safety of aggressive systemic CT with FOLFIRINOX induction treatment in patients with rectal cancer and synchronous metastases

Key patient inclusion criteria

- Rectal cancer with synchronous metastases
- ECOG PS ≤2
- No prior RT or CT

(n=65)

PRIMARY ENDPOINT(S)

- DCR at 4 months

SECONDARY ENDPOINTS

- ORR, PFS, OS, secondary resection rate
- Safety

*Oxaliplatin 85 mg/m^2 d1 + irinotecan 180 mg/m^2 d1 + leucovorin 400 mg/m^2 d1, then 5FU 400 mg/m^2 bolus d1 + 2400 mg/m^2 46h continuous infusion biweekly (8 mandatory cycles followed by investigators' choice).

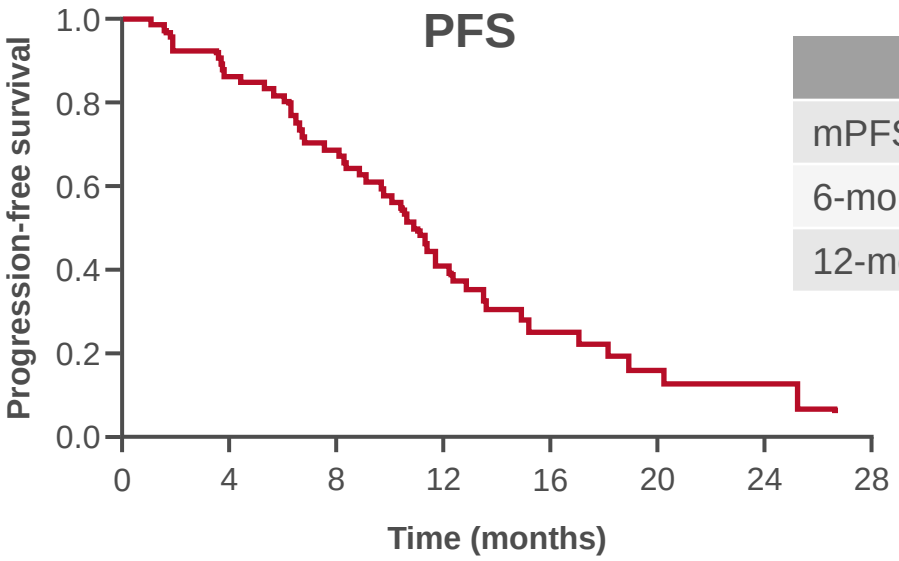
Bachet et al. J Clin Oncol 2016; 34 (suppl): abstr 3513

3513: FOLFIRINOX as induction treatment in rectal cancer patients with synchronous metastases (RCSM): Results of the FFCD 1102 phase II trial – Bachet JB, et al

Key results

Response rate, n (%)	After 4 cycles (n=64)	After 8 cycles (n=64)
PR	30 (46.9)	55 (86.0)
SD	29 (45.3)	5 (7.8)
PD	2 (3.1)	4 (6.2)
Non-evaluable	3 (4.7)	0

- DCR at 4 months: 94%



	All patients (n=65)
mPFS, months (95% CI)	10.9 (8.8, 12.3)
6-month PFS, %	82
12-month PFS, %	41

Bachet et al. J Clin Oncol 2016; 34 (suppl): abstr 3513

3513: FOLFIRINOX as induction treatment in rectal cancer patients with synchronous metastases (RCSM): Results of the FFCD 1102 phase II trial – Bachet JB, et al

Key results (continued)

Grade 3–4 AEs of interest in ≥3% of patients, n (%)	All patients (n=65)
Neutropenia	19 (29.2)
Febrile neutropenia	2 (3.1)
Nausea	3 (4.6)
Mucositis	2 (3.1)
Diarrhoea	8 (12.3)
Abdominal pain	6 (9.2)
Fatigue	5 (7.7)
Thromboembolic event	2 (3.1)

Conclusions

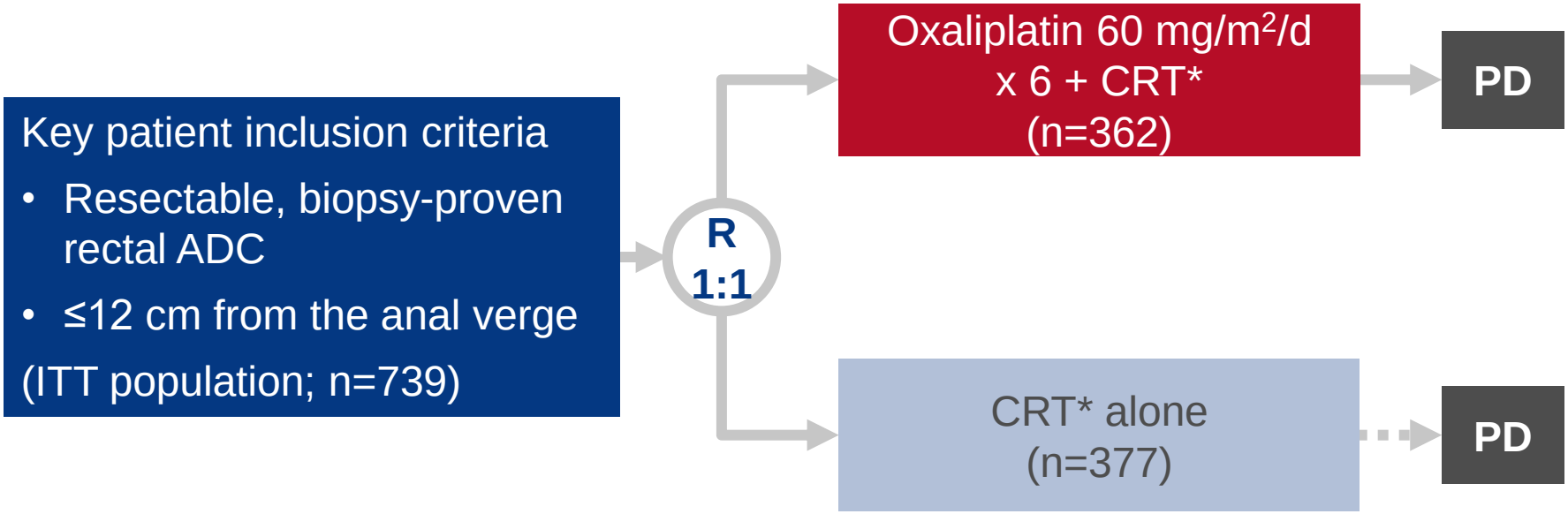
- **Aggressive CT with FOLFIRINOX allowed good control in patients with rectal cancer and synchronous unresectable metastases**
- **Such a strategy gives the opportunity to decide best locoregional treatment and surgery of metastatic legions on a controlled disease at 4 months**
- **Toxicities were acceptable and consistent with previous studies**

Bachet et al. J Clin Oncol 2016; 34 (suppl): abstr 3513

3521: Final results of STAR-01: A randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer – Aschele C, et al

Study objective

- To investigate the efficacy and safety of oxaliplatin added to preoperative CRT vs CRT alone in patients with locally advanced rectal cancer



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- EFS
- Cumulative incidence of local failure and distant metastasis

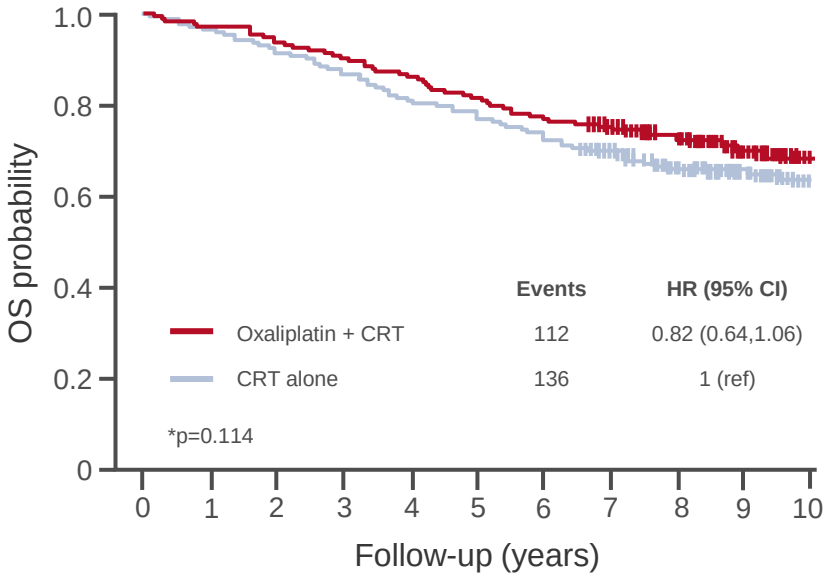
*5FU 225 mg/m²/d + external-beam pelvic (50.4 Gy in 28 daily fractions).

Aschele et al. J Clin Oncol 2016; 34 (suppl): abstr 3521

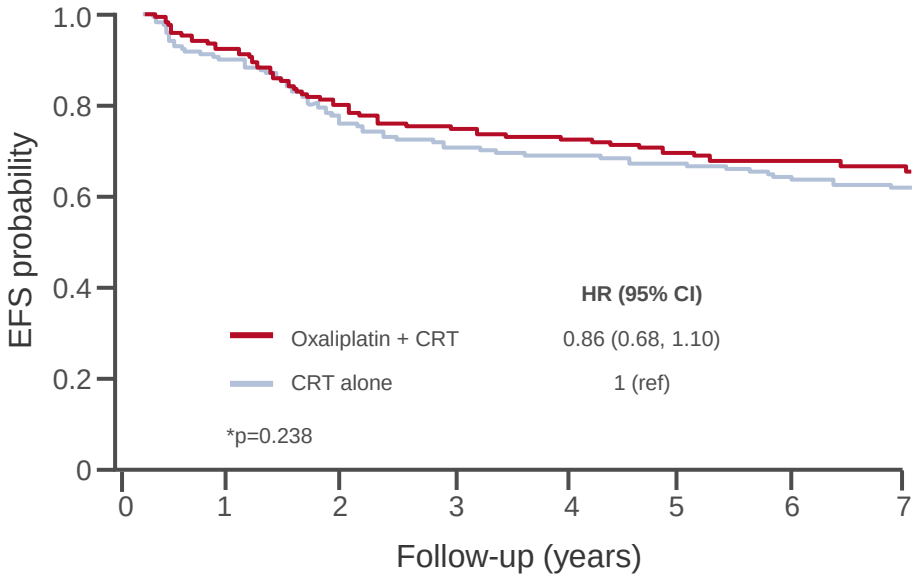
3521: Final results of STAR-01: A randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer – Aschele C, et al

Key results

OS



EFS



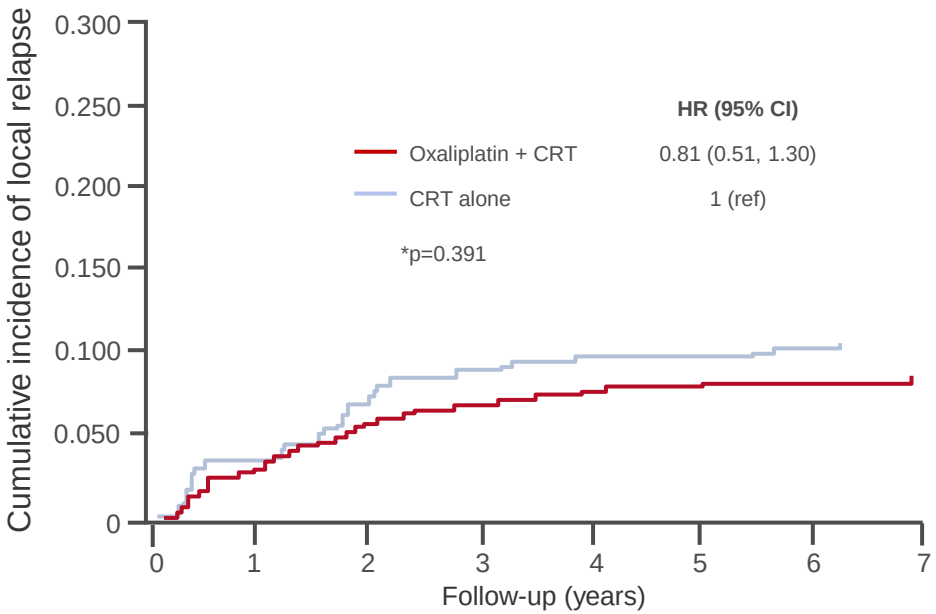
*Log-rank test.

Aschele et al. J Clin Oncol 2016; 34 (suppl): abstr 3521

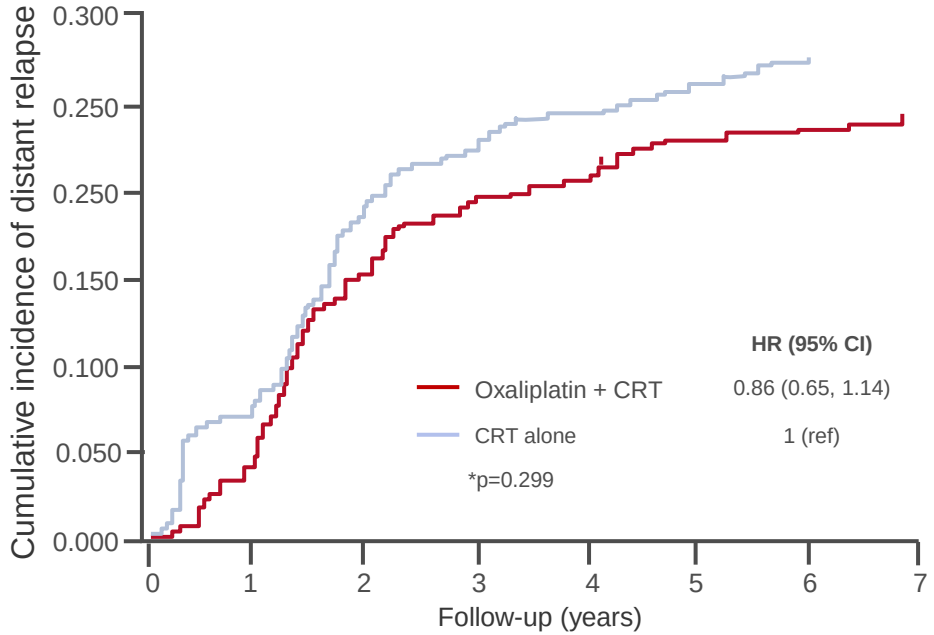
3521: Final results of STAR-01: A randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer – Aschele C, et al

Key results (continued)

Cumulative incidence of local failure



Cumulative incidence of distant metastases



Conclusions

- This study did not meet its primary endpoint of a 30% reduction in mortality rates
- Although statistical significance was not reached, findings suggest a smaller reduction in the relative reduction of death
- Similar effects were observed for local recurrence + distant metastases incidences

*Gray's test. Ref, reference.

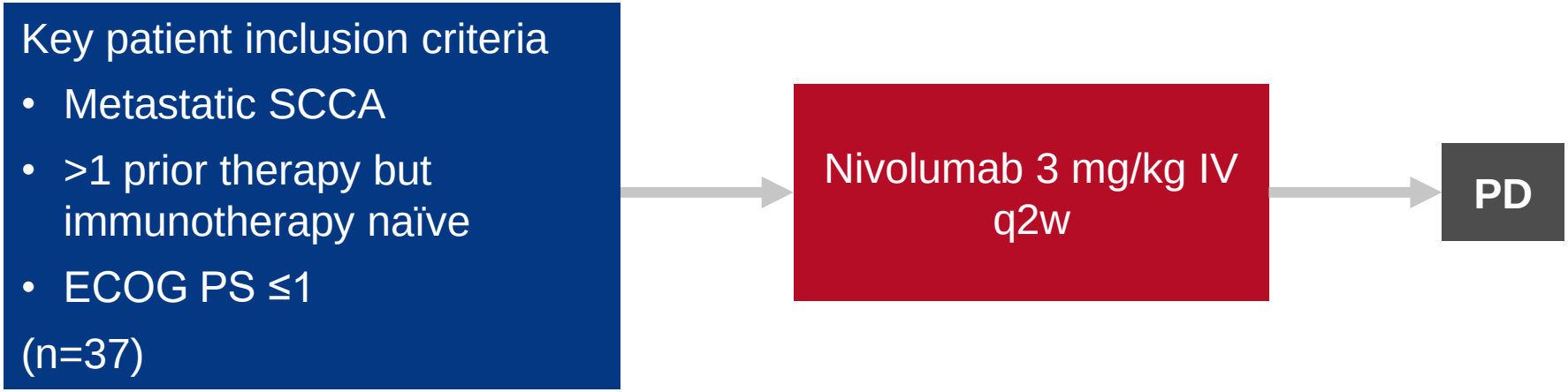
Aschele et al. J Clin Oncol 2016; 34 (suppl): abstr 3521

ANAL CANCER

3503: NCI9673: A multi-institutional eETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA) – Morris VK, et al

Study objective

- To evaluate the efficacy and safety of nivolumab in patients with refractory metastatic SCCA



PRIMARY ENDPOINT(S)

- ORR (RECIST 1.1)

SECONDARY ENDPOINTS

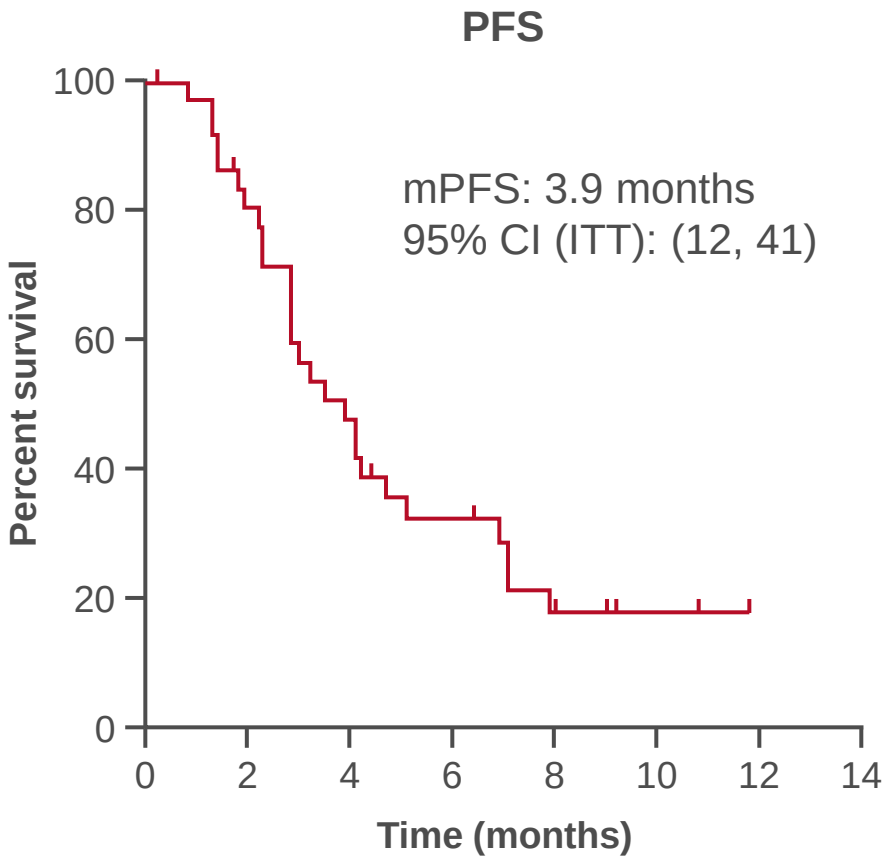
- PFS, OS
- Safety

Morris et al. J Clin Oncol 2016; 34 (suppl): abstr 3503

3503: NCI9673: A multi-institutional eETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA) – Morris VK, et al

Key results

Response rate, n (%)	
CR	2 (5.4)
PR	7 (18.9)
SD	17 (45.9)
PD	8 (21.6)
NE	3 (8.1)
ORR, ITT (n=37)	9 (24.3)
ORR, evaluable (n=34)	9 (26.5)



NE, not evaluable.

Morris et al. J Clin Oncol 2016; 34 (suppl): abstr 3503

3503: NCI9673: A multi-institutional eETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA) – Morris VK, et al

Key results (continued)

AEs in ≥15% of patients, n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	17 (46)	7 (19)	1 (3)	0
Anaemia	13 (35)	11 (30)	2 (5)	0
Rash	8 (22)	2 (5)	1 (3)	0
Constipation	8 (22)	2 (5)	0	0
Diarrhoea	8 (22)	0	0	0

Conclusions

- **This is the first prospective Phase II trial of nivolumab in patients with refractory metastatic SCCA**
- **Nivolumab monotherapy demonstrated anti-tumour activity and was well tolerated**
  - **No additional SAEs were observed in HIV^{+} patients***

*Data not shown.

Morris et al. J Clin Oncol 2016; 34 (suppl): abstr 3503

3522: Phase II trials of cetuximab plus combined modality therapy (CMT) in squamous cell carcinoma of the anal canal (SCCAC) with and without human immunodeficiency virus (HIV) infection – Garg M, et al

Study objective

- To assess the efficacy and safety of cetuximab + combined modality therapy (CMT) in patients with SCCAC with or without HIV

Key patient inclusion criteria
- Stage I–III SCCAC
- With HIV (AMC-045 study)
- Without HIV (ECOG-3205 study)

(n=106)

→ Cetuximab* + CMT† → PD

PRIMARY ENDPOINT(S)

- LRF rate

SECONDARY ENDPOINTS

- PFS, OS

- Data were analysed from two separate studies:
  - Patients with HIV infection (AMC-045)
  - Patients without HIV infection (ECOG-3205)

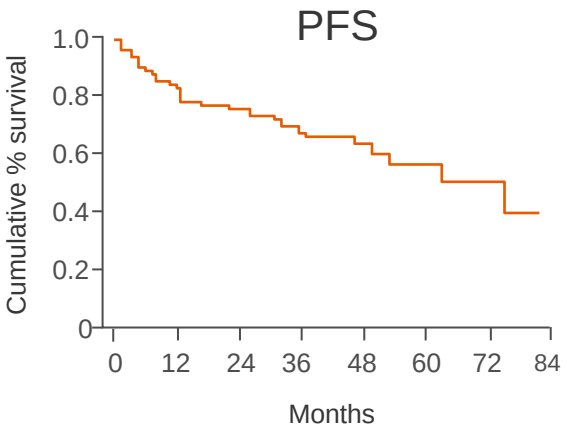
*400 mg/m^2 IV 1 week prior to CMT, then 250 mg/m^2 IV weekly x 8 weeks; †Cisplatin (75 mg/m^2) + 5FU (1000 mg/m^2/d x 4d) x 2 cycles + RT (45–54 Gy), + 2 cycles of neoadjuvant cisplatin/5FU in the first 28 patients in E3205 prior to a study amendment.

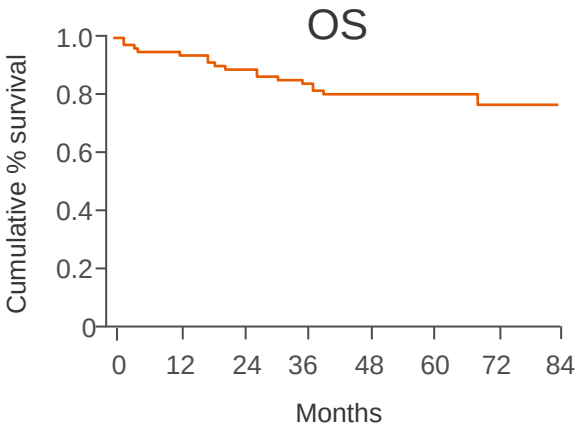
Garg et al. J Clin Oncol 2016; 34 (suppl): abstr 3522

3522: Phase II trials of cetuximab plus combined modality therapy (CMT) in squamous cell carcinoma of the anal canal (SCCAC) with and without human immunodeficiency virus (HIV) infection – Garg M, et al

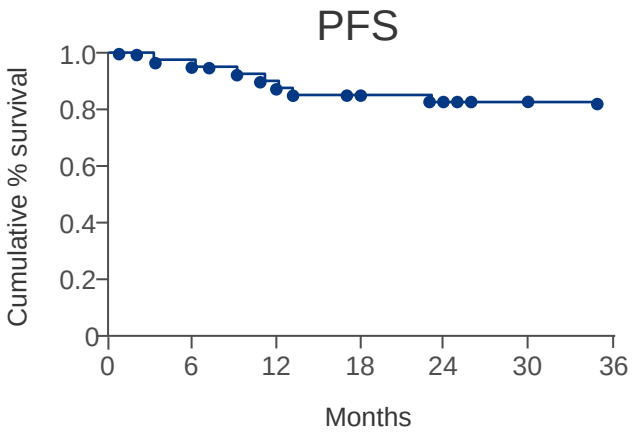
Key results

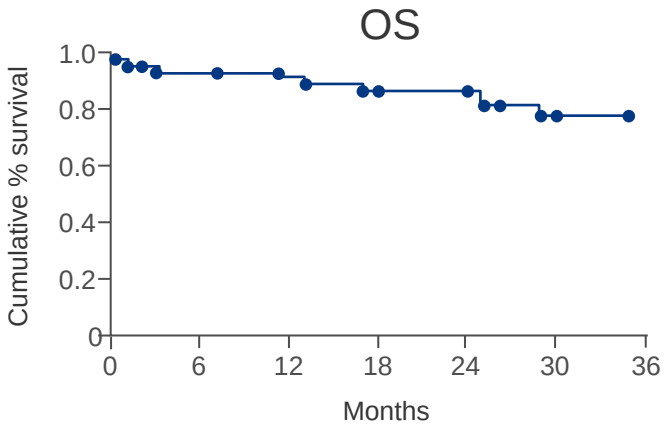
ECOG-3205





AMC-045





Garg et al. J Clin Oncol 2016; 34 (suppl): abstr 3522

3522: Phase II trials of cetuximab plus combined modality therapy (CMT) in squamous cell carcinoma of the anal canal (SCCAC) with and without human immunodeficiency virus (HIV) infection – Garg M, et al

Key results (continued)

	E3205 (n=61)	AMC045 (n=45)
3-year LRF (per protocol), % p-value	23 0.03	42 NS
3-year LRF (KM), % (95% CI)	21 (7, 26)	20 (10, 37)
3-year DFS (KM), % (95% CI)	68 (55, 79)	82 (66, 91)
3-year OS (KM), % (95% CI)	83 (71, 91)	89 (73, 89)
3-year colostomy rate, %	7	9

Conclusions

- **Patients with SCCAC with and without HIV infection had similar rates of completing therapy (80%) and clinical outcomes with cetuximab plus CMT**
- **These findings suggest that patients with Stage I–III HIV-associated SCCAC should be treated with curative intent similar to immunocompetent patients and that addition of cetuximab to CMT may reduce LRF**

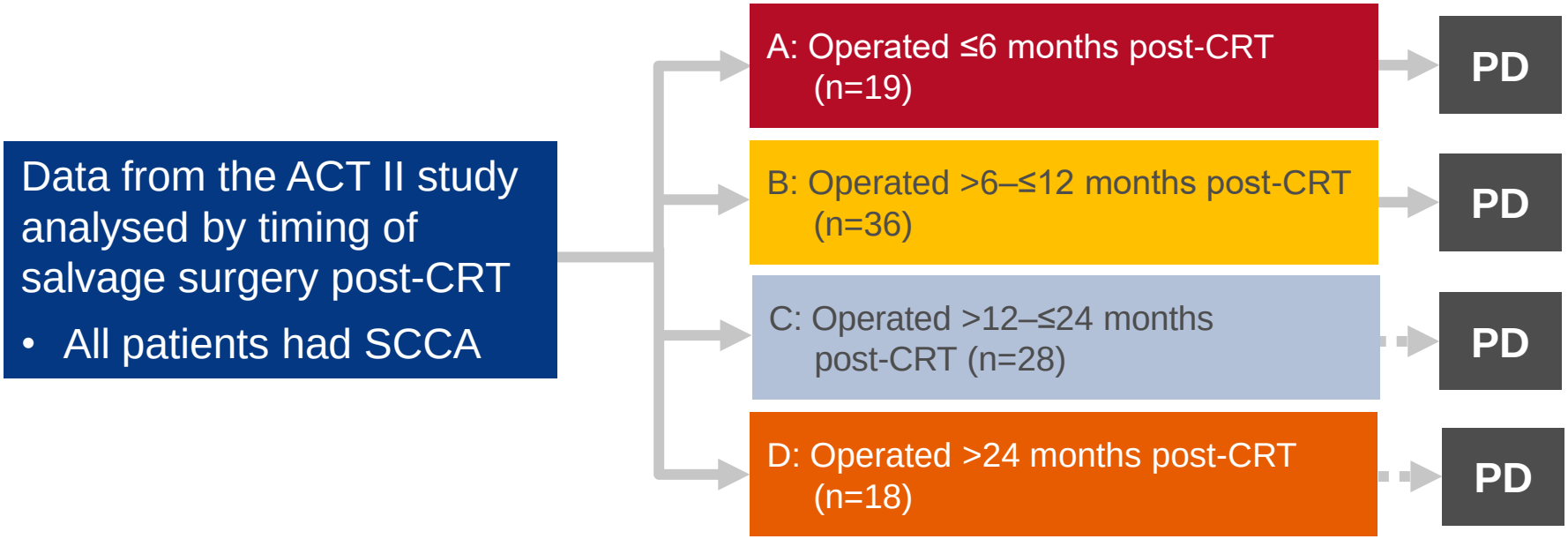
CMT, combined modality therapy.

Garg et al. J Clin Oncol 2016; 34 (suppl): abstr 3522

3523: Salvage surgery with abdominoperineal excision of the rectum (APER) following loco-regional failure after chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance 5FU/CisP chemotherapy (CT) in squamous cell carcinoma of the anus (SCCA) and the impact on long-term outcomes: Results of ACT II – Glynne-Jones R, et al

Study objective

- To determine the optimum time of cisplatin- or mitomycin-based CRT following salvage surgery with abdominoperineal excision of the rectum in patients with SCCA



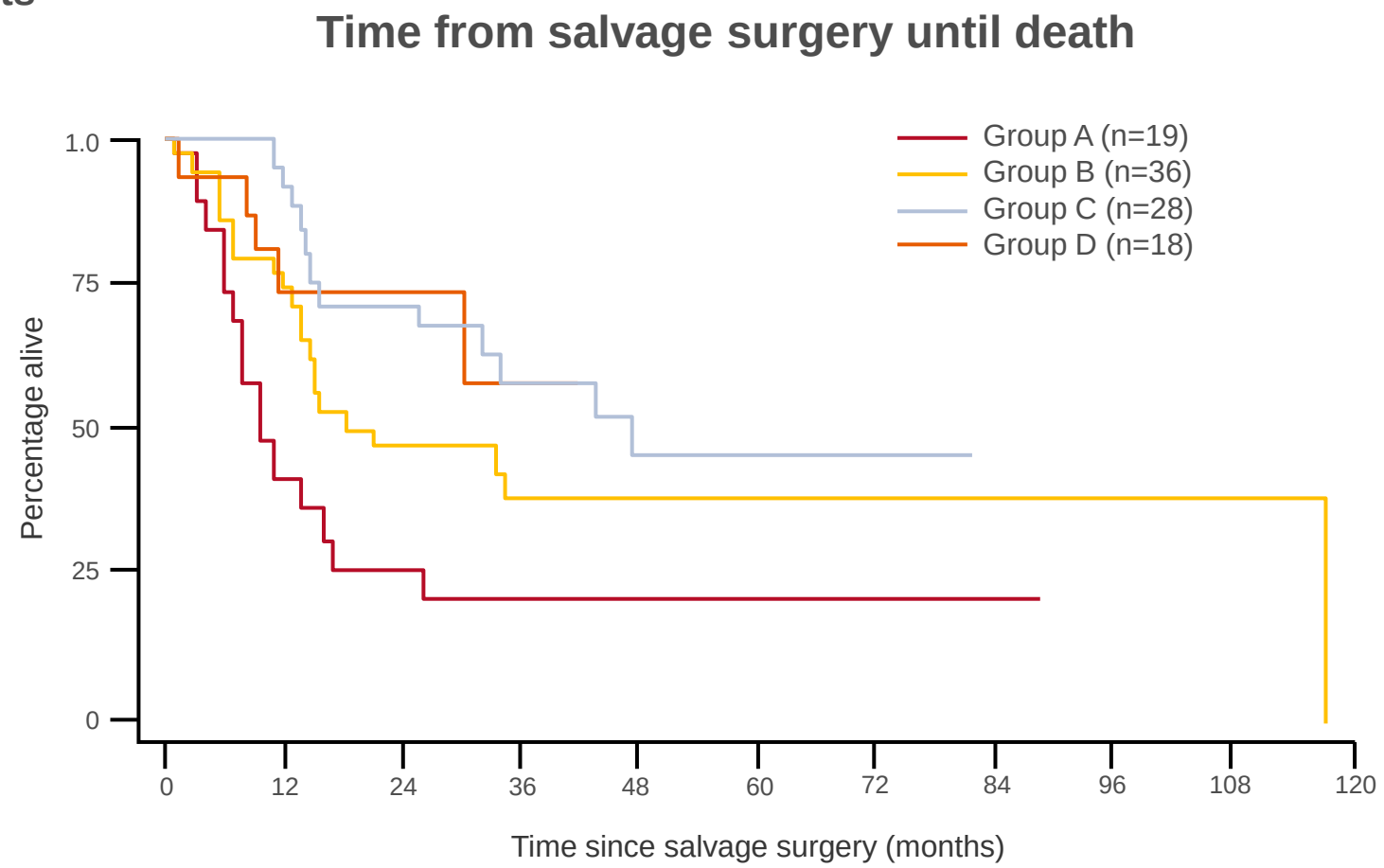
PRIMARY ENDPOINT(S)

- OS

Glynne-Jones et al. J Clin Oncol 2016; 34 (suppl): abstr 3523

3523: Salvage surgery with abdominoperineal excision of the rectum (APER) following loco-regional failure after chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance 5FU/CisP chemotherapy (CT) in squamous cell carcinoma of the anus (SCCA) and the impact on long-term outcomes: Results of ACT II – Glynne-Jones R, et al

Key results



Glynne-Jones et al. J Clin Oncol 2016; 34 (suppl): abstr 3523

3523: Salvage surgery with abdominoperineal excision of the rectum (APER) following loco-regional failure after chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance 5FU/CisP chemotherapy (CT) in squamous cell carcinoma of the anus (SCCA) and the impact on long-term outcomes: Results of ACT II – Glynne-Jones R, et al

Key results (continued)

	Group A (n=19)	Group B (n=36)	Group C (n=28)	Group D (n=18)	Overall (n=101)
Deaths, n (%)	15 (79)	21 (58)	12 (43)	5 (28)	53 (52)
mOS, months (IQR)	9.6 (5.8–26.3)	21.1 (11.7–118.1)	47.7 (15.7–NR)	NR	30.3 (11.7–118.1)
HR (95% CI)	1.00 (baseline)	0.53 (0.27, 1.03)	0.33 (0.15, 0.70)	0.31 (0.11, 0.85)	-
p-value	-	0.062	0.004	0.024	-

Conclusions

- **In patients with SCCA, the earlier timing of radical salvage surgery was associated with poor survival**
- **Local failure may benefit from early detection and salvage by radical surgery, but mainly relapse systematically**
- **Close imaging with MRI and clinical surveillance may be helpful in the first 2 years**

Glynne-Jones et al. J Clin Oncol 2016; 34 (suppl): abstr 3523