GI SLIDE DECK 2015

Selected Abstracts on **Colorectal Cancer** from:

esdo european society of digestive oncology

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Letter from ESDO

DEAR COLLEAGUES

It is my pleasure to present this ESDO slide set which has been designed to highlight and summarise key findings in digestive cancers from the major congresses in 2015. This slide set specifically focuses on Colorectal Cancer from the American Society of Clinical Oncology Annual Meeting.

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

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

Yours sincerely,

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

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european society of digestive oncology

ESDO Medical Oncology Slide Deck
Editors 2015

COLORECTAL CANCERS



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esdo

Glossary

5FU	5-fluorouracil
AE	adverse event
BSA	body surface area
CI	confidence interval
CR	complete response
(m)CRC	(metastatic) colorectal cancer
CT	chemotherapy
DCR	disease control rate
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EGFR	endothelial growth factor receptor
FFPE	formalin-fixed paraffin-embedded
FOLFIRI	leucovorin, fluorouracil, irinotecan
FOLFOX	oxaliplatin, fluorouracil, and leucovorin
GI	gastrointestinal
GFR	glomerular filtration rate
HLA	human leukocyte antigen
HR	hazard ratio
IHC	immunohistochemistry
ITT	intent-to-treat
IV	intravenous
mAb	monoclonal antibody
(d)MMR	(defective) mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSS	microsatellite stable
ORR	overall response rate
(m)OS	(median) overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
(m)PFS	(median) progression free survival
PK	pharmacokinetics
PR	partial response
PS	performance status
RECIST	Response Evaluation Criteria In Solid Tumors
RFA	radiofrequency ablation
RFS	relapse-free survival
RT	radiotherapy
(m)TTP	(median) time to progression
TTR	time to treatment response
QoL	quality of life
S-1	tegafur/CDHP/oteracil
SAR	survival after relapse
SCC	squamous cell carcinoma
SD	stable disease
SIRT	selective internal radiation therapy
UFT	uracil/tegafur
VEGF	vascular endothelial growth factor
WBC	white blood cell count
WHO	World Health Organization
WT	wild type
Xelox	oxaliplatin/capecitabine

Contents

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COLON CANCER

COLON CANCER

ADJUVANT THERAPY

3512: Randomized phase III study of adjuvant chemotherapy with S-1 versus capecitabine (cape) in patients with stage III colon cancer (CC): Results of Japan Clinical Oncology Group Study (JCOG0910) – Hamaguchi T, et al

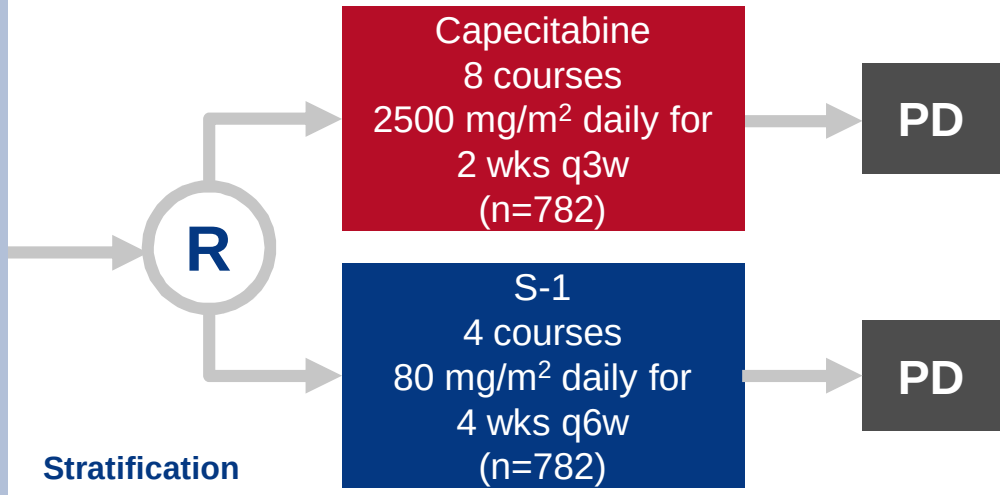
Study objective

- To assess the non-inferiority of S-1 to capecitabine as a post-operative adjuvant chemotherapy in patients with stage III colon cancer or rectal cancer

Key patient inclusion criteria

- Age 20−80 years
- Histologically proven Stage III colon cancer or rectal cancer
- Colectomy with Japanese D2 or D3 lymph node dissection, judged as R0 resection after surgery
- ECOG PS 0–1
- No prior chemotherapy or radiation therapy
- Post-operative adjuvant chemotherapy within 8 weeks after surgery

(n=1,564)



Stratification

- Tumour location (colon vs. rectum)
- Lymph node metastasis (n≤3 vs. n≤4)
- Surgical technique (conventional vs. non-touch isolation)
- Institution

PRIMARY ENDPOINT

- DFS

SECONDARY ENDPOINTS

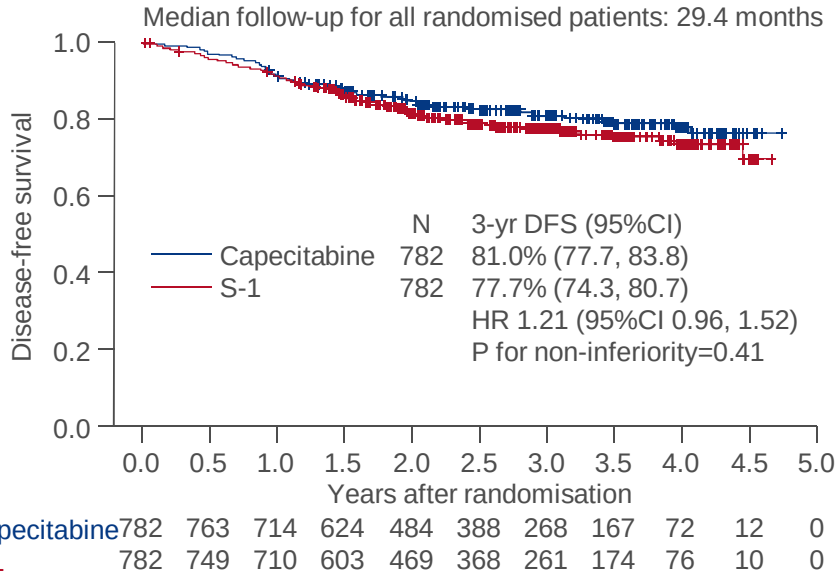
- OS, recurrence-free survival, safety

Hamaguchi et al. J Clin Oncol 2015; 33 (suppl): abstr 3512

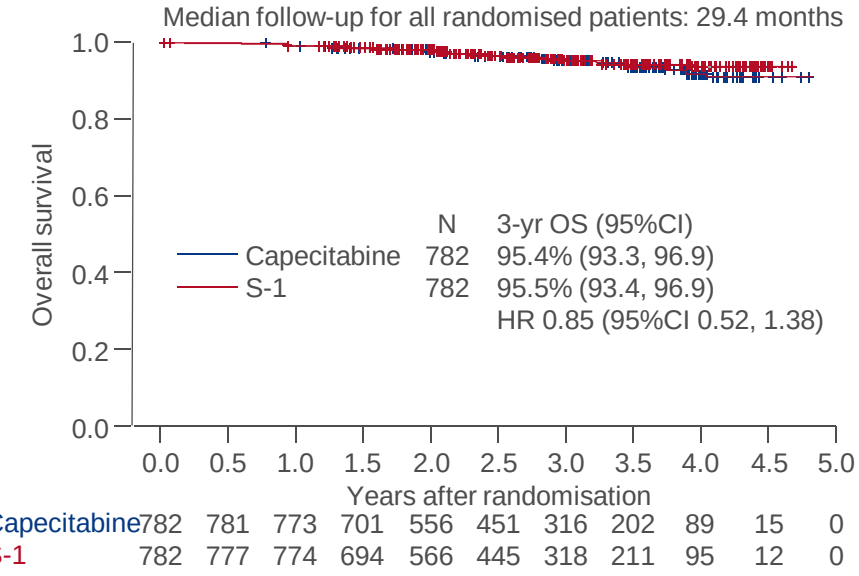
3512: Randomized phase III study of adjuvant chemotherapy with S-1 versus capecitabine (cape) in patients with stage III colon cancer (CC): Results of Japan Clinical Oncology Group Study (JCOG0910) – Hamaguchi T, et al

Key results

Disease-free survival



Overall survival



- Grade 2–4 AEs (anorexia, diarrhoea, nausea and rash) were more common in patients in the S-1 arm, whereas hand-foot syndrome was more common among patients receiving capecitabine

Conclusion

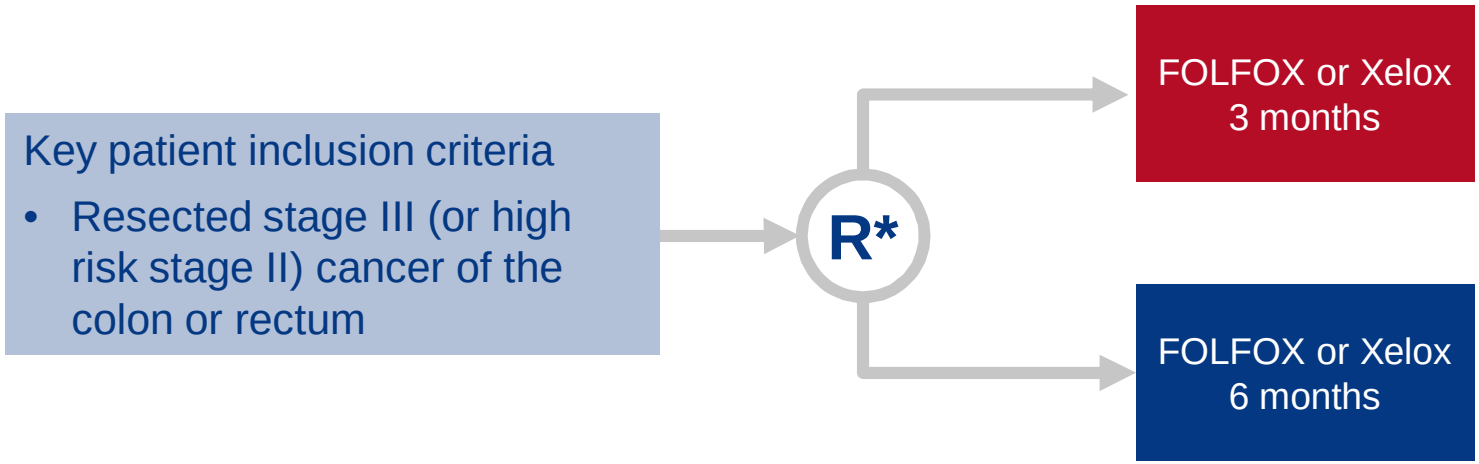
- **S-1 failed to show non-inferiority to capecitabine in DFS in a post-operative adjuvant chemotherapy setting**

Hamaguchi et al. J Clin Oncol 2015; 33 (suppl): abstr 3512

3514: Toxicity and quality of life data from SCOT: An international phase III randomized (1:1) noninferiority trial comparing 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy – Iveson T, et al

Study objective

- To investigate the efficacy and safety of 3 vs. 6 months of treatment with oxaliplatin-based adjuvant chemotherapy, either oxaliplatin plus 5FU and folinic acid (FOLFOX) or oxaliplatin plus capecitabine (Xelox) in patients with colorectal cancer



PRIMARY ENDPOINT

- Toxicity, QoL

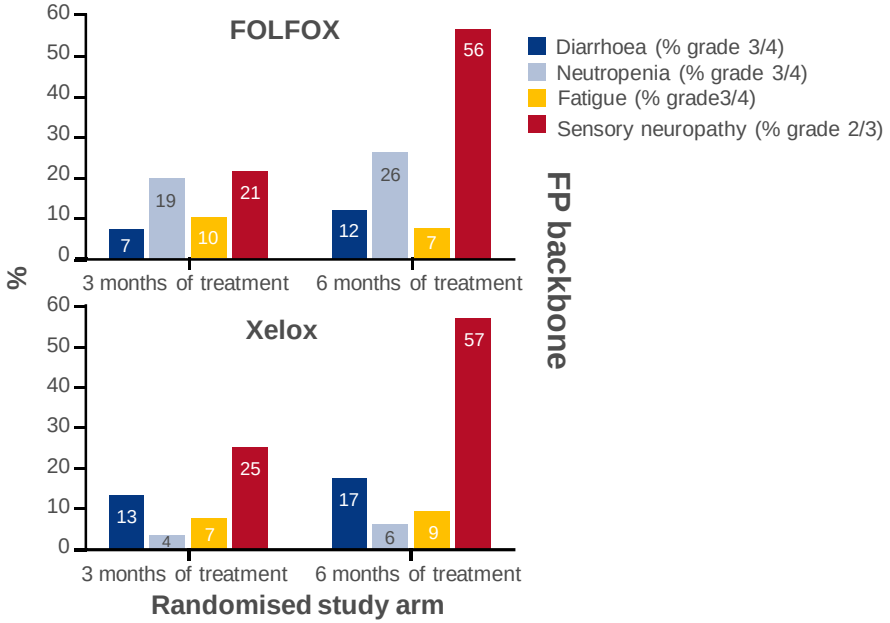
*Patients randomised using a minimisation algorithm with a random competent and minimisation factors of centre, gender, disease site, N-stage and T-stage, choice of regimen and starting dose of capecitabine for those receiving Xelox

Iveson et al. J Clin Oncol 2015; 33 (suppl): abstr 3514

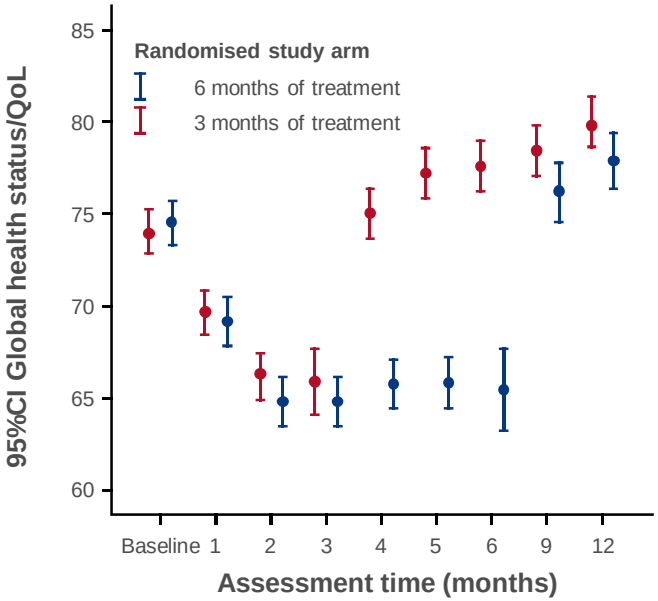
3514: Toxicity and quality of life data from SCOT: An international phase III randomized (1:1) no-inferiority trial comparing 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy – Iveson T, et al

Key results

Proportion of patients with high grade toxicity



Quality of life assessment



- Sensory peripheral neuropathy was cumulative and at 1 year was higher in the 6-month arm compared with the 3-month arm

Conclusions

- **Both FOLFOX and Xelox were safe and well tolerated**
- **Although QoL worsened while on treatment it had recovered in both treatment arms by 1 year despite persistent peripheral neuropathy**

Iveson et al. J Clin Oncol 2015; 33 (suppl): abstr 3514

Improving adjuvant therapy for colon cancer – Folprecht G

Discussion of abstract 3512

- The efficacy of S-1 in the adjuvant treatment setting in a non-inferiority study in Japanese patients with stage III colon or rectal cancer randomised to either 6 months of capecitabine or S-1 was investigated
  - Trial results published early as a result of futility with an observed HR of 1.2 for DFS
  - The inferior DFS did not translate to a worse OS (HR=0.85)
- The question of whether or not adjuvant treatment should be given or recommended remains to be determined, but survival benefit should be discussed with all non-elderly patients

Improving adjuvant therapy for colon cancer – Folprecht G

Discussion of abstract 3514

- Toxicity data from the SCOT trial, a large randomised, non-inferiority study involving >6,000 patients with stage II/III CRC comparing 3 vs. 6 months of adjuvant treatment, demonstrated that:
  - There was less neurotoxicity with the shorter treatment
  - Patients in the 6-month arm took longer to recover than those in the 3-month arm
- The SCOT trial is part of a larger project: the IDEA project – a planned meta-analysis comparing 3 vs. 6 months of adjuvant treatment in ~10,000 patients with stage III colon cancer designed to help determine whether all patients should be treated up to 6 months and in which patients the duration of the treatment should be reduced
- Overall, shorter treatment period is associated with less neurotoxicity and better QoL, however, this is not yet the standard of care because of the lack of efficacy data from all six trials participating in the IDEA project

3506: Analysis of DNA mismatch repair (MMR) and clinical outcome in stage III colon cancers from patients (pts) treated with adjuvant FOLFOX +/- cetuximab in the PETACC8 and NCCTG N0147 adjuvant trials – Zaanan A, et al

Study objective

- To examine the impact of mismatch repair (MMR) status on clinical outcome in patients with stage III colon cancer receiving adjuvant FOLFOX ± cetuximab

Study design

- Data were pooled from two large phase 3 clinical trials of adjuvant FOLFOX ± cetuximab
- Prospectively collected tumours (n=4,674) were analysed for MMR protein expression (MLH1, MSH2 and MSH6)
- Mutations in *BRAF*^{V600E} and *KRAS* were assessed
- Methylation of the MLH1 gene promoter was studied in tumours with loss of MLH1 and WT *BRAF*
- Associations of MMR status (MSI vs. MSS) with TTR, DFS and OS were analysed using a stratified Cox proportional hazards model

Zaanan et al. J Clin Oncol 2015; 33 (suppl): abstr 3506

3506: Analysis of DNA mismatch repair (MMR) and clinical outcome in stage III colon cancers from patients (pts) treated with adjuvant FOLFOX +/- cetuximab in the PETACC8 and NCCTG N0147 adjuvant trials – Zaanan A, et al

Key results

Table: Survival according to MMR status*

	Overall population		FOLFOX alone		FOLFOX + cetuximab	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
DFS	0.86 (0.71, 1.04)	0.12	0.74 (0.56, 0.98)	0.03	0.98 (0.76, 1.28)	0.91
OS	0.94 (0.75, 1.17)	0.57	0.71 (0.51, 1.00)	0.04	1.17 (0.87, 1.57)	0.29

Conclusions

- MSI was not prognostic in patients with colon cancer receiving FOLFOX-based CT
- In a subgroup analysis, MSI was prognostic for survival in patients receiving FOLFOX alone, but not in those receiving FOLFOX + cetuximab
- Further study is needed to determine why cetuximab may have reduced the prognostic impact of MSI

*HR <1 favoured MSI patients; HR>1 favoured MSS patients

Zaanan et al. J Clin Oncol 2015; 33 (suppl): abstr 3506

3507: Prognostic value of *BRAF* V600E and *KRAS* exon 2 mutations in microsatellite stable (MSS), stage III colon cancers (CC) from patients (pts) treated with adjuvant FOLFOX+/- cetuximab: A pooled analysis of 3934 pts from the PETACC8 and N0147 trials – Taieb J, et al

Study objective

- To examine the prognostic value of *BRAF* and *KRAS* mutations in patients with resected microsatellite stable (MSS) stage III colon cancer receiving adjuvant FOLFOX ± cetuximab

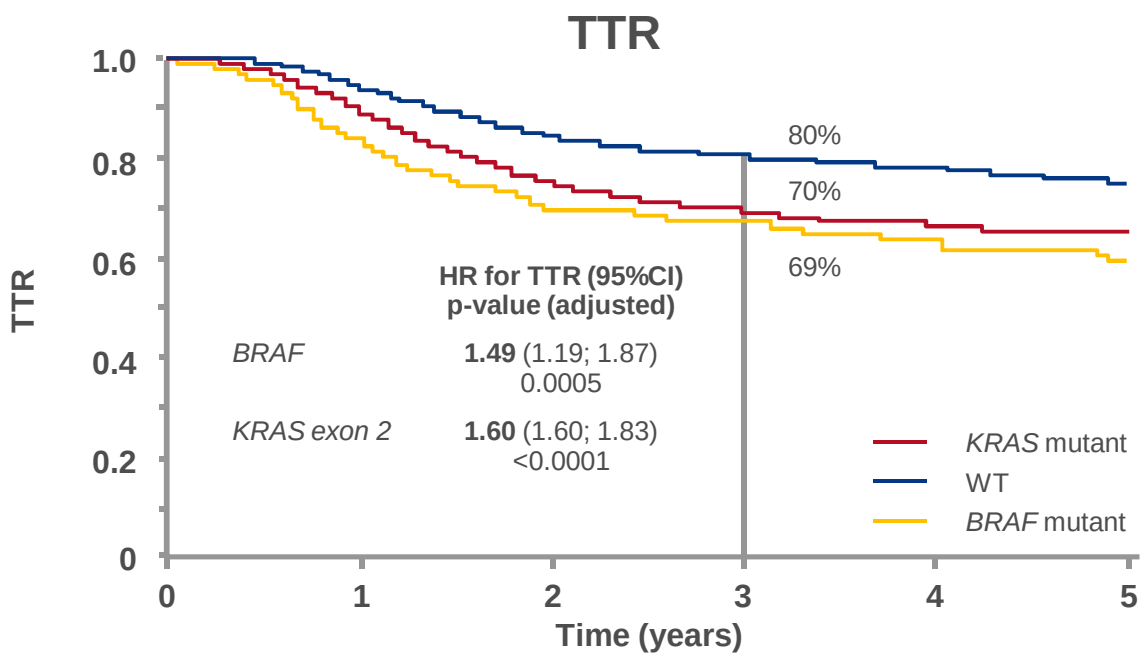
Methods

- Data were pooled from two phase 3 clinical trials in which patients received 12 cycles of FOLFOX ± cetuximab (n=5,577)
- Biospecimens from patients with MSS stage III colon cancer were collected prospectively (n=3,934)
- MSS tumours were analysed for $BRAF^{V600E}$ and *KRAS* exon 2 mutations
- Three groups were defined:
  - *BRAF* mutant (n=279 [7%]), *KRAS* mutant (1,450 [37%]), double WT (2,205 [56%])
- Associations of mutations with time to recurrence (TTR), survival after relapse (SAR) and OS were analysed

Taieb et al. J Clin Oncol 2015; 33 (suppl): abstr 3507

3507: Prognostic value of *BRAF* V600E and *KRAS* exon 2 mutations in microsatellite stable (MSS), stage III colon cancers (CC) from patients (pts) treated with adjuvant FOLFOX+/- cetuximab: A pooled analysis of 3934 pts from the PETACC8 and N0147 trials – Taieb J, et al

Key results



- OS for *BRAF* vs. WT: HR 1.72 (p<0.0001); OS for *KRAS** vs. WT: HR 1.52 (p<0.0001)
- SAR: 1.0, 2.09 and 2.57 years for *BRAF*, *KRAS* and WT tumours, respectively

Conclusions

- **In patients with resected stage III MSS colon cancer receiving adjuvant FOLFOX, mutations in *BRAF*^{V600E} or *KRAS* exon 2* predicted significantly shorter TTR, SAR, and OS**
- **Testing of MSI, *RAS* and *BRAF* should be discussed in future guidelines**

*codons 12 or 13

Taieb et al. J Clin Oncol 2015; 33 (suppl): abstr 3507

Molecular Profiling to Inform Prognosis and Treatment – Tejpar S

Discussion of abstract 3505

- A new tool for patient selection in CRC was described that can predict the emergence of new antigens based on somatic mutations in hypermutated tumours
  - Applications include improved patient selection based on mutations and neoantigen rates, functional assessments of immune environment, gene expression signatures on tissue and IHC

Discussion of abstract 3506

- Prognostic data from a large pooled analysis of patients with stage III colon cancer treated with FOLFOX-based adjuvant chemotherapy from 2 trials were reported
  - Defective mismatch repair (dMMR) was a good prognostic factor for DFS and OS in patients treated with FOLFOX alone but not in patients treated with FOLFOX + cetuximab – the reason for this is currently unknown

Discussion of abstract 3507

- Mutations in *KRAS* and *BRAF* can be used as prognostic factors for TTR and OS in patients with colon cancer and should be considered for stratification of patients in trials

RECTAL CANCER

RECTAL CANCER

NEOADJUVANT THERAPY

3500: A multi-center randomized controlled trial of mFOLFOX6 with or without radiation in neoadjuvant treatment of local advanced rectal cancer (FOWARC study): Preliminary results – Deng Y, et al

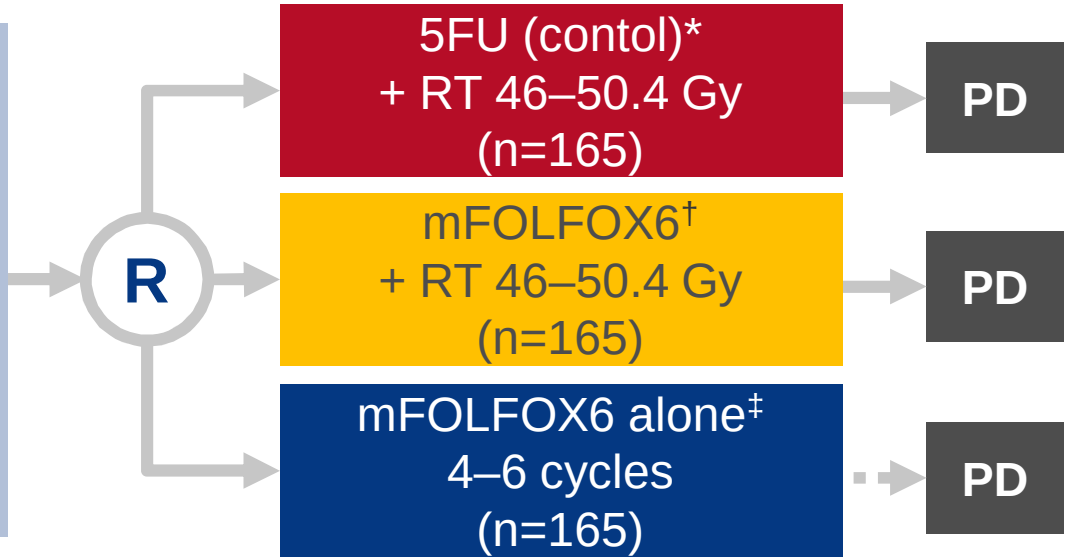
Study objective

- To determine whether perioperative mFOLFOX6 CT improves DFS in locally advanced rectal cancer

Key patient inclusion criteria

- Rectal cancer ≤12 cm from the anal verge
- T3/4 and/or N+; R0/1
- Staged by MRI
- ECOG PS 0–1

(n=495)



PRIMARY ENDPOINT

- DFS

SECONDARY ENDPOINTS

- pCR, R0 resection, sphincter preservation, local recurrence, OS, QoL, toxicity (*follow-up ongoing for recurrence/OS*)

*Leucovorin 0.4 mg/m^2 D1, 5FU 0.4 mg/m^2 bolus IV then 2.4 mg/m^2 continuous IV 48 h; †As above but with initial oxaliplatin 85 mg/m^2 2 h IV infusion. ‡Postoperative radiation permitted (physician's decision)

Deng et al. J Clin Oncol 2015; 33 (suppl): abstr 3500

3500: A multi-center randomized controlled trial of mFOLFOX6 with or without radiation in neoadjuvant treatment of local advanced rectal cancer (FOWARC study): Preliminary results – Deng Y, et al

Key results

n (%)	5FU + RT (n=133)	mFOLFOX6 + RT (n=143)	mFOLFOX6 alone (n=148)
R0 resection	120 (90.2)	128 (89.5)	132 (91.2)
pCR*	19 (14.3)	40 (28.0)	9 (6.1)
Anastomotic leakage†	28 (21.1)	26 (18.2)	10 (6.8)
Infection of incision‡	30 (22.6)	24 (16.8)	9 (6.1)

Grade 3/4 AEs, n (%)	5FU + RT (n=155)	mFOLFOX6 + RT (n=158)	mFOLFOX6 alone (n=163)
Leucopenia	19 (12.9)	29 (19.0)	9 (5.7)
Nausea/vomiting	4 (2.6)	9 (5.7)	4 (2.5)
Diarrhoea	12 (7.7)	23 (14.5)	12 (7.3)
Radiodermatitis	22 (14.1)	32 (20.3)	-

Conclusions

- mFOLFOX + RT as a neoadjuvant treatment had a higher pCR rate, increased response and slightly increased toxicity vs. 5FU in patients with locally advanced rectal cancer
- mFOLFOX alone had a similar R0 resection rate, similar good response rate and fewer surgical complications vs. 5FU
- mFOLFOX6 + RT may replace 5FU as a standard treatment in this setting
- ~35% of the patients may not need RT to create a good excision plane for surgery

*p=0.001; †p=0.02; ‡p=0.009

Deng et al. J Clin Oncol 2015; 33 (suppl): abstr 3500

3501: Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC) – Ruers T, et al

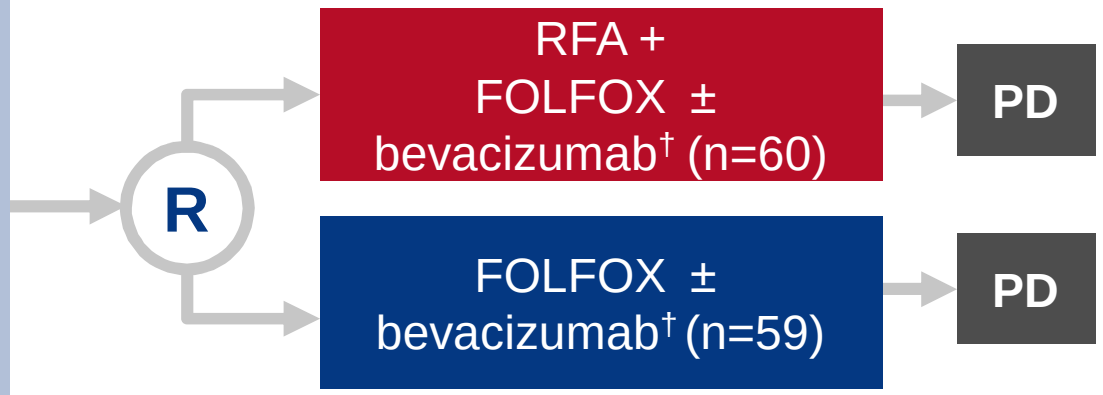
Study objective

- To evaluate the benefit of combining radiofrequency ablation (RFA) with systemic therapy in patients with unresectable CRC after a long-term median follow-up of 9.7 years*

Key patient inclusion criteria

- Unresectable CRC
- Liver metastases ≤9 lesions without extrahepatic disease
- WHO PS 0–1

(n=119)



PRIMARY ENDPOINT

- 30-month OS rate >38% for CT + RFA

SECONDARY ENDPOINTS

- PFS, OS, safety, QoL

*Initial results published in *Ann Oncol* 2012; 23: 2619–26;
†Since October 2005, ± resection if an option

Ruers et al. J Clin Oncol 2015; 33 (suppl): abstr 3501

3501: Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC) – Ruers T, et al

Key results

- The primary endpoint was met: 30-month OS was 61.7% (95%CI 48.2, 73.9) with RFA + FOLFOX ± bevacizumab vs. 57.6% (44.1, 70.4) with FOLFOX ± bevacizumab alone (the latter was higher than anticipated)

	RFA + FOLFOX ± bevacizumab	FOLFOX ± bevacizumab alone	HR (95%CI); p-value
8-year PFS, %	22.3	2.0	0.57 (0.38, 0.85); 0.005
8-year OS, %	35.9	8.9	0.58 (0.38, 0.88); 0.010
Alive at last count, %	35.0	10.2	
Dead, %	65.0	89.8	-

Conclusions

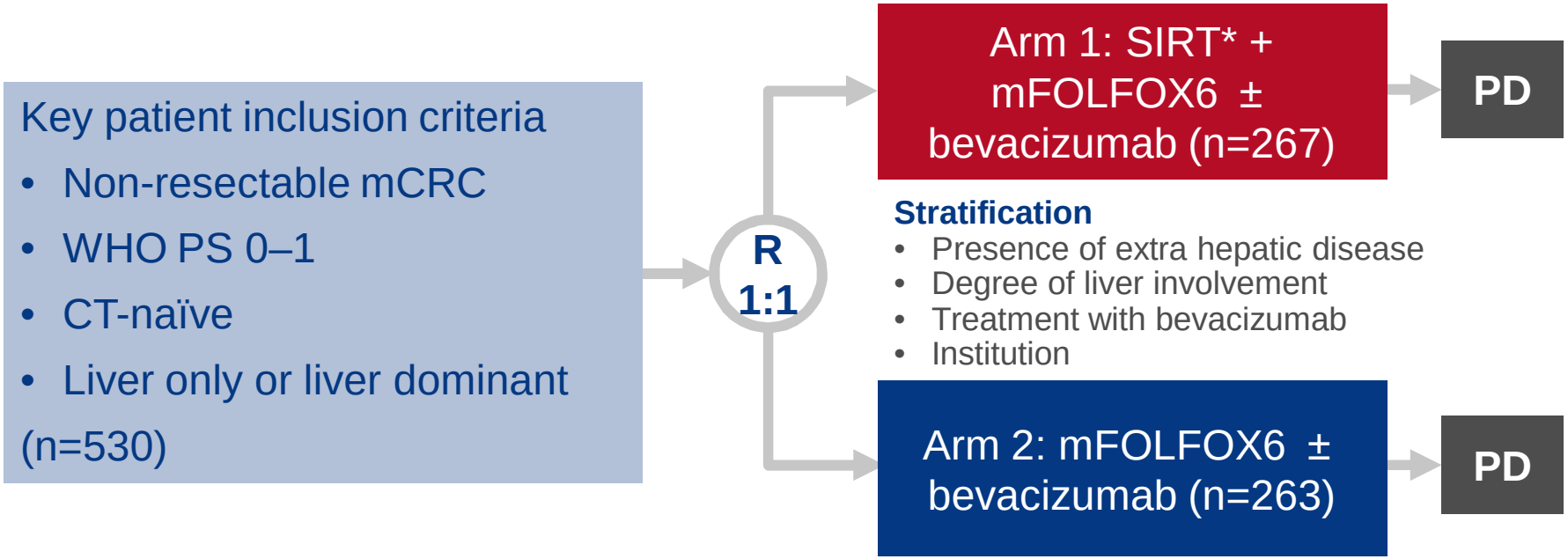
- **RFA + FOLFOX ± bevacizumab significantly improved PFS and OS vs. FOLFOX ± bevacizumab alone**
- **Despite limitations due to reduced sample size, these results suggest RFA can be used as a treatment modality in patients with unresectable CRC liver metastases**
- **Complete treatment of all liver lesions should be the aim in these patients**

Ruers et al. J Clin Oncol 2015; 33 (suppl): abstr 3501

3502: SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC) – Gibbs P, et al

Study objective

- To assess the efficacy and safety of combining FOLFOX (± bevacizumab) with SIRT* as a first-line treatment in patients with liver metastases from mCRC



PRIMARY ENDPOINT

- PFS

SECONDARY ENDPOINTS

- PFS in the liver, ORR, hepatic resection rate, safety

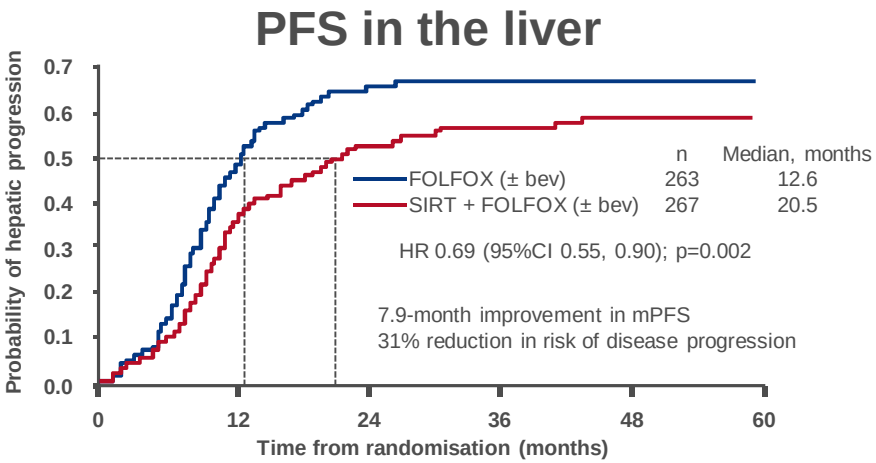
*Liver-directed therapy using Yttrium-90-labelled microspheres, administered once with cycle 1

Gibbs et al. J Clin Oncol 2015; 33 (suppl): abstr 3502

3502: SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC) – Gibbs P, et al

Key results

- mPFS at any site: 10.7 vs. 10.2 months in Arm 1 vs. Arm 2 (HR 0.93 [95%CI 0.77, 1.12]; p=0.43)



	Any site		Liver	
	Arm 1	Arm 2	Arm 1	Arm 2
ORR, %	76.4	68.1	78.7*	68.8
PR	71.9	66.5	72.7	66.9
CR	4.5	1.5	6.0*	1.9

- AEs ≥grade 3 occurred in 85.4 vs. 73.4% in Arm 1 vs. Arm 2; AEs with a significant difference between Arm 1 vs. Arm 2 were: neutropenia (40.7 vs. 28.5%), febrile neutropenia (6.1 vs. 1.9%) and thrombocytopenia (9.8 vs. 2.6%)

Conclusions

- **Liver metastases are the key disease site and cause of death in patients with mCRC**
- **The addition of SIRT† to FOLFOX (±bevacizumab) in patients with liver-dominant metastases did not improve overall PFS, but did improve PFS and ORR in the liver, and had acceptable safety**

*p<0.05 vs. Arm 2

Gibbs et al. J Clin Oncol 2015; 33 (suppl): abstr 3502

How many modalities are enough? – Sharma RA

Discussion of abstract 3500

- There was an imbalance in T4b tumours and N stage
- Data on FOLFOX + RT were hypothesis generating rather than confirmatory
- Data confirm previous studies: improved pCR but higher grade 3/4 toxicities
- Further data on primary endpoint are anticipated in 2017 (ITT analysis of DFS)

Discussion of abstract 3501

- Impressive results at 8 years, with a clear survival benefit with RFA + CT vs. CT alone
  - Unresectable patients may benefit from RFA + surgery
  - Patient follow-up should be multidisciplinary (surgery ± thermal ablation)
  - Data are required for other modalities

Discussion of abstract 3502

- 40% of patients had extrahepatic disease, which may explain why PFS did not improve
- PFS did improve in the liver (robust result), but with increased toxicity
- Further data anticipated for subgroup analyses, OS and QoL in 2015–2017

Conclusions

- **For locally advanced rectal cancer, standard of care remains CRT followed by surgery**
- **For 'clearable' liver metastases, CT, surgery + thermal ablation are required**
- **For patients with liver limited disease without extrahepatic metastases: SIRT + CT can be considered**

RECTAL CANCER

ADJUVANT THERAPY

3515: A randomized phase III trial comparing S-1 versus UFT as adjuvant chemotherapy for stage II/III rectal cancer (JFMC35-C1: ACTS-RC) – Murata A, et al

Study objective

- To investigate the efficacy and safety of S-1 vs. UFT in a superiority study in patients with rectal cancer

Key patient inclusion criteria

- Aged 20−80 years
- Histologically confirmed stage II/III rectal adenocarcinoma
- No prior chemotherapy or radiotherapy
- Curatively resected (R0 resection)

(n=959)

R

S-1 80, 100, 120 mg/day according to BSA in 2 divided doses daily
4 weeks on followed by 2 weeks off* for 1 year
(n=470)

UFT 500, 600 mg/day according to BSA in 2 divided doses daily
5 days on followed by 2 days off for 1 year
(n=479)

Stratification

- Institution
- Tumour location (above the peritoneal reflection vs below the peritoneal reflection and proctos)
- Depth of tumour invasion (T1, T2 vs. T3, T4)
- LN metastasis (N0 vs. N1, N2)

PRIMARY ENDPOINT

- Relapse-free survival

SECONDARY ENDPOINTS

- OS, safety

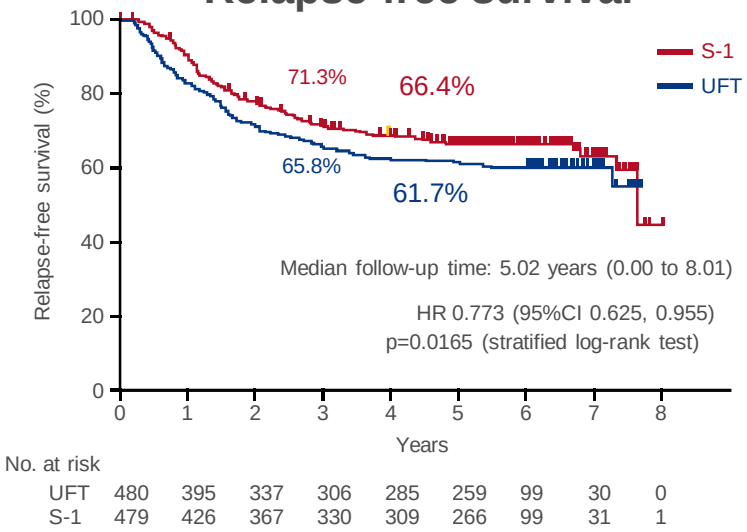
*When AEs occurred, 2 weeks on/1 week off was acceptable

Murata et al. J Clin Oncol 2015; 33 (suppl): abstr 3515

3515: A randomized phase III trial comparing S-1 versus UFT as adjuvant chemotherapy for stage II/III rectal cancer (JFMC35-C1: ACTS-RC) – Murata A, et al

Key results

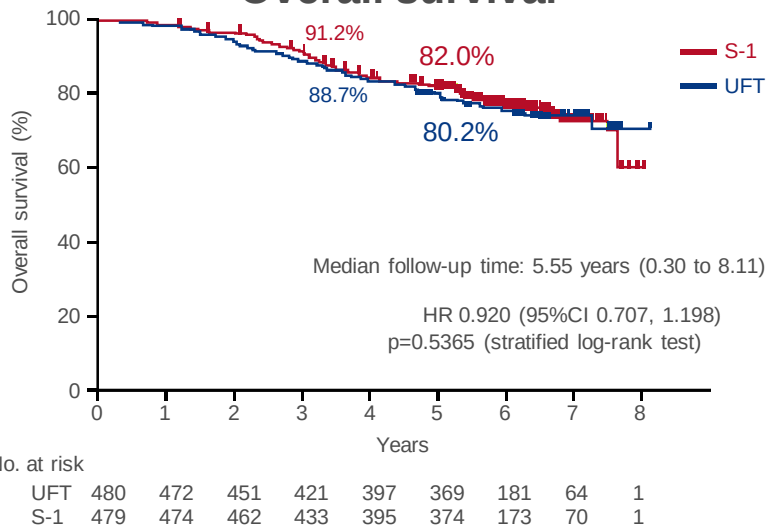
Relapse-free survival



No. at risk

UFT	480	395	337	306	285	259	99	30	0
S-1	479	426	367	330	309	266	99	31	1

Overall survival



No. at risk

UFT	480	472	451	421	397	369	181	64	1
S-1	479	474	462	433	395	374	173	70	1

- The most common grade ≥3 AEs occurring in >1% in either group were: diarrhoea, anorexia, nausea and fatigue

Conclusions

- **S-1 demonstrated superiority to UFT in relapse-free survival in patients with curatively resected stage II/III rectal cancer with no preoperative chemoradiotherapy**
- **Incidence of grade ≥3 AEs was comparable between the two treatment groups**
- **S-1 has become the standard postoperative adjuvant chemotherapy for resected stage II/III rectal cancer**

Murata et al. J Clin Oncol 2015; 33 (suppl): abstr 3515

"New" drugs in localized rectal cancer – Eng C

Discussion of abstract 3515

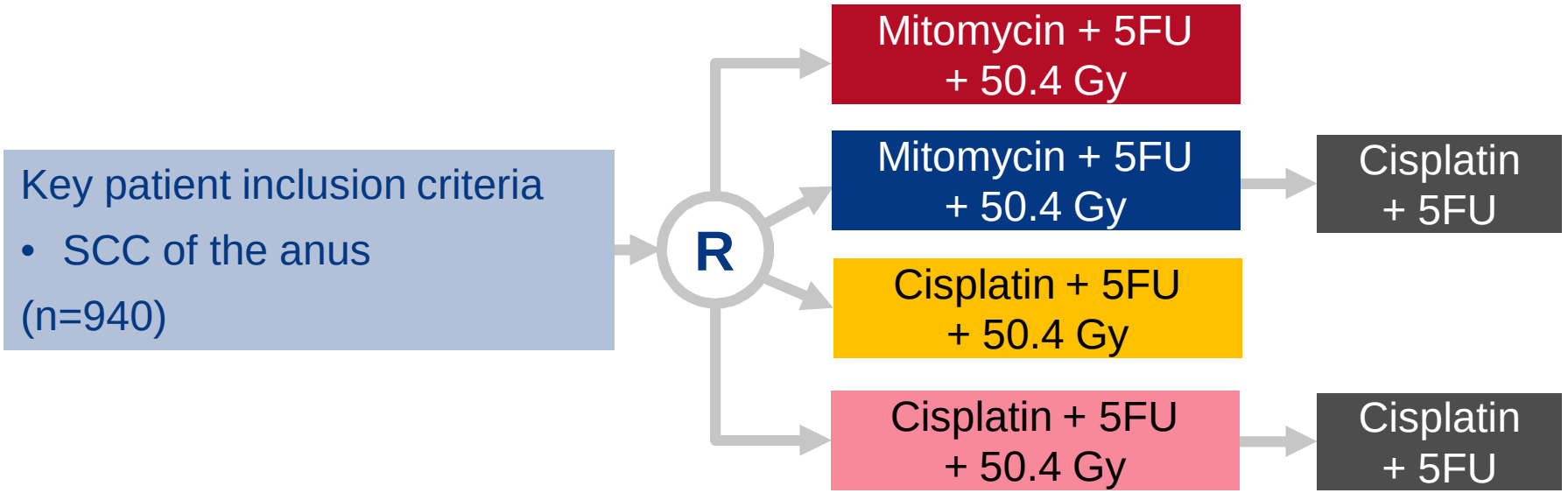
- S-1 vs. UFT was assessed for one year as adjuvant treatment for rectal cancer in patients who had not received prior chemotherapy or radiotherapy
  - S-1 showed a higher RFS than UFT, but OS was the comparable between the two treatment groups
- This study used an atypical treatment paradigm as usually patients will have received prior radiation therapy and one-year adjuvant is not typically used (3 or 6 months is preferred)
- There is limited literature regarding adjuvant treatment, however, results from the MOSAIC trial have led to the widespread adoption of adjuvant FOLFOX
- There is an unmet need in locally advanced rectal cancer for novel agents and approaches; no paradigm change since 2004
  - Lack of viable tumour tissue in postoperative chemoradiation specimens makes it hard to ascertain the biological activity of novel agents such as radiation sensitisers

ANAL CANCER

3518: Compliance to chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance 5FU/CisP chemotherapy (CT) in squamous cell carcinoma of the anus (SCCA) according to radiotherapy (RT) dose, overall treatment time (OTT) and chemotherapy (CT) and their impact on long-term outcome: Results of ACT II – Glynne-Jones R, et al

Objective

- Retrospective study to assess the association between CRT compliance and survival in patients with SCC of the anus receiving RT plus either mitomycin + 5FU or cisplatin + 5FU



For RT, patients were divided into 5 groups:

- Group 1: Per-protocol; 50.4 Gy in 28F in 38-42 days (n=786)
- Group 2: ≤40 Gy (n=18)
- Group 3: 40–48 Gy in 23–27F (n=21)
- Group 4: 50.4 Gy in >42 days (n=93)
- Group 5: >52.2 Gy (n=15)

For CT, patients were divided into 2 groups: Group A administered at Week 1 + 2 and Group B Week 1 only

Glynne-Jones et al. J Clin Oncol 2015; 33 (suppl): abstr 3518

3518: Compliance to chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance 5FU/CisP chemotherapy (CT) in squamous cell carcinoma of the anus (SCCA) according to radiotherapy (RT) dose, overall treatment time (OTT) and chemotherapy (CT) and their impact on long-term outcome: Results of ACT II – Glynne-Jones R, et al

Key results

- The following factors were borderline significant predictors of poor week 5 CT compliance:
  - Canal tumours (p=0.09), cisplatin (p=0.07), GFR <60 (p=0.06) and WBC <11 (0.08)
  - None of the baseline factors analysed, or chemotherapy type, were significant independent predictors of poor RT compliance

	3-year PFS, %	HR (95%CI)	p-value
Group 1 (n=786)	76	1.00	0.0001
Group 2 (n=18)	44	3.71 (2.01, 6.82)	
Group 3 (n=21)	56	2.26 (1.23, 4.14)	
Group 4 (n=93)	62	1.62 (1.15, 2.28)	
Group 5 (n=15)	59	1.60 (0.71, 3.61)	

Conclusions

- **Poor CT and RT compliance adversely impacted PFS**
- **Treatment interruptions should be minimised and prolonged overall treatment time compensated by hyperfractionation or possibly additional dose**
- **Patients with poor compliance to RT/CT may need closer monitoring after treatment**

Glynne-Jones et al. J Clin Oncol 2015; 33 (suppl): abstr 3518

Recent progress in anal cancer research – Wang A

Discussion of abstract 3518

- Poor RT compliance was associated with worse PFS
  - However, since non-protocol treatment is not pre-planned, it is difficult to establish cause and affect between treatment compliance and PFS
  - Groups 2, 3 and 5 also had very low numbers (n=18, n=21, n=20, respectively)
- Poor CT compliance was associated with worse PFS
- A previous study found that prolonged treatment time was associated with worse OS (RTOG trial)[1]
  - However, this was primarily due to induction CT
  - RT dose but not RT duration was a significant predictor of OS
- These differences between the RTOG[1] and ACT II trials may be due to the different treatment regimens employed in the two studies

[1]Ben-Josef E, et al. J Clin Oncol 2010; 28: 5061–6.

COLORECTAL CANCER

3504: Impact of aspirin as secondary prevention in an unselected cohort of 25,644 patients with colorectal cancer: A population-based study – Bains S, et al

Study objective

- To examine the association between aspirin use after diagnosis of CRC with CRC-specific survival and OS

Study population

- Observational, population-based, retrospective cohort study linking patients diagnosed with CRC from 2004 through 2011 (Cancer Registry of Norway) with the use of aspirin in the same patients (The Norwegian Prescription Database)
- 25,644 patients were diagnosed with CRC in the study period and 6,109 of them were defined as exposed to aspirin after the diagnosis of CRC

*Original study design included unselected patients;
†FOLFIRI or FOLFOX (investigator choice)

Bains et al. J Clin Oncol 2015; 33 (suppl): abstr 3504

3504: Impact of aspirin as secondary prevention in an unselected cohort of 25,644 patients with colorectal cancer: A population-based study – Bains S, et al

Key results

- Median follow-up was 2.2 years
- Among aspirin-exposed cases, a total of 2,088 (34.2%) deaths were recorded of which 1,172 (19.2%) were CRC specific
- Among non-exposed aspirin cases, a total of 7,595 (38.9%) deaths were recorded of which 6,356 (33.5%) were CRC specific
- In a multivariate analysis, aspirin exposure after the diagnosis of CRC was independently associated with improvements in:
  - CRC-specific survival (HR 0.53 [95%CI 0.50, 0.57]; p<0.001)
  - OS (HR 0.71 [95%CI 0.68, 0.75]; p<0.001)

Conclusion

- **Exposure to aspirin after the diagnosis of CRC is independently associated with improved cancer-specific survival and OS**

Bains et al. J Clin Oncol 2015; 33 (suppl): abstr 3504

3505: Comprehensive molecular characterization of colorectal cancer reveals genomic predictors of immune cell infiltrates – Giannakis M, et al

Study objective

- To characterise the molecular subtypes of CRC according to neoantigen* expression and to determine the prognostic value of neoantigens in patients with CRC

Study design

- Whole Exome Sequencing and microsatellite instability (MSI) analyses were performed on archived FFPE tumour samples and paired normal tissue from 689 patients with CRC
  - Samples were characterised by somatic mutations and HLA-class I expression in order to predict high affinity neoantigens
- Tumour neoantigen load was calculated and this was subsequently correlated with pathology and survival information

*Peptides resulting from somatic mutations and recognised by the immune system as foreign

Giannakis et al. J Clin Oncol 2015; 33 (suppl): abstr 3505

3505: Comprehensive molecular characterization of colorectal cancer reveals genomic predictors of immune cell infiltrates – Giannakis M, et al

Key results

- MSI-high tumours expressed more neoantigens vs. MSI-low cancers ($p<2 \times 10^{-16}$)
- Tumour neoantigen load significantly correlated with:
  - Lymphocytic score in primary CRC ($p=4.9 \times 10^{-9}$)
  - Tumor infiltrating lymphocytes ($p=1.6 \times 10^{-15}$)
  - $CD45RO^{+}$ T-cell subset ($p= 0.0003$)
- High vs. low neoantigen load predicted significantly improved CRC-specific OS (p=0.014) and OS (p=0.048)

Conclusions

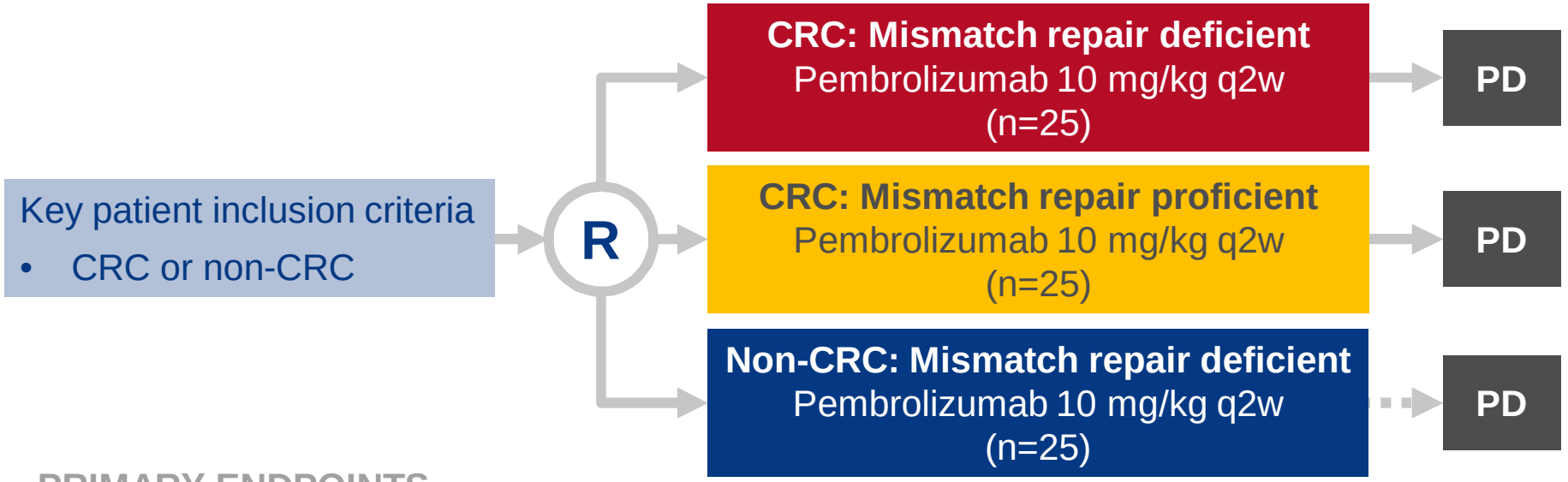
- **Tumour neoantigen load predicts greater tumour-infiltrating lymphocytes and memory T-cell infiltration in patients with CRC**
  - **Represents a novel genomic predictor of CRC survival**
- **These findings link tumour genomics to specific immune response elements and have implications for the therapeutic manipulation of the latter in CRC**

Giannakis et al. J Clin Oncol 2015; 33 (suppl): abstr 3505

LBA100: PD-1 blockade in tumors with mismatch repair deficiency – Le DT, et al

Study objective

- To determine the efficacy of anti-PD1 inhibition with pembrolizumab in patients with CRC vs. non-CRC who had mismatch repair (MMR) deficient tumours



PRIMARY ENDPOINTS

- Immune-related PFS; response rate

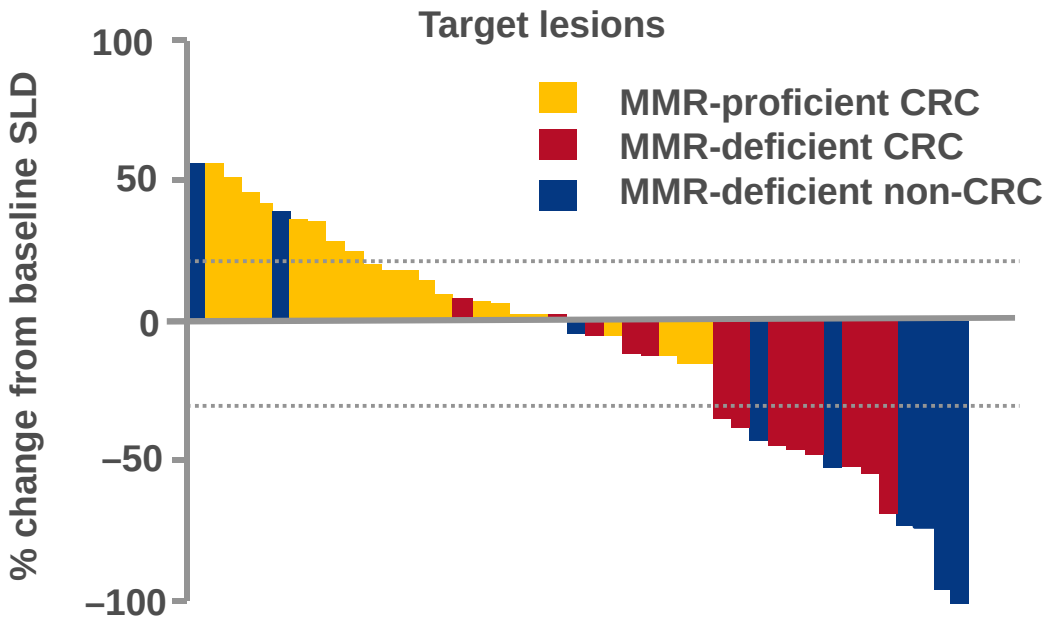
- Mismatch repair status was determined using standard PCR to ascertain microsatellite instability

Le et al. J Clin Oncol 2015; 33 (suppl): abstr LBA100

LBA100: PD-1 blockade in tumors with mismatch repair deficiency – Le DT, et al

Key results

	MMR-deficient CRC (n=13)	MMR-proficient CRC (n=25)	MMR-deficient non-CRC (n=10)
ORR, %	62	0	60
DCR, %	92	16	70

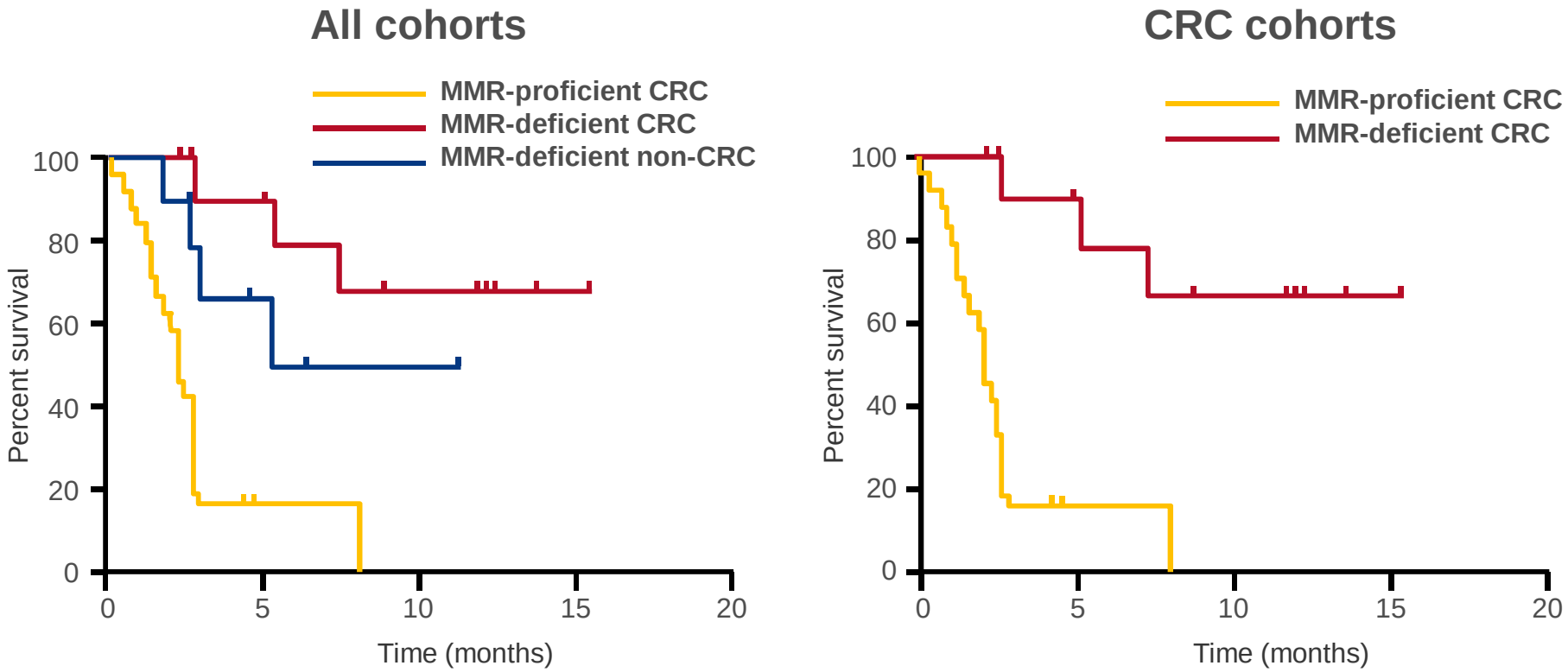


Le et al. J Clin Oncol 2015; 33 (suppl): abstr LBA100

LBA100: PD-1 blockade in tumors with mismatch repair deficiency – Le DT, et al

Key results (cont.)

PFS

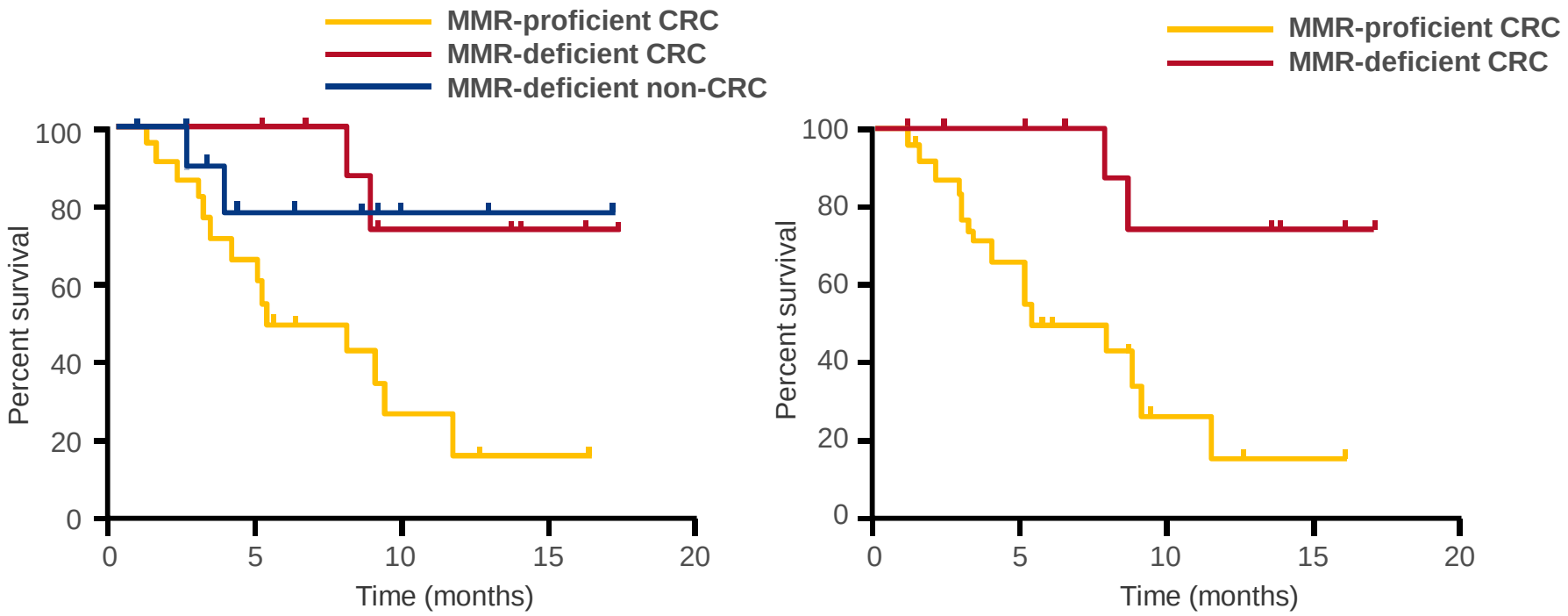


Le et al. J Clin Oncol 2015; 33 (suppl): abstr LBA100

LBA100: PD-1 blockade in tumors with mismatch repair deficiency – Le DT, et al

Key results (cont.)

OS



Le et al. J Clin Oncol 2015; 33 (suppl): abstr LBA100

LBA100: PD-1 blockade in tumors with mismatch repair deficiency – Le DT, et al

Key results (cont.)

AE, no. of events (%)	All grades (n=41)
Any	14 (34)
Generalised symptoms	3 (7)
Pancreatitis	6 (15)
Pneumonitis	1 (2)
Endocrine disorders	5 (12)
Rash/pruritus	7 (17)
Thrombocytopenia	1 (2)

- Mismatch repair deficient tumours had a higher density of invasive front CD8+ T cells (p=0.04) and greater invasive front PD-L1 expression (p=0.04) than mismatch repair proficient tumours
- In patients treated with pembrolizumab, mutation burden correlated with ORR, SD and PD (p=0.02)

Conclusions

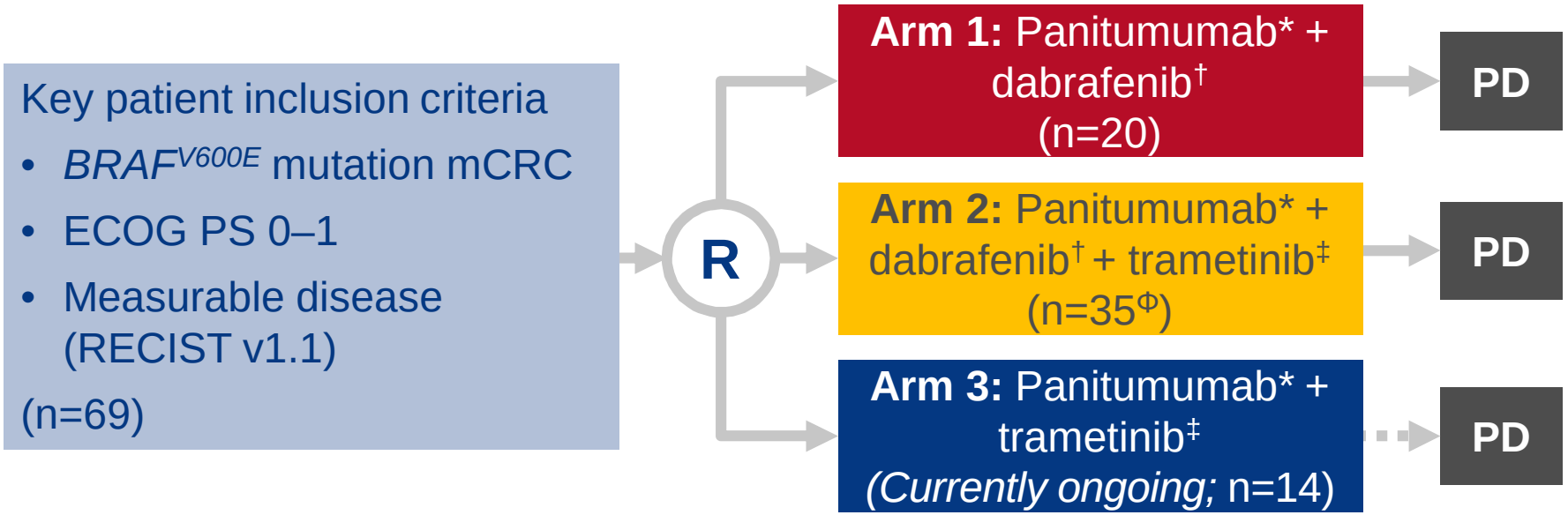
- **Mismatch repair deficient tumours are highly susceptive to anti-PD1 blockade with pembrolizumab**
- **Biochemical responses correlated with radiographic response and with PFS and OS**
- **Mismatch repair deficient tumours are highly mutated and rich in $CD8^+$ T cells and PD-L1 expression at the tumour invasive front**

Le et al. J Clin Oncol 2015; 33 (suppl): abstr LBA100

103: Phase 1/2 study of the MEK inhibitor trametinib, BRAF inhibitor dabrafenib, and anti-EGFR antibody panitumumab in patients with BRAF V600E-mutated metastatic colorectal cancer – Atreya CE, et al

Study objective

- To evaluate the efficacy and safety of panitumumab (anti-EGFR mAb) with dabrafenib (*BRAF* inhibitor) and/or trametinib (MEK inhibitor) in patients with *BRAF*-mutated mCRC



PRIMARY ENDPOINTS

- Safety, response rate, PFS

SECONDARY ENDPOINTS

- PK, duration of response

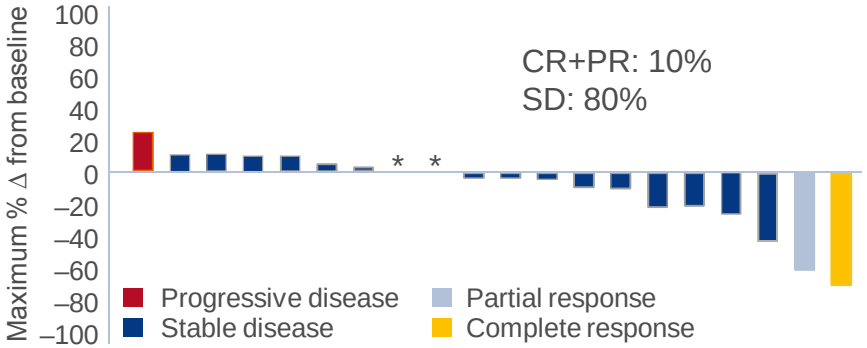
*6 mg/kg q2w; †150 mg bid; ‡2 mg/day; Φn=24 patients received the full triplet dose

Atreya et al. J Clin Oncol 2015; 33 (suppl): abstr 103

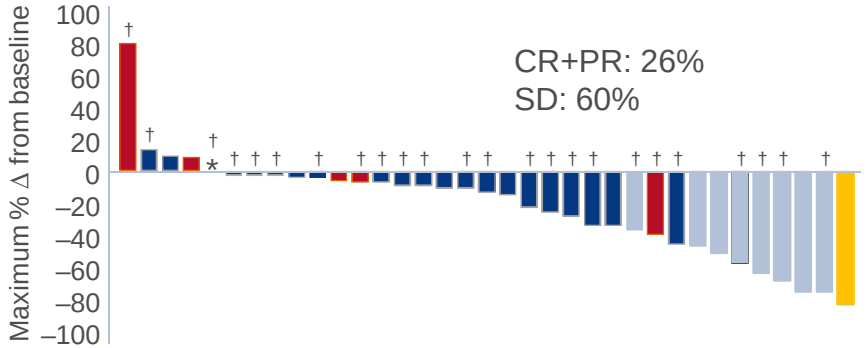
103: Phase 1/2 study of the MEK inhibitor trametinib, BRAF inhibitor dabrafenib, and anti-EGFR antibody panitumumab in patients with BRAF V600E-mutated metastatic colorectal cancer – Atreya CE, et al

Key results

Best response (Arm 1)



Best response (Arm 2)



- mPFS: 3.4 vs. 4.1 months with dual therapy (Arm 1) vs. triple therapy (Arm 2)
- Grade 3 AEs occurring in ≥5% (Arm 1 vs. 2 vs. 3): dermatitis acneiform (0 vs. 9 vs. 14%); diarrhoea (0 vs. 9 vs. 0%); fatigue (0 vs. 6 vs. 0); hypomagnesaemia (5 vs. 6 vs. 0%); dry skin (5 vs. 3 vs. 7%); and decreased appetite (0 vs. 6 vs. 0%)
- Dose reductions due to dermatological AEs (Arm 1 vs. 2 vs. 3): 11 vs. 36 vs. 54%

Conclusions

- **Triple therapy with panitumumab + dabrafenib + trametinib may be more effective than either dual therapy combinations in patients with *BRAF*-mutated mCRC**
- **Dermatologic toxicity was significant, resulting in dose reductions**

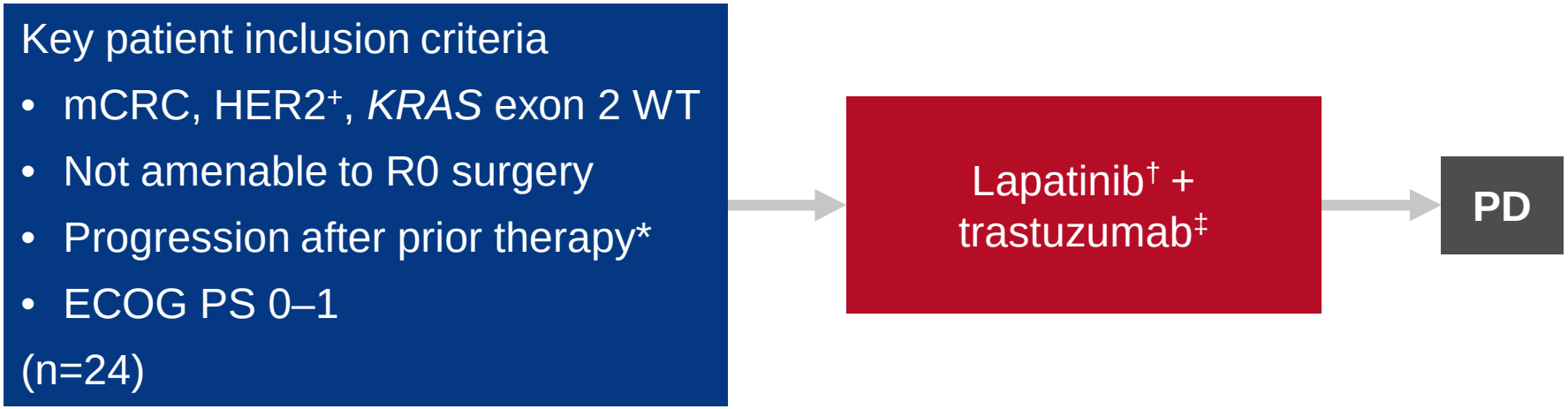
*0% reduction from baseline; †Patient received the full triplet dose

Atreya et al. J Clin Oncol 2015; 33 (suppl): abstr 103

3508: Trastuzumab and lapatinib in HER2-amplified metastatic colorectal cancer patients (mCRC): The HERACLES trial – Siena S, et al

Study objective

- To determine the efficacy and tolerability of trastuzumab and lapatinib in patients with HER2$^+$, *KRAS* exon 2 WT mCRC who were resistant to standard therapies



PRIMARY ENDPOINT

- ORR (RECIST v1.1)

SECONDARY ENDPOINTS

- TTP, safety

*Fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, cetuximab, panitumumab; †4 mg/kg IV load then 2 mg/kg/week; ‡1000 mg/day po

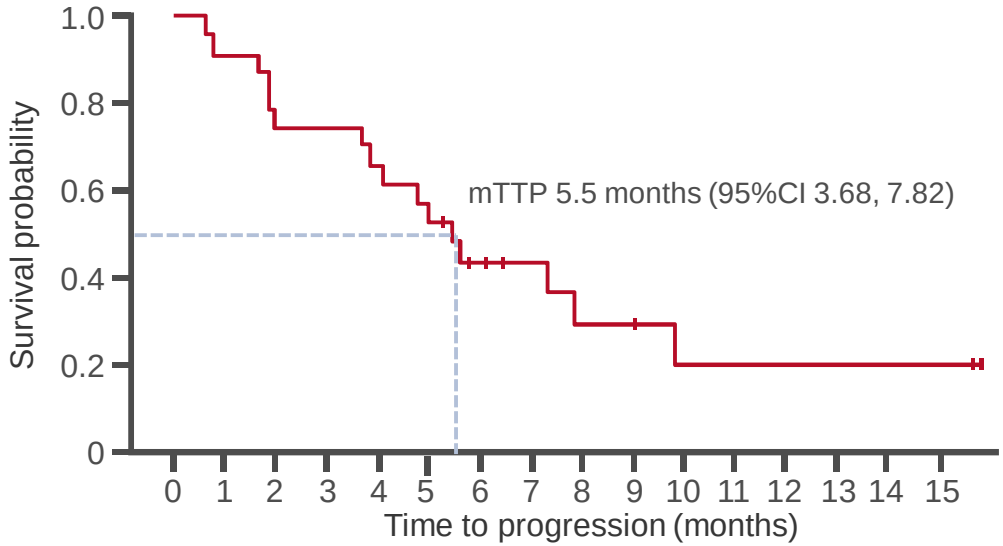
Siena et al. J Clin Oncol 2015; 33 (suppl): abstr 3508

3508: Trastuzumab and lapatinib in HER2-amplified metastatic colorectal cancer patients (mCRC): The HERACLES trial – Siena S, et al

Key results

- In total, 5.4% of the patients screened were HER2+

	L + T (n=23)
*ORR, %	34.7
CR	4.3
PR	30.4
SD ≥4 months, %	30.4
SD <4 months, %	13.0
PD, %	21.7



- Most common AEs: GI (Grade ≤2; n=16; 70%), skin (Grade 3, n=1; 4%) and fatigue (Grade 3, n=3; 13%)
- No grade 5 AEs; no withdrawal due to patient request

Conclusions

- **Lapatinib + trastuzumab was effective and well tolerated in patients with HER2$^+$ CRC**
- **Patients with HER2$^+$ mCRC were primarily resistant to cetuximab or panitumumab, supporting the use of lapatinib + trastuzumab in anti-EGFR-resistant patients**
- **Dual HER2-targeted therapy is a new valuable option for patients with HER+ mCRC**

*DCR 78%. L, lapatinib; T, trastuzumab

Siena et al. J Clin Oncol 2015; 33 (suppl): abstr 3508