GI SLIDE DECK 2018

Selected abstracts from:

esdo european society of digestive oncology

Supported by Eli Lilly and Company.
Eli Lilly and Company has not influenced the content of this publication

Lilly

Letter from ESDO

DEAR COLLEAGUES

It is our 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 2018. This slide set specifically focuses on the **2018 American Society of Clinical Oncology Annual Meeting** and is available in English, French 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 which helps to educate and inspire further advancements in our roles as scientists, clinicians and educators. We hope you find this review of the latest developments in digestive cancers of benefit to you in your practice. If you would like to share your thoughts with us we would welcome your comments. Please send any correspondence to info@esdo.eu.

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

Yours sincerely,

Eric Van Cutsem
Thomas Seufferlein
Côme Lepage
Wolff Schmiegel
Phillippe Rougier (hon.)

Ulrich Güller
Thomas Grünberger
Tamara Matysiak-Budnik
Jaroslaw Regula
Jean-Luc Van Laethem

(ESDO Governing Board)

esdo

european society of digestive oncology

ESDO Medical Oncology Slide Deck
Editors 2018

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, Kaiser-Franz-Josef Hospital, Vienna, Austria
Prof Jaroslaw Regula	Department of Gastroenterology and Hepatology, Institute of Oncology, Warsaw, Poland

PANCREATIC CANCER AND HEPATOBILIARY TUMOURS

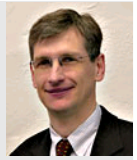


Prof Jean-Luc Van Laethem	Digestive Oncology, Erasme University Hospital, Brussels, Belgium
Prof Thomas Seufferlein	Clinic of Internal Medicine I, University of Ulm, Ulm, Germany
Prof Ulrich Güller	Medical Oncology & Hematology, Kantonsspital St Gallen, St Gallen, Switzerland

GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS


Prof Côme Lepage	University Hospital & INSERM, Dijon, France
Prof Tamara Matysiak	Hepato-Gastroenterology & Digestive Oncology, Institute of Digestive Diseases, Nantes, 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
AFP	alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
bid	twice daily
CAPOX	capecitabine + oxaliplatin
CI	confidence interval
CR	complete response
(m)CRC	(metastatic) colorectal cancer
CRT	chemoradiotherapy
CT	chemotherapy
ctDNA	circulating tumour DNA
d	day
DCR	disease control rate
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
(m)FOLFIRI	leucovorin + 5-fluorouracil + irinotecan
FOLFIRINOX	leucovorin + 5-fluorouracil + irinotecan + oxaliplatin
(m)FOLFOX	(modified) leucovorin + 5-fluorouracil + oxaliplatin
(m)FOLFOXIRI	(modified) 5-fluorouracil + leucovorin + oxaliplatin + irinotecan
GEJ	gastroesophageal junction
HCC	hepatocellular carcinoma
HR	hazard ratio
ip	intraperitoneal
ITT	intent-to-treat
iv	intravenous
mAB	monoclonal antibody
min	minute
MMR	mismatch repair proficient
MSI	microsatellite instability
MT	mutant
NE	not evaluable
NGS	next generation sequencing
NR	not reached
OR	odds ratio
ORR	overall/objective response rate
(m)OS	(median) overall survival
pCR	pathological complete response
PD	progressive disease
PD-L1	programmed death-ligand 1
(m)PFS	(median) progression-free survival
po	orally
PR	partial response
PS	performance status
pvi	protracted venous infusion
q(1/2/3/4)w	every (1/2/3/4) week(s)
QoL	quality of life
R	randomised
R0/1/2	resection 0/1/2
RCT	randomised controlled trial
(m)RECIST	(modified) Response Evaluation Criteria In Solid Tumors
RT	radiotherapy
SAE	serious adverse events
SD	stable disease
TACE	transarterial chemoembolisation
TIL	tumour-infiltrating lymphocytes
TME	total mesorectal excision
TRAE	treatment-related adverse event
VAF	variant allele frequency
wk	week
WT	wild type

Contents

Note: To jump to a section, right click on the number and ‘Open Hyperlink’

CANCERS OF THE OESOPHAGUS AND STOMACH

4062: Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial – Fuchs CS, et al

Study objective

- To assess the efficacy and safety of pembrolizumab vs. paclitaxel in previously treated patients with advanced gastric/GEJ cancer in the KEYNOTE-061 study

Key patient inclusion criteria

- Advanced gastric/GEJ cancer
- Metastatic or locally advanced
- Unresectable
- PD after 1L CT containing platinum and fluoropyrimidine
- ECOG PS 0–1

(n=592)

R 1:1

Pembrolizumab 200 mg q3w (n*=196/296)

For 35 cycles or until PD/toxicity/ withdrawal/ investigator decision

Stratification

- Geographic region
- ECOG PS (0 vs. 1)
- TTP on 1L therapy (<6 vs. ≥6 months)
- PD-L1 combined positive score (CPS <1 vs. ≥1)

Paclitaxel† (n*=199/296)

PD/toxicity/ withdrawal/ investigator decision

PRIMARY ENDPOINT

- OS‡, PFS in CPS ≥1 population

SECONDARY ENDPOINTS

- ORR, DoR in CPS ≥1 population
- Safety in all patients

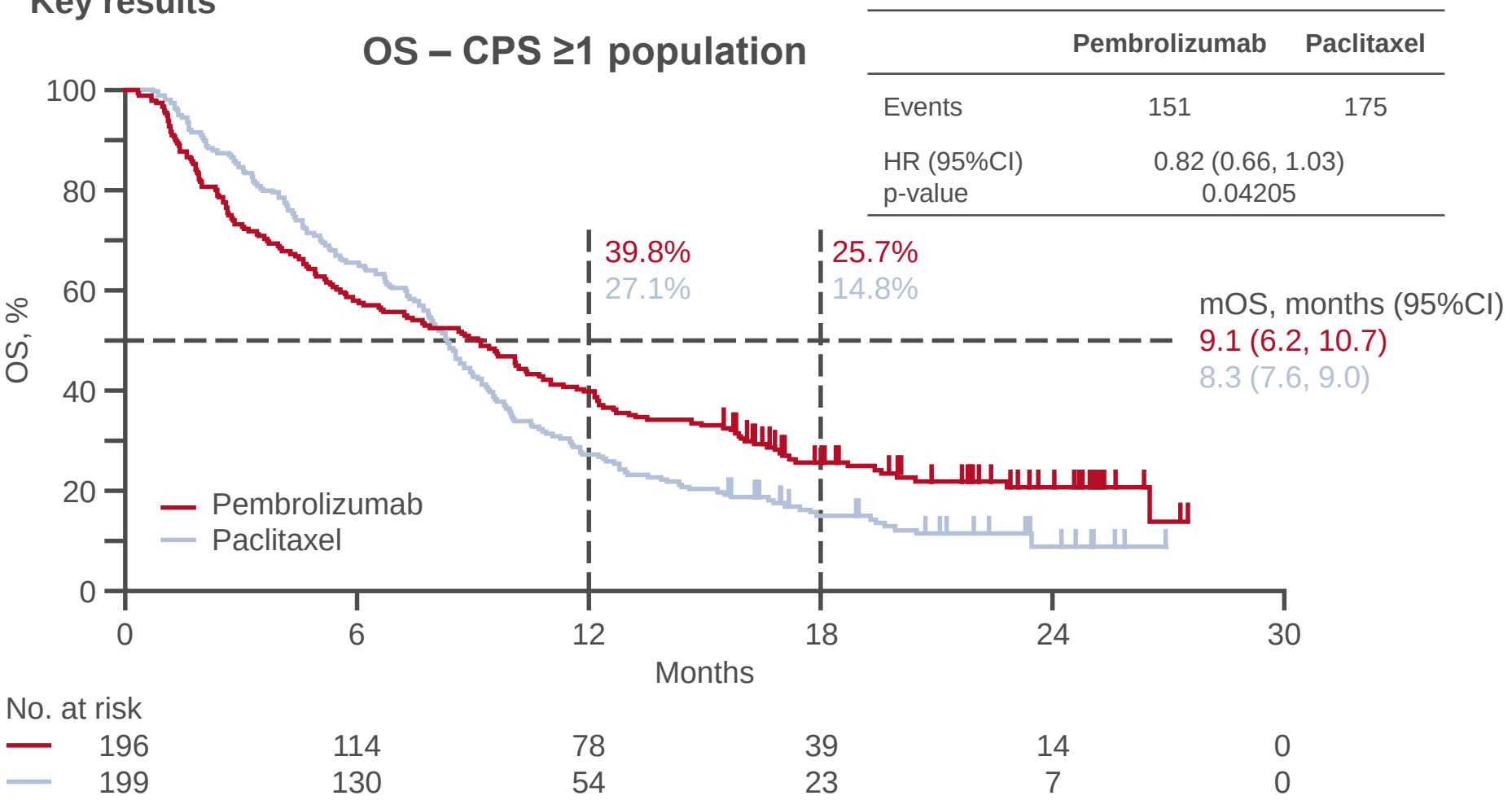
*n for CPS ≥1 population/all patients;
†80 mg/m^2 d1,8,15 of 4-week cycle;
‡pre-specified significance threshold for OS: p≤0.0135

Presented by Shitara K

Fuchs CS, et al. J Clin Oncol 2018;36(suppl):abstr 4062

4062: Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial – Fuchs CS, et al

Key results



	Pembrolizumab	Paclitaxel
Events	151	175
HR (95%CI)	0.82 (0.66, 1.03)	
p-value	0.04205	

Presented by Shitara K

Fuchs CS, et al. J Clin Oncol 2018;36(suppl):abstr 4062

4062: Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial – Fuchs CS, et al

Key results (cont.)

	Pembrolizumab	Paclitaxel	HR (95%CI)
mOS, months (95%CI)			
ECOG PS 0	12.3 (9.7, 15.9)	9.3 (8.3, 10.5)	0.69 (0.49, 0.97)
ECOG PS 1	5.4 (3.7, 7.7)	7.5 (5.3, 8.4)	0.98 (0.73, 1.32)
mOS, months (95%CI)			
CPS <1	4.8 (3.9, 6.1)	8.2 (6.8, 10.6)	1.20 (0.89, 1.63)
CPS ≥1	9.1 (6.2, 10.7)	8.3 (7.6, 9.0)	0.82 (0.66, 1.03)
CPS ≥10	10.4 (5.9, 17.3)	8.0 (5.1, 9.9)	0.64 (0.41, 1.02)
mOS, months (95%CI) MSI-high tumours	NR (5.6, NR)	8.1 (2.0, 16.7)	0.42 (0.13, 1.31)
PFS, months (95%CI)			
CPS ≥1	1.5 (1.4, 2.0)	4.1 (3.1, 4.2)	1.27 (1.03, 1.57)
ORR, %			
CPS ≥1	15.8	13.6	-
MSI-high tumours	46.7	16.7	-
mDoR, months (range)			
CPS ≥1	18.0 (1.4+–26.0+)	5.2 (1.3+–16.8)	-

Presented by Shitara K

Fuchs CS, et al. J Clin Oncol 2018;36(suppl):abstr 4062

4062: Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial – Fuchs CS, et al

Key results (cont.)

AEs in all patients, n (%)	Pembrolizumab (n=294)	Paclitaxel (n=276)
TRAEs	155 (52.7)	232 (84.1)
Grade 3–5	42 (14.3)	96 (34.8)
Led to death	3 (1.0)	1 (0.4)
Led to discontinuation	9 (3.1)	15 (5.4)
Immune-mediated AEs/infusion reactions	54 (18.4)	21 (7.6)
Grade 3–5	10 (3.4)	5 (1.8)
Led to death	2 (0.7)	0

Conclusions

- **In previously treated patients with advanced gastric/GEJ cancer, the pre-specified significance threshold for OS was not reached for pembrolizumab vs. paclitaxel**
- **Improvements in OS with pembrolizumab were greater in patients with ECOG PS 0 vs. 1, PD-L1 CPS ≥10 vs. <1 or ≥1 and MSI-high tumours**
- **Pembrolizumab did not improve PFS or ORR vs. paclitaxel although was associated with more durable responses**
- **Fewer TRAEs were reported with pembrolizumab vs. paclitaxel**

Presented by Shitara K

Fuchs CS, et al. J Clin Oncol 2018;36(suppl):abstr 4062

Gastroesophageal Cancers: What Can We Learn From Randomized Trials Discussant – Chao J

Study objective (JCOG1013: Abstract 4009 – Yamada Y, et al)

- **To compare the efficacy and safety of triplet chemotherapy with S-1 and cisplatin + docetaxel vs. doublet chemotherapy with S-1 and cisplatin as 1L therapy in patients with unresectable or recurrent gastric adenocarcinoma**

Study design

- Patients (n=740) with unresectable or recurrent gastric adenocarcinoma were randomised (1:1) to chemotherapy with S-1* and cisplatin† (d8) + docetaxel‡ (d1) vs. doublet chemotherapy with S-1* and cisplatin† (d1)

Key results

	Cisplatin (n=367)	Cisplatin + docetaxel (n=358)
1-year OS, % (95%CI)	61.5 (56.3, 66.2)	59.7 (54.5, 64.5)
Median OS, months (95%CI)	15.3 (14.2, 16.2)	14.2 (12.9, 15.9)
HR (95%CI); p-value (1-sided)	0.99 (95%CI 0.85, 1.16); 0.47	
ORR, %	56.0	59.3

*80, 100, 120 mg/body d1–21 q5w vs. 80, 100, 120 mg/body d1–14 q4w (calculated based on body surface area);
†60 mg/m^2; ‡40 mg/m^2

Yamada Y, et al. J Clin Oncol 2018;36(suppl):abstr 4009
Shah MA, et al. J Clin Oncol 2018;36(suppl):abstr 4010
Makiyama A, et al. J Clin Oncol 2018;36(suppl):abstr 4011

Gastroesophageal Cancers: What Can We Learn From Randomized Trials Discussant – Chao J

Study objective (BRIGHTER: Abstract 4010 – Shah MA, et al)

- **To assess the efficacy and safety of napabucasin + paclitaxel vs. placebo + paclitaxel as 2L therapy in patients with pre-treated, advanced GEJ adenocarcinoma**

Study design

- Patients (n=714) were randomised (1:1) to receive napabucasin (960 mg total daily dose) + weekly paclitaxel 80 mg/m^2 or placebo + weekly paclitaxel 80 mg/m^2. Interim analysis (OS follow-up) was conducted to test for superiority at 2/3 of required events (n=380)

Key results

	Napabucasin + paclitaxel (n=357)	Placebo + paclitaxel (n=357)	HR (95%CI)	p-value
Median OS, months (95%CI)	6.93 (6.28, 7.69)	7.36 (6.64, 8.15)	1.01 (0.86, 1.20)	0.8596
Median PFS, months (95%CI)	3.55 (3.22, 3.68)	3.65 (3.45, 3.71)	1.00 (0.84, 1.17)	0.9679

- No safety concerns of clinical significance were identified

Yamada Y, et al. J Clin Oncol 2018;36(suppl):abstr 4009
Shah MA, et al. J Clin Oncol 2018;36(suppl):abstr 4010
Makiyama A, et al. J Clin Oncol 2018;36(suppl):abstr 4011

Gastroesophageal Cancers: What Can We Learn From Randomized Trials Discussant – Chao J

Study objective (WJOG7112G: Abstract 4011 – Makiyama A, et al)

- **To compare the efficacy and safety of 2L weekly paclitaxel with or without trastuzumab in patients with HER2-positive advanced gastric or GEJ cancer refractory to trastuzumab combined with fluoropyrimidine and platinum**

Study design

- Patients (n=90) were randomised to receive paclitaxel 80 mg/m^2 on d1,8,15 (q4w) or paclitaxel 80 mg/m^2 d1,8,15 (q4w) + trastuzumab† on d1 (q3w)

Key results

	Paclitaxel (n=45)	Paclitaxel + trastuzumab (n=44)	Stratified HR (95%CI)	p-value
Median PFS, months (95%CI)	3.19 (2.86, 3.48)	3.68 (2.76, 4.53)	0.906 (0.674, 1.219)	0.334
Median OS, months (95%CI)	9.95 (7.56, 13.08)	10.20 (7.85, 12.75)	1.230 (0.759, 1.991)	0.199

†8 mg/kg loading dose and 6 mg/kg thereafter

Yamada Y, et al. J Clin Oncol 2018;36(suppl):abstr 4009
Shah MA, et al. J Clin Oncol 2018;36(suppl):abstr 4010
Makiyama A, et al. J Clin Oncol 2018;36(suppl):abstr 4011

Gastroesophageal Cancers: What Can We Learn From Randomized Trials Discussant – Chao J

Presenter's take-home messages

- **For 1L investigational strategies, doublet chemotherapy regimens remain a suitable backbone**
- **In the 2L setting, paclitaxel is active and for investigation in 2L therapy it is not the only combination partner**
- **Robust biomarker enrichment is required**
- **Composite testing strategies are needed to capture spatial and temporal intratumoral heterogeneity**

Yamada Y, et al. J Clin Oncol 2018;36(suppl):abstr 4009
Shah MA, et al. J Clin Oncol 2018;36(suppl):abstr 4010
Makiyama A, et al. J Clin Oncol 2018;36(suppl):abstr 4011

CANCERS OF THE PANCREAS, SMALL BOWEL AND HEPATOBILIARY TRACT

Cancers of the pancreas, small bowel and hepatobiliary tract

PANCREATIC AND BILIARY TRACT CANCERS

4000: FOLFIRINOX until progression, FOLFIRINOX with maintenance treatment, or sequential treatment with gemcitabine and FOLFIRI.3 for first-line treatment of metastatic pancreatic cancer: A randomized phase II trial (PRODIGE 35-PANOPTIMOX) – Dahan L, et al

Study objective

- To compare a 'stop-and-go' strategy of oxaliplatin with an alternative sequential strategy in patients with metastatic pancreatic cancer

Key patient inclusion criteria

- Metastatic pancreatic cancer
- No previous CT or RT
- ECOG PS 0–1

(n=273)

R 1:1:1

Arm A
FOLFIRINOX (12 cycles)
(n=91)
→ PD/ toxicity

Arm B
FOLFIRINOX (8 cycles, 4 months) then leucovorin + 5FU maintenance for SD or reintroduce FOLFIRINOX for PD (n=92)
→ PD/ toxicity

Arm C
Sequential alternating gemcitabine and FOLFIRI 3 every 2 months
(n=90)
→ PD/ toxicity

Stratification

- Centre; biliary stent; age (<65 vs. >65 yrs)

PRIMARY ENDPOINT

- 6-month PFS rate

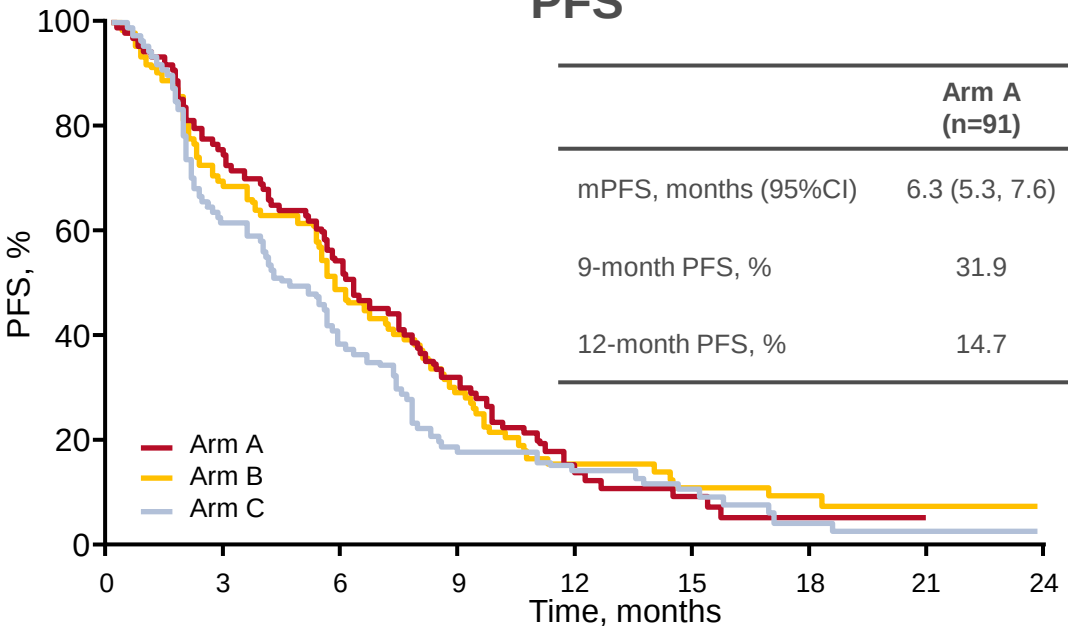
SECONDARY ENDPOINTS

- OS, PFS, best response, safety, 2L therapy

Dahan L, et al. J Clin Oncol 2018;36(suppl):abstr 4000

4000: FOLFIRINOX until progression, FOLFIRINOX with maintenance treatment, or sequential treatment with gemcitabine and FOLFIRI.3 for first-line treatment of metastatic pancreatic cancer: A randomized phase II trial (PRODIGE 35-PANOPTIMOX) – Dahan L, et al

Key results



PFS

	Arm A (n=91)	Arm B (n=92)	Arm C (n=90)
mPFS, months (95%CI)	6.3 (5.3, 7.6)	5.7 (5.3, 7.5)	4.5 (3.5, 5.7)
9-month PFS, %	31.9	29.1	16.4
12-month PFS, %	14.7	14.9	12.9

	Arm A	Arm B	Arm C
mOS, months (95%CI)	10.1 (8.5, 12.2)	11.0 (8.7, 13.1)	7.3 (5.7, 9.5)
6-month OS, %	73.6	75.0	60.0
12-month OS, %	43.3	44.1	28.5
18-month OS, %	18.5	28.0*	13.9
ORR, n (%)	31 (37.3)	31 (38.3)	20 (27.0)

*Exploratory analysis for OS: p<0.05

Dahan L, et al. J Clin Oncol 2018;36(suppl):abstr 4000

4000: FOLFIRINOX until progression, FOLFIRINOX with maintenance treatment, or sequential treatment with gemcitabine and FOLFIRI.3 for first-line treatment of metastatic pancreatic cancer: A randomized phase II trial (PRODIGE 35-PANOPTIMOX) – Dahan L, et al

Key results (cont.)

	Arm A (n=88)	Arm B (n=91)
Neurotoxicity grade 3–4, n (%)	9 (10.2)	17 (18.7)
Neurotoxicity grade 3–4 in first 6 months, n (%)	9 (10.2)	10 (11.0)
Maximum grade neurotoxicity reached, any grade		
First 6 months, n (%)	64 (94.1)	49 (70.0)
After 6 months, n (%)	4 (5.9)	21 (30.0)
Median ratio of oxaliplatin, % (range)*	83 (46.9–102.5)	92 (92.1–104.6)

Conclusions

- **FOLFIRINOX with leucovorin + 5FU maintenance after 4 months of FOLFIRINOX induction appeared to be efficacious in patients with metastatic pancreatic cancer**
- **Unexpectedly, severe neurotoxicity was higher in the maintenance arm**
  - **Neurotoxicity also occurred later in the maintenance arm**
- **Further analyses are currently in progress (QoL, DCR, subgroup analyses)**
- **A phase 3 study comparing FOLFIRINOX maintenance + 5FU vs. FOLFIRINOX alone is now needed to confirm these results**

*Ratio between received dose and targeted dose

Dahan L, et al. J Clin Oncol 2018;36(suppl):abstr 4000

LBA4001: Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas – Conroy T, et al

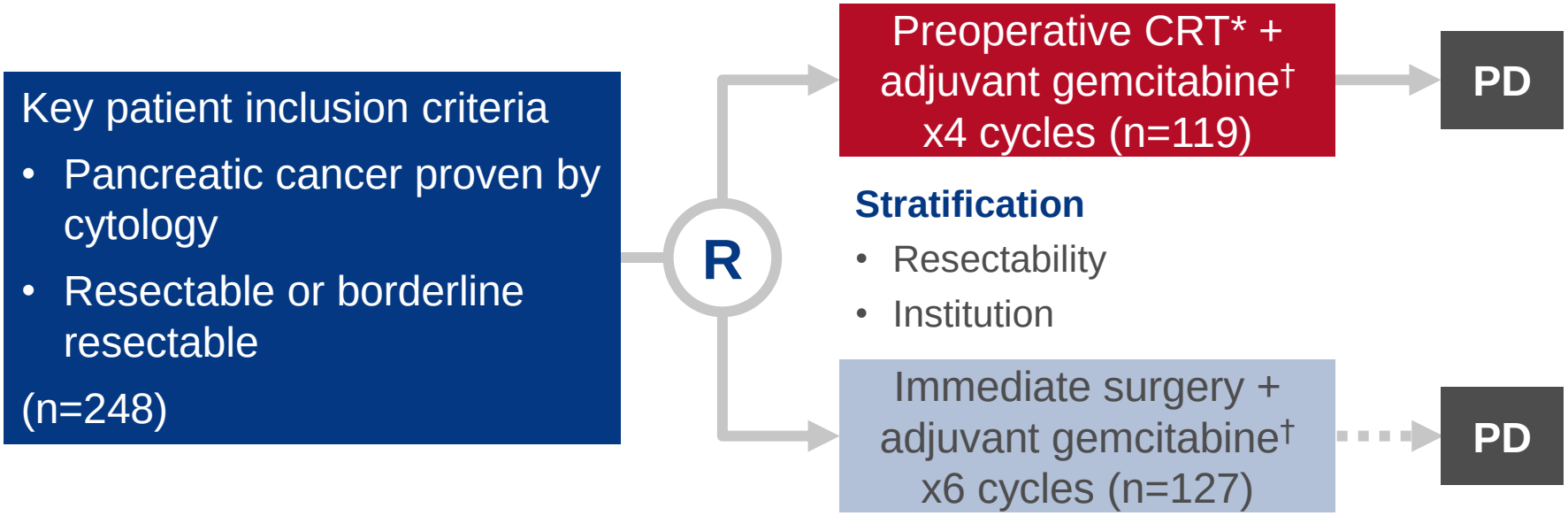
Permission to include data from PRODIGE 24 not granted

Conroy T, et al. J Clin Oncol 2018;36(suppl):abstr LBA4001

LBA4002: Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1) : A randomized, controlled, multicenter phase III trial – Van Tienhoven G, et al

Study objective

- To compare the efficacy and safety of preoperative CRT vs. immediate surgery, both followed by adjuvant CT, in patients with resectable pancreatic cancer



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- R0 resection rate, DFS, distant metastases locoregional recurrence, safety

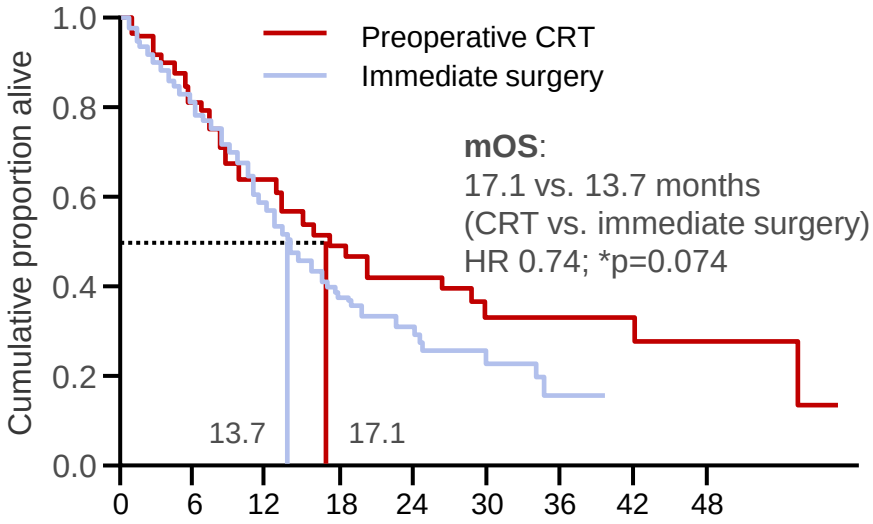
*15 fractions 2.4 Gy + gemcitabine 1000 mg/m^2 d1,8,15, preceded and followed by gemcitabine 1000 mg/m^2 d1,8 + 1 wk rest; †gemcitabine 1000 mg/m^2 d1,8,15 + 1 wk rest

Van Tienhoven, et al. J Clin Oncol 2018;36(suppl):abstr LBA4002

LBA4002: Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1) : A randomized, controlled, multicenter phase III trial – Van Tienhoven G, et al

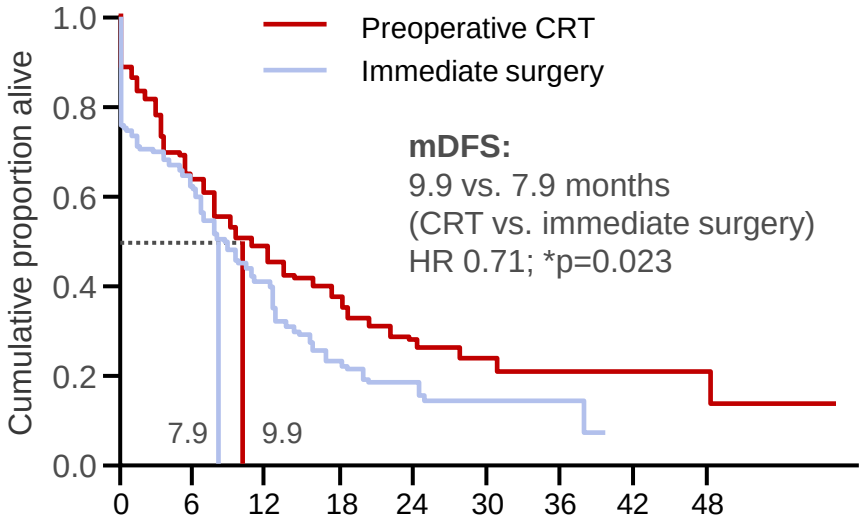
Key results

OS



No. at risk									
Immediate surgery	127	103	61	35	22	9	4	1	1
Preoperative CRT	119	98	66	43	23	11	8	7	5

DFS



No. at risk									
Immediate surgery	127	77	44	24	17	7	4	1	1
Preoperative CRT	119	76	53	35	19	9	7	6	5

- Preliminary results: 149/176 events

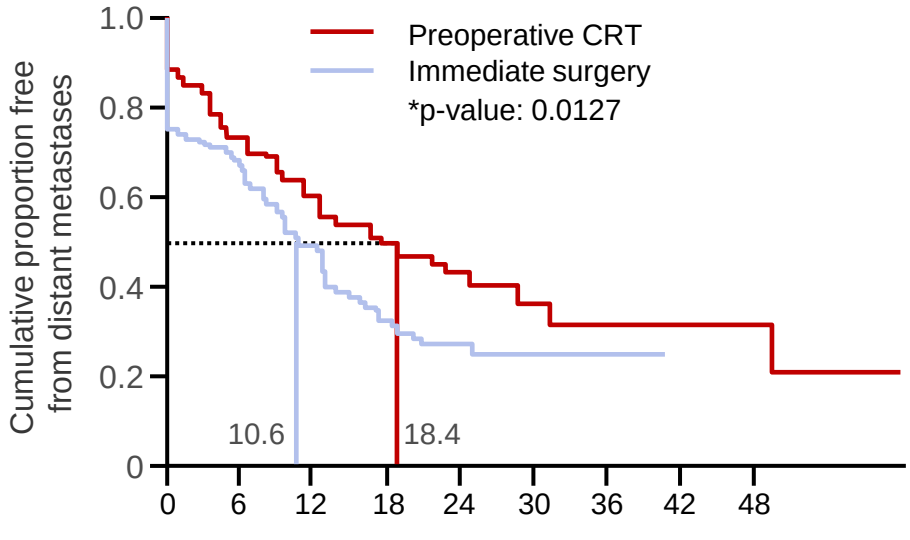
*Stratified log-rank test

Van Tienhoven, et al. J Clin Oncol 2018;36(suppl):abstr LBA4002

LBA4002: Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1) : A randomized, controlled, multicenter phase III trial – Van Tienhoven G, et al

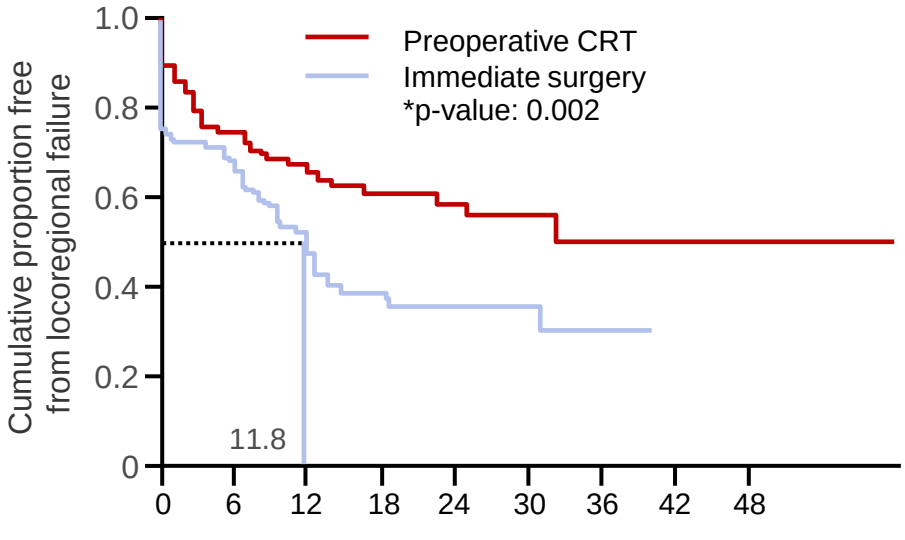
Key results (cont.)

Distant metastases-free interval



No. at risk									
Immediate surgery	127	77	44	24	17	7	4	1	1
Preoperative CRT	119	76	53	35	19	9	7	6	5

Locoregional recurrence free interval



No. at risk									
Immediate surgery	127	78	41	26	18	8	3	1	1
Preoperative CRT	119	78	57	40	23	11	7	6	4

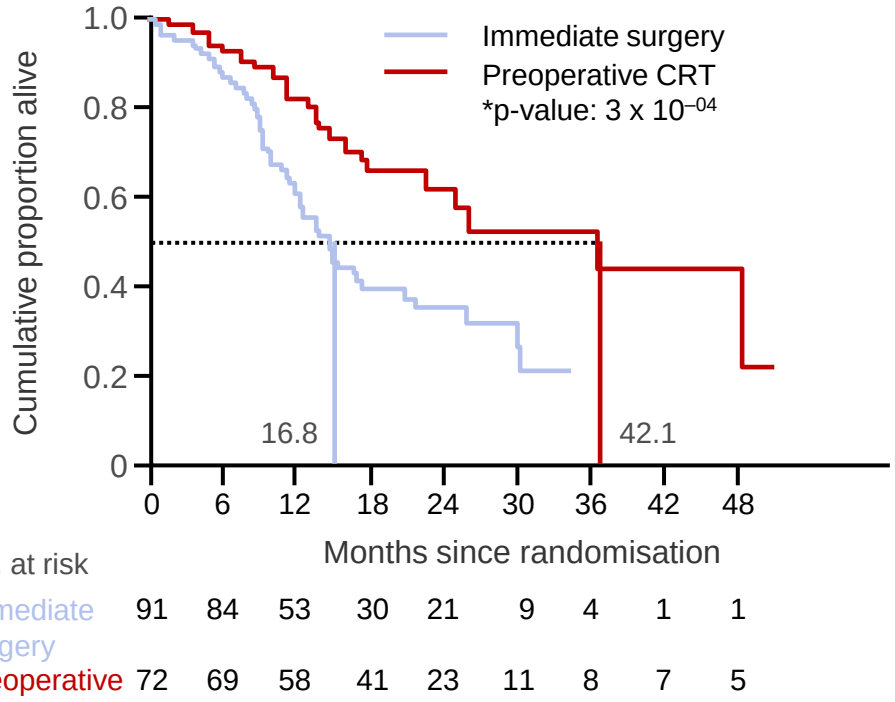
*Stratified log-rank test

Van Tienhoven, et al. J Clin Oncol 2018;36(suppl):abstr LBA4002

LBA4002: Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1) : A randomized, controlled, multicenter phase III trial – Van Tienhoven G, et al

Key results (cont.)

Patients after R0/R1 resection



	Preoperative CRT (n=119)	Immediate surgery (n=127)	p-value
Resection rate, n/N (%)	72/119 (60)	91/127 (72)	0.065
R0 resection rate, n/N (%)	45/72 (63)	28/91 (31)	<0.001
SAEs, n (%)	55 (46)	49 (39)	0.28

Conclusions

- **Neoadjuvant CRT may be beneficial vs. immediate surgery in patients with resectable pancreatic cancer**
- **Results are preliminary (149/176 events)**

Van Tienhoven, et al. J Clin Oncol 2018;36(suppl):abstr LBA4002

Moving Beyond Gemcitabine Therapy in Pancreatic and Biliary Cancers? Discussant – Shroff RT

Study objective (JCOG1113: Abstract 4014 – Ueno M, et al)

- **To compare the efficacy and safety of gemcitabine + S-1 vs. gemcitabine + cisplatin in patients with advanced biliary tract cancer**

Study design

- Patients (n=354) were randomised (1:1) to receive gemcitabine* + cisplatin† vs. gemcitabine* + S-1‡

Key results

	Gemcitabine + cisplatin (n=175)	Gemcitabine + S-1 (n=179)	HR	p-value
Median OS, months (95%CI)	13.4 (12.4, 15.5)	15.1 (12.2, 16.4)	0.945 (90%CI 0.777, 1.149)	0.0459
Median PFS, months	5.8	6.8	0.86 (95%CI 0.70, 1.07)	-

- Clinically significant AEs were observed in 35.1 vs. 29.9% of patients in gemcitabine + cisplatin vs. gemcitabine + S-1, respectively

*1000 mg/m^2 on d1,8; †25 mg/m^2 on d1,8 q3w;
‡60, 80, and 100 mg/body/day on d1–14 q3w

Ueno M, et al. J Clin Oncol 2018;36(suppl):abstr 4014
Bahary N, et al. J Clin Oncol 2018;36(suppl):abstr 4015
Picozzi VJ, et al. J Clin Oncol 2018;36(suppl):abstr 4016

Moving Beyond Gemcitabine Therapy in Pancreatic and Biliary Cancers? Discussant – Shroff RT

Study objective (Abstract 4015 – Bahary N, et al)

- **To evaluate the efficacy and safety of 1L indoximod + gemcitabine and nab-paclitaxel in treatment-naïve patients with metastatic pancreatic cancer**

Study design

- Patients (n=181) received indoximod* + gemcitabine† and nab-paclitaxel‡

Key results

	Efficacy evaluable population (n=77)	Efficacy evaluable + biopsy cohort (n=104)
Median OS, months (95%CI)	11.4 (9.4, 14.0)	10.9 (8.9, 13.7)
Median PFS, months (95%CI)	6.0 (5.1, 7.4)	5.8 (4.1, 7.3)
ORR, n (%)	33 (43)	48 (46)

- A statistically significant higher CD8:FOXp3 T-cell ratio was observed following treatment

*1200 mg orally twice daily continuously; †1000 mg/m^2 iv; ‡125 mg/m^2 iv on d1,8, 15 of a 4-week cycle

Ueno M, et al. J Clin Oncol 2018;36(suppl):abstr 4014
Bahary N, et al. J Clin Oncol 2018;36(suppl):abstr 4015
Picozzi VJ, et al. J Clin Oncol 2018;36(suppl):abstr 4016

Moving Beyond Gemcitabine Therapy in Pancreatic and Biliary Cancers? Discussant – Shroff RT

Study objective (Abstract 4016 – Picozzi VJ, et al)

- **To assess the efficacy and safety of 1L gemcitabine/nab-paclitaxel with or without pamrevlumab (an anti-CTGF human recombinant mAb) in patients with locally advanced, unresectable pancreatic cancer**

Study design

- Patients (n=37) were randomised (2:1) to receive six cycles (28 days/cycle) of gemcitabine/nab-paclitaxel + pamrevlumab (n=24) vs. gemcitabine/nab-paclitaxel (n=13)

Key results

- Resection or borderline resection was achieved in 20.8% and 7.7% of the gemcitabine/nab-paclitaxel + pamrevlumab vs. gemcitabine/nab-paclitaxel arms, respectively
- OS in eligible vs. non-eligible patients was 27.7 (95%CI 15.01, NE) vs. 18.4 (10.68, 20.21) months (p=0.0766)
- OS in resected vs. non-resected patients was NE (95%CI 15.01, NE) vs. 18.8 (13.27, 20.21) months (p=0.0141)

Ueno M, et al. J Clin Oncol 2018;36(suppl):abstr 4014
Bahary N, et al. J Clin Oncol 2018;36(suppl):abstr 4015
Picozzi VJ, et al. J Clin Oncol 2018;36(suppl):abstr 4016

Moving Beyond Gemcitabine Therapy in Pancreatic and Biliary Cancers? Discussant – Shroff RT

Presenter's take-home messages

- **Ueno et al. is the first phase 3 study in this patient population since ABC-02 and found that gemcitabine/S-1 was non-inferior to gemcitabine/cisplatin, with good tolerability and ease of administration**
- **Bahary et al. found that the addition of indoximod to gemcitabine/nab-paclitaxel did not significantly improve median OS, but there was some ORR activity – what are the next steps for indoleamine 2,3-dioxygenase inhibitors?**
- **Picozzi et al. found that the addition of pamrevlumab to gemcitabine/nab-paclitaxel may improve the potential for surgical exploration in locally advanced pancreatic cancer, but studies with a larger population size are required to confirm this**

Ueno M, et al. J Clin Oncol 2018;36(suppl):abstr 4014
Bahary N, et al. J Clin Oncol 2018;36(suppl):abstr 4015
Picozzi VJ, et al. J Clin Oncol 2018;36(suppl):abstr 4016

Cancers of the pancreas, small bowel and hepatobiliary tract

HEPATOCELLULAR CARCINOMA

4003: REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib – Zhu AX, et al

Study objective

- To assess the benefit of ramucirumab in patients with HCC and baseline AFP ≥400 ng/mL in the REACH-2 study

Key patient inclusion criteria

- HCC with BCLC stage C or B, refractory or unamenable to locoregional therapy
- Prior sorafenib
- Child-Pugh A
- Baseline AFP ≥400 ng/mL
- ECOG PS 0–1

(n=292)

R 2:1

Ramucirumab 8 mg/kg iv q2w + BSC (n=197) → PD/ toxicity

Placebo + BSC (n=95) → PD/ toxicity

Stratification

- Macrovascular invasion (yes vs. no)
- ECOG PS (0 vs. 1)
- Geographic region (Americas, Europe, Australia vs. Asia [except Japan] vs. Japan)

PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, TTP, ORR, safety

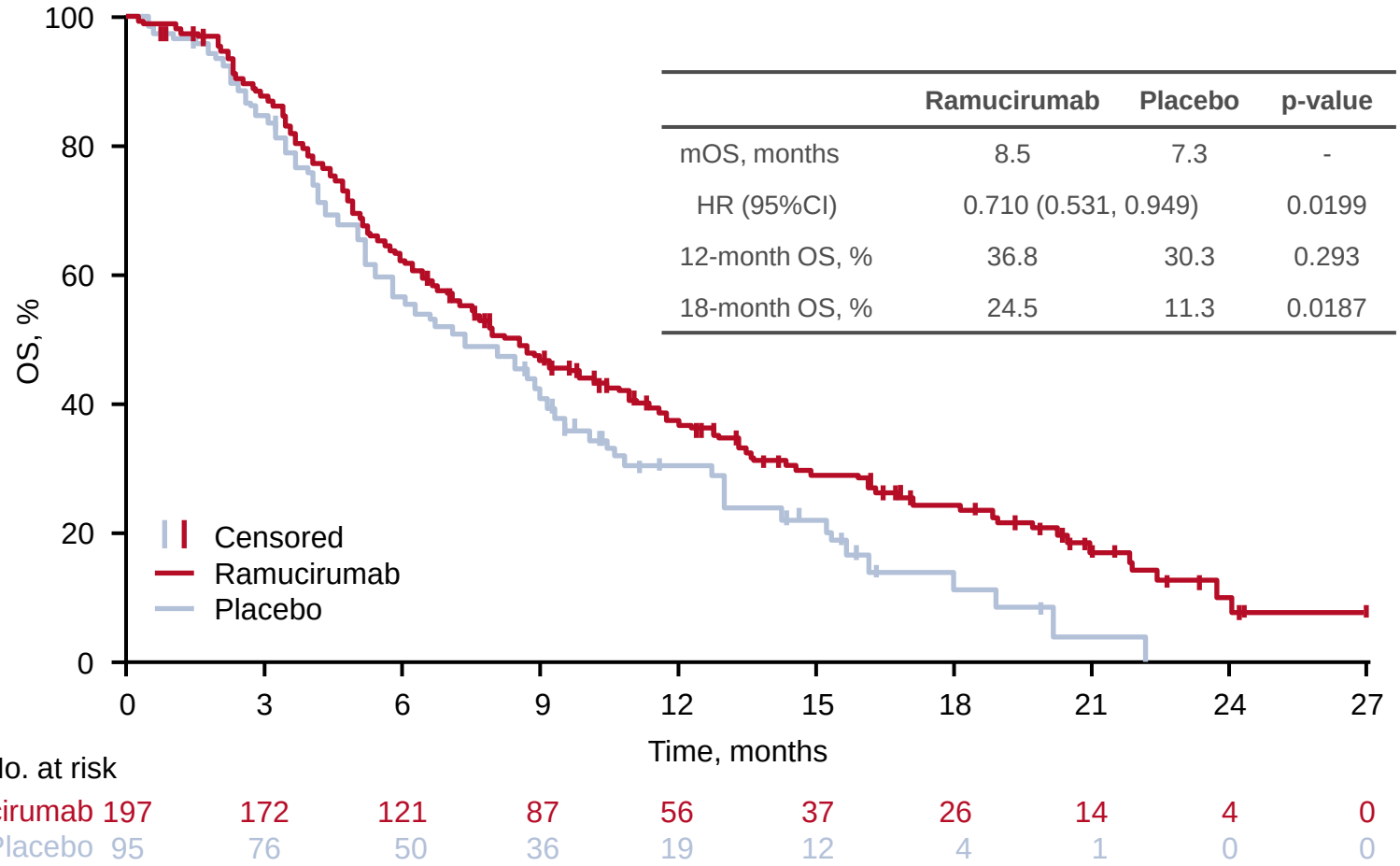
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4003

4003: REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib – Zhu AX, et al

Key results

OS

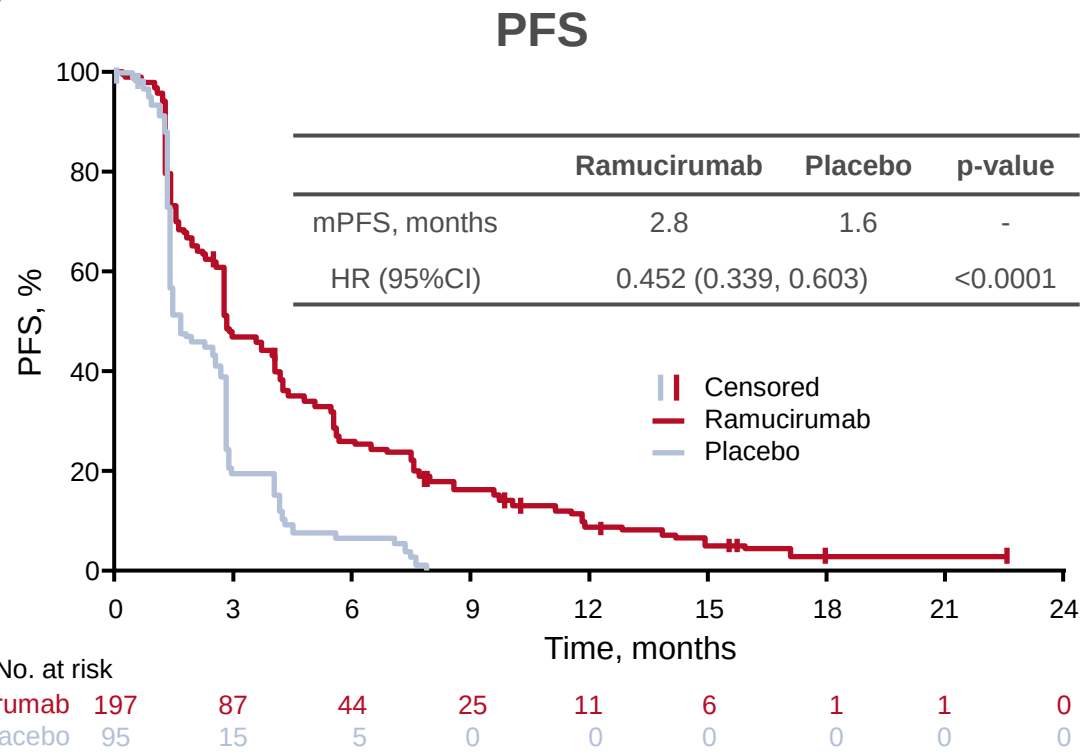
	Ramucirumab	Placebo	p-value
mOS, months	8.5	7.3	-
HR (95%CI)	0.710 (0.531, 0.949)		0.0199
12-month OS, %	36.8	30.3	0.293
18-month OS, %	24.5	11.3	0.0187



Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4003

4003: REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib – Zhu AX, et al

Key results (cont.)



	Ramucirumab	Placebo	p-value
mPFS, months	2.8	1.6	-
HR (95%CI)	0.452 (0.339, 0.603)		<0.0001

	Ramucirumab (n=197)	Placebo (n=95)	p-value
ORR, n (%) [95%CI]	9 (4.6) [1.7, 7.5]	1 (1.1) [0.0, 3.1]	0.1697
DCR	118 (59.9) [53.1, 66.7]	37 (38.9) [29.1, 48.8]	0.0006

Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4003

4003: REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib – Zhu AX, et al

Key results (cont.)

TRAE, n (%)	Ramucirumab (n=197)	Placebo (n=95)
Discontinuation due to TRAE	21 (10.7)	3 (3.2)
Dose adjustment due to AE	68 (34.5)	13 (13.7)
Deaths due to TRAE	3 (1.5)	0
≥1 TRAE in ≥15% patients in ramucirumab arm		
Any grade	191 (97.0)	82 (86.3)
Grade ≥3	116 (58.9)	42 (44.2)

Conclusions

- **Ramucirumab demonstrated significant survival benefit vs. placebo in patients with HCC and baseline AFP ≥400 ng/mL following PD or intolerance to sorafenib**
  - **Clinically meaningful benefits were also seen in PFS and DCR**
- **Ramucirumab was well tolerated with a safety profile consistent with ramucirumab monotherapy**
- **REACH-2 is the first positive study demonstrating significant and meaningful OS benefit in patients with HCC and AFP ≥400 ng/mL; a population associated with poor prognosis**

Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4003

Expanding the Treatment Landscape in Hepatocellular Carcinoma Discussant – Berlin J

Study objective (TACTICS: Abstract 4017 – Kudo M, et al)

- **To compare the efficacy and safety of sorafenib with or without TACE in patients with HCC**

Study design

- Patients (n=156) were randomised (1:1) to receive sorafenib 400 mg/day with TACE (n=80) or TACE alone (n=76)

Key results

	Sorafenib + TACE (n=80)	TACE (n=76)	HR (95%CI)	p-value
Median PFS, months	25.2	13.5	0.59 (0.41, 0.87)	0.006

- The maturity of OS results was 73.6%

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

Expanding the Treatment Landscape in Hepatocellular Carcinoma Discussant – Berlin J

Study objective (Global OPTIMIS: Abstract 4018 – Peck-Radosavljevic M, et al)

- **To assess the outcomes of TACE in patients with HCC**

Study design

- In this observational study, patients (n=507) who were eligible for TACE at baseline, eventually progressed to TACE ineligibility after ≥1 TACE and received/did not receive sorafenib upon ineligibility
- A 1:2 propensity score match on patient numbers was performed

Key results

- Unmatched, the OS was 19.8 vs. 16.2 months in those who did not receive sorafenib upon TACE ineligibility vs. those who did, respectively
- After propensity score matching, OS was 16.2 vs.12.1 months in those who received sorafenib upon TACE ineligibility vs. those who did not, respectively
- 11% and 29% of patients had deterioration in bilirubin and albumin, respectively

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

Expanding the Treatment Landscape in Hepatocellular Carcinoma Discussant – Berlin J

Study objective (CELESTIAL: Abstract 4019 – Abou-Alfa GK, et al)

- **To compare the efficacy and safety of cabozantinib vs. placebo in patients with advanced HCC who had received prior sorafenib**

Study design

- Patients (n=760) were randomised (2:1) to receive cabozantinib 60 mg/day po or placebo

Key results

	Cabozantinib (n=470)	Placebo (n=237)	HR (95%CI)	p-value
Median OS, months (95%CI)	10.2 (9.1, 12.0)	8.0 (6.8, 9.4)	0.76 (0.63, 0.92)	0.0049
Median PFS, months (95%CI)	5.2 (4.0, 5.5)	1.9 (1.9, 1.9)	0.44 (0.36, 0.52)	<0.0001
ORR, %	4	0.4	-	0.0086

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

Expanding the Treatment Landscape in Hepatocellular Carcinoma
Discussant – Berlin J

Study objective (KEYNOTE-224: Abstract 4020 – Zhu AX, et al)

- **To assess the efficacy and safety of pembrolizumab in patients with advanced HCC**

Study design

- Patients (n=104) received pembrolizumab 200 mg q3w for 2 years or until PD, intolerable toxicity, withdrawal of consent or investigator decision

Key results

	Pembrolizumab (n=104)
Median OS, months (95%CI)	12.9 (9.7, 15.5)
Median PFS, months (95%CI)	4.9 (3.4, 7.2)
ORR, n (%)	18/104 (17)

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

Expanding the Treatment Landscape in Hepatocellular Carcinoma – Berlin J

Presenter's take-home messages

- **TACE may be overused. The unmatched vs. matched results in Peck-Radosavljevic et al. indicate that those patients who require sorafenib can be easily identified**
- **Cabozantinib may be a new option for 2L treatment of HCC**
  - **Other options include nivolumab and regorafenib**
- **After TACE tumour control may be improved by sorafenib, but there does not seem to be any impact on OS**

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

Cancers of the pancreas, small bowel and hepatobiliary tract

NEUROENDOCRINE TUMOUR

4004: A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al

Study objective

- To assess the efficacy and safety of temozolomide alone or combined with capecitabine in patients with advanced pancreatic neuroendocrine tumours (pNETs)

Key patient inclusion criteria

- Metastatic or unresectable pNETs
- PD within previous 12 months
- No prior temozolomide, capecitabine, dacarbazine or 5FU
- WHO PS 1–2

(n=144)

R 1:1

Temozolomide 200 mg/m^2/day d10–14 + capecitabine 750 mg/m^2 bid d1–14 (n=72) → PD/ toxicity

Stratification

- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

Temozolomide 200 mg/m^2/day d1–5 (n=72) → PD/ toxicity

PRIMARY ENDPOINT

- PFS – local review

SECONDARY ENDPOINTS

- ORR, OS, safety

Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

4004: A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al

Key results

Baseline characteristics	Temozolomide + capecitabine (n=72)	Temozolomide alone (n=72)
Gender, female, %	45.8	43.1
Median age, years	62.5	59.5
Time from diagnosis, months	34.0	24.4
WHO grade*		
Grade 1	**68.1**	**45.1**
Grade 2	**31.9**	**54.9**
Sites of metastasis		
Liver	93.1	93.1
Bone	11.1	12.5
Lung	13.9	6.9
Peritoneum	9.7	5.6
Prior treatment		
Everolimus	36.1	34.7
Sunitinib	11.1	12.5
Concurrent octreotide	52.8	54.2

*Imbalance, p=0.013

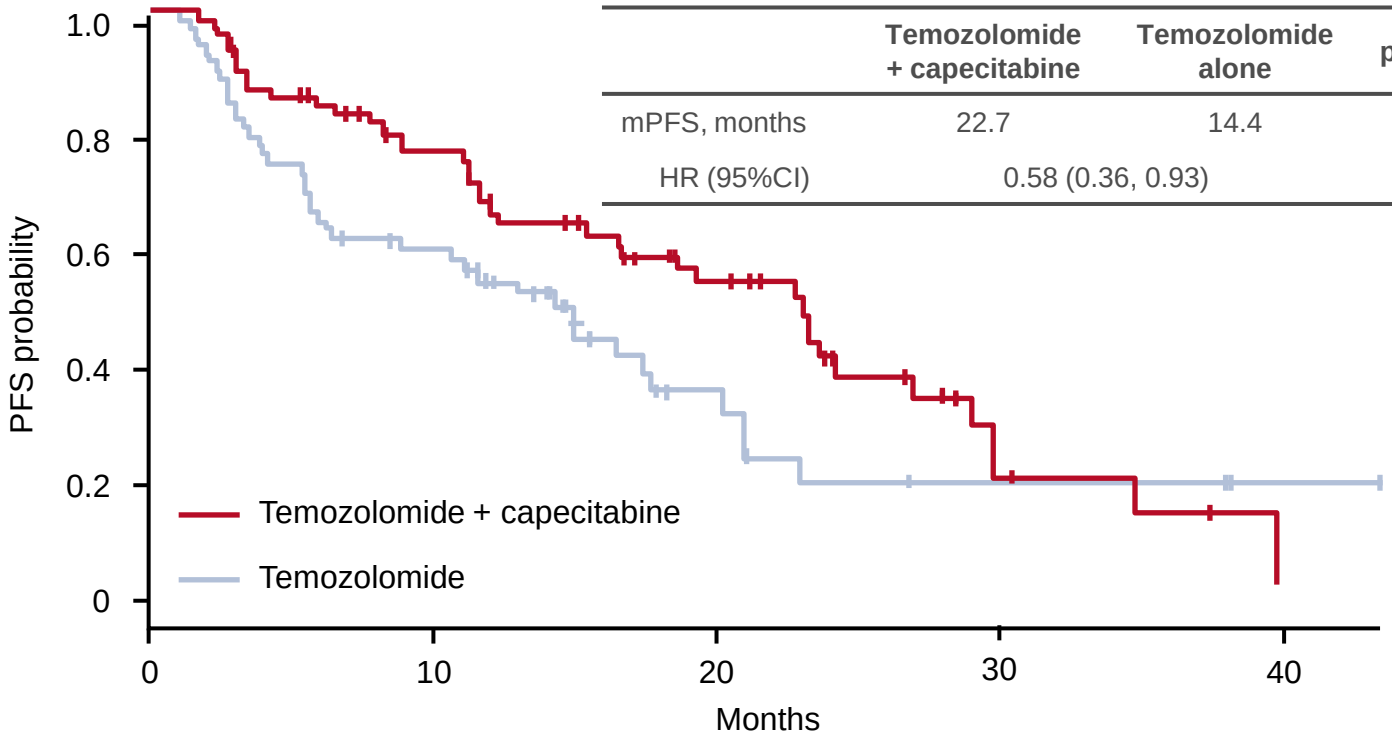
Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

4004: A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al

Key results (cont.)

PFS

	Temozolomide + capecitabine	Temozolomide alone	p-value
mPFS, months	22.7	14.4	-
HR (95%CI)	0.58 (0.36, 0.93)		0.023



	Temozolomide + capecitabine	Temozolomide alone	HR (95%CI); p-value
mOS, months	Not reached	38.0	0.41 (0.21, 0.82); 0.012

Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

4004: A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al

Key results (cont.)

	Temozolomide + capecitabine	Temozolomide alone
ORR, %	33.3	27.8
p-value	0.47	
DCR, %	81.9	68.1
Median response duration, months	12.1	9.7

%	Temozolomide + capecitabine	Temozolomide	p-value
Worst degree* for all TRAEs grade 3–4	44	22	0.007

Conclusions

- **Temozolomide + capecitabine demonstrated improved PFS vs. temozolomide alone in patients with advanced pNETs**
- **The ORR was high compared with most approved therapies, but there was no significant difference between the treatment arms**
- **AEs were as expected with rates doubled in the combination arm**
- **This is the first prospective RCT with these agents and shows the longest PFS reported for pNET-directed therapy**

*Highest grade patients achieved across all toxicities reported

Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

CANCERS OF THE COLON, RECTUM AND ANUS

3001: Anti-CD27 agonist antibody varlilumab (varli) with nivolumab (nivo) for colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results – Sanborn RE, et al

Study objective

- To assess the efficacy and safety of combination treatment with varlilumab (an anti-CD27 antibody) + nivolumab in patients with CRC or ovarian cancer

Key patient inclusion criteria

- Progressive, recurrent or refractory CRC or ovarian cancer
- No prior anti-PD-L1 therapy
- ≥3 months washout for T-cell direct mAbs
- ≤5 prior regimens for advanced disease

Phase 1

Nivolumab 3 mg/kg q2w + varlilumab escalating doses* q2w
Ovarian cancer: n=8
CRC: n=21
(n=29)

Phase 2

Nivolumab 240 mg q2w + varlilumab†
Ovarian cancer: n=58
CRC: n=21
(n=79)

PRIMARY ENDPOINT

- ORR

SECONDARY ENDPOINTS

- PFS, OS, immunogeneity, safety

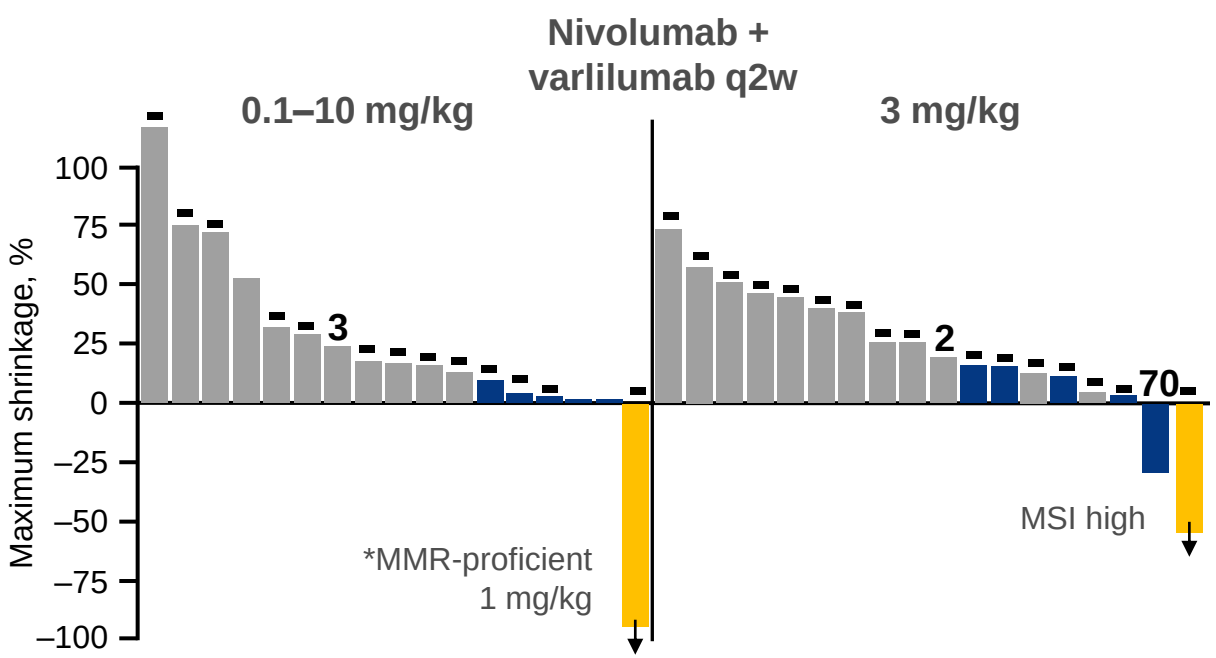
*0.1 mg/kg (n=6), 1 mg/kg (n=15), 10 mg/kg (n=15);
†CRC: 3 mg/kg q2w (n=18), ovarian (n=54): 3 mg/kg q2w (n=18), 3 mg/kg q12w (n=18), 0.3 mg/kg q4w (n=18)

Sanborn RE, et al. J Clin Oncol 2018;36(suppl):abstr 3001

3001: Anti-CD27 agonist antibody varlilumab (varli) with nivolumab (nivo) for colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results – Sanborn RE, et al

Key results

CRC tumour response



*Patient with CRC initially considered MMR-proficient

- Near CR (95% tumour shrinkage), continues at 35 months
- Molecular analysis suggests high mutational burden likely contributed to response

	Phase 1	Phase 2
ORR, n/N (%):	1/21 (5)	1/20 (5)
DCR, n/N (%):	4/21 (19)	4/20 (20)

Sanborn RE, et al. J Clin Oncol 2018;36(suppl):abstr 3001

3001: Anti-CD27 agonist antibody varlilumab (varli) with nivolumab (nivo) for colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results – Sanborn RE, et al

Key results (cont.)

TRAEs in CRC (n=42), n (%)	Grade 3–4	Grade 5
Rash maculo-papular	1 (2)	0
Lymphopenia	5 (12)	0
ALT increased	1 (2)	0
Lipase increased	1 (2)	0
Pneumonitis	0	1 (2)

- No evidence of additional toxicity for combination therapy
- Toxicity profile similar across varlilumab dosing regimens

Conclusions

- **Most tumours were PD-L1 negative or low and low TIL***
  - **Therefore, low expectation of response to checkpoint inhibition monotherapy**
- **Varlilumab 3 mg/kg appeared to have better clinical activity vs. other doses***
- **In patients with CRC, durable clinical responses were seen in a patient with MSI-high tumour and one with a high mutational burden**
- **Varlilumab + nivolumab was generally well tolerated at all doses of varlilumab**

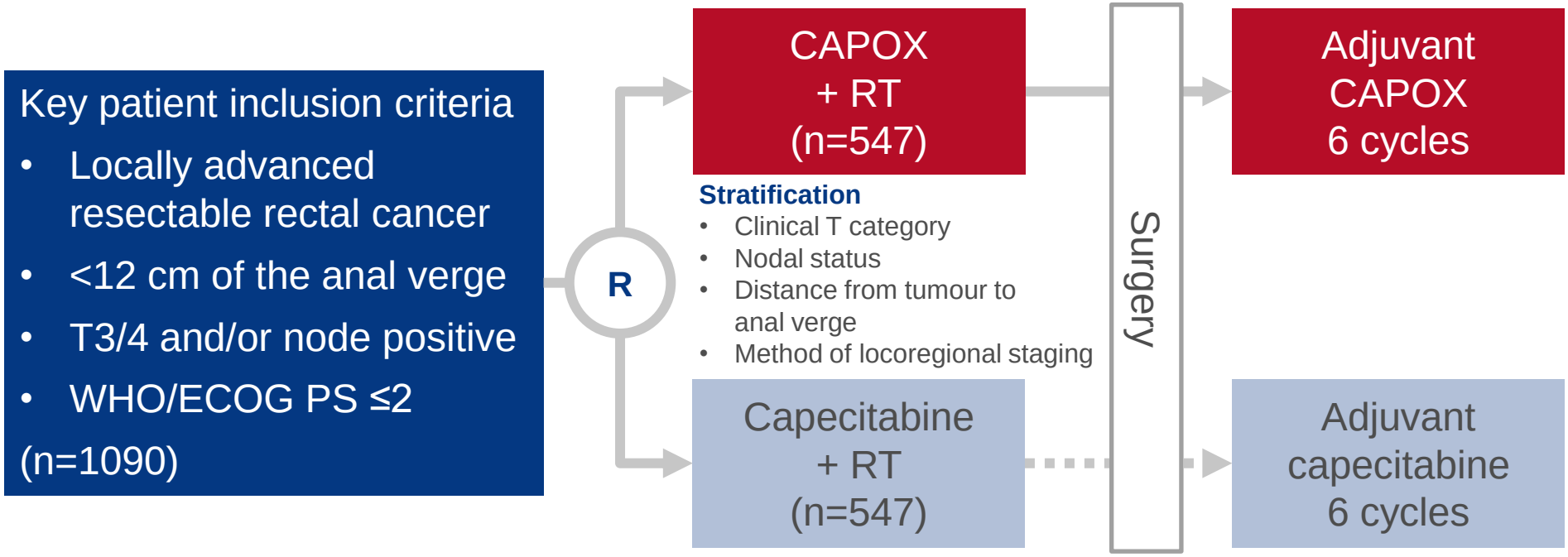
*Data not shown

Sanborn RE, et al. J Clin Oncol 2018;36(suppl):abstr 3001

3500: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: Final results of PETACC-6 – Schmoll HJ, et al

Study objective

- To assess the efficacy and safety of oxaliplatin combined with preoperative capecitabine-based CRT and postoperative capecitabine in patients with locally advanced rectal cancer



PRIMARY ENDPOINT

- 3-year DFS*

SECONDARY ENDPOINTS

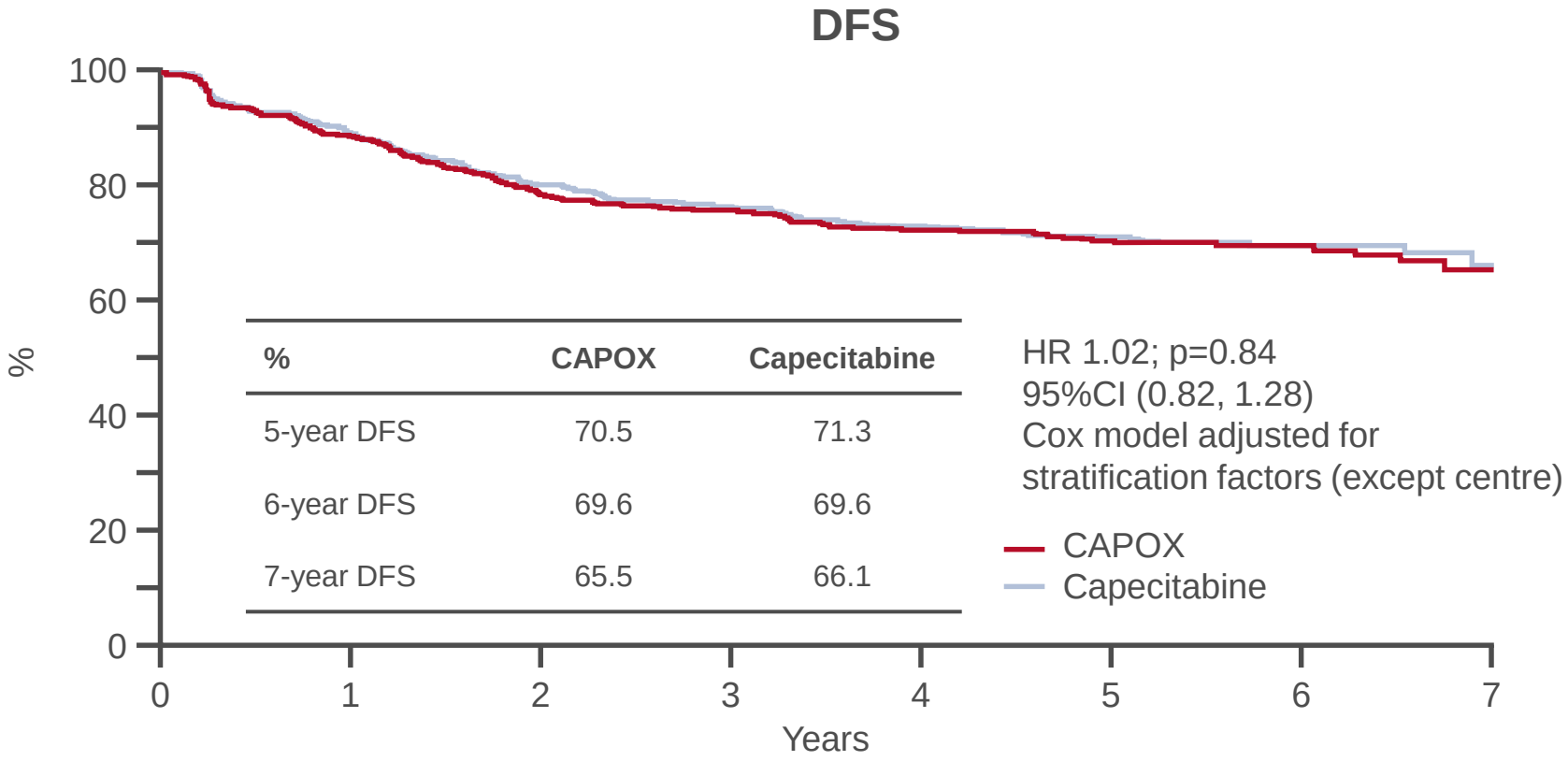
- Long-term DFS, OS, RFS, locoregional distant failure

*Reported at ASCO 2014

Schmoll H-J, et al. J Clin Oncol 2018;36(suppl):abstr 3500

3500: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: Final results of PETACC-6 – Schmoll HJ, et al

Key results



%	CAPOX	Capecitabine
5-year DFS	70.5	71.3
6-year DFS	69.6	69.6
7-year DFS	65.5	66.1

	O	N	No. at risk					
CAPOX	157	547	472	404	379	347	291	115
Capecitabine	156	547	452	388	367	324	267	111

Schmoll H-J, et al. J Clin Oncol 2018;36(suppl):abstr 3500

3500: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: Final results of PETACC-6 – Schmoll HJ, et al

Key results (cont.)

	CAPOX	Capecitabine	p-value
Locoregional relapse, %	6.0	8.7	0.238
Distant relapse, %	19.2	21.4	0.261
DFS, HR (95%CI)			
Stage II (21 of patients)		0.95 (0.59, 1.51)	0.82
Stage III (72 of patients)		1.04 (0.79, 1.36)	0.78
5-year OS, %	80.1	83.1	-
6-year OS, %	77.7	81.2	-
7-year OS, %	73.7	73.5	-
mOS, HR (95%CI)		1.17 (0.89, 1.54)	0.252
OS, HR (95%CI)			
Stage II		0.95 (0.55, 1.63)	0.84
Stage III		1.21 (0.86, 1.69)	0.27
5-year RFS, %	78.1	77.3	0.94

Schmoll H-J, et al. J Clin Oncol 2018;36(suppl):abstr 3500

3500: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: Final results of PETACC-6 – Schmoll HJ, et al

Key results (cont.)

5-year DFS by country	CAPOX, %	Capecitabine, %	HR	p-value
Germany	67.8	73.4	1.27	0.091
Not Germany	75.7	67	0.65	0.033

Conclusions

- **There was no benefit in adding oxaliplatin to CRT and adjuvant CT in patients with locally advanced rectal cancer**
- **The 7-year OS with neoadjuvant capecitabine-based CRT, surgery and adjuvant capecitabine was favourable compared with previous trials**
- **However, there was a striking and currently unexplained difference in DFS and OS* for Germany vs. non-German countries**
  - **This difference by country requires further investigation**

*OS data by country not shown

Schmoll H-J, et al. J Clin Oncol 2018;36(suppl):abstr 3500

3501: Long-term results of the ADORE trial: Adjuvant oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) versus 5-fluorouracil and leucovorin (FL) after preoperative chemoradiotherapy and surgery for locally advanced rectal cancer – Hong YS, et al

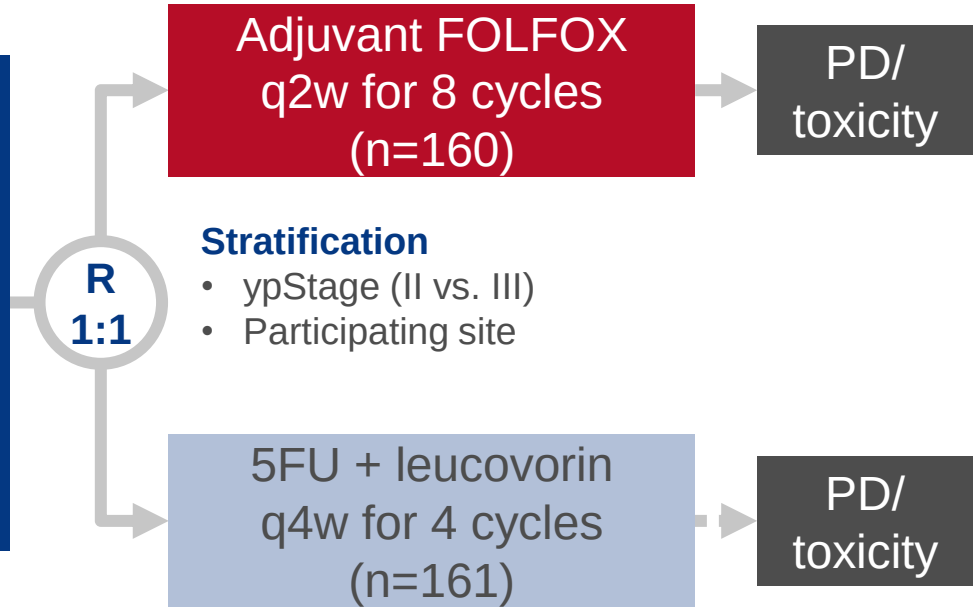
Study objective

- To assess the long-term efficacy of adjuvant FOLFOX vs. 5FU + leucovorin in patients with resected rectal cancer in the ADORE study

Key patient inclusion criteria

- Curatively resected rectal cancer
- TME
- Postoperative ypStage II/III after preoperative CRT with fluoropyrimidines alone

(n=321)



PRIMARY ENDPOINT

- DFS*

SECONDARY ENDPOINTS

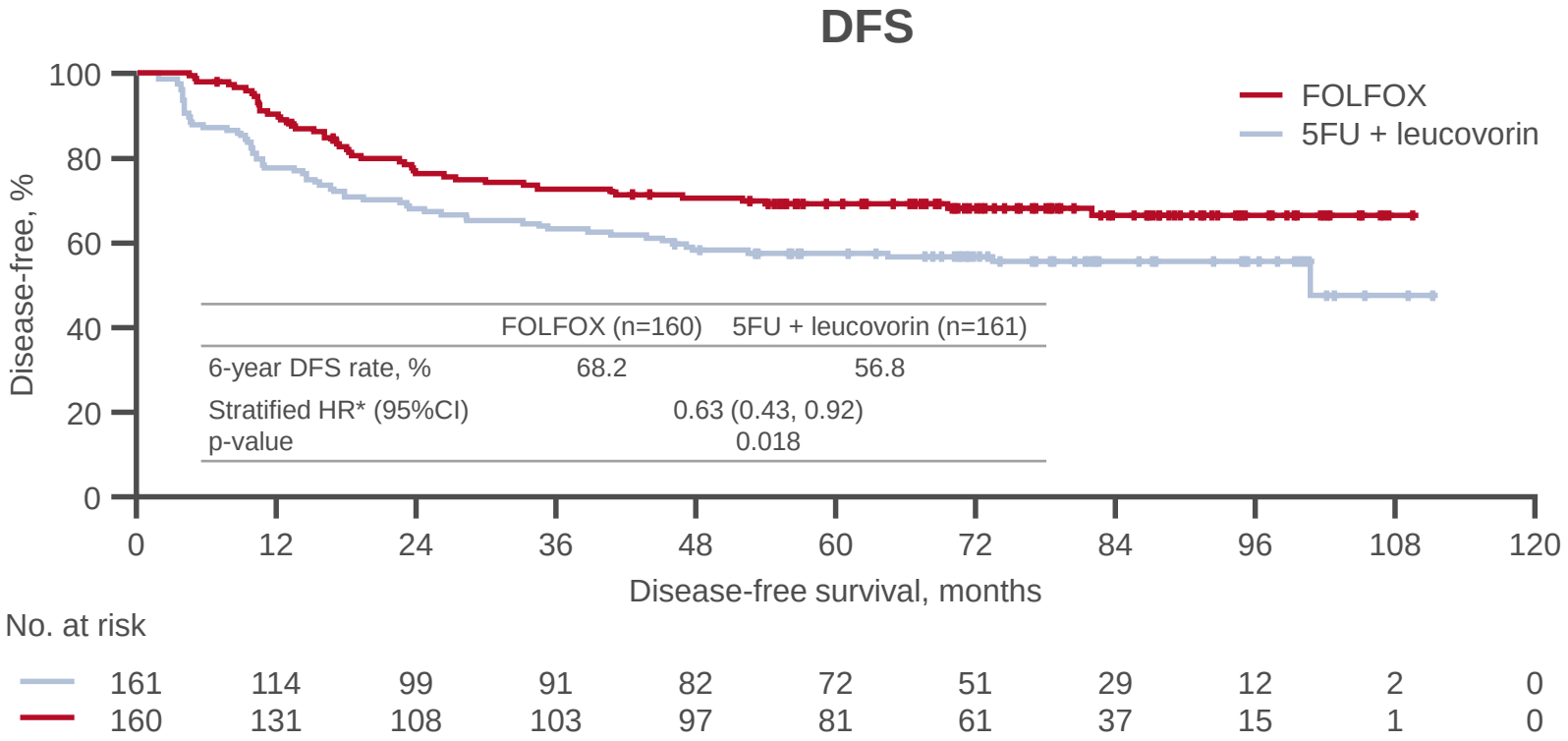
- OS, safety*, patterns of failure, QoL*

*3-year DFS, AEs and QoL reported at ASCO 2014

Hong YS, et al. J Clin Oncol 2018;36(suppl):abstr 3501

3501: Long-term results of the ADORE trial: Adjuvant oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) versus 5-fluorouracil and leucovorin (FL) after preoperative chemoradiotherapy and surgery for locally advanced rectal cancer – Hong YS, et al

Key results



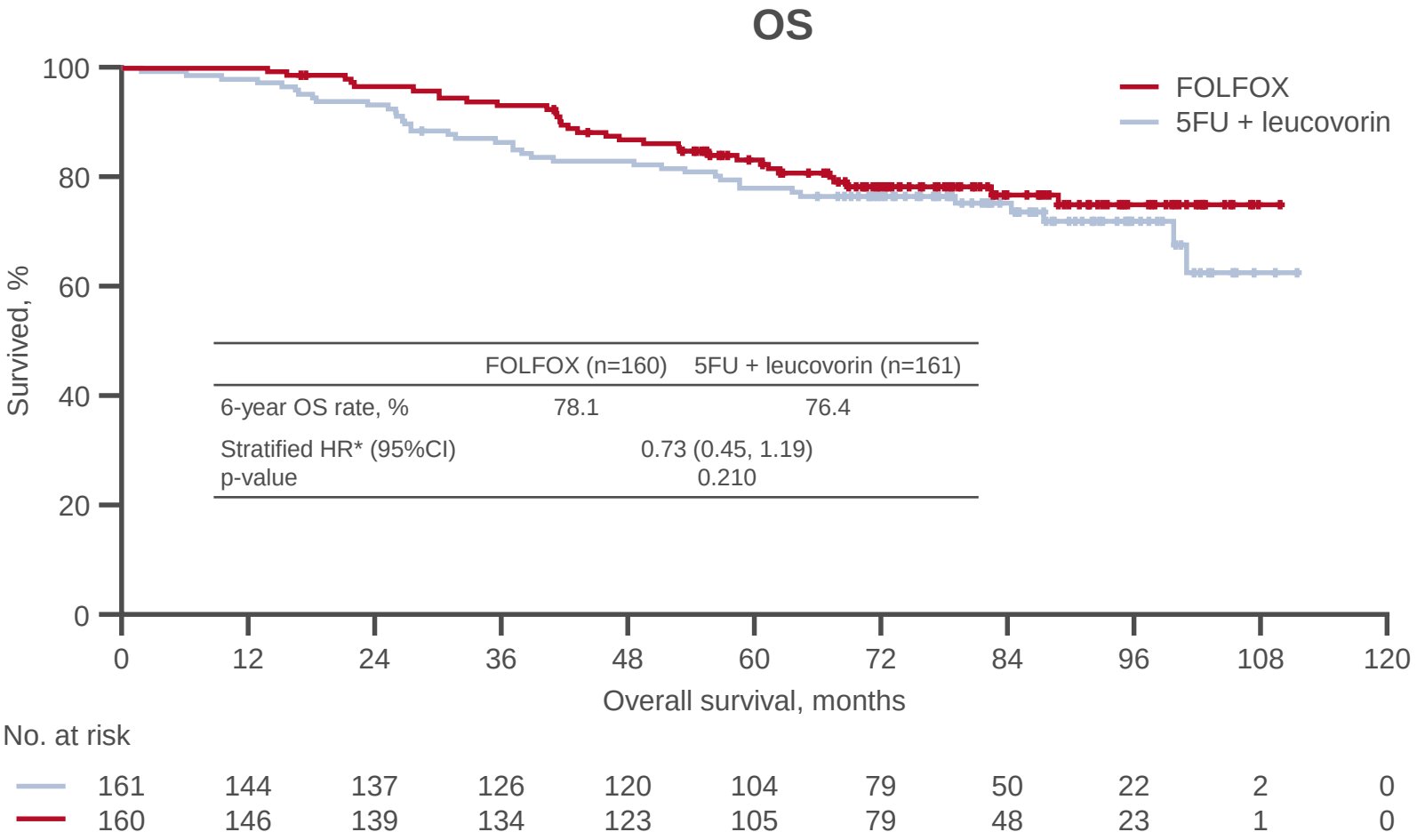
6-year DFS, %	FOLFOX	5FU + leucovorin	Difference	HR* (95%CI); p-value
ypStage III	63.2	48.3	14.9	0.59 (0.38, 0.92); 0.019
ypStage II	77.8	69.5	8.3	0.64 (0.30, 1.36); 0.245

*Stratified by ypStage and participating site

Hong YS, et al. J Clin Oncol 2018;36(suppl):abstr 3501

3501: Long-term results of the ADORE trial: Adjuvant oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) versus 5-fluorouracil and leucovorin (FL) after preoperative chemoradiotherapy and surgery for locally advanced rectal cancer – Hong YS, et al

Key results (cont.)



*Stratified by ypStage and participating site

Hong YS, et al. J Clin Oncol 2018;36(suppl):abstr 3501

3501: Long-term results of the ADORE trial: Adjuvant oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) versus 5-fluorouracil and leucovorin (FL) after preoperative chemoradiotherapy and surgery for locally advanced rectal cancer – Hong YS, et al

Key results (cont.)

Haematological AEs, grade 3–4, n (%)	FOLFOX (n=146)	5FU + leucovorin (n=149)	p-value
Leukopenia	12 (8.2)	8 (5.4)	0.363
Neutropenia	52 (35.6)	38 (25.5)	0.076
Febrile neutropenia	1 (0.7)	4 (2.7)	0.371
Thrombocytopenia	1 (0.7)	0	0.495
Anaemia	0	1 (0.7)	1.000

Conclusions

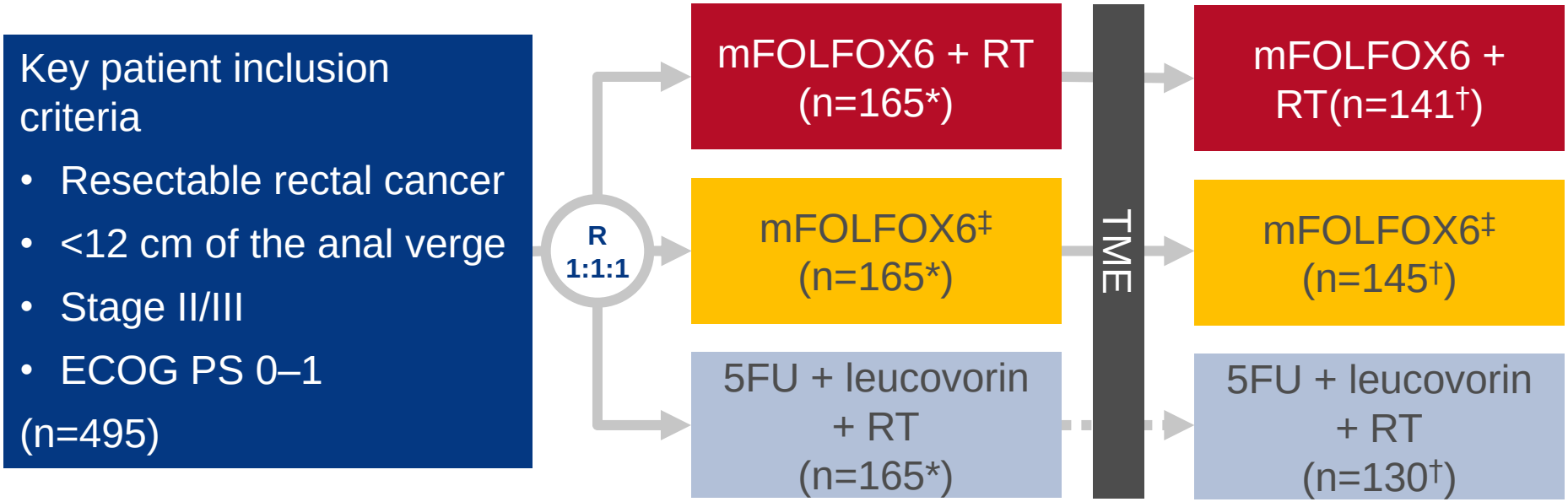
- **In patients with ypStage II–III resected rectal cancer, adjuvant FOLFOX showed improved DFS vs. 5FU + leucovorin after preoperative CRT with fluoropyrimidines**
- **Adjuvant CT selection should be based on postoperative pathologic stages after preoperative CRT and surgery**
- **Subgroup analyses may provide potential candidates of adjuvant oxaliplatin-based CT in these patients**

Hong YS, et al. J Clin Oncol 2018;36(suppl):abstr 3501

3502: Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial – Deng Y, et al

Study objective

- To assess the efficacy of mFOLFOX6 ± RT vs. 5FU CRT as neoadjuvant treatment for patients with advanced rectal cancer in the FOWARC study



PRIMARY ENDPOINT

- DFS at 3 years

SECONDARY ENDPOINTS

- Response rate, recurrence, DFS, OS

*ITT population; †per protocol population with follow-up;
‡RT was permitted according to physician's decision

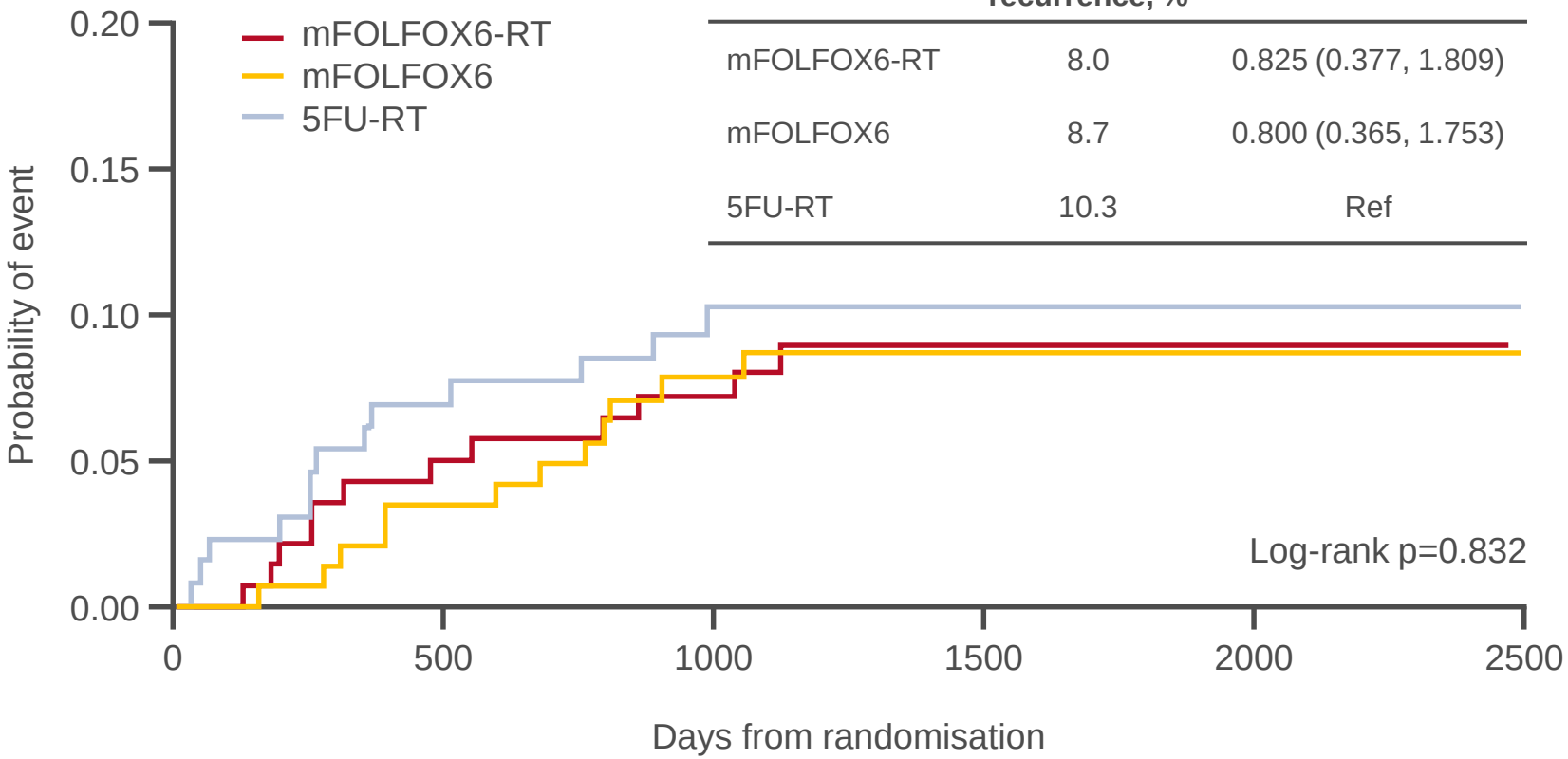
Deng Y, et al. J Clin Oncol 2018;36(suppl):abstr 3502

3502: Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial – Deng Y, et al

Key results

Local recurrence

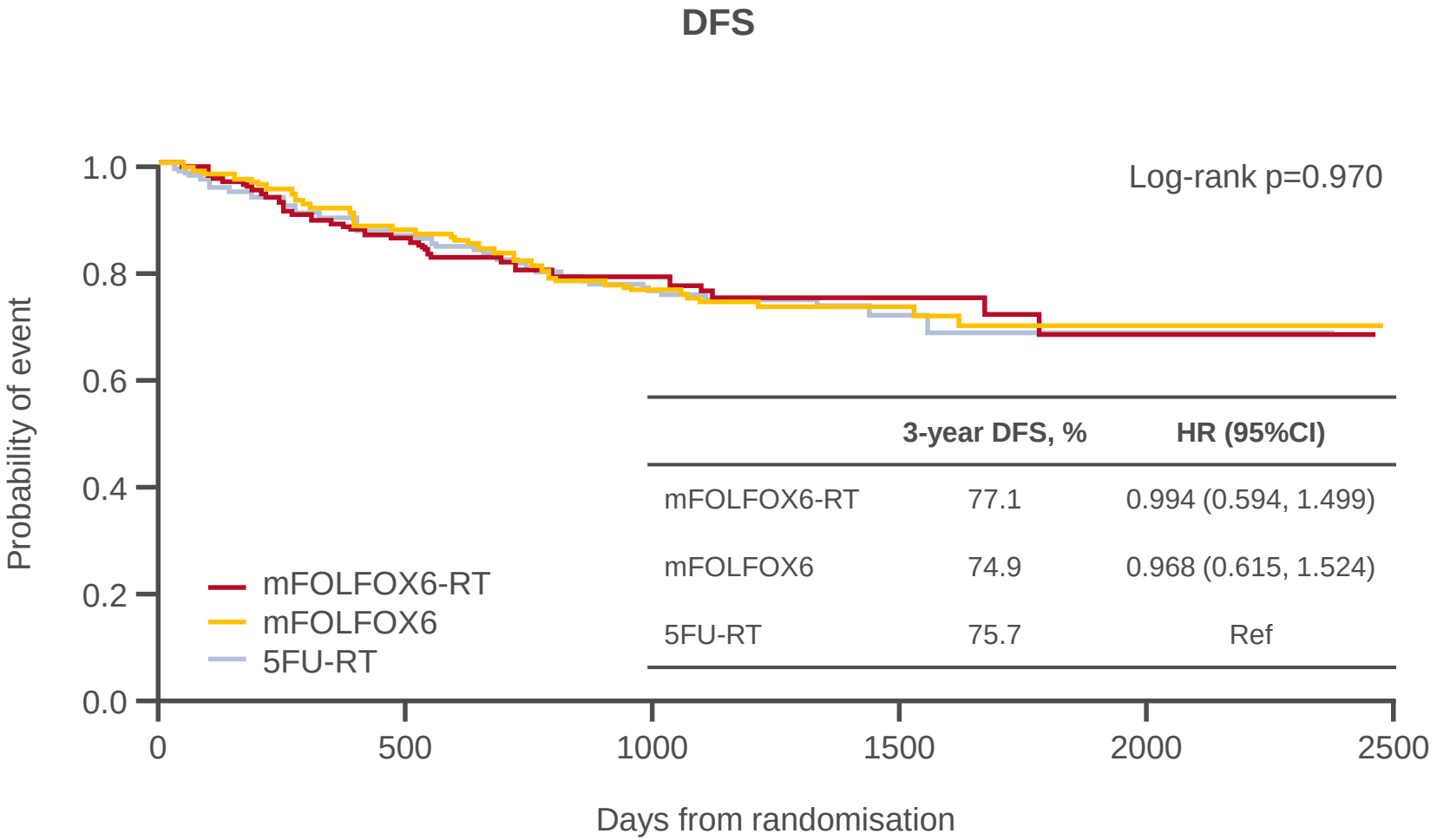
	3-year local recurrence, %	HR (95%CI)
mFOLFOX6-RT	8.0	0.825 (0.377, 1.809)
mFOLFOX6	8.7	0.800 (0.365, 1.753)
5FU-RT	10.3	Ref



Deng Y, et al. J Clin Oncol 2018;36(suppl):abstr 3502

3502: Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial – Deng Y, et al

Key results (cont.)

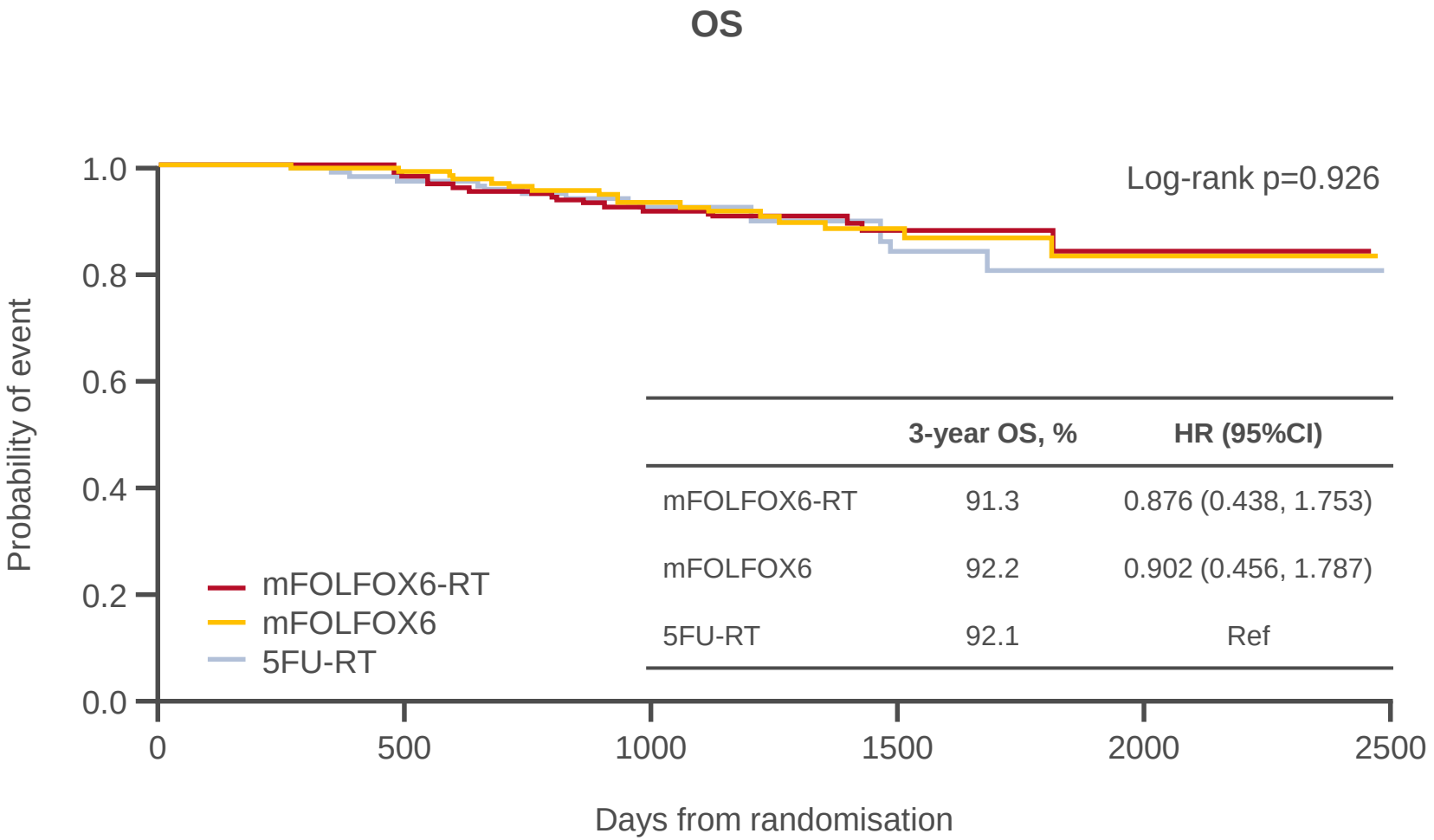


	3-year DFS, %	HR (95%CI)
mFOLFOX6-RT	77.1	0.994 (0.594, 1.499)
mFOLFOX6	74.9	0.968 (0.615, 1.524)
5FU-RT	75.7	Ref

Deng Y, et al. J Clin Oncol 2018;36(suppl):abstr 3502

3502: Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial – Deng Y, et al

Key results (cont.)



	3-year OS, %	HR (95%CI)
mFOLFOX6-RT	91.3	0.876 (0.438, 1.753)
mFOLFOX6	92.2	0.902 (0.456, 1.787)
5FU-RT	92.1	Ref

Deng Y, et al. J Clin Oncol 2018;36(suppl):abstr 3502

3502: Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial – Deng Y, et al

Key results (cont.)

n, %	FOLFOX-RT (n=141)	FOLFOX (n=145)	5FU-RT (n=130)
pCR	41 (29.1)	10 (6.9)	17 (13.1)
ypT0–2N0	80 (56.8)	53 (36.6)	47 (36.2)
TRG 0–1	97 (68.8)	48 (33.1)	63 (48.4)

Conclusions

- In patients with advanced rectal cancer, mFOLFOX6 ± RT did not improve DFS vs. 5FU CRT as neoadjuvant treatment
- mFOLFOX + RT vs. other two treatment arms:
  - Improved the rate of pCR, potentially enabling more patients to partake in a 'watch and wait' strategy
  - Decreased liver metastases*
- mFOLFOX alone did not compromise 3-year DFS or local control vs. other treatments
- Long-term follow-up is needed for OS

*Data not shown

Deng Y, et al. J Clin Oncol 2018;36(suppl):abstr 3502

LBA3503: A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7 – Quenet F, et al

Study objective

- To assess the efficacy and safety of hyperthermic intraperitoneal CT (HIPEC) after cytoreductive surgery for the treatment of colorectal peritoneal carcinomatosis

Key patient inclusion criteria

- CRC with peritoneal metastases; absence of extra-peritoneal metastases
- Peritoneal cancer index ≤25
- R0/R1 or R2 ≤1 mm
- No previous HIPEC therapy

(n=265)

R 1:1

HIPEC* + CT† (n=133) → PD

Stratification

- Centre
- Residual tumour status (R0/R1 vs. R2 ≤1 mm)
- Prior regimens of systemic CT
- Neoadjuvant CT

CT† alone (n=132) → PD

PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

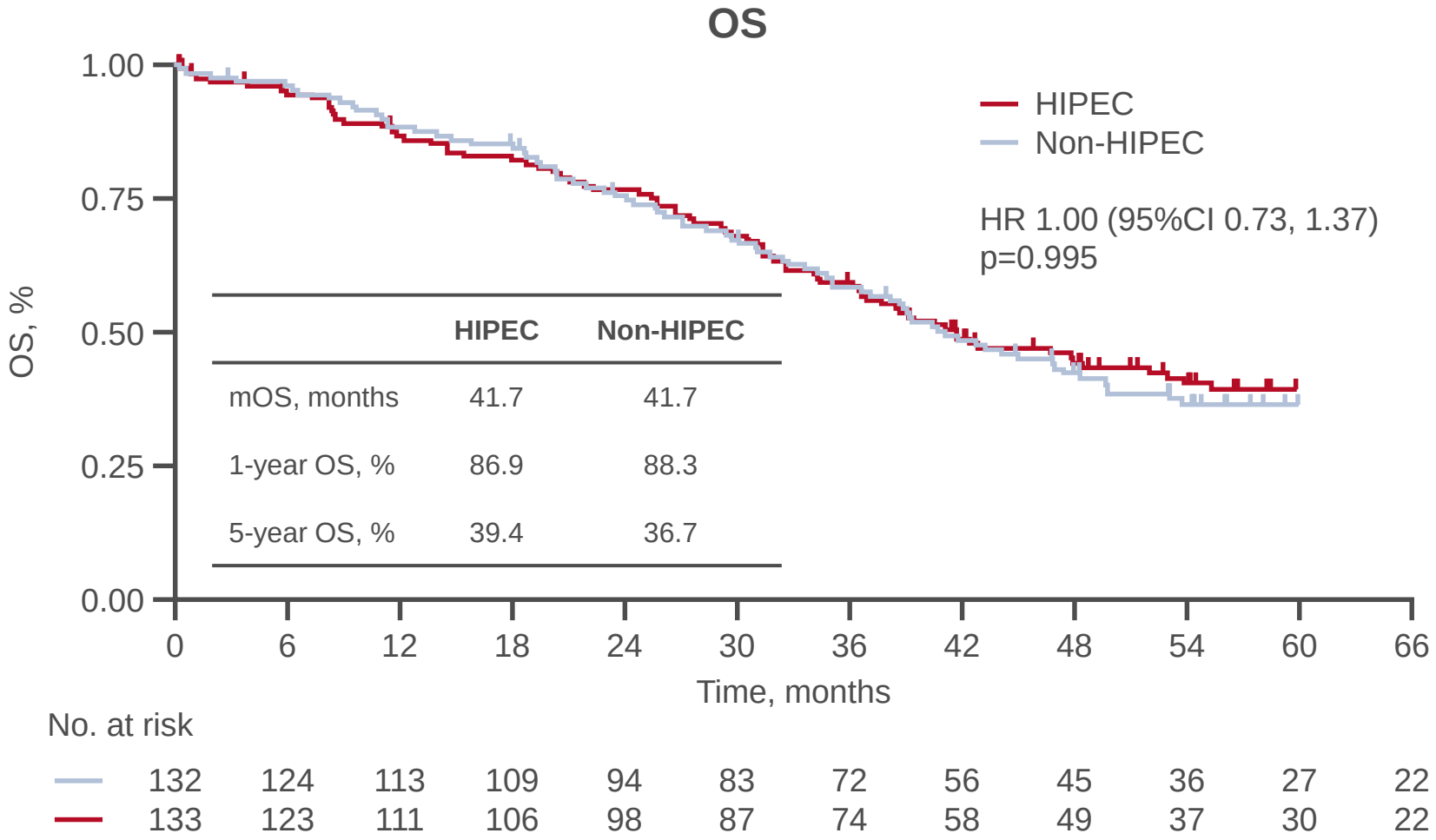
- RFS, prognostic factors or survival safety, morbidity

*Oxaliplatin 460 mg/m^2 ip (360 mg/m^2 in closed procedures), then leucovorin 20 mg/m^2 + 5FU 400 mg/m^2 ip during HIPEC; †preoperative or postoperative CT, or both, for 6 months

Quenet F, et al. J Clin Oncol 2018;36(suppl):abstr LBA3503

LBA3503: A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7 – Quenet F, et al

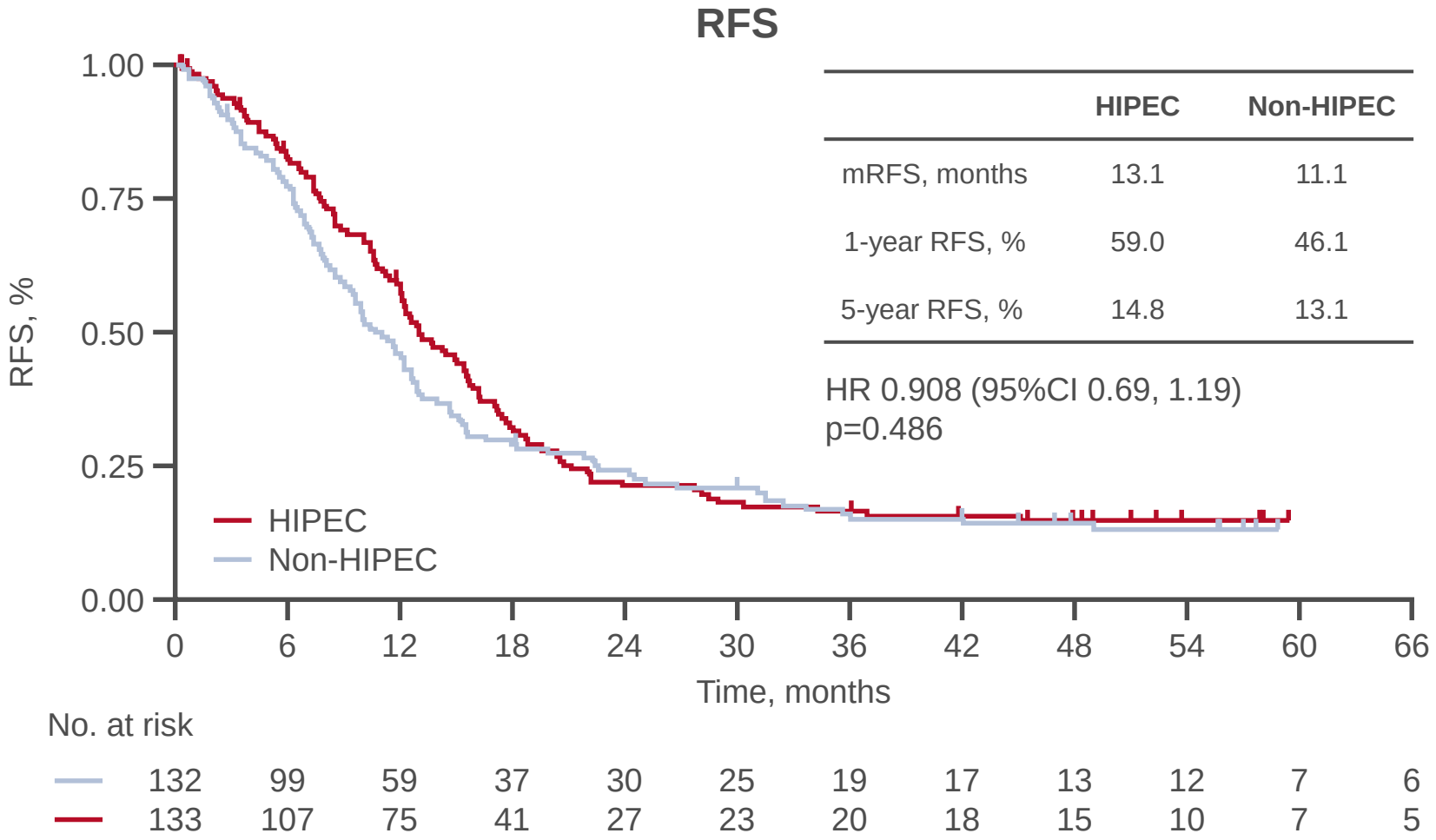
Key results



Quenet F, et al. J Clin Oncol 2018;36(suppl):abstr LBA3503

LBA3503: A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7 – Quenet F, et al

Key results (cont.)



	HIPEC	Non-HIPEC
mRFS, months	13.1	11.1
1-year RFS, %	59.0	46.1
5-year RFS, %	14.8	13.1

HR 0.908 (95%CI 0.69, 1.19)
p=0.486

Quenet F, et al. J Clin Oncol 2018;36(suppl):abstr LBA3503

LBA3503: A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7 – Quenet F, et al

Key results (cont.)

Morbidity at 30 days, n (%)	HIPEC	Non-HIPEC	p-value
All complications			
All grades	87 (65.4)	73 (55.3)	0.092
Grades 3–5	54 (40.6)	41 (31.1)	0.105
Intra-abdominal complications			
All grades	46 (35.0)	39 (29.6)	0.379
Grades 3–5	35 (26.3)	23 (17.4)	0.080
Extra-abdominal complications			
All grades	69 (51.9)	54 (40.9)	0.073
Grades 3–5	35 (26.3)	28 (21.2)	0.329

Morbidity at 60 days, n (%)	HIPEC	Non-HIPEC	p-value
All complications, grades 3–5	32 (24.1)	18 (13.6)	0.030
Intra-abdominal complications, grades 3–4	8 (6)	4 (3)	0.377
Extra-abdominal complications, grades 3–5	27 (20.3)	16 (12.1)	0.071

Quenet F, et al. J Clin Oncol 2018;36(suppl):abstr LBA3503

LBA3503: A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7 – Quenet F, et al

Key results (cont.)

	HIPEC	Non-HIPEC	p-value
Hospital stay, days (range)	18.0 (8–140)	13.0 (1–62)	<0.0001

Conclusions

- HIPEC after cytoreductive surgery for the treatment of colorectal peritoneal carcinomatosis did not improve OS or RFS vs. cytoreductive surgery alone
- There were more late postoperative complications with HIPEC
- The curative management of colorectal peritoneal carcinomatosis by curative surgery alone showed unexpectedly satisfactory survival results

Quenet F, et al. J Clin Oncol 2018;36(suppl):abstr LBA3503

3504: Randomized trial of irinotecan and cetuximab (IC) versus irinotecan, cetuximab and ramucirumab (ICR) as 2nd line therapy of advanced colorectal cancer (CRC) following oxaliplatin and bevacizumab based therapy: Result of E7208 – Hochster HS, et al

Study objective

- To assess the efficacy and safety of ramucirumab in combination with irinotecan and cetuximab as 2L therapy for patients with KRAS WT CRC compared with irinotecan and cetuximab alone

Key patient inclusion criteria

- Metastatic or advanced CRC (KRAS WT)
- 1L therapy with oxaliplatin chemotherapy + bevacizumab
- Progression

(n=97)

R 1:1

Ramucirumab + irinotecan + cetuximab* (n=50) → PD/ toxicity

Stratification

- PS (0 vs. 1–2)
- Discontinuation of oxaliplatin 1L therapy prior to progression (yes vs. no)
- Time since last bevacizumab treatment (<6 vs. ≥6 months)

Irinotecan† + cetuximab‡ (n=47) → PD/ toxicity

PRIMARY ENDPOINT

- PFS

SECONDARY ENDPOINTS

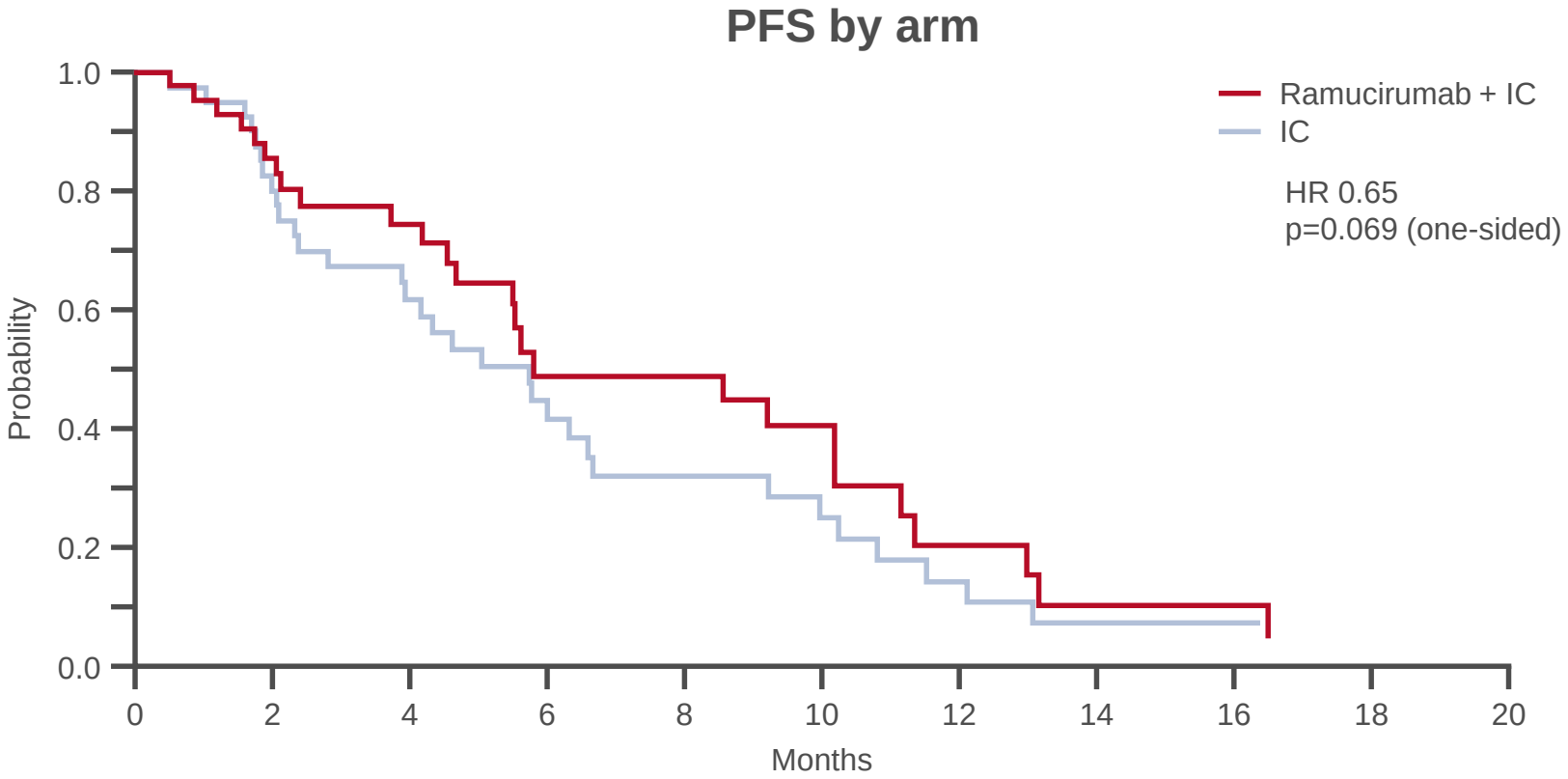
- RR; safety

*Irinotecan 150 mg/m^2 iv + cetuximab 400 mg/m^2 iv + ramucirumab 6 mg/kg iv q2w; †180 mg/m^2 iv; ‡500 mg/m^2 IV (q2w)

Hochster HS, et al. J Clin Oncol 2018;36(suppl):abstr 3504

3504: Randomized trial of irinotecan and cetuximab (IC) versus irinotecan, cetuximab and ramucirumab (ICR) as 2nd line therapy of advanced colorectal cancer (CRC) following oxaliplatin and bevacizumab based therapy: Result of E7208 – Hochster HS, et al

Key results



Treatment arm	Total	Fail	Censored	Median
Ramucirumab + IC	42	27	15	5.8
IC	40	33	7	5.7

Hochster HS, et al. J Clin Oncol 2018;36(suppl):abstr 3504

3504: Randomized trial of irinotecan and cetuximab (IC) versus irinotecan, cetuximab and ramucirumab (ICR) as 2nd line therapy of advanced colorectal cancer (CRC) following oxaliplatin and bevacizumab based therapy: Result of E7208 – Hochster HS, et al

Key results (cont.)

- AEs occurring in >5% of patients
  - Ramucirumab + irinotecan + cetuximab arm: anaemia (6%), leukopenia (10%), neutropenia (8%), mucositis (6%) and diarrhoea (13%)
  - Irinotecan + cetuximab arm: neutropenia (6%), acneiform rash (10%) and diarrhoea (10%)

Conclusions

- **In patients with KRAS WT CRC, ramucirumab added to irinotecan and cetuximab improved PFS as a 2L therapy**
- **There were, however, higher rates of toxicities (mucositis, diarrhoea, and neutropenia) with the combination along with more dose reductions**
- **Combining an anti-VEGF with an anti-EGFR should be investigated in future trials in appropriate populations such as RAS WT and left-sided disease**

Hochster HS, et al. J Clin Oncol 2018;36(suppl):abstr 3504

3505: First-line FOLFOX plus panitumumab (Pan) followed by 5FU/leucovorin plus Pan or single-agent Pan as maintenance therapy in patients with RAS wild-type metastatic colorectal cancer (mCRC): The VALENTINO study – Pietrantonio F, et al

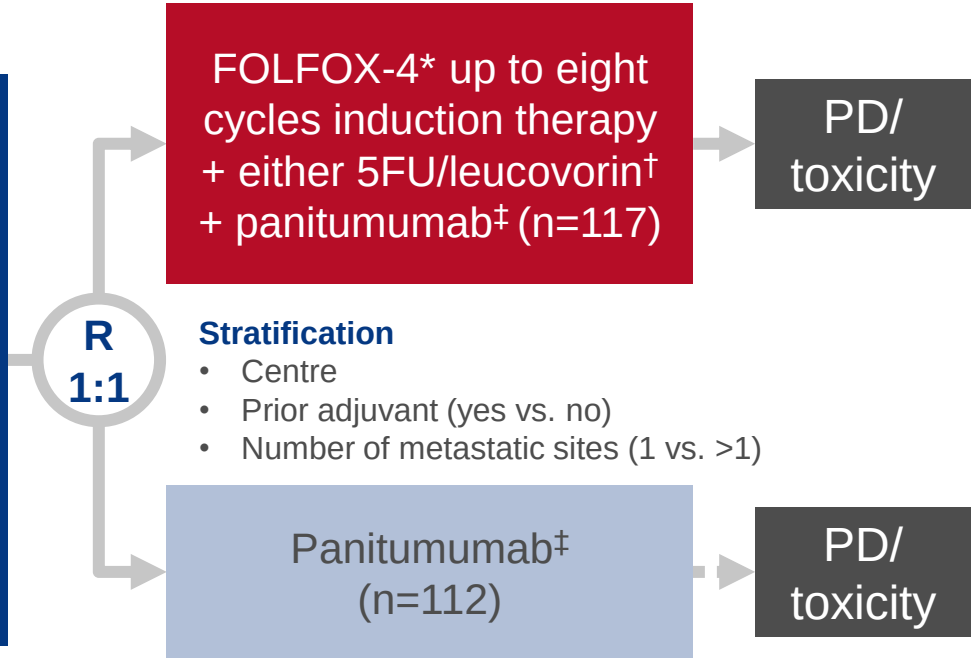
Study objective

- To examine whether "continuation maintenance" with single-agent panitumumab was non-inferior to 5FU/leucovorin + panitumumab after four months induction with FOLFOX-4 + panitumumab

Key patient inclusion criteria

- Age ≥18 years
- Histologically confirmed *RAS* WT metastatic adenocarcinoma of colon or rectum
- RECIST v1.1 metastases
- ECOG PS 0–1

(n=229)



PRIMARY ENDPOINT

- 10-month PFS

SECONDARY ENDPOINTS

- Safety, RR, OS

*Oxaliplatin 85 mg/m^2 d1 q2w; leucovorin 200 mg/m^2, d1,2 q2w; 5FU bolus 400 mg/m^2 d1,2 q2w; 5FU pvi 600 mg/m^2 d1,2 q2w; †leucovorin 200 mg/m^2 d1,2 q2w; 5FU bolus 400 mg/m^2 d1,2 q2w; 5FU pvi 600 mg/m^2 d1,2 q2w; ‡6 mg/kg d1 q2w

Pietrantonio F, et al. J Clin Oncol 2018;36(suppl):abstr 3505

3505: First-line FOLFOX plus panitumumab (Pan) followed by 5FU/leucovorin plus Pan or single-agent Pan as maintenance therapy in patients with RAS wild-type metastatic colorectal cancer (mCRC): The VALENTINO study – Pietrantonio F, et al

Key results

- The non-inferiority margin was 1.515 (upper boundary of one-sided 90%CI 1.946) in favour of 5FU/leucovorin + panitumumab
- HR 1.55 (95%CI 1.09, 2.20); p=0.011

	5FU/leucovorin + panitumumab (n=117)	Panitumumab alone (n=112)
Median PFS, months (95%CI)	13.0 (10.5, 16.0)	10.2 (8.9, 12.2)
ORR, %	65.8	67.0
DCR, %	82.9	83.9

- Skin rash of any grade was the most common AE in 54% and 46% of patients in the 5FU/leucovorin + panitumumab vs. panitumumab alone arms, respectively

Pietrantonio F, et al. J Clin Oncol 2018;36(suppl):abstr 3505

3505: First-line FOLFOX plus panitumumab (Pan) followed by 5FU/leucovorin plus Pan or single-agent Pan as maintenance therapy in patients with RAS wild-type metastatic colorectal cancer (mCRC): The VALENTINO study – Pietrantonio F, et al

Conclusions

- In patients RAS WT mCRC who achieved disease control after a 4-month induction with FOLFOX + panitumumab, maintenance with panitumumab appears to be inferior to 5FU/leucovorin + panitumumab
- In both treatment arms, the safety profile was manageable
- 5FU/leucovorin + panitumumab may be an option for patients who discontinue oxaliplatin
- Translational research is ongoing to determine the optimal maintenance strategies for individual patients

Pietrantonio F, et al. J Clin Oncol 2018;36(suppl):abstr 3505

3506: Plasma HER2 (ERBB2) copy number to predict response to HER2-targeted therapy in metastatic colorectal cancer – Bardelli A, et al

Study objective

- To assess plasma copy number as a predictor of response, explore the impact of tumour heterogeneity and determine ERBB2 copy number variation cut-off threshold, and sensitivity and positive predictive value of ERBB2 amplification detection in plasma of patients with mCRC

Methods

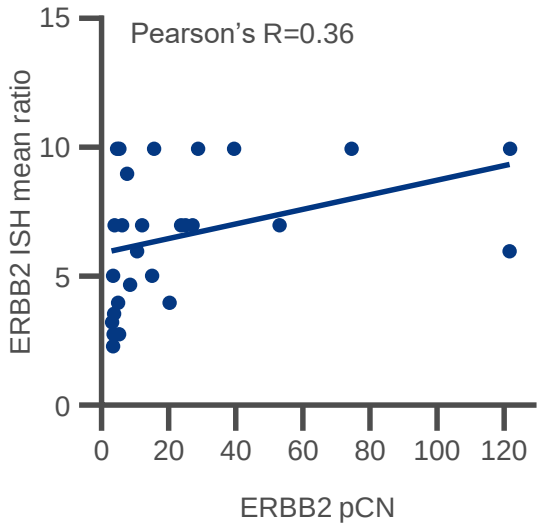
- Patients (n=33) with ERBB2-positive treatment refractory mCRC treated in the open-label phase 2 HERACLES trial of lapatinib + trastuzumab were analysed retrospectively
- Guardant360® panel was used in a retrospective cohort of 2460 ERBB2 amplified plasma samples across all tumour types to define the ERBB2 amplification threshold
- Plasma samples (n=48) were obtained from 29 patients
  - Samples were obtained at pre-treatment (n=29) and at progression (n=19)
  - 97.9% had ctDNA identified
  - 97.8% had ERBB2 amplification identified

Bardelli A, et al. J Clin Oncol 2018;36(suppl):abstr 3506

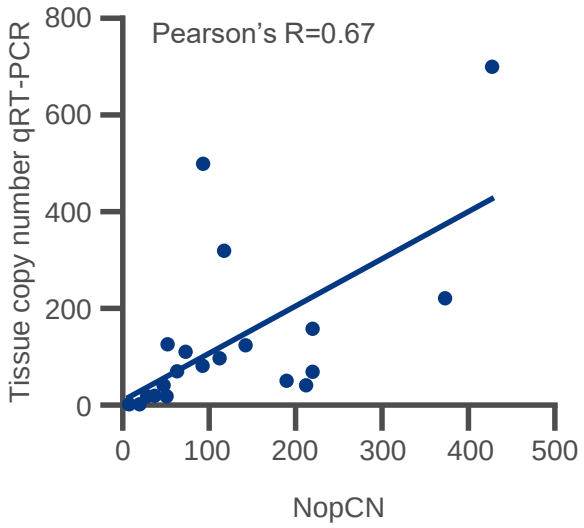
3506: Plasma HER2 (ERBB2) copy number to predict response to HER2-targeted therapy in metastatic colorectal cancer – Bardelli A, et al

Key results

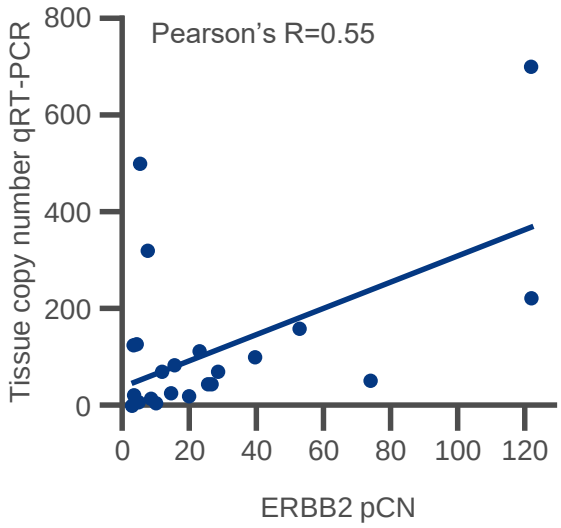
- Guardant360® accurately identified ERBB2 copy number in >97% of samples
- 100% of HERACLES pre-treatment samples had an absolute plasma copy number (pCN) of ≥2.4



Weak correlation between ABSOLUTE pCN and ISH



Strong correlation between NORMALIZED plasma copy number (NopCN) and qRT-PCR tissue copy number



Moderate correlation between ABSOLUTE pCN and qRT-PCR tissue copy number

Bardelli A, et al. J Clin Oncol 2018;36(suppl):abstr 3506

3506: Plasma HER2 (ERBB2) copy number to predict response to HER2-targeted therapy in metastatic colorectal cancer – Bardelli A, et al

Conclusions

- **In the HERACLES cohort, Guardant360® was able to detect >97% of ERBB2 amplified mCRC cases**
- **An absolute ERBB2 plasma copy number cut-off of 2.4 identified 100% of the ITT population**
- **The adjusted plasma copy number was strongly correlated with tissue copy number (qRT-PCR)**
- **These results need to be further validated in larger cohorts**

Bardelli A, et al. J Clin Oncol 2018;36(suppl):abstr 3506

3507: Actionable fusions in colorectal cancer using a cell-free circulating tumor DNA (ctDNA) assay – Clifton K, et al

Study objective

- To examine actionable fusions in CRC using a cell-free ctDNA assay

Methods

- Patients (n=4290) with CRC underwent molecular profiling at 4582 unique time points between February 2015 and December 2017 using a plasma-based ctDNA NGS assay (Guardant360®) with a 68-, 70- or 73-gene panel
- Variant allele frequency (VAF) was calculated as the number of variant calls relative to the total number of calls at a given locus
- Maximum allele frequency was defined as the highest level VAF of any aberration in the sample
  - Clonality of a given aberration was classified as VAF >50% maximum VAF (clonal) or VAF between <50% maximum VAF (subclonal)

Clifton K, et al. J Clin Oncol 2018;36(suppl):abstr 3507

3507: Actionable fusions in colorectal cancer using a cell-free circulating tumor DNA (ctDNA) assay – Clifton K, et al

Key results

- Fusions were detected in 45 patients

	Fusions detected , %
RET	36
FGFR3	29
ALK	22
NTRK1	7
ROS1	4
FGFR2	2

- A significantly higher prevalence was observed when using the ctDNA assay for RET and FGFR3 (p=0.04 vs. p=0.009, respectively)

Clifton K, et al. J Clin Oncol 2018;36(suppl):abstr 3507

3507: Actionable fusions in colorectal cancer using a cell-free circulating tumor DNA (ctDNA) assay – Clifton K, et al

Conclusions

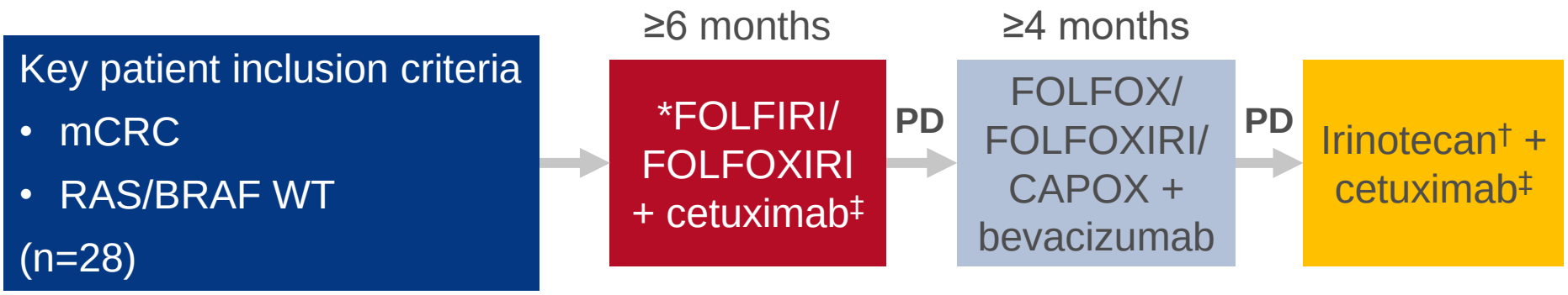
- In patients with CRC (n=4290), fusions were detected in 1.1% using a ctDNA assay, which was consistent with prior tissue-based reports
- One of the most common fusions detected was FGFR3 fusions, which have not been examined in detail in patients with CRC
- ctDNA testing may be a feasible method for identifying novel therapeutic trials in CRC because of the actionability of fusions in other solid tumours

Clifton K, et al. J Clin Oncol 2018;36(suppl):abstr 3507

12007: Liquid biopsy to predict benefit from rechallenge with cetuximab (cet) + irinotecan (iri) in RAS/BRAF wild-type metastatic colorectal cancer patients (pts) with acquired resistance to first-line cet+iri: Final results and translational analyses of the CRICKET study by GONO – Rossini D, et al

Study objective

- To assess the role of liquid biopsies to predict benefit from rechallenge with 3L cetuximab + irinotecan in patients with mCRC with acquired resistance to 1L cetuximab + irinotecan



PRIMARY ENDPOINT

- Response rate (RECIST 1.1)

SECONDARY ENDPOINTS

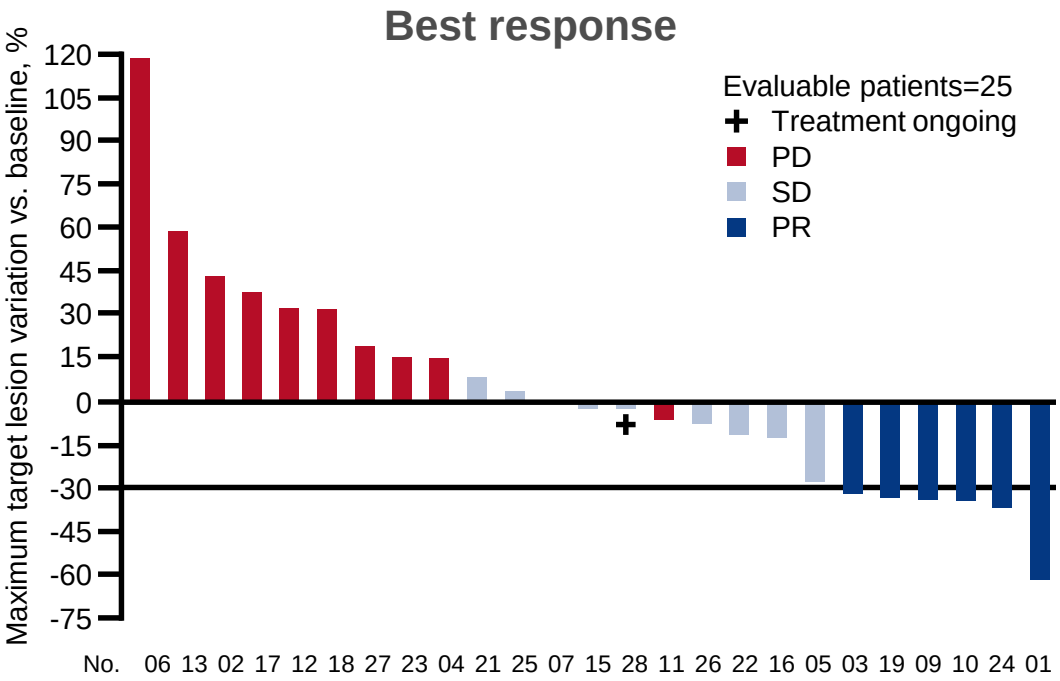
- PFS, OS, safety
- Translational analyses of RAS/BRAF mutations in ctDNA from baseline liquid biopsies

*At least a RECIST 1.1 PR, 1L PFS ≥6 months, PD to 1L cetuximab within 4 weeks after the last cetuximab administration; †180 mg/m^2 iv; ‡500 mg/m^2 iv

Rossini D, et al. J Clin Oncol 2018;36(suppl):abstr 12007

12007: Liquid biopsy to predict benefit from rechallenge with cetuximab (cet) + irinotecan (iri) in RAS/BRAF wild-type metastatic colorectal cancer patients (pts) with acquired resistance to first-line cet+iri: Final results and translational analyses of the CRICKET study by GONO – Rossini D, et al

Key results



	n=28
PR, n (%)	6 (21.5)
SD, n (%)	9 (32.1)
PD, n (%)	13 (46.4)
ORR, n (%) [95%CI]	6 (21.5) [10, 40]
DCR, n (%) [95%CI]	15 (53.6) [36, 70]

	n=28
mPFS, months (95%CI)	3.4 (1.9, 3.8)
mOS, months (95%CI)	9.8 (5.2, 13.1)

Rossini D, et al. J Clin Oncol 2018;36(suppl):abstr 12007

12007: Liquid biopsy to predict benefit from rechallenge with cetuximab (cet) + irinotecan (iri) in RAS/BRAF wild-type metastatic colorectal cancer patients (pts) with acquired resistance to first-line cet+iri: Final results and translational analyses of the CRICKET study by GONO – Rossini D, et al

Key results (cont.)

- Predictive role of ctDNA
  - RAS mutations detected in 12/25 (48%) patients; no BRAF/PI3KCA mutations detected
  - No RAS mutations were detected in patients who achieved a confirmed PR

	RAS WT ctDNA	RAS mutated ctDNA	HR (95%CI); p-value
PFS, months	4.0	1.9	0.44 (0.18, 0.98); 0.026
OS, months	12.5	5.2	0.58 (0.22, 1.52); 0.24

Conclusions

- **This is the first prospective study to demonstrate the activity of rechallenge with cetuximab + irinotecan in patients with RAS/BRAF WT tumours achieving an initial response followed by PD on 1L cetuximab + irinotecan**
- **RAS mutations in ctDNA predicted no clinical benefit from anti-EGFR rechallenge**
- **Further analyses are planned to explore other molecular events occurring during anti-EGFR rechallenge**

Rossini D, et al. J Clin Oncol 2018;36(suppl):abstr 12007

My Take: Timing of EGFR-Directed Therapy
Discussant – Sobrero AF

Study objective (FIRE-3: Abstract 3508 – Stintzing S, et al)

- **To compare the efficacy and safety of cetuximab + FOLFIRI vs. bevacizumab + FOLFIRI as 1L therapy in patients with RAS WT mCRC**

Study design

- Patients (n=352) with RAS WT mCRC were randomised (1:1) to cetuximab* + FOLFIRI (n=169) or bevacizumab† + FOLFIRI (n=183)
- Per protocol analysis

Key results

	Cetuximab + FOLFIRI (n=169)	Bevacizumab + FOLFIRI (n=183)	HR; p-value
mPFS, months (95%CI)	10.3 (9.5, 11.8)	10.7 (9.9, 11.8)	1.00; 0.99
mOS, months (95%CI)	32.5 (25.9, 38.3)	26.1 (23.7, 29.0)	0.75; 0.011

- ORR: 130 (76.9%) with cetuximab + FOLFIRI vs. 118 (64.5%) with bevacizumab + FOLFIRI; OR 1.84; p=0.014

*400 mg/m^2 iv 120 min, then 250 mg/m^2 iv 60 min q1w;
†5 mg/kg iv 30–90 min q2w

Stintzing S, et al. J Clin Oncol 2018;36(suppl):abstr 3508
Geissler M, et al. J Clin Oncol 2018;36(suppl):abstr 3509
Tsuji Y, et al. J Clin Oncol 2018;36(suppl):abstr 3510
Parseghian CM, et al. J Clin Oncol 2018;36(suppl):abstr 3511

My Take: Timing of EGFR-Directed Therapy
Discussant – Sobrero AF

Study objective (VOLFI: Abstract 3509 – Geissler M, et al)

- **To assess the efficacy and safety of panitumumab + mFOLFOXIRI vs. FOLFOXIRI alone as 1L therapy in patients with RAS WT mCRC**

Study design

- Patients with RAS WT mCRC (n=96) were randomised (2:1) to panitumumab + mFOLFOXIRI (n=63) or FOLFOXIRI alone (n=33)
  - Cohort 1: unresectable; Cohort 2: resectable (surgery then treatment for ≤12 cycles)

Key results

	Panitumumab + FOLFOXIRI (n=63)	FOLFOXIRI alone (n=33)	HR (95%CI); p-value
mPFS, months (95%CI)	9.7 (9.0, 11.7)	10.1 (7.8, 12.1)	0.920 (0.584, 1.451); 0.72

- ORR: 87.3% (95%CI 76.5, 94.4) with panitumumab + mFOLFOXIRI vs. 60.6% (95%CI 42.1, 77.1) with FOLFOXIRI alone; OR 4.5; p=0.004

Stintzing S, et al. J Clin Oncol 2018;36(suppl):abstr 3508
Geissler M, et al. J Clin Oncol 2018;36(suppl):abstr 3509
Tsuji Y, et al. J Clin Oncol 2018;36(suppl):abstr 3510
Parseghian CM, et al. J Clin Oncol 2018;36(suppl):abstr 3511

My Take: Timing of EGFR-Directed Therapy
Discussant – Sobrero AF

Study objective (REVERCE: Abstract 3510 – Tsuji Y, et al)

- **To evaluate the efficacy and safety of regorafenib followed by cetuximab vs. the reverse sequence in patients with mCRC**

Study design

- Previously treated* patients with mCRC and KRAS exon 2 WT tumours (n=180) were randomised (1:1) to regorafenib† 160 mg until PD/toxicity followed by cetuximab or cetuximab until PD/toxicity followed by regorafenib† 160 mg

Key results

	Regorafenib then cetuximab	Cetuximab then regorafenib	HR (95%CI); p-value
OS‡, months (95%CI)	17.4 (10.5, 20.7)	11.6 (8.4, 12.9)	0.61 (0.39, 0.96); 0.029
PFS, months			
PFS1‡ (PFS of treatment 1)	2.4	4.2	0.97 (0.62, 1.54); 0.91
PFS2# (PFS of treatment 2)	5.2	1.8	0.29 (0.17, 0.50); <0.0001

*Treatment failure after fluoropyrimidines + irinotecan + oxaliplatin, anti-EGFR negative; †3 weeks on, 1 week off; ‡n=101/180; #n=87/180

Stintzing S, et al. J Clin Oncol 2018;36(suppl):abstr 3508
Geissler M, et al. J Clin Oncol 2018;36(suppl):abstr 3509
Tsuji Y, et al. J Clin Oncol 2018;36(suppl):abstr 3510
Parseghian CM, et al. J Clin Oncol 2018;36(suppl):abstr 3511

My Take: Timing of EGFR-Directed Therapy
Discussant – Sobrero AF

Study objective (Abstract 3511 – Parseghian CM, et al)

- **To investigate the impact of time on the decay of RAS and EGFR mutant alleles in patients with mCRC following discontinuation of anti-EGFR therapy**

Study design

- Data were analysed from a discovery cohort (n=135) of patients with mCRC and RAS/BRAF/EGFR WT tumours treated with anti-EGFR therapy
  - Relative mutation allele frequency was determined using ctDNA sequencing
- Data were validated in an external cohort (n=267)
- The decay rate and half-life were determined using serial sampling

Key results

- RAS and EGFR MT alleles decay exponentially over time with a half-life of 4–5 months
- At progression, only 30% of cells carried a mutation in RAS/EGFR/BRAF/MAPK2K1
- This study provides a rationale for rechallenge after a period off EGFR therapy and may help guide timing of rechallenge using ctDNA monitoring

Stintzing S, et al. J Clin Oncol 2018;36(suppl):abstr 3508
Geissler M, et al. J Clin Oncol 2018;36(suppl):abstr 3509
Tsuji Y, et al. J Clin Oncol 2018;36(suppl):abstr 3510
Parseghian CM, et al. J Clin Oncol 2018;36(suppl):abstr 3511

My Take: Timing of EGFR-Directed Therapy
Discussant – Sobrero AF

Summary

- Anti-EGFR therapy increases ORR by 10–30%
- Rationale for rechallenge with anti-EGFR therapy consistent with early clinical experience

Presenter's take-home messages

- **To give 1L EGFR therapy more often**
- **To give EGFR therapy for shorter time periods, but to implement rechallenge**
- **Not to give maintenance EGFR therapy (selection pressure)**
- **To consider rechallenge with EGFR therapy before anything else**
- **It would be of interest to know the proportion of patients with true rechallenge in the FIRE-3 and CALGB studies**
- **The continuum of care becomes more complex: 'induction'**

Stintzing S, et al. J Clin Oncol 2018;36(suppl):abstr 3508
Geissler M, et al. J Clin Oncol 2018;36(suppl):abstr 3509
Tsuji Y, et al. J Clin Oncol 2018;36(suppl):abstr 3510
Parseghian CM, et al. J Clin Oncol 2018;36(suppl):abstr 3511

Molecular Subsets: Prognosis and Prediction
Discussant – Corcoran RB

Study objective (Abstract 3513 – Wang Y, et al)

- **To assess the prognostic value of KRAS, NRAS and BRAF mutations in patients with mCRC**

Study design

- Patient with mCRC who had RAS/RAF mutations were included in the study
- Clinical characteristics and survival outcomes were compared in patients with different mutations

Key results

- Mutation prevalence:
  - WT, 41.3%; KRAS, 45.6%; NRAS, 3.8%; BRAF V600, 8.0%; BRAF non-V600, 1.3%
- mPFS: BRAF V600, 11.4 months; BRAF WT, 43.0 months; BRAF non-V600, 60.7 months

	WT (n=951)	KRAS (n=1080)	NRAS (n=91)	BRAF V600 (n=160)
mOS, months	49.2	36.2	30.1	22.5

OS*	NRAS vs. WT	NRAS vs. KRAS	NRAS vs. BRAF V600
HR (95%CI)	1.830 (1.401, 2.391)	1.372 (1.059, 1.776)	0.808 (0.574, 1.136)
p-value	<0.001	0.016	0.220

*Mulivariate Cox regression, adjusting for age, sex, sidedness

Wang Y, et al. J Clin Oncol 2018;36(suppl):abstr 3513

Molecular Subsets: Prognosis and Prediction
Discussant – Corcoran RB

Presenter's take-home messages

- **In patients with mCRC, KRAS, NRAS and BRAF mutations have distinct impacts on survival**
  - **The study was well performed and the outcomes were consistent with prior trials**
  - **A key limitation of this study was that patients were only from two centres**
- **NRAS mutations have a poorer prognosis vs. KRAS mutations**
  - **However, due to the limited sample size the impact on survival of KRAS vs. NRAS are still under consideration**
- **The mutational status of mCRC tumours has prognostic and predictive value**
- **This study highlights the role of genomic analysis in mCRC**

Wang Y, et al. J Clin Oncol 2018;36(suppl):abstr 3513

Immune Therapy: Why Don't We Have the KEY for VICTORy
Discussant – Segal NH

Study objective (KEYNOTE-164: Abstract 3514 – Le DT, et al)

- **To assess the efficacy and safety of pembrolizumab in patients with MSI-high mCRC**

Study design

- Patients with MSI-high mCRC treated with ≥1 prior line of therapy (ECOG PS 0–1) received pembrolizumab 200 mg q3w for ~2 years until PD/toxicity (n=63)

Key results

	n	% (95%CI)
ORR	20	32 (21, 45)
CR	2	3 (0,11)
PR	18	29 (18, 41)
SD	16	25 (15, 38)
PD	25	40 (28, 53)
DCR	36	57 (44, 70)

- 6-month PFS: 49%; 12-month PFS: 41% (95%CI 2.1, NR)
- 6-month OS: 84%; 12-month OS: 76% (95%CI NR, NR)

Le DT, et al. J Clin Oncol 2018;36(suppl):abstr 3514
Glaire M, et al. J Clin Oncol 2018;36(suppl):abstr 3515

Immune Therapy: Why Don't We Have the KEY for VICTORy Discussant – Segal NH

Study objective (Abstract 3515 – Glaire M, et al)

- **To evaluate the prognostic values of tumour-infiltrating CD8+ lymphocyte in patients with CRC**

Study design

- Tissue microarrays were performed on samples from 1804 patients from the QUASAR2 and VICTOR trials
- The proportion of CD8+ and CD3+ cells were determined
- Data were analysed by univariate and multivariate Cox proportional hazards regression with adjustment for confounders (stage, MMR status)

Key results

Risk group	Stage	n (%)	HR: CD8 high vs. low (95%CI)	p-value
Low	T3N0	453 (25)	1.03 (0.54, 1.72)	0.91
Intermediate	T4N0; T1–3, N1/2	1035 (58)	0.69 (0.51, 0.93)	0.014
High	T4, N1/2	303 (17)	0.59 (0.39, 0.89)	0.011

Le DT, et al. J Clin Oncol 2018;36(suppl):abstr 3514
Glaire M, et al. J Clin Oncol 2018;36(suppl):abstr 3515

Immune Therapy: Why Don't We Have the KEY for VICTORy
Discussant – Segal NH

Presenter's take-home messages

- **In patients with MSI-high mCRC treated with ≥1 prior line of therapy, pembrolizumab provides meaningful benefit: no change in clinical practice**
- **Data are eagerly awaited from frontline and adjuvant clinical trials**
- **National Comprehensive Cancer Network: universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer**
- **CD8+ cell density appears to be prognostic, but does not guide clinical practice**
- **Next steps:**
  - **Determine the optimum method for quantifying immune infiltrate**
  - **Separate analysis for MSS and MSI-high**
  - **Use in determining adjuvant therapy (or not) in stage II or III CRC?**

Le DT, et al. J Clin Oncol 2018;36(suppl):abstr 3514
Glaire M, et al. J Clin Oncol 2018;36(suppl):abstr 3515

Biomarkers and New Approaches in Anorectal Cancer
Discussant – Deming DA

Study objective (Abstract 3516 – Tie J, et al)

- **To evaluate the value of ctDNA in predicting recurrence and benefit from CT in patients with stage III colon cancer**

Study design

- 95 patients with colon cancer who had received adjuvant CT were included in the study
- Blood samples were collected for ctDNA analysis post-surgery and during/after CT
- Tumour tissues were also analysed for 15 genes commonly altered in CRC

Key results

- **ctDNA positive (n=19)**:
  - ctDNA positive post-surgery: 43% 2-year RFS; CT can clear ctDNA in ~50% of patients
  - Positive then positive ctDNA: 33% 2-year RFS; positive then negative: 59% 2-year RFS
- **ctDNA negative (n=76)**:
  - ctDNA positive post-surgery: 84% 2-year RFS; ctDNA can become positive for some
  - Negative then negative ctDNA: 86% 2-year RFS; negative then positive: 25% 2-year RFS
  - Likely 25% of ctDNA negative patients remain negative due to CT

Tie J, et al. J Clin Oncol 2018;36(suppl):abstr 3516
You YN, et al. J Clin Oncol 2018;36(suppl):abstr 3517
Fernandez-Martos C, et al. J Clin Oncol 2018;36(suppl):abstr 3518

Biomarkers and New Approaches in Anorectal Cancer
Discussant – Deming DA

Study objective (Abstract 3517 – You YN, et al)

- **To validate neoadjuvant rectal cancer (NAR) score as a surrogate endpoint for OS**

Study design

- The National Cancer Database was used to identify patients with non-metastatic rectal cancer who had undergone neoadjuvant CRT (45–54 Gy) and proctectomy (n=19,831)

Key results

- After neoadjuvant CT, 12.6% of patients achieved pCR and 28.9% were downstaged

NAR score	5-year OS, %
≤8.4	88
8.5–15	81
15–26.6	75.2
>26.6	61.7

Tie J, et al. J Clin Oncol 2018;36(suppl):abstr 3516
You YN, et al. J Clin Oncol 2018;36(suppl):abstr 3517
Fernandez-Martos C, et al. J Clin Oncol 2018;36(suppl):abstr 3518

Biomarkers and New Approaches in Anorectal Cancer
Discussant – Deming DA

Study objective (GEMCAD 14-02: Abstract 3518 – Fernandez-Martos C, et al)

- **To investigate the impact of adding aflibercept to induction mFOLFOX6 followed by CRT and TME in patients with high-risk rectal cancer**

Study design

- Patients with high-risk rectal cancer (mrT3/T4/N2) were randomised (2:1) to aflibercept + mFOLFOX6 vs. mFOLFOX6 alone, prior to CRT* and TME
  - Stratification: extra-mural venous invasion and mrT4

Key results

%	Aflibercept + mFOLFOX6	mFOLFOX6 alone	p-value
pCR rate	21.7	13.8	0.1938
Preoperative grade 3–4 AEs†	50	23	-
Completion of CRT	90	96	-
Completion of surgery	90	95	-
Postoperative complications	14.7	12.3	-

*Capecitabine with 50.4 Gy in 28 fractions;
†Hypertension, mucositis, asthenia, perforation

Tie J, et al. J Clin Oncol 2018;36(suppl):abstr 3516
You YN, et al. J Clin Oncol 2018;36(suppl):abstr 3517
Fernandez-Martos C, et al. J Clin Oncol 2018;36(suppl):abstr 3518

Biomarkers and New Approaches in Anorectal Cancer
Discussant – Deming DA

Presenter's take-home messages

- **ctDNA is an exciting prognostic marker of residual disease**
- **NAR score provides a short-term readout for locally advanced rectal cancer trials**
- **Anti-angiogenic therapies could enhance neoadjuvant therapy for locally advanced rectal cancer**

Tie J, et al. J Clin Oncol 2018;36(suppl):abstr 3516
You YN, et al. J Clin Oncol 2018;36(suppl):abstr 3517
Fernandez-Martos C, et al. J Clin Oncol 2018;36(suppl):abstr 3518