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 **ESMO 2018 Congress** and is available in English, French, Japanese and Chinese.

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 I, Rudolf Foundation Clinic, Vienna, Austria
Prof Jaroslaw Regula	Department of Gastroenterology and Hepatology, Institute of Oncology, Warsaw, Poland

PANCREATIC CANCER AND HEPATOBILIARY TUMOURS

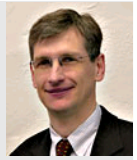


Prof Jean-Luc Van Laethem	Digestive Oncology, Erasme University Hospital, Brussels, Belgium
Prof Thomas Seufferlein	Clinic of Internal Medicine I, University of Ulm, Ulm, Germany
Prof Ulrich Güller	Medical Oncology & Hematology, Kantonsspital St Gallen, St Gallen, Switzerland

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

1/2/3L	first-/second-/third-line
5FU	5-fluorouracil
AE	adverse event
bid	twice daily
BSC	best supportive care
CBR	clinical benefit rate
CCSD	colon cancer-specific death
CEA	carcinoembryonic antigen
CI	confidence interval
CMS	consensus molecular subtype
CR	complete response
CRC	colorectal cancer
CRT	chemoradiotherapy
CT	chemotherapy
CTLA-4	cytotoxic T-lymphocyte-associated protein
D	day
DCR	disease control rate
DFS	disease-free survival
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DoR	duration of response
ECF	epirubicin, cisplatin, 5-fluorouracil
ECM	extracellular matrix
ECOG	Eastern Cooperative Oncology Group
ECX	epirubicin, cisplatin, capecitabine
ELISA	enzyme-linked immunosorbent assay
EOF	epirubicin, oxaliplatin, 5-fluorouracil
EOX	epirubicin, oxaliplatin, capecitabine
FOLFIRI	5-fluorouracil + folinic acid + irinotecan
FOLFOX	leucovorin + 5-fluorouracil + oxaliplatin
(m)FOLFOXIRI	(modified) 5-fluorouracil + oxaliplatin + irinotecan
GBC	gallbladder cancer
GEJ	gastro-oesophageal junction
GI	gastrointestinal
Gy	Gray
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
HGF	hepatocyte growth factor
HR	hazard ratio
IHC	immunohistochemistry
IQR	interquartile range
(m)ITT	(modified) intent-to-treat
iv	intravenous
LV	leucovorin
mCRC	metastatic colorectal cancer
MMR-P	mismatch repair proficient
MOMP	multi-omic molecular profiling
MSI-H	high microsatellite instability
MSS	microsatellite stable
NA	not available
NE	not evaluable
NEC	neuroendocrine carcinoma
NET	neuroendocrine tumour
NR	not reached
ORR	overall/objective response rate
(m)OS	(median) overall survival
PD	progressive disease
PD-(L)1	programmed death-(ligand) 1
(m)PFS	(median) progression-free survival
PR	partial response
PRO	patient-reported outcome
PS	performance status
q(2/3/4)w	every (2/3/4) week(s)
QoL	quality of life
R	randomised
R0	resection 0
RECIST	Response Evaluation Criteria In Solid tumours
SAE	serious adverse event
sc	subcutaneous
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SoC	standard of care
TALT	transarterial liver therapy
TEAE	treatment-emergent adverse event
TFD/TPI	trifluridine/tipiracil
tiw	three times per week
TMB	tumour mutation burden
TRAE	treatment-related adverse event
TTP	time to progression
TTR	time to response
TTRP	time to radiological progression
VEGF	vascular endothelial growth factor
WT	wild type

Contents

- Cancers of the oesophagus and stomach 6
- Cancers of the pancreas, small bowel and hepatobiliary tract 16
  - Pancreatic and biliary tract cancer 17
  - Hepatocellular carcinoma 30
  - Neuroendocrine tumour 39
- Cancers of the colon, rectum and anus 43
- Gastrointestinal cancers 86

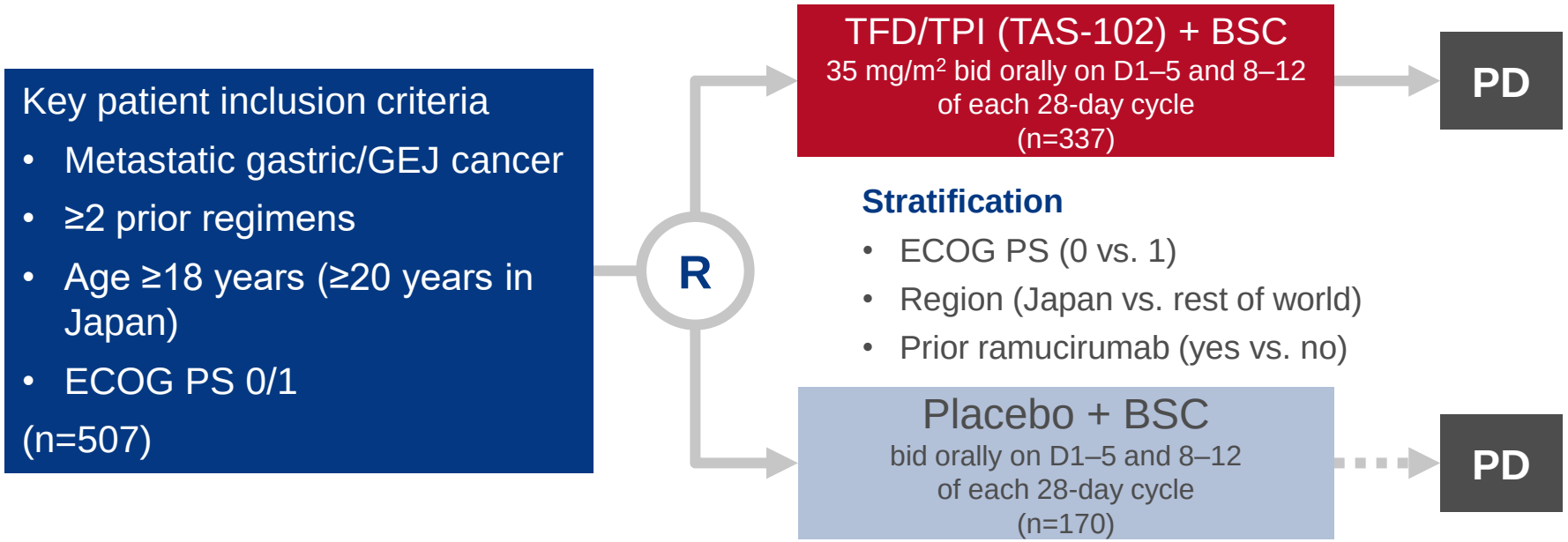
Note: To jump to a section, right click on the number and ‘Open Hyperlink’

CANCERS OF THE OESOPHAGUS AND STOMACH

LBA25: TAGS: a phase 3, randomised, double-blind study of trifluridine/tipiracil (TAS-102) versus placebo in patients with refractory metastatic gastric cancer – Arkenau H, et al

Study objective

- To assess the efficacy and safety of trifluridine/tipiracil (TFD/TPI) in heavily pre-treated patients with gastric or GEJ cancer



PRIMARY ENDPOINT

- OS

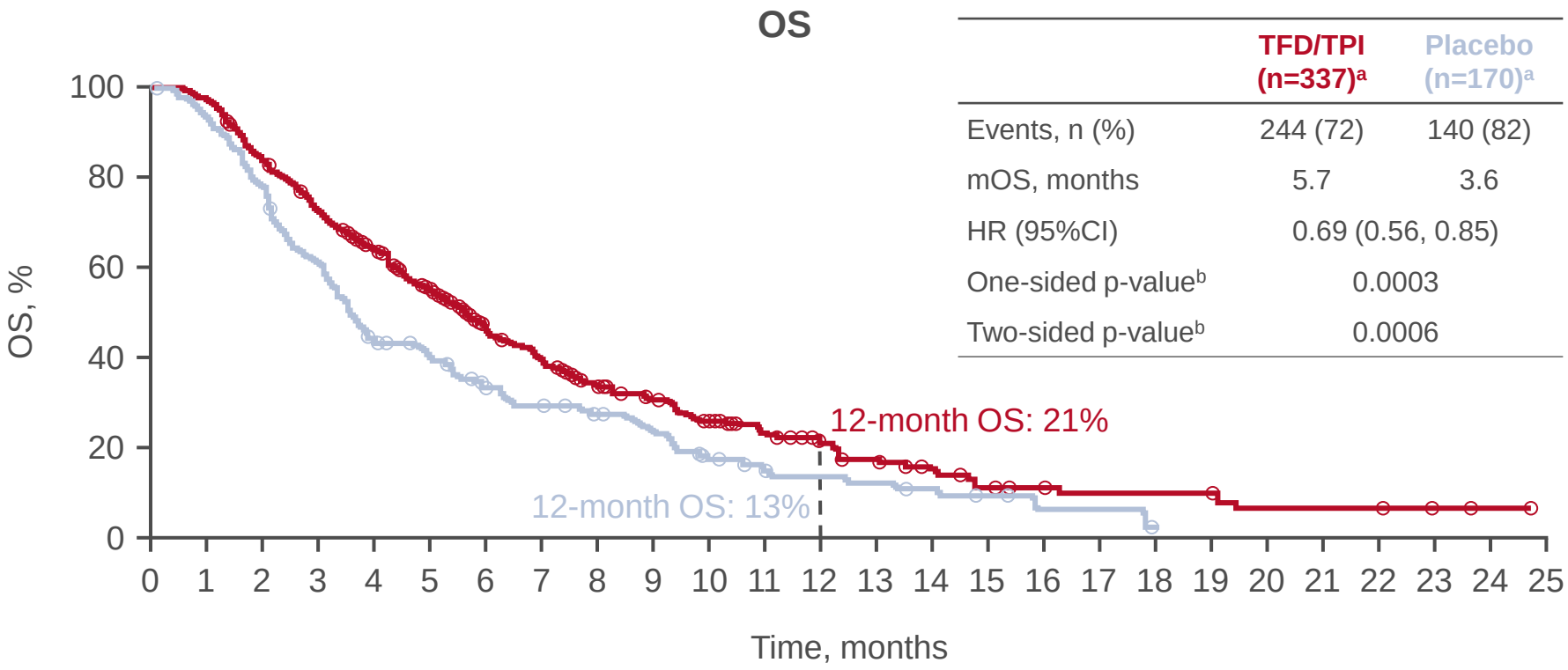
SECONDARY ENDPOINTS

- PFS, ORR, DCR, QoL, time to ECOG PS ≥2, safety

Arkenau H, et al. Ann Oncol 2018;29(suppl 5):abstr LBA25

LBA25: TAGS: a phase 3, randomised, double-blind study of trifluridine/tipiracil (TAS-102) versus placebo in patients with refractory metastatic gastric cancer – Arkenau H, et al

Key results



	TFD/TPI (n=337)[a]	Placebo (n=170)[a]
Events, n (%)	244 (72)	140 (82)
mOS, months	5.7	3.6
HR (95%CI)	0.69 (0.56, 0.85)	
One-sided p-value[b]	0.0003	
Two-sided p-value[b]	0.0006	

No. at risk

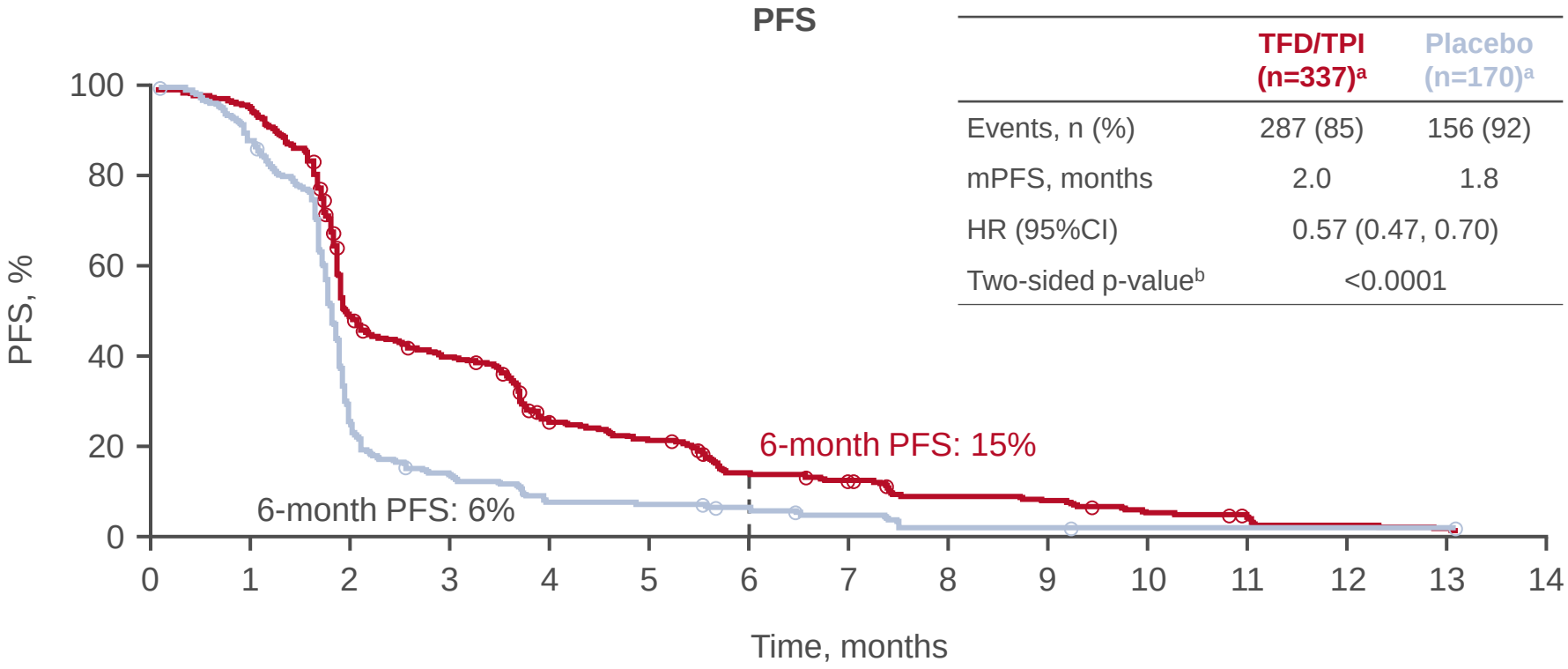
TFD/TPI	337	328	282	240	201	161	124	102	80	66	51	40	31	22	16	11	9	7	7	7	4	4	4	3	1	0
Placebo	170	158	131	101	71	60	47	40	34	29	17	12	10	9	7	5	2	2	0	0	0	0	0	0	0	0

[a]ITT population; [b]stratified log-rank test

Arkenau H, et al. Ann Oncol 2018;29(suppl 5):abstr LBA25

LBA25: TAGS: a phase 3, randomised, double-blind study of trifluridine/tipiracil (TAS-102) versus placebo in patients with refractory metastatic gastric cancer – Arkenau H, et al

Key results (cont.)



	TFD/TPI (n=337)[a]	Placebo (n=170)[a]
Events, n (%)	287 (85)	156 (92)
mPFS, months	2.0	1.8
HR (95%CI)	0.57 (0.47, 0.70)	
Two-sided p-value[b]	<0.0001	

No. at risk

TFD/TPI	337	314	154	122	72	60	37	32	20	18	12	9	4	2	0
Placebo	170	145	41	21	12	11	8	5	2	2	1	1	1	1	0

[a]ITT population; [b]stratified log-rank test

Arkenau H, et al. Ann Oncol 2018;29(suppl 5):abstr LBA25

LBA25: TAGS: a phase 3, randomised, double-blind study of trifluridine/tipiracil (TAS-102) versus placebo in patients with refractory metastatic gastric cancer – Arkenau H, et al

Key results (cont.)

- TRAEs were more common in the TFD/TPI group (81%) than placebo group (57%) as were grade ≥3 TRAEs, 53% and 13%, respectively
- The most common grade ≥3 AEs occurring in >10% of patients with TFD/TPI were neutropenia (34%) and anaemia (19%)

Conclusions

- **In heavily pre-treated patients with gastric or GEJ cancer, TFD/TPI may be considered as an effective new treatment option**
  - **Compared with placebo, TFD/TPI provided clinically meaningful and statistically significant improvements in survival and DCR and a lower risk of ECOG PS deterioration**
  - **The safety profile of TFD/TPI was manageable and similar to previous findings**

Arkenau H, et al. Ann Oncol 2018;29(suppl 5):abstr LBA25

Gastric cancer: Treatment of advanced disease
Discussant – Lordick F

Study objective (ATTRACTION-2: Abstract 617PD – Satoh T, et al)

- **To assess the efficacy and safety of 3L nivolumab vs. placebo in patients with advanced gastric or GEJ cancer (ATTRACTION-2) at two years of follow-up**

Study design

- Patients (n=493) were randomised 2:1 to receive nivolumab 3 mg/kg iv (q2w) or placebo

Key results

	Nivolumab (n=330)	Placebo (n=163)	HR (95%CI); p-value
mOS, months (95%CI)	5.26 (4.60, 6.37)	4.14 (3.42, 4.86)	0.62 (0.51, 0.76) <0.0001
mPFS, months (95%CI)	1.61 (1.54, 2.30)	1.45 (1.45, 1.54)	0.60 (0.49, 0.75) <0.0001

- The majority of patients who survived for two years in the nivolumab group had a CR or PR (19/29 [65.5%]) to treatment, whereas all patients (3/3 [100%]) in the placebo group had SD
- No new safety concerns were observed during the two years of follow-up

Satoh T, et al. Ann Oncol 2018;29(suppl 5):abstr 617PD

Gastric cancer: Treatment of advanced disease
Discussant – Lordick F

Presenter's take-home messages

- **The long-term follow-up of nivolumab in ATTRACTION-2 supports its efficacy as a 3L therapy in patients with advanced gastric or GEJ cancer**

Satoh T, et al. Ann Oncol 2018;29(suppl 5):abstr 617PD

619PD_PR: Influence of sex on chemotherapy efficacy and toxicity in oesophagogastric (OG) cancer: a pooled analysis of 4 randomised trials – Davidson M, et al.

Study objective

- To assess the influence of sex on the efficacy and toxicity of triplet chemotherapy regimens in patients with oesophagogastric cancer

Study design

- Demographic, efficacy and safety data were collected and pooled from 4 UK randomised clinical trials for patients with oesophagogastric cancer (n=1654) who had received 1L ECF, ECX, EOF or EOX chemotherapy

Key results

- There were no differences between male and female patients for PFS or OS

AEs, %	Male (n=1328)	Female (n=326)	p-value
Any grade	62.8	67.2	0.19
Nausea/vomiting	78.3	89.3	<0.001
Diarrhoea	46.9	53.8	0.027
Stomatitis	40.7	49.5	0.004
Alopecia	74.3	81.4	0.009
Peripheral neuropathy	49.3	42.6	0.03
Grade ≥3 neutropenia	40.4	45.1	-
Grade ≥3 febrile neutropenia	7.7	11.8	-

Conclusion

- **Females with oesophagogastric cancer had a significantly higher rate of toxicity than males, particularly GI related, and potentially higher rates of neutropenia with the use of 1L chemotherapy**

Davidson M, et al. Ann Oncol 2018;29(suppl 5):abstr 619PD_PR

Immune modulation/therapy
Discussant – David L

Study objective (Abstract 4PD – Hirsch L, et al)

- **To assess the immunomodulatory effects of HGF in monocytes of patients with gastric carcinoma**

Study design

- Peripheral blood mononuclear cells were isolated from patients (n=37) and cultured with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4 to stimulate dendritic cells then analysed using flow cytometry
- Interleukin-10 levels were analysed using ELISA

Key results

- No expression of cMET was detected in conventional T lymphocytes and regulatory T cells (0.36±0.13% and 0.55±0.20%, respectively)
- Monocytes expressed c-Met (15.95±2.97%)
- Expression of cMET was significantly higher in patients with a localised or metastatic tumour burden compared with those with no tumour burden (20.30±3.61 vs. 3.06±1.39, respectively; p=0.011)
- Production of HGF in plasma was high in patients with cMET expression of >5% in monocytes
- Monocytes adopted a pro-tolerogenic phenotype in the presence of HGF, potentially inducing regulatory T cell development

Hirsch L, et al. Ann Oncol 2018;29(suppl 5):abstr 4PD

Immune modulation/therapy
Discussant – David L

Presenter's take-home messages

- **Indirect targeting of HGF/cMET may interfere with immunosuppression by T regulatory cells**

Hirsch L, et al. Ann Oncol 2018;29(suppl 5):abstr 4PD

CANCERS OF THE PANCREAS, SMALL BOWEL AND HEPATOBILIARY TRACT

Cancers of the pancreas, small bowel and hepatobiliary tract

PANCREATIC AND BILIARY TRACT CANCERS

Molecular classification of biliary tract cancer leading to targeted therapy Discussant – Chau I

Study objective (Abstract LBA28 – Javle M, et al)

- **To assess the efficacy and safety of infigratinib in patients with previously treated advanced intrahepatic cholangiocarcinoma containing FGFR2 fusions**

Study design

- Patients (n=71) with histologically or cytologically confirmed advanced or metastatic intrahepatic cholangiocarcinoma with FGFR2 fusions or other FGFR genetic alterations received infigratinib monotherapy 125 mg/day (3-weeks on/1-week off) until PD

Key results

	Infigratinib (n=71)	95%CI
ORR (confirmed and unconfirmed), %	31.0	20.5, 43.1
Complete ORR, %	26.9	16.8, 39.1
DCR, %	83.6	72.5, 91.5
mOS, months	12.5	9.9, 16.6
mPFS, months	6.8	5.3, 7.6

- The most common grade 3/4 AEs occurring in >10% of patients were hypophosphatemia (14.1%) and hyperphosphatemia (12.7%)

Javle M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA28
Morizane C, et al. Ann Oncol 2018;29(suppl 5):abstr 623PD

Molecular classification of biliary tract cancer leading to targeted therapy
Discussant – Chau I

Study objective (SCRUM Japan GISCREEN: Abstract 623PD – Morizane C, et al)

- **To assess the frequency of cancer genome alterations in patients with advanced non-CRC GI cancer and facilitate enrolment of patients in clinical trials for targeted therapies in a nationwide cancer genome screening project in Japan (SCRUM)**

Study design

- In this prospective, observational study, patients (n=1656) with histologically confirmed or clinically high possibility of advanced non-CRC GI cancer were enrolled from April 2015 to March 2017

Key results

Primary tumour site	n	Median TMB, mt/Mb (range)	Frequency of TMB >20 mt/Mb, %
Intrahepatic bile duct	36	11.5 (0–57.5)	27.8
Extrahepatic bile duct	35	15.3 (3.8–49.9)	17.1
Gallbladder	14	21.1 (0–38.4)	50.0
Ampulla of Vater	7	15.3 (0–26.8)	14.3
Total	92	15.3 (0–57.5)	26.1

- Patients with FGFR2 (n=3), PTEN (n=1) and IDH1 mutations (n=1) were enrolled in clinical trials assessing an FGFR, AKT and Pan-mutant-IDH1 inhibitor, respectively

Javle M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA28
Morizane C, et al. Ann Oncol 2018;29(suppl 5):abstr 623PD

Molecular classification of biliary tract cancer leading to targeted therapy
Discussant – Chau I

Presenter's take-home messages

- **Nationwide genomic sequencing was feasible in detecting mutations in rare cancers such as advanced biliary tract cancer**
- **Enrolment of patients into biomarker-enriched prospective trials could allow for new targeted approaches to be explored**
- **There were differences in TMB between the various biliary tract sub-sites, with the highest being observed in the gallbladder primary site, so this may be a potential consideration for immuno-oncology combinations**
- **Further randomised phase III clinical trials are required to assess targeting FGFR2 genetic alterations**
  - **A placebo-controlled design may be acceptable to assess FGFR2 targeting as there would be no established active controls in 2L and 3L**
- **There is still an unmet need for FGFR2 inhibitors that can circumvent secondary resistant mutation mechanisms**

Javle M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA28
Morizane C, et al. Ann Oncol 2018;29(suppl 5):abstr 623PD

Non-CRC cancers
Discussant – O'Reilly EM

Study objective (CARRIE: Abstract LBA29 – Ko AH, et al)

- **To assess the efficacy and safety of a fixed-dose regimen of istiratumab in combination with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer and high free IGF-1**

Study design

- In CARRIE, a randomised, double-blind, placebo-controlled phase II study, patients (n=88) were randomised (2:1) to receive istiratumab 2.8 g iv (q2w) + nab-paclitaxel* and gemcitabine† vs. placebo iv (q2w) + nab-paclitaxel and gemcitabine†

Key results

- In the high IGF-1 cohort, mPFS was 3.6 vs. 7.3 months in the experimental vs. control arm

AE, n (%)	Istiratumab + nab-paclitaxel + gemcitabine (n=43)		Placebo + nab-paclitaxel + gemcitabine (n=45)	
	All grade	Grade ≥3	All grade	Grade ≥3
≥1 TEAE	43 (100)	32 (74.4)	44 (100)	33 (75.0)

- The most common TEAEs were diarrhoea, rash, decreased appetite, fatigue and nausea
- There were no SAEs leading to death in the experimental group vs. two in the control arm

Ko AH, et al. Ann Oncol 2018;29(suppl 5):abstr LBA29
Pruitt SK, et al. Ann Oncol 2018;29(suppl 5):abstr 625PD
Chang H, et al. Ann Oncol 2018;29(suppl 5):abstr 626PD

*125 mg/m^2 iv; †1000 mg/m^2 iv weekly (3-weeks on/1-week off)

Non-CRC cancers
Discussant – O'Reilly EM

Study objective (KEYNOTE-158: Abstract 625PD – Pruitt SK, et al)

- **To assess the efficacy and safety of pembrolizumab monotherapy in patients with unresectable and/or metastatic advanced biliary adenocarcinoma**

Study design

- In this single-arm, non-randomised trial of multiple cohorts, patients (n=104) received pembrolizumab 200 mg iv (q3w) for 2 years or until PD/survival follow-up after proven intolerance to standard therapy

Key results

	Overall (n=104)	PD-L1+ (n=61)	PD-L1– (n=34)
ORR*, % (95%CI)	5.8 (2.1, 12.1)	6.6 (1.8, 15.9)	2.9 (0.1, 15.3)
PR, n (%)	6 (6)	4 (7)	1 (3)
SD, n (%)	17 (16)	6 (10)	11 (32)
PD, n (%)	65 (63)	44 (72)	17 (50)

- mPFS and mOS was 2.0 months (95%CI 1.9, 2.1) and 9.1 (95%CI 5.6, 10.4), respectively
- Grade 3–4 TRAEs included increased blood alkaline phosphatase (1.9%) and pruritus, diarrhoea and pneumonitis (1.0% for each)

*Includes only confirmed responses

Ko AH, et al. Ann Oncol 2018;29(suppl 5):abstr LBA29
Pruitt SK, et al. Ann Oncol 2018;29(suppl 5):abstr 625PD
Chang H, et al. Ann Oncol 2018;29(suppl 5):abstr 626PD

Non-CRC cancers
Discussant – O'Reilly EM

Study objective (Abstract 626PD – Chang H, et al)

- **To assess the efficacy and safety of gemcitabine vs. gemcitabine + CRT in patients with curatively resected pancreatic ductal adenocarcinoma**

Study design

- Patients (n=147) were randomised to receive 6 cycles of gemcitabine 1000 mg/m^2 (n=74) vs. 3 cycles (before and after) of gemcitabine 400 mg/m^2 qw + CRT 180 cGy/28 fractions (n=73)

Key results

	Gemcitabine (n=74)	Gemcitabine + CRT (n=73)	HR (95%CI); p-value
mPFS, months	12.1	13.3	0.96 (0.67, 1.37); 0.80
mOS, months	23.5	21.5	1.07 (0.74, 1.55); 0.73
Local recurrence, %	56.8	41.1	NA; 0.056

- Grade 3/4 AEs were observed in 66% and 73% of patients in the gemcitabine vs. gemcitabine + CRT, respectively (p=0.34)

Ko AH, et al. Ann Oncol 2018;29(suppl 5):abstr LBA29
Pruitt SK, et al. Ann Oncol 2018;29(suppl 5):abstr 625PD
Chang H, et al. Ann Oncol 2018;29(suppl 5):abstr 626PD

Non-CRC cancers
Discussant – O'Reilly EM

Presenter's take-home messages

- **The CARRIE trial conducted by Ko et al. was a well-conducted randomised phase II trial that investigated selected biomarkers and carried out prospective tissue acquisition, but it had unanticipated results**
  - **The higher mPFS in the control vs. experimental arm may have been due to differences in selection, population size and toxicity in the experimental arm**
- **In Pruit et al., responses to single agent checkpoint inhibitors in patients with advanced biliary cancers appeared to be modest, but durable**
- **In Chang et al., adjuvant CRT was associated with a reduction in local recurrence, but the study had a small population size that may not be representative**
- **Combination of immuno-oncology or chemotherapy + immuno-oncology regimens should be investigated further**

Ko AH, et al. Ann Oncol 2018;29(suppl 5):abstr LBA29
Pruitt SK, et al. Ann Oncol 2018;29(suppl 5):abstr 625PD
Chang H, et al. Ann Oncol 2018;29(suppl 5):abstr 626PD

615O: Randomised phase III study of gemcitabine, cisplatin plus S-1 (GCS) versus gemcitabine, cisplatin (GC) for advanced biliary tract cancer (KHBO1401-MITSUBA) – Sakai D, et al

Study objective

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

Key patient inclusion criteria

- Histologically confirmed unresectable or recurrent biliary tract cancer
- No prior CT
- ECOG PS 0–2

(n=246)

R 1:1

GCS: Gemcitabine* + cisplatin† + S-1‡ (n=123) → PD

Stratification

- Unresectable vs. recurrent
- GBC vs. non GBC
- ECOG PS 0–1 vs. 2

GC: Gemcitabine* + cisplatin† (n=123) → PD

PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, OR, safety

*1000 mg/m^2; †25 mg/m^2 iv on D1, 8 q3w; ‡40–60 mg bid on D1–7

Sakai D, et al. Ann Oncol 2018;29(suppl 5):abstr 615O

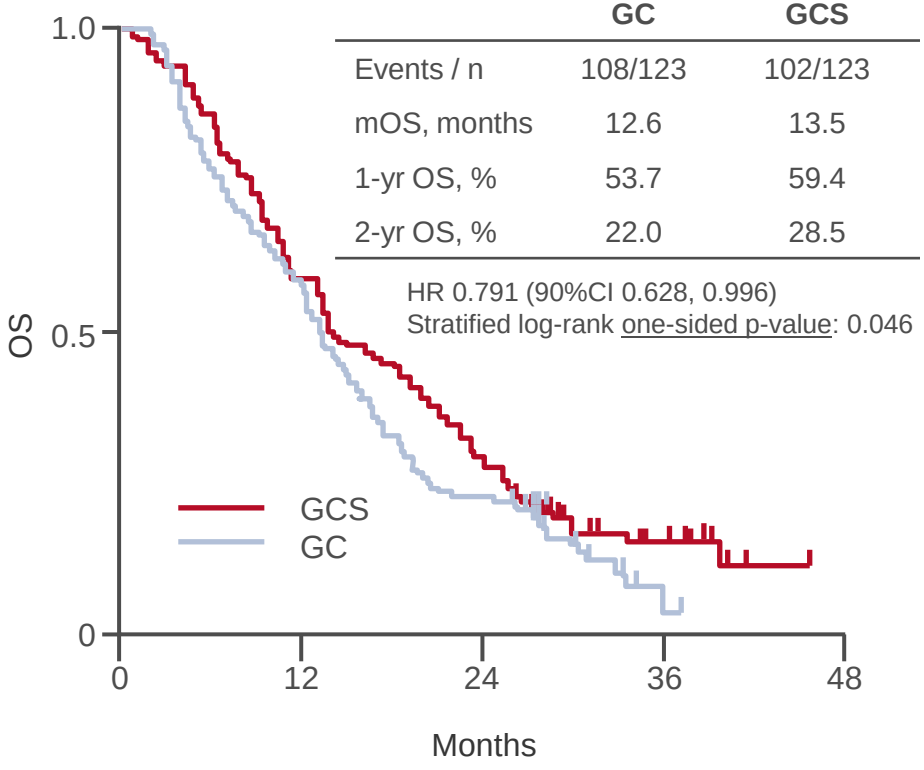
615O: Randomised phase III study of gemcitabine, cisplatin plus S-1 (GCS) versus gemcitabine, cisplatin (GC) for advanced biliary tract cancer (KHBO1401-MITSUBA) – Sakai D, et al

Key results

OS – ITT population

	GC	GCS
Events / n	108/123	102/123
mOS, months	12.6	13.5
1-yr OS, %	53.7	59.4
2-yr OS, %	22.0	28.5

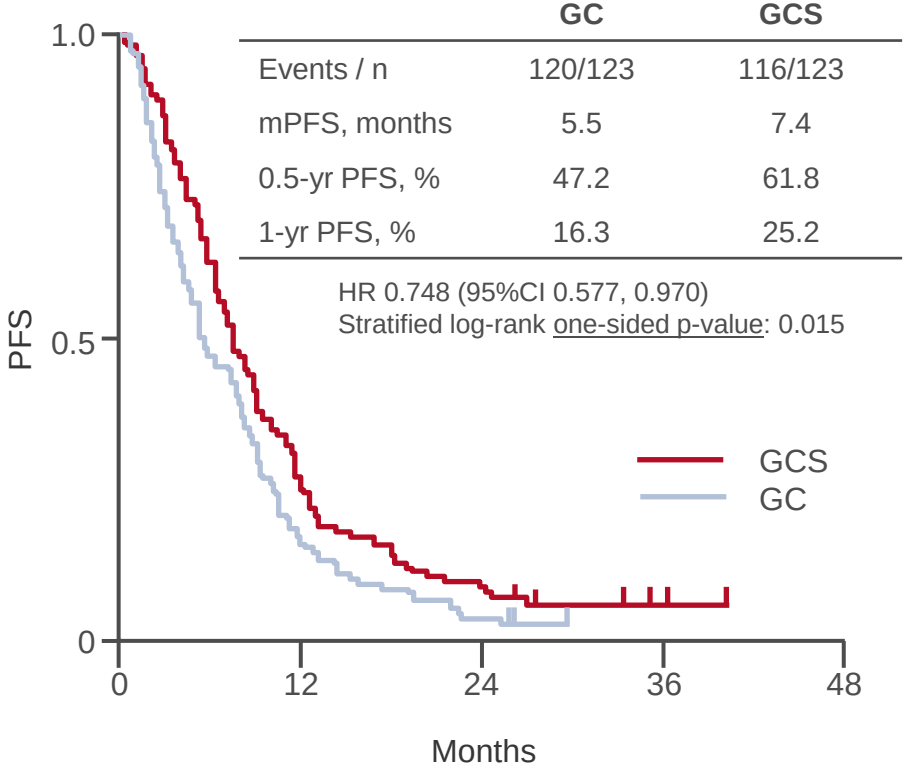
HR 0.791 (90%CI 0.628, 0.996)
Stratified log-rank one-sided p-value: 0.046



PFS – ITT population

	GC	GCS
Events / n	120/123	116/123
mPFS, months	5.5	7.4
0.5-yr PFS, %	47.2	61.8
1-yr PFS, %	16.3	25.2

HR 0.748 (95%CI 0.577, 0.970)
Stratified log-rank one-sided p-value: 0.015



GC, Gemcitabine + cisplatin; GCS, gemcitabine + cisplatin + S-1

Sakai D, et al. Ann Oncol 2018;29(suppl 5):abstr 615O

615O: Randomised phase III study of gemcitabine, cisplatin plus S-1 (GCS) versus gemcitabine, cisplatin (GC) for advanced biliary tract cancer (KHBO1401-MITSUBA) – Sakai D, et al

Key results (cont.)

Grade 3–4 AEs occurring in >10% of patients, n (%)	GC (n=122)	GCS (n=119)
Neutropenia	48	39
Anaemia	15	8
Thrombocytopenia	21	9
AST	20	15
ALT	16	13
Biliary tract infection	16	17

- There was one treatment-related death in each arm

Conclusions

- **In patients with advanced biliary tract cancer, gemcitabine + cisplatin + S-1 demonstrated improved OS compared with gemcitabine + cisplatin**
- **Based on these results, gemcitabine + cisplatin + S-1 may potentially be considered a new SoC for patients with advanced biliary tract cancer**

Sakai D, et al. Ann Oncol 2018;29(suppl 5):abstr 615O

Immunotherapy
Discussant – Keilholz U

Study objective (Abstract 1133PD – Hidalgo M, et al)

- **To assess the efficacy and safety of BL-8040, a high-affinity CXCR4 antagonist, + pembrolizumab in patients with metastatic pancreatic adenocarcinoma (COMBAT trial)**

Study design

- In this open-label, multicentre phase IIa trial, BL-8040 1.25 mg/kg sc monotherapy was administered on D1–5 followed by 3-week cycles of pembrolizumab 200 mg iv + BL-8040 1.25 mg/kg sc tiw on non-consecutive days for up to 2 years

Key results

- Modified ITT (mITT*; n=29), had a median treatment time of 72 (37–267) days
- In the mITT population, an ORR by RECIST v1.1 of PR with a ~40% reduction in tumour burden was found in 1 patient, 9 patients had SD and a total of 10 patients had disease control
- mOS in all patients (n=37) was 3.3 months with a 6-month survival rate of 34.4%
- In patients who received the treatment as 2L (n=17), mOS was 7.5 months with a 6-month survival rate of 51.5%
- There were 12 (18.9%) events of grade ≥3 TRAEs, with rash, eruptions and exanthemas the most common with 3 events followed by musculoskeletal and connective tissue pain with 2 events

*mITT refers to patients who received the combination treatment and had a post-baseline assessment for efficacy

Hidalgo M, et al. Ann Oncol 2018;29(suppl 5):abstr 1133PD

Immunotherapy
Discussant – Keilholz U

Presenter's take-home messages

- **Metastatic pancreatic adenocarcinoma has previously been shown to be unresponsive to immune checkpoint inhibitors alone, so this study should be commended for the disease control and mOS observed in patients who are heavily pre-treated**
- **Further research of this combination in patients with metastatic pancreatic cancer should be pursued**

Hidalgo M, et al. Ann Oncol 2018;29(suppl 5):abstr 1133PD

Cancers of the pancreas, small bowel and hepatobiliary tract

HEPATOCELLULAR CARCINOMA

LBA26: Updated safety and clinical activity results from a phase Ib study of atezolizumab + bevacizumab in hepatocellular carcinoma (HCC) – Pishvaian MJ, et al

Study objective

- To assess the efficacy and safety of bevacizumab combined with atezolizumab among patients with unresectable or advanced HCC

Key patient inclusion criteria

- Unresectable or advanced HCC
- Child-Pugh score ≤7
- No prior systemic therapy
- No prior treatment with anti-CTLA-4, anti-PD-(L)1 antibodies
- ECOG PS 0–1

(n=103)

→ Atezolizumab 1200 mg iv q3w + bevacizumab 15 mg/kg iv q3w →

PD/ toxicity/ loss of clinical benefit

PRIMARY ENDPOINTS

- Safety, ORR (RECIST v 1.1)

SECONDARY ENDPOINTS

- DoR, PFS, TTRP, OS

Pishvaian MJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA26

LBA26: Updated safety and clinical activity results from a phase Ib study of atezolizumab + bevacizumab in hepatocellular carcinoma (HCC) – Pishvaian MJ, et al

Key results

- There were no new safety signals were identified beyond the existing safety profile for each treatment

AEs, n (%)	n=103
Any-grade	95 (92)
Treatment-related	84 (82)
Grade 3/4	41 (40)
Treatment-related	28 (27)
Most common (occurring in ≥20% of patients)	
Decreased appetite	29 (28)
Fatigue	21 (20)
Rash	21 (20)
Pyrexia	21 (20)

ORR	
Overall, n (%)*	23/73 (32)
CR	1/73 (1)
PR	22/73 (30)
SD	33/73 (45)
PD	13/73 (18)
PFS*, months	
Median (range)	14.9 (0.5–23.9+)

*Data from 4 (6%) patients not evaluable or missing

Pishvaian MJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA26

LBA26: Updated safety and clinical activity results from a phase Ib study of atezolizumab + bevacizumab in hepatocellular carcinoma (HCC) – Pishvaian MJ, et al

Conclusions

- **In patients with HCC, atezolizumab + bevacizumab demonstrated promising activity and durable responses**
- **Atezolizumab + bevacizumab was generally tolerable with no new safety signals observed**

Pishvaian MJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA26

LBA27: A randomized multicentered phase 2 study to evaluate SHR-1210 (PD-1 antibody) in subjects with advanced hepatocellular carcinoma (HCC) who failed or intolerable to prior systemic treatment – Qin SK, et al

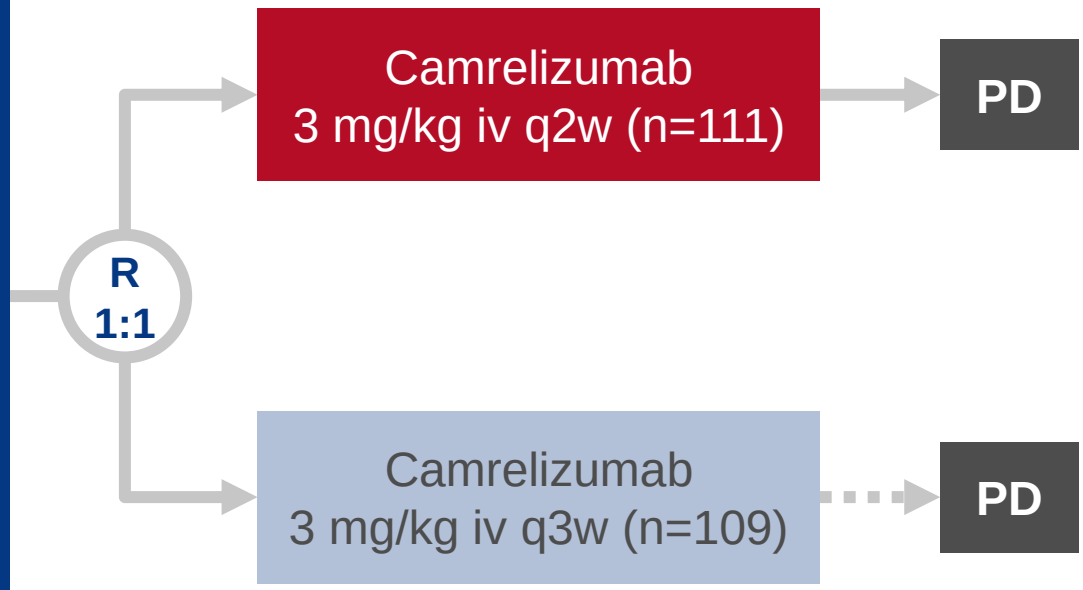
Study objective

- To assess the efficacy and safety of camrelizumab (SHR-1210) in Chinese patients with advanced HCC

Key patient inclusion criteria

- Histologically or cytologically confirmed advanced HCC
- Progressed on or intolerant to ≥1 prior systemic therapy
- Not amenable to surgery or local treatment
- Child-Pugh A or B (≤7)
- ≥1 measurable lesion
- ECOG PS 0–1

(n=220)



PRIMARY ENDPOINTS

- ORR, 6-month OS rate

SECONDARY ENDPOINTS

- DCR, DoR, TTP, TTR, PFS, OS, safety

Qin SK, et al. Ann Oncol 2018;29(suppl 5):abstr LBA27

LBA27: A randomized multicentered phase 2 study to evaluate SHR-1210 (PD-1 antibody) in subjects with advanced hepatocellular carcinoma (HCC) who failed or intolerable to prior systemic treatment – Qin SK, et al

Key results

	All (n=217)	q2w group (n=109)	q3w group (n=108)
Confirmed ORR, n (%) [95%CI]	30 (13.8) [9.5, 19.1]	12 (11.0) [5.8, 18.4]	18 (16.7) [10.2, 25.1]
Best OR, n (%)			
CR	0	0	0
PR	30 (13.8)	12 (11.0)	18 (16.7)
SD	67 (30.9)	40 (36.7)	27 (25.1)
PD	98 (45.2)	44 (40.4)	54 (50.1)
Not evaluable	22 (10.1)	13 (11.9)	9 (8.3)
OS rate at 6 months, % (95%CI)	74.7 (68.3, 79.9)	76.1 (67.0, 83.1)	73.1 (63.7, 80.5)
DCR, n (%) [95%CI]	97 (44.7) [38.0, 51.6]	52 (47.7) [38.1, 57.5]	45 (41.7) [32.3, 51.5]
Median TTR, months (range)	2.0 (1.7–6.2)	2.0 (1.7–6.1)	2.1 (1.9–6.2)
Median DoR, months (range)	NR (2.5–15.4+)	NR (2.5–15.4+)	NR (2.5–12.4+)
Ongoing responses, n/N (%)	22/30 (73.3)	9/12 (75.0)	13/18 (72.2)
Median TTP, months (95%CI)	2.6 (2.0, 3.3)	3.2 (1.9, 3.4)	2.1 (2.0, 3.4)
Median PFS, months (95%CI)	2.1 (2.0, 3.2)	2.3 (1.9, 3.2)	2.0 (2.0, 3.2)

Qin SK, et al. Ann Oncol 2018;29(suppl 5):abstr LBA27

LBA27: A randomized multicentered phase 2 study to evaluate SHR-1210 (PD-1 antibody) in subjects with advanced hepatocellular carcinoma (HCC) who failed or intolerable to prior systemic treatment – Qin SK, et al

Key results (cont.)

Patients, n (%)	All (n=217)	q2w group (n=109)	q3w group (n=108)
All grade TRAEs	197 (90.8)	99 (90.8)	98 (90.7)
Grade 3/4	42 (19.4)	21 (19.3)	21 (19.4)
Led to death	2 (0.9)	2 (1.8)	0
Serious TRAEs	21 (9.7)	14 (12.8)	7 (6.5)
Led to permanent discontinuation of treatment	6 (2.8)	3 (2.8)	3 (2.8)
Led to temporary discontinuation of treatment	30 (13.8)	18 (16.5)	12 (11.1)

Conclusions

- **In pre-treated Chinese patients with advanced HCC, camrelizumab dosed q2w and q3w provided clinically meaningful efficacy and was generally well tolerated**
- **Although sorafenib-experienced patients in this study had poorer baseline characteristics than in studies of nivolumab and pembrolizumab, camrelizumab demonstrated comparable efficacy and safety**

Qin SK, et al. Ann Oncol 2018;29(suppl 5):abstr LBA27

Discussant – Cheng A

Study objective (REACH and REACH-2: Abstract 622PD – Zhu AX, et al)

- **To assess the efficacy and safety of ramucirumab and BSC vs. placebo and BSC in two global phase III studies of patients with HCC after prior sorafenib (REACH and REACH-2)**

Study design

- Patients (n=565 in REACH; n=292 in REACH-2) were randomised (1:1 and 2:1, respectively) to ramucirumab 8 mg/kg iv q2w per cycle and BSC vs. placebo q2w per cycle and BSC
- Patients (n=250) from the REACH trial with baseline AFP ≥400 ng/mL were pooled with those from REACH-2

Key results

Time to deterioration in FHSI-8 total score	Ramucirumab (n=316)	Placebo (n=226)	HR (95%CI)	p-value
Events	154	104	0.725 (0.559, 0.941)	0.0152
Median, months	3.3	1.9		

- A significant trend towards a delay in clinically meaningful deterioration was observed with ramucirumab in the REACH (AFP ≥400 ng/mL) and REACH-2 studies

FHSI-8, FACT Hepatobiliary Symptom Index

Zhu AX, et al. Ann Oncol 2018;29(suppl 5):abstr 622PD

Discussant – Cheng A

Presenter's take-home messages

- **The investigators of the REACH studies should be commended for showing a consistent trend in reducing disease-related symptoms with ramucirumab monotherapy as a 2L treatment for patients with HCC**

Zhu AX, et al. Ann Oncol 2018;29(suppl 5):abstr 622PD

Cancers of the pancreas, small bowel and hepatobiliary tract

NEUROENDOCRINE TUMOUR

Neuroendocrine tumours
Discussant – Grande E

Study objective (Abstract 1312PD – Walter T, et al)

- **To assess the efficacy and safety of everolimus after TALT of metastases from GI NETs in patients with hepatic disease progression (FFCD 1104-EVACEL-GTE trial)**

Study design

- In this single-arm phase II study, patients (n=74) with grade 1/2 NETs of the GI tract with hepatic disease progression within one year received TALT followed 7 days later by everolimus 10 mg/day for up to 24 months or until disease progression

Key results

- Hepatic PFS rate at 24 months was 30% (95%CI 21, 40), with a median hepatic PFS of 18 (95%CI 13, 22) months and mPFS of 17 months (95%CI 12, 22)
- mOS was 51 months (95%CI 33, 60) and ORR was 54%
- The most common grade >2 AEs occurring in >10% of patients were elevated liver enzymes (55%), fatigue (18%), diarrhoea (16%) and anaemia (12%)

Walter T, et al. Ann Oncol 2018;29(suppl 5):abstr 1312PD
Okuyama H, et al. Ann Oncol 2018;29(suppl 5):abstr 1313PD

Neuroendocrine tumours
Discussant – Grande E

Study objective (Abstract 1313PD – Okuyama H, et al)

- **To assess the efficacy and safety of everolimus in patients with pancreatic neuroendocrine carcinoma refractory or intolerant to platinum-based CT**

Study design

- Patients (n=25) with histologically confirmed pancreatic NEC and ECOG PS 0–2 received everolimus 10 mg/day until disease progression or toxicity

Key results

- Median treatment duration was 35.0 days (range 3–263)
- mPFS (n=23) was 1.15 months (95%CI 0.9, 3.1) with a 3-month PFS rate of 32%
- mOS (n=23) was 7.5 months (95%CI 3.1, 13.5)
- Grade ≥3 AEs occurring in >10% of patients included hyperglycaemia (20%), anaemia (16%), thrombocytopenia (16%) and hyponatremia (12%)

Walter T, et al. Ann Oncol 2018;29(suppl 5):abstr 1312PD
Okuyama H, et al. Ann Oncol 2018;29(suppl 5):abstr 1313PD

Neuroendocrine tumours
Discussant – Grande E

Presenter's take-home messages

- **The study by Walter et al., is the first to assess everolimus after TALT in GI NETs but the primary endpoint was not met and liver toxicity appeared to be high**
- **The study did not clarify whether targeted therapy should be used immediately after TALT or until progression?**
- **In the study by Okuyama et al., the response to treatment was comparable to other targeted therapies, with a long-lasting activity observed in 2 patients and may be a potential treatment option for those patients who are ineligible to receive platinum-based CT**
- **There remains an unmet need in patients with grade 3 NETs and neuroendocrine carcinomas**

Walter T, et al. Ann Oncol 2018;29(suppl 5):abstr 1312PD
Okuyama H, et al. Ann Oncol 2018;29(suppl 5):abstr 1313PD

CANCERS OF THE COLON, RECTUM AND ANUS

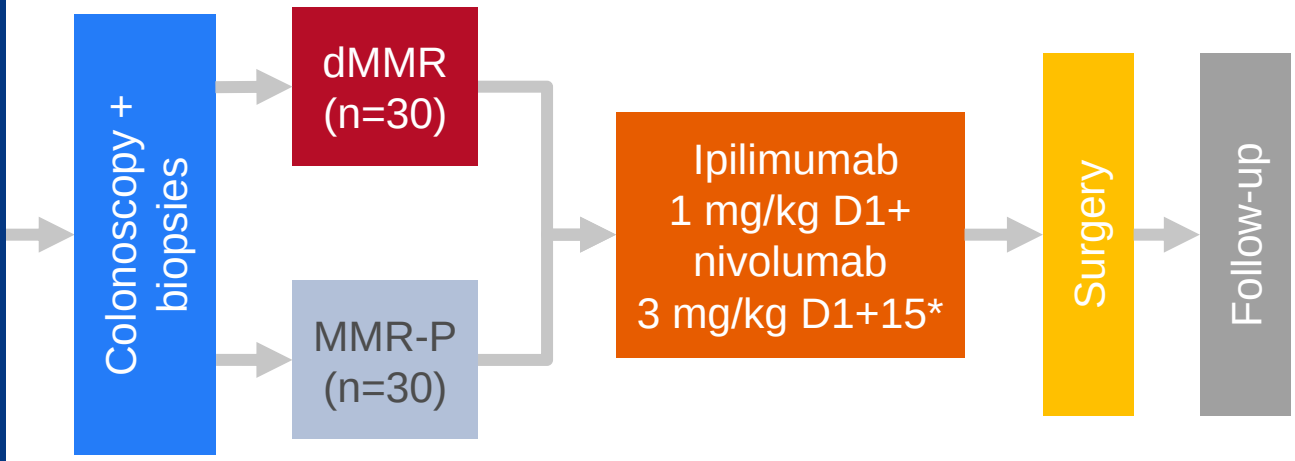
LBA37_PR: Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer – Chalabi M, et al

Study objective

- To assess the efficacy and safety of neoadjuvant ipilimumab + nivolumab in patients with early stage colon cancer

Key patient inclusion criteria

- Histologically confirmed colon cancer (no rectal cancer)
- No distant metastases
- No signs of perforation or clinical bowel obstruction



PRIMARY ENDPOINTS

- Safety/feasibility

SECONDARY ENDPOINTS

- Efficacy, association between response and TMB, IFNγ, gene signatures, T-cell infiltration, TCR clonality

*Half of the MMR-P patients received celecoxib and other combinations in addition to study treatment

Chalabi M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA37_PR

LBA37_PR: Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer – Chalabi M, et al

Key results

- Of 19 patients included, 14 were evaluable; median duration from treatment to surgery was 32 days (IQR 28–35)
- There were no delays to surgery as a result of safety

TRAEs (n=14)	Grade 1/2, n (%)	Grade 3, n (%)
Total	10 (71)	5 (36)
Sarcoid-like reaction	1 (7)	0
Abdominal pain*	0	1 (7)
Rash	0	1 (7)
Dry mouth	4 (29)	0
Infusion reaction	2 (14)	0
Dry skin	1 (7)	0
Arthritis	1 (7)	0
Diarrhoea	1 (7)	0
Abdominal infection	0	1 (7)
Anastomotic leak	0	1 (7)
Pneumonia	0	1 (7)

Post-operative**

*Abdominal pain due to pseudoprogression;
**not attributable to immune checkpoint inhibitor

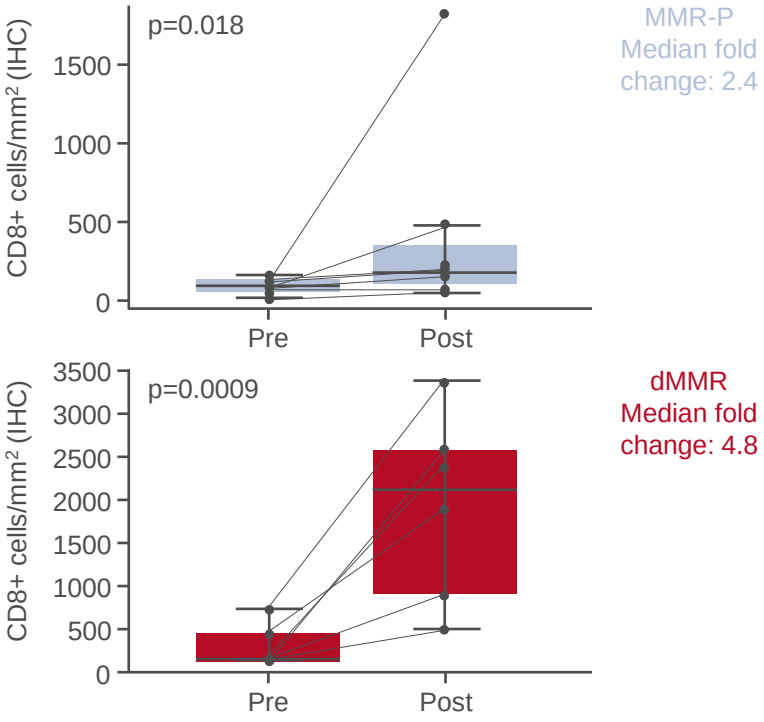
Chalabi M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA37_PR

LBA37_PR: Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer – Chalabi M, et al

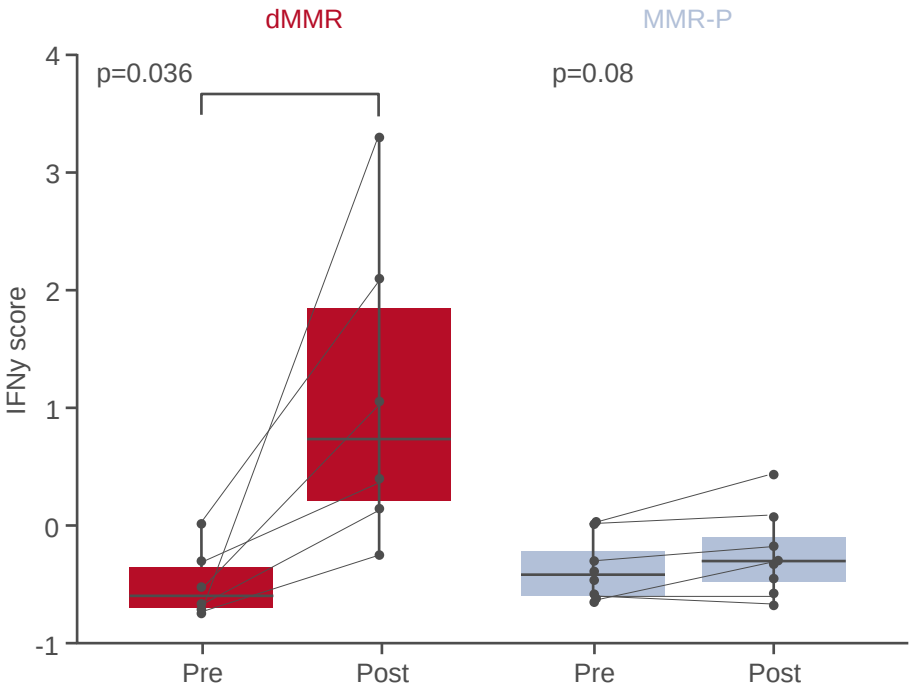
Key results (cont.)

- A major response was observed in all dMMR tumours
- Pre-treatment CD3 infiltration was not predictive of response to treatment

CD8+ T-cells increased in both dMMR and MMR-P tumours



IFNγ score significantly increased post-treatment



Chalabi M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA37_PR

LBA37_PR: Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer – Chalabi M, et al

Key results (cont.)

- TCR clonality pre- and post-treatment was not significantly different in dMMR or MMR-P
- Pre-treatment immune gene signatures were not predictive of response to treatment

Conclusions

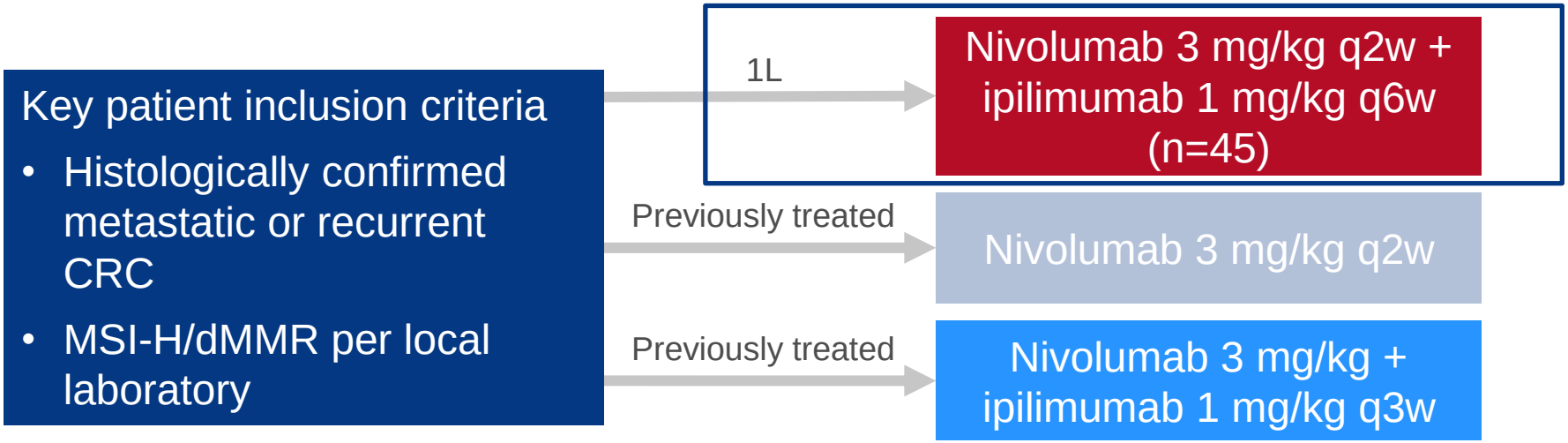
- **In patients with early stage colon caner, short pre-operative treatment with ipilimumab + nivolumab was safe and associated with major pathological responses in all dMMR tumours**
- **Tumour inflammation measures at pre-treatment were not predictive of response**
- **These findings need to be confirmed in larger trials**

Chalabi M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA37_PR

LBA18_PR: Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

Study objective

- To assess the efficacy and safety of nivolumab + low-dose ipilimumab used as 1L therapy in patients with MSI-H/dMMR mCRC in the CheckMate-142 study



PRIMARY ENDPOINT

- ORR (investigator assessed RECIST v1.1)

SECONDARY ENDPOINTS

- ORR by blinded independent review, DCR*, DoR, PFS, OS and safety

*Patients with a CR, PR or SD for ≥12 weeks divided by the number of treated patients

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

LBA18_PR: Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

Key results

Investigator-assessed	Nivolumab 3 mg/kg q2w + ipilimumab 1 mg/kg q6w (n=45)
ORR*, n (%) [95%CI]	27 (60) [44.3, 74.3]
Best OR, n (%)	
CR	3 (7)
PR	24 (53)
SD	11 (24)
PD	6 (13)
Not determined	1 (2)
DCR, n (%) [95%CI]	38 (84) [70.5, 93.5]
12-month PFS rate, % (95%CI)	77 (62.0, 87.2)
12-month OS rate, % (95%CI)	83 (67.6, 91.7)

- Responses were observed regardless of tumour PD-L1 expression, *BRAF* or *KRAS* mutation status or diagnosis of Lynch syndrome
  - In the 17 patients with a BRAF mutation, ORR was 71% and DCR was 88%

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

LBA18_PR: Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

Key results (cont.)

- A reduction in tumour burden from baseline was observed in 84% of patients

*Confirmed response per investigator assessment;
†evaluable patients per investigator assessment

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

LBA18_PR: Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

Key results (cont.)

	Nivolumab 3 mg/kg q2w + ipilimumab 1 mg/kg q6w (n=45)	
Patients, n (%)	Any grade	Grade 3–4
Any TRAE	35 (78)	7 (16)
Any serious	6 (13)	3 (7)
Any serious TRAE leading to discontinuation	3 (7)	1 (2)
TRAE reported in >10% of patients		
Pruritus	11 (24)	0
Hypothyroidism	8 (18)	1 (2)
Asthenia	7 (16)	1 (2)
Arthralgia	6 (13)	0
Lipase increased	5 (11)	0
Nausea	5 (11)	0
Rash	5 (11)	0

Conclusions

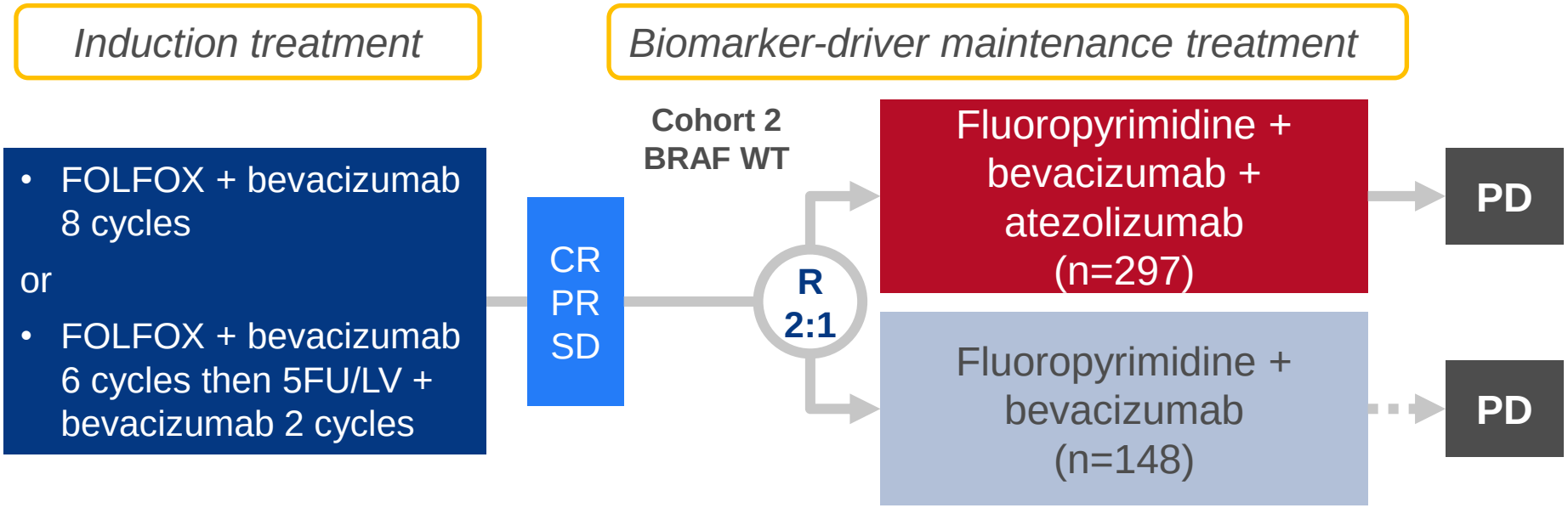
- **In patients with MSI-H/dMMR mCRC, 1L nivolumab + low-dose ipilimumab demonstrated robust and durable clinical benefit and was generally well-tolerated**
- **Nivolumab + low-dose ipilimumab may be a potential new 1L treatment option for this patient population**

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

LBA19: Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

Study objective

- To assess the efficacy and safety of fluoropyrimidine + bevacizumab + atezolizumab as a 1L maintenance treatment in patients with MSS mCRC in Cohort 2 of the MODUL study (Cohort 1, BRAF mutant; Cohort 3, HER2+; and Cohort 4, HER2-, BRAF WT)



PRIMARY ENDPOINTS

- PFS (RECIST v1.1)

SECONDARY ENDPOINTS

- OS, ORR, DCR, TTR, DoR, change in ECOG and safety

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

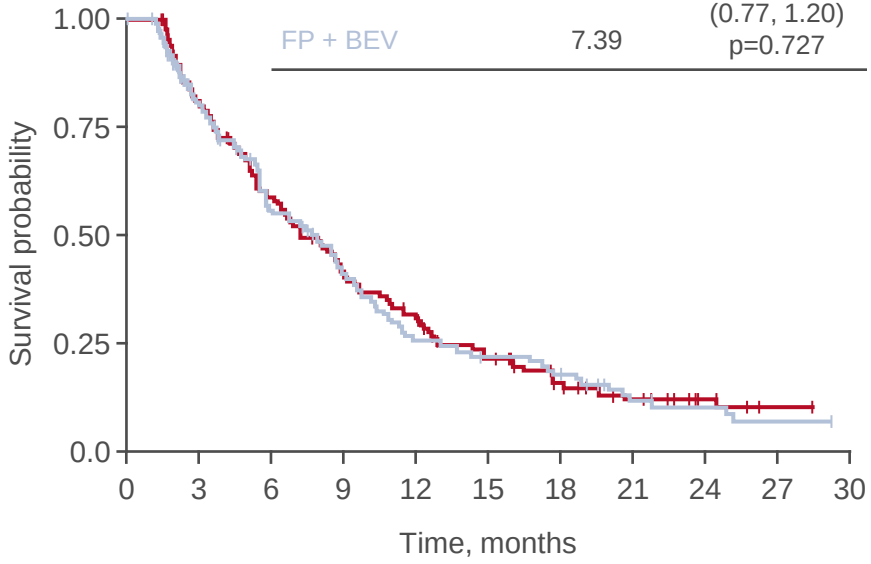
LBA19: Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

Key results

PFS and OS (median follow-up 18.7 months)

PFS

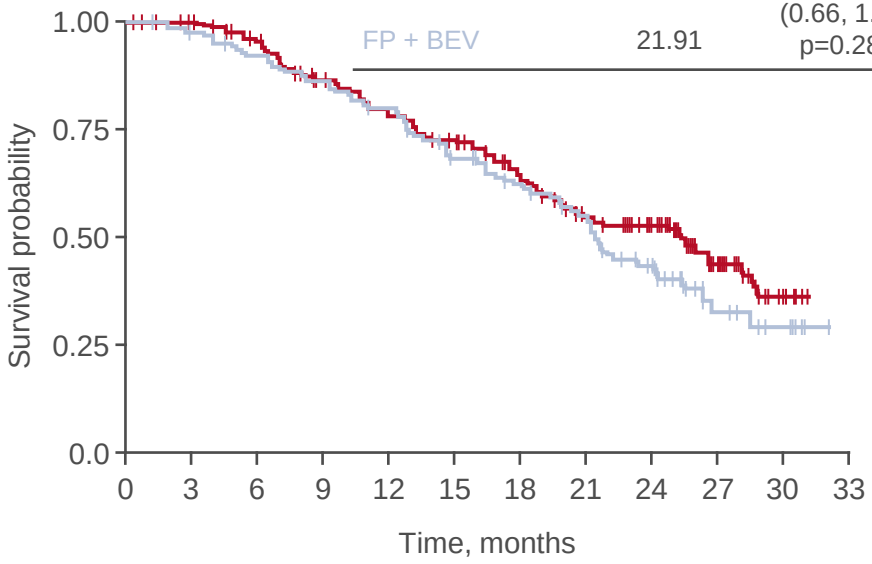
	mPFS, months	Stratified HR (95%CI)
FP + BEV + ATZ	7.20	0.96 (0.77, 1.20) p=0.727
FP + BEV	7.39	



No. at risk											
FP + BEV + ATZ	297	224	147	103	70	49	29	16	6	1	1
FP + BEV	148	109	74	55	29	21	17	6	3	1	0

OS

	mOS, months	Stratified HR (95%CI)
FP + BEV + ATZ	22.05	0.86 (0.66, 1.13) p=0.283
FP + BEV	21.91	



297	293	275	244	214	189	164	104	70	28	8	0
148	142	130	120	108	94	79	49	30	14	5	0

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

LBA19: Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

Key results (cont.)

Patients, n (%)	Fluoropyrimidine + bevacizumab + atezolizumab (n=293)	Fluoropyrimidine + bevacizumab (n=143)
TEAE	276 (94.2)	124 (86.7)
Grade ≥3	110 (37.5)	43 (30.1)
Grade 5	3 (1.0)*	1 (0.7)†
Any serious TEAE	28 (9.6)	6 (4.2)
TEAE leading to treatment discontinuation	36 (12.3)	16 (11.2)

Conclusions

- **In patients with BRAF WT mCRC, combining atezolizumab with fluoropyrimidine + bevacizumab as a 1L maintenance therapy did not lead to improvements in survival (PFS and OS)**
- **No new safety signals were identified for atezolizumab + fluoropyrimidine + bevacizumab**

*Septic shock, heart attack, recurrent pseudomonas chest infection; †colonic perforation

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

LBA20: TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts) – Cremolini C, et al

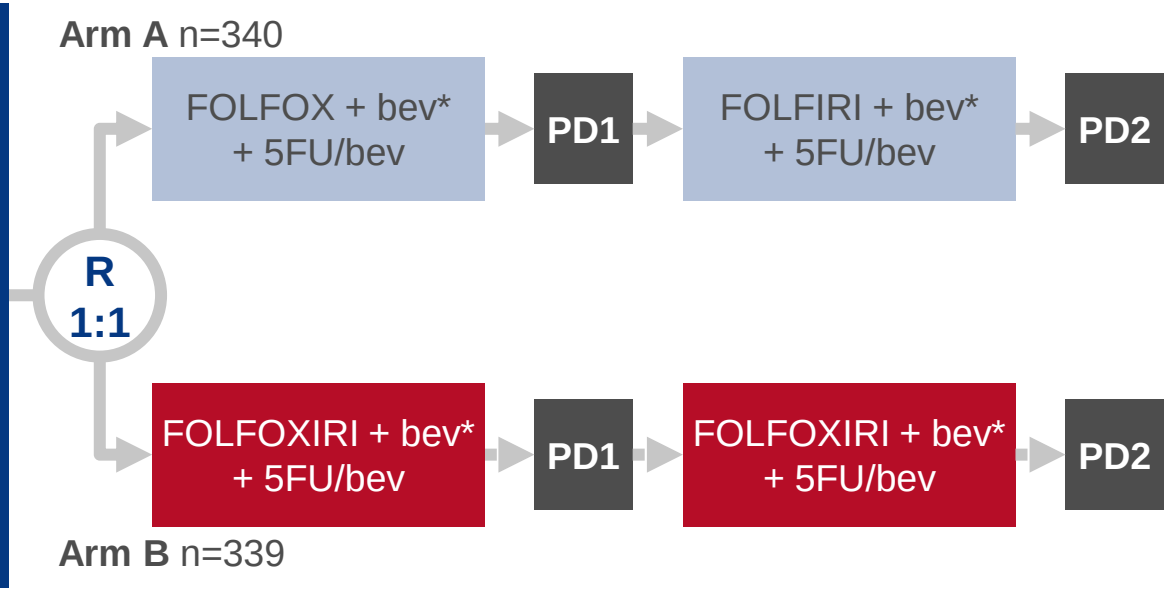
Study objective

- To assess whether three active chemotherapy agents (triplet FOLFOXIRI) upfront is more beneficial than a pre-planned sequential strategy in 2 subsequent lines of therapy (FOLFOX – FOLFIRI) combined with sustained antiangiogenic treatment

Key patient inclusion criteria

- Unresectable (locally assessed) mCRC not pre-treated for metastasis
- No adjuvant oxa-containing CT
- Adjuvant fluoropyrimidine permitted if completed >6 months before relapse
- ECOG PS ≤2 (or PS =0 if 71–75 years of age)

(n=679)



PRIMARY ENDPOINT

- PFS2

SECONDARY ENDPOINT

- PFS1

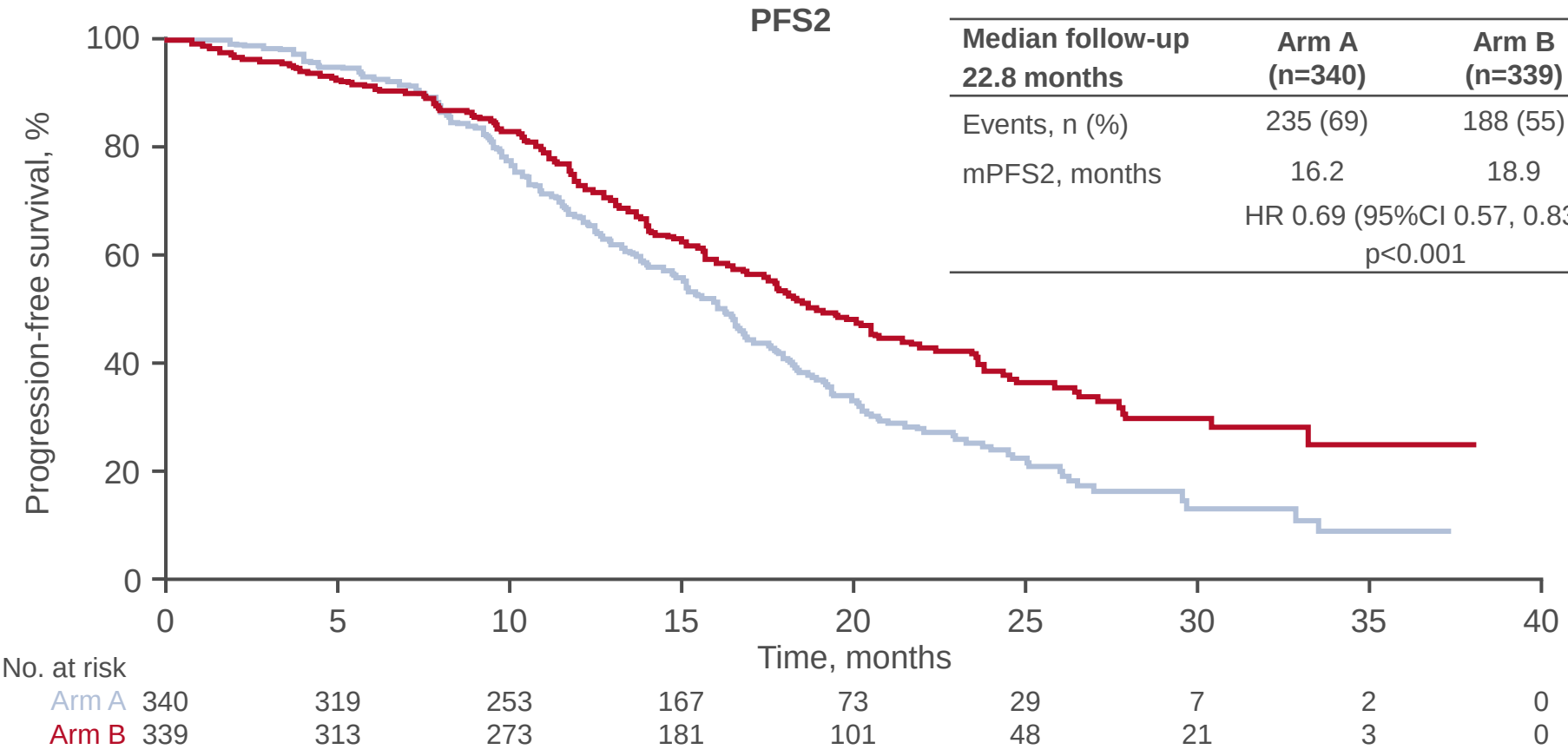
*Up to 8 cycles

Cremolini C, et al. Ann Oncol 2018;29(suppl 5):abstr LBA20

LBA20: TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts) – Cremolini C, et al

Key results

- FOLFOXIRI/bevacizumab followed by the reintroduction of the same agents after PD was superior to pre-planned sequential strategy of FOLFOX/bevacizumab followed by FOLFIRI/bevacizumab



Median follow-up 22.8 months	Arm A (n=340)	Arm B (n=339)
Events, n (%)	235 (69)	188 (55)
mPFS2, months	16.2	18.9
	HR 0.69 (95%CI 0.57, 0.83) p<0.001	

Cremolini C, et al. Ann Oncol 2018;29(suppl 5):abstr LBA20

LBA20: TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts) – Cremolini C, et al

Key results (cont.)

- 1L FOLFOXIRI/bevacizumab was associated with a higher response rate than FOLFOX/bevacizumab (61% vs. 50%; p=0.005) and a longer PFS (12.0 vs. 9.9 months, HR 0.73 [95%CI 0.62, 0.87]; p<0.001)
- OS results are immature (around 40% of events)
- AEs were similar between the two treatment groups, but compared with FOLFOX/bevacizumab, 1L FOLFOXIRI/bevacizumab was associated with a higher incidence of diarrhoea (5% vs. 17%), neutropenia (21% vs. 50%) and febrile neutropenia (3% vs. 7%)
- In total, 86% and 74% of patients received treatment after progression on FOLFOX/bevacizumab and FOLFOXIRI/bevacizumab, respectively

Cremolini C, et al. Ann Oncol 2018;29(suppl 5):abstr LBA20

LBA20: TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts) – Cremolini C, et al

Conclusions

- In patients with unresectable mCRC, FOLFOXIRI/bevacizumab was superior to a pre-planned strategy of sequential exposure of the same agents
- 1L treatment with FOLFOXIRI/bevacizumab does not compromise the feasibility and the efficacy of therapies after progression
- The findings of this study for FOLFOXIRI/bevacizumab are comparable to those of the previous phase III TRIBE study

Cremolini C, et al. Ann Oncol 2018;29(suppl 5):abstr LBA20

452O: DPYD genotype-guided dose individualization of fluoropyrimidine therapy: A prospective safety and cost-analysis on DPYD variants DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A – Henricks LM, et al

Study objective

- To assess whether upfront DPYD genotyping and dose individualisation of fluoropyrimidine treatment reduces the risk of severe (grade ≥3) fluoropyrimidine-related toxicity

Methods

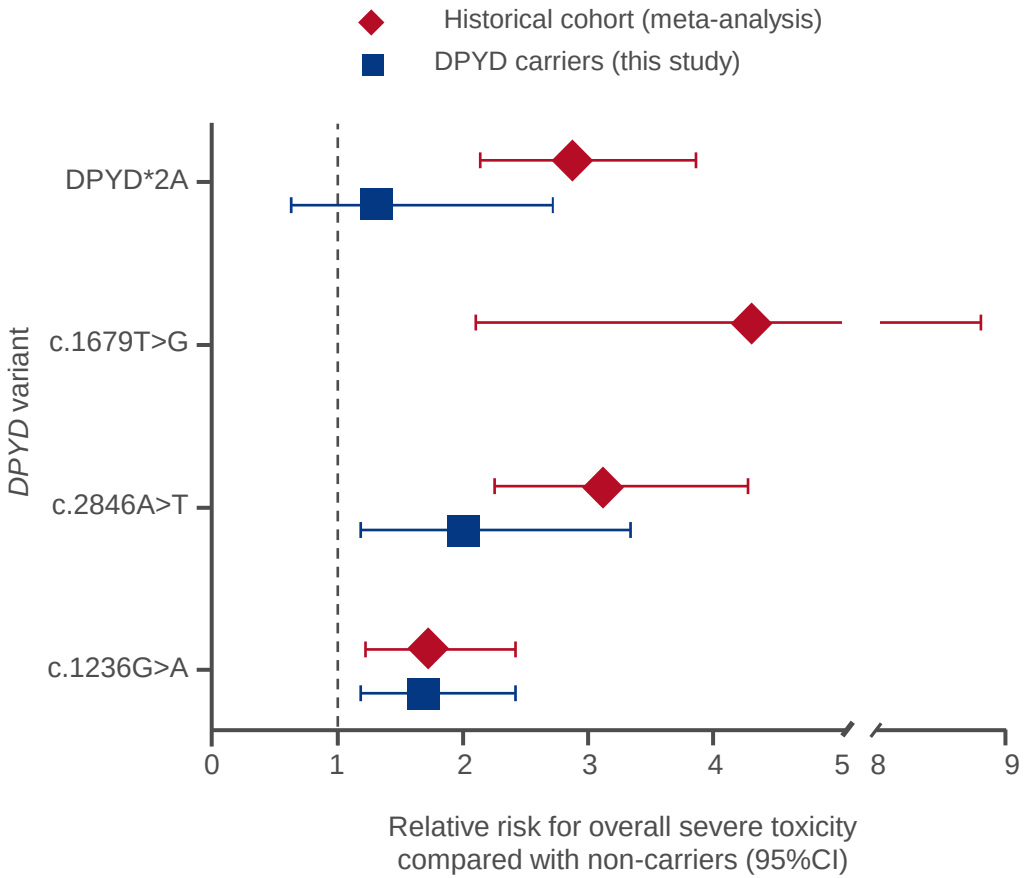
- DPYD genotyping DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A was prospectively performed in patients prior to start of fluoropyrimidine-based therapy
- Patients who were heterozygous DPYD variant carriers received an initial dose reduction of 25% (c.2846A>T, c.1236G>A) or 50% (DPYD*2A, c.1679T>G)
- Incidence of severe (grade ≥3) toxicity in DPYD variant carriers (n=85) was compared with WT patients (n=1018) in the study, as well as a historical cohort of DPYD variant carriers treated with full dose

Henricks LM, et al. Ann Oncol 2018;29(suppl 5):abstr 452O

452O: DPYD genotype-guided dose individualization of fluoropyrimidine therapy: A prospective safety and cost-analysis on DPYD variants DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A – Henricks LM, et al

Key results

- The risk of severe toxicity was decreased with DPYD genotyping
- The risk of hospitalisation was similar between DPYD carriers and WT patients in this study
- There were no toxicity-related deaths in patients with DPYD genotype-guided dosing



Henricks LM, et al. Ann Oncol 2018;29(suppl 5):abstr 452O

452O: DPYD genotype-guided dose individualization of fluoropyrimidine therapy: A prospective safety and cost-analysis on DPYD variants DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A – Henricks LM, et al

Results (cont.)

- PK analyses demonstrated that drug exposure was similar in DPYD-guided and WT patients
- The DPYD genotyping strategy was associated with cost-saving

Conclusions

- **Improvements in patient safety were achieved with the use of upfront DPYD genotyping, a strategy that is feasible in routine clinical practice and results in cost-savings**
- **These findings suggest that DPYD genotype-guided dosing should be used as the new SoC**

Henricks LM, et al. Ann Oncol 2018;29(suppl 5):abstr 452O

1O: KRAS mutant and RAS/BRAF wild type colorectal cancer cells exhibit differences in the rewiring of signal transduction that can impact on future therapeutic strategies – Georgiou A, et al

Study objective

- To assess the changes in phosphoproteins following exposure to signalling inhibitors in human CRC cell lines and determine whether or not there are any differences in signalling patterns between RAS WT and KRAS mutant cells

Methods

- A total of 15 RAS WT and 10 KRAS mutant human CRC line models were used in conjunction with pleural effusions and ascites derived from 13 patients
- Cells were exposed to targeted agents (gefitinib, pictilisib, AZD5363, everolimus, trametinib and vemurafenib) for 1 hour; Luminex200® multiplex antibody based platform was used to simultaneously quantify 55 phosphoproteins (relating to TK receptors, non-TK receptors, angiogenesis receptors, MAPK pathway, JNK pathway, P13K pathway, JAK/STAT pathway, Wnt B-catenin, cell cycle and immune response)
  - Only those changes ± 2 standard deviations of the mean (of controls) were considered important

Georgiou A, et al. Ann Oncol 2018;29(suppl 5):abstr 1O

1O: KRAS mutant and RAS/BRAF wild type colorectal cancer cells exhibit differences in the rewiring of signal transduction that can impact on future therapeutic strategies – Georgiou A, et al

Key results

- In both RAS WT and KRAS mutant cell lines, the most commonly downregulated phosphoproteins were targeted phosphoproteins (e.g. pEGFR) and effector phosphoproteins downstream of the drug targets (e.g. pRPS6, p70-S6K, pMSK1)
- Logistic regression showed that compared with RAS WT cells, pMEK upregulation was significantly higher in KRAS mutant cells following 1-hour exposure to gefitinib, pictilisib and everolimus ($p<0.05$)
- pMEK upregulation occurred in both KRAS mutant and RAS WT cells exposed to vemurafenib
- PI3K inhibition with pictilisib in KRAS mutant cells was associated with significant differences in phosphoproteins, leading to upregulation of selected phosphoproteins in the MAPK and PI3K pathways
  - P13K inhibitor GI_{50} correlated with phosphoprotein changes

Georgiou A, et al. Ann Oncol 2018;29(suppl 5):abstr 1O

1O: KRAS mutant and RAS/BRAF wild type colorectal cancer cells exhibit differences in the rewiring of signal transduction that can impact on future therapeutic strategies – Georgiou A, et al

Key results (cont.)

- EGFR inhibition with gefitinib was also associated with significant differences, namely upregulation of selected phosphoproteins in the MAPK and PI3K pathways
  - Sensitivity to gefitinib correlated with phosphoprotein changes
- The phosphoproteomic changes with EGFR inhibition observed in patient samples showed greater variability than observed in the cell lines
- Resistance was observed in RAS WT patients with previous exposure to cetuximab. The changes in phosphoproteins reflect that of KRAS mutant cell lines with additional upregulation of numerous pRTKs in RAS WT cells

Conclusions

- **Following exposure to targeted therapies, significant differences exist in the rewiring of signal transduction between KRAS mutant and RAS WT CRC cells**
- **When planning future combinations of targeted treatments, the different signal transduction findings should be considered**
  - **For example, in patients with KRAS mutant CRC, MEK or ERK inhibition should be assessed**

Georgiou A, et al. Ann Oncol 2018;29(suppl 5):abstr 1O

453PD: 1st-line mFOLFOXIRI + panitumumab vs FOLFOXIRI treatment of RAS wt mCRC: a randomized phase II VOLFI tiral of the AIO (KRK-0109) – Geissler M, et al

Study objective

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

Study design

- Patients (n=96) were randomised (2:1) to mFOLFOXIRI* + panitumumab 6 mg/kg q2w vs. FOLFOXIRI† q2w until PD, resectability or a maximum of 12 cycles

Key results

	mFOLFOXIRI + panitumumab (n=63)	FOLFOXIRI (n=33)	OR (95%CI); p-value
ORR, % (95%CI)	87.3 (76.5, 94.4)	60.6 (42.1, 77.1)	4.5 (1.6, 12.4); 0.004

- The mPFS of RAS/BRAF WT patients treated with mFOLFOXIRI + panitumumab vs. FOLFOXIRI was 12.0 (95%CI 9.6, 13.3) vs. 10.8 (95%CI 9.2, 12.2) months, respectively (HR 0.760 [95%CI 0.41, 1.40]; p=0.38)

Conclusion

- **In patients with RAS WT mCRC, mFOLFOXIRI + panitumumab significantly improved ORR, but did not lead to a prolonged PFS**

*Irinotecan 150 mg/m^2, oxaliplatin 85 mg/m^2, LV 200 mg/m^2, 5FU 3000 mg/m^2 CIV; †irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, LV 200 mg/m^2, 5FU 3200 mg/m^2 CIV

Geissler M, et al. Ann Oncol 2018;29(suppl 5):abstr 453PD

LBA22: Negative hyper-selection of RAS wild-type (wt) metastatic colorectal cancer (mCRC) patients randomized to first-line FOLFOX plus panitumumab (Pan) followed by maintenance therapy with either 5FU/LV plus Pan or single-agent Pan: translational analysis of the VALENTINO study – Morano F, et al

Study objective

- To assess the non-inferiority of 1L FOLFOX-4 + panitumumab followed by maintenance therapy with either 5FU/LV or panitumumab monotherapy in patients with RAS WT mCRC and evaluate the PRESSING panel* as a single biomarker

Study design

- Patients (n=224) with untreated, unresectable RAS WT mCRC were randomised (1:1) to receive FOLFOX-4 + panitumumab 6 mg/kg for up to 8 cycles and then either panitumumab + 5FU/LV (Arm A) or panitumumab alone (Arm B) as maintenance therapy

Results

PRESSING panel evaluable population (n=189)	PRESSING-positive (n=46) vs. negative (n=143)	PRESSING-positive: Pan (n=22) vs. Pan + 5FU/LV (n=24)	PRESSING-negative Pan (n=67) vs. Pan + 5FU/LV (n=76)
mPFS, months	7.7 vs. 12.1	7.5 vs. 11.1	11.1 vs. 13.4
HR (95%CI)	2.07 (1.43, 2.99)	2.32 (1.12, 4.81)	1.61 (1.07, 2.44)

Conclusion

- **In patients with RAS WT mCRC, maintenance with panitumumab + 5FU/LV provided greater PFS benefit than panitumumab alone**

*Including HER2 amplification/activating mutations; MET amplification, NRTK/ROS1/ALK/RET rearrangements; PIK3CA exon 20 mutations, PTEN inactivating mutations; AKT1 mutations

Morano F, et al Ann Oncol 2018;29(suppl 5):abstr LBA22

454PD: Influence of treatment with prior bevacizumab: A combined analysis of individual patient data from ASPECCT and WJOG6510G trial which compared panitumumab versus cetuximab in patients with wild-type KRAS exon 2 metastatic colorectal cancer – Taniguchi H, et al

Study objective

- To assess the efficacy and safety of panitumumab or cetuximab in patients with KRAS exon 2 WT mCRC (combined analysis of the ASPECCT and WJOG6510G trials)

Study design

- Patients (ASPECCT: n=1010; WJOG6510G: n=121) who had prior bevacizumab therapy received either panitumumab (ASPECCT: n=499; WJOG6510G: n=61) or cetuximab (ASPECCT: n=500; WJOG6510G: n=59)

Key results

	Panitumumab (n=185)	Cetuximab (n=189)	HR (95%CI); p-value
mOS, months (95%CI)	12.8 (10.8, 14.4)	10.1 (8.9, 11.7)	0.72 (0.58, 0.90); 0.0031
mPFS, months (95%CI)	4.7 (4.1, 5.0)	4.1 (3.1, 4.7)	0.79 (0.64, 0.97); 0.0207

- The most common grade ≥3 TRAE was skin toxicity* in 25/184 (13.6%) patients who received panitumumab vs. 18/188 (9.56%) patients who received cetuximab (p=0.258)

Conclusion

- **In patients with KRAS exon 2 WT mCRC, panitumumab demonstrated significant improvements in OS and PFS compared with cetuximab**

*Rash, acne, skin toxicity, dermatitis, dermatitis acneiform, and/or erythema

Taniguchi H, et al Ann Oncol 2018;29(suppl 5):abstr 454PD

Discussant – Stintzing S

Study objective (Abstract LBA23 – Hays J, et al)

- **To assess the efficacy and safety of eltanexor and determine the RP2D and dosing schedule in patients with advanced cancers**

Study design

- Patients with mCRC (n=30; ≥50% KRAS mutant) received either oral eltanexor 20 mg/day (n=7) or 30 mg/day (n=23) x5 (DLT cleared dose levels) in this dose expansion cohort

Key results

- mPFS for all patients was 3.1 months (95%CI 2.0, 4.0)
- There was no difference in the sensitivity of KRAS WT or mutant

Dose	n	PR	SD, n (%)	PD, n (%)	NE	CBR (PR + SD at ≥8 weeks)
20 mg/day	7	0	6 (86)	0	1 (14)	2 (29)
30 mg/day	23	0	14 (61)	1 (4)	8 (35)	9 (39)
Total	30	0	20 (67)	1 (3)	9 (30)	11 (37)

- The most common grade 3 TRAEs were hyponatremia, anaemia and fatigue
- Thrombocytopenia was the only grade 4 TRAE observed

Hays J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA23

Discussant – Stintzing S

Presenter's take-home messages

- **Based on these data, the RP2D is 30 mg/day**
- **The preliminary anti-tumour activity is in the anticipated range for patients with heavily pre-treated mCRC**
- **There was no signal for better outcomes in RAS mutant cases**

Hays J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA23

Colorectal gastrointestinal tumours
Discussant – Marsoni S

Study objective (CALGB/SWOG 80405: Abstract 458PD – Das RK, et al)

- **To create a multivariate causal model of mCRC OS and examine the network drivers of OS using a hypothesis-free Bayesian machine learning approach**

Study design

- This was a retrospective analysis of CALGB/SWOG 80405, a phase III trial evaluating FOLFOX or FOLFIRI with either cetuximab or bevacizumab
- An ensemble of 128 network models was built in order to estimate model uncertainty and identify key causal drivers of OS by model consensus

Key results

- Molecular pathways (angiogenesis/ECM remodelling gene signature and BRAF mutation [V600E]) drove the causal effects of the side of the primary tumour on OS
- In patients who lacked an angiogenesis signature, there were no differences in response to cetuximab vs. bevacizumab (log-rank p=0.3)
- The angiogenesis signature was a negative prognostic marker for OS, with angiogenesis more prevalent in right-sided tumours (OR 3.5, p=1.3 e-07)

Das RK, et al. Ann Oncol 2018;29(suppl 5):abstr 458PD

Colorectal gastrointestinal tumours
Discussant – Marsoni S

Presenter's take-home messages

- **The study by Das et al., puts what has previously been found for the transcriptional signatures of stromal components into therapeutic context using a modelling approach**
  - **Sidedness may be a consequence of the different stromal assets of left and right mCRC**
  - **Transcriptional signatures seemed to be sensitive to the sampling region**
  - **Is another consensus required as the transcriptional classification of mCRC is still changing?**

Das RK, et al. Ann Oncol 2018;29(suppl 5):abstr 458PD

Discussant – Adams RA

Study objective (Abstract 459PD – Li N, et al)

- **To assess the efficacy and safety of oxaliplatin combined with postoperative concurrent capecitabine + radiotherapy in patients with stage II/III rectal cancer**

Study design

- Patients (n=589) with confirmed stage II/III rectal cancer were randomised (1:1) to receive radiotherapy with concurrent capecitabine with or without oxaliplatin

Key results

	Capecitabine + oxaliplatin + radiotherapy (n=295)	Capecitabine + radiotherapy (n=294)
3-year DFS rate, %	73.7	76.1
5-year DFS rate, %	69.7	71.2

- Grade 3–4 AEs occurred in 47.1% of patients receiving capecitabine + oxaliplatin + radiotherapy and 39.5% of patients receiving capecitabine + radiotherapy

Li N, et al. Ann Oncol 2018;29(suppl 5):abstr 459PD
Wu L, et al. Ann Oncol 2018;29(suppl 5):abstr 460PD
Pernot S, et al. Ann Oncol 2018;29(suppl 5):abstr 461PD
Auclin E, et al. Ann Oncol 2018;29(suppl 5):abstr 462PD

Discussant – Adams RA

Study objective (Abstract 460PD – Wu L, et al)

- **To assess a risk survival regression model and propensity score matching method for colon cancer-specific death (CCSD) and non-CCSD in patients with stage II colon cancer treated with CT**

Study design

- In this retrospective analysis, patient data (n=53,617) were obtained from the SEER database between 1988 and 2010
- In total, 25.9% received adjuvant CT and 74.1% no CT

Key results

- In those patients who received CT there were more CCSD (HR 1.19 [95%CI 1.14, 1.24]) but less non-CCSD (HR 0.57 [95%CI 0.54, 0.60])

Li N, et al. Ann Oncol 2018;29(suppl 5):abstr 459PD
Wu L, et al. Ann Oncol 2018;29(suppl 5):abstr 460PD
Pernot S, et al. Ann Oncol 2018;29(suppl 5):abstr 461PD
Auclin E, et al. Ann Oncol 2018;29(suppl 5):abstr 462PD

Discussant – Adams RA

Study objective (FFCD 1201: Abstract 461PD – Pernot S, et al)

- **To assess the efficacy and safety of FOLFOX with intra-arterial DEBIRI as a 1L therapy for patients with non-resectable CRC and liver metastases**

Study design

- Patients (n=57) with non-resectable CRC and liver metastases were treated with 1L mFOLFOX6 and intra-arterial DEBIRI (100 mg alternating right and left lobe q2w)
- Patients had ECOG PS ≤2 and liver involvement <60%

Key results

	All patients (n=57)	R0 resected patients (n=19)
mPFS, months (95%CI)	10.8 (8.2, 12.3)	13 (8.8, 16.6)
9-month PFS rate, %	53.6 (41.8, 65.1)	73.7 (47.9, 88.1)
mOS, months (95%CI)	33.1 (25.7, 46.1)	NR

- There was one toxic death (peritonitis)
- Grade 4 AEs included neutropenia (10.5%), febrile neutropenia (3.5%), infection (1.8%), pancreatitis (1.85), small bowel obstruction (1.8%) and thrombocytopenia (1.8%)

Li N, et al. Ann Oncol 2018;29(suppl 5):abstr 459PD
Wu L, et al. Ann Oncol 2018;29(suppl 5):abstr 460PD
Pernot S, et al. Ann Oncol 2018;29(suppl 5):abstr 461PD
Auclin E, et al. Ann Oncol 2018;29(suppl 5):abstr 462PD

Discussant – Adams RA

Study objective (MOSAIC: Abstract 462PD – Auclin E, et al)

- **To validate the postoperative CEA prognostic value for DFS and OS in patients with stage II colon cancer treated with adjuvant CT and evaluate the association of CEA with DFS**

Study design

- This was a post-hoc analysis of the MOSAIC trial in which patients (n=2246) were treated with fluorouracil + LV with or without oxaliplatin
- CEA was available in 867 (96.4%) patients
- Median follow-up was 8.8 years

Key results

3-year DFS rate	n	Fluorouracil + LV	n	FOLFOX
CEA ≤2.35, % (95%CI)	333	88.2 (84.8, 91.7)	331	88.7 (85.4, 92.2)
CEA >2.35, % (95%CI)	97	76 (67.9, 85.1)	106	81.1 (74, 88.9)

- Oxaliplatin benefit was only identified in the patients with high-risk stage II colon cancer (DFS interaction term p=0.09)

Li N, et al. Ann Oncol 2018;29(suppl 5):abstr 459PD
Wu L, et al. Ann Oncol 2018;29(suppl 5):abstr 460PD
Pernot S, et al. Ann Oncol 2018;29(suppl 5):abstr 461PD
Auclin E, et al. Ann Oncol 2018;29(suppl 5):abstr 462PD

Discussant – Adams RA

Presenter's take-home messages

- **In the study by Li et al., the role for postoperative radiotherapy in patients with R0 resection seems to have no benefit**
- **In the study by Wu et al., the authors' concluded that there was no survival benefit for patients with stage II colon cancer treated with CT, but previous data do not support this conclusion**
- **In the study by Pernot et al., the results of using 1L FOLFOX and intra-arterial DEBIRI for patients with non-resectable CRC and liver metastases were not persuasive although the bar may have been set too high**
- **In the study by Auclin et al. the author's concluded that only patients with high-risk stage II colon cancer and a postoperative CEA of >2.35 ng/mL may benefit from combining oxaliplatin with fluorouracil + LV and this should be taken into consideration when treating this patient population**

Li N, et al. Ann Oncol 2018;29(suppl 5):abstr 459PD
Wu L, et al. Ann Oncol 2018;29(suppl 5):abstr 460PD
Pernot S, et al. Ann Oncol 2018;29(suppl 5):abstr 461PD
Auclin E, et al. Ann Oncol 2018;29(suppl 5):abstr 462PD

1558O: Worldwide comparison of colorectal cancer survival, by topography and stage at diagnosis (CONCORD-2) – Benitez Majano S, et al

Study objective

- To assess the long-term trends in the international survival rates in colon cancer by stage and location

Methods

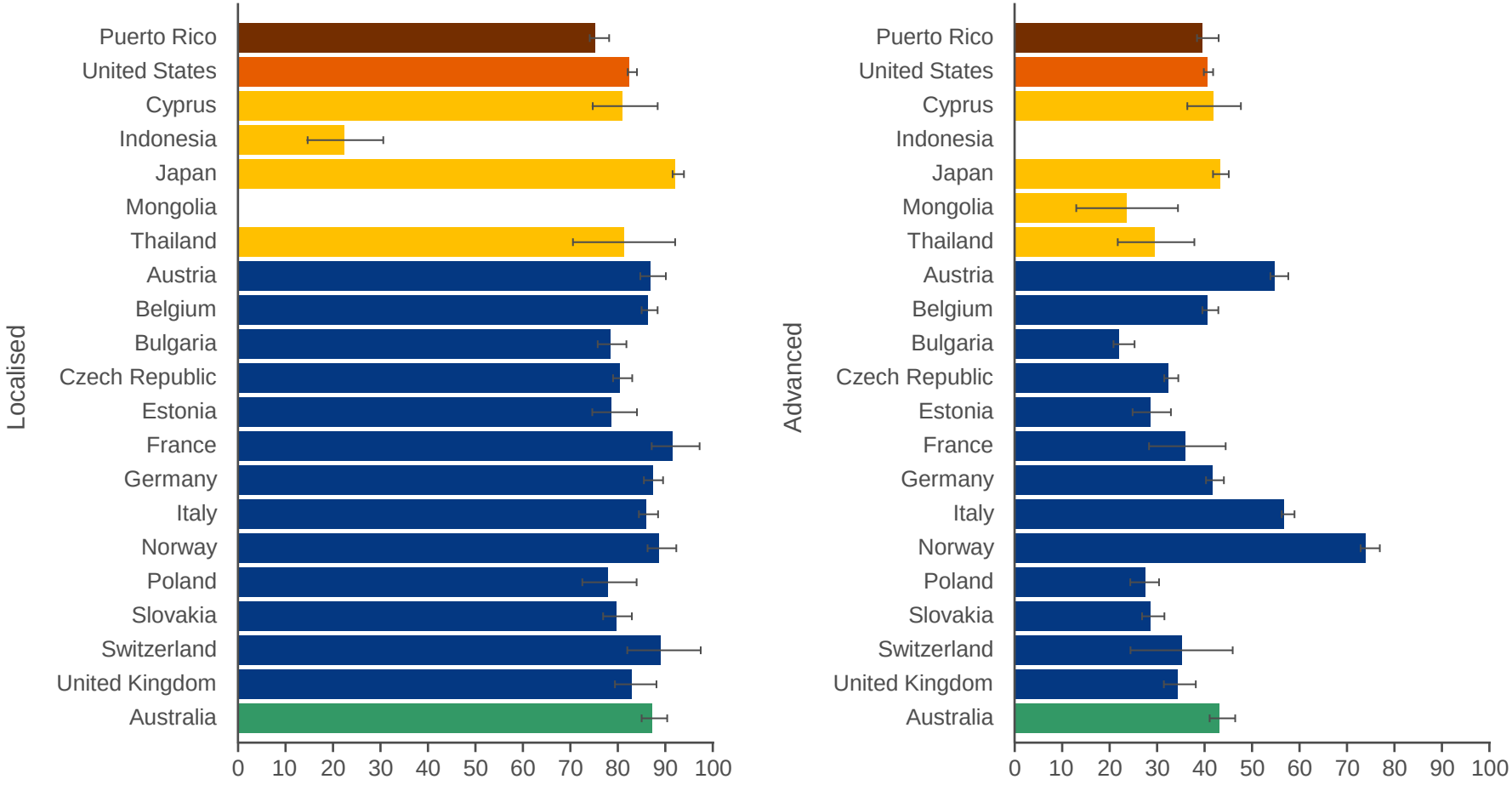
- Data were collected from a global surveillance programme consisting of 279 cancer registries from 67 countries and over 25 million patients
- Long-term trends of 10 common cancers in patients aged 15–99 years who were diagnosed between 1995 and 2009 were documented
  - It included 5,026,928 patients with CRC
- Stratified analyses were performed after excluding registries with data quality issues
  - This included 4,877,818 patients with CRC from 228 registries across 55 countries

Benitez Majano S, et al. Ann Oncol 2018;29(suppl 5):abstr 1558O

1558O: Worldwide comparison of colorectal cancer survival, by topography and stage at diagnosis (CONCORD-2) – Benitez Majano S, et al

Key results

Colon cancer 2004–2009: Age standardised 5-year net survival, by stage



Benitez Majano S, et al. Ann Oncol 2018;29(suppl 5):abstr 1558O

1558O: Worldwide comparison of colorectal cancer survival, by topography and stage at diagnosis (CONCORD-2) – Benitez Majano S, et al

Conclusions

- There was wide variation in 5-year survival for patients with CRC by stage and sub-site and particularly in patients with advanced stage disease
- Survival was similar between left and right sided colon cancer, but was lower in tumours which had ‘other’ colon cancer topographical codes

Benitez Majano S, et al. Ann Oncol 2018;29(suppl 5):abstr 1558O

1559O: Increasing colorectal cancer incidence among young adults in England diagnosed during 2001-2014 – Exarchakou A, et al

Study objective

- To describe trends in the incidence of CRC in England between 1971 and 2014 among young adults aged 20–39 years

Methods

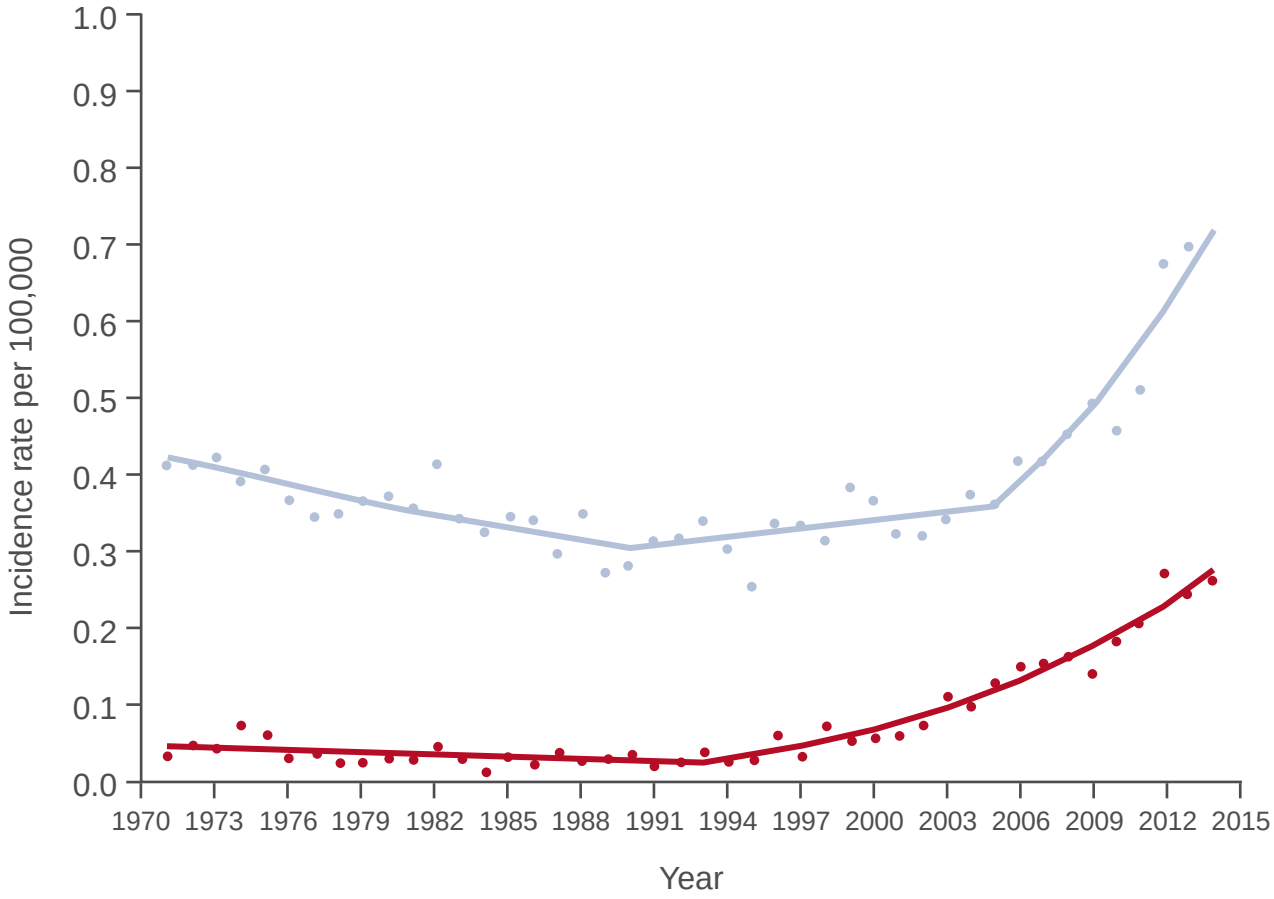
- Data were collected from the National Cancer Registry for 1,073,624 patients and stratified according to 10-year age groups (20–29 and 30–39 years) and site of cancer (left colon, right colon and rectum)
- The Index of Multiple Deprivation (IMD 2015) was used to determine social deprivation across 5 categories (1 = least deprived or most affluent; 5 = most deprived)
  - Note: population counts by deprivation were only available from 2001

Exarchakou A, et al. Ann Oncol 2018;29(suppl 5):abstr 1559O

1559O: Increasing colorectal cancer incidence among young adults in England diagnosed during 2001-2014 – Exarchakou A, et al

Key results

Incidence trends for adults by age group



	20–29 years	30–39 years
Crude incidence rates (per 100,000)		
1971	0.7	4.4
1990		3.1
1993	0.8	
2005		3.9
2014	2.8	7.6
Annual change, %		
1971–1990		–1.7
1971–1993	–1.4	
1990–2005		1.1
1993–2014	8.1	
2005–2014		8.1

Exarchakou A, et al. Ann Oncol 2018;29(suppl 5):abstr 1559O

1559O: Increasing colorectal cancer incidence among young adults in England diagnosed during 2001-2014 – Exarchakou A, et al

Key results (cont.)

Incidence among adults by CRC sub-site	Annual change, %
Right colon	
1971–1990	–2.5
1990–2009	5
2009–2014	**18**
Rectum	
1971–1990	–1.7
1990–2014	4.4
Left colon	
1971–1998	–1.7
1998–2014	5.7

Incidence of deprivation between 2001 and 2014	Annual change, %
Least deprived	7.8
Dep 2	6.1
Dep 3	6.8
Dep 4	8.5
Most deprived	4.9

Conclusions

- **Among adults aged 20–39 years in England, the incidence of CRC declined between 1971 and the early 1990s, but increased rapidly after the late 1990s in all deprivation groups**
- **The greatest increases in incidence occurred in adults aged 20–29 years and those with right colon cancer**

Exarchakou A, et al. Ann Oncol 2018;29(suppl 5):abstr 1559O

LBA21: InterAACT: A multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU) vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatment naïve disease – An International Rare Cancers Initiative (IRCI) trial – Rao S, et al

Study objective

- To assess the efficacy and safety of carboplatin + paclitaxel compared with cisplatin + 5FU as 1L maintenance treatment in patients with advanced anal cancer

Key patient inclusion criteria

- Histologically or cytologically confirmed locally recurrent inoperable or metastatic squamous cell carcinoma of the anus
- No prior systemic treatment for advanced disease
- ECOG PS 0–2

(n=91)

R 1:1

Carboplatin AUC5 D1 + paclitaxel 80 mg/m^2 D1, 8, 15 q3w → PD

Stratification

- ECOG PS 0/1 vs. 2
- HIV + vs. –
- Extent of disease locally advanced vs. metastatic
- Region UK vs. Australia vs. USA vs. Europe

Cisplatin 60 mg/m^2 D1 + 5FU 1000 mg/m^2 D1–4 q4w → PD

PRIMARY ENDPOINTS

- ORR

SECONDARY ENDPOINTS

- PFS, OS, DCR, safety, QoL, biomarker analysis

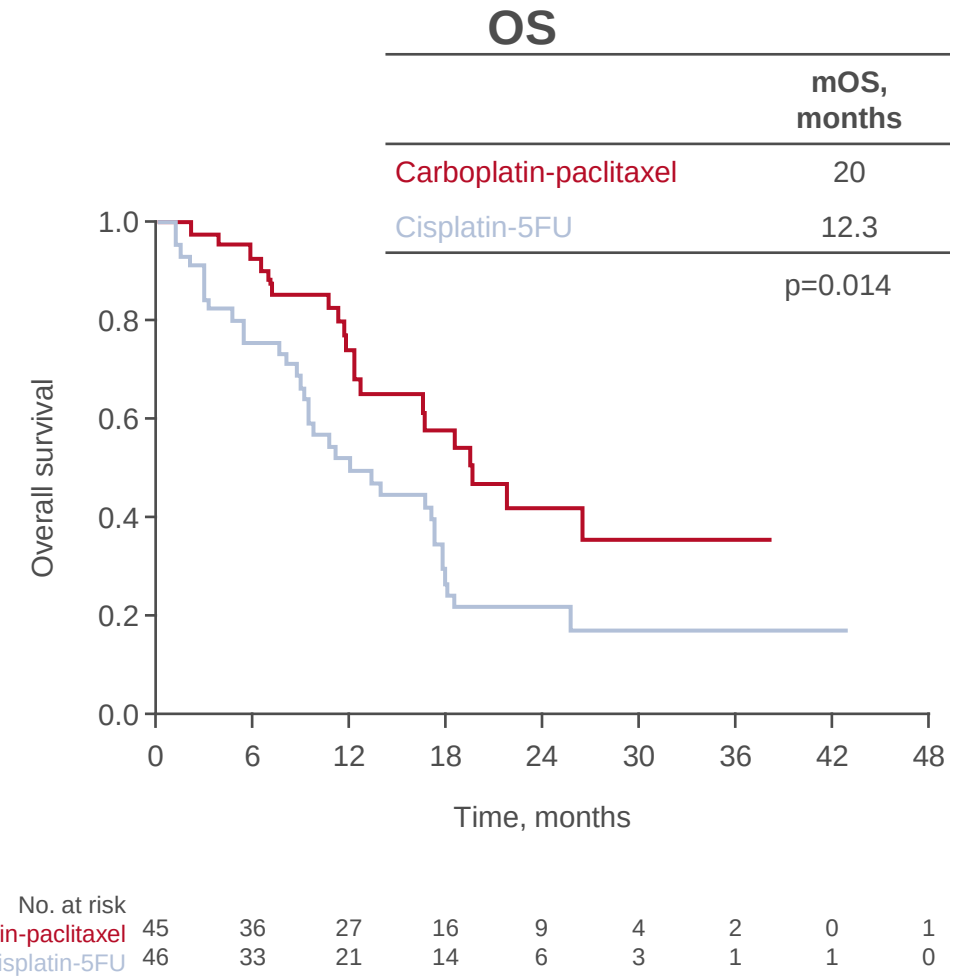
Rao S, et al. Ann Oncol 2018;29(suppl 5):abstr LBA21

LBA21: InterAACT: A multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU) vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatment naïve disease – An International Rare Cancers Initiative (IRCI) trial – Rao S, et al

Key results

- Median follow-up was 25.3 months

RECIST response, n (%)	Carboplatin + paclitaxel (n=39)	Cisplatin + 5FU (n=35)
CR	5 (12.8)	5 (14.3)
PR	18 (46.2)	15 (42.9)
SD	10 (25.6)	7 (20.0)
PD	6 (15.4)	8 (22.9)
CR/PR [95%CI] p=0.873	23 (59) [42.1, 74.4]	20 (57) [39.4, 73.7]



Rao S, et al. Ann Oncol 2018;29(suppl 5):abstr LBA21

LBA21: InterAACT: A multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU) vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatment naïve disease – An International Rare Cancers Initiative (IRCI) trial – Rao S, et al

Key results (cont.)

Grade ≥3 AEs, n (%)	Carboplatin + paclitaxel (n=42)	Cisplatin + 5FU (n=42)
Anaemia	4 (10)	2 (5)
Diarrhoea	1 (2)	2 (5)
Fatigue	4 (10)	8 (19)
Febrile neutropenia	2 (5)	4 (10)
Mucositis	0 (0)	11 (26)
Nausea	1 (2)	7 (17)
Neuropathy	1 (2)	0 (0)
Thromboembolism	1 (2)	5 (12)
SAEs	15 (36)	26 (62)

Conclusions

- **In treatment naïve patients with advanced anal cancer, carboplatin + paclitaxel demonstrated a similar ORR to cisplatin + 5FU but had a better safety profile with less toxicity**
- **Carboplatin + paclitaxel may be a new potential SoC for the management of treatment naïve patients with advanced anal cancer**

Rao S, et al. Ann Oncol 2018;29(suppl 5):abstr LBA21

GASTROINTESTINAL CANCERS

417PD: Combination therapy optimization in gastrointestinal cancers using multi-omic molecular profiling – Monge C, et al.

Study objective

- To assess the use of combination therapies in GI cancers based on MOMP cancer data obtained from a national research consortium

Study design

- In this retrospective analysis, patients with GI cancers who underwent MOMP (n=5377) and other cohorts including CRC (n=2961) were collated to assess single agents and combination therapies

Key results

- For single agent actionability, the proportion of patients with potentially actionable biomarkers was highest for PI3K/AKT/mTOR inhibitors across all GI cancers (24%) and CRC cohort (31%)

Conclusion

- **These results suggest that molecular profiling should be used in drug development strategy to assess accrual, clinical utility and both target- and disease-specific trial designs**

Monge C, et al. Ann Oncol 2018;29(suppl 5):abstr 417PD

Translational research in gastrointestinal tumours: HCC, colon cancer and mCRC
Discussant – Dienstmann R

Study objective (REFLECT: Abstract 59PD – Finn RS, et al)

- **To assess serum biomarkers in patients with unresectable HCC following 1L treatment with lenvatinib vs. sorafenib**

Study design

- In the REFLECT trial, patients (n=954) were randomised (1:1) to receive either lenvatinib (n=478) or sorafenib (n=128) and biomarkers were measured in 267 and 128 patients, respectively

Key results

- Lenvatinib was non-inferior to sorafenib in terms of mOS (13.6 vs. 12.3 months, respectively; HR 0.92 [95%CI 0.79, 1.06])
- Both treatment arms were associated with increased VEGF levels, but this was greater in patients who received lenvatinib
- OR was associated with greater observed increases from baseline in FGF19 (55% vs. 18% at Cycle 4 D1 vs. baseline, respectively; p=0.014) and FGF23 biomarker levels (48% vs. 16%, p=0.002) in those treated with lenvatinib

Finn RS, et al. Ann Oncol 2018;29(suppl 5):abstr 59PD
Laurent-Puig P, et al. Ann Oncol 2018;29(suppl 5):abstr 60PD
Berger MD, et al. Ann Oncol 2018;29(suppl 5):abstr 61PD

Translational research in gastrointestinal tumours: HCC, colon cancer and mCRC
Discussant – Dienstmann R

Study objective (PETACC-8: Abstract 60PD – Laurent-Puig P, et al)

- **To assess the prognostic impact of CMS classification accounting for intra-tumour heterogeneity using a deconvolution algorithm in patients with stage III colon cancer**

Study design

- A random Forest classifier of the CMS classification of colon cancer was applied to formalin-fixed paraffin-embedded samples (n=1779) from the PETACC08 trial

Key results

- Random Forest classification of the PETACC08 trial series confirmed CMS correlations with clinical, pathological and molecular features (CMS1: dMMR, right-sided, grade 3/4, immune infiltration; CMS2: immune desert; CMS3: RAS mutant; and CMS4: EMT/TGF-β signatures, immune/stromal infiltration, poorest prognosis)
- CMS attribution was uncertain* for 63% of samples
- Intra-tumour heterogeneity† was shown in 57% of samples

*Random Forest classifier probability <70%;
†≥1 CMS with a WISP-derived weight above 20%

Finn RS, et al. Ann Oncol 2018;29(suppl 5):abstr 59PD
Laurent-Puig P, et al. Ann Oncol 2018;29(suppl 5):abstr 60PD
Berger MD, et al. Ann Oncol 2018;29(suppl 5):abstr 61PD

Translational research in gastrointestinal tumours: HCC, colon cancer and mCRC
Discussant – Dienstmann R

Study objective (FIRE-3: Abstract 61PD – Berger MD, et al)

- **To assess the HER3 polymorphism rs2271189 as a predictive biomarker in patients with mCRC treated with 1L FOLFIRI + bevacizumab vs. FOLFIRI + cetuximab (FIRE-3)**

Study design

- Impact of four functional SNPs (within HER3, NRG1, NEDD4 and BTC) on prognostic outcome was evaluated in 585 patients

Key results

	All patients (FOLFIRI + bevacizumab)			All patients (FOLFIRI + cetuximab)		
	G/G or A/G allele (n=248)	A/A allele (n=33)	p-value	G/G or A/G allele (n=240)	A/A allele (n=52)	p-value
mPFS, months (95%CI)	10.3 (9.7, 11.8)	7.0 (4.2, 9.7)		10.0 (8.8, 10.9)	7.9 (6.5, 10.3)	
HR (95%CI)*	1 (reference)	1.64 (1.09, 2.46)	0.018	1 (reference)	1.40 (1.00, 1.96)	0.051
mOS, months (95%CI)	24.2 (21.9, 26.5)	19.0 (12.9, 29.0)		27.6 (23.5, 31.0)	20.8 (14.9, 33.6)	
HR (95%CI)*	1 (reference)	1.43 (0.93, 2.19)	0.104	1 (reference)	0.96 (0.65, 1.41)	0.819

*Multivariate analysis

Finn RS, et al. Ann Oncol 2018;29(suppl 5):abstr 59PD
Laurent-Puig P, et al. Ann Oncol 2018;29(suppl 5):abstr 60PD
Berger MD, et al. Ann Oncol 2018;29(suppl 5):abstr 61PD

Translational research in gastrointestinal tumours: HCC, colon cancer and mCRC
Discussant – Dienstmann R

Presenter's take-home messages

- **In the study by Finn et al., the differences in serum biomarker changes from baseline between patients in the lenvatinib vs. sorafenib arms showed that each drug varied in its target engagements**
- **In the study by Laurent-Puig et al., intra-tumour heterogeneity of CMS subtypes provided further insight into the prognosis of stage III colon cancer**
  - **There is no unique clonal CMS subtype in most colon cancer tumours**
  - **Based on data generated by multivariate models, CMS1 and CMS4 subclonal heterogeneity may be independent predictors of relapse**
  - **In stage III colon cancer, heterogeneity of the tumour microenvironment is a prognostic marker**
- **In the study by Berger et al., HER3 rs2271189 was found to be a prognostic biomarker, but because of a missing control arm these data should not be used to assess predictive value**

Finn RS, et al. Ann Oncol 2018;29(suppl 5):abstr 59PD
Laurent-Puig P, et al. Ann Oncol 2018;29(suppl 5):abstr 60PD
Berger MD, et al. Ann Oncol 2018;29(suppl 5):abstr 61PD