GI SLIDE DECK 2018
Selected abstracts from:

2018 ASCO Annual Meeting
1–5 June 2018 | Chicago, USA
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
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Phillippe Rougier (hon.)

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

(ESDO Governing Board)
## COLORECTAL CANCERS

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Eric Van Cutsem</td>
<td>Digestive Oncology, University Hospitals, Leuven, Belgium</td>
</tr>
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<td>Prof Thomas Gruenberger</td>
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<tr>
<td>Prof Jaroslaw Regula</td>
<td>Department of Gastroenterology and Hepatology, Institute of Oncology, Warsaw, Poland</td>
</tr>
</tbody>
</table>

## PANCREATIC CANCER AND HEPATOBILIARY TUMOURS

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
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<tbody>
<tr>
<td>Prof Jean-Luc Van Laethem</td>
<td>Digestive Oncology, Erasme University Hospital, Brussels, Belgium</td>
</tr>
<tr>
<td>Prof Thomas Seufferlein</td>
<td>Clinic of Internal Medicine I, University of Ulm, Ulm, Germany</td>
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<td>Prof Ulrich Güller</td>
<td>Medical Oncology &amp; Hematology, Kantonsspital St Gallen, St Gallen, Switzerland</td>
</tr>
</tbody>
</table>

## GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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</thead>
<tbody>
<tr>
<td>Prof Côme Lepage</td>
<td>University Hospital &amp; INSERM, Dijon, France</td>
</tr>
<tr>
<td>Prof Tamara Matysiak</td>
<td>Hepato-Gastroenterology &amp; Digestive Oncology, Institute of Digestive Diseases, Nantes, France</td>
</tr>
</tbody>
</table>

## BIOMARKERS

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Prof Eric Van Cutsem</td>
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<tr>
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<td>Clinic of Internal Medicine I, University of Ulm, Ulm, Germany</td>
</tr>
</tbody>
</table>
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 (modified) 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

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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)

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

Paclitaxel†
(n*=199/296)

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)

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/m² d1,8,15 of 4-week cycle;
‡pre-specified significance threshold for OS: p≤0.0135

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**

**OS – CPS ≥1 population**

**Pembrolizumab** vs **Paclitaxel**

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Months</th>
<th>Pembrolizumab Events</th>
<th>Paclitaxel Events</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>196</td>
<td>0</td>
<td>151</td>
<td>175</td>
<td>0.82 (0.66, 1.03)</td>
<td>0.04205</td>
</tr>
<tr>
<td>114</td>
<td>6</td>
<td>14</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>12</td>
<td>25.7%</td>
<td>14.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>18</td>
<td>39.8%</td>
<td>27.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>0</td>
<td>30</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

**mOS, months (95%CI)**

- Pembrolizumab: 9.1 (6.2, 10.7)
- Paclitaxel: 8.3 (7.6, 9.0)

Presented by Shitara K
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.)

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

Presented by Shitara K
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.)

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

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
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

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

*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/m²; ‡40 mg/m²

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/m² or placebo + weekly paclitaxel 80 mg/m². Interim analysis (OS follow-up) was conducted to test for superiority at 2/3 of required events (n=380)

Key results

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

- No safety concerns of clinical significance were identified

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/m² on d1,8,15 (q4w) or paclitaxel 80 mg/m² d1,8,15 (q4w) + trastuzumab† on d1 (q3w)

Key results

<table>
<thead>
<tr>
<th>Paclitaxel (n=45)</th>
<th>Paclitaxel + trastuzumab (n=44)</th>
<th>Stratified HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95%CI)</td>
<td>3.19 (2.86, 3.48)</td>
<td>3.68 (2.76, 4.53)</td>
<td>0.906 (0.674, 1.219)</td>
</tr>
<tr>
<td>Median OS, months (95%CI)</td>
<td>9.95 (7.56, 13.08)</td>
<td>10.20 (7.85, 12.75)</td>
<td>1.230 (0.759, 1.991)</td>
</tr>
</tbody>
</table>

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

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
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)

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

Arm A
FOLFIRINOX (12 cycles) (n=91)

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

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

PRIMARY ENDPOINT
• 6-month PFS rate

SECONDARY ENDPOINTS
• OS, PFS, best response, safety, 2L therapy

**Key results**

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

*Exploratory analysis for OS: p<0.05*
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.)

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

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  
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


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

Key patient inclusion criteria
• Pancreatic cancer proven by cytology
• Resectable or borderline resectable (n=248)

Primary endpoint
• OS

Secondary endpoints
• R0 resection rate, DFS, distant metastases, locoregional recurrence, safety

Stratification
• Resectability
• Institution

Preoperative CRT* + adjuvant gemcitabine† x4 cycles (n=119)

Immediate surgery + adjuvant gemcitabine† x6 cycles (n=127)

**Key results**

- Preliminary results: 149/176 events

**OS**

- mOS: 17.1 vs. 13.7 months (CRT vs. immediate surgery)
- HR 0.74; *p=0.074

**DFS**

- mDFS: 9.9 vs. 7.9 months (CRT vs. immediate surgery)
- HR 0.71; *p=0.023

*Stratified log-rank test* 


Key results (cont.)

**Distant metastases-free interval**

Cumulative proportion free from distant metastases

<table>
<thead>
<tr>
<th>Months since randomisation</th>
<th>No. at risk</th>
<th>Preoperative CRT</th>
<th>Immediate surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>119</td>
<td>127</td>
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<td>8</td>
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<td>24</td>
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<td></td>
<td>7</td>
<td>19</td>
<td>17</td>
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<td></td>
<td>5</td>
<td>7</td>
<td>4</td>
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<tr>
<td></td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

*p-value: 0.0127

**Locoregional recurrence free interval**

Cumulative proportion free from locoregional failure

<table>
<thead>
<tr>
<th>Months since randomisation</th>
<th>No. at risk</th>
<th>Preoperative CRT</th>
<th>Immediate surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>119</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>76</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>35</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>19</td>
<td>18</td>
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<tr>
<td></td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

*p-value: 0.002

*Stratified log-rank test

Conclusions

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

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

- 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

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine + cisplatin (n=175)</th>
<th>Gemcitabine + S-1 (n=179)</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>13.4 (12.4, 15.5)</td>
<td>15.1 (12.2, 16.4)</td>
<td>0.945 (0.777, 1.149)</td>
<td>0.0459</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>5.8</td>
<td>6.8</td>
<td>0.86 (0.70, 1.07)</td>
<td>-</td>
</tr>
</tbody>
</table>

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

**1000 mg/m² on d1,8; †25 mg/m² on d1,8 q3w; ‡60, 80, and 100 mg/body/day on d1–14 q3w

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

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

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

*1200 mg orally twice daily continuously; †1000 mg/m² iv; ‡125 mg/m² iv on d1,8, 15 of a 4-week cycle

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)

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.

HEPATOCELLULAR CARCINOMA

Cancers of the pancreas, small bowel and hepatobiliary tract
**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)

**PRIMARY ENDPOINT**

- OS

**SECONDARY ENDPOINTS**

- PFS, TTP, ORR, safety

**Stratification**

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

**Ramucirumab 8 mg/kg iv q2w + BSC**  
(n=197)  

PD/toxicity

**Placebo + BSC**  
(n=95)  

PD/toxicity
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

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months</td>
<td>8.5</td>
<td>7.3</td>
<td>-</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>0.710 (0.531, 0.949)</td>
<td>0.0199</td>
<td></td>
</tr>
<tr>
<td>12-month OS, %</td>
<td>36.8</td>
<td>30.3</td>
<td>0.293</td>
</tr>
<tr>
<td>18-month OS, %</td>
<td>24.5</td>
<td>11.3</td>
<td>0.0187</td>
</tr>
</tbody>
</table>

![OS Kaplan-Meier Curve](image_url)

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.)

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, months</td>
<td>2.8</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>0.452 (0.339, 0.603)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

PFS

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) [95%CI]</td>
<td>9 (4.6) [1.7, 7.5]</td>
<td>1 (1.1) [0.0, 3.1]</td>
<td>0.1697</td>
</tr>
<tr>
<td>DCR</td>
<td>118 (59.9) [53.1, 66.7]</td>
<td>37 (38.9) [29.1, 48.8]</td>
<td>0.0006</td>
</tr>
</tbody>
</table>
Key results (cont.)

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

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**
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

<table>
<thead>
<tr>
<th>Sorafenib + TACE (n=80)</th>
<th>TACE (n=76)</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>25.2</td>
<td>13.5</td>
<td>0.59 (0.41, 0.87)</td>
</tr>
</tbody>
</table>

• The maturity of OS results was 73.6%

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

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

<table>
<thead>
<tr>
<th></th>
<th>Cabozatinib (n=470)</th>
<th>Placebo (n=237)</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95%CI)</td>
<td>10.2 (9.1, 12.0)</td>
<td>8.0 (6.8, 9.4)</td>
<td>0.76 (0.63, 0.92)</td>
<td>0.0049</td>
</tr>
<tr>
<td>Median PFS, months (95%CI)</td>
<td>5.2 (4.0, 5.5)</td>
<td>1.9 (1.9, 1.9)</td>
<td>0.44 (0.36, 0.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>4</td>
<td>0.4</td>
<td>-</td>
<td>0.0086</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95%CI)</td>
<td>12.9 (9.7, 15.5)</td>
</tr>
<tr>
<td>Median PFS, months (95%CI)</td>
<td>4.9 (3.4, 7.2)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>18/104 (17)</td>
</tr>
</tbody>
</table>

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

Cancers of the pancreas, small bowel and hepatobiliary tract

NEUROENDOCRINE TUMOUR

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)

Primary endpoint
• PFS – local review

Secondary endpoints
• ORR, OS, safety

Stratification
• Prior everolimus
• Prior sunitinib
• Concurrent octreotide

Temozolomide 200 mg/m²/day d10–14 + capecitabine 750 mg/m² bid d1–14 (n=72)

Temozolomide 200 mg/m²/day d1–5 (n=72)

PD/Toxicity

# Key results

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

*Imbalance, \(p=0.013\)

Key results (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Temozolomide + capecitabine</th>
<th>Temozolomide alone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, months</td>
<td>22.7</td>
<td>14.4</td>
<td>-</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>0.58 (0.36, 0.93)</td>
<td>0.023</td>
<td></td>
</tr>
</tbody>
</table>

**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*
CANCERS OF THE COLON, RECTUM AND ANUS
**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

**PRIMARY ENDPOINT**

- ORR

**SECONDARY ENDPOINTS**

- PFS, OS, immunogeneity, safety

---

**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)

---

*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)
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**

**Best response:**
- **PR**
- **Single time-point PR**
- **SD**
- **PD**
- **NE**

*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**
- **ORR, n/N (%):** 1/21 (5)
- **DCR, n/N (%):** 4/21 (19)

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

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.)

<table>
<thead>
<tr>
<th>TRAEs in CRC (n=42), n (%)</th>
<th>Grade 3–4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash maculo-papular</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>5 (12)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

- 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
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

**Key patient inclusion criteria**
- Locally advanced resectable rectal cancer
- <12 cm of the anal verge
- T3/4 and/or node positive
- WHO/ECOG PS ≤2 (n=1090)

**PRIMARY ENDPOINT**
- 3-year DFS*

**SECONDARY ENDPOINTS**
- Long-term DFS, OS, RFS, locoregional distant failure

*Reported at ASCO 2014
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**

<table>
<thead>
<tr>
<th>%</th>
<th>CAPOX</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year DFS</td>
<td>70.5</td>
<td>71.3</td>
</tr>
<tr>
<td>6-year DFS</td>
<td>69.6</td>
<td>69.6</td>
</tr>
<tr>
<td>7-year DFS</td>
<td>65.5</td>
<td>66.1</td>
</tr>
</tbody>
</table>

**DFS**

HR 1.02; p=0.84
95%CI (0.82, 1.28)
Cox model adjusted for stratification factors (except centre)

**No. at risk**

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>CAPOX</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>157</td>
<td>547</td>
<td>472</td>
<td>404</td>
</tr>
<tr>
<td>156</td>
<td>547</td>
<td>452</td>
<td>388</td>
</tr>
</tbody>
</table>

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.)

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

<table>
<thead>
<tr>
<th>5-year DFS by country</th>
<th>CAPOX, %</th>
<th>Capecitabine, %</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>67.8</td>
<td>73.4</td>
<td>1.27</td>
<td>0.091</td>
</tr>
<tr>
<td>Not Germany</td>
<td>75.7</td>
<td>67</td>
<td>0.65</td>
<td>0.033</td>
</tr>
</tbody>
</table>

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

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

PRIMARY ENDPOINT

- DFS*

SECONDARY ENDPOINTS

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

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

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**

**DFS**

![DFS graph]

<table>
<thead>
<tr>
<th>Disease-free survival, months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX (n=160)</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5FU + leucovorin (n=161)</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6-year DFS rate, %</th>
<th>FOLFOX</th>
<th>5FU + leucovorin</th>
<th>Stratified HR* (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypStage III</td>
<td>63.2</td>
<td>48.3</td>
<td>0.63 (0.43, 0.92)</td>
<td>0.018</td>
</tr>
<tr>
<td>ypStage II</td>
<td>77.8</td>
<td>69.5</td>
<td>0.64 (0.30, 1.36)</td>
<td>0.245</td>
</tr>
</tbody>
</table>

*Stratified by ypStage and participating site

**No. at risk**

<table>
<thead>
<tr>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX (n=160)</td>
<td>161</td>
<td>114</td>
<td>99</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>5FU + leucovorin (n=161)</td>
<td>160</td>
<td>131</td>
<td>108</td>
<td>103</td>
<td>97</td>
</tr>
</tbody>
</table>

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.)

**OS**

<table>
<thead>
<tr>
<th>Survival, %</th>
<th>FOLFOX (n=160)</th>
<th>5FU + leucovorin (n=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-year OS rate, %</td>
<td>78.1</td>
<td>76.4</td>
</tr>
<tr>
<td>Stratified HR* (95%CI)</td>
<td>0.73 (0.45, 1.19)</td>
<td>0.210</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall survival, months

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX</td>
<td>160</td>
<td>146</td>
<td>139</td>
<td>134</td>
<td>123</td>
<td>105</td>
<td>79</td>
<td>50</td>
<td>22</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5FU + leucovorin</td>
<td>161</td>
<td>144</td>
<td>137</td>
<td>126</td>
<td>120</td>
<td>104</td>
<td>79</td>
<td>50</td>
<td>22</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Stratified by ypStage and participating site

Key results (cont.)

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

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
**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

**Key patient inclusion criteria**

- Resectable rectal cancer
- <12 cm of the anal verge
- Stage II/III
- ECOG PS 0–1

**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*

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3-year local recurrence, %</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFOX6-RT</td>
<td>8.0</td>
<td>0.825 (0.377, 1.809)</td>
</tr>
<tr>
<td>mFOLFOX6</td>
<td>8.7</td>
<td>0.800 (0.365, 1.753)</td>
</tr>
<tr>
<td>5FU-RT</td>
<td>10.3</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Log-rank p=0.832

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.)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3-year DFS, %</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFOX6-RT</td>
<td>77.1</td>
<td>0.994 (0.594, 1.499)</td>
</tr>
<tr>
<td>mFOLFOX6</td>
<td>74.9</td>
<td>0.968 (0.615, 1.524)</td>
</tr>
<tr>
<td>5FU-RT</td>
<td>75.7</td>
<td>Ref</td>
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</tbody>
</table>

DFS

Log-rank p=0.970
Key results (cont.)

### OS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3-year OS, %</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFOX6-RT</td>
<td>91.3</td>
<td>0.876 (0.438, 1.753)</td>
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<tr>
<td>mFOLFOX6</td>
<td>92.2</td>
<td>0.902 (0.456, 1.787)</td>
</tr>
<tr>
<td>5FU-RT</td>
<td>92.1</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Log-rank p=0.926

Key results (cont.)

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

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

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)

PRIMARY ENDPOINT
- OS

SECONDARY ENDPOINTS
- RFS, prognostic factors or survival safety, morbidity

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

HIPEC* + CT † (n=133)

CT † alone (n=132)

*Oxaliplatin 460 mg/m² ip (360 mg/m² in closed procedures), then leucovorin 20 mg/m² + 5FU 400 mg/m² ip during HIPEC;
†preoperative or postoperative CT, or both, for 6 months

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

OS

- **mOS**, months: 41.7 vs 41.7
- 1-year OS, %: 86.9 vs 88.3
- 5-year OS, %: 39.4 vs 36.7

HR 1.00 (95%CI 0.73, 1.37) p=0.995

No. at risk

<table>
<thead>
<tr>
<th>Time, months</th>
<th>HIPEC</th>
<th>Non-HIPEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>133</td>
<td>123</td>
</tr>
<tr>
<td>12</td>
<td>132</td>
<td>124</td>
</tr>
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<td>18</td>
<td>113</td>
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<td>24</td>
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<td>36</td>
<td>83</td>
<td>87</td>
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<tr>
<td>42</td>
<td>72</td>
<td>74</td>
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<tr>
<td>48</td>
<td>56</td>
<td>58</td>
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<tr>
<td>54</td>
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<td>60</td>
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<td>66</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>72</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

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.)

![Graph showing RFS (Relapse-Free Survival) for HIPEC and Non-HIPEC groups.]

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

**HR 0.908 (95%CI 0.69, 1.19)**

**p=0.486**

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.)

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

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

**Key results (cont.)**

<table>
<thead>
<tr>
<th></th>
<th>HIPEC</th>
<th>Non-HIPEC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay, days (range)</td>
<td>18.0 (8–140)</td>
<td>13.0 (1–62)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**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
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)

**Primary endpoint**
- PFS

**Secondary endpoints**
- RR; safety

---

*Irinotecan 150 mg/m² iv + cetuximab 400 mg/m² iv + ramucirumab 6 mg/kg iv q2w; †180 mg/m² iv; ‡500 mg/m² 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

PFS by arm

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Total</th>
<th>Fail</th>
<th>Censored</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab + IC</td>
<td>42</td>
<td>27</td>
<td>15</td>
<td>5.8</td>
</tr>
<tr>
<td>IC</td>
<td>40</td>
<td>33</td>
<td>7</td>
<td>5.7</td>
</tr>
</tbody>
</table>

HR 0.65
p=0.069 (one-sided)
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
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

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

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

- 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

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
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
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
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
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)
Key results

- Fusions were detected in 45 patients

<table>
<thead>
<tr>
<th>Fusions detected</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET</td>
<td>36</td>
</tr>
<tr>
<td>FGFR3</td>
<td>29</td>
</tr>
<tr>
<td>ALK</td>
<td>22</td>
</tr>
<tr>
<td>NTRK1</td>
<td>7</td>
</tr>
<tr>
<td>ROS1</td>
<td>4</td>
</tr>
<tr>
<td>FGFR2</td>
<td>2</td>
</tr>
</tbody>
</table>

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

**Key patient inclusion criteria**

- mCRC
- RAS/BRAF WT (n=28)

**PRIMARY ENDPOINT**

- Response rate (RECIST 1.1)

**SECONDARY ENDPOINTS**

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

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*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/m² iv; ‡500 mg/m² iv

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**

<table>
<thead>
<tr>
<th></th>
<th>n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR, n (%)</td>
<td>6 (21.5)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td>ORR, n [%] [95%CI]</td>
<td>6 (21.5) [10, 40]</td>
</tr>
<tr>
<td>DCR, n [%] [95%CI]</td>
<td>15 (53.6) [36, 70]</td>
</tr>
<tr>
<td>mPFS, months (95%CI)</td>
<td>3.4 (1.9, 3.8)</td>
</tr>
<tr>
<td>mOS, months (95%CI)</td>
<td>9.8 (5.2, 13.1)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>RAS WT ctDNA</th>
<th>RAS mutated ctDNA</th>
<th>HR (95%CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, months</td>
<td>4.0</td>
<td>1.9</td>
<td>0.44 (0.18, 0.98); 0.026</td>
</tr>
<tr>
<td>OS, months</td>
<td>12.5</td>
<td>5.2</td>
<td>0.58 (0.22, 1.52); 0.24</td>
</tr>
</tbody>
</table>

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

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

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

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

*400 mg/m² iv 120 min, then 250 mg/m² iv 60 min q1w;
†5 mg/kg iv 30–90 min q2w

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

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab + FOLFOXIRI (n=63)</th>
<th>FOLFOXIRI alone (n=33)</th>
<th>HR (95%CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, months (95%CI)</td>
<td>9.7 (9.0, 11.7)</td>
<td>10.1 (7.8, 12.1)</td>
<td>0.920 (0.584, 1.451); 0.72</td>
</tr>
</tbody>
</table>

• 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
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

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

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

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

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’

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

<table>
<thead>
<tr>
<th></th>
<th>WT (n=951)</th>
<th>KRAS (n=1080)</th>
<th>NRAS (n=91)</th>
<th>BRAF V600 (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months</td>
<td>49.2</td>
<td>36.2</td>
<td>30.1</td>
<td>22.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OS*</th>
<th>NRAS vs. WT</th>
<th>NRAS vs. KRAS</th>
<th>NRAS vs. BRAF V600</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95%CI)</td>
<td>1.830 (1.401, 2.391)</td>
<td>1.372 (1.059, 1.776)</td>
<td>0.808 (0.574, 1.136)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>0.016</td>
<td>0.220</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>20</td>
<td>32 (21, 45)</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
<td>3 (0,11)</td>
</tr>
<tr>
<td>PR</td>
<td>18</td>
<td>29 (18, 41)</td>
</tr>
<tr>
<td>SD</td>
<td>16</td>
<td>25 (15, 38)</td>
</tr>
<tr>
<td>PD</td>
<td>25</td>
<td>40 (28, 53)</td>
</tr>
<tr>
<td>DCR</td>
<td>36</td>
<td>57 (44, 70)</td>
</tr>
</tbody>
</table>

• 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)

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

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

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?

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

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

<table>
<thead>
<tr>
<th>NAR score</th>
<th>5-year OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤8.4</td>
<td>88</td>
</tr>
<tr>
<td>8.5–15</td>
<td>81</td>
</tr>
<tr>
<td>15–26.6</td>
<td>75.2</td>
</tr>
<tr>
<td>&gt;26.6</td>
<td>61.7</td>
</tr>
</tbody>
</table>

• 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

<table>
<thead>
<tr>
<th>%</th>
<th>Aflibercept + mFOLFOX6</th>
<th>mFOLFOX6 alone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate</td>
<td>21.7</td>
<td>13.8</td>
<td>0.1938</td>
</tr>
<tr>
<td>Preoperative grade 3–4 AEs†</td>
<td>50</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Completion of CRT</td>
<td>90</td>
<td>96</td>
<td>-</td>
</tr>
<tr>
<td>Completion of surgery</td>
<td>90</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>14.7</td>
<td>12.3</td>
<td>-</td>
</tr>
</tbody>
</table>

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

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