Selected abstracts from:

16 – 18 Jan 2014 | San Francisco, USA
Gastrointestinal Cancers Symposium

31 May – 3 Jun 2014 | Chicago, USA
ASCO Annual Meeting

GI SLIDE DECK 2014

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Eli Lilly and Company has not influenced the content of this publication
Dear Colleagues

It is my pleasure to present this ESDO slide set which has been designed to highlight and summarise key findings in gastric cancers from the major congresses in 2014. This slide set specifically focuses on the American Society of Clinical Oncology Gastrointestinal Cancers Symposium and 50th Annual Meeting.

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

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

Yours sincerely,

Eric Van Cutsem
Wolff Schmiegel
Phillippe Rougier
Thomas Seufferlein
Thomas Grünberger
Jean-Luc Van Laetham
Côme Lepage
(ESDO Governing Board)
Pancreatic cancer and hepatobiliary tumours

Prof Jean-Luc Van Laetham, Hôpital Erasme, Clinique Universitaire de Bruxelles, Belgium
Prof Thomas Seufferlein, Department of Internal Medicine, University of Ulm, Germany

Gastro-oesophageal and neuroendocrine tumours

Prof Philippe Rougier, Hôpital Européen Georges Pompidou, Paris, France
Prof Côme Lepage, Department of Hepatogastroenterology, University of Burgundy, France

Biomarkers

Prof Eric Van Cutsem, Digestive Oncology, University Hospitals, Leuven, Belgium
Prof Thomas Seufferlein, Department of Internal Medicine, University of Ulm, Germany
COLORECTAL CANCER
RECTAL CANCER

PERIOPERATIVE TREATMENT
3500: Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: Results of the German CAO/ARO/AIO-04 randomized phase III trial – Rodel C et al

- **Study objective**
  - To assess whether an integrated and more effective systemic treatment in patients with locally advanced rectal cancer improves survival

**Key patient inclusion criteria**
- Rectal adenocarcinoma
- cT3/4 or cN+ rectal cancer
- ECOG PS 0–2 (n=1265)

**Primary endpoint**
- DFS at 3 years

**Secondary endpoints**
- Toxicity, tumour response, recurrence and OS

**Arm 1**
- RT + 2 cycles of 5-FU followed by TME-surgery + 4 cycles of 5-FU (n=623)

**Arm 2**
- RT + 2 cycles of 5-FU + oxaliplatin followed by TME+ 8 cycles of oxaliplatin+leucovorin+5-FU (n=613)

RT, radiotherapy of 50.4 Gy

Rodel et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3500)
3500: Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: Results of the German CAO/ARO/AIO-04 randomized phase III trial – Rodel C et al

- **Key results**

<table>
<thead>
<tr>
<th>Event</th>
<th>5-FU (n=637)</th>
<th>5-FU+oxaliplatin (n=628)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from randomisation</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Incomplete local resection (R2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loco-regional recurrence after R0/R1 resection</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Distant metastases/progression</td>
<td>149</td>
<td>115</td>
</tr>
<tr>
<td>Death</td>
<td>106</td>
<td>96</td>
</tr>
<tr>
<td>First events for DFS</td>
<td>198</td>
<td>159</td>
</tr>
</tbody>
</table>

**DFS**

Mixed-effects Cox Model:
- HR (95% CI) 0.79 (0.64, 0.98)
- p=0.030
- 3-year DFS: 71.2% vs 75.9%
- 5-year DFS: 64.3% vs 68.8%

**OS**

Mixed-effects Cox Model:
- HR (95% CI) 0.96 (0.72, 1.26)
- p=0.752
- 3-year DFS: 88.0% vs 88.7%
- 5-year DFS: 78.3% vs 78.0%

Rodel et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3500)
Key results

- Grade 3–4 late overall treatment-related toxicity:
  - 22% with 5-FU alone vs 26% with 5-FU+oxaliplatin (p=0.14)

Conclusions

- Preoperative 5-FU+oxaliplatin CRT was well tolerated, with high compliance and increased pCR rate in locally advanced rectal cancer
- 5-FU+oxaliplatin significantly improved DFS compared with 5-FU alone
Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis
– Schmoll H-J et al

**Study objective**

To investigate whether the addition of oxaliplatin to preoperative oral fluoropyrimidine-based CRT followed by postoperative adjuvant fluoropyrimidine-based CT improves outcome in locally advanced rectal cancer (PETACC-6 trial).

*45 Gy (25 fractions) + capecitabine (825 mg/m² bid) days 1–33 w/o weekends; †50 mg/m² days 1, 8, 15, 22, 29; ‡1000 mg/m² bid days 1–15 q3w (6 cycles); § 130 mg/m² day 1, q3w

**Key patient inclusion criteria**

- Rectal cancer within 12 cm from the anal verge
- T3/4 and/or node-positive
- No metastatic disease
- Considered resectable at the time of entry or expected to become resectable after preoperative CRT
- WHO/ECOG PS 0–2 (n=1094)

**Arm 1**

Preoperative CRT* + adjuvant CT with capecitabine‡ (n=547)

**Arm 2**

Preoperative CRT* + oxaliplatin† then adjuvant CT with capecitabine‡ + oxaliplatin§ (n=547)

**Primary endpoint**

- DFS

**Secondary endpoints**

- OS, tumour response

Schmoll et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3501)
Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis
– Schmoll H-J et al

- Key results
  - At median follow-up of 31 months, 3-year DFS with capecitabine alone was higher than anticipated

Cox Model adjusted for stratification factors (except centre)
HR (95% CI) 1.04 (0.81, 1.33)
p=0.78

3-year DFS:
- 74.5% capecitabine
- 73.9% capecitabine+oxaliplatin

Schmoll et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3501)
3501: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis – Schmoll H-J et al

<table>
<thead>
<tr>
<th></th>
<th>Capecitabine (n=543)</th>
<th>Capecitabine+ oxaliplatin (n=526)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse at 3 years, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loco-regional</td>
<td>7.6</td>
<td>4.6</td>
<td>0.094</td>
</tr>
<tr>
<td>Distant</td>
<td>19.2</td>
<td>17.6</td>
<td>0.542</td>
</tr>
<tr>
<td>OS at 3 years, %</td>
<td>89.5</td>
<td>87.4</td>
<td>0.179</td>
</tr>
<tr>
<td>Death without progression, n</td>
<td>15</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

- **Conclusions**
  - The addition of oxaliplatin to preoperative capecitabine-based CRT:
    - Reduced treatment compliance
    - Did not improve R0 resection, pathological CR or sphincter preservation
  - The addition of oxaliplatin to pre- and post-operative capecitabine-based CRT did not improve DFS

Schmoll et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3501)
3603: Final results from NSABP protocol R-04: Neoadjuvant chemoradiation (RT) comparing continuous infusion (CIV) 5-FU with capecitabine (Cape) with or without oxaliplatin (Ox) in patients with stage II and III rectal cancer – Allegra CJ et al

**Study objective**
- To evaluate whether capecitabine can be substituted for standard of care (5-FU) in the curative setting of stage II/III rectal cancer during neoadjuvant RT and whether oxaliplatin enhances its activity

**Primary endpoint**
- Local-regional control with 3 years minimum follow-up

5-FU CIVI 225 mg/m² 5d/wk; RT 46 Gy over 5 wk + boost; Oxaliplatin 50 mg/m²/wk x5; Capecitabine 825 mg/m² po bid

Allegra et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3603)
3603: Final results from NSABP protocol R-04: Neoadjuvant chemoradiation (RT) comparing continuous infusion (CIV) 5-FU with capecitabine (Cape) with or without oxaliplatin (Ox) in patients with stage II and III rectal cancer – Allegra CJ et al

- Key results

The addition of oxaliplatin was associated with significantly more overall AEs and grade 3–4 diarrhoea (p<0.0001)  
Allegra et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3603)
3603: Final results from NSABP protocol R-04: Neoadjuvant chemoradiation (RT) comparing continuous infusion (CIV) 5-FU with capecitabine (Cape) with or without oxaliplatin (Ox) in patients with stage II and III rectal cancer – Allegra CJ et al

• Conclusions
  – The addition of oxaliplatin did not improve outcomes but led to significant rates of diarrhoea and, therefore, is not recommended to be combined with RT in the preoperative rectal setting
  – Capecitabine may be used as standard of care in the preoperative rectal setting
  – Molecular studies using this fully annotated tissue bank are ongoing
RECTAL CANCER

ADJUVANT THERAPY
3502: Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin (FL) for rectal cancer patients whose postoperative yp stage 2 or 3 after preoperative chemoradiotherapy: Updated results of 3-year disease-free survival from a randomized phase II study (The ADORE) – Hong YS et al

**Study objective**
- To investigate the addition of oxaliplatin (FOLFOX regimen) to 5-FU+leucovorin in patients with resected rectal cancer

**Key patient inclusion criteria**
- Patients with curatively resected rectal cancer
- ypStage II (ypT3-4/N0) or ypStage III (ypT any/N1–2)
- Received preoperative CRT with fluoropyrimidines alone (n=321)

**Stratification**
- ypStage (II vs III), centre

**Primary endpoint**
- DFS at 3 years

*oxaliplatin 85 mg/m², leucovorin 200 mg/m², 5-FU bolus 400 mg/m² on day 1, 5-FU infusion 2400 mg/m² for 46 hours q2w for 8 cycles

Hong et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3502)
Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin (FL) for rectal cancer patients whose postoperative yp stage 2 or 3 after preoperative chemoradiotherapy: Updated results of 3-year disease-free survival from a randomized phase II study (The ADORE) – Hong YS et al

Key results

- At median follow-up of 38.2 months patients benefitted more from FOLFOX than 5-FU+leucovorin
3502: Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin (FL) for rectal cancer patients whose postoperative yp stage 2 or 3 after preoperative chemoradiotherapy: Updated results of 3-year disease-free survival from a randomized phase II study (The ADORE) – Hong YS et al

• Conclusions
  – Adjuvant FOLFOX demonstrated improved 3-year DFS in curatively resected rectal cancer patients whose were postoperative ypStage II/III after preoperative CRT
  – Adjuvant FOLFOX remained a significant factor affecting 3-year DFS
COLON CANCER

ADJUVANT THERAPY
386: Regular aspirin (ASA) use and survival in patients with PIK3CA-mutated metastatic colorectal cancer (CRC) – Kothari N et al

• Study objective
  – A retrospective analysis of the benefits on survival of aspirin therapy in CRC and to determine the role of PIK3CA as a predictive biomarker

1019 CRC patients from Royal Melbourne and Western Hospitals (1996–2009)
112 PIK3CA mutants identified (Sanger sequencing for exons 9 and 20)
185 PIK3CA mutants

468 CRC patients from Moffitt Cancer Center and consortium sites (1998–2010)
73 PIK3CA mutants identified (targeted exome sequencing using Illumina NGS technology)

Primary endpoint
• OS

Kothari et al. J Clin Oncol 2014; 32 (suppl 3; abstr 386)
386: Regular aspirin (ASA) use and survival in patients with PIK3CA-mutated metastatic colorectal cancer (CRC) – Kothari N et al

- **Key results**
  - Of 185 patients identified with PIK3CA mutations, mean age was 72 years, median follow-up was 46 months, 107 had right-sided primary site (77 left sided and 1 unknown) and 8 had AJCC stage 1, 66 stage 2, 67 stage 3 and 44 stage 4

<table>
<thead>
<tr>
<th>CRC stage</th>
<th>Outcome</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (n=49)</td>
<td>OS</td>
<td>0.96</td>
<td>0.58, 1.57</td>
<td>0.86</td>
</tr>
<tr>
<td>No aspirin (n=136)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (n=16)</td>
<td>RFS</td>
<td>1.34</td>
<td>0.22, 5.81</td>
<td>0.67</td>
</tr>
<tr>
<td>No aspirin (n=50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (n=22)</td>
<td>RFS</td>
<td>0.85</td>
<td>0.30, 2.40</td>
<td>0.76</td>
</tr>
<tr>
<td>No aspirin (n=45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (n=9)</td>
<td>OS</td>
<td>0.40</td>
<td>0.21, 1.00</td>
<td>0.06</td>
</tr>
<tr>
<td>No aspirin (n=35)</td>
<td></td>
<td></td>
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</tbody>
</table>

Kothari et al. J Clin Oncol 2014; 32 (suppl 3; abstr 386)
Conclusions

- There was no survival benefit associated with aspirin in patients with PIK3CA mutations.
- In patients with stage 2 and 3 CRC aspirin was not demonstrated to provide any benefit on recurrence-free survival.
- There may be a trend towards survival benefit in patients with stage 4 CRC.
3507: Prognostic impact of deficient mismatch repair (dMMR) in 7,803 stage II/III colon cancer (CC) patients (pts): A pooled individual pt data analysis of 17 adjuvant trials in the ACCENT database – Sargent DJ et al

• Study objective
  – To investigate the prognostic effect of mismatch repair of proteins MLH1, MSH2 and MLH6 in patients with stage II/III colon cancer

• Study design
  – Retrospective study analysing data for 7803 patients from 17 trials
    • Patients were treated with 5-FU monotherapy, 5-FU+oxaliplatin, 5-FU+irinotecan or surgery alone
    • Tumours with MSI-high or an absent protein were classified as dMMR; remainder were pMMR
  – Primary endpoints: TTR, OS
  – All analyses were stratified by study arm
  – Median follow-up 7 years

Sargent et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3507)
dMMR, deficient mismatch repair; MSI, microsatellite instability; pMMR, MMR-proficient
Prognostic impact of deficient mismatch repair (dMMR) in 7,803 stage II/III colon cancer (CC) patients (pts): A pooled individual pt data analysis of 17 adjuvant trials in the ACCENT database – Sargent DJ et al

**Key results**
- Compared with pMMR, dMMR was associated with improved survival (table)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-year TTR</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrence-free (%)</td>
<td>HR</td>
</tr>
<tr>
<td></td>
<td>dMMR</td>
<td>pMMR</td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>89</td>
<td>74</td>
</tr>
<tr>
<td>(n=307)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU-mrx (n=1155)</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>Stage III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>60</td>
<td>47</td>
</tr>
<tr>
<td>(n=264)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU-mrx (n=2723)</td>
<td>72</td>
<td>64</td>
</tr>
</tbody>
</table>

Sargent et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3507)
3507: Prognostic impact of deficient mismatch repair (dMMR) in 7,803 stage II/III colon cancer (CC) patients (pts): A pooled individual pt data analysis of 17 adjuvant trials in the ACCENT database – Sargent DJ et al

• **Key results**

<table>
<thead>
<tr>
<th>Multivariate analysis (untreated patients)</th>
<th>TTR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markers</td>
<td>HR</td>
<td>p</td>
</tr>
<tr>
<td>Stage (III vs II)</td>
<td>3.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, 5 years increase</td>
<td>0.95</td>
<td>0.11</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.31</td>
<td>0.09</td>
</tr>
<tr>
<td>Tumor location (right vs left)</td>
<td>0.74</td>
<td>0.06</td>
</tr>
<tr>
<td>T-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 vs T2</td>
<td>3.13</td>
<td>0.05</td>
</tr>
<tr>
<td>T4 vs T2</td>
<td>7.29</td>
<td>0.02</td>
</tr>
<tr>
<td>MMR (dMMR vs pMMR)</td>
<td>0.46</td>
<td>0.01</td>
</tr>
</tbody>
</table>

• **Conclusions**

– MMR status was associated with younger, female patients; N0; T3/4; right sided
– MMR did not impact post-recurrence survival
– MMR is a prognostic marker in untreated stage II and III patients
– MMR is also prognostic in 5-FU, but with reduced impact
– Stage II dMMR patients should not be recommended for treatment due to their excellent prognosis (~90% 5-year OS)

Sargent et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3507)
3508: Impact of adjuvant chemotherapy with 5-FU or FOLFOX in colon cancers with microsatellite instability: An AGEO multicenter study – Tougeron D et al

- **Study objective**
  - To identify predictive factors of recurrence and analyse the efficacy of adjuvant CT with 5-FU or FOLFOX vs surgery alone in patients with MSI-H colon cancer

- **Study design**
  - Retrospective study of 528 patients with stage I, II or III MSI-H CRC who had undergone curative surgery between 2000 and 2011
  - High-risk stage II colon cancers were defined by one of these criteria: stage T4, bowel obstruction, tumour perforation, vascular emboli, lymphatic invasion, perinervous invasion or a number of lymph nodes examined inferior to 10
  - Prognostic factors of RFS were analysed in univariate and multivariate analysis using Cox model

MSI, microsatellite instability; RFS, relapse-free survival
**Key results**

- 3-year DFS: 76% (stage II: 2/6%, stage III: 15/23% with/without CT, respectively)

**Multivariate analysis of DFS with CT vs surgery alone:**

- 5-FU: HR (95% CI) 0.84 (0.37, 1.92), p=0.68
- FOLFOX: HR (95% CI) 0.40 (0.20, 0.79), p=0.009

**Graph:**
- DFS: 3-year DFS:
  - Surgery alone 75%
  - 5-FU 66%
  - FOLFOX 84% (p=0.02)
**3508: Impact of adjuvant chemotherapy with 5-FU or FOLFOX in colon cancers with microsatellite instability: An AGEO multicenter study – Tougeron D et al**

**Key results**
- Subgroup analysis analysing survival by TNM stage or MSI mechanism:

<table>
<thead>
<tr>
<th>Survival</th>
<th>FOLFOX</th>
<th>5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III (n=187)</td>
<td>0.32</td>
<td>0.17, 0.62</td>
</tr>
<tr>
<td>High-risk stage II (n=149)</td>
<td>0.13</td>
<td>0.02, 0.98</td>
</tr>
<tr>
<td>MSI mechanism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic (n=274)</td>
<td>0.55</td>
<td>0.29, 1.04</td>
</tr>
<tr>
<td>Lynch syndrome (n=125)</td>
<td>0.56</td>
<td>0.19, 1.67</td>
</tr>
</tbody>
</table>

**Conclusions**
- In contrast to 5-FU, patients with stage III MSI-H CRC benefit from adjuvant CT with FOLFOX, with a trend for high-risk stage II.
- There was no impact of MSI-H mechanism (sporadic vs Lynch syndrome).
- Further studies are now needed to confirm these results.

Tougeron et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3508)
3547: The 12-gene colon cancer assay validation and utility: Summary of clinical evidence – Burke E et al

- **Study objective**
  - To validate the 12-gene colon cancer assay as a reliable molecular assay to predict the risk of recurrence in stage II/III CRC

- **Study design**
  - Analysis of archived tissue from multiple large, prospectively designed studies with pre-specified methods, clinical outcomes and analysis plan
  - Data from four independent studies were analysed comprising 3315 patients:
    - QUASAR study, stage II colon cancer (n=1436)
    - CALGB 9581 study, stage II colon cancer (n=690)
    - NSABP study, stage II/III colon cancer (n=892)
    - TME trial, stage II/III rectal cancer (n=297)
3547: The 12-gene colon cancer assay validation and utility: Summary of clinical evidence – Burke E et al

- **Key results**
  - There was a significant association (p<0.05) between the assay result and outcome (e.g. recurrence risk: see figures) in all four studies

- **Conclusions**
  - The 12-gene colon assay predicts the risk of recurrence
  - The test may allow clinicians and patients to make more informed decisions regarding adjuvant CT, which may maximise treatment benefits while minimising unnecessary exposure to toxic agents

Burke et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3547)
COLORECTAL CANCER

PALLIATIVE / METASTATIC
LBA3: CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC) – Venook AP et al

- **Study objective**
  - To investigate the optimal combination of first-line CT treatment in patients with metastatic adenocarcinoma of the colon or rectum

**Key patient inclusion criteria**
- Untreated mCRC
- KRAS wild-type (codons 12 + 13)
- ECOG PS 0–1
- Preserved organ function
- FOLFIRI or mFOLFOX6 at enrollment (n=1137)

**Primary endpoint**
- OS

**Secondary endpoints**
- PFS and CT/biological interactions

**CT+cetuximab**
- (1 cycle at 400 mg/m² followed by 250 mg/m² qw)
  - (n=578)
  - PD

**CT+bevacizumab**
- 5 mg/kg q2w
  - (n=559)
  - PD

Venook et al. J Clin Oncol 2014; 32 (suppl 5; abstr LBA3)
**LBA3: CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC) – Venook AP et al**

- **Key results**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>OS (mo)</th>
<th>HR</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT+cetuximab</td>
<td>578</td>
<td>29.9</td>
<td>0.92</td>
<td>0.78, 1.09</td>
<td>0.34</td>
</tr>
<tr>
<td>CT+bevacizumab</td>
<td>559</td>
<td>29.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX+cetuximab</td>
<td>426</td>
<td>30.1</td>
<td>0.9</td>
<td>0.7, 1.0</td>
<td>0.09</td>
</tr>
<tr>
<td>FOLFOX+bevacizumab</td>
<td>409</td>
<td>26.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRI+cetuximab</td>
<td>152</td>
<td>28.9</td>
<td>1.2</td>
<td>0.9, 1.6</td>
<td>0.28</td>
</tr>
<tr>
<td>FOLFIRI+bevacizumab</td>
<td>150</td>
<td>33.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Patients rendered disease-free (n=124): median OS 66.3 (95% CI 59.8, n/a) mo
- Grade 3/4 toxicity: bevacizumab 52%/12.4%; cetuximab 54%/13.7%

- **Conclusions**

- OS with CT+cetuximab was no different from CT+bevacizumab
- FOLFIRI or FOLFOX with either bevacizumab or cetuximab is an appropriate first-line treatment for patients with KRAS wild-type mCRC
- RAS analysis not yet available

Venook et al. J Clin Oncol 2014; 32 (suppl 5; abstr LBA3)
3558: Second-line therapies in patients with *KRAS* wild-type metastatic colorectal cancer (mCRC) after first-line therapy with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK0306 (FIRE 3) trial – Modest DP et al

**Study objective**
- To investigate the choice, duration and outcome of second-line therapies in patients with *KRAS* exon 2 wild-type mCRC

**Patients with mCRC**
- First-line therapy
- *KRAS* exon 2 wild-type

**First-line**
- Arm A: FOLFIRI† + Cetuximab‡ (n=297)
- Arm B: FOLFIRI + Bevacizumab‡ (n=295)

**Second-line**
- Protocol recommended: Arm A=FOLFOX+bevacizumab
  Arm B=Irinotecan+cetuximab
  Physicians free to choose any regimen

**Primary endpoint**
- Overall response rate

**Secondary endpoints**
- PFS and OS

---

*5-FU 400 mg/m² iv bolus + 2400 mg/m² iv 46 h, folinic acid 400 mg/m², irinotecan 180 mg/m²; †cetuximab 400 mg/m² iv 120 min initial dose + 250 mg/m² iv 60 min q1w; ‡bevacizumab 5 mg/kg iv 30–90 min q2w. Modest et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3558)
3558: Second-line therapies in patients with KRAS wild-type metastatic colorectal cancer (mCRC) after first-line therapy with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK0306 (FIRE 3) trial – Modest DP et al

- **Key results**

<table>
<thead>
<tr>
<th></th>
<th>CT+cetuximab</th>
<th>CT+bevacizumab</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, %</td>
<td>62</td>
<td>58</td>
<td>0.183</td>
</tr>
<tr>
<td>PFS, months</td>
<td>10.0</td>
<td>10.3</td>
<td>0.547</td>
</tr>
<tr>
<td>OS, months</td>
<td>28.7</td>
<td>25.0</td>
<td>0.017</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Survival according to 2nd-line mAB use, mo</th>
<th>*CT+cetuximab</th>
<th>*CT+bevacizumab</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>†EGFR</td>
<td>†VEGF</td>
<td>†None</td>
</tr>
<tr>
<td>PFS of 1st-line therapy</td>
<td>9.7</td>
<td>9.7</td>
<td>11.4</td>
</tr>
<tr>
<td>OS of 1st-line therapy</td>
<td>33.5</td>
<td>23.7</td>
<td>38.3</td>
</tr>
<tr>
<td>OS of 2nd-line therapy</td>
<td>17.3</td>
<td>15.3</td>
<td>20.2</td>
</tr>
</tbody>
</table>

- **Conclusions**
  - Patients with favourable first-line PFS were more likely to be treated with no mAB as second-line treatment
  - There was, therefore, a trend towards more favourable OS and second-line OS in patients receiving no second-line mAB therapy
  - There was a trend towards longer second-line therapy in the cetuximab arm

*First-line therapy; †second-line mAB therapy; ‡log-rank  

Modest et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3558)
3550: Survival outcomes in patients (pts) with **KRAS/NRAS (RAS)** wild-type (WT) metastatic colorectal cancer (mCRC) and non-liver-limited disease (non-LLD): Data from the PRIME study – Douillard J-Y et al

- **Study objective**
  - To assess the efficacy of panitumumab+FOLFOX4 vs FOLFOX4 alone in patients with RAS wild-type mCRC whose metastases were not limited to the liver (non-LLD)

- **Study design**
  - *Post-hoc* analysis of the randomised phase III PRIME study, which evaluated panitumumab with FOLFOX4 as first-line therapy in patients with mCRC
    - Patients were randomly allocated (1:1) to panitumumab 6.0 mg/kg q2w + FOLFOX4 or FOLFOX4 alone and had no prior chemotherapy for mCRC, ECOG PS ≤2 and tumour tissue for biomarker testing
    - Exploratory analysis were conducted when ≥80% of patients had an OS event, median PFS and OS were estimated for patients with RAS wild-type mCRC (**KRAS/NRAS** exons 2–4 assessed, including codon 59) and non-LLD
    - 3-year PFS and OS rates were also evaluated
3550: Survival outcomes in patients (pts) with *KRAS/NRAS (RAS)* wild-type (WT) metastatic colorectal cancer (mCRC) and non-liver-limited disease (non-LLD): Data from the PRIME study – Douillard J-Y et al

- **Key results**
  - mPFS/OS were longer in patients receiving panitumumab+FOLFOX4 vs FOLFOX4

<table>
<thead>
<tr>
<th></th>
<th>Events (n)</th>
<th>mPFS (mo)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumab+</td>
<td>181</td>
<td>11.1</td>
<td>0.73 (0.60, 0.90)</td>
<td>0.0027</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>192</td>
<td>8.0</td>
<td></td>
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<tr>
<td>FOLFOX4</td>
<td>166</td>
<td>23.8</td>
<td>0.78 (0.63, 0.96)</td>
<td>0.0185</td>
</tr>
<tr>
<td>Panitumab+</td>
<td>186</td>
<td>18.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Conclusion**
  - The PFS and OS benefits observed with 1st-line panitumumab+FOLFOX4 vs FOLFOX4 alone in the overall PRIME population are also seen in the subgroup of patients who have non-LLD

Douillard et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3550)
Survival outcomes in the PRIME study for patients (pts) with *RAS/BRAF* wild-type (WT) metastatic colorectal cancer (mCRC), by baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) – Peeters M et al

**Study objective**
- To estimate treatment effect of panitumumab+FOLFOX4 vs FOLFOX4 alone on OS in patients with *RAS/BRAF* wild-type mCRC by baseline ECOG status

**Study design**
- *Post-hoc* analysis of the randomised phase III PRIME study, which evaluated panitumumab+FOLFOX4 as first-line treatment in patients with mCRC
  - Patients were randomly allocated to panitumumab 6.0 mg/kg q2w + FOLFOX4 or FOLFOX4 alone and had no prior chemotherapy for mCRC, ECOG PS ≤2 and tumour tissue for biomarker testing
  - Exploratory analysis was conducted when ≥80% of patients had an OS event, median PFS and OS were estimated for patients with *RAS/BRAF* wild-type mCRC, tested for *NRAS* exon 2 (codons 12/13), *KRAS/NRAS* exon 3 (codons 59/61) and exon 4 (codons 117/146) and *BRAF* exon 15 (codon 600)
  - Median PFS and OS were estimated by baseline ECOG (PS)

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3557)
3557: Survival outcomes in the PRIME study for patients (pts) with \textit{RAS/BRAF} wild-type (WT) metastatic colorectal cancer (mCRC), by baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) – Peeters M et al

- **Key results**
  - Longer mPFS/OS in patients receiving panitumumab+FOLFOX4 vs FOLFOX4

<table>
<thead>
<tr>
<th></th>
<th>Events (n)</th>
<th>mPFS (mo)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab + FOLFOX4</td>
<td>177</td>
<td>12.3</td>
<td>0.69</td>
<td>0.0007</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>181</td>
<td>9.3</td>
<td>(0.56, 0.86)</td>
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</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab + FOLFOX4</td>
<td>157</td>
<td>29.7</td>
<td>0.71</td>
<td>0.0022</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>169</td>
<td>23.1</td>
<td>(0.57, 0.88)</td>
<td></td>
</tr>
</tbody>
</table>

- **Conclusion**
  - The PFS/OS benefits observed in patients with \textit{RAS/BRAF} wild-type mCRC receiving panitumumab+FOLFOX4 are mainly confined to those with a baseline ECOG PS of 0/1

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3557)
3506: Treatment outcome according to tumor RAS mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab – Ciardiello F … Van Cutsem E et al

- **Study objective**
  - Retrospective analysis to investigate the treatment effect of FOLFIRI+cetuximab vs FOLFIRI alone in patients with mCRC

**Key patient inclusion criteria**
- mCRC
- EGFR expressing
- Previously untreated
  
  \( n=1198 \)

**Primary endpoint**
- PFS

**Secondary endpoint**
- OS

**Stratification**
- ECOG PS, region

**FOLFIRI* alone (n=599)**

**FOLFIRI* + cetuximab† (n=599)**

*Irinotecan 180 mg/m² day 1, leucovorin 200 mg/m² day 1, 5-FU 400 mg/m² bolus then 2400 mg/m² infusion over 46 h; †cetuximab 400 mg/m² initial dose then 250 mg/m² weekly

Ciardiello et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3506)

*Presented by Van Cutsem E*
3506: Treatment outcome according to tumor RAS mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab – Ciardiello F … Van Cutsem E et al

**Key results**

- Other RAS mutations were detected in 63/430 (15%) patients
- In those with RAS wild-type tumours, a significant benefit across all endpoints was associated with the addition of cetuximab to FOLFIRI (table)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RAS wild-type (all loci)</th>
<th>Other RAS mutant†</th>
<th>RAS mutant‡ (any locus)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOX4+cet (n=178)</td>
<td>FOLFOX4 (n=189)</td>
<td>FOLFOX4+cet (n=32)</td>
</tr>
<tr>
<td>Response rate, %</td>
<td>66.3</td>
<td>38.6</td>
<td>34.4</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>3.11</td>
<td>1.02</td>
<td>0.85</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.03, 4.78</td>
<td>0.33, 3.15</td>
<td>0.58, 1.25</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>0.97</td>
<td>0.40</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>11.4</td>
<td>8.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.56</td>
<td>0.81</td>
<td>1.10</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.41, 0.76</td>
<td>0.39, 1.67</td>
<td>0.85, 1.42</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0002</td>
<td>0.56</td>
<td>0.47</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>28.4</td>
<td>20.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.69</td>
<td>1.22</td>
<td>1.05</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.54, 0.88</td>
<td>0.69, 2.16</td>
<td>0.86, 1.28</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0024</td>
<td>0.50</td>
<td>0.64</td>
</tr>
</tbody>
</table>

†KRAS codon 12/13 or other RAS; ‡KRAS codon 12/13 wild-type

Ciardiello et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3506)  
*Presented by Van Cutsem E*
Conclusions

- This study supports the use of FOLFIRI+cetuximab as first-line treatment in patients with RAS wild-type mCRC
  
  - Significant improvements in PFS, OS and objective response rate
  
  - No beneficial or deleterious effects were observed with FOLFIRI+cetuximab in patients with RAS mutations

- The safety profile in the RAS wild-type and RAS mutant subgroups was similar and in-line with expectations

- The exclusion of patients with other RAS mutations from the KRAS codon 12/13 wild-type treatment population improved the benefit-to-risk ratio associated with the addition of cetuximab to FOLFIRI

Ciardiello et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3506)

Presented by Van Cutsem E
3505: Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab – Bokemeyer C et al

• Study objective
  – To investigate treatment effect of cetuximab+FOLFOX4 vs FOLFOX4 alone on survival by KRAS status (exons 3 and 4) and NRAS (exons 2, 3 and 4)

Key patient inclusion criteria
• mCRC
• EGFR-expressing
• Previously untreated (n=337)

Primary endpoint
• Objective response

Secondary endpoints
• PFS and OS

Stratification
• ECOG PS

FOLFOX* + cetuximab† (n=169) → PD
FOLFOX* alone (n=168) → PD

Primary endpoint
• Objective response

Secondary endpoints
• PFS and OS

*Oxaliplatin 85 mg/m² day 1, leucovorin 200 mg/m² days 1+2, 5-FU 400 mg/m² bolus then 600 mg/m² infusion days 1+2; †400 mg/m² initial dose then 250 mg/m² weekly

Bokemeyer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3505)
3505: Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab – Bokemeyer C et al

**Key results**

- In those with *RAS* wild-type tumours, response was significantly improved by the addition of cetuximab to FOLFOX4 (table)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RAS wild-type* (all loci)</th>
<th>Other RAS mutation†</th>
<th>RAS mutation‡ (any locus)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOX4+cet (n=38)</td>
<td>FOLFOX4 (n=49)</td>
<td>FOLFOX4+cet (n=15)</td>
</tr>
<tr>
<td>Response rate, %</td>
<td>57.9</td>
<td>28.6</td>
<td>53.3</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>3.33</td>
<td>1.50</td>
<td>0.58</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.36, 8.17</td>
<td>0.34, 6.53</td>
<td>0.31, 1.08</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0084</td>
<td>0.59</td>
<td>0.0865</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>12.0</td>
<td>5.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.53</td>
<td>0.77</td>
<td>1.54</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.27, 1.04</td>
<td>0.28, 2.08</td>
<td>1.04, 2.29</td>
</tr>
<tr>
<td>p-value§</td>
<td>0.0615</td>
<td>0.60</td>
<td>0.0309</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>19.8</td>
<td>17.8</td>
<td>18.4</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.94</td>
<td>1.09</td>
<td>1.29</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.56, 1.56</td>
<td>0.44, 2.68</td>
<td>0.91, 1.84</td>
</tr>
<tr>
<td>p-value</td>
<td>0.80</td>
<td>0.86</td>
<td>0.1573</td>
</tr>
</tbody>
</table>

* RAS evaluable population, n=118; †*KRAS* codon 12/13 or other RAS; ‡*KRAS* codon 12/13 wild-type

Bokemeyer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3505)
Conclusions

- In *RAS* wild-type patients, the addition of cetuximab to FOLFOX4 significantly improved objective response rate and has a positive impact on PFS.
- In *RAS* mutant patients, combining cetuximab with FOLFOX4 was associated with a negative effect.
- The safety profile in the *RAS* wild-type and *RAS* mutant subgroups was similar and in-line with expectations.
- Restricting cetuximab administration to patients with *RAS* wild-type tumours might help tailor therapy to maximise patient benefit.
Study objective

- To retrospectively examine the effects on survival of FOLFIRI+panitumumab compared with FOLFIRI alone in patients with wild-type KRAS (exon 2) mCRC based on RAS/BRAF mutation status

Patients with mCRC
- Documented disease progression
- No prior EGFR inhibitor or irinotecan therapy
- ECOG PS 0–2 (n=1186)

Secondary endpoints
- ORR and safety

Primary endpoints
- PFS and OS

Stratification
- ECOG PS 0–1 vs 2
- Prior oxaliplatin exposure
- Prior bevacizumab exposure

FOLFIRI q2w + panitumumab 6 mg/kg q2w

FOLFIRI q2w

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3568)
3568: Updated analysis of KRAS/NRAS and BRAF mutations in study 20050181 of panitumumab (pmab) plus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC) – Peeters M et al

- Key results

### PFS

<table>
<thead>
<tr>
<th>Efficacy analysis sets</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT KRAS Exon 2</td>
<td>597</td>
<td>0.73</td>
<td>0.59, 0.90</td>
</tr>
<tr>
<td>MT KRAS Exon 2</td>
<td>495</td>
<td>0.85</td>
<td>0.68, 1.06</td>
</tr>
<tr>
<td>WT RAS</td>
<td>421</td>
<td>0.70</td>
<td>0.54, 0.91</td>
</tr>
<tr>
<td>MT RAS</td>
<td>593</td>
<td>0.85</td>
<td>0.70, 1.05</td>
</tr>
<tr>
<td>WT KRAS Exon 2 MT RAS</td>
<td>107</td>
<td>0.89</td>
<td>0.56, 1.42</td>
</tr>
<tr>
<td>WT RAS/BRAF</td>
<td>376</td>
<td>0.69</td>
<td>0.51, 0.90</td>
</tr>
<tr>
<td>WT RAS MT BRAF</td>
<td>45</td>
<td>0.69</td>
<td>0.32, 1.49</td>
</tr>
<tr>
<td>MT RAS/BRAF</td>
<td>638</td>
<td>0.87</td>
<td>0.72, 1.06</td>
</tr>
<tr>
<td>Unevaluable RAS</td>
<td>172</td>
<td>0.83</td>
<td>0.59, 1.32</td>
</tr>
<tr>
<td>Unevaluable RAS/BRAF</td>
<td>172</td>
<td>0.83</td>
<td>0.59, 1.32</td>
</tr>
</tbody>
</table>

### OS

<table>
<thead>
<tr>
<th>Efficacy analysis sets</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT KRAS Exon 2</td>
<td>597</td>
<td>0.85</td>
<td>0.70, 1.04</td>
</tr>
<tr>
<td>MT KRAS Exon 2</td>
<td>495</td>
<td>0.94</td>
<td>0.76, 1.15</td>
</tr>
<tr>
<td>WT RAS</td>
<td>421</td>
<td>0.81</td>
<td>0.63, 1.03</td>
</tr>
<tr>
<td>MT RAS</td>
<td>593</td>
<td>0.91</td>
<td>0.76, 1.10</td>
</tr>
<tr>
<td>WT KRAS Exon 2 MT RAS</td>
<td>107</td>
<td>0.83</td>
<td>0.53, 1.29</td>
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<td>WT RAS/BRAF</td>
<td>376</td>
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<td>0.64, 1.07</td>
</tr>
<tr>
<td>WT RAS MT BRAF</td>
<td>45</td>
<td>0.64</td>
<td>0.32, 1.28</td>
</tr>
<tr>
<td>MT RAS/BRAF</td>
<td>638</td>
<td>0.93</td>
<td>0.76, 1.08</td>
</tr>
<tr>
<td>Unevaluable RAS</td>
<td>172</td>
<td>1.02</td>
<td>0.71, 1.47</td>
</tr>
<tr>
<td>Unevaluable RAS/BRAF</td>
<td>172</td>
<td>1.02</td>
<td>0.71, 1.47</td>
</tr>
</tbody>
</table>

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3568)
Conclusions

- Improvements in OS and PFS were observed with panitumumab+FOLFIRI vs FOLFIRI alone in wild-type RAS group vs wild-type KRAS exon 2 group.
- Patients with mutant RAS mCRC are unlikely to benefit by the addition of panitumumab to FOLFIRI, similar to patients with mutant KRAS exon 2 mCRC.
- BRAF mutations appear to be associated with reduced OS among patients without RAS mutations regardless of treatment arm.
- These findings support RAS testing to determine which patients with mCRC should potentially receive panitumumab treatment.

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3568)
Early predictors of prolonged overall survival (OS) in patients (pts) on first-line chemotherapy (CT) for metastatic colorectal cancer (mCRC): An ARCAD study with individual patient data (IPD) on 10,962 pts
– Sommeijer DW et al

**Study objective**
- To evaluate at the patient level the association between early response-based endpoints vs long-term outcomes in patients with mCRC treated with first-line CT

**Study design**
- A retrospective analysis of data from 10,962 patients from 16 phase III trials in the ARCAD database
- Patients were treated with 5FU-LV/capecitabine±oxaliplatin/irinotecan
- Early response at 6, 8/9 or 12 weeks, measured as:
  - Early tumour shrinkage (≥20% decrease from baseline)
  - Early objective tumour response (CR/PR by RECIST)
  - Early non-progression status (CR/PR/SD by RECIST)
were correlated with best overall response and confirmed response within the initial 26 weeks of treatment

Sommeijer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3538)
Early predictors of prolonged overall survival (OS) in patients (pts) on first-line chemotherapy (CT) for metastatic colorectal cancer (mCRC): An ARCAD study with individual patient data (IPD) on 10,962 pts

– Sommeijer DW et al

**Key results**

- Early responses were significantly associated with prolonged OS
- The association between early endpoints and OS was as strong as the associations between standard endpoints and OS

**Conclusions**

BOR, best overall response; ConfR, confirmed response

Sommeijer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3538)
Study objective
- To explore the association between clinical characteristics of mCRC and the site of the primary tumour

Study design
- Retrospective study of data from 2972 patients in the South Australian mCRC registry
- Differences in patient characteristics, treatment received and outcomes were correlated with location of the primary tumour
  - Right colon (n=1046; caecum to transverse colon)
  - Left colon (n=1103; splenic flexure to sigmoid)
  - Rectal (n=823)
- Kaplan-Meier was used for survival outcomes and Cox proportional hazards regression modeling was used to assess defined prognostic markers
3540: Survival outcomes for patients with metastatic colorectal cancer (mCRC) based on primary site, right (R) colon versus left (L) colon versus rectal (Rec) primary: Results from the South Australian Registry of mCRC – Tomita Y et al

• Key results

OS by primary site

- Right colon primary mCRC was associated with less favourable prognostic factors and poorer outcomes than left colon/rectal primary mCRC

• Conclusion

- Right colon primary mCRC was associated with less favourable prognostic factors and poorer outcomes than left colon/rectal primary mCRC

Tomita et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3540)
3503: Maintenance strategy with fluoropyrimidines (FP) plus Bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A phase III non-inferiority trial (AIO KRK 0207) – Arnold D et al

- **Study objective**
  - To investigate the optimal maintenance strategy in patients with mCRC following first-line combination CT

**Key patient inclusion criteria**
- mCRC
- First-line standard treatment FP+oxaliplatin+bevacizumab for 24 weeks (n=852)

**Primary endpoint**
- TFS

**Secondary endpoints**
- PFS1, OS and toxicity

**Stratification**
- Adjuvant treatment, CR/PR vs SD, ECOG PS

FP, fluoropyrimidines; PFS1, time to first progression; TFS, time to failure of strategy

Arnold et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3503)
3503: Maintenance strategy with fluoropyrimidines (FP) plus Bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A phase III non-inferiority trial (AIO KRK 0207) – Arnold D et al

- Key results
  - PFS1 improved with treatment intensity and FP/bevacizumab was better than bevacizumab alone and this was better than no treatment

---

**PFS1 from start of maintenance**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>Median (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP/Bev</td>
<td>141</td>
<td>6.2</td>
</tr>
<tr>
<td>Bev</td>
<td>153</td>
<td>4.8</td>
</tr>
<tr>
<td>No therapy</td>
<td>153</td>
<td>3.6</td>
</tr>
</tbody>
</table>

**mPFS1: 4.6 months**

Log rank test: p<0.0001

Arnold et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3503)
Conclusions

- Using a TFS strategy following 6 months of induction with CT demonstrated that
  - Maintenance with bevacizumab is non-inferior to FP/bevacizumab
  - Non-inferiority cannot be concluded for no active treatment
- FP plus bevacizumab or bevacizumab alone, showed prolonged TFS over no treatment
- Only a minority of patients received re-induction treatment as planned
- Preliminary OS showed no difference between the treatment arms
**Study objective**

- To examine the efficacy of observation vs maintenance treatment with capecitabine+bevacizumab after induction treatment with CAPOX-B; 6 cycles

**Key patient inclusion criteria**
- Patients with mCRC
- Stable disease or better after 1st-line CAPOX-B (6 cycles)
- No intention of radical resection of metastases (n=558)

**Primary endpoint**
- PFS2

CAPOX-B, capecitabine, oxaliplatin+bevacizumab

Koopman et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3504)
Key results

<table>
<thead>
<tr>
<th></th>
<th>Observation (95% CI), mo</th>
<th>Maintenance (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS1</td>
<td>4.1 (3.9, 4.2)</td>
<td>8.5 (6.5, 10.3)</td>
<td>0.43 (0.36, 0.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median PFS2</td>
<td>8.5 (7.4, 10.4)</td>
<td>11.7 (10.1, 13.3)</td>
<td>0.67 (0.56, 0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TT2PD</td>
<td>11.1 (10.3, 12.6)</td>
<td>13.9 (12.3, 15.6)</td>
<td>0.68 (0.57, 0.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median OS</td>
<td>18.1 (16.3, 20.2)</td>
<td>21.6 (19.4, 23.8)</td>
<td>0.89 (0.73, 1.07)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

- QoL was maintained during maintenance treatment and was clinically not inferior vs the observation arm (between group difference 3.9 [95% CI 1.2, 6.5]; p=0.004)
- A subgroup analysis showed significant survival effects for the following factors:
  - [PFS2]: Treatment arm, response to induction therapy, serum LDH and metachronous vs synchronous with/without resection of primary tumour
  - [OS]: Treatment arm, response to induction therapy, WHO PS, site of primary tumour and metachronous vs synchronous with/without resection of primary tumour

TT2PD, time to second progression of disease, time from randomisation to progression upon any treatment given after PFS1

Koopman et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3504)
3504: Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer (mCRC) – Koopman M et al

- **Key results**

  - **OS: synchronous/metachronous ± resection primary**
    - Median OS in months
      - Metachronous: 24.8 (95% CI 22.0, 29.7) n=147
      - Synchronous-R: 21.4 (95% CI 18.7, 24.2) n=180
      - Synchronous-nR: 15.7 (95% CI 13.2, 17.6) n=230
    - Log-rank p-value <0.0001
    - Induction treatment of 6x cycles CAPOX-B prior to randomisation not included (4–5 mo)

  - **OS: synchronous/metachronous ± resection primary**
    - Median OS in months
      - Metachronous: 25.8 (95% CI 19.2, 31.4) n=147
      - Synchronous-R: 18.0 (95% CI 14.6, 21.7) n=180
      - Synchronous-nR: 16.3 (95% CI 14.1, 18.3) n=230
    - Log-rank p-value <0.0001
    - Induction treatment of 6x cycles CAPOX-B prior to randomisation not included (4–5 mo)

- **Conclusions**
  - Benefits were observed in all subgroups for PFS2, PFS1 and TT2PD
  - Patients with synchronous disease with resected primary tumour and patients with a CR/PR as best response to induction treatment may benefit most from maintenance treatment in terms of OS

Koopman et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3504)
COLORECTAL CANCER

BIOMARKERS
Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) – Stintzing S et al

- **Study objective**
  - To investigate the influence of mutations on the efficacy of cetuximab in addition to standard CT in patients with mCRC

Patients with mCRC
- First-line therapy
- *KRAS* wild-type (n=592)

Primary endpoint
- ORR

FOLFIRI q2w, 5-FU: 400 mg/m² (IV bolus), folinic acid 400 mg/m², irinotecan 180 mg/m²; 5-FU 2400 mg/m² (IV 46 h)
Cetuximab: 400 mg/m² IV 120 min initial dose, then 250 mg/m² IV 60 min q1w
Bevacizumab: 5 mg/kg IV 30–90 I q2w

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)
445: Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) – Stintzing S et al

- **Key results**
  - Frequency of mutations in the EGFR pathway

<table>
<thead>
<tr>
<th>Exon</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>9</th>
<th>11</th>
<th>15</th>
<th>20</th>
<th>E17K</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS, %</td>
<td></td>
<td>wt</td>
<td>4.3</td>
<td>4.9</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NRAS, %</td>
<td></td>
<td>3.8</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3CA, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.3</td>
<td></td>
<td></td>
<td>2.0</td>
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</tr>
<tr>
<td>AKT, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
</tbody>
</table>

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)
**Key results**

<table>
<thead>
<tr>
<th>ORR</th>
<th>FOLFIRI+ cetuximab % (95% CI)</th>
<th>FOLFIRI+ bevacizumab % (95% CI)</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS exon 2 WT (ITT; n=592)</td>
<td>62.0 (56.2, 67.5)</td>
<td>58.0 (52.1, 63.7)</td>
<td>1.18 (0.85, 1.64)</td>
<td>0.183</td>
</tr>
<tr>
<td>RAS WT (n=342)</td>
<td>65.5 (57.9, 72.6)</td>
<td>59.6 (51.9, 67.1)</td>
<td>1.28 (0.83, 1.99)</td>
<td>0.32</td>
</tr>
<tr>
<td>RAS MT (n=65)</td>
<td>38.2 (22.2, 56.4)</td>
<td>58.1 (39.1, 75.5)</td>
<td>0.45 (0.17, 1.21)</td>
<td>0.14</td>
</tr>
<tr>
<td>KRAS exon 2 MT &amp; RAS MT (n=178)</td>
<td>38.0 (28.1, 48.8)</td>
<td>52.1 (40.1, 62.1)</td>
<td>0.59 (0.32, 1.06)</td>
<td>0.097</td>
</tr>
<tr>
<td>BRAF mutant (n=48)</td>
<td>52.2 (30.6, 73.2)</td>
<td>40.0 (21.1, 61.3)</td>
<td>1.64 (0.52, 5.14)</td>
<td>0.29</td>
</tr>
<tr>
<td>PIK3CA mutant (n=38)</td>
<td>47.4 (24.4, 71.1)</td>
<td>57.0 (33.5, 79.7)</td>
<td>0.65 (0.18, 2.36)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)
Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) – Stintzing S et al

### Key results

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI+ cetuximab</th>
<th>FOLFIRI+ bevacizumab</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS exon 2 WT (ITT; n=592)</td>
<td>250/297 (84.2)</td>
<td>242/295 (82.0)</td>
<td>1.06 (0.88, 1.26)</td>
<td>0.547</td>
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<tr>
<td></td>
<td>10.0 (8.8, 10.8)</td>
<td>10.3 (9.8, 11.3)</td>
<td></td>
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</tr>
<tr>
<td>RAS WT (n=342)</td>
<td>144/171 (84.2)</td>
<td>143/171 (83.6)</td>
<td>0.93 (0.74, 1.17)</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>10.4 (9.5, 12.2)</td>
<td>10.2 (9.3, 11.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF mutant (n=48)</td>
<td>22/23 (95.7)</td>
<td>25/25 (100)</td>
<td>0.87 (0.49, 1.57)</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>4.9 (2.4, 8.8)</td>
<td>6.0 (4.3, 7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3CA mutant (n=38)</td>
<td>18/19 (94.7)</td>
<td>15/19 (78.9)</td>
<td>1.61 (0.80, 3.25)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>7.8 (5.1, 10.8)</td>
<td>13.3 (4.9, 28.9)</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI+ cetuximab</th>
<th>FOLFIRI+ bevacizumab</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS exon 2 WT (ITT; n=592)</td>
<td>158/297 (53.2)</td>
<td>185/295 (62.7)</td>
<td>0.77 (0.62, 0.96)</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>28.7 (24.0, 36.6)</td>
<td>25.0 (22.7, 27.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS WT (n=342)</td>
<td>91/171 (53.2)</td>
<td>110/171 (64.3)</td>
<td>0.70 (0.53, 0.92)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>33.1 (24.5, 39.4)</td>
<td>25.6 (22.7, 28.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF mutant (n=48)</td>
<td>18/23 (78.3)</td>
<td>24/25 (96.0)</td>
<td>0.87 (0.47, 1.61)</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>12.3 (5.5, 21.7)</td>
<td>13.7 (7.8, 19.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3CA mutant (n=38)</td>
<td>13/19 (68.4)</td>
<td>11/19 (57.9)</td>
<td>1.08 (0.48, 2.43)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>26.5 (14.2, 30.6)</td>
<td>25.9 (21.0, 33.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)
Conclusions

- Comparable findings for ORR and PFS were found in both treatment groups in patients with all-RAS wild-type tumours.
- Patients with all-RAS wild-type tumours who received cetuximab as first-line therapy had a markedly superior OS.
- In patients with RAS-mutant tumours there was no difference between treatment with FOLFIRI+cetuximab or FOLFIRI+bevacizumab.
- Comparable findings for ORR, PFS and OS were demonstrated in patients with BRAF mutant tumours between the two treatment groups.
- For patients with PIK3CA mutant tumours comparable findings were observed for ORR and OS between the two treatment groups.
- In patients with PIK3CA mutant tumours PFS was longer (but not significantly) in those who received FOLFIRI+bevacizumab compared with FOLFIRI+cetuximab.
- It is recommended that RAS (KRAS and NRAS) mutation status should be determined upfront in patients with mCRC.
3539: Correlation of *PI3KCA* and extended *RAS* gene mutation status with outcomes from the phase III AGITG MAX involving capecitabine (C) along or in combination with bevacizumab (B) with or without mitomycin C (M) advanced colorectal cancer (CRC) – Price TJ et al

- **Study objective**
  - To investigate the prognostic and predictive value of extended *RAS* and *PI3KCA* mutation status in patients with advanced CRC treated with capecitabine± bevacizumab±mitomycin C

- **Study design**
  - Randomised phase III study (MAX) of patients with advanced CRC who were randomly allocated to capecitabine alone or in combination with bevacizumab with or without mitomycin C
  - DNA macrodissected from archival formalin-fixed paraffin-embedded tumour tissue
  - Mutation status for *KRAS* and *NRAS* (both exons 2, 3, 4) determined using pyrosequencing and confirmed with Sanger sequencing (for equivocal *RAS*)
  - Mutation status (wild-type vs mutated) was correlated with efficacy outcomes (RR, PFS and OS)
  - Predictive analyses were undertaken using a test for interaction

Price et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3539)
Correlation of *PI3KCA* and extended *RAS* gene mutation status with outcomes from the phase III AGITG MAX involving capecitabine (C) along or in combination with bevacizumab (B) with or without mitomycin C (M) advanced colorectal cancer (CRC) – Price TJ et al

**Key results**
- The total proportion with any *RAS* mutant was 40.9%
- *PI3K* mutant rate was 7.5% for exon 9, and 3.6% for exon 20
- *RAS* status (wild-type vs mutated) had no prognostic impact for PFS (HR 0.92)
- *RAS* status did not predict efficacy of bevacizumab for PFS (p=0.51)
- *PI3KCA* mutation was neither predictive for bevacizumab effect nor prognostic

![Graphs showing OS by RAS and PIK3CA status](image-url)
Conclusions

- *RAS* or *PI3KCA* mutation status did not appear to have any therapeutic implication when bevacizumab was given in addition to capecitabine CT.
- *RAS* or *PI3KCA* mutation status was not prognostic for PFS or OS, or predictive of bevacizumab outcome in patients with advanced CRC.
- A clinically relevant proportion of patients (11.2%) considered *KRAS* wild-type have an additional mutation in the *RAS* pathway.
3559: Cell-free DNA levels in colorectal cancer patients treated with irinotecan, healthy controls, and non-cancer patients with comorbidity – Spindler K-LG et al

- **Study objective**
  - To investigate the clinical value of total cell free DNA (cfDNA) measurement in patients with mCRC treated with second-line irinotecan monotherapy

- **Study design**
  - Patients with mCRC (n=100) treated with second-line irinotecan were compared with a cohort of healthy controls with and without comorbidity (n=70 and n=100, respectively)
  - Plasma samples drawn prior to the first cycle of chemotherapy and at time of progression were analysed for cfDNA using qPCR

Spindler et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3559)
3559: Cell-free DNA levels in colorectal cancer patients treated with irinotecan, healthy controls, and non-cancer patients with comorbidity – Spindler K-LG et al

- **Key results**
  - cfDNA levels were significantly higher in cancer patients compared with control cohort, with a clear capability for discriminating between the groups (AUC 0.82, p<0.0001)
  - Patients with high levels of cfDNA had a shorter outcome compared with those with lower levels according to upper normal limit levels
    - PFS: 2.1 vs 6.5 months for high vs low levels (HR 2.53 [95% CI 1.57, 4.06], p≤0.0001)
    - OS: 7.4 vs 13.8 months for high vs low levels (HR 2.52 [95% CI 1.54, 4.13], p<0.0001)
  - Cox regression multivariate analysis showed a PFS HR of 1.4 (95% CI 1.1, 1.7; p=0.03) for each increase in cfDNA quartile and HR of 1.6 (95% CI 1.3, 2.0; p<0.0001) for OS

- **Conclusion**
  - Measurement of cfDNA contains important clinical information and may become a useful tool for predicting outcomes from chemotherapy in mCRC

Spindler et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3559)
3606: Impact of PI3K aberrations on efficacy of perifosine (P), x-PECT: A phase III randomized study of P plus capecitabine (PC) versus placebo plus capecitabine (C) in refractory metastatic colorectal cancer (mCRC) patients – Eng C et al

- **Study objective**
  - To investigate whether patients with PI3K aberrations (*PIK3CA* and PTEN loss) would show better outcomes with perifosine, a synthetic alkylphospholipid that affects signalling pathways including PI3K/Akt, PTEN and NF-κB

Patients with mCRC
- Failed all available therapy
- Progressive disease
- *KRAS* wild-type
- EOGP PS 0–1
- Age ≥18 years (n=468)

Primary endpoint
- OS

Eng et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3606)
3606: Impact of PI3K aberrations on efficacy of perifosine (P), x-PECT: A phase III randomized study of P plus capecitabine (PC) versus placebo plus capecitabine (C) in refractory metastatic colorectal cancer (mCRC) patients – Eng C et al

• Key results
  – 45% of all patients had a KRAS mutation; NRAS (1%); BRAF (3%); PIK3CA (9%); Akt (<1%) and loss of PTEN (16%) by IHC
  – PIK3CA mutation or loss of PTEN occurred in 25% of patients

• Conclusions
  – There was no improvement in OS with perifosine+capecitabine vs capecitabine alone
  – The presence of a PI3K aberration (PIK3CA and PTEN loss) did not appear to be associated with an improved efficacy of perifosine

Eng et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3606)
PANCREATIC CANCER & HEPATOBILIARY TUMOURS
4001: Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study – Huguet F et al

- **Study objective**
  - To determine whether OS is improved with CRT in patients with locally advanced pancreatic cancer whose tumour is controlled after 4 months of induction CT

**Key patient inclusion criteria**
- Locally advanced pancreatic cancer (n=442)

**Primary endpoint**
- OS

**Secondary endpoints**
- PFS and tolerance

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1000 mg/m²/wk x3; †100 mg/day; ‡54 Gy (5x 1.8 Gy/day) + capecitabine 1600 mg/m²/day; ¥150 mg/day maintenance

Huguet et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4001)
**4001: Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study – Huguet F et al**

- **Key results**

  - **PFS**: CT 8.4 mo vs CRT 9.9 mo; HR 0.78 (95% CI 0.61, 1.01); p=0.055
  - **Site of first progression (R2 patients):**
    - Local/metastatic tumour progression: CT 46%/44% vs CRT 32%/60% (p=0.035)
  - **Time without treatment**: CT 3.7 mo vs CRT 6.1 mo (p=0.017)

Huguet et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4001)
Conclusions

- OS was not improved in the CRT arm
- There was a trend towards improved PFS and a longer period without treatment plus significantly less local tumour progression in the CRT arm, which could impact on the patients’ quality of life
- This study confirmed the value of frontline CT in patients with locally advanced pancreatic cancer to identify patients suitable for novel locoregional therapies
4122: Gemcitabine(G)/erlotinib(E) versus gemcitabine/erlotinib/capecitabine(C) in the first-line treatment of patients with metastatic pancreatic cancer (mPC): Efficacy and safety results of a phase IIb randomized study from the Spanish TTD Collaborative Group – Benavides M et al

- **Study objective**
  - To compare the efficacy and safety of gemcitabine/erlotinib/capecitabine (GEC) vs gemcitabine/erlotinib (GE) in the first-line treatment of patients with metastatic pancreatic cancer

**Key patient inclusion criteria**
- Previously untreated patients with metastatic pancreatic cancer (n=120)

- **Primary endpoint**
  - PFS

- **Secondary endpoints**
  - OS, RR, relationship of rash with PFS/OS and safety

*1000 mg/m² days 1, 8, 15; †100 mg/day po; ‡830 mg/m²/12h days 1–21

Benavides et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4122)
**4122: Gemcitabine(G)/erlotinib(E) versus gemcitabine/erlotinib/capecitabine(C) in the first-line treatment of patients with metastatic pancreatic cancer (mPC): Efficacy and safety results of a phase IIb randomized study from the Spanish TTD Collaborative Group – Benavides M et al**

- **Key results**
  - PFS and OS were significantly longer in patients with rash vs no rash (PFS: 5.5 vs 2.0 mo, HR 0.39 [95% CI 0.26, 0.6], p<0.0001; OS: 9.5 vs 4.0 mo, HR 0.51 [95% CI 0.33, 0.77], p=0.0014)
  - Treatment-related grade 3/4 AEs: 72% with GEC vs 55% with GE (p=0.0494)

- **Conclusions**
  - Gemcitabine/erlotinib/capecitabine did not improve PFS compared with gemcitabine/erlotinib
  - Skin rash strongly predicted erlotinib efficacy, deserving further study

Benavides et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4122)
4021: A phase II randomized, placebo controlled study to evaluate the efficacy of the combination of gemcitabine, erlotinib, and metformin in patients with locally advanced or metastatic pancreatic cancer – Wilmink J et al

• Study objective
  – To assess the efficacy of metformin vs placebo added to gemcitabine+erlotinib in patients with locally advanced or metastatic pancreatic cancer

Key patient inclusion criteria
• Patients with locally advanced or metastatic pancreatic cancer (n=120)

Primary endpoint
• Survival at 6 months

Secondary endpoints
• OS, PFS, ORR, toxicity and PD

Stratification
• Stage of disease (locally advanced vs metastases)
• Presence of diabetes

Gemcitabine*+erlotinib† +metformin‡ (n=60)

(Gemcitabine*+erlotinib† +placebo (n=60)

Stratification
• Stage of disease (locally advanced vs metastases)
• Presence of diabetes

Wilmink et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4021)

*1000 mg/m² on days 1, 8 and 15 q4w; †100 mg od; ‡500 mg bid in wk1, increased to 1000 mg bid if tolerated
4021: A phase II randomized, placebo controlled study to evaluate the efficacy of the combination of gemcitabine, erlotinib, and metformin in patients with locally advanced or metastatic pancreatic cancer – Wilmink J et al

**Key results**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metformin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival at 6 mo, %</td>
<td>41.2</td>
<td>38.9</td>
<td>0.38</td>
</tr>
<tr>
<td>OS (95% CI), mo</td>
<td>7.6 (6.3, 9.0)</td>
<td>6.7 (5.1, 8.3)</td>
<td>0.52</td>
</tr>
<tr>
<td>PFS (95% CI), mo</td>
<td>5.4 (4.8, 6.1)</td>
<td>3.5 (1.1, 5.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>ORR, %</td>
<td>8.9</td>
<td>9.1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

- Metformin was well tolerated with no significant differences in grade ≥3 toxicities between the two treatment groups

**Conclusion**

- The addition of metformin to gemcitabine+erlotinib did not improve outcomes for patients with locally advanced or metastatic pancreatic cancer

Wilmink et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4021)
4025: Phase II study of refametinib (BAY 86-9766), an allosteric dual MEK 1/2 inhibitor, and gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer – Van Laethem JL et al

- **Study objective**
  - To evaluate refametinib+gemcitabine in advanced pancreatic cancer

### Key patient inclusion criteria
- Locally advanced, unresectable or metastatic pancreatic cancer
- ECOG PS ≤2
- No prior systemic therapy
  - (n=60)

### Refametinib 50 mg bid po +gemcitabine*

### Primary endpoint
- ORR

### Secondary endpoints
- DOR, DCR, TTP, PFS, OS and safety

*1000 mg/m² IV weekly for 7 of 8 weeks in cycle 1, 3 of 4 weeks in subsequent cycles

Van Laethem et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4025)
4025: Phase II study of refametinib (BAY 86-9766), an allosteric dual MEK 1/2 inhibitor, and gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer – Van Laethem JL et al

- **Key results**
  - ORR: 28/48% (p=0.136), OS: 6.6/18.2 mo (HR 0.27 [95% CI 0.12, 0.62]) for mutant/wild-type, respectively
  - Most common grade 3/4 TEAEs were: neutropenia (43%), thrombocytopenia (22%), fatigues (15%), increased ALT (13%), anaemia (12%), hypertension (12%)

- **Conclusions**
  - Refametinib+gemcitabine were active in patients with advanced pancreatic cancer, with an acceptable safety profile
  - There was a trend towards improved ORR, PFS and OS in KRAS wild-type patients

Van Laethem et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4025)
Analyses of updated overall survival (OS) and prognostic effect of neutrophil-to-lymphocyte ratio (NLR) and CA 19-9 from the phase III MPACT study of nab-paclitaxel (nab-P) plus gemcitabine (Gem) versus Gem for patients (pts) with metastatic pancreatic cancer – Goldstein D et al.

- **Study objective**
  - *Post-hoc* analysis reporting updated OS data for the IMPACT trial, in which nab-paclitaxel+gemcitabine demonstrated superior OS vs gemcitabine alone in patients with metastatic pancreatic cancer.

Key patient inclusion criteria
- Metastatic pancreatic cancer
- Karnofsky PS ≥70
  - (n=861)

Primary endpoint
- OS

* nab-P 125 mg/m² + gemcitabine 1000 mg/m² on days 1, 8, 15 of each 28-day cycle; †1000 mg/m² per wk for 7 wks, then 1 wk of rest (cycle 1), then days 1, 8, 15 of each 28-day cycle (cycle ≥2)

Goldstein et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4027)
4027: Analyses of updated overall survival (OS) and prognostic effect of neutrophil-to-lymphocyte ratio (NLR) and CA 19-9 from the phase III MPACT study of nab-paclitaxel (nab-P) plus gemcitabine (Gem) versus Gem for patients (pts) with metastatic pancreatic cancer – Goldstein D et al

- **Key results**
  - Median OS: 8.7 mo nab-P+gemcitabine vs 6.6 mo gemcitabine; HR 0.72 (95% CI 0.62, 0.83); p<0.001

---

**Multivariate analysis of OS**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab-paclitaxel+gemcitabine vs gemcitabine</td>
<td>0.68 (0.57, 0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver metastases, yes vs no</td>
<td>1.65 (1.28, 2.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>KPS PS, 70–80 vs 90–100</td>
<td>1.47 (1.24, 1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NLR, ≤5 vs &gt;5</td>
<td>0.57 (0.48, 0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, &lt;65 vs ≥65 years</td>
<td>0.81 (0.69, 0.96)</td>
<td>0.016</td>
</tr>
<tr>
<td>Geographical region, Eastern Europe vs US</td>
<td>1.19 (0.99, 1.43)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

- **Conclusion**
  - Updated data confirmed the treatment effect favouring nab-paclitaxel+gemcitabine vs gemcitabine alone for OS
A phase 2, randomized trial of GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in patients with metastatic pancreatic adenocarcinoma: Updated results – Le DT et al

- **Study objective**
  - To investigate the use of heterologous prime boost vaccinations in exploiting the immunostimulatory qualities of CY (cyclophosphamide; low dose)/GVAX pancreas (an irradiated whole-cell tumour vaccine) and CRS-207 (a live-attenuated double-deleted [LADD] *Listeria monocytogenes* vaccine expressing mesothelin)

Patients with metastatic pancreatic cancer
- Failed or refused chemotherapy
- ECOG PS 0–1

R 2:1

- CY/GVAX (2 doses) followed by CRS-207 (4 doses) q3w (n=60)
- CY/GVAX (6 doses) q3w (n=30)

**Primary endpoint**
- OS

**Secondary endpoints**
- Safety, immune and clinical responses
177\(^\wedge\): A phase 2, randomized trial of GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in patients with metastatic pancreatic adenocarcinoma: Updated results – Le DT et al

- **Key results**
  - CY/GVAX in combination with CRS-207 demonstrated improved median OS compared with CY/GVAX alone:
    - 1-year survival probability for CY/GVAX in combination with CRS-207 was 24% compared with 12% for CY/GVAX alone
    - The only grade ≥3 related adverse event occurring in >5% of patients receiving CY/GVAX in combination with CRS-207 was lymphopenia (8.2% vs 3.4% for CY/GVAX alone)

### Survival probability

<table>
<thead>
<tr>
<th>OS, mo</th>
<th>CY/GVAX+CRS-207</th>
<th>CY/GVAX</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS interim analysis</td>
<td>6.0</td>
<td>3.4</td>
<td>0.4477</td>
<td>0.0057</td>
</tr>
<tr>
<td>FAS(^*)</td>
<td>6.1</td>
<td>3.9</td>
<td>0.5930</td>
<td>0.0172</td>
</tr>
<tr>
<td>PP extended analysis(^\dagger)</td>
<td>9.7</td>
<td>4.6</td>
<td>0.5290</td>
<td>0.0167</td>
</tr>
<tr>
<td>FAS 3(^{rd})-line treatment</td>
<td>5.7</td>
<td>3.7</td>
<td>0.2957</td>
<td>0.0003</td>
</tr>
<tr>
<td>PP 3(^{rd})-line treatment</td>
<td>8.3</td>
<td>4.0</td>
<td>0.2168</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

\(^*\)Received at least one dose; \(^\dagger\)Received at least 3 doses including 1 dose of CRS-207  Le et al. J Clin Oncol 2014; 32 (suppl 3; abstr 177\(^\wedge\))
Conclusions

- CY/GVAX in combination with CRS-207 demonstrated longer median OS than CY/GVAX alone in previously treated patients with metastatic pancreatic adenocarcinoma including those who received at least 3 doses.
- Both vaccines appeared to be safe and well tolerated.
- Additional studies of CY/GVAX in combination with CRS-207 are being conducted.
4000: A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC) – Hurwitz H et al

- **Study objective**
  - To assess the efficacy and safety ruxolitinib (a JAK1/2 inhibitor that blocks pro-inflammatory cytokine-mediated signalling) added to capecitabine compared with capecitabine alone in patients with metastatic pancreatic cancer refractory to initial therapy

**Key patient inclusion criteria**
- Metastatic pancreatic ductal adenocarcinoma
- Failed gemcitabine
- Karnofsky PS ≥60
  - (n=127)

**Primary endpoint**
- OS

**Secondary endpoints**
- Clinical benefit response, ORR, PFS, confirmed response, QoL and safety

**Capecitabine*+ruxolitinib† (n=64)**
- PD

**Capecitabine*+placebo† (n=63)**
- PD

**Stratification**
- Inflammation (C-reactive protein <13 mg/L)

*1000 mg/m² bid days 1–14; †15 mg bid days 1–21

Hurwitz et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4000)
A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC) – Hurwitz H et al

**Key results**

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall population</strong></td>
<td>64</td>
<td>63</td>
<td>0.79 (0.53, 1.18)</td>
<td>0.25</td>
</tr>
<tr>
<td>Median OS, days</td>
<td>136.5</td>
<td>129.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, days</td>
<td>51.0</td>
<td>46.0</td>
<td>0.75 (0.51, 1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>CRP &gt;13 mg/L subgroup</strong></td>
<td>31</td>
<td>29</td>
<td>0.62 (0.35, 1.10)</td>
<td>0.10</td>
</tr>
<tr>
<td>Median OS, days</td>
<td>83.0</td>
<td>55.0</td>
<td>0.47 (0.26, 0.85)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median PFS, days</td>
<td>48.0</td>
<td>41.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall population, n</strong></td>
<td>64</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Overall response (CR+PR)</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Disease control (CR+PR+SD)</td>
<td>26</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td><strong>CRP &gt;13 mg/L subgroup, n</strong></td>
<td>31</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Overall response (CR+PR)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Disease control (CR+PR+SD)</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Hurwitz et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4000)
4000: A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC) – Hurwitz H et al

• Key results

<table>
<thead>
<tr>
<th>AEs</th>
<th>Ruxolitinib (N=59)</th>
<th>Placebo (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean exposure, days</td>
<td>99.6</td>
<td>67.4</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>58 (98.3)</td>
<td>60 (100)</td>
</tr>
<tr>
<td>Grade ≥3 AE, n (%)</td>
<td>44 (74.6)</td>
<td>49 (81.7)</td>
</tr>
<tr>
<td>Discontinued treatment due to AE, n (%)</td>
<td>7 (11.9)</td>
<td>12 (20.0)</td>
</tr>
<tr>
<td>Grade 3/4 haematological AE, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>9 (15.3)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (1.7)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
</tbody>
</table>

• Conclusions

– Ruxolitinib in combination with capecitabine exhibited clinical activity in patients with metastatic pancreatic cancer
– Ruxolitinib appeared to improve survival in patients with inflammation
– Ruxolitinib was generally well tolerated

Hurwitz et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4000)
4022: PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT) – Gill S et al

- **Study objective**
  - To evaluate the benefit of mFOLFOX6 vs infusional 5-FU/LV in patients with advanced pancreatic cancer

Key patient inclusion criteria
- Advanced pancreatic cancer
- Previously treated with gemcitabine
- ECOG PS ≤2 (n=108)

Primary endpoint
- PFS

Secondary endpoints
- ORR, OS, QoL and safety

Gill et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4022)
4022: PANCROOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT) – Gill S et al

• Key results

<table>
<thead>
<tr>
<th>Variable</th>
<th>mFOLFOX6</th>
<th>5-FU/LV</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>65</td>
<td>67</td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Stage (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>7.4</td>
<td>5.6</td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Metastatic</td>
<td>92.6</td>
<td>94.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>3.1</td>
<td>2.9</td>
<td>1.00 (0.66, 1.53)</td>
<td>0.989</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>6.1</td>
<td>9.9</td>
<td>1.78 (1.08, 2.93)</td>
<td>0.24</td>
</tr>
<tr>
<td>ORR, %</td>
<td>13.2</td>
<td>8.5</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>EORTC-QLQ-C30*, mo</td>
<td>2.2</td>
<td>3.8</td>
<td>1.37 (0.73, 2.57)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

– Grade 3/4 AEs: 63% with mFOLFOX6 vs 11% with 5-FU/LV
– Withdrawal rate due to AE: 16.3% with mFOLFOX6 vs 1.9% with 5-FU/LV

• Conclusions

– PFS was similar and OS was inferior with mFOLFOX6 vs 5-FU/LV
– The findings suggest that oxaliplatin-based CT should primarily be used as 1st-line treatment

*Time to definite deterioration >10 patients

Gill et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4022)
BIOMARKERS

PANCREATIC CANCER
175: Pancreatic circulating tumor cells as a diagnostic adjunct in pancreatic cancer – Ankeny JS et al

• **Study objective**
  - To investigate the use of circulating tumour cells (CTCs) as a potential diagnostic biomarker in pancreatic ductal adenocarcinoma (PDAC)

- Prospective analysis of samples from 50 patients with suspicion or recent diagnosis of PDAC prior to treatment
- 2 mL venous blood samples were examined for the presence/number of CTCs
- CTCs were captured and enumerated using NanoVelcro technology improved by anti-EpCAM enrichment
- CTCs defined by size >10 µm and ICC staining pattern. KRAS mutational status was evaluated in CTCs from 3 patients to validate PDAC origin of CTCs

Ankeny et al. J Clin Oncol 2014; 32 (suppl 3; abstr 175)
175: Pancreatic circulating tumor cells as a diagnostic adjunct in pancreatic cancer – Ankeny JS et al

- Key results
  - Presence of CTCs allowed PDAC to be distinguished from non-adenocarcinoma:

<table>
<thead>
<tr>
<th>CTC cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Youden's index</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 CTC</td>
<td>0.707</td>
<td>0.950</td>
<td>0.967</td>
<td>0.594</td>
<td>0.637</td>
</tr>
<tr>
<td>≥ 2 CTC</td>
<td>0.293</td>
<td>1.000</td>
<td>1.000</td>
<td>0.408</td>
<td>0.293</td>
</tr>
<tr>
<td>≥ 4 CTC</td>
<td>0.146</td>
<td>1.000</td>
<td>1.000</td>
<td>0.377</td>
<td>0.146</td>
</tr>
<tr>
<td>≥ 5 CTC</td>
<td>0.098</td>
<td>1.000</td>
<td>1.000</td>
<td>0.357</td>
<td>0.098</td>
</tr>
<tr>
<td>≥ 10 CTC</td>
<td>0.024</td>
<td>1.000</td>
<td>1.000</td>
<td>0.339</td>
<td>0.024</td>
</tr>
</tbody>
</table>

CTC, circulating tumour cell; PDAC, pancreatic ductal adenocarcinoma

Ankeny et al. J Clin Oncol 2014; 32 (suppl 3; abstr 175)
**Key results**

- Presence of CTCs allowed local disease to be distinguished from metastatic disease, at a cut-off of ≥2 CTCs/2 mL blood, sensitivity = 68.8%, specificity = 96.0% and PPV = 92.3%:

\[
\text{CTC enumeration: PDAC stage}
\]

\[
\text{CTC enumeration: Local/regional vs metastatic}
\]

\[
\text{Discriminatory performance of CTCs: Local/regional vs metastatic PDAC}
\]
Conclusions

- When diagnosing PDAC, CTCs may be a useful biomarker.
- CTCs were shown to have high specificity and PPV for distinguishing between local and metastatic disease in patients with PDAC.
- The use of CTCs as a diagnostic biomarker may allow for improved pre-treatment staging at the time of disease presentation.
Study objective
- To determine whether a biomarker signature when using a proximity ligation assay (PLA) panel can predict response to adjuvant therapy in pancreatic cancer

Primary endpoints
- OS, DFS

Heestand et al. J Clin Oncol 2014; 32 (suppl 3; abstr 176)
176: A novel biomarker panel examining response to adjuvant pancreatic cancer therapy in RTOG 9704 – Heestand GM et al

- **Key results**
  - Univariate survival analysis demonstrated that improved OS in all patients was associated with reduced levels of CEA and CA 19-9:

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>5-FU</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CA 19-9</strong></td>
<td>1.20 (1.11, 1.30)*</td>
<td>1.20 (1.08, 1.33)*</td>
<td>1.21 (1.06, 1.39)*</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td>1.19 (1.04, 1.38)*</td>
<td>1.43 (1.12, 1.83)*</td>
<td>1.12 (0.90, 1.38)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.094</td>
</tr>
<tr>
<td><strong>MMP-7</strong></td>
<td>1.15 (0.98, 1.34)</td>
<td>0.96 (0.73, 1.25)</td>
<td>1.39 (1.05, 1.83)*</td>
</tr>
<tr>
<td></td>
<td>p=0.0054</td>
<td>p=0.58</td>
<td>p=0.0001</td>
</tr>
</tbody>
</table>

*Significance was maintained with multivariate analysis
**Key results**

- Low levels of MMP-7 were associated with significant improvement in disease-free survival and OS in the patients receiving adjuvant therapy compared with high levels; this was not observed in patients receiving 5-FU.

**MMP-7, matrix metalloproteinase-7; MST, median survival time**

Heestand et al. J Clin Oncol 2014; 32 (suppl 3; abstr 176)
Conclusions

- PLA was demonstrated to be a useful tool for identifying potential biomarkers from archived serum samples.
- The findings also suggest that MMP-7 levels may be used as a predictor for patient response to adjuvant gemcitabine.

Heestand et al. J Clin Oncol 2014; 32 (suppl 3; abstr 176)
4129: Phase II study of the MEK inhibitor refametinib (BAY 86-9766) in combination with gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer: Biomarker results – Riess H et al

- **Study objective**
  - Biomarker analysis to assess the relationship between *KRAS* mutation and treatment response in patients with advanced pancreatic cancer receiving refametinib+gemcitabine

**Key patient inclusion criteria**
- Patients with unresectable, advanced or metastatic pancreatic cancer
- ECOG PS ≤2 (n=60)

**Primary endpoint**
- ORR

**Secondary endpoints**
- PFS, OS and biomarker assessment

Reiss et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4129)
4129: Phase II study of the MEK inhibitor refametinib (BAY 86-9766) in combination with gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer: Biomarker results – Riess H et al

- **Key results**
  - *KRAS* mutation status: wild-type n=21, mutant n=39
  - ORR (at least unconfirmed PR): wild-type 48% vs mutant 28% (p=0.136)
  - There was a trend correlating allele frequency with response:
    - *KRAS* mutant allele frequency: PR 1.51 (SD 1.36)

- **Conclusion**
  - There was a trend towards improved response, median PFS and OS in the *KRAS* wild-type subset and for *KRAS* allele frequency to correlate with response

Reiss et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4129)
4006: STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC) – Bruix J et al

- **Study objective**
  - To evaluate the efficacy and safety of adjuvant sorafenib in patients with hepatocellular carcinoma

**Key patient inclusion criteria**
- Hepatocellular carcinoma
- Resected or complete local ablation
- Child-Pugh score 5–7
- ECOG PS 0
- No residual disease (n=1114)

**Arm 1**
- Sorafenib 400 mg bid for maximum of 4 years (n=556)

**Arm 2**
- Placebo (n=558)

**Stratification**
- Curative treatment, geographical region, Child-Pugh status, recurrence risk

**Primary endpoint**
- Recurrence-free survival

**Secondary endpoints**
- Time to recurrence, OS, PROs, PK and biomarkers

Bruix et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4006)
4006: STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC) – Bruix J et al

- **Key results**
  - No differences in recurrence-free survival, time to recurrence or OS were observed with sorafenib

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib (n=558)</th>
<th>Placebo (n=558)</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFS</td>
<td>33.4</td>
<td>33.8</td>
<td>0.94 (0.78, 1.13)</td>
<td>0.26</td>
</tr>
<tr>
<td>TTR</td>
<td>38.6</td>
<td>35.8</td>
<td>0.89 (0.74, 1.08)</td>
<td>0.12</td>
</tr>
<tr>
<td>OS</td>
<td>NR</td>
<td>NR</td>
<td>0.99 (0.76, 1.30)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

- Discontinuation rates with sorafenib were higher due to AEs (24% vs 7%) and withdrawal of consent (17% vs 6%)

*One-sided; NR, not reached*
4006: STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC) – Bruix J et al

• Key results

<table>
<thead>
<tr>
<th>TEAEs, n (%)</th>
<th>Sorafenib (n=559)</th>
<th>Placebo (n=548)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>545 (97.5)</td>
<td>491 (89.6)</td>
</tr>
<tr>
<td>Serious</td>
<td>225 (40.3)</td>
<td>228 (41.6)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>15 (2.7)</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td>Leading to dose modification</td>
<td>439 (78.5)</td>
<td>111 (20.3)</td>
</tr>
<tr>
<td>Leading to permanent discontinuation</td>
<td>147 (26.3)</td>
<td>59 (10.8)</td>
</tr>
</tbody>
</table>

• Conclusions

– The primary endpoint of the trial (RFS) was not met and there were also no improvements in time to recurrence or OS
– AEs were consistent with the known safety profile of sorafenib
– Sorafenib is not recommended in the adjuvant treatment of HCC

*One-sided; NR, not reached

Bruix et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4006)
HEPATOCELLULAR CARCINOMA

BIOMARKERS
4028: Biomarker analyses and association with clinical outcomes in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib with or without erlotinib in the phase III SEARCH trial – Zhu AX et al

**Study objective**

- To identify biomarkers predicting prognosis and/or response to sorafenib±erlotinib in patients with advanced HCC from the SEARCH trial

The following biomarkers were analysed in baseline plasma samples:

- VEGF-A, VEGF-C, PDGF-BB, KIT (extracellular domain), HGF, bFGF, IGF-2, amphiregulin, betacellulin, EGF, epigen, epieregulin, heregulin, hbEGF, TGF-α

- Mutations in 19 oncogenes were analysed in archival biopsies

Zhu et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4028)
4028: Biomarker analyses and association with clinical outcomes in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib with or without erlotinib in the phase III SEARCH trial – Zhu AX et al

• Key results
  – High HGF and VEGF-A baseline plasma levels were associated with poorer outcomes; high KIT and VEGF-C were associated with better outcomes

<table>
<thead>
<tr>
<th>Poorer outcome</th>
<th></th>
<th></th>
<th></th>
<th>Better outcome</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
<td></td>
<td></td>
<td>Low</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td><strong>HGF</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>KIT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>212</td>
<td>282</td>
<td></td>
<td>n</td>
<td>339</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Median OS (95% CI)</td>
<td>12.4 (10.7, 13.8)</td>
<td>7.5 (6.5, 8.5)</td>
<td>Median OS (95% CI)</td>
<td>8.7 (7.4, 10.3)</td>
<td>10.6 (8.3, 12.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI); p-value</td>
<td>1.67 (1.35, 2.07); 5e-05</td>
<td></td>
<td>HR (95% CI); p-value</td>
<td>0.71 (0.56, 0.90); p=0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VEGF-A</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>VEGF-C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>284</td>
<td>210</td>
<td></td>
<td>n</td>
<td>239</td>
<td>255</td>
<td></td>
</tr>
<tr>
<td>Median OS (95% CI)</td>
<td>12.4 (10.5, 12.0)</td>
<td>7.6 (6.3, 9.4)</td>
<td>Median TTP (95% CI)</td>
<td>2.7 (2.6, 2.9)</td>
<td>4.4 (4.0, 5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI); p-value</td>
<td>1.39 (1.12, 1.70); p=0.03</td>
<td></td>
<td>HR (95% CI)</td>
<td>0.62 (0.49, 0.77); 3e-04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Conclusions
  – HGF, VEGF-A, KIT and VEGF-C baseline plasma levels were linked with clinical outcomes in HCC patients treated with sorafenib+erlotinib
  – These biomarkers plus epigen constituted a multi-marker composite signature for improved OS

*Low vs high expression. Adj, multiplicity adjusted

Zhu et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4028)
CHOLANGIOCARCINOMA & GALLBLADDER CANCER

ADJUVANT THERAPY
4030: SWOG S0809: A phase II trial of adjuvant capecitabine (cap)/gemcitabine (gem) followed by concurrent capecitabine and radiotherapy in extrahepatic cholangiocarcinoma (EHCC) and gallbladder carcinoma (GBCA) – Ben-Josef E et al

- **Study objective**
  - To evaluate the role of adjuvant therapy after resection of EHCC or GBCA

**Key patient inclusion criteria**
- EHCC or GBCA s/p radical resection
- pT2-4, N1 or R1
- M0 and PS 0-1

**Gemcitabine** 4 cycles (1 g/m² IV, days 1, 8) + **capecitabine** (1500 mg/m²/day, days 1–14) q3w, then concurrent **CAP** (1330 mg/m²/day) + radiation (n=79)

**Stratification**
- R0 or R1
- EHCC or GBCA

**Primary endpoint**
- OS

**Secondary endpoints**
- DFS and safety

EHCC, extrahepatic cholangiocarcinoma; GBCA, gallbladder carcinoma

Ben-Josef et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4030)
4030: SWOG S0809: A phase II trial of adjuvant capecitabine (cap)/gemcitabine (gem) followed by concurrent capecitabine and radiotherapy in extrahepatic cholangiocarcinoma (EHCC) and gallbladder carcinoma (GBCA) – Ben-Josef E et al

- **Key results**
  - R0 n=54 vs R1 n=25; 62% EHCC vs 38% GBCA
  - Grade 3/4 AEs were observed in 53/11% of patients, respectively
    - Most common: neutropenia (44%), hand-foot syndrome (13%), diarrhoea (8%), lymphopenia (8%) and leukopenia (6%)
  - Median OS was 33 months (33/30 for R0/R1)

<table>
<thead>
<tr>
<th>% (95% CI)</th>
<th>All pts</th>
<th>R0 cohort</th>
<th>R1 cohort</th>
<th>EHCC</th>
<th>GBCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year OS</td>
<td>62 (50, 72)</td>
<td>65 (51, 77)</td>
<td>56 (33, 74)</td>
<td>66 (50, 78)</td>
<td>56 (37, 72)</td>
</tr>
<tr>
<td>2-year DFS</td>
<td>50 (38, 60)</td>
<td>52 (38, 65)</td>
<td>44 (23, 63)</td>
<td>51 (36, 65)</td>
<td>47 (28, 63)</td>
</tr>
<tr>
<td>2-year LR</td>
<td>12 (5, 19)</td>
<td>10 (2, 18)</td>
<td>18 (2, 33)</td>
<td>11 (2, 21)</td>
<td>13 (1, 25)</td>
</tr>
</tbody>
</table>

- **Conclusions**
  - This trial established the feasibility of adjuvant treatment in EHCC and GBCA
  - Efficacy data and completion rate are promising and warrant further study

EHCC, extrahepatic cholangiocarcinoma; GBCA, gallbladder carcinoma

Ben-Josef et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4030)
4002: ABC-03: A randomized phase II trial of cediranib (AZD2171) or placebo in combination with cisplatin/gemcitabine (CisGem) chemotherapy for patients (pts) with advanced biliary tract cancer (ABC) – Valle JW et al

**Study objective**
- To determine whether combining cediranib (a pan-VEGF receptor TKI with some activity against PDGF receptors and c-Kit) with cisplatin/gemcitabine compared with cisplatin/gemcitabine alone improves outcomes in patients with advanced biliary tract cancer

**Key patient inclusion criteria**
- Advanced biliary tract cancer
- Age ≥18 years
- ECOG PS 0–1
- Adequate bone marrow, liver and renal function

**Primary endpoint**
- PFS

Cisplatin (25 mg/m²) + gemcitabine (1000 mg/m²) days 1 and 8 of a 21-day cycle (up to 8 cycles)

**Secondary endpoints**
- OS, ORR (RECIST v1.1), toxicity and QoL

Valle et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4002)
4002: ABC-03: A randomized phase II trial of cediranib (AZD2171) or placebo in combination with cisplatin/gemcitabine (CisGem) chemotherapy for patients (pts) with advanced biliary tract cancer (ABC) – Valle JW et al

- **Key results**

  - **ORR:** 44% with cediranib vs 19% with placebo, \( p=0.0036 \)
  - **Median OS:** 14.1 mo with cediranib vs 11.9 mo with placebo (HR 0.86 [95% CI 0.58, 1.27]; \( p=0.44 \))

  Valle et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4002)
4002: ABC-03: A randomized phase II trial of cediranib (AZD2171) or placebo in combination with cisplatin/gemcitabine (CisGem) chemotherapy for patients (pts) with advanced biliary tract cancer (ABC) – Valle JW et al

• Key results

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Categories</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA19-9</td>
<td>&lt;37.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥37 to &lt;492</td>
<td>1.0 (0.6, 1.7)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>≥492</td>
<td>2.3 (1.4, 3.9)</td>
<td></td>
</tr>
<tr>
<td>CA125</td>
<td>&lt;20</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥20 to &lt;61</td>
<td>1.0 (0.6, 1.7)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>≥61</td>
<td>2.4 (1.4, 3.9)</td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>&lt;3.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3.2 to &lt;8.0</td>
<td>1.4 (0.8, 2.3)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>≥8.0</td>
<td>1.9 (1.2, 3.2)</td>
<td></td>
</tr>
</tbody>
</table>

- Patients with high (≥7515 pg/mL) vs medium (5523–7514 pg/mL)/low (<5522 pg/mL) baseline VEGFR2 levels had a shorter OS (HR 1.8 [95% CI 1.0, 3.2]; p=0.04)

<table>
<thead>
<tr>
<th>Grade 3–4 AEs, n (%)</th>
<th>Cediranib</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological</td>
<td>32 (52)</td>
<td>28 (45)</td>
<td>0.47</td>
</tr>
<tr>
<td>Non-haematological</td>
<td>55 (89)</td>
<td>46 (74)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

• Conclusions

- Cediranib did not increase PFS but appeared to improve the response rate
- Cediranib was associated with an increase in grade 3–4 toxicities
- Current and future biomarker data may reveal the potential for selecting patients most likely to benefit in future studies

Valle et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4002)
OESOPHAGEAL & GASTRIC CANCER
OESOPHAGEAL & GASTRIC CANCER

CURATIVE INTENT: SURGERY & OTHER MODALITIES
05: The effect of postoperative morbidity on survival after resection for gastric adenocarcinoma: Results from the U.S. Gastric Cancer Collaborative – Jin LX et al

• Study objective
  – A retrospective analysis to evaluate the impact of postoperative complications on survival after resection for gastric adenocarcinoma

• Study design
  – Data were collected for 965 patients between 1/1/2000 and 31/12/2012 from seven US Gastric Cancer Collaborative centres
  – In total, data from 850 patients with non-metastatic gastric or GEJ adenocarcinoma who underwent complete gross resection were analysed
05: The effect of postoperative morbidity on survival after resection for gastric adenocarcinoma: Results from the U.S. Gastric Cancer Collaborative – Jin LX et al

- **Key results**
  - The following factors were found to be associated with survival:

<table>
<thead>
<tr>
<th>Significant variables</th>
<th>Median OS (mo)</th>
<th>Univariate p-value</th>
<th>Multivariate p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=174)</td>
<td>24</td>
<td>0.012</td>
<td>0.01</td>
<td>1.7 (1.1, 2.6)</td>
</tr>
<tr>
<td>No (n=675)</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=202)</td>
<td>15</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td>1.6 (1.1, 2.5)</td>
</tr>
<tr>
<td>No (n=426)</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AJCC stage (7th edition)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3 or 4 (n=445)</td>
<td>18</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td>1.8 (1.1, 2.9)</td>
</tr>
<tr>
<td>Stage 1 or 2 (n=405)</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=342)</td>
<td>25</td>
<td>&lt;0.0001</td>
<td>0.004</td>
<td>1.6 (1.1, 2.4)</td>
</tr>
<tr>
<td>No (n=506)</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jin et al. J Clin Oncol 2014; 32 (suppl 3; abstr 05)
Key results
- OS was significantly longer (p<0.001) in patients with no complications compared with patients with complications:

Jin et al. J Clin Oncol 2014; 32 (suppl 3; abstr 05)
Conclusions

- Overall 40% of patients who had surgery for gastric adenocarcinoma suffered from complications.
- Complications were not increased by neoadjuvant therapy.
- Adjuvant therapy was less likely to be used in patients suffering from complications (48% vs. 60%).
- Overall survival was decreased in patients with complications (25 vs. 45 months, HR=1.6).
4007: RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery – Ilson DH et al

**Study objective**
- To evaluate the addition of cetuximab to concurrent chemoradiation compared with chemoradiation alone in patients with inoperable oesophageal carcinoma

**Key patient inclusion criteria**
- Oesophageal cancer
- Squamous cell or adenocarcinoma
- Curative resection and D2 lymph node dissection
- Zubrod PS 0–2
- Age ≥18–75 years (n=344)

**Primary endpoint**
- OS

**Secondary endpoints**
- Complete clinical response, safety and QoL

**Radiotherapy**

**Arm 1**
- 50.4 Gy/day + cisplatin 50 mg/m² + paclitaxel 25 mg/m² for 6 weeks + cetuximab 400 mg/m² day 1 then 250 mg/m² weekly for 6 weeks (n=168)

**Arm 2**
- 50.4 Gy/day + cisplatin 50 mg/m² + paclitaxel 25 mg/m² for 6 weeks (n=176)

**Stratification**
- Histology, cancer legion size, presence/absence of celiac node

Ilson et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4007)
4007: RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery – Ilson DH et al

• Key results

![Graph showing overall survival](image)

**OS**

Stratified log-rank p-value = 0.70

- **RT + Chemo + Cetux**
  - Failed: 97
  - Total: 159
  - 2-year rates: 44.0%

- **RT + Chemo**
  - Failed: 110
  - Total: 169
  - 2-year rates: 41.7%

HR (95% CI) 0.92 (0.70, 1.21)

Ilson et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4007)
4007: RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery – Ilson DH et al

**Key results**

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>RT+CT+cetuximab (N=157)</th>
<th>RT+CT (N=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse non-haematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>71 (45)</td>
<td>76 (45)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>21 (13)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Worse haematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>71 (45)</td>
<td>83 (49)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>35 (22)</td>
<td>28 (17)</td>
</tr>
</tbody>
</table>

**Conclusions**

– The addition of cetuximab to chemoradiation did not improve OS in patients with inoperable oesophageal carcinoma

– A number of studies indicate that there is no benefit of current EGFR-targeted agents in unselected patients with this cancer type

Ilson et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4007)
OESOPHAGEAL & GASTRIC CANCER

NEoadjuvant & Adjuvant Therapy
4014: Toxicity, surgical complications, and short-term mortality in a randomized trial of neoadjuvant cisplatin/5FU versus epirubicin/cisplatin and capecitabine prior to resection of lower esophageal/gastroesophageal junction (GOJ) adenocarcinoma (MRC OEO5, ISRCTN01852072, CRUK 02/010) – Cunningham D et al

- **Study objective**
  - To compare CF vs ECX pre-operatively, followed by oesophagectomy in patients with resectable adenocarcinoma of the lower oesophagus or GEJ

- **Key patient inclusion criteria**
  - Patients with resectable adenocarcinoma of the lower oesophagus or GEJ (n=897)

- **Primary endpoint**
  - OS (not yet reported)

- **Secondary endpoints**
  - Toxicity and mortality

CF, cisplatin/5-FU; ECX, epirubicin/cisplatin+capecitabine; GEJ, gastro-oesophageal junction

Cunningham et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4014)
4014: Toxicity, surgical complications, and short-term mortality in a randomized trial of neoadjuvant cisplatin/5FU versus epirubicin/cisplatin and capecitabine prior to resection of lower esophageal/gastroesophageal junction (GOJ) adenocarcinoma (MRC OEO5, ISRCTN01852072, CRUK 02/010) – Cunningham D et al

- **Key results**

  - Four cycles of ECX had higher CT-related toxicity vs 2 cycles of CF, but did not affect resection rates, surgical complications or 90-day mortality

- **Conclusion**

  - Four cycles of ECX had higher CT-related toxicity vs 2 cycles of CF, but did not affect resection rates, surgical complications or 90-day mortality

Cunningham et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4014)
4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

- **Primary endpoint**
  - 3-year DFS

- **Secondary endpoints**
  - OS, toxicity profile, exploratory biomarkers

- **Arm 1**
  - Capecitabine 2000 mg/m$^2$/day days 1–14 + cisplatin 60 mg/m$^2$/day 1 for 6 cycles (n=228)

- **Arm 2**
  - Capecitabine+cisplatin for 2 cycles as above, followed by radiotherapy 45 Gy with capecitabine 1650 mg/m$^2$/day for 5 weeks, followed by 2 further cycles of capecitabine+cisplatin as above (n=230)

- **Stratification**
  - Stage, type of surgery (STG vs TG)

- **Key patient inclusion criteria**
  - Gastric cancer
  - Curative resection and D2 lymph node dissection (n=458)

- **Study objective**
  - To determine whether the addition of RT to capecitabine/cisplatin CT can improve survival in patients with D2 dissected gastric cancer

Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)
4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

**Key results**

<table>
<thead>
<tr>
<th>Survival (CT+RT vs CT alone)</th>
<th>HR (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>0.74 (0.52, 1.05)</td>
<td>0.9222</td>
</tr>
<tr>
<td>OS</td>
<td>1.13 (95% CI: 0.78, 1.65)</td>
<td>0.5272</td>
</tr>
</tbody>
</table>

- 3-year DFS for CT+RT vs CT alone:
  - In lymph node-positive disease (n=396) was 76% vs 72% (p=0.04)
  - In intestinal type gastric cancer (n=163) was 94% vs 83% (p=0.001; Figure)

**DFS by Lauren classification**

Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)
4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

• Key results

<table>
<thead>
<tr>
<th>Grade 3–4 AEs, n (%)</th>
<th>CT (N=226)</th>
<th></th>
<th>CT+RT (N=227)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (12)</td>
<td>0</td>
<td>28 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (4)</td>
<td>0</td>
<td>7 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (2)</td>
<td>1 (0)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (1)</td>
<td>0</td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (1)</td>
<td>0</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>5 (2)</td>
<td></td>
<td>7 (3)</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>3 (1)</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79 (35)</td>
<td>13 (6)</td>
<td>99 (44)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

• Conclusions

– Overall, this trial was negative with no significant difference in DFS with the addition of RT to CT compared with CT alone

– Subgroup analyses showed a potential benefit of RT in patients with intestinal type and lymph node-positive gastric cancer

Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)
OESOPHAGEAL & GASTRIC CANCER

PALLIATIVE / METASTATIC
4125: A UGT1A1 genotype-guided dosing study of modified FOLFIRINOX (mFOLFIRINOX) in previously untreated patients (pts) with advanced gastrointestinal malignancies – Sharma M et al

**Study objective**
- To determine whether genotype-guided dosing of IRI (based on UGT1A1*28 in 1*1, 1*/1, 1*/28 and 28/*28 patients) in mFOLFIRINOX† improves toxicity

### Key patient inclusion criteria
- Previously untreated patients with advanced GI malignancies
- ECOG PS 0 or 1
- UGT1A1*28 in 1*1, 1*/1, 1*/28 or 28/*28 genotype (n=40)

### Primary endpoint
- DLT

### Secondary endpoint
- ORR (RECIST 1.1)

†Every 14 days; ‡5-FU dose 2400 mg/m² over 46 h (no bolus); leucovorin 400 mg/m²; oxaliplatin 85 mg/m²
DLT, dose-limiting toxicity; IRI, irinotecan

Sharma et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4125)
**Key results**

<table>
<thead>
<tr>
<th>UGT1A1 genotype</th>
<th>IRI dose</th>
<th>N</th>
<th>DLT, n (%)</th>
<th>DLT description</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>180 mg/m²</td>
<td>15</td>
<td>2 (13)</td>
<td>Neutropenic fever x 2</td>
</tr>
<tr>
<td>*1/*28</td>
<td>135 mg/m²</td>
<td>16</td>
<td>2 (13)</td>
<td>Grade 3 fatigue, diarrhoea, grade 3 fatigue</td>
</tr>
<tr>
<td>*28/*28</td>
<td>90 mg/m²</td>
<td>9</td>
<td>3 (33)</td>
<td>Neutropenic fever x 2, grade 3 abdominal pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best response</th>
<th>Pancreatic cancer (N=19)</th>
<th>Biliary tract cancer (N=13)</th>
<th>Gastric cancer (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>11 (58%)</td>
<td>4 (31%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>SD</td>
<td>6 (32%)</td>
<td>5 (38%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (10%)</td>
<td>4 (31%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Conclusions**

- mFOLFIRINOX is tolerable in UGT1A1*1/*1 patients at the standard IRI dose of 180 mg/m² and in *1/*28 patients at a reduced IRI dose of 135 mg/m²
- mFOLFIRINOX is not tolerable in UGT1A1 *28/*28 patients, even at a reduced IRI dose of 90 mg/m²

*DLT, dose-limiting toxicity*
4004: Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial – Yoon HJ et al

- **Study objective**
  - To investigate the addition of ramucirumab to FOLFOX as first-line therapy in patients with gastric or oesophageal adenocarcinoma

- **Key patient inclusion criteria**
  - Gastric, GEJ or oesophageal cancer
  - Metastatic or locally advanced unresectable
  - Previously untreated
  - ECOG PS 0–1 (n=168)

- **Arm 1**
  - mFOLFOX6* + ramucirumab 8 mg/kg on day 1 (n=84)

- **Arm 2**
  - mFOLFOX6* + placebo on day 1 (n=84)

- **Stratification**
  - Metastatic vs locally advanced unresectable
  - Oesophagus/GEJ vs gastric

- **Cycle length**: 14 days

- **Primary endpoint**
  - PFS

- **Secondary endpoints**
  - ORR, OS, time to progression and safety/toxicity

*5-FU 400 mg/m² bolus, leucovorin 400 mg/m², oxaliplatin 85 mg/m², then 5-FU infusion 2400 mg/m² (46–48 h)

GEJ, gastro-oesophageal junction

Yoon et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4004)
### Key results

<table>
<thead>
<tr>
<th>Survival</th>
<th>mFOLFOX6+ramucirumab (N=84)</th>
<th>mFOLFOX6+placebo (N=84)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (ITT population)</td>
<td>6.44</td>
<td>6.74</td>
<td>0.98 (0.69, 1.37)</td>
<td>0.98</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>5.8</td>
<td>5.8</td>
<td>1.10 (0.61, 1.97)</td>
<td>0.746</td>
</tr>
<tr>
<td>Gastric/GEJ</td>
<td>9.3</td>
<td>7.6</td>
<td>0.53 (0.29, 0.97)</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>OS, months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (ITT population)</td>
<td>11.7</td>
<td>11.5</td>
<td>1.08 (0.73, 1.58)</td>
<td>-</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>10.5</td>
<td>11.5</td>
<td>1.29 (0.75, 2.19)</td>
<td>-</td>
</tr>
<tr>
<td>Gastric/GEJ</td>
<td>14.6</td>
<td>12.5</td>
<td>0.94 (0.55, 1.61)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best overall tumour response</th>
<th>mFOLFOX6+ramucirumab (N=84)</th>
<th>mFOLFOX6+placebo (N=84)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Complete response</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Partial response</td>
<td>32</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Stable disease</td>
<td>33</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>71</td>
<td>85</td>
<td>56</td>
</tr>
</tbody>
</table>

Yoon et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4004)
4004: Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial – Yoon HJ et al

• Key results
  – Non-PD treatment discontinuation: RAM 48% vs placebo 16%; difference 32%

<table>
<thead>
<tr>
<th>Most common AEs, %</th>
<th>mFOLFOX6+ramucirumab (N=82)</th>
<th>mFOLFOX6+placebo (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>≥Grade 3</td>
</tr>
<tr>
<td>Haematological</td>
<td>Thrombocytopenia</td>
<td>56</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Peripheral sensory neuropathy</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>23</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>Decreased appetite</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia</td>
<td>20</td>
</tr>
</tbody>
</table>

• Conclusions
  – The addition of ramucirumab to mFOLFOX6 did not improve PFS
  – Ramucirumab was associated with a higher disease control rate
  – A higher non-progressive disease discontinuation rate and lower drug exposure in ramucirumab arm may have impacted PFS assessment
  – Longer PFS was observed with ramucirumab in the gastric/GEJ subgroup

Yoon et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4004)
4005: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy—Efficacy analysis in Japanese and Western patients – Hironaka S et al

- **Study objective**
  - To analyse survival outcomes in Japanese versus Western patients with metastatic gastric cancer or GEJ carcinoma receiving ramucirumab in combination with paclitaxel compared with paclitaxel alone

**Key patient inclusion criteria**
- Metastatic gastric cancer or GEJ carcinoma
- ECOG PS ≤1
- Adequate organ function
- Disease progression during or within 4 months of first-line therapy (n=665)

**Primary endpoints**
- OS and PFS

**Secondary endpoint**
- ORR

**Arm 1**
- Ramucirumab 8 kg/m²
days 1 and 15 +
paclitaxel 80 mg/m²
days 1, 8 and 15 q4w
(n=330)

**Arm 2**
- Placebo +
paclitaxel 80 mg/m²
days 1, 8 and 15 q4w
(n=335)

**R**

Hironaka et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4005)
4005: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy—Efficacy analysis in Japanese and Western patients – Hironaka S et al

- Key results

**Japanese** (N=140)

<table>
<thead>
<tr>
<th></th>
<th>RAM+PTX</th>
<th>PBO+PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/events</td>
<td>68/59</td>
<td>72/66</td>
</tr>
<tr>
<td>Median (m)</td>
<td>5.6</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.503 (0.348, 0.728)</td>
<td>0.0002 (stratified)</td>
</tr>
</tbody>
</table>

**Western** (N=398)

<table>
<thead>
<tr>
<th></th>
<th>RAM+PTX</th>
<th>PBO+PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/events</td>
<td>198/167</td>
<td>200/173</td>
</tr>
<tr>
<td>Median (m)</td>
<td>4.2</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.631 (0.506, 0.786)</td>
<td>&lt;0.0001 (stratified)</td>
</tr>
</tbody>
</table>

**PFS**

<table>
<thead>
<tr>
<th>Time from randomisation (months)</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>8</td>
<td>0.6</td>
</tr>
<tr>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>16</td>
<td>0.2</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

**Japanese**

<table>
<thead>
<tr>
<th>Ramucirumab+paclitaxel (n=68)</th>
<th>Placebo+paclitaxel (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>11.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.880 (0.603, 1.284)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.5113</td>
</tr>
</tbody>
</table>

**Western**

<table>
<thead>
<tr>
<th>Ramucirumab+paclitaxel (n=198)</th>
<th>Placebo+paclitaxel (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>8.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
</tr>
</tbody>
</table>

Hironaka et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4005)
4005: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy—Efficacy analysis in Japanese and Western patients – Hironaka S et al

- **Key results**
  - PDT: Japan 75.0 vs 75.0%; West 38.4 vs 36.0% with ramucirumab vs placebo, respectively

<table>
<thead>
<tr>
<th>Grade 3 AEs occurring in &gt;5% in any group, %</th>
<th>Japanese RAM+PTX (n=68)</th>
<th>Japanese PBO+PTX (n=71)</th>
<th>Western RAM+PTX (n=196)</th>
<th>Western PBO+PTX (n=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>66.2</td>
<td>25.4</td>
<td>32.1</td>
<td>14.7</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>45.6</td>
<td>14.1</td>
<td>9.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4.4</td>
<td>5.6</td>
<td>11.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2.9</td>
<td>5.6</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.5</td>
<td>2.8</td>
<td>16.8</td>
<td>6.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.4</td>
<td>0</td>
<td>18.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>0</td>
<td>7.1</td>
<td>4.6</td>
</tr>
</tbody>
</table>

- **Conclusions**
  - There were improvements in PFS and ORR in the Japanese population, which was consistent with the Western population
  - Prolonged post-progression survival in Japanese patients may be due to higher use of PDT and may have masked the potential OS benefit
  - The safety profile was generally comparable between Japanese and Western patients, although some AEs were more frequent in Japanese patients

PDT, post-discontinuation treatment

Hironaka et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4005)
LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Study objective**
  - To assess the efficacy of second-line treatment with ramucirumab in combination with paclitaxel compared with paclitaxel alone in patients with gastric cancer

**Patients with**
- Metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma
- Progression after 1st-line therapy
- ECOG PS 0–1

**Ramucirumab+ paclitaxel (n=330)**

- **Stratification**
  - Geographic region
  - Measurable vs. non-measurable disease
  - Time of progression on 1st-line therapy (<6 vs. ≥6 months)

**Placebo+ Paclitaxel (n=335)**

**Primary endpoint**
- OS

**Secondary endpoints**
- PFS, TTP, ORR, safety, QoL, PK, PD

Ramucirumab 8 mg/kg days 1 & 15; Paclitaxel 80 mg/m² days 1, 8 & 15 of 28-day cycle

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)
LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Key results**

  HR 0.807 (95% CI 0.678, 0.962)
  Stratified log-rank p-value=0.0169

<table>
<thead>
<tr>
<th>Patients/events</th>
<th>RAM+PTX</th>
<th>PBO+PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med OS (95% CI), mo</td>
<td>330/256 9.63 (8.48, 10.81)</td>
<td>335/260 7.36 (6.31, 8.38)</td>
</tr>
<tr>
<td>6-month OS</td>
<td>72%</td>
<td>57%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Δ mOS: 2.3 months

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)

PTX, paclitaxel; RAM, ramucirumab
LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Key results**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>( N ) (RAM+PTX)</th>
<th>( N ) (PBO+PTX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>330</td>
<td>335</td>
</tr>
<tr>
<td>Combined geo. region*</td>
<td>Region 1+2</td>
<td>221</td>
<td>221</td>
</tr>
<tr>
<td></td>
<td>Region 3</td>
<td>109</td>
<td>114</td>
</tr>
<tr>
<td>Time to PD on 1(^{st})-line therapy</td>
<td>&lt;6 months</td>
<td>250</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td>≥6 months</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>Disease measurability</td>
<td>Non-measurable</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Measurable</td>
<td>267</td>
<td>273</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>229</td>
<td>243</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>101</td>
<td>92</td>
</tr>
<tr>
<td>Age group (years)</td>
<td>&lt;65</td>
<td>204</td>
<td>212</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>126</td>
<td>123</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0</td>
<td>117</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>213</td>
<td>191</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Intestinal</td>
<td>145</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>Diffuse</td>
<td>115</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>MixMiss/Unk</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td>≤2</td>
<td>209</td>
<td>232</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>121</td>
<td>103</td>
</tr>
<tr>
<td>Primary tumour location</td>
<td>Gastric</td>
<td>264</td>
<td>264</td>
</tr>
<tr>
<td></td>
<td>GEJ</td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td>Prior gastrectomy</td>
<td>Yes</td>
<td>133</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>197</td>
<td>209</td>
</tr>
<tr>
<td>Peritoneal metastases</td>
<td>Yes</td>
<td>163</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>167</td>
<td>183</td>
</tr>
</tbody>
</table>

\( \text{HR} \) values for OS and PFS:

- OS:
  - Overall: 0.807
  - Region 1+2: 0.732
  - Region 3: 0.586
  - Time to PD on 1\(^{st}\)-line therapy:
    - <6 months: 0.871
    - ≥6 months: 0.615
  - Disease measurability:
    - Non-measurable: 1.101
    - Measurable: 0.750
  - Gender:
    - Male: 0.814
    - Female: 0.672
  - Age group (years):
    - <65: 0.753
    - ≥65: 0.861
  - ECOG PS:
    - 0: 0.778
    - 1: 0.771
  - Histologic subtype:
    - Intestinal: 0.705
    - Diffuse: 0.856
    - MixMiss/Unk: 0.955
  - Number of metastatic sites:
    - ≤2: 0.749
    - >2: 0.815
  - Primary tumour location:
    - Gastric: 0.899
    - GEJ: 0.521
  - Prior gastrectomy:
    - Yes: 0.939
    - No: 0.763
  - Peritoneal metastases:
    - Yes: 0.807
    - No: 0.758

- PFS:
  - Overall: 0.635
  - Region 1+2: 0.639
  - Region 3: 0.628
  - Time to PD on 1\(^{st}\)-line therapy:
    - <6 months: 0.586
    - ≥6 months: 0.676
  - Disease measurability:
    - Non-measurable: 0.871
    - Measurable: 0.615
  - Gender:
    - Male: 0.750
    - Female: 0.599
  - Age group (years):
    - <65: 0.572
    - ≥65: 0.673
  - ECOG PS:
    - 0: 0.663
    - 1: 0.568
  - Histologic subtype:
    - Intestinal: 0.512
    - Diffuse: 0.833
    - MixMiss/Unk: 0.599
  - Number of metastatic sites:
    - ≤2: 0.676
    - >2: 0.512
  - Primary tumour location:
    - Gastric: 0.861
    - GEJ: 0.670
  - Prior gastrectomy:
    - Yes: 0.670
    - No: 0.833
  - Peritoneal metastases:
    - Yes: 0.592
    - No: 0.599

*Region 1: Europe. United States and Australia. Region 2: Brazil, Chile, Mexico and Argentina. Region 3: Japan, South Korea, Hong, Taiwan and Singapore

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)
LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Key results**
  - Ramucirumab in combination with paclitaxel provided a consistent additive effect across all efficacy endpoints

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Ramucirumab +paclitaxel</th>
<th>Placebo+paclitaxel</th>
<th>HR p-value</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, %</td>
<td>28</td>
<td>16</td>
<td>=0.0001</td>
<td>+12</td>
</tr>
<tr>
<td>Disease control rate, %</td>
<td>80</td>
<td>64</td>
<td>&lt;0.0001</td>
<td>+16</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>4.40</td>
<td>2.86</td>
<td>HR 0.635</td>
<td>+1.5</td>
</tr>
<tr>
<td>At 6 months, %</td>
<td>36</td>
<td>17</td>
<td>&lt;0.0001</td>
<td>+19</td>
</tr>
<tr>
<td>At 9 months, %</td>
<td>22</td>
<td>10</td>
<td></td>
<td>+12</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>9.63</td>
<td>7.36</td>
<td>HR 0.807</td>
<td>+2.3</td>
</tr>
<tr>
<td>At 6 months, %</td>
<td>72</td>
<td>57</td>
<td>=0.0169</td>
<td>+15</td>
</tr>
<tr>
<td>At 12 months, %</td>
<td>40</td>
<td>30</td>
<td></td>
<td>+10</td>
</tr>
</tbody>
</table>

- Grade ≥3 TEAEs that occurred in >10% of patients and at a higher incidence with ramucirumab+paclitaxel were: neutropenia, leukopenia, hypertension and fatigue; febrile neutropenia was low and similar between the two treatment groups

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)
LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

• Conclusions
  – Ramucirumab in combination with paclitaxel provided a significant and clinically meaningful OS benefit of >2 months; risk reduction of death by 19%
  – Significant benefits were also observed for PFS and ORR
  – Ramucirumab is an effective new drug for the treatment of patients with metastatic or locally advanced unresectable gastric or GEJ cancer who have received prior chemotherapy
  – The findings demonstrate that second-line therapy improves survival of patients with metastatic or locally advanced unresectable gastric cancer

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)
4020: E2208: Randomized phase II study of paclitaxel with or without the anti-IGF-IR antibody cixutumumab (IMC-A12) as second-line treatment for patients with metastatic esophageal or GE junction cancer – Cohen SJ et al

- **Study objective**
  - To compare paclitaxel alone with paclitaxel+cixutumumab in patients as second-line treatment for patients with metastatic oesophageal or gastro-oesophageal junction (GEJ) cancer

**Key patient inclusion criteria**
- Patients with metastatic adenocarcinoma or SCC of oesophagus or GEJ
- ECOG PS 0–2
- No prior taxane
  
(n=87)

**Primary endpoint**
- PFS

**Secondary endpoints**
- OS, RR and toxicity

**Arm A:** Paclitaxel* alone (n=43)

**Arm B:** Paclitaxel* + cixutumumab† (n=44)

---

*80 mg/m² IV days 1,8,15 q4w; †10 mg/kg days 1,15 q4w

Cohen et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4020)
4020: E2208: Randomized phase II study of paclitaxel with or without the anti-IGF-IR antibody cixutumumab (IMC-A12) as second-line treatment for patients with metastatic esophageal or GE junction cancer – Cohen SJ et al

• Key results

<table>
<thead>
<tr>
<th>Most common AEs, n (%)</th>
<th>Arm A (Grade 3)</th>
<th>Arm A (Grade 4)</th>
<th>Arm B (Grade 3)</th>
<th>Arm B (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>4 (10)</td>
<td>0</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (8)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Generalised muscle weakness</td>
<td>0</td>
<td>0</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>2 (5)</td>
<td>0</td>
<td>5 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphataemia</td>
<td>2 (5)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>7 (18)</td>
<td>1 (3)</td>
<td>7 (16)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>0</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (8)</td>
<td>0</td>
<td>5 (11)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>2 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Median PFS: paclitaxel 2.6 m vs paclitaxel+cixutumumab 2.3 m (p=0.72)
- Median OS: paclitaxel 6.5 m vs paclitaxel+cixutumumab 6.4 (p=0.92)
- RR (CR+PR): 12% with paclitaxel vs 14% with paclitaxel+cixutumumab

• Conclusion

- The addition of cixutumumab to paclitaxel in second-line therapy was well tolerated, but did not improve clinical outcome

Cohen et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4020)

- Study objective
  - To assess the efficacy and safety of apatinib (a VEGFR-2 tyrosine kinase inhibitor) in patients with advanced gastric cancer who have previously failed second-line CT

Key patient inclusion criteria
- Advanced gastric cancer
- Previously failed second-line CT
  - (n=270)

Primary endpoint
- OS

Stratification
- Number of metastatic sites
  - (≥2 vs <2)

Apatinib 850 mg/day for 1 cycle (28 days)
  - (n=180)

Placebo
  - (n=90)

- **Key results**

<table>
<thead>
<tr>
<th></th>
<th>Apatinib</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, days</td>
<td>195</td>
<td>140</td>
<td>0.71 (0.54, 0.94)</td>
<td>&lt;0.016</td>
</tr>
<tr>
<td>Median PFS, days</td>
<td>78</td>
<td>53</td>
<td>0.44 (0.33, 0.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>2.8</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Apatinib was generally well tolerated
  - Most AEs were managed by dose interruptions or reductions
  - Grade 3–4 AEs that occurred in >2% of patients were: hypertension, hand-and-foot syndrome, proteinuria, fatigue, anorexia and elevated aminotransferase

- **Conclusions**
  - This study provides further evidence of the efficacy and safety of apatinib in the patients with advanced gastric cancer
  - The recommended dose of apatinib for clinical use is 850 mg/day

Qin et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4003)
RARE TUMOURS
RARE TUMOURS

NEUROENDOCRINE TUMOURS
179: Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors – Fine RL et al

- **Study objective**
  - To assess treatment with capecitabine and temozolomide in patients with progressive, metastatic, well- or moderately-differentiated neuroendocrine tumours (NETs) who failed Sandostatin LAR 60 mg

**Patients with NETs**
- Progressive disease after Sandostatin LAR 60 mg
- Ki-67 ≤20% (n=28)

**Primary endpoint**
- Response rate (RR)

**Secondary endpoints**
- PFS, OS, safety

Capecitabine 1500 mg/m²/day (PO divided BID, max 2500 mg/day) on days 1–14; temozolomide 150–200 mg/m²/day (PO divided bid, lower dose for patients who had prior chemotherapy or extensive radiation) on days 1–14

Suntharalingam et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA6)
Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors – Fine RL et al

**Key results**

- Interim findings showed an overall RR of 43% (CR 11%, PR 32%) and SD rate of 54%, with a clinical benefit in 97%
- In carcinoid tumours (typical and atypical), the ORR was 41%

<table>
<thead>
<tr>
<th></th>
<th>% SD</th>
<th>% PR</th>
<th>% CR</th>
<th>% PD</th>
<th>PFS, mo</th>
<th>OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid (total) (n=12)</td>
<td>58</td>
<td>33</td>
<td>8</td>
<td>0</td>
<td>&gt;23.9</td>
<td>&gt;31.5</td>
</tr>
<tr>
<td>Typical (n=10)</td>
<td>60</td>
<td>30</td>
<td>10</td>
<td>0</td>
<td>&gt;23.9</td>
<td>&gt;28.3</td>
</tr>
<tr>
<td>Atypical (n=2)</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>&gt;23.8</td>
<td>&gt;27.3</td>
</tr>
<tr>
<td>Pituitary (n=3)</td>
<td>0</td>
<td>33</td>
<td>67</td>
<td>0</td>
<td>&gt;41.6</td>
<td>&gt;41.6</td>
</tr>
<tr>
<td>Pancreatic NET (n=11)</td>
<td>55</td>
<td>36</td>
<td>0</td>
<td>9</td>
<td>&gt;20.0</td>
<td>&gt;24.4</td>
</tr>
<tr>
<td>Medullary thyroid (n=2)</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&gt;22.8</td>
<td>&gt;27.7</td>
</tr>
<tr>
<td>Overall (n=28)</td>
<td>54</td>
<td>32</td>
<td>11</td>
<td>3</td>
<td>&gt;22.2</td>
<td>&gt;29.1</td>
</tr>
</tbody>
</table>

- Most common grade 3/4 toxicities were lymphopenia (35%), hyperglycaemia (6%, unlikely related), thrombocytopenia (3%) and diarrhea (3%)
Conclusions

- CAPTEM was associated with significant response rates (RR 43%, SD 54%) in patients with various types of NET
- PFS and OS analysis is ongoing
- Significant responses were also observed in the traditionally chemo-resistant carcinoids (RR 42%, SD 58%) and pituitary tumours (RR 100%, CR 2/3)
RARE TUMOURS

PSEUDOMYXOMA PERITONEI
4033: Nomograms to predict prognosis in pseudomyxoma peritonei: A Peritoneal Surface Oncology Group International (PSOGI) multicenter study – Kusamura S et al

- **Study objective**
  - To determine whether clinico-pathological variables can predict survival in patients with PMP treated with cytoreductive surgery and intraperitoneal CT

- **Study design**
  - The developing set comprised data from 1715 PMP patients from 29 centres
  - The covariates were chosen according to literature data
  - Continuous variables were transformed using restricted cubic splines
  - Missing data were handled using multiple imputation with chained equations (MICE) approach
  - A Cox model was fitted in each of the different completed developing datasets generated by MICE
  - Pooled estimates of regression coefficients, variances, and models’ discriminations (bootstrap corrected Harrell C indexes) were obtained using Rubin’s rule
  - The nomograms were externally validated on 733 PMP patients (validating set)

PMP, pseudomyxoma peritonei

Kusamura et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4033)
4033: Nomograms to predict prognosis in pseudomyxoma peritonei: A Peritoneal Surface Oncology Group International (PSOGI) multicenter study – Kusamura S et al

- **Key results**
  - 5-year OS: 74.1% (95% CI 71.3, 76.8); 5-year PFS: 52.3% (95% CI 49.4, 55.2)
  - Adjusted OS/PFS were 0.80/0.74 (developing set), 0.74/0.72 (validating set)

- **Conclusion**
  - The nomograms may allow the prediction of OS and PFS, providing individualised outcome prognostication

*Corrected Harrell C indexes; CC, completeness of cytoreduction; EPIC, early postoperative CT; HIPEC, hyperthermic intraperitoneal CT; PCI, peritoneal cancer index

Kusamura et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4033)