Systemic Treatments for Esophagogastric and Pancreas Cancer in the Adjuvant and Metastatic Settings

Peter C. Enzinger, MD
Dana-Farber Cancer Institute & Harvard Medical School
Disclosure
I have nothing to disclose.

Off Label/Investigational Discussion
In accordance with Annenberg Center policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Localized Esophageal Cancer

What Can Surgery Accomplish?
Localized Esophageal Cancer Treated With Surgery

FIG. 1 Risk-adjusted survival for adenocarcinoma according to the American Joint Committee on Cancer Cancer Staging Manual, 7th edition, stage groups.

FIG. 2 Risk-adjusted survival for squamous-cell carcinoma according to the American Joint Committee on Cancer Cancer Staging Manual, 7th edition, stage groups.

Rice, Blackstone, Rusch. Ann Surg Oncol 2010
Localized Esophageal Cancer

Does (Neo)Adjuvant Chemotherapy Improve Surgical Outcomes?
### Squamous-cell carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Squamous-cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth</td>
<td>19</td>
</tr>
<tr>
<td>Nygaard</td>
<td>56</td>
</tr>
<tr>
<td>Schlag</td>
<td>22</td>
</tr>
<tr>
<td>Malphig</td>
<td>24</td>
</tr>
<tr>
<td>Law</td>
<td>74</td>
</tr>
<tr>
<td>Boomstra</td>
<td>85</td>
</tr>
<tr>
<td>Kelsen</td>
<td>103</td>
</tr>
<tr>
<td>Ancona</td>
<td>48</td>
</tr>
<tr>
<td>Allum</td>
<td>123</td>
</tr>
<tr>
<td>Total</td>
<td>554</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 14.70$, df = 8 (p = 0.07); $I^2 = 46\%$

Test for overall effect: $Z = 1.34$ (p = 0.18)

### Adenocarcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelsen</td>
<td>120</td>
</tr>
<tr>
<td>Allum</td>
<td>265</td>
</tr>
<tr>
<td>Ychou</td>
<td>85</td>
</tr>
<tr>
<td>Subtotal</td>
<td>476</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 2.83$, df = 2 (p = 0.24); $I^2 = 29\%$

Test for overall effect: $Z = 2.58$ (p = 0.01)

### Total

<table>
<thead>
<tr>
<th>Squamous-cell carcinoma</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1024</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 18.68$, df = 11 (p = 0.07); $I^2 = 41\%$

Test for overall effect: $Z = 2.71$ (p = 0.007)

Test for subgroup differences: $\chi^2 = 1.14$, df = 1 (p = 0.29); $I^2 = 12.4\%$

Localized Esophageal Cancer

Does Neoadjuvant Chemoradiation Therapy Improve Surgery Outcomes?
All-Cause Mortality Estimates for Neoadjuvant C/RT Compared with Surgery Alone

CROSS Study: Schema

- Chemoradiotherapy regimen:
  - Paclitaxel 50mg/m² + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29
  - Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy

- Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)

CROSS Study: Overall survival

HR, 0.657; 95% CI 0.495-0.871

24.0 mo 49.4 mo

**Arm A**

PLF I, PLF II, PLF III (3 weeks), Surgery

**Arm B**

PLF I, PLF II, 15 x 2 Gy in 3 weeks, Surgery, PE (1 week)

PLF: Cisplatin 50mg/m², 1h, d 1,15,29. Leukovorin/5-FU 500mg/m² 2h / 2g/m2 24h, d1,8,15,22,29,36
PE: Cisplatin 50 mg/m², 1h, d 2+8. Etoposide 80 mg/m², 1h, d 3-5

POET: Overall Survival (Long-term Results)

Median Survival:

C → C → S
C → C/RT → S

21.1 mo 30.8 mo

3yr 5yr
47% 40%
26% 24%

Hazard ratio: 0.55, CI 95%: 0.42 - 1.01
log-rank test (two-sided): p-value = 0.055

Can Surgery Improve the Outcome of Chemoradiation?
Prospective Randomized Intergroup Study:
Radiation Therapy vs Chemotherapy + Radiation Therapy for Localized SCC or ADC of the Esophagus

Schema

<table>
<thead>
<tr>
<th>Schema</th>
<th>2 x Cisplatin (75 mg/m²) + 5-fluorouracil (1000 mg/m²/d CI x 4d) + radiation therapy (5000 cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tumor size</td>
<td></td>
</tr>
<tr>
<td>histology</td>
<td></td>
</tr>
<tr>
<td>weight loss</td>
<td>radiation therapy (6400 cGy)</td>
</tr>
</tbody>
</table>

Intergroup Study

Prodige 5 - ACCORD 17 - Schema

**Inoperable esophageal cancer**

**Randomize**

- 50 Gy/5 weeks + Folfox, 3 cycles
- Folfox, 3 cycles
- 50 Gy/5 weeks + 5FU/cisplatin, 2 cy.
- 5FU/cisplatin, 2 cycles

**Stratification:**
- adenocarcinoma vs squamous cell vs adenosquamous
- pretreatment weight loss < 10% vs ≥ 10%
- performance status: 0 vs 1 vs 2
- center

FOLFOX: more gr. 1-2 PN, fewer toxic & sudden deaths, less mucositis, less alopecia, decreased renal toxicity, shorter chemotherapy (12 days vs 16-20 days) in an outpatient setting.

Chemoradiation Therapy With or Without Surgery: French Phase III Trial

• A total of 455 patients with localized esophageal cancer were given 2 courses of 5-FU/cisplatin plus radiation therapy.

• 259/455 patients experienced a “partial response”, were considered operative candidates, and entered the randomized component of the trial.

Survival
3-month mortality median
5-FU/CDDP x 3 + Radiation therapy
1%
19.3 months
40%
P=0.56

Surgery
9%
17.7 months
34%

Partial Response
(259 pts)

Chemoradiation Therapy With or Without Surgery: French Phase III Trial

Patients: (N = 177) uT3-4,N0-1, M0 with SCC

3 cycles: 5-FU/LV + Cisplatin + Etoposide

Chemoradiation: Cisplatin + Etoposide + 40 Gy RT → Surgery

Chemoradiation: Cisplatin + Etoposide + > 60 Gy RT

## Chemoradiation Therapy With or Without Surgery: German Phase III Trial - Results

<table>
<thead>
<tr>
<th>Arm</th>
<th>Completed Treatment</th>
<th>Treatment Mortality</th>
<th>3-yr Local Recurrence</th>
<th>Median Survival</th>
<th>3-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Induction Chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Responder</td>
</tr>
<tr>
<td>Arm A: C/RT → S</td>
<td>62%</td>
<td>12.8%</td>
<td>41%</td>
<td>16 mo.</td>
<td>31%</td>
</tr>
<tr>
<td>Arm B: C/RT</td>
<td>85%</td>
<td>3.5% ($P = 0.03$)</td>
<td>64% ($P = 0.004$)</td>
<td>15 mo.</td>
<td>24% ($P = 0.02$)</td>
</tr>
</tbody>
</table>

Chemoradiation Therapy With or Without Surgery:
German Phase III Trial - Survival

Median survival (N = 172):
Arm A (C/RT → S) - 16.4 months
Arm B (C/RT only) - 14.9 months

31.3% ($P = 0.02$)
24.4%

Localized Esophageal

Pre-operative cisplatin/5-FU chemotherapy offers a small survival advantage in distal esophageal and GE junction cancer.

Neoadjuvant platinum-based chemoradiation (esp. w. carbo/tax) offers a greater survival advantage with better local control but increased surgical morbidity.

Surgery may not be needed in patients who have a clinical response to chemoradiation. FOLFOX may be the best choice for these patients.
What Can Surgery Accomplish?

What are Proven Strategies to Enhance Outcomes for Surgical Resection?
Intergroup Protocol 0116
Adjuvant Therapy for Gastric Cancer

Stratify

- depth of tumor penetration
- number involved nodes
- location of tumor
- extent of surgery

Randomize:

- 5-FU/leucovorin x 1
- 5-FU/leucovorin x 2
- 4500 cGy radiation
- Observation

Intergroup Protocol 0116

MAGIC Trial: Schema


503 Patients:
15% Lower Third
12% GE Junction

Within 6 weeks

S

Resection

Follow-up

Resection

ECF x 3 q3/52
3-6 weeks

ECF x 3 q3/52
6-12 weeks

CSC

Patients: 12% GE Junction

15% Lower Third
MAGIC: Survival

Logrank $P$-value = 0.009
Hazard Ratio = 0.75
(95% CI, 0.60 - 0.93)

Cunningham.

![Survival Curve](image)

Patients at risk

<table>
<thead>
<tr>
<th>CSC</th>
<th>250</th>
<th>168</th>
<th>111</th>
<th>79</th>
<th>52</th>
<th>38</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>253</td>
<td>155</td>
<td>80</td>
<td>50</td>
<td>31</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>
FLTOT4 Study Design

Randomized, multicenter, investigator-initiated, phase II/III study

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

Stratification: ECOG (0 or 1 vs. 2), **location of primary** (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and **nodal status** (cN+ vs. cN-).

- FLOT x4 - RESECTION - FLOT x4
  - FLOT: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

- ECF/ECX x3 - RESECTION - ECF/ECX x3
  - ECF/ECX: Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Presented by: Salah-Eddin Al-Batran
FLOT4: Progression-Free Survival

**ECF/ECX vs FLOT**

- **mPFS**
  - 18 months: [15-22] vs 30 months: [21-41]

- **HR**: 0.75 [0.62-0.91], p=0.004 (log rank)

- **PFS rates**
  - 2y: 43% vs 53%
  - 3y: 37% vs 46%
  - 5y: 31% vs 41%

*Projected PFS rates*

Presented by: Salah-Eddin Al-Batran
FLOT4: Overall Survival

Overall survival (months)

Survival Probability

ECF/ECX  FLOT

mOS  35 months  50 months
[27-46]  [38-na]

HR  0.77 [0.63 - 0.94]
p=0.012 (log rank)

2y  59%  68%
3y  48%  57%
5y  36%  45%

*projected OS rates

Presented by: Salah-Eddin Al-Batrán
## FLOT 4: Toxicity

<table>
<thead>
<tr>
<th>Toxic event</th>
<th>ECF/ECX (N=354)</th>
<th>FLOT (N=354)</th>
<th>P-value (Chi-Square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE any</td>
<td>220 (62%)</td>
<td>215 (61%)</td>
<td></td>
</tr>
<tr>
<td>SAE with relation to treatment</td>
<td>137 (34%)</td>
<td>139 (35%)</td>
<td></td>
</tr>
<tr>
<td>Toxic death</td>
<td>2 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td></td>
</tr>
</tbody>
</table>

### Grade 3-4 >5%

<table>
<thead>
<tr>
<th>Toxic event</th>
<th>ECF/ECX (N=354)</th>
<th>FLOT (N=354)</th>
<th>P-value (Chi-Square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13 (4%)</td>
<td>34 (10%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (8%)</td>
<td>7 (2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>55 (16%)</td>
<td>26 (7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (11%)</td>
<td>25 (7%)</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>30 (9%)</td>
<td>63 (18%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>75 (21%)</td>
<td>94 (27%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>139 (39%)</td>
<td>181 (51%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sensory</td>
<td>7 (2%)</td>
<td>24 (7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>22 (6%)</td>
<td>9 (3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (6%)</td>
<td>9 (3%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Modified from Al-Batran et al. ASCO 2017
Localized Gastric:

Post-operative 5-FU-based chemoradiation therapy remains one standard of care for muscle-invasive or LN positive disease.

The MAGIC trial demonstrated that pre- and post-operative ECF improves survival. It may be particularly beneficial for downstaging extensive local local disease.

The peri-operative FLOT4 regimen appears to be an improvement over ECF and will likely become the new standard of care for patients of better performance status.
What are the Active Agents and Combinations for this Disease?
Evolution of Therapy in Advanced Esophagogastric Cancer

- FOLFOX
  - FOL = CF FOX
  - FOX

- DC < DCF
  - DCF > CF
  - mDCF

- IP < FOLFIRI
  - CF = FOLFIRI
  - FOLFIRI = EOX

- 5-FU < FAM
- FAM < FAMTX
- CF = ELF = FAMTX > EAP
- PELF = FAMTX < ECF
- ECF > MCF
- ECF = ECX = EOF = EOX
CALGB 80403 / ECOG E1206: Schema

Stratification:
ECOG 0-1 vs 2 ADC vs. SCC

ARM A: (ECF + cetuximab); 1 cycle = 21 days
Cetuximab 400 → 250mg/m2 IV, weekly
Epirubicin 50 mg/m2 IV, day 1
Cisplatin 60mg/m2 IV, day 1
Fluorouracil 200mg/m2/day, days 1-21

ARM B: (IC + cetuximab); 1 cycle = 21 days
Cetuximab 400 → 250mg/m2 IV, weekly
Cisplatin 30 mg/m2 IV, days 1 and 8
Irinotecan 65 mg/m2 IV, days 1 and 8

ARM C: (FOLFOX + cetuximab); 1 cycle = 14 days
Cetuximab 400 → 250mg/m2 IV, weekly
Oxaliplatin 85 mg/m2 IV, day 1
Leucovorin 400 mg/m2, day 1
Fluorouracil 400 mg/m2 IV bolus, day 1
Fluorouracil 2400 mg/m2 IV over 46hrs (days 1-2)

FOLFOX-C has similar efficacy to ECF-C in Esophageal and GEJ Cancer

Progression-Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events n/N (%)</th>
<th>Median months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF-C</td>
<td>65/67 (97.0%)</td>
<td>7.1</td>
<td>4.5-8.4</td>
</tr>
<tr>
<td>IC-C</td>
<td>72/73 (96.6%)</td>
<td>4.9</td>
<td>3.9-6.0</td>
</tr>
<tr>
<td>FOLFOX-C</td>
<td>70/73 (95.9%)</td>
<td>0.8</td>
<td>5.4-8.1</td>
</tr>
</tbody>
</table>

Log-rank test p=0.09

Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events n/N (%)</th>
<th>Median months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF-C</td>
<td>65/67 (94.0%)</td>
<td>11.6</td>
<td>8.1-13.4</td>
</tr>
<tr>
<td>IC-C</td>
<td>68/73 (93.2%)</td>
<td>8.6</td>
<td>6.0-12.4</td>
</tr>
<tr>
<td>FOLFOX-C</td>
<td>65/73 (89.0%)</td>
<td>11.8</td>
<td>8.8-13.9</td>
</tr>
</tbody>
</table>

Log-rank test p=0.61

Number of Patients at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ECF-C</th>
<th>IC-C</th>
<th>FOLFOX-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF-C</td>
<td>67</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>IC-C</td>
<td>73</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>FOLFOX-C</td>
<td>73</td>
<td>17</td>
<td>7</td>
</tr>
</tbody>
</table>

Treatment modifications:
FOLFOX-C (73%) vs IC-C (85%) vs ECF-C (91%) ($\chi^2$, p=0.013).

Discontinued treatment for adverse event or treatment-related death:
FOLFOX-C (11%) vs. ECF-C (19%) vs IC-C (26%) ($\chi^2$, p=0.17).
Phase III: DCF vs CF for Esophagogastric Cancer

Time to Progression

Overall Survival

<table>
<thead>
<tr>
<th>Grade 3-4 Toxicity</th>
<th>DCF</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>82%</td>
<td>57%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>29%</td>
<td>12%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19%</td>
<td>8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Van Cutsem et al.  
J Clin Oncol 2006
Grade 3-4 Toxicity | mDCF | DCF
---|---|---
Neutropenia w GCSF | 56% | 45%
Febrile Neutropenia | 9% | 16%
Stomatitis | 0 | 13%
Diarrhea | 6% | 3%
Vomiting | 2% | 19%
Phase 3: FOLFIRI vs ECX for Met Gastric/GEJ

Table 2. Efficacy Results for PFS and OS

<table>
<thead>
<tr>
<th>Variable</th>
<th>ECX Arm (n = 209)</th>
<th>FOLFIRI Arm (n = 207)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>PFS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.29</td>
<td></td>
<td>4.53-6.31</td>
</tr>
<tr>
<td>Range</td>
<td>4.53-6.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-month survival</td>
<td>5.03</td>
<td>2.46 to 8.97</td>
<td></td>
</tr>
<tr>
<td>OS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>9.49</td>
<td></td>
<td>8.77-11.14</td>
</tr>
<tr>
<td>Range</td>
<td>8.77-11.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-month survival</td>
<td>11.17</td>
<td>7.03 to 16.36</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; FOLFIRI, fluorouracil, leucovorin, and irinotecan; OS, overall survival; PFS, progression-free survival.
*Log-rank test.
Previously untreated patients with locally advanced or metastatic oesophago-gastric cancer

 Stratified for:
 - Center (63 centers, mainly UK, 2 Aus)
 - Locally advanced vs metastatic
 - PS 0/1 vs 2

2 x 2 design

- Epirubicin
  - Cisplatin
  - Fluorouracil

- Epirubicin
  - Cisplatin
  - Xeloda (capecitabine)

- Epirubicin
  - Oxaliplatin
  - Fluorouracil

- Epirubicin
  - Oxaliplatin
  - Xeloda (capecitabine)

REAL-2: Survival (ITT)

<table>
<thead>
<tr>
<th>Arm</th>
<th>OS (m)</th>
<th>1-year survival (95% CI)</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF</td>
<td>9.9</td>
<td>37.7 (31.8-43.6)</td>
<td>0.612</td>
<td>1</td>
</tr>
<tr>
<td>EOF</td>
<td>9.3</td>
<td>40.4 (34.2-46.5)</td>
<td>0.389</td>
<td>0.96 (0.79-1.15)</td>
</tr>
<tr>
<td>ECX</td>
<td>9.9</td>
<td>40.8 (34.7-46.9)</td>
<td>0.020</td>
<td>0.92 (0.76-1.11)</td>
</tr>
<tr>
<td>EOX</td>
<td>11.2</td>
<td>46.8 (40.4-52.9)</td>
<td></td>
<td>0.80 (0.66-0.97)</td>
</tr>
</tbody>
</table>

**IntelliDose chemotherapy order entry (COE) platform: Trends in metastatic gastric cancer chemotherapy treatment* (2005-2016)**

<table>
<thead>
<tr>
<th></th>
<th>Year of initiation of first-line therapy</th>
<th></th>
<th>Year of initiation of second-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=4,333</td>
<td></td>
<td>N=1,822</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,073</td>
<td>1,357</td>
<td>948</td>
</tr>
<tr>
<td><strong>FOLFOX (%)</strong></td>
<td>12.0</td>
<td>21.2</td>
<td>35.1</td>
</tr>
<tr>
<td><strong>ECF/EOX (%)</strong></td>
<td>13.8</td>
<td>23.0</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>DCF (%)</strong></td>
<td>22.9</td>
<td>14.3</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>CF (%)</strong></td>
<td>12.6</td>
<td>10.8</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>TAX (%)</strong></td>
<td>4.8</td>
<td>4.1</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>C+Irinotecan (%)</strong></td>
<td>9.0</td>
<td>2.8</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>C+TAX (%)</strong></td>
<td>9.8</td>
<td>12.2</td>
<td>15.6</td>
</tr>
<tr>
<td><strong>FU mono (%)</strong></td>
<td>9.2</td>
<td>7.5</td>
<td>8.1</td>
</tr>
<tr>
<td><strong>Other (%)</strong></td>
<td>5.9</td>
<td>4.1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

FOLFOX=fluoropyrimidine (FU) + oxaliplatin; ECF/EOX=epirubicin + platinum + FU; DCF=docetaxel (D) + cis/carboplatin (C) + FU; CF=C + FU; TAX=taxane; DF = D + FU

* With or without biologic agents

Abrams T et al. GI Cancers Symposium 2018
Phase III, randomized, open-label, international, multicenter study

3807 patients screened
810 HER2-positive (22.1%)

HER2-positive advanced GC (n = 584)

5-FU or capecitabine + cisplatin (n = 290)

5-FU or capecitabine\textsuperscript{a} + cisplatin + trastuzumab (n = 294)

Stratification factors
- Advanced vs metastatic
- GC vs GEJ
- Measurable vs non-measurable
- ECOG PS 0-1 vs 2
- Capecitabine vs 5-FU

\textsuperscript{a}Chosen at investigator’s discretion
GEJ, gastroesophageal junction

ToGA: Overall Survival

**HER2 3+ or 2+/FISH+**

Event | Median
--- | ---
FC + T | 13.8
FC | 11.1

---

2.7 mo.

---

(HER2 3+ or 2+/FISH+)

---

5.2 mo.
Is 2\textsuperscript{nd} line therapy of benefit?
Cougar-02: Randomized Trial of Docetaxel vs. BSC in Relapsed Esophagogastric Adenocarcinoma

168 patients:

- Docetaxel 75 mg/m² q 3 weeks
- Best supportive care

Primary Endpoint: Overall Survival

Cougar – 02: 2nd line Docetaxel vs. BSC: Overall Survival

HR: 0.67, 95% CI 0.49–0.92; p=0.01

REGARD Study Design

- Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial
- Gastric or GEJ adenocarcinoma
- Stratification factors: region, weight loss (≥10% vs. <10% over 3 months), location of primary tumor (gastric vs. GEJ)
- Global: 6 continents, 30 countries, 120 study centers

Abbreviations: BSC=best supportive care; GEJ= gastroesophageal junction

REGARD: Overall Survival

HR (95% CI) = 0.776 (0.603, 0.998)
Log rank P-value (stratified) = 0.0473

<table>
<thead>
<tr>
<th>Patients / Events</th>
<th>Ramucirumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>238 / 179</td>
<td>117 / 99</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (mos) (95% CI)</th>
<th>Ramucirumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2 (4.4, 5.7)</td>
<td>3.8 (2.8, 4.7)</td>
<td></td>
</tr>
</tbody>
</table>

| 6-month OS | 42% | 32% |
| 12-month OS | 18% | 11% |

Δ mOS = 1.4 months

**RAINBOW: Study Design**

- **Important inclusion criteria:**
  - Metastatic or loc. adv. unresectable gastric or GEJ* adenocarcinoma
  - Progression after 1st line platinum/fluoropyrimidine based chemotherapy

- **Stratification factors:**
  - Geographic region,
  - Measurable vs non-measurable disease,
  - Time to progression on 1st line therapy (< 6 mos vs. ≥ 6 mos)

---

*GEJ= gastroesophageal junction; gastric and GEJ will be summarized under the term GC

RAINBOW: Overall Survival

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

### Median (mos) (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td>Major Response Rate</td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>4.4mo</td>
<td>2.8mo</td>
</tr>
</tbody>
</table>

**Δ mOS = 2.3 months**

No benefit for angiogenesis inhibitors in frontline:

**AVAGAST:** Bevacizumab

**AVATAR:** Bevacizumab

**RAINFALL:** Ramucirumab

**ZAMEGA:** Ziv-Aflibercept
ONO-4538-12 (Attraction-2): Phase 3 Study of Nivolumab vs Placebo in Patients With Refractory GC

Key eligibility criteria:
- Age ≥20 years
- Unresectable advanced or recurrent GC or GJC
- Histologically confirmed adenocarcinoma
- Prior treatment with ≥2 regimens and refractory to/intolerant of standard therapy

Study Design and Endpoints

Nivolumab 3 mg/kg IV Q2W

Placebo

Primary endpoint
- OS

Secondary endpoints
- Efficacy
- Safety

Exploratory endpoint
- Biomarkers

N = 493

Stratification based on:
- Country (Japan vs Korea vs Taiwan)
- ECOG PS (0 vs 1)
- Number of organs with metastases (<2 vs ≥2)

Patients were permitted to continue treatment beyond initial RECIST v1.1-defined disease progression as assessed by the investigator if receiving clinical benefit and tolerating study drug.

ONO-4538-12 (Attraction-2): Response & Survival

KEYNOTE-059: Phase 2 Study of Pembrolizumab for Advanced Gastric or GEJ Adenocarcinoma

Primary end point: ORR per RECIST v1.1 by central review

COHORT 1
- PD-L1+ or PD-L1-
- ≥2 prior systemic treatments
N = 180

COHORT 2
- PD-L1+ or PD-L1-
- No prior systemic therapy
N = 40

COHORT 3
- PD-L1+ only
- No prior systemic therapy
N = 50

Pembrolizumab 200 mg Q3W
Pembrolizumab 200 mg + Cisplatin + 5FU, all Q3W
Pembrolizumab 200 mg Q3W

---

*The first 40 patients enrolled regardless of PD-L1 expression. Enrollment after the first 40 patients will be determined based on the results of an interim analysis. 20 patients from Asian sites and 20 patients from non-Asian sites will be enrolled. Analysis cut-off date: Nov. 10, 2014.

Fuchs CS et al. JAMA Oncol 2018 [Epub ahead of print]
### Cohort 1: Response by PD-L1 & MSI Expression

<table>
<thead>
<tr>
<th>Response&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PD-L1 Positive (n = 148)</th>
<th>PD-L1 Negative (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>15.5</td>
<td>10.1–22.4</td>
</tr>
<tr>
<td>CR</td>
<td>2.0</td>
<td>0.4–5.8</td>
</tr>
<tr>
<td>PR</td>
<td>13.5</td>
<td>8.5–20.1</td>
</tr>
<tr>
<td>DCR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.1</td>
<td>25.6–41.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MSI-High (n = 7)</th>
<th>Not MSI-High (n = 167)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>57.1</td>
<td>18.4–90.1</td>
</tr>
<tr>
<td>CR</td>
<td>14.3</td>
<td>0.4–57.9</td>
</tr>
<tr>
<td>PR</td>
<td>42.9</td>
<td>9.9–81.6</td>
</tr>
<tr>
<td>DCR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>71.4</td>
<td>29.0–96.3</td>
</tr>
</tbody>
</table>

Fuchs CS et al. JAMA Oncol 2018 [Epub ahead of print]
Cohort 1: Treatment Exposure\(^a\) and Duration of Response

<table>
<thead>
<tr>
<th></th>
<th>Median DoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>8.4 (1.6+(^b) to 17.3+)</td>
</tr>
<tr>
<td>PD-L1 positive</td>
<td>16.3 (1.6+ to 17.3+)</td>
</tr>
<tr>
<td>PD-L1 negative</td>
<td>6.9 (2.4 to 7.0+)</td>
</tr>
</tbody>
</table>

\(^a\)Patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 post-baseline assessment were included (n = 30). Bar length indicates time to last imaging assessment. \(^b\)No progressive disease at last disease assessment.

Data cutoff on January 16, 2017.

Fuchs CS et al. JAMA Oncol 2018 [Epub ahead of print]
**PRINCIPLES OF SYSTEMIC THERAPY**

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma

(See Principles of Pathologic Review and HER2 Testing [GAST-9])

- Combination with fluoropyrimidine and cisplatin (category 1)\[^1][^3]\)
- Combination with other chemotherapy agents (category 2B)
- Trastuzumab is not recommended for use with anthracyclines

**First Line Therapy**

Two-drug cytotoxic regimens are preferred because of lower toxicity.

Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

**Preferred Regimens:**

- Fluoropyrimidine (fluorouracil\[^1\] or capecitabine) and cisplatin\[^4\]-\[^7\] (category 1)
- Fluoropyrimidine (fluorouracil\[^1\] or capecitabine) and oxaliplatin\[^8\]-\[^10\] (category 1)

- Other Regimens:
  - Paclitaxel with cisplatin or carboplatin\[^2\]-\[^4\]
  - Docetaxel with cisplatin\[^2\]-\[^4\]
  - Fluoropyrimidine (fluorouracil\[^1\] or capecitabine) (category 1)
  - Docetaxel\[^2\]-\[^7\]
  - Paclitaxel\[^2\]-\[^7\]
  - Fluorouracil\[^1\] and irinotecan\[^3\]
  - DCF modifications
    - Docetaxel, cisplatin, and fluorouracil\[^1\] (category 1)
    - Docetaxel, oxaliplatin, and fluorouracil\[^3\]
    - Docetaxel, carboplatin, and fluorouracil (category 2B)\[^3\]
    - ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)\[^3\]
  - ECF modifications (category 2B)\[^3\]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, oxaliplatin, and capcitabine

- First-line systemic treatment with irinotecan and fluoropyrimidines should be considered in patients who have not previously received fluoropyrimidine-based chemotherapy as first-line systemic therapy.

**Second Line or Subsequent Therapy**

Dependent on prior therapy and PS:

**Preferred Regimens:**

- Ramucirumab and paclitaxel (category 1)\[^36\]
- Docetaxel (category 1)\[^27\]-\[^28\]
- Paclitaxel (category 1)\[^29\]-\[^37\]
- Irinotecan (category 1)\[^37\]-\[^40\]
- Ramucirumab (category 1)\[^41\]
- Fluorouracil\[^1\] (category 1)\[^36\],\[^42\],\[^43\]
- Pembrolizumab
  - For second-line or subsequent therapy for MSI-H or dMMR tumors\[^45\],\[^46\]
  - For third-line or subsequent therapy for PD-L1 positive adenocarcinoma\[^37\],\[^41\]
- Docetaxel and irinotecan\[^46\] (category 2B)

- Other Regimens:
  - Irinotecan and cisplatin\[^18\],\[^44\]
  - Pembrolizumab

[^1]: Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion.
[^2]: Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
[^3]: Pembrolizumab is approved for patients with gastric tumors with PD-L1 expression levels \(> 1\) as determined by an FDA-approved test.
## Pancreatic Cancer: Staging and Prognosis

<table>
<thead>
<tr>
<th>Stage classification</th>
<th>% at diagnosis</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>8</td>
<td>20%</td>
</tr>
<tr>
<td>Locally advanced/unresectable</td>
<td>31</td>
<td>8%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>61</td>
<td>2%</td>
</tr>
</tbody>
</table>
Median survival:
20 vs 11 months
($P = 0.03$)

Note: based on 43 patients only, accrued over 8 years. Study terminated prematurely before reaching original accrual goal.

ESPAC: European Study Group for Pancreatic Cancer

- N = 289
- 2 x 2 factorial design → pooled analysis

- Median survival, **chemo vs no chemo**: 20.1 vs 15.5 months
- Median survival, chemoXRT vs no chemoXRT: 15.9 vs 17.9 months

- Authors’ conclusions: chemotherapy produces survival benefit s/p pancreatic ca resection; whereas chemoradiation has *deleterious* effect

- Chemotherapy regimen: 5FU/LV monthly x 6
- Chemoradiation regimen: 4000 cGY XRT (split course) with concurrent 5-FU

CONKO-001 TRIAL

Resected pancreatic cancer
(N = 368)
Stratified by age, tumor status, nodal status, resection margin

71% node (+)
81% R0 resection

Gemcitabine x 6 months
(n = 186)

73% node (+)
85% R0 resection

Observation
(n = 182)

5yr DFS: 16.6% vs. 7.0%

5yr OS: 20.7% vs. 12.2%

ESPAC-4: Schema

Stratify: R0 vs R1, Country (UK vs rest)
Primary Endpoint: Overall survival

Stratified log-rank 5% 2-sided alpha for 10% diff 2 year survival
(47.5% ➤ 57.5%, 90% power with 480 deaths, planned N= 722)

- R0/R1 Resected Panc Adenoca WHO <2; ≤12 wks N= 730
- Gemcitabine 1,000 mg/m² d 1,8,15 q4 wks x6 (N= 366)
- Gemcitabine + Capecitabine 1,660mg/m² d1-21 q4 wks x6 (N= 364)

ESPAC-4: Overall Survival

HR = 0.82 (95% CI, 0.68-0.98)
$\chi^2(1) = 4.61, p = 0.032$

Median $S(t) = 25.5$ months (95% CI: 22.7-27.9)
Median $S(t) = 28.0$ months (95% CI: 23.5-31.5)

No. at Risk
- Gem: 366, 302, 207, 109, 61, 27, 9
- GemCap: 364, 328, 219, 139, 83, 50, 19

THEORETICAL ADVANTAGES OVER POSTOPERATIVE TREATMENT

- Improved rate of negative surgical margins

- No prolonged postoperative recovery before administering treatment
  - In older postop studies, ~20-25% of patients intended for adjuvant therapy do not end up receiving it

- Patients with distant metastases on restaging are spared the morbidity of surgery

- Allows testing of novel agents for on-target tumor effects

- MD Anderson experience: approx 66% of patients make it to surgery with a 2-4 months course of preop chemoXRT; of these, median OS = 31-34 months (Evans DB. J Clin Oncol. 2008;26:3496-3502. Varadhachary GR. J Clin Oncol. 2008;26:3487-3495.)

MAJOR CONCERN: delay of only potentially curative option (surgery)
Locally Advanced Pancreas Cancer

Distant metastasis (including non-regional lymph node metastasis)

Head/uncinate process:
- Solid tumor contact with SMA or celiac axis >180°
- Solid tumor contact with the first jejunal SMA branch
- Thrombosis of SMV or portal vein
- Contact with most proximal jejunal branch of SMV

Body and tail:
- Solid tumor contact of >180° with the SMA or celiac axis
- Solid tumor contact with the celiac axis and aortic involvement
- Thrombosis of SMV or portal vein

NCCN Guidelines Version 2.2015
1 month = Gemcitabine 1000 mg/m²/wk x 3

Capecitabine 1600 mg/m²/d plus radiation therapy 54 Gy (5 x 1.8 Gy/d)

Erlotinib with gem : 100 mg/d

150 mg/d as single agent (maintenance)

Secondary surgery allowed at any time

Overall Survival

Progression-Free Survival

HR, 0.78 (95% CI, 0.61-1.01)
Log-rank P = .06

Should FOLFIRINOX Therapy be Considered for Inoperable Disease?

MGH experience:

22 patients with LAPC treated with FOLFIRINOX between July 2010 and February 2012.

ORR was 27.3%, and median PFS was 11.7 months.

R0 resection: 5 of 22 patients (23%)

Recurrence: 3 of 5 patients with distant recurrence within 5 months.

Hospitalization: 32% on FOLFIRINOX.

Localized Pancreatic:

Adjuvant gemcitabine therapy is most important in the post-operative treatment of resected pancreas cancer. The addition of capecitabine appears to improve survival.

C/RT presently plays a lesser role and is given at most centers now at the end of an adjuvant treatment course.

Neoadjuvant C/RT remains experimental. Unresectable dz is rarely converted with this approach.

Pts with LAPC can be treated with chemo alone or chemo → C/RT. FOLFIRINOX may improve resectability but long-term survival is ?
Treatment of Metastatic Disease: Can We move beyond Gemcitabine?

- Gemcitabine approved in 1997 for first-line therapy of advanced PADC
  - Median survival (vs bolus 5-FU): 5.65 vs 4.41 mos. ($P = 0.0025$)
  - 1-yr survival: 18% vs 2%
  - Clinical benefit: 23.8% vs 4.8%
  - RR: 5.4% vs 0%

## What About Combination Therapy?: Gemcitabine/Platinum Doublets for Advanced Pancreatic Cancer (Phase III Trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Progression-free survival</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruppo Oncologia dell’Italia Meridionale Study (n = 107)</td>
<td>Gemcitabine</td>
<td>8 wks</td>
<td>5 mos</td>
</tr>
<tr>
<td>German Multicentre Study (n = 190)</td>
<td>Gemcitabine</td>
<td>3.1 mos</td>
<td>6 mos</td>
</tr>
<tr>
<td>GERCOR/GISCAD Intergroup Study (n=313)</td>
<td>Gemcitabine</td>
<td>3.7 mos</td>
<td>7.1 mos</td>
</tr>
<tr>
<td>GERCOR/GISCAD Intergroup Study (n=313)</td>
<td>Gemcitabine/oxaliplatin</td>
<td>5.8 mos (p = 0.04)</td>
<td>9.0 mos (P = 0.13)</td>
</tr>
<tr>
<td>ECOG 6201 (n=833)</td>
<td>Gemcitabine</td>
<td>N/ A</td>
<td>4.9 mos</td>
</tr>
<tr>
<td>Viret et al (n=83)</td>
<td>Gemcitabine</td>
<td>2.5 mos</td>
<td>6.7 mos</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine/cisplatin</td>
<td>2.2 mos (p=NS)</td>
<td>8.0 mos (P = 0.73)</td>
</tr>
</tbody>
</table>

**Combined analysis:**

Gemcitabine/platinum results in significant improvement in overall survival (HR 0.85, P = 0.01)

Heinemann et al, BMC Cancer 2008
### Other Gemcitabine-Based Doublets: Phase III Trials of GEM-CAP VS Gemcitabine

<table>
<thead>
<tr>
<th>Study</th>
<th>GEM-CAP</th>
<th>Gemcitabine</th>
<th>Statistically significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(SAKK study, post hoc analysis on pts with KPS 90-100)</td>
<td>N 84</td>
<td>84</td>
<td>P = 0.014</td>
</tr>
<tr>
<td>Lee HS, et al. <em>Medicine.</em> 2017;96:1 (South Korea)</td>
<td>N 108</td>
<td>106</td>
<td>P = 0.06</td>
</tr>
</tbody>
</table>

**Combined analysis:** gemcitabine/capecitabine results in significant improvement in overall survival (HR, 0.86; *P* = 0.02)

*Cunningham, J Clin Oncol 2009*
Phase 3 Meta-analysis: Gemcitabine +/- Targeted Therapy

Phase III Study of Gemcitabine +/- Erlotinib in Advanced Pancreatic Cancer (NCIC PA.3)

PFS: 3.75 vs 3.55 months ($P = 0.004$)
RR: 8.6 vs 8.0% ($P = NS$)
Prodige 4 - ACCORD 11/0402: Gemcitabine vs. FOLFIRINOX

### PRODIGE 4: Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Folfirinox N=171</th>
<th>Gemcitabine N=171</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0.6%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>31%</td>
<td>9.4%</td>
<td>0.0001</td>
</tr>
<tr>
<td>CR/PR 95% CI</td>
<td>[24.7-39.1]</td>
<td>[5.9-15.4]</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>38.6%</td>
<td>41.5%</td>
<td></td>
</tr>
<tr>
<td>Disease control</td>
<td>70.2%</td>
<td>50.9%</td>
<td>0.0003</td>
</tr>
<tr>
<td>CR+PR+SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>15.2%</td>
<td>34.5%</td>
<td></td>
</tr>
<tr>
<td>Not assessed</td>
<td>14.6%</td>
<td>14.6%</td>
<td></td>
</tr>
<tr>
<td>Median duration of response</td>
<td>5.9 mo.</td>
<td>4 mo.</td>
<td>ns</td>
</tr>
</tbody>
</table>

PRODIGE 4: Overall Survival

MPACT: Study Design

- Primary Endpoint:
  - OS

- Secondary Endpoints:
  - PFS and ORR by Independent Review (RECIST)

- Safety and Tolerability
  - by NCI CTCAE v3.0

- Planned N = 842
  - Stage IV
  - No prior treatment for metastatic disease
  - KPS ≥70
  - Measurable disease
  - Total bilirubin ≤ULN

- nab-Paclitaxel
  - 125 mg/m² IV qw 3/4 weeks
  - + Gemcitabine
  - 1000 mg/m² IV qw 3/4 weeks

- Gemcitabine
  - 1000 mg/m² IV qw for 7/8 weeks then qw 3/4 weeks

1:1, stratified by KPS, region, liver metastasis

- With 608 events, 90% power to detect OS HR = 0.769 (2-sided α = 0.049)
- 1 interim analysis for futility
- Treat until progression
- CT scans every 8 weeks

### MPACT: Response Rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>nab-P + Gem (n = 431)</th>
<th>Gem (n = 430)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent Review, % (95% CI)</td>
<td>23 (19.1–27.2)</td>
<td>7 (5.0–10.1)</td>
<td>1.1x10⁻¹⁰</td>
</tr>
<tr>
<td>Investigator Assessment, % (95% CI)</td>
<td>29 (25.0–33.8)</td>
<td>8 (5.3–10.6)</td>
<td>3.3x10⁻¹⁶</td>
</tr>
<tr>
<td><strong>Disease Control Rate by Independent Review, a %</strong> (95% CI)</td>
<td>48 (43.0–52.6)</td>
<td>33 (28.4–37.5)</td>
<td>7.2x10⁻⁶</td>
</tr>
</tbody>
</table>

*a Includes CR + PR + SD ≥16 weeks

### PRODIGE 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Folfirinox N=171</th>
<th>Gemcitabine N=171</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0.6%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>31%</td>
<td>9.4%</td>
<td>0.0001</td>
</tr>
<tr>
<td>CR/PR 95% CI</td>
<td>[24.7-39.1]</td>
<td>[5.9-15.4]</td>
<td></td>
</tr>
<tr>
<td>Disease control</td>
<td>70.2%</td>
<td>50.9%</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

MPACT: Overall Survival

### Events/N (%) Median (95% CI) 75th Percentile

<table>
<thead>
<tr>
<th></th>
<th>Events/N (%)</th>
<th>Median (95% CI)</th>
<th>75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab-P + Gem</td>
<td>333/431 (77)</td>
<td>8.5 (7.89–9.53)</td>
<td>14.8</td>
</tr>
<tr>
<td>Gem</td>
<td>359/430 (83)</td>
<td>6.7 (6.01–7.23)</td>
<td>11.4</td>
</tr>
</tbody>
</table>

**FOLFIRINOX vs. Gem**

HR = 0.72

95% CI (0.617–0.835)

P = 0.000015

### Safety: FOLFIRINOX vs. Gemcitabine vs. G+Nab-Paclitaxel

#### Prodige 4

<table>
<thead>
<tr>
<th>G3-4 Toxicity</th>
<th>FOLFIRINOX</th>
<th>Gemcitabine</th>
<th>Gemcitabine</th>
<th>G+Nab-Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>45.7%</td>
<td>18.7%</td>
<td>27%</td>
<td>38%</td>
</tr>
<tr>
<td>Febrile ANC</td>
<td>5.4%</td>
<td>0.6%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Received GCSF</td>
<td>42.5%</td>
<td>5.3%</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>Anemia</td>
<td>7.8%</td>
<td>5.4%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Plts</td>
<td>9.1%</td>
<td>2.4%</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23.2%</td>
<td>14.2%</td>
<td>7%</td>
<td>17%</td>
</tr>
<tr>
<td>Peripheral Neuro</td>
<td>9%</td>
<td>0.6%</td>
<td>&lt;1%</td>
<td>17%*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12.7%</td>
<td>1.2%</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Death</td>
<td>0.6%</td>
<td>0.6%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Median time to improvement to Grade $\leq 1 = 29$ days
NAPOLI-1 Study Design

Nano-liposomal Irinotecan

- Metastatic pancreatic cancer
- Received prior gemcitabine-based therapy

N = 417

R

1:1:1

MM-398: 120 mg/m² q3w
n = 151

5-FU/LV: 2000 mg/m² over 24 h/200 mg/m²
weekly x 4, q6w
n = 149

MM-398 + 5-FU/LV*: 80 mg/m² + 2400 mg/m²
over 46 h/400 mg/m² q2w
n = 117

- Primary endpoint: Overall survival
- Secondary endpoints: PFS, ORR, CA19-9 response, and safety
- Stratification factors: Albumin, KPS, and ethnicity

* Study was amended to add the MM-398 + 5-FU/LV arm once safety data on the combination became available; 63 patients already had been enrolled in the original 2-arm study at the time of amendment.
Response Rate:
MM-398+5FU/LV: 16%
5FU/LV: 1%


* Protocol-defined primary analysis data cut (14Feb2014, after 305 events). Survival follow-up is ongoing and the final results will be reported once all patients are off treatment and at least 90% events have taken place. Primary analysis for the study was by un-stratified log-rank test.

** Un-stratified HR: 0.67 (0.49-0.92), p = 0.0122

*** Un-stratified HR: 0.99 (0.77-1.28), p = 0.9416
## Safety

<table>
<thead>
<tr>
<th></th>
<th>Safety Population</th>
<th>PP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MM-398 + 5-FU/LV</td>
<td>5-FU/LV</td>
<td>MM-398 + 5-FU/LV</td>
</tr>
<tr>
<td>Grade ≥ 3 nonhematologic AEs in &gt; 5% patients, %</td>
<td>(N=117)</td>
<td>(N=134)</td>
<td>(N=66)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Grade ≥ 3 hematologic AEs based on laboratory values, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Patients with at least 1 AE leading to death (all causes), %</td>
<td>2</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Patients receiving at least one dose of study drug; 2 Per CTCAE Version 4; 3 Wang-Gillam et al. Lancet 2016 Feb 6;387(10018):545-57
Conclusions from these Results

**Metastatic Pancreatic:**

Gemcitabine monotherapy remains an acceptable treatment option for older or asymptomatic pts.

Addition of platinum or capecitabine boosts response and PFS but compromises 2nd line CAPOX or FOLFOX*.

Addition of Nab-paclitaxel improves OS but is more toxic. Unclear how would compare to FOLFIRINOX.

FOLFIRINOX has best response and survival but is most toxic. It should be considered for stronger, symptomatic pts or potentially resectable disease.

MM398+5FU is an option after Gem+Nab-paclitaxel. Unclear if any benefit after FOLFIRINOX.