PRACTICE CHANGING STUDIES IN GASTROINTESTINAL CANCERS IN 2017

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DISCLOSURE / CONFLICTS OF INTERESTS

Consultant/Advisory role:

Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Imclone, Lilly, MSD, Merck Serono, Merrimack, Novartis, Roche, Sanofi, Symphogen and Taiho
OUTLINE

- **Gastric cancer:**
  - Neoadjuvant setting: FLOT4 study
  - Advanced disease: JACOB study (Pertuzumab)
  - Advanced disease: ATTRACTION study (Nivolumab)

- **Colorectal cancer:**
  - Adjuvant setting: IDEA collaboration
  - Advanced setting, MSI population: Pembrolizumab, Nivolumab, Nivolumab + Ipilimumab
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FLOT4 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-).

Primary endpoint OS; HR 0.76; 2-sided log rank test a 5% significance level assuming median OS of 25 months for ECF/ECX

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: 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

n=716

Al Batran S et al.LBA27
OS in pp Population (predefined analysis)

PP Population: Eligible patients who received at least one cycles of chemotherapy, analyzed as treated

HR 0.76
P=0.0083

Al Batran S et al. LBA27
Subgroup Analysis: overall survival

P-values stands for test for interaction between treatment and subgroup variable
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JACOB: Study design

1L, first-line; 5-FU, 5-fluorouracil; CBR, clinical benefit rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FPI, first patient in; IHC, immunohistochemistry; ISH, in situ hybridisation; IV, intravenous; LPI, last patient in; mGC/GEJC, metastatic gastric or gastro-oesophageal junction cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; QoL, quality of life.

1L HER2-positive mGC/GEJC
N = 780 randomised (1:1)
FPI–LPI:
10 Jun 2013–12 Jan 2016

Follow-up

Primary endpoint: OS
Secondary endpoints: PFS, ORR, DoR, CBR, safety, PK, QoL

Study treatment
~6 treatment cycles (21-day cycle)

Study treatment
HER2-targeted therapy continues until PD or unacceptable toxicity

Key eligibility criteria:
- HER2-positive mGC/GEJC
- IHC 3+ or IHC 2+ and ISH-positive (central testing required)
- ECOG PS 0 or 1

Stratification factors:
- Geographical region (Asia [excluding Japan], Japan, North America/Western Europe/Australia, South America/Eastern Europe)
- Prior gastrectomy (yes/no)
- HER2 IHC 3+ vs IHC 2+/ISH-positive

Treatment arm A
Capecitabine or 5-FU + cisplatin
Trastuzumab + pertuzumab 840 mg IV q3w

Treatment arm B
Capecitabine or 5-FU + cisplatin
Trastuzumab + placebo IV q3w

Tabernero J et al. 6160
Overall survival

16% reduction in risk of death and 3.3 month increase in median OS; did not reach statistical significance

Stratified HR.

Median duration of survival follow-up: P + H + CT = 24.4 months (min–max, 22.3–26.1); PLA + H + CT = 25.0 months (min–max, 22.3–28.9).

CI, confidence interval; CT, chemotherapy; H, trastuzumab; HR, hazard ratio; P, pertuzumab; PLA, placebo.

ITT population  | P + H + CT (n = 388) | PLA + H + CT (n = 392)
--- | --- | ---
Events, n | 242 | 262
Median, mo | 17.5 | 14.2
HR (95% CI) | 0.84 (0.71–1.00) | 0.0565

No. at risk
P + H + CT 388 363 342 323 297 266 243 209 175 149 114 92 67 54 36 27 16 10 6 4 3
PLA + H + CT 392 359 339 306 279 252 221 175 143 118 95 76 60 47 38 31 23 14 7 4 2

Tabernero J et al. 6160
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Nivolumab in refractory GC/GEJC (ATTRACTION-02)

Key eligibility criteria:
- Age ≥ 20 years
- Unresectable advanced or recurrent gastric or gastroesophageal junction cancer
- Histologically confirmed adenocarcinoma
- Prior treatment with ≥ 2 regimens and refractory to/intolerant of standard therapy
- ECOG PS of 0 or 1

Study design

Nivolumab 3 mg/kg IV Q2W

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

Placebo

Primary endpoint:
- OS

Secondary endpoints:
- Efficacy (PFS, BOR, ORR, TTR, DOR, DCR)
- Safety

Exploratory endpoint:
- Biomarkers

Study design

• 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

• Retrospective determination of tumor PD-L1 expression, defined as positive if staining in ≥1% (or ≥5%) of tumor cells, was performed in a central laboratory using immunohistochemistry (28-8 pharmDx assay) for patients with available tumor samples

Kang YK et al. Lancet 2017
Nivolumab in refractory GC/GEJC

Overall Survival

Median OS, months (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (N = 330)</td>
<td>330</td>
<td>5.3 (4.6–6.4)</td>
</tr>
<tr>
<td>Placebo (N = 163)</td>
<td>163</td>
<td>4.1 (3.4–4.9)</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.62 (95% CI, 0.50–0.76)

P < 0.0001

12-month OS rate: 27%
24-month OS rate: 12%

*Time from first dose to data cut-off for surviving patients

Kang YK et al. Lancet 2017
Nivolumab in refractory GC/GEJC

Maximum Reduction in Tumor Burden From Baseline

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 3 mg/kg (n = 268)</th>
<th>Placebo (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>30 (11.2) [7.7–15.6]</td>
<td>0 [0–2.8]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
<td>—</td>
</tr>
</tbody>
</table>

* Patients with a change in tumor burden that exceeds 100%.

Kang YK et al. Lancet 2017
Overall survival by PD-L1 expression <1% vs ≥1%

PD-L1 evaluable patients (N=192)

**PD-L1 <1%**

- **Median OS, months (95% CI)**
  - **Nivolumab (n=114)**: 6.1 (4.8–8.6)
  - **Placebo (n=52)**: 4.3 (3.0–6.9)

  **Hazard ratio, 0.58**
  **(95% CI, 0.24–1.38)**

**PD-L1 ≥1%**

- **Median OS, months (95% CI)**
  - **Nivolumab (n=16)**: 5.2 (2.8–9.4)
  - **Placebo (n=10)**: 3.8 (0.8–5.0)

  **Hazard ratio, 0.71**
  **(95% CI, 0.24–1.38)**

---

**No. at Risk**

<table>
<thead>
<tr>
<th>Months</th>
<th>Nivolumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>114</td>
<td>52</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>27</td>
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<tr>
<td>3</td>
<td>56</td>
<td>22</td>
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<tr>
<td>4</td>
<td>49</td>
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<tr>
<td>5</td>
<td>42</td>
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<tr>
<td>6</td>
<td>37</td>
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<td>12</td>
<td>3</td>
<td>2</td>
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<tr>
<td>13</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Overall survival by PD-L1 expression <1% vs ≥1%**

Boku N et al. Proc ESMO 2017
## Ongoing Phase III Clinical Studies

<table>
<thead>
<tr>
<th>Line</th>
<th>Study</th>
<th>N</th>
<th>Treatment Arms</th>
<th>Primary EP</th>
<th>Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Line</td>
<td>KEYNOTE-062 NCT02494583 (TPS 4138)</td>
<td>750</td>
<td>Pembrolizumab 200mg Q3W vs Pembrol + Cisplatin + 5-FU/CPC vs Placebo + Cisplatin + 5-FU/CPC</td>
<td>OS, PFS (RECIST 1.1)</td>
<td>Europe/North America/Australia vs Asia vs ROW RECIST 1.1 &amp; irRECIST</td>
</tr>
<tr>
<td>1st Line</td>
<td>JAVELIN Gastric 100 NCT02625610 (TPS 4134)</td>
<td>666</td>
<td>FOLFOX/XELOX x12 weeks, thereafter: Avelumab 10mg/kg Q2W vs Continuation FOLFOX/XELOX</td>
<td>OS, PFS (from random)</td>
<td>CG &amp; CUGE, PS 0-1, PD-L1+/ HER2-</td>
</tr>
<tr>
<td>2nd Line</td>
<td>KEYNOTE-061 NCT02370498 (TPS 4137)</td>
<td>720</td>
<td>Pembrolizumab 200mg Q3W vs Paclitaxel</td>
<td>PFS (RECIST 1.1) OS in PD-L1+ (negative)</td>
<td>CG &amp; CUGE, PS 0-1 No molecular selection</td>
</tr>
<tr>
<td>3rd Line</td>
<td>JAVELIN Gastric 300 NCT02625623 (TPS4135)</td>
<td>330</td>
<td>Avelumab 10mg/kg Q2W + BSC vs Paclitaxel/Irinotecan/BSC</td>
<td>OS (negative)</td>
<td>CG &amp; CUGE, PS 0-1 No molecular selection Stratification: Asia vs non Asia Exclusion of previous immunotherapy RECIST 1.1</td>
</tr>
</tbody>
</table>
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Adjuvant Therapy (1990-2004)

6 months = 12 months
Low dose leucovorin
Elderly patients

Francini 1994
IMPACT 1995
NCCTG 1997
NCCTG-NCIC 1998
INT 0089 1998
NSABP C04 1999
QUASAR 2000

DFS

Moertel

5FU bolus + LV

5FU+lev

better safety

De Gramont A, ESMO GI 2017
Adjuvant Therapy (2004-2009)

- FOLFOX4
- DFS
- better safety
- IFL
- LV5FU/Iri
- XELOX
- Capecitabine
- FLOX
- LV5FU2
- 5FU bolus + LV
- 5FU+lev
- De Gramont A, ESMO GI 2017
International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration

- Academic collaboration of clinicians and statisticians from six randomized phase III trials (12 countries)
  - SCOT (UK, Denmark, Spain, Australia, Sweden, New Zealand), TOSCA (Italy), Alliance/SWOG 80702 (US, Canada), IDEA France, ACHIEVE (Japan), HORG (Greece)

- Total of 12,834 patients with stage III disease included in analysis
  - High number of patients needed to make sure with high confidence that we are not sacrificing efficacy of therapy for decreased toxicity
Study Overview

- **Objective:**
  Reduce side-effects of therapy without giving up (too much) anti-cancer efficacy of therapy

- **Non-inferiority design:**
  As agreed upon by patient advocates and oncologists, shorter duration of therapy should not sacrifice more than 12% of benefit of adjuvant therapy
  
  In statistical terms: upper 95% confidence interval of Hazard Ratio (HR) of disease free survival (DFS) should not exceed **1.12**

Stage III Colon Cancer

12,834 patients

*Investigator’s choice, no randomization

**R**

- 3 months
- 6 months

FOLFOX* or CAPOX*
Primary Outcomes Analysis

N Patients At risk
6424 6410
5446 5530
4464 4477
3000 3065
1609 1679
826 873
321 334

Years from Randomization

Percent Without Event

Duration
3m
6m

3-yr DFS
74.6 %
75.5 %

3-yr DFS diff. = -0.9%,
95% CI, (-2.4 to 0.6%)

DFS HR = 1.07
95% CI, 1.00 to 1.15

Presented by: Qian Shi, PhD on behalf of IDEA collaborators
DFS by risk group and duration of therapy

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Duration</th>
<th>Event</th>
<th>3 Year Est (95% CI)</th>
<th>HR (95% CI)</th>
<th>Sup p</th>
<th>NI p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-3 N1</td>
<td>3 Months</td>
<td>657</td>
<td>83.1 (81.8-84.4%)</td>
<td>1.01 (0.90-1.12)</td>
<td>0.9193</td>
<td>0.0256</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>656</td>
<td>83.3 (82.1-84.6%)</td>
<td>Reference</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>T4 or N2</td>
<td>3 Months</td>
<td>1016</td>
<td>62.7 (60.8-64.6%)</td>
<td>1.12 (1.03-1.23)</td>
<td>0.0108</td>
<td>0.5233</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>919</td>
<td>64.4 (62.6-66.4%)</td>
<td>Reference</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Years from Randomization

<table>
<thead>
<tr>
<th>T1-3 N1</th>
<th>3744</th>
<th>3313</th>
<th>2796</th>
<th>1934</th>
<th>1064</th>
<th>527</th>
<th>211</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3727</td>
<td>3336</td>
<td>2788</td>
<td>1949</td>
<td>1081</td>
<td>566</td>
<td>221</td>
</tr>
<tr>
<td>T4 or N2</td>
<td>2634</td>
<td>2099</td>
<td>1640</td>
<td>1044</td>
<td>531</td>
<td>292</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>2622</td>
<td>2151</td>
<td>1655</td>
<td>1094</td>
<td>586</td>
<td>301</td>
<td>110</td>
</tr>
</tbody>
</table>
DFS Comparison by Regimen

**FOLFOX**

- **Duration**
  - 3m: 73.6%
  - 6m: 76.0%

- **3-yr DFS diff.** = -2.4%
  - 95% CI: (-4.3 to -0.5%)

**CAPOX**

- **Duration**
  - 3m: 75.9%
  - 6m: 74.8%

- **3-yr DFS diff.** = 1.1%
  - 95% CI: (-1.3 to 3.5%)

Interaction p-value = 0.0051

Presented by: Qian Shi, PhD on behalf of IDEA collaborators
N2 & T4 within high risk stage III: 3 mo vs 6 mo according to regimen

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX</th>
<th>CAPOX</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2</td>
<td>441/1072</td>
<td>379/1049</td>
<td>1.159</td>
</tr>
<tr>
<td>N2</td>
<td>275/726</td>
<td>283/720</td>
<td>0.954</td>
</tr>
<tr>
<td>T4</td>
<td>302/709</td>
<td>265/718</td>
<td>1.221</td>
</tr>
<tr>
<td>T4</td>
<td>260/611</td>
<td>248/617</td>
<td>1.100</td>
</tr>
<tr>
<td>Overall</td>
<td>1046/3870</td>
<td>918/3893</td>
<td>1.157</td>
</tr>
<tr>
<td>Overall</td>
<td>637/2554</td>
<td>662/2517</td>
<td>0.952</td>
</tr>
<tr>
<td>Risk group</td>
<td>Regimen</td>
<td>CAPOX</td>
<td>FOLFOX</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Low-risk (T1-3 N1) ~60%</td>
<td>3 months</td>
<td>(3-6) months</td>
<td>6 months</td>
</tr>
<tr>
<td>High-risk (T4 and/or N2) ~40%</td>
<td>3(-6) months</td>
<td>6 months</td>
<td></td>
</tr>
</tbody>
</table>
ECONOMIC:
> half a billion Euros saving per annum if every stage 3 CRC patient in Europe has 3 mths CAPOX rather than 6 mths.

TOXICITY:
- Neuro: 2 to 6x lower
- Diarrhoea: 20% - 30% lower
- Mucositis: 2x lower
- HFS: 2–3x lower

The cost of 6 months therapy using CAPOX was £10,514 per patient versus £11,461 for FOLFOX. (NICE)

446,800 CRC pts diagnosed in 2012 in Europe worldwide 1,360,602 (globoCANCER)
25% stage 3: 111,700 in eu, @ £5257 saving per case = £587,206,900 per annum saving to health care system

Is this an important question?
Clinical decision making, with the patient in stage III colon cancer

1. **FATALIST:** always 3 months of CAPOX (11/11), even high risk

2. **FIGHTERS:**
   - Low risk (T1-3 N1): always 3 months of CAPOX (11/11)
   - High risk N2: usually 3 months CAPOX (8/11); 6 months (3/11)
   - High risk T4: always 6 months CAPOX (8/11) or FOLFOX (3/11)
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Pembrolizumab (anti-PD1) in mismatch repair-deficient/-proficient CRC: phase II

<table>
<thead>
<tr>
<th>Table 2. Objective Responses According to RECIST Criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Response</strong></td>
</tr>
<tr>
<td>Complete response — no. (%)</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%)‡</td>
</tr>
<tr>
<td>Objective response rate (95% CI) — %</td>
</tr>
<tr>
<td>Disease control rate (95% CI) — %§</td>
</tr>
<tr>
<td>Median duration of response — wk</td>
</tr>
<tr>
<td>Median time to response (range) — wk</td>
</tr>
</tbody>
</table>

Le DT et al. ASCO 2015, Le DT NEJM 2015
CheckMate-142 Study Design

Phase 2 Nonrandomized Study

- Histologically confirmed metastatic or recurrent CRC
- dMMR/MSI-H per local laboratory
- ≥ 1 prior line of therapy

**Primary endpoint:**
- ORR per investigator assessment (RECIST v1.1)

**Other key endpoints:**
- ORR per BICR, DCR, DOR, PFS, OS, and safety

- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses and then nivolumab 3 mg/kg Q2W)
- Nivolumab 3 mg/kg Q2W

- Median follow-up in the combination therapy cohort (N = 119) was 13.4 months (range, 9–25)\(^c\)

- Results of the monotherapy cohort (N = 74) with a similar median follow-up of 13.4 months (range, 10–32) are also presented\(^{1,c}\)

---

\(^a\)Enrollment was staggered with additional patients being enrolled if ≥ 7 of the first 19 centrally confirmed MSI-H patients had a confirmed response (CR or PR). CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison. \(^b\)Patients with a CR, PR, or SD for ≥12 weeks. \(^c\)Defined here as the time from first dose to data cutoff.

Investigator-Assessed Response and Disease Control

- DCR\textsuperscript{b} was 80\% (95\% CI: 71.5, 86.6) with combination therapy and 69\% (57.1, 79.2) with monotherapy\textsuperscript{1,d}
- Combination therapy provided a numerically higher ORR, including CRs, and DCR relative to monotherapy during a similar follow-up period\textsuperscript{d}

\textsuperscript{a}Median follow-up was 13.4 months (range, 9–25). \textsuperscript{b}Disease control was defined as patients with a CR, PR, or SD for ≥12 weeks. \textsuperscript{c}Median follow-up was 13.4 months (range, 10–32).
\textsuperscript{d}CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.

Progression-Free and Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab + ipilimumab&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Nivolumab&lt;sup&gt;1,e,f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-month rate (95% CI), %</td>
<td>76 (67.0, 82.7)</td>
<td>54 (41.5, 64.5)</td>
</tr>
<tr>
<td>12-month rate (95% CI), %</td>
<td>71 (61.4, 78.7)</td>
<td>50 (38.1, 61.4)</td>
</tr>
</tbody>
</table>

No. at Risk
Nivolumab + ipilimumab 119 95 86 78 39 12 11 10 3 0 0
Nivolumab 74 48 41 32 17 12 12 11 6 3 0

<sup>a</sup>Median follow-up was 13.4 months (range, 9–25).
<sup>b</sup>Median PFS was not reached (95% CI, not estimable).
<sup>c</sup>PFS per investigator assessment.
<sup>d</sup>Median OS was not reached (95% CI, 18.0, not estimable).
<sup>e</sup>Median follow-up was 13.4 months (range, 10–32).
<sup>f</sup>CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.

THANK YOU