ESMO SUMMIT MIDDLE EAST 2018

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

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

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

n=716

Al Batran S et al. LBA27
FLOT4: 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
FLOT4: OS - Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>716 (100%)</td>
<td>0.769</td>
<td>0.0121</td>
<td>0.8299</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>533 (74%)</td>
<td>0.760</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>183 (26%)</td>
<td>0.800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>315 (44%)</td>
<td>0.770</td>
<td></td>
<td>0.9402</td>
</tr>
<tr>
<td>60-69</td>
<td>229 (32%)</td>
<td>0.797</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=70</td>
<td>172 (24%)</td>
<td>0.723</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 0</td>
<td>500 (70%)</td>
<td>0.776</td>
<td></td>
<td>0.8080</td>
</tr>
<tr>
<td>ECOG 1/2</td>
<td>216 (30%)</td>
<td>0.736</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localization of tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEG I</td>
<td>165 (23%)</td>
<td>0.604</td>
<td></td>
<td>0.3620</td>
</tr>
<tr>
<td>AEG II/AEG III</td>
<td>233 (33%)</td>
<td>0.893</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>318 (44%)</td>
<td>0.772</td>
<td></td>
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</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
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<tr>
<td>missing</td>
<td>61 (29%)</td>
<td>0.852</td>
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<td>0.5787</td>
</tr>
<tr>
<td>diffuse</td>
<td>191 (71%)</td>
<td>0.746</td>
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<td></td>
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<tr>
<td>non-diffuse</td>
<td>464 (29%)</td>
<td></td>
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<tr>
<td>Lymph node involvement</td>
<td></td>
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<tr>
<td>cN-</td>
<td>147 (21%)</td>
<td>0.642</td>
<td></td>
<td>0.4171</td>
</tr>
<tr>
<td>cN+</td>
<td>569 (79%)</td>
<td>0.806</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT-stage</td>
<td></td>
<td></td>
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<tr>
<td>missing</td>
<td>22 (16%)</td>
<td>0.661</td>
<td></td>
<td>0.5821</td>
</tr>
<tr>
<td>T1/2</td>
<td>113 (84%)</td>
<td>0.790</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3/4</td>
<td>581 (16%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrett</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>missing</td>
<td>11 (15%)</td>
<td>0.809</td>
<td></td>
<td>0.3396</td>
</tr>
<tr>
<td>yes</td>
<td>598 (85%)</td>
<td>0.619</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signet ring cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>36 (70%)</td>
<td>0.796</td>
<td></td>
<td>0.7459</td>
</tr>
<tr>
<td>yes</td>
<td>479 (30%)</td>
<td>0.740</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values stands for test for interaction between treatment and subgroup variable

Al Batran S et al. LBA27
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JACOB: Study design

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

1L HER2-positive mGC/GEJC
N = 780 randomised (1:1)

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

Study treatment
~6 treatment cycles (21-day cycle)
- HER2-targeted therapy continues until PD or unacceptable toxicity

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

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

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.

Tabernero J et al. 6160
JACOB: 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.

Tabernero J et al. 6160
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  - Advanced setting, MSI population: Pembrolizumab, Nivolumab, Nivolumab + Ipilimumab
ATTRACTION-02: Nivolumab in refractory GC/GEJC

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

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

Primary endpoint:
• OS

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

Exploratory endpoint:
• Biomarkers

Kang YK et al. Lancet 2017
ATTRACTION-02: Nivolumab in refractory GC/GEJC

Overall Survival

Median follow-up\(^a\): 15.7 months (range, 12.1–27.2)

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

5%

\(^a\)Time from first dose to data cut-off for surviving patients

Kang YK et al. Lancet 2017
ATTRACTION-02: Nivolumab in refractory GC/GEJC

Maximum Reduction in Tumor Burden From Baseline

Nivolumab

Placebo

Patients with Tumor reduction: 37.3%

Patients with Tumor reduction: 12.4%

<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 (%) [95% CI]</td>
<td>30 (11.2) [7.7–15.6]</td>
<td>0 [0–2.8]</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
**ATTRACTION-02: OS 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) 4.2 (3.0–6.9)

**Hazard ratio, 0.71**
(95% CI, 0.50–1.01)

### 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, 0.58**
(95% CI, 0.24–1.38)

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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>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; 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>
</tr>
<tr>
<td></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>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; 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>
</tr>
<tr>
<td></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>
</tr>
</tbody>
</table>

OS: Overall Survival
PFS: Progression-Free Survival
CG & CUGE: Complete Response, Partial Response, Progressive Disease, Stable Disease
PS: Performance Status
PD-L1+/HER2-: Positive PD-L1 Expression/HER2-Negative
Stratification: Europe/North America/Australia vs Asia vs ROW
RECIST 1.1 & irRECIST: Response Evaluation Criteria in Solid Tumors 1.1 and Individualized RECIST
Exclusion: HER2+
No molecular selection: No selection based on molecular markers
Ongoing Phase III Clinical Studies
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Adjuvant Therapy (1990-2004)

DFS

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

5FU bolus + LV

5FU+lev

Moertel

better safety

6 months = 12 months
Low dose leucovorin
Elderly patients

Francini 1994
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NSABP C04 1999
QUASAR 2000

5FU bolus + LV

5FU+lev

Moertel

better safety

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

- **FOLFOX4**
- **IFL**
- **LV5FU/Iri**
- **FLOX**
- **XELOX**
- **Capecitabine**
- **LV5FU2**
- **5FU bolus + LV**
- **5FU+lev**

DFS: better safety

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

Grothey A et al. NEJM 2018; Sobrero A et al. Ann Oncol 2018
IDEA: 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

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**Stage III Colon Cancer**

- FOLFOX* or CAPOX* (Investigator’s choice, no randomization)
- 3 months vs 6 months
- 12,834 patients

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Grothey A et al. NEJM 2018; Sobrero A et al. Ann Oncol 2018
IDEA: Primary Outcomes Analysis (DFS)

Grothey A et al. NEJM 2018; Sobrero A et al. Ann Oncol 2018
IDEA: DFS by risk group and duration of treatment
IDEA: DFS comparison by regimen

**FOLFOX**

<table>
<thead>
<tr>
<th>Duration</th>
<th>3-yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3m</td>
<td>73.6%</td>
</tr>
<tr>
<td>6m</td>
<td>76.0%</td>
</tr>
</tbody>
</table>

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

**CAPOX**

<table>
<thead>
<tr>
<th>Duration</th>
<th>3-yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3m</td>
<td>75.9%</td>
</tr>
<tr>
<td>6m</td>
<td>74.8%</td>
</tr>
</tbody>
</table>

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

Interaction p-value = 0.0051

Grothey A et al. NEJM 2018
IDEA: DFS by treatment and risk group

Grothey A et al. NEJM 2018
### IDEA: DFS Comparison by Risk Group and Regimen

#### Table: 3-year DFS rate (%) and HR by regimen and risk group

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Risk group (T1–3/N1)</th>
<th>3-months DFS, % (95% CI)</th>
<th>6-months DFS, % (95% CI)</th>
<th>HR (95% CI)</th>
<th>3-months DFS, % (95% CI)</th>
<th>6-months DFS, % (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPOX</td>
<td>Low-risk (T1–3/N1)</td>
<td>85.0 (83.1 to 86.9)</td>
<td>83.1 (81.1 to 85.2)</td>
<td>0.85 (0.71–1.01)</td>
<td>81.9 (80.2 to 83.6)</td>
<td>83.5 (81.9 to 85.1)</td>
<td>1.10 (0.96–1.26)</td>
</tr>
<tr>
<td></td>
<td>High-risk (T4 and/or N2)</td>
<td>64.1 (61.3 to 67.1)</td>
<td>64.0 (61.2 to 67.0)</td>
<td>1.02 (0.89–1.17)</td>
<td>61.5 (58.9 to 64.1)</td>
<td>64.7 (62.2 to 67.3)</td>
<td>1.20 (1.07–1.35)</td>
</tr>
<tr>
<td></td>
<td>Risk groups combined</td>
<td>75.9 (74.2 to 77.6)</td>
<td>74.8 (73.1 to 76.6)</td>
<td>0.95 (0.85–1.06)</td>
<td>73.6 (72.2 to 75.1)</td>
<td>76.0 (74.6 to 77.5)</td>
<td>1.16 (1.06–1.26)</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>Low-risk (T1–3/N1)</td>
<td>81.9 (80.2 to 83.6)</td>
<td>83.5 (81.9 to 85.1)</td>
<td>1.10 (0.96–1.26)</td>
<td>83.1 (81.8 to 84.4)</td>
<td>83.3 (82.1 to 84.6)</td>
<td>1.01 (0.90–1.12)</td>
</tr>
<tr>
<td></td>
<td>High-risk (T4 and/or N2)</td>
<td>62.7 (60.8 to 64.4)</td>
<td>64.4 (62.6 to 66.4)</td>
<td>1.12 (1.03–1.23)</td>
<td>62.7 (60.8 to 64.4)</td>
<td>64.4 (62.6 to 66.4)</td>
<td>1.12 (1.03–1.23)</td>
</tr>
<tr>
<td></td>
<td>Risk groups combined</td>
<td>73.6 (72.2 to 75.1)</td>
<td>76.0 (74.6 to 77.5)</td>
<td>1.16 (1.06–1.26)</td>
<td>73.6 (72.2 to 75.1)</td>
<td>76.0 (74.6 to 77.5)</td>
<td>1.16 (1.06–1.26)</td>
</tr>
</tbody>
</table>

### Key for ‘non-inferiority’ of 3 versus 6 months of adjuvant therapy:

- Non-inferior
- Not proven
- Inferior

CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; DFS, disease-free survival; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; HR, hazard ratio; N, node; T, tumour.

Sobrero A et al. Ann Oncol 2018
IDEA: DFS Comparison by Risk Group and Regimen

- **T1-3, N1**
  - FOLFOX
  - XELOX

- **T4 or N2**
  - FOLFOX
  - XELOX

Duration
- 3 Months
- 6 Months

Percent Without Event

Years from Randomization

3-year DFS, % (95% CI)
- Low-risk (T1-3, N1): 81.9 (80.2 to 83.6)
- High-risk (T4 and/or N2): 41.1 (39.0 to 43.1)

Risk groups
- Low-risk
- High-risk

Key for 'non'
- T1-3, N1
- T4 or N2

FOLFOX, infusional 5-flurouracil and leucovorin
### IDEA: DFS Comparison by Risk Group and Regimen

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Regimen</th>
<th>CAPOX</th>
<th>FOLFOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (T1-3 N1) ~60%</td>
<td></td>
<td>3 months</td>
<td>(3-)6 months</td>
</tr>
<tr>
<td>High-risk (T4 and/or N2) ~40%</td>
<td></td>
<td>3(-6) months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Sobrero A et al. Ann Oncol 2018
IDEA: Is this an important question?

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

**ECONOMIC:**
> half a billion Euros saving per annum if every stage 3 CRC patient in Europe has 3 rather than 6 m of CAPOX

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 (globocan)
25% stage 3: 111,700 in eu, @ £5257 saving per case = £587,206,900 per annum saving to health care system
IDEA: Clinical decision making, with the patient in stage III colon cancer

1. FATALIST

2. FIGHTERS

Table 5. Voting by the expert panel of 11 clinicians in response to questions in the moderated discussion according to whether their patients were ‘fighters’ or ‘fatalists’ in terms of their reaction to their disease

<table>
<thead>
<tr>
<th>Question</th>
<th>CAPOX 3 months</th>
<th>FOLFOX 3 months</th>
<th>CAPOX 6 months</th>
<th>FOLFOX 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If you only had the choice of FOLFOX for 3 versus 6 months in low-risk T1–3/N1 patients?</td>
<td>11 for fighters</td>
<td>11 for fatalists</td>
<td>11 for both and fighters and fatalists</td>
<td></td>
</tr>
<tr>
<td>2. If you only had the choice of FOLFOX for 3 versus 6 months in high-risk T4/N2 patients?</td>
<td>11 for both fighters and fatalists</td>
<td>11 for fatalists</td>
<td>11 for both and fighters and fatalists</td>
<td></td>
</tr>
<tr>
<td>3. If you only had the choice of CAPOX for 3 versus 6 months in low-risk T1–3/N1 patients?</td>
<td>11 for fatalists and 4 for fighters</td>
<td>7 for fighters</td>
<td>1 extra vote for fighters*</td>
<td></td>
</tr>
<tr>
<td>4. If you only had the choice of CAPOX for 3 versus 6 months in high-risk T4/N2 patients?</td>
<td>11 for both fighters and fatalists</td>
<td>1 extra vote for fatalists*</td>
<td>1 extra vote for fighters*</td>
<td></td>
</tr>
<tr>
<td>5. Now you are free to decide FOLFOX or CAPOX, what do you advise to low-risk patients?</td>
<td>11 for fatalists and 4 for fighters</td>
<td>5 for fighters*</td>
<td>3 for fighters*</td>
<td></td>
</tr>
<tr>
<td>6. Now you are free to decide FOLFOX or CAPOX, what do you advise to high-risk patients?</td>
<td>11 for fatalists and 4 for fighters</td>
<td>5 for fighters*</td>
<td>3 for fighters*</td>
<td></td>
</tr>
<tr>
<td>7. Now you are free to decide FOLFOX or CAPOX, what do you advise to high-risk N2 patients?</td>
<td>11 for fatalists and 8 for fighters</td>
<td>2 for fighters*</td>
<td>3 for fighters*</td>
<td></td>
</tr>
<tr>
<td>8. Now you are free to decide FOLFOX or CAPOX, what do you advise to high-risk T4 patients?</td>
<td>11 for fatalists</td>
<td>9 for fighters*</td>
<td>3 for fighters</td>
<td></td>
</tr>
</tbody>
</table>

*Extra votes from one participant.

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IDEA: 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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OUTLINE

1. Gastric cancer:
   a. Neoadjuvant setting: FLOT4 study
   b. Advanced disease: JACOB study (Pertuzumab)
   c. Advanced disease: ATTRACTION study (Nivolumab)

2. Colorectal cancer:
   a. Adjuvant setting: IDEA collaboration
      b. Advanced setting, MSI population: Pembrolizumab, Nivolumab, Nivolumab + Ipilimumab
Pembrolizumab (anti-PD1) in mismatch repair-deficient/-proficient CRC: phase II
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)

- 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

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+r

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. a Patients with a CR, PR, or SD for ≥12 weeks. b 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</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>

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<thead>
<tr>
<th></th>
<th>Nivolumab + ipilimumab&lt;sup&gt;a,d&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>87 (80.0, 92.2)</td>
<td>78 (66.2, 85.7)</td>
</tr>
<tr>
<td>12-month rate (95% CI), %</td>
<td>85 (77.0, 90.2)</td>
<td>73 (61.5, 82.1)</td>
</tr>
</tbody>
</table>

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<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