Practice changing studies in Gastrointestinal Cancers in 2019

Andrés Cervantes
Professor of Medicine
Employment: None; Stock Ownership: None

Consultant or Advisory Role: Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas, MSD.

Research Funding: Genentech, Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas, Fibrogen, Amcure, Sierra Oncology, Astra Zeneca, Medimmune, BMS, MSD.

Speaking: Merck Serono, Roche, Angem, Bayer, Servier, Foundation Medicine. Grant support: Merck Serono, Roche.

Others: Executive Board member of ESMO, Chair of Education ESMO, General and Scientific Director INCLIVA, Associate Editor: Annals of Oncology and ESMO Open, Editor in chief: Cancer Treatment Reviews.
OUTLINE

- FLOT as neoadjuvant chemotherapy in gastroesophageal adenocarcinomas
- Preoperative CT moves to Asia
- No need for neoadjuvant treatment for MSI-high gastric tumors?
- Olaparib in BRCA-mutant pancreatic carcinomas
- Cetuximab, encorafenib and binimetinib in second-line for BRAF-mutant metastatic colorectal cancers
- Adjuvant treatment for localized biliary tract cancers
- Second line treatment for advanced biliary tract cancers
- Precision medicine for IDH-mutant biliary tract cancers
- Atezolizumab and Bevacizumab as new standard of care as first line therapy for advanced hepatocellular carcinoma
- FLOT as neoadjuvant chemotherapy in gastroesophageal adenocarcinomas
- Preoperative CT moves to Asia
- No need for neoadjuvant treatment for MSI-high gastric tumors?
- Olaparib in BRCA-mutant pancreatic carcinomas
- Cetuximab, encorafenib and binimetinib in second-line for BRAF-mutant metastatic colorectal cancers
- Adjuvant treatment for localized biliary tract cancers
- Second line treatment for advanced biliary tract cancers
- Precision medicine for IDH-mutant biliary tract cancers
- Atezolizumab and Bevacizumab as new standard of care as first line therapy for advanced hepatocellular carcinoma
Summary of trials of perioperative chemotherapy for localized Oesophago-gastric cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>No. pts</th>
<th>No. pts</th>
<th>5-year survival</th>
<th>5-year survival</th>
<th>HR (CI at 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham N Eng J Med 2006</td>
<td>ECF</td>
<td>253</td>
<td>250</td>
<td>23%</td>
<td>36%</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>No CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.60-0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.009</td>
</tr>
<tr>
<td>Ychou J Clin Oncol 2011</td>
<td>CDDP</td>
<td>111</td>
<td>113</td>
<td>24%</td>
<td>38%</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>5-FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.50-0.95</td>
</tr>
<tr>
<td></td>
<td>No CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.021</td>
</tr>
<tr>
<td>Allum J Clin Oncol 2009</td>
<td>CDDP</td>
<td>402</td>
<td>400</td>
<td>17,6%</td>
<td>25.5%</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.72-0.98</td>
</tr>
<tr>
<td></td>
<td>No CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P=0.03</td>
</tr>
</tbody>
</table>

FLOT-4 Study

Randomized, multicenter, Phase II/III Study

- Gastric or EGJ cancer type I-III
- Medically and anatomically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

Stratification: ECOG (0 or 1 vs. 2), localization (GEJ Type I vs. Type II/III vs. Gastric), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

23% had Siewert type I
33% had Siewert type II/III

n=716

FLOT: Docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; Leucovorin 200 mg/m², d1; Oxaliplatin 85 mg/m², d1, q2w

ECF/ECX: Epirubicin 50 mg/m², d1; Cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or Capecitabin 1250 mg/m² p.o. geteilt in 2 doses d1-d21), q2w

Survival FLOT vs ECF/ECX

Median follow-up time: 43 months

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS</td>
<td>35 months</td>
<td>50 months</td>
</tr>
<tr>
<td></td>
<td>[27-46]</td>
<td>[38-na]</td>
</tr>
<tr>
<td>OS rate*</td>
<td>ECF/ECX</td>
<td>FLOT</td>
</tr>
<tr>
<td>2y.</td>
<td>59%</td>
<td>68%</td>
</tr>
<tr>
<td>3y.</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>5y.</td>
<td>36%</td>
<td>45%</td>
</tr>
</tbody>
</table>

*projected OS-rates

HR 0.77 (95% CI, 0.63–0.94)
Log-rank p value = 0.012

# Summary of trials of perioperative chemotherapy for localized GEAs

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>No. pts control</th>
<th>No. pts CT</th>
<th>5-year survival control</th>
<th>5-year survival CT</th>
<th>HR (CI at 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham N Eng J Med 2006</td>
<td>ECF</td>
<td>253</td>
<td>250</td>
<td>23%</td>
<td>36%</td>
<td>0.75 (0.60-0.93) p=0.009</td>
</tr>
<tr>
<td>Ychou J Clin Oncol 2011</td>
<td>CDDP</td>
<td>111</td>
<td>113</td>
<td>24%</td>
<td>38%</td>
<td>0.69 (0.50-0.95) p=0.021</td>
</tr>
<tr>
<td>Allum J Clin Oncol 2009</td>
<td>CDDP</td>
<td>402</td>
<td>400</td>
<td>17.6%</td>
<td>25.5%</td>
<td>0.84 (0.72-0.98) P=0.03</td>
</tr>
<tr>
<td>Al-Batran ASCO 2017</td>
<td>FLOT</td>
<td>360</td>
<td>356</td>
<td>36%</td>
<td>45%</td>
<td>0.77 (0.63-0.94) P=0.012</td>
</tr>
</tbody>
</table>

## FLOT vs ECF/ECX: Toxicities

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX (n=354)</th>
<th>FLOT (n=354)</th>
<th>Difference in grade 3 or 4 events (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 or 2</td>
<td>Grade 3 or 4</td>
<td>Grade 1 or 2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>103 (29%)</td>
<td>13 (4%)</td>
<td>182 (52%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>102 (29%)</td>
<td>27 (8%)</td>
<td>113 (32%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>215 (61%)</td>
<td>55 (16%)</td>
<td>211 (60%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>86 (24%)</td>
<td>1 (&lt;1%)</td>
<td>75 (21%)</td>
</tr>
<tr>
<td>Stomatitis or mucositis</td>
<td>107 (30%)</td>
<td>10 (3%)</td>
<td>99 (28%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>175 (49%)</td>
<td>75 (21%)</td>
<td>180 (51%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>93 (26%)</td>
<td>139 (39%)</td>
<td>84 (24%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>282 (80%)</td>
<td>20 (6%)</td>
<td>283 (80%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>123 (35%)</td>
<td>11 (3%)</td>
<td>137 (39%)</td>
</tr>
<tr>
<td>Serum AST</td>
<td>41 (12%)</td>
<td>1 (&lt;1%)</td>
<td>116 (33%)</td>
</tr>
<tr>
<td>Serum ALT</td>
<td>55 (16%)</td>
<td>1 (&lt;1%)</td>
<td>127 (36%)</td>
</tr>
<tr>
<td>Fever</td>
<td>29 (8%)</td>
<td>2 (1%)</td>
<td>77 (22%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>120 (34%)</td>
<td>7 (2%)</td>
<td>228 (64%)</td>
</tr>
<tr>
<td>Pain</td>
<td>171 (48%)</td>
<td>14 (4%)</td>
<td>166 (47%)</td>
</tr>
<tr>
<td>Alopecia*</td>
<td>147 (42%)</td>
<td>74 (21%)</td>
<td>122 (35%)</td>
</tr>
<tr>
<td>Renal</td>
<td>99 (28%)</td>
<td>1 (&lt;1%)</td>
<td>38 (11%)</td>
</tr>
<tr>
<td>Infections</td>
<td>62 (18%)</td>
<td>30 (9%)</td>
<td>61 (17%)</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>31 (9%)</td>
<td>21 (6%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Toxic death†</td>
<td>..</td>
<td>2 (&lt;1%)</td>
<td>..</td>
</tr>
</tbody>
</table>
FLOT got GRADE A in the ESMO MCBS

ESMO Magnitude of Clinical Benefit Scale v1.1

Form 1: for new approaches to adjuvant therapy or new potentially curative therapies

<table>
<thead>
<tr>
<th>Name of study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug:</td>
</tr>
<tr>
<td>First author:</td>
</tr>
<tr>
<td>Name of evaluator:</td>
</tr>
</tbody>
</table>

**Grade A**

- >5% improvement of survival at ≥3 years follow-up
- Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data

A PHASE III OPEN LABEL RANDOMIZED STUDY OF NEOADJUVANT CHEMOTHERAPY WITH DOCETAXEL, OXALIPLATIN AND S-1 (DOS) FOLLOWED BY SURGERY AND ADJUVANT S-1, VS SURGERY AND ADJUVANT S-1 FOR RESECTABLE ADVANCED GASTRIC CANCER (PRODIGY STUDY)


Presenter: Professor Yoon-Koo Kang
Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Contact: ykkang@amc.seoul.kr
**STUDY DESIGN**

**Key Eligibility Criteria**
- Newly diagnosed locally advanced gastric or GEJ adenocarcinoma
- cTNM stage: cT2,3/N+[+]M0 or cT4/N[any]M0 (AJCC 7th edition)
- ECOG PS 0 or 1
- Adequate organ function

**CSC arm**: Neoadjuvant Chemotherapy + Surgery + Adjuvant Chemotherapy

**SC arm**: Surgery + Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>CSC</th>
<th>DOS</th>
<th>Surgery</th>
<th>S-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>Neoadjuvant DOS, 3 cycles</td>
<td>Gastrectomy + D2 LN dissection</td>
<td>Adjuvant S-1 8 cycles</td>
</tr>
</tbody>
</table>

**Primary endpoint**
- 3-year PFS in FAS

**Secondary endpoints**
- R0 resection rate
- Post-operative pathological stage
- OS
- Safety

* Stratification factors
1) Study site
2) cTNM stage (cT2/N+, cT3−4/N+, cT4/N−)

**Follow-up**
- Progression
- Death
- End of study

**Abbreviations**: FAS, Full analysis set; DOS, Docetaxel/Oxaliplatin/S-1

‡ Abdominopelvic CT every 6 months and esophagogastroduodenoscopy every 1 year after surgery
PRODIGY: Randomised phase III study in gastric and GEJ adenocarcinoma of peri-op vs. post-op chemotherapy

Histologically confirmed cT2, 3 / N(+) or cT4N\textsubscript{any}
gastric or GEJ adenocarcinoma

Primary endpoint: 3-year PFS

HR = 0.70 (95% CI 0.52–0.95)
p=0.0230, stratified log-rank

Median follow-up 37.4 months

Overall survival

HR = 0.84 (95% CI 0.60–1.19)
p=0.3383, stratified log-rank

<30% OS events observed thus far, therefore very low power

Kang et al ESMO 2019
PERIOPERATIVE CHEMOTHERAPY OF OXALIPLATIN COMBINED WITH S-1 (SOX) VERSUS POSTOPERATIVE CHEMOTHERAPY OF SOX OR OXALIPLATIN WITH CAPECITABINE (XELOX) IN LOCALLY ADVANCED GASTRIC ADENOCARCINOMA WITH D2 GASTRECTOMY: A RANDOMIZED PHASE III TRIAL (RESOLVE TRIAL)


Peking University Cancer Hospital, Beijing, China

Abstract 3635, LBA-42 on behalf of the RESOLVE Investigators esmo.org
Randomised phase III study in gastric and GEJ adenocarcinoma of peri-operative SOX vs. post-op SOX vs. post-op CAPOX (RESOLVE)

Histologically confirmed cT4aN1 or cT4bN\textsubscript{any} gastric or GEJ adenocarcinoma

Arm A
D2 surgery $\rightarrow$ CAPOX $\times$ 8 cycles
n=345

Arm B
D2 surgery $\rightarrow$ SOX $\times$ 8 cycles
n=340

Arm C
SOX $\times$ 3 $\rightarrow$ D2 surgery $\rightarrow$ SOX $\times$ 5 followed by S-1 $\times$ 3 cycles
n=337

Primary endpoint: 3-year DFS
Arms A vs. C: superiority; A vs. B: non-inferiority

Ji et al ESMO 2019
RESOLVE Primary comparisons

**ARMs A vs. C**

<table>
<thead>
<tr>
<th>Group</th>
<th>3y-DFS</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: D2→XELOX</td>
<td>54.78%</td>
<td>0.79 (0.62, 0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>C: SOX→D2→SOX</td>
<td>62.02%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ARMs A vs. B**

<table>
<thead>
<tr>
<th>Group</th>
<th>3y-DFS</th>
<th>HR (95% CI)</th>
<th>NI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: D2→XELOX</td>
<td>54.78%</td>
<td>0.85 (0.67, 1.07)</td>
<td>1.33</td>
</tr>
<tr>
<td>B: D2→SOX</td>
<td>60.29%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ji et al ESMO 2019
Overall Survival in stage I-III GEA according to MSI status

Martinez-Ciarpaglini C, et al. ESMO Open 2019; 4:e000470
Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

FIG 2. Kaplan-Meier curves of (A) disease-free survival and (B) overall survival according to microsatellite-instability (MSI) status (microsatellite stable [MSS]/MSI-low v MSI-high).

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

OUTLINE

- FLOT as neoadjuvant chemotherapy in gastroesophageal adenocarcinomas
- Preoperative CT moves to Asia
- No need for neoadjuvant treatment for MSI-high gastric tumors?
- **Olaparib in BRCA-mutant pancreatic carcinomas**
- Cetuximab, encorafenib and binimetinib in second-line for BRAF-mutant metastatic colorectal cancers
- Adjuvant treatment for localized biliary tract cancers
- Second line treatment for advanced biliary tract cancers
- Precision medicine for IDH-mutant biliary tract cancers
- Atezolizumab and Bevacizumab as new standard of care as first line therapy for advanced hepatocellular carcinoma
Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

3315 Patients were assessed for eligibility

247 Had a germline BRCA mutation
198 Had unknown germline BRCA mutation status before screening
49 Had known germline BRCA mutation status before screening

80 Were excluded
43 Had disease progression or died
11 Did not meet eligibility criteria
26 Were not enrolled because of patient or physician decision

167 Provided written consent to undergo randomization

13 Were excluded
11 Did not meet eligibility criteria
2 Declined to participate

154 Underwent randomization and were included in the efficacy analyses

N = 247/3351 (7.3%)

N = 154/3351 (4.6%)

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

A Progression-free Survival

<table>
<thead>
<tr>
<th>Progression-free Survival mo</th>
<th>Olaparib Group %</th>
<th>Placebo Group %</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>53.0</td>
<td>23.0</td>
</tr>
<tr>
<td>12</td>
<td>33.7</td>
<td>14.5</td>
</tr>
<tr>
<td>18</td>
<td>27.6</td>
<td>9.6</td>
</tr>
<tr>
<td>24</td>
<td>22.1</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Median, 7.4 mo vs. 3.8 mo
Hazard ratio, 0.53 (95% CI, 0.35–0.82)
P = 0.004

OUTLINE

- FLOT as neoadjuvant chemotherapy in gastroesophageal adenocarcinomas
- Preoperative CT moves to Asia
- No need for neoadjuvant treatment for MSI-high gastric tumors?
- Olaparib in BRCA-mutant pancreatic carcinomas
- **Cetuximab, encorafenib and binimetinib in second-line for BRAF-mutant metastatic colorectal cancers**
- Adjuvant treatment for localized biliary tract cancers
- Second line treatment for advanced biliary tract cancers
- Precision medicine for IDH-mutant biliary tract cancers
- Atezolizumab and Bevacizumab as new standard of care as first line therapy for advanced hepatocellular carcinoma
Triple MAPK Pathway Inhibition in \textit{BRAF}-mutant CRC

- \textit{BRAF}^{V600} mutation occurs in 10\%-15\% of patients and confers a poor prognosis\textsuperscript{1-3}
- \textit{BRAF} inhibitors alone are ineffective due to the feedback activation of EGFR, leading to continued cell proliferation\textsuperscript{4-6}
- Feedback may be overcome by targeting multiple pathway nodes, ie \textit{BRAF}/MEK/EGFR
- Preclinically, addition of MEK inhibitor improved outcomes
- In the BEACON CRC safety-lead in study, the triplet regimen of Encorafenib (ENCO) + Binimetinib (BINI) + Cetuximab (CETUX) had manageable safety profile and encouraging activity in patients with \textit{BRAF}^{V600E} mCRC\textsuperscript{7}

Patients with \textit{BRAF}^V_{600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

**Safety Lead-in**
ENCORAFENIB + BINIMETINIB + CETUXIMAB
\[ N = 30 \]
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

**Phase 3**

**Triplet therapy**
ENCORAFENIB + BINIMETINIB + CETUXIMAB
\[ n = 205 \]

**Doublet therapy**
ENCORAFENIB + CETUXIMAB
\[ n = 205 \]

**Control arm**
FOLFIRI + CETUXIMAB, or irinotecan + CETUXIMAB
\[ n = 205 \]

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

**Secondary Endpoints:** Doublet vs Control and Triplet vs Doublet - OS & ORR, PFS, Safety

**QOL Assessments:** EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change)

Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer

A  Overall Survival, Triplet Regimen vs. Control

- Median Overall Survival
  - Triplet: 9.0 (8.0–11.4) mo
  - Control: 5.4 (4.8–6.6) mo

- Hazard ratio for death, 0.52 (95% CI, 0.39–0.70)

B  Overall Survival, Doublet Regimen vs. Control

- Median Overall Survival
  - Doublet: 8.4 (7.5–11.0) mo
  - Control: 5.4 (4.8–6.6) mo

- Hazard ratio for death, 0.60 (95% CI, 0.45–0.79)

OUTLINE

- FLOT as neoadjuvant chemotherapy in gastroesophageal adenocarcinomas
- Preoperative CT moves to Asia
- No need for neoadjuvant treatment for MSI-high gastric tumors?
- Olaparib in BRCA-mutant pancreatic carcinomas
- Cetuximab, encorafenib and binimetinib in second-line for BRAF-mutant metastatic colorectal cancers
- Adjuvant treatment for localized biliary tract cancers
- Second line treatment for advanced biliary tract cancers
- Precision medicine for IDH-mutant biliary tract cancers
- Atezolizumab and Bevacizumab as new standard of care as first line therapy for advanced hepatocellular carcinoma
Three randomised controlled trials in resected biliary tract cancers: BILCAP, PRODIGE-12 and BCAT

RFS in 3 randomised controlled trials in resected biliary tract cancers: BILCAP, PRODIGE-12 and BCAT

Gain in median RFS

6.9 months

11.9 months

3.3 months

OS in 3 randomised controlled trials in resected biliary tract cancers: BILCAP, PRODIGE-12 and BCAT

Gain in median OS

14.7 months
25.0 months
1.5 months

RFS in resected biliary tract cancers: BILCAP trial

A Intention-to-treat analysis

Recurrence free survival (%)

Time since randomisation (months)

Number at risk (number censored)

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine group</td>
<td>223 (0)</td>
<td>148 (8)</td>
<td>108 (9)</td>
<td>78 (24)</td>
<td>62 (36)</td>
<td>43 (46)</td>
</tr>
<tr>
<td>Observation group</td>
<td>224 (0)</td>
<td>126 (3)</td>
<td>92 (7)</td>
<td>67 (19)</td>
<td>52 (30)</td>
<td>37 (41)</td>
</tr>
</tbody>
</table>

0-24 months (adjusted) HR
0.75 (95% CI 0.58-0.98); p=0.033

B Per-protocol analysis

Recurrence free survival (%)

Time since randomisation (months)

Number at risk (number censored)

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine group</td>
<td>210 (0)</td>
<td>145 (4)</td>
<td>107 (5)</td>
<td>78 (20)</td>
<td>62 (32)</td>
<td>43 (42)</td>
</tr>
<tr>
<td>Observation group</td>
<td>220 (0)</td>
<td>123 (3)</td>
<td>89 (7)</td>
<td>65 (19)</td>
<td>50 (30)</td>
<td>35 (41)</td>
</tr>
</tbody>
</table>

0-24 months (adjusted) HR
0.70 (95% CI 0.54-0.92); p=0.0093

RFS in resected biliary tract cancers: BILCAP trial

A Intention-to-treat analysis

- **Capecitabine group**
  - Adjusted HR: 0.81 (95% CI 0.63-1.04), p=0.097

### Number at risk (number censored)

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>223(0)</td>
<td>195(6)</td>
<td>155(7)</td>
<td>105(25)</td>
<td>83(39)</td>
<td>56(53)</td>
</tr>
<tr>
<td>Observation</td>
<td>224(0)</td>
<td>193(3)</td>
<td>137(5)</td>
<td>95(23)</td>
<td>67(34)</td>
<td>46(47)</td>
</tr>
</tbody>
</table>

B Per-protocol analysis

- **Adjusted HR**: 0.75 (95% CI 0.58-0.97), p=0.028

### Number at risk (number censored)

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>210(0)</td>
<td>190(2)</td>
<td>152(3)</td>
<td>105(21)</td>
<td>83(35)</td>
<td>56(49)</td>
</tr>
<tr>
<td>Observation</td>
<td>220(0)</td>
<td>190(3)</td>
<td>134(5)</td>
<td>92(23)</td>
<td>64(34)</td>
<td>44(47)</td>
</tr>
</tbody>
</table>

ESMO Guidelines for biliary tract cancer management

Randomised second line phase III study of FOLFOX vs. active symptom control in advanced biliary tract cancer (ABC 06)

Advanced BTC
Disease progression on 1st line GemCis
Max 6 weeks progression to randomisation

n=81
Active symptom control (ASC)
IHC: 44% pts
EHC: 28%
GB: 21%

n=81
FOLFOX + ASC
ORR= 5%
DCR= 33%

Primary endpoint: Overall survival

Lamarca A, et al ASCO 2019
• 45 publications
• Patient n=5,393
• IDH1 mutation found in IHC 13.1% EHC 0.8%
• Higher in non-Asian centres compared to Asian centres (16.5% vs. 8.8%; OR=2.06)
• Most common mutation is R132C
• Most frequent co-mutations were ARID1A (22%), BAP1 mutation or loss (15.5%) and PBRM1 (13.3%)
• mIDH1 was not a prognostic factor (OS, PFS or TTP)

ClariDHdy: Phase III study of ivosidenib vs. placebo in advanced mIDH1 biliary tract cancer

Primary endpoint: Progression free survival by IRC

Advanced cholangiocarcinoma
mIDH1 status by NGS
1-2 prior therapy (≥1 GEM or 5-FU based)

2:1 randomisation

Ivosidenib 500mg QD orally continuous
n=124

Placebo
n=61

Crossover permitted at radiological disease progression

HR=0.37 (95% CI 0.25, 0.54)
P<0.001

IHC: 91% pts
EHC: 3%
Unknown: 5%

ClariDHy
Ivosidenib
mPFS 2.7 months
ORR 2%
DCR 53%

Abou-Alfa et al ESMO 2019
ClarIDHy: Ivosidenib Overall survival

- 35 (57.4%) patients crossed over to ivosidenib in placebo group

RPSFT: Rank-preserving structural failure time method

Abou-Alfa et al ESMO 2019
OUTLINE

- FLOT as neoadjuvant chemotherapy in gastroesophageal adenocarcinomas
- Preoperative CT moves to Asia
- No need for neoadjuvant treatment for MSI-high gastric tumors?
- Olaparib in BRCA-mutant pancreatic carcinomas
- Cetuximab, encorafenib and binimetinib in second-line for BRAF-mutant metastatic colorectal cancers
- Adjuvant treatment for localized biliary tract cancers
- Second line treatment for advanced biliary tract cancers
- Precision medicine for IDH-mutant biliary tract cancers

**Atezolizumab and Bevacizumab as new standard of care as first line therapy for advanced hepatocellular carcinoma**
Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

Ann-Lii Cheng,¹ Shukui Qin,² Masafumi Ikeda,³ Peter R. Galle,⁴ Michel Ducreux,⁵ Andrew X. Zhu,⁶ Tae-You Kim,⁷ Masatoshi Kudo,⁸ Valeriy Breder,⁹ Philippe Merle,¹⁰ Ahmed Kaseb,¹¹ Daneng Li,¹² Wendy Verret,¹³ Derek-Zhen Xu,¹⁴ Sairy Hernandez,¹³ Juan Liu,¹⁴ Chen Huang,¹⁴ Sohail Mulla,¹⁵ Ho Yeong Lim,¹⁶ Richard S. Finn¹⁷

¹National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; ²People’s Liberation Army Cancer Center, Jinling Hospital, Nanjing, People’s Republic of China; ³National Cancer Center Hospital East, Kashiwa, Japan; ⁴University Medical Center Mainz, Mainz, Germany; ⁵Gustave Roussy Cancer Center, Villejuif, France; ⁶Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; ⁷Seoul National University College of Medicine, Seoul, Korea; ⁸Kindai University Faculty of Medicine, Osaka, Japan; ⁹N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; ¹⁰Hospital La Croix-Rousse, Lyon, France; ¹¹The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ¹²City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; ¹³Genentech, Inc., South San Francisco, CA, USA; ¹⁴Roche Product Development, Shanghai, People’s Republic of China; ¹⁵Hoffmann-La Roche Limited, Mississauga, ON, Canada; ¹⁶Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; ¹⁷Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA
**IMbrave150 study design**

**Key eligibility**
- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy

**Stratification**
- **Region** (Asia, excluding Japan\(^a\)/rest of world)
- **ECOG PS** (0/1)
- **Macrovascular invasion** (MVI) and/or **extrahepatic spread** (EHS) (presence/absence)
- **Baseline α-fetoprotein** (AFP; < 400/≥ 400 ng/mL)

**Treatment arms**
- **Atezolizumab** 1200 mg IV q3w + **bevacizumab** 15 mg/kg q3w
- **Sorafenib** 400 mg BID

**Outcome measures**
- **Co-primary endpoints**
  - OS
  - IRF-assessed PFS per RECIST 1.1

- **Key secondary endpoints** (in testing strategy)
  - IRF-assessed ORR per RECIST 1.1
  - IRF-assessed ORR per HCC mRECIST

---

\(^a\) Japan is included in rest of world.

\(^b\) An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.
Confirmed PFS\textsuperscript{a}: co-primary endpoint

\begin{itemize}
  \item Assessed by IRF per RECIST 1.1.
  \item 197 patients (59\%) in the Atezo + Bev arm vs 109 (66\%) in the sorafenib arm had an event.
  \item HR and \( P \) value were from Cox model and log-rank test was stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS.
  \item The 2-sided \( P \) value boundary is 0.002.
\end{itemize}

\textbf{Median PFS (95\% CI), mo}\textsuperscript{b}
\begin{tabular}{ll}
  Atezo + Bev & 6.8 (5.7, 8.3) \\
  Sorafenib & 4.3 (4.0, 5.6) \\
  \hline
  HR & 0.59 (95\% CI: 0.47, 0.76)\textsuperscript{c,d} \\
  \textit{P} & < 0.0001\textsuperscript{d}
\end{tabular}

\begin{itemize}
  \item 6-mo PFS rate: 55\% \\
  \item 6-mo PFS rate: 37\% \\
  \item mPFS: 4.3 mo \\
  \item mPFS: 6.8 mo
\end{itemize}

\textsuperscript{a} Assessed by IRF per RECIST 1.1. \textsuperscript{b} 197 patients (59\%) in the Atezo + Bev arm vs 109 (66\%) in the sorafenib arm had an event. \textsuperscript{c} HR and \( P \) value were from Cox model and log-rank test was stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. \textsuperscript{d} The 2-sided \( P \) value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.
OS: co-primary endpoint

<table>
<thead>
<tr>
<th>Median OS (95% CI), mo$^a$</th>
<th>Atezo + Bev</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NE</td>
<td>13.2 (10.4, NE)</td>
</tr>
</tbody>
</table>

HR, 0.58 (95% CI: 0.42, 0.79)$^b$  
$P = 0.0006^{b,c}$

6-mo OS rate: 85%  
6-mo OS rate: 72%  
mOS: NE  
mOS: 13.2 mo

NE, not estimable. $^a$ 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. $^b$ HR and $P$ value were from Cox model and log-rank test was stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. $^c$ The 2-sided $P$ value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.
Thanks