Biliary Tract Cancers

Miguel Navarro
Salamanca
BTCs are quite challenging to treat
BTCs Background

- Uncommon.
- Increasing incidence and mortality globally.
- Most patient are diagnosed with no resecable disease.
- Associated with poor outcomes.
- Need of new drugs.

Biliary tract cancers are a diverse set of neoplasms arising from the biliary tract epithelium ....
Why doesn´t one size fits all?

Valle et al. Cancer Discovery. 2017
Why doesn’t one size fits all?

Valle et al. Cancer Discovery.2017
Why doesn´t one size fits all?

Such differences are worth taking into account at time of treatment planning, research, and clinical trial design.
Surgery

• Biliary tract cancers usually present at an advanced stage, and only approximately **20%** of tumors are considered resectable.

• Surgery is the primary curative treatment option for early-stage biliary tract cancer.
Adjuvant therapy

- Need for effective adjuvant therapy.

- Older randomised studies were not sufficiently statistically powered to define a standard of care.

- Meta-analysis (of mostly retrospective data) has suggested improved overall survival with adjuvant treatment.

Adjuvant therapy

Two recent randomised studies did NOT show a significant benefit of:

- gemcitabine
- gemcitabine plus oxaliplatin (GEMOX regimen)

Randomized clinical trial

Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer

T. Ebata1, S. Hirano4, M. Konishi6, K. Uesaka7, Y. Tsuchiya9, M. Ohtsuka10, Y. Kacoka11, M. Yamamoto12, Y. Ambo7, Y. Shimmizu12, F. Ozawa13, A. Fukumoto14, M. Ando12, Y. Nimura1 and M. Nagino1, on behalf of the Bile Duct Cancer Adjuvant Trial (BACAT) Study Group

1Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, 2Department of Gastroenterological Surgery, Aichi Cancer Centre Hospital, and 3Centre for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, 4Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine, and 5Department of Surgery, Teine-Koenji Hospital, Sapporo, 6Department of Hepatobiliary-Pancreatic Surgery, National Cancer Centre Hospital East, Kashiwa, 7Division of 8Hepato-Biliary-Pancreatic Surgery and 9Gastroenterological Oncology, Shizuoka Cancer Centre Hospital, Shizuoka, 10Department of Surgery, Niigata Cancer Centre Hospital, Niigata, 11Department of General Surgery, Graduate School of Medicine, Chiba University, Chiba, 12Department of Surgery, Ogasawara Tribal Hospital, Ogasawara, 13Department of Surgery, Institute of Gastroenterology, Tokyo Women’s Medical University, Tokyo, and 14Department of Hepatobiliary-Pancreatic Surgery, Satsuma Medical Centre, Satsuma Medical University, Satsuma, Japan

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Gemox versus surveillance following surgery of localized biliary tract cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial.
Adjuvant therapy

Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study

John N Primrose, Richard P Fox, Daniel H Palmer, Hassan Z Malik, Raj Prasad, Darius Mirza, Alan Anthony, Pippa Corrie, Stephen Falk, Meg Finch-Jones, Harpreet Wasan, Paul Ross, Lucy Wall, Jonathan Wadsley, Jeff R Evans, Deborah Stacker, Raaj Prasadom, Yuk Ting Ma, Brian Davidson, John P Neoptolemos, Tim Iveson, James Raftory, Shihua Zhu, David Cunningham, O James Garden, Clive Stubbs, Juan W Valle, John Bridgewater, on behalf of the BILCAP study group

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Background Despite improvements in multidisciplinary management, patients with biliary tract cancer have a poor outcome. Only 20% of patients are eligible for surgical resection with curative intent, with 5-year overall survival of less than 10% for all patients. To our knowledge, no studies have described a benefit of adjuvant therapy. We aimed to determine whether adjuvant capecitabine improved overall survival compared with observation following surgery for biliary tract cancer.

Lancet Oncol 2019
Published Online
March 25, 2019
http://dx.doi.org/10.1016/S1470-2045(18)30915-X
BILCAP: Study Design

Open-label, randomized, controlled phase III trial

- **Primary endpoint:** OS
- **Secondary endpoints:** RFS, toxicity, QoL, health economics

753 patients were screened across 44 UK centres between 2006 and 2014

**Histologically confirmed biliary tract cancer**
- **intrahepatic CC**, hilar CC, muscle-invasive gallbladder cancer, and lower common bile duct CC
- **Excluded:** pancreatic, ampullary, mucosal (T1a) gallbladder cancers; incomplete recovery from prior surgery

**Stratified by surgical center, R0 vs R1 resection, ECOG PS**

- **Resection**
- **Capecitabine 1250 mg/m² BID**
  - Days 1-14 of 21-day cycle for 8 cycles
  - (n = 223)
- **Observation**
  - (n = 224)

Primary analysis after minimum 2-yr follow-up
**BILCAP: Study Design**

### Power calculation

<table>
<thead>
<tr>
<th>Version</th>
<th>Effect</th>
<th># of patients</th>
<th># of events</th>
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<tbody>
<tr>
<td>Original</td>
<td>Increase in 2 year OS from 20% → 32%, HR 0.71</td>
<td>360</td>
<td>270*</td>
</tr>
<tr>
<td>Revision 1</td>
<td>Increase in 2 year OS from ≈60% → 70%, HR 0.71</td>
<td>410</td>
<td>270*</td>
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<tr>
<td>Revision 2</td>
<td>Increase in 2 year OS from ≈60 → 71%, HR 0.69</td>
<td>410</td>
<td>234*</td>
</tr>
</tbody>
</table>

*2-sided significance level of 5% with 80% power

Observed 2 year OS of ≈60% in control group

Observed ongoing deficit of trial events

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*Images and text are speculative and not from the original document.*
Median capecitabine dose: 1250 mg/m2 BID (IQR: 1061-1250 mg/m2)

122 (55%) pts in the capecitabine arm received 8 cycles

10 (< 5%) pts received 0 cycles

**BILCAP: OS**

Unfortunately, the study did not meet its primary endpoint.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, Mos (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>51.1 (34.6-59.1)</td>
<td>0.81 (0.63-1.04)</td>
</tr>
<tr>
<td>Observation</td>
<td>36.4 (29.7-44.5)</td>
<td>P = .097</td>
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</table>

ITT Population

<table>
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<tr>
<th>Treatment</th>
<th>Median OS, Mos (95% CI)</th>
<th>HR (95% CI)</th>
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Per Protocol Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, Mos (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>52.7 (40.3-NR)</td>
<td>0.75 (0.58-0.97)</td>
</tr>
<tr>
<td>Observation</td>
<td>36.1 (29.6-44.2)</td>
<td>P = .028</td>
</tr>
</tbody>
</table>

Sensitivity analyses adjusting for further prognostic factors (gender, nodal status, disease grade) HR 0.70 (95% CI: 0.55-0.91; P = .007)

> 80% pts followed-up for 36 mos

Adjuvant therapy

Capicitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study

John N Primrose, Richard F Fox, Daniel H Palmer, Hassan Z Malik, Raj Prasad, Daruis Minna, Alan Anthony, Pippa Corrie, Stephen Folk, Mqy Fisch-Jones, Harpreet Mason, Paul Ross, Lucy Wall, Jonathan Waldron, Jeff R Evans, Deborah Slackers, Raj Prasadon, Yuk Ting Ma, Brian Davidsen, John P Kepplebohns, Tim Iveson, James Rafferty, Shihua Zhu, David Cunningham, O’James Garden, Claire Stubbs, Juan W Valle, John Brideovery, on behalf of the BILCAP study group

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Interpretation Although this study did not meet its primary endpoint of improving overall survival in the intention-to-treat population, the prespecified sensitivity and per-protocol analyses suggest that capicitabine can improve overall survival in patients with resected biliary tract cancer when used as adjuvant chemotherapy following surgery and could be considered as standard of care. Furthermore, the safety profile is manageable, supporting the use of capicitabine in this setting.
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BILCAP investigators unilaterally decide to ABANDON STATISTICAL SIGNIFICANCE, claiming a p=0.09 is practice changing!! Vinay Prasad
Table 1. Characteristics of Randomized Controlled Trials of Adjuvant Therapy for Resected Biliary Tract Carcinoma

<table>
<thead>
<tr>
<th>Study and Location</th>
<th>Study Type</th>
<th>Study Arms</th>
<th>No. of Patients</th>
<th>Median Age (years; range)</th>
<th>Male/Female (%)</th>
<th>ECOG PS (%)</th>
<th>Disease Site (%)</th>
<th>Node Status (%)</th>
<th>Margin Status (%)</th>
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</thead>
<tbody>
<tr>
<td>Primrose et al. 10, 2017 (BILCAP; UK)</td>
<td>Phase III RCT, Full publication</td>
<td>Capcitabine: 1,250 mg/m² twice a day on days 1 to 14 of a 3-week cycle for 24 weeks (8 cycles); Oxaliplatin: 85 mg/m² on day 2 for 12 cycles</td>
<td>ITT: 223; PP: 220</td>
<td>62 (55-68)</td>
<td>50/50</td>
<td>0.45</td>
<td>1: 52; 2: 3</td>
<td>Intrahepatic: 19</td>
<td>N0: 45; N1: 46; NX: 7</td>
</tr>
<tr>
<td>Observation</td>
<td>ITT: 224; PP: 210</td>
<td>64 (55-69)</td>
<td>50/50</td>
<td>0.45</td>
<td>1: 52; 2: 3</td>
<td>Intrahepatic: 18</td>
<td>N0: 48; N1: 46; NX: 6</td>
<td>R0: 63; R1: 38</td>
<td></td>
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<tr>
<td>Esteller et al. 2017 (PR002012; ACCORD 18; UNICANCER GI); France</td>
<td>Phase III RCT, Conference abstract</td>
<td>Gemcitabine: 1,000 mg/m² on days 1, 8, and 15, every 4 weeks (6 cycles)</td>
<td>95</td>
<td>63.0 (33.0-83.0)</td>
<td>60/44</td>
<td>0.54</td>
<td>1: 38; 2: 5; Unknown: 2</td>
<td>Intrahepatic: 43</td>
<td>Perihilar: 11; Distal: 28; Gallbladder: 15</td>
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<tr>
<td>Surveillance</td>
<td>99</td>
<td>63 (40.6-80.0)</td>
<td>50/50</td>
<td>0.64</td>
<td>1: 31; 2: 2; Unknown: 3</td>
<td>Intrahepatic: 45</td>
<td>Perihilar: 5; Distal: 23; Gallbladder: 21</td>
<td>Lymph node invasion: 37.2</td>
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<tr>
<td>Ebata et al. 2018, Japan</td>
<td>Phase III RCT, Full publication</td>
<td>Gemcitabine: 1,000 mg/m² on days 1, 8, and 15, every 4 weeks (6 cycles)</td>
<td>117</td>
<td>&gt; 70 years: 56%; &lt; 70 years: 44%</td>
<td>66/34</td>
<td>0.10</td>
<td>Perihilar: 44; pn0: 64; R0: 91; R1: 9</td>
<td>Lymph node invasion: 36.4</td>
<td></td>
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<tr>
<td>Observation</td>
<td>108</td>
<td>&gt; 70 years: 43%; &lt; 70 years: 57%</td>
<td>76/24</td>
<td>0.13</td>
<td>Perihilar: 47; Distal: 53; pn0: 67</td>
<td>R0: 87; R1: 33</td>
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<tr>
<td>Ben-Josef et al. 2015 (SWOG0803); United States</td>
<td>Phase II single-arm trial</td>
<td>Gemcitabine (1,000 mg/m² on days 1 and 8) and capcitabine (1,500 mg/m² per day, in divided doses twice daily on days 1 to 14) every 21 days for 4 cycles followed by concurrent capcitabine (1,330 mg/m² per day, in divided doses twice daily, 7 days per week) and radiotherapy (45 GY to regional lymphatics; 54-56.4 GY to tumor bed)</td>
<td>79</td>
<td>RO: 15 (27-85); R1: 59 (26-86); R2: 58 (44-64); R3: 59 (41-61); R4: 59 (28-72)</td>
<td></td>
<td>Distal: n = 17</td>
<td>Not reported</td>
<td>R0: 88; R1: 32</td>
<td></td>
</tr>
</tbody>
</table>
Adjuvant therapy.

Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline

Rachna T. Shroff, MD; Erin B. Kennedy, MHSc; Melinda Bachini; Tanios Bekai-Saab, MD; Christopher Crane, MD; Julien Edeline, MD, PhD; Anthony El-Khouery, MD; Mary Feng, MD; Matthew H.G. Katz, MD; John Primrose, MD; Heloisa P. Soares, MD, PhD; Juan Valle, MD; and Shishir K. Mathel, MD

Recommendation 1. Patients with resected biliary tract cancer should be offered adjuvant capecitabine chemotherapy for a duration of 6 months (Type: Evidence based; Benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Qualifying statements.

- In the BILCAP (Adjuvant Capecitabine for Biliary Tract Cancer) phase III randomized controlled trial, capecitabine was delivered at a dose of 1,250 mg/m² twice a day on treatment days 1 to 14 of a 3-week cycle for 24 weeks (eight cycles).12
- The Expert Panel agrees that the recommended dose of capecitabine may be determined by institutional and regional practices.

Recommendation 2. Patients with extrahepatic cholangiocarcinoma or gallbladder cancer and a microscopically positive surgical margin resection (R1 resection) may be offered chemoradiotherapy (Type: Evidence and Consensus based; Benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate).

Qualifying statements.

- A shared decision-making approach is recommended, considering the risk of potential harm and potential for benefit associated with radiation therapy for patients with extrahepatic cholangiocarcinoma or gallbladder cancer.
- The Expert Panel notes that in the SWOG0809 prospective single-arm trial of chemoradiotherapy, radiation was delivered at a dose of 45 Gy to regional lymphatics and 54 to 59.4 Gy to the tumor bed. However, at this time, the evidence base is not sufficiently well developed to make a recommendation for optimal dosing of radiation therapy in the context of chemoradiation therapy.

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Adjuvant therapy. Future

A trial of chemotherapy after surgery for cancer of the bile duct or gallbladder (ACTICCA-1)
Advanced disease: Liver-directed therapy

- Selected patients may be suitable for liver-directed therapy (e.g., radioembolization or external beam radiation):
  - ✔ Pending confirmation of benefit in randomized studies.

- Liver Transplant remains controversial in this setting.

Advanced or Metastatic disease therapy

• Unfortunately, most patients present with advanced or metastatic disease, when systemic chemotherapy is the only treatment option.

• Due to the paucity of effective treatments, BTCs have a dismal prognosis
Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoncy, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators*


410 Patients underwent randomization

206 Were assigned to receive gemcitabine
204 Were assigned to receive cisplatin plus gemcitabine

6 meses

SG:
11.7 Vs 8.1m

SLP:
8 Vs 5m
Gemcitabine, cisplatin plus S-1 (GCS) versus gemcitabine, cisplatin (GC) for advanced biliary tract cancer (KHBO1401-MITSUBA) – Sakai

Sample size: 240 (120 per arm) patients for 209 events

- superiority for OS
- estimated 1YS
  - 43% in GC
  - 55% in GCS
  - HR= 0.71
- one sided alpha 5%
- power 80%

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>RR</th>
<th>DCR</th>
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<tbody>
<tr>
<td>GC</td>
<td>100</td>
<td>15.0%</td>
<td>62.0%</td>
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<tr>
<td>GCS</td>
<td>94</td>
<td>41.5%</td>
<td>79.8%</td>
</tr>
</tbody>
</table>

ESMO 2018 Congress
Nab-paclitaxel plus gemcitabine-cisplatin in patients with biliary tract cancers

- Open-label, single-arm, phase 2 trial
- Gemcitabine, 1000 mg/m², cisplatin, 25 mg/m², and nab-paclitaxel, 125 mg/m², on days 1 and 8 of 21-day cycles.
- Dose reduction to G/C/N (in mg/m²) at 800/25/100.

Advanced or Metastatic disease therapy

• There is no standard second-line therapy.

• Fluoropyrimidines are frequently used in clinical practice.

• ABC-06 randomized Phase III clinical study is analyzing the role of chemotherapy FOLFOX in this setting vs symptomatic management.
  • Study positive (ASCO 2019)

Active symptom control alone or with mFOLFOX chemotherapy for locally advanced/metastatic biliary tract cancers; 2014. Available from: https://ClinicalTrials.gov/show/NCT01926236.
Significant potential targetable pathways

Valle et al. Cancer Management and Research 2019
Metastatic disease therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response rate</th>
<th>Median months</th>
<th>OS months</th>
<th>P</th>
<th>Author</th>
<th>Year</th>
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<td><strong>Cytotoxic therapies</strong></td>
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<td>GEM + CDDP</td>
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<td>S-1</td>
<td>rII 50 17</td>
<td>4.2</td>
<td>9</td>
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<td>GEM + S-1</td>
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<td>7.1</td>
<td>12.5</td>
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<tr>
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<td>5.5</td>
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<td>76 24</td>
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<tr>
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<td>62 27</td>
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<tr>
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<td>9.9</td>
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<td>21.4</td>
<td>0.35</td>
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<tr>
<td>GEM + CDDP + panitumumab</td>
<td>63 45</td>
<td>8.2</td>
<td>12.8</td>
<td></td>
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<tr>
<td>GEM + L-OHPL + Cape + panitumumab</td>
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<td>6.1</td>
<td>9.5</td>
<td>NA</td>
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<tr>
<td>GEM + L-OHPL + Cape + panitumumab + bevacizumab</td>
<td>43 18</td>
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<td>12.3</td>
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<tr>
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<td>GEM + CDDP</td>
<td>rII 124 19</td>
<td>7.4</td>
<td>11.9</td>
<td>0.44</td>
<td>Valle</td>
<td>2015</td>
</tr>
<tr>
<td>GEM + CDDP + cediranib</td>
<td></td>
<td>8.0</td>
<td>14.1</td>
<td></td>
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</tr>
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<td>Trametinib</td>
<td>rII 27 8</td>
<td>1.3</td>
<td>4.3</td>
<td>0.01</td>
<td>Kim</td>
<td>2017</td>
</tr>
<tr>
<td>SFU or Cape</td>
<td>26 10</td>
<td>2.8</td>
<td>8.0</td>
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<tr>
<td>Vandetanib</td>
<td>rII 59 4</td>
<td>3.5</td>
<td>7.5</td>
<td>0.07</td>
<td>Santoro</td>
<td>2015</td>
</tr>
<tr>
<td>GEM + vandetanib</td>
<td>58 19</td>
<td>3.7</td>
<td>9.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEM</td>
<td>56 14</td>
<td>4.9</td>
<td>10</td>
<td></td>
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</tr>
</tbody>
</table>

No agent has shown to be effective for advanced biliary tract cancer.
Metastatic disease therapy

SWOG S1310: Randomized phase II trial of single agent MEK inhibitor trametinib vs. 5-fluorouracil or capecitabine in refractory advanced biliary cancer.

- First prospective randomized study of a targeted agent versus chemotherapy for the second line treatment of BC.
- In this unselected population, the lack of response to trametinib resulted in early closure.
- The PFS and OS for trametinib were inferior to 5FU.

Genomic Landscape BTC

Liver Flukes:

*Clonorchis sinensis* – China, Korea, Vietnam

*Opisthorchis viverrini* – Thailand, Cambodia, Laos

Jusakul et al, Can Dis 2017
A number of genetic mutations have been identified in patients with BTC that open the possibility of targeted treatment for this patient population....

"Cholangiocarcinoma has a number of actionable mutations; probably more than any other gastrointestinal cancer"

Valle et al. Cancer Discovery.2017
New Horizon on Targets

- IDH-1 Mutation
- FGFR fusion rearrangements
- BRAF
- Other targets:
  - HER2 Neu alterations
  - NTRK
  - DNA alterations
  - Immunotherapy
IDH-1 mutation

• Somatic mutations within the conserved active site of isocitrate dehydrogenase (IDH) 1 and 2 occur in multiple tumors:
  • Glioma
  • Acute myeloid leukemia (AML)
  • Chondrosarcoma
  • Cholangiocarcinoma (20-25% iCCA)

• Mutation results in accumulation in
  • 2-hydroxyglutarate (oncomet)
IDH-1 mutation: AG-120

AG-120: Ivosidenib (Tibsovo®)
- IDH1 inhibitor
- Small molecule
- Oral
- Reversible
- Approved in AML

- Promising results of the Phase I study of an IDH1 inhibitor, AG-120, in 76 patients with previously treated advanced BTC.
  - Ivosidenib was given at 500 mg once daily in the dose-expansion cohort.

Lowery MA et al. Phase I study of AG-120, an IDH1 mutant enzyme inhibitor: results from the cholangiocarcinoma dose escalation and expansion cohorts. ASCO Annual Meeting 2017, Poster 4015
IDH-1 mutation: AG-120

It is estimated to be completed in August 2020.
Ivosidenib Improves PFS in IDH1-Mutant Cholangiocarcinoma

Ivosidenib demonstrated a statistically significant improvement in progression-free survival (PFS) by independent radiology review compared with placebo in patients with IDH1-mutant previously treated cholangiocarcinoma, meeting the primary endpoint of the phase III ClarIDHy trial.¹

Full findings of the study are expected to be presented at the 2019 ESMO Congress. In a press release, Agios Pharmaceuticals, the developer of the IDH1 inhibitor, stated that it plans to submit a supplemental new drug application for ivosidenib in this patient population by the end of 2019.
FGFR 2 fusions:

- FGFR genetic aberrations occur in several cancers, most notably bile duct cancers and urothelial carcinoma.
- Recurrent FGFR2 fusions in 11% to 45% of patients with ICC.
- Tested in multiple trials.
- Prognostic

Jain et al. JCO Precis oncol Jan 17, 2018
FGFR 2 fusions: BGJ398 (infigratinib)

Study objective (Abstract LBA28 – Javle M, et al)

- To assess the efficacy and safety of Infigratinib in patients with previously treated advanced intrahepatic cholangiocarcinoma containing FGFR2 fusions

Study design

- Patients (n=71) with histologically or cytologically confirmed advanced or metastatic intrahepatic cholangiocarcinoma with FGFR2 fusions or other FGFR genetic alterations received infigratinib monotherapy 125 mg/day (3-weeks on/1-week off) until PD

Key results

<table>
<thead>
<tr>
<th></th>
<th>Infigratinib (n=71)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (confirmed and unconfirmed), %</td>
<td>31.0</td>
<td>20.5, 43.1</td>
</tr>
<tr>
<td>Complete ORR, %</td>
<td>26.9</td>
<td>16.8, 39.1</td>
</tr>
<tr>
<td>DCR, %</td>
<td>83.6</td>
<td>72.5, 91.5</td>
</tr>
<tr>
<td>mOS, months</td>
<td>12.5</td>
<td>9.9, 16.6</td>
</tr>
<tr>
<td>mPFS, months</td>
<td>6.8</td>
<td>5.3, 7.6</td>
</tr>
</tbody>
</table>

- The most common grade 3/4 AEs occurring in >10% of patients were hypophosphatemia (14.1%) and hyperphosphatemia (12.7%)

FGFR 2 fusions: BGJ398 (infigratinib)

- Phase 3 Study of BGJ398 (Oral Infigratinib) in First Line Cholangiocarcinoma With FGFR2 Gene Fusions/Translocations.

Investigational Drug:
Infigratinib—oral, once daily

Comparator:
Intravenous gemcitabine with cisplatin

Primary objective is to demonstrate non-inferiority (NI) of treatment with infigratinib versus gemcitabine with cisplatin based on centrally assessed progression-free survival (PFS)
FGFR 2 fusions: TAS 120

TAS-120: Highly selective, irreversible pan-FGFR inhibitor

BRAF

• **BRAF** mutations in 5% to 7% of patients with BTC.
  • may be enriched in intrahepatic BTC

• The combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib has demonstrated efficacy in **BRAF** V600E–mutated cancers:
  • metastatic melanoma and melanoma in the adjuvant setting
  • non-small cell lung carcinoma
  • anaplastic thyroid cancer

**BRAF** kinase inhibitor dabrafenib (*Tafinlar*) and MEK inhibitor trametinib (*Mekinist*)

**Study objective**
- To assess the efficacy and safety of dabrafenib (a BRAF inhibitor) + trametinib (a MEK inhibitor) in the cohort of patients with BRAF V600E-mutated BTC in the ROAR basket trial

**Key patient inclusion criteria**
- Advanced or metastatic BTC
- BRAF V600E mutated
- Progression on gemcitabine
- ECOG PS ≤2 (n=35)

80% of patients received ≥ 2 lines of prior systemic therapy

**PRIMARY ENDPOINT**
- ORR (RECIST v1.1)

**SECONDARY ENDPOINTS**
- DoR, PFS, OS, biomarkers, safety

**BRAF** kinase inhibitor dabrafenib (*Tafinlar*) and MEK inhibitor trametinib (*Mekinist*)

In patients with **BRAF** V600E-mutated BTC, dabrafenib + trametinib provided clinical benefit with efficacy similar to 1L gemcitabine + cisplatin

Other targets: HER-2

Other targets – Her2

- Systematic review and meta-analysis of 40 studies, 3839 pts:
  - Her2 expression rate →
    EHCCA > IHCCA (20% vs ~5%)
  - Other Her family? Her3?
- Which drug may be relevant → TKI vs. mAb

Mou HB et al. Hepatobiliary Pancreat Dis Int 2018
Other targets: NTRK

Other targets: NTRK

Results per Blinded Independent Central Review (BICR)

<table>
<thead>
<tr>
<th>NTRK+ patients (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>Non-CR/PD, missing or unevaluable</td>
</tr>
</tbody>
</table>

Note: Patients (n=6) without matched pre/post therapy scans were excluded from the plot.

CI: confidence interval; CRC: colorectal cancer; MASC: mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer.
Inmunotherapy

- Microsatellite instability predict response to immunotherapy.
- About 3% of CCA patients have microsatellite instability and have had positive long-term results with checkpoint inhibitors

Inmunotherapy

Study objective (KEYNOTE-158: Abstract 625PD – Pruitt SK, et al)
- To assess the efficacy and safety of pembrolizumab monotherapy in patients with unresectable and/or metastatic advanced biliary adenocarcinoma

Study design
- In this single-arm, non-randomised trial of multiple cohorts, patients (n=104) received pembrolizumab 200 mg iv (q3w) for 2 years or until PD/survival follow-up after proven intolerance to standard therapy

Key results

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=104)</th>
<th>PD-L1+ (n=61)</th>
<th>PD-L1− (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR*, % (95%CI)</td>
<td>5.8 (2.1, 12.1)</td>
<td>6.6 (1.8, 15.9)</td>
<td>2.9 (0.1, 15.3)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>6 (6)</td>
<td>4 (7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>17 (16)</td>
<td>6 (10)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>65 (63)</td>
<td>44 (72)</td>
<td>17 (50)</td>
</tr>
</tbody>
</table>

- mPFS and mOS was 2.0 months (95%CI 1.9, 2.1) and 9.1 (95%CI 5.6, 10.4), respectively
- Grade 3–4 TRAEs included increased blood alkaline phosphatase (1.9%) and pruritus, diarrhoea and pneumonitis (1.0% for each)

*Includes only confirmed responses

Ko AH, et al  Ann Oncol 2018;29(suppl 5) abstr LBA29
Key points

• Adjuvant:
  • Bilcap/SWOG 0809
• Locally advanced:
  • Role of liver directed therapies?
• 1 line:
  • ABC-02: SOC/ Triplets?
• 2 line:
  • ABC-06: New SOC with FOLFOX? (Asco 2019)
Key points

- **IDH1 Mutations:**
  - Results of ClarIDHy positive.
  - Others agents in studies.

- **FGFR2 Fusions:**
  - Multiple drugs / Promising ORR / Phase III vs CT

- **BRAF:**
  - Lower frequency / Meaningful therapeutic option (Should be considered for routine testing).

- **Inmunotherapy:**
  - Microsatellite instability
  - Role for IO combinations?
Difficulties?

• Availability of tissue
• Simple arm studies
• Next-generation sequencing into clinical practice???
• Role of resistance.
Conclusion

• BTCs are quite challenging to treat

• Treatment paradigm for patients with advanced BTC is evolving.

• For BTCs Patients Mutations Matter.
Muchas Gracias

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