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New agents/strategies on the horizon in bile duct cancer

Michel Ducreux
Gustave Roussy Cancer Campus
France
Epidemiology

BTC =

Intrahepatic BTC Mortality rates

In the US:
Gallbladder & extrahepatic BTC new cases = 10,910, Deaths = 3,700


**BSC vs FUFOL vs GEMOX in gallbladder cancer**

- Randomised monocentric study
- Non resectable or metastatic gallbladder cancer
- ECOG 0-2, age 18-70 years (median age : 50)

<table>
<thead>
<tr>
<th></th>
<th>BSC</th>
<th>FUFOL</th>
<th>GEMOX</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>28</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>0</td>
<td>14</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>PFS (months)</td>
<td>2.8</td>
<td>3.5</td>
<td>8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SG (months)</td>
<td>4.5</td>
<td>4.6</td>
<td>9.5</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Low response rates

GEM vs GEMCIS - UK-ABC 02 trial

ABC 01
Randomized phase II, 86 patients (ASCO GI 2006)
PFS: GEM-CDDP > GEM

ABC 02
Phase III, 324 pts, 34 centers
Main endpoint: overall survival
Locally advanced disease or metastatic, age ≥18 years, WHO 0-2

Stratification
- Stage
- Tumoral site
- General status WHO
- Centre

GEMCIS x 8
(GEM 1000 mg/m² J1-8 + CDDP 25 mg/m² J1-8, J1=J21)

GEM x 6
(GEM 1000 mg/m² J1-8-15, J1=J28)

JW Valle et al. NEJM 2010;362:1273-81
GEM vs GEMCIS UK-ABC 02
Overall survival

Hazard ratio for death,
0.64 (95% CI, 0.52–0.80)
P<0.001

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>206 151 97 53 28 15 4 3 2</td>
</tr>
<tr>
<td>Cisplatin–gemcitabine</td>
<td>204 167 120 76 51 28 17 8 2</td>
</tr>
</tbody>
</table>

JW Valle et al. NEJM 2010;362:1273-81
Gemcitabine + S-1 vs GEMCIS first line: same survival, less toxicity

Overall survival

<table>
<thead>
<tr>
<th></th>
<th>GEMCIS n=175</th>
<th>GEM-S1 n=179</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year overall survival (IC 95%)</td>
<td>58.3% (50.6%-65.2%)</td>
<td>59.2% (51.6%-66.0%)</td>
</tr>
<tr>
<td>Median overall survival (IC 95%)</td>
<td>13.4 months (12.4-15.5)</td>
<td>15.1 months (12.2-16.4)</td>
</tr>
</tbody>
</table>

HR†: 0.945; IC 90%: 0.777 - 1.149  
p non-inferiority = 0.0459 < 0.05

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>GEMCIS</th>
<th>GEM-S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>175</td>
<td>179</td>
</tr>
<tr>
<td>6</td>
<td>151</td>
<td>159</td>
</tr>
<tr>
<td>12</td>
<td>102</td>
<td>106</td>
</tr>
<tr>
<td>18</td>
<td>53</td>
<td>71</td>
</tr>
<tr>
<td>24</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
<td>17</td>
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<tr>
<td>36</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>42</td>
<td>3</td>
<td>4</td>
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<tr>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

M Ueno, et al., ASCO® 2018, Abs #4014
Targeted therapies: only one phase III study. No major improvement in RR

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Phase</th>
<th>Line of Rx</th>
<th>No. of pts</th>
<th>RR (%)</th>
<th>Median PFS (mths)</th>
<th>Median OS (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEMOX + Erlotinib (A) vs. GEMOX (B)</td>
<td>Lee et al. [35]</td>
<td>III</td>
<td>1st</td>
<td>268</td>
<td>A: 30</td>
<td>A: 5.8</td>
<td>A: 9.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B: 16</td>
<td>B: 4.2</td>
<td>B: 9.5</td>
</tr>
</tbody>
</table>

Randomized

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Phase</th>
<th>Line of Rx</th>
<th>No. of pts</th>
<th>RR (%)</th>
<th>Median PFS (mths)</th>
<th>Median OS (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMOX + Cetuximab (A) vs. GEMOX (B)</td>
<td>Malka et al. [36]</td>
<td>II</td>
<td>1st</td>
<td>150</td>
<td>A: 23</td>
<td>A: 6</td>
<td>A: 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B: 29</td>
<td>B: 5.3</td>
<td>B: 12.4</td>
</tr>
<tr>
<td>GEMOX + Cetuximab (A) vs. GEMOX (B)</td>
<td>Chen et al. [37]</td>
<td>II</td>
<td>1st</td>
<td>122</td>
<td>A: 27</td>
<td>A: 6.7</td>
<td>A: 10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B: 15</td>
<td>B: 4.1</td>
<td>B: 9.8</td>
</tr>
</tbody>
</table>

Chong DQ and Zhu A Oncotarget 2016;7:46750-67
## Targeted therapies: Anti-angiogenic?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Authors [Ref]</th>
<th>Phase</th>
<th>Cycle</th>
<th>Duration</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>MRD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMOX + Bevacizumab</td>
<td>Zhu et al. [39]</td>
<td>II</td>
<td>1st/2nd</td>
<td>35</td>
<td>40</td>
<td>7</td>
<td>12.7</td>
</tr>
<tr>
<td>Bevacizumab + Erlotinib</td>
<td>Lubner et al. [40]</td>
<td>II</td>
<td>1st</td>
<td>49</td>
<td>12</td>
<td>4.4</td>
<td>9.9</td>
</tr>
<tr>
<td>Gemcitabine + Capecitabine + Bevacizumab</td>
<td>Iyer et al. [41]</td>
<td>II</td>
<td>1st</td>
<td>50</td>
<td>72</td>
<td>8.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Gemcitabine + Sorafenib (A) vs Gemcitabine (B)</td>
<td>Moehler et al. [44]</td>
<td>II</td>
<td>1st</td>
<td>102</td>
<td>A: 8 B: 6</td>
<td>A: 3 B: 4.9</td>
<td>A: 8.4 B: 11.2</td>
</tr>
<tr>
<td>Gemcitabine/ Cisplatin + Sorafenib</td>
<td>Lee et al. [46]</td>
<td>II</td>
<td>1st</td>
<td>39</td>
<td>NR</td>
<td>6.5</td>
<td>14.4</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Yi et al. [47]</td>
<td>II</td>
<td>2nd</td>
<td>56</td>
<td>9</td>
<td>1.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Gemcitabine/ cisplatin + Cediranib (A) vs Gemcitabine/ cisplatin (B)</td>
<td>Valle et al. [49]</td>
<td>II</td>
<td>1st</td>
<td>124</td>
<td>A: 44 B: 19</td>
<td>A: 8 B: 7.4</td>
<td>A: 14.1 B: 11.9</td>
</tr>
</tbody>
</table>

Chong DQ and Zhu A Oncotarget 2016;7:46750-67
Meta-analysis Gemox + ...

<table>
<thead>
<tr>
<th>Overall Survival (OS)</th>
<th>HR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>leone (2015)</td>
<td>0.83 (0.53, 1.30)</td>
<td>18.71</td>
</tr>
<tr>
<td>malka (2014)</td>
<td>1.05 (0.73, 1.50)</td>
<td>18.85</td>
</tr>
<tr>
<td>chen (2015)</td>
<td>0.87 (0.61, 1.25)</td>
<td>27.08</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.697)</td>
<td>0.91 (0.70, 1.12)</td>
<td>64.63</td>
</tr>
<tr>
<td>TKI group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lee (2012)</td>
<td>0.93 (0.69, 1.25)</td>
<td>35.37</td>
</tr>
<tr>
<td>Subtotal (I-squared = .%, p = .)</td>
<td>0.93 (0.65, 1.21)</td>
<td>35.37</td>
</tr>
<tr>
<td>Heterogeneity between groups: p = 0.912</td>
<td>0.92 (0.75, 1.08)</td>
<td>100.00</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.865)</td>
<td>P = 0.39</td>
<td></td>
</tr>
</tbody>
</table>

New drugs: Anti MEK:..Binimetinib

- Binimetinib (MEK162) selective oral MEK1/2 inhibitor,
- An expansion cohort study in patients who received ≤1 line of therapy for advanced BTC was conducted after determination of the MTD in a Phase 1 trial
- Binimetinib 60 mg twice daily.
- 28 patients
- 12 patients (43%) stable disease
- 2 objective responses (1 complete response, 1 partial response)
- Most patients (18/25; 72%) did not have KRAS, BRAF, NRAS, PI3KCA, or PTEN mutations

Finn RS et al. Invest New Drugs 2018, on line
Tribimetinib Another anti-MEK

20 refractory patients (1 line: 12, 2 lines: 8)

- 40% gallbladder
- 25% intrahepatic
- 30% bile duct, 5% ampulla of Vater
- No OR, stable disease: 65%
- Median PFS: 10.6 **weeks**
- One-year overall survival: 20%

Conclusion: **Prolonged PFS was observed in one patient having a specific biological pattern**

Pazopanib + trimetinib

25 refractory patients

- ECOG PS: 0 or 1
- Intrahepatic: 20%
- Perihilar or distal 80%
- Previous CT:
  - Median number of lines: 2
  - Range: 1 - 7

Schroff RT et al. Br J Cancer 2017:
## A biologically heterogeneous disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>IHCC (%)</th>
<th>EHCC (%)</th>
<th>GBC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine kinase signaling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td>4</td>
<td>3</td>
<td>4–18</td>
</tr>
<tr>
<td>HER2</td>
<td>1.5–3</td>
<td>11–18</td>
<td>10–16</td>
</tr>
<tr>
<td>KRAS</td>
<td>17–30</td>
<td>12–40</td>
<td>0–13</td>
</tr>
<tr>
<td>BRAF</td>
<td>4–7</td>
<td>3</td>
<td>1–6</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>5–6</td>
<td>7–9</td>
<td>8–14</td>
</tr>
<tr>
<td>FGFR2 fusions</td>
<td>6–50</td>
<td>0–5</td>
<td>0–3</td>
</tr>
<tr>
<td>IDH pathway</td>
<td>10–28</td>
<td>0–7</td>
<td>0</td>
</tr>
<tr>
<td>Chromatin-remodeling genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARID1A</td>
<td>17</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>BAP1</td>
<td>11</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>PBRM1</td>
<td>8</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>
A biologically heterogeneous disease

**INTRAHEPATIC**
- KRAS
- FGFR2 fusions
- IDH1/2

**EXTRAHEPATIC**
- KRAS
- HER2

**GALLBLADDER**
- EGFR
- HER2
- PIK3CA
Targeted therapy and targeted population...BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma

BGJ398: Pan FGFR TKI
61 patients
- ECOG PS 1 or 2
- Prior antineoplastic reg.:
  - Median: 2, Range: 1 - ≥ 4
- **FGFR status**
  - FGFR1 amplified: 1
  - FGFR2
    - Amplified: 3
    - Mutated: 8
    - Fusion: 48
  - FGFR3 amplified: 4

---

IDH1-3 in intra-hepatic cholangiocarcinoma

- Mutant IDH inhibitors are tested
- The mutant forms of IDH1/2 catalyse the non-reversible accumulation of 2-hydroxyglutarate (2HG)

MOSCATO 01: molecular screening program

1. On Purpose Tumor Biopsy
2. Molecular Screening (NGS & CGH Array & RNAseq)
3. Clinical Decision
4. Treatment

Previous Therapy

Molecular Targeted Agent (MOSCATO)

Tumor Progression

> 25% of PFS 1

PFS 1 / PFS 2

> 1.3

Presented by: Antoine Hollebecque et al., ASCO 2013
Flow chart

Patients
N = 42

Biopsies
N = 47

Fit for analysis
N = 35

Druggable molecular aberration(s)
N = 25 (71%)

Treated
N = 18 (54%)

Since November 2011

No biopsy = 3
Ongoing = 2
Cellularity < 10% = 7

Verlingue L Eur J Cancer 2017;87:122-30
Pathway-based Enrichment analysis

GO molecular functions

- Transmembrane receptor TK
- Regulator protein kinase
- Phosphatases binding
- P53 binding
- PKC binding

ClueGO plugin

Verlingue L Eur J Cancer 2017;87:122-30
TCGA, even better...

489 cholangiocarcinoma from 10 countries

- Highest SNV burden
- Enriched in TP53, ARID1A, BRCA1/2 mutations
- Enriched in H3K27me3-associated promoter mutations

Enriched in TP53 mutations

- Enriched in BAP1 and IDH1/2 mutations
- Enriched in FGFR alterations

ERBB2 amplification

- Highest CNA burden
- 1p, 2p, 2q, 7p, 16p, 19q, 20q

Gene expression

- ERBB2
- TET1
- EZH2

CTNNB1, WNT5B, AKT1

- Immune-related pathways
- PD1, PD-L2 and BTLA

Gene expression

FGFR1, FGFR2, FGFR3, FGFR4

Methylation phenotype

- CpG Island
- Hypermethylated

CpG Shore
- Hypermethylated

Prognosis

- Poorer Prognosis
- Better Prognosis

Survival probability vs. Time in days

Cancer Discov. 2017; 7(10): 1116–1135
Results for efficacy

Mean PFS ratio = 2.1
IC95 [0.08 - 7.43]
PFS ratio > 1.3 = 58%
Results for efficacy

Best responses of evaluable patients

Orientated on:
- IHC
- NGS
- CGH
- RNAseq

Out before 1st evaluation
- Ongoing

Best Response (RECIST1.1, %)

Disease control = 60%
PR+CR = 27%

Molecular targets
- NOTCH4
- PTEN, LOH
- CDH1, 11q21/C
- MET, MTAP
- ALK, EML4
- PIK3C_H1047R
- PTEN, LOH
- PIK3CA, E33K
- INI1, H340X
- KIAA1549, D11S85
- FGFR1, C521A3
- EGFR, wt
- FGFR1, CC1R1
- ERPBB2, ErbB2
- NRAS, Q61R
- TP53, R175H
- ATM
- FGFR2

Verlingue L et al. TAT 2016

Permission by author to reuse slides
Another hope: immunotherapy?

Pembrolizumab: Keynote 028

<table>
<thead>
<tr>
<th>Primary tumor location, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary tract</td>
</tr>
<tr>
<td>Gallbladder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior (neo)adjuvant therapy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lines of prior therapy for adjuvant therapy</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

Change From Baseline, %

- Biliary Tract
- Gallbladder

Time, weeks

- ORR was 17.4% (95% CI, 5.0–38.8) (Table 2)

Bang Y-J et al ECCO 2015
Another hope: immunotherapy...

• Ramucirumab + pembrolizumab
  – Phase I trial
  – Ramucirumab 8 mg/kg Day 1 and Day 8
  – Pembrolizumab 200 mg day 1
  – 26 patients
  – ORR: 4%
  – Median PFS: 1.6 months
  – Median OS: 6.4 months

Arkenau HT et al The Oncologist 2018, on line
The true hope: the European project

UK: J Bridgewater, ABC10
France: D Malka
- Evaluate the role of personalized medicine in these patients
- Molecular screening

- Failure (15%, n = 111)
  - Tumor molecular profiling
    - 1L-SoC (e.g., CisGem) (3 months)
      - No PD (85%, n = 535)
      - Frequent alterations (40%, n = 214)
        - Experimental arm (n = 160)
          - Alt A
          - Alt B
          - Alt C
          - Continuation of 1L-SoC
        - Control arm (n = 54)
          - Alt Y
          - Alt Z
          - Continuation of 1L-SoC
      - Rare alterations (10%, n = 54)
        - Continuation of 1L-SoC
    - No alteration (50%, n = 267)
- ABC (n = 740)
- PD (15%, n = 94)
- Cross-over to Tx
- 2L-Tx
Recent strategy, adjuvant treatment: Bilcap

**OS in the PP population**

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

% of patients alive

Number at risk:
- Observation: 220
- Capecitabine: 210

Time since randomization (months):
- 0: 220, 210
- 12: 190, 190
- 24: 134, 152
- 36: 92, 105
- 48: 64, 83
- 60: 44, 56

Presented by Professor John Primrose

ASCO 2017 Annual Meeting
Liver transplantation as an adjuvant treatment

- Mayo Clinic ini
  - 71 patients selected
- 38 underwent neoadjuvant brachytherapy (capecitabine)
- 26 resection
- 28 unresectable disease

Figure 1. Patient survival from start of neoadjuvant therapy (all 71 patients in transplant protocol) or resection.
Conclusion

• Biliary tract cancer remains an aggressive tumour
• Standard of care in first line therapy is Gemcitabine + Cisplatine
• AntiFGFR and Anti IDH seem to be the best candidates for further development in this disease (but only for intra-hepatic disease)
• Immunotherapy has given some promising data
• Personalized medicine programs are helpful to select targeted therapy in these patients
• In adjuvant setting, capecitabine: new standard of care?
• Liver transplantation has to be evaluated in hilar resectable tumours