GOALS OF TALK

• Going to show standard of care for localized, resectable biliary duct cancer
• Show data behind this and compare guidelines
• Discuss future directions
ADJUVANT CHEMOTHERAPY IN BTC

- Most series used 5-FU alone or with methotrexate, leucovorin, platinums, or interferon-alpha without any improvement in survival over surgery alone
- One phase III trial, both pancreas and biliary tract cancers
  - Surgery +/-mitomycin C with infusional 5-FU
  - For gallbladder cancer there was improvement in 5 year survival rate for the chemotherapy group (26%) compared with the control group (14%), p=0.0367, but the benefit appeared to be limited to those patients deemed to have a “non-curative” resection.
  - No benefit in bile duct or ampullary cancers, regardless of resection type and no benefit after curative resection of gallbladder cancer
ADJUVANT THERAPY IN BTC

• Systematic review and “meta-analysis” of 20 studies→6,712 patients
  – 17 institutional series, largely RT or CRT
  – 1 randomized trial of CT
  – 2 registry analyses
    – Ampullary cancers excluded
• Pooled data→trend to improved survival
  – Significant if registry analyses excluded
  – Suggestion that CT or CRT better than RT alone
  – Adjuvant therapy looked better for N+ or R1

Horgan, et al, ASCO 2011
ADJUVANT THERAPY IN BTC

• “meta-analysis” of 15 studies of adjuvant chemotherapy → 5,060 patients
  – All retrospective
• Improved survival
  – HR 0.66 \((p < 0.001)\) for chemotherapy
  – HR 0.72 \((p < 0.001)\) if studies with heterogeneity are removed
  – Further analyses suggested IV chemo was better and gemcitabine-containing regimens were better

Ma KW, et al Medicine 98:5-10, 2019
GEMOX vs surveillance following surgery of localized biliary tract cancer: results of the PRODIGE 12 - ACCORD 18 (UNICANCER GI) phase III trial

Design

- Biliary Tract Cancer (ICC/ECC/GBC)
- R0 or R1 surgery
- ECOG PS: 0-2
- Adequate liver function
- Randomization within 3 months of surgery

R 1:1

GEMOX 85 – 12 cycles
- Gemcitabine 1000 mg/m² D1
- Oxaliplatin 85 mg/m² D2

Surveillance only:
- ACE, CA19.9 and CT scans
- Every 3 months for 2 years, then every 6 months for 3 years

Stratification factors: tumor site (ICC vs ECC/Hilar vs GBC); R0 vs R1; N0 vs N+ vs Nx; centers

Presented by: Julien Edeline (Rennes, France, Unicancer GI)
Relapse-Free Survival

- Median FU: 44.3 months
- HR=0.83 [95% CI: 0.58-1.19], p=0.31

<table>
<thead>
<tr>
<th></th>
<th>GEMOX</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median RFS</td>
<td>30.4 months</td>
<td>22.0 months</td>
</tr>
<tr>
<td>[95% CI: 15.4-45.8]</td>
<td>[95% CI: 13.6-38.3]</td>
<td></td>
</tr>
<tr>
<td>4-year RFS</td>
<td>39.3% [95% CI: 28.4-50.0]</td>
<td>33.2% [95% CI: 23.1-43.7]</td>
</tr>
</tbody>
</table>
Adjuvant capecitabine for biliary tract cancer: the BILCAP randomized study

Study overview

- Two arm, open label, randomized, controlled clinical trial

Interventions
- Observation
- Capecitabine (1250mg/m²) twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles)

Outcome measures
- Primary; overall survival (OS)
- Secondary;
  - Relapse free survival (RFS)
  - Toxicity
  - Quality of life*
  - Health economics

*EORTC QLQ-C30 & LMC-21 (latter for patients with colorectal liver metastasis)

Minimized on surgical centre, tumour site, type of resection (RO/RI) & performance status (ECOG PS 0-2)

Primary analysis after a minimum 2 year follow-up
CONSORT diagram

n=753 patients assessed for eligibility

n=447 patients randomized

n=447

Observation arm

Capecitabine arm

n=306 Excluded

n=153 ineligible
n=133 patient declined trial
n=20 other

Randomized

n=224

n=223

Intention to treat analysis

n=224

n=223

Per protocol analysis

(n=220)

(n=210)

n=4 ineligible after randomization

n=4 ineligible after randomization

n=10 zero cycles of capecitabine

n=13*

*1 patient was both ineligible and had 0 cycles of capecitabine

PRESENTED AT:
ASCO ANNUAL MEETING '17  #ASCO17
Presented by Professor John Primrose
Treatment compliance

- Median capecitabine dose was 1250mg/kg twice daily (IQR 1061 - 1250mg/kg)

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

10 (<5%) patients received 0 cycles
OS in the ITT 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>51.1 months (34.6-59.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Observation</td>
<td>36.4 months (29.7-44.5)</td>
<td>0.63-1.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.097</td>
</tr>
</tbody>
</table>

Sensitivity analyses:
Adjusting for further prognostic factors (nodal status, disease grade, gender):
HR 0.70 (95% CI 0.55-0.91)
p=0.007
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 (0.58-0.97)</td>
</tr>
<tr>
<td>Observation</td>
<td>36.1 months (29.6-44.2)</td>
<td>p=0.028</td>
</tr>
</tbody>
</table>

Number at risk

- Observation: 220
- Capecitabine: 210

Time since randomization (months)

- Observation: 220 190 134 92 64 44
- Capecitabine: 210 190 152 105 83 56

Presented by Professor John Primrose

ASCN ANNUAL MEETING '17 | #ASCO17

NCI Designated Comprehensive Cancer Center
RFS in the ITT population

<table>
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<tr>
<th>Treatment</th>
<th>Median RFS (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>24.6 months (18.9-36.7)</td>
<td>0.76</td>
</tr>
<tr>
<td>Observation</td>
<td>17.6 months (12.8-27.6)</td>
<td>0.58-0.99</td>
</tr>
</tbody>
</table>

Number at risk:
- Observation: 224
- Capecitabine: 223

Time since randomization (months):
- 0: 224, 223
- 12: 126, 148
- 24: 92, 108
- 36: 67, 78
- 48: 52, 62
- 60: 37, 43

Presented by John Primrose at 2017 ASCO Annual Meeting
RFS in the PP population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median RFS (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>25.9 months (19.8-46.3)</td>
<td>0.71 (0.54-0.92)</td>
</tr>
<tr>
<td>Observation</td>
<td>17.6 months (12.0-23.8)</td>
<td>p=0.011</td>
</tr>
</tbody>
</table>

Number at risk
- Observation: 220, 123, 89, 65, 50, 35
- Capecitabine: 210, 145, 107, 78, 62, 43
## GUIDELINES

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>ASCO</th>
<th>ESMO</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Patients should be offered 6 months of adjuvant capecitabine. Dose is up to physician</td>
<td>Can consider adjuvant chemo, exact choice not clear</td>
<td>Gemcitabine or fluoropyrimidine-based for R0 or R1 resected disease</td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>For patients with gallbladder and extrahepatic cholangio, may consider chemoxrt</td>
<td></td>
<td>Consider for R1 disease based on SWOG study</td>
</tr>
</tbody>
</table>
CHEMO CONCLUSIONS

• Currently the only positive randomized trial we have is for adjuvant capecitabine
  – Nearly half of patients did not receive all 8 cycles
• It is hard to reconcile the issue of the Gem-ox data
• No known role for radiation but it should be investigated
  – Note that our systemic control might not be good enough to see a benefit from localized treatment such as xrt
  – Radiation oncologists need to determine the best way to treat
    • In pancreas cancer every time they have a negative trial the immediate response is that we gave the radiation wrong.
FUTURE DIRECTIONS

• Despite negative results of gem-ox, we need to consider other possible combination regimens

• We need to assess special molecular cohorts
  – IDH mutations, FGFR fusions, Braf mutations

• Radiation’s effects should be assessed prospectively in R1 resected tumors now, but should not be evaluated in R0 until we have better systemic control
QUESTIONS