ADVANCES IN HEPATOBILIARY CANCERS

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Manchester, UK
OVERVIEW

Advances in hepatobiliary cancers

**Adjuvant chemotherapy** for early-stage biliary tract cancer

New horizons for **advanced biliary tract cancer**
  - chemotherapy
  - radiotherapy
  - targeted therapy

Emerging role of **immunotherapy** in hepatocellular carcinoma
ADJUVANT CHEMOTHERAPY FOR RESECTABLE BTC
SURVIVAL IN BILIARY TRACT CANCER

Surgery is the cornerstone of cure

**Overall prognosis is poor:** 5-year survival 5-15% ¹,²

A minority of patients (<35%) present with resectable disease

Gallbladder cancer mostly curable if found incidentally (less so if presents as symptomatic RUQ mass)

Relapse rates are high

**Aims of adjuvant therapy**

- Loco-regional control
- Prevent systemic relapse
- Improve survival

BILIARY TRACT CANCER

Adjuvant chemotherapy before 2017: no conclusive evidence of benefit

<table>
<thead>
<tr>
<th>One phase III study</th>
<th>Gallbladder cancer: Possible benefit from mitomycin and 5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER studies</td>
<td>Extra-hepatic cholangiocarcinoma: No improvement in survival from XRT</td>
</tr>
<tr>
<td></td>
<td>Intra-hepatic cholangiocarcinoma: Improved survival observed from XRT</td>
</tr>
<tr>
<td></td>
<td>• Median OS 11 vs. 6 months p=0.014</td>
</tr>
<tr>
<td></td>
<td>• HR (adjusted) 0.82; 95% CI, 0.70–0.96</td>
</tr>
<tr>
<td></td>
<td>Gallbladder cancer: Improved survival observed from XRT</td>
</tr>
<tr>
<td></td>
<td>• Median OS 14-15 vs. 8 months (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>• Greatest benefit in T2+/N+ disease</td>
</tr>
<tr>
<td></td>
<td>• Updated 2011 chemo-RT better than chemo alone</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>Overall population: No benefit for adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>• OR 0.74 (95%-CI 0.55 – 1.01, p=0.06)</td>
</tr>
<tr>
<td></td>
<td>• Possible benefit from chemotherapy in LN+ disease</td>
</tr>
<tr>
<td></td>
<td>• Possible benefit from radiotherapy in resection margin-positive disease</td>
</tr>
</tbody>
</table>

# Biliary Tract Cancer

Adjuvant chemotherapy: prospective RCTs in the modern era

<table>
<thead>
<tr>
<th>Study</th>
<th>[clinicaltrials.gov ID]</th>
<th>n</th>
<th>Population</th>
<th>Arms</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRODIGE12: France</td>
<td>[NCT01313377]</td>
<td>190</td>
<td>Cholangio and GB</td>
<td>Observation vs. GemOx</td>
<td>DFS</td>
</tr>
<tr>
<td>BilCap: UK</td>
<td>[NCT00363584]</td>
<td>360</td>
<td>Cholangio and GB</td>
<td>Observation vs. capecitabine</td>
<td>OS</td>
</tr>
<tr>
<td>BCAT Japan</td>
<td>[UMIN000000820]</td>
<td>300</td>
<td>Cholangio</td>
<td>Observation vs. gemcitabine</td>
<td>OS</td>
</tr>
<tr>
<td>ASCOT (JCOG1202): Japan</td>
<td>[UMIN000011688]</td>
<td>350</td>
<td>Cholangio and GB</td>
<td>Observation vs. S1</td>
<td>OS</td>
</tr>
<tr>
<td>ACTICCA-1: Germany</td>
<td>[NCT02170090]</td>
<td>440</td>
<td>Cholangio and GB</td>
<td>Observation vs. CisGem</td>
<td>DFS</td>
</tr>
</tbody>
</table>
BILIARY TRACT CANCER

PRODIGE 12 study

Design

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

GEMOX 85 q2w – 12 cycles
Gemcitabine 1000 mg/m² D1
Oxaliplatin 85 mg/m² D2

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

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

BILIARY TRACT CANCER

PRODIGE 12 study

Relapse-free survival
- Median FU: 46.5 months
- HR=0.88 (95% CI, 0.62–1.25; p=0.47)

<table>
<thead>
<tr>
<th></th>
<th>GEMOX</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median RFS</td>
<td>30.4 months (95% CI: 15.4–43.0)</td>
<td>18.5 months (95% CI: 12.6–38.2)</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>

Edeline J, et al., Presented at ESMO Annual Meeting 2017, abstract LBA29. With permission from Dr Julien Edeline
BILIARY TRACT CANCER

PRODIGE 12 study

Most patients (63%) had N0 disease
Most patients (87%) had undergone R0 resections

Statistical calculations
Hypothesis: Increase median RFS from 18 to 30 months (HR=0.60)

Actual: Increase in RFS from 22 to 30.4 months (HR=0.83)

Ambitious hazard ratio – magnitude not seen in adjuvant studies
Patients in control arm performed better than anticipated

BILIARY TRACT CANCER

2017: BilCap study

Two-arm, open-label, randomised, 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
- Secondary;
  - Relapse free survival
  - Toxicity
  - Quality of life*
  - Health economics

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

Minimised 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

Long term analysis after a minimum 5 year follow-up

Resection

Capecitabine 8 cycles

1:1 randomisation

Primrose JN, et al., ASCO 2017; J Clin Oncol 35, suppl; abstr 4006. With permission from Prof Primrose.
BILIARY TRACT CANCER

2017: BilCap study – Improved recurrence-free survival

Benefit seen in intention-to-treat population and per-protocol analysis population [10 patients excluded in per-protocol analysis from capecitabine arm who did not receive capecitabine]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median RFS (95% CI)</th>
<th>24 months HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>24.6 months (18.9-36.7)</td>
<td>0.76 (0.58-0.99)</td>
</tr>
<tr>
<td>Observation</td>
<td>17.6 months (12.8-27.6)</td>
<td>p=0.039</td>
</tr>
</tbody>
</table>

Primrose JN, et al., ASCO 2017; J Clin Oncol 35, suppl; abstr 4006. With permission from Prof Primrose.
2017: BilCap study – Improved overall survival

Benefit seen in per-protocol analysis population only

**Sensitivity analyses** adjusting for further prognostic factors (nodal status, disease grade, gender) **HR 0.70** (95% CI 0.55–0.91) **p=0.007**

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**Capecitabine as adjuvant improves OS in patients with resected biliary tract cancer from 36 to 51 months and should become standard of care in this setting**

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Primrose JN, et al., ASCO 2017; J Clin Oncol 35, suppl; abstr 4006. With permission from Prof Primrose.
## BILIARY TRACT CANCER

Adjuvant chemotherapy: Prospective RCTs in the modern era

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NEW HORIZONS FOR ADVANCED BTC
Chemotherapy
ADVANCED BILIARY TRACT CANCER

No practice-changing studies since 2010

Best Supportive Care (no chemo)
Median OS 2.5–4.5 months\(^1,2\)

Cisplatin and gemcitabine (CisGem) improves survival (over Gem alone)
ABC-02 (n=410) OS 11.7 months\(^3\)
BT-22 (n=84) OS 11.2 months\(^4\)
Meta-analysis OS 11.6 months\(^5\)

There is an urgent need to improve outcomes

Overall survival\(^5\)
- Gemcitabine alone
- Cisplatin + gemcitabine

Hazard ratio = 0.65
95% CI 0.54–0.78
P<0.001

CHEMOTHERAPY FOR ADVANCED BILIARY TRACT CANCER

New approaches

New agents under evaluation in BTC

Gemcitabine + nab-paclitaxel

- gemcitabine 1000 mg/m² + nab-paclitaxel 125 mg/m² days 1, 8, 15 q28d
- single-arm study
- 6-mo PFS: 60.5%
- response rate: 30.1%
- median PFS: 7.7 months
- median OS: 11.2 months

1. Sahai V, et al., ASCO 2017 (abstr #4072)
CHEMOTHERAPY FOR ADVANCED BILIARY TRACT CANCER

New approaches

New agents under evaluation in BTC\(^1\)

**Acelarín**
- First-in-class nucleotide analogue
- hENT1 independent transport
- No metabolism by cytidine deaminase (reduced toxic metabolites)
- Achieves higher intracellular levels of dFdCTP than gemcitabine\(^2\)

**ABC-08 study\(^2\)**
- Phase IB study: Acelarín and cisplatin in BTC
- Phase III (BI.3) study planned

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1. Blagden SP, *et al.*, J Clin Oncol 33, 2015 (suppl; abstr 2514). With permission from Prof Blagden. 2. ClinicalTrials.gov NCT02351765
CHEMOTHERAPY FOR ADVANCED BILIARY TRACT CANCER

New approaches

New agents under evaluation in BTC

Triple combinations

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<th>Combination</th>
<th>Centre</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFIRINOX</td>
<td>USA (Chicago)</td>
<td>Basket GI study; not tolerable in BTC even with genotype (UGT1A1) dosing and G-CSF</td>
</tr>
<tr>
<td>Gem/5FU/Cis</td>
<td>USA (Ann Arbor)</td>
<td>Single-arm phase II (n=39), pancreas / BTC</td>
</tr>
<tr>
<td>Gem/Cis/S1</td>
<td>Japan (Kyoto)</td>
<td>Phase III (vs. CisGem); n=220</td>
</tr>
<tr>
<td>Gem/Cis/nab-paclitaxel</td>
<td>USA (MDA and Mayo)</td>
<td>Single-arm, phase II; n=61</td>
</tr>
</tbody>
</table>

Dosing schedule

gemcitabine 800mg/m² + cisplatin 25 mg/m² + nab-paclitaxel 100 mg/m²; D1,8 q21d

Promising early data

- median PFS (1° endpoint): 11.8 months
- response rate: 28.8%
- median OS: 18.8 months

Phase III study planned (vs. CisGem)

CHEMOTHERAPY FOR ADVANCED BILIARY TRACT CANCER

New approaches

New agents under evaluation in BTC

Triple combinations

New delivery mechanism

Chemosaturation of the liver with melphalan
Investigational platform
Most data in ocular melanoma
Study in set-up for intrahepatic CCA

ClinicalTrials.gov NCT02415036; Image property of Delcath Systems.© 2015 Delcath Systems, Inc. Available at: http://chemosat.com/about
CHEMOTHERAPY FOR ADVANCED BILIARY TRACT CANCER

New approaches

Systematic review: 14 phase II studies; 9 retrospective studies (n=895 patients)

- No conclusion regarding best approach
- Patients are willing to participate in clinical trials
- PFS correlates better with OS than RR

Eligible patients:
- Histo-/cytologically verified advanced biliary tract cancer (ABC)
- ECOG performance score 0-1
- Received prior cis / gem chemotherapy (1st-line for ABC)
- Adequate haematological, renal and hepatic function

Eligible patients* n=162

Arm A: Active symptom control*
*May include (but not limited to):
- Biliary drainage
- Antibiotics
- Analgesia
- Steroids
- Anti-emetics

Arm B: Active symptom control* + oxaliplatin/5-FU chemotherapy§
§Oxaliplatin 85 mg/m²
- L-folinic acid 175 mg
- 5-FU 400 mg/m² (bolus)
- 5-FU 2400 mg/m² (infusion)
- Every 14 days, for up to 12 cycles

Statistics
HR 0.63 (OS increase from 4 to 6.4 months)
80% power, 5% alpha, two-tailed log-rank test

Follow-up for survival [primary endpoint]

R 1:1

NEW HORIZONS FOR ADVANCED BTC
Radiotherapy
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Lesion</th>
<th>Total dose (Gy)</th>
<th>Fracs</th>
<th>Chemo (CT)</th>
<th>Local control (LC)</th>
<th>Survival</th>
<th>Median OS (mo)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herfarth</td>
<td>3</td>
<td>IHCC</td>
<td>14-26</td>
<td>1</td>
<td>No CT</td>
<td>1y LC:71% 1.5y LC:67%</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
</tr>
<tr>
<td>Tse</td>
<td>10</td>
<td>IHCC</td>
<td>28.2-48</td>
<td>6</td>
<td>N/S</td>
<td>1y LC:65% 1y OS:57%</td>
<td></td>
<td>15</td>
<td>2 biliary stenosis 2 Child A to B change 1 small bowel obstruction</td>
</tr>
<tr>
<td>Goodman</td>
<td>5</td>
<td>IHCC</td>
<td>18-30</td>
<td>1</td>
<td>N/S</td>
<td>1y LC:77% 1YS:71.4% 2YS:53.6%</td>
<td>28.6</td>
<td>No grade III toxicity</td>
<td></td>
</tr>
<tr>
<td>Kopek</td>
<td>27</td>
<td>26 Klatskin 1 IHCC</td>
<td>45</td>
<td>3</td>
<td>No CT</td>
<td>1y LC:84%</td>
<td>N/S</td>
<td>10.6</td>
<td>6 duodenal/pyloric ulcer 2 duodenal stenosis</td>
</tr>
<tr>
<td>Polistina</td>
<td>10</td>
<td>10 Klatskin</td>
<td>30</td>
<td>3</td>
<td>Gemcitabine</td>
<td>Local response ratio:80% 2YS:80% 4YS:30%</td>
<td>35.5</td>
<td>1 duodenal ulcer 2 duodenal stenosis</td>
<td></td>
</tr>
<tr>
<td>Barney</td>
<td>10</td>
<td>(12 lesions)</td>
<td>6 primary 6 recurrent</td>
<td>3 or 5</td>
<td>8 had CT but not specified</td>
<td>Local response ratio:100% 1y OS:31%</td>
<td>N/S</td>
<td>1 biliary stenosis 1 death (liver progression)</td>
<td></td>
</tr>
<tr>
<td>Welling</td>
<td>12</td>
<td>12 Klatskin</td>
<td>50-60</td>
<td>3-5</td>
<td>Capecitabine</td>
<td>CR:1/6 PR:4/6</td>
<td>1y OS:83%</td>
<td>N/S</td>
<td>14 severe adverse events</td>
</tr>
<tr>
<td>Mahadevan</td>
<td>34</td>
<td>(42 lesions)</td>
<td>31 IHCC 11 Klatskin</td>
<td>3 (3-5)</td>
<td>4 Gem 14 GemCis</td>
<td>1y:88% 4y:79% 1y OS:58%</td>
<td>17</td>
<td>12% Grade III, 2 duodenal obstruction, 2 infection</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Mahadevan A, et al., 2015 J Cancer 6(11):1099-104.
Eligible patients
n=72
- Histo-/cytologically verified locally-advanced BTC not suitable for surgery
- WHO PS 0-1
- Tumour must be ≤ 12 cm (longest dimension)

For full eligibility criteria, see protocol

CisGem
X 6 cycles
- Cis 25 mg/m² + Gem 1000 mg/m²
- On Days 1 and 8 of a 28 day cycle

CT scan after Cycle 4
SD or PR
PD: Off protocol treatment

R
1:2

CisGem x 2 cycles
- Cis 25 mg/m² + Gem 1000 mg/m²
- On Days 1 and 8 of a 28 day cycle

SBRT
- 50, 45 or 40 Gy delivered in 5 fractions over 5-15 days

Hypothesis: Local control (LC) using SBRT is comparable to surgery

Study design: Phase II with two stages
1. Feasibility of delivering SBRT in a multicentre setting in a rare disease
2. SBRT phase II single arm looking at a LC* of 70-85% at 12 months *in radiotherapy field LC

Primary endpoints
- Feasibility (recruit 1 patient/month)
- PFS @ 1 year

Status: Open, recruiting
PROTON BEAM THERAPY: PHASE 2 STUDY

Single-arm, phase II
- Patients with unresectable, biopsy-confirmed HCC (n=44) or ICC (n=39)
- Child-Turcotte-Pugh score of A or B
- ECOG PS 0-2
- No extrahepatic disease
- No prior radiation

15 fractions of proton therapy
- Max total dose of 67.5 Gy equivalent
- Obtain acceptable precision for estimating outcomes for ICC
- Median size of ICC 6 cm (range 2–11 cm)

ICC (n=39)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>8.4 months (95% CI 5.0-15.7)</td>
</tr>
<tr>
<td>OS</td>
<td>22.5 months (95% CI 12.4-49.7)</td>
</tr>
<tr>
<td>Local control rate at 2 years</td>
<td>94%</td>
</tr>
<tr>
<td>Overall 2 year survival rate</td>
<td>47%</td>
</tr>
</tbody>
</table>
PROTON BEAM THERAPY

Toxicity and future direction

<table>
<thead>
<tr>
<th>System/Condition</th>
<th>Any Grade</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/bone marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Platelets</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td>Cardiac general</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td>65 (54)</td>
<td></td>
</tr>
<tr>
<td>Dermatology/skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>12 (10)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>61 (51)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>25 (17)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Ascites (nonmalignant)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (25)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Ulcer, GI - stomach</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20 (18)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage/bleeding</td>
<td>Any</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Metabolic/laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (hyperbilirubinemia)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (8)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal/soft tissue</td>
<td>Any</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Neurology</td>
<td>Any</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-abdomen NOS</td>
<td>22 (19)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13 (11)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary/upper respiratory</td>
<td>Any</td>
<td>5 (4)</td>
</tr>
</tbody>
</table>

NCT02200042
Patients with localised unresectable ICC will receive Gem/Cis chemotherapy + 15-fraction radiation schedule (with photons or protons) or continuing chemotherapy alone.

NEW HORIZONS FOR ADVANCED BTC
Targeted therapy
TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER

EGFR inhibition: 4 negative randomised-controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens</th>
<th>Phase</th>
<th>RR (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemo alone</td>
<td>With biologic</td>
<td>Chemo alone</td>
</tr>
<tr>
<td>Malka¹</td>
<td>GemOx +/- cetuximab</td>
<td>2</td>
<td>23</td>
<td>23</td>
<td>5.5</td>
</tr>
<tr>
<td>Chen²</td>
<td>GemOx +/- cetuximab</td>
<td>2</td>
<td>15</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>Lee³</td>
<td>GemOx +/- erlotinib</td>
<td>3</td>
<td>16</td>
<td>30</td>
<td>4.2</td>
</tr>
<tr>
<td>Leone⁴</td>
<td>Gem/Ox +/- panitumumab</td>
<td>2</td>
<td>18</td>
<td>27</td>
<td>4.4</td>
</tr>
<tr>
<td>ABC-02⁵</td>
<td>CisGem (for reference)</td>
<td>26</td>
<td>8.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER

VEGF inhibition: two randomised studies

**Addition of sorafenib to gemcitabine**

Randomised phase II
N=102

- no improvement in PFS: 3.0 vs. 4.9 mo p=0.859
- no improvement in OS: 8.4 vs. 11.2 mo, p=0.775
- similar response rates: 14% vs. 10%

“treatment duration was not only shortened for sorafenib, but also fewer dose adjustments and treatment interruptions occurred in the placebo group”

**Addition of cediranib to CisGem**

Randomised phase II
N=124

- improved response rates: 44% vs. 19%, p=0.004
- improved 6-mo PFS: 71% vs. 61%
- no improvement in mPFS: 8.0 vs. 7.4 mo p=0.72
- no improvement in mOS: 14.1 vs. 11.9 mo, p=0.44
- median time on cediranib 4.6 months
- do we need a better-tolerated VEGF inhibitor?

**ramucirumab** being tested in randomised phase II study

TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER
Improving our understanding of the genetic environment of BTC

Intrahepatic cholangiocarcinoma CCA has a different profile to extrahepatic CCA or GBC\(^1,2\)

*Opisthorchis viverrini* (liver-fluke)*- associated CCA (TP53 mutations) is different from non-liver fluke associated CCA (BAP1, IDH1 and IDH2 mutations)\(^3\)

Inflammatory subclass is different from proliferative subclass\(^4\)

<table>
<thead>
<tr>
<th></th>
<th>IHCCA</th>
<th>EHCCA</th>
<th>GBCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GA/patient</td>
<td>2.9</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>CRGA/patient</td>
<td>1.1</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>ERBB2 amplification</td>
<td>3%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>BRAF substitutions</td>
<td>5%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>KRAS substitutions</td>
<td>22%</td>
<td>42%</td>
<td>11%</td>
</tr>
<tr>
<td>PI3KCA substitutions</td>
<td>5%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>FGFRI-3 fusion and amplifications</td>
<td>11%</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>CDKN2A/B loss</td>
<td>18%</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>IDHI/2 substitutions</td>
<td>20%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ARIDIA alterations</td>
<td>17%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>MET amplification</td>
<td>4%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table adapted from\(^1\)

---

\(*)\ An infection linked to an increased cancer risk, mediated by oncogenic and potentially targetable mutations

TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER

Improving our understanding of the genetic environment of BTC

Up to 70% of IH-CCA patients have an actionable mutation

IDH-1 mutations and FGFR fusion rearrangements have emerged as potential therapeutic targets

TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER

Isocitrate dehydrogenase (IDH)-1 mutations

Krebs cycle or tricarboxylic acid (TCA) cycle

IDH exists as 3 isoforms
IDH1 and 2 have cancer-associated mutations that happen early in tumour development
These mutations result in novel gain-of-function enzyme activity, which
- block normal cell differentiation
- promotes tumourigenesis

2-HG; 2-hydroxyglutarate, αKG; α-ketoglutarate.
TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER
IDH1 mutations identified in a variety of solid tumour types

2008
IDH1 mutations identified in glioblastoma

2009
Germline IDH2 mutations identified in D2HG aciduria

2010
IDH1 and IDH2 mutations identified in AML
IDH mutations identified in chondrosarcomas

2011
D2HG found to inhibit TET2 and affect DNA methylation

2012
Production of D2HG by mutant IDH enzymes discovered

2013
20% Intra-hepatic CC
First small-molecule inhibitors of mutant IDH enzyme activity developed

Reprinted from Cancer Discovery 2013;3(7):730–41, Cairns RA, Mak TW, Oncogenic Isocitrate Dehydrogenase Mutations: Mechanisms, Models, and Clinical Opportunities, with permission from AACR
TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER
IDH1 mutations identified in a variety of solid tumour types

Phase I study: cholangiocarcinoma (CCA), chondrosarcoma, glioma, others [NCT02073994]

CCA cohort: n=73 [dose escalation (n=24); dose-expansion 500 mg QD (n=49)]

No DLTs; drug-related AEs: fatigue, nausea, diarrhoea, vomiting

Activity: median PFS 3.8 months
   6-month PFS: 38.5%
   12-month PFS: 20.7%
   RR 5% (4 PRs)
   OS data not mature

Phase III study, second-line, placebo-controlled (ClarIDHy) [NCT02989857]

AG-120 is a first-in-class, potent, oral inhibitor of the mutant IDH1 enzyme

1. Lowery MA, et al., ASCO 2017 J Clin Oncol 2017; 35 (suppl; abstr 4015);
2. Lowery MA, et al., ASCO 2017 J Clin Oncol 2017;35 (suppl; abstr TPS4142)
TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER

FGRF as a potential target in intrahepatic CCA

## Targeted Therapy for Advanced Biliary Tract Cancer

FGRF as a potential target in intrahepatic CCA

<table>
<thead>
<tr>
<th>FGFR2</th>
<th>Fusion Partner</th>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BICC1</td>
<td>Wu 2013</td>
<td>2 reported cases of FGFR2-BICC1</td>
</tr>
<tr>
<td></td>
<td>TACC3</td>
<td>Borad 2014</td>
<td>3 reported cases of FGFR2-BICC1, FGFR2-TACC3, FGFR2-MGEA5 (3/6)</td>
</tr>
<tr>
<td></td>
<td>KIAA1598</td>
<td>Arai 2013</td>
<td>Translocations occur in 13.6% of 9/66 IHCCs reported FGFR2-AHCYL1, FGFR2-BICC1</td>
</tr>
<tr>
<td></td>
<td>MGEA5</td>
<td>Ross 2014</td>
<td>FGFR2-KIAA1598, FGFR2-BICC1, FGFR2-TACC3 (3/28 samples)</td>
</tr>
<tr>
<td></td>
<td>AHCYL1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPHLN1</td>
<td>Sia 2015</td>
<td>Translocations occur in ~45% of IHCCs FGFR2-PPHLN1 (16%)</td>
</tr>
</tbody>
</table>
TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER

FGRF as a potential target in intrahepatic CCA

FGFR dysregulation is associated with favourable prognosis

Javle MM, et al., 2016 ASCO J Clin Oncol 34, 2016 (suppl; abstr 109) With permission from Prof Javle
TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER
BJG398 Phase II trial

Key inclusion criteria
• Advanced or metastatic CC
• FGFR2 fusion or other genetic alterations in FGFR
• Progression following prior cytotoxic therapy

BGJ398 125 mg daily
Days 1–21, every 28 days
Treatment until disease progression, unacceptable toxicity, withdrawal of informed consent, or death

Primary endpoint | RR (RECIST v1.1)
Secondary endpoints | PFS, OS, best overall response (BOR), disease control rate (DCR), safety, and pharmacokinetics.

• 61 patients treated
• Majority of patients had ≥2 prior therapies and 11% had at ≥4 prior regimens
• FGFR2 fusions/rearrangements were present in 48 patients
• Other FGFR genetic alterations were present in 9 patients;
  – FGFR2 mutations (n=8)
  – FGFR2 amplifications (n=3)
  – FGFR3 amplifications (n=4)

TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER

BJG398 Phase II trial

Median duration of exposure was 4.7 months

All 9 patients with a partial response had an FGFR2 fusion

All patients (n=61):
- RR 14.7%
- DCR 75.4%
- mPFS 5.8 months

Patients with FGFR fusions (n=48)
- RR 18.8%
- DCR 83.3%

Commonest AEs:
Hyperphosphataemia, fatigue, stomatitis, alopecia

**All 9 patients with a partial response had an FGFR2 fusion**

TARGETED THERAPY FOR ADVANCED BILIARY TRACT CANCER

Valle JW, et al., Cancer Discovery 2017;7(9):943–62
EMERGING ROLE OF IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA
HEPATOCELLULAR CARCINOMA

The need for novel therapies

HCC is the 3rd most common cause of cancer death worldwide

Sorafenib has been the systemic standard of care for patients with advanced HCC

Further treatment options have demonstrated activity in randomised clinical trials

- Regorafenib [post sorafenib failure] - approved
- Lenvatinib [first-line; non-inferior to sorafenib]
- Ramucirumab [post sorafenib failure, in AFP >400 population – phase III ongoing]

Preclinical evidence to suggest that HCC may be responsive to immune modulation

Approaches include targeting CTLA-4 and/or PD-1/PD-L1 or both
EVOLVING THERAPEUTIC LANDSCAPE OF HCC

TREMELIMUMAB (ANTI-CTLA4)

Phase II, open-label

**Tremelimumab 15 mg/kg IV q90d**

Treatment until PD or toxicity

Patients with HCC and chronic Hep-C infection

Endpoints: **response rate** (≥3/17 with additional 4 patients for non-evaluable patients); **safety** (in cirrhosis)

---

**TREMELIMUMAB** (ANTI-CTLA4)

### Efficacy

- **Response Rate 3/17 (17.6%), all PR**
  - SD 10/17 (58.8%), 45% lasting >6 months
  - AFP response: 36% showed >50% reduction
  - TTP 6.5 months (95% CI 3.95–9.14)
  - OS 8.2 months (95% CI 4.64–21.34)
  - AFP decrease (by >50%) in 36% of patients with baseline >100 ng/mL
  - Tremelimumab also induced a decrease in viral load

### Safety

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Grade</th>
<th>Most likely cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>All N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>13 (65)</td>
<td>1 (5) Treatment</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (55)</td>
<td>0 Treatment</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10 (50)</td>
<td>0 Cirrhosis</td>
</tr>
<tr>
<td>Edema</td>
<td>7 (35)</td>
<td>0 Cirrhosis</td>
</tr>
<tr>
<td>Ascites</td>
<td>7 (35)</td>
<td>0 Cirrhosis</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (30)</td>
<td>1 (5) Treatment</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>6 (30)</td>
<td>0 Others</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>5 (25)</td>
<td>3 (15) Cirrhosis</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3 (15)</td>
<td>2 (10) Cirrhosis</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (15)</td>
<td>2 (10) Treatment</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (15)</td>
<td>0 Treatment</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (10)</td>
<td>0 Treatment</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (10)</td>
<td>0 Others</td>
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<tr>
<td>Diverticulitis</td>
<td>1 (5)</td>
<td>1 (5) Treatment</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (5)</td>
<td>1 (5) Treatment</td>
</tr>
<tr>
<td>Alopecia</td>
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<td>0 Treatment</td>
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<tr>
<td>Hypothyroidism</td>
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<td>0 Others</td>
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<tr>
<td>Arthritis</td>
<td>1 (5)</td>
<td>0 Treatment</td>
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<tr>
<td>Pleural effusion</td>
<td>1 (5)</td>
<td>0 Treatment</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>1 (5)</td>
<td>1 (5) Cirrhosis</td>
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<tr>
<td>Cholangitis</td>
<td>1 (5)</td>
<td>1 (5) Others</td>
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<tr>
<td>Pneumonia</td>
<td>1 (5)</td>
<td>1 (5) Others</td>
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<tr>
<td>Ophthalmic zoster</td>
<td>1 (5)</td>
<td>0 Others</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>1 (5)</td>
<td>0 Others</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Grade</th>
<th>Most likely cause</th>
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<td>All N (%)</td>
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<tr>
<td>Hypoalbuminemia</td>
<td>15 (75)</td>
<td>1 (5) Cirrhosis</td>
</tr>
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<td>AST</td>
<td>14 (70)</td>
<td>9 (45) Treatment</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>13 (65)</td>
<td>6 (30) Cirrhosis</td>
</tr>
<tr>
<td>ALT</td>
<td>11 (55)</td>
<td>5 (25) Treatment</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (45)</td>
<td>0 Cirrhosis</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>7 (35)</td>
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<td>Thrombocytopenia</td>
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<td>1 (5) Cirrhosis</td>
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<td>Neutropenia</td>
<td>4 (20)</td>
<td>1 (5) Treatment</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>4 (20)</td>
<td>0 Cirrhosis</td>
</tr>
</tbody>
</table>

*Only changes in CTCAE grade from baseline are considered an AE.*

NIVOLUMAB (ANTI PD-1)

Phase I/II open-label study (Checkmate 040)

Child-Pugh ≤B7 (dose escalation); ≤A6 (dose expansion)
PS 0-1
Treated Hep B (antiviral and viral load <100 IU/ml)
Antiviral therapy not required for HepC

Primary endpoint
Response rate

Reprinted from The Lancet, El-Khoueiry AB, et al., 389(1088), Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. 2492–502. , Copyright 2017, with permission from Elsevier.
NIVOLUMAB (ANTI PD-1)

Phase I/II open-label study (Checkmate 040)

Efficacy data for expansion-phase patients

<table>
<thead>
<tr>
<th></th>
<th>All patients N=214</th>
<th>PD-L1 ≥1% N=34 (20%)</th>
<th>PD-L1 &lt;1% N=140 (80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3 (1%)</td>
<td>1 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>PR</td>
<td>39 (18%)</td>
<td>8 (24%)</td>
<td>24 (17%)</td>
</tr>
<tr>
<td>RR</td>
<td>42 (20%) 95%-CI 15-26%</td>
<td>9 (26%) 95%-CI 13-44%</td>
<td>26 (19%) 95%-CI 13-26%</td>
</tr>
<tr>
<td>SD</td>
<td>96 (45%)</td>
<td>16 (47%)</td>
<td>62 (44%)</td>
</tr>
<tr>
<td>DCR</td>
<td>138 (64%)</td>
<td>25 (74%)</td>
<td>88 (63%)</td>
</tr>
</tbody>
</table>

Median OS for patients (dose-escalation phase) was 15.0 months (95% CI, 9.6–20.2)

NIVOLUMAB (ANTIPD-1)

Phase I/II open-label study (Checkmate 040)

Response by disease cohort

Reprinted from The Lancet, El-Khoueiry AB, et al., 389(1088), Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. 2492–502. © Copyright 2017, with permission from Elsevier.
IMPORTANT RCTS AWAITED

Check-Mate 459 – first-line
- Advanced HCC
- Progression post surgery or locoregional Rx
- Child-Pugh A

Nivolumab
- Primary endpoint: TTP, OS
- Secondary endpoints: RR, PFS, biomarkers
- n=726

Sorafenib

KEYNOTE 240 – second-line
- Advanced HCC (BCLC B or C)
- Not amenable/refractory to locoregional Rx
- Untreated HCV or >4 weeks of successful HCV Rx
- No systemic therapy other than sorafenib
- Child-Pugh A

Pembrolizumab + BSC
- Primary endpoint: PFS, OS
- Secondary endpoints: RR, DCR, TTP, DoR
- n=408

Placebo + BSC
SUMMARY

- Capecitabine has emerged as an adjuvant chemotherapy for biliary tract cancer.
- Cisplatin and gemcitabine remains the reference regimen for advanced biliary tract cancer.
- New chemotherapy options under investigation include new agents (nab-paclitaxel, acelarin), new combinations and delivery mechanisms; their role remains to be validated.
- The effect of targeting specific mutations (IDH-1 and FGFR fusion rearrangement) is under investigation.
- Immunotherapy is emerging as an exciting modality for advanced HCC; the results of pivotal studies in first- and second-line are awaited.
THANK YOU!