Systemic Therapy for Cholangiocarcinoma

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Discussion Points

- Current standard of care for systemic therapy in cholangiocarcinoma
- Current landscape of clinical trials in cholangiocarcinoma
- Novel targets in cholangiocarcinoma
Biliary tract cancer | Subtypes

- BTCs represent a rare and heterogeneous group of cancers with different biology and clinical behavior.
Intrahepatic cholangiocarcinoma is increasing in incidence

Cholangiocarcinoma is the most common cause of carcinoma of unknown primary

Saha, Zhu, Fuchs, Brooks, SEER 9 data, Oncologist, 2016

Hainsworth, JD, et al. JCO, 2013
Treatment of BTCs

• Surgical resection: the only potentially curative regimen
• No definitive benefit for adjuvant chemo, radiation or chemoradiation therapy
• For unresectable cancer:
  – Decompression of obstructive biliary tree: important palliative regimen
  – Consideration of local-regional therapy
  – Systemic chemotherapy
  – Best supportive care
Adjuvant therapy in the treatment of BTCs

Meta-analysis:

- 6,712 patients analyzed
- There was a nonsignificant improvement in OS with any adjuvant therapy compared with surgery alone (pooled OR, 0.74; P = .06)
- Those receiving chemo or chemoradiation derived statistically greater benefit than radiation alone (OR, 0.39, 0.61, and 0.98, respectively; P = .02).
- The greatest benefit for AT was in those with LN-positive disease (OR, 0.49; P = .004) and R1 disease (OR, 0.36; P = .002).

Ongoing randomized phase III adjuvant trials:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Targeted disease stage</th>
<th>Countries</th>
<th>Clinicaltrials.gov ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>capecitabine vs. observation</td>
<td>Resected-adjuvant</td>
<td>United Kingdom</td>
<td>NCT00363584</td>
</tr>
<tr>
<td>gemcitabine/oxaliplatin vs.</td>
<td>Resected-adjuvant</td>
<td>France</td>
<td>NCT01313377</td>
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<td>observation</td>
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<tr>
<td>gemcitabine/cisplatin vs.</td>
<td>Resected-adjuvant</td>
<td>Germany</td>
<td>NCT02170090</td>
</tr>
<tr>
<td>observation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Level 1 evidence: Cisplatin + Gemcitabine

![Graphs showing progression-free survival (PFS) and overall survival (OS) for Gem and CisGem treatments.](image)

- HR = 0.63, 95% CI 0.51-0.77, P<0.001
- HR = 0.64, 95% CI 0.52-0.80, P<0.001

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC-02</td>
<td>Valle <em>NEJM</em> 2010</td>
<td>5.0</td>
<td>8.0</td>
</tr>
<tr>
<td>BT-22</td>
<td>Okusaka <em>BJC</em> 2010</td>
<td>3.7</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Unanswered Questions from ABC-2 Study

• Is Gem/Cis the only acceptable doublet? How about GEMOX, Gem/capecitabine?

• Is the benefit similar across all BTC tumor types?

• What predicts the response to this regimen?

• How can we improve the outcomes beyond this?
Second Line Treatment for Advanced BTCs

Large retrospective study from Princess Margaret Hospital:
- 378 received fist line chemo and 96 (25%) received 2\textsuperscript{nd} chemo
- RR and SD for 2\textsuperscript{nd} line chemo: 9% and 34%, respectively
- PFS and OS for 2\textsuperscript{nd} line chemo: 2.8 m and 7.5 m respectively

Systemic review:
- 761 patients in 14 phase II trials, 9 retrospective analysis, 2 case
- The mean OS was 7.2 months (95% CI: 6.2-8.2)
- The mean PFS, RR and DCR were 3.2 months (95% CI 2.7-3.7), 7.7% (95% CI 4.6-10.9) and 49.5% (95% CI 41.4-57.7), respectively.

Phase III trial (ABC-06): FOLFOX+active symptom control vs. active symptom control alone

Walter T et al, Eur J Cancer 2013
Lamarca A et al, Ann Oncol 2014
Therapeutic Targeting of the Hallmarks of Cancer

Hanahan and Weinberg, Cell, 2011
Phase II study with GEMOX-Bevacizumab in advanced BTCs

35 patients treated
RR: 40%, SD: 29%
PFS: 7.0 months (95% CI, 5.3–10.3 months)
Median OS: 12.7 months (95% CI, 7.3–18.1 months)

ABC-03: A randomized phase II trial of cediranib or placebo in combination with cisplatin/gemcitabine (CisGem) in advanced BTCs

Chemo-naive advanced biliary tract cancers (n=124)

Primary endpoint: PFS
Secondary endpoints: RR, OS, toxicity, QOL, biomarkers, cost effectiveness analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Gem/Cis + Cediranib (n=62)</th>
<th>Gem/Cis (n=62)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, mths</td>
<td>8</td>
<td>7.4</td>
<td>0.93 (0.65-1.35)</td>
<td>0.72</td>
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<tr>
<td>OS, mths</td>
<td>14.1</td>
<td>11.9</td>
<td>0.86 (0.58-1.27)</td>
<td>0.44</td>
</tr>
<tr>
<td>ORR, %</td>
<td>44</td>
<td>19</td>
<td></td>
<td>0.0036</td>
</tr>
</tbody>
</table>

Cisplatin 25 mg/m² + Gemcitabine 1000 mg/m² Day 1 & 8 every 21 days + Cediranib 20 mg OD

Cisplatin 25 mg/m² + Gemcitabine 1000 mg/m² Day 1 & 8 every 21 days + Placebo 20 mg OD

A multicenter phase II trial of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer

- 53 patients enrolled and 49 evaluable
- Six (12%; 95% CI, 6% to 27%) had a confirmed partial response and 25 patients (51%) had SD
- Median OS was 9.9 months, and TTP was 4.4 months
- Rash was the most common grade 3 toxicity

Lubner SJ et al, J Clin Oncol. 2010
# EGFR inhibition: 3 negative randomized studies

<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>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemo alone</td>
<td>With biological</td>
<td>Chemo alone</td>
</tr>
<tr>
<td>Malka¹</td>
<td>GemOx +/- cetuximab</td>
<td>2</td>
<td>23</td>
<td>5.5</td>
<td>12.4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>23</td>
<td>6.1</td>
<td>11.0</td>
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<tr>
<td>Chen²</td>
<td>GemOx +/- cetuximab</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>8.8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td>7.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Lee³</td>
<td>GemOx +/- erlotinib</td>
<td>3</td>
<td>16</td>
<td>4.2</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>5.8</td>
<td>9.5</td>
</tr>
<tr>
<td>ABC-02⁴</td>
<td>CisGem (for reference)</td>
<td>26</td>
<td>8.0</td>
<td>11.7</td>
<td></td>
</tr>
</tbody>
</table>

Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer

RR 45%, Median PFS 10.6m, Median OS 20.3m

A randomized phase 2 trial (Vecti-BIL study)-negative  
Phase II Study of Selumetinib in Metastatic BTCs

- 28 pts treated: 39% had one prior systemic chemo
- Clinical outcome: RR 12%, SD (67%), PFS 3.7 months, OS 9.8 months
- Rash (90%) and xerostomia (54%)
- No BRAF V600E mutations were found
- Absence of pERK staining was associated with lack of response

Bekaii-Saab T et al, J Clin Oncol., 2011
Molecular Genetics of BTC

Nakamura et al, Nature Genetics, 2015
SNaPshot Mutational Profile by Gastrointestinal Organ

- Hepatocellular: n=16
- Biliary Tract: n=12
- Gastroesophageal: n=32
- Pancreatic: n=43
- Colorectal: n=184

- None Identified
- AKT1
- APC
- BRAF
- CTNNB1
- IDH1
- KRAS
- NRAS
- PIK3CA
- PTEN
- TP53

http://www.pfizerpro.com/resources/minisites/oncology/img/digestiveTract.jpg
IDH1 and IDH2 Mutations Specifically in Intrahepatic Cholangiocarcinomas

Intrahepatic CC  (n=40)
Extrahepatic CC  (n=22)

Borger et al, The Oncologist, 2011

IDH mutations found in 10-35% of ICC

Desphande *BMC Cancer* 2011
Borger *The Oncologist* 2012
Voss *Human Pathology* 2013
Sia *Gastroenterology* 2013
Ross *The Oncologist* 2014
Jiao *Nature Genetics* 2013
Chan-on *Nature Genetics* 2013
Wang *Oncogene* 2012
Riener *Genes Chromosomes Cancer* 2008
Wu *Cancer Discovery* 2013
Graham *Human Pathology* 2014
Arai *Hepatology* 2014
Sia *Nature Communications* 2015
Metabolic Gain-of-Function Activity of Mutant IDH1 in Cancer

Adapted from Lu, C., Thompson, CB. Cell Metabolism, 2012
Mutant IDH cooperates with $\text{Kras}^{\text{G12D}}$ to drive ICC pathogenesis

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Pathological Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH$^{\text{R172K}}$</td>
<td>Oval cell expansion</td>
</tr>
<tr>
<td>Kras$^{\text{G12D}}$</td>
<td>BillN I</td>
</tr>
<tr>
<td>IDH$^{\text{R172K}}$;Kras$^{\text{G12D}}$</td>
<td>BillN II</td>
</tr>
<tr>
<td>IDH$^{\text{R172K}}$;Kras$^{\text{G12D}}$</td>
<td>BillN III</td>
</tr>
</tbody>
</table>

**Image:**
- **Survival Graph:**
  - Control ($N = 7$)
  - IDH$^{\text{R172K}}$ ($N = 7$)
  - Kras$^{\text{G12D}}$ ($N = 7$)
  - IDH$^{\text{R172K}}$;Kras$^{\text{G12D}}$ ($N = 6$)

  *$P < 0.0005$*

**Diagram:**
- WT: Quiescent hepatocyte → Recovery → HNF-4α → Progenitor cell
- IDH mutant: Quiescent hepatocyte → HNF-4α → Progenitor cell → IDH mutant Progenitor cell → 2HG → Oval cell expansion → BillN → IHCC

MGH IHCC cell line/PDX protocol

1. IHCC resection
2. Implant
3. Patient-derived xenograft (PDX)
4. Digest & Culture
5. IHCC Cell line
6. Re-Implant
7. Confirm cell line Tumorigenicity

Primary IHCC → PDX → Cell line-derived Tumor
Combination drug screens in genetically-defined ICC cell lines

- multi-well 3D ICC arrays
- Add drug combinations
- Fluorescence imaging
- Rapid screening for cytotoxic and cytostatic effects
- Matrices of size-dependent response and drug-induced architectural changes
- High-content batch processing of image data.
Mutant IDH ICC lines are highly sensitive to dasatinib

*Saha et al, Cancer Discovery 2016*
Phase II trial of dasatinib in patients with isocitrate dehydrogenase (IDH)-mutant advanced intrahepatic cholangiocarcinoma

- Advanced ICC
- \textit{IDH1} or \textit{IDH2} mutations
- ECOG PS 0-1
- Good organ functions
- Dasatinib at 100 mg daily continuously
- Two stage design
- NCT02428855
Phase I Study of AG-120, a First-in-Class, Potent Inhibitor of the IDH1 Mutant Protein, in Patients with Advanced IDH1-Mutant Solid Tumors

Single-arm, dose escalation, 3+3 study (ClinicalTrials.gov NCT02073994)

Key objectives:
- Safety and tolerability
- Identify the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)
- Characterize pharmacokinetics, evaluate the pharmacokinetic/pharmacodynamic (PK/PD) relationship (2-HG)
- Characterize preliminary clinical activity

Population:
- Subjects with advanced solid tumors with an IDH1 mutation

Treatment:
- Single-agent AG-120 administered continuously, oral dosing once (QD) or twice (BID) daily in 28-day cycles
- Eight dose levels explored: 100 mg BID, and 300, 400, 500, 600, 800, 900 and 1200 mg QD

Tumor assessments:
- RECIST v1.1 criteria for solid tumors other than glioma
- RANO criteria for glioma

RECIST, response evaluation criteria in solid tumors; RANO, response assessment in neuro-oncology

Burris et al, AACR-NCI-EORTC Annual Meeting 2015
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total treated N=62</th>
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<tbody>
<tr>
<td>Median age, years (range)</td>
<td>56 (23–88)</td>
</tr>
<tr>
<td>ECOG status at baseline, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (34)</td>
</tr>
<tr>
<td>1</td>
<td>41 (66)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>29/33</td>
</tr>
<tr>
<td>Tumor types, n (%)</td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>25 (40)</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Glioma</td>
<td>20 (32)</td>
</tr>
<tr>
<td>Grade I-II</td>
<td>9</td>
</tr>
<tr>
<td>Grade III-IV</td>
<td>11</td>
</tr>
<tr>
<td>Other*</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Median prior lines of therapy, n (range)</td>
<td>3 (1–6)</td>
</tr>
</tbody>
</table>

*Colitis-associated, neuroendocrine, adenocarcinoma, small intestine, and ovarian cancers*
Most Frequent Adverse Events
(In ≥10% of Patients, Regardless of Relationship) N=62

• AG-120 well tolerated to date in this patient population

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grades, n (%)</th>
<th>Grade ≥3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients experiencing ≥1 AE</td>
<td>55 (89)</td>
<td>21 (34)</td>
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<tr>
<td>Most frequent AEs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (26)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (16)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (16)</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (15)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>9 (15)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (13)</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (11)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7 (11)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Ascites</td>
<td>6 (10)</td>
<td>1 (2)</td>
</tr>
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</tbody>
</table>
*Other Grade ≥3 events in ≥2 patients: hypophosphatemia 2 (3%), hyponatraemia 2 (3%)*
PK/PD Supports 500 mg PO QD Dose for Expansion

Pharmacokinetics

• High plasma AG-120 exposure, above projected efficacious level
• Long half life (71.4 ± 63.4 hr)
• Non-dose-proportional increases in plasma exposure above 500 mg QD

Pharmacodynamics

• 2-HG inhibition is observed
• Plasma 2-HG reduced to levels seen in healthy volunteers (up to 98% inhibition)
## Best Overall Response

(Efficacy Evaluable Subjects\(^1\))

<table>
<thead>
<tr>
<th></th>
<th>Chondrosarcoma n = 11</th>
<th>Cholangiocarcinoma n = 20</th>
<th>Glioma n = 20</th>
<th>Other n = 4</th>
<th>Total N = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td>1 (5)</td>
<td>-</td>
<td>-</td>
<td>1 (2)</td>
</tr>
<tr>
<td>SD</td>
<td>7 (64)</td>
<td>11 (55)</td>
<td>10 (50)</td>
<td>1 (25)</td>
<td>29 (53)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (18)</td>
<td>6 (30)</td>
<td>10 (50)</td>
<td>3 (75)</td>
<td>21 (38)</td>
</tr>
<tr>
<td>UNK/Not Assessed</td>
<td>2 (18)</td>
<td>2 (10)</td>
<td>-</td>
<td>-</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Clinical Benefit Rate at Month 6(^2), n/N (%)</td>
<td>5/9 (56)</td>
<td>6/14 (43)</td>
<td>4/16 (25)</td>
<td>0/2</td>
<td>15/41 (37)</td>
</tr>
</tbody>
</table>

Glioma response assessments are based on RANO criteria; non-glioma are based on RECIST v1.1 criteria

Complete responses (CR) not observed

PR, partial response; SD, stable disease; PD, progressive disease; UNK, unknown

\(^1\)Includes subjects who had baseline and at least one post baseline tumor assessment or discontinued prematurely

\(^2\)Defined as CR/PR/SD; among subjects whose treatment started at least 6 months prior to the data cut-off date of 3 Sep 2015
Duration on Treatment: Non-Glioma Solid Tumors

All 42 treated patients as of data cut-off 3 Sep 2015

PR, partial response; SD, stable disease; PD, progressive disease; UNK/NA, unknown/not assessed
FGFR2 translocations in Intrahepatic Cholangiocarcinoma

References

Wu Cancer Discovery 2013
2 reported cases of FGFR2-BICC1

Borad PLoS Genetics 2014
3 reported cases of FGFR2-BICC1, FGFR2-TACC3, FGFR2-MGEA5 (3/6)

Arai Hepatology 2013
translocations occur in 13.6% of 9/66 IHCCs
reported FGFR2-AHCYL1, FGFR2-BICC1

Ross Oncologist 2014
FGFR2-KIAA1598, FGFR2-BICC1, FGFR2-TACC3 (3/28 samples)

Sia Nat Commun 2015
Translocations occur in ~45% of IHCCs
FGFR2-PPHLN1 (16%)
Phase II BGJ in cholangiocarcinoma
Best Percentage Change From Baseline in the Size of Target Lesions With BGJ398 Treatment (n=34)

- Two patients were not included in the analysis (best percentage change could not be calculated because the scan modality changed [n = 1], patient had no postbaseline scan due to treatment discontinuation [n = 1]).
- Patients marked with an asterisk had FGFR2 mutations (n = 2) or amplification (n = 3), or FGFR3 amplification (n = 1). All other patients had FGFR2 fusions (n = 28).

Javle et al, GI ASCO Symposium 2016
Prolonged Duration of Exposure to BGJ398 (N=47)

Best Overall Response
- cPR
- uPR (pending confirmatory scan)
- uPR (confirmatory scan performed too early; patient discontinued treatment)
- uPR (response was followed by a PD assessment)

Duration of exposure, days

Patients

cPR, confirmed partial response; uPR, unconfirmed partial response.

* Data cutoff, November 4, 2015.
Ongoing targeted trials in cholangiocarcinoma

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Phase</th>
<th>Line of treatment</th>
<th>NCT number</th>
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<tbody>
<tr>
<td>IDH1</td>
<td>AG-120</td>
<td>I</td>
<td>2nd &amp; beyond</td>
<td>NCT02073994</td>
</tr>
<tr>
<td></td>
<td>IDH305</td>
<td>I</td>
<td>2nd &amp; beyond</td>
<td>NCT02381886</td>
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<tr>
<td>IDH2</td>
<td>AG-221</td>
<td>I/II</td>
<td>2nd &amp; beyond</td>
<td>NCT02273739</td>
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<td></td>
<td>BAY1187982</td>
<td>I</td>
<td>2nd &amp; beyond</td>
<td>NCT02368951</td>
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<td>ARQ087</td>
<td>I</td>
<td>2nd &amp; beyond</td>
<td>NCT01752920</td>
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<td>BAY1179470</td>
<td>I</td>
<td>Any</td>
<td>NCT01881217</td>
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<td>AZD4547</td>
<td>I</td>
<td>Any</td>
<td>NCT00979134</td>
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<td></td>
<td>BGJ398</td>
<td>II</td>
<td>2nd &amp; beyond</td>
<td>NCT02150967</td>
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<td>Ponatinib Hydrochloride</td>
<td>II</td>
<td>2nd &amp; beyond</td>
<td>NCT02265341</td>
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<tr>
<td>FGFR2</td>
<td>Selumetinib</td>
<td>II</td>
<td>1st/2nd</td>
<td>NCT00553332</td>
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<td></td>
<td>Selumetinib + Gem + Cis</td>
<td>I/II</td>
<td>Any</td>
<td>NCT01242605</td>
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<tr>
<td>MEK</td>
<td>Everolimus</td>
<td>I</td>
<td>2nd &amp; beyond</td>
<td>NCT00949949</td>
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<td>mTOR</td>
<td>MK2206</td>
<td>II</td>
<td>2nd</td>
<td>NCT01425879</td>
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<td>AKT</td>
<td>MK2206</td>
<td>II</td>
<td>2nd</td>
<td>NCT01425879</td>
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</table>

Immune therapy with checkpoint inhibitors
Cancer Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells' APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (immune and cancer cells)

Vaccination (WT-1, MUC-1)

Adoptive immunotherapy (ex-vivo activated T-cell transfer)

Tumor-infiltrating lymphocytes (CD4+T-helper against Erbb2 mutation)

Checkpoint inhibitors

Safety and Efficacy of Pembrolizumab (MK-3475) in Patients With Advanced Biliary Tract Cancer: Interim Results of KEYNOTE-028 (N=23)

<table>
<thead>
<tr>
<th>Best Response</th>
<th>n</th>
<th>% (95% CI)</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0 (0.0–14.8)</td>
</tr>
<tr>
<td>Partial response</td>
<td>4</td>
<td>17.4 (5.0–38.8)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4</td>
<td>17.4 (5.0–38.8)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12</td>
<td>52.2 (30.6–73.2)</td>
</tr>
<tr>
<td>No assessment(^b)</td>
<td>3</td>
<td>13.0 (2.8–33.6)</td>
</tr>
</tbody>
</table>

\(^a\) One patient was excluded from evaluation of best overall response because the baseline tumor scan was performed outside of the protocol-mandated period of 28 days before the first pembrolizumab dose.

\(^b\) Patients who discontinued therapy before the first postbaseline tumor evaluation because of clinical progression (n = 2) or adverse events (n = 1).

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Future perspectives and conclusions

• GemCis is the current standard systemic therapy and there is unmet need for developing more effective systemic therapies (advanced and adjuvant)

• Applying genomic technology and molecular classification critically and timely in ICC

• Genetic heterogeneity and newly identified actionable targets (IDH, FGFR) have provided the opportunity for drug development in ICC

• Immune therapy with checkpoint inhibitors represents a novel strategy in cholangiocarcinoma
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