Systemic therapies for cholangiocarcinoma: One size fits all?

RACHNA T. SHROFF, MD, MS
UNIVERSITY OF ARIZONA CANCER CENTER
RSHROFF@EMAIL.ARIZONA.EDU
Disclosures

Advisory Boards:
Exelixis, Merck, Seattle Genetics, QED Therapeutics, Debio Pharma, Clovis

Research Funding:
Halozyme, Taiho, Merck, Exelixis, Pieris
Outline

Background
Current standards for advanced disease
Why doesn’t one size fit all?
The new horizon of targets
  ◦ Isocitrate dehydrogenase 1 (IDH1) mutation
  ◦ Fibroblast growth factor receptor 2 (FGFR2) fusion
  ◦ Other targets: BRAF mutations, Her2/Neu alterations, DNA repair alterations
  ◦ Resistance
  ◦ Immunotherapy

Where to next?
Key points/Complexities
So the question really is – Is the glass half empty or half full?
Biliary Cancers

Biliary tract cancer
- >90% of cases are adenocarcinoma
- Level 1 evidence for adjuvant chemotherapy: capecitabine
- Palliative 1st-line chemotherapy: cisplatin/gemcitabine
- No 2nd-line palliative chemotherapy with a demonstrated survival benefit over active symptom control
- Median overall survival: ~12 months

Intrahepatic cholangiocarcinoma
- Risk factors: primary sclerosing cholangitis, cirrhosis, Opisthorchis viverrini or Clonorchis sinensis, obesity, diabetes, chronic hepatitis B and C, hepatolithiasis, Lynch syndrome, biliary papillomatosis, biliary duct morphologic anomalies
- Typically presents as incidental hepatic lesion(s)
- Radioembolization or radiation can be considered for liver-predominant disease

Gallbladder cancer
- Females > males
- Risk factors: gallstones, gallbladder polyps, chronic cholecystitis, Salmonella typhi, obesity, diabetes
- Typically presents as an incidental finding following cholecystectomy (localized stage) or with abdominal pain (advanced stage)

Extrahepatic cholangiocarcinoma
- Males > females
- Risk factors: primary sclerosing cholangitis, gallstones, Lynch syndrome, Opisthorchis viverrini or Clonorchis sinensis, bile duct morphologic anomalies
- Typically presents with obstructive jaundice

Valle, et al, Cancer Discov. 2017
Worldwide Distribution of Gallbladder Cancer
## Risk Factors: Biliary Cancers

<table>
<thead>
<tr>
<th>Cholangiocarcinoma</th>
<th>Gallbladder Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obesity, Metabolic Syndrome</td>
<td>• Ethnic, geographic and gender</td>
</tr>
<tr>
<td>• Chronic inflammation (hepatitis B, ETOH, smoking, occupational)</td>
<td>• Cholelithiasis (0.3-3%)</td>
</tr>
<tr>
<td>• Parasitic infections (<em>Clonorchis sinensis</em>, <em>Opisthorchis viverrini</em>)</td>
<td>• Porcelain GB (10-20%)</td>
</tr>
<tr>
<td>• IBD</td>
<td>• Bacterial infections (<em>s. typhi</em>, <em>s. paratyphi</em>)</td>
</tr>
<tr>
<td>• Cysts, Caroli’s disease</td>
<td>• Cysts, anomalous pancreatobiliary ducts, PSC</td>
</tr>
<tr>
<td>• Cholelithiasis</td>
<td>• GB polyps (&gt;10 mm)</td>
</tr>
<tr>
<td>• Genetic polymorphisms</td>
<td></td>
</tr>
</tbody>
</table>
Age-adjusted incidence of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma, 1973–2012.
Advanced disease
Advanced biliary cancers

Disease-related factors
- Uncommon malignancies
- Unwell, elderly population, infection/obstruction
- Histological / cytological confirmation difficult

Lack of evidence
- Disease often not measurable
- Primarily small phase II and one phase III study of gemcitabine-based combinations
ABC-02 - Study schema

Eligible patients (n=400*)

Randomized 1:1
(stratified by centre, primary site, PS, prior therapy and locally advanced vs. metastatic)

Arm A
Gem 1000 mg/m² D1,8,15 q 28d, 24 weeks (6 cycles)

Arm B
Cisplatin 25 mg/m² + Gem 1000 mg/m²
24 weeks (8 cycles)

Upon disease progression, management will be on clinician’s discretion (mostly best supportive care)
### ABC-02: Survival Data (ITT)

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Gem</th>
<th>Gem + Cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>n=206</td>
<td>n=204</td>
</tr>
<tr>
<td>Deaths n(%)</td>
<td>141 (68.5)</td>
<td>122 (59.8)</td>
</tr>
<tr>
<td>Median survival (mo)</td>
<td>8.3</td>
<td>11.7</td>
</tr>
<tr>
<td>Log rank p value</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.70 (0.54, 0.89)</td>
<td></td>
</tr>
</tbody>
</table>

Valle, et al, NEJM. 2010
### ABC-02: Prespecified factors

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABC trial group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>86</td>
<td>0.65 (0.42–1.01)</td>
</tr>
<tr>
<td>02</td>
<td>324</td>
<td>0.64 (0.50–0.83)</td>
</tr>
<tr>
<td><strong>Extent of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>104</td>
<td>0.47 (0.29–0.74)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>306</td>
<td>0.74 (0.57–0.95)</td>
</tr>
<tr>
<td><strong>Primary tumor site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrahepatic</td>
<td>80</td>
<td>0.57 (0.34–0.94)</td>
</tr>
<tr>
<td>Extrahepatic</td>
<td>73</td>
<td>0.73 (0.43–1.23)</td>
</tr>
<tr>
<td>Hilar</td>
<td>57</td>
<td>0.59 (0.32–1.09)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>149</td>
<td>0.61 (0.42–0.89)</td>
</tr>
<tr>
<td>Ampulla</td>
<td>20</td>
<td>0.62 (0.21–1.82)</td>
</tr>
<tr>
<td>Not specified</td>
<td>31</td>
<td>0.98 (0.46–2.11)</td>
</tr>
<tr>
<td><strong>ECOG score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>130</td>
<td>0.50 (0.33–0.77)</td>
</tr>
<tr>
<td>1</td>
<td>228</td>
<td>0.68 (0.51–0.91)</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>0.90 (0.49–1.66)</td>
</tr>
<tr>
<td><strong>Previous therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100</td>
<td>0.65 (0.41–1.01)</td>
</tr>
<tr>
<td>Yes</td>
<td>310</td>
<td>0.64 (0.49–0.82)</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>410</td>
<td>0.64 (0.52–0.80)</td>
</tr>
</tbody>
</table>

The diagram illustrates the comparison between Cisplatin and Gemcitabine in terms of better efficacy. The hazard ratios and 95% confidence intervals are provided for each subgroup.
Second-line therapy: the bar is low

• No prospective, phase III studies to date → ABC-06 is coming
• Retrospective reviews show response rates of <5% and PFS of 2-3 months
• MD Anderson data: patients with advanced cholangiocarcinoma who received 2nd line therapy from 2009-2012
  • 56 patients evaluated, majority were intrahepatic cholangiocarcinoma
  • 80% received gemcitabine-based first-line therapy
  • Mean OS was 7.2 months in Lamarca study – looked at 25 studies (14 phase II trials, 9 retrospective analyses, 2 case reports)
    • RR was 7.7%, mean PFS was 3.2 months, disease control rate of 40.5%
• Majority of patients received 5-fluorouracil in the second-line setting
  • Number of studies from Japan look at S1 as well

Rogers, et al. J Gastrointest Oncol 2014
Inclusion criteria

- Histo/cytologically verified advanced BTC
- ECOG performance score 0-1
- Progression after 1st-line CisGem
- Max 6 weeks progression to randomisation
- Adequate haematological, renal & hepatic function

Stratification factors

- Platinum sensitivity (yes vs. no; determined from first-line CisGem*)
- Serum albumin (<35 vs. ≥35 g/L)
- Stage (locally advanced vs. metastatic disease)

Arm A: Active Symptom Control (ASC)
- May include: biliary drainage, antibiotics, analgesia, steroids, anti-emetics etc
- 4-weekly clinical review

Arm B: Active Symptom Control + mFOLFOX
- Chemotherapy every 14 days for up to 12 cycles
- Day 1: Oxaliplatin 85mg/m², L-folinic acid 175 mg (or folinic acid 350 mg), 5 FU 400 mg/m² (bolus), 5 FU 2400 mg/m² 46 hours continuous infusion
- 4-weekly clinical review after chemotherapy
- 3-monthly radiological assessment

Second-line – FOLFOX (ABC-06)

Follow up

- Primary end-point: Overall Survival (OS) (ITT, adjusted for stratification factors)
- Secondary end-points: PFS, response rate, QoL, HealthEcon

* determined from first-line CisGem: sensitive (progression after three months (90 days) of day 1 of the last cycle of 1st-line CisGem), refractory (progression during 1st line CisGem), resistant (progression within the first three months (90 days) after completion of day 1 of the last cycle of 1st line CisGem)
FOLFOX improved OS after progression to CisGem with:

- A clinically meaningful reduction in risk of death (HR 0.69 (95% CI 0.50-0.97; p=0.031))
- Survival with active symptom control was greater than anticipated (5.3 vs 4 months)
- A clinically meaningful increase on OS rate:
  - at 6 months (+15%)
  - at 12 months (+15%)

FOLFOX + ASC new standard of care

---

**Overall survival by trial arm**

<table>
<thead>
<tr>
<th></th>
<th>Arm A (ASC alone)</th>
<th>Arm B (ASC + mFOLFOX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Adjusted</em> Hazard Ratio</em>*</td>
<td>0.69 (95% CI 0.50-0.97)</td>
<td>p=0.031</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>5.3 months</td>
<td>6.2 months</td>
</tr>
<tr>
<td><strong>6-month survival-rate</strong></td>
<td>35.5%</td>
<td>50.6%</td>
</tr>
<tr>
<td><strong>12-month survival-rate</strong></td>
<td>11.4%</td>
<td>25.9%</td>
</tr>
</tbody>
</table>

---

Lamarca ASCO 2019

*adjusted for platinum sensitivity, albumin and stage
## PFS and Response Rate (Arm B)

### Best response rate (RECIST v.1.1)

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>23</td>
<td>28</td>
</tr>
</tbody>
</table>

### Response rate (CR + PR)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

### Disease-control rate (CR + PR + SD)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27</td>
<td>33</td>
</tr>
</tbody>
</table>

### Progressive disease

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>37</td>
</tr>
</tbody>
</table>

### Death

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>28</td>
</tr>
</tbody>
</table>

### Not evaluable (non measurable disease)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### Median PFS

- Complete response (CR): 18.4m (SD)
- Partial response (PR): 16.0m (CR)
- Stable disease (SD): 13.3m (SD)

### Median PFS 4.0 months (95% CI 3.2-5.0)
Progress in systemic therapy

A PHASE II TRIAL OF GEMCITABINE, CISPLATIN, AND NAB-PACLITAXEL® IN ADVANCED BILIARY TRACT CANCER (GAP)
GAP: Study Schema

First line, advanced cholangiocarcinoma and gallbladder cancer
N = 60

Primary EP: PFS (data maturing)
Secondary: ORR, OS

Correlatives: Mechanisms of resistance, ERCC1, RRM

Bayesian analysis for ongoing toxicity and efficacy
PFS: from 8 to 10 months

Gemcitabine
1000 → 800 mg/m²
+ Cisplatin 25 mg/m² + Nab-Paclitaxel
125 → 100 mg/m²
IV
Days 1, 8 of a 21-day cycle

Restage every 3 cycles

30 patients on starting dose level and subsequent patients at lower dose
# GAP Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)</th>
<th>All (N = 60)</th>
<th>High-Dose Group (n = 32)</th>
<th>Reduced-Dose Group (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>58.4 (11.0)</td>
<td>58.1 (11.1)</td>
<td>58.8 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>33 (55)/27 (45)</td>
<td>16 (50)/16 (50)</td>
<td>17 (61)/11 (39)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (37)</td>
<td>12 (37)</td>
<td>10 (36)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38 (63)</td>
<td>20 (63)</td>
<td>18 (64)</td>
<td></td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHCC</td>
<td>38 (63)</td>
<td>24 (75)</td>
<td>14 (50)</td>
<td></td>
</tr>
<tr>
<td>EHCC</td>
<td>9 (15)</td>
<td>4 (13)</td>
<td>5 (18)</td>
<td></td>
</tr>
<tr>
<td>GBC</td>
<td>13 (22)</td>
<td>4 (13)</td>
<td>9 (32)</td>
<td></td>
</tr>
<tr>
<td>Disease stage(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>47 (78)</td>
<td>29 (91)</td>
<td>18 (64)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>13 (22)</td>
<td>3 (9)</td>
<td>10 (36)</td>
<td></td>
</tr>
<tr>
<td>Median CA19-9, U/mL (IQR)</td>
<td>99 (15-722)</td>
<td>99 (18-608)</td>
<td>99 (13-1053)</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: CA19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma; IQR, interquartile range.*

*SI conversion factor: To convert units per milliliter to $10^3$ units per liter, multiply by 1.0.*

\(^a\) $P = .03$ for the comparison of disease stage distribution between the high-dose and reduced-dose groups.
GAP PFS and OS: ITT

- mPFS in 58 patients – 11.8 months
- mOS in 57 patients – 19.2 months
- ORR in 50 evaluable patients – 45%
- 12 of 60 (20%) patients converted from unresectable to resectable disease and taken for curative surgery
  - 2 of 12 with pCR

GAP Efficacy

First line, advanced cholangiocarcinoma and gallbladder cancer

*Prespecified stratification factors: tumor type, PS, locally-advanced vs. metastatic

Gemcitabine + Cisplatin + Nab-Paclitaxel IV
Days 1, 8 of a 21-day cycle

Restage every 3 cycles until progression

Gemcitabine + Cisplatin IV
Days 1, 8 of a 21-day cycle

Primary EP: OS
Secondary: ORR, PFS, DCR, safety, CA 19-9 changes

Archival blood and tissue specimens to be banked
Why doesn’t one size fit all?
Clinically heterogenous
Varying etiologies
Differing presentations and complexities depending on location
Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in cholangiocarcinomas

Yeehao Ren1,2,3, Timothy F Pawe1,4,5,6, Robert A. Anders1,2,3,4,5,6, Srinivas S. Shrikant1,2,3,4,5,6, Min Donald1,2,3,4,5,6, Nadimah Nikzad7,8,9,10, Victoria Elena Gutierrez-Arcarazu11,12, Arifma Moitra9,8,7, Padma G Johan1,2,3,11,4,5,6, Lewis R. Roberts11,12, Gregory J. Garrow11,12, James T. Alcindron11,4,5,6, Simonina Dinu11,12, Matteo Fussan11,12, Michelle Simmonds11,12, Jianping Cao11,12,13, Rina T. Lau11,12,13, Andrea Brunette14,8, Alfredo Gagliardi11, Giampaolo Filippini de Bras11, Aldo Scapin1,12, William Jermy11,12, David Elmore11,12, Rachel Karch Ralph1,2,3, Bert Vogelstein1,2,3, Kenneth W. Kinzler1,2,3, Nicholas Papadopoulos1,2,3

Through exome sequencing of 12 interlobular cholangiocarcinomas, we discovered frequent inactivating mutations in multiple chromatin-modifying genes (including BAP1, ARID1A and PBRM1), and mutations in one of these genes occurred in almost half of the cholangiocarcinomas. We also identified frequent mutations, at previously unreported locations in the BAP1 and ARID2 genes encoding metastasissuppressor genes in interlobular cholangiocarcinomas. In addition, TP53 was the most frequently altered gene in a series of nine gallbladder carcinomas. These discoveries highlight the key role of deregulated chromatin remodeling in interlobular cholangiocarcinomas.

Carcinomas of the biliary tract are aggressive malignancies, with 5-year survival of less than 10% (ref. 1). These carcinomas occur throughout the biliary tree and are anatomically classified as either intraductal or interlobular cholangiocarcinomas (ICC). In addition to genetic alterations, gallbladder carcinomas also represent a major public health concern as the 5-year survival of the former entity is much lower, predominantly due to their advanced stage at diagnosis, which allows development of distant metastases.

Exome sequencing in 12 interlobular cholangiocarcinomas

Exome sequencing of liver fluke–associated cholangiocarcinoma

Choon Kiat Ong, Christine Subinuth, Chaiwut Phimolsuk, Saig Wongsupraphat, Iancu Cabiocat, White Yu, John R. McPherson, George E. Allen, Cedric Chuan Young Ng, Berrinuc Kimmy Wong, Sae Bye Myint, Nirmalraj Rajasegaran, Hong Lee Song, Anne Gao, Zhi Jiang Zeng, Yingying Wu, Jesus Wu, Ming Hui Lai, DeChae Huang, Pasolin Ong, Wanpam Chan-en, Yuf Cao, Chen-Nan Qian, Kiat Hon Lim, Aleksand Q. Gao, et al.

Affiliations: Contributions: Corresponding authors

Nature Genetics (2012) 10.1038/ng.2797
Received: 23 September 2011; Accepted: 11 April 2012; Published online: 05 May 2012

Oxphos-deficient-virus-related-cholangiocarcinoma (CA), a fatal bile duct cancer, is a major public health concern in areas endemic for this parasite. We report here exome sequencing of eight O. viverrini-related tumors and matched normal tissues. We identified and validated 236 somatic mutations in 157 genes using Sanger sequencing and selected 15 genes for mutation prevalence screening in an additional 62 individuals with CA (cases). In addition to the known cancer-related genes TP53 (mutated in 44.4% of cases), ARID2 (10.7%) and PBEF (6.9%), we identified somatic mutations in 15 newly indicated genes in 16.3-7.7% of cases. These included inactivating mutations in RELN (4.8% of cases), KDM2B (0.9%), ARID2 (0.9%) and PBEF (0.6%), and activating mutations in the SMAD3 gene (0.6%). These genes have functions that can be broadly grouped into three biological classes: (1) deregulation of histone modifications, (2) activation of G protein–coupled receptors and (3) cell growth. The study provides new insights into the mutational landscape contributing to O. viverrini-related CA.
Why does one size not fit all?
IDH1 mutation
20-25% of iCCA
Prognostic value in glioma, not clear in CCA
Mutation results in accumulation of 2-HG

Valle et al. Cancer Discov 2017;7:943-962
IDH1 mutation: ivosidenib

Oral, reversible IDH1 inhibitor, approved in AML

Phase I solid tumor study completed with N=73 CCA (89% iCCA)

Refractory population $\rightarrow$ median number of prior tx’s 2, but range 1-5
Median PFS: 3.8 mos (95% CI: 3.6, 7.3); mOS 13.8 mos (censored for 48 pts)

PFS6: 38.5%

PFS12: 20.7%

Table 2: Treatment-emergent adverse events occurring in more than 10% of patients with cholangiocarcinoma

Lowery et al. Lancet Gastroenterol Hepatol 2019
Eligible patients with mIDH1 CC (1 or 2 prior therapies) 2:1 double-blind randomization (n=186)

AG-120 500 mg QD orally Continuous 28-day cycles (n=124)

Crossover from placebo to AG-120 permitted when progressive disease documented

Matched placebo (n=62)

Assessments

Primary
- Progression free survival (PFS), assessed by independent radiology center review

Secondary
- Safety and tolerability
- Overall response rate (ORR)
- Overall survival (OS)
- Duration of response (DOR)
- Time to response (TTR)
- Pharmacokinetic and pharmacodynamic analyses on plasma
- Quality of life as assessed by:
  - EORTC QLQ-C30
  - EORTC QLQ-BIL21
  - EQ-5D-5L

Exploratory:
- TBC

ClinicalTrials.gov NCT02989857
ClarIDHy.com

Abou-Alfa et al GI ASCO 2018; TPS545
Slide courtesy of R. Katie Kelley, MD
**ClarIDHy: PFS by IRC**

**Graph:**
- Censored data represented by + symbols.
- Ivosidenib: blue line.
- Placebo: red line.

**HR = 0.37 (95% CI 0.25, 0.54)**
- **P < 0.001**

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Ivosidenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>2.7</td>
<td>1.4</td>
</tr>
<tr>
<td>6-month rate</td>
<td>32%</td>
<td>NE</td>
</tr>
<tr>
<td>12-month rate</td>
<td>22%</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Disease control rate (PR+SD)</strong></td>
<td>53% (2% PR, 51% SD)</td>
<td>28% (0% PR, 28% SD)</td>
</tr>
</tbody>
</table>

**Number of patients at risk:**
- **Ivosidenib:** 124, 105, 54, 40, 36, 28, 22, 16, 14, 10, 9, 6, 5, 4, 3, 3, 2, 1, 1
- **Placebo:** 61, 46, 11, 6, 4, 1

**Survival (months):**

**Note:**
- NE = not estimable; PR = partial response; SD = stable disease.
## ClarIDHy: Ivosidenib efficacy consistent across subgroups*

**PFS by IRC**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/N</th>
<th>Hazard ratio (HR)</th>
<th>HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>126/185</td>
<td></td>
<td>0.37</td>
<td>0.252</td>
<td>0.543</td>
</tr>
<tr>
<td><strong>Prior lines of therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>66/106</td>
<td></td>
<td>0.37</td>
<td>0.219</td>
<td>0.612</td>
</tr>
<tr>
<td>≥2</td>
<td>60/79</td>
<td></td>
<td>0.41</td>
<td>0.234</td>
<td>0.730</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>74/117</td>
<td></td>
<td>0.36</td>
<td>0.220</td>
<td>0.589</td>
</tr>
<tr>
<td>Male</td>
<td>52/68</td>
<td></td>
<td>0.45</td>
<td>0.249</td>
<td>0.811</td>
</tr>
<tr>
<td><strong>Extent of disease at screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>7/14</td>
<td></td>
<td>0.20</td>
<td>0.035</td>
<td>1.111</td>
</tr>
<tr>
<td>Metastatic</td>
<td>119/171</td>
<td></td>
<td>0.41</td>
<td>0.277</td>
<td>0.601</td>
</tr>
<tr>
<td><strong>Cancer type at initial diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrahepatic cholangiocarcinoma</td>
<td>114/169</td>
<td></td>
<td>0.38</td>
<td>0.257</td>
<td>0.567</td>
</tr>
<tr>
<td>Extrahepatic cholangiocarcinoma</td>
<td>3/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9/10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ECOG PS score at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41/68</td>
<td></td>
<td>0.26</td>
<td>0.124</td>
<td>0.540</td>
</tr>
<tr>
<td>≥1</td>
<td>85/117</td>
<td></td>
<td>0.52</td>
<td>0.332</td>
<td>0.803</td>
</tr>
<tr>
<td><strong>Regions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>83/124</td>
<td></td>
<td>0.40</td>
<td>0.249</td>
<td>0.631</td>
</tr>
<tr>
<td>Europe</td>
<td>34/49</td>
<td></td>
<td>0.39</td>
<td>0.188</td>
<td>0.830</td>
</tr>
<tr>
<td>Asia</td>
<td>9/12</td>
<td></td>
<td>0.42</td>
<td>0.110</td>
<td>1.597</td>
</tr>
</tbody>
</table>

*Subgroups with events number ≤10 were not plotted.*

Abou-Alfa et al ESMO 2019
**ClariDHy: OS by intent-to-treat (ITT)**

- Median OS based on 78 events was numerically longer with ivosidenib than placebo (10.8 vs. 9.7 months).
  - OS rates at 6 and 12 months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo.
  - Rank-preserving structural failure time (RPSFT) method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib.
  - With the RPSFT method, the median OS with placebo adjusts to 6 months.

**HR=0.69 (95% CI 0.44, 1.10); P=0.06**

**HR=0.46 (95% CI 0.28, 0.75); P<0.001 (RPSFT-adjusted)**

<table>
<thead>
<tr>
<th>Survival (months)</th>
<th>Number of patients at risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I vosidenib</td>
</tr>
<tr>
<td>24</td>
<td>61</td>
</tr>
<tr>
<td>23</td>
<td>61</td>
</tr>
<tr>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>19</td>
<td>34</td>
</tr>
<tr>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>17</td>
<td>49</td>
</tr>
<tr>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
</tr>
<tr>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
IDH1: Points to consider

Other IDH inhibitors – BAY1436032 in phase 1 with CCA cohort; What about IDH2?

Sequencing/combinations $\rightarrow$ 1\textsuperscript{st} line? Combined with chemo? Combined with PARPi? IO?

Utility in neoadjuvant/adjuvant space? Cytostatic drug
FGFR2 fusion

Seen in approximately 15-20% iCCA

Tested in multiple trials

Prognostic

Jain et al JCO Precis Oncol Jan. 17, 2018
FGFR2 fusion: BGJ398

Pan-FGFR inhibitor with strong pre-clinical rationale

Multicenter, phase II study, n = 61

Included patients with FGFR alterations → 78.7% had FGFR fusions

Javle M, Lowery M, Shroff RT, et al JCO 2017
FGFR fusion: BGJ 398

ORR was 14.8%
- Higher in FGFR fusion population → 18.8%

Median PFS was 5.8 months (95% CI: 4.3-7.6)

41% Grade 3/4 tx-related AE’s
- Hyperphosphatemia
- Fatigue
- Stomatitis
- Alopecia
- Dry eye
- Hand-foot syndrome
- Other ocular issues

Javle M, Lowery M, Shroff RT, et al. JCO 2017
54 year old male with metastatic IHCCA who had progressive, symptomatic lung metastases despite prior chemotherapy with gemcitabine and cisplatin. Tumor had \textit{FGFR2-KCTD1} fusion. Sustained partial response was noted, lasting over 7 months.
FGFR fusion: TAS-120

Total patients enrolled with advanced solid tumors (n=132)

CCA patients enrolled at the efficacious doses -16, 20, 24 mg QD (n=45):

Other FGF/FGFR aberration (n=17)
- FGF/FGFR amplification, mutations, re-arrangements
- 5 pts with prior FGFRi
- 3 extra-hepatic

FGFR2 fusion (n=28)
- FGFR2 fusion: fusions with fusion partner
- 8 pts with prior FGFRi
- 1 extra hepatic

Highly refractory patients (>40% with 3 or more prior tx’s), 28.9% with prior FGFR inhibitor
24 of pts were evaluable for efficacy (4 non evaluable)
20 pts had tumor shrinkage
7 had cPR (25% ORR)
15 had SD
DCR = 78.6%
Similar AE profile
Median duration of treatment: 7.4 m+
15/28 pts are ongoing
ARQ187 (Arqule)
IC50 FGFR2 = 1.8nM

TAS120 (Taiho)
IC50 FGFR2 = 1.3nM

IC50 FGFR2 = 1.4nM
ORR in FGFR2 fusions: 18.8%
DCR in FGFR2 fusions: 83.3%

INCB054828 (Incyte)
IC50 FGFR2 = 3-50nM

Debio1347 (Debiopharm)
IC50 FGFR2 = 7.6nM

Best Overall Response (N=28)
- PR (n=7)
- SD (n=15)
- PD (n=2)
- NE (n=4)
FGFR fusion: Points to consider

Multiple trials ongoing: BGJ398, TAS-120, ARQ 087, INCB054828, Debio 1347

How much is drug vs. natural history of FGFR fusion patients?
Role in front-line? With or without chemo?
Combinations beyond chemo?
Management of toxicities?
Deeper dive into resistance mechanisms
Other targets - BRAF

BRAF – 3-7%, Wainberg et al, Abstract #187

Dual inhibition with BRAF + MEK inhibitor

SLD, sum of the longest diameter of the target lesion.

Maximum Reduction in the SLD of Target Lesion, %

Best Confirmed Response

- PR
- SD
- PD

ITT/Evaluable Patients

SLD, sum of the longest diameter of the target lesion.
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

20-25% → DNA repair or homologous recombinant deficiency (HRD)

Alterations in HRD genes → best treated with agents against DNA repair mechanisms

PARP1 and 2 are members of the PARP family involved in DNA repair

In HRD tumor cells, PARP inhibition → sensitivity and anti-tumor activity from synthetic lethality

Phase II study of Olaparib in patients with advanced biliary tract cancer expressing aberrant DNA repair

Olaparib 300mg BID

18 patients
0 responses => stop

Additional 14 patients

1° ORR
2° OS, PFS

Treatment until disease progression per RECIST 1.1, unacceptable toxicity or withdrawal of consent

Slide courtesy of Daniel Ahn, MD
Other targets – Points to consider

Need for profiling → rare but relevant targets outside of the “traditional” ones

Combinations?

Understanding resistance

Do we need an alteration to use targeted therapy?
Other targets – Points to consider

2\textsuperscript{nd} line BTC patients

- varlitinib + capecitabine
- capecitabine

Double-blind, randomized Placebo-controlled
120 patients
Primary endpoint: ORR
Secondary endpoints: PFS, OS

- TreeTopp study (NCT03093870), randomized phase II/III study
- Varlitinib → small molecule HER1/2/4 inhibitor → studying in unselected 2\textsuperscript{nd} line population
- Phase II portion recruitment completed in US
Resistance – IDH1

A. Graph showing the sum of target lesion size (mm) over time (day) with Ivosidenib treatment.

B. Images showing tumor progression with red outlines marking changes over time: Pretreatment (day -10), Progression (day 392), Progression (day 446).

C. Genotyping data comparing tumor and blood samples before treatment (day -515) and after progression (day 461).

D. Graph depicting changes in mutant IDH1 and IDH2 copies over time with Ivosidenib.
Resistance – FGFR2 fusion

Table 1A. Clinical data of patients with FGFR2 fusion-positive cholangiocarcinoma receiving FGFR inhibitors

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>FGFR2 fusion</th>
<th>First FGFR inhibitor</th>
<th>PFS (months)</th>
<th>BOR</th>
<th>Interval between 1st and 2nd FGFR inhibitor (months)</th>
<th>Second FGFR inhibitor</th>
<th>PFS (months)</th>
<th>BOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FGFR2-SORBS1</td>
<td>BGJ398</td>
<td>12.6</td>
<td>−68.2%</td>
<td>None</td>
<td>TAS-120</td>
<td>15.8</td>
<td>−76.7%</td>
</tr>
<tr>
<td>2</td>
<td>FGFR2-ZMYM4</td>
<td>BGJ398</td>
<td>5.6</td>
<td>−49.9%</td>
<td>None</td>
<td>TAS-120</td>
<td>7.2</td>
<td>+8.3%</td>
</tr>
<tr>
<td>3</td>
<td>FGFR2-INA</td>
<td>Debio 1347</td>
<td>11.4</td>
<td>−49.5%</td>
<td>Gemcitabine/docetaxel, T11 palliative radiation</td>
<td>TAS-120</td>
<td>5.1</td>
<td>−22.1%</td>
</tr>
<tr>
<td>4</td>
<td>FGFR2-NRAP</td>
<td>BGJ398</td>
<td>7.1</td>
<td>−40.0%</td>
<td>T8 palliative radiation, pembrolizumab, resection of T8 metastasis, FOLFOX</td>
<td>TAS-120</td>
<td>17.2</td>
<td>−47.7%</td>
</tr>
</tbody>
</table>

Abbreviations: BOR, best overall response; PFS, progression-free survival.
Immunotherapy

Mismatch Repair (MMR) deficiency → 3-10%

Data with PD1 inhibitor → pembrolizumab

KEYNOTE-016 (NCT01876511)\textsuperscript{1}
- N=86 dMMR tumors, n=4 CCA
- ORR 53%, complete responses 21%
- 2-year OS 64% (95% CI: 53-78)

KEYNOTE-158 (NCT02628067)\textsuperscript{2}
- Basket trial, subgroup of n=94 dMMR solid tumors included n=9 CCA
- ORR 37%, durable

\textsuperscript{1} Le et al. Science 2017;357:409-13
\textsuperscript{2} Diaz et al ESMO 2017 Abstract 386p

Rizvi S et al. Nat Rev Clin Oncol 2018
**KEYNOTE-028:**
- Responses noted with pembrolizumab: 17%.
- Median duration of response: 40 weeks.
- **KEYNOTE-158** had a BTC cohort:
  - 104 patients enrolled, none MSI-H.
  - 58% PD-L1+.
  - ORR: 5.8%.
  - In responders, median duration of response hasn’t been reached but is > 6 months.

Presented by Ueno M et al. ESMO 2018
Immunotherapy – Points to consider

Down, but not out!

- Combinations to turn MSS tumors “hot”

Multiple ongoing trials

- ICRN IO Working Group
- NCI → ETCTN Atezo +/- Cobi (NCT03201458) → accrued < 6mths, awaiting data
- Pharma sponsored
- IITs → Phase II Pembro + GM-CSF

- ORR 19% (5/26 pts), majority MSS
- %PFS6 35% < target of 42%
- Median OS not reached
- Added biopsy cohort of 15 pts → paired bx’s
- Primary endpt now ORR for n=42

Presented by Kelley RK et al. ASCO 2018
Where to next?

Clearly a role for profiling ALL CCA patients → education

Basket trials to capture multiple targets
Where to next?

Biliary Cancer Alterations Predict Therapy Choice: The BATCH Trial
Where to next? BATCH

ABTC on first-line platinum

SOC Molecular Profiling

At Progression

e.g. HER2Neu amplification
  - BATCH HER2 Treatment Arm (Alliance)

e.g. BRCA1/2 Mutation
  - BATCH DNA Repair Treatment Arm (SWOG)

e.g. FGFR Alterations
  - BATCH FGFR Treatment Arm (ECOG-ACRIN)

No Actionable Alteration
  - Rolling Platform

Additional Alterations
  - Add new treatment arms
Key points

IDH1 mutations: Common alteration, ClarIDHy positive, other agents in early phase studies, resistance mechanisms being understood

FGFR2 fusions: Multiple agents in trials for 1st line and refractory populations, promising ORR, resistance mechanisms being understood
Key points

BRAF/Her2/DNA repair: lower frequency alterations, but still targetable, BATCH trial coming as well as others, combination strategies

Immunotherapy: single agent pembro disappointing, but role for IO combinations? awaiting results
Complexities

Tissue vs. cfDNA → availability of tissue
ABC-06 results out → new 2\textsuperscript{nd} line SOC with FOLFOX?
Single-arm studies → truly need randomized studies
Are all CCA created equal? NO → how to stratify
Basket trials → allows for nimble evaluation of rare subsets with shared controls
Role of resistance → repeat biopsy vs. cfDNA
Conclusion – One size does NOT fit all!

It is a new era in the treatment of CCA!

Sequencing can and should be done on ALL patients

Actionable targets exist → go after them with smart clinical trials
Acknowledgments

Patients, families, advocates and researchers engaged in cholangiocarcinoma research

Milind Javle, MD & MD Anderson Cancer Center
R. Katie Kelley, MD
Lipika Goyal, MD
Mitesh Borad, MD
Ghassan Abou-Alfa, MD
Cholangiocarcinoma Foundation/ICRN
University of Arizona Cancer Center, Section of GI Oncology