Current and Future Management of Advanced Biliary Tract Cancers

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Research To Practice
Hepatobiliary Cancers
San Francisco, January 24, 2020
Is cholangiocarcinoma the new nonsquamous cell lung cancer?
Advanced Biliary Tract Cancers

- Biologic subsets, response to first-line chemotherapy
- Multiplex somatic and germline testing
- IDH somatic mutations and IDH inhibitors
- Other potentially targetable mutations/alterations (EGFR/HER2, FGFR, BRAF, NTRK)
Advanced Biliary Tract Cancers

- Biologic subsets, response to first-line chemotherapy
- Multiplex somatic and germline testing
- IDH somatic mutations and IDH inhibitors
- Other potentially targetable mutations/alterations (EGFR/HER2, FGFR, BRAF, NTRK)

### Somatic IDH1 mutations
143 patients

**Targeted treatment(s)**
Ivosidenib, FGFR inhibitors, RAF inhibitors, Anti-HER2 agents, Pembrolizumab

### Somatic IDH2 mutations
22 patients

**Targeted treatment(s)**
Enasidenib, IDH1/2 inhibitor

### BRAF mutations
34 patients

**Targeted treatment(s)**
Encorafenib/binimetinib, Vemurafenib, Vemurafenib/cobimetinib, Dabrafenib/trametinib, Vemurafenib/irinotecan/cetuximab

### FGFR alterations
154 patients

**Targeted treatment(s)**
Infigratinib, Pemigatinib, TAS-120, Erdafitinib, Futibatinib

### NTRK gene fusions
1 patient

**Targeted treatment(s)**
Larotrectinib

### Somatic HER2 or EGFR mutations or fusions
37 patients

**Targeted treatment(s)**
Trastuzumab, Trastuzumab/lapatinib, Pertuzumab
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Disclosures

• Research
  ActaBiologica, Agios, Array, AstraZeneca, Bayer, BeiGene, BMS, Casi, Celgene, Exelixis, Genentech, Halozyme, Incyte, Lilly, MabVax, Novartis, Polaris, Puma, QED, Roche

• Consulting
  Agios, AstraZeneca, Bayer, BeiGene, Bioline, BMS, Celgene, CytomX, Debio, Eisai, Exelixis, Flatiron, Genoscience, Incyte, Ipsen, Jansen, LAM, Lilly, Loxo, Merck, MINA, Pfizer, QED, Redhill, Sanofi, Silenseed, Sillajen, Sobi, Targovax, twoXAR, Vicus, Yiviva
### MEGA: Mutual Exclusivity of Genetic Alterations

<table>
<thead>
<tr>
<th>Gene1</th>
<th>Gene2</th>
<th>Both genes altered (n)</th>
<th>Gene2 altered (n)</th>
<th>Gene1 altered (n)</th>
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<th>OR</th>
<th>P value</th>
<th>q value</th>
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<td>140</td>
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<tr>
<td>BAP1</td>
<td>SMAD4</td>
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<td>19</td>
<td>30</td>
<td>144</td>
<td>0.000</td>
<td>0.029</td>
<td>1</td>
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<tr>
<td>IDH1</td>
<td>FGFR2</td>
<td>1</td>
<td>19</td>
<td>47</td>
<td>128</td>
<td>0.144</td>
<td>0.030</td>
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</tr>
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<td>46</td>
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<tr>
<td>TP53</td>
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<td>1</td>
<td>19</td>
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<td>130</td>
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<td>KRAS</td>
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<td>23</td>
<td>147</td>
<td>0.000</td>
<td>0.049</td>
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</tr>
</tbody>
</table>

Lowery, M, Abou-Alfa, GK et al. Clin Cancer Res. 2018 Sep 1;24(17):4154-4161
IDH1 mutations in advanced cholangiocarcinoma

- Advanced cholangiocarcinoma is an aggressive rare cancer with treatment options limited primarily to chemotherapy\(^1\)

- IDH1 mutations occur in up to 20% of cholangiocarcinoma and do not confer a favorable prognosis\(^1\)

- Ivosidenib (AG-120) is a first-in-class, oral, targeted, small-molecule inhibitor of the mutant IDH1 (mIDH1) protein,\(^2\) and is FDA-approved for mIDH1 R/R AML and ND AML not eligible for intensive chemotherapy\(^3\)

- A phase 1 study of ivosidenib included 73 previously treated mIDH1 cholangiocarcinoma patients and was associated with: median PFS, 3.8 months; 6- and 12-month PFS rates, 40.1% and 21.8%, respectively; and median OS 13.8 months\(^4\)

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**Metabolic dysregulation**

- 2-HG=D-2-hydroxyglutarate; \(\alpha\)-KG=alpha-ketoglutarate; AML=acute myeloid leukemia; FDA=Food and Drug Administration; Me=methyl groups; ND=newly-diagnosed; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory.

ClarIDHy: Study design and endpoints

Key eligibility criteria
• ≥18 years of age
• Histologically confirmed diagnosis of cholangiocarcinoma
• Centrally confirmed mIDH1\(^*\) status by NGS
• ECOG PS score 0 or 1
• 1-2 prior therapies (at least 1 gemcitabine- or 5-FU-containing regimen)
• Measurable lesion as defined by RECIST v1.1
• Adequate hematologic, hepatic, and renal function

Primary endpoint: PFS by blinded independent radiology center (IRC)
Secondary endpoints included: safety and tolerability; PFS by local review; OS; objective response rate; quality of life (QoL); pharmacokinetics/pharmacodynamics

Sample size of ~186 patients based on hazard ratio (HR)=0.5, 96% power, 1-sided alpha=0.025

780 patients were screened for IDH1 mutations across 49 sites and 6 countries

Ivosidenib
500 mg QD orally in continuous 28-day (±2 days) cycles (n=124)

Placebo
(n=61)

NCT02989857

Crossover permitted at radiographic disease progression

An independent data monitoring committee monitored the safety data throughout the study

Abou-Alfa, GK, et al. ESMO 2019
ClarIDHy: PFS by IRC

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

<table>
<thead>
<tr>
<th></th>
<th>Ivosidenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</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>Disease control rate (PR+SD)</td>
<td>53% (2% PR, 51% SD)</td>
<td>28% (0% PR, 28% SD)</td>
</tr>
</tbody>
</table>

Number of patients at risk:

Ivosidenib: 61 46 11 6 4 1 12 11 9 6 5 4 3 2 1 1
Placebo: 124 105 54 40 36 28 22 16 10 9 6 5 4 3 2 1 1

NE=not estimable; PR=partial response; SD=stable disease.

Abou-Alfa, GK, 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

*Patients without documentation of death at the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was earlier.


Abou-Alfa, GK, et al. ESMO 2019
BGJ398 in FGFR-Altered Cholangiocarcinoma

Phase 2 open-label, single-arm study evaluating the efficacy and safety of pemigatinib in patients with previously treated locally advanced or metastatic CCA (NCT02924376)

- Sites opened in the United States, Europe, Middle East, and Asia

**FIGHT-202 STUDY DESIGN**

- **Primary endpoint:** Confirmed ORR in cohort A by independent central review

- **Secondary endpoints:** ORR in cohorts B, A + B, and C; duration of response, disease control rate, PFS, OS, and safety in all cohorts

- **Oral pemigatinib**
  - 13.5 mg QD
  - (2 weeks on, 1 week off)

**Patients**
- Adults with locally advanced or metastatic CCA
- Documented FGF/FGFR status*
- Progression after ≥1 prior therapy
- ECOG PS ≤2
- Adequate hepatic/renal function

**Cohort A (planned, N = 100)**
- FGFR2 fusions/rearrangements

**Cohort B (planned, N = 20)**
- Other FGF/FGFR genetic alterations

**Cohort C (planned, N = 20)**
- No FGF/FGFR genetic alterations

* Patients prescreened for FGF/FGFR status, documented either centrally (FoundationOne®, Foundation Medicine), based on local assessment, or an existing Foundation Medicine report. Retrospective central confirmation of locally documented FGF/FGFR status was required.

Vogel, A, ESMO 2019

Data cutoff date: March 22, 2019
Pemigatinib in FGFR2 Altered Cholangiocarcinoma

Colored bars: confirmed responses per RECIST.
* Patient had decrease in target lesion size but was not evaluable for response per RECIST.

Vogel, A, ESMO 2019
The study was not designed to compare cohorts.

Vogel, A, ESMO 2019
The study was not designed to compare cohorts.
Fusions are a product of chromosomal rearrangement
- Consistent with Foundation Medicine terminology, rearrangements are classified as fusions if the partner gene is previously described or in-frame

Among 107 patients in cohort A:
- 92 fusions; 15 rearrangements
- 56 different partner genes
- 42 partners unique to single patients
- Most common:
  - *BICC1* (29%)
  - No partner identified (5%)

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**FGFR2 FUSIONS/REARRANGEMENTS (COHORT A)**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>BICC1</td>
<td>31</td>
</tr>
<tr>
<td>None identified</td>
<td>5</td>
</tr>
<tr>
<td>KIAA1217</td>
<td>4</td>
</tr>
<tr>
<td>AHCYL1</td>
<td>3</td>
</tr>
<tr>
<td>TRIM8</td>
<td>2</td>
</tr>
<tr>
<td>TACC1</td>
<td>2</td>
</tr>
<tr>
<td>SLMAP</td>
<td>2</td>
</tr>
<tr>
<td>SHROOM3</td>
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<td>PAWR</td>
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</tr>
<tr>
<td>NRAP</td>
<td>2</td>
</tr>
<tr>
<td>NOL4</td>
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<tr>
<td>MACF1</td>
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<td>CCDC6</td>
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<td>ARHGAP24</td>
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<tr>
<td>AFF4</td>
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</tr>
<tr>
<td>Unique to single pt</td>
<td>42</td>
</tr>
</tbody>
</table>

Vogel, A, ESMO 2019
Polyclonal Secondary FGFR2 Mutations Drive Acquired Resistance to FGFR Inhibition

# FGF Landscape

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Infigratinib (BGJ398)</td>
<td>FGFR1-3 TKI</td>
<td>Cholangiocarcinoma</td>
<td>First line Phase III</td>
</tr>
<tr>
<td>Pemigatinib</td>
<td>FGFR1-3 TKI</td>
<td>Cholangiocarcinoma</td>
<td>First line Phase III</td>
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<tr>
<td>TAS-120</td>
<td>Pan-FGFR TKI</td>
<td>Solid tumors</td>
<td>Phase I</td>
</tr>
<tr>
<td>Derazantinib (ARQ 087)</td>
<td>Pan-FGFR TKI</td>
<td>Cholangiocarcinoma</td>
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<tr>
<td>Debio 1347</td>
<td>Pan-FGFR TKI</td>
<td>Solid tumors</td>
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</tr>
</tbody>
</table>
KEYNOTE-028 Phase 1b: Pembrolizumab and Bile Duct Cancers

Figure 4. Duration of exposure to pembrolizumab and summary of best overall response assessed per RECIST v1.1 by investigator review in patients who had ≥1 postbaseline tumor assessment (n = 20).

ORR = 17.4% (95% CI, 5-39) SD = 17.4% (95% CI, 5-39) The majority of patients progress rapidly

Bang et al. ESMO 2015
Conclusions

• Advanced cholangiocarcinoma systemic therapies are evolving beyond standard chemotherapy
• Next generation sequencing helped delineate genetic alterations that are targetable
• IDH1 ivosidenib has shown an improvement in PFS and OS (when adjusting for crossover using the RPSFT method) vs. placebo
• Infigratinib showed RR of 18.8% and pemigatinib treatment resulted in 35.5% RR with durable response and a median PFS of 6.9 months
• First line efforts underway
• Checkpoint inhibitors deserve further evaluation