Beyond Chemotherapy: New Treatments for Advanced Liver and Bile Duct Cancers

Katie Kelley, MD
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco (UCSF)
Disclosures

- Research funding from: Novartis, Agios, Eli Lilly, BMS, Merck, Medimmune/AZ, Exelixis, Sanofi, and Regeneron Inc. for conduct of clinical trials and/or translational/biomarker research
Objectives

1. Review current treatment options and outcomes in advanced liver and biliary cancers

2. Introduce new targets and treatments in liver and biliary cancers
   - Molecularly-targeted therapies
   - Immunotherapy

3. Looking ahead: How to combine old with new?
Anatomic Classification of Hepatobiliary Cancers

- Hepatocellular carcinoma (HCC)
- Cholangiocarcinoma (CCA)
- Intrahepatic (IHCC)
- Perihilar
- Distal extrahepatic (EHCC)

GBC
Mortality HCC+IHCC: 745,500 deaths worldwide in 2012
Objectives

1. Review current treatment options and outcomes in advanced liver and bile duct cancers
Treatment of Advanced HCC in 2016: A Review

- Before 2007: No chemotherapy had achieved survival benefit

- 2008, 2009: SHARP and Asia-Pacific trials showed survival benefit from TKI sorafenib (SOR) in Western and Asian populations\(^1,2\)
  - Median survival 10.7 vs. 7.9 mos. (SHARP)
  - Median survival 6.5 vs. 4.2 mos. (Asia-Pacific)

- 2009-2016 ~9 negative, multinational randomized phase 3 trials (sunitinib, linifanib, brivanib 1\(^{st}\), brivanib 2\(^{nd}\), SOR+erlotinib, SOR+doxorubicin, ramucirumab, everolimus, SOR adjuvant) all conducted in unselected HCC populations

- In 2016: SOR remains only FDA-labeled treatment; still no 2\(^{nd}\) line or adjuvant agents

---

Treatment of Advanced Biliary Cancers in 2016: A Review

- Before 2010: No established 1st-line chemotherapy
- In 2010: ABC-02 trial\(^1\) established gemcitabine plus cisplatin (GEMCIS) as standard of care
  - Median survival 11.7 months, PFS 8 mos. 1st line
- In 2016: Still no established 2nd line therapy
  - Median PFS in 2nd line ~3 mos., RR ~12%\(^{2-4}\)

---

NCCN Guidelines

---

What are the unique challenges in this family of cancers?

- Complex anatomy
- Competing comorbidity of organ dysfunction
  - E.g. cirrhosis, biliary obstruction, viral hepatitis
- Inherent chemoresistance?
  - MDR genes, efflux mechanisms, etc.
- Heterogeneous tumor and microenvironment biology
  - “One-size-fits-all”/unselected clinical trial designs are inadequate in highly heterogeneous populations
  - Therapeutic targets not well understood
## Impact of Tumor Location on Genetics of Biliary Cancers

<table>
<thead>
<tr>
<th>Tumor Genomic Aberrations</th>
<th>IHCC</th>
<th>EHCC</th>
<th>GBC</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>ERBB2</em> Amplification (HER2)</td>
<td>4%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td><em>BRAF</em> Substitutions</td>
<td>5%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td><em>KRAS</em> Substitutions</td>
<td>22%</td>
<td>42%</td>
<td>11%</td>
</tr>
<tr>
<td><em>PI3KCA</em> Substitution</td>
<td>5%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td><em>FGFR1-3</em> Fusions and Amplifications</td>
<td>11%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td><em>CDKN2A/B</em> Loss</td>
<td>27%</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td><em>IDH1/2</em> Substitutions</td>
<td>20%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><em>ARID1A</em> Alterations</td>
<td>18%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td><em>MET</em> Amplification</td>
<td>2%</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

N=554: IHCC n=412, EHCC n=57, GBC n=85
Oncogenic Networks in HCC

- N=503 HCC cases (including TCGA and ICGC)
- WES ± WGS, CNA, oncovirome analyses
- Identified multiple biologically distinct subgroups within HCC

Totoki et al Nat Gen 46(12) 2014
What are the clinical implications?

- There are subgroups defined by high frequency somatic mutations, pathway aberrations, and/or microenvironment within HCC and biliary cancers
- Some may be prognostic
- Some of these mutations (esp. in biliary cancers) may be driver oncogenes amenable to targeted therapies
- Signals of response can be difficult to detect in subpopulations

Need to define biologic subpopulations in hepatobiliary cancer clinical research...and in future treatment decisions?
Objectives

2. Introduce new targets and treatments in liver and biliary cancers
   - Molecularly targeted therapies
   - Immunotherapy
## High Frequency Molecular Targets in Liver and Biliary Cancers

<table>
<thead>
<tr>
<th>Target</th>
<th>Est. Incidence by Location</th>
<th>Targeted Agents</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR2 fusions</td>
<td>~20% IHCC</td>
<td>BGJ398, ARQ087, others</td>
<td>FGFR inhibition</td>
</tr>
<tr>
<td>IDH1/2 mutations</td>
<td>~20% IHCC</td>
<td>AG-120, AG-221, AG-881, IDH305, others</td>
<td>Restore differentiation</td>
</tr>
<tr>
<td>HER2</td>
<td>~15% gall bladder</td>
<td>Trastuzumab, TDM-1, others</td>
<td>HER2 inhibition, cytotoxicity</td>
</tr>
<tr>
<td>c-MET expression</td>
<td>~50% HCC</td>
<td>tivantinib</td>
<td>TKI, cytotoxicity?</td>
</tr>
<tr>
<td>Immune activation</td>
<td>Unknown: PD-L1+: 20-40%? MSI-H: &lt;10%?</td>
<td>Pembrolizumab, nivolumab, others</td>
<td>T-cell activation</td>
</tr>
</tbody>
</table>

Unknown:
- PD-L1+: 20-40%?
- MSI-H: <10%?
FGFR2 Inhibitors in IHCC: Approaching the Clinic?

- Activating FGFR2 fusions: ~20% IHCC
- Multiple agents in trials:
  - BGJ398 (Novartis)
  - ARQ 087 (ArQule)
  - INCB054828 (Incyte)
  - Others

Results: BGJ398 in FGFR2-Mutated IHCC

Figure 3. Best Percentage Change From Baseline in the Size of Target Lesions With BGJ398 Treatment (n = 34)\textsuperscript{a,b}

Disease control rate: 75%
Partial response rate: 22%

\textsuperscript{a} 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]).

\textsuperscript{b} Patients marked with an asterisk had \textit{FGFR2} mutations (n = 2) or amplification (n = 3), or \textit{FGFR3} amplification (n = 1). All other patients had \textit{FGFR2} fusions (n = 28).
Results: BGJ398 in FGFR2-Mutated IHCC

Figure 2. Prolonged Duration of Exposure to BGJ398 (N = 47)\textsuperscript{a}

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

- Median duration: 188 days

\textsuperscript{a} Data cutoff, November 4, 2015.
Results: ARQ 087 in IHCC

- N=21 IHCC
  - n=12 with FGFR2 fusion
  - n=9 wild type
- Disease control rate:
  - 75% for fusion+
  - 0 for wild type

**Figure 1. Best % Change from Baseline in Size of Target Lesions and Duration of Exposure**

Tumor control (complete or partial response or stable disease) was achieved in one of seven iCCA pts in whom FGFR2 fusions were not identified and in nine of twelve pts with iCCA with FGFR2 fusions.

Mazzaferro V. et al ESMO World GI Abstract #340 2016
Retrospective Analysis: FGFR2 Inhibitor Therapy Correlated with OS

- Pooled analysis of 412 IHCC patients across 3 centers including UCSF
  - n=54 with FGFR mutations
    - 20 received FGFR targeted therapy

Figure 6. Kaplan-Meier curves of overall survival (OS) for 54 patients with a fibroblast growth factor receptor pathway genetic aberration with (n = 20) and without (n = 34) fibroblast growth factor receptor-specific treatment.

Javle et al Cancer epub Sep 13, 2016
Case: UCSF FGFR2+ IHCC Patient Treated with FGFR Inhibition

- 1/2016: Multifocal IHCC lesions
- 8/2016: Sustained partial response, 57% reduction in multifocal liver tumors
IDH 1/2 Inhibitors for IHCC

- Activating IDH1 or 2 mutations: ~20% of IHCC, lead to dedifferentiation and uncontrolled proliferation

- IDH1/2 inhibitors being tested in cholangiocarcinoma cohorts:
  - AG-120, AG-221, AG-881 (IDH1 and IDH2 inhibitors, Agios)
  - BAY1436032 (IDH1 inhibitor, Bayer)
  - Others
Duration on AG-120 Treatment: IHCC

~mPFS2

Treatment duration (weeks)

PR  SD  PD  UNK/NA  Ongoing  Progression/death

Burris et al AACR/NCI/EORTC 2015
Case: IDH-1 Mutant IHCC with Partial Response to AG-120

- A 65 year old female with IHCC, progressed on 3 prior lines of treatment
- 98.7% reduction in tumor 2-HG level at C3D1
- 81% reduction in Ki-67 staining

<table>
<thead>
<tr>
<th></th>
<th>H&amp;E</th>
<th>Ki-67</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td><img src="image" alt="H&amp;E Screening" /></td>
<td><img src="image" alt="Ki-67 Screening" /></td>
<td><img src="image" alt="MRI Screening" /></td>
</tr>
<tr>
<td>C3D1</td>
<td><img src="image" alt="H&amp;E C3D1" /></td>
<td><img src="image" alt="Ki-67 C3D1" /></td>
<td><img src="image" alt="MRI C3D1" /></td>
</tr>
</tbody>
</table>

Burris et al AACR/NCI/EORTC 2015
c-MET Inhibition with Tivantinib (ARQ-197) in HCC with High MET Expression: Phase II Trial Results

Median OS | Patients | Events
--- | --- | ---
Tivantinib: 7.2 mo. | 22 | 17
Placebo: 3.8 mo. | 15 | 15

HR: 0.38, Log Rank: $p=0.01$

Santoro et al, Lancet 14(1), 2013
METIV-HCC Trial: Tivantinib (ARQ-197) vs. Placebo for MET-High HCC

METIV-HCC (ARQ 197-A-U303)*

Phase 3 clinical trial in the Americas, Australia, Europe, New Zealand

Approximately 303 adult pts with:
- MET-High, measurable HCC
- Child-Pugh A, ECOG PS 0-1, inoperable, progressed or intolerant to 1 prior therapy with sorafenib

2:1 Randomization

Oral Tivantinib 120mg BID
202 pts

Oral Placebo BID
101 pts

Overall Survival

Eligibility and IHC criteria comparable to the ARQ 197-215 phase 2 RCT (except METIV-HCC selected MET-High patients only). Accrual completed in December 2015

Rimassa et al GI ASCO 2016
Objectives

2. Introduce new targets and treatments in liver and biliary cancers
   - Molecularly targeted therapies
   - Immunotherapy
Immune Checkpoint Inhibitors

- “Checkpoint inhibitors” boost anti-tumor immune response
  - PD-1/PD-L1 inhibitors
  - CTLA-4 inhibitors
- PD-1/-L1 inhibitors now approved by FDA for many cancers: melanoma, lung, kidney, bladder, head and neck, Hodgkin’s
  - Pembrolizumab, nivolumab, atezolizumab; others pending

- Promising early results in HCC and biliary cancers have led to rapid development of multiple ongoing registration trials
CheckMate 040: Phase 1/2 Trial of PD-1 Inhibitor Nivolumab in Advanced HCC

Figure 1. Study design

<table>
<thead>
<tr>
<th>Dose Escalation (n = 48)</th>
<th>Expansion (n = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uninfected</strong></td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 0.1 mg/kg (n = 1)</td>
<td>Sorafenib naïve/intolerant Nivo Q2W 3 mg/kg (n = 54)</td>
</tr>
<tr>
<td>Nivo Q2W 0.3 mg/kg (n = 3)</td>
<td>Sorafenib progressors Nivo Q2W 3 mg/kg (n = 58)</td>
</tr>
<tr>
<td>Nivo Q2W 1 mg/kg (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 3 mg/kg (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 10 mg/kg (n = 13)</td>
<td></td>
</tr>
<tr>
<td><strong>HCV-infected</strong></td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 0.3 mg/kg (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 1 mg/kg (n = 4)</td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 3 mg/kg (n = 3)</td>
<td></td>
</tr>
<tr>
<td><strong>HBV-infected</strong></td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 0.1 mg/kg (n = 5)</td>
<td>Nivo Q2W 3 mg/kg (n = 51)</td>
</tr>
<tr>
<td>Nivo Q2W 0.3 mg/kg (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 1 mg/kg (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Nivo Q2W 3 mg/kg (n = 4)</td>
<td></td>
</tr>
</tbody>
</table>

El-Khoueiry et al ASCO 2016 Abstract 4012; Sangro et al ILCA 2016 Abstract O-019
CheckMate 040: Safety and Efficacy Nivolumab in Advanced HCC (N=48)

- Response rate: 17%, including 3 complete responses
- Median duration of response: 17 months

---

Figure 2. Maximal change in target lesions from baseline

- Uninfected (n = 22): Nivo 0.1–10 mg/kg
- HCV (n = 10): Nivo 0.3–3 mg/kg
- HBV (n = 14): Nivo 0.1–3 mg/kg

*Complete response
*Partial response

El-Khoueiry et al ASCO 2016 Abstract 4012
Of 214 patients, five were not evaluable (two in the uninfected sorafenib progressor cohort and three in the HCV cohort), and data for percent maximal change in target lesion from baseline were missing for a further five (one in the uninfected sorafenib naïve/intolerant cohort, two in the uninfected sorafenib progressor cohort, one in the HCV cohort, and one in the HBV cohort).

Response rate: 16%
Median duration of response: NR

Sangro et al ILCA 2016 Abstract O-019 9-11 September 2016 - Vancouver, Canada
Figure 5. OS by prior sorafenib

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Naive</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at Risk</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>Time Since First Dose (Months)</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Proportion Survival

- Censored
- Naive
- Treated

Group | Died/Treated | Median (95% CI) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib-naive</td>
<td>7/11</td>
<td>14.1 (3.2, 28.6)</td>
</tr>
<tr>
<td>Sorafenib-treated</td>
<td>22/37</td>
<td>15.0 (5.0, 18.9)</td>
</tr>
</tbody>
</table>
Case: PD-1 Inhibition by Nivolumab in UCSF Patient with Nonviral HCC

- 28yo male with nonviral HCC with lung, bone, and scalp/dermal metastases, progressed after surgery, TACE, Y90, and 6 prior lines of systemic therapy

12/2015: AFP 46,051, bilirubin 3.8
8/2016: AFP 766, bilirubin 1.1
Case: Combined PD-L1 plus CTLA-4 Inhibition in UCSF Patient with Nonviral HCC

- 6/2016: AFP 8264
- 9/2016: AFP 46
Pembrolizumab (MK-3475, anti-PD-1) in Cholangiocarcinoma: KEYNOTE-028

- Screened 87 patients:
  - 41% tumor PD-L1+
  - Enrolled 24
    - CCA 83%
    - Gall bladder 17%

- Outcomes:
  - Partial response 17%
  - Stable disease 17%
  - Treatment-related grade 3 AE: 17%

Bang et al ESMO 2015, Abstract 525
Case: Complete Response to PD-1 Inhibition in UCSF Patient with IHCC

- 66yo female with CCA with liver, bone, lymph node, dermal, and cardiac metastases after surgery, progressed on 1st line GEMCIS chemotherapy

- Treated with 2nd line therapy on clinical trial of PD-1 inhibitor mAb
- Dramatic, durable response (“super-responder”); completed 2 years on treatment, no toxicity; now off treatment without recurrence since 6/2016
Case: PD-1 Inhibition plus GM-CSF in UCSF Patient with Mixed HCC-Cholangiocarcinoma

- 6/2016
- 8/2016
Immunotherapy: Ongoing Studies of Biomarkers, Combinations

- **Biomarkers:**
  - Microsatellite instability (MSI-high)/deficient mismatch repair (e.g. Lynch/HNPCC or sporadic cases of tumor MSI)
  - Tumor PD-L1 expression level, mutational burden, specific gene signatures?

- **Combination strategies for PD-1/-L1 inhibitors:**
  - CTLA-4 inhibitors, other immunotherapy agents
  - Chemotherapy?
  - Local therapies such as radiation, arterial therapies, ablation?
High Response Rates to PD-1/PD-L1 Inhibition in Mismatch-Repair Deficient Tumors

Response rate: 47%; 7 of 8 responders still ongoing at reporting
Immunotherapy: Immune-Related Adverse Events

- Immune-mediated adverse events can range from mild to severe (rare, generally <5% grade ≥3 each) including:
  - Endocrinopathies (thyroid, diabetes, pituitary, etc.)
  - Colitis including bleeding and perforations
  - Hepatitis, liver failure
  - Pneumonitis, respiratory failure
  - Myocarditis, pericardial effusions
  - Encephalitis, neuropathy, myasthenic syndrome
  - Nephritis including renal failure
  - Dermatitis, rashes
  - Allograft rejection *(cannot be used before/after transplant)*
Objectives

3. Looking ahead: How to integrate the old with the new?
Advanced HCC: Integrating Old and New

- Sorafenib remains current/only standard of care
- Multiple ongoing pivotal trials reporting soon:
  - 1\textsuperscript{st} line sorafenib versus PD-1 inhibitor nivolumab trial ongoing (CheckMate 459, NCT02576509)
  - 2\textsuperscript{nd} line: regorafenib, cabozantinib after sorafenib failure
  - MET-high: tivantinib phase 3 trial due to report late 2016
- Combination immunotherapy trials including PD-1/-L1 plus CTLA-4 inhibition suggest promise to improve response rates over PD-1/-L1 alone
- Role for immunotherapy in earlier stage disease and/or in combination with liver-directed therapies?
  - Immune-related toxicity is a significant concern in early-stage disease
  - Not thought safe before/after transplant
Advanced Biliary Cancers: Integrating Old and New

- GEMCIS remains current/only standard of care
- Emerging data support obtaining tumor sequencing for advanced biliary cancers:
  - Our practice is to obtain sequencing at diagnosis/during 1st line therapy
    - If positive for FGFR2, IDH1/2, BRAF, HER2, NTRK, ROS1, or other actionable mutation: Refer to targeted therapy trials
    - FGFR2-targeted therapy may be approved by FDA for FGFR2+ in future?
  - If known MSI-high/mismatch-repair deficient advanced biliary cancer: Refer for immunotherapy trials
    - Anti-PD-1 immunotherapy may be FDA-approved MSI-high/mismatch repair deficient advanced cancers in future?
Summary: Take-Home Points

- We recommend obtaining next-generation sequencing of advanced biliary cancer patients at diagnosis or during 1\textsuperscript{st} line therapy; refer for clinical trials if targetable aberration such as FGFR2, IDH1/2, BRAF, HER2, NTRK, ROS1, ALK1, MSI-high

- Immunotherapy studies show subset with extraordinary responses in both HCC and biliary cancers
  - Lynch syndrome/MSI have \(~50\%) response rate or higher
  - Toxicity issues: Cannot use before/after transplant; caution in earlier stages of disease
  - Many studies are underway to identify predictive biomarkers and combinations/strategies to augment response

These are promising times in hepatobiliary cancer treatment!
Acknowledgments

- GI Oncology Site Committee and research coordinators
- Colleagues in Hepatology/GI, IR, Surgery, Radiology, Radiation Oncology, and basic science research…
- The Bili Project Foundation, Inc.
- Cholangiocarcinoma Foundation
- Our patients and their families