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

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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 integrate the old with the new?

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 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
  - 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 1st, brivanib 2nd, SOR+erlotinib, SOR+doxorubicin, ramucirumab, everolimus, SOR adjuvant) all conducted in unselected HCC populations
- In 2016: SOR remains only FDA-labeled treatment; still no 2nd 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 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%

Sources:
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>ERBB2 Amplification (HER2)</td>
<td>4%</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 Substitution</td>
<td>5%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>FGFR1-3 Fusions and Amplifications</td>
<td>11%</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>CDKN2A/B Loss</td>
<td>27%</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>IDH1/2 Substitutions</td>
<td>20%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ARID1A Alterations</td>
<td>18%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>MET Amplification</td>
<td>2%</td>
<td>0</td>
<td>1%</td>
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</tbody>
</table>

N=554: IHCC n=412, EHCC n=57, GBC n=85

Javle et al Cancer epub Sep 13, 2016

Oncogenic Networks in HCC

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

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 unselected populations

Need to define relevant biologic subpopulations for clinical research and treatment
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, ARQ 087, 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>

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

![Image of results graph]

Disease control rate: 75%
Partial response rate: 22%
Results: BGJ398 in FGFR2-Mutated IHCC

- Median duration: 188 days

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

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

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

Randomized trial of AG-120 versus placebo expected to open in early 2017

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C-MET Inhibition with Tivantinib (ARQ-197) in HCC with High MET Expression: Phase II Trial Results

<table>
<thead>
<tr>
<th>Median OS</th>
<th>Patients</th>
<th>Events</th>
</tr>
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<tbody>
<tr>
<td>Tivantinib: 7.2 mo.</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Placebo: 3.8 mo.</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>HR: 0.38, Log Rank: p&lt;0.01</td>
<td></td>
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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

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

CheckMate 040: Safety and Efficacy Nivolumab in Advanced HCC (N=48)

Figure 2. Maximal change in target lesions from baseline

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

El-Khoueiry et al ASCO 2016 Abstract 4012;
Sangro et al ILCA 2016 Abstract O-019
CheckMate 040 Expansion Cohorts: Maximal Change in Target Lesions From Baseline

Response rate: 16%
Median duration of response or stable disease: NR

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 lesion volume from baseline were missing for a further five (one in the uninfected sorafenib naive/intolerant cohort, two in the uninfected sorafenib progressor cohort, one in the HCV cohort, and one in the HBV cohort).

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

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

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**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

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**Case: PD-1 Inhibition plus GM-CSF in UCSF Patient with Mixed HCC-Cholangiocarcinoma**

- 6/2016
- 8/2016

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**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

Objectives

3. Looking ahead: How to integrate the old with the new?

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 (avoid use before/after transplant)

Advanced HCC: Integrating the Old and New

- Sorafenib remains current/only standard of care
- Multiple ongoing pivotal trials reporting soon:
  - 1st line sorafenib versus PD-1 inhibitor nivolumab trial ongoing (CheckMate 459, NCT02576509)
  - 2nd line: regorafenib, cabozantinib after sorafenib failure
  - MET-high: tivantinib phase 3 trial due to report late 2016
- Combination immunotherapy trials suggest promise to improve response rates over PD-1/L1 alone
  - CTLA-4 plus PD-1/L1
- 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
  - Contraindicated before/after transplant due to rejection risk
Advanced Biliary Cancers: Integrating Old and New

- GEMCIS remains current/only standard of care
- Emerging data support obtaining tumor DNA sequencing for advanced biliary cancers:
  - Our practice is to obtain NGS panel at diagnosis/during 1st line therapy
    - If positive for FGFR2, IDH1/2, BRAF, HER2, NTRK, ROS1, or other actionable mutation: Refer to targeted therapy clinical 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 tumor DNA sequencing in advanced biliary cancer patients at diagnosis or during 1st 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 due to immune toxicities
  - Many studies are underway to identify predictive biomarkers and combinations/strategies to augment response

There is progress ahead for hepatobiliary cancer treatment

Acknowledgments

- GI Oncology Site Committee and research coordinators
- Colleagues in Hepatology/GI, IR, Surgery, Radiology, Radiation Oncology, and basic sciences
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- Cholangiocarcinoma Foundation
- Our patients and their families