Molecular alteration and new drugs in bile duct cancer

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Biliary tract cancer: epidemiology

BTC =

Intrahepatic BTC Mortality rates

In the US
Gallbladder & extrahepatic BTC
new cases = 10,910, Deaths = 3,700
A complete failure of “targeted therapies”
A biologically heterogeneous disease

Table 1: Prevalence of key genetic alterations in biliary tract cancers

<table>
<thead>
<tr>
<th>Variables</th>
<th>IHCC (%)</th>
<th>EHCC (%)</th>
<th>GBC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine kinase signaling</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EGFR</td>
<td>4</td>
<td>3</td>
<td>4–18</td>
</tr>
<tr>
<td>HER2</td>
<td>1.5–3</td>
<td>11–18</td>
<td>10–16</td>
</tr>
<tr>
<td>KRAS</td>
<td>17–30</td>
<td>12–40</td>
<td>0–13</td>
</tr>
<tr>
<td>BRAF</td>
<td>4–7</td>
<td>3</td>
<td>1–6</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>5–6</td>
<td>7–9</td>
<td>8–14</td>
</tr>
<tr>
<td>FGFR2 fusions</td>
<td>6–50</td>
<td>0–5</td>
<td>0–3</td>
</tr>
<tr>
<td>IDH pathway</td>
<td>10–28</td>
<td>0–7</td>
<td>0</td>
</tr>
<tr>
<td>Chromatin-remodeling genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARID1A</td>
<td>17</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>BAP1</td>
<td>11</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>PBRM1</td>
<td>8</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>
A biologically heterogeneous disease

- **INTRAHEPATIC**
  - KRAS
  - FGFR2 fusions
  - IDH1/2

- **EXTRAHEPATIC**
  - KRAS
  - HER2

- **GALLBLADDER**
  - EGFR
  - HER2
  - PIK3CA
Targeted therapy and targeted population...BGJ398 (infigratinib) in patients with FGFR-altered advanced cholangiocarcinoma

BGJ398: Pan FGFR MKI
61 patients
- ECOG PS 1 or 2
- Prior antineoplastic regimens:
  - Median: 2, Range: 1 - 4
- **FGFR status**
  - FGFR1 amplified: 1
  - FGFR2
    - Amplified 3
    - Mutated 8
    - Fusion 48
  - FGFR3 amplified: 4

On the opposite all-comers: Tribimetinib: anti-MEK

20 refractory patients (1 line: 12, 2 lines: 8)
• 40% gallbladder
• 25% intrahepatic
• 30% bile duct, 5% ampulla of Vater
• No OR, stable disease: 65%
• Median PFS: 10.6 weeks
• One-year overall survival: 20%

Conclusion: Prolonged PFS was observed in one patient having a specific biological pattern

IDH1-3 in intra-hepatic cholangiocarcinoma

- Mutant IDH inhibitors are tested
- The mutant forms of IDH1/2 catalyse the non-reversible accumulation of 2-hydroxyglutarate (2HG)
- Enasidenib, Ivosidenib (AG-120), on-going phase III
A step forward: MOSCATO 1 screening molecular program

- ON PURPOSE TUMOR BIOPSY
- MOLECULAR SCREENING NGS & CGH ARRAY & RNAseq
- CLINICAL DECISION
- TREATMENT

Tumor Progression

Previous Therapy

Molecular Targeted Agent (MOSCATO)

> 25% of PFS 1

PFS 2

> 1.3
Flow chart

Patients
N = 42

Biopsies
N = 47

Fit for analysis
N = 35

Druggable molecular aberration(s)
N = 25 (71%)

Treated
N = 18 (54%)

Since November 2011

No biopsy = 3
Ongoing = 2
Cellularity < 10% = 7
Alterations in biliary tract cancer: MOSCATO trial

Results for efficacy

Change from baseline (RECIST1.1, %)

Molecular targets

Altered pathway:
- MAPK
- EMT
- DNA damage
- TKR
- Metabolism

- Ongoing
- Same patient

Exemple…

Trastuzumab + lapatinib

Baseline
10-14-2015

1st evaluation
01-11-2016

Confirmation
02-12-2016

-54%
PFS ratio was 2.1 (versus 1.3 in MOSCATO main endpoint)

Overall survival...
TCGA: different prognostic groups

489 cholangiocarcinoma from 10 countries

- Highest SNV burden
- Enriched in TP53, ARID1A, BRCA1/2 mutations
- Enriched in H3K27me3-assoc. promoter mutations

Enriched in TP53 mutations

- Highest CNA burden
  1p, 2p, 2q, 7p, 16p, 19q, 20q

ERBB2 amplification

- TET1
- EZH2

CTNNB1, WNT5B, AKT1

- Immune-related pathways
  PD1, PDL2 and BTLA

FGFR1
FGFR2
FGFR3
FGFR4

CpG Island
Hypermethylated

CpG Shore
Hypermethylated

Prognosis

Poorer Prognosis

Better Prognosis
The true hope: the European project

UK: J Bridgewater, ABC10
France: D Malka

• Evaluate the role of personalized medicine in these patients
• Molecular screening

Flowchart:
- Failure (15%, n = 111)
  - Tumor molecular profiling
    - 1L-SoC (e.g., CisGem) (3 months)
      - No PD (85%, n = 535)
        - No alteration (50%, n = 267)
          - Experimental arm (n = 160)
            - Alt A
            - Alt B
            - Alt C
          - Continuation of 1L-SoC
            - Tx A
            - Tx B
            - Tx C
        - Frequent alterations (40%, n = 214)
          - Control arm (n = 54)
            - Alt Y
            - Alt Z
          - Continuation of 1L-SoC
            - Tx Y
            - Tx Z
      - Rare alterations (10%, n = 54)
        - PD (15%, n = 94)

2L-Tx

PD

Cross-over to Tx

R

3:1
Pembrolizumab and refractory bile ducts cancers

- Multicentric single arm phase II trial:
  - pembrolizumab (200 mg IV/3 weeks)

- Inclusion criteria:
  - Cholangiocarcinoma with progressive disease after at least one line of treatment (59% ≥ 2 lines)
  - ECOG PS 0-1
  - Tissue sample available for PDL1 IHC evaluation.

- Endpoints
  - Main endpoint: Objective response rate
  - Secondary: PFS, OS, Tolerance
## Pembrolizumab and refractory bile ducts cancers

<table>
<thead>
<tr>
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<th>Population N=104</th>
<th>PLD1+ N = 61</th>
<th>PLD1- N = 34</th>
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<tbody>
<tr>
<td><strong>Objective response</strong></td>
<td></td>
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<tr>
<td>Partial response</td>
<td>5.8%</td>
<td>6.6%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Stabilisation</td>
<td>6 (6%)</td>
<td>4 (7%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>17 (16%)</td>
<td>6 (10%)</td>
<td>11 (32%)</td>
</tr>
<tr>
<td>PFS</td>
<td>65 (63%)</td>
<td>44 (72%)</td>
<td>17 (50%)</td>
</tr>
<tr>
<td>OS</td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

→ Median duration of response: not reached
Immunotherapy: durvalumab + tremelimumab

<table>
<thead>
<tr>
<th></th>
<th>Bile duct cancers (n=12)</th>
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<tbody>
<tr>
<td>OR</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>PFS</td>
<td>3.1 months</td>
</tr>
<tr>
<td>OS</td>
<td>5.45 months</td>
</tr>
</tbody>
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Side effects, Grade > 3: 14%

Charalampos S et al GI ASCO 2019 abs 316
Conclusion

• Among GI cancers bile duct tumours are probably the best candidates for personalized medicine
• Druggable targets have already been identified
  – IDH1 for intrahepatic cholangiocarcinoma
  – FGFR fusion for intrahepatic cholangiocarcinoma
  – HER2 for PI3K for gallbladder carcinoma
  – HER2 for extrahepatic cholangiocarcinoma
• Biologically-driven trials are starting…