CLINICAL UPDATE ON DIGESTIVE RARE CANCERS

BILIARY TUMORS

MONICA NIGER, MD
Medical Oncology Department
FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI
MILANO

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AGENDA

✓ BILIARY TRACT TUMORS
  ✓ Numbers and classification
  ✓ Standard treatments
  ✓ Heterogeneity
  ✓ Molecular profiling

✓ PROMISING NEW TARGETS AND THERAPIES FOR CCA
  ✓ IDH
  ✓ FGFR
  ✓ BRAF
  ✓ Immunotherapy
What’ to know about BTC?

➢ Group of rare diseases
  < 3% of GI tract cancers

➢ Complex anatomy
  Anatomy can impact the molecular features, complications, surgical approach etc..

➢ Various different causes
  Liver fluke infection, biliary duct diseases, viral hepatitis, lifestyle etc..
Classification

✓ Intrahepatic Cholangiocarcinoma (ICC)  
53% of all CC – Rates *increasing*

✓ Extrahepatic Cholangiocarcinoma (ECC)  
47% of all CC – Rates *relatively stable*
  • Hilar (Klatskin), 5%  
  • Distal tumors, 42%

✓ Gallbladder Carcinoma  
*Rates decreasing*
Prognosis

Percent Surviving 5 Years

< 20%
mPFS Cis + Gem 8.0 months (95% CI, 6.6 to 8.6)
mOS Cis + Gem 11.7 months (95% CI, 9.5 to 14.3)

**1st Line: one fits all**

**STANDARD 1L-DRUG THERAPY SINCE 2010!**

Valle et al, NEJM 2010

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"There is insufficient evidence to recommend specific regimens for second-line therapy in this group of patients, and prospective randomized trials are needed. “
HETEROGENEITY and TUMOR PROFILING

489 CCAs from 10 countries

Jusakul et al, Cancer Discovery 2017
TGCA TUMOR PROFILING

➢ Mostly iCCA, All Fluke-Neg

➢ IDH mutants CCA have distinct mRNA, copy number and DNA methylation features

➢ The association between the mitochondrial gene signature and IDH was not observed upon analysis of other TCGA datasets

Particular to CCA

Farshidfar et al, Cell 2017
195 pts, iCCA (81%), eCCA (19%), 410-gene panel

- Commonly mutated genes: IDH1 (25%), TP53 (24%), ARID1A (21%), BAP1 (15%), KRAS (13%), PBRM1 (12%), SMAD4 (9%) and ATM (8%)

- One tumour (0.5%) had MSI-H

- **BAP1 mutations and FGFR2 gene fusions were exclusive in iCCA**
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POTENTIAL TARGETS FOR CCA

- IDH 1/2 mutations
  - IDH inhibitors
  - PARP inhibitors
  - Dasatinib

- FGFR2 aberrations
  - FGFR inhibitors

- CDKN2A/B aberration and CCDN1 amplification
  - CDK4/6 inhibitors

- PIK3CA, AKT, PTEN mutations
  - AKT, mTOR inhibitors

- BRCA1/2 or BAP1 mutations
  - PARP/ATM inhibitors

- dMMR/MSI, high TMB
  - Immune-checkpoint inhibitors

- BRAF mutations
  - BRAF + MEK inhibitors

- Mutations of Chromatin remodeling genes (e.g., IDH1/2, ARID1A/B, BAP1, PBRM1)
  - EZH2, HDAC, DNMT and PARP inhibitors
IDH1/2 mutation in cholangiocarcinoma

- Wang et al (2013): better prognosis
- Zhu et al (2014): no difference
- Goyal et al (2015): no difference

IDHm 15%-20%
IDH1/2 INHIBITORS FOR CCAs

Ivosidenib (AGI-120) is an oral mutant IDH1 inhibitor

73 CCAs (89% iCCAs) in the Phase I trial → RR 5%, SD 56%, PFS at 6 months 38.5%

ClarIDHy: a phase 3, multicenter, randomized, double-blind study of AG-120 vs placebo in patients with an advanced cholangiocarcinoma with an IDH1 mutation
ONCOMETABOLITE-INDUCED BRCAness

AKG – dependent enzymes

➢ Homologous Repair Defect (HRD)
➢ Genomic Instability via HRD
➢ Radiation and Chemo Sensitivity
➢ PARPi Synthetic Lethality

Sulkowski et al, STM 2017

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EXPLOITING ONCOMETABOLITE-INDUCED BRCAness

A Phase 2 Study of the PARP Inhibitor Olaparib in IDH1 and IDH2 Mutant Advanced Solid Tumors (NCT03212274)

- **IDH1/2 mutant glioma**
  - Pre-treated with IDH inhibitors
  - Not pre-treated with IDH inhibitors

- **IDH1/2 mutant cholangiocarcinoma**
  - Pre-treated with IDH inhibitors
  - Not pre-treated with IDH inhibitors

- **IDH1/2 other mutant solid tumors**
  - Pre-treated with IDH inhibitors
  - Not pre-treated with IDH inhibitors

Olaparib 300 mg q12hrs each day, 28-day cycle
Until disease progression/unacceptable toxicity/other discontinuation criteria

**CORRELATIVE STUDIES** include:
- tumor biopsies, DNA/RNA sequencing, liquid biopsy
FGFR2 gene aberrations: clinical features

- Earlier stage disease, Predominantly G2
- Longer OS
- **BUT** PFS with 1st line CT showed no differences

# FGFRi in CCAs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>TARGET</th>
<th>RR</th>
<th>DCR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCB054828 (Pemigatinib)</td>
<td>Selective SMKI FGFR1-3</td>
<td>33% (3/9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BGJ398 (Infigratinib)</td>
<td>Selective SMKI panFGFR</td>
<td>25.4% (18/71)</td>
<td>83.6%</td>
<td>6.8 months</td>
</tr>
<tr>
<td>ARQ087 (Derazantinib)</td>
<td>Selective SMKI panFGFR</td>
<td>20.7% (6/29)</td>
<td>82.8%</td>
<td>5.7 months</td>
</tr>
<tr>
<td>JNJ-42756493 (Erdafitinib)</td>
<td>Selective SMKI panFGFR</td>
<td>27.3% (3/11)</td>
<td>55%</td>
<td>5.1 months</td>
</tr>
<tr>
<td>TAS-120</td>
<td>Selective irreversible SMKI panFGFR</td>
<td>25% (7/28) - FGFR2 fusion 18% (3/17) - other FGF/FGFR GA 31% (4/13) - pretreated with FGFRi</td>
<td>79% (overall)</td>
<td>-</td>
</tr>
</tbody>
</table>

Saleh et al ENA 2017; Javle et al, ESMO 2018; Mazzaferro et al, BJC 2018; Soria et al ASCO 2017; Tran et al ESMO GI 2018
Targeting BRAF mutations

ROAR: A Phase 2, Open-label, Multicenter Study (NCT02034110)

- Anaplastic thyroid cancer
- Gastrointestinal stromal tumor
- Germ cell tumor
- WHO grade 1 or 2 glioma
- WHO grade 3 or 4 glioma
- Hairy cell leukemia
- Multiple myeloma
- ASI

**Patients with BRAF V600E–mutated cancers**

**Primary Analysis**

Patients with BTC
- Dabrafenib (150 mg BID) + Trametinib (2 mg QD)
- Disease progression, death, or unacceptable toxicity

**Expansion Phase**

Patients with BTC
- n = 15

Dose

- Primary endpoint: Investigator-assessed ORR by RECIST v1.1
- Secondary endpoints: PFS, DOR, OS, safety

**Primary Analysis**

Patients with ASI
- n = 3

A Bayesian hierarchical statistical design was used to address the small sample size

**Primary endpoint:** Investigator-assessed ORR by RECIST v1.1

**Secondary endpoints:** PFS, DOR, OS, safety

DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; WHO, World Health Organization.

Presented at ENA 2018
Targeting BRAF mutations

mOS: 11.3 months (95% CI, 7.3-17.7 mo)
mPFS: 7.2 months by investigator assessment (95% CI, 4.6-10.1 mo)

Presented at ENA 2018

BRAFm 5%-7% of iCCA

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MSI AND IMMUNOTHERAPY

MMRD predicts response to immunotherapy...

MSI CCAs
0.5-2.5%

Le et al, N Eng J Med 2015
Pembrolizumab for Advanced Biliary Adenocarcinoma: Results From the Multicohort, Phase 2 KEYNOTE-158 Study

Figure 2. Best Percentage Change From Baseline in Target Lesion Size (RECIST version 1.1 by Independent Central Review)

Table 2. Summary of Response (RECIST version 1.1 by Independent Central Review)

<table>
<thead>
<tr>
<th></th>
<th>Overalla</th>
<th>PD-L1-positive</th>
<th>PD-L1-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>N = 104</td>
<td>n = 61</td>
<td>n = 34</td>
</tr>
<tr>
<td>ORR, (%) (95% CI)</td>
<td>5.8 (2.1–12.1)</td>
<td>6.6 (1.8–15.9)</td>
<td>2.9 (0.1–15.3)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (5.8)</td>
<td>4 (6.6)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17 (16.3)</td>
<td>6 (9.8)</td>
<td>11 (32.4)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>65 (62.5)</td>
<td>44 (72.1)</td>
<td>17 (50.0)</td>
</tr>
<tr>
<td>Nonevalualec</td>
<td>2 (1.9)</td>
<td>2 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>No assessmentd</td>
<td>14 (13.5)</td>
<td>5 (8.2)</td>
<td>5 (14.7)</td>
</tr>
</tbody>
</table>

Figure 3. Time to and Duration of Response Assessed per RECIST version 1.1 by Independent Central Review

PD-L1-positive
PD-L1-negative
Unknown
PR
PD
Ongoing Response

Presented at ESMO 2018
WHAT ABOUT THE OTHER 97.5%?

<table>
<thead>
<tr>
<th>Agents/Approach</th>
<th>NCT</th>
<th>Population/Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + TIL’s</td>
<td>NCT01174121</td>
<td>Includes cholangio</td>
</tr>
<tr>
<td>Nivolumab/ Ipilimumab</td>
<td>NCT03101566, NCT02834013</td>
<td>Includes cholangio</td>
</tr>
<tr>
<td>Durvalumab/ Tremelimumab</td>
<td>NCT01938612</td>
<td>Includes cholangio</td>
</tr>
<tr>
<td><strong>Checkpoint + Local Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremelimumab + TACE, RFA, Cyro, SBRT</td>
<td>NCT01853618</td>
<td>HCC, cholangioca</td>
</tr>
<tr>
<td>Durvalumab, tremelimumab + TACE, RFA, Cyro</td>
<td>NCT02821754</td>
<td>HCC, cholangioca</td>
</tr>
<tr>
<td><strong>Checkpoint + Targeted Approach</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab + XL888 (HSP-90i)</td>
<td>NCT03095781</td>
<td>Includes cholangioca</td>
</tr>
<tr>
<td>Pembrolizumab + INCB054828 (FGFR1-3i)</td>
<td>NCT02393248</td>
<td>Includes cholangioca</td>
</tr>
<tr>
<td>Atezolizumab +/- Cobimetinib (MEKi)</td>
<td>NCT03201458</td>
<td>Rand phase II, PFS</td>
</tr>
</tbody>
</table>
Conclusions

✓ BTC is a group of rare and heterogeneous diseases, with poor prognosis

✓ Platinum – based regimens are the standard option as 1st line therapy for advanced disease

✓ There is no 2nd line treatment established

✓ Molecular characterization opened the door for new targeted therapies → FGFR rearrangements, IDH1/2 mutations, BRAF mutations, MSI can lead to potentially effective treatments

✓ ALWAYS consider sequencing/testing for MSI and refer your patients to Clinical Trials
Thank you!
to be continued...

monica.niger@istitutotumori.mi.it