UPDATE ON DIGESTIVE RARE CANCERS

BILIARY TUMORS

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AGENDA

✓ BILIARY TRACT TUMORS (BTCs)
  ✓ Numbers, classification & risk factors
  ✓ Update on Resected disease
  ✓ Update on Unresectable/metastatic disease

✓ MOLECULAR PROFILING AND FUTURE PERSPECTIVES
  ✓ Heterogeneity & Molecular profiling
  ✓ IDH
  ✓ BRAF
  ✓ FGFR2
What’ to know about BTC?

➢ Rare cancers
  3% of GI cancers

➢ Poor prognosis
  < 20% pts alive at 5 years

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

➢ Complex anatomy
  Extrahepatic ≠ Intrahepatic ≠ Gallbladder
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
Risk Factors

**Established Risk Factors**
- Parasitic infections
- Gallstones/Bile Duct Stones
- Primary Sclerosing Cholangitis
- Congenital Bile Duct Abnormalities
  - Choledochal cyst
  - Caroli’s disease
- Inflammatory Bowel Disease

**Possible Risk Factors**
- Cirrhosis
- Viral hepatitis (HCV, HBV)
- Diabetes
- Smoking
- Alcohol
- Obesity
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What’s to know about Resected BTC?

Radical Surgery is the only cure, **BUT**...

- **Unresectable disease** at diagnosis → 60 - 80%
- **High Recurrence rate** → 60 - 70%
- **Retrospective studies** provide conflicting evidence regarding Adjuvant Therapy

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Adjuvant therapy: BILCAP is the “new” standard

A. Intention-to-treat analysis

B. Per-protocol analysis

Primrose et al, Lancet Oncology 2019
**PRODIGE 12**

- Log-rank $p=0.74$
- At 36 months

No trend toward benefit in any subgroup

- Significantly worse survival in GBC, $HR=3.39$, $p=0.025$

**BCAT**

- $HR=1.08$ [0.70-1.66], $p=0.74$

No trend toward benefit in any subgroup

*Edeline et al ESMO 2017, **Ebata et al Br J Surg 2018*
✓ Adjuvant chemotherapy for resected biliary tract cancer is established and should be offered

✓ Capecitabine chemotherapy for a duration of 6 months is the new standard of care

✓ Chemoradiotherapy can be considered, especially for R1 and/or N+ cases
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1st Line: one fits all

Hazard ratio for death, 0.64 (95% CI, 0.52–0.80)  
P < 0.001

Overall Survival (%)

No. at Risk
Gemcitabine: 206 115 56 18 4 3 1 1 1  
Cisplatin–gemcitabine: 204 140 95 36 18 10 4 1 1 1

mOS Cis + Gem 11.7 months (95% CI, 9.5 to 14.3)

mPFS Cis + Gem 8.0 months (95% CI, 6.6 to 8.6)

Valle et al, NEJM 2010

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STANDARD 1° LINE THERAPY SINCE 2010!
1\textsuperscript{st} Line: Establishing a new standard?

1. Single arm, Phase II study (74 pts): Nab-Paclitaxel + Gemcitabine as first line for CCA
1\textsuperscript{st} Line: Establishing a new standard?

1. Single arm, Phase II study (74 pts): \textbf{Nab-Paclitaxel + Gemcitabine} as first line for CCA

\textbf{mPFS 7.7 months (95\% CI 5.4 – 13.1)}

\textbf{mOS 12.4 months (95\% CI 9.2 – 15.9)}

Primary endpoint (70\% PFS rate at 6 months) \textbf{NOT MET}

\textit{Sahai et al, JAMA Oncology 2018}
1\textsuperscript{st} Line: Establishing a new standard?

2. Single arm, Phase II study (60 pts): \textbf{Nab-Paclitaxel + Gemcitabine – Cisplatin} as First line for CCA

**Progression-free survival**
- Median PFS = 11.8 mo (95% CI, 6.0 to 15.6 mo)

**Overall survival**
- Median OS = 19.2 mo (95% CI, 13.2 mo to not estimable)
1st Line: Establishing a new standard?

3. Phase II (41 pts): Selective Internal Radiotherapy (SIRT) + Cisplatin + Gemcitabine*

*Edeline et al, JAMA Oncology 2019, **Cercek et al, JAMA Oncology 2019
1\textsuperscript{st} Line: Establishing a new standard?

3. Phase II (41 pts): Selective Internal Radiotherapy (SIRT) + Cisplatin + Gemcitabine*

4. Phase II (38 pts): Hepatic Arterial Infusion (HAI) floxuridine + Gemcitabine + Oxaliplatin**

*Edeline et al, JAMA Oncology 2019,  **Cercek et al, JAMA Oncology 2019
2nd Line: no good options...

Second-line chemotherapy in advanced biliary cancer: a systematic review

A. Lamarca¹, R. A. Hubner¹, W. David Ryder² & J. W. Valle³

¹Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester; ²MAHSC Clinical Trials Unit, The Christie NHS Foundation Trust, Manchester, UK

“There is insufficient evidence to recommend specific regimens for second-line therapy in this group of patients, and prospective randomized trials are needed. “
Primary end-point: Overall Survival (ITT)

- The **primary end-point was met**: adjusted* HR was 0.69 (95% CI 0.50-0.97; p=0.031) for OS in favour of ASC + mFOLFOX arm (vs ASC)

- No marked evidence was identified against the key proportional hazards assumption**, which confirmed the validity of using the Cox Regression analysis

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*adjusted for platinum sensitivity, albumin, and stage
**proportional hazards assumption test p-value 0.129

ITT=intention-to-treat analysis; ASC=activity of control
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✓ BILIARY TRACT TUMORS (BTCs)
  ✓ Numbers, classification & risk factors
  ✓ Current treatment for resected disease
  ✓ Current treatment for advanced disease

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  ✓ Heterogeneity & Molecular profiling
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Heterogeneity and Tumor Profiling

489 CCAs from 10 countries
Potential targets for CCA

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

- **FGFR2 aberrations**
  - FGFR inhibitors

- **CDKN2A/B aberration and CCND1 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
Targeting IDH1 mutations

Ghassan K. Abou-Alfa et al ESMO 2019

IDHm 15%-20%

<table>
<thead>
<tr>
<th></th>
<th>Ivosidenib</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>PFS</td>
<td></td>
<td></td>
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<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>
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<tr>
<td>12-month rate</td>
<td>22%</td>
<td>NE</td>
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<tr>
<td>Disease control rate (PR+SD)</td>
<td>53% (2% PR, 51% SD)</td>
<td>28% (0% PR, 28% SD)</td>
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HR=0.37 (95% CI 0.25, 0.54)  
P<0.001
Targeting BRAF mutations

ROAR: Phase 2 Study of Dabrafenib/Trametinib in BRAF V600E mutant iCCA

- ORR = 42% by investigator assessment, 36% by independent review
- Median PFS: 9.2 months by investigator assessment (95% CI, 5.4-10.1 months)
- Median OS was 11.7 months (95% CI, 7.5-17.7 months)

5%-7% of iCCA
Targeting FGFR2 fusions

**Infigratinib**

![Graph showing best change from baseline for Infigratinib.](image)

**Derazantinib**

**Pemigatinib**

![Graph showing best change from baseline for Pemigatinib.](image)

* Javle et al, JCO 2018; ** Mazzaferro et al, BJC 2018; Vogel A ESMO 2019*
MSI and Immunotherapy

MMRD predicts response to immunotherapy...

0.5 – 2.5% CCAs

Le et al, N Eng J Med 2015
Conclusions

✓ BTCs are heterogeneous and aggressive diseases, with poor prognosis

✓ Multidisciplinary assessment is essential

✓ ALWAYS consider refer your pts to Referral centers to assess for Molecular Characterization and Clinical Trials

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to be continued...