Treatment strategy in Pancreatic Cancer and Biliary Tract Cancer

ESO-ESMO masterclass
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Prof Eric Van Cutsem, MD, PhD
Digestive Oncology
Leuven, Belgium

Eric.VanCutsem@uzleuven.be
Pancreatic cancer:
2\textsuperscript{d} cause of death by cancer in 2020

Rahib L. Cancer Res 2014
Ferlay J. Acta Oncologica 2016
Pancreatic adenocarcinoma: a very tough disease!

- ~85% of patients are diagnosed with advanced unresectable disease
- ~80% of patients who have resection and adjuvant therapy relapse
- “Cure” rate is only ~5%
- Median survival of patients with metastases without treatment is only about 3 months
- Incidence numbers and numbers of deaths are almost identical

- Often rapid progression with a lot of symptoms: so optimal symptom management and palliative care is crucial
  - Cachexia, anorexia
  - Jaundice: bile duct obstruction
  - Gastric outlet obstruction
  - Pain
Evolution in Pancreatic Ductal adenocarcinoma & Role of Stroma in the Development

Figure 2. Biologic Features of Pancreatic Cancer.
Pancreatic cancers have a complex microenvironment that might be a target for therapy. TCA denotes tricarboxylic acid.
4 sub-types:
1. Squamous: more aggressive and spread more quickly
2. Pancreatic progenitor: triggered by errors in the cells that should guide the development of the pancreas
3. Immunogenic
4. Aberrantly differentiated endocrine exocrine (ADEX): subtype of pancreatic progenitor tumours, where specific genes are upregulated

- Subtypes correlate with histopathologic characteristics and may provide rationale for therapeutic strategies
Pancreatic adenocarcinoma: treatment strategy
clinical grouping

- Metastatic disease
  - Chemotherapy: modest progress

- Resectable disease
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease
Treatment of Pancreatic Cancer

Key Milestones

But despite improvements:

Median survival remains under 1 year in advanced stage
In early stage, 5-year survival rate is only about 20-25%

- Gemcitabine 1994
- Erlotinib + gemcitabine 1998
- FOLFIRINOX 2002
- nab-Pacl + gemcitabine 2006
- S1 (Japan) + gemcitabine 2010
- Adjuvant gemcitabine + capecitabine 2012
- Adjuvant FOLFIRINOX 2016
- Pembrolizumab MSI-H/dMMR (US) 2018
- Olaparib in germline BRCA 2019
Treatment of Metastatic Pancreatic Cancer is Palliative

Benefits
- Prolong survival
- Improve clinical symptoms
- Improve quality of life

Toxicity
Incremental Benefits With New Agents in Frontline

**ACCORD trial: Gemcitabine vs FOLFIRINOX**

### Outcomes

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX</th>
<th>Gem</th>
<th>HR</th>
<th>P</th>
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<tbody>
<tr>
<td>RR</td>
<td>31.6%</td>
<td>9.4%</td>
<td>.57</td>
<td>&lt;.001</td>
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<tr>
<td>PFS, months</td>
<td>6.4</td>
<td>3.3</td>
<td>.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OS, months</td>
<td>11.1</td>
<td>6.8</td>
<td>.57</td>
<td>&lt;.001</td>
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</tbody>
</table>

**12-month OS**
- FOLFIRINOX: 48.4%
- Gem: 20.5%

**18-month OS**
- FOLFIRINOX: 18.6%
- Gem: 6%

---

MPACT trial:
Gemcitabine ± Nabplacitaxel

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>nab-P + Gem</th>
<th>Gem</th>
<th>HR</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>RR</td>
<td>23%</td>
<td>7%</td>
<td>0.72</td>
<td>.001</td>
</tr>
<tr>
<td>PFS, months</td>
<td>5.5</td>
<td>3.7</td>
<td>0.69</td>
<td>&lt;.001</td>
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<tr>
<td>OS, months</td>
<td>8.5</td>
<td>6.7</td>
<td>0.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>24-month OS</td>
<td>10%</td>
<td>5%</td>
<td>0.69</td>
<td>.021</td>
</tr>
<tr>
<td>42-month OS</td>
<td>3%</td>
<td>0%</td>
<td>0.72</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

HR = 0.72
95% CI (0.617-0.835)
P = 0.000015

Strategy in metastatic PDAC

**Very fit:**
Pressure for rapid regression

**Fit:**
But reduced PS

**Unfit:**
poor PS

- **FOLFIRINOX** or **GEM + Nab-paclitaxel**
- **GEM + Nab-paclitaxel** or **GEM mono ? / mFOLFIRINOX?**
- **BSC** or **GEM mono**

Clinical trials:
- GEM + nab-paclitaxel
- Or possibly FOLFIRINOX backbone

Clinical trials:
- GEM + nab-paclitaxel backbone
Treatment selection depends on a wide range of factors.
NAPOLI-1 Results in second line

OS

PFS

New Subgroups

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

Recommendation 3.1. **Routine testing for dMMR or MSI-H is recommended, using IHC, PCR, or NGS for patients who are considered to be candidates for checkpoint inhibitor therapy** (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.2. **PD-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested positive for dMMR or MSI-H** (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

MSI-high/dMMR across 12 tumor types
N = 86

- Aprox. 1% mPCA
  MSI-H/dMMR (IHC, PCR, NGS)

ORR for all patients were 53% (21% CR), responses were durable, mPFS and mOS not reached.

CR, complete response; DCR, disease control rate IHC, immunohistochemistry; NGS, next generation sequencing; PCR, polymerase chain reaction

BRCA Mutations May Predict Benefit of Platinum Therapy and PARP Inhibitors

POLO: A Phase III International PARPi Maintenance Study in \textit{gBRCA} Mutated Patients

- mPCA
- Prior platinum therapy
- Germline \textit{BRCA} mutated
- ECOG 0-1

N = 145
Primary endpoint = PFS

Press release: March 2019: study meets primary endpoint

Future developments?

- Targeting the stroma:
  - PEGylated-rHuPH20 (PEGPH20): hyaluronic acid
  - Hedgehog inhibitors
  - Stromal FAK

- Targeting stem cells:
  - napabucasin

- Exploiting DNA repair defects:
  - PARP inhibitors in gBRCA mutants

- Immunotherapy:
  - MSI tumors: anti-PD(L) AB
  - Combination & new approaches

- Targeting abnormal metabolism:
  - CPI-613: selectively blocks PDH and KGDH triggering cell death that is highly selective to tumor Cells

- Bruton kinase inhibitors:
  - ibrutinib

- Targeting CDK4/6:
  - abemaciclib, ribociclib

- Mesothelin-based Immunotherapy

- Asparaginase loaded RBC

- ....
**Pancreatic adenocarcinoma:**

**treatment strategy**

**clinical grouping**

- **Metastatic disease**
  - Chemotherapy: modest progress

- **Resectable disease**
- **Borderline resectable disease**
- **Locally advanced, but clearly not resectable disease**
Metastatic disease

Resectable disease: resection in experienced teams/high volume
  ✓ resection plus adjuvant treatment
  ✓ Evolution towards trials with neo-adjuvant treatment

Borderline resectable disease
Locally advanced, but clearly not resectable disease
Anatomy of pancreatic cancer

Figure 3. Anatomy and Surgical Resectability of Pancreatic Cancer.
Pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases.
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Survival</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>43</td>
<td>Observation</td>
<td>10% at 2 yr</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorouracil plus radiotherapy</td>
<td>20% at 2 yr</td>
<td></td>
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<tr>
<td>EORTC</td>
<td>218</td>
<td>Observation</td>
<td>26% at 2 yr</td>
<td>0.10</td>
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<td></td>
<td></td>
<td>Fluorouracil plus radiotherapy</td>
<td>34% at 2 yr</td>
<td></td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>289</td>
<td>Observation</td>
<td>16.9 mo (median)†</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemoradiotherapy</td>
<td>13.9 mo</td>
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<tr>
<td></td>
<td></td>
<td>Fluorouracil</td>
<td>21.6 mo</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Chemoradiotherapy plus fluorouracil</td>
<td>19.9 mo</td>
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</tr>
<tr>
<td>CONKO-01</td>
<td>368</td>
<td>Observation</td>
<td>10.4% at 5 yr</td>
<td>0.01</td>
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<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>20.7% at 5 yr</td>
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<tr>
<td>ESPAC 3</td>
<td>1088</td>
<td>Fluorouracil</td>
<td>23.0 mo (median)†</td>
<td>0.39</td>
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<tr>
<td></td>
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<td>Gemcitabine</td>
<td>23.6 mo</td>
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<tr>
<td>RTOG 9704</td>
<td>451</td>
<td>Fluorouracil plus radiotherapy</td>
<td>22% at 5 yr</td>
<td>0.12</td>
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<td></td>
<td></td>
<td>Gemcitabine plus radiotherapy</td>
<td>18% at 5 yr</td>
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<tr>
<td>JASPAC-01</td>
<td>378</td>
<td>5-FU (oral fluoropyrimidine)</td>
<td>70% at 2 yr</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>53% at 2 yr</td>
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</table>

* CONKO-01 denotes Charité, EORTC European Organization for Research and Treatment of Cancer, ESPAC European Study Group for Pancreatic Cancer, GITSG Gastrointestinal Tumor Study Group, JASPAC-01 Japan Adjuvant Study Group for Pancreatic Cancer, and RTOG 9704 Radiation Therapy Oncology Group 9704.

† The estimated 5-year survival rate was 10% among patients who received chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy (P=0.05). The 5-year survival rate was 21% among patients who received chemotherapy and 5% among patients who did not receive chemotherapy (P=0.009).
Adjuvant Gemcitabine After Complete Tumor Resection

Statistically significant improvement in 5 and 10 year OS rates vs observation
- 5-year OS: 10.3% improvement (20.7% vs 10.4%)ª
- 10-year OS: 4.5% improvement (12.2% vs 7.7%)ª

95% CI for gemcitabine and observation, respectively
ª(95% CI: 14.7%-26.6%) vs (95% CI, 5.9%-15.0%)
b(95% CI: 7.3%-17.2%) vs (95% CI: 3.6%-11.8%)

Treatment with adjuvant gemcitabine for 6 months leads to 24% improvement in OS over observation

PRODIGE 24/CCTG PA.6

Disease-Free Survival

Presented By Thierry Conroy at 2018 ASCO Annual Meeting

Primary endpoint

PRODIGE 24/CCTG PA.6

Disease-Free Survival

Presented By Thierry Conroy at 2018 ASCO Annual Meeting

Primary endpoint
PRODIGE 24/CCTG PA.6

**Overall Survival**

- A. Gemcitabine
- B. mFolfirinox

Stratified HR = 0.64, [95% CI: 0.48-0.86], p=0.003

**Median overall survival:**
- 54.4 months [95% CI: 41.8-NR] with mFolfirinox
- 35.0 months [95% CI: 28.7-43.9] with Gemcitabine

**3-year overall survival:**
- No OS events=192
- 63.4% (mFolfirinox) vs 48.6% (Gem)

**Specific Survival**

- A. Gemcitabine
- B. mFolfirinox

Stratified HR = 0.63, [95% CI: 0.47-0.85], p=0.003

**Disease Specific Survival** is the time delay between the date of randomization and the patient’s death due to the treated cancer or a treatment-related complication.

**3-year specific survival:**
- No OS events=180
- 66.2% (mFolfirinox) vs 51.2% (Gem)
Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05)

Study objective
- To assess the efficacy and safety of neoadjuvant chemotherapy compared with upfront surgery in patients with resectable pancreatic ductal adenocarcinoma

Key patient inclusion criteria
- Pancreatic ductal adenocarcinoma
- Treatment naïve
- R0/R1 resectable
- ECOG PS 0–1 (n=364)

Neoadjuvant chemotherapy (gemcitabine + S-1)* + surgery + adjuvant (S-1)† (n=182)

Stratification
- CA19-9
- Institutions

Surgery + adjuvant (S-1)† (n=180)

PRIMARY ENDPOINT
- OS

SECONDARY ENDPOINTS
- Resection rate, RFS, safety


*Gemcitabine 1 g/m² D1, 8 + oral S-1 40 mg/m² bid D1–14 for 2 cycles; †S-1 for 6 months in patients with curative resection and fully recovered within 10 weeks of surgery
Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05)

Key results


- Neoadjuvant chemotherapy:
  - OS: 36.7 months (95%CI 28.7, 43.3)
  - HR 0.72 (95%CI 0.55, 0.94); log-rank test p=0.015
  - 2-year OS: 63.7% vs. 52.5%

- Upfront surgery:
  - OS: 26.7 months (95%CI 21.0, 31.3)
  - 2-year OS: 63.7% vs. 52.5%
Adjuvant treatment in PDAC

- Optimal surgery in experienced team and high volume centers

- Adjuvant treatment is still the standard, although neo-adjuvant treatment has a good rationale and is being explored

- Adjuvant treatment: Fit patients
  - West: FOLFIRINOX for 6 months in very fit patients
  - Gemcitabine (± capecitabine) for 6 months
  - Japan: S1

- Other regimens are being explored: gem/nab-paclitaxel
  - press release march 2019: no significant DFS benefit (primary endpoint), but survival benefit
Pancreatic adenocarcinoma: treatment strategy
clinical grouping

- Metastatic disease
- Resectable disease

- Borderline resectable disease: definition issues
  - Neoadjuvant treatment
    - Chemotherapy
    - Chemoradiotherapy

- Locally advanced, but clearly not resectable disease
Continuum between technically resectable and unresectable disease

**RESECTABLE tumor**
- No distant metastasis
- No tumor contact with CA, SMA or CHA
- No tumor contact with SMV or PV or contact ≤ 180°

**BORDERLINE resectable tumor**
- No distant metastasis
- Solid tumor contact with SMV/PV >180°
- Solid tumor contact with CHA or with SMA or CA ≤ 180°

**Locally Advanced UNRESECTABLE tumor**
- Distant metastasis
- Unreconstructible SMV/PV involvement or occlusion
- Solid tumor contact of >180° with the SMA or CA

National Comprehensive Cancer Network 2016 www.nccn.org
Currently available induction strategies

Staging: Borderline Resectable Pancreatic Cancer

1. Chemoradiation → Surgery

2. Combination chemotherapy → Surgery → Adjuvant chemotherapy

3. Combination chemotherapy → Chemoradiation → Surgery
## Treatment For Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Stage</th>
<th>Study Design</th>
<th>N</th>
<th>ORR, %</th>
<th>Resection rate, %</th>
<th>R0 resections, %</th>
<th>1-year PFS, %</th>
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<tr>
<td>FOLFIRINOX(^1)</td>
<td>BL or unresectable</td>
<td>Retrospective</td>
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<td>83</td>
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<td>54</td>
<td>42</td>
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<td>37</td>
<td>41</td>
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<tr>
<td>FOLFIRINOX(^6)</td>
<td>laPC</td>
<td>Phase II(^b)</td>
<td>8</td>
<td>63</td>
<td>37</td>
<td>---</td>
<td>---</td>
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<tr>
<td>Nab-paclitaxel + gemcitabine(^7)</td>
<td>BL or resectable</td>
<td>Phase II</td>
<td>16</td>
<td>31(^c)</td>
<td>56(^d)</td>
<td>89(^e)</td>
<td>---</td>
</tr>
</tbody>
</table>

\(^b\)Sequential regimen including FOLFIRINOX and nab-paclitaxel plus gemcitabine  
\(^c\)1 complete pathological response and 4 near complete responses (few (<5%) residual tumor)  
\(^d\)At the time of the analysis  
\(^e\)Of patients who had been operated on at the time of the analysis

Dutch PREOPANC Trial: resectable & borderline resectable PDAC

**Trial design**

- **Surgery**
  - **Gem:** gemcitabine 1000 mg/m² day 1, 8, 15, one week rest
  - **Gem':** gemcitabine 1000 mg/m² day 1, 8, one week rest
  - **RT:** 36 Gy in 15 fractions of 2.4 Gy

**Statistics:** stratification: resectability/institution  
Primary endpoint: Overall survival (ITT)  
Expected trial duration: 36 months + 12 months FUP  
Hypothesis: improvement in median survival from 11 to 17 months

80% power assuming 10% dropouts; 244 patients / 176 events
Dutch PREOPANC Trial

Disease-Free Survival

Overall DFS (ITT)

Distant Metastasis Free Interval

Locoregional Recurrence Free Interval

DFS: 7.9 vs 9.9 Months, HR 0.71; p=0.023

HR 0.71; p = 0.013

HR 0.55; p = 0.002

Presented By Geertjan Van Tienhoven at 2018 ASCO Annual Meeting
Overall Survival Analyses

Intention to Treat

- Exploratory laparotomy
- Radiochemotherapy followed by exploratory laparotomy

P-value stratified logrank test: 0.0742

Median: 13.7 vs 17.1 Months, HR 0.74; p = 0.074

Post Resection

- Exploratory laparotomy
- Radiochemotherapy followed by exploratory laparotomy

P-value stratified logrank test: 3e-04

Median Survival 16.8 vs 29.9 Months, p = 0.001

Presented By Geertjan Van Tienhoven at 2018 ASCO Annual Meeting
Does neoadjuvant chemoradiation therapy benefit patients with resectable or borderline resectable disease?

- Trial design cannot definitively define that neoadjuvant CRT better than direct surgical resection.

- The results of this trial in aggregate with other recently published prospective trials demonstrate that the benefit of radiation therapy is in the neoadjuvant setting.

- Neoadjuvant CRT based therapy is associated with higher R0 resection rate.

- What is the impact of Resectable vs Borderline Resectable disease as well as R1 resection on outcome?

- Will the use of modern combination chemotherapy increase the magnitude of the effect associated with neoadjuvant/perioperative CRT-based therapy.
  - Alliance Trial – Total Neoadjuvant FOLFIRINOX vs FOLFIRINOX plus SBRT
  - SWOG 1505 – Perioperative FOLFIRINOX vs Gemcitabine + nab-Paclitaxel
  - AGICC – Perioperative Gemcitabine + nab-Paclitaxel plus SBRT
Borderline resectable/unresectable pancreatic cancer

- Prospective data support the use of induction chemotherapy and/or chemoradiation before resection, but convincing data from randomized studies are still lacking.

- The treatment of BRPC remains a multidisciplinary challenge and staging/restaging results must be regularly discussed in multidisciplinary team meetings in high volume centers.

- Decline in CA 19.9 may help the assessment of response.

- The optimal strategy for induction therapy for patients with BRPC has not been established. FOLFIRINOX seems to be the most promising approach.

- The best management for these patients occurs in a clinical trial.
Pancreatic adenocarcinoma: treatment strategy
clinical grouping

- Metastatic disease
- Resectable disease
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease
1 month = Gemcitabine (1000 mg/m²)/wkX3

Erlotinib: 100 mg/d with gem 150 mg/d as single agent

Secondary surgery allowed at any time

Hammel P et al, JAMA 2016
Overall Survival and Progression-Free Survival, According to the First Randomization (primary endpoint)

- Gemcitabine alone: 13.6 mo (95% CI, 12.3-15.3)
- Gemcitabine plus Erlotinib: 11.9 mo (95% CI, 10.4-13.5)

Overall Survival and Progression-Free Survival, According to the Second Randomization

- Gemcitabine alone: 16.5 mo (95% CI, 14.5-18.5)
- Gemcitabine plus Erlotinib: 15.2 mo (95% CI, 13.9-17.3)
Pancreatic adenocarcinoma: treatment strategy
clinical grouping

- Metastatic disease
- Resectable disease
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease
Biliary Tract Cancers are Heterogeneous

- Adenocarcinomas (95%) +/- mucin, 3% of all GI cancers
- Overall prognosis is poor: 5-year survival 5-15% \(^1,2\)
- <35% of patients present with resectable disease and relapse rates are high
- IntraHepatic Cholangiocarcinoma vs. ExtraHepatic Cholangiocarcinoma vs Gallbladder cancer

**IHCCA**

<table>
<thead>
<tr>
<th>Specific Targetable GAs</th>
<th>Prevalence</th>
<th>Targeted Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR2 Fusions</td>
<td>10% to 20%</td>
<td>BGJ398, Ponatinib, SORafenib, LINIPLA403, PHX1131, TACE, 200, FGFR antibodies and FGFR trap molecules</td>
</tr>
<tr>
<td>IDH1/2</td>
<td>22% to 28%</td>
<td>AG-120, AG-881</td>
</tr>
<tr>
<td>BAP1</td>
<td>15% to 25%</td>
<td>Histone Deacetylase (HDC) inhibitors like vorinostat and panobinostat</td>
</tr>
</tbody>
</table>

**EHCCA**

<table>
<thead>
<tr>
<th>Specific Targetable GAs</th>
<th>Prevalence</th>
<th>Targeted Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERTGlu (mutation)</td>
<td>11% to 20%</td>
<td>Tyrosine Kinase inhibitors like sunitinib, nanobis, and sorafenib</td>
</tr>
<tr>
<td>P53/TP53</td>
<td>9%</td>
<td>Protein Kinase A inhibitors under development</td>
</tr>
<tr>
<td>ARID1A</td>
<td>5% to 13%</td>
<td>Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat</td>
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</table>
Randomized phase III studies
gemcitabine ± cisplatin

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tbody>
<tr>
<td>ABC-02</td>
<td>Valle <em>NEJM</em> 2010</td>
<td>5.0</td>
<td>8.1</td>
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<tr>
<td>BT-22</td>
<td>Okusaka <em>BJC</em> 2010</td>
<td>3.7</td>
<td>7.7</td>
</tr>
</tbody>
</table>
Genomic Alterations In Biliary Cancers

Potential druggable alterations

- BRAF
- HER2
- MSI
- IDH
- FGFR
- NTRK

Study objective
To determine whether capecitabine improves OS compared with observation following radical surgery in cholangiocarcinoma or gallbladder cancer

Key patient inclusion criteria
• Completely resected cholangiocarcinoma or gallbladder cancer (including liver and pancreatic resection, as appropriate)
• Adequate biliary drainage
• ECOG PS ≤2
(n=447)

Capecitabine
1250 mg/m² bid
D1–14 q3w
8 cycles (n=223)

Stratification
• Tumour resection status
• ECOG PS
• Tumour site
• Surgical centre

Observation
(n=224)

PRIMARY ENDPOINT
OS

SECONDARY ENDPOINTS
RFS, TTP, toxicity, QoL

*Primary analysis after a minimum 2-year follow-up

The BILCAP randomized study
Adjuvant treatment for biliary tract cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, months (95%CI)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>51.1 (34.6, 59.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Observation</td>
<td>36.4 (29.7, 44.5)</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Sensitivity analyses
Adjusting for further prognostic factors (nodal status, disease grade, gender)
HR 0.70 (95%CI 0.55, 0.91); p=0.007

>80% patients followed-up for 36 months
Surgery is the only option for curative treatment: expert centers!

New data suggest benefit of adjuvant chemotherapy

Chemotherapy is associated with modest benefit in advanced disease
- Standard option in fit patients in 2019: gemcitabine/cisplatin
- Future molecular analysis: FGR, IDH, BRAF, HER2, MSI, NTRAK fusions….