Standard of care in pancreatic adenocarcinoma in 2020

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Disclosures

- participation to advisory boards for Array, Astrazeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, GSK, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier, Sirtex, Taiho
- research grants from Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier paid to institution
Leuven, Belgium

- 25 km east of Brussel: ~ 100,000 inhabitants
- KUL: University founded in 1425: > 60,000 students:
  - Reuters World Ranking of Most Innovative Universities: Nr 7 in world; Nr 1 in Europe
- Largest Beer Brewery in world (>25% of world production)
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
- ~75-80% of patients who have resection and adjuvant therapy relapse
- “Cure” rate is only ~5%; 5 year survival 10-15%
- 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

Many druggable alterations

But very few with proven clinical activity in PDAC
**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

Bailey P. Nature 2016
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%: expertise, high volume, laparoscopic
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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>FOLFIRINOX</th>
<th>Gem</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>31.6%</td>
<td>9.4%</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>PFS, months</td>
<td>6.4</td>
<td>3.3</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td>OS, months</td>
<td>11.1</td>
<td>6.8</td>
<td>.57</td>
<td></td>
</tr>
<tr>
<td>12-month OS</td>
<td>48.4%</td>
<td>20.5%</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>18-month OS</td>
<td>18.6%</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MPACT trial:**

**Gemcitabine ± Nabplcitaxel**

![Graph showing survival rates over months for different treatment groups.](image)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>nab-P + Gem</th>
<th>Gem</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>23%</td>
<td>7%</td>
<td>0.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PFS, months</td>
<td>5.5</td>
<td>3.7</td>
<td></td>
<td>.69 &lt;.001</td>
</tr>
<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></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>42-month OS</td>
<td>3%</td>
<td>0%</td>
<td></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

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

Treatment Strategies: ESMO Guidelines

Diagnosis of pancreatic carcinoma

Adequate staging (Fig 1.)

- Resectable pancreatic cancer
  - Surgery
  - Adjuvant chemotherapy 5FU + LV or Gemcitabine
    - If resectable: Resection + adjuvant chemotherapy
    - If non-resectable: Chemotherapy

- Borderline resectable pancreatic cancer
  - Neoadjuvant ChT +/− RT
  - Surgical exploration
    - Therapeutic goal: R0 resection

- Locally advanced pancreatic cancer
  - Chemotherapy Gemcitabine 6 months
  - PS 0 or 1
  - PS2 and/or bilirubin level higher than 1.5 x ULN
  - PS 3-4 or comorbidities

- Metastatic pancreatic cancer
  - Gemcitabine alone
  - Best supportive care
  - FOLFIRINOX
  - Gemcitabine + nab-paclitaxel

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-placlitaxel backbone
Treatment selection depends on a wide range of factors.

- Medical comorbidities
- ECOG/KPS, Age
- Toxicity, Side Effects
- Liver function
- Patient preference
- Practical considerations
- Physician’s experience

Treatment decision
NAPOLI-1 Results in second line: nano-liposomal irinotecan (=Naliri) +5FU/FA

OS

PFS

Rationale for PARP inhibition in BRCA-deficient tumours

Olaparib traps PARP at sites of DNA single-strand breaks

Accumulation of DNA double-strand breaks

HRR-deficient cancer cell, e.g. gBRCAm

Reliance on error-prone pathways

Homologous recombination repair

Cell death

Cell survival

Normal cell

Demonstrated clinical efficacy in gBRCAm ovarian and breast cancers\(^2,3\)

BRCA, BRCA1 and/or BRCA2; HRR, homologous recombination repair; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase

BRCA Mutations May Predict Benefit of Platinum Therapy and PARP Inhibitors

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D., Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D., Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O’Reilly, M.D., David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D., Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

Key eligibility criteria
Metastatic pancreatic cancer
Deleterious or suspected deleterious germline BRCA1 or BRCA2 mutation
≥16 weeks first-line platinum-based chemotherapy with no limit to duration, without progression (CR, PR or SD)*

Study design

First-line chemotherapy

Randomization

Maintenance treatment

Discontinuation

≥16 weeks
4–8 weeks
Follow-up

Randomized 3:2
No stratification factors

Olaparib tablets 300 mg bid or Placebo

Until investigator-assessed disease progression or unacceptable toxicity

38% of gBRCAm patients had disease progression, were ineligible, or declined randomization

*There was no maximum limit to the duration of first-line chemotherapy. bid, twice daily; CR, complete response; PR, partial response; SD, stable disease
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=92)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.0 (37–84)</td>
<td>57.0 (36–75)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53 (57.6)</td>
<td>31 (50.0)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>65 (70.7)</td>
<td>38 (61.3)</td>
</tr>
<tr>
<td>1</td>
<td>25 (27.2)</td>
<td>23 (37.1)</td>
</tr>
<tr>
<td>BRCA mutation status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>29 (31.5)</td>
<td>16 (25.8)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>62 (67.4)</td>
<td>46 (74.2)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Time from diagnosis to randomization</td>
<td>6.9 (3.6–38.4)</td>
<td>7.0 (4.1–30.2)</td>
</tr>
<tr>
<td>Duration of first-line chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months (range)</td>
<td>5.0 (2.5–35.2)</td>
<td>5.1 (3.4–20.4)</td>
</tr>
<tr>
<td>16 weeks to 6 months, n (%)</td>
<td>61 (66.3)</td>
<td>40 (64.5)</td>
</tr>
<tr>
<td>&gt;6 months, n (%)</td>
<td>30 (32.6)</td>
<td>21 (33.9)</td>
</tr>
<tr>
<td>First-line platinum-based chemotherapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRINOX variants</td>
<td>79 (85.9)</td>
<td>50 (80.6)</td>
</tr>
<tr>
<td>Gemcitabine/cisplatin</td>
<td>2 (2.2)</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (10.9)</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Best response on first-line chemotherapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete or partial response</td>
<td>46 (50.0)</td>
<td>30 (48.4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>45 (48.9)</td>
<td>31 (50.0)</td>
</tr>
<tr>
<td>Disease status following first-line chemotherapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurable</td>
<td>78 (84.8)</td>
<td>52 (83.9)</td>
</tr>
<tr>
<td>Non-measurable or no evidence of disease</td>
<td>13 (14.1)</td>
<td>6 (9.7)</td>
</tr>
</tbody>
</table>
### Patient disposition

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=92)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screened, n</strong></td>
<td>3315</td>
<td></td>
</tr>
<tr>
<td><strong>Found to have a gBRCAm, n (%)</strong></td>
<td>247 (7.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Excluded, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression or death</td>
<td>93</td>
<td>43</td>
</tr>
<tr>
<td>Ineligible</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>Patient or physician decision</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td><strong>Randomized, n</strong></td>
<td>92</td>
<td>62</td>
</tr>
<tr>
<td><strong>Treated, n</strong></td>
<td>90</td>
<td>61</td>
</tr>
<tr>
<td><strong>Discontinued treatment, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression by BICR</td>
<td>60 (65.2)</td>
<td>53 (85.5)</td>
</tr>
<tr>
<td>Disease progression by investigator assessment</td>
<td>43 (46.7)</td>
<td>40 (64.5)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>12 (13.0)</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>Patient decision</td>
<td>4 (4.3)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Ineligible</td>
<td>1 (1.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td><em><em>Continuing assigned treatment at data cut-off</em>, n (%)</em>*</td>
<td>30 (32.6)</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td><strong>Median follow-up for progression, months (range)†</strong></td>
<td>9.1 (0–39.6)</td>
<td>3.8 (0–29.8)</td>
</tr>
</tbody>
</table>

*15 January 2019. †Censored patients. BICR, blinded independent central review.
Primary endpoint: PFS by blinded independent central review

<table>
<thead>
<tr>
<th>Olaparib (N=92)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>7.4</td>
</tr>
<tr>
<td>HR 0.53</td>
<td>95% CI 0.35, 0.82;</td>
</tr>
</tbody>
</table>

Progression-free at data cut-off:†
30 olaparib patients (32.6%)
12 placebo patients (19.4%)
POLO TRIAL: olaparib vs placebo in gBRCA mutant PDAC

Golan T., Van Cutsem E et al, NEJM 2019
Two olaparib arm patients had a complete response to olaparib following first-line chemotherapy:
• One had a partial response
• One had stable disease
Both complete responses were ongoing at the data cut-off†

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response* in patients with measurable disease by blinded independent central review</td>
<td>23.1%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Olaparib patients</td>
<td>n=18</td>
<td>n=6</td>
</tr>
<tr>
<td>Placebo patients</td>
<td>n=78</td>
<td>n=52</td>
</tr>
</tbody>
</table>

Median duration of response:
- Olaparib: 24.9 months
- Placebo: 3.7 months

Median time to onset of response:
- Olaparib: 5.4 months
- Placebo: 3.6 months

*By modified RECIST v1.1. †January 15, 2019
## Most common AEs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Olaparib (N=91)</th>
<th>Placebo (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>60.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>45.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>28.6</td>
<td>23.3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28.6</td>
<td>15.0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>27.5</td>
<td>16.7</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>23.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19.8</td>
<td>15.0</td>
</tr>
<tr>
<td>Back pain</td>
<td>18.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15.4</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Incidence (%)
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)

8 mPCA patients
- ORR 62% (2/8 CR)
- DCR 75%

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

**KEYNOTE-164 and KEYNOTE-158 Studies**

**MSI-H Tumor Types**

- **Pancreatic cancer is non-immunogenic because:**
  - immunosuppressive cells and cytokines
  - low tumor mutational burden
  - paucity of T cells in tumor (number and function)
  - ~1% of PDAC are MSI

---

Diaz L, ... Van Cutsem E et al, ESMO 2019: oral presentation
### Antitumor Activity Across Tumor Types

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>N</th>
<th>CR, n</th>
<th>PR, n</th>
<th>ORR, % (95% CI)</th>
<th>Median (95% CI) PFS, months</th>
<th>Median (95% CI) OS, months</th>
<th>Median (range) DOR, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial</td>
<td>49</td>
<td>8</td>
<td>20</td>
<td>57.1 (42.2–71.2)</td>
<td>25.7 (4.9–NR)</td>
<td>NR (27.2–NR)</td>
<td>NR (2.9–27.0+)</td>
</tr>
<tr>
<td>Gastric</td>
<td>24</td>
<td>4</td>
<td>7</td>
<td>45.8 (25.6–67.2)</td>
<td>11.0 (2.1–NR)</td>
<td>NR (7.2–NR)</td>
<td>NR (6.3–28.4+)</td>
</tr>
<tr>
<td>Cholangio-carcinoma</td>
<td>22</td>
<td>2</td>
<td>7</td>
<td>40.9 (20.7–63.6)</td>
<td>4.2 (2.1–NR)</td>
<td>24.3 (6.5–NR)</td>
<td>NR (4.1+–24.9+)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>22</td>
<td>1</td>
<td>3</td>
<td>18.2 (5.2–40.3)</td>
<td>2.1 (1.9–3.4)</td>
<td>4.0 (2.1–9.8)</td>
<td>13.4 (8.1–16.0+)</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>19</td>
<td>3</td>
<td>5</td>
<td>42.1 (20.3–66.5)</td>
<td>9.2 (2.3–NR)</td>
<td>NR (10.6–NR)</td>
<td>NR (4.3+–31.3+)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>15</td>
<td>3</td>
<td>2</td>
<td>33.3 (11.8–61.6)</td>
<td>2.3 (1.9–6.2)</td>
<td>NR (3.8–NR)</td>
<td>NR (4.2–20.7+)</td>
</tr>
<tr>
<td>Brain</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0.0 (0.0–24.7)</td>
<td>1.1 (0.7–2.1)</td>
<td>5.6 (1.5–16.2)</td>
<td>–</td>
</tr>
</tbody>
</table>

Efficacy analyses included all patients who received at least one dose of pembrolizumab. Only confirmed responses are included. Response was assessed per RECIST version 1.1 by independent central radiological review. Data cutoff: Sept 4, 2018 (KN164); Dec 6, 2018 (KN158).

Diaz L, … Van Cutsem E et al, ESMO 2019: oral presentation
The Tumor Microenvironment Defines the Molecular Properties of PDAC

Transcriptome of resected PDAC samples

Unraveling the PDAC transcriptomic landscape

Redefining PDAC molecular subtypes

5 PDAC subtypes defined by specific characteristics in tumor & tumor microenvironment

New classification integrating the stromal and neoplastic compartments of PDAC

RNA-determined subtypes can reflect patient outcomes → clinical applicable setting

Targeting of:

✓ Stroma- and CAF (Cancer-Associated fibroblasts) - derived factors
✓ Tumor cell–derived factors
✓ Cytoskeletal regulators
✓ Structural components of the stroma
✓ Cellular and other components of the microenvrionment
✓ The stroma-associated immune system

HALO 301 Study: Gem/nab-Paclitaxel +/- PEGPH20 in HA-High Untreated PDAC

**Phase 3 trial**

- 1L metastatic PDCA
- High-HA
- N = 420-570

**Primary endpoints:** PFS and OS
**Secondary endpoints:** ORR, DOR, and safety

**Randomization (R 2:1):**
- **PAG**
  - PEGPH20 + nab-P + Gem
- **AG**
  - nab-P + Gem

ClinicalTrials.gov. NCT02715804.
PI's: Eric Van Cutsem & Margaret Temperov
Macrophages contribute to the squamous subtype of PDAC.

Inhibition of CSFR1 alters the tumor microenvironment and leads to enhanced T cell immune response.

Loss of macrophages leads to change in PDAC gene expression and switches subtype and results in prolonged survival.

Marked differences between targeting macrophages and neutrophils.

Colony stimulating factor 1 receptor (CSF1R), also known as macrophage colony-stimulating factor receptor (M-CSFR), and CD115 (Cluster of Differentiation 115)


CPI-613: Selectively Blocks PDH and KGDH Triggering Cell Death That Is Highly Selective to Tumor Cells

Pilot clinical trial

CPI-613 + lower-dose FOLFIRINOX

Oxaliplatin 65 mg/m²
Irinotecan 140 mg/m²
5FU 2400 mg/m²


PDH: pyruvate dehydrogenase
KGDH: α-ketoglutarate dehydrogenase
Eryaspase Prolongs Survival in a Pilot Trial in Patients After Failure of Front-Line Therapy


Eryaspase = L-asparaginase encapsulated in erythrocytes

Study design:
- OS advantage regardless of asparaginase synthetase (ASNS) expression level
- Similar safety profiles in both groups

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy Plus</th>
<th>Chemotherapy Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events n (%)</td>
<td>79 (83%)</td>
<td>40 (87%)</td>
</tr>
<tr>
<td>Censored n (%)</td>
<td>16 (17%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.60 (0.40, 0.88)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.009</td>
<td></td>
</tr>
<tr>
<td>Median OS (weeks)</td>
<td>26.1</td>
<td>19.0</td>
</tr>
<tr>
<td>OS rate at 24 weeks</td>
<td>46%</td>
<td>37%</td>
</tr>
<tr>
<td>OS rate at 52 week</td>
<td>15%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Targeting metabolic pathways

\[ \text{Eryaspase = L-asparaginase encapsulated in erythrocytes} \]
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 2. Adjuvant Therapy for Pancreatic Cancer.*

<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>GITSG⁵⁸</td>
<td>43</td>
<td>Observation</td>
<td>10% at 2 yr, 20% at 2 yr</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorouracil plus radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC⁵⁹</td>
<td>218</td>
<td>Observation</td>
<td>26% at 2 yr, 34% at 2 yr</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorouracil plus radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPAC-1⁶⁰</td>
<td>289</td>
<td>Observation, Chemoradiotherapy</td>
<td>16.9 mo (median)†, 13.9 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorouracil, Chemoradiotherapy &amp; Fluorouracil</td>
<td>21.6 mo, 19.9 mo</td>
<td></td>
</tr>
<tr>
<td>CONKO-01⁵¹</td>
<td>368</td>
<td>Observation, Gemcitabine</td>
<td>10.4% at 5 yr, 20.7% at 5 yr</td>
<td>0.01</td>
</tr>
<tr>
<td>ESPAC 3⁶²</td>
<td>1088</td>
<td>Fluorouracil, Gemcitabine</td>
<td>23.0 mo (median), 23.6 mo</td>
<td>0.39</td>
</tr>
<tr>
<td>RTOG 9704⁶³</td>
<td>451</td>
<td>Fluorouracil plus radiotherapy, Gemcitabine plus radiotherapy</td>
<td>22% at 5 yr, 18% at 5 yr</td>
<td>0.12</td>
</tr>
<tr>
<td>JASPAC-01⁶⁴</td>
<td>378</td>
<td>S-1 (oral fluoropyrimidine), Gemcitabine</td>
<td>70% at 2 yr, 53% at 2 yr</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* CONKO-01 denotes Charité Onkologie 01, 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 of 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 8% among patients who did not receive chemotherapy (P=0.009).
Adjuvant Gemcitabine After Complete Tumor Resection

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

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%)\(^b\)

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%)

Gemcitabine: 22.8 months
Observation: 20.2 months

HR, 0.76 [95% CI, 0.61 - 0.95], P=.01

Log-rank P=.01

Primary endpoint

Disease-Free Survival

No DFS events: 314
Median DFS:
- 21.6 mths [95%CI: 17.7-27.6] with mFolfinox
- 12.8 mths [95%CI: 11.7-15.2] with Gemcitabine

3-year DFS:
- 39.7% [95%CI: 32.8-46.6] with mFolfinox
- 21.4% [95%CI: 15.8-27.5] with Gemcitabine

stratified HR=0.58 [95%CI: 0.46-0.73], p<0.0001

Presented By Thierry Conroy at 2018 ASCO Annual Meeting
PRODIGE 24/CCTG PA.6

**Overall Survival**
- A: Gemcitabine
- B: 5-FU/mFolinic acid (5-FU/mFolinic acid) vs Gemcitabine

**Specific Survival**
- A: Gemcitabine
- B: 5-FU/mFolinic acid (5-FU/mFolinic acid) vs Gemcitabine

**Median overall survival:**
- 54.4 months [95% CI: 41.8-NR] with 5-FU/mFolinic acid
- 35.0 months [95% CI: 28.7-43.9] with Gemcitabine

**3-year overall survival:**
- No OS events=192
- 63.4% (5-FU/mFolinic acid) vs 48.6% (Gemcitabine)

**3-year specific survival:**
- No OS events=180
- 66.2% (5-FU/mFolinic acid) vs 51.2% (Gemcitabine)

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.

Presented By Thierry Conroy at 2018 ASCO Annual Meeting
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)

Surgery + adjuvant (S-1)† (n=180)

Stratification
- CA19-9
- Institutions

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


OS

Neoadjuvant chemotherapy: 
36.7 months (95%CI 28.7, 43.3)

Upfront surgery: 
26.7 months (95%CI 21.0, 31.3)

HR 0.72 (95%CI 0.55, 0.94); log-rank test p=0.015

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
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>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRINOX(^1)</td>
<td>BL or unresectable</td>
<td>Retrospective</td>
<td>18</td>
<td>---</td>
<td>39</td>
<td>28</td>
<td>83</td>
</tr>
<tr>
<td>FOLFIRINOX(^2)</td>
<td>laPC</td>
<td>Retrospective</td>
<td>16</td>
<td>50</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>FOLFIRINOX(^3)</td>
<td>laPC or BL</td>
<td>Registry</td>
<td>23</td>
<td>34</td>
<td>---</td>
<td>---</td>
<td>75</td>
</tr>
<tr>
<td>FOLFIRINOX(^4)</td>
<td>laPC or BL</td>
<td>Retrospective</td>
<td>43</td>
<td>---</td>
<td>54</td>
<td>42</td>
<td>---</td>
</tr>
<tr>
<td>FOLFIRINOX(^5)</td>
<td>BL or unresectable</td>
<td>Phase II</td>
<td>32</td>
<td>37</td>
<td>41</td>
<td>---</td>
<td>---</td>
</tr>
<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>
</tr>
<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

Statistics: stratification: resectability/institution
Primary endpoint: Overall survival (ITT)
Expected trial duration: 36 months + 12 months FUP
Hypothesis: improvement 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)**
- DFS: 7.9 vs 9.9 Months, HR 0.71; p=0.023

**Distant Metastasis Free Interval**
- HR 0.71; p = 0.013

**Locoregional Recurrence Free Interval**
- HR 0.55; p = 0.002
Dutch PREOPANC Trial

Overall Survival Analyses

**Intention to Treat**
- Explorative laparotomy
- Radiochemotherapy followed by explorative laparotomy
- P-value stratified logrank test: 0.0742

**Post Resection**
- Explorative laparotomy
- Radiochemotherapy followed by explorative laparotomy
- P-value stratified logrank test: 3e−04

Median: 13.7 vs 17.1 Mos. HR 0.74; p=0.074
Median Survival 16.8 vs 29.9 Months, p = 0.001
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

  chemotherapy alone or chemotherapy followed by chemoradiotherapy
CAPECITABINE PLUS RADIATION
Quality assurance

Secondary surgery allowed at any time

Hammel P et al, JAMA 2016

1 month = Gemcitabine (1000 mg/m²)/wkX3

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

Until progression
Overall Survival and Progression-Free Survival, According to the First Randomization (primary endpoint)

Gem: 13.6 mo (95% CI, 12.3-15.3)
Gem/Erlotinib: 11.9 mo (95% CI, 10.4-13.5)

LAP 07 study

Hammel P et al, JAMA 2016
Pancreatic adenocarcinoma: treatment strategy

Clinical grouping

❖ Metastatic disease
✓ Modest progress

❖ Resectable disease
✓ High quality surgery followed by adjuvant chemotherapy: folfirinox

❖ Borderline resectable disease
✓ Preoperative chemotherapy (folfirinox)

❖ Locally advanced, but clearly not resectable disease
✓ Strategy of chemotherapy


- Gemcitabine
- 5FU/LV
- Erlotinib + gemcitabine
- FOLFIRINOX
- nab-Paclitaxel + gemcitabine
- S1 (Japan)
- Adjuvant gemc./cap.
- Adjuvant FOLFIRINOX
- n-IRI +FU/LV
- Pembrolizumab
- MSI-H/dMMR (US)
- Laroctenib in NTRK fusions
- Olaparib in gBRCAm

Adjuvant chemotherapy:
JOIN US IN 2020
1–4 JULY
BARCELONA