Update on Pancreatic Cancer

Farshid Dayyani, MD, PhD
Associate Clinical Professor, Department of Medicine, UC Irvine School of Medicine
February 2nd, 2018
Overview

- Current Systemic Treatments
  - Adjuvant Chemotherapy in resected PDAC
  - Neoadjuvant Treatment
  - Metastatic Disease
- New Developments
### Principles of Multidisciplinary Treatment Based on Resectability

**NCCN Guidelines Version 3.2017**  
Pancreatic Adenocarcinoma

**Criteria Defining Resectability Status**

<table>
<thead>
<tr>
<th>Resectability Status</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resectable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).</td>
<td>No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.</td>
<td></td>
</tr>
</tbody>
</table>
| **Borderline Resectable**² | **Pancreatic head/uncinate process:**
• Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.
• Solid tumor contact with the SMA of ≤180°
• Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning.
• Pancreatic body/tail:
• Solid tumor contact with the CA of ≤180°
• Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category]. | • Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.
• Solid tumor contact with the inferior vena cava (IVC). |
| **Unresectable**² | **Head/uncinate process:**
• Distant metastasis (including non-regional lymph node metastasis)
  **Head/uncinate process:**
• Solid tumor contact with SMA >180°
• Solid tumor contact with the CA >180°
• Solid tumor contact with the first jejunal SMA branch
  **Body and tail**
• Solid tumor contact of >180° with the SMA or CA
• Solid tumor contact with the CA and aortic involvement | **Head/uncinate process:**
• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)
• Contact with most proximal draining jejunal branch into SMV
  **Body and tail**
• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) |
Q: Which Patients Need Chemotherapy???

A: All Patients!!!

- Resectable:
  - Before (=neoadjuvant) OR after surgery (adjuvant)
  - Borderline resectable / locally advanced
  - Neoadjuvant, followed by surgery if resectable
- Metastatic
  - Combo or single agent based on patient’s status

**Important:** Discuss Goals of Chemotherapy (potentially curable vs life extending vs palliative) ahead of time

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Q: If the patient is symptomatic from the cancer (abdominal pain, anorexia, nausea/vomiting, weight loss etc), and the chemo shrinks the tumor, what will happen?

A: The patient actually starts feeling better!!! First symptom to improve is usually the pain.

Main side effects expected:

- Fatigue
- Diarrhea
- Constipation
- Nausea
- Vomiting
- Numbness
- Tingling
- Cytopenia
Adjuvant Chemotherapy

Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial

Prof John P Neoptolemos, MD, Prof Daniel H Palmer, PhD, Prof Paula Ghaneh, MD, Eftychia E Psarelli, MSc, Juan W Valle, MD, Christopher M Halloran, MD, Olusola Faluyi, MD, Derek A O'Reilly, MD, Prof David Cunningham, MD, Prof Jonathan Wadsley, MD, Suzanne Darby, MD, Prof Tim Meyer, MD, Roopinder Gillmore, MD, Alan Anhoney, MD, Pehr Lind, MD, Bengt Glimelius, MD, Stephen Falk, MD, Prof Jakob R Izbicki, MD, Gary William Middleton, MD, Sebastian Cummins, MD, Paul J Ross, MD, Harpreet Wasan, MD, Alec McDonald, MD, Tom Crosby, MD, Yuk Ting Ma, MD, Kinnari Patel, MD, David Sherriff, FRCR, Rubin Soomal, MD, David Borg, MD, Sharmila Sothi, MD, Prof Pascal Hammel, MD, Thilo Hackert, MD, Richard Jackson, PhD, Prof Markus W Büchler, MD

The Lancet
Volume 389, Issue 10073, Pages 1011-1024 (March 2017)
DOI: 10.1016/S0140-6736(16)32409-6
ESPAC-4

Hazard ratio for death: 0.82 (95% CI 0.68-0.98); stratified log-rank p=0.037

Overall survival (%)

Number at risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>At Risk</th>
<th>Time</th>
<th>Number at Risk</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>366</td>
<td>0</td>
<td>364</td>
<td>80</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine</td>
<td>364</td>
<td>0</td>
<td>328</td>
<td>80</td>
</tr>
<tr>
<td>Median survival time: 25.5 months (95% CI 22.7-27.3)</td>
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<tr>
<td>Median survival time: 28.0 months (95% CI 23.5-31.5)</td>
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<tbody>
<tr>
<td>Gemcitabine-positive</td>
<td>219</td>
<td>0</td>
<td>178</td>
<td>83</td>
</tr>
<tr>
<td>Gemcitabine-negative</td>
<td>147</td>
<td>0</td>
<td>124</td>
<td>83</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine-positive</td>
<td>221</td>
<td>0</td>
<td>193</td>
<td>83</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine-negative</td>
<td>143</td>
<td>0</td>
<td>135</td>
<td>83</td>
</tr>
<tr>
<td>Median survival time: 23.0 months (95% CI 21.6-26.2)</td>
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<td>Median survival time: 27.0 months (95% CI 23.8-31.4)</td>
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<td>Median survival time: 39.5 months (95% CI 32.0-58.0)</td>
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</table>

X^2(1) trend-14.83, p=0.0001

UC Irvine Health
Locally Advanced Pancreatic Cancer: LAP-07 study

Random 1

EVALUATION: non progressive

EVALUATION: non progressive

Random 2

Cape

RT

EVALUATION

EVALUATION

EVALUATION

Until Progression

4 months

1 month = Gemcitabine 1000 mg/m²/wk x 3

Cape

RT

Capcitabine 1600 mg/m²/d plus radiation therapy 54 Gy (5 x 1.8 Gy/d)

Erlotinib with gem: 100 mg/d

150 mg/d as single agent (maintenance)

Secondary surgery allowed at any time
OS and PFS by Second Randomization

Local Progression: 32% CRT vs 46% Chemo

Time to treatment reintroduction: 6.1 m CRT vs 3.7 m Chemo

Meta-analysis FOLFIRINOX in LAUPC

11 studies / 315 patients
RT: 30-100%
Resection: 26% / R0 74%
OS: range 10-33 mos
PFS: range 3-20 mos

Contemporary LAUPC Trials

LAPACT (Phase II)
- Nab-Paclitaxel Gemcitabine X 6 cycles
  - 1° Endpoint: TTF
  - 2° Endpoint: DCR in pts who completed induction
  - N=110 completed

NEOPAN (Phase III)
- Nab-Paclitaxel Gemcitabine until PD
  - SX
  - CRT
- FOLFIRINOX
- Gemcitabine
  - N=170 Est 2020
LAPACT Trial

- N= 101 pts included
- N= 60 (59%) completed induction
- N= 93 evaluable; DCR= 82% (n= 33 PR)
- N=14 (13.9%) underwent surgery (R0, n = 4; R1, n = 6; R2, n = 1; 3 missing)
- Multi-agent chemotherapy such as FOLFIRINOX or nab-Paclitaxel / Gemcitabine

- Induction chemotherapy – adequate course (NCCN)
  - at least 6 months (ASCO)

- Unknown if CRT benefits after induction FOLFIRINOX or NabP/Gem (not after Gem)

- If local PD (no mets) after induction chemo: CRT or SBRT

- If PR or SD after induction chemo but + toxicity: CRT or SBRT

- If no benefit from 1st line induction chemo: 2nd line chemo (~ metastatic regimen)

Recurrent/Metastatic

**FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer**

*The NEW ENGLAND JOURNAL of MEDICINE*

Overall Survival

Hazard ratio, 0.57 (95% CI, 0.45–0.73)
P < 0.001 by stratified log-rank test

mOS: 11.1 mo vs 6.8 mo
ORR: 31.6% vs 9.4%

**Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.**

<table>
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<tr>
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<td></td>
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<td>35/167 (21.0)</td>
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<td>0.03</td>
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<td>15/165 (9.1)</td>
<td>6/168 (3.6)</td>
<td>0.04</td>
</tr>
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<td>Anemia</td>
<td>13/166 (7.8)</td>
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</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
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</tr>
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<td>0/169</td>
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</tr>
<tr>
<td>Elevated level of alanine aminotransferase</td>
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Recurrent/Metastatic- 1st Line

**FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer**

The New England Journal of Medicine

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Recurrent/Metastatic- 1st Line

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

The New England Journal of Medicine

mOS: 8.5mo vs 6.7mo
ORR: 23% vs 7%

UC Irvine Health
NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV—OS

mOS: 6.2mo vs 4.2mo

ORR: 16% vs 1%

<table>
<thead>
<tr>
<th>AEs, %</th>
<th>Safety Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nal-IRI + 5-FU/LV</td>
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<tr>
<td></td>
<td>(n = 117)</td>
</tr>
<tr>
<td>Grade ≥ 3 nonhematologic AEs†</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7</td>
</tr>
<tr>
<td>Grade ≥ 3 hematologic AEs‡</td>
<td></td>
</tr>
<tr>
<td>ANC decrease</td>
<td>20</td>
</tr>
<tr>
<td>Anemia</td>
<td>6</td>
</tr>
</tbody>
</table>
## New Directions in the Treatment of Pancreatic Cancer

### Investigational Agents for Advanced Pancreatic Cancer

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel cytotoxics</td>
<td>• TH-302 (evofosfamide, hypoxia-activated mustard) did not improve OS in pancreatic trial (2015)—negative trial results</td>
</tr>
<tr>
<td>Stromal-depleting agents</td>
<td>• PEGPH20 (recombinant hyaluronidase)</td>
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<td></td>
<td>• Vitamin D analogues</td>
</tr>
<tr>
<td></td>
<td>• Necuparanib</td>
</tr>
<tr>
<td>Signal transduction inhibitors</td>
<td>• JAK inhibitors (ruxolitinib)—negative trial results</td>
</tr>
<tr>
<td></td>
<td>• MM-141 (bispecific anti-IGFR/HER3 antibody)</td>
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<td></td>
<td>• BTK inhibitors (ibrutinib)</td>
</tr>
<tr>
<td></td>
<td>• Notch inhibitors (eg, demcizumab, tarextumab)—negative trial results</td>
</tr>
<tr>
<td></td>
<td>• PARP inhibitors (eg, olaparib)</td>
</tr>
</tbody>
</table>
PEGPH20 Degrades Hyaluronan in the Tumor Microenvironment

**Hyaluronan (HA)**

- Naturally occurring, linear, megadalton polysaccharide and major component of the tumor stroma
  - HA accumulation increases tumor interstitial gel-fluid pressure, which in turn compresses blood vessels and compromises blood flow
  - HA accumulation is associated with accelerated tumor growth and is an independent negative predictor of survival in PDA

**PEGPH20 (pegvorhyaluronidase alfa)**

- A PEGylated form of recombinant human hyaluronidase PH20, which degrades HA and remolds the tumor stroma

---

HALO-202: Phase 2 Randomized Multicenter Study

Stage IV PDA
KPS: 70-100
n = 279

PAG
PEGPH20 + nab-Paclitaxel + Gemcitabine

AG
nab-Paclitaxel + Gemcitabine

Primary Endpoints:
- PFS
- Thromboembolic Event Rate

Secondary Endpoints:
- PFS by HA Level
- ORR
- OS

Exploratory Endpoints:
- OS by HA Level
- DoR
- DCR (CR+PR+SD)

Primary & Secondary PFS Endpoints: 80% power at 2-sided alpha level of 0.1
Primary Efficacy Endpoint: PFS (Stages 1 & 2)

K-M Estimate of Progression-Free Survival (%)

- 30% HA-High

At Risk, n
PAG 166 101 79 55 36 22 9
AG 113 62 42 26 9 4 2

Study Duration (months)

Events
PAG 102
AG 67

Median PFS, mo
PAG 6.0
AG 5.3

HR (95% CI)
PAG 0.73 (0.53-0.99)

P value
PAG 0.0448

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17
Presented by: Sunil R. Hingorani, MD, PhD

UC Irvine Health
Secondary Endpoint: Progression-Free Survival HA-High (Combined Stages 1 & 2)

- **PAG** (n = 49)
  - Events: 24
  - Median PFS, mo: 9.2
  - HR (95% CI): 0.51 (0.26-1.00)
  - P value: 0.048

- **AG** (n = 35)
  - Events: 19
  - Median PFS, mo: 5.2

**K-M Estimate of Progression-Free Survival (%)**

**At Risk, n**
- **PAG**: 49, 31, 24, 18, 15, 9, 4, 4, 1, 0
- **AG**: 35, 20, 11, 7, 2, 1, 1, 0, 0, 0

**Study Duration (months)**
- To 18 months

Presented by: Sunil R. Hingorani, MD, PhD

UC Irvine Health
HALO-301: Ongoing Phase 3 Global Multicenter Study

Randomized 2:1 DB / PC
Stage IV PDA HA-High
n = 420

PAG
PEGPH20 + nab-Paclitaxel + Gemcitabine

AG
Placebo + nab-Paclitaxel + Gemcitabine

Primary Endpoints:
- PFS
- OS

Secondary Endpoints:
- ORR
- DoR
- Safety

This Trial is currently available at UC Irvine (UCI 15-94)

UC Irvine Health
New Trials for Pancreatic Cancer at UCI

- **UCI-17-103**: Irinotecan liposomial injection (lip-IRI)-containing Regimens in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma

- **UCI-17-109**: Durvalumab +/- Treme in combination with Gemcitabine and Abraxane in First Line Pancreatic Ductal Adenocarcinoma

- **UCI-15-94**: PEGPH20 in combination with Gemcitabine and Abraxane in First Line Pancreatic Ductal Adenocarcinoma with Hyaluronan-High

UC Irvine Health
Summary

Improving options for all treatment settings

• “Chemo for everybody”
• Adjuvant: Gem-Cap x 6 months
• LAPC: no randomized phase 3 trial (yet); gemcitabine/nab-paclitaxel (LAPACT phase II) and FOLFIRINOX have shown activity
• Metastatic: 2 first-line regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel, have demonstrated survival benefit (vs gemcitabine alone) in phase III studies
• Second-line/salvage treatment benefit with nanoliposomal irinotecan and 5-FU after gemcitabine-based therapy

Novel therapeutics

• Active area of research
• Multiple ongoing randomized phase II/III trials at UCI
Thank You

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