Contemporary Treatment Approaches for Patients with Pancreatic Cancer

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Sequencing therapy in metastatic disease

First-line treatment

• “Younger older” patients
• Patients who have received prior neoadjuvant therapy

Later-line treatment (Nal-IRI)
What is your usual first-line therapy recommendation for a 75-yr patient with newly diagnosed metastatic pancreatic cancer who is ambulatory but unable to work (PS 2)?

- Gemcitabine/nab paclitaxel: 13
- Gemcitabine: 7
- Modified FOLFIRINOX: 1
- Palliative care: 2

A 77-yr patient who is not considered a candidate for FOLFIRINOX receives gemcitabine/nab paclitaxel for metastatic pancreatic cancer and experiences disease progression after 5 months. What second-line therapy would you recommend?

- Nal-IRI + 5-FU/LV: 14
- FOLFOX: 7
- FOLFIRI: 2

In general, which treatment would you recommend for a 65-yr patient (PS 0) who receives first-line FOLFIRINOX followed by second-line gemcitabine/nab paclitaxel for metastatic pancreatic cancer and experiences disease progression?

- Nal-IRI + 5-FU/LV: 9
- Capecitabine: 2
- FOLFIRI: 1
- Palliative care: 2

Sequencing therapy in metastatic disease

**First-line treatment**
- “Younger older” patients
- Patients who have received prior neoadjuvant therapy

**Later-line treatment (Nal-IRI)**
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### Disclosures

<table>
<thead>
<tr>
<th>Advisory Committee</th>
<th>ASLAN Pharmaceuticals, BioLineRx, Caris Life Sciences, Celgene Corporation, Eisai Inc, Erytech Pharma, Halozyme Inc, Ipsen Biopharmaceuticals Inc, Merck, TriSalus Life Sciences</th>
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<td>Consulting Agreements</td>
<td>AbbVie Inc, Merck, Rafael Pharmaceuticals Inc, TriSalus Life Sciences</td>
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<td>Contracted Research</td>
<td>Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene, BioLineRx, Boston Biomedical Inc, Bristol-Myers Squibb Company, Caris Life Sciences, Celgene Corporation, Halozyme Inc, Incyte Corporation, Lilly, Novartis, Novocure, QED Therapeutics, Rafael Pharmaceuticals Inc, Roche Laboratories Inc, Taiho Oncology Inc</td>
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<td>Data and Safety Monitoring Board/Committee</td>
<td>ASLAN Pharmaceuticals, Blueprint Medicines, Erytech Pharma, Lexicon Pharmaceuticals Inc</td>
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<tr>
<td>Speakers Bureau</td>
<td>Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Ipsen Biopharmaceuticals Inc, Merck</td>
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Incremental improvement in systemic therapies that are largely based on cytotoxic drugs

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

Initial Assessment

• The goals of care
  • Include discussion of an advance directive

• Patient preferences

• Support systems should be discussed with every patient with metastatic pancreatic cancer and his or her caregivers

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

Treatment recommendations

- ECOG PS 0-1
- Favorable comorbidity profile
- Patient preference
- Support system for aggressive medical therapy → FOLFIRINOX

- ECOG PS of 2, or
- A comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy → Gem

- ECOG PS 0-1
- Favorable comorbidity profile
- Patient preference
- Support system for *a relatively aggressive* medical therapy → Gem Nab-paclitaxel

- ECOG PS >3, or
- with poorly controlled comorbid conditions despite ongoing active medical care → Supportive care

Second-Line Oxaliplatin-Based Regimens: Conflicting Results From Phase III Trials

<table>
<thead>
<tr>
<th>Patients (N = 268)</th>
<th>CONKO-003 PD on Gem Therapy (n = 160)</th>
<th>PANCREOX Previous Gem Therapy (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>OFF (n = 76)</td>
<td>mFOLFOX6 (n = 54)</td>
</tr>
<tr>
<td></td>
<td>5-FU/LV (n = 84)</td>
<td>5-FU/LV (n = 54)</td>
</tr>
<tr>
<td>OS, median</td>
<td>5.9 months</td>
<td>6.1 months</td>
</tr>
<tr>
<td></td>
<td>HR 0.66 (95% CI, 0.48–0.91)</td>
<td>HR 1.78 (95% CI, 1.08–2.93)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .01</td>
<td><em>P</em> = .02</td>
</tr>
<tr>
<td>PFS, median</td>
<td>2.9 months</td>
<td>3.1 months</td>
</tr>
<tr>
<td></td>
<td>HR 0.68 (95% CI, 0.50–0.94)</td>
<td>HR 1.00 (95% CI, 0.66–1.53)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .02</td>
<td><em>P</em> = .99</td>
</tr>
</tbody>
</table>

Phase 3 trial of Nano-liposomal irinotecan + 5-FU/LV as 2\textsuperscript{nd}-line therapy for metastatic pancreatic cancer (NAPOLI-1)

- Metastatic pancreatic cancer
- Received prior gemcitabine-based therapy
- N=417

Primary endpoint: OS
Secondary endpoints: PFS, ORR, CA19-9 response, safety

- **Nal-IRI**
  - (120 mg/m\textsuperscript{2} Q3W)
  - n=151

- **5-FU/LV**
  - (2000 mg/m\textsuperscript{2} over 24 h / 200 mg/m\textsuperscript{2} weekly Q6W)
  - n=149

- **Nal-IRI + 5-FU/LV**
  - (80 mg/m\textsuperscript{2} + 2400 mg/m\textsuperscript{2} over 46 h / 400 mg/m\textsuperscript{2} Q2W)
  - n=117

Stratification: Albumin, KPS, ethnicity

NAPOLI-1: Study outcome

<table>
<thead>
<tr>
<th>Grade 3 or 4 Toxicity</th>
<th>Nano-liri-5FU/LCV</th>
<th>5FU/LCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13 %</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Appetite</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27%</td>
<td>1%</td>
</tr>
</tbody>
</table>

NAPOX: moving Nal-Iri to the front line

Nal-Iri/5FU/LV/Oxaliplatin

Cohort A
70/2400/400/60

Cohort B
50/2400/400/60

Cohort C
50/2400/400/85

Cohort D
55/2400/400/70

No grade 3 or higher fatigue or neuropathy

Wainberg et al, ESMO GI, 2019

Phase III

N = 750, Overall Survival

Nal-Iri 50 mg/m²
5FU 2,400 mg/m²
Oxaliplatin 60 mg/m²
Q 2 weeks

Gemcitabine/
Nab-paclitaxel
standard

Phase III

No grade 3 or higher fatigue or neuropathy

Wainberg et al, ESMO GI, 2019

NCT04083235
PRODIGE 24/CCTG PA.6:
Phase III adjuvant trial in resected pancreatic cancer

Stratification, by:
- Center
- CA 19-9
- pN status
- Resection margin

Primary endpoint = DFS
CT scans Q 3 months

Modified FOLFIRINOX
Oxaliplatin 85 mg/m²
Irinotecan 180 (150) mg/m²
5FU 2,400 mg/m²
X 12 cycles

Gemcitabine
Standard dose
X 6 cycles

Disease-free survival and overall survival were significantly improved with modified FOLFIRINOX

APACT: Phase III, Open-Label, Randomized Trial of Adjuvant nab-Paclitaxel plus Gemcitabine vs Gemcitabine for Resected Pancreatic Adenocarcinoma

Resected PDAC
R0/R1; ECOG PS 0 or 1; CA19-9 < 100

Randomized 1:1

Arm A
nab-Paclitaxel 125 mg/m² qw 3/4 +
Gemcitabine 1000 mg/m² qw 3/4
× 6 cycles

Arm B
Gemcitabine 1000 mg/m² qw 3/4
× 6 cycles

866 patients; 179 sites; 21 countries

- Patients were randomized no later than 12 weeks post surgery
- Stratification factors: R0 vs R1; LN+ vs LN−; North America, Europe and Australia vs Asia Pacific

Tempero et al, Abstract #4000, ASCO, 2019
APACT did not meet the primary endpoint but demonstrated significant improvement in OS.

Temperature et al., Abstract #4000, ASCO, 2019.
Evolution of adjuvant therapies in pancreatic cancer: median overall survival times in months

- Observe: 19 months
- RTOG: 20.5 months
- ESPAC1: 21.6 months
- CONKO1: 22.8 months
- ESPAC3: 23.6 months
- EORTC: 24.5 months
- ESPAC4: 28.0 months
- IMPRESS: 30.4 months
- CONKO5: 28.0 months
- JASPAC1: 46.5 months
- APACT: 40.5 months
- PRODIGE: 54.4 months

Treatments: S1, Nab-paclitaxel/gemcitabine, FOLFIRINOX
It Is a Challenge to Give Enough Combination Chemo After Surgery!

<table>
<thead>
<tr>
<th></th>
<th>PRODIGE\textsuperscript{[a]}</th>
<th>ESPAC-4\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFIRINOX</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Completed all cycles</td>
<td>66.4</td>
<td>79.0</td>
</tr>
<tr>
<td>Relative dose intensity of $&gt; 0.70$</td>
<td>48.7%</td>
<td>91.4%</td>
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</tbody>
</table>

More Patients Will Receive Effective Systemic Therapy With the Neoadjuvant Approach

100 Newly diagnosed resectable

100% receive chemo.

80 R0/R1

15% spared futile surgery

85 Surgery

50 Adjuvant chemo

50 Complete adjuvant

≤ 50% receive chemo.

50 Adjuvant chemo

15 Relapsed

> 15% futile surgery

15 Progression

15% spared futile surgery
S-1505: picking a winner neoadjuvant regimen for resectable disease

- RESECTABLE
  - mFOLFIRINOX 12 weeks
  - Gemcitabine Nab-paclitaxel 12 weeks
- RESTAGING
- SURGERY
  - mFOLFIRINOX 12 weeks
  - Gemcitabine Nab-paclitaxel 12 weeks

Primary endpoint is survival at 20 months

N = 150

Off study if,
Toxicity
Unresectability
# Role of Multimodality Therapy: The Literature Helps, But Also Confusing!

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients [n]</th>
<th>Regimen</th>
<th>Resection rate [%]</th>
<th>R0 rate [% of resected]</th>
<th>Median OS [months]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neoadjuvant trials of upfront chemoradiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoffman et al. (1998)</td>
<td>62</td>
<td>FU + Mitomycin + 50.4 Gy</td>
<td>45.3</td>
<td>70.8</td>
<td>16</td>
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<tr>
<td>Mornex et al. (2006)</td>
<td>41</td>
<td>PF + 50 Gy</td>
<td>63.4</td>
<td>80.7</td>
<td>12</td>
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<tr>
<td>Turrini et al. (2009)</td>
<td>102</td>
<td>PF + 45 Gy</td>
<td>60.8</td>
<td>91.8</td>
<td>23</td>
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<tr>
<td>Evans et al. (2008)</td>
<td>86</td>
<td>Gem + 30 Gy</td>
<td>64.4</td>
<td>86.4</td>
<td>34</td>
</tr>
<tr>
<td>Pisters et al. (2002)</td>
<td>37</td>
<td>PXL + 30 Gy (IORT)</td>
<td>54.1</td>
<td>70</td>
<td>19</td>
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<tr>
<td>Golcher et al. (2015)</td>
<td>29</td>
<td>PG + 55.8 Gy</td>
<td>65.5</td>
<td>89.5</td>
<td>25</td>
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<tr>
<td>Pisters et al. (1998)</td>
<td>35</td>
<td>FU + 30 Gy (IORT)</td>
<td>57</td>
<td>51</td>
<td>37</td>
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<tr>
<td>Sho et al. (2013)</td>
<td>61</td>
<td>Gem + 50.4-54Gy</td>
<td>97</td>
<td>92</td>
<td>NR</td>
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<tr>
<td>Van Buren et al. (2013)</td>
<td>59</td>
<td>Gem + Bev + 30 Gy</td>
<td>73</td>
<td>88</td>
<td>17</td>
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<tr>
<td><strong>Neoadjuvant trials of chemotherapy alone</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Palmer et al. (2007)</td>
<td>50</td>
<td>Gem vs. PG</td>
<td>37.5 (Gem) 69.2 (PG)</td>
<td>75</td>
<td>28</td>
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<tr>
<td>Heinrich et al. (2008)</td>
<td>28</td>
<td>PG</td>
<td>89.3</td>
<td>80</td>
<td>27</td>
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<tr>
<td>O’Reilly et al. (2014)</td>
<td>38</td>
<td>GemOx</td>
<td>71</td>
<td>74</td>
<td>27</td>
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<tr>
<td>Tajima et al. (2012)</td>
<td>34</td>
<td>Gem + S1</td>
<td>100</td>
<td>85</td>
<td>56% at 24</td>
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<td><strong>Neoadjuvant trials of chemotherapy followed by chemoradiation therapy</strong></td>
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<td>Varadhachary et al. (2008)</td>
<td>90</td>
<td>PG - &gt; 30 Gy + Gem</td>
<td>57.8</td>
<td>96.2</td>
<td>31</td>
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<td>Talamonti et al. (2006)</td>
<td>20</td>
<td>Gem - &gt; 36Gy</td>
<td>85</td>
<td>80</td>
<td>26 (resected)</td>
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<td>Faris et al. (2013)</td>
<td>22</td>
<td>FOLFIRINOX +/- CRT</td>
<td>55</td>
<td>42</td>
<td>NR</td>
</tr>
</tbody>
</table>
Conclusions

- FOLFIRINOX and gemcitabine/nab-paclitaxel are appropriate regimens for first line therapy with comparable efficacy
- Careful patient assessment and discussion is very important
- Nal-Iri/5FU/LCV improves survival in patients after gemcitabine based therapy
  - Current development of Nal-Iri in frontline therapy
- mFOLFIRINOX is preferred adjuvant treatment, other options include gemcitabine/capecitabine, gemcitabine/nab-paclitaxel, or gemcitabine
- Neoadjuvant therapy is preferred in patients with potentially resectable pancreatic cancer