# PANCREATIC ADENOCARCINOMA TREATMENT REGIMENS (Part 1 of 4)

**Clinical Trials:** The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

## Metastatic Disease[1]

**Note:** All recommendations are category 2A unless otherwise indicated.

| REGIMEN | DOSING |
|---|---|
| **Gemcitabine**[2] | **Cycle 1 (8-week cycle)**<br>• **Days 1, 8, 15, 22, 29, 36 and 43:** Gemcitabine 1,000mg/m² IV administered over 30 minutes, followed by a 1-week rest<br>**Subsequent cycles (4-week cycle)**<br>• **Days 1, 8 and 15:** Gemcitabine 1,000mg/m² IV administered over 30 minutes, followed by a 1-week rest. Fixed-dose gemcitabine (10mg/m²/minute IV) can be substituted for standard infusion of gemcitabine over 30 minutes. |
| **Gemcitabine + erlotinib**[3] | **Cycle 1 (8-week cycle)**<br>• **Days 1, 8, 15, 22, 29, 36 and 43:** Gemcitabine 1,000mg/m² IV followed by a 1-week rest, **plus**<br>**All days:** Erlotinib 100mg/day or 150mg/day PO, **followed by**<br>**Subsequent cycles (4-week cycle)**<br>• **Days 1, 8 and 15:** Gemcitabine 1,000mg/m² IV over 30 minutes.<br>• **All days:** Erlotinib 100mg/day or 150mg/day orally. |
| **Gemcitabine + cisplatin**[4] | **Days 1 and 15:** Gemcitabine 1,000mg/m² IV + cisplatin 50mg/m² IV. Repeat cycle every 4 weeks. |
| **GEMOX** (fixed-dose rate gemcitabine + oxaliplatin)[5,6] | **Day 1:** Gemcitabine 1,000mg/m² IV, **plus**<br>**Day 2:** Oxaliplatin 100mg/m² IV.<br>Repeat cycle every 2 weeks until disease progression. |
| **Gemcitabine + fluoropyrimidine** (capecitabine)[7] | **Days 1–21:** Gemcitabine 1,000mg/m² IV once weekly + capecitabine 1,660mg/m² PO (830mg/m² twice daily).<br>Repeat cycle every 4 weeks until disease progression. |
| **FOLFIRINOX** (oxaliplatin + irinotecan + 5-fluorouracil [5-FU]/leucovorin)[8,9] | **Day 1:** Oxaliplatin 85mg/m² IV + irinotecan 180mg/m² IV + leucovorin 400mg/m² IV, **followed by** a 5-FU bolus of 400mg/m² and a 46-hour continuous 5-FU infusion of 2,400mg/m².<br>Repeat cycle every 2 weeks. |

## Second-Line Therapy[1]

| | |
|---|---|
| **Gemcitabine** (in gemcitabine-naïve patients)[2] | **Cycle 1 (8-week cycle)**<br>• **Days 1, 8, 15, 22, 29, 36 and 43:** Gemcitabine 1,000mg/m² IV administered over 30 minutes, followed by a 1-week rest<br>**Subsequent cycles (4-week cycle)**<br>• **Days 1, 8 and 15:** Gemcitabine 1,000mg/m² IV administered over 30 minutes, followed by a 1-week rest. Fixed-dose gemcitabine (10mg/m²/minute IV) can be substituted for standard infusion of gemcitabine over 30 minutes |
| **Capecitabine**[10] | **Days 1–14:** 1,000mg/m² PO twice daily.<br>Repeat cycle every 3 weeks for up to 52 weeks. |
| **5-FU + leucovorin + oxaliplatin**[11] | **Days 1, 8, 15 and 22:** 5-FU 2,000mg/m² IV + leucovorin 200mg/m² IV, **plus**<br>**Days 8 and 22:** Oxaliplatin 85mg/m² IV<br>Repeat cycle every 6 weeks. |

*continued*

## PANCREATIC ADENOCARCINOMA (Part 2 of 4)

| REGIMEN | DOSING |
|---|---|
| **Second-Line Therapy**[1] (continued) | |
| **CapeOx** (capecitabine + oxaliplatin)[12] | **Age ≤ 65 years and ECOG performance status 0 to 1**<br>• **Days 1–14:** Oxaliplatin 130mg/m² + capecitabine 1,000mg/m² twice daily. Repeat cycle every 3 weeks.<br>**Age > 65 years and ECOG performance status 2**<br>• **Days 1–14:** Oxaliplatin 110mg/m² + capecitabine 750mg/m² twice daily. Repeat cycle every 3 weeks |
| **Locally Advanced Disease**[1] | |
| **Gemcitabine or gemcitabine-based combination therapy**<br>• May be considered as initial therapy prior to 5-FU-based chemoradiation for patients with locally advanced, unresectable disease. | |
| **Adjuvant Therapy**[1] | |
| **5-FU**[13] | **Prior to chemoradiation**<br>• **Days 1–21:** 5-FU 250mg/m²/day continuous IV infusion; initiate 1–2 weeks prior to chemoradiation (50.4Gy + 5-FU 250mg/m²/day).<br>**After chemoradiation**<br>• **Days 1–28:** 5-FU 250mg/m²/day continuous IV infusion; initiate 3–5 weeks following chemoradiation.<br>Repeat cycle every 6 weeks for 3 months. |
| **Gemcitabine**[13] | **Prior to chemoradiation**<br>• **Days 1, 8 and 15:** Gemcitabine 1,000mg/m² IV; initiate 1–2 weeks prior to chemoradiation (50.4Gy + 5-FU 250mg/m²/day).<br>**After chemoradiation**<br>• **Days 1, 8 and 15:** Gemcitabine 1,000mg/m² IV; initiate 3–5 weeks following chemoradiation.<br>Repeat cycle every 4 weeks for 3 months. |
| **Post-operative gemcitabine**[14] | **Days 1, 8 and 15:** Gemcitabine 1,000mg/m² IV.<br>Repeat cycle every 4 weeks for 6 months. |
| **Leucovorin + 5-FU**[15] | **Days 1–5:** Leucovorin 20mg/m² IV bolus, **followed by** 5-FU 425mg/m² IV bolus.<br>Repeat cycle every 4 weeks. |

### Principals of Chemotherapy[1]

Systemic therapy is used in the neoadjuvant or adjuvant setting and in the management of locally advanced unresectable and metastatic disease.

- Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.
- Close follow-up of patients undergoing chemotherapy is indicated.

**Metastatic Disease**

- Acceptable chemotherapy combinations for patients with good performance status include:
  - FOLFIRINOX[9] (category 1)
  - Gemcitabine + nab-paclitaxel[16] (category 1)
  - Gemcitabine + erlotinib[17] (category 1)*
  - Gemcitabine + capecitabine[18]
  - Gemcitabine + cisplatin[19] (especially for patients with possible hereditary cancers)
  - Fixed-dose rate gemcitabine, docetaxel, capecitabine (GTX regimen)[20] (category 2B)
  - Fluoropyrimidine + oxaliplatin (category 2B; e.g., 5-FU/leucovorin/oxaliplatin[21] or CapeOx[22])
- Acceptable monotherapy options for patients with poor performance status include:
  - Gemcitabine at 1,000mg/m² over 30 minutes, weekly for 3 weeks cycled every 28 days (category 1).
  - Fixed-dose rate gemcitabine (10mg/m²/minute) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B).
  - Capecitabine or continuous infusion 5-FU (category 2B)
- Second-line chemotherapy may consist of gemcitabine-based therapy for those previously treated with fluoropyrimidine-based therapy, and fluoropyrimidine-based therapy for those previously treated with gemcitabine-based therapy. Results of the CONKO-003 trial demonstrated a significant improvement in overall survival with the addition of oxaliplatin to 5-FU/leucovorin.[21]

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## Principals of Chemotherapy[1] (continued)

**Locally Advanced Disease**

- Depending on performance status, monotherapy or combination systemic chemotherapy, as noted above, may be considered as initial therapy prior to chemoradiation for appropriate patients with locally advanced, unresectable disease.†
- Patients should be evaluated for recovery from hematologic and nonhematologic toxicity prior to initiation of chemoradiation.
- Patients who progress with metastatic disease are not candidates for chemoradiation unless required for palliative purposes.

**Adjuvant Therapy**

- The CONKO-001 trial demonstrated significant improvements in disease-free survival and overall survival with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[23]
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[24]
- The use of gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU-based chemoradiotherapy.
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment.[25]
- For patients who relapse after receiving adjuvant therapy, subsequent therapy may consist of gemcitabine or gemcitabine-based combination therapy for patients previously treated with fluoropyrimidine-based therapy, or fluoropyrimidine-based therapy (e.g., 5-FU/ leucovorin/oxaliplatin[21] or CapeOx)[22] for patients previously treated with gemcitabine-based therapy.

**Neoadjuvant Therapy**

- Although there is insufficient evidence to recommend specific neoadjuvant regimens, most published neoadjuvant studies that were done prior to the introduction of more effective combination chemotherapy incorporated chemoradiation. Studies of these more effective regimens (i.e., FOLFIRINOX or gemcitabine and nab-paclitaxel) without chemoradiation are in progress.

* Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

† Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy.[26]

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