Occult Primary (Cancer of Unknown Primary)
Treatment Regimens

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 health care 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 provided only to supplement the latest treatment strategies. These Guidelines are a work in progress that may be refined as often as new significant data become 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 NCCN 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.

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

### Adenocarcinoma

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSING</th>
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<tbody>
<tr>
<td><strong>Preferred Regimens</strong></td>
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</table>
| CapeOX₂,₃,a-c | Day 1: Oxaliplatin 130mg/m² IV over 2 hours  
Day 1-15: Capecitabine 850–1,000mg/m² orally twice daily beginning evening of Day 1 until the morning of Day 15.  
Repeat cycle every 3 weeks for 16 cycles. |
| Gemcitabine + Cisplatin⁴,₅,e | Days 1,₈: Gemcitabine 1,000-1,250mg/m² IV over 30 minutes  
Day 1: Cisplatin 75mg/m² IV over 1 hour.  
Repeat cycle every 3 weeks for 6 cycles. |
| FOLFIRI⁶,₁₀,a,c,f,i | Day 1: Irinotecan 180mg/m² IV over 30-90 minutes, **with:**  
Day 1: Leucovorin 400mg/m² IV over 30-90 minutes, **followed by:**  
Day 1: Fluorouracil 400mg/m² IV push, **followed by:**  
Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion daily (2,400mg/m² IV over 46-48 hours).  
Repeat cycle every 2 weeks. |
| mFOLFOX⁶,₁₁,a-c,h,j | Day 1: Oxaliplatin 85mg/m² IV over 2 hours, **with:**  
Day 1: Leucovorin 400mg/m² IV over 2 hours, **followed by:**  
Day 1: Fluorouracil 400mg/m² IV push, **followed by:**  
Days 1-2: Fluorouracil 1200mg/m² IV continuous infusion over 24 hours (total 2,400mg/m² over 46–48 hours).  
Repeat cycle every 2 weeks for 24 cycles. |
| mFOLFOX6 + Radiation¹²,a,c,b,j | Day 1: Oxaliplatin 85mg/m² IV over 2 hours, **with:**  
Day 1: Leucovorin 400mg/m² IV over 2 hours, **followed by:**  
Day 1: Fluorouracil 400mg/m² IV push, **followed by:**  
Days 1-2: Fluorouracil 800mg/m² IV continuous infusion over 24 hours daily (total 1,600mg/m² over 46–48 hours).  
Repeat cycle every 2 weeks for 3 cycles with radiation. |
| Paclitaxel + Carboplatin¹³,a,k,l | Day 1: Paclitaxel 175-200mg/m² IV over 3 hours, **followed by:**  
Day 1: Carboplatin AUC 5-6 IV over 30 minutes.  
Repeat cycle every 3 weeks for 8 cycles. |

| Other Recommended Regimens | |
| Capecitabine¹⁴,₁₃,l,c,d | Days 1-14: Capecitabine 850-1,250mg/m² orally twice daily.  
Repeat cycle every 3 weeks. |
| Capecitabine + Radiation¹⁴,₁₆,c,d | Days 1-5: Capecitabine 625-825mg/m² orally twice daily.  
Repeat cycle every week for 5 weeks with radiation.  
OR  
Days 1-7: Capecitabine 625-825mg/m² orally twice daily.  
Repeat cycle every week for 5 weeks with radiation. |
| Docetaxel + Carboplatin¹²,₁₈,a,m | Day 1: Docetaxel 65mg/m² IV over 1 hour, **followed by:**  
Day 1: Carboplatin AUC 5-6 IV over 30 minutes.  
Repeat cycle every 3 weeks for 8 cycles. |
| Docetaxel + Cisplatin¹₈,₂₀,a,m | Day 1: Docetaxel 60-75mg/m² IV over 1 hour, **followed by:**  
Day 1: Cisplatin 75mg/m² IV over 1 hour.  
Repeat cycle every 3 weeks for 6 cycles. |

continued
## Occult Primary (Cancer of Unknown Primary)
### Treatment Regimens

**Adenocarcinoma** (continued)

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| **Fluorouracil**<sup>21,24,81</sup> | Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by:  
Day 1: Fluorouracil 400mg/m² IV push, followed by:  
Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion daily (2,400mg/m² IV over 46-48 hours).  
Repeat cycle every 2 weeks.  
OR  
Days 1,8,15,22,29,36: Leucovorin 500mg/m² IV over 2 hours  
Days 1,8,15,22,29,36: Fluorouracil 500mg/m² IV push administered 1 hour after the start of Leucovorin infusion.  
Repeat cycle every 4 weeks (6 weeks on followed by 2 weeks off treatment).  
OR  
Day 1: Leucovorin 20mg/m² IV over 2 hours  
Day 1: Fluorouracil 500mg/m² IV push administered 1 hour after the start of Leucovorin infusion.  
Repeat cycle every week.  
OR  
Day 1: Leucovorin 500mg/m² IV over 2 hours  
Day 1: Fluorouracil 2,600mg/m² IV continuous infusion over 24 hours.  
Repeat cycle every week. |
| **Fluorouracil + Radiation**<sup>25,c,g,h</sup> | Days 1-5: Fluorouracil 200-250mg/m² IV continuous infusion over 24 hours daily.  
Repeat cycle every week for 5 weeks with radiation.  
OR  
Days 1-7: Fluorouracil 200-250mg/m² IV continuous infusion over 24 hours daily.  
Repeat cycle every week for 5 weeks with radiation. |
| **Gemcitabine + Docetaxel**<sup>5,18,26,m</sup> | Day 1,8: Gemcitabine 1,000mg/m² IV over 30 minutes  
Day 8: Docetaxel 75mg/m² IV over 1 hour.  
Repeat cycle every 3 weeks for 6 cycles. |
| **Irinotecan + Carboplatin**<sup>10,27,a,f,l</sup> | Days 1,8,15: irinotecan 60mg/m² IV over 90 minutes daily  
Day 1: Carboplatin AUC 5-6 IV over 30 minutes.  
Repeat cycle every 4 weeks for 6 cycles. |
| **Useful in Certain Circumstances** |
| **FOLFIRINOX (for patients with presumed GI primary site and for patients with ECOG performance status 0-1)**<sup>38,44,66</sup> | Day 1: Oxaliplatin 85mg/m² IV over 2 hours, followed by:  
Day 1: Leucovorin 400mg/m² over 2 hours, followed by:  
Day 1: Irinotecan 180mg/m² over 90 minutes (begin 30 minutes after start of leucovorin infusion).  
Day 1: Fluorouracil 400mg/m² IV push, followed by:  
Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (total 2,400mg/m² over 46 hours).  
Repeat cycle every 2 weeks for 4-12 cycles. |
| **Irinotecan + Gemcitabine**<sup>30,12,74,66</sup> | Days 1 and 8: Irinotecan 100mg/m² IV over 90 minutes  
Days 1 and 8: Gemcitabine 1,000mg/m² IV over 30 minutes.  
Repeat cycle every 3 weeks for 6 cycles. |
| **Paclitaxel + Carboplatin + Etoposide (for patients with ECOG performance status 0-1)**<sup>30,64</sup> | Day 1: Paclitaxel 175-200mg/m² IV over 3 hours, followed by:  
Day 1: Carboplatin AUC 5-6 IV over 30 minutes  
Days 1,3,5,7,9: Etoposide 50mg orally once daily  
Days 2,4,6,8,10: Etoposide 100mg orally once daily.  
Repeat cycle every 3 weeks for 8 cycles. |
| **Pembrolizumab (dMMR/MSI-H tumors or TMB-H [>10 mut/ Mb] tumors)**<sup>31,34</sup> | Day 1: Pembrolizumab 200mg IV over 30 minutes  
Repeat cycle every 3 weeks or until up to 2 years.  
OR  
Day 1: Pembrolizumab 400mg IV over 30 minutes  
Repeat cycle every 6 weeks or until up to 2 years. |

*continued*
Occult Primary (Cancer of Unknown Primary)
Treatment Regimens

▶ Squamous Cell Carcinoma

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<tr>
<td>mFOLFOX6[2,3,8,a,c,h]</td>
<td>Day 1: Oxaliplatin 85mg/m² IV over 2 hours. with: Day 1: Leucovorin 400mg/m² IV over 2 hours. followed by: Day 1: Fluorouracil 400mg/m² IV push, followed by: Days 1-2: Fluorouracil 1200mg/m² IV continuous infusion over 24 hours daily (total 2,400mg/m² over 46–48 hours). Repeat cycle every 2 weeks for 24 cycles.</td>
</tr>
<tr>
<td>mFOLFOX6 + Radiation[2,a,c,h]</td>
<td>Day 1: Oxaliplatin 85mg/m² IV over 2 hours. with: Day 1: Leucovorin 400mg/m² IV over 2 hours. followed by: Day 1: Fluorouracil 800mg/m² IV continuous infusion over 24 hours daily (total 1,600mg/m² over 46–48 hours). Repeat cycle every 2 weeks for 3 cycles with radiation.</td>
</tr>
<tr>
<td>Paclitaxel + Carboplatin[3,9,a,n]</td>
<td>Day 1: Paclitaxel 175-200mg/m² IV over 3 hours Day 1: Carboplatin AUC 5-6 IV over 30 minutes. Repeat cycle every 3 weeks for 8 cycles.</td>
</tr>
</tbody>
</table>

**Other Recommended Regimens**

| Capecitabine[3,4,13,c,d] | Days 1-14: Capecitabine 850-1,250mg/m² orally twice daily. Repeat cycle every 3 weeks. |
| Capecitabine + Radiation[3,16,c,d] | Days 1-5: Capecitabine 625-825mg/m² orally twice daily. Repeat cycle every week for 5 weeks with radiation. OR Days 1-7: Capecitabine 625-825mg/m² orally twice daily. Repeat cycle every week for 5 weeks with radiation. |
| Cisplatin + Fluorouracil[35,d,g,h] | Days 1-5: Cisplatin 20mg/m² IV over 1 hour Daily 1-5: Fluorouracil 700mg/m² IV continuous infusion over 24 hours daily. Repeat cycle every 4 weeks. |
| Cisplatin + Fluorouracil + Radiation[36-38,a,g,h] | Days 1,29: Cisplatin 75-100mg/m² IV over 1 hour. Days 1-4,29-32: Fluorouracil 750-1,000mg/m² IV continuous infusion over 24 hours daily. Administer for one 5-week cycle with radiation. OR Days 1-5: Cisplatin 15mg/m² IV over 60 minutes daily Days 1-5: Fluorouracil 800mg/m² IV continuous infusion over 24 hours. Repeat cycle every 3 weeks for 2 cycles with radiation. |
| Docetaxel + Carboplatin[38,39,a,l,m] | Day 1: Docetaxel 75mg/m² IV over 30 minutes followed by: Day 1: Carboplatin AUC 5-6 IV over 30 minutes. Repeat cycle every 3 weeks for 8 cycles. |
| Docetaxel + Cisplatin[18,20,a,m] | Day 1: Docetaxel 60-75mg/m² IV over 1 hour, followed by: Day 1: Cisplatin 75mg/m² IV over 1 hour. Repeat cycle every week for 6 cycles. |
| Fluorouracil[21,24,c,e] | Day 1: Leucovorin 400mg/m² IV over 2 hours. followed by: Day 1: Fluorouracil 400mg/m² IV push. followed by: Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion daily (2,400mg/m² IV over 46-48 hours). Repeat cycle every 2 weeks. OR Days 1,8,15,22,29,36: Leucovorin 500mg/m² IV over 2 hours Days 1,8,15,22,29,36: Fluorouracil 500mg/m² IV push administered 1 hour after the start of Leucovorin infusion. Repeat cycle every 8 weeks (6 weeks followed by 2 weeks off treatment). OR Day 1: Leucovorin 20mg/m² IV over 2 hours Day 1: Fluorouracil 500mg/m² IV push administered 1 hour after the start of Leucovorin infusion. Repeat cycle every week. OR Day 1: Leucovorin 500mg/m² IV over 2 hours Day 1: Fluorouracil 2,600mg/m² IV continuous infusion over 24 hours. Repeat cycle every week. |
### Squamous Cell Carcinoma

**REGIMEN**

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<tr>
<td><strong>Fluorouracil + Radiation</strong>&lt;sup&gt;25,c,g,h&lt;/sup&gt;</td>
<td>Days 1-5: Fluorouracil 200-250mg/m² IV continuous infusion over 24 hours daily. Repeat cycle every week for 5 weeks with radiation. OR Days 1-7: Fluorouracil 200-250mg/m² IV continuous infusion over 24 hours daily. Repeat cycle every week for 5 weeks with radiation.</td>
</tr>
<tr>
<td><strong>Gemcitabine + Cisplatin</strong>&lt;sup&gt;4,5,a&lt;/sup&gt;</td>
<td>Days 1: Gemcitabine 1.000-1.250mg/m² IV over 30 minutes Day 1: Cisplatin 75mg/m² IV over 1 hour. Repeat cycle every 3 weeks for 6 cycles.</td>
</tr>
<tr>
<td><strong>Paclitaxel + Cisplatin</strong>&lt;sup&gt;60,i,k&lt;/sup&gt;</td>
<td>Day 1: Paclitaxel 175mg/m² IV over 3 hours. <strong>followed by:</strong> Day 1: Cisplatin 60mg/m² IV over 1 hour. Repeat cycle every 3 weeks for 8 cycles.</td>
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</tbody>
</table>

### Useful in Certain Circumstances

**Docetaxel + Cisplatin + Fluorouracil (for patients with ECOG performance status 0-1)**<sup>31-34,a</sup>

**Regimen:**

**Day 1:** Docetaxel 75mg/m² IV over 1 hour. **followed by:** Day 1: Cisplatin 75mg/m² IV over 1 hour. Days 1-5: Fluorouracil 750mg/m² IV continuous infusion over 24 hours. Repeat cycle every 3 weeks for 3 cycles.

**Pembrolizumab (for TMB-H [>10 mut/Mb] tumors only)**<sup>35-34,a</sup>

**Regimen:**

**Day 1:** Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 3 weeks or until up to 2 years. OR Day 1: Pembrolizumab 400mg IV over 30 minutes. Repeat cycle every 3 weeks or until up to 2 years.

### Neuroendocrine Tumors<sup>5</sup>

- For poorly differentiated (high-grade or anaplastic) or small cell subtype, refer to the NCCN Small Cell Lung Cancer guidelines.
- For well-differentiated neuroendocrine tumors, refer to the NCCN Neuroendocrine Tumors guidelines (Carcinoid tumors).

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**References**

5. Gemcitabine (Gemzar) [package insert]. Indianapolis, IN: Lilly USA, LLC, 2019.
Occult Primary (Cancer of Unknown Primary) Treatment Regimens

References (continued)