

# 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<sup>1</sup>

REGIMEN	DOSING
<b>Preferred Regimens</b>	
CapeOX <sup>2-4,a</sup>	<b>Day 1:</b> Oxaliplatin 130mg/m <sup>2</sup> IV over 2 hours <b>Day 1-15:</b> Capecitabine 850–1,000mg/m <sup>2</sup> orally twice daily beginning evening of Day 1 until the morning of Day 15. Repeat cycle every 3 weeks for 16 cycles.
Gemcitabine/Cisplatin <sup>5-7b</sup>	<b>Days 1,8:</b> Gemcitabine 1,000-1,250mg/m <sup>2</sup> IV over 30 minutes <b>Day 1:</b> Cisplatin 75mg/m <sup>2</sup> IV over 1 hour. Repeat cycle every 3 weeks for 6 cycles.
FOLFIRI <sup>8-13,a</sup>	<b>Day 1:</b> Irinotecan 180mg/m <sup>2</sup> IV over 30-90 minutes, <b>concurrent with:</b> <b>Day 1:</b> Leucovorin 400mg/m <sup>2</sup> IV over 30-90 minutes, <b>followed by:</b> <b>Day 1:</b> Fluorouracil 400mg/m <sup>2</sup> IV push, <b>followed by:</b> <b>Days 1-2:</b> Fluorouracil 1,200mg/m <sup>2</sup> IV continuous infusion daily (2,400mg/m <sup>2</sup> IV over 46-48 hours). Repeat cycle every 2 weeks.
mFOLFOX6 <sup>2,4,8,14,a,c</sup>	<b>Day 1:</b> Oxaliplatin 85mg/m <sup>2</sup> IV over 2 hours, <b>with:</b> <b>Day 1:</b> Leucovorin 400mg/m <sup>2</sup> IV over 2 hours, <b>followed by:</b> <b>Day 1:</b> Fluorouracil 400mg/m <sup>2</sup> IV push, <b>followed by:</b> <b>Days 1-2:</b> Fluorouracil 1200mg/m <sup>2</sup> IV continuous infusion over 24 hours daily (total 2,400mg/m <sup>2</sup> over 46–48 hours). Repeat cycle every 2 weeks for 24 cycles.
Paclitaxel/Carboplatin <sup>15-18,d,e</sup> <i>Paclitaxel requires premedication.</i>	<b>Day 1:</b> Paclitaxel 175-200mg/m <sup>2</sup> IV over 3 hours, <b>followed by:</b> <b>Day 1:</b> Carboplatin AUC 5-6 IV over 30 minutes. Repeat cycle every 3 weeks for 8 cycles. <b>OR</b> <b>Days 1,8,15:</b> Paclitaxel 80mg/m <sup>2</sup> IV over 1 hour, <b>followed by:</b> <b>Days 1,8,15:</b> Carboplatin AUC 2 IV over 30 minutes. Repeat cycle every 4 weeks.
<b>Other Recommended Regimens</b>	
Capecitabine <sup>3,9,20</sup>	<b>Days 1-14:</b> Capecitabine 850-1,250mg/m <sup>2</sup> orally twice daily. Repeat cycle every 3 weeks.
Capecitabine + RT <sup>3,21,a</sup>	<b>Days 1-5:</b> Capecitabine 625-825mg/m <sup>2</sup> orally twice daily. Repeat cycle every week for 5 weeks with radiation.
Docetaxel/Carboplatin <sup>15,22,23,d,g</sup> <i>Docetaxel requires premedication.</i>	<b>Day 1:</b> Docetaxel 65mg/m <sup>2</sup> IV over 1 hour, <b>followed by:</b> <b>Day 1:</b> Carboplatin AUC 5-6 IV over 30 minutes. Repeat cycle every 3 weeks for 8 cycles.
Docetaxel/Cisplatin <sup>7,23-25,b,d,g</sup> <i>Docetaxel requires premedication.</i>	<b>Day 1:</b> Docetaxel 60-75mg/m <sup>2</sup> IV over 1 hour, <b>followed by:</b> <b>Day 1:</b> Cisplatin 75mg/m <sup>2</sup> IV over 1 hour. Repeat cycle every 3 weeks for 6 cycles.

continued

# Occult Primary (Cancer of Unknown Primary) Treatment Regimens

## ► Adenocarcinoma<sup>1</sup> (continued)

REGIMEN	DOSING
<b>Other Recommended Regimens</b> (continued)	
Fluorouracil <sup>8,26-29</sup>	<p><b>Day 1:</b> Leucovorin 400mg/m<sup>2</sup> IV, <b>followed by:</b>  <b>Day 1:</b> Fluorouracil 400mg/m<sup>2</sup> IV push, <b>followed by:</b>  <b>Days 1-2:</b> Fluorouracil 1,200mg/m<sup>2</sup> IV continuous infusion daily (2,400mg/m<sup>2</sup> IV over 46-48 hours). Repeat cycle every 2 weeks.</p> <p><b>OR</b></p> <p><b>Days 1,8,15,22,29,36:</b> Leucovorin 500mg/m<sup>2</sup> IV over 2 hours  <b>Days 1,8,15,22,29,36:</b> Fluorouracil 500mg/m<sup>2</sup> IV push administered 1 hour after the start of Leucovorin infusion. Repeat cycle every 8 weeks (6 weeks on followed by 2 weeks off treatment).</p> <p><b>OR</b></p> <p><b>Day 1:</b> Leucovorin 20mg/m<sup>2</sup> IV over 2 hours  <b>Day 1:</b> Fluorouracil 500mg/m<sup>2</sup> IV push administered 1 hour after the start of Leucovorin infusion. Repeat cycle every week.</p> <p><b>OR</b></p> <p><b>Day 1:</b> Leucovorin 500mg/m<sup>2</sup> IV over 2 hours  <b>Day 1:</b> Fluorouracil 2,600mg/m<sup>2</sup> IV continuous infusion over 24 hours. Repeat cycle every week.</p>
Fluorouracil + RT <sup>8,30,a</sup>	<p><b>Days 1-5:</b> Fluorouracil 200-250mg/m<sup>2</sup> IV continuous infusion over 24 hours daily. Repeat cycle every week for 5 weeks with radiation.</p>
Gemcitabine/Docetaxel <sup>6,23,31,d,g</sup> <i>Docetaxel requires premedication.</i>	<p><b>Day 1,8:</b> Gemcitabine 1,000mg/m<sup>2</sup> IV over 30 minutes  <b>Day 8:</b> Docetaxel 75mg/m<sup>2</sup> IV over 1 hour.  Repeat cycle every 3 weeks for 6 cycles.</p>
Irinotecan/Carboplatin <sup>10,15,32,d</sup>	<p><b>Days 1,8,15:</b> Irinotecan 60mg/m<sup>2</sup> IV over 90 minutes daily  <b>Day 1:</b> Carboplatin AUC 5-6 IV over 30 minutes.  Repeat cycle every 4 weeks for 6 cycles.</p>
<b>Useful in Certain Circumstances</b>	
Dostarlimab-gxly (only in tumors that are dMMR/MSI-H) <sup>33,34,a,h,i</sup>	<p><b>Day 1:</b> Dostarlimab-gxly 500mg IV over 30 minutes. Repeat cycle every 3 weeks for 4 cycles, <b>followed by:</b>  <b>Day 1:</b> Dostarlimab-gxly 1,000mg IV over 30 minutes. Repeat cycle every 6 weeks (beginning with Cycle 5, starting 3 weeks after Cycle 4).</p>
FOLFIRINOX (for patients with presumed GI primary site and for patients with ECOG performance status 0-1) <sup>4,8,10,35,a,c,f</sup>	<p><b>Day 1:</b> Oxaliplatin 85mg/m<sup>2</sup> IV over 2 hours, <b>followed by:</b>  <b>Day 1:</b> Leucovorin 400mg/m<sup>2</sup> over 2 hours  <b>Day 1:</b> Irinotecan 180mg/m<sup>2</sup> over 90 minutes (begin 30 minutes after start of leucovorin infusion)  <b>Day 1:</b> Fluorouracil 400mg/m<sup>2</sup> IV push, <b>followed by:</b>  <b>Days 1-2:</b> Fluorouracil 1,200mg/m<sup>2</sup> IV continuous infusion over 24 hours daily (total 2,400mg/m<sup>2</sup> over 46 hours). Repeat cycle every 2 weeks for 4-12 cycles.</p>
Irinotecan/Gemcitabine (for patients ineligible to receive platinum-based chemotherapy) <sup>6,10,36</sup>	<p><b>Days 1,8:</b> Gemcitabine 1,000mg/m<sup>2</sup> IV over 30 minutes  <b>Days 1,8:</b> Irinotecan 100mg/m<sup>2</sup> IV over 90 minutes.  Repeat cycle every 3 weeks for 6 cycles.</p>
mFOLFIRINOX (for patients with presumed GI primary site and for patients with ECOG performance status 0-1) <sup>4,8,10,35,38,a,c,f</sup>	<p><b>Day 1:</b> Oxaliplatin 85mg/m<sup>2</sup> IV over 2 hours  <b>Day 1:</b> Leucovorin 400mg/m<sup>2</sup> IV over 2 hours  <b>Day 1:</b> Irinotecan 150mg/m<sup>2</sup> IV over 30-90 minutes  <b>Days 1-2:</b> Fluorouracil 1,200mg/m<sup>2</sup> IV continuous infusion daily (total 2,400mg/m<sup>2</sup> IV over 46 hours). Repeat cycle every 2 weeks for 12 cycles.</p>
Paclitaxel/Carboplatin/Etoposide (for patients with ECOG performance status 0-1) <sup>15,16,39,40,a,d,e</sup> <i>Paclitaxel requires premedication.</i>	<p><b>Day 1:</b> Paclitaxel 175-200mg/m<sup>2</sup> IV over 3 hours, <b>followed by:</b>  <b>Day 1:</b> Carboplatin AUC 5-6 IV over 30 minutes  <b>Days 1,3,5,7,9:</b> Etoposide 50mg orally once daily  <b>Days 2,4,6,8,10:</b> Etoposide 100mg orally once daily.  Repeat cycle every 3 weeks for 8 cycles.</p>
Pembrolizumab (dMMR/MSI-H tumors or TMB-H [ $>10$ mut/Mb] tumors) <sup>41-44,a,h</sup>	<p><b>Day 1:</b> Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 3 weeks or until up to 2 years.</p> <p><b>OR</b></p> <p><b>Day 1:</b> Pembrolizumab 400mg IV over 30 minutes. Repeat cycle every 6 weeks or until up to 2 years.</p>

continued

# Occult Primary (Cancer of Unknown Primary) Treatment Regimens

## ► Squamous Cell Carcinoma<sup>1</sup>

REGIMEN	DOSING
<b>Preferred Regimens</b>	
mFOLFOX6 <sup>2,4,8,14,a,c</sup>	<p><b>Day 1:</b> Oxaliplatin 85mg/m<sup>2</sup> IV over 2 hours, <b>concurrent with:</b>  <b>Day 1:</b> Leucovorin 400mg/m<sup>2</sup> IV over 2 hours, <b>followed by:</b>  <b>Day 1:</b> Fluorouracil 400mg/m<sup>2</sup> IV push, <b>followed by:</b>  <b>Days 1-2:</b> Fluorouracil 1200mg/m<sup>2</sup> IV continuous infusion over 24 hours daily (total 2,400mg/m<sup>2</sup> over 46–48 hours).                      Repeat cycle every 2 weeks for 24 cycles.</p>
Paclitaxel/Carboplatin <sup>15-18,d,e</sup> <i>Docetaxel requires premedication.</i>	<p><b>Day 1:</b> Paclitaxel 175-200mg/m<sup>2</sup> IV over 3 hours, <b>followed by:</b>  <b>Day 1:</b> Carboplatin AUC 5-6 IV over 30 minutes.                      Repeat cycle every 3 weeks for 8 cycles.  <b>OR</b>  <b>Days 1,8,15:</b> Paclitaxel 80 mg/m<sup>2</sup> IV over 1 hour, <b>followed by:</b>  <b>Days 1,8,15:</b> Carboplatin AUC 2 IV over 30 minutes.                      Repeat cycle every 4 weeks.</p>
<b>Other Recommended Regimens</b>	
Capecitabine <sup>2,19,20</sup>	<p><b>Days 1-14:</b> Capecitabine 850-1,250mg/m<sup>2</sup> orally twice daily.                      Repeat cycle every 3 weeks.</p>
Capecitabine + RT <sup>3,21,a</sup>	<p><b>Days 1-5:</b> Capecitabine 625-825mg/m<sup>2</sup> orally twice daily.                      Repeat cycle every week for 5 weeks with radiation.  <b>OR</b>  <b>Days 1-7:</b> Capecitabine 625-825mg/m<sup>2</sup> orally twice daily.                      Repeat cycle every week for 5 weeks with radiation.</p>
Cisplatin/Fluorouracil <sup>7,8,45,b</sup>	<p><b>Days 1-5:</b> Cisplatin 20mg/m<sup>2</sup> IV over 1 hour daily  <b>Days 1-5:</b> Fluorouracil 700mg/m<sup>2</sup> IV continuous infusion over 24 hours daily.                      Repeat cycle every 4 weeks.</p>
Cisplatin/Fluorouracil + RT <sup>7,8,46-48,a,b</sup>	<p><b>Days 1,29:</b> Cisplatin 75-100mg/m<sup>2</sup> IV over 1 hour.  <b>Days 1-4,29-32:</b> Fluorouracil 750-1,000mg/m<sup>2</sup> IV continuous infusion over 24 hours daily.                      Administer for one 5-week cycle with radiation.  <b>OR</b>  <b>Days 1-5:</b> Cisplatin 15mg/m<sup>2</sup> IV over 60 minutes daily  <b>Days 1-5:</b> Fluorouracil 800mg/m<sup>2</sup> IV continuous infusion over 24 hours.                      Repeat cycle every 3 weeks for 2 cycles with radiation.</p>
Docetaxel/Carboplatin <sup>15,22,23,d,g</sup> <i>Docetaxel requires premedication.</i>	<p><b>Day 1:</b> Docetaxel 75mg/m<sup>2</sup> IV over 30 minutes <b>followed by:</b>  <b>Day 1:</b> Carboplatin AUC 5-6 IV over 30 minutes.                      Repeat cycle every 3 weeks for 8 cycles.</p>
Docetaxel/Cisplatin <sup>7,23-25,b,d,g</sup> <i>Docetaxel requires premedication.</i>	<p><b>Day 1:</b> Docetaxel 60-75mg/m<sup>2</sup> IV over 1 hour, <b>followed by:</b>  <b>Day 1:</b> Cisplatin 75mg/m<sup>2</sup> IV over 1 hour.                      Repeat cycle every 3 weeks for 6 cycles.</p>
Fluorouracil <sup>8,26,29</sup>	<p><b>Day 1:</b> Leucovorin 400mg/m<sup>2</sup> IV over 2 hours, <b>followed by:</b>  <b>Day 1:</b> Fluorouracil 400mg/m<sup>2</sup> IV push, <b>followed by:</b>  <b>Days 1-2:</b> Fluorouracil 1,200mg/m<sup>2</sup> IV continuous infusion daily (2,400mg/m<sup>2</sup> IV over 46-48 hours).                      Repeat cycle every 2 weeks.  <b>OR</b>  <b>Days 1,8,15,22,29,36:</b> Leucovorin 500mg/m<sup>2</sup> IV  <b>Days 1,8,15, 22,29,36:</b> Fluorouracil 500mg/m<sup>2</sup> IV push administered 1 hour after the start of Leucovorin infusion.                      Repeat cycle every 8 weeks (6 weeks followed by 2 weeks off treatment).  <b>OR</b>  <b>Day 1:</b> Leucovorin 20mg/m<sup>2</sup> IV  <b>Day 1:</b> Fluorouracil 500mg/m<sup>2</sup> IV push administered 1 hour after the start of Leucovorin infusion.                      Repeat cycle every week.  <b>OR</b>  <b>Day 1:</b> Leucovorin 500mg/m<sup>2</sup> IV  <b>Day 1:</b> Fluorouracil 2,600mg/m<sup>2</sup> IV continuous infusion over 24 hours.                      Repeat cycle every week.</p>

continued

# Occult Primary (Cancer of Unknown Primary) Treatment Regimens

## ► Squamous Cell Carcinoma<sup>1</sup> (continued)

REGIMEN	DOSING
<b>Other Recommended Regimens</b> (continued)	
<b>Fluorouracil + RT</b> <sup>8,30,a</sup>	<b>Days 1-5:</b> Fluorouracil 200-250mg/m <sup>2</sup> IV continuous infusion over 24 hours daily. Repeat cycle every week for 5 weeks with radiation.
<b>Gemcitabine + Cisplatin</b> <sup>5,7b</sup>	<b>Days 1,8:</b> Gemcitabine 1,000-1,250mg/m <sup>2</sup> IV over 30 minutes <b>Day 1:</b> Cisplatin 75mg/m <sup>2</sup> IV over 1 hour. Repeat cycle every 3 weeks for 6 cycles.
<b>Paclitaxel/Cisplatin</b> <sup>716,49,b,d,e</sup> <i>Paclitaxel requires premedication.</i>	<b>Day 1:</b> Paclitaxel 175mg/m <sup>2</sup> IV over 3 hours, <b>followed by:</b> <b>Day 1:</b> Cisplatin 60mg/m <sup>2</sup> IV over 1 hour. Repeat cycle every 3 weeks for 8 cycles.
<b>Useful in Certain Circumstances</b>	
<b>Docetaxel/Cisplatin/Fluorouracil</b> (for patients with ECOG performance status 0-1) <sup>7,8,23,50,a,b,d,g</sup> <i>Docetaxel requires premedication.</i>	<b>Day 1:</b> Docetaxel 75mg/m <sup>2</sup> IV over 1 hour, <b>followed by:</b> <b>Day 1:</b> Cisplatin 75mg/m <sup>2</sup> IV over 1 hour. <b>Days 1-5:</b> Fluorouracil 750mg/m <sup>2</sup> IV continuous infusion over 24 hours daily. Repeat cycle every 3 weeks for 3 cycles.
<b>Pembrolizumab (only in tumors that are dMMR/MSI-H or have TMB-H [≥10 mut/Mb])</b> <sup>41-44,a,h</sup>	<b>Day 1:</b> Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 3 weeks or until up to 2 years. <b>OR</b> <b>Day 1:</b> Pembrolizumab 400mg IV over 30 minutes. Repeat cycle every 6 weeks or until up to 2 years.

### Neuroendocrine Tumors<sup>1</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).

<sup>a</sup> AUC= Area under the curve; CapeOx = Capecitabine/oxaliplatin; CSF = colony-stimulating factor; dMMR = Deficient mismatch repair; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = Fluorouracil continuous; FOLFIRINOX = Fluorouracil continuous infusion/leucovorin/irinotecan/oxaliplatin; GI = gastrointestinal; FOLFIRI = Fluorouracil continuous infusion/leucovorin/irinotecan; mFOLFOX6 = Fluorouracil continuous infusion/leucovorin/oxaliplatin (modified regimen); MSI-H = High level microsatellite instability; Mut/mb = mutations/megabase; RT = radiation therapy; TMB-H = Tumor mutational burden-high.

<sup>b</sup> Hydration is required with supplemental electrolytes pre- and post-administration of Cisplatin.

<sup>c</sup> Discontinuation of oxaliplatin should be strongly considered after 3-4 months of therapy (or sooner if neurotoxicity grade 2 or greater develops) while maintaining other agents until time of tumor progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.

<sup>d</sup> CSFs may be considered for primary prophylaxis based on the febrile neutropenia (FN) risk of the chemotherapy regimen.

<sup>e</sup> For Paclitaxel: Premedication for hypersensitivity is required. The recommended dosing is:

- H<sub>2</sub> antagonist
  - Famotidine 20mg IV or orally (or equivalent H<sub>2</sub> blocker) 30-60 minutes pre-Paclitaxel AND
- H<sub>1</sub> antagonist
  - Diphenhydramine 12.5-50mg IV or orally 30-60 minutes pre-Paclitaxel AND
- Dexamethasone (for 21-day regimen):
  - Dexamethasone 20mg orally approximately 12 and 6 hours pre-Paclitaxel OR
  - Dexamethasone 20mg IV 30 minutes pre-Paclitaxel
- Dexamethasone (for weekly regimens):
  - Dexamethasone 10mg IV 30 minutes pre-Paclitaxel

<sup>f</sup> Myeloid growth factor therapy should be administered with the regimen.

<sup>g</sup> For Docetaxel: Premedication with dexamethasone for fluid retention is required. One recommended dosing strategy is dexamethasone 8mg orally twice daily for three consecutive days starting 1 day prior to docetaxel administration.

<sup>h</sup> Early- and late-onset immune-related adverse events affecting multiple organ systems can occur in patients receiving immune checkpoint inhibitors. Patients with neurologic or life-threatening autoimmune disorders as well as those receiving high levels of immunosuppression for their underlying disease should be approached with caution when considering immunotherapy. All patients will require extensive resources including ongoing intensive monitoring and supportive care.

<sup>i</sup> For patients with recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. Note, patients who had received prior immune checkpoint inhibitor therapy were excluded from the dostarlimab-gxly clinical trial.

## References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Occult Primary V.1.2023: Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/occult.pdf](https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf). Accessed August 30, 2022.
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