

# 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>2,3,a-c</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>4,5,e</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>6-10,a,c,f-i</sup>	<b>Day 1:</b> Irinotecan 180mg/m <sup>2</sup> IV over 30–90 minutes, <b>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>2,11,a-c,h-j</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.
mFOLFOX6 + Radiation <sup>12,a-c,h-j</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 800mg/m <sup>2</sup> IV continuous infusion over 24 hours daily (total 1,600mg/m <sup>2</sup> over 46–48 hours). Repeat cycle every 2 weeks for 3 cycles with radiation.
Paclitaxel + Carboplatin <sup>13,a,k,l</sup>	<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>Other Recommended Regimens</b>	
Capecitabine <sup>3,14,15,c,d</sup>	<b>Days 1-14:</b> Capecitabine 850–1,250mg/m <sup>2</sup> orally twice daily. Repeat cycle every 3 weeks.
Capecitabine + Radiation <sup>3,16,c,d</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. <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.
Docetaxel + Carboplatin <sup>17,18,a,m</sup>	<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>18-20,e,m</sup>	<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>21-24,c,g,i</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.</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 + Radiation <sup>25,c,g,h</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> <p><b>OR</b></p> <p><b>Days 1-7:</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>5,18,26,m</sup>	<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>10,27,a,f,i</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>	
FOLFIRINOX (for patients with presumed GI primary site and for patients with ECOG performance status 0-1) <sup>28,a,c,f,h,j</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>followed by:</b>  <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 <sup>5,10,29,f,n</sup>	<p><b>Days 1 and 8:</b> Irinotecan 100mg/m<sup>2</sup> IV over 90 minutes  <b>Days 1 and 8:</b> Gemcitabine 1,000mg/m<sup>2</sup> IV over 30 minutes.            Repeat cycle every 3 weeks for 6 cycles.</p>
Paclitaxel + Carboplatin + Etoposide (for patients with ECOG performance status 0-1) <sup>30,a,k,l</sup>	<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>31-34,a</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>2,11,a-c,h-j</sup>	<p><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.</p>
mFOLFOX6 + Radiation <sup>12,a-c,h-j</sup>	<p><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 800mg/m<sup>2</sup> IV continuous infusion over 24 hours daily (total 1,600mg/m<sup>2</sup> over 46–48 hours).                      Repeat cycle every 2 weeks for 3 cycles with radiation.</p>
Paclitaxel + Carboplatin <sup>13,a,k,n</sup>	<p><b>Day 1:</b> Paclitaxel 175-200mg/m<sup>2</sup> IV over 3 hours  <b>Day 1:</b> Carboplatin AUC 5-6 IV over 30 minutes.                      Repeat cycle every 3 weeks for 8 cycles.</p>
<b>Other Recommended Regimens</b>	
Capecitabine <sup>3,14,15,c,d</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 + Radiation <sup>3,16,c,d</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>35,d,g,h</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 + Radiation <sup>36-38,e,g,h</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>18,39,a,l,m</sup>	<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>18-20,e,m</sup>	<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>21-24,c,g,i</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 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 followed by 2 weeks off treatment).  <b>OR</b>  <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.  <b>OR</b>  <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>

continued

# Occult Primary (Cancer of Unknown Primary) Treatment Regimens

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

REGIMEN	DOSING
<b>Other Recommended Regimens</b> (continued)	
Fluorouracil + Radiation <sup>25,c,g,h</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>OR</b> <b>Days 1-7:</b> Fluorouracil 200-250mg/m <sup>2</sup> IV continuous infusion over 24 hours daily. Repeat cycle every week for 5 weeks with radiation.
Gemcitabine + Cisplatin <sup>4,5,e</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.
Paclitaxel + Cisplatin <sup>40,e,k</sup>	<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>	
Docetaxel + Cisplatin + Fluorouracil (for patients with ECOG performance status 0-1) <sup>5,41,a,c,e,g,h</sup>	<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. Repeat cycle every 3 weeks for 3 cycles.
Pembrolizumab (for TMB-H [ $>10$ mut/Mb] tumors only) <sup>31,34,a</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; 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; TMB-H = Tumor mutational burden-high.
- <sup>b</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>c</sup> Patients with dihydropyrimidine dehydrogenase (DPD) deficiency are unable to metabolize capecitabine or fluorouracil normally and may have severe unexpected toxicity.
- <sup>d</sup> This agent has multiple potential drug-drug and/or drug-food interactions.
- <sup>e</sup> Hydration is required with supplemental electrolytes pre- and post-administration of cisplatin.
- <sup>f</sup> Patients who are homozygous for the UGT1A1\*28 allele or who have a clinical diagnosis of Gilbert's Syndrome have an increased risk of neutropenia when started on irinotecan.
- <sup>g</sup> Fluorouracil is administered as a continuous infusion over multiple days with this regimen.
- <sup>h</sup> IV continuous infusion fluorouracil requires a central venous access device.
- <sup>i</sup> Levoleucovorin is not interchangeable with leucovorin, and doses are not equivalent.
- <sup>j</sup> Leucovorin infusion time should match the infusion time of oxaliplatin when these are given concurrently.
- <sup>k</sup> Premedication for hypersensitivity is required for paclitaxel: famotidine 20 mg IV or orally (or equivalent H2 blocker) 30 – 60 minutes pre-paclitaxel AND diphenhydramine 12.5 – 50 mg IV or orally 30 – 60 minutes pre-paclitaxel AND dexamethasone 20 mg IV 30 minutes pre-paclitaxel OR dexamethasone
- <sup>l</sup> The maximum dose for carboplatin is based on GFR estimate that is capped at 125mL/min for patients with normal renal function.
- <sup>m</sup> Docetaxel should be administered through non-PVC tubing. 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>n</sup> For patients ineligible to receipt platinum-based chemotherapy.

## References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Occult Primary V.2.2021: Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/occult.pdf](https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf) Accessed July 14, 2021.
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