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# Cleveland Clinic

## Clinical Rx Forum

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## Onivyde™ in Metastatic Pancreatic Cancer

By: Thomas S. Achey, Pharm.D.

**Background:** Pancreatic cancer is a debilitating disease with a poor prognosis as life expectancy is measured in months.<sup>1</sup> Metastasis is observed early in its progression and patients commonly experience cachexia and asthenia. Risk factors for developing pancreatic cancer include advanced age and cigarette smoking. Systemic chemotherapy provides benefits to patients with metastatic pancreatic cancer including symptomatic relief and survival.<sup>2</sup> First-line therapies include FOLFIRINOX (leucovorin, fluorouracil, irinotecan, oxaliplatin) or gemcitabine (GEM) with or without albumin-bound paclitaxel. FOLFOX (leucovorin, fluorouracil, oxaliplatin) has been evaluated as a second-line option; however, it is associated with various toxicities including, but not limited to, peripheral neuropathy.<sup>3</sup> Optimal second-line regimens are unknown; however, irinotecan liposome shows promising results. Irinotecan liposome (Onivyde™; Merrimack Phar-

maceutical), a topoisomerase 1 inhibitor antineoplastic agent, was approved by the Food and Drug Administration (FDA) in October 2015, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following GEM-based therapy.<sup>4</sup>

**Mechanism of Action:** Irinotecan liposome inhibits the activity of topoisomerase I resulting in DNA damage and subsequent apoptosis.<sup>1,2</sup> Following administration, irinotecan liposome remains 95% encapsulated within a lipid bilayer vesicle. Its liposomal bilayer shelters irinotecan from conversion to its active SN-38 metabolite in the circulation, thereby increasing the intratumoral levels of both irinotecan and SN-38.<sup>4</sup> Local metabolic activation increases its therapeutic window and potentially minimizes toxicity.<sup>5,6</sup> The

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## Movantik™ for Opioid-Induced Constipation

By: Molly Ellen Amos, Pharm.D.

**Introduction:** Opioid analgesics are often used for the treatment of chronic pain, and it is estimated that approximately 3% of the United States population is on long-term opioid therapy for this indication.<sup>1</sup> These opioid analgesics are associated with adverse effects, the most common of which are gastrointestinal (GI) upset and constipation.<sup>1</sup> Opioid-induced constipation is estimated to affect half of patients receiving chronic opioid therapy, and is mediated via action at the  $\mu$ -opioid receptor in the GI tract.<sup>1,2</sup>

**Novel Drug:** Naloxegol (Movantik™; AstraZeneca Pharmaceuticals) is an oral peripherally-acting  $\mu$ -opioid receptor antagonist (PAMORA) indicated for the treatment of opioid-induced constipation in patients being treated with opioids for nonmalignant pain.<sup>3</sup> This drug contains a polyethylene glycol moiety, which decreases its permeability and increases its efflux by P-glycoprotein.<sup>3</sup> These properties make it less likely to enter the central nervous system (CNS) and interfere

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metabolism of irinotecan liposome formulation has not been evaluated. However, following intravenous administration, standard irinotecan undergoes metabolism via esterases to SN-38. This metabolite is subsequently activated by uridine diphosphate glucuronosyl transferase (UGT1A1). Patients homozygous for the UGT1A1\*28 allele achieve higher levels of the SN-38. Those individuals may require lower dosages of irinotecan.<sup>7,8</sup>

**Key Clinical Trials:** Forty patients with metastatic, GEM-refractory pancreatic cancer were included in a randomized, open-label evaluation of irinotecan liposome monotherapy.<sup>9</sup> The primary endpoint was 3-month survival rate. Thirty-five (75%) patients survived at least 3 months. The median progression-free and overall survival were 2.4 and 5.2 months, respectively. Ten (25%) patients survived 1 year after initiation of therapy. The authors concluded that irinotecan liposome demonstrates moderate antitumor activity in patients with metastatic pancreatic adenocarcinoma previously treated with GEM-based therapy. The FDA approval of irinotecan liposome for use in pancreatic cancer was based on the results of an international, open-label trial: **Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous-gemcitabine therapy (NAPOLI-1).**<sup>5</sup> The trial evaluated the efficacy of irinotecan liposome, alone (n=151) or in combination with 5-FU/LV (n=117), compared with the control, 5-FU/LV (n=149). The primary endpoint was overall survival. Irinotecan liposome plus 5-FU/LV significantly improved overall survival in patients previously treated with GEM-based therapy compared to the control group (6.1 versus 4.2 months).<sup>4</sup> The median progression-free survival was 3.1 months in patients randomized to combination therapy versus 1.5 months in patients receiving 5-FU/LV alone. Common adverse effects included: diarrhea, fatigue, nausea, anorexia, neutropenia, and vomiting.

**Dosing and Administration:** The recommended starting dose of irinotecan liposome is 70 mg/m<sup>2</sup> administered intravenously over 90 minutes every 2 weeks prior to leucovorin and fluorouracil.<sup>4</sup> In patients known to be homozygous for the UGT1A1\*28 allele, the starting dose is 50 mg/m<sup>2</sup> administered by intravenous infusion over 90 minutes; doses may be increased to 70 mg/m<sup>2</sup> as tolerated in subsequent cycles. Irinotecan liposome is classified as an antineoplastic irritant.<sup>10</sup>

**Availability and Cost:** Irinotecan liposome is available as a 43 mg, 10 mL vial with a suggested wholesale price (SWP) of \$1944.<sup>10</sup> The cost of one dose of irinotecan liposome for an average patient who weighs 1.73/m<sup>2</sup> would be approximately \$6000.

**Role in Therapy:** Irinotecan liposome, in combination with leucovorin and fluorouracil, may be an acceptable second-line option in patients with metastatic pancreatic cancer previously treated with GEM-based therapy. The irinotecan liposome regimen is a much more expensive treatment option than FOLFOX, another second-line treatment option. Despite its higher cost, this regimen may represent a possible alternative in patients with disease regression who may not be able to tolerate FOLFOX therapy.

**Formulary Status:** Irinotecan liposome, which was FDA-approved in 2015, is being reviewed for formulary addition.

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with centrally-mediated opioid analgesia.<sup>3</sup> Naloxegol has an estimated bioavailability of 60% and reaches peak plasma concentrations within 2 hours of administration.<sup>3,4</sup> Metabolism of naloxegol occurs via the CYP3A4 enzymes into metabolites, with undefined activity. Naloxegol is excreted in the urine and feces and has a half-life of 8 hours.

**Efficacy and Safety:** There were three randomized controlled studies conducted to evaluate the efficacy of naloxegol, one phase II and two replicate phase III trials (KODIAC-04 and KODIAC-05). The phase II trial included patients with non-malignant or cancer-related pain, and showed that naloxegol, when compared to placebo, significantly increased the number of spontaneous bowel movements from baseline to the end of the first week of treatment at 25 mg (2.9 versus 1.0;  $P=0.002$ ) and 50 mg (3.3 versus 0.5;  $P=0.0001$ ) daily.<sup>5</sup> The replicate phase III trials included only patients with non-cancer pain, and showed that naloxegol significantly increased response rate in KODIAC-04 in both the 12.5 mg ( $RR=1.38$ ,  $95\%CI:1.06-1.80$ ;  $P=0.02$ ) and 25 mg ( $RR=1.51$ ,  $95\%CI:1.17-1.95$ ;  $P=0.001$ ) daily dose groups, and in the 25 mg ( $RR=1.35$ ,  $95\%CI:1.05-1.74$ ;  $P=0.02$ ) dose group in KODIAC-05.<sup>6</sup> A subgroup analysis of KODIAC-04 and KODIAC-05 showed that this improved response was also observed in patients who had inadequate response to other laxative therapies.<sup>7</sup> Another randomized controlled trial, called KODIAC-08, evaluated the long-term safety of naloxegol over a 52-week period, and found that the most common adverse effects of naloxegol dosed at 25 mg daily were GI-related, and that there were no adverse events that appeared during the 52-week period that did not also appear during the 12-week phase III trials.<sup>8</sup>

**Dosing and Administration:** Recommended dosing for naloxegol is 25 mg by mouth once daily.<sup>3</sup> Naloxegol is renally excreted and the dose must be renally adjusted; renal dosing starts at 12.5 mg daily and may be increased if tolerated and ineffective at producing a spontaneous bowel movement. Naloxegol dosing must also be adjusted to 12.5 mg daily if taken concomitantly with moderate CYP3A4 inhibitors or inducers.

**Clinical Pearls:** Naloxegol is contraindicated for concomitant use with strong CYP3A4 inducers or inhibitors.<sup>3</sup> Labeling for naloxegol also contains warnings for risk of GI perforation and opioid withdrawal; therefore, patients should be monitored for the occurrence of these adverse effects. Naloxegol is rated pregnancy category C; no adverse events were observed in animal reproductive studies. It may be secreted into the breast milk and should be discontinued in a breastfeeding woman. Absorption of naloxegol is

increased when administered with a high fat-content meal, and it is recommended to be taken on an empty stomach.

**Availability and Cost:** Naloxegol is available as 12.5 mg and 25 mg oral tablets with a suggested wholesale price (SWP) of \$329.17 for 30 tablets.<sup>3,9</sup>

**Formulary Status:** Naloxegol was recently added to the CCHS Adult Formulary restricted to patients currently on opioid therapy who have failed at least two other scheduled laxative therapies for 48 hours.

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