Formulary Drug Reviews

Irinotecan Liposome Injection

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Generic Name:	Irinotecan liposome injection
Proprietary Name:	Onivyde (Merrimack Pharmaceuticals, Inc.)
Approval Rating:	SPO
Therapeutic Class:	Antineoplastic agents, DNA topoisomerase inhibitors
Similar Drugs:	Irinotecan hydrochloride
Sound- or Look-Alike Names:	Irinotecan hydrochloride

INDICATIONS

Irinotecan liposome injection (PEP02, MM-398) is indicated in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas that has progressed following gemcitabine-based therapy.¹

Ongoing clinical trials evaluating irinotecan liposome injection in the treatment of other advanced metastatic cancers include a phase 2 study comparing irinotecan liposome injection with a gemcitabine-based regimen in patients with previously untreated metastatic pancreatic adenocarcinoma.^{2,3} Irinotecan

liposome has also been evaluated in phase 2 studies as second-line therapy for metastatic colorectal cancer and advanced or metastatic gastric cancer.^{4,5}

Irinotecan liposome injection should not be substituted for conventional irinotecan hydrochloride injection (Camptosar, Pharmacia and Upjohn Company LLC).¹ Irinotecan hydrochloride injection is indicated in combination with fluorouracil and leucovorin as first-line therapy for patients with metastatic carcinoma of the colon or rectum and for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.⁶

CLINICAL PHARMACOLOGY

Irinotecan liposome injection is formulated with irinotecan into a liposomal dispersion.^{1,4,7} The liposome is a unilamellar lipid bilayer vesicle that encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrose octasulfate salt.¹

Irinotecan is a topoisomerase I inhibitor.¹ Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase I-DNA complex and prevent repair of single-strand breaks, leading to exposure

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time-dependent, double-strand DNA damage and cell death.¹ Administration via a liposomal formulation results in prolonged intratumor exposure at levels above the threshold for antitumor activity.⁸ In animal models, irinotecan liposome produced similar intratumor SN-38 exposure at doses 5-fold lower than irinotecan hydrochloride, with enhanced antitumor activity.^{1,8} In addition to activity in pancreatic cancer, irinotecan liposome injection has demonstrated antitumor activity in animal models of glioblastoma, Ewing sarcoma, and colon carcinoma; in early clinical trials, it demonstrated activity in colorectal cancer and gastric cancer.^{4,5,9,10}

Additional lipid-based formulations of irinotecan either previously or currently under preclinical and clinical evaluation include another liposomal nanoformulation (Irinophore C), a pegylated liposomal formulation (IHL-305), and a lipid-coated mesoporous silica nanoparticle formulation.¹¹⁻²⁰

PHARMACOKINETICS

Over the irinotecan liposome dose range of 50 to 155 mg/m², peak concentration (C_{max}) and area under the curve (AUC) of total irinotecan increase with dose. The C_{max} of total SN-38 also increases proportionally with dose, although the AUC of total SN-38 increases less than proportionally with dose.¹ Compared with administration of irinotecan hydrochloride, the pharmacokinetics of SN-38 following administration of irinotecan liposome were characterized by lower C_{max} , prolonged terminal half-life, and higher AUC.⁷ The ratios of total and encapsulated irinotecan did not change with time after administration; 95% of the irinotecan remained liposome encapsulated. Plasma protein binding of total irinotecan in irinotecan liposome is negligible (less than 0.44%).¹ Age, gender, and mild to moderate renal impairment had no effect on exposure to irinotecan or SN-38.¹ East Asian patients had a 56% lower total irinotecan average steady-state concentration and an 8% higher total SN-38 average steady-state concentration than white patients.¹

The metabolism of irinotecan liposome has not been evaluated. Compared with irinotecan hydrochloride, irinotecan liposome administration results in a longer half-life for both irinotecan (25.8 vs 11.7 hours) and the active metabolite (67.8 vs 21 hours).^{1,6} Irinotecan is extensively metabolized via esterases to form the active metabolite SN-38, via UGT1A1-mediated glucuronidation of SN-38 to form the inactive metabolite SN-38G, and via cytochrome P450 (CYP-450) 3A4-mediated oxidative metabolism to form several inactive oxidation products.¹

The excretion of irinotecan liposome has not been evaluated. Following administration of irinotecan hydrochloride, the urinary excretion of irinotecan is 11% to 20%, excretion of SN-38 is less than 1%, and excretion of SN-38G is 3%.¹

COMPARATIVE EFFICACY

Indication: Metastatic Pancreatic Cancer That Has Progressed Following Gemcitabine-Based Therapy

Guidelines

Guideline: Metastatic pancreatic cancer: American Society of Clinical Oncology clinical practice guideline

Reference: Sohal DP, et al, 2016²¹

Comments: The guideline recommends that leucovorin-fluorouracil-irinotecan-oxaliplatin (FOLFIRINOX) or gemcitabine plus albumin-bound paclitaxel be offered as first-line therapy to patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1. Gemcitabine monotherapy is recommended as first-line therapy for patients with ECOG performance status 2 or with a comorbidity profile that precludes therapy with other preferred regimens. Gemcitabine plus albumin-bound paclitaxel is recommended as second-line therapy in patients who received first-line treatment with FOLFIRINOX and who have ECOG performance status 0 to 1, a relatively favorable comorbidity profile, and patient preference and support system for aggressive therapy. Fluorouracil plus oxaliplatin, irinotecan, or irinotecan liposome is recommended as second-line therapy for patients who received first-line treatment with gemcitabine plus albumin-bound paclitaxel and who have ECOG performance status 0 to 1, a relatively favorable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services. Gemcitabine or fluorouracil should be offered as second-line therapy to patients with ECOG performance status 2 or a comorbidity profile that precludes other therapies. The guideline advises that second-line therapy should generally consist of a regimen the patient was not exposed to in the first-line regimen, but acknowledges there is insufficient data regarding second-line therapy for patients with disease progression with current first-line regimens (FOLFIRINOX or gem-

citabine plus albumin-bound paclitaxel). Second-line therapy selection should be guided by the patient's performance status, comorbidities, organ function, and residual toxicities from the first-line regimen, as well as patient preference and presence of a support system for aggressive medical therapy.

Studies

Drug: Irinotecan Liposome plus Fluorouracil-Leucovorin or Irinotecan Liposome Monotherapy vs Fluorouracil-Leucovorin

Reference: Wang-Gillam A, et al, 2016 (NAPOLI-1 study)^{1,22,23}

Study Design: Randomized, open-label, phase 3 multicenter study

Study Funding: Merrimack Pharmaceuticals

Patients: Patients with metastatic pancreatic adenocarcinoma with disease progression after gemcitabine or gemcitabine-based therapy. Patients had a Karnofsky performance status score of at least 70 (90 to 100 in 53% of patients), normal serum bilirubin, and albumin of at least 3 g/dL (mean, 3.97 g/dL). Median patient age was 63 years (range, 34-81 years); 58% were men; and 63% were white and 30% were Asian. Liver metastases were present in 67% of patients and lung metastases were present in 31%. Patients previously treated with irinotecan or fluorouracil were permitted.

Intervention: 417 patients were randomized (1:1:1) to irinotecan liposome plus fluorouracil-leucovorin ($n = 117$), irinotecan liposome monotherapy ($n = 151$), or fluorouracil-leucovorin ($n = 149$). Patients randomized to the 3-drug regimen received irinotecan liposome 70 mg/m² as an intravenous (IV) infusion over 90 minutes, followed by leucovorin 400 mg/m² IV over 30 minutes, then fluorouracil 2,400 mg/m² IV over 46 hours, every 2 weeks. Patients randomized to monotherapy received irinotecan liposome 100 mg/m² as an IV infusion over 90 minutes every 3 weeks. Patients randomized to the 2-drug regimen received leucovorin 200 mg/m² IV over 30 minutes followed by fluorouracil 2,000 mg/m² IV over 24 hours on days 1, 8, 15, and 22 of a 6-week cycle. Patients homozygous for the UGT1A1*28 allele received a reduced irinotecan liposome dose (50 mg/m² if given with fluorouracil-leucovorin or 70 mg/m² if given as a single agent). If the dose of irinotecan liposome was held or reduced, the dose of fluorouracil was also held or reduced.

Results

Primary Endpoint(s)

- Overall survival, assessed in the intention-to-treat (ITT) population, was greater in patients receiving the 3-drug regimen than in the 2-drug regimen arm (6.1 months vs 4.2 months; hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.49 to 0.92; $p = .012$). There was no difference in overall survival between the monotherapy and 2-drug regimen arms (4.9 months vs 4.2 months; HR, 0.99; 95% CI, 0.77 to 1.28; $p = .94$).

Secondary Endpoint(s)

- Progression-free survival was greater in patients receiving the 3-drug regimen than in the 2-drug regimen arm (3.1 months vs 1.5 months; HR, 0.56; 95% CI, 0.41 to 0.75; $p < .001$). There was no difference in progression-free survival between the monotherapy and 2-drug regimen arms (2.7 months vs 1.6 months; HR, 0.81; 95% CI, 0.63 to 1.04; $p = .1$).
- The median time to treatment failure was 2.3 months in patients receiving the 3-drug regimen compared with 1.4 months in the 2-drug regimen arm (HR, 0.6; 95% CI, 0.45 to 0.78; $p < .001$). There was no difference in time to treatment failure between the monotherapy and 2-drug regimen arms (1.7 months vs 1.4 months; HR, 0.82; 95% CI, 0.65 to 1.03; $p = .1$).
- The objective response rate (best overall response of complete or partial response as assessed by the investigator) was 16% with the 3-drug regimen compared to 1% with the 2-drug regimen (difference, 15.4%; 95% CI, 8.5% to 22.3%; $p < .001$), and was 6% with monotherapy compared with 1% with the 2-drug regimen (difference, 5.3%; 95% CI, 1.3% to 9.3%; $p = .02$). The confirmed objective response rate (confirmed complete or partial response) was 7.7% with the 3-drug regimen and 0.8% with the 2-drug regimen.
- Serum carbohydrate antigen 19-9 (CA19-9) response (at least a 50% reduction in amount of CA19-9 from baseline at least once during the treatment period) was achieved in 29% of patients treated with the 3-drug regimen compared with 9% treated with the 2-drug regimen ($p < .001$), and was achieved in 24% of patients treated with monotherapy compared with 11% with the 2-drug regimen ($p = .024$).
- Clinical benefit response (achievement of pronounced and sustained improvement in pain

intensity, analgesic consumption, or performance status without worsening of these factors, or stability of these factors with pronounced and sustained weight gain) was less than 20% and did not differ among treatment groups.

- Quality-of-life measures did not differ substantially from baseline in any treatment group.

Comments: Randomization was stratified by ethnicity (white vs East Asian vs other), KPS (70 to 80 vs 90 to 100), and baseline albumin (4 g/dL or greater vs 3 to 3.9 g/dL). Patients were enrolled in 14 countries, including the United States; approximately 17% were enrolled in North American study centers. Results were consistent across preplanned subgroup analyses.

Limitations: The irinotecan liposome plus fluorouracil-leucovorin arm was added in a protocol amendment after the start of the study. The initial study design assessing irinotecan liposome monotherapy was due to a phase 2 study in which monotherapy demonstrated moderate activity in patients with metastatic, gemcitabine-refractory pancreatic cancer.²⁴ The irinotecan liposome combination regimen is consistent with current guideline-recommended second-line therapies.²¹ Data are not available directly comparing this regimen with other recommended regimens (eg, fluorouracil plus oxaliplatin or irinotecan) after a first-line gemcitabine-based regimen.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

The contraindications, warnings, and precautions associated with irinotecan liposome injection and irinotecan hydrochloride are similar.^{1,6}

Contraindications

Irinotecan liposome injection is contraindicated in patients who have experienced a severe hypersensitivity reaction to the product or to irinotecan hydrochloride.¹

Warnings and Precautions

Irinotecan liposome injection has been associated with severe or life-threatening neutropenia and fatal neutropenic sepsis. Severe or life-threatening neutropenia occurred in 20% of patients receiving irinotecan liposome injection in combination with fluorouracil-leucovorin compared to 2% of patients receiving fluorouracil-leucovorin. Severe or life-threatening neutropenic fever or sepsis occurred in 3% of patients treated with irinotecan liposome

injection in combination with fluorouracil-leucovorin. Fatal neutropenic sepsis occurred in 0.8% of patients treated with irinotecan liposome injection. The incidence of grade 3 or 4 neutropenia was higher among Asian patients than white patients (55% vs 18%), as was the incidence of neutropenic fever or neutropenic sepsis (6% vs 1%). Patients homozygous for the UGT1A1*28 allele are at increased risk for irinotecan-induced neutropenia and should receive a reduced starting dose. Therapy should be withheld in patients with absolute neutrophil counts below 1,500/mm³ or if neutropenic fever occurs. Complete blood cell counts should be monitored on days 1 and 8 of every cycle and more frequently if clinically indicated.¹

Diarrhea, which can be severe or life-threatening, has been associated with irinotecan liposome injection. Severe diarrhea occurred in 13% of patients treated with irinotecan liposome injection in combination with fluorouracil-leucovorin. Irinotecan liposome injection should not be administered to patients with bowel obstruction and should be withheld for diarrhea of grade 2 to 4 severity. Late-onset diarrhea, occurring more than 24 hours after chemotherapy, should be treated with loperamide. Early-onset diarrhea, occurring within 24 hours of chemotherapy, should be treated with IV or subcutaneous atropine 0.25 to 1 mg.¹

Irinotecan can cause severe and fatal interstitial lung disease. Therapy should be withheld in patients with new or progressive dyspnea, cough, and fever pending diagnostic evaluation. Discontinue therapy upon confirmation of interstitial lung disease.¹

Severe hypersensitivity reactions, including anaphylactic reactions, have occurred with irinotecan hydrochloride therapy. Irinotecan liposome therapy should be discontinued if a severe hypersensitivity reaction occurs.¹

Irinotecan can cause fetal harm if administered to a pregnant woman. Embryotoxicity and teratogenicity have been observed in animal models. Females of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose. Males with female partners of reproductive potential should be advised to use condoms during treatment and for 4 months after the final dose.¹

It is not known if irinotecan liposome, irinotecan hydrochloride, or the active metabolite are excreted in human milk; however, because of the risk of serious adverse reactions in breastfeeding infants, women

should be advised not to breastfeed during treatment with irinotecan liposome and for 1 month after the final dose.¹

Safety and effectiveness of irinotecan liposome have not been established in pediatric patients.

ADVERSE REACTIONS

The most common adverse reactions observed during irinotecan liposome injection therapy (occurring at an incidence of at least 20%) included diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. Grade 3 or 4 lymphopenia and neutropenia occurred in more than 10% of patients. The most common serious adverse reactions (occurring in at least 2% of patients) were

diarrhea, vomiting, neutropenic fever or sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.¹

Table 1 compares the incidence of common adverse reactions and laboratory abnormalities observed with irinotecan liposome injection in combination with fluorouracil-leucovorin with that observed with fluorouracil-leucovorin alone.¹

Irinotecan liposome has also been associated with cholinergic reactions, manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis. Early-onset diarrhea tends to be related to a cholinergic reaction.¹

Table 1. Irinotecan liposome adverse reactions and laboratory abnormalities¹

Adverse reactions	Irinotecan liposome + Fluorouracil-leucovorin (<i>n</i> = 117)		Fluorouracil-leucovorin (<i>n</i> = 134)	
	Grades 1 to 4	Grades 3 to 4	Grades 1 to 4	Grades 3 to 4
Anemia	97%	6%	86%	5%
Lymphopenia	81%	27%	75%	17%
Diarrhea	59%	13%	26%	4%
Early-onset	30%	3%	15%	0%
Late-onset	43%	9%	17%	4%
Fatigue/Asthenia	56%	21%	43%	10%
Neutropenia	52%	20%	6%	2%
Vomiting	52%	11%	26%	3%
Nausea	51%	8%	34%	4%
Increased ALT	51%	6%	37%	1%
Decreased appetite	44%	4%	32%	2%
Hypoalbuminemia	43%	2%	30%	0%
Thrombocytopenia	41%	2%	33%	0%
Hypomagnesemia	35%	0%	21%	0%
Stomatitis	32%	4%	12%	1%
Hypokalemia	32%	2%	19%	2%
Hypocalcemia	32%	1%	20%	0%
Hypophosphatemia	29%	4%	18%	1%
Hyponatremia	27%	5%	12%	3%
Pyrexia	23%	2%	11%	1%
Increased creatinine	18%	0%	13%	0%
Weight loss	17%	2%	7%	0%
Alopecia	14%	1%	5%	0%

Note: ALT = alanine aminotransferase.

Infusion reactions including rash, urticaria, periorbital edema, or pruritus were reported in 3% of patients receiving irinotecan liposome monotherapy or irinotecan liposome in combination with fluorouracil-leucovorin.¹

Adverse reactions most commonly leading to permanent discontinuation of therapy (11% of patients) included diarrhea, vomiting, and sepsis. Adverse reactions most commonly leading to dose reductions (33% of patients) included neutropenia, diarrhea, nausea, and anemia.¹

DRUG INTERACTIONS

Exposure to irinotecan and its metabolite is reduced with coadministration of CYP3A4 inducers and irinotecan hydrochloride. Concomitant use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John's wort) should be avoided with irinotecan liposome if possible. Non-enzyme-inducing alternatives should be substituted at least 2 weeks prior to initiation of irinotecan liposome therapy.¹ This group of drug interactions is associated with both the irinotecan hydrochloride and irinotecan liposome formulations.^{1,6}

Increased exposure to irinotecan and SN-38 has been observed following administration of irinotecan hydrochloride with ketoconazole, a CYP3A4 inhibitor, and a UGT1A1 inhibitor. Coadministration of irinotecan liposome with CYP3A4 or UGT1A1 inhibitors may increase systemic exposure to irinotecan or SN-38. The concomitant use of strong CYP3A4 or UGT1A1 inhibitors should be avoided if possible. The use of strong CYP3A4 inhibitors should be discontinued at least 1 week prior to initiation of therapy with irinotecan liposome.¹

RECOMMENDED MONITORING

Monitor complete blood cell counts on days 1 and 8 of every cycle and more frequently if clinically indicated.¹ Patients should be closely monitored for adverse effects; treatment for diarrhea should be promptly initiated.

DOSING

The recommended dose of irinotecan liposome injection is 70 mg/m² administered by IV infusion over 90 minutes every 2 weeks; a reduced starting dose of 50 mg/m² is recommended for patients homozygous for the UGT1A1*28 allele. A corticosteroid and antiemetic should be administered 30 minutes

prior to the irinotecan liposome dose. Irinotecan liposome should be administered prior to leucovorin and fluorouracil.¹

Dose modifications are recommended for patients with grade 3 or 4 adverse reactions; discontinuation of therapy is recommended after the third occurrence of a grade 3 or 4 adverse reaction or if patient develops interstitial lung disease or an anaphylactic reaction.¹

The recommended dose should be diluted in 500 mL of dextrose 5% injection or sodium chloride 0.9% injection prior to administration. The dose is infused over 90 minutes without use of in-line filters. The diluted solution should be protected from light and administered within 4 hours of preparation if stored at room temperature or within 24 hours if refrigerated.¹

PRODUCT AVAILABILITY

Irinotecan liposome injection received US Food and Drug Administration approval on October 22, 2015.²⁵ It is available in a single-dose 10 mL vial containing 43 mg of irinotecan free base as a liposomal dispersion.¹ The liposomal vesicles are composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE); also present are excipients 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer and sodium chloride as an isotonicity reagent.¹

Irinotecan liposome injection should be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from freezing and light.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for irinotecan liposome injection.²⁵ Special handling and disposal procedures for cytotoxic drugs should be observed.¹

CONCLUSION

Irinotecan liposome injection is indicated for use in conjunction with fluorouracil and leucovorin as second-line therapy of metastatic pancreatic cancer that has progressed following gemcitabine-based therapy. The liposomal formulation improves intratumor delivery of the active metabolite, resulting in prolonged exposure, which may enhance antitumor activity. Head-to-head studies comparing the 2 irinotecan formulations have not been conducted. As with irinotecan hydrochloride therapy, patients should be closely monitored for hematologic adverse effects and severe diarrhea.

REFERENCES

1. *Onivyde* (irinotecan liposome injection) [prescribing information]. Cambridge, MA: Merrimack Pharmaceuticals Inc.; October 2015.
2. Merrimack Pharmaceuticals. Study of nanoliposomal irinotecan (Nal-IRI)-containing regimens in patients with previously untreated, metastatic pancreatic adenocarcinoma. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT02551991>. Updated July 28, 2016. Accessed September 14, 2016. NLM Identifier: NCT02551991.
3. MM-398. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/results?term=MM-398&Search=Search>. Accessed September 14, 2016.
4. Chibaudel B, Maindrault-Göbel F, Bachet JB, et al. PEPOL: A GERCOR randomized phase II study of nanoliposomal irinotecan PEP02 (MM-398) or irinotecan with leucovorin/5-fluorouracil as second-line therapy in metastatic colorectal cancer. *Cancer Med*. 2016;5(4):676-683.
5. Roy AC, Park SR, Cunningham D, et al. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. *Ann Oncol*. 2013;24(6):1567-1573.
6. *Camptosar* (irinotecan hydrochloride injection) [prescribing information]. New York: Pharmacia & Upjohn Co.; April 2016.
7. Chang TC, Shiah HS, Yang CH, et al. Phase I study of nanoliposomal irinotecan (PEP02) in advanced solid tumor patients. *Cancer Chemother Pharmacol*. 2015;75(3):579-586.
8. Kalra AV, Kim J, Klinz SG, et al. Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor prodrug conversion. *Cancer Res*. 2014;74(23):7003-7013.
9. Chen PY, Ozawa T, Drummond DC, et al. Comparing routes of delivery for nanoliposomal irinotecan shows superior anti-tumor activity of local administration in treating intracranial glioblastoma xenografts. *Neuro Oncol*. 2013;15(2):189-197.
10. Kang MH, Wang J, Makena MR, et al. Activity of MM-398, nanoliposomal irinotecan (nal-IRI), in Ewing's family tumor xenografts is associated with high exposure of tumor to drug and high SLFN11 expression. *Clin Cancer Res*. 2015;21(5):1139-1150.
11. Baker JH, Lam J, Kyle AH, et al. Irinophore C, a novel nanoformulation of irinotecan, alters tumor vascular function and enhances the distribution of 5-fluorouracil and doxorubicin. *Clin Cancer Res*. 2008;14(22):7260-7271.
12. Hare JJ, Neijzen RW, Anantha M, et al. Treatment of colorectal cancer using a combination of liposomal irinotecan (Irinophore C™) and 5-fluorouracil. *PLoS One*. 2013;8(4):e62349.
13. Infante JR, Keedy VL, Jones SF, et al. Phase I and pharmacokinetic study of IHL-305 (PEGylated liposomal irinotecan) in patients with advanced solid tumors. *Cancer Chemother Pharmacol*. 2012;70(5):699-705.
14. Konishi H, Takagi A, Kurita A, Kaneda N, Matsuzaki T. PEGylated liposome IHL-305 markedly improved the survival of ovarian cancer peritoneal metastasis in mouse. *BMC Cancer*. 2012;12:462.
15. Liu X, Situ A, Kang Y, et al. Irinotecan delivery by lipid-coated mesoporous silica nanoparticles shows improved efficacy and safety over liposomes for pancreatic cancer. *ACS Nano*. 2016;10(2):2702-2715.
16. Neijzen R, Wong MQ, Gill N, et al. Irinophore C™, a lipid nanoparticulate formulation of irinotecan, improves vascular function, increases the delivery of sequentially administered 5-FU in HT-29 tumors, and controls tumor growth in patient derived xenografts of colon cancer. *J Control Release*. 2015;199:72-83.
17. Ramsay EC, Anantha M, Zastre J, et al. Irinophore C: A liposome formulation of irinotecan with substantially improved therapeutic efficacy against a panel of human xenograft tumors. *Clin Cancer Res*. 2008;14(4):1208-1217.
18. Verreault M, Strutt D, Masin D, et al. Irinophore C, a lipid-based nanoparticulate formulation of irinotecan, is more effective than free irinotecan when used to treat an orthotopic glioblastoma model. *J Control Release*. 2012;158:34-43.
19. Waterhouse DN, Sutherland BW, Santos ND, et al. Irinophore C, a lipid nanoparticle formulation of irinotecan, abrogates the gastrointestinal effects of irinotecan in a rat model of clinical toxicities. *Invest New Drugs*. 2014;32(6):1071-1082.
20. Wu H, Infante JR, Keedy VL, et al. Factors affecting the pharmacokinetics and pharmacodynamics of PEGylated liposomal irinotecan (IHL-305) in patients with advanced solid tumors. *Int J Nanomedicine*. 2015;10:1201-1209.
21. Sohal DP, Mangu PB, Khorana AA, et al. Metastatic pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34(23):2784-2796.
22. Merrimack Pharmaceuticals. Study of MM-398 with or without 5-FU/LV, versus 5-FU/LV in patients with metastatic pancreatic cancer (NAPOLI-1). ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT01494506>. Updated June 16, 2016. Accessed September 13, 2016. NLM Identifier: NCT01494506.
23. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): A global, randomised, open-label, phase 3 trial. *Lancet*. 2016;387(10018):545-557.
24. Ko AH, Tempero MA, Shan YS, et al. A multinational phase 2 study of nanoliposomal irinotecan sucrosfate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. *Br J Cancer*. 2013;109(4):920-925.
25. Keegan P. NDA approval letter: Irinotecan liposome injection (NDA 207793). US Food and Drug Administration website. October 22, 2015. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207793Orig1s000ltr.pdf. Accessed September 14, 2016. ■