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The State of the Management of Metastatic Pancreatic Cancer—A Focus on Recent Real-World Clinical & Economic Evidence With Liposomal Irinotecan

KEY TAKEAWAYS:

- Pancreatic cancer is an aggressive disease with a low survival rate that frequently presents in advanced stages and is associated with significant economic burden.[1-5]
- Among American Society of Clinical Oncology (ASCO) Clinical Practice Guideline recommended, FDA-approved, National Comprehensive Cancer Network® (NCCN®) category 1 therapies for the treatment of metastatic pancreatic cancer, the most commonly prescribed are first-line gemcitabine + nab-paclitaxel, first-line FOLFIRINOX (fluorouracil [5-FU] + leucovorin + oxaliplatin + irinotecan), and second-line liposomal irinotecan (in combination with 5-FU and leucovorin) which was approved in 2015.[6-10]
- Real-world data on the use of second-line liposomal irinotecan determined it to be similar in total cost of care to first-line therapies, and through budget impact modeling, to be cost neutral when factoring in medical cost–offsets of fewer adverse events (AEs) and lower administration costs compared with alternatives.[10-15]

INTRODUCTION

Pancreatic cancer is an aggressive disease that commonly presents in advanced stages.[1] From 1997 to 2017, the incidence of pancreatic cancer in the United States increased; however, mortality rates remained relatively unchanged.[2] Survival estimates for patients diagnosed with pancreatic cancer are very low; most patients die of the disease by the end of the first

INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

BOXED WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

- **Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment**
- **Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity**

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year after diagnosis. Based on Surveillance, Epidemiology, and End Results Program data from 2016, only 37.0% of patients were expected to survive the first year after diagnosis, and the 5-year survival estimate is 10.0%.[2]

Recent (2020) data indicate pancreatic cancer is only the eleventh leading cause of new cancers annually in the United States, accounting for 3.2% of all new cancer cases; however, it is the third leading cause of cancer deaths annually. The mortality rate is 11 deaths per 100,000 men and women patients (based on age-adjusted deaths from 2013 through 2017). The median age at diagnosis of pancreatic cancer is 70 years.[2]

In 2020, approximately 57,600 individuals in the United States are expected to be diagnosed with pancreatic cancer, and about 47,050 individuals are expected to die from it.[2] By 2030, pancreatic cancer is expected to become the second leading cause of cancer-related deaths in the United States.[16] This anticipated increase in mortality is likely due to factors such as few tests for screening, poor efficacy of currently available chemotherapeutic agents, and frequent diagnosis of pancreatic cancer at late stages.[1]

RISK FACTORS

Risk factors include a family history of pancreatic cancer, chronic pancreatitis, smoking and the use of smokeless tobacco, type 2 diabetes, obesity, heavy alcohol consumption, and certain genetic mutations (eg, those associated with *BRCA1*, *BRCA2*, and *ATM* mutations, which have been found in approximately 5.5% of patients with pancreatic cancer [95% CI, 4.7%-6.4%]).[1,17]

SYMPTOMS AND BIOMARKERS

Symptoms or signs often fail to be diagnosed at the early stages of pancreatic cancer. As the disease progresses, the presenting symptoms are generally nonspecific and include weight loss, loss of appetite, jaundice, light-colored stools or dark urine, upper or middle abdominal or back pain, and fatigue.[1,6] Routine screening is not recommended for asymptomatic individuals.[6]

NCCN has stated the biomarker CA-19, a blood group antigen, may be a useful biomarker for the early detection of pancreatic cancer. However, because the antigen is expressed and shed by various types of malignant tumors, it is not specific to pancreatic cancer.[6]

CLINICAL FEATURES

Pancreatic ductal adenocarcinomas account for approximately 90% of all pancreatic malignancies.[6] Pancreatic cancer residing solely at the primary site (ie, localized disease) at diagnosis is associated with the highest 5-year survival estimate (39.4%), whereas disease that has already spread to regional lymph nodes (ie, regional disease) or metastasized (ie, distant disease) is associated with much lower estimates (13.3% and 2.9%, respectively).[2] At diagnosis, most tumors are distant (52%) or regional (30%); few tumors are localized (11%) or unstaged (7%).[2]

For patients with metastatic pancreatic cancer, the recommended treatment selection is based on performance status.[6] Surgery is a potentially curative treatment for pancreatic ductal adenocarcinoma; however, less than 20% of patients present with potentially operable disease.[1]

TREATMENT LANDSCAPE AND NCCN RECOMMENDATIONS

Two general principles should be considered when selecting treatment for a patient with pancreatic cancer. First, the efficacy and toxicity of the therapy, the patient's preferences, and tumor characteristics should be considered when choosing an appropriate therapy.[18] Second, NCCN recommends specific regimens by line of therapy and performance status as well as the consideration of investigational options for all phases of management of pancreatic cancer because of the relatively high likelihood of a poor outcome.[6]

Chemotherapy

According to NCCN, systemic therapy should be used for all stages of pancreatic cancer, even when surgical resection is possible. The goals of systemic therapy should be discussed with the patient before therapy begins, and close follow-up during systemic therapy is required. Patient participation in a clinical study is highly recommended.[6]

Of the NCCN recommended regimens for metastatic pancreatic adenocarcinoma in patients with good performance status, the category 1 recommended regimens include FOLFIRINOX, gemcitabine monotherapy, the combination of gemcitabine + nanoparticle albumin-bound paclitaxel (nab-paclitaxel) or the combination of gemcitabine and erlotinib (**Table 1**). FOLFIRINOX or modified FOLFIRINOX should

IMPORTANT SAFETY INFORMATION (*continued*)

Contraindication

- ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl

be reserved for patients who have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, whereas gemcitabine + nab-paclitaxel may be a reasonable option for patients whose ECOG performance status is 0 to 2.[6]

The first-line treatment recommendations for metastatic pancreatic adenocarcinoma are supported by results from the MPACT and PRODIGE trials.[6] MPACT was a phase 3 open-label, international, randomized study that investigated the efficacy and safety of gemcitabine + nab-paclitaxel in the treatment of metastatic pancreatic cancer.[19] The combination of gemcitabine + nab-paclitaxel resulted in a median overall survival (OS) of 8.5 months, whereas the median OS for the group given gemcitabine was 6.7 months (hazard ratio [HR] for death, 0.72; 95% CI, 0.62-0.83; P <.001). In MPACT (NCT00844649), the most frequently reported AEs of at least grade 3 were neutropenia (38% in the gemcitabine + nab-paclitaxel group), fatigue (17% in the gemcitabine + nab-paclitaxel group), and neuropathy (17% in the gemcitabine + nab-paclitaxel group).[19]

The phase 2/3 PRODIGE trial (NCT00112658) compared FOLFIRINOX with gemcitabine monotherapy as first-line therapy for metastatic pancreatic cancer. Compared with gemcitabine monotherapy, FOLFIRINOX resulted in longer OS (median, 11.1 vs 6.8 months; HR for death, 0.57; 95% CI, 0.45-0.73; P <.001) and longer progression free survival (PFS) (median, 6.4 vs 3.3 months; HR for progression, 0.47; 95% CI, 0.37-0.59; P <.001]; however, AEs such as, the incidence of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy, were significantly greater in the FOLFIRINOX group [$P \leq .04$ for all]).[20]

Recommendations for second-line therapy for patients who have good performance status and received prior gemcitabine-based therapy include the following[6]: FOLFIRINOX or modified FOLFIRINOX, liposomal irinotecan + 5-FU + leucovorin, 5-FU + leucovorin + irinotecan (FOLFIRI), leucovorin + 5-FU + oxaliplatin (FOLFOX), oxaliplatin + 5-FU + leucovorin (OFF), capecitabine + oxaliplatin (CapeOx), capecitabine monotherapy, and continuous infusion of 5-FU.

Although a variety of regimens are available as second-line therapy for pancreatic adenocarcinoma, liposomal irinotecan + 5-FU + leucovorin is the only regimen with an NCCN category 1 recommendation in patients with metastatic cancer who previously received gemcitabine-based therapy (Table 1).[6] ASCO guideline recommended liposomal irinotecan + 5-FU + leucovorin as preferred second-line therapy in patients who desire this treatment and who meet all of the following criteria: first-line treatment with gemcitabine + nab-paclitaxel, an ECOG performance status of 0 to 1, a favorable comorbidity profile, access to management services for a chemotherapy port and infusion pump, and a network to support them while they are going through therapy with the potential for serious AEs.[7]

Table 1. FDA-Approved/NCCN Category 1 Recommended Treatment Options for Good PS First-Line and Second-Line Chemotherapy for Metastatic Pancreatic Cancer[6,a,b]

First-Line Chemotherapy
FOLFIRINOX
Gemcitabine monotherapy
Gemcitabine + nab-paclitaxel
Gemcitabine + erlotinib[c]
Second-Line Chemotherapy
5-FU + leucovorin + liposomal irinotecan[d]

5-FU, fluorouracil; FOLFIRINOX, 5-FU + leucovorin + oxaliplatin + irinotecan; nab, nanoparticle albumin-bound; NCCN, National Comprehensive Cancer Network; PS, performance status.

[a]Recommendations for patients with *BRCA1/2* or *PALB2* mutations not included.

[b]Please note this table is not comprehensive or detailed and additional treatment recommendations can be found within the NCCN Guidelines®.

[c]Only a small subset of patients may benefit.

[d]After first-line gemcitabine-based therapy.

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Liposomal Irinotecan

Irinotecan liposome injection (ONIVYDE, Ipsen Biopharmaceuticals, Inc) was approved in 2015, in combination with 5-FU and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.[21,22] ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.[21] The prescribing information for ONIVYDE includes a boxed warning on the risk of severe neutropenia and severe diarrhea.[23]

Liposomal irinotecan is a topoisomerase-1 inhibitor encapsulated in a lipid bilayer vesicle or liposome (**Figure 1**).[23-26] Topoisomerase-1 relieves torsional strain in DNA by inducing single-strand breaks.

IMPORTANT SAFETY INFORMATION (*continued*)

Warnings and Precautions

- **Severe Neutropenia: See Boxed WARNING.** In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients

Figure 1. Liposome Encapsulation of Irinotecan[23-26]

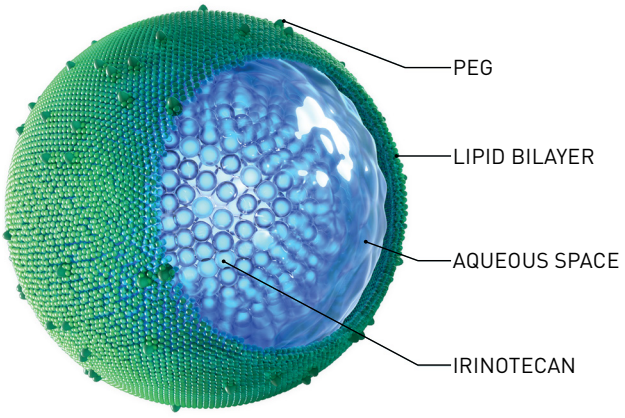

Image courtesy of Ipsen Biopharmaceuticals, Inc. 2019.

Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase-1-DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. In mice bearing human tumor xenografts, irinotecan liposome administered at irinotecan HCl–equivalent doses lower than irinotecan HCl achieved similar intratumoral exposure of SN-38.[23]

The approval of liposomal irinotecan was based on findings from the phase 3, randomized, open-label, multicenter, international NAPOLI-1 trial.[8,21,23,27] A total of 417 patients with metastatic pancreatic ductal adenocarcinoma who had been previously treated with gemcitabine-based therapy were randomly assigned to liposomal irinotecan monotherapy (n = 151), 5-FU + leucovorin (n = 149), or liposomal irinotecan + 5-FU + leucovorin (n = 117).[8] OS, the primary endpoint (cutoff date, February 14, 2014), was longer for patients treated with liposomal irinotecan + 5-FU + leucovorin than for patients treated with 5-FU + leucovorin (median, 6.1 vs 4.2 months; HR, 0.67; 95% CI, 0.49-0.92; *P* = .012). The OS estimates did not differ much between patients given liposomal irinotecan monotherapy and those given 5-FU + leucovorin (median, 4.9 vs 4.2 months; HR, 0.99; 95% CI, 0.77-1.28; *P* = .94). The median PFS was 3.1 months versus 1.5 months for patients treated with liposomal irinotecan + 5-FU + leucovorin and for patients treated with 5-FU + leucovorin, respectively (HR, 0.56; 95% CI, 0.41-0.75; *P* = .0001). No significant difference was seen in PFS for patients treated with liposomal irinotecan monotherapy and those treated with 5-FU + leucovorin (median, 2.7 vs 1.6 months; HR, 0.81; 95% CI, 0.63-1.04; *P* = .1).[8]

Of the treatment-emergent AEs of any grade, the most common for the 398 patients who received some kind of liposomal irinotecan therapy were diarrhea (59%-70% of patients), nausea (51%-61% of patients), and vomiting (52%-54% of patients). Alopecia was reported for 16 of 117 patients (14%) treated with liposomal irinotecan + 5-FU + leucovorin, 32 of 147 patients (22%) treated with liposomal irinotecan monotherapy, and 6 of 134 patients (5%) treated with 5-FU + leucovorin. The most frequent grade 3 or 4 AEs for the 117 patients treated with liposomal irinotecan + 5-FU + leucovorin were neutropenia (32 patients [27%]), diarrhea (15 patients [13%]), vomiting (13 patients [11%]), and fatigue (16 patients [14%]).[8]

Analysis of longer follow-up data from NAPOLI-I (updated cutoff date, November 16, 2015) demonstrated the advantage in OS associated with liposomal irinotecan + 5-FU + leucovorin vs 5-FU + leucovorin continued over time for patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy (OS, 6.2 vs 4.2 months; unstratified HR, 0.75; 95% CI, 0.57-0.99; *P* = .039; stratified HR, 0.63; 95% CI, 0.47-0.85; *P* = .002).[9] Patients given liposomal irinotecan + 5-FU + leucovorin also had longer median PFS than those given 5-FU + leucovorin (3.1 vs 1.5 months, respectively; HR, 0.57; 95% CI, 0.43-0.76; *P* <.0001).[9] The safety profile of liposomal irinotecan + 5-FU + leucovorin seen during long-term follow-up was similar to that seen during the primary analysis.[9] Neutropenia, diarrhea, vomiting, and fatigue were the most frequent AEs grade 3 and higher reported during long-term follow-up for patients treated with liposomal irinotecan + 5-FU + leucovorin.[9] Neuropathy, which has been seen with the use of the first-line combination of gemcitabine + nab-paclitaxel,[19] was not seen with the use of liposomal irinotecan in NAPOLI-1.[8,9]

It should be noted that randomized controlled trials (RCTs) are used to establish causality among a small homogenous sample of patients. Although this lends itself to an unbiased distribution of confounders, results are not generalizable to a broad population of

IMPORTANT SAFETY INFORMATION (*continued*)

Warnings and Precautions (*continued*)

- **Severe Diarrhea: See Boxed WARNING.** Severe and life-threatening late-onset (onset >24 hours after chemotherapy [9%]) and early-onset diarrhea (onset ≤24 hours after chemotherapy [3%], sometimes with other symptoms of cholinergic reaction) were observed
- **Interstitial Lung Disease (ILD):** Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD

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patients. In the NAPOLI-1 follow-up, long-term survivor analyses were limited by the small sample size, and as such, it was not possible to statistically analyze prognostic factors between long-term survivors and all treated patients.[9]

Given the low survival estimates for patients with metastatic pancreatic cancer,[2] patients' health-related quality of life (HRQOL) was measured as a secondary endpoint in NAPOLI-1. Hubner and colleagues captured patient responses using the European Organisation for Research and Treatment of Cancer quality of life core questionnaire C30 (EORTC QLQ-C30) within 7 days of starting treatment (baseline), and then every 6 weeks, ending 30 days after the completion of treatment. Among the 128 patients in the patient-reported outcomes (PRO) population for whom HRQOL was assessed up to week 12, a total of 71 patients received liposomal irinotecan + 5-FU + leucovorin and 57 patients received 5-FU + leucovorin.[28]

Baseline global health status and functional scale scores across both arms ranged from 58 to 83 while baseline symptom scale scores ranged from 0 to 33. The observed median change from baseline to week 6 in the physical functioning score was 6.7 points in both arms. The proportion of patients whose HRQOL improved or deteriorated was not significantly different between the arms (**Figure 2**).[8,28]

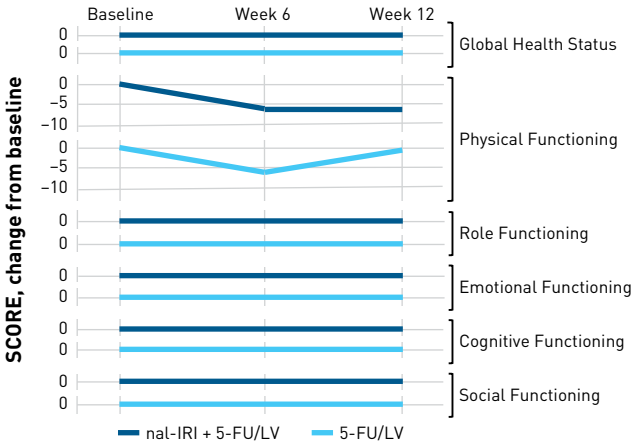
The observed median change from baseline was 10 points at weeks 6 and 12 in global health status or functional and symptom scale scores, except for fatigue, which deteriorated by 11.1 points with liposomal irinotecan + 5-FU + leucovorin but did not change versus 5-FU + leucovorin (**Figure 3**).[8,28]

In this study, HRQOL was maintained with liposomal irinotecan + 5-FU + leucovorin in patients with metastatic pancreatic adenocarcinoma previously treated with a gemcitabine-based regimen, while survival was significantly extended.[28]

Differentiating Liposomal Irinotecan from Nonliposomal Irinotecan: Mechanism of Delivery and Safety

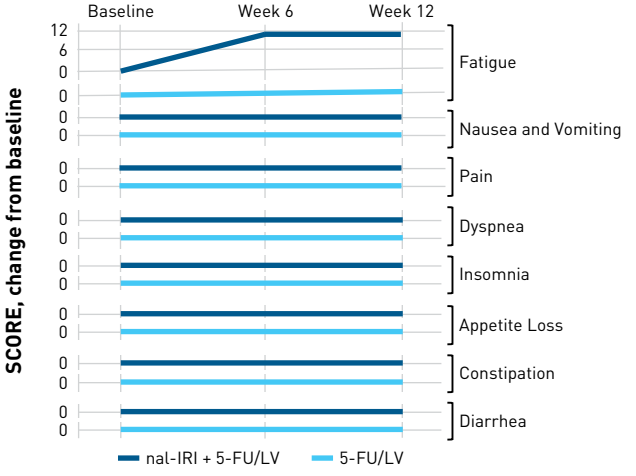
Nonliposomal irinotecan is an antitumor compound with highly variable efficacy (ie, due in part to suboptimal pharmacokinetics) and toxicity, in part because of variation in the pharmacogenetics related to the clearance of its active metabolite, SN-38.[29] For these reasons, nonliposomal irinotecan has generally had limited use in pancreatic cancer. Interest in the use of irinotecan-containing regimens in pancreatic cancer resurfaced when results of the PRODIGE

Figure 2. NAPOLI-1 Global Health Status and Functional Scale Scores: Medical Change Over Time.[8,28]



5-FU, fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.

Figure 3. NAPOLI-1 Symptom Scale Scores: Medical Change Over Time.[8,28]



5-FU, fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.

IMPORTANT SAFETY INFORMATION (*continued*)

Warnings and Precautions (*continued*)

- **Severe Hypersensitivity Reactions:** Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction
- **Embryo-Fetal Toxicity:** ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment

Table 2. Animal Model Differences Between Liposomal and Nonliposomal Irinotecan[31,a]

	Conventional Irinotecan	Nal-IRI
Nonpharmacokinetic		
Tumor growth inhibition	~40%	~110%
Pharmacokinetic		
Exposure in plasma	Irinotecan and SN-38 plasma levels cleared from circulation within 8 hours	Irinotecan and SN-38 remained in circulation for more than 50 hours
Exposure in tumors	More than 90% of irinotecan was cleared from tumors within 24 hours SN-38 exposure in tumors was less than 48 hours	Irinotecan levels persisted above 10,000 nmol/L for 168 hours in tumors SN-38 exposure above activity threshold for up to 168 hours
Dose needed to achieve similar in SN-38 exposure in plasma and tumors	50 mg/kg	10 mg/kg

nal-IRI, liposomal irinotecan.

[a]This table does not represent a clinical comparison of conventional irinotecan versus nal-IRI.

study demonstrated how FOLFIRINOX, which includes nonliposomal irinotecan, led to longer OS and PFS than did gemcitabine monotherapy as first-line therapy.[20]

Liposomal irinotecan was developed with the aim of improving the distribution of the drug while avoiding premature metabolism of it; thereby, intentionally maximizing efficacy while minimizing toxicity.[30] Liposomal encapsulation of irinotecan stabilizes the prodrug, increases its time in systemic circulation, and improves its biodistribution.[24] Greater permeability of tumor blood vessels and altered lymph drainage are thought to enhance the preferential accumulation of liposomal irinotecan in tumors.[29] The presence of polyethylene glycol on the liposome surface blocks circulating plasma proteins from binding to the liposome; subsequently, the premature elimination of liposomal irinotecan from circulation is reduced.[29] In a preclinical in vivo study, liposomal irinotecan remained in plasma circulation for more than 50 hours, whereas nonliposomal irinotecan was cleared within 8 hours of administration.[26,31] Similar doses resulted in longer tumor exposure with the use of liposomal irinotecan than with nonliposomal irinotecan (168 vs <48 hours) (**Table 2**).[31]

While pre-clinical differences in formulations have been observed as stated above, numerical differences in laboratory abnormalities have been observed in a real-world clinical setting. The next section of this article will explore real-world evidence of how the medical cost–offsets of these reduced AEs, when taken into account with lower administration costs, demonstrate second-line liposomal irinotecan is similar to first-line therapies in terms of total costs, and through budget impact modeling, is cost neutral.

EXPLORING REAL-WORLD CLINICAL & ECONOMIC CONSIDERATIONS ASSOCIATED WITH USE OF LIPOSOMAL IRINOTECAN

Whereas RCTs are used to establish causality among a small homogenous sample of patients, observational studies utilize real-world data, such as electronic health records (EHRs), and medical and administrative claims databases that represent the heterogeneity of usual care. As such, they generate real-world evidence of an association between a given treatment and an event, yielding insights that may not have been addressed in RCTs and describe what actually occurs outside of a controlled setting.[32-36]

Real-world evidence can be generalizable to a broader population and have economic implications. It is used by US payers in population health management and decision making for comparative effectiveness analyses, further safety considerations not gleaned from RCTs, and more.[37] Herein, we discuss real-world clinical and economic evidence associated with the use of liposomal irinotecan, as well as the resulting medical cost offsets and budget impact.

IMPORTANT SAFETY INFORMATION (*continued*)

Adverse Reactions

- The most common adverse reactions (≥20%) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%)
- The most common Grade 3/4 adverse reactions (≥10%) were diarrhea (13%), fatigue/asthenia (21%), and vomiting (11%)

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Real-World Clinical Evidence Associated with Use of Liposomal Irinotecan

The outcomes of the first large-scale US retrospective observational study on the effectiveness of liposomal irinotecan + 5-FU + leucovorin in the real-world setting were similar to those seen in the controlled NAPOLI-1 trial, even though patients were older, sicker, and had more lines of therapy.[38]

Using longitudinal, deidentified EHR data from more than 265 community-based cancer treatment clinics and academic hospitals in the Flatiron Health database, Barzi and colleagues identified patients aged 18 years or older with stage IV or progressive metastatic pancreatic cancer on or before January 1, 2014.[38] To be included in the analysis, patients also were required to have at least 2 documented clinic visits on or after this date, and had received treatment with liposomal irinotecan at least 90 days before the data cutoff date of August 31, 2017. As in the NAPOLI-1 trial, most patients (n = 242) in the Flatiron study received prior treatment with gemcitabine therapy.[8,38]

Of the 257 total patients included in the Flatiron study, the median age was 68 years, and most patients (58.5%) had an ECOG score of 0 or 1. When started on treatment with liposomal irinotecan, the majority of patients (n = 230) received liposomal irinotecan + 5-FU + leucovorin. The mean dose intensity was 177.8 mg/m^2 and the median duration of exposure for all patients was 7.3 weeks. Patients treated with liposomal irinotecan + 5-FU + leucovorin in NAPOLI-1 (n = 117) were a median age of 63 years. The mean dose intensity in NAPOLI-1 was 167.5 mg/m^2, and the median duration of exposure was 8.7 weeks.[8,38]

Although no formal statistical comparison was made, the data suggest that compared with patients in NAPOLI-1, a higher proportion of patients in the Flatiron study had an ECOG score of at least 2 and had experienced at least 2 prior lines of therapy (**Table 3**).[8,38]

Taken in context, results of median OS in patients who received liposomal irinotecan + 5-FU + leucovorin in the first- or second-line were comparable to NAPOLI-1: 5.6 months (95% CI, 4.8-7.3 months) versus 6.1 months (95% CI, 4.8-8.9 months), respectively.[9,38]

The most common AE (all grades) during the treatment period was diarrhea in both the Flatiron study and NAPOLI-1; 46.3% and 59% of patients, respectively. A total of 18.7% of patients in the Flatiron study and 39% in NAPOLI-1 experienced neutropenia. As seen in NAPOLI-1, most patients (57%) in the Flatiron study discontinued treatment due to progression (or progressive disease), followed by disease-related symptoms not due to therapy, or clinical deterioration (17%) (**Table 4**).[8,38]

Table 3. ECOG Score, Number of Prior Lines of Therapy, Mean DI, and Median DOE in the Metastatic Setting for Flatiron Health and NAPOLI-1[8,38,a]

	FLATIRON	NAPOLI-1
Total cohort	257	117
Age at initiation: median (IQR)	68 (61 – 74)	63 (57 – 70)
ECOG Score[b]		
0	16.0%	15.38%
1	42.8%	76.07%
≥2	**14.8%**	8.55%
Missing	26.5%	-
Number of prior lines of therapy in the metastatic setting[c]		
0-1	56.4%	66%
≥2	**43.6%**	34%
Key dosing results		
Mean DI over 6 weeks (mg/m^2)	177.8[d]	167.5
Median DOE, weeks (IQR)	7.3 (3.4-17.1)	8.7 (5.4-22.0)
Median dose at initiation, mg/m^2 (range)	69.4 (65 to <75)	70.0 (70.0 – 70.0)

DI, dose intensity; DOE, duration of exposure; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

[a]Descriptive only; no statistical testing performed.

[b]ECOG Score converted from Karnofsky Performance Status for NAPOLI-1 study. A total of 5% of patients may not have had sufficient prior records.

[c]Patients received neoadjuvant, adjuvant, or locally advanced treatment, but no previous therapy for metastatic disease; 94.2% had documented prior gemcitabine therapy.

[d]DI over 6 weeks is the cumulative dose administered (in mg/m^2) in the first 6 weeks (42 days) after initiating liposomal irinotecan. The mean DI was similar between patients who initiated liposomal irinotecan as first- or second-line therapy (176.4 mg/m^2) versus later lines (179.6 mg/m^2).

The results of a study by Kim and colleagues also demonstrated patients treated with liposomal irinotecan in an earlier treatment sequence had improved outcomes, specifically OS. For the study, presented at the 2019 annual international conference for ISPOR—The Professional Society for Health Economics and Outcomes Research, investigators compared clinical characteristics and OS of 2 sets of patients: (1) those in sequence 1 who had received liposomal irinotecan as third-line therapy (or beyond) after treatment

IMPORTANT SAFETY INFORMATION (*continued*)

Adverse Reactions (*continued*)

- Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; The most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis

Table 4. Comparison of Select Adverse Events, Disease-Related Symptoms Not Due to Therapy, Progression, and Toxic Effect of Therapy for Flatiron Health and NAPOLI-1[8,38]

	FLATIRON N = 257	NAPOLI-1 N = 117
Select adverse events during treatment with liposomal irinotecan (all grades)		
Neutropenia	48 (18.7%)	46 (39%)
Diarrhea	119 (46.3%)	69 (59%)
Reasons for discontinuation[a]		
Disease-related symptoms not due to therapy / clinical deterioration	32 (17%)	13 (13%)
Progression / progressive disease	106 (57%)	57 (55%)
Toxic effect of therapy	26 (14%)	11 (11%)

[a]Among the 186 patients in the Flatiron Health study and 103 patients in NAPOLI-1 for whom these data were available.

with 5-FU and gemcitabine-based therapy, and (2) those in sequence 2 who had received liposomal irinotecan as second-line therapy after gemcitabine-based first-line therapy. Patients in sequence 1 (n = 121) had a median OS estimate of 4.1 months, whereas patients in sequence 2 (n = 129) had a median OS estimate of 6.3 months.[39]

Real-World Evidence: Economic Impact of Pancreatic Cancer

To best evaluate the economic impact of any treatment, an understanding of the baseline economic burden is required. Multiple studies have investigated real-world economic factors associated with pancreatic cancer, including metastatic disease. For example, in a retrospective, claims-based analysis for a commercially insured US population and Medicare Advantage enrollees (2001-2010), DaCosta and colleagues estimated the costs and resource use associated with treatment. For this study, 5262 patients with pancreatic cancer were matched with 15,786 controls; for each patient, medical and pharmacy claims data and enrollment information were available from a national managed care organization database (Optum Research Database). The mean total all-cause healthcare costs per member per month (PMPM) were significantly higher for patients with pancreatic cancer than for controls ($15,480 vs $1001 [Consumer Price Index–adjusted 2010 US dollars {USD}]; P <.001). The single largest cost driver was mean inpatient costs ($9917 PPPM). Additionally, mean all-cause healthcare costs were more than 2 times higher during treatment of metastatic disease than during the initial treatment of nonmetastatic disease ($21,637 PMPM vs $10,358 PMPM; P <.001).[3]

In another study, Chang and colleagues used large nationwide claims databases containing medical and pharmacy claims for 3 million individuals with employer-sponsored private health insurance, who were commercially insured or insured through Medicare (MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases), to investigate the cost associated with pancreatic cancer at its initial diagnosis and the additional costs incurred with disease progression. For this retrospective cohort study, a total of 412 patients newly diagnosed with pancreatic cancer between January 1, 1999, and November 30, 2000, were demographically matched to a control group of 1236 patients enrolled between January 1, 1998, and November 30, 2000. The overall healthcare costs for patients with pancreatic cancer were more than 20 times those for the matched controls. The incremental regression-adjusted monthly costs attributable to pancreatic cancer were $7279, of which more than 60% resulted from hospitalization-related costs. Compared with patients with no disease progression (n = 183), patients who experienced progression (n = 171; 51.7%) incurred additional costs of $15,143 per month and $47,437 over the 2-year study period. For disease progression costs, the main driver was hospitalization: the inpatient costs for patients with disease progression were almost twice that for patients without progression ($11,222 vs $6485, respectively; P <.05).[4]

Furthermore, in a retrospective study of patient data in a SEER–Medicare database, O'Neill and colleagues estimated the direct medical costs of pancreatic cancer treatment for a population-based cohort of Medicare beneficiaries (aged ≥66 years). Costs attributable to pancreatic cancer were estimated using the difference between the costs of medical care for patients with pancreatic cancer and those for the matched cohort of beneficiaries without cancer. For the 15,037 patients with pancreatic adenocarcinoma diagnosed between 2000 and 2007 included in the study, mean total direct medical costs were $65,500 (all reported costs were in 2009 USD). These costs were greater for patients with respectable locoregional disease ($134,700) than for patients with unresectable locoregional disease ($65,300) and those with distant disease ($49,000). Hospitalizations and cancer-directed procedures drove the largest expenditures of healthcare costs.[5]

IMPORTANT SAFETY INFORMATION (*continued*)

Adverse Reactions (*continued*)

- Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia

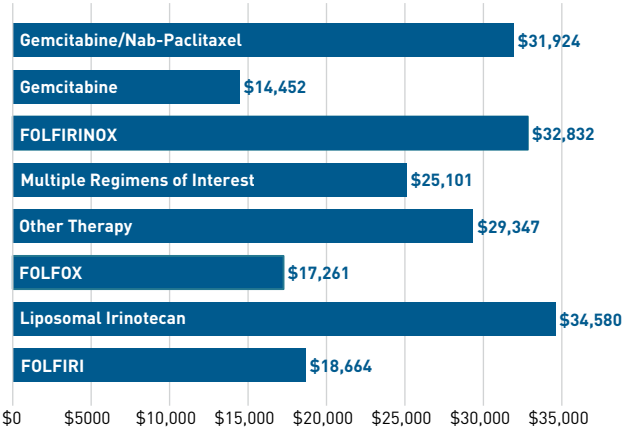
Real-World Evidence: Economic Impact Associated with Use of Liposomal Irinotecan

Recent studies using real-world evidence of the economic benefits of using liposomal irinotecan as therapy for metastatic pancreatic cancer have shown the cost of liposomal irinotecan is similar to the first-line agents, FOLFIRINOX and gemcitabine + nab-paclitaxel in total cost of care.

The results of a study by Muldoon and colleagues indicated 90-day survival rates decreased modestly across lines of treatment, from 79% with first-line treatment to 73% with third-line treatment. For the study, presented at the ISPOR 2019 annual international conference, investigators reviewed the treatment patterns, costs, and survival rates for 10,874 Medicare fee-for-service beneficiaries with metastatic pancreatic cancer from 2014 through 2017 by line of therapy and chemotherapy regimen. Average line of therapy costs varied by regimen from less than $15,000 to more than $30,000 with the average costs for FOLFIRINOX, liposomal irinotecan, and gemcitabine + nab-paclitaxel being comparable (**Figure 4**).[12]

The results of an analysis by Hirsch and colleagues also demonstrated the average total cost of second-line liposomal irinotecan did not significantly differ from first-line gemcitabine + nab-paclitaxel or first-line FOLFIRINOX. For the study, presented as a poster at the Academy of Managed Care Pharmacy Nexus 2019 annual meeting, investigators analyzed treatment patterns, total costs, and survival rates by line of therapy for Medicare fee-for-service patients who had metastatic pancreatic cancer treated with FDA-approved/NCCN Category 1 Recommended regimens. More than 28,000 patients and more than 15,000 lines of therapy were identified. Gemcitabine monotherapy, gemcitabine + nab-paclitaxel, and FOLFIRINOX were most commonly used as first-line therapies (87%, 81%, and 79%, respectively), whereas liposomal irinotecan was most commonly used as second-line therapy (53%). The average total cost for first-line gemcitabine monotherapy ($20,462) was significantly lower than first-line gemcitabine + nab-paclitaxel ($40,390) and first-line FOLFIRINOX ($40,325), which were comparable to second-line liposomal irinotecan ($41,600) ($P < .05$). In addition, the 90-day OS rate did not significantly differ between first-line gemcitabine-based regimens and second-line liposomal irinotecan (gemcitabine monotherapy, 73%; gemcitabine + nab-paclitaxel, 78%; liposomal irinotecan, 74%), despite disease progression and/or later lines of therapy.[10]

Figure 4. Average Cost of Line of Therapy by Treatment Regimen[12]



FOLFIRI, leucovorin + fluorouracil (5-FU) + irinotecan hydrochloride; FOLFOX, leucovorin + 5-FU + oxaliplatin; FOLFIRINOX, 5-FU + leucovorin + oxaliplatin + irinotecan.

Reprinted with permission from Muldoon LD, Hirsch J, Dieguez G, Valderrama A, Cockrum P. Presented at: ISPOR 2019; May 18-22, 2019; New Orleans, LA.

Muldoon and colleagues demonstrated the total cost of care associated with liposomal irinotecan as a second-line therapy was similar to the total cost of care associated with first-line therapies and was budget-neutral. For the study, presented during the ASCO 2019 annual meeting, the results of an analysis of Medicare-based claims from 2013 through 2017, showed the mean total Medicare Part A and Part B costs (excluding professional costs) totaled $32,447 for first-line gemcitabine + nab-paclitaxel and $33,628 for first-line FOLFIRINOX. These were similar to the cost of liposomal irinotecan ($36,350) in the second-line setting. The 90-day survival rates for second- and third-line treatment with liposomal irinotecan were lower (68% and 73%, respectively) than with first-line gemcitabine (76%-79%) and FOLFIRINOX (86%), but the differences were modest.[13]

Medical Cost Offsets & Budget Impact with Use of Liposomal Irinotecan

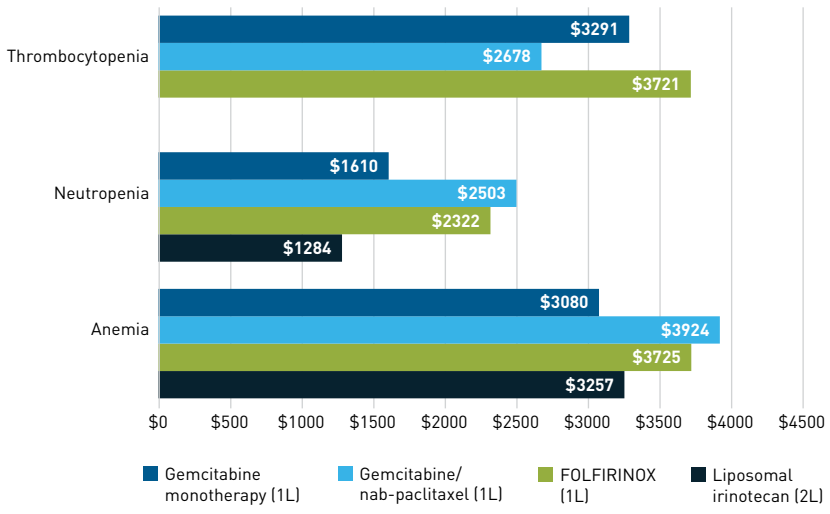
Although inpatient care is a primary economic driver in overall costs surrounding pancreatic cancer, drug and treatment costs remain a

IMPORTANT SAFETY INFORMATION (*continued*)

Adverse Reactions (*continued*)

- ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia

Figure 5. Mean 30-Day Incremental Costs of Adverse Events by Chemotherapy Regimen and Line of Therapy[14,a]



1L, first-line therapy; 2L, second-line therapy; AE, adverse event; FOLFIRINOX, fluorouracil (5-FU) + leucovorin + oxaliplatin + irinotecan.

[a]Mean 30-day AE incremental costs were calculated relative to controls through the use of recycled projects and bootstrapped 95% CI, which determined statistical significance relative to zero.[14]

Reprinted with permission from Hirsch J, Dieguez G, Cockrum P. Presented at: ASHP Midyear Clinical Meeting 2019; December 8-12, 2019; Las Vegas, NV.

focus as they represent interventions that are open to evaluation and differentiation. The value of a treatment goes beyond its acquisition cost when it is assessed by its impact on medical outcomes. This includes a scenario where factors such as the reduction in AEs as well as reduced administration costs can result in overall medical cost offsets equivalent to a regimens higher cost, thus conveying its use to be budget-neutral.

Mean Incremental Costs of AEs: Differences Among Regimens

The result of an analysis of claims data for a Medicare fee-for-service population from 2013 through 2017 demonstrated that first-line therapies were associated with substantial mean 30-day incremental costs for the AEs of anemia, neutropenia, and thrombocytopenia (**Figure 5**). For the study, presented as a poster at the American Health-Systems Pharmacists Midyear 2019 meeting, Hirsch and colleagues evaluated the mean incremental costs of AEs by line of therapy for patients with metastatic pancreatic cancer treated using FDA-approved/NCCN Category 1 Recommended regimens (n = 9185). The most common AE was anemia, experienced by 41% of patients on first-line therapy with gemcitabine + nab-paclitaxel, 35% of patients receiving first-line gemcitabine monotherapy, 33% of those receiving first-line FOLFIRINOX, and 32% of patients receiving liposomal irinotecan. Neutropenia was observed for 16% of those receiving first-line gemcitabine monotherapy, 19% of patients receiving second-line liposomal irinotecan, 20% of patients receiving first-line gemcitabine + nab-paclitaxel, and 32% of those receiving first-line FOLFIRINOX. Mean 30-day incremental costs for neutropenia were $2503 for first-line gemcitabine + nab-paclitaxel; $1610 for first-line gemcitabine monotherapy; and $2322 for first-line FOLFIRINOX, all of which were statistically significant. The mean 30-day incremental cost for neutropenia for second-line liposomal irinotecan was $1284, which was not statistically significant, and there were few cases.[14]

An additional validation of real-world observational data, by Dieguez and colleagues, indicated the use of liposomal irinotecan was associated with lower incremental costs, and lower grade 3 and 4 hematologic AEs. For the study presented at the ASCO Gastrointestinal Cancers 2019 Symposium, investigators examined rates of AEs recorded in EHRs of patients with metastatic pancreatic cancer between 2014 and 2019, as well as the AE-related costs from a claims analysis of Medicare patients with the same disease from 2013 through 2017.[11]

Of the 4592 patients included in the analysis, 2295 patients were treated with first-line gemcitabine + nab-paclitaxel, 1138 were treated with first-line FOLFIRINOX, 218 patients were treated with second-line FOLFOX, 178 patients were treated with second-line liposomal irinotecan, and 56 patients were treated with second-line FOLFIRI.

IMPORTANT SAFETY INFORMATION (*continued*)

Adverse Reactions (*continued*)

- The most common laboratory abnormalities (≥20%) were anemia (97%), lymphopenia (81%), neutropenia (52%), increased ALT (51%), hypoalbuminemia (43%), thrombocytopenia (41%), hypomagnesemia (35%), hypokalemia (32%), hypocalcemia (32%), hypophosphatemia (29%), and hyponatremia (27%)

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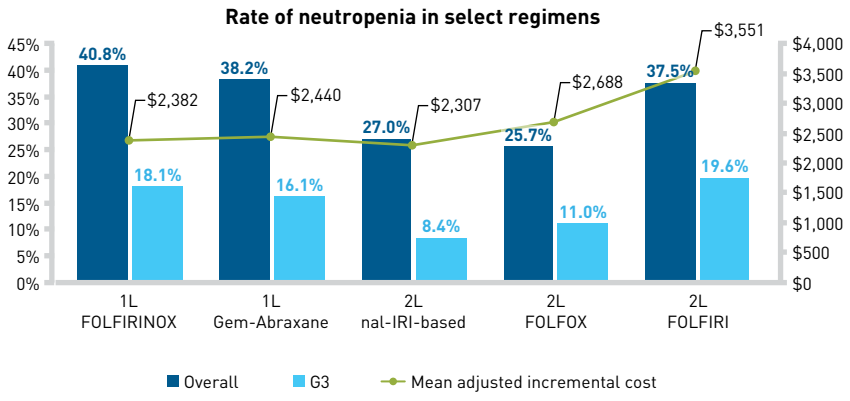
The rates of any grade of neutropenia ranged from 25.7% (FOLFOX) to 40.8% (FOLFIRINOX). The rates of anemia (any grade) were similar and ranged from 82.6% (FOLFOX) to 91.1% (FOLFIRI). The incremental costs associated with any grade neutropenia and any grade anemia were lower for liposomal irinotecan than for the other first- or second-line therapies ($2307 and $2963, respectively) (**Figure 6** and **Figure 7**).[11] These low incremental costs were consistent with the low rates of neutropenia and grade 3 or greater anemia seen in the study. The rate of grade 3 or greater neutropenia was 8.4% for liposomal irinotecan and 11.0% to 19.6% for the other first- or second-line therapies. The rate of grade 3 or greater anemia was 7.3% for the second-line therapy of liposomal irinotecan vs 6.4% to 19.6% for the other first- or second-line therapies. Rates of lymphopenia were found to be similar across all regimens and these incremental costs were not statistically significant.[11]

Budget Impact of Adding or Increasing Access to Liposomal Irinotecan

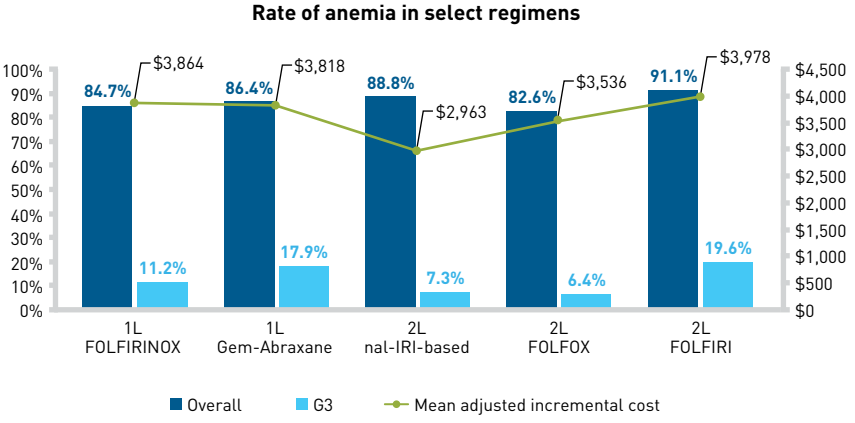
Herrara-Restrepo and colleagues reported the budget impact of adding or increasing access to liposomal irinotecan for patients with disease progression after receiving gemcitabine-based therapy in the first, second, and third lines of therapying presented at the ISPOR 2019 annual international conference. Epidemiologic inputs reflecting a US population of patients with metastatic pancreatic cancer were applied to a hypothetical plan population of 1 million members to calculate the number of patients who were eligible for treatment with liposomal irinotecan. The perspective was that of a US commercial

Figure 6. Real-World Experience with nal-IRI + 5-FU/LV: Flatiron and Medicare Perspective (Economics of Neutropenia)[11]



1L, first-line therapy; 2L, second-line therapy; 5-FU, fluorouracil; FOLFIRI, 5-FU + leucovorin (LV) + irinotecan; FOLFIRINOX, 5-FU + LV + oxaliplatin + irinotecan; FOLFOX, LV + 5-FU + oxaliplatin; G3, grade 3; G4, grade 4; Gem-Abraxane, gemcitabine + abraxane; nal-IRI, liposomal irinotecan.

Figure 7. Real-World Experience with nal-IRI + 5-FU/LV: Flatiron and Medicare Perspective (Economics of Anemia)[11]



1L, first-line therapy; 2L, second-line therapy; 5-FU, fluorouracil; FOLFIRI, 5-FU + leucovorin (LV) + irinotecan; FOLFIRINOX, 5-FU + leucovorin + oxaliplatin + irinotecan; FOLFOX, leucovorin + 5-FU + oxaliplatin; G3, grade 3; Gem-Abraxane, gemcitabine + abraxane; nal-IRI, liposomal irinotecan.

IMPORTANT SAFETY INFORMATION (*continued*)

Drug Interactions

- Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE
- Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy

payer. The base-case market share consisted of the most frequently prescribed treatment options for metastatic pancreatic cancer (ie, liposomal irinotecan + 5-FU + leucovorin, FOLFIRI, FOLFIRINOX, FOLFOX, gemcitabine, and gemcitabine + nab-paclitaxel). Treatment costs were derived from a commercially available database (Medi-Span Price Rx), and the administration costs were taken from the 2019 Medicare Physician and Laboratory Fee Schedules. AE rates and related costs were calculated for each regimen, and the rates and costs associated with prophylactic use of granulocyte colony-stimulating factor (G-CSF) were also factored into the modeled calculations for each regimen. The base-case calculations were based on a 100% commercial plan with 1 million members, and with an increasing liposomal irinotecan treatment uptake of 1.4% with first-line treatment, 21.5% with second-line treatment, and 40.2% with third-line treatment relative to the current utilization. Although a modest incremental budget impact was associated with the addition of liposomal irinotecan to the plan's formulary, this increase in drug cost was offset by a 0.3% savings each in drug administration, the cost of G-CSF, and patient monitoring costs, as well as a 0.1% savings in AE management, which ultimately rendered the net budget impact neutral.[15]

LIMITATIONS

EHR Data Limitations

Although EHR RWE reflects real-world treatment utilization and decision making across practice settings, regardless of formal labeling recommendations, true comorbidity may be underestimated because diagnosis codes from structured data might not capture all comorbid conditions. Several limitations inherent in the analyses of real-world data should be considered. Nonrandom allocation and bias in the frequency and availability of data (for example, systematic differences in terms of missing data or data-collection frequency) are general limitations and cannot be controlled completely with statistical methods. Additional limitations can occur in retrospective chart reviews: potential entry errors in the structured lab data, leading to extreme values; abstraction of certain variables, leading to data being exploratory and underreported. Results may not be generalizable outside of the community oncology setting. Additionally, specific to Flatiron data, age is capped at 85 years for de-identification reasons; thus, the true age of some older patients with mPC and their associated clinical outcomes is unknown.

Claims Data Limitations

There are no head-to-head trials comparing Irinotecan liposome injection (ONIVYDE) + 5-FU + leucovorin to other metastatic pancreatic cancer treatments included. Because of the inherent restrictions of claims data, there is no adjustment for individual regimen dosing periods. Since this analysis uses claims data and not EHR data, the authors could not control for clinical covariates; thus, specific disease characteristics and patient demographics may influence which treatment regimens patients receive. The authors did not study whether patients who received liposomal irinotecan also received concomitant 5-FU + leucovorin and/or prior gemcitabine-based therapy. Thus, patients who may have received therapy without a gemcitabine sequence are not excluded from these data. Analysis of different populations or time periods can yield different results.

Budget Impact Models Data Limitations

Budget impact models (BIMs) are intended to be a tool to aid in planning and is primarily based on the assumptions. Results depend on the quality and accuracy of model inputs, and known data limitations exist, including those around published data for commercial payers (ie, uncertainty surrounding model inputs for G-CSF use and AE rates and costs). The results should be interpreted with consideration of these limitations.

The BIM reviewed recognizes dosing regimens may vary widely in actual practice. It was not, however, capable of fully assessing the impact one treatment regimen over another when frequency of use or dosing strength differences are considered. The user must recognize that these, and other limitations, are inherent in this model, and this model should therefore be considered as only one factor in the overall analysis and cannot be relied upon as the absolute predictor of budget impact. Additionally, some chemotherapy regimens are administered with concomitant medications and this model does not account for that variable.

A payer may experience a different budget impact if negotiated prices differ from published prices. This model does not account for any differences in product reimbursement. Referenced prices are derived from published price lists and do not necessarily reflect actual prices paid by consumers, payers, or dispensers. Wholesale acquisition cost price differences do not necessarily reflect a cost advantage in the use of a product because there are other variables

IMPORTANT SAFETY INFORMATION (*continued*)

Use in Specific Populations

- **Pregnancy and Reproductive Potential:** See WARNINGS & PRECAUTIONS. Advise males with female partners of reproductive potential to use condoms during and for 4 months after ONIVYDE treatment
- **Lactation:** Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment

that affect relative net costs to payers and consumers. Drug costs were last accessed January 2019 and are subject to change without notice.

This analysis is limited to a US healthcare setting; results are not generalizable to other patient subgroups, disease indications, or geographies.

CONCLUSIONS

Irinotecan liposome injection (ONIVYDE) + 5-FU and leucovorin is an ASCO guideline recommended treatment and the first and only FDA-approved, and only NCCN category 1 chemotherapy option, recommended for treatment of metastatic pancreatic cancer after disease progression following gemcitabine-based therapy. When compared with other regimens, liposomal irinotecan provides similar 90-day OS rates and total cost of care to front-line therapies with minimal budget impact, despite patients using this regimen in later lines of therapy.

Disclosure

All the studies referenced herein were supported by Ipsen Biopharmaceuticals, Inc., the manufacturer of ONIVYDE.

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