# Encapsulated irinotecan provides novel option for hard-to-treat pancreatic cancer

In the fall of 2015, the US Food and Drug Administration approved the addition of a novel, much-needed treatment option for patients with metastatic pancreatic cancer, a particularly hard-to-treat form of the disease, in the second-line setting following progression on gemcitabine-based chemotherapy.[1] MM-398 is a modified version of the chemotherapeutic agent irinotecan, in which the drug is encapsulated in a nanoliposomal construct that is designed to improve delivery to the tumor and enhance antitumor efficacy while minimizing side effects in the rest of the body.

Approval was based on the global, randomized, open-label phase 3 NAPOLI-1 trial performed at 76 sites in 14 countries between January 11, 2012 and September 11, 2013, which demonstrated improved survival for patients with metastatic pancreatic cancer who were treated with a combination of MM-398 and fluorouracil plus leucovorin compared with fluorouracil-leucovorin alone, in the second-line setting following progression on gemcitabine-based chemotherapy.[2]

Eligible patients were aged 18 years or older, with histologically or cytologically confirmed pancreatic ductal adenocarcinoma; had documented measurable or non-measurable distant metastatic disease that progressed after previous gemcitabine-based therapy in the neoadjuvant, adjuvant, locally advanced, or metastatic setting; had a Karnofsky Performance Status score of ≥70 (100, perfect health); and had adequate hematologic, hepatic, and renal function.

Patients were initially randomized 1:1 to receive nanoliposomal irinotecan (n = 151) or fluorouracil-leucovorin (n = 149; protocol version 1), but that was subsequently amended to include a third arm (1:1:1) in which nanoliposomal irinotecan was administered in combination with fluorouracil-leucovorin (n = 117; protocol version 2). Randomization was performed according to a prespecified scheme generated by an independent statistician using a computerized interactive web response system and was stratified according to baseline albumin levels (≥40 g/L or <40 g/L), Karnofsky Performance Status (70 and 80 or ≥90), and racial or ethnic origin (white, East Asian, or all others). Of the 417 patients, 63 were enrolled under protocol version 1 before all sites were switched to version 2.

Patients in the combination arm were given an intravenous infusion of nanoliposomal irinotecan over 90 minutes at a dose of 80 mg/m$^2$, followed by leucovorin 400 mg/m$^2$ over 30 minutes, then fluorouracil 2400 mg/m$^2$ over 46 hours every 2 weeks. In the monotherapy arm, patients were administered nanoliposomal irinotecan at a dose of 120 mg/m$^2$ every 3 weeks and in the control arm, leucovorin was given as a 30-minute infusion at a dose of 200 mg/m$^2$, followed by 2000 mg/m$^2$ fluorouracil over 24 hours every week for the first 4 weeks of each 6-week cycle.

Genetic variations in the uridine diphosphate glucoronosyltransferase 1A1 (*UGT1A1*) gene, which encodes the enzyme that deactivates irinotecan's active metabolite (SN-38), can affect the metabolism and excretion of irinotecan and place patients at increased risk of severe toxicity, therefore all patients received *UGT1A1* genotype testing. Patients homozygous for the *UGT1A1*28* allele were given

## What's new, what's important

Therapeutic options for metastatic pancreatic cancer are still limited, and the prognosis remains poor. So any improvement in this scenario is welcome news for our patients. Late last year, the US FDA approved irinotecan liposome injection, a topoisomerase inhibitor, in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma.

The approval was based on findings from a 3-arm, randomized study of 417 patients with metastatic pancreatic adenocarcinoma whose cancer had progressed after treatment with gemcitabine. The study was designed to determine whether patients who received irinotecan liposome injection plus fluorouracil-leucovorin or irinotecan liposome injection alone lived longer than those who received fluorouracil-leucovorin. The study showed that the combination arm had a survival advantage of 2 months.

The most common side effects of treatment with irinotecan liposome injection included diarrhea, fatigue, vomiting, nausea, decreased appetite, stomatitis, and fever. The injection was also found to cause neutropenia. Death due to sepsis following neutropenia has been reported in patients treated with Irinotecan liposome injection.

The recommended dose of irinotecan liposome injection is 70 mg/m$^2$ intravenous infusion over 90 minutes every 2 weeks. The recommended starting dose of irinotecan liposome injection in patients who are homozygous for UGT1A1*28 is 50 mg/m$^2$ every 2 weeks.

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## Mechanism of action

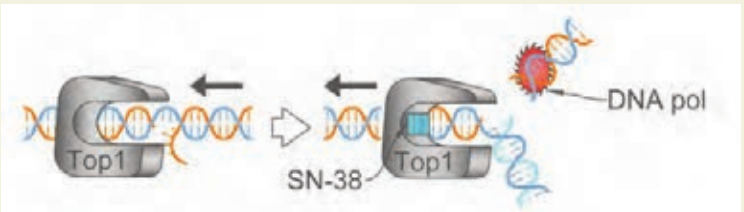
### Novel formulation boosts antitumor efficacy, reduces side effects

Pancreatic carcinoma is among the most lethal of all solid tumors. Despite improved outcomes following the approval of several chemotherapy regimens, the outlook for most patients remains poor, and there is no consensus on the treatment of patients whose disease progresses on front-line therapy.

Irinotecan is a semisynthetic camptothecin derivative that inhibits the function of the DNA topoisomerase I enzyme. DNA is normally found in a coiled double helix, but is periodically uncoiled for the genetic code to be replicated during cell division, repaired when damage occurs, or read during translation into protein. DNA topoisomerases play a key role in the uncoiling and recoiling process, by cutting and resealing the DNA, and ensure the DNA doesn't get overwound.

Inhibitors of these enzymes bind to the topoisomerase enzyme and prevent it from functioning so that the DNA cannot be stuck back together after it has been cut. These unrepaired cuts ultimately lead to cell death, thus topoisomerase inhibitors were proposed as a way to induce cell death in cancer cells that are rapidly dividing.

Irinotecan demonstrated modest activity in patients with pancreatic cancer and was explored as both a single agent and in combination therapy, but not found to be superior to standard of care. MM-398 is a novel formulation of irinotecan, in which the drug is encapsulated in a nanoparticle/liposome construct that shields it from conversion into its active metabolite, SN-38, until it reaches the tumor. Increased levels of SN-38 in the tumor and decreased levels in the circulation helps to improve antitumor efficacy while reducing off-target side effects.




The enzyme DNA topoisomerase I (Top1) cleaves and unwinds DNA to prevent twisting and supercoiling during replication and transcription. The active metabolite of irinotecan, SN-38, forms a complex with DNA and Top1 that prevents the DNA strand from sticking back together, causing a double-strand break that inhibits DNA replication and induces cell death. In MM-398, irinotecan is encapsulated in a nanoliposomal construct that shields it from activation until it reaches the tumor, increasing antitumor efficacy while limiting systemic toxicity.

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a reduced initial dose of MM-398 (20 mg/m$^2$), which was increased to standard dosing after the first cycle in patients who did not experience drug-related toxicities.

Treatment was continued until disease progression or intolerance of side effects and patients were evaluated using serial imaging studies, measurement of carbohydrate antigen 19-9 (CA19-9) levels, radiographic tumor response assessment (performed according to Response Evaluation Criteria in Solid Tumors, version 1.1), and measurement of quality of life using European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire. Baseline demographics and clinical characteristics were similar in the 3 treatment groups.

The primary endpoint of the trial was overall survival (OS) and, at a cut-off of February 14, 2014, the median OS was 6.1 months in the combination arm, compared with 4.2 months in the fluorouracil-leucovorin monotherapy arm (unstratified hazard ratio [HR], 0.67; $P$ = .012), whereas median OS did not differ significantly for MM-398 monotherapy compared with fluorouracil-leucovorin monotherapy. Preplanned subgroup analyses showed that the survival benefit for combination therapy was consistent across most subgroups and it maintained a strong treatment effect on OS after adjusting for prognostic factors (HR, 0.58).

Median progression-free survival (PFS) was 3.1 months, compared with 1.5 months in the combination and fluorouracil-leucovorin arms, respectively (unstratified HR, 0.56; $P$ = .0001). Median time-to-progression was 2.3 months, compared with 1.4 months, respectively. Objective response rates were 16% and 1%, and the CA19-9 response rates (defined as a decrease of 50% or more in the amount of CA19-9 from baseline occurring at least once during the treatment period) for the 2 groups were 29% and 9%. In a subanalysis that assessed patients who received at least 80% of the target dose in the first 6 weeks (a per protocol population), there was an even greater OS benefit with combination therapy.

Overall, 95% of patients received at least 1 dose of the study drug and were included in the safety analysis. Common treatment-emergent adverse events (TAEs) associated with nanoliposomal irinotecan were diarrhea, nausea, and vomiting. Adverse events resulted in dose reduction in 33% of patients in the combination arm, 31% of patients who took nanoliposomal irinotecan monotherapy, and 4% in the fluorouracil-leucovorin arm; those leading to discontinuation occurred in 11%, 12%, and 7% of patients, respectively. Grade 3/4 neutropenic sepsis (including febrile neutropenia) occurred in 3%, 4%, and 0% of patients, respectively, whereas grade 4 TAEs occurred in

10%, 16%, and 7%, respectively. The 30-day mortality rate was low in all groups. Of the 47 deaths that occurred, 30 resulted from pancreatic cancer, 16 from adverse events (1 of which was related to nanoliposomal irinotecan), and 1 from an unknown cause.

MM-398 is being marketed as Onivyde by Merrimack Pharmaceuticals Inc. The recommended dose is 70 mg/m$^2$, administered as an intravenous infusion over 90 minutes every 2 weeks, except in patients with homozygous *UGT1A1*28* for whom the starting dose should be 50 mg/m$^2$ every 2 weeks.[3] The prescribing information includes a boxed warning to alert health care providers to the risks of severe neutropenia and diarrhea. Complete blood cell counts should be obtained on days 1 and 8 of every cycle (more frequently if clinically indicated) and MM-398 withheld when absolute neutrophil count is below 1500/mm$^3$ or if neutropenic fever occurs. MM-398 should not be given to patients with bowel obstruction and antidiarrheal treatment should be administered if needed. There are also warnings and precautions relating to the risk of interstitial lung disease, severe hypersensitivity reactions, and embryofetal toxicity.

**References**


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