The American Cancer Society has estimated that approximately 45,220 new cases of pancreatic cancer would be diagnosed in the United States in 2013 and approximately 38,460 patients would die of pancreatic cancer in 2013.1 Despite being the tenth most common cancer, pancreatic cancer is the fourth most common cause of cancer deaths, in part because a large majority of patients present with nonresectable advanced disease.2,3

Although adjuvant chemotherapy with gemcitabine or with 5-fluorouracil (5-FU) confers a small survival advantage for patients with early-stage pancreatic cancer, the vast majority will relapse and die from their disease.3 Only approximately 4% of patients with pancreatic cancer will be alive and disease free at 5 years.3 With statistics like these, there is clearly an urgent unmet need for more effective therapies for patients with pancreatic cancer.4

Because pancreatic cancer results in substantial morbidity and mortality, the financial burden associated with patient management can be significant. US researchers recently reported the direct medical costs of pancreatic cancer treatment based on an analysis of a population-based cohort of Medicare beneficiaries.5 Using the 2001 to 2007 Surveillance, Epidemiology, and End Results–Medicare database, more than 15,000 patients (aged ≥66 years) with pancreatic cancer were identified.5 The total mean direct medical cost was $65,500, with greater costs ($134,700) for patients with resectable locoregional pancreatic cancer compared with patients with unresectable locoregional or distant disease ($65,300 and $49,000, respectively).5

Hospitalizations and cancer-directed procedures were the largest cost drivers in this analysis.5 Demographic trends and the increasing use of targeted therapies are likely to affect treatment patterns, as well as increase the costs of managing pancreatic cancer in the future, the investigators suggest.5

Today, the only potentially curative technique for pancreatic cancer is surgical resection.6 Cytotoxic chemotherapy and radiation therapy are relevant options in the neoadjuvant and adjuvant settings, as well as in patients with unresectable and metastatic disease. The current National Comprehensive Cancer Network (NCCN) guidelines for patients with metastatic or locally advanced unresectable pancreatic cancer include several category 1 recommendations, including clinical trials, the 4-drug regimen FOLFIRINOX (leucovorin, 5-FU, irinotecan, and oxaliplatin), the combination of gemcitabine and erlotinib, other gemcitabine-based combinations, and gemcitabine monotherapy.6 For patients whose performance status is poor (Eastern Cooperative Oncology Group 2 or higher), the NCCN suggests gemcitabine monotherapy or best supportive care.6

**Abraxane a New Treatment Option**

In September 2013, the US Food and Drug Administration (FDA) approved the cytotoxic agent nab-paclitaxel (paclitaxel protein-bound particles for injectable suspension, albumin-bound; Abraxane; Celgene Corporation) for first-line treatment of patients with metastatic adenocarcinoma of the pancreas in combination with gemcitabine.7 Nab-paclitaxel is also approved for first-line treatment of locally advanced or metastatic non–small-cell lung cancer in combination with carboplatin and for breast cancer after failure with combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.8

The FDA’s approval of nab-paclitaxel for advanced pancreatic cancer was based on the demonstration of a significant increase in overall survival (OS) in a phase 3 multicenter clinical trial of 861 patients with metastatic pancreatic cancer conducted in more than 150 centers throughout the world.9,10 “This large, randomized, international, phase 3 study showed that the nab-paclitaxel plus gemcitabine led to a significant improvement in survival at all time points,” said Daniel D. Von Hoff, MD, Physician-in-Chief, Translational Genomics Research Institute, Phoenix, AZ, and Chief Scientific Officer, Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare, AZ. “The rate of survival was significantly higher in the nab-paclitaxel-gemcitabine group than in the gemcitabine group,” he added. Dr Von Hoff served as the principal investigator of the Metastatic Pancreatic Adenocar-
cinoma Clinical Trial (MPACT), which included sites in North America, Europe, and Australia.\textsuperscript{10}

**Mechanism of Action**

Nab-paclitaxel is a cytotoxic agent that stabilizes microtubules in cancer cells and protects them from disassembly. This stability inhibits normal microtubule network functions that are essential for cell division.\textsuperscript{8} Compared with the original formulation of paclitaxel, nab-paclitaxel or albumin-bound paclitaxel is a solvent-free formulation that utilizes albumin to deliver the taxane, resulting in an advantageous pharmacokinetic profile.\textsuperscript{11}

**Dosing and Administration**

For patients with newly diagnosed metastatic pancreatic cancer, the recommended dose and schedule for nab-paclitaxel is 125 mg/m\textsuperscript{2} intravenously over 30 to 40 minutes on days 1, 8, and 15 of each 28-day cycle.\textsuperscript{8} Gemcitabine should be administered on days 1, 8, and 15 of each 28-day cycle immediately after nab-paclitaxel.\textsuperscript{8}

**Phase 3 Clinical Trial**

The multicenter MPACT trial enrolled 861 patients with newly diagnosed advanced pancreatic cancer. Patients were randomly assigned to nab-paclitaxel 125 mg/m\textsuperscript{2} followed by gemcitabine 1000 mg/m\textsuperscript{2} on days 1, 8, and 15 every 4 weeks or to gemcitabine monotherapy 1000 mg/m\textsuperscript{2} weekly for 7 of 8 weeks (cycle 1), and then on days 1, 8, and 15 every 4 weeks (cycle 2 and subsequent cycles).

Patients were treated until disease progression. Patients with pancreatic cancer who had received cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting were excluded from study participation.\textsuperscript{9}

The primary end point of this trial was OS duration. Secondary end points included progression-free survival (PFS), overall response rate (ORR), and safety.\textsuperscript{9} Tumor scans were assessed every 8 weeks by investigators, as well as by independent reviewers.\textsuperscript{9}

**Patient Population**

The median age of patients enrolled in this phase 3 clinical trial was 63 years.\textsuperscript{9} Of the patients, 10% were aged \(\geq 75\) years.\textsuperscript{9} The majority of the patients were male (58%) and white (87%), with Karnofsky performance scores of 80 to 100 (92%).\textsuperscript{9} Overall, 46% of the patients had 3 or more metastatic sites, and most patients (84%) had liver metastasis.\textsuperscript{9} Demographic and clinical characteristics were well balanced between the 2 study arms at baseline.\textsuperscript{9}

**Efficacy**

The OS benefit, the study’s primary end point, was significant for patients receiving the combination of nab-paclitaxel and gemcitabine. In the intent-to-treat population, the median OS was 8.5 months (95% confidence interval [CI], 7.89-9.53) for the nab-paclitaxel plus gemcitabine group compared with 6.7 months (95% CI, 6.01-7.23) for the gemcitabine monotherapy group (hazard ratio for death, 0.72; 95% CI, 0.62-0.83; \(P < 0.001\)).\textsuperscript{9} The Figure illustrates these significant OS advantage findings in the combination of nab-paclitaxel and gemcitabine using a Kaplan-Meier curve. Of note, these survival curves separated early, with a median improvement of 1.8 months and an improvement of 3.4 months at the time point when 25% of the patients were alive.\textsuperscript{9} In addition, survival rates were significantly higher in the nab-paclitaxel plus gemcitabine group than in the gemcitabine monotherapy group at 1 year (35% vs 22%, respectively) and 2 years (9% vs 4%, respectively).\textsuperscript{9}

The secondary end points of PFS and ORR were also significantly improved in the nab-paclitaxel plus gemcitabine arm relative to the gemcitabine monotherapy arm. The median PFS was 5.5 months in patients receiving the nab-paclitaxel plus gemcitabine combination (95% CI, 4.5-5.9) versus 3.7 months for the patients receiving gemcitabine monotherapy (95% CI, 3.6-4.9).\textsuperscript{9} At 1 year, the PFS rate was 16% in the group receiving nab-paclitaxel plus gemcitabine compared with 9% in the group receiving gemcitabine.\textsuperscript{9} According to independent review, the ORR was also significantly improved with nab-paclitaxel combined with gemcitabine relative to gemcitabine alone (23% vs 7%; \(P < 0.001\)).\textsuperscript{9} The Table summarizes these data and relevant statistical analyses.
Safety and Serious Adverse Events

In the nab-paclitaxel plus gemcitabine group, the median duration of treatment was 3.9 months (0.1-21.9 months) compared with 2.8 months (0.1-21.5 months) in the gemcitabine group.8 The median relative dose intensity was 85%.9

The incidence rates of anemia (13% in the nab-paclitaxel plus gemcitabine group vs 12% in the gemcitabine monotherapy group) and thrombocytopenia (13% vs 9%) were similar in the 2 treatment arms.9 Febrile neutropenia was rare in both groups (3% vs 1%).9

Peripheral neuropathy was the most notable difference in AEs between the 2 treatment groups.8 It was cumulative and rapidly reversible in most patients after temporary discontinuation of nab-paclitaxel and subsequent dose reduction. None of the patients experienced grade 4 peripheral neuropathy. The rate of discontinuation of nab-paclitaxel secondary to peripheral neuropathy (all grades) was 8%.9 Overall, 10% of the patients had dose reduction of nab-paclitaxel as a result of peripheral neuropathy.9

In the MPACT trial, 50% of the patients receiving nab-paclitaxel plus gemcitabine and 43% of the gemcitabine recipients experienced serious AEs.9 Fatal events were reported for 4% of the patients in each treatment group.9 Patients in the nab-paclitaxel plus gemcitabine group were more likely to experience pneumonitis (4% vs 1%, respectively), as well as sepsis (5% vs 2%, respectively) compared with the gemcitabine group.9

A limitation of the MPACT study was that quality of life was not assessed.9

Warnings and Precautions

Hematologic effects. Bone marrow suppression—primarily neutropenia—is a dose-dependent and dose-limiting toxicity associated with nab-paclitaxel. In the phase 3 trial comparing nab-paclitaxel and gemcitabine with gemcitabine monotherapy in metastatic pancreatic cancer, grade 3 to 4 neutropenia occurred in 38% of patients receiving the combination.8,9

Patients with pancreatic cancer who receive nab-paclitaxel and gemcitabine should undergo frequent complete blood cell counts to monitor for myelotoxicity, including before drug dosing on days 1, 8, and 15.9 The combination of nab-paclitaxel and gemcitabine should not be given to patients with pancreatic cancer whose baseline absolute neutrophil count (ANC) is <500 cells/mm3 or whose platelets are <50,000 cells/mm3.8 Initiation of the next treatment cycle should be delayed if ANC is <1500 cells/mm3 or if the platelet count is <100,000 cells/mm3 on day 1.8 Treatment can be resumed with appropriate dose reduction if recommended.8

Nervous system. Sensory neuropathy is also a dose-dependent and dose-limiting toxicity associated with nab-paclitaxel. Grade 1 or 2 sensory neuropathy typically does not require dose modification.8 If grade 3 or higher sensory neuropathy develops in a patient with pancreatic cancer, withhold nab-paclitaxel treatment until it resolves to grade 1 or lower.8 The dose of nab-paclitaxel should be reduced in all subsequent treatment courses.8

Sepsis. Sepsis with or without neutropenia occurred in 5% of patients with pancreatic cancer who received nab-paclitaxel in combination with gemcitabine.8,9 Risk factors for severe or fatal sepsis included biliary obstruction and the presence of a biliary stent.8 Patients who become febrile regardless of ANC should receive treatment with broad spectrum antibiotics.8 If febrile neutro-

<table>
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<th>Table</th>
<th>Selected Efficacy Results from the MPACT Study in Patients with Adenocarcinoma of the Pancreas (ITT Population)</th>
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<tr>
<td>Efficacy end point</td>
<td>Nab-paclitaxel 125 mg/m2 and gemcitabine (N = 431)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
</tr>
<tr>
<td>Death or progression, N (%)</td>
<td>277 (64)</td>
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<tr>
<td>Median progression-free survival, mo</td>
<td>5.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>4.5-5.9</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.69 (0.58-0.82)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
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<tr>
<td>Overall response rate</td>
<td></td>
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<tr>
<td>Confirmed complete or partial response, N (%)</td>
<td>99 (23)</td>
</tr>
<tr>
<td>95% CI</td>
<td>19%-27%</td>
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<tr>
<td>P value</td>
<td>&lt;.001</td>
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penia is detected, nab-paclitaxel and gemcitabine should be withheld until fever resolves and ANC increases to ≥1500 cells/mm³. Treatment with nab-paclitaxel can then be resumed at reduced dose levels.⁸

**Pneumonitis.** Of patients with pancreatic cancer, 4% receiving nab-paclitaxel in combination with gemcitabine experienced pneumonitis, including some fatal cases.⁵,⁹ Patients exhibiting signs and symptoms of pneumonitis should not receive nab-paclitaxel and gemcitabine during evaluation. If an infectious etiology is ruled out and pneumonitis is diagnosed, treatment with nab-paclitaxel and gemcitabine should be permanently discontinued.⁸

For patients with advanced pancreatic cancer, the combination of nab-paclitaxel and gemcitabine offers clinically and significant efficacy benefits, with an acceptable tolerability profile.

**Hypersensitivity.** Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with nab-paclitaxel. Patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be rechallenged.⁸

**Hepatic impairment.** Dose adjustments are not necessary for patients with mild hepatic impairment. However, nab-paclitaxel should be withheld if aspartate aminotransferase is greater than 10 times the upper limit of normal (ULN) or if bilirubin is greater than 5 times the ULN.⁸ The starting dose of nab-paclitaxel should be reduced in patients with moderate-to-severe hepatic impairment.⁸ Dose reductions or discontinuation may be appropriate if severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities occur.⁸

**Albumin (human).** Because nab-paclitaxel contains human albumin, a derivative of human blood, it carries a remote risk for viral disease transmission.⁸

**Use in pregnancy.** Based on animal studies, nab-paclitaxel can cause fetal harm when administered to a pregnant woman. Women of childbearing age should avoid becoming pregnant while receiving nab-paclitaxel.⁸

**Conclusion**
For patients with advanced pancreatic cancer, the combination of nab-paclitaxel and gemcitabine offers clinically and significant efficacy benefits, with an acceptable tolerability profile. Experts suggest that this combination may represent an alternative to FOLFIRINOX in patients who are unlikely to tolerate the toxicities associated with this regimen.¹⁰ Studies are under way to elucidate the optimal dosing schedule of the nab-paclitaxel and gemcitabine combination for pancreatic cancer, as well as the efficacy and safety of triple-drug regimens combining these 2 cytotoxic drugs with novel targeted agents.¹²

**References**
8. Abraxane (paclitaxel protein-bound particles for injectable suspension) (albumin bound) [prescribing information]. Summit, NJ: Celgene Corporation; September 2013.