Pancreatic cancer

NEW COMBINED-THERAPY OPTION FOR METASTATIC DISEASE

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TRIAL SUMMARY: Combined nab-paclitaxel plus gemcitabine provides superior efficacy vs gemcitabine alone for metastatic PC


In preclinical models of pancreatic cancer (PC), nab-paclitaxel (nab-P; 130 nm albumin-bound paclitaxel) has demonstrated both single-agent activity and synergy with gemcitabine (G). A phase I/II study in metastatic PC (J Clin Oncol 2011; 4548–54) also reported promising efficacy for nab-P + G, warranting a phase III study of nab-P + G vs G alone in this setting.

In this large, international study conducted at 151 community and academic centres, 861 patients with metastatic PC and a Karnofsky performance status (KPS) ≥70 were randomized 1:1 to receive nab-P 125 mg/m² + G 1000 mg/m³ on days 1, 8 and 15 every 4 weeks, or G alone 1000 mg/m³ weekly for 7 weeks followed by 1 week of rest (cycle 1) and then on days 1, 8 and 15 every 4 weeks (cycle ≥2). The primary endpoint was overall survival (OS); secondary endpoints were progression-free survival (PFS) and overall response rate (ORR) by independent review.

Patients’ median age was 63 years (range 27–88). KPS increased toxicity. Patients had advanced disease with liver metastases (84%), ≥3 metastatic sites (46%) and Cancer Antigen (CA) 19-9 ≥59 × upper limit of normal (ULN) (46%). Nab-P + G was superior to G for all efficacy endpoints: median OS 8.5 vs 6.7 months (HR 0.72; 95% CI 0.617–0.835; p=0.000015); median PFS 5.5 vs 3.7 months (HR 0.69; 95% CI 0.581–0.821; p=0.000024); ORR 23% vs 7% (p=1.1 × 10–10) by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0. Metabolic response assessed by positron emission tomography (PET) in 257 patients was 63% for nab-P + G vs 38% for G (p=0.000051). CA19-9 response (≥90% decrease) was 31% for nab-P + G vs 14% for G (p=0.00001). Grade 3 and worse adverse events (AEs) with nab-P + G vs G included neutropenia (38% vs 27%), fatigue (17 % vs 7%), diarrhea (6% vs 1%) and febrile neutropenia (3% vs 1%). Grade 3 and higher peripheral neuropathy (PN) occurred in 17% vs 1% of patients who received nab-P + G vs G, respectively; for nab-P + G, PN improved to grade ≤1 in a median of 29 days, and 44% of patients resumed nab-P treatment. Median treatment duration was 3.9 months for nab-P + G and 2.8 months for G.

The study concluded that nab-P + G was superior to G across all efficacy endpoints, had an acceptable toxicity profile and is a new standard for treatment of metastatic PC that could become the backbone for new regimens.

COMMENTARY: Approximately 45,000 people in the United States and 4,700 in Canada will be diagnosed with pancreatic cancer in 2013. The majority will have adenocarcinoma histology and about 80% will present with advanced, nonoperable disease. Treatments in this setting aim to control disease and treat symptoms using systemic therapies, radiation and in some cases, palliative surgery. Metastatic and locally advanced, nonoperable pancreatic cancers have poor survival rates, with very few patients alive at two years. New therapies to improve patient longevity are needed.

In the late 1990s, gemcitabine was approved and became standard of care over single-agent 5-fluorouracil (5-FU), based on the Burris trial that enrolled 126 previously untreated patients with locally advanced or metastatic pancreatic cancer. Gemcitabine had significantly better clinical response (24% vs 5%), median OS (5.6 vs 4.4 months) and one-year survival (18% vs 2%). In 2011, our first-line standard of care for good-performance patients with adequate liver function changed to FOLFIRINOX (infusional 5-FU, leucovorin, oxaliplatin and irinotecan) from gemcitabine, based on the ACCORD 11 trial. In this study, 342 patients with chemotherapy-naive metastatic pancreatic cancer, performance status 0–1, serum total bilirubin <1.5 times the upper limit of normal were randomly assigned to gemcitabine alone vs FOLFIRINOX. FOLFIRINOX showed superior objective response rate (32% vs 9%), median PFS (6.4 vs 3.3 months) and OS (11.1 vs 6.8 months). Importantly, there was no decline in quality of life despite higher rates of neutropenia, febrile neutropenia, sensory neuropathy, vomiting, fatigue and diarrhea with FOLFIRINOX. How much irinotecan contributes to the cytotoxicity of FOLFIRINOX is debatable, given the encouraging phase II data of FOLFOX6 (infusional 5-FU, leucovorin with oxaliplatin). Attempts have been made to improve first-line activity of gemcitabine by combining it with other chemotherapies and targeted agents; examples include, but are not limited to, capecitabine and erlotinib. A meta-analysis of two phase III trials and one phase II trial showed a statistically significant survival benefit for gemcitabine with capecitabine over gemcitabine alone (HR 0.86; 95% CI 0.75–0.98). The combination of gemcitabine and erlotinib showed a 2-week OS improvement compared to gemcitabine alone. These were modest improvements in outcomes at a cost of increased toxicity.
MPACT examined the outcomes of another gemcitabine doublet, nab-P + G, based on preclinical data showing synergy of these 2 agents, single-agent activity and a promising phase II trial. This well-conducted multinational randomized phase III trial found clinically meaningful improvements in OS (8.5 vs 6.7 months), PFS (5.5 vs 3.7 months) and ORR (23% vs 7%) with nab-P + G over G. PET and CA 19-9 were found to correlate with survival. As well, in subgroup analysis, patients with poorer performance status, liver metastatic disease and higher CA 19-9 values seemed to do better with nab-P + G. The survival data were robust such that subsequent lines of therapy did not impact conclusions. As expected, there were predictable additional ≥ grade 3 AEs in the experimental arm. Unlike in the FOLFIRINOX trial, however, quality of life data were not reported so the full impact on patients is unknown. In addition, cost-effectiveness data have yet to be reported. Despite these limitations, this trial represents another key milestone in the treatment of metastatic pancreatic cancer. This is the first phase III study showing clinically meaningful OS data with a gemcitabine chemotherapy combination.

For the first time, we have improved first-line chemotherapy choices over single-agent gemcitabine when treating metastatic pancreatic cancer patients. These include FOLFIRINOX, presented in 2011, and now nab-P +G, offering 11.1- and 8.5-month median OS, respectively. The next step is to identify subgroups and molecular markers that predict response and help to determine the appropriateness of one regime over the other. While nab-P + G and FOLFIRINOX had similar patient populations — metastatic with good performance status and liver function — nab-P + G allowed patients over the age of 75 years and had slightly more Eastern Cooperative Oncology Group (ECOG) performance status 2 patients. Performance of nab-P + G in the locally advanced, neoadjuvant and adjuvant settings is unknown. These data are also lacking for FOLFIRINOX, although a large multinational adjuvant study is currently underway.

**Disclosure**

Dr. Goodwin reports no conflict of interest relevant to this article.

**References**