

## U.S. Food and Drug Administration Approves Paclitaxel Protein-Bound Particles (Abraxane®) in Combination with Gemcitabine as First-Line Treatment of Patients with Metastatic Pancreatic Cancer

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On September 6<sup>th</sup>, 2013, the U.S. Food and Drug Administration (FDA) approved paclitaxel protein-bound particles (albumin-bound) (Abraxane® for injectable suspension, Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Co., Summit, NJ, USA), in combination with gemcitabine for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas based on the MPACT study which demonstrated a clinically meaningful increase in overall survival [1].

The promising results of a phase I/II study led to the performance of this phase III study named MPACT [2]. MPACT was a multi-center, international, open-label, randomized trial that enrolled 861 patients with metastatic pancreatic cancer. Patients were randomized to receive either the combination of Abraxane® plus gemcitabine (n=431) or gemcitabine alone (n=430). Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), performance status, and presence of liver metastasis. The primary endpoint was overall survival (OS) and secondary objectives included progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using Response

Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.0) [3].

The demographic characteristics were well-balanced between the arms. The median age of the patients was 63 years (range: 27-88 years) with 42% aged 65-years or older, 58% were men, and the Karnofsky performance was 90 or 100 in 60%. Nearly half (46%) of the patients had three or more sites of metastatic disease and 84% had liver metastases. The primary lesion was located in the pancreatic head in 43%, the body in 31%, or tail in 25% of patients. The results are summarized in Table 1.

Grade  $\geq 3$  adverse events were more common in the combination arm compared to single agent gemcitabine and included neutropenia (38% vs. 27%), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). However, the grade  $\geq 3$  neuropathy improved to grade 1 or less within 29 days.

The recommended dose and schedule for Abraxane® is 125 mg/m<sup>2</sup> administered as an intravenous infusion over 30-40 minutes on days 1, 8 and 15 of each 28-day cycle until disease progression or if no longer tolerated by the patient. Gemcitabine is administered immediately after Abraxane® on days 1, 8 and 15 of each 28-day cycle. Full prescribing information is available in the FDA web-site [4].

This regimen now offers a new option for first line treatment of advanced pancreatic cancer. *Nab*-paclitaxel has already been approved to treat advanced breast cancer and non-small-cell lung cancer. A non-gemcitabine regimen, FOLFIRINOX (combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) has already emerged recently and adopted by many oncologists

**Keywords** Carcinoma; Drug Therapy; gemcitabine; Neoplasm Metastasis; Pancreas; Pancreatic Neoplasms; Therapeutics

**Abbreviations** FOLFIRINOX: combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; SPARC: secreted protein acidic and rich in cysteine

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**Table 1.** Results of the MPACT study.

Intent-to-treat	<i>Nab</i> -paclitaxel plus gemcitabine (n=431)	Gemcitabine (n=430)	Hazard ratio (95%CI)	P value
<b>Overall survival:</b>				
- Median	8.5 months	6.7 months	0.72 (0.62–0.84)	0.000015
- 1-year	35%	22%		0.000200
- 2-year	9%	4%		0.021234
<b>Median progression-free survival</b>	5.5 months	3.7 months	0.69 (0.58–0.82)	0.000024
- 1-year	16%	9%		0.031876
<b>Overall response rate</b>	99 patients (23%)	31 patients (7%)	3.19 (2.18–4.66)	1.1x10 <sup>-10</sup>

**Table 2.** Summary results of MPACT study and FOLFIRINOX treatment.

Efficacy parameters	<i>Nab</i> -paclitaxel plus gemcitabine	FOLFIRINOX
<b>Median overall survival</b>	8.5 months	11.1 months
<b>Median progression-free survival</b>	5.5 months	6.4 months
<b>Response rate</b>	23%	33%

worldwide [5]. A number of factors influence which drug combination that clinicians will chose in the future. One can question that the median survival with *nab*-paclitaxel plus gemcitabine (8.5 months) is almost three months less than that of FOLFIRINOX (Table 2). However, it is difficult to draw any conclusions since these two regimens were not compared directly in the same trial.

Both studies have well-balanced demographic characteristics and none of those features seem to help us identifying the right patient for an individual regimen. The toxicities are different (Table 3) for these two regimens. Toxicity has been a concern with the 4-drug combination. While the overall survival of patients treated with gemcitabine and Abraxane® does not reach the level seen in patients treated with FOLFIRINOX, the toxicity profile of this combination seems more favorable, especially with respect to neutropenia and fatigue.

Another important factor to consider is the financial burden. The New York Times reported that *nab*-paclitaxel will cost \$6,000 to \$8,000 a month for a pancreatic cancer patients, a cost likely to be more expensive than FOLFIRINOX [6]. On the other hand, FOLFIRINOX is a toxic regimen if given in full doses and requires the patient to wear an infusion pump

**Table 3.** Toxicities associated with *nab*-paclitaxel plus gemcitabine and FOLFIRINOX treatment.

Adverse events (grade ≥3)	<i>Nab</i> -paclitaxel plus gemcitabine	FOLFIRINOX
<b>Fatigue</b>	17%	24%
<b>Diarrhea</b>	6%	13%
<b>Neutropenia</b>	38%	46%
<b>Febrile neutropenia</b>	3%	5%
<b>Peripheral neuropathy<sup>a</sup></b>	17%	9%
<b>Thrombocytopenia</b>	13%	9%

<sup>a</sup> Different type of neuropathy with each regimen

for 5-fluorouracil. It is my expectation that both regimens will be used by the physicians in selected patients and their preferences. FOLFIRINOX may be best used in younger patients younger with a good performance status.

There is a need to identify which patients will ultimately benefit from one of these regimens (Table 4). The correlation between secreted protein acidic and rich in cysteine (SPARC) expression and outcome is pending on MPACT study.

**Conflict of interest** The author has no potential conflicts of interest

**References**

1. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* 2011; 29:4548-54. [PMID 21969517]
2. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; Oct 16. [PMID 24131140]
3. Therasse P, Arbuuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92:205-16. [PMID 10655437]

**Table 4.** Summary.

- IMPACT study showed that gemcitabine plus Abraxane® improves overall survival, progression-free survival and overall response rate
- More toxic vs. gemcitabine
- Quality of life not evaluated
- Cost-effective not assessed
- Secreted protein acidic and rich in cysteine (SPARC) data not presented yet
- Better than gemcitabine but not superior to FOLFIRINOX (No randomized study between these two regimens)
- We need to understand data FOLFIRINOX delays worsening of quality of life
- It is nice to have choices
- Which regimen will you choose for your patients?
- Prospective studies of Abraxane® and gemcitabine in adjuvant, neoadjuvant, and in locally advanced patients with pancreatic cancer are warranted

4. U.S. Food and Drug Administration. FDA approved drug products: Abraxane. Label Information. September 6th, 2013.

5. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic

pancreatic cancer. *N Engl J Med* 2011; 364:1817-25. [PMID 21561347]

6. Pollack A. Drug is shown to help pancreatic cancer cases. *The New York Time* 2013; January 22. (Last accessed on October 26, 2013)

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