

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## Albumin-Bound Nanoparticle Paclitaxel

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### **H&O** What is albumin-bound nanoparticle paclitaxel?

**WG** Albumin-bound nanoparticle paclitaxel (ABI-007; Abraxane, Abraxis) is a novel chemotherapeutic agent that incorporates paclitaxel and nanoparticle technology, enmeshing the drug molecule in albumin. With conventional paclitaxel, the drug is combined with Cremophor (polyoxyethylated castor oil, BASF) in order to enable uptake. However, Cremophor is associated with certain disadvantages. Patients undergoing paclitaxel therapy experience Cremophor-associated neurotoxicity. Also, enhanced microscopic images have shown that Cremophor causes micelle formation, which limits the amount of drug that is taken up by the tumor. The paclitaxel becomes segregated at the location of the micelle and as a result does not penetrate the tumor tissues.

ABI-007 eliminates the need for Cremophor. Interestingly, with conventional paclitaxel, no significant improvement has been observed in association with escalating doses, most likely due to the micelle formation, which makes less of the drug available and therefore prevents any potential benefit that increasing the amount of the drug might have. By contrast, preclinical studies in animal models have found that with ABI-007 more of the drug reaches tumor tissue, suggesting that the antitumor effect might also be increased with this alternative formulation. In addition, while premedication with steroids is required to decrease the hypersensitivity reactions associated with paclitaxel, this premedication is not necessary with the albumin-bound formulation.

### **H&O** Does ABI-007 correlate with any structures in the cell that might account for its ability to access tumor tissues?

**WG** This story is still evolving. Tumor vasculature is generally leaky; it is possible for molecules to pass between endothelial cells. There are albumin receptors, also known as albondin, in tumor vasculature, which facilitate the transport of ABI-007 across the vasculature.

Also, it appears that there is another albumin-binding protein in the interstitium between the vasculature and tumor tissue referred to as SPARC that may also facilitate the transport of the ABI-007 toward the tumor tissue. Thus, it appears that it is not just the bioavailability of ABI-007 that is of relevance; there appear to be other internal aspects related to its activity.

### **H&O** Could you describe the pivotal trial on which approval of this agent was based?

**WG** ABI-007 has been most thoroughly evaluated in breast cancer, and these studies served as the basis for US Food and Drug Administration approval of the agent for second-line treatment of breast cancer. This agent is now being explored in a variety of disease settings. Potential cancers where this agent may be of use include any for which paclitaxel might be effective, including lung, prostate, ovarian, and others. However, data are still limited in these areas. The pivotal trial was in breast cancer, as were the preceding phase I and II dose-finding and safety studies.

The phase III trial compared paclitaxel 175 mg/m<sup>2</sup> every 3 weeks given as a 3-hour infusion versus ABI-007 260 mg/m<sup>2</sup> every 3 weeks given as a 30-minute infusion. Growth factor support was not allowed. The majority of patients enrolled in this trial were from outside the United States, but the results were carefully evaluated by an international contract research organization. According to the study findings, patients who received the albumin-bound formulation had a higher response rate, a longer time to disease progression, and less neutropenia compared to the standard formulation arm. A surprising outcome was a 10% incidence of neuropathy on the experimental arm, compared with 4% on the standard-therapy arm. However, neuropathy that occurs in association with ABI-007

appears to resolve fairly quickly, enabling patients to resume treatment sooner.

### **H&O** What other clinical studies have been conducted?

**WG** Recently, at both the 2004 San Antonio Breast Cancer Symposium and the 2004 Annual Meeting of the American Society of Clinical Oncology (ASCO), data were presented from a phase II clinical trial evaluating weekly schedules of ABI-007. This trial involved patients whose disease had progressed while they were undergoing therapy with paclitaxel, docetaxel, or both, or who had received adjuvant therapy with a taxane shortly before trial enrollment. The vast majority of patients were taxane-refractory, a patient population considered to have a fairly poor prognosis. According to the data presented, a fraction of patients receiving the novel taxane benefited from this therapy. The response rate was low, but the fact that a clinical benefit was observed is certainly of interest.

### **H&O** Is the response time faster with albumin-bound paclitaxel than with standard paclitaxel?

**WG** It is not clear whether the response time is faster; this aspect has not been studied as of yet.

### **H&O** What prompted your cost-effectiveness study presented at the 2004 ASCO meeting, and what were the findings?

**WG** The idea behind this study was to consider all of the ancillary costs related to the use of ABI-007 and standard paclitaxel. As mentioned above, the novel agent does not require premedication. In addition, paclitaxel requires special tubing, which the novel taxane does not. The cost-effectiveness study accounted for the longer infusion time required with paclitaxel, the management of hypersensitivity reactions, if they occur, the comparative rates of neutropenia, and all other ancillary factors in order to create a cost profile. This profile was created before the novel agent was approved, and so drug cost was kept as a neutral factor in the analysis. According to the cost profile calculations, ABI-007 is associated with a cost savings compared with standard paclitaxel.

### **H&O** Might this agent be used as first-line therapy in the future?

**WG** The use of this new taxane will likely evolve over time. Based on data from studies with taxane-refractory patients, it appears that some of these patients will respond. However, this agent might be most effective in patients who are not heavily pretreated with taxanes, and so it might be moved up to first-line therapy in time.

### **H&O** What additional clinical trials of this agent are being planned?

**WG** There are plans to study this agent as first-line therapy compared with standard weekly therapy with paclitaxel. Adjuvant therapy trials are also being considered, although nothing has yet been initiated. There are more questions than answers right now, and all of these questions are likely to be evaluated in clinical trials.

### **H&O** Do you foresee the success with this agent leading to similar drug development with other already available agents?

**WG** Yes. The development of ABI-007 is exciting because it is associated with an improved response rate, time to disease progression, shorter infusion time, no hypersensitivity reactions, and no need for premedication. However, the other significant consideration is that nanoparticle technology is not restricted to paclitaxel. It is likely that this platform will be explored with a range of compounds to see if they are more effectively taken up by tumor cells when wrapped in albumin. No data with other agents are available, but such studies are underway.

### **H&O** Is this agent having an impact on drug development in terms of emphasizing the potential of already existing drugs?

**WG** Yes. The nanoparticle technology delivery system is one example of a way to enhance paclitaxel. Examples with other agents include the development of capecitabine (Xeloda, Roche), an oral 5-fluorouracil (5-FU) agent, which also enables more 5-FU to reach the tumor tissue. Obviously, clinicians are very interested in targeted therapies, but chemotherapy will not become obsolete going forward. Most likely, chemotherapy research will focus on finding ways to improve not only efficacy but also tolerability.

### **Suggested Reading**

O'Shaughnessy J, Tjulandin S, Davidson N, et al. ABI-007 (ABRAXANE), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs taxol in MBC: a phase III trial [abstract]. Presented at: the 26th Annual San Antonio Breast Cancer Symposium; December 3-6, 2003; San Antonio, Tex. Abstract 44.

O'Shaughnessy JA, Blum JL, Sandbach JF, Savin M, Fenske E, Hawkins M. Weekly nanoparticle albumin paclitaxel (Abraxane) results in long-term disease control in patients with taxane-refractory metastatic breast cancer [abstract]. Presented at: the 27th Annual San Antonio Breast Cancer Symposium; December 8-11, 2004; San Antonio, Tex. Abstract 1070.

Desai N, Trieu V, Yao R, Frankel T, Soon-Shiong P. SPARC expression in breast tumors may correlate to increased tumor distribution of nanoparticle albumin-bound paclitaxel (ABI-007) vs taxol [abstract]. Presented at: the 27th Annual San Antonio Breast Cancer Symposium; December 8-11, 2004; San Antonio, Tex. Abstract 206.

Gradishar W, Wolinsky S, Vishalpura T, Nightengale B, Bram T. Cost-effectiveness of nanoparticle albumin-bound (nab) paclitaxel (ABX) vs Cremophor-based paclitaxel (CP) in the treatment of metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol*. 2004;23. Abstract 635.