# *Summary Minutes of the Oncologic Drugs Advisory Committee*
September 7, 2006:

The summary minutes for the September 7, 2006 meeting of the Oncologic Drugs Advisory Committee were approved on September 13, 2006.

I certify that I attended the September 7, 2006 meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

| | |
|---|---|
| /s/ | /s/ |
| Johanna Clifford, M.Sc., RN<br>Executive Secretary, ODAC | Maha Hussain, M.D., Acting Chair, ODAC |

The meeting of the Oncologic Drugs Advisory Committee was held in the Maryland Ballroom, Hilton Washington DC/Silver Spring, Silver Spring, MD. Approximately 75 people were in attendance. The meeting was chaired by Maha Hussain, M.D.

The committee met to discuss new drug application (NDA) 21-660, proposed trade name ABRAXANE ® (paclitaxel protein-bound particles for injectible suspension) (albumin-bound), Abraxis Bioscience, Incorporated, including trial design issues for adjuvant treatment of node-positive breast cancer.

**Attendance:**
**Oncologic Drugs Advisory Committee Members Present (voting):**
Ronald Bukowski, M.D., Maha Hussain, M.D. (Chair), David Harrington, Ph.D., Pamela Haylock, M.D., Alexandra Levine, M.D., Michael Perry, M.D., Maria Rodriguez, M.D.,

**Oncologic Drugs Advisory Committee Consultants (voting):**
John Carpenter, M.D.; Nancy Davidson, M.D.; Natalie Compagni-Portis (patient representative); Michael Link, M.D., Gary Lyman, M.D., MPH; Richard Simon, D.Sc., Sandra Swain, M.D.; Jurgen Venitz, M.D.

**Industry Representative (non-voting):**
Antonio Grillo-Lopez, M.D.

**Oncologic Drugs Advisory Committee Members Absent:**
James Doroshow, M.D., S. Gail Eckhardt, M.D., Joanne Mortimer, M.D.

**FDA Participants:**
Richard Pazdur, M.D., Robert Justice, M.D.; John R. Johnson, M.D.; Patricia Cortazar, M.D.; Brian Booth, M.D.; Rajeshwari Sridhara, Ph.D.

**Open Public Hearing Participants:**
Terri F. Jones, RN, BSN, OCN, Nurse Manager, Montgomery Cancer Center-East
Carolina Hinestrosa, Executive Vice President of Programs Planning, National Breast Cancer Coalition
Helen Schiff, M.L.S., B.A.

The agenda proceeded as follows:

| | |
|---|---|
| **Sponsor Presentation** | **Pfizer, Inc** |
| Abraxane®: Background & PK/Safety Comparisons with Taxol® | Michael J. Hawkins, M.D.<br>Chief Medical Officer |
| Results of the Phase 3 Clinical Trials of Abraxane® vs. Taxol® in Metastatic Breast Cancer | William J. Gradishar, M.D., F.A.C.P.<br>Professor of Medicine<br>Northwestern University |
| Perspectives on the use of Abraxane® in Node-Positive Breast Cancer | Clifford A. Hudis, M.D.<br>Chief, Breast Cancer Medicine Service<br>Memorial Sloan Cancer Center |
| **FDA Presentation** | **NDA 21-986** |
| Proposal for Abraxane Use in Adjuvant Breast Cancer | Patricia Cortazar, M.D., Medical Officer<br>Division of Drug Oncology Products<br>OODP,CDER, FDA |

| | |
|---|---|
| A Pharmacokinetic Comparison of Abraxane vs. Taxol® | Brian Booth, Ph.D., Clinical Phamacology Acting Team Leader for Oncology Drugs, Division of Clinical Pharmacology 5, Office Of Clinical Pharmacology, CDER, FDA |
| Trial Design Considerations | Rajeshwari Sridhara, Ph.D., Statistical Team Leader for Oncology Drug Products, Division of Biometrics V, Office of Biostatistics, CDER, FDA |

Open Public Hearing

*Questions to the Committee*

***MEETING QUESTIONS***

**Proposed Development Plan for a New Indication:** ABRAXANE® is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.

**Company:** Abraxis BioScience

**Original Approval:** January 7, 2005

**Approved Indication:** ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

**Abraxis BioScience Proposal:** Although adjuvant breast cancer indications have been supported by large randomized trials adequately characterizing the safety and efficacy of a new drug in the adjuvant population, Abraxis BioScience is requesting approval of Abraxane for the above indication without performing a randomized efficacy trial.

The Abraxis BioScience plan relies upon Section 505(b)(2) of the Food, Drug and Cosmetic Act. This section of the Act allows the FDA, **where appropriate**, to base approvals of new drugs entirely or partially on studies not conducted by the applicant and for which the applicant has not obtained a right of use. Approval under Section 505(b)(2) is requested because Abraxane and Taxol are both paclitaxel formulations. Clinical studies with Taxol might be used as the basis (either partially or completely) for Abraxane approval. Their request includes the following components. Items 1 and 2 below are the 505(b)(2) components. The remaining items are studies that have been or will be conducted by Abraxis BioScience.

1) Results of the randomized INTERGROUP study that was the basis for Taxol approval for adjuvant treatment of node-positive early breast cancer.

2) Taxol's preclinical genetic toxicology studies.

3) A comparison of the pharmacokinetics of the Abraxane and Taxol paclitaxel formulations.

4) Results of a study comparing Abraxane and Taxol in advanced metastatic breast cancer that served as the clinical trial supporting the 2005 approval of Abraxane's metastatic breast cancer indication.

5) A 400 patient randomized safety study comparing Abraxane to Taxol in the adjuvant treatment of node-positive early breast cancer was initially proposed. This proposal has recently been changed to a post-approval study of unspecified size.

6) A 30-patient, single arm safety study (CA030), using a different schedule than the proposed indication: Adriamycin plus Cytoxan every 2 weeks for 4 cycles followed by Abraxane 260 mg/m$^2$ every 2 weeks for 4 cycles.

***Background***

1) The pharmacokinetics of Abraxane and Taxol are different. More importantly, the pharmacokinetic studies have measured **total** paclitaxel (free + bound), while **free** or unbound paclitaxel is believed to mediate drug effect. Information comparing free paclitaxel concentrations from Abraxane and Taxol is not available. In addition, information on the comparative biodistributions of Abraxane and Taxol is not available.

2) Abraxane does not contain Cremophor. Therefore, Abraxane administration does not require the specialized intravenous tubing required for Cremophor-containing products.

3) Abraxane is given as a 30 minute infusion at a dose of 260 mg/m$^2$ without premedication. Taxol is administered as a 3-hour infusion at a dose of 175 mg/m$^2$ and requires premedication.

4) In the randomized trial that was the basis for approval of Abraxane for treatment of advanced metastatic breast cancer, Abraxane had an improved tumor response rate compared to Taxol (21.5% versus 11.1%). Abraxane had more neurotoxicity, nausea, vomiting, diarrhea and asthenia, while Taxol had more hypersensitivity reactions and neutropenia; however, no differences in infections or febrile neutropenia were observed. The different toxicity profiles and tumor response rates indicate Abraxane and Taxol are different drugs.

5) In the INTERGROUP trial that was the basis for Taxol approval for adjuvant treatment of node-positive breast cancer, Taxol resulted in better disease-free survival (22% reduction in the risk of disease recurrence) and better overall survival (26% reduction in the risk of death).

***Questions for the Committee*:**

The question is whether Abraxane should be approved for adjuvant treatment of node-positive early breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy *without a randomized controlled trial showing Abraxane's efficacy and safety in this setting.* In the adjuvant setting cure is achievable. Thus, the FDA is concerned with *any* decrease in efficacy in this setting. In addition, a *comparative* safety evaluation in the adjuvant setting has not been performed and the FDA is concerned with the extrapolation of safety data from the metastatic disease setting to the adjuvant setting.

1) DISCUSS: The FDA believes that *any* potential risk should be offset by a well characterized and clinically meaningful benefit. Does the current information on Abraxane without a well designed trial examining both comparative efficacy and safety provide adequate information and justification for use in the adjuvant setting?

*The committee felt that the evidence provided did not provide adequate information of safety and assured efficacy and felt that abraxane did warrant further study in the adjuvant setting. Specifically, the committee had concerns with dose-related toxicities of neutropenia and neuropathy and the lack of data showing the advantage of Abraxane® over Taxol®.*

2) VOTE: The Sponsor has proposed a development plan that would rely on safety and efficacy data derived from Abraxane's approved metastatic indication and Taxol's known effect in the adjuvant setting to obtain marketing authorization for the above adjuvant indication. The sponsor does not plan to conduct a randomized trial of sufficient size to compare Taxol and Abraxane's efficacy and safety in the adjuvant treatment of node-positive breast cancer.

**Should the Sponsor conduct an adequate and well controlled randomized trial of sufficient size to characterize Abraxane's efficacy and safety in the adjuvant setting?**

***Yes = 13*** ***No = 1***

*The committee was not satisified with the safety or efficacy of Abraxane based on the current information and agreed that the sponsor should conduct a trial comensurate with other trials being performed in the adjuvant setting looking at efficacy and safety.*

3) DISCUSS: If the answer to question #2 is yes, please discuss potential designs of adjuvant trials. Please note that efficacy can be demonstrated either in superiority or non-inferiority trials. In general, superiority trials produce new standards of treatment. Non-inferiority trials are indirect measures of efficacy and must preserve a percent (percent retention) of a known treatment effect of the standard drug (Taxol). The lower the required percentage retention of the effect, the smaller the trial size; however, the greater the potential loss of efficacy.

*The committee suggested that additional evidence of efficacy can be obtained using the following designs as potential alteratives:*

- *Using a high risk population of patients, e.g.hormone receptor negative patients or Stage III patients.;*
- *Conducting a supportive trial in the neoadjuvant setting, examining tumor levels of paclitaxel.*
- *Aligning with a cooperative group already using Taxol ® in the adjuvant setting and perform a subrandomization to those patients receiving taxol.*

The meeting adjourned by 12:00 noon.