Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE CDER PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

October 20, 2005

Members Present
Gregory Reaman, M.D. (Committee Chair)
Pamela Haylock, R.N.

Consultants to the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

Victor Santana, M.D.	Charles Reynolds, M.D.	James Boyett, Ph.D.
Jerry Finklestein, M.D.	Michael Link, M.D.	Malcolm Smith, M.D., Ph.D.
Clinton Stewart, Ph.D.	Jeffrey Barrett, Ph.D.	Cindy Schwartz, M.D.
Naomi Winick, M.D.		

Federal Government Employee Consultant
Anne Zajicek, M.D.

FDA Participants

Karen Weiss, M.D.	Ramzi Dagher, M.D.	Rick Pazdur, M.D.
Robert Justice, M.D.	Marty Cohen, M.D.	Joe Gootenberg, M.D.
Jeff Summers, M.D.	Lisa Mathis, M.D.	Patricia Keegan, M.D.

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Patient Representatives
Cathy O'Connell
Marilyn Eichner

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Industry Representative
Eugene Sun, M.D.

Executive Secretary
Victoria Ferretti-Aceto, Pharm.D.

These summary minutes for the October 20, 2005 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee were approved on October 28, 2005.

I certify that I attended the October 20, 2005 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, and that these minutes accurately reflect what transpired.

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Victoria Ferretti-Aceto, Pharm.D.	Gregory Reaman, M.D.
Executive Secretary	Chair

The Committee had received a briefing document from the FDA. There were 90 persons in attendance. There was one speaker for the Open Public Hearing sessions. The meeting was called to order at 8:05 a.m. by the Chair, Gregory Reaman, M.D. The subcommittee members and discussants introduced themselves. Victoria Ferretti-Aceto, Executive Secretary of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee read the Meeting Statement. A welcome was provided by Karen Weiss, M.D., Deputy Director, Division of Oncology Drug Products.

Open Public Hearing Speaker:
Sadhana Dhruvakumar

Issues:
During the morning session, the Subcommittee listened to a presentation on the structure and function of the Office of Oncology Drug Products in CDER and considered issues involved with the conduct of post-marketing studies for products approved for oncologic indications. Products discussed included Clolar™ (clofaribine), Neulasta® (pegfilgrastim), Kepivance® (palifermin). The afternoon session included a review of the status of studies for specific off-patent drugs for pediatric oncology, and consideration of other off-patent oncology drugs for which pediatric studies are needed, as mandated by the Best Pharmaceuticals for Children Act (BPCA).

FDA Presentation	
Opening Remarks	**Karen Weiss, M.D.** Deputy Director, Office of Oncology Drug Products
Introduction of CDER's Office of Oncology Drug Products	**Richard Pazdur, M.D.** Director, Office of Oncology Drug Products
Clolar™ (Clofaribine)	**Martin Cohen, M.D.** Medical Officer, Division of Drug Oncology Products
Sponsor Presentation	
Genzyme Corporation	**Rekha Abichandani, M.D.** Medical Director, Clinical Research, Genzyme Corporation
FDA Presentation	
Pediatric Drug Development Initiatives	**Lisa Mathis, M.D.** Acting Director, Division of Pediatric Drug Development, Office of Counterterrorism and Pediatrics

Neulasta® (pegfilgrastim)	**Jeff Summers, M.D.** Medical Officer, Division of Biologic Oncology Products
Sponsor Presentation Amgen, Inc.	**Lyndah Dreiling, M.D.** Director, Clinical Development, Amgen, Inc.
FDA Presentation Kepivance™ (palifermin)	**Joseph Gootenberg, M.D.** Medical Team Leader, Division of Biologic Oncology Products
Sponsor Presentation Amgen Presentation	**Dietmar Berger, M.D., Ph.D.** Director, Clinical Development, Amgen, Inc.
FDA Presentation The Best Pharmaceuticals for Children Act (BPCA)	**Anne Zajicek, M.D., Pharm.D.** Pediatric Medical Officer, National Institute of Child Health and Human Development, NIH
Actinomycin-D/Vincristine in Pediatric Oncology Trials	**Jeffery Barrett, Ph.D., FCP** Division of Clinical Pharmacology & Therapeutics, The Children's Hospital of Philadelphia
Future Subcommittee Topics	**Karen Weiss, M.D.**

Questions for the Subcommittee

Regarding required postmarketing studies as a condition of accelerated approval for clofarabine:

1. Are the proposed patient populations (ALL, first or second relapse) and primary efficacy endpoint (4 month EFS) feasible and will the design permit an adequate assessment of clofarabine's clinical benefit?

   The subcommittee consensus was that the proposed patient populations and primary efficacy endpoints do not permit an adequate assessment of clofaribine's clinical benefit. Suggestions included focusing on first relapse patients and evaluating them in the context of known active agents in a controlled setting. It

was also suggested that remission induction rate and/or MRD be considered as potential primary endpoint(s).

2. To what extent can the data generated in adult patients with relapsed/refractory AML support efficacy in pediatric patients with ALL?

   The Subcommittee expressed the opinion that using adult AML data to support efficacy of clofaribine in pediatric ALL patients does not seem plausible based on what is known about the differing biology of AML and ALL. More evidence would be required to prove that there is enough correlation between these 2 diseases that would allow generalization or extrapolation from one disease to the other. Suggestions include looking closely at the 2 populations and assessing for portability of data from one population to the other.

Regarding pegfilgrastim postmarketing requirements under PREA:

3. Please comment on Amgen's ongoing study in patients with sarcoma treated with VAdriac/IE. Will this study allow for extrapolation of activity and safety findings across all age groups and to different pediatric cancers?

   Comments by the Subcommittee centered around the difficulty of enrolling this population of patients in these studies, particularly those in the younger age group. Difficulty in administering filgrastim (especially to younger patients) in a randomized setting and the issue of competition with other studies were brought up as factors contributing to low enrollment in these studies. The largest population of children treated with a similar chemotherapy regimen were required to receive protocol described growth factor. Earlier communication may have prevented the problem of slow accrual. Among the suggestions made were for patients to serve as their own controls, to randomize for the first cycle, to consider studies in patients with rhabdomyosarcoma and neuroblastoma to assure broader age range of study subjects.

Regarding palifermin postmarketing requirements under PREA:

4. Please comment on the suitability and feasibility of the proposed pediatric program; specifically: need for dose escalation, need for collection of pharmacokinetic data, choice of patient population (homogenous vs heterogeneous with regard to underlying disease, source of stem cells, cytotoxic regimen, etc.).

The general perception of the Subcommittee was that there is great need for data to be collected from pediatric populations. They suggested decreasing the number of doses tested in the dose escalation portion and to consider evaluating other schedules. The committee suggested that a study in patients with acute leukemia receiving allogeneic transplantation would be useful and feasible to conduct. The committee saw no reason not to combine autologous and allogeneic transplant recipients for study.
Adult pharmacokinetic (PK) data ideally should be used as a guideline to determine when and how to sample and should only serve as a framework for pediatric dosing. Very long follow up would be needed to assess concerns about tumor induction.

Regarding ongoing studies of vincristine/actinomycin-D

5. Please comment on the approach to the generation of safety/efficacy and pharmacokinetic information on vincristine and actinomycin-D. Does the subcommittee have suggestions about additional data that should be collected?

The Subcommittee made several comments and posed several questions for general consideration:

●*Could the frequency of toxicity be minimized with a dose cap? Might dose capping cause underdosing and subsequent lack of efficacy (esp in older children).*

●*Could mathematical models be used for dose finding?*

Regarding vincristine, the difficulty of quantifying toxicity and the pitfalls to using peripheral neuropathy given the lack of standard assessment measures and scoring system as a measure of toxicity were highlighted. The issue of whether tests should be required for measuring or whether it should simply be monitored was brought up.

Regarding the off-patent BPCA process:

6. Please discuss additional off-patent drugs (and/or therapeutic drug classes) used in pediatric patients with malignancies for which additional data in labeling could provide health benefits.

The Subcommittee expressed a need for dosage adjustment guidelines for numerous off-patent drugs, specifically in obese children (for example, corticosteroids, in addition to anthracyclines). Additionally, suggestions by which methods of administration might make certain drugs less toxic (such as less frequent dosing intervals) would be helpful . Other topics include: the need to focus on dose optimization by using more systematic methods, patient specific pharmacogenomics-based methods, tools to measure early toxicity so that interventions can take place before serious toxicity develops, arbitrary age groups (for example, they suggested studies focused on patients in the two age ranges of 0-1 month and 1-3month) during the first year of life, then 1 – 5 and 5 - 10.

The following suggestions were also made:

- *Issues in pain control, including symptom management in neonates*
- *Drug delivery systems*
- *Long term sequelae*
- *Orphan drug indications*
- *End of life care/palliative care, pain control*
- *Indications that are waived from the requirement for conducting pediatric studies*
- *Therapies that do not result in tumor shrinkage – role of stable disease*
- *Endpoints for pediatric cancer*
- *Pre-clinical predictors of clinical outcomes*
- *Re-formulations, rounding off errors*
- *Look at past 7 years; have there been any changes in getting drugs into pediatric cancer patients earlier?*