Food and Drug Administration  
Center for Drug Evaluation and Research  

Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs  
Advisory Committee Meeting  
December 11, 2014  

Location:  FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland  

Topic:  Information was presented to gauge investigator interest in exploring potential pediatric development plans for three products in various stages of development for adult cancer indications. The subcommittee considered and discussed issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use. The discussion also provided information to the Agency pertinent to the formulation of written requests for pediatric studies. The products under consideration were: (1) GANETESPIB, application submitted by Synta Pharmaceuticals Corp. (2) Etririnotecan, application submitted by Nektar Therapeutics, and (3) RO5503781, application submitted by Hoffmann-La Roche, Inc.  

These summary minutes for the December 11, 2014, meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on March 3, 2015.  

I certify that I attended the December 11, 2014, meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.  

/S/  
Caleb D. Briggs, PharmD  
Designated Federal Officer, ODAC  

/S/  
Alberto Pappo, MD  
Acting Chairperson, pedsODAC
Summary Minutes of the Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee  
December 11, 2014

The following is the final report of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) meeting held on December 11, 2014. A verbatim transcript will be available in approximately six weeks, sent to the Office of Hematology and Oncology Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm394134.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 11, 2014 from 8 a.m. to 3:30 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503, Section A), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA, and the Sponsors. The meeting was called to order by Alberto Pappo, MD, (Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Designated Federal Officer). There were approximately 50 people in attendance. There were no Open Public Hearing speakers.

**Issue:** Information was presented to gauge investigator interest in exploring potential pediatric development plans for three products in various stages of development for adult cancer indications. The subcommittee considered and discussed issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use. The discussion also provided information to the Agency pertinent to the formulation of written requests for pediatric studies. The products under consideration were: (1) GANETESPIB, application submitted by Synta Pharmaceuticals Corp. (2) Etitinotecan, application submitted by Nektar Therapeutics, and (3) RO5503781, application submitted by Hoffmann-La Roche, Inc.

**Attendance:**

**ODAC Members Present (Voting):** Jane Zones, PhD (Consumer Representative) (Sessions 1 and 2 only)

**ODAC Members Present (Non-Voting):**  
Howard Fingert, MD, FACP (Industry Representative)

**ODAC Members Not Present (Voting):** Deborah K. Armstrong, MD; Harold J. Burstein, MD, PhD; Aman Buzdar, MD; Bernard F. Cole, PhD; Louis F. Diehl, MD; Tito Fojo, MD, PhD; James Liebmann, MD; Michael Menefee, MD; Bruce J. Roth, MD

**Temporary Members (Voting):** Carola Arndt, MD (Sessions 1 and 2 only); Ira Dunkel, MD (Sessions 1 and 2 only); Julia Glade Bender, MD (Sessions 1 and 2 only); Nancy Goodman (Patient Representative); Richard Gorlick, MD (via phone); Beverly Lange, MD (Sessions 1 and 3 only); Leo Mascarenhas, MD, MS (Session 1 only); Kathleen Neville, MD; Alberto Pappo, MD (Acting Chairperson); Carlos Rodriguez-Galindo, MD; Malcolm Smith, MD, PhD (Session 1 and 2 only)
FDA Participants (Non-Voting): Richard Pazdur, MD; Gregory Reaman, MD; Leigh Marcus, MD (Session 1 only); Amy Barone, MD (Session 2 only); Denise Casey, MD (Session 3 only)

Designated Federal Officer (Non-Voting): Caleb Briggs, PharmD

Open Public Hearing Speakers: None

The agenda proceeded as follows:

Call to Order and Introduction of Committee

Alberto Pappo, MD
Acting Chairperson, Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (PedsODAC)

Conflict of Interest Statement

Caleb Briggs, PharmD
Designated Federal Officer, ODAC

FDA Introductory Remarks

Gregory Reaman, MD
Associate Director for Oncology Sciences Division of Hematology Products (DHP) Office of Hematology and Oncology Products (OHOP) Office of New Drugs (OND), CDER, FDA

SESSION 1: GANETESPIB - SYNTA PHARMACEUTICALS CORP.

SPONSOR PRESENTATIONS

Synta Pharmaceuticals Corp.

Ganetespib and Hsp90 Inhibition
Vojo Vukovic, MD, PhD
Chief Medical Officer
Synta Pharmaceuticals Corp.

SARC 023 Study
AeRang Kim, MD, PhD
Assistant Professor of Pediatrics
The George Washington School of Medicine

Clarifying Questions from Subcommittee

Questions to the Subcommittee and Subcommittee Discussion

SESSION 2: ETIRINOTECAN PEGOL - NEKTAR THERAPEUTICS

Conflict of Interest Statement
Caleb Briggs, PharmD

Announcement of Change to Participants
Alberto Pappo, MD
**Sponsor Presentations**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nektar Therapeutics</td>
<td>Etirinotecan Pegol: Nonclinical Pharmacology, Pharmacokinetics and Clinical Review</td>
</tr>
<tr>
<td>Carlo Di Fonzo, PhD</td>
<td>Vice President Drug Development and Regulatory Affairs</td>
</tr>
<tr>
<td></td>
<td>Nektar Therapeutics</td>
</tr>
<tr>
<td>Alison Hannah, MD</td>
<td>Consultant</td>
</tr>
<tr>
<td></td>
<td>Nektar Therapeutics</td>
</tr>
</tbody>
</table>

Clarifying Questions from Subcommittee

Questions to the Subcommittee and Subcommittee Discussion

**Session 3: RO5503781 – Hoffman-La Roche, Inc.**

**Conflict of Interest Statement**

Caleb Briggs, PharmD

**Announcement of Change to Participants**

Alberto Pappo, MD

**Sponsor Presentation**

Hoffman-La Roche, Inc.

The MDM2 Antagonist RO5503781

Gwen Nichols, MD

Site Head, Translational Medicine Oncology
Roche Pharmaceutical Research and Early Development

Clarifying Questions from Subcommittee

Open Public Hearing

Questions to the Subcommittee and Subcommittee Discussion

Questions to the Committee:

---

**Session 1: GANETESPIB**

**Sponsor:** Synta Pharmaceuticals Corp.

1. **Discussion:** Does the panel consider ganetespib a viable drug candidate for further study in pediatric patients? Please comment on the specific diseases where ganetespib would be of interest to the investigator community.

**Committee Discussion:** Members of the subcommittee generally agreed that ganetespib is a viable drug candidate for further study in pediatric patients. There was interest in seeing more clinical data in patients with neuroblastoma, tumors that are driven by mutations in anaplastic lymphoma kinase (ALK),
and sarcomas - notably Ewing’s and acute myeloid leukemia (AML). Some members of the subcommittee also stated that it would be worthy to gather more pre-clinical data in larger subsets of pediatric populations in order to potentially inform other specific diseases for research.

2. DISCUSSION: Please comment on potential study designs, including combinations of drugs, for clinical trials evaluating ganetespib.

Committee Discussion: Members of the subcommittee agreed that ganetespib would need to be cautiously studied in combination with other agents to be able to determine additive, synergistic or clinical activity. Members of the subcommittee stated that strong evidence would need to be produced for clinical activity of ganetespib as monotherapy in phase 1 clinical trials. Once the activity of ganetespib as a single agent was established from robust phase 1 clinical studies, other agents could be added to ganetespib to evaluate the tolerability and effectiveness of combination therapies. Some members commented that historical control regimens may be necessary as comparators to ganetespib combination therapy regimens, while others noted that using historical controls maybe difficult due to the current salvage approach in these diseases. Specific endpoints suggested by subcommittee members for study included objective response, tumor regression, time to progression, and overall survival, depending on the type of study and population to be investigated.

3. DISCUSSION: Please comment on any concerns relating to the use of ganetespib in pediatric patients given the current levels of excipients PEG-300, polysorbate 80, and alcohol.

Committee Discussion: The subcommittee agreed that there is always a concern for levels of excipients, especially in very young patients. Subcommittee members did not describe particular concern with the levels of excipients in ganetespib, given the alternative of death due to disease. The subcommittee agreed that, if ganetespib showed substantive effect in pediatric populations, that they would urge the sponsor to find and study more appropriate pediatric formulations along with their pharmacokinetics, and toxicities.

Session 2: ETIRINOTECAN PEGOL

SPONSOR: Nektar Therapeutics

1. DISCUSSION: Does the panel consider etirinotecan pegol a good candidate for study in pediatric patients with solid tumors?

Committee Discussion: The subcommittee agreed that etirinotecan pegol was a good candidate for study in pediatric patients with solid tumors.

2. DISCUSSION: Please comment on potential study designs for development of etirinotecan pegol in pediatric cancers, including specific pediatric solid tumors (e.g. neuroblastoma, bone tumors, etc.).

Committee Discussion: The subcommittee agreed that etirinotecan pegol is a good candidate for study in pediatric patients with solid tumors. Specific tumors that were described by subcommittee members as possibilities for study include relapsed neuroblastomas, Ewing’s sarcoma, rhabomyosarcomas, brain tumors and liver tumors. Subcommittee members stated that prospective combination therapy studies would be the preferred type of trial design in relapsed or front line observation. Some of the
subcommittee members also mentioned that patient reported or health economic outcomes were important to include as study endpoints. Other subcommittee members noted that robust pharmacokinetic data would need to be gathered as well in these studies due to our current dearth of evidence in the pediatric population. They also noted that, due to the long half-life of the pegylated etirinotecan, the current administration protocols for therapy would need to be altered to account for delayed metabolism.

3. DISCUSSION: Dosing irinotecan in children is often limited by severe diarrhea which may have an impact on efficacy. Please comment on the expected toxicities of etirinotecan pegol compared to irinotecan, and mitigation strategies.

Committee Discussion: The subcommittee noted that diarrheal toxicity might be lower with etirinotecan pegol compared to irinotecan due to the altered metabolism. Members of the subcommittee commented that they would suggest mitigating or treating the diarrhea with what is currently standard in the use irinotecan, which is antibiotics and loperamide. One committee member did note that, due to the longer half-life of etirinotecan pegol compared to irinotecan, the potential administration protocols might need to be prolonged to account for the delayed metabolism.

4. DISCUSSION: Please comment on the potential for combination of etirinotecan pegol with other agents in the pediatric population.

Committee Discussion: The subcommittee described enthusiasm about novel combinations with the use of etirinotecan pegol and currently used therapies. Potential combination agents specifically mentioned by subcommittee members include poly ADP ribose polymerase (PARP) inhibitors, temozolomide, pegylated interferon, temsirolimus, or topoisomerase-1 inhibitors. Subcommittee members explained that the selection of combination agents would ultimately depend on the groups designing the trails and what specific diseases were going to be studied. One subcommittee member reiterated that etirinotecan pegol has a longer half-life and this would also need to be accounted for in combination therapies with regard to administration protocols.

Session 3: RO5503781

SPONSOR: Hoffman-La Roche, Inc.

1. DISCUSSION: Given the available data from nonclinical and adult studies of RO5503781, does the panel consider the current pediatric development plan appropriate to address the unmet medical need of pediatric patients with acute leukemias and solid tumors?

Committee Discussion: The subcommittee agreed that there was promising data with AML patients given the current lack of effective therapies in that patient population. The subcommittee also discussed that it was currently unclear which solid tumors populations would benefit from RO5503781 and robust trials would be needed to inform that determination.

2. DISCUSSION: Pre-clinical data generated with MDM2 antagonists, including RO5503781, suggests that this product may be effective in the treatment of some pediatric cancers. Does the panel have any suggestions for how appropriate subpopulations in pediatric patients may be selected?
Committee Discussion: The subcommittee agreed that different solid tumors would need to be studied separately and one could not include all solid tumor types into one trial. Members of the subcommittee further stated that patients included in trials would have to have an intact p53 tumor suppressor gene.

3. DISCUSSION: Please comment on any theoretic concerns regarding normal growth and development in younger children with the use of RO5503781.

Committee Discussion: The subcommittee agreed that there were concerns with risks for normal growth in pediatric patients with the use of any agent. They agreed and stressed to the sponsor that long term monitoring would be critical to evaluate potential disruptions to normal growth and development. Some subcommittee members stated that there is potential concern for late secondary malignancies and hematologic toxicities with the use of the agent and wondered if using this agent could select for p53 mutant clones.

4. DISCUSSION: Given the "on target" cytopenias, does the panel have any suggestions for how best to develop combination strategies that insure patient safety; particularly in pediatric tumors where treatment also causes marrow suppression?

Committee Discussion: Some subcommittee members noted that one has to determine the risk benefit with the use of agents and know the overall efficacy to determine the risk-benefit profile. One member of the subcommittee stated that there are potential strategies for mitigating cytotoxicity if an agent demonstrates overwhelming efficacy in a given area of treatment. This member further stated that strategies to overcome toxicity would need to be determined after the signals are determined for efficacy with use of the agent.

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 3:00 p.m.