



The Oncologic Drugs Advisory Committee (ODAC) of the Center for Drug Evaluation and Research met on May 2, 2013 from 8 a.m. to 12 noon at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and the Sponsor, AVEO Pharmaceuticals, Inc. The meeting was called to order by Mikkael Sekeres, MD, MS (Committee Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Designated Federal Officer). There were approximately 120 persons in attendance. There were nine (9) speakers for the Open Public Hearing session.

Issue: During the morning session, the committee met to discuss new drug application (NDA) 204408, with the established name tivozanib capsules, submitted by AVEO Pharmaceuticals, Inc. The proposed indication (use) for this product is for the treatment of advanced renal (kidney) cell carcinoma.

Attendance:

**Oncologic Drugs Advisory Committee Members Present (Voting):**

Deborah K. Armstrong, MD, Frank Balis, MD, Aman Buzdar, MD, FACP, Louis Diehl, MD, Tito Fojo, MD, PhD, James Liebmann, MD, Brent Logan, PhD, Michael Menefee, MD, Mikkael Sekeres, MD, MS (Chairperson), David Steensma, MD, Jane Zones, Ph.D. (Consumer Representative)

**Temporary Members Present (Voting):**

Lori Dodd, PhD, Marc Garnick, MD, Dan Lumley, EdD (Patient Representative)

**Oncologic Drugs Advisory Committee Member Present (Non-Voting):**

Howard Fingert, MD, FACP (Industry Representative)

**FDA Participants (Non-Voting):**

Richard Pazdur, M.D., Amna Ibrahim, MD, V. Ellen Maher, MD, Jonathan Jarow, MD, J. Dawn Arrington, MD

**Oncologic Drugs Advisory Committee Members Not Present:**

Julie M. Vose, MD, Antoinette J. Wozniak, MD, FACP

**Designated Federal Officer:**

Caleb Briggs, PharmD

**Open Public Hearing Speakers:**

Holly Johnston

Jennifer Yttri, PhD – Cancer Prevention and Treatment Fund

Sheila Hewitt

Trish Creel, RN, OCN, CCRP – Duke University Medical Center

Lori Andrews, RN – Baylor Sammons Cancer Center

Dena Battle

Richard Bruno

Christopher Battle

Jim Kaya

**The agenda was as follows:**

Call to Order Introduction of Committee	<b>Mikkael Sekeres, MD, MS</b> Chairperson, Oncologic Drugs Advisory Committee (ODAC)
Conflict of Interest Statement	<b>Caleb Briggs, PharmD</b> Designated Federal Officer, ODAC
Opening Remarks	<b>Amna Ibrahim, MD</b> Deputy Director, Division of Oncology Products 1 (DOP1), Office of Hematology and Oncology Products (OHOP), Office of New Drugs (OND), CDER, FDA
<b><u>Sponsor Presentation</u></b> Introduction	<b><u>AVEO Pharmaceuticals, Inc.</u></b> <b>William Slichenmyer, MD</b> Chief Medical Officer AVEO Oncology
Background on Renal Cell Carcinoma and Unmet Need	<b>Daniel George, MD</b> Associate Professor of Medicine Division of Medical Oncology; Division of Urology Duke University Medical Center
Efficacy and Safety	<b>Anna Berkenblit, MD</b> Vice President, Clinical Development AVEO Oncology
Clinical Interpretation & Benefit-Risk	<b>Robert Motzer, MD</b> Professor of Medicine Attending Physician Memorial Sloan-Kettering Cancer Center, NY Weil College of Medicine, Cornell University, NY
<b><u>FDA Presentation</u></b> NDA 204408 tivozanib capsules	<b>Jonathan Jarow, MD</b> Medical Officer DOP1, OHOP, OND, CDER, FDA
	<b>J. Dawn Arrington, MD</b> Medical Officer DOP1, OHOP, OND, CDER, FDA
Clarifying Questions from Committee	

Open Public Hearing

Questions to the Committee and Committee Discussion

Adjournment of morning session

**Question to the Committee:**

**NDA 204408  
tivozanib capsules**

**APPLICANT: AVEO Pharmaceuticals, Inc.**

**PROPOSED INDICATION:** For the treatment of advanced renal (kidney) cell carcinoma

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The Applicant conducted a single randomized trial in which patients with metastatic renal cell carcinoma were randomly allocated to tivozanib (N = 260) or sorafenib (N = 257). The analysis of PFS (Progression-Free Survival), the primary endpoint, showed a statistically significant improvement with tivozanib [hazard ratio = 0.80, p = 0.04]. The analysis of overall survival showed a trend towards a detrimental effect on survival with tivozanib [hazard ratio = 1.25, p = 0.11].

Although, the trial achieved its primary endpoint of progression-free survival, the analysis of overall survival demonstrated a potential 25% increase in the risk of death with tivozanib. The safety profile of tivozanib was consistent with that of other vascular endothelial growth factor inhibitors. The incidence of hypertension and dysphonia was higher on the tivozanib arm, where as the incidence of diarrhea and plantar-palmar dysesthesia was greater on the sorafenib arm. There are multiple drugs approved for the treatment of patients with renal cell cancer.

**VOTE:** Has the Applicant demonstrated a favorable benefit to risk evaluation for the treatment of renal cell carcinoma in an adequate and well-controlled trial?

**YES: 1**

**NO: 13**

**ABSTAIN: 0**

*During discussion, many committee members expressed a lack of confidence in the benefit to risk evaluation, citing the observed negative trend in overall survival as a significant source of concern. Members described difficulty with assessing data as a whole due to confounding aspects of the trial, including a unilateral crossover of patients to the sorafenib arm for post-study treatment. One committee member summarized the study results as demonstrating a questionable improvement in progression-free survival with no demonstrated impact on quality of life and no demonstrated improvement in overall survival, with that impact possibly being negative.*

*Some committee members acknowledged that tivozanib may have potential but criticized the design of the trial, citing the imbalance and unilateral crossover in post-study treatments as a significant barrier to interpreting the overall survival results of the trial. A committee member expressed that any drug approval which is based on progression-free survival should require a clear lack of*

*ambiguity in the other aspects of the trial, which was not demonstrated in this case. Several committee members expressed caution in generalizing the results of the trial to the United States, because enrollment from U.S. was low. Concern was expressed with the ethics of this one-way crossover design, based on limited access in other countries to the effective agents. The choice of sorafenib as a comparator in trials for first-line treatment of patients with advanced renal cell cancer was also questioned because sorafenib is not routinely used in the first line setting in the U.S. In addition, one member discussed uncertainty regarding the magnitude of the progression-free survival effect due to dose reductions on the sorafenib arm to what may be considered an ineffective dose. Another committee member questioned the limited exposure data in African-American patients, describing these patients as having unique needs in the areas of kidney cancer and hypertension.*

*Committee members who voted “no” cited uncertainty with the results from the phase 3 trial and lack of confidence in the safety of tivozanib. Several committee members summarized their consideration of benefit to risk in terms of how they would describe the product to a patient with renal cell carcinoma if it were approved. These members stated that it would be difficult to recommend to a patient a treatment option that may shorten their survival, particularly when multiple other therapies were available. Some committee members expressed that more treatment options continue to be needed in this area, but that the results of this phase 3 trial did not elucidate an impact that included more good than harm.*

*The committee member who voted “yes” briefly cited the differing side effect profile of tivozanib as having been persuasive.*

(Please see official transcript for details.)

Morning session adjourned at approximately 12 noon.

===== Lunch Break =====

The Oncologic Drugs Advisory Committee (ODAC) of the Center for Drug Evaluation and Research met on May 2, 2013 from 1 p.m. to 5 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and the Sponsor, Delcath Systems, Inc. The meeting was called to order by Mikkael Sekeres, MD, MS (Committee Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Designated Federal Officer). There were approximately 70 persons in attendance. There was one (1) speaker for the Open Public Hearing session.

Issue: During the afternoon session, the committee met to discuss NDA 201848, a drug/device combination product with the proposed trade name Melblez Kit (Melblez (melphalan) for Injection for use with the Delcath Hepatic Delivery System), submitted by Delcath Systems, Inc. The proposed indication (use) for this product is for the treatment of patients with unresectable ocular melanoma that is metastatic to the liver.

Attendance:

**Oncologic Drugs Advisory Committee Members Present (Voting):**

Deborah K. Armstrong, MD, Frank Balis, MD, Aman Buzdar, MD, FACP, Louis Diehl, MD, Tito Fojo, MD, PhD, James Liebmann, MD, Brent Logan, PhD, Michael Menefee, MD, Mikkael Sekeres, MD, MS (Chairperson), David Steensma, MD, Antoinette J. Wozniak, MD, FACP, Jane Zones, Ph.D. (Consumer Representative)

**Temporary Members (Voting):**

Cynthia Chauhan (Patient Representative), Wen-Jen Hwu, MD, PhD, Kenneth Najarian, MD (participated via telephone), Takami Sato, MD, PhD

**Oncologic Drugs Advisory Committee Member Present (Non-Voting):**

Howard Fingert, MD, FACP (Industry Representative)

**FDA Participants (Non-Voting):**

Richard Pazdur, MD, Patricia Keegan, MD, Joseph Gootenberg, MD, Martin Cohen, MD, Geoffrey Kim, MD

**Oncologic Drugs Advisory Committee Member Not Present:**

Julie M. Vose, MD

**Designated Federal Officer:**

Caleb Briggs, PharmD

**Open Public Hearing Speaker:**

Daniel J. Becker, MD

**The agenda was as follows:**

Call to Order  
Introduction of Committee

**Mikkael Sekeres, MD, MS**  
Chairperson, ODAC

Conflict of Interest Statement

**Caleb Briggs, PharmD**  
Designated Federal Officer, ODAC

**Sponsor Presentation**

Introduction

**Delcath Systems, Inc.**

**John Purpura**

Executive Vice President,  
Regulatory Affairs  
Delcath Systems, Inc.

Medical Need

**Steven O'Day, MD**

Director, Clinical Research  
The Beverly Hills Cancer Center

Procedure, Phase 1 Study

**Richard Alexander, MD, FACS**

Professor of Surgery  
Associate Chairman for Clinical Research  
University of Maryland Medical Center

Phase 3 Efficacy

**Krishna Kandarpa, MD, PhD**

Chief Scientific Officer  
Delcath Systems, Inc.

Safety, Risk Management & REMS

**Krishna Kandarpa, MD, PhD**

Clinical Perspective

**Richard Alexander, MD, FACS**

**FDA Presentation**

NDA 201848

Melblez Kit

**Geoffrey Kim, MD**

Medical Officer  
DOP1, OHOP, OND, CDER, FDA

Clarifying Questions from Committee

Open Public Hearing

Questions to the Committee and Committee Discussion

Adjournment of afternoon session

**Question to the Committee:**

**NDA 201848**

**Melblez Kit**

**a drug/device combination product, containing Melblez (melphalan hydrochloride) for injection and the Delcath Hepatic Delivery System**

**APPLICANT: Delcath Systems, Inc.**

**PROPOSED INDICATION:** For the treatment of patients with unresectable ocular melanoma that is metastatic to the liver

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Given the 5.4 month improvement in median hPFS (hepatic Progression-Free Survival), the 3 month improvement in median overall PFS and a trend suggesting a detrimental effect on overall survival, along with the 7% incidence of toxic death and the observed risks of serious cardiovascular, hepatic, gastrointestinal, and bone marrow toxicities:

**VOTE:** For patients with hepatic-dominant metastatic ocular melanoma, do the benefits of treatment with Melblez Kit (clinical trial-version) outweigh the risks?

**YES: 0**

**NO: 16**

**ABSTAIN: 0**

*The committee agreed that the high risk of side effects raised significant concern when evaluating the benefit to risk profile of the product. Several committee members discussed the toxicity of the product as being severe, to the point that the treatment may be more toxic than the disease itself. One member described a worry that the quality of life for patients who have a good performance status may be more negatively impacted by side effects such as gastrointestinal perforation or stroke than by the disease itself. Another committee member stated her own similar concern with this toxicity by reiterating the medical tenet of “do no harm.” Several members of the committee described a need for more and better treatment options in this area of care, but a feeling that the data did not support this product meeting that need. The Patient Representative summarized this perspective by explaining a fear that approval of this product may offer “false hope” to patients with this disease, a statement that was supported by other members of the committee.*

*Patient selection in both trial design and selection of treatment was also mentioned as an important consideration by multiple members of the committee.*

(Please see official transcript for details.)

Afternoon session adjourned at approximately 4:45 p.m.