U.S. Food and Drug Administration

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Summary Minutes of the
Oncologic Drugs Advisory Committee
December 16, 2009
Location: Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the December 16, 2009 Meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on ___January 11, 2010____

I certify that I attended the December 16, 2009 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

___/s/_____
Nicole Vesely, Pharm.D.
Designated Federal Official, ODAC

_____/s/_____
Wyndham Wilson, M.D.
Acting Committee Chair

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 16, 2009 at the Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Wyndham Wilson, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Official). There were approximately 200 persons in attendance. There were three speakers for the Open Public Hearing session.

Issue: On December 16, 2009, during the morning session, the committee met to discuss supplemental new drug application (sNDA) 021-743/S-016, TARCEVA (erlotinib) tablets, by OSI Pharmaceuticals, Inc. The proposed indication (use) for this product is first-line maintenance, monotherapy (first-choice, single drug) treatment in patients with a form of lung cancer called non-small cell lung cancer (NSCLC) that is either locally advanced (has spread regionally within the lung and/or within chest lymph nodes) or metastatic (has spread beyond the lung), and who have not progressed (including those patients with stable disease) on first-line treatment with platinum-based chemotherapy (a regimen including a platinum drug (cisplatin or carboplatin) plus another chemotherapy drug).

Attendance:
Oncologic Drug Advisory Committee Members Present (Voting):
Ralph Freedman, M.D., Ph.D., William Kelly, D.O., Michael Link, M.D., Gary Lyman, M.D., M.P.H. Virginia Mason, R.N. (Consumer Representative), Ronald Richardson, M.D., Mikkael Sekeres, M.D., M.S., Margaret Tempero, M.D., Wyndham Wilson, M.D. (Acting Chair)

Special Government Employee Consultants (Temporary Voting Members):
Thomas Fleming, Ph.D., Steven H. Krasnow, M.D. Brent Logan, Ph.D., Pamela Moffitt (Patient Representative)

Non-voting Participants:
Richard Hubbard, M.D. (Acting Industry Representative)

Oncologic Drugs Advisory Committee Members Not Present:
S. Gail Eckhardt, M.D.
Jean Grem, M.D., F.A.C.P
Patrick Loehrer, Sr., M.D.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Robert Justice, M.D., John Johnson, M.D., Martin Cohen, M.D., Somesh Chattopadhyay, Ph.D.

Designated Federal Official:
Nicole Vesely, Pharm.D.

Open Public Hearing Speakers:
Peter Matloff
Maureen Rigney, LICSW, Director of Community and Support Services, Lung Cancer Alliance
Susan C. Mantel, Executive Director, Uniting Against Lung Cancer

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The agenda was as follows:

Call to Order Introduction of Committee	**Wyndham Wilson, M.D.** Acting Chair, ODAC
Conflict of Interest Statement	**Nicole Vesely, Pharm.D.** Designated Federal Official, ODAC
Sponsor Presentation Introduction and Regulatory History	**OSI Pharmaceuticals, Inc.** **Karsten Witt, MD** Senior Vice President Oncology Development OSI Pharmaceuticals, Inc.
Rationale for NSCLC Maintenance Therapy & SATURN: Study Design	**Federico Cappuzzo, MD** Principal Investigator, SATURN Professor and Vice Director Department of Medical Oncology Istituto Clinico Humanitas IRCCS Rozzano, Italy
SATURN: Efficacy and Safety Results	**Angela Davies, MD** Vice President Clinical Development OSI Pharmaceuticals, Inc.
Lung Cancer: Maintenance Therapy	**Paul Bunn, Jr., MD** Dudley Professor University of Colorado Cancer Center

	Aurora, Colorado USA
Concluding Remarks	**Karsten Witt, MD** Senior Vice President Oncology Development OSI Pharmaceuticals, Inc.
FDA Presentation	**(sNDA) 021-743/S-016** **Martin Cohen, M.D.** Medical Officer, Division of Drug Oncology Products (DDOP), OODP, OND, CDER, FDA
Questions to the Presenters	
Open Public Hearing	
Questions to the ODAC and ODAC Discussion	

Question to the Committee:

The full question is included after the vote below for completeness.

Question (VOTE)

- The study was not optimally designed to demonstrate that maintenance therapy with erlotinib after initial chemotherapy is better than therapy with erlotinib at disease progression
- Results of the study demonstrated a modest improvement in OS.

VOTE: Based on these results, should Erlotinib be approved for the proposed indication?

PROPOSED INDICATION

"Tarceva monotherapy is indicated as first-line maintenance treatment in patients with locally advanced or metastatic NSCLC who have not progressed (including stable disease) on first-line treatment with platinum-based chemotherapy."

Vote : ***Yes=1*** ***No = 12*** ***Abstain = 0***

- ***Members had issues that there was only one trial with a marginal favorable survival improvement and felt that this study had design flaws and limitations because patients in the control arm were not offered Tarceva at disease progression.***

- ***Members had difficulty determining whether maintenance treatment was as good as treatment at relapse based on the data presented.***

- ***Members agreed that the overall survival benefit was modest with most questioning whether this simply reflected access to Tarceva in the treatment arm. It was mentioned that with other products currently on the market that the bar for future products for review is higher.***

- ***It was noted that the study had a modest overall survival.***

- ***It was felt that the subgroups that would benefit from maintenance therapy needed to be studied further and defined. Some members questioned the use of Tarceva in patients who were EGFR (IHC) negative and those patients with squamous cell carcinoma.***

Please see the transcript for detailed discussion.

The meeting adjourned @ approximately 2:30 p.m.

Question for the
Oncologic Drugs Advisory Committee Meeting
December 16, 2009

NDA 21743/S016
Tarceva® (erlotinib) tablets oral
Applicant: OSI Pharmaceuticals, Inc.

PROPOSED INDICATION

"Tarceva monotherapy is indicated as first-line maintenance treatment in patients with locally advanced or metastatic NSCLC who have not progressed (including stable disease) on first-line treatment with platinum-based chemotherapy."

BACKGROUND

One randomized trial is submitted, comparing Erlotinib with Placebo (randomized 1:1) as maintenance treatment in 889 patients with locally advanced or metastatic NSCLC who have not progressed after 4 cycles of first-line treatment with platinum-based chemotherapy. Patients were stratified prior to randomization, using the adaptive method of Pocock and Simon, to ensure balance between treatment groups for EGFR protein expression by IHC (EGFR Positive versus EGFR Negative versus EGFR Undetermined); Stage of disease at start of chemotherapy (IIIb versus IV); ECOG PS (0 versus 1); Chemotherapy regimen (gemcitabine plus cisplatin versus carboplatin plus docetaxel versus other); Smoking status (current smoker [includes patients who had stopped smoking within a year] versus former smoker versus never smoked); and Region (North America, South America, Western Europe, Eastern Europe, South East Asia and Africa). All patients were required to provide a tumor sample for analysis of EGFR protein expression by IHC. Treatment was continued until progression, death or unacceptable toxicity.

The protocol specified co- primary endpoints are progression-free survival (PFS) in all patients and PFS in the EGFR (IHC) Positive subgroup. At a Special Protocol Assessment on 4/20/05 the FDA indicated that "To demonstrate the value of maintenance targeted therapy superiority of survival will have to be demonstrated". The study was conducted entirely outside of the United States.

Erlotinib is superior to Placebo for both co-primary endpoints, i.e., PFS in all patients and PFS in the EGFR (IHC) Positive subgroup. Using the protocol-specified unadjusted Log Rank Test, Erlonitib is also superior to Placebo for overall survival (OS) in all patients and in the EGFR (IHC) Positive subgroup. Using the Stratified Log Rank Test, Erlotinib is not superior to Placebo for OS.

A confirmatory OS analysis was performed, censoring at the date of first open-label Erlotinib or second or further line Tyrosine Kinase Inhibitor (TKI) treatment. The HR in this analysis is 0.80 versus 0.81 in ITT analysis. The LR in this analysis is p=0.0087 versus p=0.0088 in the ITT analysis.

PFS and OS results are shown in Table 1.

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Table 1 PFS and OS Results

	PLACEBO N Median (Mo)	ERLOTINIB N Median (Mo)	DIFFERENCE IN MEDIANS (Mo)	HR (95% CI) LR P Value Unadjusted
Progression-Free Survival				
All Patients	**N=451** 2.6	**N=438** 2.8	0.2	0.71 (0.62,0.82) p<0.0001
EGFR (IHC +)	**N=313** 2.6	**N=308** 2.8	0.2	0.69 (0.58,0.82) p<0.0001
EGFR (IHC) –	**N=59** 2.1	**N=62** 2.5	0.4	0.77 (0.51,1.14) p=0.1768
EGFR Mutation + (PFS Cut-Off)	**N=27** 3.0	**N=22** 10.3	7.3	0.10 (0.04,0.25) p<0.0001
EGFR Mutation + (OS Cut-Off)	**N=27** 3.0	**N=22** 11.0	8	0.23 (0.12,0.45) p>0.0001

EGFR Mutation – PFS Cut-Off)	**N=189** 2.0	**N=199** 2.8	0.8	0.78 (0.63,0.96) p=0.0182
Overall Survival				
All Patients	**N=451** 11.0	**N=438** 12.0	1	0.81 (0.70,0.95) p=0.0088
All patients Stratified LR	**N=451** 11.0	**N=438** 12.0	1	0.85 (0.71,1.02) p=0.0839 *
EGFR (IHC +)	**N=313** 11.0	**N=308** 12.8	1.8	0.77 (0.64,0.93) p=0.0063
EGFR (IHC –)	**N=59** 11.1	**N=62** 10.6	-0.5	0.91 (0.59,1.38 p=0.6482
EGRF Mutation +	**N=27** 23.8	**N=22** 23.6	-0.2	1.01 (0.47-2.16) p=0.9870
EGRF Mutation –	**N=189** 10.2	**N=199** 11.3	1.1	0.77 (0.61,0.97) p=0.0243
Adenoca	**N=198** 11.6	**N=205** 13.9	2.3	0.77 (0.61,0.97) p=0.0249
Squamous	**N=194** 11.1	**N=166** 11.3	0.2	0.86 (0.68,1.10) p=0.2369
Other NSCLC	**N=59** 9.1	**67** 10.6	1.5	0.85 (0.57,1.27) p=0.4219
Non-Squamous	**N=257** 10.5	**N=272** 13.7	3.2	0.79 (0.64,0.96) P=0.0194

*Stratified LR Test

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Figure 1 PFS in All Patients

Applicant Figure

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Figure 2 PFS in EGFR (IHC) Positive Subgroup

Applicant Figure

Figure 3 OS in All Patients

Applicant Figure

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Figure 4 OS in EGFR (IHC) Positive Subgroup

Applicant Figure

Main Issue

The **main issue** concerns other available treatment options for patients in this randomized trial. Both single agent Erlotinib and Docetaxel are approved for treatment of NSCLC after failure of prior chemotherapy. Erlotinib and Docetaxel have a statistically significant improvement in median survival over Placebo of 2-3 months in this setting, compared to a 1 month improvement in median survival in the Erlotinib versus Placebo maintenance trial (See Table 2). In both the Erlotinib and Docetaxel trials after failure of prior chemotherapy, the treated population is more difficult than in the Erlotinib maintenance trial. This is because the population includes both responders and non-responders to initial chemotherapy, while the Erlotinib maintenance trial includes only responders or stable disease. In addition, Pemetrexed was recently approved for maintenance therapy of non-squamous cell NSCLC in patients who did not progress on platinum-based initial chemotherapy based on a 5 month improvement in median survival (See Table 5). This raises the question whether treatment with single agent Erlotinib or Docetaxel after progression or Pemetrexed maintenance therapy are better options than treatment with Erlotinib as maintenance.

Table 2 NSCLC After Failure of Prior Chemotherapy

	Median Survival	Diff in	Hazard Ratio	Log Rank P Value

	(mo)	Medians (mo)	(95% CI)	Unadjusted
Erlotinib	6.7	2	0.73 (0.61-0.86)	<0.001
Placebo	4.7			
Docetaxel	7.5	2.9	0.56 (0.35-0.88)	0.01
BSC	4.6			

Other Issues

Although Erlonitib is superior to Placebo in the maintenance study, the findings in some subgroups may be issues for the wording of any approved indication or other sections in the package insert. The **first issue** is that the OS HR in the EGFR (IHC) Negative subgroup is 0.91. Notably in the Erlotinib advanced NSCLC trial after failure of at least one prior chemotherapy regimen, the OS HR of Erlonitib versus Placebo was 1.01 in the EGFR (IHC) Negative subgroup (See Table 3). Thus Erlonitib appears to have at best a weak OS effect in this subgroup. This raises the question whether the EGFR (ICH) Negative subgroup should be included in any approval.

Table 3 NSCLC EGFR (IHC) Negative Subgroup

	Median Survival (mo)	Diff in Medians (mo)	Hazard ratio (95%CI)	Log Rank P Value Unadjusted
Maintenance				
Erlotinib	10.6	-0.5	0.91 (0.59-1.38)	0.6482
Placebo	11.1			
Failure at least one prior chemotherapy				
Erlotinib	5.35	-2.15	1.01 (0.7-1.6)	0.958
Placebo	7.5			

The **second issue** is that in the squamous cell subgroup of the Erlotinib maintenance trial the Erlonitib effect on OS is very modest with median OS Erlotinib 11.3 months and Placebo 11.1 months, HR 0.86 (0.68,1.10), p=0.2369. Pemetrexed is the only drug approved for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy. Pemetrexed is approved for maintenance only in the non-squamous cell subgroup (Approved 7/2/09). In the trial with all histological subgroups the median OS was Placebo 10.6 months and Pemetrexed 13.4 months, HR=0.79 (0.65, 0.95), LR p=0.012. In the squamous cell subgroup median OS was Placebo 10.8 months and Pemetrexed 9.9 months, HR 1.07 (0.77,1.50), LR p=0.23 (See Table 4). This raises the question whether the squamous cell subgroup should be included in any approval. However, when Erlotinib was compared with Placebo after NSCLC progression on prior chemotherapy, in the squamous cell subgroup the HR=0.67 (0.5-0.9) favoring Erlotinib.

Table 4 Squamous Cell Subgroup Maintenance Rx

	Median Survival (mo)	Diff in Medians (mo)	Hazard Ratio (95% CI)	Log Rank P Value Unadjusted
Erlotinib	11.3	0.2	0.86 (0.68-1.10)	0.2369
Placebo	11.1			
Pemetrexed	9.9	-0.9	1.07 (0.77-1.50)	0.23
Placebo	10.8			

In the Erlotinib Maintenance trial in the non-squamous cell subgroup median OS was Placebo 10.5 months and Erlotinib 13.7 months, HR 0.79 (0.64-0.96). In the Pemetrexed Maintenance trial in the non-squamous cell subgroup OS was Placebo 10.3 months and Pemetrexed 15.5 months, HR 0.7 (0.56-0.88) (See Table 5). This raises the question whether any Erlotinib approval should be limited to only the non-squamous cell subgroup.

Table 5 Non-Squamous Cell Subgroup Maintenance Rx

	Median Survival (mo)	Diff in Medians (mo)	Hazard Ratio (95% CI)	Log Rank P Value Unadjusted
Erlotinib	13.7	3.2	0.79 (0.64-0.96)	0.0194
Placebo	10.5			
Pemetrexed	15.5	5.2	0.70 (0.56-0.88)	0.0020
Placebo	10.3			

The **third issue** is that although Erlotinib has a large improvement in PFS (HR=0.10) in the EGFR Mutation Positive subgroup, this is not reflected in OS (HR=1.01) (See Table 6). This disparity may be partly accounted for by the lack of mature survival data in the EGFR Mutation Positive subgroup (55% dead) because of the longer survival in this subgroup. However, it seems unlikely the results will change greatly with more events.

The Applicant attributes the lack of an Erlotinib OS effect to subsequent systemic therapy at progression. After progression any subsequent systemic therapy was given to 89% of patients in the Placebo group and 73% of patients in the Erlotinib group. After progression TKI therapy was given to 70% of patients in the Placebo group and 27% of patients in the Erlotinib group.

The Applicant's argument that in the EGFR Mutation + subgroup, OS in the Placebo group is prolonged to equal OS in the Erlotinib group by Tyrosine Kinase Inhibitor treatment at progression contradicts the Applicant's claim that Erlotinib maintenance has clinical benefit.

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Table 6 EGFR Mutation Positive Subgroup

PFS	Median (mo)	Diff in Medians (mo)	Hazard Ratio	Log Rank P Value Unadjusted
Erlotinib	10.3	7.3	0.10 (0.04-0.25)	<0.0001
Placebo	3.0			
OS				
Erlotinib	23.6	-0.2	1.01 (0.47-2.16)	0.99
Placebo	23.8			

The EGFR Mutation Positive subgroup is a small minority of NSCLC patients in this study. Only 11% of patients with known EGFR Mutation status were EGFR Mutation Positive. Additional follow-up is needed in this subgroup.

The **fourth issue** is that in the Erlotinib trial in patients with advanced NSCLC after failure of at least one prior chemotherapy regimen, 47% of the patients with known EGFR (IHC) status were EGFR (IHC) Negative. However, in the Erlotinib maintenance trial only 16% of patients with known EGFR (IHC) status were EGFR (IHC) Negative. This apparent discrepancy is concerning. We can not have personalized therapy if the tests are not reliable.

Bevacizumab is approved for treatment of locally advanced, metastatic or recurrent non-squamous NSCLC in combination with carboplatin and paclitaxel for 6 cycles and Bevacizumab continues alone after 6 cycles until progression or unacceptable toxicity (approved 10/11/06). There was no randomization at the start of the maintenance phase, so there are no data supporting Bevacizumab for maintenance therapy.