



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 24, 2006
To: NCCTG Primary Clinical Research Associates
From: Lori Bratvold
Protocol Development Coordinator
Re: N0177, A Phase I/II Study of OSI-774 and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with OSI-774 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_2006000005

Please note that all risks currently cited in the NCCTG consent form can not be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Lori Bratvold at 507-266-3549.

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enclosure

Drug Safety Department

Tarceva® (erlotinib, OSI-774)

Serious Adverse Event Report – 15 Day Investigator Notification

Report # 2006000005

Preferred Term: Oesophagobronchial fistula

17-Jan-2006

Re: Protocol 5411: A Phase I Study of OSI-774 (NSC# 718781) Based Multimodality Therapy for Inoperable Stage III Non-Small Cell Lung Cancer.

Dear Investigator:

This letter is to advise you that we have submitted a report to local regulatory authorities regarding a patient who was hospitalized due to oesophagobronchial fistula that was considered possibly related to erlotinib therapy. This patient was treated in NCI Protocol 5411: A Phase I Study of OSI-774 (NSC# 718781) Based Multimodality Therapy for Inoperable Stage III Non-Small Cell Lung Cancer. This report, from the USA, was received at OSI Pharmaceuticals on 03-Jan-2006. Please include a copy of this letter with your study records and forward a copy to your Institutional Review Board/Ethics Committee as required by local regulations.

Event Narrative

This 61-year old male patient enrolled into protocol 5411, a phase I study of OSI-774 based multimodality therapy for inoperable stage III non-small cell lung cancer. The patient was diagnosed with non-small cell lung cancer in Jul-2005. Protocol therapy consisted of induction chemotherapy, with carboplatin AUC 6 IV on days 1 and 22 and paclitaxel 200 mg /m² IV on days 1 and 22 for 2 cycles (cycle =21 days) followed by paclitaxel 50 mg/m² IV on days 43, 50, 57, 64, 71, 78 and 85, carboplatin AUC 2 IV on days 43, 50, 57, 64, 71, 78 and 85 and erlotinib 150 mg PO QD on days 43-91 and 6600 cGY given as 5 fractions/week continuing for 7 weeks beginning on day 43. The first course of protocol therapy commenced on 14-Sep-2005. The patient received no prior interventions for the underlying disease. Medical history is significant for multiple thromboses in multiple locations and mild gastroesophageal reflux disease. Concomitant medications included warfarin and enoxaparin.

On 02-Dec-2005 the patient was removed from study because he was unable to complete radiation therapy due to the fact that any further radiation would damage the left ventricle.

On 27-Dec-2005, the patient presented to the emergency room complaining of dysphagia and pain and edema in the left lower leg. He was admitted for observation. On 29-Dec-2005 a fistula between the esophagus and the left mainstem bronchus was found via an esophagram. A thrombosis was confirmed by venous ultrasound on 27-Dec-2005. However, this was a continuation from a previous clot. He has been treated with enoxaparin and warfarin and will continue with this treatment.

The events are serious. Thrombosis is expected in the IB and considered by the investigator to be unlikely related to erlotinib. Esophageal fistula is not expected and considered by the investigator to be possibly related to erlotinib, possibly related to carboplatin, possibly related to paclitaxel, probably related to radiation and probably related to the NSCLC.

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Drug Safety Department

Company Medical Assessment

Thrombosis and esophagobronchial fistula were serious due to hospitalization. Thrombosis is expected in the erlotinib IB; fistula is not. The thrombosis was an ongoing problem in this patient and started prior to the use of erlotinib; therefore, it is probably due to underlying disease and not due to erlotinib treatment. The fistula is most likely related to radiation treatment. However, the patient had other factors that may have contributed including prior gastroesophageal reflux disease and the use of chemotherapy (especially paclitaxel) that has been associated with mucositis and GI perforation. Erlotinib has been associated with GI bleed and there have been a small number of reports of esophagitis; an association of erlotinib with the fistula cannot be ruled out.

Similar Events:

The OSI and Roche erlotinib clinical safety databases were searched for all reports with the preferred terms of acquired tracheo-oesophageal fistula or pharyngeal fistula. The search found two cases of pharyngeal fistula and one case of acquired tracheo-oesophageal fistula. All three cases were considered by the investigator to be unrelated to erlotinib and related to the underlying disease. In two of the cases, the patients were being treated for head and neck cancer. In the third case, the patient was being treated for non-small cell lung cancer and had received radiation and high dose steroids for metastases to the brain, mediastinum and groin.

Conclusion

After review of the clinical details and investigator comments pertaining to this adverse event and based upon the experience of erlotinib to date, the sponsor does not believe that changes to the conduct of this clinical trial are warranted.

Please feel free to contact the OSI Drug Safety Department or your local clinical contact with any questions or concerns you may have in this regard. We appreciate your continuing efforts and cooperation in the conduct of our clinical trials.

Sincerely,

Drug Safety Department
OSI Pharmaceuticals, Inc.
Telephone: (303) 546-7869
e-mail: safetygroup@osip.com

* A safety report or other information submitted by a sponsor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the drug caused or contributed to an adverse experience." [CFR 312.32]

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