



September 17, 2010

Dear Investigator,

RE: Patients with Bacterial Sepsis in Study CA046: "A Randomized Phase III Study of Weekly ABI-007 plus Gemcitabine versus Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas"

Pharmacovigilance monitoring of the above-mentioned study has identified the incidence of ten (10) events of sepsis which require attention and the immediate institution of preventive measures. In a total of 322 patients enrolled to date, nine (9) patients with septic episodes were reported in the experimental arm (Abraxane + gemcitabine) and one (1) patient in the control arm (gemcitabine alone), for a total of ten (10) cases. Out of the nine (9) patients, five (5) of the cases were not fatal and were in non-neutropenic patients. Four (4) cases were fatal (all 4 of these patients were neutropenic). Two (2) of the deaths were reported in patients older than eighty (80) years. Among the four (4) deceased patients, one (1) had a biliary stent in place. Among the ten (10) events of sepsis, four (4) occurred in patients with biliary stents. A noteworthy observation was that the non-neutropenic patients had experienced an abrupt descent of their CA 19.9 levels with attending lesion shrinkage just before the onset of the septic event, possibly indicating acute tumor stromal collapse. Stromal collapse has been demonstrated in preclinical human pancreatic cancer xenograft models treated with Abraxane + gemcitabine. It is postulated that the sudden tumor collapse may have outpaced the speed of surrounding tissue to re-fill the vacated stromal spaces, and facilitated bacterial penetration into the bloodstream thus inducing sepsis in non-neutropenic patients. Neutropenia adds another risk factor to that of stromal collapse. We thus believe that bacterial invasion may be a risk associated with the antitumor activity of this regimen, which can be compounded by neutropenia in the induction of clinical sepsis.

Two of the patients succumbing to sepsis were older than 80 years. Candidate patients in this age group should be thoroughly evaluated before enrollment in the study, to ensure they are fit to receive chemotherapy. In addition to meeting all of the baseline patient selection criteria, clinical judgment on their susceptibility to infection and expected stability of their performance status as to receive repeat weekly chemotherapy cycles, should be paid special attention to. Patients should not be enrolled in the study should there be any hesitation on any of these considerations. Baseline criteria for all patients enrolled on the study must be carefully evaluated and all criteria followed appropriately.

In order to prevent and/or minimize the re-occurrence of septic events, the measures listed below will be implemented from now on in **both** arms of the study. These measures are effective immediately upon receipt of this notification, and will be formally introduced in an upcoming Protocol Amendment and accompanying Informed Consent Form:

1. Protocol Section 4.2.3.4: Dose Modification Tables

- For Grade 4 neutropenia within a treatment cycle (ANC < 500) in the absence of fever, Abraxane dosing is not to be interrupted and G-CSF (Neupogen®) is recommended) may be initiated as per institutional guidelines. Patients not experiencing resolution of their neutropenia in 14 days, despite uninterrupted G-CSF treatment, will be discontinued from the study.
- Gemcitabine should be resumed at the next lower dose according to Table 5 in the protocol
- Should a second instance of Grade 4 Neutropenia occur, dosage of ABI-007 and gemcitabine will be resumed at the next lower dose according to Table 5 in the protocol

2. Due to the instances of non-neutropenic sepsis, at the first occurrence of fever of at least 38.5 degrees Celsius (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally 2 times daily) or amoxicillin/ clavulanate (Augmentin, 500 mg orally 2 to 3 times daily, in patients with allergy to fluoroquinolones) should be initiated. On their first visit, patients are to be provided with enough supplies of ciprofloxacin (or the alternative antibiotic) for use at home, and instructed to initiate its intake at the first recorded temperature of at least 38.5 degrees Celsius or if they feel they are developing a fever and a thermometer is not available. They should also immediately contact their physician for guidance on where to go for blood counts to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation.
3. Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 2 weeks despite uninterrupted antibiotic treatment will be discontinued from the study. Febrile neutropenic patients can also receive G-CSF in addition to antibiotic treatment, for hastening the resolution of their febrile neutropenia, following current institutional guidelines. In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.
 - Upon resolution of febrile neutropenia, ABI-007 and gemcitabine treatment can be resumed at the next lower dose
 - Should a second instance of Grade 4 Febrile Neutropenia occur, dosage of ABI-007 and gemcitabine will be resumed at the next lower dose according to Table 5 in the protocol
4. Administration of long-term prophylactic ciprofloxacin (or the alternate antibiotic) to prevent recurrences in patients already having experienced a first febrile episode (and managed as above) will be at the discretion of the treating physician.
5. Administration of prophylactic antibiotics to otherwise uncomplicated patients with biliary stents will be at the discretion of the treating physicians. Biliary stents should be monitored closely to determine need for replacement.

Please submit this letter to your Ethics Committees in advance of receiving the amended protocol and revised informed consent document, and inform any new patients to be enrolled in the study about these newly implemented safety measures, as part of their consenting process.

Please do not hesitate to contact us should you have any questions or concerns.

Kind regards,



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