

North Central Cancer Treatment Group

N0682: A Phase II Clinical Trial of Denileukin Diftitox in Combination with Rituximab in Previously Untreated Follicular B-cell Non-Hodgkin's Lymphoma

Addendum 2– October 3, 2008

Summary

- Statistician has been updated
- Section 15.0 and consent form revisions based on review of Denileukin Diftitox package insert dated April 2007.
- Administrative/Editorial changes.

Replacement protocol is provided. Please replace the current copy with the one attached. Please keep this addendum with your protocol.

Title page Updated NCI version date and addition of Addendum 2 have been added.

Matthew J. Maurer, M.S. has replaced Eric W. Schaefer as the current statistician. Contact information has been revised to reflect this change.

Protocol Resources Page

Page 2: Title change has occurred for the 'Protocol document, consent form, regulatory issues' contacts. Revisions are as follows:
Sara M. Braun
NCCTG *Research Base* **Research Protocol Specialist** ~~Development Coordinator~~

Patricia A. Aggen
NCCTG *Research Base* **Research Protocol Specialist** ~~Coordinator~~

Section 14.0 **Body Fluid Biospecimens**

Page 31: The following paragraph has been newly added for clarification concerning residual blood:

14.47 A portion of the blood products will initially be analyzed as described above in Dr. Ansell's laboratory. According to patient consent information (see Section 6.25), remaining blood products will be transferred to the NCCTG BAP Shared Resource, and stored frozen until specific analyses are identified. As protocols are developed, they will be presented for NCCTG and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of NCCTG studies.)

Repagination has occurred from this point forward due to large amount of text.

Section 15.0 Drug Information

Page 35: Based on review of Denileukin Diftitox (ONTAK) Package Insert dated April 2007, the following text has been revised in Section 15.254:

15.254 Known adverse events (reported in greater than 5% of patients): Infection, impaired immune function, chills/fever, asthenia, pain, headache, chest pain, flu-like syndrome, hypotension, vasodilatation, tachycardia, thrombotic events, hypertension, arrhythmia, anorexia, diarrhea, nausea, vomiting, constipation, dehydration, dyspepsia, dysphagia, anemia, thrombocytopenia, leukopenia, hypoalbuminemia, increased transaminase, edema, hypocalcemia, weight decrease **or increase**, hypokalemia, myalgia, arthralgia, dizziness, paresthesia, nervousness, confusion, insomnia, dyspnea, cough increase, pharyngitis, rhinitis, lung disorder, rash, pruritus, sweating, hematuria, albuminuria, pyuria, creatinine increase, **lymphadenopathy, liver function changes, somnolence, skin carcinoma, hypoglycemia, right heart failure or heart attack.**

Section 16.0 Statistical Considerations and Methodology

Page 38: The following text has been added to the end of Section 16.12 for clarification:

We anticipate pre-registering 63 patients to register/randomize a total of 53 patients necessary for the study design and allotted over accrual.

Appendix I Consent Form

Pages 8-9: Based on review of Denileukin Diftitox (ONTAK) Package Insert dated April 2007, the following text has been added (note - no new risks, only expanded upon or removed duplication):

Likely risks of Denileukin diftitox (*events occurring greater than 20% of the time*)

- Chills
- Fever
- Weakness, lack of energy, loss of strength (asthenia)
- Infection
- Pain
- Headache
- Chest pain
- Low blood pressure, **which can lead to lightheadedness and dizziness, and cause you to pass out** (hypotension) (*risk expanded due to package insert review*)
- Widening of the blood vessels (vasodilation)
- **Feeling sick to your stomach** (~~N~~-nausea) (*risk expanded due to package insert review*)
- **Throwing up** (~~V~~ vomiting) (*risk expanded due to package insert review*)
- Loss of appetite or inability to eat (anorexia)
- **Loose stools** (~~D~~ diarrhea) (*risk expanded due to package insert review*)

- Low blood albumin (hypoalbuminemia)
- **Increases Changes** in liver function tests (**specifically such as** aspartate aminotransaminase – AST, **lactate dehydrogenase – LDH, alkaline phosphatase – ALP**, and alanine aminotransaminase - ALT) (*duplication of risk-LDH and ALP moved from less likely and verbiage changed to match NCCTG risk template*)
- **Swelling or extra fluid buildup in areas such as the hands and feet (edema)** (*risk expanded due to package insert review*)
- Dizziness
- Shortness of breath (dyspnea)
- Cough
- Rash
- Itching (**pruritus**) (*risk expanded due to package insert review*)
- Allergic reactions (hypersensitivity reactions). Side effects from being overly sensitive to the drug may occur during or within 24 hours of infusion. Symptoms include low blood pressure, shortness of breath, flushed appearance, rash, chest pain or tightness, rapid heart rate, difficulty swallowing or tightness in the throat, dizziness, fainting, allergic reaction, or anaphylaxis. These events may require medications such as IV antihistamines, corticosteroids, or epinephrine.
- Vascular leak syndrome is reported with low blood pressure, swelling and low blood albumin. The start of symptoms is delayed, usually occurring within the first two weeks of infusion; symptoms may persist or worsen after stopping treatment.
- Flu-like symptoms

Less likely risks of Denileukin diftitox (*events occurring less than or equal to 20% of the time*)

- Injection site reaction **which could include redness or soreness at the site of injection** (*risk expanded due to package insert review*)
- Rapid heart rate (tachycardia)
- High blood pressure (hypertension)
- Irregular heart beat (arrhythmia)
- Fainting (syncope)
- **Difficulty passing stool** (€ constipation) (*risk expanded due to package insert review*)
- Heartburn (dyspepsia)
- Low levels of red blood cells **which can cause fatigue and shortness of breath** (anemia) (*risk expanded due to package insert review*)
- Low platelet count **which can increase the risk for bleeding** (thrombocytopenia) (*risk expanded due to package insert review*)
- Low white blood cell count **which can increase the risk for infection** (leukopenia) (*risk expanded due to package insert review*)
- Enlarged lymph nodes/ swollen glands (lymphadenopathy)
- Low blood calcium (hypocalcemia)

- Weight decrease
- **Loss of body fluids** (~~⊖~~ dehydration) (*risk expanded due to package insert review*)
- Low blood potassium (hypokalemia)
- Abnormal levels of bilirubin in the blood (bilirubinemia)
- ~~Increase in liver enzymes (specifically lactate dehydrogenase—LDH) (risk removed due to duplication and parentheses have been added to the likely risk “Changes in liver function tests”)~~
- ~~Increase in liver bone or intestinal enzymes (specifically Alkaline Phosphatase—ALP) (risk removed due to duplication and parentheses have been added to the likely risk “Changes in liver function tests”)~~
- Weight increase
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Numbness, tingling or burning sensation on the skin (paresthesia)
- Nervousness
- Difficulty sleeping (insomnia)
- Confusion
- Sleepiness (somnolence)
- Sore throat (pharyngitis)
- Inflammation of the nose (rhinitis)
- ~~Lung disorder/problems {removed due to duplication of risk listed under likely risks as “Shortness of breath (dyspnea)}~~
- ~~Breathing disorder/problems {removed due to duplication of risk listed under likely risks as “Shortness of breath (dyspnea)}~~
- Sweating
- Skin cancer (**squamous cell**) (*added due to clarification from PI*)
- Skin sores or ulcers
- ~~Ear problems (removed due to duplication of risk under likely risks as “Dizziness”)~~
- Blood in the urine (hematuria)
- Protein in the urine (albuminuria)
- Urinary infection or white blood cells in the urine, **which may cause pain with passing urine** (pyuria) (*risk expanded due to package insert review*)
- Increased levels of creatinine in the blood that may mean kidney problems
- Blood clots (thrombotic events including deep vein thrombosis, pulmonary embolus, arterial thrombosis, and superficial thrombophlebitis)

Rare but serious risks of Denileukin diftitox (*events occurring less than 2-3% of the time*)

- Low blood sugar levels (hypoglycemia)
- Inflamed or **pain in joints** (**including, but not limited to** ~~⊖~~ gout) (*risk expanded due to package insert review*)
- Mouth sores (mucous membrane disorder)

- Decrease in hearts ability to pump blood (right heart failure)
- **Decreased blood supply to the heart, which causes heart muscle damage or muscle death (H heart attack)** (*risk expanded due to package insert review*)
- ~~Death~~ (*removed as this risk is stated at the beginning of “What side effects or risks can I expect from being in the research study?”*)
- Loss of color vision has been reported. Recovery was reported, but some patients reported long lasting changes in their vision.