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TO: ALL PRINCIPAL INVESTIGATORS/NURSES/DATA MANAGERS

FROM: MEG COLAHAN
PROTOCOL SECTION

DATE: JUNE 24, 2009

RE: GOG-0219-REVISION #8

Protocol Title: A Phase III Randomized Trial of Weekly Cisplatin and Radiation versus Cisplatin and Tirapazamine and Radiation in Stage IB2, IIA, IIB, IIIB and IVA Cervical Carcinoma Limited to the Pelvis *NCI Version Date: 06/05/2009*

Study Chairs:

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IRB Review Recommendation:

- No review required
- Expedited review; however, site IRB requirements take precedence*
- Full board review recommended because there have changes to the consent.

***For the studies affected by this Action Letter, CTEP considers all the proposed protocol and informed consent changes to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the IRB Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor.**

Patients currently on study may continue on study provided they are informed of the new and/or modified risk information. This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may related to a patient's willingness to continue participation and per the Office of Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are approved to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. Please note that all IRB approvals obtained before the

date of this amendment are now considered expired. IRB approval of this amendment and the revised informed consent must be submitted to the CTSU before enrolling any patients. Please fax Revision #8 IRB approval and revised Informed Consent to the CTSU at 215-569-0206.

This amendment is in response to an **Action Letter for Tirapazamine dated June 22, 2009**. The following changes have been made and become effective June 24, 2009:

- Title Pages - NCI Version Date is now 06/05/2009.
- Includes Revisions #1-8.
- Section 10.26 - The Comprehensive Adverse Event and Potential Risks list (CAEPR) has been replaced with the updated version 1.1 CAEPR for tirapazamine. Specific changes to the CAEPR are as follows:
- Added New Risk:
 - Possible:
 - Opportunistic Infections associated with \geq Grade 2 Lymphopenia
 - Pain-NOS
 - Reported on tirapazamine trials with relationship to tirapazamine still undetermined:
 - CNS cerebrovascular ischemia
 - GGT (Gamma-Glytimyl transpeptidase)
 - Hemorrhage, pulmonary/upper respiratory-Nose
 - Hypoxia
 - Infection with normal ANC or Grade 1 or 2 neutrophils-Select
 - Lymphopenia
 - Mucositis/stomatitis (functional/symptomatic)-Oral cavity
 - Neuropathy: motor
 - Pneumonitis/pulmonary infiltrates
 - Thrombosis/thrombus/embolism; Vasovagal episode
 - Increase in Risk Attribution:
 - Events Moved from Reported but Undetermined to Possible:
 - Anorexia
 - Constipation
 - Cough
 - Dyspnea (shortness of breath)
 - Fatigue (asthenia, lethargy, malaise)
 - Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9/L$)
 - Hypertension
 - Infection with unknown ANC- Select

- Injection site reaction/extravasation changes
- Pain-Abdomen NOS
- Rash/desquamation
- Tinnitus
- Deleted Risk
 - Reported on tirapazamine trials with relationship to tirapazamine still undetermined:
 - Sudden Death
- Decrease in Risk Attribution
 - Events Moved from Possible to Reported but Undetermined:
 - Dysphagia (difficulty swallowing)
- Modified Agent Specific Adverse Events List (ASAEL) reporting requirements:
 - Added:
 - Anorexia
 - Constipation
 - Fatigue
 - Injection site reaction/extravasation changes
 - Rash/desquamation
 - Tinnitus

- Informed Consent
- NCI Version Date is now 06/05/2009.
 - Under Risks and Side Effects Related to Tirapazamine:
 - Added to Likely:
 - “Visual disturbances, flashing lights and/or floaters
 - “muscle cramps” changed to “muscle pain.”
 - Added to Less Likely:
 - “swelling of” was changed to “Irritation or sores in” the lining of the mouth.
 - “or flaking of outer layer of skin” was added after “skin rash.”
 - “that causes fever, aches and pains in the joints, skin rash and swollen lymph glands” was added after “allergic reaction.”
 - Belly pain
 - Constipation
 - Cough
 - Fatigue or tiredness
 - Fever that may or may not be associated with dangerously low levels of a type of white blood cell (neutrophils)
 - High blood pressure
 - Infection

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- Injection site reaction/leaking of some blood into tissue
- Loss of appetite
- Pain
- Shortness of breath
- Removed from Less Likely:
 - Painful swallowing, difficulty swallowing

Please update all copies of the protocol at your institution with these changes. Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.