

Nemours Oncology IRB MEETING MINUTES

July 2, 2008

Videoconference

The meeting was called to order on July 2, 2008 at 8:05 AM and a quorum was present.

ATTENDANCE

Voting Members Present:

[REDACTED]	Co-Chair
[REDACTED]	Scientific
[REDACTED]	Scientific
[REDACTED]	Non-Scientific
[REDACTED]	Scientific
[REDACTED]	Scientific
Tim Wysocki	Chair

Non-Voting Attendees, Staff and Guests Present:

[REDACTED]	Institutional Official
[REDACTED]	Prospective New Member
[REDACTED]	IRB Assistant

Recording:

[REDACTED]	IRB Coordinator
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ITEMS

1 Welcome and Opening Remarks

It was noted that this was the last meeting for [REDACTED] who has resigned from the IRB due to workload and the departure of doctors in her department. The IRB thanked her for her excellent service to the IRB while she was a member.

[REDACTED] attended the meeting and was introduced as a prospective member of the IRB. He is an Epidemiologist who came to Nemours from MD Anderson in Delaware and who was also an IRB member of the MD Anderson IRB.

All members received the review material before the meeting, had time for adequate review and had adequate access to the material for the meeting.

2 **Next Meeting Date and General Announcements: Next meeting is scheduled for August 6 2008**

3 **Review of Previous Minutes: Minutes from the June 4 2008 meeting.**

The Minutes from the June 4, 2008 IRB meeting were reviewed and approved.

4 **Conflict of Interest**

The IRB Chair reminded the Committee about the need for confidentiality and to disclose any conflict of interest. There were no disclosures.

5 **Continuing Education**

The committee members were given the most recent edition of the Human Research Report and the IRB Ethics & Human Research Report. The Chair gave a brief summary of the reports.

5.1 **Human Research Report**

6 **Amendments**

6.1 **[82228-4] ACNS0331: A Study Evaluating Limited Target Volume Boost Irradiation and Reduced Dose Craniospinal Radiotherapy (18.00 Gy) and Chemotherapy in Children with Newly Diagnosed Standard Risk Medulloblastoma: A Phase III Double Randomized Trial**

PI: [REDACTED]

IRB Number: 06-065

Sponsor: Children's Oncology Group

Submission Type: Modification/Amendment

Action: Modifications Required

Effective Date: July 2, 2008

Vote: Total = 7; For = 7; Opposed = 0; Abstained = 0;

Primary Reviewer: [REDACTED]

Discussion and Remarks:

This is an amendment to a current study that is initiated because adjustments are necessary for lower than expected accrual and for changes in eligibility subsequent to findings from an earlier study that were not available at accrual projection time. The changes outlined in the updated protocol based on the COG memo include: 1) decrease target accrual because uniform imaging guidelines identify metastases more accurately and children with metastatic disease are not eligible, 2) decrease target accrual because results from a previous study, A9961, led to better definition of standard risk and resulted in most centers excluding children with anaplastic medulloblastoma, so study guidelines now uniformly exclude this diagnosis, 3) adding the Dutch Oncology Group, and 4) making some administrative changes on the primary investigative team. The treatment-related changes involve correcting the administration time for Cisplatin and clarifying some dosing

guidelines. Thus, while there are a number of changes that should improve the specificity of treatment, most of these changes are primarily important to the clinician and do not impact on children who are currently enrolled and would not be reflected in the consent. The amendment is approved with modifications, pending a satisfactory response from the investigator.

The modifications required for approval are: Section 5: Consent still states that 600 patients will be enrolled, but this amendment changes the accrual goals to 455. Please change. Section 8: Changes outlined in COG amendment memo include a change for Cisplatin from 8 hours to 6 hours. The consent still says 8 hours (pg. 4, Cycle A) . Pg. 5, paragraph 1 - 2nd sentence should read "To measure the effects of radiation on brain function and ability to learn and to assess..." Section 9: All risk and side effects tables seem to have been revised to reflect formatting changes. Not sure that the statement on pg 9, 1st paragraph should be included, as this is one of the things the study is examining. It does say "may" experience, but perhaps "but we do not know this for sure" or something like it. In section 10, the statement says your child might benefit, with might underlined. Did any of the changes in the amendment affect the assent forms? If so, please submit the assent with the tracked changes for review.

6.2 **[82397-5] AALL0232: High risk B-precursor acute lymphoblastic leukemia**

PI: [REDACTED]
IRB Number: 07-020
Sponsor: Children's Oncology Group
Submission Type: Modification/Amendment

Action: Modifications Required
Effective Date: July 2, 2008
Vote: Total = 7; For = 7; Opposed = 0; Abstained = 0;
Primary Reviewer: [REDACTED]

Discussion and Remarks:

Amendment #5 dated May 23, 2008 proposes to: re-open AALL0232 (suspended April 2008) to patient accrual effective Monday, June 2, 2008. Amend the protocol in light of ongoing osteonecrosis (ON) analyses that have revealed higher than expected incidences of this side effect. Exclude patients with Down syndrome and - Make administrative/editorial changes. Amendment summary: ON is being reported at significantly increased frequency for all patients greater than 10 years of age on AALL0232 versus CCG 1961. Much of the increase in incidence appears to reflect the administration of dexamethasone, clearly during Induction and possibly during Maintenance. As noted above, the rate of ON remains low among patients 1-9 years of age and there is no difference between those randomized to dexamethasone vs. prednisone in Induction. Accordingly, the following changes are being proposed to decrease the incidence of ON while preserving efficacy: 1. All patients 10+ years of age will receive prednisone during Induction. The Induction steroid randomization will continue for patients 1-9 years of age.

Amendment #5 dated May 23, 2008 proposes to: re-open AALL0232 (suspended April 2008) to patient accrual effective Monday, June 2, 2008. Amend the protocol in light of ongoing osteonecrosis (ON) analyses that have revealed higher than expected incidences of this side effect. Exclude patients with Down syndrome and - Make administrative/editorial changes. Amendment summary: ON is being reported at significantly increased frequency for all patients greater than 10 years of age on AALL0232 versus CCG 1961. Much of the increase in incidence appears to reflect the administration of dexamethasone, clearly during Induction and possibly during Maintenance. As noted above, the rate of ON remains low among patients 1-9 years of age and there is no difference between those randomized to dexamethasone vs. prednisone in Induction. Accordingly, the following changes are being proposed to decrease the incidence of ON while preserving efficacy: 1. All patients 10+ years of age will receive prednisone during Induction. The Induction steroid randomization will continue for patients 1-9 years of age. As discussed below, study duration will be extended to accrue sufficient patients to answer the steroid question among those 1-9 years of age. 2. All patients will receive discontinuous dexamethasone during the DI phase(s). 3. All patients will receive every 4-week 5-day prednisone pulses, rather than dexamethasone pulses, during Maintenance. Exclusion of patients with Down syndrome; Enrollment of children with Down syndrome to AALL0232 was suspended on 11/04/05 due to excessive toxic deaths. The protocol was re-opened for patients with Down syndrome on 11/06/06 following amendment of the study, designed to reduce toxicity in this patient group. Since re-opening AALL0232 to patients with Down syndrome there have been 3 additional deaths out of 21 patients. This rate is clearly higher than in previous HR ALL protocols, particularly CCG-1961 which involves similar therapy. Therefore, patients with Down syndrome are no longer eligible to enroll onto AALL0232. Patients with Down syndrome currently on-study will be closely monitored particularly during periods of neutropenia and in-patient observation will be seriously considered particularly during Induction. No specific recommendations for the clinical management of this vulnerable population are planned. The study is approved, with modifications, for a period of one year pending a satisfactory response from the investigator.

The modifications required for approval are: Amendment Form, #7: The amendment form states that this amendment does not affect risk, benefits or scientific merit. This is not the case. Please revise this section of the Amendment Form.

Please clarify if any active Down Syndrome participants are enrolled in this study?

Although current participants received a letter in April that informed them of the suspension and changes in treatment, any patients in active treatment at this time, need to be reconsented.

Consent: Children 10 years of age and older: Please see the attached highlighted PPF/ICF attached with 'you' your child' issues.

Section 8: First paragraph about randomization. Talks about 4 arms. Should be two for this age group, please change. Consistently use, either the terms HD MTX and Capizzi, or PC and PH (through out the PPF). The terms HD MTX and Capizzi are easier to understand.

Unless there are Down Syndrome patients enrolled at Nemours and who need to be reconsented, then delete all reference to Down Syndrome treatment.

Page 8 and 9. Change the statement about osteonecrosis (explained in attachment) to (explained in Risk section.) The method of drug administration is in the main text, and in attachment #1. Choose one.

Section 10: The main risks of study participation need to be included in the risk section. Not in Attachment #2. This includes the overall risks that are listed at the bottom of attachment #1. Also, the possible increased toxicities related to the different treatment arms.

Signature Section: The signature page needs to be replaced. This is a template issue. As written, the signature page is for a PPF and would not work if used as a ICF.

Assent is not required because few children will be able to understand the purpose of the research enough to make any type of informed decision, and COG oversight and monitoring assures a level of safety that could not be provided outside of this study. Also, COG procedures like MRD are not available outside of the study. The investigator may choose to obtain assent if the child is determined to be capable. The investigator will be reminded that if he or she chooses to obtain assent, that the assent or dissent of the child must be honored. If the investigator chooses to obtain assent, please make the following changes.

7-11 Assent: Delete the word 'great' before medical care. Use the purpose statement in the child information sheet in the COG protocol.

12-17 Assent: Use the purpose statement in the child information sheet in the COG protocol.

Consent: Children 10 years of age and younger: Please see the attached highlighted PPF/ICF attached with 'you' your child' issues.

Section 8: Fix formatting of table on page 8.

Page 10. Correct the information given about continuous vs discontinuous dexamethasone for children under 10. Which is it?

7-11 Assent: Delete the word 'great' before medical care. Use the purpose statement in the child information sheet in the COG protocol.

12-17 Assent: Use the purpose statement in the child information sheet in the COG protocol. Signature Section:

The signature page needs to be replaced. This is a template issue. As written, the signature page is for a PPF and would not work if used as a ICF.

7.1 **[82397-6] AALL0232: High risk B-precursor acute lymphoblastic leukemia**

PI: [REDACTED]

IRB Number: 07-020

Sponsor: Children's Oncology Group

Submission Type: Continuing Review/Renewal

Action: Modifications Required

Effective Date: July 2, 2008

Vote: Total = 7; For = 7; Opposed = 0; Abstained = 0;

Primary Reviewer: [REDACTED]

Discussion and Remarks:

AALL0232 is a COG group-wide phase III study designed for NCI high risk patients with acute lymphoblastic leukemia (ALL) from 1-30 years of age. Although event free survival and overall survival continue to increase for children with high risk ALL, CNS disease has become an increasing cause of treatment failure. There is evidence that both dexamethasone and high dose methotrexate prevent CNS relapse. To specifically address the relative increase in CNS events this study will test safety and efficacy of these two therapeutic interventions. The last Nemours CR was 11/07.

The review is early in order to add Delaware as a site. (Recommend approval of that amendment). JAX: 10 (9 active, 1 LTFU) (Plus 2 since last CR) PNS: 3 (2 LTFU, 1 Death following withdrawal due to relapse) (consistent with last CR) DEL: 8 (5 active, 2 LTFU, 1 discontinued by PI for progressive disease, in LTFU). (last CR was at Christiana)

The modifications required for approval are:

Continuing Renewal Application: The continuing review application should include information about the April suspension of the study and the concurrent amendment that made major revisions to the protocol (treatment plan, eligibility, PPF / ICF).

Please clarify if any active Down Syndrome participants are enrolled in this study?

Although current participants received a letter in April that informed them of the suspension and changes in treatment, any patients in active treatment at this time, need to be reconsented.

Consent: Children 10 years of age and older: Please see the attached highlighted PPF/ICF attached with 'you' your child' issues.

Section 8: First paragraph about randomization. Talks about 4 arms. Should be two for this age group, please change. Consistently use, either the terms HD MTX and Capizzi, or PC and PH (through out the PPF). The terms HD MTX and Capizzi are easier to understand. Unless there are Down Syndrome patients enrolled at Nemours and who need to be reconsented, then delete all reference to Down Syndrome treatment.

Page 8 and 9. Change the statement about osteonecrosis (explained in attachment) to (explained in Risk section.) The method of drug administration is in the main text, and in attachment #1. Choose one.

Section 10: The main risks of study participation need to be included in the risk section. Not in Attachment #2. This includes the overall risks that are listed at the bottom of attachment #1. Also, the possible increased toxicities related to the different treatment arms.

Signature Section: The signature page needs to be replaced. This is a template issue. As written, the signature page is for a PPF and would not work if used as a ICF.

Assent is not required because few children will be able to understand the purpose of the research enough to make any type of informed decision, and COG oversight and monitoring assures a level of safety that could not be provided outside of this study. Also,

COG procedures like MRD are not available outside of the study. The investigator may choose to obtain assent if the child is determined to be capable. The investigator will be reminded that if he or she chooses to obtain assent, that the assent or dissent of the child must be honored.

If the investigator chooses to obtain assent, please make the following changes.

7-11 Assent: Delete the word 'great' before medical care. Use the purpose statement in the child information sheet in the COG protocol.

12-17 Assent: Use the purpose statement in the child information sheet in the COG protocol.

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Section 8: Fix formatting of table on page 8.

Page 10. Correct the information given about continuous vs discontinuous dexamethasone for children under 10. Which is it?

7-11 Assent: Delete the word 'great' before medical care. Use the purpose statement in the child information sheet in the COG protocol.

12-17 Assent: Use the purpose statement in the child information sheet in the COG protocol. Signature Section: The signature page needs to be replaced. This is a template issue.

As written, the signature page is for a PPF and would not work if used as a ICF.

7.2 [82324-4] AEPI04C1: Low Birth Weight and Other Risk Factors for Hepatoblastoma

PI: [REDACTED]

IRB Number: 06-168

Sponsor: Children's Oncology Group

Submission Type: Continuing Review/Renewal

Action: Modifications Required

Effective Date: July 2, 2008

Vote: Total = 7; For = 7; Opposed = 0; Abstained = 0;

Primary Reviewer: [REDACTED]

Discussion and Remarks:

This is a continuing review of an epidemiology study that seeks to determine if there is an association between low birth weight, other factors and the occurrence of hepatoblastoma. One family enrolled in and completed the study in Pensacola. SAE reporting is irrelevant to a study of this type. The Mothers and Fathers (Living Child) consent forms are identical and I don't believe that this was as intended. There should be one PPF-ICF for use when the child is entered into the study, which both parents can sign if both wish to provide cheek cells and/or be interviewed. The second consent (currently labelled "Fathers") should only be used when there is a biological father who wishes to enroll and provide cheek cells. The fathers consent should not duplicate the process of getting parental permission for the

This is a continuing review of an epidemiology study that seeks to determine if there is an association between low birth weight, other factors and the occurrence of hepatoblastoma. One family enrolled in and completed the study in Pensacola. SAE reporting is irrelevant to a study of this type. The Mothers and Fathers (Living Child) consent forms are identical and I don't believe that this was as intended. There should be one PPF-ICF for use when the child is entered into the study, which both parents can sign if both wish to provide cheek cells and/or be interviewed. The second consent (currently labelled "Fathers") should only be used when there is a biological father who wishes to enroll and provide cheek cells. The fathers consent should not duplicate the process of getting parental permission for the aspects of the study that the first parent has already consented to. Allowing duplicate, sequential consents for the two parents to separately approve obtaining cheek cells from the child, abstracting the child's medical record and doing a medical history interview creates the possibility that the two signed parental consents may be contradictory. This second consent should be limited to getting a father's consent to provide cheek cells for DNA testing, nothing more. See the accompanying consent form reviews for details. The study is approved, with modifications, for a period of one year per Subpart D of 45CFR46, Section 404, and 21CFR50, Section 41, pending a satisfactory response from the investigator.

The modifications required for approval are:

The title of the consents should be: Consent for mothers of living children: Consent for fathers of living children: Consent for mothers of deceased children: Consent for fathers of deceased children.

Continuing Renewal Form:

The continuing review summary does not specify that children diagnosed between 01/01/2000 and 5/31/2005 will be studied retrospectively (perhaps this information was included on the initial application). Also, the summary talks about asking mothers to participate in a one hour telephone interview, and to give a sample of cheek cells from mother and child. It does not mention anything about fathers. However, there are two separate consent forms for mothers and fathers whose children have died, and 2 more for mothers and fathers whose children are alive.

Living Mother's Consent: One consent form should be used when new families enter this study with space for either or both to sign. This would prevent confusion and possible contradictions between the two parents' intentions.

The current "Fathers" consent should more accurately be labelled "Second Parent's Consent" and it should be limited to obtaining their permission for collection of that parent's cheek cells for DNA analysis.

The Fathers consent should not repeat seeking the parent's consent for the aspects of the study that the mother has already either consented to or opted out of.

The current "Mothers" PPF-ICF should cover the collection of cheek cells from the child, the collection of information from the child's medical record, the agreement for the parent to be interviewed about other possible etiologic factors and space for both parents to agree to collection of their own cheek cells to be collected for DNA testing. This consent document

should be signed whenever possible by both parents and both should enter the study simultaneously. The current "Fathers" PPF-ICF should be renamed as above and used only in the circumstance in which the second parent decides later to join the study. It should have the sole purpose of obtaining that parent's consent for collection of that parent's cheek cells for DNA testing and should not duplicate the parental permission process that has already occurred to allow cheek cells to be collected from the child, to collect medical record information about the child and to agree to an interview about other possible factors in the etiology of the child's hepatoblastoma.²

The PPF-ICF gives no indication that participation in only selected parts of the study is allowable until after the signature page. Parents will reach the signature page and sign, which to me indicates agreement to all aspects of the study. On the page after the signature page, they are then offered the option to participate or not in each of three segments of the study. So, if they now indicate that they only want to take part in some aspects of the study, what does their signature mean? The optional checkboxes need to appear before the signature page and the consent document needs to make clear early on that they will be allowed to choose which, if any, aspects of the study they wish to participate in.

Section 8: In this section it should be made clear that participants have the choice to participate in any, or none, of the study procedures.

Section 13: This section needs to make clear that participants can choose to take part in selected aspects of the study, that they don't have to participate in all parts.

Section 19: Optional checkboxes needed to be moved to precede the signature page.

Living Father's Consent: The current "Mothers" PPF-ICF should cover the collection of cheek cells from the child, the collection of information from the child's medical record, the agreement for the parent to be interviewed about other possible etiologic factors and space for both parents to agree to collection of their own cheek cells to be collected for DNA testing. This consent document should be signed whenever possible by both parents and both should enter the study simultaneously.

The current "Fathers" PPF-ICF should be renamed as above and used only in the circumstance in which the second parent decides later to join the study. It should have the sole purpose of obtaining that parent's consent for collection of that parent's cheek cells for DNA testing and should not duplicate the parental permission process that has already occurred to allow cheek cells to be collected from the child, to collect medical record information about the child and to agree to an interview about other possible factors in the etiology of the child's hepatoblastoma.

For the "Fathers" PPF-ICF, the optional check boxes at the end should be removed, since the only purpose of this document should be to obtain consent for collection of that parent's cheek cells, not repetition of the parental permission process regarding the child's involvement in the study.

All aspects of the "Fathers" PPF-ICF that make reference to parental permission for the child's participation should be removed from the document. If parental permission has not already been signed by the mother, the father will not be offered this consent document. It

is not necessary for this to be duplicated since permission by one parent is adequate in this type of study and it could create confusion and complications if the two parents have differing opinions about the nature of child's involvement.

Section 8: This section should be reduced to indicate that this parent is being asked only for consent to obtain the parent's cheek cells for DNA testing. At most, reference to the child's involvement should be limited to what data have or will be collected from/about the child since the child is ostensibly already enrolled by the time the father sees this consent document.

Section 18: Should say: "What Information about me and my child will be disclosed". Same section, next to last paragraph on page 4, add "you and.." your child...

Section 19: Optional checkboxes needed to be removed. They do not pertain to this parent's involvement and they duplicate and potentially contradict the previously signed consent document.

Add "mine and.." my child's individually...etc. Optional check boxes on page 7 need to be moved before signature on page 6.

Consent for Fathers of deceased children:

Section 6: Because the parents being asked to participate have lost their child, adding to the sentence "...genes of children with hepatoblastoma, and those who died with the disease..." or something to that effect would be appropriate.

Section 8: Are fathers also answering telephone interviews, or only mothers? Section 12, second paragraph: eliminate second "by contacting".

Section 16: Mothers consent stated that they will get paid \$10.00 - Fathers consent states that they will not get paid. Maybe it should state that payment is one per family.

Section 18: Page 4: eliminate the word "and" at the end of the 4th bullet.

At the end of section 18, on page 5 it talks about "Tumor Registrar" and in the box it calls the position "Cancer Registrar" - For clarity purposes there should be consistency.

Section 19: If fathers are only being asked to give genetic samples of their cells, the mention to child and relationship to participant, etc. should be eliminated.

If fathers are being asked to participate in an interview and to have their medical records reviewed, optional check boxes on page 7 need to be moved before signature on page 6.

7.3 **[82418-4] AHOD0521: A Randomized Phase II Study of Bortezomib (PS-341, Velcade) 1/2; IND 58443, NSC 681239) in Combination with Ifosfamide/Vinorelbine in Pediatric Patients with Relapsed/Refractory Hodgkin Disease**

PI: [REDACTED]
IRB Number: 07-038
Sponsor: Children's Oncology Group
Submission Type: Continuing Review/Renewal

Action: Modifications Required
Effective Date: July 2, 2008
Vote: Total = 7; For = 7; Opposed = 0; Abstained = 0;
Primary Reviewer: [REDACTED]

Discussion and Remarks:

This is a 1 year CR of a phase II COG-sponsoifosfamide/vinorelbinned study aimed at establishing safety and efficacy of the addition of bortezomib to ifosfamide/vinorelbine alone (historic control) for refractory Hodkin's. Also some biological goals: 1-effect on the number of blood stem cells collected for stem cell transplantation 2-to collect biologic specimens for other biological experiments specific for this Rx. The study did not recruit in any of the Nemours sites and according to the application it is closed to accrual at Nemours. It remains open nationally since according to the 2/08 COG Progress report the recruitment has been 10/48 needed. There have not been any concerning toxicities. The DSMB report determined continuation of the study. It is not clear why the application indicates closure to accrual @ Nemours.

The study is approved, with modifications, for a period of one year per Subpart D of 45CFR46, Section 405, and 21CFR50, Section 52 pending a satisfactory response from the investigator.

Question to be answered

The study did not recruit subjects in any of the Nemours sites and according to the application it is closed to accrual at Nemours. It is not clear why the application indicates closure to accrual @ Nemours. Please clarify. If this study is closed to accrual, there is no need for consent and assents.

7.4 **[82416-4] ACNS0232: Radiotherapy Alone vs. Chemotherapy Followed By Response-based Radiotherapy For Newly Diagnosed Primary CNS Germinoma**

PI: [REDACTED]
IRB Number: 07-036
Sponsor: Children's Oncology Group
Submission Type: Continuing Review/Renewal

Action: Approved
Effective Date: July 2, 2008
Expiration Date: July 1, 2009
Vote: Total = 7; For = 7; Opposed = 0; Abstained = 0;
Primary Reviewer: [REDACTED]

Discussion and Remarks:

This is a randomized study where subjects with CNS germinoma will be randomized into a standard therapy (radiation) group, or a standard therapy plus chemotherapy(Cisplatin, cyclophosphamide, MESNA, Filgrastim). Outcome measures include assessing reduced severity and frequency of late side effects without reducing likelihood of cure, tracking GCF in blood and CSF, and differences in cure rate or recurrence between the two therapies. A Study Progress Report dated 2/4/08 states that 4 patients have been enrolled in the trial. There has been only one subject enrolled at any Nemours site. One patient in

Jacksonville is currently participating in the trial. The Study Progress Report recommended continuation of the trial. The COG DSMC met in October 2007 and recommended continuation of the trial.

The approval criteria are met. The study is approved for a period of one year per Subpart D of 45CFR46, Section 405 and 21CFR50, Section 52.

A copy of the signed PPF/ICF and research data must be included in the Nemours' electronic medical record (EMR).

8 New Studies

8.1 [86700-1] ADVL06B1: A Pharmacokinetic-Pharmacodynamic-Pharmacogenetic Study of Actinomycin-D and Vincristine in Children with Cancer

PI: [REDACTED]

IRB Number: 08-118

Submission Type: New Study

Action: Modifications Required

Effective Date: July 2, 2008

Vote: Total = 7; For = 7; Opposed = 0; Abstained = 0;

Primary Reviewer: [REDACTED]

Discussion and Remarks:

This is a NCI-COG sponsored trial in infants, children and adolescents with cancer. The primary aims are to characterize the pharmacokinetics of anti-neoplastic agents; actinomycin-D (Act-D) and vincristine (VCR) and identify demographic or physiological factors that are determinants of Act-D and VCR deposition. The study will also explore the pharmacodynamic and pharmacogenetic relationships of Act-D and VCR. Despite Act-D's longstanding use in pediatric oncology, there is very little PK information from which safe and appropriate age-based dosing can be derived. The consequences of this lack of fundamental knowledge were evident in 2002, when COG suspended 3 active protocols for the treatment of children with rhabdomyosarcoma after four Act-D associated deaths from hepatotoxicity. While there is PK data available on VCR, there are no universal guidelines on pediatric dosing in infants and children. The investigators' objectives are to describe the PK, PD, and PG characteristics of Act-D and VCR in pediatric patients diagnosed with various childhood cancers using a limited sampling schema, and to estimate population PK parameters for these drugs in these patients, evaluate the impact of covariate clinical and demographic factors including body size and composition, tissue distribution and binding, cancer type, age and gender. They hope to enroll 140-260 participants from around the country. NCC-J, NCC-P, and NCC-D are participating sites. The study is approved, with modifications, for a period of one year per Subpart D of 45CFR46, Section 406 and 21CFR50, Section 53, pending a satisfactory response from the investigator.

The decision for the 406/53 determination was because the ports will be accessed multiple times and the participants will be immunosuppressed. The permission of both parents is required if both parents are alive, known, competent, reasonably available, and have legal responsibility for the care and custody of the child. Otherwise the permission of one parent is required.

A copy of the signed PPF/ICF and research data must be included in the Nemours' electronic medical record (EMR).

Pg 3, Participating in this study a second time, 1st sentence: Add the word "to" after choose.

Make sure there are 2 signature lines in the ICF/PPF.

Section 7: 1st sentence: Change "Your child will be treated on study for 4 days..." to "Your child will participate in this study...."

5th sentence: change "receive" to "receives".

Section 11: 6th sentence: add a comma after Nemours.

Section 13: Delete the various treatment options.

Section 14: 1st sentence: Remove the word treatment. If study is stopped your child will continue in the follow-up phase. Delete because there is not a follow-up phase.

Section 15: Move the last 2 sentences of the first paragraph to the section 16, Will People be Paid.

7-11 and 12-17 Assents: Last paragraph, the first 2 sentences should be deleted as there is no direct benefit to the child.

8.2 **[87152-1] ASCT0631(PBMTC SCT051) A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation**

PI: Eric Sandler, MD
IRB Number: 08-119
Sponsor: COG
Submission Type: New Study

Action: Deferred
Effective Date: July 2, 2008
Vote: Total = 7; For = 7; Opposed = 0; Abstained = 0;
Primary Reviewer: [REDACTED]

Discussion and Remarks:

This is an NCI approved COG study for leukemia patients who are going to receive stem cell transplant. The study has two arms, Arm A is the experimental arm in which G-CSF bone marrow from the donor will be transplanted and Arm B which is standard treatment with recipients receiving bone marrow from a donor who did not receive G-CSF. The idea is to see whether donors treated with granulocyte cell stimulating factor will yield bone marrow that is higher in stem cell quantity and if someone receiving that treated marrow will have a higher chance of survival. The study anticipates 425 patients total and they will undergo standard treatment only getting stem cell transplant if they would have during their standard treatment anyway but half will get donor marrow from someone who was treated with G-CSF and half will receive marrow from a donor not treated with G-CSF. Treatment lasts only through the day of marrow transplant but the study plans to follow recipients for up to 10 years after the marrow is given.

The approval criteria are not met by the current application. Approval is deferred pending significant revision to the current application and re-review by the convened IRB.

The documentation (and/or process) of assent is waived because the children are not capable of providing assent based on the age, maturity, or psychological state, the capability of the children is so limited that they could not reasonably be consulted and The intervention or procedure involved in the research holds out a prospect of direct benefit that was important to the health or well being of the children and is available only in the context of the research. The investigator may choose to obtain assent if the child is determined to be capable. The investigator will be reminded that if he or she chooses to obtain assent, that the assent or dissent of the child must be honored.

There was discussion regarding if there is any benefit to the donor participants. There are many risks to G-CSF. The only benefit stated is an altruistic benefit. The IRB feels this is a valuable study to do and would help kids get benefit from bone marrow transplants. Please submit more detail to allow us to determine the risk level of G-CSF. Please justify what the benefit would be for the donor.

The modifications required for approval are: Please submit the COG central IRB justification for approval.

Donor Consent: Section 10: Pg 7 of 16, 1st real paragraph: says no direct benefit but potential benefit could include prolonging your child's survival and getting rid of his cancer

for a long time. This consent is for the donor child so won't prolong their life necessarily because they don't have leukemia, but if it is referring to prolonging the life of the sibling to the donor, the sibling who does have leukemia it almost sounds coercive. Please reevaluate.

Recipient Consent: Section 8: Although the harvest of marrow from the donor is described in the recipient consent on pg 3 of 27, not sure that it needs to be there but are ok with it if the investigator feels there is a good reason. Seems leaving it runs the risk of confusing the recipient and family into thinking they would undergo the harvest.

Pg 5 of 27 - 2nd to last paragraph - 1st line: you and your use is inappropriate. Please change throughout the consent.

Typos: Pg 6 of 27 - 2nd to last line of page - change 'better chance of a getting rid of cancer' to 'better chance of getting rid of cancer'.

9 **Adverse Events**

10 **INTERIM ACTIVITY**

10.1 **[86419-2] AOST06B1, A Children's Oncology Group Protocol for Collecting and Banking Osteosarcoma Specimens**

PI: [REDACTED]
IRB Number: 08-092
Sponsor: COG
Submission Type: Revision

Action: Approved
Effective Date: May 7, 2008
Expiration Date: May 6, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

All of the required changes to the consent have been completed. The study may be approved provided Dr Wysocki agrees. thanks, [REDACTED]

10.2 **[82416-3] ACNS0232: Radiotherapy Alone vs. Chemotherapy Followed By Response-based Radiotherapy For Newly Diagnosed Primary CNS Germinoma**

PI: [REDACTED]
IRB Number: 07-036
Sponsor: Children's Oncology Group
Submission Type: Modification/Amendment

Action: Approved
Effective Date: June 18, 2008
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The revisions are satisfactory. Please extend executive approval. Carlos

10.3 **[82520-6] HLMCC 0402: Glutamic Acid to Decrease Vincristine Toxicity in Children with Cancer**

PI: [REDACTED]
IRB Number: 07-114
Sponsor: NCI - H. Lee Moffitt Cancer Center CCOP Research B
Submission Type: Researcher

Action: Approved
Effective Date: June 4, 2008
Expiration Date: June 5, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

I reviewed the revised version resulting from IRB stipulation and find them satisfactory. Approve CR and amended consent document.

10.4 **[87272-4] A Multi-Center Phase I Study of AP23573 in Pediatric Patients with Advanced Solid Tumors**

PI: [REDACTED]
IRB Number: 08-091
Submission Type: Researcher

Action: Approved
Effective Date: May 7, 2008
Expiration Date: May 6, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

I reviewed the list of revisions made by the investigators following IRB stipulations as well as the requests from the company to delete NCI/COG references as well as adding the CRO (PPD) in the consent. I find those revisions satisfactory. The study CR is then approved.

10.5 **[87088-2] AAML05P1: Killer Immunoglobulin-like Receptor (KIR) Incompatible Unrelated Donor Hematopoietic Cell Transplantation (HCT) for Refractory and Relapsed AML and Newly Diagnosed AML with Monosomy 7 or -5/5q- in Children**

PI: [REDACTED]
IRB Number: 08-107
Sponsor: COG
Submission Type: Researcher

Action: Approved
Effective Date: June 4, 2008
Expiration Date: June 3, 2009

Primary Reviewer: [REDACTED]

Discussion and Remarks:

I have reviewed the rebuttal or response to the IRB in regard to our requested changes to the above referenced studies. The research team has addressed the issues we raised and I would recommend approval of the study.

10.6 **[87272-3] A Multi-Center Phase I Study of AP23573 in Pediatric Patients with Advanced Solid Tumors**

PI: [REDACTED]

IRB Number: 08-091

Submission Type: Other

Action: Acknowledged

Effective Date: June 12, 2008

Primary Reviewer: [REDACTED]

Discussion and Remarks:

The updated Investigator Brochure (Version 6.0, 4-30-08) is accepted as information.

10.7 **[82590-8] ADVL0525: A Phase II Study of Pemetrexed in Children with Recurrent Malignancies**

PI: [REDACTED]

IRB Number: 07-174

Sponsor: Children's Oncology Group

Submission Type: Adverse Event

Action: Approved

Effective Date: June 10, 2008

Discussion and Remarks:

The following AE's have been accepted as information.

US200804006797 Initial 5/6/2008

DE200802000020 Initial 5/6/2008

DE200802002043 Follow-up 4/28/2008

PT200805001720 Initial 5/12/2008

CA200711000761 Follow-up 5/13/2008

IT200805003183 Initial 5/21/2008

PT200805001720 Follow-up 5/16/2008.

10.8 **[82409-5] AALL0434: Intensified Methotrexate, Nelarabine (Compound 506U78, IND 52611) and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia (ALL)**

PI: [REDACTED]

IRB Number: 07-029

Sponsor: Children's Oncology Group
Submission Type: Modification/Amendment

Action: Information
Effective Date: June 12, 2008
Primary Reviewer: [REDACTED]

Discussion and Remarks:

I am confused about what is being submitted here. The consent documents are labelled as "Consent for Optional Pharmacokinetic Study", yet the amendment is for the protocol as a whole. Unclear why the overall PPF-ICF was not submitted. Also, it is unclear to me whether prior participants enrolled without signing the Pharmacokinetic consent. A clearer and more complete explanation of the submission is needed.

10.9 **[89951-1] Children's Oncology Group Commercial Agent Monograph**

PI: [REDACTED]
IRB Number: 08-125
Sponsor: COG
Submission Type: Other

Action: Acknowledged
Effective Date: June 12, 2008
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The COG Commercial Agents Monograph is accepted as information.

10.10 **[82518-4] A Phase II Study of Combotox in Children with Refractory/Relapsed CD19+, CD22+ B-Precursor Acute Lymphoblastic Leukemia (ALL)**

PI: [REDACTED]
IRB Number: 07-112
Sponsor: Scott/Sherwood/Brindley Found.
Submission Type: Continuing Review/Renewal

Action: Approved
Effective Date: June 4, 2008
Expiration Date: June 3, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The IRB's remaining stipulations for approval of this protocol have been addressed satisfactorily. The researchers have clarified why the Nemours Florida IRB's ICF-PPF

template was used rather than the Oncology template. The revisions to the various consent documents are acceptable. The protocol is approved for 1 year under Subpart D, Section 405 (52). Consent documents and study data should be placed in the EMR for each participant.

10.11 **[82359-5] AALL0331: Standard Risk B-precursor Acute Lymphoblastic Leukemia Part I Induction Therapy**

PI: [REDACTED]
IRB Number: 06-199
Sponsor: Children's Oncology Group
Submission Type: Continuing Review/Renewal

Action: Approved
Effective Date: June 4, 2008
Expiration Date: June 3, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The IRB's minor stipulations for approval have been addressed satisfactorily. The study is approved under Subpart D, Section 405 (52) for one year. The consent documents and study data should appear in each participant's medical record.

10.12 **[87505-2] ANBL0532, Phase III Randomized Trial of Single vs. Tandem Myeloablative Consolidation Therapy for High-Risk Neuroblastoma**

PI: [REDACTED]
IRB Number: 08-101
Sponsor: COG
Submission Type: Researcher

Action: Approved
Effective Date: June 4, 2008
Expiration Date: June 3, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The IRB's required stipulations have been addressed satisfactorily. The protocol is approved by expedited review for one year under Subpart D, Section 405 (52).

10.13 **[82282-3] ASCT0521: Soluble Tumor Necrosis Factor Receptor: Enbrel (Etanercept) for the Treatment of Acute Non-Infectious Pulmonary Dysfunction (Idiopathic Pneumonia Syndrome) Following Allogeneic Stem Cell Transplantation.**

PI: [REDACTED]
IRB Number: 06-138

Sponsor: Children's Oncology Group
Submission Type: Continuing Review/Renewal

Action: Approved
Effective Date: June 4, 2008
Expiration Date: June 3, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The IRB's required changes to the consent documents have been addressed satisfactorily. The protocol is approved for one year under Subpart D, Section 405 (52).

10.14 **[90100-1] EPIDEMIOLOGIC CHARACTERIZATION OF ETIOLOGIC AND PREDISPOSING FACTORS IN DELAWARE PROSTATE CANCER CLUSTERS: CASE COHORT INVESTIGATION**

PI: [REDACTED]
IRB Number: 08-116
Sponsor: Potential - Department of Defense (DOD)
Submission Type: New Study

Action: Exempt
Effective Date: June 18, 2008
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The IRB Chair has determined that his activity does not constitute human subjects research since he is not interacting with data contributed by or about identifiable people. No further IRB oversight is needed as long as he implements his plans as indicated in the submitted documents. Any significant change in procedures should be reported in advance to the IRB.

10.15 **[82478-3] ANHL04B1: Rare and Cutaneous Non-Hodgkin Lymphoma Registry**

PI: [REDACTED]
IRB Number: 07-073
Sponsor: Children's Oncology Group
Submission Type: Revision

Action: Approved
Effective Date: May 7, 2008
Expiration Date: May 6, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

Most of the required changes and suggested changes have been made to the various

documents, with the exception of changing the "Previous Approval Date" from 6/6/2008 to 6/6/2007 - Once this change is made I recommend we approve the Continuing Renewal.e approve the Continuing Renewal

10.16 **[82268-3] ANHL01P1, A Pilot Study to Determine the Toxicity of the Addition of Rituximab to the Induction and Consolidation Phases and the Addition of Rasburicase to the Reduction Phase in Children with Newly Diagnosed Advanced B-Cell Leukemia/Lymphoma Treated with LMB/FAB Therapy-Initial Treatment with Rasburicase**

PI: [REDACTED]
IRB Number: 06-126
Sponsor: Children's Oncology Group
Submission Type: Revision

Action: Approved
Effective Date: May 7, 2008
Expiration Date: May 6, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The stipulations for approval imposed by the IRB at its May meeting have been resolved satisfactorily. The amendment form, continuing review application and consent documents have all been edited in accord with the required changes. I approve the study under Subpart D, Section 405(52) for 12 months. The signed consent document should be placed in the EMR.

10.17 **[82314-3] AHOD0031: A Phase III Group-Wide Study Of Dose-Intensive Response-Based Chemotherapy And Radiation Therapy For Children And Adolescents With Newly Diagnosed Intermediate Risk Hodgkin Disease.**

PI: [REDACTED]
IRB Number: 06-165
Sponsor: Children's Oncology Group
Submission Type: Continuing Review/Renewal

Action: Approved
Effective Date: May 7, 2008
Expiration Date: May 6, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

Concerns have been addressed adequately. Would recommend approval at this time.

10.18 **[82234-4] HEAD START III: A Dose Intensive Chemotherapy for children less than ten years of age newly-diagnosed with Malignant Brain Tumors: A Pilot Study of two alternative intensive induction chemotherapy regimens, followed by consolidation**

with Myeloablative chemotherapy (Thiopeta and carboplatin, with or without Etoposide) and autologous stem cell rescue

PI: [REDACTED]
IRB Number: 06-072
Sponsor: Children's Hospital Los Angeles
Submission Type: Continuing Review/Renewal

Action: Approved
Effective Date: May 7, 2008
Expiration Date: May 6, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

I believe the changes made to the Continuing Review application and the various consent documents are sufficient to meet the stipulations imposed by the IRB during its May meeting. I approve the study under Subpart D Section 405 for 12 months. The signed consent should be placed in the EMR.

10.19 **[86583-2] miRNA Screening of Pediatric Solid Tumors to Identify Signature Patterns of Tumorigenesis**

PI: [REDACTED]
IRB Number: 08-076
Sponsor: Nemours Biomedical Research
Submission Type: New Study

Action: Approved
Effective Date: June 2, 2008
Expiration Date: June 1, 2009
Primary Reviewer: [REDACTED]
Secondary Reviewer: [REDACTED]

Discussion and Remarks:

Study on existing clinically obtained stored tissue from biopsy and resection of Wilm tumors. Reviewed under category 5. The investigators will de-identify and make Master key WITHIN Department. Tissue (both snap frozen and paraffine embedded) will be given a code and the miRNA signature studied and correlated with clinical data obtained at the time of de-ident. This study could have a waiver of consent but cannot be exempted until the master key is destroyed @ the end. Approve under 404 x 1yr.

This is a tissue repository study in which stored tissue samples of pediatric solid tumors will be provided in a de-identified manner to the investigator by the pathology department together with pertinent details of each patient's clinical diagnosis and course. A third party not involved in the study will retain the code linking the identities of the patients back to their respective clinical information and tissue samples. The protocol involves characterization of the tissue samples via miRNA screening in an effort to specify processes associated with tumorigenesis. The accompanying application for waiver of the

requirement for informed consent makes clear that the study would not be practicable without the waiver and that participants would not sacrifice any of their rights by virtue of the waiver since the data are to be de-identified.

Waiver of consent is allowable because the research could not be practicably conducted without the waiver and implementation of the waiver will not unduly deprive participants of any of their rights.

10.20 **[82520-5] HLMCC 0402: Glutamic Acid to Decrease Vincristine Toxicity in Children with Cancer**

PI: [REDACTED]
IRB Number: 07-114
Sponsor: NCI - H. Lee Moffitt Cancer Center CCOP Research B
Submission Type: Revision

Action: Approved
Effective Date: May 27, 2008
Primary Reviewer: [REDACTED]

Discussion and Remarks:

This is a minor amendment to change the study coordinator. This change does not affect the risks, benefits or scientific merit of the study. I approve the amendment by expedited review.

10.21 **[82571-3] N3698g: A Phase III, Randomized, Double-Blind Placebo-Controlled Study of Tenecteplase for Restoration of Function in Dysfunctional Central Venous Access Catheters**

PI: [REDACTED]
IRB Number: 07-158
Sponsor: Genentech, Inc.
Submission Type: Reportable Event (Non-AE)

Action: Approved
Effective Date: May 29, 2008

Discussion and Remarks:

The following AE has been accepted as information.
Report Number Type Date
260842 Follow up 05/23/03

10.22 **[82261-2] AAML03P1: Treatment of newly diagnosed childhood AML using intensive MRC-based therapy and Gemtuzumab Ozogamicin (GMTZ): A COG Pilot Study and Primary Induction Failure, unrelated transplantation as salvage therapy for children with AML and primary induction Failure: A collaborative COG/NMDP study**

PI: [REDACTED]

IRB Number: 06-118
Sponsor: Children's Oncology Group
Submission Type: Reportable Event (Non-AE)

Action: Acknowledged
Effective Date: June 4, 2008
Primary Reviewer: [REDACTED]

Discussion and Remarks:

This patient who is enrolled on the Long Term Follow-up Tool and is not on active protocol therapy has been incarcerated in a juvenile detention center indefinitely. He will turn 18 in a few months. The IRB has concluded that this patient should be withdrawn from the Long Term Follow-up Tool. He could be re-consented at such time that he is released from incarceration. No further data about this patient should be collected or distributed for research purposes during this incarceration.

10.23 **[87063-2] AEWS07P1, A Pilot Study of Chemotherapy Intensification by Adding Vincristine, Topotecan and Cyclophosphamide to Standard Chemotherapy Agents with an Interval Compression Schedule in Newly Diagnosed Patients with Localized Ewing Sarcoma Family of Tumors**

PI: [REDACTED]
IRB Number: 08-088
Sponsor: COG
Submission Type: Researcher

Action: Approved
Effective Date: May 7, 2008
Expiration Date: May 6, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The IRB's stipulations for approval have been addressed adequately. The risk section of the PPF now more clearly lays out each of the risks associated with the study design. I approve the amended protocol under Subpart D, Section 405 (52).

10.24 **[87058-2] ACNS0332: Efficacy of Carboplatin Administered Concomitantly With Radiation and Isotretinoin as a Pro-Apoptotic Agent in Other Than Average Risk Medulloblastoma/PNET Patients**

PI: [REDACTED]
IRB Number: 08-095
Sponsor: COG
Submission Type: Researcher

Action: Approved
Effective Date: May 7, 2008
Expiration Date: May 6, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

The IRB's stipulations for approval have been fulfilled. I approve the protocol under Subpart D, Section 405 (52) for 12 months. Consent documents and study data should be entered into the EMR.

10.25 **[82530-3] ACNS0222: A Phase II Study of Motexafin-Gadolinium (NSC 695238, IND #55583) and Involved Field Radiation Therapy for Intrinsic Pontine Glioma of Childhood**

PI: [REDACTED]
IRB Number: 07-123
Sponsor: Children's Oncology Group
Submission Type: Continuing Review/Renewal

Action: Approved
Effective Date: June 4, 2008
Expiration Date: June 3, 2009
Primary Reviewer: [REDACTED]

Discussion and Remarks:

As required by the IRB, the Parental permission Form has been revised to offer a clearer explanation of the study drug dosing schedule relative to radiotherapy. The protocol is approved for One year under Subpart D, Section 405 (52). The consent documents and study data should appear in each participant's medical record.

The meeting adjourned on July 2, 2008 at 10:05 AM.