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Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Enclosed please find Amendment #8A to protocol AALL1731, *A Phase 3 Trial Investigating Blinatumomab (IND#, NSC# 765986) in Combination with Chemotherapy in Patients with Newly Diagnosed Standard Risk or Down syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients with Localized B-Lymphoblastic Lymphoma (B-LLy)*.

Amendment #8A includes administrative corrections to the protocol that were made in response to a clinical information request by the FDA. These changes are noted in the summary of changes table for the protocol below. In addition, an exploratory aim was revised per the recommendation from the CTEP Protocol Information Office (PIO) of the last protocol review for AALL1731.

Additional administrative changes have been made; specific changes are detailed in the Summary of Changes table below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

Please let me know if you have any questions or need additional information.

Sincerely,

Rachel Vasquez, Protocol Coordinator (for)

Sumit Gupta, M.D., AALL1731 Study co-Chair,
Rachel Rau, M.D., AALL1731 Study co-Chair,
John Kairalla, Ph.D., AALL1731 Study Statistician
David Teachey, M.D., Acute Lymphoblastic Leukemia Committee Chair, and
Douglas S. Hawkins, MD, COG Group Chair

SUMMARY OF CHANGES: B-LLy INFORMED CONSENT

In accordance with the above discussion, the following specific revisions have been made to the consent. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	All	Updated version date of consent to match the current version of the protocol.
2.	Attachment 2	19 20	Updated the risk insert tables for the following agents: • Asparaginase Erwinia chrysanthemi (recombinant) or Asparaginase Erwinia/crisantaspase • Pegaspargase or Calaspargase pegol

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions must use the sections of this document that are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

AALL1731, A Phase 3 Trial Investigating Blinatumomab (IND#, NSC# 765986) in Combination with Chemotherapy in Patients with Newly Diagnosed Standard Risk or Down Syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients with Localized B-Lymphoblastic Lymphoma (B-LLy)

Study title for study participants: A study to compare the addition of Blinatumomab in combination with chemotherapy in patients diagnosed with standard risk B-cell Acute Lymphoblastic Leukemia (B-ALL), Down syndrome B-ALL and the treatment of patients with localized B-cell lymphoblastic lymphoma (B-LLy)

Consent for Subjects with Localized B-cell Lymphoblastic Lymphoma (B-LLy) with or without Down syndrome (DS)

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say “you” in this consent form, we mean you or your child; “we” means the doctors and other staff.

Overview

You are being asked to take part in this research study because you have been diagnosed with localized B-cell Lymphoblastic Lymphoma (B-LLy).

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

The overall goal of this study is to see if children with localized B-LLy receiving “standard risk” B-ALL therapy maintain good treatment outcomes

The treatment involves cancer fighting medicines called chemotherapy. The treatment on this study takes about 2 years. It is divided into 6 phases.

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is

usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished. The risks of the individual drugs are listed in **Attachment 2**.

You can ask your study doctor questions about side effects at any time.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you associated with participation in this study are described in the Section **Are there benefits to taking part in the study?**

You have a choice between another treatment for B-LLy disease and this clinical trial. Please take your time to make your decision. You may want to discuss it with your family and friends. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

The rest of this form provides detailed information about the study and what to expect should you decide to participate.

Why am I being invited to take part in this study?

You are being asked to take part in this research study because you have been diagnosed with localized B-cell Lymphoblastic Lymphoma (B-LLy), with or without Down syndrome.

Localized B-cell Lymphoblastic Lymphoma (B-LLy) is a cancer of the lymph system and other lymphoid tissue throughout the body. Lymphoid tissues make and store infection fighting white blood cells called lymphocytes. These cells become cancerous when a person has B-LLy. Your B-LLy is localized because your lymphoma is restricted to one particular area of the body.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for B-LLy disease and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this disease?

Standard treatment for localized B-LLy has several phases. In the first phase of treatment, called Induction, we try to remove all visible signs of lymphoma and allow normal blood cells to be restored (this is called remission). In the remainder of therapy called post-Induction, we try to get rid of any remaining lymphoma cells to keep them from coming back. Post-Induction therapy

has several phases that are called Consolidation, Interim Maintenance (IM), Delayed Intensification (DI), and Maintenance. During Consolidation, IM, and DI, we try to eliminate any remaining lymphoma cells. In the final phase called Maintenance, we try to keep the lymphoma from coming back. All phases of treatment are very important.

Why is this study being done?

Historically, localized B-LLy was treated similarly to “high risk” B lymphoblastic leukemia (B-ALL) with good results. B-ALL is a kind of cancer that occurs in the bone marrow and is more common than B-LLy. The treatment used for B-LLy subjects on this study is less intense in some ways than standard treatment for B-LLy and is similar to that used currently in COG centers for children and young adults with “standard risk” B-ALL. We want to see if using the same kind of therapy used to treat “standard risk” B-ALL results in the same good outcomes while decreasing side effects.

The overall goal of this study is to see if children with localized B-LLy receiving “standard risk” B-ALL therapy maintain good treatment outcomes

What will happen on this study that is research?

The treatment used on this study for children, teenagers, and young adults with localized B-LLy or DS localized B-LLy is similar to that used currently in COG centers for children with “standard risk” B-ALL and is described in **Attachment 1.**

This clinical trial eliminates the dose of daunorubicin and reduces the dose of cyclophosphamide historically given to patients with localized B-LLy in the United States. In Interim Maintenance, methotrexate will be given at a higher dose by vein instead of by mouth. Also, the Interim Maintenance phase of therapy has historically been given once but on this study will be repeated to happen twice. These changes are being done to see if they can reduce side effects. The treatment on this study takes about 2 years and is divided into the following six phases. The details of these phases are described in **Attachment 1.**

- Induction
- Consolidation
- Interim Maintenance I
- Delayed Intensification
- Interim Maintenance II
- Maintenance

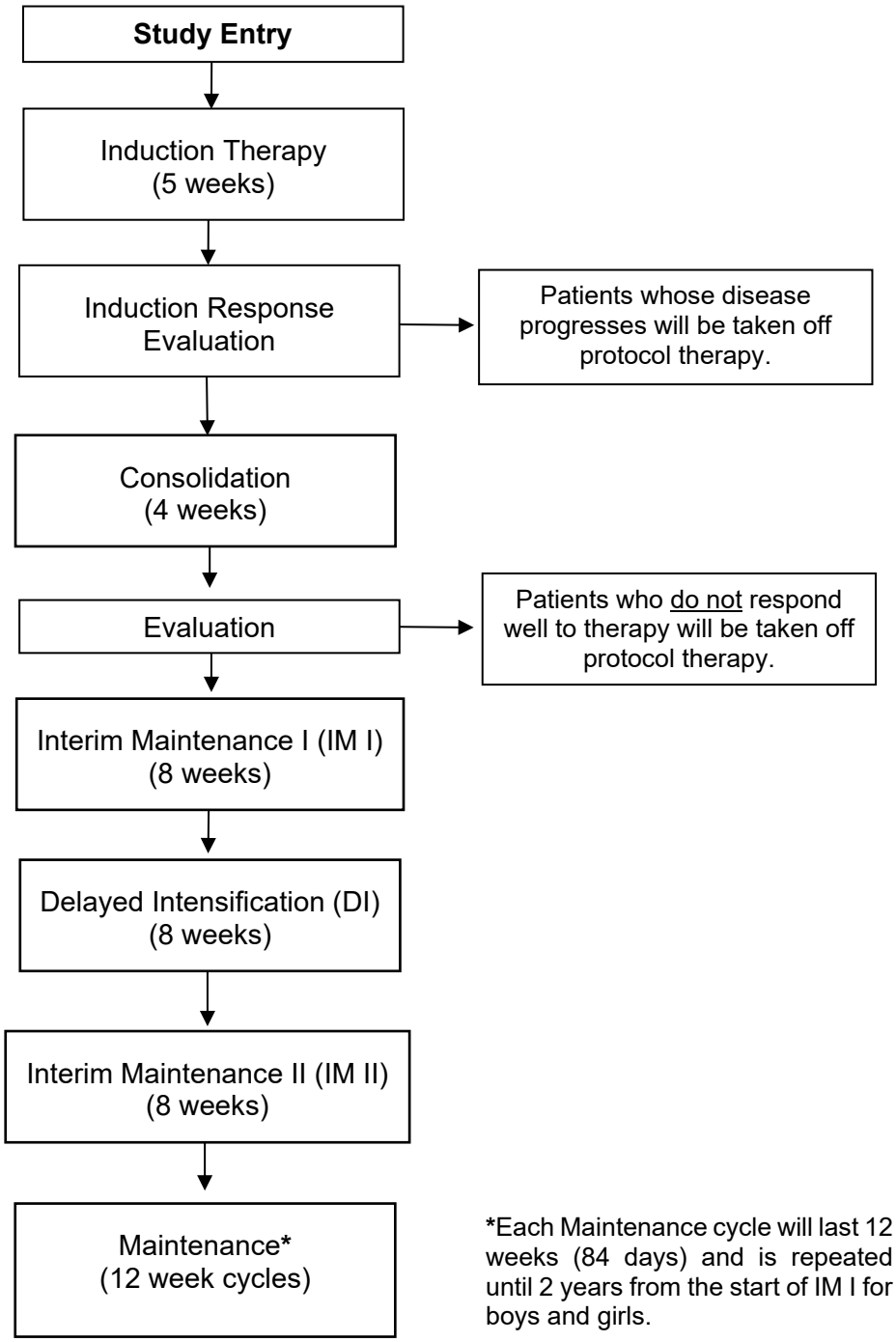
Before starting treatment on this study, a routine diagnostic bone marrow sample will be taken from you to stage the lymphoma (determine how widespread it is).

At the end of Induction and end of Consolidation therapy (for some subjects), imaging studies (scans) will be done to find out how well the treatment is working.

You will continue with post-Induction treatment on this study only if your response to Induction therapy is good. Subjects with poor response to Induction therapy will be removed from the study.

Diagram of Treatment

This chart shows the treatment on this study.



Treatment that is Research

The experimental part of the study is the elimination of daunorubicin, and reduced dose of cyclophosphamide typically given to patients with B-LLy and DS B-LLY. This study will also give methotrexate at a higher dose and by vein instead of by mouth and will include a second Interim Maintenance phase of therapy. Treatment for B-LLy or DS B-LLy on this study is described in **Attachment 1**.

Required Research Study Tests

The following tests will be done because you are part of this study. If you were not in the study, you would probably not have these tests performed.

Response Evaluation

For some subjects, scans will be done to find out how well the treatment is working at the end of Induction and end of Consolidation therapy. You will continue with treatment on this study after Induction only if your response to Induction therapy is good. Subjects with poor response to Induction therapy will be removed from the study. If this occurs, your doctor will discuss options with you. You will also only be able to continue with treatment on this study after Consolidation if you are in remission (visible signs of lymphoma have resolved) at the end of Consolidation. Subjects not in remission at the end of Consolidation therapy will be removed from the study. If this occurs, your doctor will discuss options with you. These scans are part of standard of care treatment and would be performed whether or not you are in this study. You or your health insurance provider will be responsible for the cost of these tests.

Optional Research Study Tests

We would also like to do some tests called biology studies. These tests are important to help us learn more about B-LLy and may help children and young adults in the future. The information learned would not change the way you are treated, and the results of these tests will not be given to you. You do not have to do these tests if you do not want to. You can still be in the study if you do not want to do these tests. At the end of this consent form, there is a place to record your decision about taking part in each test. There will be no extra cost to you or your health insurance provider for the optional studies.

Banking for Future Research

We would like to take some of your tumor tissue for future research. This is called “specimen banking” or “tissue banking.” A tissue bank is a lab where specimens (such as tumor, blood or bone marrow) are kept for use in future research studies. This sample will be collected at diagnosis and at relapse (if it occurs) and will not require any extra procedures. We are also asking for your permission to use any leftover tissue from biopsies that will be part of your standard care.

Minimal Marrow Disease – only for patients receiving treatment in the U.S.

As part of your regular care, your doctor may remove some of your bone marrow for disease testing at certain times throughout the study. With your permission, we would like to collect 5 mL (about 1 teaspoon) of bone marrow at diagnosis for this study. The purpose of this study is to measure very small levels of lymphoma cells in the bone marrow, called minimal marrow disease (MMD), in patients with B-LLy and compare it with outcomes to see if these tests can help doctors predict how B-LLy patients will respond to treatment. This test will not affect the treatment you receive and results from this test will not be returned to you.

What side effects or risks can I expect from being in the study?

Treatment Risks

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

The risks of the individual drugs given as standard treatment are listed in **Attachment 2**.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished.

Though combining chemotherapy drugs is the most effective way to kill lymphoma cells, side effects can also be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in the COG Family Handbook for Children with Cancer. Parents will be taught more about caring for their child when his or her blood counts are low.

Risks of Study

The treatment that is being studied could be less effective than historical treatment used for localized B-LLy. The study will be closely monitored for the potential increased risk of relapse and will be stopped if this is seen.

You may lose time at school, work or home and spend more time in the hospital or doctor's office than usual. You may be asked sensitive or private questions which you normally do not discuss. You may not be able to take part in future studies.

The chemotherapy used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs/study approach. Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

You can ask your study doctor questions about side effects at any time.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.
- The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drugs.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Reproductive risks

Women should not become pregnant, and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

You will also be provided with a clinical trial wallet card for this study at enrollment. The card contains important clinical trial information that your other healthcare providers need to know. It's a convenient wallet-sized information card for you to cut out and retain at all times.

Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

Potential benefits to you could include:

- getting rid of your cancer for a long time or for the rest of your life,
- fewer side effects,
- fewer long term side effects (for example, being less likely to develop problems with the heart, lungs, kidneys; being less likely to have learning problems, or, less risk of getting another cancer later as a result of treatment).

With any cancer treatment, sometimes treatment does not make the cancer go away. Or, sometimes treatment makes the cancer go away for a while but the cancer comes back later.

We expect that the information learned from this study will benefit other patients in the future.

What other options are there?

Instead of being in this study, you have these options:

- **Current standard therapy even if you do not take part in the study.**
- **Taking part in another study**

Please talk to your doctor about these and other options.

How many people will take part in the study?

The total number of people enrolled on this study is expected to be 6,720. The number of people with B-LLy expected to enroll on this study is 50.

How long is the study?

People in this clinical trial are expected to receive treatment on this study for about 2 years. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health every year for about 10 years after you enter this study. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:
- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you
- if you become pregnant

What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. However, we cannot guarantee total privacy. The *Children's Oncology Group* has a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the *Children's Oncology Group* will do their best to make sure that any information that goes out to others will not identify who you are. Information about this Certificate of Confidentiality is included in **Attachment 3**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**

- **The Institutional Review Board of this hospital**
- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

This study includes providing specimens to the researcher. There are no plans for you to profit from any new product developed from research done on your specimens.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. A summary of the study results will also be posted on the Children's Oncology Group website at http://www.childrensoncologygroup.org/. To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all people on the study is completed, and not only when you complete treatment.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* IRB Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

Visit the NCI's Web site at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Specimens for optional research tests

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

If you decide now that your specimens can be used for research and banking, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

If you want to learn more about tissue research with banked specimens, the NCI website has an information sheet called "Providing Your Tissue For Research: What You Need To Know." This sheet can be found at: https://www.cancer.gov/publications/patient-education/providing-tissue.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

#1 **If receiving treatment in the US:** My bone marrow may be collected and studied for the Minimal Marrow Disease study.

Yes_____ No_____ _____ / _____
Initials Date

Specimens for optional biobanking

If you agree to Biobanking, your sample will be stored *in the Biopathology Center at Nationwide Children's Hospital, in a locked freezer*. The samples *will be kept until they are used up*, unless you request that they be destroyed. Some information from your medical record, including your name, date of birth, and unique COG identifier, will also be kept in secure databases at the Biobank and updated from time to time. The information and samples will be kept under a code, not your name.

This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. Qualified researchers can submit a request to use the materials stored in the Biobank. The research may be about your type of cancer, about other cancers, or even about conditions unrelated to cancer. A science committee at the Children's Oncology Group,

and/or the National Cancer Institute, will review each request. Researchers will not be given your name or any other information that could directly identify you. Your sample will not be sold to third parties. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples, unless something is discovered that could directly affect your health. If that happens your study doctor will be notified and will decide whether and how to contact you.

Right now, we don't know what research may be done in the future using your samples. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

Some of your genetic and health information may be placed in central databases that may be made available to qualified researchers, along with information from many other people. Information that could directly identify you will not be included.

Even without your name or other identifiers, your genetic information is unique to you. If you agree to Biobanking, there is a risk of a data security breach and that someone could trace the genetic information in a central database back to you. Although this has never happened in real life and we have many safeguards in place to prevent it from happening, the risk may change in the future as people come up with new ways of tracing information. There are laws against the misuse of genetic information, but they may not give full protection. In some cases, misuse of the information could be used to make it harder for you to get or keep a job or insurance.

There can also be risks in learning about your own genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. Sometimes this is upsetting to families or they wish they didn't know the information. We encourage you to discuss this study with your relatives before you decide whether to participate in the Biobanking part.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

Check YES if you agree to have tumor sample kept (banked) for use in research to learn about, prevent, or treat cancer or other health problems (for example: diabetes, Alzheimer's disease, or heart disease). Check NO if you do not want any new samples banked.

Yes _____ No _____ _____ / _____
Initials Date

Signature

I have been given a copy of all _____ pages of this form. The form includes three (3) attachments.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

Attachment 1

Treatment and Procedures Common to all Patients with B-LLy

Methods for Giving Drugs

Various methods will be used to give drugs:

- **PO** - Drug is given by tablet or liquid swallowed through the mouth.
- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").
- **SubQ** - Drug is given by inserting a needle just under the skin.
- **IT** - Drug used to treat the brain and spinal cord is given using a needle inserted through the back into the fluid surrounding the spinal cord.
- **IM** - Drug is given into a muscle using a needle.

Central Line

Your doctor may recommend that you get a special kind of IV called a "central line." This is a kind of IV placed into a big vein in your body, usually in the chest, that can stay in for a long time. The risks connected with central lines will be explained to you and all of your questions will be answered. If you are to have a central line inserted, you will be given a separate informed consent document to read and sign for this procedure. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

Treatment Tables

The treatment described below is study treatment for patients with localized B-LLy or DS B-LLy.

Studies have shown that subjects who have DS are more likely to suffer serious side effects from treatment with chemotherapy than subjects without DS. Subjects with DS are particularly sensitive to certain chemotherapy medications, such as methotrexate. To help lessen the side effects of methotrexate, you will be given a medicine called leucovorin, 24 and 30 hours after you are given methotrexate into your spinal fluid. Although leucovorin may help with side effects, it may also make methotrexate less effective in treating lymphoma.

Induction

Induction therapy starts on Day 1 and lasts about 35 days (or about 5 weeks).

Drug	How the drug will be given	Days
Cytarabine	IT	1
VinCRIStine	IV infusion using a minibag over several minutes	1, 8, 15, and 22
Pegaspargase [1]	IV over 1-2 hours or IM	4
or Calaspargase pegol [1,2]	IV over 1-2 hours	
Dexamethasone [3]	PO twice a day or IV	1-28
Prednisone or Prednisolone [4]	PO twice a day	1-28
Methotrexate	IT	8 and 29
Leucovorin[5]	PO or IV	24 and 30 hours after each IT MTX

[1] If you develop an allergy to pegaspargase or calaspargase pegol, a different form of asparaginase may be substituted for each dose of pegaspargase or calaspargase pegol.

[2] Calaspargase pegol can only be administered to patients less than 22 years of age.

[3] For non-Down syndrome patients at all ages, and Down syndrome patients < 10 years old only.

[4] For Down syndrome patients ≥ 10 years old only. IV methylprednisolone may be substituted for prednisolone.

[5] For Down syndrome patients only.

You will be examined at the end of Induction therapy to find out how well your cancer has responded to treatment. Depending on your response to Induction, you may be able to continue to receive treatment on this study.

Consolidation

Consolidation therapy starts after Induction and lasts about 28 days (or about 4 weeks)

Drug	How the drug will be given	Days
Mercaptopurine	PO	1-28
VinCRIStine	IV infusion using a minibag over several minutes	1
Methotrexate	IT	1, 8, and 15
Leucovorin [1]	PO or IV	24 and 30 hours after each IT MTX

[1] For Down syndrome patients only.

If there was still some tumor at the end of Induction you may have scans done again at the end of Consolidation. If your disease is in remission, you will move on to the next phase of therapy which is Interim Maintenance. If your disease is not in remission, you may be removed from protocol therapy. Your doctor will speak more to you about this.

Interim Maintenance I

Interim Maintenance I with escalating methotrexate lasts about 56 days (or about 8 weeks)

Drug	How the drug will be given	Days
Methotrexate	IV over 2-5 minutes (if medicine is undiluted) or 10-15 minutes (if medicine is diluted). Each dose is increased from the previous one as tolerated.	1, 11, 21, 31 and 41
VinCRIStine	IV infusion using a minibag over several minutes	1, 11, 21, 31 and 41
Methotrexate	IT	31
Leucovorin [1]	PO or IV	24 and 30 hours after each IT MTX

[1] For Down syndrome patients only.

Delayed Intensification

Delayed Intensification lasts about 56 days (or about 8 weeks)

Drug	How drug will be given	Days
Methotrexate	IT	1 and 29
Dexamethasone	PO twice a day or IV	1-7 and 15-21
VinCRIStine	IV infusion using a minibag over several minutes	1, 8, and 15
DOXOrubicin	IV over 3-15 minutes	1, 8, and 15
Leucovorin [1]	PO or IV	24 and 30 hours after each IT MTX
Pegaspargase [2] or Calaspargase pegol[2, 3]	IV over 1-2 hours or IM	4
	IV over 1-2 hours	
Cyclophosphamide	IV over 30-60 minutes	29
Thioguanine	PO once a day	29-42
Cytarabine	IV over 1-30 minutes or SubQ	29-32 and 36-39

[1] For Down syndrome patients only.

[2] If you develop an allergy to pegaspargase or calaspargase pegol, a different form of asparaginase may be substituted for each dose of pegaspargase or calaspargase pegol.
[3] Calaspargase pegol can only be given to patients under the age of 22 years.

Interim Maintenance II

Interim Maintenance II with escalating methotrexate lasts about 56 days (or about 8 weeks)

Drug	How the drug will be given	Days
Methotrexate	IV over 2-5 minutes (if medicine is undiluted) or 10-15 minutes (if medicine is diluted). Each dose is increased from the previous one as tolerated.	1, 11, 21, 31 and 41
VinCRIStine	IV infusion using a minibag over several minutes	1, 11, 21, 31 and 41
Methotrexate	IT	1 and 31
Leucovorin [1]	PO or IV	24 and 30 hours after each IT MTX

[1] For Down syndrome patients only.

Maintenance

Maintenance therapy cycles last 12 weeks (84 days) are repeated until 2 years from the start of IM I.

Maintenance for non-Down syndrome patients

Drug	How drug will be given	Day of cycle
VinCRIStine	IV infusion using a minibag over several minutes	Every 12 weeks
Dexamethasone	PO twice a day or IV	5 days every 12 weeks
Methotrexate	PO	Once a week [1]
Mercaptopurine	PO once a day	1-84
Methotrexate	IT	1

[1] Except when IT methotrexate is administered on Day 1.

Maintenance for Down syndrome patients

Drug	How drug will be given	Day of cycle
VinCRIStine	IV infusion using a minibag over several minutes	Every 12 weeks
Dexamethasone	PO twice a day or IV	5 days every 12 weeks
Methotrexate	PO	Once a week [1]
Mercaptopurine	PO once a day	1-84
Methotrexate	IT	1
Leucovorin	PO or IV	24 and 30 hours after each IT MTX

[1] Except when IT methotrexate is administered on Day 1.

Standard Tests and Procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- Frequent labs to monitor your blood counts and blood chemistries.
- Urine tests to measure how your kidneys are functioning.
- Pregnancy test for females of childbearing age before treatment begins.
- X-rays and scans to monitor your response to treatment.

- Tests to monitor your heart and lung function.
- Bone marrow aspiration tests to see if the cancer is responding to treatment. The bone marrow procedure is described in the COG Family Handbook for Children with Cancer.
- Spinal Taps to check for cancer cells in the spinal fluid and to give chemotherapy into the spinal fluid. This is described in the COG Family Handbook for Children with Cancer.

Attachment 2

Risks of Chemotherapy Drugs Used to Treat B-LLy

Possible Side Effects of Asparaginase erwinia chrysanthemi (recombinant) or Asparaginase erwinia/crisantaspase

COMMON, SOME MAY BE SERIOUS In 100 people receiving Asparaginase erwinia chrysanthemi (recombinant) or Asparaginase erwinia/crisantaspase, more than 20 and up to 100 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Belly pain, nausea, diarrhea, decreased appetite** • **Infection, especially when white blood cell count is low** • **Bleeding** • **Sores in mouth which may cause difficulty swallowing** • **Pain in muscles** • **Tiredness** • **Heachache** • **Fever**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Asparaginase erwinia chrysanthemi (recombinant) or Asparaginase erwinia/crisantaspase, from 4 to 20 may have:
• **Abnormal heartbeat which may cause fainting** • **High blood pressure which may cause headaches, dizziness, blurred vision** • **Low blood pressure which may cause feeling faint** • **Pain including in the bone** • **Acute respiratory distress syndrome which may cause damage to the lungs and shortness of breath** • **Fluid around lungs which may cause shortness of breath** • **Cough** • **Kidney damage which may cause swelling, may require dialysis** • **Possible changes in mental status** • **Dehydration** • **Bloating, constipation** • **Feeling of “pins and needles” in arms and legs** • **Muscle cramp, muscle weakness** • **Difficulty walking** • **Restlessness, difficulty sleeping** • **Worry, irritability** • **Dizziness** • **Itching** • **Swelling and redness at the site of the medication injection** • **Blood clot, including in the brain, which may lead to stroke**

RARE, AND SERIOUS In 100 people receiving Asparaginase erwinia chrysanthemi (recombinant) or Asparaginase erwinia/crisantaspase, 3 or fewer may have:
• **Sinusoidal obstructive syndrome (SOS) which may cause damage to the liver, yellowing of the eyes and skin, swelling**

Possible Side Effects of Pegaspargase or Calaspargase pegol

COMMON, SOME MAY BE SERIOUS In 100 people receiving Pegaspargase or Calaspargase pegol, more than 20 and up to 100 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Nausea, vomiting** • **Chills, fever** • **Tiredness** • **Hives, rash**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Pegaspargase or Calaspargase pegol, from 4 to 20 may have:
• **Abnormal heart beat** • **Blood clot, including in the brain, which may lead to stroke** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Anemia which may require blood transfusions** • **Liver damage which may cause yellowing of eyes and skin** • **Belly pain, damage to the pancreas** • **Diabetes**

RARE, AND SERIOUS In 100 people receiving Pegaspargase or Calaspargase pegol, 3 or fewer may have:
• **Sinusoidal obstructive syndrome (SOS) which may cause damage to the liver, yellowing of the eyes and skin, swelling**

Possible Side Effects of Cyclophosphamide

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, more than 20 and up to 100 may have:
• **Hair loss, skin changes, rash, change in nails** • **Nausea, vomiting, diarrhea, loss of appetite, pain in belly** • **Sores in mouth which may cause difficulty swallowing** • **Infection, especially when white blood cell count is low** • **Absence of menstrual period which may decrease the ability to have children** • **Blood in urine** • **Anemia which may cause tiredness, or may require transfusion** • **Bruising, bleeding**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, from 4 to 20 may have:
• **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions** • **Loss or absence of sperm which may lead to an inability to father children** • **Fluid around the heart**

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, 3 or fewer may have:
• **Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness** • **A new cancer (including leukemia) resulting of treatment of a prior cancer** • **Swelling of the body including the brain which may cause dizziness, confusion** • **Damage to the lungs or scarring of the lungs which may cause shortness of breath** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Sinusoidal obstructive syndrome (SOS) which may cause damage to the liver, yellowing of eyes and skin, swelling** • **Kidney damage which may cause swelling, may require dialysis** • **Stevens-Johnson syndrome which may cause severe skin rash with blisters and peeling which can involve mouth and other parts of the body**

Possible Side Effects of Cytarabine when given into the spinal fluid (intrathecal)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, more than 20 and up to 100 may have:
• **Nausea, vomiting** • **Fever** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, from 4 to 20 may have:
• **Anemia which may cause tiredness, or may require blood transfusions** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Tiredness, dizziness, loss of coordination** • **Numbness and tingling of the arms and legs** • **Inflammation of the lining of the brain that can lead to headache, numbness and tingling**

RARE, AND SERIOUS In 100 people receiving Cytarabine, 3 or fewer may have:
• **Seizure** • **Paralysis** • **Blurred vision with a chance of blindness** • **Damage to the brain that may result in a decrease in the ability to learn**

Possible Side Effects of Cytarabine by vein or under the skin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, more than 20 and up to 100 may have:
• **Infection, especially when white blood cell count is low** • **Anemia which may cause tiredness, or may require blood transfusions** • **Bruising, bleeding** • **Blood clot** • **Rash** • **Diarrhea, loss of appetite, nausea, vomiting, pain in belly** • **Sores in mouth, throat, and GI tract including rectum which may cause difficulty swallowing or pain** • **Fever**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, from 4 to 20 may have:
• **Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness** • **Abnormal heartbeat which may cause fainting** • **Damage to the lungs which may cause shortness of breath** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Numbness and tingling of the arms and legs** • **Muscle pain** • **Severe blood infection** • **Kidney damage which may cause swelling, may require dialysis** • **Headache** • **Dizziness, confusion** • **Flu-like syndrome with fever, bone pain, rash, redness of eyes, or chest pain** • **Chest pain** • **Hair loss** • **Liver damage which may cause yellowing of skin or eyes** • **Swelling and redness of the eye** • **Hives** • **Itching** • **Infection at injection site which may cause rash** • **Difficulty emptying the bladder or urinating**

RARE, AND SERIOUS In 100 people receiving Cytarabine, 3 or fewer may have:
• **Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness** • **Difficulty speaking, trouble standing or walking, coma** • **Swelling and redness at the site of the medication injection (SubQ)**

Possible Side Effects of Dexamethasone

COMMON, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, more than 20 and up to 100 may have:
• **High blood pressure which may cause headaches, dizziness** • **Skin changes, rash, acne** • **Swelling of the body, tiredness, bruising** • **In children and adolescents: decreased height** • **Pain in belly, heartburn** • **Infection** • **Damage to the bone which may cause joint pain, loss of motion, or broken bones** • **Difficulty sleeping** • **Mood swings** • **Diabetes** • **Increased appetite and weight gain in belly, face, back and shoulders** • **Loss of bone tissue** • **Restlessness, worry**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, from 4 to 20 may have:
• **Blood clot which may cause swelling, pain, shortness of breath** • **Glaucoma** • **Cloudiness of the eye, visual disturbances, blurred vision** • **A tear or a hole in the bowels which may cause pain or that may require surgery** • **Numbness, pain and tingling of the arms, legs, fingers and/or toes** • **Muscle weakness** • **Non-healing wound**

RARE, AND SERIOUS In 100 people receiving dexamethasone, 3 or fewer may have:
• **None**

Possible Side Effects of Doxorubicin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, more than 20 and up to 100 may have:
• **Hair loss** • **Nausea, vomiting** • **Red colored urine, saliva, or sweat**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, from 4 to 20 may have:
• **Heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose** • **Abnormal heartbeat** • **Damage to the lungs which may cause shortness of breath when combined with radiation** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Anemia which may cause tiredness, or may require transfusion** • **Kidney damage which may require dialysis** • **Swelling and redness at the site of the medication injection or area of previous radiation** • **Belly pain** • **Diarrhea, dehydration** • **Sores in the mouth or throat** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Absence of menstrual period or early menopause** • **Damage to sperm** • **Muscle weakness** • **Damage to the skin which may cause pain** • **Changes to the nails** • **Darkening of the nail beds or skin or hands and feet** • **Darkening of the gums**

RARE, AND SERIOUS In 100 people receiving Doxorubicin, 3 or fewer may have:
• **Severe blood infection** • **Cancer of the bone marrow, caused by chemotherapy, which may result in leukemia (cancer of the bone marrow)**

Possible Side Effects of Leucovorin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Leucovorin, more than 20 and up to 100 may have:
• **Diarrhea, nausea, vomiting, loss of appetite** • **Sores in mouth which may cause difficulty swallowing** • **Tiredness** • **Blisters on the skin**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Leucovorin, from 4 to 20 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**

RARE, AND SERIOUS In 100 people receiving Leucovorin, 3 or fewer may have:
• **None**

Possible Side Effects of Mercaptopurine

COMMON, SOME MAY BE SERIOUS In 100 people receiving Mercaptopurine, more than 20 and up to 100 may have:
• **Anemia which may cause tiredness, or may require transfusion** • **Bruising, bleeding** • **Infection, especially when white blood cell count is low** • **Rash** • **Loss of appetite, nausea, vomiting, diarrhea** • **Fatigue**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Mercaptopurine, from 4 to 20 may have:
• **Damage to the liver which may cause pain, bleeding, confusion, yellowing of eyes and skin** • **Increased risk of sunburn** • **Fever**

RARE, AND SERIOUS In 100 people receiving Mercaptopurine, 3 or fewer may have:
• **Scarring of the lungs which may cause shortness of breath** • **Damage to the pancreas causing belly pain** • **A new cancer resulting from treatment** • **Loss or absence of sperm**

Possible Side Effects of Methotrexate when given into the spinal fluid (intrathecal)

COMMON, SOME MAY BE SERIOUS In 100 people receiving methotrexate when given into the spinal fluid, more than 20 and up to 100 may have:
• **Nausea** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving methotrexate when given into the spinal fluid, from 4 to 20 may have:
• **Swelling of the brain which may cause blurred vision, and/or confusion** • **Damage to the brain which may cause changes in thinking** • **Confusion, dizziness** • **Vomiting** • **Rash** • **Tiredness** • **Pain** • **Anemia which may require blood transfusions** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Difficulty with speaking**

RARE, AND SERIOUS In 100 people receiving methotrexate when given into the spinal fluid, 3 or fewer may have:
• **Seizure** • **Damage to the brain which could lead to coma** • **Paralysis, weakness** • **Bleeding into the space of the spine at the site of the injection**

Possible Side Effects of Methotrexate when given by mouth or by vein

COMMON, SOME MAY BE SERIOUS In 100 people receiving methotrexate, more than 20 and up to 100 may have:
• **Loss of appetite** • **Increased risk of sunburn, rash** • **Hair loss**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving methotrexate, from 4 to 20 may have:
• **Heart failure, which may cause shortness of breath, swelling of ankles, cough, or tiredness** • **Fluid around heart** • **Internal bleeding which may cause belly pain, black tarry stool, blood in vomit** • **Blood in urine** • **Sores in mouth which may cause difficulty swallowing** • **Nausea, vomiting, diarrhea, weight loss, heartburn, belly pain** • **Menstrual changes** • **Flu-like symptoms, including fever, chills, body aches, muscle pain, tiredness** • **Headache** • **Numbness and tingling of the skin** • **Hepatitis or damage to the liver which may cause yellowing of eyes and skin, swelling** • **Scarring of the lungs or damage to the lungs, which may cause shortness of breath, cough** • **Bruising, bleeding** • **Infection, including pneumonia, especially when white blood cell count is low** • **Anemia which may cause tiredness, or may require transfusion** • **Seizure** • **Kidney damage which may require dialysis** • **Low blood pressure, which may cause feeling faint** • **Blurred vision or other visual changes, possibly including temporary blindness** • **Swelling and redness of the whites of the eye** • **Blood clot, possibly in the brain or lung, which may cause swelling, pain, shortness of breath** • **Damage to the brain, which may cause tiredness, confusion, changes in mood, anxiety, dizziness, lightheadedness, ringing in the ears, difficulty speaking or understanding speech** • **Weakness on one or both sides of the body** • **Low blood oxygen, which may cause shortness of breath, headache, confusion, or restlessness**

RARE, AND SERIOUS In 100 people receiving methotrexate, 3 or fewer may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Stevens Johnson syndrome which may cause severe skin rash with blisters and peeling which can involve mouth and other parts of the body**

Possible Side Effects of Methylprednisolone

COMMON, SOME MAY BE SERIOUS In 100 people receiving methylprednisolone, more than 20 and up to 100 may have:
• **In children and adolescents: decreased height** • **Loss of bone tissue which may lead to increased bone fractures** • **Joint pain** • **Mood swings, depression, worry** • **Skin changes, acne, rash** • **Increased sweating** • **Changes in hair growth, hair loss** • **Swelling of the body from fluid retention, tiredness, bruising** • **High blood pressure which may cause headaches, dizziness, blurred vision** • **Pain in belly, bloating, nausea, hiccups** • **Increased appetite and weight gain in the belly, face, back and shoulders** • **Difficulty sleeping, restlessness** • **Dizziness**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving methylprednisolone, from 4 to 20 may have:
• **Blood clot which may cause swelling, pain, shortness of breath** • **Fluid around lungs which may cause shortness of breath** • **Cloudiness of the eye, visual disturbances, blurred vision** • **Glaucoma** • **Infection** • **A tear or a hole in the bowels which may cause belly pain or that may require surgery** • **Non-healing wound** • **Diabetes** • **Numbness and tingling of the arms, legs, and upper body** • **Muscle weakness** • **Heartburn**

RARE, AND SERIOUS In 100 people receiving methylprednisolone, 3 or fewer may have:
• **Bleeding from sores in the stomach**

Possible Side Effects of Prednisone or Prednisolone

COMMON, SOME MAY BE SERIOUS In 100 people receiving prednisone or prednisolone, more than 20 and up to 100 may have:
• **In children and adolescents: decreased height** • **Loss of bone tissue** • **Mood swings** • **Skin changes, acne** • **Swelling of the body, tiredness, bruising** • **High blood pressure which may cause headaches, dizziness, blurred vision** • **Pain in belly** • **Increased appetite and weight gain in the belly, face, back and shoulders** • **Difficulty sleeping**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving prednisone or prednisolone, from 4 to 20 may have:
• **Irregular heartbeat** • **Heart failure** • **Blood clot which may cause swelling, pain, shortness of breath** • **Cloudiness of the eye, visual disturbances, blurred vision** • **Glaucoma** • **Infection** • **Non-healing wound** • **Diabetes** • **A tear or a hole in the bowels which may cause belly pain or that may require surgery** • **Damage to the bone which may cause joint pain and loss of motion** • **Numbness and tingling of the arms, legs and upper body** • **Muscle weakness** • **Heartburn**

RARE, AND SERIOUS In 100 people receiving prednisone or prednisolone, 3 or fewer may have:
• **Tiredness and low blood pressure which may cause feeling faint** • **Bleeding from sores in the stomach** • **Broken bones**

Possible Side Effects of Thioguanine

COMMON, SOME MAY BE SERIOUS In 100 people receiving thioguanine, more than 20 and up to 100 may have:
• **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Anemia which may cause tiredness, or may require transfusion** • **Increased risk of sunburn**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving thioguanine, from 4 to 20 may have:
• **Nausea, vomiting, loss of appetite** • **Sores in mouth which may cause difficulty swallowing** • **Damage to the bowels** • **A tear or a hole in the bowels which may cause pain or that may require surgery** • **Fluid in belly, which may cause belly pain, swelling** • **Sinusoidal obstruction syndrome (SOS) which may cause damage to the liver, yellowing of skin, swelling** • **Tumor lysis syndrome which may cause kidney damage which may require dialysis**

RARE, AND SERIOUS In 100 people receiving thioguanine, 3 or fewer may have:
• **None**

Possible Side Effects of Vincristine

COMMON, SOME MAY BE SERIOUS In 100 people receiving Vincristine, more than 20 and up to 100 may have:
• **Constipation, which may be severe, as a result of a bowel blockage** • **Nausea, vomiting, diarrhea** • **Hair loss** • **Pain or redness at the site of injection** • **Numbness and tingling of fingers or toes** • **Headache, jaw pain and/or bone/muscle pain** • **Muscle weakness and difficulty walking** • **Swelling of lower legs**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Vincristine, from 4 to 20 may have:
• **High blood pressure which may cause headaches, dizziness, blurred vision** • **Low blood pressure which may cause feeling faint** • **Anemia which may cause tiredness, or may require blood transfusions** • **Swelling that may be accompanied by confusion, and dizziness** • **Paralysis** • **Drooping eyelids, abnormal eye movement** • **Hoarseness** • **Difficulty with balance and hearing** • **Loss of appetite, weight loss** • **Difficulty emptying the bladder or urinating, excessive, frequent, or painful urination**

RARE, AND SERIOUS In 100 people receiving Vincristine, 3 or fewer may have:
• **Seizure** • **Coma** • **Visual loss with a chance of blindness** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**

Attachment 3

Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.