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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 #4 to protocol ANHL1931, **A Randomized Phase 3 trial of Nivolumab (NSC# 748726 IND# [redacted]) in Combination with Chemo-immunotherapy for the Treatment of Newly Diagnosed Primary Mediastinal B-cell Lymphoma**.

Amendment #4 addresses the CTEP amendment request to revise prior malignancy eligibility criteria to ASCO/Friends Modernizing eligibility and the CTEP amendment request to expand study accrual. Sections of the protocol and consent were updated to reflect this change.

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,

Jenna Braun, Protocol Coordinator (for)
Lisa Roth, M.D., ANHL1931 Study Chair,
Carl Allen, M.D., Non Hodgkins Lymphoma Committee Chair, and
Douglas S. Hawkins, MD, COG Group Chair

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SUMMARY OF CHANGES: 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.	Overview	2	Revised common side effects to align accurately with nivolumab side effects.
3.	Reproductive Risks	10	Removed reproductive risk language for men
4.	Attachment 1	17-18	Added clarifying language for subq administration
5.	Attachment 2	19-24	• Updated Possible Side Effects of Rituximab • Updated Possible Side Effects of CHOP • Updated Possible Side Effects of EPOCH

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

ANHL1931 A Randomized Phase 3 trial of Nivolumab in Combination with Chemo-immunotherapy for the Treatment of Newly Diagnosed Primary Mediastinal B-cell Lymphoma

Study title for study participants: A study combining nivolumab and chemo-immunotherapy as a treatment option for Primary Mediastinal B-cell lymphoma (PMBCL).

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 clinical trial because you have been diagnosed with Primary Mediastinal B-cell lymphoma (PMBCL).

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 compare the effects, good and/or bad, of nivolumab with chemo-immunotherapy on people diagnosed with PMBCL.

The treatment involves cancer fighting medicines called chemotherapy plus an immunotherapy medicine with or without the study drug, nivolumab. You may also receive a treatment called radiotherapy (also called radiation therapy) which is usually used to kill cancer cells and shrink tumors. The treatment on this study takes about 4-6 months.

In this study you will get 1 of 3 treatment plans. Treatment #1 is the chemo-immunotherapy regimen DA-EPOCH-R (Etoposide + Prednisone + Vincristine + Cyclophosphamide + Doxorubicin + Rituximab) with or without the study agent, nivolumab. The “DA” stands for dose-adjusted. Treatment #2 is the chemo-immunotherapy regimen R-CHOP (Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone), with or without the study agent, nivolumab. Treatment #3 is the chemo-immunotherapy regimen R-CHOP in combination with radiotherapy with or without nivolumab.

The chemo-immunotherapy regimen treatment that you receive will be decided by your treating doctor.

Whether or not you receive the study drug nivolumab in addition to chemo-immunotherapy regimen is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer. You and your doctor will not pick if you receive nivolumab.

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

This study uses the investigational drug nivolumab. Common side effects of this drug are fatigue (tiredness).Some less common but notable side effects are swelling and redness of the eye, pain, nausea, diarrhea, dry mouth, fever, loss of appetite, lowering of the number of blood cells resulting in anemia, and bleeding tendency**.** Nivolumab may also cause your immune system to attack normal organs and cause side effects in many parts of the body. The full list of risks for nivolumab are available in the section What side effects or risks can I expect from being in the study?

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 a standard treatment for PMBCL and this research study.

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 Primary Mediastinal B Cell Lymphoma (PMBCL).

PMBCL is a type of cancer that occurs in the upper chest between the lungs and behind the breast bone, in an area called the mediastinum. PMBCL is considered an aggressive (fast-growing) form of another type of cancer known as large B-cell lymphoma.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This trial is part of the national NCI Clinical Trials Network (NCTN) program which is sponsored by the National Cancer Institute (NCI). The trial will be conducted by the network of NCTN researchers, led by the Children’s Oncology Group (COG).

It is common to enroll children, adolescents, and adults with conditions such as PMBCL in a clinical trial that seeks to improve treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for PMBCL and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. For children with PMCBL, 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 is the treatment that most cancer doctors would recommend you receive even if you decide not to participate in a clinical trial. Chemotherapy is mainly used as the standard treatment for PMBCL. Two common standard chemotherapy regimens are R-CHOP (a combination of chemotherapy drugs: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and DA-EPOCH-R (a combination made up of the chemotherapy drugs etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin, and the immunotherapy drug, rituximab). The “DA” stands for “dose-adjusted.” Radiation therapy is often used in combination with R-CHOP and occasionally with DA-EPOCH-R when disease is left after completion of chemotherapy.

Why is this study being done?

Treatment for PMBCL involves chemotherapy combined with an immunotherapy called rituximab. This combination is also known as the chemo-immunotherapy regimen. There are two types of chemo-immunotherapy regimens for PMBCL: either R-CHOP or DA-EPOCH-R.

These drugs effectively treat PMBCL, but are known to cause long-term side effects at high doses. Side effects are unintended and unwanted results of treatment. Study doctors are interested in finding an effective treatment that improves the outcome of PMBCL.

Nivolumab is a type of cancer treatment which uses the immune system to fight cancer. We will be using nivolumab with chemo-immunotherapy and comparing the results with only chemo-immunotherapy in newly diagnosed PMBCL. By doing this study, we are hoping that we can figure out the best way to treat PMBCL while also improving outcomes.

This study looks at how well the addition of nivolumab to chemo-immunotherapy works when given to children, adolescents, and adults with PMBCL. Nivolumab is experimental because it has not been proven to work in people with PMBCL.

The overall goals of this study are to

- **Compare the effects, good and/or bad, of nivolumab with chemo-immunotherapy versus chemo-immunotherapy alone on people with PMBCL to find out which is better. In this study, you will get either the nivolumab with the chemo-immunotherapy or the chemo-immunotherapy alone.**

Other goals of this study include understanding the biology and treatment of PMBCL.

What will happen on this study that is research?

The treatment involves cancer fighting medicine called chemo-immunotherapy with or without nivolumab. The treatment on this study takes about 6 cycles or 4-6 months (each cycle is 21 days).

Most of the treatment in this study is standard or regular therapy for people with PMBCL. Treatment that is standard for PMBCL is described in **Attachment 1**.

Some parts of the treatment on this study are different from standard therapy. These parts are experimental and include the drug, nivolumab, as described below.

Summary of Study Treatments

The chemo-immunotherapy treatment that you receive will be decided by your treating physician. This chemo-immunotherapy treatment will either be R-CHOP or DA-EPOCH-R.

In this study you will get 1 of 3 treatment plans. Treatment #1 is the chemo-immunotherapy regimen DA-EPOCH-R with or without the study agent, nivolumab. Treatment #2 is the chemo-immunotherapy regimen R-CHOP, with or without the study agent, nivolumab. Treatment #3 is the chemo-immunotherapy regimen R-CHOP in combination with radiation treatments with or without nivolumab. There will be imaging tests (scans) after various cycles of treatment to evaluate how the tumor has responded to treatment. Depending on the results of the tests, you may be taken off the study. After 6 cycles of treatment, you will have another imaging test. Based on the results of the imaging test, you may either receive radiation treatments, be placed under observation, or receive a biopsy. If the biopsy is positive, you will go on to receive radiation treatments regardless of your treatment plan. If you get treatment #3, you will receive radiation regardless of imaging results.

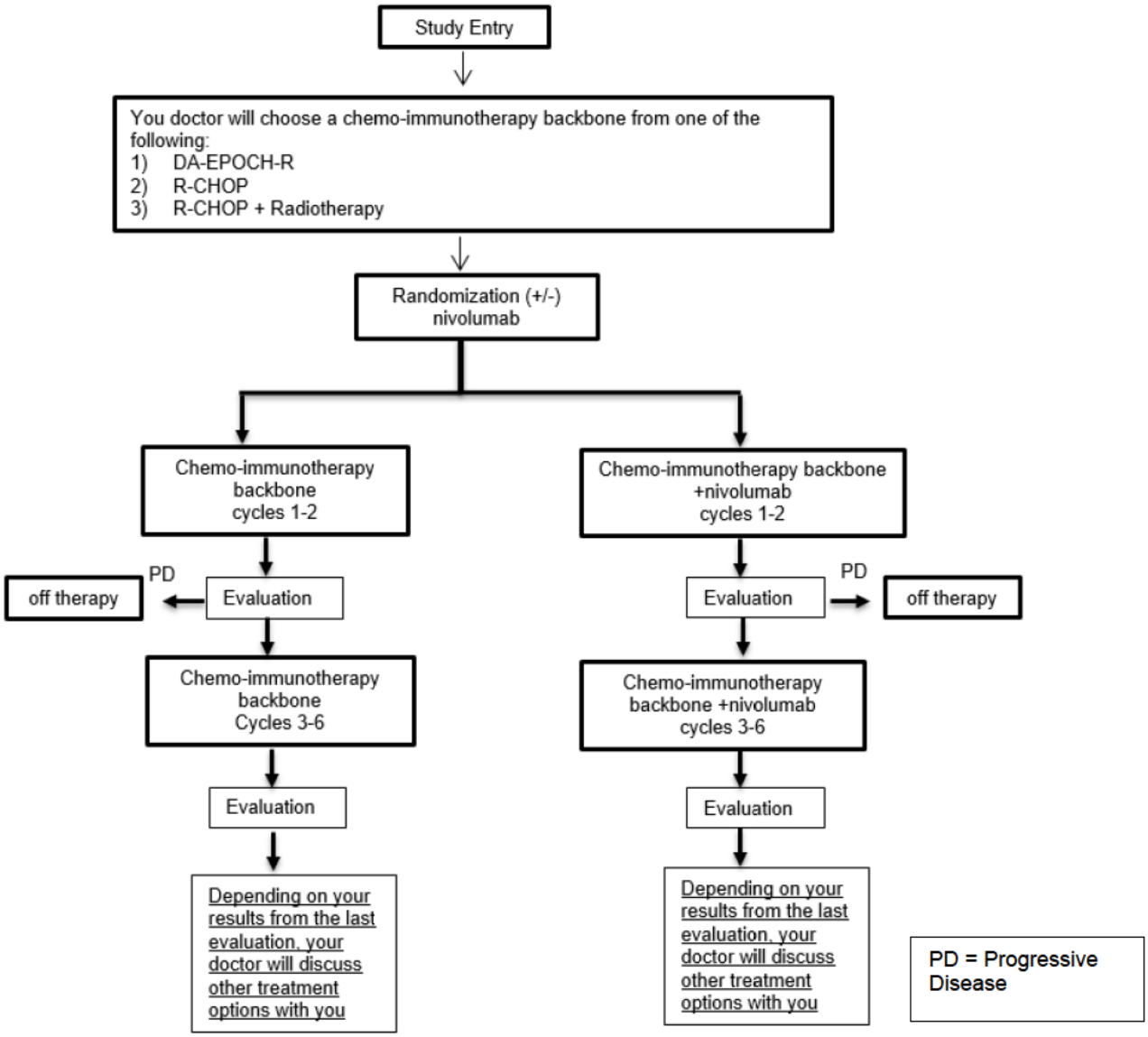
Random Assignment
Whether or not you receive the study drug nivolumab is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer. You and your doctor will not pick whether you get nivolumab or not. The randomization process is described in the COG Family Handbook for Children with Cancer.

Subjects will be randomized to receive nivolumab with a chemo-immunotherapy regimen, or to receive the chemo-immunotherapy regimen without nivolumab.

The treatment plans are listed as follows:

- **Arm A:** DA-EPOCH-R
- **Arm B:** DA-EPOCH-R with nivolumab
- **Arm C:** R-CHOP
- **Arm D:** R-CHOP with nivolumab
- **Arm E:** R-CHOP + radiation
- **Arm F:** R-CHOP + radiation with nivolumab

Diagram of Treatment
This chart shows the treatments on this study.



Treatment that is Research
The addition of the drug nivolumab to a standard chemo-immunotherapy regimen (DA-EPOCH-R or R-CHOP) is considered research and is described below. Standard Chemo-Immunotherapy treatment is described in Attachment 1.

Experimental Treatment for subjects who are on Arm B, D, or F

Drug	How the drug will be given	Days
Nivolumab	IV infusion over 30 minutes	Day 1

Research Study Tests and Procedures
The sections below describe tests that will be done because you are part of this study. If you were not part of the study, you would probably not have these tests. More information on these tests are as follows:

Required Research Study Tests

Central Review of Diagnostic Material
Some of the bone marrow and tumor tissue, already taken and used to diagnose PMBCL will be sent to a review center to help confirm findings. The results of these reviews will not be returned to you.

Optional Research Study Tests

We would also like to do some tests called biologic studies. These tests are important to help us learn more about the effect of nivolumab in treating PMBCL and may help children, adolescents, and adults with PMBCL 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.

Immune profile and Biomarker Testing
Study doctors would like to learn more about how your immune system responds to treatment. We also want to see whether we can predict a patient's response to treatment based on certain markers in the blood. If you agree to this testing, we will draw additional blood at the following timepoints:

At the start of therapy:
- Immune Tests: about 3 tablespoons (or 40 mL) of blood will be drawn
- Biomarker Tests: about 4 teaspoons (or 20 mL) of blood will be drawn

At the start of Cycle 2:
- Immune Tests: about 3 tablespoons (or 40 mL) of blood will be drawn

At the start of Cycle 3:
- Biomarker Tests: about 4 teaspoons (or 20 mL) of blood will be drawn

At the end of therapy:
- Immune Tests: about 3 tablespoons (or 40 mL) of blood will be drawn
- Biomarker Tests: about 4 teaspoons (or 20 mL) of blood will be drawn

If your PMBCL returns:
- Biomarker Tests: about 4 teaspoons (or 20 mL) of blood will be drawn

Optional Specimen Banking
As part of your regular care, your doctor may have removed some tissue and bone marrow. If any of this tissue is left over and no longer needed for your medical care, we would like to use it to study PMBCL.

We would like to take some of your tissue and bone marrow 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.

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 cells and produce side effects.

The risks of the individual drugs given as standard treatment and risks of radiation therapy 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.

Side effects can 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 use of nivolumab together with standard chemo-immunotherapy may cause more complications.

The nivolumab treatment together with standard chemo-immunotherapy that is being studied could be less effective than the current standard treatment.

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.

The table(s) below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible side effects of nivolumab:

Special precautions Side effects of nivolumab may happen anytime during treatment or even after your treatment has ended. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**
COMMON, SOME MAY BE SERIOUS In 100 people receiving nivolumab, more than 20 and up to 100 may have:
• **Tiredness**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving nivolumab, from 4 to 20 may have:
• **Anemia which may require blood transfusion** • **Swelling and redness of the eye** • **Pain** • **Diarrhea, nausea** • **Dry mouth** • **Fever** • **Swelling and redness at the site of the medication injection** • **Bruising, bleeding** • **Pain or swelling of the joints** • **Loss of appetite** • **Reaction during or following a drug infusion which may cause fever, chills, rash** **Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:** • **Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.** • **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase**

in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.

- **Skin: itching; rash, blisters including inside the mouth; loss of skin pigment**
- **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly**
- **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.**

RARE, AND SERIOUS

In 100 people receiving nivolumab, 3 or fewer may have:

- **Swelling of arms and legs which may cause a feeling of heaviness and tightness**
- **Dry eyes**
- **Sores in the mouth which may cause difficulty swallowing**
- **A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss**
- **Swelling of the bowels**

Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness**
- **A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma**
- **Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.**
- **Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.**
- **Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine**
- **Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)**

- **Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement**
- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**
- **Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.**

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 are a woman who can get pregnant, it is important for you to use birth control or not have sex while on this study and for 5 months after the last dose of. 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 doctor 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).

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 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.

Information learned from this study may 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 a study. Standard therapy is described in Attachment 1.**
- **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 244 patients.

How long is the study?

People in this clinical trial are expected to receive treatment on this study for about 6 months. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health 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. 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 and research partners**
- **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**

- **The study sponsor and any drug company supporting the study or their designated reviewers.**

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.

There is no charge for the central review of diagnostic material testing.

The NCI will supply nivolumab at no charge for this study. The NCI does not cover the cost of getting the nivolumab ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the NCI may not be able to continue to provide the nivolumab for some reason. If this does happen, the study may have to close. Your study doctor will talk with you about this, if it happens.

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 (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..

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* Institutional Review Board (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 that your specimens can be used for research, some of your health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.

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 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.) My blood may be sent to a COG laboratory and studied for Immune Profile and Biomarker Testing to see whether we can predict a patient's response to treatment based on certain markers in the blood.

*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 location*. The Biopathology Center is supported by the NCI. The samples will be kept until they are used up, unless you request that they be destroyed. Some information from your medical record 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. The goal of this is to make more research possible that may improve people's health. 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.

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) Check YES if you agree to have tissue and/or blood 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 samples banked.

Yes _____ No _____ _____ / _____
Initials Date

Signature

I have been given a copy of all _____ pages of this form. The form includes 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 PMBCL

Methods for Giving Drugs ~only include relevant methods. Remove if no treatment described below~

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").
- **IM** - Drug is given into a muscle using a needle.
- **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.

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.

Standard Treatment Tables

The treatment described below is standard treatment for patients with PMBCL

DA EPOCH-R

Drug	How the drug will be given	Days
Prednisone	PO	Days 1 - 5
Rituximab	IV titration/infusion per institutional policy OR SubQ* over 5 minutes per institutional policy (≥ 18 years of age, Cycle ≥ 2)	Day 1 or Day 5
Etoposide	IV continuous infusion over 24 hours (total 96 hours)	Days 1 - 4
Doxorubicin	IV continuous infusion over 24 hours (total 96 hours)	Days 1 - 4
Vincristine	IV continuous infusion over 24 hours (total 96 hours)	Days 1 - 4
Cyclophosphamide	IV over 30 – 60 minutes	Day 5

*SubQ administration is only an option for patients ≥ 18 years receiving rituximab and hyaluronidase formulation in Cycles 2-6.

R-CHOP

Drug	How the drug will be given	Days
Prednisone	PO	Days 1 - 5

Rituximab	IV titration/infusion per institutional policy OR SubQ* over 5 minutes per institutional policy (≥ 18 years of age, Cycle ≥ 2)	Day 1 or Day 5
Doxorubicin	IV push/infusion over 3-15 min	Day 1
Vincristine	IV infusion per institutional standards or IV push over 1 minute	Day 1
Cyclophosphamide	IV over 30 – 60 minutes	Day 1

*SubQ administration is only an option for patients ≥ 18 years receiving rituximab and hyaluronidase formulation in Cycles 2-6.

Radiation Therapy

In addition to chemo-immunotherapy, patients may be treated with radiation therapy over 3.5 to 5 weeks. Arms E and F will receive radiation therapy regardless of end of therapy test results. Arms A, B, C, and D will receive radiation therapy depending on end of therapy test results. For these arms, radiation therapy will be started within 6-8 weeks after completing cycle 6 of chemo-immunotherapy. During radiation therapy, you may be asked to take a deep breath hold to help optimize results.

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.
- PET or CT scans to monitor your response to treatment.
- Tests to monitor your heart and lung function.
- Bone marrow aspiration tests to see if the cancer has spread to the bone marrow. 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

Attachment 2

Risks of Chemotherapy Drugs and Radiation Used to Treat PMBCL

Possible Side Effects of Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP), more than 20 and up to 100 may have:
• **High blood pressure which may cause headaches, dizziness, blurred vision** • **Infection, possibly in the blood, especially when white blood cell count is low** • **Anemia which may cause tiredness, or may require transfusion** • **Bruising, bleeding** • **Blood in urine** • **In children and adolescents: decreased height** • **Loss of bone tissue** • **Increased appetite and weight gain in the belly, face, back and shoulders** • **Nausea, vomiting, diarrhea, loss of appetite, pain in belly** • **Constipation, which may be severe, as a result of a bowel blockage** • **Sores in mouth or throat which may cause difficulty swallowing** • **Absence of menstrual period or early menopause which may decrease the ability to have children** • **Muscle weakness and difficulty walking** • **Numbness and tingling of fingers or toes** • **Headache, jaw pain and/or muscle pain** • **Swelling of the body, tiredness, bruising** • **Difficulty sleeping** • **Mood swings** • **Swelling and redness at the site of the medication injection or area of previous radiation** • **Red colored urine, saliva, or sweat** • **Hair loss, skin changes, rash, change in nails**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),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** • **Blood clot which may cause swelling, pain, shortness of breath** • **Fluid around the heart** • **Low blood pressure which may cause feeling faint** • **Damage to the lungs or scarring of the lungs which may cause shortness of breath** • **Diabetes** • **Kidney damage which may cause swelling, may require dialysis** • **Heartburn**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),from 4 to 20 may have:
• **A tear or a hole in the bowels which may cause belly pain or that may require surgery** • **Difficulty emptying the bladder or urinating, excessive, frequent, or painful urination** • **Swelling of the body including the brain which may cause dizziness, confusion** • **Paralysis** • **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions** • **Damage, loss or absence of sperm which may lead to inability to father children** • **Dehydration** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Damage to the bone which may cause joint pain and loss of motion** • **Cloudiness of the eye, visual disturbances, blurred vision** • **Glaucoma** • **Difficulty with balance and hearing** • **Non-healing wound** • **Weight loss** • **Darkening of the gums** • **Drooping eyelids, abnormal eye movement** • **Hoarseness**

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),3 or fewer may have:
• **Sinusoidal obstructive syndrome (SOS) which may cause damage to the liver, yellowing of eyes and skin, and swelling** • **Seizure** • **Coma** • **Bleeding from sores in the stomach** • **Visual loss with a chance of blindness** • **A new cancer (including leukemia) resulting from treatment** • **Broken bones** • **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 EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin)

COMMON, SOME MAY BE SERIOUS In 100 people receiving EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin), more than 20 and up to 100 may have:
• **High blood pressure which may cause headaches, dizziness, blurred vision** • **Infection, especially when white blood cell count is low**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin), more than 20 and up to 100 may have:

- **Bruising, bleeding**
- **Anemia which may cause tiredness, or may require blood transfusions**
- **Blood in urine**
- **Swelling of the body, tiredness, bruising**
- **In children and adolescents: decreased height**
- **Nausea, vomiting, diarrhea, loss of appetite, pain in belly**
- **Constipation, which may be severe, as a result of a bowel blockage**
- **Increased appetite and weight gain in the belly, face, back and shoulders**
- **Sores in mouth or throat which may cause difficulty swallowing**
- **Absence of menstrual period which may decrease the ability to have children**
- **Loss of bone tissue**
- **Muscle weakness and difficulty walking**
- **Mood swings**
- **Numbness and tingling of fingers or toes**
- **Headache, jaw pain and/or muscle pain**
- **Difficulty sleeping**
- **Swelling of lower legs**
- **Swelling and redness at the site of the medication injection or area of previous radiation**
- **Red colored urine, saliva, or sweat**
- **Hair loss, skin changes, rash, change in nails**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, and 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**
- **Fluid around the heart**
- **High blood pressure which may cause headaches, dizziness, blurred vision**
- **Low blood pressure which may cause feeling faint**
- **Damage to the lungs or scarring of the lungs which may cause shortness of breath**
- **Blood clot which may cause swelling, pain, shortness of breath**
- **Kidney damage which may cause swelling, may require dialysis**
- **Difficulty emptying the bladder or urinating, excessive, painful or frequent urination**
- **Swelling of the body including the brain which may cause dizziness, confusion**
- **Paralysis**
- **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions**
- **Diabetes**
- **Cloudiness of the eye, visual disturbances, blurred vision with chance of blindness**
- **Glaucoma**
- **A tear or a hole in the bowels which may cause belly pain or that may require surgery**
- **Heartburn**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin), from 4 to 20 may have:
• **Damage, loss or absence of sperm which may lead to an inability to father children** • **Dehydration** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Damage to the bone which may cause joint pain and loss of motion** • **Numbness and tingling of the arms, legs, and upper body** • **Difficulty with balance and hearing** • **Weight loss** • **Darkening of the gums** • **Drooping eyelids, abnormal eye movement** • **Hoarseness** • **Non-healing wound**

RARE, AND SERIOUS In 100 people receiving EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin), 3 or fewer may have:
• **Sinusoidal obstructive syndrome (SOS) which may cause damage to the liver, yellowing of eyes and skin, and swelling** • **Seizure** • **Coma** • **Visual loss with a chance of blindness** • **Bleeding from sores in the stomach** • **A new cancer (including leukemia) resulting from treatment of a prior cancer** • **Stevens-Johnson syndrome which may cause severe skin rash with blisters and peeling which can involve mouth and other parts of the body** • **Broken bones**

Possible Side Effects of Rituximab

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rituximab, more than 20 and up to 100 may have:
• **Infection, possibly in the blood, especially when white blood cell count is low** • **Anemia which may require blood transfusion** • **Nausea** • **Reaction during or following infusion of the drug** • **Numbness and tingling of the arms, legs, fingers, and/or toes** • **Chills, fever** • **Tiredness**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rituximab, 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**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rituximab, from 4 to 20 may have:
• **Swelling of arms, legs** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Swelling and redness of the throat and sinuses (might not be caused by infection) which may cause difficulty breathing and swallowing** • **Bruising, bleeding** • **Prior liver infection that returns which may cause yellow eyes and skin, tiredness** • **Prior liver infection that returns which may cause yellow eyes and skin, tiredness** • **Tumor lysis syndrome which may cause kidney damage which may require dialysis** • **A tear or a hole in the bowels that may require surgery** • **Sores in mouth which may cause difficulty swallowing** • **Belly pain, diarrhea, vomiting** • **Depression** • **Headache, dizziness** • **Pain in back, muscles, joints** • **Cold symptoms such as stuffy nose, sneezing, sore throat** • **Itching, rash, blisters on the skin**

RARE, AND SERIOUS In 100 people receiving Rituximab, 3 or fewer may have:
• **Heart attack which may cause chest pain, shortness of breath** • **Heart stops beating** • **Brain damage, progressive multifocal leukoencephalopathy (PML), which may cause tiredness, changes in thinking** • **Damage to the lungs which may result in shortness of breath, cough, wheezing** • **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 Research Radiation Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 and up to 100 may have:
• **Reddening, tanning, or peeling of the skin** • **Mild pain** • **Hair loss** • **Tiredness** • **Diarrhea, nausea** • **Anemia, which may require transfusion** • **Infection, especially when white blood cell count is low**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• **Thickening and numbness of the skin** • **Sores or ulcers on the skin or near the cancer location** • **Permanent hair loss** • **Bleeding from the skin** • **Sores in mouth which may cause difficulty swallowing**

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• **Damage to internal organs** • **Abnormal opening in internal organs which may cause pain and bleeding**

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.