

North Central Cancer Treatment Group

N078D: Phase I/II Trial of Rituximab, Cladribine, and Temozolomide (RCT) Therapy in Newly Diagnosed Mantle Cell Lymphoma (MCL).

Addendum 11 – February 10, 2012

**Summary**

- This addendum is in response to a Request for Amendment (RA) from the National Cancer Institute (NCI) for Temozolomide. Therefore, the Drug Information section and consent form have been revised accordingly.
- Administrative/editorial changes.

**Replacement pages are included. Please incorporate into the protocol and keep this addendum with your protocol.**

**Title page** Addendum 11 has been added and the NCI version date has been revised.

**Protocol Resources**

Page 2: The fax number for Patricia Koenig has been updated as follows:  
507/284-~~9628~~ **1902**

The name of the NCCTG Research Base Research Protocol Specialist has been updated to reflect Tamra L. ~~Chonjak~~ **Losinski**.

~~Patricia A. Aggen~~ has been removed as the second NCCTG Research Base Research Protocol Specialist.

**Section 14.0** **Body Fluid Biospecimens**

Page 39: The shipping instructions in Section 14.256 have been updated as follows:  
BAP ~~Receiving-Freezer~~ will forward specimens to the NCCTG Research Base Biospecimens Accessioning and Processing (BAP) Laboratory, ~~Stable 13-10A~~  
**Hilton CL-21**, Attention: BAP Supervisor.

**Section 15.0** **Drug Information**

Pages 49-52: Due to the receipt of the RA from NCI for Temozolomide, Section 15.37 has been replaced in its entirety.

**Appendices IA and IB Consent Forms**

Pages 9-10: Due to the receipt of the RA from NCI for Temozolomide, the risks sections of the consent forms have been updated as follows:

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

- Decreased number of blood cells that help to clot blood (platelet)
- Tiredness, fatigue
- Rash; flaking or sloughing of skin or with the presence of macules (flat discolored area) and papules (raised bump)
- Diarrhea
- Irritation or sores in the lining of the gastrointestinal tract (for example: mouth, throat, stomach, intestine, **anus, rectum, small bowel, voice box, windpipe**) (*newly added*)
- Feeling sick to your stomach, nausea
- Increased blood cholesterol level
- Decrease in the part of the red blood cells that carries oxygen in the body, may cause tiredness (**anemia**) (*wording expanded*)
- Loss of appetite

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

- Abnormal reaction of the body to substances, called allergens, that are contacted through the skin, inhaled into the lungs, swallowed, or injected (allergic reaction)
- Decreased number of white blood cells (for example reduced total leucocytes, lymphocytes, or neutrophils/granulocytes), which may cause increased risk of infection
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- High blood pressure
- Low blood pressure
- Abnormal amount of blood protein needed for blood clotting
- Fever
- Difficulty sleeping or falling asleep
- Chills, shivering
- Dry skin
- Loss of some or all of the fingernails or toenails
- Itching
- Acne, pimples
- Hives
- Decreased level of the hormone testosterone
- Abnormal control of blood sugars
- Constipation
- Taste changes
- Throwing up, vomiting
- Nosebleed
- Infection
- Condition where the blood contains more acid than normal
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (GGT)
- Decreased blood calcium level
- Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine

- High blood sugar level
- High lipid (fat) levels in the blood
- Decreased blood phosphate level
- Decreased blood potassium level
- Increased blood level of a form of fat called triglyceride
- Feelings of sadness, worthlessness, thoughts of suicide or death (depression)
- Sleepiness
- Pain – for example pain in the stomach, back, chest, head, joint, muscle, **headache or head pain** (*newly added*)
- Cough
- Shortness of breath
- Runny/stuffy nose or sneezing
- Inflammation of the lungs
- Impotence, inability to have or maintain an erection during sexual intercourse
- Decrease in sexual desire
- Flu type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Poor wound healing
- Premature opening of a wound along surgical stitches after surgery
- Weight loss
- Edema or swelling of the face, hands or feet
- Excess accumulation of fluid between the layers of tissue that lines the lungs and chest cavity
- Distention/bloating of the belly (swelling or feeling of fullness and tightness in the abdomen)
- Problem of the sinuses
- Difficulty swallowing

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

- ~~A sudden or traumatic injury to the kidney~~ **Sudden decrease of kidney function** (*reworded*)
- ~~Perforation/hole in the bowel/digestive tract~~ (*separated into the following entries*)
- **Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair**
- **Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue**
- **Formation of a Bblood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung** (*wording expanded*)

## North Central Cancer Treatment Group

**Phase I/II Trial of Rituximab, Cladribine, and Temsirolimus (RCT) Therapy in Newly Diagnosed Mantle Cell Lymphoma (MCL).**

*For any communications regarding this protocol,  
please call the protocol resource person on the following page.*

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507/284-4101  
507/284-5280 (FAX)  
e-mail: [inwards.david@mayo.edu](mailto:inwards.david@mayo.edu)

Paul A .S. Fishkin, MD (NCCTG)

Study Cochairs: Matthew T. E. Drake, MD, PhD  
Scott H. Kaufmann, MD  
Thomas E. Witzig, MD  
Paul J. Kurtin, MD (*pathology – Mayo*)  
Ahmet Dogan, MD, PhD (*pathology – Mayo*)

Statistician: Betsy R. LaPlant, MS<sup>√</sup>  
(507)284-8803

<sup>√</sup>Study contributor(s) not responsible for patient care.

**Drug Availability:**

**Commercial Agents:** Rituximab, cladribine

**Drug Company Supplied:** Temsirolimus supplied by Pfizer, Inc. (IND Exempt.)

<b>Document History</b>	<b>(Effective Date)</b>	<b>Document History</b>	<b>(Effective Date)</b>
Activation	April 3, 2009	Addendum 6	July 30, 2010
Addendum 1	July 3, 2009	Addendum 7	October 22, 2010
Addendum 2	September 11, 2009	Addendum 8	February 4, 2011
Addendum 3	February 5, 2010	Addendum 9	February 4, 2011
Addendum 4	June 25, 2010	Addendum 10	May 13, 2011
Addendum 5	June 25, 2010	Addendum 11	February 10, 2012

**Study Participants**    **Date Activated**

Entire NCCTG    April 3, 2009

NCI Version Date: February 1, 2012

Add 8

**Protocol Resources**

<b>Questions:</b>	<b>Contact Name:</b>
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	Patricia A. Koenig, R.N. NCCTG <i>Research Base</i> Quality Control Specialist Phone: 507/284-4642 Fax: 507/284-1902 E-mail: <a href="mailto:koenig@mayo.edu">koenig@mayo.edu</a>
Drug administration, infusion pumps, nursing guidelines	Sherry Looker, R.N. NCCTG <i>Research Base</i> Nurse Phone: 507/284-2459 E-mail <a href="mailto:looker.sherry@mayo.edu">looker.sherry@mayo.edu</a>  Mary Wilwerding, R.N. NCCTG Member Nurse Phone: 402/991-8070 x202 E-mail: <a href="mailto:mwilwerding@mvcc.cc">mwilwerding@mvcc.cc</a>
Forms completion and submission	Mary B. Husby NCCTG Member Clinical Research Associate Phone: 218/786-3308 E-mail: <a href="mailto:mhusby@smdc.org">mhusby@smdc.org</a>
Protocol document, consent form, regulatory issues	Tamra L. Losinski NCCTG <i>Research Base</i> Research Protocol Specialist Phone: 507/284-0195 Fax: 507/284-5280 E-mail: <a href="mailto:losinski.tamra@mayo.edu">losinski.tamra@mayo.edu</a>
Paraffin-embedded tissue pathology	Jenny Mentlick NCCTG <i>Research Base</i> Pathology Coordinator phone: 507-293-3928 Fax: 507-284-9628 E-mail: <a href="mailto:mentlick.jennifer@mayo.edu">mentlick.jennifer@mayo.edu</a>
Non-paraffin biospecimens	Roxann Neumann, RN, BSN, CCRP NCCTG <i>Research Base</i> Biospecimen Resource Manager Phone: (507) 538-0602 Fax: (507) 266-0824 E-mail: <a href="mailto:neumann.roxann@mayo.edu">neumann.roxann@mayo.edu</a>
Adverse Events (AdEERS, MedWatch, Non-AER, AML/MDS)	Patricia G. McNamara NCCTG <i>Research Base</i> SAE Coordinator Phone: (507) 266-3028 Fax: (507) 284-9628 E-mail: <a href="mailto:mcnamara.patricia@mayo.edu">mcnamara.patricia@mayo.edu</a>

Add  
11Add  
10,11

\*No waivers of eligibility per NCI

- Add 2,4 14.255 The BAP kits will contain a smart shipper label (white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by NCCTG if this shipping box is used for shipping specimens to BAP.
- Add 4,11 14.256 BAP Freezer will forward specimens to the NCCTG Research Base Biospecimens Accessioning and Processing (BAP) laboratory, Hilton CL-21, Attention: BAP Supervisor.
- 14.257 BAP will process specimens according to Appendix III instructions.
- 14.3 Other Body Fluids Handling (None)
- 14.4 Study Methodology and Storage Information
- 14.41 Blood/blood product samples will be collected for the following research
- 14.411 **Serum free light chains:** Serum will be processed from the red top tube and will be frozen, batched, and analyzed for serum free light chains in Dr. Thomas E. Witzig's research laboratory, Mayo Clinic Rochester, Stable 6-13. In a recent publication by Martin et al. (Translational Research 149(4): 231 - 235, 2007) 36% of patients with mantle cell lymphoma had positive serology for serum free light chains. In this study we will assay for serum free light chains at on study and after two cycles of treatment. All samples will be evaluated with the Freelite serum free light chain assay (The Binding Site, Birmingham, UK). This is a commercial assay run routinely in Dr. Witzig's laboratory.
- 14.412 **Single nucleotide polymorphisms (SNPs) in host immune genes:** Genomic DNA from patients at on study will be obtained from peripheral blood from the EDTA tube and cryopreserved. DNA and buffy coat will be isolated in the Biospecimen Accessioning and Processing (BAP) Shared Resource. We have previously demonstrated our ability to analyze SNPs in patients with lymphoma. For example, Cerhan et al. (Blood 109: 5439 - 46) demonstrated that host gene SNP profiles could predict prognosis in follicular lymphoma. This information is not yet available for mantle cell lymphoma; therefore we will study that in this protocol. Genomic DNA samples will be batched and analyzed in the Mayo Clinic Cancer Center Genotyping Shared Resource.
- 14.413 **Vitamin D metabolites:** Serum from the red top tube will be cryopreserved and batched for 25 hydroxy vitamin D levels. These will be studied in the laboratory of Matthew T. E. Drake, M.D., Ph.D., Mayo Clinic Rochester, by liquid chromatography/tandem mass spectrometry. The rationale to study vitamin D in lymphoma comes from the finding that lymphoma is more common in climates with less sunshine. A recent study in the Journal of Clinical Oncology (26:2984 - 2991, 2008) demonstrated a significant improvement in overall survival in colon cancer patients with a higher level of vitamin D.
- 14.414 **PI3K Pathway Member Expression:** We will collect cells (from ACD whole blood) for PI3K pathway member expression after pre-registration, but prior to treatment and at restaging after cycle 2. Malignant cells will be analyzed under R01 CA127433 (Witzig/Kaufman) in Dr. Thomas E. Witzig's research laboratory, Mayo Clinic Rochester, Stable 6-13.

15.37 **Known potential toxicities:**

**Comprehensive Adverse Events and Potential Risks list (CAEPR)  
For Temsirolimus (CCI-779, NSC 683864)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. *Frequency is provided based on 1288 patients.* Below is the CAEPR for temsirolimus (CCI-779).

**NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.3, December 15, 2011<sup>1</sup>**

Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 4.0 Term) [n= 1288]			Specific Protocol Exceptions to Expedited Reporting (SPEER)  (formerly known as ASael)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>			
Anemia			<b><i>Anemia (Gr 3)</i></b>
	Febrile neutropenia		<b><i>Febrile neutropenia (Gr 3)</i></b>
<b>ENDOCRINE DISORDERS</b>			
	Endocrine disorders - Other (decreased testosterone)		<b><i>Endocrine disorders - Other (decreased testosterone) (Gr 2)</i></b>
<b>GASTROINTESTINAL DISORDERS</b>			
	Abdominal distension		<b><i>Abdominal distension (Gr 2)</i></b>
	Abdominal pain		<b><i>Abdominal pain (Gr 3)</i></b>
Anal mucositis <sup>2</sup>			<b><i>Anal mucositis<sup>2</sup> (Gr 2)</i></b>
	Constipation		<b><i>Constipation (Gr 3)</i></b>
Diarrhea			<b><i>Diarrhea (Gr 3)</i></b>
		Gastrointestinal fistula <sup>3</sup>	
		Gastrointestinal perforation <sup>4</sup>	<b><i>Gastrointestinal perforation<sup>4</sup> (Gr 4)</i></b>
Mucositis oral <sup>2</sup>			<b><i>Mucositis oral<sup>2</sup> (Gr 3)</i></b>
Nausea			<b><i>Nausea (Gr 3)</i></b>
Rectal mucositis <sup>2</sup>			<b><i>Rectal mucositis<sup>2</sup> (Gr 2)</i></b>
Small intestinal mucositis <sup>2</sup>			<b><i>Small intestinal mucositis<sup>2</sup> (Gr 2)</i></b>
	Vomiting		<b><i>Vomiting (Gr 3)</i></b>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
	Chills		<b><i>Chills (Gr 2)</i></b>
	Edema face		<b><i>Edema face (Gr 2)</i></b>
	Edema limbs		<b><i>Edema limbs (Gr 3)</i></b>
Fatigue			<b><i>Fatigue (Gr 3)</i></b>
	Fever		<b><i>Fever (Gr 2)</i></b>
	Flu like symptoms		<b><i>Flu like symptoms (Gr 2)</i></b>
	Non-cardiac chest pain		<b><i>Non-cardiac chest pain (Gr 2)</i></b>
<b>IMMUNE SYSTEM DISORDERS</b>			
	Allergic reaction <sup>5</sup>		<b><i>Allergic reaction<sup>5</sup> (Gr 2)</i></b>
<b>INFECTIONS AND INFESTATIONS<sup>6</sup></b>			
	Infection <sup>7</sup>		<b><i>Infection<sup>7</sup> (Gr 3)</i></b>

INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Wound dehiscence <sup>8</sup>	<b>Wound dehiscence<sup>8</sup> (Gr 2)</b>
INVESTIGATIONS		
	Alanine aminotransferase increased	<b>Alanine aminotransferase increased (Gr 3)</b>
	Alkaline phosphatase increased	<b>Alkaline phosphatase increased (Gr 2)</b>
	Aspartate aminotransferase increased	<b>Aspartate aminotransferase increased (Gr 3)</b>
Cholesterol high <sup>9</sup>		<b>Cholesterol high<sup>9</sup> (Gr 4)</b>
	Creatinine increased	<b>Creatinine increased (Gr 2)</b>
	Fibrinogen decreased	<b>Fibrinogen decreased (Gr 2)</b>
	GGT increased	<b>GGT increased (Gr 2)</b>
	Lymphocyte count decreased	<b>Lymphocyte count decreased (Gr 4)</b>
	Neutrophil count decreased <sup>10</sup>	<b>Neutrophil count decreased<sup>10</sup> (Gr 4)</b>
Platelet count decreased <sup>10</sup>		<b>Platelet count decreased<sup>10</sup> (Gr 3)</b>
	Weight loss	<b>Weight loss (Gr 3)</b>
	White blood cell decreased	<b>White blood cell decreased (Gr 3)</b>
METABOLISM AND NUTRITION DISORDERS		
	Acidosis	<b>Acidosis (Gr 2)</b>
Anorexia		<b>Anorexia (Gr 3)</b>
	Glucose intolerance <sup>11</sup>	<b>Glucose intolerance<sup>11</sup> (Gr 2)</b>
	Hyperglycemia <sup>11</sup>	<b>Hyperglycemia<sup>11</sup> (Gr 3)</b>
	Hypertriglyceridemia <sup>9</sup>	<b>Hypertriglyceridemia<sup>9</sup> (Gr 4)</b>
	Hypocalcemia	<b>Hypocalcemia (Gr 3)</b>
	Hypokalemia	<b>Hypokalemia (Gr 3)</b>
	Hypophosphatemia	<b>Hypophosphatemia (Gr 3)</b>
	Metabolism and nutrition disorders - Other (hyperlipidemia) <sup>9</sup>	<b>Metabolism and nutrition disorders - Other (hyperlipidemia)<sup>9</sup> (Gr 2)</b>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	<b>Arthralgia (Gr 2)</b>
	Back pain	<b>Back pain (Gr 2)</b>
	Myalgia	<b>Myalgia (Gr 2)</b>
NERVOUS SYSTEM DISORDERS		
	Depressed level of consciousness	<b>Depressed level of consciousness (Gr 2)</b>
	Dysgeusia	<b>Dysgeusia (Gr 2)</b>
	Headache	<b>Headache (Gr 3)</b>
PSYCHIATRIC DISORDERS		
	Depression	<b>Depression (Gr 2)</b>
	Insomnia	<b>Insomnia (Gr 2)</b>
	Libido decreased	<b>Libido decreased (Gr 2)</b>
RENAL AND URINARY DISORDERS		
		<b>Acute kidney injury<sup>12</sup></b>
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
	Erectile dysfunction	<b>Erectile dysfunction (Gr 2)</b>
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Allergic rhinitis	
	Cough	<b>Cough (Gr 2)</b>
	Dyspnea	<b>Dyspnea Gr 3)</b>
	Epistaxis	<b>Epistaxis (Gr2)</b>
Laryngeal mucositis <sup>2</sup>		<b>Laryngeal mucositis<sup>2</sup> (Gr 2)</b>

Pharyngeal mucositis <sup>2</sup>			<b>Pharyngeal mucositis<sup>2</sup> (Gr 2)</b>
	Pleural effusion		<b>Pleural effusion (Gr 2)</b>
	Pneumonitis <sup>13</sup>		<b>Pneumonitis<sup>13</sup> (Gr 3)</b>
	Sinus disorder		<b>Sinus disorder (Gr 2)</b>
Tracheal mucositis <sup>2</sup>			<b>Tracheal mucositis<sup>2</sup> (Gr 2)</b>
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>			
	Dry skin		<b>Dry skin (Gr 2)</b>
	Nail loss		<b>Nail loss (Gr 2)</b>
	Pruritus		<b>Pruritus (Gr 2)</b>
	Rash acneiform		<b>Rash acneiform (Gr 2)</b>
Rash maculo-papular			<b>Rash maculo-papular (Gr 3)</b>
	Urticaria		<b>Urticaria (Gr 2)</b>
<b>VASCULAR DISORDERS</b>			
	Hypertension		<b>Hypertension (Gr 3)</b>
	Hypotension		<b>Hypotension (Gr 2)</b>
		Thromboembolic event	<b>Thromboembolic event (Gr 4)</b>

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup>Mucositis/stomatitis: Gingivitis, mucositis/stomatitis, ulcers in mouth and throat, pharyngitis, and dysphagia have been reported in subjects receiving temsirolimus.

<sup>3</sup>Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

<sup>4</sup>Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. GI perforation (including fatal outcome) has been observed in subjects who received temsirolimus.

<sup>5</sup>Hypersensitivity /infusion reactions (including some life threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity, and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored early during infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical care administered. A risk-benefit assessment should be done prior to the continuation of temsirolimus therapy in patients with severe life-threatening reactions.

<sup>6</sup>Infections: Bacterial and viral infections including opportunistic infections have been reported in subjects. Infections may originate in a variety of organ systems/body regions and may be associated with normal or grade 3-4 neutropenia. Bacterial and viral infections have included cellulitis, herpes zoster, herpes simplex, bronchitis, abscess, pharyngitis, urinary tract infection (including dysuria hematuria, cystitis, and urinary frequency), rhinitis folliculitis, pneumonia, and upper respiratory tract infection.

<sup>7</sup>Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

<sup>8</sup>Wound Dehiscence: The use of temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of temsirolimus in the perisurgical period.

<sup>9</sup>Cholesterol High: The use of temsirolimus in subjects has been associated with increases in serum levels of triglycerides and cholesterol. This may require initiation of or increase in the dose of lipid-lowering agents.

<sup>10</sup>Thrombocytopenia and Neutropenia: Grades 3 and 4 thrombocytopenia and/or neutropenia have been observed at higher frequency in subjects with mantle cell lymphoma (MCL).

<sup>11</sup>Hyperglycemia/Glucose Intolerance: The use of temsirolimus in subjects was associated with increases in serum glucose level. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral

hypoglycemic agent therapy.

<sup>12</sup>Acute Kidney Injury: Renal failure (including fatal outcome) has been observed in subjects receiving temsirolimus for advanced RCC and/or with pre-existing renal insufficiency.

<sup>13</sup>Interstitial Lung Disease: There have been cases of nonspecific interstitial pneumonitis, including rare fatal reports. Some subjects were asymptomatic with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, and fever. Some subjects required discontinuation of temsirolimus or treatment with corticosteroids and/or antibiotics, while some subjects continued treatment without additional intervention.

<sup>14</sup>Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

**Also reported on temsirolimus (CCI-779) trials but with the relationship to temsirolimus (CCI-779) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Hemolysis

**CARDIAC DISORDERS** - Left ventricular systolic dysfunction; Pericardial effusion; Right ventricular dysfunction; Sinus tachycardia

**EYE DISORDERS** - Blurred vision; Conjunctivitis

**GASTROINTESTINAL DISORDERS** - Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Gastritis; Gastrointestinal hemorrhage<sup>14</sup>; Oral pain; Pancreatitis; Periodontal disease

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Gait disturbance

**HEPATOBIILIARY DISORDERS** - Hepatic failure

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Fracture

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood bilirubin increased; INR increased (potential interaction with Coumadin); Investigations - Other (lactic dehydrogenase increased)

**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hypercalcemia; Hyperkalemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (hypoproteinemia)

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (bursitis)

**NERVOUS SYSTEM DISORDERS** - Ataxia; Cognitive disturbance; Dizziness; Intracranial hemorrhage; Ischemia cerebrovascular; Peripheral sensory neuropathy; Seizure; Syncope

**PSYCHIATRIC DISORDERS** - Anxiety; Confusion; Personality change; Psychosis

**RENAL AND URINARY DISORDERS** - Cystitis noninfective; Hematuria; Proteinuria; Renal hemorrhage; Urinary frequency; Urinary tract pain

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Hematosalpinx; Irregular menstruation; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal hemorrhage

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Bronchopulmonary hemorrhage; Hypoxia; Pleuritic pain; Pulmonary hypertension; Respiratory failure

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Hyperhidrosis

**Note:** Intracerebral Bleeding: Subjects with central nervous system (CNS) tumors (primary CNS tumors or metastases) and/or receiving anticoagulation therapy may be at an increased risk of intracerebral bleeding (including fatal outcomes) while receiving therapy with temsirolimus.

**Note:** Temsirolimus (CCI-779) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Add 4,8 15.38 **Drug procurement:** The NCCTG Research Base pharmacist will obtain an investigational supply of temsirolimus from Pfizer, Inc.

Each participating main membership will order temsirolimus from the NCCTG Research Base pharmacist, as needed. Fax or mail the NCCTG Clinical Drug Order/Return Form request to:

Medical Oncology Pharmacist  
Mayo Clinic  
Gonda 10-178  
Rochester, MN 55905  
FAX (507) 284-3464

Each participating main membership will be responsible for monitoring their supply of temsirolimus and must use the NCCTG Clinical Drug Order/Return Form to order additional vials as needed.

Add 5

Outdated or remaining temsirolimus are to be destroyed on-site as per procedures in place at

**NCI Informed Consent Template for Cancer Treatment Trials  
(English Language)**

**\*NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]**

The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>

A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.

Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer...What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.

Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*\*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

**Phase I/II Trial of Rituximab, Cladribine, and Tamsirolimus (RCT) Therapy in Newly Diagnosed Mantle Cell Lymphoma (MCL).**

(Phase I Consent Form)

Add 2

**This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.**

**This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.**

You are being asked to take part in this research study because you have newly diagnosed mantle cell lymphoma (MCL). MCL is a cancer which is generally thought to not be curable by standard therapies. Treatments used include combinations of chemotherapy, antibody therapy, and aggressive chemotherapy with stem cell transplant.

**Why is this research study being done?**

The purpose of this research study is to:

- Test the safety of tamsirolimus at different dose levels in combination with rituximab and cladribine.
- Determine what effects, good and/or bad, this combination has on you and your lymphoma.
- Additional research testing will be done as part of this study to better understand what effects the study drugs have on your body as well as seeing if minor differences in your genes change your cancer's response to the treatment.

Add 2

Side effects from the combination of rituximab, cladribine, and tamsirolimus will be closely monitored. The use of this combination in this study is considered investigational.

Add 2

**How many people will take part in the research study?**

At least 9 people and at most 30 people will take part in the first part of this study. A total of about 74 people will take part in this study overall (Phase I and Phase II combined).

At the beginning of the study, 3 patients will be treated with a low dose of the drug. If this dose does not cause bad side effects, it will slowly be made higher as new patients take part in the study. A total of 30 patients are the most that would be able to enter the phase I part of this study.

**What will happen if I take part in this research study?**

**Before you begin the study ...**

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

**Before entering study:**

<p>≤ 28 days before entering study</p>	<ul style="list-style-type: none"> <li>• Routine blood tests</li> <li>• CT scans</li> <li>• Bone marrow biopsy</li> <li>• PET Scan (if clinically indicated)</li> <li>• Mandatory tumor biopsy - tumor tissue collected previously during a biopsy (or surgery) will be reviewed to confirm the results of your local laboratory review.</li> <li>• Mandatory research tissue – The tumor biopsy tissue (listed above) will also be used for mandatory research tests, no additional biopsies will be done for the research tests.</li> </ul>
<p>≤ 14 days before entering study</p>	<ul style="list-style-type: none"> <li>• Doctor’s appointment for history and examination</li> <li>• Routine blood tests</li> <li>• Mandatory research blood draw, about 2 tablespoons of blood will be drawn after pre-registration, but prior to starting study treatment.</li> <li>• If it is not known if you have hepatitis B you will need to have a blood test done. If your hepatitis B test result is positive, you may not be able to take part in the study. The test result will also be put in your medical record.</li> </ul>
<p>≤ 7 days before entering study</p>	<ul style="list-style-type: none"> <li>• Pregnancy test (if applicable)</li> </ul>

Add 3

**During the study...**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures which are part of regular cancer care.

During the study you will be given the following combination of study drugs: rituximab, cladribine and temsirolimus.

You will receive rituximab, cladribine and temsirolimus at various time points during a 28 day period. This period of time is called a cycle. You will receive 2-6 cycles of therapy, depending on the response of your lymphoma to the treatment. Each cycle is numbered in order. The chart below shows what will happen to you during each cycle as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day. Prior to each rituximab treatment you will be given acetaminophen by mouth and diphenhydramine either by mouth or through your vein. Prior to each temsirolimus dose you will be given diphenhydramine either by mouth or through your vein.

You should not drink grapefruit juice or eat grapefruit while you are enrolled in the study, because there may be possible drug interactions. Temsirolimus could interact with other medicines. Please provide your doctor or nurse with a list of all your medications to check for any potential interactions.

**Study treatment summary**

<b>Day</b>	<b>What you need to do</b>
Before receiving chemotherapy at the start of each cycle	<ul style="list-style-type: none"> <li>• Doctor's appointment for history and examination</li> <li>• Routine blood tests</li> </ul>
Day 1 each cycle	<ul style="list-style-type: none"> <li>• Acetaminophen will be given prior to each rituximab dose.</li> <li>• Diphenhydramine will be given prior to each rituximab or temsirolimus dose.</li> <li>• One dose of rituximab will be given into a vein over several hours as fast as tolerated</li> <li>• One dose of temsirolimus will be given into a vein over 30 minutes.</li> </ul>
Days 1-5 each cycle	<ul style="list-style-type: none"> <li>• One dose of cladribine will be given into a vein over 2 hours each day for 5 days in a row</li> </ul>
Days 6-15 each cycle	<ul style="list-style-type: none"> <li>• Filgrastim under the skin daily-Days 6-15 OR pegfilgrastim injected under the skin on Day 6. These drugs may be given on Day 7 or 8 if there is a weekend or holiday on Day 6.</li> </ul>
Days 8, 15 & 22 each cycle	<ul style="list-style-type: none"> <li>• On these days <u>you may or may not</u> receive diphenhydramine and a dose of temsirolimus. This will depend on which dose level of temsirolimus you are assigned to.</li> <li>• Routine blood tests will be done before each dose of temsirolimus.</li> </ul>
Day 15 each cycle	<ul style="list-style-type: none"> <li>• Routine blood tests</li> </ul>
Day 28	<ul style="list-style-type: none"> <li>• End of current cycle</li> </ul>
After cycles 2, 4 and 6	<ul style="list-style-type: none"> <li>• Doctor's appointment for history and examination</li> <li>• Routine blood tests</li> <li>• Repeat CT or PET scans and/or bone marrow biopsy if test showed lymphoma when last done</li> <li>• Mandatory research blood draw (after cycle 2 only). Approximately 2 tablespoons of blood will be drawn.</li> </ul>

**When I am finished taking the study drugs....**

You will be asked to take study drugs for 2-6 months depending on how your cancer responds to the study drugs.

**How long will I be in the research study?**

After you are finished taking study drugs the study doctor will ask you to visit the office for follow-up exams according to the table below:

First and second year after treatment	<ul style="list-style-type: none"> <li>• Doctor's appointment for history and examination, blood tests (may include research tests), and CT scans every 3 months</li> </ul>
Third year after treatment	<ul style="list-style-type: none"> <li>• Doctor's appointment for history and examination, blood tests (may include research tests), and CT scans every 4 months</li> </ul>

You will be followed for a maximum of 5 years.

**Can I stop being in the research study?**

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drugs. In some cases, side effects can be serious, long lasting, or may never go away. There may be a risk of death.

### **You should talk to your study doctor about any side effects that you have while taking part in the study.**

Cladribine is a powerful drug that affects both normal and cancer cells. Risks and side effects related to the cladribine include those which are:

Add 1,4

#### **Likely risks of cladribine** (*events occurring greater than 10% of the time*)

- Low number of white blood cells (infection fighting cells), which could put you at risk for infection (neutropenia)
- Decrease in red blood cells (oxygen carrying cells) which could make you feel tired (anemia)
- Low number of a particular white blood cell, which is important to the immune system and may be long term (lymphopenia)
- Infection
- Fever, particularly when white blood counts are low (neutropenic fever)
- Headache
- Tiredness (fatigue)
- Feeling sick to your stomach (nausea)
- Skin rash
- Reduced number of bone marrow cells and may be long term (hypocellular bone marrow)
- Abnormal breathing sounds
- Decreased production within the bone marrow that causes decreased production of red cells, white cells, or platelets (myelosuppression)
- Decreased number of blood cells (platelets) that help to clot the blood, which could put you at increased risk of bleeding (thrombocytopenia)
- Redness at the site of the intravenous line (injection site reaction)
- Throwing up (vomiting)
- Poor appetite, not feeling hungry (anorexia)

Add 1,4

#### **Less likely risks of cladribine** (*events occurring 1-10% of the time*)

- Serious infection with risk of death
- A painful, blistering red rash that is confined to one side of the body, similar to chicken pox (herpes zoster or shingles)
- Chills (rigors)
- Sweats
- Body aches
- Weakness (asthenia)
- Feeling unwell (malaise)

- Loose stool (diarrhea)
- Difficulty passing stool (constipation)
- Belly (abdominal) pain
- Bruising
- Small purple dots on the skin (petechiae)
- Nose bleed (epistaxis)
- Sensation of lightheadedness or vertigo (spinning sensation) (dizziness)
- Difficulty falling or staying asleep (insomnia)
- Swelling in your arms or legs (edema)
- Rapid heartbeat (tachycardia)
- Cough
- Shortness of breath or difficulty breathing (dyspnea)
- Itching sensation (pruritus)
- Pain
- Redness of the skin (erythema)
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Blood clot (thrombosis)
- Inflammation of the veins (phlebitis)
- Abnormal chest sounds

Add 1,4

**Rare but serious risks of cladribine** (*events occurring less than 1% of the time*)

- Kidney damage, when used at higher doses; may be long term. Not reported at standard doses (renal failure).
- Brain, spinal cord and nerve damage, when used at higher doses; may be long term. Rarely seen after standard doses (demyelinating disease, axonal peripheral polyneuropathy, paraparesis, and quadriplegia).
- Involuntary changes in body movement or function, sensation, awareness, or behavior, when used at higher doses (seizures).
- A complication that may occur if the cancer cells die too quickly that includes inappropriate increase or decrease of various natural chemicals in the blood stream (uric acid, phosphorus, potassium, creatinine, and calcium) which can result in kidney failure and may harm muscle or nerve function (tumor lysis syndrome).
- Abnormal blood counts from bone marrow damage long after cladribine use which may be long term (myelodysplasia).
- Cancer of the bone marrow (leukemia)
- Anemia from red blood cell destruction (hemolytic anemia)
- Anemia in which the bone marrow fails to produce adequate numbers of peripheral blood elements (aplastic anemia)
- Hives (urticaria)
- Severe rash which causes blistering and peeling of the skin (Stevens-Johnson syndrome and toxic epidermal necrolysis).
- Bilirubin increase (hyperbilirubinemia)
- A disease characterized by a marked increase in the white blood cell count (hypereosinophilia)
- Reduced red blood cells (can make you feel tired), white blood cells (can put you at risk for infection), and platelets (can put you at risk for bleeding) (pancytopenia)
- Infection of the lungs (pneumonia)
- Changes in lungs seen on chest x-ray showing abnormal shadows, resembling pneumonia (pulmonary interstitial infiltrates)
- Increase in blood level of liver enzymes (ALT/AST)
- Increased risk of unusual infections due to lowered immunity (opportunistic infections)

Risks and side effects related to the rituximab include those which are:

Add 5

**Likely:**

- Chills
- Fever
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Decreased number of a type of white blood cell (lymphocyte)

Add 5

**Less Likely:**

- Lack of enough red blood cells (anemia)
- Thickening of blood/serum as found in Waldenstrom's macroglobulinemia (a cancer of certain blood cells)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Heart attack caused by a blockage of a blood vessel supplying part of the heart
- Fast heartbeat; regular rhythm
- Fast heartbeat usually originating in an area located above the ventricles
- Belly pain
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Swelling of the arms and/or legs
- Fatigue or tiredness
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Allergic reaction to certain medications, injected proteins, or antisera (blood product) used to treat certain medical conditions (such as an infectious or poisonous substance)
- Infection
- Awakening of viruses which have been latent/dormant
- Infection in HIV positive patients
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Decrease in the total number of white blood cells (leukocytes)
- Increased blood sugar level
- Decreased blood level of calcium
- Decreased blood level of potassium
- Joint pain
- Back pain
- Muscle pain
- Pain in the area of the tumor
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Headache or head pain
- Abnormal drowsiness or sluggishness, an unusual lack of energy
- Convulsion or seizure
- Sudden or traumatic injury to the kidney
- Stuffy or runny nose, sneezing

- Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath
- Cough
- Shortness of breath
- Decrease in the oxygen supply to a tissue
- Inflammation of the lungs that may cause difficulty breathing and can be life-threatening
- Sore throat
- Excess sweating
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Swelling of body tissue underneath the skin
- Hives
- Sudden reddening of the face and/or neck
- High blood pressure
- Low blood pressure

Add 5,7

**Rare but Serious:**

- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure
- Disease affecting brain tissue, caused by the JC virus
- Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure or even death. The risk of hepatitis B virus flaring up may continue for several months after you stop. Most of these patients were taking rituximab in combination with chemotherapy. If you are at risk of hepatitis B reactivation, you should speak with your doctor before you enroll in this study. If you are a carrier of hepatitis B, you will be monitored for signs of active infection throughout your study participation. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor immediately.

**Risks and side effects related to the temsirolimus include those which are:**

Add 4,11

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

- Decreased number of blood cells that help to clot blood (platelet)
- Tiredness, fatigue
- Rash; flaking or sloughing of skin or with the presence of macules (flat discolored area) and papules (raised bump)
- Diarrhea
- Irritation or sores in the lining of the gastrointestinal tract (for example: mouth, throat, stomach, intestine, anus, rectum, small bowel, voice box, windpipe)
- Feeling sick to your stomach, nausea
- Increased blood cholesterol level
- Decrease in the part of the red blood cells that carries oxygen in the body, may cause tiredness (anemia)
- Loss of appetite

Add  
4,8,11**Less likely risks of temsirolimus** (*events occurring less than or equal to 20% of the time*)

- Abnormal reaction of the body to substances, called allergens, that are contacted through the skin, inhaled into the lungs, swallowed, or injected (allergic reaction)
- Decreased number of white blood cells (for example reduced total leucocytes, lymphocytes, or neutrophils/granulocytes), which may cause increased risk of infection
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- High blood pressure
- Low blood pressure
- Abnormal amount of blood protein needed for blood clotting
- Fever
- Difficulty sleeping or falling asleep
- Chills, shivering
- Dry skin
- Loss of some or all of the fingernails or toenails
- Itching
- Acne, pimples
- Hives
- Decreased level of the hormone testosterone
- Abnormal control of blood sugars
- Constipation
- Taste changes
- Throwing up, vomiting
- Nosebleed
- Infection
- Condition where the blood contains more acid than normal
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (GGT)

- Decreased blood calcium level
- Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine
- High blood sugar level
- High lipid (fat) levels in the blood
- Decreased blood phosphate level
- Decreased blood potassium level
- Increased blood level of a form of fat called triglyceride
- Feelings of sadness, worthlessness, thoughts of suicide or death (depression)
- Sleepiness
- Pain – for example pain in the stomach, back, chest, head, joint, muscle, headache or head pain
- Cough
- Shortness of breath
- Runny/stuffy nose or sneezing
- Inflammation of the lungs
- Impotence, inability to have or maintain an erection during sexual intercourse
- Decrease in sexual desire
- Flu type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Poor wound healing
- Premature opening of a wound along surgical stitches after surgery
- Weight loss
- Edema or swelling of the face, hands or feet
- Excess accumulation of fluid between the layers of tissue that lines the lungs and chest cavity
- Distention/bloating of the belly (swelling or feeling of fullness and tightness in the abdomen)
- Problem of the sinuses
- Difficulty swallowing

Add  
4,11

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

- Sudden decrease of kidney function
- Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Gastrointestinal fistula: Abnormal hold between an organ of the digestive tract and another organ or tissue
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Allergic reaction: Some patients have had an allergic reaction during CCI-779/temsirolimus infusion. Life threatening reactions (including fatal) have occurred. Patients with allergic reactions have had chest pain and tightness, difficulty breathing, feeling hot, flushed and anxious, swelling around the eyes, dizziness, feeling sick to the stomach, a fall in blood pressure, back pain, and numbness and tingling. These symptoms went away a few minutes after the infusion was stopped, and in some cases, after treatment was given. Because an allergic reaction may happen, an antihistamine drug (e.g. diphenhydramine (Benadryl) is given before CCI-779/temsirolimus. If you are given an antihistamine and still have an allergic reaction, the study doctor may stop or slow down the infusion and may give you other intravenous medication.

**Risks and side effects related to the filgrastim include those which are:**

**Common side effects**

- Bone pain

**Less common side effects**

- Fluid or blood collecting in the sac around the heart
- Increased blood levels of uric acid, LDH, alkaline phosphatase

- Enlargement of the spleen
- Worsening of skin rashes, hair loss, and ability for blood to clot

**Rare but serious side effects**

- Fluid retention
- Lowering of blood pressure which lasts only for a little while
- Acute inflammation of blood vessels
- Allergic-type reactions

**Risks and side effects related to pegfilgrastim include those which are:**

**Common side effects**

- Bone pain

**Less common side effects**

- Allergic-type reactions

**Rare but serious side effects**

- Rupture of the spleen
- Sickle cell crisis in patients who have sickle cell disease

To help prevent reactions to the chemotherapy; you will get acetaminophen and diphenhydramine at the same time you get rituximab.

Add 1 The combination of cladribine and rituximab may worsen the side effects of each drug in comparison to when the drugs are given separately. This combination may also result in unexpected, severe permanent, debilitating, or even fatal toxicities.

Adult Respiratory Distress Syndrome (ARDS) has been reported in neutropenic patients with sepsis (bacteria in your blood or tissue) who get filgrastim. If you get a fever or have trouble breathing, you should contact your doctor. If you get ARDS, filgrastim and pegfilgrastim will be stopped until you get better.

Bone marrow biopsies (sample taken from large bones in your hip with a needle) may cause pain and a small risk of bleeding, bruising, or infection at the needle site.

Frequent blood draws will be part of this study. A blood drawing may cause minimal discomfort and a small risk of bleeding, bruising, or infection at the needle site.

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important for you to understand that you need to use birth control while on this study and for up to 12 months after taking your last dose of study drug. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future. Women who can become pregnant must have a pregnancy test before taking part in this study. This test must be done within 7 days before you enter the study. You will be told if you are pregnant or not. If you are pregnant, you will not be able to take part in the study.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the research study?**

Taking part in this study may or may not make your health better. While doctors hope the study drugs will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the study drugs as a treatment for cancer. This information could help future cancer patients.

### **What other choices do I have if I do not take part in this research study?**

You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

### **Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

- The local Institutional Review Board
- The North Central Cancer Treatment Group
- Pfizer, Inc., who is providing support for the study
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

Add 8

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

### **What are the costs of taking part in this research study?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Add 8 Pfizer, Inc. is supplying temsirolimus at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the (drug).

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

### **What happens if I am injured because I took part in this research study?**

It is important that you tell your study doctor, \_\_\_\_\_ [*investigator's name(s)*], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at \_\_\_\_\_ [*telephone number*].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

### **What are my rights if I take part in this research study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_ [*name(s)*] at \_\_\_\_\_ [*telephone number*].

For questions about your rights while taking part in this study, call the \_\_\_\_\_ [*name of center*] Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ (*telephone number*). [*Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.*]

\*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*\*Only applies to sites using the CIRB.*]

**About Using Biological Samples for Research**

This study has research tests that will be performed to study small samples of blood and biopsy tissue. You are required to participate in these studies in order to participate in this study.

A blood sample will be done by drawing some blood from a vein. The research blood samples will be drawn after registering for the study but before treatment starts. Research blood will be drawn again at the end of cycle two. Approximately 2 tablespoons of blood will be drawn for each of these time points.

You are going to have or may already have had a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these clinical tests will be given to you by your doctor and will be used to plan your care. If you agree to participate in this study, your original biopsy tissue sample will be used for additional research tests as a part of this study. No additional biopsies will be done to get this tissue.

For the research tests to be done, your tissue will be sent to Dr. Ahmet Dogan's laboratories which are associated with NCCTG. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these research tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

We would like to store your blood and/or tissue samples for future research. If you agree, your samples will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research (<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>).

The research that may be done with your samples is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

**Things to Think About**

The choice to let us store your samples for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your samples can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your samples. Then any samples that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). Even if your samples are used for this kind of research, the results will not be put in your health records.

Your samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future.

**Benefits**

The benefits of research using samples may include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**Risks**

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Making Your Choice**

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number. No matter what you decide to do, it will not affect your care.

1. My blood sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

Yes  No Please initial here: \_\_\_\_\_  
 Date: \_\_\_\_\_

2. My blood sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes  No Please initial here: \_\_\_\_\_  
 Date: \_\_\_\_\_

3. My tissue sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

Yes  No Please initial here: \_\_\_\_\_  
 Date: \_\_\_\_\_

4. My tissue sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes  No Please initial here: \_\_\_\_\_  
 Date: \_\_\_\_\_

If you want your sample(s) destroyed at any time, write to the Secretary of the \_\_\_\_\_ Institutional Review Board \_\_\_\_\_.  
 NCCTG has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of NCCTG. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

**How do outside researchers get the sample?**

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, who will contact you.

***Please read the following statements and mark your choice:***

I permit NCCTG to give my blood sample(s) to outside researchers:

Yes  No Please initial here: \_\_\_\_\_  
Date: \_\_\_\_\_

I permit NCCTG to give my tissue sample(s) to outside researchers:

Yes  No Please initial here: \_\_\_\_\_  
Date: \_\_\_\_\_

Two of the investigators associated with this project and Mayo Clinic have a financial interest in technology used in the research, and the investigators and Mayo Clinic may stand to gain financially from the successful outcome of the research.

Both the Mayo Clinic Conflict of Interest Review Board and the Institutional Review Board have reviewed the financial interest for two of the investigators and/or Mayo Clinic related to this research and they have determined that this financial interest poses no additional significant risk to the welfare of participants in this research project or to the integrity of the research.

Additional information is available to any interested study participant regarding the details of this financial interest and how it is being managed by contacting the study coordinator or the Office of Conflict of Interest Review at 507-284-0075.

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**Where can I get more information?**

**You may call the National Cancer Institute's Cancer Information Service at:**

**1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615**

**You may also visit the NCI Web site at <http://cancer.gov/>**

- **For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>**
- **For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>**
- **For NCI's general information about cancer in Spanish, go to <http://www.cancer.gov/espanol>**

**You will get a copy of this form. If you want more information about this study, ask your study doctor.**

**Signature**

**I have been given a copy of all \_\_\_\_\_ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

**Printed Participant Name:** \_\_\_\_\_

**Participant Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Printed name of person obtaining informed consent:**

\_\_\_\_\_

**Signature of person obtaining informed consent:**

\_\_\_\_\_

**Date** \_\_\_\_\_

*Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.*

*Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.*

**NCI Informed Consent Template for Cancer Treatment Trials  
(English Language)**

**\*NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]**

The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>

A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.

Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer...What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.

Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*\*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

**Phase I/II Trial of Rituximab, Cladribine, and Temsirolimus (RCT) Therapy in Newly Diagnosed Mantle Cell Lymphoma (MCL).**  
(Phase II Consent Form)

**This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.**

**This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.**

You are being asked to take part in this research study because you have newly diagnosed mantle cell lymphoma (MCL). MCL is a cancer which is generally thought to not be curable by standard therapies. Treatments used include combinations of chemotherapy, antibody therapy, and aggressive chemotherapy with stem cell transplant.

**Why is this research study being done?**

The purpose of this research study is to:

- Determine what effects, good and/or bad, this combination has on you and your lymphoma.
- Additional research testing will be done as part of this study to better understand what effects the study drugs have on your body as well as seeing if minor differences in your genes change your cancer's response to the treatment.

Side effects from the combination of rituximab, cladribine, and temsirolimus will be closely monitored. The use of this combination in this study is considered investigational.

**How many people will take part in the research study?**

About 44 people will take part in the second part of this study. About 74 people will take part in this study overall (Phase I and Phase II combined).

**What will happen if I take part in this research study?**

**Before you begin the study ...**

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

**Before entering study:**

≤ 28 days before entering study

- Routine blood tests
- CT scans
- Bone marrow biopsy
- PET Scan (if clinically indicated)
- Mandatory tumor biopsy - tumor tissue collected previously during a biopsy (or surgery) will be reviewed to confirm the results of your local laboratory review.
- Mandatory research tissue – The tumor biopsy tissue (listed above) will also be used for mandatory research tests, no additional biopsies will be done for the research tests.

Add 3

≤ 14 days before entering study

- Doctor's appointment for history and examination
- Routine blood tests
- Mandatory research blood draw, about 2 tablespoons of blood will be drawn after pre-registration, but prior to starting study treatment.
- If it is not known if you have hepatitis B you will need to have a blood test done. If your hepatitis B test result is positive, you may not be able to take part in the study. The test result will also be put in your medical record.

≤ 7 days before entering study

- Pregnancy test (if applicable)

**During the study...**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures which are part of regular cancer care.

During the study you will be given the following combination of study drugs: rituximab, cladribine and temsirolimus.

You will receive rituximab, cladribine and temsirolimus at various time points during a 28 day period. This period of time is called a cycle. You will receive 2-6 cycles of therapy, depending on the response of your lymphoma to the treatment. Each cycle is numbered in order. The chart below shows what will happen to you during each cycle as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day. Prior to each rituximab treatment you will be given acetaminophen by mouth and diphenhydramine either by mouth or through your vein. Prior to each temsirolimus dose you will be given diphenhydramine either by mouth or through your vein.

You should not drink grapefruit juice or eat grapefruit while you are enrolled in the study, because there may be possible drug interactions. Temsirolimus could interact with other medicines. Please provide your doctor or nurse with a list of all your medications to check for any potential interactions.

**Study treatment summary**

<b>Day</b>	<b>What you need to do</b>
Before receiving chemotherapy at the start of each cycle	<ul style="list-style-type: none"> <li>• Doctor's appointment for history and examination</li> <li>• Routine blood tests</li> </ul>
Day 1 each cycle	<ul style="list-style-type: none"> <li>• Acetaminophen will be given prior to each rituximab dose.</li> <li>• Diphenhydramine will be given prior to each rituximab or temsirolimus dose.</li> <li>• One dose of rituximab will be given into a vein over several hours as fast as tolerated</li> <li>• One dose of temsirolimus will be given into a vein over 30 minutes.</li> </ul>
Days 1-5 each cycle	<ul style="list-style-type: none"> <li>• One dose of cladribine will be given into a vein over 2 hours each day for 5 days in a row</li> </ul>
Days 6-15 each cycle	<ul style="list-style-type: none"> <li>• Filgrastim under the skin daily-Days 6-15 OR pegfilgrastim injected under the skin on Day 6. These drugs may be given on Day 7 or 8 if there is a weekend or holiday on Day 6.</li> </ul>
Days 8, 15 & 22 each cycle	<ul style="list-style-type: none"> <li>• On these days <u>you may or may not</u> receive diphenhydramine and a dose of temsirolimus. This will depend on which dose level of temsirolimus you are assigned to.</li> <li>• Routine blood tests will be done before each dose of temsirolimus.</li> </ul>
Day 15 each cycle	<ul style="list-style-type: none"> <li>• Routine blood tests</li> </ul>
Day 28	<ul style="list-style-type: none"> <li>• End of current cycle</li> </ul>
After cycles 2, 4 and 6	<ul style="list-style-type: none"> <li>• Doctor's appointment for history and examination</li> <li>• Routine blood tests</li> <li>• Repeat CT or PET scans and/or bone marrow biopsy if test showed lymphoma when last done</li> <li>• Mandatory research blood draw (after cycle 2 only). Approximately 2 tablespoons of blood will be drawn.</li> </ul>

**When I am finished taking the study drugs....**

You will be asked to take study drugs for 2-6 months depending on how your cancer responds to the study drugs.

**How long will I be in the research study?**

After you are finished taking study drugs the study doctor will ask you to visit the office for follow-up exams according to the table below:

First and second year after treatment	<ul style="list-style-type: none"> <li>• Doctor's appointment for history and examination, blood tests (may include research tests), and CT scans every 3 months</li> </ul>
Third year after treatment	<ul style="list-style-type: none"> <li>• Doctor's appointment for history and examination, blood tests (may include research tests), and CT scans every 4 months</li> </ul>

You will be followed for a maximum of 5 years.

**Can I stop being in the research study?**

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drugs. In some cases, side effects can be serious, long lasting, or may never go away. There may be a risk of death.

### **You should talk to your study doctor about any side effects that you have while taking part in the study.**

Cladribine is a powerful drug that affects both normal and cancer cells. Risks and side effects related to the cladribine include those which are:

Add 1,4

#### **Likely risks of cladribine** (*events occurring greater than 10% of the time*)

- Low number of white blood cells (infection fighting cells), which could put you at risk for infection (neutropenia)
- Decrease in red blood cells (oxygen carrying cells) which could make you feel tired (anemia)
- Low number of a particular white blood cell, which is important to the immune system and may be long term (lymphopenia)
- Infection
- Fever, particularly when white blood counts are low (neutropenic fever)
- Headache
- Tiredness (fatigue)
- Feeling sick to your stomach (nausea)
- Skin rash
- Reduced number of bone marrow cells and may be long term (hypocellular bone marrow)
- Abnormal breathing sounds
- Decreased production within the bone marrow that causes decreased production of red cells, white cells, or platelets (myelosuppression)
- Decreased number of blood cells (platelets) that help to clot the blood, which could put you at increased risk of bleeding (thrombocytopenia)
- Redness at the site of the intravenous line (injection site reaction)
- Throwing up (vomiting)
- Poor appetite, not feeling hungry (anorexia)

Add 1,4

#### **Less likely risks of cladribine** (*events occurring 1-10% of the time*)

- Serious infection with risk of death
- A painful, blistering red rash that is confined to one side of the body, similar to chicken pox (herpes zoster or shingles)
- Chills (rigors)
- Sweats
- Body aches
- Weakness (asthenia)
- Feeling unwell (malaise)

- Loose stool (diarrhea)
- Difficulty passing stool (constipation)
- Belly (abdominal) pain
- Bruising
- Small purple dots on the skin (petechiae)
- Nose bleed (epistaxis)
- Sensation of lightheadedness or vertigo (spinning sensation) (dizziness)
- Difficulty falling or staying asleep (insomnia)
- Swelling in your arms or legs (edema)
- Rapid heartbeat (tachycardia)
- Cough
- Shortness of breath or difficulty breathing (dyspnea)
- Itching sensation (pruritus)
- Pain
- Redness of the skin (erythema)
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Blood clot (thrombosis)
- Inflammation of the veins (phlebitis)
- Abnormal chest sounds

Add 1,4

**Rare but serious risks of cladribine** (*events occurring less than 1% of the time*)

- Kidney damage, when used at higher doses; may be long term. Not reported at standard doses (renal failure).
- Brain, spinal cord and nerve damage, when used at higher doses; may be long term. Rarely seen after standard doses (demyelinating disease, axonal peripheral polyneuropathy, paraparesis, and quadriplegia).
- Involuntary changes in body movement or function, sensation, awareness, or behavior, when used at higher doses (seizures).
- A complication that may occur if the cancer cells die too quickly that includes inappropriate increase or decrease of various natural chemicals in the blood stream (uric acid, phosphorus, potassium, creatinine, and calcium) which can result in kidney failure and may harm muscle or nerve function (tumor lysis syndrome).
- Abnormal blood counts from bone marrow damage long after cladribine use which may be long term (myelodysplasia).
- Cancer of the bone marrow (leukemia)
- Anemia from red blood cell destruction (hemolytic anemia)
- Anemia in which the bone marrow fails to produce adequate numbers of peripheral blood elements (aplastic anemia)
- Hives (urticaria)
- Severe rash which causes blistering and peeling of the skin (Stevens-Johnson syndrome and toxic epidermal necrolysis).
- Bilirubin increase (hyperbilirubinemia)
- A disease characterized by a marked increase in the white blood cell count (hypereosinophilia)
- Reduced red blood cells (can make you feel tired), white blood cells (can put you at risk for infection), and platelets (can put you at risk for bleeding) (pancytopenia)
- Infection of the lungs (pneumonia)
- Changes in lungs seen on chest x-ray showing abnormal shadows, resembling pneumonia (pulmonary interstitial infiltrates)
- Increase in blood level of liver enzymes (ALT/AST)
- Increased risk of unusual infections due to lowered immunity (opportunistic infections)

Risks and side effects related to the rituximab include those which are:

Add 5

**Likely:**

- Chills
- Fever
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Decreased number of a type of white blood cell (lymphocyte)

Add 5

**Less Likely:**

- Lack of enough red blood cells (anemia)
- Thickening of blood/serum as found in Waldenstrom's macroglobulinemia (a cancer of certain blood cells)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Heart attack caused by a blockage of a blood vessel supplying part of the heart
- Fast heartbeat; regular rhythm
- Fast heartbeat usually originating in an area located above the ventricles
- Belly pain
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Swelling of the arms and/or legs
- Fatigue or tiredness
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Allergic reaction to certain medications, injected proteins, or antisera (blood product) used to treat certain medical conditions (such as an infectious or poisonous substance)
- Infection
- Awakening of viruses which have been latent/dormant
- Infection in HIV positive patients
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Decrease in the total number of white blood cells (leukocytes)
- Increased blood sugar level
- Decreased blood level of calcium
- Decreased blood level of potassium
- Joint pain
- Back pain
- Muscle pain
- Pain in the area of the tumor
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Headache or head pain
- Abnormal drowsiness or sluggishness, an unusual lack of energy
- Convulsion or seizure
- Sudden or traumatic injury to the kidney
- Stuffy or runny nose, sneezing

- Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath
- Cough
- Shortness of breath
- Decrease in the oxygen supply to a tissue
- Inflammation of the lungs that may cause difficulty breathing and can be life-threatening
- Sore throat
- Excess sweating
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Swelling of body tissue underneath the skin
- Hives
- Sudden reddening of the face and/or neck
- High blood pressure
- Low blood pressure

Add  
5,7

**Rare but Serious:**

- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure
- Disease affecting brain tissue, caused by the JC virus
- Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure or even death. The risk of hepatitis B virus flaring up may continue for several months after you stop. Most of these patients were taking rituximab in combination with chemotherapy. If you are at risk of hepatitis B reactivation, you should speak with your doctor before you enroll in this study. If you are a carrier of hepatitis B, you will be monitored for signs of active infection throughout your study participation. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor immediately.

**Risks and side effects related to the temsirolimus include those which are:**Add  
4,11**Likely risks of temsirolimus** (*events occurring greater than 20% of the time*)

- Decreased number of blood cells that help to clot blood (platelet)
- Tiredness, fatigue
- Rash; flaking or sloughing of skin or with the presence of macules (flat discolored area) and papules (raised bump)
- Diarrhea
- Irritation or sores in the lining of the gastrointestinal tract (for example: mouth, throat, stomach, intestine, anus, rectum, small bowel, voice box, windpipe)
- Feeling sick to your stomach, nausea
- Increased blood cholesterol level
- Decrease in the part of the red blood cells that carries oxygen in the body, may cause tiredness (anemia)
- Loss of appetite

Add  
4 8 11**Less likely risks of temsirolimus** (*events occurring less than or equal to 20% of the time*)

- Abnormal reaction of the body to substances, called allergens, that are contacted through the skin, inhaled into the lungs, swallowed, or injected (allergic reaction)
- Decreased number of white blood cells (for example reduced total leucocytes, lymphocytes, or neutrophils/granulocytes), which may cause increased risk of infection
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- High blood pressure
- Low blood pressure
- Abnormal amount of blood protein needed for blood clotting
- Fever
- Difficulty sleeping or falling asleep
- Chills, shivering
- Dry skin
- Loss of some or all of the fingernails or toenails
- Itching
- Acne, pimples
- Hives
- Decreased level of the hormone testosterone
- Abnormal control of blood sugars
- Constipation
- Taste changes
- Throwing up, vomiting
- Nosebleed
- Infection
- Condition where the blood contains more acid than normal
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (GGT)

- Decreased blood calcium level
- Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine
- High blood sugar level
- High lipid (fat) levels in the blood
- Decreased blood phosphate level
- Decreased blood potassium level
- Increased blood level of a form of fat called triglyceride
- Feelings of sadness, worthlessness, thoughts of suicide or death (depression)
- Sleepiness
- Pain – for example pain in the stomach, back, chest, head, joint, muscle, headache or head pain
- Cough
- Shortness of breath
- Runny/stuffy nose or sneezing
- Inflammation of the lungs
- Impotence, inability to have or maintain an erection during sexual intercourse
- Decrease in sexual desire
- Flu type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Poor wound healing
- Premature opening of a wound along surgical stitches after surgery
- Weight loss
- Edema or swelling of the face, hands or feet
- Excess accumulation of fluid between the layers of tissue that lines the lungs and chest cavity
- Distention/bloating of the belly (swelling or feeling of fullness and tightness in the abdomen)
- Problem of the sinuses
- Difficulty swallowing

Add  
4,11

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

- Sudden decrease of kidney function
- Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Allergic reaction: Some patients have had an allergic reaction during CCI-779/temsirolimus infusion. Life threatening reactions (including fatal) have occurred. Patients with allergic reactions have had chest pain and tightness, difficulty breathing, feeling hot, flushed and anxious, swelling around the eyes, dizziness, feeling sick to the stomach, a fall in blood pressure, back pain, and numbness and tingling. These symptoms went away a few minutes after the infusion was stopped, and in some cases, after treatment was given. Because an allergic reaction may happen, an antihistamine drug (e.g. diphenhydramine (Benadryl) is given before CCI-779/temsirolimus. If you are given an antihistamine and still have an allergic reaction, the study doctor may stop or slow down the infusion and may give you other intravenous medication.

**Risks and side effects related to the filgrastim include those which are:**

**Common side effects**

- Bone pain

**Less common side effects**

- Fluid or blood collecting in the sac around the heart
- Increased blood levels of uric acid, LDH, alkaline phosphatase

- Enlargement of the spleen
- Worsening of skin rashes, hair loss, and ability for blood to clot

**Rare but serious side effects**

- Fluid retention
- Lowering of blood pressure which lasts only for a little while
- Acute inflammation of blood vessels
- Allergic-type reactions

**Risks and side effects related to pegfilgrastim include those which are:**

**Common side effects**

- Bone pain

**Less common side effects**

- Allergic-type reactions

**Rare but serious side effects**

- Rupture of the spleen
- Sickle cell crisis in patients who have sickle cell disease

To help prevent reactions to the chemotherapy; you will get acetaminophen and diphenhydramine at the same time you get rituximab.

Add 1 The combination of cladribine and rituximab may worsen the side effects of each drug in comparison to when the drugs are given separately. This combination may also result in unexpected, severe permanent, debilitating, or even fatal toxicities.

Adult Respiratory Distress Syndrome (ARDS) has been reported in neutropenic patients with sepsis (bacteria in your blood or tissue) who get filgrastim. If you get a fever or have trouble breathing, you should contact your doctor. If you get ARDS, filgrastim and pegfilgrastim will be stopped until you get better.

Bone marrow biopsies (sample taken from large bones in your hip with a needle) may cause pain and a small risk of bleeding, bruising, or infection at the needle site.

Frequent blood draws will be part of this study. A blood drawing may cause minimal discomfort and a small risk of bleeding, bruising, or infection at the needle site.

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important for you to understand that you need to use birth control while on this study and for up to 12 months after taking your last dose of study drug. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future. Women who can become pregnant must have a pregnancy test before taking part in this study. This test must be done within 7 days before you enter the study. You will be told if you are pregnant or not. If you are pregnant, you will not be able to take part in the study.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the research study?**

Taking part in this study may or may not make your health better. While doctors hope the study drugs will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the study drugs as a treatment for cancer. This information could help future cancer patients.

### **What other choices do I have if I do not take part in this research study?**

You do not have to be in this study to receive treatment for your cancer. Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

### **Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

- The local Institutional Review Board
- The North Central Cancer Treatment Group
- Pfizer, Inc., who is providing support for the study
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

Add 8

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

### **What are the costs of taking part in this research study?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Add 8

Pfizer, Inc. is supplying temsirolimus at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the (drug).

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

### **What happens if I am injured because I took part in this research study?**

It is important that you tell your study doctor, \_\_\_\_\_ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at \_\_\_\_\_ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

### **What are my rights if I take part in this research study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_ *[name(s)]* at \_\_\_\_\_ *[telephone number]*.

For questions about your rights while taking part in this study, call the \_\_\_\_\_ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ *(telephone number)*. *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

\*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[\*Only applies to sites using the CIRB.]*

**About Using Biological Samples for Research**

This study has research tests that will be performed to study small samples of blood and biopsy tissue. You are required to participate in these studies in order to participate in this study.

A blood sample will be done by drawing some blood from a vein. The research blood samples will be drawn after registering for the study but before treatment starts. Research blood will be drawn again at the end of cycle two. Approximately 2 tablespoons of blood will be drawn for each of these time points.

You are going to have or may already have had a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these clinical tests will be given to you by your doctor and will be used to plan your care. If you agree to participate in this study, your original biopsy tissue sample will be used for additional research tests as a part of this study. No additional biopsies will be done to get this tissue.

For the research tests to be done, your tissue will be sent to Dr. Ahmet Dogan's laboratories which are associated with NCCTG. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these research tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

We would like to store your blood and/or tissue samples for future research. If you agree, your samples will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research (<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>).

The research that may be done with your samples is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

**Things to Think About**

The choice to let us store your samples for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your samples can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your samples. Then any samples that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). Even if your samples are used for this kind of research, the results will not be put in your health records.

Your samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future.

**Benefits**

The benefits of research using samples may include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**Risks**

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Making Your Choice**

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number. No matter what you decide to do, it will not affect your care.

1. My blood sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

Yes  No Please initial here: \_\_\_\_\_  
Date: \_\_\_\_\_

2. My blood sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes  No Please initial here: \_\_\_\_\_  
Date: \_\_\_\_\_

3. My tissue sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

Yes  No Please initial here: \_\_\_\_\_  
Date: \_\_\_\_\_

4. My tissue sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes  No Please initial here: \_\_\_\_\_  
Date: \_\_\_\_\_

If you want your sample(s) destroyed at any time, write to the Secretary of the \_\_\_\_\_  
Institutional Review Board \_\_\_\_\_.  
NCCTG has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of NCCTG. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

**How do outside researchers get the sample?**

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, who will contact you.

***Please read the following statements and mark your choice:***

I permit NCCTG to give my blood sample(s) to outside researchers:

Yes  No Please initial here: \_\_\_\_\_  
Date: \_\_\_\_\_

I permit NCCTG to give my tissue sample(s) to outside researchers:

Yes  No Please initial here: \_\_\_\_\_  
Date: \_\_\_\_\_

Two of the investigators associated with this project and Mayo Clinic have a financial interest in technology used in the research, and the investigators and Mayo Clinic may stand to gain financially from the successful outcome of the research.

Both the Mayo Clinic Conflict of Interest Review Board and the Institutional Review Board have reviewed the financial interest for two of the investigators and/or Mayo Clinic related to this research and they have determined that this financial interest poses no additional significant risk to the welfare of participants in this research project or to the integrity of the research.

Additional information is available to any interested study participant regarding the details of this financial interest and how it is being managed by contacting the study coordinator or the Office of Conflict of Interest Review at 507-284-0075.

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**Where can I get more information?**

**You may call the National Cancer Institute's Cancer Information Service at:**

**1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615**

**You may also visit the NCI Web site at <http://cancer.gov/>**

- **For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>**
- **For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>**
- **For NCI's general information about cancer in Spanish, go to <http://www.cancer.gov/espanol>**

**You will get a copy of this form. If you want more information about this study, ask your study doctor.**

**Signature**

**I have been given a copy of all \_\_\_\_\_ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

**Printed Participant Name:** \_\_\_\_\_

**Participant Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Printed name of person obtaining informed consent:**

\_\_\_\_\_

**Signature of person obtaining informed consent:**

\_\_\_\_\_

**Date** \_\_\_\_\_

*Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.*

*Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.*