Title: Safety and Efficacy of Intrathecal Rituximab in Patients with Lymphoid Malignancies Involving the Central Nervous System

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Centers: M. D. Anderson Cancer Center

Number of Patients: 25

Objectives: to determine the safety and efficacy of intrathecal rituximab in patients with relapsed and/or refractory lymphoid malignancies with involvement of the central nervous system.

Background:

Leptomeningeal / Central Nervous System Disease

Leptomeningeal disease (LMD) or central nervous system (CNS) disease in leukemia occurs when blast cells invade the walls of the leptomeningeal veins over superficial surfaces of the brain. Utilization of prophylactic intrathecal chemotherapy and high-dose systemic chemotherapy reduces the incidence of CNS disease. However, development of CNS disease is still a problem, because if it occurs, the prognosis overall tends to be poor (1, 2).

Diagnosis

Diagnosis of CNS leukemia involves assessing the cerebrospinal fluid (CSF) by lumbar puncture (LP) or intraventricular sampling. Signs and symptoms include headache, mental status changes, motor deficits, and seizures. In most patients, the CSF is abnormal (protein concentration greater than 50 mg/dL, leukocyte count greater than 4 per mm^3, and positive cytology). A positive cytology by itself is diagnostic of LMD. In leukemias and lymphomas, the yield of positive cytology following one or two lumbar punctures is approximately 70% (3).

Neuroradiographic imaging can also be involved in the diagnostic workup, to include cranial computed tomography (CT), magnetic resonance imaging (MRI), CT-myelography, and radionuclide CSF flow studies (4). However, imaging studies have a high false negative rate.

Treatment of Leptomeningeal Disease

Treatment of LMD involves the entire neuroaxis, therefore treatment must be designed to encompass the entire subarachnoid space. Radiation therapy to the entire neuroaxis produces severe bone marrow suppression and has generally not been effective in controlling active CNS disease even in radiosensitive malignancies (4). Systemic chemotherapy for LMD is limited in its utility due to poor penetration of the blood brain barrier (with the exception of the administration of high dose methotrexate or cytarabine) and due to difficulties attaining prolonged intra-CSF drug exposure. Determining the response to therapy primarily involves the clearance of blasts from the CSF along with clinical improvement.

The incidence of CNS relapse with or without bone marrow recurrence in adults with ALL is approximately 7% (1). In this series, patients were treated with intensive chemotherapy and/or CNS prophylaxis with IT methotraxate and cytarabine. Despite a high response rate (clearing CNS disease), median survival for these patients was 6 months, and the 1-year survival rate was 28%.

In our institution, patients who are diagnosed with CNS leukemia are started on intrathecal chemotherapy on a twice weekly schedule of administration. This continues until two consecutive CSF samples are negative for the presence of blast cells. After the patient's CSF cytology is negative, patients commence on maintenance intrathecal chemotherapy weekly for one month, followed by one intrathecal injection with chemotherapy administration every other week thereafter. Methotrexate has been the most widely employed drug for intrathecal treatment of LMD. The terminal half-life of intrathecal methotrexate is 14 hours. The toxicities of intrathecal methotrexate can be exacerbated by the administration of concurrent systemic chemotherapy or radiation. Cytarabine is another active agent administered intrathecally in the treatment of LMD. Typically, these two agents are given on an alternating schedule to potentially minimize toxicity and maximize effectiveness.

Monoclonal antibody therapy has drastically improved the outlook for several malignancies, including adult acute lymphoblastic leukemia. Recently, Thomas and colleagues reported an increased overall survival in younger patients who received the CD20 specific monoclonal antibody rituximab (5). However, the molecule is large, making it difficult to deliver the agent to the central nervous system. Recently, several reports have been published on intrathecal administration of rituximab. Therefore, we would like to conduct a prospective investigation on the safety and effectiveness of this strategy.

Background Drug Information:

Systemic Rituximab

Rituximab is a chimeric monoclonal antibody directed at the CD20 antigen. It was initially approved for systemic use in 1997 to treat non-Hodgkin's lymphoma (6). Subsequent to the drug's approval, it has been studied in a number of different oncologic situations, including chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and as part of the mobilization program for hematopoietic stem cell transplantation. Recently, the addition of rituximab to chemotherapy has been shown to improve overall survival (OS) in younger patients with CD20 positive ALL (5). Moreover, in CLL, rituximab

combined with fludarabine and cyclophosphamide has also improved the outcome of patients compared to conventional chemotherapy programs (7).

The major toxicities of systemically administered rituximab are primarily related to the infusion of the drug, and may include fever, chills, rigors, rash, headache, and hypotension (6). These reactions are potentially fatal, and are typically seen during the first infusion. Most infusion reactions can be ameliorated by administering the drug slowly, and escalating the infusion rate only as the patient tolerates. Premedications are also vital, and might include histamine blocking agents, acetaminophen, and/or corticosteroids. Other potential toxicities include tumor lysis syndrome and mucocutaneous eruptions. Rarely, reactivation of JC virus leads to progressive multifocal leukoencephalopathy.

Penetration of rituximab across the blood brain barrier is a problem due to the drug's large molecular size. Investigators have conducted pharmacokinetic analyses showing that CSF levels of rituximab are 0.1 – 4% of the concomitant serum concentration (8, 9). Rituximab, while highly effective as a systemic therapy, does not reduce the risk of lymphoma recurrence in the central nervous system (10).

Intrathecal Rituximab

There is preclinical and clinical experience directly infusing rituximab into the CSF. Rubenstein and colleague have first explored the safety and pharmacokinetics of intraventricular rituximab in four female cynmologus monkeys (11). The authors noted that high concentrations were able to be achieved, and there was no evidence of neurotoxicity observed. The animals received up to two intraventricular rituximab infusions.

Encouraging animal data led to several instances where intrathecal rituximab was employed in humans. A group from the University of California San Francisco and Memorial Sloan Kettering Cancer Center conducted a phase 1 dose finding study of intraventricular rituximab in patients with recurrent CNS and intraocular lymphoma (12). Patients were to receive 10 mg, 25 mg, or 50 mg for up to nine administrations. Most patients on this study had the drug administered through an Ommaya reservoir. Five out of the six patients initially assigned to the 10 mg and 25 mg cohorts received all nine scheduled rituximab treatments. The dose limiting toxicity in the 50 mg cohort was grade 3 hypertension. These patients also complained of diplopia and chest discomfort that resolved with careful observation and supportive care. Very little toxicity was noted in patients who received 25 mg of intraventricular rituximab. However, one patient in the 10 mg cohort did experience what was defined as white matter changes on MRI raising the possibility of leukoencephalopathy. One patient who received rituximab 25 mg administered via lumbar puncture experienced parasthesias in the sacral distribution that resolved within 10 minutes after drug administration.

The remainder of the experience with intrathecal rituximab has been presented or published in case reports or case series. Most of the reports describe administration of rituximab through an Ommaya reservoir (13). Only one case series to date (to our knowledge) describe the use of intrathecal rituximab in patients with B-cell ALL (14). A group from Mexico tested the efficacy of intrathecal rituximab in the

setting of CNS leukemia refractory to conventional intrathecal therapy (combination of methotrexate, cytarabine, and corticosteroids) (Jaime-Perez). Before the rituximab, these patients had undergone a median of 23 intrathecal lumbar punctures with administration of chemotherapy and steroids. These patients received rituximab 10 mg diluted in 6 mL of saline solution intrathecally weekly for 4 weeks. After the fourth dose, all 7 patients' CSF samples were negative for leukemia cells. No neurotoxicity was observed. After 24 months of follow up, 5 of the 7 patients remained without CNS involvement of the leukemia.

Inclusion Criteria

Patients must have relapsed or refractory CD20+ lymphoid malignancies with either documented CNS involvement or peripheral nerve infiltration.

Patients 3 years of age and older are eligible after 3 patients (age 15 or older) have been treated and did not experience a dose limiting toxicity. Patient 3 to 15 years of age will follow the dose escalation schema independent of the adults.

ECOG performance status measure will be used. (ECOG Performance Status less than or equal to 3)

Adequate liver function (bilirubin less than or equal to 3 mg/dL within 24 hours of enrollment)

Adequate renal function (serum creatinine less than or equal to 3 mg/dL within 24 hours of enrollment)

Urine pregnancy test for women of childbearing potential (defined as *not* post-menopausal for 12 consecutive months or no previous surgical sterilizations). A negative urine pregnancy test is required within 48 hours of initiating study drug.

Signed informed consent

Exclusion Criteria

Known active meningeal infection

History of severe infusion reaction to any monoclonal antibody

Treatment Plan

Rituximab will be administered via lumbar puncture at a dose of 10 – 25 mg according to the dose escalation procedures outlined below.

Standard premedications for each lumbar puncture will be administered (benzodiazepine for anxiolysis as well as a topical anesthetic)

Additional premedication will be administered to prevent infusion related complications. 30 minutes prior to each lumbar puncture, patients should receive diphenhydramine (12.5 – 50 mg IV), famotidine (20 – 40 mg IV, and acetaminophen 650 mg PO). Patients may also receive corticosteroid as a premedication at the discretion of the Attending Physician. If in the best interest of the patient, as judged by the Attending Physician, any of the above premedications can be omitted with documentation of the reason why a particular medication was not to be prescribed.

After each intralumbar administration, the patient will be instructed to lie flat for one to two hours, and longer if possible

Rituximab is commercially available, patient and/or insurance provider will be responsible for the cost of the drug. Rituximab will be commercially supplied as a 10 mg/mL solution

Drug Preparation: the 10 mg dose of rituximab will be diluted to a total volume of 5 mL with preservative free 0.9% sodium chloride. The 25 mg dose of rituximab will be diluted to a total volume of 6.3 mL with preservative free 0.9% sodium chloride.

Selection of Patients:

Patients will be eligible for the study if they relapsed and/or refractory CD20+ lymphoid malignancies (all patients beyond complete remission 1 are considered eligible). Upon suspicion of LMD, the patients will be screened for the protocol. The preference at this point will be for the patient to receive a diagnostic lumbar puncture (i.e., no chemotherapy administered). However, if it is deemed necessary to instill conventional chemotherapy (e.g., methotrexate or cytarabine) during the first lumbar puncture, these patients will still be eligible for the protocol. The two groups will be analyzed separately for all outcomes (i.e., patients who received no intrathecal chemotherapy prior to receiving intrathecal rituximab, and patients who received cytarabine or methotrexate before commencing intrathecal rituximab). If a patient had received IT methotrexate or cytarabine and is subsequently enrolled, at least 48 hours should elapse from the administration of methotrexate or cytarabine to the first application of IT rituximab.

Once enrolled, the patients will go on to receive rituximab 10 mg intrathecally twice weekly until 2 consecutive CSF samples are negative for the presence of blast cells 48 hours must elapse between intrathecal rituximab doses**.** Thereafter, rituximab 10 mg intrathecally will be administered weekly for an additional 4 weeks, followed by intrathecal rituximab 10 mg administered once every other week for an additional 8 weeks.

After the first three patients are enrolled and followed for at least 2 weeks, if no dose limiting toxicity is experienced, all subsequent patients will be given rituximab 25 mg intrathecally on an identical schedule as described above. This dose was identified as the maximum tolerated dose in the phase I study

conducted by Rubenstein and colleagues. If excessive toxicity is noted in the first 3 patients given rituximab 25 mg (with at least two weeks of follow up), we will move back to the 10 mg dose, and that will be the final dose employed going forward.

Supportive Care

While intrathecal rituximab has been well tolerated in all previously published reports, there are a number of potential toxic effects that will be anticipated. Since hypertension was the dose limiting toxicity in the phase 1 trial, specific aims will be outlined to manage changes in blood pressure around the time of rituximab administration.

Vital signs will be checked every 15 minutes for one hour after each intrathecal administration of rituximab (after one hour, vital signs will return to "routine" unless clinically warranted). For systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg, labetalol 20 mg IV will be administered. An alternative agent will be prescribed if the patient's heart rate is less than 70 beats per minute (e.g. hydralazine, enalaprilat). The management of hypertension can be further individualized if necessary at the discretion of the treating physician. For nausea or vomiting, ondansetron can be considered. If the patient is not over-sedated, a dopamine receptor blocking agent such as promethazine or prochlorperazine can be ordered. These agents will be available on an as needed basis only.

If a patient experiences any chest discomfort, a 12-lead electrocardiogram will be ordered.

For any shortness of breath, bronchodilators such as albuterol will be administered via nebulizer. Supplemental oxygen will be provided to maintain the oxygen saturation greater than 92%, and diagnostic imaging studies (e.g., chest x-ray or chest CT) will be ordered at the discretion of the treating physician or the PI of the study.

Any acute or subacute changes in mental status will warrant magnetic resonance imaging of the brain to rule out leukoencephalopathy.

Concomitant Medications/Therapy

If warranted, patients will be able to commence treatment with systemic chemotherapy. If at all possible, high dose cytarabine and high dose methotrexate will be avoided while patients are undergoing intrathecal rituximab injections. However, this may not always be avoidable, and any patient that receives concomitant intrathecal rituximab and potentially neurotoxic systemic chemotherapy will be monitored closely for any toxicity that is out of the ordinarily expected effects from chemotherapy. If needed, whole brain or cranio-spinal irradiation will be permitted during this study. Concomitant medications/therapy will be entered into the electronic case report form (PDMS/CORe).

Patient Evaluation

Pre-Treatment Evaluation

- History and physical examination, including vital signs, height, weight and performance status.
- Blood will be drawn for routine tests.
- Diagnostic lumbar puncture
- Concomitant drugs and side effects will be evaluated and recorded.

During Treatment Evaluation

Twice weekly evaluations until two consecutive CSF samples are negative for the presence of blast cells. After the patient's CSF cytology is negative, patients will be evaluated weekly for one month, then every other week thereafter.

- Physical examination, including vital signs, weight and performance status.
- Blood will be drawn for routine tests.
- Concomitant drugs and side effects will be evaluated and recorded.

Follow-Up

- Serious adverse events will be captured until 30 days after the last dose of drug.

Long-term Follow-up

- Patients will be followed for survival every 6 to 12 months after completion of active treatment and while still on study or be enrolled on the leukemia department long-term follow-up umbrella protocol.

Adverse Events

We will use the CTCAE version 4 for toxicity and adverse event reporting. A copy of this can be found at: http://ctep.info.nih.gov

Criteria for Response

Patients will considered as responding to therapy if the CSF is without evidence of blast cells after four lumbar punctures with rituximab. Clinical improvement and diagnostic imaging may also be used to support a patient's response to therapy.

Criteria for Removal from Study

Progressive or resistant disease (defined as CSF with persisting blasts after four intra-lumbar administrations of rituximab, which is after 2 weeks of therapy)

Unacceptable severe (grade 3-4) toxicity that is possibly related to the study drug and persists despite dose optimization and optimal management of toxicity.

Patient choice

Failure to comply with study schedule

Statistical Considerations

The primary outcome of the study will be response rate. Time to recurrence of CNS leukemia and overall survival will be secondary outcomes. Time to recurrence and survival will be considered from the date of CNS relapse diagnosis.

There is no well-defined metric to measure response to treatment in patients with peripheral nerve involvement only. Clinical and radiologic response will be recorded and it is expected that few to no patients with only peripheral nerve involvement will actually be involved and therefore the statistical analysis will not be affected.

A maximum of 25 patients will enrolled in this phase I/II study, with about 12 patients/year.

Phase I

First, phase I study is performed to assess the safety of two dose levels for rituximab: 10mg and 25mg. These two dose levels have been previously in a small series (12). A 3+3 design will be used to for dose escalation. Detailed dose escalation rules are described in the following section. A maximum of 12 patients will enroll in the phase I study.

Dose Escalation Procedures

The dose of treatment agent will be escalated in successive cohorts of patients. The starting dose is at dose 0 as shown in table 1. Enroll 3 patients at the dose level and proceed to the next higher dose level with a cohort of 3 patients until at least 1 patient experiences a dose-limiting toxicity (DLT).

DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and meeting the NCI common terminology criteria that are CTCAE Grade 3 or 4.

An adverse event must be clinically significant to define DLT e.g. alopecia, study drug-related fever, electrolyte abnormalities (including K, Na, Cl, HCO3, Mg, Ca) that are < Grade 3 will not define the DLT. Drug-related Grade 3-4 nausea and vomiting not controlled with adequate therapy will be considered DLTs.

If only 1 of 3 patients experiences a DLT at a given dose level, enter 3 additional patients at the current dose level. If only 1 of 6 patients experiences a DLT at a given dose level, proceed to the next higher dose level with a cohort of 3 patients. If at least 2 of 3 or 2 of up to 6 patients experience a DLT at a

given dose level, then the MTD has been exceeded (stopping dose). Once the MTD has been exceeded, treat another 3 patients at the previous dose level if there were only 3 patients treated at that dose level. The MTD is defined as the highest dose level in which 6 patients were treated with at most 1 experiencing a DLT during the 1st cycle.

In summary, our dose escalation plan is as follows: during phase I, the starting dose is 10 mg and dose escalation will follow a 3 + 3 design. After three patients have received 10 mg, if there is no DLT, the next cohort of three patients will receive 25 mg. If there is one DLT in the initial three patients, an additional three patients will be treated at 10 mg. If 2/6 patients experience a DLT at 10 mg, the study will be closed. If less than or equal to 1/6 at 10 mg experience a DLT, we will enroll the next three patients at 25 mg. The maximum dose on this protocol is 25 mg, thus, no further dose escalation will occur. If 1/3 patients at 25 mg experience a DLT, we will enroll three additional patients at 25 mg. If 2/6 experience a DLT, all subsequent patients will receive 10 mg, and that will be the final dose. If less than or equal to 1/6 experience a DLT at 25 mg, the remainder of the patients enrolled will receive 25 mg. If 2/3 or 2/6 patients experience a DLT at the 10 mg dose, the study will be terminated.

Table 1. Dose levels of rituximab

Dose level	rituximab
0 (starting dose)	10 mg
1	25 mg

Phase II

Phase II part is a single arm study using the dosage level recommended from phase I. The patients treated at the MTD in phase I will be included in phase II part, and the sample size for phase II can be up to 22. The trial will be continuously monitored for efficacy and toxicity (non-hematological ≥grade 3). The method of Thall, Simon, and Estey will be used to perform interim efficacy and safety monitoring (15).

Efficacy

The primary endpoint is the response defined as the CNS is without evidence of blast cells after four lumbar punctures with rituximab. The historical data suggested the response rate by chemotherapy (methotrexate and/or cytarabine) is about 10%. The targeted improved overall response rate is 25%, The trial will be continuously monitored. The study will be stopped early if the data suggest that:

$$\Pr(\pi > 0.1 \mid \text{data}) < 0.05$$

Here π is the response rate. That is, if at any time during the study we determine that there is a less than 5% chance that the response rate is greater than 10%, we will terminate the study. The response

rate is assumed to follow a non-informative prior of Beta (0.2, 1.8). The study will be stopped early if (The number of responders)/ (The number of patients evaluated) ≤0/9.

Table 2: Operating characteristics for monitoring of overall response rate

True Response Rate	Early Stopping Probability	Median Sample size (interquantile)
0.05	0.63	9 (9, 22)
0.1	0.40	22 (9,22)
0.15	0.23	22 (22,22)
0.2	0.14	22 (22,22)
0.25	0.08	22 (22,22)

Monitoring Of non-hematological ≥grade 3 toxicities

With the concern of treatment related toxicity, the non-hematological toxicity (**≥**grade 3) will also be closely monitored during the study. Since the 6 patients treated at MTD in phase I will be included for efficacy evaluation in phase II, the toxicity monitoring in phase II start either with the 7th patient or with the 1st patient treated at the MTD.

Denote the probability of toxicity by P_E. We assume P_E ~ beta (0.6,1.4). Our stopping rule is given by the following probability statement: $Pr(P_E > 0.3 \mid data) > 0.9$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 90% chance that the toxicity is more than 30%. The study will be stopped early if (The number of non-hematological toxicities being grade 3 or higher)/ (The number of patients evaluated) ≥4/6/, 5/8, 6/10, 7/13, 8/15, 9/18, 10/21. The operating characteristics are summarized in table 3.

Table 3: Operating characteristics for monitoring of non-hematological ≥grade 3 toxicities

True Toxicity Rate	Early Stopping Probability	Median Sample size (interquantile)
0.2	0.05	22 (22,22)

0.3	0.22	22 (22, 22)
0.4	0.54	19 (7, 22)
0.5	0.82	7 (6, 17)

Analysis method

Data analysis will be performed using SAS or S-plus, as appropriate. All patients who received at least 1 dose of the agent will be included in the intent-to-treat analysis for efficacy. Demographic and disease characteristics of the patients at registration will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Overall response rates will be presented with 95% confidence intervals. The association between response and patient and disease characteristics will be examined by two-sample t-test or Chi-square test.

The data from all patients who received the therapy during the study will be included for safety analysis. Safety data will include laboratory, physical exam, and adverse event reports on study patients. These descriptive summaries will be provided for all patients for each safety parameter by intrathecal rituximab dose #, grade, and relationship to treatment.

Patient Data Confidentiality

Patient data will be collected, analyzed, distributed and managed in accordance with the M. D. Anderson Confidentiality Policy. Only the PI and research staff will have access to the data. The data will be stored on a password protected computer in a locked office.

Reporting Requirements

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

- Refer to Appendix C for Leukemia-Specific Adverse Event Recording and Reporting Guidelines. Only unexpected AEs will be recorded in the Case Report Form (CRF). The Principal Investigator will sign and date the PDMS Case Report Form toxicity pages per each patient at the completion of each intrathecal rituximab dose #. Following signature, the Case Report Form will be used as source documentation for the adverse events for attribution. PDMS /CORe will be used as the electronic case report form.

Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

(Please see Appendix C regarding data capturing of adverse events and adverse events source documentation.)

Reporting to FDA:

· Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

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