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Title of Study: **A pilot study of ^{18}F fluorothymidine (FLT) PET/CT in lymphoma**

Abbreviated Title: ^{18}F fluorothymidine (FLT) in lymphoma

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Study Sponsor: CIP/NCI
IND number/name of investigational drug: **# 71,260** /3'-deoxy-3'-^{18}F fluorothymidine (FLT)

NCI Supplied Agent:

3'-deoxy-3'-^{18}F fluorothymidine (FLT) (NSC 743, 144)

Participating Institution Information

This protocol includes the participation of an affiliate institution to facilitate patient imaging as authorized by the Principal Investigator and approved by the Cancer Therapy Evaluation Program. The Principal Investigator will make all treatment decisions related to the protocol and these will be conveyed to the affiliated investigator. The Principal Investigator is responsible for the research data and for the appropriate use of the study agent. The affiliate investigator has obtained IRB approval to participate in this CTEP-sponsored trial.

Affiliated Institution: Walter Reed National Military Medical Center (Nuclear Medicine Department)

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PRECIS

Background:

- FLT PET/CT has been shown to correlate with the rate of cellular/tumor proliferation.
- The Imaging Subcommittee of the International Harmonization Project in Lymphoma recommends performing FDG PET at least 3 weeks, and preferably 6-8 weeks after chemotherapy or chemoimmunotherapy therapy and 8- 12 weeks after radiation or chemoradiation therapy due to high FDG accumulation in inflammatory tissues.
- FLT uptake in inflammatory lesions is less prominent than FDG and it is likely that FLT PET/CT can better differentiate inflammation from tumor.
- FLT PET/CT imaging is expected to better differentiate between treatment induced inflammation and malignancy and should enable early prediction of therapeutic response.
- FLT PET/CT imaging is expected to differentiate between residual inflammatory residual masses from residual malignancy and therefore guide appropriate treatment.

Primary Objectives:

- To estimate the diagnostic accuracy of FLT PET/CT as an early indicator of complete response to therapy in B and T cell lymphoma.
- To estimate the diagnostic accuracy of FLT PET/CT in the evaluation of residual masses after therapy.

Eligibility:

- Participant must be enrolled in a lymphoma therapy study at the NIH Clinical Center OR be enrolled in the CALGB 50303 study at another site OR undergoing a new course of treatment of lymphoma at another facility. The NCI Laboratory of Pathology will confirm diagnosis for subjects enrolled at all CALGB study sites.
- Participants must have a clinical course consistent with lymphoma and have available documentation of lymphoma from either the NCI or from an outside pathology laboratory.
- Subjects enrolling in the early response arm must undergo baseline FLT PET prior to receiving a new course of lymphoma therapy.
- Subjects enrolling in the residual mass evaluation arm can be enrolled at the time the FDG avid residual mass is discovered (i.e. no pre-therapy FLT image is required).
- Subjects can enroll in both arms of the study.
- Participant must be 18 years or older.
- ECOG Performance score of 0 or 1
- SGOT, SGPT <5x ULN
- bilirubin ≤2x ULN

Design:

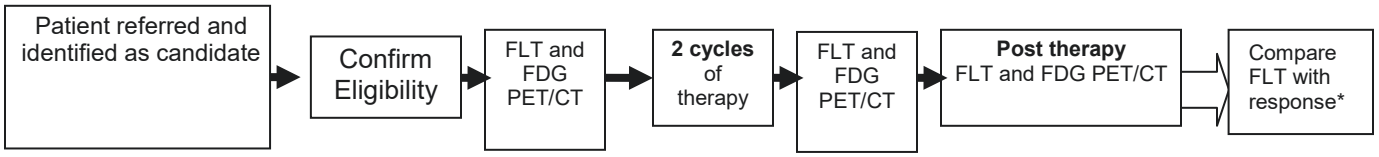
- There are 2 arms in this study
    - The first arm will assess FLT as an early predictor of tumor response to therapy (treatment naive or recurrent disease). Subjects are imaged with FLT and FDG PET pre-therapy, following 2 cycles of therapy and post therapy.
    - The second arm will assess lymphoma patients with FDG PET positive residual mass. Subjects are imaged with FLT PET prior to standard of care biopsy of residual mass. If initial FDG PET data is not available in DICOM format or is of

suboptimal image quality, a repeat FDG PET/CT at the study site may be required.

- We will accrue 70 participants (40 in the early response arm and 30 in the residual mass arm) to this study.

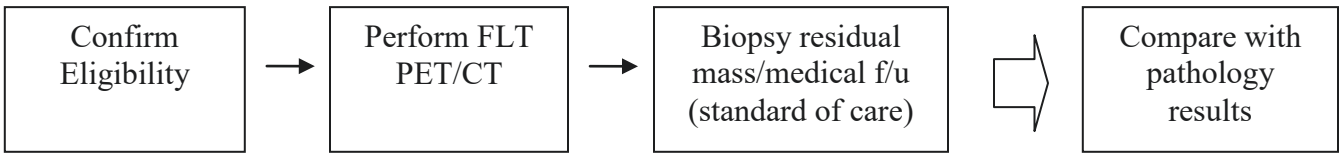
Study Schema

Early response arm



*Complete response as defined by the Cheson revised response criteria and FDG PET/CT Imaging Subcommittee of the International Harmonization Project in Lymphoma

Residual FDG PET positive residual mass arm



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1 INTRODUCTION

1.1 Objectives

1.1.1 Primary Objectives

- To estimate the diagnostic accuracy of FLT PET/CT as an early indicator of complete response to therapy in B and T cell lymphoma.
- To estimate the diagnostic accuracy of FLT PET/CT in the evaluation of residual masses after therapy.

1.1.2 Secondary Objectives

- To compare the diagnostic accuracy of FLT PET/CT with that of FDG PET/CT as indicators of tumor response to therapy
- To evaluate whether FLT tumor uptake either prior to therapy and/or following completion of therapy are in dependent predictors of complete response to therapy
- To evaluate whether there is a significant difference in tumor, selected normal organs ,and mediastinal blood pool FLT dynamic influx parameter (Ki),SUV at 1 hours and 2 hours post injection
- To estimate the diagnostic accuracy of percent change in SUV between pre-treatment and mid-treatment FLT PET/CT as an indicator of complete response to therapy

1.2 Background

Malignant lymphomas are the fifth most frequently occurring type of cancer in the United States accounting for approximately 5 % of all malignancies. In 2007, it is estimated that 8,190 new cases of Hodgkin's lymphoma (HL) and 63,190 new cases of non-Hodgkin's lymphoma (NHL) will be diagnosed.(1, 2)

The appropriate management of lymphomas greatly depends on an accurate staging and evaluation of histologic features.(3, 4) For a long time, CT has been the imaging gold standard for the staging of lymphomas but offers only structural information. CT has excellent resolution; however, disease is frequently assessed on the basis of size criteria. For example, lymph nodes less than 1 cm in diameter are not considered abnormal by most current criteria.(5, 6) In addition, CT may demonstrate residual masses on follow-up that represent fibrosis rather than active disease. Therefore, while computed tomography remains a valuable imaging method for the assessment of disease status, it provides no understanding of the metabolic or functional parameters of the disease.

Nuclear medicine techniques permit the evaluation of functional status, and nuclear medicine is likely to have its greatest impact in the detection of viable tumor in persistent masses. Nuclear imaging can be conducted using single photon agents, such as ^{67}Ga-citrate with SPECT (single photon emission computed tomography),(7, 8) or with positron emitters, such as ^{18}F-fluorodeoxyglucose (FDG) with PET (positron emission tomography).

In comparison with ^{67}Ga, ^{18}F-FDG PET has proved to be far superior in the assessment of disease status and evaluation of the efficacy of different treatment modalities (9-11). PET has better resolution and is especially more accurate for detection of disease below the diaphragm. The basic principle of ^{18}F-FDG imaging is based on Warburg's observation that the increased metabolic demands of rapidly dividing tumor cells required adenosine triphosphate generated by

glycolysis.(12) FDG is actively transported into cells and converted into FDG-6-phosphate by hexokinase. FDG-6-phosphate, because it is not a substrate for the enzyme responsible for the next step in glycolysis, is then trapped in the cell.

In 2001, the first commercial PET/CT was introduced combining the ability to assess function and anatomy in a single study (13-15) . A preliminary study(16) to evaluate ^{18}F-FDG PET/CT versus CT and PET performed separately in patients with lymphoma showed an incremental improvement, with patient-based sensitivities of 78%, 86%, and 93% and region-based sensitivities of 61%, 78%, and 96% for CT, PET, and PET/CT, respectively. The patient-based specificities were 54%, 100% and 100% for CT, PET, and PET/CT, respectively. Whereas the region-based specificities were 89%, 98%, and 99%. Another study(17) showed PET/CT to be more accurate for staging (93%) than was PET alone (84%), with discordant image interpretation between PET and PET/CT in approximately 10% of patients.

1.3 FDG PET for Response Assessment of Lymphoma at the Conclusion of Therapy

Numerous studies have demonstrated the value of [^{18}F]FDG PET and PET/CT for response assessment of lymphomas at the conclusion of front-line, salvage, or high-dose therapy(2, 18-26). Based on the meta-analysis by Zijlstra et al(18), pooled sensitivity and specificity of FDG-PET for detection of residual disease after completion of first-line therapy were 84% (95% CI, 71% to 92%) and 90% (95% CI, 84% to 94%), respectively, for Hodgkin's lymphoma (HL), and 72% (95% CI, 61% to 82%) and 100% (95% CI, 97% to 100%), respectively, for aggressive Non-Hodgkin's lymphoma (NHL). Accurate information regarding tumor status after treatment of these lymphoma subtypes is critical because these are curable malignancies.

The value of [^{18}F]FDG PET in this setting is its ability to distinguish between viable tumor and necrosis or fibrosis in residual masses. Conventional anatomic imaging modalities frequently are unable to make this distinction because the morphologic features of these tissues are usually indistinguishable (Figure 1 and **Figure 2**). Moreover, biopsy of a specific site may not be representative of disease activity since areas of necrosis/fibrosis might be interspersed among areas of viable tumor (**Figure 3**).

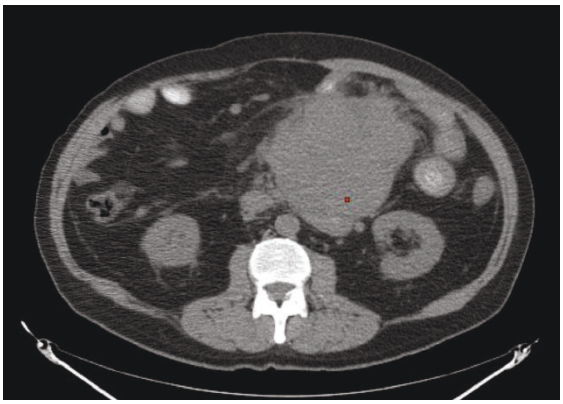


Figure 1 CT scan of the abdomen prior to chemotherapy demonstrating a large mesenteric mass consistent with biopsy proven lymphoma.

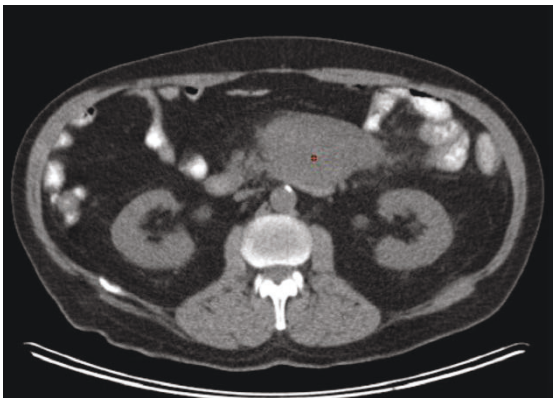


Figure 2 CT scan after chemotherapy demonstrating a decrease in size of the mass but without biopsy, it is impossible to know if there is complete response to treatment.

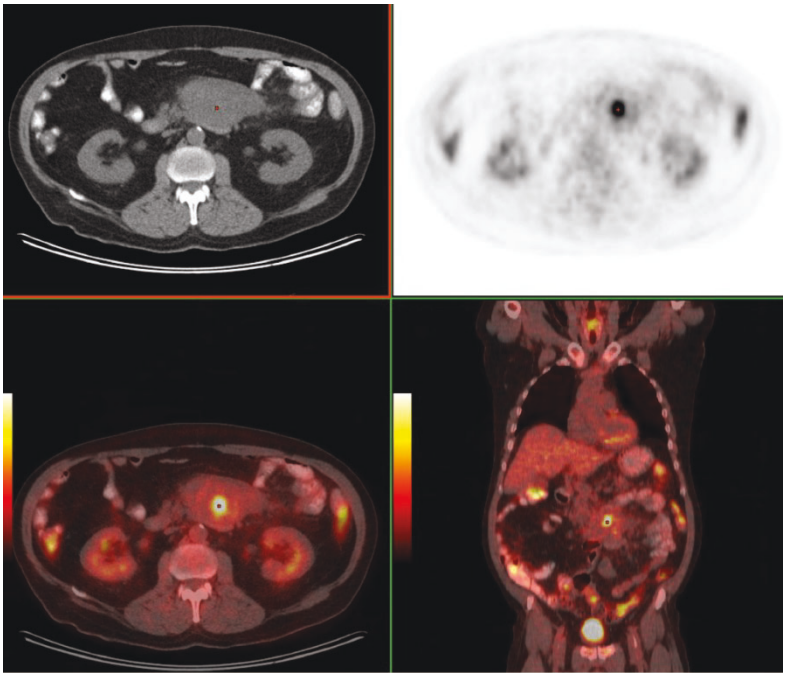


Figure 3[18F] FDG PET scan after chemotherapy demonstrating the residual mesenteric mass with a central area of viable tumor. Even if a needle biopsy were performed there was a good chance of missing the viable tissue.

1.4 FDG PET for Response Assessment of Early Treatment Response

Less than half of all patients with aggressive NHL are cured with standard chemotherapy. [^{18}F]FDG PET or PET/CT scanning during treatment of patients with HL and aggressive NHL may be justified as an early indicator of treatment efficacy as the information provided might be used to alter patient management and avoid unnecessary and ineffective chemotherapy.

Changes in [^{18}F]FDG uptake have been correlated with response to antitumor therapy by several authors (27-29). Several studies have also demonstrated a correlation between a visual normalization of [^{18}F]FDG uptake as early as after one to four cycles of chemotherapy and patient outcome. In a study by Spaepen et al (25), 70 patients with newly diagnosed aggressive NHL were treated with doxorubicin-containing chemotherapy and underwent [^{18}F]FDG PET

scan at mid-treatment. Presence or absence of abnormal [^{18}F]FDG uptake was correlated with progression-free survival (PFS) and overall survival (OS) (**Figure 4** and **Figure 5**). Of the 37 patients with a negative scan early during chemotherapy, 31 were still in complete remission (CR) after a median follow-up of 1107 days (range 595–1572). Thus, all patients who had a durable complete remission (CR-Cont) became FDG-negative after only three to four cycles of chemotherapy. Of 33 PET-positive cases early during chemotherapy, no patient maintained a durable complete response (CR-Cont) after completion of first line treatment. [^{18}F]FDG-PET delineated patients who failed to achieve a complete response from other categories. Eight patients progressed during first-line therapy and all these patients died during further treatment (median OS 107 days; range 10–360). 15 patients achieved a partial response. During further treatment, nine of these 15 patients died of progressive disease, with a median OS of 333 days (range 74–1100). The other 6/15 patients had successful additional therapy and were momentarily in CR (median follow-up 1308 days; range 553–1500). The remaining 10 patients in this group achieved a complete response but subsequently relapsed (CR-Rel) after a median PFS of 175 days (range 89–838) at the sites as seen on the interval PET scan.

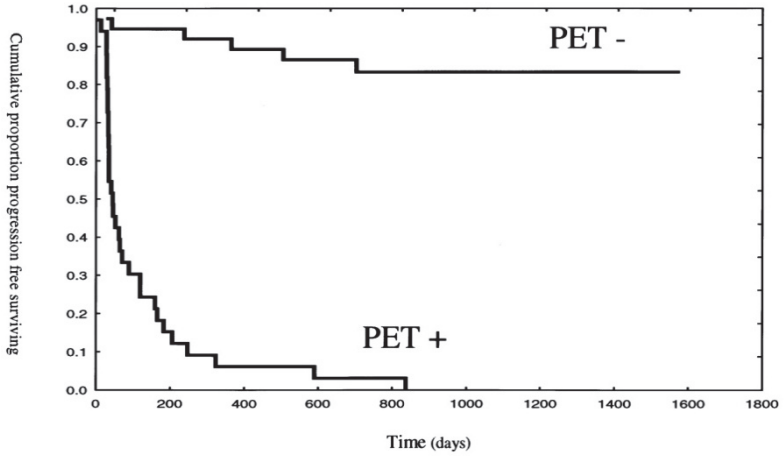


Figure 4 Kaplan-Meir curve demonstrating differences of progression free survival in 33 patients with positive mid-treatment [^{18}F] FDG scan compared with 37 patients with negative mid-treatment FDG-PET scan (30)

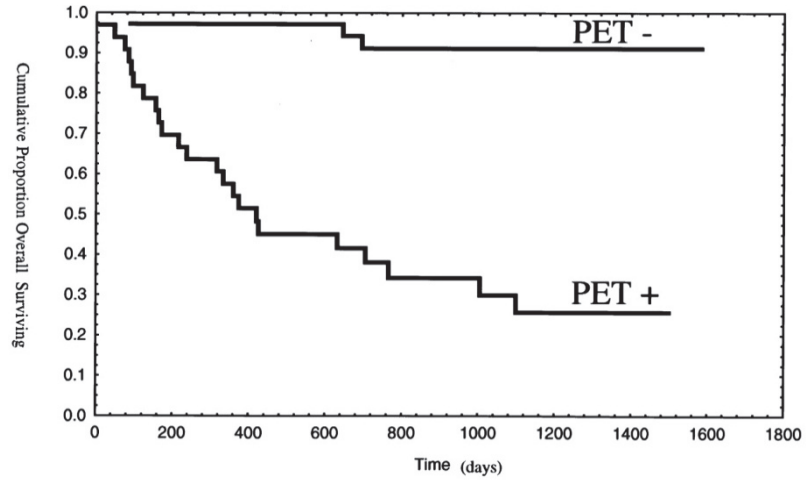


Figure 5 Kaplan–Meier estimate of overall survival (OS) in 33 patients with a positive mid-treatment [^{18}F] FDG scan compared with 37 patients with a negative mid-treatment FDG-PET scan (30)

In another study, Kostakoglu et al(31) evaluated the predictive value of [^{18}F]FDG-PET as an early response indicator after 1 cycle of chemotherapy for progression-free survival (PFS) in diffuse large cell lymphoma (DLCL) and classic Hodgkin disease (HD). Results demonstrated that all [^{18}F]FDG PET negative patients after 1 cycle (n= 31) had sustained complete remission with a median follow-up of 28 months. Fourteen of sixteen PET positive patients after 1 cycle had refractory disease or relapsed (median PFS= 5.5 months).

1.5 FLT scanning for early response to therapy

3'-deoxy-3'-^{18}F fluorothymidine ([^{18}F]FLT) is a structural analog of the DNA constituent, thymidine (**Figure 6**). It is a radiolabeled imaging agent that has been proposed for investigating cellular proliferation with positron emission tomography (PET). Although [^{18}F]FLT is not incorporated into DNA, it is trapped in the cell due to phosphorylation by thymidine kinase, a part of the proliferation pathway. As such, it has potential as a marker of proliferating tumor in proportion to the DNA synthesis rate. Therefore, [^{18}F]FLT is proposed as a radiolabeled imaging probe for *in vivo* assessment of cellular proliferation in malignant tumors using PET.

Figure 6(from the investigator's brochure 1-03-05)

One objective of this study is to evaluate the ability of [^{18}F]FLT as an early predictor of treatment response and progression free survival. Several studies evaluating the utility of FDG PET in the early assessment of tumor response have been performed; however, as FDG accumulates in inflammatory tissues as well as malignant tissues, differentiation between treatment induced tumor inflammation and tumor response becomes complicated. Pre-clinical studies suggest that FLT PET can differentiate between inflammation and malignancy. These results are expected as FLT uptake is dependent on cellular proliferation, which is a less prominent feature of inflammation.

FLT PET was recently successfully used to detect early response to chemotherapy in mice bearing a follicular lymphoma xenotransplant.(32) Another study by Hermann et. al. show that FLT PET imaging 2-7 days after completion of R-CHOP/CHOP show a significant difference in mean SUV value between partial (2.6) and complete (1.5) responders. In one group of six subjects with high-grade non-Hodgkin's lymphoma, the FLT SUV decreased 77% seven days after therapy with a total decrease in FLT SUV of 85% 40 days after therapy. In a study of breast cancer patients following 1 cycle of chemotherapy, the mean change in FLT SUV from baseline correlated with later (mean 5.8 months) changes in tumor marker (CA27.29).(33)

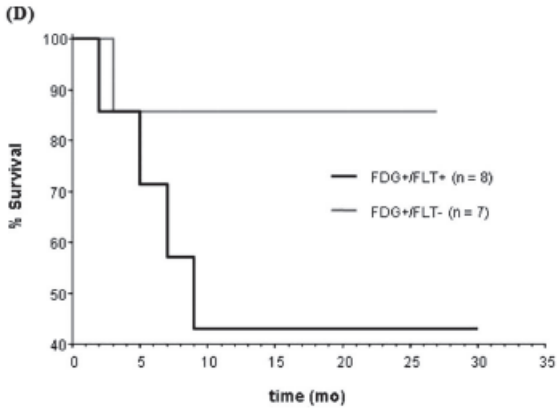
1.6 FLT PET imaging compared with FDG PET imaging

Even though [^{18}F]FDG PET/CT imaging has revolutionized the modern management of lymphomas, [^{18}F]FDG is not 100% specific for tumor cells and accumulation can be seen in

inflammation, apoptotic cells, granulomas, abscesses, and sarcoidosis (34-37). To overcome these problems several new radiotracers are currently under development. Recently, the thymidine analogue [^{18}F]FLT has been suggested as an in-vivo marker of tumor's proliferative activity and possible a more specific tumor imaging agent(38). An initial clinical trial comprising 34 patients (39) indicated a significant correlation of [^{18}F]FLT uptake in lymphoma and proliferation fraction in biopsied tissues as indicated by Ki-67 immunohistochemistry. In this particular study, patients were admitted for pre-therapeutic staging (25 patients) or restaging (9 patients). [^{18}F]FLT images were compared with routine staging which included clinical examination, laboratory screening, chest X-ray, CT of the chest and abdomen, and bone marrow biopsy. In 21 patients, [^{18}F]FDG imaging was also performed. Data analysis demonstrated that [^{18}F]FLT PET detected a total of 490 lesions compared with 420 lesions revealed by routine staging and the authors concluded that [^{18}F]FLT PET may be suitable for imaging malignant lymphomas.

In a study by Kasper et. al.(40), 48 patients with residual masses >2 cm were studies with FLT and FDG PET, 15 subjects were FDG + and 10 were FLT +. Two subjects who were FDG negative were FLT + and seven subjects who were FDG positive were FLT negative. Unfortunately they did not obtain pathologic confirmation of all subjects. Another difficulty in evaluating this data lies in the selection of a 1.5 SUV cut-off for both FDG and FLT (normal background activity can have an SUV as high as 3 in some body regions).

Figure 7 Kaplan Meier plot of FDG and FLT positive mass versus FDG positive and FLT negative patients(40)



Even though these initial studies appear promising, the evaluation of residual masses after standard chemotherapy in lymphomas continues to present as a clinical dilemma. We therefore intend to investigate the ability of [^{18}F]FLT PET to differentiate between residual viable tumor and non-viable masses after the conclusion of standard chemotherapy. In this protocol we will include individuals with FDG positive residual masses to determine if they represent active disease based on biopsy or clinical follow-up.

1.7 Findings as of March 1, 2013:

To date, we have 22/30 patients in the residual mass arm and 8/40 patients in the early response arm. After review of data we have noted that [^{18}F]-FLT PET/CT appears to better differentiate viable lymphomatous masses from benign inflammatory processes than [^{18}F]-FDG. This

suggests that in specific settings [^{18}F]-FLT may help [^{18}F]-FDG in predicting response to therapy.

2 Rationale

FDG PET/CT has emerged as a powerful functional imaging tool for staging, restaging, and response assessment of lymphomas. In 2007, the American Society of Clinical Oncology, released new guidelines incorporating FDG PET in the evaluation of treatment response in non-Hodgkin's and Hodgkin's lymphoma.(21) It is well known that FDG PET/CT imaging improves differentiation between viable and non-viable residual masses; however FDG accumulates in inflammatory lesions also, limiting its specificity. FLT PET/CT, with uptake correlation with cellular proliferation, may serve as a more accurate predictor of early (intra therapy) therapy response and be more accurate than FDG PET/CT in differentiating between residual tumor and non-viable mass post therapy.

3 Imaging Agent Information

3'-deoxy-3'-18F fluorothymidine (FLT)

3.1 Pharmacology and Toxicology

FLT is a structural analog of the DNA constituent, thymidine. Thymidine has previously been labeled with C-11 for studies in cell culture and animals; results have shown that it is rapidly incorporated into newly synthesized DNA.(38) Radiolabelled thymidine has been used for noninvasive evaluation of tumor proliferation. Shields *et al* determined that [C-11] thymidine demonstrated a response to chemotherapy faster than ^{18}F-FDG in 6 patients with malignancy.(38) However, because C-11 has a half-life of 20 minutes,(38) it is not practical for routine clinical use and other radiolabels are being investigated. ^{18}F-FLT is radiolabelled with F-18, which has a half-life of 110 minutes.(38)

The pharmacology of FLT is based on its action as an inhibitor of DNA synthesis.(41-43) Intracellular metabolism of FLT produces nucleotides that inhibit endogenous DNA polymerases because they lack a 3'-hydroxyl substituent. This results in premature chain termination of DNA synthesis.(44, 45) These biochemical properties can account for FLT's prominent hematological and liver toxicity.(45-47) The pharmacology of FLT closely parallels that of the widely used prescription HIV-antiviral drug azidothymidine (AZT).(48, 49) Both FLT and AZT are 3'-deoxythymidine analogs that act as inhibitors of DNA synthesis and are cleared from the body in the same way. However, FLT is significantly more cytotoxic than AZT in test cell lines.(47) Cellular uptake of FLT and thymidine is greater than that of AZT. Transport of FLT and thymidine across cell membranes occurs by active transport and passive diffusion.(49)

3.2 Toxicity of FLT in Humans

FLT was investigated as an anti-AIDS drug in humans.(46) Toxic effects and death were reported for some subjects who received FLT during randomized concentration-controlled trials during a 16-week treatment of oral multi-dosing. Doses of 0.125 mg/Kg every 12h produced a mean cumulated drug exposure (AUC12: area under curve) of 417 ng-h/mL. At this level, serious (grade 3) hematologic toxicity occurred in 6 of 10 subjects. At 300 ng-h/mL, grade 2 or greater (fall in hemoglobin to < 9.4 g/dL) developed within 4 weeks in 9 of 12 subjects. At 200 ng-h/mL almost no clinically significant anemia developed, but dose-limiting granulocytopenia (< 750 granulocytes/mm^3) occurred in 5 of 15 subjects. Mild peripheral neuropathy occurred in

2 of 10 subjects at 50 ng-h/mL, but was not dose-limiting. FLT drug trials were terminated after the unexpected death of 2 subjects of hepatic failure. One patient assigned to 200 ng-h/mL developed progressive liver failure and died after 12 weeks of FLT therapy. A second subject, who received a fixed dose of 10 mg/day, developed progressive liver failure and died at about the same time. All surviving subjects were followed closely for 4 weeks after stopping FLT and none had evidence of clinically significant liver disease or other adverse effects. Overall, 25 of the 44 subjects receiving at least two doses of FLT completed the 16 week study without clinically significant adverse effects.

Unlabelled FLT was initially investigated as a treatment for HIV and AIDS, and toxicity studies of the unlabeled compound have been performed at substantially higher doses than those proposed for imaging. Hematologic, hepatic and peripheral nerve toxicities were observed after administration of therapeutic doses (≥ 10 mg) of FLT for several weeks (See Section **3.1**). In comparison, the proposed ^{18}F-FLT PET studies use a maximum injection of 10μg, a factor of 1,000 times lower(50). The dose of FLT to be administered in this imaging trial is 1400-fold lower than the dose that led to serious toxicity in the studies described above.

3.3 Dosimetry

An [^{18}F]FLT dose of 0.07 mCi/Kg with a maximum of 5 mCi was selected based on a prior human dosimetry study performed in 18 patients at the University of Washington(51). With this dose, the individual organ and total-body radiation dose associated with [^{18}F]FLT is comparable to or lower than those reported for widely used clinical nuclear medicine procedures. There is ample preliminary evidence that a dose of 5 mCi is sufficient for imaging. The actual dosing, 0.07 mCi/kg was determined by assuming average body weight of 70 Kg and dividing by the maximum total dose. As FLT is not lipid soluble, no upward adjustments are expected to be needed for subjects > 70 Kg. These details are specified in the IND. A summary of the relevant human dosimetry for 2 different voiding scenarios from the investigator's brochure is included in **Table 1**. For more details, the reader is referred to the IND.

Table 1 Human dosimetry estimates

Organ of Interest	Men mGy/MBq (mrad/mCi)			Women mGy/MBq (mrad/mCi)		
Total Body Dose	Scenario 1	1.23E-02	(46)	Scenario 1	1.56E-02	(58)
	Scenario 2	1.26 E-02	(47)	Scenario 2	1.59 E-02	(59)
Bladder	Scenario 1	1.79E-01	(662)	Scenario 1	1.74E-01	(646)
	Scenario 2	7.91E-02	(293)	Scenario 2	7.76E-02	(287)
Liver	Scenario 1	4.51E-02	(167)	Scenario 1	6.42E-02	(238)
	Scenario 2	4.54 E-02	(168)	Scenario 2	6.45 E-02	(239)

Scenario 1: Single bladder voiding at 6 h after [^{18}F]FLT administration with a 10% post-voiding bladder residual decayed to infinity. This scenario assumed no urine re-accumulation after 6 h.

Scenario 2: First bladder voiding at 2 h after [^{18}F]FLT administration with a 10% post-voiding residual; urine re-accumulation between 2 and 6 h at a rate determined by the bladder curve fit; second bladder voiding at 6 h with a 10% post-voiding residual decayed to infinity. This scenario assumed no urine re-accumulation after 6 h.

The first scenario is conservative, whereas the second has a more realistic voiding scheme.

3.4 Previous human [^{18}F]FLT imaging studies

Several preliminary studies using [^{18}F]FLT imaging in human subjects have been performed in Germany and the United States (UCLA, University of Washington in Seattle, Wayne State University)(51-56). The imaging protocols were pre-approved by their respective regulatory committees and conducted under the RDRC process, with patients receiving between 1.4 and 13 mCi of [^{18}F]FLT. Some of the imaging results have been published (**Table 2**). The group in Seattle, which has the most experience with this agent in the US, has performed numerous studies in patients with lung cancer as well as a few in patients with primary brain tumors. Their findings demonstrate the feasibility and merit of tumor imaging with [^{18}F]FLT. [^{18}F]FLT PET showed increased uptake in tumor lesions outside the liver or bone marrow with standardized uptake values (SUV) of 4-7, enabling differentiation from surrounding tissues (SUV 0.5-2).

Table 2 Summary of published manuscripts reporting [^{18}F]FLT human imaging studies

Year	Organ System	# of pts	mCi injected	MBq Injected	Specific Activity	nmole injected	Reference (#)	Previous Chemotherapy	Time post injection
2006	Brain	10	4	104-202	37-222GBq/umol	N.C.	Yamamoto, 2006 (57)	10 previous chemo	Dynamic 60 min; constant from 10-60min
2006	Lymphoma	34	9.3	265-370	Not reported	N.C.	Buck 2006 (39)	25 none, 9 restaging	60 min
2006	Lung and SPN	22	5	185.2	Not reported	N.C.	Yap, 2006 (58)	none	60 min
2006	Breast	14	4	150	74 TBq/mmol	N.C.	Pio, 2006 (33)	Pre-,after 1-cycle, and post-chemo	Dynamic 45min
2005	Brain	23	8.6	111-370 (321)	Not reported	N.C.	Jacobs,2005 (59)	10 previous chemo	Dynamic 90min
2005	Esophageal	10	11.1	340-450 (410)	>10TBq/mmol	N.C.	vanWestreenen, 2005 (60)	None	60 min
2005	Lung	47	9.5	265-370	Not reported	N.C.	Buck 2005 (61)	none	60 min
2005	Breast	10		390-420 (3 patients) 60-250 (7 patients)	>10TBq/mmol	N.C.	Been 2006 (62)	None	3 patients at 30,120,180, and 240 min; others at 120 min
2005	Brain	25	4.7	141-218 (174)	~74 Bq/mmol	N.C.	Chen, 2005 (63)	None	75: 11 patients 35:13 patients (uptake peaks at 5- 10min)
2005	Brain	26	10	370	0.1-0.3TBq/mmol	N.C.	Choi, 2005 (64)	None	60 min
2004	Lymphoma	7	4.3 - 13.2	Mean = 324	Not reported	N.C.	Buchmann 2004 (65)	Not reported	50-70 min

Year	Organ System	# of pts	mCi injected	MBq Injected	Specific Activity	nmole injected	Reference (#)	Previous Chemotherapy	Time post injection
				159 - 489					
2004	Lung	17	5.7	Mean=210 130-420	>10TBq/mmol =10GBq/umol	40 nmol	Cobben 2004 (66)	None	60 min
2004	Lung	28 (a)	9	Mean=334 265-370	Not reported	N.C.	Halter 2004 (67)	None	80-120min
2004	Breast	12	8.1-12.1	300-450	Not reported	N.C.	Smyczek-Gargya 2004 (68)	None	80-120 min
2004	Colorectal	18	9.7	360 $\pm$ 25	Not reported	N.C.	Visvikis 2004 (69)	Not reported	Dynamic 60 min
2004	HEENT	21	9.2	Mean=340 165-650	>10TBq/mmol =10GBq/umol	40 nmol	Cobben 2004 (70)	Not reported	60 min
2004	Soft Tissue	19	10.8	Mean=400 115 -430	>10TBq/mmol =10GBq/umol	40 nmol	Cobben 2004 (71)	Not reported	60 min
2003	Lymphoma	11	7.5	280	Not reported	N.C.	Wagner 2003 (72)	Not reported	60 min
2003	Colorectal	10 (b)	9.5	351 $\pm$ 52	Not reported	N.C.	Francis 2003 (73)	Not reported	57+/-10 min
2003	Colorectal	17 (b)	9.4	Mean=360 312-412	Not reported	N.C.	Francis 2003 (74)	Not reported	57-69 min
2003	Dosimetry (Lung)	18	5	185 MBq max	> 37 GBq/umol	5 nmol	Vesselle 2003 (75)	Not reported	2 hour dynamic
2003	Lung	16	5.4 - 10.8	200 - 400	Not reported	N.C.	Dittmann 2003 (76)	None	114+/-20 min

Year	Organ System	# of pts	mCi injected	MBq Injected	Specific Activity	nmole injected	Reference (#)	Previous Chemotherapy	Time post injection
2003	Melanoma	10	10.8	Med= 400 185-430	>10TBq/mmol =10GBq/umol	40nmol	Cobben 2003 (77)	None	60 min
2003	SPN	26 (c)	9	Mean=334 265-370	Not reported	N.C.	Buck 2003 (78)	None	45 min
2002	SPN	30 (c)	9	Mean=334 265-370	Not reported	N.C.	Buck 2002 (79)	None	45 min
2002	Lung	10	5	185 max	1Ci/umol = 37GBq/umol	5 nmol	Vesselle 2002 (80)	None	2-hr dynamic
Total No. Subjects:		380*							

N.C. = not calculated
(a) There appear to be 10 additional unique patients who were not described in the Buck 2002 and 2003 manuscripts.
(b) It is unclear if the same patients are being described for both of the Francis manuscripts.
(c) It is unclear if the same patients are being described for both of the Buck, 2002 and 2003, manuscripts.
* Due to the possibility that the same patients are being described in some reports, the total # of unique patients studied in these published studies appears to be 198.

As evidenced in **Table 2**, many of the published studies did not report the specific activity of the [^{18}F]FLT, so it is not possible to determine the amount of FLT that was actually administered to the patient. Furthermore, none of the published studies addressed safety issues by describing laboratory results post injection or assessing for neurological sequelae such as mild peripheral neuropathy.

3.5 Reported Adverse Events and Potential Risks

No adverse events have been reported for [^{18}F]FLT at the dose to be used for this study. As described in Section **3.2**, non-radioactive FLT has been investigated as an anti-AIDS drug, and some adverse effects, namely, reversible peripheral neuropathy, were observed in subjects exposed to 50 ng-h/mL plasma over a course of 16 weeks (15µg/kg q12h). The FLT dose anticipated for this study will be <6.1µg for a single injection. Assuming a 70kg individual, the maximum concentration of FLT would be expected to be equivalent to 0.29 ng-h/mL. The radiation exposure associated with this study is described in Section **3.6** and is comparable to the dose for other widely used clinical nuclear medicine procedures.

3.6 [^{18}F]FLT Administered Dose

The administered dose will be 0.07 mCi/kg with a maximum of 5 mCi. The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and has an expiration time of 8 hours. The injectable dose of [^{18}F]FLT for most studies will be ≤ 0.07 mCi/kg of fluorine-18, not to exceed 5 mCi with a specific activity greater than 200 Ci/mmol at the time of injection. In the dose of [^{18}F]FLT, only a small fraction of the FLT molecules are radioactive. The amount of injected drug is ≤ 6.1 µg (≤ 25 nmol per dose) of FLT. [^{18}F]FLT is administered to subjects by intravenous injection of ≤ 10 mL. There is no evidence that nonradioactive and radioactive FLT molecules display different biochemical behavior.

3.7 Agent Availability

[^{18}F]FLT will be provided by IBA, or Cardinal Health under an IND held by the Cancer Imaging Program (CIP)/NCI.

4 Eligibility assessment and enrollment

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

- Participant must be enrolled in a lymphoma therapy study at the NIH Clinical Center OR be enrolled in the CALGB 50303 study at another site OR undergoing a new course of treatment of lymphoma at another facility.
- Participants must have a clinical course consistent with lymphoma and have available documentation of lymphoma from either the NCI or from an outside pathology laboratory.
- Participant must be 18 years or older
- ECOG Performance score of 0 or 1
- Ability to provide informed consent. All patients must sign a document of informed consent indicating their understanding of the investigational nature and risks of the study before any protocol related studies are performed.

For subjects enrolling in early response arm

- Must be enrolled in CALGB 50303 or a lymphoma therapy study at the NIH Clinical Center or undergoing a new course of treatment of lymphoma at another facility

- Must not have begun lymphoma therapy for this tumor occurrence/ relapse
- Prior completed therapy does NOT affect eligibility

For subjects enrolling in the residual FDG avid mass arm

- Must have a residual FDG PET positive mass ≥1cm, with uptake greater than that of mediastinal blood pool (81)
- Participant will undergo a repeat FDG PET/CT scan if the original FDG/PET imaging performed at an outside institution is not of adequate imaging quality for subjects enrolling in the residual FDG mass arm.

4.1.2 Exclusion Criteria

- Known allergy to fluorothymidine
- Participants for whom enrollment would significantly delay (> 2 weeks) the scheduled standard of care therapy.
- Participants with any coexisting medical or psychiatric condition that is likely to interfere with study procedures and/or results are excluded
- Participants with severe claustrophobia not relieved by oral anxiolytic medication or patients weighing >136 kg (weight limit for scanner table)
- Other medical conditions deemed by the PI or associates to make the patient ineligible for protocol procedures.

4.1.3 Research eligibility evaluation (required within 2 weeks of each investigational agent (FLT) injection)

- Liver enzymes: Should be completed within 14 days before injection of the radiopharmaceutical
- SGOT, SGPT <5x ULN
- bilirubin ≤2x ULN
- Negative urine or serum HCG

4.2 Registration Process

4.2.1 NCI Patient Registration

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://intranet.cancer.gov/ccr/welcome.htm) must be completed and faxed to 301-480-0757. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

4.2.2 Patient Registration for Participating Site:

All patients must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. A protocol registration form and cover memo will be supplied by the Coordinating Center, NCI CCR and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To register a subject, send the completed registration checklist to Coordinating Center's Research Nurse, Yolanda McKinney RN, 301-443-6913, and ymckinney@mail.nih.gov. Please indicate on the protocol registration form whether the patient is screening or is eligible to start treatment. The CRO will notify you either by e-mail or fax that the protocol registration form has been received. The CRO will assign a unique patient/subject

ID number for each subject that will be used to enter data into the C3D data base. Questions about eligibility should be directed to the Coordinating Center's Research Nurse, Yolanda McKinney RN, 301-443-6913, and ymckinney@mail.nih.gov. Technical questions about the form should be directed to the Central Registration Office (301-402-1732).

5 Study implementation

5.1 Overall Trial Design

A member of the research team will perform the initial eligibility screening.

Informed consent will be obtained prior to the first FLT imaging study. If not obtained within 3 weeks of scheduled FLT imaging, liver enzymes will be drawn.

5.1.1 For subjects enrolling in early response arm

- Participants in this arm will undergo a pre-treatment FLT PET/CT and FDG PET/CT (+/- 2 weeks of each other) imaging prior to beginning lymphoma therapy.
- They will then continue in a lymphoma therapy trial at the NIH Clinical Center or receive a new course of treatment at their home institution.

- Repeat FDG and FLT PET/CT studies will be performed following 2 cycles of chemotherapy.
    - The FDG PET/CT study should be performed as close as possible (i.e. within 4 days) before the subsequent cycle; for example, on days 17 to 21 of a 21-day cycle.
    - The repeat FLT PET/CT imaging should be performed within +/- 2 weeks of the FDG PET/CT study.
- Post treatment FDG and FLT PET/CT studies will be performed
    - The FDG PET/CT study will be performed >=3 weeks after the completion of chemotherapy
    - The FLT PET/CT scan will be performed within +/- one week of the 3rd FDG PET/CT.
- Patients in this arm with residual FDG positive mass following completion of therapy may be enrolled in the residual mass arm.
- The target lesion will be defined as the hypermetabolic (uptake > background) lesion $\geq$1cm with the highest SUV_{max} at 1 hour post injection
- Primary analyses will be performed on the target lesion and compared with complete response (CR or Cr_u, **Table 6**).

5.1.2 For subjects enrolling in the residual mass arm

Patients enrolled in an NIH Clinical Center lymphoma therapy protocol having a residual mass $\geq$ 1 cm in longest dimension as measured by the CT component of the PET/CT with FDG uptake greater than that of mediastinal blood pool will undergo an FLT PET/CT within 2 weeks of the post treatment FDG PET/CT study. Patients on other lymphoma therapies from outside institutions, must have a FDG PET/CT positive mass $\geq$1cm, with uptake greater than that of mediastinal blood pool (81). Participant will undergo a repeat FDG PET/CT scan if the original FDG/PET imaging performed at an outside institution is not of "adequate imaging quality" for subjects enrolling in the residual FDG mass. The patient will undergo an FLT PET/CT within 2

weeks of the FDG PET/CT. Patients will undergo clinically indicated biopsy of the residual mass after FLT PET/CT imaging. Fine needle aspiration (FNA) will be performed when biopsy is not possible. If a biopsy is not medically indicated, then the patient will be followed medically by the Lymphoma Team or by their outside oncologist.

The FLT SUV will be compared with pathological response, with the presence of any viable lymphoma cells on biopsy being considered positive for malignancy. For patients who do not undergo biopsy, the absence of tumor will be assessed by lack of lesion progression on routine medical follow-up. An FLT SUV greater than mediastinal background will be considered positive for malignancy.

5.2 [^{18}F]FLT PET/CT imaging

5.2.1 Investigational agent

[^{18}F]FLT will be provided by IBA or Cardinal Health pharmacies.

5.2.1.1 Investigational agent administration:

The [^{18}F]FLT will be brought by shielded carrier to the PET/CT scanner and will be injected intravenously over a 10-15 seconds period using an intravenous catheter under the supervision of an authorized user of radiopharmaceuticals.

Qualified staff or clinical research nurse will be in attendance during the infusion. In the event of an emergency such as an allergic response immediate treatment will be initiated using emergency medication kits available in the Nuclear Medicine/PET Departments. If the participant requires admission due to the severity of the reaction, the participant will be admitted to the Lymphoma service for observation for the NCI site and the appropriate standard operating procedures should be followed for the participating site.

5.2.2 FLT PET/CT Imaging protocol

Immediately following the IV infusion of [^{18}F]FLT, a dynamic 2D PET emission imaging with the target lesion in the field of view (FOV) will be performed for 60 minutes, immediately followed by a whole body static image. An additional 2D PET emission imaging acquisition will be performed 120 minutes (+/- 10 minutes) post infusion. A corresponding transmission CT will be acquired immediately before each emission scan.

5 ml of venous blood will be obtained ~1 hour and ~2 hours post injection to correct the measured F-18 counts for the % metabolized F-18 FLT. The simplified TLC (thin layer chromatography) method described by Shields et. al.(82) will be performed to determine fraction of parent F-18 FLT remaining in the venous blood at those times.

5.2.3 FDG PET/CT Imaging protocol

Standard image acquisition will be performed approximately 1 hour post injection of F18 FDG.

5.3 Pathology (residual mass arm only)

In patients with FDG avid residual masses (uptake greater than mediastinal blood pool) who would routinely undergo biopsy or fine needle aspiration (FNA), the pathology results will be collected and compared with the corresponding FLT SUV. The presence of any viable lymphoma cells will be considered positive for residual malignancy. Biopsy is not medically

indicated in many patients undergoing therapy and therefore, determination of active disease will be based on clinical follow-up in those patients.

5.4 Treatment modifications

The expected dose of [^{18}F]FLT is 5 mCi. Due to potential unpredictable delays, the total dose administered may be reduced at the discretion of the PI.

5.5 Imaging Interpretation

[^{18}F]FLT PET/CT

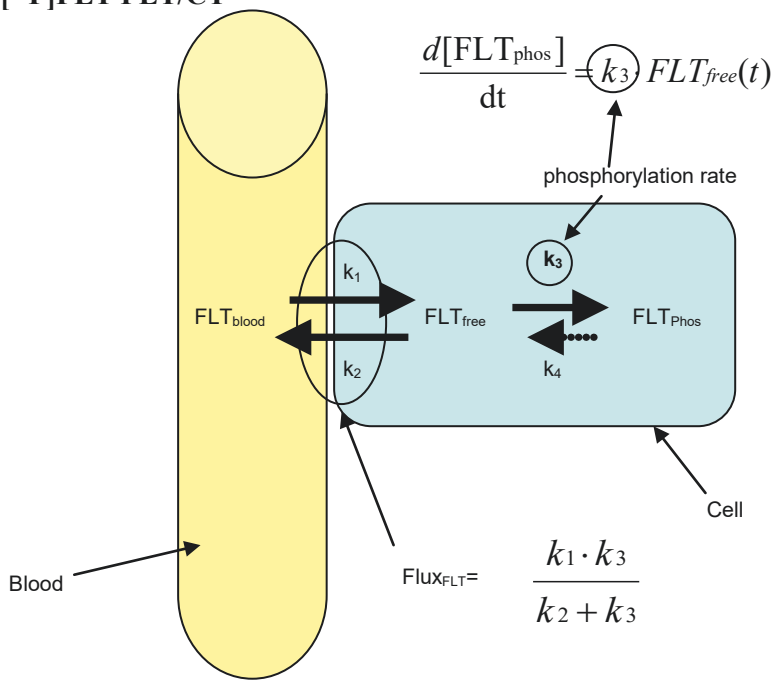


Figure 8 Kinetic model for [^{18}F]FLT. k_4 is assumed to be negligible at later time points. k_1 and k_2 are assumed to be equal, k_3 is assumed to be the dominate factor in [^{18}F]FLT accumulation in tumors over time.

Preliminary data suggests that [^{18}F]FLT is essentially irreversibly phosphorylated and trapped inside cells (similar to [^{18}F]FDG) during the imaging period. Prior to this point, however, there is a flux of unphosphorylated [^{18}F]FLT (reversible component). If the rate of phosphorylation (k_3) is low, then the early contribution of perfusion to the measured tumor activity is high. Assuming the phosphorylation rate correlates to the proliferative rate, a high rate of phosphorylation means that the cumulative measured tumor activity should be representative of cellular proliferation. The kinetics of FLT distribution has been evaluated in lung(53), brain(63, 83), colon(69) and other tumor types previously.(38, 54, 55) A comparison between the dynamic influx parameter (Patlak graphical analysis (below) and the standardized uptake values (SUV) at 1 and 2 hours post injection will be made. 5cc venous blood samples will be obtained just prior to the 1 and 2 hour imaging sessions to measure for metabolites and measure blood radioactivity. To improve the accuracy of the SUV measurements, the SUV values measured will be corrected for the fraction of non-metabolized FLT remaining in the blood at the time of image acquisition using thin layer chromatography estimation of metabolized fraction as described by Shield et. al.(82)

5.5.1 Compartmental and Patlak(84-87) Graphical Analysis

A 3-compartment data analysis will be performed to estimate values for the rate constants and [^{18}F] FLT flux parameters base on the model in **Figure 4** and **Figure 5**.

The Patlak graphical method enables estimation of the influx rate constant (K_i) and the volume of distribution (V_d) of unphosphorylated [^{18}F] FLT within the ROI from the data. The plot of ROI activity/Plasma Activity vs. $\int (PlasmaActivity * dt) / PlasmaActivity$ will become linear for irreversible systems. The slope of the linear portion is K_i and the y-intercept is V_d. The primary assumptions of these estimations are that the uptake of tracer is irreversible and that exchange of [^{18}F] FLT between the plasma and extracellular compartments has reached equilibrium. The rate of clearance of [^{18}F] FLT from the blood is equal to the Patlak influx rate constant (K_i) and is equal to $k_1k_3/(k_2+k_3)$.

A plasma activity function (the *input function*) is classically obtained from the arterial blood samples. Alternative methods of non-invasively deriving the plasma input function include ROIs drawn over the left atrial cavity (LA)/ basal portion of the left ventricular cavity (LV) or from a normalized population-based input function. Because obtaining an arterial or venous input function would likely adversely effect patient enrollment, for this study an LV image derived input function will be used. (87-90)

5.5.2 General image parameter extraction

- FLT and FDG uptake greater than surrounding background will be considered positive.
- The "target" will be identified, as a lesion ≥1cm with the highest SUV (amongst all identified hypermetobolic lesions).
- All regions/volumes of interest will be saved as DICOM-RT structure sets. Region volumes, and SUV values will be output to an Excel spreadsheet using MIMVista imaging software (www.mimvista.com)
- For the hypermetabolic lesions, an estimated smoothed maximum SUV (SUV_{max}) will be reported as the mean SUV value of an automated 85% maximum pixel value threshold based volume of interest (i.e. the average SUV of the "hottest" 15% of pixels in the user defined lesion). This method reduces the chances of the SUV_{max} value being dominated one or more "noisy" pixel values.
- All lesions will be followed from baseline with the same lesion number, even if they have resolved.
- For quality control, mediastinal and left ventricular blood pool (BP) SUV means, spleen, and liver SUV mean will be measured in all FLT and FDG scans.
    - To measure the left ventricular cavity BP SUV_{mean}, the mean SUV of a 1 cm spherical volume of interest (VOI) will be placed in the left ventricular cavity, avoiding the myocardial wall
    - For liver and spleen SUV_{mean}, a spherical VOI of 2 to 5 cm in diameter will be placed in a homogeneous area in the center of the organ (excluding the central hilum of the liver), and the mean SUV recorded.
- For the FLT images, the K_i Patlak influx parameter will be extracted from the 60 minute dynamic data. SUV values (corrected for the fraction of unmetabolized FLT (as

determined by thin layer chromatography (TLC)) will be recorded for the 1- and 2- hour static images.
  - For the primary analyses, the 1- hour SUV (SUV_1) parameters will be used
- For the FDG images SUV values will be recorded for the 1 hour static images.
- On transmission CT, lesion dimensions will be determined in perpendicular planes where the lesion appears largest.

5.5.3 Early response arm

- The percent of decrease or increase in SUV uptake in post cycle 2 and end of treatment scans in comparison with baseline scans will be calculated as follow:

$$\frac{SUV_{max} \text{ post cycle 2 or end of treatment} - \text{baseline } SUV_{max}}{\text{Baseline } SUV_{max}}$$

Table 3 Image Analysis Parameters for Early Response Arm

Pre-treatment	Mid-treatment	Post Treatment
FLT (K_i, SUV_1, SUV_2)	FLT (K_i, SUV_1, SUV_2)	FLT (K_i, SUV_1, SUV_2)
FDG (SUV_1)	FDG (SUV_1)	FDG (SUV_1)
CT (bidirectional measurements)	CT (bidirectional measurements)	CT (bidirectional measurements)

5.5.4 Residual mass arm

- The size of the residual mass will be determined on CT and will include the entire length of the mass visible on CT (i.e. if only a portion of the mass is hypermetabolic, the anatomical size will be determined by the entire mass length, not just the portion which appears hypermetabolic)
- The length used for the inclusion criteria is the longest measureable length

Table 4 Image Analysis Parameters for the Residual Mass arm

FLT (K_i, SUV_1, SUV_2)
FDG (SUV_1)
CT (bidirectional measurements)

6 Protocol evaluations

6.1 Study Calendar

Table 5

	Pre-study	Pre-therapy (biopsy for the Residual Mass arm)	Post 2-cycles	End of study
Enroll in CALGB 50303 or other lymphoma therapy trial or undergoing a new course of treatment of lymphoma at another	**X**			

	Pre-study	Pre-therapy (biopsy for the Residual Mass arm)	Post 2-cycles	End of study
facility				
Informed Consent	**X**			
Check Liver Function	**X**	**X**	**X**	**X**
Urine or Serum HCG	**X**	**X**	**X**	**X**
Early Response Arm				
FDG PET/CT	**X**	**X**[c]	**X**	**X**
FLT PET/CT		**X**[c]	**X**	**X**[a]
Residual Mass Arm				
FDG PET/CT	**X**[b]			
FLT PET/CT		**X**		

[a.] The FLT PET/CT scan will be performed at least 12 hours after, and +/- 2 weeks of, the FDG PET/CT study

[b.] If not performed at NIH or WRNMMC a repeat FDG PET/CT will be performed according to the prescribed FGD PET/CT protocol within 2 weeks of the FLT PET/CT study

[c.] Baseline FDG and FLT PETs must be performed prior to initiation of the current/new therapy in patients in the Early Response arm

6.2 Concurrent Therapies

No restrictions

6.3 Surgical Guidelines

FDG PET imaging must be performed >2 week following any surgical procedure to the target lesion.

6.4 Radiation Therapy Guidelines

In patients in whom the target lesion received radiation therapy, the FDG PET imaging must be performed >8 weeks following the completion of radiation therapy.

6.5 Supportive care guidelines

In the event that a patient has a reaction (allergic) to the contrast agent or radiotracer, all appropriate medical measures will be taken immediately. In rare instances, this may entail admission to the hospital on the Medical Oncology (Inpatient Lymphoma) service for observation and the appropriate standard operating procedures should be followed for the participating site.

6.6 Off Study Criteria

Subjects will be enrolled in the study beginning with their consent for [^{18}F]FLT imaging and ending following completion of all FLT PET/CT imaging. Correlative clinical response data will also be obtained from data collected from the lymphoma therapy trial.

Once a subject is taken off study, no further data can be collected, with the exception of follow-up clinical data from the patients referring physicians. Patients will be taken off the study if:

- Patient experiences an adverse event that prohibits them from completing the [^{18}F]FLT imaging sessions
- Patients voluntarily withdraw from the study

- Patient completes all FLT PET/CT imaging
- Death

6.6.1 Directions for NCI

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site **(**http://intranet.cancer.gov/ccr/welcome.htm) main page must be completed and faxed to 301-480-0757.

6.6.2 Directions for participating site

All subjects must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. An off-study form will be supplied by the Coordinating Center, NCI CCR. Send the completed off-study form to the Coordinating Center's Research Nurse; insert name, telephone number, and email.

7 Data collection and evaluation

7.1 Data collection

Demographic and summary data will be collected by research nurse or designee and entered in a password protected file in NCI C3D. The data will be entered at least on a weekly basis. Participating institutions will be trained in the use of NCI C3D and database access will be provided to site staff based on their designated duties.

The following is a list of specific data elements that **will** be collected or recorded in the database:

- demographics,
- histological type and disease stage,
- diagnosis date
- history of previous therapy (including dates of therapy)
- Date Informed Consent signed
- ECOG Status
- Labs
- Radiotracer dose amount & time.
- The following adverse events of any grade:
    - Localized discomfort at the IV injection site
    - Pain
    - Respiratory difficulties
    - Flushing
    - Dizziness
    - Itching/rash
    - Any other symptoms that could be secondary to an anaphylactic reaction
    - Any sign of illness or symptoms that appear or worsen after the F-18 FLT infusion

Imaging data will include storage of the images from each time point and intensity measurements from the tumor will be stored on a secure, password protected lab imaging database. Dr. Peter Choyke will serve as the study monitor responsible for the protocol.

The images will be stored on a secure database completely anonymized and administered by the Cancer Imaging Program, NCI. Access to these systems is restricted to authorized users.

Please note that follow-up clinical data may be collected from the patients referring physicians.

7.2 Response Criteria:

7.2.1 Early Treatment Arm

Overall response will be assessed according to the Cheson revised response criteria, 2007.(91). This data will be collected under the therapy trial in which the patient is also enrolled. For primary analyses, CR and Cru will be considered positive for response.

Table 6 **Summary of the response criteria**

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

7.2.2 Residual Mass arm

The presence of viable lymphoma cells on biopsy/FNA or absence of lesion progression on medical follow-up will be considered positive for residual malignancy.

8 Statistical Section

8.1 Objectives

8.1.1 Primary Objectives

- 1.a. To estimate the diagnostic accuracy of FLT PET/CT as an early indicator of complete response to therapy in B and T cell lymphoma.
- 1.b To estimate the diagnostic accuracy of FLT PET/CT in the evaluation of residual masses after therapy.

8.1.2 Secondary Objectives

- 2.a.To compare the diagnostic accuracy of FLT PET/CT with that of FDG PET/CT as an indicator of tumor response to therapy
- 2.b. To evaluate whether FLT tumor uptake prior to therapy or following completion of therapy are independent predictors of complete response to therapy
- 2.c. To evaluate whether there is a significant difference in tumor, selected normal organs ,and mediastinal blood pool FLT dynamic influx parameter (Ki),SUV at 1 hours and 2 hours post injection

- 2.d To estimate the diagnostic accuracy of percent change in SUV between pre-treatment and mid-treatment FLT PET/CT with regard to complete response to therapy

8.1.3 Analysis Plan

For the primary analyses, sensitivity and specificity will be estimated and 95% confidence intervals provided. Subjects with an FLT SUV greater than mediastinal blood pool activity will be considered FLT positive. In the early response arm, subjects with complete response (CR or Cr_u, **Table 6**) as determined by the CHESON revised response criteria will be considered disease negative (all others will be considered disease positive). In the residual mass arm, subjects with any malignant cells on biopsy will be considered disease positive.

For secondary objectives 2a and 2d, empirical ROC curves will be estimated, along with non-parametric AUCs and corresponding 95% confidence intervals. For 2b, we will evaluate the ability of FLT to predict clinical response independent of other known predictors using logistic regression. For aim 2c, we will test for differences using signed-rank tests.

No stratification based on lymphoma histology or treatment is planned due to the small amount of expected variability in treatments available.

8.1.4 Sample size

We plan to enroll 40 participants in the first arm and 30 participants in the residual tumor arm.

In the first arm, we assume that patients enrolled in this trial come from a randomized trial of DA-EPOCH-R vs. R-CHOP. With DA-EPOCH-R treatment, the expected response rate is 74%(92), while with R-CHOP it is 50%. (21). If we assume half of the patients enrolled in this trial will receive DA-EPOCH-R and the other half will receive R-CHOP, the average response rate is 62%, which will provide about 25 responders, who will contribute to estimates of sensitivity. About 15 patients will be non-responders and will contribute to estimates of specificity. The lower bounds for sensitivity are given in **Table 7**. Lower bounds for specificity are given in **Table 8**.

For the second primary objective, we assume that the 50% of patients with FDG positive residual disease will have positive pathology.(93) This provides 15 positives and 15 negatives. **Table 8** provides lower bounds for confidence intervals for sensitivity and specificity for this objective.

The following table provides expected lower bounds for 95% confidence intervals given observed values of sensitivity and specificity for a sample size of 15.We anticipate sensitivity and specificity to be about 85% and 90%, respectively. Hence, the sample size will provide lower bounds above the chance threshold of 50%.

Table 7

Sensitivity (n=25)	Expected lower bound of exact 95% CI
20/25(=.80)	0.59
21/25(=.84)	0.64
22/25(=.88)	0.69

Table 8

Sensitivity/Specificity (n=15)	Expected lower bound of exact 95% CI
12/15 (=0.8)	0.52
13/15 (=0.87)	0.60
14/15 (=0.93)	0.68

8.2 Data and Safety Monitoring Plan (DSMP)

No adverse events are expected for the [^{18}F]FLT PET/CT imaging study. The PI and research nurse will monitor the study for adverse events. Safety reporting will be performed as described in section **10.3**. Should there be more than 3 instances of Grade 3 or greater toxicities that increase the risks to participants, the study will be suspended or closed depending on the severity of the adverse events. Due to the minimal risk of this study we will not have a formal DSMP, however, the PI and Study Chair will re-evaluate the protocol after each patient.

The images will be stored on a secure database completely anonymized and administered by the Cancer Imaging Program, NCI. Access to these systems is restricted to authorized users.

Low level image analysis data and will be recorded in a password protected MS Access database on a secure server to allow for easy data manipulation.

9 Human subjects protection

9.1 Rationale for Subject Selection

All subjects must first be enrolled in a lymphoma treatment trial at the NIH Clinical Center OR be enrolled in the CALGB 50303 study at another site OR undergoing a new course of treatment of lymphoma at another facility. Both males and females will be eligible to enroll in this study. All ethnic groups/ race categories would be represented as they are represented in the disease as a whole. Cognitively impaired individuals will not be included in this study, if they are unable to understand the informed consent. Physically impaired persons who otherwise satisfy eligibility criteria will be included in this study.

This study is considered more than minimal risk to subjects and offers NO direct benefit to individual subjects. Information gained from this study is expected to benefit future patients with lymphoma. We anticipate that a thorough discussion of the study at the time informed consent is obtained will minimize any susceptibility to undue influences and unnecessary risks as research subjects.

9.2 Participation of Children

Subjects must be 18 years of age or older. Because no dosing or adverse event data are currently available on the use of FLT in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.

9.3 Evaluation of Benefits and Risks/Discomforts

Risks and discomforts of the experimental procedure are expected to be small and related to the risks of [^{18}F]FLT injection and PET/CT imaging. Specific risks and potential complications will be clearly outlined in a separate consent form at the time of each procedure. Most complications are expected to be minor and require no treatment. Risks and discomforts associated with

[^{18}F]FLT PET imaging are discomfort of an IV placement and the theoretical effects of additional radiation exposure (ED estimated at 1.2 rads for each FLT PET/CT scan and 1.88 rads for the additional FDG PET/CT). The subject will be required to lay still on their back for back for up to 95 minutes for the longest scan.

9.4 Risks/Benefits Analysis

The risks of participation are minimal based on the tracer doses of FLT. The benefits are similarly minimal as the participant is unlikely to derive any personal benefits. However, the knowledge derived from the study could benefit future patients with similar clinical presentations.

9.5 Consent and Assent Process and Documentation

The subject will be informed of the study by a member of the research team. The subject will contact the study research staff who will explain the study in detail. A member of the research team will send the consent form and protocol (if requested) to the participant. If the participant has any questions they will be answered by telephone. A signed consent will be obtained on the day of the study. The informed consent process will be documented in the patient's medical record and on the informed consent document. This process will be performed by the local Principal Investigator or designee.

10 Data reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html).

10.1 Patient registration form

See Sections **4.2.1** and **4.2.2**.

10.2 Data submission

10.2.1 Clinical Data

The investigators will provide quarterly reports of clinical data on the C3D clinical trial software. Cumulative C3D will be submitted quarterly to CIP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

10.2.2 Imaging Data

DICOM datasets (or digital datasets for non-DICOM studies) - of the PET, PET-CT and pertinent anatomic studies the patients undergo on the trial will be submitted quarterly to CIP via the NCIA (NCI Imaging Archive). The electronic transfer of image datasets is due January 31, April 30, July 31, and October 31.

Demographic information, correlative data and summary data will be entered into C3D weekly.

Data may be reported in laboratory publications as derived from pilot studies. Patients will not be identified by name.

10.3 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study

Coordinator) and the procedures for auditing are presented in **APPENDIX A: CTEP MULTICENTER GUIDELINES**.

The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

10.4 Safety reporting

10.4.1 Adverse Events

No adverse events have been reported for [^{18}F]FLT at the strength to be used for this study. As described in Section **3.2**, non-radioactive FLT has been investigated as an anti-AIDS drug, and some instances of reversible peripheral neuropathy were observed in subjects exposed to 50 ng-h/mL plasma over a course of 16 weeks (15µg/kg q12h). The FLT dose anticipated for this study will be <6.1µg for a single injection. Assuming a 70kg individual, the maximum concentration of FLT would be expected to be equivalent to 0.29 ng-h/mL. The administration of a total 10-15 mCi of [F-18]FLT over several imaging time points required to assess the effects of therapeutic intervention (baseline and typically two time points during therapy) to humans poses a minimal risk for an adverse effect. Therefore, the risk profile for [F-18] FLT used as described in the Investigator's Brochure consists of allergic reaction/anaphylaxis, which appears to be highly unlikely, and risks that would be associated with any clinical IV infusion/injection. The radiation exposure associated with this study is comparable to the dose for other widely used clinical nuclear medicine procedures.

Subjects will be monitored for adverse events during each [^{18}F]FLT imaging session. Adverse events are defined as any signs of illness or symptoms that have appeared or worsened since the infusion of [^{18}F]FLT. At the beginning and end of the [^{18}F]FLT imaging session, subjects will be questioned regarding any appearance or change in signs and symptoms. The adverse events to be specifically monitored during the infusion include localized discomfort at the IV injection site, pain, respiratory difficulties, flushing, dizziness, itching/rash, and any other symptoms that could be secondary to an anaphylactic reaction.

10.4.2 STUDY SPECIFIC RISKS/ADVERSE EVENT REPORTING

Qualifying Adverse Events (AEs), including Serious Adverse Events (SAEs), as defined herein, will be reported via the Adverse Event Expedited Reporting System (AdEERS) application. All Adverse Events, as defined herein, will, in addition, be reported via CDUS Complete, C3D, or other AE reporting system as specified below.

AdEERS is an electronic, internet based expedited Adverse Event reporting system operated by NCI/CTEP. It is generally used to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. However, it may be used to report adverse events of all types if AdEERS reporting is required per protocol.

For this study, Adverse Event reporting must follow the guidelines and timing requirements below. The latest version of the NCI/CTEP Adverse Event Reporting Requirements document, which is available at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf

provides additional details, and may be consulted as a reference, but **does not supersede AE reporting as specified in this protocol.**

The electronic-AdEERS AE system is to be used for all 'expedited reporting' events as defined herein.

10.4.3 General Definitions

10.4.3.1 Adverse Event (AE)

For the purpose of this study, an Adverse Event is an untoward medical condition experienced by a study participant **during the Adverse Event reporting period defined in Table 9 of the protocol**, or by applicable guidance, regulation, or policy. An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with participation in the study, **regardless of exposure to an agent or procedure, and regardless of whether it is considered to be caused by the agent, device, or process under investigation.**

If there is thought to be a conflict between the protocol and a regulatory or guidance source, consult the CIP Clinical Trials Branch. If a decision must be made pending final clarification, the stricter requirement should be applied.

10.4.3.2 Life-Threatening Adverse Event

A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

10.4.3.3 Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

- Results in death or is life-threatening at the time of the event
- Requires inpatient hospitalization, or prolongs a hospitalization
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in a participants offspring)

NOTE: Any event that:

- Follows IND agent administration, AND
- Occurs within the Expedited AE reporting period defined in the Reporting Table [See **Table 9** Below], AND
- Meets the definition of a Serious Adverse Event (SAE), as described above

MUST be reported through the AdEERS system.

All SAEs are to be followed by the investigator until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology, or until subject is lost to follow up.

10.4.3.4 Adverse Event Expedited Reporting System (AdEERS)

AdEERS is a web-based system created by NCI for electronic submission of expedited AE reports & is to be used in this study.

10.4.3.5 Investigational Agent

An investigational agent is any agent held under an Investigational New Drug (IND) application. For purposes of this study 3'-deoxy-3'-18F fluorothymidine (FLT) is an investigational agent.

10.4.3.6 Clinical Data Update System (CDUS/Complete CDUS)

CDUS/Complete CDUS is a data collection system used to capture clinical data. Complete CDUS is capable of capturing Adverse Event Data and is not being used in this study.

10.4.3.7 C3D

C3D is an integrated clinical trial data collection and AE reporting system for reporting of ALL Adverse Events, including those also requiring expedited reporting via (e)-AdEERS. Trials that will use C3D have been developed using C3D to create customized eCRFs.
This trial will use C3D. [See CDUS above.]

10.4.3.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved study procedures in a research protocol that **does not** have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

10.4.3.9 Protocol Violation (NIH Definition)

Any change, divergence, or departure from the IRB-approved study procedures in a research protocol that **does** have a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data.

10.4.3.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**

- Places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.4.4 AE Reporting Requirements

The Investigator's Brochure has been consulted in compiling the Adverse Events list in this protocol and the Informed Consent for the study.

<u>NOTE:</u> 24-Hour Notification for CIP IND Trials

The adverse event 24-hour notification requirement provides an early detection system for potential safety problems. Adverse events that must be reported within 24-hours of learning of the event are dependent upon the phase of trial, the agent/intervention (investigational or commercial), whether the event is expected or unexpected, the grade, and attribution. **Table 9** and footnotes to the table outline 24-hour notification requirements for AEs in trials utilizing an agent under a CIP IND. Adverse events that fulfill the 24-hour reporting requirement must be reported electronically via AdEERS. To ensure vigilance for AEs that require 24-hour notification, AdEERS is programmed to facilitate complete, timely submission.

10.4.5 Comprehensive Adverse Events & Potential Risks Lists (CAEPR) for 3'-deoxy-3'-[F-18]fluorothymidine (NSC 743144)

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 Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for 3'-deoxy-3'-[F-18]fluorothymidine.

Version 1.0, July 1, 2010 [1]

Category (Body System)	Adverse Events[2] with Possible Relationship to 3'-deoxy-3'-[F-18]fluorothymidine (CTCAE v4.0 Term)	EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)
	No AEs reported in human studies[2,3].	

[1]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. Your name, the name of the investigator, the protocol, and the agent should be included in the e-mail.

[2]No adverse events have been attributed to Positron-Emission Tomography (PET) imaging/diagnostic administration of [3'-deoxy-3'-[F-18]fluorothymidine at the levels described in the Investigators Brochure. Therefore, no adverse events are expected as a result of the intravenous (IV) administration of 3'-deoxy-3'-[F-18]fluorothymidine for typical PET imaging applications.

[3]As with many intravenously administered agents, 3'-deoxy-3'-[F-18]fluorothymidine could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in limited human exposure to date. Reasonable precautions should be taken, consistent with normal radiologic and clinical facility practice. The patient should be monitored

until the PET procedure is completed, and trained personnel and emergency equipment should be available per facility standards.

10.4.6 Adverse Event Characteristics

Expected Adverse Event: An expected AE is an event that is listed in the protocol or the Investigator's Brochure.

Unexpected Adverse Event: An unexpected AE is an event that is NOT listed in the protocol or the Investigator's Brochure.

Attribution: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure

NOTE: Attribution is part of the assessment of an adverse event. Determining that an event is 'unlikely related' or 'unrelated' to a study agent or procedure does NOT make the event unreportable, or disqualify the event as an AE. As defined above, an AE is reportable as specified herein if it occurred:

"during the Adverse Event reporting period defined in Table 9 of the protocol, or by applicable guidance, regulation, or policy."

Grade: Grade denotes the **severity** of the AE. An AE is graded using the following categories:

- Mild
- Moderate
- Severe
- Life-threatening or disabling
- Fatal

10.4.7 CTCAE term (AE description and grade)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate clinical areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).

10.4.8 Expectedness

AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. 'Expected' AEs, obtained from the Investigators Brochure, are as follows: allergic reaction/anaphylaxis, which appears to be highly unlikely, and risks that would be associated with any clinical IV infusion/injection.

10.4.9 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use electronic AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). Site personnel will be trained in required AE identification and reporting procedures. These requirements are briefly outlined in **Table 9** below.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.4.10 Expedited Reporting Guidelines

Table 9 **Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]**

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.4.11 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine C3D study data submissions. **AEs reported through AdEERS must also be reported in routine study data submissions.**

10.5 NCI-IRB Reporting

10.5.1 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

The Protocol PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

10.5.2 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

The protocol PI will report to the NCI-IRB:

1. All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
2. All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
3. All Grade 5 events regardless of attribution;
4. All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

10.5.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that require a sponsor recommended change to the protocol or the consent form or in the opinion of the PI increases risks to study participants will need to be reported to the NCI IRB.

10.6 NCI Guidance for Reporting Expedited Adverse Events for Multi-Center Trials

The reporting requirements for adverse events in multi-center trials when the NCI PI is responsible for the research and the coordination of the other research sites is the same as with any NCI intramural research protocol. The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 48 hours of PI awareness of the

event. The Site PI must also report any protocol deviations or violations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

11 Pharmaceutical information

11.1 [18F]FLT (IND # 71,260)

Product Description

11.1.1 How Supplied

Unit dose

11.1.2 Route of Administration

[^{18}F]FLT will be administered by intravenous injection.

11.1.3 Method of Administration

[^{18}F]FLT is administered by intravenous injection over 10-15 seconds with a saline flush. Appropriate shielding to meet the Radiation Safety Guidelines will be used.

11.1.4 Availability

[^{18}F]FLT will be synthesized by IBA or Cardinal Heath Pharmacies.

11.1.5 Agent Ordering

See **APPENDIX A: CTEP MULTICENTER GUIDELINES**

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13 APPENDIX A: CTEP MULTICENTER GUIDELINES

13.1 Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

13.2 Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

13.3 Agent Ordering

Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

The WRNMMC study coordinator or designee will fax a copy of the eligibility checklist, consent, and supporting source documentation to the Molecular Imaging Program. All investigational agents will be ordered by the Molecular Imaging Program Staff.

Once eligibility is verified and a scan date is arranged, the Molecular Imaging Program Staff will order the [^{18}F]FLT from IBA and Cardinal Heath Pharmacies.

Doses of the investigational agent ordered for patients admitted to the NIH CC, [^{18}F]FLT will be delivered to the Clinical Center Nuclear Medicine Department. Doses of the investigational agent ordered for patients admitted to the WRNMMC, [^{18}F]FLT will be delivered to the WRNMMC Nuclear Medicine Department.

14 Appendix B: Participating Site Expedited Event Report Form

NCI IRB Report Form	PROTOCOL No.	Site investigator (Name, Contact Telephone Number):

PROTOCOL TITLE:

PARTICIPATING SITE LOCATION:

Date Site Investigator Notified of Event: Click here to enter a date.
Description of Participant:
Sex: ☐ Male ☐ Female Age: Diagnosis:

Is this an Initial or a Follow-Up Report? ☐ Initial ☐ Follow up
For Follow up, AE reference # provided by NIH, if applicable:

If this is a Follow-up report, describe what was updated from the initial report:

Category of Report (*select all that apply*):

☐ Unexpected Serious Adverse Event that is possibly, probably, or definitely related to research

☐ Death, except due to progressive disease

☐ Protocol Violation

☐ Protocol Deviation

☐ Unanticipated Problem

If reporting a Serious Adverse Event, please select appropriate outcome category:

☐ Death

☐ Life Threatening

☐ Required or Prolonged Hospitalization

☐ Caused Persistent or Significant Disability/Incapacity

☐ Resulted in Congenital Anomalies or Birth Defects

☐ Required Intervention to Prevent Permanent Impairment or Death

Did this result in? (*select all that apply*)

☐ Harm or significant or substantive risk of harm to the research subject

☐ A compromise in the scientific integrity of the data collected for the study

☐ A breach of human subject protection regulations, policies or procedures

☐ Non-compliance with human subject protection regulations, policies or procedures

☐ A Protocol Deviation that does not impact the safety or welfare of subjects, or protocol integrity

Have similar adverse events occurred on this protocol at this site? ☐ Yes ☐ No

Description of similar events:

Brief description of the event/incident being reported:

Is this event "unexpected"? *(i.e., not described in protocol, consent, or Investigator Brochure)*

☐ YES ☐ NO If yes, explain:

Does the event suggest the research places subjects or others at a greater risk of harm?

☐ YES ☐ NO If yes, explain:

What steps do you plan to take as a result of this report? Select all that apply.

- ☐ No Action Required
- ☐ Amend protocol
- ☐ Amend consent document
- ☐ Inform current participants and document in the medical record
- ☐ Terminate protocol
- ☐ Educate staff
- ☐ Conduct audit

☐ Suspend enrollment

☐ Other

Specify other steps taken:

In addition to the NCI IRB, is this report being submitted to the local IRB?

☐ Yes

☐ No

Adverse Event Information:

CTCAE Term	**Date of Event**	**Location of Event**	**CTCAE Version**	**CTCAE Grade**	**Attribution to Research**	**Attribution to IND Agent**	**Expected**
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
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	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No

CTCAE Term	**Date of Event**	**Location of Event**	**CTCAE Version**	**CTCAE Grade**	**Attribution to Research**	**Attribution to IND Agent**	**Expected**
	date.						

REPORTED BY: _____

Printed Name: _____

Date: _____

15 Appendix C: Model Informed Consent Document (Residual Mass)

NIH CC Protocol #: 08C0200
NCI CTEP #: 8333
Local Protocol #: pending_____

A pilot study of ^{18}F fluorothymidine (FLT) PET/CT in lymphoma

***NOTES FOR INFORMED CONSENT AUTHORS:**

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term 'study doctor' has been used throughout the template because the Principal Investigator of a cancer treatment trial is a physician. If this template is used for a trial where the Principal Investigator is not a physician, another appropriate term should be used instead of 'study doctor'.
- The template date in the header is for reference to this template only and should not be included in the informed consent form given to the prospective research participant.

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

INTRODUCTION

We invite you to take part in a research study at the (*your institution*).
First, we want you to know that:

Taking part in (*your institution*) is entirely voluntary**.**
You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.
You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your (*your institution*) or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at (*your institution*), or with family, friends or your personal physician or other health professional.

Description of Research Study

You have been invited to participate in this study because you have lymphoma. Response to treatment in lymphomas may be difficult to assess by conventional PET/CT scans. Conventional PET/CT scans are typically done using a sugar-like radioactive tracer called FDG and low dose x-rays. In many instances, FDG PET/CT scans can show uptake suggestive of active disease and presence of a mass after chemotherapy despite the fact that no live cancer cells are present. Doctors have particular problems in evaluating response to treatment when this happens because

they can't tell if this mass is just dead tumor cells or active cancer. We hope that a new PET radioactive tracer called ^{18}F- Fluorothymidine (FLT) may help us to better evaluate treatment response. This is why we have asked you to participate in this study.

Positron emission tomography (PET) is a type of scan that uses a large donut shaped detection device. The scanner contains crystals that pick up tiny radiation signals given off by radioactive substances (tracers) that have been injected into the vein. The images generated by the scanner show where the radioactive tracer is in the body. The CT portion of the PET/CT is performed with low dose x-rays that go through your body and help us to better localize where the radioactive tracer is concentrating.

If your original FDG PET/CT imaging was performed at an outside institution and is not of adequate imaging quality, you may be asked to undergo a repeat FDG PET/CT study at NIH. If this is the case, you will undergo the routine 1- hour post injection imaging.

FLT is an experimental tracer which has high uptake in tissues involved in cellular division such as tumors. By injecting a small amount intravenously, we can image where FLT accumulates in the body.

Numerous small PET studies using FLT have been performed with no adverse effects ever reported. The amount of radiation is within the NIH radiation safety guidelines for protection of research volunteers.

By enrolling is this study, you will be asked to perform an additional FLT PET/CT scan at the end of your chemotherapy. This is in addition to standard of care FDG PET/CT studies ordered by your doctor.

Patients with a mass that can be seen on FDG PET/CT routinely have a biopsy performed as standard of care to determine if there are live tumor cells remaining.

There may be additional blood tests performed before the FLT PET scan can be scheduled. These are to be as certain as we can that the injection of FLT will not cause side effects. These tests will be performed to assess your liver function and will require about two teaspoonfuls of blood. Women able to have children will have an additional teaspoonful of blood collected in order to test for pregnancy. Pregnant women cannot participate in this study due to potential negative health effects to the unborn baby.

On the day of your FLT PET/CT study, you will come to the Nuclear Medicine Department at NIH and an intravenous line will be placed in your arm. You will be asked to lie on your back at the PET/CT scanner table. The table will then be advanced into the scanner. FLT will be injected in the vein over a 10-15 second period. Subsequently, PET/CT imaging over the tumor will be performed for 60 minutes, and immediately afterwards, a whole body scan will be performed (an additional 25-35 minutes). It is important that you remain still during these scans. 120 minutes after the injection, a regional (with your target tumor in the field of view) PET/CT images will be performed in a similar fashion for 25-35 minutes. Please note that for the additional sets of

images re-injection of tracer is not necessary. Doctors and nurses will be supervising the whole procedure and you should ask them any questions you have concerning this study. Additional blood samples (two teaspoons) will be collected from your vein at 60 and 120 minutes after the FLT injection to determine the amount of FLT that remains in your blood.

Up to 30 subjects will be enrolled in this arm of the trial. Patients will be enrolled at either the NIH Clinical Center or the Walter Reed National Military Medical Center.

Alternative Approaches or Treatments
You are not obligated to participate in this study. If you decide not to participate, it will not alter your planned treatment.

Risks or Discomforts of Participation
There are a few possible risks of [F-18]FLT PET and PET/CT scans. The most common ones are not considered serious. Any serious risks of [F-18]FLT PET or PET/CT scans are considered very unlikely. All of the known risks are described below.
Possible risks from having an intravenous (IV) injection:

- Bruising, pain, or infection at the injection site
- Leaking of IV fluid into tissues near the injection
- Inflammation of the vein at the injection site
- Allergic reaction, which could be serious or life threatening
- Dizziness if you stand up quickly

Possible risks from having a PET scan in general:

- Claustrophobia (feeling anxious and 'closed in')
- Discomfort from lying still on your back for a total of about 95 minutes during the scans

Possible risks from radiation exposure:
Each dose of [F-18]FLT will expose you to about [e.g. one-half to three –quarters] of the amount of radiation in a routine CT scan of a large body area such as your abdomen. Because we also need to do a CT, along with the [F-18]FLT PET, you could get up to another full CT dose of radiation at each scan depending on the scanner used.

Using the standard way of describing radiation dose, from participating in this study, you will receive a total of approximately 3.2 rem to your liver, 2.7 rem to your pancreas, your stomach, and adrenal glands,2.6 rem to your small and upper large intestines. All other organs will receive smaller amounts of radiation.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of 1.5 rem. This calculated value is known as the "effective dose" and is used to relate the dose received by each

organ to a single value. The amount of radiation received in this study is within the dose guidelines established by the NIH Radiation Safety Committee for research subjects. The guidelines is an effective dose of 5 rem (or 5,000 mrem) received per year.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the Earth's air and soil. The dose that you will receive from this research study is about the same amount you would normally receive in 4.6 years from these natural sources.

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effects to have been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

If you are pregnant or breastfeeding you will not be permitted to participate in this protocol. The unborn or nursing children are more sensitive to radiation than children or adults.

If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects.

Please tell your doctor if you have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

Experimental FLT PET imaging may reveal new information that would result in further studies (e.g., biopsies) and interventions that might not be necessary. The decision to act on findings on the experimental FLT PET study will be made by you and your referring physician.

It is possible that you may experience some side effects that we cannot anticipate. For that reason, you will be watched closely so that we can treat any side effects early.

Potential Benefits of Participation
As this is NOT a treatment protocol, **you are not likely to have any direct benefits.**

Alternative Treatments:
You should discuss your condition and prognosis with other doctors. Ask your doctor any questions you have and the choices that are available to you. Possible options are to proceed with the embolization procedure without participating in the study or not to have the embolization

procedure at all. Alternatives to the standard procedure will be explained elsewhere and are not related to this particular study.

Can I stop being in the study?
Yes. You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first. It is important to tell the study doctor if you are thinking about stopping so any risks from the intervention can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up 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 are the costs of taking part in this study?
(If applicable, inform the patient of any tests or procedures for which there is no charge. Indicate if the patient and/or health plan is likely to be billed for any charges associated with these 'free' tests or procedures.)

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.

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

- *[List relevant organizations like study sponsor(s), pharmaceutical company collaborators, local IRB, etc.]*
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

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

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]
[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 happens if I am injured because I took part in this 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 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 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].*

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)

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/

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

16 Appendix D: Model Informed Consent Document (Early Response)

NIH CC Protocol #: 08C0200
NCI CTEP #: 8333
Local Protocol #: pending_____

A pilot study of ^{18}F fluorothymidine (FLT) PET/CT in lymphoma

***NOTES FOR INFORMED CONSENT AUTHORS:**

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term 'study doctor' has been used throughout the template because the Principal Investigator of a cancer treatment trial is a physician. If this template is used for a trial where the Principal Investigator is not a physician, another appropriate term should be used instead of 'study doctor'.
- The template date in the header is for reference to this template only and should not be included in the informed consent form given to the prospective research participant.

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

INTRODUCTION

We invite you to take part in a research study at the (*your institution*).
First, we want you to know that:

> Taking part in (*your institution*) is entirely voluntary**.**
> You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.
> You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your (*your institution*) or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at (*your institution*), or with family, friends or your personal physician or other health professional.

Description of Research Study

You have been invited to participate in this study because you have lymphoma. As standard of care, your doctor will obtain conventional PET/CT scans to evaluate your response to chemotherapy. Conventional PET/CT scans are typically done using a sugar-like radioactive tracer called FDG and low dose x-rays. They are usually performed before treatment and after

the completion chemotherapy. Even though, FDG PET/CT is valuable in monitoring treatment response, we hope that a new PET radioactive tracer called ^{18}F- fluorothymidine (FLT) PET/CT will be better able predict final response to treatment. We, the study team, will work with your clinical provider to see if this early imaging helped predict your response to therapy. This is why we have asked you to participate in this study.

Positron emission tomography/computed tomography (PET/CT) is a type of scan that uses a large donut shaped detection device. The scanner contains crystals that pick up tiny radiation signals given off by radioactive substances (tracers) that have been injected into the vein. The images generated by the scanner show where the radioactive tracer is in the body. The CT portion of the PET/CT is performed with low dose x-rays that go through your body and help us to better localize where the radioactive tracer is concentrating.

FLT is an experimental tracer which has high uptake in tissues involved in cellular division such as tumors. By injecting a small amount intravenously, we can image where FLT accumulates in the body.

Numerous small PET studies using FLT have been performed with no adverse effects ever reported.

By enrolling is this study, you will be asked to undergo an FLT PET/CT scan: before beginning therapy, after 2 cycles of therapy and following completion of your chemotherapy. It is generally standard of care to undergo FDG PET/CT imaging prior to beginning treatment and at the completion of therapy. Some small studies have suggested that FDG PET/CT performed during therapy may be predictive of outcome. For this study, we are asking you to undergo an additional mid-therapy FDG PET/CT study, which will be compared with the mid treatment FLT PET/CT. You will also be giving us permission to collect follow-up information regarding your progress for up to three years after treatment.

There may be additional blood tests performed before the FLT PET scan can be scheduled. These are to be as certain as we can that the injection of FLT will not cause side effects. These tests will be performed to assess your liver function and will require about two teaspoonfuls of blood. Women able to have children will have an additional teaspoonful of blood collected in order to test for pregnancy. Pregnant women cannot participate in this study due to potential negative health effects to the unborn baby.

On each day of your FLT PET/CT studies, you will come to the Nuclear Medicine Department at (*your institution*) and an intravenous line will be placed in your arm. You will be asked to lie on your back at the PET/CT scanner table. The table will then be advanced into the scanner. FLT will be injected in the vein over a 10-15 second period. Subsequently, PET/CT imaging over the tumor will be performed for 60 minutes, and immediately afterwards, a whole body scan will be performed (an additional 25-35 minutes). It is important that you remain still during these scans. 120 minutes after the injection, another regional (with your target tumor in the field of view) PET/CT images will be performed in a similar fashion for 10 minutes. Please note that for the additional sets of images re-injection of tracer is not necessary. Doctors and nurses will be supervising the whole procedure and you should ask them any questions you have concerning

this study. Additional blood samples (two teaspoons) will be collected from your vein at 60 and 120 minutes after the FLT injection to determine the amount of FLT that remains in your blood.

For the mid-therapy FDG study, you will also come to the Nuclear Medicine Department at (*your institution*) and an intravenous line will be placed in your arm. You will be asked to lie on your back at the PET/CT scanner table. The table will then be advanced into the scanner. FDG will be injected in the vein over a 10-15 second period. One hour after injection a whole body PET/CT will be performed (lasting ~25-35 minutes).

Up to 40 subjects will be enrolled in this arm of the trial. Patients will be enrolled at either the NIH Clinical Center or the Walter Reed National Military Medical Center.

Alternative Approaches or Treatments
You are not obligated to participate in this study. If you decide not to participate, it will not alter your planned treatment.

Risks or Discomforts of Participation
There are a few possible risks of [F-18]FLT PET and PET/CT scans. The most common ones are not considered serious. Any serious risks of [F-18]FLT PET or PET/CT scans are considered very unlikely. All of the known risks are described below.

Possible risks from having an intravenous (IV) injection:

- Bruising, pain, or infection at the injection site
- Leaking of IV fluid into tissues near the injection
- Inflammation of the vein at the injection site
- Allergic reaction, which could be serious or life threatening
- Dizziness if you stand up quickly

Possible risks from having a PET scan in general:

- Claustrophobia (feeling anxious and 'closed in')
- Discomfort from lying still on your back for a total of about 95 minutes during the scans

Possible risks from radiation exposure:

Each dose of [F-18]FLT will expose you to about [e.g. one-half to three –quarters] of the amount of radiation in a routine CT scan of a large body area such as your abdomen. Because we also need to do a CT, along with the [F-18]FLT PET, you could get up to another full CT dose of radiation at each scan depending on the scanner used.

A total of 3 FLT PET/CT scans will be performed.

Using the standard way of describing radiation dose, from participating in this study and undergoing all 3 FLT PET/CT scans, you will receive approximately 9.7 rem to your liver, 8.2

rem to your stomach, and your adrenals, 8.1 rem to your pancreas, and 7.9 rem to your small intestines. All other organs will receive smaller amounts of radiation.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of 4.2 rem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is within the dose guidelines established by the NIH Radiation Safety Committee for research subjects. The guidelines is an effective dose of 5 rem (or 5,000 mrem) received per year.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. The dose that you will receive from this research study is about the same amount you would normally receive in 13.7 years from these natural sources.

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effects were ever observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects. Please tell your doctor if you have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

Experimental FLT PET imaging may reveal new information that would result in further studies (e.g., biopsies) and interventions that might not be necessary. The decision to act on findings on the experimental FLT PET study will be made by you and your referring physician.

It is possible that you may experience some side effects that we cannot anticipate. For that reason, you will be watched closely so that we can treat any side effects early.

Alternative Treatments:
You should discuss your condition and prognosis with other doctors. Ask your doctor any questions you have and the choices that are available to you. Possible options are to proceed with the embolization procedure without participating in the study or not to have the embolization procedure at all. Alternatives to the standard procedure will be explained elsewhere and are not related to this particular study.

Can I stop being in the study?
Yes. You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first. It is important to tell the study doctor if you are thinking about stopping so any risks from the intervention can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up 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 are the costs of taking part in this study?
(If applicable, inform the patient of any tests or procedures for which there is no charge. Indicate if the patient and/or health plan is likely to be billed for any charges associated with these 'free' tests or procedures.)

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.

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

- *[List relevant organizations like study sponsor(s), pharmaceutical company collaborators, local IRB, etc.]*
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
-

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

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]
[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 happens if I am injured because I took part in this 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 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 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]*.

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)

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/

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