AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6678

FDG-PET/CT as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in Non-small Cell Lung Cancer

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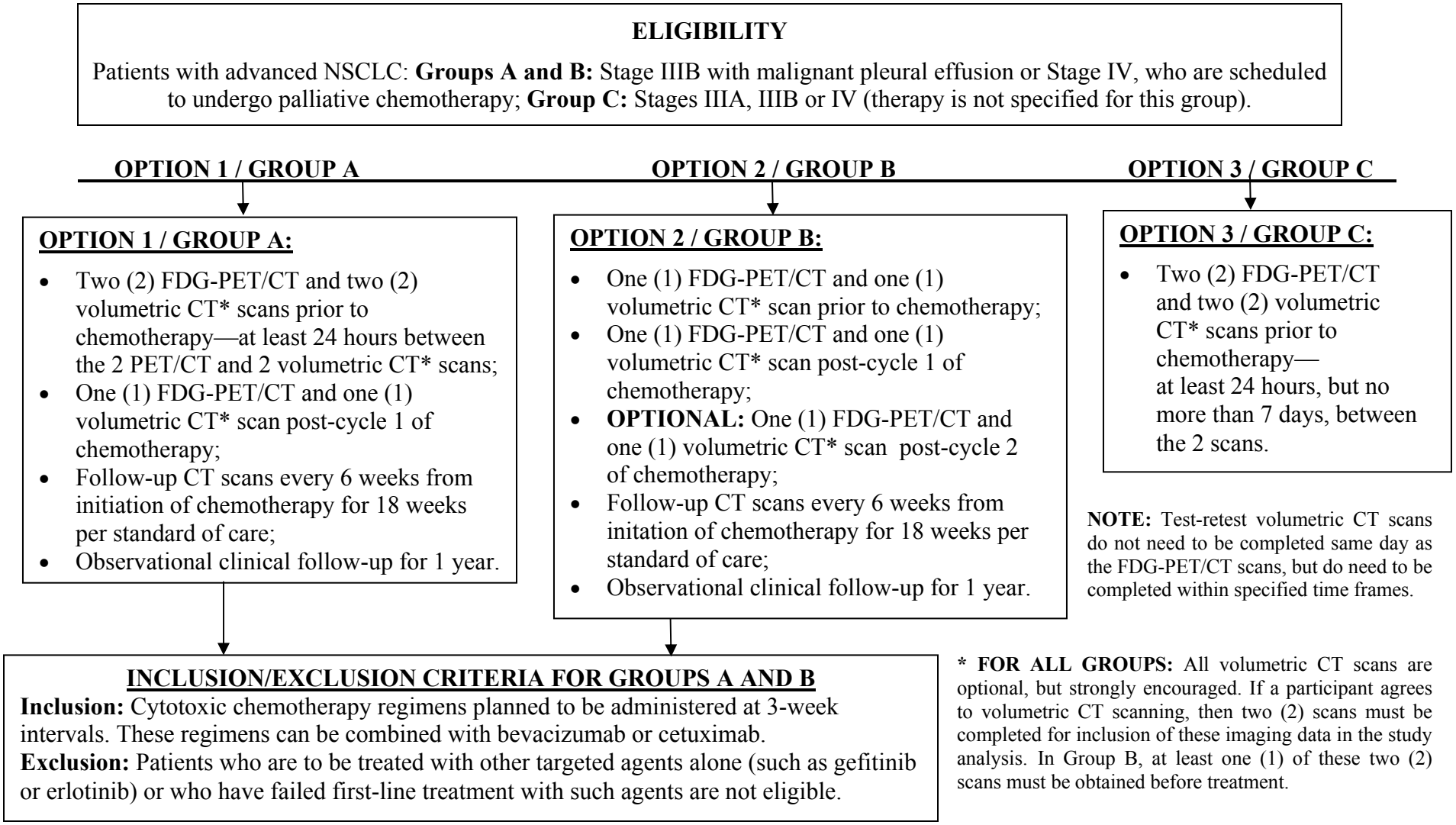
SCHEMA



NOTE: The first FDG-PET/CT scan may be completed prior to registration if: a) the PET/CT scanner has been qualified for the 6678 protocol; b) all parameters and scanning techniques are completed per protocol guidelines; and c) all subsequent PET/CT scans are performed on the same scanner or the same scanner model. Please note that the PET scan must include serum glucose testing prior to scanning and the timing and scheduling of the scan must fall within protocol guidelines.

NOTE: See Section 8.0.5 for examples of test-retest imaging scenarios for Groups A and C.

SPECIFIC HYPOTHESES

1. A metabolic response, defined as a $\geq$ 25% decrease in peak tumor SUV post-cycle 1 of chemotherapy, provides early prediction of treatment outcome (tumor response and patient survival).
2. Tumor glucose utilization can be measured by FDG-PET with high reproducibility.

SAMPLE SIZE

In this prospective, multi-center trial, a maximum of 285 eligible participants will be registered to achieve the following accrual targets:

- Combined total accrual of 228 participants to Groups A and B, with at least 171 of these in Group B.
- Combined total accrual of 57 participants to Groups A or C.

1.0 ABSTRACT

Background: Several studies have suggested that positron emission tomography (PET) with the glucose analog fluorodeoxyglucose (FDG) may be used to monitor tumor response very early in the course of therapy. However, further validation is necessary before FDG-PET can be used as a new marker for tumor response in clinical trials or for the management of individual patients.

Aim: The trial aims to show that quantitative changes in FDG uptake during chemotherapy provide an early readout for the effectiveness of therapy in patients with advanced non-small cell lung cancer (NSCLC).

Rationale for validating FDG-PET in NSCLC: To lay the foundation for quantitative FDG-PET as a potential biomarker for drug development, we have selected advanced NSCLC because it is a common disease with a poor prognosis. In the United States, more patients die of lung cancer than of breast cancer, prostate cancer, colorectal cancer, and lymphoma combined. This indicates that new tools for drug development and clinical patient management are urgently needed. From a methodological point of view, the poor prognosis of NSCLC significantly facilitates correlating tumor response in FDG-PET and patient survival, since only a relatively small patient population needs to be recruited and only a brief follow-up period is necessary. Correlating metabolic changes during chemotherapy with patient survival is the most stringent approach to validate FDG-PET as a predictive marker for treatment outcome. Another methodological consideration is that NSCLC almost universally demonstrates intense FDG uptake, which facilitates the quantitative analysis of PET studies.

Design: The trial will examine the correlation between changes in tumor FDG uptake during chemotherapy and subsequent patient survival. Furthermore, it will determine the test-retest reproducibility of quantitative measurements of tumor FDG uptake. The trial will also evaluate the time course of changes in tumor glucose metabolism during chemotherapy and measure changes in tumor FDG uptake after one *and* two cycles of chemotherapy, because the optimal time point to predict patient outcome by FDG-PET is currently unknown.

Since it is not practical for participants to undergo a total of four (4) FDG-PET/CT scans (two prior to therapy and two during therapy), study participants will be enrolled into one of three groups. Group A will undergo two FDG-PET/CT scans prior to chemotherapy and one FDG-PET/CT scan after the first chemotherapy cycle. Group B will undergo one FDG-PET/CT prior to chemotherapy and one FDG-PET/CT scan after the first chemotherapy cycle; an ***optional*** FDG-PET/CT scan may be completed after the second chemotherapy cycle. For both Groups A and B, standard of care follow-up CT imaging after every other chemotherapy cycle will be used to determine best clinical response according to RECIST criteria. Group C participants will undergo two FDG-PET/CT scans prior to treatment to support the test-retest reproducibility aim.

NOTE: Volumetric CT scans are optional at each FDG-PET/CT time point for each group throughout the trial, and are strongly encouraged. If a participant agrees to volumetric CT scanning, then two (2) scans must be completed for inclusion of these imaging data in the study analysis.

Hypotheses: The two hypotheses underlying this trial are that (i) a metabolic response, defined as a 25% or greater decrease in peak tumor SUV post-cycle 1 of chemotherapy, provides early prediction of treatment outcome (tumor response and patient survival) and (ii) tumor glucose utilization can be measured by FDG-PET with high reproducibility.

Endpoints: The primary endpoint of this study is the prediction of one-year overall survival by monitoring the metabolic response of the tumor following one cycle of chemotherapy. Secondary endpoints are (i) the correlation between a metabolic response after one cycle of chemotherapy and subsequent best tumor response according to standard anatomic response using the RECIST evaluation criteria, (ii) correlation between a metabolic response after the first chemotherapy cycle and progression-free survival, (iii) a comparison of the predictive value of FDG-PET for one-year overall survival after one and two cycles of chemotherapy, (iv) the test-retest reproducibility of standardized uptake values (SUVs).

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Introduction

Assessment of tumor response to therapy plays a central role in drug development as well as clinical patient management. Currently response is mainly evaluated by measuring tumor size in CT and classifying tumor shrinkage according to standard criteria, such as those of the World Health Organization (WHO) or Response Evaluation Criteria for Solid Tumors (RECIST) criteria (1, 2). However, response rates as assessed by these criteria are not well correlated with patient survival. Furthermore, response is evaluated not earlier than 2-3 months after start of therapy. This represents a significant clinical problem, since many treatment regimens are only active in the minority of the patients, meaning that the majority of patients undergo prolonged therapy without benefits. Several studies have suggested that positron emission tomography (PET) with the glucose analog fluorodeoxyglucose (FDG) may be used to monitor tumor response very early in the course of therapy. Quantitative changes in tumor FDG uptake 2-3 weeks after start of therapy have been shown to correlate well with subsequent tumor shrinkage and patient survival (see Section 2.3.2). Thus, FDG-PET has the potential to improve patient management by signaling the need for early therapeutic changes in non-responders, thereby avoiding the side effects and costs of ineffective treatment. Furthermore, as an early indicator of clinical benefit, FDG-PET may also facilitate oncologic drug development by shortening Phase II trials and detecting clinical benefit earlier in Phase III investigations. The availability of such a sensitive measurement could streamline clinical trials of putative therapeutics for lung cancer and, hence, accelerate new drug approvals.

However, further validation is necessary before FDG-PET can be used for these two applications. In this study, we propose to validate treatment monitoring with FDG-PET in patients with NSCLC. Specifically, this trial is designed to show that changes in FDG uptake, as measured by the standardized uptake value (SUV) during therapy for advanced lung cancer, provide an early predictor of the effectiveness of therapy. Lung cancer is the leading cause of cancer deaths in the U.S., with more than 160,000 deaths occurring annually. More patients die of lung cancer than of breast cancer, prostate cancer, colon cancer and lymphoma combined (3). The majority of patients presents with advanced disease and undergoes palliative chemotherapy. However, approximately only one third of the patients respond to chemotherapy. Therefore, new approaches to monitor tumor response early in the course of therapy are particularly relevant for NSCLC.

2.2 Lung Cancer: Challenges in Assessing Treatment Response

In lung cancer, standard response assessment is largely anatomic, using CT imaging as the primary modality, from which uni- or bidimensional diameters of malignant lesions are measured and summed as surrogates of tumor burden. Therapeutic response to treatment is evidenced by decreases or increases in these measurements.

The original WHO response criteria were based on bidimensional measurements of the tumor and defined response as a decrease of the sum of the product of the longest perpendicular diameters of measured lesions by at least 50%. The rationale for using a 50% threshold value for definition of response were data evaluating the reproducibility of measurements of tumor size by palpation and on planar chest x-rays (1, 4). The more recent RECIST criteria introduced by the National Cancer Institute (NCI) and the European Organisation for Research and Treatment of Cancer (EORTC) standardized imaging techniques for anatomic response assessment by specifying minimum size thresholds for measurable lesions and considered other imaging modalities beyond CT. As well, the RECIST criteria replace longest bidirectional diameters with longest unidimensional diameter as the representation of a measured lesion (2). RECIST defines response as a 30% decrease of the largest diameter of the tumor. For a spherical lesion, this is equivalent to a 50% decrease of the product of two diameters.

Meta-analyses combining the results of several large Phase II and Phase III studies have shown that tumor response according to WHO or RECIST criteria is correlated with patient survival for some tumor types (5). However, there is considerable variability between individual studies, and the same response rate can be associated with completely different survival rates in different studies (6). For some tumor types, meta-analyses found no or only a very weak correlation with patient survival (7, 8). Given the history of response criteria outlined above, these observations are probably not unexpected. Current response criteria were designed to ensure a standardized classification of tumor shrinkage after completion of therapy. They have not been developed on the basis of clinical trials correlating tumor shrinkage with patient outcome. While tumor shrinkage may generally be expected to be associated with a better outcome of therapy, it is also clear that there are diseases and treatment-specific differences with respect to the necessary degree of tumor shrinkage; one definition of response may not be adequate for prediction of patient outcome across all tumor types. Furthermore, morphologic alterations may not be adequate for evaluating physiologic or other biological responses that may precede significant tumor shrinkage or the response to newer cytostatic agents, in which anatomic changes may be absent or slow to manifest relative to therapeutic benefit.

In addition to size measurements, tumor response has also been evaluated histopathologically. Histopathologic response is defined as the percentage of viable tumor relative to therapy-induced fibrosis. This percentage is then expressed as a regression score. Such scoring systems have been established for various tumor types, including NSCLC (9). Histopathological regression scores have shown a close correlation with patient survival and patients with no or only minimal (less than 10%) residual tumor have been found to have a markedly better prognosis than patients without a histopathologic response (9-12). Therefore, histopathologic response is often used as the gold standard for the evaluation of imaging techniques. However, complete resection of the tumor is necessary for a valid histopathological response evaluation. Thus, histopathological response can only be determined for patients undergoing *preoperative* chemo- or radiotherapy and it cannot be used to modify treatment.

2.3 Experience with FDG-PET for Treatment Monitoring

2.3.1 Assessment of Tumor Response after Several Cycles of Therapy

In recent years, numerous studies have evaluated the use of FDG-PET for monitoring tumor response to chemo- and radiotherapy. These studies have shown that treatment-induced changes in tumor FDG uptake and residual FDG uptake after completion of therapy are highly significantly correlated with patient survival. Table 1 gives an overview of 9 studies evaluating the predictive value of FDG-PET after completion of chemo- or chemoradiotherapy in a total of 455 patients with NSCLC (13–22).

MacManus et al. studied the use of FDG-PET after chemoradiotherapy in patients with locally advanced NSCLC. Seventy-three (73) patients were prospectively evaluated for tumor response to chemoradiotherapy by CT and FDG-PET (13). Complete response in FDG-PET was defined as normalization of all sites with abnormal FDG uptake and partial response as a significant reduction in FDG uptake of all known lesions without the appearance of new lesions. Tumor response assessed by FDG-PET predicted better patient survival than response by CT criteria, the pre-treatment tumor stage, or patient performance status. The correlation between tumor FDG uptake after chemoradiotherapy and patient outcome was confirmed in a series of studies evaluating tumor response to chemoradiotherapy (Table 1). Only one of these studies contradicts this result: Tanvetyanon did not find a correlation between metabolic changes after neoadjuvant chemotherapy and patient survival (14). In contrast to the other studies, this study included patients with stage I disease. In addition, Tanvetyanon et al. used less intensive chemotherapy regimens resulting in relatively low response rates on PET, but also on CT and on histopathology. As a consequence, tumor response to chemotherapy had only a minor effect on

outcome, which was mainly determined by pretherapeutic stage and the completeness of surgical resection.

Table 1. Response assessment on FDG-PET and survival of patients with NSCLC

						Survival (months)[a]		
First Author/ Year	**N**	**Stage**	**Treatment**	**Timing of PET**	**Criterion**	**PET Responders**	**PET Nonresponders**	**P-value**
Vansteenkiste (1998) (15)	18	IIIA-N2	3xCTx -> surgery or RTx	Before and after CTx	ΔSUV > 50%	> 25	< 9	0.03
MacManus (2003) (13)	73	I-III	RTx or CRTx	Before and after RTx/CRTx	Visual[b]	24	4	< 0.0001
Hellwig (2004) (16)	47	IIB-IIIB	CRTx->surgery	After CRTx	SUV < 4	>56	9	<0.001
Hoekstra (2005) (17)	47	IIIA-N2x	3xCTx->surgery or RTx	Before CTx and after 1st and 3rd cycle	ΔSUV > 35% (after 1st cycle) ΔSUV > 50% (after 3rd cycle)	39 39	16[c] 14[c]	0.04 0.007
Poettgen (2006) (18)	50	III	3xCTx->CRTx-> surgery	Before and after CRTx	ΔSUV > 50%	>36	9[d]	0.045
Eschmann (2007) (19,20)	70	III	4xCTx->CRTx-> surgery	Before and after CRTx; 65 pts also after CTx	ΔSUV > 80% (after CRTx) ΔSUV > 60% (after CTx)	>60 >60	12 12	0.0001 0.0007
Dooms (2007) (21)	30	IIIA-N2	3xCTx->surgery	Before and after CTx	ΔSUV > 60%	58	18	0.009
Tanvetyanon (2008) (14)	89	I-III	2xCTx->surgery	Before and after CTx	ΔSUV > 30% or visual	>36	>36	0.7
Decoster (2008) (22)	31	III	3xCTx-RTx	Before and after CTx	Visual	>40	14	0.004

N, number of patients included; CTx, chemotherapy cycle; RTx, radiotherapy; CRTx, chemoradiotherapy; SUV, standardized uptake value; ΔSUV, fractional decrease in SUV.

[a] Median overall survival data are shown, except when indicated otherwise. If median survival times were not presented in the manuscript, these data were estimated from survival curves.

[b] Criteria for visual analysis: CR, no tumor FDG uptake or uptake less intense than in the mediastinum; PR, decrease in tumor FDG uptake from the pretherapeutic scan and no new lesions; NR, no appreciable change in intensity of tumor FDG uptake; PD, increase in tumor FDG uptake or volume or new metastatic sites.

[c] Data are for changes in glucose metabolic rates, but SUVs are shown in the paper to be similarly predictive for survival.

[d] Freedom from extracranial progression was analyzed in this study. In a subgroup of patients, PET was also repeated after induction CTx. SUV changes at this point in time were predictive for histopathologic response, but no survival data are presented for this group of patients.

In several other studies, FDG uptake after chemoradiotherapy and/or changes during chemoradiotherapy have been correlated with histopathologic tumor regression. All these studies report a significant correlation between the findings in FDG-PET and histopathological tumor regression (Table 2). The individual values for sensitivity and specificity, however, vary widely (58%–100%). This is likely due to the use of different criteria for histopathologic response in these studies (no viable tumor cells, less than 10% viable tumor cells). Furthermore, the number of patients with a histopathological response was generally small in these studies; as a consequence the values for the specificity of FDG-PET to detect residual tumor tissue (non-responders) must be interpreted with caution (Table 2).

Table 2. Sensitivity and specificity of FDG-PET for assessment of histopathologic response to preoperative chemoradiotherapy in patients with locally advanced NSCLC				
Author	**Year**	**N**	**Sensitivity**	**Specificity**
Akhurst(23)	2002	52	90%	67% [a,d]
Ryu(24)	2003	21	88%	67% [b,d]
Cerfolio(25)	2004	56	95%	100% [c,d]
Port(26)	2004	23	58%	100% [c,e]
Hellwig(16)	2004	37	81%	64% [b,d]
Poettgen(18)	2006	51	86%	85% [c,e]

[a]Visual analysis
[b]Quantitative analysis (absolute SUV)
[c]Quantitative analysis (Δ SUV)
[d]Criterion for histopathologic response: ypT0
[e]Criterion for response: less than 10% tumor cells

2.3.2 FDG-PET as an Early Predictor of Treatment Response and Survival

Perhaps even more interestingly, several studies have indicated that in responding tumors, FDG uptake markedly decreases within the first chemotherapy cycle (3-4 weeks after start of therapy). Conversely, the absence of a measurable decrease in tumor FDG uptake after the first chemotherapy cycle has been found to predict lack of tumor shrinkage and poor patient survival. This suggests that FDG-PET may be used to identify nonresponding tumors early in the course of therapy and to adjust treatment regimens according to the individual chemo- and radiosensitivity of the tumor tissue. Table 3 summarizes the results of recent studies correlating early changes in tumor FDG uptake with patient survival.

In NSCLC, Hoekstra et al. evaluated prediction of tumor response in a multicenter trial including 79 patients with locally advanced disease scheduled to undergo chemotherapy followed by surgical resection or radiotherapy (17). FDG-PET was performed prior to preoperative therapy and after the first and third cycle of chemotherapy. In 56 evaluable patients, reduction of tumor FDG uptake after one cycle of chemotherapy by more than 35% was significantly correlated with overall median survival ($p=0.04$, Table 2). Absolute tumor metabolic activity at the time of the second PET scan as expressed by metabolic rates derived from Patlak analysis was an even stronger prognostic factor ($p=0.01$). The quantitative evaluation of the third PET study provided a similar predictive value for patient outcome. Importantly, this study was performed at four Oncology and two Nuclear Medicine centers in two different countries. Thus, this study also indicates the feasibility of performing quantitative FDG-PET studies in a multicenter setting.

We have recently evaluated the prognostic implications of a measurable change in tumor glucose utilization in patients with advanced NSCLC, who were treated with palliative platinum-based chemotherapy. A "metabolic response" in PET was prospectively defined as decrease of the SUV of the primary tumor by at least 20%. This definition was based on the test-retest reproducibility of FDG-PET (see Section 2.6). A total of 57 patients were included in the study and 28 tumors showed a metabolic response after the first chemotherapy cycle. Median progression-free survival of metabolic

nonresponders was only 1.8 months versus 5.9 months for metabolic responders. Median overall survival of metabolic responders was 8.4 months and only 5.0 months for metabolic nonresponders (27). The sensitivity and specificity of a metabolic response for prediction of best response according to RECIST criteria were 95% and 74%, respectively. These data indicate that a measurable change in tumor FDG uptake after the first cycle of chemotherapy is associated with a palliative effect of therapy.

Although these data are encouraging, it is clear that the patient populations studied so far are obviously small and heterogeneous. Furthermore, the techniques and criteria for assessment of tumor response in FDG-PET vary significantly (Table 3). Therefore, there is a great need for validation of FDG-PET in larger patient populations and for standardization of response criteria.

Table 3. Prognostic relevance of quantitative changes in tumor FDG uptake during chemo- or chemoradiotherapy

Tumor	Author	Year	N	criteria	median survival		p-value
					responder	non-responder	
Esophagus	Weber(28)	2001	37	-35%	>48	20	0.04
	Wieder(29)	2004	22**	-30%	>38	18	0.011
Gastric	Ott(30)	2002	35	-35%	>48	17	0.001
Head and Neck	Brun(31)	2002	47**	median*	>120	40	0.004
Ovarian	Avril (32)	2005	33	-20%	38	23	0.008
Lung	Weber(27)	2003	57	-20%	9	5	0.005
	Hoekstra(17)	2005	56	-35%	43	18	0.04
	de Geus-Oei(33)	2007	51	-35%	17	9	0.018
	Nahmias(34)	2007	16	SUV slope	>20	5	0.0016

* Median metabolic rate at the time of the follow-up study.
** Chemoradiotherapy, otherwise chemotherapy.

2.4 Tumor Measurements Using RECIST and WHO Criteria

Although anatomic measurements are the standard for characterizing treatment response, there are several factors that contribute to variability in uni- and bidimensional measures of response assessment. Technical factors known to influence nodule size and anatomic response assessment include slice thickness, the axial plane on which the lesion is visible and measured, the use and timing of intravenous contrast administration, and the measurement technique used to determine tumor diameter (e.g., electronic calipers, automated techniques, etc.) (35–40). Patient-related factors such as the state of

respiration during scan acquisition and tumor margin also influence response assessment. Although not consistently observed, response assessment may be more variable with irregularly marginated tumors than smooth-edged tumors (41).

Reader variability is a well known cause of measurement error in anatomic response assessment. Erasmus et al. estimated both inter- and intraobserver variability and resulting response assessment misclassification rates among five experienced radiologists who independently measured 40 tumors (mean size 4.4 cm; range 1.8 – 8.0 cm), in double readings separated in time. Uni- and bidimensional measures were obtained. Misclassification rates were estimated based on the differences between measures of the same lesions within and between readers for both RECIST and WHO criteria for response and progressive disease. Table 4 summaries the misclassification rates between intra- and interobserver settings and RECIST vs. WHO criteria for progressive disease and treatment response.

Table 4. Reader misclassifications of response using RECIST and WHO criteria (41)

Reader	Measure	RD between 1st and 2nd measures Median (Mean minimum – mean maximum)	Mean No. Misclassifications	% of tumors per reader
Intra	RECIST PD	5.46 (0.00 – 59.64)	3.8 per reader	9.50
	WHO PD	10.64 (0.00 – 126.76)	8.2 per reader	20.50
Inter	RECIST PD	12.34 (0.00 – 116.91)	11.9 per reader	29.75
	WHO PD	20.76 (0.75 – 287.88)	17 per reader	42.50
Intra	RECIST PR	5.17 (0.00 – 44.44)	1.2 per reader	3.00
	WHO PR	9.61 (0.00 – 69.70)	1.0 per reader	2.50
Inter	RECIST PR	10.87 (0.00 – 51.93)	5.5 per reader	13.75
	WHO PR	16.98 (0.72 – 71.95)	3.3 per reader	8.25

RD = relative difference between first and second (comparative) measurement; Intra = intraobserver; Inter = interobserver; PD = progressive disease [RECIST > 20%; WHO > 25%]; PR = partial response [RECIST >30%; WHO > 50%].

Analysis of variance showed a significant difference among readers and among the measured nodules for both uni- and bidimensional measurements ($p<0.05$). Interobserver misclassification rates exceeded intraobserver rates for both progressive disease and response criteria. Intraobserver misclassifications were least common in the setting of response (3% RECIST | 3% WHO); interobserver misclassifications were greatest for progression (30% RECIST | 43% WHO). The greater consistency seen with same reader measurements has supported the concept of centralized readings for cancer clinical trials (42).

Measurement variations were also observed by Tran et al. in a retrospective study assessing differences in response category resulting from 1D, 2D, and 3D volumetric measurements of cancer patients in whom sequential chest scans were reviewed (38). Studies were interpreted by one of two radiologists with no attempt to assess intra- or interreader variability, but rather, the degree of concordance between RECIST, WHO, and volumetric measurements, the latter obtained by using a semi-automated software program. The authors used the kappa statistic (K) to determine the level of agreement between the different criteria. The 1D and 3D measurements were concordant in 29 of 30 classifications with K =

0.739 ± 0.345 (visits 1 & 2) and K = 0.273 ± 323 (visits 2 & 3). There was less concordance between 1D vs. 2D measurements and 2D vs. 3D measurements (38).

2.4.1 Volumetric Measures of Response

The variability of RECIST and WHO criteria has encouraged volumetric approaches to the anatomic measure of response assessment. The rationale for volumetric approaches is multi-factorial. First, lung cancers may grow *and* regress irregularly in three dimensions. Measurements obtained in the axial plane fail to account for growth or regression in the longitudinal axis, whereas volumetric measurements incorporate changes in all dimensions. Secondly, changes in volume are less subject to either reader error or interscan variations. For example, partial response using the RECIST criteria requires a greater than 30% decrease in tumor diameter, which corresponds to greater than 50% reduction in volume of tumor. If one assumes a 21 mm diameter lesion (of 4850 mm^3 volume), partial response would result in a diameter of 18 mm, but a decrease in volume to 2145 mm^3. The much greater magnitude of volumetric changes is less prone to measurement error than changes in diameter, particularly if the lesions are irregularly shaped or spiculated (Figure 1).

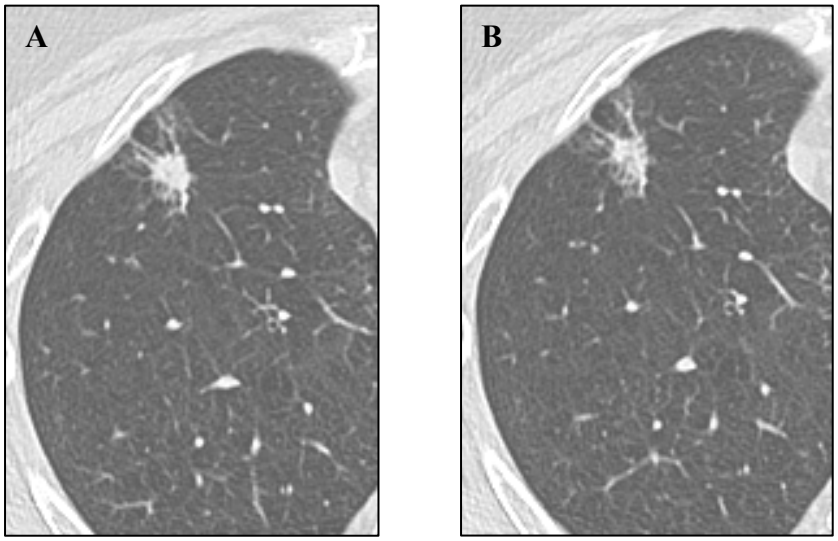


Figure 1: Axial CT scans of a lesion in a patient with non small cell carcinoma at (A) baseline and (B) following 2 cycles of chemotherapy. The spiculations may obscure the "edge" of the lesion, making 1D or 2D measures more prone to error than 3D measures based on gray level thresholding techniques.

Volumetric measurements of lung lesions have been compared to uni- and bidimensional measures of therapeutic response in several studies and have also been shown to result in different response categories (38, 43, 44). A mapping of the measurements for the four response categories is shown in Table 5 below:

Table 5. Comparison between Tumor Measurement Techniques and Treatment Response Categories

Category	Bidimensional	Unidimensional	Volumetric *
Complete Response	Tumor disappearance	Tumor disappearance	Tumor disappearance
Partial Response (PR)	> 50% reduction in cross-product	> 30% reduction in diameter	> 65% reduction in volume
Stable Disease	Size between PR and PD	Size between PR and PD	Size between PR and PD
Progressive Disease (PD)	> 25% increase in cross product	> 20% increase in diameter	> 44% increase in volume

***** Treatment response using the volumetric technique is extrapolated from unidimensional (RECIST) criteria and assumes a spherical lesion.

Anatomic response assessment using tumor volume rather than 1D or 2D measurements could provide more accurate and reproducible results. However, to date, there have been no systematic analyses of volumetric measurements relative to survival or other therapeutic outcomes in patients with NSCLC. Such prospective studies will be necessary to confirm the utility and accuracy of volumetric response assessment.

Currently, there are several computer aided diagnosis (CAD) systems for lung nodule detection. These have been tested primarily as primary or second readers to improve the sensitivity of lung nodule detection (45–47). Study results are not directly comparable due to differences in methodological design and analysis. However, there is general agreement that CAD systems increase the sensitivity of lung nodule detection, albeit at the expense of some increase in false positive nodules. Three FDA-approved, commercially available software programs offer automated or semi-automated methods of nodule detection and segmentation. These programs also report volumetric measurements and are thus potential software platforms for change analysis. The programs are: (1) Siemens LungCARE (Siemens Medical Systems; Malvern, PA); (2) Lung VCAR software (GE Healthcare Technologies; Waukesha, WI); and (3) R2 ImageChecker CT Lung System (R2 Technology; Sunnyvale, CA).

Acceptable accuracy (agreement with truth) of 3D measurements has been reported for volumetric software programs using simulated nodules (48), but there have been very few reports of the accuracy of these systems *in vivo* due to the lack of an anatomic truth standard. While absolute nodule volume is important, measurement precision (reproducibility) will be more important because proportional change in volume over time is more clinically relevant than the absolute change in volume (49). Furthermore, no comparisons between tumor volumetry and clinical outcomes have been reported. Nor have any of these software systems been systematically compared to assess their relative accuracies on a standard image dataset; therefore performance characteristics *between* these programs are unknown. Before promoting tumor volumetry as a more meaningful anatomic measure of treatment response, prospective studies will be necessary to compare these software systems in assessing change and in predicting clinical outcomes.

2.4.2 Reproducibility of 3D Measurements

For any software system, measurement variability may result from the interaction between the reader and the software system (i.e., the interobserver variability between independent readers using the same software to measure the same lesions) or from inter-scan variability (i.e. the repeatability of volume measurements from a software system for a nodule scanned multiple times contemporaneously). Different investigators have found very low interobserver variability (repeatability) in the measurement of 3D volumes, suggesting that the way in which the user interacts with the software to perform nodule segmentation produces very little variation in the final measurement. More of the variation relates to precision, as observed by differences in volumetric measures of nodules scanned multiple times in a single setting (49–51). Goodman et al. scanned nodules less than 20 mm diameter (size range 49.3-1434 mm^3) and observed a mean interobserver variability of 0.018% (standard deviation [SD] = 0.73%) (49). Precision, as measured by the SD of the mean volume for three contemporaneous scans, was 13.1% (confidence limits ± 25.6%). Not surprisingly, both the SD and confidence limits narrowed as nodule volume increased. Similarly, Wormanns et al. serially scanned 151 nodules of mean diameter 7.4 ± 4.5 mm (range 2.2-20.5 mm) and observed a mean intraobserver variability of 0.9% [95% confidence interval: 0.2-1.6%], mean interobserver variability of 0.5% (95% confidence interval: -0.3 to 1.4%) and an interscan variability of approximately ± 20% (51).

Compelling, the data for 3D measures of treatment response are scant, involve relatively few numbers, and are not readily comparable. This trial provides an important opportunity to assess several questions with respect to change analysis with tumor volumetry: (a) is volumetric analysis feasible in the multicenter trial setting; (b) can volumetric change analysis early in the course of therapy offer improvement as an independent or complementary variable with FDG-PET in predicting early therapeutic response or long term survival; (c) is volumetry reproducible; and (d) does volumetry improve on existing anatomic assessment? This trial, which will follow a well characterized cohort of patients with advanced stage NSCLC receiving chemotherapy, provides an excellent opportunity to address these important questions.

2.5 Rationale for Evaluating FDG-PET/CT in Patients with Advanced NSCLC Undergoing Palliative Chemotherapy

Although encouraging data have been reported for several tumor types (see Tables 1 and 2), prospective validation of FDG-PET as a predictive marker for tumor response appears most promising in NSCLC. The use of FDG-PET for staging and re-staging has been studied more extensively in NSCLC than in any other tumor type. The utility of FDG-PET for NSCLC imaging has been confirmed in several large surgical studies of preoperative staging as well as meta-analyses (52–54). From these studies, it is well established that—with the exception of pure bronchioloalveolar cell carcinoma—NSCLC demonstrates intense FDG uptake and can be detected by PET imaging with high sensitivity.

Sufficient baseline tumor FDG uptake is an important prerequisite for the use of FDG-PET for treatment monitoring. In tumors with low baseline metabolic activity, quantitative assessment of relative changes in tumor FDG uptake tends to be unreliable since image noise can significantly influence the measured signal. Furthermore, treatment induced changes in tumor FDG uptake are necessarily small when there is only low contrast between tumor and surrounding normal tissues. Even in a completely responding tumor, the tumor FDG-signal cannot decrease below background activity. For example, if the baseline signal is only 40% above background, the maximum decrease in the signal can only be 29% ([140%-100%]/140%). As a consequence, differences between tumors with a favorable or unfavorable response to therapy become small and are difficult to separate. Therefore, the high metabolic activity of NSCLC will significantly facilitate the quantitative analysis of the FDG-PET studies in this trial.

The second reason for selecting NSCLC as a model disease for validating FDG-PET for treatment monitoring is the high incidence of NSCLC. The incidence of lung cancer is the third highest of all malignant tumors in the US. NSCLC accounts for approximately 80% of all lung cancers. Only prostate and breast cancer have higher incidence rates than lung cancer. However, prostate cancer frequently demonstrates only low FDG uptake. Therefore, FDG-PET cannot be used for treatment monitoring. FDG uptake of breast cancer is on average significantly lower than of lung cancer, which makes quantitative evaluation of FDG-PET studies more challenging. Furthermore, most patients with breast cancer present with local disease and are primarily treated by surgery, whereas systemic therapy is used in an adjuvant setting. In contrast, the majority of patients with NSCLC presents with metastatic disease or develop metastatic disease after surgical therapy. Therefore, patients with NSCLC represent the largest group of patients to evaluate therapy response monitoring by FDG-PET.

The third reason is the poor prognosis of patients with advanced NSCLC and the lack of efficient second line therapies. With standard chemotherapy regimens, the one-year survival rate of advanced NSCLC is approximately 33% (55). From a clinical perspective, this clearly indicates the need for more efficient tools to aid the development of new therapeutic approaches. On one hand, the poor prognosis of patients with advanced NSCLC allows us to study the correlation between early metabolic changes and survival in a relatively small patient population with only a short follow-up period. Malignant diseases

that are more responsive and for which more therapeutic options are available, such as breast cancer, would mandate significantly larger patient populations and longer follow up to validate FDG-PET as a predictive marker for patient outcome. Second-line therapies are available for patients with NSCLC who progress after first line chemotherapy. These include docetaxel, pemetrexed, and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). However, in unselected patient populations, the response rates to second line treatments are in the range of 10% (56, 57). Therefore, second line therapy is not expected to significantly confound the predictive value of tumor response to first line chemotherapy.

2.5.1 Selection of Chemotherapy Regimens

Several treatment regimens are currently considered as "standard of care" for patients with advanced NSCLC (58). All these regimens are characterized by a similar response rate and randomized studies have not shown that any of these regimens provides a significant survival benefit (59). Alternatives to cisplatin and carboplatin, including non-platinum-based doublets, may be efficacious while imposing lesser toxicity, particularly for elderly patients with NSCLC (60–61). A meta-analysis of third-generation (paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan) versus second-generation platinum-based chemotherapeutic agents for late-stage NSCLC showed equivalency in survivorship (60). Rajeswaran et al. found “slightly higher” survival at 1 year and better partial response with platinum-based regimens in comparison with non-platinum-based doublets, but also a higher risk of anemia, nausea and vomiting, and neurotoxicity among the older-generation treatments (61). Gemcitabine-based doublets may be particularly appropriate for consideration among elderly patients with advanced NSCLC. A meta-analysis of the literature showed efficacy with significantly reduced thrombocytopenia in gemcitabine-based doublets by comparison with single agents among elderly patients for whom a full-dose platinum-based regimen might not be suitable (62). Therefore, we are not planning to restrict the study to one chemotherapy regimen, but will include patients scheduled to undergo a variety of frequently used chemotherapy regimens as described in Section **8.8**.

Although all these treatment regimens are characterized by similar response rates and survival data, one potential concern is that individual chemotherapeutic drugs may affect tumor metabolism in a different way. Therefore, including patients undergoing different chemotherapy regimens could potentially confound the correlation between changes in tumor metabolism and patient survival. However, all clinical FDG-PET studies published so far universally indicate that the decrease in the FDG-signal is a measure of the loss of viable tumor cells (data reviewed in references 63, 64). *In-vitro* studies have indicated that during the first hours after drug administration some chemotherapeutic drugs have specific acute effects on tumor metabolism including a temporary increase in cellular FDG uptake. In the present study, however, the earliest follow-up PET study will be performed 3 weeks after start of chemotherapy. Considering these data, it appears very unlikely that at this point in time drug-specific effects are still predominant (63, 64). Treatment with gemcitabine-based regimens has been monitored with FDG-PET in several tumor types including soft tissue sarcomas (65), breast cancer (66), and pancreatic cancer (67). These studies found no evidence for gemcitabine-specific effect on tumor metabolism when PET imaging was performed 1 to 2 cycles after start of therapy.

In a previous study, there were no significant differences with respect to changes in tumor FDG uptake in response to cisplatin/vinorelbine and carboplatin/taxol for responding and non-responding tumors (27). A metabolic response (≥ 20% decrease in tumor FDG uptake) was significantly correlated with patient survival for both chemotherapy regimens (27). de Geuss-Oei found that changes in FDG uptake measured 5-8 weeks after start of chemotherapy were significantly correlated with patient survival in a heterogeneous group of 51 NSCLC patients. In

this study of tumor stages ranging from IB to IV, 15 patients were treated with induction chemotherapy followed by surgery or chemoradiotherapy in curative intent and 36 patients were treated in a palliative setting. As a consequence of this heterogeneous patient population, 7 different chemotherapy regimens were used in this study. Despite all these potentially confounding factors, a change in FDG uptake (SUV) by more than 25% was significantly correlated with overall and progression-free survival (33). These data indicate that a metabolic response is a remarkably robust parameter that is not influenced by the chemotherapy regimen.

The Eastern Cooperative Oncology Group (ECOG) trial (E4599) has indicated that the vascular endothelial growth factor (VEGF) antibody bevacizumab significantly improves patient survival when added to paclitaxel/carboplatin chemotherapy (68). Based on these data, bevacizumab is used in addition to platinum-based chemotherapy at several centers in subgroups of patients with advanced NSCLC. Recently, FDG-PET has also been evaluated for monitoring treatment with EGFR kinase inhibitors and bevacizumab. Langen et al. studied 15 patients with FDG-PET before and after 3 weeks of treatment with bevacizumab and erlotinib (69). These investigators found a significant correlation between tumor metabolic activity at 3 weeks after start of therapy and patient survival ($p=0.03$).

Recently, the results of the FLEX trial have indicated that the EGFR-targeted monoclonal antibody, cetuximab, significantly improves patient survival when added to cisplatin/vinorelbine chemotherapy (70). Accordingly, this combination therapy is now being offered as a standard treatment option for some patients with advanced NSCLC.

Given the large variety of chemotherapy regimens used for treatment of advanced NSCLC, limiting the study to only one chemotherapy regimen would significantly affect patient recruitment. Furthermore, it could then be questioned whether the results could be generalized to different chemotherapy regimens.

2.6 Rationale for Assessing the Test-Retest Reproducibility of FDG-PET

Validating imaging methods as potential biomarkers for tumor response to treatment requires the demonstration of a high degree of test-retest reproducibility for the imaging method. Therefore, test-retest reproducibility will also be an important element of this trial. Test-retest reproducibility of FDG-PET and volumetric CT imaging will be assessed only prior to therapy in Groups A and C. During therapy, it would be difficult to separate random measurement errors from the effects of therapy.

Table 6. Studies evaluating the test-retest reproducibility of FDG-PET or PET/CT scans in various tumor types

First Author	Year	N	Setting	Technique	Tumor type	Measure of reproducibility	Result
Minn(71)	1995	10	Single center	PET	NSCLC	Percentage of absolute value of differences in Ki and SUV	10% for SUV and Ki
Weber(72)	1999	16	Single center	PET	Various metastatic solid tumors	Standard deviation of differences in Ki and SUV normalized by average value	10% for SUV and Ki

Hoekstra(73)	2002	10	Dual center	PET	NSCLC	Intraclass correlation coefficient	0.95
Nahmias(74)	2008	26	Single center	PET/CT	NSCLC	Standard deviation of SUV differences	0.27 SUV
Kamibayashi(75)	2008	45	Single center	PET and PET/CT	Lung tumors	Absolute value of differences in SUV normalized by average value	16%
Velasquez(76)	2009	62	Multi center	PET and PET/CT	Advance GI cancers	Standard deviation of differences in Ki and SUV normalized by average value	11%–16%

Four single-center studies (71, 72, 74, 75) have evaluated the test-retest reproducibility of FDG-PET or PET/CT scans in various tumor types (Table 6). In addition, there is a small two-center study and a larger multicenter study including patients with advanced gastrointestinal cancers (73, 76). Although different measurements of test-retest reproducibility have been used in these studies, FDG-PET has been found to be highly reproducible in single-center studies. The coefficient of variation for relative SUV changes and the SUV difference were 10% and 0.27 SUV, respectively. Larger variability has been reported by Kamibayashi et al. (75). However, in this study the two PET scans were performed on two different camera systems (a PET/CT and PET). This likely explains the higher coefficient of variation observed. In the current protocol, we are therefore requesting that the baseline and the follow-up PET/CT studies be performed on the same PET/CT system.

Velasquez et al. have recently published the results of a multicenter trial evaluating the test-retest reproducibility of FDG-PET in patients with metastatic GI cancers (76). They found a higher coefficient of variation (16%) than in the previous single-center studies. This variability was explained partly by inconsistent scan protocols (e.g., differences in the uptake period between the baseline and the follow-up scan). When only scans passing a strict quality control procedure were analyzed, the coefficient of variation decreased to 11%. Similar data from multicenter studies are missing in lung cancer. Furthermore, the test-retest reproducibility that can be achieved prospectively in a multicenter protocol with strict criteria for acquisition and analysis of PET scans needs to be determined.

2.7 Rationale for Studying the Time Course of Tumor FDG Uptake During Chemotherapy

A previous study has indicated that, in patients with advanced NSCLC, changes in tumor FDG uptake after one cycle of chemotherapy are well correlated with patient survival (27). In addition, a study evaluating neoadjuvant chemotherapy has also shown that metabolic activity after one chemotherapy cycle is highly predictive of patient survival (17). A second study in patients undergoing neoadjuvant chemoradiotherapy retrospectively analyzed PET scans of patients with locally advanced NSCLC imaged after three cycles of induction chemotherapy and after completion of chemoradiotherapy (45 Gy) (18). Changes in tumor FDG uptake at both time points were predictive of patient survival. However, most of the patients underwent only two and not three PET studies. There are some data in locally advanced breast and esophageal cancer that PET imaging after one cycle of chemotherapy may be a slightly better predictor of patient survival than PET after 2-6 cycles (29, 77, 78).

Ultimately, the "best" time point to assess tumor response by FDG-PET has not been identified in these single center studies, because the statistical power allowed the detection of only marked differences in the predictive value of FDG-PET after one or several cycles of chemotherapy. Therefore, this trial will measure changes in tumor FDG uptake after one and two cycles of chemotherapy.

2.8 Definition of a Metabolic Response in FDG-PET

Based on the reproducibility of the FDG-signal in untreated tumors, relative changes of approximately 20% are very unlikely to be due to measurement errors or spontaneous fluctuations of tumor metabolic activity (71, 72). These data establish the minimal effect of treatment on tumor metabolic activity that can be assessed by FDG-PET. However, a measurable change in metabolic activity does not necessarily imply that treatment has a beneficial effect for the patient. Therefore, we have recently evaluated the prognostic implications of a measurable change in tumor glucose utilization in patients with advanced NSCLC, who were treated with palliative platinum-based chemotherapy. A "metabolic response" in PET was prospectively defined as decrease of the SUV of the primary tumor by at least 20%. A total of 57 patients were included in the study and 28 tumors showed a metabolic response after the first chemotherapy cycle. Median progression-free survival of metabolic nonresponders was only 1.8 months versus 5.9 months for metabolic responders. Median overall survival of metabolic responders was 8.4 months and only 5.0 months for metabolic nonresponders (27). The sensitivity and specificity of a metabolic response for prediction of best response according to RECIST criteria were 95% and 74%, respectively.

These data indicate that a measurable change in tumor FDG uptake after the first cycle of chemotherapy is associated with a palliative effect of therapy. These data and the data on the test-retest reproducibility of FDG-PET suggest that a 20% decrease in tumor FDG uptake may be used to define a metabolic response in patients with NSCLC. However, we will use slightly stricter criteria for a metabolic response in the present study and define a metabolic response as a decrease of tumor FDG uptake by 25%. The rationale for this definition is that the test/retest reproducibility of FDG-PET in a multicenter trial may be lower than previously reported in single-center studies. Therefore, a 20% threshold may not be robust enough for a multicenter trial. Defining a metabolic response as a 25% decrease of tumor FDG uptake makes this study also consistent with previous recommendations by the EORTC (69).

Some previous studies (Table 3) have used even stricter criteria and have defined a metabolic response as a decrease of tumor FDG uptake by more than 30%, to 35%. However, these studies have evaluated patients undergoing neoadjuvant and not palliative chemotherapy. In this context, the gold standard for a favorable response was a histopathologic response, defined as no less than 10% viable tumor cells in the resected specimens. Thus, treatment had, on average, a much more pronounced effect on tumor viability than we expect in the present study. Therefore, a SUV change of 30% or more appears to be too high a target for this trial.

Although data in the literature support the use of a 25% decrease in tumor FDG uptake as a criterion for a metabolic response, we cannot exclude that other threshold values may allow a better prediction of patient outcome. Therefore, receiver operating characteristic (ROC) curves will be calculated for prediction of best response and one-year survival by quantitative changes in FDG uptake after one cycle of chemotherapy. Predictive accuracy will be evaluated through 95% confidence intervals for the area under the ROC curve (79). Furthermore, we are determining the test-retest reproducibility of FDG-PET in this trial.

2.9 Potential Problems of Using FDG-PET/CT for Treatment Monitoring

2.9.1 Inflammatory Reactions and Activation of Repair Mechanisms in Response to Therapy

In-vitro studies have suggested that chemo- and radiotherapy may cause a "metabolic flare phenomenon" (80, 81). This phenomenon has been attributed to the activation of energy dependent cellular repair mechanisms. In addition, inflammatory reactions have been observed in an animal model of chemotherapy of malignant lymphoma (82). Clinically, "sarcoid-like reactions" following chemotherapy have been described in some patients with malignant lymphomas and NSCLC (83, 84). These lesions can result in false-positive FDG-PET scans. However, sarcoid-like reactions appear to be rare. Few cases have been reported in the literature.

Because of the potential interference of a metabolic flare phenomenon and inflammatory reactions, some investigators have recommended that assessment of tumor response should not be performed until several weeks after completion of therapy. However, in the *in-vitro* studies indicating the presence of a flare phenomenon, FDG uptake was measured per *surviving* cells after chemotherapy or radiation therapy. This differs from the clinical situation, where the change in the PET signal is determined by a combination of decreased FDG uptake due to cancer cell death plus potentially increased FDG uptake by surviving tumor cells. In clinical studies, a mild to moderate increase in tumor FDG uptake has only been observed in the first hours after high-dose radiotherapy of brain tumors (85, 86). In contrast, several studies in a variety of malignant tumors, including NSCLC, have shown that tumor FDG uptake significantly decreases after the first chemotherapy cycle (Table 3). Even many eventually non-responding tumors show a slight decrease in FDG uptake at this point in time. Therefore, all clinical evidence indicates that inflammatory reactions or activation of repair mechanisms do not significantly limit the accuracy of FDG-PET for assessment of tumor response after one cycle of chemotherapy.

2.9.2 Accuracy of Quantitative Assessment of Tumor FDG Uptake

Quantification of tumor metabolic activity by FDG-PET is complicated by the fact that several factors other than tumor glucose use have an impact on the FDG signal. Partial volume effects can cause a marked underestimation of the true activity concentration within small tumors (diameter less than 2 cm). Furthermore, the activity concentration may be considerably underestimated even in large tumors due to heterogeneous FDG uptake (64).

In addition to these principal physical limitations of PET imaging, the processing of PET images and the definition of regions of interest affects the results of quantitative measurements of tumor FDG uptake. For example, smoothing of images will decrease the measured FDG uptake and the mean measured tumor FDG uptake will decrease when the size of the region of interest used to define the tumor is increased. On the other hand, image noise will lead to larger random errors of the measured tracer uptake when the size of the region of interest is decreased. Boellaard et al. recently reported that these factors may cause an increase or decrease of the measured tracer uptake by at least 50% (87).

Furthermore, it must be considered that FDG uptake of malignant tumors is time dependent. In most tumors, tracer uptake increases for at least 90 minutes after injection of FDG (88). Thus, FDG uptake will generally be considerably higher at later time points than at earlier. For some tumor types, up to 50% increase in tumor FDG uptake has been shown to occur between 40 and 90 minutes post injection (88).

Considering all these factors, it is clearly very challenging to quantify tumor FDG uptake *in absolute units* in a multicenter trial. However, this does not mean that it is equally difficult to measure *relative changes* in tumor glucose utilization over time. In this case, only intraindividual comparison of two studies is performed. This significantly reduces the number of factors that may confound the FDG signal. Therefore, the accuracy of FDG-PET for measuring

changes in tumor glucose utilization is considerably better than its accuracy to quantify tumor glucose utilization in absolute units (71, 72). Simulations studies and clinical data have shown that relative changes in tumor FDG uptake are much more robust to changes in the acquisition and reconstruction parameters than absolute SUVs (87, 89). In the present study, we will ensure a high accuracy of quantitative measurements of tumor FDG uptake by applying a strict protocol for data acquisition and image analysis. Inter-observer variability in definition of regions of interest will be minimized by performing the data analysis centrally at the ACRIN core lab.

2.9.3 Use of PET/CT for Treatment Monitoring

During the last 5 years, PET/CT has almost replaced PET at many institutions. PET/CT provides the ability to combine functional and anatomical measurements of the tumor. Therefore, we will use PET/CT and not PET in this study. PET/CT improves the anatomical localization of abnormalities identified in PET and reduces the number of false-positive studies by facilitating the identification of physiologic FDG accumulation in normal organs, such as skeletal muscles or the genitourinary tract. Several studies in a variety of cancers indicate that PET/CT significantly improves staging accuracy when compared to PET or CT alone. Perhaps most importantly, the anatomical information of PET/CT has made it much easier to communicate the findings in FDG-PET to the referring physicians and has markedly improved their confidence in the results of FDG-PET. In summary, tumor staging by PET/CT has many advantages and no apparent disadvantages when compared to standalone PET.

The situation is different for quantitative analysis of FDG-PET scans and treatment monitoring. PET/CT scan also offers several potential advantages, but there are also some technical challenges that may limit the accuracy of PET/CT for assessing treatment effects. The major concern is that the CT-based attenuation may be inaccurate due to differences in the photon energies used for PET and CT, and misregistration of the PET and CT data sets (90–92). These factors may increase the variability of quantitative measurements of tumor FDG uptake by PET/CT as compared to standalone PET.

However, studies have shown that accurate attenuation maps for correction of the PET emission data can be obtained by segmenting and scaling the CT images (93, 94). These algorithms have been implemented by all manufacturers of PET/CT systems. Misregistration of PET and CT images represents a problem for small pulmonary nodules and may result in considerable errors in the measured activity concentrations. However, for the large and frequently immobile pulmonary masses in patients with advanced NSCLC, errors due to misregistration of PET and CT data sets are small. One recent study in patients with locally advanced NSCLC treated by preoperative chemoradiotherapy has indicated that quantitative analysis of contrast enhanced FDG-PET/CT studies is feasible. In this study, quantitative changes in tumor FDG uptake after induction chemotherapy were highly predictive of histopathologic tumor response as well as recurrence-free survival (18). PET/CT scans were acquired during shallow breathing and no respiratory gating was employed.

The use of PET/CT imaging will allow exploratory analysis of changes in tumor metabolic activity with changes in tumor volume. Conceptually, tumor volume is a more attractive parameter to assess the effects of therapy than measurements of tumor diameters. Since tumors are frequently irregularly shaped, measurements in one or two dimensions may not capture the effects of therapy on the tumor mass. Furthermore, tumor volume is expected to be a more sensitive parameter for assessment of therapeutic effects than tumor diameters. For example, the volume of a spherical tumor decreases by 66% when its diameter decreases by 30%. In esophageal cancer, changes in tumor volume measured three weeks after start of preoperative

chemotherapy have been shown to be predictive of histopathologic response, whereas changes in tumor diameters were not correlated with histopathologic response (95). Therefore, combined analysis of metabolic and volumetric changes by PET/CT may improve the accuracy for assessing tumor response. One attractive approach to combine anatomic and functional information is to multiply the tumor volume in CT with FDG uptake in PET. This parameter proposed by Larson et al. provides an estimate of the "total lesion glycolysis" and its changes should reflect both decreased metabolic activity of the tumor tissue as well as reduction of tumor size (96).

2.10 Significance of ACRIN 6678 Trial

As outlined above, a number of small studies have indicated that quantitative assessment of tumor FDG uptake by PET imaging may provide an early indication for the effectiveness of therapy. Thus, FDG-PET has the potential to improve patient management by signaling the need for early therapeutic changes in non-responders, thereby avoiding the side effects and costs of ineffective treatment. Furthermore, as an early indicator of clinical benefit, the modality also has the potential to facilitate oncologic drug development by shortening Phase II trials and detecting clinical benefit earlier in Phase III investigations. The availability of such a sensitive measurement could significantly streamline clinical trials of putative therapeutics for lung cancer and, hence, accelerate new drug approvals.

However, the use of FDG-PET/CT for these promising applications requires systematic validation in multicenter studies. NSCLC represents an ideal model for this validation of FDG-PET, because it is a highly metabolically active tumor that has been extensively studied by PET imaging and is a common disease with a poor prognosis. In the US, more patients die of lung cancer than of breast cancer, prostate cancer, colorectal cancer and lymphoma combined, which indicates an urgent need for new tools for drug development and clinical patient management. Methodologically, the unfavorable prognosis of NSCLC makes this study tractable, and significantly facilitates correlating tumor response in FDG-PET with patient survival, since only a relatively small patient population needs to be recruited and the follow-up period can be brief. Correlating metabolic changes during chemotherapy with patient survival is the most stringent approach to validate FDG-PET as a predictive marker for treatment outcome.

Currently, therapeutic options in patients with NSCLC not responding to chemotherapy are limited. However, second line chemotherapy and treatment with EGFR TKIs are effective in subgroups of patients refractory to first line chemotherapy. If prospectively validated by the present study, FDG-PET may, therefore, be used to change patient management in patients with advanced NSCLC. The use of FDG-PET/CT as a "surrogate endpoint" to shorten the duration of Phase II and III trials will require further validation. In order to qualify as a surrogate endpoint, changes in tumor FDG uptake do not only need to correlate with patient survival, but also need to capture the net effect of treatment on patient survival (97). A series of randomized trials will be necessary in order to demonstrate whether treatment regimens with a higher metabolic response rate also lead to improved patient survival. However, the present study will provide the data necessary for the planning of such studies (97).

3.0 STUDY OBJECTIVES

This study has four objectives:

1. To test whether a metabolic response, defined as a $\geq$ 25% decrease in peak tumor SUV post-cycle 1 of chemotherapy, provides early prediction of treatment outcome (tumor response and patient survival).
2. To determine the test-retest reproducibility of quantitative assessment of tumor FDG uptake by SUVs.

3. To study the time course of treatment-induced changes in tumor FDG uptake.
4. To evaluate in an exploratory analysis changes in tumor volume during chemotherapy by multislice CT.

The two specific hypotheses underlying this trial are (i) a metabolic response, defined as a ≥ 25% decrease in peak tumor SUV post-cycle 1 of chemotherapy, provides early prediction of treatment outcome (tumor response and patient survival) and (ii) tumor glucose utilization can be measured by FDG-PET/CT with high reproducibility.

3.1 Primary Endpoint

The primary endpoint of this study is the prediction of one-year overall survival by monitoring changes in tumor metabolic activity during the first chemotherapy cycle, where metabolic response is classified as ≥ 25% decrease in SUV of the primary tumor relative to baseline (pre-chemotherapy).

3.2 Secondary Endpoints

3.2.1 Assessment of the association between a metabolic response after one cycle of chemotherapy and subsequent best tumor response according to standard anatomic response evaluation criteria (RECIST).

3.2.2 Assessment of the association between a metabolic response after the first chemotherapy cycle and progression-free survival.

3.2.3 Assessment of the test-retest reproducibility of SUVs measured by PET/CT systems.

3.3 Exploratory Data Analysis

In addition to the specific endpoints described above, the trial provides data for hypothesis-forming analyses. Specifically, the following questions will be addressed:

3.3.1 Will the ability of FDG-PET/CT to predict one-year survival be comparable after one and two cycles of chemotherapy?

3.3.2 Could ROC analysis be used to estimate an optimal threshold for the SUV differences in defining a metabolic response?

3.3.3 Can changes in tumor volume be assessed by multi-detector CT early during the course of chemotherapy?

3.3.4 Are tumor volumetric changes correlated with patient outcomes?

3.3.5 Can one develop parameters that combine metabolic and volumetric data and do these parameters allow a better prediction of patient outcome than metabolic changes alone?

3.3.6 How does the prognostic value of a metabolic response in PET compare with the prognostic value of tumor response according to standard tumor response assessment according to RECIST?

3.3.7 What is the correlation between metabolic changes in the primary tumor and in metastatic lesions?

3.3.8 How should changes in FDG uptake of multiple metastatic lesions be quantified?

4.0 STUDY OVERVIEW

4.1 Groups and Trial Accrual

In this prospective, multicenter trial, a minimum of 228 and a maximum of 285 eligible participants, excluding those who have been classified as off-study per Section 8.6, will be registered to achieve the following accrual targets: combined total accrual of 228 participants to Groups A and B, with at least 171 of these in Group B; combined total accrual of 57 participants to Groups A and C. Accrual to Groups A and C will be closed once a combined total of 57 cases has been accrued. However, should a participant drop out of Group A or C, that participant will need to be replaced to ensure 57-total accrual.

NOTE: Group A participants who do not complete the test-retest pre-treatment imaging requirements can be considered for Group B participation (which would require new consent for this group, enrollment in this arm, and a note to file). This is an acceptable protocol variation.

4.2 FDG-PET/CT Scans

Eligible participants in Group A will undergo a total of three (3) FDG-PET/CT scans. Eligible participants in Group B will undergo two (2) FDG-PET/CT scans and optionally may undergo a third FDG-PET/CT scan as described below. Eligible participants in Group C will undergo a total of two (2) FDG-PET/CT scans.

Group A will undergo two (2) FDG-PET/CT scans within 14 days prior to chemotherapy for test-retest reproducibility of SUVs and one (1) FDG-PET/CT scan after the first chemotherapy cycle. Group B will undergo one (1) FDG-PET/CT prior to chemotherapy and one (1) FDG-PET/CT scan after the first chemotherapy cycle; one (1) *optional* FDG-PET/CT scan may be completed after the second chemotherapy cycle. For both Groups A and B, standard of care follow-up CT imaging after every other chemotherapy cycle will be used to determine best clinical response according to RECIST criteria. Group C participants will undergo two (2) FDG-PET/CT scans before any treatment to treatment to support the test-retest reproducibility aim. See detailed procedures in Section 8.0 for specifics for all images by group.

4.3 Optional Volumetric CT Scans

Volumetric CT scans are optional at each FDG-PET/CT time point for each group throughout the trial, and are strongly encouraged. If a participant agrees to volumetric CT scanning, then two (2) scans must be completed for inclusion of these imaging data in the study analysis. In Group B, at least one (1) of these optional volumetric CT scans must be obtained before treatment. Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. See Section 8.0 for detailed procedures, including Section 8.0.5 for examples of possible timing scenarios.

4.4 Image Data Overview

All image data will be transmitted in digital form to the ACRIN Image Management Center for central analysis (Appendices VI and VII). Investigators analyzing the FDG-PET/CT images will be blinded to patient outcomes, namely CT findings and patient survival. Similarly, investigators analyzing the CT scans will be unaware of the PET findings and patient survival. Treating physicians will be blinded to the results of the CT and FDG-PET/CT scans completed post-cycle 1. Only potentially life threatening CT findings or other serious complications, such as impending fractures will be reported after cycle 1. For ethical reasons, treating physicians will not be blinded to the results of the later FDG-PET/CT scan (post-cycle 2), since tumor response is routinely assessed at this time.

4.5 Per Case Reimbursement

A per case reimbursement rate will be established based on the group and the number of PET/CT scans performed. Additional reimbursement will be provided when the optional volumetric CT scans are completed. As well, if a participant has to have a repeat baseline FDG-PET/CT scan to qualify for participation in the study, additional reimbursement for the repeat PET/CT scan will be provided.

5.0 PARTICIPANT SELECTION

Participants interested in the trial will be consented to one of the three study arms depending on their eligibility evaluation, personal preference, and their ability to adhere to the timing sequences for each arm. The decision will be made by the referring physician, the study PI, and the research staff consenting the patient to determine the appropriate enrollment path. Eligibility is based on the option/group for which the participant is eligible and chosen. Criteria that do not apply to Group C are noted below with "(Groups A and B ONLY)".

5.1 Inclusion Criteria

5.1.1 Histologically or cytologically proven NSCLC;

5.1.2 Participant meets one of the following criteria:

5.1.2.1 Newly diagnosed Stage IIIB (with malignant pleural effusion) or Stage IV **(Groups A and B ONLY)** or newly diagnosed Stage IIIA, IIIB, or IV **(Group C ONLY)**;

5.1.2.2 Recurrent or metastatic NSCLC, if surgery or radiation therapy for treatment of the primary tumor and locoregional disease were performed ≥ three (3) months prior to study enrollment and there is a measurable lesion in the chest (see Section 5.1.5 for a definition of "measurable lesions");

5.1.2.3 Recurrent or metastatic NSCLC, having received chemotherapy in the adjuvant setting or as part of combined modality therapy for locoregional disease ≥ three (3) months prior to diagnosis of recurrence/metastatic disease, and there is a measurable lesion in the chest (see Section 5.1.5 for a definition of "measurable lesions").

5.1.2.4 In a previously irradiated participant, the recurrent lesion(s) must be outside the prior radiation port or if within a prior radiation port, the lesion(s) must demonstrate radiologic progression by RECIST criteria.

5.1.3 Participant is being considered for a cytotoxic chemotherapy regimen planned to be administered at 3-week intervals; this regimen can be combined with bevacizumab OR cetuximab **(Groups A and B ONLY)**;

5.1.4 Participant has undergone the following minimum workup to confirm tumor stage:

5.1.4.1 CT or MR scan of the chest;

NOTE: If necessary to determine/confirm stage of disease, an upper abdomen CT scan (to include liver and adrenal glands);

5.1.4.2 History/physical examination within 6 weeks prior to registration;

5.1.4.3 CT or MR scan of the brain within 4 weeks prior to registration if there are headache, mental/physical impairment, or other signs or symptoms suggesting brain metastases within the past two months **(Groups A and B ONLY)**;

5.1.5 At least one measurable primary or other intrathoracic/supraclavicular lesion ≥ 2 cm, according to Response Evaluation Criteria in Solid Tumors (RECIST);

5.1.6 Performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) scale **(Groups A and B ONLY)**;

5.1.7 Age 18 years or older;

5.1.8 Participant must use medically appropriate contraception if sexually active; women of childbearing potential must not be pregnant or breastfeeding;

5.1.9 Able to give study-specific informed consent;

5.1.10 Able to tolerate PET/CT imaging required by protocol, to be performed at an ACRIN-qualified facility.

5.2 Exclusion Criteria

5.2.1 Small cell carcinoma histology;

5.2.2 Pure bronchioloalveolar cell carcinoma histology;

5.2.3 Thoracic radiotherapy, lung surgery or chemotherapy within three (3) months prior to inclusion in the study.

NOTE: Radiotherapy or surgery for a non-thoracic metastatic lesion within three (3) months prior to inclusion in the study is not an exclusion criterion.

5.2.4 Poorly controlled diabetes (defined as fasting glucose level > 150 mg/dL) despite attempts to improve glucose control by fasting duration and adjustment of medications. Patients with diabetes will preferably be scheduled in the morning and instructions for fasting and use of medications will be provided in consultation with the patients' primary physicians.

5.2.5 Prior malignancy; however, participants with basal cell or squamous cell carcinoma of the skin, or carcinoma in situ, or other cancer from which the participant has been disease free for more than 3 years are still eligible **(Groups A and B ONLY)**;

5.2.6 Patients of reproductive potential, who are sexually active but unwilling and/or unable to use medically appropriate contraception, or women who are pregnant or breastfeeding;

5.2.7 Patients with intent to undergo chemoradiotherapy **(Groups A and B ONLY)**;

5.2.8 Clinical or radiographic signs of post-obstructive pneumonia;

5.2.9 Symptomatic brain metastases **(Groups A and B ONLY)**;

5.2.10 Treatment planned with any targeted or biologic therapy alone, such as gefitinib and erlotinib, or failure of first-line treatment with such agents **(Groups A and B ONLY)**.

5.3 Recruitment and Screening

The investigative team at each participating site includes a primary medical oncologist specializing in lung cancer, a nuclear medicine physician, and a radiologist. Potential participants will be referred by medical oncologists as well as physicians from the primary care, pulmonary medicine, and surgical oncology disciplines. Additional sources of accrual may be obtained from regional community oncology groups to whom study investigators have provided descriptions of the trial and eligibility criteria.

The Protocol Specific Application (PSA) will require site investigators to record:

1. The investigative team members along with acknowledgements of each member's role and responsibilities.
2. Historical data for the past three years – from all anticipated referral sources – documenting the numbers of patients with advanced NSCLC, Stage IIIB (with pleural effusion), and Stage IV who were treated.

3. A strategy for educating potential referrers and their staff about the trial and the process for participant identification and consent.

ACRIN will develop a trial communications plan that will describe the production of materials to aid participant recruitment. All materials used for participant recruitment will be reviewed and approved by each institution's Institutional Review Board (IRB).

Understanding the additional time and effort involved in collaborating on and referring patients to a trial such as this, ACRIN will provide additional resources to referring oncologists to supplement support staff that will be necessary to discuss this protocol with potential participants, schedule imaging examinations, and collect and provide requisite clinical information on a per case basis. Referring physicians will provide the documentation on potential participants of the criteria required for eligibility (see Inclusion Criteria, Section 5.1).

6.0 SITE SELECTION

6.1 Institution Requirements

The potential sites for this study are ACRIN participating institutions that meet qualifications for participating in this study. Each institution must complete a PSA (Appendix IV) and have the PET/CT scanner and dedicated CT scanner (if one will be used for this trial) approved prior to the institution participating in the study (Appendix V). Detailed information for PET/CT and CT Qualification Procedures and the PSA can be accessed at www.acrin.org/6678_protocol.aspx. All regulatory documentation must be submitted to ACRIN Headquarters (via fax: 215-717-0936, ATTN: ACRIN Protocol Development and Regulatory Compliance Department).

6.1.1 PET/CT Qualification

To participate in this study, the site must be able to conform to all of the criteria described in the PSA and the ACRIN PET Qualifying Application which are available on the ACRIN web site, www.acrin.org/6678_protocol.aspx. This process includes submission of test images to ACRIN. The test images will be reviewed by one or more of the study investigators for compliance. Only after approval by ACRIN can an institution enroll participants on this study. Centers that have received PET/CT approval for other ACRIN studies may be eligible for expedited qualification.

6.2 IRB Approval and Informed Consent

All institutions must have study-specific Institutional Review Board (IRB) approval for the protocol and site-specific informed consent forms. The informed consent form templates are included in this protocol as Appendix I. The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. A copy of the IRB approval letter and the IRB-approved, institutional study-specific informed consent forms must be on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: ACRIN Protocol Development and Regulatory Compliance Department) prior to enrolling the first study participant.

6.3 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any recruitment barriers. In particular, starting approximately one month after a site is approved to begin participant enrollment, the site's actual accrual will be compared to the average monthly accrual potential described in their PSA. If a site's actual accrual falls below 60% of what is reported in the

PSA, the Protocol Support Enrollment Committee (PSEC) comprised of the trial PI and his or her designees will determine a follow up action plan to identify site accrual barriers and develop strategies to support the site in meeting accrual goals.

The ACRIN Steering Committee regularly reviews the overall trial accrual and may request information about a trial's accrual performance to better understand general accrual barriers or issues. Accrual and safety information will be presented to the ACRIN Data Safety and Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the DSMC may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

7.0 ONLINE REGISTRATION

7.1 Using the Online Registration System

Once the investigator-designated research staff (i.e. the Research Associate [RA]) has completed the eligibility checklist (Appendix II) and the participant has been found to be eligible to participate in the trial, the participant will be consented to either Group A, B, or C based on inclusion/exclusion criteria and choice. Upon obtaining a signed informed consent form, the information of the study participant will be registered by logging onto the ACRIN web site (www.acrin.org), which is available 24 hours a day, 7 days a week**.**

7.2 Unsuccessful Registrations

7.2.1 ACRIN and protocol-specific requirements for Institution participation are maintained within the Administrative database. The protocol specific attributes are then interfaced with the web application for on-line verification of site participation acceptance. If the institution has not met all the regulatory requirements based on the required attributions within the database, a screen that includes a brief explanation of the failure to gain access to the registration screens is projected. If during the completion of the eligibility questions a participant is deemed ineligible based on a response, a message box appears to instruct the research staff to contact the Data Management Center.

7.2.2 In the unlikely event that the ACRIN web registration site is not accessible, participating sites may still register a participant by faxing the completed eligibility checklist to the DMC at the ACRIN (215-717-0936, ATTN: PARTICIPANT REGISTRATION). ACRIN staff will either fax or email a response to the registering site with the confirmation of registration and participant case number as soon as possible.

8.0 STUDY PROCEDURES

The schedule of the imaging studies is described in Sections 8.9.1, 8.9.2, and 8.9.3.

8.0.1 Scanner Technical Specifications

All FDG-PET/CT and volumetric CT scans will be performed on equipment specifically qualified for this trial using the same image acquisition parameters as described in Appendices VI and VII and summarized in Section 10. All FDG-PET/CT and CT scans for an individual participant will be performed on the same scanner throughout the trial. In the rare instance of equipment malfunction, follow-up scans on an individual participant can be performed on the same type of platform provided that it has been qualified for use in ACRIN 6678 protocol.

8.0.2 Baseline FDG-PET/CT Scan

Minimum Acceptable Tumor FDG Uptake. If the FDG uptake of the tumor tissue is too low for quantitative analysis (SUV < 4.0), the participant will be removed from participation and replaced with another eligible study participant. In participants whose measurable tumor has a baseline SUV of less than 4.0, a 25% relative decrease of tumor FDG uptake would result in a decrease in SUV of ≤ 1 to the tumor. Data on the test-retest reproducibility of FDG-PET suggest that in an individual patient such a small absolute change in tumor FDG uptake cannot be reliably identified by PET imaging. Therefore, a baseline SUV of at least 4.0 is required for the present study which defines a metabolic response as a 25% decrease in tumor FDG uptake. We expect that the tumor SUV will be less than 4.0 in fewer than 5% of patients (27). This estimate is based on data on FDG uptake of untreated, advanced NSCLC. SUVs lower than 4.0 are observed in small lesions and in patients with bronchioloalveolar cell carcinomas (BAC). For these reasons, patients with these tumor types will not be included in the present study (see Section 8.6).

NOTE: The first FDG-PET/CT scan may be completed prior to registration if: a) the PET/CT scanner has been qualified for the 6678 protocol; b) all parameters and scanning techniques are completed per protocol guidelines; and c) all subsequent PET/CT scans are performed on the same scanner or the same scanner model.

Please note that the PET scan must include serum glucose testing prior to scanning and the timing and scheduling of the scan must fall within protocol guidelines.

In addition, if the first FDG-PET/CT scan is completed prior to registration as noted above, the participant may undergo a volumetric CT scan after consent and registration to the trial is complete. Volumetric CT scans are optional at each FDG-PET/CT time point for each group, but are strongly encouraged. If a participant agrees to undergo volumetric CT scanning, then two (2) scans must be completed for inclusion of these imaging data in the study analysis. In Group B, at least one (1) of these two (2) scans must be obtained before treatment. Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. For Groups A and C, the first volumetric CT should be completed at least 24 hours before Imaging Visits A2 or C2. For Group B, the first volumetric CT must be completed within 7 days before treatment start.

Please refer to Section 8.9 for the study procedure calendar.

8.0.3 Number and Timing of FDG-PET/CT Scans

Eligible participants for the study Groups A and B will generally need to undergo at least 2 cycles of first-line chemotherapy. Eligible participants for Group C will be recruited regardless of intended therapy. All participants in Group A will undergo three (3) FDG-PET/CT studies; participants in Group B will undergo two (2) FDG-PET/CTs and may undergo an optional third FDG-PET/CT; participants in Group C will undergo two (2) FDG-PET/CT studies.

Participants in Group A will undergo a total of three FDG-PET/CT scans: two pre-chemotherapy FDG-PET/CT scans (the second pre-chemotherapy FDG-PET/CT scan can be performed on the day of treatment, but must be done prior to administration of pre-medication or chemotherapy to exclude acute drug effects on tumor FDG uptake and

FDG biodistribution) and another FDG-PET/CT scan post-cycle 1 of chemotherapy (on days 19, 20, 21, or 22 before the start of chemotherapy cycle 2).

Participants in Group B will undergo a total of two FDG-PET/CT scans: one pre-chemotherapy and one post-cycle 1 of chemotherapy (on days 19, 20, 21, or 22 before the start of chemotherapy cycle 2). An ***optional*** third FDG-PET/CT may be completed for participants post-cycle 2 of chemotherapy (on days 19, 20, 21, or 22 before the start of chemotherapy cycle 3).

NOTE: Days are listed based on a 21-day chemotherapy cycle; assume first day of chemotherapy = day 1. Note also that if the beginnning of chemotherapy cycle 2 or cycle 3 is to be delayed (e.g., because of hematologic toxicity from the prior cycle), the FDG-PET/CT scan still must be obtained on day 19, 20, 21, or 22 of the prior cycle. Details of the acquisition and analysis of the FDG-PET/CT scans are described in Appendices VI and VII, and an overview is provided in Section 10.

Participants in Group C will undergo a total of two pre-chemotherapy FDG-PET/CT scans. The two pre-chemotherapy FDG-PET/CT scans will be performed at least 24 hours apart, but no longer than seven (7) days between scans. Subsequent treatment for NSCLC is not mandated for this trial group.

8.0.4 CT Scans

Volumetric CT. Within similar timeframes as each FDG-PET/CT study, participants will undergo a non-contrast chest CT scan according to specified parameters (Appendix VII) for tumor volumetry. This will ensure that research studies are performed at the same time point. For participants undergoing volumetric CT scanning, two (2) scans must be completed for for inclusion of these imaging data in the study analysis. In Groups A and C, the test-retest reproducibility of volumetric measurements will be determined only prior to treatment. Volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within the specified time frames between scans and prior to treatment initation. The site investigator and treating physicians will determine whether a participant will undergo the optional volumetric scans based upon the health of the participant and scheduling barriers. In Groups A and B, changes in tumor volume after one cycle of chemotherapy will be correlated with patient survival, best response according to RECIST, and time to progression. In Group B, the time course of metabolic changes post-cycles 1 and 2 of chemotherapy will be determined. **See Note above in Section 8.0.2 regarding performance and timing of baseline volumetric CT study if the FDG-PET/CT scan is completed prior to registration.**

Diagnostic CT. Diagnostic CT scans for response assessment using RECIST criteria will be collected if performed within 28 days prior to treatment initiation and otherwise will need to be repeated for Groups A and B only; diagnostic CTs will be performed every other cycle in Groups A and B, as part of standard clinical practice. These diagnostic CT scans will be performed on the PET/CT platform unless logistical or workflow issues prevent this, in which case, the diagnostic CT scans may be completed on dedicated CT platforms that meet the equipment requirements of this protocol. Guidelines for acquisition parameters for the diagnostic CT scans will be provided to ensure standardization (Appendix VII).

Contrast Media. Iodinated intravenous (IV) contrast media may be administered for diagnostic CT scans per standard of practice unless contraindicated. The decision not to use IV contrast for CT will be made at the discretion of the performing radiologist. If IV contrast is *not* administered for these scans, then these non-contrast CT series can be used for both RECIST and volumetric measurements by prospectively reconstructing the image data into both thick (2.5 to 5 mm) and thin-section (1 to 1.25 mm) series, respectively; this will alleviate the need for any additional research-related CT scans (specifically, those done for volumetrics only).

8.0.5 Timing Scenario Guidance for Test-Retest FDG-PET/CT and Optional Volumetric CT Scans (Groups A and C Only)

The following provides clarifying guidance and examples of possible timing scenarios to accommodate the test-retest scan requests for Groups A and C. They are not all inclusive, but provide some potential scenarios to aid in completion of the test-retest component of the trial. Note that all volumetric CT scans are optional. Two volumetric CT scans need to be completed for inclusion of these imaging data in the study analysis.

Guidance A: The test-retest FDG-PET/CT and volumetric CT scans do not need to be completed within the **same** 7-day window—there can be no more than 7 days between the FDG-PET/CT scans and no more than 7 days between the optional volumetric CT scans—but all do need to be completed within a 14-day timeframe prior to any cancer treatment.

Guidance B: If the participant is able, all four scans (two FDG-PET/CT scans within 7 days of each other and two volumetric CT scans within 7 days of each other—see NOTE below) can be completed on separate days.

Guidance C: If no treatment is planned for Group C, all scans still need to be completed within a 14-day timeline.

Guidance D—Example Timeline: In the event that a pre-registration scan is acceptable for the A1 or C1 FDG-PET/CT scan, the first volumetric CT scan can be completed the same day as the A2 or C2 FDG-PET/CT scan. The second volumetric CT scan could then be completed at any time within the following 7 days, still prior to any treatment initiation—or even the same day of treatment initiation as long as it is completed prior to treatment initiation.

8.0.6 Submission of Images to ACRIN

All imaging studies (research and standard of care) will be transmitted in digital form to the ACRIN Imaging Management Center for central analyses (Section 11.0 and Appendices VI and VII).

8.1 Registration Visit (≤ 28 Days Before the Start of Chemotherapy)

Once a patient has been identified to be eligible to participate in one of the three study groups:

- Obtain a signed informed consent form specific to the group to which the patient will be registered (see Appendix I);
- Confirm that the patient met all the eligibility criteria;
- Obtain a medical history;

- Review clinical laboratory tests completed within 4 weeks of registration to document that there are no contraindications to beginning the planned chemotherapy regimen (Groups A and B only; this measure is not necessary for Group C participants);
- Perform a physical examination if one has not been performed in the last 6 weeks per inclusion criteria;
- Perform a serum pregnancy test, if applicable;
- Obtain pathology reports to confirm the histopathologic diagnosis and stage of NSCLC;
- Confirm that participant is fit for the chemotherapy regimen (Groups A and B only);
- Collect CT scan for baseline RECIST (images for Groups A and B only and CT scan results for Group C; imaging per standard clinical practice—must have been completed within 28 days prior to treatment initiation);
- Register the study participant.

A copy of the report for each of the above studies, in addition to medical records verifying eligibility, needs to be maintained as source documents and filed in each participant's study chart.

8.2 Group A Participants

Participants in Group A will undergo two FDG-PET/CT scans for research purposes only (see Section 10.4 for details). Each FDG-PET/CT study includes a PET emission scan and a low-dose CT scan for attenuation correction. Participants in Group A also may undergo up to three optional volumetric CT scans of the chest beyond the standard of care for research purposes. At least two optional volumetric CT scans will need to be completed for inclusion of these imaging data in the study analysis.

8.2.1 Imaging Visit A1: Pre-Chemotherapy - ≤ 14 Days Before the Start of Chemotherapy and ≤ 7 Days Before Imaging Visit A2

Imaging Visit A1 will occur fourteen (14) days or fewer from start of chemotherapy, and 7 days or fewer before Visit A2 imaging. All A1 and A2 imaging must be completed prior to chemotherapy administration (Section 8.8). The volumetric CT images are optional but strongly encouraged. Each participant will undergo FDG-PET/CT and CT scans, as described in Appendices VI and VII, using the same scanner at each study visit.

- Perform serum glucose test prior to administration of FDG*;
- Perform optional pre-chemotherapy, non-contrast CT scan for tumor volumetry*;
- Perform pre-chemotherapy FDG-PET/CT scan.*

If RECIST CT needs to be repeated on Imaging Visit A1 (only necessary if no diagnostic CT is available within 28 days prior to treatment), then the FDG-PET/CT scan, the RECIST CT scan, and the CT scan for tumor volumetry can be performed in any order. However, if the RECIST CT scan is performed before either the FDG-PET emission scan or the volumetric CT scan, the acquisition of these studies must be delayed for at least 30 minutes after IV contrast agent administration.

***NOTE:** The first FDG-PET/CT scan may be completed prior to registration; please see Note in Section 8.0 for specific guidelines and instructions. In addition, if the first FDG-PET/CT scan is completed prior to registration, participants may need to undergo the optional volumetric CT scans per the protocol guidelines after consent and registration to the trial is complete. Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be

completed within specified time frames between scans and in relation to treatment. Please refer to Section 8.0.5 for timing guidance and Section 8.9 for the study procedure calendar.

See Section 8.0.2 regarding minimum acceptable tumor FDG uptake necessary for participant to continue on study.

8.2.2 Imaging Visit A2: Pre-Chemotherapy - ≤ 7 Days Before the Start of Chemotherapy Cycle 1 and ≥ 24 Hours After Visit A1 Scan

Imaging Visit A2 will occur seven (7) days or fewer before the start of chemotherapy, and at least 24 hours after the Visit A1 FDG-PET/CT scan, but before the participant has received any chemotherapy. The volumetric CT scans are considered optional, but are strongly encouraged. The scans can be done on the same day of administration of chemotherapy (but must be done prior to administration of pre-medication or chemotherapy to exclude acute drug effects on tumor FDG uptake and FDG biodistribution).

Each participant will undergo FDG-PET/CT and CT scans, as described in Appendices VI and VII, using the same scanner as his/her Visit A1 scan(s).

- Perform serum glucose test prior to administration of FDG;
- Perform optional pre-chemotherapy, non-contrast CT scan for tumor volumetry*;
- Perform pre-chemotherapy FDG-PET/CT scan*;
- Assess for any adverse events since Imaging Visit A1.

*** NOTE:** Optional test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. See Section 8.0.5 for timing guidance.

NOTE: Group A participants who do not complete the test-retest pre-treatment FDG-PET/CT imaging requirements can be considered for Group B participation (which would require new consent for this group, enrollment in this arm, and a note to file). This is an acceptable protocol variation. However, to ensure the 57-participant sample size, an additional participant would need to be accrued to Group A or C.

8.2.3 Imaging Visit A3: Post-Cycle 1 of Chemotherapy - On Days 19, 20, 21, or 22 (Before the Start of Chemotherapy Cycle 2) When the First Day of Chemotherapy = Day 1 of 21-Day Cycle

Imaging Visit A3 will occur after the first chemotherapy cycle, on days 19, 20, 21, or 22 (of 21-day cycle) before the start of chemotherapy cycle 2. Each participant will undergo FDG-PET/CT and CT scans, as described in Appendices VI and VII, using the same scanner as his/her Visit A1 and A2 scan(s).

- Perform serum glucose test prior to administration of FDG;
- Perform optional post-cycle 1 of chemotherapy, non-contrast CT scan for tumor volumetry;
- Perform post-cycle 1 of chemotherapy FDG-PET/CT scan;
- Assess for any adverse event since Imaging Visit A2.

8.3 Group B Participants

In Group B, participants will undergo two FDG-PET/CT studies for research purposes (see Section 10.4 for details). In addition participants will undergo up to three optional CT scans of the chest for measurement of tumor volume. Two (2) optional volumetric CT scans will need to be completed for inclusion of these imaging data in the study analysis. At least one (1) of these optional volumetric CT scans must be obtained before treatment. Thus the maximum number of research scans and the maximum effective dose will be identical to Group A.

8.3.1 Imaging Visit B1: Pre-Chemotherapy - ≤ 7 Days Before the Start of Chemotherapy Cycle 1

Imaging Visit B1 will occur seven (7) days or fewer prior to the start of chemotherapy cycle 1 (same as Imaging Visit A2 for Group A). Each participant will undergo FDG-PET/CT and CT scans, as described in Appendices VI and VII, using the same scanner for each visit.

- Perform serum glucose test prior to administration of FDG*;
- Perform optional pre-chemotherapy, non-contrast CT scan for tumor volumetry*;
- Perform pre-chemotherapy, FDG-PET/CT scan*.

If RECIST CT needs to be repeated on Imaging Visit B1 (only necessary if no diagnostic CT is available within 28 days prior to treatment), then the FDG-PET/CT scan, the RECIST CT scan, and the CT scan for tumor volumetry can be performed in any order. However, if the RECIST CT scan is performed before either the FDG-PET emission scan or the volumetric CT scan, the acquisition of these studies must be delayed for at least 30 minutes after IV contrast agent administration.

***NOTE:** The first FDG-PET/CT scan may be completed prior to registration; please see Note in Section 8.0 for specific guidelines and instructions. In addition, if the first FDG-PET/CT scan is completed prior to registration, participants may still need to undergo the optional volumetric CT scans per the protocol guidelines after consent and registration to the trial is complete. Please refer to Section 8.9 for the study procedure calendar.

See Section 8.0.2 regarding minimum acceptable tumor FDG uptake necessary for participant to continue on study.

8.3.2 Imaging Visit B2: Post-Cycle 1 of Chemotherapy - On Days 19, 20, 21, or 22 (Before the Start of Chemotherapy Cycle 2) When the First Day of Chemotherapy = Day 1 of 21-Day Cycle

Imaging Visit B2 will occur after the first chemotherapy cycle, on days 19, 20, 21, or 22 of 21-day chemotherapy cycle (day 1 = start of chemotherapy) and before the start of chemotherapy cycle 2 (same as Imaging Visit A3 for Group A). Each participant will undergo FDG-PET/CT and CT scans, as described in Appendices VI and VII, using the same scanner as his/her Visit B1 scan(s).

- Perform serum glucose test prior to administration of FDG;
- Perform optional post-cycle 1 of chemotherapy, non-contrast CT scan for tumor volumetry;

- Perform post-cycle 1 of chemotherapy, FDG-PET/CT scan;
- Assess for any adverse events since Imaging Visit B1.

8.3.3 OPTIONAL Imaging Visit B3: Post-Cycle 2 of Chemotherapy - On Days 19, 20, 21, or 22 (Before the Start of Chemotherapy Cycle 3) When the First Day of Chemotherapy = Day 1 of 21-Day Cycle

Optional Imaging Visit B3 will occur after the second chemotherapy cycle, on days 19, 20, 21, or 22 of 21-day chemotherapy cycle (day 1 = start of chemotherapy) and before the start of chemotherapy cycle 3. Participants will undergo FDG-PET/CT and CT scans, as described in Appendices VI and VII, using the same scanner as his/her Visit B1 and B2 scan(s).

- Perform serum glucose test prior to administration of FDG;
- Perform optional post-cycle 2 of chemotherapy, non-contrast CT scan for tumor volumetry;
- Perform post-chemotherapy cycle 2 FDG-PET/CT scan;
- Perform CT scan for RECIST (standard clinical practice);
- Assess for any adverse events since Imaging Visit B2.

8.4 Participant Follow-up Visits (Both Groups A and B)

All participants will be treated and followed clinically per the institution's standard of care or per the recommendations of the participant's treating physician.

- Perform diagnostic follow-up imaging visits per the institution's standard of care at every 6 weeks (i.e. every other chemotherapy cycle) from the baseline CT scan performed for RECIST for a maximum of 18 weeks or until participant shows progression.

  NOTE: ACRIN will collect the diagnostic images for a maximum of 18 weeks or until the participant shows progression, at which point the secondary endpoint of progression-free survival has been reached.

- Contact the participant's treating physician every three months (at a minimum) after post-cycle 2 of chemotherapy for one year or until death for information pertaining to disease progression and vital status.

  NOTE: All participants will be followed for one year or until death, whichever occurs first, in order to determine progression and the primary endpoint of one-year overall survival. A copy of the source documents should be filed in the participants' study chart.

8.5 Group C Participants

Participants in Group C will undergo two FDG-PET/CT scans, the first obtained per standard of care and the second for research purposes only. Each FDG-PET/CT study includes a PET emission scan and a low-dose CT scan for attenuation correction. Participants in Group C also may undergo two optional—but strongly encouraged—volumetric CT scans of the chest beyond the standard of care for research purposes.

8.5.1 Imaging Visit C1: Pre-Treatment

Imaging Visit C1 will occur 7 days or fewer before Visit C2 imaging. All C1 or C2 imaging must be completed prior to treatment. Each participant will undergo FDG-

PET/CT scans and may undergo optional volumetric CT scans (strongly encouraged), as described in Appendices VI and VII, using the same scanner at each study visit.

- Perform serum glucose test prior to administration of FDG*;
- Perform optional pre-treatment, non-contrast CT scan for tumor volumetry*;
- Perform pre-treatment FDG-PET/CT scan.*

***NOTE:** The first FDG-PET/CT scan may be completed prior to registration; please see Note in Section 8.0 for specific guidelines and instructions. In addition, if the first FDG-PET/CT scan is completed prior to registration, participants may need to undergo the optional volumetric CT scans per the protocol guidelines after consent and registration to the trial is complete. Both optional volumetric CT scans will need to be completed for inclusion of these imaging data in the study analysis. Optional test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. See Section 8.0.5 for timing guidance. Please refer to Section 8.9 for the study procedure calendar.

8.5.2 Imaging Visit C2: Pre-Treatment — ≥ 24 Hours After Visit C1 Scan and No More Than 7 Days Between Scans

Imaging Visit C2 will occur at least 24 hours but no more than seven (7) days after the Visit C1 FDG-PET/CT scan, before the participant has received any treatment. The scan can be done on the same day of start of treatment (but must be done prior to administration of pre-medication, chemotherapy, or radiotherapy to exclude acute effects on tumor FDG uptake and FDG biodistribution).

Each participant will undergo FDG-PET/CT scans and may undergo optional volumetric CT scans (strongly encouraged), as described in Appendices VI and VII, using the same scanner as his/her Visit C1 scan(s).

- Perform serum glucose test prior to administration of FDG;
- Perform optional pre-treatment, non-contrast CT scan for tumor volumetry*;
- Perform pre-treatment FDG-PET/CT scan*;
- Assess for any adverse events since Imaging Visit C1.

NOTE: If a clinical diagnostic CT scan is performed on the same day as the FDG-PET/CT scan or the CT scan for tumor volumetry, the acquisition of the latter studies must be delayed for at least 30 minutes after IV contrast agent administration.

*** NOTE:** Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. See Section 8.0.5 for timing guidance. Both optional volumetric CT scans will need to be completed for inclusion of these imaging data in the study analysis.

8.6 Off-Study Criteria

Participants will go off-study for the reasons identified below and will need to be replaced with other eligible participants. Participants going off-study will not undergo any additional FDG-PET/CT scan or CT scan for tumor volumetric imaging nor will the study follow-up visits continue. An End of Study Form should be submitted to the ACRIN DMC.

8.6.1 The baseline SUV of the tumor (measured at the first PET/CT study) is less than 4.0. In this case, relative changes by 25% cannot be reliably measured in individual participants (Section 8.0.2). The frequency of participants with low baseline FDG uptake will be recorded.

8.6.2 There are significant protocol variations or image artifacts, as described on the Checklist for PET/CT Image Quality (Appendix VI), which result in an unrepeatable and inadequate PET/CT exam.

8.6.3 If a participant in Group A or C does not undergo both test-retest FDG-PET/CT imaging requirements, an additional participant will need to be recruited for either Group A or C to ensure the 57-participant sample size for the FDG-PET/CT component; imaging will continue as scheduled for the Group A participant or the participant can be enrolled in Group B (see Note in Sections 4.0 and 8.2.2).

8.6.4 Participant undergoes the baseline pre-chemotherapy/treatment FDG-PET/CT scan(s) after the initiation of chemotherapy.

8.6.5 Participant undergoes the post-chemotherapy cycle 1 FDG-PET/CT scan after initiation of chemotherapy cycle 2 (for Groups A and B only).

8.6.6 Participant refuses the FDG-PET/CT scan(s) at the study Imaging Visits and/or refuses study follow-up visits.

8.7 Off-Protocol Imaging Criteria

Participants will be taken off-protocol imaging (will not undergo any additional FDG-PET/CT scan[s] or CT tumor volumetric scan[s]) for the reasons identified below, but we will continue to collect survival data for these participants as itemized below. These participants will remain on-study.

- Groups A and B Only: Participants who receive less than 2 cycles of first-line chemotherapy. These participants will go off-imaging, and will not undergo any additional FDG-PET/CT studies. For these participants, overall survival will be determined and correlated with changes in tumor FDG uptake from the baseline FDG-PET/CT scan compared to FDG-PET/CT scan completed after one cycle of chemotherapy.
- Groups A and B Only: Participants are expected to have diagnostic follow-up imaging visits every 6 weeks from initiation of chemotherapy (i.e. every other chemotherapy cycle) for a maximum of 18 weeks, however, the participant will go off-protocol imaging if the participant shows progression, at which point, the secondary endpoint of progression-free survival has been reached.
- All Groups: Participants experience any serious adverse events related to the investigational component of the trial. These participants will go off-protocol imaging (no additional study imaging will be performed) but will be followed for progression and one-year survival.

8.8 Chemotherapy Regimens (Groups A and B Only)

8.8.1 Selection of Chemotherapy Regimens

8.8.1.1 Background

Several treatment regimens are currently considered as "standard of care" for patients with advanced NSCLC (58). All these regimens are characterized by a similar response rate and randomized studies have not shown that any of these regimens provides a significant survival benefit (61). Median survival across the cohorts ranged from a minimum of 6.7 months to a

maximum of 12.3 months, with the majority of median survivorship between 8 and 10 months. Response rates ranged from 12% to 42%, with more than half of rates concentrated between 25% and 35% (59). Newer data show similar efficacy among third-generation non-platinum-based regimens (60–62); including these alternative therapies in the trial cohort will make the data more generalizable to current care.

Therefore, we are not planning to restrict the study to one chemotherapy regimen, but will include participants scheduled to undergo a variety of frequently used chemotherapy regimens as specified below.

Although all these treatment regimens are characterized by similar response rates and survival data, one potential concern is that individual chemotherapeutic drugs may affect tumor metabolism in a different way. Therefore, including participants undergoing different chemotherapy regimens could potentially confound the correlation between changes in tumor metabolism and patient survival. On the other hand, since a variety of regimens are in common use clinically, inclusion of newer options—non-platinum-based doublets in particular—will allow us to obtain results more generalizable to current clinical practice. All clinical FDG-PET studies published so far universally indicate that the decrease in the FDG signal is a measure for the loss of viable tumor cells (63, 64). *In-vitro* studies have indicated that during the first hours after drug administration some chemotherapeutic drugs have specific acute effects on tumor metabolism, including a temporary increase in cellular FDG uptake. In the present study, however, the earliest follow-up PET study will be performed 3 weeks after start of chemotherapy. Considering the data published in the literature, it appears very unlikely that at this point in time drug-specific effects are still predominant (63 , 64).

8.8.1.2 Treatment Regimens Studied in the ACRIN 6678

In order to reduce the number of confounding factors, the study is limited to **cytotoxic chemotherapy regimens administered at 3 week cycles, which can be combined with bevacizumab or cetuximab, in Groups A and B; Group C can be scheduled for any therapeutic regimen.** Most of the published studies on treatment monitoring with FDG-PET have been performed in patients undergoing platinum-based chemotherapy. We have previously studied changes in FDG uptake after one cycle of chemotherapy in patients with advanced NSCLC treated with platinum-based chemotherapy. Thirty-one (31) patients received carboplatin in combination with paclitaxel, whereas 26 patients were treated with cisplatin in combination with vinorelbine (n=22) or other chemotherapeutic agents (n=4). In that study, a metabolic response in FDG-PET was defined as 20% decrease in tumor FDG uptake (5). There were no significant differences in relative changes in tumor FDG uptake for patients receiving cisplatin or carboplatin based regimens ($p>0.2$). In the whole group of patients (n=57), a metabolic response was highly significantly correlated with patient survival ($p=0.005$). This correlation remained significant when patients were stratified by chemotherapy regimens (cisplatin or carboplatin based, $p=0.004$). One year survival rates of metabolic responders treated with cisplatin and carboplatin were 53% and 40% respectively. Median survival of metabolic non-responders treated with cisplatin or carboplatin were 9% and 11%, respectively. Thus, these data suggest that, in patients with advanced NSCLC treated with platinum-based chemotherapy, the accuracy of FDG-PET for prediction of patient survival is independent of the individual chemotherapy regimen.

Some chemotherapy regimens used in advanced NSCLC are administered at 4 week cycles. However, these are not commonly used and we do not expect that exclusion of these treatment regimens will significantly affect participant recruitment. These treatment regimens include, but

are not limited to: paclitaxel/carboplatin, vinorelbine/cisplatin, docetaxel/cisplatin, docetaxel/carboplatin, gemcitabine/cisplatin, gemcitabine/carboplatin.

Patients treated with chemotherapy in combination with bevacizumab or cetuximab will be included in the study. Although the experience in using FDG-PET in patients treated with bevacizumab is limited (98, 99), current evidence suggests that bevacizumab therapy also causes significant changes in tumor metabolism within 3 weeks after start of therapy (69). Since bevacizumab has become generally accepted as the standard of care for treatment of advanced NSCLC, the protocol will allow inclusion of patients treated with bevacizumab. Excluding these patients could potentially bias the results of the study, because patients treated with bevacizumab are on average characterized by a better performance status and have fewer comorbidities than patients who do not receive bevacizumab.

8.8.2 Monitoring for Drug Toxicity Per Institutional Standard of Care

Drug toxicity will be monitored according to the routine clinical standards of the referring oncologist. The results of these studies should be maintained as source documents. All these studies will be repeated before every chemotherapy cycle per standard of care.

8.8.3 Duration of Chemotherapy

In order to remain eligible for the study, participants generally need to undergo at least 2 cycles of first-line chemotherapy. Participants who cannot tolerate a second chemotherapy cycle due to drug toxicity or who decline further treatment with the first-line chemotherapy regimen after the first cycle will be excluded from the analysis of the primary endpoint. Participants who progress after the first cycle will not be excluded. These participants will not undergo additional PET/CT studies, but overall survival will be determined and correlated with changes in tumor FDG uptake from the baseline to the first follow-up PET/CT study.

8.9 Overview of the Study Procedures

8.9.1 GROUP A: Two (2) FDG-PET/CT scans with two (2) optional CT tumor volumetry scan(s) prior to chemotherapy cycle 1; one (1) FDG-PET/CT scan with one (1) optional CT tumor volumetry after the first chemotherapy cycle; follow-up CT scans per standard of care.

STUDY PROCEDURES	REGISTRATION VISIT	IMAGING VISIT A1: Pre-Chemo	IMAGING VISIT A2: Pre-Chemo Cycle 1	IMAGING VISIT A3: Post-Chemo Cycle 1	FOLLOW-UP DIAGNOSTIC IMAGING	FOLLOW-UP
Time Frames	≤ 28 days before start of chemotherapy	≤ 14 days before start of chemotherapy	≤ 7 days before start of chemotherapy and 1 to 7 days between A1 and A2 scans	Days 19, 20, 21, or 22[7] of 21-day chemotherapy cycle where day 1 = start of chemotherapy	Every 6 weeks from initiation of chemotherapy for maximum of 18 weeks	Every 3 months for 1 year or until death whichever occurs first
Signed Informed Consent Form	X					
Confirmation of Eligibility	X					
Medical History, including Lab results	X					
Physical Examination	X					
Confirmation of Diagnosis[1]	X					
Registration	X					
Serum Pregnancy Test	X					
Serum Glucose[2]		X	X	X		
FDG-PET/CT[3]		X[5] (Standard of Care)	X (Research)	X (Research)		
Non-Contrast CT Tumor Volumetry[3]		X[6] (Research-Optional)	X[6] (Research-Optional)	X[8] (Research-Optional)		
Diagnostic CT (RECIST)	X (Standard of Care)				X (Standard of Care)	
Clinical Assessment[4]						X
Adverse Event Assessment		X	X	X	X	

[1]Confirmation by histopathologic diagnosis.

[2]Prior to each FDG administration.

[3]At a minimum, two optional volumetric CT scans must be completed for inclusion of these imaging data in the study analysis. Test-retest FDG-PET/CT and volumetric CT scans do not need to be completed on the same days, but do need to be completed within the specified time frame between scans and prior to treatment initiation. See Section 8.0.5 for timing guidance.

[4]Contact with the oncologist treating the participant to determine progression and the primary endpoint of one-year overall survival.

[5]Note: The first FDG-PET/CT scan may be completed prior to registration if: a) the PET/CT scanner has been qualified for the 6678 protocol; b) all parameters and scanning techniques are completed per protocol guidelines; and c) all subsequent PET/CT scans are performed on the same scanner or the same scanner model. Please note that the PET scan must include serum glucose testing prior to scanning and the timing and scheduling of the scan must fall within protocol guidelines.

[6] For Group A, the first optional volumetric CT must be completed within 14 days before treatment starts, and the second optional volumetric CT scan within 7 days before treatment starts.

[7] Day 22 is defined as day 1 of the next chemotherapy cycle immediately prior to administration of pre-medication and chemotherapy in the next cycle.

[8] The optional volumetric CT scan on Imaging Visit A3 should only be performed if at least one optional volumetric CT scan was obtained on Imaging Visit A1 or A2.

8.9.2 GROUP B: One (1) FDG-PET/CT scan with optional CT tumor volumetry prior to chemotherapy cycle 1; one (1) FDG-PET/CT scan with optional CT tumor volumetry after the first chemotherapy cycle; and one (1) optional FDG-PET/CT scan with optional CT tumor volumetry after the second chemotherapy cycle; diagnostic follow-up CT scans per standard of care.

STUDY PROCEDURES	REGISTRATION VISIT	IMAGING VISIT B1: Pre-Chemo	IMAGING VISIT B2: Post-Chemo Cycle 1	*OPTIONAL* IMAGING VISIT B3: Post-Chemo Cycle 2	FOLLOW-UP DIAGNOSTIC IMAGING	FOLLOW-UP
Time Frames	≤ 28 days before start of chemotherapy	≤ 7 days before start of chemotherapy	Days 19, 20, 21, or 22[5] of 21-day chemotherapy cycle where day 1 = start of chemotherapy	Days 19, 20, 21, or 22[6] of 21-day chemotherapy cycle where day 1 = start of chemotherapy	Every 6 weeks from initiation of chemotherapy for maximum of 18 weeks	Every 3 months for 1 year or until death whichever occurs first
Signed Informed Consent Form	X					
Confirmation of Eligibility	X					
Medical History, including Lab results	X					
Physical Examination	X					
Confirmation of Diagnosis[1]	X					
Registration	X					
Serum Pregnancy Test	X					
Serum Glucose[2]		X	X	X		
FDG-PET/CT		X[4] (Standard of Care)	X (Research)	X (Research-Optional)		
Non-Contrast CT Tumor Volumetry[5]		X (Research-Optional)	X[7] (Research-Optional)	X[7] (Research-Optional)		
Diagnostic CT (RECIST)	X (Standard of Care)			X (Standard of Care)	X (Standard of Care)	
Clinical Assessment[3]						X
Adverse Event Assessment		X	X	X	X	

[1]Confirmation by histopathologic diagnosis.

[2] Prior to each FDG administration.

[3]Contact with the oncologist treating the participant to determine progression and the primary endpoint of one-year overall survival.

[4] Note: The first FDG-PET/CT scan may be completed prior to registration if: a) the PET/CT scanner has been qualified for the 6678 protocol; b) all parameters and scanning techniques are completed per protocol guidelines; and c) all subsequent PET/CT scans are performed on the same scanner or the same scanner model. Please note that the PET scan must include serum glucose testing prior to scanning and the timing and scheduling of the scan must fall within protocol guidelines.

[5] For Group B, the first optional volumetric CT must be completed within 7 days before treatment starts. At a minimum, two optional volumetric CT scans must be completed for inclusion of these imaging data in the study analysis.

[6] Day 22 is defined as day 1 of the next chemotherapy cycle immediately prior to administration of pre-medication and chemotherapy in the next cycle.

[7] The optional volumetric CT scan on Imaging Visits B2 or B3 should only be completed if the Imaging Visit B1 scan has been completed prior to therapy initiation. The Imaging Visit B3 optional volumetric CT scan should be completed only if the optional FDG-PET/CT for that same visit also is completed.

8.9.3 GROUP C: Two (2) mandatory FDG-PET/CT scans with two (2) optional CT tumor volumetry prior to start of treatment (at least 24 hours between scans).

STUDY PROCEDURES	REGISTRATION VISIT	IMAGING VISIT C1: Pre-Treatment	IMAGING VISIT C2: Pre-Treatment
Time Frames	Before start of treatment	Before start of treatment	≥ 24 hours after C1 scans, but no more than 7 days later (before start of treatment)
Signed Informed Consent Form	X		
Confirmation of Eligibility	X		
Medical History	X		
Physical Examination	X		
Confirmation of Diagnosis[1]	X		
Registration	X		
Serum Pregnancy Test	X		
Collection of Diagnostic CT Results[2]	X (Standard of Care)		
Serum Glucose[3]		X	X
FDG-PET/CT[4]		X[5] (Standard of Care)	X (Research)
Non-Contrast CT Tumor Volumetry[4]		X[6] (Research-Optional)	X[6] (Research-Optional)
Clinical Assessment			
Adverse Event Assessment		X	X

[1]Confirmation by histopathologic diagnosis.

[2] Baseline diagnostic CT scan results will need to be confirmed at registration.

[3] Prior to each FDG administration.

[4] Test-retest FDG-PET/CT and volumetric CT scans do not need to be completed on the same days, but do need to be completed within the specified time frame between scans and prior to treatment initiation, if applicable. See Section 8.0.5 for timing guidance.

[5] NOTE: The first FDG-PET/CT scan may be completed prior to registration if: a) the PET/CT scanner has been qualified for the 6678 protocol; b) all parameters and scanning techniques are completed per protocol guidelines; and c) all subsequent PET/CT scans are performed on the same scanner or the same scanner model. Please note that the PET scan must include serum glucose testing prior to scanning and the timing and scheduling of the scan must fall within protocol guidelines.

[6] At minimum, two optional volumetric CT scans must be completed for inclusion of these imaging data in the study analysis. For Group C participants agreeing to undergo optional volumetric CT scans, the first volumetric CT (Imaging Visit C1) must be completed at least 24 hours before the second (Imaging Visit C2), but no more than 7 days between scans.

9.0 DATA COLLECTION AND MANAGEMENT

9.1 General

9.1.1 The ACRIN web address is **www.acrin.org.**

9.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at the Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at ACRIN in Philadelphia, PA.

9.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case-specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the DMC before attempting a re-registration.

9.2 Clinical Data Submission

9.2.1 Upon successful participant registration, a confirmation e-mail containing the registration and case-specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant-specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN web site. The research associate (RA) may use the calendar as a case management tool for data submission and follow-up scheduling.

9.2.2 The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as open/alive or until the study is terminated. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.

9.2.3 To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, data that are out of range, and data that are in the wrong format (e.g. character data in a field requiring numeric

responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form Submission" button is depressed.

9.2.4 Once data entry of a form is complete, and the summary form reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form Submission" button on the form summary screen and the data are transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or RA listing all of the data completed and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or RA should contact the DMC for resolution of the submission.

9.2.5 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, ACRIN can serve as an ISP.

9.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

9.4 Electronic Data Management

9.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Brown BC and the DMC. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC. The validation program generated by BC produces a log of errors, which is sent to the DMC for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC for resolution. All BDMC communication with the participating sites is normally done through the DMC.

9.4.2 If checks at DMC or BC detect missing or problematic data, the DMC sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC updates the participant's data submission calendar with the due date for the site RA or investigator's response.

9.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as-needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool.

9.6 Data Quality Assurance

9.6.1 The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the DMC. The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

9.6.2 A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the BDMC will apprise ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance (PDRC) department, until the problem has been resolved. If the BDMC, along with the PDRC, cannot find a resolution to the problem, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

9.6.3 In addition, the ACRIN QA Monitor will review case report forms and source documents at several different time points: after the first few participants are enrolled and during the conduct of the trial, including in the event of staff changes at the participating sites. In addition, the QA Monitor will review the initial and annual regulatory documents and any revised regulatory documents. This monitoring process ensures protocol and regulatory compliance, participant's welfare and safety, and provides resources to sites for clarification to the protocol and guidance in completion of the case report forms.

10.0 IMAGING PROTOCOL: PET AND CT SCANS

10.1 Overview of PET and CT Data Acquisition

Acquisition protocols of the PET and CT studies are described in Appendices VI and VII, respectively. Study participants will undergo a static whole body PET/CT study sixty (60) minutes after injection of FDG. Photon attenuation will be corrected by a low-dose CT scan. In addition to this scan used for attenuation correction only (acquired during shallow breathing), participants will be asked to undergo optional CT scans of the chest in full inspiration for measurement of tumor volume.

As part of their clinical care, participants will undergo CT imaging for assessment of tumor response according to RECIST. Guidelines for acquisition parameters for these diagnostic CT studies are provided in Appendix VII.

10.2 Image Interpretation

10.2.1 Blinding

Investigators measuring tumor FDG uptake will be blinded to patient outcome, namely tumor shrinkage and patient survival. Treating physicians will be blinded to the results of the FDG-PET/CT done after cycle 1. In order to ensure that treating physicians are blinded, sites will need to take appropriate measures to prevent these digital images from being accessible in their institution's PACS system. A full written report of the results of CT should also not be made available to the treating physicians, but a limited report indicating there were no life threatening or serious changes may be made available after chemotherapy cycle 1. For ethical reasons, it is not possible to blind the treating physicians also to the results of the later PET and CT studies, since this represents a routine time point for response assessment.

10.2.2 Analysis of FDG-PET/CT Scans

FDG uptake of the primary tumor will be quantified by SUVs, normalized to the body weight of the participant. In a subgroup of participants, the primary tumor may be small (< 2 cm) and show only low FDG uptake in PET due to partial volume effects or it may have been resected in participants with recurrent NSCLC. In this case, the metastatic lesion with the highest FDG uptake will be used for analysis. Regions of interest for measuring tumor FDG uptake will be defined as previously described in patients with advanced NSCLC and other tumor types (27). Briefly, "peak" tumor SUV will be determined by placing small regions of interest in the area of tumor with highest FDG uptake in three consecutive axial slices and calculating the average SUV in this volume. All data analysis of the FDG-PET/CT scans will be performed blinded at the ACRIN Image Management Center. Details of the data analysis are described in Appendix VI.

For quality control purposes, a local read of the FDG-PET/CT scans will also be performed (see Appendix VI). This read will include SUV measurements for the primary tumor and normal liver. However, only the results of the central read will be used for correlation with the primary or secondary endpoints and for further statistical analysis.

10.2.3 Measurement of Tumor Volume

As part of exploratory analyses, optional CT scans will be acquired in full inspiration according to a standardized protocol to enable assessment of change in volume of the

primary tumor as a predictor of therapeutic response. Details of these optional CT scans and their analysis are described in Appendix VII.

10.2.4 Response Assessment According to RECIST

Appendix VII provides guidelines for acquisition and reconstruction parameters for the CT scans used to assess tumor response according to RECIST. Images will be transferred in digital form to ACRIN for blinded reading and response classification.

Local assessment of tumor response will be used to guide patient management. This local assessment of tumor response will be recorded. However, only the central blinded read of the CT scans will be correlated with metabolic changes in FDG-PET/CT (secondary endpoint one).

10.3 FDA Preliminary Public Health Notification for CT Scans

As of July 14, 2008, the FDA has released a preliminary public health notification to health professionals regarding possible malfunction of electronic medical devices caused by CT scanning. Please refer to the FDA website for the notification (http://www.fda.gov/cdrh/safety/071408-ctscanning.html) and to Section 12.5.3 for adverse event reporting requirements.

10.4 Radiation Dose to the Participant

Participants will be injected with 370-740 MBq of FDG (10-20 mCi) for each research PET scan. The exact amount of FDG injected depends on the characteristics of the PET/CT system used and will be adjusted by the participating sites. According to ICRP Report 80, a typical dose of 15 mCi results in an effective dose of 10.6 mSv (1.06 rem) per PET scan. The critical organ is the bladder, which according to ICRP Report 80 receives a radiation dose of 90 mSv (9 rem). However, several studies have demonstrated that the radiation dose to the bladder can be reduced by approximately 50% if participants void after completion of the PET study (99–103). The effective dose of a whole-body low-dose CT for attenuation correction of the PET data is in the range of 3 mSv (0.3 rem) (104). The effective dose due to the diagnostic CT scan of the chest for measurements of tumor volume is in the range of 6 mSv (0.6 rem) (105). The critical organ are the lungs, which will receive a radiation dose of approximately 15 mSv (1.5 rem) (105). These figures compare with the annual background radiation in the US, which is approximately 3.6 mSv (0.36 rem). It can also be compared to the annual amount of radiation allowed for a radiation worker, such as a CT technologist or radiologist, which equals 50 mSv (5 rem) per year.

Participants in Group A will undergo two FDG-PET/CT scans for research purposes only. Each FDG-PET/CT study includes a PET emission scan and a low-dose CT scan for attenuation correction. In Group A, these FDG-PET/CT scans are the second scan prior to initiation of therapy (for assessment of the test-retest reproducibility) and the scan post-cycle 1 of chemotherapy (early metabolic response). Participants in Group A will undergo up to three volumetric CT scans of the chest beyond the standard of care for research purposes. (All volumetric CT scans are optional, but strongly encouraged.) At minimum, two optional volumetric CT scans must be completed for inclusion of the imaging data in the study analysis. Unless the diagnostic pre-chemotherapy FDG-PET/CT scan has been conducted prior to registration, these optional volumetric CT scans will be performed at the same time as the FDG-PET/CT studies, i.e., two studies pre-chemotherapy cycle 1 and one study post-chemotherapy cycle 1.

In Group B, participants will undergo a maximum of two FDG-PET/CT studies for research purposes. These include the scan post-cycle 1 of chemotherapy for assessment of the early metabolic response to chemotherapy and an optional scan post-cycle 2 of chemotherapy to study the time course of metabolic

changes. In addition, participants will undergo up to three optional volumetric CT scans of the chest beyond the standard of care for research purposes. At minimum, two optional volumetric CT scans must be completed for inclusion of the imaging data in the study analysis; at least one of these two scans must be performed prior to initiation of chemotherapy. Unless the diagnostic pre-chemotherapy FDG-PET/CT scan has been conducted prior to registration, these optional scans are performed at the same time as the FDG-PET/CT studies, i.e. pre-chemotherapy, post-chemotherapy cycle 1, and post-chemotherapy cycle 2. Thus the maximum number of research scans and the maximum effective dose will be identical to those in Group A.

In Group C, participants will undergo one FDG-PET/CT scans per standard of care and one for research purposes only. Each FDG-PET/CT study includes a PET emission scan and a low-dose CT scan for attenuation correction. In Group C, these FDG-PET/CT scans are for assessment of test-retest reproducibility, both conducted prior to any chemotherapy, if such treatment is scheduled. Participants in Group C also may undergo two volumetric CT scans of the chest beyond the standard of case for research purposes; these volumetric CT scans are optional, but strongly encouraged.

Additionally, note that if the baseline FDG-PET/CT scan obtained clinically before participant consent and registration does meet the technical parameters required for this protocol, this can be repeated as a research-related examination. The radiation exposure in such a case will be further increased (since the participant will have three research-related FDG-PET/CT scans).

11.0 IMAGE SUBMISSION

The protocol required images must be in DICOM format on CD/DVD-ROM or submitted via the internet using secure File Transfer Protocol (sFTP), and transmitted along with an Imaging Transmittal Worksheet (ITW) which can be found on the ACRIN 6678 web site (www.acrin.org/6678_protocol.aspx). The required images must be submitted to ACRIN Imaging Core Lab. ACRIN can provide electronic image submission and anonymization utilities for participating institutions via TRIAD software. For support in sending the images via the internet using TRIAD, contact the representatives of the Image Management Center via email at Triad-Support@acr-arrs.org or via phone: 215-940-8820.

11.1 If required and part of the protocol, images maintained at ACRIN Headquarters Image Archive may be distributed to other participating sites, using sFTP, or CD-ROM where appropriate, for purposes of secondary review.

11.1.1 Removal of Confidential Participant Information: The header record on DICOM formatted image data, which often contains information identifying the participant by name, MUST be scrubbed before the data are transferred. This involves replacing the Participant Name tag with the ACRIN Institution ID or number, replacing Participant ID tag with the ACRIN case number and putting the study number into the Other Participant ID tag.

11.1.2 sFTP Transfer: Digitally generated image files in DICOM v3.0 format can be transmitted to the ACRIN Image Management Center via sFTP directly to the image archive. This can be performed using a customized software program or by using TRIAD software available from ACRIN. An ITW must be faxed at the time images are transmitted. Contact Image Management Center for additional details at Triad-Support@acr-arrs.org

11.1.3 Please fax the ITW to:

ACRIN Core Lab ATTN: 6678 Imaging Specialist at (215) 923-1737

11.1.4 In the event that the transfer of scrubbed image headers is not available, images may also be sent on a CD/DVD-ROM to the ACRIN Image Management Center for transfer to the image archive. Please contact ACRIN prior to sending the media to confirm compatibility.

11.1.5 Mail Images and the ITW to:

American College of Radiology Imaging Network
MR/CT Core Laboratory
Attn: 6678
1818 Market Street 16th floor
Philadelphia, PA 19103

12.0 ADVERSE EVENTS REPORTING

12.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal results of diagnostic procedures are considered to be adverse events (AEs) if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

12.2 Definition of Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- results in death, or
- is life-threatening (at the time of the event), or
- requires inpatient hospitalization or prolongation of an existing hospitalization, or
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

12.3 Adverse Event Grading

Grade is used to denote the severity of the adverse event.

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

12.4 Adverse Event Attribution

Attribution is used to determine whether an adverse event is related to a study treatment or procedure.

Attribution categories are:

Definite – AE ***is clearly related*** to the study treatment or procedure.
Probable – AE ***is likely related*** to the study treatment or procedure.
Possible – AE ***may be related*** to the study treatment or procedure.
Unlikely – AE ***is doubtfully related*** to the study treatment or procedure.
Unrelated – AE ***is clearly NOT related*** to the study treatment or procedure.

12.5 Expected Adverse Events from FDG-PET

12.5.1 Expected Adverse Events from injection of FDG:

- Bruising;
- Bleeding;
- Phlebitis;
- Infection at the site of injection;
- Allergic-type or other adverse reaction to FDG.

12.5.2 Expected Adverse Events from PET scan:

- Discomfort;
- Claustrophobia.

12.5.3 Expected Adverse Events from CT scan:

- Discomfort;
- Claustrophobia;
- Malfunction of implanted electronic medical devices, e.g., pacemakers, neurostimulators, insulin pumps (see note below).

NOTE: As of July 14, 2008, FDA released a preliminary public health notification of possible malfunction of electronic medical devices caused by CT scanning. Site should use CT scout views to determine if implanted or externally worn electronic medical devices are present and if so, their location relative to the programmed scan range. See Section 10.3 for FDA warning and their recommendations.

12.6 Reporting of Adverse Events

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular adverse event should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance. However, an adverse event report should be submitted if there is a reasonable suspicion of the medical treatment or imaging procedure.

Routine reporting is defined as documentation of adverse events on source documents and AE case report form (CRF), and submission to ACRIN for preparation of a report for DSMC review, quarterly reports to CDUS, and the final study report.

Expedited reporting is defined as immediate notification of NCI and ACRIN per Section 12.7. Routine reporting requirements also apply.

Since this is a diagnostic study that does not involve any experimental forms of cancer therapy, adverse event reporting will be minimal. ACRIN will collect and report only those adverse events considered possibly, probably, or definitely related to the trial with the severity level of Grades 3, 4, 5 that occur during study participation and up to 30 days after the last study procedure. Local IRBs and/or institutions may stipulate additional adverse events reporting based upon their review of the protocol.

All expected (Section 12.5) and unexpected adverse events considered possibly, probably, or definitely related to PET/CT Scan and FDG, and serious adverse events will be documented in the study participant's chart and AE CRFs, in addition to meeting all study-specific reporting requirements of ACRIN, National Cancer Institute's Cancer Imaging Program (NCI/CIP), and the local IRB (per local IRB policy).

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse events are otherwise explained. Any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may be reasonably related to the study imaging effect should be reported.

The following table summarizes the reporting requirements for AEs for the FDG-PET Trial:

Adverse Events that occur during study participation (from the first study procedure and up to 30 days after the last study procedure)	**Type of Report**		
	Routine Reporting	**Expedited Written in 10 days**	**Telephonic Report to NCI-CIP and ACRIN within 24 hours of knowledge of AE**
Grade 3 **(Attribution of possible, probable, or definite)**	**X** Expected and Unexpected		
Hospitalization/Prolongation of hospitalization** **(Attribution of possible, probable, or definite)**	**X** Expected and Unexpected	**X** Unexpected	
Grade 4 **(Attribution of possible, probable, or definite)**	**X** Expected and Unexpected	**X** Unexpected	
Grade5/Death **(Attribution of possible, probable, or definite)**	**X** Expected and Unexpected	**X** Expected and Unexpected	**X** Expected and Unexpected

**All unexpected hospitalizations (or prolongation of existing hospitalization) for adverse events with the severity (intensity) level of Common Terminology Criteria for Adverse Events (CTCAE, most recent version) Grade 3, 4, 5 with attribution of possible, probable, or definite.

Assignment of grades (severity level) and attribution for each AE is to be completed at the site by the Site Principal Investigator.

12.7 Expedited Reporting To NCI and ACRIN

12.7.1 Investigator or investigator-designee must use expedited adverse event reporting for **deaths** with attribution of possible, probable, or definite occurring during study participation and up to 30 days after the last study procedure. Deaths should be reported by telephone to NCI/CIP and ACRIN within 24 hours of first knowledge of the event and followed by an expedited written report within ten (10) days. These reports should be sent to ACRIN, NCI/CIP, and the local IRB, in addition to documentation in participant chart and AE CRF.

12.7.2 All life-threatening/disabling unexpected adverse events (considered possibly, probably, or definitely related to the FDG-PET/CT trial) occurring during study participation and up to 30 days after the last study procedure will reported within ten (10) working days of first knowledge of the event. These reports should be sent to ACRIN, NCI/CIP, and the local IRB, in addition to documentation in participant chart and AE CRF.

12.7.3 All hospitalizations (or prolongation of existing hospitalization) for adverse events with the severity (intensity) level of CTCAE Grade 3, 4, 5 and attribution of possibly, probably, or definitely related to the FDG-PET/CT trial must be reported within ten (10) working days of first knowledge of the event, in addition to documentation in participant chart and AE CRF.

12.7.4 All other serious adverse events with attribution of possibly, probably, or definitely related to the FDG-PET/CT trial which include AEs that results in persistent or significant disability or incapacity, or congenital anomaly (birth defect) in the offspring of the study participant must be reported within ten (10) working days of first knowledge of the event during study participation and up to 30 days after the last study procedure, in addition to documentation in participant chart and AE CRF.

12.7.5 Significant new information and/or follow-up information (e.g., test results, autopsy, discharge summary) on any on-going serious adverse events should be promptly reported to ACRIN.

12.8 When to Report

12.8.1 All unexpected and expected Grade 5 events require expedited adverse event reporting within 10 working days of knowledge of the event occurring within 30 days of the study procedure with attribution of possible, probable, or definite. These fatal (Grade 5) adverse events should also be reported by telephone to NCI/CIP and ACRIN within 24 hours of knowledge of the event. Routine reporting also applies.

12.8.2 All unexpected Grade 4 require expedited adverse event reporting within 10 working days of knowledge of the event for occurring within 30 days of the study procedure with attribution of possible, probable, or definite. Routine reporting is required for all unexpected and expected Grade 4 events with attribution of possible, probable, or definite.

12.8.3 An expedited report is required for unexpected Grade 3, 4, or 5 hospitalizations with attribution of possible, probable, or definite and must be reported within 10 working days. Routine reporting also applies.

12.8.4 Expected Grade 3 adverse events with attribution of possible, probable, or definite require only routine reporting.

12.8.5 These reports should be sent to ACRIN, NCI/CIP, and the local IRB. Copies of each report and documentation of the notification and receipt will be kept in the study participant's file.

12.9 How to Report

12.9.1 An expedited adverse event report requires submission to the NCI/CIP and ACRIN using the paper templates "Adverse Event Expedited Report—Single Agent" available on the CTEP home page, http://ctep.info.nih.gov.

Protocols involving only imaging procedures must be submitted using a paper version. Investigators following those protocols should omit the Course Information section and the Protocol Agent section, even though the template indicates those as mandatory. (Do not try to send the form via the web site; it will not accept a form without those fields filled in.)

General questions regarding completion of the AdEERS report or submission can be sent to CIPSAEReporting@tech-res.com. AdEERSMD helpline is available for any questions via phone at 301-897-7497.

12.9.2 To make an expedited telephone report to NCI/CIP, contact TRI staff at (301) 897-1704, available 24 hours a day (recorder after hours from 7:30 PM to 7:30 AM Eastern Time).

12.9.3 An expedited adverse event report must be sent with the above-mentioned timeframe to NCI/CIP by fax at (301) 897-7402. All fatal adverse events should be reported by telephone within 24 hours of the event.

12.9.4 A copy of all expedited adverse event reports should be sent to ACRIN by fax at (215) 717-0936 and the original signed and dated report must be sent to ACRIN.

ACRIN 6678 Adverse Event
Attn: ACRIN Adverse Events Coordinator
1818 Market Street, 16th Floor
Philadelphia, PA 19103

12.9.5 All unexpected fatal adverse events with attribution of possible, probable, or definite and unexpected life-threatening/disabling unexpected adverse events with attribution of possible, probable, or definite should be reported by telephone within 24 hours of the first knowledge of the adverse event. To make a telephone report to ACRIN, call (215) 717-2763, available 24 hours a day (recorder after hours from 4:30 PM to 8:00 AM Eastern Time).

12.9.6 All expedited adverse event reports should be sent to your local IRB per your local IRB policies and procedures. Adverse events not requiring expedited reporting are normally reported to the local IRB in an annual report.

13.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonisation [ICH] guidelines), applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or IRB for a formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study. The investigator will provide ACRIN with the institution's federal wide assurance (FWA) number, along with the IRB approval letter and copies of the IRB-approved informed consent forms. The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

All study participants in this study will be provided an IRB-approved, site-specific informed consent form describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for sample informed consent forms). The informed consent forms will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with an EC/IRB approved informed consent form before the participant is subjected to any study procedures. The approved consent form MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent.

14.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN policies and applicable federal, state, and local laws and regulations.

15.0 PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of ACRIN and the Study Chair. Any investigator involved in this study is obligated to provide ACRIN with complete test results and all clinical data obtained from participation in this protocol. Investigators will follow ACRIN Publication Policy (available on the web at www.acrin.org/PublicationsPolicy.aspx).

16.0 INSTITUTIONAL MONITORING AND AUDITS

The investigator will permit study-related monitoring, auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. The investigator will ensure the capability for inspection of all participating site's study-related facilities (e.g. imaging center, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct audit visits.

Monitoring ensures protocol and regulatory compliance and provides any clarification to the protocol and guidance to the completion of the CRFs. Institutional monitoring will be implemented at several different time points: after first participant enrolled and during the conduct of the study. Instructions for preparation for the monitoring will be sent to the site prior to the implementation of monitoring. The instructions will specify regulatory document and participant case records to be monitored. CRFs and source documents of selected study participants enrolled at each site will be reviewed. In addition, the initial regulatory documents and any revised regulatory documents also will be monitored.

All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 20% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.

Subsequent audits will be scheduled per the outcome of the initial audit. The audits will be conducted per procedures established by the NCI/CIP. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms also will be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org/pdrc.aspx.

To help sites prepare for monitoring and audits and assure that the investigator and the research staff maintain records appropriately, the ACRIN Headquarter staff will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial.

16.1 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN. Source documents must verify the eligibility criteria and data submitted on all CRFs.

Research records for each case should contain copies of the source documents for the data collected and reported to ACRIN. If data is abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol. This will prevent any discrepancies and the inability to verify the document and the data reported.

16.2 Case Report Forms

CRFs, both web-based and paper form, are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank on paper CRFs because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case "N/A" must be noted. All entries on paper CRFs must be printed legibly in black ink on the paper case report forms. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the correction, recording the date** when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that is more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and is acceptable source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s). Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of CRFs as source documentation when the protocol has designated the medical record documentation as source data will be considered a deficiency.

17.0 STATISTICAL CONSIDERATIONS

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Appendix I

Informed Consent Form Templates:
Instruction to Participating Sites Regarding Consent Forms

This Appendix contains three (3) consent form templates for Groups A, B and C, respectively. These consent form templates describe the research procedures that will be done if the patient has all imaging studies after consent and registration to the trial or, per the protocol guidelines, the research procedures that will be done if it is possible to use an FDG-PET/CT scan that the participant had on a qualified scanner prior to consent and registration.

If, per protocol guidelines, you are UNABLE to use the FDG-PET/CT scan that was done recently prior to consent and registration to the trial, template consent language also has been provided to create consent forms for patients having to repeat the first FDG-PET/CT scan just for study purposes; this baseline scan would otherwise have been considered a standard-of-care examination.

If a Group A participant is unable to complete both pre-treatment test-retest FDG-PET/CT scans, that participant can be reassigned to Group B. It may be necessary to re-consent a participant to the appropriate group in these cases. It may also be possible to draft your site-specific informed consent form so that, in instances when a participant can switch from Group A to Group B, a re-consent is not necessary because the participant has already consented to three FDG-PET/CT and three volumetric CT scans total.

The following are options, based on site-specific Institutional Review Board requirements, for consent forms that will need to be created for this trial:

Option 1:
Have six (6) consent forms prepared for this trial; the patient will sign one (1) consent form, applicable to the group and situation:

- One consent form for Group A.
- One consent form for Group B.
- One consent form for Group C.
- One consent form for Group A, describing the additional procedures and risks if it is necessary to repeat a previously performed clinical FDG-PET/CT scan to obtain the baseline scan for the trial.
- One consent form for Group B, describing the additional procedures and risks if it is necessary to repeat a previously performed clinical FDG-PET/CT scan to obtain the baseline scan for the trial.
- One consent form for Group C, describing the additional procedures and risks if it is necessary to repeat a previously performed clinical FDG-PET/CT scan to obtain the baseline scan for the trial.

Option 2:
Have three (3) consent forms prepared for this trial; the patient will sign one (1) consent form, applicable to the group:

- One consent form for Group A, also describing the additional procedures and risks if it is necessary to repeat a previously performed clinical FDG-PET/CT scan to obtain the baseline scan for the trial.
- One consent form for Group B, also describing the additional procedures and risks if it is necessary to repeat a previously performed clinical FDG-PET/CT scan to obtain the baseline scan for the trial.
- One consent form for Group C, also describing the additional procedures and risks if it is necessary to repeat a previously performed clinical FDG-PET/CT scan to obtain the baseline scan for the trial.

NOTE: The consent form templates in the protocol are designed to accommodate Options 1 and 2 easily.

Option 3:
Have one (1) consent form prepared for this trial; the patient will sign one (1) consent form, applicable to all possible situation:

- One consent form that covers Group A, B and C, also describing the additional procedures and risks if it is necessary to repeat a previously performed clinical FDG-PET/CT scan to obtain the baseline scan for the trial.

Option 4:
Have two (2) consent forms prepared for this trial; the patient will sign one (1) consent form, applicable to the situation:

- One consent form that covers Groups A, B and C.
- One consent form that covers Groups A, B and C, describing the additional procedures and risks if it is necessary to repeat a previously performed clinical FDG-PET/CT scan to obtain the baseline scan for the trial.

Option 5:
Have two (2) consents prepared for this trial; the patient will sign two (2) consent forms:

- One consent form that covers Group A, B and C.
- One SEPARATE consent form specifically for a repeat FDG-PET/CT scan to obtain the baseline scan for the trial.

Option 6:
Have four (4) consent forms prepared for this trial; the patient will sign two (2) consent form, applicable to the group and situation:

- One consent form for Group A.
- One consent form for Group B.
- One consent form for Group C.
- One SEPARATE consent form specifically for a repeat FDG-PET/CT scan to obtain the baseline scan for the trial.

Appendix I: Informed Consent Form Templates

Informed Consent Form Template For Group A Patients

ACRIN 6678

FDG-PET/CT as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in Non-small Cell Lung Cancer

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

If you want more information about participating in clinical trials, ask your study doctor for the National Cancer Institute (NCI) booklet *Taking Part in Cancer Treatment Research Studies*. Also, you can learn more about clinical trials at http://cancertrials.nci.nih.gov or by calling the NCI's help line at 1-800-4-cancer (1-800-422-6237 or TTY: 1-800-332-8615).

You are being asked to take part in this study because you have advanced lung cancer. This clinical trial for advanced lung cancer involves FDG-PET/CT scans.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if FDG-PET/CT scans can help doctors decide if chemotherapy is working to control your lung cancer.

PET stands for Positron Emission Tomography and CT stands for Computed Tomography. PET/CT is a novel imaging technology that combines two imaging modalities (PET images and CT images) into one image.

About FDG-PET Scan

PET is a nuclear medicine medical imaging technique that produces a 3-D image of functional processes in the body.

About CT Scan

A CT scanner is a special kind of X-ray machine. Instead of sending out a single X-ray through your body as with ordinary X-rays, several beams are sent simultaneously from different angles. The computer processes the results, displaying them as a two-dimensional picture shown on a monitor.

About FDG-PET/CT Scan

Many PET scanners also include a CT scanner. This allows images of both anatomy (CT) and function (PET) to be taken during the same examination. The FDG-PET/CT scan has the benefit of combining the PET scan information about cell function with the CT scan information about the size and shape of abnormal cells. Alone, each test has its limitations but when the results of the scans are fused together they provide the most complete information on cancer cell function and location.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Up to 57 people will take part in study Group A, and up to 285 people will participate in all three study groups.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

Overall, this study has three groups. In each group the timing of the imaging tests is different, so you and your doctor have to discuss and choose which group you will be enrolled in. You and your doctor have considered these choices and your planned therapy, and have decided that that you will participate in study Group A.

If you agree to take part in this study:

Standard medical procedures that are part of regular cancer care and would probably be done even if you do not join the study:

- Chemotherapy (cancer fighting drugs) through a vein in your arm
- Diagnostic CT scan
- Physical examination
- Clinical labs related to your treatment (within 4 weeks of registration to the trial)
- Pregnancy test (if applicable)

Standard medical procedures that are being done specifically because you are in this study (these may or may not be done if you were not in this study):

- PET/CT scan with FDG
- CT scan without contrast

You will be asked to have two (2) FDG-PET/CT scans (1 to 7 days apart) and two (2) other CT scans (also 1 to 7 days apart) before you begin your cancer treatment and one (1) FDG-PET/CT and one (1) other CT scan after you receive your first cycle of chemotherapy. Your study doctor will try to take imaging scans on the same day as possible, or on days when you are already scheduled to be at the facility for care. If you have already had an FDG-PET/CT scan before agreeing to participate in this clinical trial, it is possible that scan may be used as the first one for the trial. If for any reason you cannot have both FDG-PET/CT scans before beginning treatment, your doctor may ask you to join Group B of this trial. You may not receive all of the CT scans if your study and treating doctors decide it is in your best interest or if time becomes an issue.

You will have routine follow-up CT scans, every six (6) weeks from initation of chemotherapy, as recommended for your cancer treatment. These CT scans will be collected by the study doctor, for up to eighteen (18) weeks, in addition to the study FDG-PET/CT scans. You will continue to see and follow up with your regular doctor. Your study doctor will also follow-up with your regular doctor, at least every three (3) months, for up to one (1) year, to see how you are doing. Normally, the results of the FDG-PET/CT scan obtained after your first cycle of chemotherapy will not be given to you or your regular doctor who is caring for you. But, if the study CT scan images show potentially serious or life threatening findings, your regular doctor will be told of the results.

[ADD THIS PARAGRAPH AS A GUIDE IF A PREVIOUSLY PERFORMED BASELINE FDG-PET/CT SCAN NEEDS TO BE REPEATED AS A RESEARCH PROCEDURE.] In order to

participate in this research project, the FDG-PET/CT scans done before and after treatment must be obtained on the same scanner with a specific technique. The FDG-PET/CT scans must also be done within the timeframe outlined for this trial. Although you had a previous FDG-PET/CT scan, it cannot be used for this trial, because it was done at another hospital or imaging facility, or was done with a technique different from that required by the research protocol, or is outside the timing needed for this protocol. Thus, if you would like to participate in this research project, funds are available to repeat your FDG-PET/CT scan at *INSERT INSTITUTION NAME*. The PET scan would be performed exactly as described in the consent form for the trial but would be specifically for research purposes, and would not be charged to you or your insurance company.

Preparation for a PET/CT Scan: Before each FDG-PET/CT scan, do not eat for 4 to 6 hours before your appointment time and drink only water. You will be given details of what to do to prepare for your PET/CT scan.

During the Exam: On the day of your FDG-PET/CT scan, you first will be given an injection of a small amount of a radioactive drug/tracer (a chemical similar to sugar which is called FDG) into a vein in your arm or hand. The amount of radiation is very small, no more than what you would have during a normal x-ray. It only stays in your body for a few hours. The FDG will travel to particular parts of your body. It travels to places where glucose is used for energy. It can show cancer because the cancer cells use glucose in a different way from normal tissue.

The PET/CT scanner is a large machine with a hole in the middle. It looks like a donut with a table in the middle. Approximately 50-70 minutes after the injection of FDG, you will be asked to go to the bathroom (urinate) and then lie on a partially enclosed scanning table. The table will slide into the machine. You will be asked to remain still during the scan. You will hear buzzing or clicking sounds during the scan. You will need to lie still for about 20-60 minutes before coming off of the scanning table.

The size of the opening is 27 to 30 inches. How much space you feel you have around you will depend on your body size and the scanner. If you feel any anxiety over being in enclosed spaces, let your study doctor know. A mild sedative may be used to help you feel more comfortable during the exam.

Time Required: The entire FDG-PET/CT scan procedure is expected to take about 2 hours.

Once you have had your FDG-PET/CT scan(s), you will receive chemotherapy. The chemotherapy that you will be getting is not a part of this study. It will be the usual treatment for your kind of cancer. You and your regular doctor will decide how many chemotherapy treatments you will get. You are consenting to have two (2) FDG-PET/CT scans (1 to 7 days apart) and two (2) other CT scans (also 1 to 7 days apart) before you begin your cancer treatment and one (1) FDG-PET/CT and one (1) other CT scan after you receive your first cycle of chemotherapy. However, the other CT scans are optional. You may not undergo all of these scans, depending on what you and your study and regular doctors decide is in your best interest. The scans will be done exactly the same way as described above.

You will continue to see your regular doctor once the chemotherapy treatments have ended. You will see your regular doctor at regular intervals according to her/his recommendations and usual practice. This will include a diagnostic CT scan every six (6) weeks throughout your cancer treatment. Information gathered by your regular doctor as part of your normal follow-up visits will be given to your study doctor(s) so they can find out more about your health. Your follow-up care will be decided between you and your regular doctor.

Study Chart

What you do if you are in Group A:

At Registration/ Baseline Visit	• Sign an informed consent form (ICF); • Have a physical examination; • Have a pregnancy test, if applicable; • Provide medical history.
Visit A1: Pre-Chemotherapy Imaging Visit, Within 14 Days of Start of Chemotherapy	• Follow instructions provided at Registration/Baseline Visit in preparation for the FDG-PET/CT; • Have a blood sugar test before the FDG injection; • Have a CT scan (may not be on the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*; • Have a FDG-PET/CT scan†.
Visit A2: Pre-Chemotherapy Imaging Visit, Within 7 Days Before Start of Chemotherapy Cycle 1	• Follow instructions provided at Registration/Baseline Visit in preparation for the FDG-PET/CT; • Have a blood sugar test before the FDG injection; • Have a CT scan (may not be on the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*; • Have a FDG-PET/CT scan†.
Visit A3: Post-Chemotherapy Cycle 1 Imaging Visit, Within 4 Days Before Start of Chemotherapy Cycle 2	• Follow instructions provided at Registration/Baseline Visit in preparation for the FDG-PET/CT; • Have a blood sugar test before the FDG injection; • Have a CT scan (may not be on the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*; • Have a FDG-PET/CT scan†.
Imaging Follow-up Visits: Every 6 Weeks from Initiation of Chemotherapy for Maximum of 18 Weeks	• Have a diagnostic CT scan at time intervals based on the recommendation and standard practice of your regular doctor.
Clinical Follow-up Visits	• Have a physical examination, at time intervals based on the recommendations and standard practice of your regular doctor.

In most cases, you will have the FDG-PET/CT and CT scans on the same imaging device and during the same imaging session. You do not have to make separate appointments for the FDG-PET/CT and the CT scans. However, some FDG-PET/CT devices may not be able to take CT images meeting the special requirements for this research study. In this case, you will be asked to have the CT scan done on a separate scanner and possibly on a separate day.

* Even if you agree to the other CT scans, you may not receive them if your study and regular doctors decide it is in your best interest or if time becomes an issue.

† It is important to the study to make sure you have completed the first two FDG-PET/CT scans before you start any treatment and the third FDG-PET/CT scan after your first cycle of chemotherapy.

HOW LONG WILL I BE IN THE STUDY?

We expect that you will be an active participant for about 6 months/24 weeks while you receive chemotherapy. You will then need to see your regular doctor(s) for follow-up visits as he/she recommends.

You can stop participating in this study at any time. However, if you decide to stop participating, we encourage you to talk to the study doctor and your regular doctor(s) first.

The study doctor may decide to take you off this study if your cancer gets worse or if the side effects of the cancer treatment are very serious. The study doctor may also take you off if new information becomes available that suggests that participating in this study will be unsafe for you. It is unlikely, but the study may also be stopped early due to lack of funding or participation.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

In addition to the side effects of your chemotherapy treatment, you may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the FDG-PET/CT scan. In some cases, side effects can be serious, long lasting or may never go away.

Risks Associated with Radiation Exposure from FDG-PET/CT and CT Scans:

<<Each site may need to modify this section to quote the correct CT dosimetry for its own PET/CT and CT scanners in accordance with its own institutional policies and procedures. This section may necessitate further revision if three (3) FDG-PET/CTs (i.e., one [1] more than presented in the radiation exposure details below) must be conducted for research purposes.>>

This research study involves a maximum exposure to radiation from *2* FDG-PET/CT scans and *3* volumetric CT scans. *[Note that if the first FDG-PET/CT has to be repeated for research, then the number of FDG-PET/CT scans will increase to three (3).]* The radiation exposure you will receive from each FDG-PET/CT scan is equal to a uniform whole-body exposure of approximately *14* mSv (a measure of radiation exposure), with approximately *11* mSv from the injected radioactive FDG and *3* mSv from the CT component). The radiation exposure you will receive from each volumetric CT scan is equal to a uniform whole-body exposure of approximately *6* mSv. The total radiation exposure from all of these procedures is *46* mSv. This is about *92%* of the allowable annual dose of 50 mSv for radiation workers (for example, x-ray technicians). The risk from this level of radiation exposure is too small to be measured and is small when compared with other everyday risks.

If you would like more information about radiation exposure associated with the PET and CT scans, please speak with your study doctor.

Other Risks Associated with PET Scans and Injection of FDG:

Less Likely

Discomfort from lying still on the enclosed scanning table;
Bruising or bleeding at the site of injection of FDG;
Infection at the site of injection of FDG.

Rare

An allergic-type or other adverse reaction to the radioactive drug (FDG) has not been documented so far, but cannot be entirely excluded.

Other Risks Associated with CT Scans:

Rare

Malfunction of worn or implanted electronic medical devices. If you wear or have electronic medical devices implanted, such as a pacemaker or a drug pump, please make sure you tell your study doctors

and research staff. It was recently reported by the FDA that the CT scan may cause the malfunction of electronic medical devices.

Reproductive Risks:
Because the radiation from PET scans or CT scans can damage an unborn baby, you should not become pregnant or father a baby while on this study. (The risks of fetal injury, however, are far greater from the chemotherapy that will be used to treat your cancer.) These days, some doctors tell PET scan patients that they should not have close contact with pregnant women, babies and young children for a few hours after their scan. If you are breast feeding, you have to express enough milk beforehand to get your baby through the first 6 hours after the scan. This is not because there will be radiation in the milk. It is because the mother should not be holding the baby closely during the time the radiation is in her body. Some doctors recommend you get someone else to feed the baby for 24 hours, although it is safe for you to express more milk for those feeds from 6 hours after the scan. It is important you understand that you need to use birth control while on this study. Ask your study doctor about what kind of birth control methods to use and how long to use them. If you are a woman who can become pregnant, you must agree to a pregnancy test (blood test) before starting chemotherapy treatment, and later on if your physician considers it necessary.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, your study doctor(s) may learn more information from the FDG-PET/CT scans about how best to treat your cancer and whether the chemotherapy treatment is working in fighting your cancer. Please discuss with your regular doctor the findings from the scans being completed and the information that is available to you at that time. Taking part in this study may or may not make your health better. The information from this study will help your study doctors learn whether FDG-PET and the FDG-PET/CT scans will help identify cancer that has spread to your lungs. This knowledge will help doctors decide on the best treatment for patients with lung cancer. In some participants, a change in treatment may better treat your lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

You may choose to not participate in this study. You could have PET/CT scans done without participating in this study. Please talk to your regular doctor about this and other options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Records of your participation in this study, your progress, and images submitted (such as FDG-PET/CT scan or CT scan) while you are on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia. Your personal information may be given out if required by law.

Authorized representatives of ACRIN, Center for Statistical Sciences at Brown University, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the Institutional Review Board (IRB) of *<<Institution>>*, and other groups or organizations that have a role in this study will have access to and may inspect and/or copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare. If

any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner such that you cannot be identified.

Your research records and images will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number. The research that may be done with the information will not specifically help you. But, it might help people who have cancer and other diseases in the future.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study may lead to added costs to you or your insurance company. FDG-PET/CT scans for lung cancer are usually covered by most insurance companies, but this is not guaranteed. Please ask your study doctor(s) about any expected added costs or insurance problems.

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

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, *<<insert name>>*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at *<<insert 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.

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, *<<insert name>>*, at *<<insert telephone number>>*.

For questions about your rights while taking part in this study call the *<<insert name IRB contact person>>* at *<<insert name of the IRB>>* Institutional Review Board (a group of people who review the research to protect your rights) at *<<insert telephone number>>*.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at **1–800–4–CANCER (1–800–422–6237)** or **TTY: 1–800–332–8615.**

Visit the NCI's Web sites for clinical trials information http://cancertrials.nci.nih.gov**,** or for cancer information visit http://cancernet.nci.nih.gov. ACRIN's Web site is www.acrin.org.

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You also have had the opportunity to take this consent form home for review or discussion if you want to. A copy of the signed consent will be given to you.

_____ _____

Signature of Participant (or Legal Representative) Date

<Insert other signature and date lines as appropriate per local IRB policies and procedures>

Informed Consent Form Template for Group B

ACRIN 6678

FDG-PET/CT as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in Non-small Cell Lung Cancer

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

If you want more information about participating in clinical trials, ask your study doctor for the National Cancer Institute (NCI) booklet *Taking Part in Cancer Treatment Research Studies*. Also, you can learn more about clinical trials at http://cancertrials.nci.nih.gov or by calling the NCI's help line at 1-800-4-cancer (1-800-422-6237 or TTY: 1-800-332-8615)

You are being asked to take part in this study because you have advanced lung cancer. This clinical trial for advanced lung cancer involves FDG-PET/CT scans.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if FDG-PET/CT scans can help doctors decide if chemotherapy is working to control your lung cancer.

PET stands for Positron Emission Tomography and CT stands for Computed Tomography. PET/CT is a novel imaging technology that combines two imaging modalities (PET images and CT images) into one image.

About FDG-PET Scan

PET is a nuclear medicine medical imaging technique that produces a 3-D image of functional processes in the body.

About CT Scan

A CT scanner is a special kind of X-ray machine. Instead of sending out a single X-ray through your body as with ordinary X-rays, several beams are sent simultaneously from different angles. The computer processes the results, displaying them as a two-dimensional picture shown on a monitor.

About FDG-PET/CT Scan

Many PET scanners also include a CT scanner. This allows images of both anatomy (CT) and function (PET) to be taken during the same examination. The FDG-PET/CT scan has the benefit of combining the PET scan information about cell function with the CT scan information about the size and shape of abnormal cells. Alone, each test has its limitations but when the results of the scans are fused together they provide the most complete information on cancer cell function and location.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Up to 171 people will take part in study Group B, and up to 285 people will participate in all three study groups.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you agree to take part in this study:

Standard medical procedures that are part of regular cancer care and would probably be done even if you do not join the study:

- Chemotherapy (cancer fighting drugs) through a vein in your arm
- Diagnostic CT scan
- Physical examination
- Clinical labs related to your treatment (within 4 weeks of registration to the trial)
- Pregnancy test (if applicable)

Standard medical procedures that are being done specifically because you are in this study (These may or may not be done if you were not in this study):

- PET/CT scan with FDG
- CT scan without contrast

You will be asked to have one (1) FDG-PET/CT scan and one (1) CT scan before you begin your cancer treatment, one (1) FDG-PET/CT scan and one (1) CT scan after your first cycle of chemotherapy, and one (1) FDG-PET/CT scan and one (1) CT scan after your second cycle of chemotherapy. You may not receive all of these scans if you and your study and treating doctors decide it is in your best interest or if time becomes an issue. Your study doctor will try to take imaging scans on the same day as possible, or on days when you are already scheduled to be at the facility for care. If you have already had an FDG-PET/CT scan before agreeing to participate in this clinical trial, it is possible that scan may be used as the first one for the trial. If you were already enrolled in Group A of this trial but were unable to have two (2) pre-treatment FDG-PET/CT scans, you may be asked to participant in Group B instead.

You will have routine follow-up CT scans, every six (6) weeks from initiation of chemotherapy, as recommended for your cancer treatment. These CT scans will be collected by the study doctor, for up to eighteen (18) weeks, in addition to the study FDG-PET/CT scans. You will continue to see and follow up with your regular doctor. Your study doctor will also follow-up with your doctor, at least every three (3) months, for up to one (1) year, to see how you are doing. Normally, the results of the FDG-PET/CT scan obtained after your first cycle of chemotherapy will not be given to you or your regular doctor who is caring for you. But, if the study CT scan images show potentially serious or life threatening findings, your regular doctor will be told of the results.

[ADD THIS PARAGRAPH AS A GUIDE IF A PREVIOUSLY PERFORMED BASELINE FDG-PET/CT SCAN NEEDS TO BE REPEATED AS A RESEARCH PROCEDURE.] In order to participate in this research project, the FDG-PET/CT scans done before and after treatment must be obtained on the same scanner with a specific technique. The FDG-PET/CT scans must also be done within the timeframe outlined for this trial. Although you had a previous FDG-PET/CT scan, it cannot be used for this trial, because it was done at another hospital or imaging facility, or was done with a technique different from that required by the research protocol, or is outside the timing needed for this protocol. Thus, if you would like to participate in this research project, funds are available to repeat

your FDG-PET/CT scan at *INSERT INSTITUTION NAME*. The PET scan would be performed exactly as described in the consent form for the trial but would be specifically for research purposes, and would not be charged to you or your insurance company.

Preparation for a PET/CT Scan: Before each FDG-PET/CT scan, do not eat for 4 to 6 hours before your appointment time and drink only water. You will be given details of what to do to prepare for your PET/CT scan.

During the Exam: On the day of your FDG-PET/CT scan, you first will be given an injection of a small amount of a radioactive drug/tracer (a chemical similar to sugar which is called FDG) into a vein in your arm or hand. The amount of radiation is very small, no more than what you would have during a normal x-ray. It only stays in your body for a few hours. The FDG will travel to particular parts of your body. It travels to places where glucose is used for energy. It can show cancer because the cancer cells use glucose in a different way from normal tissue.

The PET/CT scanner is a large machine with a hole in the middle. It looks like a donut with a table in the middle. Approximately 50-70 minutes after the injection of FDG, you will be asked to go to the bathroom (urinate) and then lie on a partially enclosed scanning table. The table will slide into the machine. You will be asked to remain still during the scan. You will hear buzzing or clicking sounds during the scan. You will need to lie still for about 20-60 minutes before coming off of the scanning table.

The size of the opening is 27 to 30 inches. How much space you feel you have around you will depend on your body size and the scanner. If you feel any anxiety over being in enclosed spaces, let your study doctor know. A mild sedative may be used to help you feel more comfortable during the exam.

Time Required: The entire FDG-PET/CT scan procedure is expected to take about 2 hours.

Once you have had your FDG-PET/CT scan(s), you will receive chemotherapy. The chemotherapy that you will be getting is not a part of this study. It will be the usual treatment for your kind of cancer. You and your regular doctor will decide how many chemotherapy treatments you will get. You are consenting to one (1) FDG-PET/CT and one (1) other CT scan before you begin your cancer treatment, one (1) FDG-PET/CT and one (1) other CT scan after your first cycle of chemotherapy, and one (1) FDG-PET/CT and one (1) other CT scan after your second cycle of chemotherapy. One of the FDG-PET/CT scans (post-cycle 2 of chemotherapy) and all of the other CT scans are optional. You may not undergo all of these scans, depending on what you and your study and treating doctors decide is in your best interest. The scans will be done exactly the same way as described above.

You will continue to see your regular doctor once the chemotherapy treatments have ended. You will see your regular doctor at regular intervals according to her/his recommendations and usual practice. This will include a diagnostic CT scan every six (6) weeks throughout your cancer treatment. Information gathered by your regular doctor as part of your normal follow-up visits will be given to your study doctor(s) so they can find out more about your health. Your follow-up care will be decided between you and your regular doctor.

Study Chart

What you do if you are in Group B:

At Registration/ Baseline Visit	• Sign an informed consent form (ICF); • Have a physical examination; • Have a pregnancy test, if applicable; • Provide medical history.
Visit B1: Pre-Chemotherapy Imaging Visit, Within 7 Days Before Start of Chemotherapy Cycle 1	• Follow instructions provided at Registration/Baseline Visit in preparation for the FDG-PET/CT; • Have a blood sugar test before the FDG injection; • Have a CT scan (may not be on the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*; • Have a FDG-PET/CT scan†.
Visit B2: Post-Chemotherapy Cycle 1 Imaging Visit, Within 4 Days Before Start of Chemotherapy Cycle 2	• Follow instructions provided at Registration/Baseline Visit in preparation for the FDG-PET/CT; • Have a blood sugar test before the FDG injection; • Have a CT scan (may not be on the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*; • Have a FDG-PET/CT scan†.
Visit B3: Post-Chemotherapy Cycle 2 Imaging Visit, On Days 19, 20, 21, or 22 Before Start of Chemotherapy Cycle 3	• Follow instructions provided at Registration/Baseline Visit in preparation for the FDG-PET/CT; • Have a blood sugar test before the FDG injection; • Have a CT scan (may not be on the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*; • Have a FDG-PET/CT scan.
Imaging Follow-up Visits: Every 6 Weeks from Initiation of Chemotherapy for Maximum of 18 Weeks	• Have a diagnostic CT scan at time intervals based on the recommendation and standard practice of your regular doctor.
Clinical Follow-up Visits	• Have a physical examination, at time intervals based on the recommendations and standard practice of your regular doctor.

In most cases, you will have the FDG-PET/CT and CT scans on the same imaging device and during the same imaging session. You do not have to make separate appointments for the FDG-PET/CT and the CT scans. However, some FDG-PET/CT devices may not be able to take CT images meeting the special requirements for this research study. In this case, you will be asked to have the CT scan done on a separate scanner and possibly on a separate day. The FDG-PET/CT scan after your second cycle of chemotherapy (Visit B3) and the other CT scans are optional. You and your study and treating doctors will decide if it is in your best interest to undergo some or all of these scans during the trial.

* Even if you agree to the other scans, you may not receive them if your study and treating doctors decide it is in your best interest or if time becomes an issue.
† It is important to the study to make sure you have completed the first two FDG-PET/CT scans—one before you start any treatment and the second after your first cycle of chemotherapy.

HOW LONG WILL I BE IN THE STUDY?

We expect that you will be an active participant for about 6 months/24 weeks while you receive chemotherapy. You will then need to see your regular doctor(s) for follow-up visits as he/she recommends.

You can stop participating in this study at any time. However, if you decide to stop participating, we encourage you to talk to the study doctor and your regular doctor(s) first.

The study doctor may decide to take you off this study if your cancer gets worse or if the side effects of the cancer treatment are very serious. The study doctor may also take you off if new information becomes available that suggests that participating in this study will be unsafe for you. It is unlikely, but the study may also be stopped early due to lack of funding or participation.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

In addition to the side effects of your chemotherapy treatment, you may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the FDG-PET/CT scan. In some cases, side effects can be serious, long lasting or may never go away.

Risks Associated with Radiation Exposure from FDG-PET/CT and CT Scans:

<<Each site may need to modify this section to quote the correct CT dosimetry for its own PET/CT and CT scanners in accordance with its own institutional policies and procedures. This section may necessitate further revision if three (3) FDG-PET/CTs (i.e., one [1] more than presented in the radiation exposure details below) must be conducted for research purposes.>>

This research study involves a maximum exposure to radiation from *2* FDG-PET/CT scans and *3* volumetric CT scans. *[Note that if the first FDG-PET/CT has to be repeated for research, then the number of FDG-PET/CT scans may increase to three (3).]* The radiation exposure you will receive from each FDG-PET/CT scan is equal to a uniform whole-body exposure of approximately *14* mSv (a measure of radiation exposure), with approximately *11* mSv from the injected radioactive FDG and *3* mSv from the CT component. The radiation exposure you will receive from each volumetric CT scan is equal to a uniform whole-body exposure of approximately *6* mSv. The total radiation exposure from all of these procedures is *46* mSv. This is about *92%* of the allowable annual dose of 50 mSv for radiation workers (for example, x-ray technicians). The risk from this level of radiation exposure is too small to be measured and is small when compared with other everyday risks.

If you would like more information about radiation exposure associated with the PET and CT scans, please speak with your study doctor.

Other Risks Associated with PET Scans and Injection of FDG:

Less Likely

Discomfort from lying still on the enclosed scanning table
Bruising or bleeding at the site of injection of FDG
Infection at the site of injection of FDG

Rare

An allergic-type or other adverse reaction to the radioactive drug (FDG) has not been documented so far, but cannot be entirely excluded.

Other Risks Associated with CT Scans:

Rare
Malfunction of worn or implanted electronic medical devices. If you wear or have electronic medical devices implanted, such as a pacemaker or a drug pump, please make sure you tell your study doctors and research staff. It was recently reported by the FDA that the CT scan may cause the malfunction of electronic medical devices.

Reproductive Risks:
Because the radiation from PET scans or CT scans can damage an unborn baby, you should not become pregnant or father a baby while on this study. (The risks of fetal injury, however, are far greater from the chemotherapy that will be used to treat your cancer.) These days, some doctors tell PET scan patients that they should not have close contact with pregnant women, babies and young children for a few hours after their scan. If you are breast feeding, you have to express enough milk beforehand to get your baby through the first 6 hours after the scan. This is not because there will be radiation in the milk. It is because the mother should not be holding the baby closely during the time the radiation is in her body. Some doctors recommend you get someone else to feed the baby for 24 hours, although it is safe for you to express more milk for those feeds from 6 hours after the scan. It is important you understand that you need to use birth control while on this study. Ask your study doctor about what kind of birth control methods to use and how long to use them. If you are a woman who can become pregnant, you must agree to a pregnancy test (blood test) before starting chemotherapy treatment, and later on if your physician considers it necessary.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, your study doctor(s) may learn more information from the FDG-PET/CT scans about how best to treat your cancer and whether the chemotherapy treatment is working in fighting your cancer. Please discuss with your regular doctor the findings from the scans being completed and the information that is available to you at that time. Taking part in this study may or may not make your health better. The information from this study will help your study doctors learn whether FDG-PET and the FDG-PET/CT scans will help identify cancer that has spread to your lungs. This knowledge will help doctors decide on the best treatment for patients with lung cancer. In some participants, a change in treatment may better treat your lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
You may choose to not participate in this study. You could have PET/CT scans done without participating in this study. Please talk to your regular doctor about this and other options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Records of your participation in this study, your progress, and images submitted (such as FDG-PET/CT scan or CT scan) while you are on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia. Your personal information may be given out if required by law.

Authorized representatives of ACRIN, Center for Statistical Sciences at Brown University, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the Institutional Review Board (IRB) of <<*Institution*>>, and other groups or organizations that have a role in this study will have access to

and may inspect and/or copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner such that you cannot be identified.

Your research records and images will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number. The research that may be done with the information will not specifically help you. But, it might help people who have cancer and other diseases in the future.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study may lead to added costs to you or your insurance company. FDG-PET/CT scans for lung cancer are usually covered by most insurance companies, but this is not guaranteed. Please ask your study doctor(s) about any expected added costs or insurance problems.

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

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, *<<insert name>>*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at *<<insert 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.

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, *<<insert name>>*, at *<<insert telephone number>>*.

For questions about your rights while taking part in this study call the *<<insert name IRB contact person>>* at *<<insert name of the IRB>>* Institutional Review Board (a group of people who review the research to protect your rights) at *<<insert telephone number>>*.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at **1–800–4–CANCER (1–800–422–6237)** or **TTY: 1–800–332–8615.**

Visit the NCI's Web sites for clinical trials information http://cancertrials.nci.nih.gov**,** or for cancer information visit http://cancernet.nci.nih.gov. ACRIN's Web site is www.acrin.org.

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You also have had the opportunity to take this consent form home for review or discussion if you want to. A copy of the signed consent will be given to you.

_____ _____

Signature of Participant (or Legal Representative) Date

<Insert other signature and date lines as appropriate per local IRB policies and procedures>

Informed Consent Form Template for Group C

ACRIN 6678

FDG-PET/CT as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in Non-small Cell Lung Cancer

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

If you want more information about participating in clinical trials, ask your study doctor for the National Cancer Institute (NCI) booklet *Taking Part in Cancer Treatment Research Studies*. Also, you can learn more about clinical trials at http://cancertrials.nci.nih.gov or by calling the NCI's help line at 1-800-4-cancer (1-800-422-6237 or TTY: 1-800-332-8615)

You are being asked to take part in this study because you have advanced lung cancer. This clinical trial for advanced lung cancer involves FDG-PET/CT scans.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if FDG-PET/CT scans can help doctors decide if chemotherapy is working to control your lung cancer. Before FDG-PET/CT can be used for this purpose it is necessary to know how stable (reproducible) FDG-PET/CT measurements of tumor metabolism are. Therefore the purpose of this study is to determine by how much the results of FDG-PET/CT scans differ when scans are performed at 2 different visits up to 1 week apart.

PET stands for Positron Emission Tomography and CT stands for Computed Tomography. PET/CT is a novel imaging technology that combines two imaging modalities (PET images and CT images) into one image.

About FDG-PET Scan

PET is a nuclear medicine medical imaging technique that produces a 3-D image of functional processes in the body.

About CT Scan

A CT scanner is a special kind of X-ray machine. Instead of sending out a single X-ray through your body as with ordinary X-rays, several beams are sent simultaneously from different angles. The computer processes the results, displaying them as a two-dimensional picture shown on a monitor.

About FDG-PET/CT Scan

Many PET scanners also include a CT scanner. This allows images of both anatomy (CT) and function (PET) to be taken during the same examination. The FDG-PET/CT scan has the benefit of combining the PET scan information about cell function with the CT scan information about the size and shape of abnormal cells. Alone, each test has its limitations but when the results of the scans are fused together they provide the most complete information on cancer cell function and location.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Up to 57 people will take part in study Group C, and up to 285 people will participate in all three study groups.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you agree to take part in this study:

Standard medical procedures that are part of regular cancer care and would probably be done even if you do not join the study:

- Chemotherapy (cancer fighting drugs) through a vein in your arm
- Radiation therapy
- Diagnostic CT scan
- Physical examination
- Pregnancy test (if applicable)

Standard medical procedures that are being done specifically because you are in this study (These may or may not be done if you were not in this study):

- PET/CT scan with FDG
- CT scan without contrast

You will be asked to have two (2) FDG-PET/CT scans (1 to 7 days apart) and two (2) other CT scans (also 1 to 7 days apart) before you begin your cancer treatment. Your study doctor will try to take imaging scans on the same day as possible, or on days when you are already scheduled to be at the facility for care. You may not receive the two (2) pre-treatment CT scans if your study and treating doctors decide it is in your best interest or if time becomes an issue. If you have already had an FDG-PET/CT scan before agreeing to participate in this clinical trial, it is possible that scan may be used as the first one for the trial. You will continue to see and follow up with your regular doctor.

[ADD THIS PARAGRAPH AS A GUIDE IF A PREVIOUSLY PERFORMED BASELINE FDG-PET/CT SCAN NEEDS TO BE REPEATED AS A RESEARCH PROCEDURE.] In order to participate in this research project, the FDG-PET/CT scans done before and after treatment must be obtained on the same scanner with a specific technique. The FDG-PET/CT scans must also be done within the timeframe outlined for this trial. Although you had a previous FDG-PET/CT scan, it cannot be used for this trial, because it was done at another hospital or imaging facility, or was done with a technique different from that required by the research protocol, or is outside the timing needed for this protocol. Thus, if you would like to participate in this research project, funds are available to repeat your FDG-PET/CT scan at *INSERT INSTITUTION NAME*. The PET scan would be performed exactly as described in the consent form for the trial but would be specifically for research purposes, and would not be charged to you or your insurance company.

Preparation for a PET/CT Scan: Before each FDG-PET/CT scan, do not eat for 4 to 6 hours before your appointment time and drink only water. You will be given details of what to do to prepare for your PET/CT scan.

During the Exam: On the day of your FDG-PET/CT scan, you first will be given an injection of a small amount of a radioactive drug/tracer (a chemical similar to sugar which is called FDG) into a vein in your arm or hand. The amount of radiation is very small, no more than what you would have during a normal x-ray. It only stays in your body for a few hours. The FDG will travel to particular parts of your

body. It travels to places where glucose is used for energy. It can show cancer because the cancer cells use glucose in a different way from normal tissue.

The PET/CT scanner is a large machine with a hole in the middle. It looks like a donut with a table in the middle. Approximately 50-70 minutes after the injection of FDG, you will be asked to go to the bathroom (urinate) and then lie on a partially enclosed scanning table. The table will slide into the machine. You will be asked to remain still during the scan. You will hear buzzing or clicking sounds during the scan. You will need to lie still for about 20-60 minutes before coming off of the scanning table.

The size of the opening is 27 to 30 inches. How much space you feel you have around you will depend on your body size and the scanner. If you feel any anxiety over being in enclosed spaces, let your study doctor know. A mild sedative may be used to help you feel more comfortable during the exam.

Time Required: The entire FDG-PET/CT scan procedure is expected to take about 2 hours.

Once you have had your FDG-PET/CT scan(s), you may receive treatment. The treatment that you will be getting is not a part of this study. It will be the usual treatment for your kind of cancer. You and your regular doctor will decide what treatments you will get, if any. You are consenting to two (2) FDG-PET/CT scans (1 to 7 days apart) and two (2) other CT scans (also 1 to 7 days apart) before you begin your cancer treatment. However, the two (2) other CT scans are optional. You may not undergo all of these scans, depending on what you and your study and treating doctors decide is in your best interest. The scans will be done exactly the same way as described above.

You will see your regular doctor at regular intervals according to her/his recommendations and usual practice. Information gathered by your regular doctor as part of your normal follow-up visits will be given to your study doctor(s) so they can find out more about your health. Your follow-up care will be decided between you and your regular doctor.

Study Chart

What you do if you are in Group C:

At Registration/ Baseline Visit	• Sign an informed consent form (ICF); • Have a physical examination; • Have a pregnancy test, if applicable; • Provide medical history.
Visit C1: Pre-Treatment Imaging Visit	• Follow instructions provided at Registration/Baseline Visit in preparation for the FDG-PET/CT; • Have a blood sugar test before the FDG injection; • Have a CT scan (may not be the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*; • Have a FDG-PET/CT scan†.
Visit C2: Pre-Treatment Imaging Visit, More Than 24 Hours Between Imaging Scans, But Within 7 Days of Visit C1	• Follow instructions provided at Registration/Baseline Visit in preparation for the FDG-PET/CT; • Have a blood sugar test before the FDG injection; • Have a CT scan (may not be the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*; • Have a FDG-PET/CT scan†.
Clinical Follow-up Visits	• Have a physical examination, at time intervals based on the recommendations and standard practice of your regular doctor.

In most cases, you will have the FDG-PET/CT and CT scans on the same imaging device and during the same imaging session. You do not have to make separate appointments for the FDG-PET/CT and the CT scans. However, some FDG-PET/CT devices may not be able to take CT images meeting the special requirements for this research study. In this case, you will be asked to have the CT scan done on a separate scanner and possibly on a separate day.

*Even if you agree to the CT scans, you may not receive them if your study and treating doctors decide it is in your best interest or if time becomes an issue.
† It is important to the study to make sure you have completed the two FDG-PET/CT scans before you start any treatment.

HOW LONG WILL I BE IN THE STUDY?

We expect that you will be an active participant for up to 1 week before you receive treatment. You will then need to see your regular doctor(s) for follow-up visits as he/she recommends.

You can stop participating in this study at any time. However, if you decide to stop participating, we encourage you to talk to the study doctor and your regular doctor(s) first.

The study doctor may decide to take you off this study if your cancer gets worse. The study doctor may also take you off if new information becomes available that suggests that participating in this study will be unsafe for you. It is unlikely, but the study may also be stopped early due to lack of funding or participation.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side

effects. Many side effects go away soon after the FDG-PET/CT scan. In some cases, side effects can be serious, long lasting or may never go away.

Risks Associated with Radiation Exposure from FDG-PET/CT Scans:
<<Each site may need to modify this section to quote the correct CT dosimetry for its own PET/CT and CT scanners in accordance with its own institutional policies and procedures. This section may necessitate further revision if two (2) FDG-PET/CTs (i.e., one [1] more than presented in the radiation exposure details below) must be conducted for research purposes.>>

This research study involves a maximum exposure to radiation from *1* FDG-PET/CT scans and *2* volumetric CT scans. *[Note that if the first FDG-PET/CT has to be repeated for research, then the number of FDG-PET/CT scans will increase to two (2).]* The radiation exposure you will receive from each FDG-PET/CT scan is equal to a uniform whole-body exposure of approximately *14* mSv (a measure of radiation exposure), with approximately *11* mSv from the injected radioactive FDG and *3* mSv from the CT component. The radiation exposure you will receive from each volumetric CT scan is equal to a uniform whole-body exposure of approximately *6* mSv. The total radiation exposure from all of these procedures is *24* mSv. This is about *48%* of the allowable annual dose of 50 mSv for radiation workers (for example, x-ray technicians). The risk from this level of radiation exposure is too small to be measured and is small when compared with other everyday risks.

If you would like more information about radiation exposure associated with the PET and CT scans, please speak with your study doctor.

Other Risks Associated with PET Scans and Injection of FDG:
Less Likely
Discomfort from lying still on the enclosed scanning table
Bruising or bleeding at the site of injection of FDG
Infection at the site of injection of FDG

Rare
An allergic-type or other adverse reaction to the radioactive drug (FDG) has not been documented so far, but cannot be entirely excluded.

Other Risks Associated with CT Scans:
Rare
Malfunction of worn or implanted electronic medical devices. If you wear or have electronic medical devices implanted, such as a pacemaker or a drug pump, please make sure you tell your study doctors and research staff. It was recently reported by the FDA that the CT scan may cause the malfunction of electronic medical devices.

Reproductive Risks:
Because the radiation from PET scans or CT scans can damage an unborn baby, you should not become pregnant or father a baby while on this study. (The risks of fetal injury, however, are far greater from the chemotherapy that will be used to treat your cancer.) These days, some doctors tell PET scan patients that they should not have close contact with pregnant women, babies and young children for a few hours after their scan. If you are breast feeding, you have to express enough milk beforehand to get your baby through the first 6 hours after the scan. This is not because there will be radiation in the milk. It is because the mother should not be holding the baby closely during the time the radiation is in her body. Some doctors recommend you get someone else to feed the baby for 24 hours, although it is

safe for you to express more milk for those feeds from 6 hours after the scan. It is important you understand that you need to use birth control while on this study. Ask your study doctor about what kind of birth control methods to use and how long to use them. If you are a woman who can become pregnant, you must agree to a pregnancy test (blood test) before starting chemotherapy treatment, and later on if your physician considers it necessary.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, your study doctor(s) may learn more information from the FDG-PET/CT scans and how they change or stay the same within 1 week of each scan. Please discuss with your regular doctor the findings from the scans being completed and the information that is available to you at that time. Taking part in this study may or may not make your health better. This knowledge will help doctors decide on the best treatment for patients with lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

You may choose to not participate in this study. You could have PET/CT scans done without participating in this study. Please talk to your regular doctor about this and other options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Records of your participation on this study, your progress, and images submitted (such as FDG-PET/CT scan or CT scan) while you are on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia. Your personal information may be given out if required by law.

Authorized representatives of ACRIN, Center for Statistical Sciences at Brown University, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the Institutional Review Board (IRB) of *<<Institution>>*, and other groups or organizations that have a role in this study will have access to and may inspect and/or copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner such that you cannot be identified.

Your research records and images will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number. The research that may be done with the information will not specifically help you. But, it might help people who have cancer and other diseases in the future.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study may lead to added costs to you or your insurance company. FDG-PET/CT scans for lung cancer are usually covered by most insurance companies, but this is not guaranteed. Please ask your study doctor(s) about any expected added costs or insurance problems.

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

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, *<<insert name>>*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at *<<insert 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.

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, *<<insert name>>*, at *<<insert telephone number>>*.

For questions about your rights while taking part in this study call the *<<insert name IRB contact person>>* at *<<insert name of the IRB>>* Institutional Review Board (a group of people who review the research to protect your rights) at *<<insert telephone number>>*.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at **1–800–4–CANCER (1–800–422–6237)** or **TTY: 1–800–332–8615.**

Visit the NCI's Web sites for clinical trials information http://cancertrials.nci.nih.gov**,** or for cancer information visit http://cancernet.nci.nih.gov. ACRIN's Web site is www.acrin.org.

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You also have had the opportunity to take this consent form home for review or discussion if you want to. A copy of the signed consent will be given to you.

_____ _____

Signature of Participant (or Legal Representative) Date

<Insert other signature and date lines as appropriate per local IRB policies and procedures>

Appendix II

ACRIN 6678 Eligibility Checklist

The ACRIN 6678 Eligibility Checklist is available on the ACRIN web site at ACRIN 6678 Protocol web page (www.acrin.org/6678_protocol.aspx). For more detailed information, contact the ACRIN 6678 Data Manager at ACRIN. The contact information can also be found on the above-mentioned web page.

Appendix III

ACRIN 6678 Participating Institutions

A minimum of eight (8) participating institutions, Site Principal Investigators will be identified upon review and approval of completed ACRIN Protocol Specific Application (PSA).

Appendix IV

ACRIN 6678 Protocol-Specific Application Information

Application Process

All participating institutions must be ACRIN-approved institutions prior to study participation and accrual. The approval process for ACRIN 6678 includes submitting an ACRIN Protocol Specific Application (PSA), having the PET scanner credentialed for study imaging, and obtaining qualification from ACRIN for the CT Volumetric imaging. Detailed information is available on the ACRIN web site (www.acrin.org) under list of current protocols (ACRIN 6678). The complete Protocol-Specific Application is on the ACRIN web site at www.acrin.org/6678_protocol.aspx.

Appendix V

ACRIN Qualification Procedures for PET Imaging

Details of the ACRIN Qualification Procedures for PET Imaging are available on the ACRIN web site at ACRIN 6678 Protocol web page (www.acrin.org/6678_protocol.aspx). For more detailed information, send an email to petcorelab@acr-arrs.org.

Appendix VI

PET Imaging Acquisition Parameters and Image Data Analysis
(Detailed criteria/specifications for performance of PET scanning in the study)

Additional information for PET Imaging Acquisition Parameters and Analysis are available on the ACRIN web site at (www.acrin.org/6678_protocol.aspx). For more detailed information, send an email to petcorelab@acr-arrs.org.

Acquisition and Analysis of FDG-PET/CT Scans

FDG-PET/CT scans will be performed according to the guidelines for NCI-sponsored studies as recently published by Shankar et al. (1).

1. Participant Preparation

Participants must fast for a minimum of 4 hours prior to the injection of FDG for the PET scan. However, they will be encouraged to drink water to ensure adequate hydration.

- Upon arrival at the PET facility, the participant's weight and height will be measured and recorded. Serum glucose should be measured to determine that the blood glucose concentration is within the normal range.
- If the serum glucose concentration is found to be greater than 150 mg/dL, the study should be rescheduled. The referring oncologist or the primary physician of the patient will be contacted to optimize blood glucose control.
- The participant should be placed in a comfortable position, either supine or semi-recumbent. A large-bore intravenous line (21-gauge or greater) should be placed in an arm or hand vein. The room should be kept warm to avoid shivering and temperature effects that may increase muscular or fat uptake. The participant should move as little as possible and should not talk more than necessary in the first 30 min following FDG injection.
- Prior to positioning the participant on the PET scanner the participant should be asked to urinate.

2. Injection of [^{18}F] Fluorodeoxyglucose (FDG)

- The dose of FDG to be administered should be 10 to 20 millicuries (mCi), adjusted according to weight as suggested by the scanner manufacturer.
- FDG will be synthesized and prepared in accordance with USP compendial standards.
- The exact time of calibration of the dose should be recorded and the exact time of injection noted to permit correction of the administered dose for radioactive decay. In addition, the dose remaining in the tubing or syringe, or that was spilled during injection should be recorded. The injection should be performed through an intravenous catheter.

3. FDG-PET/CT Imaging

- PET scanning must begin 60 ± 10 minutes after FDG injection. The time between injection and the start of the PET scanning for the second and third scans should be matched as closely as possible to that for the first scan (less than 10 min difference in uptake times).
- Participants will generally be positioned in the PET/CT scanner with their arms raised above the head. If participants cannot tolerate this position for the duration of the PET/CT study, a different participant positioning may be chosen. However, arms should be positioned in the same way at the baseline and the follow-up studies.
- A low-dose CT scan will be acquired for attenuation correction and anatomical localization of findings in the PET scan.
- The acquisition parameter for the low-dose CT scan for attenuation correction should be: kV = 120; effective mAs = 30-80 (patient dependent); gantry rotation time ≤ 0.5 sec; maximum reconstructed width = 3-5 mm without overlap; standard reconstruction algorithm, minimum reconstruction diameter = outer arm to outer arm; and without iodinated contrast (86).
- The axial field of view of the CT scan for attenuation correction will range from the mid thighs to the base of the skull. Arm positioning will be the same as for the PET scan, typically above the head.
- The CT scan will be performed during "shallow breathing" as described previously (21). No respiratory gating will be applied.
- After the CT scan, a PET scan covering the same axial field of view will be performed. This scan will start at the mid thighs. The number of bed positions and the acquisition time per bed position will be scanner specific. Typical parameters are 6 bed positions and an acquisition of 2-5 min per bed position.

4. Image Reconstruction

- The PET data will be corrected for dead time, scatter, randoms and attenuation using standard algorithms provided by the scanner manufacturers.
- Image reconstruction will be performed as specified in the ACRIN certification of the PET/CT scanner.

5. Blinded Central Image Analysis

- Activity concentrations in the attenuation-corrected PET images will be converted to standardized uptake values (SUVs) by dividing the activity concentrations by the decay-corrected injected dose and multiplying with the body weight of the participant.
- The intrathoracic lesions with the highest FDG uptake in the pre-chemotherapy PET scan (scan 2 in group A and scan 1 group B) will be analyzed in order to determine the metabolic response of the participant (primary endpoint).
- A circular region of interest (ROI) with a diameter of 0.75 to 1.5 cm will be centered at the site of maximum FDG uptake within this lesion. ROIs of the same size will be placed in the slices immediately above and below, at the same transverse location.

- The average SUV within the volume encompassed by these three ROIs will be determined and recorded. This approach for definition of ROIs has been successfully used for assessment of tumor response in patients with advanced NSCLC (26) and a variety of other malignant tumors (26-29, 31, 93-95). In total these studies include more than 300 patients and more than 600 PET scans. As part of the exploratory analyses, the maximum SUV and glucose-corrected average and maximum SUVs (25) will be recorded and analyzed.
- In most patients the primary tumor will show the highest FDG uptake. However, in a small subgroup of participants the primary tumor may be small (< 2cm) and show only low FDG uptake in PET or it may have been resected in participants with recurrent NSCLC. In this case, the intrathoracic metastatic lesion with the highest FDG uptake will be used for analysis.
- As part of an exploratory analysis, ROIs will be placed in the same way in up to 6 metastatic lesions. In participants with more than 6 metastatic lesions in several organs a maximum of 3 lesions should be in the same organ. In each organ, the lesions with the highest FDG uptake will be selected for analysis.
- For quality control purposes, a large circular ROI (diameter >= 5 cm) will be placed in normal liver tissue. The mean SUV in this ROI will be recorded.
- In the case of multiple liver metastases, it may not be feasible to place one large ROI in normal liver tissues. In this case, several small ROIs, including the same number of pixels as one 5-cm ROI, may be placed in normal liver tissue. FDG uptake within these lesions will be averaged and used for further analysis.
- If the mean SUV within the liver changes by more than 1.0 between two scans, the SUV calculation will be checked for errors. Specifically, the scanner cross calibration, the decay correction of the injected activity, and the participant's body weight will be checked (see checklist below for details)
- Previous studies have shown that this approach for quantitative analysis of tumor FDG uptake is highly reproducible (9). Nevertheless, quantitative analysis will be performed independently by two observers in order to minimize random errors in SUV measurements. Discrepant findings will be discussed and resolved by consensus.

6. Local Image Interpretation

- Describe the location of the primary tumor and of metastatic lesions.
- Measure and record the maximum SUV in the primary tumor. If maximum SUV is less than 4.0, contact ACRIN Image Management Center (IMC) to determine whether the participant should remain in the study or not.
- If the diameter of the primary tumor is less than 2 cm or the primary tumor demonstrates only low FDG uptake, measure the maximum SUV of the lesion with the highest FDG uptake in the chest.
- Measure and record the mean SUV in the liver as described in Section 5 above.
- Check image quality according to the checklist below.

Checklist for PET/CT Image Quality Control

7. SUV Calculations

7.1 Time of Injection and Scan Start Time

7.1.1 Data Correctly Recorded and Entered?

Check whether the time of injection and the scan start time have been correctly recorded. If the PET scanner software performs decay correction for the time interval between injection and imaging, check whether the time of injection and the start time of the scanner have been correctly entered.

7.1.2 Data correctly recorded and entered: Proceed to 7.2

7.1.3 Injection Time Missing

7.1.3.1 Time between injection and start of scan known: Record time between injection and start of scan and proceed to 7.2

7.1.3.2 Time between injection and start of scan unknown: Record a protocol violation and try to repeat the scan. If the scan cannot be repeated, the participant goes off study.

7.1.4 Scan Start Time Missing

7.1.4.1 Time between injection and start of scan known: Record time between injection and start of scan and proceed to 7.2

7.1.4.2 Time between injection and start of scan unknown: Record a protocol violation and try to repeat the scan. If the scan cannot be repeated, the participant goes off study.

7.2 Is the Time between FDG injection and Start of the PET Emission Scan within the Specifications of the Protocol?

7.2.1 All Scans (Baseline and Follow-up Scans)

7.2.1.1 Time between injection and start of PET scan within 50-70 min: If it is a baseline scan, proceed to 7.3. If it is a follow-up scan, proceed to 7.2.2

7.2.1.2 Time between injection and start of PET scan >=45 and < 50 min: Record a protocol variation. Participant remains in the study.

7.2.1.3 Time between injection and start of PET scan >70 min and <= 80 min: Record a protocol variation. Participant remains in the study.

7.2.1.4 Time between injection and start of PET scan < 45 min: Record a protocol violation and try to repeat the scan. If the scan cannot be repeated, the participant goes off study.

7.2.1.5 Time between injection and start of PET scan > 80 min: Record a protocol violation and try to repeat the scan. If the scan cannot be repeated, the participant goes off study.

7.2.2 Follow-up Scans

7.2.2.1 Time between injection and PET imaging differs by 10 min or less between the baseline and the follow-up scan: Proceed to 7.3

7.2.2.2 Time between injection and PET imaging differs by more than 10 min, up to 15 min: Record a protocol variation. Participant remains in the study.

7.2.2.3 Time between injection and PET imaging differs by more than 15 min: Record a protocol violation and try to repeat the scan. If the scan cannot be repeated, the participant goes off study.

7.3 Injected Dose

Has the injected dose been correctly calculated and entered in the header of the PET data set?

7.3.1 Injected dose known and correctly entered: Proceed to 7.4

7.3.2 Injected dose unknown or incorrectly entered: Correct image header information. If injected dose is unknown, but the dose at the time of imaging is known, record this dose and use it for SUV calculations. Proceed to Section 7.4. If the dose at the time of imaging is also unknown, try to repeat the scan. If the scan cannot be repeated the participant goes off study.

7.4 Body Weight

7.4.1 Body weight of the participant correctly recorded and entered into the header of the PET data set: Proceed to Section 8.

7.4.2 Body weight incorrect or unknown: Record a protocol violation. Retrieve body weight from participant chart.

8. Check Fasting State and Blood Glucose Levels

8.1 Participant fasted for > 4 hours: Proceed to 8.3

8.2 Participant fasted for <= 4 hours

8.2.1 Blood glucose levels <= 150 mg/100mL: Participant remains in the study.

8.2.2 Blood glucose levels > 150 mg/100mL: Try to repeat the scan. If the scan cannot be repeated the participant goes off study.

8.3 Blood glucose level <= 150 mg/100mL: Proceed to 9

8.4 Blood glucose level > 150 mg/100mL: Try to repeat the scan. If the scan cannot be repeated the participant goes off study.

9. Measure Liver SUV

(Internal quality control, see Section 5 above for details of this measurement)

9.1 All Studies (Baseline and Follow-up Studies)

9.1.1 Mean liver SUV within 1.5 – 4.0 (expected variability): Proceed to 9.2.

9.1.2 Mean liver SUV < 1.5 or > 4.0: Check scanner calibration and cross calibration of dose calibrator and PET scanner. Are there signs of partially paravenous tracer administration in the images? Record protocol variation, if no explanation for the unusual liver SUV can be found or there is evidence of partially paravenous tracer administration.

9.2 Follow-up Scans

9.2.1 Difference in mean liver SUV between the baseline and follow-up scan less than 1.0: Proceed to 10.

9.2.2 Difference in mean liver SUV between the baseline and follow-up scan greater than 1.0: Check scanner calibration and cross calibration of dose calibrator and PET scanner. Are there signs of partially paravenous tracer administration in the images? Record protocol variation, if no explanation for the unusual liver SUV can be found or there is evidence of partially paravenous tracer administration.

10. Artifacts in the Reconstructed Images

10.1 Beam hardening artifacts in CT

10.1.1 Are there any metal implants or other structures with high density in the chest? No, proceed to 10.1.2

10.1.1.1 Do the implants cause beam hardening artifacts on CT that are visible on the reconstructed PET emission images? No, proceed to 10.1.2

10.1.1.2 Are the beam hardening artifacts overlying the tumor region? No, proceed to 10.1.2

10.1.1.3 Is there an alternative lesion in the chest that could be used for quantitative measurements in PET (e.g. pulmonary metastasis or lymph node metastasis): If yes, use this lesion for quantitative analysis. If no, the participant goes off study.

10.1.2 Was the scan acquired with the arms raised above the head? Yes, proceed to 10.2.

10.1.2.1 Are the resulting beam hardening artifacts visible on the PET images and over the tumor region? No, proceed to 10.2

10.1.2.2 Is there an alternative lesion in the chest that could be used for quantitative measurements in PET (e.g. pulmonary metastasis or lymph node metastasis): If yes, use this lesion for quantitative analysis. If no, the participant goes off study.

10.2 Participant Movement

10.2.1 Is there any visible mis-registration between the outer contours of the tumor as seen on CT and the outer contours seen on PET? This is checked on the PET/CT fusion images.

10.2.1.1 If yes, estimate the degree of misregistration by counting the number of slices that the tumor is visible on CT, but not on PET. If there is misregistration by more than 3 slices of the PET scan (about 1 cm), report a protocol variation.

10.2.2 Can the volume of interest for quantitative analysis of the PET scans be placed in an area where PET and CT images overlap? If yes, use this area for quantitative analysis. If no, proceed to 10.2.1.

10.2.3 Is there another lesion that can be used to quantify FDG uptake (see Appendix VI for criteria)? If no, try to repeat the PET scan. If it is not possible to repeat the scan, the participant goes off study.

References

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Appendix VII

CT Acquisition Parameters and Image Data Analysis

Additional Information for the CT Acquisition Parameters and Volumetric Analyses are also available on the ACRIN web site at (www.acrin.org/6678_protocol.aspx). For more detailed information, contact the Image Management Center at 215-940-8820.

Acquisition and Analysis of the CT Scans

The CT scans serve three purposes: (a) attenuation correction and registration with PET scans for anatomic localization of FDG uptake; (b) response assessment using RECIST; and (c) high spatial quality data sets for central volumetric analyses of lung lesions. Depending upon considerations of workflow and the need for intravenous contrast, individual institutions may have different processes for completing the chest CT scans used for RECIST and tumor volumetric assessments. The following are potential scenarios:

- **Single Platform**: fusion PET/CT scanner: All studies are performed on a fusion PET/CT scan, including the PET/CT scanner, and one single inspiratory CT without contrast for both RECIST criteria and tumor volumetry.
- **Single Platform**: fusion PET/CT scanner: All studies are performed on a fusion PET/CT scan, including the PET/CT scanner, an inspiratory CT with contrast for RECIST criteria, and an inspiratory CT without contrast for tumor volumetry.
- **Dual Platforms**: Fusion PET/CT scanner used to perform a PET/CT scan and an inspiratory CT without contrast for tumor volumetry as well as a dedicated, standalone CT scanner to perform a CT with contrast for RECIST criteria.

1. Low Dose CT for PET Attenuation Correction

Parameters for these CT scans are described in Appendix VI (Acquisition Parameters and Analysis of the PET/CT Scans), since the primary purpose of these scans is to correct the PET emission data for photon attenuation.

2. CT Volumetry: Optional (Participant May Not Undergo Volumetric CT Scans/Decision Left to Clinicians and Participants)

2.1 Image Acquisition

To ensure the level of spatial quality necessary for tumor volumetric analyses, the scanner platforms must be able to perform prospective reconstructions of a single helical sequence at different slice thicknesses. The following are representative PET/CT systems:

- Siemens Biograph PET/CT (CT scanners 6,16, 64-slice); Siemens Medical Solutions | Malvern, PA.
- GE Discovery PET/CT scanners; GE Healthcare Technologies | Waukesha, WI, USA
- Philips Gemini PET/CT scanners (Brilliance CT: 6, 10, 16, 40-slice; 40 and 64 channel); Philips Medical Systems | Andover, MA, USA

Research CT scans for tumor volumetric analysis will be performed on equipment qualified for this trial, and all CT scans for an individual participant should be performed on the same platform throughout the trial. In the rare instance of equipment malfunction, follow-up scans on an individual participant can be performed on the *same type* of platform.

In Groups A and C, the optional CT component of the two baseline (pre-chemotherapy) PET-CT scans will provide a basis for determining the inter-scan precision (reproducibility) of volumetric measurements. In addition, for Group A, changes in tumor volume will be assessed post-cycle 1 in order to assess early changes in tumor volume in response to chemotherapy. In Group B, measurement of tumor volume by CT will be performed at baseline and may occur at both or either timepoint—post-cycle 1 or 2 of chemotherapy. These optional CT scans will allow us to evaluate the time course of changes in tumor volume during chemotherapy.

Each scanner platform has slightly different technical specifications and user inputs for imaging parameters. The following table provides specifications for the acquisition and reconstruction parameters for the CT series performed for tumor volumetry.

Table 1. Parameters for the CT scans used to measure tumor volume.

Parameter	Diagnostic CT Scan for Tumor Volumetry
KV	120
Gantry rotation time	≤ 0.5 sec
Scanner Effective mAs (Regular-large size patient)	100-260
Maximum scan | breath-hold time (40 cm long thorax)	≤ 15 sec
Number of active channels (N)	≥ 6
Maximum Reconstructed slice width	1-1.5 mm
Reconstruction interval	0 – 20% overlap
Reconstruction algorithm*	Standard
Reconstruction diameter (dFOV)	outer rib to outer rib
Intravenous contrast media	None
Arm positioning	Above the head

Parameters for tumor volumetry should provide an in-plane voxel size of 0.55-0.75 mm.

All CT datasets will be transmitted to ACRIN Imaging Management Center for archive and distribution to Image Volumetric Analysis CORE (V-CORE) facilities for volumetric analyses using one or more volumetric software programs.

2.2 Volume Measurements and Image Analysis Core Credentialing

Up to four software programs may be used to provide volumetric measurements of all measurable disease within the lung parenchyma. No attempt will be made to perform manual volumetric analyses of measurable disease in the mediastinum or other anatomic regions of low surrounding contrast. The software programs may include:

- Siemens Leonardo Lung Processing Program; Siemens Medical Solutions (Malvern, PA).
- Lung VCAR software; GE Healthcare (Waukesha, WI)
- R2 ImageChecker CT Lung System; R2 Technology (Sunnyvale, CA)

- Lung Imaging Database Consortium Image Analysis Software; UCLA Thoracic Imaging Research Group

Each software platform will be run as described by the vendor | software developers. Measurable disease on PET/CT scans of all participants will be measured according to the protocol schema using each software system by independent readers blinded to all clinical and imaging information. Measurable lesions will be defined on the baseline (pre-chemotherapy cycle 1) CT scan. The textual description of these lesions will be used to identify them on subsequent scans. Volumetric analyses on subsequent scans will be performed without knowledge of measurements performed at the local sites or the results of FDG PET uptake changes.

All CT image series will be transmitted to ACRIN Imaging Management Center for archive and distribution to distributed CORE facilities for volumetric analyses using one or more of the different software programs.

A distributed V-CORE includes the ACRIN CORE Laboratory as well as individual sites that maintain and have documented expertise in the use of the analysis workstations | software that will perform the tumor volumetry in this trial. One V-CORE laboratory will perform all measurements using a given image analysis platform. Volumetric measurements will be performed only by radiologists certified for protocol 6678; a single reader will analyze images for a given participant at all time points. All readers will be trained on the ACRIN V-CORE SOP and sign off to document training. The expertise of a V-CORE laboratory and its compliance with image transmission, de-identification, and mark-up procedures will require documentation of the following capabilities:

- Ability to send and receive DICOM formatted image data archived at ACRIN Image Management Center (IMC) using sFTP. Sites must be able to receive de-identified data with scrubbed headers from ACRIN IMC.
- Documentation of the specific volumetry software platform by vendor, version, and other specifications, as well as brief description of the software segmentation steps.
- Documentation of prior CORE experimental analyses using this software, anticipated number of analyses per unit time, and guaranteed access to the software for purposes of this study.
- Compliance with transmission procedures and performance of volumetric measurements using the specific image analysis software in three test cases, consisting of one ACRIN test case and two cases from the V-CORE that have been scrubbed of identifiers prior to transmission to ACRIN IMC.
- Satisfactory credentialing for completion of RECIST criteria on CT scans (see below).

Each volumetry platform achieves nodule segmentation and volumetric measurement with different proprietary image processing routines and knowledge base. A detailed understanding of the analytical basis underlying the segmentation process is beyond the scope of this trial. The objectives of the V-CORES are to perform volumetric analyses of: (a) Groups A and C two baseline CT components of PET/CT scans to assess interscan variability; and (b) Group B sequential CT components of PET/CT scans and Group A CT components of PET/CT scans immediately pre-chemotherapy and post-cycle 1, to analyze volume changes in support of the exploratory objectives and to identify differences in performance between software platforms.

2.2.1 Baseline Scans

All CT scans from PET/CT studies will be transferred from the participating sites to ACRIN IMC. IMC will distribute the scrubbed data sets to V-COREs for analyses. The cores will receive neither the results of local image interpretations nor any clinical information beyond the cycle associated with the data set. The primary lung lesion will be defined on the baseline scan; multifocal lung lesions may be defined as the primary lung lesion depending on the individual case. The target lesion will be segmented according to the requirements of the individual software program and the volume calculated. Manual editing in regions of complex anatomy, such as the juxtapleural or juxtavascular regions, will be allowed if this is a routine feature of the software. Software programs that provide 3D volumetric renditions of the nodule will be captured and these 3D volumetric renditions will be archived. In studies with more than one lesion, lesions will be numbered craniocaudally and, if multiple nodules are present in the same axial plane, from medial to lateral. The x and y coordinates of the target centroid will also be captured. This indexing will be used on all subsequent reads to ensure concordance of lesions on follow up.

2.2.2 Follow-up Interpretations

When interpreting all subsequent follow-up CT scans, the baseline (pre-chemotherapy) annotated scan will be reviewed for: the number of the target lesion, the location of the lesion (x, y coordinates) and the target volume. This will provide the reader with a basis for assessing measurement change. Readers will review all available images for the current time point prior to making a measurement. The target lesion will be segmented according to the requirements of the individual software program, the volume calculated, and target location by number and x, y coordinates recorded. All image metadata (results of image analysis) will be entered into the ACRIN analysis database.

3. Tumor Response Evaluation According To RECIST

3.1 Image Acquisition

Response assessment using RECIST criteria will be performed on: CT scans pre-chemotherapy cycle 1, the CT scans pre-chemotherapy cycle 3 and, thereafter, at every other chemotherapy treatment cycle. Scans will be performed after administration of oral and IV contrast agents according to institutional practices.

Iodinated intravenous (IV) contrast media may be administered for diagnostic CT scans per standard institutional practice, unless contraindicated. The decision not to use IV contrast for CT is at the discretion of the performing radiologist. If IV contrast is *not* administered for these scans, then these non-contrast CT series can be used for both RECIST and volumetric measurements by prospectively reconstructing the image data into both thick (2.5 to 5 mm) and thin-section (1 to 1.25 mm) series, respectively; this will alleviate the need for any additional research-related CT scans (specifically, those done for volumetrics only).

The CT scan with contrast is obtained with arms elevated above the head and at suspended maximal inspiration to provide optimal relative contrast of lung lesions within aerated lung. CT scans for RECIST interpretations may be acquired on the fusion PET/CT scanners or dedicated CT system, depending upon the workflow practices, but in all instances, the scanner platforms will be qualified for this trial by ACRIN. Typical parameters for image acquisition and reconstruction are shown in Table 2.

Table 2: Parameters for the CT scans used to assess tumor response according to RECIST

Parameter	Dedicated CT for RECIST*
KV	120

Gantry rotation time	≤ 0.5 sec
Scanner Effective mAs (Regular-large size patient)	100-260
Maximum scan | breath-hold time (40 cm long thorax)	≤ 15 sec
Number of active channels (N)	≥ 6
Maximum Reconstructed slice width	5 mm[1]
Reconstruction interval	0-20% overlap
Reconstruction algorithm	Standard
Reconstruction diameter (dFOV)	outer rib to outer rib
Intravenous contrast media	Per institution practice | indication[2]
Arm positioning	Above the head

1 If the inspiratory scan of the PET/CT is non-contrast, it *also* should be used for tumor volumetry, and prospectively reconstructed at 1-1.25 (volumetry) and 2.5-5 mm (diagnostic interpretation using RECIST) slice thicknesses.

2. Intravenous contrast should be administered according to standard practices with respect to amount, flow rates, and timing with respect to image acquisition, depending upon the body parts imaged. The same method of contrast administration should be followed with all subsequent scans.

3.2 Image Data Analysis

3.2.1 Local CT Interpretation

Local CT interpretations generally will be provided to treating physicians for purposes of managing therapy. However, treating physicians will be blinded to the results of the first follow-up CT scan (scan 3 in group A and scan 2 in group B) except when the scan shows potentially life threatening tumor progression, impending fractures or other serious complications. In order to ensure that treating physicians are blinded, sites will need to take appropriate measures to prevent these digital images from being accessible in their institution's PACS system. Also, a full written report of the results of CT should not be made available to the treating physicians, but a limited report indicating there were no life threatening or serious changes may be made available after chemotherapy cycle 1. Response assessment by CT after 2 cycles of therapy will be communicated to the physicians as part of the routine clinical care of participants with advanced NSCLC treated with chemotherapy.

3.2.2 Response Evaluation Criteria in Solid Tumors (RECIST)

The following categories of disease will be used in determining response to treatment by RECIST:

- **Measurable disease:** The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology | histology.
- **Measurable lesions**: Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm with helical CT.
- **Non-measurable lesions**: all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with helical CT scan), i.e., bone lesions, leptomeningeal disease, Ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic cutis | pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

All measurements will be taken and recorded in metric notation on a calibrated diagnostic imaging workstation at full resolution using electronic calipers. The baseline measurements will be performed within one week of the start of treatment; measurements obtained following chemotherapy cycles will be obtained on scans performed within 1-3 days of the next cycle of treatment. The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Lung lesions will be evaluated on lung windows; mediastinal and or soft tissue lesions will be evaluated on soft tissue windows. The acquisition parameters provided above serve as guidelines for CT technique.

"Target" and "Non-Target" lesions will be documented according to the following guidelines:

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter and their suitability for accurate repeated measurements.
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

The following summarizes the categories of response:

Response Criteria	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since treatment start
	Evaluation of Non-Target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response; Stable Disease (SD)	Persistence of one or more non-target lesions(s) or/and maintenance of tumor marker level above the normal limits
Progressive disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)
(1) Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by follow-up imaging.	

Evaluation of Best Overall Response: The best overall response recorded from the start of the treatment until disease progression | recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	Evaluation of Non-Target Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete Response | SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Confirmation:

- To be assigned the status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- To be assigned the status of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of Overall Response: This is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started. The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the study population.

3.2.3 Blinded CT Reading

Central blinded reading of all CT scans according to RECIST criteria will be used for correlation with metabolic changes seen on PET and CT tumor volumetry.

3.2.4 Baseline Interpretations

Target lesions on scans for Group A and B participants will be defined on the baseline scan. A maximum of 10 target lesions will be defined with no more than 5 lesions per single organ. The 10 target lesions will be chosen with representation from all organs with measurable disease.

A screen capture of each target lesion annotated with a pointer and a lesion reference number assigned to the target lesion will be generated and archived. This will be used on subsequent reads to ensure concordance between lesions on follow up exams. The reader will identify the axial slice on the baseline exam that represents the largest axial equator of the lesion and will choose the orientation of longest axis diameter measurement to be approximated on subsequent scans. Measurements will be made from the axial post-contrast scan that best demonstrates the lesion as distinct from background.

All measurements will be made by electronic calipers; images that capture the actual measurement axis with calipers will be saved and archived with the exam.

3.2.5 Follow-up Interpretations

When interpreting all subsequent follow-up CT scans, the baseline (pre-chemotherapy) annotated scan will be reviewed for: the axial equator (slice location) from which the maximum diameter was obtained, the axis of the diameter, and the measurement. This will provide the reader with a basis for assessing measurement change. Readers will review all available images for the current time point prior to making a measurement. Measurements will be made from the axial post contrast scan that best demonstrates the lesion as distinct from background. Unless there is an obvious change in lesion shape, the reader will identify the slice on the current exam that best matches the lesion anatomy used for the prior measurement as well as an axis for diameter measurement that best approximates the axis used for prior measurements. If lesions undergo an obvious change in shape, a new axis (and axial equator) corresponding to longest diameter will be measured. All measurements will be made by electronic calipers; images that capture the actual measurement axis with calipers will be saved and archived with the exam.

3.2.6 Reader Qualification for RECIST

Central reads will be performed by certified core radiologists, and will employ a single reader for each participant for all time points. All readers will be trained on the ACRIN RECIST SOP and sign off to document training.

Training includes the following reads from one archive test case:

- One Baseline test scan to ensure compliance with | understanding of the use of RECIST criteria and the method of annotating index lesions for purposes of future comparison.
- Three test follow-up scans to ensure compliance with SOPs for follow-up reads and target definitions. All three lesion diameters in the test set must be within 10% of a standard established for the test case defined by the ACRIN Imaging Management Center.

4. Qualification of CT Scanners

Participating sites will be required to submit two (2) CT scans of the lungs using the volumetric parameters outlined on page 113 (Appendix VII, Section 2.1, Table 1), before enrolling any study participants to this trial.

4.1 Image Data Sets

Two (2) image data sets will be evaluated. Images produced at an image thickness of 3-5mm will be used for measurements employing RECIST criteria. Images produced at an image thickness of 1-1.5mm will be used for volumetric analyses. Both image data sets may be produced from a single PET/CT acquisition provided that the PET/CT scanner is capable of prospective reconstruction at varying image thicknesses.

4.2 Reconstructing Volumetric Images for RECIST Measurements

Images produced for volumetric analyses can be used for RECIST measurements if the PET/CT scanner is capable of producing prospective reconstructed slices. Images must first be prospectively reconstructed at an image thickness of 3 mm before measurements are made using RECIST criteria.

4.3 Reconstructing CT Images Produced on a PET/CT for Volumetric Analyses

CT Images produced on a PET/CT scanner also may be used for volumetric analyses if:

1. The CT scan is acquired on inspiration; and
2. The PET/CT scanner can prospectively reconstruct images at 1-1.5 mm.

4.4 Required CT Test Case Submission

The required CT test cases must be submitted to the ACRIN MR/CT Imaging Core Lab. All imaging submissions must be in DICOM format via CD/DVD-ROM or via the internet using a secure File Transfer Protocol (sFTP).

Removal of Confidential Participant Information

The header record on DICOM formatted image data, which often contains information identifying the participant by name, MUST be scrubbed before the image is transferred. This involves replacing the Participant Name tag with the ACRIN Institution ID or number, replacing Participant ID tag with the ACRIN case number and putting the study number into the Other Participant ID tag. This can be performed using a customized software program or by using TRIAD software available from ACRIN. Contact the ACRIN Image Management Center for additional details at Triad-Support@acr-arrs.org.

sFTP Transfer

Digitally generated image files in DICOM v3.0 format can be transmitted to the ACR Image Management Center (IMC) via sFTP directly to the image archive. ACRIN can provide electronic image submission and anonymization utilities for participating institutions via TRIAD software. For support in sending the images via the internet using TRIAD, contact the representatives of the Image Management Center via email at Triad-Support@acr-arrs.org or via phone: 215-940-8820.

An Imaging Transmittal Worksheet (ITW), which can be found on the ACRIN 6678 web site (www.acrin.org/6678_protocol.aspx), must be faxed at the time of all image submissions according to the instructions on the ITW.

Fax ITW to:
ACRIN Core Lab
ATTN: 6678 Imaging Specialist
215-923-1737

DICOM CD/DVD-ROM Transfer

In the event that the electronic transfer of scrubbed image headers is not available, images may also be sent on a CD/DVD-ROM to the ACRIN Image Management Center for transfer to the image archive. Please contact ACRIN prior to sending the media to confirm compatibility.

Mail Images and ITW to:

American College of Radiology Imaging Network
MR/CT Core Laboratory
Attn: ACRIN 6678
1818 Market Street, 16th floor
Philadelphia, PA 19103