DEPARTMENT OF THE ARMY
HEADQUARTERS, MADIGAN ARMY MEDICAL CENTER
TACOMA, WASHINGTON 98431-5000

REPLY TO
ATTENTION OF

ARM1.941116.019

HSHJ-CI

18 October 1993

MEMORANDUM FOR: Commander, US Army Medical Department Center and School, ATTN: HSMC-GCI, Clinical Investigation Regulatory Office, 1608 Stanley Road, Sam Houston, TX 78234-6060

SUBJECT: Research Protocol: A Multicenter Clinical Study to Compare Imaging of Non-Small Cell Lung Cancer With A Technetium-Labelled Monoclonal Antibody Produced by Two Different Manufacturers by MAJ Mark E. Robson, MC

1. This protocol has been closed to patient entry by the sponsor due to sufficient subject accrual.

2. Therefore, it has been terminated at MAMC. The protocol never received final approval at MAMC because the principal investigator did not furnish the required paperwork (DA Form 1572 and clinical brochure). No patients were entered at MAMC.

3. The protocol was forwarded to CIRO, 16 Sep 93.

DAN C. MOORE, M.D.
COL, MC
C, Department of Clinical Investigation

MADIGAN ARMY MEDICAL CENTER
CLINICAL INVESTIGATION PROTOCOL

Title: A MULTICENTER CLINICAL STUDY TO COMPARE IMAGING OF NON-SMALL CELL LUNG CANCER WITH A TECHNETIUM-LABELLED MONOCLONAL ANTIBODY PRODUCED BY TWO DIFFERENT MANUFACTURERS

Personnel Involved:

a. **Principal Investigators:** Mark Robson, MAJ, MC
Hematology-Oncology
968-2505

John Bauman, LTC, MC
Nuclear Medicine
968-1645

b. **Associate Investigator(s):** Hematology-Oncology 968-2505
Luke M. Stapleton, LTC, MC
Howard Davidson, COL, MC
Patrick L. Gomez, MAJ, MC
Kenneth A. Bertram, MAJ, MC
Robert O. Ellis, MAJ, MC
Jennifer L. Cadiz, CPT(P), MC
Richard C. Tenglin, MAJ(P), MC
James Hu, CPT(P), MC
Robert Vallion, LTC, MC
Diana Willadsen, CPT, MC

Nuclear Medicine 968-1645
Stephen E. Budd, MAJ, MC
Stanton R. Brown, COL, MC
Terry R. Minton, LTC, MS

Facilities to be used: Department of Hematology-Oncology,
Department of Nuclear Medicine,
Madigan Army Medical Center

Anticipated start date: August 1993

Anticipated completion date: August 1994

Anticipated Number of Patients: 6-10

Age Range of Patients: Greater than 18 years old

Source of Patients: Hematology-Oncology Clinic, MAMC
Pulmonary Clinic, MAMC

Objective(s): To compare, in patients with non-small cell lung cancer, the normal biodistribution and tumor localization of ^{99m}-TC labelled NR-LU-10 Fab monoclonal antibody prepared with a NeoRx "OncoTrac" kit produced by two different manufacturers.

Hypothesis: Similar biodistribution and tumor localization will be obtained from kits produced by different manufacturers.

Title: A Multi-Center Clinical Study to Compare Imaging of Non-Small Cell Lung Cancer With a Technetium-Labelled Monoclonal Antibody Produced by Two Different Manufacturers

Synopsis: See enclosed protocol, pages 6-9. Briefly, patients will undergo standard staging to determine extent of disease. This staging will, at a minimum, consist of a CT scan of the chest, liver, and adrenals. Additional staging tests may be requested by the primary physician but are not required by the protocol. In addition, patients will undergo two scans 3-7 days apart using the technetium-labelled monoclonal antibody NR-LU-10. The two scans will be performed with kits from two different manufacturers. Sites of disease as determined by the monoclonal antibody scans will be compared with each other and with those delineated by conventional staging techniques. No therapeutic decisions will be made on the basis of the investigational scan.

Medical application: See pages 3-5 of enclosed protocol. Briefly, the curability of non-small cell lung cancer depends heavily upon the amenability of the patient's disease to surgical resection. One of the major determinants of such resectability is the presence or absence of mediastinal lymph node metastases. Patients without such metastases have up to 80% disease-free survival after complete surgical resection. The presence of lymph node disease reduces the probability of survival dramatically. The two modalities currently available for pre-thoracotomy staging of the mediastinum, CT scan and mediastinoscopy, suffer from significant limitations. Computed tomography suffers from a significant incidence of false-positive and false-negative results. Mediastinoscopy, while more accurate, requires a surgical procedure. Furthermore, mediastinoscopy may be falsely negative due to sampling error. An accurate, non-invasive staging test, specifically directed at dtermining the presence or absence of mediastinal node disease, would be extremely useful.

NeoRx Corporation has developed a monoclonal antibody (NR-LU-10) that recognizes a surface glycoprotein present on the cell membrane of many carcinomas, including non-small cell lung cancer. This antibody can be linked to a radioisotope (^{99m}Tc). Using conventional nuclear medicine technology, sites of uptake of this antibody, presumably representing sites of disease, can then be imaged with a single scan. Trials documented by NeoRx have demonstrated that the antibody can safely be administered to human subjects, and that imaging with the antibody can detect disease in primary lesions, mediastinal nodal metastases, and distant metastatic sites. The current study is designed to compare the imaging characteristics of NR-LU-10 antibody produced by two different manufacturers.

The advent of a reliable test for mediastinal (and potentially distant) disease that is as or more sensitive than conventional staging, but that does not require multiple studies or invasive procedures, would be immensely helpful to pulmonologists, thoracic surgeons, and clinical oncologists treating this disease. Such a test would allow certain patients to avoid a fruitless thoracotomy, and would also allow the identification of minimal metastatic disease patients who might be candidates for aggressive investigational treatment approaches.

Status: See pages 3-5, page 15 of enclosed protocol.

References: See page 15 of attached protocol

FUNDING

FUNDING REQUIREMENT	COST
Personnel: No additional	$0.00
Equipment: No additional	$0.00
Consumable Supplies: No additional	$0.00
Travel: No additional funds required	$0.00
Modification of Facilities: None required	$0.00
Other: None	$0.00
TOTAL:	**$0.00**

The monoclonal antibody kits will be provided by NeoRx.

Title: A Multi-Center Clinical Study to Compare Imaging of Non-Small Cell Lung Cancer With a Technetium-Labelled Monoclonal Antibody Produced by Two Different Manufacturers

IMPACT STATEMENT

Bed Occupancy: Outpatient procedures, no impact

Nursing: No additional impact

Pathology: Patients will undergo standard staging laboratory evaluation. In addition, if they are females of child-bearing age, they will have to have a serum beta-hCG. This is standard procedure in Nuclear Medicine before administering isotopes. The only lab studies required by study that would not be performed normally are thyroid function tests. Thus, the study will have minimal impact on Pathology.

ok
re-page 2
para 5b. (3)
& page 93-45

Pharmacy: ^{99m}-Technetium is a standard isotope in the Nuclear Medicine Pharmacy. The monoclonal antibody kits will be provided by NeoRx. Mixing isotope and antibody will require approximately 1-2 hours of time from the Nuclear Medicine pharmacist. There will be no financial impact on Pharmacy, and minimal resource (man-hour) impact.

Radiology: No radiographic studies beyond those normally performed in the staging of these patients will be required. Thus, there will be no impact on Radiology.

Clinical investigation: No impact beyond standard administration

Title: A Multi-Center Clinical Study to Compare Imaging of Non-Small Cell Lung Cancer With a Technetium-Labelled Monoclonal Antibody Produced by Two Different Manufacturers

Hematology-Oncology

L. Michael Stapleton, LTC, MC
C, Hematology-Oncology

Nuclear Medicine

J. Bauman, LTC, MC
C, Nuclear Medicine

Pharmacy

Richard J. Ferrell, COL, MS
C, Pharmacy

Title: A Multi-Center Clinical Study to Compare Imaging of Non-Small Cell Lung Cancer With a Technetium-Labelled Monoclonal Antibody Produced by Two Different Manufacturers

AR 40-38, Paragraph 2-10c

Investigators will -

(1) Prepare a protocol following the policies and procedures in this regulation.
(2) Prepare and maintain adequate records on -
    (a) Receipt, storage, use, and disposition of all investigational drugs issued to the investigator by the pharmacy and investigation devices issued to the investigator by the activity responsible for storing them.
    (b) Case histories that record all observations and other data important to the study.
    (c) Volunteer informed consent documents.
(3) Prepare progress reports, including annual reports (Clinical Investigation Program, RCS MED-300(R1)), as determined by the approving authority and regulatory agencies.
(4) Prepare and file an investigator sponsored Investigational New Drug or Investigational Drug Exemption as appropriate.
(5) Promptly notify the approving official, through the medical monitor and the Human Use Committee, of adverse effects caused by the clinical investigation.
(6) Report serious and unexpected adverse experiences involving the use of investigational drugs or devices to the sponsor or the FDA in accordance with AR 40-7.
(7) Ensure that the clinical investigation has been approved by the proper review committee(s) before starting, changing, or extending the investigation.
(8) Ensure that all subjects or their representatives, including subjects used as controls, are fully informed of the nature of the investigation to include potential risks to the subject.
(9) Ensure that investigational drugs or devices are administered only to subjects under the investigator's personal supervision or that of a previously approved associate investigator.
(10) Ensure that a new principal investigator (PI) is appointed if the PI cannot complete the clinical investigation for reasons such as permanent change of station (PCS) or retirement.
(11) Apprise the HUC of any investigator's noncompliance with the Clinical Investigation protocol.

(12) Seek HUC approval for other investigators to participate in the Clinical Investigation.
(13) Ensure that studies involving attitude or opinion surveys are approved in accordance with AR 600-46.

I agree to conduct this study in accordance with the policies set forth in AR 40-38, paragraph 2-10c.

Principal Investigator	Date 6/2/93
Principal Investigator	Date 6/2/93

I have reviewed this protocol with the investigators for:
  a. scientific merit
  b. experimental design
  c. expenditure of money and man-hours
  d. risks and safeguards in the use of human subjects

This proposal is forwarded with my full support and approval

5 June 93

NeoRx Corporation
410 West Harrison Street
Seattle, Washington 98119

A MULTICENTER CLINICAL STUDY TO COMPARE IMAGING OF NONSMALL CELL LUNG CANCER WITH A TECHNETIUM-LABELED MONOCLONAL ANTIBODY PRODUCED BY TWO DIFFERENT MANUFACTURERS

(BB-IND #2633)

PROTOCOL 9206-_____

November 1992

Principal Investigator(s):

CONFIDENTIALITY STATEMENT

This protocol is provided to you as a principal investigator, potential investigator, or consultant for review by you, your staff, and Institutional Review Board. The information contained in this document is regarded as confidential and except to the extent necessary to obtain informed consent, may not be disclosed unless such disclosure is required by federal or state law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Table of Contents

1.0 Introduction

1.1 Nonsmall Cell Lung Cancer

Approximately 168,000 new cases of lung cancer are estimated to occur in 1992 with estimated lung cancer deaths of 145,000. The two major histologic groups of lung cancers are nonsmall cell carcinomas and small cell carcinoma. About 75-80% of all lung cancers are of nonsmall cell histology and 20-25% are of small cell histology. Nonsmall cell lung cancer includes epidermoid carcinomas, adenocarcinomas, bronchoalveolar carcinoma, and large cell carcinomas. These are usually grouped together because of the major differences between the clinical and pathological features of these tumors and those of small cell lung cancer.[1,2,3]

The rate of cure for nonsmall cell lung cancer is low and can be obtained only by surgery in early cases. The overall cure rate following surgery alone is approximately 13%, but long-term survival rates may be as high as 60-70% depending on the stage and histologic type of the tumor.[4]

Because many patients are heavy smokers with compromised pulmonary function, the morbidity and risks of surgery must be carefully weighed against the potential gains. Thus, an accurate determination of prognosis is important for determining treatment plans in these patients. Clinical staging may assist the physician in the initial choice between surgical and other approaches; pathologic staging at the time of surgery helps to guide future treatment strategies, such as radiotherapy or investigational adjuvant therapy.

Current approaches for determining whether patients are candidates for surgery include studies to rule out distant metastases and to evaluate whether the patient's pulmonary function will allow for resection of the tumor and the adjacent lung (lobectomy or pneumonectomy). Lymph nodes in the mediastinum are usually evaluated by computerized tomography (CT) and mediastinoscopy, because mediastinal spread is associated with a greater risk of recurrence. Both of these methods of evaluating the mediastinum have shortcomings. CT may not distinguish whether enlarged nodes are non-specifically reactive or involved with tumor and may be inconclusive in as many as 20% of patients.[1,5] This has led to the consensus that a positive CT alone should not determine inoperability.[6,7,8] Mediastinoscopy provides only a sampling of accessible nodes and requires an additional invasive procedure before thoracotomy. A monoclonal antibody imaging procedure that could identify tumor in the mediastinum without an invasive procedure might be useful in this setting.

1.2 Antibody Imaging

There are several underlying reasons for developing agents with specific targeting properties for imaging of carcinoma. Patients with cancer require evaluation to determine whether particular complaints are secondary to their tumor or another disease process. CT scans, bone scans, liver scans and MRI are frequently used to evaluate the extent of the disease. The ability to detect disease in multiple organs at earlier times has an impact on patient management.

Monoclonal antibodies offer specificity, purity and consistency among lots.[9] These factors coupled with the wide availability of these agents have led to a resurgence of interest in the labeled antibody approach to detection and treatment of cancer. Other studies have employed ^{111}Indium, ^{131}Iodine or ^{123}Iodine as the radionuclide label.[10,11]

Technetium (^{99m}Tc) is the ideal radioisotope for use in *in vivo* imaging. It has a 140 keV gamma ray energy with a high photon flux that provides superior image resolution. Its short (6-hour) physical half-life and lack of beta particle emission permits the safe administration of large doses (up to 30 mCi). It is inexpensive and is readily available in nuclear medicine departments, facilitating the use of cold kits. It is used in more than 80% of nuclear medicine imaging studies.

NeoRx Corporation has developed a method of stably linking ^{99m}Tc to proteins and has tested one of these methods in multicenter clinical trials using monoclonal antibodies directed against melanoma and small cell and non-small cell lung cancers. In these studies ^{99m}Tc was linked irreversibly to protein by a diamide dithiolate (N_2S_2) system developed by Fritzberg.[12] Confirmed known, viable disease and previously unsuspected disease have been detected in skin, lymph node, lung, bone, liver, adrenal glands, spleen and brain.

NR-LU-10 Antibody

NeoRx Corporation has tested a murine IgG2b antibody (Muromonab NR-LU-10) that recognizes a glycoprotein expressed on both small cell and nonsmall cell lung cancer, as well as other carcinomas. Immunoperoxidase staining of tumor cells demonstrates antigen expression in the vast majority of samples from all carcinomas including nonsmall cell and small cell lung cancers tested. Immmunoperoxidase staining of frozen human tissues also demonstrates antigen expression in normal thyroid, salivary glands, pituitary and pancreas, and in some other normal tissues.

After establishing seed lots, the hybridomas are grown and tested for purity, non-pyrogenicity, sterility and general safety. The antibody, ligand and other components are supplied as a cold kit with instructions for labeling the antibody with Technetium ^{99m}Tc.

Among 500 patients in Phase I, II, and III clinical trials using the NR-LU-10 imaging agent, there have been no clinically significant adverse reactions. Mild temperature elevations occurred in 4 patients and these returned to normal within 4 - 24 hours without treatment. Transient asymptomatic elevations of amylase or lipase were observed in fewer than 5% of patients.

The NR-LU-10 Imaging Agent has demonstrated safety when prepared and administered in accordance with the manufacturer's instructions. No unexpected reactions occurred, clinically evident allergic reactions were rare, and no patients were dropped from the studies due to an adverse event related to the product.

NeoRx has conducted a multicenter study for its OncoTrac® ^{99m}Tc monoclonal antibody imaging kit for the detection of small cell lung cancer. Analysis of 96 SCLC patients in the pivotal study demonstrated that it is the best first test for staging: it detects more lesions and more diseased organs than any other test; it stages 85% of patients with extensive disease (98% PPV); 15% of patients diagnosed as limited disease by the complete battery of standard tests were upstaged from limited to extensive disease by this test.[13]

Among 44 patients in Phase II nonsmall cell lung cancer imaging trials, 96% of primary lung tumors, 81% of mediastinal lymph node regions, and 72% of distant organs were detected.[14]

2.0 Objective

2.1 To compare in patients with nonsmall cell lung cancer the normal biodistribution and tumor localization of ^{99m}Tc-Labeled NR-LU-10 Fab using the OncoTrac® Imaging Kit produced by two different manufacturers.

3.0 Patient Eligibility

3.1 A new diagnosis of nonsmall cell lung cancer confirmed by histology or cytology with no prior chemotherapy or radiotherapy.

If histological or cytological confirmation has not been obtained, patients should have a history and clinical findings strongly suggestive of nonsmall cell lung cancer, such as a history of smoking or asbestos exposure, or suspicious cytology (Class IV). Other possible diagnoses (tuberculosis,

lymphomas, abscess or metastasis from a different primary tumor) should be considered unlikely.

3.2 At least one known lesion present, evaluable by standard diagnostic techniques.

3.3 Performance status of at least 60% on the Karnofsky scale.

3.4 Ability to understand and give informed consent.

3.5 Grossly preserved renal function (creatinine not more than 2.5 mg/dL) and hepatic function (bilirubin not more than 2.0 mg/dL).

4.0 Patient Exclusions

4.1 Prior chemotherapy or radiotherapy for this tumor.

4.2 Pregnancy (confirmed by pregnancy test).

4.3 Inability to understand informed consent.

4.4 Age less than 18 years.

4.5 Resection of the only known lesion.

4.6 History of previous exposure to a murine monoclonal antibody and current antibody titer against NR-LU-10 Fab that is more than two standard deviations above the geometric mean of a control population not exposed to murine monoclonal antibody.

4.7 Any other investigational agent administered within 72 hours before and 24 hours after administration of the radiolabeled antibody.

5.0 Study Plan

The overall plan is shown in Table 1. Patients will have pre-study investigations including a standard staging evaluation within 15 days of the first antibody administration. After baseline laboratory evaluations, each patient will undergo two imaging procedures, two to seven days apart (i.e. Day 1 and Day 3-8). The two procedures will be identical, however one procedure will use the OncoTrac Imaging Kit produced by manufacturer A and the other procedure will use the OncoTrac® Kit produced by manufacturer B.

TABLE 1: Study Outline

	Pre-Study	Each Imaging Procedure					After Second Imaging Procedure	
		Minutes		Hours		Wks	Weeks	
		0	5-10	1	14-17	1	3	Follow-up
Consent Form	X							
History and Physical Examination	X							
Confirmation of Pathology Report	X[1]							
Clinical Staging Studies	X[2]							
Pregnancy Test (if indicated)	X							
Chem, CBC, UA[3]	X				X[4]			
Amylase, Lipase	X				X[4,5]	X[5]		
T3, T4, TSH	X							
7 cc Red Top Tube for Serum Antiglobulin Level	XX[4]					X	X	X (q 4 wk)[7]
Vital Signs (T,P,R,BP)		X	X	X	X			
Administration of Antibody (NR-LU-10)		X						
Cathartic				X[6]				
Imaging					X			
Vital Status								X (q 6 mo)[8]

1. If histologic or cytologic confirmation is not obtained pre-study for nonsmall cell lung cancers it should be obtained on follow-up.
2. Within 15 days of first administration of ^{99m}Tc-labeled NR-LU-10 Fab.
3. Electrolytes, BUN, glucose, bilirubin, creatinine, phosphorous, calcium, bicarbonate, LDH, SGOT, SGPT, alkaline phosphorus, total protein, albumin; CBC (Hgb, Hct, WBC, RBC) with differential and platelet counts; urinalysis.
4. Repeated for second administration of ^{99m}Tc-labeled NR-LU-10 Fab.
5. Abnormal values in either sample following test agent administration require weekly evaluation until the value returns to normal or baseline.
6. Cathartic to be given at an appropriate time to be effective before imaging (see Section 5.3.3).
7. Collect serum samples every 4 weeks for 4 months (from week 7 to week 27).
8. To be monitored at six month intervals.

5.1 Pre-study investigations:

- History and physical examination
- Urinalysis
- Complete blood count with differential and platelet count
- Biochemical profile (electrolytes, BUN, bicarbonate, glucose, creatinine, bilirubin, calcium, phosphorous, alkaline phosphatase, SGOT, SGPT, LDH, total protein, albumin), amylase, lipase
- TSH, T_3, T_4.
- Pregnancy test for women of child-bearing potential
- Two 7 cc serum samples for antiglobulin assays before each antibody administration.

5.2 Lesion evaluation and staging procedures.

- Chest CT scan (with mediastinal windows)
- Abdominal CT (or CT of the chest that includes liver and adrenal views).

5.3 Schedules for Each Imaging Procedures:

The first administration of ^{99m}Tc NR-LU-10 Fab takes place on the afternoon of the first day (Day 1) of the study (e.g. Monday). The first gamma camera imaging session occurs the morning of the second day (Day 2; e.g. Tuesday). The second administration of ^{99m}Tc NR-LU-10 takes place no sooner than the afternoon of the third day (e.g. Wednesday afternoon) and no later than the afternoon of the eighth day (e.g. the following Monday).

5.3.1 First Imaging Procedure (Day 1)

Time

Draw serum for antiglobulin before injection.

0 hr. 5-10 mg NR-LU-10 Fab labeled with 15-30 mCi ^{99m}Tc

(see 5.4.3) Cathartic

14-17 hrs. Imaging

5.3.2 Second Imaging Procedure (Day 3-8)

Time

Draw serum for antiglobulin before injection.

0 hr. 5-10 mg NR-LU-10 Fab labeled with 15-30 mCi ^{99m}Tc

(See 5.4.3) Cathartic

14-17 hrs. Imaging

5.4 Antibody Imaging Procedure:

5.4.1 Epinephrine 1:1000 (0.3 cc) and diphenhydramine (50 mg) will be drawn up in separate syringes before the injection of antibody in case of an idiosyncratic anaphylactic response.

5.4.2 Patients will receive 5.0-10.0 mg NR-LU-10 (Fab), labeled with 15-30 mCi ^{99m}Tc, diluted according to the radiolabeing instructions and administered by intravenous injection over 3-5 minutes. The antibody will be administered within 4 hours of the completion of radiolabeling, and must have 15-30 mCi at the time of infusion.

5.4.3 Before imaging, the patient will receive as a cathartic 2 liters of Go-Lytely® or 1-2 bottles of magnesium citrate, or an alternative laxative in order to purge the large bowel of radioactivity that is excreted via the hepatobiliary route. The timing of the administration will depend on the cathartic used, to ensure an effective response before images are obtained.

5.4.4 Images will be obtained with a gamma camera 14-17 hours after injection according to the general protocol for imaging in Appendix II. The data will be acquired, stored and processed with a dedicated computer.

5.5 If the antibody images reveal an abnormality in an otherwise unsuspected area, further diagnostic studies will be performed to evaluate the abnormality. Biopsies will be performed when feasible for histologic and immunohistochemical analysis.

5.6 Because this is an investigational procedure, the results (whether positive or negative) should not be used alone for determining patient care.

6.0 Serial Observations

6.1 On the day following each radiolabel injection, a complete blood count, platelet count, a biochemical profile (as described in Item 5.1) and urinalysis will be performed. Amylase and lipase will be obtained additionally at one week after the last injection, and if abnormal, repeated weekly until returning to normal range or baseline levels. Additional routine toxicity monitoring is not planned because the administered total body radiation is equal to commonly employed single procedures (Appendix I), such as bone scan, and because no major toxicity has occurred in other trials with this agent or other similar antibodies developed by NeoRx Corporation.

6.2 Serial blood studies will be performed for antiglobulin titer. A serum sample will be drawn at the following times after the second imaging procedure: one week, three weeks, and every four weeks for six months. Specimens will be drawn in a 7 cc red top vacutainer clot tube, and mailed by standard mail in packages supplied by NeoRx. If the sample is not mailed on the day of drawing, it should be refrigerated until mailing.

Sample to be shipped to:

NeoRx Corporation
410 West Harrison Street
Seattle, Washington 98119
Attention: Bob Mallett

6.3 Patients will be followed for six months after the imaging procedure. Follow-up information will be requested at three months and six months.

6.4 Vital Status will be requested on patients every six months after patients are off-study.

7.0 Review of Gamma Camera Images

7.1 The scintiscans will be evaluated by an experienced nuclear medicine physician at each clinical site and this analysis recorded.

7.2 The scintigraphs will then be evaluated independently by two blinded nuclear medicine physicians (consultants to NeoRx) to compare the two sets of images from each patient.

7.3 All reviewers will score the degree to which each known or suspected lesion is seen in each image set and the quality of each imaged lesion.

8.0 Statistical Considerations

The objective of this study is to provide a qualitative assessment to determine if images of nonsmall cell lung cancer lesions obtained using the OncoTrac® Imaging Kit produced by one manufacturer are comparable to images of the same lesions obtained using the OncoTrac® Imaging Kit produced by a second manufacturer. The study is designed to include one sample of patients where each patient undergoes two imaging procedures, one by each manufacturer. The experimental unit is a known or suspected nonsmall cell lung cancer lesion. Each lesion will be evaluated for each of the two antibody imaging procedures according to whether it is seen or not seen, based on a blinded, doubly reviewed analysis comparing the two sets of images from each patient.

To diminish any contributing bias from the order in which patients receive the Kits from the two different manufacturers, each alternating patient will receive the Kits in opposing order [e.g. Patient #1 will receive manufacturer A's Kit for the first procedure, and manufacturer B's Kit for the second procedure. Patient #2 will receive manufacturer B's Kit for the first procedure and manufacturer A's Kit for the second procedure.] Each site will be required to call the NeoRx study monitor prior to patient entry onto study. At this point eligibility will be checked and the order of Kit administration will be assigned.

9.0 Toxicity Monitoring

9.1 Classification of Toxicity

Parameter	I (mild)	II (moderate)	III (severe)	IV (life-threatening)
Fever	100-102.9°F	103-105°F (transient, less than six hours)	103-105°F (persistent, more than six hours)	More than 105°F
Allergic Pruritus		Urticarial rash	Swelling of pharyngeal tissues or extensive urticarial rash	Hypotension
Pulmonary	Shortness of breath or mild wheezing	Moderate wheezing	Moderate wheezing and tachypnea with normal pCO_2	Hypoxemia and/or hypercapnia
Other	(To be described and graded as appropriate)			

9.2 Level of unacceptable toxicity and study termination.

9.2.1 If a grade I (mild) toxicity occurs during administration of antibody, administer 50 mg diphenhydramine IV and continue antibody infusion if toxicity is controlled.

9.2.2 If a grade II (moderate) toxicity occurs, administer 50 mg diphenhydramine IV and continue antibody infusion if toxicity is controlled. If grade II toxicity continues after treatment, stop the antibody infusion and remove the patient from the study. Similarly, if a patient received diphenhydramine before the study because of concerns about the potential for development of an allergic reaction in that particular patient, stop the antibody infusion if a grade II (moderate) toxicity develops, and remove the patient from the study.

9.2.3 If any patient experiences a grade III or IV toxicity (severe or life-threatening) with or without premedication, the patient should be removed from the study.

9.3 Any patient who develops signs of acute toxicity (grade I or greater) will have serum samples collected in a 7 cc red top vacutainer clot tube at the time of the reaction, 7-8 hours later, and 20-24 hours later. These samples will be mailed to NeoRx Corporation for immunologic assays. If the sample is not mailed on the day of drawing it should be refrigerated until mailing.

9.4 Adverse Experiences

An adverse experience is any undesirable event including toxicity, sensitivity reaction, injury or any significant failure of pharmacological action thought to be associated with the use of the test agent. An adverse experience may be expected (known) and will have been previously reported or associated with the use of the test agent. An adverse experience may be unexpected (unknown), i.e., not identified in nature, severity or frequency in the current investigator brochure or general investigational plan. A serious adverse reaction is one that is fatal or life threatening, requires inpatient hospitalization, is permanently or severely disabling, or is a congenital anomaly, cancer or overdose.

The investigator is to report immediately all serious expected or unexpected adverse reactions by telephone to the study monitor or Terry Lesley, R.N. or Darrell Salk, M.D.in the Department of Medical and Regulatory Affairs, NeoRx Corporation, (206-281-7001). All unexpected adverse reactions,

regardless of grade of toxicity and suspected etiology, must be reported to NeoRx by telephone within 24 hours of occurrence.

This should be followed by an Investigator's written summary of the incident which should be received at NeoRx Corporation within five days.

Written summaries of adverse reactions must include the patient identification code number; reaction onset day; duration of reaction; a description of the reaction and grade of toxicity; laboratory data or tests confirming the reaction; drug dose, route, time and rate of administration diluent and concentration of product; premedication and other medication; patient hospitalization or not and patient outcome; intervention and therapy to treat the reaction.

NeoRx will report this information to the Center of Biologics Evaluation and Research, Food and Drug Administration (FDA). Serious adverse drug reactions will be reported to the Institutional Review Board by the Principal Investigator.

9.5 Patient Deaths

All patient deaths, from all causes, are to be reported to NeoRx Corporation for any patient on study through the six month follow-up period. Deaths should be reported by phone call to the study monitor within 24 hours of notification.

10.0 Investigator's Agreement with Protocol

I agree to conduct the study entitled "A Multicenter Clinical Study to Compare Imaging of Nonsmall Cell Lung Cancer with a Technetium-labeled Monoclonal Antibody Produced by Different Manufacturers" as outlined in the above protocol (number 9206-_____).

I agree that no alterations to the protocol may be made without the written agreement of NeoRx Corporation.

Signature:_____

Print Name:_____

Date: _____

_____ _____

Darrell Salk, M.D. Date
Vice President
Medical and Regulatory Affairs
NeoRx Corporation

REFERENCES

1. Piro AJ, Grillo H, Huberman M: Primary Carcinoma of the Lung in Cancer Manual. Boston: American Cancer Society, 1982.

2. Boring CC, Squines TS, Tong T: Cancer Statistics, 1992. Ca-A Cancer Journal for Clinicians, 42:19-28, 1992.

3. Minna JD, Higgins GA, Glatstein EJ: Cancer: Principles and Practice of Oncology, Third Edition. deVita VT, Hellman S, Rosenberg SA (eds) J.B. Lippincott Company 591-687, 1989.

4. Minna JD, Higgins GA, Glatstein EJ: Cancer: Principles and Practice of Oncology, Second Edition. deVita VT, Hellman S, Rosenberg SA (eds.) J.B. Lippincott Company, Philadelphia, 507-597, 1985.

5. Baron RL, Levitt RG, Sagel SS, et al: Radiology, 145:727-732, 1982.

6. Glazer GM, Orringer MB, Gross BH, et al: AJR, 142:1101-1105, 1984.

7. Daly BD Jr., Faling J, Bite G, et al: J Thoracic Cardiovasc Surg, 94:664-672, 1987.

8. Libshitz HI, McKenna RJ, Haynie TP, et al: Radiology, 151:295-299, 1984.

9. DeLand FH, Goldenberg DM: Seminars in Nuclear Medicine, 15:2-11, 1985.

10. Kohler G, Milstein C: Nature, 256:495-297, 1975.

11. Larson SM, Carrasquillo JA, Krohn KA, et al: J Clin Inv., 72:2101-2114, 1983.

12. Eary J, Schroff RW, Kasina S, et al: Clinical Nuclear Medicine, 9, 1986 (abstract).

13. Salk D, Reno J, et al: The Third Conference on Radioimmunodetection and Radioimmunotherapy of Cancer, November 15-17, 1990; abstract.

14. Friedman S, Sullivan K, Salk D, et al: Hematology/Oncology Clinics of North America, 4(6):1069-1078, 1990.

APPENDIX I

Estimate of Radiation Dosimetry

The radiation dose to each organ resulting from the administration of ^{99m}Tc labeled Muromonab NR-LU-10 Fab fragment was calculated using biokinetic data derived subjects receiving the product.

The distribution of ^{99m}Tc activity in the major body organs was determined by gamma camera imaging of the subject with comparison to a quantitative standard of ^{99m}Tc. The standard was counted at each patient measurement time using a fixed geometry. All data were stored on a dedicated computer.

Activity in the thyroid gland was measured with a single anterior gamma camera image using computer-generated areas of interest to outline the organs. Background was subtracted from the organ activity using an equal area of interest in adjacent tissue, and the amount of ^{99m}Tc activity in the organ was estimated using an attenuation correction for the average mid-plane depth of the organ.

Absolute activity in the major internal organs (liver, lungs, kidney) was measured with the gamma camera using the method described by Hammond (Med. Physics 11:778, 1984). At each imaging point, reproducible regions of interest (ROI) were selected to represent the various organs, and the activity in μCi was calculated over time.

All images were inspected visually. There was no visualization of discrete activity in the pancreas, adrenals, ovaries, bone marrow, or liver. The thyroid, pituitary, and testes were routinely visualized.

The biokinetic data derived from these calculations are shown in the following table "Biokinetic Data Obtained from Patients Receiving ^{99m}Tc NR-LU-10 Fab". From these data were derived the effective half life of radioactivity in the various organs and regions of interest and the radiation dose estimates calculated using MIRD dosimetry methodology for rad/mCi and standard international units, mGy/MBq (see the table on page 18, "The Final Dose Estimates for an Average Patient".

Biokinetic Data Obtained from Patients Receiving ^{99m}Tc NR-LU-10 Fab Used for Radiation Dose Estimates				
Organ/Sample	**Time Post Injection**	**Number of Subjects**	**% Dose/ Organ**	**Standard Deviation**
Liver	0*	5	11.25	± 2.08
	3	6	5.79	± 1.67
	8	6	6.17	± 1.50
	24	4	3.75	± 1.39
Lungs (2)	0*	7	5.76	± 0.94
	3	7	3.47	± 1.03
	8	7	2.47	± 0.72
	24	7	1.71	± 0.68
Kidney (1)	0*	8	4.06	± 2.00
	3	8	6.14	± 3.44
	8	8	4.10	± 2.01
	24	6	1.59	± 1.03
Thyroid	0*	9	0	
	3	6	0.27	± 0.30
	8	6	0.33	± 0.37
	24	6	0.24	± 0.36
Testes	0*	3	0.02	± 0.02
	3	3	0.04	± 0.03
	8	3	0.05	± 0.02
	24	3	0.00	± 0.01
Whole Body	0*	9	100.00	--
	3	8	79.75	± 11.03
	8	8	60.50	± 11.32
	24	7	38.57	± 9.95

* Time 0 is defined as immediately after injection which may range up to one-half hour after Technetium 99mTc NR-LU-10 Fab administration.

The final dose estimates for an average patient (70 kg) receiving 30 mCi Technetium ^{99m}Tc NR-LU-10 Fab.			
	Absorbed Dose		
Target Organ	mGy/MBq	rad/mCi	Total Dose rad/30 mCi
Kidney	0.0382	0.1410	4.230
Liver	0.0098	0.0361	1.083
Lungs	0.0061	0.0226	0.678
Ovaries	0.0038	0.0141	0.423
Red Marrow	0.0037	0.0136	0.408
Spleen	0.0050	0.0184	0.552
Testes	0.0029	0.0108	0.324
Thyroid	0.0191	0.0706	2.118
Uterus	0.0038	0.0142	0.42[illegible]
Total Body	0.0036	0.0132	0.396

APPENDIX II

Methods of Gamma Camera Imaging of Technetium ^{99m}Tc-labeled NR-LU-10

In order to establish consistency among different institutions in the study the following methods must be used during this study. In particular, in order to establish consistency between the first and second imaging procedures, the methods indicated in bold face type are especially important and must be followed.

The Technetium ^{99m}Tc antibody images should begin at 14-17 hours following injection. Each patient should have a total body survey. The body survey can be done by multiple anterior and posterior planar LFOV views or with full length anterior and posterior total body views and left and right lateral views of the head. In each case selective spot views of areas of known disease or suspected occult lesions should be done to augment lesion visualization or verify lesion position. The same gamma camera and collimator will be used for both imaging procedures in a single patient. SPECT images will be obtained of the lungs and mediastinum, if there are known or suspected lesions present. Additional SPECT images are strongly encouraged of other areas if they may improve the detection or positioning of a lesion.

Quality Assurance (QA) testing of planar cameras should be done on the day of imaging to confirm good field uniformity; adequate linearity of the camera should have been confirmed within the week. It is best to check these parameters with at least 2 x 10^6 counts/ image. Tests should be done using Technetium ^{99m}Tc sources; alternatively ^{57}Co can be used. Standard QA procedures for SPECT equipment should be performed as specified at each institution; a description of these procedures should be sent to NeoRx. Since several types of cameras will be used in the various participating institutions, individual questions regarding the QA procedures should be addressed to the study monitor at NeoRx.

SPECT Imaging

SPECT imaging of the lungs is to be performed first before the total body survey when activity is greatest. A complete set of SPECT images should be obtained and processed in coronal, saggital, and transverse sections. A high sensitivity collimator should be used. Because of the short half-life of technetium and the late imaging times, it may require up to twice the amount of time usually spent for a 360° acquisition to obtain good quality images. CARE SHOULD BE TAKEN TO ALIGN PATIENTS SO THAT ALL PORTIONS OF THE RIGHT AND LEFT LUNGS ARE INCLUDED SO THEY CAN BE FULLY PROCESSED AND DISPLAYED ON THE SPECT IMAGES.

Planar Images

For planar imaging the highest resolution collimator should be used consistent with reasonable sensitivity. For images obtained at 14-17 hours, a general purpose collimator should be used to keep acquisition times reasonable. The energy window should be 15% centered at 140 Kev (132.5 Kev - 147.5 Kev) or should be on the full width at half the maximum of the photopeak (FWHM).

The planar images should begin with an anterior thorax view to obtain 500,000 total counts (approximately 8-10 minutes) or for a maximum of 10 minutes, whichever is shortest. All subsequent survey views should then be done using the same acquisition time as used in the anterior thorax view. The abdomen should be shielded with a lead apron to the level of the xiphoid before acquiring 500,000 counts over the chest in the first planar view of the study; this will provide optimal lung views and the most appropriate acquisition time in other views.

The views obtained and the positioning of the patient must be the same for the two imaging procedures. The images from the first procedure must be used at the time of the second imaging procedure for guidance.

Special spot views (including obliques and laterals) of individual lesions should use individualized count acquisitions and intensities to best elucidate the lesions, etc.

Frequently in heavier subjects, subtle hot area artifacts may be noted in skin folds of the axilla or breast. These artifacts are caused by low angle forward scattering near a skin fold with little attenuation at the skin surface. Such artifacts in the axilla for examples can be eliminated by positioning the patient with the arms extended overhead and should not be confused with localization of radiolabeled antibody in lymph nodes or other sites.

You may wish to acquire and view your images in direct analog form. However, all image sets also must be computer acquired to a dedicated nuclear medicine computer for digital storage and subsequent processing and filming. This will preserve the image data, provide the opportunity for optimal viewing, filming and contrast enhancement of the images and provides a means to make duplicate film copies of equal quality and contrast.

Image Processing

Processing of the images should be as follows: the first set of images should be processed to give the interpreter of the images the best visualization. The second set of images should then processed using the same background cutoff and contrast on the processor as was used for preparing the first set of images. Image sizes and the exposure time of the films in the processor should be the same.

All images used for interpretation must be forwarded immediately to the study monitor at NeoRx for a blinded review. Two duplicate sets (not copies) of digital images are to be forwarded to NeoRx; one unmarked for a blinded review and one very carefully marked with lesions circled or otherwise noted and labeled with lesion identification numbers or letters from lesion diagrams. The duplicate sets of films should be made at the time of the original exposure and processing.

If analog images are used (in part or full) for interpretation, the originals of these films (not copies) must be sent to NeoRx for the blinded review.

For SPECT images, the level of the section and the orientation (transverse, coronal, or saggital; anterior, posterior, left, right, rostral, and caudal) must be clearly indicated on each of the images.

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority:	10 USC 3013, 44 USC 3101 and 10 USC 1071-1087
Principle Purpose:	To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purpose.
Routine Uses:	The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs, teaching, adjudication of claims, and for the mandatory reporting of medical condition as required by law. Information may be furnished to Federal, State and local agencies.
Disclosure:	The furnishing of SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN _____ having full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in the research protocol A Multicenter Clinical Study to Compare Imaging of Non-Small Cell Lung Cancer With a Technetium-Labelled Monoclonal Antibody Produced by Two Different Manufacturers under the direction of MAJ Mark E. Robson, M.D., US Army Medical Corps, conducted at Madigan Army Medical Center.

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by _____.

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. **Should any further questions arise concerning my rights on study-related injury I may contact the Center Judge Advocate at Madigan Army Medical Center, (206) 968-3113.**

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits; however, I may be required (*military volunteer*) or requested (*civilian volunteer*) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

Part B - Explanation of What Is To Be Done

INTRODUCTION: You have been invited to participate in a clinical research study conducted at Madigan Army Medical Center. It is very important that you read and understand the following general principles that apply to all participants in our studies: (a) your participation is entirely voluntary; (b) you may withdraw from participation in this study or any part of the study at any time by calling Dr. Robson at (206) 968-2405; withdrawal from the study or refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled; (c) after you read the explanation, please feel free to ask any questions that will allow you to clearly understand the nature of the study.

Your physicians have determined that you are suffering from a type of lung cancer known as "non-small cell" lung cancer. This

Initials of volunteer _____

Robson/non-small cell/NR-LU-10

Revised - 16 Sep 93 - MTF IRB

particular type of lung cancer has frequently spread to the lymph nodes in the center of the chest, or even outside the chest, even when patients are first diagnosed. It is very important to determine whether or not your disease has spread in order to determine the likelihood that you will benefit from a surgical operation to remove the tumor.

Physicians routinely perform a variety of tests in patients with non-small cell lung cancer to determine whether the disease has spread to the lymph nodes in the center of the chest or to other areas outside the chest. This process is called "staging." The tests that are routinely performed are: (1) a thorough physical examination, (2) blood tests, including liver and kidney function tests and a complete blood count, (3) a chest x-ray, and (4) a CT scan of the chest and abdomen. In certain circumstances, your physician may request that other tests be performed. All of these tests are routine in the evaluation of non-small cell lung cancer, and are not a part of this research study.

Unfortunately, after all of these conventional staging studies, your physician may still be unsure whether or not you have disease in the nodes in the center of your chest. For this reason, many patients are asked to undergo a procedure known as "mediastinoscopy" before they can proceed to a resection of their tumor. A mediastinoscopy is a surgical procedure where in the thoracic surgeon inserts a lighted tube into the center of your chest through an incision in your neck. Using this tube, the surgeon takes biopsy samples of the nodes in the center of your chest to determine whether there is cancer there. Not all patients undergo this test. The mediastinoscopy is recommended only if, after all the conventional staging studies, your physician are uncertain whether or not your disease has spread. It would be helpful if there were a test, which did not require surgery, to detect this spread.

PURPOSE: Such a test is called NR-LU-10. The purpose of this study is to compare the imaging characteristics of two versions of NR-LU-10. **NR-LU-10 is an investigational test.** This means that it has not been approved by the Food and Drug Administration for routine use, but the FDA has agreed to its use in this study to determine how effective it is in detecting the spread of non-small cell cancer. This test involves "monoclonal antibody imaging." An antibody is a protein that can attach to tumor cells directly. Highly purified single antibodies are called monoclonal antibodies (abbreviated MoAb). MoAbs have been developed by injecting mice with tumor cells. The MoAbs bind to most tumor cells, but to very few normal cells. In an earlier study, it shown that these MoAbs can be linked to a metal called "technetium." This metal is radioactive so its presence can be detected by a special type of camera. The metal is the same one as used in the routine bone scan and the imaging procedure is very similar. It has already been shown that the technetium-linked NR-LU-10 antibody is able to detect metastasis (spread) of lung cancer. This information could potentially be useful in treating patients in the future, although not specifically for you. Since we are not certain about these characteristics, we will not be able to use the information from this study to plan

the treatment you will receive for your cancer.

PROCEDURES: This study will involve the administration of antibody on one day, with CT images obtained early the following day. The other staging procedures described above that you would undergo as a matter of routine medical practice will also be performed. A second antibody administration (identical to the first except made by a different manufacturer) and imaging procedure will be performed 3-7 days after the first procedure. The results of the monoclonal antibody imaging tests will be evaluated and compared with the standard tests. If the experimental test detects an abnormality not seen on the standard tests, you may be asked to undergo further standard tests to evaluate these findings further. These tests may include additional CT scans, magnetic resonance imaging (MRI) scans, and possibly a biopsy.

You will receive the monoclonal antibody IV (into a vein) over 3-5 minutes. Before the injection you will undergo a standard medical history and physical examination and standard blood tests, requiring about 2 tablespoons of blood.

After the injection, you will be asked to take a strong laxative to clear the bowel of any radioactive material. You should have a bowel movement before the scans are done.

Approximately 14-17 hours after the antibody injection, you will be asked to come to the Nuclear Medicine Service for a series of scans. These scanning procedures are similar to those routinely performed by nuclear medicine clinics across the country and require lying on a table while a special camera takes pictures of your body. The standard blood tests will also be repeated. You will be asked to have ~~a~~ blood samples (1 teaspoonful each) taken at one and three weeks and ~~the~~ every three weeks for six months after the imaging procedures. A blood sample (1 teaspoon) will also be ~~dan~~ one week after the imaging procedure to evaluate your pancreas.

POTENTIAL BENEFITS: This is an experimental study and we can not predict, nor guarantee, that you will personally benefit from participation. As mentioned above, this experimental test cannot be used by itself to make ~~a~~ decision about the type of treatment you should receive for your cancer. The information gathered, however, may provide data that may be of help to you or other patients in the future. Although the imaging studies are being conducted, in part, to help develop treatments based on these antibodies in the future, there is no guarantee that such treatments will either be available to you or, if available, successful.

RISKS, INCONVENIENCES, AND DISCOMFORTS: The side effects of this antibody in humans are not entirely known at this point. Based on prior studies with other antibodies, however, these side effects may include, but are not necessarily limited to, allergic reactions, including fever, hives, wheezing, inflammation, and damage to blood vessels (breaking and clogging of small vessels).

There is a small risk of a major allergic reaction, such as that seen in some people after bee stings. This is called anaphylaxis. Such a reaction poses a small risk of death. Your physicians will be prepared to deal with this reaction immediately, should it occur. Usually, treatment reverses the reaction.

Possible, but not previously seen, reactions include lowering of the white blood count or platelet count with an increased risk of infection or bleeding, and possible damage to the kidney or liver.

Among 500 patients who received a prior version of this antibody (NR-LU-10), there were no clinically significant adverse reactions. Mild temperature elevations occurred in 4 patients, which returned to normal within 4 to 24 hours without treatment. Temporary elevations of amylase or lipase (pancreas enzymes) were seen in less than 5% of patients and were not associated with any symptoms.

The radiation you will receive from the imaging procedure is less than 500 millirems to the whole body. This is similar to that received during standard nuclear medicine scans.

The scanning procedures require lying on a bed for up to 20 minutes in one position which might be slightly uncomfortable.

There is some discomfort associated with the blood drawing procedure. Possible complications of blood drawing include excessive bleeding externally or into the skin or underlying tissue, blood clots in the blood vessel resulting in loss of blood flow to or from the hand, and infections of the skin, soft tissue, or blood vessel.

There will be some discomfort associated with taking the laxative to clear your bowels. This would include bloating, cramping, and diarrhea.

Some patients receiving monoclonal antibodies develop immunity against these antibodies. While such immunity is not harmful, it could prevent you from entering future monoclonal antibody studies.

As with any experimental treatment, there is a possibility that previously unknown side effects may occur.

Although there is no evidence that monoclonal antibodies or the dose of radiation used in this study is harmful to either the fetus or mother, it is unknown what effect monoclonal antibodies would have on an unborn baby. Therefore, pregnant women are not eligible to enter this study, and they should not become pregnant while in the study. If you are a women of childbearing age, you will have a blood test to make sure that you are not pregnant before you receive the antibody. The information regarding unknown risks also applies to fathering a child. Therefore, male subjects entering this study should avoid fathering children during the course of the study and should either abstain from

sexual relations or practice a method of birth control. Surgical removal of a woman's uterus is the only totally effective method to prevent pregnancy. Therefore, the only ways to completely avoid drug-associated risk to an unborn baby are (1) for a woman not to become pregnant or (2) for the subject not to receive this drug.

ALTERNATIVES TO PARTICIPATION: If you choose not to participate in this study, you will receive the usual routine evaluation as stated above.

CONFIDENTIALITY OF RECORDS: The case records from this study will be available for review by members of the Institutional Review Board at Madigan, by representatives of the Food and Drug Administration, and by NeoRex (the sponsor of this study). Otherwise, only the physicians conducting this study will have access to the records from this study. Information gained from this study may be used as part of a scientific publication, but you will in no way be personally identified.

OTHER INFORMATION: Significant findings that occur during this study that might affect your decision to participate in the study will be discussed with you. Any significant findings developed from this study will be available to you and may be obtained from Dr. Robson. Your participation in this study may be terminated without your consent if conditions occur which make your continued participation detrimental to your health.

If you should require medical care for injuries or disease which result from participation in this study, the medical care to which you will be entitled is the same as that to which you are already entitled as a DoD health care beneficiary. This does not include domiciliary or nursing home care.

You are encouraged to ask any questions, at any time, that will help you to understand how this study will be performed and/or how it will affect you. You may contact Dr. Robson at (206) 968-2505 or Dr. Bauman (co-investigator) at (206) 968-1645.

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING THIS FORM.

I do ☐ do not ☐ (check one & initial) consent to the inclusion of this form in my outpatient medical treatment record.

You will be given a signed copy of this form to keep.

SIGNATURE OF VOLUNTEER	DATE	SIGNATURE OF LEGAL GUARDIAN

PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS SIGNATURE OF WITNESS DATE SIGNED

As approved

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority:	10 USC 3013, 44 USC 3101 and 10 USC 1071-1087
Principle Purpose:	To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purpose.
Routine Uses:	The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs, teaching, adjudication of claims, and for the mandatory reporting of medical condition as required by law. Information may be furnished to Federal, State and local agencies.
Disclosure:	The furnishing of SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN _____ having full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in the research protocol **A Multicenter Clinical Study to Compare Imaging of Non-Small Cell Lung Cancer With a Technetium-Labelled Monoclonal Antibody Produced by Two Different Manufacturers** under the direction of MAJ Mark E. Robson, M.D., US Army Medical Corps, conducted at Madigan Army Medical Center.

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by _____.

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. **Should any further questions arise concerning my rights on study-related injury I may contact the Center Judge Advocate at Madigan Army Medical Center, (206) 968-3113.**

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits; however, I may be required (*military volunteer*) or requested (*civilian volunteer*) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

Part B - Explanation of What Is To Be Done

INTRODUCTION: You have been invited to participate in a clinical research study conducted at Madigan Army Medical Center. It is very important that you read and understand the following general principles that apply to all participants in our studies: (a) your participation is entirely voluntary; (b) you may withdraw from participation in this study or any part of the study at any time by calling Dr. Robson at (206) 968-2405; withdrawal from the study or refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled; (c) after you read the explanation, please feel free to ask any questions that will allow you to clearly understand the nature of the study.

Your physicians have determined that you are suffering from a type of lung cancer known as "non-small cell" lung cancer. This

Revised - 16 Sep 93 - PMI IRB

particular type of lung cancer has frequently spread to the lymph nodes in the center of the chest, or even outside the chest, even when patients are first diagnosed. It is very important to determine whether or not your disease has spread in order to determine the likelihood that you will benefit from a surgical operation to remove the tumor.

Physicians routinely perform a variety of tests in patients with non-small cell lung cancer to determine whether the disease has spread to the lymph nodes in the center of the chest or to other areas outside the chest. This process is called "staging." The tests that are routinely performed are: (1) a thorough physical examination, (2) blood tests, including liver and kidney function tests and a complete blood count, (3) a chest x-ray, and (4) a CT scan of the chest and abdomen. In certain circumstances, your physician may request that other tests be performed. All of these tests are routine in the evaluation of non-small cell lung cancer, and are not a part of this research study.

Unfortunately, after all of these conventional staging studies, your physician may still be unsure whether or not you have disease in the nodes in the center of your chest. For this reason, many patients are asked to undergo a procedure known as "mediastinoscopy" before they can proceed to a resection of their tumor. A mediastinoscopy is a surgical procedure where in the thoracic surgeon inserts a lighted tube into the center of your chest through an incision in your neck. Using this tube, the surgeon takes biopsy samples of the nodes in the center of your chest to determine whether there is cancer there. Not all patients undergo this test. The mediastinoscopy is recommended only if, after all the conventional staging studies, your physician are uncertain whether or not your disease has spread. It would be helpful if there were a test, which did not require surgery, to detect this spread.

PURPOSE: Such a test is called NR-LU-10. The purpose of this study is to compare the imaging characteristics of two versions of NR-LU-10. NR-LU-10 is an investigational test. This means that it has not been approved by the Food and Drug Administration for routine use, but the FDA has agreed to its use in this study to determine how effective it is in detecting the spread of non-small cell cancer. This test involves "monoclonal antibody imaging." An antibody is a protein that can attach to tumor cells directly. Highly purified single antibodies are called monoclonal antibodies (abbreviated MoAb). MoAbs have been developed by injecting mice with tumor cells. The MoAbs bind to most tumor cells, but to very few normal cells. In an earlier study, it shown that these MoAbs can be linked to a metal called "technetium." This metal is radioactive so its presence can be detected by a special type of camera. The metal is the same one as used in the routine bone scan and the imaging procedure is very similar. It has already been shown that the technetium-linked NR-LU-10 antibody is able to detect metastasis (spread) of lung cancer. This information could potentially be useful in treating patients in the future, although not specifically for you. Since we are not certain about these characteristics, we will not be able to use the information from this study to plan

the treatment you will receive for your cancer.

PROCEDURES: This study will involve the administration of antibody on one day, with CT images obtained early the following day. The other staging procedures described above that you would undergo as a matter of routine medical practice will also be performed. A second antibody administration (identical to the first except made by a different manufacturer) and imaging procedure will be performed 3-7 days after the first procedure. The results of the monoclonal antibody imaging tests will be evaluated and compared with the standard tests. If the experimental test detects an abnormality not seen on the standard tests, you may be asked to undergo further standard tests to evaluate these findings further. These tests may include additional CT scans, magnetic resonance imaging (MRI) scans, and possibly a biopsy.

You will receive the monoclonal antibody IV (into a vein) over 3-5 minutes Before the injection you will undergo a standard medical history and physical examination and standard blood tests, requiring about 2 tablespoons of blood.

After the injection, you will be asked to take a strong laxative to clear the bowel of any radioactive material. You should have a bowel movement before the scans are done.

Approximately 14-17 hours after the antibody injection, you will be asked to come to the Nuclear Medicine Service for a series of scans. These scanning procedures are similar to those routinely performed by nuclear medicine clinics across the country and require lying on a table while a special camera takes pictures of your body. The standard blood tests will also be repeated. You will be asked to have ~~a~~ blood samples (1 teaspoonful each) taken at one and three weeks and ~~the~~ every three weeks for six months after the imaging procedures. A blood sample (1 teaspoon) will also be ~~dan~~ one week after the imaging procedure to evaluate your pancreas.

POTENTIAL BENEFITS: This is an experimental study and we can not predict, nor guarantee, that you will personally benefit from participation. As mentioned above, this experimental test cannot be used by itself to make ~~a~~ decision about the type of treatment you should receive for your cancer. The information gathered, however, may provide data that may be of help to you or other patients in the future. Although the imaging studies are being conducted, in part, to help develop treatments based on these antibodies in the future, there is no guarantee that such treatments will either be available to you or, if available, successful.

RISKS, INCONVENIENCES, AND DISCOMFORTS: The side effects of this antibody in humans are not entirely known at this point. Based on prior studies with other antibodies, however, these side effects may include, but are not necessarily limited to, allergic reactions, including fever, hives, wheezing, inflammation, and damage to blood vessels (breaking and clogging of small vessels).

There is a small risk of a major allergic reaction, such as that seen in some people after bee stings. This is called anaphylaxis. Such a reaction poses a small risk of death. Your physicians will be prepared to deal with this reaction immediately, should it occur. Usually, treatment reverses the reaction.

Possible, but not previously seen, reactions include lowering of the white blood count or platelet count with an increased risk of infection or bleeding, and possible damage to the kidney or liver.

Among 500 patients who received a prior version of this antibody (NR-LU-10), there were no clinically significant adverse reactions. Mild temperature elevations occurred in 4 patients, which returned to normal within 4 to 24 hours without treatment. Temporary elevations of amylase or lipase (pancreas enzymes) were seen in less than 5% of patients and were not associated with any symptoms.

The radiation you will receive from the imaging procedure is less than 500 millirems to the whole body. This is similar to that received during standard nuclear medicine scans.

The scanning procedures require lying on a bed for up to 20 minutes in one position which might be slightly uncomfortable.

There is some discomfort associated with the blood drawing procedure. Possible complications of blood drawing include excessive bleeding externally or into the skin or underlying tissue, blood clots in the blood vessel resulting in loss of blood flow to or from the hand, and infections of the skin, soft tissue, or blood vessel.

There will be some discomfort associated with taking the laxative to clear your bowels. This would include bloating, cramping, and diarrhea.

Some patients receiving monoclonal antibodies develop immunity against these antibodies. While such immunity is not harmful, it could prevent you from entering future monoclonal antibody studies.

As with any experimental treatment, there is a possibility that previously unknown side effects may occur.

Although there is no evidence that monoclonal antibodies or the dose of radiation used in this study is harmful to either the fetus or mother, it is unknown what effect monoclonal antibodies would have on an unborn baby. Therefore, pregnant women are not eligible to enter this study, and they should not become pregnant while in the study. If you are a women of childbearing age, you will have a blood test to make sure that you are not pregnant before you receive the antibody. The information regarding unknown risks also applies to fathering a child. Therefore, male subjects entering this study should avoid fathering children during the course of the study and should either abstain from

sexual relations or practice a method of birth control. Surgical removal of a woman's uterus is the only totally effective method to prevent pregnancy. Therefore, the only ways to completely avoid drug-associated risk to an unborn baby are (1) for a woman not to become pregnant or (2) for the subject not to receive this drug.

ALTERNATIVES TO PARTICIPATION: If you choose not to participate in this study, you will receive the usual routine evaluation as stated above.

CONFIDENTIALITY OF RECORDS: The case records from this study will be available for review by members of the Institutional Review Board at Madigan, by representatives of the Food and Drug Administration, and by NeoRex (the sponsor of this study). Otherwise, only the physicians conducting this study will have access to the records from this study. Information gained from this study may be used as part of a scientific publication, but you will in no way be personally identified.

OTHER INFORMATION: Significant findings that occur during this study that might affect your decision to participate in the study will be discussed with you. Any significant findings developed from this study will be available to you and may be obtained from Dr. Robson. Your participation in this study may be terminated without your consent if conditions occur which make your continued participation detrimental to your health.

If you should require medical care for injuries or disease which result from participation in this study, the medical care to which you will be entitled is the same as that to which you are already entitled as a DoD health care beneficiary. This does not include domiciliary or nursing home care.

You are encouraged to ask any questions, at any time, that will help you to understand how this study will be performed and/or how it will affect you. You may contact Dr. Robson at (206) 968-2505 or Dr. Bauman (co-investigator) at (206) 968-1645.

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING THIS FORM.

I do ☐ do not ☐ (check one & initial) consent to the inclusion of this form in my outpatient medical treatment record.

You will be given a signed copy of this form to keep.

SIGNATURE OF VOLUNTEER	DATE	SIGNATURE OF LEGAL GUARDIAN

PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS SIGNATURE OF WITNESS DATE SIGNED