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*A Review of Selected Radiopharmaceuticals
Approved by the FDA During 1996-1997*

by:

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A REVIEW OF SELECTED RADIOPHARMACEUTICALS APPROVED BY THE FDA DURING 1996-1997

STATEMENT OF OBJECTIVES

The purpose of this lesson is to provide a general review of radiopharmaceutical products approved by the FDA in 1996 and 1997. Specifically, this unit will review the following products: nofetumomab merpentan (Verluma®), capromab (Prostascint®), arcitumomab (CEA-Scan®), Tc99m sestamibi (Miraluma™), and samarium-153 lexidronam (Quadramet®).

Upon completion of this continuing education unit, the reader should be able to:

1. Recall the normal adult dosage for each of the products discussed. List the clinical indications for each of the products discussed.
2. Describe the basic pharmacokinetics, elimination and biodistribution for each of the products discussed.
3. Describe the basic imaging protocol for each of the agents discussed.
4. List the critical or dose-limiting organ for each of the agents discussed.
5. Recall the compounding and quality control procedure for each of the agents discussed.
6. Describe factors that contribute to the development of the HAMA response following monoclonal antibody administration.
7. Discuss the basic principles of radiolabeling monoclonal antibody-based radiopharmaceuticals.

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A REVIEW OF SELECTED RADIOPHARMACEUTICALS APPROVED BY THE FDA DURING 1996-1997

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INTRODUCTION

The purpose of this continuing education unit is to review the radiopharmaceutical products approved for use by the FDA in 1996 and 1997. Specifically, this unit will review the following products: nofetumomab merpentan (Verluma®), capromab (Prostascint®), arcitumomab (CEA-Scan®), Tc99m-sestamibi (Miraluma™), and samarium-153 lexidronam (Quadramet®). For each product, a brief discussion of the pharmacology, chemistry, pharmacokinetics, preparation parameters, dosimetry and clinical applications will follow. As this article represents a hodge-podge of products, specific disease states and epidemiologic data will be only briefly discussed. Given that several of the radiopharmaceutical products released in 1996-97 are monoclonal antibodies, the authors feel it necessary to present an overview of this class of agents prior to discussing specifics about each monoclonal product.

The reader is also encouraged to reflect upon the fact that each of the products discussed has clinical application in the oncological patient, whether as a diagnostic adjunct in combination with other imaging modalities, or as palliative therapy. The use of nuclear medicine imaging in staging, evaluation, follow-up

or treatment in certain cancer patients represents an area of growth for the industry. Given that in 1996, the American Cancer Society estimated that 1.3 million people would be diagnosed with cancer, there is great interest in the potential role of nuclear medicine in oncology.¹

MONOCLONAL ANTIBODIES

A review of monoclonal antibody production and radiolabeling is presented in the text that follows. A comparison of antibody fragments and intact antibodies is also discussed. This section is intended to provide a framework under which to group the specific monoclonal-based radiopharmaceutical products.

Monoclonal production^{2,3}

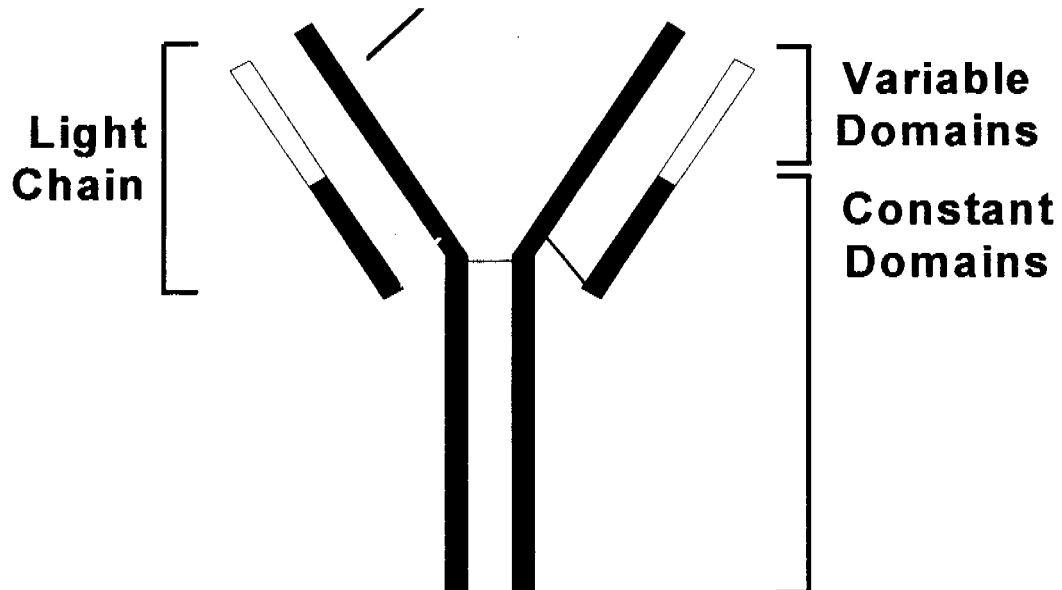
Large-quantity production of monoclonal antibodies became a fairly straightforward process as the hybridoma technique was refined. To review this technique, a specific antigen is injected into a mouse, stimulating antibody production by B-lymphocytes. These B-lymphocytes are harvested from the animal's spleen and incubated with myeloma cells in culture.

The resultant hybridoma is capable of producing large quantities of antibody and may be maintained over a long time period (immortal cell line). The hybridomas are carefully screened to

determine which particular cell line has the most desirable uptake, binding and

cross-reactivity profile. The structure of a monoclonal antibody is illustrated below in Figure 1.

Figure 1. Monoclonal antibody



HAMA (Human anti-mouse antibody) Response^{2,4,5}

It is the use of the murine-based technique described above which may initiate the HAMA (human anti-mouse antibody) response to foreign protein. Improper storage, rough handling during labeling or specific patient disease states may increase the likelihood of the HAMA, as well. Initiation of the HAMA response is undesirable because of its effect on subsequent diagnostic tests or radiolabeled antibody scans. HAMA formation may interfere with diagnostic tests that employ murine-based immunoassay techniques, such as tumor markers like PSA, CEA or CA125. For this reason, it is advisable to wait seven days post injection of a

monoclonal imaging agent to draw blood levels for immunoassay. Additionally, induction of a HAMA response from a previous exposure to a murine-product may adversely affect the biodistribution of the injected labeled antibody. If the injected antibody is complexed to HAMA, the complex clears from the body more quickly and is routed to the RE system instead of traveling to the area of interest. Many institutions routinely draw HAMA titer prior to injection of a monoclonal-based product, and repeat the titer when serial studies are planned.

“Designer” Antibodies²

In an attempt to avoid generating the HAMA response by decreasing

immunogenicity, alternate monoclonal production methods may be utilized. A fully human antibody may be genetically engineered, as may be a "chimeric" (partial human/ partial murine) product. Both are less likely to elicit HAMA. These genetically engineered antibodies are more expensive than those obtained from mass-produced hybridomas, but can be altered to optimize affinity for the target and decrease cross-reactivity with normal tissue or other types of cancer.

Whole Antibodies vs. Fragments^{2,4}

The variable regions of the antibody largely govern the specificity of the monoclonal for a particular target. The Fc portion (constant domain of the antibody) remains relatively constant among species and is thought to be primarily responsible for the HAMA response. The Fc portion is responsible for effector function like antibody dependent cell cytotoxicity and complement fixation. Whole antibodies may be broken into fragments using proteolytic enzymes, like papain or pepsin. Antibody fragments may be referred to as Fab' or F(ab')₂, referring to one "arm" of the "Y" or both arms of the "Y," respectively. These fragments retain the antigen binding portion, but lose the immunogenic Fc portion. Thus, the molecular weight of an intact antibody is on the order of 150,000 Daltons (Da), while that of a Fab' fragment is about 50,000 Da.

In addition to the advantage of decreasing the likelihood of HAMA formation, the use of fragments results in other desirable characteristics. Fragments clear the blood pool very rapidly, while intact antibodies diffuse to the target site more slowly and have a much longer serum half-life. The serum half-life of intact antibodies is on the

order of 24-30 hours, whereas the fragments have a serum half-life of about 90 minutes allowing for early imaging. Additionally, fragments tend to yield higher tumor to background ratio, improving image quality. Intact antibodies have a lower tumor to blood ratio because of their slower diffusion and clearance, but may achieve higher absolute tumor levels because of their higher specificity for the antigen.

Ultimately, the choice of fragment versus intact antibody is governed by the uptake characteristics of the target antigen, as well as the radionuclide used for labeling. (i.e., a shorter-lived label like Tc99m may be better suited for use with an antibody fragment than an intact antibody, depending on the uptake kinetics of the target). The bottom line is to choose a radionuclide for labeling that parallels the biologic half-life of the fragment or intact antibody.

Antibody Mass⁶

An additional consideration with some antibodies is the mass of product that must be administered to achieve adequate tumor levels. That is, there is non-specific uptake in binding sites of normal organs that must be saturated so that the tumor uptake can be distinguished. Each antibody product is tested to determine at what level the antibody dose is optima. Too much antibody increases the likelihood of HAMA formation, while too little may not achieve adequate target levels for imaging. In many cases, a fairly large mass of antibody must be administered to overcome this nonspecific binding, particularly in the liver.

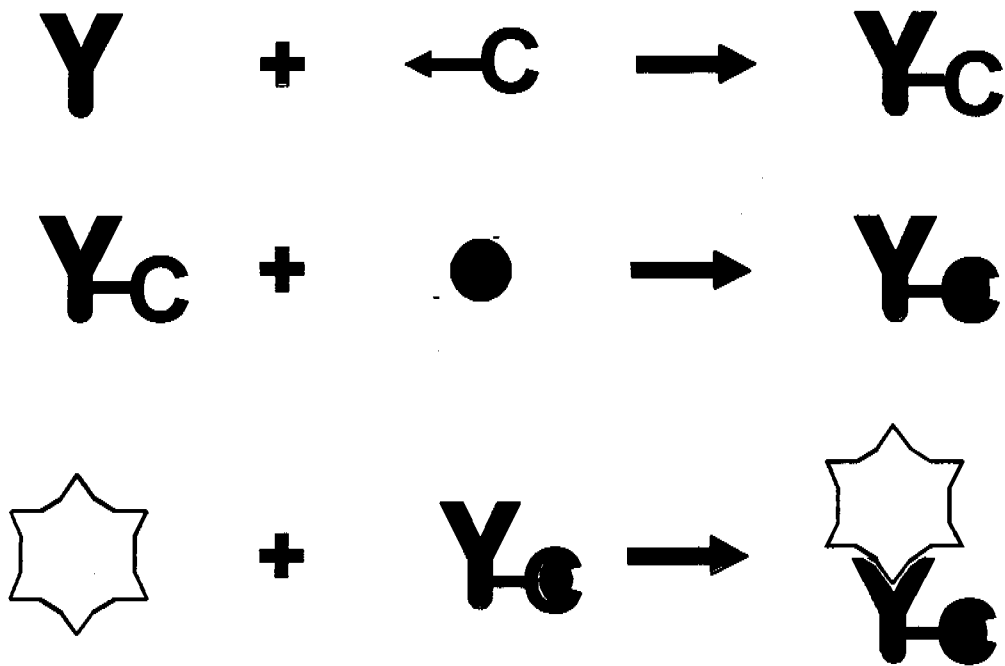
Radiolabeling^{4,6}

Figure 2 below presents a schematic representation of radiolabeling a

monoclonal antibody and its subsequent attachment to a target cell. Because the antibody molecule is a protein, there are a variety of potential attachment sites for drugs and radionuclides. However, the radionuclide must be attached in such a way that the reactivity with the antigen target is not affected. An additional consideration that must be made when radiolabeling is the half-life of the radionuclide, which must allow adequate

target to background contrast within a reasonable time frame. Furthermore, it also is desirable in order to minimize the radiation dose to the patient. A short half-life nuclide is preferred unless the tumor uptake or background clearance requires the use of a longer-lived nuclide to get adequate counting statistics for imaging. The agents presented in this lesson utilize In-111 or Tc-99m labeling.

Figure 2. Radiolabeling of Monoclonal Antibody



PROSTASCINT® (CAPROMAB PENDETIDE)⁷⁻¹⁶

Indications and Disease State Information

ProstaScint®, manufactured and distributed by Cytogen, is indicated for newly diagnosed patients with prostate

cancer thought to be localized, and in post-prostatectomy patients with rising PSA, negative or equivocal standard evaluations, like bone scan, and who have a high suspicion of occult disease. It is not to be used without confirmation of disease because of the high false positive and false negative rate in clinical

trials. See Figure 3 for ProstaScint® utilization in patient work-up.

Cytogen has restricted access to this product to institutions who are enrolled as "PIE" (Partners in Excellence) sites. Enrolling in this Cytogen-sponsored program gives the physicians and technologists in the institution access to training materials and a speaker's bureau. The program is designed to increase demand for the product and avoid having technical image difficulties in image acquisition and interpretation.

There are 244,000 newly diagnosed prostate cancer patients each year, with 40,000 cancer-related deaths. Serum blood levels of prostate specific antigen (PSA) are often used to monitor therapy and disease progression in these patients. However, the PSA is normal in approximately 21% of patients with recurrent disease. Also problematic is the fact that CT and MRI only detect 30% of prostate metastases. Treatment options for recurrent prostate cancer include hormonal therapy if the disease recurs outside the prostate fossa, or radiation therapy if localized to the prostate fossa.

Pharmacology, Biodistribution and Dosimetry

ProstaScint® has a small volume of distribution and a slow clearance; $8 \pm 3\%$ is excreted in the urine during the 72 hour period post administration. Its serum half-life is 68 ± 28 hours. Fecal excretion ultimately accounts for 25% of the injected activity. Thus, a bowel prep the night before the scan and an enema 2-4 hours prior to the scan are recommended. Catheterization during the procedure is also recommended. The liver has the highest organ residence time for the drug and is the critical organ, receiving 18.5 rads/5 mCi.

Areas of normal uptake include blood pool, liver, spleen, kidney, bone marrow, bowel and genitalia. The liver spleen activity is probably secondary to catabolism.

Reported causes of false positive uptake include ostomy sites, abdominal aneurysms, post-operative bowel adhesions and degenerative joint disease. Reported causes of false negative lesions include small lymph nodes, especially those less than 5mm in size.

Compounding and Quality Assurance

Compounding is fairly straightforward. The initial step is to buffer the indium chloride with acetate, prior to adding 6-7 mCi to the reaction vial containing the capromab. A 30-minute incubation at room temperature completes the labeling process. The pH is adjusted with the remaining acetate and the product is filtered. The kit must be used within 8 hours of compounding and requires refrigeration prior to compounding. Radiochemical purity must be greater than 90%. The quality control procedure is similar to that used with OncoScint®, and involves mixing the final product with an equimolar amount of DTPA prior to spotting the sample on the ITCL-SG strip. The strip is developed in 0.9% saline; the labeled antibody product remains at the origin.

Dosage and Administration

The normal adult dose is 0.5 mg of ProstaScint labeled with 5 mCi indium-111 administered IV over 5 minutes. Adverse reactions reported in the package insert include: 1% of patients experienced an increase in bilirubin, hypo or hypertension, 8% of patients developed HAMA following a single injection. As many as 19% of patients were found to have HAMA titer upon

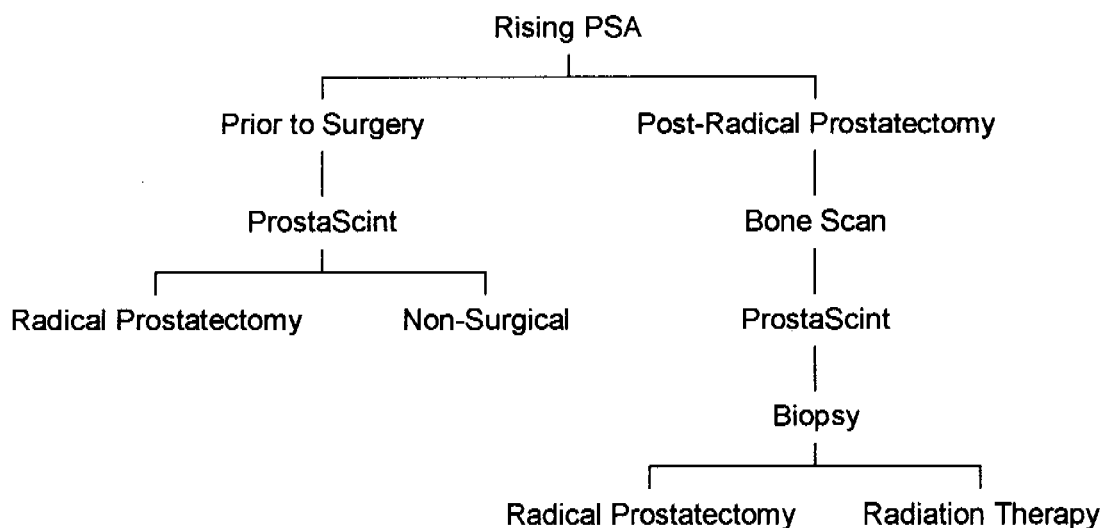
repeat injection in clinical trials. The antibody may also interfere with PSA and digoxin assays.

Imaging Considerations

Initial SPECT images are performed 30 minutes post injection to obtain a blood pool image. Whole body planar images are obtained at 3-5 days. Delayed

images may be acquired out to 6-7 days to distinguish bowel activity from recurrence of cancer. It is important to do SPECT of the pelvis to look at activity adjacent to, but separate from the bladder and blood pool. Blood pool images may also be co-registered in order to do a background subtraction.

Figure 3. ProstaScint® Patient Management⁸



VERLUMA® (NOFETUMOMAB)¹⁷⁻²¹

Indications and Disease State Information

Verluma®, manufactured by Thomae and distributed by DuPont, is indicated for detection of extensive disease in patients with biopsy-proven small cell lung cancer (SCLC). It is not indicated for screening, nor is it recommended to confirm limited disease. Extensive disease indicates there is evidence of distant metastasis. Limited disease indicates that the disease is confined to one hemithorax without distant new cases per year. Eighty-seven percent of those who die are smokers.

metastases. The prognosis for the patient with lung cancer is quite poor. Those with limited disease have a 10-25% 2-year survival rate; those with extensive disease have a 0-2% 2-year survival rate. Two-thirds of patients present with extensive disease that, by definition, has metastasized at the time of first diagnosis.

Lung cancer is the leading cause of cancer death in both sexes, with 177,000 Of the 177,000 cases, approximately 20% have SCLC, 20% have mixed small

cell and non-small cell cancer. The majority of patients, therefore, have NSCLC, for which Verluma® is not indicated.

In order that the patient receive proper treatment, it is necessary to correctly stage the progression of the cancer. Patients with limited disease may respond to surgery, radiation therapy, or chemotherapy. Those with extensive disease often have chemotherapy as the sole option due to the extent of spread of their disease. Staging is an involved process, which includes CT of the abdomen and head, bone scan and bone

marrow biopsy/aspiration, physical exam, chest X-ray and biopsy. Verluma® has the highest accuracy (82%) for clinical staging of any single diagnostic test and the highest sensitivity. See Table 1, from the Verluma® package insert. The intent of adding Verluma® to the standard diagnostic modalities is to avoid the expense of further testing in patients confirmed to have extensive disease as determined by the monoclonal scan. It is recommended that patients with limited disease still undergo further standard tests to assure that Verluma® did not underestimate the extent of their disease.

Diagnostic Evaluation	Extensive Disease	Limited Disease	Overall Accuracy
Verluma® Imaging	44/57	29/32	73/89 (82%)
CT Abdomen	33/57	30/32	63/89 (71%)
Bone Scan	24/57	32/32	56/89 (63%)
Bone Marrow (asp/bx)	16/57	32/32	48/89 (54%)
CT Head	12/57	32/32	44/89 (49%)
Physical Exam	8/57	31/32	39/89 (44%)
CT Chest	5/57	32/32	37/89 (42%)
Chest X-Ray	2/57	32/32	34/89 (38%)

Pharmacology, Biodistribution and Dosimetry

Verluma® is a Fab' fragment of the monoclonal antibody NR-LU-10 that reacts with a 40 kD glycoprotein antigen expressed by a variety of cancers including SCLC, NSCLC, and adenocarcinomas of the colon, ovary and breast. It is expressed on virtually all

SCLC, unlike the other types of cancer. This Fab' fragment is rapidly distributed and clears from the body fairly quickly. Elimination is via the urine with about 64% of the injected amount cleared in the first 24 hours. A secondary route of excretion is the hepatobiliary system.

Nonspecific uptake occurs in areas of high vascularity including the midline

nasal area and testes. The antibody also exhibits very distinct cross-reactivity with the thyroid, salivary and pituitary glands. The thyroid will be seen very clearly on the images. The critical organ is the gall bladder wall (5.6 rads/30 mCi), followed by the kidney (3.9 rads/30 mCi), and upper and lower large intestine (2.7 rads/30 mCi and 2.0 rads/30 mCi, respectively). False positive images may occur in areas of high blood flow, such as recent surgery or inflammation. Additional uptake of an artifactual nature occurs at the skin folds of the axilla, breast and lower abdomen, particularly in obese patients. It may be desirable to image with the arms overhead to minimize this uptake. False negative images may occur in areas like the brain and bone, where Verluma® is not taken up to any great extent. Verluma® may miss small liver lesions, as well.

Compounding and Quality Assurance

The procedure for compounding Verluma® requires several complex manipulations and takes about 90 minutes to complete the labeling process. Temperature and incubation times are critical, as are the concentration of the reactants used. It is also important to realize that there are several required ancillary supplies that are not listed in the package insert. Detailed coverage of this procedure is beyond the scope of this lesson. It may be found in the package insert. See Figure 4 for a graphic explanation of the labeling process.

The basic steps in compounding are:

- I. Formation of ligand
- II. Formation of the ligand ester
- III. Reaction of the ligand ester with the antibody

IV. Purification and filtration of the labeled antibody via ion exchange column.

The Verluma® labeling reaction is accomplished by forming a Tc99m gluconate ligand that acts as an intermediate chelate to stabilize the Tc99m until it is transferred to the phenthioate ligand. This transchelation requires the proper temperature, pH and reaction time. The Tc-ligand complex is added to the antibody vial, the pH is adjusted and the antibody is conjugated to the phenthioate ligand to form the final product. Careful attention must be paid to the age of the generator eluate and the contamination of the reactants by trace metals. Trace metals, such as those that leach from rubber stoppers, interfere with the transchelation process. There is very little tin in the initial reaction of gluconate with Tc99m, necessitating the use of "fresh" Tc99m with little Tc99 to interfere with tagging.

Careful handling of the antibody product is necessary to avoid the loss of product to "plating out" on the froth produced by vigorous agitation of the vial. Careful filtration is necessary to assure that the integrity of the filter is maintained. The final product should be >85% radiochemically pure and be used within 6 hours of preparation. The quality control procedure requires a 12% trichloroacetic acid solution and a silica gel glass fiber sheet cut into 2x10 cm strips. Following strip development in the solvent, the strip is cut into three pieces. The labeled product remains at the origin, while the non-protein bound Tc99m labeled impurities and unbound pertechnetate migrate with the solvent front.

Dosage and Administration

The adult dose of Verluma® is 5-10 mg nofetumomab labeled with 15-30 mCi of Tc99m, infused in a total volume of 15-20 mL over 3-5 minutes. Some institutions prefer to administer the dose in a smaller total volume. IV bags should not be used for administration, but three-way stopcock assemblies are acceptable.

Adverse reactions were rare and consisted of self-limited elevations in temperature, mild urticaria or allergic reaction, transient changes in serum lipase or amylase; 6% of patients had a HAMA response that subsequently normalized within 3-4 months.

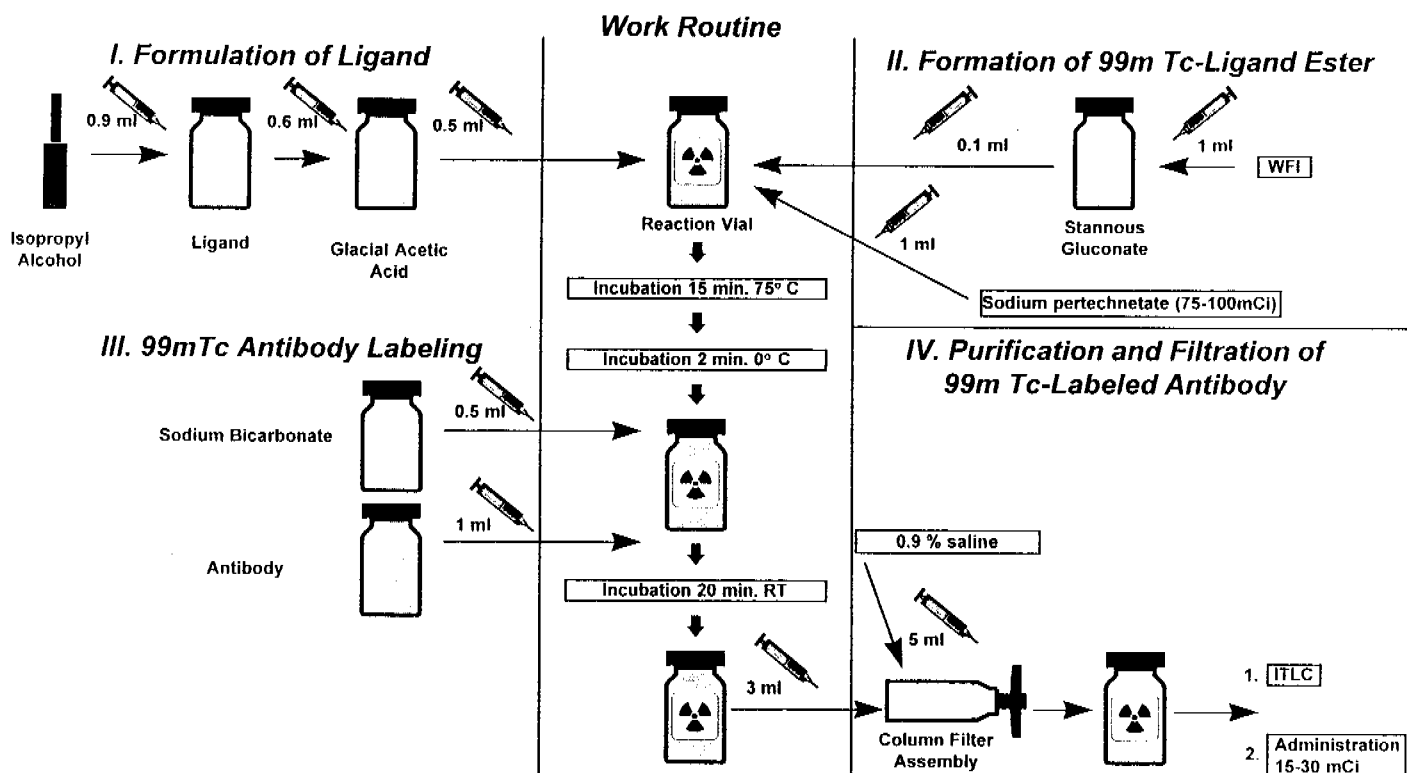
Imaging Considerations

Imaging is performed 14-17 hours post injection. Whole body planar views of the anterior and posterior are obtained

routinely. SPECT in areas of interest and lateral skull views may be useful, as well.

Verluma® performs well in patients with extensive disease, however understaged those thought to have limited disease 10% of time. In another 15%, however, antibody imaging uncovered metastatic sites missed by other modalities. Verluma's® positive predictive value (PPV) in extensive disease was 95-100%, comparable to that of the 96-100% obtained with all other diagnostic modalities combined. Therefore, in a patient thought to have limited disease after Verluma® scan, the standard battery of tests is still necessary to confirm the staging. Those found to have extensive disease with Verluma® may be spared the cost of further diagnostic tests, as the PPV is so high.

Figure 4. Radiolabeling of Verluma®



CEA-SCAN® (ARCITUMOMAB)²²⁻³²

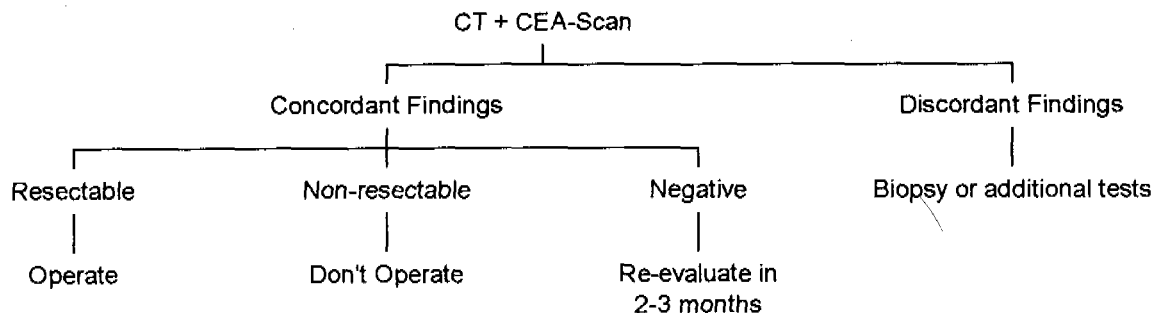
Indications and Disease State Information

CEA-Scan®, manufactured and distributed by Immunomedics, is indicated for use with standard diagnostic modalities to detect the presence, location and extent of recurrent or metastatic colorectal cancer involving the liver, abdomen and pelvis in patients with a histologically confirmed diagnosis of colorectal carcinoma. It is not indicated as a screening or follow-up tool and is recommended only in patients with confirmed disease.

Colorectal cancer has an annual incidence of 133,500 cases with 54,000 related deaths each year. The only chance for cure is surgery. In those patients who have localized disease, the 5-year survival rate following surgery is 90%. Survival decreases as the disease spreads. Unfortunately, many patients already have metastatic disease at the time of diagnosis. Up to 50% have micrometastasis and will eventually die of the disease.

Accurate staging is important to avoid the unnecessary morbidity and cost of surgery or chemotherapy in a patient who will not ultimately benefit. Staging of colorectal cancer requires an extensive work-up prior to surgery, including CT, barium enema, chest X-ray, MRI, colonoscopy, endoscopy with biopsy, ultrasound and sometimes liver/spleen scanning. After surgery, patients are generally followed with a physical exam, CEA levels, liver function tests, chest X-ray and yearly colonoscopy. CT and MRI may be performed at follow-up, as well. Unfortunately, standard staging modalities, such as CT, may miss micrometastatic lesions in normal-sized nodes. The intent of monoclonal antibody imaging then is to improve the diagnostic accuracy and staging. The manufacturer has developed a patient management paradigm, as shown in Figure 5, for physician use in using the results of CT and CEA-Scan in order to make decisions about resection.

Figure 5. Suggested Patient Management Paradigm



Pharmacology, Biodistribution and Dosimetry

CEA-scan® is a Fab' fragment of an IMM-4 IgG antibody directed at the 200,000 Da membrane-bound form of carcinoembryonic antigen(CEA). This carcinoembryonic antigen is expressed by normal tissues, as well as a variety of cancers and circulates in the bloodstream. The circulating antigen is primarily a 180,000 Da form and is normally present at levels less than 2 ng/mL of serum. These levels increase 10-20 fold as a cancer grows. CEA-Scan® has little cross-reactivity with this circulating 180,000 Da form and binds instead to the 200,000 Da form present on the surface of the cell membrane.

Following injection, CEA-Scan® is very rapidly cleared by the glomerulus, with about 28% excreted in the urine over the first 24 hours. About 23% of the original amount remains in the blood at 5 hours, and 7% at 24 hours. The serum half-life of Fab' is about 4 hours. There is some catabolism of the Fab' by the kidneys and the resultant Tc99m-labeled peptide products may clear more slowly than intact Fab'. There is also some dimerization of Fab' to form Fab₂' during labeling, so there will be a small percentage (<5%) of hepatobiliary excretion, as well. The critical organ is the kidney(~0.5rads/mCi), followed by the bladder (~0.08rads/mCi), spleen (~0.08rads/mCi) and liver(~0.05 rads/mCi).

Potential causes of false positive uptake listed in the package insert and literature include: adenoma with atypia, gall bladder and gut in late images, uterine activity in patients with hypermenorrhea, IM injection site, nonspecific uptake at surgical scar/incision, blood pool on early

images and adhesions. False negative lesions may result from small lymph node and peritoneal mets, ovarian mets, and any recurrence less than 1 cm in size.

Compounding and Quality Assurance

Compounding is fairly straightforward. The Fab' fragment was formulated to have an intrinsic receptor with a high affinity for binding Tc99m. In preclinical studies, this receptor was demonstrated to quantitatively bind up to 50mCi of Tc99m within 5 minutes. Compounding involves the addition of 25-30 mCi of pertechnetate to the lyophilized vial that has been allowed to equilibrate to room temperature following its storage in the refrigerator. An incubation period of 5 minutes is sufficient to obtain very high binding efficiency. The kit may be diluted to final volume with saline and stored at room temperature for up to 4 hours post compounding. The product must be 90% radiochemically pure. The package insert recommends a quality control procedure using ITLC-SG and acetone to determine the radiochemical purity.

Dosage and Administration

The recommended adult dose is 1mg arcitumomab labeled with 20-30 mCi of pertechnetate. It may be administered IV in 2 mL of volume or infused over a 5-20 minutes period in a 30 mL volume. Adverse reactions are generally minor, with fever, minor GI upset, transient eosinophilia, headache, itching and rash listed in the package insert. There was one case report of an unwitnessed seizure in a severely hypertensive patient that could not be directly attributed to the drug's administration.

Imaging Considerations

Initial planar and SPECT images are obtained of the chest, abdomen and pelvis at 2-5 hours post administration. Delayed planar and SPECT images are acquired of the head, chest, abdomen and pelvis at 18-24 hours. It is recommended that images be read from a computer, as up to 1/3 of liver metastases were missed on plain film. The cine mode may help distinguish bowel from tumor and the intensity may be adjusted to improve the image contrast, as the kidneys will be very hot. Liver metastases may be seen on the scan as hot, iso-intense with a hot rim, or cold with a hot rim. Late images are useful because the "rims" of these liver lesions get hotter with time.

CEA-Scan® is indicated in conjunction with other diagnostic modalities. CT + CEA-Scan® together more accurately predict surgical outcome following tumor detection than either test alone. In 122 patients with surgical/ histological confirmation of disease, CEA-Scan® showed a sensitivity of 78%, specificity of 86%, accuracy of 79%, PPV of 99% and negative predictive value (NPV) of 19%. When used in conjunction with standard diagnostic modalities, the sensitivity was 97%, specificity 29%, accuracy 93%, PPV 96% and NPV 33%. Both sensitivity and specificity decreased in recurrent disease. CT is more sensitive for detecting liver lesions due to the normal uptake of In111 in the liver as was discussed earlier.

NON-MONOCLONAL ANTIBODIES: MIRALUMA™³³⁻⁴¹

Indications and Disease State Information

Miraluma™, which is manufactured and distributed by DuPont, is indicated for

use in planar breast imaging (scintimammography). Miraluma™ is a second-line diagnostic drug to be used after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass. It is not indicated for breast cancer screening or to confirm the presence or absence of malignancy. It is not indicated as an alternative to biopsy.

Breast cancer is the second leading cause of cancer related deaths in women of all ages and the leading cause of death in women ages 40-55. One in every 8 women will develop breast cancer sometime during their lifetime. Each year, one of every 33 breast cancer patients will die of the disease. Five or six women will have a negative biopsy (benign) for every one patient diagnosed with cancer.

Nearly 20 million women will see physicians for potential breast cancer each year. Fifty-six percent of all women over 50 years of age will have a mammogram study performed routinely. This test continues to be the best screening tool available for diagnosing breast cancer. One study reported mammography sensitivity of 80% specificity of 20-50%, a false negative rate of 10-15% and a positive predictive value of 15-30%. Each patient with a palpable mass and/or questionable mammogram requires additional evaluation to determine if treatment is necessary. Mammography's low specificity infers that the 50-80% false positives go to biopsy unnecessarily. Mammography in patients with dense breasts has an even lower specificity of 20%. In patients with difficult to interpret mammograms, such as those with dense breasts, scarring from

previous biopsy, breast implants, or fibrocystic disease, many breast cancers are missed (35.7%) due to a false negative mammogram.

The need for accurate diagnosis and staging has resulted in a variety of additional breast cancer screening tools.

With additional adjunct screening, many unnecessary biopsies could be prevented. Scintimammography with sestamibi has demonstrated significant improvement in sensitivity, specificity, negative predictive value and positive predictive value, as indicated below in Table 2.

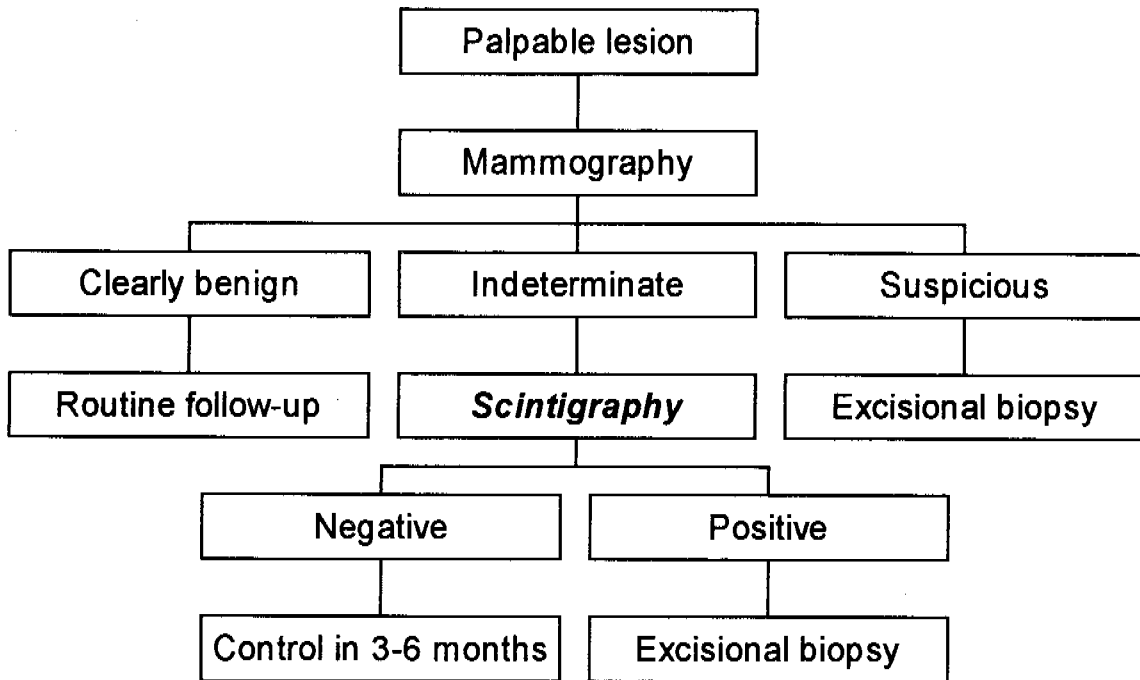
Table 2: Sestamibi Statistics from Multi-Center Trials of 673 women ⁽³⁷⁾

	Sensitivity	Specificity	PPV	NPV
Palpable lesion	95%	74%	77%	94%
Nonpalpable lesion	72%	86%	70%	87%
Overall	85%	81%	74%	90%
Fatty breast	84%	81%	76%	88%
Dense breast	86%	80%	72%	91%

The literature concludes that high-quality imaging with sestamibi has a high diagnostic accuracy for the detection of primary breast cancer in patients who have palpable lesions. When used as a complementary method to conventional

mammography, scintimammography can help diagnose breast cancer at an earlier stage in women with dense breasts. An example of the role of sestamibi mammography in patient management is shown in Figure 6.

Figure 6. Patient Work-up Example



Pharmacology, Biodistribution and Dosimetry

Tc99m-sestamibi, the active ingredient of Miraluma™ is well established as Cardiolite®, a cardiac imaging agent. An isonitrile derivative, it also localizes in many malignant tumors, including most malignant breast cancer tumors. After injection, Miraluma™ is distributed throughout the body in proportion to blood flow. It is cleared from the bloodstream rapidly and is fixed intracellularly in proportion to the vascularity. Since malignant cells have a higher metabolic activity than normal cells, lesions appear on the images as “hot spots”. Elimination is primarily via the hepatobiliary system. Twenty-seven percent of the injected dose is excreted in the urine and about thirty-three percent is cleared through the feces in 48 hours. The critical organ for this procedure is the upper large intestine wall, receiving a

radiation dose of 5.4 rads/30 mCi. The breasts receive a radiation dose of 0.2 rads/30 mCi.

Compounding and Quality Assurance

Readers are most likely very familiar with the compounding procedure from experience with Cardiolite®. After reconstitution with Tc-99m, the vial is heated for ten minutes. Radiolabeling occurs through a series of ligand exchange reactions. Quality control is TLC using ethanol and aluminum oxide plates.

Dosage and Administration

The dosage of Miraluma is 20-30 mCi injected in the arm contralateral to the suspected lesion. If bilateral lesions are suspected, the patient should be injected through the dorsal veins. The choice of an inappropriate injection site could result in activity localizing in the axillary

lymph nodes. No drug interactions have been reported. Adverse reactions include transient parosmia and taste perversion. Other mild reactions, such as headache, flushing and hypersensitivity have been reported.

Imaging Considerations

In order to achieve the best separation of breast tissue from the chest wall, the patient's breast should be freely suspended with no compression. This may be accomplished with a special overlay for the imaging table. Beginning five minutes post-injection, a ten-minute lateral image of both the abnormal and normal breast is acquired. This is followed by a ten-minute anterior image of both breasts.

As the only radiopharmaceutical with an approved indication for breast imaging, Miraluma, as an adjuvant to mammography, may offer an answer for those patients with difficult or questionable mammograms or those reluctant to have a biopsy. The improvement in patient management may also decrease health care costs by avoiding unnecessary biopsies.

NON-MONOCLONAL ANTI-BODIES: QUADRAMET® (SAMARIUM SM 153 LEXIDRONAM)⁴²⁻⁴⁸

Indications and Disease State Information

Quadramet® is manufactured by Dow and distributed by DuPont under license from Cytogen. It is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions. The exact mechanism by which Quadramet® relieves bone pain is unknown. A routine radionuclidic bone scan is used to

confirm lesions before administering Quadramet® to patients.

Bone metastases are the most common cause of cancer pain and predispose patients to immobility, pathological fractures, bone marrow failure, neurological symptoms and hypercalcemia. The reported incidence of bone metastases varies according to tumor type. Post-mortem studies indicate that up to 85% of patients with breast or prostatic carcinoma develop bone metastases. The management of skeletal metastases is directed toward pain palliation and demands a multi disciplinary approach. Traditional treatments include chemotherapy, hormonal therapy, radiotherapy, surgery, and high dose analgesics. Each of the traditional treatments has inherent adverse reactions that significantly impact the patient's quality of life.

The use of radionuclides for palliative therapy of bone malignancies, was reported in the earliest days of the nuclear era. Both Sr-89 and P-32 were investigated in the early 1940's. The underlying principle of any form of unsealed source therapy is that the absorbed dose to the lesion should be high enough to produce a significant clinical effect. The dose to the critical organ, usually bone marrow, should be low enough to avoid significant adverse events. The duration of response should be prolonged and the onset should occur soon after administration. In theory, the agent is incorporated into areas of growing bone. Bone growth rate is slowed with the beta emission cellular ablation. Slowing the metastatic bone invasion will reduce the pain. The appropriate administered dosage is determined after consideration of beta energy, physical and effective half-lives.

The FDA approved Strontium-89 chloride for bone pain palliation in 1993 and Sm-153 leixidronam in 1997. Both of these agents emit beta-particles during

decay and avidly seek areas of growing bone. A comparison of the approved radiopharmaceuticals used for bone pain palliation is provided in Table 3.

	Strontium-89 chloride	Quadramet®
Half-life	50.5 days	46.3 hours
Dosage	4 mCi	1 mCi/kg
Emissions	1.4 MeV beta	640 , 710 & 810 keV beta 103 keV gamma
Onset of action	7-20 days	7 days
Excretion	66% renal, 33% fecal	100% renal
Dosimetry: bone surface	63 rad/mCi	26 rad/mCi
Dosimetry: bone marrow	40.7 rad/mCi	5.7 rad/mCi

Pharmacology, Biodistribution and Dosimetry

Quadramet® is a therapeutic agent of radioactive samarium and a tetrphosphonate chelator. The reactor produced radionuclide emits three betas and a 103 keV gamma ray. Quadramet® has an affinity for bone and concentrates in areas of bone turnover in association with hydroxyapatite with a lesion-to-normal bone ratio of approximately 5 to 1. The bone surface is the critical organ for Quadramet®, receiving 25 rads/mCi. The radiation dose to the red marrow, which receives a radiation dose of 5.7 rads/mCi, limits the dosage of Quadramet administered to a patient. The skeletal uptake varies with the number of metastatic lesions. A patient with 5 lesions had a skeletal uptake of 56% of the injected dose, while a patient with 52 lesions had uptake of 76% of the injected dose. There is no metabolism of Quadramet®. "Free" radiopharmaceutical, which is not taken up by bone, is promptly excreted renally with less than 1% of the dose remaining in the bloodstream after 5 hours.

Handling Considerations

There is no compounding of Quadramet®, as it arrives ready for administration from the manufacturer. Prior to dispensing, the product must be thawed at room temperature, having been shipped and stored frozen. The product expires 8 hours after thawing or 48 hours after calibration, whichever is earlier. Those who handle Quadramet® should use radiation safety procedures appropriate to beta emitting isotopes. Dose calibrators may need to be adjusted to accurately assay patient doses. Contaminated waste products should be stored separately from other isotopes since Quadramet® contains microcurie amounts of Europium-154 with a half-life of 8.8 years.

Dosage and Administration

A patient dose of 1 mCi/kg administered by slow IV injection is recommended. The patient should be well hydrated and urged to void frequently. There is a delayed onset of pain relief, usually 7 days post injection. Many patients have reported a transient increase in pain followed by relief. This

“flare response” can be treated with analgesics. Well-hydrated patients can be imaged as soon as 6 hours post injection.

No drug interactions have been studied, but those drugs that interfere with routine bone scans would most likely alter the biodistribution of Quadramet®. Adverse reactions include the “flare response”, and reversible myelosuppression. White blood cell and platelet counts will decrease to a nadir of 40-50% of baseline within 3-5 weeks. Blood counts should be monitored weekly for at least 8 weeks, or until recovery of adequate bone marrow function.

As an adjuvant to traditional therapy, Quadramet® is effective in bone pain management in cancer patients. Since much of the morbidity and mortality associated with cancer can be attributed to skeletal metastases, any improvement in effective treatment for metastatic bone pain must therefore represent a major advance in cancer management.

Patient Considerations

Patient instructions following the administration of Quadramet® include

personal hygiene instructions similar to those given following therapeutic doses of I-131. Patients are instructed about the importance of follow-up blood counts and cautioned to report signs or symptoms that might indicate a fall in WBC or platelet count. (i.e., sore throat, bleeding or bruising, infection) It may be advisable to warn patients of the “flare phenomenon,” and its management with traditional pain medications. Many clinicians encourage patients to keep a record of pain medication use, and the duration, intensity and frequency of their pain. As Quadramet® begins to provide pain relief, the patient’s use of other medications should begin to decrease.

CONCLUSION

The information presented in this article is intended to provide a cursory overview of the radiopharmaceutical products released by the FDA in 1996-1997. Prior to dispensing or making recommendations about the clinical use of these products, the reader is encouraged to consult the manufacturer’s package insert and nuclear medicine literature for further detail.

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QUESTIONS:

1. Which of the following factors contributes to increased likelihood of HAMA formation following IV administration?
 - a. slow IV infusion
 - b. use of chimeric antibody product
 - c. use of an antibody fragment
 - d. harsh labeling conditions
2. Monoclonal agent XB has a serum half-life of 90 minutes and clears the blood pool very rapidly. Imaging will be performed shortly after administration. Which of the following radionuclides would be most desirable for labeling Monoclonal XB?
 - a. I-131
 - b. Tc-99m
 - c. Ga-67
 - d. In-111
3. Staging of colorectal cancer involves the use of several diagnostic tests. Unfortunately, these standard diagnostic modalities may miss metastases in
 - a. liver
 - b. lower abdomen
 - c. normal-sized nodes
 - d. lungs
4. CEA-Scan is primarily eliminated from the body via the
 - a. hepatobiliary system
 - b. feces
 - c. urine
 - d. spleen

5. Labeling of CEA-Scan involves attaching Tc99m to the antibody via a/an
 - a. sulfhydryl group
 - b. DTPA chelate
 - c. phenthioate ligand
 - d. intrinsic receptor

6. The normal adult dosage of CEA-Scan is _____.
 - a. 1 mCi arcitumomab
 - b. 1 mg nofetumomab
 - c. 20-30 mCi pertechnetate-labeled antibody
 - d. 15-30 mCi pertechnetate-labeled antibody

7. Which of the following is a characteristic of extensive small cell lung cancer?
 - a. limited to one hemithorax
 - b. spread of metastasis
 - c. no distant metastasis
 - d. 25% 2-year survival rate

8. Verluma™ is indicated for the detection of _____.
 - a. limited small-cell lung cancer
 - b. non-resectable prostate cancer
 - c. extensive small cell lung cancer
 - d. small-cell lung cancer without metastasis

9. Which of the following organs are considered to be part of the normal biodistribution pattern seen on Verluma™ images?
 - a. brain
 - b. pancreas
 - c. thyroid
 - d. bone

10. The compounding of Verluma™ is labor-intensive and involves several manipulations to achieve labeling. Which of the following terms best describes the chemistry of the labeling reaction?
 - a. isotopic exchange
 - b. transchelation reaction
 - c. ligand extraction
 - d. substitution reaction

11. The normal adult dose of Verluma™ is _____.
 - a. 1 mg arcitumomab labeled with 20 mCi pertechnetate
 - b. 15-30 mg nofetumomab labeled with 5-10 mCi pertechnetate
 - c. 5-10 mg nofetumomab
 - d. 15-30 mCi imciromab

12. Which of the following patients would meet the package insert criteria for use of ProstaScint®?
 - a. Patient A: unconfirmed localized prostate cancer
 - b. Patient B: rising PSA following successful prostatectomy
 - c. Patient C: equivocal bone scan with unconfirmed disease
 - d. Patient D: low suspicion of disease with rising PSA

13. Which of the following best describes the elimination of ProstaScint® from the body?
 - a. approximately 50% excreted via kidneys during first 72 hours
 - b. renal accounts for 25% during the first 24 hours

- c. fecal accounts ultimately for 25% of injected activity
- d. fecal elimination accounts for 50% of injected activity
14. _____ is a recommended patient preparation for a ProstaScint™ study.
- barium enema
 - oral cathartic
 - NPO x 12 hours
 - CEA blood levels
15. What is the purpose for adding acetate to the InCl₃ vial prior to labeling ProstaScint®?
- Increase solubility
 - Decrease reaction time
 - Minimize competitive interference
 - pH adjustment
16. Whole body planar images are obtained _____ post-administration of ProstaScint®.
- 30-45 minutes
 - 3-5 hours
 - 8-10 days
 - 3-5 days
17. The proper injection technique for Miraluma™ includes injection _____
- by rapid bolus IV injection
 - into the arm proximal to the suspected lesion
 - into the arm contralateral of the suspected lesion
 - through a central line
18. The critical organ for Miraluma™ is the
- liver
 - bladder
 - large intestine
 - bone marrow
19. The quality control test for Miraluma™ uses
- ITLC-SA and acetone
 - ITLC-aluminum oxide plate and ethanol
 - ITLC-SG and saline
 - ITLS-SG and methanol
20. Scintimammography using Miraluma™ in a patient work-up is best described as
- an effective tool for breast cancer screening
 - an effective method to confirm malignancy
 - a second line diagnostic drug for use after an indeterminate mammogram
 - a second line diagnostic drug for use after physical examination
21. The usual dosage of Miraluma™ is
- 10-20 mCi
 - 20-30 mCi
 - 1-5 mCi
 - determined from patient statistics
22. The purpose of the tetrphosphonate chelator in Quadramet® is
- To sequester any Eu-154 contaminants
 - To bind samarium to hydroxyapatite

- c. To function as an antioxidant
 - d. To function as a reducing agent
23. The dose-limiting organ for Quadramet® is
- a. red bone marrow
 - b. bladder
 - f. large intestine
 - g. thyroid
24. The recommended patient dosage of Quadramet is
- a. 4 mCi
 - b. 1.0 mCi/kg
 - c. 0.57 mCi/kg
 - d. 20 mCi
25. When compared to Strontium-89, the recommended patient dosage of Quadramet® is much higher because of its
- a. shorter physical half-life and higher energy beta emissions
 - b. shorter effective half-life, lower energy beta emissions and reduced dosimetry
 - c. shorter effective half-life, reduced dosimetry and delayed onset of action
 - d. longer effective half-life, reduced dosimetry and rapid onset of action