

1 buying a pig in a poke, you have to believe in the basic
2 integrity of the thing and in the observations and all kinds
3 of things, which you never do get to check, which is sort of
4 why the robustness of the findings and anything that can
5 make it seem less dependent on day-to-day differences adds
6 to the persuasiveness for me, and the things you cited, the
7 evidence of control group, the knowledge that there is
8 quality control in the system that generated the data, all
9 those things certainly help us.

10 CHAIRMAN BUNN: For the consumers on the
11 Committee, one of the things when the FDA approves an agent,
12 it allows a manufacturer to market or advertise, you know,
13 their product, whereas, they are not allowed to do that
14 without the FDA approval.

15 Most of the time when a company comes in with an
16 extra indication, it is because they feel it is important to
17 advertise or market, and that has been the case in the past.
18 Now we have these new things where companies are just
19 denying drugs, saying, well, the FDA hasn't approved it,
20 therefore, we are not going to pay for it, and that is an
21 unfortunate thing that I think consumers and physicians,
22 even the FDA, as we have just heard, is really not in favor
23 of that type of approach to medical care.

24 DR. DELAP: I would just reiterate that there is
25 no way that we can fully keep up with the medical practice

1 and that it is really unfortunate when insurance companies
2 make decisions based on FDA approvals, which are always
3 going to be -- despite our best efforts -- are always going
4 to be a little bit behind the cutting edge of clinical
5 science.

6 So I think we should represent ourselves as trying
7 to keep the labeling up to date for the use of the insurance
8 companies because I don't really see that as an appropriate
9 use of labeling to make a decision about payment.

10 CHAIRMAN BUNN: But for those in the audience, I
11 think we all agree that this was an appropriate use of
12 literature-based and important for the FDA, important for
13 physicians, and important for consumers, and this is an
14 appropriate way to do things. Hopefully, it won't be
15 extended to how insurers should pay for drugs.

16 That being the case, we will take a break for
17 lunch until 12:15.

18 [Whereupon, at 11:15 a.m., the proceedings were
19 recessed, to be resumed at 12:15 p.m.]

20

- - -

AFTERNOON PROCEEDINGS

[12:30 p.m.]

DR. DEVOUS: Let's start to introductions to begin. Steve Pollitt, actually, needs to talk about a voting conflict.

MR. POLLITT: Dr. James Ingle has recused himself from voting on this issue after finding out that his institution is doing a study on NR-LU-10. He will be allowed to participate in discussion but will not vote on the issues at hand.

Dr. Devous?

DR. DEVOUS: On my right, I want to introduce Barbara Sortino who is here as a Patient Representative and is a non-voting member in that regard. Perhaps the best thing for us to do to get on firm footing first is to just do some personal introductions.

George, Could you start and we will just go around the table.

DR. MILLS: I am Dr. George Mills from the Center for Biologics.

MR. BERKOWER: Ira Berkower from the Center for Biologics.

DR. BOTSTEIN: Paula Botstein, the Center for Drug Evaluation and the Office of Drug Evaluation III. One of our Divisions is the Medical Imaging Division.

1 DR. JAY SIEGEL: Jay Siegel, Office of
2 Therapeutics in the Center for Biologics.

3 DR. KEEGAN: Patricia Keegan, Center for
4 Biologics.

5 DR. GELBER: I'm Rich Gelber a biostatistian on
6 the ODAC Committee from Boston.

7 DR. FORASTIERE: Arlene Forastiere, medical
8 oncologist from Johns Hopkins.

9 DR. INGLE: James Ingle, Professor of Oncology,
10 Mayo Clinic.

11 DR. OCHS: Judy Ochs, pediatric oncology, Arkansas
12 ODAC.

13 MR. POLLITT: Steven Pollitt. I am the Executive
14 Secretary for the Committee.

15 DR. SWAIN: Sandra Swain, medical oncology,
16 Bethesda.

17 DR. OZOLS: Bob Ozols, Fox Chase, medical
18 oncology, ODAC.

19 DR. KROOK: James Krook, Duluth, medical oncology,
20 ODAC.

21 MS. BEAMAN: Carolyn Beaman, science educator,
22 Consumer Representative, ODAC.

23 DR. DEVOUS: We have introduced Barbara. I am
24 Mike Devous, University of Texas, Southwestern Medical
25 School, Dallas. I am the Chairman of MIDAC and, for five or

1 ten minutes or so, the Acting Chairman here until Dr.
2 Parkinson arrives.

3 DR. MARILYN SIEGEL: Marilyn Siegel, pediatric
4 radiologist, Mallinckrodt Institute of Radiology, St. Louis.

5 DR. ABBITT: Pat Abbitt, radiologist, University
6 of Florida in Gainesville.

7 DR. MALCOLM: Arnold Malcolm, member of MIDAC, a
8 radiation oncologist.

9 DR. BARRY SIEGEL: Barry Siegel, nuclear medicine,
10 from Washington University. I am a consultant to MIDAC.

11 DR. DEVOUS: Thank you. I have seen the agenda.
12 for about 30 seconds, so I will struggle through with this.
13 If I make any gross mistakes, somebody please raise your
14 hand and jump in there.

15 This is the post-lunch session. My understanding
16 is the first order of business is George's presentation; is
17 that correct? The sponsor presentation? Oh; I'm sorry. It
18 does say that.

19 MR. POLLITT: As people come to the podium, would
20 you please state your name and your affiliation.

21 **PLA 94-1308, NR-LU-10**

22 **KARL THOMAE PRESENTATION**

23 **DR. DAVID BRILL**

24 DR. DAVID BRILL: My name is David Brill. I am
25 the Director Drug Regulatory Affairs at the sponsor,

1 Boehringer Ingelheim. I would like to say, to start, good
2 afternoon and an early "Happy holidays" to the members of
3 ODAC, the consulting members from MIDAC, the representatives
4 from the Food and Drug Administration and all the attending
5 industry colleagues that are sitting in the audience today.

6 As I said, my name is David Brill and I am
7 representing the sponsor, Boehringer Ingelheim. That is
8 hard to say. It shouldn't be. It is my pleasure and true
9 privilege to be introducing and opening today's Advisory
10 Committee meeting discussion on Verluma.

11 [Slide.]

12 Verluma is a kit for the preparation of Technetium
13 99 nofetumomab merpentan. I have to tell you that is not
14 easy for me to say, as well. Verluma, which you may have
15 seen or heard about under a different name such as Oncotrac
16 or NR-LU-10 or, as we finally refer it to as "narlu-10," is
17 a product opportunity which has come to be based on a very
18 extensive collaboration involving many organizations.

19 [Slide.]

20 Verluma was developed by the NeoRx Corporation in
21 Seattle, Washington. The manufacturer of Verluma is Dr.
22 Karl Thomae GmbH which is an affiliated company of
23 Boehringer Ingelheim International GmbH. I should say that
24 it is Dr. Karl Thomae who is the official sponsor of the
25 pending PLA and will be the holder of the license following

1 approval of that application.

2 In North America, Verluma will be distributed by
3 the Radiopharmaceutical Division of the DuPont Merck
4 Pharmaceutical Company in Billerica, Massachusetts.

5 [Slide.]

6 The development of Verluma, as you can see, was a
7 collaborative effort. So, too, is today's Advisory
8 Committee presentation. I would like to just very briefly
9 introduce some of our participants.

10 We have already met. Dr. Darrell Salk is
11 currently with the consulting firm Biotech Med/Reg.
12 However, during the majority of the development of Verluma,
13 he served as a Vice-President of Medical and Regulatory
14 Affairs at NeoRx Corporation.

15 Dr. Wil Nelp of the University of Washington
16 Medical Center is a nuclear-medicine physician who served on
17 the Verluma development team since its inception. Dr. Nelp
18 participated in the Phase I and II clinical trials. He
19 assisted in the development of the Phase-III protocol design
20 and also served as a blinded reviewer during that Phase-III
21 study.

22 Dr. Andrew Turrisi of the Medical University of
23 South Carolina is an oncologist and brings to the Verluma
24 Program that critical perspective of how, where and under
25 what conditions fits in that clinical community.

1 We have additional team members here that will be
2 available to answer some questions as deemed necessary.
3 They are Dr. Paul Abrams who is the President of the NeoRx
4 Corporation; Dr. Hermann Allgaier, who will serve as the
5 responsible Head in Dr. Karl Thomae, GmbH; Dr. Michael Bjorn
6 who is the Director of Clinical Research at the NeoRx
7 Corporation; Dr. Brent Blumenstein of the Fred Hutchinson
8 Cancer Center who is our consulting biostatistician; and Dr.
9 Alan Fritzberg of the NeoRx Corporation who designed the
10 Technetium labeling technology.

11 Let me move, then, very quickly into the agenda.
12 and get us started.

13 [Slide.]

14 Dr. Darrell Salk will give a clinical introduction
15 and profile of Verluma and give a brief background on small-
16 cell lung cancer. Dr. Wil Nelp will present some images
17 which might typically be seen using the product and, also,
18 go through the image-review procedure and other product
19 performance characteristics.

20 Dr. Salk will present the pivotal-study results
21 and will focus in on what are the key results and
22 conclusions from that Phase III study. Dr. Andrew Turrisi,
23 as I mentioned before, will present the critical
24 oncologist's perspective and will really focus in on issues
25 related to clinical benefit and relevance of Verluma.

1 Dr. Darrell Salk will then return and serve as
2 moderator for the remaining section of this discussion and
3 will take measures to insure that all your questions are
4 adequately answered.

5 So, having adequately, I hope, set the stage for
6 the rest of the presentation, it is my pleasure to introduce
7 Dr. Darrell Salk, and I would like to turn over the
8 microphone and the presentation to him.

9 Dr. Salk?

10 **DR. DARRELL SALK**

11 DR. SALK: Good afternoon. Thank you, Dr. Brill.
12 My name is Darrell Salk. I was, as Dr. Brill said, formerly
13 Vice-President of Medical and Regulatory Affairs at NeoRx
14 Corporation and, from 1987 to 1994, my primary
15 responsibility was in the Phase-III clinical development of
16 Verluma. Since 1994, I have continued my involvement in the
17 Verluma project as a consultant to NeoRx. I currently
18 consult through Biotech Med/Reg in Seattle and I am an
19 Affiliate Associate Professor of Pediatrics and Pathology at
20 the University of Washington.

21 Today, we want to describe for you a product that
22 we have developed for staging patients with small-cell lung
23 cancer in a non-invasive way. We are very confident of the
24 safety and efficacy of this product.

25 We have focussed initially on small-cell lung

1 cancer in the clinical development of Verluma because
2 accurate staging is so important in the treatment of this
3 disease. The antibody that we chose to radiolabel and to
4 use for imaging small-cell lung cancer was actually derived
5 originally using small-cell lung-cancer tumor cells. It is
6 an FAB fragment of an IgG 2B murine monoclonal antibody that
7 is specific for a 40 kiloDalton glycoprotein expressed on
8 the surface of small-cell lung-cancer cells as well as the
9 surface of many other epithelial cancers.

10 [Slide.]

11 This is a molecular model of an FAB fragment.
12 This is where the antibody attaches to the antigen. We
13 developed a labeling method that tightly binds Technetium
14 99m in a defined and stable way that does not affect the
15 immunoreactivity of the molecule.

16 As you know, Technetium 99m is a radionuclide that
17 is routinely used in clinical nuclear medicine. We show
18 here, at the same scale, a model of the Technetium chelate
19 at an exposed lysine amine of the protein. The structure of
20 the Technetium N2S2 chelate is shown here with the side
21 chain for formation of an amide linkage with the FDA
22 fragment.

23 This chemistry results in an attachment of a
24 stable metal Technetium chelate using a defined covalent
25 linkage to the protein.

1 Today, we want to summarize for you the key points
2 from our work that demonstrate the usefulness of this
3 diagnostic agent and support the following indication.

4 [Slide.]

5 Verluma imaging is indicated for initial staging
6 of patients with small-cell lung cancer. It establishes a
7 diagnosis of extensive disease in 77 percent of patients
8 with extensive disease -- in other words, it has a
9 sensitivity of 77 percent -- with a positive predictive
10 value of 94 percent which is very high. For these patients,
11 no further staging tests are needed before moving on to
12 therapy.

13 [Slide.]

14 If there is no evidence of extensive data by
15 Verluma imaging, then additional tests can be done to
16 accurately establish the diagnosis of limited disease which
17 is a diagnosis of exclusion. Of course, for a diagnosis of
18 exclusion, the more tests that are done that are
19 complementary to each other and remain negative, the greater
20 the accuracy of that diagnosis.

21 [Slide.]

22 Verluma imaging should not be used for
23 differential diagnosis of small-cell lung cancer because it
24 also localizes to other carcinomas. This precaution is
25 important because Verluma images must be interpreted with

1 this cross-reactivity in mind just as radiologic images and
2 those from other diagnostic imaging procedures must be
3 interpreted, recognizing that the histology of any observed
4 abnormality is presumed rather than defined.

5 [Slide.]

6 Like all Technetium-labeled nuclearmedicine
7 imaging agents, Verluma is provided as a cold kit with all
8 of the components necessary for the addition of Technetium
9 99m in the radiopharmacy at the clinical site.

10 By the way, the name NR-LU-10 stands for NeoRx
11 Lung Antibody No. 10. Despite rumors to the contrary, there
12 is no mythological or astrological significance to that name
13 and Elvis was not involved in creating it.

14 [Slide.]

15 Verluma imaging is performed as an outpatient
16 procedure with administration to the patient in the
17 afternoon and then routine gamma-camera imaging 14 to 17
18 hours later the following morning. Our safety experience
19 with Verluma is actually quite extensive. It has been used
20 in many Phase I-II studies with a variety of different tumor
21 types.

22 Among 515 patients, Verluma has been shown to be
23 very safe with only a very small percentage of patients
24 showing laboratory changes without any clinical
25 significance. Other clinical events have been very rare and

1 insignificant.

2 [Slide.]

3 53 patients in the pivotal study had blood
4 collected at baseline, 6 weeks and 9 weeks after imaging
5 and, thus, were evaluable for the development of HAMA --
6 that is, human anti-mouse antibodies which may occur in
7 response to administration of a murine protein.

8 As it turns out, 50 of 53 small-cell lung-cancer
9 patients had no evidence of HAMA response when tested with
10 an antibody-specific and very sensitive ELISA. Only three
11 patients had low-level responses that were transient.

12 [Slide.]

13 A small-cell lung cancer represents 20 to
14 25 percent of all lung cancers. There are about 40,000 new
15 cases in the United States every year. It is an aggressive
16 disease and, if not treated, survival is only a few months.
17 Chemotherapy is the mainstay of treatment in this disease
18 with a very high response rate. However, staging, accurate
19 staging, is critical for determining prognosis and the
20 choice of therapy.

21 [Slide.]

22 Small-cell lung cancer is staged as limited
23 disease or extensive disease based on the distribution of
24 the lesions and diseased organs. A limited disease is that
25 in which the disease is within a single radiation port, one

1 hemithorax, the mediastinum and ipsilateral supraclavicular
2 lymph nodes.

3 Extensive disease, on the other hand, is disease
4 when there is any metastasis outside of this limited region.

5 [Slide.]

6 For patients with limited disease, the intent of
7 treatment is curative using chest radiation therapy within
8 that radiology port in addition to combination chemotherapy.
9 Patients with extensive disease, on the other hand, the
10 intent of treatment is palliative using chemotherapy alone.

11 The reason for this difference in approach to
12 treatment is because patients with limited disease who are
13 treated with chest radiation therapy in addition to
14 chemotherapy demonstrate an increased long-term survival
15 compared to patients who are treated with chemotherapy
16 alone.

17 On the other hand, patients with extensive disease
18 gained no benefit from the additional chest radiation
19 therapy and its attendant cost, acute toxicity and potential
20 morbidity.

21 [Slide.]

22 Because of the importance of accurate staging in
23 small-cell lung cancer, current staging procedures that are
24 necessary include four diagnostic-imaging tests and an
25 invasive procedure evaluation of the bone marrow.

1 [Slide.]

2 The objective of our pivotal study was to evaluate
3 the ability of Verluma imaging to stage patients with small-
4 cell lung cancer in comparison with current staging
5 modalities.

6 Before discussing the pivotal trial and its
7 results, Dr. Nelp will describe the characteristics of the
8 images obtained with Verluma. As Dr. Brill mentioned, Dr.
9 Nelp was involved in the Phase I-II studies of Verluma,
10 defined the pharmacokinetics, biodistribution and dosimetry
11 and he was also one of two nuclearmedicine consultants who
12 read blindly all of the images in the pivotal study.

13 Dr. Nelp.

14 **DR. WIL B NELP**

15 DR. NELP: Thank you, Dr. Salk. I am Wil B. Nelp,
16 Professor of Medicine and Professor of Radiology at the
17 University of Washington School of Medicine in Seattle. I
18 have been the Director of the Nuclearmedicine Programs there
19 for a number of years.

20 What I will do is show you the basic
21 biodistribution and kinetics and excretion of the NR-LU-10
22 Technetium-labeled FAB product and then I will show you some
23 examples of tumor labeling as it has been applied to small-
24 cell lung cancer.

25 [Slide.]

1 This is done immediately after injection. This is
2 an anterior gamma-camera imaging planar view of the chest.
3 As you would expect with this protein, you see predominantly
4 vascular distribution, cardiac blood pool, major vessels of
5 the neck, lungs, liver.

6 [Slide.]

7 If we look lower in the abdomen, we, again, see a
8 blood-pool image, faint visualization of the kidneys, the
9 renal blood pool, other vascularity. Notice in the left
10 lobe of the liver sort of a defect. This is a large
11 metastatic lesion from carcinoma of the colon. This was a
12 Phase-II study where we did a lot of the biodistribution
13 studies, a Phase-II patient.

14 This image was probably made 20 minutes after
15 injection. You can see very early peripheral adherence of
16 antibody to the tumor.

17 [Slide.]

18 If we come back in three hours and look at the
19 head and neck region, now we see this image. We see the
20 thyroid. This is not free pertechnetate. This is a cross
21 reaction between the antibody and a naturally occurring
22 antigen that is in normal thyroid tissue so you always see
23 the normal thyroid as part of the image picture.

24 Up here, the pituitary. This is also another
25 cross-reactive antigen in the anterior pituitary and, very

1 often, one can define that.

2 [Slide.]

3 If we go down into the abdomen, now, at three
4 hours, we notice now we have fairly intense activity in the
5 kidneys because this is the major route of excretion of the
6 product. Some slight clearance in vascularity and, note,
7 there has been increased labeling of that tumor mass now at
8 the three-hour period.

9 [Slide.]

10 Eight hours; some further clearance, continued
11 activity in the kidneys. This is relatively more intense
12 compared to surrounding tissue. And now we see
13 radioactivity in the bowel. This is because, as the product
14 is degraded, the lysine portion, which is linked to the
15 chelate which traps the Technetium, comes off and is
16 excreted. Part of that excretion goes through the liver
17 into the biliary system and is excreted into the bowel.

18 [Slide.]

19 If we look further down at 8 hours, this is
20 bladder, lower abdomen, we see activity in the testes. This
21 is a non-specific uptake in the testes, not specific for
22 this antibody but it is seen with a number of antibodies.
23 We can't identify cross-reactive antigens, but it will be
24 seen in the images.

25 [Slide.]

1 If we go out to 24 hours, which was what our
2 biodistribution studies did, now we can see much clearance
3 of general activity, still prominence of the kidneys,
4 residual activity in the gut and then this tumor now is
5 sitting pretty much in very high contrast to the surrounding
6 tissues.

7 If we put all this information together, we get
8 biodistribution data that looks something like this.

9 [Slide.]

10 This is serum clearance over time, 24 hours, very
11 rapid disappearance of activity from the serum due to
12 immediate distribution of the product and early excretion.
13 This dominates the curve, has a T1 half of about one-and-a-
14 half hours, and then there is a minor longer-phase component
15 here.

16 [Slide.]

17 If we do total body counting on subjects, we get
18 this kind of a pattern. This is the disappearance of
19 activity from the total body over a period of 24 hours at
20 which time, on average, about 38 percent remains in the body
21 and the reciprocal of that, of course, is the urinary
22 excretion curve, the major route of excretion.

23 What comes out in the urine initially? The
24 preformed FAB intact, and that continues to come out. And
25 then degradation products, again, predominantly the lysine

1 adduct with the chelate and Technetium still bound together.
2 There is really no free Technetium, per se, that comes out
3 in the urine.

4 Now, I am going to show you some images of small-
5 cell lung cancer. These images were done at the 14-hour
6 time period which was the way the study was carried out. I
7 will show you the following.

8 [Slide.]

9 This is a patient with a pleural-based lung
10 lesion, primary tumor here, soft-tissue mass here,
11 supraclavicular lymph nodes, small-cell cancer of the lung.

12 [Slide.]

13 This image was done at 14 hours and it is in the
14 posterior projection. So this is the head, the thorax, the
15 tumor. The lymph nodes are on the right side now, which is
16 over here. Notice the intense labeling in the diseased
17 lymph nodes here. This is the pleural-based lesion which
18 looks somewhat more extensive that was appreciated on the X-
19 ray and on CT.

20 Notice these multiple discrete areas of activity
21 down the spine. This is distinctly abnormal. This
22 patient's bone scan was completely normal. This is activity
23 in marrow, but to confirm this, an MRI was done and showed
24 diffuse and punctate areas of marrow invasion of small-cell
25 lung tumor corresponding to these areas and several areas

1 where bony invasion had also take place. But the bone scan
2 remained negative.

3 In this patient, bone-marrow aspiration did show
4 small-cell lung-cancer cells.

5 [Slide.]

6 The liver. The chest is up here, not much
7 activity seen. It is cleared. This is the region of the
8 liver. This patient has multiple hepatic metastases
9 demonstrated on CT imaging. You can see these discrete
10 areas of tumor labeling within the liver that correspond to
11 those abnormal findings, and you note the good contrast :
12 between the lesion and the surrounding normal tissue.

13 Here is the bowel, again, you see. This activity
14 could be further reduced by a very successful catharsis.
15 However, it is variably present and invariably present to
16 some degree.

17 [Slide.]

18 If we look at this patient's anterior view of the
19 chest, we see this type of image. Here is the primary lung
20 tumor. Here are some mediastinal nodes. Here is, actually,
21 a small lymph node next to the thyroid.

22 We can do SPECT, which is a tomographic image
23 where we take slice through the chest and we can, then, go
24 through the area of interest and remove activity above and
25 remove activity behind the lesion and enhance the contrast.

1 [Slide.]

2 SPECT on this patient shows these two lung lesions
3 more dramatically and separates them out a little bit
4 better. This image is rather blurry, but that is the nature
5 of the instrument that was used by this investigator.

6 [Slide.]

7 Another anterior view of the chest. This is the
8 primary tumor, pleural-based and extending toward the
9 mediastinum. But notice thyroid. Notice all of the
10 activity in the ribs, sternum, et cetera. This, again, is
11 distinctly abnormal.

12 [Slide.]

13 If we look at the posterior view of this patient,
14 it looks like a normal bone scan. This is distinctly
15 abnormal. Notice that there is activity down here in the SI
16 joints and in the pelvis, as well. The kidneys, of course,
17 are seen.

18 This is marrow tumor. This patient did have an
19 abnormal bone scan but, as it turns out, only one vertebral
20 body was abnormal and several ribs. The bone-marrow
21 aspiration on this patient, however, showed heavy invasion
22 with small-cell lung tumor.

23 So this is part of the learning process to learn
24 these patterns. What else did we see? We can see some
25 artifacts.

1 [Slide.]

2 This is an anterior lesion. These are the
3 axillary folds. These are not abnormal lymph nodes. This
4 is an artifact where skin folds come together and you get
5 forward-angle scattering commonly recognized in Technetium
6 images procedures. This can be eliminated by simply
7 elevating the arms at the time of imaging.

8 [Slide.]

9 This is an interesting case here. Here the
10 investigator put the intensity very high on this film to
11 illustrate the point. So this is a posterior view of the
12 chest that had -- this is upscatter from the kidneys because
13 the intensity is so high. Here is the spin. Now, this
14 little triangular area, which is sort of in the posterior
15 basilar segment of the lung, clearly has abnormal deposition
16 of activity. It was noted so by the blinded reviewer. But
17 this is a post-operative site. This patient had surgery in
18 this tissue three days prior to the image.

19 The investigative reviewer, who was not blinded,
20 realized this and properly identified it as an operative
21 artifact. But what happens is the tissue is injured, and
22 there is some edema. There is a protein leak into that
23 space. So you will see collections of antibody under those
24 circumstances.

25 It can also happen in sites of intramuscular

1 injection and other infectious areas but, if you know the
2 clinical history, these things are usually relatively easy
3 to sort out.

4 How is the learning process for interpreting these
5 images in the nuclearmedicine community? I had the
6 opportunity to visit many of the participating sites, talk
7 with the investigators and, in particular, the
8 nuclearmedicine physicians. Nuclearmedicine physicians
9 spend about 80 percent of their time, at least, interpreting
10 images of Technetium. So they have -- this is a familiar
11 isotope energy. Their equipment is very well designed to do
12 Technetium imaging, and I would go through biodistribution
13 artifacts, tumor labeling and so forth with them.

14 I would characterize the learning curve as fairly
15 straightforward and relatively simple.

16 Thank you. I am going to turn the podium back to
17 Dr. Salk.

18 DR. PARKINSON: Can we just ask some questions
19 while you are there?

20 DR. INGLE: As in a bone scan, a very sensitive
21 but not specific as a Technetium bone scan, say, in breast
22 cancer, in lung cancer, you have described a number of, I
23 guess, false positives -- that is, areas of increased uptake
24 that are not tumor. Do you have any other thoughts on this?
25 Trauma, you said, will do it. How about arthritis, other

1 benign conditions. Will they give increased uptake such
2 that if you have an abnormal scan, you need to corroborate
3 the abnormal findings with some other images technique.
4 Just any comments on that.

5 DR. NELL: The false-positive rate, actually, was
6 quite small in this pivotal study, but we do see deposition
7 of protein in spaces where injury occurs and the best answer
8 to your question is, in the practice of medicine, you
9 usually evaluate the patient, you usually examine the
10 patient, you get the correlative information, and if you
11 have an inflammatory joint or if you have a traumatic
12 arthritis of the joint or if you have a post-operative
13 region, these things are usually easily identified.

14 But false positives in terms of what looks like
15 tumor localization, like in the marrow and this sort of
16 thing, those are not false positives. But I think it is
17 easy to sort out at the practical-application level.

18 DR. PARKINSON: I am going to suggest that we have
19 further discussion after the full presentation and we have a
20 chance to look at the data.

21 DR. SALK: That question will be answered, in
22 part, by some of the data that you are going to see now.
23 Basically, in the pivotal study, there were only three
24 instances of inadvertent false positives. There were two
25 axillary skin folds and one, that patient you saw with the

1 post-cervical thing.

2 The other kinds of things that Dr. Nelp referred
3 to are either theoretical or have been observed with other
4 antibodies in other situations as non-specific hyperemia
5 inflammation. But it was not a problem in this study.

6 **DR. DARRELL SALK**

7 [Slide.]

8 DR. SALK: The objective of the pivotal study, as
9 I said before, was to evaluate the ability of Verluma
10 imaging as shown to you by Dr. Nelp, to stage people with
11 small-cell lung cancer in comparison with current imaging
12 methodologies.

13 [Slide.]

14 All patients had a new diagnosis of biopsy-
15 confirmed small-cell lung cancer and they underwent a series
16 of non-invasive tests including physical examination and
17 four diagnostic imaging procedures, traditional ones, and
18 including a Verluma imaging.

19 The results of the physician exam and traditional
20 imaging tests define the traditional stage. The results of
21 the Verluma imaging, by itself, defined the Verluma stage.
22 These traditional tests were evaluated and read as routinely
23 practiced in clinical medicine; that is, in an unblinded
24 manner with access to all clinical and laboratory
25 information as well as the results of other tests.

1 In what we report here today, the Verluma images
2 were interpreted in a single blinded review performed
3 centrally by one of two nuclearmedicine consultants. No
4 information was available about the imaging procedure
5 including information about the patient, other tests or, as
6 we mentioned, any technical information related to the
7 imaging procedure, itself.

8 Thus, the data that we present to you here today
9 represent the most stringent challenge for Verluma, the
10 comparison of a completely blinded review of a single test
11 with an unblinded assessment of four tests, a physical
12 examination, and access to complete clinical and laboratory
13 information.

14 [Slide.]

15 96 patients were enrolled in the study and 89 were
16 evaluable. Among the 89 evaluable patients, there were 610
17 individual lesions and 333 affected organs; in other words,
18 organs that had at least one lesion. It was these 333
19 affected organs that formed the basis of the staging
20 analysis in this study.

21 These demographic characteristics are similar to
22 the general population of patients with newly diagnosed
23 small-cell lung cancer. There were no apparent sampling
24 anomalies.

25 [Slide.]

1 This slide summarizes the statistical results for
2 staging patients with small-cell lung cancer using Verluma
3 imaging as a single test read unblinded in comparison with
4 the unblinded reading of four tests plus a physical exam.

5 The sensitivity for detection of extensive disease
6 was 77 percent for Verluma imaging by itself with a very
7 high positive predictive value compared with 88 percent for
8 the full battery of standard tests. The specificity for
9 detection of extensive disease is also quite high with a
10 negative predictive value of 69 percent.

11 Thus, a fully blinded reading of Verluma images
12 alone compares very favorably with an unblinded assessment
13 of four imaging tests in a physical examination.

14 [Slide.]

15 For purposes of illustration, here is a clinical
16 model that uses the study data to predict what would be
17 expected to be the outcome of staging 100 patients in
18 clinical practice using either the full battery of non-
19 invasive tests or Verluma imaging read in a blinded manner.

20 With the full battery of traditional tests, 56
21 percent of the patients are accurately identified as having
22 extensive disease and 34 percent of the patients are
23 accurately staged as having limited disease, for an overall
24 accuracy of staging of 90 percent.

25 With a blinded reading of Verluma images, the

1 overall accuracy of staging is 82 percent, 49 for extensive
2 disease and 33 for limited disease. A very small percentage
3 of patients is overstaged; that is, they are said to have
4 extensive disease when, in fact, they have limited disease.
5 Such patients might not receive potentially beneficial chest
6 radiation therapy.

7 This false-positive rate is the same for
8 traditional methods and for a fully blinded reading of
9 Verluma images. Thus, a low rate of false positives is a
10 problem for all staging methods of small-cell lung cancer
11 and it points out the need for good clinical judgment in
12 making critical staging decisions that are based on a single
13 positive finding.

14 As Dr. Nelp pointed out, and we discussed a moment
15 ago, some of the false-positive findings experienced in an
16 artificially blinded reading of Verluma images were due to
17 technical artifact that would be recognized and properly
18 interpreted in an actual clinical setting.

19 These 8 percent of patients would be understaged
20 by the traditional battery of non-invasive tests. Thus,
21 they would be said to have limited disease although they
22 actually have extensive disease. Such patients might
23 undergo costly, potentially toxic, chest radiation therapy
24 that would be of no benefit.

25 The patients that were understaged by this full

1 battery of traditional tests, of course, would not have been
2 identified as false negatives if Verluma imaging had not
3 been available. Because Verluma imaging is complementary to
4 other staging tests, it identifies some disease that may not
5 be seen initially by other tests.

6 In our study, when a positive Verluma finding
7 suggested the possibility of a false negative by the
8 standard battery, we did additional evaluations to confirm
9 whether the tumor site was positive or not and only if those
10 evaluations corroborated the Verluma finding was the lesion
11 defined as positive.

12 Although this model shows that Verluma alone
13 understages 15 percent of patients, in practice, all
14 patients who have no evidence of extensive disease would
15 continue to have additional standard tests until either, by
16 exclusion, all tests are negative and a diagnosis of limited
17 disease is made or these 15 would be recognized to have
18 extensive disease.

19 Thus, in practice, using Verluma imaging first and
20 then following with additional tests as needed, both these
21 sets of false negatives would be eliminated, reducing,
22 therefore, the number of patients exposed to non-beneficial
23 non-radiation therapy.

24 Having evaluation Verluma alone against an entire
25 battery of standard tests, we compared Verluma images

1 against each individual test in order to assess which test
2 provides the most information.

3 [Slide.]

4 It is not surprising, since it is a whole-body
5 imaging agent that is not limited to a single anatomic
6 region or organ system, Verluma imaging identifies the most
7 number of lesions, the most diseased organs and, therefore,
8 the largest number of patients with extensive disease, more
9 than any other single test.

10 This fact may appear to be self-evident, but the
11 analysis here illustrates why Verluma imaging is, therefore,
12 the best test to use first in staging patients with small-
13 cell lung cancer. More patients can move rapidly on to
14 therapy after only a single test.

15 In addition, this analysis suggests that CT of the
16 abdomen is the next-best test to use which does, indeed,
17 turn out to provide the most additional information when
18 added to Verluma imaging.

19 [Slide.]

20 In summary, Verluma is safe. Verluma is the most
21 sensitive single test for establishing the diagnosis of
22 extensive disease with a high positive predictive value.
23 For staging patients with small-cell lung cancer, a single
24 blinded reading of Verluma images is comparable to an
25 unblinded evaluation of all four traditional imaging tests

1 plus a physical examination.

2 [Slide.]

3 These conclusions support the indication that
4 Verluma can be used for the initial staging of patients with
5 small-cell lung cancer.

6 I will now ask Dr. Turrisi to take the microphone
7 and he will comment on the usefulness of Verluma as seen
8 from the perspective of an oncologist.

9 **DR. ANDREW TURRISI**

10 DR. TURRISI: Good afternoon. My name is Andrew
11 Turriši. I am Professor and Chairman of the Department of
12 Radiation Oncology at the Medical University of South
13 Carolina. I am trained as a medical oncologist and I began
14 my radiation training here in Bethesda and, subsequently,
15 have spent my last 13 or so years involving myself in
16 clinical trials.

17 I have had an interest in small-cell lung cancer
18 since medical school days when a patient that I cared for
19 with extensive disease responded to chemotherapy and had a
20 Lazarus-like response. He got out of the bed and walked.

21 [Slide.]

22 Some of this may be gratuitous to most of you that
23 are here, but I just want to focus on the fact that we deal
24 with limited and extensive and not this traditional AJC
25 systems of staging with the TN&M system. This is used in

1 lung cancers and, sometimes, on small-cell for patients
2 going to surgery, but is not routinely useful.

3 Why do we do it this way? Because the limited and
4 extensive categories provide prognosis. In limited disease,
5 we believe that goal is the cure and that, in extensive
6 disease, the goal is palliation, a worthy goal. But
7 distinguishing these two different sets of patients is the
8 first step in how we go on to treat these patients.

9 Dr. Salk kindly provided you some what I will
10 charitably call "dated information" about outcomes in small-
11 cell lung cancer published in the DeVita textbook. But the
12 cure rates now for limited disease in group studies in 1995
13 show a 40 percent 2-year survival and, perhaps, a 20 to
14 30 percent 5-year survival in patients with limited disease.

15 This year, at the ASCO Meeting, in the Program
16 Book, there is going to be an abstract that also shows that
17 a reanalysis of extensive disease shows that we haven't made
18 much progress in the last 20 years. So, separating out that
19 group of who has got extensive and who has got limited, is
20 very crucial.

21 Why is it crucial? Because it is going to guide
22 treatment and, as I have just mentioned, it influences
23 prognosis.

24 [Slide.]

25 I would like to categorize for the next couple of

1 minutes what this distinction does for patients and then
2 what it does for physicians. For patients, they are
3 generally in a hurry to get going on treatment. They are
4 scared and they want to move because they think that the
5 therapy is going to provide them with their best measure and
6 hope for cure.

7 So staging, now, will consume less of that time if
8 we have Verluma. The process becomes a little bit more
9 efficient. We get accurate staging with that study
10 82 percent of the time by the data Darrell Salk showed you a
11 few minutes ago. And it is the most sensitive test to use
12 first. We can identify that extensive group of patients
13 77 percent of the time.

14 Once Verluma is positive, you don't have to bother
15 to do all those other -- and I have phrased it "meaningless"
16 -- studies at that time. That eliminates, or certainly
17 should reduce, the cost of unhelpful tests in three-quarters
18 of the patients.

19 Another important feature is about the feature of
20 false positives. At least in the study that we have shown
21 you today, that of the three false positives with clinical
22 input, those false positives are eliminated. But I think it
23 is safe to say that the frequency of false positives is very
24 small.

25 [Slide.]

1 What are physician benefits, and, I guess, health-
2 care benefits, for that matter. We now can use tests much
3 more efficiently. We have got a test that shows us that
4 with a positive Verluma image, there is no need for tests in
5 extensive disease save for if you want to get that test to
6 further confirm and follow that lesion to see if it has
7 improved with therapy.

8 Again, in this study that we showed today, three
9 false positives were eliminated once you knew that the
10 clinical input said the patient had surgery or their arms
11 were down and it was a technical artifact. So we had an
12 accurate staging of 82 percent of the patients screened.
13 Again, the sensitivity for extensive disease had picked up
14 77 percent of the patients.

15 If you have a negative Verluma image, that means,
16 in many cases, that the patients have limited disease and
17 only these patients require further testing. More extensive
18 staging procedures in this group can pick up some of the
19 patients that are "understaged," and we can accurately
20 diagnose those patients as was shown by Dr. Salk's
21 presentation. It shows you that the traditional stages
22 don't always pick these things up, so the tests are
23 complementary. This one merely is better to use first.

24 [Slide.]

25 So, to summarize this, and what I have just told

1 you, is that Verluma decreases the overutilization of
2 staging procedures, reduces the time spent defining stage
3 and that should lead to a reduction in cost. Only the
4 negative Verluma gets the full battery of tests. This leads
5 to an increased comfort for patients and eliminates, or at
6 least decreases, the frequency of bone marrows which, in and
7 of itself, takes three days to do, to decalcify, to read and
8 then interpret.

9 And all of this you get with no compromise in
10 accuracy.

11 I think I can say, as a clinician and as an
12 investigator, that I will find having Verluma around,
13 particularly in these days when we are asked to be efficient
14 and use resources more carefully, a great boon and something
15 that I look forward to having.

16 I thank you for your attention.

17 DR. SALK: We would like to take questions now.

18 DR. PARKINSON: Sure, if you are ready. At this
19 point, I think it is appropriate for me to, first of all,
20 apologize for being what I thought was half an hour early
21 for this meeting -- the last schedule that I had had. I
22 haven't been half an hour early for anything in years and I
23 guess the record still continues.

24 At this point, I think it is appropriate to open
25 up for questions to the sponsor. Dr. Siegel, you had a

1 question earlier.

2 DR. BARRY SIEGEL: Actually, I had a comment
3 earlier, and I will use it to start, namely in response to
4 Dr. Ingle. I agree with what Dr. Nelp said completely. In
5 routine clinical practice in nuclearmedicine, we do chat
6 kind of image problem-solving all the time every day where
7 we see things that look like they are conforming to the line
8 of a glenohumeral joint, where we go out and talk to the
9 people, look at the available chest radiograph, figure out
10 that it is osteoarthritis and go on from there.

11 So I really am not troubled by the concept, that
12 the kinds of things like recent surgical incisions that Dr.
13 Nelp pointed out, are going to cause problems, significant
14 problems, in clinical practice. So that is my first
15 comment.

16 Question for Dr. Turrisi, actually. The way you
17 all have built your model, assuming that the prior
18 probability of limited disease in patients who would be
19 subjected to imaging is going to be somewhere around
20 30 percent. What fraction of people who walk in the door
21 with small-cell lung cancer have clinically evident
22 extensive disease right at the time they are first seen so
23 that they really wouldn't be candidates for imaging at all,
24 because they come in with a superior venacaval syndrome, and
25 the initial chest film shows bilateral mediastinal and

1 hyaler adenopathy, or they have a seizure and the CT scan
2 shows a brain metastasis.

3 I am actually wondering if this will apply to a
4 smaller fraction of small-cell lung cancer than you
5 intimated in your broader modeling approach.

6 DR. TURRISI: I think that is a good question and
7 I am going to refer back to Dr. Salk because I think he has
8 some specific data on this, but it is not overwhelmingly
9 common that the simple things, like chest X-ray and physical
10 examination, make the diagnosis as extensive. But, you are
11 absolutely right. If you have that information in today's
12 world, unless there are specific requirements for someone to
13 go around and study.

14 But, in the real world, if you know that they have
15 extensive disease, you probably don't need those imaging
16 tests.

17 DR. BARRY SIEGEL: But you wouldn't have found it
18 in this trial.

19 DR. TURRISI: I agree with that.

20 DR. BARRY SIEGEL: Because those patients probably
21 wouldn't have ever gotten into the study because they would
22 have been undergoing radiation therapy within two hours of
23 getting to the hospital.

24 DR. SALK: That is a possibility. Those patients
25 were not excluded from the study. They could participate,

1 but there may have been some selection beforehand. It turns
2 out, in this study, if you actually look at what is added to
3 Verluma by physical examination and chest X-ray or,
4 conversely, what Verluma adds to a physician exam and chest
5 X-ray, it is not a great deal either way.

6 Do you have that slide available? I will tell you
7 which one it is. It is M-1, Slot 53.

8 [Slide.]

9 As I said, this shows the information that is
10 added to a physical examination and chest X-ray by Verluma
11 or, conversely, to Verluma by physical examination and chest
12 X-ray. The vertical axis shows the number of diseased
13 organs. It may be hard for you to read, so I will read
14 across the bottom here. This is lung, mediastinal lymph
15 nodes, pleura, bone, liver, abdominal masses and lymph
16 nodes, other abdominal lesions, brain, other head, neck,
17 axillary lymph nodes, other categories and bone marrow.

18 You can see here the purple is that information
19 that was collected by a physical examination and chest X-
20 ray, in other words, in the patient's first walk in the
21 door. The green is what is added by Verluma imaging.

22 Conversely, this is the Verluma imaging, the red.
23 And you can see the blue, the additional information from a
24 physical examination and chest X-ray. It is interesting
25 that in such areas as in the neck and axillary lymph nodes

1 where the physical examination picks up a lot, this non-
2 invasive procedure also is very good at picking up those
3 things which would normally be found only on physical
4 examination. They are not very well defined by other
5 imaging modalities.

6 Similarly, the bone marrow you see here, Verluma
7 alone and, again, here Verluma alone, is picked up and it is
8 obviously, other than a full-body MRI, the only non-invasive
9 test that will give you an assessment of bone marrow.

10 Does that answer your question?

11 DR. BARRY SIEGEL: Yes; I think so.

12 DR. FORASTIERE: I am wondering if you have that
13 same data for physical examination and CT because most
14 people who have an abnormal chest X-ray, nobody does a
15 bronch on them or a percutaneous needle aspiration until
16 they have gotten a chest CT. That includes, usually, the
17 upper abdomen.

18 So, since that really is the baseline evaluation,
19 a physical examination and at least a minimum of a chest CT
20 and, most of us, if you suspect lung cancer, do the full
21 abdomen anyway. But let's say it is just the chest CT and
22 upper abdomen, how much would Verluma add in that situation
23 to defining someone who has extensive disease?

24 DR. SALK: Verluma imaging adds, in that
25 situation, as well because it reads something beyond what

1 you see just in the chest. Dr. Abrams, do you have a
2 comment on that?

3 DR. PAUL ABRAMS: My name is Paul Abrams. I am a
4 medical oncologist as well as President of NeoRx. The
5 comment I would make on that is that today I certainly
6 accept what you say as what the procedures are. I think
7 that what we are trying to show here is that the data
8 suggest that if you have a chest X-ray from which you
9 suspect small-cell lung cancer, if you have a needle biopsy
10 that shows small-cell lung cancer, that Verluma, in fact, is
11 a more efficient way of staging patients because, not only
12 will you find what is in the abdomen, but you will also find
13 what is in other tissues, as has been defined by Dr. Salk.

14 So the question is which one to do. Our
15 suggestion, based on the data, is that Verluma, in fact, is
16 a more powerful test and that fewer patients, following the
17 CT of the chest and following the CT of the abdomen, would
18 require any further evaluation.

19 DR. FORASTIERE: But how many further? That is
20 what I was asking, how much of a difference does it make
21 because, the fact is that you wouldn't do the scan until you
22 have the diagnosis and you wouldn't make the diagnosis until
23 you had the chest CT.

24 DR. ABRAMS: That really depends on how you want
25 to practice. If you have a chest X-ray and you do a needle

1 biopsy of the lung, or a fiberoptic bronchoscopy or a lymph
2 node that is needed, and you have the diagnosis, you then
3 have a choice of what test to do. It can be a CT of the
4 chest and abdomen. It could be a CT of the head. It could
5 be a bone scan or it could be Verluma.

6 Again, as the data shows, Verluma is the most
7 powerful test to use in order to find out whether the
8 patient has extensive disease or not. Specifically, to
9 answer her question --

10 DR. SALK: Let me ask you to flip it over a little
11 bit because in the study that we did here, we did look at
12 what happens if you do contrast of the abdomen in addition
13 to Verluma, the two tests together versus Verluma alone, et
14 cetera. It turns out that when we do this fully blinded
15 analysis, a single reading under the settings that I
16 describe, the CT of the abdomen and Verluma together have
17 essentially the same negative predictive value as the entire
18 battery of standard tests.

19 So, under these stringent conditions, your
20 negative predictive value or evaluation of limited disease
21 is equivalent. When we do the analysis according to the
22 design we had in the protocol which we felt provides a
23 better estimate of what is liable to happen in practice --
24 in other words, it takes in to consideration the technical
25 artifacts and so forth -- the antibody imaging alone was

1 equivalent in its negative predictive value to the full
2 battery of standard tests.

3 And those numbers are 80 percent, 80 and 81
4 percent, or 74 and 77 percent, under the two different forms
5 of analysis.

6 DR. FORASTIERE: I understand what you are saying.
7 I am just making the point that current practice for a
8 pulmonologist to do bronchoscopy or someone to do a needle
9 aspiration, they have the information from the a chest CT
10 before they proceed to make the diagnosis. You wouldn't do
11 the Verluma scan until you have the diagnosis.

12 DR. SALK: Absolutely. We certainly can't dictate
13 clinical practice here. If somebody already has a diagnosis
14 of extensive disease, they shouldn't get Verluma any more
15 than the other way around.

16 DR. OZOLS: I think Dr. Forastiere makes a good
17 point. I think that is really the crux of the matter about
18 the clinical utility. You are talking about the
19 sensitivities tests; we are certainly going to do a physical
20 examination. This test, Verluma, doesn't appear to be very
21 good for head problems, so you are going to have to do a CT
22 scan of the head.

23 You are likely, as you point out, going to want to
24 do that CT scan of the chest before you do anything. If you
25 do those tests as part of the routine practice right now, it

1 seems that you are really coming down to a very small number
2 of indications or instances where Verluma would help you.

3 The standard of care when somebody walks in with a
4 diagnosis of suspected lesion, what are you going to do? In
5 your study, in your pivotal study, what was done before you
6 got the tissue biopsy. Any one of these tests; right -- for
7 your new diagnosis of small-cell.

8 DR. SALK: We didn't control for that.

9 DR. OZOLS: Right. So a lot of tests were done
10 before that.

11 DR. SALK: No, not necessarily. Typically, I :
12 think the histologic diagnosis was made very early on, that
13 patients may have come to a tertiary center already with
14 that diagnosis made. But the point about, for instance,
15 sensitivity in the head, you are right. Based on the
16 numbers that we show here, the very small number of brain
17 lesions -- there were only 12 in the entire study -- the
18 detection rates are low.

19 However, when you look at staging the entire
20 patient, there is very little impact from that because there
21 are very few times that a brain lesion alone defines
22 extensive disease.

23 DR. OZOLS: That's correct.

24 DR. SALK: Therefore, you only have to go on and
25 do your CT of the head if you have still have not found

1 extensive disease by other tests. One thing I want to
2 emphasize again is that with Verluma imaging, anywhere in
3 the process, if you have done all of these things and you
4 still have no extensive disease, then your diagnosis of
5 limited disease is more accurate than the one that is
6 available just with the traditional battery of tests
7 currently.

8 Dr. Turrisi, do you have a comment?

9 DR. TURRISI: The point I would make is that that
10 is a good observation that maybe if you did things the way
11 we have always done them, it doesn't add that much, if you
12 have already expended all four imaging tests. But if you
13 look at it the other way, it accurately picks up three-
14 quarters of them and that means you only need to do that
15 battery of four extra tests or two extra tests if I give you
16 that they have a chest CT ahead of time and maybe even some
17 of the abdomen.

18 But, it reduces the number of total tests that you
19 have to do and you only get the head CT scan in that small
20 proportion rather than all 100 percent of the patients.

21 DR. OZOLS: Then what would you do first before
22 you did the biopsies, right now?

23 DR. TURRISI: If I were to see these patients now
24 and they a lesion that looks like a lung cancer, you get,
25 probably a chest CT scan, today. I don't know what you get

1 in California, whether you have to go to bronch first or you
2 get a needle on that before you are allowed to do the
3 expensive image.

4 But if we know that patient has small-cell by
5 either getting the CT or getting the bronch next, the next
6 test for me would be to get the Verluma because after the
7 Verluma, you get two nicely divided groups of patients. The
8 three-quarters that have extensive don't need any more tests
9 and then the one-quarter to one-third that does have limited
10 disease apparently then gets the rest of the battery of the
11 test to find out whether, in fact, they really are limited,
12 about a quarter of the patients, or that understaged group
13 of patients that you then need to find out and prove that
14 they have got extensive disease.

15 DR. OZOLS: If the Verluma showed extensive
16 disease, you are not interested in the CT scan of the head?

17 DR. TURRISI: As a radiation oncologist, if that
18 person is clinically asymptomatic, there is actually data
19 now suggesting that you don't need to intervene with
20 radiotherapy off the top. But managing those with systemic
21 chemotherapy is a reasonable first go around for those
22 patients.

23 Clearly, if they develop a symptom, then you would
24 come to the beam and you would, in that case -- I am going
25 to tell you, half of the patients, ultimately, are going to

1 go on to have brain metastasis so those patients are going
2 to have an MRI or a CT. But it can be down the road because
3 we don't know today, even, if it is negative or positive
4 what that influence is.

5 DR. PARKINSON: Let me ask you a related question.
6 What about subsequent therapy. How important do you think
7 it might be to a medical oncologist or radiation therapist
8 to have baseline scans? We have no information on the
9 utility of Verluma in following patients, presumably. So
10 would you do subsequent scans without a baseline scan?

11 DR. TURRISI: Second-line therapy in small-cell
12 lung cancer does not work very effectively. If you want to
13 find out how that person is going to progress, I think
14 getting a battery of tests, the time that someone loses
15 performance status, has a new symptom, in order to guide
16 prognosis or further therapy to symptomatic lesions, that is
17 a sensible approach.

18 But, as I was trained, we did -- in the era when
19 cost was not considered, you would do all of these screening
20 tests. I think, today, that is going to be relooked at. In
21 cooperative groups, we are asked, regularly, now to go back
22 and see do we really need to repeat the test with the
23 frequencies that we have had or, in fact, should we start to
24 back off and really think about, good and hard, whether we
25 need those extra tests.

1 So, to directly answer your question, I don't know
2 if I need the baseline anymore. I used to, modeling things
3 after other diseases where it was important. I am really
4 not sure I need it today.

5 DR. MALCOLM: Actually, it is the same question,
6 Dr. Turrisi. But I am not sure if it was clear to me what
7 you were saying. If you have the patient "staged," with the
8 Verluma study, that question is with that patient's response
9 to therapy, what do you use to evaluate the response. I am
10 not saying for returns. But, to evaluate that patient, I am
11 not clear if you answered that.

12 DR. TURRISI: Let me answer it because that is
13 slightly different. But if I knew that I had a Verluma-
14 positive patient and, let's say, it was only the bone
15 marrow. I will use one of Dr. Nelp's examples where the
16 vertebral bodies of the spine were positive. If I wanted to
17 have a followable test, I would order an MRI on that patient
18 to see the way the marrow looked. And then you would have
19 to MRI to follow that patient rather than Verluma.

20 The other side of the coin; let's say it was a
21 liver lesion that glowed. You get a liver scan, or an
22 abdominal CT scan, and you can then follow that study from
23 that point forward. But you don't need a full battery of
24 every other test known to man, at least the way I look at
25 this.

1 DR. SALK: Also, what lesions do you follow
2 clinically most of the time? Is it, indeed, one of these
3 distant metastases or what you have seen in the chest?

4 DR. TURRISI: The most common thing you would
5 follow and, actually, even in extensive disease, the most
6 common site of failure is the chest. I guess the point has
7 been made but I will make it again; the brain is the other
8 thing that shows up with increasing frequency. This is not
9 a time to academe in whether PCI should be used or not. I
10 won't get into that.

11 DR. SWAIN: I wanted to get back to the questions
12 we asked at the beginning. Since it is established that you
13 do get a chest and abdominal CT in these patients before
14 diagnosis, how many patients with small-cell lung cancer
15 actually have a negative abdominal CT or negative liver and
16 positive bone scan? Do you know that?

17 DR. TURRISI: We don't get 58 percent.

18 DR. SWAIN: But in the literature. I don't know
19 the data, myself. I don't take care of lung cancer
20 patients. Negative liver and positive bone.

21 DR. TURRISI: How common is that?

22 DR. SWAIN: How common is that, because that would
23 be the group

24 DR. TURRISI: Negative liver scan and a positive
25 bone scan?

1 DR. SWAIN: Right.

2 DR. TURRISI: A positive bone scan, as an isolated
3 finding, is not a very common feature. On the study, if you
4 looked at the bone scan, it was, perhaps, the least
5 sensitive test to establish distant disease. But the other
6 question is how common is the abdominal CT negative in
7 extensive-disease patients, Dr. Swain?

8 DR. SWAIN: No. I am trying to get at the group
9 that this is going to help. If we have an abdominal CT that
10 is negative, then you would normally go on to do the other
11 scans like the Verluma --

12 DR. TURRISI: The premise is not entirely correct.
13 I don't think we would have to get an abdominal CT scan. I
14 will just correct the illusion that the simple CT from chest
15 down through adrenals is a good enough evaluation of the
16 liver. If you really want to look at the liver, you have
17 got to ask for it and you have to get a separate contrast
18 injection as the scan goes through that spot.

19 But your point about abdominal CT scans; there are
20 a fair number that are negative. Certainly, all of the
21 limiteds are negative. But I don't have a good handle on
22 which ones are negative of the rest of the group. It would
23 be the sensitivity of the CT on the --

24 DR. ABRAMS: I think it is worth pointing out that
25 if you just look at the abdominal CT, it only detected

1 58 percent of all those patients with extensive disease.
2 So, without picking it out by whether it is bone or bone
3 marrow or whatever, it is only detecting 58 percent whereas
4 the Verluma test is detecting 77 percent.

5 So you have almost a 20 percent improvement in the
6 pickup of patients with extensive disease through one or
7 more of those organs.

8 DR. OZOLS: I think that takes it out of context
9 of what you do when you see the patient. You are still
10 going to have the physical examination which is about
11 18 percent. You are going to do a chest X-ray and that is
12 going to put some of these -- so just to say that you have
13 got the Verluma scan at 77 percent may overstate, in light
14 of what you are going to do anyway. You are going to get
15 some of these tests before you make that diagnosis, and you
16 are certainly going to do a physical examination and a chest
17 X-ray and, likely, a CAT scan as well.

18 I just don't see how you are going to avoid doing
19 those tests.

20 DR. SALK: I can make a couple of points about
21 that. The first is that in the study, we did evaluate what
22 other information was provided first and how much was added
23 by each of the tests when mixed together and combined. The
24 data that was showed you indicate that the Verluma gives you
25 the most information of any test with a single test.

1 And, in fact, it does so more than any combination
2 of the other tests. Clearly, people are going to practice
3 as they see and we can't advocate that everybody change
4 their practice and you do what we suggest.

5 We, nevertheless, feel that the data that we have
6 here indicate that Verluma provides the most information of
7 any test and, therefore, done first, is beneficial.

8 DR. OZOLS: I am not advocating to do the test
9 before you have the diagnosis. We are talking about what
10 the minimum that you would do before you did the diagnosis.
11 And before you did the diagnostic tests, you are not going
12 to do the Verluma.

13 DR. SALK: Before you do the histologic diagnosis.

14 DR. OZOLS: Right. That is your indication. It
15 says after the diagnosis is made. So what are you going to
16 do before you make that diagnosis? You are certainly going
17 to do a physical exam and you are certainly going to do a
18 chest X-ray and a CT scan.

19 DR. SALK: Right. And based on the data that we
20 have here, the physical examination, the CT, still allows
21 Verluma to provide a great deal of information. I am going
22 to ask Dr. Turrisi and Dr. Kyle Bryan to comment because
23 they are both oncologists.

24 DR. TURRISI: I just want to bring this one up
25 because I know it is not that long ago, but the CT scan

1 wasn't around forever. We used to diagnosis small-cell lung
2 cancer on the basis of a bronchoscopy and a chest X-ray. If
3 you ask me to define what the role is of CT scans and how
4 they have aided our management, they are like something that
5 we know we want them, but we don't know exactly why we have
6 to use them.

7 I can't argue you out of the idea that today our
8 clinical practice is to get CT scans, both the chest and the
9 abdominal. But I ask you to take that look into the future.
10 Will we be allowed to do those in all people if there is
11 another test and a better test, a more sensitive test, that
12 says you don't need to do those.

13 If you could make the diagnosis without doing a
14 chest CT scan, which is a little bit larger leap, you
15 certainly can make the diagnosis without doing an abdominal
16 CT scan. That, by itself, is a good enough reason as far as
17 I am concerned, not to mention not needing to do a head CT
18 or a bone marrow or a bone scan.

19 DR. SALK: Dr. Kyle Bryan is a physician at NeoRx
20 Corporation.

21 DR. KYLE BRYAN: My name is Kyle Bryan. I am a
22 physician. I work at the NeoRx Corporation. In addition, I
23 have a clinical oncology practice within a managed-care
24 setting. I think I can address a couple of the issues that
25 were brought up.

1 First, the issue of the negative liver CT scan
2 with the positive bone images. To my recollection, I
3 believe the last addition of DeVita mentions 15 to
4 20 percent where a positive bone scan is the only evidence
5 of extensive disease.

6 With regard to following and the issue of the CT
7 scan versus chest X-ray and the timing within the diagnosis,
8 most of the patients, at the point when I see them, have
9 often had a chest X-ray followed by bronchoscopy. But many,
10 many of them have had chest CT scanning done at times
11 including the liver and adrenals.

12 But, as Dr. Turrisi pointed out, to get an
13 accurate assessment of the liver for full evaluation, you do
14 need to have a special contrast injection and you need to
15 tell the scanner that you are looking for liver lesions.
16 Often, at this point, the diagnosis is not made and so you
17 have to go back and scan again to get a better look at the
18 abdomen.

19 With regard to how to follow this, these patients
20 have some evidence of disease. Either they have had a
21 peripheral supraclavicular node that has been aspirated.
22 There was a chest X-ray lesion that detected, or a chest CT
23 lesion.

24 We rarely, in the absence of any clinical evidence
25 of bone pain or a neurologic finding, need to get a CT scan

1 of the head in order simply to have a lesion to follow to
2 assess response to therapy. There is always some type of
3 lesion that you can follow.

4 DR. PARKINSON: Dr. Forastiere, I think that this
5 may be the last question before we go on.

6 DR. FORASTIERE: I was wondering if you have any
7 information on the development of HAMA with multiple
8 injections because I could envision a scenario, if this were
9 approved, where a patient received their first injection; it
10 was negative and they were shown to have limited-stage
11 disease, and they go on and receive treatment. Then they
12 might be restaged down the road. It might be very useful to
13 do this one test to get an indication of whether or not they
14 were still in a complete response or not because of the
15 sensitivity.

16 So if you were to do repeated restagings and use
17 this, would there be a problem with HAMA?

18 DR. SALK: First, I want to point out that in this
19 application, we specifically limit it to a single use of the
20 product.

21 DR. FORASTIERE: Okay.

22 DR. SALK: The very limited information we have is
23 difficult to come by because HAMA happens so infrequently
24 that any repeat imaging very rarely is done in a patient who
25 has had it before. We did happen to have one patient who

1 had -- one of the three patients there, that I described,
2 that had a transient HAMA that then went down -- who went on
3 to reimaging and the HAMA level, once again, went up and
4 came back down.

5 This is essentially one anecdote but, again, this
6 indication is for a single use of the product.

7 DR. FORASTIERE: Thank you.

8 DR. PARKINSON: Thank you very much.

9 DR. JAY SIEGEL: Just a brief comment about the
10 issue under discussion. In the FDA briefing package, it is
11 Page 14 of the draft I have. I don't know if everybody else
12 has the same draft and table. There is some data addressing
13 the impact of SSU. If the 57 patients in this study who had
14 a clear clinical extensive stage, there were only two where
15 that was identifiable by chest X-ray, suggesting, perhaps,
16 that there was some tendency not to include such patients in
17 the trial.

18 There were an additional 9, or only 8 correct,
19 that were identified on physical examination. I shouldn't
20 actually say additional. We don't know that those 8 might
21 not also have included a tumor with chest X-ray.

22 There are 5 identified by CT scan of the chest
23 which probably includes those who are positive on chest X-
24 ray so there may be anywhere from 8 to 13 patients there.
25 There are, certainly, far more where the CT of the abdomen,

1 had it been done, would have give evidence of disease.

2 DR. SALK: Very few patients are identified by
3 physical exam or chest X-ray to have extensive disease. The
4 reason the chest CT and chest X-ray do not frequently
5 identify extensive disease is not because of some bias in
6 entering the study but because it is relatively uncommon to
7 have bilateral lung disease which is the only instance of
8 extensive disease in small-cell lung cancer detectable in
9 the chest.

10 DR. PARKINSON: Thank you.

11 The first FDA presentation is by Dr. Berkower.

12 **FDA PRESENTATION**

13 **MR. IRA BERKOWER**

14 MR. BERKOWER: My name is Ira Berkower. I am in
15 the Center for Biologics of FDA. I will be presenting the
16 first part of the FDA perspective on this product.

17 I would like to begin this afternoon by telling
18 you the Committee members which will be on the first slide.

19 [Slide.]

20 I will be presenting the chronology and the
21 findings of the early Phase I and Phase II studies and then
22 George Mills, who is one of the Cochairmen of the Committee,
23 will be presenting the Phase III pivotal trial.

24 I will just say that the PLA Committee consisted
25 of the two Cochairmen, George Mills and Tom Bull and also

1 included the other members, Satish Mishra, Florence
2 Kaltovich, Chris Joneckis, Dennis Klinman and myself, Ira
3 Berkower.

4 [Slide.]

5 The slide that was before this said NR-LU-10 is a
6 FAB fragment of a monoclonal antibody that is to be used for
7 imaging small-cell lung cancer. This slide shows a brief
8 chronology of the application. The Phase-I and Phase-II
9 studies were initiated with the filing of an IND application
10 in May of 1987. I will be discussing the 47 patients in
11 this study.

12 This led to a Phase-III trial in August of 1988
13 involving 89 evaluable patients. That will be presented by
14 Dr. Mills. In December of 1989, these studies led to the
15 filing of a PLA. In January of 1992, for business reasons,
16 manufacturing of the monoclonal antibody was suspended for a
17 period of time. In September of 1993, a new manufacturer
18 took up this product and that sponsor filed the current PLA
19 in March of 1994.

20 So I will just be describing the Phase-I and
21 Phase-II studies.

22 [Slide.]

23 This is a list of the questions addressed during
24 these studies. The first question was the dose of the
25 protein which was found to be 10 mg, the dose of the

1 radiolabel, which was 15 to 30 mCi, and the optimum time of
2 imaging, which was found to be 14 to 20 hours. I will go
3 into this a bit more on the next slide in terms of
4 pharmacokinetics leading to these parameters being chosen.

5 The safety was evaluated in these studies both in
6 terms of clinical safety, which there were very few adverse
7 reactions, human antibodies to mouse which, in the Phase I
8 and II was detected in 5 out of 48 patients and, as well,
9 the radiation dose absorbed by these patients, indicated as
10 RADs; the radioactivity was that 4 RADs were absorbed in the
11 kidneys, 1 RAD in the thyroid, and all the other organs were
12 1 or less, which was considered a very good profile for this
13 type of imaging agent.

14 The other thing that had to be evaluated at this
15 phase was which tumor type to go after since
16 immunohistochemistry studies revealed that this antigen is
17 found on a number of different tumors. Of course, these
18 studies led to small-cell lung cancer. Other lung cancers
19 were evaluated as well.

20 [Slide.]

21 So, on the next few slides, I would just like to
22 go into a little more detail on some of these issues.
23 First, the half life of the Technetium-labeled FAB fragment,
24 both in terms of its biological half life, which the
25 excretory phase was 10.5 hours, and the physical half life

1 of the radiolabel, which was 6 hours.

2 The good match between these two times, in part,
3 accounts for the equality of the images obtained because the
4 material was cleared from the blood pool relative quickly
5 for an antibody fragment, faster than in a whole antibody,
6 and yet the 6-hour half life limited the total amount of
7 time available for imaging, and most imaging is done at
8 about 3 half-lives.

9 [Slide.]

10 This slide shows some of the artifacts that were
11 observed right from the first Phase-I and -II trials, the
12 imaging artifacts. Some of these could be attributed to
13 specific binding, recognizing the antigen on tissues. These
14 included, as was shown by Dr. Nelp, the thyroid gland, which
15 seems to have an antigen-specific binding. Salivary glands
16 are sometimes picked up and the anterior pituitary.

17 As well, non-specific localization has been
18 observed on organs such as the testes and nasopharynx.
19 Finally, an imaging artifact occurs due to the excretion
20 pathway which is roughly two-thirds renal so there is a
21 strong renal image, kidney image, and the hepatobiliary tree
22 leading to some artifacts in the GI tract at various times
23 after imaging.

24 It is a very important point that has persisted
25 with this product through all the trials, that there is an

1 education process so that the reader will be able to take
2 these artifactual images into account in looking for tumor
3 images.

4 [Slide.]

5 Finally, in the Phase-I and -II trials, they
6 address the question of which tumors were the most likely to
7 succeed in terms of imaging. What I am showing here are a
8 variety of tumors that were tested. There were roughly 10
9 patients for this one, this one, this one and this one. I
10 am just showing the detection rate of involved sites.

11 This is not really an indicator of specificity or
12 efficiency of detecting them, just simply getting an idea
13 which were the good tumors to go for. As you can see,
14 small-cell lung cancer, 12 out of 21 sites, were detected
15 even in these early studies.

16 Non-small-cell lung cancer is also detected, as is
17 colon, breast, kidney, prostate, liver and cancers of
18 undetermined origins. Some of them were detected less well.
19 So the results of the Phase-I and -II study were interpreted
20 as showing that small-cell lung cancer would be the target
21 for further studies and this was pursued in a Phase-III
22 trial which will now be discussed by Dr. Mills.

23 **DR. GEORGE MILLS**

24 DR. MILLS: I am George Mills with the Center for
25 Biologics. We are going to discuss the pivotal Phase-III

1 trial.

2 [Slide.]

3 This is PLA 94-0308. It was submitted into the
4 Center for Biologics on March 28, 1994. Under IND 2633, all
5 the clinical trials we will be discussing were performed.
6 Our sponsor is Dr. Karl Thomae.

7 [Slide.]

8 The pivotal Phase-III trial was titled a trial of
9 Technetium-labeled monoclonal antibodies for staging a
10 small-cell cancer. The dates of this trial were July 6,
11 1988 through July 6, 1989. All of the patients that are
12 accrued under the pivotal Phase-III trial that are submitted
13 in this PLA were performed at that time.

14 There were 24 sites in the United States. This is
15 a single-arm, open label, multi-center trial.

16 [Slide.]

17 The sponsor's proposed indication has been
18 reviewed by the sponsor, but let me take you through it
19 again, that the proposal for NR-LU-10 is for initial staging
20 of patients with biopsy-confirmed small-cell lung cancer.
21 For those patients with no evidence of extensive disease --
22 that is, staged as limited disease by NR-LU-10 -- the
23 sponsor is recommending that they have the standard
24 diagnostic tests in order to continue staging because the
25 standard diagnostic tests have demonstrated that they will

1 find additional sites of disease which are not apparent by
2 NR-LU-10.

3 [Slide.]

4 NR-LU-10 also, as noted by the sponsor, is not
5 indicated for differential diagnosis of suspected lung
6 cancer or suspected metastases. Clinical trials have shown,
7 in their Phase I-II studies, that they can image other
8 tumors with NR-LU-10; non-small-cell lung cancer, primary
9 and metastatic tumors, also of breast, ovary, colorectum,
10 prostate, kidney and liver.

11 [Slide.]

12 The sponsor had three objectives in the pivotal
13 Phase-III trial. The first was the comparison of NR-LU-10
14 FAB imaging with the current standard diagnostic imaging
15 tests to assess the utility of NR-LU-10 for staging of
16 patients with small-cell lung cancer.

17 The second objective was estimation of sensitivity
18 and positive predictive value of NR-LU-10. The third was
19 the evaluation of safety for NR-LU-10.

20 [Slide.]

21 The population in the pivotal Phase-III trial were
22 adults, newly diagnosed, histologically confirmed, small-
23 cell lung cancer. They had to have a least one known lesion
24 detected by physical exam or standard diagnostic evaluation.
25 They were to have no prior history of chemotherapy,

1 radiation therapy, or other investigational agents.

2 [Slide.]

3 The treatment plan began with the standard staging
4 evaluation, physical examination, CT of the chest, head and
5 abdomen, whole-body bone scan and bone-marrow aspiration
6 and/or biopsy.

7 [Slide.]

8 The second step in the treatment plan was a single
9 intravenous administration of NR-LU-10 FAB label with
10 Technetium. There was a maximum of 10 mg of the NR-LU-10
11 FAB fragment and a minimum of 5 mg; a minimum of 15 mCi and
12 a maximum of 30 mCi of Technetium-99, pertechnetate as the
13 label; total volume of administration is 15 to 20 ml, and it
14 was chelated with normal saline to get that volume; and it
15 was administered over 3 to 5 minutes.

16 [Slide.]

17 The imaging protocol in the treatment plan was
18 ideally to image these patients at 14 to 17 hours. Imaging
19 was regional, planar imaging; whole-body planar imaging, and
20 SPECT to the chest was optional and performed in many
21 patients.

22 [Slide.]

23 The interpretation of the scintiscans; the
24 original treatment protocol identified that all of these
25 studies would be evaluated at the clinical site unblinded.

1 A second step was all of the scintiscans were to be
2 evaluated in a completely blinded evaluation. Comparison
3 between the first and second steps were then to make sure
4 that they agreed.

5 If there was a disagreement, then they were
6 submitted to a third interpreter and that third interpreter
7 would evaluate those sites that were in question and then
8 render an unblinded third opinion.

9 The Center for Biologics, noting that this is
10 being proposed as a first-best test for evaluating patients
11 with small-cell lung cancer, have chosen to go with the
12 fully blinded interpretation for the evaluation of this
13 trial.

14 That evaluation; all scintiscans from all
15 investigational sites were moved to an independent
16 interpretation. There was no consultation between the
17 interpreters. They had no knowledge or access to the
18 clinical history, the findings of the standard diagnostic
19 imaging, nor did they know the technical imaging findings or
20 artifacts, which is significant when we talk about false
21 positives, especially.

22 [Slide.]

23 The treatment protocol for safety evaluation;
24 patient monitoring was first with observation and vital
25 signs. Next was serial laboratory evaluation with

1 hematology, serum chemistry and HAMA evaluations, and
2 urinalysis.

3 [Slide.]

4 The results of the pivotal study Phase-III trial;
5 first of all, the demographics and patient characteristics.
6 We started with 96 patients being entered on this trial.
7 89 patients were evaluable for efficacy. The mean age of
8 the population is 60.9 years ranging from 34 to 88 years.
9 77 percent of the patients being admitted on the trial were
10 male.

11 [Slide.]

12 Seven patients who did not qualify for efficacy
13 analysis. One did not undergo gamma-camera imaging. One
14 did not complete the standard diagnostic studies. One
15 patient received chemotherapy prior to the antibody
16 injection. One patient had a second malignancy, a colon
17 cancer. Three patients had primary tumors, not small-cell
18 lung cancers. Two were non-small-cell lung cancers of the
19 lung. One was a small-cell carcinoma of the parotid.

20 [Slide.]

21 This summarizes the evaluation of the Phase-III
22 trial. We start with 89 patients in this trial and we
23 notice, on the left side, final stage being determined. The
24 final stage is different from those patients in terms of the
25 standard diagnostic modalities.

1 Seven patients plus 2, a total of 9, were
2 reevaluated, sometimes based upon the imaging from NR-LU-10,
3 other times in terms of re-review of bone marrow as well as
4 CT evaluations. Therefore, when we look across for the
5 final stage of extensive disease, we have 57 patients who
6 were staged as extensive disease, 32 patients who were
7 staged as limited disease, totalling the 89.

8 Looking on the bottom, NR-LU-10, extensive
9 disease, identified 47 patients as extensive disease. Of
10 these, they were correct on 44 patients as extensive
11 disease. They were incorrect on 3 patients as extensive
12 disease. These were overstaged and we will review those
13 initially for you in just a moment.

14 Looking at NR-LU-10 for limited stage, they
15 identified 42 patients as limited stage. They were correct
16 on 29 patients. They were incorrect and understaged on
17 13 patients and we will review those.

18 [Slide.]

19 Sensitivity for NR-LU-10 imaging. Of 57 patients
20 with extensive disease, they identified 44 correctly,
21 77 percent sensitivity. All standard diagnostic tests;
22 those 57 patients. All standard diagnostic tests identified
23 50 for a sensitivity of 88 percent. Specificity; 32
24 patients identified with limited stage, NR-LU-10 imaging
25 correctly identified 29 for a specificity of 91 percent.

1 All standard diagnostic tests; of the 32, they correctly
2 identified 30 for 94 percent.

3 [Slide.]

4 Comparative performance for extensive disease;
5 accuracy, PPV and NPV may vary with the prevalence of the
6 disease and the population. In our review, in the briefing
7 document, you will notice that CBER went forward and looked
8 at different population prevalences, at 60 percent,
9 69 percent and 75 percent to compare and see if we could
10 feel that the accuracy, PPV and NPV reported in this patient
11 population for the clinical trial could be reliable.

12 The population prevalence in this trial was
13 64 percent and we determined that the accuracy PPV and NPV
14 had minimal variations and, therefore, we could rely on the
15 values for this clinical trial as being representative.

16 The accuracy for NR-LU-10 imaging, 82 percent.

17 All standard diagnostic modalities, 90 percent. PPV for NR-
18 LU-10 imaging, 94 percent. All standard diagnostic
19 modalities, 96 percent. NPV, 69 percent for NR-LU-10
20 imaging, 81 percent for all standardized diagnostic tests.

21 [Slide.]

22 This is a comparative example of the accuracy of
23 single diagnostic modalities. You have seen this before.
24 It lists, on the left column, each of the individual
25 diagnostic modalities that were in this clinical trial. NR-

at

168

1 LU-10 is at the top. CTV abdomen is No. 2. And the others
2 are listed below.

3 Limited stage, the number correct as compared to
4 the total, is in the second column, extensive stage in the
5 third column, and accuracy in the fourth. As we see,
6 accuracy at 82 percent for NR-LU-10 is the leading accuracy
7 of all of the single standard diagnostic tests as compared
8 to NR-LU-10..

9 This is somewhat artificial. You are not going to
10 use the individual tests alone. But, from that standpoint,
11 it is the most accurate individual single test in this
12 trial. Extensive disease; it identified 44 of 57. The next
13 closest is CT of the abdomen, identifying 33 of 57. As a
14 comparison to that 82 percent accuracy for NR-LU-10, CT of
15 the abdomen demonstrated an accuracy of 71 percent.

16 ~~The other diagnostic modalities below all decline~~
17 in accuracy and all decline in the number of extensive-stage
18 disease identified. Of note, in the limited stage; actually
19 NR-LU-10 was the lowest in terms of identifying limited-
20 stage correctly.

21 [Slide.]

22 This is a sensitivity, a secondary analysis, if
23 you will, of NR-LU-10 by organ evaluation. In the top
24 column, you will see the white listing. All of this area
25 above, all of these areas, were identified with a detection

1 rate or sensitivity greater than 75 percent, in the lung,
2 neck, axilla, mediastinum, bone and bone marrow.

3 Liver and pleura demonstrated a detection rate or
4 sensitivity at 63 percent and 53 percent, respectively.

5 Noted is brain which has a relatively insensitive
6 demonstration of 3 of 12 at 25 percent. And there were
7 9 metastatically involved adrenal glands in the trial. None
8 of them were detected by NR-LU-10.

9 [Slide.]

10 False positives. There were 3 patients who were
11 overstaged in a fully blinded evaluation. The interpreters
12 had no knowledge of the technical artifacts and these of 3
13 patients that were overstaged, one had a recent surgery
14 site, and Dr. Nelp demonstrated that scan to you. There is
15 no need to show it to you again. Indeed, it is positive
16 and, if you were on the clinical site, you would have
17 identified that and easily detected it.

18 There were two skin folds in the axilla. This
19 product does demonstrate positive localization of the skin
20 folds. It should be recommended for this agent that always
21 the arm should be elevated. But they weren't in the trial,
22 as you saw in the picture.

23 In the opinion, therefore, in my review, all three
24 of these false-positive patients would have been properly
25 staged in a clinically competent or routine clinical

1 setting, so the false positives here were three. I feel all
2 of them are represented because of the fully blinded
3 evaluation.

4 [Slide.]

5 False negatives; 13 patients were understaged. Of
6 these 13 patients, 5 were because they did not identify
7 brain metastatic disease primarily. Remember that 3 of 12
8 that I showed you before. It will detect brain in some
9 patients but it is relatively insensitive. It is a whole-
10 body imaging technique and, as a result, it is not and it
11 cannot be expected that it is going to identify brain
12 metastasis with a high efficiency.

13 4 patients were missed because of liver metastatic
14 disease which was not identified. 4 patients, 4 bone
15 metastasis, total of 13. All of these patients were
16 ~~correctly staged and identified for the metastatic disease~~
17 at the same time by the standard diagnostic modalities as
18 they were missed by NR-LU-10 in this evaluation.

19 [Slide.]

20 Review of the imaging. Dr. Nelp has given you an
21 excellent set of images. I will go through and step through
22 what I consider to be the significant findings for, number
23 one, imaging and confirmed tumor sites; yes, NR-LU-10 will
24 identify tumor sites as demonstrated.

25 Adequate target to non-target imaging resolution

1 is apparent in the studies. The earliest image tumor that I
2 could identify in the scans that were submitted to me was at
3 3 hours and the latest were 24 hours.

4 [Slide.]

5 Non-tumor localization is in three areas in these
6 studies, and he has reviewed those for you, also. First of
7 all, the clearance routes and we will step through those in
8 just a moment. Antigen-specific localization; remember, we
9 are working with an antigen-antibody response and non-
10 antigen-specific localization.

11 [Slide.]

12 Clearance routes were two. The first and the
13 predominant is through the kidneys and the urinary bladder.
14 It is seen as early as 3 hours in the images and it is
15 intense through the 24-hour set of images. Gall bladder,
16 ~~small bowel~~ and large bowel and liver are a second route of
17 clearance. It is significant with approximately one-third
18 of the clearance going this route. It is seen as early as
19 3 hours through 24 hours.

20 [Slide.]

21 Antigen-specific localization; salivary glands,
22 thyroid and adenohypophysis have all been demonstrated on
23 imaging. A fourth is also known in terms of
24 immunohistochemistry and that is the pancreas. We were not
25 able to identify pancreas localization on the scans, but

1 this may well be because of the overlying bowel in the area
2 that we were not able to define the structure.

3 [Slide.]

4 Non-specific localization; typical for
5 nuclearmedicine-type imaging. Normal structures in the
6 heart, vascular structures, nasopharynx, spleen, testis and
7 skin folds. Inflammatory responses; we have noted the
8 recent surgical site that you have seen. I would anticipate
9 that you are going to see this agent in injection sites as
10 common with any type of Technetium-labeled material.

11 I would also anticipate you are going to see this
12 in inflammatory responses and you have to be concerned that,
13 with any type of agent that sees inflammatory responses, the
14 potential for abscess localization is there, too. Neither
15 of those last two, though, were identified in the clinical
16 trial for us.

17 [Slide.]

18 Non-tumor localization. NR-LU-10's interpretation
19 will be of limited value for detection of potential
20 metastatic disease in regions of non-tumor localization.
21 The extrahepatic abdomen presents one concern in terms of
22 the amount of activity clearing through the bowel as well as
23 in the region of the kidney and bladder, remembering those
24 adrenal glands; they were 0 for 9 in terms of identifying
25 metastatic disease.

1 [Slide.]

2 Integrated safety summary; 515 single patient
3 intravenous doses reviewed. These are in multiple trials in
4 multiple different types of tumor. Their experience from
5 those 515, 30 patients, 6 percent showing minor adverse
6 events.

7 [Slide.]

8 The safety summary in terms of those events;
9 clinical events, mild and transient, fevers in 2 patients.
10 Allergic reactions in three patients. Laboratory value
11 increases, low-level and transient. Amylase in 10 patients
12 and lipase in 13 patients, remembering this agent is
13 targeting salivary glands and pancreas. And whether one or
14 both of these organs are demonstrating slight elevations in
15 amylase and lipase would be determined.

16 - - Thyroid-function studies were elevated and changed
17 in 2 patients transiently, remembering also that this
18 antibody targets specifically the thyroid and there is some
19 change. No adverse events were considered of clinical
20 significance.

21 [Slide.]

22 HAMA response evaluated in 53 of 89 patients in
23 the pivotal, Phase-III trial. Of those 53 patients that
24 were evaluated, 3 patients developed elevated HAMA tests.
25 Of those levels, one was a two-fold increase over baseline.

1 One was a six-fold increase over baseline, and one was 40-
2 fold increase over baseline.

3 The 2 patients with two-fold and six-fold both
4 returned to the baseline within 4 months. The third patient
5 was declining but did not return to the baseline at 4 months
6 and was lost to follow up.

7 [Slide.]

8 Dosimetry; total body radiation exposure is 0.47
9 RAD/30 mCi. The kidney exposure, our first route of
10 clearance, is 3.9 RAD/30 mCi. Our gall bladder, second
11 route of clearance, 5.6 RAD/30 mCi. And the thyroid, 0.91
12 RAD/30 mCi. From this standpoint, all of these are within
13 acceptable limits with Technetium products and represent no
14 concern in terms of a medical or clinical evaluation.

15 [Slide.]

16 Summary points. Tech NR-LU-10 FAB whole-body
17 imaging identified extensive disease in 44 of 57 patients
18 for a sensitivity of 77 percent. Those patients had a PPV
19 of 94 percent. There was a low rate of false positive
20 interpretation in 3 of 47, and I have reviewed those false
21 positives for you, in terms of being probably representative
22 from the fully blinded evaluation. There were 13 of 57
23 patients understaged.

24 [Slide.]

25 NR-LU-10 images small-cell lung cancer, other

1 malignancies, inflammatory sites at recent operative site,
2 we know from this trial; benign neoplasms, as we know from
3 immunohistochemistry; and normal tissues. Readministration
4 has not been evaluated for safety or efficacy. And the
5 performance characteristics of NR-LU-10 who have received
6 anti-neoplastic therapy, chemotherapy and/or radiation
7 therapy, are unknown.

8 [Slide.]

9 NR-LU-10 FAB imaging is safe for clinical use with
10 a 6 percent adverse-events reported in 515 single-patient
11 injections and no adverse events were clinically
12 significant.

13 That concludes the pivotal study Phase-III trial.

14 DR. PARKINSON: Thank you, Dr. Mills. I think it
15 is appropriate at this point to ask if there are any
16 questions either for Dr. Berkower or for Dr. Mills.

17 DR. GELBER: In the pivotal study, could you
18 comment on the determination of the final stage? How was
19 that actually achieved?

20 DR. MILLS: In terms of the final stage whereby
21 standard diagnostic modalities -- and, again, there were
22 9 patients who were actually rereviewed on bone marrow as
23 well as CT, sometimes being led back by the NR-LU-10,
24 sometimes by other clinical findings, that were final stage
25 changed from the initial on-study staging.

1 DR. GELBER: I see -- because your comment about
2 using the test study to go back over caught my attention.

3 DR. MILLS: It caught my attention, too, in terms
4 of when we initially started reviewing this that you will,
5 from time to time, find sites on NR-LU-10 during that
6 clinical trial which would refocus their attention and go
7 back looking at CT or looking at bone marrow. So, from that
8 standpoint, while we consider the standard diagnostic
9 modalities to be a gold standard, it may have a slight tinge
10 of brass to it in terms of interpretation.

11 DR. GELBER: Just to push that a little bit :
12 further; if you didn't use the evidence from the agent we
13 are evaluating to restage, what would the parameters of the
14 test performance look like?

15 DR. MILLS: In terms of if we had not done that?
16 Actually, when we compared, when we were looking at the
17 sensitivity, we were looking the standard diagnostic
18 modalities on stage evaluation for that comparison of
19 sensitivity and specificity.

20 DR. GELBER: So it wouldn't change it.

21 DR. MILLS: No. We were comparing that because we
22 wanted to identify final stage in terms of the outcome for
23 it. But when we compared sensitivity and specificity, we
24 used the on-trial staging as initially being evaluated.

25 DR. GELBER: So, did you recalculate positive

1 predictive value, then, using sensitivity and specificity
2 and putting in a prevalence, because the 94 percent, I
3 assume, comes out of the data in the table.

4 DR. MILLS: That is correct.

5 DR. GELBER: Rather than a recalculation.

6 DR. MILLS: That's correct. We estimated that
7 prevalence rate only to make sure with this trial, because
8 we had 89 patients, that the prevalence would not move those
9 accuracy PPV and NPV values.

10 DR. GELBER: And your lowest prevalence for that
11 sensitivity was 60 percent?

12 DR. MILLS: We attempted 60 percent, 69 percent
13 and 75 percent.

14 DR. GELBER: Was the 60 percent a reasonable lower
15 limit for the portion of patients with extensive disease?

16 DR. MILLS: We felt it was. If someone, in terms
17 of difference, in terms of that -- but we felt that those
18 would extend to any type of prevalence rate that we would
19 expect to see clinically.

20 DR. GELBER: And a last question about the study.
21 The 7 patients who were excluded. Did you go back and take
22 a look at what their small-cell lung-cancer stage would have
23 been?

24 DR. MILLS: No; I did not. From that standpoint,
25 they were excluded from it. I reasonably went back and

1 evaluated each one of them in terms of the reason for
2 exclusion to make sure there was a reasonable reason to move
3 those patients off.

4 DR. INGLE: For the indication, the positive
5 predictive-value indications sought -- the positive
6 predictive value is very important. What you are telling us
7 is that if you have the clinical material available, and the
8 way it would be used was approved, that, in fact, the
9 positive predictive value is 100 percent; is that right?

10 That is what I am assuming from the data; that is,
11 there were 3 false positives that, in fact, if you had the
12 clinical data, you would have called them negatives.

13 DR. MILLS: I would have.

14 DR. INGLE: So your positive predictive value,
15 with all the clinical information, is 100 percent. That
16 almost sounds too good to be true.

17 DR. MILLS: As a nuclearmedicine imager, it is too
18 good to be true. But, from that standpoint, in terms of a
19 fully blinded interpretation, the three false positives were
20 correctable in terms of standard clinical evaluation. It is
21 a remarkable one in terms of being able to do extensive
22 disease evaluation. It is, obviously, not, in terms of
23 limited disease.

24 DR. INGLE: That is correct. But they are not
25 seeking that as an indication.

1 DR. MILLS: That's correct.

2 DR. INGLE: I know that the studies were blinded.
3 Did you review the studies that were called negative?

4 DR. MILLS: Yes.

5 DR. INGLE: You have got uptake from the neck and
6 the head and down into the abdomen and the bowel, et cetera
7 -- well, thank you. I feel much better.

8 DR. MILLS: From that standpoint, number one, is
9 we did review all 89 scans in terms of being able to
10 determine if we could evaluate that. Number one is that if
11 you are looking for extensive disease, when you are looking
12 for multiple organ involvement, this study does quite well.
13 When you see that much activity, limited-stage disease
14 presents a problem for you in terms of determining it.

15 Looking at the abdomen -- and one of the concerns
16 -- I have about this study is it clears through into the small
17 bowel, large bowel, and shows quite a bit of activity over
18 the abdomen. What that did, in terms of the evaluation, was
19 that the interpreters became insensitive in that area and
20 actually under-read adrenal areas.

21 So, from that standpoint, the experienced
22 reviewer, if you will, became very cognizant of those areas
23 that were of concern and down-read them and, so, tended to
24 understage patients.

25 DR. INGLE: Just one last question, if I could.

1 Whenever you have a test that has 100 percent positive
2 predictive value, it opens the door for basically
3 overstaging somebody; that is, you gave the example that you
4 would expect it to be taken up in benign lesions such as
5 abscess.

6 DR. MILLS: Absolutely.

7 DR. INGLE: Any thoughts about suggestions if it
8 was used in positive as a part of clinical practice that one
9 uses, focuses in one lesion to prove metastatic disease with
10 a more conventional diagnostic test, anything to really
11 protect patients so that you don't overstage somebody?

12 DR. MILLS: I think what will happen with this
13 study --

14 DR. INGLE: That's what will happen.

15 DR. MILLS: Absolutely. They will understage
16 these patients, characteristically, and that is what you saw
17 in this trial evaluation. There is so much activity in the
18 field and you know where the positive areas are going to be
19 which are going to confuse you, that abdomen, that activity,
20 both kidneys.

21 So what we see is that the interpreters were
22 actually understaging patients. So what is going on is that
23 they have a degree of confidence in the extensive. They
24 were able to call that.

25 DR. INGLE: One point regarding that that I am

1 sure will be reflected in the labeling is that although one
2 might argue that no incidences of false positives were
3 observed, when one looks at the confidence interval around
4 either specificity or PPV, given that you are talking 30 or
5 40 people in the group, even with no observation, the
6 confidence interval for specificity drops down as low as
7 about 90 percent, meaning that 10 percent of patients with
8 limited disease may be positive and it just may not have
9 shown up on this.

10 Similarly, if you look at the PPV, the confidence
11 interval could be as low as 92 percent. So I don't think
12 the data yet are strong enough where, even based on these
13 readings, one would write a labeling saying they are not
14 going to occur if this is approved.

15 DR. MILLS: To offer to you, the same way. My
16 concern of having dealt with nuclearmedicine images for
17 many, many years is that nothing has 100 percent. But, from
18 the standpoint of looking at this, the natural tendency of
19 the reviewer who is experienced and who has been trained
20 will be to under-read these images, not over-read these
21 images.

22 DR. BARRY SIEGEL: I certainly agree that nothing
23 in nuclearmedicine has 100 percent with confidence. Dr.
24 Gelber, I think, was trying to get at an issue of
25 verification bias as it entered into the assessment of the

1 final extensive versus limited disease classification. I
2 think that is an important problem. But there is another
3 twist to it and that is, since, the data were available at
4 the clinical site, since the scans were read and it was an
5 open-label study at the clinical site, do you all have a
6 feel, or has the sponsor presented data, as to what extent
7 verification bias operated in the actual clinical
8 interpretation of the standard diagnostic tests and prompted
9 additional workup?

10 How often did the scan results lead to something
11 that wouldn't have been done in routine clinical practice or
12 change the interpretation of the CT scans?

13 DR. MILLS: We know that there were 7 patients who
14 had CT re-reviewed in terms of that interpretation, if you
15 wanted to draw that. We did not come back in terms of
16 additional ---I'm seeing -- Dr. Salk is at the ready to give
17 me some input. As soon as we can get him seen, he is going
18 to tell us.

19 DR. BARRY SIEGEL: Part of the point of the
20 question is that, in a way, the design of this trial is
21 stacked against NR-LU-10 and stacked in favor of the
22 conventional diagnostic test.

23 DR. JAY SIEGEL: It is my understanding, though,
24 that if a CT was re-read and the CT or biopsy are ultimately
25 confirmed disease, the reading for the standard diagnostic

1 test, however, was the initial reading not the re-read --

2 DR. BARRY SIEGEL: But even the initial reading --

3 DR. JAY SIEGEL: Might have been informed --

4 DR. BARRY SIEGEL: If the NR-LU-10 showed a lesion
5 in the left lobe of the liver and the initial CT scan showed
6 only a subtle hypodense lesion of the left lobe of the
7 liver, the CT interpreter, knowing that NR-LU-10 was
8 positive, might well have called that a metastasis that he
9 would have skipped otherwise.

10 DR. JAY SIEGEL: I think they were done
11 sequentially, though, where the standard tests were all done
12 before the NR-LU-10, at least that was a protocol.

13 DR. SALK: Yes. Almost invariably, all the
14 standard tests were done before the Verluma imaging. There
15 were a very few exceptions that were made because of
16 scheduling reasons.

17 Can you get me Slot No. 42.

18 DR. MILLS: By the way, just as you are getting
19 your Slot 42, one of the things to understand is that we,
20 indeed, stacked this against NR-LU-10 as stringently as we
21 could in terms of making sure there was no bias introduced
22 in terms of knowledge from the site. That is why I
23 specifically wanted a fully blinded interpretation with this
24 study.

25 We have data that we were originally presented in

1 the trial in terms of the on-site. We did not want to have
2 that influencing because of the performance characteristics.

3 DR. SALK: I want to show you two slides that I
4 think will help to see what is going on here. One of them -
5 - 22 will come after this one.

6 [Slide.]

7 This shows you the previously unsuspected true
8 positives. In other words, these were the false-negative
9 lesions, organs or patients, those three different levels of
10 analysis, by the traditional imaging test, by the standard
11 evaluation. These are all of them in the study.

12 Among 610 lesions, there were 39 lesions that were
13 seen in NR-LU-10 images that had not been previously seen,
14 and raise the question of whether they were real or not. In
15 contradistinction to what you said, Dr. Mills, in fact, all
16 of these were first seen by the Verluma imaging.

17 Because they were seen, we went back and either
18 reread the baseline CT, obtained another test, went and did
19 an MRI, and, in one instance where we found a positive bone
20 marrow in the Verluma images, went back and looked at the
21 original bone marrow and found abnormal cells that had been
22 missed previously.

23 Those were the only instances in which, when it
24 was corroborated by a standard modality, most of the time
25 that was because it just didn't happen to be seen in the

1 first reading, there were only 6 percent of those in the
2 entire study in the lesions. At the organ level, among 333,
3 only 5 percent and, at the patient staging level, the 7
4 patients that Dr. Mills has been referring to were the
5 unsuspected positives.

6 [Slide.]

7 This shows the detection rates for positive
8 disease, the percentage detection of lesions, affected
9 organs or patients with extensive disease at the three
10 different review levels. The patterns are similar at all of
11 these. Let me just stick with this one.

12 The orange one is what we referred to as R-1.
13 That is the primary investigator at the clinical site. This
14 is the person for whom we did not control blinding. He had
15 access to everything. One or two investigators chose to
16 read everything blinded, but we had no control or any
17 information about that.

18 All of the images were then sent, submitted, to
19 NeoRx and were read, fully blinded, as I said before, by
20 either Dr. Nelp or Dr. Grief. They alternated odd and even
21 cases. That reading is referred to as the R2 reading. That
22 is the one we report to you here today. As you see, those
23 blinded reviewers tend to be more conservative in the
24 reading of the images.

25 As Dr. Mills mentioned, in order to try the

1 protocol design for this review process, it was fairly
2 complicated. In order for us to try and define something
3 unlike an artificial blinded situation, it would give us a
4 more accurate prediction of what the experience would be in
5 clinical practice.

6 It, therefore, went to when there was difference
7 between the first and second reviewers, it went to a third
8 reviewer which actually was fully blinded, initially, in
9 order to make a final determination of the stage. We did
10 add an extra step related to unblinding in order to identify
11 those three cases in which technical artifact played an
12 impact, put that back in.

13 So this, what we referred to as our final blinded
14 analysis, is the result of that blinded review process.
15 This was designed this way in the original protocol in an
16 attempt to make a better prediction of what would happen in
17 practice. As you can see, all of these are very similar to
18 each other and the pattern is that a reviewer on site with
19 all information tends to identify more disease. A fully
20 blinded reviewer is more conservative.

21 When you put in technical information and other
22 things, and you increase uniformity -- because this, again,
23 was done by two reviewers centrally as opposed to the
24 variety of reviewers with a variety of different equipment
25 throughout the many sites. When you increase uniformity,

1 you get this experience. They are all very similar to each
2 other.

3 DR. GELBER: I don't know how to summarize this.
4 I am just a little confused about the seven cases. I don't
5 know how it would turn out. You mentioned that this
6 analysis you did was conservative, if you will. You stacked
7 the deck against it.

8 On the other hand, part of the information we are
9 presented is the hierarchy of what the individual studies
10 can produce with respect to the different sensitivities and
11 accuracies. It is against those that people are going to
12 carry away the message, "This is much better." I haven't
13 done all the math and so on, but, if out of the 44 patients
14 that are in the cell and table that are extensive disease,
15 final stage, plus extensive disease by the test, seven of
16 those got into that cell because the test stimulated a
17 reevaluation of previous studies based on CAT scan.

18 Therefore, when you look at the results of
19 sensitivity, specificity here and you compare it to the
20 results if you look at other types of studies that were done
21 you might suspect, because you are using that information to
22 define your final stage, you could, again, get a better test
23 performance for the test agent that you are using to
24 stimulate.

25 That is just my first feeling. On the other hand,

1 you might say, "Well, there really was a gold standard of
2 disease present and this agent was better able to pick it
3 up." So my question, really, is, besides looking at the
4 images, was there any other further evaluation of the status
5 and what summary numbers can we take away with respect to
6 sensitivity, specificity for the different tests given that
7 you are using your test to classify the final stage.

8 How do we get around that issue to report the
9 characteristics?

10 DR. MILLS: Remember, the sensitivity and
11 specificity are based upon the initial evaluation by the
12 standard diagnostic modalities that we presented to you, not
13 the final stage numbers.

14 DR. SALK: Let me also comment. You have
15 identified something which is a problem for the evaluation
16 of every diagnostic test we have available for which --

17 DR. GELBER: I don't mean to pick on you. You
18 just happen to be up there.

19 DR. SALK: -- for which a true gold standard
20 doesn't exist. Particularly in this disease, with small-
21 cell lung cancer, you can't do biopsies of the entire body
22 and slice it up and know exactly what all of your -- it is
23 difficult to get that past a review committee.

24 So this is, indeed, a problem that one has. It is
25 uniform for all studies like this. Our feeling is that what

1 we did was we tried to define the best truth that we could
2 and to use that in order to come up with a reasonable
3 prediction of what the experience is liable to be.

4 DR. GELBER: I guess the bottom line comment is it
5 would be useful, because people will be using the numbers
6 that are reported here in a comparison way, to perform some
7 type of a sensitivity analysis. For example, you did one on
8 the prevalence. That was very nicely presented and an
9 important question to ask.

10 But, also, with respect to some of the other
11 statistics that come out of the study, with respect to how
12 you classify -- in addition to the 95 percent confidence
13 intervals, take a look at what those numbers would be if you
14 used other kinds of evaluations.

15 DR. GELBER: I think it is very interesting
16 suggestion. I am going to suggest that you get together
17 with Dr. Blumenstein afterwards and discuss it because we
18 have spent many, many hours discussing this kind of thing.
19 I terms of making comparisons with other agents, remember,
20 the other agents are also tested within the same kind of
21 setting where the gold standard doesn't exist and may be
22 influenced.

23 DR. JAY SIEGEL: I think part of that question,
24 which I didn't hear answered, is, on those 7 patients who
25 were, at least by initial standard diagnostic modalities

1 negative but wound up positive, do you know how many of
2 those were histologically confirmed as positive as opposed
3 to confirmed by rereading the standard methodology?

4 DR. MILLS: We had two of them. Bone marrow.

5 DR. SALK: I think, perhaps, two. It was a small
6 number and those were, like, bone marrows for which you can
7 do histology in this disease or biopsy.

8 DR. MILLS: The others were reinterpretation of
9 scans which were quite apparent.

10 DR. PARKINSON: I think we may get additional
11 clarification. Could you please use the microphone and
12 identify yourself, please.

13 DR. SATISH MISHRA: Satish Mishra from CBER.
14 Regarding the sensitivity analysis, I looked at the numbers
15 very carefully. There were 8 persons who were identified as
16 extensive by physical examination, alone. Two patients were
17 identified as extensive by chest X-ray, so making up
18 10 percent identified as having extensive disease by
19 physical examination and chest X-ray alone. And they were
20 identified as extensive by other tests like this --

21 DR. OZOLS: That is an important point that we
22 keep coming back to. If you take the test of a single test,
23 the Verluma test, and you get 44 patients who were
24 identified out of the 57 as extensive stage, that is very
25 impressive. But, if you take into account that everybody is

1 going to have a physical examination, everybody with small-
2 cell is going to have a chest X-ray, and then you compare
3 those 8 patients with physical examination, 2 patients with
4 chest X-ray, to CT of the abdomen, you are left with
5 43 patients.

6 So, in the real world, is this test any better
7 than a chest X-ray, a CT scan of the abdomen and a physical
8 examination?

9 DR. MISHRA: This analysis I did not do. But if
10 we exclude those persons, maybe we could get some number
11 indicative. I think that the numbers will not change that
12 much. That is my feeling. But, again, sample size, too, is
13 small. That is one comment.

14 Another comment I wanted to make was the on-site
15 reviewer had identified two different patients than the
16 blinded reviewer as having false false positives. So there
17 was some reader-to-reader variability seen also in this.

18 DR. SALK: Dr. Ozols, I have a series of slides
19 which may help to answer that question.

20 DR. OZOLS: I would actually like the FDA's
21 opinion on that.

22 DR. SALK: Oh; I'm sorry. If you want to know the
23 truth, it is the slides that were prepared by Dr. Mills. He
24 asked us to make them.

25 DR. MILLS: Why don't you go ahead and bring them

1 up. I anticipated what we were going to have.

2 DR. SALK: L-1 through L-6; that's 46 through 51.

3 DR. PARKINSON: Those are the contract slides.

4 DR. SALK: We went to the trouble to make them for
5 him and he didn't show them, so I wanted to make sure they
6 were here.

7 DR. MILLS: It is good grist for the response,
8 now. Go for it.

9 [Slide.]

10 This is, again, a similar diagram to what I showed
11 you before and that is the number of diseased organs here
12 and the different organ systems down here. The top of the
13 bar represents the total number of organs, effected organs,
14 in the study. And the orange indicates the number of those
15 organs that were detected by, in this case, chest X-ray or
16 CT of the chest.

17 [Slide.]

18 The next one shows what happens if you move on to
19 CT of the abdomen.

20 [Slide.]

21 Bone scan.

22 [Slide.]

23 CT of the head.

24 [Slide.]

25 And when you add all of those together, this is

1 the pattern that you get. You will notice that the bone
2 marrow and neck and axillary lymph nodes are not marked very
3 much. So, after stepping through that whole series, you end
4 up with this information.

5 By comparison with the Verluma imaging, with a
6 single test, this is the information which you get including
7 evaluation of the bone marrow in a non-invasive manner and
8 either confirmation or new identification of neck and
9 axillary lymph nodes which are otherwise not well
10 identified.

11 DR. MILLS: One of the more interesting things of
12 these tables is to identify that NR-LU-10 imaging is the
13 second best test in each organ system. Its constellation of
14 findings is where it is able to perform for extensive
15 disease. Its limitation, therefore, is why it is limited in
16 limited staging.

17 DR. PARKINSON: Are there additional questions
18 either for the FDA or Dr. Salk?

19 DR. MALCOLM: We were just discussing the fact
20 that, in clinical practice, many times, individuals get
21 chest CT scans which include the abdomen. The question we
22 wanted to get clarified here; were these actually separate
23 tests? What I am saying was a CT scan of the chest and then
24 a separate CT scan of the abdomen --

25 DR. PARKINSON: Or was it a CT to include

1 adrenals.

2 DR. MALCOLM: Right.

3 DR. MILLS: I can't confirm if every one of them
4 was divided separately. We had reports but whether they
5 were done at the same setting or as a continuous, that I
6 cannot tell you for sure. Depending on the clinical
7 practice site as to whether or not they are going to
8 continue right on down.

9 DR. MALCOLM: I would beg to venture that the
10 majority of these patients had a CT scan of their chest
11 which included the upper abdomen which is the standard way
12 to do it and the patient did not undergo a separate CT scan
13 of the abdomen.

14 DR. SALK: Actually, remember this study was
15 performed back in 1988 and that was not the routine practice
16 every place. So, in many, many, many instances, it was an
17 independent CT of the abdomen that had to be performed.

18 DR. BOTSTEIN: I wanted to ask the sponsor
19 something. If this were a drug, we would be asking you to
20 have two adequate and well-controlled clinical trials, the
21 second one replicating, scientifically, the findings of the
22 first. So really the only exception to that would be if a
23 product were of such major medical importance that you
24 couldn't go and do the second trial once you had the results
25 of the first trial.

1 So what is different here in the requirements for
2 a biological, or in the scientific setup, that makes you
3 think one study is enough? This isn't a situation where you
4 could look at the findings from separate study sites and say
5 they replicated each other because there aren't enough
6 numbers for you to get sensitivity and specificity and all
7 that sort of stuff.

8 DR. SALK: Actually, Dr. Mills, would you like to
9 comment on that?

10 DR. MILLS: I was going to say Dr. Siegel -- at
11 that level, will discuss that.

12 DR. JAY SIEGEL: I think one of the issues here is
13 that this isn't an issue of hypothesis testing, of looking
14 for a p value to reject the null hypothesis. This is a
15 issue of estimation -- two things; estimating past
16 performance in terms of sensitivity, specificity, predictive
17 values, accuracy and so forth and, also, estimating utility
18 in a clinical setting.

19 I would argue, in biologics in general where we
20 obviously are very interested in replication or in how
21 convincing the data are -- we don't have quite as, perhaps,
22 consistent a view as to the multiplicity of trials, but I
23 think in a case where you are trying to get estimates of
24 statistical values, that one can certainly make, as opposed
25 to hypothesis testing, the case that one can get more

1 precise data from one larger trial than from a larger number
2 of smaller trials each yielding rather inaccurate data.

3 It is, of course, important, I think, to look at
4 the data that insure that there aren't local either biases
5 or techniques that may have caused some sites to perform
6 differently from others. Although that hasn't been
7 addressed, that is a routine part of our review.

8 DR. SALK: Our experience at NeoRx has primarily
9 been with biologics rather than drugs. This obviously was a
10 question that we discussed pre-Phase-III, early on, about
11 the design of the study. The resolution was to do it the
12 way we did. Our experience in looking at other biologic
13 products is that many of them are also handled that way.

14 So your general question of whether drugs are
15 different from biologics and why, I am not going to attempt
16 to answer.

17 DR. PARKINSON: Is there data on performance at
18 different sites? I guess it was unremarkable enough that it
19 --

20 DR. MILLS: There were 24 sites. We did not see a
21 difference in terms of that remarkable presentation. But,
22 remember, you have very small experiences at any one site
23 with 89 patients.

24 DR. SALK: The other important thing is that all
25 of these images were ready in one place by one pair of

1 blinded reviewers so that the variability from site to site,
2 et cetera, is eliminated by the review process. Unlike some
3 other studies where either none or a sampling of images are
4 read by a blinded way, we read 100 percent of the images in
5 this blinded process.

6 DR. BARRY SIEGEL: That doesn't actually address
7 the clinical problem in the real world because unless you
8 have Dr. Nelp read all the scans, you can't be sure -- and
9 that would keep him busy for a long time to come -- but you
10 can't be sure that you can replicate this level of observer
11 performance at multiple sites.

12 You have the opportunity with at least several
13 sites to look at the data because you have several sites
14 that have large enough n values to try to get some estimate
15 of lesion sensitivity and specificity. You can't do it on a
16 patient basis.

17 DR. SALK: It, certainly, potentially, could be
18 done. The experience we actually had in training physicians
19 for the trial was a session, not unlike what Dr. Nelp did
20 for you here today. They were either done personally or,
21 sometimes, with a book. We sent a book of images with some
22 descriptions. A nuclearmedicine physician read through
23 that, looked at the normal biodistribution, saw a few
24 examples of the types of artifact, and they were very
25 comfortable.

1 There was no obvious -- nothing jumped out
2 obviously as people having particular problems at one site
3 compared to another. So, practically speaking, it was not
4 apparent.

5 DR. PARKINSON: Can I now consider myself
6 certified to be able to read these scans?

7 DR. SALK: Not necessarily, but you can be
8 comfortable.

9 DR. BARRY SIEGEL: You can't be licensed to
10 possess the radioactive material, but you can be certified
11 to read the studies. That is an NRC --

12 DR. PARKINSON: There are people who could be
13 certified immediately.

14 DR. TOM BULL: I am Tom Bull. I am with CBER. IN
15 addition to the reading of these images that they have
16 mentioned today, we also had three radiologists at CDER, the
17 Center for Drugs, read these images, read 22 of them. They
18 were Dr. Lionel Lieberman, Dr. David Woodbury, and Dr. Eric
19 Jones. George has looked at 100 percent of them, and your
20 assistant has looked at 100 percent of them.

21 So we have had five radiologists within the Food
22 and Drug Administration look at them and they are all
23 getting the same answers. So I think that is a fairly good
24 certification that the reading results can be replicated.

25 DR. GELBER: Did you also review all the CAT scans

1 that were done?

2 DR. MILLS: From the FDA's standpoint, no, we did
3 not. We have all the source documents for all of the
4 interpretations from them, but we did not actually review
5 all of the CT scans. From that standpoint, we would have to
6 have a record room fairly extensive to do that in any of
7 these trials.

8 DR. GELBER: It, again, goes to the issue of the
9 comparability --

10 DR. MILLS: Absolutely. From our standpoint, we
11 have to rely on the on-site interpretation of the comparable
12 gold-standard studies.

13 DR. SALK: And, as you said, we stacked the deck
14 against Verluma by using the routine evaluations on site
15 rather than attempting to do a very, very difficult thing
16 which would be to make uniform all of the other tests as
17 well and to review those centrally.

18 DR. GELBER: I guess that last comment is the one
19 that I haven't -- I am going to need more time to convince
20 myself that that is the way the deck has been stacked
21 because if one can conjecture, with 24 sites, maybe three
22 patients from each site, studies done in '88, '89, in terms
23 of the uniform reading of the other diagnostic tests against
24 a test that has been reviewed and reviewed and reviewed by
25 experts in the field who train themselves and are really

1 clued in to evaluating that scan, and then to look at the
2 performance characteristics of that procedure against the
3 performance characteristics of detecting extensive disease
4 at local institutions.

5 That is the standard that we are comparing against
6 and I am just a little uncomfortable.

7 DR. SALK: Remember, once again, when I showed you
8 the Verluma experience at the sites compared to the central
9 blinded reading, at the sites, they were higher. I would
10 expect that, in general, an unblinded reading, for instance
11 of the traditional imaging tests, is going to be higher than
12 a blinded reading.

13 So this is why I feel that we stacked the deck
14 against Verluma by that method of analysis.

15 DR. DEVOUS: I would reinforce that. In
16 diagnostic imaging, in general, blinded readings always do
17 worse, often substantially worse, than informed ones. So, I
18 understand that question you are asking, but,
19 experientially, the notion of giving a lot of clinical
20 information to somebody frequently makes them more accurate.

21 So, in this particular case, while that is an
22 appropriate challenge in a diagnostic imaging setting, I
23 think I would agree with his perspective that this is an
24 anti-Verluma design.

25 DR. GELBER: One last question related to that,