then. The pickup on the CAT scans as an individual -- because there is that list of individual studies, not taken as a group. And I am focussing on that hierarchy which, I imagine, is going to be impressive feature of something that comes out of this. Do you think that the pickup on the CAT scans that were done in the individual centers, '88 to '89, given the fact that they are unblinded, represents about what you would expect from those kinds of studies?

Is it high enough, or do you think that part of what we are seeing is misdiagnosis in individual centers that wasn't re-reviewed, that if those CAT scans were drawn in -- even blinded, if you looked at the CAT scans, you might say, "Ah; something was missed here. Something was missed here."

I just wonder about that. I hear everything you are saying, but I am concerned about the one study and the way it was done and a sense of being biased against. But I am not sure that is real.

DR. SALK: Are you raising the question as to whether there has been technology advancement that would make the standard tests more sensitive and accurate then they were in 1988, 1989?

DR. GELBER: That is not fundamental. The fundamental is that the results of the CAT-scan findings were not going through the same kind of review by experts

that the test agent went through in order to detect areas of disease. That is my concern in looking at the data presented to us.

DR. SALK: Once again, I would just not personally want to claim that the people at the sites who read the radiographs, et cetera, were not experts. I think they might question that. And the nuclearmedicine imagers on-site who read it were experts only to the extent of what their knowledge was from the training and the experience that they had with the Verluma.

So, once again, you are stacked the wrong way.

DR. MILLS: I think, also, to emphasize, remember, in this type of clinical trial, these are not the typical community hospital, necessarily. We would anticipate that the radiograph interpretations would probably be at a higher level than typically found in the general community only in as much that they are in academic centers, from that standpoint.

So, we would expect them to be slightly elevated, if anything. Going back and re-reviewing would be setting a different standard in terms of doing that from what we see here. I think you can feel comfortable that they are representative and, if anything, at a level at least adequate to the community if not higher then what you would expect in the community.

DR. PARKINSON: Thank you. I would like to move on at this point to the discussion. To lead that off, Dr. Ozols, you are prepared to make additional comments?

COMMITTEE DELIBERATION

DR. OZOLS: No; I think most of the things have been raised. I guess the real issue, again, that I am concerned about is not whether this test is a good individual test, which I think it is a good, accurate test. I think the question comes into the situation where you have already got the diagnosis made and you have got to put that in context with the chest X-ray, the physical exam, and a CT of the abdomen.

Again, if you add all those three things together, what have you really gained? Many of these patients, in fact, will wind up also having a CT scan of the head. These are elderly patients, often with the symptoms, and so forth. You are going to do a lot of that. So, it seems to me, that if you ask the question is this test better than the standard armamentarium that we have, I think the answer is no.

DR. PARKINSON: We will have some questions in a second, so you can't need to create your own. But, thank you.

DR. BARRY SIEGEL: I am not sure we are asking that question. This is not a test in pharmacoeconomics.

This is a discussion of safety and effectiveness of this drug. The added yield of this approach will depend on the strategy you choose for using this drug. If you use this drug as the first test beyond everything else you do short of a needle biopsy, it will be affected in a very large fraction of the population.

If you use this drug only in those patients who haven't already had extensive disease diagnosed by the things that we all logically believe might have been done before they come to the point of nuclearmedicine imaging, then it will be a smaller fraction of the population.

If you feel that you can't change your current practice, then it will be a tiny fragment of the population and the marketplace will figure that out very, very quickly. I think the cut point here is really between physical examination, chest X-ray and chest CT which most of us think everybody will have which, likely, in the latter, will include an improperly contrast-enhanced look at the liver and the adrenals versus whether or not you add in a formal, properly contrast-enhanced, helical CT study of the abdomen. That is really the key.

So those who feel that they are not going to give up the helical CT of the abdomen are going to almost never use this drug and those who feel that they are willing to drop back to the CT, chest X-ray and physical examination,

are going to use it a lot of the time.

If you look at George's Table 6, and some of these patients may be the same, it looks as if there are 8 -- Page 14 of the FDA write-up -- 8 patients in whom extensive disease was detected by physical examination, 5 by chest CT and 2 by chest X-ray. So that is 15 patients and some of them are probably the same people, out of 57.

So maybe 75 percent of the people with extensive disease would still go on to be staged by NR-LU-10 if you chose the "I'm not going to do a formal abdominal CT approach" and it might turn out to be a perfectly effective strategy.

I think, based on the discussion we had at the October 17 meeting, it really is a question of where you want to draw the decision criterion. Do you want to draw it at one of sensitivity and specificity? If we are accepting performance standards, this is a very effective drug as a nuclearmedicine radiopharmaceutical goes.

If we are requiring a standard that this has the potential to alter clinical management accurately, I think we have met that standard. If we want to know whether it is cost-effective and whether it unequivocally changes outcomes, the study wasn't designed to answer that question and we don't have the data yet. The marketplace will answer that question in relatively short order.

DR. JAY SIEGEL: We discussed three standards at that time, I would just remind the group. The imaging performance of clinical benefit, but, also, of clinical utility in which one would take presumptions about restaging, given the importance of staging, indicative of probably benefit.

As we have been assessing, in the past, and, of course, we are rethinking the role of all of these standards, but as we have been assessing clinical utility, we include in that, also, issues such as the proposal here that this may be a first-best test that would avoid significant numbers of additional tests as a marker of, albeit limited, potentially real utility. So there is that as a potential standard.

Addressing one other question I had raised which is that table on Page 14. If you exclude those 15 patients, or if you exclude those 13 patients, we will be able to get data on that tomorrow. I think it is 13. I don't think the two positive chest X-rays would have had negative chest CT scans.

So it is a maximum of 13, and it is possibly 8. And, even if all of those were ones that NR-LU-10 picked up so that you decrease -- when you exclude those, you decrease the number that the NR-LU-10 would pick up. Under those assumptions, that you are left with 31 of 44, or about

70 percent, which is on the order of where the CT optimum is likely to be.

DR. BARRY SIEGEL: It would be nice to see this sort of stepwise analysis of the patient population to know, assuming you did this, what are you left with; and then you do this, what are you left with. So then you can get estimates of sensitivity and specificity at different cut points in the diagnostic evaluation strategy.

You have got the data. You just haven't presented it in that way.

DR. PARKINSON: Are we ready to consider the questions? Are there slides for the questions? Overheads, whatever? Audiovisual enhancements, I think is the word.

DR. MILLS: I have got some.

DR. PARKINSON: Would you like me just to read them? Doesn't everybody have a copy? Can everyone here read? The first part of Question 1, basically, is a summary of the data. It comments on the sensitivity. Do you want me to read all these things? Okay; thank you.

This is a very important question. 1(a); "Are the data from the Phase-III trial sufficient to demonstrate the efficacy of NR-LU-10, the Technetium conjugate, FAB whole-body imaging, for initial staging of patients with biopsy-proven small-cell lung cancer." So that is the signal question to address this afternoon.

Comments on this? Are we ready to vote on this?

DR. GELBER: I would like to offer an amendment, perhaps. The term "efficacy," I think gets at, really, the issue --

DR. PARKINSON: Of clinical utility.

DR. GELBER: Yes.

DR. PARKINSON: Would you like to change that to -

DR. GELBER: It depends on if we want to vote yes or no. If we want to vote yes, one way is to replace efficacy with performance characteristics or sensitivity and specificity. Or, an alternative, is replace efficacy with clinical utility, or replace it with clinical benefit, which were the three categories that were described as the level of evidence for a test.

DR. JAY SIEGEL: I think that what would be most useful to us would be probably to replace it with clinical utility as the proposal of the sponsor is that this is useful as a first test in screening those patients. Should the vote be no, I think what we would, perhaps, also like to hear more directly about whether, based on performance characteristics or other standards, it should be approved.

DR. GELBER: I will accept that recommendation.

DR. PARKINSON: The alternative would be that 1(c) really address --

DR. OZOLS: That is diagnostic, actually.

DR. PARKINSON: Oh; is it really a little bit different? Okay. So, as written, then, and if people agree, the question is now, "Are the data from the Phase-III trials sufficient to demonstrate the clinical utility of this agent for whole-body imaging for initial staging?"

DR. BARRY SIEGEL: And we are defining clinical utility as indicating that the data support the proposed indication; is that correct? Isn't that what this process is all about?

DR. JAY SIEGEL: Yes.

DR. PARKINSON: I think we ought to be really clear before we vote on this.

DR. BARRY SIEGEL: It is not just some vague notion of utility, it is that the data support the notion that this can be first staging test for patients with small-cell carcinoma of the lung with our innate recognition that if you have already figured it out by the things that you have done, you won't order the test.

I add that as a demur. I think we all know that.

DR. PARKINSON: Dr. Gelber, are you thinking this through? Are you comfortable with that? I think we ought to all agree on what we are talking about with clinical utility before we vote on whether or not --

DR. GELBER: Could you repeat that language exactly again.

DR. PARKINSON: A little more slowly, Dr. Siegel, please, just so we are really clear on this.

DR. BARRY SIEGEL: The real issue is whether or not we believe the data support the proposed clinical indication. That is what the law is all about in this case. I am not a lawyer, but just speaking to that issue. The proposed indication is that this can be used as -- I don't have the language right in front of me --

DR. PARKINSON: The proposed indication for initial staging of patients with biopsy-confirmed small-cell lung cancer.

DR. BARRY SIEGEL: Right. And then the only caveat I added to that was I think we all recognize, as a matter of clinical sensibility, that if, by physical exam, chest X-ray, chest CT and a brain CT that you have already done because the patient has a seizure, you already know the patient has extensive disease, you won't order this test.

We can't necessarily -- well, if you do, it is not very good medicine. But it is not likely you will. We can't, necessarily, answer how big that subset is from the data as they have been presented to us. But I think that is something we have to recognize will be in the background in the use of this drug.

DR. PARKINSON: I am comfortable with that. It defines clinical utility in view of the absolute specific

indication that we are being asked to address this afternoon. Okay. Do we have concordance on this. Okay.

All in favor of the fact that data is sufficient, please raise your hands.

[Show of hands.]

Don't be shy. Either high or -- the "maybes" are hard to see. We have 9.

All against, please raise your hands.

[Show of hands.]

Four. Does that add up to the correct number? Thank you. The question carries, 9 to 4.

Question 1(b); "Does the Committee recommend the approval," I am just going to call it "this agent," "whole-body imaging for initial staging of patients as stated in the sponsor's proposed indication?" What is the difference?

DR. BARRY SIEGEL: That is the same question.

DR. PARKINSON: We just redefined it. Thank you. Is this like an IQ test or something?

1(c); "Please comment on the potential for clinical use of this agent in the diagnostic evaluation of patients with small-cell lung cancer."

DR. BARRY SIEGEL: We already have.

DR. PARKINSON: If there is anybody who is not clear on that, we don't want to know.

Question 2 has a descriptor of the data and then

the last sentence, basically, is that "The sponsor recommends that patients initially staged by this agent as limited disease should have the standard diagnostic evaluation." Do you remember this discussion and the recommendation based on the data from Dr. Salk." Does the Committee concur with the sponsor's recommendation?"

Is there anyone who does not concur with that recommendation? Okay. That was straightforward. Thank you.

Question 3. Again, it is the basic information which we have seen presented including the data from Dr. Berkower in the Phase-I/II clinical trial.

Then we have, "CBER and Thomae agree that the agent imaging should not be used for diagnosis of lung masses or suspected metastatic sites without histologic confirmation of small-cell lung cancer and that the labeling should so indicate." Does the Committee concur? Is there anyone who would speak against this?

I might get perfect on this test. No. 4; it is then a description of the kind of imaging data that we saw from Dr. Nelp and described quantitatively by Dr. Salk. "CBER and Thomae agree that the agent imaging should not be used for detection of the extrahepatic intra-abdominal metastases and that the labeling should so indicate. Does the Committee concur?"

Dr. Siegel?

DR. BARRY SIEGEL: Just a comment, although I concur based on the data as we have seen it, my guess is that things will change because there are a couple of things that are likely to occur in the real clinical practice. Whether this belongs in the labeling based on conjecture versus based on what you already know is a tougher question.

My guess is that, given the pharmacokinetics of this agent, given that uptake in tumors occurs relatively rapidly even though blood clearance is a little bit slower than you would like, people are going to start doing imaging in the 4-to-6-hour window or the 3-to-6-hour window.

They are going to use SPECT and they are going to find these lesions with much higher sensitivity than has been found in this 1989 technology, planar-imaging, study. So I concur with this based on what we know from what has been submitted in the PLA, but I can tell you that in the real world, this will evolve very quickly.

DR. MILLS: A couple of items. No. 1 is I have worked with the sponsor in terms of this concern and question because I think that the same will happen. No. 1, we are going to want to see this in the precautions because we don't want overinterpretation. The interpreters have typically under-read these areas.

No. 2 is asking them, because of their 14- to 17-

hour image time, I fully expect that they are going to walk down this imaging curve. They felt, in their original Phase-I/II studies that they did not get good performance at that time. That is 1988, 1989.

I would anticipate the same. It will be listed as a precaution so that people will not overinterpret loops of bowel as potentially a mass that they are seeing by some other modality.

DR. SWAIN: I just had a question. Should it not also include brain?

DR. MALCOLM: That was my question. I am very concerned. The data that I saw, one of the areas in which this drug particularly is a weak aspect, is the brain. That is my next question before we moved on. Somehow, I think there needs to be some type of information with regards to the reliability --

DR. PARKINSON: I think that is a important point. Is there general concurrence on this?

DR. MILLS: Let me bring back to you No. 2 because, as we are discussing, we are getting farther and farther into labeling considerations. Obviously, as my presentation focussed on that, I will be telling you that, indeed, we will identify this in the package insert. The concern here is not to overrely on this study in certain areas such as the adrenals and such as the brain.

DR. BARRY SIEGEL: One is the false-positive question which is what the abdomen addresses. The other is a false-negative question. That is already addressed in the labeling; namely, that if you get a negative NR-LU-10 result, you go on and do conventional diagnostic tests.

DR. PARKINSON: Okay. The final question talks about future studies and it suggests that we, "Please discuss the potential use of this agent to evaluation response to medical therapy." That gets back to some comments from before.

DR. OZOLS: I think that is a concern because if that is the only test you are going to use, and you can stop with all other tests when you use this test to diagnose advanced disease, extensive disease, then you feel comfortable in giving the patient a couple cycles of treatment because you know that the response rate is only going to be about 40, 50 percent in patients with advanced disease and you are going to stop therapy after two cycles, in the traditional sense, if you had followable disease.

So what are you going to use to follow those patients? I think that is a real concern. Are you going to repeat this test after two cycles? If the test is positive, aren't you going to feel comfortable or feel that you need to have something to give you some followable disease so you know whether to continue after two cycles or not?

DR. PARKINSON: Or knowing that you are going to have to do subsequent imaging studies, like a CT scan.

DR. OZOLS: But if you do one after two cycles, you want to know what the baseline is.

DR. PARKINSON: You want to know what it looked like before.

DR. OZOLS: So you will probably go back and do the CT scans anyway.

DR. DEVOUS: I am confused. Aren't you talking about treating the limited-disease patient in whom you have actually got all the other tests as baseline anyway? You are talking about treating the NR-LU-10-negative patients, aren't you?

DR. PARKINSON: All of them are going to be treated.

DR. OZOLS: You are talking about treating the NR-LU-10-positive patients as well. They are going to get treated with chemotherapy.

DR. DEVOUS: I guess the ones I am asking about are the ones that you would be reimaging.

DR. OZOLS: You reimage extensive disease to make sure that you don't overtreat them.

DR. PARKINSON: That is the clinical consideration here that I would see. Additional comments by the Committee?

DR. GELBER: The question reads, "Are there future studies planned for this potential extension of the indication?" Usually, when we hear about drugs presented, we also hear a little bit about ongoing research. Are there studies ongoing?

DR. PARKINSON: Do you have a "future studies" slide, Dr. Salk?

DR. ABRAMS: It is possible. We already have some data. When we finish with this, we will be taking a look at that to see if the data is either sufficient or if it is insufficient, we will be the first to --

DR. GELBER: So there is no prospective trial that is planned to evaluate this?

DR. ABRAMS: There has been a study that has been done, but it hasn't been analyzed to see whether it was sufficient to submit to such an august body.

DR. PARKINSON: Said augustly. Any other comments from the Committee? Dr. Siegel? Colleagues?

DR. JAY SIEGEL: Is it the sense of this Committee from the discussion that we should pursue with Company the importance of evaluating the utility of this scan for serial --

[Several "yeses."]

DR. MILLS: One of the questions I would have from the clinical design if, indeed, they do proceed with it, is

what would be an appropriate interval for suggestions or recommendations for the design of a readministration trial. In other words, what should we ask the sponsor to be looking for in terms of time interval from the time of chemotherapy and/or radiation therapy.

Those of us who have worked with such things as gallium know that certain tumors would not reimage even in the face of growing in the field. So these are the concerns and that questions and, possibly, if we have some input in terms of the timing appropriateness for it, that would be a question, noting that we did have three patients who did develop positive HAMAs on the first administration, knowing that there may be potential that we are going to have to face that reality that, on the second or third readministration, we are going to have a declining group of patients.

So we were hoping maybe some additional input, if you have any, or suggestions in that design.

DR. OZOLS: That is one of the reasons why I think there is this issue about whether a test like this should be approved on the basis of just simply sensitivity, specificity tests versus the bigger context of clinical utility.

I am still concerned that you are going to want some type of other tests to follow disease in this group of

patients. As Dr. Siegel pointed out, do you really cut the number of tests, diagnostic tests, you do if this is positive? I am not so certain because you want to know what happens after a couple of cycles of treatment.

If the Verluma scan is positive, you may wind up doing the same number of tests anyway just to give you a handle on what your chemotherapy is doing. Then, if that is the case, then there is no utility for this thing.

DR. JAY SIEGEL: If somebody has extensive disease, would it be standard to evaluate the response of all lesions and all types of scans? Or, if you have a positive chest X-ray, would you look at the chest X-ray?

DR. OZOLS: But you are saying the chest X-ray is only positive two out of the --

DR. BARRY SIEGEL: No, no.

DR. JAY SIEGEL: Well, no, no, no. It is positive for extensive disease. I think there was disease in the --

DR. BARRY SIEGEL: My guess is that virtually all of these people have extensive disease in the chest and mediastinum which means you have followable disease by chest X-ray or CT in nearly everyone. You don't measure the response of every single lesion when you follow a response to chemotherapy. You look to see what is going on on the lesions you can get an easy assessment on.

So I really think that we are making this sound

more complicated than it really is in terms of how these people will be followed if they don't get all the other full battery of tests, especially when you acknowledge, as I think we sort of did, that most of them are going to have the chest CT anyway before they even get to the point where they are eligible for this drug.

In answer to your question about using this as a means to follow these patients, this is actually a situation where the disease has a lousy enough prognosis that you actually can use a survival endpoint to look at whether the change in the NR-LU-10 scan after two or three cycles of therapy is predictive of how the patient is really responding to therapy.

I think you can design the trial in a way that you can really look at a very hard endpoint if you chose to do so. If the sponsor doesn't do that trial, I may try to just see if I can write a grant to do it myself.

DR. PARKINSON: Any other comments? If not, thank you all very much.

[Whereupon, at 3:15 p.m., the meeting was adjourned.]

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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