We are now going to proceed --

DR. KENT: Madam Chairman, if I could just add one other thing? Kenneth Kent.

CHAIRPERSON DUTCHER: Okay.

DR. KENT: Relative to the measurements, the whole science of saliva is something which has been blossoming within the last 10 years and there have been major changes in the quantification of the salivary measurements. There currently are no hard and fast gold standards. The best gold standards that exist state that any patient that receives radiation therapy to the salivary glands in excess of 45 Gray will have extremely deleterious morbidity. The major measure is a quality of life issue for these patients. Quality of life issue measures are very difficult for patients because they can only compare themselves to their existing experience. Dr. Lo Presti presents a very valid example. He perceived that he was very dry. His perception. However, when he compared himself to his peer group of patients who received radiotherapy without the benefit of medication, he realized that his morbidity was not nearly as great as

anyone else. It is standard that when a patient sits for an interview, they are constantly sipping water. It is very unusual that a patient can get up and give a 20-minute dissertation after receiving high dose radiotherapy to the salivary glands without having to take a single drink. I think this testifies very strongly to the quality of life change that can occur with this medication.

CHAIRPERSON DUTCHER: Thank you. Thank you very much. Okay. Does anybody need anything else further clarified? I would like to just go with the discussion and then if there are issues that need clarification, we will clarify them. Because it sounds like some of us are confused and we don't want to be confused. Any comments or questions? I will proceed. Ready?

Okay. This application seeks approval for ethyol to reduce the incidence of severe radiation-induced xerostomia, severe being defined as greater than or equal to RTOG Grade 2 acute and late xerostomia. Efficacy data come from a single multi-center randomized Phase III trial in patients with

head and neck cancer. It compares ethyol plus standard fractionated radiotherapy with radiotherapy alone in 303 patients. The patient characteristics were generally well-balanced on the study arms.

The primary efficacy endpoints were acute and late xerostomia, Grade 2 or higher, and acute mucositis Grade 3. There was no difference between the study arms and the incidence of acute Grade 3 mucositis. However, acute and late xerostomia, Grade 2 or higher, were significantly more common on the radiotherapy alone arm. And there you have the tables showing acute and late xerostomia.

Although patients on the RT plus ethyol arm received a higher median dose of radiation therapy than patients on the RT arm, a higher proportion of patients randomized to the RT arm received higher total doses of radiation greater than 6500 Centigray. When patients were grouped according to radiation dose received, an advantage for ethyol was apparent in each group. And there is a table showing incidence of late xerostomia by dose.

Does the trial provide substantial

evidence that ethyol decreases the incidence of moderate to severe xerostomia in patients undergoing radiation treatment for head and neck cancer?

Dr. Simon?

DR. SIMON: I just want to make a general comment. I guess not just specific to this question, but I have a lot of concern about -- I think the whole analysis is data-driven because the sponsor decided to present this at a time prior to the stated time of definitive analysis in the protocol, presumably because of what they believed the study showed, even though it was at a time when according to the curves we see, there are lots of patients who are censored at around 15 months. And I don't believe that that is the way to analyze clinical trials. I don't believe it leads to reliable analysis.

DR. WILLIAMS: Rich, I would like to make a comment. That may be true for tumor data, but I believe for efficacy, when the primary endpoint -- all the data is collected by one year, that these data wouldn't have changed.

DR. SIMON: We are seeing 18-month data

here.

DR. HARWOOD: As a radiation oncologist, I absolutely agree with that. You see xerostomia develop in less than six months and then starts improving after that. So in terms of this drug's ability to protect the salivary glands from the effect of radiation, you will see this at 6 months, 12 months, and probably see even more improvement as the time goes out. So I think in terms of this drug having an effect, and it certainly seems to me that it is having a beneficial effect on xerostomia and acute mucositis, then I think we will have seen it by the time that these patients have been followed. As I have indicated earlier, I think there is somewhat of a concern about tumor protection, but I think that that is less of a concern in the patients that are receiving post-operative radiation, as has been demonstrated from the data from the RTOG. But I have residual concerns about tumor protection in definitive radiotherapy patients. But I really do think that the evidence that has been presented -- and anybody who has ever done quality of life studies in head and neck

cancer know how difficult it is. I started doing this 20 years ago, and I had difficulty demonstrating differences in quality of life between patients who had had their larynxes preserved by radiation and those that had had laryngectomies, believe it or not. So quality of life studies are very hard.

One might suggest that we should initiate the bagel test. Because I agree with the patient advocate that this is one of the most significant effects of radiation in the inability to eat dry bread. This has been amply demonstrated that amifostine in his particular case has improved his quality of life. So forgive me for being a simple man, but I would have understood it better if they had asked the patients randomized into the trial, can you eat a bagel or a piece of toast in the morning or can you not? And I kind of suspect the evidence would have been strongly in favor of amifostine.

DR. WILLIAMS: I'd like to go back to Rich's question, which I believe if we are addressing question number one, as the protocol defined it and as we analyzed it, it was the months 9 through 12 data

that we used to determine late xerostomia, and that was the primary endpoint in the protocol. So for the purposes of that endpoint, additional follow-up would not be helpful.

However, I believe there was an amendment to the protocol changing analysis to later and the purpose of that was to collect more tumor data. But for the purposes of question one, I don't know that that applies.

DR. HARWOOD: I completely agree. You have to look at all the data together. There is a lot of data been produced on this, including the information. The reason that the salivary gland was chosen was that that was protected the most, I think, in the original U.S. Department of Defense data from 25 years ago, and I am sure that is what has led to this trial being done.

DR MARGOLIN: I realize we are not supposed to talk about the package insert before we vote, but I think it is important because the question has been raised by the FDA and by Dr. Harwood and some of us are also concerned about the inability or the

underpowered state of the current data to really reassure us that tumor protection is not being afforded. And if this gets out, obviously with all of the other kinds of things that are being done in head and neck cancer, and the use of platinum which is a drug for which this protector is already approved, one can just imagine all the other situations that it will be used for very different than the patients that were in this study. So the question is whether that package insert will say something specific about postoperative resected head and neck patients undergoing radiation alone, for example, as opposed to chemoradiotherapy or as opposed to patients with primary definitive therapy being given for an unresectable tumor.

DR. HARWOOD: I was actually -- I actually prepared a few comments and you have kind of hit the nail on the head. I think that this -- it is my opinion that the drug is protecting salivary function. It is also my opinion that there is enough data in the trial to support its use in patients who are receiving postoperative radiation. I personally would be

hesitant to recommend it at this point in time in definitive radiotherapy patients because I don't think that we have enough patients entered into the trial to permit us to be absolutely confident that there is no tumor protection, even though I think it is very unlikely to be the case.

One interesting piece of information is that this drug has been approved in renal protection and ovarian cancer for cisplatin, and there is five-year data on that to suggest that there is no tumor protection. Interestingly in head and neck cancer, increasingly cisplatin plus or minus 5FU is used as a predictor of radiation responsiveness, in that in the VA laryngeal cancer study patients who are given up-front chemo, primarily cisplatin, and if they responded they went on to radiation and had laryngeal preservation, and if they didn't, they went on to surgery. So I regard the ovarian cancer study as very significant in that we have five-year data to support the fact that amifostine is not protecting and producing a lower responsiveness in the ovarian cancer patients. But I personally would be hesitant to

recommend it right now until more data is accumulated in the definitive radiotherapy patients.

This drug, I think, also becomes more important because more and more patients are now receiving hyperfractionated radiotherapy and chemotherapy and radiation, which all of us know produces significantly increased mucosal toxicity. There has been some discussion here about toxicity of amifostine, but the toxicity and morbidity of amifostine is vastly less than what one sees in patients getting simultaneous chemo and radiation for head and neck cancer.

I remember an early study in chemo and radiation in head and neck cancer, and one would start off with 150 patients and due to the lifestyle of these patients, of which we are all aware, only 25 completed the study. So I find it absolutely extraordinary that in fact the sponsor has in fact been able to get as many patients through this study as in fact they have.

So I also would think that it probably could be approved in the chemoradiation advanced head

and neck patients, because those patients get profound mucositis. And in the two supporting studies, I think they showed a significant reduction in mucositis in them. So I really am personally in favor of some kind of limited approval, but not blanket approval such as they gave in the United Kingdom.

DR. WILLIAMS: It is quite possible to go ahead and answer this question number one just for the efficacy and then have some other answers for others such as tumor control.

CHAIRPERSON DUTCHER: I think we have to remember that the question is asking only about xerostomia. Only about salivary production, not about mucositis. So does this trial provide substantial evidence that ethyol decreases the incidence of moderate to severe xerostomia in patients undergoing radiation treatment for head and neck cancer, and I guess through endpoints months 9 through 12. All those who would vote yes? 11 yes. Voting no? Okay, one no. Carolyn Beaman voted no. So two no. Okay.

The next issue is salivary measurements. Clinically meaningful levels of saliva production in

time categories for saliva collection analysis were defined retrospectively. In the analysis of unstimulated saliva collection, the applicant used greater than .1 gram of saliva as the cutoff for adequate function. They used the time window of one year's follow-up defined as 6 to 15 months after treatment, and noted a significant difference in favor of the ethyol arm. 63 patients with adequate function on the ethyol arm versus 43 patients in the RT arm with a P value of .003. The analysis of stimulated saliva collections by the applicant and longitudinal analysis of unstimulated saliva collections by the FDA did not show statistically significant differences between study arms.

Do the results of the salivary measurements provide supportive evidence that ethyol reduces the incidence and severity of late xerostomia? Dr. Margolin?

DR MARGOLIN: I am sorry, I must either be misinterpreting this slide or these numbers may be wrong. But on page 19, again these bars suggest that the total number studied was only 63 in the amifostine

arm and the number studied was 43 in the RT alone arm, and that these are the percentages of --

CHAIRPERSON DUTCHER: I think those are the n's.

DR MARGOLIN: Can those be clarified?

CHAIRPERSON DUTCHER: Those are the n's, I believe, on the slides, correct?

DR. WILLIAMS: I believe you are looking at a different analysis. This was the sponsor's analysis, not the one done by Gani.

DR MARGOLIN: But the numbers were identical. That is why I was querying that.

CHAIRPERSON DUTCHER: Those are the n's.

DR MARGOLIN: So in the question, what do 63 and 43 --

DR. RUSSELL: Let her comment on the slide first.

DR. RUSSELL: The n's are actually the numbers of patients who had more than .1 gram. So it is 72 percent of those patients who were actually analyzed for this endpoint and 49 percent of those patients analyzed for this endpoint respectively.

CHAIRPERSON DUTCHER: And what are those denominators?

DR MARGOLIN: Is 63 the denominator or the numerator?

DR. RUSSELL: The numerator.

DR MARGOLIN: So the 22 percent is the previous number that the patients -- the 97 and the 106 is the denominator?

DR. RUSSELL: The level -- approximately those numbers. They are slightly less in both treatment arms.

CHAIRPERSON DUTCHER: It says late xerostomia -- on page 15, late xerostomia at one year patients available data, n equals 97 for amifostine and n equals 106 for RT. And then here we have unstimulated saliva at one year, 63 had the number that was .1 gram or greater. So that 63 is 72 percent of the 97 roughly speaking. Close enough. Is that right? That is right. Okay. So, a comment, Dr. Lippman?

DR. LIPPMAN: I do think the salivary measurements are supportive. I was concerned initially

when I saw the .1 cutoff and it was defined unfortunately later on. But I think when -- listening to the presentation and seeing the median saliva levels, it looks as though -- this data looked at from several angles seems to be supportive. So I do feel that the salivary data is supportive and that there is no accepted standard.

DR. SIMON: Well, I think it is difficult to make a judgment here. When two different analyses give what appears to be two totally different answers, I think there needs to be some assessment as to why they are giving different answers. And what it is about the data that is -- does doing things from baseline just add a lot of variability to data? I think there needs to be a more in-depth analysis myself before I could make a judgment. I think it is difficult. There is a lot of missing data, which is very understandable. But for myself, I think that really when you -- I don't like the use of cutoffs like that. I would have rather just seen sort of a more straight forward analysis without introducing thresholds, particularly when you haven't defined the

thresholds prospectively in the protocol. So I am just left with concern one way or the other.

DR. HARWOOD: I hate to come back to this, but you have to understand the patient population that you are dealing with. And I think -- and one has to look at the lifestyle of the patients that we are studying. And this is different. And it is very difficult, let me tell you, to have the follow-up levels. As a clinician that has treated hundreds and hundreds of these patients, it is very hard to get these patients to come back for follow-up, and it is very hard to get them to do these various studies of saliva functions. So I personally think the numbers of patients that they have got to measure the saliva is extraordinarily high given the patient population that you are dealing with. I really do.

DR. SIMON: I meant to imply that. That it was not a criticism of the study. That for this patient population, I think that was good. But still you do not want to be left with doing the analysis two ways and getting two totally different answers.

DR. LIPPMAN: But at least in terms of the

unstimulated saliva, on page 18, the medians are different as well. So the cutoff issue I have the same concern, but it does look as though when you look at the data in different ways, at least the unstimulated data seems to be consistently supportive.

DR. SIMON: As long as the pre-treatment medians wouldn't be different also.

CHAIRPERSON DUTCHER: Dr. Schilsky?

DR. SCHILSKY: Just one other comment about that. I mean I guess looking at it from the clinical perspective, there doesn't seem to me to be any particular rationale to have chosen the FDA's analysis method of looking at change from baseline. I personally actually was quite persuaded by the comments from the sponsor that what is important is where you end up at the end of the treatment. Because the bottom line is is your mouth wet or dry when you have completed all the treatment. And who cares how wet it was when you started.

DR. HARWOOD: Exactly right. And it comes down to can you eat a bagel or can you not.

CHAIRPERSON DUTCHER: So the Phase IV

study is going to be bagels. Other comments? All right. Do the results of the salivary measurements provide supportive evidence that ethyol reduces the incidence and severity of late xerostomia. All those who would vote yes? 12 yes and one no. Carolyn votes no. Okay.

Patient benefit questionnaire. As described in the presentations, analytical plans for this parameter were submitted retrospectively. Consequently, the applicant and the agency chose different methods of analysis. The applicant evaluated the overall mean of the 7 subscales of the PVQ and found a statistically significant difference in favor of ethyol 7 months and one year after completion of therapy. The longitudinal analyses by the FDA looked at three discrete areas identified by the reviewers as most clinically significant -- functional well-being, global assessment of dryness and use of external aids and found trends in favor of ethyol.

Do the results of the patient benefit questionnaire provide support to this application?

Dr. Sledge?

DR. SLEDGE: This kind of gets back to the methodologic question I was asking earlier. If this scale has been used previously and has been used in the way that the sponsor used it previously, then I don't see any particular reason why we should take the FDA as opposed to the sponsor way of analyzing this. If it hasn't, then it is a flip of the coin as to which one to accept. But my understanding from what I heard was that it has indeed been used before and it has been used in head and neck cancer.

DR. WILLIAMS: We certainly had no evidence submitted to us that it had been used in another trial and that it had been connected up to a particular clinical event. I mean our tendency to frown upon lumping of a bunch of different subscales is we don't know what it means when you get through. I mean, what does it change on the scale versus a particular subscale may ask a question and you can at least calibrate it to that question. There is a 2 point change on this question dealing with a specific name. So that is where our philosophy came from. But

we had nothing submitted to us to indicate it had been used in other trials in support of it.

CHAIRPERSON DUTCHER: I want to make one comment from the sponsor.

DR. MACKOWIAK: Sorry, just to clarify. The instrument had been used in other studies, pilocarpine studies. However, non-significant findings, of course, are rarely published. And we talked about the difficulty of finding a difference. So when we looked to the literature to find publications of instruments, we are not going to see it there. So it has been used.

CHAIRPERSON DUTCHER: Thank you. Dr. Nerenstone?

DR. NERENSTONE: I think even the FDA said that their analysis was trending in favor of it. It is descriptive. I think that is all you can say. Does it tend to support the application? Yes, it does. In a statistical hard-nosed way, no it doesn't. Next question.

CHAIRPERSON DUTCHER: She has to get out of here.

DR. HARWOOD: Amen to that.

CHAIRPERSON DUTCHER: Okay. We are voting. Do the results of the patient benefit questionnaire provide support for this application? Those who would vote yes? 11 yes. I am abstaining. And the patient rep voted no.

Tumor control. In the evaluation of cytoprotective agents such as ethyol, one must consider the adequacy of evidence demonstrating that the cytoprotective agent is not protecting the tumor from anticancer treatment. In this case, the FDA determined that relatively large trials in patients with head and neck cancer would be needed to rule out such a tumor protective effect relative to radiation therapy. The most relevant data submitted is from the randomized control study discussed above. In this trial, no difference was noted between the arms in time to local/regional recurrence, disease-free survival and overall survival. The lower bound of the 95 percent confidence intervals cannot exclude the possibility that ethyol is 36 percent, 31 percent, and 13 percent inferior respectively.

The sponsor also cites data from a 100 patient randomized study of radiation therapy plus/minus ethyol in rectal cancer, and data from a randomized trial of chemotherapy plus/minus ethyol in ovarian cancer.

Is there adequate evidence that ethyol does not protect tumors during treatment of head and neck cancer with radiation therapy?

DR. HARWOOD: This is where I have expressed concerns already. I think that the problem with the trial to some degree was the large number of patients who were postoperative patients who have been resected for cure, albeit though they have a fairly high frequency of recurrence. And the relatively small number, one-third I think, of definitive radiotherapy patients entered into the trial. I have already talked about this. So I believe that there is enough data to say this drug is not tumor protective in the post-operative patients. But I personally would prefer to see more definitive radiotherapy patients treated and followed for a longer period of time. Because it is those patients who I think

conceivably could be at risk from three to five years out of having a 5 to 10 percent difference in survival. I don't know that that is the case, and there is no evidence that that will be the case. But I think that there has just not been enough follow-up on that group of patients for me personally to recommend its use in that area.

So I would think that we do have enough information on the postoperative patients, because that is the large group in the trial. And those patients do, as has been discussed, tend to recur early. But in the definitive group of patients, I would be somewhat more hesitant because there are just not that many patients that have been entered. And the supporting studies, the rectal cancer study, I think, is really irrelevant. These are patients being treated palliatively with radiation for rectal cancer. There are two other supporting studies which are chemoradiation studies, but the follow-up in those patients is short and the number of events and recurrences are less than 5, I do believe.

So I think that we have enough patients

followed for long enough who are postoperative, but in the definitive radiotherapy patients, I would personally prefer to see larger numbers of patients followed for longer periods of time to be absolutely certain on that issue. And I think that is a very important issue.

CHAIRPERSON DUTCHER: Dr. Williams?

DR. WILLIAMS: Could you clarify what you mean by -- I mean wording you might use in labeling by a postoperative patient? Which patients who are going to have surgery and radiation do you think this might be indicated for?

DR. HARWOOD: These are patients that have had a curative resection and had all gross tumor removed but have positive margins or extracapsular extension and things like that. The definitive patients are patients who have never had surgery and who are receiving radiation for cure, of course. So the postoperative patients, both the high and low risk -- and I think they had a good definition of the -- the sponsor had a good definition of this.

CHAIRPERSON DUTCHER: Dr. Margolin?

DR MARGOLIN: Yes. I would like to strongly agree with that and support that. And I think it would be very, very unwise for us to take any -- to put any faith in the data against tumor protection in other histologies for which other treatments are given. We have many examples in oncology where things that would appear to be interchangeable are not.

CHAIRPERSON DUTCHER: Mr. Gruett?

MR. GRUETT: I think the key word here is adequate, and I don't think that has been demonstrated.

CHAIRPERSON DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I think we all have the same concerns. And I guess one thing I am unclear about is I suspect that the design of this trial was based upon the total number of patients entered with respect to ability to look at non-inferiority. So once you start to break-out these subsets, I don't know that we have any sufficient power in any subset to be able to conclude with a reasonable level of confidence that there is not an inferior outcome for

the amifostine-treated patients. Maybe somebody could comment further on that. But I am just -- I mean I think that the concerns are completely valid about we don't have enough events yet to determine that there is not actual tumor protection. But I don't know that the solution to that problem is to start to break it out into subsets. Because I have a feeling then that the patient numbers are going to be too small to be able to draw any conclusion with confidence.

DR. HARWOOD: Well, I think that we have 200 patients, I believe, give or take that are the postoperative patients. And as has been discussed and I completely agree with that 90 percent of these recurrences occur within the time frame of these patients that have been followed. And I think the additional supplemental RTOG data that was presented is very supportive of that. So I really do think that we have enough patients followed for long enough in that group. And there is absolutely -- I would add that there is absolutely no hint of tumor protection in any of this data, nor in any of the other data that has been accumulated through the years. So I kind of

have a feeling that my worries about the definitive radiotherapy group are kind of theoretical, and in the fullness of time will not prove to be correct. But I really think that it will be prudent to do that.

But I really strongly believe, as a radiation oncologist treating many head and neck cancer patients, that I would be comfortable treating the postoperative patients with amifostine.

CHAIRPERSON DUTCHER: Dr. Lippman?

DR. LIPPMAN: I have a real concern similar to Dr. Schilsky about taking out subsets from this trial to make recommendations. I mean, this was a very well-designed, well-powered large trial for this disease, and I would just be very concerned to make recommendations from subset analyses within this trial. And that was why I made the comment, because you addressed this earlier about the chemoradiation. I don't think we can make any comments about that. I think that needs to be clarified in the recommendation. But in this case, to subsect based on any of these stratification factors I think is going to be problematic.

CHAIRPERSON DUTCHER: Dr. Margolin?

DR MARGOLIN: I think you are absolutely right about that. Because this is -- what we were talking about was actually a subset and not the complete patient population here. But I think what you end up having to do in the package insert is not to put it in the first sentence of the indication that it is only for post-op NED patients, but rather to go into extensive detail in the package insert that certain populations of patients were not studied in sufficient detail to allow this indication to apply to them or to recommend it, such as chemoradiation or definitive radiation patients.

CHAIRPERSON DUTCHER: Dr. Ozols?

DR. OZOLS: Dr. Chico, you concluded that it was premature. But since most of the events have taken place, do you think there will be more data coming from this trial with longer follow-up?

DR. CHICO: I would think there would be, although the cutoff point that was determined was up to 18 months, and that was the extent they provided to the agency.

DR. WILLIAMS: It sort of depends on what kind of patients were entered and how long -- I am not sure -- maybe the sponsor might have a comment.

DR. BRIZEL: Thank you very much. I think we are getting to the crux of the issue here which is what is the natural history of this disease. And in other diseases -- prostate cancer and breast cancer, for example -- the natural history of the disease may be 15 or 20 years. And certainly within that context, absolutely with longer follow-up, you would expect to see more events. But in head and neck cancer, not just through the RTOG data base, but if you look at the article that I published in the New England Journal. If you look at articles or institutional experiences and cooperative group experiences just about anywhere, you see that 80 to 90 percent of all of the events that are going to occur do so within this 12 to 18 month framework. So with all due respect, I think that the likelihood of seeing more events with longer follow-up is probably pretty small. And again, the events that we have seen have been local/regional events. And so when I look at this, I

see the natural history of the disease again. The problem with not having "enough events" is that compared with ovarian cancer or the Liu study, which was unresectable rectal cancer, a much greater proportion of these patients are cured of their disease. So there aren't as many events to occur. And in order -- I am no statistician and I don't pretend to be, but if we want to look at the number of events that we are talking about to prove non-inferiority, we are looking at a very minimum of doubling the size of the study population, if not a tripling or a quadrupling. And to put that in the proper perspective for this group of patients, the largest study randomized trial in head and neck cancer was an RTOG forearm randomized trial that accrued 1,100 patients on it. Only 1,100 and took six years to get there. The next largest was the British chart study, which again took many, many years and only had 900 patients. So I think it is very important to keep these issues to frame the context of the discussion. Thank you.

CHAIRPERSON DUTCHER: Yes, Mr. Gruett?

MR. GRUETT: I am a cancer survivor. I had throat cancer. My entire throat has been removed. And I worry about this drug. My doctor has told me that my chances now -- I am in recovery for two years -- are very good. I am probably 98 percent cancer free. But if I was on this drug, I would worry because we don't have information that goes beyond two years, and I am a patient. And for my own self, the benefits I don't think overcome the gamble that takes place in this unknown period of time between the two and five year period that I was explained that cancer could reoccur. So my feelings are I am afraid of it. Because we don't have enough information. I guess fear is the unknown and we are lying in an unknown area right here. Because maybe it has suppressed the cancer, but it didn't remove it. So I don't think there is enough info yet.

CHAIRPERSON DUTCHER: Dr. Simon?

DR. SIMON: I think the issues are difficult. Dr. Chico quoted a figure before of 190 or 200 events needed for an equivalence trial, and that is the kind of thing you might calculate ahead of time

once you actually have data that power doesn't really become the definitive issue because you have some of the data already. On the other hand, I personally always like to see two studies, just because one study can and has been sometimes a fluke. And in this particular case, the study looks pretty convincing. But in terms of -- I looked at what was shown for the RTOG data and it was not true that 80 or 90 percent of the events occurred by 12 to 15 months. Once you got to 2 years, yes, the curves plateaued then. But certainly not at 12 months. So I think some points are being stretched here. I think there was sort of a rush to present this at a time when we could have had a little bit more follow-up, although probably not enough to make a difference.

Personally I am torn between the fact that I really like to see two studies, because I think one can be misleading, and on the other hand I know that studies in this population are very difficult to do and this is a drug that looks like it has some real advantages to offer to the patient. So I think it is a difficult judgment.

I think with regard to the issue that was raised in terms of subset analysis, I don't -- a lot of times we say we want to stay away from subset analysis, and that is in a situation where we see ineffectiveness sort of across the board except possibly for a subset. And there, I think it is very compelling to sort of stay away from subset analysis and then recommend some approval for some subset which may just be a random finding. Here I think we have reason to believe that some subset of patients really warrant longer follow-up and that they were not well represented in this trial. I think the cautious thing -- it may be appropriately cautious to not recommend approval of the drug for that subset. And also that may lead to then another study in that group of patients, which I think would really be good to me for a drug that really offers something to cancer patients where most drugs don't. I think it is appalling that we should not be able -- for a common disease, we should not be able to have two good studies.

CHAIRPERSON DUTCHER: Dr. Wasserman?

DR. WASSERMAN: Yes. Todd Wasserman,

again, radiation oncologist from NSU. Gail Broder eluded to the fact this morning that there was an ASCO panel which has deliberated over the last roughly year and a half and whose report has gone through the board and is pending publication. And we wrestled with the issue -- I was on the panel too and we wrestled with the issue of tumor protection. And one, we recognized that tumor protection was a theoretical risk only. I mean, there was really never any data to suggest that tumor protection would occur. There was always a worry that it could occur. And so you had to prove the null effect essentially, the lack of any effect on the tumor. And it was concluded that this was something that would just take forever, number one, and has been part of the baggage that this drug has carried around all this time. So I can tell you that the writing in the ASCO report, for whatever it is worth, is that it is a theoretical risk only.

DR. LIPPMAN: I'd just like to address the issue of two studies. This is the area that I work in and I would like to sort of highlight what Dr. Brizel just said. In head and neck cancer, this would be

considered a very large, well-done definitive trial. The trials that usually come out are like the ones mentioned with 40 patients randomized and things of this sort. And the VA cooperative study program larynx preservation trial, which was really a landmark trial, had 330 patients. So personally I would go with a well-designed large randomized trial as opposed to two or three studies of 50 patients, which is common in the head and neck literature. It doesn't address the issue we are talking about in terms of tumor control, but in terms of definitive studies in this area.

CHAIRPERSON DUTCHER: Okay. Is there adequate evidence that ethyol does not protect tumors during treatment of head and neck cancer with radiation therapy?

DR. WILLIAMS: Janice, do you want to modify the -- yes, that is what I wanted to ask. There has been some talk about modifying the question.

CHAIRPERSON DUTCHER: All right. Are you ready? Turn the page. Is there adequate evidence that ethyol does not protect resected tumors? I guess

it wouldn't. Would you like to make a stab at this question?

DR. WILLIAMS: Dr. Harwood, you are on.

DR. HARWOOD: Is there adequate evidence -- sorry, just give me the first part and I will go on from there.

CHAIRPERSON DUTCHER: Oh, you don't have the question?

DR. HARWOOD: Is there adequate evidence that ethyol does not protect tumors during treatment -- during postoperative radiation treatment of head and neck cancer with radiation therapy? Now I am doing a double positive there, but I think that is -- or is there adequate evidence that ethyol does not protect tumor during postoperative radiation treatment of head and neck cancer?

CHAIRPERSON DUTCHER: All those who would vote yes? 8 yes. All those who would vote no? One -- and we have two from the other two members. Three, no. Abstain? Did you vote? What did you vote?

MR. GRUETT: Yes.

CHAIRPERSON DUTCHER: You voted yes. So

then 9 yes. 9 yes and 2 no. All right. Now to safety profile. There were significantly more severe adverse events, more missed radiotherapy sessions, and more hospitalizations in the amifostine plus radiotherapy arm. Adverse events attributed to ethyol are listed in the following table. Regulations require that substantial evidence of effectiveness be demonstrated through adequate and well-controlled investigations. In most cases, the FDA has required more than a single trial. As noted in the 1998 FDA guidance for industry, providing clinical evidence of effectiveness for human drug and biologic products, in other cases FDA has relied on only a single adequate and well-controlled efficacy study to support approval. Generally only in cases in which a single multi-center study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit such as an effect on survival and a confirmatory study would have been difficult to conduct on ethical grounds.

DR. WILLIAMS: Janet, I would like to make an additional comment. The comment here is from a

guidance on clinical effectiveness for drugs, and the sponsor was very attentive to this guidance and noted on page 13 that it expands a little bit on the survival and also mentions irreversible morbidity as a suitable endpoint. So we could add that in there if you wanted.

CHAIRPERSON DUTCHER: That's a good term. So an important clinical benefit such as an effect on irreversible morbidity, et cetera. Considering the efficacy evidence presented from this single randomized Phase III study, considering the safety data and considering the data on tumor protection, should ethyol be approved to decrease the incidence of moderate to severe xerostomia in patients undergoing radiation treatment for head and neck cancer? All those --

DR. WILLIAMS: You are going to amend the question to be postoperative again, aren't you?

CHAIRPERSON DUTCHER: Postoperative. Undergoing postoperative radiation treatment for head and neck cancer. Is that what you were -- Dr. Simon, is that what your comment was? Other comments? Dr.

Lippman?

DR. LIPPMAN: Although it is unusual to give simultaneous chemotherapy with postoperative, it is occasionally done and maybe later on in the description, as you pointed out, you could indicate that it is for single modality radiation alone.

CHAIRPERSON DUTCHER: I think the FDA pretty much understands that. Any other comments? No. All those who would vote yes on question 5? 9 yes and one qualified yes and one very narrow indication yes. So that was 11, I think. Any no? One no. And I think the qualified yes, again, is the same issues that came up and the narrow indication seems to be the same issues that related to postoperative. So 11 yes and one no. Thank you very much.

(Whereupon, at 4:38 p.m., the meeting was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: 62ND MEETING

Before: ONCOLOGIC DRUGS ADVISORY COMMITTEE

Date: JUNE 8, 1999

Place: SILVER SPRING, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Irene Gray

Look-See Concordance Report

- - -

UNIQUE WORDS: **3,934**
TOTAL OCCURANCES: **23,448**
NOISE WORDS: **385**
TOTAL WORDS IN FILE: **59,068**

- - -

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CASE SENSITIVE

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- - -

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