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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

RADIOLOGICAL DEVICES PANEL MEETING

OPEN SESSION

Monday, November 6, 2000

10:00 a.m.

Room 020B
9200 Corporate Boulevard
Rockville, Maryland

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Ernest L. Stern, Industry Representative

TEMPORARY VOTING MEMBERS

Geoffrey S. Ibbott, Ph.D.
Minesh Mehta, M.D.

TEMPORARY NON-VOTING MEMBER

Robert Ayres

FDA

Daniel Schultz, M.D.

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P R O C E E D I N G S

Introductory Remarks

DR. GARRA: I call this meeting of the Radiological Devices Panel to order and would request everyone in attendance to be sure and sign in on the attendance sheet that is available outside the door.

I note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14.

At this time I would like each panel member at the table to introduce him or herself and state his or her specialty, position, title, institution, and status on the panel.

I am starting out with myself. I am Brian Garra. I am Professor of Radiology at University of Vermont, College of Medicine, and I am the chairman of this panel.

DR. MALCOLM: My name is Arnold Malcolm. I am a radiation oncologist in California. I am the Director of Radiation Oncology Department, St. Joseph Medical Center, also Cancer Center Director at California Hospital Medical Center in Los Angeles.

DR. TOLEDANO: My name is Alicia Toledano. I am a biostatistician. I am on the faculty at Center for Statistical Sciences at Brown University, and I am a regular voting member on the panel.

DR. HARMS: I am Steve Harms. I am Professor of

1 Radiology, University of Arkansas. I do primarily
2 diagnostic radiology, mainly MRI. I am a regular panel
3 member.

4 DR. SCHULTZ: My name is Dan Schultz. I am a
5 general surgeon by training, currently the Deputy Office
6 Director for the Office of Device Evaluation and the Acting
7 Director of the Division of Reproductive Abdominal and
8 Radiological Devices here at CDRH.

9 MR. STERN: I am Ernest Stern. I am the President
10 of Thomson Components, industry member, non-voting.

11 MS. PETERS: My name is Marilyn Peters. I am the
12 Patient Health Education Coordinator for the Department of
13 Veterans Affairs, West Los Angeles Medical Center, and I am
14 a consumer representative and non-voting member.

15 MR. AYRES: I am Robert Ayres, U.S. Nuclear
16 Regulatory Commission, guest panel member and non-voting
17 with corresponding regulatory interest in these products.

18 DR. IBBOTT: I am Geoff Ibbott. I am the Director
19 of Medical Physics at the University of Kentucky Medical
20 Center in the Department of Radiation Medicine there, and I
21 am temporary voting member on the panel.

22 DR. MEHTA: I am Minesh Mehta. I am a radiation
23 oncologist. I am Associate Professor and Chair of the
24 Department of Human Oncology at the University of Wisconsin.
25 I am also a temporary voting member on the panel.

1 MR. DOYLE: I am Bob Doyle. I am the Executive
2 Secretary of this panel.

3 DR. GARRA: What I would like to do now is
4 introduce Dr. Bernard Statland, Director of the Office of
5 Device Evaluation, who would like to say a few words and
6 just make a small presentation.

7 **Service Award Presentation**

8 DR. STATLAND: Good morning. Many of you I have
9 seen only for the first time and I welcome you. This is my
10 fourth month on the job, so I am relatively new. I am the
11 Director of the Office for Device Evaluations, and the good
12 news is you are in the same building where I am located, so
13 it is relatively easy for me to come down one floor and also
14 to our visitors, we welcome you, as well. It sounds like
15 there is a very exciting day ahead of you.

16 As life has it, the snowstorm prevented the
17 recipient of an award from being here, someone that you know
18 well, Dr. Patricia Romilly-Harper, her term is going to
19 expire the coming year. She will continue to work as a
20 consultant I guess as needed, and I would just like to
21 acknowledge the time and effort that she has put into this
22 effort. Unfortunately, she can't be here, but we will
23 certainly send her her plaque.

24 Without any further ado, I would like to program
25 to continue, welcome you, and wish you a very good day.

1 Thank you.

2 DR. GARRA: Thank you, Dr. Statland, and welcome
3 onboard, a little bit belated, though.

4 Next on the agenda, Dr. Robert Phillips, the Chief
5 of the Radiology Branch of the Office of Device Evaluation,
6 would like to give a brief update on FDA radiology
7 activities.

8 While he is setting up, I would like to mention
9 there is a handout out in front of the room. It is titled
10 "Discussion Points for SIR-Spheres," and the discussion
11 points on that sheet are incorrect compared to the one that
12 the panel has, so if you notice some discrepancies, somehow
13 the wrong form got copied, so there will be some other
14 discussion points that are brought up.

15 MR. DOYLE: At noontime I will make some copies of
16 the actual fine points that we are going to have, and I will
17 have them out on the table, so you can pick them up at noon.

18 **Update on FDA Radiology Activities**

19 DR. PHILLIPS: Good morning. What I would like to
20 do is bring you up to date on what has happened in the
21 Center in Radiology regarding our major approvals.

22 Since the last meeting, which was December 16th,
23 we have gone ahead and approved the General Electric
24 Senographe, which was a digital mammography system. In that
25 case, you have in your packages, copies of the approval

1 letter and the Summary of Safety and Effectiveness.

2 I don't know how much you know about our internal
3 processing, but when we approve a PMA, we have to write what
4 is called a Summary of Safety and Effectiveness, and it is
5 the Center's rationale for the approval. You have that in
6 your package.

7 Other devices that we have approved: from McCue
8 PLC, which is a Bone Sonometry System; from Sunlight
9 Ultrasound Technology, the Sunlight Omnisence, which again
10 is a Bone Sonometer; from Metra Biosystems, the QUS-2
11 Calcaneal Ultrasonometer; and from Osteometer Medtech, the
12 DTU-ONE Ultrasound Scanner.

13 So, we did the Senographe, which was the digital
14 mammography, and four ultrasound sonography machines. If
15 you are interested in getting more background information on
16 any of these, the summaries and all supporting information
17 is located at these web sites which I have listed.

18 We don't have the Osteometer material up yet, but
19 it will be up there very soon.

20 Thank you.

21 DR. GARRA: Are there any questions?

22 [No response.]

23 DR. GARRA: Thank you, Bob.

24 At this point, Mr. Doyle would like to make some
25 introductory comments and remarks.

FDA Introductory Remarks

MR. DOYLE: Thank you.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government. Therefore, waivers have been granted for Drs. Arnold Malcolm and Steven Harms for their interest in firms that could potentially be affected by the panel's recommendations.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the Agency also took into consideration a matter regarding Dr. Geoffrey Ibbott's who reported an interest in a firm at

1 issue, but in a matter that is unrelated to today's agenda.
2 The Agency has determined therefore that he may fully
3 participate in all discussions.

4 In the event that the discussions involve any
5 other products or firms not already on the agenda for which
6 an FDA participant has a financial interest, the
7 participants should excuse him or herself from such
8 involvement, and the exclusion will be noted for the record.

9 With respect to all other participants, we ask in
10 the interest of fairness that all persons making statements
11 or presentations disclose any current or previous financial
12 involvement with any firm whose products they may wish to
13 comment upon.

14 Now I would like to read the appointment to
15 temporary voting status.

16 Pursuant to the authority granted under the
17 Medical Devices Advisory Committee charter, dated October
18 27th, 1990, and as amended August 18th, 1999, I appoint the
19 following individuals as voting members of the Radiological
20 Devices Panel for the meeting of November 6, 2000, and the
21 two are Geoffrey S. Ibbott, Ph.D., and Minesh P. Mehta, M.D.

22 For the record, these individuals are special
23 government employees and consultants to this or other panels
24 under the Medical Devices Advisory Committee. They have
25 undergone the customary conflict of interest review and have

1 reviewed the material to be considered at this meeting.

2 This appointment is signed by David W. Feigle,
3 Jr., Director, Center of Devices and Radiological Health.

4 One other thing I will point out for those who
5 picked up a list of participants at this meeting, as Dr.
6 Statland mentioned, Dr. Romilly-Harper, who had intended to
7 come but was caught in a snowstorm, is not here today, and
8 Lawrence W. Way, who is also listed, could not make the
9 meeting.

10 Thank you.

11 DR. GARRA: Thank you.

12 MR. DOYLE: Now, if anyone has anything to discuss
13 concerning these matters, please advise me now and we can
14 leave the room to discuss them.

15 The FDA seeks communication with industry and the
16 clinical community in a number of different ways. First,
17 FDA welcomes and encourages pre-meetings with sponsors prior
18 to all IDE and PMA submissions.

19 This affords the sponsor an opportunity to discuss
20 issues that could impact the review process. Second, the
21 FDA communicates through the use of guidance documents.
22 Towards this end, FDA develops two types of guidance
23 documents for manufacturers to follow when submitting Pre-
24 Market Application.

25 One type is simply a summary of the information

1 that has historically been requested on devices that are
2 well understood in order to determine substantial
3 equivalence.

4 The second type of guidance document is one that
5 develops as we learn about new technology. FDA welcomes and
6 encourages the panel and industry to provide comments
7 concerning our guidance documents.

8 I would also like to remind you that the meeting
9 of the Radiological Devices Panel tentatively scheduled for
10 the first half of next year are February 5th and May 14th.
11 You may wish to pencil in these dates on your calendar, but
12 please recognize that these dates are tentative at this
13 time.

14 That is all I have, Dr. Garra.

15 **Open Public Hearing**

16 DR. GARRA: We now are ready to proceed with the
17 first of two half-hour open public hearing sessions for this
18 meeting. The second half-hour public hearing session will
19 occur following the panel discussion.

20 At these times, public attendees are given an
21 opportunity to address the panel and to present data or
22 views relevant to the panel's activities.

23 Are there any attendees here today that wish to
24 address the panel?

25 [No response.]

1 DR. GARRA: I don't see any. Does anyone else?
2 Okay. I guess that shortens that section of the
3 meeting considerably.

4 **Charge to the Panel**

5 DR. GARRA: We now are ready to proceed with the
6 open committee portion of the meeting. This meeting has
7 been called for consideration of PMA 990065 for an embolic
8 radiation therapy device.

9 We are now ready to proceed with the sponsor's
10 presentation of the PMA. The first speaker from SIRTEX
11 Medical Ltd. will be Ms. Monica Hope.

12 MR. DONALD: May I make some introductory
13 comments?

14 DR. GARRA: Yes. Go ahead.

15 **Presentation on P990065 by Sponsor**

16 **Introduction**

17 MR. DONALD: My name is Alan Donald. I am a
18 regulatory and clinical affairs consultant stationed in San
19 Diego, California, and I have been asked by SIRTEX
20 management to give a brief introduction today.

21 First of all, thank you all for being here today.
22 We have a rather interesting product to discuss. First of
23 all, to introduce SIRTEX, SIRTEX is a company based in
24 western Australia, in Perth, and the acronym SIRT stands for
25 selective ionizing radiation therapy, and this product is

1 specifically designed for patients with inoperable liver
2 cancer and the device itself consists of resinous beads
3 which are coated with yttrium 90, which is injected into the
4 patient via the hepatic artery, and the microspheres
5 themselves become permanently embedded in the vasculature
6 and therefore selectively place the ionizing radiation at
7 the site of the tumor.

8 You will hear from three speakers from SIRTEX
9 today. The agenda calls for four. The three you will hear
10 from are Dr. Monica Hope, who is the head of Regulatory
11 Affairs, has a doctorate degree in Clinical Pharmacy.

12 You will hear from Dr. Bruce Gray, who is the
13 medical director, and Dr. Val Gebiski, who is the
14 statistician for the company, who will discuss the results
15 from a statistical perspective.

16 Due to time limits, what we are trying to do today
17 actually is to compress approximately 18 years of work into
18 an hour and 10 minutes. It is a difficult compression job.
19 In hopes of meeting that time limit, we have asked Mr.
20 Sutton, the CEO of the company, to be available for
21 questions, but not to be a speaker today.

22 A regulatory perspective also is that the Food and
23 Drug Administration approved a similar device in December of
24 1999. The sponsor of that device was Nordion, and the
25 device is called TheraSpheres, which is a device which has

1 an analogous application.

2 We are hoping by the end of this meeting that the
3 panel will make a similar recommendation for approval of the
4 SIRTEX device. In hopes of moving things along, I request
5 that the panel please save questions until the end of all
6 the presenters, so that we may take the time to present the
7 information to you uninterruptedly.

8 Let me introduce the speakers now and give you
9 some further detail as to each one of them.

10 [Slide.]

11 Dr. Hope has a degree in Clinical Pharmacy, is a
12 lecturer at Curtin University in pharmacy, and has been the
13 head of Regulatory Affairs at SIRTEX Medical and essentially
14 the company correspondent, the one in closest contact with
15 the Food and Drug Administration on this product.

16 [Slide.]

17 Dr. Bruce Gray has many accomplishments in
18 academia and in industry. He is, as you can see, the
19 Medical Director of the Lions Cancer Institute in Australia.
20 He is Professor and Head of Surgery at the University of
21 Western Australia, Director for the Centre of Applied Cancer
22 Studies, Chair of the Australian Gastrointestinal Tumor
23 Study Group, and in the GI Core Committee for the Eastern
24 Cooperative Oncology Group, which United States is a
25 participant in, and the Medical and Research Director of

1 SIRTEX Medical.

2 [Slide.]

3 The final speaker from SIRTEX is the statistician,
4 Dr. Val Gebski, who is a senior statistician and fellow at
5 the National Health and Medical Research Council in Clinical
6 Trials, statistician to a number of Australian health and
7 research groups, holds a number of publications and has
8 specific expertise in clinical trial design and data
9 analysis.

10 With that, I pass things to Dr. Monica Hope.

11 **Device Description**

12 DR. HOPE: Good morning. Thank you very much.

13 Dr. Gray will spend some time following my
14 description of the device to discuss with you the problem of
15 liver cancer and provide some perspective on the variety of
16 treatment options available to patients.

17 [Slide.]

18 Suffice it to say, liver cancer is a significant
19 health issue with a very poor prognosis for most patients at
20 the time of diagnosis. An approach to treatment of liver
21 tumors that are not suitable for surgical cure would be a
22 device capable of delivering a tumoricidal dose of radiation
23 to such tumors.

24 [Slide.]

25 Identification of this approach resulted in the

1 concept of a device with four main characteristics.

2 Firstly, the device would need to selectively
3 place a radioactive source in intimate contact with liver
4 tumors. This was considered necessary to ensure that high
5 radiation doses were delivered to the actively growing
6 cancer.

7 Secondly, the radiation source must be capable of
8 delivering a cytocidal radiation dose. The choice of
9 isotope is therefore important.

10 Thirdly, healthy liver tissue must be spared high
11 radiation doses. Continuing adequate hepatic function is
12 particularly important in these patients.

13 Fourthly, the adjacent organs must be spared
14 significant radiation exposure and distant organs should
15 receive little or no radiation at all.

16 [Slide.]

17 To meet these concepts, a device with the
18 following features was developed. The device has to be an
19 implantable radioactive source. This will allow the
20 intimate contact with tumors to provide the high radiation
21 dose locally while sparing the remaining liver and other
22 tissues.

23 In addition, as liver cancer in non-resectable
24 patients frequently presents with multiple tumor sites, the
25 device must be capable of delivering radiation to all tumors

1 regardless of the number and their location within the
2 liver. Inability to do so would severely limit the
3 potential benefits of treatment.

4 Ordinarily, treating disease with multiple sites
5 would involve invasive methods to locate and treat each
6 tumor. In cases of disseminated disease throughout the
7 liver, as that very first slide demonstrated to you, it is
8 clearly difficult, if not impossible, and a minimally
9 invasive implantation procedure is required.

10 [Slide.]

11 The solution to disseminated but selective liver
12 placement of the radioactive source was microspheres, and as
13 mentioned earlier, this concept is not new and certainly
14 other microsphere technology is available for the treatment
15 of cancer in the liver.

16 [Slide.]

17 The concepts and requirements outlined on the
18 previous slides for us became the device that we call SIR-
19 Spheres, and SIR-Spheres has two components. These are the
20 microspheres themselves and the isotope yttrium-90. The
21 device is supplied in water for injection, and this allows
22 the required activity for an individual patient to be
23 measured as a volume in a shielded syringe.

24 [Slide.]

25 The microspheres have three significant features

1 contributing to device performance. Firstly, they are
2 biocompatible. This was determined through a program of in
3 vitro and in vivo studies undertaken by an independent
4 research laboratory. As an implantable device,
5 biocompatibility is mandatory.

6 Secondly, they are sterilizable. This has been
7 well established from product development in the needs of
8 production, and this feature is also mandatory.

9 The size of the microspheres allows lodgment in
10 the vasculature of the tumors. The microspheres predominate
11 in the arterials of the growing rim of the tumor delivering
12 the ionizing radiation to these cells and the rim of the
13 healthy tumor immediately adjacent to the tumor edge.
14 Microspheres will also distribute to the central part of the
15 tumor depending on the vascularity of the tumor core, which
16 is frequently necrotic in large tumors.

17 Microspheres must be small enough to reach the
18 terminal arterials. They must also, however, be
19 sufficiently large to prevent them passing through the very
20 small vessels and entering the systemic circulation. The
21 size of the microspheres is a key parameter in entrapment of
22 the microspheres within the tumor vasculature where it is
23 required.

24 This provides the radiation dose to the tumor and
25 reduces the radiation dose to the remaining healthy liver.

1 Entrapment also prevents distribution of the microspheres to
2 other organs in significant amount, thereby preventing
3 damaging radiation doses to the extrahepatic sites.

4 The size of the microspheres is also fundamental
5 to a noninvasive implant procedure. Microspheres can be
6 delivered via a catheter placed into the hepatic artery.
7 Therefore, the microspheres must be small enough to traverse
8 this catheter. In addition, they must be small enough to
9 reach those terminal arterials of the tumor, and not remain
10 trapped out in the large vessels of the healthy liver.

11 [Slide.]

12 Yttrium-90 is the isotope used in this device.
13 Yttrium has a number of desirable features which make it
14 suitable for this application.

15 Firstly, yttrium-90 is a pure beta emitter with an
16 average energy of 0.93 MeV. This high-energy emission is
17 capable of causing sufficient cell damage to result in cell
18 death. For this reason, the isotope must be confined to the
19 area of desired damage, that being the tumor.

20 Confinement of radioactivity is further enhanced
21 by the minimal penetration depth of emissions in tissue,
22 which is an average of 2.5 mm or about a tenth of an inch.
23 The half-life of approximately 64 hours allows radiation to
24 be delivered over a period of approximately two weeks, and
25 this is a comparable dose per unit time to other forms of

1 radiation therapy.

2 [Slide.]

3 SIR-Spheres is presented in a sealed glass vial
4 with 3 gigabecquerels or 3 GBq activity per 5 ml vial at the
5 time and date of calibration, and two such vials comprise
6 the 6 GBq device.

7 The label includes the time and date of
8 calibration. I think you can see that on the slide in front
9 of you. The glass vial contains the microspheres. They are
10 packed into the yellow container, which is a lead pot, for
11 transport, and the microspheres have been decanted into a
12 vial, so that you can actually see the microspheres in the
13 water for injection.

14 Currently, calibration time is always 0900 hours
15 Sydney, Australia time on the day of calibration. Labeling
16 for the U.S. will reflect the relevant time zone and be
17 deliberately labeled, so you won't always have to figure out
18 what time it is in Sydney, although that could be important.

19 Calibration date is generally the day the
20 microspheres are to be implanted. They may not be implanted
21 prior to the time and date of calibration as they are
22 released parametrically because they are a decaying product
23 and this allows a safety lockout period.

24 [Slide.]

25 SIR-Spheres is intended for implantation into

1 liver tumors. Implantation is by way of a catheter placed
2 into the hepatic artery. The catheter can either be
3 surgically implanted prior to the use of SIR-Spheres or
4 simply passed via the trans-femoral artery up into the
5 hepatic artery on the day of the implantation.

6 [Slide.]

7 On the scan in front of you, you can see that
8 there is catheter placed. This is a trans-femoral catheter
9 and it just hooks around and into the hepatic artery.

10 [Slide.]

11 What you are looking at here is the microspheres
12 being delivered into an implanted catheter connected to a
13 port, so the catheter has been surgically implanted,
14 connected to a port on the upper abdomen or lower chest, and
15 the port is accessed to implant the microspheres.

16 [Slide.]

17 In this slide, the microspheres are being
18 delivered via a trans-femoral catheter that has to be placed
19 under radiographic guidance. In this situation,
20 implantation of microspheres will take place in an
21 angiography suite.

22 That completes my description of the device and
23 its use and I will now hand it to Dr. Gray who will continue
24 with clinical information.

25 **Liver Cancer and the Pivotal Study**

1 DR. GRAY: Thank you, Monica.

2 I would like to thank the FDA and the panel for
3 the opportunity of presenting to you this morning. In the
4 introductory remarks, Mr. Donald said what we are trying to
5 do is present a synopsis of 18 years' experimentation in two
6 universities.

7 What I would like to do is walk with the panel
8 through three areas, first of all, to look at the clinical
9 problem of liver cancer, and then, secondly, to take you on
10 a very brief description about the physiological basis that
11 underpins the use of the device, how it works, and finally,
12 to present to you the Phase II, non-randomized, and then
13 finally, the Phase III randomized results from our last
14 clinical trial.

15 The panel pack that has been handed out to people
16 is obviously a condensate of a very large application of
17 over 3,000 pages that went to the FDA. In the panel pack,
18 there is no evidence in there for use of the device in
19 primary liver cancer, however, that was part of our
20 submission. So, I will talk very briefly at the end on some
21 experience in the use of this device in primary liver
22 cancer.

23 [Slide.]

24 If we look at liver cancer, obviously, it is a
25 major cause of morbidity and mortality. These are United

1 States figures. You can see that cancer here is the second
2 leading cause of death in the U.S. The proportional death
3 rate from cancer is rising in all societies. For instance,
4 in my country, in Australia, cancer has now exceeded heart
5 disease as a cause of death.

6 [Slide.]

7 If we look at the different cancers that are
8 actually causing death, it varies obviously between men and
9 women, but you will find that diseases or cancer of the
10 large bowel is prominent in both sexes. In fact, it ranks
11 only after carcinoma of the lung as a total cause of cancer
12 mortality.

13 [Slide.]

14 For the non-clinicians, it is important to note
15 that when people die of colon cancer or of pancreas cancer
16 or of esophageal cancer or even breast cancer, they don't
17 die of the cancer in the large bowel or the pancreas or the
18 esophagus or the breast, they die because the malignancy
19 metastasizes, and the liver is a prime site for metastatic
20 spread.

21 If we take just large bowel cancer and look just
22 at that as a subset, we can find that overall, in the United
23 States, there is about 6 percent lifetime risk of getting
24 large bowel cancer and about a 40 percent overall mortality
25 if you do get the disease.

1 If you look at why these people are dying, one
2 finds that more than 50 percent of deaths from colorectal
3 cancer are due either solely or predominantly to the liver
4 metastases. If you simply distill that down, you will find
5 that in the United States, you have slightly less than a 2
6 percent chance of dying from metastatic liver cancer just
7 from the colorectum.

8 If we looked at all of the patients that have been
9 treated with SIR-Spheres, it amounts to about 700 people in
10 four different countries. We have published data on around
11 3- or slightly less than 300 of those. Some of that data,
12 but not all of that data was gathered in western Australia
13 in my institute.

14 Many of the patients that we have treated did, in
15 fact, have metastatic disease that comes from the large
16 bowel, because it is a particular clinical problem. When
17 one manages cancer, it is important to look at the whole
18 disease, it's a wholistic approach, but if we look at
19 colorectal cancer, we find that because the liver metastases
20 are such a predominant cause of death, that the ability to
21 prevent the growth or the progress of liver metastases
22 should, in fact, translate into a significant patient
23 benefit.

24 [Slide.]

25 For the last 25 years, the mainstay, in fact, even

1 now, the mainstay of the treatment--and now we are
2 concentrating on colorectal cancer--has been chemotherapy,
3 and there has been very little change in that.

4 Just to digress and talk briefly about
5 hepatocellular cancer, hepatocellular cancer is not early as
6 common in the United States, but is particularly common in
7 Asia. However, it is rising substantially.

8 This is an abstract of an article in The New
9 England Journal from last year that clearly demonstrated
10 that there was a substantial rise in the incidence, and
11 consequently the death rate, from hepatocellular cancer or
12 primary liver cancer, in fact, a 70 percent increase in this
13 15-year period. That is driven by the rapid rise in
14 hepatitis C in particular.

15 [Slide.]

16 I would like to emphasize also that the disease we
17 are talking about is not this. This is a CT scan showing
18 the top segment 7 and 8 of the liver with a single tumor
19 sitting in segment 8, which in this case happens to be
20 filled with lipiodol.

21 This represents about 1 in 10, or 10 percent, of
22 the patients that actually present with metastatic cancer.
23 The vast majority of patients present with widespread
24 disease, and not that.

25 [Slide.]

1 There are already a number of ways of treating
2 localized liver cancer, and it is something that we do in
3 our institute and it is something that is done in every
4 major hospital throughout the United States.

5 So, we already have relatively effective
6 mechanisms for dealing with localized liver cancer -
7 surgical excision, absolutely standard these days, injecting
8 sclerotherapeutic agents into the cancer or passing probes
9 in and destroying them with laser ablation. Radiofrequency
10 ablation has recently been popularized in which a probe,
11 which emits a radiofrequency beam into the tumor, can be
12 used, and, of course, cryotherapy has been around for the
13 best part of a decade or so.

14 [Slide.]

15 All of these techniques are addressing 10 percent
16 of the problem. This is 90 percent of the problem, and that
17 is what we are about addressing. There is no application
18 for any of those locally ablative treatments for managing
19 this disease. The management of this disease has to be some
20 technique that will manage all of the tumors in the liver
21 regardless of where they are.

22 [Slide.]

23 I mentioned briefly before that the mainstay of
24 treatment of metastatic liver cancer from the colorectum
25 although my comments would also apply equally well to many

1 other sites, such as the pancreas, gallbladder cancer,
2 esophageal cancer, et cetera, but let's just concentrate for
3 clarity on colorectal cancer. The mainstay of treatment is
4 chemotherapy and has been for at least 25 years, and that
5 chemotherapy consists of fluorouracil and leucovorin. That
6 is absolutely the mainstay of treatment.

7 Again, I will quote from The New England Journal
8 of Medicine. This is an abstract from about four weeks ago.
9 This was considered so important. It was a large randomized
10 study, it was a three-arm randomized study by the irinotecan
11 Study Group enrolling over 600 patients that demonstrated
12 that if you added irinotecan to a regimen of fluorouracil
13 and leucovorin, then, you got a benefit, there was a patient
14 benefit.

15 This was considered so important that it even got
16 an editorial in The New England Journal saying at last we
17 have made a breakthrough. Well, I am happy about that
18 because my institution was one of the two non-U.S.
19 institutions that actually participated in this study.

20 The response, in fact, by adding irinotecan went
21 from 21 to 39 percent, which is significant indeed. The
22 disease-free interval or the progression-free interval
23 increased from four months to seven months, and perhaps if
24 you could just try and remember some of these because using
25 SIR-Spheres, I will be telling you later, in a randomized

1 study, that we can increase disease-free interval of the
2 order of 19 months, and survival was a very modest increase,
3 but it just reached statistical significance, so there was a
4 survival increase of the order of about eight or nine weeks.

5 Now, this is heralded, quite appropriately so, as
6 a significant and important breakthrough, and this will
7 become one of the new baseline treatments for the management
8 of widespread metastatic cancer.

9 [Slide.]

10 The other technique involves regional
11 chemotherapy. Because the colorectal cancer when it
12 metastasizes in particular often goes to the liver and
13 nowhere else, there is a role for regional treatment and
14 hepatic artery chemotherapy has been popularized for more
15 than 30 years.

16 In fact, it came out of the Lahey Clinic when I
17 was there nearly 30 years ago, and it involves implanting
18 surgical ports, which are plumbed into the hepatic artery
19 and then they are either connected to an external pump or,
20 in some cases, the pump itself is actually implanted into
21 the patient, and you deliver through that usually one of the
22 fluorinated pyrimidines, such as floxuridine.

23 That technique would be regarded in the year 2000
24 as the most aggressive treatment for disease in the liver
25 from, in particular, the large bowel. This forms the

1 control arm of the Phase III randomized study that I will
2 talk about a little later.

3 [Slide.]

4 If we are to look very briefly at primary liver
5 cancer or hepatocellular cancer, we can summarize the
6 world's experience in three lines, and I say this in all
7 sincerity. There is very good data to confirm that apart
8 from surgical resection, no treatment of any sort has ever
9 been shown to affect survival. It is a particularly
10 difficult disease to treat effectively.

11 [Slide.]

12 Let's just go on now and perhaps walk through
13 where we have been in the last 18 years. The research
14 program that we started goes back to 1982 when we first
15 started looking at mechanisms by which we could implant
16 small particles into the vascular milieu of malignancies in
17 the liver regardless of where they are.

18 It started at the University of Melbourne, we
19 transferred it to the University of Western Australia, and
20 subsequently to the Cancer Research Institute. Through a
21 series of sequential investigations, we moved through until
22 1987, we felt that we were confident enough to start Phase I
23 and II clinical trials in patients, so we treated our first
24 patient in 1987.

25 Because liver cancer or primary liver cancer is so

1 common in Asia, we actually transplanted the technology to
2 the Chinese University in Shatin where they have
3 subsequently undertaken numerous studies.

4 In that time period, we have published over 40
5 articles in the scientific press that allude to the
6 physiological basis behind it all, a little bit about the
7 characterization of the particles, radiation dosimetry, and
8 protection, and more recently, we have been talking about
9 Phase II and Phase III clinical trials.

10 Now, the pivotal study, the Phase III study is in
11 press at the moment, but has not actually reached the
12 shelves.

13 [Slide.]

14 If we look at how this technique works, let me
15 take you back to some physiology of blood flow in the liver
16 because it is highly dependent on blood flow and our ability
17 to manipulate blood flow.

18 The liver is an unusual organ, i.e., in that it is
19 the receptacle for so many cancers to metastasize to, but
20 also because it has a dual blood supply. About 80 percent
21 of the bulk of blood that flows through the liver comes from
22 the portal vein, which drains the gastrointestinal tract,
23 and about 20 percent of it comes from arterial blood coming
24 from the aorta.

25 [Slide.]

1 But when cancers develop in the liver, regardless
2 of whether they are primary cancers and regardless of where
3 they come from, if they are metastatic cancers, they suck in
4 a blood supply that comes exclusively, and it is more than
5 99 percent of the blood supply, comes only from the artery
6 which normally supplies about 20 percent of the liver's
7 blood, so now it is supplying 100 percent of the tumor's
8 blood. That has been known obviously for very many years.

9 That gives us a therapeutic opportunity in which,
10 if we were to implant into the hepatic artery anything that
11 was not noxious to the cancer, it would hit the cancer in a
12 higher proportion than it would hit the normal liver just by
13 virtue of blood flow.

14 In fact, we can manipulate that blood flow and
15 actually increase the proportion of arterial blood that goes
16 to tumors rather than the normal liver parenchyma regardless
17 of where they are. If this was a real live patient, we
18 would excise that. That would be a patient we would say we
19 can treat with the potential of cure.

20 [Slide.]

21 The radiologists have known this, of course, for a
22 long time, and you can demonstrate it very easily and very
23 graphically on a CT scan. Here, we have a CT scan of the
24 same patient, in fact, it is the same slice of the liver of
25 a patient with a number of metastases throughout the liver.

1 In the top CT scan here, you can see that is the
2 liver here that has a contrast agent in the portal venous
3 system. The catheter has been placed in the superior
4 mesenteric artery, a pulse of contrast has been injected.
5 It goes down into the gut and back up into the portal vein,
6 and it outlines the normal liver parenchyma. You can see
7 there is very little contrast, in fact, in the tumor.

8 We now take the catheter and we simply move it and
9 put it into the hepatic artery and inject contrast, and you
10 get a mirror image of this. Now the contrast agent is
11 picking out the tumor in preference to the normal liver
12 parenchyma. That is the body's own physiological targeting
13 mechanism which we exploit by the use of SIR-Spheres.

14 [Slide.]

15 If we were to inject drugs into the artery, we
16 would undoubtedly get some beneficial effect, and that is
17 why hepatic artery chemotherapy has been so popular over the
18 last couple of decades, but, of course, the blood flows
19 through the liver very quickly.

20 What we would like to do is to implant particles
21 into the liver that would concentrate in the tumor and which
22 would stay there, and not pass through. That is where we
23 were 15 or so years ago developing these SIR-Spheres which
24 have characteristics which are proprietary, which we feel
25 are ideal for embolization into the vascular bed of tumors

1 by simply placing a catheter into the hepatic artery and
2 injecting them through a syringe.

3 [Slide.]

4 In this schematic representation, what we see is
5 that microparticles that are injected into the artery will
6 pass into the tumors regardless of where they are and they
7 will lodge in the microvasculature, not always capillaries,
8 in fact, they often lodge in precapillary arterials, but
9 they will not pass through in large numbers into the vein
10 and back into the general circulation because they have been
11 designed to be of a size that will get entrapped in much the
12 same way that tea leaves get caught in a tea strainer when
13 you pour tea through.

14 [Slide.]

15 If we look histologically, we find them
16 individually sometimes in capillaries, but very frequently
17 trapped in small precapillary arterials. We have lots of
18 data which is in the public press to show that these
19 microparticles concentrate in particular in the rim, the
20 growing rim of tumors, and the ratio of concentration
21 between microparticles in the rim of tumors as opposed to
22 the normal liver often varies widely, that can be up to 100
23 to 1, so you can get enormous amounts of particles
24 concentrating in the growing edge, and you can demonstrate
25 that in patients.

1 [Slide.]

2 This is a patient's liver here in which we have
3 performed a sulfur colloid liver scan. It is not a common
4 test these days. It was something that was done more
5 frequently perhaps 20 years ago, and the sulfur colloid has
6 concentrated in the normal functioning liver parenchyma, but
7 you can see it looks a little moth-eaten and, of course,
8 there are defects here that don't have reticuloendothelial
9 cells, and they show up as areas of paucity of the sulfur
10 colloid.

11 We take that same patient and we inject
12 microparticles into the liver. In this case, they have been
13 tagged with technetium, so you can actually see them on a
14 stick camera, and we take a stick image, and we see that the
15 particles have picked out the tumors regardless of where
16 they are in the liver, you don't need to know that. The
17 targeting mechanism of the blood flow will find them.

18 So, you can imagine that these tumors here would
19 be getting a very high dose of the ionizing radiation.

20 [Slide.]

21 I would like to talk now and move on to talk about
22 some of our Phase II data. This is not our pivotal data,
23 but this is data which has only very recently been
24 published. It was published, in fact, a couple of months
25 ago in GI Cancer.

1 Again, I have only looked at a selected subgroup
2 of patients who had colorectal metastases only, so that we
3 are comparing apples with apples. There were 87 patients,
4 and these are sequential, unselected patients who we treated
5 with SIR-Spheres, who had advanced non-resectable liver
6 metastases that weren't in the context of some other
7 randomized trial.

8 In the initial stages, we treated patients with
9 SIR-Spheres alone, but subsequently, we found that if we
10 added hepatic artery chemotherapy, we actually prolonged the
11 response, and so after the first 16, it has been our
12 practice to not only treat people with SIR-Spheres, but to
13 actually add ongoing either hepatic artery chemotherapy or,
14 more recently, systemic chemotherapy in order to potentiate
15 the ionizing radiation.

16 The drugs that happened to be effective against
17 colorectal cancer, not very effective, but they have some
18 effect, are also very good at potentiating radiation, the
19 fluorinated pyrimidines in particular. So, we found that we
20 could potentiate ionizing radiation, as of course radiation
21 oncologists frequently do using drugs like fluorouracil. In
22 our case we have used floxuridine, which is an analog of
23 fluorouracil, as the hepatic artery chemotherapy agent.

24 So, I will just give you very briefly the results
25 of what we found when we treated these 16 patients with SIR-

1 Spheres, one shot only, just only one injection, usually
2 given as an outpatient or an overnight stay, and then 71
3 patients who were treated with the combination.

4 [Slide.]

5 We found if we treated patients with SIR-Spheres
6 alone--and this is our initial data which we did publish in
7 1992--we found that if we measured responses by serial CT
8 scans, that the majority of people we actually saw a
9 response in. We could demonstrate in slightly under three-
10 quarters of patients that there would be some diminution in
11 the size of the tumor on serial monthly CT scans with an
12 average decrease of about 50 percent.

13 If we looked at CEA, and CEA is carcinoembryonic
14 antigen, which is a very widely used serologic marker for
15 colorectal cancer, oncologists use it routinely to monitor
16 the progress or regress of malignancy, if we did that, that
17 we found 100 percent of people in fact had a fall in CEA, so
18 in everybody, we were getting at least some evidence of a
19 biological effect. The average fall was around about 80
20 percent, 78 percent.

21 [Slide.]

22 So, we then moved on, and these are the other
23 patients, the 71 patients who were treated, not with SIR-
24 Spheres alone, but in whom we added ongoing cycles of
25 hepatic artery chemotherapy, so these patients had a port

1 implanted, they had their SIR-Spheres injected through the
2 port, as we showed in one of the earlier slides, and then
3 they had ongoing cycles of hepatic artery chemotherapy.
4 Again, we found high response rates.

5 If we look at CT scan responses, we found that
6 almost 9 out of 10 people we could demonstrate a decrease in
7 size of the tumor on serial CT scans, and in three-quarters
8 of them, they would qualify as a partial response or a
9 complete response.

10 Now, a complete response in this scenario is a
11 disappearance of all evidence of tumor on serial CT scans
12 and maintained for a minimum of one month, whereas a partial
13 response means a decrease in the size of the tumor by 50
14 percent, that has to be maintained for at least one month.

15 If we looked at CEA before it was 100 percent--and
16 I think this is just variation in the different trials--
17 again, we were seeing that the vast majority of people in
18 fact had a decrease in CEA and almost 90 percent of them now
19 qualified for either partial or complete response.

20 So, by the early 1990's, we were pretty confident
21 that we were seeing responses that we just had not seen
22 before.

23 [Slide.]

24 Many of these patients I would add, in fact, the
25 majority of these patients had already been pretreated, in

1 the early days we were getting patients who had been
2 pretreated usually with systemic chemotherapy and had
3 failed, so these were chemotherapy failures that were
4 treating.

5 Survival, again, was significantly longer than
6 perhaps we would have assumed it would have been if they
7 hadn't been treated, but it wasn't a randomized study, but
8 the results of survival impressed us.

9 If we looked, for instance, from diagnosis, the
10 average survival was around 21 months, and the median
11 survival was a year and a half. If you look at that
12 previous slide that we have just published in The New
13 England Journal in irinotecan, the median survival there is
14 14.8 months. So, we thought we were doing reasonably well.

15 All of these studies were undertaken under GMP,
16 under the auspices of a program run by the Therapeutic Goods
17 Administration in Australia, which is the Australian federal
18 government body that supervises the conduct of clinical
19 experimentation in that country.

20 [Slide.]

21 So, we then went on and said let's structure a
22 Phase III trial, and that was undertaken under the
23 imprimatur of the University of Western Australia. I must
24 declare, in fact, I should have done so at the beginning,
25 that I have a financial interest in the company and I am

1 employed by the company, SIRTEX Medical, but at the stage
2 all this was happening, I did not, and I was one of the
3 principal investigators, not the only, but one of the
4 principal investigators on the Phase III trial.

5 It was undertaken in Western Australia at the two
6 major teaching hospitals.

7 [Slide.]

8 So, the structure of the Phase III trial was we
9 said the most aggressive treatment that you could have for
10 advanced nonresectable liver metastases from the large bowel
11 would be hepatic artery chemotherapy, and fairly aggressive
12 chemotherapy, too, 0.3 mg/kg/day in 12 day/monthly cycles is
13 fairly aggressive chemotherapy.

14 So, that would be our control arm, and to that we
15 would add one single dose or one single administration of
16 SIR-Spheres administered through the port either on an
17 outpatient basis or usually with an overnight stay, and that
18 was given up-front. That is the only difference between the
19 two arms. Otherwise, they are identical.

20 We stratified patients according to the extent of
21 liver involvement, whether it was less than 25 percent of
22 the liver involved with tumor, 25 to 50, or greater than 50.

23 I would like to now stop for a moment and ask Dr.
24 Val Gebski, who is the chief statistician at the Australian
25 National Clinical Trials Center, to talk about the analytic

1 techniques that were used to analyze the study and then
2 perhaps I can sum up by giving you the results of the study.

3 **Statistical Analysis of the Pivotal Study**

4 DR. GEBSKI: Thank you, ladies and gentlemen, Mr.
5 Chairman.

6 DR. GARRA: Excuse me. Could you identify
7 yourself, also, if you have a financial interest.

8 DR. GEBSKI: I am sorry. Val Gebski. I have no
9 financial interest in SIRTEX. I am just a consultant for
10 them. As Dr. Gray intimated, I am the statistician at the
11 Clinical Trials Center.

12 Let me just walk you through some of the design
13 issues of the Phase III study and perhaps even relate to
14 some of the issues back to the Phase II.

15 [Slide.]

16 The Phase III study, its original sample size was
17 95 patients. After six years, unfortunately, accrual
18 ceased, and it ceased after 74 patients had been entered
19 into the study and there was some difficulty in retaining
20 accrual primarily because the referring clinicians were sort
21 of sending the patients or recommending that patients get
22 the SIRT arm. The patients were almost demanding that arm,
23 and that made randomization difficult, if not impossible,
24 and it was extremely slow.

25 [Slide.]

1 But around about the same time, the FDA also
2 published, sort of accepted the fact that objective
3 endpoints other than survival would still be acceptable look
4 at treatment efficacy.

5 So, the objectives of this study were then looking
6 at tumor response. We will talk about that in a minute.
7 Also, time to disease progression in the liver or, if you
8 like, local control, survival toxicity, and quality of life.

9 Now, the quality of life was not necessarily aimed
10 at saying it defined an advantage in quality of life, that
11 would have been very good, but the idea was to reassure us
12 that because as you saw in the sort of schema, the patients
13 were getting pretty well the same treatment in both arms
14 except for the SIRT up-front, the idea was to really
15 reassure us that the quality of life was not going to be
16 compromised in the experimental arm.

17 [Slide.]

18 So, our primary analysis was, as almost everybody
19 would use, an intention-to-treat analysis, but our response
20 differed quite rigorously from what was acceptable or what
21 usually was common in medical oncology.

22 We defined a complete response as the
23 disappearance of all evidence of disease, and that had to be
24 maintained for at least three months, and also no new
25 lesions being evident. A partial response was a decrease in

1 measure of the disease by at least 50 percent, and again
2 still maintained for three months and no new lesions
3 becoming evident.

4 [Slide.]

5 So, therefore, our sort of endpoints or measures
6 of treatment efficacy were now tumor response and time to
7 disease progression. They are rigorous and also we used not
8 just response in terms of what the medical oncologists and
9 what was the common way of doing it was simply by using
10 tumor area, we also had two other criteria, and that CEA
11 response and tumor volume to just see whether the results
12 were consistent.

13 Nevertheless, the early termination of the study
14 at 74 patients still allowed us to detect a 33 percent
15 increase in the response rate with 80 percent power.

16 [Slide.]

17 All the data were recorded on clinical record
18 forms from source documentation, and all source data were
19 independently monitored and audited by an external clinical
20 research organization.

21 The tumor sizes were all recorded in a blinded
22 fashion, and the tumor volume was determined by two
23 independent observers, and if their values differed by more
24 than 10 percent from the average from the middle, a third
25 observation was made with a third person, and then the

1 closest to the average of the closest was taken to represent
2 the tumor volume.

3 [Slide.]

4 The comparisons for tumor response, which were
5 essentially ordered responses by treatment, were compared
6 using a test called the Kruskal-Wallis.

7 [Slide.]

8 Looking at the data, testing for normality, we
9 used the Shapiro-Wilk test. These are sort of statistical
10 tests that checked whether the data are consistent with the
11 normal distribution.

12 A test of two proportions was the conditional
13 binomial exact test, and that is very similar to the
14 Fisher's exact test, which is pretty common.

15 [Slide.]

16 Time to event data, which is survival, time to
17 disease progression, the treatments were compared using the
18 log-rank test, which is a common test used in biostatistics,
19 and the actuarial curves were constructed using the Kaplan-
20 Meier method. Hazard ratios and time dependent effects were
21 analyzed using essentially time dependent Cox models of
22 proportional hazards, sometimes known as the Mantel
23 biotests.

24 [Slide.]

25 Now, quality of life was a patient self-assessed

1 measure on linear analog scale, and there were 10 measures.
2 These were fairly common at the time - physical well-being,
3 a lot of these are chemotherapy measures of how people feel
4 with receiving chemotherapy, mood, pain, and also the last
5 one, which is a good one, was an overall quality of life,
6 how you feel overall or sometimes called the Quality of Life
7 Uniscale.

8 The quality of life was measured at 3 monthly
9 intervals, and the average quality of life was compared at
10 each time point.

11 [Slide.]

12 Now, we defined survival as the time from the date
13 of randomization to the date last known alive or the date of
14 death. The time to disease progression was from the date of
15 randomization to the date of first evidence of tumor
16 recurrence.

17 [Slide.]

18 Now, our overall survival benefit for SIRT did not
19 reach statistical significance, and you will see this as Dr.
20 Gray presents some of the data. After 15 months, patients
21 on the SIRT arm appeared to live longer, and so we looked at
22 some exploratory analysis and found that there was little
23 difference between the treatments up to 15 months.

24 We looked at why this was happening, and this was
25 due to the fact that the patients were actually going from

1 distant disease, and these were essentially regional
2 treatments, so we couldn't help them anyhow, the disease had
3 spread to outside the liver.

4 But for those patients who did live up to 15
5 months, those who originally got SIRT seemed to have a
6 survival benefit.

7 So, one of the things that these data will show,
8 and Dr. Gray will now go through the primary results of the
9 study, is that you will notice that they are highly
10 consistent with the Phase II data, in other words, it seemed
11 that it didn't really matter whether the patients were
12 within a controlled trial or not, we got highly consistent
13 results.

14 **Conclusions from all Clinical Evidence**

15 DR. GRAY: Thank you. As I was one of the
16 principal investigators, I will continue on and perhaps give
17 you the results of this analysis.

18 [Slide.]

19 When we presented the data to the FDA, we analyzed
20 the data fairly extensively and gave it all to the FDA. The
21 conventional way of measuring tumor responses is to sum the
22 cross-sectional areas in order to find out whether or not
23 there is going to be a response.

24 There is good evidence, although the evidence
25 isn't widely used, in fact, measuring tumor volumes is much

1 more accurate, so we have presented both to the FDA and I
2 will present it to you here today. The reality is, of
3 course, they both end up with very similar results.

4 [Slide.]

5 If we look at the number of patients that
6 developed either a complete response or a partial response--
7 and this is, just to recap, this means complete
8 disappearance of all evidence of tumor, with no new lesions,
9 maintained for a minimum of three months, and this means
10 decrease in the sum of the products of the cross-sectional
11 areas by at least 50 percent and maintained for at least
12 three months--we found that 18 percent of the patients,
13 those getting hepatic artery chemotherapy, qualified as
14 either a CR or a PR in comparison to 44 percent who had a
15 single administration of SIR-Spheres added to the hepatic
16 artery chemotherapy. Of course, that is significant.

17 [Slide.]

18 If we looked at the same analysis, but using what
19 we would consider to be more accurate, we get very similar
20 results. The numbers are, in fact, slightly larger, but the
21 differences are the same, 24 percent of people who received
22 hepatic artery chemotherapy versus 50 percent of people who
23 had the combination treatment.

24 So, regardless of how we were looking at response,
25 we were getting substantially greater responses.

1 [Slide.]

2 If we looked at CEA, and CEA is a serologic
3 objective measure of tumor load, we found the data was very
4 similar to what we were finding if we were measuring tumor
5 areas or tumor volumes, but the numbers are actually
6 greater, but the proportions are similar.

7 So, nearly 50 percent of the people here qualified
8 for either a PR or a CR if they got HAC. If they got the
9 combination of hepatic artery chemotherapy plus a single
10 injection of SIRT, then, that rose to 72 percent. Of
11 course, that is significant.

12 [Slide.]

13 One of the questions you might be asking, why did
14 we use such rigorous criteria, and the answer was that this
15 trial was conducted in the two major teaching hospitals in
16 Western Australia and we simply weren't allowed to do
17 monthly CT scans. They said that it would not be
18 appropriate in a teaching hospital to subject patients to
19 monthly CT scans and therefore we were required to do three-
20 monthly CT scans, so our data is rigorous.

21 When we presented to the FDA, they asked us to go
22 back and look at the data again, but use slightly softer or
23 less stringent definitions of what response was, and, in
24 fact, when we did that, the data got even stronger.

25 So, here we have the control arm of hepatic artery

1 chemotherapy and the experimental arm, but now we have a
2 decrease in tumor size from nothing up to 25 percent
3 decrease, 25 to 50, 50 to 99 or 100 percent, which of course
4 is a complete response.

5 We found that using these slightly softer
6 criteria, the response rates went up in this case to 32
7 percent, and over here, to 69 percent with a p value using a
8 two-tailed test.

9 [Slide.]

10 If we look at the other parameter of treatment
11 efficacy, which was time to disease progression, and this
12 means that if a response was recorded, how long did it take
13 for that tumor to subsequently progress, and progression has
14 a hard definition. It means an increase in the size of the
15 measure that you are using by greater than 25 percent of the
16 nadir, of the lowest point. That is a very standard, widely
17 accepted definition of time to disease progression.

18 If we use cross-sectional tumor areas, we got an
19 increase in the mean from 10 to 19 months, and if we look at
20 median, from 10 to 16 months, and, of course, it is very
21 significant.

22 [Slide.]

23 If we measure it by tumor volumes, the numbers are
24 essentially the same, from, say, 10 to 17 months, and 7 1/2
25 to 12 months.

1 [Slide.]

2 If we measure it by CEA, again, we see the same
3 sort of response, but, in fact, it is not quite as dramatic,
4 and the reason it is not quite as dramatic is that CEA is
5 not only measuring what is happening in the liver, it is
6 measuring disease at any other site.

7 So, you might get a dramatic response in the
8 liver, but if you get progress in the lung, then, the CEA
9 will go up, so this is picking up responses at any site, but
10 the treatments are both regional treatments. Again, we see
11 the increase in mean from 6 to 12, and median from 5 1/2 to
12 16 months.

13 [Slide.]

14 These are the actuarial survival figures, which
15 Dr. Gebski already said didn't quite reach statistical
16 significance, and the survivals over that period of time
17 were greater in the experimental arm than the hepatic artery
18 chemotherapy control arm alone.

19 [Slide.]

20 That is the Kaplan-Meier analysis. There are the
21 curves that reflect those figures in the actuarial survival
22 table.

23 [Slide.]

24 Dr. Gebski also referred to an exploratory
25 analysis in which we looked at patients after 15 months, and

1 we found that there was a divergence of the curves at that
2 stage, so we looked at that to find out why that should be
3 so.

4 What we found is what is commonly found in
5 oncology. This curve is commonly seen in medical oncology
6 in which the curves hug themselves and then they split
7 apart. What is happening is that there is a cohort of
8 people up here in whom you have very little effect from your
9 treatment. These are regional treatments, and what is
10 happening here is these people are dying, not of progression
11 of liver disease, but of disseminated disease, and that is
12 exactly what we found when we, in fact, looked at why they
13 are dying.

14 So, if we looked at why are people dying,
15 particularly what are they dying of after 15 months, we
16 found that the number of people that were actually dying of
17 progression of the cancer in their liver was quite common in
18 the hepatic artery chemotherapy arm, but relatively uncommon
19 when the experimental treatment was added in, and that is
20 simply reflecting all the other data that has gone before
21 both in the Phase II and in the Phase III that I presented,
22 demonstrating a high response rate in the liver and the
23 ability of SIRT to maintain control of the tumor in the
24 liver.

25 [Slide.]

1 There was no difference in quality of life between
2 SIRT and HAC, and I would emphasize again what Val Gebski
3 said, that both of these patient groups had HAC. In fact,
4 the amount of HAC they had was very similar when we analyzed
5 that between the two same groups, and most of the toxicity
6 is associated with HAC, and not SIRT, and therefore, any
7 impact on quality of life could only be diminution of
8 quality of life, we couldn't actually make it better, and,
9 in fact, we didn't compromise quality of life, so we are
10 would regard that very much as a positive outcome.

11 [Slide.]

12 I am sorry, this is not a very clear slide, but
13 the next two slides are going to be toxicity and severe
14 adverse events. All of this data has been externally
15 audited.

16 If we look at toxicity of any stage, and this is
17 using the UICC rating scale which is very similar to the WHO
18 scale, we find that there are more toxic events using the
19 SIRT plus HAC arm, but they are nearly all Grade 1 and 2.

20 For instance, the biggest one is an increase in
21 alkaline phosphatase in the combination arm, and that merely
22 reflects exactly what you would expect if you delivered
23 ionizing radiation to the liver, the liver will swell a bit,
24 the pressure in the bile canaliculi will go up, and so you
25 will get a rise in alkaline phosphatase.

1 Grade 1 and 2 toxicities are not trivial, but they
2 are not clinically important. What is important are Grade 3
3 and 4 events, and when we looked at the Grade 3 and 4
4 events, there was no difference at all. So, while there was
5 more Grade 1 and 2 events here, they are of little clinical
6 significance, and that confirmed our previous experience
7 that this treatment was actually well tolerated.

8 [Slide.]

9 If we look at serious adverse events--and a
10 serious adverse event is, by definition, an event which
11 requires hospitalization even for a very short period of a
12 few hours, or is potentially life-threatening--once again
13 there was no difference between the two.

14 The pattern of serious adverse events was slightly
15 different, but the numbers were relatively small, and if you
16 look at what these events are, they are, in fact, generally
17 not terribly important either.

18 For instance, the removal of the port, well, if a
19 port got blocked, we might remove it. If we had finished
20 the chemotherapy and the patient didn't like the lump under
21 the skin, we might remove it, which might mean a local
22 anesthetic or as a day case, but that would get flagged as a
23 serious adverse event.

24 [Slide.]

25 So, in conclusion, we have quite a lot of data

1 which has been collected from published studies that have
2 now come out of three different countries. I presented our
3 Phase II and our only single pivotal Phase III study, and
4 those studies have addressed the issues of efficacy, of
5 safety, and of toxicity, and we believe that there is good
6 evidence to support all of those three outcomes.

7 [Slide.]

8 I would like to address one other thing before I
9 close. We are seeing something--and this is perhaps where
10 this might be in the future--we are seeing something more
11 commonly now that we didn't think was possible sometime ago.

12 Generally, around the world there is a fairly
13 aggressive attitude to resecting liver cancer. What we are
14 finding more and more is that we are down-staging patients
15 from a position where initially they would be regarded as
16 incurable because the tumor couldn't be removed, to a point
17 where the tumor becomes resectable.

18 This is not only our experience, it is the
19 experience of others, and they have documented that in the
20 literature.

21 [Slide.]

22 This is an anecdotal case of one patient who was
23 actually in the trial. This is one of our long-term
24 survivors in the clinical trial which we have already
25 presented. There are four patients in the clinical study

1 who are still alive, one in the HAC arm and three in the
2 SIRT plus HAC arm, and this is one of our early patients who
3 had a large tumor in the right lobe of his liver and, in
4 fact, there was another tumor in the left lobe of the liver
5 in segment 3, which is not reflected on that particular
6 slice of the CT scan.

7 If you can see--you probably can't see--but there
8 is the number 1991. This was one of our very first
9 patients.

10 [Slide.]

11 Over the ensuing 12 months, the tumor shrunk
12 substantially, and these are the CT scans that show this
13 particular tumor, so that it was possible a year later to go
14 in and surgically resect that and to remove the tumor out of
15 segment 3, and this is the post-resection CT scan, and this
16 patient remains disease-free, and we would have to consider
17 that patient cured. This is becoming increasingly common as
18 we treat more and more people using the SIRT technique.

19 The last time I resected somebody having been
20 down-staged by SIRT was about 10 days ago.

21 [Slide.]

22 In conclusion, although I have presented very
23 little data on primary hepatocellular carcinoma, it is
24 included in the PMA application. I will refer you just
25 briefly to the results from a sequential 71 patients treated

1 at the Chinese University of Hong Kong with injection of
2 SIR-Spheres via trans-femoral catheter and no other
3 treatment published last year in International Journal of
4 Radiation Oncology and Physics, 71 patients, and they found
5 that nearly 90 percent of patients responded with a decrease
6 of at least 50 percent in the alpha fetoprotein level, and
7 in 27 percent of those, it actually decreased to qualify as
8 at least a partial response on serial CT scans.

9 They also found what we are finding, that they
10 actually down-staged 6 percent of their patients to the
11 point where they could then go in and operate on them with
12 the expectation of potentially getting long-term cure. I
13 also documented the relative low toxicity of the correctly
14 administered SIR-Spheres

15 That really concludes the presentation. I think I
16 would like to hand it over to either the panel or to our
17 moderator.

18 MR. DONALD: Thank you, Dr. Garra, and the panel
19 members. That concludes the presentation from SIRTEX, and
20 the members of SIRTEX are open for questions should the
21 panel have any.

22 DR. GARRA: What I would like to do at this point,
23 and thank you very much for your presentation, the FDA
24 presentation should take around a half-hour or maybe
25 slightly more by some estimates I have gotten, and we can do

1 the FDA presentation and then have a question period for
2 both groups afterwards. I think that will move us along
3 nicely and we will get to see some other questions may come
4 up for us.

5 So, I would like to move ahead with the FDA
6 presentations. Jack Monahan is going to do an overview with
7 some preclinical data and then there will be a clinical data
8 review and a statistical analysis.

9 We will let them get organized and proceed with
10 that.

11 **Presentations on P990065 by FDA**

12 **PMA Overview and Preclinical Data**

13 MR. MONAHAN: Good morning. I am Jack Monahan. I
14 am the lead reviewer for this particular PMA. The question
15 that often comes up is what does a lead reviewer do. It can
16 best be described as herding cats, but for the purposes of
17 this PMA, I was lucky to have a group of very good
18 reviewers, so it wasn't too difficult to do.

19 [Slide.]

20 We had a number of people actually look at the
21 various aspects of this PMA. Andy Kang reviewed clinical
22 portion of the PMA, and he is in our Radiology group.

23 Jerry Sokol from the Center for Drugs, who is an
24 oncologist, also took a look at the clinical aspects of this
25 particular PMA because we wanted his clinical expertise in

1 evaluating the studies.

2 Lakshmi Vishnuvajjala was our statistician. Frank
3 Cerra, from the Office of Science and Technology, looked at
4 dosimetry. Raju Kammula looked at the compatibility
5 studies. Cathy Nutter examined sterility issues. Jay
6 Rachlin did the patient labeling, and Shawn Boyd, from our
7 Office of Compliance, did the manufacturing.

8 [Slide.]

9 Prior to initiating these studies, as Dr. Gray
10 alluded to, a number of studies examined various aspects of
11 liver tumors, and they began by looking at the physiology of
12 blood flow to liver cancers. They then examined the
13 distribution of various tracer microspheres within tumors.

14 They examined blood flow as a function of tumor
15 size, examined the distribution of different sized
16 microspheres in an attempt to evaluate what would be the
17 appropriate size.

18 They looked at the vasculature of micrometastases,
19 and finally, they examined the radiation dosimetry in normal
20 liver tissue in an attempt to see whether, in fact, normal
21 liver tissue would be significantly impacted by this
22 approach to the cancer.

23 All of these studies were done in preparation for
24 the clinical trials that were discussed earlier, and I think
25 that these studies laid a good foundation for those trials.

1 [Slide.]

2 In addition to those preclinical studies, a number
3 of studies were done to look at the biocompatibility. This
4 is a particularly relevant issue because the microspheres
5 lodge in the microvasculature and consequently are there
6 permanently.

7 The sponsor examined mutation, cytogenetic
8 activity, hemocompatibility, cytotoxicity, sensitization,
9 tissue toxicity, and also systemic toxicity.

10 [Slide.]

11 From these studies, the only one which showed any
12 effect was the mild dermal sensitization study. In looking
13 over the clinical trial data, we do not see that this
14 appeared to be a problem for patients since no adverse
15 events of that nature cropped up. However, the sponsor has
16 decided to enter a precaution in the labeling which
17 addresses this issue.

18 At this point, I would like to turn the podium
19 over to Dr. Andy Kang who will be discussing the clinical
20 portion of the PMA.

21 **Clinical Data Review**

22 DR. KANG: Good morning, members of the Panel. My
23 name is Andrew Kang. I am a medical officer in the Office
24 of Device Evaluation and Radiological Device Branch. Today,
25 I am going to present a summary, clinical review of this

1 interesting device, a SIR-Spheres yttrium-90 therapy for
2 metastatic liver cancer.

3 Previous speakers mostly described the general
4 principle of the device, as well as a device description and
5 the procedure for the therapy, so I am not going to
6 duplicate the same slide set. I am going to reduce my
7 presentation to the evaluation of the protocol for the
8 interest of the time.

9 [Slide.]

10 The first slide shows a summary of the current
11 statistics of the colon cancer which have already been
12 presented by a previous speaker, 130,000 new patients
13 annually develop a colon cancer and among them, about 50,000
14 patient will develop liver metastases. Among them, about
15 less than 30 percent of the tumor can be surgically
16 resectable. Most of the patient survival time is less than
17 one year.

18 I was going to discuss the study protocol, but I
19 may go away with it, and I am going to go directly into
20 safety assessment, as well as the effectiveness assessment,
21 which will consist of adverse event analysis, the radiation
22 safety, and the material safety and the clinical concerns,
23 and effectiveness assessment including tumor regression
24 rate, time to tumor progression, and the patient's quality
25 of life and survival time. I will conclude with the

1 summary.

2 [Slide.]

3 As the previous speaker mentioned, Dr. Gray
4 mentioned, the original study was designed for 95 patients
5 for the period of three years. The goal was to achieve the
6 median survival rate increase of 30 percent in the SIRT arm
7 over the chemotherapy arm, but the study ended with 70
8 patients--actually, it was 74 patients entered, but 4
9 patients were determined as ineligible--in about six years
10 due to some previously mentioned reason.

11 [Slide.]

12 The protocol was designed as a randomized,
13 controlled trial with the patients with proven metastases in
14 the liver and the tumor is surgically unresectable, and also
15 there was no proven extrahepatic metastasis.

16 So, the eligible patients among the 70 patients,
17 investigational arm consist of 36 patients treated with SIR
18 therapy plus with hepatic arterial chemotherapy, and the
19 control arm consist of 34 patients treated with chemotherapy
20 only.

21 [Slide.]

22 The study objective is also again described
23 before. Primary objective was assessment of the overall
24 survival, quality of life. Secondary objective was to
25 assess the toxicity and the tumor response rate.

1 [Slide.]

2 Tumor was stratified in three different groups -
3 less than 25 percent involvement of the tumor in the liver
4 by volume, 25 to 50 percent, and a patient involving more
5 than 50 percent of the liver volume.

6 According to the stratification, the dosimetry was
7 arranged from 2 gigabecquerels of yttrium-90 up to 3
8 gigabecquerels.

9 [Slide.]

10 If you look at the distribution of the patient
11 numbers between these three different groups, less than 25
12 percent involvement was about 67 percent of the 70 patients.
13 Between the 25 to 50 percent, tumor involvement was about 26
14 percent of the 70 patients, and more than 50 percent
15 involvement was only 7 percent.

16 But if you look at the two different arms, very
17 similar distribution, 23 versus 24, 10 versus 8, 3 versus 2.

18 [Slide.]

19 For the safety assessment, as I mentioned, we are
20 going to look at the adverse event, the radiation safety
21 issues, and the material safety issues.

22 [Slide.]

23 The adverse events, as mentioned before, are the
24 acute and subacute toxicity graded by the European Grading
25 System UICC, but I found out that it is very similar to our

1 system in the United States, and also serious adverse events
2 including some radiation event.

3 [Slide.]

4 I think this slide has already been shown by the
5 sponsor. The only thing we can look at is that the Grade I
6 and II, there is some difference in the SIR therapy group in
7 the temporary increase of the alkaline phosphatase. Other
8 than that, the more important things are Grade III and IV,
9 which is more clinically significant grade, showing, as
10 there, 23 to 22, very similar toxicity rate.

11 [Slide.]

12 In the serious adverse events, it is defined as an
13 event required hospitalization, including all these events,
14 removal of the port, re-siting the port, infection or
15 blockage or the fever of unknown origin, GI symptoms, or the
16 surgical complications.

17 If you quickly look at the number, between the two
18 arms, is again very similar.

19 [Slide.]

20 The radiation safety issue. Since they are giving
21 empirical dose of 2 to 3 gigabecquerels, I believe the
22 dosage to the liver has been predetermined through their
23 previous study, like a Phase I and Phase II clinical trial,
24 and averaged dose to the liver is estimated to about 60 to
25 80 Gy.

1 The interesting issue is that as most of the
2 oncologists would know, the external radiation to the liver,
3 the dosimetry about the 40 Gy is to be a 50 percent
4 morbidity rate, developing a radiation hepatitis.

5 So, how are we going to answer that the high dose
6 like a 60 to 80 Gy can be delivered without any incident? I
7 think there is several articles written for this, and one of
8 the articles actually is provided by the sponsor suggested
9 that there is a less radiation effect on the normal liver
10 tissue with the SIRT than the radiation effect with the
11 external radiation.

12 [Slide.]

13 And the cited reasons are I think the previous
14 speaker mentioned, the target to non-target ratio, it
15 varies, but 1 to 2, to 10 to 1, so the tumor gets more,
16 about 10 times more radiation than the normal tissue.

17 Also, the article suggested autoradiographic
18 findings showing very significant effect, that is,
19 clustering effect, it is not a uniformly distributed, it is
20 maybe 30 to 60 particles clumping together, and between the
21 island of the clump, there is normal liver tissue still
22 remaining.

23 So, after the radiation effect has been effective
24 to the normal liver, the normal area of the liver
25 regenerating very quickly compared to the external

1 radiation.

2 Another issue is the peripheral aggregation of the
3 SIR particles, if you look at the hepatic lobule, the center
4 vein area is pretty much reserved, and the SIR particles
5 usually attack the periphery of the hepatic lobule, so that
6 again that enhance the hepatic recovery quickly.

7 Also, it mentioned the liver is one of the high
8 regeneration capability it has, so depending on the liver
9 capability of regeneration, it may be probably better than
10 the external radiation effect.

11 [Slide.]

12 Another reference I would mention is that just a
13 few weeks ago, the October issue of the Journal of Nuclear
14 Medicine presented one article very similar to this, but
15 from the Toronto General Hospital, it mentioned that 22
16 patients with the feasibility study, with the yttrium-90
17 microspheres, not the SIR-Spheres, but other similar product
18 with 22 patients, injected only the brachytherapy, not any
19 chemotherapy mixed, and the result is their final conclusion
20 regarding the radiation safety has the same conclusion.

21 They used over 50 Gy to 150 Gy to the primary
22 liver cancer, and they found out much less radiation effect
23 than external radiation, so as far as the radiation
24 safetywise, there are several articles concluding the same
25 conclusion.

1 [Slide.]

2 Another issue I can mention, the radiation safety,
3 in this trial, with the 70 patients, there is no serious
4 radiation related toxicity event observed, such as radiation
5 pneumonitis or the radiation either gastritis or duodenitis.

6 Of course, the radiation pneumonitis, I didn't
7 mention the protocol, but they had a pre-study evaluation
8 for the pulmonary shunting procedure by injecting
9 technetium-99M into the hepatic artery and measure the ratio
10 by doing nuclear scan, the ratio between the lung and the
11 liver, as well as the GI area, and they eliminated high
12 shunting patient, tried to avoid the radiation pneumonitis.

13 [Slide.]

14 The material safety, what I am trying to say is
15 that we are presently here, since we are injecting about the
16 30 to 60 million particles, permanently injecting hepatic
17 artery, how much of that will affect the liver physiology.

18 It has no evidence, but there is some suggestion
19 saying that the number of the arteriolar blockage, when
20 compared to the arterioles in the liver, it is very small
21 numbers. Also, some microscopic findings suggest that the
22 collateral circulation developing so quickly after blocking
23 some of the arterioles, so that there will be all the
24 arterial blood can bypass easily.

25 Also, the recent clinical trial, including this

1 study, shows there is no permanent deterioration of any
2 liver function in this regard.

3 [Slide.]

4 Effectiveness assessment, as mentioned before, we
5 are going to look at four different issues - tumor
6 regression rate, time to tumor progression, patient's
7 quality of life, and survival time.

8 [Slide.]

9 Tumor regression is measured by tumor volume,
10 tumor area, and CEA level. Among these three, I have to
11 mention that FDA do not consider CEA level as reliable as
12 either tumor volume or the tumor area. So, we are mainly
13 looking at the tumor volume or the tumor area.

14 Among the tumor volume or tumor area, both are
15 acceptable measurement by FDA. In the study done, both of
16 them, volume and tumor area, obviously, tumor volume is more
17 reliable.

18 The Partial Response and the Complete Response
19 have been already described by the sponsor.

20 [Slide.]

21 The tumor regression result by volume, as you can
22 see here, the chemotherapy group with the 34 patients, SIRT
23 therapy plus chemotherapy is 36 patients. Among the
24 complete response and the partial response all added
25 together, got a 23.5 percent response, and the SIRT therapy

1 has a 50 percent response, so there is some significant
2 improvement of response rate.

3 [Slide.]

4 If you look at the tumor stratification and the
5 response rate by volume, then, you can also conclude that
6 there is some improvement of the SIRT therapy group, such as
7 at less than 25 percent tumor improved, about doubled the
8 response rate, same as the 25 to 50 percent range, also
9 improved about 2-fold.

10 [Slide.]

11 Time to first disease progression is defined as a
12 25 percent increase of the tumor size, by volume or area, or
13 the 25 percent decrease of the serum CEA. The result
14 showed, again the median and the mean both shows some
15 improvement, but again, FDA considered median value as more
16 reliable than mean, because mean can be very skewed by a few
17 patients one way or another. So, median value is more
18 important.

19 But anyway, the time to first disease progression
20 has improved, I mean delayed, 233 days versus 366 days, so
21 there is some significant improvement of the median.

22 [Slide.]

23 Quality of Life Assessment. As mentioned before,
24 it did not show any difference between the overall result
25 showed equivalent result in the investigational and the

1 control group.

2 I may add one comment, is that FDA considered
3 quality of their life is a part of the efficacy assessment,
4 but I believe the company assessed it as a part of the
5 safety assessment. In other words, I know that it should be
6 very difficult to measure quality of life in this kind of a
7 complicated case for the assessment of the effectiveness,
8 but again the quality of life is part of the effectiveness
9 assessment, not the safety assessment.

10 [Slide.]

11 The survival assessment, survival is defined as
12 the time from the randomization to death of the patient, and
13 it shows again median value 487 days versus 519 days, only
14 maybe 30-some days improvement, which is percentagewise
15 maybe 6.6 percent increase at the median survival in the
16 SIRT arm, but the number is so small, so we cannot conclude.

17 [Slide.]

18 The survival assessment again by year, if you look
19 at it, first year survival rate is 23 versus 26, and the
20 second year 9 to 14, third year 2 to 5, fourth year 2 to 2,
21 and the fifth year 0 to 1. Although the number is very
22 small, but there seems to be a tendency of longer survival
23 time in the SIRT therapy group although I am not sure that
24 these are statistically significant.

25 [Slide.]

1 [Slide.]

2 Most of the things I am going to say you already
3 heard one place or the other, but this is more from the
4 reviewing statistician's perspective. These are the
5 original outcome measures proposed by the sponsor. There
6 are two primary endpoints and two secondary endpoints, and
7 the objective is to show that the overall survival and tumor
8 regression are superior for the treated arm, and quality of
9 life and treatment complications are no worse.

10 Quality of life is self-assessed on a visual
11 analog scale, and no formal statistical analysis were
12 performed. Tumor response and treatment complications are
13 secondary endpoints, so the trial is basically sized for
14 detecting an increase in the overall survival.

15 [Slide.]

16 For the control group, at six months, 50 percent
17 of the patients had expected to be surviving. The SIRT
18 treated group is expected to have a 30 percent improvement
19 in median survival over that of the control group, and 95
20 patients will detect this improvement with 90 percent power
21 and one-sided significance of 5 percent. The 95 patients
22 had expected to be recruited over three years.

23 What actually happened later in the trial is the
24 30 percent improvement over the 50 percent, which is the 80
25 percent survival for the treated group at six months, did

1 happen, but what also happened was the control group also
2 survived at six months, over 80 percent of the patients.
3 So, you did not have the difference between the two groups
4 to be statistically significant.

5 [Slide.]

6 In the trial design, the patients are stratified
7 into three groups - where the tumor is less than 25 percent,
8 between 25 and 50, and greater than 50 percent. It is
9 blocked randomization, and the analysis is based on intent-
10 to-treat.

11 [Slide.]

12 The trial actually stopped after recruiting 74
13 patients over six years. Of these 74 patients, 4 of the
14 patients were deemed to be ineligible because they had
15 disseminated cancer detected at the time of randomization,
16 so we only have 70 patients who are eligible.

17 The study was stopped due to difficulties in
18 recruiting patients who were willing to be randomized to the
19 control arm and the financial burden on the public health
20 system under which the study was conducted.

21 [Slide.]

22 For survival, the SIRT therapy arm is higher, but
23 not significantly higher, but the mean and the median are
24 higher for the SIRT therapy arm. Because of the high
25 variability of the data that can be seen from the large

1 standard deviations, the median is a better measure, and the
2 difference between the medians is not statistically
3 significant log-rank test.

4 [Slide.]

5 The survival in the individual strata, as you can
6 see, both the mean and the median are higher for the SIRT
7 therapy compared to chemotherapy alone, but because of the
8 small numbers in each of these groups, none of the
9 differences are statistically significant.

10 [Slide.]

11 The cause of death, as you can see, in all the
12 groups you have the same number of patients basically dying.
13 It is the cause that is different. Most patients in the
14 chemotherapy arm died of progression of liver disease and
15 more patients in the SIRT therapy arm died of disseminated
16 cancer. This is even more pronounced in the group of
17 patients that survived at least 15 months.

18 So, some post-hoc analysis were also done on
19 survival of patients who survived at least 15 months, which
20 was significantly different between the two groups. Since
21 overall survival is also dependent on other causes of death,
22 other than just the liver cancer, Gray's test for competing
23 risks, which regarded the progression of liver metastasis as
24 primary cause and progression of cancer at extrahepatic
25 sites as a competing risk, has a p value of 0.07.

1 [Slide.]

2 Tumor regression by volume, most patients in the
3 SIRT therapy had complete and partial regression of the
4 tumor compared to the chemotherapy group, and this is the
5 average of three different technicians. The Kruskal-Wallis
6 test comparing the two groups excluding the category Other,
7 shows a statistically significant difference between the two
8 groups with a p value of 0.033, but it should be noted that
9 a good number of patients in the other category here, 8
10 patients out of 70, and in the next slide, which is for the
11 area, we see even more patients in the Other category.

12 [Slide.]

13 The test compares the four categories not counting
14 the Other. For the area, the significance is 0.011.

15 [Slide.]

16 Time to progressive disease is longer for patients
17 in the SIRT therapy group compared to the chemotherapy
18 group, and the log-rank test statistic has a p value of
19 0.043.

20 [Slide.]

21 The number of serious adverse events is similar
22 for the two groups, 14 in the chemotherapy-alone group and
23 13 in the SIRT therapy group.

24 [Slide.]

25 The quality of a life was a self-assessed measure,

1 and all these measures were assessed by the patients on a
2 visual analog scale, and the measures were similar for the
3 two groups. They basically have a scale saying zero is the
4 best and 10 is the worst, and they just put a mark on the
5 line, and that was interpreted as whatever number that
6 happened to be.

7 Most measures improved from baseline for both
8 treatment groups with the exception of sexual interest or
9 ability, which has decreased in both the groups, and no
10 statistical analysis was done on these data, and the data
11 for the two groups appear to be similar.

12 [Slide.]

13 The expected improvement in the survival did not
14 materialize. The survival for the SIRT therapy arm, even
15 though better, it is not significantly better. Tumor
16 regression is statistically significant, significantly
17 better both by volume and area for the SIRT therapy group.
18 Complications and Quality of Life measures were similar.

19 Time to disease progression, which was not
20 included as an endpoint initially, but analyzed in the
21 submission, is included as an endpoint in the revised
22 objectives.

23 [Slide.]

24 Again, the primary endpoint did not show a
25 statistically significant difference for the SIRT therapy

1 group even though it did show an improvement.

2 Time to disease progression is included in the
3 revised measures now.

4 [Slide.]

5 The revised study objectives now are the tumor
6 response rate, time to disease progression in the liver,
7 overall survival, toxicity of the two treatment regimens,
8 and quality of life.

9 The only new objective here is the time to disease
10 progression. The other four were the endpoints in the
11 original objectives, but the difference is in the original
12 objectives we have two measures which were listed as primary
13 endpoints and two as the secondary endpoints.

14 In the revised objectives, we have five measures
15 which all seem to have the same importance.

16 [Slide.]

17 If we look at the original objectives, survival,
18 which is the primary endpoint, did not achieve statistical
19 significance, but tumor regression, which is the secondary
20 endpoint, is significantly better for the SIRT therapy
21 group. The other two endpoints, with only descriptive data,
22 showed no difference between the two groups.

23 [Slide.]

24 In the revised objectives, we have tumor response
25 rate, which is significantly better, and the disease

1 progression, which is also significantly better for the SIRT
2 therapy group. Survival was better, but not significantly
3 better, and complications and quality of life were similar
4 between the two groups.

5 Thank you.

6 DR. GARRA: Thank you very much.

7 At this point, it is time for lunch. What we are
8 going to do is take a break. We want to reconvene promptly
9 at 10 minutes after 1:00 to begin the question session, and
10 Dr. Malcolm will be conducting much of the afternoon
11 session.

12 MR. DOYLE: I would like to just take this
13 opportunity to remind the panel members to be back, you will
14 probably want to get your lunch and bring it in here, and
15 there will be a closed session starting at 12:30, promptly
16 at 12:30 for all the panel members, and the public will not
17 be allowed to attend that, but the panel can come back at 1
18 o'clock when we resume the open session.

19 [Whereupon, at 12:05 p.m., the proceedings were
20 recessed, to be resumed at 1:10 p.m.]

AFTERNOON PROCEEDINGS

[1:10 p.m.]

DR. GARRA: While this portion of the meeting is open to public observation, public attendees may not participate unless specifically requested to do so by the Chair.

What we are going to do now, since we have done the FDA presentations, is I am going to turn the control of this meeting over to Dr. Malcolm, and he is going to first start off with a question session that we didn't have in the morning and then there will be a discussion period, as well.

Panel Discussion

DR. MALCOLM: Are there any general questions from the panel members? Dr. Mehta.

DR. MEHTA: I had a specific question regarding response analysis. We heard both from the FDA and the sponsor that they used multiple methodologies for response analysis including bi-dimensional product or area and a volumetric definition of response.

We also heard some remarks being made that volumetric assessments are superior, therefore, they enhance the data.

A very simple mathematical modeling would suggest that if you take a sphere, a 50 percent reduction in area, it requires a corresponding 67 percent reduction in volume

1 to be equivalent, yet, we were not shown any data for volume
2 versus area response comparisons looking at 50 versus 67
3 percent. All the volume reduction data were at 50 percent.

4 I am wondering if the 67 percent volume reduction
5 data for response analysis are available.

6 DR. GRAY: I am Bruce Gray from SIRTEX Medical.
7 You are quite correct. They are measuring slightly
8 different events. It is not that the volume measurements
9 are more sensitive, they are more accurate. It is in the
10 literature that measurements of volumes actually give you a
11 more accurate estimation of response than areas, and they
12 are less subject to objective discrepancies between
13 observers.

14 What we can do is we can look at the comparisons
15 between the responses using areas and the responses using
16 volumes, and as in the slides that I presented, the volume
17 responses are usually higher than the area, and that is
18 reflected in the fact that it is easier to get a reduction
19 of 50 percent in a volume than an area, but the comparison
20 between the two groups holds up regardless of how you do it.

21 So, at the end of the day, regardless of which
22 technique you use, it is the comparison between the control
23 arm and the treatment arm or the investigational arm that is
24 important, and that difference, and the statistical
25 significant difference between the two holds up regardless

1 of how you measure it.

2 What we haven't done--and I think it probably
3 wouldn't have legitimacy--is to say reduce the volume effect
4 to, say, a 50 percent volume reduction rather than 67
5 percent. We haven't done that.

6 DR. MEHTA: So, let me rephrase my question. If
7 you want to state that you have an X percent response using
8 volume, the criterion should be 67 percent, as alluded to by
9 Chappell, et al., in JCO of January 1999.

10 For example, in your area responses, you suggest
11 that it is 44 percent response rate in patients treated with
12 combined modality therapy versus 18 percent in those treated
13 with chemotherapy alone. This is based on area.

14 Since you have the volume data in the database,
15 would it be possible to access what would have occurred if
16 the 67 percent volumetric reduction had been used as a
17 parameter for response analysis?

18 DR. GRAY: Yes, absolutely. We could quite easily
19 provide that.

20 DR. MEHTA: Another question on response. There
21 are some discrepancies in terms of responses. For example,
22 in the FDA slides that were shown, we were shown a complete
23 responder based on volumetric analysis, but not on area.
24 Complete response is a complete response. It doesn't matter
25 how you look at it, all the tumor is gone.

1 How can you get a complete response by volume, but
2 not by area?

3 DR. GRAY: Because the observations were made
4 between observers. In examining CT scans, one observer
5 might think that there is nothing present, and the other
6 might say, well, there is a shadow present that may
7 represent a tumor. It is a subjective assessment complete
8 response.

9 DR. MEHTA: I thought you took three people to
10 assess the responses and took the two best.

11 DR. GRAY: That is correct. In volumes, that is
12 what happened. When we were assessing volumes, we took two
13 separate independent observers, and if there was discrepancy
14 of more than 10 percent of either, we then took a third, and
15 then we took the closest two, the average of the closest
16 two. All of them were blinded. But for areas, there was a
17 single observer, not two.

18 DR. MALCOLM: So, you are saying for the area
19 evaluation, it was a single observer; for the volume
20 analysis, it was we will say potential triple observers, is
21 that correct?

22 DR. GRAY: That is correct.

23 DR. TOLEDANO: I will keep going on this topic.
24 Dr. Gray, you just made a statement that you found the
25 volume measurements to be higher in reliability than the

1 area measurements. Do I have that accurately?

2 DR. GRAY: No. In the literature, there is
3 evidence, particularly from the work of Ettinger from about
4 a decade ago, suggesting that areas have an inherent
5 subjective variation which you can overcome if, in fact, you
6 measure the total volume of the tumor rather than measuring
7 the areas.

8 I am not saying that in our study, one is more
9 accurate than the other. So, what we have done is we have
10 done both areas and volumes.

11 DR. TOLEDANO: Could you provide some rationale
12 for doing the volume with two out of three, but the area
13 with a single observer?

14 DR. GRAY: Manpower resources. It was as simple
15 as that.

16 DR. MALCOLM: Other questions? Dr. Mehta.

17 DR. GRAY: Perhaps I can just finishing answering
18 that. In the data that we have provided to the FDA, we
19 provided all of the data, not just the average of the two or
20 the three. We actually provided in the individual
21 recordings of every observer, so you can take any one you
22 want.

23 DR. TOLEDANO: So, I will respond to that.
24 Depending on which one I take for volume, I get a different
25 answer as to statistical significance, and that is in the

1 PMA actually filed by SIRTEX. So, if I take JA's readings
2 on eligible patients, the p is greater than 0.05, but if I
3 take PM's readings, the p is 0.02, and then if I take the
4 average, which is the best two out of three, then, the p is
5 0.03. Two of those are statistically significant, one is
6 not.

7 DR. GRAY: Correct.

8 DR. TOLEDANO: That makes me uncomfortable.

9 DR. GRAY: That is just inter-observer variation,
10 and the way we have tried to address that is by having
11 multiple observers and taking means, and the data that I
12 presented on the slides today were the means.

13 DR. TOLEDANO: What impact do you think that has
14 on clinical practice because when this comes off study, in
15 actual clinical daily practice, you are going to have inter-
16 observer variability.

17 Do you think that the conclusions will be robust
18 to this inter-observer variability when they are placed out
19 into the field?

20 DR. GRAY: Yes, I do because if you look at the
21 variations between observers, the trend is always the same.
22 There may be slight individual variations in any particular
23 measurement, but the direction is the same throughout all
24 the observations. Sometimes it will hover on statistical
25 significance and other times it won't.

1 DR. MALCOLM: Dr. Mehta.

2 DR. MEHTA: Continuing on the tumor regression
3 since that is one of the major endpoints that has been shown
4 to potentially favor the treatment arm, we have 11 patients
5 all together for whom the category Other is applied. In
6 other words, we don't have data for response for these 11
7 patients.

8 That leaves us with a total of 59 patients on
9 study, 27 on one arm, 32 on the other, for whom we have
10 response data. What happened to these other 11 patients?

11 DR. GRAY: May I ask Dr. Hope to answer that?

12 DR. HOPE: I haven't got the individual data in
13 front of me, but the vast majority of those are patients
14 where there was not a follow-up scan, which you need to
15 assign a status, so you cannot say whether they had no
16 change, whether they had progressive disease, or whether
17 they, in fact, had a response. So, they only had a single
18 baseline scan in the majority of cases. So, we had to say
19 Other.

20 DR. GRAY: For instance, if a patient had a 50
21 percent reduction in volume, area, or whatever you want to
22 measure it, and subsequently died six weeks later, they
23 would not be recorded as a response because there wasn't a
24 supporting subsequent scan.

25 DR. HOPE: These are people who just have a

1 baseline without a follow-up scan, because we had a three-
2 monthly gap in the scans, not one-monthly, which is more
3 usual.

4 DR. TOLEDANO: To follow up on that question
5 again, so following up on the small sample size and the
6 question of the patients who fell into the Other category,
7 if even one or two of those fell differentially into the
8 responders or not responders across the two arms, you would
9 often lose the statistical significance that you see in
10 these tables. These results are very fragile.

11 Can you have perhaps your statistician address
12 what would happen if a few patients fell differently?

13 DR. GEBSKI: The problem of analyzing response
14 versus non-responses is always very difficult because it is
15 hard to know what you, say, do, as Dr. Gray said, with early
16 deaths, whether you classify them as responders or non-
17 responders, and what do you do with patients who aren't
18 eligible for response, in other words, you have lost them,
19 and you can actually induce a bias by making decisions one
20 way or another.

21 Perhaps one could do a sensitivity analysis where
22 you could assume, say, that they all did respond, and I gave
23 them all a PR or CR, or you could say, well, no, they all
24 didn't respond and never would, or you can omit them.

25 I think experience has shown that you are never

1 going to necessarily please everybody by doing any one of
2 these, and we sort of have chose to take a course of saying,
3 well, let us exclude the patients in unknown category rather
4 than perhaps arbitrarily give them status.

5 Now, it is not too difficult to do the sensitivity
6 analysis, you could evenly divide them, but we assume that
7 that randomization would have perhaps to some extent
8 balanced the bias by excluding them, would just give us
9 perhaps a more reasonable picture of what the underlying
10 response rate was.

11 DR. MALCOLM: Additional questions?

12 MR. AYRES: I had a question on a different topic.
13 Under Device Failures and Replacements, you quoted a
14 leaching of a tenth of a percent, and from very early
15 studies in this area, it is known that if you get a lot of
16 free yttrium-90, you have got a real problem. That is only
17 one point.

18 Have you studied the leaching as a function of
19 time particularly due to autoradiolysis? I am assuming you
20 are planning on shipping the material from Australia to the
21 U.S., which would allow a significant time between
22 production and use. Do you know whether the free yttrium-90
23 changes is a function of time during the decay of the
24 material?

25 DR. HOPE: You had two questions in there?

1 MR. AYRES: Well, one was concerned about the time
2 between production and use, and all of it was related do you
3 have a time-dependent study on the free yttrium ingrowth
4 into the material or if there is any?

5 DR. HOPE: Currently, our interaction in terms of
6 how the microspheres are constructed is considered
7 proprietary and we would be happy to talk to you about that
8 separately. However, I can tell you that there is no
9 alteration with time. We have certainly got some data on
10 that, that is available, which we would be happy to talk to
11 you about.

12 The second question was regarding shipping and
13 duration, and the question there is related to the time--

14 MR. AYRES: It was the same. It was just
15 qualifying why my concern and interest in the ingrowth of
16 free yttrium, if any, as a function of time, because one
17 would expect a greater length of time between manufacture
18 and use when shipping to the U.S.

19 DR. HOPE: There isn't an issue, and we can
20 certainly talk to you regarding that.

21 DR. MALCOLM: Geoff.

22 DR. IBBOTT: A couple of small questions. Your
23 calculation of lung shunting, I am wondering, in the
24 denominator of your equation, you have the activity taken up
25 by the liver, but you don't include the activity taken up by

1 the tumor, and I am wondering why not.

2 DR. GRAY: We do, and if that is an
3 interpretation, then, we obviously have a problem in making
4 it clear. The amount that goes to the lung is the
5 percentage of the total amount that ends up in the lung, and
6 the denominator is both the amount in the tumor and the
7 amount in the normal liver.

8 DR. IBBOTT: I suspected that, but the way that
9 equation is written next to the others didn't make that very
10 clear.

11 Another question about radiation safety issues.
12 You ship the activity in a glass vial encased in a lead pig
13 with fairly high-energy beta particles in high-Z materials.
14 You get a fair amount of bremsstrahlung.

15 What sort of exposure rates or air-kerma rates do
16 you expect outside the shipping container?

17 DR. GRAY: It certainly falls within all of the
18 safety guidelines. I can't give you the exact details, but
19 it is shipped from the Australian nuclear reactors, the
20 government reactor at Sydney. I can provide you with those
21 figures, but I can't give them off the top of my head. It
22 is true that about 1 1/2 percent of it will come off the
23 secondary as bremsstrahlung and gammas.

24 DR. IBBOTT: Related to that, in the labeling you
25 mentioned that patients are advised to avoid contact with

1 women of child-bearing age and children, what do you expect
2 the dose to those people to be in the vicinity?

3 DR. GRAY: Virtually nil. It is almost to protect
4 ourselves from litigation. It is absolutely a precaution.
5 There is no radiation safety reason why that should happen
6 other than as a general overall global precaution.

7 DR. IBBOTT: Thank you.

8 DR. MEHTA: I have a question regarding the Phase
9 II study, but I want to ask a clarification first before I
10 ask the question. The patients who went on the Phase II
11 study with liver metastasis, were they a comparable
12 population to the Phase III population?

13 DR. GRAY: In general, yes, they were all patients
14 who had non-resectable advanced liver cancer. In the Phase
15 III, we restricted it more tightly to people that did not
16 have disease outside their liver.

17 There was a substantial cohort of people in the
18 Phase II that also had extrahepatic disease, as well, but a
19 clinical decision was made that it was the liver metastases
20 that was the life-threatening event, and therefore, control
21 of the liver metastases should translate into patient
22 benefit. So, they actually selected a slightly worse
23 population than the patients in the Phase II trial.

24 Now, with time, with the egress of time, our
25 indications for local regional ablation have actually

1 expanded, so some of the patients that were treated in the
2 early Phase II studies in the year 2000 would be subjected
3 to fairly radical surgery.

4 So, it is actually a mixture.

5 DR. MEHTA: So, let me go and ask my question. In
6 the Phase II study, you had 16 patients that were treated
7 with spheres alone, they got no chemotherapy.

8 DR. GRAY: Correct.

9 DR. MEHTA: These 16 patients had a response rate
10 of 73 percent.

11 DR. GRAY: Correct.

12 DR. MEHTA: In the Phase III study, the response
13 rate on the combined modality arm is 44 percent, the
14 chemotherapy response is 18 percent.

15 DR. GRAY: Yes.

16 DR. MEHTA: If you subtract those numbers, you get
17 a number of 26 percent, which is the response rate that can
18 be ascribed to the spheres alone. So, you have gone from a
19 73 percent response rate in a potentially worse population
20 to a 26 percent response rate in a more favorable
21 population.

22 DR. GRAY: Yes.

23 DR. MEHTA: Does this imply that the response rate
24 is highly dependent on patient selection variables?

25 DR. GRAY: No, I don't think so, but the criteria

1 used for response in the Phase II was slightly different
2 from that in the Phase III. The response data in the Phase
3 II was based on volumes, and not on areas.

4 DR. MEHTA: The numbers I gave you are area based,
5 44 minus 18.

6 DR. GRAY: Yes, but in the Phase II, it was based
7 on -- sorry, it was based on volumes, but in the Phase III,
8 it was based on either volumes and areas, and in the Phase
9 III study, it was necessary to maintain a diminution in the
10 size of the tumor either completely or by 50 percent for at
11 least three months, and in the Phase II study it was one
12 month.

13 We were restricted in the Phase III study by our
14 inability to do CT scans at monthly intervals because of
15 cost constraints. So, the criteria used in the Phase III
16 were much harder to achieve.

17 DR. MALCOLM: I was actually leading to that same
18 question, but perhaps this also will fit. I couldn't
19 distinguish which patients--this is a clinical question--
20 which patients would undergo a surgical procedure, i.e., the
21 placement of a catheter, hepatic catheter, versus those who
22 have femoral approach. I didn't know if that was patient
23 selection again, sicker patients, I couldn't distinguish the
24 two at all.

25 DR. GRAY: In the data that I presented in the

1 Phase II studies, all of those patient that had additional
2 chemotherapy, had hepatic artery catheters placed. In the
3 Phase III study, they also had hepatic artery catheters
4 placed. We have treated many patients outside of the
5 context of the Phase III study over the last eight years,
6 and in reality, for instance in the year 2000, you wouldn't
7 actually get an hepatic artery catheter, you would get
8 systemic chemotherapy, and you would probably get it in the
9 context of another trial that is running at the moment.

10 In other centers, such as in New Zealand and in
11 Hong Kong, for instance, it is now universally delivered via
12 a trans-femoral catheter.

13 DR. GARRA: I have a couple of questions, one of
14 them relating to technique. There are comments in the
15 labeling about positioning of the catheter for delivery of
16 the material, flow rates. These were determined, were they
17 just ad hoc or were they determined experimentally?

18 For instance, you say don't deliver at a rate more
19 than 5 cc per second, I think, to avoid reflux into the
20 gastroduodenal artery. Were those determined just by
21 talking with your angiographers and using contrast material
22 to simulate it or what?

23 DR. GRAY: Yes, they were. We have not done any
24 studies in terms of reflux and flow rates.

25 DR. GARRA: You did not report any adverse

1 reactions that would suggest that there was necrosis of the
2 duodenum, so I presume that there was no case of reflux into
3 the gastroduodenal artery that you know of.

4 DR. GRAY: Not within the data that we have
5 presented. We have got experience of one patient with that
6 about eight months ago, and there has been several cases
7 reported from Hong Kong, but not from our data.

8 DR. GARRA: Okay. One other question I had
9 regarding technique, and that has to do with multiple doses
10 of this agent. It is mentioned in the submission that a few
11 patients have received multiple hits of this material, but
12 it wasn't clear to me what happened to them, whether they
13 did better or they did worse. Since it is reasonable to
14 assume that a person who gets the agent and then responds
15 and then after a period of time doesn't seem to be doing as
16 well, they might be pressured to do a second dosage.

17 I would like to hear your comments about those
18 patients.

19 DR. GRAY: There is two lots of experience there.
20 There is our own experience in Australia, and there is again
21 the experience that is coming from the Chinese University.
22 It is common practice at the Chinese University to repeat
23 doses. In fact, they have one patient where they have
24 actually administered five doses.

25 In our experience, it generally isn't required.

1 Off the 200-odd patients that we have treated in Perth,
2 approximately seven have had repeat doses on one second
3 occasion. The reason it is not required is that on clinical
4 indications, it is an unusual scenario to have progression
5 of disease in the liver without progression of disease at
6 another site.

7 So, they get regression in the liver, and if there
8 is subsequently progression, the vast majority of the time
9 there is disease at other sites, as well, and on clinical
10 grounds we would say that would mitigate against giving a
11 second dose. Most people would then pass on to systemic
12 chemotherapy if, in fact, they hadn't had it already.

13 The scenario I think is different with primary
14 hepatocellular cancer. In that situation, it is common that
15 the cancer stays inside the liver, and they die of
16 progression of the disease after a period of remission. In
17 that situation, causing subsequent regression is considered
18 to be potentially beneficial to the patient.

19 So, you are much more likely in primary
20 hepatocellular cancer to consider second dosing.

21 DR. GARRA: Thank you.

22 DR. HARMS: The lack of a statistical difference
23 between the experimental arm and the control arm in survival
24 presumably was due to extrahepatic disease. You didn't
25 elaborate on that, but I wonder if there was a difference in

1 those two arms in terms of people with liver failure, you
2 would presume the people on the experimental arm would have
3 less liver failure than on the control arm. Do you know
4 about that?

5 DR. GRAY: Yes. I actually did show a slide on
6 that. Very much so. If you look at, for instance, the
7 patients that die in the first 15 months after
8 randomization, the pattern of disease failure is quite
9 different from those that die subsequent to that.

10 There is a much higher likelihood of dying of
11 extrahepatic disease before 15 months than after 15 months,
12 particularly in the experimental arm. I am trying to think
13 back to the slide, but it actually reaches statistical
14 significance, so patients who actually don't develop
15 extrahepatic disease after 15 months, and they are the ones
16 that survive greater than 15 months, the chances of them
17 actually dying or progressive liver disease is substantially
18 less if they received the experimental treatment even though
19 eventually, at the end of the day, the vast majority of
20 these people are going to die of disseminated cancer, but
21 that pattern is quite different.

22 MR. AYRES: I noticed in reading through the data,
23 and then you confirmed it earlier this morning, that the
24 patient had been administered the SIR-Spheres in two
25 different manners, one by syringe injection, and the other

1 with the infusion set that you document on page 1809.

2 I guess it just boiled down to the question, what
3 are you applying for approval for, both, or just the
4 infusion set method of administering the materials?

5 DR. HOPE: The PMA submission is for the use of
6 SIR-Spheres. The method of administration is the choice of
7 the physician.

8 MR. AYRES: I confused a little bit then. It
9 seems like the infusion set is part of your labeling.

10 DR. HOPE: Can I comment on that?

11 MR. AYRES: Okay.

12 DR. HOPE: In Australia, we do use that, and we
13 have put it in there as a helpful prompt for the physician's
14 information. It is a separate device.

15 MR. AYRES: You believe either method, physician's
16 choice, would be appropriate then, and that is what you are
17 asking for approval for.

18 DR. HOPE: Yes.

19 MR. AYRES: And the patient data includes a
20 mixture of both types of methods of administering the
21 material in the Phase III trials?

22 DR. HOPE: Yes, it does.

23 DR. GARRA: The FDA, the people who reviewed the
24 proposal, they have the same understanding of the exact
25 mechanism of administration?

1 MR. MONAHAN: It is my understanding from looking
2 at the PMA that the administration set is included as part
3 of the PMA, so that when we approve the PMA for the device,
4 that the administration set would be part of that approval.

5 How the treating physician chooses to administer
6 the SIR-Spheres, whether using that administration set or
7 using a syringe is the physician's option. Does that make
8 sense?

9 DR. GARRA: That makes total sense. Just a brief
10 comment. The manufacturer is aware that the FDA will not
11 regulate the physicians, but the NRC can regulate the
12 physicians on exactly how they do it.

13 MR. AYRES: That was my comment. We may parallel
14 the panel and the FDA's approval process, which would
15 mandate the one system, if that is all the FDA ends up
16 approving.

17 DR. TOLEDANO: If the FDA, the panel, the NRC,
18 whoever, decides to go with the infusion set through the
19 port, how many of your 700 total patients would be relevant?

20 DR. GRAY: Who would have used the disposable
21 infusion set? It is not used, for instance, at all in Asia.
22 We have been using it in Australia for six years, I suppose,
23 approximately six years, so it may be 25 percent. It
24 matters little in terms of delivery. It is simply a more
25 convenient way of doing it.

1 MR. AYRES: A radiation safety related question.
2 Do you have any idea of the difference in the dose the
3 physician receives between the two methods of administering
4 the material?

5 DR. GRAY: We do have data on that, but I don't
6 have it at my fingertips, but I could certainly provide it
7 for you.

8 DR. GARRA: That would be of significant interest
9 to me as a person who does angiography on occasion, knowing
10 how much exposure I am getting to betas on my hands would be
11 really important, and I am sure the NRC will probably be
12 interested in seeing that information.

13 DR. MALCOLM: Dr. Mehta.

14 DR. MEHTA: I would like to change my endpoints
15 from response to something different at this point. One of
16 the other interesting endpoints that was presented was time
17 to disease progression.

18 As I jotted my notes down, I wrote that down as
19 approximately 7.7 versus 12 months in terms of time to
20 disease progression between the two arms of the study, but I
21 also understand that this is time to disease progression
22 only in the responders.

23 Do you have time to disease progression in the
24 entire cohorts on both arms?

25 DR. GRAY: No, we don't. The time to disease

1 progression -- I am sorry --

2 DR. MALCOLM: Please clarify the point. Do you
3 have the data?

4 DR. HOPE: I will just double-check that for you,
5 but I do believe it was time to disease progression for all
6 patients randomized.

7 DR. MEHTA: So, let me just clarify to make that I
8 understand it correctly. The 7.7 versus 12 months
9 represents all patients on both arms with no exception?

10 DR. HOPE: I shall just double-check that for you.

11 DR. MALCOLM: Page 1695. Are there any other
12 questions while we are waiting to clarify this one?

13 DR. HOPE: On page 1694 is the time from
14 randomization to the time at which progressive disease was
15 recorded. The bottom paragraph, page 1694.

16 DR. VISHNUVAJJALA: I did find it. It is based on
17 all the patients. It is 34 patients with the chemotherapy
18 arm and 36 for the SIRT therapy arm.

19 DR. IBBOTT: You have to forgive me if I am not
20 understanding the submission correctly, but I think this is
21 related to the previous question. In the June 2000 response
22 to the FDA, you have a similar table on page 15 describing
23 the responses for patients receiving chemotherapy-only and
24 those receiving the SIR-Spheres plus chemotherapy.

25 I don't understand the number in that table. If

1 those are numbers of patients, there appear to be too many;
2 if they are percentages, they are not enough.

3 DR. GRAY: I agree. That is a confusing table.

4 DR. HOPE: Page 15. The table that we put up
5 today was those separated out. This one is a cumulative
6 table saying if we counted only these patients, we would
7 have that many, if we then softened the responses, we would
8 take patients that had a reduction of between 50 and 25, and
9 we add those in, so that is why the numbers, it's a
10 cumulative table.

11 DR. GRAY: So, a patient who had a 50 percent
12 response would also be included in the table, but all
13 patients who got at least a 25 percent response. It is not
14 a well-structured table.

15 DR. IBBOTT: In that case, are there only 12
16 patients in the chemotherapy arm and 22 in the combined arm?

17 DR. HOPE: Who received a response.

18 DR. TOLEDANO: It is 12 out of the 34, and the
19 remaining 22 had progressive disease or stable disease.

20 DR. IBBOTT: So, then it is really more than zero
21 percent response. That confused me.

22 I didn't read anything in here relating to quality
23 assurance. Do you make any recommendations for procedures
24 to be followed in the hospital when they receive the
25 material or draw it up to verify the activity?