Dr. Stacey Brennan: Thank you. Welcome back, I'd like to turn things over to Dr. Julie Kessel, who is the Chair of our CAC panel. She is going to lead the remainder of the meeting, starting with questions from the panel for the Novocure presenters, Dr. Julie Kessel.

Dr. Julie Kessel: So, thank you everybody. Thank you to our Novocure representatives and to you, especially, sir for your sharing your personal story with us. We're going to have about an hour and a half or so, 12:15, 12:30 for our CAC panel to direct questions at you related to any of the five questions, in any order. And, hopefully, this will be a robust discussion, then we'll break for lunch, and then we'll come back, and the CAC members will deliberate publicly, but amongst ourselves and then record the assessments for each answer, and then we will share them with you.

Dr. Julie Kessel: So, I'd like to open it up, I'd like to make this informal for our CAC panelists, and let's see how it goes if you would like to ask a question, just go ahead and do it, and we'll see if we can share the space without much more formality than that.

Dr. Julie Kessel: Would someone like to open with a question?

Parashar Patel: I guess I'll ... go ahead.

Parashar Patel: So, I'm just kind of curious, you had mentioned numbers of prescribing physicians, 1,042 I think something like that. What's the denominator? So, in other words how many ... Is that 10% of the universe of physicians treating these patients, or is it 20%, 80%?

Bill Doyle: Figure out how we do this with the ... And I think what we've decided to do, we'll hold the mic, and we'll pass it back and forth. So again, I'll start with the fact that as we said, 59 of the 62 NCCI cancer centers are now certified in prescribing, so in terms of the academic centers, it's the vast majority.

Bill Doyle: Sixty percent of newly diagnosed GBM is treated in the community, this is why it's a little harder for me to give the denominator; because for some of the community physicians, they may see one or two GBMs a year.

Bill Doyle: But for the academic centers where it's more concentrated, and where the other 40% are seen in the 200 or so academic centers, it's certainly a substantial majority of those clinicians who are certified and prescribe.

Dr. Julie Kessel: Yes.

Dr. Henry Fishman: Go right ahead.

Dr. Julie Kessel: Just go-ahead doctor.

Dr. Henry Fishman: I believe there's evidence that suggests that tumor treatment fields may be synergistic if given with radiation therapy instead of sequentially. Are there ongoing trial looking at that?

Bill Doyle: Yeah so, of course, today we're here to focus on the on-label indication, which is the use of tumor treating fields as adjutant therapy with Temozolomide after radiotherapy. The data that we showed you, the .63 hazard ratio P001 data were in that indication.

Bill Doyle: There are indications that tumor treating fields is a radiosensitizer, and there are today investigator-sponsored trials. In fact, there's one at Johns Hopkins, which is leading the efforts in this area that are underway. So, we expect the community clinicians to report first on this, and they we'll consider whether a phase three trial to prove it, prospectively, is warranted.

Dr. Julie Kessel: Thank you. Is there a question from the side? Yes.

Dr. Cary Gross: I was glad to hear of this connection with Johnson & Johnson because, as you're probably aware, the Institute of Medicine has recommended sharing patient level clinical trial data with the scientific community.

Dr. Cary Gross: In addition to that, the International Council of Medical Journal Editors has recommended clinical trial data sharing. Yeah, we have a collaboration with J&J where they have agreed to share the patient level data in over 200 clinical trials.

Dr. Cary Gross: Other industry sponsors including Lilly, GSK, Roche, Novartis, Sanofi all have made commitments to sharing their clinical trial data. Given the importance of the EF-14 trial to the scientific community, would you be willing to commit today to making de-identified patient level trial available to the scientific community for their analysis?

Bill Doyle: So again, I'll repeat what I said before. That, of course, we're here today to consider the Medicare LCD reconsideration for the use of Optune® therapy for newly diagnosed GBM patients as directed based on the data.

Bill Doyle: As I mentioned during my presentation, all of that data, and it's now delivered electronically but if it were in paper, it's basically a forklift full of data that was delivered to FDA and was evaluated.

Bill Doyle: What I will commit to today is we'll consider that because, as you say, the EF-14 is the only successful phase three trial in newly diagnosed GBM since the original Temozolomide trial. It clearly is important for the community, there are very interesting aspects to study, so I will commit to taking that under consideration and reporting that soon to the community.

Dr. Julie Kessel: Thank you doctor.

Dr. Annick Desjardins: So, the same type of idea, just question about EF-14. So, 1,019 patients were screened, and 324 patient were excluded. Some of them were excluded from good reason, they didn't mean eligibility.

Dr. Annick Desjardins: But some patients just refused to go in the trial, didn't want to use the device. So, what we calculate is about 182 patient, we really don't know why they were screen failure. What do you have the characteristic of those patients? What were their age, their KPS, information about those patients that you could share?

Bill Doyle: Let me turn this to-

Dr. Adrian Kenzel: Yeah, so we do have all the numbers of these and 324 patients who were excluded of the trials, so most of the patients due to early progression.

Dr. Adrian Kenzel: So, 82 patients were excluded due to early progression. Back to your question, how many patients did not want to use the device? Forty-six, so 5% of the whole patient population.

Dr. Annick Desjardins: Okay, but what I was asking is, do we have the characteristic? What I'm trying to figure out is why were they refusing to go on the trial? Did they feel that it was too demanding on them? So that's why I was asking. Caregivers support, KPS, and age, things like that. Trying to figure out why.

Dr. Adrian Kenzel: No, we just know that 46 patients didn't want to use the device.

Dr. Annick Desjardins: Okay.

Dr. Julie Kessel: Thank you. Yes, doctor.

Dr. Arnab Chakravarti: Yes. We're moving more towards an era of personalized care where we like to tailor the treatment towards an individual's tumor; that's our ideal, at least. So, in that context, what are the predictive biomarkers of response to TTF?

Dr. Arnab Chakravarti: You presented some data on MGMT methylation, and just a quick read on that data seemed to indicate that there was maybe greater efficacy in MGMT methylated versus un-methylated patients. Are you proposing that MGMT methylation might be a predictive marker in that setting? Either way, are there other predictive biomarkers that may guide TTF therapy for this patient population?

Bill Doyle: So maybe I'll let Matt take the first crack at this, and then I'll follow up.

Dr. Matthew Ballo: I mean, it's clear that both MGMT methylated and un-methylated benefit from-

Dr. Arnab Chakravarti: But there is a dramatic difference, right?

Dr. Matthew Ballo: There is-

Dr. Arnab Chakravarti: There is methylated patients, it was 31 months versus like whatever-

Dr. Matthew Ballo: Right.

Dr. Arnab Chakravarti: Twelve months.

Dr. Matthew Ballo: There is a difference. There are-

Dr. Arnab Chakravarti: For un-methylated patients, the difference was a month and a half or so.

Dr. Matthew Ballo: Right. And there were differences in some of the other subgroups, the older than 65, less than 65, also in the patients that had biopsy only. So, there are differences in those subgroups that may just be statistical.

Dr. Matthew Ballo: But I absolutely understand the question, and I think that that's an active area of interest. I mean, everyone is very interested in being able to figure out who is responding and who isn't responding.

Dr. Matthew Ballo: But the thing that I have been most interested in is trying to understand the physical property, and trying to understand the intensity through the tumor bed, and trying to figure out if that is a predictor of who's responding and who's not responding.

Bill Doyle: Maybe I'll just-

Dr. Julie Kessel: Yeah.

Bill Doyle: Follow up briefly. If you'll recall from the discussion of the mechanism of action, this is an antimitotic. So, where many of the therapies that are also advancing through the research pathway are focused on specific genotypes, phenotypes, microenvironments, we really are focused on a very fundamental aspect of cell division.

Bill Doyle: As Dr. Matthew Ballo said, the biggest correlation we see is with dose density. And so those patients who both, today, have a tumor that is receiving greater than this 1.1 milliwatts per CC, and have a long duration perform better regardless of a specific biomarker.

Bill Doyle: We do personalize the therapy so, in our case, we personalize it as was discussed based on the placement of the arrays. Based on the work that Dr. Matthew Ballo and his colleagues have performed on these maps from the EF-14 trial, we are now improving and making the maps more sophisticated in a way to increase the dose density for all patients. So, this does give us, like all therapies, we do have paths to improve further beyond the results that we have reported today.

Dr. Arnab Chakravarti: So, all patients on EF-14 received the same dose of TTF, or do they receive different doses?

Bill Doyle: It depends on their location of their tumors.

Dr. Matthew Ballo: Right, and no not at all. So, what we're finding is that when we went through, there were 466 patients who received the Optune® device. And then we looked at the 340 patients that we had sufficient MRI to be able to do the calculations of their tumor treating field dose, and who had used the device for more than two months.

Dr. Matthew Ballo: So that was in the paper that we're currently working on. And patients had a customized array layout that would try to increase the field intensity through the region of the tumor. And then now that we're actually doing patient specific calculations, we are finding that the interface between high conductivity and low conductivity tissues is actually having a very large influence on the field intensity distribution.

Dr. Matthew Ballo: And that that interface between different tissues, fluid, or gray matter/white matter, or contrast enhancing tumor, that interface may actually be more important than the array layout.

Dr. Matthew Ballo: So, the array layout is kind of the first step, but what we're seeing in these calculations is that it's the interface between tissues that has a much bigger influence.

Dr. Arnab Chakravarti: If I could interrupt-

Bill Doyle: I'll just mention one more statistic and then-

Dr. Arnab Chakravarti: I just want to follow up on that point.

Bill Doyle: Yeah, the statistic I wanted to mention is just to underline 86% of all treated patients in the trial benefited beyond the control. The degree of that benefit was a function of intensity, as Dr. Matthew Ballo described.

Dr. Kevin Camphausen: So, the calculations that Dr. Matthew Ballo is describing are based on the MRI images of the patient. And I've asked several times, through the committee, to have data of measurements from within the patient. So, the calculations that are doing are a mathematical calculation based on an enormous number of assumptions. What measurements do we have of the dose?

Bill Doyle: Sure, so as you described this is physics, and we know the key property is called the dielectric constant. And we know the dielectric constant of skin, we know the dielectric constant of skull, we know the dielectric constant of the various tissues in the brain, including tumor that allow us to make these calculations.

Bill Doyle: Early in the development of tumor treating fields, in order to confirm the value of these models, as I mentioned during operations ... So, a patient who was undergoing brain surgery, we would place arrays on the skull and, with a probe, measure the field strength in the brain. So, we were able to confirm what the physical modeling and calculations provide.

Dr. Kevin Camphausen: So, you said that; where's the data for that measurement?

Bill Doyle: We have that data within the company. As-

Dr. Kevin Camphausen: Has it been published?

Bill Doyle: I don't believe those data have been published.

Dr. Kevin Camphausen: Okay. So, the assumptions we're going off of, you're asking us that the company is holding data about the dose that's actually measurable within a patient, that we're using to do mathematical calculations, that the paper that you sent to us says there's roughly a 60% variability in the dose across various regions within the brain. But we're not sure if that's true, if that's been measured?

Bill Doyle: No, we, again, we're very confident. And these data were all provided to the FDA in their review of the PMA. So, as I said, that was a many month review, and they had all the basic measurement data as part of their review.

Dr. Julie Kessel: Let's go Dr. Jonathan Sherman, then Dr. Edjah Nduom, and then Dr. Freeman.

Dr. Jonathan Sherman: Got two quick questions. One, related to the placement of the arrays for multi-focal glioblastoma, do you have the data that shows efficacy? Was it subgroup analysis in the F-14? Because it didn't look like that was exclusion criteria for multi-focal here.

Dr. Matthew Ballo: No, I don't believe there's been any subgroup analysis of that so far.

Dr. Jonathan Sherman: And what about biopsy versus subtotal, versus gross total, and degree of outcome related to using the TTP?

Dr. Matthew Ballo: Sure, in that forest plot that all three groups benefited from the therapy.

Dr. Jonathan Sherman: [inaudible 00:16:03]

Dr. Matthew Ballo: There was no subgroup that didn't benefit. Those who have biopsy only benefited from the therapy, those who had gross total benefited, subtotal benefited. Those were actually-

Dr. Jonathan Sherman: Was that equal benefit between or is there a differential?

Dr. Matthew Ballo: I mean, the magnitude of that hazard ratio seemed to be actually the largest for the patients that had biopsy only.

Dr. Jonathan Sherman: Okay.

Dr. Matthew Ballo: But it was positive for all three groups.

Dr. Jonathan Sherman: Okay.

Dr. Julie Kessel: Just one correction, Dr. Paul Zeltzer, go ahead.

Dr. Paul Zeltzer: I had a question related to how this might be used in the community in the population that's under discussion here. In the community, older patients may sometimes receive a decreased dose of radiation compared to the usual dose; 60 versus 40 for three or four weeks versus six weeks.

Dr. Paul Zeltzer: Were there any patients that you know of that, in fact, received less radiation? And do you have any information about that subgroup? Or was there a subgroup that was it ... Or were they excluded if they had-

Dr. Matthew Ballo: My understanding is everyone was treated per protocol, and that was 60 gray of radiation therapy was the protocol treatment.

Dr. Paul Zeltzer: So as far as you know, there were none that were treated with the lower dose?

Dr. Matthew Ballo: Are you aware of it?

Dr. Adrian Kenzel: So, some patients there was a range but, overall, it was 60 gray.

Dr. Julie Kessel: Dr. Edjah Nduom.

Dr. Edjah Nduom: Sorry, I was trying to follow up with Kevin's comments because mine is similar. I was an engineer in college, this stuff is fascinating to me. In the 2007 PNAS paper, you referred to a single patient who was having resection for a large [inaudible 00:17:44] region meningioma and said that fields were similar within about 10% by direct measurement.

Dr. Edjah Nduom: It's down in the methods but, again, that data in that field isn't presented. Was that submitted to PNAS? Was that in some sort of supplemental information? Because that's the reference throughout the rest of everything that we received, that you keep going back to say that there was direct measurement within humans to say that the fields were what they were. So, it's just kind of follow-

Dr. Matthew Ballo: Yeah.

Dr. Edjah Nduom: The data seems to ... it's referred to many times, and that's the basis of the claim is that 2007 PNAS paper, but that information isn't in that specific reference. So what format was that information provided to anyone to back up that claim?

Dr. Adrian Kenzel: Okay, so you can [inaudible 00:18:33].

Dr. Adrian Kenzel: So, in the reference, you just referred to, and we are explaining the situation. So, in this reference, it clearly says that there was a patient undergoing surgery. He received a vp shunt, and during this procedure, we were able to confirm the analysis that we've done before. So, it's, I mean, it is in this publication that you just mentioned.

Dr. Edjah Nduom: But there are multiple patients, not just that single patient that there is data from direct measurements?

Dr. Adrian Kenzel: Direct measurements were performed in this single patient, in many animal models, and so there's ongoing research on this end as well.

Bill Doyle: I guess I failed to mention that, as well, of course we did this during the pre-clinical animal phase with large animals with skulls that are approximately human size skulls. So, this, as I said, the physics here is fairly established. In all the data, both the pre-clinical data and the clinical data were all in the data package that was reviewed by the FDA.

Dr. Edjah Nduom: Were the large animal data published? Because same thing, the PNAS papers, the paper that's referred to, and there's none of the large animal-

Bill Doyle: No-

Dr. Edjah Nduom: Field-

Bill Doyle: These data have not been published. They're provided to the FDA, but not published.

Dr. Edjah Nduom: All right, thank you.

Dr. Julie Kessel: Dr. Holdhoff.

Dr. Holdhoff: Yeah, so I'm a medical oncologist treating brain cancer patients, and most of my patients are patients with high grade gliomas and with glioblastoma. I'm not an engineering person by background.

Dr. Adrian Kenzel: It's all right.

Dr. Matthias Holdhoff: And so first of all, I want to say that all of us here in the room, especially the ones who treat primary brain cancers, we want something that really works and that can push the needle forward.

Dr. Matthias Holdhoff: So, we take any published positive results very, very seriously. However, they're a little bit differently from the way we perceived it has been presented. There is ongoing skepticism in the neuro oncology community regarding whether the data that represented in EF-14 are actually true.

Dr. Matthias Holdhoff: And the main concern that's brought up is that this was not a placebo-controlled trial. You can make an argument that, certainly, Temozolomide was not a placebo-controlled trial.

Dr. Matthias Holdhoff: However, wearing the Novo TTF device or the TTFT versus taking a pill really makes a difference for patients. And we know a number of patients who wear the device or most patients who don't want to wear the device because of the reasons mentioned: shaving your head, wearing it 22 to ... More than 18 hours a day, wearing the backpack; those data are not captured.

Dr. Matthias Holdhoff: So, you mentioned the acceptance in the neuro oncology community, and the NCCN guidelines are one guideline as published in the Washington State Healthcare Authority Report. There were other guidelines that did not endorse Novocure for the treatment of these patients.

Dr. Matthias Holdhoff: We really want this concept to work. The skepticism we have, the problem we have in really making recommendations as often, and this is shared by many colleagues in the field. Do we feel that the data really support what's going on?

Dr. Matthias Holdhoff: So, we understand that they were considerations for a sham controlled trial, and that there were reasons for not doing it. The hypothesis is that we know that there are data in non-brain tumors that showed an effect from Novocure.

Dr. Matthias Holdhoff: Wouldn't it be, for example, an option to a sham controlled trial there and, I mean, we would love to see data from a sham controlled trial in patients with glioblastoma. If the data positive, I think it would be much easier for everybody to adapt the concept, and I think it would serve the neuro oncology community a great deal. Are you planning such as trial?

Dr. Matthew Ballo: I can't speak to whether or not that trial's being planned. But what I can speak to is that question of the sham device into the NCCN guidelines; the two questions you've kind of posed.

Dr. Matthew Ballo: As far as I'm concerned, the NCCN guidelines really are the guidelines; those are the guidelines that are nationally accepted. Sure, there are other guidelines, there used to be MD Anderson guidelines, there used to be Mayo Clinic guidelines. But I mean, really, the NCCN guidelines are the guidelines that most

of the payers are looking towards and most clinicians are looking towards. So that's what, across the board, we really stress.

Dr. Matthew Ballo: As far as the sham goes, that's an excellent question. And that is really why I got involved in looking at dose. Because I think what we're now finding is that, one sugar pill made the difference, but two sugar pills that looked identical actually improved survival even further. And three sugar pills that also looked identical improved the overall survival even further.

Dr. Matthew Ballo: So, it's hard to say now that a sham device is really necessary if the mathematical modeling is robust enough; which it is. Because remember, we're not talking about ionizing radiation therapy that's measured in the subatomic particle, we're talking about a very large wave; and it's a fairly simple calculation, actually.

Dr. Matthew Ballo: There are some assumptions, but there aren't a ton of assumptions. There are some assumptions that are made, of course, but these calculations are fairly straightforward. I mean, you're calculating the propagation of a force across the interfaces of different tissues; and it's fairly straightforward really. And like I said, now that we have this dose response data coming out, I think the sham device argument really is no longer valid.

Dr. Matthias Holdhoff: But this is all based on the same trial and the data are coming from ... I know this one is [inaudible 00:25:06] again. So, one clarification about the NCCN, so that the academic community, when we have more time to look at guidelines, and we're focused on one tumor at a time, for the most part, we have more time to dissect the data.

Dr. Matthias Holdhoff: If somebody's in the community basing their judgment on NCCN guidelines, I think the importance of NCCN guidelines affects more the community of prescribers. So, I think I would want to mention that the NNCN guidelines [crosstalk 00:25:33].

Dr. Matthew Ballo: The panels made [crosstalk 00:25:34] the panel NCCN.

Dr. Matthias Holdhoff: They are not to be taken [inaudible 00:25:36] as granted by experts in the field, necessarily.

Dr. Matthew Ballo: Well, last time I looked at the panel members of the NCCN, I mean, they're all the people who are in this room. I mean, they're the same academicians, the NCCN panel's not made up of a community cancer center. These are large academic programs, nationally.

Bill Doyle: So maybe a couple more comments, because I agree, it is an excellent question. And as I mentioned earlier during my years at J&J and, subsequently, this is always a question that we ask with a medical device, whether a sham is necessary or whether it's not necessary.

Bill Doyle: Also, this trial was designed in conjunction with the FDA, so this was an active topic of discussion with the FDA before; so, let me mention a couple of things.

Bill Doyle: One of the aspects that was very important to us and to the FDA, in the trial, was this notion of a parallel quality of life study. Because this was a new therapeutic modality, because there was the shaving of the head and the carrying of the box, we really needed to provide the data to the community that's very often counterintuitive that, in fact, deterioration of quality of life was prolonged. You, obviously, can't do a quality of life study with a sham control.

Bill Doyle: The second thing that I'll underline is that the primary endpoint was progression-free survival. The secondary endpoint was the powered analysis of overall survival, but not only would you have to believe that dose density is a function of placebo, but you'd have to believe that progression of a glioblastoma that is somehow a function of placebo.

Bill Doyle: So, we think the weight of the evidence from dose response, the blinded reading of progression-free survival, the need for a quality of life survival is more than sufficient to justify the current NCCN guidelines.

Bill Doyle: We are planning to invest and, again, we're a small company, but we are planning to invest in more studies in GBM; we think they're warranted. But we think that investment would be much better deployed in some of the new areas that have been discussed. The potential synergy with radiation, the potential synergy with other emerging compounds where we can, together, provide even better results for these patients.

Dr. Julie Kessel: Dr. Friedman, and then Parashar Patel.

Dr. Henry Friedman: First of all, truly excellent presentation, laying out the facts we want to explore. And so, I had just a couple of different areas, and if I go too long, you can stop me and let some other people talk, and then come back to me. I don't want to take the rest of the time.

Dr. Henry Friedman: You're correct when you said 13,800, approximate, newly diagnosed glioblastoma patients annually in the United States; that's the incidents. You said only 9,300 were eligible, so I'm confused at that drop down.

Dr. Henry Friedman: You said 40% were patients that are given prescriptions, that's 3,720, you showed 3,741; that's here nor there. So why the drop down in the eligible patients and all those 3,741 represent newly diagnosed patients who got TTF?

Bill Doyle: Yeah, so I can take this one, and I can give it to Adrian for follow up. So, everyone will recall that we are providing, on label, the therapy after radiotherapy. And as we know with this disease from the total incidence, there is a fraction that deteriorates so quickly and recur during radiotherapy, or are not able to handle the therapy.

Dr. Henry Friedman: Have we seen that at Duke? I'm not sure, no keep going, sorry.

Bill Doyle: But that's the reason for the drop off. It's the percent of patients who cannot handle the therapy by the time they've reached the end of radiation.

Dr. Henry Friedman: Okay. The second is a little bit of a deeper dive into EF-14. And Dr. Matthew Ballo, I guess this would go to you. You say, totally appropriately, that the best way to look at a randomized trial is to look at the controls and to see what happened.

Dr. Henry Friedman: That Celldex learned when the controls was so much better that the Celldex V3 trial fell apart because controls embedded prior controls. And yet, you say that the Stupp five-year survival was 10%, which is what was in Lancet oncology in a five year follow up. In your trial, you show a 5% at five years versus 13% for the TTF patients, so doesn't that show there's a difference in the controls?

Dr. Adrian Kinzel: So, I think there's no difference in the controls in the end, because you cannot really compare those trials directly with each other. I think this is, first of all, really important to know, because you cannot compare two trials with each other directly. So, and the 5% you mentioned in our control, I think this is still in the range that you've seen in the Stupp previous trial as well.

Dr. Henry Friedman: That was 10%, 9.8%.

Dr. Adrian Kinzel: Yeah, but nevertheless, I mean, you saw the delta and you saw all the baseline characteristics. I mean, they are still the same in both trials.

Dr. Henry Friedman: Not a point worth arguing. Another question, you are absolutely correct, Dr. Matthew Ballo, when you said, I think you said, that when Temozolomide came out, it was embraced immediately.

Dr. Matthew Ballo: Yes.

Dr. Henry Friedman: It became a global standard of care-

Dr. Matthew Ballo: Yes.

Dr. Henry Friedman: Across the board. You said that at your institution TTF is standard of care. But then you went a step further and you made a very bolder statement that it is the global, or at least the United States, standard of care.

Dr. Henry Friedman: And I don't think that the data really support that, because if I look at www.clinicaltrials.gov, and look at the newly diagnosed trials, I'm not seeing the academic institutions; maybe just because of time.

Dr. Henry Friedman: But I'm not seeing the academic institutions when they build randomized phase three trials consider the standard of care to be surgery, radiation, TEMODAR,

and TTF. So, I don't know that that's been adopted by virtually anyone, so I guess the question is, why not?

Dr. Matthew Ballo: Well, I mean, we're kind of getting off topic a little bit, but I've always thought that it's because the results of the EF-14 really caught a lot of people off guard. And that, basically, you have a situation where the basic science really supported tumor treating fields; and it's very robust basic science.

Dr. Matthew Ballo: And then there was a translation to the clinic, and that's rarely seen, right? We see stuff that's positive in phase one trials compared to a historical cohort, for example; we see that all the time.

Dr. Matthew Ballo: But to actually see something go from bench to bedside, I think caught the academic community, maybe, off guard because this is really in some respects ... I don't want to overstate it, but it's transformational in that it's completely different than anyone was thinking.

Dr. Henry Friedman: Just to refine that, temozolomide, carmustine wafers, bevacizumab, every one of those went from pre-clinical basic data, VEGF expression for example in cells, to pre-clinical animal models to the clinic.

Dr. Henry Friedman: And it's true that temozolomide captured the world immediately. It's also true that bevacizumab and carmustine wafers have not. And so, I don't know exactly where things are going to go with TTF, because a previous speaker or questionnaire was right about the fact that the neuro oncology community has had a, shall we say, a robust response one way or another passionate to TTF.

Dr. Henry Friedman: And so, I guess the last question for me would be, you're right in that all these academic institutions are training in TTF, our institution we're all trained, every one of our faculty is trained. But the question, though, is just because they're trained, what is your perception of academic community embracement of this?

Dr. Henry Friedman: It only takes two patients to be treated at an institution, and you can say it's being used at the center. So, have you done a deeper dive at the academic world to really see is it simply that everybody's trained and occasional patients are treated, or it's something that's being adopted more robustly?

Bill Doyle: So, Dr. Freeman, let me touch on your previous question, and then-

Dr. Henry Friedman: Good.

Bill Doyle: Move to the second question. So first of all, with respect to your question about clinical trials, so I will go back to my experience in the med tech industry because, again, we're dealing with here a medical device, at the end of the day, which is different than a new drug.

Dr. Henry Friedman: Yes,

Bill Doyle: And if you look across all med tech, the adoption curves are very different than the adoption curves for new drugs because, at the end of the day, if a new drug is developed, the data are good.

Bill Doyle: It's consistent with existing medical practice, meaning you write your script if it's a pill, you write your script, and you hang the bag if it's an infusion, and you don't have to change your medical practice. So, we see, generally, with data like ours a more rapid adoption of drugs.

Bill Doyle: For medical devices, it's a change of medical practice. And particularly TTF, which I won't say came out of left field, but it came out of Israel from a cardiac electrophysiologist, who had a notion about forces and microtubule spindles.

Bill Doyle: This is not what was being discussed at SNO year, after year, after year. It came as something very new and even after the data were presented, the question among the clinic, "Now what do I do? How do I ... Do I have to stack these boxes up in my office? Do I have to ..."

Bill Doyle: So, there's a period of time ... And this is, as I said, true of every medical device where it has to be integrated into medical practice. And, importantly, because this is a home-use device, clinicians have to become comfortable enough with the science in order to describe it to their patients.

Bill Doyle: And clinicians are very comfortable, typically, with molecular mechanisms, but to start talking about forces in the brain, and dipole moments, it's just a different vocabulary than we're used to in medical oncology. That said, and if I go back to the reference point 2014, when we first applied, tumor treating fields was almost universally excluded from clinical trials.

Dr. Henry Friedman: Right.

Bill Doyle: It was a complication, and it makes a trial harder to ... Today, it's almost universally not included, but accepted; so, it's not not excluded. So, we've moved to a point from where it's excluded to where it's very hard to actually run a trial in GBM where it is excluded.

Bill Doyle: And, again, we see this, and I would expect, over time, that we will reach the phase where it is included, or their arms as this becomes more routinely adopted. But there is no doubt it's trickier to run a trial if you have to manage the device-

Dr. Henry Friedman: Sure.

Bill Doyle: So, I think that's largely the extent. But we're making this pathway and, again, I emphasize this, but this is the fastest of any medical device. So, it always seems slow to us, and we're very, of course, eager to have this, at least, presented as an option to patients.

Bill Doyle: And, again as Matt mentioned, surgery's an option, radiotherapy's an option, the chemotherapy regimens are options. We just don't want CMS patients to be excluded from that option as they're having their conversations with their clinicians.

Dr. Julie Kessel: Dr. Patel, and then Dr. Fishman, and then we'll go back to Dr. Zeltzer.

Parashar Patel: So just a correction for the record, I'm not a physician. Although many times, both at CMS and elsewhere, folks have called me Dr. Patel.

Parashar Patel: I want to go back to the 14,000 number for a minute and sort of parse that out a little bit more. Can you confirm, how does the FDA label compare in terms of patients with what's in the EF-14 study? In other words, is the FDA label broader than the patients that were studied in the EF-14 study?

Bill Doyle: No, the label is completely consistent with the trial, including the exclusion criteria for the trial are incorporated in the label.

Parashar Patel: Okay, so you're not asking for coverage beyond what's in the label, and beyond the patients that were studied in the F-14?

Bill Doyle: Correct.

Parashar Patel: Okay, thank you.

Dr. Julie Kessel: Dr. Fishman.

Dr. Henry Fishman: First, I'm a hematologist/oncologist and I don't have the deep knowledge of glioblastoma that my esteemed colleagues have. I've been tracking Novocure probably since the beginning, I find it very, very interesting; the data's fascinating.

Dr. Henry Fishman: But as a medical oncologist, I've learned to look very carefully at industry-sponsored studies. And there's a sentence in EF-14 that, to me, raises a red flag; and it's in the introduction, not in the data.

Dr. Henry Fishman: And I'd like to read the sentence that makes me wonder. And it's referring back to use in recurrent glioblastoma and it says, "Although no survival difference was observed, the higher objective response rate, 12% versus 7% percent, suggested single modality activity of TTF fields." and then it's referenced.

Dr. Henry Fishman: Personally, I'm not sure that really belonged in this paper, but since it's here, it makes me wonder. And then the elephant in the room, and certainly in medical oncology, is economics and how economics impacts quality of life.

Dr. Henry Fishman: If we're talking about 12% versus 77%, we're talking about 93% who are paying a copay or 88%. So, if CMS supports the use as initial therapy, as part of the

protocol for EF-14 and then a patient progresses, would Novocure continue to make Optune® available and invoice CMS for continued maintenance therapy when CMS has already said that they don't support it?

Bill Doyle: Okay, so I'm going to try and parse that question a little bit. First of all, the trial that you just read from is not the trial that we're discussing today. That is the EF-11 trial that was in recurrent-

Dr. Henry Fishman: But it's referenced in the EF-14, it's in the introduction.

Bill Doyle: Yeah, the paper is there because often were asked why did we conduct a trial in newly diagnosed GBM? And among the reasons that we conducted a trial in newly diagnosed GBM is that we did observe this significant dose response in the recurrent trial.

Bill Doyle: The recurrent trial, by the way, recruited very sick patients. Ninety percent of the patients in the recurrent trial were second, third, fourth, fifth, we even had sixth recurrence GBM patients in that trial.

Bill Doyle: So, it was important to us to analyze those data to determine whether we move forward. And the conclusion was based on the dose response observed, that it made sense to go to the healthier patients.

Bill Doyle: I think with respect to your second question, the trial design and, again, the design that we're ... and the trial that we're discussing today ... Because this is a physical modality, and you saw that the curves separate almost immediately and continue to separate.

Bill Doyle: We are killing dividing cancer cells. In some patients, we're killing above 50% of the dividing cells, in which case you see a response. In other patients, because of the location of the tumor and the intensity, we may be killing fewer than 50%, which case you're still prolonging the survival, but you may not be actually getting to response. So, the trial was designed so that the patients would have that benefit.

Bill Doyle: At the end of the day, whether a patient continues through first recurrence, or stops at first recurrence is, of course, a decision between the clinician treating the patient and the patient.

Bill Doyle: And we don't want to and, of course, we never would mandate what that should be, but we want to have for the Medicare eligible population, the physician and patient to have the option to determine whether that's the therapy that's appropriately in the specific case.

Dr. Julie Kessel: Dr. Zeltzer.

Dr. Paul Zeltzer: Yeah, I'd like to address the issue of when a product becomes part of the normal accepted landscape for when this is the basic therapy that everything else should be compared to.

Dr. Paul Zeltzer: Between 1982 and the year 2000, I headed the medulloblastoma trial for the Children's Oncology Group. And it was a randomized controlled trial, and we published about 15 papers during that period of time. And half of those papers dealt with the fact that although we were comparing two different chemotherapy regimes, it turns out the neurosurgeon was the most prognostic factor.

Dr. Paul Zeltzer: And in fact, if the neurosurgeon was able to leave less than 1.5 centimeters of tumor, there was a 30% difference in survival. If there was more than one and a half cc's versus less than one and a half cc's.

Dr. Paul Zeltzer: So, imagine you can increase the survival of children with medulloblastoma and young adults with medulloblastoma at the neurosurgeons spending more hours in the OR, in many cases, to get that last bit of tumor.

Dr. Paul Zeltzer: It took 10 years for that to evolve in the sense that that then became a more standard practice. And the idea here that I'm trying to say is that physicians and medical centers are conservative institutions, and they really want to be convinced.

Dr. Paul Zeltzer: And I think it takes time to adopt new therapies and accept data, and I think we have to recognize what time/space we're in. And I'm not saying that this will be the standard, but what I'm saying is that the initial data is ... I think we're all here because it looks quite interesting. But that we also need to know what point in time we are in terms of when something becomes generally accepted in the medical community.

Bill Doyle: So, I'll just underline a few comments that were made before. So, the first is that of the eligible patients, 40% are now receiving a prescription; and that number increases each year.

Bill Doyle: There are no doubt that there are skeptics, this is a new therapy, a completely new modality. We can debate issues of the trial, whether quality of life is more important than sham. I think we've tried to present dose response data that will help people become more comfortable.

Bill Doyle: Dr. Friedman, one of the questions that, or assertions that you made, or the questions that you made is what about the adoption in academic medical schools? We see a steady progression.

Bill Doyle: It's interesting and, as I said, I've done this for a long time in a lot of different areas, and I suspect every innovation since Avicenna has had people who had to

be proven twice before they adopted; particularly when it's an unfamiliar modality.

Bill Doyle: But I think that if we look at the number of institutions that I would say were staunch opponents, versus now are trained and presenting, versus those who have adopted a standard of care, we see a steady progression.

Bill Doyle: The other thing about academic institutions, of course, this is where we conduct our clinical trials, and many patients in academic centers will be at least presented with various clinical trial alternatives as well; we believe that that's critical.

Bill Doyle: We discussed that we are working now with academic centers, in fact, those of you who received a call from me which was, you mentioned, all of which were before I knew who was on this panel. I'm going out now because we're planning a new round of clinical investigations in GBM, and I'm looking for the feedback from the key centers as to what will be the most valuable next step, if you will.

Bill Doyle: And I think there is something to that, as well, in terms of acceptance. There's what I view is the core trial for newly diagnosed GBM that allows clinicians to present this to patients, but now we definitely want to explore other aspects of the therapy with other modalities.

Bill Doyle: We have anti-aneugenics, we have viruses, we have immunotherapeutic options. All of these plus radiation, the combinations with radiation, all of these, we want to explore to provide, ultimately, the best options for patients. And no doubt in the years to come, we'll be back here for more evolved indications based on new data that will be developed in the future.

Dr. Julie Kessel: Dr. Gross.

Dr. Cary Gross: Thanks. I'm interested in a real-world experience that the patients who have been using the device have had. So, it's just like reading tea leaves, I was looking through the annual report, and it looks like in the first three quarters of 2018, 3,700 new patients were started on treatment during that time.

Dr. Cary Gross: At the end of that three-quarter period, 2,200 patients were still on it. So, 3,700 started, and the 2,200 patients were on treatment at the end. So, it looks like ... It's hard to really understand that because some patients were on treatment prior to that period.

Dr. Cary Gross: But just my quick back of the envelope conversation ... I should say calculation, looks as though there's a significant number of patients who may be stopping the treatment after just a few months. I was wondering if you could tell us about what actually has been happening in the real world as far as duration of treatment?

Bill Doyle: Sure. So, I'll let Matt talk about his experience in his clinic, and then I'll give the overall statistics.

Dr. Matthew Ballo I mean, there is some attrition, I mean, that's true of any therapy. But in our clinic, what we do is we introduce the concept of tumor treating fields early on, when the patient is first diagnosed, because we have a multidisciplinary approach where the neurosurgeon starts the discussion.

Dr. Matthew Ballo Our neuro oncologist, medical oncologist will then bring that up again at the first consult, and sort of reiterate that we're going to do this once we're done; this is part of the standard of care.

Dr. Matthew Ballo And then during the radiation therapy ... We see our patients weekly, and I will talk to them about the benefits and they start to lose their hair. And remember, with radiation therapy, the hair loss is permanent. So, they start to lose their hair, but I'll say, "Well don't forget you shave your head when you go on the tumor treating field therapy as well."

Dr. Matthew Ballo And our numbers of patients who start therapy are very high. So, we have about 70% of our patients will start the therapy, and there is some attrition over time, but there's a myriad of reasons why that can happen.

Dr. Matthew Ballo I always kind of say we have two types of patients; but we don't quite have two, we have 70% who use it, and we have 30% who don't. But I always sort of say there's two types of people, there's people who, literally, won't take the device off because they really feel like it's working. Then we have some who just for whatever reason, don't want to use it.

Dr. Matthew Ballo The only predictor I have ever found is a patient who was also on oxygen. I've had a couple of patients who, when I talk to them about going on to the device, they'll pick up their oxygen tank and say, "I really can't do both of these."

Dr. Matthew Ballo That's the only thing I've really found as a factor for why people don't use it. But their reasons for going off the therapy are also all over the map. Sometimes people are progressing, and they decide they just want to try something else; but I haven't really been able to put my finger on any one thing.

Bill Doyle: So, with respect to the statistics that you quote so, first of all, that total number includes patients who start at the time of diagnosis; and we do have some patients who will start after recurrence.

Bill Doyle: That they may have gone on a clinical trial, or they may have made some other decision at the time of diagnosis, but when they do recur they say, "Okay, now I'm ready for tumor treating fields."

Bill Doyle: What we see, on average, is that if a patient starts at the time of diagnosis ... And by diagnosis, again, this is after radiotherapy, that they'll stay on therapy, on average, for eight to nine months.

Bill Doyle: And if a patient starts at first recurrence, they'll stay on therapy for about four months. There are patients who will start and stop immediately; that's a very small percentage that for whatever reason they decide that they're not comfortable with the technology. That's a decision that they make, typically, very quickly.

Bill Doyle: And then otherwise what we see, and Matt can confirm this, they typically will stay on until the point where they have progressed to where handling the equipment is no longer convenient and easy. So, it tends to be at a point where the physical and the neurological deterioration render it less practical.

Dr. Julie Kessel: Dr. Peña.

Dr. Carlos Peña: Sure. Thank you, Dr. Carlos Peña, FDA. So, two comments and a question, one is on slide five you had talked about requested coverage is a match to the FDA PMA (pre-market approval) IFUdecision process.

Dr. Carlos Peña: And I think they can be framed as related, but they are different questions, they are different agencies. One is safety and effectiveness, the other one is necessary and reasonable.

Dr. Carlos Peña: They have different questions when we look at risks and benefits, another agency takes into consideration reimbursement. And we have different populations, sometimes, that we are studying.

Dr. Carlos Peña: So, there's differences in both agencies that I think are significant, and specific, and there are different standards. And the reason I'm sort of walking through that is because if there is a data set that would be helpful to one entity or another, it should be provided.

Dr. Carlos Peña: I am not at liberty to provide information to entities, I can't really talk about investigation device exemptions, I will be spending my time in a much smaller room than we're all in today if I do that.

Dr. Carlos Peña: But if there's information that I think sponsors have that would help address questions about a specific population as it relates to the mission of an agency, that might be worthwhile to consider.

Dr. Carlos Peña: The one question I did have was on slide 58, increase dose correlated with increased survival, which I think has been resonating with some of the questions here. Is there any additional information that you have?

Dr. Carlos Peña: It's a very interesting data set that I think if you could expand upon with regard to real world evidence, or other studies that have looked at both dose as well as compliance, that would be very helpful to hear.

Bill Doyle: So, I'll respond first to your initial two comments, and then I'll let Dr. Ballo respond to the evidence question. The point that I was trying to make here is not that FDA and CMS are the same; we know they're very different.

Bill Doyle: The only point I was making is that the coverage that we're looking for is coverage that consistent the FDA label. Often sponsors may ask for broader coverage or different coverage; this is completely consistent with the label so that's the only point I wanted to mention.

Bill Doyle: With respect to the science question, I'm going to smile up here, but we received these questions Friday afternoon at 5:00; we didn't even know science was going to be discussed here.

Bill Doyle: I will tell you that a lot of people sitting behind me worked all weekend to pull together the information that we have here. And I think that there's no hesitation to provide this deep CRF level data, it's just with four days' notice our focus was on the key questions that were being asked you.

Dr. Carlos Peña: Right. I just wanted to make sure that the panel ... Everyone knows that when you say, "FDA has the data." Well, if there's data out there, that would be helpful for other groups to know about; you share that data.

Bill Doyle: And, again, my only point is ... And you know this because your team was a big team, they spent a lot of time, and they had access to everything, including all the pre-clinical data and the CRF level data. That's my only point and as of 5 p.m. Friday, we did the best ... And I think we brought the relevant data for the question at hand.

Dr. Julie Kessel: Yes.

Dr. Edjah Nduom: Glad I was able to go after Dr. Peña, because I have questions that I suspect you won't be able to answer, but I want to ask them anyway, and then they can bounce back.

Dr. Edjah Nduom: Because your name was invoked earlier, the FDA was in the design of the trials, having been through the IND process myself, I know that we got several inquiries about our trial design and some suggestions; some more firm than others. Did the FDA suggest sham device use in this trial? So, is that a question you can answer? If not, could you answer that?

Dr. Carlos Peña: Yep, so a couple of comments on that question. One, I am unable to discuss investigational device exemption type discussions.

Dr. Edjah Nduom: Right.

Dr. Carlos Peña: Two. In general, when a sponsor comes to us with a trial design, we can recommend different study designs. We can't mandate those designs unless there's a safety issue involved. Then we can, potentially, stop a study or recommend some other alternative path.

Dr. Carlos Peña: And then, at the end of the day, once the sponsor does the study we are, by law, required to look at the valid scientific evidence from that study. We don't have a choice on whether to accept that submission based upon how it's been designed, what we're required to look at that study and make a determination about the safety effectiveness of that product and make a judgment.

Dr. Edjah Nduom: So, could you share any-

Bill Doyle: Sure. So first of all, I'm glad you've gone through the IND process because you know what it's all about. Particularly with a new modality where, again, when we started this, there were all sorts of safety questions, "Do these electric fields interfere with cardiac activity?" The answer is, "No, they don't at a high frequency." But question's asked.

Bill Doyle: "Do they interfere with the rapidly dividing healthy cells?" "No, they do not." But question's asked. A lot of pre-clinical data on these topics, and the issue with the sham control was discussed extensively with the FDA.

Bill Doyle: And again, the collective opinion was, and determination was that the quality of life study was critical. And that because the primary endpoint was progression-free survival with GBM, and there's no evidence that there's a placebo effect with progression-free survival, and that it was measured by blinded radiology panel, that it was not necessary.

Bill Doyle: And now, again, now that we've provided the dose response that I think clearly show that there is a profound dose response with the therapy, I think that we validated the IND discussions that we had with the FDA.

Dr. Edjah Nduom: So, along the dose response, I have to ask engineer type questions. I told my son that I was an engineer kind of, so I have to stay on that realm for at least a little while.

Dr. Edjah Nduom: The location of the tumor would affect the dose that the tumor receives, right? And just based on my understanding, just all the different factors that are involved, a deep tumor would be likely to get a lower dose in many cases based on how the arrays, and how the energy would get there. Is that correct?

Dr. Matthew Ballo No.

Dr. Edjah Nduom: Not correct?

Dr. Matthew Ballo No, it's not. It's not quite that simple. So, remember the force is going to be going through the path of least resistance, and so you actually see a very high intensity along the ventricles.

Dr. Matthew Ballo And it depends on whether or not you're looking at the right left array, versus the APPA array of where you're going to get those hot spots. So, it's predictable, but it's non-uniform, and it's not as simple as you're going to get less dose to the midline structures.

Dr. Edjah Nduom: So, but if you look at the correlation between location and dose, was there a location relate ... Could you say that a frontal lesion versus a thalamic lesion, versus a parietal? Were you able to parse out that data?

Dr. Matthew Ballo That's something that I'm looking at in my own data, but I don't believe that was looked at in EF-14; it was not separated in that way.

Dr. Edjah Nduom: Because I think all of us would say that there are certainly different survival differences for patients based on the location of their tumor, deep, surface.

Dr. Edjah Nduom: And that would also affect the resection capability of the lesion and the extent of resection for those patients. So, it would also be an interesting variable and important variable in that dose response study to know what the extent of resection was for those various patients, and whether that was related to location, whether that was related to -

Dr. Matthew Ballo Yeah.

Dr. Edjah Nduom: Dose that they received, and then whether there was survival benefit with all those variables in your array. I'm sorry you-

Dr. Adrian Kinzel: We just want to add that, I mean, besides the fact that we did not take a closer look into this specific question, the tumor location is well balanced between those groups, and this is what you can see in EF-14 trial. So, this is why I think tumor location, in general, did not play a critical role in the outcome. And, I mean, the 0.63 hazard ratio is still there. So, I mean-

Dr. Edjah Nduom: Right, but we're also making this argument that the dose ... So, I just wanted to follow up on that question as well, I'm sorry.

Bill Doyle: So, I am the engineer in the room and my thesis work was on the effects of electric fields on white cap semiconductors, so I'm very facile in this area. First point I want to underline that Matt made because, as we think about ionizing radiation, we do think about a dose that decreases with penetration.

Bill Doyle: Okay, that is not the case here. We have parallel plates and the field distributes itself between those plates based on, as Matt said, based on the conductivity of the tissue.

Bill Doyle: So, in the follow-up analyses in order to continue to improve the therapy, we've done all this work that Matt's led. So, it's not about how close it is, or how far it is, it's much more about its position within the conductive matter.

Bill Doyle: And as was discussed, this was all very well balanced. By the way, the resection status was stratified in the results, so I think that's all been taken care of.

Bill Doyle: This doesn't mean that we're at the end of this development, and our goal is, certainly, to get the therapeutic dose, ultimately, throughout the brain so that we can present patients with even better potential outcomes than what was presented in the EF-14 trial.

Dr. Julie Kessel: Doctor. Yes.

Parashar Patel: So, you'll have to forgive this question, it may be in the body of the literature that we were provided. But clearly the dose matters in terms of how the patient is going to respond to the therapy.

Parashar Patel: Does the length of time of treatment matter? And if so, is there like a minimum point in the study or in your post market analysis, if they're on at least a month, they're going to get some benefit, and then the benefit goes on forever, etc.?

Parashar Patel: Because I noticed in the trial, the median duration time was eight months, which seems like ... What did you say currently patients are on, eight or nine months?

Bill Doyle: About the same in the real world as in the trial.

Parashar Patel: And so, I'm kind of curious if that's the median, what's happening to the patients underneath? Are there deriving any benefit? Is there a cliff that you saw? Can you talk a little bit about this? And if the data are available for real world patients, is that something you can provide?

Bill Doyle: So, a couple of things, and then I'll let my colleagues comment on this as well. So, in the trial, dose is a function of duration of therapy and the intensity; so, it's both. And this is similar to concepts and radiation oncology.

Bill Doyle: In our trial, as I think I mentioned before, we saw that 86% of the patients benefited from the therapy. We did see a cut off, not in terms of the number of months, but in terms of the hours of the day. That patients who use it 12 hours a day, or more, had a statistically significant improvement over the control.

Bill Doyle: It looks like if you didn't use it at least 12 hours a day ... We don't have enough patients to really do the statistics but, with the number of patients in the trial, that was the time.

Parashar Patel: But you do now, right, with post market? Do you track those patients afterwards, or can you collect that information post market?

Bill Doyle: So, we do collect the time of the start of the trial, the duration of the therapy, and the date of death, but we have not published a post market analysis of the newly diagnosed patients yet. It's a huge amount of data, and our focus here today is on the randomized clinical trial.

Dr. Julie Kessel: Dr. Camphausen.

Dr. Kevin Camphausen: Yeah, one more question from the clinical angle and having seen patients on the trial receiving the device. The big question, the skeptics or how I think of them, have been questioning, "How much of this could be placebo effect? How much could be real effects? How big can a placebo effect be if the data in an orderly done trial it says show an overall survival benefit?"

Dr. Kevin Camphausen: One of the points that are frequently criticized about this trial, which I believe have not been formally addressed, and I would be interested what you have in your databases is that patients on the control arm of the temozolomide, but they had no further interactions with the Novocure team.

Dr. Kevin Camphausen: The patients on the intervention arm had open access to the company. You could say those were technicians part of the company, they were not oncologists, but the frequent contact, the phone call, "If something's not quite right, I could call that person." I think it's a significant aspect that needs to be considered.

Dr. Kevin Camphausen: So, if you have an extra person, let's say if you treat a patient and you have, let's say, an extra person which you often don't have in real life to medical practice for financial reasons, and other reasons. If you had, let's say, another provider who always check in with a patient that could potentially provide a meaningful difference that may or may not have impact on survival. So, what are your thoughts?

Bill Doyle: So, I'll start my thoughts and then I'll give it to Adrian; so first some clarifying points. I want to go back to the fact that the primary endpoint was progression-free survival of a glioblastoma tumor as measured by blinded radiology.

Dr. Kevin Camphausen: Right.

Bill Doyle: Number two, we had a significant separation of curves from the beginning, all the way to the end with a significant improvement in hazard ratio and a significant P value; P000.1; this was not a close call in these data.

Bill Doyle: Furthermore, because of this question we've gone back ... and this was also a question that was very much studied by the FDA, although you can't confirm it. We went back to the patient level data that showed that the medical therapy that was delivered to these patients, in both groups, was extremely well matched.

Bill Doyle: So, in other words, the times that they were interacting with their doctors, the times that they were getting medical follow up ... And remember, these patients are being followed up, they're coming back and they're getting an MRI every month. So, it's not as if the control patients are receiving their temozolomide and then going home, they're frequently interacting with the medical community.

Bill Doyle: What we provide is a technician, and the technician goes to the patient's house, or the care facility, and trains the patient how to use the device. And Steve can talk about that, but learn how to change the batteries, learn how with the caregiver, how to place the arrays; this is a training that usually takes a few hours.

Bill Doyle: And then we follow up once a month to download the compliance data, because this was part of the follow-up. But these are technicians, it's not medical care, and it was no more frequent or less frequent than the monthly medical therapy that every patient in the control arm and the treatment arm was receiving.

Bill Doyle: So, our view is that based on the preponderance of the evidence that having a tech show up with a new batch of arrays once a month is not a significant factor in the results.

Dr. Arnab Chakravarti: We're considering TTF in the context of maintenance therapy today. It seems that, I guess, the underlying hypothesis is that TTF might be a chemotherapy sensitizer as well, is that correct? And do you have data showing that TTF sensitizes to temozolomide chemotherapy?

Dr. Arnab Chakravarti: And I guess the follow-up question to that is there are certain patients who might not be able to tolerate temozolomide chemotherapy, may pursue other types of chemotherapies or no chemotherapy. What is the data with regards to TTF in the absence of any type of chemotherapy?

Bill Doyle: I've been doing all the talking, so I'm going to give it to Dr. Kinzel ... sorry.

Dr. Adrian Kinzel: Yeah. So, let's start with the first part of the question. So, we do have data, or there is data available from independent researchers showing that, first of all, there seems to be kind of an additional or synergistic effect between temozolomide and tumor treating reading fields. And secondly, that even in temozolomide resistant cells, adding tumor treating fields seems to have a positive effect on these cells.

Dr. Adrian Kinzel: So there seems to be kind of an interaction that temozolomide, or the treating fields, work in cells that are temozolomide resistant; so, I think this is something to keep in mind.

Dr. Adrian Kinzel: Regarding the other question, what data do we have for monotherapy? Of course, we have the EF-11 data that showed similar results; and we discussed it before. And I think more, importantly, in the EF-11 is in the objective response rate, which was definitely higher in the tumor treating fields group compared to the control group. And the control group received chemotherapy only, and the treatment group treating fields alone.

Dr. Julie Kessel: Dr. Camphausen.

Dr. Kevin Camphausen: Dr. Ballo, after doing your measurements now, are there patients that you won't recommend TTF fields to?

Dr. Matthew Ballo No, no because any customized array layout is going to increase the field intensity through that region of the brain. There are places where the intensity would be lower, but there are no places that can't be reached, so to speak.

Dr. Kevin Camphausen: So, it's only going to be good, better, better, there's not going to be ones that you think shouldn't get it?

Dr. Matthew Ballo That's right.

Dr. Julie Kessel: Dr. Gross.

Dr. Cary Gross: Can I ask you to clarify the difference between the two clinical trials? So, there are two Stupp trials, one in which there was a survival benefit in new disease, and there is the earlier one where there is no survival benefit among the patients with recurrent disease. So just in layman's terms, why did it work in one instance and not in the other?

Bill Doyle: So, as is often the case in development of any therapy, in interactions with the FDA, you often start at the second line, if you will, or particularly when safety is yet unexplored.

Bill Doyle: So, in conjunction with the FDA, we performed a first phase three clinical trial in recurrent GBM. This trial was designed for patients who, in the treatment arm, would receive Optune® alone; so, without any chemotherapy compared to best physicians choice chemotherapy in the recurrent arm.

Bill Doyle: And that was typically re-exposure to temozolomide, BCNU, or CCNU, or Vastin; those were the three most common salvage chemotherapies, if you will.

Bill Doyle: As I mentioned before, the patients that were recruited were extremely sick. Only 10% were first recurrence, 90% were beyond first recurrence. Those of you who treat these patients you know the status of the patient beyond first recurrence; so extremely sick. And their ability to comply with therapy was highly limited.

Bill Doyle: What we did show, nonetheless, and was the result of an FDA approval in second line therapy, was that the two are equivalent. So that the patients who received the salvage chemos that I described, did the same as the patients who received Optune® therapy.

Bill Doyle: We weren't superior, but we showed ... And there was a huge statistical discussion and we showed a statistical equivalence. Now what we saw, and what you see in the subgroup analysis which of those very sick patients, those patients who were able to actually use the device, and there was a per protocol endpoint, the patients on protocol were superior to the chemotherapy arm.

Bill Doyle: So, again, I'm the engineer, not the doctor but my view is if you have a patient, regardless of recurrence, who is healthy enough to comply with therapy, this is an option. If you have a patient who is, obviously, not healthy enough to comply with the therapy, then this is not an option for that, so.

Dr. Matthew Ballo Right, yeah, just to clarify the discussion I was having with Dr. Camphausen, when you're looking at the dose alone, there's no patient where I wouldn't recommend it. But I mean, of course, if we would look at clinical characteristics of the patient, for most patients it's an option. As I had said, the debilitated patient in a wheelchair, elderly, absolutely an option for that patient.

Dr. Matthew Ballo But there are some patients where I pause. The one patient would be somebody who has absolutely no caregiver at home, somebody who is completely alone, and completely unable to put the arrays on.

Dr. Matthew Ballo I mean, that's the kind of patient where I do start to pause in using the device. But as long as someone is able to use the device, there's really no other ... As long as it falls within the FDA approval of the device, I have recommended it.

Dr. Julie Kessel: Dr. Paul Zeltzer, and then Dr. Nduom, and then Dr. Friedman.

Dr. Paul Zeltzer: Yeah, wasn't there a crossover design here? The patients that when they were censored from progression-free survival, and on the temozolomide alone, they were able to get the Optune® device?

Dr. Adrian Kinzel: So-

Dr. Paul Zeltzer: Can you talk about that? Am I correct in that?

Dr. Adrian Kinzel: So, patients were allowed to cross over after FDA approval, so and these crossover patients, I mean, in the end all the measurements are done in the ITT population.

Dr. Adrian Kinzel: So therefore, I think there's no doubt that the crossover patients are included very well, and so this is why we showed the results in the ITT populations instead of per protocol. So, and the 0.63 hazard ratio and the significant amount of survival benefit is shown in the ITT population, including the crossover patients.

Dr. Julie Kessel: Dr. Nduom.

Dr. Edjah Nduom: One quick question I'm going to ask you to speculate. Why do you think that tumor treating fields is an option in the NCCN guidelines as opposed to every patient should get it, as opposed to a recommendation? Because temozolomide, if you look at all the groups, it's-

Dr. Matthew Ballo Sure.

Dr. Edjah Nduom: They all get temozolomide but not TTF.

Dr. Matthew Ballo Well, I mean, these are consensus guidelines. I think there were a lot of people ... I have not participated in the NCCN discussions, but if all it takes is one person to sort of feel, "Well maybe this isn't the recommendation." It only takes one person to change the results, so this is a consensus guideline in that respect; and so, it does allow for other things.

Dr. Matthew Ballo In fact, NCCN has gotten much better in that respect because when NCCN first came out, there were 100 different options for every disease, and they've really pared it down to the real winners.

Bill Doyle: And by the way, this is a statistic that I learned recently, only 6% of all FDA approved cancer therapies are NCCN category one.

Dr. Edjah Nduom: Another one of these lay engineer questions. There's something in your FDA submission that says that bone marrow is not affected by tumor treating fields. And the reason that it gives is that it's shielded by the bone, which has a very high resistance. Why does that not apply to the skull?

Bill Doyle: Yeah, okay so this is a very interesting point and one that we've discussed many times. So, as we underline it ... Again, I apologize we don't have the PhD seminar to really go into these details.

Bill Doyle: But an electric field will travel in the area of, or in the direction of, the least electrical resistance. So, in the long bones, the path of least electrical resistance is through the muscle around the long bones.

Bill Doyle: When you put the arrays on the side of the head, the path of greatest resistance is actually through the skin all the way around to the other side. So, it's a function of the fact that with the long bones there is a convenient, low resistance pathway that goes around the bone; and in the case of the skull, there is not.

Bill Doyle: Now if we were to take a long bone out of the body so there was no muscle and tissue around it, and put the arrays side to side, then we could force an electric field through the bone. But the long bone in the tissue on the body acts as a natural shield because of that path of least resistance.

Dr. Edjah Nduom: And the last question. Do you have a registry of patients that are continuing to receive this therapy and have results from that, or have you collaborated with any centers that have their own registries that are following patients to start to see how the ongoing survival from patient use of this is looking?

Bill Doyle: Yeah, so as I said before, every patient who starts Optune® therapy, at the same time consents to allow us to use the compliance data and the survival data, so we're not tracking all the medical characteristics that you would in a randomized clinical trial.

Bill Doyle: We have published the data, the registry data, from our recurrent cohort, because we started earlier, and this is a very large data set that is publicly available. We have not yet compiled and published the registry or ... because registry you have to stop at a particular time and then look at the data.

Bill Doyle: Everything that we see is consistent with the label, as I said ... Pardon me, with the clinical trial, as I said, we see the same average durations of therapy. So, there's nothing that stands out, but those data are being captured and, ultimately, could be published in a non-randomized registry.

Dr. Julie Kessel: Dr. Friedman.

Dr. Henry Friedman: Okay, let me bring this over here; a question and a point. We're not all physicians on this table, and I recognize on this side of the table, and not that side of the room, but I nevertheless have to make a point that I think the clinicians know and the others should know.

Dr. Henry Friedman: That there are patient population who have no ability to tolerate any chemotherapy because their bone marrow is so damaged, that they can't receive chemotherapy, they do have the option for TTF. That has nothing to do with voting or anything, that's just a reality; and I think we all need to understand.

Dr. Henry Friedman: The second is where I'm more on this side of the table, NCCN are guidelines, they are things that people look at and they say, "Yeah, maybe I'll pay attention, maybe I won't." If you're an academic center, if you're in the community, you may be more in tune with doing that, or you may be talking to your local neuro oncology center of excellence; but they're guidelines.

Dr. Henry Friedman: There are insurance companies who use that to decide who they're going to pay for or not, and that's absolutely inappropriate; totally. They're guidelines, I fought that fight a number of times.

Dr. Henry Friedman: They merely give what a consensus group of people come together, not necessarily all agreeing to give what they think is the best information they can provide to the community. So, I understand why you're happy, you have NCCN level one approval, but to the community that treats these patients, they're simply guidelines that don't necessarily bind us to do anything.

Bill Doyle: Dr. Friedman, absolutely. And, in fact, we're hanging our hat on the science here, the pre-clinical science, and the results of the largest trial run in newly diagnosed GBM.

Bill Doyle: I think there's every trial under the sun because, unfortunately, you can't measure everything. If you want quality of life, you can't have a sham control, so you have to make some trade-offs in any trial design.

Bill Doyle: But this nonetheless is a trial that was exceptionally well thought through, at the time of design, it was a large international trial, was conducted at 80 centers internationally, including centers in South Korea; so, we have data in all ethnic groups.

Bill Doyle: We have a large age spread, so there were very few exclusions. We excluded for things like bullet fragments in the brain, we excluded KPS patients who couldn't handle this; but this is not a trial that was narrowly applied. And I think the fact that it's recognized at the NCCN is great, but that is one factor of many I think that supports your decision today.

Dr. Julie Kessel: Dr. Sherman.

Dr. Jonathan Sherman: I know that today we're talking about approval for the developed brain over 18 years old, and just from a scientific perspective, with the knowledge that there are neural stem cells, and even though it's a small percentage, do you have any data that sees an effect of the tumor treating fields on the neural stem cells that could still be present in the adult brain?

Dr. Adrian Kinzel: No negative effect at all. So, I think it's mainly related to the cell size in the end.

Dr. Jonathan Sherman: Is that data available?

Dr. Adrian Kinzel: In ongoing research from independent institute's like, for example, the University of Zurich did some research on this, and so it's all in the [inaudible 01:25:12] that we submitted to you.

Dr. Julie Kessel: Dr. Desjardins.

Dr. Annick Desjardins: So, when we're later we'll be discussing and what we're being asked is really Medicare eligible population. And so most of my patient with a KPS of 90 and 100 are really happy to work, and I'm proud of it because this is who they are right? Otherwise they'll lose who they are as a human being.

Dr. Annick Desjardins: So, I know you still showed efficacy in KPS 80 and lower population, but only a third of the patient had a KPS of 80 and lower. Same thing 65 and older, only 19% of the population was 19% was 65 and older.

Dr. Annick Desjardins: So, which means it's small subgroup analysis still positive and EF-14 with republish agree with that. Any interest though, in looking forward or into the elderly population? A little bit like the same work that has been done in hypofractionated radiation or something like? Really answering that question that we are being asked today. [crosstalk 01:26:17]

Bill Doyle: So, I am going to pass the microphone after my comments to Steve, who can talk about his experience in going to work, and because we have someone here who's lived it.

Bill Doyle: As you stated, the trial encompassed the whole population, including elderly. Our cut-off was 80, I think, which is beyond most trials; we showed the positive effects in every subgroup.

Bill Doyle: One of the reasons ... to your specific question, the mechanism of action here does not suggest that there's a difference in the way that a microtubule spindle will respond based on age.

Bill Doyle: We think there may be something to the frequency because, again, as Adrian said, depending on the cell size, if we found that ... And I've heard things like this, "If, there's a difference in cell size, on average, between younger and older people, there may be things that we can fine tune."

Bill Doyle: And as I said before, we're now right at the point where we're very interested in taking the next step, and that's why I and my colleagues are out to ask the key opinion leaders where they think the investment should be made.

Bill Doyle: And if there's a consensus that that is the most important question, then that may be a question that we answer. But again, if we come back to the Medicare eligible population, it is the over 65, which are included in the trial. It's also, in this case, anyone under 65 that is disabled.

Bill Doyle: And so, I think it is important for the CAC to look at the totality of the data, because of that fact. And Steve, maybe just a comment or two about your work at [inaudible 01:28:06]

Steve W: Well, I think you heard that I ... If you back calculate from where I am now, I was 56 when I was diagnosed. And I went from being on the ground, not being able to move anything on my left side and started through the process. And as time went on, I was able to get to where I needed to be, today, with a small deficit in my left leg.

Steve W: But one of the things that I learned was that I needed to continue to push myself in more ways than just dealing with whatever therapy I had. I had to do all the things that kept me mentally strong, kept me physically strong, and all those other things.

Steve W: So, I think those are factors in being able to determine whether you can go beyond whatever these thresholds that people are talking about right now. And I think that, with any doctors that are considering this, you have to talk about that beyond the basic therapy.

Steve W: And I had that conversation with my doctor all the time, "Am I doing the right things? Am I able to maybe put this thing off a little bit further by continuing to work out, hike through the canyons in Alaska, and do all the other things that I enjoy?"

Steve W: I think that it's critically important to the process. And as I get older, I ask myself, "What is it going to mean to me?" I sit here, and I think, "Well, I'm not eligible right now, but what happens when I..."

Steve W: Because I'm going to get there. What happens when I get there, and what will I have to face in terms of questions about will I be able to afford it to be able to at least get people to stand behind it? So, I think it's very important.

Dr. Julie Kessel: Dr. Holdoff, and then Dr. Nduom.

Dr. Matthias Holdoff: Yeah, thank you. And sorry for going back to the sham device question, because I think that, for a lot of us, really the key point where we have trouble really adjusting to accepting the data as they are.

Dr. Matthias Holdoff: And we do discuss the option of the device with every single patient we see, based on the FDA approval and positive published trial. But if the sham device intervention is so difficult to do, for obvious reasons, in patients with glioblastoma because you can see the device, there should be no real reason not to do it in patients with pancreatic cancer, GI malignancies and, for example, lung cancer.

Dr. Matthias Holdoff: To my knowledge, and please correct me if I'm wrong, there's so far, no trial that uses a sham arm in these patients, and it will be really important to know whether there might be a sham bias or not.

Dr. Matthias Holdoff: If there was not, I think it would be much easier for us to accept the data and say, "Well, this is really working." So, are you planning to use a sham device in patients with non-CNS tumors?

Bill Doyle: So again, I appreciate the sham issue is very important to you.

Dr. Matthias Holdoff: And not only to me, actually, to a lot of colleagues who are not all in this room.

Bill Doyle: Yeah, and as I said, I have spent over 25 years now developing medical technologies. Shams aren't used in, for instance, radiation therapy trials, the vast majority of physical modalities, and even if you look at the vast majority of the phase three GBM drug trials, there're shams and some, but in the majority, there aren't.

Bill Doyle: And I think this is because there is a consensus that progression-free survival of GBM is not observed, and it's not observed in these failed trials, either. Now, when we look at a blinded review of the radiological data, we look at dose response.

Bill Doyle: Again, I'm not going to convince you today because that's, clearly, an important issue for you. But as we design other trials, and we are conducting trials that you mentioned in tumors now in the trunk, the existing designs do not include a sham for similar reasons that progression-free survival of pancreatic cancer, for instance, is not shown to be affected by sham.

Bill Doyle: But I will take this under advisement; at the end of the day, I decide. As I said, I've been now out in the community, I'd love to come and get your opinion one-on-one in what you think the best trial for the community would be.

Bill Doyle: Our strong, very strong opinion is today, based on the data that are available, it's important that Medicare beneficiaries have access to this therapy. That doesn't mean that we won't continue to develop evidence and take your considerations into account.

Bill Doyle: That's certainly true for temozolomide, the original Stupp trial was not the end of the temozolomide study, it's been studied and studied since then. And I think we've narrowed down the patient populations where it's ideal and other patient populations where may be used with other things.

Bill Doyle: We're not suggesting that this is the end of the development, but we do believe that the substantial body of evidence here suggests that Medicare beneficiaries should have the same access as the rest of Americans to this therapy.

Dr. Edjah Nduom: Just while we're talking future trials, a couple comments. One, one thing you may consider, maybe you already did from the deep brain stimulation literature, the kind of on/off/on type studies where there, again, there is a sham, but the sham is something's implanted, maybe not in use for a period of time to try and get around some of those issues that you might have with ethics and that sort of thing. Again, because I do think that'd be nice information to have.

Dr. Edjah Nduom: And then just one thing on the demographics, which I wasn't going to bring up, but you commented that you had every race and everything that's kind of a pet issue of mine. There were only three African American patients that received the tumor treating fields with temozolomide and one in the sham arm. That's not just you, that's every trial that's done in glioblastoma. I think, in general, as a field we need to do better, but I just had to make that comment.

Bill Doyle: Yeah, so first of all taking it back first. We had a significant number of centers in the US, obviously, we don't pick the patients. I agree with you. I think that we need to figure out how to have greater representation of underrepresented patients of every ethnic heritage; so completely agree with that.

Bill Doyle: You know we're now a little bit far afield, back to the experience with medical devices, anytime there's a surgery, now you have a real possibility of a placebo effect because you're ... And in the case of deep-brain stimulators, you're cutting the patient open, you're threading a catheter into the appropriate area that you want to stimulate. Those trials, absolutely, require a sham control.

Bill Doyle: In this case, again, we've made the observations why we, in conjunction with the FDA, chose the trial design. I think the quality of life data are critical for the community, but we will take this under advisement as we always do when we have these conversations as we go forward.

Dr. Julie Kessel: Doctor.

Dr. Arnab Chakravarti: Our published data from RTOG 9802 and 9813 indicate that some of the IDH wild type grade two and three tumors behave, essentially, like molecular glioblastomas, especially some of the grade threes may creep up into the Medicare population and certainly disabled populations; both can be represented. What is the data with regards to TTF in patients with recurrent grade two and grade three or IDH wild type?

Bill Doyle: [inaudible 01:36:16].

Dr. Henry Fishman: Your mic is off. AP? AP? There you go.

Dr. Julie Kessel: Can we get some AP support?

Dr. Henry Friedman: Just grab one of his mics. [inaudible 01:36:36]

Dr. Adrian Kenzel: Thank you. So, I think basically, this is not the context of today's discussion. So about recurring or low grade glioma or whatever. So, I think we should focus on newly diagnosed glioblastoma and there, as you've seen in the-

Dr. Arnab Chakravarti: But I think moving forward and the field is changing pretty rapidly, IDH wild type tumors are going to be perhaps molecular glioblastomas. I mean, there's not going to be that just a pathologic barrier in the very near future, perhaps. So, I'm just curious, what is the data with regards to TTF in that particular group of patients?

Bill Doyle: Yeah, so first of all, we are very much aware of the work that's being done in reclassification of GBM; and we encourage it. Because I think it was mentioned some of the trials that look very promising in phase two and then, ultimately, don't pan out in phase three.

Bill Doyle: That may have a lot to do with the fact that in the small trial, there was maybe a more concentrated sub-population that was not represented the same way in the larger population.

Bill Doyle: As Dr. Kessel said today we're focused on the EF-14 data in newly diagnosed GBM. However, as the classifications evolve ... And, again, this is part of our commitment to ongoing development in the neuro-oncology community, we will certainly focus on that and developing whatever data may be appropriate in those new patient populations as the classifications are adjusted.

Dr. Julie Kessel: And Dr. Holdoff, and then after that, we may have time for a couple more questions. We'll go to as late as 12:45. Doctor.

Dr. Kevin Camphausen: You meant me?

Dr. Julie Kessel: Yes, I did.

Dr. Kevin Camphausen: Camphausen. So just one comment, I guess, for Bill Doyle. So, you said that really the EF-14 trial, the biggest thing that we want to focus on is the progression-free survival. Because the radiologists were blinded to that, so they didn't have any idea which side the patient was on, which gets back to our placebo-controlled trial.

Dr. Kevin Camphausen: So, if we're really going to focus on that bullet point, the progression-free survival and the patients with TTF plus temozolomide was 6.7 months. In the original 2005 Stupp trial, the progression-free survival was 6.9 months; so that's the same.

Bill Doyle: Again, we all know-

Dr. Adrian Kinzel: You have to add 3.8 months from diagnosis. So, because-

Dr. Kevin Camphausen: The randomization-

Dr. Kevin Camphausen: Was late?

Dr. Adrian Kinzel: Yes.

Dr. Adrian Kinzel: Right.

Dr. Adrian Kinzel: So, 6.7 is from randomization, so this is what you have to add 3.8 months.

Dr. Kevin Camphausen: Great. Thank you.

Dr. Julie Kessel: Are there any other questions from our CAC members? Okay, thank you then we will.

Dr. Henry Friedman: [inaudible 01:39:49] the broken one.

Dr. Julie Kessel: Break for lunch. We'll reconvene it at 1:30. We'll review the questions, and we'll get started with our CAC deliberation. CAC members, please stay back just for a moment before we go to lunch. Thank you.

Bill Doyle: And we'd like to thank the CAC for your thoughtful questions this morning. Thank you very much.

Dr. Julie Kessel: Sorry.