Robert Hoover: ... as well. There'll be a written comment period and an in-person opportunity for people to come, and that will be the open public meeting. At this point in the CAC, it's really an open closed discussion if you want to call it that. It's an open discussion amongst the CAC members, but there's not an interaction with the audience or other people here. In terms of the numbers here, we just had to do advanced registration for the in-person to get people. We left it open as long as we could to give as many people the opportunity to come. But at some point, we had to close it because CMS security had to do their piece of it.

Dr. Julie Kessel: Sure. Thank you for that clarification. There won't be any interaction with the audience unless CAC members need some clarification. There will be five Key Questions. We'll review and, hopefully, we'll have a robust discussion. Each of you has been provided with a yellow form. We're going to go over the rating of those forms in a minute. But as the discussion progresses, you'll have the opportunity to fill in the form. It's a level of confidence rating around each of the five Key Questions. Because the discussion may ebb and flow or move from one topic to another, you are free to fill that in at whatever time during this deliberation that you choose. At the end, of course, we'll have another minute for you to finalize your ratings. Those ratings will be delivered back to me. I will summarize them, hand them back. They'll be projected onto the screen, the average ratings for each of the five Key Questions, and then the meeting will conclude. It will conclude at about 3:30, possibly 3:45, depending on the robustness of the discussion.

Dr. Julie Kessel: Just to reiterate, the scoring is to go as follows. It'll be scored on a rating scale of five with one reflecting a low level of confidence in the Key Question itself. Each Key Question is written in such a way that you can score the response as you have a low level of confidence in the question, you have an intermediate, or high. It's on a Likert Scale of five. First question, I'm going to go over all five and then we'll we'll go back to start at one. “How confident are you that there is sufficient evidence to determine that TTFT for newly diagnosed GBM can provide positive health outcomes in the Medicare-eligible population?”

Dr. Julie Kessel: Number two, “How confident are you that the available evidence demonstrates adequate predictors of success in Medicare-eligible population?” Number three, “How confident are you that the evidence is sufficient to state that TTFT is generally accepted by the medical community for newly diagnosed GBM?” Number four, “How confident are you that scientific evidence supports mitotic spindle disruption and cellular apoptosis as the mechanism of action of TTFT?” Finally, “How confident are you that there are no significant evidence gaps that may impact positive health outcomes in the Medicare-eligible population?” We'll have some discussion questions to drive discussion around the Key Questions and, of course, they can be expanded at your will. Pretty much any discussion element is game.

Dr. Julie Kessel: Let's get started. We can float between the questions. That's fine. I'll make sure we come back and make sure that all the discussion points have been reviewed before we conclude this afternoon. Let's get started. “How confident are you that there is sufficient evidence to determine that the TTFT for newly diagnosed GBM can provide positive health outcomes in the Medicare-eligible population?” Some of the things that we'll be talking about include the quality of the Sentinel studies, the outcome measures use, progression-free survival, overall survival, quality of life, et cetera, safety issues, strengths and weaknesses of the studies including potential bias, and statistical assessments particularly relevant to the Medicare-eligible population. I will open it up now to the panel to get our questions and discussion started. To the extent that I can, I will back out, except to corral the team. Okay. Let's get started on question number one.

Dr. Arnab Chakravarti: I guess I just have a general question about the degree of benefit. By net positive benefit, are we talking about a major advancement or any benefit whatsoever? How is this traditionally experienced?

Dr. Julie Kessel: You're questioning what the definition of net positive health outcomes is? I think that that is part of the discussion. In fact, that's a wonderful place to start the discussion. What should net positive health outcomes actually mean and how well does the information that we have address that issue?

Dr. Arnab Chakravarti: Can we have some guidance as far as historically how that's been defined?

Dr. Julie Kessel: No.

Dr. Arnab Chakravarti: No? We have to come up with that ourselves.

Dr. Julie Kessel: Here's what I would suggest. I'd suggest that net health outcomes could be measured in overall survival certainly as an actual health outcome, or progression-free survival as a proxy health outcome. Quality of life, of course, becomes relevant to the number of months of life extension that occurs. I think that those are the points of discussion.

Parashar Patel: In my experience with payers and assessment bodies, net positive health outcomes, they are usually taking into account safety profiles versus the clinical benefits, et cetera. Then in essence, through quantitative or subjective scores, trying to determine if there's a net. I don't know if that helps.

Dr. Julie Kessel: Does that provide a decent framework to begin?

Dr. Arnab Chakravarti: Kind of.

Dr. Julie Kessel: Kind of? Okay. Would anybody else like to comment on-

Dr. Marc Fishman: As a clinician, I can't ignore economics. I don't know which patients when I'm seeing them in a study, which patients can afford copays, which ones can't. I can say that as a clinician, when I know that, I'll have patients say, "If I have to pay this, I'll never see my grandson in California." That happened. Or, "I'm losing weight because I can't afford food." Then if they don't take the treatment, that's a negative because maybe the treatment works. If they do take it, they can't afford other things, including things that add to quality of life, like going out for dinner or a movie. When you're looking at a study, you don't know the answers to that. You don't know what plans have copays. You don't know who can afford copays. You don't know any of that stuff. But when you're in private practice, that's real.

Dr. Paul Zeltzer: The question is, how is that pertinent for purpose that we're here in terms of Medicare approving funding for this? Or am I missing the point?

Dr. Marc Fishman: I don't know how to quantitate it. I don't even know if it should be considered in this question because we know what the science is looking at. But when you use the word net, you have to look at the positives and the negatives. Financial distress is a negative, we just can't quantify it, we don't know who has it, who it impacts.

Dr. Henry Friedman: I don't think it's relevant. But I think if you can't quantify it, you can't identify it, you're not sure what it means, it has no value.

Parashar Patel: Even if you could, I think that's a second-order decision the clinicians make based on a whole array of other factors. This is for a coverage policy as to whether Medicare as a payer should, in fact, pay for this, whether the physician and patient then decide to take them up, I think is a second order. But they don't have that option if there's no coverage in the first place.

Dr. Henry Friedman: I totally agree with that position. I think that it's a secondary thing that the physician and patient decides. It's not our job to factor that in, because it's unfactorable, we just can't do it.

Dr. Paul Zeltzer: I'll frame it from going back to being an oncologist. There are medications that were very helpful for progression-free survival. Avastin, I believe, one of those CCNU, several others. But they didn't have an effect on overall survival. I'm looking here and I'm saying they had an endpoint that looked at progression-free survival and that would determine if the study went on further in terms of analysis. In fact, there was a difference in overall survival with the addition of the treatment, and for now, I'm ignoring the sham issue. I'm not in the sham camp as a discovery item. It seems if we're just looking in terms of was there a net benefit, I think survival is a net benefit. Speaking just very grossly and very superficially, the lack of significant ... Compared to the things that we do to patients with glioblastoma multiforme, the toxicity of this therapy is minimal. I'll start the discussion there, saying I see a net positive.

Dr. Henry Friedman: Two points. You can't use Avastin because the Avastin studies were flawed with crossover of 50% each arm. The Avastin survival issue has never been resolved. The fact that, unwarranted, the national study got approved is probably irrelevant, except it's not. On the other hand, what is relevant is the primary endpoint was progression-free survival. The secondary endpoint was survival. One could argue in a glioblastoma population that any intervention, be it Avastin, be it TTF, that produces a meaningful increase in progression-free survival, even if overall survival is not attained, it's still a significant achievement because the longer it takes to progress, the longer you maintain your neurological quality of life. I have argued for 20 years that PFS is an acceptable endpoint for approval, independent of survival. For the most part, the FDA has taken that posture to heart, as you can see by a number of different agents that are approved every week on a basis of PFS. Yes, it's a surrogate for overall survival, but the bottom line is, in the brain tumor population, when you progress, your life goes badly.

Dr. Paul Zeltzer: Here, we have both.

Dr. Julie Kessel: Yes?

Dr. Cary Gross: This is a really interesting situation, because here, I think the bar needs to be higher when we were looking at evidence around an entirely new treatment modality. I don't want to switch the subject to the mechanism of action in the biologic plausibility. However, because it's new, I think we need to really be thinking about the science more carefully. If this is just another “me-too” checkpoint inhibitor. We might all feel more comfortable saying, okay, there's one trial. It has potential flaws. But we have a body, a very sound body of independently conducted, unbiased biologic evidence over 10, 20 years upon which this is being based.

Dr. Cary Gross: I think that the bar needs to be higher for this particular instance because a lot of the basic studies are sponsored by industry. A lot of the investigators that are performing these studies are not independent. They're also receiving sponsorship by industry. The only trial is an industry-sponsored trial. I asked that the data be made publicly available as is the current standard for many pharmaceutical trials. We were told that that would be considered. But I would strongly urge, if there's a hope that this trial be considered as a potential pivotal and practice-changing trial, that the patient-level data be made publicly available to the scientific community. The fact that these data are not out there being analyzed by us as a community, not by us personally, adds to my skepticism.

Dr. Paul Zeltzer: I think that's an interesting point. When you say raise the bar, can you help us in terms of to where? If we're going to say raise the bar, what needs to happen concretely to get over the bar?

Dr. Cary Gross: I want to see another randomized trial with a sham control. I would like to see that trial include enough older patients that we can have a firm understanding of the benefits in older versus younger patients as well. That's my opinion.

Dr. Edjah Nduom: My personal, if I was going to keep it short, just going off with what Dr. Friedman said and what's been said so far, there's a progression-free survival benefit. With all the kind of engineering stuff and questions that I have, and I still have, I'm still fascinated by this and I still don't fully understand, and we'll get to that later in some of the other questions. The healthy dose of skepticism that I have from some people I've interacted with and the many questions that we have unanswered, I have not been able to figure out with the centrally blinded review how you get around the fact that even with, you can say, the extra doses of temozolomide, right? But they didn't progress, so then they stayed on the temozolomide. That's the other way that you explain away the progression-free survival benefit.

Dr. Edjah Nduom: I haven't been able to come up with a clever way to explain how the MRIs don't get worse with the patients that are on the treatment if it's not doing something. That's my fundamental problem, to try and attack the progression-free survival endpoint. So, with that, if you see a progression-free survival increase, given all the flaws and everything we've talked about, there seems to be some clinical benefit that I may not be able to fully explain, but it seems to be there.

Dr. Matthias Holdhoff: I'm actually in direct connection to that. I think I agree with that. Most treatments that are eventually used in the community, they don't have absolutely perfect data. I think we discussed the limitations of this study. But this is, as you pointed out, research with a significant body of data behind it. If we think that this is positive data presented, if we think this is clearly different from a drug trial, but just hypothetically, if this was not the Novocure device, the TTFT, if this was a pill, would we have the same discussion? We would see these curves. We would probably say they look pretty good, would be great to do another trial to confirm it. But the discussion would be probably less complex because we have done this with other drugs.

Dr. Henry Friedman: You go first, I'll go second.

Dr. Annick Desjardins: No, I have to agree with what has been said so far. The improvement in progression-free survival and overall survival in the EF-14 study, in this patient population, I think, is there. There is a benefit there. But we need to be really careful in the fact that I think that the main concern is making sure what has been mentioned before, which is that there is enough elderly patients. We have to remember this is a patient population where they had resection, radiation, Temodar, were stable after a radiation and Temodar, and then enroll in study. For that population, it's clear there is a benefit. I'm good with that. I'm absolutely okay with that. But I do think that I want to have more information on the other patients, so the patients that are older, their poor quality of life data.

Dr. Annick Desjardins: That's my main concern, because I think that everyday life, when you see a patient, a patient that sees this degree of improvement in overall survival and progression-free survival, a patient who doesn't have caregiver support, a patient that doesn't have the quality of life to put the device themselves. They feel very guilty of not being able to do it. While the patients that are very good, for them, they're passionate about it. It's really, really good. I think that's fantastic. But I think that I'm mostly thinking about, I want that to be clear, the benefit that we see in a clearly defined population, which are stable after radiation and Temodar, with a good quality of life, and are dedicated and using the device. I do not want the other patients to feel guilty if they cannot do that.

Dr. Paul Zeltzer: But that's the indication.

Dr. Annick Desjardins: I agree with that. But the problem is that part of the feeling ... I completely agree that's the indication and I'm really glad that and Novocure made it clear that's what they were asking for. I'm really, really happy with that. But it's just when you approve something, I think we need more data for the other patients. But I have no problem with the good patients, the study population. The benefit is there.

Dr. Julie Kessel: Yes, Doctor.

Dr. Henry Friedman: Okay. I may say a couple things that may not agree with it, that not everyone in the committee may agree with. But I'll start from scratch. I don't think EF-14 is a particularly terrific clinical trial. I think that there are holes in it. I think we've talked about it. But overall, I do believe that there's something there, there's a signal. On the FDA panel, had I been there, would I on NCCN done the things that were done? I'm not sure. I don't envy the FDA. They've done a difficult job, and I admire them. But nevertheless, we are where we are.

Dr. Henry Friedman: Now, you've got a situation where you've got a large population of Americans that are under 65, where every major payer is providing this. Many people only have Medicare coverage, don't even have a supplement. The problem is that I agree with Annick that we don't really know with hardcore data about the elderly population. I don't like the word elderly since I'm in that population, I just say that in their prime, okay? If you don't laugh, you're not getting anything.

Dr. Henry Friedman: But for those people that are in their prime of life, I think it would be a challenge to not have that group of patients have access to the same things that the younger, the babies, really do. That's not meaning that I think the data is terrific. I don't. That doesn't mean that I think this is the most brilliant study ever conducted. I don't. But I'm conscious of the fact that we see so many patients who are over 65 that do, probably because it's warm and sunny and we're the best, that I think that it's a difficult position to be. It's not just the data, it's the reality of setting up a dichotomy within the country of who's going to get something and who's not going to get something. For me, that makes me willing to lower the bar rather than raise the bar, although I don't think the bar has to be changed at all.

Dr. Julie Kessel: Dr. Peña.

Dr. Carlos Peña: Another way to look at this is when you think of net-

Dr. Henry Friedman: You have the mic.

Dr. Henry Friedman: Can you talk into the mic?

Dr. Carlos Peña: ... net positive health outcomes per patient, the wording is interesting because you're saying net, so you're trying to add up a number of factors such as the risks, the benefits that we know of, the safety data set, the effectiveness on PFS and overall survival and activities of daily living and the quality of life. You're adding this all up to see where the net is. Then you're also adding up the challenges, the limitations, the limitations of the trial design or the sub-population that people are interested in. But I guess my comment is that we should all be adding up all these different things and seeing if there's a net benefit to that patient, because that's an important calculus that I think we should all do, which we've heard about today.

Dr. Paul Zeltzer: According to Dr. Friedman, I'm past my prime, but I'm going to voice anyway.

Dr. Henry Friedman: No. You're not in your prime yet.

Dr. Paul Zeltzer: What I'm thinking is I'm getting a subtext of we need more data, more information. In many drug trials, you only find out what the real side effects of the drug, and sometimes even the therapeutic effects on a post-marketing phase four-type trial. In the first thousand, you didn't see and then you start to notice things after that. What I'm wondering is, and I don't know if this is the right time to talk about this. Would it help the committee if we knew that there was going to be a phase four component to this in terms of collecting outcome data and following the patients so that we know our original hypotheses really bearing out on 2,000, 3,000 patients as opposed to 670? Given the questions and difference of opinion about the study design, but still looking at net benefit or deducing an opinion based on the net positive effect, would a phase four add to that component to allay some of the concerns?

Dr. Cary Gross: It's kind of hard to respond to things like three comments ago, but a couple of issues. One, I actually don't think that our deliberations around the strength of the science supporting this intervention should be in any way affected by what other private payers have done. They have their own considerations with their coverage decisions. My personal opinion is that shouldn't affect how Medicare makes decisions or how we evaluate the strength of evidence. Secondly, with regard to the relation of age and the interaction with the effectiveness and risk of interventions, the FDA has called very recently for, really, this whole lifespan approach, both in age, but the FDA has specifically called for enrolling more older patients into trials, recognizing the paucity of elderly.

Dr. Cary Gross: In light of that, I think it's in keeping with other federal initiatives that we should strongly consider that data derived directly from older patients should really inform the way Medicare is making decisions, should inform the way that we are evaluating the evidence. Again, I really just think that if something hasn't been studied much in the older population, that is very relevant to our decisions.

Dr. Henry Friedman: The only thing I would say, and I'll stop belaboring the point, is that Annick and I and others in this table are the ones in the clinic seeing patients who are in different degrees of complexity and sensitivity to the intervention. When you get into the approaching your prime age where Medicare kicks in, I'm never going to concede the word elderly, there's no question that toleration of chemotherapy is more challenging. It's a more difficult proposition to treat patients with chemotherapy, the exception probably being Avastin which is more tolerated in the elderly. That's a whole separate controversy, but it's used.

Dr. Henry Friedman: You find yourself in a position where maybe you have less options than you might otherwise have because of the approach that you're talking about. I just bring it up there as a counterpoint when you're really looking at patient in the eye and saying, "I'm sorry, you can't get CCNU. You can't get temozolomide because your counts are too low. You can't get Avastin because your platelet count's 30 and you've had your radiotherapy. We're helpless." I don't want to be in that position.

Parashar Patel: I understand the desire for more data, right? To some extent, I kind of agree with more data is always better so you can better identify which patients are going to respond. But I think we have to seriously consider whether asking for another randomized study is practically possible and even doable. You've got a case here where you're going to randomize patients to no treatment with TTF or treatment with an FDA-approved therapy which at least one study has shown some efficacy. What type of doctors are going to recruit patients in? If I'm a patient with that consent form in front of me, am I going to sign that consent form, or wouldn't I just say, "Well, why can't I get therapy?" How long would it take to recruit patients into that type of study, et cetera? I think we've got to balance the need for more data. Device companies, I know, always do post-market studies either independently. I'm kind of curious, is there a post-market requirement for this approval?

Male: I think so.

Parashar Patel: Do you have a post-market study requirement?

Male: Yeah. I think they complete it. Is that correct?

Dr. Paul Zeltzer: No whispering, come on. [crosstalk 00:27:58].

Parashar Patel: Sorry?

Dr. Paul Zeltzer: He's saying something, he's whispering. I don't want to hear whispers. [crosstalk 00:28:04]

Male: A post-market requirement.

Parashar Patel: There is a post-market requirement?

Bill Doyle: No. For this newly diagnosed therapy, again, we weren't sure whether we're allowed to respond.

Parashar Patel: Fair enough.

Dr. Julie Kessel: Please provide a clarifying response.

Parashar Patel: Maybe the microphone will help folks out in the Internet.

Bill Doyle: We were whispering. We were only whispering because we weren't sure whether we were allowed to respond. For this EF-14 study, the FDA approved it without the requirement for a post-market study. What I can say is we've now treated over 10,000 patients in the community, so that's a large number of patients. For medical devices, every device has a registry for safety. We're talking about net. There've been no safety signals that have been reported. Back to your net equation of safety versus efficacy, that hasn't been seen. We are recording, however, the usage and the overall survival. We don't get progression-free survival of these patients, we only get overall survival. Those data are being compiled and will ultimately be available.

Dr. Julie Kessel: Thank you.

Parashar Patel: It's helpful to keep that context in mind, that we're probably past the point we're going to get a randomized study for this population.

Dr. Kevin Camphausen: If I could just say something quick, I'm sorry. The only thing is that the treatment in this population is moving really fast, too. Somebody had mentioned earlier that a lot of these patients that are in the prime of their life are getting 40 and 15, so 40 gray and 15 fractions. It's a larger radiation dose. It's a faster dose, it gets them done in about three weeks, versus 60 gray which is what this study did. That's changing. We don't know that a higher radiation dose, I assume it's exactly the same, but we don't know that.

Dr. Kevin Camphausen: The other thing is, is recently, they've published that that's concurrent with temozolomide is better also. The standard of care in people in the prime of their life has moved very quickly over the last two years and isn't represented in the EF-14 trial, because that was 60 gray. I can't tell you what the number is, but every patient that walks in the door in their time of their life, the first thing is "Are we doing 40 and 15?" That's the default now, not "Are we doing 60 gray?" Then we argue over the temozolomide. There might be room for another randomized trial because that standard of care is changing so fast that this isn't either the control arm or the experimental arm for people in the prime of their life. It's slipping that way.

Dr. Edjah Nduom: The phrase that keeps bouncing around in my head really all day is the whole thought of trying to put the toothpaste back in the tube, which I know a lot of my questions, I think, were deliberately going in that. Could the trial have been done differently, could we have gotten the data on the fields? Could we validate the models as far as everything? Because it would have been really nice to have all that. This would have been a much shorter meeting and I'd have less sound bites to maybe show my son later about how I really am an engineer.

Dr. Edjah Nduom: But we're here with this amount of data. For this specific question with the data that's presented, the benefit is what it is. It's dirty in some ways, but it's what's in front of us and it's what the FDA had to deal with, irrespective of what their advice may have been on how the trial should have been run, that the data they got back was this. We have that same data. I don't know. Again, I've twisted my head around in different ways to get around the positivity. Because of that visceral, it doesn't make enough sense to me yet, but the benefit seems to be in the paper.

Dr. Julie Kessel: Other comments around this issue. It sounds like a lot of the discussion was around this particular trial and what could or could not have been done better and what we're left with. I just want to bring to the foreground that it's largely been about this trial.

Dr. Jonathan Sherman: I'll just say just from my personal perspective, as the initial introduction of everyone, my research is on cold atmospheric plasma. You don't have to know what that is. But we are studying the mechanism because we feel like we're 15 years behind where you guys are and we're using Optune® as our example. I just find that I was really keen on the basic science. I think one of the main points of today's discussion is on the basic science. I just gave a grand rounds on our research. We were talking about P53 relationship or independence. Just like your data, ours is similar. We're essentially electrifying healing and regenerating plasma, which is a state of matter, and you're doing it differently but at the same point.

Dr. Jonathan Sherman: We're P53-independent just like you guys are. We have G2 MRS just like you guys do. We've actually studied aquaporins, your literature on the actual increase and the porosity of the membrane. I don't know if you looked into that with aquaporin. That's what we did. We haven't studied it enough to really look at the cell membrane itself like you did. But based on your literature, that's what we're going to do next. We're following some of the same footprints that you guys did just based on our early experience with this cold plasma. We've seen efficacy selectively to tumors.

Dr. Jonathan Sherman: We can't get NIH funding for our researches because the mechanism is still in process. It's a challenge I find personally to get grant funding when you don't have a great mechanism. We're so far behind where you guys are where you have pretty interesting basic science. Even from a basic science perspective when I look at the pathways that you've shown are impacted for proliferation one, you still ask, "How is that possible?" You still don't have the mechanism even to get to why the pathways are impacted in the first place, but they are. Even just like the trial, the basic science isn't perfect either, but it's there.

Dr. Jonathan Sherman: Our cold plasma research relates to electromagnetic pulse. You're generating a different type of magnetic field. But there's enough similarities that, I would just say personally, we're using a lot of your basic science research to study our own area of treating cancer. While not perfect and while there's a lot of holes even in your own basic science understanding of how it works, I think there's enough positive answers that I glean from reading all your literature that it gives ... Personally, maybe I'm a little biased because I actually would love to have NIH funding. As we strive for that perfect mechanism, so they'll give it to us, I find that that the data is good enough for me to say that I understand where it's coming from and there's background to support the clinical finding. I think that should not be taken lightly.

Dr. Henry Friedman: You can't ask them for money, you know that?

Dr. Jonathan Sherman: I'm not. This isn't a pitch, but before reading all this data, I only thought of tumor-treating fields related, obviously, with change in mitosis. But there's so much more to it than that, and so why we don't really understand it. I just was impressed with the similarities between what we're studying and what you're studying. I think there's something to be said. Even though it's not perfect, that doesn't mean it shouldn't be accepted.

Dr. Julie Kessel: Thank you. Any other comments? We can come back to this. But if there aren't any other specific comments around this particular question, let's go ahead and move into the related question of “How confident are you that the available evidence demonstrates adequate predictors of success in the Medicare-eligible population?” The discussion questions relevant to this item really include patient selection in terms of performance, methylation status, adjuvant therapy, cycles of therapy, and any other predictors that we may think are relevant to discuss.

Dr. Arnab Chakravarti: I was actually very impressed with the data, the methylated population with TTF. I think the median survival time was doubled, 32 months versus 12 months or something like that. The unmethylated population, there was more of a subtle difference, but I think it was still a significant difference. I thought that those data were pretty impressive by themselves. I wish that there were true predictive biomarkers to identify which specific patients would benefit, but it looks like that's a future direction.

Dr. Julie Kessel: Yes?

Dr. Henry Friedman: I don't want to over-talk, but it's hard not to. Under 65, MGMT has no predictive value. I know there are people who say that it does, and they're wrong. It's merely got prognostic value. You take 100 patients with and without methylation. The methylated patients are going to do better, tumors that are methylated. Over 65 to 70, the data would appear that it does have predictive value, that truly patients who have tumors that are unmethylated do worse, and you can make individual decisions about that. You can't do that under 65. The fact that there's anything in the unmethylated population is important, which is a particularly higher risk group in your prime group of patients.

Dr. Paul Zeltzer: I was interested in terms of the eligibility criteria, they in fact entered older patients. It was up to 80, where a lot of trials cherry-pick in terms of high KPS and under 70. I think the fact that you do that and you're willing to take that and you were able to look at that, I think, is important for us to consider.

Dr. Julie Kessel: Yes?

Dr. Matthias Holdhoff: I want to underline that I think a lot of trials including the EORTC and CRC trial.

Dr. Paul Zeltzer: Can you talk in the microphone? I can't hear you.

Dr. Matthias Holdhoff: Oh, sorry. I'm actually saying exactly the same thing as you, sir. I think that the original EORTC and CRC trial had age cut off at 70. Here, we have an open-ended study which we would, at least for the most part, all agree that we should enroll older patients so that we can say that population was included. It was not an older-adult-specific trial, but which trial is designed like this due to the first randomized control trial.

Dr. Edjah Nduom: Essentially the same thing as I said before with the caveats that were expressed before about the fact that this wasn't focused on that sub-population of older patients. It would be nice if we had that and the new standard of care as far as radiation for patients in their prime. But even in that subgroup, with the data that's available, there appeared to be some evidence.

Dr. Annick Desjardins: No, I have to agree with what has been said. I think that it's clear the methylated patient has much better data, the KPS, everything, longer exposure to chemotherapy. The data is there. Despite all the flaws we discussed about already, there is the benefit and we cannot dispute that.

Dr. Julie Kessel: I want to clarify that some of the things that we said so far had to do with methylation status in the older folks. Then there were comments that benefit looks positive. How about with some of these other discussion points: Performance score, concurrent therapies, history of therapies, and adherence in terms of predicting success?

Dr. Edjah Nduom: Again, I'd just say narrowly, the trial-eligible population with the clarifications of good KPS, newly diagnosed, that that sub-population appeared to have some benefit. I don't think we can say anything about patients that were not on support KPS. Patients that had had other chemotherapeutic agents wouldn't have been eligible, so we can't really say anything about that. Adherence to therapy, I think you made a great point earlier about it. If patients don't have the supportive therapy, then again, it would seem they would not get benefit.

Dr. Annick Desjardins: I think that what is clear for the adherence therapy part, I think that paper is very interesting in showing that, in effect, the patients that had 0% to 30% adherence to the therapy, that's where the highest number or the lower KPS is, that's where there is the largest number of biopsy-only patients. It just shows the lower your KPS is, less you will be able to adhere, those patient didn't have the benefit. But in the patients that do adhere to the therapy clearly, and most patients were able, this patient population was selected that most patients were able to do the therapy more than 75% of the time.

Dr. Cary Gross: Just a quick note about adherence to therapy. We've alluded to this idea before, that people who are adherent maybe just somehow different from those who are not. For instance, in some of the larger cardiovascular disease trials, adherence in the placebo group, adherence to the placebo, people in the upper quartile of being really adherent or not adherent, sometimes the hazard ratio is as good as 0.6. 40% lower mortality if you're adherent to placebo in some of those other studies. It's just important for us to keep in mind that when we're thinking about the dose response curve, there's also this adherence curve. That's why I'm interested in this other issue of there's an intensity above and beyond adherence. Can I pose a question? You raised the issue of tumor resectability and how you had a concern about how that might relate to how we're understanding, I guess, the relation between dose and outcome. Can you elaborate on that a little bit? Does that affect the way you evaluate this data?

Dr. Edjah Nduom: Yeah. We can get into that more on the specific mechanism stuff and parsing out the data on the dose response. The maps are the maps. Yes, on the surface in some of the maps, depending on where the field was coming, they didn't get that high of a feeling the field would be particularly high next to the ventricles and the deep white matter because of the conductivity of those areas. But there are hot and cold spots based off location. It'd be difficult for me not having looked at all the maps, just only seeing a couple examples, to know where the cold spots are relative to a frontal polar tumor versus an insular glioma versus wherever else the lesion might be.

Dr. Edjah Nduom: This whole thing about dosing, the patients that had better dosing might do better. The geographic nature of the brain and the conductivity of different regions is going to be different. One could theorize that if you did parse out the data by location and depth and resectability that there could be, I don't have the data in front of me, there could be some overlap between unresectable tumors, for example, and locations that are difficult to treat by tumor-treating fields. If that were the case, then the dose response curves would be difficult to parse out, because then, if you look at it, then that could wash away because, potentially, the unresectable tumors maybe weren't getting as good of a tumor-treating fields dose. Maybe if there's tumor left, the conductivity is worse. I don't know. That was where that all came from.

Dr. Paul Zeltzer: One of the questions you posed was, are there predictors or are there prognostic markers for who's going to respond or not respond? If we look at other tumor systems that most of us had contact with, especially on the pediatric side, the only thing that knocks out prognostic markers is effective therapy. Once you have an effective therapy, the prognostic markers disappear. I think we have to remember what we're trying to do, we're incrementally adding here. If, in fact, when we can study what happens to 10,000 patients, some of those predictive factors, in fact, and the things that we're talking about in terms of location, tumor intensity, et cetera, we may learn an awful lot of that, but it's only going to be on large numbers of patients to parse that out.

Dr. Paul Zeltzer: I think we're too early to really talk about predictive factors. I think we can say predictive factors, probably a Karnofsky of 10, we're not going to put that patient on study. But barring entry on study, I think we're just too early to look at. My opinion is that we're just too early to look at what might be a prognostic factor at this point in terms of choosing who should go on and who should not.

Dr. Julie Kessel: No other comments about this? Okay. We can come back to it if something comes up. Next question is, “How confident are you that the evidence is sufficient to state that TTFT is generally accepted by the medical community for newly diagnosed GBM?” The discussion question around that is, “What factors support that assessment in the Medicare-eligible population?”

Dr. Arnab Chakravarti: I think they presented data that the majority of practitioners at comprehensive cancer centers employ TTF at some point. I'm not sure that that necessarily means that every practitioner agrees that TTF is accepted therapy for this patient population. I think there's still some heterogeneity in terms of practice. I don't think all practitioners have adopted TTF. I think maybe part of it is due to the fact that I think there's perhaps some confusion as far as lack of mechanism or skepticism of mechanism. I think there's also the convenience issue for certain patients as well. I guess in terms of scoring this question, yes, it's out there being utilized, but is the question implying that they want the majority of patients to be treated with this device or what is considered widely accepted?

Dr. Julie Kessel: I think that the interpretation here of the question is ... I'll read into this a little bit because it's not exactly what the question says. But it seems to me that the question gets out, “How comfortable are providers understanding the technology enough to choose to use it or to choose not to use it knowingly?”

Parashar Patel: The other thing, I think, to consider, this is a tough question especially with a new technology that comes into a place where physicians aren't used to this mechanism of action. On top of which, you have coverage issues. Interpreting this question four years out, I know you've done a good job on coverage, I don't know what the ramp was. But having been on the other end trying to launch new technology, acceptance is a double-edged thing because they're willing to accept it if the patient's going to get covered. It's a chicken and egg thing. It's one thing to consider.

Parashar Patel: The other thing to consider is, again, getting physicians comfortable with a new method of action, understanding it, being comfortable enough with it. At least from what I saw of the evidence, it seems like they've got enough physicians. They're not pockets of physicians, it appears, from the geographic data, if they are spread out over the country, that they are both in community practices and academic medical centers. Is it 100% of the docs? I don't know. That was a question we ask. We don't know what the denominator is, but it seems to be at least enough and not just sort of confined to one place. Maybe with Medicare coverage, that number may go up again.

Dr. Julie Kessel: Yes?

Dr. Marc Fishman: I found it very interesting as a medical oncologist that physicians don't make any money on prescribing Optune®. I think that's a credit.

Dr. Paul Zeltzer: Microphone.

Dr. Marc Fishman: I don't know how many patients, how many physicians prescribe, but I think the fact that many physicians are prescribing in many different locations and that none of them are being compensated, I think speaks well.

Dr. Julie Kessel: Yes, Dr. Friedman?

Dr. Henry Friedman: I don't think you can lump medical community into one pocket. I think there are three pockets. There are the private practice medical oncologists and those rare private practice neuro-oncologist who have no real affiliation with an academic center. There are academic centers that are basically doing patient care, but not necessarily conducting trials. Then there are other brain tumor centers of excellence which are conducting trials. Each one has to be looked at separately. I think the general population of physicians will tend to look at whatever is FDA-approved. Whatever is FDA-approved, I think they're going to be interested in using because they want to do something better for their patients.

Dr. Henry Friedman: I frankly don't think they should be treating those patients alone, I think they should all go to academic centers. But that's my bias academic admission. I think they should go to an academic center every time. If they go to an academic center that is not a program that is conducting clinical trials, then they're probably going to use this as another weapon. If they're at a center that's conducting clinical trial, and I think someone made a comment about this, you can't go on a clinical trial for an immunotherapy for modified poliovirus or anything else and get a confounding variable. Because if you've got an FDA-approved intervention, then you can't use it by definition in that clinical trial.

Dr. Henry Friedman: I think you have to look at each of them separately. Let's look at each of them separately. General population of people who are medical oncologists who treat patients, I think there's a penetration now. The academic centers that don't run their own trials, I think there's some penetration. I think the least penetration, at least my bias, is that is going to be at the academic centers who run their own trials, because you can't do it with TTF unless, of course, it's a TTF trial. I think lumping them all together is hard. But since the majority of patients sadly for any adult tumor don't go to an academic center, it's like 3% as opposed to my background in pediatrics, where it's 90%, which is why I act somewhat immature up here. I think you can say that there is a pretty good penetration now into the medical community, looking at it in three different ways.

Dr. Cary Gross: I just have a question for my colleagues on the board. I'm about to make a statement that I don't have firm evidence for, but I did a lot of talking with people and some back-of-the-envelope type of a research preparing for this meeting. They say if you build a better mousetrap, the world will beat a path to your door. My question is, is this a better mousetrap? Because the concern I have is that there are a lot of industry, specifically Novocure, relationships with oncology providers and that they have a reputation for being very aggressive at reaching out to providers and speaking to them about, "Hey could we have you come give talks for us? Can we talk to you about our product?"

Dr. Cary Gross: I guess a question is, is this widespread dissemination a result of acceptance about the efficacy of this intervention at the community, or is this increasing dissemination the result of a very aggressive marketing? I'm hoping some of you all that are more directly involved with this type of clinical care could shed light on your thoughts about the potential impact of marketing savviness as opposed to grassroots clinicians clamoring to use the device.

Dr. Paul Zeltzer: What physician hasn't been contacted about Keytruda or another checkpoint inhibitor recently?

Male: I have not.

Dr. Paul Zeltzer: Yes, the exception. It's a fact of life in terms of this wasn't developed by the government, it was developed by private industry in the same way Herceptin is promoted for breast cancer. I think that's just a reality of the world. It's hard for me to judge whether that's malignant, malign, benign or not. But I don't know if that's ... Help me in terms of, is there a phase of that that you think truly does impact our decision-making here?

Dr. Cary Gross: If we're being asked to evaluate the degree to which this is becoming accepted standard practice, the implicit assumption behind that is that it's accepted standard practice because clinicians believe this is in the best interest of their patients. My question to the group is whether you believe that the prevalence of this use of the intervention is because of widespread belief of the efficacy, I think it's very relevant to talk about, or is it because of just some other mechanism?

Dr. Edjah Nduom: It was interesting. This is one of the things I had a question on, one of the CAC calls is how we're supposed to parse this question out, because I think it is difficult because of the different practice environments and that sort of thing. I'm a surgeon so I don't typically prescribe anything. No one asks me about this stuff. I work for the NIH, and so we probably beat them out the door anyway before they could come in. That hasn't been a factor for me personally, but I don't prescribe it. I think that the scientific discussion we had earlier with the company reflected the level of skepticism there is when you are looking at a lot of the academic centers towards this thing, because I really would like to understand it better and I don't understand it as well as I would like to, because I think some of the data is not there. Some of the data wasn't provided. Some of the data was not published. It is what it is.

Dr. Edjah Nduom: Nevertheless, one of the documents we had that we're supposed to look at is guidelines. It's one of the reasons I kept coming back to the NCCN guidelines. Again, that's not a mandate or whatever, but guidelines. I actually looked at that. They have on the NCCN website the conflicts of interest for the people that are on the guidelines committee. Two had a Novocure conflict. But that was out of something like 30 people on the committee. It wasn't most of them. There were certainly some people in the room who may or may not have been vociferously in favor of Novocure for their own personal benefit. I don't know.

Dr. Edjah Nduom: I asked them about why they think it's an option and not of a mandate. I think some patients want to use it, some patients don't, whatever, it's tough to parse out from there. But it's in the guideline that a lot of people who aren't in academic centers use to make their decisions on what to do for therapy. That's what I have. I actually thought about doing a survey before this. I've been doing some surveys for the tumor section, but the length of time it takes to get through the IRB at the NIH would not permit me to even do a survey of my colleagues of what they think of this.

Dr. Edjah Nduom: There was a survey that was included in our data, it was on elderly treatment of glioblastoma. I was actually surprised because in that survey, I think it was something like 40% said they were already prescribing those who responded to the survey which surveys other problems. Then there was an additional 20% who said they were making progress towards providing. Then there were 40% that had no interest whatsoever. That's still, in theory, about 60%. What is generally accepted? I don't I don't know. I think a lot of people that I talk to, it's like, "Well, what do you think about it?" It's like, "I don't know." I think they similarly say they don't know. But many of them prescribe it anyway.

Dr. Matthias Holdhoff: In similar notes, I think it's a very complex question. I think it's a broad spectrum. It's not just two-dimensional. It's like it depends on how many patients you see with this disease, how much experience you had with the device, how much time you had to study the actual data as a treating clinician, what does the patient bring in, and what would the regulatory body say. Is it FDA-approved? What would the different guidelines say? One guideline, NCCN guideline is in favor. There's certainly a continuum. What I understand with this compound and with this device is that it depends on how the discussion is like with the patient. If a patient comes in, has no idea about the device, and the treating physician is clearly in favor of the device, that discussion will go, especially if nobody is prepared to be diagnosed with a glioblastoma. You depend on the advice from people in the field and from other patients who have the same tumor. You rely on their experience and opinion.

Dr. Matthias Holdhoff: Patients often come in. Some people have never heard about Optune®, many have heard about Optune®, so TTFT. They look at the picture. Some patients know exactly they want to be on this trial, receive the device, and others don't. It is certainly a complex question. I would agree that there's this difference between academic institutions, but we have the luxury a lot of time to review the data, ask this kind of questions, and critically review, and we see only one tumor type versus in the community, and you rely on essentially summarized opinions in the form of guidelines. I think that's important to consider. There's no perfect answer, I think, to this question.

Dr. Paul Zeltzer: There's a new phenomenon that I don't know if all of you are aware of, but there are at least three organizations now that our navigators specifically for patients with brain tumors. The thing that these three that I know of have in common is that they collate the foundation in genetic-type studies and the patient's condition and then advise both standards of treatment, as well as possible clinical trials that patients may be eligible on. It's not statistical, it's just based on discussions. Each of those three have Optune® as part of their recommendations. In terms of the dissemination, the dissemination of the option for Optune® is not just coming from the penetration of the company, but rather it's also coming from these navigator groups that are helping patients.

Dr. Julie Kessel: Yes.

Dr. Henry Friedman: No, you go first.

Dr. Annick Desjardins: Go ahead.

Dr. Henry Friedman: Okay. Two points. There's a lot more than three groups. The ones that we work with basically do not give patients recommendations. They basically send them to centers of excellence. I won't name them because they don't need the publicity on YouTube, it's not fair to those I don't mention. But they basically just leave the plans up to us. Then there are some high-tier medical triage groups. Even there, they basically will leave the decision to the centers that they choose to use. Again, look at the medical community in three ways. I don't think that the private practice groups are going to be in any real way enticed by anything Novocure has got to offer. An office lunch doesn't cut it. The academic centers that are brain tumor centers of excellence, similarly, are going to do what they want to do based on the trials they want to run.

Dr. Henry Friedman: The middle ground is a little shakier. The institutions that don't have their own trials would potentially be more likely to curry favor from Novocure if, as part of that relationship, they not only use it for patients not on trial but were offered trials of the product in whatever clinical trials Novocure and that institution agreed to do. That's the weak link. That's the vulnerable group of people who could be manipulated. I don't fault Novocure. This has been done by every single pharmaceutical companies since the history of man. They're going to fight their fiduciary responsibility to make money. They want to do something good. That's one way to get their product out there. It happens all the time. I'm not condoning it, I'm just noting it as a phenomenon. But that's the group that there would be potentially an impact of any company, not just Novocure, Genentech, whatever it is, Merck, all of them, Pfizer. They all do that to help promote their studies at institutions. That's just the way it is.

Parashar Patel: I agree with what you said. I guess I'll pose a hypothetical alternative. In a capitalist society that we live in, and combined with the information flow directed at doctors through peer-reviewed journals and everything else and a quick pace of change that we see in healthcare, I'm not sure what companies can and can't do if they can't at least go out and talk about their product. If that's at least going to be the standard that sort of disqualifies you, I think we just have to be careful about setting that type of a bar, where we're trying to actually get information out in front of docs because, otherwise, they may not even see it, even if it is groundbreaking and everybody loves it. Again, I would urge the committee to sort of balance these considerations as you think about this.

Dr. Julie Kessel: Before we end this discussion, are there any comments related to the NCCN's designation or other guideline organizations and what they do or do not say about tumor treatment fields? Did you want to say something?

Dr. Annick Desjardins: I think it has been said right. The NCCN guideline is a recommendation. It's not a mandate, it's a recommendation. All the groups, in fact, the patient support group are quite fantastic in giving information to the patient, but I've never heard any of them mandating a patient to do anything. They are there to bring information, to bring support. It's mostly caregiver support. I'm not concerned with that, absolutely.

Dr. Julie Kessel: Any other comments before we move from this particular question? Okay. Let's go on to the fourth question, which addresses the cellular mechanism of action. “How confident are you that scientific evidence supports mitotic spindle disruption and cellular apoptosis as the mechanism of action?” The discussion question revolves around, “Is the mechanism of action or actions sufficiently accepted in the basic science literature?”

Dr. Arnab Chakravarti: I think the preclinical data that was published and presented is very compelling with regards to mechanism of action in the preclinical models. But I haven't seen any human tissue data or correlative data to support that. That's the big grain of salt, because mice are not men and vice versa. But I would also have to state that, looking forward, there's almost more of a rationale for radiosensitization versus chemosensitization because the mitotic mechanism is a major mechanism of radiation-induced cell death. I'm still a little bit confused about the specific mechanism of sensitization with temozolomide and chemotherapies. I don't think that's 100% rock solid and convincing. But I think the preclinical data that was published with regards to mechanism seems pretty solid just on itself. It's going to be hard to translate that into actual clinical data and clinical reality.

Dr. Edjah Nduom: I'll just say in my very short career thus far, this is one of my many platforms that I'd like to talk about, is figuring out how we translate therapies from mice into humans and validate that they work the same way that they did in our models. I think that we can do better in general as far as validating that drugs get to the target, do the same thing in the target, do very elegant, single-cell RNA sequencing in mice and then noting in patients. I think that we can do a little bit better in our patient population. I think that applies here. I think that that probably followed another line of questioning that I had earlier. It would have been nice to get some of the data so that beyond models which are fantastic, it would have been really nice to have just a little bit more of that validation that everything worked the way it does.

Dr. Edjah Nduom: Now, I feel pretty confident on how it works in mice. As far as the mechanism of action in murine models, I feel very confident about that. I can't say that I'm very confident in exactly how it works in humans. I don't know how we're supposed to parse that out for the question. The question doesn't say humans or mice or models or in vitro versus in vivo or whatever. But that's my two cents on that.

Dr. Matthias Holdhoff: I would agree with what my colleague says. Very often, we find out about the precise mechanism of the drug. Much later, much more data. From a clinical trial, patient/physician perspective. As long as something's happening and the tumor cells die, the main thing is we hope they die. That's clear. I think it's really interesting to follow the development of additional data. There were two recent publications from South Korea that also showed some additional interesting aspects. That being said, virtually, all larger trials are based on really good preclinical data that are promising and it usually doesn't translate into a real benefit. I think that's what I would have to add.

Dr. Henry Friedman: In a younger life, I spent 25 years doing preclinical translation, thanks to the FDA, NIH and ACS, and lots of other groups that gave us money, gave me money, us money. All I can tell you is a mouse is not a man, and so things that work in a mouse don't always work in a man, and things that don't work in mice, less commonly can work in a man depending on metabolism and things like that. CPT-11, for example, is phenomenal in mice. I never saw a better drug ever. There's never been a better drug. Every single xenograph, every single tumor goes away, but the metabolism, different in humans. CPT-11 in glioblastoma proved to be a trivial agent. I'm going to steal your line. I might as well tell you about putting the toothpaste back into the tube. I'm going to use that now. I'm just telling you right now. It's great. I wish we had the data. I don't think it impacts on how we're going to make a decision today. It is a good line.

Dr. Julie Kessel: Other comments about this? Okay. Our last question before we potentially wrap around to any leftover items is, “How confident are you that there are no significant evidence gaps that may impact positive health outcomes in the Medicare-eligible population?” Our discussion questions will revolve around “Are there evidence gaps that impact important health outcomes in the

Medicare-eligible population? If there are evidence gaps, what evidence gaps require additional study and what other comments may you make about that?"

Dr. Jonathan Sherman: I think some of it that's mentioned in the papers that we were provided talks about some of the gaps which relates to the mutational analysis and the various different subsets of glioma patients that haven't been studied individually. It's a gap in the data that says, is there a select group that benefits more than others? It's not necessarily a negative group or would benefit not at all because it seems that there's a general group. Generally, most people benefit from it, but there could possibly be a group that, just like you when you talk about temozolomide and MGMT, there might be a group that you would not recommend providing it for. That's a lot to do for a patient to wear 18 hours plus a day. If you're in that subset, we don't realize yet. That might not benefit.

Dr. Paul Zeltzer: In terms of ethnic groups, when I looked at the demographic breakdown, there were very few African American that were on the study. I don't know what in terms of post-marketing. This relates to the Medicare population because I think there may have, in fact, been a financial bias and prejudice in not referring those patients for the benefit of this device. I think whether the African American population responds differently or not, we don't know because they're not having access. As a note, I would say that the ability to have Medicare reimburse for this device would help that disadvantaged population.

Dr. Julie Kessel: I'm sorry. Would you please clarify the statement about financial bias and not referring what subgroup?

Dr. Paul Zeltzer: Excuse me. I spoke improperly. I meant those people could not afford it or afford the copay that may be on private insurance. Disadvantaged in that sense, not in the sense that physicians didn't offer to them more on a financial access basis.

Dr. Julie Kessel: Were you referring to Medicare patients is what I meant?

Dr. Paul Zeltzer: No. What I was saying is that the ability for those patients, if Medicare funded this, then that group would be eligible for this modality. That's the point I'm trying to make.

Dr. Julie Kessel: Thank you. Yes?

Dr. Marc Fishman: There's lots of gaps, but it's not surprising. I don't think that that should really impact whether or not-

Dr. Carlos Peña: Microphone right there.

Dr. Marc Fishman: Sorry. Whether or not Medicare should cover. But when we look at the pharmaceuticals and how they're used and in what combination and what dose densities, you could just go through a lot of things. It be is it better to be used with a hypofractionation or not? Should it start with treatment or not? If not, when? Should it start with chemotherapy? Should there be sequential chemotherapy because there's some data to suggest that VEGF may potentiate TTFs? Should you perhaps use TTFs with temozolomide, and at some point, maybe it relapsed, maybe not, use it with VEGFs? There's just no shortage of questions. I'm not sure about the importance of question five.

Dr. Carlos Peña: Sort of this question resonates with question one again, where we're looking at the evidence gaps in net positive health outcomes if I just add the word net. But if we take into consideration what we know with what's in front of us with regard to the safety and effectiveness and the risks and the benefits in the patient population, and we add the limitations, should we all be factoring a net positive health outcome? I think it's very resonant with number one.

Dr. Julie Kessel: Yes?

Dr. Cary Gross: Yeah. This question, it sounds kind of double negatives. How confident are you in the absence of gap? Yeah, I do think there are gaps that are relevant to the Medicare population, because I don't know, I was going to say this by now, I guess. We've beaten the trial to death. I think there are weaknesses in the trial. I won't elaborate on those. In the trial design, the inclusion of older patients in this study is they're markedly underrepresented compared to the US population. Roughly half of the newly diagnosed patients with glioblastoma are over the age of 65, just under half.

Dr. Cary Gross: Whereas in the study, about 25% of study enrollees were over the age of 65, and adds up to 134 patients in this study were 65 and over. We're talking about a Medicare policy based not entirely on this subgroup, but the subgroup is 134 patients who are treated all over the world, mind you. Some of them might have had slightly different health systems and slightly different standards of care. One other gap that we've alluded to earlier is the real-world outcomes because it's a rapidly evolving field. A gap is that we're not sure how the intervention in question interacts with how we are currently treating patients. Maybe it's different. Maybe it's more effective, maybe it's less effective.

Dr. Julie Kessel: Yes?

Dr. Edjah Nduom: Actually, Kevin, I was curious. Let's say whatever, we all decide that it ends up being approved our input notwithstanding whatever it is. But we have this data now on people in their prime and how you're going to treat them radiation-wise that's different. Do you then go back to previous standard of care radiation so that they do this, or you're still going to do the the shorter, the 15 days 40 over 15 instead of what was done previously, which was done with this trial? One of the reasons they-

Dr. Kevin Camphausen: Are you asking me if this gets approved, and then I see a 65-year-old patient, but I treat him with 40 and 15 plus temozolomide or go back to 60 gray plus temozolomide plus this?

Dr. Edjah Nduom: Right.

Dr. Kevin Camphausen: Yeah. I would probably do the 40 and 15. The whole point of the short course is it's only keeping the patient with us for three weeks. That's the biggest impact on quality of life, is the amount of time they have to be in the hospital.

Dr. Edjah Nduom: I don't know the answer to this, but if this is approved for the particular indication that it is, does it affect what radiation course they would "need to have" before they got this device? Would a patient who gets the short course still be eligible to receive this if that's not how the patients were treated on this trial?

Dr. Kevin Camphausen: I don't know what the FDA [crosstalk 01:20:08]. I don't know what the FDA qualification is, but I would doubt it says 60 gray plus 150 to 200. I bet it says chemoradiation.

Dr. Arnab Chakravarti: But my understanding is that this is used in the maintenance phase with temozolomide. This is not used concurrently with radiation upfront. I think that's a moot point. I'd still give it to my patients in the maintenance stage.

Dr. Edjah Nduom: Right. But they would be reaching that maintenance phase having had a different treatment.

Dr. Kevin Camphausen: A different way of getting there.

Dr. Arnab Chakravarti: Yeah. But I think that's-

Dr. Kevin Camphausen: That's not the question I thought he was going to ask. The question I thought you were going to ask was, would I put TTF as part of my standard treatment in one of my clinical trials?

Dr. Edjah Nduom: No.

Dr. Kevin Camphausen: Because I do put radiation and Temodar plus my experimental agent, so that's the question I thought you were going to ask. Thank for not asking.

Dr. Arnab Chakravarti: I think in any case that we're not approving, we're not deciding on the TTF in combination with radiation whatever the fractionation is. This is TTF in combination with the maintenance phase, with temozolomide.

Dr. Edjah Nduom: Just the question, how they get to the maintenance phase, does that make a difference at all?

Dr. Julie Kessel: What was your question again?

Dr. Edjah Nduom: How they get to the concurrent chemotherapy and radiation that they get, does that at all affect the approval of the subsequent treatment, that maintenance phase? Do they have to have reached the maintenance phase in the standard way in order for this to be-

Dr. Kevin Camphausen: In the EF-14 way.

Dr. Edjah Nduom: Correct, because that's how the trial was conducted. It was conducted in that way with that concurrent chemotherapy and radiation over six weeks. That's where the benefit was definitively seen. Do they have to get to that TTF phase in that way in order for this to be covered? Does that make sense? I don't know.

Dr. Kevin Camphausen: It absolutely makes sense because, right now, there's a lot of trials out there in the elderly doing five fractions of radiation. Monday, Wednesday, Friday, and the next week Tuesday, Thursday, and be done. That's experimental, but it's not going to surprise me if that actually isn't good for patients because, again, it gets them home really quick. The question is a valid one of what is the approval. Is the approval that you've had EF-14 treatment first and then you get this, or are you just showing up having completed some form of standard radiation and chemo?

Dr. Matthias Holdhoff: One question, and that is not something that the panel numbers are to judge on, but I think it is a fact that this is a very costly intervention. Over $20,000 for one month of treatment, it's a very high price. Does that factor into the decision on the CMS side? If this device was $500, would the discussion have been differently or not?

Dr. Julie Kessel: The purpose of our discussion today doesn't factor in cost at all and we're just making our conclusions around confidence related to the evidence and what is presented in the evidence. Did you have a comment?

Dr. Annick Desjardins: I've been mentioning a lot elderly population, doing this more study in older patients. It was really not based on wanting to see the increase in survival, the increase in progression-free survival. But mostly, I'm interested in looking on the impact on the quality of life of those patients and the quality of life. I understand that there is no impact on EF-14 and that, in fact, other than the itchiness, being itchy, people did really well. But I think that another thing I'm very interested is not only on the patient in a social role, but also the caregiver. Because an elderly patient, or a patient in his prime, is someone that rely a lot on his children, his or her children, and those children have children of their own that they need to raise. This is a different population in the fact that your caregiver is a caregiver already to a young patient. I'm not saying that I don't agree, it's mostly I'm asking that it's just to really understand how does it impact older patient and their family. That's what I would like to know to be honest.

Dr. Henry Friedman: To the question regarding the kind of radio therapy that's used and whether it should impact on the way that, assuming if this is approved, how it should move forward, the answer is we pay no attention to the upfront therapy. Because if you had to do a trial for every single drug that's going to follow radiation, recognizing that the radiation could be one of a thousand different ways. There goes medical research and medical progress. The answer is no. I don't think you pay any attention to what comes first. You simply use the therapy as it's approved based on EF-14.

Dr. Henry Friedman: Having said that, I have some degree of confidence that what works in the younger population works in the patients in their prime. The reason for that is that you're hard-pressed to find something in the absence of a biomarker relationship, like MGMT unmethylated, where it is, again, as I said, predictive where something that was effective in the younger people are not effective in the people in their prime. I can't think of any. In fact, I can think of the reverse. I can think of Avastin which is more effective and less toxic in the older population, prime, than in the younger population. I slipped. Anyway, I don't have any concerns.

Parashar Patel: We've got member from the FDA, and maybe the company actually has the FDA label which presumably may say something about what type of radiation therapy has to occur before?

Dr. Carlos Peña: Right. I thought that the label said that this was after radiation and surgery options were performed. This is during the maintenance.

Bill Doyle: I'm happy to clarify because I have the label.

Parashar Patel: Does it got any specific details?

Bill Doyle: Optune® with temozolomide is indicated for the treatment of adult patients with newly diagnosed supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy, together with concomitant standard of care chemotherapy. It's exactly as Dr. Friedman mentioned, they can receive whatever radiation course their radiation oncologist believes is most effective for them. It's after that, that they'll receive Optune® therapy with their temozolomide maintenance therapy.

Dr. Julie Kessel: Thank you. Yes?

Dr. Jonathan Sherman: Not that it would directly relate to upfront treatment, but just because it's something that I'm thinking about. I know it was brought up earlier, but if you progress and then you're on new treatment, would Medicare ... how it's written so that Medicare A or B would or would not cover the treatment when you get on to the next treatment if the patient wants to stay on it?

Bill Doyle: The label states that Optune® can be used through the first progression. Newly diagnosed, first progression, and then they would stop at second progression.

Dr. Julie Kessel: Other questions about this or clarifications requested? Okay. Let's take this time to just look at any of the other questions and see if there are any things that anybody would like to discuss that they may have missed. On question one, related to the evidence, things we might consider are obviously pivotal studies, relevance studies, quality of study, volume study, safety issues, intermediate and not intermediate outcomes, primary and secondary outcomes, statistics, strengths and weaknesses of the studies available, and a statistical subset of Medicare-eligible patients. Any other comments or concerns about this? Everyone have their opportunity to offer comments.

Dr. Julie Kessel: Okay. For the second question where we talked about predictors of success in the Medicare-eligible population, we talked briefly about tumor methylation status, the performance scores, therapeutic regimens, adherence to therapy. We did not really talk about other genetic or molecular markers. Are there any other questions or comments in this area? Okay. In the third area, we were talking about the acceptance of the medical community. There did seem to be quite a bit of discussion around this in the different groups of practitioners and how they would be characterized as community academic and then academic with clinical trials, and the impact of the sales force and other things. Are there any other questions about this, questions, comments, or concerns about this area? We also talked about guidelines in this during this topic.

Dr. Julie Kessel: Okay. Then we went on to talk about the mechanism of action. There seem to be some issues or comments raised around preclinical versus clinical translation of effects that seemed pretty well-established in the preclinical environment, and that may or may not matter when thinking about the clinical impact or the outcome of the use of TTF. Any other questions or comments? Okay. Finally, we talked about the evidence gaps and what we would like to see. There's a whole plethora of things that would be optimal to see, including controlled trials, sequencing trials, sequencing therapeutic trials, real-world evidence information collection, and any sort of variation of those three things, including additional populations, including Medicare population. Are there any other comments, questions, or concerns around this topic?

Dr. Julie Kessel: Okay. Why don't we take a few minutes, if you haven't already, and consider how you want to fill in your yellow sheets on a scale of one to five? Are there any questions about how the sheet should be filled in or how you might measure your level of confidence? Okay. We'll just take a minute then.

Dr. Julie Kessel: When you're through, you can pass them over to me from each direction. I don't want to rush anybody. If you need the extra time, please take it. [crosstalk 01:33:10]

Dr. Julie Kessel: Thank you. [crosstalk 01:33:55]

Robert Hoover: All right. While they're scoring, why don't I do this, and it'll help us to all get out of here because I know we have some CAC members that have some time frames to meet. First, I want to thank everybody today. Not only our CAC members for coming here, but the Novocure folks. This is the first one of these that we've done. It's a new experience for us. It was a new experience for CMS and the staff. I want to say I really appreciate the discussion that went on today. Not only the questions that were asked of the Novocure panel, but the way you guys challenged your fellow experts. It's what we were looking for, is to have an open discussion about the issues around this technology. Thank you very much, and thanks to the CMS staff that have worked a lot over the past several weeks as we've gotten this together. Again, a new process for them. We tried to do it somewhat based on the MEDCAC process, but we wanted it to be different for the way the DME MACs did it.

Robert Hoover: You heard me talk a little bit more about next steps earlier in the day. I'll just go over those again. We'll take the information from this meeting. We're going to sit back. We're going to look at the literature again and other materials that we have, and we'll come out with a proposed LCD. Once that proposed LCD is out, that will be the start of the open comment period. We'll take written comments. We'll have an open meeting. When the proposed LCD comes out, it has three new sections to it that we haven't done before. One is a rationale for decision, a summary of the evidence, and the full bibliography of the information we consider. You'll have that in there.

Robert Hoover: We'll have 45 days of public comment. Then we we take those comments and consider them, make any changes to the proposed LCD, and then we'll publish a final LCD along with a response to comments document. Very similar to what you might see in the Federal Register in a proposed rule when it comes out in final. We got 16 letters. We answered this. We do the same thing in our response to comments documents. We'll go through, we'll categorize the comments. We try to kind of put them together in broad buckets, because most of the time, the comments come out in buckets.

Robert Hoover: I can see I'm no longer looked at anymore here or listened to because I see numbers up on the board. But, again, once that comment period is over, then we have 45 days of notice before the policy becomes effective. I will let everybody take a look at the questions.

Dr. Paul Zeltzer: Can you read off the last column? It's tough to see from here [inaudible 01:38:21]. Thank you.

Dr. Julie Kessel: It says score average.

Male: I can't see anything. [crosstalk 01:38:27]

Dr. Julie Kessel: Bob, do you want to read them?

Robert Hoover: Yeah, I'll read them. For those that can't see the last column or had questioned, we anonymized all this data. You just see CAC member, but each CAC member knows what column they were on. We just do an average scoring or rating at the end. For the first question, how confident are you that there is sufficient evidence to determine that TTFT for newly diagnosed GBM can provide net positive health outcomes in the Medicare-eligible population? The score was 3.82, and recall that this was scoring on a one to five scale.

Robert Hoover: Second question, how confident are you that the available evidence demonstrates adequate predictors of success in the Medicare-eligible population? Average score was 3.45. How confident are you that TTFT is generally accepted by the medical community for newly diagnosed GBM? 2.91. How confident are you that scientific evidence supports mitotic spindle disruption and cellular apoptosis as the mechanism of action for TTFT? 3.27. How confident are you that there are no significant evidence gaps that may impact positive health outcomes in the Medicare-eligible population? 2.91 is the average score.

Robert Hoover: We will have these scores in our proposed LCD when it comes up as part of our CAC summary. We'll also have the summary from the CAC chair that we'll hang kind of the highlight of the proceedings today. Are there any questions for me before we wrap up? All right. Thank you very much. We'll conclude this meeting.

Dr. Julie Kessel: Thank you.

Robert Hoover: Thank you.

Dr. Julie Kessel: Safe travels home.