WORKSHOP ON PRODUCT DEVELOPMENT FOR CNS METASTASES

Co-Sponsored by the FDA and

National Brain Tumor Society

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Building 31

The Great Room

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P R O C E E D I N G S

(8:31 a.m.)

Opening Remarks

MR. ARONS: Good morning, everybody. Welcome. Thanks for finding your seats, and we're live.

Welcome and thank you for being here today for the CNS Metastasis Product Development Workshop. I'm David Arons with National Brain Tumor Society. As we get started, just a few logistical points.

First, number one, please mute your cell phones. That would be appreciated. Second, this is a public event, and thanks to the FDA, it is being livestreamed. Third, your participation is wanted, encouraged, and frankly expected.

This is a working meeting in the truest sense of the word. At the end of the day, we hope that new ideas, opportunities, and recommendations are brought forward so that action steps can be identified. In fact, during the Q&A session, we hope that you'll take a robust role, and Wendy may

even call on you.

Now about the disease itself we're talking about or this collection of diseases. Brain metastases are the most common type of intracranial neoplasm, with the total number diagnosed annually outnumbering all other intracranial tumors combined.

They outnumber primary brain tumors by a ratio of 10 to 1 according to some studies and occur in about 25 to 45 percent of all patients with cancer. Conservative estimates suggest that 100,000 to upwards of 180,000 new cases of brain metastases are diagnosed every year in the United States.

As brain tumor and cancer patient advocates, we know firsthand this is a highly vulnerable population with significant unmet medical need. There are not enough therapeutic options, let alone cures, for CNS metastasis patients. Today is a very important opportunity to work together to identify ideas, opportunities, and realistic strategies, and even innovative out-of-the-box

thinking to advance clinical research in this area. In addition to bringing our collective expertise to bear on the subject, let us all be driven by a sense of urgency and spirit of collaboration to make positive change.

A big thank you to the Food and Drug Administration for hosting this workshop and for partnering to plan the workshop. Thank you to partner organizations that formed the planning committee. They are Accelerate Brain Cancer Cure; American Brain Tumor Association; Friends of Cancer Research; Kidney Cancer Research Alliance; LUNGevity Foundation; National Brain Tumor Society; Metastatic Breast Cancer Alliance; Melanoma Research Alliance; RANO; and Society for Neuro-Oncology.

Thank you to additional organizations that helped the workshop come about, including Bayer; BMS; Celgene; Edison; Elekta; Lilly; Merck; Novocure; and Seattle Genetics. We are truly grateful to the workshop steering committee, including Dr. Joohee Sul, Nancy Lin, and Patrick

Wen.

In addition, we thank the content committee members that are quite numerous, and a lot of appreciation goes to our presenters and those who volunteered many hours to prepare information, including the videos, in preparation for this that will advance our workshop's goals, and a big thanks to Wendy Selig, our project director from WSCollaborative, who led the entire planning process, and also to Sarah O'Connor from NBTS, Dianne Spillman, and Joan Todd from the FDA, who were instrumental.

A very special thanks here to all the patients. This is about you, and it's about all the CNS metastasis patients worldwide. The patients traveled here today, and they have a lot they can contribute, and we really look forward to hearing your perspectives and views in this conversation. We value your experience and want to hear it.

Now, it is an honor to introduce Dr. Rick Pazdur, the director of FDA's Oncology Center of

Excellence. We thank Dr. Pazdur for his leadership, innovation, and for also being a patient advocate himself. Thank you, Dr. Pazdur.

(Applause.)

DR. PAZDUR: Thank you very much. I welcome you here to the White Oak Campus at the FDA. For many of you, this has probably been an initial visit here, and it's a campus that we've been here for a little more than 10 years.

I think what's special about this conference is that it brings a lot of diverse groups of people together that perhaps never have worked here before together. Generally, when we have meetings, we have meetings centering on lung cancer, colon cancer, breast cancer, myeloma, and melanoma, but we very rarely bring groups of people together to look at a site of metastatic disease or an approach to a particular problem that joins various diseases together. So this is somewhat of a unique conference, and I hope that we will have a very productive meeting.

I'm very interested in this meeting. As a

practicing oncologist years ago, one of the things I dreaded most in approaching patients, especially in discussing with them when they had disease progression, was when they had brain metastases, because I think delivering this news to patients is a really devastating discussion that one has to have. It's a special site of metastatic disease, and I think we should consider what is unique about brain metastasis versus other sites of metastatic disease.

This goes to how we approach this in drug development, and I hope that this will be one of the avenues that we will discuss here, what are novel clinical trial designs to look and assess the effects of therapy.

What I'm hoping for is that we will have some form of guidance that will come from the FDA after this meeting, at least a formulation of a guidance, that will direct sponsors and other clinical developers in this area to have a better understanding of what it would take to get a drug developed in a particular indication for a brain

metastases.

I again would like to thank you for being here. I hope this is a productive meeting. It's something that I'm very interested in. Our staff is represented from all of the disease specific areas here, and I really would like to thank them for their efforts, those members in the FDA that have worked on this, as well as the organizing committee and the various organizations that have already been stated, that have participated in formulating this conference.

I'm going to turn it over to Wendy, to Joohee, and Patrick. Thank you.

(Applause.)

Presentation - Patrick Wen

DR. WEN: On behalf of my co-chair, Joohee Sul, I'd like to welcome all of you. I want to echo David's thanks to the FDA, Dr. Pazdur and Joohee. I want to thank the National Brain Tumor Society, David Arons and Wendy Selig, and all the patient organizations and sponsors that have made this meeting possible.

In 2014, the neuro-oncology community had a couple of workshops with the FDA, and we found those workshops incredibly useful and increasing our understanding of what is required to develop drugs, in this case for gliomas. As a result of the workshop, we developed this brain tumor standardized imaging protocol that was led by Ben Ellingson, which has now become the imaging protocol used in the vast majority of glioblastoma trials.

I think we all know about the significant morbidity and mortality from brain metastases, and it's been over two years ago that I talked to Joohee about potentially having a workshop to clarify what we need to do to develop more effective therapies for brain metastases patients and provide some clarity in terms of trial design and endpoints, both in the place of brain metastases in the general development of drug in oncology and also specifically for developing treatments for brain metastases, both local therapies and systemic therapies. That hopefully

will be the goal of the meeting today.

There are a lot of things we can talk about in brain metastasis, but the focus should be on these issues. In the last couple of years, there have been two important papers that have tried to clarify these issues.

One, the ASCO Friends of Cancer Research brain metastases working group has provided some guidance on how to incorporate metastases patients in the general development in oncology, dividing them into patients with treated or stable metastases, with active metastases, and also to try to incorporate those that have leptomeningeal metastases.

The RANO group has also published a paper providing guidance on the same issue, dividing brain metastases patients and drugs into three categories: agents that have a high likelihood of helping brain metastases; those that have a low likelihood of helping brain metastases; and those where we're not sure about the efficacy.

In today's meeting, I hope that we will talk

about whether we should incorporate these guidances routinely into drug development strategies, and also whether we should incorporate the RANO brain metastases criteria routinely into clinical trials for brain metastasis, and then also to define the optimal endpoints for clinical trials.

I think by the end of today, our hope is that we have more clarity on what trials and endpoints should be performed to develop new treatments for brain metastases. Just like with the glioma workshops, we want to identify issues that still need to be addressed. One of them will be the standardized brain imaging protocols for brain metastases and develop a roadmap to address these issues. In addition to the FDA guidance, the hope is that we will also have a paper that comes out of this meeting.

We look forward to a really productive day, and thank you so much to all of you. I know you're all incredibly busy, and we're very fortunate to have all of you here today to help us find better treatments for our patients, so thank you.

I also wanted to mention that the Society for Neuro-Oncology and the RANO group is committed to continuing this effort. This is not just a one-off meeting. So as a follow-on later this summer, The Society for Neuro-Oncology will have our inaugural brain metastases meeting to continue this conversation and to push the development of better treatments for brain metastases, and hopefully many of you will be able to come, so thank you.

(Applause.)

Presentation - Joohee Sul

DR. SUL: Good morning. For those of you who don't know me, my name is Joohee Sul, and I'm a medical reviewer here at the FDA and a neuro-oncologist. I'm going to be brief because I know we're short on time; we're crunched on time. But I just want to echo Dr. Pazdur, David Arons, and Patrick Wen in thanking everyone for coming and for participating, and that we're looking forward to a lively discussion about some of the topics and issues and challenges that we face with evaluating

brain metastases.

Dr. Wen has nicely I think provided an overview of the goals. Just one thing I think would be important to keep in mind, and one thing I think I've come to realize being here at the FDA, is that for all these issues we're going to discuss today, the context is incredibly important, that these endpoints in study designs don't exist in a vacuum, and although data can often be fixed, the context in which they're interpreted can be very variable. I think that has a huge impact on how we view these types of therapies and their impact on patients.

The last point I'd like to make is I know it can be difficult to speak up in a public setting. I personally have always dreaded public speaking, but I encourage everyone to please speak up and present your ideas. I know that sometimes it can be tough to say something that might go against the crowd, but if there are dissenting opinions out there, we need to bring all these aspects to light so that we can have a fruitful discussion. So

thank you very much.

(Applause.)

Session I

Presentation - Michael Davies

DR. DAVIES: Good morning. My name is Dr. Michael Davies. Thank you very much for the opportunity to talk today. As Dr. Pazdur mentioned, it's really, again, a unique experience today. We not only have people from multiple different disease sites but actually also from different therapeutic approaches. So one of the things in the discussion about this meeting was to actually think about starting the day off with trying to give everybody a framework to understand where we are in different diseases and with different treatment modalities.

So as has been mentioned, it was my honor to participate with the other speakers you've seen here and recording webinars that are available through the FDA website. And again, I personally have benefited tremendously from being able to review these other talks. These are my

disclosures.

What, again, I would just like to reinforce, as David said, is, again, the significance of the problem of brain metastasis. Indeed, the estimates are that up to 170,000 patients are diagnosed with CNS involvement per year, and we expect that CNS involvement actually is the cause of up to 100,000 deaths per year from cancer. I actually think that these rates, at least in incidence, are probably rising as we've developed therapies that are achieving better and better control of extracranial disease.

What I'd like to do in the next few minutes, then, is just to again provide some of the highlights from the webinars. And again, I hope that people have had a chance to look at these webinars or have a chance to go back after the meeting, but to really talk about, again, where we stand in the management of CNS disease, both in terms of standard-of-care options and also clinical investigations for radiation therapy, systemic therapy, for breast cancer, lung cancer, and

melanoma. And then finally to talk upon what's probably our final frontier, which is leptomeningeal disease.

Just to start off with Dr Brown's talk about the role of radiotherapy in the management of brain metastasis, this again is an area where clearly we've moved from the era of whole-brain radiation therapy to stereotactic radiosurgery. This in many ways is the standard of care for patients with oligometastatic disease and very effective at achieving local control in tumors that are less than 2 centimeters.

The real limitation is the fact that we know that it doesn't do a good job of controlling tumors that were not radiating, and the key question is how can we improve control throughout the brain in addition to that local control. And while we know that whole-brain radiotherapy will increase controlling the CNS, it comes at the expense of worsening neurocognitive function and quality of life without impact on overall survival.

So whole-brain radiation therapy is

something that's really primarily reserved for patients with diffuse brain metastasis with research and new strategies to reduce the neurotoxicity from this therapeutic modality.

Again, there are really a number of key questions, particularly now that we're moved into an era where we have effective systemic therapies for patients with CNS involvement. What is the optimal utilization of radiotherapy approaches? What are the appropriate combinations? What is the appropriate sequencing? And as Paul really pointed out as we move into this era is as a field, what are going to be the best primary endpoints for us to use as we try to evaluate these different strategies?

One of the things that I think also stands out about the development of radiotherapy has been the importance of evaluating neurocognitive function, which is something we haven't really done as much of with our systemic therapies.

Dr. Lin reported, again, a very nice summary of the current systemic therapy for breast cancer

brain metastasis. Just to highlight a couple of the key points, Dr. Lin really reinforced the fact that there are currently no systemic therapies with an FDA approved indication for the treatment of breast cancer brain metastases, and in actual fact, there are no strategies at this point that have actually been proven to reduce the incidence of developing brain metastasis; so two real key deficits that we have.

Actually, again, really sort of stunningly, is a review of almost 1500 trials for patients with breast cancer identified only 16 that were specifically designed for breast cancer patients with new or progressing brain metastases, representing less than 1 percent of all of those clinical trials. So again, a theme that we'll hear throughout these talks, underrepresentation of trials for patients with active brain metastases.

Now again, breast cancer is really divided into three different subcategories, as Dr. Lin explained, really it's in the HER2 positive breast cancer and triple negative breast cancer that we

see a higher risk of brain metastasis. Again, she did a very nice job of summarizing both the commercially available therapies we have for each of those subtypes, as well as a number of the ongoing clinical trials.

I don't think I'm going to try to go through all of those approaches, but just really to say that, again, clearly in the HER2 space it's building upon a backbone of HER2 targeted therapies, triple negative cancer at this point, Really building upon chemotherapy, and now in the realm of ER/PR positive starting to add things like CDK4 inhibitors and other targeted therapies to our hormonal therapies.

So again, just to summarize our challenges here in the HER2 positive space, multiple active regimens, but these are regimens that often have relatively transient benefit with progression-free survival on the range of approximately 6 months. Again, this is a disease that has shown that chemotherapy absolutely can have a role in the management of patients with CNS involvement, but

how can we do better or how can we build upon the current activity; and certainly the idea that there's now multiple new targets of interest, including both targeted therapies and immunotherapies, and increasingly bringing these different types of strategies together.

I'd like to just in particular highlight that she discussed future directions, questions, and opportunities, that one of the things that we'll talk about later today is the need for better preclinical models to help us develop, validate, and prioritize new therapeutic strategies is I think one of the other great unmet needs that we have in our field.

So moving on, Dr. Ross Camidge gave what he called the State of the Tumor Address for patients with non-small cell lung cancer and brain metastasis, again, really a wonderful summary that he provided. As he pointed out, really our understanding of lung cancer has evolved quite rapidly over the last few years such that we now have multiple molecularly defined subtypes of lung

cancer driven by oncogenic targets, and in particular EGFR mutations and out fusions that have really provided new therapeutic opportunities.

Actually, as we think about the management of patients with stage 4 and non-small cell lung cancer, we now sort of divide patients into those who have these driver oncogenes that are targetable, and those patients really are getting treated with targeted therapy up front. For the rest of the patients, what we are really moving into is an era now where the standard upfront therapy is immune therapy, either by itself or in combination with chemotherapy.

In addition to really talking about the number of the key trials, I think what was really sort of nice about his presentation was also talking about how the lung cancer field has learned and progressed over the last decade about how to appropriately design and interpret these clinical trials, and as he goes into in depth, a number of rookie mistakes that were learned from that can really inform I think our other fields where we

sometimes haven't really dealt with some of these challenges yet, including not separating treated versus untreated brain metastases; whether patients got whole-brain or stereotactic radiosurgery.

I think one that we've seen is a particular challenge is the impact of variation in the frequency and modality of CNS surveillance or even CNS screening before patients are enrolled into clinical trial and the impact that can have on the difficulty of interpreting the results from some of these clinical studies.

In addition to those overall concepts, I just wanted to highlight two key clinical trials and the lessons that were learned that I think are particularly impactful for thinking about this in the future. This is a slide presented at ESMO 2018, a randomized trial of brigatinib versus crizotinib in ALK-driven tumors, and what we can see on the left are the outcomes in patients with brain metastases; on the right, patients without brain metastases.

What we can see here is that very early it

became clear in patients with brain metastases, that there was a marked difference in the efficacy of these two agents that actually wasn't detectable at early time points in patients without CNS involvement.

This again actually highlights the challenge that we have clinically in managing patients with brain metastasis but also highlight the opportunity to learn much quicker which agents are going to be effected by including patients with brain metastases in these trials; that again, there's particular opportunity and really a need not to deny patients these types of agents that have such impressive activity.

Building upon that, he talked about how laratinib was actually approved in November of 2018 for patients with ALK-driven tumors who were refractory to other therapies, where interestingly, this is a therapy that actually had higher response rates in the brain than it actually extracranially, again, reinforcing where there's actually really tremendous opportunities for drug development in

patients with active and progressing brain metastases.

Again, it was really a beautiful lecture, multiple key points, and I would just highlight the real take-home message is that capturing robust CNS efficacy data is becoming increasingly important as CNS active drugs emerge in non-small cell lung cancer, and particularly, again, the question of as we move into this era, the rationale for how we start to do randomized trials, not just with multiple targeted therapies and immunotherapies, but how we incorporate radiation therapy in these patients as well.

Moving onto my easy topic, which is melanoma, since that's what I take care of, brain metastasis is always been a huge problem in this disease, even before we had effective therapy. In the old era in which all we had was chemotherapy, the median survival for melanoma patients with brain involvement was about 4 months.

The treatment of melanoma has been absolutely revolutionized, and we had 11 targeted

and immune therapies approved for stage 4 patients between 2011 and 2018. And I would point out that all of the registration studies for those agents that led to those approvals excluded patients with active brain metastases. Not a single patient with active brain metastasis was included in those studies, and as I'll show, we have clear evidence that those treatments can benefit patients with CNS metastasis.

Again, like lung cancer, we actually talk about both targeted therapy and immune therapy are driver mutations, the BRAF mutation that's present in about 50 percent of patients. Our standard of care for those patients in the targeted therapy era is combined BRAF and MEK inhibitors. And although we have three regimens that have been approved, we only have data for one of them in patients with brain metastases, dabrafenib and trametinib.

As you can see in the waterfall plot, when we treated patients with BRAF mutant brain metastases, we saw disease control rates of almost 80 percent, very similar to what we see in

extracranial disease, but the duration of these responses was about 7 months. That's half of what we see in patients without brain metastases. And in this study, 50 percent of patients progressed in the brain while their extracranial disease was controlled. So we're still struggling to learn why this happens and, again, how to overcome that type of differential activity.

In parallel, we've been revolutionized by the development of effective immune therapies. We had initial clinical trials with single-agent checkpoint inhibitors with ipilimumab and pembrolizumab, which showed the proof of concept that immunotherapy can achieve responses in patients with brain metastases.

Both achieved responses in about 20 percent in patients who don't require steroids. We've actually seen in patients that require steroids to control cerebral edema much inferior results. But what we've also seen is that when these responses happen, they can be quite durable.

What really revolutionized our expectations

for patients with brain metastases were two trials that look to combined immunotherapy with ipilimumab and nivolumab, patients, again, who did not require steroids, where we saw response rates of close to 50 to 60 percent. And what's been so striking is the fact that almost all of those responses are still ongoing such that we saw a one-year overall survival rate of 81 percent in the CheckMate 204 study.

Importantly -- and I think this is something that we went in looking very carefully -- these studies showed no increase in adverse events or CNS related toxicities in either study; that it was absolutely safe to use these immunotherapies in patients with brain metastases.

While we're very excited about the progress we've made with immunotherapy, we recognize that these therapies haven't actually shown yet any data that they can improve outcomes in patients who require steroids, which is quite common. We still have 40 percent of patients who blow right through these, and aren't benefiting from them, and clearly

looking for less toxic regimens.

Again, our key challenge with targeted therapy, how do we extend the duration of responses? We actually will have our first randomized trial comparing standard versus higher dosing of BRAF-MEK combinations in the coming year. What we're really looking at now as a field is combinatorial approaches, not only combining different immune therapies but immune and targeted therapies, and again, the role of radiation therapy as well.

Finally, we have the final frontier, I would call it, which is leptomeningeal disease. Again, Dr. Le Rhun is really one of the world's experts in this. For those of you who aren't as familiar with this, this is, again, when you have disease not focally in the brain but on the leptomeninges, so a diffuse problem.

The striking data is the median survival of these patients is actually in the range of 2 to 3 months. I know in melanoma, we actually measure our outcomes in weeks instead of months because of

how aggressive this is. It's also a field that's very challenging because there aren't standards for neurologic examination. They're still moving standards in terms of imaging assessment and even CSF cytological diagnosis.

There is a dearth of clinical trials. All of the trials that I talked about for patients with brain metastasis actually excluded patients with leptomeningeal disease, so it's a huge unmet need. But there are also key challenges we have as a field of optimizing the design of these trials, including the inclusion criteria, and actually defining the endpoints for these studies is going to be very important for us moving forward.

Just to summarize all of this, I know it was a quick and brief overview, but hopefully it provides you at least a bit of a taste of what those webinars actually have. Again, I encourage you to go back and watch them. Some of the themes are certainly this consistent underrepresentation or delay for patients with CNS disease for inclusion in clinical trials and early therapeutic

development. This is a particular problem for brain mets, but even amongst the patients with CNS involvement, and an even worse problem for patients with leptomeningeal disease.

That being said, we now have clear proof of concept for the efficacy of systemic therapies in these patients, and as we saw in lung cancer, there is the potential to identify effective regimens earlier or even regimens that have enhanced activity in the CNS. We'll talk a little bit later about what we know about the unique biology and immunology of brain metastasis, which may provide unique therapeutic opportunities as well.

As we move forward, we still, though, today, I think we'll focus a lot on our key questions and challenges around trial design, including what are the patient characteristics, inclusion and exclusion criteria, and what are the best clinical trial endpoints, and finally, moving from an era of single-agent, single modalities, non-randomized studies into combinatorial approaches, bringing different therapeutic modalities together, and I

hope learning from each other what we've learned in different diseases to accelerate more effective treatments and better trials. Thank you very much.

(Applause.)

Panel Discussion

DR. AMIRI-KORDESTANI: Thank you, Dr. Davies. Excellent talk.

Now, we actually have excellent panelists we have from pharma, patient, and actually also academia. I wanted to actually give the opportunity to each of them to introduce themselves and give a few words, and then we can actually open it up to questions and also take questions from the audience. Thank you.

MR. QUEEN: Hi. Good morning. My name is Derrick Queen, and I'm here to tell you about my experience with brain metastases. Through my life, great health was a part of my self-identity. I'd always played athletics. I was captain of my college hockey team, and I continued to play competitive ice hockey after college.

I had a stressful job. I was working as a

hedge fund portfolio manager in New York. Three years ago, about exactly three years ago, I experienced a very debilitating headache that was unusual, that ultimately led to an MRI. At that MRI, the doctors took me aside, what was a very unusual experience for me because I was always used to doctor's telling me you're in incredible physical shape, and you're were really healthy and go home.

But that was not what they told me. On that day, they put up scans of my brain and said these are the images that we just took of your brain, and you've got 3 brain tumors and tumors in both lungs. The tumors in your brain have progressed to a state where one is so large, it's pushing everything from the left side of your head over to the right side of your head, and we can't let you leave the hospital, and we need to operate immediately.

So here I was. Nobody in my family had ever had cancer before, and this was the first news that I had. I had to understand what this was and how to cope with it, so I had brain surgery to remove

that largest tumor but then had to figure out how to address the rest of the cancer that had spread to my body.

As part of that process, when the potential treatments were outlined to me -- and actually as part of that, just in my own research, I learned that for somebody like me, the median survival rate was about 4 and a half months. So I knew I had to act quickly. I had two young kids. They were 12 and 14 years old. Besides thinking about how to fight for my life, the other thought that went through my head was what do I need to teach my two boys before I die?

So there became the quest of how to beat this disease. I was BRAF positive. Two drugs that worked for me with incredible efficacy, I took those drugs, but as Mike Davies just said, these drugs for melanoma patients can last 6 months. In my case, it was even shorter. It was 3 months where they began to shrink my tumors, and after 3 months, that was it. My body became resistant to them, and then new tumors appeared.

One of the things that was really disturbing to me as a patient is that, at that time, there were about 11 drugs on clinical trials for patients like me, but because I had brain metastases, I was not eligible for any of them. So one set of drugs had done what they could, and then I had exhausted that outcome. So it naturally begs the question of what other drugs are there and what could they do for me, and will I exhaust them also to the point where I have no more options but death?

I consider myself incredibly lucky because we tried something new, that was relatively new at that time, where I got a dose of pembrolizumab combined with stereotactic radiation. And again, I was lucky because when I showed up to the hospital that first day that I told you about, my brain mets were just on the border of 2 centimeters, and that was verging on becoming too big for stereotactic radiation, so I got in under the wire.

That was in September 2016, and 3 months later on Christmas Eve of 2016, I found out that that treatment was actually working and my tumors

were responding and had shrunk by greater than 50 percent, and 5 months later, I was completely off pembrolizumab. So my last dose was in May of 2017, and so I'm coming up on two years where I'm back to playing competitive hockey and haven't had a treatment since May of 2017.

(Applause.)

DR. WALKER: Hi. I'm Luke Walker. I'm with Seattle Genetics and lead the tucatinib clinical program there. Tucatinib is an oral anti-HER2 agent that we've been developing with hopes of being able to treat patients with HER2 positive brain metastases. From the very early-phase 1 trials, I've included patients with active as well as treated brain metastases.

I think the take-home that we have so far is that it does take some extra care and attention, and there are certainly extra complexities in this endeavor, but it's certainly achievable. We're currently in a registrational trial that we expect to have data on this year of 600 patients, about half of whom we expect to have brain metastases.

I'll say that some of the challenges that we've come across, and I think that we'll hear from many of the other speakers today about some of the details around this, are really around clinical endpoints and about the use of RECIST, for instance.

For instance, the approach to patients with small changes in the brain that might lead to clinical actions like radiation may not conform exactly with the standards that are put forward with RECIST, and we probably need to think about how we might look at those types of patients, especially if they have controlled extracranial disease at that time.

We know that these patients come in to trials with very complex histories if they've had brain metastases in the past, with maybe SRS, and whole brain, and surgery, and selecting those lesions for assessment in RECIST really depends upon pulling together all that complex history across many disciplines with radiation oncologists, surgeons, and maybe across different institutions,

and that requires extra care.

We also know that the use, for instance, of MRIs of the brain for an independent blinded review can be challenging, generally, but when you add in that we're using brain MRIs in a non-neuro-oncology trial, and the average medical oncologist is not maybe as well versed in the nuances of the different sequences of the MRIs, and making sure that you really have good information and that they're working with the radiology group at their institution and so forth to get good quality data, all that requires a bit of extra work.

I think that in the end that extra work is worth it and it's doable, and I hope that with some of the actions that we're able to talk about today, we can make that still easier and make these trials more accessible to patients like Derrick.

DR. EBIANA: I'm Victoria Ebiana, and I'm a clinical director at Merck. I'm actually a neuro-oncologist by training, and I don't think it's an accident that I'm sitting next to Derrick. I'm really incredibly touched by his story. He was

telling me a little bit before we got started, and I'm just really blown away by his response. And I'm so grateful to be able to work on a drug and be able to have that opportunity to hear his story.

One of the things that really touched me about hearing his story is how a lot of the trials that he was looking at did not include brain metastases patients and why that is. I think that especially for melanoma, there are a lot of issues that come up there potentially surrounding safety, especially with the immunotherapy.

One of the things that I really like about how we do things at Merck is that we do allow patients with brain mets who meet certain criteria that allow for them to safely receive immunotherapy, to get immunotherapy and to allow patients like Derrick to be here and tell us about his story. So I'm excited to be here and talk more about that later.

DR. DAVIES: Good morning. Again, my name is Mike Davies. I'm a medical oncologist, melanoma medical oncology at MD Anderson. I'm also a

physician scientist and run a lab that does a lot of work on what really are the factors that predict the development of brain metastasis, that are unique to brain metastasis, and that drive therapeutic resistance in brain metastasis.

I would say that one of the things that we've seen is that, again, we have the clear proof of concept now that the agents that are safe and effective extracranially are generally safe and effective intracranially. There absolutely can be unique challenges in thinking about what else we need to do in settings where they're not as effective, but I think we really need to reset the expectations on therapeutic development to really include these patients as early as possible.

I think some of the unique challenges we do run into are this is a group of patients where often we really feel very uncomfortable waiting our normal period that we wait to get patients started on a therapy and thinking are there ways we can facilitate designs to allow patients get treated sooner.

The other thing that's really exciting at our institution is in January we opened our brain metastasis clinic. We're now seeing patients with brain metastasis from any disease, and patients come into a room and actually get to meet at the same time with a medical oncologist and neurosurgeon and radiation oncologist to talk about the multidisciplinary management of these tumors, talking both about standard of care and about clinical trials.

We think this is a really powerful way to optimize the care we can to deliver to these patients and hopefully provides a really unique platform for really facilitating and expediting new clinical trials for these patients. So something I think that is afield, hopefully is another place that we can get to, to help improve their outcomes.

DR. AHLUWALIA: Good morning, everyone. I'm Manmeet Ahluwalia. I'm a medical neuro-oncologist, and I work at Cleveland Clinic. My interests are treating both primary brain tumors and brain metastases with a primary interest of clinical

trials, and also primarily looking at combinatorial efforts with radiosurgery and some of these newer agents.

First of all, a great story by Derrick. I'm really heartened to see a great response that you've had, so I congratulate you on your success. I'm so excited because when I started doing this 10 years back as a medical oncologist, we had a very limited role actually in the management of brain metastases. It primarily was a neurosurgeon's game where they would take the brain mets out, and then it would be followed mostly by radiation.

Most of the talk really was, would we give whole-brain radiation or would we do stereotactic radiosurgery? As Mike had shown work from Paul Brown, I think the field has moved that at least in the radiation, there are now efforts because neurocognition is a big problem with these patients. So the field is moving towards how can you decrease the neurocognitive side effects when you treat these patients. As Derrick's case proves, these patients are living longer.

Previously, like a decade back, most of these patients lived 6 months or so, and when you did your research, you found it out to be 4 and a half months. Now we know our patients are living multiple years, so congratulations again on being off treatment for two years.

So neurocognition becomes a big part of the picture, and a lot of efforts now are looking at how can we decrease the neurotoxicity. There new ways of looking at whole-brain radiation with hippocampus sparing. There are efforts to do radiosurgery, which can help you preserve neurocognition because the worst thing for neurocognition is the brain tumor growing actively, but then some of the treatments we do induce neurocognitive side effects.

So the efforts that we lead actually, looking at how do we minimize radiation to the brain and how do we effectively use some of these therapies, as Mike had alluded to, there are a number of exciting agents which are now working in the brain. Though, what we also tried to look at

are two points, and Nancy Lin's talk also highlighted that at least, which Mike Davies covered, is not only do you need to look at these agents and their response rates, you also need to look at what's the duration of response, because as in your case, these two agents work beautifully before we see that, but the challenge is the duration of response is not there.

So we actually had recently published our experience of over 150 patients where we treated them with combined radiosurgery and immune checkpoint blockade. A number of these patients were treated actually with pembrolizumab but also nivolumab.

What we found was when we were able to combine the stereotactic radiosurgery with the immune checkpoint blockade, within 3 weeks of treatment, we saw the best response, actually completed responses naught of 50 percent. That's higher than what we see with pembrolizumab alone, which is around 30 percent in non-small cell and 20 percent in melanoma. Now we know the combinatorial

efforts are better, but we also need to look at one with the neurotoxicities when we combine this.

The other thing we like to look at is whether the patient is asymptomatic or symptomatic. I think that plays a critical role of which therapy to do. We also at Cleveland Clinic have a multidisciplinary program just like Mike Davies said, because one thing I would definitely want to stress on today is it takes a village to take care of a patient with brain mets just like brain tumors. So neurosurgeons, radiation oncologists, medical neuro-oncologists, neuropsychologists, they all have to work together to optimize the treatment for these patients.

So I'm very excited to be here and looking forward to excellent talks. Thank you.

DR. RIELY: I'll introduce myself as well. I'm Greg Riely. I'm a medical oncologist who treats primarily patients with lung cancer. As you saw in Mike's presentation, patients with lung cancer have the plurality of brain metastases that we diagnose each year, so it's a critical problem

for patients with lung cancer who develop brain metastases.

I think we've heard a lot of interesting beginning thoughts on defining the problem of CNS metastases. I wanted to step back for a second. I think we've really heard a lot about how we've made dramatic improvements and now enrolling patients with brain metastases into our clinical trials.

Why didn't we do that before? What's the -- and I think this is really just to educate more than anything. Mike, maybe you can elaborate on why patients with brain metastases were excluded from trials before.

DR. DAVIES: Certainly one of the issues has always been concerns about whether these drugs will actually penetrate the blood-brain barrier and have activity. Dabrafenib was, again, a drug that is a mutant selected BRAF inhibitor that was in some ways selected for clinical development specifically because it didn't cross an intact blood-brain barrier in preclinical development, and therefore it was thought this was an agent that wouldn't have

neurologic toxicities.

Therefore, in the initial development, there was a thought not to include patients with brain metastases. And I can tell you melanoma investigators around the world really harped on the fact, well by the time you can see a brain metastasis on an MRI, we know the blood-brain barrier has been disrupted.

So in the actual fact, the reason that we initially saw activity in patients with brain metastases is because there were clinical trials that were ongoing that didn't require CNS imaging in asymptomatic patients.

So there were some patients who even though PET scan is not the best way to actually look at response to treatment in the brain, patients who had PET scans had undiagnosed brain mets that clearly shrunk on dabrafenib, and that really changed the paradigm from saying that you couldn't treat these patients to absolutely recognizing this was a huge unmet need. Therefore, even though dabrafenib was the second BRAF inhibitor to be

improved, we ended up with data for it almost two years before we had data for the first FDA approved BRAF inhibitor in patients in the brain.

Certainly, I think the other concern has been historically the very poor outcomes in these patients. I think sometimes people have just been intimidated in thinking about how they're going to talk about the efficacy of their drug if testing it in patients who have had very poor outcomes. If anything, I think we in the community harp on the fact, well that's the population that we are most desperately needing new treatments for and in fact are most impressed by when we see activity.

I think, again, this idea that in the lung cancer space, in particular this new paradigm, that absolutely this may be a place where you can see activity the earliest I think is a really important concept and lesson that I hope drives further assessment.

In terms of toxicities, I would say that we had lots of concerns going in with immunotherapy about whether we would see toxicity from increased

inflammation in the CNS. I have to say that hasn't really been much of an issue. It's an issue that we deal with anyways in routine clinical practice.

So I think those barriers, at least in terms of concerns about efficacy and safety, I think those are sort of falling away, so I really hope that as we move forward, we are able to change that paradigm.

DR. RIELY: Manmeet, Mike mentioned this notion of a blood-brain barrier. I think this is kind of a fundamental concept as we think about treating brain tumors and treating brain metastases. What's a blood-brain barrier and what challenges does that --

DR. AHLUWALIA: Yes, sure. Just basically, blood-brain barrier is the lining around the brain that exists actually. It's basically what we think is so that the toxins don't get into the brain. So it's the natural protection that exists in the body. This has also been challenged traditionally with the chemotherapies that tend to be large molecules or the antibodies which tend to be large

molecules. If you have a small molecule less than 400 dalton rate, you would probably traverse the blood-brain barrier.

But as Mike alluded to, and we see this in primary brain tumors as well as brain metastasis, that actually when you're seeing brain mets, there is a disruption of the blood-brain barrier. Then it actually gets into the point of how potent the agent is that is going to be able to traverse.

We also in our own practice have used radiosurgery selectively to artificially disrupt the blood-brain barrier. So what we know when we use radiation -- at least in primary brain tumors, we use a lot of that knowledge to translate it to our brain metastases practices.

When you use radiation, there is a phenomena of pseudoprogression, which is due to more further disruption of the blood-brain barrier, and people like Ben Ellingson can tell you better; but then there's more gadolinium that actually spreads out, and this basically tells you that there's a disruption of the blood-brain barrier.

So we tried to use some combinatorial approaches where we are at least trying to increase the blood-brain barrier penetration, and there's also now interested in using ultrasounds, focused ultrasounds of the brain actually, where you can use high frequency or low frequency, which can noninvasively disrupt the blood-brain barrier.

So I think this has been a major challenge for the neuro-oncology community, how to get drugs to get in. But a number of these small molecule inhibitors, actually the good part is they have good blood-brain barrier berry penetration, and tucatinib now has excellent blood-brain barrier penetration.

So I think companies are really picking up on this, that brain metastases is a significant clinical problem. A large number of patients have brain metastases, especially from lung cancer, melanoma, and breast cancer and a significant unmet need, and they're focusing on how to develop agents.

DR. DAVIES: If I could add just one point

to that. Again, we were really thrilled with the activity we saw with these immunotherapies, which again are all antibody based at this point. It's actually unknown at this point whether these antibodies actually have to get into the brain to work or whether actually inducing a response in the extracranial disease is sufficient to be able to get trafficking of immune cells into the brain. It's an unanswered question at this point.

One of the things we do know is that when we see responses in brain mets to immunotherapy, we almost always see can concordant responses in the body as well; that it's not that those usually sort of separate.

That being said, we do actually see with immunotherapies that we do have patients who are responding in the body who progress in the brain or have mixed responses. So I think there's still a lot of questions around this that haven't been answered to this point, but it is an open question with immunotherapy; do you even have to cross the blood-brain barrier with your drug or is it

sufficient to stimulate a T cell to do the work for you?

DR. AMIRI-KORDESTANI: I wanted to go back to the issue with the patients with leptomeningeal disease, that still actually a majority of them are being excluded from the majority of the clinical trials. From your perspective, how could you actually see that they could actually be enrolled in the trials? Maybe you could start.

DR. WALKER: That remains probably the last frontier I think for these types of patients. For our registrational trial, for instance, we did exclude patients with leptomeningeal disease but are currently exploring that, for instance, in an investigator initiated trial.

So I think that there probably needs to be a little bit more data around the use of systemic agents for leptomeningeal disease to make sure that there's comfort that these patients can be enrolled and also receive benefits.

I certainly think that if we can get some comfort there, and then define are we talking about

patients with radiologic leptomeningeal disease or is this cytologic leptomeningeal disease, to ensure that these patients have access as well; or if there is still a differentiation, is there a way to include cohorts within trials that might include leptomeningeal disease that could be assessed differently so that we can maintain access even if the outcomes remain different.

DR. DAVIES: If I could just add to that, with Dr. Le Rhun not here, again, to your point, it's one of the things that if you include cohorts of those patients in your study, if you see activity in patients with leptomeningeal disease, that is something where there is such an unmet need.

Priscilla Brastianos is at the other end of the table, and Mass General and MD Anderson, and I'll let Priscilla talk about her experience. We have an experience with immunotherapy for leptomeningeal disease, actually intrathecal immunotherapy, for a long time with IL-2, and now a trial, first in-human study of intrathecal plus

systemic nivolumab, including patients who've progressed on PD-1.

One of the things that was a bit of a challenge in getting the trial up and running was the concern that there weren't enough patients to conduct these studies. It is actually always different to mine from the literature how many patients there are with leptomeningeal disease. I can tell you that once we opened the trial, the number of patients who had leptomeningeal disease who came to our front door went up probably 5 to 10-fold.

These patients are out there. They absolutely need studies. I would say also as physicians, we absolutely need therapies to offer to these patients. So I think this is a huge untapped opportunity, and maybe Priscilla can talk about her experience.

DR. BRASTIANOS: Sure. Actually, thanks Mike. So yes, as Mike mentioned, we're also looking at immunotherapy and leptomeningeal disease, and I'd like to second Mike's point.

We added this as a separate cohort as part of our immunotherapy trials. We have two trials right now. We have a pembro and brain met trial, but then we added an additional cohort; so to speak to your point, adding additional cohorts with a separate endpoint. Our endpoint is overall survival for the leptomeningeal cohort, where's the other brain met cohorts we have, we have RANO for brain mets as the endpoint, so we added a separate cohort.

We filled up the leptomeningeal cohort in a year and a half. For the pembro study, with patients coming from all over the country, actually, people fly to Boston with leptomeningeal disease to get on studies because there are so few leptomeningeal studies. We very quickly transitioned to opening an ipi-nivo study for leptomeningeal disease, again filling up really quickly.

Last year, we presented the result at ASCO, and we're going to be submitting a manuscript very soon, as we met primary endpoint for the

pembrolizumab and leptomeningeal cohort, which we presented at ASCO last year.

So just a plug for, yes, the patients are out there. The patients are willing to travel to come to these trials. It would be great if as a community we opened up more multicenter trials. And Mike and I have talked about joining forces, but we'd love to join forces with more institutions to allow these patients to go on study because they're out there and they're in great need of going on these trials.

DR. AHLUWALIA: To add to that, I agree completely with some of the sentiments that have been echoed. I think leptomeningeal disease, as has been called the last frontier, is obviously I think one of the biggest challenges in the whole of solid-tumor oncology, how to treat patients with leptomeningeal disease.

I think during our investigations of patients with brain metastases, we have tried to add cohorts of leptomeningeal disease in the past. There's a trial -- actually Priya Kumthekar is here

in the audience, and there's actually a full study, which I'll be looking at ANG1005, an agent that was looked at in brain metastases but showed very nice activity in leptomeningeal disease. Also, osimertinib is a drug that we have looked at a trial ongoing right now, combining radiosurgery and osimertinib. Obviously, there's a lot of active data with the BLOOM study showing that leptomeningeal patients actually get a response.

I think the different tumor types are different. Sometimes you have to act very quickly with patients with leptomeningeal disease. I think the window of opportunity is really short in these patients, but as has been expressed with prior experience, if you do have cohorts, you'll see patients will fly in and will come because they don't have too many options.

DR. BRASTIANOS: And to add to that, I think it's incredibly important -- and I'll talk more about this later -- to add in translational studies so we can understand these patients more particularly for the leptomeningeal study. I know

Mike is doing this, and our group, again, joining forces, but understanding responses and biomarkers for the leptomeningeal cohort is especially important, too.

DR. DAVIES: The other thing I'll vouch for as well is, just reinforcing Dr. Lin's point, leptomeningeal disease is a place where we absolutely need models to be developed for us to help with therapeutic development, and again, an area that's very difficult to get funding for at this point because of the perception that it's a rare entity.

MS. SELIG: I wanted to take facilitator's prerogative here and go back, if I could, to the question -- and I see Luke's microphone on -- really for our industry friends up here and in the room of why haven't we been doing this before. And you used the word "comfort," and I would really love to hear some discussion about how can we get to a place where there is more comfort, especially with our industry colleagues, for opening these kinds of trials. So maybe you could

start.

DR. WALKER: Well, I think some of it relates to some of the comments that were made earlier about the need for these patients to have treatment very, very quickly. Sometimes in a clinical trial setting, it can take weeks for all of the necessary things to be done to get a patient on clinical trials, and some of these patients may not have that type of time.

So there may need to be a different approach to these types of patients because of the nature of their disease. But I think if we can work very closely with our investigator colleagues to come up with ways to make sure that we're safely getting the patients on trial, obviously, but at the same time making it to where it's really feasible to do so and get them access to trials, that that's what really needs to be done.

DR. RIELY: I think sometimes in clinical development, it's a bit of a catch-22. You have a new drug, you're not sure it's going to work in the CNS, so you don't want to put those patients on,

and then you develop an efficacy profile, and you say it looks like it's working, we're not sure how it works in the brain; let's keep those patients out and go forward.

So I think from the industry perspective, it's hard from the trial design perspective to think about how we do that.

One more thing I wanted to address on the trial front, and you alluded to it for leptomeningeal disease, when you're thinking about enrolling patients like that, how do you determine response and how do you identify it, that sort of thing. I think that's been a real limitation up until very recently. We now have the RANO criteria for leptomeningeal disease.

I think one of your key decisions when you're developing a drug is trying to find a surrogate endpoint that will help you. Do you think that's probably the overriding issue in terms of leptomeningeal disease or is it a more of the fact that those patients are the sickest?

DR. WALKER: It's both, but I think that

perhaps the big concerns is the patients are not going to have -- I think it's been more that these patients don't respond to systemic therapy. And I think that that's still ingrained in people's thoughts.

So it's the worry about exposing these patients to potentially ineffective therapies, even though nobody's ever really tried them in a clinical trial setting. I think if we can get to the point where we have some level of clinical evidence, even if it's not a randomized trial, that some of these agents could be a beneficial.

I think your point about the availability of patients is also a very important one because it is difficult to come up with a clinical trial if you think you're going to enroll one patient every 6 months. But I think the reality is that these patients are actually much more available and the need is really much greater than that, and that makes the trials easier to do.

DR. EBIANA: I'd just like to add to that we'd have to think about criteria that would make

it less likely that the patient would need to get something like radiation that would then confound our ability to really tell if the agent was working. A lot of patients with leptomeningeal disease need to get radiation to control symptoms or disease, and that would really make it extremely difficult to tell if the therapy was working and makes it almost impossible to really design a trial that we can interpret the results from.

So that's another potential challenge, but again, we do have trials that examine leptomeningeal disease, mostly through our investigator-initiated program specifically for that reason. It's much easier to do that when all of the patients are being treated at a single institution and can be assessed rapidly.

DR. RIELY: I think the investigator-initiated trials is a nice opportunity to get investigators who are wholly devoted to this, and I think that's an important aspect of it.

I'll move to the microphone here.

DR. NDOUM: Hey. How's it going? Edjah

Ndoum. I'm a neurosurgical oncologist at the NIH. Thank you for allowing me to be here. I was one of the few neurosurgeons here. You knew we weren't going to be silent the entire time.

One point I did want to make out is in looking through the list of people, I don't think there were any neurosurgeons on the panels or speakers today, which to me is a little interesting, because I know, as you mentioned, I think neurosurgeons were very involved early on in treatment of brain metastases, and I think we've been kind of pushed to the side in a lot of cases.

I was talking with Dr. de Groot about the clinic that you guys have at MD Anderson as you mentioned earlier about having brain metastases' patients seen by a neurosurgeon and an oncologist and an radiation oncologist. I think that's a fantastic model. I think it's something that could be adopted more broadly.

Where this ties in is when we're talking about designing trials for brain metastasis patients and figuring out how the drugs work in

brain metastasis patients, personally in the glioblastoma space, my kind of mini soap box has been talking about actually measuring how drugs work in the tumor. The preclinical models are fantastic, but we actually need to know how they work in patients because the models aren't perfect.

So I think that insofar as particularly leptomeningeal. Dr. Brastianos mentioned that you're working on actually getting biomarkers with that CSF or tissue that actually sees why the drugs are getting there or having an effect.

I think that sort of model is something that might be needed in small pilots that drug companies can maybe consider supporting, where there is a small subset of patients on a much bigger trial that you're doing, where these are patients that we know are going to resect the single tumor like Mr. Queen, it had done for him. But you're getting a dose of the drug ahead of time. We're taking the tumor out, seeing what changes there might be or what targets are there, and what concentrations the drug has there.

So I just wanted to put that in for the discussion and see where we go from there. Thanks for having me.

DR. BRASTIANOS: Just to add to that -- and Mike mentioned this before -- absolutely, we need our neurosurgical collaborators. As part of our multiclinic at Mass General, we work closely. A lot of these patients get shunted, both for ICP, but also it allows us to collect CSF.

So absolutely, these brain met patients need neurosurgical input, and the leptomeningeal disease patients, too. And I'm sure others would absolutely agree.

DR. DAVIES: We actually designed a trial in melanoma around this question of why were brain metastases not responding as durably to the BRAF inhibitors. We're taking patients. We said, well, this is a patient who is going to undergo surgical resection. They haven't received BRAF inhibitor before. Actually, what we did is we did the study to treat for basically 10 to 14 days before neurosurgery, and actually planned to get, when

possible, biopsies of extracranial tumors essentially before the start of treatment and then on the day of neurosurgery.

The challenge we had is in the current era, it became so hard to find that patient who was going to undergo surgery, who could wait for a clinical trial, because often we're doing surgery in patients who are highly symptomatic, and again, the part about the time it takes to put patients onto a trial where there wasn't a plan basically to do gamma knife and where there wasn't a plan basically to do systemic therapy.

I have to say the small number of patients that we accrued, we've already had remarkable insights in the difference that we've seen in the brain met and the extracranial met on therapy, that I think we'll reinvigorate interest in this. But as we've talked about, the question is how can we design those studies such that we actually can successfully accrue patients, because that's a huge challenge to those types of studies. But we're very jealous of the GBM and the window studies;

absolutely.

DR. AHLUWALIA: Just to add to that, I think that's a great point. We have tried this approach as well, having a strong neurosurgery program, and typically these patients used to be operated on much more before. Then, as the radiosurgery equipment and the ability to do radiosurgery changed, a lot of these patients actually ended up undergoing radiosurgery rather than a resection.

Also, the other thing that has changed is because we do MRI screenings much more often now compared to a decade back, we tend to catch these lesions generally when they're smaller as compared to when they used to be larger before, where they absolutely needed to come out.

When we have this discussion on our tumor boards, whether someone who has a 1.5 centimeter or a 2-centimeter lesion, the neurosurgeon says, yeah, I can take it out, but at the same time I can do radiosurgery and they'll be home, and you can carry on the systemic treatments at the same time.

I think with us learning a little bit more

about the biology of the disease, the fact that that it's different in the brain as compared to extracranially, I think there is, again, gain an evolving role of the neurosurgeon, and we have seen much more receptiveness on the part of the neurosurgeons to take these patients to surgery. Also, in this era of immunotherapy, you want the mass effect to be decreased rapidly because you don't like steroids, because steroids impact the efficacy of most of the immunotherapies that we use in our clinic.

So I think the role of neurosurgeons is coming back actively in terms of removing these tumors, and obviously we are also in the process of actually designing phase zero trials. I think we have done this much more successful in the GBM space, and I think in brain makes this a little bit more challenging.

MS. SELIG: Dr. Sul, did you have a comment you wanted to make?

DR. SUL: Yes. I think a lot of this discussion is also highlighting a point that was

brought out by Mr. Queen's story. One of the issues is this whole idea of radiation and where to put it in the continuum of treatment. We have this therapy that we know can be quite effective for a short period of time. So it can be helpful for patients who need some kind of intervention, but where do we fit that in with clinical trials, and at what point do you allow patients to forego radiation and try a clinical trial?

The other topic I wanted to touch on briefly was what Dr. Riely had brought up, going back to the problem of CNS medicine and why have they not been included. There are all the standard reasons that we know about, the side effects. People are afraid that their drug will result in bad outcomes, so they don't want to develop it in this patient population.

It seems that the other reason is that we haven't looked, and that's a really I think important point that Dr. Ahluwalia just brought up, is that we haven't done screening in the past as much as we do now. It's sort of been this don't

ask/don't tell. You don't want to know. You don't want to go there and look. But it seems that we really need to if we're going to count it along with the other systemic mets. We've kind of left it behind.

Those are just the two points I wanted to bring up.

DR. DAVIES: Just to follow on to that, again, Dr. Lin brought this up in talking about breast cancer. One of the other things is about strategies for patients that we know are at risk of developing brain metastasis; how can we develop trials and strategies to reduce that risk? That's incredibly dependent upon coming up with standardized ways that patients are surveilled for brain metastasis.

DR. LIN: I'll add that part of the don't ask/don't tell really has to do with if you diagnose a patient with a small asymptomatic brain metastasis, they're now excluded from their next clinical trial. It's a huge disincentive, from a clinical perspective, to screen that patient.

In breast cancer, all of the guidelines basically say don't screen patients with brain MRI on a regular basis. Yael Lazer [ph] in our group is the radiation oncologists is going to launch a randomized trial to actually look at the question of screening in breast cancer patients. But a huge part of that really has to do with we're worried we're going to do a patient a disservice.

You find an 8-millimeter lesion and they can't go on to the next trial of a HER2 TKI, which may be perfectly effective against that brain met, and they lose out on this next option. I think these two things are linked. If we actually allow more patients with brain metastases on clinical trials, you're going to reduce the disincentive to screen.

DR. RIELY: In the limited time we have left, I wanted to get to the microphone for another question.

AUDIENCE MEMBER: Thank you so much. My name is Simon Tooma [ph], hematologist/oncologist. I was at academia, so I'm currently working at

Lilly. I'd like to pose a question certainly to the panelists today. Certainly, I'm so glad to hear that there's definitely a lot of discussions around getting patients with brain mets during the early phases of clinical development as soon as possible, but maybe if I could ask the panelists for some guidance and maybe from our industry colleagues here as well.

It's good to certainly put patients in. Many times, many of the drug companies certainly have overlapping drugs specific to a specific target, and we know that they have different profiles going to the brain, and we don't know, a priori, based on their TPU, their likelihood of going to the brain.

In that particular circumstance, can the panel give some guidance in terms of when is it time, on the other hand, to say maybe we shouldn't continue to do it because as you're going through dose escalation or the dose expansion stage of your study, you may not be seeing activity if you allow patients with brain mets.

When is the right time to somehow say, you know what, for our drug specifically, maybe it's not time to put patients with brain mets because chances are it's probably not going to benefit them?

DR. RIELY: I'll jump in first on that. I think the key thing when I approach this is that you don't go in with the a priori assumption that drug's not going to work for people with brain metastasis, so you have to have to keep your mind open to that. But you also have to keep your mind open to the observation that it's not working in patients with brain metastases.

So you begin the development with inclusion/exclusion criteria, which allows safe development of the drug, so you allow patients with brain metastases, but they're not large brain metastases, for instance; they're small ones. Then, if you see that the majority of patients who progress are progressing in the CNS, then you realize that's not the place you want to be, and then you can refine this. But I think you build

that from data in the drug development experience, not from just sort of an a priori assumption that it ain't going to work there.

DR. LIN: I can comment as well. That's part of what the RANO group has tried to put together, a framework for this, and Ross Camidge was the first author of the trial design publication. The idea is there are many ways to mitigate this concern. You could have expansion cohorts that are specific in the phase 1 for brain metastasis patients. There are many -- if you don't want a specific expansion cohort, you could have a minimum number of brain met patients that you're going to enroll in a more generalized expansion.

So I think there are ways to certainly look at this a little bit better in that early-phase setting. We'll have the case discussion, and the afternoon will be on in the ALK story. I think what it really highlights is that if you include patients early on in the drug development, then you actually have data on which to base a decision

whether or not to enroll such patients in your registration trial.

If you don't generate that data, you're left with this catch-22, which is where most drugs are at this point, where you want to be conservative. You don't want to let those patients on registration trials. But then it means that patients with brain mets don't have access to these agents until well after drugs are developed, and that's something we hope we can change.

MS. SELIG: I'm going to jump in here again. You've heard my voice. I forgot to introduce myself. I'm Wendy Selig, and I'm going to be keeping the trains running here. We're about to let this panel go, but there will be an opportunity for you to come back with your question after the next set of talks.

I just thought, can I take one more prerogative and give Derrick a very quick last word so we keep the voice of our patient as we go into the next session? The next session is going to be for individual talks. That's what these folks up

here are doing up here. I just want to summarize what I heard some people are thinking in terms of themes in the problem area that we're then going to be wanting to solve.

We heard about inclusion of patients. We heard about timing of inclusion of patients. We heard about how to address radiation in this discussion. We need to be thinking of whether we're actually looking in the right places, and then we heard from Dr. Riely about our assumptions. So just be thinking of those concepts as we move forward.

Derrick, a very quick last point, and then we're going to go into the next session, which is for individual talks from over here. You guys can use the podium or stay at your seats, as you will; except for Nancy. Your microphone I think is the one that's buzzing, so during the break, we'll address it, but maybe you could use one of the other ones.

Derrick?

MR. QUEEN: Wendy, thanks. I don't have

anything else to add. I think in the interest of time, we'll just keep it moving. But it's fantastic to hear and see so many concerned people to address this issue, which is clearly a solvable problem, and I think it's in everyone's interest to find a solution. Thank you.

MS. SELIG: Okay. So we're going to move on to the next session. Our two chairs are right there. If you guys want to introduce it briefly, and then we'll go right into the talks.

Session II

DR. WEINSTOCK: Thank you very much. That was an excellent session. I think it really helped to define what we're going to be discussing in Session II.

I'm Chana Weinstock. I'm one of the GU oncology team leaders here, and I think the inclusion of a GU oncologist I think brings to light what Dr. Pazdur stated at the beginning of this workshop, which is that we're trying to get many voices involved here that maybe don't traditionally think about

brain metastases in drug development. So I'm very interested in hearing how this evolves.

DR. LIN: I'm Nancy Lin. I'm a medical oncologist focusing on breast cancer at Dana Farber Cancer Institute and have been very involved with Patrick in the RANO efforts, as well as in the ASCO Friends of Cancer initiative for eligibility criteria.

MS. SELIG: We have four talks and we're going to keep on schedule. We've asked each speaker to have a relatively parsimonious representation of slides so we leave time for discussion.

Presentation - Priscilla Brastianos

DR. BRASTIANOS: Thanks so much for the invitation to speak today. As I mentioned, my name is Priscilla Brastianos. I'm a physician scientist at Mass General Hospital. I also lead a multidisciplinary brain metastasis clinic there. Just to put a plug in for what Mike said, the patients are out there. With this multidisciplinary clinic, we started the clinic

four years ago, and our patient volume has exploded by -- we've 5 times increased patient volume in the clinic since we started this four years ago. So there's a huge unmet clinical need, and it's wonderful that we're all here together to try to figure this out together.

Today with my talk, what I hope to show is how preclinical work can lead to new drug targets, and I'm going to show that, again, it's an unmet clinical need, and we do need more preclinical models as well as more molecular studies to try to understand what the therapeutic targets are for brain metastases patients.

These are my disclosures. Briefly, molecular epidemiology of brain metastases, we've already talked briefly about this earlier. About 30 to 40 percent of advanced HER2 positive breast cancer patients will develop brain mets; 40 to 50 percent of metastatic triple negative patients will develop brain mets; 25 to 40 percent of advanced EGFR positive disease will develop brain mets; and about 27 to 40 percent of ALK positive

patients at baseline will have brain mets; and 35 to about 70 percent in the second-line setting will develop mets. In melanoma, about 40 to 50 percent of advanced BRAF positive disease will develop brain metastases. These are some of the important targets we need to be thinking about.

However, as Dr. Davies had said earlier, patients will often develop progressive brain metastases in the setting of stable extracranial disease. This is an example of a 24-year-old patient of mine with brain metastases with stable extracranial disease and this devastating scan here. We have a number of unanswered clinical questions.

Number one, do we see intracranial progression because of incomplete drug penetration or are there different genetic drivers? What are the targetable mutations in brain metastases? And finally, can we rely on a primary tumor biopsy to make decisions for systemic targeted therapies in brain metastases, which is what standardly often done now as we do rely on a primary biopsy to make

decisions for systemic targeted therapies in brain metastases patients. Historically, we've had a limited understanding of how brain metastases genetically evolved from their primary tumors.

There have been a few studies to try to answer this question. The first study, to use next-generation sequencing technology to try to understand differences between brain metastases and primary tumors, had One patient sample and showed few de novo genetic alterations in brain metastases.

This very nice work by Dr. Davies group did proteomic analysis in resected brain mets and extracranial mets for melanoma patients and showed PI3 kinase pathway activation in CNS metastases.

Now we've brought together a team of collaborators nationally and internationally to try to understand the issues and try to understand what are the targets in brain metastases, and we've now collected more than 1500 match brain metastases primary tumors in normal DNA.

This has been an enormous collaborative

effort and actually funded by some of the funders here today, such as American Brain Tumor Association and Melanoma Research Alliance. As part of these efforts now, we're genomically characterizing brain metastases primary tumors to try to identify new therapeutic targets. As part of this collaboration, we share data back to the collaborators so that each of the collaborative can then develop preclinical models and validate these studies.

Just again, how important it is and how critical it is that we joined forces to try to answer these questions.

As part of these efforts, this is the first study we published on this. We had done whole exome sequencing of a hundred brain metastases matched with primary and normal tissue, and this included additional extracranial sites, as well as temporally, regionally, and anatomically separated brain metastases.

For each matched brain metastasis and primary tumor from the same patient, we mapped out

the genomic evolution to try to figure out where different genetic alterations occur. Are they in the brain metastasis only, depicted by the red; are they in the primary tumor only, depicted by the blue; or are they shared depicted, by the gray line here?

What we found across all the cases was this pattern of divergent or branched evolution where the brain metastasis and the primary tumor shared a common ancestor, but there was significant genetic evolution such that there were new oncogenic mutations in the brain metastasis.

Why is this such an important concept? Well, we need to know if the therapeutic targets are different in the brain compared to the extracranial sites. This is the pattern we saw across all our brain metastases. Charles Darwin depicted this in his notebook in 1837 showing this pattern of branched evolution. This is exactly the pattern we're seeing in brain metastases.

Take this back to the clinic. Do brain metastases harbor clinically significant genetic

differences compared to their primary tumors? Indeed they do. This is an example of a patient that had a brain metastasis from a renal cell carcinoma developed synchronously with the primary tumor.

There's a shared common ancestor, so there are shared mutations; yet the brain metastasis had PIK3CA mutation and loss of CDKN2A that was not detected in the primary tumor biopsy. This was the case across the entire cohort. More than half the cases had a clinically actionable alteration in the brain metastasis that was not detected in the primary tumor biopsy.

Were there commonalities? So we can start thinking about clinical trials for these patients and that's why we're all here today. We found that more than half the cases had alterations in the CDK pathway. This included loss of CDKN2A and CDK46 amplifications. Forty-three percent of cases with alterations associated with sensitivity to PI3 kinase inhibitors, so PIK3CA mutations, PIK3R1, et cetera, and about a third of cases with

alterations in HER2 and EGFR.

Not surprising, many of these patients were breast and lung patients. What was surprising is that it was not uncommon to see ERBB2 amplifications or EGFR amplifications or mutations in the brain metastasis and not detected in the primary tumor sample.

Genetic divergence between primary metastatic samples, it creates a major challenge to clinical decision making in oncology. What about regional heterogeneity within the brain itself? How representative of both CNS disease as a single brain metastasis sample? To answer that question, we sequenced regionally, anatomically, and temporally distinct areas of brain metastases.

Here's an example of a patient with a salivary gland ductal carcinoma that had a cerebellar tumor taken out before whole brain, and then a parietal metastasis taken out after whole-brain radiation. And you can see the red are the brain metastases. They were all more genomically homogenous with each other and shared

the same clinically actionable drivers that were not detected in the primary tumor sample.

What we're seeing is that CNS metastases are relatively homogenous and we're validating this across the larger cohort of samples. This actually is another plug for why we need surgical intervention, too, is because we are seeing that brain metastases do harbor new mutations that are not in the extracranial or in the primary tumor.

However, central nervous system disease may be difficult to access in many cases or craniotomies are not trivial in every patient. Then we looked at extracranial sites and how well do they recapitulate genetic vulnerabilities in brain metastases.

Here's an example of a patient with an ovarian cancer. This patient had a primary tumor, a lymph node, and a brain metastasis. Here we showed the brain metastasis in the regional lymph node sharing this common ancestor, yet the brain metastasis harbors this long branch, so lots of genetic divergence, and this aura kinase

amplification not detecting the primary tumor or the regional lymph node.

Similarly, here's another example of a lung adeno, so just as lymph nodes were not reliable surrogates, nor were distal mets. Here's an example of a lung cancer patient where we had the brain metastasis, the primary tumor, and the bony metastasis, and you can see here this genetic divergence of this brain metastasis harboring these alterations that are not in the primary tumor or the brain metastasis.

This is very nice work by Mike Davies group that was just published, where they actually looked at melanoma brain metastases and patient matched extracranial metastases and did RNA-seq analysis and actually found oxidative phosphorylation being enriched in melanoma brain metastases compared to patient-matched extracranial metastases. So the theme you're seeing here is that brain metastases are evolving. They are distinct from their primary tumors.

I just told you about this divergent

evolution and how is this important to us? If we were to exclusively sample the primary tumor or an extracranial site, one may miss those potentially clinically actionable drivers since our data showed that clinically actual drivers occur in the brain metastasis branch more than 50 percent of the time.

The other point I made earlier was that many brain metastases patients do develop progressive intracranial disease in the setting of extracranial disease being stable. The question has always been, is it a blood-brain barrier issue or is it an oncogenic; is it a heterogeneity or genetic heterogeneity issue?

So our data suggest that at least in part it is a genetic heterogeneity issue, and there are additional oncogenic alterations in the brain metastasis that are contributing to this divergence of therapeutic responses.

However, now we need to answer the question, will targeting those molecular drivers in CNS metastases lead to improved overall survival? We just showed that there are genetic differences.

Will targeting those differences lead to improved overall survival?

Actually, another plug for doing more preclinical studies, our group and others are creating patient derived xenograft models of brain metastases, and again another place where the fields can join forces.

This is a study that we published in the last month. We developed patient-derived xenograft models of breast cancer brain metastases and actually looked at the efficacy of this PI3 kinase inhibitor, the CNS penetrant PI3 kinase inhibitor in most models, and showed that GDC-0084 does inhibit tumor growth in vivo in a PIK3CA mutant cell line and not in a PIK3CA wild type cell line.

Mike Davies' group, following up on their work, they actually looked at the efficacy of an OXPHOS inhibitor in a patient-derived xenograft model of melanoma brain metastases. Here they treated nude mice with human xenografts with either an OXPHOS inhibitor or with a vehicle and showed that mice treated with this inhibitor lived

significantly longer. Again, we need to be developing patient-derived xenograft models and looking for inhibitors in these models.

How does this apply to patients? Now we're starting a national biomarker-driven trial in brain metastases, so we need to show that targeting what we see in the brain leads to improved outcomes. This trial just got approved from the FDA -- thank you -- and a central IRB. It's set to open in about a month to be activated nationally. It's going to be an Alliance NCI trial, and many people in this room have contributed to this trial, including Carey Anders sitting in the audience and Priya Kumthekar, and we're grateful. This has been a massive, multidisciplinary and multi-institutional effort to get this trial up and running, so thank you, thank you to everyone.

Basically, we're going to be targeting patients by what we see in the brain, and these are patients that had brain metastasis tissue taken out as part of clinical care and will go on to this study. Actually, the primary endpoint will be a

response rates by RANO brain met criteria, so we encourage all sites to get this trial open. The idea is as we discover more therapeutic targets in these patients with our genomics, we can actually add additional arms. And we've partnered with pharmaceutical companies to actually expand this trial.

In conclusion, what we're seeing is that brain metastases harbor distinct clinically actionable genetic alterations compared to their primary tumors. Different brain metastases regions are relatively homogenous. Extracranial mets are not a reliable surrogate for brain metastases when it comes to clinically actionable genetic drivers, and alterations in the CDK pathway and PI3 kinase pathways are frequent, and now work from Mike Davies showing OXPHOS being enriched in brain metastases and a national genomically guided trial is planned.

Of course, I'd like to acknowledge a number of individuals who have contributed to all of this. I guess we'll take some questions now or we'll do

questions later.

(Applause.)

MS. SELIG: Thank you. We are going to hold the questions until the end of all the talks.

Dr. Lin?

Presentation - Nancy Lin

DR. LIN: Good morning, and thank you all for joining. I'm going to talk for a few minutes about selecting drug candidates for treatment of brain metastases. These are my disclosures. What I wanted to organize this talk around really is around two historical paradigms, and I hope that we can reexamine whether or not we should follow these or not follow these in the years ahead.

The first historical paradigm is that patients with brain metastases experience very poor survival, and the corollaries to this from a drug development standpoint have been, one, the assumption that by the time brain metastases occur, the cancer is highly refractory and unlikely to respond to any systemic therapy, and the second corollary or assumption has been that patients with

brain metastases will not be good candidates for clinical trials, as the competing risk of death or deterioration will prevent proper evaluation of a new therapeutic strategy, so we'll look at that.

The second historical paradigm is that penetration across the intact blood-brain barrier is required for activity in the CNS. So again, the first assumption or corollary to that is that if a drug does not show good CNS penetration across the intact blood-brain barrier in animal models, it is futile to study the drug for treatment of brain metastases, and by extension, all those patients should be excluded from all phases of drug development. The reality is that is sort of the paradigm that we've gone through over the last few decades.

The second corollary assumption to the blood-brain barrier penetration is as or more important than the mechanism of action or targeted to the drug. So often when people are thinking about whether or not to consider their drug for treatment of brain metastases, the order of

questions usually is does it penetrate the blood-brain barrier, and only as a secondary, does it have activity against the disease in question?

I am certain many of you in the audience have had people come to you with drugs that they're developing, and they say, "Well, we have this drug that penetrates the blood-brain barrier." And you ask, "Well, why do you think it might work in breast cancer or lung cancer melanoma?" And then the answer may be a little more sketchy. So I think hopefully towards the end of this talk, we can really flip that paradigm around and ask perhaps the questions in a different order

The end results of these assumptions is that patients with brain metastases have largely been excluded from cancer clinical trials despite a very high prevalence in some tumor types. You saw data that Mike Davies presented from the breast cancer literature. Only 1 percent of all phase 1 or 2 trials in many, many decades have specifically focused on breast cancer brain metastases, and similar, looking at lung cancer trials, even with

clinicaltrials.gov searches in the relatively recent years.

So the question is, are these assumptions true? If so, how true or how not true, and how should we really be selecting drug candidates for clinical trials? In terms of assumption number 1, patients with brain metastases experience very poor survival; how true is that? I'm showing you data from breast cancer for melanoma and from lung adenocarcinoma, really showing that at least for some subsets of patients, survival after brain metastasis diagnosis has substantially improved.

This is an academic collaboration led by Paul Sperduto, pooling data from radiation oncology databases across the United States. This focused on breast cancer. What you can see is that for the best prognosis group, which were patients with a good performance status, HER2 positive subtype and age less than 60, the median survival from a diagnosis of brain metastasis was about 2 years.

So certainly these are patients who could enter clinical trials where the endpoints would be

reached before their survival endpoint would be reached. And remember, these patients were entered between 1985 and 2007, so if anything, there's been 10 more years or 10 plus more years of progress.

Some have criticized this, quite rightly, as being really a selected population of patients who made it to an academic cancer center. Badi Alazor [ph], who's a radiation oncologist in our group has recently recapitulated this analysis with a SEER database and in the SEER database looking at patients presented with stage 4 de novo breast cancer where we do have sites of disease. In fact, the median survival almost completely lines up with what was seen in the Sperduto analysis.

If we look at lung adenocarcinoma, again, here the prognostic factors that came out were different: age performance status, extracranial disease, as well the number of brain metastasis, and importantly the gene status, whether or not there was an either an EGFR are mutation or ALK rearrangement. Again, you can see for the best prognosis group, those patients with either EGFR or

ALK rearrangement with a good performance status and young age experience actually quite substantial median survival compared to our historical assumptions.

Finally, the poster child of this major shift is melanoma. These are data from the CheckPoint [sic] 204 study that you heard about that was published in the New England Journal last year. This is looking at overall survival in patients treated with combination checkpoint inhibition, and you can see that the numbers are really quite astounding in comparison to what all of our assumptions have been over the last decade.

So I think, for sure at this point, for some subsets of patients, the survival after brain metastasis diagnosis has substantially improved, and even among those patients where it has not, I would argue that these are patients who still have a tremendous unmet medical need, and we don't want to ignore those patients as well.

Now let's move into assumption number 2, that penetration across the intact blood-brain

barrier is required for CNS activity, and we'll look to see how true or not true that is. The first point is that penetration of the blood-brain barrier is really irrelevant if the drug is inactive against the target cancer.

I just can't stress that point enough. The idea that the target is very important, as you heard about from Priscilla, is so critical. These are data looking at temozolomide, which obviously is a very commonly used drug in neuro-oncology based upon its PK characteristics, but these are data looking at temozolomide for the use of established active breast cancer brain metastases.

The first is a trial from NCIC Canada, which basically was stopped for futility, no responses seen in the first stage; another trial from Italy looking at 51 patients with a 4 percent response rate; and finally a randomized trial assessing whether temozolomide may be a radio sensitizer, a hundred patients enrolled in this study and no difference in any of the outcomes. So again, I think the target is really critical in selecting

the drug.

The second point is that it appears quite clearly that lack of penetration across the intact blood-brain barrier does not preclude activity against established brain metastases. These are data looking at whole body audio radiograph of lapatanib penetration in male rats after a single dose. You can see that there's almost nothing that gets in. The brain plasma ratio is less than 0.13.

But in fact, lapatinib is quite active in the brain. These were data from our very first study looking at lapatinib and monotherapy. The third person treated on the study, you can see clearly that there's activity in the pre-baseline versus the post with lapatinib monotherapy despite the rat data that I showed you. And if combined with chemotherapy, particularly in patients who had not received previous radiation, so less heavily pretreated patients, we see response rates in excess of 60 percent.

How could this be? It's really this point that came out earlier, which is that there is a

difference in biodistribution in normal brain versus brain metastases. This was a study actually using radiolabeled lapatinib as a PET tracer; 6 patients were recruited, 3 of these patients had brain metastases. In normal brain, you can see there's very little uptake, however, in brain metastases there's substantially more uptake; although in one of the patients, as you see, there was heterogeneity between different lesions.

Akiko Morikawa, who is here in the audience today, also led a study where rather than using a PET tracer, they directly measured lapatanib concentrations in a brief presurgical exposure study, again, showing that lapatanib does reach therapeutic levels in brain metastases, although in a heterogeneous fashion, across and between metastases.

This is a list of a few examples of drugs which we know do not freely penetrate an intact blood-brain barrier. In fact, some of them, including for melanoma, were designed not to penetrate the blood-brain barrier, but there's

clear anti-CNS tumor activity. You can see this is for anti-HER2 two agents, for chemotherapy, for BRAF inhibitors; perhaps immune checkpoint inhibitors may not need to get in to exert their effect; EGFR inhibitors, and ALK inhibitors, as well as VEGF inhibitors.

So we really I think have enough data at this point to be quite convincing that blood-brain barrier penetration across an intact blood-brain barrier is not required for activity.

The question that this raises is whether blood-brain barrier penetration is relevant at all. So again, existing data tells us that lack of penetration across an intact blood-brain barrier does not preclude efficacy. And I would argue that because of these data, we really should not use these types of preclinical models to exclude patients from clinical trials.

However, this still raises the question of whether better blood-brain barrier penetration might lead to more or more durable CNS efficacy or could correlate with prevention affects. Here I

think we don't fully know the answers, but I'm going to show you some data, and we can think about how convinced we are.

I'm going to show you data from the lung cancer arena. This is data looking at crizotinib versus alectinib in ALK rearranged lung cancer. Crizotinib, we know very little crosses the intact blood-brain barrier. There were interestingly early observations of CNS-only progression leading to a concern that this may be a liability of the compound. And although CNS responses were seen, numerically the systemic response rates were higher.

In contrast, alectinib has excellent CNS penetration, including into the CSF in preclinical models, and in the early-phase studies, there were high and similar response rates in a brain versus extracranial sites. I will note that I'm only able to make this slide because patients with active brain metastases were allowed onto the early-phase trials, so we had this data going into the registration trial designs.

This shows the design of the ALEX trial, which looked at ALK rearranged non-small cell lung cancer Patients were enrolled who are untreated with advanced disease with a performance status 0 to 2, and they could have had asymptomatic brain metastases or leptomeningeal disease and still be eligible. Patients without brain metastases were also eligible.

Patients were randomized to either alectinib or crizotinib, and the primary endpoint was investigator assessed PFS across both compartments, brain and body. Importantly, the stratification factors included the presence or absence of CNS disease at baseline.

Notably, 40 percent of the study population had brain metastasis at baseline, speaking to the prevalence of this problem in patients, and also notably in the protocol, there was CNS imaging at baseline in every 8 weeks mandated across all patients regardless of whether brain metastases were present at baseline or not, so this is very different than many of the trial designs that we

see. Interestingly, despite the fact that crizotinib does not cross the intact blood-brain barrier, 50 percent of patients achieved a CNS response with crizotinib, but it was significantly higher with alectinib at 81 percent.

You can see in terms of their primary endpoint of progression free survival that this favored alectinib over crizotinib, and because of the mandated CNS imaging, they were able to actually create proper curves looking at the cumulative incidence of CNS progression and demonstrate a prevention effect of alectinib.

So I think that this study is very instructive. You will hear more about the ALK story in a later session; but really, in terms of both the study design and the inclusion, what led up to the study to allow these patients to enroll, to really help us learn something very important about this patient population in which brain metastases are so common.

I'm going to contrast that with the KATHERINE data. For those of you who are not

breast cancer medical oncologist, TDM1 is an antibody drug conjugate that conjugates trastuzumab, a monoclonal antibody that targets HER2, along with a payload of emtansine. In the metastatic setting, TDM1 is approved for treatment of HER2 positive metastatic breast cancer, and there was an attempt to bring it into the early-stage setting.

In the metastatic setting, after the approval of TDM1 for treatment of general HER2 positive metastatic breast cancer, a number of groups put together a case series to demonstrate that there is activity in the CNS in the range of 20 to 50 percent in terms of response rate across the various studies.

I will point out that none of the either phase 1, phase 2, or registration trials of TDM1 included patients with active brain metastases. They were excluded from all phases of their drug development, but nevertheless, we do know that it has some activity in the CNS, and presumably because of its size, it does not cross the intact

blood-brain barrier.

The KATHERINE trial looked at patients who were treated with curative intent with new adjuvant chemotherapy, and then at the time of surgery if there was residual disease, the randomization was trastuzumab, which is the standard of care or switch to TDM1.

You can see in terms of the overall endpoint of invasive disease-free survival, there was a substantial advantage of TDM1 more than 10 percent absolute delta and that there was also a substantial decrease in the risk of distant recurrence. But somewhat disappointingly, there was actually no change in the incidence of CNS disease as first site of relapse, raising the question of whether CNS penetration is required for prevention effect. I don't know that we know; we don't have that many data points to look at, but certainly does raise that question.

The other point from this study to note is that if we think about -- these are our highest risk patients at this point, the patients who are

eligible for neoadjuvant therapy, and you can see that if we were to march into the future, given that about half of the distant recurrences were in the brain, and of these patients where the distant recurrence was not in the brain, probably somewhere between 20 and 50 percent will eventually develop brain metastases; that in the future as breast cancer medical oncologists, we are going to be -- for the HER2 positive metastatic patients, they're going to be brain metastases patients, and again, really stressing the point that studying this patient population is so very important.

Finally, and Priscilla has touched on this as well, is whether better preclinical models can help with drug selection. I think it's very clear at this point that just simply doing audio radiographs studies or studies to look at distribution of drug in normal animals really does not help us determine which drugs will be effective in the brain. I've shown you many examples of that. The question is can we develop better preclinical models?

There are 3 strains of preclinical models, major strains. One is to take established cell lines, inject them intracranially, and then test the drug in those intracranial models, and that's still probably the most common way that these studies are done.

Pat Keegan at the NCI has pioneered the use of these brain metastatic cell lines where she takes normal breast cancer cell lines and injects them intracardiac. They then spontaneously metastasize to the brain, select out those brain metastases, put them back intracardiac, and over multiple passages have created several lines that are very highly metastatic to the brain in a more spontaneous fashion and does not require intracranial, so that's one additional strain.

Finally, I think more and more we're seeing people start to put together patient-derived xenograft models, and this is an example of how that works. A patient who is undergoing a clinical resection at the time of resection can sense that tumor is put in a mouse brain and also can be put

in a mammary fat pad. They can be grown out. They recapitulate the genomic and IC characteristics of the original patient's tumor, and then you can run mouse clinical trials, really testing a number of different combinations and trying to prioritize which combinations or strategies to take into the clinic.

At this point in time, because there are a relative dearth of trials in terms of breast cancer or other brain metastases that have reported out, relative to corresponding models, I think it's hard to conclude at this point which model is going to be the most predictive. But hopefully, if we continue to do these experiments in parallel, then in the future we'll have better ways to select which drugs to prioritize for drug development.

In conclusion, I hope that we will take away some ability to rethink our assumptions. I think that that is really going to be key into changing how we take care of patients with brain metastases relative to clinical trials. In terms of conditions for efficacy of systemic therapy against

established brain metastases, I think, number one, is there needs to be a rational target. It needs to be active against the underlying disease, and either achieve therapeutic levels in tumor tissue or exert effects independent of penetration in tumor tissue. That may be the case with checkpoint inhibitors. But it's very clear that penetration across an intact blood-brain barrier is not required.

What are the conditions for prevention effect? Again, you'd like a rational target, but here there actually may be the opportunity to look at agents that actually directly affect brain metastatic potential. So there may be agents that actually are not necessarily effective against established metastases, but if we can identify the underlying factors that allow cancer to go to the brain, there may be the ability to target those pathways as well.

I would argue that at least for right now, the existing data suggests, although it does not prove, that penetration across an intact

blood-brain barrier may be associated with a better prevention, a potential at least for those drugs that need to exert their action at the tumor site.

Finally, in terms of preclinical models, again, I would argue that standard drug distribution studies in normal animals is not enough and really should not be used solely as an exclusion for patients to enter into early-phase trials. Intracranial models are probably better, although which model and under what circumstance, I think we still need to work out. So thank you.

(Applause.)

DR. WEINSTOCK: Thank you very much. Our next talk is by Dr. Margolin about issues with conducting brain metastases clinical trials.

Presentation - Kim Margolin

DR. MARGOLIN: Thank you very much. I think that I was asked to really put together some concepts, very briefly, that will jump start or kick start a discussion for later on rather than giving you the definitive answers to any questions. By this time of the morning, I think you've heard

almost all of the things that I'm going to say in my slide set anyway or seen most of these slides, so we'll keep it brief.

So why are we here? Do we really need regulatory criteria for the approval of agents that treat brain metastases? Actually I'm going to go back for a second just to point out the fact that I underlined this comment, that this is to talk about issues in conducting clinical trials for patients with brain metastases rather than treating brain metastases.

I think that's really super important as we talk about the two compartments and the idea of competing risks of death or morbidities from cancer, being the extracranial disease versus the intracranial disease, including leptomeningeal disease. So we have multiple challenges that are all interacting with each other.

So back to why we're here, yes, it would appear, based on the number and nature of the people in this group, that we do need some regulatory criteria for the development and the

approval of agents that treat patients with brain metastases, and it has to be put into context as I just said.

How do we define these needs and how do we define the regulatory strategies, which rather complicated challenges? We know from history that the gold standard for all of what we do in cancer patients is of course overall survival and certainly has been traditionally the standard for a criterion for FDA approval of a new agent. Certainly in the days when I was on ODAC, that was really the be-all and end-all, and it was with great trepidation that we ever talked about fuzzy endpoints like progression-free survival and all of the challenges to using those endpoints, but they do have some pros and cons.

We talked already about some of the concepts of looking at intracranial response rates in progression-free survival. And for those of you who had the time and pleasure of looking at Ross Camidge's webcast, it was really quite amazing. I think you'll be hearing more about that later on

today talking about drugs and brain metastases and some interesting concepts about assessing.

There are other endpoints, of course, neurologic quality of life. Patient reported outcomes are also important and maybe harder in some ways and easier in some ways to quantitate. There are indirect criteria but equally important such as patients coming off of steroids.

We've talked very little about the interactions of steroids with some of the endpoints and some of the therapeutic strategies, but for those of us who are more in the immunotherapy world, that's a really critical concept and challenge that has to be addressed uniquely; combination strategies with stereotactic radiosurgery and with neurosurgery and other ways to combine therapeutic strategies, and maybe even in my world, in melanoma, some of the targeted agents with immunotherapies are going to be very important.

Then how can we define other surrogate endpoints that may support accelerated approvals if

we're truly going to look at drug approvals that are uniquely designed for patients with brain metastases? What about the use of concepts like when can you discontinue some of the adjunctive therapies? We haven't talked about therapeutic strategies like bevacizumab as well. Importantly, there are currently no comparators, so we're kind of forging or blazing a new trial here and using approved therapies as benchmarks.

I think you've really heard a lot about the incidence of brain metastases in various solid tumors, but I just want to point out a couple of things. There are patients in whom brain metastases are found at the first presentation of metastatic disease, particularly in melanoma where it may be as high as 20 percent of patients or even more with melanoma. Then of course there is the other cohort, which is at the time of progression on their first or subsequent therapies for metastatic disease.

In melanoma, pretty routinely, every time a patient has the first metastatic disease or first

progression in need of another, we look at the brain. From what I've heard this morning, I think that's going to be more and more true for the two other big diseases that metastasize to the brain; that is lung cancers and breast cancers.

Then of course the concept of looking for escape metastases, how often and what type of scanning should be done in patients with these diseases who appear to be responding to our systemic therapy for disease outside the brain who've never had known disease in the brain. Sometimes you get surprised.

What are some of the biologies of brain metastases? You heard a very elegant explanation from Priscilla Brastianos and as well from my Mike Davies who have really done pioneering work in the field. This is one of my favorite slides from a somewhat older now review by Mike Davies' group where I fixed the captions a little bit, but really sort of speaks to the concepts of when and where some of the mutations or non-mutational changes that may occur, that predispose to or facilitate

the growth of certain clones in the brain that can occur. I'm not going through all the details here, but there are many opportunities for clones to become prone to CNS metastases and thriving in the brain.

You've really heard about this. I don't think we should focus heavily on this slide, and you've heard about lung cancer brain metastases, and you've heard about breast cancer brain metastases, so I don't want to dwell on what you've already heard or will be hearing about more today.

What about clinical trial design today? There's a lot of retrospective literature about the sequencing versus the simultaneous modalities, particularly SRS and systemic therapy for various tumors metastatic to the brain. But with all due respect to my colleague, Dr. Ahluwalia and others, it's really critical to really prospectively study these sequences and these combinations. All of the principles in the first slide must be considered, and I won't regroup that.

The challenges in the imaging are also

important, and you'll be hearing about that in the next speaker's talk. So again, I won't dwell on that, but timing, size, alterations and appearance, peritumoral edema, hemorrhage, new lesions, pseudoprogression, obviously the critical importance of defining the compartments and how you use those data to determine the value of a particular therapeutic intervention.

Then of course the whole problem of radionecrosis from prior SRS and whether you believe that some of our systemic therapies are enhancing that and how can that be addressed and how can it be identified, treated, prevented, and so forth.

These are some of the categories of metastatic disease in the CNS and outside the CNS. It looks like a complicated slide, but this is the true clinical world where each patient's disease really does need to be customized and thought about, and it does take a village. All of these categories are the underlying groups and cohorts that we have to think about in terms of clinical

trial design, as well as in the design of some of the pathways, for example, for the NCCN and ASCO, and so on and so forth. So clinical trial design reflects real decisions and real decisions reflect the clinical trial design.

This is my last slide. I told you I'd keep it brief, and this is just the title and the authorship of -- and the first line kind of snuck in there -- for systemic agents in patients with brain metastases from solid tumors, which is the guideline by the -- and now I know how to pronounce it -- RANO working group. It's a living dynamic group of individuals that are really trying to define this field in primary brain tumors and brain metastases, and happy to be a member of that group that meets every year at ASCO with quite an important output.

So I'll stop there and listen to Dr. Ellingson next. Thank you.

(Applause.)

Presentation - Ben Ellingson

DR. ELLINGSON: Thank you. My name is Ben

Ellingson. I'm a professor of radiology at UCLA, and I've done a lot of work in standardizing brain mets response assessment, particularly radiographic, and radiographic measurement, and how we're going to actually judge these things. Unlike tumors in other parts of the body, which you're all familiar with, serial biopsies are not really possible. They're safe when we talk about CNS metastases. So there are really few pathologically confirmed responses.

We rely heavily on imaging, particularly MRI, but sometimes PET imaging, for routine clinical monitoring and response assessment for new therapeutics. MRI has exquisite soft tissue contrast, so we can see different aspects of the brain biology. It doesn't use ionizing radiation, unlike CT and other modalities. And really, there's a variety of different flavors that we can use to evaluate anatomy and physiology, so it makes it particularly attractive.

Now, When we talk about response assessment, and again, particularly radiographic response

assessment, there are really two components that we have to consider. The first part is image acquisition. That typically requires T2 weighted or T2-weighted FLAIR scan. What these measures are is really water content within the brain. They're used to identify brain metastases that maybe don't have blood-brain barrier disruption.

The second set of sequences that we consider our pre- and post-contrast T1-weighted images. These are kind of your classic contrast enhancing lesions that we typically see or define emergence of these brain tumors. But really what they do, what they're measuring, is disruption of the blood-brain barrier and gadolinium or your contrast agent leaking into the extravascular space.

The last set of images that are used quite routinely are diffusion and perfusion MRI, and these typically reflect cell density in the case of diffusion and perfusion vascularity within the tumor because we know these tumors tend to be highly vascular.

Now, once we have that information, that's

only one piece of the puzzle, the other part of the puzzle really is quantifying disease burden and interpreting that in terms of its clinical meaning. In terms of disease quantification, we do size measurements, we do quantification, maybe total lesion volume; and then in response to determination, this is the thresholds that we set up that's really a meaningful change, and these make up our critical endpoints.

About a month ago, there was an article in the New York Times that talked about The Joy of Standards. It was an opinion article, and it really talked a lot about how, although very boring and not talked about enough, life is a lot easier when you have standards and you can plug your devices into any outlet.

We really need to make these standards to make meaningful progress. There are standards all around us, electrical outlets and gasoline pumps. Even cinderblocks that make up structures have standards that they comply with. The modern laptop, for example, has over 250 standards that

they comply with.

Many of these standards, the vast majority of them, are really voluntary consensus recommendations much like we've done or are going to do in this field. So really building and improving upon a set of standards, it may not be the greatest set of tools we have, but building upon those is really the path to tangible progress, so having a concrete baseline in which to build is critical.

Our first attempt at standardizing brain tumor imaging protocol came in 2015, and it was really the result of a workshop much like this. This was designed for primary brain tumor clinical trials, primarily high-grade gliomas like glioblastoma. It was designed after a lot of meetings, a lot of phone calls, and a lot of people invested a lot of time in this.

It was designed to be synergistic and used in cooperative group settings and allowed for use in community and academic medical centers, so there's a lot of flexibility. It was supposed to

be compatible with most clinical MRI protocols, so it wasn't burdensome to the different institutions and the different medical facilities that are going to be conducting these trials.

I already touched upon this, but really the minimum standards that we came up with were pre- and post-contrast, T1-weighted images to look at contrast enhancing lesions, and we wanted these to be volumetric. Typically, we acquire in the brain prior to this thick slices, 2-dimensional axial slices, and then we try to make some measurements on those.

What we required is 1 to 1 and a half millimeter isotropic, meaning equal in all sizes, resolution so we can really accurately measure these lesions. The second aspect was 2-dimensional T2 or FLAIR imaging. I mentioned this before. This is to look at non-enhancing disease or cerebral edema.

We were pushing the limits of the manufacturer saying we want thinner slices so we can really see the true extent of the disease. The

other aspect of these consensus protocols was really requiring diffusion MRI to be acquired in addition to these anatomic scans. That was for a variety of reasons, one being to rule out stroke, and the other to look at cell density and what's going on within the tumor.

There are unique challenges associated with brain mets that are not necessarily true for high-grade gliomas. Thin 3D images are absolutely critical to accurately quantify the extent of disease. So unlike high-grade gliomas that may have one or even a few target lesions, there can be many target lesions or many small lesions throughout the brain in patients with brain mets. So there's a requirement for high resolution 3D imaging of the brain and spine if we're looking at leptomeningeal spread.

There's also a need for better contrast to noise, and some anecdotal evidence or some evidence from the literature suggests that in order to detect really small lesions, we may want to move from our traditional standardized gradient echo to

a more spin echo based approach, which again is not standardized across vendors, so it could be particularly challenging in a multicenter, multisite study, but there seems to be evidence that that might provide additional value. Again, this can be extra cost to the institutions to get these types of sequences; it's not standardized. And there's a big difference between high field and low-field scanners.

In general, 3D turbo spin echo seems to be the best to delineate these lesions followed by 3D gradient echo, which is part of the standardized brain tumor protocol to date, followed by 2-dimensional turbo spin echo, which is the previous standard of care acquisition.

In building upon the standards that we already established a few years back, Tim Kauffman at the Mayo Clinic, and in myself playing a small part, were leading this effort to try to build upon that protocol and integrate some of the recommendations for the RANO brain met recommendations in order to be compliant with those

standards as well.

Really, the two main pieces -- and again, this is still a work in progress and we're setting up meetings to try to hammer this out, but the two pieces that are added to this are dynamic susceptibility contrast perfusion MRI, so look at vasculature within these lesions.

This is particularly important when we look at SRS and other things that we've alluded to before that may disrupt the blood-brain barrier as a result of damaging the vasculature, as well a delayed contrast-enhanced T1-weighted scan using the turbo spin echo to see the added value of this additional sequence; again, building upon what we have previously done.

The second part of response assessment or radiographic response assessment is the interpretation. Now that you have these measurements or you have these images, what do you do with them? At about the same time, in 2015, Nancy Lin and a variety of others in the RANO group came up with a RANO criteria for brain mets,

specifically for brain mets.

This really focuses only on parenchymal mets only, so not leptomeningeal spread or anything like that. It was based on RECIST 1.1. It looks at the longest single diameter of contrast-enhancing lesions. They have to be measurable disease, which again is a criteria of traditional RANO and other response assessment criteria as well, greater than 1 centimeter with relatively thin slices. You're not supposed to include the cystic, or any resection cavity, or any tumor that's taken out. The idea is to sum up 5 target lesions if there's more than that, then you only look at the 5 largest lesions, and you add them up as a sum total lesion burden.

You then use this rubric. And I'm not going to go into a lot of detail, but the idea is very similar. If you're familiar with RECIST or you're familiar with RANO. A complete response is complete elimination of all target lesions or shrinkage to the point they disappear. Non-target lesions are gone. The patients aren't on any

steroids, and clinically they're either neurologically stable or they're actually improved.

Partial response is a little bit lower bar, so that's more than 30 percent decrease in the sum of those longest diameter measurements. They may have stable or improved non-target lesions, and, again, with corticosteroids, they have to be stable or decreasing, and the same thing with neurological status.

Progressive disease is defined as more than 20 percent increase in those lesions or any of these things that are on the list here. You may have unequivocal progressive disease in non-target lesions. You may see new lesions become present or they may have declining neurological status, which isn't realizable on radiographic scans.

There are some special considerations, and I mentioned a couple of those before. Immunotherapies and SRS, there's a need to verify progressive disease. So just because the lesion gets bigger doesn't necessarily mean the drug isn't working. There are a couple of ways to mitigate,

but, again, this is still a work in progress. There's the iRANO criteria that focuses mostly on high-grade gliomas, mostly in the upfront setting. But the idea behind that is to give approximately a 6-month window or allow for evaluation period in order to see what's going on with the lesion. If it's getting bigger and the patient is stable, let's just keep watching and see what happens.

There's another strategy that kind of builds on the iRANO and the RANO criteria that we've developed with Patrick and Tim Cloughesy that we call the modified RANO. The idea there is very similar to iRECIST, where you want confirmed sequential progressive disease events and then go back and back date when that first progressive disease event happened. That way we can mitigate and actually define pseudoprogression and radionecrosis.

Lastly, I just want to touch on some advanced imaging and promises of the near future. I've only talked really about anatomic imaging and to some degree perfusion imaging, but there are a

lot of things on the horizon that can add different aspects to what's going on with an individual patient disease.

There seems to be some evidence that a DSC perfusion imaging provides additional value, so again looking at the vascular components of the enhancing lesion. MR spectroscopy allows you to look at other metabolites within the tumor, and that might be important to understand whether or not the tumor is proliferating rapidly and whether or not the cells are breaking down.

Lastly, PET imaging, there's a wide variety of radionuclearized available, but the most common being FDG PET systemically used, as well as in the brain, we find a lot of value in amino acid PET, so looking at methionine, and phenylalanine, and other neutral amino acids.

Again, there is still this need for standardization and large multicenter data sets to really determine feasibility and the value of both RANO BM and a standardized brain tumor protocol, but there are a lot of efforts ongoing to kind of

set those in place so we have a standard to move forward to evaluate new drugs in CNS mets. Thank you.

(Applause.)

Panel Discussion

DR. WEINSTOCK: Thank you very much to our presenters for those excellent talks to help frame the discussion. I'm going to turn it over to our patient rep for comment.

MR. QUEEN: Well, thanks. It's clear that there's a lot of talented people working on this problem, and I think, as I said earlier, it's solvable. I think I'd be remiss, though, as a patient not to reiterate one point that hasn't really been touched upon. I touched upon it initially in my initial comments.

That is, from the patient perspective, I'm a firm believer in modern medicine on all the things that we're talking about here, but there's another element of being a patient that we've not talked about, and that's an element of hope and what important role

that hope plays in all of this. It gives the patient a will to live, to fight, to find the best doctors, to seek out the best cures.

As a patient, I know from my personal experience, as I said, there was a stable of drugs that were out there that I did not have access to. And what does that do? It completely extinguishes that hope in a patient, and I think it's really important that we keep that in mind as we want to make the latest technology available to the sickest patient pool.

(Applause.)

DR. WEINSTOCK: I think there have been some very interesting and thought provoking questions raised. I'm going to start by touching on the intact blood-brain barrier and how important that is in thinking about drug development in the metastatic space, whether the data that we have so far is convincing enough to maybe think about targets first and then blood-brain barrier penetration next; so wondering if any of our panelists had some thoughts in that regard.

DR. AHLUWALIA: Clearly, I think that's a perennial question that we all struggle with, at least in primary glioblastoma or glioma patients. Some of the efforts that we have done, which definitely we can learn from, is that we have paid -- this is not directly related to brain mets, but to put it in perspective is that we have patients who have an enhancing component of the disease, and we have patients who have a non-enhancing component.

What we have done through the American Brain Tumor Consortium are multiple trials actually looking at the drug penetration in the enhancing component, but also looking at what's the drug concentration in the non-enhancing component. Certainly, if there are drugs which would have a target that can be looked at both in gliomas or in brain mets, I think that would be an easy thing. We do phase zero trials all the time, so I think that would be something to piggy back in learning about the drugs. Obviously, as related to other people on the panel and some stellar docs earlier

on, there are not good mouse models, so I think utilizing some of the patients.

In brain mets, the challenge, it's very difficult to do the same because if someone has brain mets, they have a blood-brain barrier that's broken. So if you're going to resect, you resect that. But to the neurosurgeon and the team, how comfortable they are intersecting a small part of the brain, which may not have an eloquent component, which is next to where the enhancing component is. I think it's easier done in the glioma world than in the brain mets world.

DR. DAVIES: I wanted to follow up on a concept that
Dr. Lin had talked about in terms of some of the subtleties of looking at the clinical data. Again, I've talked about the dabrafenib data, the proof of concept that a drug that couldn't cross the intact blood-brain barrier had activity in patients with established brain metastases. At the same time, we know the most common site of progression in patients who are receiving a dabrafenib is the

development of new brain metastasis.

I think that the idea is that for patients with established brain metastases, even for drugs that don't cross the blood-brain barrier, we may get the proof of concept that a pathway is important in brain metastases with the activity we see, that doesn't exclude the possibility as you discussed, that we might get even better results with drugs that penetrate the blood-brain barrier to a greater degree, or -- and this is one of the things we're going to test in an upcoming trial -- by pushing drugs to higher doses than what's the FDA-approved dose. There's actually a significant experience with this with EGFR inhibitors.

So again, I really do agree with that concept -- not being overly discouraged -- of this idea that you can see CNS escape doesn't mean the drugs can't be effective there. And in the same way, it's also the disappointing fact that some of these drugs that show activity in patients with established brain mets on the other hand didn't

show efficacy in preventing the development of brain metastasis.

So the concept of blood-brain barrier, as you said, may be very important in prevention of brain mets, but I don't think excludes the possibility of activity in established brain mets where the blood-brain barrier has been disrupted.

DR. LIN: Just speaking to our advocate's point -- patient's point, I think the slide that I showed with all the drugs that we know don't go into the brain and there is activity that has been reported, that activity by and large has been reported in either ISTs [ph], or case series, or some sort of little experience that was published after the drug got an indication for the underlying metastatic disease.

Speaking from the patient perspective, that's like incredibly hard to see. There's no data for brain metastasis until the drug's already been through every hoop that there is and managed to get through phase 3 and get an FDA label. I think we just really have to change that. That

timing is just not acceptable timing.

DR. BRASTIANOS: Just to add, for our pharmaceutical collaborators who are here, I think focusing on the target is important, but we shouldn't forget focusing on CNS penetrant compounds also. We certainly see -- Pat Keegan has done some beautiful work where she's shown heterogeneous uptake and established mouse models with multiple brain metastases.

Certainly, we do see response in the brain for agents that we didn't expect responses in the brain, as Dr. Davies and Dr. Lin mentioned, but certainly with an IATA [ph] we should also -- looking at the already established inhibitors in brain metastases patients, we should in parallel be developing agents that do have CNS penetration, too, while we're focusing on the right targets.

DR. MARGOLIN: Yes, I think that's really important because I think even when you talk about this concept where there's tumor, if it's over a certain size or micro size, the integrity of the

blood-brain barrier's loss, there's probably areas of minimal residual disease that are still not getting the drug, and I would think that could be a focus for escape.

DR. WEINSTOCK: So we're going to go to our audience.

DR. ANDREWS: Hi. It's a great discussion, and my tribute to the panel. My name is David Andrews. I'm a career academic neurosurgeon in Philadelphia, and I'm joining my landsman from building 10, Dr. Nuwam [ph] here, to represent neurosurgery. Our forum includes the public and courageous patients like Derrick Queen.

I would frame this disease this way. Brain metastases are the most threatening phase of any cancer and therefore are the highest priority for treatment, either because of potential increased intracranial pressure or actual increased intracranial pressure. We also know that when we treat patients with brain mets, it bifurcates into two separate teams because of the unique physiology and danger of brain mets. So it's usually a

neurologic team that deals with the mets and then the systemic team, who are the medical oncologists that manage the systemic disease. So immediately for patients, often they're dealing with two separate teams.

The third and very obvious thing is we're dealing with a disease in which, still, systemic cancer is treated with radiation, surgery, and chemotherapy, so as a neurosurgeon, I'm going to frame the surgical side of this.

Single mets were sort of immortalized as a surgical operation by Roy Patchell's landmark paper in 1990 where you remove a single met with an improved overall survival. That's carried forward to date, although there's now question when the systemic cancer is now known, we can simply radiate that metastasis.

So what about all oligometastasis? Certainly, if there's one symptomatic met, we as neurosurgeons will take it out; otherwise stereotactic radiosurgery I think is now more the standard of care than whole-brain radiation. I

think that's very strongly supported.

What about a cerebellar metastasis? They're unique in one sense. They're more of a challenge. The posterior fossa is more constrained. I think we have a lower threshold for operating because of concerns of obstruction of the fourth ventricle. But Ray Sawaya, actually at MD Anderson, was the first to point out that when you take out a cerebellar met, you can actually spread the disease, particularly if you do a piecemeal resection.

So that's raised the issue that particularly we have to be more multidisciplinary to consider neoadjuvant radiosurgery first to sterilize tumor cells at resection to minimize the chance of peeled [ph] spread or leptomeningeal spread.

The final couple of issues are the number of metastases and the size of metastases. So again, we're getting into the realm of radiosurgery. Most of us as neurosurgeons practicing radiosurgery are comfortable with radiosurgery for up to 4 metastases. As kind of a quaint vignette, one of

our early international meetings at ISRS in Madrid in 1997 included a Japanese neurosurgeon by the name of Doctor Yamamoto. Back then, the gamma knife was the way to treat brain mets as the mode for radiosurgery.

Well, he would put a frame on, and he would treat up to 30 brain metastases over about two days, which was sort of outlandish. But he was sort of laughed off the podium, but 25 years later, he actually had a prospective randomized trial that actually showed noninferiority of treatment of up to 5 to 10 metastases compared to oligometastases for overall survival in these patients, so that was an important advance.

The latest evolution in radiosurgery is one of single isocenter treatment of multiple metastases within an hour, and quite precisely. So the radiosurgery aspect of management of metastases has become a very important part of our armamentarium.

I'll conclude by actually what Dr. Margolin has stated so well, and all of you have, that this

is a multidisciplinary effort, and I think multidisciplinary clinics should include the neurosurgeon, the radiation oncologist, the neuro-oncologist, the neuropathologist, and the neuroradiologist. It's only together that collectively our wisdom can carry these patients forward. Thank you.

DR. WEN: I wanted to follow up on Ben's talk. When the RANO BM criteria was proposed, the hope was that it would become the standardized response criteria in the field. I wanted to see what the feeling of the panel and the FDA is. Should we use RANO BM for all trials going forward or are there issues that we need to address? Another issue that you may want to comment on is the size, whether the 1 centimeter is required for the trials or whether we can go down to half a centimeter. Thank you.

DR. ELLINGSON: I think the two questions that Patrick asked first was maybe for the FDA, but I can answer it, my opinion, but should RANO BM be used as the response criteria for trials moving

forward and brain mets? The second question was should the size requirements be as large as they are? I think that were your questions. I think Luke brought this up as well.

One of the challenges I think when you have large trials that include mets and systemic disease is the expertise in the person doing the measurements. If you don't have not even diagnostic radiologists but oncology trained neuro-oncology radiologists to do those measurements, at least in gliomas, you can run into pitfalls, and I think that that's something to consider.

One of the things I like about the RANO BM criteria is it piggybacks on RECIST, which people may have, at least in these trials, more experience with. I think if we flop back and forth between two different criteria, one that's a bidirectional measurement, one that's unidirectional, and have different criteria, there's at least a possibility of some competing things. I think maybe something that would allow that to synergize with whatever

the systemic response criteria is and kind of integrate into that would be important.

I think with the second question, it all depends on the acquisition and the timing that you get with respect to the size of the lesions. Traditionally, we've made those lesions the minimum size being 1 centimeter because we relied on suboptimal imaging and what we could reliably measure over and over and over again. So I think it's a valid question, what's the minimum size to get into these studies and whether or not --

MS. SELIG: We have a few people here [inaudible - off mic].

AUDIENCE MEMBER: My name is [indiscernible], biopharma, clinical stage and [indiscernible] and Duke, Mayo Clinic. My father died of a brain metastasis at age 65. My question is actually to Nancy. You show two ALK tyrosine kinase inhibitor difference. Is that simply due to a dose difference with no [indiscernible], and the dose of 600 milligram BID with 250 milligram?

DR. LIN: Greg might actually be the right

person to answer the question since I will go on a limb and talk about lung cancer. It's a little bit of comparing not exactly apples to apples because alectinib even extracranially a better drug than crizotinib, yet we see that effect both in the brain and in the body.

How much of the additional effect that we see in the brain is related to its better blood-brain barrier penetration effects and how much is just that it's a better drug I think the trial can't really sort out. I don't really think it's necessarily a dosing issue, personally. I think it's just in more general terms a better drug.

I do think that the prevention data that I showed you was, to me, one of the more striking data points from that study, really showing that we actually can prevent brain metastases. I think that that to me was one of the most striking findings, that we don't have to be satisfied with simply treating established brain metastases.

MS. SELIG: Great. Go ahead.

AUDIENCE MEMBER: Eric Yonas [ph], MD Anderson. Fantastic speakers and incredible presentations.

MS. SELIG: Can you get a little closer to the microphone?

AUDIENCE MEMBER: Yes. Two questions. One is really looking at the molecular determinants of metastatic progression across diseases versus what the definitions of lethality are within diseases, how much commonality is really across these diseases? If you did an unsupervised clustering, what's actually brain metastasis specific and what's actually disease specific?

The question's important from a standpoint of therapy development. Are we developing a pan-metastasis treatment or are we improving treatments for diseases?

My second question is just a comment from the group on the immune microenvironment. The brain immune microenvironment from a standpoint of its basal state, what do brain metastases do and how should we change our immunotherapy approaches

for these metastases?

MS. SELIG: So we'll take one quick response and two quick comments, and then give our moderators a chance. We'll have time later to get back to some of these questions; otherwise you're going to get no break.

DR. BRASTIANOS: Do you want me to answer the question?

MS. SELIG: One quick answer.

DR. BRASTIANOS: I'll do it first, and then, Mike, you can take the second question. First question, in our work right now, we're looking across diseases, what are the commonalities? In the initial data set of a hundred brain mets across all histologies, CDK pathway seems to be important and PI3 kinase pathway seems to be important.

Many of these could be important drivers of progression in general, but we are seeing that they are very common in brain metastases across the histologies. With our larger data set, we'll be able to answer that more fully, but certainly CDK/PI3 kinase in both our work and Mike Davies'

work is important.

If you want to comment on your work and the immune --

DR. DAVIES: I think what's relevant for both the molecular biology of brain mets and the immunology of brain mets, it's actually clear that the tumor microenvironment impacts these tumors differently than what we see in other sites in the body.

An actual fact, the differences that we saw in melanoma, we actually recapitulate in animal models just by injecting tumors into the brain versus subQ; not a clonal selection, not genetically driven, but epigenetically driven. And there's no reason to think that that is actually specific to melanoma, and we have work going on across other diseases that preliminarily supports that.

MS. SELIG: Great. Last two comments over here.

AUDIENCE MEMBER: Hi. This is an excellent presentation. My name is Jill Mancuso. I'm a

patient advocate and also an individual member of the Metastatic Breast Cancer Alliance. Just briefly, I was diagnosed with advanced breast cancer in 2007 -- and not de novo -- in the lung, then in the brain in 2008. The lung was treated with VATS and then RFA when it recurred, and the brain was treated with craniotomy and IMRT. I haven't had any sign of the disease since then.

My question is, when I got the report, the MRI report, on the brain metastasis, it said that it was a cystic metastasis. I believe that was the word, and I didn't really understand that. I knew what a cyst was, but I didn't understand. I asked the surgeon, and she said that it was -- well, it wasn't a solid.

That was basically the first and the last time I've ever really heard about this. So I'm wondering is any work or anything ever done in the lab to understand what drives either getting a cystic brain metastasis or a solid brain metastases, which I know can occur sometimes in the different cancers that go to the brain; that it

could be maybe 50/50 or maybe it occurs more in one than the other. But I don't know whether there's any work done in the lab to understand what drives this that could eventually lead to maybe differentiating the types of drugs people should get, depending, and also lead to maybe controlling it in the body.

MS. SELIG: I don't know if we can have a quick answer to that or we can just pose that. Is that a quick answer?

DR. DAVIES: I don't think anybody knows the answer to your question.

MS. SELIG: That's what I was afraid of. It's a good point to come back to further subtyping.

Last comment?

MS. COLLYAR: Hi. Deborah Collyar with Patient Advocates and Research, and I really appreciate everyone's comments. It's been good presentations. I wanted to reiterate the important points I think that Kim Margolin brought out about study endpoints, and PFS really is not a good one

for patients in lots of ways. So there are ways I think that we do need to have discussions together about how to get better endpoints.

One point that did not come out that may this afternoon is the design of the clinical trials is actually very important to the patient communities as well. I'll just bring one example, and that's in phase 1's. We want to try to get away from 3 plus 3's if at all possible and consider intra-patient dosing as well, so that's just one example.

MS. SELIG: Hold those thoughts. We have a panel coming up on endpoints and a panel coming up on trial designs after the break. To our moderator, I just want to say we have about 115 people listening and following along on the webcast. This is terrific, the full room here and a lot of people paying attention.

Dr. Weinstock, do you want to have the last couple of thoughts about what you heard, and then we'll go into about a 10-minute break, and we'll start again at 11:15.

Session Recap - Chana Weinstock

DR. WEINSTOCK: Thank you. I think some of the thoughts that occurred to me over the first two sessions, I would encapsulate them as if you design these trials, they will enroll since patients with brain metastases are out there and have previously faced many barriers to trial enrollment, and from the patient perspective, this is vitally important. If you study CNS disease early on, it will inform our ability to select drugs and develop them appropriately.

Then to the last comment, if you collect trial data thoughtfully and via standardized assessment with endpoints that are clinically meaningful and take the patient's perspective into account, then that will help inform our reporting of study results and future patient care.

So I think we heard a lot of very good discussion on some interesting data about genetic divergence of brain metastases, from the primary and how that's been shown by us in really good rapid autopsy studies that have demonstrated this

quite elegantly. Then we talked a little bit about rethinking our assumptions about how to choose drugs in the best way possible to develop in this space and whether blood-brain barrier penetration needs to be the primary means by which we select these drugs.

We talked about moving away from overall survival as possibly the only gold standard endpoint in this setting, and we're going to really touch on that in the afternoon. But as a regulator, endpoints and how we define them is a very important conversation to have, so I think we'll get into that in the afternoon.

Then we talked about standardizing radiographic endpoints to look at how to develop these endpoints thoughtfully and how efforts towards this have started with the RANO assessment criteria. So I think that's very important, and using that going forward will be important as well.

Then just the role of hope in thinking about patients and how we develop these trials with the patients in mind. Like I said, I'm a GU

oncologist. I think if a patient came to me with brain metastases and wanted to know what to expect from some of the approved drugs, I think that would be a difficult conversation to have. But if we design these trials going forward so that there is more data, the conversation could be better informed and hopefully the results are better. I think the melanoma data is astonishing, just that overall survival of 80 percent plus 12 months can give everyone a lot of hope, and hopefully we'll take that going forward.

Thank you. I think it's break time.

MS. SELIG: We will come back at 11:20 to get started right away. Thank you so much to everybody here for an amazing job. This was a terrific first two panels. Thank you.

(Whereupon, at 11:08 a.m., a recess was taken.)

MS. SELIG: Okay. If everyone could take their seats please. I know that was a short break, but you'll all thank me at the end of the day when it's Friday, late afternoon, and you can get where

you need to go. We're going to start now with Session III. The morning was really an opportunity to set the table, and we're now tasking our next set of panels and moderators with really aiming at now what do we do and concrete suggestions for how we move forward as a community on brain mets.

Just the format here, Session III has two parts. The first part happens before lunch. The second part happens after lunch. Each part is kicked off by a very brief 10-minute talk from an FDA colleagues who's going to set the stage for that panel, and each panel, again, is moderated by a clinician and an FDA colleague.

So with that, I'm going to turn it over to Dr. Anders and Dr. Prowell, and to Dr. Kluetz for the first talk.

Session III

DR. PROWELL: Good morning. It's such a pleasure to be here this morning. We've already had such a rich conversation. The title of our session is Clinical Benefit in Patients with Brain Metastases, and we're going to start by hearing

Dr. Kluetz talk about regulatory definition of clinical benefit, and we'll follow that with a panel presentation.

Presentation - Paul Kluetz

DR. KLUETZ: Thank you very much. My name is Paul Kluetz. I'm a medical oncologist within the Oncology Center of Excellence and also a genital urinary specialist. So it's interesting, again, to span the histologic diseases for this brain metastasis symposium. Today I'm going to talk a little bit about clinical benefit and how we look at clinical benefit, and the fact that it isn't just the primary efficacy endpoint; that it's a constellation of things, and there's multiple facets of this concept.

I think everyone knows that in the United States, in order to market a drug, you need to have the drug approved through one of two pathways. There's a traditional approval pathway and an accelerated approval pathway. I think probably in the clinical trial design section of today, it will really talk about how it comes down to the primary

endpoint of the clinical trial. What are you able to show in an adequate well-controlled trial, that you either prolong life, you create a better life for the patient, or you have an established surrogate endpoint effect that's large enough to predict a downstream direct clinical benefit.

An accelerated approval, we use surrogate endpoints that are, quote, "reasonably likely to predict clinical benefit." So these are endpoints that aren't directly measuring clinical benefits themselves, but they intend to predict a downstream benefit in how patients feel or function, and because there's some residual uncertainty regarding this endpoint, postmarketing clinical trials are typically done to verify that benefit. And in oncology, that's typically been response rate, durable response rate in single-arm trials.

When I think about an efficacy endpoint, I think about it in three buckets. I think about what is being measured, I think about how accurately is it being measured, and I think about how much of an effect has been demonstrated in a

trial. What is being measured is actually the primary endpoint or the efficacy endpoint; what are you actually measuring? Again, direct benefit measures survival or how someone feels or functions.

Symptom or functional benefits are considered more meaningful, however, how accurately is something being measured also needs to be taken into consideration. What is the accuracy of the assay that you're using? How susceptible is this endpoint to bias? How accurate is the timing of the event if it's a time-to-event endpoint?

Finally, if there's a very large magnitude of benefit, that can overcome some of the limitations of an endpoint. Conversely, if there's a very small benefit, even in survival, you may wonder whether that risk-benefit is reasonable.

To demonstrate this idea of how something's measured and how important it is to understand the measurement characteristics, we'll use survival all the way through presenting more of the procedures as an idea of when you have more interpretation or

subjectivity in your assay or in your endpoint, it can lead to more variability in the measure, and it can actually increase your risk for bias. So survival has the lowest potential for bias. Why? Because there really is no interpretation required. We know the event time to the day, and therefore it's a very strong endpoint.

Progression-free survival in measurable tumors, standard RECIST type of progression-free survival is also pretty objective and relatively easy to measure. As a prostate cancer doc, we have a challenge with progression-free survival, and I think it's very similar to the challenge that you have within this community, which is that this is not a very easy to measure lesion. Ninety percent of prostate cancer metastases are to the bone, and if anyone's read a bone scan, they know that it's not quite as easy to interpret as a CT scan.

So now we have two additional lesions that a nuclear medicine doc needs to understand is this progression or not, so a lot more interpretation there.

Finally, this idea of preventing morbid procedures or preventing or delaying the supportive care medications, again, germane to what you do with steroids, this is an important endpoint. Clinically, it's pretty meaningful, but there's a lot of subjectivity in the decision of a physician whether or not to undergo a procedure or whether or not to give a supportive care med.

I guess what I'm trying to say is there's no free lunch, obviously, with an endpoint. There are pluses and there are minuses for each of these types of endpoints, and we just need to understand what the strengths and limitations are.

With overall survival, it's a direct measure of clinical benefit. It's a strong clinical outcome. As I mentioned, it has the lowest potential for bias, but there are feasibility problems with overall survival. As we all know, there's crossover in trials. If it's a very rare disease, it's hard to get a randomized set of patients, et cetera.

Tumor endpoints are interesting because

there's a little bit of controversy. Is this a direct clinical benefit or is it a surrogate endpoint? We've gone back and forth about this. If you look at our most recent clinical benefit guidance, we call it clinical benefit as well as a surrogate because it is a little bit of both. While it's not a direct measure of clinical benefit, it is a direct measure of the disease. You're directly looking at the tumor. So it's a challenging one. There's a little bit of a plus or minus there.

It does have a relatively low risk for bias, it's an objective measure, and it's imminently feasible, so this is an endpoint that we use very commonly in oncology, not surprisingly.

Clinical outcomes, patient-reported outcomes, are one type, but there's also now potentially wearable devices and other digital health types of applications and are directly measuring how someone feels or functions, so their symptom or functional outcome measures. They are pretty feasible, although there can be some

operational challenges for those in industry that there are well aware of and making sure their completion rate is high for patient-reported outcomes, et cetera.

Again, with the risk for bias, it's a little bit of a plus minus. Minus, there is subjectivity, and there's going to be some variability in these PRO instruments. But then again, there's no other assay currently that can measure how you are feeling, so it's kind of what we have.

Finally, this idea of clinical outcomes as health care utilization, reducing health care utilization or preventing something like a cystectomy in bladder cancer, which is a very morbid procedure, has a very big clinical outcome component to it. It is feasible as a measure, however, there is this issue of bias with respect to what is the trigger to undergo this procedure.

So I really want to bring home the fact that when we look at clinical benefit, that was efficacy. But clinical benefit, whether we approve a drug or not, efficacy is only one component. It

has to be done in an acceptable safety profile, and then there's the clinical context. The clinical context has to do with the rarity of the disease. The clinical context has to do with the unmet need, the available therapies, and many different things.

I'm going to end with the idea of response rate, not being response rate, not being response rate. If there's a 30 percent response rate, it can be mean very different things in two different kinds of tumors.

Here's a cross-sectional CT scan of the pelvis, and you can see that a 2.2 centimeter pelvic lymph node has been reduced by more than 50 percent. That's a RECIST response, but it is quite uncertain whether or not this would lead to downstream benefit.

Conversely, where the tumors are located is obviously very important. Here we have two areas of skin disease that are quite disfiguring and likely to be quite symptomatic. You have basal Cell carcinoma and CTCL, cutaneous T-cell lymphoma. Both of these drugs were granted approval based on

a response rate with the idea that there's such a high likelihood of obviously cosmetic improvement and potentially symptomatic improvement. Now, would we like sponsors to directly measure those symptoms and other kinds of improvements? Yes, and we are seeing that more often.

To give you an example of this totality of data approach and that we shouldn't rely on one endpoint, especially where there's some uncertainty surrounding its measure, for instance, response in the brain tumor, COUGAR 302 was a trial done that was the second approved indication for abiraterone in prostate cancer.

As I said, prostate cancer's measure for tumor measures, progression free survival, there's a lot of uncertainty in that because it was two new bone lesions. It was a very kind of complicated algorithm for the assay. It wasn't our typical PFS, so it was really considered kind of an unestablished surrogate endpoint at the time.

The trial showed a statistically significant improvement in the delay in this radiographic

progression with a nonsignificant trend for OS. So we had one primary endpoint, which was a kind of an unestablished surrogate, and if they had not measured anything else, they may have gotten an accelerated approval rather than a regular approval.

But look how they designed this trial. There was a delay in the time to first opiate use. There was a delay in the time to cytotoxic chemotherapy, which had a more safety profile in that agent. Time to patient-reported pain was delayed. Time to ECOG performance status was delayed, performance decline, and there was a very favorable safety profile.

So in the totality of data, this was given a regular approval. And I just want to leave you with the fact that you should make sure that you paint a picture of your therapy that you're trying to show is clinically beneficial to patients using more than one endpoint.

What does this mean for what we're doing today? I think brain metastases has some

similarities I guess to this prostate cancer example. The tumor location is obviously very important in this particular situation. We've already heard, and we will continue to hear, that the functional and symptomatic declines that you can see in these either primary brain tumors or metastases are large.

So location, depth of response, duration of response are taken into account. I think there's plenty of clinical outcomes that can be measured in this disease: survival, obviously cognitive and physical function, pain, ability to carry out activities, walking, et cetera. And then this idea of events, treatment related events or delaying healthcare utilization or preventing healthcare utilization that has its own morbidity is important.

We talked about steroids. Could you delay or prevent cranial radiation; could you delay or prevent pain meds like opiates; and of course seizures are a big problem, and can you delay or prevent those.

So my take-home message should be, I think for all you to take home, is that there's no perfect efficacy endpoint. It's always going to be a balance between meaningfulness and risk for bias and feasibility. I think all available data should be used, and you should be thinking about that up front in your trial design because we need to determine clinical benefit based on a totality approach, especially in diseases that are hard to quantify.

Radiographic response rate is not the same across diseases. We have approved drugs based on the endpoint because the location was so important, and I think that is consistent with where these tumors are located in the brain tumor situation.

I think technology is really improving our ability to do a better job with functional and symptom measurements, whether that's electronically captured patient-reported outcomes, whether that's wearable devices, or whether that's an iPad type of cognitive function assay.

I've left you with a slide also that it has

some common terminology that I won't go over, but we have our own language, and if we can all stick to similar language in our clinical trial design and our publications, it would do a service to everyone. So thank you for your attention.

(Applause.)

Panel Discussion

DR. ANDERS: Excellent. Well, thank you for that fantastic framework as we move into the panel discussion today. We had a fascinating exchange and call as we were preparing for our session today amongst the members, and I'm looking forward to what each of the members has to say based on the varying backgrounds and complementary expertise.

Our charge was to discuss the design of endpoint framework for CNS metastasis, and as we considered this, we realized before we discussed endpoints, we really needed to go back to what our individual goals were for the many different scenarios for trials designed for CNS metastasis studies, the phase of the study, whether or not it was early phase, phase 1, or registrational

phase 3; whether or not the intervention was local or systemic or a neurocognitive protectant, just to name a few.

I think I'll start with Terri Armstrong here at the NCI, just introductions and thoughts.

DR. ARMSTRONG: Well, thanks so much. I appreciate the opportunity to be here. I head up the outcome section in the neuro-oncology branch, and I've learned a lot since being here. I think a couple of things that have framed my thoughts from earlier, this idea of maintaining hope and this idea of access that we don't want to lose track of as we talk about the nitty-gritty of the outcomes that are key messages that, Mr. Queen shared with us.

I think also, importantly, we heard from Dr. Brastianos on the differences in the metastasis in terms of what the mutational burden and load is, and those compared to other parts of the body and the significance of that as we start to plan trials; and from Dr. Margolin about understanding that patients come to this from different places;

20 percent of the time, a diagnosis, if it's at the end stage of disease and this idea of escape metastasis and how do we monitor for that. I think typically we find those when patients are symptomatic, and then how does that then impact the outcome of patients if we're waiting for that.

My personal thoughts are to remember that the brain is not disassociated from the body, at least for most of us, and most of these patients are going to have disease in their brain and their bodies, so we don't want to lose sight of the importance of those two. And the work that we know from people like Ethan Basch, that if we can improve symptoms, we can improve survival and that we need to understand that, and focus on that, and measure that in our trials.

These ideas may influence our ideas about clinical outcomes assessment going forward, but I think rationally we have to identify a small subset of things that we can measure, including how the patient functions that I think will be integral to understanding the benefit of therapy going forward

and introducing those early in trial. Thank you.

MS. ENGFER-TRIEBENBACH: Good morning. My name is Shelly Engfer-Triebenbach, and I have a little bit of laryngitis, so bear with me. I'm coming to you as a patient advocate from Minnesota. I was so excited to see rain yesterday as opposed to snow, that we've seen in the last six months.

(Laughter.)

MS. ENGFER-TRIEBENBACH: I am a stage 4 lung cancer survivor, activist, patient advocate, whatever you want to call me. My experience with brain mets started after 9 months on crizotinib. I knew as a patient that it did not cross the blood-brain barrier, and that information was given to me by other patients who had been on this drug prior to me. So that patient-to-patient communication is so important and should be a part of any type of clinical trial.

I have asked and tried to get this going, but so far it has not happened because I know the HIPAA and blah, blah, blah.

But anyway, patients do talk, and because of that,

my brain mets were found when I was asymptomatic because I more or less demanded a brain scan after 6 months, lo and behold, I had 7 brain mets.

During this time, alectinib and brigatinib both were on a clinical trial, so after talking to Dr. Camidge and Dr. Shah [ph] about options and availabilities, I decided to go on brigatinib and was on it for 28 months, and it was wonderful. It did not have an exclusion, obviously, for brain mets because I came into it with 7, so I know not of what my esteemed patient advocate before me spoke. I was fortunate that they accepted patients with brain metastases.

I had a great run on that 28 months. I wasn't disease-free all the time, but it started developing the last 6 months. We were slowly watching it grow, and if that isn't something, sitting by and waiting until your next scan to see, oh, how much has it grown this time, and what will we do, and different things like that.

The next option that I went to was a clinical trial specifically designed for brain

mets. In fact, you had to have brain mets to get into this trial. I now am seeing Dr. Shah [ph] at Mass General. Even the lorlatinib drug has been approved, my arm of the trial still continues, as they want to get more information about this particular drug and its ability to control brain mets.

There is one pesky brain met that, unfortunately, it has not controlled in my brain. I had SRS last May and so far so good. Everything has been stable to this point, but I continue on in the lorlatinib trial. That goes without saying about the different types of side effects you can have from the lorlatinib drug, but I am fortunately not one of those patients that experiences that.

I notice on my bio -- I forgot to mention my wonderfully supportive family. I have a great husband and two children, and they were 10 years old and 7 years old when I was diagnosed, so they've been through the gamut with me with scans and ups and downs, and they love to meet the doctors and oncologists that I encounter and get to

see.

Talking about what you were saying about hope, seeing all these people coming together from such different entities, that's what gives patients hope because you guys care about this, and it's important to you as well, so thank you.

(Applause.)

DR. KALIDAS: Hello. I'm Chitkala Kalidas. I lead the global regulatory affairs organization for oncology and in vitro diagnostics at Bayer. First off, I'd like to thank the FDA as well as the National Brain Tumor Society for bringing so many multiple stakeholders together today to address this very important issue in oncology, so thank you very much.

Being in drug development and in regulatory affairs in particular, I'm used to the drug development process allowing for the study of special populations and vulnerable populations. Examples would be the pediatric population and also understanding how a drug works in patients with renal insufficiency or hepatic insufficiency.

So this enables a drug to be used in a safe manner so that the patients that this drug is targeted for can derive benefit from the drug. I see the discussion today as a natural progression of that. Oncology is all about an unmet medical need, and the patient population that we are talking about has a very high unmet medical need.

Today's discussion, in conjunction with the draft guidance that the FDA has just very recently issued on the cancer clinical trial eligibility criteria for CNS mets, I think is very helpful, especially for sponsors to have a very thoughtful and informed discussion with the FDA on early clinical trials as well as registrational trials. So I'm really looking forward to this discussion on the endpoints and how to bring this forward.

DR. LEVY: I'm Ben Levy. I'm a thoracic medical oncologist from Johns Hopkins primarily based out of Sibley Memorial Hospital. I'm humbled to be on this esteemed faculty and panel, and perhaps more humbled by the complexity of the topic of really trying to tease out how we manage

patients and how we create endpoints specifically for patients with brain metastases.

I can give you my comments through the prism of being a lung cancer doctor for the past 10 to 15 years. There's a lot of complexity with therapies that we give with our patients in lung cancer. We have patients like Shelly who received drugs that have a very high chance of getting into the brain and eliciting responses in the brain, and it's really changed the way that we think about treating the brain.

These genotype directed therapies like alectinib, or brigatanib, or osimertinib, there's a high chance that they can get in, and it has, again, altered the way that we think about treating these patients. Then we have, of course, other drugs like immunotherapy, which have created these fascinating tales of the curve, but we still remain unclear about what chances these drugs really have of getting into the brain and eliciting responses in the brain.

So we have such divergent therapies within

lung cancer, and I think that really leads to the discussion of how do we create endpoints for trials. This has been pitched forth by RANO and published recently, is that perhaps endpoints have to be designed based on how likely we think the drugs are going to get into the brain, and that can be challenging because oftentimes we don't have a lot of data on this.

The last thing I'll say is just in terms of quality of life, which I think we all know is so important for our patients, I'm all for looking at not only overall survival, as was discussed in the nice talk at the beginning, but putting that in the context of tolerability of the drug but also quality of life.

I'll say as a clinician, as much as we're in favor of this, it's extremely hard to capture at times. And how to tease out quality of life related to neurocognitive problems versus quality of life overall for their cancer is exceptionally challenging, and it's something that I think we'll have to think through as we begin to have more of a

discussion about this.

DR. WEFEL: Hello. My name is Jeff Wefel. I'm a neuropsychologist at MD Anderson Cancer Center, and I have focused a lot of time and effort on trying to make cognitive endpoints in clinical trials feasible and accessible to multinational clinical trial settings and have been fortunate to work with a lot of really motivated and intelligent investigators to share this aspect of clinical trials with them.

To the benefit of patients, I think we've changed standard of care a couple of times and that we hope to do that a couple more times, of course, in the space of cognition as it contributes to the disease experience that patients have.

So I think this is a really compelling and exciting session that maybe we can hammer out some standardization around clinical outcome assessments for this space as well, as we tried to do in the glioma space just a couple of years ago through these same sort of meetings and mechanisms. So I'm looking forward to this, and I appreciate the

invitation to be here.

DR. YANG: Hi. My name's Arvin Yang. I'm the development lead for our melanoma and are genital urinary cancers at BMS. I'm actually representing BMS on behalf of our broad development program that we have across multiple tumor types, including actually those that are primary within CNS, including GBMs and so forth.

From the standpoint of -- actually I wanted to make probably a couple of different points. First, I'm privileged actually for the opportunity to see the union of all these different groups that are coming together.

I think it's been highlighted earlier, but it highlights the unmet need and the urgency in regards to what's actually becoming probably more of an urgency or an emergency in relationship to this disease area, because as we control this disease more extracranially, you'll see -- I think melanoma was highlighted as one example -- that this will become more and more of a higher percentile or frequency in relationship to those

patients that are being impacted specifically by the intracranial disease.

So I think actually the focus hopefully today will be about a framework because from a development perspective, at least my personal lens, how can we establish what's the most clinically meaningful endpoint in such a way that we can meet the needs of different stakeholders, first and foremost being obviously the patient?

So what's most meaningful to the patient, but then you have additional stakeholders at hand, including regulators, including payers, and otherwise, that have perhaps potentially different thresholds in relationship to understanding what would be an acceptable endpoint for them.

At a minimum, if we can understand actually how to establish that framework, to establish that the surrogate is acceptable as an endpoint that could lead to ultimately approval and access to the patients, I think that will be a critical landmark that we could potentially try to achieve today.

Two things, actually, just as an aside that

through the morning discussion for me has emerged as actually quite impactful, are some of the points mentioned earlier in regards to that even in the screening of patients, there's a tendency not to screen them in order to preserve options.

I think that's actually a critical element that we have to think carefully about, but it's in the context of the full extent of drug development whereby there are elements in regards to the benefit-risk, and the safety, and the tolerability that come into play, but we need to probably think more carefully about how can we effectively do that and have patients actually capable or able to access these experimental regimens, but in a way that doesn't limit then the potential to uncover the true activity of those regimens.

The other actually novel point I'll just mention, we've probably not directly pointed out is there something biologically distinct in regards to the CNS mets in a way that perhaps we could then identify tumor-specific or region-specific endpoints that may then be a novel endpoint by

which we could then move forward in a more rapid fashion, because we have to think about it potentially from a positive perspective, that if the intracranial disease is so unique, is there some way that we can actually provide some incentive, or otherwise, for development in that sphere and potentially through some type of surrogate? So let me stop there.

DR. ANDERS: Excellent. I appreciate everybody's comments from the different viewpoints. As I'm sitting here thinking about all the different things we've heard, there are a lot of topics to cover. But I thought we could start by really thinking about endpoints more from an early-phase development perspective and then a later phase development perspective.

This comment that you brought up, Arvin, the concept of a surrogate, which I almost hesitate to say because I don't know that we have a great or perfect surrogate, but I'd be curious to hear what the panel members have to say about how we should be approaching endpoints in the early phase, first

in man, first in human, as opposed to a later stage when we're really thinking about registrational strategies; and this concept we heard of earlier and when we believe there is a signal that is appropriate to move forward and when we believe the signal is not appropriate to move forward.

Anyone want to take that? Anyone from the audience?

DR. YANG: I guess I can probably start the conversation.

DR. ANDERS: Sure.

DR. YANG: Hopefully there will be more to be added. Obviously, naturally within early development in regards to a drug, it's always a question of understanding the signal or proof of concept related also to this toxicity and safety profile. Just by way of example -- and this may be more of a late-stage example, but I think it's relevant -- is from the standpoint, even before the guidance came out recently, in relationship to the type of patients that could be incorporated into clinical trials.

I'll give you a history lesson in relationship to even Yervoy and Opdivo development. The initial Yervoy phase 3 trials, they did not include patients that incorporated brain mets, even those that were treated, because there was the potential for questions in relationship to the safety aspects. But also as you choose patients or put criteria in order to reveal the potential benefits, you don't potentially want a scenario where there could be factors that blunt that ability to detect that activity.

So there's that balance in relationship to as you do the early drug development, is there a scenario whereby you have risk in relationship to not determining the signal because of the poor prognosis and so forth.

The history lesson is this, though. As we then developed Opdivo, we did actually incorporate patients that had previously treated brain mets. We moved from not including them at all to then actually including those that had stable brain mets in a way because we understood then that there were

some level of activity. We could then reveal the activity of the agent itself without potentially -- including a broader population.

So there was a natural evolution I think is the point that I'm trying to make here. So in the early space, there's probably opportunities by which you can still reveal the activity of the molecule itself but not jeopardizing either safety or other efficacy signals that otherwise would be blunted if you include a broad population.

DR. PROWELL: I can make a comment on that. Maybe because we don't have a statistical perspective, I'm realizing here when we're looking at drugs in very early development where the design of the trials is likely to be a single-arm trial. I think that's a place where response is going to be more important because that's interpretable even in the absence of a control arm.

I think in later phase development, and maybe particularly in more refractory patient populations or settings where the prognosis of the disease overall is poor, overall survival becomes

interpretable and also really important because, as Dr. Lin highlighted earlier, the prognosis of patients with brain mets has changed for the better a lot in the last two decades, but nonetheless, the median remains about two years, which is not great, and certainly not great for the very young patients that we often see being diagnosed with this condition.

DR. KLUETZ: I know there's a lot of enthusiasm about clinical outcomes and I think there's rightly a lot of enthusiasm in this setting, but what I would mention to echo Tatiana is that especially in early-phase development, you need to make an upfront decision on whether you're developing a supportive care medication or are you developing an anticancer drug?

We need to make sure that this drug is reducing the tumor. And when we do that through response rate, we can then say, and in addition to clinical benefit to the patient was a functional improvement or a cognitive improvement. It would be a very challenging regulatory action for, say, a

reduction in pain alone with no evidence of antitumor activity.

I can't imagine what the endpoint would be other than a tumor measure in early stage. The question is, back to the previous panel, is it RANO? As a community, you really need to figure out what your response rate is because that is going to drive early development.

DR. LEVY: Just to piggyback that, in terms of the phase 1 experience, again is it wise to have a cohort specifically just of brain metastases patients so you can gain further signal? If you see an early signal with some of these drugs, do you want to open that up and have a cohort specifically for -- if we're looking at response rate and we need a denominator in these early stages, do we want to open it up and have a specific cohort if there is an early signal?

DR. ANDERS: The question at the microphone or comment?

DR. ATKINS: I just wanted to make a little correction to Arvin's statement. The actual early

ipi trials from Medarex actually included patients with treated brain metastases. It was actually the observation in those patients that we didn't see additional brain metastases forming. In some of the patients who had some swelling around their brain metastases, who then underwent surgical resection, there was no viable tumor left there that led to the initial trial of ipilimumab in patients with active brain metastases that Kim Margolin led to.

I think there is value in including patients with treated brain metastases in those early trials once you know you have a drug that has efficacy. At least from my view, if you have no efficacy in the systemic situation -- I can't think of any situation where something would work in the brain that didn't work systemically, but once you establish that the drug works, I think it's reasonable to include patients with treated brain metastases.

Also, I think when it comes to melanoma, I assume all of our patients with metastatic melanoma

have brain metastases. It's just that our MRIs can't show them yet. So if you're treating patients with systemic disease and not seeing recurrence in the brain after you see a response systemically, that means you're having some effect in the brain and it's certainly reasonable to take patients with untreated brain metastases that are asymptomatic and enroll them as well, and actually see whether or not you're actually producing shrinkage.

To me, though, the endpoint that is most relevant, in addition to seeing whether you can actually see shrinkage, is to go back to Kim's statement where you're actually treating patients with brain metastases and not necessarily treating brain metastases. I can think of situations where you've controlled the systemic disease and you have alternative ways of treating the brain disease, where eventually that leads to a better survival for those patients even if the treatment itself doesn't get into the brain. But you wouldn't learn that unless those patients were included on the

clinical trials.

DR. YANG: Michael, just to clarify, you're absolutely accurate, but I was referring to pivotal phase 3's, not the exploratory work.

DR. ATKINS: That was the one that led to the FDA approval.

DR. ANDERS: Thank you. Can you please state your name and affiliation? You can go ahead.

DR. MARGOLIN: Thanks. I didn't come up here to rebut what Mike was saying or thank him. I think it was Dr. Levy Who said something that triggered a thought that I've been having all along, and maybe Mike Davies wants to address this or Priscilla Brastianos.

I think not only is it important to study new drug development in a new agent or strategy development in patients with active brain metastases, but there may be, at least in some diseases and some groups, differences in the biology of all disease in the patients who develop brain metastases. It may be true what Mike just said that everyone with melanoma is a candidate for

brain mets, but there might be other diseases -- we certainly know in some of the subsets of breast and lung cancer -- that have a predisposition based on certain mutations and other biology to go to the brain. So we should include patients but not lump them altogether, and we should have different strata and different cohorts so that we can analyze them separately, I think.

DR. ANDERS: Thank you. Dr. Kumthekar?

DR. KUMTHEKAR: I'm Priya Kumthekar from Northwestern and I have half a voice, so I'm going to whisper my way through my comments. Definitely, over the past 10 years had an evolution -- I'll speak specifically to leptomeningeal metastases -- over how we want to design our early phase versus now we have a registrational phase 3 in the making and hopefully soon to open.

So I really think moving forward when we're looking at the phase 1 studies, it's important to get a depth of info, even if it's a shorter breadth of patients. What I mean by that is we presented an intrathecal herceptin's study just this last

year, and when I look back at that with patients with ommayas [ph] in their brains, we should be getting circulating tumor cells. We should be getting that peripherally in the CSF. We should be getting drug bioavailability and a greater depth.

This is like a lesson learned for me, just looking at that phase 1/phase 2. Really, again, it's not so much the number of patients always for those early phases, it's the depth of info that we gain.

Fast forwarding that to now our phase 3 AngioChem study that we've been working on for years now, I think the key that I've learned there is early involvement of the FDA, early involvement of agency -- and I can speak to my experience that the first time I came on this campus was a meeting for that study, and it was about three years ago. And working on that special protocol agreement over the past couple of years taught me that the agency is very much on our side -- of course the reason we're at this meeting here today -- and wants more drugs developed in this area.

So it's really important to get them early involved so that we can create special protocol agreements, just like we have with that study, so that these drugs are quick hopefully to hit the market if we have successful studies. So looking at those in two different ways with early phase and late phase I think are quite important.

DR. ANDERS: Priya, can you just share you endpoint for your study?

DR. KUMTHEKAR: Sure. With the lack of validated endpoints from an imaging perspective in the phase 3 study, for me it was really important that overall survival was the primary endpoint for exactly the reasons that were outlined in the initial talk.

DR. ARMSTRONG: Can I add a comment?

DR. ANDERS: Absolutely.

DR. ARMSTRONG: I would just add to Priya's comment that in addition to things like circulating DNA, that we consider those outcomes in terms of how the patient is doing. Do we shrink the tumor without improving the person is really important.

And I think related to Dr. Kluetz's comment, that of course we want to see response, but in diseases like LMD, we don't do a good job of measuring that.

So if we don't at least look at those clinical outcomes at the same time, we'll never know what that association is. I think although it wouldn't be the reason it would be approved, I think inclusion of that at that time is really critical in these patient populations.

DR. KUMTHEKAR: And that is a secondary endpoint on our registrational study.

DR. KLUETZ: A response or a clinical outcome?

DR. KUMTHEKAR: There are PROs as well as response.

DR. KLUETZ: I was going to say, just like translational work that was previously brought up, we need to learn as much as we can with this huge phase 3 trial. If you were to do a survival endpoint and not further develop a RANO type of response or something, it would be really a missed opportunity and really understanding your clinical

outcomes.

I hope at some point we'll get to be able to power our clinical outcomes based on previous studies and understanding what that time to deterioration, for instance, would be.

DR. KUMTHEKAR: Well, the hope would be to validate some of these right now unvalidated outcome measures in leptomeningeal disease.

DR. ANDERS: Thank you. Front microphone?

DR. TAWBI: Hussein Tawbi, MD Anderson. Actually, I think from my perspective, I just want to address what Paul is mentioning about the endpoints. I really think what's important for us is to really be pragmatic for this population. This is a population that comes to us, and we have days to manage them and to figure out what we should do for them.

The proximal endpoint should be response. We want to shrink tumor, but we also should be careful about progression and when it happens, and be able to actually adjust our therapy quickly if we need to. We need to have our endpoints allow us

for SRS-ing one or two lesions and continue patients on therapy, and see when they actually progress.

So having objective response rate as the primary endpoints is the proximal one, but then kind of adding that PFS is going to be secondary. And then if they live long enough, neurocognitive assessment is going to be really important for us. I think in that way, we kind of address this in a hierarchical way and a pragmatic way.

I think one of the important issues we really need to address as a group here is as much as it's important to actually identify what response looks like, I'm really interested in the thoughts of the panel on all of our expertise here and what we are going to call progression, and when is that progression going to actually drive our next clinical decision making. When are we going to introduce SRS? And do we have to take those patients off that study and move on to something else or just allow them to continue moving on?

DR. LEVY: I just wanted to add to that.

Again, giving you my thoughts through the prism of a clinician who does research, we've got these wonderful drugs now, targeted agents that can get into the brain. And similar to your comment, we often have patients who have really good disease control in the brain on these agents, but then they progressed systemically, and what do we do with those patients?

I think all of us who do lung cancer are very reluctant to take patients off of these therapies, and I think the trials need to be designed so that we can allow these drugs to continue when we layer in the next line of therapy, if tolerable, so that these patients aren't censored and we can still follow how much disease control there is in the brain with these targeted agents, even in the context and the setting of systemic progression. So I think that's a very good point.

DR. ANDERS: Just thinking about the converse as well, increasingly I've seen clinical trials where if there was intracranial progression,

standard-of-care radiosurgery could be employed and then maintained on the clinical trial with continued systemic disease control; so kind of the converse as well and really thinking these through. In fact, I think earlier it was said best that we're treating the patient with brain metastasis, not the brain metastases themselves.

Back microphone?

DR. ANDREWS: David Andrews, once again, from Philadelphia, Jefferson. I just want to first assert that we all agree that neurologic death is the accepted overall survival endpoint for brain met phase 3 trials. If we all agree that's the case, I may be going off the rails a little bit, but I would just be asking the FDA if they would consider neurologic death for primary intracranial malignancies, particularly since comorbidities associated with treatment or unassociated comorbidities really does dilute the intention-to-treat population. And I'll accept going offline if you want to answer that.

DR. ANDERS: Does anyone want to answer that

one?

DR. PROWELL: I think that talking about primary CNS malignancies is a little outside of the scope of this workshop, and interpreting neuro death is complex. With most of these solid tumors that we're talking about -- I'm a breast oncologist. I didn't introduce myself yet, but I'm Tatiana Prowell, breast oncologist at FDA and Johns Hopkins.

It's pretty rare scenario that we have patients who have only CNS disease and that that remains the case for a very long time. We do see that sometimes in the HER2 positive patients who are treated early stage and then have an isolated CNS relapse. But it's a challenge to think about how to do that outside of a primary CNS tumor setting because the status of the other diseases are equally important in most solid tumors. If you develop fulminant hepatic failure from liver metastases, your intracranial control becomes not relevant.

So, I don't know. Probably others want to

comment on this.

DR. SUL: I just wanted to touch also on the point about the rest of the systemic disease And also going back to the question that Patrick had posed at the last session about what do we think about RANO. I didn't realize I was pronouncing it incorrectly this entire time, but what do we think about the RANO brain mets criteria.

I think that they're actually very well thought out, that people put a lot of thought into trying to figure out how to measure and assess disease. I think one of the issues, though, that potentially relates to that is sort of balancing this idea of how much do we compartmentalize brain mets versus disease in the rest of the body.

That's something that we discuss internally and we struggle with as well. I've had discussions with other clinical reviewers about what's the significance of a small response in the brain if, as Tatiana said, you've got fulminant liver disease that's rapidly progressing.

That also goes back to the second part of

Patrick's question, which was could we actually start to assess or include lesions that are even smaller? I think, again, going back to the purpose of this session and thinking about early versus late, certainly if you're looking for activity, it makes sense to include any size lesion, even a non-measurable disease, if you're looking for activity.

If you're starting to look for what is clinical benefit and what is clinically meaningful, would it make sense -- and this is something I'd be interested in hearing from the panel and the audience about -- would it make sense to maybe try and define a set of clinically meaningful brain lesions?

For instance, when we see patients in clinic, what are the brain lesions that I know I definitely want to get on? So anything that happens in the posterior fossa or in the brain stem, regardless of the size, that's not something you necessarily want to sit around on. Leptomeningeal disease, there's a lot of debate

about whether or not to even treat asymptomatic patients and should this just be done in a palliative fashion.

Then in the hemispheres, the lesions that I am concerned about are the ones in eloquent cortex, the ones that I know patients are symptomatic from, and any lesion that I know is beyond a certain size that I know I want to get right on because I know that even if patients are not symptomatic now, they are going to be imminently symptomatic.

So is there some way that maybe we could define a set of potentially "clinically meaningful," quote/unquote, tumors to follow for response to look for benefit?

DR. LEVY: I think you just did.

(Laughter.)

DR. LEVY: I think you have to create broad categories that are flexible. You mentioned the ones that I look at when patients come in, and we talk about are they symptomatic or not and what's the size and location. I probably learned more from you in that statement than I have from my

radiation oncologists on whether or not they're going to radiate or not. But I think it would be educational to create some broad categories that may set some criteria and understanding that there's such heterogeneity even within those categories.

DR. KLUETZ: I would just mention -- first of all, I think it's a really fascinating idea because as I mentioned in my talk, location is so important. And the reason it's important is because it portends clinical benefit down the road. But it is going to make it a lot more challenging, and in that subjectivity category, it's going to create a lot more, sort of, is that exactly in the cerebellum or is that a little closer? Where is it exactly?

So I think there's going to be a lot more radiographic complexity to bidding those as such, so maybe the consideration should be more of what are you actually trying to measure; cerebellar walking, speech? Again, we keep getting back to these clinical outcomes, and if we can measure

those, that's really what you're getting at and acknowledging how hard it is to measure those, to the point you made.

DR. JUL: I'm just going to counter that really quickly. Neurologists are infamous for localization and for anatomy, so I think we can be somewhat more precise. It's different than trying to identify a specific area in the liver or the lung. There's a large region that's a middle lobe or a lower lobe. But I think in the brain, neurologists and neuro-oncologists are very specific about describing regions, so I think it's possible to do that.

DR. ANDERS: Another way to think about that is based on the NCI guidelines that recently were reported in the fall. The term was lesions that are not in need of immediate therapy. And that really does get at what you're saying, these very worrisome posterior fossa brain stem, the motor cortex lesions. So that may be another way to frame that as opposed to having to think about every single region of the brain.

DR. KLUETZ: It's also got some precedent as far as response and defining a response as the number of CRs, for instance. In this case you'd have, well, we have a response rate, but the response rate in posterior fossa or whatever that particular region is would add value to the response rate itself, I guess.

DR. YANG: Could I ask a question just from the standpoint -- this is wonderful. From a technical perspective, there may be challenges in relationship to identifying essentially these high-risk patients, but I'm trying to bridge this back to ultimately a determination of true clinical benefit.

Maybe, Jeff, I'll put you on the spot, but are there other mechanisms by which we could then make that bridge beyond identifying that high-risk population, but really then being able to establish whatever results you see and actually then support an established surrogate in relationship to whether it be overall survival or otherwise? What are the bins in a way that we could think about?

DR. PROWELL: I wanted to respond to Dr. Sul's comment earlier. As I think about this and trying to define what lesions we would put into a collection of important things, these all make perfect sense clinically to say posterior fossa, motor cortex and whatnot. But it seems to me that what you're really trying to get is measurable, and that is who are the patients that we're going to have to take to either another round of SRS or whole-brain radiotherapy because the lesions they have are problematic enough that we can't afford to wait any longer to see if this drug is going to work?

You can just measure that. You can measure time to local therapy or time to deterioration requiring some sort of local intervention. I wonder if it's more valuable to simply measure that thing, recognizing that there's bias of course, and who actually does get referred for that. But nonetheless, I do think that there's a certain amount of consistency in what prompts us to say to our local therapy colleagues, okay, it's time. We

need your help.

MS. SELIG: Can I just jump in for a second and maybe just ask Shelly to comment on what's important to you as a patient and what you think should be measured about any of this, in terms of how successful is a therapy.

DR. ENGFER-TRIEBENBACH: Obviously, the survival is key, but linked with that survival is your everyday life and your quality of life, which is hand in hand as far as I'm concerned. They interplay with each other so much, so I don't see one outweighing the other as far as a benefit to patients. We want it all.

MS. SELIG: What kinds of things in terms of quality of life? I'm just interested. I think people would like to hear.

DR. ENGFER-TRIEBENBACH: Well for me, avoiding whole-brain radiation is top on my list. I want to be able to -- even though it's not as -- how should I say this? Just from a cognitive standpoint, I don't want to lose anything going into any type of treatment option. I have had the

SRS treatment, but that was down the line several years after my brain mets first appeared. So I guess, yeah, that's of the utmost importance.

DR. ANDERS: Excellent. Fantastic conversation. Why don't we move to Dr. Lin?

DR. LIN: I have two questions. One is a question actually to Paul. We've sort of toyed around with this idea that if you measure let's say 15 symptoms at baseline and over time, you potentially dilute out any signals that you see because everybody has their own constellation, personal constellation of symptoms.

Is there a way that we could come to a little bit of what other areas neurology used? For example, MS you might pick a dominant symptom for that patient and you follow it over time. So every patient actually gets followed a different way, but the endpoint is improvement. I just wonder if there's some way that clinical benefit could get to that point for brain mets.

The second point is really just related back to the issue of CNS-only progression and allowing

SRS. I think we try to be very thoughtful about this in the RANO criteria really distinguishing your primary endpoint determination and how you manage the patient, really keeping the patient in mind, the idea being that if your primary endpoint is progression-free survival and you have a CNS progression event, you get counted to progression-free survival. It goes to the endpoint. There's nothing funny about it, but then you let the patient have SRS, and then you follow how they do over time.

We probably can learn a lot from those. In the TM1 studies where that was allowed, what was found is that when patients had CNS-only progression and they had SRS, they were on median and able to stay on TM1, the disease control, for another 9 months. Remember, these are patients who ordinarily in the past would all have been kicked off the trial. So A, there was clinical benefit to patients, and B, you actually got to document that. So I think that's a really important point.

DR. ANDERS: Excellent points. Why don't we

go to the back of the room?

DR. HELLER: Thank you. I'm Kevin Heller. I work at NextCure, a local biotech. I'm a pediatric oncologist by training, so I will just also say I think this might be a little bit out of the scope but it really speaks to, Wendy, your last question and, Shelly, your response about the relevance of surrogate endpoints in pediatric malignancies.

For example, the goal perhaps ought to be how long we can prolong whole-brain radiation because with children, especially under the age of 5, you really are curtailing their development. It's been written about.

Tom Merchant from St. Jude, who's a radiation oncologist, if we could use as an endpoint -- and I'm really curious to know from our FDA colleagues whether or not there's a way that we could have prolongation prior to starting whole-brain or even focal radiation and is that even practical because that really relies on the patient-reported outcomes. And then certainly if

we get patients through the therapy, they want to have their cognitive state with them.

DR. KLUETZ: I was going to mention, we just did a workshop -- again, there's a lot of parallels in prostate cancer. But we did a workshop about how do we develop drugs in local prostate cancer where the median survival is decades, and the time you get to metastatic disease is a long time, so it was a really challenging space.

What all men said was we would love to not a radical prostatectomy or XRT, which portends sexual dysfunction and urinary dysfunction. The challenge, which was actually something we kind of looked at -- and there's a sample clinical trial on that site too -- was, yes, the delay or the prevention of the RP or XRT was clinically beneficial, but how you trigger that intervention was going to need to be objectively clarified.

How we went about that is there are lots of active surveillance programs out there and when your pathology gets to a certain point, it's just sort of standard of care that that triggers your

intervention, Gleason 7, et cetera. If there's some kind of objective criteria that could be used that would trigger whole-brain radiation therapy and you could integrate that into your decision making that would provide it, that would make it a stronger endpoint.

DR. WEFEL: I might offer an alternative to this, is to remove the surrogacy on this question. You're saying you want to avoid whole-brain radiation therapy because that might cause memory disorder for example, so might the systemically administered therapy.

We see this in this concept of chemo brain, so why not just follow memory? It's how we function, and I think that could be a compelling outcome as opposed to a surrogate that we assume might have an effect on memory, which it doesn't always in everybody.

DR. ANDERS: A very good point.

First microphone?

DR. MARGOLIN: Well, I was just going to make the comment that it sounds like having not

only composite endpoints but multiple parallel points, and then going back and studying how well the endpoints function, would be really critical.

After a few years on ODAC, I realize that when you review the sponsor package, let's say it's a new drug, you're looking for sometimes the difference between drug X and Y doesn't meet, or doesn't quite meet, or barely meets the original discussions with the FDA, but you have several other secondary endpoints. And if everything is going in the same direction, then it's far more compelling than if you have a split.

However, having quantitative endpoints that are readily and accurately saleable would be critical, and I would think that memory might be awfully difficult and very challenging.

DR. WEFEL: So it's not.

DR. MARGOLIN: Oh, good.

(Laughter.)

DR. WEFEL: That's a big reveal. Certainly, this is something that's been done for hundreds of years in the practice of psychology and

neuropsychology. We do have ways to do that.

I think the dilemma had been in the clinical trials space that we don't have neuropsychologists at every single site, so what we've tried to do is to find ways to train healthcare providers to be able to assess this in their patients, kind of like the neuroradiology example where we acquire scans but we may need help processing them or centrally reviewing them in some way to make this disseminable and accessible. It also takes a little bit more time. We don't have an e-version of this yet, so there's some time in the clinic that's required to do this, but it's otherwise tractable.

DR. ANDERS: All right. We have about 10 more minutes before lunch. We have two folks at the microphone. Why don't we start at the back.

DR. ATZBERGER: My name is Alexander Atzberger, and I'm a PhD student at the department of neurosurgery at the Brigham and Women's Hospital in Boston. I have a question about steroids in brain mets trials. Steroids, dexamethasone mainly,

they're probably the most prescribed drug historically for patients with brain mets. They've been prescribed for about half a century, and yet there's very little standardization of regimens. And there's increasing evidence that these drugs -- we know that they have some nasty side effects, but they also have -- probably they interact with immunotherapy in a negative rate. And there was even a study published in Nature this week that said that steroids can have inherent metastasis promoting capacities in breast cancer.

So my question is, do you think that steroid dependency is going to be an increasingly important a surrogate endpoint or study outcome in brain mets trials, especially in the era of immunological treatments?

DR. PROWELL: This is a challenging point in that it sort of is related to what Paul was talking about earlier when we think about criteria for referring people for radiation. I think in order to be able to use these sorts of things as endpoints, you really have to have some algorithm

for how they're applied, and that involves telling clinicians what to do, which is hard. We know this as regulators. We don't regulate practice of medicine, and I can tell you that whenever we do a drug approval and the label is written to a T to be very precise, as soon as that drugs out in the community, people are like, "I don't really like Taxotere; I like taxol," and people start making everything up.

So even within the context of a clinical trial, something like these are the criteria for which you can get steroids and here's which one you have to use and how you have to dose it, are you going to be able to get clinicians participating in that clinical trial to be on board with that? I don't know. And what about the patient who shows up in the ER, and now they have a protocol violation because they got steroids in a way that wasn't allowed or prescribed in the clinical trial?

I think that in order to do that, it's an interesting idea, and there are compelling reasons to want to do it, for the reasons you just said,

but you have to be able to have clinicians who are going to be on board with a protocol telling them how they have to do things that typically we felt were outside the scope of how directive we should be in clinical trials. I don't know how likely that is to work. Clinicians are pretty independent minded. That's what I've discovered.

DR. ATZBERGER: Thank you.

DR. ANDERS: Excellent. First microphone?

DR. EBIANA: Hi. I'm Victoria Ebiana from Merck again. Actually, I completely agree with Dr. Margolin's point, and she actually stole what I was going to ask, so I'm going to turn it back around to the regulators and ask you what your opinion is of the idea of collecting parallel pieces of data such as the radiographic data time to SRS or whole-brain radiation, things like the mini-mental status as an example of cognitive function and just using those as parallel endpoints rather than trying to use one as a surrogate for the other.

Would you accept that as a part of a trial

design and maybe as part of a packaging label, or what do you think about that?

DR. KLUETZ: I gave an example of COUGAR 302, which was the prostate cancer trial that did just that. So yeah, we do this all the time. The question is really much more about being very, very careful with your statistical hierarchy because I have seen many times that someone will put survival up at the very top of a hierarchical secondary endpoint list where there was really no chance they were going to get survival because they were offering crossover, and you were like who was that statistician?

So just be very, very careful about what your hierarchy is to make sure that the thing that you believe is most likely to be significant is on top, and then paint the picture, just as I mentioned. And I think that's absolutely how these trials should be run, with many, many multiple important -- both clinically beneficial as well as super objective, potentially more surrogate endpoints.

DR. PROWELL: I would add to that. I think it shouldn't be only that the thing you can win on should be first. There are obvious reasons to want to do that so that you can be able to look at the other things and for drug developers to be able to try to get your drug approved. But I think at the top of the hierarchy should also be the things that you actually think count as a clinician, and things that, more importantly, that patients think count should be at the top of your list. If you feel like you can't demonstrate those things statistically, then you either need a different trial design or you need a different drug.

DR. KLUETZ: Just to counter that, the things that are often most important and most clinically meaningful are the things that have the most variability in their measure, as I tried to describe before. Therefore, sometimes we're stuck to describe how you're affecting the tumor first, and then you may even have non-statistically significant but directionally important corroborating evidence.

So I totally get what Tatiana says, and in the ideal world, we'd only be getting big effects on cognitive function or big effects on whatever your functional outcome is. But I think the reality is the best assays we have right now are tumor measures, honestly, and then the question is, is that reduction in tumor or that delay in tumor portending clinical benefit through your subsequent endpoints.

So I think you can do it either way. If you have really strong activity in the early phases, you could try to put your clinical benefit endpoint first. But as I said before, a clinical benefit endpoint in the absence of any tumor activity is a supportive care medication, which has a vastly different safety tolerance.

DR. ANDERS: We agree.

MS. SELIG: Dr. Anders, I wonder if you could maybe let Dr. Kalidas speak last, and then we can have you wrap up. If you want to hold your comments for after lunch.

FEMALE VOICE: We don't.

MS. SELIG: Sorry. We're running out of time here, so we need to wrap up. Go ahead.

DR. KALIDAS: I just want to add to the discussion that Tatiana and Paul just had. I think the example that Paul had used from prostate cancer, that would be a great example for later stage development discussion with the FDA for a registration trial.

To inform ourselves about how to come up with all of those tests in the hierarchical testing, we would need to have a more streamlined set of tests, as Tatiana mentioned, maybe response rate to something that we include in the expansion cohort stage, along with the duration of response.

Maybe depending on what tumor type it is and the prevalence of certain type of CNS mets patients, we include other relevant clinical measures so that we can ultimately inform what we include in the registration trial, especially when it comes to hierarchical testing.

So we do need multiple measures in the late-stage trials, but perhaps in the early trials

we have a more streamlined approach with response rate definitely included.

DR. ANDERS: That was actually a fantastic summary.

AUDIENCE MEMBER: I have a very quick question. When Dr. Lin talked about local control and trials that do allow for brain mets and have a progression in the brain, why is that specific to SRS? Why doesn't it include surgery? Especially because when you do surgery, you can get a pathology and you can find out exactly what that is.

FEMALE VOICE: [Inaudible - off mic].

FEMALE VOICE: The comment, I know not everyone could hear, was you definitely could include surgery.

Panel Recap - Carey Anders

DR. ANDERS: Correct. Excellent.

Well, thank you to the panelists for a very rich conversation. I think we've certainly, as we think through the past hour and 15 minutes, have defined a lot of challenges with endpoints. The

endpoints are clearly going to differ by the stage of the study and the type of intervention. These can range from response rate earlier on.

I think we all agree overall survival is our gold standard and really incorporating the totality of the data to incorporate symptom burden along the way. And I think, just has been thematic throughout our morning, hope and access. I think that's certainly being addressed by all the individuals in this room.

I will turn it over to Wendy for, I believe, lunch.

MS. SELIG: Great. Please thank the panel. You guys did a great job.

(Applause.)

MS. SELIG: Joohee, did you have any parting shots on that discussion? Patrick? Nothing?

(No response.)

MS. SELIG: Okay. Food for thought plus food for everything else outside. Thirty minutes for lunch. I know it's brief, but we want to start right up again at 1:00. You should have signed up

for some sort of a sandwich or salad. They should be outside. There are all kinds of places to eat out there, and we'll see you all back here.

(Whereupon, at 12:31 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:59 p.m.)

MS. SELIG: We are going to get started. I know it was a quick lunch break. Thank you all for getting back and getting in your seats. If you're still eating, no problem. We want to stay on time here.

As I mentioned before, this is the second part of Session III, and I'm sure we will circle back around to some of the topics we were discussing in the first panel. We're going to start off with a brief regulatory presentation, Dr. Marur, and we're also really delighted that Dr. Keegan was able to join us today; welcome. You two have about 10 minutes to talk about regulatory challenges, and then the second panel in this session is moderated by Dr. Prowell and that focuses on rethinking trial designs.

I do want to put out there for our industry colleagues in the room, we're going to want to put you on the spot either as part of this discussion or part of Session IV, or both. We really want to

hear from you about something you've heard today that can incentivize and motivate you to move forward in the direction of product development for CNS metastasis; something you haven't heard today that you need to hear in order to be able to do that or something that you heard today that is raising concerns that need to be addressed.

We have our regulatory colleagues in the room. We have our clinician colleagues in the room. We really need to hear from you about what you're going to need in order to be able to move this forward, so just putting it out there.

Dr. Marur and Dr. Keegan, turning it to you. Thank you.

Presentation - Shanthi Marur

DR. MARUR: Good afternoon. My name is Shanthi Marur. I'm a medical officer with the Division of Oncology Products, and Dr. Keegan is here, who is the director of the Division of Oncology Products, too. Together, today we want to go over what are the regulatory challenges with trials that are seeking CNS efficacy claims, and

I'm going to focus pretty much on registrational trials so that we can come to a consensus today or at least stimulate a discussion with these trials.

This is just an overview of the challenges that we come across. Of these, the most challenging is the efficacy endpoints, and then of course all the others that are down the list, such as the eligibility criteria, the CNS imaging, the assessment of CNS lesions, criteria used to assess the CNS response, and then the study design. They all in some ways just tie in with the most burning, challenging issue, which is the efficacy endpoint.

So what is it about the efficacy endpoint that is so challenging for, especially for CNS efficacy claims? The most common ones that come across to us are the CNS-ORR, objective response rate and the duration of response. Then of course, some trials will include CNS-PFS and CNS-OS.

We have to remember that CNS-ORR and duration of response, we will take into consideration, provided the response rate looks -- the magnitude of the effect and the

durability of the response, if it looks great, we are open to putting this in the label. But for an FDA full approval, it has based on the demonstration of clinical benefit, and that is improvement in survival or how the patient feels or functions. ORR and duration of response does not automatically translate into having an improvement in survival or how the patient feels or functions. Please keep that in mind.

The next is the demonstration of effects on survival or quality of life requires randomized trials. The way the current trials are designed, it's not designed in a way that it shows such effects. Let me elaborate on that a little bit more

If you are coming in with the CNS efficacy claim, if this is a randomized trial, often we see that these trials and not stratified by presence or absence of CNS mets or treated or untreated CNS mets, so then when we want to analyze this data, it becomes less and less interpretable. The effects on the tumor in one organ site, one

compartment -- for example, with using CNS-ORR or CNS-PFS, we believe that this may not always confer clinical benefit in a disease that is more systemic and widespread.

Once you've chosen your efficacy endpoint, we then look at who were included in this trial and who were excluded in this trial, and we see that the majority of the patients that are included in the trial are asymptomatic patients, were locally treated, and are stable at study entry, have known neurological dysfunction, and are not on any steroids or any kind of supportive medications.

So we have a group of patients who are already good actors, and we see that patients who are excluded are those who are the untreated symptomatic brain mets patients. Some trials will allow leptomeningeal disease, but most trials do not, and we had this discussion in the sessions in the morning; and not all patients have an assessment of CNS involvement at study entry. Each one of these can be a challenge to us when we interpret the data.

This takes us to the CNS imaging. I'll go to the first point, which is about baseline CNS imaging. It's not done in all patients who get enrolled into the trial. Requiring baseline CNS imaging and documenting the CNS disease, it will limit the patient's eligibility, so many of these patients then turn out to be ineligible for at least a systemic benefit. And we can understand why not everyone has a baseline CNS imaging.

Then comes the question about the on-treatment evaluations. We often see that the CNS imaging assessments are not scheduled at the same frequency as the extracranial disease assessments, whether it's planned or unplanned. Sometimes you have unplanned extracranial disease assessments, and those time points, these patients don't have a CNS imaging disease.

That leads to a high censoring rate for the CNS tumor endpoints, so the patient would have progressed as a result of systemic disease, or had an event because of the systemic disease and comes off the trial. Those patients are censored, and

they have not had another scan at that time point of the CNS imaging.

Next is the assessment of the CNS lesions. I'll go to the second bullet, which is basically there is no agreement upon the selection of the CNS lesions; that's the target lesions. What lesions are you going to use as the target lesions? Have these lesions been previously radiated? If they have been previously radiated, how long ago was there prior radiation to the study entry and was their documented progression of that lesion at the time of study entry? These become major challenges in attributing the treatment effect to the study drug.

I'm going to go to the first bullet, which is the discordance between the investigator assessment and the independent review committee, specifically categorizing the measurable and the non-measurable lesions. What the investigator might think is non-measurable may turn out to be measurable by IRC or vice versa. This high rate of discrepancy in CNS-ORR between investigator an IRC

is more with the CNS rather than for the systemic disease.

Of course the assessment of intracranial response, what criteria do you want to use? It's different across the trials. Every trial that hits our [indiscernible] it's either RECIST or it's RECIST plus RANO, or RANO plus RANO LM, or sometimes it's just RANO LM alone sometimes when they come in for an leptomeningeal indication.

Then comes the study design challenges. Since we're talking about registrational trials, I'm going to focus only on randomized trials. The randomized trials that we see, as I've mentioned before, are not stratified by the presence or absence of brain mets, treated versus untreated brain mets, and we see that there is no justification for the sample size that you want for the CNS efficacy population. I'm specifically talking about that population; no prespecified assumptions of the treatment effects or prespecified analysis plan.

Of course, again, I come back to this issue

of high rate of censoring due to systemic progression. In these patients, what is the clinical benefit of intracranial objective response rate in the face of systemic progression? We keep forgetting that when we come in only for the CNS efficacy.

So with this, I hope we will kick off the discussion. Given that the trials must demonstrate the clinical benefit of treatment, what endpoints do we want to capture for clinical benefit of treatment, focused on an involved site of systemic disease? Who should be included in these trials to seek claims for treatment of patients with CNS metastases?

A discussion on the appropriate criteria. Should it just be RECIST or RECIST plus RANO to characterize the clinically important reduction in intracranial metastases, and then a discussion on adequately designed trials to support claims that are attributable to intracranial overall response rate, independent of the effects on the systemic disease.

With this, I'm going to let the panel takeover and move this discussion further. Thank you.

Panel Discussion

DR. PROWELL: Thank you so much for those introductory comment. I just want to offer one minute or so of comments, and then I'm going to open this up for the panel members to introduce themselves and offer their initial remarks.

When I have tried for a long time to persuade people to include patients with brain metastases in the clinical trials, before this was being commonly done, the reasons that people would tell me they were not going to include them were things I had heard again and again, which actually made no sense whatsoever, now that I've been thinking about it for a longer time. They would tell me we can't include these patients because their prognosis is so poor; they don't live very long, which really makes no sense. That's exactly in whom we need to be developing drives and studying.

They would tell me, we don't know enough about these patients. We don't know enough about how they do. We don't know enough about how drugs might work in them or why they have brain mets that are progressing when their extracranial disease is stable. Again, that's why we do clinical trials, to learn things in places where we don't know.

So I'm happy that this is a sympathetic crowd and I don't have to persuade anyone that we should be including patients with brain mets to begin with, but nonetheless, even when everyone agrees on that, I find that there are a lot of differences about at what stage in drug development patients with brain mets should be included and what exactly we mean by patients with brain mets. Do we mean the newly diagnosed patient? Do we mean the stable patient? Do we mean the unstable patient? Do we even mean patients with leptomeningeal disease?

So I hope that we're going to get into a lot of issues about trial design but also about eligibility criteria, which I think is really

critical to move this field forward.

I would actually like to give the whole panel an opportunity to introduce themselves, but because I thought it was so powerful in the first panel, I want to start with hearing from our patient, Lynda Weatherby.

MS. WEATHERBY: Hi, everybody. I'm a little nervous. I wanted to start today and tell you that I've been a metastatic breast cancer patient advocate for about five years, and today probably marks the most meaningful day on that whole half so far. To be in the room with all of you is really -- it inspires three emotions. It's very emotional.

The first is gratitude for everybody and the way you're working on this. The second is fear and terror at some of the things I see on these slides. And the only way I cope with that is to keep in mind the words of my doctors, Julie Gralow at Seattle Cancer Care Alliance and Leah Hallis [ph] as my radiation oncologist at University of Washington. They advise me and other friends of

mine who see them that despite all the statistics, I'm not a statistic. I'm in the tail of the curve, and I intend to stay there.

Lastly, it's the hope thing. I really have to actively push down fear, and turn away from it, and stay in trust that it's been okay for me so far. I do everything my doctors tell me, and then I go after naturopathic care and I pay attention to everything that goes into my body, and so far it's been okay.

I am not typical of anything in breast cancer. In 2001, I was an early-stage patient with a 3 year old and a 6 year old diagnosed with stage 0 DCIS and had a bilateral mastectomy. And because I was placed at a 2 to 3 percent risk of recurrence, after many conflicting opinions, I did not do chemo or radiation at the time, and believe me, I got lots of opinions.

I proceeded to raise my kids. I'm a healthcare professional, healthcare administrator, always been in health care, and lived a healthy lifestyle. Twelve years later, my 6 year old, he

was in kindergarten at the time, and as he was graduating high school, the long silent scream in my body, that was accelerating slowly and then very rapidly as I approached diagnosis, revealed that I had metastatic disease, which was widespread in my skeleton, on my spine, pressing on my spinal cord to my brain.

I had a fractured rib from a met. The lesions in my brain were tiny to the cerebellum, but I also had, most troubling of all, a tumor on my left trigeminal nerve, and my husband and I laughed that I might be the only person who gets breast cancer on their face, but I managed to do it.

I knew nothing about a trigeminal nerve until this diagnosis, and I was stuck in between my bone scan with my husband in Japan and him arriving home on Saturday that this nerve, after a couple of weeks of giving me terrible symptoms, simply locked up my face, dropped me to my knees, sent me to the ER. Nobody knew what was going on. I had no idea that it could be breast cancer, and I thought I had

another problem going on that weekend before we got the diagnosis of metastatic breast cancer. I was rushed in for radiation to my spine. I had gamma knife right away to treat the brain lesions, and then this nerve.

It took all summer. The trigeminal nerve was so problematic for a long complicated series of events. I will tell you that I ended up in a neuro-oncologist office who explained to me that I was really possibly facing leptomeningeal disease. That was the only appointment my husband did not go to with me.

If you can imagine, if you're not a patient, you are sitting in your chair, and then it's kind of like in StarWars where the whole structure opens up and you're just free falling you. That is how it feels. Everything goes away and you have nothing to hold on to.

Fortunately, my oncologist and my radiation oncologist stepped in and got me pulled back together and said we're not going to go there yet, and suffice it to say my first-line treatments of

Tamoxifen and now an aromatase inhibitor, following hysterectomy, have been working really well.

Having said that, I'm in the middle of scan anxiety right now because I go in on Tuesday. Last year, I had to have my second gamma knife radiation um, for some things that had been on watch that Dr. Hallis and I agreed we should go ahead and go after. And as I was in for that second gamma knife, we discovered the cause of shooting pain down my neck, like a stinger pain down my neck, was a brand new skull metastasis. I said to my husband -- it had been present -- the pain down my neck had been present for about a month, and you just go through thinking, what did I do? Did I exercise? Every time I turned to drive, it's shooting pain, and here it's a metastasis. My tumor markers were normal, everything else is quiet, and here it's a metastasis.

It's hard to live in that space where you don't want to overreact, but then it's a metastasis. So fortunately, it was treated that day and hopefully I won't hear any more from it

even though there is still permanent pain going down my neck.

I guess I just want to say I have not done a clinical trial yet. I keep an eye on it. I will try to speak for the patients that I know that have done them, and I am very aware of the patient friends that I've lost to leptomeningeal disease and brain metastases as I sit here today. So thank you very much for having me.

(Applause.)

DR. PROWELL: Thank you so much for those opening comments, and I'm struck by your saying that you felt like you didn't have anything to hold on to. So I think the goal of this day is for you and every patient facing what you've been facing to have something to hold on to at the end of this day.

Maybe we could just start from that end and have people just introduce themselves, say their name and affiliation and a brief remark.

DR. WEN: I'm actually not on this panel. I'm just a spectator.

DR. PROWELL: Please, go ahead.

DR. TAWBI: You were supposed to start on the other end, but that's fine. My name is Hussein Tawbi. I'm a melanoma medical oncologist at the University of Texas MD Anderson Cancer Center. I've been fortunate to actually lead trials that have helped patients with brain metastases, and it's really amazing to have Lynda here, and earlier Derrick, and hear about your experiences.

I really want to actually highlight the fact that Derrick started with the hope and you're talking about the fear. And I really think as a group here, our job is to make sure that nobody's afraid of hoping, and that we can actually bring these trials to patients and be able to actually impact not just their survival but their daily lives as well.

I'll just say that I started my career as a phase 1 drug development person in melanoma. I guess I was always the kid that drove everybody nuts by asking the why question; why, why, why. It was really important to me that every time I tried

to put a patient on a clinical trial to go through, my coordinator would look at me and say, "Can't; exclusion criterion," and to ask why was this exclusion criteria actually in this study? Why do we have to say your platelets have to be more than 100,000?

Well, that made sense for some of our patients, but then you got to brain metastases. You got to, again, organ dysfunction. You got to just rare diseases that were not allowed. So I kind of made it a mission of mine to kind of go after these whys and really try to understand how can we turn those around.

I've done some work in organ dysfunction studies, but then turning to patients with brain metastases, it was clear to us that those are patients that are just being excluded based on existing dogma rather than actual evidence, and I think over time with some courageous actually clinical researchers. Actually, I have to also shout out for some of the companies that have been involved to say, look, we can actually include

those patients on trials. We can design trials specifically for those patients and actually answer the questions in an inappropriate way.

So I'm really looking forward to hear the rest of the discussion and really to come out of today with very clear guidelines so that our colleagues across all diseases, not just in melanoma, and obviously across oncology, to try to actually demystify brain metastases and allow them on trials more freely, and really allow for this data to be generated. Because the answer that we don't want to have is that we don't know. Thank you.

DR. PROWELL: Thank you so much.

DR. MISHRA-KALYANI: Good afternoon. My name is Pallavi Mishra-Kalyani, and I'm a statistician at the FDA. I work in the Division of Biometrics V, which is the group that supports the statistical review of applications or INDs for oncology and hematology products. My own experience has been mostly with solid tumors and review of protocols and applications for solid

tumors, including lung cancer and melanoma.

I'm going to pause on my comments on what Shanthi has presented mostly because I am in agreement mostly there. I don't know if I'll add anything substantial quite yet, but hopefully I can help address some of the statistical concerns and questions that may come up as we're discussing trial designs.

DR. PROWELL: Thank you so much.

DR. GONDI: My name is Vinai Gondi. I'm a radiation oncologist at Northwestern. I specialize in the management of patients with brain and spine tumors, both in adults and pediatrics. My focus of research, my real passion has been shared earlier today, and that is how do we treat tumors, and specifically brain metastases, with this really effective modality called radiotherapy in a safe as way as possible.

A lot of my focus has been on neuroprotective strategies and most recently hippocampal sparing. So I'll weigh in on some of that as it relates to drug development, but I'll

also weigh in on my clinical experience, as was discussed before, and some of the frustrations sometimes we face in clinic when we know we have this really effective treatment like radiosurgery or radiotherapy for someone with brain metastases, but then we have to really consider should we use it because then they may not be eligible for a trial. We can talk about that.

DR. KEEGAN: Hi. I'm Patricia Keegan. I'm with the Division of Oncology Products II, and we're responsible for the oversight of drug development in a variety of solid tumors. The area where I face this issue has primarily been with the lung cancer clinical trials in drug development, but I think I bring a perspective in the sense that we're also responsible for consulting with other parts of the agency, for instance, on trials to give liver-directed therapies and other things. So I think that that experience will help, and it does help me inform my considerations for this specific focus.

I'd like to say just a little word about the

issue of patients not being enrolled in clinical trials, not just related to CNS malignancies, but that I think, based on my experience with FDA, that probably the single greatest limiting factor to patients not getting into clinical trials based on eligibility criteria is that people just recycle clinical protocols, and they don't look at the drugs that they're studying and make a specific decision on each eligibility criteria as to why this makes sense to be here or not to be there.

Much of that has led to the reason that we're regularly excluding patients with CNS metastases or other conditions, not because they need to be, but because we're not focusing on what is absolutely necessary to conduct the clinical trial. So I guess we should probably try and refocus our energies on being a little less academically lazy about clinical trial development and trying to be more considerate of when we developed eligibility criteria, what's the real thinking behind that in light of both the disease and the drugs being studied.

DR. BLACKWELL: I'm Kim Blackwell. I'm currently a vice president, and at Eli Lilly, I oversee the early-phase oncology and immuno-oncology efforts there. I should disclose some people might think I have a multiple personality because I just joined Lilly a year ago, after 25 years of clinical practice running both the breast cancer program and ultimately founding the Center for Solid Tumor Brain Mets at Duke University.

Prior to leaving my university appointment, I actually founded a company that's focused on the treatment of early solid tumor brain mets. So I have academic experience, I have early life science experience, and I now have big pharma experience, so I'll try to say, "And now I'm speaking from this role, and now I'm speaking from this role." But I think I'm uniquely equipped to try to speak on the pharma perspective, both big and early-life science, just from an investment and how do you start a company that's focused on this.

I became passionate about this, in part,

because I worked at a university that had the world's largest brain tumor center, and I remember Carey and I having a discussion probably 20 years ago saying we have all these tools that they're using for GBM. Why don't we apply them to the treatment of solid tumor brain metastases in the GU neurosurgery, cool radiation techniques.

Treatments for breast cancer, and in particular HER2 positive breast cancer, got a lot better; so much so that over the past 7 to 10 years of my career at Duke, I watched women not die of their HER2 positive metastatic breast cancer, but actually die of the consequences of the radiation that was required to keep their brain mets under control.

So I think now's a good time to have this conference. I'm honored to be here, and hopefully I can contribute to some of the discussions. I don't think I can represent all pharma, but I can certainly give you what my experience has been in the first year having joined Lilly and what we worry about and what we don't worry about in

developing pharmaceuticals in this space.

DR. ATKINS: I'm Michael Atkins. I am a medical oncologist and deputy director of the Georgetown Lombardi Cancer Center here in the D.C. area. My major interests are in melanoma treatment, kidney cancer treatment, and immunotherapy.

Being a longstanding clinical trialist, I've sort of taken the general idea that industry's job when they're developing drugs is to get the drugs approved as fast as possible, and it's academic medicine's job to figure out how to use those drugs along the way, and that's including subsets of patients with Comorbidities; how to develop biomarkers; how to sequence them or combine them with other agents; and also whether they are effective in specific organs such as the CNS.

I do think that the experience I've had with immunotherapy and melanoma suggests that you can, while you're developing drugs and getting them approved, potentially address some of those questions along the way without delaying

development or approval of the drugs, or in some points cases, even expediting the approval by allowing more patients to be eligible for one's trials, while at the same time getting some real-world, or closer to real-world, experience.

I think as Hussein and Kim have proven in the ipi-nivo 204 trial for patients with melanoma and brain metastases, when it comes to immunotherapy for patients with melanoma, there is no effective blood-brain barrier.

I think taking that approach, I don't know why that same statement wouldn't apply to every other cancer where immune therapy has efficacy, and certainly that would be justification for taking patients with treated brain metastases or asymptomatic brain metastases, as was in the 204 trial, and allowing them to be part of earlier clinical trials in other cancers, and also, if it's a poor prognostic factor, then one could stratify for that.

Because patients with brain metastases have generally had such poor outcome, I think it lends

itself perfectly to have overall survival be an endpoint in randomized trials in patients with brain metastases and having neurologic function be the secondary endpoint.

Although it's nice to see tumor shrinkage and may be great to see PFS being prolonged in the CNS, I think you might not always see those things, but you may see an impact on survival, particularly in patients who otherwise would have had short survival. If your drugs really work, then they should work better than the standard of care in the patients who are at the greatest risk.

DR. PROWELL: Great. Thank you for all those introductions. We have about 45 minutes or so, and I want to try to focus our panel discussion around four main topics. I'll just outline what those are briefly, and then maybe we can comment on them, and of course we encourage the audience to ask questions or contribute from the microphone.

The first is when we should include patients with brain metastasis or leptomeningeal disease, because I don't want to forget about those

patients. When should we include them, and by when, I mean when in drug development, at what point? How early are we comfortable including them?

Second is I want to think about how we should include them. And by how I mean do they go into the overall trial population, particularly in settings where brain metastases are very prevalent, certain diseases where they're very prevalent, or do they belong in their own separate cohort?

The third is how do we incorporate local therapy into clinical trials? And then the fourth is how do we move beyond this mind-set of letting patients with brain mets be in our clinical trials to actively pursuing drug development in patients with brain mets or leptomeningeal disease? I think it is a different question and an important kind of reframing of our thought process.

So one of the complaints I've heard early on, I was involved with a lot of people in this room, Dr. Amiri, Dr. Sul, Dr. Lin, with the ASCO friends' effort to modernize eligibility criteria

in brain mets. One of the concerns that we heard when we started thinking about how we were going to address that topic was people saying, well, patients who have brain mets are different. They have different efficacy, they have different safety, and that makes it really complex to put them in clinical trials. And that's why we've not done it and that's why we don't want to do it.

One solution that came out of literally years of people sitting around talking around tables and on phones was the notion of including these patients in separate cohorts, which addresses many of the issues. There are statistical considerations that this brings up, and there are pragmatic considerations about trial design, and analysis, and size of the trial, and so on.

I'd like to have the panel maybe begin by thinking about that issue, responding to the idea that patients with CNS involvement should be their own separate cohort, and maybe we can start -- whoever wants to go first. We don't necessarily have to go down the whole row, but

whoever wants to take that. Go ahead.

DR. MISHRA-KALYANI: I'll start. I can't, of course, again, speak to the clinical side and the safety concerns exactly, but I will mention one thought about -- or a couple of thoughts about having patients with brain metastases in a separate cohort, and that would be a question of equipoise.

If you're not sure that the patients with brain mets will actually benefit from the standard of care because there's evidence that it won't be effective therapy for them, then you may consider having a separate non-randomized cohort for those patients so that you can just look at the effect of the experimental therapy.

I think separate from that, if you do feel like there is effective standard-of-care therapy that you can compare to, the concept of having patients either in a separate cohort or in the overall population with a stratification factor for whether or not patients have brain metastases isn't necessarily going to make too much of a difference in how we interpret that data, at least from a

statistical perspective because you can make arguments on how you can look at the data together or look at them separately, and there are a lot of different statistical methods for doing that.

So really, I think the concern first needs to be whether or not you can do a randomized design for those patients. And if you can -- and I'm assuming that we're talking, again, as Shanthi mentioned, in the phase 3 randomized study setting. If you can randomize them, then I don't see why you couldn't include them in the overall population with a stratification factor to kind of cover yourself.

DR. GONDI: Can I take off -- oh, sorry.

DR. TAWBI: If you don't mind, I really do want to address two very important points. I think one very important point that we all kind of faced throughout the morning and throughout our careers so far is the dearth of knowledge in this field and the fact that less than 1 percent of our patients that represent, really, 30 percent of metastatic disease population, less than 1 percent of them are

represented anywhere in a clinical trial. So my answer to when is as early as possible and as often as possible should be the answer.

Now in terms of how do you address the fact that this is a different population, I actually will take what Pat said about not being lazy in our clinical development and clinical trials. I don't think there's a blanket statement for that.

I think we really have to think about which drug are we using, what are the targets that we're considering, what do we know about its penetration for the blood brain or not, and then based on that, try to include those in the early phases, either dose escalation's completed, to have a small cohort in which you can look at this; or even have a separate dose escalation.

As Mike Davies earlier mentioned, maybe for those patients, you do need a higher dose, and maybe some of the toxicities can be -- we all are oncologists and treat patients with chemotherapy and give them awful toxicities all the time if their goal is benefit. So sometimes maybe our

threshold for toxicity for that population may be slightly different as well.

Then when we go later in the development, stratifying should be a must, actually. It's very easy. I'll talk for melanoma. A lot of those patients screen fail because of brain mets. Imagine if those people that screen fail just go on a study, and they're just in their own separate cohort, and then you can answer the question right there. You can design your trial in a way that the primary endpoint isn't the cohort that's not brain mets if you're worried about their poor outcomes. But at the end of the study, you'll have all the answers that you need.

DR. PROWELL: I'll let Dr. Gondi in just one moment. I just want to say one thing. Part of the reason that industry has historically not included these patients is that we've allowed them to not include these patients, despite the fact that for some of these diseases, the prevalence of brain mets is as high as 40 or 50 percent.

One thing that I want to get back to you

later in the discussion, and maybe I'll ask Dr. Blackwell to comment on this from an industry perspective, is what sort of incentives, in terms of either being able to differentiate a product from other drugs in class maybe that haven't studied brain mets, or what sort of concerns or potential carrot and stick, if you will -- what sort of regulatory things would lead companies to preferentially include these patients in their clinical trials?

Dr. Gondi?

DR. GONDI: I wanted to go back to something that was mentioned earlier about being practical, too, with clinical trial design and development. I see brain metastases different but in a positive way, to some extent. Again, as one of two radiation oncologists in the room, I can say that we have very effective treatment for brain metastases, and that's radiosurgery, and it's safe, and it's effective for the timeline of most clinical trials.

So we can leverage that. In fact, we should

leverage that in a way that allows us to include these patients on trials. For later-phase studies, I agree a hundred percent, putting my biostatistics hat on, it makes sense to stratify patients to enable them to be treated with radiosurgery before they enroll on trial, and for small asymptomatic mets in non-eloquent locations, not requiring corticosteroids, to not have to necessarily treat those lesions and stratify and be able to watch that.

At the end of the day, if the primary endpoint is survival, one thing that we have trouble showing in brain metastases management is that anything we do for brain metastases actually has an impact at survival. There have been a lot of challenges in demonstrating that. So if we know that and we all agree on that, why not just allow those patients, monitor them closely with MR surveillance, treat the troublesome lesions with radiosurgery, safe and effective.

In terms of earlier phase studies -- oh sorry, one more thing about that. I'm going to put

on my radiation oncologist hat now, because I have hats, too --

(Laughter.)

DR. GONDI: -- this washout period really troubles me as a radiation oncologist. I've never understood it. It was in this JCO paper that you asked us to read in advance of this, and in most trials, it's a couple months. I think the JCO paper said 1 month post-radiosurgery. Radiobiologically, there is no washout period.

What happens in 1 month radiobiologically when you treat a met? You usually get a little FLAIR, it calms down with steroids, and they're fine. In fact, if you scan that patient a month later, which we don't normally do, that tumor's probably shrunk. So why do we need a washout period? Why not enroll that patient right away so that we're not sitting there for a month watching their disease outside of the brain continue to progress?

As it relates to earlier phase studies, the thing I struggle with the most in my clinical

practice is so many of the patients who do earlier phase studies have failed several prior systemic therapies, and usually by that point, it's not 30 percent of them have brain mets; it's like 60 or 70 percent of them have brain mets by that point.

I think our patient advocate earlier today really echoed this and it's really important. The patients who've had brain mets treated should be able to go on earlier phase studies. It doesn't make sense to me biologically or clinically why that should not be possible.

I can understand why there may be some concern about if they have intracranial progression at that time, and how do things interact with radiotherapy, which I'd like to spend some time weighing in on, maybe for an earlier phase study that may need to be delicately looked at. But if they've already been treated for their brain mets and their scan is stable, they should be able to go on an earlier phase study.

DR. ATKINS: A couple of comments. I agree with Hussein that when should be as early as

possible. The only qualification I would say is I'd like to see that the agent has some systemic disease activity before exposing patients with CNS mets, because if it doesn't work systemically, it's not going to work in the brain.

I do agree with Dr. Gondi that -- and the one objection I had to the article that you distributed and asked us to read is I don't see why it's necessary to wait 4 weeks after radiation of brain mets before enrolling patients on trial. In the national cooperative group trial that I lead, we decided to completely eliminate the repeat MRI in patients with treated brain metastasis for melanoma and just enroll them as soon as they were off steroids for getting immune therapy.

I don't know that if you're treating every lesion in the brain, you're not going to be measuring those lesions. If you go put them on study right away, there shouldn't be a chance for new brain disease to develop. So that's the best time to treat them, and I don't know why you would wait on treating their systemic disease because

that's what keeps some patients off of trials, is they have to get their brain met radiated, and then they don't want to wait 4 weeks to actually enroll.

DR. PROWELL: Dr. Keegan, do you want to comment on the issues from a regulatory standpoint of letting people get radiation and then go right into this study, in terms of our being able to interpret endpoint design?

DR. KEEGAN: Right. And I think that's why we -- when Dr. Marur led off, we talked about the endpoints because what you want to show often drives who gets in the trial. If all you want to do is show level of activities, systemic activity, and if there are treated brain lesions in there but you're not necessarily focusing on that, there would be no reason to wait.

So the reason is usually because people are focused on looking at activity in the CNS as well, but it's simply a matter of how you design the trial and what you want to be able to include at the end. There's no regulatory reason, generally speaking, why you would have to have a washout as

long as you would understand that those would not be lesions that could evaluate for drug activity.

I actually have a quick question. Maybe you can answer this. Why not include patients in the first in-human clinical trials if there's a reason -- if there's no specific safety concern, why would you want to wait until you have evidence of systemic activity before you would enroll those patients?

I would say they're taking a lot of chances regardless, in the very early-phase studies patients are, and they don't know if they're going to respond systemically either. So with close monitoring, I would challenge that perhaps those patients could be enrolled in phase 1 studies as well.

DR. PROWELL: I just want to say this is regulators being more liberal than academics.

(Laughter.).

DR. PROWELL: You might never see this again --

(Laughter.)

DR. PROWELL: -- so mark this in your calendar, friends.

DR. ATKINS: Yes, and maybe other people are going to challenge me on that statement, but I don't want to compromise the initial study that looks at whether or not there's efficacy in a drug. If you put in your phase 1 trial, where you're trying to define what the doses that you're going to use, and it's compromised because patients have toxicity issues or you don't see any activity because a large percentage of the patients were patients who couldn't respond to that agent, then you may slow down the development of that drug. But I'm willing to listen to comments otherwise because I suppose if you saw a response in the brain, nothing would speed up the development of that drug any faster.

DR. PROWELL: So what about if we had those patients in a separate cohort even in dose escalation, where it's baked into the protocol that if there's excessive toxicity, if you're seeing seizures, if you're seeing bleeds, you're seeing

whatever, that cohort built into the protocol is going to close. You're going to stop, and that's going to be the end of it, and there's no need to pause, and amend, and reconsent people because that was built into the protocol right from day one; likewise, looking at the efficacy or even the dose requirement, which, as someone alluded to earlier, might be different for patients who've got intracranial compartment disease.

I want to ask Kim to comment on one thing in a minute from a pharma perspective, and then I'll get you. But Nancy Lin, who was a lead author of these eligibility criteria guidelines, I want to have her comment on the 4-week washout period. We talked about this a lot.

DR. LIN: There's a story behind it as there is with many things, and I actually agree with the panelists. You have to remember where we're starting from, which is that almost all standard templates had a 3-month washout from radiation, which completely makes no sense. If you're trying to include people who are less least likely to have

a CNS progression event when they enter a trial, you want to have 3 months go by because, honestly, most of the time in 3 months after radiation, nothing happens in those first 3 months.

So we really wanted to get rid of the 3-month threshold. We had a lot of debate about what that threshold would be, ranging from no time, to 7 days, to 4 weeks. We felt very strongly that it couldn't be any more than 4 weeks. Ultimately, the consensus was that everyone felt comfortable with 4 weeks, which is why that's in the guideline, but in the text, there's a note that based on the situation, it could be less than 4 weeks.

So I don't want anyone to feel like it has to be 4 weeks. The guidelines, they could be really anything, but we recommend a maximum of 4 weeks is the way that I would think about it because I entirely agree, it makes no sense the way that it was written before; it really makes no sense.

DR. ATKINS: What about the issue, Nancy, about repeat imaging? Obviously, if it's less than

4 weeks, you're not going to repeat image.

DR. LIN: I totally agree. And again, it has to do with where we were trying to move the needle from, which was really from this 3-month or 6-month kind of a time frame. I think if somebody's had SRA a week ago, does it make any sense to repeat it? No.

DR. GONDI: I just want to clarify again, it's a semantic thing, but it's what causes us to think about it. There's no such thing as washout after radiation. The radiation is done.

DR. LIN: Agreed.

DR. PROWELL: Sorry. We're using this in a shorthand way to mean you got to wait a little while. Yes, but thank you.

I want to ask Dr. Blackwell the comment on the pragmatism of this, a bunch of people who are not in pharma saying, "It's really simple. Just have another cohort." You're going to have separate dose escalation for them, you're going to have separate stopping rules for them potentially for toxicity.

How practical is this in both early-stage development where you're still on the dose-finding and toxicity-gathering stage, and how practical is this in late-stage development? How much does this add to cost, and risk, and time to accrue, and so on?

DR. BLACKWELL: Well, that's a lot of questions. I tend to try to break this down because I think sometimes when we blur what we're talking about, it's hard to find solutions. In terms of inclusion of patients that have treated CNS mets on a trial where the sole intent is not to look at CNS activity, I think that's a very different discussion than how do we design trials where we're intending to look at CNS activity.

So I'll address the first. In the context of early drug development, I actually -- so I'm going to take the contrary here. I actually think we need to include patients that have worst disease in our dose-finding study because if we see a signal, then we're going to want to develop that drug.

You put a bunch of patients on whose disease was going to not progress for a year anyway, then you're going to fool yourself into thinking a drug has activity when it really doesn't, and you set yourself up for failure as you move that on at whatever dose you find.

Now I think precision medicine is going to help us with that, so if you know what the driving mutation is and you know how that disease performs in a different cohort, then you can actually say, okay, these patients should do this and on our drug, they actually did this, so there's a signal of activity there.

So I do think science is actually going to help us sort this out as opposed to, gosh, if your hemoglobin's okay and your platelets are okay, then you're the patient we want to study a drug in. So I see hope in biology and science helping us understand how patients would have done had they not received our drug, even in the earliest stage. So I actually think that patients facing brain mets should be allowed.

I would say that Pat brings up a good point. The reason we have excluded them, both pharma -- even in the trials I participated in prior to joining pharma was a cut and paste phenomenon, which is we didn't want to be bold enough or brave enough to include those patients on the trial. The 25 years of my practice, I think I might've seen 7 seizures and I focused on the care of women with brain metastases. It's just an urban legend. It happens, don't get me wrong, but the problem, as much as it's discussed, is very unusual in the day-to-day clinical practice.

So in terms of early phase, I see where there'd be no problem, and in fact I think this is where patients, and the regulatory agencies, and the investigators can push and say we're not going to put people on this trial unless you -- I'm probably going to get in trouble back at work, but we're not going to put patients on a trial if you don't allow patients with stable brain metastases to go on it.

These patients are sacrificing a lot.

Sometimes they're the first human dose. We have very few signals of what the safety is. We have it in preclinical models, but in people we don't. So I feel pretty strongly. And you have to realize that it takes a little while to change, so we have to be a community and push to allow for these patients to go on the early-phase trials.

I feel about the same as the phase 3 studies. I will say, though -- I've wrote down this list of things pharma worries about, so maybe I can just tell you what they are really quickly. We worry about the endpoints in a phase 3 study. We worry about the complexity of the patient and heterogeneity. And patients who have had SRS-to-1 lesion is a very different patient than someone that's had SRS to 5, or even whole-brain radiation therapy.

Just like we try to homogenize patient enrollment, everyone's only had 2 lines of therapy, it's very hard to control that in a setting of a randomized phase 3 study. So we worry about patient population, heterogeneity, lines of

therapy, and in particular burden of disease.

The biggest thing -- I have to say this before I get cut off -- the lack of preclinical models makes it very hard for me to argue to do trials in this space, having joined a large pharma a year ago. It's just the way that big pharma makes decisions, which is did it work in the cell lines? Did it work in the animals xenografts? Did it work in this? Obviously, there's safety in the preclinical models, but you can't just say it's because I think it's a good idea.

So I think we need to work together to figure out what those preclinical models would look like, and I think we're going to speak about the multidisciplinary buy-in. I just have a couple of points of what we don't worry about because I've heard it a couple of times.

We don't worry that the patients are too sick. The presence or absence of brain mets in a setting of 4 pages of eligibility criteria is probably the least of our worries. I do think it's a cut and paste phenomenon, which is that's just

how our protocol writers have always written it, and there's not a voice to say don't forget, and I'm pushing investigators to say that.

We don't worry about the size of the patient population. We recognize it's a huge unmet need. Even in a molecular era of precision medicine, there's still a huge opportunity to make improvements, and pharma actually wants to improve the care of patients as well.

Then the third thing we don't worry about is figuring out if the drug should cross the blood-brain barrier or not, and this is my last point. I worked for a company that's had spent 20 years in the neurocognitive space, the Alzheimer's space, the depression space. I've got teams of hundreds of chemists that could tell you with 92 percent precision whether or not that drug gets across the blood-brain barrier. We have imaging companies and that's all they do is look to see if the drug gets across the blood-brain barrier and people.

So as much as we talk about the blood-brain

barrier from a big pro pharma perspective, we don't worry about that too much because we actually have whole teams of people that have thought about that outside of cancer for three decades. So probably I took up more of my time but I did want to make those points because I don't think they'd been made earlier in the day.

DR. PROWELL: Thank you. I think that's very appropriate. I asked you like 12 questions. You responded to me in 4 minutes or something, so good job.

I want to take some questions from the audience. We'll just maybe go front/back.

DR. ABREY: Lauren Abrey, Novartis oncology. I actually wanted to make a comment, and I think I'm going to build on what Kim said. You have to think what are we trying to do? Are we trying to include brain metastases patients or are we trying to develop intentional drugs for brain metastases? I think it actually gets to what do you want your label to look like?

Do you want your brain mets to be included

as under the umbrella of metastatic disease and they've been represented in the trial? Then, in my view, they don't belong in a separate cohort. If you want to do intentional brain met development either to differentiate your product or because there's something unique about the patient population or the product, then you need to develop it quite differently.

I guess I would actually rebut a little bit what Kim said in that the selection for entry into human, at least at my current company and my last company for oncology products, would often select the drug that doesn't cross the blood-brain barrier. So yes, people know, but there's often a bias to, for safety reasons, pick some of the ones that don't cross the blood-brain barrier to try to limit the possibility that you also end up with seizures or something else when you take your first step into human.

So I think it's something we could manipulate while we sit there or try to influence; maybe not manipulate. That's not such a positive

word. But I think that's a little bit -- maybe we need to frame thinking about this because my first thought when Tatiana -- was we want to allow patients. I want to allow patients in trial. If we want to make a difference here, we need to move the needle, but then we need to be thoughtful about where are we moving it and what are we doing.

DR. PROWELL: This is a regulatory issue that I think will be interesting to talk about maybe as we go on, which is that because historically we have allowed companies to exclude and there's no limitation of use in the indication. The indication would be for whatever line, non-small cell lung cancer or something, but it doesn't say for patients without brain mets, or we've not specifically been granting indications for treatment of patients with this and brain mets, or even necessarily including a lot of that data in the label.

So the question is for companies that are coming into this now with multiple other drugs already approved in that line of therapy or in the

same class, how do we provide that incentive to really include these patients?

DR. TAWBI: I'll be more than happy to address this. I really think that's a great point, and we're actually talking about two separate things, and you're absolutely right. If you look at what we've been doing so far, is we've been trying to prove the things that have already been approved, that are already available to everybody in the community, then prove that they have activity in the brain. And obviously this has been a long and arduous journey.

I can tell you, having had the honor of leading the CheckMate 204 trial with ipi-nivo, this trial had 15 patients on when ipi-nivo got FDA approved. So we actually were concerned that people won't put patients on study because they have access to the drugs. So it took a lot of sweat and blood and a lot of investigators being convinced that this is an important study to do, and to actually finish it. There were 90 patients and now soon 119; we changed the practice. I think

in a lot of ways, for those drugs that we think are close enough to change practice for all metastatic patients, that's when we need to allow patients with brain metastases.

However, the other aspect is that I want to focus back on what are the targets we're going after, what is the actual biology that we are trying to modulate. We are in a place where we should start thinking about what's specific about the brain and what targets do we want to go after. You heard Priscilla, you heard Mike earlier today, and even in immune oncology, the tumor microenvironment in the brain may need completely different modulators. So for those targets, for those pathways, we need to develop studies that are specific for that population.

DR. MISHRA-KALYANI: I actually wanted to address something specific you said about having a different cohort. I think that there are two things that I would consider there, and it goes back to your discussion as to what is it that we're trying to include in the label.

If you were trying to include your endpoint in the label that shows that you have a clinical benefit due to this treatment, if you have a lot of heterogeneity in your population, you might not be able to adequately size or power your analysis to find a clinically meaningful benefit in your population if there's a lot of difference in what we would expect for the clinical benefit in patients with those brain metastases versus those who do not have them.

So if you're getting a mixed model of what you actually are finding, then what you're indicating in your label is the clinical benefit may not be what it truly is. So in that respect, there may be some real reason for you to include a separate cohort. It doesn't mean that you're allowing the patients -- you're pursuing them. You're just pursuing them to also characterize the benefit for those patients because you're recognizing that it's a prognostic factor just as we might with histology, squamous versus non-squamous, et cetera. There usually it's a

stratification factor, but it's just a reason that you might want to consider, so pursuing them but having them in a separate cohort for that reason.

The second part of that would be if you wanted to specifically look at the activity in the brain or in CNS metastases, then there may be a reason, then, to also look at those patients separately for many of the reasons that have been discussed. There may be local treatments or radiation, and those things may affect how well you're able to characterize the clinical benefit or the treatment effect, and you don't want that diluting whatever you're able to find in the overall population.

DR. ABREY: So it could be really helpful in defining some of those clinical benefit endpoints from the last session.

DR. PROWELL: I'm going to let Dr. Gondi respond, and we'll take the question at the back microphone. Thank you, all standing up, for being so patient. You live longer if you don't sit so much, so we're doing this for you.

(Laughter.)

DR. GONDI: And by the way, the chairs up here are so much more comfy than the chairs out there.

(Laughter.)

DR. GONDI: So for CNS directed therapy, if I may, I think the challenge we face in later stage trials is to some extent, we are trying to show CNS-directed therapy for what purpose? Speaking as a radiation oncologist, if we have a modality such as radiotherapy that is very effective in managing brain metastases, how do we supersede that? How do we improve upon that? That's hard to show.

So that's why I think it's important, as was mentioned here, when you're designing a trial, that it's going to be hard in the early/late phase studies to really show benefit over what is considered standard of care right now.

I would say that allowing those patients on those studies, though, allows us to make important secondary observations. A lot of the secondary observations we now make for trials that have not

included brain metastases patients is based on multi-institution retrospective series, where people said, okay, well let's just try this in brain metastases patients, some of whom got radiosurgery, some whom didn't, and see if it makes a -- and that's really hard to -- there's so much bias there, it's hard to really extrapolate much from that. So if we can include that within those later phase studies, that really gives us much more data from which to build.

Related to that, I think on the last session we talked about patient-reported quality of life and the challenges of assessing that. We actually now have, and we're just going to present later this year, an intervention radiotherapy related that actually has shown in a randomized trial better preservation of patient-reported quality of life. So it is possible to look at that as an endpoint.

But related to CNS-directed therapy, I think there's a dearth of knowledge as it relates to patients whose metastases fail effective local

therapy. In my experience, most of my brain metastases patients when they have issues down the road, it's not necessarily from the radiations because eventually their tumor grows years down the road after the radiation, and then we're stuck. We try surgery or LITT, but a lot of those tumors aren't resectable or it's too much to ask of a patient.

If there is something earlier phase that we should consider, I actually think it should be an earlier phase study of CNS-directed therapies with higher dose intensification for patients who have lesions that have failed all forms of local therapy, and we're really out of options, because you could see a home run in that situation.

DR. PROWELL: Thank you. I'm going to take a question from the back microphone, and then I want to get back to Lynda to move into our next topic, which is going to be about this issue of incorporating local therapy and should we be enrolling patients with active, meaning previously untreated or potentially progressing, having had

local therapy, and what are the ethical and pragmatic issues of that.

So we're going to come to Lynda in a second, but a question from the back microphone, please.

AUDIENCE MEMBER: Thank you. As a neurosurgeon, I probably stand up more than a lot of you, so I'm doing okay on that front, but I do appreciate the exercise today. I'll start with a kind of slight rebuttal to my radiation oncology colleague in that I think there is a way to improve on radiation therapy for brain metastases, which would be to obviate the need by giving therapies that keep them from developing brain metastasis in the first place.

That's where I think developing therapies that are specifically targeted to get into the brain and treat the brain beyond the breakdown of the brain blood-brain barrier within the tumor itself are important. So getting to this question of including brain metastasis patients in early trials, again, I'm a hammer, so I sound like a hammer, but everything's a nail.

I do think it's important when we're thinking about these early-phase trials to think about ways to bring in patients and also have potential endpoints where we're looking at the tissue to see what the drug is actually doing in the tissue and/or the brain around it.

There was a comment earlier about envy of the window opportunity studies that are being done in glioblastoma. There's no reason for anyone in this room to envy the glioblastoma field. I spent a lot of time in it. We envy a lot of the response rates that you see in these things.

You're talking about shrinkage or you're talking about objective responses. We don't see a lot of that, so we're starting to get creative on how we're doing our trials to try and stack the deck a little bit and see which drugs are going to work. And that's why we're doing these window of opportunity trials to understand things better.

In some of these brain metastases patients, I think we need to do the same thing. We're seeing great responses, but there are still these large

numbers of patients whose brain metastases aren't responding, and I think it's exactly because we aren't designing trials that are specifically designed to answer the question of what does it do in the brain metastases patients.

So it would seem to me to suggest that in those early phases beyond just separating out a cohort of metastasis patients and seeing what the objective response is, I think if you did have a few of those patients who we know are going need a resection with that solitary metastasis that is symptomatic, if you did design that trial where -- maybe it doesn't have to be 2 weeks, maybe it's a week, which most patients can tolerate, where you're giving the one dose of the drug and doing a resection.

I would even posit myself as something I'm pushing in glioblastoma community that a needle biopsy, which is very low morbidity, can be done in a lot of these cases, in and out, 1 percent risk of hemorrhage, and get some pre-tissue and post-tissue before you give the drug and then after. And then

really have an idea of that biologic endpoint.

Now you've done 10 patients, and I said, hey, in each of these 10 patients, it got into the tumor, and in each of these 10 patients, I saw a change in the endpoint that I was looking at. Maybe now I want to enrich for brain metastasis patients when we're going to these big registration trials because I know that we're going to see some effect in the tissue.

The last thing that I wanted to just ask from the regulatory perspective -- these things interest me. My wife actually works at the FDA. But I saw that there's a draft guidance on including metastasis patients in a lot of these clinical trials going forward, and one of the things you mentioned is that you let industry and the investigators not include the metastasis patients.

So is there a point at which you now start getting these boilerplate protocols that don't include brain metastasis patients, will you then send it back and say why? You need to justify the

exclusion.

DR. PROWELL: We're there, and we're doing this rather -- we've seen exclusion of men, for example, from breast cancer trials. I'm a breast oncologist, and that was something we didn't even blink at when I started here in 2006, and now anybody in this room who submitted a protocol knows that if we get an IND where they propose to exclude patients, we will always send a comment back and say you need to have a scientific rationale for why you don't think this drug is going to be effective in them or you need to include them. The fact that there aren't that many of them is not a good reason to not include them, so we're there. We're there already.

AUDIENCE MEMBER: The last thing I'll say is if you're at an institution and you think there's no neurosurgeons that are interested in doing the window of opportunity study at your trial, and part of the tumor section, and the [indiscernible] INS, I assure you I can find you one.

DR. PROWELL: Perfect.

AUDIENCE MEMBER: Can I just add one more point to what he said?

DR. PROWELL: Sure. I do want to make sure we get to the next topic, but please.

DR. YUNG: I'm Al Yung. I'm from MD Anderson. Just one more point is I totally agree with Pat Keegan and [inaudible], that there is no reason not to include brain met patients in the phase 1 trial while we are in the signal seeking stage for drug development sake. Besides, you can build in the window opportunity trial into that stage, as well as when you see failure or brain met when you have systemic response. You actually can also take that brain met by surgery and begin to study the reason why you failed.

So there is really no reason in the early phase. We just need to separate the early-phase study from the later phase when we're looking at efficacy for specific indication or targeted drug you have the precision medicine endpoint also there.

DR. PROWELL: It has become abundantly clear

that we should have had a neurosurgeon sitting in the front all day.

(Laugher.)

DR. PROWELL: So we apologize. These comments have been really terrific.

Actually, did you want to respond to that?

DR. MOSS: Just one tiny corollary of the same point. Nelson Moss, neurosurgeon at Memorial Sloan Kettering. I'm also happy to provide tissue. Just one more plug for more data.

Why don't we consider all cancer patients, potential metastasis patients, potential brain metastasis patients, and mandate MRIs at the end, at late time points in our late-stage trials? We don't have enough understanding of how these tumors behave over time. We've all seen ER positive breast cancer act in a very latent fashion on hormonal therapy, and then 13 years later giving us these tiny, slow-growing mets. Why don't we collect more data? Why don't we require this of all of our trials?

DR. PROWELL: I want to move to a next

topic, and I promise I will come back to you guys. I want to move to a next topic, which is it seems like there's pretty good consensus in the room that we want to be including these patients, and we want to be including them pretty actively and aggressively, and we want to include them early in the sense of early in drug development, like phase 1.

But I want to ask this who question now, and the one question of how do we feel about including patients who might have either not yet treated brain metastases, meaning no local therapy, no surgery yet, or patients who've had local therapy and are progressing? I want to get your comments on that from a patient perspective.

MS. WEATHERBY: Yes And yes. I know I don't understand all the complexities, but speaking for patients -- and I spent a lot of time talking to other patient advocates at a weekend long meeting last week. Yes. When you're in this situation, we don't have a lot to lose. I know that might sound crude, but we don't. Probably the harder thing is

to know that there -- I mean, I'm hearing this makes no sense. This makes no sense. We need to work on it, and probably the hardest thing of all is to know that something's poised for change but it hasn't happened yet.

The only other comment I wanted to make as an advocate -- and I want to point out I'm with metastatic breast cancer advocacy, which is way different than early-stage breast cancer advocacy, and I hope everybody in the room kind of gets that. The metastatic breast cancer advocacy movement has really gotten a lot of momentum lately and is really looking to work with the other metastatic cancers to create these changes.

I want to assure you that the patients are ready, not every patient, but they're ready. Especially in metastatic breast cancer, from the ones that I meet, they tilt young, desperately young, and they are ready for anything. We are organizing -- part of the Metastatic Breast Cancer Alliance's work right now is to launch a patient enrollment tool and database that. It's called

MBC Connect, which we're enrolling now. And shortly in another 4 to 6 weeks, we're going to roll out the 2.0 version, which is actively going to match them to clinical trials based on the data that they enter.

So our whole purpose is to bring the clinical trial information to the patients so they don't have to struggle so hard to find out about clinical trials. Once this momentum builds and builds and spreads across cancers, can you imagine how it would feel as a patient to be able to find the trials and then still see that maybe these blockades are in place? So yes and yes.

DR. PROWELL: Thank you. I actually want to ask Dr. Keegan to comment on that, and then I'm going to ask Dr. Blackwell to comment on that. One of the things that we struggle with as regulators is when investigators or companies want to have patients potentially forego known effective therapy to get an investigational agent. There are real ethical concerns with that.

Maybe I'll ask Dr. Keegan and then

Dr. Blackwell to comment from a regulatory and an industry perspective on that idea, potentially enrolling patients who've got progressing brain mets after stereotactic radiosurgery in lieu of going on whole brain or taking patients who maybe in the slightly simpler scenario just have brain mets and haven't yet had any local therapy at all. Your thoughts on that?

DR. KEEGAN: So my thought is that, yes, there is an ethical consideration and argument to be made, and there are ways to mitigate that. Some of those mitigations are adequate informed consent. By and large, we should be trying not to take the judgment out of the hands of the patient and their physician from making a decision under adequate informed consent.

So I do believe that it would be possible to allow a patient, adequately counseled, to make that judgment. I would like to try this therapy knowing that there are other therapies available and that the trial should have certain safeguards built into it for adequate monitoring to take patients off at

the earliest opportunity. But with those kinds of conditions in mind, I don't see any reason why one could not have a trial like that and consider it to be ethical.

DR. MISHRA-KALYANI: Could I add to that, to Dr. Keegan's comment? And I know she's going to agree with me.

(Laughter.)

DR. MISHRA-KALYANI: There are also statistical trial design considerations that you could include in those cases like adaptive design, and early stopping rules, and things like that, so that you can not only have informed consent for patients and investigators, but you can also very closely monitor your trial to make sure it doesn't go too far without having a good idea of what benefit the patients are getting.

DR. PROWELL: Right, Dr. Keegan?

DR. KEEGAN: Yes.

DR. PROWELL: Thank you.

Dr. Blackwell, do you want to comment from an industry perspective on this?

DR. BLACKWELL: Yes. I agree with both. In the setting of adequate consent, knowing and stating that there's an appropriate standard of care in the consent makes it at least acceptable to me. And I can't speak for all of Lilly.

I do want to say something that's in -- and I'm not going to go off on my list again. But it's very interesting, this dynamic that I'm seeing. And now I'm speaking from my history as a practicing clinician, which is most doctors do what they do because they think it helps people.

The way that patients with newly diagnosed brain mets get into the system typically is they have a problem. They know they have cancer. They go to the emergency room. And honestly, their treatment is dictated by who they see in the emergency room if it's truly an emergency. So if they see a radiation oncologist because, unfortunately, there's not a neurosurgeon on call and they need emergent therapy, then they'll get radiation.

DR. PROWELL: No offense to radiation

oncology intended or taken.

DR. BLACKWELL: Yes, no offense, or neurosurgery. I think the point is that what happens -- and now I'm speaking from industry and clinician -- is you have a patient that's facing a new brain met, perhaps asymptomatic, although, again, frequently they're symptomatic. That's how you pick them up. I've always struggled with the term "asymptomatic."

So you have a symptomatic brain met. The patient comes in. They maybe see me as a medical oncologist first. I say I have this great trial. You can go on drug X. I know you're afraid of getting more SRS or you're afraid of radiation in general. And we sign them up, and it's, again, industry speaking, too, which is it costs money to just screen patients for trials. Then in the criteria it says "doesn't require radiation," or you feel as a clinician you have to refer them to a radiation oncologist.

So here's the choice the patient has to make, which is you can go on this trial that we

think might help you or you can have radiation, which we know will help you. And in fact, that's a tough decision and it's a tough place to put patients.

I actually thought -- some of the randomized studies that reported out in 2016-17, which really demonstrated that at least for whole brain compared to best and supportive care, with all the caveats of the trial design, it might help in this discussion, Which is although we can do this, it's not been shown -- and I'm talking about whole brain now -- it's not been shown to improve survival, so I as your practitioner am willing to say let's try this; you can always have this.

So I just think we need to be aware -- and now I'm speaking from an industry standpoint -- of where that dynamic is, which is patients get treated by the doctors they see, by the modality that those doctors use. So I think that is something we're going to have to address, and educate the ER physicians, and the neurosurgeons -- not all neurosurgeons but

radiation oncologists, and even the medical oncologists.

I frequently had discussions conducting trials of patients that had new brain mets, where the radiation oncologist actually said -- and this is the truth, "You're going to feel bad if the patient goes home and has a seizure and you didn't give them radiation." That's a true story.

So these are the forces that -- and I'm sure there are other stories here, but we just need to be very practical about how patients get referred to these trials and enrolled on the trials.

DR. PROWELL: Dr. Tawbi, respond, and then the person at the back microphone who is the single most patient human I've ever known --

(Laughter.)

DR. PROWELL: -- and then I'm going to invite you to respond.

DR. TAWBI: And happens to be my patient, so I apologize, Christina.

I really just want to address the issue of who sees the patients and at what point. Actually,

I think that's where the value of multidisciplinary care is so important. I co-direct the brain metastases clinic at MD Anderson, and that's exactly the point; that we all see the patient together at the same time, and we really look in each other's faces about how comfortable we are about waiting for SRS to happen.

The way we built our clinical trials is actually if we have a trial that's for patients with untreated brain metastases, I actually include in it that they have to be evaluated by the radiation oncologist that can tell me that they can do it. And actually Dr. Chung is sitting right in the audience and has herself overruled me on some of those patients, and said, "This cannot wait; let's do it," versus now you can do systemic therapy.

What we've included in those studies was very early imaging assessments, as early as 3 weeks or 6 weeks, depending on the specific regimen, so that we can -- as I said in my earlier comment, we have days to manage these patients; we don't have a

lot of time -- so that we can act on it relatively quickly.

DR. PROWELL: Would you like to acknowledge your patient by name and invite her --

DR. TAWBI: Christine Baum, one of the most patient patients, as you said, but the most bright as well and very well represented on social media, I should say.

MS. BAUM: Thank you. As my oncologist, Dr. Tawbi said, I'm having my third recurrence of melanoma, second metastatic, first brain met. I'm an active clinical trial right now. This is my second clinical trial. I'm one of nivolumab and cyberknife radiation.

My question has more to do with NRAS, the NRAS genetic mutation of brain mets. I'm an NRAS patient, which is separate than BRAF, as most of you know. I know FDA has done some work with NRAS mutation tumors specifically. Just to double down a little bit of what my friend Derrick said this morning on just making more clinical trials available to brain mets patients -- but I also

wanted to ask, is there a potential trial designed to break it down into genetic mutation? Certain of these clinical trial drugs could be made available to NRAS patients or different genetic mutation tumor of patients, that could be a way to further the ball.

How does that kind of comes together in trial design?

DR. PROWELL: Do you want to come up? We're going to have Dr. Brastianos address this question probably related to the Alliance trial I'm guessing.

MS. SELIG: Dr. Prowell, I'm just going to say maybe take the last two comments after this, and then if you could summarize. Then those of you who are on Session IV panel, we're going to do a quick reset without anybody in the audience getting up and leaving the room, and see if we can do that.

DR. BRASTIANOS: That's a great question. Actually, we're starting an Alliance trial and actually --

DR. PROWELL: Can you speak into the mic?

You can turn around if you want.

DR. BRASTIANOS: We're starting a national trial, precision medicine trial, with that design that will allow all histologies. And if you have a CDK path filtration, you'll get a CDK inhibitor regardless of pathology, and the same with PI3 kinase pathway.

That's the design, and it's a biomarker-driven trial for brain metastases based on the science, showing that these are markers that do seem to be common in brain metastases. So that's a trial that is coming in a month.

AUDIENCE MEMBER: Thank you. And just let the record show, to all the neurosurgeons, I win the standing contest today.

(Laughter.)

DR. PROWELL: Absolutely.

(Applause.)

DR. BRASTIANOS: Kim just wanted me to mention also that we're looking for mutations in the brain metastases themselves, so we are hoping that it will target the patients with the brain

metastases.

DR. PROWELL: Thank you. And we'll take the question on the mic.

AUDIENCE MEMBER: This may be a combination comment and question brought up by, really, the first real reference to informed consent and the patient landing in the ER and those combinations. The informed consent, et cetera or the patient landing in the ER carries with it the question of whether the patient's options offered them, whether ER or in the trial, are really given to a patient who can make consent, because very often there's that emergent need, and in the clinical trial there's a lack of information on the total perspective of the options that are available.

This is an issue that hits every patient. I'm seeing this kind of doctor. I'm directed into this treatment whether in the ER or in a clinic. The informed consent is usually quite narrow; "Yes, I want to be fixed tonight in the ER," or "Yes, I want to be treated in this category of response."

So I'm going to always be pushing that the

patient not just have informed consent but to be able to make an educated choice with the full range of options available. And that is something that is beyond this specific brain met issue but hits every patient and every trial in complex diseases, and every patient going into treatment where he or she has perhaps been diagnosed and sent in one direction when there were 10 or a lack of clarity from that initial doctor, so educated options.

DR. PROWELL: Thank you. Absolutely, a terrific comment.

I'll just maybe spend 30 seconds summarizing this panel's discussion. And I believe you actually want the panels to switch -- is that right -- while I'm talking?

MS. SELIG: That's okay. You can talk first, and then we're going to take 60 seconds and switch.

Panel Recap - Tatiana Prowell

DR. PROWELL: Okay, great.

Just to summarize this really terrific discussion, I think what we've heard from across

all the sectors is that there's really enthusiasm for including patients broadly who have CNS involvement in clinical trials and that we'd like to see that happening not only robustly, but earlier in the drug development process in the sense of kind of phase 1, 2, 3, but also earlier potentially even including patients who may not necessarily have had definitive local therapy.

We feel that there are ways that this can be accomplished both safely and without compromising -- either compromising patient safety or posing excessive risk to the companies developing these drugs in terms of having patients in separate cohorts that that may enable us to look at their efficacy and safety, and even their dosing requirements distinct from the main group, and hopefully without too much disruption to the overall trial if we do in fact discover that it's not safe or it's not effective to develop these drugs in patients with brain mets.

I think that we had hoped to get to -- but it actually really leads into Session IV well, how

do we provide the incentive to really include these patients; what's in it for patients to go on these trials; and what's in it for an industry to include these patients in their trials? I think that that'll be a big focus in Session IV.

So I'd like to thank all the panelists and thank the audience for being so engaged.

(Applause.)

MS. SELIG: Please if you're sitting in the room, just take a moment to check your phone or whatever you need to do, but don't leave. And if you are on Session IV and you're not already up there, please make your way, and we'll move everybody closer together.

Joohee?

DR. SUL: I also wanted to add that we felt so terrible for Edjah having to stand for so long that we actually invited him up to join panel 4, so he'll be joining to represent the neurosurgeon's perspective.

Session IV

DR. WEN: I think we'll get started on the

final session. We've had a lot of great discussion today. This final session, I think what we hope will come out of this are concrete steps that we can take forward on how to include brain metastasis patients.

I guess the tradition is we started excluding brain metastases patients, and now we're slowly letting them in. Maybe the flip is that everybody should be allowed in, and this is a good reason that they shouldn't be in the trial, and how can we get to that stage. I think in this final session we want to be concrete. We want to come out of this with clarity, both in terms of who's eligible, what are the trials, and what are the endpoints.

Before we get going, though, maybe I'll have the new people who joined the panel introduce themselves. The first one, Peggy's Zuckerman.

MS. ZUCKERMAN: I'm a kidney cancer patient, or at least I like to say I used to be a kidney cancer patient. I am 15 years, nearly to the day, from having had a radical nephrectomy because I had

a 10-centimeter tumor that also included metastases throughout my lungs, and I was clearly a goner, I think is the technical term, and all I wanted to do, with so many other patients, was live long enough to see, in my case, my son graduate, my youngest graduate from high school. That was all I thought I could begin to hope for.

I was one of those miracle responders to high-dose interleukin. All of you will know more about it, of course, than I; except that I would have in many cases been precluded from even considering it because it wasn't a medication -- though it was the only agent, which was FDA approved at the time, it wasn't one which had much support in the clinic.

Certainly, had I not gone to an academic center, would not have even heard of it, period. Obviously, it was very easy for me to make the choice to enter into that treatment, and with other patients very often enter into a clinical trial because that is the only version of a treatment.

I do remember very clearly, and thought

about this the moment I heard of this workshop, that I would not have been allowed to go into that treatment had I any brain metastases. So the moment I got the call that said "it's clear," I knew it's clear meant my brain was clear of any mets, and it was clear that I was heading into the first thing that gave me any hope that I would see that boy graduate.

I obviously responded. I quit asking why me? Why did I get kidney cancer? Then I could finally ask, why me? Why did I respond? Why are there not more like me? Why was I so lucky to be just dropped into a place where they would grant me that one hopeful treatment? And that has pushed me to where I am today, lucky to be here, in the most essential terms, to be here on this good earth and here hoping that I can add some insight into the patient's role, and what options can be brought to patients, and how to bring those two patients.

So thank you, and I always have more to say, so somebody close.

(Applause.)

DR. WEN: Thanks so much. Dr. Ndoum?

DR. NDOUM: Edjah Ndoum. I'm a neurosurgical oncologist at the NIH and happy to be here. I came here to learn and listen, actually, and not to talk.

DR. WEN: Caroline?

DR. CHUNG: I'm Caroline Chung. I'm from MD Anderson. I'm a radiation oncologist, cross appointed to diagnostic radiology. I'm the director of imaging technology and innovation, and I'm hoping to contribute to this great discussion. It clearly shows how complicated brain metastasis can be, as well as how strong a mission we have to actually make things better. I think that, hopefully, we can start to wrap up with some key action items as we move forward. Thank you.

DR. ABREY: I'm Lauren Abrey. I currently work at Novartis oncology, where I lead the solid tumor group and medical affairs. Previous to that, I think I can say I started my career making some of those working mistakes that someone brought up in the first session. I think I did a bunch of

Temodar studies in brain met patients, and I think it's been true ever since then. Brain met patients are out there and participate, but I do think we have to be mindful that sometimes what we ask for in trials are a pretty selected group of patients if we look at it that way.

I really want us to start to think how does what we're talking about connect to all the brain met patients who are treated in the community because we've got a lot of specialized centers here, and not everybody has access to these multidisciplinary clinics, and we really need to think how they're getting treatment when they're out there in the real world.

DR. WEN: Thank so much.

Maybe what we'll do is divide this into trial design and eligibility, and then we'll talk about endpoints. In the first spot, in terms of trying to allow all or as many as possible brain metastasis patients into general oncology development, maybe, Dr. Prowell, if you could give us your thoughts on this, and also whether we

should try to get the ASCO Friends of Cancer guidelines and the RANO guidelines uniformly adopted as a recommendation and earlier thoughts on this.

DR. PROWELL: Sure. I think there's been movement in that direction already. We've seen NCI come out with standardized templates a few months ago that were based upon BM [ph], ASCO Friends eligibility criteria. Although there's templated language available in these manuscripts, I'm not sure that that's been -- in fact, I'm sure that has not been uniformly adopted by industry, but I would like to see it done.

As a clinician, it's hard for me to understand why we actually allowed this to happen for so long. Why did we allow these patients to be excluded when they represent, in some cases, half or more than half of the intended-use population? It doesn't make a lot of sense to me.

So I feel like we should be compelling these patients to be included. Anybody here who's an industry, or anybody here who's an investigator at

all, knows that the reason that we put clinical trials on hold is because of deficiencies, and those tend to be safety issues.

So I would actually say that maybe this requires recharacterizing how we think about exclusion of brain mets patients to be a safety issue, because the reality is these patients will be treated with these drugs, and the experiment will occur, and the only question is will it occur on a clinical trial where safety data are being rigorously collected and patient safety as being rigorously monitored by a specialized team, or is it going to occur in someone's outpatient practice.

The experiment's going to happen, so maybe that's the issue, is we need to recharacterize failing to include brain mets patients as a safety issue and as a deficiency, and not just a comment, "Hey, you need to think about including these people."

DR. CHUNG: I'd just like to add a comment to that. I completely agree with you, and I think that one of the things that we do have to think

about is when we think about when we started excluding brain metastases patients and the era in which we were imaging these patients, and when you compare someone who doesn't have brain metastases on a brain CT versus an MRI, I'm pretty sure a good proportion of those patients actually did have brain metastases.

So we were including patients with brain metastases from the start. For some reason, we continue to keep that exclusion criteria, but our imaging got better, and I think that there's a continued improvement in that image quality. So if you find a 1-millimeter spot in the brain today, is that the same thing as someone who has a sizeable brain metastasis that we were finding on older imaging? So I think that we do have to be thoughtful about what we're saying when we're saying we're excluding these patients.

DR. SUL: Yes, I absolutely agree with that statement. There's a big difference between excluding someone based on information you don't know versus information you do. I would bet my

house and my car that all these trials, some of the industry reps have said, well, we excluded patients with lepto. I can guarantee that there were patients with lepto on that study, because if you didn't look, it doesn't mean that it's not there.

So we are doing these studies; we're just kind of I think fooling ourselves, and in that process, we're not getting the data.

This goes back to I think one of the questions I had asked earlier about screening and looking, are we just not looking enough? I understand the reasons why we don't. Sometimes we say, okay, if you're not symptomatic, we're not even going to go there and look, and I know that's standard for patients with breast cancer, but should we actually start looking more? When we do all these staging screening exams, it stops right at the neck with CTs and PETs, and we're not including the brain as part of the entire body.

DR. CHUNG: Just to add to that, I think as Hussein had mentioned earlier, the patients who are in the studies where there seems to be a good

efficacy signal, where we're probably going to say this is going to become a mainstream drug, similarly, even in the upfront setting when patients may have metastatic disease but don't have known brain metastases, if we don't continue to follow them -- or if we do continue to follow them and the pharma companies are willing to fund these trials, and we can continue to follow them with brain imaging, that will help answer our preventative questions without designing a whole new trial.

Kim had mentioned the whole cost of screening patients, and we have patients who we're following who have been screened, who are on this trial. And by following them, we are getting a secondary endpoint that's clinically very meaningful in terms of brain mets prevention.

DR. SUL: Kim?

DR. MARGOLIN: I agree with that, and I think I even mentioned it earlier. It's been nice for my career, Hussein, et cetera, that we've been in -- melanoma has sort of been the vanguard

because of the bad news that melanoma has such a high brain met 2 case rate, that all along I think we've -- and immunotherapy has been important, and steroids.

So we've been in this mind-set of for many years of looking for brain metastases basically anytime there's a first recurrence metastatic disease. Some of the surgeons I work with are even scanning people's brains as soon as they have a sentinel node metastasis, which we could quibble about that, but that's not what we're here for.

But the idea of not lulling yourself, just like you were saying about assuming that patient's don't have brain mets and including them when they may, these patients who were in remission who didn't have visible brain metastases at the beginning of whatever their current therapy is, and they're doing well on it.
extracranially, you can't forget the importance of occasionally looking at their brain. I don't know that we can legislate that.

But I wanted to make a couple of other

points if you'll permit. These are more global and little bit off this topic, so you may choose to ignore it or come back to it. I'd like to propose that there are really two purposes here.

One is that if we're looking at the concept of approving drugs with a specific idea that they're going to be for patients with a given disease and brain metastasis, then we have to show, as so elegantly gone over in the Camidge video and earlier talks this morning -- I think it was Mike -- that they really should demonstrate an improvement in patients with brain metastases over the available options in patients with brain metastases.

So all these amazing mutations in lung cancer are the area where that's already started to be shown, because otherwise the drug doesn't have an advantage in those patients, and that's an FDA issue.

What's not an FDA issue that I think is more of a market penetration if you're talking from the industry point of view, or a usage, and maybe even

a safety issue, is the idea that available drugs being used more in patients with brain metastases are safe and may be synergistically effective with other modalities such as stereotactic radiosurgery, or certain sequences are ideal, and so on and so forth. That I don't think is for the FDA to have to legislate.

DR. LIN: The two points that I would add are I would distinguish two kinds of trials, the trials where the patient's CNS disease has been treated, and then you enter them, and your primary purpose is to control the extracranial disease. I think the argument there is, really, unless there's a very good safety reason, those patients should just be allowed on all phases of all trials just as a blanket statement.

I think right now that's still not -- I mean it's happening more, but it's still not happening enough. We would never allow a trial for metastatic breast cancer to exclude liver metastasis patients. That's a completely ridiculous concept, but we routinely allow trials

to exclude brain metastases patients even if they've been treated.

So I would like to see that just completely go away. I still think we need specific -- whether it's an individual trial, or a cohort in a trial, or subset in a trial, these patients do have to be looked at separately in some way because you're going to be potentially looking at different secondary endpoints. You might have different ways that you're going to assess their CNS.

So I think it's so important to do those trials, but I would kind of distinguish between these two types of trials. I personally think for a patient who has treated brain mets that any exclusions should really go away unless you really know that there's a safety issue.

DR. ABREY: If I could follow up on that, if you're interested in thinking how do you incentivize industry to want to do two very different things there, I think one is breaking an old habit, and whether you take Pat Keegan's comment that a lot of what we do in industry comes

out of a standard template, what's probably not cut and paste. There's just a template for phase 3 trials in solid tumors, and then you adapt what you need, and that exclusion lives in there.

I think it was the same when I was at Sloan Kettering, and I cut and paste from my last protocol, sometimes horribly, even to the statistics section just to provoke the statisticians to give me what I needed. So I think some of it is just breaking old bad habits, and unfortunately that's a little bit more the stick than the carrot I think probably.

I do think the other side, though -- and I think the alectinib, brigatinib stories, osimertinib start to really say why would industry care about developing drugs that have unique efficacy in the brain, and it's because it helps you differentiate your product from the other products on the market. And that's not hard for my scientists to understand or my commercial team to understand.

So I think those stories and those examples

are really terrific and thinking how we can build on whether it's specifically the alectinib story or another to say how do we do that in other disease areas and other specific mutations in a similar fashion, and how much of that was intentional, and how much of that was a little bit luck. I think maybe some of the early alectinib was observing early luck, and I think maybe some of the brigatinib, lorlatinib story was a little bit more intentional as the follow-on. So I think we've got opportunities on both.

DR. BRASTIANOS: Just a quick comment, just to add to it, I completely agree, there are two issues. One is we should be running brain metastases trials because we are seeing that brain metastases do differ from their primary and extracranial sites, so that's really important, and then the other issue of including the primary tumors. But I think we can't forget that brain metastases are genetically distinct, and we should be considering brain metastases trials, and just a comment to add to what you're saying.

DR. ABREY: I think that's something even -- there was a third thing, Priscilla. I think we really need to be intentional about the drug development for brain tumors, including brain metastasis because we suffer from the same problem in the primary brain tumor, that we try to piggyback on other oncology drugs and make them good enough. Good enough isn't good enough for this disease.

DR. RIELY: I think one thing to really bear in mind, and as a lung cancer doc, I think about the ALK story as something that taught us a lot. I think one way it helps to teach us is we look at ALK and we say it was really a great story about developing drugs in patients with brain metastases. A big part of that is because brain metastases are very common in ALK-positive lung cancer. So it's inherently about treating this disease as you're treating people with brain metastases, a significant number of people with brain metastases.

So maybe that's how we can figure out whether this is merely having an arm, a cohort, for

brain metastases patients or trying to include them in every step of the drug development process, and basically how frequent is it, and is that number 10 percent, is that number 20 percent? I'm not sure where the cut-point is, but that's kind of how I'm beginning to think about it.

DR. LeBLANG: Hi. My name is Suzanne LeBlang, and I'm a neuroradiologist, one of few in the room here, so I've been eagerly listening to the discussions all day, and I have a few thoughts that I'd like to share.

First of all, I do believe that doing more screening, MRI scans in patients that are at these high-risk levels of disease is mandatory, and I think the problem lies on both sides, on the clinician side not wanting to prescribe or order the MRI scan because you don't know -- you won't have to deal with the results, and the clinical trial enrollment is an issue. And on the other hand, radiologists have some blame in this as well.

I think sometimes we do limited protocols for orbis [ph] and not a whole brain, and I think

we can tailor an MRI screening exam so we're not doing 6 or 8 different sequences and making it too expensive to add to a clinical trial design.

So perhaps just do a volume 3DT1 pre-imposed contrast and 1 T2-weighted image, like a FLAIR image, and really cut the cost down of that, and it could be more amenable to entering all these patients in clinical studies, obviously to enroll them and screen them before, as well as following them during the study to see if they respond or not. So we can tailor the protocol down.

The second thing I'd like to bring up is that I'm currently working for the Focused Ultrasound Foundation, and a few people have brought up the new technology called focused ultrasound. And what it can do is temporarily reversibly and safely now open the blood-brain barrier. This allows big pharma to start considering either drugs that don't cross the blood-brain barrier that may work for CNS mets, so now we can get those drugs into the brain in localized fashion, or even taking drugs that may

get in there to elevate their concentrations.

So I wanted to know your thoughts on actually even opening the blood-brain barrier more with this focus ultrasound and how that will enable a more systemic therapy to possibly play a role in between radiation oncologists, neurosurgeons, and what we have today. So any thoughts on opening the blood-brain barrier directly to allow these drugs to enter?

DR. ABREY: I'm from New York originally. I live in Switzerland now, sometimes I start from skepticism. I feel like trying to open the blood-brain barrier has been a long conversation, so we've tried to disrupt it with various osmotic agent. We've done other things where we've given intra-arterial, including catheters threaded right to the site of the tumor and infusing. I think to date, it hasn't consistently shown us benefit, although individual patients clearly have derived massive benefit from it, but it's more stories than data.

I don't want to write it off, but I think

it's still kind of an area that needs to be considered experimental, and I guess I'm still worried that we need better drugs to give the patients more than we need to open the blood-brain barrier, but others might disagree with me.

DR. NDOUM: I was just going to say, when I was looking at -- I was talking to somebody earlier about Visualase as well. That's another thing that hasn't really been discussed a lot, but I know it's very frequently discussed in neurosurgical literature. So there are better local therapies or alternative local therapies, and we have some local therapies that seem pretty effective.

So focused ultrasound would fall into the category of another local option. Maybe if radiosurgery had failed or something like that, and you're looking for an option, you know that there's a systemic drug that's very promising, but we know it doesn't cross the blood-brain barrier.

So maybe with the focused ultrasound, we could get the contrast enhancing lesion plus a slight margin around it in a different local way.

So I think there may be a role. I think as we're talking broadly about metastases, it wouldn't be the first thing that I'd focus on, but I think it'd be something that could be adjunctive and helpful.

DR. WEN: Mike?

DR. DAVIES: Mike Davies, MD Anderson. I was just thinking, as we talked before, about the concept of do we need separate cohorts versus just stratifying. I do think the one argument that I would argue for the cohorts, as we talked about, there are actually endpoints that are unique to the brain metastasis patients, so making sure that we designed the trial so we capture those, whether it's the neurocognitive dysfunction or whether it's the incidence of radiation necrosis.

I just wonder if we'd be able to efficiently or effectively capture those if we just go to stratification where we're using the same endpoints on everybody and miss those sort of CNS specific endpoints. So I think that could be an argument for why it might make sense to use cohorts specifically.

The other argument, just coming back to it, not argument, but about the phase 1 question of how early to go in. Again, as we talked about, we all know that if these drugs get approved, even if it doesn't specifically say brain mets, they're going to get used in patients with brain mets. So getting a safety signal in brain mets in phase 1 is absolutely a straightforward justification for doing that.

MS. ZUCKERMAN: I'd like to comment to that because we focused quite a bit on the breast, on lung cancer, and little on the other solid tumors, and of course my favorite being kidney cancer. We are finding out that there are probably far more brain mets in that group than anticipated, and historically.

Again, because we have better reasons perhaps to go in and look, suddenly it's not just a small percentage, but an increasingly large percentage. As the technology improves, we'll find more. And if we don't know the impact of the medications, all of them on brain mets and the

responses that may or may not come, we will have more failed trials in general.

The reality is, of course, even if we don't know the patient has brain mets, he's in the population that's being served by perhaps a less experienced doctor who then provides one or more medications and perhaps with some safety issues that could have been anticipated had we done proper and complete involvement and participation of all those patients without regard to brain mets.

DR. PROWELL: Can I ask a question, actually, to Dr. Abrey or anybody else in the room from industry. I'm curious what you think, from a large pharmaceutical company perspective, what do you think is more motivating to companies? Is it the incentive of being able to have a labeling claim of saying here's the activity in brain mets or even an indication in brain mets, or is it the fear or the desire to avoid a limitation of use?

What is more -- is it the consequence avoiding or the reward seeking that drives behavior?

DR. ABREY: This could be a whole study in human psychology.

(Laughter.)

DR. ABREY: Just a disclaimer, I spent half of my career or more in academic medicine, so I might not answer very straight. No, I think the incentive to me would be the possibility to differentiate around an enhanced labeling claim because I think that's how you stand out from the background. Having to either have a limitation of use or some sort of restrictive comment in your label is something that puts you on the defensive, and nobody likes to be in that position. We want to be better or competitive. I think we're all competitive, before, in those rooms, so sorry.

DR. SUL: I think given the audience here today, it's no surprise that we're all in agreement that more patients should be enrolling in clinical trials and that there should be more access allowed, and we've talked a little bit about incentives for industry, and wanted to know if we could hear from Peggy a little bit about the

patient perspective on incentives and barriers to enrolling in clinical trials.

MS. ZUCKERBERG: Well, first, there's endless barriers, and a lot of it is simply that we're not properly diagnosed as a group. I know I'm speaking always from a kidney cancer perspective, but I've got a feeling that most other cancers are very much the same.

You're suddenly told you have cancer. You're desperate to get it out or get it treated, whatever that cancer is, and rarely do you hear from your doctor that I can't do this or I won't do this, you better go onto a clinical trial. If you've got that far in your conversation to understand that you might need a clinical trial, unless you're from one of the many lovely centers that have just been mentioned today, and within 100 miles or maybe 20 miles or so, chances are, you're in a community setting, where your family is, where your support system is, and where you're unlikely to leave comfortably in his new stunning, terrifying situation you found yourself.

So access to trials starts with that doctor in that office and what I will call a complete diagnosis, and that includes not just where the tumor landed, where else it is, and I'm going to start with the brain on down. And then to find what those options are for you, and then a meaningful way to find all the clinical trials that might be available.

You and your doctor may not even properly characterize your disease to be able to search on clinicaltrials.gov or any of the other helpful sites. So that alone, just knowing that what you've got, where you can go, what your disease is really called, how it's characterized in the literature, all these are barriers; not even to understand what a clinical trial means, which is one of the pushes that every patient forum and every disease group wants to work with.

But that is why we don't get the numbers of patients into trials that we need, and then to be really desperate because your head's at risk, it's far more concerning that I would have had brain

mets than my liver was going to give me grief. And I was living quite nicely with my lung mets all over the place, but to think that your brain is going to go, is going to be chewed up by this cancer, is so frightening, so stunning, it is the game changer.

Then to find out you've got a limited number of choices in a trial, and you're now excluded because of the thing that's most threatening to your essential self is a betrayal of the medical system and the clinical trial system to the patient, in my thinking.

You've already been betrayed perhaps by your own body, perhaps by the doctor who misdiagnosed you, perhaps by the limitations of where you live and what you can afford, and now the clinical trial world that's supposed to be the foundation for the new and improved care won't let you in because you have brain mets, that's unethical, and it adds to the terrible distrust we have in our society for the medical world, which includes everybody from patient advocates, to doctors, and to the pharmas

who really suffer from that.

I think I have probably said enough, but that's enough of the barriers, and just not to understand what a clinical trial is.

DR. WEN: Thank you. A question at the back?

MS. SELIG: Can I pose a question on behalf of a colleague who was here, but I think she had to leave, and represents the lung cancer community, a thought that came up -- and maybe this would be something good for the regulators and the clinicians to respond to.

She was listening to the discussion of, well, we should measure this, and we should measure that, and we should know these things, and we should do all these tests. The flip side of that is the burden on the patient that's actually in the trial to go through all these tests.

So back to what Joohee was saying earlier, could we identify those things that we all agree are most important that we'd be measuring versus study everything, put the patient through a zillion

tests to gather all this information? Is there some way to balance the need to know more and to evaluate these therapies in the brain with the burden on the patient of actually participating in these trials?

DR. MARGOLIN: Wendy, I'm not going to try to answer this, but I want a part B to that. Just as Tatiana's question, you can't ask one person to represent the whole drug company industry, there are patients who want to be scanned every 5 minutes, who want to know. There are patients who don't ever want to know. So I'm not even sure that this kind of a question can be applied here; just saying.

DR. LIN: I'll add one point to that also. Patrick has been thinking about this a lot as part of this snow physician paper on barriers to trial enrollment. I think that more so -- I'm speaking for patients now, and there are patients here who can tell me what they think. I think more so than, okay, there's an MRI, there's a CAT scan, there's a blood test, travel is a big issue.

So I think whatever we can do when we design trials to minimize travel, to me that feels -- that's what I hear from patients, is that makes the biggest difference in their ability to go on a trial. So if you have day 1, day 4, day 8, day 11, day 16 blood draws, do they have to be done at the site? Can they be done at a local lab? Those very practical issues are I think really important in allowing better access to trials.

DR. PROWELL: I'll just comment on one thing. We hear you and we've heard this from patients as well. This is actually a huge topic of interest, not only in oncology but we've heard a lot about this from the neurodegenerative diseases community who have even more challenges and difficulty traveling that are metastatic cancer patients in many cases.

Just to make people aware, there actually is a decentralized clinical trials working group at FDA that's in the process of finalizing a draft guidance that we expect to come out late summer, and we're also going to have one of our two plenary

sessions at the AAADV workshop that's sponsored by FDA, Duke, ASCO, ACR in Bethesda on May 9th. The middle day of that workshop, we're actually having a plenary session on decentralized trials that Rich Schelsky from ASCO and I will be co-chairing, and we'll be talking about this issue.

DR. RIELY: That's a great effort to be part of because I think the question gets at the patient experience, and that's critical. But I think we need to get together and figure out what the best tests to do are, because if you ask all the investigators up here, we can tell you about 10 things that we do all the time that are dumb, and getting an MRI brain is not one of them. That's smart. The day 4 PK test, that's probably dumb. But we all have to agree on what's important, and I think that's hard.

DR. WEN: I'm going to take the two questions really quickly, and then I want to switch and talk about trials specifically for brain metastases, and then talk about endpoints. We have 20 minutes left, so I think we want to get to

those. The person in the back, you've been waiting a long time.

AUDIENCE MEMBER: Thank you. My name is [indiscernible]. I have been running for office for many times, [indiscernible] to U.S. Congress and U.S. Senate, plus Maryland state comptroller. As a patient myself before, I think as a mother, as a consumer, as a government employee, I have seen a lot of problems in our health care area, including the [indiscernible] data set. All the research is meaningless and this data should have accountability.

So many times I just say if the researcher wants to collect the data, first thing first. You have to have independent accountability to have good, accurate data. So I hope you can put this in mind, first of all. To do that, you've got to be independent sponsors, so you can see all those sites. Those are sponsors, and some of those I can testify they don't have independent or best interest of the general public.

DR. WEN: Thank you.

AUDIENCE MEMBER: The second is I would like to let you know after you have a drug, it's not necessary [indiscernible] best and efficient. These costs to the patients. I think now our health care is in trouble because all pharmacy and industry, even mergers, are a revolving door and don't have accountability for the best interest of our general public. Certainly, it's less affordable, and pharmacy, or hospital, or rehab center to get patient care.

DR. WEN: Thank you. Thank you very much for that comment.

AUDIENCE MEMBER: Pay attention to health care to consumers that complain. All this information -- put a consumer group up front rather than putting a pharmaceutical up front. Thank you.

DR. WEN: Thank you. Dr. Weinstock?

DR. WEINSTOCK: Thank you. I wanted to touch on a topic that came up in terms of endpoints in Session III, and I want to circle back to how that might apply to something that we were talking about in this session. And that's the use of an

endpoint, sort of avoidance of whole-brain radiation type of endpoint and how that might fit into a regulatory framework in a bit of a different way than the other kind of surrogate endpoints that you might think about traditionally.

The way we define an endpoint that's used in a regulatory framework for regular approval, there has to be demonstration of direct clinical benefit. In the prostate cancer setting, we were trying to wrap our heads around how to define an avoidance of harm endpoint and direct clinical benefit endpoint into maybe an earlier clinical endpoint that could possibly, when designed appropriately -- and I think we're not there quite yet -- could possibly even lead to a regular approval based on avoidance of harm or direct clinical benefit.

I think that could be presented to sponsors as a possible incentive because if you look at a brain specific endpoint like this, it's sort of a different way of looking at the endpoint, rather than looking at a surrogate, which would need to lead to an accelerated approval, this may be a

regular approval endpoint that weeds out earlier than more conventional measures of direct clinical benefit.

I'm not sure if I'm getting my point across because this is a very regulatory framework, but I'm just saying that this could be used as an incentive to enroll these trials.

DR. MARGOLIN: But you still have to have really good control comparator.

DR. WEINSTOCK: This would have to be in a -- certainly in the prostate setting, this is in the context of a randomized controlled trial, but my point is that it's a much earlier readout than you necessarily have with the more conventional measures of clinical benefit.

DR. LIN: We thought about this a lot. Yael Lazer [ph], who's a radiation oncologist in our group, is launching a screening brain MRI trial for patients with metastatic breast cancer, and we thought a lot about the right endpoint. We tossed around time to radiation, time to whole-brain radiation, time to SRS, time to symptom

deterioration.

One of the problems, practically speaking, with the time to whole-brain radiation endpoint is that people are doing now SRS to more and more lesions, so it's kind of subjective when somebody gets whole-brain radiation in a way. I mean, if somebody has 30 lesions, not so subjective.

So ultimately, we actually came around to Jeff Wefel's conclusion, which is that we just really have to look at neurocognitive endpoints. So that's actually what the study is powered to, because I think it is. I think this time to whole-brain radiation is tricky because of the availability of SRS and multiple lesions, especially now that we can do this with single ICE [ph] center and do this with many, many lesions in one session.

DR. ABREY: Thank you. And also for the sponsor's point of view, be limiting the trial to a very U.S. focus in that situation, so just thinking about where whole-brain radiation is still used. And also I want to put a little bit of caution

here.

It's still a very effective therapy and I don't think we should make all patients so terribly afraid of it that when you need to use it, it's somehow the worst thing that could ever happen to them. But I think the extreme use of radiosurgery is not seen across the world, and then you'd be focusing on a very limited potential market, which drives a lot of the choices in pharma right now but not great for patients necessarily.

DR. PROWELL: We were talking during the break about what is the real possibility of persuading investigators in a large randomized trial, or particularly in a global trial, of coming up with a uniform algorithm to how they would administer steroids and to which patients would receive radiation, recognizing that you really are dictating practice of medicine and is that even something that's possible. And the neuro-oncologists all said impossible; there's no way you can get them to all agree on this.

But I'd be curious to hear perspectives of

others in the room if they think that that's something that you could even get people to rally around and say we recognize that we all do this differently in our own clinic, but from the standpoint of this clinical trial, here are criteria that we can all agree upon, which might enable us to use certain endpoints like time to whole-brain radiation, for example.

DR. WEN: Just a quick comment from Dr. Gondi and Dr. Chung, and I really want to move on to the other two topics that we need to discuss.

DR. GONDI: Two comments I'd say for the time to whole-brain radiotherapy, but I just want to make it also clear that it actually nicely presented with Doctor Brown's online session. I agree that whole-brain radiotherapy does have some cognitive issues, but we've come a long ways in preventing those cognitive issues. We didn't really spend a lot of time talking about this today, but hippocampal sparing, which is coming out and been submitted to ASCO and prophylactic [indiscernible], we're seeing fairly significant

cognitive benefits with these interventions. So I think to Dr. Abrey's point, sometimes the metastatic disease is really what drives the cognition as we try to involve safer radiotherapy approaches.

Secondly, as a question to the panel, as we talk about all these endpoints and challenges of these trials, some of the best brain met trials have actually been run by the NCI, and I wonder what type of opportunities we have in collaborating with the NCI and industry to run basket trials in the area of brain metastases.

Dr. Brastianos' trial is a great example of moving in that direction; did a great job with the MATCH trial, which did not include brain metastases. But how do we allow various industries to work together in basket trials to address all these other endpoints that may not have enough resources to address.

DR. WEN: Thank you. Let's talk briefly about trials specifically for brain mets. Maybe Nancy and Kim, if we could have your thoughts.

What does a trial look like and what are the endpoints, if we had this magic drug X that's going to be great for brain mets?

DR. MARGOLIN: I'll take a shot first because I want Nancy to be the finisher and the one who says the final words of wisdom, because I wrote down a couple notes, and I actually wanted to say that I agree with something Mike Atkins said earlier and would like to expand on that just a little, which is the concept that for many, not all necessarily, patients with brain metastases from most of the tumors we're talking about, lung, breast and melanoma, the presence of brain metastases, at least when they're symptomatic and of a substantial size requiring steroids, et Cetera, is not always but often going to be considered the overall lifespan limiting factor in that patient's natural history.

So the use of a survival endpoint, at least as one of the endpoints, but really maybe the primary endpoint in many of the trials, I really think is a good idea, even though I was arguing for

many composite and parallel endpoints as long as they go the same direction, and I don't think those two things are incompatible depending on the kinds of patients.

Also, we often talk about the fact that you can't use survival as an endpoint in randomized trials because of the high likelihood that patients who are assigned to one treatment will end up crossing over, whether it's on study, or outside of a study, to the other arm or something like it, and thus that sort of blurs the ability to dissect out survival as an endpoint.

But I think there are times when that's not altogether true, if you think about the idea that the first therapy that you give somebody may be the most definitive one, and that may be the one that alters or defines the survival benefit. Even if you could get that drug later, it may not catch up. I'm going to turn the rest over to Nancy.

DR. LIN: Here, I would think of two kinds of studies, and I think the considerations are different. I think there's the ALK kind of story,

which is patients with brain metastases, included in their early-phase trials, seeing CNS responses, and then those patients included actively in the phase 3 registration strategies, and they were enrolled with the purpose of treating both their CNS and their extracranial disease.

So there, if they're going to be included as part of the overall set, you'll have a certain type of endpoint that you need to pick that will be relevant to all patients entering on a trial, and then you may have secondary endpoints that are important for the brain metastasis subset. So that's kind of one type of study I think of.

The other type of study is the study that really only exclusively enrolls patients with active brain metastases, where the goal is to treat their brain metastasis. I think there, you can obviously choose more CNS-directed endpoints. You could always choose overall survival because these are patients where you are probably more likely to see an overall survival advantage given the dearth of other therapies that the patients can receive.

But here I think, from a practical standpoint, in addition to the endpoint challenges, it's really the control arm because speaking for breast cancer, there's no obvious control arm. You could have a control arm of radiation, I guess, but then you have all these considerations of what's the right endpoint.

I think that that's a challenge, and I'm interested from a regulatory perspective under what circumstances, for example, a single-arm experience might have to gain regulatory approval; what sort of endpoint would be sufficient understanding it's a non-randomized experience, so survival is a little hard unless you hit it out of the park. I think the considerations are different depending on whether you're including the patient or you are doing a brain met specific study.

DR. SUL: I think some of this goes back to what we started out with in thinking about context. I think that's probably one of the most common questions we get asked, is can I use an objective response rate to get approval? I think it's more

helpful to think about it in terms of in which situations does looking at objective response rate make the most sense to look at benefits.

For instance, if you're looking at a drug that has no track record and you have no idea that the mechanism of action ties in with the effect of the drug, it's harder to look at these single-arm studies. I think if you are looking at a drug that has a well-proven track record in other malignancies, your response rate is -- Paul was saying sometimes the robustness of the data or the effect can help overcome some of the uncertainties, so you have a really robust response rate. You're seeing CRs, which we don't see in patients with brain mets, then I think those kinds of aspects are helpful in helping us interpret.

It's not so much is it endpoint; it's the data that comes from it and how we interpret it. That's one of those questions I always struggle with, is can I use PFS? Can I use ORR? And the answer's always, well, it depends, and the circumstances really are what shape the outcome,

and nobody likes that answer.

DR. NDOUM: Can I -- sorry.

DR. PROWELL: I was going to say, you can always measure it. The question is can we interpret it when you submit it to us?

DR. NDOUM: So back to being a hammer. If such a single-arm submission was backed up with biological data -- say you had preclinical data that every time you use drug X, you get this biological response Y within the tumor, and then you had an actual window of opportunity study in this single-arm setting where you gave the drug and you saw the exact same biological response, and then you were additionally seeing these objective responses in these patients in this single arm, would that help support a potential filing for metastatic drug-specific indication?

DR. SUL: I think specifically for preclinical data, that's always helpful. Regardless of whether you're talking about interpreting the endpoint or designing the study, I think that's absolutely important. But again, I

think it really depends a lot on the magnitude, the patient population.

I'm not sure how many different ways to put it, but we have to take the totality of the information into account when we evaluate the effects of the drugs. And I know it's not the most satisfying answer, but you can do it, and we'd have to sit and interpret the data.

DR. NDOUM: Translating, she said it would work.

DR. ANDERS: Carey Anders from Duke. I just wanted to follow up on what Nancy brought up as the second part of her conversation, and that's the control arm. I think many of us have designed single-arm, stage 2 studies with response rate or a PFS compared to historical control, but many times our historical control is very difficult to interpret. So whether or not you actually have a signal is hard to know.

In thinking about this, particularly in breast cancer not having a gold standard, the thought process around physician's best choice or

MD discretion and what that would look like, I recognize from a patient perspective and talking to my own patients about that, that's not the most attractive trial design unless there is a way to crossover and still allow patients access to hopefully promising investigational agents.

So I just wanted to open up conversation around control arms and how we should be thinking about this as we're designing our own studies.

DR. WEN: Dr. Tawbi? Did anybody want to comment?

DR. ANDERS: I'm kind of following up on the EMBRACE data in breast cancer. That's always been very striking to me. For those who don't do breast cancer every day, eribulin was FDA approved based on a survival advantage compared to physician's best choice. I use that every week in my practice to select eribulin when I'm stuck with that.

So I'm just curious if that could be something we could be thinking about, also recognizing that the studies are going to be larger. It's a comparative design, so to have

appropriate power, we'd need larger studies.

DR. PROWELL: I think part of what made that trial successful was the fact that they were going in very refractory patients, so those were people who had had I think at least 3 lines of therapy, but the median was 5. So these were patients who really had a very poor prognosis for metastatic breast cancer, and overall survival was the endpoint.

I think that was a very pragmatic clinical trial where you said, look, this is what's going to happen, is you're going to give them either capecitabine, or this, or this, or this, or whatever the whole list of drugs that were in the menu that one could choose from for treatment of physician's choice.

One thing that we've considered when we look at trials using treatment of physician's choice as a control arm is that you have to choose the treatment of physician's choice before the randomization. That may introduce some complexity when you're talking about a brain mets trial that

isn't present necessarily in a conventional metastatic breast cancer trial. We can maybe talk about that.

I'm not a neuro-oncologist, though I'm sitting up here half the day. But the neuro-oncologists would be the better ones to really comment on that issue of the feasibility of selecting that standard therapy before randomization.

DR. SUL: I think that also kind of goes back to your earlier question about how much can we dictate what goes on in a clinical trial. I think the more options you have -- A, the more difficult it is for physician's best choice, the more difficult it is potentially to interpret that data. It's also harder to design the trial to say you have to choose from these two or three. But I think that those are definitely things to consider, that could be considered as potential control arms.

DR. WEN: Dr. Tawbi?

DR. TAWBI: Hussein Tawbi, MD Anderson. I actually just wanted to follow up on Kim and

Nancy's points about which kind of buckets of clinical trials we have and which endpoints we choose. I really think, even within brain metastases specific clinical trials, we actually should allow for different endpoints in case you have IO versus non-IO. Even thinking about being pragmatic and combining with SRS, SRS plus IO may actually modulate the response, and you may have longer term outcomes just because you added SRS 6 months later or even 3 months later.

So we do need to kind of think about the quality of the response to the immunotherapy and use as compared to a targeted therapy.

DR. MARGOLIN: I think sometimes the more brilliant and the more creative at trial is the less practical it's going to be for an approval endpoint, but it's still a great comment.

DR. TAWBI: Sort of a constant debate --

DR. WEN: One final comment from Caroline.

DR. CHUNG: I just want to make a comment that we've mentioned a number of times that composite endpoints would be really helpful in

developing a surrogate that is a composite that reflects both patient function as well as the imaging response, et Cetera. I think the one thing that I would propose that we could potentially agree to do today is I think most of us would know which of those endpoints that we would want to include in most brain metastases trials.

I think, to sort of echo Ben's message around standardization, if we can actually standardize which key endpoints we will include in every brain metastasis trial, we can actually -- we're in the modern era, as Paul mentioned, using technology to our benefit, and I think that we're in the modern era where we can use computational oncology. We can use big data approaches. We have electronic health records that will allow us to bring this data together from multiple trials.

So it's not necessarily a retrospective meta-analysis, but if we're actually collecting standardized structured data across these trials, we can actually start to not necessarily create

definitive conclusions, but we will actually develop meaningful data-driven hypotheses about surrogate endpoints that we can validate in future trials.

Until we actually come to that consensus of which of those structured endpoints we're going to include in every brain mets trials, that just wouldn't happen. But I think that would be a meaningful conclusion, or meaningful product from this meeting because I think we're all very motivated to do it. There's going to be many different trials that are going to come down the pipeline, but if we can actually collaborate and actually cohesively come up with a list of specific endpoints we want to include, we could go a lot further along in the long run.

DR. LIN: I totally agree, and just as an example, even just for imaging, which we think is very simple, or maybe not so simple, RECIST and RANO are in a collaboration to actually -- and EORTC is funding the data center to pull in actually radiology imaging across multiple brain

metastasis trials. We're finalizing the legal language of the request letters, and many of you in the audience may start getting these letters asking for your trial data to be able to answer some of these questions.

The reason that we actually have to pull in all the primary imaging data is that unbeknownst -- I didn't realize this, but when the RECIST criteria were developed, nobody pulled in scans, they just pulled in the case report forms, because everybody basically around world collected the target lesions the same way. They measured them the same way. They did them all on CT scans. So no one ever had to do primary image analysis. They just took the data, and they rerun it a bunch of different ways, and that's why we look at 2 target lesions and not 5 target lesions, et cetera.

You can't even do that with just the imaging of brain metastasis trials because everybody collected a different way. They did different scans. Some of them did MRIs; some of them CTs. Some collected 5-target lesions. Some collected 2.

Some collected 10. Some collected volume only. Some collected linear dimension only.

I mean, the data itself is a mess, and then you can't actually combine any data sets. You actually have to start from scratch, go to the original imaging, and do it all over again. So I think if we maybe learn from that and do it better, we can do better in the future.

DR. CHUNG: I think we can do it over and over again more easily because we now have automated methods of reanalyzing the data. So if we build the algorithms, we can evaluate across studies to see whether these measurements that we've done manually versus in an automated way fashion really agree.

DR. WEN: Thank you.

DR. AMIRI-KORDESTANI: Thank you. I just wanted to actually make a clarifying comment. I'm sorry. I forgot to introduce myself earlier. My name is Laleh Amir. I'm a hematologist/oncologist at the Division of Oncology Products I.

We have two pathways for approval. And as

you know, the accelerated approval pathway basically relies on an endpoint that is not really a validated endpoint, and it doesn't need to show a direct clinical benefit. So basically, it doesn't really need to have a surrogate endpoint that is already validated. As long as you come in and basically discuss it with the FDA and the endpoint is appropriate for that patient population, We actually accept that for an accelerated approval pathway.

That goes back also to the other comment that was about in a single-arm trial like a response rate be acceptable? Yes. We have actually approved many drugs only based on a response rate, even as a regular approval more recently. So yes, it could be accepted. It really depends on -- we look at, for example, duration of response. We also look at what is available therapy for that patient population. In a totally refractory patient population that has nothing available, it sounds like it should be acceptable.

So I really encourage, actually, that if you

see some encouraging results, like even an intracranial response rate when the drug is actually controlling the disease also outside, you just come in and actually bring the results in because, really, we like to see those studies happen, and it may actually be adequate for an accelerated approval, and then we can strategize and design it more like a confirmatory study so that actually the benefit could be later on proven in a more randomized fashion if it is necessary.

Sometimes actually, more recently, because of some scenarios that you couldn't even do randomized trials, we may actually not even require that. So it really depends on the context, as was mentioned by many of the colleagues here. That's basically what I was adding.

DR. WEN: Thanks so much.

I want to thank the panel for the excellent discussion.

DR. AMIRI-KORDESTANI: Did you want to ask me a question?

DR. WEN: I think we're going to have to

move on.

MS. SELIG: I'm going to propose the following. We are coming to the end. Patrick and Joohee are going to have some comments also at the end. I wanted to give you both a chance on this panel to make any kind of final comments about this discussion. Then we have a 10-minute brief presentation from the American Brain Tumor Association, one of the sponsoring organizations, and then some closing comments.

Would all of you just stay there so that we just can keep going, if you don't mind, and then you don't get to leave early. You have to stay and listen to the ending comments, too.

Joohee, Patrick, did you want to make any comments now or do you want to --

DR. WEN: Maybe in the interest of time, we'll do it --

MS. SELIG: Contemplate them. Okay.

We now have Ralph DeVito and Nicole Willmarth from the American Brain Tumor Association, one of the sponsoring organizations.

They have been doing some excellent work that's very complementary to all of this discussion, so we're going to take a few minutes -- just a few minutes, you guys -- to talk about it.

Presentation - Ralph DeVito

MR. DeVITO: Everything's running very smoothly. Thank you, Wendy. Thanks to David, the National Brain Tumor Society, for the FDA for convening this group. Great conversation; just absolutely wonderful.

I am Ralph DeVito, CEO of the American Brain Tumor Association. Nicole Willmarth is our chief mission officer. We'll take just a few minutes with a few slides to tell you about some work that really began before I started. I've been on the board about a year with ABTA, and they had envisioned a real in-depth, survey-based analysis of the brain mets issue.

So there is a brain metastasis issue at ABTA, in coordination with others, that has been in effect for a while. So we just wanted to quickly highlight it. I'll give an overview, and then

Nicole will talk a little bit about some preliminary high-level findings and then some next steps. I also want to put a plug in for the SNO brain mets conference in New York this August. This should be a pretty exciting session, and it's wonderful to see this issue being given great in-depth focus.

Let me go to the first slide. Let me just, in the interest of time, skip ahead to show you our collaborators, our science, our clinicians, our patient advocate that's helped us with the survey development. We have a third-party vendor that's been working with us. Nicole and her team have been working hard, and we have moved through a lot of our work.

We're going to do three panels of surveys. We have already surveyed over 200 patients, we have surveyed over 200 caregivers, and our next step is to survey over 200 oncologists. With that data, we're going to be developing new programs and new services. And I do want to say that currently the ABTA is providing high-risk, innovative research

that we're doing in this area, and we're also offering currently to patients brochures and information, webinars, and other information today. With these findings, there's so much more that we and you can do to serve patients far more.

Nicole?

Presentation - Nicole Willmarth

DR. WILLMARTH: Thank you, Ralph. And I also want to second his thank you to the FDA and for the National Brain Tumor Society bringing everybody together. I think bringing all these perspectives in one room today to have these discussions is so important. I feel humbled listening to the conversations that we've had today. I've learned so much and really appreciate everybody being here.

I think we've been noticing a lot of themes today, one of which is hope and making sure that we keep that in the back of our minds for the patient perspective. But then also I think there's a theme of considering that we're treating a patient with brain metastases and not just treating the brain

metastases. Those are things that we want to keep considering as we come full circle with bringing in the patient perspective.

I'm going to just, as Ralph said, do a very high-level overview of some of the initial findings from our survey just so that we can give you a little piece of that. A lot of this probably won't be of any surprise considering what we've discussed today.

Just to start out with the patient caregiver surveys, we did two online quantitative surveys. One was to 237 cancer patients, which was a representative mix of patients with brain metastases, and then also another survey to 211 caregivers of cancer patients who have brain metastases. This was conducted back at the end of 2018. The sample was provided by -- we worked with our survey vendor. They had a panel that was surveyed as well as working with our advocacy partners that Ralph just mentioned, and I'm going to go through this very quickly. I apologize, but considering the time constraints.

To summarize just high level, the patient survey, this again won't come as any surprise probably to most people here, but a diagnosis of brain metastases was a surprise to 9 in 10 of the patients that we surveyed. Their top concerns upon learning of their diagnosis was the impact on their quality of life as well as the likelihood of treatment success. I think this goes hand in hand with what was discussed today, is you can't really separate the importance of those to a patient. Those are really both top priorities.

Also, what came out of the survey was that fewer than half sought a second opinion, and they really felt that -- actually most said that they felt that they received enough information from their oncologist, and 81 percent actually were diagnosed with brain mets from the same doctor who diagnosed their primary.

So what this suggests is that they didn't really seek out a second opinion as to what type of treatment to pursue for the brain metastases, so I think there's a lot we could learn there.

This goes along with what we were talking about with clinical trial exclusion. Some of the patients did report being denied participation in clinical trials, and the experience for them was emotionally taxing.

Twenty-four percent said they were denied participation in a clinical trial related to their primary form of cancer because of their brain metastases, and 19 percent said that they were denied participation in a clinical trial related to brain metastases because of previous treatments of their primary form of cancer.

Some of the comments that were written into the survey we have here. "It was so disheartening to be close to a possible treatment only to be rejected. It was a very brutal and emotionally taxing experience, and I was interested in pursuing a particular clinical trial, but it excluded people with brain metastasis."

Then just a summary of some of the highlights from our caregivers survey, most of the caregivers -- just a little bit about the

profile -- had a personal relationship with the patient. The patient was in most cases their parent. Caregivers expressed many of the same reactions to learning of the diagnosis as the patient's did. Many expressed shock and depression.

Over 6 in 10 said they were familiar with brain metastases before becoming caregivers, however, that means about 40 percent were not familiar with brain metastases.

Caregivers were most concerned about the effect on the quality of life of the person under their care and the likely success of treatments, which mirrors what the patient perspective was as well. And nearly 9 in 10 caregivers said that there was an emotional impact on them as a result of caring for a brain metastasis patient.

So quickly to wrap up, because I know I've already gone over, for the next steps, as Ralph mentioned, we would like to also do an oncologist survey, so we're currently developing a survey to understand from the doctors who treat these brain

metastases patients, from their point of view, what the journey is like when treating these patients. That way we can understand better if there's agreement or disagreement and the knowledge or perception from the patient perspective and the oncologist perspective.

Once all the survey results have been compiled and analyzed, we hope to present the data at the Society for Neuro-Oncology meeting in November, so stay tuned for that. That's it.

(Applause.)

MS. SELIG: Thank you so much. It's really, really important to understand the patient perspective and the patient experience, so thank you guys.

We're going to ask Joohee and Patrick, our fearless co-chairs, to make some wrap-up closing comments and in particular what you heard that you think is actionable, and then the final uh, next-steps discussion will come from David Arons, and then we will conclude and get everybody on their way. Thanks for sticking it out.

Summary and Next Steps

DR. WEN: I wanted to thank everybody for coming today. It's been a really great discussion. We're so lucky to have all of you here. I think today we heard hopefully things that will move us closer to significantly increasing the participation of brain metastases patients both in all oncology trials and also the development of more trials specifically for brain metastases.

I think Nancy gave a really nice talk earlier about perhaps the limited importance of blood-brain barrier penetration for a therapeutic effect. Perhaps it's more important for prevention, but that's something that should lower the barrier of drugs being evaluated for brain mets.

I think ideally, all patients with brain metastasis should be considered eligible for oncology clinical trials, whether they should have treated lesions or whether we would include patients with small asymptomatic lesions where they could be on drug for a month or two and closely

monitored, and taken off it if there's progression.

I think we need to also think about whether we should recommend routine adoption of the Friends of Cancer Research recommendations and the RANO recommendations for eligibility into trials. I think there needs to be guidance on eligibility to reduce the restrictions, including time from radiation and a number of other factors.

In terms of the trials specifically for brain metastases, I think we heard that potentially in some situations, objective response rate might be a path to approval, and if we use that, is the RANO BM criteria the one that we should use instead of all these variations that are still being considered in different trials. There was also discussion on the need for randomization for the more definitive trials and the challenges of the control arm.

Going forward, there are some things that clearly we need to do. We need a standardized brain metastases imaging protocol that will be similar to the one that's been used for

glioblastoma but with some minor differences. Hopefully, that would be used for all brain metastases studies so that there's less variability.

I think we need guidance on eligibility criteria for these trials on the optimal endpoints, as Carolyn discussed. I think we need to continue -- this is an audience that really cares about this issue, but there's a whole world out there that is still thinking several years back where brain metastases patients should just be excluded from all these trials, and we need to educate them and spread the message.

So going forward, I think SNO and RANO are definitely committed to doing this and partnering with all with you, and our conference in August is one step in this direction. So thank you all so much for coming today. It's been a really important step forward, and we're grateful to all of you.

DR. SUL: Thank you, Patrick.

I'm going to actually start with my thank

yous first because I know I'll run out of time and then I'll forget to thank people. I want to thank everybody who participated in the planning and also in the development of the workshop. I also want to thank all the patients and the patient advocates and representatives who came here today to give a voice to all the patients who enroll on these studies that we review but we don't actually get to meet the patients face to face.

I also want to thank my FDA colleagues for participating and helping, and also for having discussions with me about a lot of these issues, sometimes heated, sometimes controversial, and really being interested in this topic, so I want to start with that.

I think a couple of the common or recurring themes that I've heard today, one of them is standardization, whether or not that's an approach to how we use steroids, or decide on radiation, or what studies should be included, or whether it's an imaging protocol. I want to go back to what Ben Ellingson said it at the very beginning, that

standardization really makes interpretation of information much easier, and it's essential to get a clear picture of what's going on; so that's one thing.

The second is these different baskets of trials, trying to separate out the populations. We sort of touched on that, but we didn't get to really delve into how we would do that. So how do you separate out the untreated versus the treated patients? When do we decide that SRS should be the point at which patients are not included on trials? What's the, quote/unquote "washout period"? I know that Dr. Gondi doesn't like that term, but we're just going to use it because it's familiar.

Timing of therapy sort of ties in with that as well because there are therapies like radiation therapy, which are not really regulated in the same way by FDA but are still considered standard of care. So we need to figure out how to smartly include those as well.

One comment I did want to make, because it came up a couple of times, is it seems that people

are really afraid of seizures because people kept saying, well, somebody had a seizure. This is going to circle back to having a multidisciplinary approach.

Neurologists in general are not afraid of seizures. I mean, we see patients have seizures. Status epilepticus, that's a different story. And not to say that it's not serious, but it shouldn't be the reason why you don't want to develop a drug because guess what? We have great treatments for seizures. We don't have great treatments for brain metastases. So don't let that be the reason why you don't want to move forward with development, and ask the neurologist and the neuro-oncologist to collaborate with you on these studies to make it safe to include these patients and to evaluate them.

DR. WEN: Thank you.

MR. ARONS: Thanks Patrick and Joohee. Wendy told me to come here so that's what I'm doing. I generally do what I'm told.

Thank you all for being here today. Thank

you so much to the FDA and to all the partners and experts that came together. I'll have a few more thank yous, but just a few points that I wrote down in my notes from a patient advocacy perspective.

We started out the day with a theme of hope, and Mr. Queen brought that. And I really want to thank him for starting us out with the perfect theme of the day and his story. But as we know, hope is not a strategy, but what hope can do is bring a sense of determination to create one. And we certainly started to build the ingredients for a realistic strategy to move forward against this disease today in this room.

We recognize this is a very vulnerable population, a population at great risk, but yet it's very numerous. So what we began to do today was to take a situation that's really a problem, and try to figure out how can we use this population and use what we know as assets to flip this on its head and say, what can we do that can work.

We talked about some really big points from

a patient advocacy perspective; include patients in trials, period end. Let's just start including the patients in the trials. No more excuses, no more barriers, let's move forward and begin to do that. And if there's a reason against it scientifically or medically, figure that out, but the default status should be include patients in trials.

Dr. Brastianos brought up a very important point scientifically, and that is, is there biological considerations that make this disease different from the systemic disease, that ultimately not really -- her point was not harmonized throughout the day, so there seems like there's going to be more work to figure out when is this disease uniquely different, warranting a different kind of trial, different issues than say the regular disease outside of the brain.

The FDA opened up a tremendous opportunity for science today, and Paul Kluetz and others talked about it, is the opportunity to develop patient-focused endpoints and clinical outcomes assessments that really reflect what patients want

to see in new medicines, new therapies, new devices for that matter.

So we should try to drive a truck through this opportunity and come up with new medicines, new therapies that both extend survival but really reflect the kinds of domains and general concepts that that patients wants, like what was said by a patient earlier. She wanted to retain her brain's functioning, period, end. She wanted to keep her cognition. That would be really awesome if we could see more therapies do that.

There's great traction to move forward in this era of precision medicine with basket trials and even adaptive trial design that is very patient focused, and that could be done in this disease. I'm agreeing with all the action items and ideas that Patrick and Joohee mentioned but just wanted to add those.

I'm hopeful that the group of nonprofit organizations listed up there will all stay together now kind of as a loose coalition to see this through the next phase, which is getting the

summary together, working collaboratively with the FDA on a guidance document. If the FDA wants any help from all of us as a team, we're happy to do it. And then to try to take this forward as a scientific and product development agenda into the future.

To the companies in the room, really, thank you for being here today. That's huge, and we're really grateful for your expertise. And as you think about product development as a company and the investigators thinking about product development in investigator-driven trials, I think all the nonprofits and patient advocacy groups here would like to be of assistance to you to discuss how to do this together and to reduce the barriers to making new therapies possible.

Finally, I get to echo what Joohee said. Thank you to the patients who have been here today who have spoken up and who are adding so much to this discussion. So thank you again, really appreciate everybody who was here today and everybody who patched in by the webcast for that.

Thank you to all those who helped make the technology possible. Thanks again. Appreciate your time.

(Applause.)

(Whereupon, at 3:57 p.m., the meeting was concluded.)