

1 WORKSHOP ON PRODUCT DEVELOPMENT FOR CNS METASTASES

2

3

4

5

6

Co-Sponsored by the FDA and
National Brain Tumor Society

7

8

9

10

11

Friday, March 22, 2019

12

8:33 a.m. to 3:57 p.m.

13

14

15

16

FDA White Oak Campus

17

Building 31

18

The Great Room

19

10903 New Hampshire Avenue

20

Silver Spring, Maryland

21

22

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Opening Remarks	
4	David Arons, JD	8
5	Richard Pazdur, MD	12
6	Presenting the Challenge	
7	Patrick Wen, MD	14
8	Joohee Sul, MD	18
9	Session I: Defining the Problem of	
10	CNS Metastases	20
11	Moderators - Laleh Amiri-Kordestani, MD	
12	Greg Riely, MD	
13	Discussant Presentations:	
14	Clinical Management of CNS Metastasis	
15	2019: Current Strategies,	
16	Investigations, and Key Challenges	
17	Michael Davies, MD, PhD	20
18		
19		
20		
21		
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Panel Discussion	
4	Derrick Queen, MD, PhD	37
5	Luke Walker, MD	41
6	Victoria Ebianana, MD	43
7	Michael Davies, MD, PhD	44
8	Manmeet Ahluwalia, MD	46
9	Session II: Key Issues for Clinical	83
10	Development for Brain	
11	Moderators - Chana Weinstock, MD	
12	Nancy Lin, MD	
13	Discussant Presentations:	
14	Identifying Targets for Brain Mets	
15	Clinical Studies	
16	Priscilla Brastianos, MD	84
17	Selecting Drug Candidates for	
18	Brain Mets	
19	Nancy Lin, MD	98
20	Issues with Conducting Brain Mets	
21	Clinical Trials	
22	Kim Margolin, MD	117

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Standardizing Brain Mets	
4	Response Assessment	
5	Ben Ellingson, MD	125
6	Panel Discussion	138
7	Session Recap	
8	Chana Weinstock, MD	159
9	Session III: Clinical Benefit in	
10	Patients with Brain Mets	162
11	Moderators - Carey Anders, MD	
12	Tatiana Prowell, MD	
13	Discussant Presentations:	
14	Regulatory Definition of "Clinical Benefit"	
15	Paul Kluetz, MD	163
16	Panel Discussion	175
17	Terri Armstrong, PhD	176
18	Shelly Engfer-Triebebach	178
19	Chitkala Kalidas, PhD	181
20	Benjamin Levy, MD	182
21	Jeffrey Wefel, MD	185
22	Arvin Yang, MD, PhD	186

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Panel Recap	
4	Carey Anders, MD	229
5	Discussant Presentations:	
6	Regulatory Challengers for CNS	
7	Metastases	
8	Shanthi Marur, MD	233
9	Panel Discussion	241
10	Lynda Weatherby	243
11	Hussein Tawbi, MD, PhD	249
12	Palavi Mishra-Kalyani, PhD	251
13	Vinai Gondi, MD	252
14	Patricia Keegan, MD	253
15	Kim Blackwell, MD	255
16	Michael Atkins, MD	257
17	Panel Recap	
18	Tatiana Prowell, MD	314
19		
20		
21		
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Session IV: Therapy Development:	
4	Challenges and Opportunities	316
5	Moderators - Joohee Sul, MD	
6	Patrick Wen, MD	
7	Panel Discussion	
8	Peggy Zuckerman	317
9	Edjah Ndoum, MD	320
10	Caroline Chung, MD	320
11	Lauren Abrey, MD	320
12	Tatiana Prowell, MD	322
13	Kim Margolin, MD	326
14	Nancy Lin, MD	329
15	Overview of the American Brain Tumor	
16	Association's Metastatic Brain Tumor	
17	Initiative	
18	Ralph DeVito	375
19	Nicole Willmarth, PhD	377
20		
21		
22		

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Summary and Next Steps	
Patrick Wen, MD	383
Joohee Sul, MD	385
David Arons, JD	388

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

1 even call on you.

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

8 They outnumber primary brain tumors by a
9 ratio of 10 to 1 according to some studies and
10 occur in about 25 to 45 percent of all patients
11 with cancer. Conservative estimates suggest that
12 100,000 to upwards of 180,000 new cases of brain
13 metastases are diagnosed every year in the United
14 States.

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

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

6 A big thank you to the Food and Drug
7 Administration for hosting this workshop and for
8 partnering to plan the workshop. Thank you to
9 partner organizations that formed the planning
10 committee. They are Accelerate Brain Cancer Cure;
11 American Brain Tumor Association; Friends of Cancer
12 Research; Kidney Cancer Research Alliance;
13 LUNGeivity Foundation; National Brain Tumor Society;
14 Metastatic Breast Cancer Alliance; Melanoma
15 Research Alliance; RANO; and Society for
16 Neuro-Oncology.

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

1 Wen.

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

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

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

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

4 (Applause.)

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

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

22 I'm very interested in this meeting. As a

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

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

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

1 metastases.

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

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

14 (Applause.)

15 **Presentation - Patrick Wen**

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

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

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

1 will be the goal of the meeting today.

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

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

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

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

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

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

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

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

11 (Applause.)

12 **Presentation - Joohee Sul**

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

1 brain metastases.

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

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

1 thank you very much.

2 (Applause.)

3 **Session I**

4 **Presentation - Michael Davies**

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

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

1 disclosures.

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

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

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

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

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

22 So whole-brain radiation therapy is

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 In addition to those overall concepts, I
13 just wanted to highlight two key clinical trials
14 and the lessons that were learned that I think are
15 particularly impactful for thinking about this in
16 the future. This is a slide presented at ESMO
17 2018, a randomized trial of brigatinib versus
18 crizotinib in ALK-driven tumors, and what we can
19 see on the left are the outcomes in patients with
20 brain metastases; on the right, patients without
21 brain metastases.

22 What we can see here is that very early it

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

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

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

1 patients with active and progressing brain
2 metastases.

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

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

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

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

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

19 As you can see in the waterfall plot, when
20 we treated patients with BRAF mutant brain
21 metastases, we saw disease control rates of almost
22 80 percent, very similar to what we see in

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

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

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

22 What really revolutionized our expectations

1 for patients with brain metastases were two trials
2 that look to combined immunotherapy with ipilimumab
3 and nivolumab, patients, again, who did not require
4 steroids, where we saw response rates of close to
5 50 to 60 percent. And what's been so striking is
6 the fact that almost all of those responses are
7 still ongoing such that we saw a one-year overall
8 survival rate of 81 percent in the CheckMate 204
9 study.

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

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

1 looking for less toxic regimens.

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

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

19 The striking data is the median survival of
20 these patients is actually in the range of 2 to
21 3 months. I know in melanoma, we actually measure
22 our outcomes in weeks instead of months because of

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

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

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

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

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

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

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

4 (Applause.)

5 **Panel Discussion**

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

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

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

22 I had a stressful job. I was working as a

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

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

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

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

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

14 So there became the quest of how to beat
15 this disease. I was BRAF positive. Two drugs that
16 worked for me with incredible efficacy, I took
17 those drugs, but as Mike Davies just said, these
18 drugs for melanoma patients can last 6 months. In
19 my case, it was even shorter. It was 3 months
20 where they began to shrink my tumors, and after
21 3 months, that was it. My body became resistant to
22 them, and then new tumors appeared.

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

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

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

1 were responding and had shrunk by greater than
2 50 percent, and 5 months later, I was completely
3 off pembrolizumab. So my last dose was in May of
4 2017, and so I'm coming up on two years where I'm
5 back to playing competitive hockey and haven't had
6 a treatment since May of 2017.

7 (Applause.)

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

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

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

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

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

1 and that requires extra care.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 for patients with lung cancer who develop brain
2 metastases.

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

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

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

1 neurologic toxicities.

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

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

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

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

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

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

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

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

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

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

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

1 molecules. If you have a small molecule less than
2 400 dalton rate, you would probably traverse the
3 blood-brain barrier.

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

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

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

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

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

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

22 DR. DAVIES: If I could add just one point

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

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

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

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

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

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

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

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

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

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

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

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

3 One of the things that was a bit of a
4 challenge in getting the trial up and running was
5 the concern that there weren't enough patients to
6 conduct these studies. It is actually always
7 different to mine from the literature how many
8 patients there are with leptomenigeal disease. I
9 can tell you that once we opened the trial, the
10 number of patients who had leptomenigeal disease
11 who came to our front door went up probably 5 to
12 10-fold.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 start.

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

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

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

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

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

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

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

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

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

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

13 I think your point about the availability of
14 patients is also a very important one because it is
15 difficult to come up with a clinical trial if you
16 think you're going to enroll one patient every
17 6 months. But I think the reality is that these
18 patients are actually much more available and the
19 need is really much greater than that, and that
20 makes the trials easier to do.

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

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

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

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

21 I'll move to the microphone here.

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

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

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

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

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

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

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

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

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

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

10 So absolutely, these brain met patients need
11 neurosurgical input, and the leptomenigeal disease
12 patients, too. And I'm sure others would
13 absolutely agree.

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

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

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

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

1 absolutely.

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

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

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

22 I think with us learning a little bit more

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 Derrick?

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

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

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

11 **Session II**

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

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

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

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

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

14 **Presentation - Priscilla Brastianos**

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

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

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

14 These are my disclosures. Briefly,
15 molecular epidemiology of brain metastases, we've
16 already talked briefly about this earlier. About
17 30 to 40 percent of advanced HER2 positive breast
18 cancer patients will develop brain mets; 40 to
19 50 percent of metastatic triple negative patients
20 will develop brain mets; 25 to 40 percent of
21 advanced EGFR positive disease will develop brain
22 mets; and about 27 to 40 percent of ALK positive

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

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

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

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

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

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

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

22 This has been an enormous collaborative

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

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

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

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

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

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

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

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

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

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

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

1 alterations in HER2 and EGFR.

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

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

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

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

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

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

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

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

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

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

22 I just told you about this divergent

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

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

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

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

1 Will targeting those differences lead to improved
2 overall survival?

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

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

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

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

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

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

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

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

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

1 questions later.

2 (Applause.)

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

5 Dr. Lin?

6 **Presentation - Nancy Lin**

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

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

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

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

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

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

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

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

1 clinicaltrials.gov searches in the relatively
2 recent years.

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

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

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

1 reached before their survival endpoint would be
2 reached. And remember, these patients were entered
3 between 1985 and 2007, so if anything, there's been
4 10 more years or 10 plus more years of progress.

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

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

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

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

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

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

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

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

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

1 the drug.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 This shows the design of the ALEX trial,
2 which looked at ALK rearranged non-small cell lung
3 cancer. Patients were enrolled who are untreated
4 with advanced disease with a performance status
5 0 to 2, and they could have had asymptomatic brain
6 metastases or leptomeningeal disease and still be
7 eligible. Patients without brain metastases were
8 also eligible.

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

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

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

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

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

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

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

9 In the metastatic setting, after the
10 approval of TDM1 for treatment of general HER2
11 positive metastatic breast cancer, a number of
12 groups put together a case series to demonstrate
13 that there is activity in the CNS in the range of
14 20 to 50 percent in terms of response rate across
15 the various studies.

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

1 blood-brain barrier.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 (Applause.)

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

16 **Presentation - Kim Margolin**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 The challenges in the imaging are also

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

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

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

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

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

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

20 (Applause.)

21 **Presentation - Ben Ellingson**

22 DR. ELLINGSON: Thank you. My name is Ben

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

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

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

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

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

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

22 Now, once we have that information, that's

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

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

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

1 they comply with.

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

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

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

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

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

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

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

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

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

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

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

10 In general, 3D turbo spin echo seems to be
11 the best to delineate these lesions followed by 3D
12 gradient echo, which is part of the standardized
13 brain tumor protocol to date, followed by
14 2-dimensional turbo spin echo, which is the
15 previous standard of care acquisition.

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

1 standards as well.

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

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

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

1 specifically for brain mets.

2 This really focuses only on parenchymal mets
3 only, so not leptomeningeal spread or anything like
4 that. It was based on RECIST 1.1. It looks at the
5 longest single diameter of contrast-enhancing
6 lesions. They have to be measurable disease, which
7 again is a criteria of traditional RANO and other
8 response assessment criteria as well, greater than
9 1 centimeter with relatively thin slices. You're
10 not supposed to include the cystic, or any
11 resection cavity, or any tumor that's taken out.
12 The idea is to sum up 5 target lesions if there's
13 more than that, then you only look at the 5 largest
14 lesions, and you add them up as a sum total lesion
15 burden.

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

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

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

10 Progressive disease is defined as more than
11 20 percent increase in those lesions or any of
12 these things that are on the list here. You may
13 have unequivocal progressive disease in non-target
14 lesions. You may see new lesions become present or
15 they may have declining neurological status, which
16 isn't realizable on radiographic scans.

17 There are some special considerations, and I
18 mentioned a couple of those before.

19 Immunotherapies and SRS, there's a need to verify
20 progressive disease. So just because the lesion
21 gets bigger doesn't necessarily mean the drug isn't
22 working. There are a couple of ways to mitigate,

1 but, again, this is still a work in progress.
2 There's the iRANO criteria that focuses mostly on
3 high-grade gliomas, mostly in the upfront setting.
4 But the idea behind that is to give approximately a
5 6-month window or allow for evaluation period in
6 order to see what's going on with the lesion. If
7 it's getting bigger and the patient is stable,
8 let's just keep watching and see what happens.

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

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

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

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

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

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

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

4 (Applause.)

5 **Panel Discussion**

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

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

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

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

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

12 (Applause.)

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

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

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

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

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

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

1 development of new brain metastasis.

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

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

1 show efficacy in preventing the development of
2 brain metastasis.

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

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

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

1 timing is just not acceptable timing.

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

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

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

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

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

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

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

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

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

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

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

1 think that's very strongly supported.

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

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

17 The final couple of issues are the number of
18 metastases and the size of metastases. So again,
19 we're getting into the realm of radiosurgery. Most
20 of us as neurosurgeons practicing radiosurgery are
21 comfortable with radiosurgery for up to
22 4 metastases. As kind of a quaint vignette, one of

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. LIN: Greg might actually be the right

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

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

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

22 MS. SELIG: Great. Go ahead.

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

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

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

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

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

1 for these metastases?

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

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

9 MS. SELIG: One quick answer.

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

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

1 work is important.

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

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

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

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

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

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

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

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

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

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

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

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

16 Last comment?

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

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

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

12 MS. SELIG: Hold those thoughts. We have a
13 panel coming up on endpoints and a panel coming up
14 on trial designs after the break. To our
15 moderator, I just want to say we have about
16 115 people listening and following along on the
17 webcast. This is terrific, the full room here and
18 a lot of people paying attention.

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

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

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

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

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

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

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

12 Thank you. I think it's break time.

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

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

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

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

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

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

17 **Session III**

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

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

4 **Presentation - Paul Kluetz**

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

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

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

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

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

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

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

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

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

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

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

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

1 Finally, this idea of preventing morbid
2 procedures or preventing or delaying the supportive
3 care medications, again, germane to what you do
4 with steroids, this is an important endpoint.

5 Clinically, it's pretty meaningful, but there's a
6 lot of subjectivity in the decision of a physician
7 whether or not to undergo a procedure or whether or
8 not to give a supportive care med.

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

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

22 Tumor endpoints are interesting because

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 (Applause.)

7 **Panel Discussion**

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

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

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

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

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

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

1 20 percent of the time, a diagnosis, if it's at the
2 end stage of disease and this idea of escape
3 metastasis and how do we monitor for that. I think
4 typically we find those when patients are
5 symptomatic, and then how does that then impact the
6 outcome of patients if we're waiting for that.

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

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

1 and introducing those early in trial. Thank you.

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

8 (Laughter.)

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

19 I have asked and tried to get this going,
20 but so far it has not happened because I know the
21 HIPAA and blah, blah, blah.
22 But anyway, patients do talk, and because of that,

1 my brain mets were found when I was asymptomatic
2 because I more or less demanded a brain scan after
3 6 months, lo and behold, I had 7 brain mets.

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

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

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

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

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

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

1 see.

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

7 (Applause.)

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

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

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

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

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

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

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

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

22 So we have such divergent therapies within

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

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

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

1 discussion about this.

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

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

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

1 invitation to be here.

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

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

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

1 patients that are being impacted specifically by
2 the intracranial disease.

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

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

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

22 Two things, actually, just as an aside that

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

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

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

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

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

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

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

7 Anyone want to take that? Anyone from the
8 audience?

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

11 DR. ANDERS: Sure.

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

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

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

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

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

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

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

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

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

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

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

1 reduction in pain alone with no evidence of
2 antitumor activity.

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

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

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

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

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

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

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

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

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

1 clinical trials.

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

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

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

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

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

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

9 DR. ANDERS: Thank you. Dr. Kumthekar?

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

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

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

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

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

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

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

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

16 DR. ARMSTRONG: Can I add a comment?

17 DR. ANDERS: Absolutely.

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

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

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

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

12 DR. KLUETZ: A response or a clinical
13 outcome?

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

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

1 outcomes.

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

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

9 DR. ANDERS: Thank you. Front microphone?

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

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

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

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

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

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

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

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

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

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

8 Back microphone?

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

22 DR. ANDERS: Does anyone want to answer that

1 one?

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

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

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

1 comment on this.

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

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

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

22 That also goes back to the second part of

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

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

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

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

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

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

15 DR. LEVY: I think you just did.

16 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

1 need your help.

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

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

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

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

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

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

6 DR. LIN: I have two questions. One is a
7 question actually to Paul. We've sort of toyed
8 around with this idea that if you measure let's say
9 15 symptoms at baseline and over time, you
10 potentially dilute out any signals that you see
11 because everybody has their own constellation,
12 personal constellation of symptoms.

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

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

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

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

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

1 go to the back of the room?

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

10 For example, the goal perhaps ought to be
11 how long we can prolong whole-brain radiation
12 because with children, especially under the age of
13 5, you really are curtailing their development.
14 It's been written about.

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

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

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

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

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

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

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

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

19 DR. ANDERS: A very good point.

20 First microphone?

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

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

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

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

17 DR. WEFEL: So it's not.

18 DR. MARGOLIN: Oh, good.

19 (Laughter.)

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

1 neuropsychology. We do have ways to do that.

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

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

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

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

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

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

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

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

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

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

8 DR. ATZBERGER: Thank you.

9 DR. ANDERS: Excellent. First microphone?

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

22 Would you accept that as a part of a trial

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

3 DR. KLUETZ: I gave an example of COUGAR
4 302, which was the prostate cancer trial that did
5 just that. So yeah, we do this all the time. The
6 question is really much more about being very, very
7 careful with your statistical hierarchy because I
8 have seen many times that someone will put survival
9 up at the very top of a hierarchical secondary
10 endpoint list where there was really no chance they
11 were going to get survival because they were
12 offering crossover, and you were like who was that
13 statistician?

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

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

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

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

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

17 DR. ANDERS: We agree.

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

22 FEMALE VOICE: We don't.

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

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

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

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

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

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

3 DR. ANDERS: That was actually a fantastic
4 summary.

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

13 FEMALE VOICE: [Inaudible - off mic].

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

17 **Panel Recap - Carey Anders**

18 DR. ANDERS: Correct. Excellent.

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

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

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

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

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

15 (Applause.)

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

18 (No response.)

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

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

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

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

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

(12:59 p.m.)

1
2
3 MS. SELIG: We are going to get started. I
4 know it was a quick lunch break. Thank you all for
5 getting back and getting in your seats. If you're
6 still eating, no problem. We want to stay on time
7 here.

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

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

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

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

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

15 **Presentation - Shanthi Marur**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Of course, again, I come back to this issue

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

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

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

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

4 **Panel Discussion**

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

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

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

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

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

1 critical to move this field forward.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 (Applause.)

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

18 Maybe we could just start from that end and
19 have people just introduce themselves, say their
20 name and affiliation and a brief remark.

21 DR. WEN: I'm actually not on this panel.
22 I'm just a spectator.

1 DR. PROWELL: Please, go ahead.

2 DR. TAWBI: You were supposed to start on
3 the other end, but that's fine. My name is Hussein
4 Tawbi. I'm a melanoma medical oncologist at the
5 University of Texas MD Anderson Cancer Center.
6 I've been fortunate to actually lead trials that
7 have helped patients with brain metastases, and
8 it's really amazing to have Lynda here, and earlier
9 Derrick, and hear about your experiences.

10 I really want to actually highlight the fact
11 that Derrick started with the hope and you're
12 talking about the fear. And I really think as a
13 group here, our job is to make sure that nobody's
14 afraid of hoping, and that we can actually bring
15 these trials to patients and be able to actually
16 impact not just their survival but their daily
17 lives as well.

18 I'll just say that I started my career as a
19 phase 1 drug development person in melanoma. I
20 guess I was always the kid that drove everybody
21 nuts by asking the why question; why, why, why. It
22 was really important to me that every time I tried

1 to put a patient on a clinical trial to go through,
2 my coordinator would look at me and say, "Can't;
3 exclusion criterion," and to ask why was this
4 exclusion criteria actually in this study? Why do
5 we have to say your platelets have to be more than
6 100,000?

7 Well, that made sense for some of our
8 patients, but then you got to brain metastases.
9 You got to, again, organ dysfunction. You got to
10 just rare diseases that were not allowed. So I
11 kind of made it a mission of mine to kind of go
12 after these whys and really try to understand how
13 can we turn those around.

14 I've done some work in organ dysfunction
15 studies, but then turning to patients with brain
16 metastases, it was clear to us that those are
17 patients that are just being excluded based on
18 existing dogma rather than actual evidence, and I
19 think over time with some courageous actually
20 clinical researchers. Actually, I have to also
21 shout out for some of the companies that have been
22 involved to say, look, we can actually include

1 those patients on trials. We can design trials
2 specifically for those patients and actually answer
3 the questions in an inappropriate way.

4 So I'm really looking forward to hear the
5 rest of the discussion and really to come out of
6 today with very clear guidelines so that our
7 colleagues across all diseases, not just in
8 melanoma, and obviously across oncology, to try to
9 actually demystify brain metastases and allow them
10 on trials more freely, and really allow for this
11 data to be generated. Because the answer that we
12 don't want to have is that we don't know. Thank
13 you.

14 DR. PROWELL: Thank you so much.

15 DR. MISHRA-KALYANI: Good afternoon. My
16 name is Pallavi Mishra-Kalyani, and I'm a
17 statistician at the FDA. I work in the Division of
18 Biometrics V, which is the group that supports the
19 statistical review of applications or INDs for
20 oncology and hematology products. My own
21 experience has been mostly with solid tumors and
22 review of protocols and applications for solid

1 tumors, including lung cancer and melanoma.

2 I'm going to pause on my comments on what
3 Shanthi has presented mostly because I am in
4 agreement mostly there. I don't know if I'll add
5 anything substantial quite yet, but hopefully I can
6 help address some of the statistical concerns and
7 questions that may come up as we're discussing
8 trial designs.

9 DR. PROWELL: Thank you so much.

10 DR. GONDI: My name is Vinai Gondi. I'm a
11 radiation oncologist at Northwestern. I specialize
12 in the management of patients with brain and spine
13 tumors, both in adults and pediatrics. My focus of
14 research, my real passion has been shared earlier
15 today, and that is how do we treat tumors, and
16 specifically brain metastases, with this really
17 effective modality called radiotherapy in a safe as
18 way as possible.

19 A lot of my focus has been on
20 neuroprotective strategies and most recently
21 hippocampal sparing. So I'll weigh in on some of
22 that as it relates to drug development, but I'll

1 also weigh in on my clinical experience, as was
2 discussed before, and some of the frustrations
3 sometimes we face in clinic when we know we have
4 this really effective treatment like radiosurgery
5 or radiotherapy for someone with brain metastases,
6 but then we have to really consider
7 should we use it because then they may not be
8 eligible for a trial. We can talk about that.

9 DR. KEEGAN: Hi. I'm Patricia Keegan. I'm
10 with the Division of Oncology Products II, and
11 we're responsible for the oversight of drug
12 development in a variety of solid tumors. The area
13 where I face this issue has primarily been with the
14 lung cancer clinical trials in drug development,
15 but I think I bring a perspective in the sense that
16 we're also responsible for consulting with other
17 parts of the agency, for instance, on trials to
18 give liver-directed therapies and other things. So
19 I think that that experience will help, and it does
20 help me inform my considerations for this specific
21 focus.

22 I'd like to say just a little word about the

1 issue of patients not being enrolled in clinical
2 trials, not just related to CNS malignancies, but
3 that I think, based on my experience with FDA, that
4 probably the single greatest limiting factor to
5 patients not getting into clinical trials based on
6 eligibility criteria is that people just recycle
7 clinical protocols, and they don't look at the
8 drugs that they're studying and make a specific
9 decision on each eligibility criteria as to why
10 this makes sense to be here or not to be there.

11 Much of that has led to the reason that
12 we're regularly excluding patients with CNS
13 metastases or other conditions, not because they
14 need to be, but because we're not focusing on what
15 is absolutely necessary to conduct the clinical
16 trial. So I guess we should probably try and
17 refocus our energies on being a little less
18 academically lazy about clinical trial development
19 and trying to be more considerate of when we
20 developed eligibility criteria, what's the real
21 thinking behind that in light of both the disease
22 and the drugs being studied.

1 DR. BLACKWELL: I'm Kim Blackwell. I'm
2 currently a vice president, and at Eli Lilly, I
3 oversee the early-phase oncology and
4 immuno-oncology efforts there. I should disclose
5 some people might think I have a multiple
6 personality because I just joined Lilly a year ago,
7 after 25 years of clinical practice running both
8 the breast cancer program and ultimately founding
9 the Center for Solid Tumor Brain Mets at Duke
10 University.

11 Prior to leaving my university appointment,
12 I actually founded a company that's focused on the
13 treatment of early solid tumor brain mets. So I
14 have academic experience, I have early life science
15 experience, and I now have big pharma experience,
16 so I'll try to say, "And now I'm speaking from this
17 role, and now I'm speaking from this role." But I
18 think I'm uniquely equipped to try to speak on the
19 pharma perspective, both big and early-life
20 science, just from an investment and how do you
21 start a company that's focused on this.

22 I became passionate about this, in part,

1 because I worked at a university that had the
2 world's largest brain tumor center, and I remember
3 Carey and I having a discussion probably 20 years
4 ago saying we have all these tools that they're
5 using for GBM. Why don't we apply them to the
6 treatment of solid tumor brain metastases in the GU
7 neurosurgery, cool radiation techniques.

8 Treatments for breast cancer, and in
9 particular HER2 positive breast cancer, got a lot
10 better; so much so that over the past 7 to 10 years
11 of my career at Duke, I watched women not die of
12 their HER2 positive metastatic breast cancer, but
13 actually die of the consequences of the radiation
14 that was required to keep their brain mets under
15 control.

16 So I think now's a good time to have this
17 conference. I'm honored to be here, and hopefully
18 I can contribute to some of the discussions. I
19 don't think I can represent all pharma, but I can
20 certainly give you what my experience has been in
21 the first year having joined Lilly and what we
22 worry about and what we don't worry about in

1 developing pharmaceuticals in this space.

2 DR. ATKINS: I'm Michael Atkins. I am a
3 medical oncologist and deputy director of the
4 Georgetown Lombardi Cancer Center here in the D.C.
5 area. My major interests are in melanoma
6 treatment, kidney cancer treatment, and
7 immunotherapy.

8 Being a longstanding clinical trialist, I've
9 sort of taken the general idea that industry's job
10 when they're developing drugs is to get the drugs
11 approved as fast as possible, and it's academic
12 medicine's job to figure out how to use those drugs
13 along the way, and that's including subsets of
14 patients with Comorbidities; how to develop
15 biomarkers; how to sequence them or combine them
16 with other agents; and also whether they are
17 effective in specific organs such as the CNS.

18 I do think that the experience I've had with
19 immunotherapy and melanoma suggests that you can,
20 while you're developing drugs and getting them
21 approved, potentially address some of those
22 questions along the way without delaying

1 development or approval of the drugs, or in some
2 points cases, even expediting the approval by
3 allowing more patients to be eligible for one's
4 trials, while at the same time getting some
5 real-world, or closer to real-world, experience.

6 I think as Hussein and Kim have proven in
7 the ipi-nivo 204 trial for patients with melanoma
8 and brain metastases, when it comes to
9 immunotherapy for patients with melanoma, there is
10 no effective blood-brain barrier.

11 I think taking that approach, I don't know
12 why that same statement wouldn't apply to every
13 other cancer where immune therapy has efficacy, and
14 certainly that would be justification for taking
15 patients with treated brain metastases or
16 asymptomatic brain metastases, as was in the 204
17 trial, and allowing them to be part of earlier
18 clinical trials in other cancers, and also, if it's
19 a poor prognostic factor, then one could stratify
20 for that.

21 Because patients with brain metastases have
22 generally had such poor outcome, I think it lends

1 itself perfectly to have overall survival be an
2 endpoint in randomized trials in patients with
3 brain metastases and having neurologic function be
4 the secondary endpoint.

5 Although it's nice to see tumor shrinkage
6 and may be great to see PFS being prolonged in the
7 CNS, I think you might not always see those things,
8 but you may see an impact on survival, particularly
9 in patients who otherwise would have had short
10 survival. If your drugs really work, then they
11 should work better than the standard of care in the
12 patients who are at the greatest risk.

13 DR. PROWELL: Great. Thank you for all
14 those introductions. We have about 45 minutes or
15 so, and I want to try to focus our panel discussion
16 around four main topics. I'll just outline what
17 those are briefly, and then maybe we can comment on
18 them, and of course we encourage the audience to
19 ask questions or contribute from the microphone.

20 The first is when we should include patients
21 with brain metastasis or leptomeningeal disease,
22 because I don't want to forget about those

1 patients. When should we include them, and by
2 when, I mean when in drug development, at what
3 point? How early are we comfortable including
4 them?

5 Second is I want to think about how we
6 should include them. And by how I mean do they go
7 into the overall trial population, particularly in
8 settings where brain metastases are very prevalent,
9 certain diseases where they're very prevalent, or
10 do they belong in their own separate cohort?

11 The third is how do we incorporate local
12 therapy into clinical trials? And then the fourth
13 is how do we move beyond this mind-set of letting
14 patients with brain mets be in our clinical trials
15 to actively pursuing drug development in patients
16 with brain mets or leptomeningeal disease? I think
17 it is a different question and an important kind of
18 reframing of our thought process.

19 So one of the complaints I've heard early
20 on, I was involved with a lot of people in this
21 room, Dr. Amiri, Dr. Sul, Dr. Lin, with the ASCO
22 friends' effort to modernize eligibility criteria

1 in brain mets. One of the concerns that we heard
2 when we started thinking about how we were going to
3 address that topic was people saying, well,
4 patients who have brain mets are different. They
5 have different efficacy, they have different
6 safety, and that makes it really complex to put
7 them in clinical trials. And that's why we've not
8 done it and that's why we don't want to do it.

9 One solution that came out of literally
10 years of people sitting around talking around
11 tables and on phones was the notion of including
12 these patients in separate cohorts, which addresses
13 many of the issues. There are statistical
14 considerations that this brings up, and there are
15 pragmatic considerations about trial design, and
16 analysis, and size of the trial, and so on.

17 I'd like to have the panel maybe begin by
18 thinking about that issue, responding to the idea
19 that patients with CNS involvement should be their
20 own separate cohort, and maybe we can
21 start -- whoever wants to go first. We don't
22 necessarily have to go down the whole row, but

1 whoever wants to take that. Go ahead.

2 DR. MISHRA-KALYANI: I'll start. I can't,
3 of course, again, speak to the clinical side and
4 the safety concerns exactly, but I will mention one
5 thought about -- or a couple of thoughts about
6 having patients with brain metastases in a separate
7 cohort, and that would be a question of equipoise.

8 If you're not sure that the patients with
9 brain mets will actually benefit from the standard
10 of care because there's evidence that it won't be
11 effective therapy for them, then you may consider
12 having a separate non-randomized cohort for those
13 patients so that you can just look at the effect of
14 the experimental therapy.

15 I think separate from that, if you do feel
16 like there is effective standard-of-care therapy
17 that you can compare to, the concept of having
18 patients either in a separate cohort or in the
19 overall population with a stratification factor for
20 whether or not patients have brain metastases isn't
21 necessarily going to make too much of a difference
22 in how we interpret that data, at least from a

1 statistical perspective because you can make
2 arguments on how you can look at the data together
3 or look at them separately, and there are a lot of
4 different statistical methods for doing that.

5 So really, I think the concern first needs
6 to be whether or not you can do a randomized design
7 for those patients. And if you can -- and I'm
8 assuming that we're talking, again, as Shanthi
9 mentioned, in the phase 3 randomized study setting.
10 If you can randomize them, then I don't see why you
11 couldn't include them in the overall population
12 with a stratification factor to kind of cover
13 yourself.

14 DR. GONDI: Can I take off -- oh, sorry.

15 DR. TAWBI: If you don't mind, I really do
16 want to address two very important points. I think
17 one very important point that we all kind of faced
18 throughout the morning and throughout our careers
19 so far is the dearth of knowledge in this field and
20 the fact that less than 1 percent of our patients
21 that represent, really, 30 percent of metastatic
22 disease population, less than 1 percent of them are

1 represented anywhere in a clinical trial. So my
2 answer to when is as early as possible and as often
3 as possible should be the answer.

4 Now in terms of how do you address the fact
5 that this is a different population, I actually
6 will take what Pat said about not being lazy in our
7 clinical development and clinical trials. I don't
8 think there's a blanket statement for that.

9 I think we really have to think about which
10 drug are we using, what are the targets that we're
11 considering, what do we know about its penetration
12 for the blood brain or not, and then based on that,
13 try to include those in the early phases, either
14 dose escalation's completed, to have a small cohort
15 in which you can look at this; or even have a
16 separate dose escalation.

17 As Mike Davies earlier mentioned, maybe for
18 those patients, you do need a higher dose, and
19 maybe some of the toxicities can be -- we all are
20 oncologists and treat patients with chemotherapy
21 and give them awful toxicities all the time if
22 their goal is benefit. So sometimes maybe our

1 threshold for toxicity for that population may be
2 slightly different as well.

3 Then when we go later in the development,
4 stratifying should be a must, actually. It's very
5 easy. I'll talk for melanoma. A lot of those
6 patients screen fail because of brain mets.

7 Imagine if those people that screen fail just go on
8 a study, and they're just in their own separate
9 cohort, and then you can answer the question right
10 there. You can design your trial in a way that the
11 primary endpoint isn't the cohort that's not brain
12 mets if you're worried about their poor outcomes.
13 But at the end of the study, you'll have all the
14 answers that you need.

15 DR. PROWELL: I'll let Dr. Gondi in just one
16 moment. I just want to say one thing. Part of the
17 reason that industry has historically not included
18 these patients is that we've allowed them to not
19 include these patients, despite the fact that for
20 some of these diseases, the prevalence of brain
21 mets is as high as 40 or 50 percent.

22 One thing that I want to get back to you

1 later in the discussion, and maybe I'll ask
2 Dr. Blackwell to comment on this from an industry
3 perspective, is what sort of incentives, in terms
4 of either being able to differentiate a product
5 from other drugs in class maybe that haven't
6 studied brain mets, or what sort of concerns or
7 potential carrot and stick, if you will -- what
8 sort of regulatory things would lead companies to
9 preferentially include these patients in their
10 clinical trials?

11 Dr. Gondi?

12 DR. GONDI: I wanted to go back to something
13 that was mentioned earlier about being practical,
14 too, with clinical trial design and development. I
15 see brain metastases different but in a positive
16 way, to some extent. Again, as one of two
17 radiation oncologists in the room, I can say that
18 we have very effective treatment for brain
19 metastases, and that's radiosurgery, and it's safe,
20 and it's effective for the timeline of most
21 clinical trials.

22 So we can leverage that. In fact, we should

1 leverage that in a way that allows us to include
2 these patients on trials. For later-phase studies,
3 I agree a hundred percent, putting my biostatistics
4 hat on, it makes sense to stratify patients to
5 enable them to be treated with radiosurgery before
6 they enroll on trial, and for small asymptomatic
7 mets in non-eloquent locations, not requiring
8 corticosteroids, to not have to necessarily treat
9 those lesions and stratify and be able to watch
10 that.

11 At the end of the day, if the primary
12 endpoint is survival, one thing that we have
13 trouble showing in brain metastases management is
14 that anything we do for brain metastases actually
15 has an impact at survival. There have been a lot
16 of challenges in demonstrating that. So if we know
17 that and we all agree on that, why not just allow
18 those patients, monitor them closely with MR
19 surveillance, treat the troublesome lesions with
20 radiosurgery, safe and effective.

21 In terms of earlier phase studies -- oh
22 sorry, one more thing about that. I'm going to put

1 on my radiation oncologist hat now, because I have
2 hats, too --

3 (Laughter.)

4 DR. GONDI: -- this washout period really
5 troubles me as a radiation oncologist. I've never
6 understood it. It was in this JCO paper that you
7 asked us to read in advance of this, and in most
8 trials, it's a couple months. I think the JCO
9 paper said 1 month post-radiosurgery.
10 Radiobiologically, there is no washout period.

11 What happens in 1 month radiobiologically
12 when you treat a met? You usually get a little
13 FLAIR, it calms down with steroids, and they're
14 fine. In fact, if you scan that patient a month
15 later, which we don't normally do, that tumor's
16 probably shrunk. So why do we need a washout
17 period? Why not enroll that patient right away so
18 that we're not sitting there for a month watching
19 their disease outside of the brain continue to
20 progress?

21 As it relates to earlier phase studies, the
22 thing I struggle with the most in my clinical

1 practice is so many of the patients who do earlier
2 phase studies have failed several prior systemic
3 therapies, and usually by that point, it's not 30
4 percent of them have brain mets; it's like 60 or 70
5 percent of them have brain mets by that point.

6 I think our patient advocate earlier today
7 really echoed this and it's really important. The
8 patients who've had brain mets treated should be
9 able to go on earlier phase studies. It doesn't
10 make sense to me biologically or clinically why
11 that should not be possible.

12 I can understand why there may be some
13 concern about if they have intracranial progression
14 at that time, and how do things interact with
15 radiotherapy, which I'd like to spend some time
16 weighing in on, maybe for an earlier phase study
17 that may need to be delicately looked at. But if
18 they've already been treated for their brain mets
19 and their scan is stable, they should be able to go
20 on an earlier phase study.

21 DR. ATKINS: A couple of comments. I agree
22 with Hussein that when should be as early as

1 possible. The only qualification I would say is
2 I'd like to see that the agent has some systemic
3 disease activity before exposing patients with CNS
4 mets, because if it doesn't work systemically, it's
5 not going to work in the brain.

6 I do agree with Dr. Gondi that -- and the
7 one objection I had to the article that you
8 distributed and asked us to read is I don't see why
9 it's necessary to wait 4 weeks after radiation of
10 brain mets before enrolling patients on trial. In
11 the national cooperative group trial that I lead,
12 we decided to completely eliminate the repeat MRI
13 in patients with treated brain metastasis for
14 melanoma and just enroll them as soon as they were
15 off steroids for getting immune therapy.

16 I don't know that if you're treating every
17 lesion in the brain, you're not going to be
18 measuring those lesions. If you go put them on
19 study right away, there shouldn't be a chance for
20 new brain disease to develop. So that's the best
21 time to treat them, and I don't know why you would
22 wait on treating their systemic disease because

1 that's what keeps some patients off of trials, is
2 they have to get their brain met radiated, and then
3 they don't want to wait 4 weeks to actually enroll.

4 DR. PROWELL: Dr. Keegan, do you want to
5 comment on the issues from a regulatory standpoint
6 of letting people get radiation and then go right
7 into this study, in terms of our being able to
8 interpret endpoint design?

9 DR. KEEGAN: Right. And I think that's why
10 we -- when Dr. Marur led off, we talked about the
11 endpoints because what you want to show often
12 drives who gets in the trial. If all you want to
13 do is show level of activities, systemic activity,
14 and if there are treated brain lesions in there but
15 you're not necessarily focusing on that, there
16 would be no reason to wait.

17 So the reason is usually because people are
18 focused on looking at activity in the CNS as well,
19 but it's simply a matter of how you design the
20 trial and what you want to be able to include at
21 the end. There's no regulatory reason, generally
22 speaking, why you would have to have a washout as

1 long as you would understand that those would not
2 be lesions that could evaluate for drug activity.

3 I actually have a quick question. Maybe you
4 can answer this. Why not include patients in the
5 first in-human clinical trials if there's a
6 reason -- if there's no specific safety concern,
7 why would you want to wait until you have evidence
8 of systemic activity before you would enroll those
9 patients?

10 I would say they're taking a lot of chances
11 regardless, in the very early-phase studies
12 patients are, and they don't know if they're going
13 to respond systemically either. So with close
14 monitoring, I would challenge that perhaps those
15 patients could be enrolled in phase 1 studies as
16 well.

17 DR. PROWELL: I just want to say this is
18 regulators being more liberal than academics.

19 (Laughter.).

20 DR. PROWELL: You might never see this
21 again --

22 (Laughter.)

1 DR. PROWELL: -- so mark this in your
2 calendar, friends.

3 DR. ATKINS: Yes, and maybe other people are
4 going to challenge me on that statement, but I
5 don't want to compromise the initial study that
6 looks at whether or not there's efficacy in a drug.
7 If you put in your phase 1 trial, where you're
8 trying to define what the doses that you're going
9 to use, and it's compromised because patients have
10 toxicity issues or you don't see any activity
11 because a large percentage of the patients were
12 patients who couldn't respond to that agent, then
13 you may slow down the development of that drug.
14 But I'm willing to listen to comments otherwise
15 because I suppose if you saw a response in the
16 brain, nothing would speed up the development of
17 that drug any faster.

18 DR. PROWELL: So what about if we had those
19 patients in a separate cohort even in dose
20 escalation, where it's baked into the protocol that
21 if there's excessive toxicity, if you're seeing
22 seizures, if you're seeing bleeds, you're seeing

1 whatever, that cohort built into the protocol is
2 going to close. You're going to stop, and that's
3 going to be the end of it, and there's no need to
4 pause, and amend, and re consent people because that
5 was built into the protocol right from day one;
6 likewise, looking at the efficacy or even the dose
7 requirement, which, as someone alluded to earlier,
8 might be different for patients who've got
9 intracranial compartment disease.

10 I want to ask Kim to comment on one thing in
11 a minute from a pharma perspective, and then I'll
12 get you. But Nancy Lin, who was a lead author of
13 these eligibility criteria guidelines, I want to
14 have her comment on the 4-week washout period. We
15 talked about this a lot.

16 DR. LIN: There's a story behind it as there
17 is with many things, and I actually agree with the
18 panelists. You have to remember where we're
19 starting from, which is that almost all standard
20 templates had a 3-month washout from radiation,
21 which completely makes no sense. If you're trying
22 to include people who are less least likely to have

1 a CNS progression event when they enter a trial,
2 you want to have 3 months go by because, honestly,
3 most of the time in 3 months after radiation,
4 nothing happens in those first 3 months.

5 So we really wanted to get rid of the
6 3-month threshold. We had a lot of debate about
7 what that threshold would be, ranging from no time,
8 to 7 days, to 4 weeks. We felt very strongly that
9 it couldn't be any more than 4 weeks. Ultimately,
10 the consensus was that everyone felt comfortable
11 with 4 weeks, which is why that's in the guideline,
12 but in the text, there's a note that based on the
13 situation, it could be less than 4 weeks.

14 So I don't want anyone to feel like it has
15 to be 4 weeks. The guidelines, they could be
16 really anything, but we recommend a maximum of
17 4 weeks is the way that I would think about it
18 because I entirely agree, it makes no sense the way
19 that it was written before; it really makes no
20 sense.

21 DR. ATKINS: What about the issue, Nancy,
22 about repeat imaging? Obviously, if it's less than

1 4 weeks, you're not going to repeat image.

2 DR. LIN: I totally agree. And again, it
3 has to do with where we were trying to move the
4 needle from, which was really from this 3-month or
5 6-month kind of a time frame. I think if
6 somebody's had SRA a week ago, does it make any
7 sense to repeat it? No.

8 DR. GONDI: I just want to clarify again,
9 it's a semantic thing, but it's what causes us to
10 think about it. There's no such thing as washout
11 after radiation. The radiation is done.

12 DR. LIN: Agreed.

13 DR. PROWELL: Sorry. We're using this in a
14 shorthand way to mean you got to wait a little
15 while. Yes, but thank you.

16 I want to ask Dr. Blackwell the comment on
17 the pragmatism of this, a bunch of people who are
18 not in pharma saying, "It's really simple. Just
19 have another cohort." You're going to have
20 separate dose escalation for them, you're going to
21 have separate stopping rules for them potentially
22 for toxicity.

1 How practical is this in both early-stage
2 development where you're still on the dose-finding
3 and toxicity-gathering stage, and how practical is
4 this in late-stage development? How much does this
5 add to cost, and risk, and time to accrue, and so
6 on?

7 DR. BLACKWELL: Well, that's a lot of
8 questions. I tend to try to break this down
9 because I think sometimes when we blur what we're
10 talking about, it's hard to find solutions. In
11 terms of inclusion of patients that have treated
12 CNS mets on a trial where the sole intent is not to
13 look at CNS activity, I think that's a very
14 different discussion than how do we design trials
15 where we're intending to look at CNS activity.

16 So I'll address the first. In the context
17 of early drug development, I actually -- so I'm
18 going to take the contrary here. I actually think
19 we need to include patients that have worst disease
20 in our dose-finding study because if we see a
21 signal, then we're going to want to develop that
22 drug.

1 You put a bunch of patients on whose disease
2 was going to not progress for a year anyway, then
3 you're going to fool yourself into thinking a drug
4 has activity when it really doesn't, and you set
5 yourself up for failure as you move that on at
6 whatever dose you find.

7 Now I think precision medicine is going to
8 help us with that, so if you know what the driving
9 mutation is and you know how that disease performs
10 in a different cohort, then you can actually say,
11 okay, these patients should do this and on our
12 drug, they actually did this, so there's a signal
13 of activity there.

14 So I do think science is actually going to
15 help us sort this out as opposed to, gosh, if your
16 hemoglobin's okay and your platelets are okay, then
17 you're the patient we want to study a drug in. So
18 I see hope in biology and science helping us
19 understand how patients would have done had they
20 not received our drug, even in the earliest stage.
21 So I actually think that patients facing brain mets
22 should be allowed.

1 I would say that Pat brings up a good point.
2 The reason we have excluded them, both
3 pharma -- even in the trials I participated in
4 prior to joining pharma was a cut and paste
5 phenomenon, which is we didn't want to be bold
6 enough or brave enough to include those patients on
7 the trial. The 25 years of my practice, I think I
8 might've seen 7 seizures and I focused on the care
9 of women with brain metastases. It's just an urban
10 legend. It happens, don't get me wrong, but the
11 problem, as much as it's discussed, is very unusual
12 in the day-to-day clinical practice.

13 So in terms of early phase, I see where
14 there'd be no problem, and in fact I think this is
15 where patients, and the regulatory agencies, and
16 the investigators can push and say we're not going
17 to put people on this trial unless you -- I'm
18 probably going to get in trouble back at work, but
19 we're not going to put patients on a trial if you
20 don't allow patients with stable brain metastases
21 to go on it.

22 These patients are sacrificing a lot.

1 Sometimes they're the first human dose. We have
2 very few signals of what the safety is. We have it
3 in preclinical models, but in people we don't. So
4 I feel pretty strongly. And you have to realize
5 that it takes a little while to change, so we have
6 to be a community and push to allow for these
7 patients to go on the early-phase trials.

8 I feel about the same as the phase 3
9 studies. I will say, though -- I've wrote down
10 this list of things pharma worries about, so maybe
11 I can just tell you what they are really quickly.
12 We worry about the endpoints in a phase 3 study.
13 We worry about the complexity of the patient and
14 heterogeneity. And patients who have had SRS-to-1
15 lesion is a very different patient than someone
16 that's had SRS to 5, or even whole-brain radiation
17 therapy.

18 Just like we try to homogenize patient
19 enrollment, everyone's only had 2 lines of therapy,
20 it's very hard to control that in a setting of a
21 randomized phase 3 study. So we worry about
22 patient population, heterogeneity, lines of

1 therapy, and in particular burden of disease.

2 The biggest thing -- I have to say this
3 before I get cut off -- the lack of preclinical
4 models makes it very hard for me to argue to do
5 trials in this space, having joined a large pharma
6 a year ago. It's just the way that big pharma
7 makes decisions, which is did it work in the cell
8 lines? Did it work in the animals xenografts? Did
9 it work in this? Obviously, there's safety in the
10 preclinical models, but you can't just say it's
11 because I think it's a good idea.

12 So I think we need to work together to
13 figure out what those preclinical models would look
14 like, and I think we're going to speak about the
15 multidisciplinary buy-in. I just have a couple of
16 points of what we don't worry about because I've
17 heard it a couple of times.

18 We don't worry that the patients are too
19 sick. The presence or absence of brain mets in a
20 setting of 4 pages of eligibility criteria is
21 probably the least of our worries. I do think it's
22 a cut and paste phenomenon, which is that's just

1 how our protocol writers have always written it,
2 and there's not a voice to say don't forget, and
3 I'm pushing investigators to say that.

4 We don't worry about the size of the patient
5 population. We recognize it's a huge unmet need.
6 Even in a molecular era of precision medicine,
7 there's still a huge opportunity to make
8 improvements, and pharma actually wants to improve
9 the care of patients as well.

10 Then the third thing we don't worry about is
11 figuring out if the drug should cross the
12 blood-brain barrier or not, and this is my last
13 point. I worked for a company that's had spent 20
14 years in the neurocognitive space, the Alzheimer's
15 space, the depression space. I've got teams of
16 hundreds of chemists that could tell you with 92
17 percent precision whether or not that drug gets
18 across the blood-brain barrier. We have imaging
19 companies and that's all they do is look to see if
20 the drug gets across the blood-brain barrier and
21 people.

22 So as much as we talk about the blood-brain

1 barrier from a big pro pharma perspective, we don't
2 worry about that too much because we actually have
3 whole teams of people that have thought about that
4 outside of cancer for three decades. So probably I
5 took up more of my time but I did want to make
6 those points because I don't think they'd been made
7 earlier in the day.

8 DR. PROWELL: Thank you. I think that's
9 very appropriate. I asked you like 12 questions.
10 You responded to me in 4 minutes or something, so
11 good job.

12 I want to take some questions from the
13 audience. We'll just maybe go front/back.

14 DR. ABREY: Lauren Abrey, Novartis oncology.
15 I actually wanted to make a comment, and I think
16 I'm going to build on what Kim said. You have to
17 think what are we trying to do? Are we trying to
18 include brain metastases patients or are we trying
19 to develop intentional drugs for brain metastases?
20 I think it actually gets to what do you want your
21 label to look like?

22 Do you want your brain mets to be included

1 as under the umbrella of metastatic disease and
2 they've been represented in the trial? Then, in my
3 view, they don't belong in a separate cohort. If
4 you want to do intentional brain met development
5 either to differentiate your product or because
6 there's something unique about the patient
7 population or the product, then you need to develop
8 it quite differently.

9 I guess I would actually rebut a little bit
10 what Kim said in that the selection for entry into
11 human, at least at my current company and my last
12 company for oncology products, would often select
13 the drug that doesn't cross the blood-brain
14 barrier. So yes, people know, but there's often a
15 bias to, for safety reasons, pick some of the ones
16 that don't cross the blood-brain barrier to try to
17 limit the possibility that you also end up with
18 seizures or something else when you take your first
19 step into human.

20 So I think it's something we could
21 manipulate while we sit there or try to influence;
22 maybe not manipulate. That's not such a positive

1 word. But I think that's a little bit -- maybe we
2 need to frame thinking about this because my first
3 thought when Tatiana -- was we want to allow
4 patients. I want to allow patients in trial. If
5 we want to make a difference here, we need to move
6 the needle, but then we need to be thoughtful about
7 where are we moving it and what are we doing.

8 DR. PROWELL: This is a regulatory issue
9 that I think will be interesting to talk about
10 maybe as we go on, which is that because
11 historically we have allowed companies to exclude
12 and there's no limitation of use in the indication.
13 The indication would be for whatever line,
14 non-small cell lung cancer or something, but it
15 doesn't say for patients without brain mets, or
16 we've not specifically been granting indications
17 for treatment of patients with this and brain mets,
18 or even necessarily including a lot of that data in
19 the label.

20 So the question is for companies that are
21 coming into this now with multiple other drugs
22 already approved in that line of therapy or in the

1 same class, how do we provide that incentive to
2 really include these patients?

3 DR. TAWBI: I'll be more than happy to
4 address this. I really think that's a great point,
5 and we're actually talking about two separate
6 things, and you're absolutely right. If you look
7 at what we've been doing so far, is we've been
8 trying to prove the things that have already been
9 approved, that are already available to everybody
10 in the community, then prove that they have
11 activity in the brain. And obviously this has been
12 a long and arduous journey.

13 I can tell you, having had the honor of
14 leading the CheckMate 204 trial with ipi-nivo, this
15 trial had 15 patients on when ipi-nivo got FDA
16 approved. So we actually were concerned that
17 people won't put patients on study because they
18 have access to the drugs. So it took a lot of
19 sweat and blood and a lot of investigators being
20 convinced that this is an important study to do,
21 and to actually finish it. There were 90 patients
22 and now soon 119; we changed the practice. I think

1 in a lot of ways, for those drugs that we think are
2 close enough to change practice for all metastatic
3 patients, that's when we need to allow patients
4 with brain metastases.

5 However, the other aspect is that I want to
6 focus back on what are the targets we're going
7 after, what is the actual biology that we are
8 trying to modulate. We are in a place where we
9 should start thinking about what's specific about
10 the brain and what targets do we want to go after.
11 You heard Priscilla, you heard Mike earlier today,
12 and even in immune oncology, the tumor
13 microenvironment in the brain may need completely
14 different modulators. So for those targets, for
15 those pathways, we need to develop studies that are
16 specific for that population.

17 DR. MISHRA-KALYANI: I actually wanted to
18 address something specific you said about having a
19 different cohort. I think that there are two
20 things that I would consider there, and it goes
21 back to your discussion as to what is it that we're
22 trying to include in the label.

1 If you were trying to include your endpoint
2 in the label that shows that you have a clinical
3 benefit due to this treatment, if you have a lot of
4 heterogeneity in your population, you might not be
5 able to adequately size or power your analysis to
6 find a clinically meaningful benefit in your
7 population if there's a lot of difference in what
8 we would expect for the clinical benefit in
9 patients with those brain metastases versus those
10 who do not have them.

11 So if you're getting a mixed model of what
12 you actually are finding, then what you're
13 indicating in your label is the clinical benefit
14 may not be what it truly is. So in that respect,
15 there may be some real reason for you to include a
16 separate cohort. It doesn't mean that you're
17 allowing the patients -- you're pursuing them.
18 You're just pursuing them to also characterize the
19 benefit for those patients because you're
20 recognizing that it's a prognostic factor just as
21 we might with histology, squamous versus
22 non-squamous, et cetera. There usually it's a

1 stratification factor, but it's just a reason that
2 you might want to consider, so pursuing them but
3 having them in a separate cohort for that reason.

4 The second part of that would be if you
5 wanted to specifically look at the activity in the
6 brain or in CNS metastases, then there may be a
7 reason, then, to also look at those patients
8 separately for many of the reasons that have been
9 discussed. There may be local treatments or
10 radiation, and those things may affect how well
11 you're able to characterize the clinical benefit or
12 the treatment effect, and you don't want that
13 diluting whatever you're able to find in the
14 overall population.

15 DR. ABREY: So it could be really helpful in
16 defining some of those clinical benefit endpoints
17 from the last session.

18 DR. PROWELL: I'm going to let Dr. Gondi
19 respond, and we'll take the question at the back
20 microphone. Thank you, all standing up, for being
21 so patient. You live longer if you don't sit so
22 much, so we're doing this for you.

1 (Laughter.)

2 DR. GONDI: And by the way, the chairs up
3 here are so much more comfy than the chairs out
4 there.

5 (Laughter.)

6 DR. GONDI: So for CNS directed therapy, if
7 I may, I think the challenge we face in later stage
8 trials is to some extent, we are trying to show
9 CNS-directed therapy for what purpose? Speaking as
10 a radiation oncologist, if we have a modality such
11 as radiotherapy that is very effective in managing
12 brain metastases, how do we supersede that? How do
13 we improve upon that? That's hard to show.

14 So that's why I think it's important, as was
15 mentioned here, when you're designing a trial, that
16 it's going to be hard in the early/late phase
17 studies to really show benefit over what is
18 considered standard of care right now.

19 I would say that allowing those patients on
20 those studies, though, allows us to make important
21 secondary observations. A lot of the secondary
22 observations we now make for trials that have not

1 included brain metastases patients is based on
2 multi-institution retrospective series, where
3 people said, okay, well let's just try this in
4 brain metastases patients, some of whom got
5 radiosurgery, some whom didn't, and see if it makes
6 a -- and that's really hard to -- there's so much
7 bias there, it's hard to really extrapolate much
8 from that. So if we can include that within those
9 later phase studies, that really gives us much more
10 data from which to build.

11 Related to that, I think on the last session
12 we talked about patient-reported quality of life
13 and the challenges of assessing that. We actually
14 now have, and we're just going to present later
15 this year, an intervention radiotherapy related
16 that actually has shown in a randomized trial
17 better preservation of patient-reported quality of
18 life. So it is possible to look at that as an
19 endpoint.

20 But related to CNS-directed therapy, I think
21 there's a dearth of knowledge as it relates to
22 patients whose metastases fail effective local

1 therapy. In my experience, most of my brain
2 metastases patients when they have issues down the
3 road, it's not necessarily from the radiations
4 because eventually their tumor grows years down the
5 road after the radiation, and then we're stuck. We
6 try surgery or LITT, but a lot of those tumors
7 aren't resectable or it's too much to ask of a
8 patient.

9 If there is something earlier phase that we
10 should consider, I actually think it should be an
11 earlier phase study of CNS-directed therapies with
12 higher dose intensification for patients who have
13 lesions that have failed all forms of local
14 therapy, and we're really out of options, because
15 you could see a home run in that situation.

16 DR. PROWELL: Thank you. I'm going to take
17 a question from the back microphone, and then I
18 want to get back to Lynda to move into our next
19 topic, which is going to be about this issue of
20 incorporating local therapy and should we be
21 enrolling patients with active, meaning previously
22 untreated or potentially progressing, having had

1 local therapy, and what are the ethical and
2 pragmatic issues of that.

3 So we're going to come to Lynda in a second,
4 but a question from the back microphone, please.

5 AUDIENCE MEMBER: Thank you. As a
6 neurosurgeon, I probably stand up more than a lot
7 of you, so I'm doing okay on that front, but I do
8 appreciate the exercise today. I'll start with a
9 kind of slight rebuttal to my radiation oncology
10 colleague in that I think there is a way to improve
11 on radiation therapy for brain metastases, which
12 would be to obviate the need by giving therapies
13 that keep them from developing brain metastasis in
14 the first place.

15 That's where I think developing therapies
16 that are specifically targeted to get into the
17 brain and treat the brain beyond the breakdown of
18 the brain blood-brain barrier within the tumor
19 itself are important. So getting to this question
20 of including brain metastasis patients in early
21 trials, again, I'm a hammer, so I sound like a
22 hammer, but everything's a nail.

1 I do think it's important when we're
2 thinking about these early-phase trials to think
3 about ways to bring in patients and also have
4 potential endpoints where we're looking at the
5 tissue to see what the drug is actually doing in
6 the tissue and/or the brain around it.

7 There was a comment earlier about envy of
8 the window opportunity studies that are being done
9 in glioblastoma. There's no reason for anyone in
10 this room to envy the glioblastoma field. I spent
11 a lot of time in it. We envy a lot of the response
12 rates that you see in these things.

13 You're talking about shrinkage or you're
14 talking about objective responses. We don't see a
15 lot of that, so we're starting to get creative on
16 how we're doing our trials to try and stack the
17 deck a little bit and see which drugs are going to
18 work. And that's why we're doing these window of
19 opportunity trials to understand things better.

20 In some of these brain metastases patients,
21 I think we need to do the same thing. We're seeing
22 great responses, but there are still these large

1 numbers of patients whose brain metastases aren't
2 responding, and I think it's exactly because we
3 aren't designing trials that are specifically
4 designed to answer the question of what does it do
5 in the brain metastases patients.

6 So it would seem to me to suggest that in
7 those early phases beyond just separating out a
8 cohort of metastasis patients and seeing what the
9 objective response is, I think if you did have a
10 few of those patients who we know are going need a
11 resection with that solitary metastasis that is
12 symptomatic, if you did design that trial
13 where -- maybe it doesn't have to be 2 weeks, maybe
14 it's a week, which most patients can tolerate,
15 where you're giving the one dose of the drug and
16 doing a resection.

17 I would even posit myself as something I'm
18 pushing in glioblastoma community that a needle
19 biopsy, which is very low morbidity, can be done in
20 a lot of these cases, in and out, 1 percent risk of
21 hemorrhage, and get some pre-tissue and post-tissue
22 before you give the drug and then after. And then

1 really have an idea of that biologic endpoint.

2 Now you've done 10 patients, and I said,
3 hey, in each of these 10 patients, it got into the
4 tumor, and in each of these 10 patients, I saw a
5 change in the endpoint that I was looking at.
6 Maybe now I want to enrich for brain metastasis
7 patients when we're going to these big registration
8 trials because I know that we're going to see some
9 effect in the tissue.

10 The last thing that I wanted to just ask
11 from the regulatory perspective -- these things
12 interest me. My wife actually works at the FDA.
13 But I saw that there's a draft guidance on
14 including metastasis patients in a lot of these
15 clinical trials going forward, and one of the
16 things you mentioned is that you let industry and
17 the investigators not include the metastasis
18 patients.

19 So is there a point at which you now start
20 getting these boilerplate protocols that don't
21 include brain metastasis patients, will you then
22 send it back and say why? You need to justify the

1 exclusion.

2 DR. PROWELL: We're there, and we're doing
3 this rather -- we've seen exclusion of men, for
4 example, from breast cancer trials. I'm a breast
5 oncologist, and that was something we didn't even
6 blink at when I started here in 2006, and now
7 anybody in this room who submitted a protocol knows
8 that if we get an IND where they propose to exclude
9 patients, we will always send a comment back and
10 say you need to have a scientific rationale for why
11 you don't think this drug is going to be effective
12 in them or you need to include them. The fact that
13 there aren't that many of them is not a good reason
14 to not include them, so we're there. We're there
15 already.

16 AUDIENCE MEMBER: The last thing I'll say is
17 if you're at an institution and you think there's
18 no neurosurgeons that are interested in doing the
19 window of opportunity study at your trial, and part
20 of the tumor section, and the [indiscernible] INS,
21 I assure you I can find you one.

22 DR. PROWELL: Perfect.

1 AUDIENCE MEMBER: Can I just add one more
2 point to what he said?

3 DR. PROWELL: Sure. I do want to make sure
4 we get to the next topic, but please.

5 DR. YUNG: I'm Al Yung. I'm from MD
6 Anderson. Just one more point is I totally agree
7 with Pat Keegan and [inaudible], that there is no
8 reason not to include brain met patients in the
9 phase 1 trial while we are in the signal seeking
10 stage for drug development sake. Besides, you can
11 build in the window opportunity trial into that
12 stage, as well as when you see failure or brain met
13 when you have systemic response. You actually can
14 also take that brain met by surgery and begin to
15 study the reason why you failed.

16 So there is really no reason in the early
17 phase. We just need to separate the early-phase
18 study from the later phase when we're looking at
19 efficacy for specific indication or targeted drug
20 you have the precision medicine endpoint also
21 there.

22 DR. PROWELL: It has become abundantly clear

1 that we should have had a neurosurgeon sitting in
2 the front all day.

3 (Laughter.)

4 DR. PROWELL: So we apologize. These
5 comments have been really terrific.

6 Actually, did you want to respond to that?

7 DR. MOSS: Just one tiny corollary of the
8 same point. Nelson Moss, neurosurgeon at Memorial
9 Sloan Kettering. I'm also happy to provide tissue.
10 Just one more plug for more data.

11 Why don't we consider all cancer patients,
12 potential metastasis patients, potential brain
13 metastasis patients, and mandate MRIs at the end,
14 at late time points in our late-stage trials? We
15 don't have enough understanding of how these tumors
16 behave over time. We've all seen ER positive
17 breast cancer act in a very latent fashion on
18 hormonal therapy, and then 13 years later giving us
19 these tiny, slow-growing mets. Why don't we
20 collect more data? Why don't we require this of
21 all of our trials?

22 DR. PROWELL: I want to move to a next

1 topic, and I promise I will come back to you guys.
2 I want to move to a next topic, which is it seems
3 like there's pretty good consensus in the room that
4 we want to be including these patients, and we want
5 to be including them pretty actively and
6 aggressively, and we want to include them early in
7 the sense of early in drug development, like
8 phase 1.

9 But I want to ask this who question now, and
10 the one question of how do we feel about including
11 patients who might have either not yet treated
12 brain metastases, meaning no local therapy, no
13 surgery yet, or patients who've had local therapy
14 and are progressing? I want to get your comments
15 on that from a patient perspective.

16 MS. WEATHERBY: Yes And yes. I know I don't
17 understand all the complexities, but speaking for
18 patients -- and I spent a lot of time talking to
19 other patient advocates at a weekend long meeting
20 last week. Yes. When you're in this situation, we
21 don't have a lot to lose. I know that might sound
22 crude, but we don't. Probably the harder thing is

1 to know that there -- I mean, I'm hearing this
2 makes no sense. This makes no sense. We need to
3 work on it, and probably the hardest thing of all
4 is to know that something's poised for change but
5 it hasn't happened yet.

6 The only other comment I wanted to make as
7 an advocate -- and I want to point out I'm with
8 metastatic breast cancer advocacy, which is way
9 different than early-stage breast cancer advocacy,
10 and I hope everybody in the room kind of gets that.
11 The metastatic breast cancer advocacy movement has
12 really gotten a lot of momentum lately and is
13 really looking to work with the other metastatic
14 cancers to create these changes.

15 I want to assure you that the patients are
16 ready, not every patient, but they're ready.
17 Especially in metastatic breast cancer, from the
18 ones that I meet, they tilt young, desperately
19 young, and they are ready for anything. We are
20 organizing -- part of the Metastatic Breast Cancer
21 Alliance's work right now is to launch a patient
22 enrollment tool and database that. It's called

1 MBC Connect, which we're enrolling now. And
2 shortly in another 4 to 6 weeks, we're going to
3 roll out the 2.0 version, which is actively going
4 to match them to clinical trials based on the data
5 that they enter.

6 So our whole purpose is to bring the
7 clinical trial information to the patients so they
8 don't have to struggle so hard to find out about
9 clinical trials. Once this momentum builds and
10 builds and spreads across cancers, can you imagine
11 how it would feel as a patient to be able to find
12 the trials and then still see that maybe these
13 blockades are in place? So yes and yes.

14 DR. PROWELL: Thank you. I actually want to
15 ask Dr. Keegan to comment on that, and then I'm
16 going to ask Dr. Blackwell to comment on that. One
17 of the things that we struggle with as regulators
18 is when investigators or companies want to have
19 patients potentially forego known effective therapy
20 to get an investigational agent. There are real
21 ethical concerns with that.

22 Maybe I'll ask Dr. Keegan and then

1 Dr. Blackwell to comment from a regulatory and an
2 industry perspective on that idea, potentially
3 enrolling patients who've got progressing brain
4 mets after stereotactic radiosurgery in lieu of
5 going on whole brain or taking patients who maybe
6 in the slightly simpler scenario just have brain
7 mets and haven't yet had any local therapy at all.
8 Your thoughts on that?

9 DR. KEEGAN: So my thought is that, yes,
10 there is an ethical consideration and argument to
11 be made, and there are ways to mitigate that. Some
12 of those mitigations are adequate informed consent.
13 By and large, we should be trying not to take the
14 judgment out of the hands of the patient and their
15 physician from making a decision under adequate
16 informed consent.

17 So I do believe that it would be possible to
18 allow a patient, adequately counseled, to make that
19 judgment. I would like to try this therapy knowing
20 that there are other therapies available and that
21 the trial should have certain safeguards built into
22 it for adequate monitoring to take patients off at

1 the earliest opportunity. But with those kinds of
2 conditions in mind, I don't see any reason why one
3 could not have a trial like that and consider it to
4 be ethical.

5 DR. MISHRA-KALYANI: Could I add to that, to
6 Dr. Keegan's comment? And I know she's going to
7 agree with me.

8 (Laughter.)

9 DR. MISHRA-KALYANI: There are also
10 statistical trial design considerations that you
11 could include in those cases like adaptive design,
12 and early stopping rules, and things like that, so
13 that you can not only have informed consent for
14 patients and investigators, but you can also very
15 closely monitor your trial to make sure it doesn't
16 go too far without having a good idea of what
17 benefit the patients are getting.

18 DR. PROWELL: Right, Dr. Keegan?

19 DR. KEEGAN: Yes.

20 DR. PROWELL: Thank you.

21 Dr. Blackwell, do you want to comment from
22 an industry perspective on this?

1 DR. BLACKWELL: Yes. I agree with both. In
2 the setting of adequate consent, knowing and
3 stating that there's an appropriate standard of
4 care in the consent makes it at least acceptable to
5 me. And I can't speak for all of Lilly.

6 I do want to say something that's in -- and
7 I'm not going to go off on my list again. But it's
8 very interesting, this dynamic that I'm seeing.
9 And now I'm speaking from my history as a
10 practicing clinician, which is most doctors do what
11 they do because they think it helps people.

12 The way that patients with newly diagnosed
13 brain mets get into the system typically is they
14 have a problem. They know they have cancer. They
15 go to the emergency room. And honestly, their
16 treatment is dictated by who they see in the
17 emergency room if it's truly an emergency. So if
18 they see a radiation oncologist because,
19 unfortunately, there's not a neurosurgeon on call
20 and they need emergent therapy, then they'll get
21 radiation.

22 DR. PROWELL: No offense to radiation

1 oncology intended or taken.

2 DR. BLACKWELL: Yes, no offense, or
3 neurosurgery. I think the point is that what
4 happens -- and now I'm speaking from industry and
5 clinician -- is you have a patient that's facing a
6 new brain met, perhaps asymptomatic, although,
7 again, frequently they're symptomatic. That's how
8 you pick them up. I've always struggled with the
9 term "asymptomatic."

10 So you have a symptomatic brain met. The
11 patient comes in. They maybe see me as a medical
12 oncologist first. I say I have this great trial.
13 You can go on drug X. I know you're afraid of
14 getting more SRS or you're afraid of radiation in
15 general. And we sign them up, and it's, again,
16 industry speaking, too, which is it costs money to
17 just screen patients for trials. Then in the
18 criteria it says "doesn't require radiation," or
19 you feel as a clinician you have to refer them to a
20 radiation oncologist.

21 So here's the choice the patient has to
22 make, which is you can go on this trial that we

1 think might help you or you can have radiation,
2 which we know will help you. And in fact, that's a
3 tough decision and it's a tough place to put
4 patients.

5 I actually thought -- some of the randomized
6 studies that reported out in 2016-17, which really
7 demonstrated that at least for whole brain compared
8 to best and supportive care, with all the caveats
9 of the trial design, it might help in this
10 discussion, which is although we can do this, it's
11 not been shown -- and I'm talking about whole brain
12 now -- it's not been shown to improve survival, so
13 I as your practitioner am willing to say let's try
14 this; you can always have this.

15 So I just think we need to be aware -- and
16 now I'm speaking from an industry standpoint -- of
17 where that dynamic is, which is patients get
18 treated by the doctors they see, by the modality
19 that those doctors use. So I think that is
20 something we're going to have to address, and
21 educate the ER physicians, and the
22 neurosurgeons -- not all neurosurgeons but

1 radiation oncologists, and even the medical
2 oncologists.

3 I frequently had discussions conducting
4 trials of patients that had new brain mets, where
5 the radiation oncologist actually said -- and this
6 is the truth, "You're going to feel bad if the
7 patient goes home and has a seizure and you didn't
8 give them radiation." That's a true story.

9 So these are the forces that -- and I'm sure
10 there are other stories here, but we just need to
11 be very practical about how patients get referred
12 to these trials and enrolled on the trials.

13 DR. PROWELL: Dr. Tawbi, respond, and then
14 the person at the back microphone who is the single
15 most patient human I've ever known --

16 (Laughter.)

17 DR. PROWELL: -- and then I'm going to
18 invite you to respond.

19 DR. TAWBI: And happens to be my patient, so
20 I apologize, Christina.

21 I really just want to address the issue of
22 who sees the patients and at what point. Actually,

1 I think that's where the value of multidisciplinary
2 care is so important. I co-direct the brain
3 metastases clinic at MD Anderson, and that's
4 exactly the point; that we all see the patient
5 together at the same time, and we really look in
6 each other's faces about how comfortable we are
7 about waiting for SRS to happen.

8 The way we built our clinical trials is
9 actually if we have a trial that's for patients
10 with untreated brain metastases, I actually include
11 in it that they have to be evaluated by the
12 radiation oncologist that can tell me that they can
13 do it. And actually Dr. Chung is sitting right in
14 the audience and has herself overruled me on some
15 of those patients, and said, "This cannot wait;
16 let's do it," versus now you can do systemic
17 therapy.

18 What we've included in those studies was
19 very early imaging assessments, as early as 3 weeks
20 or 6 weeks, depending on the specific regimen, so
21 that we can -- as I said in my earlier comment, we
22 have days to manage these patients; we don't have a

1 lot of time -- so that we can act on it relatively
2 quickly.

3 DR. PROWELL: Would you like to acknowledge
4 your patient by name and invite her --

5 DR. TAWBI: Christine Baum, one of the most
6 patient patients, as you said, but the most bright
7 as well and very well represented on social media,
8 I should say.

9 MS. BAUM: Thank you. As my oncologist,
10 Dr. Tawbi said, I'm having my third recurrence of
11 melanoma, second metastatic, first brain met. I'm
12 an active clinical trial right now. This is my
13 second clinical trial. I'm one of nivolumab and
14 cyberknife radiation.

15 My question has more to do with NRAS, the
16 NRAS genetic mutation of brain mets. I'm an NRAS
17 patient, which is separate than BRAF, as most of
18 you know. I know FDA has done some work with NRAS
19 mutation tumors specifically. Just to double down
20 a little bit of what my friend Derrick said this
21 morning on just making more clinical trials
22 available to brain mets patients -- but I also

1 wanted to ask, is there a potential trial designed
2 to break it down into genetic mutation? Certain of
3 these clinical trial drugs could be made available
4 to NRAS patients or different genetic mutation
5 tumor of patients, that could be a way to further
6 the ball.

7 How does that kind of comes together in
8 trial design?

9 DR. PROWELL: Do you want to come up? We're
10 going to have Dr. Brastianos address this question
11 probably related to the Alliance trial I'm
12 guessing.

13 MS. SELIG: Dr. Prowell, I'm just going to
14 say maybe take the last two comments after this,
15 and then if you could summarize. Then those of you
16 who are on Session IV panel, we're going to do a
17 quick reset without anybody in the audience getting
18 up and leaving the room, and see if we can do that.

19 DR. BRASTIANOS: That's a great question.
20 Actually, we're starting an Alliance trial and
21 actually --

22 DR. PROWELL: Can you speak into the mic?

1 You can turn around if you want.

2 DR. BRASTIANOS: We're starting a national
3 trial, precision medicine trial, with that design
4 that will allow all histologies. And if you have a
5 CDK path filtration, you'll get a CDK inhibitor
6 regardless of pathology, and the same with PI3
7 kinase pathway.

8 That's the design, and it's a
9 biomarker-driven trial for brain metastases based
10 on the science, showing that these are markers that
11 do seem to be common in brain metastases. So
12 that's a trial that is coming in a month.

13 AUDIENCE MEMBER: Thank you. And just let
14 the record show, to all the neurosurgeons, I win
15 the standing contest today.

16 (Laughter.)

17 DR. PROWELL: Absolutely.

18 (Applause.)

19 DR. BRASTIANOS: Kim just wanted me to
20 mention also that we're looking for mutations in
21 the brain metastases themselves, so we are hoping
22 that it will target the patients with the brain

1 metastases.

2 DR. PROWELL: Thank you. And we'll take the
3 question on the mic.

4 AUDIENCE MEMBER: This may be a combination
5 comment and question brought up by, really, the
6 first real reference to informed consent and the
7 patient landing in the ER and those combinations.
8 The informed consent, et cetera or the patient
9 landing in the ER carries with it the question of
10 whether the patient's options offered them, whether
11 ER or in the trial, are really given to a patient
12 who can make consent, because very often there's
13 that emergent need, and in the clinical trial
14 there's a lack of information on the total
15 perspective of the options that are available.

16 This is an issue that hits every patient.
17 I'm seeing this kind of doctor. I'm directed into
18 this treatment whether in the ER or in a clinic.
19 The informed consent is usually quite narrow; "Yes,
20 I want to be fixed tonight in the ER," or "Yes, I
21 want to be treated in this category of response."

22 So I'm going to always be pushing that the

1 patient not just have informed consent but to be
2 able to make an educated choice with the full range
3 of options available. And that is something that
4 is beyond this specific brain met issue but hits
5 every patient and every trial in complex diseases,
6 and every patient going into treatment where he or
7 she has perhaps been diagnosed and sent in one
8 direction when there were 10 or a lack of clarity
9 from that initial doctor, so educated options.

10 DR. PROWELL: Thank you. Absolutely, a
11 terrific comment.

12 I'll just maybe spend 30 seconds summarizing
13 this panel's discussion. And I believe you
14 actually want the panels to switch -- is that
15 right -- while I'm talking?

16 MS. SELIG: That's okay. You can talk
17 first, and then we're going to take 60 seconds and
18 switch.

19 **Panel Recap - Tatiana Prowell**

20 DR. PROWELL: Okay, great.

21 Just to summarize this really terrific
22 discussion, I think what we've heard from across

1 all the sectors is that there's really enthusiasm
2 for including patients broadly who have CNS
3 involvement in clinical trials and that we'd like
4 to see that happening not only robustly, but
5 earlier in the drug development process in the
6 sense of kind of phase 1, 2, 3, but also earlier
7 potentially even including patients who may not
8 necessarily have had definitive local therapy.

9 We feel that there are ways that this can be
10 accomplished both safely and without
11 compromising -- either compromising patient safety
12 or posing excessive risk to the companies
13 developing these drugs in terms of having patients
14 in separate cohorts that that may enable us to look
15 at their efficacy and safety, and even their dosing
16 requirements distinct from the main group, and
17 hopefully without too much disruption to the
18 overall trial if we do in fact discover that it's
19 not safe or it's not effective to develop these
20 drugs in patients with brain mets.

21 I think that we had hoped to get to -- but
22 it actually really leads into Session IV well, how

1 do we provide the incentive to really include these
2 patients; what's in it for patients to go on these
3 trials; and what's in it for an industry to include
4 these patients in their trials? I think that
5 that'll be a big focus in Session IV.

6 So I'd like to thank all the panelists and
7 thank the audience for being so engaged.

8 (Applause.)

9 MS. SELIG: Please if you're sitting in the
10 room, just take a moment to check your phone or
11 whatever you need to do, but don't leave. And if
12 you are on Session IV and you're not already up
13 there, please make your way, and we'll move
14 everybody closer together.

15 Joohee?

16 DR. SUL: I also wanted to add that we felt
17 so terrible for Edjah having to stand for so long
18 that we actually invited him up to join panel 4, so
19 he'll be joining to represent the neurosurgeon's
20 perspective.

21 **Session IV**

22 DR. WEN: I think we'll get started on the

1 final session. We've had a lot of great discussion
2 today. This final session, I think what we hope
3 will come out of this are concrete steps that we
4 can take forward on how to include brain metastasis
5 patients.

6 I guess the tradition is we started
7 excluding brain metastases patients, and now we're
8 slowly letting them in. Maybe the flip is that
9 everybody should be allowed in, and this is a good
10 reason that they shouldn't be in the trial, and how
11 can we get to that stage. I think in this final
12 session we want to be concrete. We want to come
13 out of this with clarity, both in terms of who's
14 eligible, what are the trials, and what are the
15 endpoints.

16 Before we get going, though, maybe I'll have
17 the new people who joined the panel introduce
18 themselves. The first one, Peggy's Zuckerman.

19 MS. ZUCKERMAN: I'm a kidney cancer patient,
20 or at least I like to say I used to be a kidney
21 cancer patient. I am 15 years, nearly to the day,
22 from having had a radical nephrectomy because I had

1 a 10-centimeter tumor that also included metastases
2 throughout my lungs, and I was clearly a goner, I
3 think is the technical term, and all I wanted to
4 do, with so many other patients, was live long
5 enough to see, in my case, my son graduate, my
6 youngest graduate from high school. That was all I
7 thought I could begin to hope for.

8 I was one of those miracle responders to
9 high-dose interleukin. All of you will know more
10 about it, of course, than I; except that I would
11 have in many cases been precluded from even
12 considering it because it wasn't a
13 medication -- though it was the only agent, which
14 was FDA approved at the time, it wasn't one which
15 had much support in the clinic.

16 Certainly, had I not gone to an academic
17 center, would not have even heard of it, period.
18 Obviously, it was very easy for me to make the
19 choice to enter into that treatment, and with other
20 patients very often enter into a clinical trial
21 because that is the only version of a treatment.

22 I do remember very clearly, and thought

1 about this the moment I heard of this workshop,
2 that I would not have been allowed to go into that
3 treatment had I any brain metastases. So the
4 moment I got the call that said "it's clear," I
5 knew it's clear meant my brain was clear of any
6 mets, and it was clear that I was heading into the
7 first thing that gave me any hope that I would see
8 that boy graduate.

9 I obviously responded. I quit asking why
10 me? Why did I get kidney cancer? Then I could
11 finally ask, why me? Why did I respond? Why are
12 there not more like me? Why was I so lucky to be
13 just dropped into a place where they would grant me
14 that one hopeful treatment? And that has pushed me
15 to where I am today, lucky to be here, in the most
16 essential terms, to be here on this good earth and
17 here hoping that I can add some insight into the
18 patient's role, and what options can be brought to
19 patients, and how to bring those two patients.

20 So thank you, and I always have more to say,
21 so somebody close.

22 (Applause.)

1 DR. WEN: Thanks so much. Dr. Ndoum?

2 DR. NDOUM: Edjah Ndoum. I'm a
3 neurosurgical oncologist at the NIH and happy to be
4 here. I came here to learn and listen, actually,
5 and not to talk.

6 DR. WEN: Caroline?

7 DR. CHUNG: I'm Caroline Chung. I'm from MD
8 Anderson. I'm a radiation oncologist, cross
9 appointed to diagnostic radiology. I'm the
10 director of imaging technology and innovation, and
11 I'm hoping to contribute to this great discussion.
12 It clearly shows how complicated brain metastasis
13 can be, as well as how strong a mission we have to
14 actually make things better. I think that,
15 hopefully, we can start to wrap up with some key
16 action items as we move forward. Thank you.

17 DR. ABREY: I'm Lauren Abrey. I currently
18 work at Novartis oncology, where I lead the solid
19 tumor group and medical affairs. Previous to that,
20 I think I can say I started my career making some
21 of those working mistakes that someone brought up
22 in the first session. I think I did a bunch of

1 Temodar studies in brain met patients, and I think
2 it's been true ever since then. Brain met patients
3 are out there and participate, but I do think we
4 have to be mindful that sometimes what we ask for
5 in trials are a pretty selected group of patients
6 if we look at it that way.

7 I really want us to start to think how does
8 what we're talking about connect to all the brain
9 met patients who are treated in the community
10 because we've got a lot of specialized centers
11 here, and not everybody has access to these
12 multidisciplinary clinics, and we really need to
13 think how they're getting treatment when they're
14 out there in the real world.

15 DR. WEN: Thank so much.

16 Maybe what we'll do is divide this into
17 trial design and eligibility, and then we'll talk
18 about endpoints. In the first spot, in terms of
19 trying to allow all or as many as possible brain
20 metastasis patients into general oncology
21 development, maybe, Dr. Prowell, if you could give
22 us your thoughts on this, and also whether we

1 should try to get the ASCO Friends of Cancer
2 guidelines and the RANO guidelines uniformly
3 adopted as a recommendation and earlier thoughts on
4 this.

5 DR. PROWELL: Sure. I think there's been
6 movement in that direction already. We've seen NCI
7 come out with standardized templates a few months
8 ago that were based upon BM [ph], ASCO Friends
9 eligibility criteria. Although there's templated
10 language available in these manuscripts, I'm not
11 sure that that's been -- in fact, I'm sure that has
12 not been uniformly adopted by industry, but I would
13 like to see it done.

14 As a clinician, it's hard for me to
15 understand why we actually allowed this to happen
16 for so long. Why did we allow these patients to be
17 excluded when they represent, in some cases, half
18 or more than half of the intended-use population?
19 It doesn't make a lot of sense to me.

20 So I feel like we should be compelling these
21 patients to be included. Anybody here who's an
22 industry, or anybody here who's an investigator at

1 all, knows that the reason that we put clinical
2 trials on hold is because of deficiencies, and
3 those tend to be safety issues.

4 So I would actually say that maybe this
5 requires recharacterizing how we think about
6 exclusion of brain mets patients to be a safety
7 issue, because the reality is these patients will
8 be treated with these drugs, and the experiment
9 will occur, and the only question is will it occur
10 on a clinical trial where safety data are being
11 rigorously collected and patient safety as being
12 rigorously monitored by a specialized team, or is
13 it going to occur in someone's outpatient practice.

14 The experiment's going to happen, so maybe
15 that's the issue, is we need to recharacterize
16 failing to include brain mets patients as a safety
17 issue and as a deficiency, and not just a comment,
18 "Hey, you need to think about including these
19 people."

20 DR. CHUNG: I'd just like to add a comment
21 to that. I completely agree with you, and I think
22 that one of the things that we do have to think

1 about is when we think about when we started
2 excluding brain metastases patients and the era in
3 which we were imaging these patients, and when you
4 compare someone who doesn't have brain metastases
5 on a brain CT versus an MRI, I'm pretty sure a good
6 proportion of those patients actually did have
7 brain metastases.

8 So we were including patients with brain
9 metastases from the start. For some reason, we
10 continue to keep that exclusion criteria, but our
11 imaging got better, and I think that there's a
12 continued improvement in that image quality. So if
13 you find a 1-millimeter spot in the brain today, is
14 that the same thing as someone who has a sizeable
15 brain metastasis that we were finding on older
16 imaging? So I think that we do have to be
17 thoughtful about what we're saying when we're
18 saying we're excluding these patients.

19 DR. SUL: Yes, I absolutely agree with that
20 statement. There's a big difference between
21 excluding someone based on information you don't
22 know versus information you do. I would bet my

1 house and my car that all these trials, some of the
2 industry reps have said, well, we excluded patients
3 with lepto. I can guarantee that there were
4 patients with lepto on that study, because if you
5 didn't look, it doesn't mean that it's not there.

6 So we are doing these studies; we're just
7 kind of I think fooling ourselves, and in that
8 process, we're not getting the data.

9 This goes back to I think one of the
10 questions I had asked earlier about screening and
11 looking, are we just not looking enough? I
12 understand the reasons why we don't. Sometimes we
13 say, okay, if you're not symptomatic, we're not
14 even going to go there and look, and I know that's
15 standard for patients with breast cancer, but
16 should we actually start looking more? When we do
17 all these staging screening exams, it stops right
18 at the neck with CTs and PETs, and we're not
19 including the brain as part of the entire body.

20 DR. CHUNG: Just to add to that, I think as
21 Hussein had mentioned earlier, the patients who are
22 in the studies where there seems to be a good

1 efficacy signal, where we're probably going to say
2 this is going to become a mainstream drug,
3 similarly, even in the upfront setting when
4 patients may have metastatic disease but don't have
5 known brain metastases, if we don't continue to
6 follow them -- or if we do continue to follow them
7 and the pharma companies are willing to fund these
8 trials, and we can continue to follow them with
9 brain imaging, that will help answer our
10 preventative questions without designing a whole
11 new trial.

12 Kim had mentioned the whole cost of
13 screening patients, and we have patients who we're
14 following who have been screened, who are on this
15 trial. And by following them, we are getting a
16 secondary endpoint that's clinically very
17 meaningful in terms of brain mets prevention.

18 DR. SUL: Kim?

19 DR. MARGOLIN: I agree with that, and I
20 think I even mentioned it earlier. It's been nice
21 for my career, Hussein, et cetera, that we've been
22 in -- melanoma has sort of been the vanguard

1 because of the bad news that melanoma has such a
2 high brain met 2 case rate, that all along I think
3 we've -- and immunotherapy has been important, and
4 steroids.

5 So we've been in this mind-set of for many
6 years of looking for brain metastases basically
7 anytime there's a first recurrence metastatic
8 disease. Some of the surgeons I work with are even
9 scanning people's brains as soon as they have a
10 sentinel node metastasis, which we could quibble
11 about that, but that's not what we're here for.

12 But the idea of not lulling yourself, just
13 like you were saying about assuming that patient's
14 don't have brain mets and including them when they
15 may, these patients who were in remission who
16 didn't have visible brain metastases at the
17 beginning of whatever their current therapy is, and
18 they're doing well on it.

19 extracranially, you can't forget the importance of
20 occasionally looking at their brain. I don't know
21 that we can legislate that.

22 But I wanted to make a couple of other

1 points if you'll permit. These are more global and
2 little bit off this topic, so you may choose to
3 ignore it or come back to it. I'd like to propose
4 that there are really two purposes here.

5 One is that if we're looking at the concept
6 of approving drugs with a specific idea that
7 they're going to be for patients with a given
8 disease and brain metastasis, then we have to show,
9 as so elegantly gone over in the Camidge video and
10 earlier talks this morning -- I think it was
11 Mike -- that they really should demonstrate an
12 improvement in patients with brain metastases over
13 the available options in patients with brain
14 metastases.

15 So all these amazing mutations in lung
16 cancer are the area where that's already started to
17 be shown, because otherwise the drug doesn't have
18 an advantage in those patients, and that's an FDA
19 issue.

20 What's not an FDA issue that I think is more
21 of a market penetration if you're talking from the
22 industry point of view, or a usage, and maybe even

1 a safety issue, is the idea that available drugs
2 being used more in patients with brain metastases
3 are safe and may be synergistically effective with
4 other modalities such as stereotactic radiosurgery,
5 or certain sequences are ideal, and so on and so
6 forth. That I don't think is for the FDA to have
7 to legislate.

8 DR. LIN: The two points that I would add
9 are I would distinguish two kinds of trials, the
10 trials where the patient's CNS disease has been
11 treated, and then you enter them, and your primary
12 purpose is to control the extracranial disease. I
13 think the argument there is, really, unless there's
14 a very good safety reason, those patients should
15 just be allowed on all phases of all trials just as
16 a blanket statement.

17 I think right now that's still not -- I mean
18 it's happening more, but it's still not happening
19 enough. We would never allow a trial for
20 metastatic breast cancer to exclude liver
21 metastasis patients. That's a completely
22 ridiculous concept, but we routinely allow trials

1 to exclude brain metastases patients even if
2 they've been treated.

3 So I would like to see that just completely
4 go away. I still think we need specific -- whether
5 it's an individual trial, or a cohort in a trial,
6 or subset in a trial, these patients do have to be
7 looked at separately in some way because you're
8 going to be potentially looking at different
9 secondary endpoints. You might have different ways
10 that you're going to assess their CNS.

11 So I think it's so important to do those
12 trials, but I would kind of distinguish between
13 these two types of trials. I personally think for
14 a patient who has treated brain mets that any
15 exclusions should really go away unless you really
16 know that there's a safety issue.

17 DR. ABREY: If I could follow up on that, if
18 you're interested in thinking how do you
19 incentivize industry to want to do two very
20 different things there, I think one is breaking an
21 old habit, and whether you take Pat Keegan's
22 comment that a lot of what we do in industry comes

1 out of a standard template, what's probably not cut
2 and paste. There's just a template for phase 3
3 trials in solid tumors, and then you adapt what you
4 need, and that exclusion lives in there.

5 I think it was the same when I was at Sloan
6 Kettering, and I cut and paste from my last
7 protocol, sometimes horribly, even to the
8 statistics section just to provoke the
9 statisticians to give me what I needed. So I think
10 some of it is just breaking old bad habits, and
11 unfortunately that's a little bit more the stick
12 than the carrot I think probably.

13 I do think the other side, though -- and I
14 think the alectinib, brigatinib stories,
15 osimertinib start to really say why would industry
16 care about developing drugs that have unique
17 efficacy in the brain, and it's because it helps
18 you differentiate your product from the other
19 products on the market. And that's not hard for my
20 scientists to understand or my commercial team to
21 understand.

22 So I think those stories and those examples

1 are really terrific and thinking how we can build
2 on whether it's specifically the alectinib story or
3 another to say how do we do that in other disease
4 areas and other specific mutations in a similar
5 fashion, and how much of that was intentional, and
6 how much of that was a little bit luck. I think
7 maybe some of the early alectinib was observing
8 early luck, and I think maybe some of the
9 brigatinib, lorlatinib story was a little bit more
10 intentional as the follow-on. So I think we've got
11 opportunities on both.

12 DR. BRASTIANOS: Just a quick comment, just
13 to add to it, I completely agree, there are two
14 issues. One is we should be running brain
15 metastases trials because we are seeing that brain
16 metastases do differ from their primary and
17 extracranial sites, so that's really important, and
18 then the other issue of including the primary
19 tumors. But I think we can't forget that brain
20 metastases are genetically distinct, and we should
21 be considering brain metastases trials, and just a
22 comment to add to what you're saying.

1 DR. ABREY: I think that's something
2 even -- there was a third thing, Priscilla. I
3 think we really need to be intentional about the
4 drug development for brain tumors, including brain
5 metastasis because we suffer from the same problem
6 in the primary brain tumor, that we try to
7 piggyback on other oncology drugs and make them
8 good enough. Good enough isn't good enough
9 for this disease.

10 DR. RIELY: I think one thing to really bear
11 in mind, and as a lung cancer doc, I think about
12 the ALK story as something that taught us a lot. I
13 think one way it helps to teach us is we look at
14 ALK and we say it was really a great story about
15 developing drugs in patients with brain metastases.
16 A big part of that is because brain metastases are
17 very common in ALK-positive lung cancer. So it's
18 inherently about treating this disease as you're
19 treating people with brain metastases, a
20 significant number of people with brain metastases.

21 So maybe that's how we can figure out
22 whether this is merely having an arm, a cohort, for

1 brain metastases patients or trying to include them
2 in every step of the drug development process, and
3 basically how frequent is it, and is that number
4 10 percent, is that number 20 percent? I'm not
5 sure where the cut-point is, but that's kind of how
6 I'm beginning to think about it.

7 DR. LeBLANG: Hi. My name is Suzanne
8 LeBlang, and I'm a neuroradiologist, one of few in
9 the room here, so I've been eagerly listening to
10 the discussions all day, and I have a few thoughts
11 that I'd like to share.

12 First of all, I do believe that doing more
13 screening, MRI scans in patients that are at these
14 high-risk levels of disease is mandatory, and I
15 think the problem lies on both sides, on the
16 clinician side not wanting to prescribe or order
17 the MRI scan because you don't know -- you won't
18 have to deal with the results, and the clinical
19 trial enrollment is an issue. And on the other
20 hand, radiologists have some blame in this as well.

21 I think sometimes we do limited protocols
22 for orbis [ph] and not a whole brain, and I think

1 we can tailor an MRI screening exam so we're not
2 doing 6 or 8 different sequences and making it too
3 expensive to add to a clinical trial design.

4 So perhaps just do a volume 3DT1 pre-imposed
5 contrast and 1 T2-weighted image, like a FLAIR
6 image, and really cut the cost down of that, and it
7 could be more amenable to entering all these
8 patients in clinical studies, obviously to enroll
9 them and screen them before, as well as following
10 them during the study to see if they respond or
11 not. So we can tailor the protocol down.

12 The second thing I'd like to bring up is
13 that I'm currently working for the Focused
14 Ultrasound Foundation, and a few people have
15 brought up the new technology called focused
16 ultrasound. And what it can do is temporarily
17 reversibly and safely now open the blood-brain
18 barrier. This allows big pharma to start
19 considering either drugs that don't cross the
20 blood-brain barrier that may work for CNS mets, so
21 now we can get those drugs into the brain in
22 localized fashion, or even taking drugs that may

1 get in there to elevate their concentrations.

2 So I wanted to know your thoughts on
3 actually even opening the blood-brain barrier more
4 with this focus ultrasound and how that will enable
5 a more systemic therapy to possibly play a role in
6 between radiation oncologists, neurosurgeons, and
7 what we have today. So any thoughts on opening the
8 blood-brain barrier directly to allow these drugs
9 to enter?

10 DR. ABREY: I'm from New York originally. I
11 live in Switzerland now, sometimes I start from
12 skepticism. I feel like trying to open the
13 blood-brain barrier has been a long conversation,
14 so we've tried to disrupt it with various osmotic
15 agent. We've done other things where we've given
16 intra-arterial, including catheters threaded right
17 to the site of the tumor and infusing. I think to
18 date, it hasn't consistently shown us benefit,
19 although individual patients clearly have derived
20 massive benefit from it, but it's more stories than
21 data.

22 I don't want to write it off, but I think

1 it's still kind of an area that needs to be
2 considered experimental, and I guess I'm still
3 worried that we need better drugs to give the
4 patients more than we need to open the blood-brain
5 barrier, but others might disagree with me.

6 DR. NDOUM: I was just going to say, when I
7 was looking at -- I was talking to somebody earlier
8 about Visualase as well. That's another thing that
9 hasn't really been discussed a lot, but I know it's
10 very frequently discussed in neurosurgical
11 literature. So there are better local therapies or
12 alternative local therapies, and we have some local
13 therapies that seem pretty effective.

14 So focused ultrasound would fall into the
15 category of another local option. Maybe if
16 radiosurgery had failed or something like that, and
17 you're looking for an option, you know that there's
18 a systemic drug that's very promising, but we know
19 it doesn't cross the blood-brain barrier.

20 So maybe with the focused ultrasound, we
21 could get the contrast enhancing lesion plus a
22 slight margin around it in a different local way.

1 So I think there may be a role. I think as we're
2 talking broadly about metastases, it wouldn't be
3 the first thing that I'd focus on, but I think it'd
4 be something that could be adjunctive and helpful.

5 DR. WEN: Mike?

6 DR. DAVIES: Mike Davies, MD Anderson. I
7 was just thinking, as we talked before, about the
8 concept of do we need separate cohorts versus just
9 stratifying. I do think the one argument that I
10 would argue for the cohorts, as we talked about,
11 there are actually endpoints that are unique to the
12 brain metastasis patients, so making sure that we
13 designed the trial so we capture those, whether
14 it's the neurocognitive dysfunction or whether it's
15 the incidence of radiation necrosis.

16 I just wonder if we'd be able to efficiently
17 or effectively capture those if we just go to
18 stratification where we're using the same endpoints
19 on everybody and miss those sort of CNS specific
20 endpoints. So I think that could be an argument
21 for why it might make sense to use cohorts
22 specifically.

1 The other argument, just coming back to it,
2 not argument, but about the phase 1 question of how
3 early to go in. Again, as we talked about, we all
4 know that if these drugs get approved, even if it
5 doesn't specifically say brain mets, they're going
6 to get used in patients with brain mets. So
7 getting a safety signal in brain mets in phase 1 is
8 absolutely a straightforward justification for
9 doing that.

10 MS. ZUCKERMAN: I'd like to comment to that
11 because we focused quite a bit on the breast, on
12 lung cancer, and little on the other solid tumors,
13 and of course my favorite being kidney cancer. We
14 are finding out that there are probably far more
15 brain mets in that group than anticipated, and
16 historically.

17 Again, because we have better reasons
18 perhaps to go in and look, suddenly it's not just a
19 small percentage, but an increasingly large
20 percentage. As the technology improves, we'll find
21 more. And if we don't know the impact of the
22 medications, all of them on brain mets and the

1 responses that may or may not come, we will have
2 more failed trials in general.

3 The reality is, of course, even if we don't
4 know the patient has brain mets, he's in the
5 population that's being served by perhaps a less
6 experienced doctor who then provides one or more
7 medications and perhaps with some safety issues
8 that could have been anticipated had we done proper
9 and complete involvement and participation of all
10 those patients without regard to brain mets.

11 DR. PROWELL: Can I ask a question,
12 actually, to Dr. Abrey or anybody else in the room
13 from industry. I'm curious what you think, from a
14 large pharmaceutical company perspective, what do
15 you think is more motivating to companies? Is it
16 the incentive of being able to have a labeling
17 claim of saying here's the activity in brain mets
18 or even an indication in brain mets, or is it the
19 fear or the desire to avoid a limitation of use?

20 What is more -- is it the consequence
21 avoiding or the reward seeking that drives
22 behavior?

1 DR. ABREY: This could be a whole study in
2 human psychology.

3 (Laughter.)

4 DR. ABREY: Just a disclaimer, I spent half
5 of my career or more in academic medicine, so I
6 might not answer very straight. No, I think the
7 incentive to me would be the possibility to
8 differentiate around an enhanced labeling claim
9 because I think that's how you stand out from the
10 background. Having to either have a limitation of
11 use or some sort of restrictive comment in your
12 label is something that puts you on the defensive,
13 and nobody likes to be in that position. We want
14 to be better or competitive. I think we're all
15 competitive, before, in those rooms, so sorry.

16 DR. SUL: I think given the audience here
17 today, it's no surprise that we're all in agreement
18 that more patients should be enrolling in clinical
19 trials and that there should be more access
20 allowed, and we've talked a little bit about
21 incentives for industry, and wanted to know if we
22 could hear from Peggy a little bit about the

1 patient perspective on incentives and barriers to
2 enrolling in clinical trials.

3 MS. ZUCKERBERG: Well, first, there's
4 endless barriers, and a lot of it is simply that
5 we're not properly diagnosed as a group. I know
6 I'm speaking always from a kidney cancer
7 perspective, but I've got a feeling that most other
8 cancers are very much the same.

9 You're suddenly told you have cancer.
10 You're desperate to get it out or get it treated,
11 whatever that cancer is, and rarely do you hear
12 from your doctor that I can't do this or I won't do
13 this, you better go onto a clinical trial. If
14 you've got that far in your conversation to
15 understand that you might need a clinical trial,
16 unless you're from one of the many lovely centers
17 that have just been mentioned today, and within 100
18 miles or maybe 20 miles or so, chances are, you're
19 in a community setting, where your family is, where
20 your support system is, and where you're unlikely
21 to leave comfortably in his new stunning,
22 terrifying situation you found yourself.

1 So access to trials starts with that doctor
2 in that office and what I will call a complete
3 diagnosis, and that includes not just where the
4 tumor landed, where else it is, and I'm going to
5 start with the brain on down. And then to find
6 what those options are for you, and then a
7 meaningful way to find all the clinical trials that
8 might be available.

9 You and your doctor may not even properly
10 characterize your disease to be able to search on
11 clinicaltrials.gov or any of the other helpful
12 sites. So that alone, just knowing that what
13 you've got, where you can go, what your disease is
14 really called, how it's characterized in the
15 literature, all these are barriers; not even to
16 understand what a clinical trial means, which is
17 one of the pushes that every patient forum and
18 every disease group wants to work with.

19 But that is why we don't get the numbers of
20 patients into trials that we need, and then to be
21 really desperate because your head's at risk, it's
22 far more concerning that I would have had brain

1 mets than my liver was going to give me grief. And
2 I was living quite nicely with my lung mets all
3 over the place, but to think that your brain is
4 going to go, is going to be chewed up by this
5 cancer, is so frightening, so stunning, it is the
6 game changer.

7 Then to find out you've got a limited number
8 of choices in a trial, and you're now excluded
9 because of the thing that's most threatening to
10 your essential self is a betrayal of the medical
11 system and the clinical trial system to the
12 patient, in my thinking.

13 You've already been betrayed perhaps by your
14 own body, perhaps by the doctor who misdiagnosed
15 you, perhaps by the limitations of where you live
16 and what you can afford, and now the clinical trial
17 world that's supposed to be the foundation for the
18 new and improved care won't let you in because you
19 have brain mets, that's unethical, and it adds to
20 the terrible distrust we have in our society for
21 the medical world, which includes everybody from
22 patient advocates, to doctors, and to the pharmas

1 who really suffer from that.

2 I think I have probably said enough, but
3 that's enough of the barriers, and just not to
4 understand what a clinical trial is.

5 DR. WEN: Thank you. A question at the
6 back?

7 MS. SELIG: Can I pose a question on behalf
8 of a colleague who was here, but I think she had to
9 leave, and represents the lung cancer community, a
10 thought that came up -- and maybe this would be
11 something good for the regulators and the
12 clinicians to respond to.

13 She was listening to the discussion of,
14 well, we should measure this, and we should measure
15 that, and we should know these things, and we
16 should do all these tests. The flip side of that
17 is the burden on the patient that's actually in the
18 trial to go through all these tests.

19 So back to what Joohee was saying earlier,
20 could we identify those things that we all agree
21 are most important that we'd be measuring versus
22 study everything, put the patient through a zillion

1 tests to gather all this information? Is there
2 some way to balance the need to know more and to
3 evaluate these therapies in the brain with the
4 burden on the patient of actually participating in
5 these trials?

6 DR. MARGOLIN: Wendy, I'm not going to try
7 to answer this, but I want a part B to that. Just
8 as Tatiana's question, you can't ask one person to
9 represent the whole drug company industry, there
10 are patients who want to be scanned every
11 5 minutes, who want to know. There are patients
12 who don't ever want to know. So I'm not even sure
13 that this kind of a question can be applied here;
14 just saying.

15 DR. LIN: I'll add one point to that also.
16 Patrick has been thinking about this a lot as part
17 of this snow physician paper on barriers to trial
18 enrollment. I think that more so -- I'm speaking
19 for patients now, and there are patients here who
20 can tell me what they think. I think more so than,
21 okay, there's an MRI, there's a CAT scan, there's a
22 blood test, travel is a big issue.

1 So I think whatever we can do when we design
2 trials to minimize travel, to me that
3 feels -- that's what I hear from patients, is that
4 makes the biggest difference in their ability to go
5 on a trial. So if you have day 1, day 4, day 8,
6 day 11, day 16 blood draws, do they have to be done
7 at the site? Can they be done at a local lab?
8 Those very practical issues are I think really
9 important in allowing better access to trials.

10 DR. PROWELL: I'll just comment on one
11 thing. We hear you and we've heard this from
12 patients as well. This is actually a huge topic of
13 interest, not only in oncology but we've heard a
14 lot about this from the neurodegenerative diseases
15 community who have even more challenges and
16 difficulty traveling that are metastatic cancer
17 patients in many cases.

18 Just to make people aware, there actually is
19 a decentralized clinical trials working group at
20 FDA that's in the process of finalizing a draft
21 guidance that we expect to come out late summer,
22 and we're also going to have one of our two plenary

1 sessions at the AAADV workshop that's sponsored by
2 FDA, Duke, ASCO, ACR in Bethesda on May 9th. The
3 middle day of that workshop, we're actually having
4 a plenary session on decentralized trials that Rich
5 Schelsky from ASCO and I will be co-chairing, and
6 we'll be talking about this issue.

7 DR. RIELY: That's a great effort to be part
8 of because I think the question gets at the patient
9 experience, and that's critical. But I think we
10 need to get together and figure out what the best
11 tests to do are, because if you ask all the
12 investigators up here, we can tell you about 10
13 things that we do all the time that are dumb, and
14 getting an MRI brain is not one of them. That's
15 smart. The day 4 PK test, that's probably dumb.
16 But we all have to agree on what's important, and I
17 think that's hard.

18 DR. WEN: I'm going to take the two
19 questions really quickly, and then I want to switch
20 and talk about trials specifically for brain
21 metastases, and then talk about endpoints. We have
22 20 minutes left, so I think we want to get to

1 those. The person in the back, you've been waiting
2 a long time.

3 AUDIENCE MEMBER: Thank you. My name is
4 [indiscernible]. I have been running for office
5 for many times, [indiscernible] to U.S. Congress
6 and U.S. Senate, plus Maryland state comptroller.
7 As a patient myself before, I think as a mother, as
8 a consumer, as a government employee, I have seen a
9 lot of problems in our health care area, including
10 the [indiscernible] data set. All the research is
11 meaningless and this data should have
12 accountability.

13 So many times I just say if the researcher
14 wants to collect the data, first thing first. You
15 have to have independent accountability to have
16 good, accurate data. So I hope you can put this in
17 mind, first of all. To do that, you've got to be
18 independent sponsors, so you can see all those
19 sites. Those are sponsors, and some of those I can
20 testify they don't have independent or best
21 interest of the general public.

22 DR. WEN: Thank you.

1 AUDIENCE MEMBER: The second is I would like
2 to let you know after you have a drug, it's not
3 necessary [indiscernible] best and efficient.
4 These costs to the patients. I think now our
5 health care is in trouble because all pharmacy and
6 industry, even mergers, are a revolving door and
7 don't have accountability for the best interest of
8 our general public. Certainly, it's less
9 affordable, and pharmacy, or hospital, or rehab
10 center to get patient care.

11 DR. WEN: Thank you. Thank you very much
12 for that comment.

13 AUDIENCE MEMBER: Pay attention to health
14 care to consumers that complain. All this
15 information -- put a consumer group up front rather
16 than putting a pharmaceutical up front. Thank you.

17 DR. WEN: Thank you. Dr. Weinstock?

18 DR. WEINSTOCK: Thank you. I wanted to
19 touch on a topic that came up in terms of endpoints
20 in Session III, and I want to circle back to how
21 that might apply to something that we were talking
22 about in this session. And that's the use of an

1 endpoint, sort of avoidance of whole-brain
2 radiation type of endpoint and how that might fit
3 into a regulatory framework in a bit of a different
4 way than the other kind of surrogate endpoints that
5 you might think about traditionally.

6 The way we define an endpoint that's used in
7 a regulatory framework for regular approval, there
8 has to be demonstration of direct clinical benefit.
9 In the prostate cancer setting, we were trying to
10 wrap our heads around how to define an avoidance of
11 harm endpoint and direct clinical benefit endpoint
12 into maybe an earlier clinical endpoint that could
13 possibly, when designed appropriately -- and I
14 think we're not there quite yet -- could possibly
15 even lead to a regular approval based on avoidance
16 of harm or direct clinical benefit.

17 I think that could be presented to sponsors
18 as a possible incentive because if you look at a
19 brain specific endpoint like this, it's sort of a
20 different way of looking at the endpoint, rather
21 than looking at a surrogate, which would need to
22 lead to an accelerated approval, this may be a

1 regular approval endpoint that weeds out earlier
2 than more conventional measures of direct clinical
3 benefit.

4 I'm not sure if I'm getting my point across
5 because this is a very regulatory framework, but
6 I'm just saying that this could be used as an
7 incentive to enroll these trials.

8 DR. MARGOLIN: But you still have to have
9 really good control comparator.

10 DR. WEINSTOCK: This would have to be in
11 a -- certainly in the prostate setting, this is in
12 the context of a randomized controlled trial, but
13 my point is that it's a much earlier readout than
14 you necessarily have with the more conventional
15 measures of clinical benefit.

16 DR. LIN: We thought about this a lot. Yael
17 Lazer [ph], who's a radiation oncologist in our
18 group, is launching a screening brain MRI trial for
19 patients with metastatic breast cancer, and we
20 thought a lot about the right endpoint. We tossed
21 around time to radiation, time to whole-brain
22 radiation, time to SRS, time to symptom

1 deterioration.

2 One of the problems, practically speaking,
3 with the time to whole-brain radiation endpoint is
4 that people are doing now SRS to more and more
5 lesions, so it's kind of subjective when somebody
6 gets whole-brain radiation in a way. I mean, if
7 somebody has 30 lesions, not so subjective.

8 So ultimately, we actually came around to
9 Jeff Wefel's conclusion, which is that we just
10 really have to look at neurocognitive endpoints.
11 So that's actually what the study is powered to,
12 because I think it is. I think this time to
13 whole-brain radiation is tricky because of the
14 availability of SRS and multiple lesions,
15 especially now that we can do this with single
16 ICE [ph] center and do this with many, many lesions
17 in one session.

18 DR. ABREY: Thank you. And also for the
19 sponsor's point of view, be limiting the trial to a
20 very U.S. focus in that situation, so just thinking
21 about where whole-brain radiation is still used.
22 And also I want to put a little bit of caution

1 here.

2 It's still a very effective therapy and I
3 don't think we should make all patients so terribly
4 afraid of it that when you need to use it, it's
5 somehow the worst thing that could ever happen to
6 them. But I think the extreme use of radiosurgery
7 is not seen across the world, and then you'd be
8 focusing on a very limited potential market, which
9 drives a lot of the choices in pharma right now but
10 not great for patients necessarily.

11 DR. PROWELL: We were talking during the
12 break about what is the real possibility of
13 persuading investigators in a large randomized
14 trial, or particularly in a global trial, of coming
15 up with a uniform algorithm to how they would
16 administer steroids and to which patients would
17 receive radiation, recognizing that you really are
18 dictating practice of medicine and is that even
19 something that's possible. And the
20 neuro-oncologists all said impossible; there's no
21 way you can get them to all agree on this.

22 But I'd be curious to hear perspectives of

1 others in the room if they think that that's
2 something that you could even get people to rally
3 around and say we recognize that we all do this
4 differently in our own clinic, but from the
5 standpoint of this clinical trial, here are
6 criteria that we can all agree upon, which might
7 enable us to use certain endpoints like time to
8 whole-brain radiation, for example.

9 DR. WEN: Just a quick comment from
10 Dr. Gondi and Dr. Chung, and I really want to move
11 on to the other two topics that we need to discuss.

12 DR. GONDI: Two comments I'd say for the
13 time to whole-brain radiotherapy, but I just want
14 to make it also clear that it actually nicely
15 presented with Doctor Brown's online session. I
16 agree that whole-brain radiotherapy does have some
17 cognitive issues, but we've come a long ways in
18 preventing those cognitive issues. We didn't
19 really spend a lot of time talking about this
20 today, but hippocampal sparing, which is coming out
21 and been submitted to ASCO and prophylactic
22 [indiscernible], we're seeing fairly significant

1 cognitive benefits with these interventions. So I
2 think to Dr. Abrey's point, sometimes the
3 metastatic disease is really what drives the
4 cognition as we try to involve safer radiotherapy
5 approaches.

6 Secondly, as a question to the panel, as we
7 talk about all these endpoints and challenges of
8 these trials, some of the best brain met trials
9 have actually been run by the NCI, and I wonder
10 what type of opportunities we have in collaborating
11 with the NCI and industry to run basket trials in
12 the area of brain metastases.

13 Dr. Brastianos' trial is a great example of
14 moving in that direction; did a great job with the
15 MATCH trial, which did not include brain
16 metastases. But how do we allow various industries
17 to work together in basket trials to address all
18 these other endpoints that may not have enough
19 resources to address.

20 DR. WEN: Thank you. Let's talk briefly
21 about trials specifically for brain mets. Maybe
22 Nancy and Kim, if we could have your thoughts.

1 What does a trial look like and what are the
2 endpoints, if we had this magic drug X that's going
3 to be great for brain mets?

4 DR. MARGOLIN: I'll take a shot first
5 because I want Nancy to be the finisher and the one
6 who says the final words of wisdom, because I wrote
7 down a couple notes, and I actually wanted to say
8 that I agree with something Mike Atkins said
9 earlier and would like to expand on that just a
10 little, which is the concept that for many, not all
11 necessarily, patients with brain metastases from
12 most of the tumors we're talking about, lung,
13 breast and melanoma, the presence of brain
14 metastases, at least when they're symptomatic and
15 of a substantial size requiring steroids,
16 et Cetera, is not always but often going to be
17 considered the overall lifespan limiting factor in
18 that patient's natural history.

19 So the use of a survival endpoint, at least
20 as one of the endpoints, but really maybe the
21 primary endpoint in many of the trials, I really
22 think is a good idea, even though I was arguing for

1 many composite and parallel endpoints as long as
2 they go the same direction, and I don't think those
3 two things are incompatible depending on the kinds
4 of patients.

5 Also, we often talk about the fact that you
6 can't use survival as an endpoint in randomized
7 trials because of the high likelihood that patients
8 who are assigned to one treatment will end up
9 crossing over, whether it's on study, or outside of
10 a study, to the other arm or something like it, and
11 thus that sort of blurs the ability to dissect out
12 survival as an endpoint.

13 But I think there are times when that's not
14 altogether true, if you think about the idea that
15 the first therapy that you give somebody may be the
16 most definitive one, and that may be the one that
17 alters or defines the survival benefit. Even if
18 you could get that drug later, it may not catch up.
19 I'm going to turn the rest over to Nancy.

20 DR. LIN: Here, I would think of two kinds
21 of studies, and I think the considerations are
22 different. I think there's the ALK kind of story,

1 which is patients with brain metastases, included
2 in their early-phase trials, seeing CNS responses,
3 and then those patients included actively in the
4 phase 3 registration strategies, and they were
5 enrolled with the purpose of treating both their
6 CNS and their extracranial disease.

7 So there, if they're going to be included as
8 part of the overall set, you'll have a certain type
9 of endpoint that you need to pick that will be
10 relevant to all patients entering on a trial, and
11 then you may have secondary endpoints that are
12 important for the brain metastasis subset. So
13 that's kind of one type of study I think of.

14 The other type of study is the study that
15 really only exclusively enrolls patients with
16 active brain metastases, where the goal is to treat
17 their brain metastasis. I think there, you can
18 obviously choose more CNS-directed endpoints. You
19 could always choose overall survival because these
20 are patients where you are probably more likely to
21 see an overall survival advantage given the dearth
22 of other therapies that the patients can receive.

1 But here I think, from a practical
2 standpoint, in addition to the endpoint challenges,
3 it's really the control arm because speaking for
4 breast cancer, there's no obvious control arm. You
5 could have a control arm of radiation, I guess, but
6 then you have all these considerations of what's
7 the right endpoint.

8 I think that that's a challenge, and I'm
9 interested from a regulatory perspective under what
10 circumstances, for example, a single-arm experience
11 might have to gain regulatory approval; what sort
12 of endpoint would be sufficient understanding it's
13 a non-randomized experience, so survival is a
14 little hard unless you hit it out of the park. I
15 think the considerations are different depending on
16 whether you're including the patient or you are
17 doing a brain met specific study.

18 DR. SUL: I think some of this goes back to
19 what we started out with in thinking about context.
20 I think that's probably one of the most common
21 questions we get asked, is can I use an objective
22 response rate to get approval? I think it's more

1 helpful to think about it in terms of in which
2 situations does looking at objective response rate
3 make the most sense to look at benefits.

4 For instance, if you're looking at a drug
5 that has no track record and you have no idea that
6 the mechanism of action ties in with the effect of
7 the drug, it's harder to look at these single-arm
8 studies. I think if you are looking at a drug that
9 has a well-proven track record in other
10 malignancies, your response rate is -- Paul was
11 saying sometimes the robustness of the data or the
12 effect can help overcome some of the uncertainties,
13 so you have a really robust response rate. You're
14 seeing CRs, which we don't see in patients with
15 brain mets, then I think those kinds of aspects are
16 helpful in helping us interpret.

17 It's not so much is it endpoint; it's the
18 data that comes from it and how we interpret it.
19 That's one of those questions I always struggle
20 with, is can I use PFS? Can I use ORR? And the
21 answer's always, well, it depends, and the
22 circumstances really are what shape the outcome,

1 and nobody likes that answer.

2 DR. NDOUM: Can I -- sorry.

3 DR. PROWELL: I was going to say, you can
4 always measure it. The question is can we
5 interpret it when you submit it to us?

6 DR. NDOUM: So back to being a hammer. If
7 such a single-arm submission was backed up with
8 biological data -- say you had preclinical data
9 that every time you use drug X, you get this
10 biological response Y within the tumor, and then
11 you had an actual window of opportunity study in
12 this single-arm setting where you gave the drug and
13 you saw the exact same biological response, and
14 then you were additionally seeing these objective
15 responses in these patients in this single arm,
16 would that help support a potential filing for
17 metastatic drug-specific indication?

18 DR. SUL: I think specifically for
19 preclinical data, that's always helpful.
20 Regardless of whether you're talking about
21 interpreting the endpoint or designing the study, I
22 think that's absolutely important. But again, I

1 think it really depends a lot on the magnitude, the
2 patient population.

3 I'm not sure how many different ways to put
4 it, but we have to take the totality of the
5 information into account when we evaluate the
6 effects of the drugs. And I know it's not the most
7 satisfying answer, but you can do it, and we'd have
8 to sit and interpret the data.

9 DR. NDOUM: Translating, she said it would
10 work.

11 DR. ANDERS: Carey Anders from Duke. I just
12 wanted to follow up on what Nancy brought up as the
13 second part of her conversation, and that's the
14 control arm. I think many of us have designed
15 single-arm, stage 2 studies with response rate or a
16 PFS compared to historical control, but many times
17 our historical control is very difficult to
18 interpret. So whether or not you actually have a
19 signal is hard to know.

20 In thinking about this, particularly in
21 breast cancer not having a gold standard, the
22 thought process around physician's best choice or

1 MD discretion and what that would look like, I
2 recognize from a patient perspective and talking to
3 my own patients about that, that's not the most
4 attractive trial design unless there is a way to
5 crossover and still allow patients access to
6 hopefully promising investigational agents.

7 So I just wanted to open up conversation
8 around control arms and how we should be thinking
9 about this as we're designing our own studies.

10 DR. WEN: Dr. Tawbi? Did anybody want to
11 comment?

12 DR. ANDERS: I'm kind of following up on the
13 EMBRACE data in breast cancer. That's always been
14 very striking to me. For those who don't do breast
15 cancer every day, eribulin was FDA approved based
16 on a survival advantage compared to physician's
17 best choice. I use that every week in my practice
18 to select eribulin when I'm stuck with that.

19 So I'm just curious if that could be
20 something we could be thinking about, also
21 recognizing that the studies are going to be
22 larger. It's a comparative design, so to have

1 appropriate power, we'd need larger studies.

2 DR. PROWELL: I think part of what made that
3 trial successful was the fact that they were going
4 in very refractory patients, so those were people
5 who had had I think at least 3 lines of therapy,
6 but the median was 5. So these were patients who
7 really had a very poor prognosis for metastatic
8 breast cancer, and overall survival was the
9 endpoint.

10 I think that was a very pragmatic clinical
11 trial where you said, look, this is what's going to
12 happen, is you're going to give them either
13 capecitabine, or this, or this, or this, or
14 whatever the whole list of drugs that were in the
15 menu that one could choose from for treatment of
16 physician's choice.

17 One thing that we've considered when we look
18 at trials using treatment of physician's choice as
19 a control arm is that you have to choose the
20 treatment of physician's choice before the
21 randomization. That may introduce some complexity
22 when you're talking about a brain mets trial that

1 isn't present necessarily in a conventional
2 metastatic breast cancer trial. We can maybe talk
3 about that.

4 I'm not a neuro-oncologist, though I'm
5 sitting up here half the day. But the
6 neuro-oncologists would be the better ones to
7 really comment on that issue of the feasibility of
8 selecting that standard therapy before
9 randomization.

10 DR. SUL: I think that also kind of goes
11 back to your earlier question about how much can we
12 dictate what goes on in a clinical trial. I think
13 the more options you have -- A, the more difficult
14 it is for physician's best choice, the more
15 difficult it is potentially to interpret that data.
16 It's also harder to design the trial to say you
17 have to choose from these two or three. But I
18 think that those are definitely things to consider,
19 that could be considered as potential control arms.

20 DR. WEN: Dr. Tawbi?

21 DR. TAWBI: Hussein Tawbi, MD Anderson. I
22 actually just wanted to follow up on Kim and

1 Nancy's points about which kind of buckets of
2 clinical trials we have and which endpoints we
3 choose. I really think, even within brain
4 metastases specific clinical trials, we actually
5 should allow for different endpoints in case you
6 have IO versus non-IO. Even thinking about being
7 pragmatic and combining with SRS, SRS plus IO may
8 actually modulate the response, and you may have
9 longer term outcomes just because you added SRS
10 6 months later or even 3 months later.

11 So we do need to kind of think about the
12 quality of the response to the immunotherapy and
13 use as compared to a targeted therapy.

14 DR. MARGOLIN: I think sometimes the more
15 brilliant and the more creative at trial is the
16 less practical it's going to be for an approval
17 endpoint, but it's still a great comment.

18 DR. TAWBI: Sort of a constant debate --

19 DR. WEN: One final comment from Caroline.

20 DR. CHUNG: I just want to make a comment
21 that we've mentioned a number of times that
22 composite endpoints would be really helpful in

1 developing a surrogate that is a composite that
2 reflects both patient function as well as the
3 imaging response, et Cetera. I think the one thing
4 that I would propose that we could potentially
5 agree to do today is I think most of us would know
6 which of those endpoints that we would want to
7 include in most brain metastases trials.

8 I think, to sort of echo Ben's message
9 around standardization, if we can actually
10 standardize which key endpoints we will include in
11 every brain metastasis trial, we can
12 actually -- we're in the modern era, as Paul
13 mentioned, using technology to our benefit, and I
14 think that we're in the modern era where we can use
15 computational oncology. We can use big data
16 approaches. We have electronic health records that
17 will allow us to bring this data together from
18 multiple trials.

19 So it's not necessarily a retrospective
20 meta-analysis, but if we're actually collecting
21 standardized structured data across these trials,
22 we can actually start to not necessarily create

1 definitive conclusions, but we will actually
2 develop meaningful data-driven hypotheses about
3 surrogate endpoints that we can validate in future
4 trials.

5 Until we actually come to that consensus of
6 which of those structured endpoints we're going to
7 include in every brain mets trials, that just
8 wouldn't happen. But I think that would be a
9 meaningful conclusion, or meaningful product from
10 this meeting because I think we're all very
11 motivated to do it. There's going to be many
12 different trials that are going to come down the
13 pipeline, but if we can actually collaborate and
14 actually cohesively come up with a list of specific
15 endpoints we want to include, we could go a lot
16 further along in the long run.

17 DR. LIN: I totally agree, and just as an
18 example, even just for imaging, which we think is
19 very simple, or maybe not so simple, RECIST and
20 RANO are in a collaboration to actually -- and
21 EORTC is funding the data center to pull in
22 actually radiology imaging across multiple brain

1 metastasis trials. We're finalizing the legal
2 language of the request letters, and many of you in
3 the audience may start getting these letters asking
4 for your trial data to be able to answer some of
5 these questions.

6 The reason that we actually have to pull in
7 all the primary imaging data is that
8 unbeknownst -- I didn't realize this, but when the
9 RECIST criteria were developed, nobody pulled in
10 scans, they just pulled in the case report forms,
11 because everybody basically around world collected
12 the target lesions the same way. They measured
13 them the same way. They did them all on CT scans.
14 So no one ever had to do primary image analysis.
15 They just took the data, and they rerun it a bunch
16 of different ways, and that's why we look at 2
17 target lesions and not 5 target lesions, et cetera.

18 You can't even do that with just the imaging
19 of brain metastasis trials because everybody
20 collected a different way. They did different
21 scans. Some of them did MRIs; some of them CTs.
22 Some collected 5-target lesions. Some collected 2.

1 Some collected 10. Some collected volume only.

2 Some collected linear dimension only.

3 I mean, the data itself is a mess, and then
4 you can't actually combine any data sets. You
5 actually have to start from scratch, go to the
6 original imaging, and do it all over again. So I
7 think if we maybe learn from that and do it better,
8 we can do better in the future.

9 DR. CHUNG: I think we can do it over and
10 over again more easily because we now have
11 automated methods of reanalyzing the data. So if
12 we build the algorithms, we can evaluate across
13 studies to see whether these measurements that
14 we've done manually versus in an automated way
15 fashion really agree.

16 DR. WEN: Thank you.

17 DR. AMIRI-KORDESTANI: Thank you. I just
18 wanted to actually make a clarifying comment. I'm
19 sorry. I forgot to introduce myself earlier. My
20 name is Laleh Amir. I'm a hematologist/oncologist
21 at the Division of Oncology Products I.

22 We have two pathways for approval. And as

1 you know, the accelerated approval pathway
2 basically relies on an endpoint that is not really
3 a validated endpoint, and it doesn't need to show a
4 direct clinical benefit. So basically, it doesn't
5 really need to have a surrogate endpoint that is
6 already validated. As long as you come in and
7 basically discuss it with the FDA and the endpoint
8 is appropriate for that patient population, We
9 actually accept that for an accelerated approval
10 pathway.

11 That goes back also to the other comment
12 that was about in a single-arm trial like a
13 response rate be acceptable? Yes. We have
14 actually approved many drugs only based on a
15 response rate, even as a regular approval more
16 recently. So yes, it could be accepted. It really
17 depends on -- we look at, for example, duration of
18 response. We also look at what is available
19 therapy for that patient population. In a totally
20 refractory patient population that has nothing
21 available, it sounds like it should be acceptable.

22 So I really encourage, actually, that if you

1 see some encouraging results, like even an
2 intracranial response rate when the drug is
3 actually controlling the disease also outside, you
4 just come in and actually bring the results in
5 because, really, we like to see those studies
6 happen, and it may actually be adequate for an
7 accelerated approval, and then we can strategize
8 and design it more like a confirmatory study so
9 that actually the benefit could be later on proven
10 in a more randomized fashion if it is necessary.

11 Sometimes actually, more recently, because
12 of some scenarios that you couldn't even do
13 randomized trials, we may actually not even require
14 that. So it really depends on the context, as was
15 mentioned by many of the colleagues here. That's
16 basically what I was adding.

17 DR. WEN: Thanks so much.

18 I want to thank the panel for the excellent
19 discussion.

20 DR. AMIRI-KORDESTANI: Did you want to ask
21 me a question?

22 DR. WEN: I think we're going to have to

1 move on.

2 MS. SELIG: I'm going to propose the
3 following. We are coming to the end. Patrick and
4 Joohee are going to have some comments also at the
5 end. I wanted to give you both a chance on this
6 panel to make any kind of final comments about this
7 discussion. Then we have a 10-minute brief
8 presentation from the American Brain Tumor
9 Association, one of the sponsoring organizations,
10 and then some closing comments.

11 Would all of you just stay there so that we
12 just can keep going, if you don't mind, and then
13 you don't get to leave early. You have to stay and
14 listen to the ending comments, too.

15 Joohee, Patrick, did you want to make any
16 comments now or do you want to --

17 DR. WEN: Maybe in the interest of time,
18 we'll do it --

19 MS. SELIG: Contemplate them. Okay.

20 We now have Ralph DeVito and Nicole
21 Willmarth from the American Brain Tumor
22 Association, one of the sponsoring organizations.

1 They have been doing some excellent work that's
2 very complementary to all of this discussion, so
3 we're going to take a few minutes -- just a few
4 minutes, you guys -- to talk about it.

5 **Presentation - Ralph DeVito**

6 MR. DeVITO: Everything's running very
7 smoothly. Thank you, Wendy. Thanks to David, the
8 National Brain Tumor Society, for the FDA for
9 convening this group. Great conversation; just
10 absolutely wonderful.

11 I am Ralph DeVito, CEO of the American Brain
12 Tumor Association. Nicole Willmarth is our chief
13 mission officer. We'll take just a few minutes
14 with a few slides to tell you about some work that
15 really began before I started. I've been on the
16 board about a year with ABTA, and they had
17 envisioned a real in-depth, survey-based analysis
18 of the brain mets issue.

19 So there is a brain metastasis issue at
20 ABTA, in coordination with others, that has been in
21 effect for a while. So we just wanted to quickly
22 highlight it. I'll give an overview, and then

1 Nicole will talk a little bit about some
2 preliminary high-level findings and then some next
3 steps. I also want to put a plug in for the SNO
4 brain mets conference in New York this August.
5 This should be a pretty exciting session, and it's
6 wonderful to see this issue being given great
7 in-depth focus.

8 Let me go to the first slide. Let me just,
9 in the interest of time, skip ahead to show you our
10 collaborators, our science, our clinicians, our
11 patient advocate that's helped us with the survey
12 development. We have a third-party vendor that's
13 been working with us. Nicole and her team have
14 been working hard, and we have moved through a lot
15 of our work.

16 We're going to do three panels of surveys.
17 We have already surveyed over 200 patients, we have
18 surveyed over 200 caregivers, and our next step is
19 to survey over 200 oncologists. With that data,
20 we're going to be developing new programs and new
21 services. And I do want to say that currently the
22 ABTA is providing high-risk, innovative research

1 that we're doing in this area, and we're also
2 offering currently to patients brochures and
3 information, webinars, and other information today.
4 With these findings, there's so much more that we
5 and you can do to serve patients far more.

6 Nicole?

7 **Presentation - Nicole Willmarth**

8 DR. WILLMARTH: Thank you, Ralph. And I
9 also want to second his thank you to the FDA and
10 for the National Brain Tumor Society bringing
11 everybody together. I think bringing all these
12 perspectives in one room today to have these
13 discussions is so important. I feel humbled
14 listening to the conversations that we've had
15 today. I've learned so much and really appreciate
16 everybody being here.

17 I think we've been noticing a lot of themes
18 today, one of which is hope and making sure that we
19 keep that in the back of our minds for the patient
20 perspective. But then also I think there's a theme
21 of considering that we're treating a patient with
22 brain metastases and not just treating the brain

1 metastases. Those are things that we want to keep
2 considering as we come full circle with bringing in
3 the patient perspective.

4 I'm going to just, as Ralph said, do a very
5 high-level overview of some of the initial findings
6 from our survey just so that we can give you a
7 little piece of that. A lot of this probably won't
8 be of any surprise considering what we've discussed
9 today.

10 Just to start out with the patient caregiver
11 surveys, we did two online quantitative surveys.
12 One was to 237 cancer patients, which was a
13 representative mix of patients with brain
14 metastases, and then also another survey to 211
15 caregivers of cancer patients who have brain
16 metastases. This was conducted back at the end of
17 2018. The sample was provided by -- we worked with
18 our survey vendor. They had a panel that was
19 surveyed as well as working with our advocacy
20 partners that Ralph just mentioned, and I'm going
21 to go through this very quickly. I apologize, but
22 considering the time constraints.

1 To summarize just high level, the patient
2 survey, this again won't come as any surprise
3 probably to most people here, but a diagnosis of
4 brain metastases was a surprise to 9 in 10 of the
5 patients that we surveyed. Their top concerns upon
6 learning of their diagnosis was the impact on their
7 quality of life as well as the likelihood of
8 treatment success. I think this goes hand in hand
9 with what was discussed today, is you can't really
10 separate the importance of those to a patient.
11 Those are really both top priorities.

12 Also, what came out of the survey was that
13 fewer than half sought a second opinion, and they
14 really felt that -- actually most said that they
15 felt that they received enough information from
16 their oncologist, and 81 percent actually were
17 diagnosed with brain mets from the same doctor who
18 diagnosed their primary.

19 So what this suggests is that they didn't
20 really seek out a second opinion as to what type of
21 treatment to pursue for the brain metastases, so I
22 think there's a lot we could learn there.

1 This goes along with what we were talking
2 about with clinical trial exclusion. Some of the
3 patients did report being denied participation in
4 clinical trials, and the experience for them was
5 emotionally taxing.

6 Twenty-four percent said they were denied
7 participation in a clinical trial related to their
8 primary form of cancer because of their brain
9 metastases, and 19 percent said that they were
10 denied participation in a clinical trial related to
11 brain metastases because of previous treatments of
12 their primary form of cancer.

13 Some of the comments that were written into
14 the survey we have here. "It was so disheartening
15 to be close to a possible treatment only to be
16 rejected. It was a very brutal and emotionally
17 taxing experience, and I was interested in pursuing
18 a particular clinical trial, but it excluded people
19 with brain metastasis."

20 Then just a summary of some of the
21 highlights from our caregivers survey, most of the
22 caregivers -- just a little bit about the

1 profile -- had a personal relationship with the
2 patient. The patient was in most cases their
3 parent. Caregivers expressed many of the same
4 reactions to learning of the diagnosis as the
5 patient's did. Many expressed shock and
6 depression.

7 Over 6 in 10 said they were familiar with
8 brain metastases before becoming caregivers,
9 however, that means about 40 percent were not
10 familiar with brain metastases.

11 Caregivers were most concerned about the
12 effect on the quality of life of the person under
13 their care and the likely success of treatments,
14 which mirrors what the patient perspective was as
15 well. And nearly 9 in 10 caregivers said that
16 there was an emotional impact on them as a result
17 of caring for a brain metastasis patient.

18 So quickly to wrap up, because I know I've
19 already gone over, for the next steps, as Ralph
20 mentioned, we would like to also do an oncologist
21 survey, so we're currently developing a survey to
22 understand from the doctors who treat these brain

1 metastases patients, from their point of view, what
2 the journey is like when treating these patients.
3 That way we can understand better if there's
4 agreement or disagreement and the knowledge or
5 perception from the patient perspective and the
6 oncologist perspective.

7 Once all the survey results have been
8 compiled and analyzed, we hope to present the data
9 at the Society for Neuro-Oncology meeting in
10 November, so stay tuned for that. That's it.

11 (Applause.)

12 MS. SELIG: Thank you so much. It's really,
13 really important to understand the patient
14 perspective and the patient experience, so thank
15 you guys.

16 We're going to ask Joohee and Patrick, our
17 fearless co-chairs, to make some wrap-up closing
18 comments and in particular what you heard that you
19 think is actionable, and then the final uh,
20 next-steps discussion will come from David Arons,
21 and then we will conclude and get everybody on
22 their way. Thanks for sticking it out.

Summary and Next Steps

1
2 DR. WEN: I wanted to thank everybody for
3 coming today. It's been a really great discussion.
4 We're so lucky to have all of you here. I think
5 today we heard hopefully things that will move us
6 closer to significantly increasing the
7 participation of brain metastases patients both in
8 all oncology trials and also the development of
9 more trials specifically for brain metastases.

10 I think Nancy gave a really nice talk
11 earlier about perhaps the limited importance of
12 blood-brain barrier penetration for a therapeutic
13 effect. Perhaps it's more important for
14 prevention, but that's something that should lower
15 the barrier of drugs being evaluated for brain
16 mets.

17 I think ideally, all patients with brain
18 metastasis should be considered eligible for
19 oncology clinical trials, whether they should have
20 treated lesions or whether we would include
21 patients with small asymptomatic lesions where they
22 could be on drug for a month or two and closely

1 monitored, and taken off it if there's progression.

2 I think we need to also think about whether
3 we should recommend routine adoption of the Friends
4 of Cancer Research recommendations and the RANO
5 recommendations for eligibility into trials. I
6 think there needs to be guidance on eligibility to
7 reduce the restrictions, including time from
8 radiation and a number of other factors.

9 In terms of the trials specifically for
10 brain metastases, I think we heard that potentially
11 in some situations, objective response rate might
12 be a path to approval, and if we use that, is the
13 RANO BM criteria the one that we should use instead
14 of all these variations that are still being
15 considered in different trials. There was also
16 discussion on the need for randomization for the
17 more definitive trials and the challenges of the
18 control arm.

19 Going forward, there are some things that
20 clearly we need to do. We need a standardized
21 brain metastases imaging protocol that will be
22 similar to the one that's been used for

1 glioblastoma but with some minor differences.
2 Hopefully, that would be used for all brain
3 metastases studies so that there's less
4 variability.

5 I think we need guidance on eligibility
6 criteria for these trials on the optimal endpoints,
7 as Carolyn discussed. I think we need to
8 continue -- this is an audience that
9 really cares about this issue, but there's a whole
10 world out there that is still thinking several
11 years back where brain metastases patients should
12 just be excluded from all these trials, and we need
13 to educate them and spread the message.

14 So going forward, I think SNO and RANO are
15 definitely committed to doing this and partnering
16 with all with you, and our conference in August is
17 one step in this direction. So thank you all so
18 much for coming today. It's been a really
19 important step forward, and we're grateful to all
20 of you.

21 DR. SUL: Thank you, Patrick.

22 I'm going to actually start with my thank

1 you first because I know I'll run out of time and
2 then I'll forget to thank people. I want to thank
3 everybody who participated in the planning and also
4 in the development of the workshop. I also want to
5 thank all the patients and the patient advocates
6 and representatives who came here today to give a
7 voice to all the patients who enroll on these
8 studies that we review but we don't actually get to
9 meet the patients face to face.

10 I also want to thank my FDA colleagues for
11 participating and helping, and also for having
12 discussions with me about a lot of these issues,
13 sometimes heated, sometimes controversial, and
14 really being interested in this topic, so I want to
15 start with that.

16 I think a couple of the common or recurring
17 themes that I've heard today, one of them is
18 standardization, whether or not that's an approach
19 to how we use steroids, or decide on radiation, or
20 what studies should be included, or whether it's an
21 imaging protocol. I want to go back to what Ben
22 Ellingson said it at the very beginning, that

1 standardization really makes interpretation of
2 information much easier, and it's essential to get
3 a clear picture of what's going on; so that's one
4 thing.

5 The second is these different baskets of
6 trials, trying to separate out the populations. We
7 sort of touched on that, but we didn't get to
8 really delve into how we would do that. So how do
9 you separate out the untreated versus the treated
10 patients? When do we decide that SRS should be the
11 point at which patients are not included on trials?
12 What's the, quote/unquote "washout period"? I know
13 that Dr. Gondi doesn't like that term, but we're
14 just going to use it because it's familiar.

15 Timing of therapy sort of ties in with that
16 as well because there are therapies like radiation
17 therapy, which are not really regulated in the same
18 way by FDA but are still considered standard of
19 care. So we need to figure out how to smartly
20 include those as well.

21 One comment I did want to make, because it
22 came up a couple of times, is it seems that people

1 are really afraid of seizures because people kept
2 saying, well, somebody had a seizure. This is
3 going to circle back to having a multidisciplinary
4 approach.

5 Neurologists in general are not afraid of
6 seizures. I mean, we see patients have seizures.
7 Status epilepticus, that's a different story. And
8 not to say that it's not serious, but it shouldn't
9 be the reason why you don't want to develop a drug
10 because guess what? We have great treatments for
11 seizures. We don't have great treatments for brain
12 metastases. So don't let that be the reason why
13 you don't want to move forward with development,
14 and ask the neurologist and the neuro-oncologist to
15 collaborate with you on these studies to make it
16 safe to include these patients and to evaluate
17 them.

18 DR. WEN: Thank you.

19 MR. ARONS: Thanks Patrick and Joohee.
20 Wendy told me to come here so that's what I'm
21 doing. I generally do what I'm told.

22 Thank you all for being here today. Thank

1 you so much to the FDA and to all the partners and
2 experts that came together. I'll have a few more
3 thank yous, but just a few points that I wrote down
4 in my notes from a patient advocacy perspective.

5 We started out the day with a theme of hope,
6 and Mr. Queen brought that. And I really want to
7 thank him for starting us out with the perfect
8 theme of the day and his story. But as we know,
9 hope is not a strategy, but what hope can do is
10 bring a sense of determination to create one. And
11 we certainly started to build the ingredients for a
12 realistic strategy to move forward against this
13 disease today in this room.

14 We recognize this is a very vulnerable
15 population, a population at great risk, but yet
16 it's very numerous. So what we began to do today
17 was to take a situation that's really a problem,
18 and try to figure out how can we use this
19 population and use what we know as assets to flip
20 this on its head and say, what can we do that can
21 work.

22 We talked about some really big points from

1 a patient advocacy perspective; include patients in
2 trials, period end. Let's just start including the
3 patients in the trials. No more excuses, no more
4 barriers, let's move forward and begin to do that.
5 And if there's a reason against it scientifically
6 or medically, figure that out, but the default
7 status should be include patients in trials.

8 Dr. Brastianos brought up a very important
9 point scientifically, and that is, is there
10 biological considerations that make this disease
11 different from the systemic disease, that
12 ultimately not really -- her point was not
13 harmonized throughout the day, so there seems like
14 there's going to be more work to figure out when is
15 this disease uniquely different, warranting a
16 different kind of trial, different issues than say
17 the regular disease outside of the brain.

18 The FDA opened up a tremendous opportunity
19 for science today, and Paul Kluetz and others
20 talked about it, is the opportunity to develop
21 patient-focused endpoints and clinical outcomes
22 assessments that really reflect what patients want

1 to see in new medicines, new therapies, new devices
2 for that matter.

3 So we should try to drive a truck through
4 this opportunity and come up with new medicines,
5 new therapies that both extend survival but really
6 reflect the kinds of domains and general concepts
7 that that patients wants, like what was said by a
8 patient earlier. She wanted to retain her brain's
9 functioning, period, end. She wanted to keep her
10 cognition. That would be really awesome if we
11 could see more therapies do that.

12 There's great traction to move forward in
13 this era of precision medicine with basket trials
14 and even adaptive trial design that is very patient
15 focused, and that could be done in this disease.
16 I'm agreeing with all the action items and ideas
17 that Patrick and Joohee mentioned but just wanted
18 to add those.

19 I'm hopeful that the group of nonprofit
20 organizations listed up there will all stay
21 together now kind of as a loose coalition to see
22 this through the next phase, which is getting the

1 summary together, working collaboratively with the
2 FDA on a guidance document. If the FDA wants any
3 help from all of us as a team, we're happy to do
4 it. And then to try to take this forward as a
5 scientific and product development agenda into the
6 future.

7 To the companies in the room, really, thank
8 you for being here today. That's huge, and we're
9 really grateful for your expertise. And as you
10 think about product development as a company and
11 the investigators thinking about product
12 development in investigator-driven trials, I think
13 all the nonprofits and patient advocacy groups here
14 would like to be of assistance to you to discuss
15 how to do this together and to reduce the barriers
16 to making new therapies possible.

17 Finally, I get to echo what Joohee said.
18 Thank you to the patients who have been here today
19 who have spoken up and who are adding so much to
20 this discussion. So thank you again, really
21 appreciate everybody who was here today and
22 everybody who patched in by the webcast for that.

1 Thank you to all those who helped make the
2 technology possible. Thanks again. Appreciate
3 your time.

4 (Applause.)

5 (Whereupon, at 3:57 p.m., the meeting was
6 concluded.)

7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22