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CONSIDERATIONS FOR PROGRESSIVE MULTIFOCAL
LEUKOENCEPHALOPATHY (PML) CLINICAL TRIAL DESIGNS FDA
WORKSHOP
SEPTEMBER 21, 2021

Job No. CS4500544

1 P R O C E E D I N G S

2 DR. BIRNKRANT: Good morning. My name is
3 Debbie Birnkrant, and I am the director of the
4 Division of Antivirals at CDER FDA.
5 I'd like to welcome everyone to this virtual
6 workshop on considerations for PML clinical trial
7 designs.

8 PML is such an important topic, that the
9 Division of Antivirals has continued our efforts to
10 support PML therapeutic development throughout the
11 COVID-19 pandemic, despite the considerable demands,
12 COVID-19 has brought on the division and our
13 colleagues.

14 Because PML is also a complex disease,
15 today's workshop brings together a multidisciplinary
16 team of specialists in infectious diseases,
17 neurology, virology, rare diseases, and
18 biostatistics from the FDA, NIH, EMA, academia,
19 along with industry representatives and PML patients
20 to address this important topic.

21 We want to thank our speakers and

1 panelists for their efforts and preparing for the
2 workshop today.

3 Next slide, please.

4 So let's start with a brief background to
5 set the stage for today's presentations and
6 discussions. We are here today because there is an
7 unmet medical need for PML therapeutics. PML is a
8 devastating, rare, opportunistic brain infection
9 that occurs in patients with impaired cellular
10 immunity.

11 It presents with a variety of serious
12 neurologic symptoms, including mental status
13 changes, hemiparesis, gait ataxia, and visual
14 symptoms. The only PML treatment is to reconstitute
15 the immune system when possible.

16 Unfortunately, immune reconstitution is
17 not always possible or rapid enough to prevent death
18 or devastating neurologic complications. Of those
19 who survive, approximately 80% will not have
20 recovery from their neurologic deficits.

21 Importantly, there are no approved or

1 effective medical products available for the
2 treatment of PML, and that is why we are holding
3 this workshop today.

4 Next slide, please.

5 The FDA is committed to helping support
6 the development of PML therapeutics. One essential
7 aspect to successful and efficient product
8 development is optimal clinical trial design. FDA
9 is hosting today's workshop because we recognize
10 that design in clinical trials for PML is
11 challenging for several significant reasons.

12 First, as I mentioned, PML is rare. NORD
13 estimates that the incidence is 1 in 200,000, and
14 there are approximately 4,000 new cases per year in
15 the U.S. and Europe. Clinical trial design is often
16 more difficult to address for rare diseases for
17 which there's limited medical and scientific
18 knowledge, natural history data, and drug
19 development experience.

20 PML is rapidly progressive and often
21 fatal, which makes it also difficult to study.

1 Diagnosis of PML is often made late into disease and
2 presentation, and neurologic presentation in course
3 varies based on location and characteristics of
4 brain lesions.

5 Another challenge is that natural history
6 differs by underlying immune disease and impairment.
7 And, lastly, mobility and communications
8 difficulties, although common, may be difficult to
9 quantify.

10 Next slide, please.

11 So the purpose of today's workshop is to
12 foster an exchange of ideas on addressing the
13 challenges and clinical trial design considerations
14 for developing products for the treatment of PML.
15 It is not product specific, and we will not be
16 making regulatory decisions at this meeting. All
17 opinions, recommendations and proposals are
18 unofficial and non-binding an FDA, NIH, and all
19 other participants.

20 We very much hope that today's meeting
21 will serve to move the field of PML therapeutics

1 forward by building on prior collaborative efforts,
2 which will be discussed, and we are also looking
3 forward to hearing from all of you on this topic.

4 So now I would like to turn the program
5 over to my colleague, Dr. Virginia Sheikh, who will
6 provide a brief background on FDA's recent efforts
7 to support PML therapeutic development, and then
8 address housekeeping items before we get started.

9 Virginia, I turn it over to you.

10 DR. SHEIKH: Thank you, Dr. Birnkrant.

11 Next slide, please.

12 Good morning, everyone. As Dr. Birnkrant
13 mentioned, I'm Virginia Sheikh, and I'm a medical
14 officer in the Division of Antivirals at FDA CDER.
15 As Dr. Birnkrant alluded to in her remarks, today's
16 workshop is part of a collaborative,
17 multidisciplinary effort between the FDA, NIH and
18 academic experts, that began more than two years
19 ago.

20 The collaboration began with a product
21 nonspecific discussion between the FDA and NINDS

1 clinicians focused on how PML Phase Three clinical
2 trials might be designed. It was immediately
3 evident that PML presented several significant
4 challenges to clinical trial design, and that these
5 challenges were likely to deter industry engagement
6 and hamper product development.

7 We determined that considerable work would
8 be required to flesh out the existing scientific
9 evidence and to establish consensus on key PML
10 clinical trial design issues.

11 Soon after, we established the PML
12 clinical trial design collaboration. This is an
13 informal, collaborative effort designed to
14 facilitate clinical development of effective
15 therapeutic products for the treatment of PML.

16 We focused on five key areas for which we
17 created working groups; JC virus biomarkers; brain
18 imaging; patient-focused drug development; clinical
19 outcomes, and clinical trial design.

20 The collaboration has two main aims, the
21 first is to identify knowledge gaps and develop

1 plans for filling those knowledge gaps. Today
2 representatives from each of the project working
3 groups will provide talks meant to summarize the key
4 findings of the working groups, and to set the stage
5 for the discussion sessions.

6 The second aim and ultimate goal of this
7 project was to develop one or more phase three
8 clinical trial designs for PML that might be
9 acceptable to regulators, clinicians and patients,
10 and it might foster industry engagement.

11 Please keep these aims in mind as you
12 participate in today's workshop. As members of the
13 small, but dedicated, PML clinical research
14 community, each of your perspective is needed to
15 overcome PML clinical trial design challenges.

16 Next slide.

17 Today's workshop is organized into five
18 parts. We will begin the workshop with several
19 essential PML background talks; thereafter, we will
20 cover for main topic areas; potential endpoints for
21 PML clinical trials; PML patient perspectives;

1 selection of control groups for PML clinical trials,
2 and, finally, clinical trial designs for PML
3 treatment trials.

4 Some of the most essential work of today's
5 workshop will take place during three panel
6 discussions. Each of the panel discussions will be
7 moderated by an FDA reviewer and will include five
8 to six PML experts from academia, and an industry
9 panelist.

10 Each of the discussions will be preceded
11 by brief talks designed to provide background for
12 the discussions. Panelists will be asked to weigh
13 in on key PML clinical trial design challenges.

14 In addition to the perspectives provided
15 by panelists, we encourage workshop participants to
16 contribute to these important panel discussions
17 using Zoom's Q and A function.

18 Next slide.

19 Now some workshop logistics. This meeting
20 is being recorded. Speaker slides, transcripts and
21 recordings will be available in the coming days.

1 Next, I am very pleased and proud of the
2 range of expertise and experience we have in today's
3 workshop speakers and panelists; however, in the
4 interest of time, we're going to keep introductions
5 very brief. I encourage all of you to view the
6 workshop website for speaker and panelist
7 affiliations, disclosures, and, frankly, impressive
8 biographies.

9 If you are not a workshop speaker or
10 panelist, your microphone and video are
11 automatically turned off today; however, as I
12 mentioned, we still very much want to hear from you.
13 Please use the Q and A function at the bottom of
14 your screen to ask questions and provide comments
15 for the panel discussions.

16 We encourage you to use the chat function
17 for networking and for exchanging ideas, as you
18 would in an in-person event; however, questions and
19 comments entered into the chat will not be actively
20 collated for panelists or moderators. If you're
21 experiencing any Zoom difficulties today, please

1 reach out to the public meetings team at the email
2 address provided here.

3 Next slide.

4 With that, we'll begin the workshop.

5 Next slide.

6 I would like now to introduce the three
7 speakers tasked with providing us background for
8 today's workshop. First, we will hear about JC
9 virus virology and PML pathogenesis from Dr. Gene
10 Major, Senior Advisor to NINDS, Director of the CLIA
11 Laboratory of Molecular Medicine and Neuroscience,
12 and Scientist Emeritus at NINDS.

13 Second, we will hear about PML drug
14 development history, current standard of care, and
15 the PML therapeutic landscape from Dr. David
16 Clifford. Dr. Clifford is the Melba and Forest Seay
17 Professor of Clinical Neuro Pharmacology and
18 Neurology at Washington University in St Louis.

19 Third, we will hear about clinical
20 outcomes among PML patients from Dr. Bryan Smith,
21 head of the Clinical Neuro HIV Research Program at

1 NINDS.

2 Next slide.

3 Dr. Major, the floor is yours.

4 DR. MAJOR: Thank you very much, Virginia.

5 And it's a real pleasure to be amongst my colleagues
6 and to participate in this tremendously important
7 workshop and conference.

8 So we're going to start by looking at
9 something of a basic science view of the causative
10 agent of the disease PML, that's the human
11 polyomavirus JC, and we'll look at some details on
12 how a viral infection leads to a demyelinating
13 disease.

14 And could I have the next slide?

15 These are just the disclosures. You can
16 take a few seconds to look at this.

17 And then we can have the next slide.

18 This is what I call the cast of
19 characters, and in the middle you see an MR scan of
20 a PML patient brain with the classic definition of
21 subcortical white-matter lesions. We'll have much

1 more imaging in one of the talks later by Mike. And
2 if you look at at just to the left of that MR scan,
3 you see the plaque lesions in a Luxol fast blue
4 stain from that brain tissue, the D for
5 demyelination, and you can see some of the lesions
6 that are there that are small, but they do enlarge
7 and they have a tendency to coalesce into those
8 larger lesions, as you see in the box in the scan.

9 Right below demyelinating Luxol fast blue
10 stain is the histopathology where you have
11 bizarre-looking astrocytes, that's the A, and
12 sometimes they can be misdiagnosed as being gliomas
13 at gliomas, and there are several cases like that
14 that are quite important in the literature, they're
15 bizarre astrocytes, but they are -- they can be JC
16 infected. There are also macrophages in the
17 histology of this disease.

18 To the right of that and below the MR scan
19 is the incitu DNA hybridization using biotin-labeled
20 JC DNA probes. Those are in the -- they're in the
21 nucleus of an infected oligodendrocyte, and the

1 density of that staining reflects a concentration of
2 the viral DNA, which we can find in the nucleus of
3 the infected aligo. And we quantitated that some
4 years ago, so you can find 10 to the 10th to 10 to
5 the 12th viral genome copies per cell in some of
6 these PML brain tissues.

7 To the right of that, again, in the
8 nucleus of an oligodendrocyte is a pact series of
9 what we call crystallization of the virion
10 particles, the newly multiplication of variance.
11 And, again there, any single cell can have 10 to the
12 8th to perhaps 10 to the 10th virion particles in
13 the nucleus of a single oligodendrocytes.

14 Just above that are not infectious
15 particles, but what they are are assembly of the
16 variant protein, capsid protein, which is the
17 structure that you see in the box in the corner
18 there, and these are variolite particles. We had
19 cloned out the gene for the VP-1 for JC, and
20 purified the protein. And if you put that in a test
21 tube with a little calcium and other buffers,

1 actually, the VP-1 will self-assemble into these 40
2 nanometers hexahedral particles.

3 And if you look hard enough in that box,
4 there is the tip of one of these icosahedral
5 particles that's called aCAP somewhere, and we know
6 a good deal about the structure of VP-1 and where
7 antibody responses are made to.

8 So those are the cast of characters. Now,
9 how does all of this work so that you finally get
10 PML as a disease.

11 So we could have the next slide.

12 This is what I call, putting the pieces of
13 the puzzle together. We'll go through the steps,
14 which is really the heart of the matter here for
15 this particular talk today.

16 In order for anyone to develop PML, you
17 first have to become infected with JC.

18 Seroepidemiologic studies tell us that with
19 advancing ages, the percent of individuals in a
20 population increases, so that, for example, in
21 individuals in their teens or their 20s, they're

1 perhaps somewhere in the vicinity of 15 to 25% of
2 the population may have come in contact with JC and
3 developed antibodies.

4 By the time that you go into your third
5 decade, fourth, fifth, sixth, and so forth, there is
6 a higher percent of the population that's
7 serologically positive. So what happens, we think,
8 is approximately 30% of the population that is
9 seropositive can develop a persistent latent
10 infection in the kidney.

11 And that's evidenced by the fact that
12 individuals become biuric. And you can excrete
13 tremendous amounts of variant particles in the
14 urine, but for reasons that we really don't
15 understand, there's no pathology associated with
16 that infection.

17 In some -- in about 30%, and that's
18 looking at a variety of different studies that have
19 been done, and that's globally because JC is a virus
20 that's represented throughout the world.

21 In a number of individuals who are

1 latently or persistently infected, or from initial
2 infection perhaps, infection then can escape from
3 the kidney and can be found in the peripheral
4 circulation, approximately 2 to 3% if you do
5 cross-sectional studies will find that the
6 population is viremic.

7 And the virus is disseminated, and we feel
8 as if it's disseminated into lymphoid organs,
9 including the bone marrow. And it could be other
10 tissues as well, but these are what we would
11 consider the functional sites of latency. And it's
12 within these cells we're particularly -- we have
13 been particularly interested in the bone marrow, and
14 where rearrangements -- and we'll see this in the
15 viral genome -- of the regulatory region may take
16 place.

17 Now, interestingly enough, in MS patients
18 treated with natalizumab, there are a population of
19 bone marrow cells, CD-34 hematopoietic progenitor,
20 which migrate out into the peripheral circulation in
21 concentrations that are perhaps as much as 10-fold

1 higher than normal physiology of the immune system
2 would be.

3 So, for example, if we had 1 or 2 or 10,
4 or whatever the number could be, of those cells from
5 the marrow that could be latently infected, they're
6 now found in peripheral circulation. Those cells
7 have a tendency to differentiate the CD-34s into
8 lymphocytic pathways and not monocytic pathways.
9 And in those that are pre-B, CD-19, CD-20, they're
10 very good hosts for the growth of JC virus, and so
11 the virus continues to grow in those type of cells.

12 With time, it looks as if natalizumab has
13 an effect on the up regulation and down regulation
14 on a number of genes, and micro RNAs that regulate
15 the differentiation of these cells.

16 And this was not identified by our
17 laboratory, but it was identified by Raija Lindbergh
18 in Livacabos's (sp) laboratory in Basel. The pala
19 domain is very important in B cell differentiation,
20 and spy B is used by -- it's a transcription factor
21 that's used by JC in order to grow.

1 As these cells then multiply, and as the
2 cells differentiate, then the virus continues to
3 grow. In some cases then it could be in a mature
4 CD-19, CD-20 B cell, or -- and you find these in the
5 peripheral circulation.

6 What happens at that particular point is
7 that the virus then can enter into the brain. And
8 we really don't have exactly the mechanism behind
9 that. The Atwood Laboratory at Brown University
10 seems to think that the virus can be found in
11 cellular vesicles that can gain entrance, perhaps,
12 to the choroid plexus, but there's ample evidence to
13 say that it's certainly a hematogenous spread into
14 the brain.

15 So the virus then gets into the brain; it
16 infects the astrocyte, and it effects the
17 oligodendrocyte. There is another transcription
18 factor, which is very important, called NF-1X, there
19 are four class member of nuclear factor one that are
20 transcription factors, ABC and X oligodendrocytes,
21 astrocytes have a high concentration of NF-1X and

1 not AB and C, and that makes those cells, almost by
2 definition, susceptible to infection.

3 And then that infection proceeds, and as
4 we have seen on the previous slide, that PML
5 initiates as the virus destroys the allogos by
6 alitic necrotic cell death, JC can be carried into
7 the CSF, and that's what we look for, of course, in
8 the diagnostic PCR.

9 So that's putting the pieces of the puzzle
10 together. A lot of things have to happen here in
11 order for successful infection to take place.

12 Can we have the next slide?

13 I wanted to show you this particular slide
14 because it was a very interesting case. It was
15 actually from several decades ago, and it was one of
16 Dr. Joe Berger's patients.

17 On the left-hand panel there is another
18 INCYTO DNA hybridization of the autopsy tissue have
19 a PML patient, it was a young man, with
20 Wiskott-Aldrich Syndrome, and the density of the
21 staining tells us that there was a high copy number

1 of the virus that was there.

2 On the right-hand side -- and we received
3 that brain tissue into the laboratory on the
4 right-hand side. We also found a bone marrow biopsy
5 from that patient, and you can see the bone on the
6 right-hand side, you can see a
7 hybridization-positive cell there in the middle of
8 that panel.

9 We did the nucleotide sequencing of the
10 virions both from the brain and the bone marrow, and
11 they were virtually identical. The reason I wanted
12 to show this is because, interestingly enough, that
13 bone marrow biopsy was taken four years prior to the
14 time that that patient developed PML.

15 And we have a number of other sets like
16 that, so that really started our investigation of
17 the linkage with the cells of the -- infected cells
18 of the immune system and cells of the nervous system
19 as well.

20 And the next slide.

21 Let's take a look at the viral genome, and

1 there are two points we want to make with this
2 particular slide. One is just to do something of an
3 explanation of the variants that occur during the
4 course of infection, and the other is just to show
5 you where the targets are for the PCR assay for the
6 detection of a viral DNA, principally what's found
7 in the CSF.

8 And there will be a lot of discussion
9 about that later on. So let's take a look at what's
10 called the archetype. And just for ease of
11 discussion then, we like to kind of block those
12 nucleotide sequences in the genome. To the left of
13 the genome, as you see there, they're the sequences
14 which make the viral T protein, that's a
15 non-structural protein, it has about 12 functions,
16 on the left-hand side.

17 On the right-hand side there are the
18 sequences for the capsid proteins that make up the
19 structure. The intergenic region there, which is
20 blown up there for archetype of prototype, is the
21 non-coding regulatory region, and that's really the

1 engine that drives the infection.

2 For the archetype is what we find in the
3 kidney and in the urine, and it's generally
4 considered non-pathogenic, and it's in the sequences
5 which we define as blocks A, B, C, D and E, F goes
6 on a little bit later.

7 And since it's generally considered as
8 being non-pathogenic, what seems to occur, and
9 perhaps this -- tissues, is that you have deletions
10 of the B region; you have a deletion of the D
11 region; you have duplication of then those blocks A,
12 C and E, and they turn out to then be the prototype,
13 which is the vastly majority of the arrangement of
14 the nucleotide sequences in the PML brain tissue.

15 And so then you have the difference in
16 these variants, and we'll call them variants, that
17 can be found during the course of infection.

18 Archetype generally considered non-pathogenic; the
19 prototype considered what's now being called the
20 neurotropic variant, and those are the general
21 specific ones that we look for.

1 In the PCR assay that we had developed in
2 the laboratory quite a number of years ago, we
3 target that T-protein region because it's unique to
4 JC and it's conserved, so that if an individual has
5 JC DNA in their peripheral circulation and in the
6 brain, which we find also in the CSF, then if we
7 receive a sample, for example, for -- you know, from
8 these individuals, then that's the region that we
9 quantitate the amount of DNA that's there where we
10 detect it.

11 We also have primer pairs and probes in
12 the D region of the archetype in the same test tube
13 so that, for example, if we get a CSF, we're able to
14 tell the treating neurologist in the viral DNA is in
15 the tissue, in the CSF, in the brain, in the plasma
16 or serum, how much is there, and that's done by
17 those targeted sequences in the T-protein, and also
18 we can -- we can say what the variant is; is it the
19 non-pathogenic archetype or the pathogenic
20 neurotrophic prototype by the detection of that
21 particular region there.

1 At the Atrimus (sp) meeting a number of
2 years ago in Paris, we also introduced another
3 series of prime repairant probes looking at the
4 VP-1, and that was for different reasons, just in
5 case we missed something in T-protein coding
6 sequences, but that hasn't been used very much at
7 all.

8 So there are two things that are important
9 from this slide, one is the differentiation between
10 the archetype in the prototype, and the other is to
11 take a look at the fact that in this particular PCR
12 assay, which is -- continues to be, perhaps, one of
13 the most sensitive of assays because we can detect
14 viral DNA and determine what the variant is at 10
15 copies per Ml.

16 So could we have the next slide?

17 There are several factors that I like to
18 divide these into, post-factors and viral-factors
19 that are typical characteristics in PML patients.
20 Those factors include ineffective T-cell responses,
21 in some cases, anti-inflammatory-type responses,

1 finding IL-10, for example, in the CSF.

2 In a series of studies that we did with
3 our colleagues at the Vaccine Research Center and
4 with Daniel Duick -- Danny Duick and our group, we
5 looked at a number of T-cell populations in PML
6 patients, and we find that generally PML patients
7 will have a lack of CD-4 and CD-8 responses.

8 And in the very early days of looking at
9 these immune responses, Igor Koralnik's group did --
10 started a great deal of understanding of what these
11 T-cell responses were like, and I think that's a
12 critical, important point here in terms of
13 understanding how individuals and patients control
14 the infection.

15 We have expressions of the DNA-binding
16 proteins that are used by JC, particularly cell
17 types that may become infected that have the
18 appropriate transcription factor DNA-binding
19 proteins that the virus needs to grow. And, of
20 course, evidence of viremia in the plasma or serum,
21 and cell components, if we choose to monitor

1 individuals for viremia, and we can now tell the
2 difference between the variance, the archetype or
3 the prototype.

4 Viral factors, as we've talked about, is
5 the arrangement of the regulatory region, again, the
6 nucleotide sequence in these tandem repeats, is it
7 neurotrophic, is it not. Latent cytes and immune
8 system cells, I think is another critically
9 important point to look at in terms of where the
10 virus may be in an individual.

11 And also there are some hyper-variable
12 regions in the capsid VP-1 protein as well, which
13 may give you an idea, in some cases, of what the
14 oncoming pathology may look like. So there are host
15 and viral factors that take place here.

16 In the last slide -- if we can have the
17 next slide?

18 There's a summary of these points one, two
19 and three that we've just discussed. I do like to
20 say a few things about risk assessment markers for
21 PML, that you can measure in the blood, and there

1 are several that can be done relative -- which can
2 be done relatively routinely.

3 I think if you have a patient who may be a
4 risk patient because of underlying disease, and the
5 treatment for that underlying disease, which either
6 modulates or depresses the immune system, I think if
7 that individual has a rise in antibody -- to the
8 virus, that usually is an indication of an active
9 infection.

10 And so that should be a kind of warning
11 sign if that individual is viremic, for example,
12 with a pathogenic genotype and not the
13 non-pathogenic genotype, which our multiplex assay
14 can determine, that's also another sign, and
15 ineffective T-cell responses as well. And I think
16 we have to pay a little bit more attention to that
17 in terms of monitoring patients.

18 So that concludes kind of like an
19 Olympic-speed event here and trying to get through
20 the pathophysiology of PML and how a viral-induced
21 demyelinating disease can occur. I think I've got

1 maybe 30 seconds left to be able to say I'm glad to
2 pass the baton here to my good friend and colleague
3 Dr. David Clifford, who will tell us more about
4 treatment in PML patients. So thank you all for
5 your attention.

6 DR. CLIFFORD: Great. Well, thanks, Gene,
7 and it's a real honor for me to be here to share
8 this very important meeting with this group of
9 friends and colleagues.

10 Next slide.

11 Just background, and primarily an NIH
12 supported researcher, but have consulted with many
13 companies around issues with PML.

14 Next slide.

15 My objectives in this discussion are going
16 to be just to remind again the challenges we face in
17 developing therapeutics for PML to review a few of
18 the leading clinical efforts that have been done at
19 trials, and then to outline what I consider current
20 manage.

21 The next slide.

1 Is just an endorsement of this effort for
2 developing real clinical trials. We're often
3 tempted by our clinical experience grappling with
4 dangerous diseases, to believe we can see the truth
5 through individual observations, in my experience,
6 is a really dangerous phrase for a clinician to use,
7 and I just think it's really critical, especially
8 for a slippery and dangerous disease like PML that
9 trials that are appropriately designed and powered
10 be designed, so thanks to all those that arranged
11 this discussion to optimize that approach.

12 The next slide just goes over, once again,
13 some of the challenges. It has not been for lack of
14 interest or passion that those of us that have taken
15 care of patients with this terrible disease have not
16 come up with an approvable intervention
17 therapeutically.

18 And so the challenges are very real and,
19 you know, it will not be easy to get this trial
20 designed. This is a rare disease, but with a rapid
21 time course, so it's a subacutely progressive

1 disease.

2 And it really takes your breath away as a
3 clinician to see how rapidly patients will progress,
4 and so there's very little time to identify the
5 disease; to decide what you're going to do, and
6 implement it. And when you're doing experimental
7 interventions, it's cumbersome, so this is very
8 challenging to approach.

9 The next slide emphasizes, again, how
10 unpredictable it is; where it's going to occur; what
11 part of the sky is that shooting star going to be
12 in, and so prior knowledge of the people that
13 develop it is usually not available, and the
14 progression and background is highly variable.

15 The next slide would just point out that
16 doing clinical assessment of the patients that
17 develop PML is also very challenging because it
18 doesn't develop in perfectly healthy people, it's
19 not the only problem that's happening at the time it
20 develops. These are people with often malignancies
21 or severe immunodeficiency, and may have multiple

1 active problems, so dissecting out what you're doing
2 to PML in this setting is particularly challenging.

3 Next slide emphasizes that the correlation
4 of the clinical manifestation of the disease, which
5 is what everybody really cares about at the end of
6 the day, and the amount of disease in the brain is
7 not a -- it's not a tight correlation, you can have
8 massive lesions, like in this scan, in the frontal
9 lobes that may have minimal symptoms, whereas, just
10 a tiny portion of a cubic centimeter of tissue
11 involved in critical regions of the motor system or
12 brainstem can be lethal.

13 So it's very hard to correlate the amount
14 of disease that you're fighting biologically with
15 the clinical outcomes that you're seeing.

16 Next slide just is to emphasize that you
17 don't get multiple shots-on-goal with each of these
18 rare patients that have this disease. This is a
19 disease that causes, essentially, permanent
20 disability, and so you really have one chance to do
21 your best game with treating it, and that is -- that

1 is -- compounds difficulty. On more chronic
2 disease, you could try variable approaches or delay
3 the onset of therapy, but it's much more dangerous
4 to do that with this disease.

5 And the next slide is just to emphasize
6 that this is -- this is really a brain disease, and
7 so testing the therapeutics requires getting them
8 into the brain, which has, as we all know, real
9 problems because the blood-brain barrier and the
10 unique environment of the brain.

11 So the next slide, I'm just going to point
12 out that while treating it is so difficult, it would
13 be ideal if we could just prevent PML so
14 therapeutics that might arrest this virus before it
15 causes disease and prevent it would be ideal.

16 And, again, this has been non-trivial, the
17 usual approach to preventing a viral disease is sort
18 of vaccination, you know, give the individual the
19 antigens so that the immune system can work out a
20 system for controlling this virus.

21 But that happens in almost all of us, and

1 it fails in the people with PML, and so that's not
2 an easy approach. And if you have a novel way to
3 modify that preventive approach, it still is going
4 to be very costly because the rare -- the rarity of
5 the disease in even a high-risk population.

6 So we need windows of opportunity, and at
7 present we'll have to discuss what the best windows
8 are, but they're are none of them easy.

9 Next slide I believe we get into the list
10 of the trials that I wanted to just briefly touch
11 on. But it's not been, as I said, for lack of
12 interest in developing therapeutics that we don't
13 have an ideal approach.

14 The first one in the next slide is our
15 effort to test cytosine arabinoside, which I think
16 is one of the best trials that we've ever designed
17 and I'm proud of it. The neurologic aids research
18 consortium and the ACG ran this randomized
19 multicenter trial in which patients with AIDS and
20 developing what looked like PML were rapidly
21 biopsied and entered into this trial.

1 And they were randomized either to the
2 most active anti-retroviral therapy we could offer
3 in this pre-cart era, or that therapy plus either
4 intravenous or intrathecal cytarabine.

5 And the background, of course, is that the
6 best therapy we had was usually Zidovudine with
7 either didanosine or stavudine, and people were all
8 generally already resistant to Zidovudine through
9 mono therapy before we added the second aggressive
10 therapy for their anti-retroviral therapy.

11 And then the next slide, this was a
12 decisive and impactful trial, first, it allowed us
13 to really map out what is the natural history of PML
14 rapidly diagnosed and actively followed, and the
15 answer was this dreadful disease that had a median
16 survival time of only 15 weeks after the hurried,
17 rapid diagnosis of the disease. And so people die
18 uniformly and rapidly when the immune system can't
19 be modified.

20 And, essentially, the trial did show that
21 cytarabine was not able to influence that course.

1 We think probably because the delivery of the drug
2 was inadequate to the brain tissue where it needed
3 to get.

4 The other thing the trial did was to give
5 really, I think, the first systematic look at CSF
6 viral load, and Gene Major lead and effort to study
7 viral load, and we could really already see that
8 lower viral burden in the CSF was correlated to
9 better survival times in this disease.

10 So the next slide.

11 You know, a good clinical trial, even if
12 it doesn't succeed in finding a successful drug, can
13 be impactful, and this trial did change practice
14 such that cytarabine really fell off the map as a
15 sensible approach to treat PML patients, and it also
16 set the stage for understanding how Cart, when it
17 was introduced just as this trial ended, changed the
18 natural history.

19 So the next slide just notes, Dr. Walter
20 Royal lead this effort to try to study and Topotecan
21 drug to treat PML. Again, in-vitro evidence

1 suggested that it could be active against JC virus,
2 and so a phase-two trial was designed. And the
3 important thing for us thinking about trial designs
4 was this trial was designed to look at immediate
5 versus delayed institution of the intervention.

6 And then the next slide.

7 Unfortunately, it turned out that
8 Topotecan was quite toxic and it really was a trial
9 that had to be abandoned, and it also suggested
10 almost everybody was randomized or had to be started
11 on immediate therapy, and so there really wasn't an
12 adequate comparative experience by this immediate
13 versus delayed design. So that flamed out,
14 unfortunately, rather quickly.

15 The next slide has to do with the risks of
16 historical controls. And so of course we're
17 thinking of a viral disease, and interferon is a
18 kind of elementary school antiviral approach, and we
19 didn't miss that thought, and so we had alpha
20 interferon in our therapeutic regimen.

21 So a number of people lead by a group at

1 Hopkins looked at alpha interferon in consecutive
2 patients treated with it that had developed PML in
3 the setting of HIV.

4 And the initial impression was, wow, you
5 know, maybe we've got something, the median
6 survivals in the treated patients with alpha
7 interferon were longer than we'd seen in untreated
8 patients; however, the experience that, oh, you
9 know, our active anti-retroviral therapy is changing
10 the biology of the disease came into play, and when
11 the data was re-analyzed looking at the use of
12 antivirals in CD-4 counts, the impact of interferon
13 went away.

14 So, again, a reminder of the danger of
15 historical controls in a landscape where therapeutic
16 approaches is changing.

17 The next slide is about the second of our
18 NARC ACDG-lead efforts to treat PML, and it was lead
19 by Dr. Christina Marra, and it was an effort to look
20 at cidofovir, a DNA antiviral active drug given IV,
21 and it was primarily designed as a safety trial, but

1 I think one of the contributions in terms of trial
2 design that this trial contributed was we built
3 outcomes at eight weeks on the neurologic exam,
4 hypothesizing if we had an active good drug that
5 would show improvement in neurologic outcomes after
6 a couple of months of therapy with a good drug.

7 And so the next slide shows that scale,
8 and I think that in discussions about grading
9 clinical change, this could be at least a good
10 starting point because we spent considerable time
11 trying to build a scale that weighted scores of
12 clinical impact of disease around the areas that we
13 know PML could affect. So this, I think, could be
14 brought out and looked at again.

15 And the next slide, unfortunately, again,
16 this intervention didn't seem to work. It was done
17 in a messy period, it was open-label, and most of
18 the patients got anti-HIV therapy, and you can see
19 the outcomes were that as we went from baseline to
20 week eight in the first and second column, that the
21 CD-4 counts were tending to rise, and in the next

1 line, the plasma HIV RNA was falling.

2 So we had an active treatment of HIV,
3 which is what you will always have because you can't
4 deny the use of the HIV therapy, and indeed in that
5 setting it looked like there was a trend for the JC
6 DNA to fall and, in fact, all of the median JC DNA
7 at eight weeks was already down to undetectable DNA.

8 Unfortunately, the neurologic exam didn't
9 improve with survival to eight weeks, in fact, it
10 got worse, as did the MRI. Now we could probably
11 interpret that experience by the onset of some IRIS
12 and worsening clinical status, but in the setting of
13 controlling the infection.

14 So we had an over 50% survival to 12
15 weeks, and that really was a critical time in this
16 trial, certainly hopeful in terms of that.

17 But in the next slide, cidofovir was sort
18 of put in better perspective by pooling our study
19 with five other cohort studies that Andrea De Luca
20 pulled together.

21 And in the next slide you can see that in

1 terms of survival, the impact of adding cidofovir to
2 CART really -- it made no difference. So although
3 it was a reasonably nontoxic therapy, it was
4 cumbersome to give, and it really did not impact at
5 all the outcome in terms of patient survival.

6 But we can see here that instead of having
7 people dying almost always, at least 90%, as had
8 been done in the pre-CART era, now there's long-term
9 survival out to several years in the CART era. So
10 the biology of the disease clearly, clearly changed
11 by active anti-retroviral therapy, and could that be
12 better.

13 And so the next slide was, I think, a very
14 impactful study where the French ANRS group lead by
15 Jacques Coslo tried to push the envelope of what's
16 the most aggressive HIV therapy we can design in the
17 late 90s, and they added Enfuvirtide to at least
18 three active CART drugs, assumed that maybe that 50%
19 survival that I showed you in the cidofovir trial
20 was what would happen without aggressive therapy.

21 But with aggressive therapy, in the next

1 slide, you can see that they actually got about 75%
2 survival, so up the ante even further by aggressive
3 use of CART. They also showed the biology of the
4 CART era PML, which was that really the deaths that
5 happened were all in the first four months.

6 This disease, the shooting star, the rapid
7 course, the disease plays itself out, certainly in
8 the first six months and, in fact, all the deaths
9 from disease were in the first four months of this
10 actively-followed group.

11 And as they went through the first six
12 months, most of the survivors got undetectable JC
13 DNA simply from active HIV therapy. Better
14 responses in terms of CD-4 count and lower JC DNA
15 were associated with better survival in the
16 univariant analysis.

17 So in the next slide, this is the
18 background that we have for modern CART therapy, and
19 with protease inhibitors and modern therapy of any
20 sort you don't have Enfuvirtide, I would say that
21 we're really looking at 75% survival is what you

1 could get from HIV alone, which makes the HIV group
2 of patients a difficult one to add in therapy to
3 because, at least for survival, there's very little
4 room for improvement. And with a very small study,
5 it's hard to prove a change of survival that's going
6 to be that small.

7 Next slide.

8 The final trial that I will bring up is
9 our Mefloquine trial. Now, this came out of the
10 effort led by Biogen in response to the issues
11 around PML with Natalizumab to seek out other
12 interventions. And in a high-throughput study of
13 many available drugs, somewhat surprisingly
14 Mefloquine fell out as having efficacy in inhibiting
15 JC DNA in vitro, and in concentrations that we knew
16 we could get in the brain of patients in a nontoxic
17 way.

18 So this was a trial where we compared
19 standard of care without Mefloquine to standard of
20 care plus Mefloquine randomizing all coming PML
21 patients. And the important part of this trial is

1 it was a trial in which the endpoint was selected to
2 be the JC DNA copy number in the CSF at the baseline
3 and under therapy.

4 Unfortunately, in the next slide you will
5 see that, while the randomization worked
6 beautifully, the standard of care in Mefloquine
7 groups and essentially identical viral loads in the
8 CSF baseline.

9 Unfortunately, as we went forward, we
10 could see no impact of the addition of Mefloquine to
11 standard of care. However, you know, four weeks is a
12 very short time to clear DNA from the CSF, and the
13 power of this study to tell us anything at eight
14 weeks was minimized, you can see only three patients
15 remained in the standard of care analysis at eight
16 weeks.

17 So the study was -- turned out to be
18 underpowered for the endpoint that we were
19 interested in, and eight weeks may be a little bit
20 too short to study the endpoint of JC DNA viral
21 load, but an impactful study.

1 So I'm going to just move forward one
2 slide in and say that this study doesn't rule out
3 the use of Mefloquine because it didn't prove it was
4 inactive, but it certainly doesn't support it as a
5 highly-active intervention.

6 In the next slide I was asked to just
7 mention what the standard of care is, and I'm really
8 going to stop because this panel has expert people,
9 I think that my approach to care of PML is to make a
10 really clean, clear diagnosis with MRI and JC
11 detected in the central compartment, to stage the
12 disease to understand where we are in the setting of
13 immunodeficiency and immune response so that you can
14 think about the active interventions that you can
15 offer.

16 To offer immune reconstitution to
17 everybody, that's clearly advantageous clinically,
18 and where it can be done, and often can be done, can
19 be life saving.

20 To support these patients through, the
21 outcome is not as bad in everybody as our early

1 results suggested, so I'm supportive, and then to
2 use -- care to actively treat IRIS where it's
3 present and support these patients, encouraging
4 people to have hope that they can combat this
5 disease.

6 But clearly we need active treatment for
7 the virus, and that's what this conference, I hope,
8 is going to set up the approach that we can do that.

9 And so having burned up my time, as usual,
10 I'm going to stop with that and we can flip through
11 my other slides, and I will thank my other folks, so
12 just going right through just the next one, I've
13 really covered each of these points, and you can
14 review them in the slides later on, but they're
15 standard points that experts know about this
16 disease, and I would just sort of stop and thank all
17 of my friends and supporters and teachers.

18 And I'll pass it on to Dr Smith who's
19 gonna carry on.

20 DR. SMITH: Thanks, Dr. Clifford.
21 I'm Bryan Smith, I'm at the NIH. I'm currently in

1 D.C. where there's a lot of construction outside, so
2 I apologize in advance if there's too much noise.
3 So I'm going to talk about clinical outcomes among
4 PML patient populations, and this is on behalf of
5 our Clinical Outcomes Working Group, which I'll
6 introduce momentarily.

7 Next slide.

8 So I'm going to go over our working group
9 structure and objectives, I'll talk about PML
10 patient populations, specifically thinking about
11 clinical outcomes and how much the underlying
12 disease really dictates those outcomes. I'll talk
13 about outcomes over time, when we've collected data,
14 we've certainly seen that what era we're collecting
15 data from, again, dictates what the outcomes are for
16 patients with PML.

17 Survival is really at the heart of PML
18 clinical outcomes, but I want to think beyond that,
19 and what has been collected so far in terms of
20 disability and functional status, in addition to
21 survival. And then I also want to briefly touch on

1 IRIS and how that certainly impacts clinical
2 outcomes in these patients.

3 Next slide.

4 So historically survival in patients with
5 PML has been uniformly dismal, unfortunately, and
6 limited attention has been paid to establishing
7 measurements of functional outcomes in PML, those
8 related to disability or activities of daily living.

9 Next slide.

10 And it really depends on the population,
11 so for some patients with PML who have a poor
12 prognosis, survival is a meaningful outcome measure,
13 and really the only outcome measure that we would
14 need for a clinical trial. But for others, those in
15 whom PML has much higher survival rates, measuring
16 the PML-related disability is a much more meaningful
17 outcome measure.

18 Next slide.

19 So we established a PML Clinical Outcomes
20 Working Group at the NIH and the FDA with these
21 members with the purpose of evaluating the

1 differences in outcomes that are reported among PML
2 disease populations to see which measures have been
3 used previously in the literature, and for which
4 diseases.

5 And then really to think ahead to evaluate
6 the measures that are currently out there, how
7 suitable are these for endpoints in PML trials, and
8 what potentially is missing from the field in terms
9 of establishing clinically-relevant outcomes.

10 Next slide.

11 So we did this with a systematic review
12 that is ongoing. We started with more than 1,300
13 Pub Med hits that potentially could relate to
14 clinical outcomes in PML, and we ended up with 121
15 studies. And all of these included at least three
16 cases, and all had data related specifically to
17 clinical outcomes in patients with PML.

18 Next slide.

19 So of the 121 studies, the median
20 publication year was 2009, we actually had over
21 6,500 individual patients whose clinical outcomes

1 were reported. The mean cohort size of each
2 individual publication was about 54 participants
3 with PML. And then you can see that the vast
4 majority of the studies were small cohorts or small
5 case reports of patients.

6 There were somewhat surprisingly a good
7 number of very large studies, some more than 50
8 participants with PML. We had about a little over
9 25% of our studies had a relatively large number of
10 participants, so that was very helpful.

11 Next slide.

12 And here is the breakdown by underlying
13 disease, so not surprisingly, cohorts with HIV --
14 with patients with HIV and multiple sclerosis made
15 up the vast majority of the clinical outcomes
16 reports.

17 You can see that for some of the other
18 diseases, they're certainly relevant for research
19 studies, but there are very few reports in the
20 literature from patients with these various
21 underlying conditions, idiopathic CD for

1 lymphopenia, non-hematologic oncological cases,
2 transplant cases. There's certainly very -- groups
3 of patients with the dire need for PML-specific
4 therapies, but it's relatively rare in the
5 literature.

6 Next slide.

7 So what we found, and what I think is at
8 the heart of our results across the board, was that
9 the underlying disease is critical. So when we look
10 at the percent survival, the underlying disease
11 really dictates the percentage of patients with PML
12 that will survive. So in MS here on the left,
13 survival is just over 90%, and this is an average
14 across all of the reports that we found.

15 On the other end of the spectrum we have
16 primary immunodeficiencies that are already
17 diagnosed, and survival for those patients is about
18 10%, again, very small numbers of patients, but very
19 poor prognosis. So for those conditions on the
20 right side of the graph, survival would be a very
21 easy outcome measure for a trial because the natural

1 history of the disease has uniformly low survival.

2 Those diseases on the left side of the
3 graph would be the opposite, so if you measure
4 survival, you're probably not going to get a good
5 measure of whether your drug is working or your
6 product is working, because the natural history
7 survival is so high for those diseases.

8 Next slide.

9 So we also know that the time when the
10 study was published dictates the clinical outcome as
11 well, in this case percent survival still. So just
12 as probably the most important example would be HIV,
13 and we Apriori (sp) did a binary cut off of 2006
14 when CART ace inhibitors became available, and again
15 this is just publication date, but you can see that
16 there's a general linear curve upward here with
17 improved percent survival as time goes on.

18 And so down below you can see that percent
19 survival 2006 and onward is 52.5%, probably higher
20 now, and pre-2006 it was only about 30% of patients
21 with HIV.

1 Next slide.

2 So there is limited data on survival
3 beyond percent survival, so certainly it's relevant
4 to think about the time to death or risk factors for
5 death, but those outcomes are more inconsistent in
6 the literature, the summary methods that people used
7 for these measures is very inconsistent.

8 But even with those inconsistencies, we do
9 see that the underlying disease probably dictates
10 those outcomes as well, so thinking about the time
11 to death, for example, really varies mostly by the
12 underlying disease.

13 Next slide.

14 So it's important to think beyond
15 survival, we want to think about disability. So
16 survival doesn't capture the full spectrum of
17 clinical outcomes across PML populations, so we want
18 to measure function. And we can do that with
19 measuring a patient's symptoms; we can measure the
20 neurologic exam abnormalities and quantify that,
21 potentially, and also we can measure the functional

1 status, how someone is doing in terms of his or her
2 daily living activities.

3 And these are all things that might be
4 relevant for clinical trials because they're all
5 quantifiable.

6 Next slide.

7 So there are a few commonly-used scales in
8 the literature, and Dr. Baldassari is going to
9 discuss these in much more detail, so I'll just skim
10 over them for now, but a lot of these vary by the
11 patient groups. So, for example, in neurology we
12 use the modified ranking quite a bit; in cancer,
13 oncologists use the Karnofsky Performance Scale
14 pretty frequently, or versions of that, and then in
15 MS there's a disease-specific scale, the EDSS,
16 that's commonly used.

17 And so it's not surprising in patients who
18 have MS and PML, that commonly the EDSS is reported
19 as a disability scale or a disease-specific scale
20 when measuring how the PML is affecting them.

21 There are advantages and disadvantages to

1 each of these, but the main point is really none of
2 these could be used it as a sole clinical outcome
3 measure in a PML clinical trial, and I think this
4 really highlights the need for a PML
5 disease-specific scale that incorporates different
6 aspects of these existing scales that could be used
7 for a clinical trial.

8 Next slide.

9 So, for example, again, this common theme,
10 the underlying disease really dictates the outcomes.
11 So, for example, we have HIV and multiple sclerosis,
12 we did see that the Karnofsky Performance Score was
13 lower in patients with HIV compared to multiple
14 sclerosis, and, similarly, in those studies that did
15 report the EDSS, certainly a smaller number in the
16 HIV group compared to MS, we do see that the EDSS is
17 higher and, in a sense worse, in the HIV group.

18 Next slide.

19 So I briefly want to talk about IRIS so
20 IRIS is Immune Reconstitution Inflammatory Syndrome.
21 For patients who start a therapy that's working

1 against the disease, commonly he or she will have a
2 clinical worsening as the therapy might be working,
3 so, for example, anti-retroviral therapy. So it's
4 important to know that IRIS might negatively impact
5 a disability scale, despite the product actually
6 working, despite a positive effect.

7 So the likelihood of IRIS during a
8 clinical trial will depend on the intervention and,
9 of course, the underlying disease, so we really need
10 a standardized way in the field to define and report
11 IRIS for trials.

12 Next slide.

13 So in conclusion, PML prognosis varies
14 widely, most of this is related to the underlying
15 disease that defines the natural history of the PML
16 prognosis. There's currently no ideal clinical out
17 point -- I'm sorry, endpoint for use in a trial,
18 though we do think a disease-specific scale will be
19 of tremendous value.

20 And IRIS must be recognized and accounted
21 for when measuring and reporting clinical outcomes,

1 because it's going to confound the results quite
2 significantly unless it's accounted for.

3 Next slide.

4 So this is a collaborative effort, this
5 systematic review that is being conducted, and all
6 the discussions and conclusions that we come up with
7 have been a very large collaborative effort, and I
8 just want to acknowledge and thank our group here.
9 Thank you.

10 DR. SHEIKH: Thank you so much, Dr. Smith.
11 So we're going to go on a 10-minute break right now,
12 so if we could all return to the meeting at 11:15.
13 So I guess a nine-minute break. We'll talk to you
14 all in nine minutes.

15 (Whereupon, a short break was taken.)

16 DR. SHEIKH: Welcome back from break
17 everyone. We're now going to dive deep into
18 considering endpoints for PML clinical trials.
19 To make sure that we're on the same page as we
20 prepare for the first panel discussion, I'm going to
21 provide a brief overview of what we want our focus

1 to be on, and some key considerations for endpoint
2 selection for PML.

3 Next slide.

4 So first, the endpoints discussion today
5 is meant to focus on primary and key endpoints that
6 could be used in clinical trials designed to
7 establish PML product and efficacy and safety.
8 These discussions are not meant to preclude the
9 inclusion of exploratory or secondary endpoints that
10 might inform future trials.

11 Additionally, we want the discussion to
12 focus on information that is available currently.
13 So, for example, although there may be other
14 biomarkers that are scientifically interesting and
15 that weren't for their study, we want to focus a
16 discussion on endpoints that could be incorporated
17 as a primary endpoint into a PML clinical trial
18 today.

19 Next slide.

20 As we embark on discussions about clinical
21 trial endpoints, please keep these important

1 endpoint characteristics in mind, first, the
2 selected clinical trial endpoint should be well
3 defined.

4 Second, the endpoint should be reliable.
5 Thirdly, the endpoint should be clinically
6 meaningful. So what do I mean by this exactly? So
7 the most straightforward examples of clinically
8 meaningful endpoints are direct measures of clinical
9 benefits, such as mortality or survival or another
10 measure of how people feel, function or survive.

11 For PML, a measure of neurologic outcomes,
12 as Dr. Smith was just referring to, would fall into
13 this category of a direct clinical benefit -- direct
14 measure of clinical benefit.

15 But clinical trials can also use
16 biomarkers that had been established as clinically
17 meaningful endpoints. An important example in
18 virology is HIV viral load, which is now used as an
19 endpoint from most clinical trials leading to HIV
20 drug approval.

21 In some cases biomarkers that are

1 reasonably likely to predict clinical benefit, but
2 are not yet established as clinically meaningful
3 trial endpoints, can be used to support drug
4 approval. In the U.S., this is via the accelerated
5 approval pathway. Drug companies whose products are
6 approved via this pathway are required to conduct
7 confirmatory trials, and products can be removed
8 from the market if the confirmatory trials do not
9 show the product provides clinical benefit.

10 Next slide.

11 So although Dr. Smith just covered this to
12 a great extent, I just want to clarify why we're
13 talking about something other than survival when
14 survival is such an important outcome for anyone,
15 and particularly in the setting of PML, like why are
16 we even having this discussion.

17 So mortality rates are generally high in
18 PML, and survival is clearly a clinically meaningful
19 objective endpoint, and it's generally considered to
20 be a gold-standard clinical trial endpoint; however,
21 using a survival as an endpoint for PML clinical

1 trials might confer some disadvantages.

2 And some of those disadvantages might
3 include the following: So, first, survival and
4 mortality do not capture the full spectrum of
5 serious and clinically meaningful PML clinical
6 outcomes. For example, the clinical outcome of a
7 patient who becomes permanently bed bound is not
8 captured by survival outcome alone.

9 Additionally, as Dr. Smith mentioned,
10 survival rates are already high in certain patient
11 groups. For example, PML mortality is relatively
12 infrequent in the MS patient population in whom a
13 PML diagnosis might be made promptly, and for whom a
14 reversal of immunosuppression is often possible.
15 Nonetheless, evaluating whether this patient
16 population may benefit from an investigational PML
17 treatment maybe warranted.

18 And, finally, the use of a survival
19 endpoint may require a larger sample size for an
20 adequately-powered clinical trial. This may be
21 problematic in a rare disease like PML for which

1 clinical trial recruitment and retention is likely
2 to be challenging.

3 Next slide.

4 As I mentioned earlier, neurologic
5 progression is another important clinical endpoint
6 for PML, and Dr. Smith mentioned this going into
7 some detail about this; however, there's also some
8 challenges inherent to the selection of this type of
9 trial endpoint; namely, the use of neurologic
10 progression as an endpoint requires a selection of a
11 reliable, well-defined, meaningful scale.

12 Furthermore, neurologic scales, also
13 called functional scales, and disability measures
14 that measure neurologic progression, should
15 adequately capture meaningful clinical outcomes for
16 PML specifically, and Dr. Smith talked about that
17 previously.

18 Dr. Baldassari will describe a lot -- the
19 various disability outcome measures in more detail
20 in her upcoming talk.

21 Next slide.

1 Scientifically valid biomarkers have also
2 been used to accelerate therapeutic product
3 development in many disease areas, including viral
4 diseases. Developing biomarkers for PML could be
5 very valuable; however, we also have to overcome
6 challenges in this area, too. The first challenge
7 is that currently no biomarkers have been
8 established as predictors of clinical benefit in the
9 setting of PML.

10 Second, the use of biomarkers, for
11 example, brain imaging and the results of molecular
12 tests, would have to be supported by strong
13 scientific evidence supporting the biomarkers use as
14 a predictor of clinical benefit.

15 To inform our discussions about biomarkers
16 as endpoints for PML clinical trials, we'll hear a
17 talk on MRI imaging of the brain, and a talk on JC
18 virus DNA in the CSF later this morning.

19 Next slide.

20 With that, I will introduce our next
21 series of speakers. First, Dr. Laura Baldassari,

1 Medical Officer for CDER's Division of Neurology II,
2 will provide a talk on PML disability outcome
3 measures.

4 Then Dr. Mike Wattjes, Professor of Neuro
5 Radiology at Hanover Medical School in Hanover,
6 Germany, will provide an overview of brain imaging
7 in PML, and third, Dr. Irene Cortese, Director of
8 the Experimental Immuno Therapeutics Unit of NINDS,
9 Ms. Gina Norato, Statistician at the NINDS Clinical
10 Trials Unit, and Dr. Paola Cinque, Senior Physician
11 at the San Raffaele Scientific Institute in Milan,
12 Italy, will together provide a talk summarizing
13 available data on JC virus DNA in the CSF as a
14 predictor of PML clinical outcomes.

15 Next slide.

16 Dr. Baldassari, you have the floor.

17 DR. BALDASSARI: Thank you so much,
18 Dr. Sheikh. Morning everyone, my name is Laura
19 Baldassarri, and I'm a clinical reviewer in the
20 Division of Neurology II at FDA. I'll be speaking
21 about clinical disability outcome measures in PML on

1 behalf of the PML Clinical Outcomes Working Group.

2 Next slide.

3 As discussed by Dr. Smith and Sheikh
4 earlier, assessment of PML-related disability may be
5 more meaningful to some patient populations in
6 survival, but a standardized assessment has not been
7 developed. Our working group sought to evaluate the
8 use of disability measures for PML in the literature
9 in order to determine whether any existing measures
10 would be suitable for use as a key clinical trial
11 endpoint.

12 Next slide, please.

13 To accomplish this goal, as Dr. Smith
14 discussed previously, we conducted a systematic
15 review to evaluate the use of clinical outcomes in
16 PML in articles from 1990 to the present that
17 included at least three patients. Our key outcomes
18 of interest for survival, which was discussed by
19 Dr. Smith, clinical disability outcomes, and the
20 prevalence of PML symptoms within key neurological
21 domains.

1 Next slide.

2 Ultimately, 121 studies were included in
3 our analysis, which comprised approximately 6,500
4 patients. Most studies were retrospective cohorts
5 or case series, and studies most commonly reported
6 data from populations with HIV and multiple
7 sclerosis or were mixed populations of various
8 underlying diseases.

9 Next slide.

10 I first wanted to highlight our findings
11 related to common signs and symptoms of PML, which
12 inform further discussion of appropriate outcome
13 measures. Among approximately 2,200 patients for
14 whom clinical symptom data were available, the most
15 common signs and symptoms were reported in the motor
16 and cognitive domains, with approximately 50 and 40%
17 prevalence, respectively.

18 I would also like to highlight that visual
19 were symptoms reported in approximately 23% of
20 patients.

21 Next slide.

1 The second key finding that I will be
2 discussing is that of disability outcomes utilized
3 in the existing literature. Of the 121 studies
4 included in our analysis, 72% did not report a
5 quantitative clinical disability outcome; however,
6 many studies reported more of a global impression of
7 neurologic improvement or worsening without a
8 quantitative or standardized assessment.

9 Of the studies that did report clinical
10 disability outcome, the most commonly reported scale
11 were the Expanded Disability Status Scale or EDSS,
12 the Karnofsky Performance Score and the Modified
13 Rankin Scale. A few studies also reported a novel
14 scale, including the PML clinical score from the
15 Cidofovir trial discussed by Dr. Clifford earlier.

16 As it was discussed by Dr. Smith
17 previously, the disability scale used, as well as
18 the severity of disability, varied by underlying
19 disease.

20 Next slide.

21 Our group, therefore, evaluated the three

1 clinical disability scales that were most commonly
2 used in further detail. The EDSS or Expanded
3 Disability Status Scale, is a 10-step scale based on
4 a standardized neurological exam, which was
5 developed by Dr. John Christie for use in patients
6 with multiple sclerosis. The overall score, which
7 ranges from zero to 10, is determined by the
8 quantitative evaluation of eight functional systems,
9 including ambulation.

10 Each functional system is graded on a
11 scale from zero to five or six, and the number of
12 domains in which the patient has varying degrees of
13 disability determines the overall score. For
14 example, a patient with moderate disability in one
15 functional system who is fully ambulatory would
16 receive a score of three, as indicated in the table
17 on the right side of the slide.

18 This table and figure below also
19 demonstrates that above a score of a four, the score
20 is driven primarily by ambulation, and that a score
21 of six, unilateral assistance is required for

1 ambulation. Above the six, the steps reflect
2 increasing levels of disability related to
3 ambulation, use of arms, communication, and the
4 ability to eat.

5 Next slide, please.

6 So when we considered applying the EDSS to
7 PML, we noted several potential advantages and
8 disadvantages. The EDSS does account for
9 multi-focal central nervous disease -- system
10 disease, and has a broad range of outcomes.
11 Additionally, clinical meaningful changes in the
12 EDSS are relatively well defined, and it is a
13 commonly utilized outcome in phase three trials for
14 multiple sclerosis.

15 However, limitations to the application of
16 EDSS in PML include its intended specificity for MS,
17 the lack of formal assessment of PML-relevant
18 domains specifically related to behavior, cognition,
19 cortical visual function and seizures. It's focused
20 on ambulation, the integrator of variability, as
21 well as statistical properties.

1 Next slide, please.

2 Next, we consider the Karnofsky
3 Performance Score, which is an 11-point functional
4 scale developed for use in patients with cancer that
5 is based upon the ability to perform activities of
6 daily living. The table on the right side of the
7 slide shows that a score can range from 100, which
8 is normal, to zero, which is death, in increments of
9 ten. Patients who are able to work, but can live at
10 home, receive a score from 50 to 70, and those who
11 are unable to care for themselves and require
12 specialized or hospital care, receive a score of 40
13 or lower.

14 Next slide, please.

15 So when considering applying the Karnofsky
16 Performance Score to PML, we again noted several
17 potential advantages and disadvantages. This scale
18 is not specific to an underlying disease, it
19 assesses a broad range of outcomes and is a
20 reasonable assessment of overall disability, and is
21 also commonly utilized.

1 However, limitations include lack of
2 assessment of domains relevant to PML, and the
3 course nature of the categories may not capture a
4 clinically meaningful change in patients with PML.

5 Next slide.

6 Finally, the Modified Rankin Scale is a
7 seven-point functional scale originally developed
8 for use in patients with stroke. Scoring is based
9 upon the ability of patients to perform activities
10 of daily living. As indicated by the table on the
11 right, the score can range from zero, which is no
12 symptoms, to six, which is death.

13 Patients who could walk unassisted are
14 assigned a score of three or lower, those who cannot
15 attend to their activities of daily living without
16 assistance or walk, receive a four, and those who
17 require constant care due to severe disability
18 receive a five.

19 Next slide, please.

20 So when considering applying the Modified
21 Rankin to PML, we again noted several potential

1 advantages and disadvantages, several of which
2 overlapped with our assessment of the EDSS and
3 Karnofsky Performance Score.

4 Similar to the Karnofsky Performance
5 Score, the Modified Rankin is not specific to an
6 underlying disease, it assesses a broad range of
7 outcomes and there's a reasonable assessment of what
8 overall disability and ability to conduct activities
9 of daily living.

10 Clinically meaningful changes in the
11 Modified Rankin are defined as well; however, also
12 similar to the Karnofsky Performance Score,
13 limitations include lack of assessment of domains
14 relevant to PML, and the course nature of the
15 categories may not capture a clinically meaningful
16 change in patients with PML.

17 Next slide, please.

18 We therefore determined that none of the
19 existing functional or disability scales previously
20 utilized in PML were ideal for us as a key clinical
21 endpoint in a therapeutic trial, as discussed by

1 Dr. Smith earlier. We then considered development
2 of a PML-specific scale for this purpose, which
3 would ideally quantify and weight the severity of
4 common neurological symptoms associated with PML in
5 terms of their overall contribution to disability.

6 However, we do recognize several
7 challenges to the development of such a scale,
8 including the rarity of PML, which may limit the
9 availability of patients for scale development; the
10 choice of an appropriate anchoring scale, and the
11 dedicated process of scale development.

12 Next slide.

13 So in summary, our systematic review the
14 literature demonstrated limited and heterogeneous
15 application of clinical outcome measures across PML
16 clinical studies. The clinical outcome measures
17 that were previously applied to PML lack granularity
18 and specificity for relevant domains commonly seen
19 and leading to disability in patients with PML.

20 Development of a PML-specific scale would
21 be ideal for use in the clinical trials setting, but

1 may be logistically challenging.

2 In terms of our next steps, our systematic
3 review is currently ongoing to allow for
4 comprehensive assessment of PML clinical outcomes in
5 the medical literature.

6 Next slide, please.

7 I would like to end by acknowledging the
8 members of the PML Clinical Outcomes Working Group.
9 Thank you all for your time and attention this
10 morning. And I will now turn things over to
11 Dr. Mike Wattjes to discuss brain imaging in PML.
12 Thank you.

13 DR. WATTJES: Thanks, Laura. Many thanks
14 for your kind invitation to this monumental meeting.

15 Next slide, please.

16 These are my disclosures.

17 Next slide, please.

18 So this is the agenda. So I will start
19 with some introduction words, and then I will focus
20 on the standardized acquisition for PML not only for
21 diagnostic purposes, but also for disease and

1 treatment monitoring.

2 And then we will discuss the imaging
3 features, very important to understand the MR
4 methodology in terms of diagnosis and treatment
5 monitoring, of course, and then we will focus on the
6 lesion evolution and whether or not the outcome
7 measures -- the imaging-based outcome measures are
8 ready for clinical trials.

9 Next slide.

10 So, first of all, it's very important that
11 imaging is part of the Holy Trinity of diagnosis of
12 PML, including the clinical assessment, the CSF
13 analyzes and, of course, imaging.

14 And next slide.

15 And this has been incorporated in the --
16 diagnostic criteria facilitating very early and also
17 a very specific diagnosis of PML.

18 Next slide.

19 So in terms of the standardized image
20 acquisition, we know that the flare has a high
21 sensitivity in terms of the PML lesion detection,

1 T-2 can detect certain imaging features quite
2 specific for PML, at least very small intra-lesional
3 nodules or vacuoles at T-1 was able to detect the
4 stage of the disease in terms of your irreversible
5 demyelination, but also in terms of detection of
6 finding imagery finding suggestive information in
7 DWI is able to detect the architects of viral
8 replication, and particularly on the border of the
9 lesion where the oligodendrocyte swelling is taking
10 place.

11 Next slide.

12 So for monitoring -- well, for screening
13 purposes in patients with a higher risk of
14 developing PML like a -- treated patients, we can
15 use a -- scan protocol skipping the T-1 post -- or
16 if you're able to apply or to acquire a 3D flare.

17 Next slide.

18 You can even more shorten the protocol
19 like suggested by the recent MNCMC guidelines by
20 using our 3D flare in detail on the y.

21 Next slide.

1 So, in terms of image methodology, we are
2 differentiating two different types, very roughly
3 classically -- classic PML having these very nice
4 hyperintense -- T-2 hyper-intense lesion in the
5 subcortical white matter, but also involving the
6 cortical gray matter, hypo-intensity on the T-1, and
7 a hyper-intensic intensity on the -- and
8 particularly at the border of the lesion where
9 active viral replication takes place.

10 In contrast to that, we have also the so
11 called inflammatory PML showing imaging findings
12 suggestive of inflammation, including contrast
13 enhancement for lesional edema and provisional
14 swelling.

15 Next slide.

16 In terms of lesion evolution, this is an
17 example of a white matter onset PML, so this is a
18 treated patient, you see at some moment new lesions
19 are occurring in the deep white matter or in the --
20 cortical white matter and then spreading along
21 the -- fibers or other white matter tracks, and then

1 becoming confluent and very dark on the T-1.

2 However, considering PML as an exclusive
3 white matter disease, it would be a failure of
4 imagination because PML is not an exclusive white
5 matter disease, it's also a cortical gray matter
6 disease.

7 Next slide.

8 And these lesions can start in the
9 cortical gray matter, like here very nicely
10 demonstrated, and then subsequently can involve the
11 oxi-cortical white matter and DHWC -- adjacent deep
12 white matter. And this is very important, not only
13 in terms of making the correct diagnosis, but also
14 in terms of understanding the lesion evolution for
15 clinical trials.

16 Next slide.

17 We can also have sort of selective tropism
18 of the virus, almost exclusively focusing on the
19 cortical gray matter, like seen in this patient
20 here, coining the term GC virus-related
21 encephalopathy. I call it sometimes cortical

1 phenotype, and the very end is the heliotropism of
2 the granule cells in the cerebellum accordingly, so
3 the term GCN granule cell neuropathy.

4 Next slide.

5 So in terms of the relationship between
6 imaging finding and -- detection of -- in the CSF,
7 it's very important that there is a relationship
8 between imaging and CSF findings.

9 Now, this is exclusively present at the
10 time of the diagnosis, so we know that the number of
11 copies detected in the CSF is related to a lesion
12 volume, and that the lesion volume has also some
13 predictive value in terms of the prediction of
14 whether or not the GC virus can be detected and the
15 CSF are not.

16 So when the lesion volume gets smaller --

17 Next slide.

18 -- the likelihood that we are able to
19 detect GC virus in the CSF and the copy number of GC
20 virus on the CFS is going down, and it can be the
21 case that we see a PML lesion -- a small PML lesion

1 on the MRI and the GC virus is negative.

2 And this limits our ability to facilitate
3 a very early PML diagnosis while we're not able to
4 detect GC virus in the CSF.

5 Next slide.

6 So in terms of lesion evolution, imaging
7 can serve as a method to demonstrate lesion
8 progression and lesion dissemination, like shown in
9 this picture here, very nicely shown the
10 dis-cortical phenotype of PML, and then subsequently
11 involving also the white matter in the contralateral
12 hemisphere over a period of several months.

13 But not only the lesion evolution in terms
14 of volume changes is very important --

15 Next slide.

16 -- but also to detect other phenotypes
17 like the PML IRIS phenomenon that can occur after
18 the reconstitution of the immune system, which is
19 reflected by T cell mediated immune response against
20 the virus leading to imaging findings suggestive of
21 inflammation like contrast enhancement and appeared

1 lesional edema.

2 Next slide.

3 This is an example of PML IRIS, the lesion
4 grows rapidly and then as someone was showing, a
5 mess of imaging findings suggestive of inflammation,
6 particularly on the border of the original PML
7 lesions, but also elsewhere, particularly in the
8 perivascular spaces.

9 So this is a sort of complication of
10 immune reconstitution, which can occur during
11 treatment of PML and, therefore, I think for safety
12 reasons, imaging is very important to facilitate a
13 very early detection of PML IRIS lesions on the MRI.

14 Next slide.

15 Another example how imaging can facilitate
16 a very precise lesion evolution is during the virus
17 T-cell treatment from our local cohort in the early
18 stage the flare images are able to demonstrate the
19 progression of the disease at some moment the lesion
20 volume is stabilized, and then at some moment we see
21 an improving in terms of lesion volume on the flare.

1 It's not clear what kind of lesions do
2 shrink or what the underlying pathology really is,
3 but these imaging findings in terms of resolution of
4 RT lesions or partial resolution of T-2 lesions is
5 quite conclusive, at least in our cohort.

6 Next slide.

7 And this is also demonstrated in this
8 patient very nicely showing a huge PML manifestation
9 in the posterior fossa, also with a lot of imaging
10 findings suggest the inflammation, you see at some
11 moment that the inflammatory signs, so the contrast
12 enhancement is decreasing and also the T-2 lesion
13 demonstrated here on the lateecho2 is decreasing.

14 And it's very important to understand
15 using quantitative MRI techniques, what kind of
16 pathology already shrinks on the T-2, whether this
17 is edema or whether this is really a partial
18 remyelination.

19 So therefore --

20 Next slide.

21 -- it's very important to move on to the

1 next step to use quantitative MRI techniques, in
2 particular volumetric measurements, but also MRI
3 techniques focusing on microstructural changes,
4 including -- transfer ratio and -- imaging to really
5 understand what kind of changes can show an
6 improvement on MRI, as nicely shown on the T-2 image
7 in the slide before.

8 A very nice example to further increase
9 the precise measurement of lesion progression is
10 the --

11 Next slide.

12 -- artificial-intelligence based automated
13 segmentation technique introduced by Irene Cortese's
14 group, very nicely shown here, the GC net methods
15 very nicely showing the automatic -- very precise
16 automatic segmentation of the lesion here in the
17 deep exo-cortical white matter, which is very close
18 to the manual segmentation done by an expert.

19 So this, I think, is the future we have to
20 address to very precisely document and monitor the
21 lesion burden occurring over time, and the next step

1 to understand whether or not these lesions can show
2 some neuronal repair mechanism based on
3 microstructural MRI using myelin water fraction
4 imaging or MTR.

5 Next slide.

6 To sum up, I think a multi-sequence brain
7 MRI not only facilitate a very early PML diagnosis
8 according to the -- criteria, but it's also a good
9 screening tool for high-risk patients like
10 Natalizumab MS patient, for example.

11 And MRI-based treatment monitoring in PML
12 really requires a standardized MRI acquisition
13 protocol. The increase of TT lesion burden is a
14 reliable marker in terms of disease progression.
15 The detection and the monitoring of imaging findings
16 successive of inflammation like contrast enhancement
17 is very important, not only for safety purposes, but
18 also for monitoring of disease progression and
19 partial resolution.

20 I showed you this example when the
21 inflammation went away in the case we treated the

1 patient with BK-specific T-cells.

2 Disability and decrease of patient
3 progression, like shown in the examples I showed
4 you, is quite suggestive of treatment effect;
5 however, this has to be validated in conclusion with
6 other outcome measures like CSF findings and
7 clinical findings, of course.

8 And I think the major future challenge is
9 to more precisely assess the lesion burden by
10 artificial-intelligence based automated segmentation
11 tools like shown in the slide before, but also to
12 implement quantitative MRI techniques focusing on
13 the microstructural changes suggestive of neuronal
14 repair and remyelination to understand which kind of
15 pathology really improves during treatment to better
16 understand the real pharmacal dynamic effect of
17 experimental treatment, the treatments in the
18 clinical trial setting.

19 Having said this, many thanks for your
20 kind attention.

21 Next slide.

1 And many thanks to my collaborators in
2 Hanover Medical School in particular, to my
3 colleague Thomas Siplets (sp) -- Thank you very
4 much.

5 DR. SHEIKH: Thank you, Dr. Wattjes. And
6 now I'll ask, I believe, it's Dr. Cortese who's
7 going to start the next talk.

8 DR. CORTESE: Thank you for the
9 opportunity to speak here today, and a really
10 special thank you to Virginia Sheikh for all her
11 work on this project and in leading up to this
12 workshop.

13 The talk here today is a shared
14 presentation between myself, Gina Norato and Paola
15 Cinque, and we will be presenting on behalf of our
16 working group, the members are listed here. Our
17 working group was tasked with the evaluation of the
18 potential of JCV DNA in the CSF as a biomarker for
19 PML product development. and while the working group
20 explored the role of JCV DNA more broadly and is
21 putting together a detailed report of our findings,

1 today we will really focus on the question of
2 suitability of JCV DNA as an efficacy endpoint for
3 clinical trials.

4 And I just want to make note that this
5 question is asked independently of details of a
6 specific treatment approach, which could, in itself,
7 shape how such an endpoint might need to be defined
8 and used.

9 Next slide, please.

10 As this audience knows, CSF JCV PCR has an
11 established role as a diagnostic biomarker for PML,
12 whether and how CSF JCV PCR might move beyond the
13 diagnostic biomarker, and whether quantitative
14 assessments of CSF JCV DNA might provide usable
15 information about a patient's disease course or
16 response to treatment, has not been established.

17 Next slide, please.

18 And so a question today is whether JCV DNA
19 in the CSF could also serve as a predictive
20 biomarker, defined as a biomarker that reflects the
21 likelihood of a treatment effect of a specific

1 intervention.

2 Next slide, please.

3 Conceivably, a subset of predictive
4 biomarkers might be able to very reliably predict
5 the true clinical outcome of interest. That is, how
6 a patient feels, functions or survives, and could
7 then effectively serve as a surrogate outcome
8 substituting for the true clinical outcome.

9 Validated surrogate outcomes can lead to various
10 advantages, they might simplify trial design, reduce
11 required sample size or shorten a study's duration.

12 But the bar for qualification of a
13 predictive, and certainly have a surrogate endpoint,
14 is very high.

15 So our working group set out first to
16 explore how well longitudinal measurements of JCV
17 DNA in CSF correlate with clinical outcome, and then
18 as we'll hear from my co-speakers, we explored
19 practical ways a JCV DNA endpoint might be defined
20 and applied.

21 Next slide, please.

1 Up front we need to recognize an important
2 limitation of JCV DNA measurements represented by
3 technical variability, and this is both over time
4 across studies and across laboratories. Some of the
5 most important sources of this variability stemmed
6 from changes in PCR methodology over the last
7 decades, variability in assay sensitivity over time
8 and across labs, which even today easily range from
9 10 copies per mil to some 500 copies per mil, and
10 also from a lack of common assay standards used
11 across labs.

12 So taken together, this creates a major
13 challenge in evaluating existing data, and is a
14 reason why true meta analysis is not possible.
15 So if CSF JCV DNA copy number is to be used as a
16 biomarker, some level of standardization will
17 certainly be required.

18 That said, hopefully we're still able to
19 appreciate consistent patterns in the data and
20 across patient cohorts that might inform on how CSF
21 JCV DNA can best be used as a measure of PML

1 disease.

2 Next slide, please.

3 So our working group tackled these
4 questions in two ways, first of all, by a review of
5 existing literature focusing on reports that
6 contained sufficient detail to describe the
7 relationship between quantitative CSF JCV DNA and
8 clinical outcomes.

9 Next slide, please.

10 Our second approach was a primary analysis
11 of samples submitted to a single laboratory the NIH
12 LMN CLIA Laboratory, which was under the
13 directorship of Gene Major from 1999 to 2019. In
14 this analysis we included 942 samples submitted to
15 the lab for testing between 2005 and 2019 derived
16 from 452 unique patients.

17 While the underlying disease is known for
18 most of these samples, information is otherwise
19 limited in terms of clinical course or ultimate
20 outcomes.

21 Next slide, please.

1 A subset of the samples included in this
2 database were derived from patients enrolled in the
3 NIH PML clinical cohort, patients for whom we do
4 have detailed longitudinal follow up, including
5 clinical and radiological data. Forty-eight
6 patients from this data set were analyzed, and they
7 were selected as those who were tested while the LMN
8 CLIA Lab was active.

9 Next slide.

10 Here we see it depicted more detail of
11 this cohort. On the left we see a distribution by
12 calendar year, and on the right, the case
13 distribution by underlying disease. As we will hear
14 later in this talk, we were additionally able to
15 take advantage of two validation cohorts with
16 testing performed in different centers.

17 Next slide, please.

18 Looking at the published literature, there
19 are remarkably few reports detailing longitudinal
20 quantitative JCV DNA in the CSF and its relationship
21 to clinical outcomes. Representative figures from

1 two studies are shown here. Overall, the pattern
2 that emerges is that declining CSF copy number is
3 seen in patients with clinical stabilization, but
4 not in untreated patients or those having
5 progression of PML.

6 And, similarly, a decline of CSF copy
7 numbers associated with improved disability
8 outcomes.

9 Next slide, please.

10 Analysis of the LMN CLIA database
11 specifically for the endpoint suitability question
12 allowed to appreciate the longitudinal course of JCV
13 copy number across the largest categories of
14 underlying disease in this database.

15 Although clinical outcome is not available
16 for these patients, we observed, as you see on the
17 far left, that the greatest uniformity of decline in
18 copy number was achieved among MS Natalizumab PML,
19 also associated with longer duration of follow up
20 available, which might be inferred to indicate
21 longer survival in these patients.

1 And while in the middle panel and on the
2 right panel we observe somewhat mixed copy number
3 trajectories in other major disease categories,
4 perhaps again consistent with the variable clinical
5 outcomes seen in these diseases.

6 Next slide, please.

7 Analysis of the NIH PML clinical cohort
8 for whom ultimate clinical outcome is known, shows
9 that all the patients that ultimately died, depicted
10 in red and on your left, had an increase in CSF copy
11 number over time, while about 87% of those that
12 survived had a decreased or stabilization of CSF
13 copy number over the time sampling was performed.

14 Now I'll now hand over the mic to Gina.

15 MS. NORATO: Thank you. So to further
16 investigate --

17 Oh, next slide.

18 To further investigate CSF JCV DNA as a
19 biomarker, we used this observational retrospective
20 data and identified three time points of interest,
21 the 30, 60 and 90 days, each with a 14-day window

1 around each of those time points. Individuals were
2 classified as having a decline in log 10 JCV DNA
3 copy number of either a quarter, half or full log 10
4 decline, and individuals were classified as
5 surviving greater than six months, nine months or 12
6 months, based on the survival data.

7 Next slide, please.

8 So just to give a brief overview of the
9 results, we found that survival at six months may
10 not be of particular interest. We calculated
11 six-month data -- survival data, but we are not
12 showing it for this talk. Survival was not
13 different between nine months and 12 months, so we
14 calculated the nine-month data, but it's not shown
15 here since it is redundant.

16 And there were also some futility measures
17 that we investigated, such as increases in copy
18 number, but these are not shown here for brevity.

19 Next slide, please.

20 So this demonstrates how we compiled the
21 data so all of the data can be put into,

1 essentially, a two-by-two table of whether or not
2 they survived past six months, and whether or not
3 they had a decline that was greater or less than
4 each of those specified declines, a quarter log, a
5 half log or a full log.

6 Next slide.

7 And we can see how we can develop this
8 table again for the half log 10 decline.

9 Next slide.

10 And also a full log 10 decline. And all
11 of the data will be used in this two-by-two fashion
12 to help us collect data, such as sensitivity,
13 specificity and positive and negative predictive
14 value, and also to perform formal testing using
15 Fisher's effect test.

16 Next slide, please.

17 So this is a compilation of those results
18 that existed across all those little two-by-two
19 tables, and in the NIH cohort in particular, again
20 to separate that from the validation cohorts that
21 we'll be talking about. And to briefly orient you

1 to the table, on the first column we have the time
2 points of interest, day 30, day 60, day 90, and we
3 also described baseline behavior.

4 The second column is the -- each of those
5 definitions of interest, as far as which would be
6 most useful biomarkers, so that's our quarter log,
7 half log and full log ten decline.

8 The third column is the number of
9 individuals who -- the number of individuals who had
10 data at each of those time points.

11 And then the five remaining columns
12 describe the actual results, the data, so the first
13 of those is survival among those who meet the
14 definition, this is what we call positive predictive
15 value.

16 And then we see survival among those not
17 meeting the definition, this is the inverse of
18 negative predictive value, specifically we're
19 talking about survival here, so it's the inverse.
20 And then we see sensitivity and specificity, and
21 sensitivity is those who meet the definition who

1 also survivor are a true positive rate. And
2 specificity is those who do not meet the definition
3 out of those who die, so that's the true negative
4 rate.

5 And the final column we have the P value
6 for the Fisher's Exact test, as I noted before.

7 Next slide.

8 So just to go over some of the results in
9 particular, at day 60 we can see that as we increase
10 the cutoff here as we have a higher cut off for
11 decline, we see a higher number of -- a higher
12 survival rate among those not meeting the
13 definition, or in other words, a lower negative
14 predictive value, and we also see more sensitivity.
15 So our better sensitivity is existing at the quarter
16 or 0.25 log 10 decline and in our half log 10
17 decline.

18 Next slide, please.

19 And we can also use our P value as a
20 marker for possibly predictive results here, so we
21 see low P values, which are good, at our quarter log

1 declines of both day 30 and day 60.

2 Next slide, please.

3 And we can see across those results, high
4 positive predictive value, as noted 89% and 100%. A
5 low survival rate in those groups, 43% and 46%, and
6 decently high sensitivity and specificity.

7 Next slide, please.

8 And again, we can see similar strong
9 results also for the half log greater than --
10 greater than or equal to half log 10 decline, again
11 with very high positive predictive value, somewhat
12 worse survival predictability among those not
13 meeting the definition, lower sensitivity, somewhat,
14 but still decent, and very good specificity.

15 Next slide, please.

16 And at day 90 we can see a similar pattern
17 of results; however, overall these are somewhat less
18 convincing than at the other time points.

19 Next slide, please.

20 So broadly we summarize our NIH findings as the
21 behavior at 30 and 60 days for this biomarker may be

1 the most predictive of survival, and also in that
2 way, the quarter or half log 10 declines might be
3 the most predictive.

4 Now I'll hand it over to Dr. Cinque.

5 DR. CINQUE: Thank you, Gina. Thank you
6 Irene, and also to the organizer for inviting me.
7 To present some data based on previous findings
8 given by Gina, I'm going to continue with showing
9 the data of the value of the reduction of JCV DNA in
10 CSF for predicting survival in two different
11 cohorts.

12 And next slide. please.

13 So these two cohorts were one from Milano
14 at San Raffaele Hospital, and Multicenter cohort
15 that was including patients put together by
16 Martin-Blondel in Toulouse and receiving I7 cohort
17 PD-1 blockers. And these are the two -- what we
18 call the two validation cohorts.

19 Next slide, please.

20 So this is a representation of the cases
21 in the cohort of Milan, including 73 patients with

1 longitudinal evaluation of CSF samples, 46 had two
2 samples taken 30 days apart, and 39 had samples
3 taken at 60 days apart.

4 So as we see here, the timeframe is quite
5 large. We started collecting samples in 1992 and we
6 ended two years ago in 2019. So we have a
7 distribution of cases with a lot of cases with HIV
8 infections in the first years of the survey, and we
9 can see on the right part of the slide that most of
10 the patients actually were HIV, and most of them
11 were observed after the introduction of
12 anti-retroviral treatment.

13 But we have a number of patients with HIV
14 infection in PML that were observed before 1996,
15 then we have the other patients that we can see here
16 belonging to patients with idiopathic
17 lymphocytopenia, MS, primary immunodeficiency, blood
18 neoplasms or other diseases.

19 So one simple connection to the PCR assay,
20 we have used as the samples, the same assay that was
21 a real time PCR --with a low volume detection of 100

1 copies for ML.

2 The next slide, please.

3 So here is a simplified table that shows
4 the predictive value of a reduction of either or .25
5 or 0.5 log, JCV DNA in CSF either at 30 or 60 days,
6 and the predictive value for survival, and the
7 negative predictive value or disease and sensitivity
8 and specificity, and also we evaluated the value of
9 the JCV DNA level at the baseline samples or
10 predicting survival.

11 The next one, please.

12 And we can see that the best predictive
13 values -- positive predictive values and specificity
14 actually were observed at base 16 at -- looking at
15 the decline of 0.25 or 0.5 between two CSF samples.
16 So we had a predictive value of 62 and 87,
17 respectively, and a quite good specificity.

18 So this is meaning that if you -- if we
19 see a decline of JCV DNA at 60 days, this patient is
20 likely to survive, but other patients will survive
21 despite not reducing their DNA in CSF.

1 The next one, please.

2 This is the second cohort, it includes 56
3 patients, and 21 and 20, respectively, had a
4 follow-up sample at 30 and 60 days, and these
5 patients were included 31 patients who would be
6 receiving a recombinant JURMI7 --7, and 22 were
7 treated with anti PD-1 -- plaques.

8 So this is a multicenter cohort, so the
9 PCR assay used was different in different center,
10 but each patients were evaluated at the same center
11 in the same laboratory with the same assay, so the
12 case distribution by calendar year, you can see here
13 that we go from 2010 to 2020.

14 And most of the cases were observed during
15 the last years, and the majority of the patients
16 belonging to this cohort were patients with
17 hematological malignancies or HIV infections
18 receiving -- but we have quite a significant number
19 of patients with combined immunodeficiency or
20 idiopathic CD-4 deficit.

21 So the next one.

1 Again, so this was the same representation
2 as before -- and I think there is another one --

3 Next one, please.

4 Yes, so that is highlighted highlighting
5 the data about predictive -- positive predictive
6 value for survival that was 90% and good specificity
7 at day 60 for both the 0.25 lot decline and 0.5 lot
8 decline in this cohort as well.

9 So the next one.

10 And this slide is one that summarizes the
11 value for predictive value for survival, negative
12 predictive value, inverse of these calculations,
13 sensitivity and specificity in the NIH cohort, the
14 Milano cohort and in the Multicenter cohort.

15 And if we look at sensitivity and
16 specificity, we see the specificity was high in all
17 the three cohorts, with the highest value found in
18 the NIH cohort. And sensitivity was -- for
19 sensitivity we saw values that were more different
20 between the three different cohorts and were ranging
21 from 29 to 71%, with the lowest and the highest

1 values in the NIH cohort for, respectively, 0.5 and
2 0.25 log decline.

3 So these differences may be due to a
4 number of reasons that we may want to discuss, and
5 these are including, of course, the PCR assay that
6 was used, the characteristics of the cohorts, and
7 also the timing of the CSF sampling related to the
8 onset of disease and also different interventions
9 that were applied to patients included in these
10 cohorts.

11 So I'd like to conclude with the next
12 slide.

13 And we can see that both 0.25 and 0.5 log
14 JCV DNA copy numbers in CSF declines at 60 days
15 predictive for survival at 12 months.

16 On the other hand, the baseline CSM JCV
17 DNA copy number was not related strongly to
18 survival, and these data were sort of reduced in the
19 validation cohorts that -- supporting for these
20 initial finding that was observed in the NIH cohort,
21 and of course differing cohorts may account for

1 differences in values that we found by calculating
2 survival.

3 And I think there is a last, final slide.
4 Yes.

5 And I'd like to thank you on behalf of the
6 whole group, all the laboratories and people in the
7 lab that did the PCR assay and all our colleagues at
8 NIH, at San Raffaele Hospital, and all the
9 collaboration for the multi-centric PD-1 I7 cohorts.
10 And thank you for your attention.

11 DR. HARRINGTON: Okay. Well, thank you
12 all. We will now move to the panel discussion. So,
13 first of all, I'd like to thank all of this
14 morning's speakers for the excellent presentations,
15 that certainly helped to set the stage for what I
16 think will be a very interesting and important panel
17 discussion. I just want to make sure everybody can
18 hear me okay. Looks like we're good.

19 So my name is Patrick Harrington, and I am
20 a Senior Clinical Biology Reviewer in the Division
21 of Anti-virals at FDA CDER. Our goal over the next

1 45 minutes or so is to dive a bit deeper into the
2 topic of potential PML endpoints in clinical trials,
3 and of course we're focusing on efficacy endpoints
4 specifically.

5 And to discuss this topic, we have a very
6 distinguished panel of PML experts representing
7 academia, government and industry, and I'm just
8 going to introduce very briefly each of the panel
9 members, so that we can spend as much time as
10 possible on the task at hand.

11 Members of the audience can find more
12 details about each panelist on the website for this
13 meeting, so please feel free to look over the bios
14 and disclosures and all those other materials.

15 So on the panel, hopefully, all the
16 panelists have their cameras on and their mics
17 ready. And so I'll just introduce each of the
18 panelists in no particular order.

19 So first we have Dr. Igor Koralnik, who is
20 the Archibald Church Professor of Neurology and the
21 Chief of the Division of Neuro Infectious Diseases

1 and Global Neurology at Northwestern University; we
2 have Dr. Roland Martin, who is a professor and head
3 of the Multiple Sclerosis Center at the University
4 Hospital Zurich in Switzerland; we have Dr. Clemens
5 Warnke, who is a consultant of neurology at the
6 Department of Neurology, University Hospital of
7 Cologne in Germany.

8 We have Dr. Serena Spudich, who is the
9 Gilbert Glazer Professor of Neurology and the Chief
10 of the Division of Neurological Infections and
11 Global Neurology at Yale University; we have
12 Dr. Avindra Nath, who is the Clinical Director at
13 the U.S. National Institute of Neurological
14 Disorders and Stroke at the NIH; we have
15 Dr. Christina Marra, who is a Professor Emeritus and
16 Vice Chair for Academic Affairs in Neurology at the
17 University of Washington in Seattle.

18 And finally, we have Dr. Jennifer Lyons,
19 who's a Senior Medical Director in Global Medical
20 Safety at Biogen.

21 Well, thank you all for being here. So

1 does everybody have their -- okay, so we've got our
2 cameras on ready to start our discussion.

3 Again, thank you all for being here. I
4 will also note that the previous speakers are
5 available on standby to answer any clarifying
6 questions on their presentations that the panelists
7 may have. Members of the audience can also use the
8 Q and A function to ask questions of the panelists,
9 and we will collect those questions and try to get
10 as many answered as we can.

11 I see there are already a few questions
12 that we will hopefully address. The panelists can
13 use the chat to communicate with each other during
14 the session so, you know, to decide who might be
15 able to answer the questions that are being asked,
16 but the audience comments and questions in the chat
17 will not be collated for this panel discussion, so
18 if you really have a burning question, use the Q and
19 A function for that.

20 So I'm going to start our discussion with
21 probably the broadest and most challenging question,

1 and I'm hoping that each of you on the panel will be
2 willing to provide a response, and when you do
3 respond, please keep it to just one or two minutes
4 to allow time for discussion.

5 So, as we all know, it's important that
6 efficacy endpoints in clinical trials of
7 investigational PML therapies really, like any
8 therapies, are adequately designed to determine if
9 the investigational products are effective and
10 provide clinically meaningful benefits to patients.

11 The primary efficacy endpoints in PML
12 clinical trials may be based on a direct and clear
13 clinical outcome, such as survival or a reliable
14 measure of disability, as has been discussed by the
15 previous speakers.

16 A primary efficacy endpoint may also be
17 based on a laboratory marker, which we would call a
18 surrogate marker, such as the JCV DNA levels in CSF,
19 also discussed by this morning's speakers. But that
20 surrogate measure can only be used as a primary
21 endpoint if that laboratory marker is reasonably

1 expected to inform a clinical outcome.

2 So the question is, based on your
3 experience and your expertise and your assessment of
4 the data discussed by the previous speakers, which
5 efficacy endpoints do you feel are most clinically
6 relevant and feasible for clinical trials evaluating
7 PML treatments.

8 And I'd really like, if at all possible,
9 please specifically comment on what you think might
10 be the single most appropriate and feasible primary
11 efficacy endpoint and discuss why.

12 And so if the panelists want to raise your
13 hands, I will take volunteers to begin addressing
14 this question, otherwise, I will just start calling
15 on people. Do I have any volunteers for this yet?

16 DR. MARRA: I'll volunteer.

17 DR. HARRINGTON: Thank you, Dr. Marra.

18 DR. MARRA: First of all, I want to say
19 that I've never seen you in a tie before.

20 DR. HARRINGTON: It happens sometimes.

21 DR. MARRA: You look great. You know, I

1 don't know that I can answer this question, which is
2 why I decided to go first. I think survival is the
3 most objective, but people have pointed out that in
4 the MS population, that probably isn't a reasonable
5 outcome. But, again, people in the chat have talked
6 about the different groups of people who get PML,
7 and I think we need -- we probably can't lump them
8 all together.

9 So for whoever showed that nice graph of,
10 you know, the half of people who don't do well, for
11 them, survival would be a great outcome. So I think
12 we can't lump everybody together. Survival is the
13 most objective. I think disability is a really
14 important outcome, and that we haven't done enough
15 for that.

16 I don't think that following neuro exam or
17 following volume of lesions is probably going to be
18 that useful because those lag behind what you're
19 eventually going to get, and I think that the PCR is
20 very compelling, although I think that the numbers
21 are really small, I was pointing out that the

1 confidence intervals, even around those hundred
2 percent estimates, are going to be really wide.

3 And the thing I would pitch to the rest of
4 the panel, because I'm really interested in what
5 they have to say, is how we take into account immune
6 reconstitution. I think a bunch of us are on a
7 Delphi Panel that's looking at how to identify
8 immune reconstitution, and one of the things that's
9 come up there is that can you still have detectable
10 pathogen and have IRIS at the same time.

11 And I think that's a really important
12 question that we're going to have to address, maybe
13 with a DNA outcome it isn't as difficult, but I
14 still think that IRIS is going to be the real
15 confounder here, I mean, that's -- I think that's
16 why people, obviously, with MS do so much better.

17 So I'm really interested in what the panel
18 has to say about taking into account IRIS and what
19 kind of disability outcomes they think would be
20 good, and how they feel about the PCR in general.

21 DR. HARRINGTON: Okay. Thank you very

1 much, Dr. Marra.

2 Dr. Koralnik, do you have any comments on
3 your favorite primary endpoint for a PML clinical
4 trial?

5 DR. KORALNIK: Well, first I want to
6 congratulate all the speakers and all the organizers
7 for putting this workshop together. An amazing
8 amount of work that's going to be very useful, you
9 know, going forward.

10 I agree with Christina in terms of the
11 major endpoint being survival and disability, the
12 issue is that there is such variability in survival,
13 as we have seen in the different underlying
14 pathologies that lead to PML that you need to have a
15 very large group of patients, and so you can't just
16 lump them all together, you need to differentiate
17 those with HIV and those with underlying malignancy.

18 I think it's important to realize that the
19 length of follow up needs to be, you know, probably
20 more than just 30 or 60 days, because we've seen
21 that a lot of patients end up having burnt out PML

1 and will be able to stabilize the disease in time.

2 And it's also important to define which
3 medication, you know, you're giving to the patients.
4 If you're giving something that is immune active
5 like Natalizumab or Nivolumab, for example, that
6 will be able to reinvigorate the T-cell against JC
7 virus, then you need to also measure an endpoint
8 which would be the T-cell function of these
9 patients.

10 I hope that I answered the question
11 succinctly.

12 DR. HARRINGTON: I think we'll probably
13 get back to you. I'm sensing a theme already that
14 there may not be one-size-fits-all, but we'll
15 continue on the question as far as, you know, what
16 you think are the most important primary endpoints
17 for PML trials in general, and then maybe we'll
18 focus on specific sub groups after that.

19 So maybe we'll go to Dr. Spudich.

20 DR. SPUDICH: Sure. And I'm going to
21 echo, you know, this is such a disease which is

1 always a terrible diagnosis to give a patient, and
2 I'm so glad that we're doing this meeting because I
3 think we just -- it's absolutely imperative that
4 these clinical trials can be designed.

5 You know, my thought is actually I think
6 neuro imaging is quite valuable in the patients that
7 I followed, and I'll say that I've never been
8 involved in clinical trials for PML, I've only taken
9 care of patients with PML clinically.

10 But I do think that it's very helpful to
11 follow neuro imaging, partly because it's incredibly
12 revealing about the IRIS phase, and I think it's one
13 of the things that can help sort of us understand
14 the timing of IRIS, and also prognosticate when you
15 see IRIS on your imaging, which sometimes is
16 difficult to assess clinically when you're looking
17 at a patient.

18 It can be informative, both in terms of if
19 the patient's doing poorly at that time, that may
20 not mean they're going to be doing poorly six weeks
21 later, and it also -- you know, I think we still

1 have an understanding of whether IRIS actually helps
2 with long-term outcomes.

3 So when I'm taking care of a patient, I do
4 use neuro imaging as an endpoint, but usually not at
5 the six-week time point, more sort of at the three
6 month time point or so.

7 The other thing I'll say is that, you
8 know, even making things more complicated, I don't
9 think looking at a patient who has HIV who's on
10 anti-retroviral therapy, who has PML, who's been on
11 stable therapy and gets PML, can actually be lumped
12 with someone who has a new diagnosis of HIV and is
13 starting therapy for the first time.

14 In my experience those patients often do a
15 lot better in terms of their PML prognosis than
16 someone who, unfortunately, gets PML when they have
17 well-treated HIV where you have less to do for
18 immune reconstitution.

19 But, you know, I think that the -- I'm
20 very interested in the CSF biomarkers, and I think
21 that thinking about JC virus DNA, as well as

1 potentially other markers of injury in the CNS might
2 be important, but I think those are still
3 exploratory.

4 DR. HARRINGTON: Okay. Thank you.

5 Dr. Martin, do you have some comments on
6 this?

7 DR. MARTIN: Yeah. And also thank you for
8 having me, and I think a lot of interesting and
9 important things have already been said. I believe
10 that probably one cannot lump all the different
11 therapies and all the aims together.

12 If you had a trial that is more
13 exploratory with a new approach and tries to
14 establish efficacy on a surrogate with more
15 immunology, more biology and imaging, but is not
16 definitive on the long term in the clinical outcome,
17 then probably the trial has to include slightly
18 different outcome measures or sets of outcome
19 measures than a trial that would be considered
20 definitive proof of efficacy on the most important
21 outcome, which is long-term survival, elimination of

1 the virus, and stabilization of disability or even
2 improvement of quality of life of neurological
3 exams.

4 So I think the type of trial and the
5 approach, and whether it's more exploratory or it's
6 already getting close to providing approval data, is
7 a very important consideration, but the outcomes, to
8 me, have to be combinations of markers that depict
9 the biology of the disease, as well as imaging and
10 clinical data.

11 DR. HARRINGTON: Okay. Interesting. So a
12 combination endpoint approach. Okay. We might come
13 back to that. So let's see if Dr. Lyons has any
14 thoughts on this question.

15 DR. LYONS: Yeah, sure. Thanks. And I
16 would also like to echo what everyone has said about
17 how well put together this conference is, and thank
18 you for inviting me to be a part of it.

19 I would also just mention that, you know,
20 what everyone has said, I agree with that this
21 one-size-fits-all approach, it poses a challenge

1 because, as Dr. Smith had noted, there are very
2 different outcomes based on what the baseline
3 disease is, and so for that, the fact in and of
4 itself, it makes it very difficult to have a single
5 outcome measure that would be useful for every
6 population.

7 However, if you separate the populations,
8 then it becomes a very difficult objective to enroll
9 patients in your trial. So I think that is just one
10 challenge at the very beginning that has to be sort
11 of sorted out. That said, in an ideal world, I do
12 like the idea of having a PML-specific clinical
13 endpoint, a scale that could take into account the
14 common findings that are seen with PML and could be
15 used as marker for improvement.

16 Again, because in some populations
17 survival is likely, but disability is actually where
18 the long-term issues arise. I also -- I like the
19 idea of MRI endpoints; however, I think for patients
20 who have severe disease, it becomes a little bit of
21 a -- it could become a little bit of a logistic

1 issue if you are trying to measure -- trying to do
2 volumetric analysis and you have a patient who
3 actually can't tolerate an MRI, then that could pose
4 logistical challenges just to the study in and of
5 itself.

6 And then for the CSF biomarker, that is
7 also a -- you know, it's a great idea; however,
8 again, noting that there are differences in the
9 populations, so one of the things that I have seen,
10 you know, when I was treating patients was that CSF
11 viral load in HIV, it can be different from CSF
12 viral load in, say, a patient who has an underlying
13 disease of MS.

14 And if you have variability in the
15 quantity at baseline of their CSF viral load, then I
16 think that would potentially pose a challenge in
17 using that as an outcome's biomarker, again, if
18 you're pooling populations.

19 So my favorite in an ideal world, and I
20 know it doesn't exist yet, would probably be to --
21 for us to develop a PML-specific -- or a PML-quasi

1 specific -- as specific as we can be with the
2 variability in clinical manifestations of PML, but a
3 clinical functional outcomes score.

4 DR. HARRINGTON: Okay. Thank you.

5 Dr. Warnke, could you comment on the
6 question?

7 DR. WARNKE: Thank you very much, and
8 thanks also for inviting me.

9 It's a very interesting discussion, and I
10 like to try and argue to choose a surrogate
11 biomarker for the key clinical trial outcome
12 measure. And what I was wondering, we didn't
13 discuss so much clearance of JC DNA from CSF, so no
14 copies at a certain time point as possible
15 biomarker, I think this is related to maybe lack of
16 sufficient data on this.

17 But let's say at a time point of 12 or 24
18 weeks, this could be a good surrogate of that the
19 infection is under control, and also the MRI might
20 also aid in this respect, so no new lesion at a
21 certain time point could be a nice additional

1 endpoint. Maybe these two together are the time
2 points or the outcome measures I would look at,
3 because this is what I clinically would also do in
4 my single patients.

5 DR. HARRINGTON: Okay. Thank you very
6 much.

7 And, finally, Dr. Nath.

8 DR. NATH: Thanks very much. First of all
9 I want to start by thanking all the organizers and
10 speakers, I know they put in a huge amount of
11 effort, they've been working on it for over a year
12 and trying to put all this together. And I
13 particularly want to thank Dr. Sheikh for her
14 leadership, without which this would never have
15 happened.

16 So now with regards to endpoints, I think
17 one consensus seems to be emerging, that there is no
18 one single clear winner here, each of these
19 potential endpoints have their drawbacks. And the
20 idea also seems to be emerging that maybe some sort
21 of a composite endpoint may be worthy of

1 consideration.

2 So, you know, our usual fallback is to
3 consider clinical endpoints in a neurological
4 disease, but the problem with that is that as soon
5 as you do the sample size calculations, the study
6 becomes so huge that it will be almost impossible to
7 conduct.

8 So then your next best choice biomarkers,
9 the problem with the biomarkers are that they aren't
10 really very well standardized, there's lots of
11 variability and they vary from investigator to
12 investigator and institution to institution.

13 So it's a viral disease, one would think
14 that measuring the virus should be the answer, but,
15 as Paolo showed that -- you know, the variability
16 between regions and labs is so much that it
17 becomes -- even within a single lab the variability
18 is enough to whereby a single end point, it becomes
19 hard.

20 However, I think what is critical is that
21 in the context of whatever clinical study we do, we

1 need to try and standardize these biomarkers because
2 ultimately that's the only way that we'll be able to
3 do small sample size patients and really test a
4 large number of compounds or drugs or antibodies or
5 whatever it might be -- therapeutic agents might be.

6 And without that, I don't think we're
7 going to make any progress. So I think we need to
8 put a huge amount of effort and develop a reliable
9 biomarker that is reproducible, and unless we have
10 surrogate endpoints, I don't think this field is
11 going to move too much further.

12 DR. HARRINGTON: Okay. Well, thank you
13 all for the comments. I want to dive a little bit
14 deeper into the JCV DNA potential endpoint, and just
15 throw in a couple comments just because I was on
16 that working group, so I'm pretty familiar with the
17 data, and maybe some of the previous speakers can
18 come in and expand that discussion as well.

19 But, you know, one of the things that we
20 considered with the JCV DNA levels in CSF as a
21 potential endpoint is, of course, what many of you

1 have mentioned, Dr. Lyons in particular mentioned
2 that, you know, depending on the underlying disease,
3 the -- you know, the baseline level could be quite
4 variable, which creates a challenge with using that
5 as a surrogate measure.

6 And that's part of the reason why we
7 focused on not -- not the absolute level, but the
8 change from baseline. So we're looking at the
9 change from baseline as an indicator of how the
10 patient might be responding virologically.

11 And I wonder if others on the panel can
12 kind of comment on whether that change from baseline
13 value, you know, which can be used regardless of
14 your baseline level as long as it's a quantitative
15 measure, does that help to make that a more widely
16 applicable surrogate marker that could be used for,
17 you know, the broad PML patient population.

18 Again, bringing up the issue that if you
19 start dividing up everybody into smaller groups,
20 that they become almost too small to conduct a trial
21 or it just becomes really challenging to power a

1 trial for efficacy.

2 So does anybody have any thoughts on that
3 as far as just a specific change from baseline to
4 say, you know, day 60 or, you know, a particular
5 time point as a potential measure of how the patient
6 is responding.

7 DR. MARRA: Well, even though -- I asked
8 this question in the chat -- even though baseline
9 DNA doesn't seem to be a marker, it seems to me that
10 you still would need to take into account baseline
11 value because 25% of the person starts with 100, and
12 25% of the person starts at a million strikes me as
13 sort of a different situation.

14 I don't know that you can lump -- again, I
15 know we don't want to lump everybody together so we
16 have greater power, but I would like to see an
17 analysis of that that took into account people with
18 low numbers and people with high numbers.

19 DR. KORALNIK: So, Patrick, if I may?

20 I think we also have to consider where the
21 patient is in their disease when they are enrolled

1 in the trial. Because, you know, diagnosing PML is
2 not easy for people who don't see that every day in
3 their clinic or on the ward, and so, you know, on
4 more than 100 patients where we had exactly the time
5 of symptom onset and time of diagnosis, the medium
6 delay to diagnosis was two and a half months, right.

7 So when you have somebody who's already
8 advanced when they are diagnosed, then they may not
9 have, you know, a high level of JCV DNA in the CSF,
10 and they may already have advanced disease. So it's
11 difficult to measure, you know, a difference from
12 baseline if somebody is already severely affected
13 clinically to the point that the family is
14 considering even going to hospice rather than to
15 going to a clinical trial and follow up.

16 Plus, it's not trivial to do serial LPs,
17 you know, in those patients, especially when they're
18 severely affected. So to rely too much on the
19 change in DNA value of a time may be putting
20 ourselves in a corner, which is going to be
21 difficult to enroll patients, right, in those

1 trials, yeah.

2 DR. HARRINGTON: Okay. Thank you for your
3 comments.

4 DR. MARTIN: Patrick, I have one comment.
5 One thing that was alluded to a little bit, but
6 which I think is also important, what kind of
7 treatment one is examining.

8 So, for example, an antiviral monochrome
9 antibody that would not change the host's immune
10 responsiveness to the virus, one would probably need
11 to look at different things, and if you have a
12 treatment where you reinvigorate or reactivate the
13 immune system that was not fully functioning before,
14 and really clearly have something in the trial that
15 considered that.

16 DR. HARRINGTON: Okay. I'm going to
17 let -- Dr. Clifford has his hand raised, if he wants
18 to ask a question.

19 Go ahead, Dr. Clifford.

20 DR. CLIFFORD: Thanks. You know, as I
21 reflected, really wonderful comments about the

1 selection of these markers, but as a gray-haired
2 clinician, I'm increasingly backing off into saying
3 what's the long-term value that we can get out of a
4 trial, and I think that it may be that we will want
5 to think about a delayed final outcome sort of
6 assessment as the primary value that we place on --
7 on a planned intervention.

8 Because there's so much noise in all of
9 the issues of, you know, staging the patient
10 initially; how much virus we're dealing with; how
11 much of the brain is already damaged.

12 The change and the final outcome in the
13 clinical status after the dust is settled, which
14 means, I think, nine months or longer into the
15 disease, because we know that it's going to take
16 some months for the virus to be controlled.

17 And that the immune reconstitution
18 response goes on for at least six months, and you
19 can see the functional improvement in the
20 Natalizumab patients in the second six months of
21 follow up after the disease.

1 And so, you know, how much permanent
2 damage is done by the IRIS, you know, is there a
3 balance of stimulating too much IRIS or too little,
4 all of those things are going to be part of a
5 successful therapy, and so I would -- I would
6 encourage our field -- and I'm guilty, too, I want
7 to know in the first three months if I'm on the
8 right track.

9 But as I said, this is a disease where you
10 may only have one shot per patient, and we should
11 make smart trials to give patients a good
12 opportunity for therapy.

13 But I think maybe we ought to settle back
14 and just say, you know, we have to be satisfied,
15 we're going to have to compare the final outcome and
16 how well we do in the end. Because at an interim
17 point, we're not going to be able to act on
18 effectively for that patient.

19 So I just would put that thought into the
20 consideration of when you want your primary outcome,
21 maybe we're struggling to have it too early, and

1 that's just not practical for a disease of this
2 kind.

3 DR. HARRINGTON: And just to clarify, when
4 you say your primary outcome later on at six or nine
5 months, you're talking about survival or disability?

6 DR. CLIFFORD: Percentage of loss of
7 function that has accrued in the course of living
8 through this disease and surviving it. So I think
9 that's very important, but, you know, because we're
10 starting with very different baselines, the ultimate
11 outcome, short of survival --

12 I mean, we all -- we want to have our
13 patients, but we also want to prevent as much
14 disability as we can, and whether the disability is
15 caused by PML or by the virus or by IRIS or by side
16 issues that we've brought up by some powerful
17 therapy that, you know, both gave us an immune
18 system, but also damaged our patients in the
19 process, you know, the ultimate integration of what
20 the outcome is is really important.

21 And I would say maybe this field has tried

1 to have quick answers that are possible in diseases
2 like HIV where you can see viral loads in
3 correlations with outcomes, but maybe it's just too
4 much to ask for this disease.

5 DR. HARRINGTON: All right. Thank you.
6 There are a bunch of questions about, you know,
7 what's the impact of baseline JCV DNA levels, for
8 example, or other baseline factors, and whether for
9 the surrogate marker, for example, if you stratify
10 patients by their baseline disease, do you lose that
11 potential association with clinical outcomes.

12 And I wonder if one of the earlier
13 speakers would comment on that.

14 And I see Paola Cinque has her hand raise,
15 maybe she could answer that and ask her question at
16 the same time, if that's possible.

17 Dr. Cinque?

18 DR. CINQUE: Yes. Well, I was interested
19 on the issue of the -- virus to your answer that you
20 raise, and also some of the panelists, and because
21 as you anticipated, it's very difficult in clinical

1 practice to identify patterns among patients because
2 it looks like every individual patient has his own
3 kinetics or trajectories.

4 So for clinical trials actually it is
5 really difficult to have a glioses an endpoint
6 because the clearance is the ultimate goal, I agree,
7 because this is a viral disease for remission, but
8 then it might be reached after maybe six or nine
9 months, and there's also -- Igor was underlined that
10 was very important, we don't know at what stage of
11 disease we get patient for the first time, so we
12 don't know actually the baseline -- objectively.

13 And I'd also like to make a very short
14 comment to link the CSF finding to MRI, because I do
15 believe MRI is fantastic now for conditions like --
16 where CSF examination is a bit insensitive, although
17 our experience that was quite proven over time, is
18 that the follow up -- the changes in MRI
19 longitudinally occur with some delay after clinical
20 improvements and viral declines.

21 There may be one exception, that is when

1 we have an IRIS, so the viral load is maybe already
2 in downhill and MRI is more real time, and I think
3 this is also important. So it seems like in our
4 experience that clinical changes and CSF changes go
5 parallel, and MRI changes show up a bit later. And
6 I don't know whether you have the same experience
7 with that.

8 DR. HARRINGTON: Go ahead, Dr. Spudich.

9 DR. SPUDICH: You know, we haven't talked
10 about, I don't think today, is whether or not
11 following systemic immune parameters in combination
12 is predictive. And, you know, we've talked about
13 IRIS as being a negative thing, but of course the
14 positive immune reconstitution that we've seen when
15 people either stop their immunosuppressants or they
16 have an improvement in their HIV control, for
17 example.

18 And, you know, I think that conceptually I
19 think of that as being predictive of outcome, but I
20 don't know if that's being shown to be predictive of
21 outcome, and so should some sort of systemic immune

1 monitoring be part of an outcome that one's
2 carefully following to assess efficacy overall for
3 PML.

4 DR. HARRINGTON: All right. Dr. Nath, did
5 you have a comment about that? I noticed your
6 expression.

7 DR. NATH: No, no, I was distracted a bit.

8 DR. HARRINGTON: Oh, sorry.

9 DR. NATH: I think the points are made,
10 you know, it's true, I think the clinical endpoints
11 always -- and it's very hard to argue against them,
12 and that's what affects the patient's ultimate
13 outcome. And I do agree that, you know, things --
14 course and trajectory is going to differ from
15 patient to patient, and that it's going to take a
16 while before you know the ultimate answer.

17 And I think because of those
18 variabilities, the problem with that is that when we
19 did the sample size calculation, and maybe -- exact
20 numbers here, it just seemed like the sample size
21 was so large, you needed like 200 patients or

1 something of that nature, that you'd never be able
2 to do the clinical trial, you know.

3 And it doesn't matter what kind of agent
4 you're going to use, I think you're going to run
5 across those kinds of problems. So you need some
6 kind of composite whereby you've got some biomarkers
7 to go with it.

8 As I mentioned earlier, despite the
9 drawbacks of all the biomarkers, if you have good
10 biomarkers, you can decrease the sample size. So
11 you have to look at that aspect, it has to be
12 taken -- I mean, into account. You may have the
13 best wish list, but the practicality of how to do
14 these studies is going to be important.

15 And if you have a very large study, then
16 you're going to be able to study only one compound
17 every few years.

18 So we want to study a large number of
19 these things and multiple candidates simultaneously,
20 so somehow we need to factor in how we're going to
21 decrease the sample size and yet study various

1 agents.

2 And we can't just be doing exploratory
3 studies on five patients and ten patients here and
4 make very little headway, you know.

5 DR. HARRINGTON: Thank you. Those are
6 excellent points. And that's really why we work so
7 hard to try to see if, you know, there is a
8 surrogate marker out there that, you know, would
9 potentially reduce the need for a certain sample
10 size that just becomes not feasible for PML.

11 I'm going to let Dr. Cortese comment. She
12 has her hand raised.

13 DR. CORTESE: Thanks. Hi. I just wanted
14 to follow up on some of the comments that were made,
15 and I wanted to add that surrogate outcomes also
16 have another important value, which is by shortening
17 the duration of trial participation, it also
18 increases acceptability for the patients. And so it
19 increases a very real problem in trials in a rapidly
20 progressive disease where patients maybe have little
21 confidence that they're getting better or that

1 they're going to survive, that it helps to retain
2 them till the end of the study.

3 And so if we were able to identify some
4 sort of a surrogate that could reliably -- and this
5 would obviously have to be validated, and we have to
6 prove that it actually does predict the ultimate
7 true clinical endpoint, but it might make it so that
8 actually running trials is more feasible and
9 practical, in addition to possibly reducing sample
10 sizes.

11 The other thing I just wanted to mention
12 responding to Serena and Roland earlier about
13 immunological outcomes, I mean, these are obviously
14 incredibly important, but it depends, you know, on
15 the treatment intervention. So an immune -- sort of
16 way to measure immune reconstitution and achievement
17 of immune reconstitution probably is more or less
18 valuable depending on the intervention that's being
19 used.

20 So it's kind of difficult to speak sort of
21 agnostically without an actual treatment in mind,

1 but, obviously, you know, that does play a role in
2 which endpoint is chosen.

3 DR. HARRINGTON: All right. Thank you.
4 Dr. Martin, do you have a comment?

5 DR. MARTIN: No, you just reiterated what
6 I tried to say before, of course the mechanism of
7 the treatment is very important.

8 And also along Dr. Spudich's comments,
9 it's also very important to consider what kind of
10 immunocompromised the patient has, a
11 Natalizumab-treated MS patient is a typical example,
12 they are fully immunocompetent, they are always able
13 to deal with JCV, their immune cells just don't
14 enter the compartment where they're needed.

15 So you have a disease where just taking
16 that block away will usually get rid of PML, and
17 then you have a CD-4 lymphopenia patient or somebody
18 who has received antiCD20 and is immunocompromised
19 for quite some time or for a longer period of time,
20 so in each of these you need to consider exactly
21 what the immunological compromise or which assay to

1 use to text for what your drug does and what the
2 patient's problem is.

3 And I was just thinking along Avi's and
4 Irene's comments also for shorter trials, PML is so
5 heterogenous with all the facets that you have
6 mentioned and shown, that one always wonders
7 whether --

8 I don't know whether you know Nicholas
9 Shock from Squibs who advocates one-patient trials,
10 so taking individuals are very well defined where
11 one characterizes all this in a single individual
12 and tries an intervention and documents again in
13 great deal what's going to happen through surrogates
14 and imaging to viral load to immunology, and then
15 draws conclusions from that.

16 So there's an interesting nature paper
17 from him positioning this concept, and it would be
18 for -- at least for the exploratory trials that he
19 wants to conduct many, would be something worth
20 considering.

21 DR. HARRINGTON: Okay. We can maybe

1 tackle that last part of your comments in one of the
2 later panel discussions about clinical trial design
3 in general. But, you know, just here we just really
4 want to focus on the specific endpoints.

5 And, Dr. Berger. you have your hand
6 raised?

7 DR. BERGER: I do. And perhaps these
8 comments are best for later in the afternoon when we
9 talk about clinical trial design. But I think that
10 as Roland mentioned, the heterogeneity -- as all the
11 speakers have mentioned -- the heterogeneity of this
12 illness makes it extraordinarily difficult to design
13 a meaningful clinical trial. And the sample sizes
14 are going to be enormous.

15 Recall that all the studies that David
16 mentioned earlier this morning had difficulty
17 recruiting even small numbers of patients to them.
18 So the exploratory study is the way to go and to
19 have as homogeneous a population as possible;
20 therefore, you might consider doing a study in just
21 individuals with underlying hematologic disease with

1 PML where you know that the outcome is going to be
2 vested with lamentable results and that, you know,
3 the study would be -- would likely give you some
4 answers.

5 The other thing, and I agree with Roland
6 that, you know, these small studies, maybe even
7 one-patient studies, where people are extremely well
8 characterized may be a way to go with -- in terms of
9 the exploratory studies. And the biomarkers like
10 are being developed in MS may turn out to be very
11 important, things like neural filament light chain
12 or GFAP, may be very helpful for us in determining
13 whether or not people are seeing response.

14 And then one last comment I'd make, we
15 certainly see people who still have JC virus
16 detectable in their spinal fluid, yet have done
17 beautifully and they're long-term survivors, so I'm
18 not sure that, you know, trying to eliminate the
19 virus entirely is going to be a likely outcome for
20 us. It may be that we can never do that. It might
21 be just like the herpes viruses, you know, you're

1 just never going to get rid of it in its entirety.

2 So those are the comments I had with
3 respect to this morning.

4 DR. HARRINGTON: Okay. Thank you.

5 Dr. Koralnik, I see your hand is raised.
6 Before I get to you, I just wanted to ask one
7 question, it was a follow up to an earlier point
8 that Dr. Cortese was making. So, you know, a
9 surrogate measure or a laboratory marker or
10 something that can be measured a little bit earlier
11 in the trial, you know, even if it's not used as a
12 primary efficacy endpoint, you know, the conversion
13 is maybe it could be used as a futility endpoint.

14 And one potential benefit of having a
15 futility endpoint is that, for example, one may be
16 able to identify study volunteers early who are
17 unlikely to meet the primary efficacy endpoint, so
18 that these volunteers could then be unblinded, if
19 it's a blinded trial, and then have access to an
20 experimental treatment if they happen to be in a
21 control arm.

1 So I guess my question is, should we
2 consider any of these endpoints as potential
3 treatment futility rules to help make earlier
4 decisions in clinical trials, and maybe make those
5 protocols more, you know, acceptable to patients.

6 Do you want to comment on that,
7 Dr. Koralnik?

8 DR. KORALNIK: Yes. Well, it's a
9 completely different question. I think it's, you
10 know, has many level of answers, obviously, to
11 stratify best how we include patients in the study
12 to begin with is going to be very important because,
13 obviously, patients are too advanced than any
14 intervention is going to be futile by definition,
15 right.

16 And then we can decide, you know, how we
17 apply those futility analysis to all the different
18 parameters that we discussed, which is going to be
19 also another level of complexity in the organization
20 of a trial.

21 Just wanted to say another thing about the

1 immunological endpoint. I think it would be great to
2 include them, but we need to have a good baseline,
3 for example, especially if we use medication like
4 Pembrolizumab or Nivolumab that will reinvigorate
5 the T-cells like in JC virus, but it's only
6 predicated about the presence of these T-cells in
7 the first place in the patients, right, and so that
8 could be a way to decide which patient we would want
9 to include in the trial in the first place.

10 I think that those should be combined with
11 the MRI aspects since the definition of IRIS is very
12 important if we use immunological active
13 medications, and we should be careful when we do
14 volumetric analysis on MRI to make sure that we
15 don't look only at the size of the lesion, but also
16 at atrophy in the area of the lesion, because,
17 unfortunately, remyelination really doesn't appear
18 in a patient with PML.

19 DR. HARRINGTON: Okay. Thank you. We are
20 pretty much out of time, but I wanted to just give,
21 you know, another minute to any of the other

1 panelists if you have any other comments to add to
2 this discussion. I know we could go for hours, but
3 I'm sure there are a lot of people who want to take
4 a lunch break before coming back to the afternoon
5 sessions.

6 Anyone else on the panel want to --

7 DR. MARRA: Well, one thing that came out
8 in the discussion was the idea of dividing people
9 out, which is sort of a little bit more than an --
10 of one, but the same idea of maybe considering all
11 Natalizumab patients as a group rather than
12 combining them with others since, as this one
13 pointed out, they have an obvious treatment for PML.

14 DR. HARRINGTON: Right. And what would
15 you propose for their endpoint for that particular
16 population?

17 DR. MARRA: I think you could use an
18 immunologic endpoint. I would ask Igor what he
19 could do with them, but I think that they would
20 potentially have an immunologic out point --
21 endpoint that could be assessed in blood.

1 DR. HARRINGTON: Okay. Dr. Lyons, I think
2 you will be the last one to comment before lunch.

3 DR. LYONS: Okay. Sure. I just wanted to
4 come back to your point about using a biomarker as
5 futility, and I like that idea, I like the idea of,
6 you know, potentially using CSF JCV DNA
7 quantification as a futility marker, not in terms of
8 lack of a drop in the viral load, but if you have at
9 four weeks or eight weeks your virus level is going
10 up, then obviously whatever you're doing is not
11 working.

12 So operationally though, I don't know that
13 that's ever been looked at in terms of how useful
14 that would be, meaning, how common it is that, you
15 know, when you start to do worse, your JCV level
16 actually goes up as opposed to you might start to do
17 worse and it's because of IRIS or it's because you
18 have extensive damage that is irreversible in the
19 brain.

20 But I think just as an initial thought in
21 terms of, you know, something that is quick and easy

1 to sort of determine if there's futility in your
2 study, I like that idea.

3 DR. HARRINGTON: Okay. Thank you very
4 much. I'm sorry we did not get to all of the --
5 there are several other questions that we couldn't
6 get to before the end of the session, but we're
7 going to take a break now, and I think we come back
8 at, what is it -- it looks like 1:20, so we have
9 time for a brief lunch. Thank you all. Thank you
10 to all the panelists for your helpful comments.
11 We'll certainly take all of this under
12 consideration.

13 And I'm sure some of this will come up in
14 the subsequent panel discussions as well today. So
15 thank you again, and we will take a break until
16 1:20.

17 (Whereupon, a lunch break was taken until
18 1:20 p.m.)

19 DR. SHEIKH: Welcome back everyone. I
20 hope you're refreshed and ready for a productive and
21 thought provoking afternoon or, for our European

1 colleagues, early evening. You're about to hear
2 about the PML patient perspective. First Joan
3 Ohayon, Senior Nurse Consultant and Certified MS
4 Nurse at NINDS will provide you with a summary of
5 what we've learned through FDA NIH efforts to elicit
6 the PML patients' perspectives on clinical trial
7 design.

8 Thereafter, we'll hear from two PML
9 survivors, Suzanne Tobin, an accomplished copy and
10 layout editor for the Washington, D.C. region, and
11 Luca Isabella, a management advisor who is
12 participating today from his home country of Italy.

13 I'll hand the mic over now to Ms. Ohayon.

14 The floor is yours.

15 MS. OHAYON: Thank you, Virginia. I'm
16 very honored to be able to represent our working
17 group and share with you the work that we've done
18 with the patient-focused drug development for PML.

19 Next slide, please.

20 So, by definition, patient-focused drug
21 development is a systematic approach to help ensure

1 that patients experiences, perspectives, needs and
2 priorities are captured and meaningfully
3 incorporated into drug development and evaluation.
4 As we know, patients are uniquely positioned to
5 inform the understanding of the therapeutic context
6 of drug development and evaluation.

7 Next slide, please.

8 However, PML creates significant
9 challenges for obtaining the patient's voice. As we
10 know, there is high mortality in rapid disease
11 progression, survival rate varies. One publication
12 shows that with HIV, the survival rate is 50% at two
13 years; with multiple sclerosis, 77% at three years,
14 but with hematological malignancies, only 10% at two
15 months.

16 We know there are delays in diagnosis, so
17 that often there is significant disease burden by
18 the time diagnosis is made.

19 Additionally, the neurological impairment
20 from the symptoms of PML creates huge obstacles
21 often affecting mobility, mentation, and speech.

1 Next slide, please.

2 So our working group, with others, had two
3 major initiatives, we conducted patient listening
4 sessions, which took place summer and -- late
5 summer, early fall of 2020, and external crowd
6 sourcing, which took place this past summer, July
7 2021.

8 Patient listening sessions or small,
9 informal non-regulatory, non-public discussions
10 about disease experiences, not about the specific
11 medical product that are of interest to FDA medical
12 staff and others. And we did this in collaboration
13 with the FDA Office of Patient Affairs.

14 On the contrary, external crowd sourcing
15 is a web-based platform providing opportunities for
16 patients and caregivers to engage with each other
17 and share experiences with the guidance of
18 moderators from FDA. Again, we collaborated with
19 the FDA Office of Patient Affairs, as well as with
20 FDA CDER Office of Strategic Programs.

21 Next slide, please.

1 So for the patient listening sessions our
2 working group developed a survey to elicit thoughts
3 and challenges to gather opinions and perspectives
4 from the patients and caregivers about their
5 experience living in coping with multiple sclerosis
6 with PML.

7 From the results of these surveys, we
8 identified a group of PML patients and their
9 caregivers representing the diverse spectrum of
10 perspectives and diseases, underlying diseases, and
11 experiences.

12 From there we conducted sessions, a
13 moderator from Office of Patient Affairs asked
14 questions -- the same questions to all participants
15 regarding their experiences with PML. FDA and NIH
16 members participated as listeners to gain insight.
17 And I will share with you that our first session was
18 extremely powerful; participants are very candid.

19 As a listener, it was very tough
20 emotionally to hear these stories, but because of
21 the success that we had with this first session, we

1 opted to have a second session to offer to the
2 remainder of the survey respondents.

3 Again, with the second session, we had
4 engaging conversations with similar themes presented
5 as the first, and summaries of both of these
6 sessions are available at the FDA link that is
7 posted on this slide.

8 Next slide, please.

9 So in total we had 17 participants in both
10 listening sessions, five PML and 12 caregivers, and
11 you can see here how close they were relative to
12 their PML experience. Of note, five of the PML
13 patients represented had died. You can also see the
14 underlying disease varied from HIV to MS to primary
15 immune deficiency disease.

16 Note that hematological malignancies were
17 represented by seven different people, as well as
18 idiopathic CD-4 lymphocytopenia sarcoidosis
19 autoimmune, so we had a really nice variety.

20 Next slide, please.

21 So before sharing the responses from the

1 patient listening sessions, I just want to touch on
2 external crowd sources, as both initiatives really
3 resulted in similar themes.

4 So as I shared, external crowd sourcing
5 provides an opportunity for individuals with PML to
6 share their experiences and, in particular, this
7 demonstrated the platform's ability to function as a
8 listening mechanism for CDER, and this allows
9 participants to comment on their own time, rather
10 than having to be available for a specific meeting.

11 Outreach was made by our working group and
12 others to encourage potential participants to use
13 the platform to share their stories. A moderator
14 from the FDA then asked questions and provided
15 follow up as needed.

16 And these responses are being shared today
17 at today's workshop, as well as planning for a
18 future report and manuscript.

19 Next slide, please.

20 So there were five submissions during the
21 two-week period of external crowd sourcing, four of

1 the five were family or caregivers, and you can see
2 on the first graph here how they were relative to
3 the PML diagnosis, and then the second graph shows
4 the spectrum of underlying diseases with the
5 submissions from the external crowd sourcing.

6 Next slide, please.

7 With both initiatives, there were similar
8 themes shared from the patients' and caregivers'
9 stories. In here they are summarized as barriers to
10 participation in clinical trial.

11 So lack of knowledge of studies; lack of
12 availability of studies, as I've shared; rapid
13 disease progression and mortality; painful
14 procedures; onerous tests, frequent LPs was
15 mentioned by numerous people several times;
16 ineligibility to participate due to perhaps
17 treatment history related to their underlying
18 diseases; limitations in mobility; challenges of
19 travel; family responsibilities; finances;
20 challenges of just the overall neurological
21 manifestations of PML, and as we've said before,

1 delayed diagnosis.

2 So often by the time these patients reach
3 the opportunity to potentially participate in a
4 clinical trial, their disease burden and their
5 ability to participate is just too much.

6 Next slide, please.

7 So when asked about the use of placebo in
8 research, there were mixed responses with over half
9 of the participants in a listening session
10 expressing reluctance to participate in placebo
11 controlled trials. Some believe the placebo would
12 be a waste of valuable time and would defeat the
13 purpose of treatment, although they did express
14 understanding the necessity for the placebo, but
15 would prefer not to participate.

16 And then a few would have taken any
17 opportunity to delay, reverse, stop progression of
18 symptoms, including participating in a clinical
19 trial with placebo stating that there's --
20 placebo-controlled trial is better than no other
21 options.

1 Next slide, please.

2 With both initiatives, there were positive
3 comments shared about motivations for participating
4 in clinical trial; access to PML expert; access to
5 an earlier diagnosis; increasing knowledge for both
6 the family, the participants and, of course, the
7 general public; the fact that they were just limited
8 options and, of course, the desire to contribute.

9 And many expressed the desire to
10 contribute, regardless of the outcome, if it would
11 help their loved ones or themselves, perhaps it
12 would help somebody in the future.

13 Next slide, please.

14 So in summary, our patient listening
15 session demonstrated that it is possible to elicit
16 the PML patient voice to inform PML clinical trial
17 design considerations. External crowd sourcing
18 showed similar themes to the listening sessions
19 regarding the barriers and motivators among
20 participants, so I think overall we had two very
21 successful initiatives.

1 We learned that the PML patients and their
2 caregivers are willing to share their perspectives,
3 even when doing so is challenging emotionally. I
4 think that all of us that participated in these
5 initiatives will agree that we were very pleased and
6 grateful for the openness and the details shared
7 among the participants.

8 Hearing the voices in the listening
9 session and reading the comments and the crowd
10 sourcing were extremely powerful and provided really
11 personal insight into each one's own experience;
12 they were not easy to hear or easy to read.

13 As we've shared previously, the take-home
14 messages from this work is that this is a disease of
15 high mortality, rapid disease progression, really
16 emphasizing the rapidness, time is of the essence.
17 Neurological symptoms are obviously a burden on the
18 patient, but the caregiver as well; travel; family
19 responsibilities; finances, create huge challenges.

20 And it's important for patients and
21 caregivers to have realistic expectations of what to

1 expect with the disease and any potential research
2 participation, so that they can make their best
3 decisions, ultimately keeping quality of life as the
4 top priority.

5 Next slide, please.

6 So, moving forward with clinical trial
7 development, we know it's essential to integrate the
8 PML patient voice in trial development in order to
9 recruit and retain patients. This information --
10 there's some guidance provided by the FDA, so
11 clinical trial lists and product sponsors should
12 refer to the link that's on this slide.

13 Next slide.

14 And lastly, but most importantly, I would
15 like to, on behalf of our working group, thank all
16 of the PML patients and caregivers that
17 participated, and especially those that participated
18 in the listening sessions and crowd sourcing, they
19 were both such remarkable experiences. I would like
20 to thank FDA Office of Patient Affairs, CDER Office
21 of Strategic Programs, NORD, our working group

1 members, and overall FDA CDER, CBER, NIH and
2 referring clinicians.

3 So we had way too many people involved in
4 here to list by name, but really appreciate all of
5 the participation and we're very pleased with the
6 success that we had with these initiatives, and look
7 forward to continuing the work.

8 So thank you. And with that, I will turn
9 this over to Suzanne Tobin so you can get a
10 first-hand experience about the patient perspective.
11 Suzanne we're very grateful and happy to have you
12 here with us today, so thank you very much.

13 DR. SHEIKH: Ms. Tobin, you're not on
14 audio or video right now.

15 MS. TOBIN: Okay. I'm good now, I think.
16 That seems to have done for the audio, I hope.

17 DR. SHEIKH: We can hear you and see you
18 now.

19 MS. TOBIN: (there were some audio
20 difficulties with this speaker) Oh, wonderful.
21 Okay. I just can't see myself for some reason.

1 Thank you for allowing me to present a patient's
2 perspective to doctors and researchers -- who might
3 access this webinar, you are heroic lifesavers.

4 My name is Suzanne Tobin, and I was born
5 and still live in the Washington D.C. area.
6 December will mark eight years since my PML
7 diagnosis. That part of my story is a months' long
8 one, so in the interest of time, I will refer you to
9 the Washington Post Medical Mystery article link in
10 my bio.

11 As for life in general, I have my share of
12 good and bad days. For the PML and -- are ever
13 present clouds over my life. On many days since my
14 illness began, my sense of humor has sustained me
15 and allowed me to laugh instead of cry -- dead
16 anyway, and I totally agree with her.

17 Here's what I hope to impress upon you,
18 one, continue to search for -- drugs for PML. We
19 see -- survivors need you to cast the widest net
20 possible to find a treatment. My -- MRIs have been
21 stable since 2015, the JC virus continues to show a

1 presence in my yearly LPs, but is negligible
2 compared to when I was diagnosed.

3 Okay. Neuro plasticity will help
4 survivors recover over the long term, but we need to
5 have a treatment that stops the virus from doing
6 anymore damage so we can focus on our recovery. I
7 have regained many physical functions I lost to PML,
8 which paralyzed my whole left side. The fine motor
9 skills of my left hand and my short-term memory
10 still pose challenges.

11 As for my mental health, my NIH
12 neurologists told me that some of the PML caused
13 lesions showed significant, permanent damage to the
14 frontal lobe, that controls mood, so it's difficult
15 to manage my chronic clinical depression. I have
16 yet to find medications that work as well as they
17 did prior to PML.

18 In my case Mefloquine, an anti-malarial
19 drug, had an almost immediate positive impact. I
20 believe the progression of my PML was halted within
21 a day of starting it. My -- which had been my first

1 symptom, improved over night. While it was not
2 validated in clinical trials, Johns Hopkins had had
3 some success with Mefloquine killing JC virus in the
4 lab. I believe it saved my life, and for that, I am
5 grateful.

6 I have taken Mefloquine once a week since
7 2013. The experts don't know why I got sick or why
8 I got better, but as the saying goes, if ain't
9 broke, don't fix it, so I continue to do what works
10 for me. Two, we need more attention for PML as it
11 looks like more people will be at risk for PML with
12 the continued development immune-suppressing drugs.

13 Even though PML may have declined with the
14 progress that's been made with HIV AIDS treatment,
15 immune-suppressing drugs are now putting more people
16 at risk. One person in our survivors' Facebook group
17 said that, quote, developers and prescribers of
18 immune-modulating drugs like oncologists, need to
19 realize that regular testing for the JC virus and
20 CD-4 counts should be routine procedure for anyone
21 on these drugs.

1 Another patient comment was that if
2 scientists could develop a vaccine for the JC virus,
3 they could vaccinate all patients prior to any
4 immune-modulating therapies. We aren't scientists,
5 so we don't even know if that's possible, but it's
6 worth mentioning. Every time I see a TV
7 advertisement for a drug that mentions PML as a
8 possible side effect, I just want to scream, "don't
9 take it" at my television.

10 Unless users of being actively monitored
11 for PML, it's not worth risking the health of your
12 brain, which is the very essence of who you are, for
13 clearer skin or anything that is not immediately
14 life threatening. Obviously, transplant patients
15 and MS patients are a different story.

16 Three, spread the word about PML any way
17 you can. Many of you specialize in PML, but the
18 awareness of the disease is far from universal.
19 The next speaker, Luca Isabella, will talk about
20 using social media to spread awareness of the
21 disease. Over the last eight years, I've noticed

1 that more doctors seem to at least know about PML,
2 that's progress.

3 Four, urge your colleagues to listen to
4 their patients. We patients know our bodies better
5 than you do. Use your clinical skills and do not
6 rely on diagnostic tests to the inclusion --
7 exclusion of listening to your patients. Ask
8 yourself whether the diagnostic tests default
9 diagnosis is consistent with the progression of
10 symptoms.

11 Repeatedly, I raised the inconsistency of
12 my symptom progression versus the original diagnosis
13 of stroke, and was repeatedly told that BMI
14 indicated stroke, period, end of discussion.
15 If you have five MRI snapshots of brain lesions,
16 each in isolation may look a lot like a stroke, but
17 taken together with progressive increases in the
18 same lesion, they are not typical of a series of
19 strokes, particularly if small lesions spread widely
20 throughout the brain.

21 Over time I was getting incrementally

1 worse each day, rather than in the stepwise manner
2 of a series of strokes.

3 If I would have had a lumbar puncture when
4 I visited the Johns Hopkins ER in October, instead
5 of telling the resident that I had an LP scheduled
6 the next month at my local hospital, I could have
7 been diagnosed two months earlier.

8 Having always been phobic about needles, I
9 was terrified of lumbar puncture. If I had known it
10 was the key to the correct diagnosis and that all
11 LPs are not created equal, I would have insisted on
12 it.

13 When I had my scheduled LP at my local
14 hospital, they didn't test for the JC virus. Once I
15 was an in-patient at Johns Hopkins, they did.
16 When I saw my local neurologist after my hospital
17 stay, and told him of the PML diagnosis, he admitted
18 that he had never even heard of the disease.

19 Five continue to develop ways to
20 differentiate between PML lesions and other types of
21 lesions. My NIH neurologist told me there is

1 research on how to differentiate PML lesions from
2 other types, and it's possible that PML lesions may
3 have an iron ring, of sorts, around them, but the
4 data is inconclusive yet.

5 Keep up the good work. Early diagnosis
6 would be a huge deal for someone like me who doesn't
7 fit the normal profile of someone at risk for PML.

8 My sixth and final idea is a far-fetched
9 one, but I figured it never hurts to ask. Since PML
10 is so rare, is it possible to have some sort of
11 mobile lab for clinical trials that could go to the
12 survivor or is there some way to help defray travel
13 costs for trail participants?

14 I live within an hour's drive of two
15 state-of-the-art medical institutions, NIH and Johns
16 Hopkins, but how could you make it easier for others
17 to get access to trials? This idea may not be
18 feasible in the entire United States, but it might
19 work in individual states or countries in Europe
20 where the land mass is not so great. Depending on
21 the severity of the patient's symptoms, travel may

1 be difficult, if not impossible, particularly with
2 the added challenge of COVID.

3 Cost is another obstacle. I have private
4 disability insurance that paid me two-thirds of my
5 previous salary, but many people don't. During my
6 worst phase, my whole left side was paralyzed. This
7 made travel difficult and required an able-bodied
8 person to drive and accompany me to appointments.
9 Long-distance travel by air or rail would have been
10 even more daunting.

11 Defraying travel costs might have more
12 survivors participate in clinical trials.

13 In closing, I want to give you a gift and
14 I'll try not cry. It's the gift of -- it is a thing
15 that many -- nine years of rehabilitation, I would
16 tell myself I can't walk without a cane yet; I can't
17 drive yet; you haven't found a vaccine yet; the
18 clinical trial hasn't produced the perfect -- yet.
19 Yet is a hopeful word that has been the key to my
20 continuing recovery.

21 Thank you again for your work to help us

1 PML survivors, we are so grateful.

2 DR. SHEIKH: Thank you very much,
3 Ms. Tobin. That was really special, thank you very
4 much.

5 Mr. Isabella?

6 MR. ISABELLA: (there were some audio
7 difficulties with this speaker) Okay. Here I am.
8 Okay. Good evening, my name is Luca Isabella. It's
9 a little bit touching to see -- to hear the
10 testimonial by the -- but, okay. Thank you very
11 much for the opportunity to share my experience as a
12 PML survivor.

13 My name is Luca Bella, I live in Milano in
14 Italy. Sorry if I cannot speak as well, but okay,
15 Italian, but also I had aphasia, so now I am -- I
16 have some difficulty. In ten minutes I want to
17 focus on how social media can be useful to help the
18 awareness of this disease.

19 I will be -- something from my personal
20 story related to PML. In 2015 I began experiencing
21 constant headaches and severe fatigue that had been

1 attributed work stress. This -- next few months I
2 began to have some neurological symptoms, and I was
3 hospitalized for stress. At first the news is it
4 was ischemia, even if the doctors don't want to --
5 very confused. Later I had MRI scan and confirmed
6 a -- brain tumor.

7 They gave me a lot of steroids, and took
8 me to another hospital to be quickly operated on.
9 Since I have a -- my situation went downhill. In
10 the new hospital, they -- and after the lumbar
11 puncture, the -- news was and became HIV and PML.
12 That can track progress -- over the weeks, and
13 include mental deterioration, visual problems,
14 aphasia, lack of coordination and paralysis.

15 From then on, I've been followed by the --
16 department, and after ten months I've been
17 discharged. Aside from the infectious department
18 specialists, ever time I -- the doctor, no one knows
19 what PML is. The rehab they give me -- and
20 therefore, I was not adequately followed. How many
21 times I heard a doctor say, "what do you expect, you

1 have AIDS and PML, it will not last long".

2 Slide, please.

3 Okay. This is my MRI scan when I was in
4 the hospital.

5 Next slide.

6 When I slowly started to read again, the
7 first needed was to get in touch with the people who
8 had PML. I searched for it on the Internet, not in
9 Italian, my native language, but in English, and I
10 found everything in -- making my search less --
11 scary.

12 Next slide, please.

13 At one point I found myself a Yahoo group,
14 PML Survivors and Supporters. -- I found
15 information I need, I no longer felt the only one
16 who had PML and, above all, the stories of the
17 survivors were somewhat comforting. -- were not --
18 but someone -- survive for many years. I found a
19 small community of peer support.

20 Next slide, please.

21 After one year a former year, including

1 me, created an information page on Facebook and a --
2 group. Patients and caregivers all over the world
3 ask me to join a group of survivors, patients
4 with -- survival -- one year -- five years, and
5 we're always available to give information -- and
6 practical advice.

7 Next slide, please.

8 Obviously, we do not give medical
9 opinions, and we suggest that doctors -- but we are
10 often thanked for the -- little support we give.

11 Next slide, please.

12 Some topics we discuss in the group are
13 difficulty in finding doctors in training in PML --
14 of PTLT, speech therapy, caregiving, lifestyle,
15 effective medical treatments, recovery --
16 relationship struggles, finding employment,
17 experience on confirmatory -- above all, in this
18 communication with the physicians to disseminate
19 information for any new therapeutic approaches and
20 accessibility.

21 Next slide, please.

1 So we go for the -- this patient a
2 promotion of the patients' associations to support
3 patients and carers -- an important source of
4 information by which PML can orient themselves,
5 their -- for -- and complex needs. Furthermore,
6 our -- they can provide patients and caregivers who
7 have been affected by or at least an opportunity to
8 share their -- about --

9 Next slide, please.

10 Each patient has his own journey, and each
11 patient is different. Recently a researcher from --
12 in molecular biology from Zaged (sp) say that we do
13 very valuable, and the best source of information is
14 the experiences of the survivors. Please, a small
15 acknowledgment that we are doing the right thing.

16 Next slide.

17 Thank you for the -- I want to especially
18 thank the people, all the survivors that are every
19 day they are working on the group, and especially
20 Paola Cinque, my neurologist. Thank you.

21 DR. SHEIKH: Thank you, so much. That was

1 really wonderful, Ms. Tobin and Mr. Isabella, and
2 before that, Ms. Ohayon, that was terrific.

3 And now I think this will be a nice
4 transition to our next portion of the talk, which we
5 mentioned previously about how important clinical
6 trial acceptability needs to be for patients, and
7 this involves a tough subject, which is placebo or
8 at least finding the selection of a control group.

9 And for that, we're going to have a
10 discussion about this in about 20 minutes. But
11 before that, Dr. Paul Lee, Deputy Director of the
12 Division of Neurology 2 will provide an overview of
13 key considerations for control group selection for
14 PML.

15 So the floor is yours, Dr. Lee.

16 DR. LEE: (there were some audio
17 difficulties with this speaker) Thank you, Virginia.
18 Thanks everyone. Good afternoon. It's really an
19 honor to follow these amazing personal perspectives
20 in PML. As Virginia introduced, I'm Paul Lee, I'm a
21 Deputy Director and Team Leader for the Neuro Immune

1 Group in the Division of Neurology 2 at the FDA.

2 And the topic I'll discuss today is the
3 selection of control groups for PML clinical trials.

4 And I'd really like to thank the organizers of this
5 excellent symposium for the opportunity to discuss
6 this important topic with you.

7 Next slide.

8 So I have no relevant financial
9 disclosures.

10 Next slide.

11 So PML presents unique challenges to
12 clinical trial design. By any reasonable
13 definition, PML constitutes a rare disease.

14 As a rare disease, PML presents the
15 typical challenges in rare disease research, meaning
16 there are few patients available to study; there's a
17 relative possible disease-related research available
18 to form a natural history and understanding of PML,
19 and there are no large repositories or databases
20 that can serve as a source of historical clinical
21 control data.

1 While immune suppression appears intrinsic
2 to the pathophysiology of PML, depending on the
3 etiology of this immune suppression, there are
4 differences in natural history and outcomes of PML
5 that further complicate outcome assessment.

6 Finally, there are no approved therapies
7 for PML, which means we do not have a history of
8 successful development programs to inform trial
9 design, and we do not have clearly established
10 effective -- therapies to serve as active
11 comparators in clinical trials.

12 Next slide.

13 It's a scientific truism that a clinical
14 trial's quality is intrinsically tied to the quality
15 of it's control group. The regulatory standard of
16 two adequate and well-controlled trials codifies the
17 importance of this precept. The quote in this slide
18 is taken verbatim from the E10 guidance for industry
19 regarding choice of clinical control group
20 design-related issues of the trials.

21 And this is intended to suggest that the

1 primary purpose of a control group is to allow
2 discrimination of patient outcomes, so that there's
3 ultimately a control group's ability to discriminate
4 between the treatment effect and in the outcomes
5 only attributable to experimental manipulation --
6 experimental treatment are -- net result of the
7 ability of the control group to serve as an
8 appropriate comparator and baseline for the
9 evaluation and establishment of these outcomes.

10 Next slide.

11 The E-10 guidance for industry document
12 provides a list of potential control groups that can
13 be acceptable in an adequate and well-controlled
14 trial. Of course, the gold standard of a
15 placebo-controlled trial is the gold standard for
16 good reason, because it -- minimizes many sources of
17 bias in other designs and it is readily
18 interpretable.

19 And the treatment comparator arm option
20 exists, and it is now typically represented in
21 historical external control data, which we can

1 discuss further in subsequent slides, and in a
2 setting of diseases with no established treatment or
3 when quality database of untreated patients is
4 available potentially used for -- from the same
5 limitations and biases of external historical
6 controls.

7 Finally, active comparator, either using
8 the same experimental treatment and different dose
9 strength or regimen or a different active treatment
10 with a known established affect can serve as
11 potential treatment options in a perspective
12 clinical trial.

13 The challenge of that for comparatives --
14 trial design is appropriate to demonstrate the
15 accepted treatment -- expectation is that the
16 experimental treatment will be superior or as
17 effective -- designs the control treatment --
18 addressed adequately within the trial design which
19 predetermines the -- comparisons.

20 This, therefore, renders a -- complication
21 when you introduce an active comparator that does

1 not have established effects independent of that --
2 the trial in which -- because then you really don't
3 have an expectation or ability to objectively
4 evaluate the treatment effect we've seen in this
5 trial relative to it's known established --
6 previously established treatment effect.

7 Next slide.

8 In PML trial design where you need -- PML
9 itself -- it must be considered. While
10 placebo-controlled remain arguably the most
11 interpretable and readily acceptable designs, we've
12 heard from patients, caregivers and investigators
13 who treat placebo -- therapies considered to be
14 standard of care in widespread use, but not approved
15 for the treatment of PML, would be excluded or not
16 appealing for enrollment, and this is certainly an
17 understandable consideration.

18 However, the agency and our Division of
19 Neurology have a great deal of experience with
20 trials in which experimental therapy is superimposed
21 on to other clinical treatments, and one message

1 that I wish to convey clearly today is that at
2 add-on trials can be placebo-controlled trials, so
3 an add-on trial being the adding on of a potential
4 investigative therapy to a -- considered to be
5 standard of care, and the Division of Neurology has
6 experience in this trial design, and when done with
7 fair and thoughtful design, these trials can
8 interpretable and actionable.

9 We've been discussing some examples to
10 such trials in the slides to follow, but even
11 suggest that the -- standard of care should be
12 defined to the fullest extent possible, and
13 therapies that -- would be represented in trials --
14 a focus list and if -- contributions of such
15 therapies -- comparison -- treatment of -- of the
16 treatment, specifically, what are the effects to be
17 used as an additive to experimental treatment, and
18 if there's any potential for deleterious
19 interactions that would impact the interpretability
20 of the overall trial.

21 But I just emphasize that the use of

1 unapproved therapies in the context of an add-on
2 trial is a potentially acceptable approach to trial
3 design in PML.

4 Next slide.

5 As discussed previously, historical
6 patient data are available -- potentially use such
7 data as a historical external control population in
8 a trial. The rare disease guidance in the industry
9 quoted on this slide is -- are appropriate for
10 consideration -- there must be unmet medical need --
11 in certain -- with PML in the absence of any proven
12 effective treatments.

13 The natural history of the disease should
14 also be well described and uniformly predictable,
15 and this natural history -- should suggest objective
16 outcome assessments. This is a bit more complicated
17 with respect to PML, given some of the issues with
18 the natural history.

19 Finally, any expected effect of -- should
20 be large and -- therapies used -- so generally this
21 is a good -- for any clinical trial design -- in a

1 rare disease setting, you don't want to be looking
2 at the most effective treatments you have on the
3 table at that particular time to be -- clinical
4 trial.

5 Next slide.

6 The rare disease guidance elaborates --
7 patients -- historical controls -- trials -- merits
8 further discussion. Historical database is
9 typically incomplete and primitive in its
10 comparability. These databases will reflect the
11 technology and knowledge available at the time of
12 the data collection.

13 Whatever bias exists in these historical
14 databases will be flexible and cannot be
15 mitigated -- opportunity to go back and revise the
16 trial or allow -- the guidance -- even the most
17 well-characterized diseases -- used relevant factors
18 that are unknown and not capturable at the time of
19 the data collection, which further limits their
20 comparability and interpretability.

21 Next slide.

1 All the guidance has general concerns but
2 certainly relevant to PML. Speakers today have
3 discussed the -- literature and natural history
4 efforts undertaken with PML, and it's clear that
5 while considerable efforts were made to capture that
6 natural history data, no one complete database
7 exists in any form that can serve as an adequate
8 source for a trial.

9 Even considering the smaller scale, less
10 ambitious approach, we have heard that the risk
11 factors of PML -- lead to different patient
12 populations to -- data sources -- varied
13 accessibility and all the usual limitations in the
14 data collected.

15 We're also faced with the -- circumstances
16 of the natural history of PML has been evolution,
17 specifically the -- in therapies with treatment of
18 multiple sclerosis and the risk of PML are the
19 changes in labeling and practice -- PML -- and
20 multiple sclerosis patient population with a
21 relatively short time if the risk is identified,

1 such as the data from just a few years ago may not
2 have high fidelity with more recent actual data even
3 in the multiple sclerosis patient population.

4 In a longer timeframe, same could be said
5 about PML and the HIV AIDS Community where one
6 examines outcomes before and after the advent of
7 highly active anti-retroviral therapies, data from
8 these areas may not be -- there's also -- PML --
9 clinical assessment measure and had no accepted
10 biomarker, and so any database available --
11 standardized -- exists. Until biomarkers are
12 identified, no matter how comprehensive --

13 Next slide.

14 Now, even understanding the challenges we
15 face in finding control groups for PML trials, there
16 is valuable feedback from many stakeholders in mind,
17 I'd like to discuss potentially -- examples from
18 another rare disease, neuro-myelitis optica spectrum
19 disorders, also known as NMOSD. NMOSD is a rare
20 autoimmune disease characterized by paroxysms of
21 inflammatory regions in the optic nerves and spinal

1 cord.

2 NMOSD is extremely disabling and can be
3 fatal in instances where lesions -- critical
4 portions of the brain stem involved in regulation of
5 temperature and breathing. NMOSD shares much in
6 common with PML, until 2019 NMOSD had no proven
7 effective therapies to do -- considered standard of
8 care treatments for this disease.

9 To further the similarity, there's no --
10 specific outcome assessment tool, and instead
11 NMOSD -- identified as being relevant to other --
12 autoimmune disease -- central nervous system, most
13 specifically multiple sclerosis. There really isn't
14 natural history database -- as an external control
15 database suitable for substitution for -- control
16 group at least at the time when -- were being
17 designed previous to -- therapy --

18 My only feedback from many stakeholders in
19 the agency is unified in the assertion that --
20 potentially fatal consequences of NMOSD -- trials
21 lacking in standard of care treatment,

1 specifically -- in broad use, were not acceptable
2 and might not even be practical for enrollment.

3 Next slide.

4 The first example I'd like to discuss
5 is -- or Eculizumab, which is an antibody
6 directed -- compliment C-5, which is involved in --
7 is involved in part of the disease process relevant
8 to NMOSD -- in 2019 Eculizumab became the first
9 therapy approved as an effective treatment for
10 NMOSD.

11 The single trial would serve as a basis
12 for approval of -- the small trial population, only
13 137 patients, but thanks to a very robust treatment
14 effect, the trial was able to demonstrate a highly
15 statistically significant finding in the primary
16 outcome measure at the time -- and trial.

17 And it's important for this discussion,
18 the trial -- is the basis for approval allowed
19 patients to enroll in the trial while remaining on
20 their baseline -- immunosuppressing therapies. The
21 Eculizumab and placebo treatment arms were add one

1 to a patients background therapy.

2 Next slide.

3 Therefore, as shown on this slide, there
4 were many different concurrent treatment regimens
5 were out in this trial. In the smaller -- trial
6 size, that meant that after -- the number of
7 patients who would need treatment -- thus, because
8 the small sample size -- is not possible to make any
9 comments about the interactions between background
10 therapies and -- however, the treating effect of --
11 is consistently replicated across all groups, which
12 likely spoke to the overwhelming, robust treatment
13 effect of -- itself.

14 However, I cite this trial as an example
15 of how one can achieve a successful interpretive
16 trial in a rare disease by adding a single, highly
17 effective treatment or placebo into a broad range of
18 other considered -- treatments, and resulting in an
19 interpretable trial.

20 Next slide.

21 Another example from the NMOSD experience

1 is a development program for Enspryng
2 (satralizumab). The sponsor this therapy conducted
3 two trials, one that allowed a limited number of
4 concurrent immune suppressant therapies, and another
5 trial that was a true placebo-controlled trial, and
6 did not permit concurring immunosuppressants in the
7 population.

8 Unlike the -- program, instead of allowing
9 all possible concurrent treatments, this program
10 restricted allowed treatments to just three immune
11 suppressant treatments that were considered to be
12 the most commonly used at the time of the trial's
13 design, azathioprine -- and corticosteroids.

14 Next slide.

15 This slide depicts the -- Enspryng and
16 demonstrates that the treatment effect that's
17 been -- in both studies. The treatment effect in
18 patients using -- worked like the steroids or
19 similar, but they -- again not possible evaluate
20 interactions between Enspryng and -- and treatment;
21 however, as we saw -- the strong treatment effect in

1 Enspryng seemed to be the dominant treatment at date
2 of trial, as was confirmed in the placebo-controlled
3 trial that did not allow concurrent immune
4 suppression of the --

5 Obviously, a takeaway is that having
6 therapy and strong treatment effect relative to
7 concurrent -- therapy -- interoperability is a
8 consideration -- and this is, of course, a
9 consideration of PML trial design -- therapies
10 are -- in trials.

11 Next slide.

12 -- is a rare disease with heterogeneous
13 risk factors and variable outcomes -- etiology and
14 also a uniquely challenging disease with respect to
15 trial design. Natural history of PML is evolving,
16 which further competence considerations from the
17 appropriate control condition and defies -- use
18 historical data uniquely.

19 In searching for an appropriate control
20 option for PML clinical trials, there is no single
21 source of high-quality data which -- an

1 acceptable -- historical control in a clinical
2 trial.

3 Therefore, a clinical trial in PML will
4 likely have to have a concurrent, contemporary
5 control group -- since there are no approved
6 treatments for PML, there are no options presently
7 for therapy -- serving as true active comparators
8 with a known established affect of the -- trial --
9 investigated, therefore, placebo -- still appears
10 represent the best option for a controlled trial.

11 Next slide.

12 There are many therapies considered
13 standard of care, which the stakeholders -- should
14 be included in trials to ensure enrollment and
15 practicability, and in a true placebo -- such
16 therapies -- not acceptable.

17 In considering an example of another rare
18 potentially fatal disease, NMRSC, several lessons
19 are clear, first, placebo-controlled trials and
20 allowance of inclusion of unproven therapies are
21 acceptable, practicable and interpretive. These

1 add-on trials are standard of care treatments and --
2 an approval as an effective treatment.

3 The Division of Neurology has experience
4 and comfort in this trial design in rare diseases
5 like PML and encourages sponsors to utilize the
6 appropriate mechanisms for the -- discuss specifics
7 of such a trial. Our goal, collectively, and which
8 we all agree upon is to provide patients with PML
9 proven effective treatments identified as such
10 through rigorous high-quality research endeavors.

11 So I thank you for your attention today.

12 DR. SHEIKH: Thank you very much, Dr. Lee.

13 So it's now my pleasure to introduce our
14 panelists for the next discussion panel, which will
15 be focused on the selection of control groups for
16 PML clinical trials.

17 And so if I can now -- hopefully all of
18 our speakers are getting on video, it looks like
19 that's happening. So I am going to introduce
20 everyone.

21 So, first, we have Dr. Joseph Berger --

1 this is in no particular order, I shouldn't have
2 said first -- Dr. Joe Berger, who is a professor of
3 neurology and Associate Chief of the MS Division at
4 the Perelman School of Medicine at the University of
5 Pennsylvania; Dr. Farrah Mateen, associate professor
6 at Harvard Medical School; Dr. Kiran Thakur,
7 Winifred Mercer Pitkin assistant professor of
8 neurology, and Director of the Program in Neuro
9 Infectious Diseases at Columbia University, Irving
10 Medical Center, New York Presbyterian Hospital.

11 Dr. Guillaume Martin-Blondel, professor of
12 infectious diseases at the Toulouse University
13 Hospital and University of Toulouse; Dr. Gloria von
14 Geldern, associate professor of neurology at the
15 University of Washington in Seattle, and Dr. Derrell
16 Porter, founder and CEO of Cellevolve, an early
17 stage cell therapy commercialization company.

18 So thank you all, panelists. Before we
19 all begin, I want to remind participants to use the
20 Q and A feature if you would like to ask a question
21 of the panelists, or provide a comment for the

1 panelists.

2 And questions and comments for people who
3 are panelists, please submit them via the chat or
4 raise your hand.

5 So to begin that session out, I'm going to
6 begin with a potentially easier question, which is,
7 what do you believe -- from your perspective, what
8 do you consider to be the standard of care for PML,
9 and particularly that might include things like
10 Mefloquine, which Ms. Tobin talked about, or other
11 therapies that are now given throughout -- you know,
12 throughout the world for the treatment of PML.

13 And then Dr. Porter, for you, my question
14 for you would be, you know, what are the your
15 considerations from the sponsor, from the industry
16 perspective in deciding what those standards of care
17 could be, and how it might impact the functioning of
18 your trial.

19 So do I have any volunteers from panelists
20 before I begin calling on people randomly?

21 DR. BERGER: I'll volunteer.

1 DR. SHEIKH: Okay. Dr. Berger.

2 DR. BERGER: So I think it's highly
3 dependent on the patient and what the underlying
4 disease is. You know, obviously the individuals
5 that have multiple sclerosis and are being treated
6 with a drug like Natalizumab or Fingolimod, the
7 discontinuation of a drug in and of itself may be
8 sufficient.

9 Whereas, in other instances, as
10 Shakespeare said, diseases desperate grown or by
11 desperate measures relieved or not at all, you want
12 to throw the kitchen sink at them. And, you know,
13 many of these therapies that we have available to us
14 pretty benign, so I will often employ Mefloquine;
15 I'll use Mirtazapine, and then with increasing
16 frequency, I've been using Pembrolizumab as a
17 therapy in patients.

18 And, you know, I find that it's going to
19 be -- at least in my opinion, it's going to be very
20 difficult to carve out a placebo arm where there's
21 no treatment at all.

1 Dr. Lee mentioned the Eculizumab trial,
2 which I was a part of, we kept those patients on the
3 drugs that they were on, and as a doctor who treats
4 MS patients as well, I can tell you that I've been
5 extraordinarily reluctant to start patients in
6 placebo trials for relapsing remitting disease,
7 because of the importance of controlling the disease
8 as quickly as you can, and the value of the drugs
9 that we have currently.

10 So those are just some of my editorial
11 comments.

12 DR. MARTIN-BLONDEL: Maybe I can reply
13 also?

14 As Joe Berger just said, the standard of
15 care is depending on the underlying condition, and
16 it's could be easy if you could interrupt the
17 immunosuppressive treatments the patient received as
18 Natalizumab or other immunosuppressive treatments to
19 initiate -- in patient living with HIV, it's much
20 more difficult for patients with primary
21 immunodeficiencies with no alternative to restore

1 immune responses against JC virus, and particularly
2 for those patients.

3 It sounds for me quite difficult, as Joe
4 said, to not use something, even though we do not
5 have any proof of efficacy using I7 or CPD1
6 monoclonal antibodies, but using clearly placebo
7 controlled group, particularly for those patients
8 with no other way to -- for -- restoration sounds
9 really difficult for me.

10 DR. SHEIKH: So just before we move on, I
11 just want to clarify that what we're talking about
12 here is the standard of care, so that would not
13 include, for example, not starting HIV therapy for a
14 patient with HIV, that would not -- we're not
15 talking about not withdrawing Natalizumab. I just
16 wanted to make sure that I was clear about that
17 before we move on there.

18 So the problem with not -- with having a
19 clinical trial, that if we are -- the standard of
20 care includes everything that's available, then we
21 don't really have a comparator group.

1 So I just want to clarify, so it sounds
2 like people are definitely considering Mefloquine
3 and Mirtazapine mostly because the side effects --
4 we're not sure if they could work, but the side
5 effects seem to be low, but does the standard of
6 care also include IL7 and Pembrolizumab?

7 MR. MARTIN-BLONDEL: Not for me, at least.

8 DR. SHEIKH: Okay. So what is --

9 DR. BERGER: And for me as well.

10 DR. SHEIKH: It does not include those; is
11 that right?

12 GLORIA VON GELDERN: I think I agree as
13 well.

14 DR. SHEIKH: So, Dr. von Geldern, can you
15 specify what you think that standard -- what is the
16 standard of care from your perspective?

17 GLORIA VON GELDERN: Well, I agree with
18 what the two previous speakers have said, it depends
19 on the underlying disease and standard of care in
20 individual cases may include trying something to
21 restore the immune system if there's a primary

1 immunodeficiency, but I think standard of care
2 primarily focuses, at this point in my mind, on
3 restoring the immune system, depending on the
4 underlying disease.

5 In some cases, maybe that includes an
6 addition, things like Mirtazapine or Mefloquine, I'm
7 not usually super excited about those, but I think
8 the other aspect of standard of care is treatment of
9 PML IRIS in those patients where the immune system
10 comes back, and so that then further complicates
11 trials, but I think steroids to combat IRIS is
12 another piece that is part of standard of care in my
13 mind.

14 DR. SHEIKH: Thank you. Dr. Thakur, would
15 you please comment?

16 DR. THAKUR: Yeah. You know, I think I
17 agree with the prior speakers, I think that, you
18 know, perhaps one difference between PML in NMO
19 spectrum is just the heterogeneity of underlying
20 conditions that can cause the disease, and so that
21 then triggers us to treat the condition of PML

1 somewhat differently, so there is this kind of
2 individualized approach, certainly.

3 And our tools are limited in terms of
4 effective tools, and, you know, I will say that I
5 think we use somewhat experimental kind of
6 non-evidence based or pilot-based treatments in an
7 effort to treat a condition we know has a
8 significant morbidity and mortality.

9 And so I think that, you know, your
10 question, which I think is a lot more complex about
11 kind of standards of care, I think it's -- it's --
12 at least that piece when we're looking at it, I
13 think Paul did a great job in thinking about how we
14 can use NMO as kind of a model, I think this is a
15 bit different, you know, there's not one category of
16 disease entities, there's not kind of one category
17 of treatment.

18 DR. SHEIKH: Dr. Mateen:

19 DR. MATEEN: Yeah, I mean, I think in
20 terms of the discussion on standard of care, I think
21 I agree with what's already been said, and it is

1 technically appropriate as long as you're addressing
2 the offending agent, not to give Mefloquine or
3 Mirtazapine.

4 And I think we have a very, like, frank
5 discussion that we don't really know or think that
6 those may work, but they're also, as Dr. Berger
7 said, you know, limited harm, and so we often give
8 them as a sort of -- maybe for the doctor as much as
9 the patient -- feel like we're doing something for
10 them. But nowadays I actually would refer a patient
11 to a clinical trial as a first pass because I think
12 that what we have isn't sufficient.

13 And then just building on Dr. Thakur's
14 comments on the NMO studies, I think it's a really
15 interesting comparison, and one of the similarities,
16 besides the rarity of the disease, is the biomarker
17 itself doesn't necessarily need to change for the
18 patient to be treated, so people can have no relapse
19 and they can continue to have --

20 But I was just thinking about the prevent
21 trial, and it was, you know, enrolled in 18

1 countries, the Secura Star and Secura Sky, the
2 enrolled in about 12, and, you know, one of those
3 was -- for the Satralizumab, one of those was
4 placebo, and that had a recruitment yield into the
5 trial above 56%, and then for everyone that had an
6 active comparator, the recruitment into the trial
7 was closer to 80%.

8 And so I think if you're really going to
9 do a clinical trial, first of all, you can have more
10 than one control group, and if we have historical
11 controls, now might be a good time to start building
12 that database.

13 But if you're really going to do this, I
14 think we're talking about 20 countries, and maybe
15 you use the time to event analysis as well, just
16 like the Eculizumab, but there's a lot of -- I think
17 this is going to have to be global in order to do it
18 properly.

19 DR. SHEIKH: Thank you, Dr. Mateen.

20 I probably -- Dr. Porter, now you kind of
21 have it a little bit difficult here as the industry

1 representative, but I don't know if you have any
2 thoughts on how this could work in PML and what the
3 standard of care is and how that might impact, you
4 know, a clinical trial and the feasibility of a
5 clinical trial.

6 MR. PORTER: Oh, absolutely. Well, first
7 of all, thank you to the organizers for setting up
8 this meeting, it's been fantastic and, obviously
9 very, very important topics that we're covering. So
10 I think in terms of background therapy and standard
11 of care, you know, I don't have anything new to add
12 than the previous comments.

13 The one thing I will highlight, and the
14 previous speaker just hit a very important point
15 about the NMO trial being in 18 countries with a
16 fairly well-established, well-funded organization
17 being a lexicon that supported that trial, and so I
18 think part of the considerations and, frankly, the
19 challenge that we're facing, you know, as a private
20 small biotech interested in getting a product
21 approved for PML, you know, conducting a study in 18

1 markets is challenging, obviously, very expensive,
2 and very time consuming.

3 And so what we've been thinking through
4 is, you know, how do you balance a smaller
5 population with a smaller set of countries, on the
6 other hand, trying to clearly demonstrate benefit
7 for the therapeutic question.

8 So I don't have any unique insights on
9 this right now, our perspective is to go a smaller
10 set of countries, probably a global trial, but not
11 18 markets, probably more like eight to ten, with a
12 placebo-controlled arm is what we're considering at
13 this point.

14 All of the challenges that, frankly, have
15 been discussed in the last, you know, 45 minutes to
16 an hour, are things that we struggle with with many
17 of the participants in this conference. We've
18 talked to many of you, both individually and
19 collectively, and we landed on doing a randomized
20 placebo-controlled trial with all the
21 considerations.

1 DR. BERGER: I would just like to say that
2 I think the heterogeneity of the illness,
3 particularly the heterogeneity in the diseases that
4 predispose to PML make this particularly difficult,
5 that is having a placebo arm.

6 The thing that you want to do is to offer
7 the patient hope, and if you have somebody who has
8 an illness associated with a PML for which there's
9 really no hope, and the endpoint is going to be
10 death, to put them in a placebo arm I think is going
11 to be ethically very difficult, and I think it's
12 going to be very difficult for recruitment.

13 So I would say that those individuals that
14 are on drugs like MS drugs that predispose to PML,
15 there's hope there because taking them off the drug
16 is going to improve their survival, and their
17 ultimate outcome. And the same is true particularly
18 of the anti-retroviral therapy -- HIV patient where
19 establishing anti-retroviral therapy -- but then you
20 don't have the large numbers in order to decide
21 whether the drug really works or not, because those

1 people do so well.

2 On the other hand, those individuals who
3 have underlying illnesses where there's little
4 available, other than the things that we've just
5 mentioned, it's going to be enormously difficult
6 doing a study with a placebo arm when there is a
7 body of literature suggesting that the PD-1
8 inhibitors and the off-the-shelf T-cell therapies,
9 et cetera, and the IL7 whatever, it can offer some
10 hope to those patients.

11 So, you know, I'm not an ethicist, I think
12 that we probably should have had an ethicist on the
13 panel, but it makes -- I think it's difficult to do
14 those studies in that population with a placebo arm.

15 DR. MARRA: Oh, I so I disagree with you,
16 and I was waiting for Virginia to call on me, but
17 she didn't.

18 DR. SHEIKH: Sorry, Dr. Marra.

19 DR. MARRA: You're taking us back to
20 heresy and cidofovir, you know, in five patients it
21 worked, so we wasted all that time and all those

1 people who gave their bodies for us to test things
2 that didn't work. We need to have controlled trials
3 before we take everything that gives people hope
4 into primary care. We don't know that those drugs
5 work, there haven't been controlled trials. We
6 waste our patients goodwill by doing this.

7 I just so disagree with you and I think
8 you're just taking us back to where we were before,
9 and all you guys said the same thing, we should give
10 Aisle7 and Pembrolizumab, come on, they're unproven
11 therapies.

12 DR. VON GELDERN: But do these trials need
13 to be placebo controlled or can you test two
14 different treatments against each other to --

15 DR. MARRA: You can do that.

16 DR. von GELDERN: That would then that
17 improve enrollment and ethically maybe be better.

18 DR. MARRA: We just can't take something
19 that has a good idea and say that it's standard of
20 care.

21 DR. BERGER: Well, I didn't say it was

1 standard of care. What I said --

2 DR. MARRA: No, you did. You did say it
3 was standard of care.

4 DR. BERGER: I said it depends on the
5 patient.

6 DR. SHEIKH: So a couple of comments, one
7 is, I think that what we're talking about here is
8 equipoise, when we don't know whether something can
9 work or not, then generally is not unethical to not
10 provide that if you don't know if it will work or
11 not.

12 So, for example, offering -- you know,
13 offering Cidofovir, you know, it's not unethical to
14 enroll in clinical trial when you don't whether it
15 will work or not. And that's the case here with
16 Pembrolizumab and Aisle7 and other products that
17 haven't been evaluated in clinical trials.

18 So that's my personal view, and also, you
19 know, what we've seen in other disease areas where
20 that's -- that's been an issue; however, that
21 doesn't mean that, you know, patients aren't going

1 to be concerned about enrolling in
2 placebo-controlled trials, and then that's not going
3 to be a disincentive to participation.

4 But one thing I thought was really good
5 about Dr. Lee's talk is that he talked about
6 standard of care, rather than placebo, so if we can
7 work out what might be the standard of care, then
8 the comparator group can be standard of care,
9 provided it doesn't negatively impact the, you know,
10 the investigational agent.

11 And then one other comment with the two --
12 Dr. von Geldern, you mentioned comparing
13 two things. The problem is, if you offer two
14 different treatments and both of them do the same,
15 then you don't know whether or not they're --
16 actually both of them don't work or whether both of
17 them do work.

18 DR. SHEIKH: Dr. Martin-Blondel, do you
19 have any comments about the thoughts on what might
20 be a comparator arm or control arm?

21 DR. MARTIN-BLONDEL: Yeah, this is

1 difficult really. Once again, it's a difficult
2 question, this field. Just to come back to the
3 standard of care. To my opinion, standard of care
4 is only treating the underlying condition -- HIV,
5 stopping immunosuppressive drugs in others, and the
6 issue is that for the patient with primary
7 immunodeficiency -- okay.

8 What about selecting underlying conditions
9 where we know that the prognosis is clearly dismal,
10 and this did not change according to time, and
11 specifically patient with primary immune
12 deficiencies.

13 And to compare two or more therapeutic
14 interventions -- because we know that in those type
15 of patients, we have nothing done this for 90% of
16 them at one year, and this did not change according
17 to time in the last 20 years.

18 DR. SHEIKH: Thank you. Dr. Mateen, do
19 you have any additional thoughts since the
20 conversation has evolved since we last talked to
21 you?

1 DR. MATEEN: You know, I think that it's
2 been a really exciting conversation actually about
3 controls, but I think what are we not doing now that
4 we could be doing, besides launching on a trial. So
5 since PML is not a reportable disease officially,
6 like is this an opportunity to start pooling data in
7 a database for historical controls, if that ever
8 becomes valuable.

9 Just thinking ahead about, you know, what
10 do we have right now or if we don't know what the
11 standard of care is, should we be asking a group of
12 neurologists what the standard of care is, if it is
13 controversial. I don't know if it is, but there's
14 just -- I think we have opportunities at this
15 second.

16 I actually think historical controls would
17 be a very appropriate control group. I think that,
18 you know, there's a separation between HIV and some
19 other illnesses versus the rest, but, in general,
20 historical controls, I think, are an appropriate
21 choice, and I agree that placebo feels difficult.

1 It felt more wrong in NMO than it would in PML, but
2 I worry that it's such a rare disease, people
3 wouldn't actually enroll in various placebo.

4 DR. SHEIKH: Dr. von Geldern, with this
5 issue of historical controls has come up, and I know
6 that in the past you worked on trying to establish a
7 registry, which, you know is something that could be
8 used for historical control, but do you have any
9 comments about, you know, the logistics there, you
10 know, why it hasn't happened already, despite the
11 fact that there's been clinical trials going on --
12 or I'm sorry, there's been PML care problems for
13 over 40 years?

14 DR. VON GELDERN: Exactly. Thank you for
15 letting me speak to that. I completely agree with
16 that that it would be wonderful to have more data,
17 which is why, Dr. Major in particular, tried to
18 bring forward many years ago a registry for PML to
19 collect this -- exactly this data.

20 One of the big challenges in PML and in
21 getting the historical control data is that the

1 underlying diseases are so varied, and so these are
2 patients that are not necessarily always cared for
3 by the same even medical community or medical
4 providers, so there might be hematologists taking
5 care of people with PML; there might be oncologist,
6 obviously there's overlap; there might be
7 neurologists, hopefully neurologists will be very
8 involved.

9 But sometimes these patients have
10 underlying -- diseases, underlying rheumatologic
11 diseases, so I think the -- it's not just a -- not a
12 reportable disease, but it's also treated by so many
13 different providers, and it is rare. So it's not
14 that there are centers where thousands of people are
15 treated.

16 So what we found is that it's really
17 challenging for collecting this data to get buy-in
18 by enough people to actually be willing to submit
19 this without -- especially if there's no funding to
20 actually put effort and time into this.

21 So I think it would be hugely important to

1 collect historical data and learn from these various
2 patients with very different underlying diseases,
3 but it's been -- I think it's worthwhile to pursue
4 this, but it has been really challenging I think to
5 do this, it's not as simple as for some other
6 diseases that are maybe more in the hand of one
7 specialty or in the hand of -- I don't know -- one
8 entity that you can tap to try to provide this data.

9 The other thing I wanted to comment is
10 that I wonder if, contrary to what
11 Dr. Martin-Blondel just said, maybe we should study
12 a large group that's available, either HIV or, let's
13 say, MS patients where outcome is not as abysmal and
14 do a trial there where standard of care is removing
15 the offending agent like Natalizumab or giving hard
16 therapy, and then having an add-on of either agent
17 that you're interested in studying, either one or
18 it's multiple, because it's maybe less unethical in
19 patients who have a relatively good outcome to try
20 this.

21 So almost like the compliment to studying

1 these patients with primary immunodeficiencies and
2 not having a placebo group there. That's just one
3 other thought.

4 DR. BERGER: Yeah, I'm strongly in favor
5 of that, and had suggested, I thought. I agree.

6 DR. VON GELDERN: Sorry if I didn't
7 understand that then.

8 DR. BERGER: Yeah, no, no. I think that's
9 what we should do.

10 DR. SHEIKH: Dr. Berger and Dr. von
11 Geldern, you're both suggesting, I think, that the
12 group to be -- or at least if you were to study the
13 patients who probably have the best outcomes, which
14 is patients who are on -- who you can start HIV
15 therapy or who can stop Natalizumab, in other words,
16 they have a reversible immunosuppression, you know,
17 immunosuppression that can be reversed, and then you
18 use that as the standard of care, and you add on
19 additional therapy; is that correct?

20 DR. BERGER: Well, I think that that would
21 be the cleanest and the most palatable to a lot of

1 people, because you know that the prognosis is
2 reasonable if you're able to restore the immune
3 system.

4 I do think that, as I mentioned earlier
5 this morning, I think we're going to have to
6 homogenize our study populations, otherwise you're
7 going to have to have a huge study that's going to
8 be very, very difficult to recruit into, and then
9 the hope is the that you hit a home run with
10 whatever therapeutic agent you have so that you see
11 a clear signal that the thing works.

12 And if you have a drug that will provide a
13 home run, it would seem to me that you could do that
14 in the HIV or the MS population, although the
15 numbers in PML in the MS population are dwindling,
16 so you may be stuck with HIV. The alternative,
17 though, is to do a comparative trial, in my opinion,
18 a for group like the individuals that have an
19 underlying hematologic malignancy, because as a
20 treating physician, I just feel very uncomfortable
21 not -- not doing anything.

1 DR. SHEIKH: So in the standard of care,
2 you would consider not doing anything; is that
3 right, Dr. Berger?

4 DR. BERGER: Well, I think the standard of
5 care -- look, it's difficult to say what I do is
6 necessarily the standard of care, it isn't, and we
7 all have our -- there's nothing formulaic about the
8 treatment of PML right now.

9 And I will tell you that there's no
10 consistency in my treatment of PML patients, none.
11 It's not like you're going to find it in the back of
12 Up-To-Date, you're not, there's just nothing
13 formulaic because there's no accepted therapy.
14 Although I do offer patients the therapies that I
15 mentioned, particularly in those instances where I
16 can't reverse the immune system.

17 DR. SHEIKH: So, Dr. Thakur -- oh, go
18 ahead, Dr. Porter.

19 DR. PORTER: I was just going to ask the
20 opposite question. So -- and I believe it was
21 mentioned before, both for Dr. Berger and von

1 Geldern -- what if you did the opposite, so instead
2 of large group where the outcome is not as abysmal,
3 what if you went to a more targeted, homogenous
4 group where, unfortunately, the outcome is more
5 challenging and abysmal, would that be a more ideal
6 population to study with the objective of trying to
7 have an approved agent in this fatal disease?

8 DR. BERGER: I think you'll arrive at an
9 answer sooner with a smaller number of patients, but
10 convincing patients and treating physicians that
11 this is acceptable may be difficult.

12 DR. SHEIKH: So I'm going to call on
13 Dr. Thakur because I haven't heard from her, and I
14 know that this is a difficult time to weigh in, but
15 I guess my question would be so, you know, we're in
16 a place where it sounds like there's -- that
17 different treating people who are expert at PML feel
18 differently about what the standard of care is and
19 feel uncomfortable -- some feel uncomfortable with,
20 you know, not giving something like AISLE7 or
21 Pembrolizumab, which we don't know whether they work

1 or not.

2 So the question is, you know, for you
3 Dr. Thakur, is do you see a future moving from not,
4 you know, giving treatments where we don't know
5 whether they work or not, to being able to find out
6 whether they work and, you know, where do you -- if
7 you see that future, where do you where do you think
8 it could come, from what angle?

9 DR. THAKUR: Yeah, I mean, I think maybe
10 this is -- some of the discussion, which I think is
11 really fruitful, is around kind of what we mean by
12 standard of care, I mean, certainly what I think
13 we've all shown as we do more of individualized,
14 personalized medicine approach, and we're often
15 using therapies on an individualized basis that
16 doesn't have a lot of experimental evidence.

17 But I don't think that means that we
18 cannot develop trials that are robust and provide
19 information about efficacy of treatments. And I
20 really think that maybe the idea that we somewhat
21 homogenize the underlying kind of population that

1 Gloria mentioned, you know, perhaps with kind of one
2 underlying condition, that might be a way for us to
3 kind of understand what works.

4 I think the HIV population and response
5 and kind of after they've been given
6 anti-retrovirals, I think, with all the kind of
7 issues around, you know, potential for PML IRIS is
8 one population that we know could -- we could study
9 really effectively, especially in a global
10 population.

11 I think there's two other issues, one is,
12 you know, we heard from the patients, and I think we
13 always have to think about or what is their voice.
14 We had, I think, a great study looking at responses
15 to surveys and how they would feel about clinical
16 trial design, and greater than 50% being concerned
17 and would not enroll in a placebo-controlled trial,
18 I think, is one that we really have to think
19 carefully about before we decide to do it, because
20 that is going to affect our enrollment and
21 recruitment.

1 And that perspective, I think, really --
2 really has to be taken very seriously.

3 And then I think, secondly, if we're going
4 to consider a global study of, you know,
5 HIV-infected patients, I think that we really also
6 have to consider the applicability of the treatment
7 itself.

8 And if we're looking at resource limited
9 settings, you know, this isn't talking about the
10 control population necessarily, but it's really
11 important that we don't ignore that issue as well in
12 terms of whether this potential treatment could be
13 deployed to this patient population.

14 DR. SHEIKH: Dr. Marra, do you want to --
15 it sounds like there's a chat going on, would you
16 mind explaining what your ideas are that you've
17 discussed in the chat?

18 DR. MARRA: Well, I was just suggesting
19 that, based on what our industry person said, that
20 we could pose a trial where we had newly-diagnosed
21 HIV infected people with PML, because that's

1 truthfully what I see the most of anyway, and we
2 would randomize them to combination and a retroviral
3 therapy versus combination and a retroviral therapy
4 with Pembrolizumab or with Aisle 7.

5 That would be a group that would be
6 expected to do probably poorly, so you could get an
7 answer pretty quickly, and you could also get some
8 information about IRIS, I think, with that, and you
9 maybe wouldn't have to have a huge number of people.
10 But that was my pitch now that all the coffee I
11 drink has worn off.

12 DR. SHEIKH: So now what about -- I think
13 that I'd also like to talk about the other groups
14 that we haven't discussed too much right now. We've
15 talked about patients with underlying HIV, and we've
16 talked about people with MS, but can we talk a
17 little bit more about patients who really don't have
18 a reversible -- don't have immune suppression that
19 is readily reversible?

20 So I'd like to ask Dr. Mateen to weigh in
21 on, you know, how -- if we were to think of clinical

1 trials for this patient population, you know, what
2 would the standard of care be for these patients,
3 and would that include in those patients, say,
4 patients who have a history of lymphoma or had ICL,
5 would that include ICL as a standard -- would that
6 include Aisle 7 or Pembrolizumab as a standard of
7 are and, if so, how would that be integrated into
8 something like a cell therapy trial.

9 DR. MATEEN: Yeah, that's a good question.
10 So I think the two groups that we haven't talked
11 very much about are the hematological malignancies
12 and potentially the transplants. And it brings to
13 light that many patients who have PML have more than
14 one risk factor for PML, so they may have both
15 malignancy and a history of transplant and multiple
16 immunosuppressive onboard, for example, and so it's
17 hard to know.

18 For example, you might reduce the degree
19 of immunosuppression in those patients, but they
20 still have two other underlying risk factors for
21 PML.

1 So in terms of -- you know, they're a more
2 homogenous group, and I think that that makes a lot
3 of sense to actually focus on those. As was said
4 earlier, the number of people with MS who have PML
5 is exceedingly small now because of vigilance for
6 it, and HIV -- I guess I don't know the incidents of
7 PML in HIV now, but I understand that it's much less
8 than what it was.

9 And so -- and I think Dr. Spudich earlier
10 mentioned, PML at the time of presentation versus
11 PML in somebody with well-controlled HIV may
12 actually be very different groups. So the
13 hematology patient population is, I think, a ripe
14 group for study; transplant is itself homogenous
15 so -- or heterogenous in the sense that they could
16 be solid or not.

17 So I don't think there is -- any group is
18 actually not that homogenous within itself, so the
19 more you know about the group, the more difficult it
20 looks.

21 But, you know, if I had to design a trial,

1 I think that HIV is still of interest, but the hema
2 malignancies I would also focus heavily on or even
3 people on specific drugs, no matter what their
4 underlying disease.

5 DR. THAKUR: I think this is where the
6 historical controls could be really useful. And I
7 know you, I'd love to hear more -- I know Gloria
8 kind of started -- large natural history study
9 that's bring run through the NIH, but this also
10 depends on our outcome measures but, you know, for
11 those kind of rare underlying conditions, using that
12 historical control, I think, could be really, really
13 valuable, depending on the kind of variables that
14 have been collected.

15 DR. SHEIKH: So I think for the -- the
16 problem with the historical control is we need to
17 identify a group that can be the historical
18 controls, and I am not aware, other than I know --
19 other than Gloria von Geldern's attempt to establish
20 a registry, I'm not aware of any true historical
21 control database that would be, you know,

1 non-biased. I'm not sure if -- is there anyone on
2 the panel who's aware of any of these kind -- where
3 this database might be, if there is one?

4 DR. THAKUR: I wonder if Irene can speak
5 about the ongoing NIH that -- the details of which
6 I'd like to --

7 DR. CORTESE: So we do have a natural
8 history study at NIH and, you know, ongoing
9 collection of data, but, you know, it's still
10 relatively limited, and I think that there would be
11 much to gain from being able to pull, you know, from
12 different sources.

13 Also, the patient population that we see
14 might have Certain biases, you know, for referral to
15 our center, and we certainly wouldn't want to carry
16 those forward too much, so, again, I think it's
17 really important to pool resources, and probably as
18 we'll be talking about later as well, I think what
19 would be really helpful is as a community, you know,
20 to develop standardized core set of outcomes that
21 we're all collecting and that will facilitate, you

1 know, going forward, you know, trial design and so
2 on.

3 What we've also seen at NIH, at least, is
4 that when our natural history study was going
5 forward without the possibility of offering a
6 treatment option, we were getting mostly long-term
7 survivors of PML and not so much active PML, which
8 is where we really need to focus if we want to
9 develop biomarkers and learn about trial designs
10 and, you know, appropriate interventions.

11 And so I think that trial design -- sorry,
12 clinical trials interventional studies themselves
13 are the way to learn how to design clinical trials
14 better and -- yeah. So I think we need to make more
15 efforts in that direction a well. I don't think I
16 really answered your question.

17 DR. SHEIKH: Thank you, Irene, I think
18 that does answer the question about what you have in
19 terms of a natural history, you know, a database or
20 historical data.

21 I will also mention, Carey Jolie of rare

1 diseases at CDER, has put in a link in the chat for
2 everyone that there is a new -- I think it's been
3 two years ago that this was launched by the FDA --
4 funding through the FDA for the rare disease cures
5 accelerator data and analytics platform, so this is
6 a platform which is a centralized and standardized
7 infrastructure to support and accelerate rare
8 disease characterization with the goal of developing
9 accelerating therapy development.

10 So it was funded through an FDA grant to
11 the Critical Path institute and was developed in
12 collaboration with NORD. And so essentially what
13 this is an opportunity to share databases, and I
14 would really encourage everyone here if we think
15 that historical controls are very important, then we
16 need to develop this and this is potentially a way
17 of getting information about the natural history of
18 PML without starting a registry, which also might be
19 an important thing to do.

20 So that's my plug for RDCA Dap. So before
21 I --

1 DR. VON GELDERN: Can I give one --

2 DR. SHEIKH: We have about --

3 DR. VON GELDERN: -- on this problem of
4 getting the control data. So I think we heard from
5 the patients in both their stories that diagnosis is
6 often delayed, and I think maybe one effort needs to
7 somehow go to spreading the word about PML -- this
8 sounds silly to ask here -- but I think if more
9 non-neurologists or non-PML experts were recognizing
10 the disease or were at least referring patients for
11 PML, maybe we would collect more meaningful data.

12 Because I think a lot of patients with PML
13 are not collected because we don't even know that
14 somebody -- I saw patients who had some malignancy,
15 and as soon as there was any concern for PML they
16 say, well, we've stopped treatments, you have PML,
17 that's it. So I think we are missing a lot of
18 patients that we don't even ever hear about.

19 DR. SHEIKH: That definitely makes sense.
20 And I think the patients -- every patient who's
21 communicated with us about their perspectives would

1 agree with you, Dr. von Geldern, that, you know, the
2 word needs to get out, we need to get patients
3 diagnosed earlier, that would facilitate clinical
4 trial participation, and also likely increase the
5 likelihood that an intervention could have an affect
6 also.

7 So before we wrap up this session, I
8 believe we have only five more minutes, and I don't
9 think we've gotten to the bottom of this, but I'm
10 going to ask again, just I'm going to reframe the
11 question.

12 So in order to get products approved in
13 the United States or in order to know that something
14 works, we need to have confidence that whatever
15 intervention it is, is actually doing better than
16 what would have happened had we not given the
17 intervention.

18 And the problem with the historical
19 controls, number one, we don't really have
20 historical controls for PML right now, we have a
21 heterogeneity of patient populations with differing

1 outcomes; we have changing things -- changing
2 therapies over time for those underlying diseases.

3 So in the last four minutes, if I can have
4 just a 30 second -- ask each of you to -- each of
5 the panelists to give me your opinion about how we
6 can move forward, what is the best, most appropriate
7 control for PML.

8 And I'm going to use the example of the
9 patients without reversible immunosuppression
10 because I think that's the area where, you know,
11 that's going to be the hardest ethically. I'm going
12 to ask you all to just weigh in for 30 seconds on
13 which -- what control can we use, is it historical
14 control or is it placebo or a standard of care, and
15 if so -- if it's a standard of care, what's that
16 standard of care.

17 So, Dr. von Geldern, I'll start with you
18 since you're on my screen right now.

19 DR. VON GELDERN: I think what's come out
20 of this discussion is that we don't know. I think
21 my -- would be for a placebo-controlled trial in a

1 patient group that has a reasonable survival rate or
2 where we are doing other interventions, like
3 restoring the immune system, whether it's HIV or
4 Natalizumab, and maybe trying out as much as there's
5 limits to that, different treatments without a
6 placebo group in patients where we can't restore the
7 immune system.

8 DR. SHEIKH: Thank you.

9 And Dr. Berger?

10 DR. BERGER: Well, if I understood the
11 question right, Virginia, you're really looking at
12 that group of individuals who has PML, who do not
13 have an immune deficiency that's readily reversible.

14 DR. SHEIKH: Correct.

15 DR. BERGER: And if that's the group
16 you're talking about, what I would suggest is
17 looking at historical controls. I'd be quite
18 comfortable with that knowing that these are
19 individuals that, by and large, do not recover and
20 end up dying.

21 And I would think that, you know, the hope

1 is that you have a strong signal from whatever drug
2 you're giving where, you know, maybe the survival is
3 50% or 80% and you could say quite comfortably that
4 there's clearly an effect from the drug.

5 DR. SHEIKH: So, Dr. Mateen?

6 DR. MATEEN: Yeah, I guess I would just
7 say that perfect is the enemy of the good here, and
8 I think we can get historical controls, you know, I
9 think that that is just a matter of investment and
10 effort and collaborations. I don't think not having
11 them as a good enough excuse, I think we should try
12 to get them and work on it.

13 But I like historical controls because
14 it -- I think ethically it is the appropriate thing
15 to do here, and we don't have to worry about
16 enrollment in the same way. And I think the disease
17 is very rare, I think this study could be like
18 several years long, so we'll just have to hold on
19 for results.

20 DR. SHEIKH: And Dr. Thakur?

21 DR. THAKUR: Yeah, I agree with Dr. Berger

1 and Dr. Mateen. As I said earlier, and I do think
2 there is an opportunity here, we have a model of a
3 natural history study at NIH to expand across sites
4 in which the number -- the places that are practiced
5 still see a lot of PML across different populations,
6 especially at places that have high volumes of
7 transplanted patients.

8 So I think there is a real opportunity, as
9 Dr. Mateen said, and I think historical controls are
10 going to be one component. I know you didn't ask
11 this, but I do think that a trial looking at, you
12 know, new diagnosis of HIV starting retroviral
13 therapy and then doing a real kind of treatment
14 trial would be, you know, a good idea. I think
15 that's really important for the field to advance as
16 well.

17 DR. SHEIKH: Dr. Martin-Blondel?

18 DR. MARTIN-BLONDEL: If we need a
19 controlled trial with a control group with a -- I
20 would rely -- I would say, as Christina said,
21 newly-diagnosed HIV patients with -- only and --

1 plus anything else as the experimental group, and I
2 would not rely for those kind of patients on
3 historical controls because they changed according
4 to time, except for patients with no reversible
5 immunodeficiency.

6 DR. SHEIKH: And Dr. von Geldern? Oh, I
7 think I asked you this already.

8 DR. VON GELDERN: You did.

9 DR. SHEIKH: Dr. Porter?

10 DR. VON GELDERN: I might not have
11 answered your question exactly, but I think that's
12 all I have to say.

13 DR. SHEIKH: Sorry. Dr. Porter?

14 DR. PORTER: I'll keep this brief. SO I
15 agree with Dr, Berger and Dr. Mateen, for this
16 patient population that you specified in your
17 question, I think historical controls seems like it
18 balances all considerations.

19 DR. SHEIKH: All right. Thank you. So we
20 are now going to enter -- thank you all, panelists,
21 this was a very interesting conversation. It

1 doesn't seem like we've worked out everything for
2 PML, but hopefully we've moved the bar forward a
3 little bit.

4 Now we're going to go on a break for nine
5 minutes until 3:05 Eastern Standard Time. So I'll.

6 (Whereupon, a break was taken.)

7 DR. SHEIKH: Okay. Welcome back from your
8 last break of the day before the workshop concludes.
9 We're going to now dive right into the last session,
10 which is focused on putting all this discussion, all
11 the topics we've discussed today, together into
12 trial designs.

13 And we'll have the panel experts, which
14 will be moderated by Dr. Baldassari, who you met
15 earlier. But to put everything into perspective to
16 try to put all the pieces together, including some
17 of the aspects of clinical trial design that we
18 haven't discussed already today, we're going to have
19 Dr. Irene Cortese come back from NINDS, and along
20 with Ken Cheung, who's a of biostatistics at
21 Columbia University.

1 Dr. Cortese?

2 DR. CORTESE: So thank you. And today
3 I'll be speaking together with Ken Cheung on behalf
4 of the Clinical Trials Working Group, whose members
5 are listed here in this slide.

6 As we've heard throughout the day,
7 obviously, PML poses several specific challenges
8 that impact trial design, and we've also heard
9 pretty clearly that it seems unlikely that we're
10 going to be able to identify a one-size-fits-all
11 approach, and most approaches will be compromised on
12 some level.

13 And so just to review again in the next
14 slide, PML is a rare disease, which has clearly
15 contributed to the limited availability of reliable
16 natural history data and, therefore, also to the
17 lack of established clinically meaningful
18 biomarkers, and also generally limits feasible
19 sample sizes for clinical trials.

20 Next.

21 It's commonly a rapidly fatal disease,

1 which can impact recruitment and retention to
2 clinical trials. The lack of any validated therapies
3 limits options for control arm, as we've heard, and
4 can, therefore, also impact acceptability of a
5 concurrent control arm. And generally acceptability
6 and feasibility of a complex studies schedule is
7 impacted by patients with rapid accrual of
8 disability.

9 Next slide.

10 The patient population is very
11 heterogeneous with heterogeneous outcomes, which
12 impacts most aspects of clinical trial design from
13 decisions over eligibility criteria to appropriate
14 endpoint selection, selection of the interventional
15 approach itself, and also simply a need really to
16 account for complex clinical outcomes, such as IRIS
17 or progression of underlying disease.

18 So in the next slides, Ken Cheung and I
19 will give a high-level outline of how some of these
20 factors might need to be taken into account when
21 designing a clinical trial for PML, and much of this

1 has already been hashed out in the previous panel
2 sessions and will be talked about, surely, in the
3 final panel session.

4 And to be clear, this discussion is not
5 intended to be prescriptive, nor really
6 comprehensive, and the goal is really more to
7 broadly bring together what we've heard today and go
8 a little deeper with an overview of statistical
9 efficiency, and essentially list some of the
10 tradeoffs that need to be considered when designing
11 trials.

12 So in the next slide we'll start with
13 patient heterogeneity.

14 Next slide.

15 Patient heterogeneity can affect
16 considerations for inclusion in trials for PML in a
17 number of ways, and perhaps most importantly,
18 because a given treatment approach might be more or
19 less appropriate for different patient populations.
20 So for example --

21 Next.

1 A JCV antiviral drug might be conceivably
2 offered to all patients with PML from the time of
3 first diagnosis.

4 Next.

5 While on the other hand, experimental
6 immune rescue strategies might be risky in patients
7 likely to develop PML IRIS with standard of care,
8 and so strategies might be more appropriately
9 reserved for patients with PML that have clearly not
10 responded to standard of care approaches attempting
11 to reverse the immune suppressed state, such as,
12 anti-retroviral agents in HIV-related PML or
13 discontinuation of immune suppressive agents, or
14 simply reserved for patients for whom no true
15 standard of care approach is available.

16 The type of intervention and the patient
17 population to which it's most appropriately applied
18 will in turn impact other aspects of trial design.

19 Next.

20 While including a narrowly-defined patient
21 population might lead to more uniform expectation of

1 outcome, as we've talked about, inclusion of the
2 more heterogeneous population with wide expectation
3 of outcome would likely require a stratification to
4 ensure that study arms are balanced. And here among
5 the recognized prognostic factors that might be
6 considered would be --

7 Next.

8 -- the underlying predisposing disease
9 and --

10 Next.

11 -- the level of disability at study entry
12 and --

13 Next.

14 -- the JCV CSF copy number at study entry,
15 and possibly last --

16 Next.

17 -- even the extent or location of PML
18 lesion burden or perhaps other MRI features.

19 Next slide, please.

20 As we've heard in earlier talks, inclusion
21 of heterogeneous populations could also greatly

1 affect the selection of an appropriate
2 clinically-relevant endpoint.

3 Next.

4 Such as survival being appropriate for
5 some populations with the worst prognosis or --

6 Next.

7 -- a measure of disability for others with
8 less severe prognosis or --

9 Next.

10 -- even consideration of some sort of a
11 ranked outcome that might take into consideration a
12 broader spectrum of disability, and also survival
13 or --

14 Next.

15 -- possibly even a surrogate endpoint
16 might be feasible in some clinical trial designs.

17 As we've also heard today, patients with
18 PML can present a complex clinical course that could
19 confound and point interpretation, and specifically
20 a PML clinical trial would need to consider ways to
21 clearly identify and distinguish between such

1 events.

2 So next slide.

3 Next.

4 Such as definition of PML IRIS --

5 Next.

6 -- progression of the PML itself --

7 Next.

8 -- of the underlying disease, including,
9 for example, situations brought up earlier in the
10 chat box of how to weigh in situations of withdrawal
11 of supportive care or --

12 Next.

13 -- simply identifying adverse drug
14 reaction. And since often the distinction between
15 these events might not be straightforward,
16 consideration might be given to establishment of
17 adjudication committees to provide objective
18 determinations.

19 Next.

20 The lack of robust natural history data
21 and lack of established clinically-meaningful

1 outcomes urges development of consensus and
2 standardization of a core set of key secondary
3 outcomes that might be applied across clinical
4 trials, and also to allow pooling of data across
5 studies, as we talked about earlier.

6 Next slide.

7 And so such outcomes would likely include
8 --

9 Next. Next. Next. And next.

10 -- standardization of PCR assays of MRI
11 protocols, development of clinical disability
12 scales, and also identification and validation of
13 key immunological measures. And this would also
14 surely offer the opportunity to develop maybe a
15 combined clinical outcome or a combined biomarker in
16 clinical outcome, as has been mentioned earlier, as
17 well as to learn more about pathophysiology of the
18 disease, as also discussed earlier today.

19 Next slide.

20 Increasing patient acceptability to
21 participate in clinical trials is obviously

1 essential for recruitment and retention.

2 Next.

3 And so integrating concerns voiced by
4 patients and caregivers, as we heard earlier today,
5 including --

6 Next.

7 -- limiting requirements for travel to
8 study sites, developing and validating decentralized
9 outcome collection, limiting frequency of invasive
10 study procedures, increasing acceptability of
11 control arm, as we'll hear a little bit later, and,
12 more generally, improving access to information
13 about available trials and about disease in general.

14 Next.

15 And simply conducting more trials to
16 increase available options.

17 And I'll now hand over to Ken Cheung, who
18 will continue.

19 DR. CHEUNG: Thank you, Irene. First, I'd
20 like to say that it is my pleasure to work with this
21 working group for this important effort to see how

1 we can improve visibility of doing trials in PML.

2 So in the next few minutes I'm going to talk about
3 the range of sample size requirement --

4 Oh, maybe next slide.

5 Yes. So in the next few minutes, I'm
6 going to talk about the range of sample size
7 requirement that we may anticipate in the PML trial,
8 and how we may make efficient use of data from a
9 statistical perspective.

10 We're going to look at sample size in
11 relation to two aspects of clinical trial design.
12 First, in relation to choice of endpoint, second, in
13 relation to the control arm.

14 So next slide.

15 So first we'll look at sample size
16 associated with different endpoints.

17 Next -- maybe next two as well. Thank
18 you.

19 So for PML, as in other fatal conditions,
20 the specific survival is obviously clinically
21 relevant, but the question is whether it's feasible

1 in terms of sample size requirements. So this is
2 one of the questions that we're going to explore.
3 In addition to survival, the functions and
4 disability also clinically relevant.

5 The Modified Rankin Scale, for example, is
6 a composite score that includes death and disability
7 on a single scale, but for PML, it's likely that
8 such a composite scale will mainly be driven by the
9 death outcomes, so the impact on the sample size by
10 including disability might be very minimal.

11 I'd like to emphasize that this is -- my
12 discussion is purely based on a sample size
13 perspective, clinically it's definitely very
14 important to track the quality of life, disability
15 of the patient.

16 A third possibility is that we're going to
17 use a biological endpoint, which we will define and
18 explore on the next slide.

19 So next.

20 Oh, and one more -- and finally, we will
21 actually look at how increasing criteria together

1 with the choice of endpoint will effect sample size.

2 Next slide.

3 We will consider JCV copy number as an
4 example of a biological measurement, which has been
5 demonstrated to assist with survival. As my
6 colleagues here my know, that JCV copy number is a
7 measurement, not an endpoint. We need to define how
8 the measurements are used to calculate a JCV-based
9 endpoint. So there are many ways to do it, and we
10 have considered three approaches.

11 So next. Next.

12 Yes, so the first approach is to consider
13 a biological response defined with respect to a
14 pre-specified threshold. For example, we call it a
15 JCV responder when the JCV DNA decreases by a
16 quarter on a -- scale over 60 days from baseline, so
17 this is how we can define a JCV base response. And
18 the advantage of using a respondent analysis is that
19 it provides a very clear clinical interpretation and
20 guidance.

21 Next.

1 The second approach, we find the
2 respondent analysis by adding JCV categories to
3 reflect more granularity. In addition to the
4 improvement defined by a decline in JCV, we may add
5 a category to -- defenses these patients with
6 worsening JCV from those with stable JCV values over
7 time.

8 In other words, it is an ordinal scale
9 with three levels, which also offers clear
10 interpretation, albeit, slightly more complicated
11 than the responder analysis.

12 The third way to define a JCV-based
13 endpoint is to look at the ratio between JCV DNA on
14 day 60, and based on JCV. A small ratio of forward
15 change will indicate improvement; however, you could
16 be unclear what -- for change would be considered
17 clinical important, so there may be some gray area
18 in interpretation.

19 These are the three ways that we have
20 considered on how to use JCV measurement as an
21 endpoint.

1 Next slide.

2 This slide gives the range of sample size
3 that we may anticipate when different endpoints are
4 used. Let's start from the Left, where survival
5 time is at the endpoint. If we include patients
6 from all disease categories, one estimate is that
7 patients under standard of care may have about 47%
8 one year survival, and the assumed relative risk of
9 a .6 by an intervention, which is a large effect
10 size. The required sample size is 137 per arm in
11 order to achieve 80% power in a one-to-one
12 randomization RCT.

13 Now, if we include patients with worse --
14 prognosis, say having a 20% one-year survival under
15 standard of care, the required sample size will be
16 86 per arm under the same relative risk assumption,
17 so it's a much smaller sample size. And this point
18 has been noted by some previous panelists.

19 How about the use of JCV-based endpoint?
20 If you use a responded analysis, as we defined in
21 the previous slide, and if you assume an -- of 2.5

1 by the intervention, the requested sample size will
2 be 86 per arm to achieve 80% power. Under the
3 same -- assumption, if you use an ordinal endpoint,
4 that would reduce sample size slightly to -- per arm
5 in the one-to-one RCT.

6 Now, if you we use a continuous -- as an
7 endpoint, the sample size reduction can be dramatic,
8 as you're requiring only 32 patients per arm. So we
9 see actually quite a range here in terms of a sample
10 size requirement, depending on how we choose the
11 endpoint.

12 While these assumptions on this effect
13 size are not directly comparable for different
14 endpoints, they represent effect size that is large,
15 but not unrealistic based on some of the JCT data
16 that we have seen in the pilot.

17 Next.

18 So here's a few points that I'd like to
19 recap. First, the use of our PML-specific survival
20 as an endpoint is clinically relevant, but it may
21 require a large sample size that will put visibility

1 in question. And the sample size requirement can be
2 reduced quite a bit by including patients with poor
3 survival prognosis only, but that will also mean
4 reducing the pool of patients that we may enroll
5 from.

6 Next.

7 Second, the use of JCV-based endpoint
8 reduces sample size requirement to varying degrees,
9 depending on how we define it. In general, it may
10 be more feasible than using a server for endpoint,
11 not only because of the smaller sample size
12 required, but also because of the possibility of a
13 large effects when the biological measurement is
14 a -- target of an intervention.

15 And in addition, because we anticipate
16 changes in JCV or any other biological measurements
17 to occur over a much shorter period of time, we can
18 complete a proof concept trial using a JCV endpoint
19 much more quickly.

20 And having said that, we still need to
21 correlate each biological endpoint with survival in

1 the trial as a secondary analysis.

2 Next.

3 And the last point is, as I mentioned, the
4 incorporation of disability score with that may have
5 a minimal impact on sample size, simply because of
6 the fact that the scale will be mainly driven by the
7 death outcome.

8 So next.

9 So the second aspect I'd like to talk
10 about is sample size and the choice of the control
11 arm.

12 Next, please. Thanks.

13 There have been quite a few discussions
14 about the use of historic control, so the
15 consideration here is that whether it exists, and if
16 such a cohort exists, it would definitely reduce the
17 sample size substantially. Of course, using a
18 historical control is often tricky due to difficulty
19 in interpretating causation of the --

20 So in the next scenario --

21 Next.

1 -- we would compare the intervention with
2 a concurrent control arm in a randomized study. In
3 my sample size calculations, I assume a one-to-one
4 randomization ratio, which would offer the most
5 power for the same sample size as an -- we may
6 conduct a trial with a two-to-one randomization
7 ratio, this approach may improve patient
8 acceptability because patient will more likely get a
9 treatment that they perceive that will work;
10 however, it will be achieved at the expense of
11 requiring a larger sample size.

12 So there's a trade off between efficiency
13 versus whether patient will accept the trial.

14 And that leads to the next scenario where
15 we will compare multiple candidate interventions to
16 a shared control arm.

17 So now, the design of a trial with
18 multiple interventions is more complicated than a
19 trial with only one intervention versus the control,
20 but it also offers an opportunity for -- design
21 concept that would lessen sample size requirement

1 overall.

2 We're going to go over two concepts.

3 Next.

4 So the first design concept we would like
5 to consider is a use of -- study. In the phase two
6 portion of this trial, patients will be randomized
7 through all interventions and the standard of care,
8 which was service the shared control arm. At the
9 end of the phase two trial, one intervention will be
10 selected based on the biological endpoint, and you
11 may be moved forward to a phase three trial.

12 In the phase three portion, then we will
13 compare survival of the two -- of the standard of
14 care versus the selected intervention. This design
15 can be adaptive in the sense that the sample size of
16 the phase three trial, maybe we estimate it based on
17 the phase two data, and this design can be efficient
18 In that the final analysis, by the end of the phase
19 three trial, when you encrypt data collected in the
20 phase two trial, as well as data in the phase three
21 trial.

1 So we're not -- so these are two trials in
2 one concept, but we're going to be able to use data
3 from two trials in the final analysis. So this is
4 the first design concept on the next slide. We're
5 going to have a second design concept that is
6 related to running a platform trial under a massive
7 protocol where multiple interventions may enter a
8 trial in a staggered and, again, they'll be compared
9 to a shared control arm.

10 There are many advantages of running a
11 platform trial, it creates an infrastructure that
12 can move new treatments through -- quickly, the data
13 management system is already in place, so there's
14 some building efficiency in the infrastructure, and,
15 importantly, the enrollment network is established
16 so that we don't need to get like a new number every
17 time we establish a new trial.

18 And there are also statistical advantages,
19 specifically, a platform trial can serve as a large
20 screen platform where interventions can be stopped
21 for lack of efficacy through continuous monitoring,

1 so that we can direct resources and patients to the
2 more promising treatments, and use head-to-head
3 comparisons between interventions, if possible. We
4 may also adapt a randomization ration in a way that
5 favor arms that look superior based on interim data.

6 So these are all the possibilities that is
7 enabled by the use of one shared control arm by
8 multiple interventions.

9 Next slide.

10 In our working group, we've actually
11 considered some design concepts that may not work,
12 but in the interest of time, I probably want to skip
13 this slide for now.

14 So maybe next. And next.

15 Yeah, so let's go through a few summary
16 points.

17 So next.

18 So, again, we made this comment about the
19 use of -- endpoint, the question is whether it's
20 clinically meaningful, and for the server for
21 endpoint, choosing a study population with high

1 mortality rate, poor survival prognosis would
2 require sample size.

3 And next.

4 And towards the end I also talk about the
5 use of a shared control arm in a similar phase
6 two/phase three study or a platform trial. And
7 these approaches will allow us to optimize
8 resources.

9 And the only new point I'd like to make is
10 that while these design concepts will optimize the
11 use of data and resources, given how rare PML is, we
12 need to have a long -- in way, we need to have a
13 long game and we need to have a multi-center
14 consortium to reach any evidence-based conclusions.
15 So with all these design tools, it could -- to
16 having a massive protocol under which we want to
17 establish an enrollment network and -- operations.

18 So with that, I'd like to stop here and
19 thank you for listening.

20 DR. BALDASSARI: Thank you so much, Drs.
21 Cortese and Cheung. We'll now move on to our final

1 panel discussion about clinical trial designs for
2 PML treatments this afternoon.

3 So first, reminders to the audience that
4 for the panel discussion, you can submit any
5 questions you would like to be addressed by the
6 panelists using the Q and A feature at the bottom
7 center of the screen in Zoom.

8 Please note that questions and comments
9 submitted via the chat function will not be collated
10 for panelists.

11 So here with us today we have seven
12 panelists participating in this discussion, who I
13 will introduce briefly, but I'd like to refer you to
14 the meeting materials for their full affiliations,
15 disclosures and biographies.

16 Dr. Paola Cinque is the head of the
17 Clinical Neuro-virology Research Institute and
18 Division of Infectious Diseases at the San Raffaele
19 Scientific Institute in Milan, Italy; Dr. David
20 Clifford is the Melba and Forest Seay professor of
21 Clinical Neuropharmacology and Neurology at

1 Washington University in St. Louis; Dr. Lori Dodd is
2 the section chief for the Clinical Trials Research
3 Section with the Biostatistics Research Branch in
4 the Division of Clinical Research at the National
5 Institute of Allergy and Infectious Disease.

6 Dr. Andrew Goodman is a professor of
7 neurology and chief of the Neurology Division at the
8 University of Rochester Medical Center; Dr. NgocDiep
9 Lee is the Executive Vice President and Chief
10 Medical Officer at NeoImmune Tech; Dr. Walter Royal
11 is a professor and Chair of the Department of
12 Neurobiology and the Director of the Neuroscience
13 Institute at Morehouse School of Medicine.

14 And Dr. Sabrina Tan is a physician
15 scientist at the Division of Infectious Diseases and
16 Center of virology and Vaccine Research at the Beth
17 Israel Deaconess Medical Center of Harvard Medical
18 School.

19 I'd like to ask our panelists to turn on
20 their videos at this time.

21 So with that, just to get things started,

1 I'd like to open with a general question we would
2 like each panelist to provide a one-to-two minute
3 response to kind of get the discussion started.

4 The question is, based on your experience
5 and expertise, what trial design elements do you
6 consider to be the most important, feasible and
7 appropriate for PML clinical trial designs and why?

8 So would anybody like to volunteer to
9 respond first?

10 DR. ROYAL: I'll go ahead and get started.
11 I'll say --

12 DR. BALDASSARI: Thank you, Dr. Royal.

13 DR. ROYAL: -- like the second clinical
14 trial design, the staggered enrollment approach.
15 And I'm a bit biased because with our study we had
16 the main enrollment that I think works well with a
17 HIV population, especially one that has, you know,
18 better clinical status, it allows one the
19 opportunity to have a control group built in.

20 I would say that in doing that, it's
21 important to be prepared to modify treatment as the

1 trial goes along using the different biomarkers that
2 are used not only for identifying candidates, but
3 also to be prepared to modify depending on what the
4 drug that's being used in the clinical trial to
5 modify treatment, much as what you might see done a
6 cancer -- clinical trial.

7 DR. BALDASSARI: Thank you so much.

8 Would anyone like to go next?

9 DR. TAN: I can speak next. I think we
10 learned a whole lot from the COVID trials, we were
11 running them left and right and we literally threw
12 the kitchen sink at it. The NIH model of the
13 Platform design for the COVID active trials is a
14 good model to follow, which exactly is the platform
15 where you can plug into the different drugs in one
16 study.

17 And I think that eventually came into play
18 in the COVID studies that we've been doing, because
19 initially we were just doing one-offs, and then we
20 were just so desperate to treat patients.

21 And I do think we do learn from that also

1 that just treating them doesn't really help us
2 answer any questions. You know, a lot of the things
3 that we have tried, Aisle 6, even Remdesivir, we did
4 them without a good control arm, not necessarily
5 placebo, but a good control arm, we still are up in
6 the air whether they work or not, we whiplashed, you
7 know, back and forth in the entire year.

8 So I think those have been -- us in doing
9 PML -- it's a rare disease, we can't afford that
10 whiplashing back and forth, so we should have a good
11 control arm that's shared by everyone. And then
12 have a centralized consortium, have everything set
13 up, would be great.

14 And having done studies with centralized
15 IRB and that will move amendments and changes
16 through really fast to off sites, and it's much more
17 efficient than doing individual trials with
18 different sponsors.

19 DR. LE: I'll go next. First of all, I'd
20 like to thank the organizer and the speakers for
21 having this very educational workshop and for

1 inviting me to participate in today's discussion. I
2 should also mention that my comments are more
3 pertinent to the clinical trials that are designed
4 for potential registration, if there is a court and
5 not for trial design for exploratory purpose only.

6 So with that in mind, of the two study
7 designs that Dr. Cheung presented, I prefer the
8 seamless of phase two/phase three study design,
9 preferably with one active -- but maybe different
10 dose level other regimen. Hopefully, two or maybe
11 up to three, but more than that is -- can be
12 prohibitive because of a large sample size.

13 And the reason I prefer the seamless phase
14 two/phase three study design, because I think that
15 it provides the line of sight towards registration.
16 And logistically, it may be easier to conduct
17 compared to the platform study design. So during
18 the phase two portion of the study, for example, in
19 addition to establish the safety profile for the
20 drug, we can determine the right dose level or --
21 regimen to bring toward the phase three portion of

1 the study.

2 We can also assess what are the clinical
3 endpoints that are clinically meaningful, but
4 obtainable, and have an estimate -- a more accurate
5 estimate of the magnitude of improvement.

6 In addition to that, we can potentially
7 also use the data information that we get from the
8 phase two portion to refine or revise the
9 eligibility criteria, as appropriate.

10 We can also have a better and hopefully more
11 realistic estimate of the accrual enrollment, et
12 cetera.

13 So for all of that reason, if we were to
14 design a trial for potential registration, I would
15 prefer the seamless phase two/phase three design.

16 DR. BALDASSARI: Thank you very much. And
17 I just wanted to take a minute and remind the panel
18 that -- I wanted to clarify the purpose of the
19 question is not necessarily to kind of, you know,
20 how you select one of the two design strategies that
21 were presented in the previous presentation, but

1 really just kind of a broad question related to
2 anything -- any clinical trial design element you'd
3 like to speak about, so patient population,
4 endpoints, elements related to feasibility, we'll
5 try to get into all of those, but just wanted to
6 make sure you weren't limiting your responses to
7 just picking between one of those two.

8 But feel free to respond however you'd
9 like. Thank you.

10 Would anyone like to go next?

11 DR. CLIFFORD: I can go next.

12 DR. BALDASSARI: Thanks, Dr. Clifford.

13 DR. SMITH: Sure. You know, I think
14 having wrestled with this problem for the last three
15 decades or so, I've realized that the devil is in
16 the details with designing these trials, and so I
17 think, you know, one of the questions going into
18 what's the ideal trial is what are we trying to
19 study, what are we trying to prove we can do that
20 might benefit the outcome of this disease.

21 And so I think it is going to be different

1 depending on the kind of intervention that we're
2 proposing to use. That said, I think because of the
3 widespread network that you have to construct in
4 order to enroll a number of patients, keeping things
5 quite simple and controllable is -- is very
6 important in a successful ultimate study.

7 And I think that getting a standard of
8 care for underlying condition that we could agree
9 on, which, you know, obviously, our discussion
10 showed that's not simple, but I still think, you
11 know, we ethically have to find where's the
12 equipoise with this condition, we can't just sit and
13 let the disease kill our patients as good
14 physicians.

15 At the same time, we have to have an
16 equipoise of where we're quite convinced that we can
17 offer benefit to a set of patients, and then either
18 add something to it or not, and do it as a trial so
19 that we come out smarter at the end of the day,
20 rather than spending years and years poisoning
21 patients in this way and that way, and not making

1 progress.

2 So I think as a group we need to organize
3 and we need to systematically say, okay, this is the
4 standard care. And people will come to us as the
5 network because we can apply that, we can diagnose
6 quickly and get care underway, but then we either
7 add or we don't add something where there's an
8 equipoise and we don't know whether we're going to
9 do more damage or good and in what way.

10 So I think that that's how I would like to
11 see the field go forward. I do think that -- that
12 looking at what we're doing to the virus, so the
13 trajectory of what's happening to JC in the central
14 compartment is the most measurable sort of interim
15 marker that -- that we're either on the right track
16 or not.

17 But, ultimately, I do think that longer
18 trials that look at the nine or 12-month outcome and
19 really try to do a multi-factor analysis of have we
20 made the population we chose to give this therapy to
21 or didn't, have we made those outcomes better. If

1 we have, then that's something that we could endorse
2 and that we hope the FDA would endorse.

3 So it's not a simple answer, but that's
4 where I am going at this point in time.

5 DR. BALDASSARI: Thank you.

6 Dr. Goodman, I see your hand raised.
7 Would you like to weigh in?

8 DR. GOODMAN: Yes, please. So firstly,
9 I'd like to thank the organizers for doing a great
10 job and a great service for this very thoughtfully
11 put together workshop. And I agree that the unmet
12 need here is actually really desperate because I
13 don't think the prognosis for PML in people who
14 don't have an easily reversible immunocompromised
15 has changed in the 40 years that I've been doing
16 neurology.

17 But also as I'm looking at myself, I would
18 like to apologize for the lighting because I really
19 don't have the same coloring as our recent past
20 president, but that's what it seems to look like
21 here today. I'm sorry for that.

1 In any case, what I would like to -- I
2 think the important feature for trial design was
3 already brought up by Joe Berger and Roland Martin
4 earlier today, and that is really trying to have as
5 homogeneous a patient population selected if we
6 really want to get a clear answer.

7 And I would also like to push back on the
8 notion that we don't -- we don't have good natural
9 history. I think that we learned from the trials
10 that David and Walter and Joe and others have worked
11 on over the decades, they weren't failed studies,
12 the drug failed to work, but we learned from them.
13 We learned, unfortunately, that -- you know, that
14 the prognosis is as horrible as it is, other than,
15 again, for the correctable immunodeficiencies.

16 So we build on that, and if we have, for
17 example, a homogeneous population of people with,
18 again, uncorrectable immunodeficiencies, then if
19 there is a treatment that, you know, beats the known
20 15-week median survival that David mentioned
21 earlier, you know, then we know we're on to

1 something.

2 I have other ideas about the study design
3 as Dr. Cheung put forth, but I'd like to focus on
4 homogeneity of the study population and using what
5 we know, particularly if we use the most hopeless
6 group, which is the most desperate situation, I
7 think, and we use the biomarkers for futility is --
8 I think Jennifer Lyons brought up this morning -- as
9 a start in survival, I think, that's a start.

10 DR. BALDASSARI: Thank you so much.

11 Dr. Cinque, would you like to weigh in?

12 DR. CINQUE: Hello. Yes. Well, I like
13 very much Irene and Ken's presentation, that was so
14 rich and smart and also practical. I'd like to go
15 through very quickly three points -- main points,
16 very practical again.

17 So one first, maybe it was implied, but I
18 like to stress that the clinical trial of PML should
19 really be intercontinental, so should include all
20 the countries all over the world, because, well, it
21 will need more resources, but we need to enroll a

1 lot of patients.

2 Second point is that I -- well, the
3 question would we want to also consider for
4 inclusion in a clinical trial patients with PML who
5 are JCV DNA negative in CSF, because 20 to 30% of
6 patients at presentation are negative, but now we
7 have very good neuro ideologies and a lot of
8 experience to clinically classify PML or based on
9 clinical and radiological criteria, so I would not
10 discharge this opportunity.

11 And the third point was about outcomes,
12 because I always been very -- very strong supporter
13 of a virological endpoint, and I still am because --
14 well, because it -- because it's viral disease
15 because if you use an antiviral so it's good to have
16 an anti-virologic endpoint.

17 But there are some concerns, and one is
18 that if we decide to include -- we cannot include
19 JCV negative patients, that if we use that as a
20 primary point, and also -- time into a couple of
21 clinical trials of PML, and I have to say that a

1 major problem was involvement of patients because of
2 the real rapid progression of these cases.

3 So you are a patient with PML, you want
4 to -- and the physician wants him to enter a
5 clinical trial, then you start all the screening
6 tests, and then you have to get the lumbar puncture,
7 and then you have to send to the reference lab, it
8 takes time for shipping for everything and maybe
9 just in one week or ten days or two weeks, so PML is
10 really worsened dramatically.

11 So I think we should keep it as simple as
12 possible, especially with clinical -- with
13 outcomes, and I would not discharge for this reason a
14 clinical outcome or so there might be other problems
15 because, well, biological marker is objective and
16 clinical outcomes not so objective.

17 DR. BALDASSARI: Okay. Thank you. Thank
18 you so much.

19 Dr. Dodd?

20 DR. DODD: Yeah, thank you. So in my
21 notes I have listed the key design features that I

1 think are important, in general, and in particular
2 listening to the very interesting discussion today,
3 it was a really energizing day for me, so thank you
4 all.

5 The first is a clinically meaningful
6 endpoint that's -- I'm repeating what -- some of
7 what's been said, but that's subjectively measured,
8 not necessarily completely objectively measured, but
9 you don't want to be in a position where the measure
10 changes over time, which we know happens, and you
11 have to guard against that. Randomization with a
12 standard of care control arm, I think stratification
13 is an excellent idea, in particular I was thinking
14 early on, stratifying by the underlying condition.

15 I often caution against having too many
16 strata, because you can sometimes create imbalances,
17 and we had that happen in our Act One Trial in
18 COVID.

19 The other things I have in my notes are I
20 have concerns about the virologic results at this
21 point, the numbers were small and the correlation

1 with the outcome, I thought, was likely to depend on
2 the underlying condition, so I don't know how much
3 you would -- how comfortable you would feel saying a
4 point of .25 in HIV was similar to a cut point of a
5 .25 log reduction in MS, you know, so those are just
6 things to think of.

7 I think more data is needed to really
8 understand the relevant cut points and whether you
9 could apply a single cut point universally across
10 the different underlying populations.

11 And then, finally, you know, one thing --
12 well two other points, one is why not increase the
13 type one error rate? Point 05 is, you know, sort
14 of -- it was an arbitrary choice.

15 And I'm a statistician, we talk about this
16 all the time, we love .05, but in rare diseases
17 there's precedent for setting a higher type one
18 error rate, so rare pediatric cancers is one setting
19 that I think the FDA has experience with approvals
20 in, so why not choose .1 or consider something
21 higher.

1 So if you go from .05 to .1, I think you
2 end up reducing your sample size by about 20%, you
3 know, so maybe this is an area that you -- you all
4 are willing to say, I'm willing to take a higher --
5 you know, have a higher false positive rate, and
6 that can help out a lot.

7 And then the last comment I wanted to make
8 is that, you know, I like platform trials, I've been
9 involved in a couple of them, not all of them are
10 the same, you know, the devil is in the details
11 about how the platform trials are designed.

12 I was involved in an Ebola trial in the
13 Congo, where we had a four arm trial, and we started
14 the fourth arm a few months after the original
15 three, and that agent was a little bit behind,
16 right, it's like holding the horse back from the
17 race to get started, and that created a lot of
18 headaches for me because I thought we weren't
19 giving -- potentially, we weren't giving that drug
20 the same fair chance because you could only compare
21 it to its concurrently enrolled standard of care

1 arm.

2 So you just have to think about, you know,
3 when you're going to roll in a new agent, and
4 whether you were -- I think you're probably not able
5 to compare the new agent to the standard of cares
6 from the previous period.

7 And so, you know, I think there's a lot to
8 be thought through about how you do a platform
9 trial. I certainly like the idea of a trial that
10 you can, you know, roll out different eras or epics
11 of comparators, because it's -- you know, just
12 programmatically it's a lot easier to implement a
13 trial in that way. So I'll stop with that. Thank
14 you.

15 DR. BALDASSARI: Thank you so much. Those
16 are all wonderful points and I really thank
17 everybody for tackling such a complicated and
18 diverse topic. So I think at this point I think
19 we've had some common themes arise in everybody's
20 responses, I think, you know, the overall trial
21 design concept, but also as the previous panels have

1 discussed, the degree of patient heterogeneity and
2 who would be appropriate for inclusion in a single
3 trial under what design.

4 So given the differences in PML natural
5 history, there are patient populations with PML,
6 what patient populations do you feel could
7 reasonably included in an individual trial, and what
8 endpoints do you feel that would be the most
9 appropriate there.

10 And I also wanted to tie in an audience
11 question as well with the patient population
12 heterogeneity, particularly including more disabled
13 patients to see if they could be included in the
14 trial as well. Thanks. If anybody wants to start,
15 please feel free.

16 DR. CINQUE: Well, I can start. If we
17 want to restrict to one single population, I would
18 exclude those like MS patients who are going to
19 respond better to withdrawal of Natalizumab and
20 include the largest group of patients. But I do
21 believe in this case is patients with HIV just

1 diagnosed who are going to start anti-retroviral
2 treatment because they will have a similar baseline
3 point, all of them, or almost all of them.

4 Differently, people with meta-logic malignancies,
5 actually they are also heterogenous inside the
6 group, like all the other diseases, so probably.

7 And of course it would be great to include
8 that sort of mandatory and really ethical to have
9 patience with -- well, congenital disease or
10 conditions for which there is no chance to reduce
11 immunosuppression.

12 DR. CLIFFORD: I think I could comment
13 just walking through the eligible populations for
14 studies, which is a -- I'm really struck with how we
15 keep changing the populations that potentially are
16 most important that are having to deal with PML. I
17 agree with Paola that the newly diagnosed HIV
18 patient, AIDS patient that's fallen through the
19 cracks and presents with PML and hasn't started HIV
20 therapy is an available and relatively frequent
21 population, although it used to be upwards of 80%,

1 and now I'm sure it's much less than half of all PML
2 patients.

3 So the total numbers are declining, and as
4 we're successful in starting HIV therapy earlier and
5 more widely in populations at risk, this AIDS
6 population that's fallen through the treatment
7 cracks is largely populated by people that have
8 either significant psychiatric co-morbidity or drug
9 use or other issues that make them a complicated and
10 difficult study population to continue to follow for
11 a PML study.

12 So I think there are real problems with
13 the HIV population. Someone earlier mentioned sort
14 of successfully-treated HIV patients, and believe
15 me, we'll never have a study because they're -- you
16 know, there are virtually no cases of people that
17 have good HIV control that developed PML, that's
18 just a really rare entity, so don't hold your breath
19 for that.

20 In regard to the MS population, there's
21 been really marked decline, it appears to me, maybe

1 folks from Biogen can tell us, but my impression is
2 that with the availability of alternative MS
3 therapies and risk stratification, that the numbers
4 of Natalizumab patients have really fallen, and
5 that's not a very promising population and, you
6 know, the -- and Dimethyl fumarate, PML and so on
7 are a very small number that you're not going to
8 have a study in either.

9 I'm tending still to think that, like Joe
10 Berger, that this very
11 bad-prognosis-hematologic-malignancy-cancer
12 population is one to test hypotheses about
13 interventions and, albeit, it is also very
14 complicated.

15 The other autoimmune disease population,
16 we see a fair number of lupus patients, a few
17 rheumatoid arthritis patients and the like, those
18 are worrisome because a lot of what we do is immune
19 stimulation, and their underlying disease might well
20 be adversely impacted by that strategy, so, you
21 know, the equipoise for the intervention there is a

1 problem.

2 So it really is -- it's challenging, but I
3 think the HIV population versus the malignancy
4 population are where the next studies really
5 probably ought to go.

6 DR. GOODMAN: So I've already weighed in
7 on this, I think, but I'll just embellish a little
8 bit. I agree with what I think I just heard from
9 David, is that we ought to focus on the population
10 with -- again, not easily or impossible to treat
11 immunodeficiency like hematologic conditions.

12 I would also just -- to say that there
13 seems to be a paucity of hematology input in this
14 workshop today, and maybe we're overweighted with
15 people like me, neurologists, so I think that's just
16 something to consider as this moves forward, that we
17 need hematologists and clinical immunologists who
18 are also dealing with these people.

19 And it was mentioned earlier today, and I
20 think it's true, there are a lot of patients who are
21 never diagnosed or missed, simply because they're

1 in -- with all due respect -- in cancer centers
2 where they don't think to call neurology or do an
3 MRI scan or an LB, they're never diagnosed or
4 certainly diagnosed too late, so that's an issue, so
5 I think hematology is important to include in this
6 project as it moves forward.

7 Yeah, I think I'll stop there.

8 DR. TAN: Yeah, I think what Irene
9 presented earlier makes a lot of sense, and it
10 really depends on the product were trying, you know,
11 if it's an antiviral, it would seem to me that, you
12 know, we would include allcomers, right, regardless.
13 But if it's an anti-immune modulator, it -- when we
14 have to really look at which group we're talking
15 about because then the HIV group and MS group would
16 be different.

17 And then, furthermore, among the --
18 malignancy, they're really different with what their
19 immune composite is. And then compare those to the
20 autoimmune people, if you're giving an immune
21 stimulant, you also need to understand that their

1 baseline immune factor or modulation is also
2 different.

3 And so it seems to me that it's a little
4 bit difficult to design a trial where we don't know
5 the exact product, but whereas, if we do have an
6 infrastructure in place that will allow us to look
7 carefully at, you know, each product and plug into
8 the baseline infrastructure where the IRB is already
9 in place as more inclusive and people didn't qualify
10 them for this rare disease, perhaps it could be
11 important to our historical control group or even
12 just collecting the registry so we can understand
13 PML better.

14 DR. LE: Hi. I'd like to follow up on Dr.
15 Clifford's suggestion to potentially focus on a PML
16 patient with -- malignancy as the underlying
17 disease. So I have to admit I'm a medical
18 oncologist by training, so I love the idea, but my
19 concern is -- and I know very limited about PML
20 compared to all of you -- so my concern for that
21 patient population is the incident, would it be

1 feasible to accrue patient for the specific sample
2 size in an acceptable timeline for us to develop new
3 treatment?

4 So essentially compare this, say, HIV
5 patient with a newly-diagnosed PML, for patient with
6 PML and hema malignancy, how do you compare the
7 number there in terms of the incident and the new
8 cases, et cetera?

9 DR. CLIFFORD: So the numbers are
10 substantially less, and that's the problem. I mean,
11 we're caught between a rock and a hard place. With
12 one set of patients, we need a vast number, although
13 there are quite a few available; with the other, we
14 need a smaller number, but there are a smaller
15 number available.

16 But I think that, you know, sort of this
17 notion of intensive study and understanding what
18 happens, a little bit of an N equals 1 or 3 or 4,
19 but really intensively studying them, that some of
20 these patients we might be able to learn quite a lot
21 in a relatively small trial, simply because there --

1 they have such a uniformly poor outcomes overall.

2 DR. BALDASSARI: I wanted to revisit a
3 point Dr. Cinque mentioned earlier about the
4 logistics of having an incidence trial, essentially,
5 in a patient population that's relatively rapidly
6 progressing and, you know, getting worse, especially
7 depending on which underlying patient population you
8 choose.

9 And that goes back to Dr. Thakur's
10 question in the chat, how would you feel that -- or
11 how would you say that this issue, basically, of
12 having a rapidly-progressing population with poor
13 prognosis would factor into your decision for an
14 overall clinical trial design. She mentioned
15 specifically about a platform trial design. So what
16 do you think?

17 DR. ROYAL: So for me, having such a
18 population takes me back to my earlier comment
19 related to being prepared to do some -- modification
20 and other interventions to -- based on, you know,
21 validated biomarkers wherever possible to try to

1 counteract some adverse effect of the drug or some
2 feature of the underlying disease that might prevent
3 that person from being able to stay in the trial and
4 survive as long as they would otherwise, of course,
5 do that, one should try to build in as much as
6 possible such interventions into the initial
7 protocol.

8 DR. BALDASSARI: Thank you. And Dr. Dodd,
9 I see your hand raised. Would you like to respond?

10 DR. DODD: No, I wasn't -- this is not my
11 domain. I'm sorry.

12 DR. BALDASSARI: No worried. Dr. Le, I
13 see your hand raised as well.

14 DR. LE: No, I already asked the question
15 that I was planning to ask.

16 DR. BALDASSARI: Okay. Dr. Cinque?
17 Dr. Cinque, I see your hand raised as well. Did you
18 want to comment?

19 DR. CINQUE: Yeah, I think that your
20 question was very important because when we refer
21 patients for inclusion in a possible experimental

1 intervention, so one of the first consideration with
2 patients and families is about the -- how advanced
3 is the disease, because, especially for -- or
4 approaches that are not antiviral, so they are
5 expected to act immediately on the viral
6 replication, so with immune interventions it will
7 take time -- well, not months, but not days.

8 So one has also to consider time from the
9 start of treatment to the moment a new approach will
10 be effective. And if we save lives, technically,
11 and a drug is working, the patient is really left
12 with terrible neurological deficits, then -- well,
13 we don't have to get to that point.

14 So stage of disease or -- I don't know how
15 to call it, how the disease is advanced, and we
16 probably need criteria to define these no return
17 point.

18 DR. BALDASSARI: That's a great point.
19 Thank you. And getting back to what Dr. Dodd was
20 saying earlier about stratification factors, I think
21 that kind of stems nicely from what you were just

1 saying, Dr. Cinque, about, you know, how do we
2 decide, you know, what stratification factors, how
3 many to use in individual trial design, based on
4 what we know about PML. What does the group think
5 about stratification factors? Which ones would be
6 the most important?

7 DR. MARRA: How about supra-tentorial
8 versus infratentorial disease?

9 DR. BALDASSARI: Thank you.

10 DR. MARRA: -- talked about that.

11 DR. CLIFFORD: And I'm not sure there's
12 that much difference between posterior-fossa and
13 hemispheril disease, frontal disease perhaps, but I
14 do think the underlying disease and sort of the
15 readiness of an intact or relative intact immune
16 system is one of the key factors in prognosis.

17 When the patient enters the trial, to know
18 that that slide that I had about staging the
19 disease, you know, how much immunosuppression; how
20 much immune reconstitution has gone on so far, and
21 somehow placing the patient starting the trial on my

1 plot as to where they are in their immune
2 suppression, immune reconstitution continuum, which
3 is a continuum, it's not a yay or nay presence or
4 absence.

5 You know, I think if we could quantify
6 that in a useful way, that would give us a very nice
7 way to look at prognosis and the opportunity to save
8 lives.

9 I wanted to divert just a minute, though,
10 Dr. Cinque and I almost always agree on most things,
11 but I heard her say something about sort of JC
12 negative inclusion, and I am a little bit alarmed at
13 that. I really -- I really am uncomfortable with
14 clinical trials where the diagnosis is in question.

15 We've heard the flip side of confusion
16 around PML diagnosis where, you know, one of our --
17 our really informative patients told us about having
18 a stroke misdiagnosed -- her PML misdiagnosed as a
19 stroke, and, you know, having a bunch of small
20 strokes included in a PML trial would be
21 disastrously uninformative for a therapy.

1 And so I am really alarmed and think that
2 I would very much want to insist, unless it's a
3 trivial intervention, to make sure we know the
4 diagnosis truly is PML.

5 DR. CINQUE: May I?

6 Well, David I'm been thinking exactly same
7 as you until a few years ago. What we have
8 witnessed in the last, let's say, five years, with
9 the Natalizumab epidemic, and then there was a new
10 generation of neuroradiologists that were very,
11 very, very competent and easy to recognize early PML
12 lesions and to differentiate the PML lesions from
13 other lesions.

14 I'm not talking in general, let's say, in
15 typical PML cases, so -- and if we put together this
16 information with the clinical information, and the
17 fact that there is an underlying disease with the
18 insidious presentation and a lot of clinical
19 elements, I think we can make a diagnosis of PML
20 without having JCV DNA in CSF. I'm more and more
21 convinced of that.

1 Perhaps it's just because I'm fortunate
2 and lucky that in our -- well, local situation we
3 have a very good neuroradiologist that has persuaded
4 me and my colleagues of this. And I don't know if
5 there are here people who do neuro imaging that are
6 with me in these --

7 DR. MARRA: Maybe another certification
8 factor could be, you know, definite versus possible
9 or probably and most likely or something like that?

10 DR. CLIFFORD: -- I agree with that and --

11 DR. CINQUE: For clinical trial, I think
12 we need diagnosis --

13 DR. CLIFFORD: In the high-risk
14 Natalizumab population where they're being
15 surveilled very frequently with scans and picking up
16 very small lesions that are hard to diagnose
17 virologically, you know, I see where you're coming
18 from and the importance of that early recognition is
19 very critical, but I remain, you know, sort of quite
20 cautious about trusting the radiologist to make this
21 diagnosis, as good and as friendly as they are.

1 DR. MAJOR: Let me make the comment here,
2 and I've waited until the end of the day to barge
3 into these clinical discussions, although I do have,
4 you know, five pages of notes that are going to be
5 extensively reviewed by Irene and Virginia and Pat
6 and that.

7 So I was concerned also, as David had
8 said, Paola, you had said that you see 20 to 30% of
9 PML patients diagnosed than whose CSF has
10 undetectable amounts of JC DNA over the last number
11 of years. I think that was the percentage that you
12 said.

13 DR. CINQUE: Yeah, that was from the
14 literature, Gene.

15 DR. MAJOR: Yeah, so the literature on
16 some of that is so poor that I stopped reading it.
17 And so that has not been our experience over 20
18 years of directing the CLIA Laboratory.

19 I will say over the last more recent
20 times, before we had to close our operation, that a
21 large number of samples that we got, you know, CSF

1 samples that were just sent to us without any
2 pre-warning, were sent to us because the treating
3 neurologist was still concerned about the diagnosis
4 of PML, even though whatever laboratory tested the
5 CSF said that it was undetectable.

6 Now, are there some cases of PML where you
7 simply can't find the JC DNA at the time the sample
8 is set? And Dr. Goodman had a patient a number of
9 years ago that was clearly not diagnosed, I mean,
10 you know, it was a biopsy and we found a lot of
11 viral DNA in there, but we never -- I don't know,
12 Andy, what is it, maybe had five samples of CSF that
13 we could never find it.

14 DR. GOODMAN: Five LPs that were negative.
15 But she was very -- she had very restricted sort of
16 mono-focal disease. And so as David just points
17 out, there are these cases -- and this was an
18 Natalizumab patient, and there are these cases of
19 these tiny, tiny lesions that are, you know,
20 foreign -- I would guess, of PML, and she was one.
21 But she had millions of copies in the pathology

1 specimen.

2 DR. MAJOR: So at least we've not had that
3 experience, Paola. Does it happen occasions? Yes.
4 On the other hand, the laboratory over the decades
5 worked very hard to be able to go ahead and make
6 sure that we had a very robust and reproducible
7 assay, and that's to the credit of the lab folks.

8 And, again, I don't know how many of these
9 samples that we got where we did find, let's say, 15
10 copies or 22 copies or something that was just above
11 our level of detection, and as a matter of fact, if
12 you look back in the literature after Natalizumab
13 was put back on the market and there were several --
14 there were several cases that ultimately got
15 published in the New England Journal, and where --
16 and I had been one of the co-authors on that because
17 no one -- this was in Germany -- no one could find
18 the detectable levels of JC DNA.

19 We finally got the CSFs and, sure enough,
20 I mean, it was there, and so that does happen. It's
21 a concern as the DNA as a marker was talked about

1 before, and Irene had mentioned this, is that, you
2 know, there's variability in the assays, and you
3 have to trust them -- you have to be rather
4 vigilant, if that's the word to use these days, to
5 make sure that you have a highly reproducible and a
6 very sensitive assay, and that's why we spent a good
7 deal of time doing that.

8 So, David, I'm glad you raised that point,
9 it gave me an opportunity to go ahead and extend
10 this whole afternoon.

11 DR. CLIFFORD: And I think anchoring
12 changes of anybody status in the central compartment
13 would be another alternative that would add to the
14 spectrum of associatedness to JC virus that we --
15 would make me more comfortable. Anyway, interesting
16 discussion.

17 DR. BALDASSARI: Okay. Sorry about that,
18 everyone. I didn't mean to cut anybody off, but
19 we're unfortunately out of time for our session
20 today. I wanted to thank everybody for a really
21 thoughtful and thought provoking discussion this

1 afternoon, hopefully conversations can continue
2 offline, you know, we're capturing all the questions
3 and everything in the chat.

4 So I will now turn to Dr. Sheikh for
5 closing remarks. Thank you. everyone.

6 DR. SHEIKH: Yes, thank you so much,
7 Dr. Baldassari and panelists, that was a really good
8 way to end the day. So I just want to thank you,
9 all panelists, moderators and speakers for helping
10 us finish out today's workshop. Before we close,
11 I'm going to try to provide a very brief summary of
12 today's workshop; however, I have to say I kind of
13 worked on how to summarize each of the discussion
14 sessions in one sentence, and I failed, so I'm not
15 going to do it.

16 We'll have to -- I'll really need to think
17 about it and have you all give input on to really
18 how to summarize all those really interesting
19 conversation.

20 But we started this morning with Drs.
21 Major, Clifford and Smith who laid out the

1 groundwork for the meeting by summarizing PML
2 virology and pathogenesis, PML drug development
3 history, current therapeutic landscape and clinical
4 outcomes among PML patient populations.

5 For the next portion of the workshop we
6 focused on potential primary and key efficacy
7 endpoints for PML clinical trials, Drs. Baldassari,
8 Cortese, Cinque, Wattjes and Ms. Norato provided us
9 with excellent summaries of the strengths and
10 weaknesses of various potential endpoints.

11 And following those talks, we had a lively
12 discussions between Dr. Koralnik, Martin, Warnke,
13 Spudich, Nath, Marra and Lyons on potential PML
14 trial endpoints. I'll just summarize that by saying
15 that we have not found a perfect endpoint for all
16 patient populations yet, but hopefully we moved the
17 needle in terms of that discussion, and that these
18 discussions will continue offline.

19 After lunch we heard about our FDA NIH
20 efforts to elicit the PML patient's perspectives on
21 clinical trial design by Ms. Ohayon, followed by

1 thought-provoking perspectives from PML survivors
2 Suzanne Tobin and Luca Isabella.

3 For the next portion of the workshop, we
4 focused on the selection of control groups for PML
5 clinical trials, Dr. Lee provided an overview of
6 several approaches to control groups, including some
7 promising examples of successful outcomes in neuro
8 mellitus optical spectrum disorder, another rare
9 neurologic disorder.

10 Following those talks, we had a very
11 lively discussion with Dr. Berger, Mateen, Thakur,
12 Martin-Blondel, von Geldern and Porter, as well as
13 other guest appearances, who all provided their
14 perspectives on control groups in the setting of
15 PML.

16 Again, we have not -- I don't think we've
17 come to complete consensus on the perfect -- how to
18 select the perfect control group for PML, hopefully
19 we've understood at least each other's perspectives
20 and can move forward with clinical trial designs in
21 the future.

1 And then the final portion of today's
2 meeting was focused on how to put all the elements
3 of PML clinical design together to create phase
4 three PML clinical trial designs that might be
5 acceptable to regulators, clinicians and patients,
6 and that might foster industry engagement.
7 Dr. Cortese and Dr. Cheung did a fantastic job
8 summarizing the pros and cons of key trial design
9 features.

10 After that we heard from Drs. Royal,
11 Clifford, Dodd, Goodman, Tan, Cinque and Le, who
12 each provided their perspectives on the elements
13 they felt to be most important.

14 Hopefully we'll be able to -- after all of
15 us have had an opportunity to really think through
16 what happened today and all the discussion and what
17 the conclusions will be, we'll be able to move
18 forward with continuing this discussion in the
19 future.

20 So speaker slides, transcripts and
21 recordings will be available on the meeting's web

1 page in the coming days, and we also plan to
2 summarize the meeting for publication, probably in
3 the spring of 2022.

4 Next slide.

5 On behalf of my colleagues at the FDA, I
6 would like to thank you all for your participation
7 in today's workshop. Thank you, speakers, for doing
8 such an excellent job concisely summarizing key
9 considerations for PML clinical trial designs.
10 Thank you, panelists, for your insightful comments
11 and your vigorous discussion, and your perspectives.

12 And a special thanks to PML survivors,
13 Luca Isabella and Suzanne Tobin for sharing your
14 personal perspectives on PML and PML clinical
15 trials.

16 And thank you, workshop participants, for
17 your attention and thoughtful comments and
18 questions. I'm sorry we didn't get to all of them,
19 there were actually a lot of comments and questions
20 that we did not get to address, and I apologize for
21 that. We'll try to incorporate that into any future

1 publications and thoughts, and also in summarizing
2 in the meeting summaries, if possible.

3 I'd like to particularly acknowledge
4 workshop participants from timezones far away from
5 the Eastern Standard Time who woke up either
6 particularly early this morning, like Dr. Marra, or
7 are participating late into the night right now,
8 like those from Europe.

9 I'd like to thank the CDER public meetings
10 team and our technical support team for facilitating
11 today's meeting, it went really well, thank you very
12 much.

13 Next slide.

14 More generally, I'd like to thank the many
15 members of the PML clinical research community, both
16 in the U.S. and internationally, and the people
17 throughout the FDA who've been steadfast in their
18 support of our efforts to reach consensus on key PML
19 clinical trial and considerations.

20 Next slide.

21 Please continue all your great work,

1 keeping in mind the important issues that were
2 discussed today. Please take advantage of FDA's
3 many resources for rare diseases, some of which are
4 highlighted on this slide today.

5 Lastly, especially in the areas where we
6 have not reached consensus, which is potentially
7 most of the issues, please continue your discussions
8 amongst yourselves, engage with regulators at the
9 FDA and elsewhere with potential brainstorming and
10 potential solutions.

11 Next slide.

12 Thank you very much for participating and
13 have a good evening.

14 (Whereupon, meeting adjourned at 4:22 p.m.)
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21

1 State of Maryland, to wit:

2
3 I, Jean M. Townsend, a Notary Public of
4 the County of Montgomery, do hereby certify that the
5 within-named witness, personally appeared before me
6 at the time and place herein set out, and after
7 having been duly sworn by me, according to law, was
8 examined by counsel.

9 I further certify that the examination was
10 recorded stenographically by me and this transcript
11 is a true record of the proceedings.

12 I further certify that I am not of counsel
13 to any of the parties, nor in any way interested in
14 the outcome of this action.

15 As witness my hand this 21st day of
16 September, 2021.

17 

18 Jean M. Townsend

19 Notary Public

20 My Commission expires:

21 October 8, 2025

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