CONSIDERATIONS FOR PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) CLINICAL TRIAL DESIGNS FDA WORKSHOP

SEPTEMBER 21, 2021

Job No. CS4500544

P R O C E E D I N G S

DR. BIRNKRANT: Good morning. My name is Debbie Birnkrant, and I am the director of the Division of Antivirals at CDER FDA.

I'd like to welcome everyone to this virtual workshop on considerations for PML clinical trial designs.

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

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

We want to thank our speakers and

panelists for their efforts and preparing for the workshop today.

Next slide, please.

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

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

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

Importantly, there are no approved or

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

Next slide, please.

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

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

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

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

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

Next slide, please.

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

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

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

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

Virginia, I turn it over to you.

DR. SHEIKH: Thank you, Dr. Birnkrant.

Next slide, please.

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

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

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

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

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

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

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

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

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

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

Next slide.

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

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

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

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

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

Next slide.

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

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

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

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

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

Next slide.

With that, we'll begin the workshop.

Next slide.

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

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

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

NINDS.

Next slide.

Dr. Major, the floor is yours.

DR. MAJOR: Thank you very much, Virginia. And it's a real pleasure to be amongst my colleagues and to participate in this tremendously important workshop and conference.

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

And could I have the next slide?

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

And then we can have the next slide.

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

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

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

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

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

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

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

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

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

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

So we could have the next slide.

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

In order for anyone to develop PML, you first have to become infected with JC. Seroepidemiologic studies tell us that with advancing ages, the percent of individuals in a population increases, so that, for example, in individuals in their teens or their 20s, they're

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

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

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

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

In a number of individuals who are

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

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

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

higher than normal physiology of the immune system would be.

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

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

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

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

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

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

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

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

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

Can we have the next slide?

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

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

of the virus that was there.

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

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

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

And the next slide.

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

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

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

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

engine that drives the infection.

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

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

And so then you have the difference in these variants, and we'll call them variants, that can be found during the course of infection. Archetype generally considered non-pathogenic; the prototype considered what's now being called the neurotropic variant, and those are the general specific ones that we look for.

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

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

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

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

So could we have the next slide?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Next slide.

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

Next slide.

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

The next slide.

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

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

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

disease.

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

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

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

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

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

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

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

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

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

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

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

But that happens in almost all of us, and

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

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

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

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

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

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

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

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

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

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

So the next slide.

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

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

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

And then the next slide.

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

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

So a number of people lead by a group at

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

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

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

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

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

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

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

line, the plasma HIV RNA was falling.

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

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

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

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

And in the next slide you can see that in

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

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

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

But with aggressive therapy, in the next

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

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

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

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

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

Next slide.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Next slide.

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

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

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

Next slide.

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

Next slide.

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

Next slide.

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

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

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

Next slide.

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

Next slide.

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

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

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

Next slide.

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

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

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

Next slide.

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

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

history of the disease has uniformly low survival.

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

Next slide.

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

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

Next slide.

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

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

Next slide.

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

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

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

Next slide.

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

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

There are advantages and disadvantages to

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

Next slide.

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

Next slide.

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

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

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

Next slide.

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

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

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

Next slide.

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

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

(Whereupon, a short break was taken.)

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

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

Next slide.

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

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

Next slide.

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

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

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

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

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

In some cases biomarkers that are

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

Next slide.

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

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

trials might confer some disadvantages.

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

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

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

clinical trial recruitment and retention is likely to be challenging.

Next slide.

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

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

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

Next slide.

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

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

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

Next slide.

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

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

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

Next slide.

Dr. Baldassari, you have the floor.

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

behalf of the PML Clinical Outcomes Working Group.

Next slide.

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

Next slide, please.

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

Next slide.

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

Next slide.

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

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

Next slide.

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

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

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

Next slide.

Our group, therefore, evaluated the three

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

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

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

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

Next slide, please.

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

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

Next slide, please.

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

Next slide, please.

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

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

Next slide.

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

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

Next slide, please.

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

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

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

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

Next slide, please.

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

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

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

Next slide.

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

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

may be logistically challenging.

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

Next slide, please.

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

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

Next slide, please.

These are my disclosures.

Next slide, please.

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

treatment monitoring.

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

Next slide.

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

And next slide.

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

Next slide.

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

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

Next slide.

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

Next slide.

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

Next slide.

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

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

Next slide.

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

becoming confluent and very dark on the T-1.

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

Next slide.

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

Next slide.

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

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

Next slide.

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

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

So when the lesion volume gets smaller --

Next slide.

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

on the MRI and the GC virus is negative.

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

Next slide.

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

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

Next slide.

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

lesional edema.

Next slide.

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

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

Next slide.

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

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

Next slide.

And this is also demonstrated in this patient very nicely showing a huge PML manifestation in the posterior fossa, also with a lot of imaging findings suggest the inflammation, you see at some moment that the inflammatory signs, so the contrast enhancement is decreasing and also the T-2 lesion demonstrated here on the lateechot2 is decreasing.

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

So therefore --

Next slide.

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

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

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

Next slide.

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

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

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

Next slide.

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

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

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

patient with BK-specific T-cells.

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

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

Having said this, many thanks for your kind attention.

Next slide.

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

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

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

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

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

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

Next slide, please.

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

Next slide, please.

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

intervention.

Next slide, please.

Conceivably, a subset of predictive biomarkers might be able to very reliably predict the true clinical outcome of interest. That is, how a patient feels, functions or survives, and could then effectively serve as a surrogate outcome substituting for the true clinical outcome. Validated surrogate outcomes can lead to various advantages, they might simplify trial design, reduce required sample size or shorten a study's duration.

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

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

Next slide, please.

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

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

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

disease.

Next slide, please.

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

Next slide, please.

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

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

Next slide, please.

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

Next slide.

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

Next slide, please.

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

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

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

Next slide, please.

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

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

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

Next slide, please.

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

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

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

Oh, next slide.

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

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

Next slide, please.

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

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

Next slide, please.

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

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

Next slide.

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

Next slide.

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

Next slide, please.

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

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

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

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

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

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

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

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

Next slide.

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

Next slide, please.

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

declines of both day 30 and day 60.

Next slide, please.

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

Next slide, please.

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

Next slide, please.

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

Next slide, please.

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

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

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

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

And next slide. please.

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

Next slide, please.

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

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

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

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

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

copies for ML.

The next slide, please.

So here is a simplified table that shows the predictive value of a reduction of either or .25 or 0.5 lot, JCV DNA in CSF either at 30 or 60 days, and the predictive value for survival, and the negative predictive value or diverse and sensitivity and specificity, and also we evaluated the value of the JCV DNA level at the baseline samples or predicting survival.

The next one, please.

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

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

The next one, please.

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

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

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

So the next one.

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

Next one, please.

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

So the next one.

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

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

values in the NIH cohort for, respectively, 0.5 and 0.25 lot decline.

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

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

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

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

differences in values that we found by calculating survival.

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

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

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

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

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

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

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

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

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

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

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

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

Well, thank you all for being here. So

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

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

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

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

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

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

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

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

expected to inform a clinical outcome.

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

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

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

DR. MARRA: I'll volunteer.

DR. HARRINGTON: Thank you, Dr. Marra.

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

DR. HARRINGTON: It happens sometimes.

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

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

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

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

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

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

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

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

DR. HARRINGTON: Okay. Thank you very

much, Dr. Marra.

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

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

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

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

and will be able to stabilize the disease in time.

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

I hope that I answered the question succinctly.

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

So maybe we'll go to Dr. Spudich.

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

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

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

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

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

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

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

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

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

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

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

DR. HARRINGTON: Okay. Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. HARRINGTON: Okay. Thank you.

Dr. Warnke, could you comment on the question?

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

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

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

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

DR. HARRINGTON: Okay. Thank you very much.

And, finally, Dr. Nath.

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

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

consideration.

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

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

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

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

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

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

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

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

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

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

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

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

trial for efficacy.

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

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

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

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

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

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

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

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

trials, yeah.

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

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

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

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

Go ahead, Dr. Clifford.

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

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

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

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

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

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

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

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

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

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

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

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

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

And I would say maybe this field has tried

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

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

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

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

Dr. Cinque?

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

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

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

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

There may be one exception, that is when

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

DR. HARRINGTON: Go ahead, Dr. Spudich.

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

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

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

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

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

DR. HARRINGTON: Oh, sorry.

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

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

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

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

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

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

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

agents.

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

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

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

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

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

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

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

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

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

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

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

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

So you have a disease where just taking that block away will usually get rid of PML, and then you have a CD-4 lymphopenia patient or somebody who has received antidCD20 and is immunocompromised for quite some time or for a longer period of time, so in each of these you need to consider exactly what the immunological compromise or which assay to

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

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

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

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

DR. HARRINGTON: Okay. We can maybe

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

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

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

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

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

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

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

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

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

DR. HARRINGTON: Okay. Thank you.

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

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

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

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

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

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

Just wanted to say another thing about the

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

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

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

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

Anyone else on the panel want to --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The floor is yours.

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

Next slide, please.

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

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

Next slide, please.

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

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

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

Next slide, please.

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

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

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

Next slide, please.

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

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

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

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

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

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

Next slide, please.

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

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

Next slide, please.

So before sharing the responses from the

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

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

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

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

Next slide, please.

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

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

Next slide, please.

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

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

delayed diagnosis.

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

Next slide, please.

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

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

Next slide, please.

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

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

Next slide, please.

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

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

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

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

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

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

Next slide, please.

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

Next slide.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Over time I was getting incrementally

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you again for your work to help us

PML survivors, we are so grateful.

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

Mr. Isabella?

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

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

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

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

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

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

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

Slide, please.

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

Next slide.

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

Next slide, please.

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

Next slide, please.

After one year a former year, including

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

Next slide, please.

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

Next slide, please.

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

Next slide, please.

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

Next slide, please.

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

Next slide.

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

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

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

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

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

So the floor is yours, Dr. Lee.

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

Group in the Division of Neurology 2 at the FDA.

And the topic I'll discuss today is the selection of control groups for PML clinical trials. And I'd really like to thank the organizers of this excellent symposium for the opportunity to discuss this important topic with you.

Next slide.

So I have no relevant financial disclosures.

Next slide.

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

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

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

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

Next slide.

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

And this is intended to suggest that the

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

Next slide.

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

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

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

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

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

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

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

Next slide.

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

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

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

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

But I just emphasize that the use of

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

Next slide.

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

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

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

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

Next slide.

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

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

Next slide.

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

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

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

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

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

Next slide.

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

cord.

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

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

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

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

Next slide.

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

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

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

to a patients background therapy.

Next slide.

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

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

Next slide.

Another example from the NMOSD experience

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

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

Next slide.

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

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

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

Next slide.

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

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

acceptable -- historical control in a clinical trial.

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

Next slide.

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

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

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

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

So I thank you for your attention today.

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

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

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

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

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

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

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

panelists.

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

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

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

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

DR. BERGER: I'll volunteer.

DR. SHEIKH: Okay. Dr. Berger.

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

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

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

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

So those are just some of my editorial comments.

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

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

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

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

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

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

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

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

DR. SHEIKH: Okay. So what is --

DR. BERGER: And for me as well.

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

GLORIA VON GELDERN: I think I agree as well.

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

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

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

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

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

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

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

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

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

DR. SHEIKH: Dr. Mateen:

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

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

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

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

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

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

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

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

DR. SHEIKH: Thank you, Dr. Mateen.

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

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

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

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

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

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

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

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

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

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

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

people do so well.

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

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

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

DR. SHEIKH: Sorry, Dr. Marra.

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

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

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

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

DR. MARRA: You can do that.

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

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

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

standard of care. What I said --

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

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

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

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

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

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

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

And then one other comment with the two --

Dr. von Geldern, you mentioned comparing two things. The problem is, if you offer two different treatments and both of them do the same, then you don't know whether or not they're -- actually both of them don't work or whether both of them do work.

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

DR. MARTIN-BLONDEL: Yeah, this is

difficult really. Once again, it's a difficult question, this field. Just to come back to the standard of care. To my opinion, standard of care is only treating the underlying condition -- HIV, stopping immunosuppressive drugs in others, and the issue is that for the patient with primary immunodeficiency -- okay.

What about selecting underlying conditions where we know that the prognosis is clearly dismal, and this did not change according to time, and specifically patient with primary immune deficiencies.

And to compare two or more therapeutic interventions -- because we know that in those type of patients, we have nothing done this for 90% of them at one year, and this did not change according to time in the last 20 years.

DR. SHEIKH: Thank you. Dr. Mateen, do you have any additional thoughts since the conversation has evolved since we last talked to you?

DR. MATEEN: You know, I think that it's been a really exciting conversation actually about controls, but I think what are we not doing now that we could be doing, besides launching on a trial. So since PML is not a reportable disease officially, like is this an opportunity to start pooling data in a database for historical controls, if that ever becomes valuable.

Just thinking ahead about, you know, what do we have right now or if we don't know what the standard of care is, should we be asking a group of neurologists what the standard of care is, if it is controversial. I don't know if it is, but there's just -- I think we have opportunities at this second.

I actually think historical controls would be a very appropriate control group. I think that, you know, there's a separation between HIV and some other illnesses versus the rest, but, in general, historical controls, I think, are an appropriate choice, and I agree that placebo feels difficult.

It felt more wrong in NMO than it would in PML, but I worry that it's such a rare disease, people wouldn't actually enroll in various placebo.

DR. SHEIKH: Dr. von Geldern, with this issue of historical controls has come up, and I know that in the past you worked on trying to establish a registry, which, you know is something that could be used for historical control, but do you have any comments about, you know, the logistics there, you know, why it hasn't happened already, despite the fact that there's been clinical trials going on -- or I'm sorry, there's been PML care problems for over 40 years?

DR. VON GELDERN: Exactly. Thank you for letting me speak to that. I completely agree with that that it would be wonderful to have more data, which is why, Dr. Major in particular, tried to bring forward many years ago a registry for PML to collect this -- exactly this data.

One of the big challenges in PML and in getting the historical control data is that the

underlying diseases are so varied, and so these are patients that are not necessarily always cared for by the same even medical community or medical providers, so there might be hematologists taking care of people with PML; there might be oncologist, obviously there's overlap; there might be neurologists, hopefully neurologists will be very involved.

But sometimes these patients have underlying -- diseases, underlying rheumatologic diseases, so I think the -- it's not just a -- not a reportable disease, but it's also treated by so many different providers, and it is rare. So it's not that there are centers where thousands of people are treated.

So what we found is that it's really challenging for collecting this data to get buy-in by enough people to actually be willing to submit this without -- especially if there's no funding to actually put effort and time into this.

So I think it would be hugely important to

collect historical data and learn from these various patients with very different underlying diseases, but it's been -- I think it's worthwhile to pursue this, but it has been really challenging I think to do this, it's not as simple as for some other diseases that are maybe more in the hand of one specialty or in the hand of -- I don't know -- one entity that you can tap to try to provide this data.

The other thing I wanted to comment is that I wonder if, contrary to what Dr. Martin-Blondel just said, maybe we should study a large group that's available, either HIV or, let's say, MS patients where outcome is not as abysmal and do a trial there where standard of care is removing the offending agent like Natalizumab or giving hard therapy, and then having an add-on of either agent that you're interested in studying, either one or it's multiple, because it's maybe less unethical in patients who have a relatively good outcome to try this.

So almost like the compliment to studying

these patients with primary immunodeficiencies and not having a placebo group there. That's just one other thought.

DR. BERGER: Yeah, I'm strongly in favor of that, and had suggested, I thought. I agree.

DR. VON GELDERN: Sorry if I didn't understand that then.

DR. BERGER: Yeah, no, no. I think that's what we should do.

DR. SHEIKH: Dr. Berger and Dr. von Geldern, you're both suggesting, I think, that the group to be -- or at least if you were to study the patients who probably have the best outcomes, which is patients who are on -- who you can start HIV therapy or who can stop Natalizumab, in other words, they have a reversible immunosuppression, you know, immunosuppression that can be reversed, and then you use that as the standard of care, and you add on additional therapy; is that correct?

DR. BERGER: Well, I think that that would be the cleanest and the most palatable to a lot of

people, because you know that the prognosis is reasonable if you're able to restore the immune system.

I do think that, as I mentioned earlier this morning, I think we're going to have to homogenize our study populations, otherwise you're going to have to have a huge study that's going to be very, very difficult to recruit into, and then the hope is the that you hit a home run with whatever therapeutic agent you have so that you see a clear signal that the thing works.

And if you have a drug that will provide a home run, it would seem to me that you could do that in the HIV or the MS population, although the numbers in PML in the MS population are dwindling, so you may be stuck with HIV. The alternative, though, is to do a comparative trial, in my opinion, a for group like the individuals that have an underlying hematologic malignancy, because as a treating physician, I just feel very uncomfortable not -- not doing anything.

DR. SHEIKH: So in the standard of care, you would consider not doing anything; is that right, Dr. Berger?

DR. BERGER: Well, I think the standard of care -- look, it's difficult to say what I do is necessarily the standard of care, it isn't, and we all have our -- there's nothing formulaic about the treatment of PML right now.

And I will tell you that there's no consistency in my treatment of PML patients, none. It's not like you're going to find it in the back of Up-To-Date, you're not, there's just nothing formulaic because there's no accepted therapy. Although I do offer patients the therapies that I mentioned, particularly in those instances where I can't reverse the immune system.

DR. SHEIKH: So, Dr. Thakur -- oh, go ahead, Dr. Porter.

DR. PORTER: I was just going to ask the opposite question. So -- and I believe it was mentioned before, both for Dr. Berger and von

Geldern -- what if you did the opposite, so instead of large group where the outcome is not as abysmal, what if you went to a more targeted, homogenous group where, unfortunately, the outcome is more challenging and abysmal, would that be a more ideal population to study with the objective of trying to have an approved agent in this fatal disease?

DR. BERGER: I think you'll arrive at an answer sooner with a smaller number of patients, but convincing patients and treating physicians that this is acceptable may be difficult.

DR. SHEIKH: So I'm going to call on Dr. Thakur because I haven't heard from her, and I know that this is a difficult time to weigh in, but I guess my question would be so, you know, we're in a place where it sounds like there's -- that different treating people who are expert at PML feel differently about what the standard of care is and feel uncomfortable -- some feel uncomfortable with, you know, not giving something like AISLE7 or Pembrolizumab, which we don't know whether they work

or not.

So the question is, you know, for you Dr. Thakur, is do you see a future moving from not, you know, giving treatments where we don't know whether they work or not, to being able to find out whether they work and, you know, where do you -- if you see that future, where do you where do you think it could come, from what angle?

DR. THAKUR: Yeah, I mean, I think maybe this is -- some of the discussion, which I think is really fruitful, is around kind of what we mean by standard of care, I mean, certainly what I think we've all shown as we do more of individualized, personalized medicine approach, and we're often using therapies on an individualized basis that doesn't have a lot of experimental evidence.

But I don't think that means that we cannot develop trials that are robust and provide information about efficacy of treatments. And I really think that maybe the idea that we somewhat homogenize the underlying kind of population that

Gloria mentioned, you know, perhaps with kind of one underlying condition, that might be a way for us to kind of understand what works.

I think the HIV population and response and kind of after they've been given anti-retrovirals, I think, with all the kind of issues around, you know, potential for PML IRIS is one population that we know could -- we could study really effectively, especially in a global population.

I think there's two other issues, one is, you know, we heard from the patients, and I think we always have to think about or what is their voice. We had, I think, a great study looking at responses to surveys and how they would feel about clinical trial design, and greater than 50% being concerned and would not enroll in a placebo-controlled trial, I think, is one that we really have to think carefully about before we decide to do it, because that is going to affect our enrollment and recruitment.

And that perspective, I think, really -- really has to be taken very seriously.

And then I think, secondly, if we're going to consider a global study of, you know, HIV-infected patients, I think that we really also have to consider the applicability of the treatment itself.

And if we're looking at resource limited settings, you know, this isn't talking about the control population necessarily, but it's really important that we don't ignore that issue as well in terms of whether this potential treatment could be deployed to this patient population.

DR. SHEIKH: Dr. Marra, do you want to -- it sounds like there's a chat going on, would you mind explaining what your ideas are that you've discussed in the chat?

DR. MARRA: Well, I was just suggesting that, based on what our industry person said, that we could pose a trial where we had newly-diagnosed HIV infected people with PML, because that's

truthfully what I see the most of anyway, and we would randomize them to combination and a retroviral therapy versus combination and a retroviral therapy with Pembrolizumab or with Aisle 7.

That would be a group that would be expected to do probably poorly, so you could get an answer pretty quickly, and you could also get some information about IRIS, I think, with that, and you maybe wouldn't have to have a huge number of people. But that was my pitch now that all the coffee I drink has worn off.

DR. SHEIKH: So now what about -- I think that I'd also like to talk about the other groups that we haven't discussed too much right now. We've talked about patients with underlying HIV, and we've talked about people with MS, but can we talk a little bit more about patients who really don't have a reversible -- don't have immune suppression that is readily reversible?

So I'd like to ask Dr. Mateen to weigh in on, you know, how -- if we were to think of clinical

trials for this patient population, you know, what would the standard of care be for these patients, and would that include in those patients, say, patients who have a history of lymphoma or had ICL, would that include ICL as a standard -- would that include Aisle 7 or Pembrolizumab as a standard of are and, if so, how would that be integrated into something like a cell therapy trial.

DR. MATEEN: Yeah, that's a good question. So I think the two groups that we haven't talked very much about are the hematological malignancies and potentially the transplants. And it brings to light that many patients who have PML have more than one risk factor for PML, so they may have both malignancy and a history of transplant and multiple immunosuppressive onboard, for example, and so it's hard to know.

For example, you might reduce the degree of immunosuppression in those patients, but they still have two other underlying risk factors for PML.

So in terms of -- you know, they're a more homogenous group, and I think that that makes a lot of sense to actually focus on those. As was said earlier, the number of people with MS who have PML is exceedingly small now because of vigilance for it, and HIV -- I guess I don't know the incidents of PML in HIV now, but I understand that it's much less than what it was.

And so -- and I think Dr. Spudich earlier mentioned, PML at the time of presentation versus PML in somebody with well-controlled HIV may actually be very different groups. So the hematology patient population is, I think, a ripe group for study; transplant is itself homogenous so -- or heterogenous in the sense that they could be solid or not.

So I don't think there is -- any group is actually not that homogenous within itself, so the more you know about the group, the more difficult it looks.

But, you know, if I had to design a trial,

I think that HIV is still of interest, but the hema malignancies I would also focus heavily on or even people on specific drugs, no matter what their underlying disease.

DR. THAKUR: I think this is where the historical controls could be really useful. And I know you, I'd love to hear more -- I know Gloria kind of started -- large natural history study that's bring run through the NIH, but this also depends on our outcome measures but, you know, for those kind of rare underlying conditions, using that historical control, I think, could be really, really valuable, depending on the kind of variables that have been collected.

DR. SHEIKH: So I think for the -- the problem with the historical control is we need to identify a group that can be the historical controls, and I am not aware, other than I know -- other than Gloria von Geldern's attempt to establish a registry, I'm not aware of any true historical control database that would be, you know,

non-biased. I'm not sure if -- is there anyone on the panel who's aware of any of these kind -- where this database might be, if there is one?

DR. THAKUR: I wonder if Irene can speak about the ongoing NIH that -- the details of which I'd like to --

DR. CORTESE: So we do have a natural history study at NIH and, you know, ongoing collection of data, but, you know, it's still relatively limited, and I think that there would be much to gain from being able to pull, you know, from different sources.

Also, the patient population that we see might have Certain biases, you know, for referral to our center, and we certainly wouldn't want to carry those forward too much, so, again, I think it's really important to pool resources, and probably as we'll be talking about later as well, I think what would be really helpful is as a community, you know, to develop standardized core set of outcomes that we're all collecting and that will facilitate, you

know, going forward, you know, trial design and so on.

What we've also seen at NIH, at least, is that when our natural history study was going forward without the possibility of offering a treatment option, we were getting mostly long-term survivors of PML and not so much active PML, which is where we really need to focus if we want to develop biomarkers and learn about trial designs and, you know, appropriate interventions.

And so I think that trial design -- sorry, clinical trials interventional studies themselves are the way to learn how to design clinical trials better and -- yeah. So I think we need to make more efforts in that direction a well. I don't think I really answered your question.

DR. SHEIKH: Thank you, Irene, I think that does answer the question about what you have in terms of a natural history, you know, a database or historical data.

I will also mention, Carey Jolie of rare

diseases at CDER, has put in a link in the chat for everyone that there is a new -- I think it's been two years ago that this was launched by the FDA -- funding through the FDA for the rare disease cures accelerator data and analytics platform, so this is a platform which is a centralized and standardized infrastructure to support and accelerate rare disease characterization with the goal of developing accelerating therapy development.

So it was funded through an FDA grant to the Critical Path institute and was developed in collaboration with NORD. And so essentially what this is an opportunity to share databases, and I would really encourage everyone here if we think that historical controls are very important, then we need to develop this and this is potentially a way of getting information about the natural history of PML without starting a registry, which also might be an important thing to do.

So that's my plug for RDCA Dap. So before I --

DR. VON GELDERN: Can I give one --

DR. SHEIKH: We have about --

DR. VON GELDERN: -- on this problem of getting the control data. So I think we heard from the patients in both their stories that diagnosis is often delayed, and I think maybe one effort needs to somehow go to spreading the word about PML -- this sounds silly to ask here -- but I think if more non-neurologists or non-PML experts were recognizing the disease or were at least referring patients for PML, maybe we would collect more meaningful data.

Because I think a lot of patients with PML are not collected because we don't even know that somebody -- I saw patients who had some malignancy, and as soon as there was any concern for PML they say, well, we've stopped treatments, you have PML, that's it. So I think we are missing a lot of patients that we don't even ever hear about.

DR. SHEIKH: That definitely makes sense. And I think the patients -- every patient who's communicated with us about their perspectives would

agree with you, Dr. von Geldern, that, you know, the word needs to get out, we need to get patients diagnosed earlier, that would facilitate clinical trial participation, and also likely increase the likelihood that an intervention could have an affect also.

So before we wrap up this session, I believe we have only five more minutes, and I don't think we've gotten to the bottom of this, but I'm going to ask again, just I'm going to reframe the question.

So in order to get products approved in the United States or in order to know that something works, we need to have confidence that whatever intervention it is, is actually doing better than what would have happened had we not given the intervention.

And the problem with the historical controls, number one, we don't really have historical controls for PML right now, we have a heterogeneity of patient populations with differing

outcomes; we have changing things -- changing therapies over time for those underlying diseases.

So in the last four minutes, if I can have just a 30 second -- ask each of you to -- each of the panelists to give me your opinion about how we can move forward, what is the best, most appropriate control for PML.

And I'm going to use the example of the patients without reversible immunosuppression because I think that's the area where, you know, that's going to be the hardest ethically. I'm going to ask you all to just weigh in for 30 seconds on which -- what control can we use, is it historical control or is it placebo or a standard of care, and if so -- if it's a standard of care, what's that standard of care.

So, Dr. von Geldern, I'll start with you since you're on my screen right now.

DR. VON GELDERN: I think what's come out of this discussion is that we don't know. I think my -- would be for a placebo-controlled trial in a

patient group that has a reasonable survival rate or where we are doing other interventions, like restoring the immune system, whether it's HIV or Natalizumab, and maybe trying out as much as there's limits to that, different treatments without a placebo group in patients where we can't restore the immune system.

DR. SHEIKH: Thank you.

And Dr. Berger?

DR. BERGER: Well, if I understood the question right, Virginia, you're really looking at that group of individuals who has PML, who do not have an immune deficiency that's readily reversible.

DR. SHEIKH: Correct.

DR. BERGER: And if that's the group you're talking about, what I would suggest is looking at historical controls. I'd be quite comfortable with that knowing that these are individuals that, by and large, do not recover and end up dying.

And I would think that, you know, the hope

is that you have a strong signal from whatever drug you're giving where, you know, maybe the survival is 50% or 80% and you could say quite comfortably that there's clearly an effect from the drug.

DR. SHEIKH: So, Dr. Mateen?

DR. MATEEN: Yeah, I guess I would just say that perfect is the enemy of the good here, and I think we can get historical controls, you know, I think that that is just a matter of investment and effort and collaborations. I don't think not having them as a good enough excuse, I think we should try to get them and work on it.

But I like historical controls because it -- I think ethically it is the appropriate thing to do here, and we don't have to worry about enrollment in the same way. And I think the disease is very rare, I think this study could be like several years long, so we'll just have to hold on for results.

DR. SHEIKH: And Dr. Thakur?

DR. THAKUR: Yeah, I agree with Dr. Berger

and Dr. Mateen. As I said earlier, and I do think there is an opportunity here, we have a model of a natural history study at NIH to expand across sites in which the number -- the places that are practiced still see a lot of PML across different populations, especially at places that have high volumes of transplanted patients.

So I think there is a real opportunity, as Dr. Mateen said, and I think historical controls are going to be one component. I know you didn't ask this, but I do think that a trial looking at, you know, new diagnosis of HIV starting retroviral therapy and then doing a real kind of treatment trial would be, you know, a good idea. I think that's really important for the field to advance as well.

DR. SHEIKH: Dr. Martin-Blondel?

DR. MARTIN-BLONDEL: If we need a controlled trial with a control group with a -- I would rely -- I would say, as Christina said, newly-diagnosed HIV patients with -- only and --

plus anything else as the experimental group, and I would not rely for those kind of patients on historical controls because they changed according to time, except for patients with no reversible immunodeficiency.

DR. SHEIKH: And Dr. von Geldern? Oh, I think I asked you this already.

DR. VON GELDERN: You did.

DR. SHEIKH: Dr. Porter?

DR. VON GELDERN: I might not have answered your question exactly, but I think that's all I have to say.

DR. SHEIKH: Sorry. Dr. Porter?

DR. PORTER: I'll keep this brief. SO I agree with Dr, Berger and Dr. Mateen, for this patient population that you specified in your question, I think historical controls seems like it balances all considerations.

DR. SHEIKH: All right. Thank you. So we are now going to enter -- thank you all, panelists, this was a very interesting conversation. It

doesn't seem like we've worked out everything for PML, but hopefully we've moved the bar forward a little bit.

Now we're going to go on a break for nine minutes until 3:05 Eastern Standard Time. So I'll.

(Whereupon, a break was taken.)

DR. SHEIKH: Okay. Welcome back from your last break of the day before the workshop concludes. We're going to now dive right into the last session, which is focused on putting all this discussion, all the topics we've discussed today, together into trial designs.

And we'll have the panel experts, which will be moderated by Dr. Baldassari, who you met earlier. But to put everything into perspective to try to put all the pieces together, including some of the aspects of clinical trial design that we haven't discussed already today, we're going to have Dr. Irene Cortese come back from NINDS, and along with Ken Cheung, who's a of biostatistics at Columbia University.

Dr. Cortese?

DR. CORTESE: So thank you. And today I'll be speaking together with Ken Cheung on behalf of the Clinical Trials Working Group, whose members are listed here in this slide.

As we've heard throughout the day, obviously, PML poses several specific challenges that impact trial design, and we've also heard pretty clearly that it seems unlikely that we're going to be able to identify a one-size-fits-all approach, and most approaches will be compromised on some level.

And so just to review again in the next slide, PML is a rare disease, which has clearly contributed to the limited availability of reliable natural history data and, therefore, also to the lack of established clinically meaningful biomarkers, and also generally limits feasible sample sizes for clinical trials.

Next.

It's commonly a rapidly fatal disease,

which can impact recruitment and retention to clinical trials. The lack of any validated therapies limits options for control arm, as we've heard, and can, therefore, also impact acceptability of a concurrent control arm. And generally acceptability and feasibility of a complex studies schedule is impacted by patients with rapid accrual of disability.

Next slide.

The patient population is very heterogeneous with heterogeneous outcomes, which impacts most aspects of clinical trial design from decisions over eligibility criteria to appropriate endpoint selection, selection of the interventional approach itself, and also simply a need really to account for complex clinical outcomes, such as IRIS or progression of underlying disease.

So in the next slides, Ken Cheung and I will give a high-level outline of how some of these factors might need to be taken into account when designing a clinical trial for PML, and much of this

has already been hashed out in the previous panel sessions and will be talked about, surely, in the final panel session.

And to be clear, this discussion is not intended to be prescriptive, nor really comprehensive, and the goal is really more to broadly bring together what we've heard today and go a little deeper with an overview of statistical efficiency, and essentially list some of the tradeoffs that need to be considered when designing trials.

So in the next slide we'll start with patient heterogeneity.

Next slide.

Patient heterogeneity can affect considerations for inclusion in trials for PML in a number of ways, and perhaps most importantly, because a given treatment approach might be more or less appropriate for different patient populations. So for example --

Next.

A JCV antiviral drug might be conceivably offered to all patients with PML from the time of first diagnosis.

Next.

While on the other hand, experimental immune rescue strategies might be risky in patients likely to develop PML IRIS with standard of care, and so strategies might be more appropriately reserved for patients with PML that have clearly not responded to standard of care approaches attempting to reverse the immune suppressed state, such as, anti-retroviral agents in HIV-related PML or discontinuation of immune suppressive agents, or simply reserved for patients for whom no true standard of care approach is available.

The type of intervention and the patient population to which it's most appropriately applied will in turn impact other aspects of trial design.

Next.

While including a narrowly-defined patient population might lead to more uniform expectation of

outcome, as we've talked about, inclusion of the more heterogeneous population with wide expectation of outcome would likely require a stratification to ensure that study arms are balanced. And here among the recognized prognostic factors that might be considered would be --

Next.

-- the underlying predisposing disease and --

Next.

-- the level of disability at study entry and --

Next.

-- the JCV CSF copy number at study entry, and possibly last --

Next.

-- even the extent or location of PML lesion burden or perhaps other MRI features.

Next slide, please.

As we've heard in earlier talks, inclusion of heterogeneous populations could also greatly

affect the selection of an appropriate clinically-relevant endpoint.

Next.

Such as survival being appropriate for some populations with the worst prognosis or --

Next.

-- a measure of disability for others with less severe prognosis or --

Next.

-- even consideration of some sort of a ranked outcome that might take into consideration a broader spectrum of disability, and also survival or --

Next.

-- possibly even a surrogate endpoint might be feasible in some clinical trial designs.

As we've also heard today, patients with PML can present a complex clinical course that could confound and point interpretation, and specifically a PML clinical trial would need to consider ways to clearly identify and distinguish between such

events.

So next slide.

Next.

Such as definition of PML IRIS --

Next.

-- progression of the PML itself --

Next.

-- of the underlying disease, including, for example, situations brought up earlier in the chat box of how to weigh in situations of withdrawal of supportive care or --

Next.

-- simply identifying adverse drug reaction. And since often the distinction between these events might not be straightforward, consideration might be given to establishment of adjudication committees to provide objective determinations.

Next.

The lack of robust natural history data and lack of established clinically-meaningful

outcomes urges development of consensus and standardization of a core set of key secondary outcomes that might be applied across clinical trials, and also to allow pooling of data across studies, as we talked about earlier.

Next slide.

And so such outcomes would likely include --

Next. Next. Next. And next.

-- standardization of PCR assays of MRI protocols, development of clinical disability scales, and also identification and validation of key immunological measures. And this would also surely offer the opportunity to develop maybe a combined clinical outcome or a combined biomarker in clinical outcome, as has been mentioned earlier, as well as to learn more about pathophysiology of the disease, as also discussed earlier today.

Next slide.

Increasing patient acceptability to participate in clinical trials is obviously

essential for recruitment and retention.

Next.

And so integrating concerns voiced by patients and caregivers, as we heard earlier today, including --

Next.

-- limiting requirements for travel to study sites, developing and validating decentralized outcome collection, limiting frequency of invasive study procedures, increasing acceptability of control arm, as we'll hear a little bit later, and, more generally, improving access to information about available trials and about disease in general.

Next.

And simply conducting more trials to increase available options.

And I'll now hand over to Ken Cheung, who will continue.

DR. CHEUNG: Thank you, Irene. First, I'd like to say that it is my pleasure to work with this working group for this important effort to see how

we can improve visibility of doing trials in PML. So in the next few minutes I'm going to talk about the range of sample size requirement --

Oh, maybe next slide.

Yes. So in the next few minutes, I'm going to talk about the range of sample size requirement that we may anticipate in the PML trial, and how we may make efficient use of data from a statistical perspective.

We're going to look at sample size in relation to two aspects of clinical trial design. First, in relation to choice of endpoint, second, in relation to the control arm.

So next slide.

So first we'll look at sample size associated with different endpoints.

Next -- maybe next two as well. Thank you.

So for PML, as in other fatal conditions, the specific survival is obviously clinically relevant, but the question is whether it's feasible

in terms of sample size requirements. So this is one of the questions that we're going to explore. In addition to survival, the functions and disability also clinically relevant.

The Modified Rankin Scale, for example, is a composite score that includes death and disability on a single scale, but for PML, it's likely that such a composite scale will mainly be driven by the death outcomes, so the impact on the sample size by including disability might be very minimal.

I'd like to emphasize that this is -- my discussion is purely based on a sample size perspective, clinically it's definitely very important to track the quality of life, disability of the patient.

A third possibility is that we're going to use a biological endpoint, which we will define and explore on the next slide.

So next.

Oh, and one more -- and finally, we will actually look at how increasing criteria together

with the choice of endpoint will effect sample size.

Next slide.

We will consider JCV copy number as an example of a biological measurement, which has been demonstrated to assist with survival. As my colleagues here my know, that JCV copy number is a measurement, not an endpoint. We need to define how the measurements are used to calculate a JCV-based endpoint. So there are many ways to do it, and we have considered three approaches.

So next. Next.

Yes, so the first approach is to consider a biological response defined with respect to a pre-specified threshold. For example, we call it a JCV responder when the JCV DNA decreases by a quarter on a -- scale over 60 days from baseline, so this is how we can define a JCV base response. And the advantage of using a respondent analysis is that it provides a very clear clinical interpretation and guidance.

Next.

The second approach, we find the respondent analysis by adding JCV categories to reflect more granularity. In addition to the improvement defined by a decline in JCV, we may add a category to -- defenses these patients with worsening JCV from those with stable JCV values over time.

In other words, it is an ordinal scale with three levels, which also offers clear interpretation, albeit, slightly more complicated than the responder analysis.

The third way to define a JCV-based endpoint is to look at the ratio between JCV DNA on day 60, and based on JCV. A small ratio of forward change will indicate improvement; however, you could be unclear what -- for change would be considered clinical important, so there may be some gray area in interpretation.

These are the three ways that we have considered on how to use JCV measurement as an endpoint.

Next slide.

This slide gives the range of sample size that we may anticipate when different endpoints are used. Let's start from the Left, where survival time is at the endpoint. If we include patients from all disease categories, one estimate is that patients under standard of care may have about 47% one year survival, and the assumed relative risk of a .6 by an intervention, which is a large effect size. The required sample size is 137 per arm in order to achieve 80% power in a one-to-one randomization RCT.

Now, if we include patients with worse -- prognosis, say having a 20% one-year survival under standard of care, the required sample size will be 86 per arm under the same relative risk assumption, so it's a much smaller sample size. And this point has been noted by some previous panelists.

How about the use of JCV-based endpoint? If you use a responded analysis, as we defined in the previous slide, and if you assume an -- of 2.5

by the intervention, the requested sample size will be 86 per arm to achieve 80% power. Under the same -- assumption, if you use an ordinal endpoint, that would reduce sample size slightly to -- per arm in the one-to-one RCT.

Now, if you we use a continuous -- as an endpoint, the sample size reduction can be dramatic, as you're requiring only 32 patients per arm. So we see actually quite a range here in terms of a sample size requirement, depending on how we choose the endpoint.

While these assumptions on this effect size are not directly comparable for different endpoints, they represent effect size that is large, but not unrealistic based on some of the JCT data that we have seen in the pilot.

Next.

So here's a few points that I'd like to recap. First, the use of our PML-specific survival as an endpoint is clinically relevant, but it may require a large sample size that will put visibility

in question. And the sample size requirement can be reduced quite a bit by including patients with poor survival prognosis only, but that will also mean reducing the pool of patients that we may enroll from.

Next.

Second, the use of JCV-based endpoint reduces sample size requirement to varying degrees, depending on how we define it. In general, it may be more feasible than using a server for endpoint, not only because of the smaller sample size required, but also because of the possibility of a large effects when the biological measurement is a -- target of an intervention.

And in addition, because we anticipate changes in JCV or any other biological measurements to occur over a much shorter period of time, we can complete a proof concept trial using a JCV endpoint much more quickly.

And having said that, we still need to correlate each biological endpoint with survival in

the trial as a secondary analysis.

Next.

And the last point is, as I mentioned, the incorporation of disability score with that may have a minimal impact on sample size, simply because of the fact that the scale will be mainly driven by the death outcome.

So next.

So the second aspect I'd like to talk about is sample size and the choice of the control arm.

Next, please. Thanks.

There have been quite a few discussions about the use of historic control, so the consideration here is that whether it exists, and if such a cohort exists, it would definitely reduce the sample size substantially. Of course, using a historical control is often tricky due to difficulty in interpretating causation of the --

So in the next scenario --

Next.

-- we would compare the intervention with a concurrent control arm in a randomized study. In my sample size calculations, I assume a one-to-one randomization ratio, which would offer the most power for the same sample size as an -- we may conduct a trial with a two-to-one randomization ratio, this approach may improve patient acceptability because patient will more likely get a treatment that they perceive that will work; however, it will be achieved a the expense of requiring a larger sample size.

So there's a trade off between efficiency versus whether patient will accept the trial.

And that leads to the next scenario where we will compare multiple candidate interventions to a shared control arm.

So now, the design of a trial with multiple interventions is more complicated than a trial with only one intervention versus the control, but it also offers an opportunity for -- design concept that would lessen sample size requirement

overall.

We're going to go over two concepts.

Next.

So the first design concept we would like to consider is a use of -- study. In the phase two portion of this trial, patients will be randomized through all interventions and the standard of care, which was service the shared control arm. At the end of the phase two trial, one intervention will be selected based on the biological endpoint, and you may be moved forward to a phase three trial.

In the phase three portion, then we will compare survival of the two -- of the standard of care versus the selected intervention. This design can be adaptive in the sense that the sample size of the phase three trial, maybe we estimate it based on the phase two data, and this design can be efficient In that the final analysis, by the end of the phase three trial, when you encrypt data collected in the phase two trial, as well as data in the phase three trial.

So we're not -- so these are two trials in one concept, but we're going to be able to use data from two trials in the final analysis. So this is the first design concept on the next slide. We're going to have a second design concept that is related to running a platform trial under a massive protocol where multiple interventions may enter a trial in a staggered and, again, they'll be compared to a shared control arm.

There are many advantages of running a platform trial, it creates an infrastructure that can move new treatments through -- quickly, the data management system is already in place, so there's some building efficiency in the infrastructure, and, importantly, the enrollment network is established so that we don't need to get like a new number every time we establish a new trial.

And there are also statistical advantages, specifically, a platform trial can serve as a large screen platform where interventions can be stopped for lack of efficacy through continuous monitoring,

so that we can direct resources and patients to the more promising treatments, and use head-to-head comparisons between interventions, if possible. We may also adapt a randomization ration in a way that favor arms that look superior based on interim data.

So these are all the possibilities that is enabled by the use of one shared control arm by multiple interventions.

Next slide.

In our working group, we've actually considered some design concepts that may not work, but in the interest of time, I probably want to skip this slide for now.

So maybe next. And next.

Yeah, so let's go through a few summary points.

So next.

So, again, we made this comment about the use of -- endpoint, the question is whether it's clinically meaningful, and for the server for endpoint, choosing a study population with high

mortality rate, poor survival prognosis would require sample size.

And next.

And towards the end I also talk about the use of a shared control arm in a similar phase two/phase three study or a platform trial. And these approaches will allow us to optimize resources.

And the only new point I'd like to make is that while these design concepts will optimize the use of data and resources, given how rare PML is, we need to have a long -- in way, we need to have a long game and we need to have a multi-center consortium to reach any evidence-based conclusions. So with all these design tools, it could -- to having a massive protocol under which we want to establish an enrollment network and -- operations.

So with that, I'd like to stop here and thank you for listening.

DR. BALDASSARI: Thank you so much, Drs. Cortese and Cheung. We'll now move on to our final

panel discussion about clinical trial designs for PML treatments this afternoon.

So first, reminders to the audience that for the panel discussion, you can submit any questions you would like to be addressed by the panelists using the Q and A feature at the bottom center of the screen in Zoom.

Please note that questions and comments submitted via the chat function will not be collated for panelists.

So here with us today we have seven panelists participating in this discussion, who I will introduce briefly, but I'd like to refer you to the meeting materials for their full affiliations, disclosures and biographies.

Dr. Paola Cinque is the head of the Clinical Neuro-virology Research Institute and Division of Infectious Diseases at the San Raffaele Scientific Institute in Milan, Italy; Dr. David Clifford is the Melba and Forest Seay professor of Clinical Neuropharmacology and Neurology at

Washington University in St. Louis; Dr. Lori Dodd is the section chief for the Clinical Trials Research Section with the Biostatistics Research Branch in the Division of Clinical Research at the National Institute of Allergy and Infectious Disease.

Dr. Andrew Goodman is a professor of neurology and chief of the Neurology Division at the University of Rochester Medical Center; Dr. NgocDiep Lee is the Executive Vice President and Chief Medical Officer at NeoImmune Tech; Dr. Walter Royal is a professor and Chair of the Department of Neurobiology and the Director of the Neuroscience Institute at Morehouse School of Medicine.

And Dr. Sabrina Tan is a physician scientist at the Division of Infectious Diseases and Center of virology and Vaccine Research at the Beth Israel Deaconess Medical Center of Harvard Medical School.

I'd like to ask our panelists to turn on their videos at this time.

So with that, just to get things started,

I'd like to open with a general question we would like each panelist to provide a one-to-two minute response to kind of get the discussion started.

The question is, based on your experience and expertise, what trial design elements do you consider to be the most important, feasible and appropriate for PML clinical trial designs and why?

So would anybody like to volunteer to respond first?

DR. ROYAL: I'll go ahead and get started. I'll say --

DR. BALDASSARI: Thank you, Dr. Royal.

DR. ROYAL: -- like the second clinical trial design, the staggered enrollment approach. And I'm a bit biased because with our study we had the main enrollment that I think works well with a HIV population, especially one that has, you know, better clinical status, it allows one the opportunity to have a control group built in.

I would say that in doing that, it's important to be prepared to modify treatment as the

trial goes along using the different biomarkers that are used not only for identifying candidates, but also to be prepared to modify depending on what the drug that's being used in the clinical trial to modify treatment, much as what you might see done a cancer -- clinical trial.

DR. BALDASSARI: Thank you so much.

Would anyone like to go next?

DR. TAN: I can speak next. I think we learned a whole lot from the COVID trials, we were running them left and right and we literally threw the kitchen sink at it. The NIH model of the Platform design for the COVID active trials is a good model to follow, which exactly is the platform where you can plug into the different drugs in one study.

And I think that eventually came into play in the COVID studies that we've been doing, because initially we were just doing one-offs, and then we were just so desperate to treat patients.

And I do think we do learn from that also

that just treating them doesn't really help us answer any questions. You know, a lot of the things that we have tried, Aisle 6, even Remdesivir, we did them without a good control arm, not necessarily placebo, but a good control arm, we still are up in the air whether they work or not, we whiplashed, you know, back and forth in the entire year.

So I think those have been -- us in doing PML -- it's a rare disease, we can't afford that whiplashing back and forth, so we should have a good control arm that's shared by everyone. And then have a centralized consortium, have everything set up, would be great.

And having done studies with centralized IRB and that will move amendments and changes through really fast to off sites, and it's much more efficient than doing individual trials with different sponsors.

DR. LE: I'll go next. First of all, I'd like to thank the organizer and the speakers for having this very educational workshop and for

inviting me to participate in today's discussion. I should also mention that my comments are more pertinent to the clinical trials that are designed for potential registration, if there is a court and not for trial design for exploratory purpose only.

So with that in mind, of the two study designs that Dr. Cheung presented, I prefer the seamless of phase two/phase three study design, preferably with one active -- but maybe different dose level other regimen. Hopefully, two or maybe up to three, but more than that is -- can be prohibitive because of a large sample size.

And the reason I prefer the seamless phase two/phase three study design, because I think that it provides the line of sight towards registration. And logistically, it may be easier to conduct compared to the platform study design. So during the phase two portion of the study, for example, in addition to establish the safety profile for the drug, we can determine the right dose level or -- regimen to bring toward the phase three portion of

the study.

We can also assess what are the clinical endpoints that are clinically meaningful, but obtainable, and have an estimate -- a more accurate estimate of the magnitude of improvement.

In addition to that, we can potentially also use the data information that we get from the phase two portion to refine or revise the eligibility criteria, as appropriate.

We can also have a better and hopefully more realistic estimate of the accrual enrollment, et cetera.

So for all of that reason, if we were to design a trial for potential registration, I would prefer the seamless phase two/phase three design.

DR. BALDASSARI: Thank you very much. And I just wanted to take a minute and remind the panel that -- I wanted to clarify the purpose of the question is not necessarily to kind of, you know, how you select one of the two design strategies that were presented in the previous presentation, but

really just kind of a broad question related to anything -- any clinical trial design element you'd like to speak about, so patient population, endpoints, elements related to feasibility, we'll try to get into all of those, but just wanted to make sure you weren't limiting your responses to just picking between one of those two.

But feel free to respond however you'd like. Thank you.

Would anyone like to go next?

DR. CLIFFORD: I can go next.

DR. BALDASSARI: Thanks, Dr. Clifford.

DR. SMITH: Sure. You know, I think having wrestled with this problem for the last three decades or so, I've realized that the devil is in the details with designing these trials, and so I think, you know, one of the questions going into what's the ideal trial is what are we trying to study, what are we trying to prove we can do that might benefit the outcome of this disease.

And so I think it is going to be different

depending on the kind of intervention that we're proposing to use. That said, I think because of the widespread network that you have to construct in order to enroll a number of patients, keeping things quite simple and controllable is -- is very important in a successful ultimate study.

And I think that getting a standard of care for underlying condition that we could agree on, which, you know, obviously, our discussion showed that's not simple, but I still think, you know, we ethically have to find where's the equipoise with this condition, we can't just sit and let the disease kill our patients as good physicians.

At the same time, we have to have an equipoise of where we're quite convinced that we can offer benefit to a set of patients, and then either add something to it or not, and do it as a trial so that we come out smarter at the end of the day, rather than spending years and years poisoning patients in this way and that way, and not making

progress.

So I think as a group we need to organize and we need to systematically say, okay, this is the standard care. And people will come to us as the network because we can apply that, we can diagnose quickly and get care underway, but then we either add or we don't add something where there's an equipoise and we don't know whether we're going to do more damage or good and in what way.

So I think that that's how I would like to see the field go forward. I do think that -- that looking at what we're doing to the virus, so the trajectory of what's happening to JC in the central compartment is the most measurable sort of interim marker that -- that we're either on the right track or not.

But, ultimately, I do think that longer trials that look at the nine or 12-month outcome and really try to do a multi-factor analysis of have we made the population we chose to give this therapy to or didn't, have we made those outcomes better. If

we have, then that's something that we could endorse and that we hope the FDA would endorse.

So it's not a simple answer, but that's where I am going at this point in time.

DR. BALDASSARI: Thank you.

Dr. Goodman, I see your hand raised. Would you like to weigh in?

DR. GOODMAN: Yes, please. So firstly, I'd like to thank the organizers for doing a great job and a great service for this very thoughtfully put together workshop. And I agree that the unmet need here is actually really desperate because I don't think the prognosis for PML in people who don't have an easily reversible immunocompromised has changed in the 40 years that I've been doing neurology.

But also as I'm looking at myself, I would like to apologize for the lighting because I really don't have the same coloring as our recent past president, but that's what it seems to look like here today. I'm sorry for that.

In any case, what I would like to -- I think the important feature for trial design was already brought up by Joe Berger and Roland Martin earlier today, and that is really trying to have as homogeneous a patient population selected if we really want to get a clear answer.

And I would also like to push back on the notion that we don't -- we don't have good natural history. I think that we learned from the trials that David and Walter and Joe and others have worked on over the decades, they weren't failed studies, the drug failed to work, but we learned from them. We learned, unfortunately, that -- you know, that the prognosis is as horrible as it is, other than, again, for the correctable immunodeficiencies.

So we build on that, and if we have, for example, a homogeneous population of people with, again, uncorrectable immunodeficiencies, then if there is a treatment that, you know, beats the known 15-week median survival that David mentioned earlier, you know, then we know we're on to

something.

I have other ideas about the study design as Dr. Cheung put forth, but I'd like to focus on homogeneity of the study population and using what we know, particularly if we use the most hopeless group, which is the most desperate situation, I think, and we use the biomarkers for futility is -- I think Jennifer Lyons brought up this morning -- as a start in survival, I think, that's a start.

DR. BALDASSARI: Thank you so much.

Dr. Cinque, would you like to weigh in?

DR. CINQUE: Hello. Yes. Well, I like very much Irene and Ken's presentation, that was so rich and smart and also practical. I'd like to go through very quickly three points -- main points, very practical again.

So one first, maybe it was implied, but I like to stress that the clinical trial of PML should really be intercontinental, so should include all the countries all over the world, because, well, it will need more resources, but we need to enroll a

lot of patients.

Second point is that I -- well, the question would we want to also consider for inclusion in a clinical trial patients with PML who are JCV DNA negative in CSF, because 20 to 30% of patients at presentation are negative, but now we have very good neuro ideologies and a lot of experience to clinically classify PML or based on clinical and radiological criteria, so I would not discharge this opportunity.

And the third point was about outcomes, because I always been very -- very strong supporter of a virological endpoint, and I still am because -- well, because it -- because it's viral disease because if you use an antiviral so it's good to have an anti-virologic endpoint.

But there are some concerns, and one is that if we decide to include -- we cannot include JCV negative patients, that if we use that as a primary point, and also -- time into a couple of clinical trials of PML, and I have to say that a

major problem was involvement of patients because of the real rapid progression of these cases.

So you are a patient with PML, you want to -- and the physician wants him to enter a clinical trial, then you start all the screening tests, and then you have to get the lumbar puncture, and then you have to send to the reference lab, it takes time for shipping for everything and maybe just in one week or ten days or two weeks, so PML is really worsened dramatically.

So I think we should keep it as simple as possible, especially with clinical -- with outcomes,and I would not discharge for this reason a clinical outcome or so there might be other problems because, well, biological marker is objective and clinical outcomes not so objective.

DR. BALDASSARI: Okay. Thank you. Thank you so much.

Dr. Dodd?

DR. DODD: Yeah, thank you. So in my notes I have listed the key design features that I

think are important, in general, and in particular listening to the very interesting discussion today, it was a really energizing day for me, so thank you all.

The first is a clinically meaningful endpoint that's -- I'm repeating what -- some of what's been said, but that's subjectively measured, not necessarily completely objectively measured, but you don't want to be in a position where the measure changes over time, which we know happens, and you have to guard against that. Randomization with a standard of care control arm, I think stratification is an excellent idea, in particular I was thinking early on, stratifying by the underlying condition.

I often caution against having too many strata, because you can sometimes create imbalances, and we had that happen in our Act One Trial in COVID.

The other things I have in my notes are I have concerns about the virologic results at this point, the numbers were small and the correlation

with the outcome, I thought, was likely to depend on the underlying condition, so I don't know how much you would -- how comfortable you would feel saying a point of .25 in HIV was similar to a cut point of a .25 log reduction in MS, you know, so those are just things to think of.

I think more data is needed to really understand the relevant cut points and whether you could apply a single cut point universally across the different underlying populations.

And then, finally, you know, one thing -- well two other points, one is why not increase the type one error rate? Point 05 is, you know, sort of -- it was an arbitrary choice.

And I'm a statistician, we talk about this all the time, we love .05, but in rare diseases there's precedent for setting a higher type one error rate, so rare pediatric cancers is one setting that I think the FDA has experience with approvals in, so why not choose .1 or consider something higher.

So if you go from .05 to .1, I think you end up reducing your sample size by about 20%, you know, so maybe this is an area that you -- you all are willing to say, I'm willing to take a higher -- you know, have a higher false positive rate, and that can help out a lot.

And then the last comment I wanted to make is that, you know, I like platform trials, I've been involved in a couple of them, not all of them are the same, you know, the devil is in the details about how the platform trials are designed.

I was involved in an Ebola trial in the Congo, where we had a four arm trial, and we started the fourth arm a few months after the original three, and that agent was a little bit behind, right, it's like holding the horse back from the race to get started, and that created a lot of headaches for me because I thought we weren't giving -- potentially, we weren't giving that drug the same fair chance because you could only compare it to its concurrently enrolled standard of care

arm.

So you just have to think about, you know, when you're going to roll in a new agent, and whether you were -- I think you're probably not able to compare the new agent to the standard of cares from the previous period.

And so, you know, I think there's a lot to be thought through about how you do a platform trial. I certainly like the idea of a trial that you can, you know, roll out different eras or epics of comparators, because it's -- you know, just programmatically it's a lot easier to implement a trial in that way. So I'll stop with that. Thank you.

DR. BALDASSARI: Thank you so much. Those are all wonderful points and I really thank everybody for tackling such a complicated and diverse topic. So I think at this point I think we've had some common themes arise in everybody's responses, I think, you know, the overall trial design concept, but also as the previous panels have

discussed, the degree of patient heterogeneity and who would be appropriate for inclusion in a single trial under what design.

So given the differences in PML natural history, there are patient populations with PML, what patient populations do you feel could reasonably included in an individual trial, and what endpoints do you feel that would be the most appropriate there.

And I also wanted to tie in an audience question as well with the patient population heterogeneity, particularly including more disabled patients to see if they could be included in the trial as well. Thanks. If anybody wants to start, please feel free.

DR. CINQUE: Well, I can start. If we want to restrict to one single population, I would exclude those like MS patients who are going to respond better to withdrawal of Natalizumab and include the largest group of patients. But I do believe in this case is patients with HIV just

diagnosed who are going to start anti-retroviral treatment because they will have a similar baseline point, all of them, or almost all of them. Differently, people with meta-logic malignancies, actually they are also heterogenous inside the group, like all the other diseases, so probably.

And of course it would be great to include that sort of mandatory and really ethical to have patience with -- well, congenital disease or conditions for which there is no chance to reduce immunosuppression.

DR. CLIFFORD: I think I could comment just walking through the eligible populations for studies, which is a -- I'm really struck with how we keep changing the populations that potentially are most important that are having to deal with PML. I agree with Paola that the newly diagnosed HIV patient, AIDS patient that's fallen through the cracks and presents with PML and hasn't started HIV therapy is an available and relatively frequent population, although it used to be upwards of 80%,

and now I'm sure it's much less than half of all PML patients.

So the total numbers are declining, and as we're successful in starting HIV therapy earlier and more widely in populations at risk, this AIDS population that's fallen through the treatment cracks is largely populated by people that have either significant psychiatric co-morbidity or drug use or other issues that make them a complicated and difficult study population to continue to follow for a PML study.

So I think there are real problems with the HIV population. Someone earlier mentioned sort of successfully-treated HIV patients, and believe me, we'll never have a study because they're -- you know, there are virtually no cases of people that have good HIV control that developed PML, that's just a really rare entity, so don't hold your breath for that.

In regard to the MS population, there's been really marked decline, it appears to me, maybe

folks from Biogen can tell us, but my impression is that with the availability of alternative MS therapies and risk stratification, that the numbers of Natalizumab patients have really fallen, and that's not a very promising population and, you know, the -- and Dimethyl fumarate, PML and so on are a very small number that you're not going to have a study in either.

I'm tending still to think that, like Joe Berger, that this very bad-prognosis-hematologic-malignancy-cancer population is one to test hypotheses about interventions and, albeit, it is also very complicated.

The other autoimmune disease population, we see a fair number of lupus patients, a few rheumatoid arthritis patients and the like, those are worrisome because a lot of what we do is immune stimulation, and their underlying disease might well be adversely impacted by that strategy, so, you know, the equipoise for the intervention there is a

problem.

So it really is -- it's challenging, but I think the HIV population versus the malignancy population are where the next studies really probably ought to go.

DR. GOODMAN: So I've already weighed in on this, I think, but I'll just embellish a little bit. I agree with what I think I just heard from David, is that we ought to focus on the population with -- again, not easily or impossible to treat immunodeficiency like hematologic conditions.

I would also just -- to say that there seems to be a paucity of hematology input in this workshop today, and maybe we're overweighted with people like me, neurologists, so I think that's just something to consider as this moves forward, that we need hematologists and clinical immunologists who are also dealing with these people.

And it was mentioned earlier today, and I think it's true, there are a lot of patients who are never diagnosed or missed, simply because they're

in -- with all due respect -- in cancer centers where they don't think to call neurology or do an MRI scan or an LB, they're never diagnosed or certainly diagnosed too late, so that's an issue, so I think hematology is important to include in this project as it moves forward.

Yeah, I think I'll stop there.

DR. TAN: Yeah, I think what Irene presented earlier makes a lot of sense, and it really depends on the product were trying, you know, if it's an antiviral, it would seem to me that, you know, we would include allcomers, right, regardless. But if it's an anti-immune modulator, it -- when we have to really look at which group we're talking about because then the HIV group and MS group would be different.

And then, furthermore, among the -- malignancy, they're really different with what their immune composite is. And then compare those to the autoimmune people, if you're giving an immune stimulant, you also need to understand that their

baseline immune factor or modulation is also different.

And so it seems to me that it's a little bit difficult to design a trial where we don't know the exact product, but whereas, if we do have an infrastructure in place that will allow us to look carefully at, you know, each product and plug into the baseline infrastructure where the IRB is already in place as more inclusive and people didn't qualify them for this rare disease, perhaps it could be important to our historical control group or even just collecting the registry so we can understand PML better.

DR. LE: Hi. I'd like to follow up on Dr. Clifford's suggestion to potentially focus on a PML patient with -- malignancy as the underlying disease. So I have to admit I'm a medical oncologist by training, so I love the idea, but my concern is -- and I know very limited about PML compared to all of you -- so my concern for that patient population is the incident, would it be

feasible to accrue patient for the specific sample size in an acceptable timeline for us to develop new treatment?

So essentially compare this, say, HIV patient with a newly-diagnosed PML, for patient with PML and hema malignancy, how do you compare the number there in terms of the incident and the new cases, et cetera?

DR. CLIFFORD: So the numbers are substantially less, and that's the problem. I mean, we're caught between a rock and a hard place. With one set of patients, we need a vast number, although there are quite a few available; with the other, we need a smaller number, but there are a smaller number available.

But I think that, you know, sort of this notion of intensive study and understanding what happens, a little bit of an N equals 1 or 3 or 4, but really intensively studying them, that some of these patients we might be able to learn quite a lot in a relatively small trial, simply because there --

they have such a uniformly poor outcomes overall.

DR. BALDASSARI: I wanted to revisit a point Dr. Cinque mentioned earlier about the logistics of having an incidence trial, essentially, in a patient population that's relatively rapidly progressing and, you know, getting worse, especially depending on which underlying patient population you choose.

And that goes back to Dr. Thakur's question in the chat, how would you feel that -- or how would you say that this issue, basically, of having a rapidly-progressing population with poor prognosis would factor into your decision for an overall clinical trial design. She mentioned specifically about a platform trial design. So what do you think?

DR. ROYAL: So for me, having such a population takes me back to my earlier comment related to being prepared to do some -- modification and other interventions to -- based on, you know, validated biomarkers wherever possible to try to

counteract some adverse effect of the drug or some feature of the underlying disease that might prevent that person from being able to stay in the trial and survive as long as they would otherwise, of course, do that, one should try to build in as much as possible such interventions into the initial protocol.

DR. BALDASSARI: Thank you. And Dr. Dodd, I see your hand raised. Would you like to respond?

DR. DODD: No, I wasn't -- this is not my domain. I'm sorry.

DR. BALDASSARI: No worried. Dr. Le, I see your hand raised as well.

DR. LE: No, I already asked the question that I was planning to ask.

DR. BALDASSARI: Okay. Dr. Cinque? Dr. Cinque, I see your hand raised as well. Did you want to comment?

DR. CINQUE: Yeah, I think that your question was very important because when we refer patients for inclusion in a possible experimental

intervention, so one of the first consideration with patients and families is about the -- how advanced is the disease, because, especially for -- or approaches that are not antiviral, so they are expected to act immediately on the viral replication, so with immune interventions it will take time -- well, not months, but not days.

So one has also to consider time from the start of treatment to the moment a new approach will be effective. And if we save lives, technically, and a drug is working, the patient is really left with terrible neurological deficits, then -- well, we don't have to get to that point.

So stage of disease or -- I don't know how to call it, how the disease is advanced, and we probably need criteria to define these no return point.

DR. BALDASSARI: That's a great point. Thank you. And getting back to what Dr. Dodd was saying earlier about stratification factors, I think that kind of stems nicely from what you were just

saying, Dr. Cinque, about, you know, how do we decide, you know, what stratification factors, how many to use in individual trial design, based on what we know about PML. What does the group think about stratification factors? Which ones would be the most important?

DR. MARRA: How about supra-tentorial versus infratentorial disease?

DR. BALDASSARI: Thank you.

DR. MARRA: -- talked about that.

DR. CLIFFORD: And I'm not sure there's that much difference between posterior-fossa and hemispheril disease, frontal disease perhaps, but I do think the underlying disease and sort of the readiness of an intact or relative intact immune system is one of the key factors in prognosis.

When the patient enters the trial, to know that that slide that I had about staging the disease, you know, how much immunosuppression; how much immune reconstitution has gone on so far, and somehow placing the patient starting the trial on my

plot as to where they are in their immune suppression, immune reconstitution continuum, which is a continuum, it's not a yay or nay presence or absence.

You know, I think if we could quantify that in a useful way, that would give us a very nice way to look at prognosis and the opportunity to save lives.

I wanted to divert just a minute, though, Dr. Cinque and I almost always agree on most things, but I heard her say something about sort of JC negative inclusion, and I am a little bit alarmed at that. I really -- I really am uncomfortable with clinical trials where the diagnosis is in question.

We've heard the flip side of confusion around PML diagnosis where, you know, one of our -- our really informative patients told us about having a stroke misdiagnosed -- her PML misdiagnosed as a stroke, and, you know, having a bunch of small strokes included in a PML trial would be disastrously uninformative for a therapy.

And so I am really alarmed and think that I would very much want to insist, unless it's a trivial intervention, to make sure we know the diagnosis truly is PML.

DR. CINQUE: May I?

Well, David I'm been thinking exactly same as you until a few years ago. What we have witnessed in the last, let's say, five years, with the Natalizumab epidemic, and then there was a new generation of neuroradiologists that were very, very, very competent and easy to recognize early PML lesions and to differentiate the PML lesions from other lesions.

I'm not talking in general, let's say, in typical PML cases, so -- and if we put together this information with the clinical information, and the fact that there is an underlying disease with the insidious presentation and a lot of clinical elements, I think we can make a diagnosis of PML without having JCV DNA in CSF. I'm more and more convinced of that.

Perhaps it's just because I'm fortunate and lucky that in our -- well, local situation we have a very good neuroradiologist that has persuaded me and my colleagues of this. And I don't know if there are here people who do neuro imaging that are with me in these --

DR. MARRA: Maybe another certification factor could be, you know, definite versus possible or probably and most likely or something like that?

DR. CLIFFORD: -- I agree with that and --

DR. CINQUE: For clinical trial, I think we need diagnosis --

DR. CLIFFORD: In the high-risk Natalizumab population where they're being surveilled very frequently with scans and picking up very small lesions that are hard to diagnose virologically, you know, I see where you're coming from and the importance of that early recognition is very critical, but I remain, you know, sort of quite cautious about trusting the radiologist to make this diagnosis, as good and as friendly as they are.

DR. MAJOR: Let me make the comment here, and I've waited until the end of the day to barge into these clinical discussions, although I do have, you know, five pages of notes that are going to be extensively reviewed by Irene and Virginia and Pat and that.

So I was concerned also, as David had said, Paola, you had said that you see 20 to 30% of PML patients diagnosed than whose CSF has undetectable amounts of JC DNA over the last number of years. I think that was the percentage that you said.

DR. CINQUE: Yeah, that was from the literature, Gene.

DR. MAJOR: Yeah, so the literature on some of that is so poor that I stopped reading it. And so that has not been our experience over 20 years of directing the CLIA Laboratory.

I will say over the last more recent times, before we had to close our operation, that a large number of samples that we got, you know, CSF

samples that were just sent to us without any pre-warning, were sent to us because the treating neurologist was still concerned about the diagnosis of PML, even though whatever laboratory tested the CSF said that it was undetectable.

Now, are there some cases of PML where you simply can't find the JC DNA at the time the sample is set? And Dr. Goodman had a patient a number of years ago that was clearly not diagnosed, I mean, you know, it was a biopsy and we found a lot of viral DNA in there, but we never -- I don't know, Andy, what is it, maybe had five samples of CSF that we could never find it.

DR. GOODMAN: Five LPs that were negative. But she was very -- she had very restricted sort of mono-focal disease. And so as David just points out, there are these cases -- and this was an Natalizumab patient, and there are these cases of these tiny, tiny lesions that are, you know, foreign -- I would guess, of PML, and she was one. But she had millions of copies in the pathology

specimen.

DR. MAJOR: So at least we've not had that experience, Paola. Does it happen occasions? Yes. On the other hand, the laboratory over the decades worked very hard to be able to go ahead and make sure that we had a very robust and reproducible assay, and that's to the credit of the lab folks.

And, again, I don't know how many of these samples that we got where we did find, let's say, 15 copies or 22 copies or something that was just above our level of detection, and as a matter of fact, if you look back in the literature after Natalizumab was put back on the market and there were several -- there were several cases that ultimately got published in the New England Journal, and where -- and I had been one of the co-authors on that because no one -- this was in Germany -- no one could find the detectable levels of JC DNA.

We finally got the CSFs and, sure enough, I mean, it was there, and so that does happen. It's a concern as the DNA as a marker was talked about

before, and Irene had mentioned this, is that, you know, there's variability in the assays, and you have to trust them -- you have to be rather vigilant, if that's the word to use these days, to make sure that you have a highly reproducible and a very sensitive assay, and that's why we spent a good deal of time doing that.

So, David, I'm glad you raised that point, it gave me an opportunity to go ahead and extend this whole afternoon.

DR. CLIFFORD: And I think anchoring changes of anybody status in the central compartment would be another alternative that would add to the spectrum of associatedness to JC virus that we -- would make me more comfortable. Anyway, interesting discussion.

DR. BALDASSARI: Okay. Sorry about that, everyone. I didn't mean to cut anybody off, but we're unfortunately out of time for our session today. I wanted to thank everybody for a really thoughtful and thought provoking discussion this

afternoon, hopefully conversations can continue offline, you know, we're capturing all the questions and everything in the chat.

So I will now turn to Dr. Sheikh for closing remarks. Thank you. everyone.

DR. SHEIKH: Yes, thank you so much, Dr. Baldassari and panelists, that was a really good way to end the day. So I just want to thank you, all panelists, moderators and speakers for helping us finish out today's workshop. Before we close, I'm going to try to provide a very brief summary of today's workshop; however, I have to say I kind of worked on how to summarize each of the discussion sessions in one sentence, and I failed, so I'm not going to do it.

We'll have to -- I'll really need to think about it and have you all give input on to really how to summarize all those really interesting conversation.

But we started this morning with Drs. Major, Clifford and Smith who laid out the

groundwork for the meeting by summarizing PML virology and pathogenesis, PML drug development history, current therapeutic landscape and clinical outcomes among PML patient populations.

For the next portion of the workshop we focused on potential primary and key efficacy endpoints for PML clinical trials, Drs. Baldassari, Cortese, Cinque, Wattjes and Ms. Norato provided us with excellent summaries of the strengths and weaknesses of various potential endpoints.

And following those talks, we had a lively discussions between Dr. Koralnik, Martin, Warnke, Spudich, Nath, Marra and Lyons on potential PML trial endpoints. I'll just summarize that by saying that we have not found a perfect endpoint for all patient populations yet, but hopefully we moved the needle in terms of that discussion, and that these discussions will continue offline.

After lunch we heard about our FDA NIH efforts to elicit the PML patient's perspectives on clinical trial design by Ms. Ohayon, followed by

thought-provoking perspectives from PML survivors Suzanne Tobin and Luca Isabella.

For the next portion of the workshop, we focused on the selection of control groups for PML clinical trials, Dr. Lee provided an overview of several approaches to control groups, including some promising examples of successful outcomes in neuro mellitus optical spectrum disorder, another rare neurologic disorder.

Following those talks, we had a very lively discussion with Dr. Berger, Mateen, Thakur, Martin-Blondel, von Geldern and Porter, as well as other guest appearances, who all provided their perspectives on control groups in the setting of PML.

Again, we have not -- I don't think we've come to complete consensus on the perfect -- how to select the perfect control group for PML, hopefully we've understood at least each other's perspectives and can move forward with clinical trial designs in the future.

And then the final portion of today's meeting was focused on how to put all the elements of PML clinical design together to create phase three PML clinical trial designs that might be acceptable to regulators, clinicians and patients, and that might foster industry engagement. Dr. Cortese and Dr. Cheung did a fantastic job summarizing the pros and cons of key trial design features.

After that we heard from Drs. Royal, Clifford, Dodd, Goodman, Tan, Cinque and Le, who each provided their perspectives on the elements they felt to be most important.

Hopefully we'll be able to -- after all of us have had an opportunity to really think through what happened today and all the discussion and what the conclusions will be, we'll be able to move forward with continuing this discussion in the future.

So speaker slides, transcripts and recordings will be available on the meeting's web

page in the coming days, and we also plan to summarize the meeting for publication, probably in the spring of 2022.

Next slide.

On behalf of my colleagues at the FDA, I would like to thank you all for your participation in today's workshop. Thank you, speakers, for doing such an excellent job concisely summarizing key considerations for PML clinical trial designs. Thank you, panelists, for your insightful comments and your vigorous discussion, and your perspectives.

And a special thanks to PML survivors, Luca Isabella and Suzanne Tobin for sharing your personal perspectives on PML and PML clinical trials.

And thank you, workshop participants, for your attention and thoughtful comments and questions. I'm sorry we didn't get to all of them, there were actually a lot of comments and questions that we did not get to address, and I apologize for that. We'll try to incorporate that into any future

publications and thoughts, and also in summarizing in the meeting summaries, if possible.

I'd like to particularly acknowledge workshop participants from timezones far away from the Eastern Standard Time who woke up either particularly early this morning, like Dr. Marra, or are participating late into the night right now, like those from Europe.

I'd like to thank the CDER public meetings team and our technical support team for facilitating today's meeting, it went really well, thank you very much.

Next slide.

More generally, I'd like to thank the many members of the PML clinical research community, both in the U.S. and internationally, and the people throughout the FDA who've been steadfast in their support of our efforts to reach consensus on key PML clinical trial and considerations.

Next slide.

Please continue all your great work,

keeping in mind the important issues that were discussed today. Please take advantage of FDA's many resources for rare diseases, some of which are highlighted on this slide today.

Lastly, especially in the areas where we have not reached consensus, which is potentially most of the issues, please continue your discussions amongst yourselves, engage with regulators at the FDA and elsewhere with potential brainstorming and potential solutions.

Next slide.

Thank you very much for participating and have a good evening.

(Whereupon, meeting adjourned at 4:22 p.m.)

State of Maryland, to wit:

I, Jean M. Townsend, a Notary Public of the County of Montgomery, do hereby certify that the within-named witness, personally appeared before me at the time and place herein set out, and after having been duly sworn by me, according to law, was examined by counsel.

I further certify that the examination was recorded stenographically by me and this transcript is a true record of the proceedings.

I further certify that I am not of counsel to any of the parties, nor in any way interested in the outcome of this action.

As witness my hand this 21st day of September, 2021.

Jean M. Townsend

Notary Public

My Commission expires:

October 8, 2025

f

g