ACTTION - Chemotherapy-Induced Peripheral Neuropathy (CIPN) Trial Design Considerations

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ACTTION

ANALGESIC, ANESTHETIC, AND ADDICTION CLINICAL TRIAL TRANSLATIONS, INNOVATIONS, OPPORTUNITIES, AND NETWORKS

Chemotherapy-Induced Peripheral Neuropathy (CIPN) Trial Design Considerations

Thursday, March 23, 2017
8:13 a.m. to 3:59 p.m.

Westin City Center
Washington, D.C.

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:13 a.m.)

Introduction and Meeting Objectives

DR. FREEMAN: Good morning. Welcome to the ACTTION meeting on chemotherapy-induced peripheral neuropathy. My name is Roy Freeman, and on behalf of my co-chair and myself, I'd like to welcome you.

I see a lot of new faces, and it's great to have new faces at this meeting. I also see a number of familiar faces. I, of course, was not going to say old faces.

For the new faces, as the meeting evolves, I will give you some sense of how these kinds of meetings go, and they are quite unique meetings where everybody is a participant, everybody is involved. This is not the kind of meeting where you slip out for an hour or two and pay your respects to the White House.

You are here throughout the meeting. You contribute whether you're on the podium, whether you're a panel member, whether you're a speaker, or whether you're in the audience, and everybody is

involved in the final work product.
I want to introduce Bob Dworkin, who is the president of ACTTION, who will give a brief overview of ACTTION and its goals, role, and contributions.
Bob.
Introduction to ACTTION
DR. DWORKIN: Thanks, Roy.
I do have to set the record straight, especially in Washington, D.C. I am not the president of ACTTION. I'm the director.
I just want to spend a couple of minutes for those of you who aren't familiar with ACTTION, saying just a few brief words about what it is. You can see from the slide what the acronym stands for.
It's a public-private partnership that was established by the FDA about six or seven years ago. At the University of Rochester, we've essentially been the coordinating center for ACTTION for the past six or seven years. So I'll just give you an overview of it.

Housekeeping, you can read this yourself. I assume that it says that the restrooms are outside in the hall somewhere, and please do silence your cell phones.
The meeting -- and this is important, and if you don't like this, unfortunately, you have to leave. The FDA has asked us to record all of these meetings that ACTTION sponsors and prepare transcripts that are then posted on our website. Whatever you say will eventually appear on our website in a very detailed 600-page transcript. We're not sure that anyone actually reads those transcripts, but they're there.
This is a quote from Dr. Janet Woodcock from, as you can see, back in 2007 that I think is really excellent in providing the overarching rationale for public-private partnerships in general and also ACTTION. And I think it's worth reading, and I'll read it.
What Dr. Woodcock said back then is, "The science base necessary to evaluate and predict safety and efficacy is different from the science

that generates the new idea for drug, biologic, or device."
In general, NIH and academia do not perform research in this area of efficacy and safety, indicating the need to develop mechanisms and incentives to foster research directed in improving the scientific base for what came to be called "the critical path." In fact, the examples she gives us is for analgesic drug development, which is one of the emphases of ACTTION.
So the mission of this public-private partnership is to identify, prioritize, sponsor, coordinate, and promote innovative activities, and this meeting exemplifies it, a particular interest in optimizing the design of clinical trials. That is across four different therapeutic areas: pain, analgesia, anesthesia and sedation, treatment of various types of addiction, and disease modification if a peripheral neuropathy.
So ACTTION has a large portfolio of activities across those four different therapeutic areas. And of course, this meeting today fits in

the peripheral neuropathy bucket.
These activities of ACTTION are coordinated by consortia and various collaborations, and this one I highlighted on the slide is the Consortium on Clinical Endpoints and Procedures for Peripheral Neuropathy Trials. We like acronyms. The acronym is CONCEPPT. We have other acronyms, and also a large number of working groups.
Because ACTTION originated with a focus on pain, there's been a greater amount of activity involving analgesic treatments and methods for analgesic clinical trials. Sedation and anesthesia, addiction medicine, and disease modification in peripheral neuropathy were added after ACTTION was originally established, and so we just haven't had as much time to ramp up activities to the extent that we've done in pain. But that's all forthcoming, and of course this meeting is an example of that.
Overall, I think our research objective crosscutting those four different therapeutic areas has been to develop an evidence-based approach to

Page 9

design, execution, analysis, and interpretation of clinical trials of analgesic, anesthetic, sedation, peripheral neuropathy clinical trials.

I love the phrase "evidence-based approach to design of clinical trials," and I have to acknowledge Nat Katz as being the source of that I think really felicitous phrase. I hadn't heard of it until Nat exposed me to it, but I've used it with abandon since learning this from Nat several years ago.

We've got a bunch of partners reflecting diverse professional societies, U.S. government agencies, and industry. There are multiple industry sponsors, supporters of ACTTION. The two I've put on this slide are the two companies that have provided support for this meeting and for the CONCEPPT peripheral neuropathy initiative.

So we all have to express our appreciation to Mundipharma and Regenacy for supporting this meeting, and we really appreciate it. It goes without saying, but I'll say it anyway, that ACTTION wouldn't be able to do the things it does

Page 10

without the support of industry and, of course, the FDA.

The CONCEPPT peripheral neuropathy consortium had a meeting a year and a half or so ago. One publication has just appeared from that meeting in Muscle and Nerve. There are several other publications in the pipeline that many of you in this room know about, are co-authors on, as Roy will say more about in a moment, I'm sure. One of the major deliverables' objectives of this meeting will be a publication that you are all invited to serve as co-authors on.

Finally, if you're all interested in learning more about what ACTTION is doing, has done, plans to continue to do for at least another five years, we are in the beginning of a second five-year cooperative agreement from the FDA. The website has a wealth of information about all of our activities.

Thank you very much. It's probably worthwhile for me to take any -- if there are any questions about ACTTION and to address that.

Page 11

(No response.)

DR. DWORKIN: Well, okay. Without further ado, I'd like to turn this back over to Roy. Thank you.

DR. FREEMAN: Next set of slides.

This meeting is in large part a consequence of success. Few would argue about the major success of the treatment of cancer over the past few decades. The number of cancer survivors are in the tens of millions, and this has necessitated a change in focus, that one now needs to focus not only on the treatment of cancer but on the quality of life of those surviving cancer.

Chemotherapy-induced peripheral neuropathy is one of the issues that is directly related to quality of life. There is, unnecessary to say to this audience, a substantial prevalence, disability, reduced quality of life of patients who have received chemotherapy, had a peripheral neuropathy, even years after treatment. The numbers are not well worked out. The predictors are not well worked out, but there is a substantial

Page 12

prevalence.

Chemotherapy-induced peripheral neuropathy also results in reduction or even discontinuation of chemotherapy with possible long-term consequences, and it is these two aspects that we will deal with during the meeting.

Now, it seems ostensibly simple. We have a group of patients who will receive a neurotoxin. We do not precisely know the number or exactly who, but a number of them will develop a chemotherapy-induced peripheral neuropathy.

What could be simpler than to design a trial to prevent that happening? But as you will hear when my co-chair, Jennifer Gewandter, gives her talk later today, there are a number of challenges. And she will dissect with the precision of a surgeon those challenges. You will leave that talk thinking that this is perhaps too challenging to accomplish.

I want to disabuse all of us of that notion immediately because we, as Bob said, want to finish this meeting with a product, with a potential

Page 13

publication, and again, as you heard all earlier, every one of you, if you wish, will be involved in the development of that publication.

The goal, and this is the ball upon which I want you to keep your eyes throughout the meeting despite the challenges, is to come up with something, which is I think in the long run going to be a lot more simple than the challenges you will hear will suggest.

We want to establish what would be a clinical trial or what would be clinical trials to evaluate disease modification of chemotherapy-induced peripheral neuropathy, that is, to prevent or delay the appearance or attenuate the features of chemotherapy peripheral neuropathy.

We want to evaluate symptomatic treatment of chemotherapy peripheral neuropathy and design a clinical trial to do that. We want to attempt to design a clinical trial to evaluate chemotherapy disruption during the receipt of chemotherapy. And there will, of course, many unknowns, and we want to define a research agenda to deal with those

Page 14

unknowns.

This is the ball that I want you to keep your eye on throughout the proceedings because what we want to do at the end of this is come up with a product that will address these issues and allow us to go forward in this area.

As I mentioned earlier, this is a meeting in which everybody is a participant. We purposefully have a relatively small number of invitees so that people, whether they are delivering a talk, on a panel, or sitting in the audience, are contributing.

I want just to set the tone for this -- and the meeting is sort of in between, just a little bit too big for a roundtable and perhaps a little too small for an auditorium -- but to set the tone of participation. I'd like to begin by having everybody, starting on the right in the front row, introduce themselves so that we know who each other are.

DR. DWORKIN: Bob Dworkin.

DR. GEWANDTER: Jennifer Gewandter.

Page 15

DR. FREEMAN: Maybe one line, two lines if you can.

(Laughter.)

DR. DWORKIN: I just want to reiterate, in Washington, D.C. that I am not president of ACTTION. I'm on the faculty at the University of Rochester School of Medicine.

DR. GEWANDTER: I am an assistant professor at University of Rochester and an assistant director of ACTTION, and CIPN is my main area of clinical research interest.

DR. FREEMAN: Simon?

DR. HAROUTOUNIAN: Simon Haroutounian. I'm from Washington University in St. Louis, Department of Anesthesiology in Washington University Pain Center. CIPN is one of the areas of my clinical research.

DR. KATZ: Nathaniel Katz. I'm a neurologist from Boston, and I actually am president of a small company called Analgesic Solutions. It's not in Washington, so I guess we're all okay.

Page 16

DR. BRELL: I'm Joanna Brell. I'm a medical oncologist formerly with the Division of Cancer Prevention at NCI, National Cancer Institute. And now I'm a medical oncologist at a safety net hospital in Cleveland associated with Case Western Reserve University.

DR. CAVALETTI: I'm Guido Cavaletti from University of Milan, Italy. I'm the coordinator of the CI PeriNorms Study Group that is international network of neurologists and oncologists from Europe, U.S., and Australia, and I'm the head of the experimental neurology unit in my university.

DR. FREEMAN: Daniela?

DR. DASTROS-PITEI: I am Daniela Dastros-Pitei. I'm the head of medical science, pain, and new products at Mundipharma in Europe. We have a product, which we are very interested in developing in CIPN. So thank you for allowing me to participate.

DR. ZHOU: I am Yan Zhou. I am a statistical reviewer at DAAAP.

DR. DOUGHTERTY: Hi. I'm Pat Dougherty from

Page 17

the MD Anderson Cancer Institute, and I do both patient-based and animal-based CIPN research.

DR. GAUTHIER: I'm Lynn Gauthier, an assistant professor from Laval University in Quebec, Canada; professor and scientist in palliative care, and CIPN is one of my areas of interest.

DR. WILTROUT: Hi. I'm Lisa Wiltrout. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products at the FDA.

DR. FIELDS: Good morning. I'm Ellen Fields, deputy director in the same division.

DR. McDERMOTT: I'm Mike McDermott, a professor of biostatistics at the University of Rochester.

DR. EVANS: Good morning. Scott Evans, biostatistics at Harvard.

DR. JARPE: I'm Matt Jarpe from Regenacy Pharmaceuticals, a company primarily focused on treatments for peripheral neuropathy.

DR. G. SMITH: I'm Gordon Smith. I'm a neurologist at the University of Utah interested in

Page 18

peripheral neuropathy.

DR. HOWIE: I'm Lynn Howie. I'm a medical oncologist and a medical officer at the Food and Drug Administration in the Division of Oncology Products.

DR. O'MARA: I'm Ann O'Mara. I'm a program director at the National Cancer Institute and manage a portfolio of symptom management of which CIPN is one of them.

DR. LAVOIE SMITH: I'm Ellen Smith. I'm an associate professor at the University of Michigan, and I study CIPN treatment and measurement.

DR. LOPRINZI: Charles Loprinzi, medical oncologist, Mayo Clinic, been involved with the cooperative groups, been involved with a number of treatment and/or prevention clinical trials with chemotherapy-induced peripheral neuropathy.

DR. CLEARY: I'm James Cleary. I'm a medical oncologist at Dana Farber. I specialize in gastrointestinal malignancies and give a lot of oxaliplatin, which causes neuropathy.

DR. WEN: I'm Patrick Wen. I'm a

Page 19

neurologist. I direct the neuro-oncology program at Dana Farber.

DR. FREEMAN: Thank you for that.

I'd like to now hand back to Bob, who will begin the first session.

DR. DWORKIN: The format of the se meetings, as you can see from the agenda, is we have presentations. But the most important part of the meeting is the discussion periods that follow the presentations, so we try to have as much time for discussion as possible at these meetings.

As a consequence, I think the best format, at least for this morning's session that I'll be chairing, is we'll have a series of four presentations. And after each one, maybe we should take just a couple of questions before the next presentation. So if you don't get to ask your question after the presentation, don't worry about it because we'll have lots of time during the Q&A period before lunch.

It's a great pleasure to introduce Dr. Joanna Brell, our first speaker, who is going

Page 20

to be presenting an overview of chemotherapy-induced peripheral neuropathy. As you just heard, Joanna spent some time at the National Cancer Institute and is now on the faculty at Case Western Reserve University School of Medicine in Cleveland.

Presentation – Joanna Brell

DR. BRELL: Good morning. Thank you, Dr. Dworkin, Dr. Freeman, for the invitation to speak.

The title of my talk is An Overview, and then we've had over 55 years of neuropathic toxicity with the agents we use to treat patients with, so if not now, when are we going to take action? And I think it was outlined very clearly this morning that we are taking action.

What I am going to do is a 30,000-foot view. There are a few people in here that may not be as familiar with CIPN. I'm going to give a case report, which will really help us understand the impact and the significance of this and then talk about the American Society of Clinical Oncology approach to CIPN.

Page 21

It's hard to define. You know it when you see it. To describe CIPN, it's the most common dose-limiting toxicity for chemotherapeutic agents. When I say chemotherapy, I mean any of the drug agents, any of the anti-cancer agents.

No FDA treatments or prevention and further preclinical data is needed to help inform development of treatments. As stated earlier, it's a very serious unmet clinical need, and I think we really need to work at some point getting a definition of this condition, though you can take any definition of sensory neuropathy right now.

What is also needed is being on a typical chemotherapeutic agent that could cause neuropathy, and the onset of the disease and the symptoms are based on which type of chemotherapy one is receiving. And of course, the symptoms simply range from having sensory problems to having pain to having both.

Of course, those symptoms really depend on which peripheral nerves are involved. You can see that sensory nerves are the A alpha, beta, larger

Page 22

fibers, and the A delta and C fibers are smaller. They're most involved with pain, which we don't see with some cases, and thermal sensations.

This is just a schematic to remind us of some of the mechanisms of peripheral neuropathy. There's multiple points along the axon and DRG where these agents can work. There's still much research going on in this area as needed.

As far as what was said this morning, this is really a serious condition. It's a large condition, but it's really difficult to enumerate it. It's difficult because it really depends on the symptom types. We have a whole range of symptoms and a whole range of agents that could cause this.

The percentage looking at each different chemotherapeutic agent ranges from 25 percent to 90 percent. There's a few clinical trials with cisplatin that 100 percent of the patients developed peripheral neuropathy.

There are factors that can play into this as well. It depends on what stage of cancer, meaning

Page 23

that then depends on what treatment you're on. Some people may be on a clinical trial that's not known to cause peripheral neuropathy, but they develop it, so there's a cohort of patients with the neuropathy that we don't really know about and don't really count.

If you had several lines of therapy already with CIPN-inducing treatments, it's possible if you get another one that you may be a little more predisposed to having neuropathy. And it's been shown that the dose, the route of administration, and the infusion rate of some of these agents can really make a difference on the development, and there are host risk factors.

We think it's under-reported just because we don't always have the best tools to diagnose it. What we can do to estimate the incidence is look at the 2017 new cases of cancer, and you can see these are the top 10 malignancies for men and women. Within the purple circles, you can see agents that are treated with CIPN-inducing drugs. That's really 57 percent of the top 10 cancers in 2017

Page 24

that could potentially be exposed to these agents. That's almost 1 million patients.

Of course, there's other malignancies. Many of the GI malignancies are treated with CIPN agents, gastric, esophagus, and those didn't make the top 10.

There are estimates floating around of 30 to 40 percent, so that's about 300,000, 400,000 patients annually. With some of the agents such as oxaliplatin, you know the percentage of patients that would be able to receive chemotherapy, you know the incidence of oxaliplatin-induced neuropathy, so you can get some estimates. Maybe 50,000 patients with colorectal cancer will develop CIPN.

As you know, there are several different ways we diagnose CIPN right now. That depends on the type of anti-cancer therapy. It depends on patient report, clinical examination, neurologic testing. At this point, I'm not aware that we have any serum biomarkers, any imaging studies that can help us. Some studies are using intraepidermal

Page 25

nerve fiber density studies, and germline mutations are being assessed.

This is a short list of the anti-cancer therapies that are associated with CIPN. On the left are the mechanisms or class, and the drugs themselves are on the right. The drugs themselves are just examples because there are many others that cause the disease but I don't have listed here.

If you go towards the bottom, some of these newer therapies, some of them are approved, some of them are still in testing. Targeted therapies, crizotinib is a new targeted therapy for lung cancer. It's also being tested in other cancers, and we're seeing peripheral neuropathy with that.

Then you need the patient report so the patient can tell you what the symptoms are and what the issues are. You can grade in the office on a numeric rating scale.

Here's five other scales or instruments, tools that we use to assess CIPN. The most common is the EORTC quality of life survey that has 20

Page 26

questions on CIPN. As you can see, I didn't get my circles right there, but sensory, motor, and autonomic questions are assessed.

This may not always be appropriate for all chemotherapeutic agents. There are some that don't cause any autonomic problems, for example. But some of these PROs, patient-reported outcomes, suffer for lack of validation.

Though there are weaknesses and strengths in using patient-reported outcomes as the main diagnosis for chemotherapy-induced peripheral neuropathy, obviously, it's an individually experienced condition, so it's the patient that's the only person that's really going to be able to tell you what's going on.

Some of the clinical assessments that we use aren't always specific enough or sensitive enough to help identify peripheral neuropathy in general, and obviously getting a patient-reported outcome is very easy to do in the clinic.

Some of the weaknesses is that the patient, of course with anything, can have some confusion

Page 27

about the questions or the scales, have some confusion about how to respond. Sometimes it's difficult to discern on that spectrum between sensory symptoms both in pain where their symptoms actually are.

Expectations of the patient can sometimes influence what they say. My best example is a patient of mine telling me he had severe, very painful -- well, numb, severe numbness peripheral neuropathy. And he said he couldn't even button his own clothes, yet he was putting his shirt back on and expertly buttoning his shirt without any difficulty, correctly, easily.

So without talking to him, I would have said this is terrible. He's at 3. We have to dose reduce. But by observing him, I was able to see that he was probably a grade 1. He was able to do the thing he said he couldn't do.

Then of course, we talked about validation of instruments.

As far as clinician's assessment, what's been used in the past is the NCI common terminology

Page 28

criteria for adverse events. There's multiple versions. The name has changed from terminology to toxicity and back and forth.

This was created just to assess toxicities due to drug therapy, so it was used a lot in clinical trials to assess new agents. But unfortunately, it's being used as a diagnostic tool, and sometimes it's being used as outcome. And there's a whole literature where the CTCAE was unfortunately used for outcomes for neuropathy trials. And this is just one reference at the bottom of the slide about discordance between patient report and this particular scale.

What is going to, I think, be the best way to capture CIPN is composite scales like this. Dr. Cavaletti will talk about this some more tomorrow, but you can see on the left-hand side that there are symptoms from the patient. There's physical examination with deep tendon reflexes, vibration sense, and then there's also some particular testing such as quantitative sensory testing focusing on vibration and sural nerve

Page 29

amplitudes.

What will eventually need to happen is the total neuropathy score can be used in research, and then eventually as time goes on, hopefully, we'll be able to find the couple points of this that will help us diagnose CIPN easily in the clinic.

I'm going to talk about a case study just to illustrate what happens in the clinic. This is a typical case, but it will bring up a couple of points about oxaliplatin-induced peripheral neuropathy.

This is a 69-year-old African American woman who works part-time as a seamstress. She's sedentary, lives alone. She has type 2 diabetes for 5 years, has never been on insulin, and does not have any neuropathy.

She was diagnosed with adenocarcinoma of the colon, and she underwent a complete resection hemicolectomy. She was found to have stage IIIB disease. She's at high risk for recurrence of this cancer, approximately 50 percent, and there are even other factors in the tumor that make her even

Page 30

a higher risk.

Her priority is to extend her life, so she's interested in adjuvant therapy. The standard off-study adjuvant chemotherapy for colorectal cancer in the United States is FOLFOX. This includes oxaliplatin at 85 milligrams meters squared. It's given every 2 weeks as a cycle, and it takes about 6 months to get through the total 12 cycles.

These are some of her symptoms. Cycle 1 before she even leaves the cancer center, she's complaining of shortness of breath, laryngospasm. She has some perioral sensations. She's distressed. Even though she's short of breath, she's not hypoxic, and we give her IV steroids. Whether the natural history of this was that she was going to get better or whether she responded to the steroids is unclear.

Then also after cycle 1, a couple hours later, she has cold-induced sensations. If she touches anything cold with her hands, she gets parathesias. If she swallows anything that's cold,

Page 31

she gets parathesias. Patients have described this as feeling like there's glass, breaking glass in their mouths and throat, so obviously not a good sensation, obviously distressing again to the patient.

She comes back for her cycles. These cold-induced symptoms that I just described, they're now lasting instead of a couple days, over a week, and she's beginning to feel some mild parathesias in her toes.

She comes back a couple cycles later, and she's now having parathesias with a little bit of numbness in her fingers and toes, but it's still mild, according to her, and she's still functioning well. But by the time she comes for cycle 7, she's dropping things. She cannot button her clothes very well. She can't pick up the needles to sew as a seamstress.

This is more of a grade 2 because she can do all of her other activities of daily living but she's not able to perform other things. This is a distress to her. It's hard to know. Some grade 2s

Page 32

have to be dose reduced, and so we decided to dose reduce her oxaliplatin. We don't have any disease-modifying agents, so there was nothing we can do at that time. She had no pain, so we did not start any analgesics for her.

When she comes back for subsequent cycles, she says she's stable or improved with the dose reduction, and that's a red flag that she's not reporting her symptoms because there's no expectation that you would improve with a dose reduction in chemotherapy. So you have to question her more. You have to try to find out what's going on.

She came back for her last cycles and says she's stable. Later on, she admits that her symptoms had been worsening the whole time, but she feared dose reduction. So 6, 8 weeks later, she comes back with an abrupt worsening of her symptoms.

Now, several months later, she has numbness in her fingers and toes. She's not able to return to work, and six months later, she comes back with

Page 33

a diabetic foot ulcer on the first digit. She's not able to feel her feet.

This illustrates some of the risk factors that we think we know for CIPN: older age, history of diabetes. Her diabetes probably wasn't in as good of control as she thought; obesity and being female.

She also had symptoms of acute oxaliplatin neurotoxicity, and these are experienced by almost every patient that has oxaliplatin. It can happen right after the infusion. It can happen hours later, but it's particularly involving the head and neck. Not sure exactly what causes it, whether it's a hypersensitive reaction where it's ion channel dysfunction, but these patients will experience this right away, again, very distressing.

They feel short of breath, but we know they're not hypoxic, but the sensation is poor. And that's most likely related to the other symptoms that they're having such as laryngospasm.

She has then developed the chronic sensory

Page 34

peripheral neuropathy, and that's what we focus on. There are some reports in the literature saying it can be predicted by at least acute symptoms or early onset of parathesias. She did not have any burning pain. Sometimes patients don't report accurately. They fear the dose reduction, and you really have to spend time and talk to them about getting their symptoms.

Then it looks like she had some experience with coasting where the neuropathy gets worse even though the agent has been stopped, and that most likely was the cause of her abrupt symptoms.

That was during treatment. So now she's a cancer survivor. If you look, we think in 2016, there are about 15.5 million cancer survivors in the United States. The overall survival rate for all cancers is 67 percent, so we're just accumulating more and more survivors, which is positive.

Two-thirds of the survivors are 5 years out from their disease, so they're getting away from the period where they're going to relapse, so that

Page 35

group of survivors is going to accumulate as well. But look at the types of survivors, and she is this type. After treatment for many years, she has chronic late conditions.

Some of the consequences of having peripheral neuropathy to simply state, we talked about dose reduction or dose continuation. And as stated earlier, we don't really know the clinical manifestation of what that really means. With some drugs, that may not be as problematic. With other agents, it really could be a serious problem. We just don't know.

We mentioned that it takes a couple years to recover. Some patients do not resolve at all. There's certainly increased healthcare utilization, and functional rate is diminished completely. So they need more support from family and friends if they still have severe neuropathic pains.

These are just a few references on multiple studies showing that chemotherapy-induced peripheral neuropathy interferes with quality of life. If you look at the bottom one, this is very

Page 36

interesting, one we don't think of. This was spiritual pain from patients in Japan, and a lot of this came from not being able to return to the workforce, not being able to continue their usual roles and function. And that was really difficult, and I don't think we think about that ramification very often.

There's certainly financial toxicity, and if you're unable to return to the workforce or unable to perform your societal roles as caregivers, as students. So the caregivers to these patients have been shown to have lost productivity. But if I'm a caregiver and I have CIPN, I can't take of myself; as well I can't take care of children very well, then someone has to step in for me. So that's involving even more family and friends down the line.

These are older studies, but in 2010, there was an estimated $2 billion spent on peripheral neuropathy, CIPN. These were outpatients but also took into account lost wages and lost time from the family members, friends and family that had to be

Page 37

caregivers. That was the biggest division of the money. There was hardly any of this money that was spent on treatments, symptomatic treatments, or the multiple clinic visits. That was about $5,000 per patient.

In 2012, this study looked at not only outpatient visits and caregiver lost wages and time utilization, but it looked at inpatient and all total healthcare utilization for these patients. They looked at just some of the most common cancers, and they found about $17,000 per patient per year. About 8,000 of this was in outpatient, and this was a rough estimate of the total cost. So we're talking about billions of dollars.

I'd like to switch gears a little bit and talk now about the American Society for Clinical Oncology approach to CIPN, ASCO. That's our lead organization for medical oncologists. There was in 2014 a publication. A group of experts met to ascertain best practices for CIPN and then provide some research guidance.

They did look at 48 eligible randomized

Page 38

trials from the time period of 1990 to 2013 and found what we know, that a lot of these clinical trials with CIPN are small sample size. There's different eligibility criteria, different populations are used, multiple different outcomes and instruments, different time points for when the objectives are assessed. So it's hard to really compare any of these trials, unfortunately.

They made some recommendations based on the quality and quantity of evidence, and I don't want to go through that slide. But there was no recommendation for any agent that would be able to prevent peripheral neuropathy. This is concordance with another review that was published the same year that also showed that there were no agents that could prevent neuropathy.

These were the six trials that they assessed that were treatment trials, and only the top one on duloxetine had statistical significance. But you can see on the right all these various scales that were used. Unfortunately, some of these were smaller trials, but this is the only agent that,

Page 39

not surprisingly, has shown some benefit in neuropathic pain.

This ASCO group also put forward some recommendations and a research agenda, and of course, the goal was to develop a comprehensive and standardized approach to assessment of CIPN, for obvious reasons, to help with data acquisition and to also help the clinician in the clinic.

The research agenda is listed below. They believe that we can get more benefit from some topical treatments for peripheral neuropathy. They thought that another phase 3 trial of gabapentin or pregabalin was warranted. I'm not sure if this is the right way to go or not, and I'm afraid that we won't get the FDA indication for peripheral neuropathy just like we didn't get it for the duloxetine.

There's work on electrocutaneous nerve stimulation that's going on, and there's a lot of clinical trials going on that are looking at complementary and alternative therapies.

A lot of this information on CIPN and a lot

Page 40

of studies come from the NCI-sponsored Community Oncology Research Program called the NCORP. These are peer-reviewed grants that go either to cancer centers or academic centers, and they are the point for developing clinical trials. And these trials are performed out in the community with a very large network of support of physicians that are able to perform the clinical trials.

Of course, these medical oncologists are in the community, and they have the time restrictions that all of us have. There's competing interest when a medical oncologist sees a patient. The patient has other toxicity. You really tend to focus on the treatable toxicity. We can fix nausea and vomiting. We can hydrate for renal insufficiency. There's not too much to do for the peripheral neuropathy, so there's less time to focus on that.

This may not be the best environment for complex clinical studies. I think when we get closer to having better treatments, this is the perfect network in which to study that.

Page 41

NCI has a major investment, of course, in NCORP, and that's where their CIPN investment is for the most part. Over the years, there's been clinical trial planning meetings sponsored by NCI. The first one looked at clinical trial research and knowledge gaps, and there was a CIPN workshop in 2011. That was focused on mechanistic research recommendations, and that led to some translational and basic science funding announcements to further the science.

Then just a few weeks ago, some of us in the room were at another clinical trials planning meeting, and this was focusing on developing novel trials incorporating translational research. We had some excellent translational research talks with this. We had a diverse group as we have here, neurologists, PhD researchers, advocates, community members, community oncologists.

Then we broke into two groups, and one was looking at longitudinal study recommendations. There's a hope for a database with lots of information, mainly phenotype, any other

Page 42

assessments, a real focus on drug levels and dosing of drugs, and to really look at exactly what amount of drug the patient receives and how that relates to the development of their neuropathy.

SWOG, under the leadership of Dawn Hershman from Columbia, is already thinking about this, and so they're going to be the lead for developing this type of database.

Then we had an interventional study group, which recommended looking at phase 2 studies and smaller studies. Hopefully, some of these new drugs will become available to us, and so far, that's not yet the case. But there's a focus on exercise studies which really shows some promise, and then perhaps looking at duloxetine prevention, although that may not be the best trial to perform right now due to lack of mechanistic evidence.

In summary, this is a chronic debilitating condition. It's a huge problem, millions of patients, millions of dollars in the long run. There's absolutely no expectation that CIPN will decrease.

Page 43

There's a study that's being assessed right now looking at oxaliplatin, the 12 cycles versus the 6 cycles, and we don't have the data back on that. But even with 6 cycles using FOLFOX, oxaliplatin, that's still within the timeframe that people develop peripheral neuropathy.

Of course, there's increasing interest. We're here. The NCI is gathering groups, multidisciplinary, but we need to keep in mind that vincristine was FDA approved about 55 years ago, so patients have been suffering at least 55 years with peripheral neuropathy.

I think, as beautifully said by Dr. Freeman and Dr. Dworkin, that now is the time, and we're going to make some headway in this meeting and move forward. Thank you.

(Applause.)

DR. DWORKIN: Just a few questions.

DR. FREEMAN: Maybe let me start with a question. I'm going to frame the question within the context of the meeting and then ask the question.

Page 44

The way I'm thinking about this meeting is in a number of very specific boxes. The one is prevention, disease modification. And with respect to disease modification, the way I think of disease modification is either prevent the appearance, delay the appearance, or slow the progression of chemotherapy-induced peripheral neuropathy. And that's going to be one issue, probably the most important and biggest challenge for the meeting.

The other is the acute symptom treatment, and I think the patient you presented embodied the typical presentation so very clearly. Then there's the chronic symptom treatment, which is not going to be a focus of this meeting. And then finally, the third box is chemotherapy disruption and how to assess that, how to measure that.

Here's the question. With regard to that third one, you made a statement that dose reduction or discontinuation of chemotherapy may be more important with some chemotherapeutic agents than with others.

Can you elaborate on that? If we want to

Page 45

address that, somehow measure that, value that in terms of its long-term consequences, where should we focus? Where is the area of --

DR. BRELL: I think certainly not on oxaliplatin because there was some data from Europe showing that maybe we may get by with 6 cycles instead of 12 cycles. So the only way that's going to be used clinically is to make sure there's no difference in survival.

So oxaliplatin may not be the best drug for that, but certainly there's many people on paclitaxel for a lot of different reasons for breast cancer. And I think that drug or that family of drugs would be the drugs we would want to look at.

Of course, it's going to be a long-term proposition. If you look at adjuvant therapy patients, you're going to have to wait a long time to look at overall survival, and even disease recurrence unless you look at those that are at very high risk for disease recurrence. You could look at a metastatic group of patients and look at

Page 46

issues like disease progression, but we're going to have to really figure out which drug to use and the timing of the outcomes.

DR. RICHARDSON: If I could add to that, in the myeloma space, we have established clearly now that continuous therapy results in survival benefit. So for us, it's a different paradigm altogether because we continue therapy. We have an incurable malignancy, and adjuvant therapy has no role. It's essentially induction, remission therapy, and then maintenance.

So to your point, that's a specific area where neurotoxicity of continuous therapy, and how you abrogate dose and schedule to minimize neurotoxicity is a paradigm of how we treat the disease, recognizing that some of our newer drugs that we've developed to target similar -- targets like the proteasome, for example, where we see less neurotoxicity with carfilzomib.

We're struck, however, that we steal from Peter to pay Paul because with carfilzomib, for example, we see really unacceptable cardiovascular

Page 47

toxicity even though we have much less neurotoxicity. So we're revisiting how can we optimize dose and schedule around first in class like bortezomib and second generation boronate peptides like ixazomib. So it's a very interesting area in our space, what you just asked.

DR. BRELL: Dr. Richardson, could you comment a little bit on the peripheral neuropathy that's disease induced in myeloma?

DR. RICHARDSON: Yes, it's a great question. Thank you for asking that.

The incidence -- and it's great to be with Patrick right here because we did some of the original work showing this -- clinically, it's around 20, 25 percent clinical manifestation of peripheral neuropathy that's typically small fiber from myeloma itself.

When we do nerve conduction studies, we realized that the actual incidence is probably much higher, and certainly in some preliminary work we did and published some years ago, if you looked at newly diagnosed patients and studied them

Page 48

carefully, the incidence of documentable neurotoxicity from the disease was probably approaching 50 percent.

DR. BRELL: Thank you.

DR. LOPRINZI: From our standpoint, clinically I think that 80 percent of neuropathy we see is from paclitaxel and oxaliplatin both because they cause a lot of neuropathy and they're used very, very commonly.

We have to make decisions about dose modifying, I think, in our patients. There are some patients who get neuropathy, and particularly with oxaliplatin, there's a coasting phenomenon. When you stop the oxaliplatin, it gets worse for three months. It's actually the same slope as it was in the three months before they ended. So in my mind, it's not because of stopping that makes it get worse, although people have fought that process, but rather it just takes three months for the last dose to actually get the maximal effect from it is the way I see it.

I virtually never dose reduce. I virtually

Page 49

never dose reduce. I don't have many patients with very much neuropathy. I see breast cancer, and taxane is what we use, paclitaxel. And the reason why I say I never dose reduce is I either stop or continue. This 20 percent dose reduce, you're still getting more of this neurotoxic agent process in there.

I think we'll get data from the IDEA trial. All rumors are that it will come out at this year's ASCO. It will be very interesting from there.

In practice, to help figure out, what I do with my patients at the end of therapy, if they've had 8 doses of paclitaxel, I have to estimate how much more benefit would be 12, which is our standard versus the 8. And maybe it's a percentage point or so in terms of 10-year survival and that sort of stuff. Then you put that up against the bout of neuropathy they have, which can be long-term neuropathy for things, so you make choices along those sorts of ways.

DR. DWORKIN: Seems like we'll have no trouble with that material for discussion. Thanks

Page 50

very much.

DR. BRELL: Thank you.

DR. DWORKIN: It's a pleasure to introduce our next speaker, Dr. Pat Dougherty from MD Anderson Cancer Center in Houston. Pat's done really landmark studies, both preclinical and clinical, of chemotherapy-induced peripheral neuropathy. So it's a great pleasure to have him here, and he'll be speaking for the next half hour on predictors of CIPN.

Presentation – Patrick Dougherty

DR. DOUGHERTY: Thank you for that introduction, and thank you very much for the invitation just to participate. As I commented to a few folks, when I saw the list of participants, I was kind of surprised actually that I was included, so I'm very appreciative.

I knew I was coming after Joanna, and Bob already told you that I do both clinical and preclinical studies. So please don't be shocked when I don't spend an entire half hour on the predictors because again, Joanna has just hit some

Page 51

of them.

I will bring up a few, and one that I think is very surprising, it came from our own data, and I had never really paid much attention to this in the past. But it opens up a whole new kettle of fish, I think, when we get into the predictors.

We're all aware and familiar with this picture. And again, some of you may not have heard me talk in the past, so for those that are familiar with my work, I apologize for doing a little bit of review, but I wanted to get everyone up to the rationale of what we're doing.

I began a number of years ago looking at CIPN patients, and we began with the chronic patients. One of the things I had them do, of course, was give me a drawing to show where their symptoms were located.

Here's the typical presentation. This is not surprising to anybody, but what we did is we laid out then, as we did our psychophysical test, trying to target in this particular patient where they've colored solid is where they actually had

Page 52

ongoing pain. Then you notice there's a stripe in their palm, and that's where they said they went from overt pain to numbness and tingling. It was bothersome but not necessarily painful.

You notice how this patient in particular was very interesting because they drew a line right at their ankles and their wrists saying that above that point, they're symptom free. The fact is, as you further talk to folks, they really complain about the glabrous surface of their hands being affected, not as much the hairy backside of the hands.

So we set up then to do some psychophysical studies directed at both the fingertip -- so that will be labeled the painful area -- this numbness, tingling area that's not necessarily painful but symptomatic, we call that the border area, and then we picked an area outside the area of pain, up in the volar forearm.

We did primarily hands just because it's easier for the patients, but we get very much the same data if we target the feet. What we found,

Page 53

using again these sorts of tests -- and I'll get into that one with the little colored dots in a second because I think that's a really intriguing test. But each of these different tests are designed to get at the different subtypes of fibers.

So touch is mediated by A beta fibers. Pinprick is mediated by A delta fibers, and then overt pain is mediated by C fibers. And the different tools that we use are directed at those.

I've also put this in just to remind you that the dorsal root ganglion is where all those cell bodies live, and I'm going to come back at the end with some new findings as to what we think is going on in the ganglia, or what we've observed going on in the ganglia, that I think may point future directions to potential therapies.

The initial psychophysical test we did, and the white bars, the open bars, that's data from you or I, and then the colored bars, the black being our initial test, then the gray being a test that we did a year after the first. It shows, number

Page 54

one, there's compromise of touch fiber, so A beta fibers seem to get sick. There's some compromise of A delta fibers. The sharpness detection is increased in that pain area, marginally in some of the other areas. Then there's variable changes in the percept for hot and cold.

The gray tells you that once these folks get to a chronic condition, we don't see them getting better. The idea that we're going to somehow put folks back together and cure them of CIPN is going to be quite the challenge, which again then I think pushes the emphasis to perhaps prevention as being the key here ultimately.

The other take-home message is that there is a sparing of sensibility. Folks don't go completely numb. So what that tells you is that the treatments are not just uniformly neurotoxic. There's some element of selectivity in the types of nerves that are affected. That then gets to important issues related to underlying mechanisms, which I won't get too much into that.

That level of impairment that we saw in the

Page 55

chronicity is what led us initially to do skin biopsies. This picture here is a very nice pretty picture, and this was in collaboration with a guy named Bill Kennedy, who taught us how to do this sort of work on our own.

The blue stain that you see there, that's for the stratum basale keratinocytes. Then down below, you can see the red. Those are the blood vessels down in the dermis, and then the green is a stain for what's called PGP 9.5. It's just a pan neuronal marker.

The little squiggly lines that are going from the dermis up into the blue is the free nerve endings, so those would either be C fibers or A delta fibers. And then the big swirly things that you see, those are Meissner's corpuscles, so those are A-beta-type fibers.

There's your nice normal skin, and there's your skin on chemotherapy. So the reason folks are getting numb is because those fibers are becoming largely obliterated. Not all the fibers, you can still see there's some down there around the blood

Page 56

vessels. But right in the center, just next to that blood vessel right in the center, you can see there's a sick Meissner's corpuscle, and then there's very few fibers going up past the blue line, showing that the A deltas and C in this little section at least are remarkably knocked out.

I just thought the picture shows us a couple of things. Number one, the fibers are gone, but number two, as I was looking at this, this picture here, I was looking at this because we were counting these fibers. And it suddenly occurs to me that we've talked about die-back neuropathy. I thought, you know what, those free nerve endings are getting up into the stratum spinosum. That's where tight junctions form.

Does that mean then that that axon is trapped into the skin? Meaning that to keep this innervation intact, the nervous system needs to be constantly extending into that tissue. So these neurons are being renewed all the time.

So it's not that the axons so much retract as what potentially is going on is that the axons

Page 57

are failing to reextend for some period of time. And if the tissue is sloughing, well, then that means that eventually those axons are going to get cut off.

In this particular slide here, there's just a little bit of a picture all the way down at the bottom -- and I guess it's on your right -- where you can see the dermal plexuses down there. And if you count those -- Gary Bennett actually went in and did some counting of the dermal plexus down in there, and he could not find any change in axon content. We found the same thing.

But the interesting thing about that then is that if the C fibers are broken off, then somewhere down in that dermal plexus is the original axon. Everyone remembers from their neuroembryology -- of course it's vivid in all of our imaginations still -- a growing axon, if those axons eventually try to regrow, they form growth cones on them.

Growth cones cause spontaneous discharges. So there's one substrate, then down potentially in that dermal plexus of axons that are somehow trying

Page 58

to find their way back to mama, the growth factor is being released by the keratinocytes. They're not finding it, so they're continuing to grow around down that dermal plexus, potentially discharging all the time. Indeed, there have been studies showing that there are peripheral generators, discharge generators, that are down in there.

So of course, we did the counts. And the striking thing that came out of the counts in these five here -- with this actually we're ramping up the study now again to get this pushed out the door so everyone can actually get these.

This table here is showing the three areas that we took biopsies from, the fingertip, the thenar eminence, and then the volar forearm. So that's sample A, B, and C, as you can see there.

The 1 and 2 patient, they're starred, those patients actually had chronic pain in their feet, not in their hands, so they were biopsied off target. The four at the bottom are all biopsied on target, and what that's telling us is

Page 59

quantitatively what you just saw in the picture. In the areas of pain, those fibers dramatically depleted. As you move proximal, then the fiber numbers start to recover.

When we looked at normal people -- and by the way, I'll tell you, if you want to do biopsies in patients, you're going to get one try, one chance at doing that. Here, we had our normal volunteers, and I asked a couple folks if they would do it again. Under no circumstances will they do that again.

The volar forearm is not a big deal. The fingertips, particularly if they're still healthy, hurts like hell the next day. Don't tell anybody that as they're signing the form.

(Laughter.)

DR. DOUGHERTY: But they'll all remember you the next time they're sitting in clinic and that guy comes in. Don't go with him. He's going to hurt you.

The interesting thing that came out of our volunteer counts is you look through there, and the

Page 60

number one thing that jumps out, ENF density, free nerve endings are lowest in your fingertips and then recover as you come proximal. If you're doing something that's depleting ENFs, essentially what you're doing is we're built in, we're hard wired, for the clinical phenotype of CIPN. If you knock out those ENFs, you're going to knock them out down to zero in your fingertips first, and then you're going to have reserve as you move proximal.

Now, as I presented that data in the past, people have said hold on, that's completely counterintuitive. My fingertips are most sensitive, and then I'm less sensitive. But that's for light touch.

We all presumably took showers today. If you stick your hand in the hot water, it doesn't feel nearly as hot as when it hits your back, right? So you already know that this is actually true.

Number one, we're put together sort of hard wired for the development of CIPN. Number two, look through that column A from the volunteers.

Page 61

Some of those folks are walking in with very low ENF at baseline, which made me think immediately, wow, this is cool. What we've got here is this is a clear risk factor, is that if folks are latently put together with a low functional reserve, then they're likely to be the ones that are going to show symptoms when they go to therapy.

That's what we focused on. And that picture there, I'll get to it in a second why that picture is there. So that's what we decided to do, is initially we were just biopsy a whole bunch of folks, send them off to therapy, and then we'll sort them out later.

The table shows -- because again, I said how this hurts, so I knew we would have a heck of a time trying to recruit people if the entry criteria was you got to give me a chunk of skin. But the table showed that, in fact, the Meissner corpuscle density more or less parallels your ENF density. What saved us is this because we could find a noninvasive way of counting Meissner corpuscles using a confocal laser reflectance microscopy.

Page 62

That's, in fact, my fingerprint there. You can see the bumps coming up at you, and then the dark spots is the valleys going down. The little arrows are all pointing at little Meissner corpuscles, so you can count those noninvasively.

That's what we did. We began in our psychophysical study. And as Paul was just mentioning, one of the things that came out when we started doing these baseline studies is that lo and behold, when we look at patients and we look at healthy volunteers, in fact, patients have subclinical neuropathies.

Initially, I saw this in non-small cell lung cancer patients, then we saw it in myeloma patients, and I wasn't particularly surprised because of the idea that there may be subclinical paraneoplastic syndrome running around out there. So that wasn't really surprising.

This slide, though, was surprising to me because this comes from colorectal cancer patients. Even in a group not associated with paraneoplastic, we're finding these subclinical neuropathies. It

Page 63

panicked me a little bit because I initially thought that all of our tools were simply out of calibration, so we quickly recruited some more healthy volunteers, and sure enough, the data came out consistent.

So this seemed to be a reliable data point that, in fact, it really is true. There is something about the disease process of cancer itself that seems to start to impact your ENF density and presumably then predisposes you to the onset later then of treatment-related neuropathies.

One of the big critiques of trying to do QSTs is that it's too time consuming. It's going to take too long to work up each patient. Well, in panel C, that's a slotted pegboard test. It takes roughly for any of us 70 seconds or so to do that test. The patients, you see, take considerably longer, but still, it's under 2 minutes to get this done. So that's something that can be quickly done.

In panel B is where we're showing this bumps test. Now, that bumps test is here, and again,

Page 64

it's something that can be done really quick. This was developed by Bill Kennedy in Minnesota along with Don Simone at University of Minnesota. They promised me they got this very close; actually they can mass produce this.

The test is basically -- you can see the finger there is on one of the dots. Over one of those dots is a little cylinder that I think is 550 microns in diameter, and then they vary from a half micron tall to 22 and a half microns tall. And the task is for each dot, tell me where is the bump.

I'm actually terrible at this because I get so competitive, I want to find that doggone dot, that I end up just messing up. But you guys would all probably perform at roughly 3 microns for your age. Kids can go all the way down to that half micron tall. Patients, though, they end up more or less somewhere in double that. They're walking in somewhere in the 7 to 8 micron range.

Again, this is something that can be done relatively quickly. So if Bill can just push this

Page 65

out the door as a product, it's something again that could be applied.

This then is showing you as we move forward -- and now we're actually looking at going out into the study where we're showing then this number of out-of-range measures. I'm going to actually skip that.

This is the picture I wanted to get to, where when we look at then the correlation of folks' ability to detect the bumps back to their Meissner corpuscle counts, we find that those things are correlated to one another. So the long and the short, you can use simple QST measures to get at what those patients' underlying ENF and density might be.

Looking prospectively, this is again colorectal cancer patients, and one of the take-home messages I'd give you is that once you start doing these therapies -- so here we're looking at again colorectal cancer patients, pegboard time, which we thought was very sensitive to initially detect folks.

Page 66

As you go through therapy, it didn't tend to get worse, which is what I would have expected. In fact, patients practiced at it. They tend to get a little bit better. But the bumps test -- it's all the way at the bottom -- you can see as they went further and further into therapy, in fact, that was a good metric of showing that they're starting to compile a loss of the ability to detect those little bumps.

Our initial trial looking at trying to prevent CIPN in a myeloma cohort with minocycline -- and I'll get into the rationale for that later perhaps -- didn't work because we used a QST as a primary outcome. If we would have stuck to patient-reported pain, numbness, tingling, in fact, we were getting signal there.

So I wouldn't use necessarily QST as your primary outcome. I would potentially use it as an entry screening tool to make sure that you get both cohorts stratified correctly. But as a tool to look at how well your particular intervention might be working, I think I would stick with patient-

Page 67

reported outcome that we found was much more sensitive, in fact, than the rate at which folks changed their QST function.

I think the next slide I have that. Yes, I have a little more QST data.

Here, you're showing touch gets worse over time slowly. The sharpness threshold doesn't really change much. Similar with warm and cool, they really don't change that fast. There is some changes over time, but it's relatively slow.

This is, I thought, the more important slide. So as you look at the total neuropathy score, that does tend to build up over time. That's just giving a score of 1 to each QST measure that changes over time, so that builds up.

But the center is what I thought was more interesting. It gets to what Joanna was talking about a little bit ago. On oxaliplatin, you can see that numbness builds up fairly rapidly over time. And we ended up with roughly 80 percent of our patients by the end of the trial showing some degree of numbness and tingling. Only about

Page 68

20 percent of patients started to show pain.

There's one measure of what the expected percentages of patients might be. Again, pain for this particular cohort is not that prevalent, but there is a lot of numbness. It is often really bothersome to the patients. And along with that numbness, you start to show -- at least they start to complain of difficulty with buttoning, stuff like that, but also most especially problems walking, and they start to become predisposed to falling. That's one of the areas that we thought --

At the bottom, you can see the incidence for the folks that started off with a preclinical deficit and not. And clearly, the folks that walked in the door with deficits -- and again, this was QST deficit at baseline -- tended to do worse than those folks that came in with normal QST function. So we think then that that may be an important way to stratify based on that risk factor.

Coming back to multiple myeloma, we

Page 69

basically found the same data, that if you walked in the door with a subclinical deficit at baseline, you tended to have more numbness, tingling, and pain. This was on Velcade. So these folks actually developed over pain, so again, an important risk factor.

This is the slide that when I -- and again, it's my own data, and I was so bummed out to see this, that I hadn't caught this ahead of time. So the top part of the table where it says "touch detection, sensory motor function," that's data that I already showed you.

It's the bottom part that blew me away, particularly the very bottom line. Opioid use was a significant predictor of folks that developed pain, numbness, tingling, neuropathy during treatment. I look at that, and I thought to myself, golly, how many of these folks are all in the adjuvant setting? They've all had surgery. What's postoperative pain been in these folks that have gone on to chemotherapy? How much opioid use are we talking about? Did these folks get opioid

Page 70

use later on during therapy, and does that make things worse?

To me, I find this to be a really shocking and important observation that folks in the lab got a flash traffic from Pat, quick, to let everyone -- quick, start doing opioids with CIPN work.

I think that that's a really, really important finding. It bumps up against the idea that opioids now in any cancer setting seem to be predisposing folks to micrometastases, and it also now underscores the importance of this enhanced recovery after surgery in limiting opioid use, particularly if it's going to be a risk factor as folks move forward into chemotherapy.

That's one of the new things that I thought I would bring to share with folks, that that could be a really interesting thing.

This is implicit in the data all the way through. If you go back and you sort -- and this is Shelley [ph] Long's data. She likes to partition folks out this way -- is whether they had

Page 71

a high numbness or a low numbness. In fact, you can predict that again based on baseline QST, which is where that previous table came from.

I want to jump past now -- I don't know where I'm at. I'm running out of time so I'm going to have to flash real fast. This is going to be preclinical data, and I want to hit a couple of things. I'm not going to go through these slides nearly as slowly as I did previously.

One of the first things that we found here in the preclinical setting is that the infiltration of the dorsal root ganglion occurs by macrophages during the chemotherapy. If you kill those macrophages, the CIPN stops to develop. So that tells us then that the potentially in patients, the strength of their pro-inflammatory response may be another predictor of whether they're going to have a strong reaction to the chemotherapy and show rapid onset of symptoms.

This picture here is -- and both of these were collaborative with Annemieke Kavelaars and Cobi Heijnen at MD Anderson. They went on to show

Page 72

that following this infiltration by macrophages, the ganglia becomes infiltrated by T cells, CD3-positive T cells.

Those T cells, if you deplete them, prevent the recovery from CIPN. So this was in a Taxol model. Normally, we see these animals get better by about 60 days or so. They start to show recovery. If you deplete the T cells, then folks don't get better.

The center panel there showing the spontaneous activity, I'm going to touch on that real fast. But what that shows there is that these T cells seem to start producing IL-10. The IL-10 switches the macrophages from an M1 to a M2 phenotype, and that's what promotes recovery.

So that tells us a couple of things. Number one, there are a couple of immune mechanisms within each of us potentially. How strong is our M1 response, and how strong is our M1 to M2 conversion? Then as well if we have a chronic patient, we may be able to actually -- immunotherapy may be another path

Page 73

forward to treat folks.
The other thing -- and I'll leave this as the last tidbit -- we found preclinically, this is dorsa root ganglia from animals treated with paclitaxel, and they developed spontaneous activity in the soma, in the ganglion cells themselves.
This previously was in large cells using a sharp electrode preparation where we were able to sample large cells. This is where we were using disassociated neurons so now we can better sample the small cells.
So we're seeing activity in both large and small neurons, and the shocker, we're able to get dorsal root ganglia out of people at MD Anderson, basically patients going in for vertebrectomies in the thoracic dermatomes, so the dorsal root is often sacrificed, and we were able then to collect those.
We found spontaneous activity in ganglia of patients but only in dermatomes where they had pain. If we got these ganglia out of dermatomes where patients did not have pain, there was no

Page 74

spontaneous activity. So exactly like we're seeing in animals, we're getting the same type of spontaneous activity occurring in patients.
I want to blow past this one, and I want to get to this point right here. And there are two flavors of that activity. In large neurons -- and the picture is probably too small for you to see. But the isoelectric line should be flat in these cells when they're not active, but it becomes -- and you can see in panel B -- real squiggly, and those are in small neurons. Those are called sub-threshold fluctuations, and in A is activity from a large cell. Those are called sub-threshold oscillations.
The important thing is that the underlying ionic mechanisms are different between the two. So in large neurons, they're voltage dependent. So something like gabapentin might work in those cells, but it wouldn't touch the small cells.
This is why some of the compounds that we've been using are potentially not effective because you're treating only one set of cells that have

Page 75

become spontaneously active. There are still other groups of neurons that aren't affected that treatment. So in fact, you may need combination treatments to actually get an effective block of this activity.
Then some data showing you some of the interventions that we've tried to suppress this activity. I'm not going to get into that. Then as well, we've been doing now some in vitro culture work focusing on the mechanisms of this activity that I'm not going to get into.
I'm going to stop right there because I'm right on time and potentially going to take a few questions. Thank you.
Hold on. Let me blast all the way through to the people that did all the work.
(Applause.)
DR. DWORKIN: We have time for a couple questions.
DR. RICHARDSON: Patrick, I'm very interested in that immune observation that you made. Could you just go over that? Because you

Page 76

moved through it rather quickly. But what was the implication of the macrophage function that you talked about?
DR. DOUGHERTY: I won't get into the history of it, but the bottom line is we found that early in chemotherapy treatment, the ganglion becomes infiltrated by macrophages. Those are M1 phenotype pro-inflammatory-type macrophages. So they're pumping out things like TNF, IL-6, IL-1.
Following that, so a week or 10 days following that, the ganglion becomes infiltrated by T cells, and they're T reg cells. And they drive those macrophages from an M1 pro-inflammatory phenotype to an M2 restorative, healing phenotype. Those macrophages then start to produce things like IL-10 that suppresses the spontaneous activity that I showed you.
So that's the bottom-line story is that we have both an immune component that drives the onset, and then there's an important immune component that drives recovery.
DR. RICHARDSON: We're just about to publish

Page 77

in the British Journal of Hematology a meta-analysis from our bortezomib experience showing that you must partner dexamethasone on the day of bortezomib administration and the day after. Previous adaptations of the regimen had moved to a weekly schedule dislocating steroid from bortezomib, and we saw a spike in grade 3 neuropathy in the meta-analysis.

Your observation is extremely pertinent because it exactly correlates with what we see clinically.

DR. DOUGHERTY: It'd be interesting, and I've given a lot of thought to that steroid treatment because, again, the macrophages are resistant to steroids.

DR. RICHARDSON: Right, but it's downstream. It's cytokines and --

DR. DOUGHERTY: Your T cells would potentially be sensitive to steroids. So it'd be very interesting to see whether the T regs are less sensitive, say, than T helpers. And so you're actually augmenting the activity of those T regs,

Page 78

so a lot of interesting immunology based on that observation as well. Thank you.

DR. CAVALETTI: Pat, may I ask a question? Guido Cavaletti. You mentioned that blocking macrophages, killing macrophages, stops CIPN. Would it be more correct to say it stops pain? Because we have the same data you provided us in bortezomib, and we also have infiltration with macrophages in the dorsal ganglia and in the nerve. We have a complete prevention from allodynia when we kill macrophages, but we have no effect at all on nerve conduction, for instance.

So my question is, are those macrophages producing pain or producing CIPN?

DR. DOUGHERTY: Boy, that's a tough question, Guido. So my interpretation of the animal behavior is that they're not moving their paw out of the way as much. I'm not really sure what that animal -- why it moves its paw.

Patients don't usually have touch-evoked pain. Most of them are numb. They'll walk in. They've got jewelry on. You put your hand out.

Page 79

They'll shake your hand.

Why do the animals move their paw quicker? I'm not sure. One of the things that I can guess at is, again, this spontaneous activity that we see and we think about what the patients tell us. A lot of folks have spontaneous pain. That's what they got. And if they walk or they use their hands, it makes their spontaneous pain worse, and then it lingers.

The animals, I suspect, are learning to avoid a stimulus. Now, is that because they also would have a spontaneous dysesthesia pain, that they know that if you touch them, you're going to make it worse and it's going to linger? That's my interpretation.

I would say that we're preventing the onset of the CIPN itself. Now, we have not done the nerve counts. We have not done the ENF counts, et cetera, other things that we could measure to look at, but that's my suspicion.

DR. DWORKIN: Last question from Ellen.

DR. LAVOIE SMITH: You mentioned that you

Page 80

thought that a patient-reported outcome measure would be more sensitive than the bumps test. Can you elaborate on why you think that's true?

DR. DOUGHERTY: Just based on the rate of change. So if you're going to use an objective functional measure to say, all right, we're preventing CIPN, I just think that that's less sensitive.

The patients are going to tell you -- and that's going to be at the end of the day -- if you're making them not have numbness, tingling, and pain, your patient is going to be happy. If they still can't button their shirt, they may be able to get on with life, but what they don't want is to have pain or numbness. Really, at the end of any clinical trial, that's going to be the most important endpoint.

Again, I think that the nerves get sick and start to discharge spontaneously before their function declines. So I just think that the symptom onset, the sickness in the nervous symptom, the spontaneous activity that I've been talking

Page 81

about, I think that comes on faster than the deterioration in function.

DR. DWORKIN: (Inaudible – off mic).

DR. DOUGHERTY: That's my impression. That's the result that we have is if you look at the PRO data and the patient's complaint of numbness, tingling, and then later pain precedes an objective decline in sensory function.

DR. DWORKIN: (Inaudible – off mic).

DR. DOUGHERTY: Haven't done that.

DR. DWORKIN: Thanks very much.

Next speaker, before the coffee break, which will be in about a half hour, it's my pleasure to introduce Dr. Lynn Howie. She's from the Division of Oncology Products at the Food and Drug Administration and will be giving an overview on the regulatory perspective involving the development of therapeutics for CIPN.

Thanks very much for joining us.

Presentation – Lynn Howie

DR. HOWIE: Thank you, Dr. Dworkin. Thank you for allowing me to be here.

Page 82

I'm actually going to give one regulatory perspective. These agents are now going through two divisions. Dr. Horn will speak after the coffee break, and she's the primary division that these drugs are going through.

We primarily can serve as consultants, but up until 2015 were reviewing these products. So I take a lot of this talk from the wisdom of one of our longtime reviewers, Dr. Schecter, in providing the oncologist's perspective and the FDA oncology regulatory perspective on development of agents for CIPN.

As a medical oncologist and a medical officer, I first want to just acknowledge how much supportive care is crucial for cancer treatment, and we have FDA-approved supportive care agents in the area of antiemetics, growth factors, bone health agents, agents to reduce mucositis, and antidiarrheals.

These have helped to reduce symptoms and side effects, and as Dr. Brell and Dr. Freeman have both talked about, have helped to improve the delivery of chemotherapy, many of which are given with curative intent.

Page 83

We have had lots of talk about the incidence. The numbers range greatly, as Dr. Brell had talked about. Platinums tend to be one of the highest rates of the incidence of chemotherapy-induced peripheral neuropathy, and this can lead to dose reductions, delays, and/or early discontinuation.

Manifestations are broad. It can be pain, numbness. Some people end up having difficulty with proprioception and balance. There can be difficulty with motor symptoms and then autonomic symptoms as well. As was well described by Dr. Brell in her description of her patient, these can be detrimental to function as well as quality of life.

Moreover, we have little evidence of agents that can actually prevent or even treat chemotherapy-induced peripheral neuropathy. As a practicing physician, I find that there are few evidence-based options that I can offer to patients

Page 84

to prevent or treat CIPN, and this makes this an unmet clinical need.

Now I want to put my regulator hat on and talk about what's important to FDA oncology when we're evaluating these products. First and foremost, we need evidence that these therapies do not attenuate or interfere with anti-cancer therapies. Sometimes the mechanism of action for the neurotoxicity is the mechanism of action that's treating the tumor, and so we need to figure out how to balance those two things.

We also in clinical trials design want to have awareness of the variability of chemotherapy agents and various mechanisms of action of causation of CIPN. And putting all of these chemotherapy agents together in a basket to treat in a trial to evaluate an agent is probably not going to lead to much success because of these variations.

We also want to encourage trial designs and patient selection that are focused on helping to tease out the impact of the drug that is used to

Page 85

prevent or treat CIPN as opposed to the myriad of factors that can affect the development and persistence of these symptoms.

We want to also say that when you get an approval for a drug, it's probably going to be chemotherapy specific. Because of these different mechanisms of action, we want to be clear that approval for one chemotherapy type or chemotherapy regimen and potentially even in one tumor type may not mean approval for use in all chemotherapies or chemotherapy regimens.

We want to strongly encourage the development process be focused on agents that are used to prevent or treat peripheral neuropathy for common chemotherapies and common malignancies. So as we've talked about already, the two that come to mind most readily are breast cancer and colon cancer with the use of taxanes and platinums respectively.

As Dr. Brell covered, there are multiple agents that are associated with CIPN. Interestingly and going back to Dr. Dougherty's

Page 86

comments, immunotherapies, the pembrolizumab and nivolumab, are also associated with the development of autoimmune neuropathies. So all of these can affect the peripheral nerves, however, they may do so in different ways.

We just want to talk about within classes. So within the platinums, oxaliplatin, cisplatin, and carboplatin all have variable incidences of peripheral neuropathy and may have slightly different mechanisms of action as well as manifestations. So combining these platinums together in one trial is unlikely to lead to an effective evaluation of a therapy.

Same with the taxanes, docetaxel has a reduced incidence of peripheral neuropathy compared to paclitaxel. So combining those two agents within the context of a clinical trial may lead to not good outcomes for the evaluation of the agent.

There are multiple risk factors for the development of chemotherapy-induced peripheral neuropathy. We encourage that clinical trials try to minimize the incidence of comorbidities that can

Page 87

be associated with this in order to better evaluate the outcome of interest.

Getting back to the cancer, we want preclinical data that shows that the agent would not interfere with the anti-tumor activity of the chemotherapy. So that includes data in the preclinical setting that gives a good and strong scientific rationale that the mechanism of action will not interfere with the anti-cancer agent and/or pharmacologic studies that demonstrate that there is no evidence of detriment to the anti-tumor activity.

As far as the clinical studies go, we strongly encourage that the initial clinical studies be done in the metastatic setting. This would likely be in the first-line metastatic setting as we know that cumulative chemotherapy increases the risk for CIPN. This is because we need to know that the agent does not have an effect on tumor-related endpoints such as survival or progression-free survival.

Well-designed, randomized placebo-controlled

Page 88

trials with a homogenous patient population, meaning the same tumor, the same stage of disease, and the same treatment with appropriate endpoints that assess both symptom severity as well as functional measurements, are what are most likely to be compelling evidence for the FDA to grant an approval.

Unlike our cancer therapies where we're often willing to give approval based on one trial, we would like multiple trials to show that there is both safety and efficacy in these agents.

For the endpoints, we feel very strongly that both symptom and functional assessments are important. We have the clinical outcomes assessment group that can get advice on endpoints, including PROs as well as functional assessments.

Then from a safety perspective, we want to show that there is no increased adverse events by CTCAE criteria as well as no detriment to tumor-related outcomes, including overall and progression-free survival. Balancing the safety and efficacy of the drug is key for successful

Page 89

development.

For symptom measurement scales, we strongly encourage that the symptoms that are measured are validated in the disease studied and in the chemotherapy studied. In other words, if you are concerned about pain, make sure that the primary manifestation of peripheral neuropathy from that agent is pain and not numbness, tingling, or other things. If it is those other manifestations, make sure that you have measures that account for that because you're not going to show a change in a symptom that is not the primary manifestation of CIPN.

We recommend that you conduct focus groups of patients in the same disease and same stage that you intend to test the agent in as that can help inform what PRO measures are selected, and that can be tested in a larger group to demonstrate whether the change in those symptoms occurs at a frequency great enough that that could be detected as an outcome measure for the study.

Additionally, we want to show that the drug

Page 90

can improve impacts on function. We are not prescribing any particular measures per se, but measures that will be sensitive enough to show a difference between the two arms are important measures that can be validated as functional outcomes that are associated regularly with the treatment are important. And the challenge is to develop a group of functional assessments that can be used in clinical trials across different populations.

Additional considerations are that studies should be long enough to detect the onset, progression, and possible improvement in the chronic neuropathy, if that is the goal. This would be different in studies where you're looking at maybe reducing the acute effects of oxaliplatin. Those could be different and potentially shorter endpoints. But we also want the study duration to be long enough to ensure that there's adequate information about the safety and tumor-related endpoints associated in the population.

Then given the lack of relationship between

Page 91

acute neuropathic syndromes and chronic syndromes, it's not clear that targeting neuropathic syndromes is a surrogate for the prevention of chronic chemotherapy-induced peripheral neuropathy, but it may be an endpoint in and of itself.

Then just to give a brief mention to the agency or the office within the agency that deals with non-drug modalities, that's the Center for Devices and Radiologic Health.

As Dr. Brell mentioned earlier, there have been multiple devices that have been evaluated for treatment. This is actually treatment of pain associated with chronic chemotherapy-induced peripheral neuropathy, and to get labels for these particular things, you would go through the CDRH for the development and approval of those devices.

So the take-home messages from the FDA oncology perspective are safety first. We want evidence that these agents do not attenuate anti-cancer therapy and do not negatively affect tumor-related outcomes. We recommend trials that have patients with the same underlying malignancy,

Page 92

the same anti-cancer therapy, and that we minimize the number of patients who have comorbidities associated with increased risk to show that we're treating the chemotherapy-induced peripheral neuropathy and not necessarily other types.

Then we want endpoints that measure both patient symptoms as well as change in function related to treatment as well as the hopefully improvement of both of these with new agents that are evaluated.

I just want to thank folks from the Division of Oncology Products I. I want to thank Dr. Gewandter and Dr. Freeman for inviting me, and then folks from the clinical outcomes assessment group as well. I'm happy to take questions.

(Applause.)

DR. DWORKIN: I've been asked to use the microphone, so that's why I'm standing here with this.

Let's take just one or two questions. I think there are probably a whole lot of questions. It was a wonderful talk. We appreciate it greatly.

Page 93

Because I think what we really want to do is also get the perspective from the Division of Anesthesia and Analgesia and Addiction Products, so we can see overlaps and differences, but one or two questions.

DR. CLEARY: That was a good talk. One of the things I think holds back oncology drug development is the CTCAE with neuropathy. It's really vague, and it's really hard to score. I think your emphasis on trying to come up with a validated symptom and also functional assessment for neuropathy is important. Maybe we can also translate that over to oncology trials as well, but I think that's going to be really important.

DR. HOWIE: I agree, and I have actually been working with patient-reported outcomes in oncology as well, not from the COA perspective but from the oncologist perspective. And one of the hard things about many of those are that there are item questions that include so many things, that you can't show a change in the overall score because everything is gemisched together.

So you want to be able to have things,

Page 94

particularly for neuropathy, that tease out the specific symptoms that are causing the most pain because if you can show a difference in those symptoms, that would be what would be our measure of efficacy along with a functional assessment.

DR. DWORKIN: Roy, then Simon, and then we'll have coffee.

DR. FREEMAN: That was a great talk. So two questions, the one related to the exclusion or minimization of patients at risk, there are two issues with regard to that question, and I just want to maybe clarify. And this will crop up all the time. In a way, this ties the previous two talks to what you said.

If you think of any clinical trial, on the one hand, you want to maximize generalizability, and on the other hand, you want it to be efficient, which means including the smallest number of subjects possible. And one of the ways to run an efficient clinical trial, particularly with chemotherapy-induced peripheral neuropathy, is to actually include at-risk patients, particularly if

Page 95

you are pretreating before a neuropathy develops where your sample size might need to be very large.

I want you to maybe elaborate a little on your views on why you think you wish to exclude those patients at risk.

DR. HOWIE: It's not necessarily exclude them per se but to make sure that they're -- so for diabetes, have patients who have a hemoglobin a1c that's within -- below 8 per se and are well controlled otherwise defined.

I think part of the thing that -- and this was what was strongly encouraged by Dr. Schecter, my mentor, is that when you're trying to tease out the effect of the drug, these patients actually, while they are efficient for accrual, are not very efficient for figuring out the change in the endpoint. Because if you have people who have severe neuropathy in both arms, you're not able to tease out what is the chemotherapy and also not necessarily able to show a difference in the end.

So that's the primary reason to minimize these patients. It's not to make it less

Page 96

generalizable. It's basically to try to help determine the effect of the drug as well as the degree to which the chemotherapy and the treatment for the CIPN are complementary to one another.

DR. FREEMAN: That's very helpful. Can I ask one very quick question just to get an elaboration?

You mentioned a trial needs to be of sufficient duration with respect to assessing the safety of chemotherapy-related or cancer-related endpoints. That's a wonderfully vague term.

Can you be more specific as far as sufficient duration?

DR. HOWIE: If you're doing your first trials in the metastatic setting, that actually is not going to be, for most chemotherapies, that long. Most progression-free survivals are within the less than two-year-range, but it's more than the three-month range.

It also depends on what your indication is. If you're trying to get an indication for prevention of the acute neurotoxicity of

Page 97

oxaliplatin, your endpoints could be shorter. But again, we would want that primarily in a first-line metastatic setting to be able to show that you were not also minimizing the anti-cancer effect of the drug.

DR. DWORKIN: There's undoubtedly going to be a lot more discussion of these issues.

DR. HOWIE: Yes.

DR. DWORKIN: So we hope you're going to stay here through tomorrow afternoon.

Last question from Simon.

DR. HAROUTOUNIAN: Thank you for a wonderful talk. I just wanted to ask about the preclinical safety data. My question is, how much confidence do you have in the translational value of data that comes from in vitro experiments or maybe an animal model of cancer, which have very little to do with a true cancer, with human immunological setting, et cetera -- if your intervention does not interfere with oxaliplatin, et cetera, in a mouse, or in vitro, how much confidence do you really have that it's a safety --

Page 98

DR. HOWIE: That's why we want our first clinical trials to be in patients with metastatic disease. We don't have enough confidence to say go out and take this agent and test it in all patients who are receiving adjuvant therapy.

DR. HAROUTOUNIAN: A clinical study in a metastatic setting where you have clear safety outcomes would probably be a more clinically relevant way for --

DR. HOWIE: Exactly, that's where we would recommend the first studies to be, yes.

DR. HAROUTOUNIAN: Thank you.

DR. DWORKIN: But after some preclinical or in vitro --

DR. HOWIE: Exactly. One example is palifermin. Palifermin is an agent that reduces mucositis in patients who are receiving stem cell transplant. It was thought to be something that could be used also in patients who were receiving combined chemo and radiation for head and neck cancer. However, its mechanism of action is that it is a keratinocyte growth factor stimulant, and

Page 99

keratinocyte growth factors are on epithelial-derived tumors. And that is why FDA approved it only in the hematologic malignancy setting, is because we were concerned that because it could potentially promote tumor growth, it would be less safe in that patient population.

DR. DWORKIN: Thank you.

There's going to be lots more. Let's have a coffee break now. Please return promptly at 10:30 because we're going to have one more talk and then discussion at 11:00. Thank you all.

(Whereupon, at 9:58 a.m., a recess was taken.)

DR. DWORKIN: Thank you all for returning from the coffee break. It's a pleasure for me to introduce our next speaker, Dr. Pamela Horn. Dr. Horn is at the FDA's Division of Anesthesia, Analgesia, and Addiction Products, and she'll be giving a second regulatory perspective on the development of treatments for chemotherapy-induced peripheral neuropathy.

Dr. Horn.

Page 100

Presentation – Pamela Horn

DR. HORN: Good morning. Thank you, Dr. Dworkin. It's a pleasure to be here.

I am going to pick up where Dr. Howie left off, around 2016 when we in the Division of Anesthesia, Analgesia, and Addiction Products took over the primary responsibility for CIPN drug development. I will start off with the outline of what I'm going to cover.

First of all, I'm going to talk very quickly about a patient-focused drug development meeting that we had last year where CIPN patients were very well represented, and we learned some interesting things from them.

Then I'm going to touch on drug approval standards, the approved therapies for peripheral neuropathic pain in other conditions, and a little bit about the division roles that we have, and then the rest of my talk I'm going to spend on different trial design issues that have come up in our work, and really give you as much as I can about what we've encountered in our division.

Page 101

This meeting is part of the last PDUFA legislation that was passed. FDA committed to having a little more than 20 of these meetings where patients had the opportunity to tell us about their disease and the available treatments and their experience.

This one that we had on peripheral neuropathy was June 10, 2016. It was attended by 37 patients in person, and then there were a few more that had a live webcast and were able to participate in real time. There were quite a few CIPN patients, and they had a lot to offer. They contributed a lot, so it was very interesting for me to learn about it. And anybody who's interested, the summary report was posted last month.

I will just give you a little summary of what was said. One interesting thing, the first bullet there, that's not an error. People actually did -- even though we were asking, prompting for painful sensations and how to describe them, numbness was described as well as burning and

Page 102

stabbing. Most commonly, what was described was hands and feet, so similar to what we've heard already about CIPN in particular.

Numbness was really emphasized as having a high impact because of what would happen with loss of balance, falls. There was an impact on daily activities, work, and relationships, and almost all of the patients said that their pain was not well managed and their other symptoms of neuropathy were not well managed on their current regimens.

They also gave us some insight into what they were being treated with, and the most common drugs that came up were pregabalin and gabapentin, not unsurprisingly. We also asked them a little bit about what adverse reactions were the most important, disruptive, notable to them. The ones that came out in the discussion were dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and problems with concentration and attention.

The other drug therapies that came up, NSAIDs, opioids, and then also some of the

Page 103

alternative routes of administration other than oral route were being used by some patients.

A lot of the patients were using additional therapies like massage, physical therapy, acupuncture. A lot of them were taking vitamin supplements and making lifestyle modifications through diet and exercise.

Now I'll shift gears and just talk briefly about the drug approval standards, and highlight in our analgesic guidance for the peripheral neuropathic pain conditions, the general standard is for two adequate and well-controlled trials. So that is consistent with what Dr. Howie talked about in her talk.

The other thing is that if there are three successful trials in three separate neuropathic pain indications, there may be an opportunity for a general neuropathic pain indication.

In addition to the efficacy, there needs to be an adequate assessment of safety, and it needs to be in enough individuals to characterize the safety and for adequate duration of exposure. Then

Page 104

we have to look at the risk-benefit balance and determine that it's favorable.

This is just a quick summary of the drugs that are approved for peripheral neuropathic pain. You can see that CIPN is not on there. The only three peripheral neuropathies that are on there are the diabetic peripheral neuropathy, postherpetic neuralgia, and trigeminal neuralgia. The only drug that's approved for more than one indication is pregabalin.

Briefly, the division roles, so as we previously heard, DAAAP is reviewing and providing advice primarily for the development of these drugs for CIPN, and then we consult with Division of Oncology Products as well as the COA staff, which Dr. Howie also mentioned.

Now I'm going to touch briefly on how we are thinking about CIPN indications. The purpose of this slide is to illustrate the fact that there are differences in the different drugs and when they cause neuropathy, and it affects when in the process of receiving chemotherapy would be the

Page 105

opportunity to initiate and measure the effective drugs for prevention and treatment.

The bottom left, there are some of these chemotherapy agents that actually could cause the neuropathy very early on with the first dose perhaps of chemotherapy, and in that case, you might be starting the preventative treatment before chemotherapy, certainly by the first dose of chemotherapy. Then you could also have a situation where you're trying to treat the acute manifestations of the neuropathy and starting treatment very early and having it potentially be concurrent with the chemotherapy.

Then the other extreme would be that the symptoms could be appearing after the chemotherapy regimen is completed and maybe even delayed by a number of weeks after the end of chemotherapy in which case your treatment period wouldn't start until well after the chemotherapy is ended. Also, potentially if you're trying to target chronic CIPN, which is very clinically important to patients, then you also might be starting the

Page 106

treatment period after the end of the chemotherapy regimen.

Then the other aspect of the CIPN indication is that one might be seeking an indication for CIPN pain, or it might be a more general indication. Then there may be assessments needed for other symptoms or signs of CIPN, and we know for sure that there are a lot of other important symptoms for CIPN like numbness.

The next slides, so the rest of my talk really is going to be touching on what we have seen proposed, and all of these things that I'm going to be talking about are things that are publicly available. The range of proposals for the number of different chemotherapy agents to include in one study, everything from a single agent to multiple classes within the same trial. I think Dr. Howie touched on historically what the advice that the oncology division has given about that.

In terms of entry criteria, the things that often come up are the cancer diagnosis, the life expectancy, the planned chemotherapy regimen, all

Page 107

important for defining the study population in the proposals that we see. Then the entry criteria for treatment, so now we're looking at people who already have a neuropathy; baseline pain scores defined by a 11-point NRS; NCI CTCAE criteria, which is obviously unique to this particular indication compared to other painful conditions; and then also clinical diagnosis based on symptoms and neurological signs might be part of the criteria, and the timing of the chemotherapy regimen with respect to the treatment period.

Next, I'm going to sum up what has been proposed and what has been studied for dose and dosing. Some dosing considerations for dose selection, it may be that a drug has been tested as a chemotherapy agent, and then it's possible that the next step would be to test it at the same dosing as was used in the chemotherapy trials for CIPN.

There also could be that we'll be seeing some phase 2 work for pain or neuropathy endpoint, and that's what the dose selection is based on,

Page 108

generally, placebo-controlled double-blind trials. And we know that there could be a flexible dosing interval that isn't common. For the dosing and the strength, it could be fixed or flexible. There have been patient administered as well as clinician administered models for the trial design.

Concomitant analgesic use and rescue medication use are very important to consider, and generally what we have seen is that they've been allowed in trials.

The next part of the trial design that I'm going to talk about is outcome measures. Again, these are things that have been proposed and that can be found publicly. One approach is to look at pain only on an 11-point NPRS or BPI. Short forms are very common, and I think we're all probably very familiar with those.

Some of the ones that are more unique to CIPN would be a patient-reported outcome that tries to incorporate multiple manifestations of the disease in one instrument. I'll show you the FACT/GOG one, but the EORTC, the CIPN 20 scale, is

Page 109

proprietary, wasn't publicly available. What it is, is a 3-domain scale, and it's a quality-of-life questionnaire. Then of course, there could be proposals for novel PRO development, and then there's the Sanofi NCI scale, which is clinician reported.

This is the 11-point NPRS that we're very familiar with, the BPI short form. This is version 4 of this scale, which you can see is definitely specific to neuropathy and has been used in trials in this setting. Then this one comes from the eloxatin program and is a clinician-administered scale, and the setting that it was used for was advanced colorectal cancer patients.

That is the breadth of what we can talk about in terms of what we have been seeing proposed. So in summary, we know that the CIPN is not being adequately managed for many patients and that we need treatment options. There have been a range of proposals made that we've encountered, and when we've seen the proposals, it's brought up some unique study design issues that are unique to CIPN.

Page 110

Thank you.

(Applause.)

DR. DWORKIN: Let's follow our format and take a couple of questions for Dr. Horn, and then we'll have a panel discussion. Pat?

DR. DOUGHERTY: It was interesting that in your initial study design that you wanted that restricted to a single agent, but some of the groups of patients that have still poor outcomes and a lot of neuropathy, in fact, get combination therapies -- I'm thinking the GU cancer cohort, for example -- how do you follow along --

DR. HORN: I can go back to that slide. I definitely didn't mean to say that we prefer that.

DR. DOUGHERTY: Right here, single class. So a lot of folks, in fact, get a taxane/platinum combination. So why would you want to restrict that to a single class?

DR. HORN: I wouldn't. Those are the range of proposals that we've seen for study design.

DR. DOUGHERTY: Oh, okay. So you're summarizing the studies that have been done --

Page 111

DR. HORN: I'm summarizing, yes.

DR. DOUGHERTY: -- not that are allowed.

DR. HORN: Correct.

DR. DOUGHERTY: Oh, okay. Great.

DR. HORN: Right. So everything here that I've presented is trying to give you a flavor for what we see right now to allow you to have that context for your discussion. I have not presented anything in terms of what we're recommending.

DR. FIELDS: Hi. It's Ellen Fields from FDA. I also think we can talk about that during the panel discussion, and Dr. Howie may have some input into some of those questions about single class versus multiple classes at the same time.

DR. DWORKIN: Another question?

DR. FREEMAN: You made it quite clear earlier on and then now, you're not saying what you are recommending, and you're not saying also what you're not recommending or recommending against.

Do you intend to do that?

(Laughter.)

DR. HORN: In terms of when we're

Page 112

interacting with sponsors --

DR. FREEMAN: If I could maybe ask it much more specifically. Can you give us some sense of the sort of thing that you might recommend, or the sort of thing that you might recommend definitely against?

DR. HORN: I could, but in which part of the study design?

DR. FREEMAN: It's really pretty open because I think -- for example, just looking at this slide over here, Joanna Brell mentioned in her talk the issues related to even within class trial, that there are quite marked differences within each class, which may make a design issue. Now, that's not a regulatory issue, but that's a design issue.

But if we say when do you start a prevention study, do you wait? Do you not wait? Are you happy about -- there are so many issues that it would be nice to hear what you say. How do you feel about exposing patients who will never get a chemotherapy-induced peripheral neuropathy to a drug, which may or may not have toxicity?

Page 113

So it would be nice to hear just some sense of your views on the kinds of things that you would say this is acceptable even though there are risks involved and it may not be the perfect efficient trial design, or the kind of thing where you would say, this is the kind of thing that we would find just totally unacceptable.

DR. HORN: Okay.

DR. FREEMAN: I understand I'm asking not an easy question.

DR. FIELDS: You want me to respond?

DR. HORN: You can respond.

DR. FIELDS: Appreciate the question. We're very early in our regulatory experience with these products, and we base a lot of our recommendations on the science and what the sponsor comes to us with. We look at the potential risk-benefit for an individual product.

So there's not going to be a single -- we can't give you we'll definitely allow treatment with all preventive chemotherapy-induced peripheral neuropathy products starting prior to chemotherapy.

Page 114

It's going to depend on the product, it's going to depend on the population, it's going to depend on the mechanism of action.

All these things depend on a variety of variables, and I don't think we can give you one answer for that. Sponsors come to us with a lot of science behind what they're saying, and we listen to that. We talk to them about it, and between our division and the oncology division and the sponsor, we try to come up with the best approach balancing risk-benefit and furthering the science. So it's hard to give an answer to what you asked.

DR. DWORKIN: So we have Charles, and then we'll have panel discussion.

DR. LOPRINZI: So as opposed to a question, I just wanted to make a comment. I love that answer there because this is a new area, and it's either prevention, early treatment, or treatment of far established. There are all sorts of different things going on here with incidence of neuropathies so that looking at the science as you go along there and evaluating the actual science and what's

Page 115

put forward to make sure safety and potential efficacy and all that stuff, makes a ton of sense to me.

DR. DWORKIN: What I'd like to do is invite the other three presentation speakers from this morning up to the table, and also Daniela and Dr. Fields, who will be substituting for Dr. Sharon Hertz, who has to deal with a failure to resolve pain from oral surgery, is my understanding.

DR. FIELDS: She's on her way.

Q&A and Panel Discussion

DR. DWORKIN: I thought a reasonable way to begin this session, it's really Q&A and discussion, but to start by asking the two people who are up here who didn't present this morning if they have anything they would like to add to what they've heard.

Could we start with Ellen. Is there anything else you'd like to add to what you heard this morning, any thoughts you have, any questions for the four presenters, and then we'll give Daniela a chance, also.

Page 116

DR. FIELDS: I think in my last comment, I said our overall approach. I don't have anything specific to add; possibly as the questions come in I think.

DR. DWORKIN: Okay. Daniela.

DR. DASTROS-PITEI: I would like to thank very much the agency for coming forward and presenting what you've seen in the past and the future. We all recognize that this is a new area, and we're all learning. I think the reason for today's meeting is exactly that.

What would be very helpful I think to discuss today is to understand the role of PROs, which are incipient in this area and perhaps how we can best address this need for long-term follow-up in an indication, which is focused on neuropathy.

DR. FIELDS: I think tomorrow, isn't there going to be an extended discussion about PROs? And there will be presentations from our COA staff who are actually the experts on the PROs. But the key thing is that the patient-reported outcomes need, as both Dr. Howie and I think Dr. Horn said it,

Page 117

encompass both symptoms and functions. And we hear from our oncologists that that's crucial in evaluating the PRO. The PROs need to be clinically relevant. What's important to the patient? What are their most disturbing symptoms?

I don't want to over-speak because I'm not part of the CRO staff, and I don't want to say something wrong. But there was a second part to your question about follow-up?

DR. DASTROS-PITEI: Yes. Perhaps the oncology aspect because obviously this is a disease which is so correlated with an oncology treatment many times, right?

DR. FIELDS: Right.

DR. DASTROS-PITEI: It's more how we assess from a clinician perspective when to stop or to delay and how would you be convinced that measuring clinical studies will enable the clinicians to make that decision.

So in the past, we used NCI CTCAE for neuropathy as a decision making, perhaps for oxaliplatin, it's on the label, but how would you

Page 118

see the future? Because we're focusing more on the patient signs and function, but would we want to see measures of oncology treatment?

I understand overall, this is perhaps much harder to achieve for a neurology drug, right? So how would you balance this? I think this is probably where we're struggling a bit.

DR. HOWIE: I think those are all really great points because I think we don't know what the optimal timing is. I think part of the thing about PROs and symptom-related issues in cancer patients is that they often wax and wane with time in and of themselves.

So I think as we develop measures, it's going to be important to understand not so natural history as meaning kind of what are the effects without the agent to better understand what the optimal time period for measure would be. Does that make sense?

Then one of the things that we have done on the oncology perspective from PRO assessment has been to look at the patient as their own control,

Page 119

and so some of our analyses have been looking at what the patient is at baseline versus change within that patient as one of the ways that we can better understand what their symptom burden is over time.

DR. FIELDS: I don't know if you're actually asking also about the duration of follow-up in the studies?

DR. DASTROS-PITEI: That's right, yes.

DR. FIELDS: From our oncology colleagues, I think in a perfect world, you'd want years of follow-up to see is the neuropathy being prevented, is it being delayed --

DR. HOWIE: Is it being reduced --

DR. FIELDS: Is it being reduced, and along with that, the outcomes of the cancer treatment, we need to see both. So we're still working on how long that follow-up should be in the clinical studies.

DR. DASTROS-PITEI: Considering the natural progression of the disease, which is related to the chemotherapy injury --

Page 120

DR. FIELDS: Right, so --

DR. HOWIE: That's part of the reason too that we encourage there to be homogeneity among the patients who are in the initial clinical trials is because with the known data about what the duration of follow-up is as well as survival data, can help inform the duration of the study needed.

Because it's not likely to say -- I can't say oh, if you follow the patient up for 2 years, that's enough because that's going to be very different in metastatic hormone receptor positive breast cancer versus metastatic triple negative breast cancer versus ovarian cancer.

DR. DASTROS-PITEI: Yes, and I think many of the drugs which were mentioned earlier, the taxanes, oxaliplatin, and the platinums, which are the most often associated with CIPN, really these days are used in an adjuvant setting. And that means the duration would be even longer for these patients in terms of disease progression.

DR. HOWIE: Correct.

DR. DASTROS-PITEI: So I think we need to

Page 121

find a way to learn when the difference occurs, when it is important for the patients and for the agency.

DR. HOWIE: I think that that's going to be disease specific. Does that help? At least in the initial trials, I think it's going to be disease specific.

DR. FIELDS: There's also the option of following the patient in the clinical trial for a certain period of time to get the drug out there and have a postmarketing requirement after the drug is on the market to gain more information about the product to learn more about its behavior.

DR. DASTROS-PITEI: Which will make sense.

DR. FIELDS: Those are also options.

DR. DWORKIN: I'm going to preempt into tomorrow's discussion, but it sounds like -- and this goes back to what Roy was asking for in terms of recommendations. It sounds like we've heard from Drs. Horn, Howie, and Fields that one agency recommendation perspective is for co-primary endpoints in clinical trials of pain and some

Page 122

functional measure.

That seems like a very clear perspective we're hearing from the three speakers representing FDA; is that correct?

DR. FIELDS: Well, the COA can talk about whether they're co-primaries. Those terms get sometimes -- it's not exactly what we'd call it, but including domains for those different aspects.

DR. DWORKIN: We will table for tomorrow afternoon the discussion of whether these are co-primary endpoints or multiple endpoints. I think Mike and Scott are smiling because they educated me at the coffee break about that distinction, which we will return to tomorrow.

Charles, yes?

DR. LOPRINZI: You mentioned pain and something else, but it's neuropathy. Because again, the point made again several times today, for chemotherapy neuropathy, numbness, tingling, pain, pain is the last thing that comes. Sometimes it's the worst thing, but many times it's not. So we want to look at all of those things, not just

Page 123

necessarily pain.

DR. DWORKIN: I'm corrected. So symptoms and function.

DR. LOPRINZI: You just come from your pain background. I know I've got to keep you honest there.

DR. DWORKIN: Yes, you do. Thank you. You're absolutely right. I meant symptoms, but I said pain.

DR. DOUGHERTY: Let me just chime in. So co-primaries is clearly not the way you want to go because if you use a functional measure that's going to be expressed at a year, you're going to end up being forced to stop early because nothing is changing early on. You got to be really careful of that part of the design.

The other comment -- and so Joanna and I decided to talk off-line because she was surprised by this opioid potential risk factor. So what that means is that your definition of homogeneity in your population is, in fact, I think a lot more complex than what we might be actually trying to

Page 124

look at first blush.

Joanna and I started talking about, well, what about the number of patients running around with hyperglycemia? How many of our patients are running around with sugars of 200 all the time? Is that a risk factor? We don't even know for sure.

As each of these studies progress, all of these little characteristics potentially could have major impact depending on whether they're stratified evenly or not between the two arms or three arms or four arms, however it is you decide to do this.

As well, some of the physiology indicates, as I mentioned at the very tail end of my talk, that single-agent interventions may not work. They'll work on a portion of the underlying pathophysiology but not all. So instead of trying a single agent at a time, in fact, some of the trials may want to be using more than one intervention.

Just to make your life a little more complicated, I'll just toss those points out for

Page 125

consideration.
DR. CAVALETTI: Pat, I think this is a very, very good point. I saw a list of potential risk factors in one of the slides, and I think that actually as a neurologist, the only way to stratify this population which is very, very non-homogenous by definition, is to stratify based on some neurological aspect, maybe bumps or maybe something else.
But I wouldn't care about the fact that one is smoking or is not smoking because someone in one single trial showed that smoking is a risk factor for most severe CIPN. I would like to understand which is the biology of this kind of association, so probably is not the true association. But if a patient has used innervation or is unable to feel the same level of thickness or the bumps, probably is more reasonable to me to stratify according to that point.
All the rest, obesity, age, who knows? We have patients older than me that is much better than me in terms of peripheral nerves probably. So

Page 126

I think that we should carefully consider the fact that they should stratify according to some neurological indicator because we are looking for a neurological side effect.
DR. RICHARDSON: May I make a comment, though, Guido? Because one thing that struck me from all of this, and Patrick and I were talking about this as well as with Joanna, do you think a lot of this unifies -- you mentioned smoking. You mentioned obesity, diabetes.
I'm very struck by the importance of microvasculature because that would be a unifying concept. That would explain why neoplasia, it's so broad because obviously, the microvasculature broadly in cancer is profoundly disturbed. Certainly in myeloma, for example, we realize microangiopathy is real.
So I just wondered. And wonder, Pat, if you had some comments on that.
DR. DOUGHERTY: Please do let me comment on that. One of the things that's always struck me that I've not been able to reconcile is, again, why

Page 127

are these symptoms so focused in glabrous skin. Clearly there, the autonomics are quite different than they are in hairy skin.
Another piece of QST data I didn't present is that in our experience, the areas of pain are associated by markedly colder skin. The fingertips in a patient with painful CIPN are anywhere from at least 3 if not 5 degrees centigrade cooler than their volar forearm where they're asymptomatic.
I absolutely agree. I think the microvasculature is a major contributor.
DR. RICHARDSON: That's a great point, Pat, because in myeloma, we see this all the time, that the colder weather brings this.
The other thing is we've had great success with very simple emollients, which I think is what one of the FDA speakers was touching on with the therapeutic massage. We just recommend this regular vigorous hand massage and feet massage using simply cocoa butter and coconut oil. I know it sounds slightly implausible, but it really does seem to work anecdotally.

Page 128

Pat's had this experience from our collaboration in myeloma, this simple therapeutic massage with an appropriate emollient that penetrates the skin. Patients anecdotally reported that for the soles of the feet, they find cocoa butter oil because it penetrates the skin better than they do for the creams on the hand. I know it sounds ridiculously simple, but we found it very effective.
DR. DOUGHERTY: That would also approximate Marie Fallon's claim concerning the topical menthol being massaged in.
DR. RICHARDSON: Exactly.
DR. BRELL: Just to reiterate what Patrick was saying earlier, this can be as simple as we want or it can be as involved and complex as we want. And unfortunately, I think it's going to be complex.
But going back to medications and Pat's suggestion that analgesics may have a role in peripheral neuropathy, I think we've not been looking at all the medications the patients are

Page 129

taking. They come in with polypharmacy, and we are not even looking to see what other medications could cause neuropathy.

So I think we're going to have to delve a lot deeper into patient characteristics and what their concomitant diseases are and what the medications are.

DR. WEN: Can I ask Pat --

DR. DWORKIN: Gordon, yes?

DR. G. SMITH: I think someone was ahead of me.

DR. DWORKIN: Dr. Wen, then Gordon.

DR. WEN: Pregabalin has been useful in a number of other neuropathies, but it hasn't been useful in chemotherapy-induced peripheral neuropathy. So what are the potential mechanistic differences you think that might account for this?

DR. DOUGHERTY: Between other neuropathies and CIPN, I think that's part of the issues in previous neuropathy studies. The etiologies for most of the neuropathies -- excluding PHN, clearly, the etiology there is pretty clear, but if you get

Page 130

into any of the other and diabetic neuropathy -- but in fact, we don't even know what the mechanisms of diabetic neuropathy are. Those are people who have had diabetes for years. What causes that is really unclear, and I'm not sure how much overlap or not there is in those mechanisms. I just don't think we know enough yet.

Now, that being said, CIPN patients, you put them on pregabalin, put them on Lyrica, and you may have a small impact on their pain ratings, but you're knocking them down from a daily max of 6 to 8 down to a 4 or 5. You can get an impact, it's just not really enough to have any functional importance.

I know basically I sound like a politician up here. I'm wandering all around your question without giving you a straight answer. But I just don't think we have enough data to give you a straight answer, unfortunately.

To Joanna's point, I don't think that we've tracked enough of the variables around all of our patients to really determine did Lyrica fail or did

Page 131

we not have the two arms adequately balanced to each other? That could be just an underlying problem in the original study design.

DR. DWORKIN: I'll give a simple-minded answer. I don't think there's been a high quality clinical trial of pregabalin in this condition, not that I know of. So I'm not sure that we really know whether it works for pain in CIPN.

I personally wouldn't expect it to work for numbness, which is an issue we heard a lot about. The drugs that are efficacious for peripheral neuropathic pain may have zero efficacy for numbness associated with peripheral neuropathy. But I think it would be a fascinating trial to do, to do a large well-designed clinical trial of pregabalin in patients with chronic painful CIPN.

DR. DOUGHERTY: Good point.

DR. DWORKIN: Gordon?

DR. G. SMITH: I have to congratulate you on having a neuropathy meeting where we're at 11:00 o'clock and no one's mentioned biomarkers. So I guess I'm going to ruin it by doing so.

Page 132

I work in the diabetes world primarily, and the FDA, at least in diabetic neuropathy trials, expects biomarkers, particularly nerve conduction studies, both as an efficacy outcome measure but also a safety outcome measure even in pain trials.

I understand that this discussion is largely focused on neuropathic pain, and therefore, perhaps these are somewhat less relevant. But I'm just curious from the FDA perspective, the role of biomarker surrogate measures, and there have been discussions of nerve conduction studies and INFD and Meissner corpuscle imaging, which is very interesting in CIPN, particularly prevention trials.

(Laughter.)

DR. FIELDS: Companies have come, not about CIPN, I don't think, but have talked to us about biomarkers about other issues, and we're certainly happy to entertain discussion and try to -- we don't have any biomarkers yet for any of the neuropathic pain conditions that we're relying on, but we're happy to have sponsors come discuss that

Page 133

with us.
DR. HORN: We have applied some of the same advice that we've given for DPN to companies interested in looking at CIPN in terms of looking at those objective measures for safety and to see whether there's any deleterious effects going on, on the nerves.
Then also, we have to really consider carefully, and the advice we give often is that it needs to be clinically meaningful, whatever you're looking at, your primary measure. The thing that you're going to try to demonstrate efficacy with has to be correlated with or in itself be clinically meaningful to the patients, and that, we have not gotten very far with any of these with that.
DR. DWORKIN: Let me ask a follow-up question. If I was a sponsor and I had a drug that I thought could promote reinnervation of the epidermis -- I'm thinking of Pat's wonderful slides. And let's say the drug did that versus placebo, is that an indication? It's a biomarker,

Page 134

I guess, right? We show on skin-punch biopsy reinnervation. That's not feeling. That's not function. It's not survival. Is it an indication?
DR. FIELDS: Well, the sponsor would have to -- we'd have to have data that showed that reinnervation could be correlated with the actual clinical outcome.
DR. DWORKIN: So you'd have to validate the biomarker with a clinical outcome?
DR. FIELDS: Correct.
DR. FREEMAN: Which may be a good time for me to ask a question. During Pat's talk, I may have missed it, but was there a link between your functional measures and the skin biopsy data that you acquired?
DR. DOUGHERTY: Are you talking about what we've done with preclinical models or clinical models?
DR. FREEMAN: No, no, no. In the clinical models -- don't let me leave the microphone without making another point -- you showed in your studies of the glabrous skin biopsies, the thenar eminence,

Page 135

the fingertip, and the forearm, you showed data, and then you showed functional data, the pegboard.
DR. DOUGHERTY: Right, right.
DR. FREEMAN: What I missed -- and maybe you mentioned it and maybe you didn't -- was whether there was any correlation between what you -- because this addresses the point that Bob is making. What is the relationship between the more objective measures, the histopathology, and the functional measures?
DR. DOUGHERTY: Yes, I did not address that directly, but yes, each of our patients that were biopsied had marked psychophysical deficits. We didn't line them up and try to correlate whether the counts exactly matched because at the fingertip, the counts were basically zero or one. They're just absent.
So as you get to that end of the graph for the function, it's not going to correlate because it's zero to whatever function that that patient had. There is a variability in that. Some people are profoundly impaired to the point where they

Page 136

have a positive Romberg sign essentially in their hands. They can't tell where their fingers are. Others have markedly elevated touch threshold, et cetera, again in their fingertips, but they still have some sensibility.
It will more or less correlate, but it may not be a one-to-one correlation. You see what --
DR. FREEMAN: I understand, yes. So clearly, more data is needed to answer that question.
I do want to make one I think rather important point. One of the issues always -- and this will come up in the symposium tomorrow, one of the late symposia, is the difficulty of recruiting for these clinical trials. I think it's probably -- of the neuropathy and neuropathic pain trials, I think it's one of the most difficult trials to recruit for.
One of many reasons is that the oncologists are very protective of their patients and the discomfort that is involved in these assessments, and I want to very strongly make the point about

Page 137

skin biopsy because this may one of the measures that is used.

Clearly, glabrous skin biopsy is uncomfortable, but skin biopsy in and of itself is not. And if we are looking at non-glabrous skin, there are many patients and many controls and many members of my lab who have 5, 6, 7 biopsies and are quite willing to have more. And I'm not at this point suggesting that this is of necessity a measure that we will be using or should be using in a clinical trial, but skin biopsy is not a heart transplant. It's a benign procedure

DR. DOUGHERTY: As long as you're not doing the fingertips, these closed compartments, they're going to hurt, and patients I don't think will sign up for that.

Now, your comment about the clinical trial, we have not -- number one, let me address the issue of the oncologists. Absolutely, I think that a breast oncologist, you're going to have to have real convincing evidence that you're going to improve his outcomes, and they have pretty good

Page 138

outcomes, which is why I asked the question about the GU cancers. The outcomes there are still not so great, and those oncologists, in my experience, are much more interested in getting their patients into experimental paradigms.

So that's where you're probably going to have your best traction is where right now outcomes aren't that great. Where outcomes are really good, then you're going to have more difficulty, and particularly the more difficult you make it on the patient. But as long as the patients aren't put under -- A, number one, don't hurt them because they don't like that obviously.

But at least in our center, there's a lot of down time for the patients. So I have my clinical data coordinators actually meet folks at the door from the parking lot, escort them to their clinic. From there they go to my lab. Then they're escorted to their next clinic so that they almost have their own little personal shepherd and friend there at the medical center. That greatly facilitates keeping people in trials.

Page 139

DR. RICHARDSON: If I may echo, Pat, just echo your point, we did a prospective study. Patrick was a collaborator, and we published in the JCO in 2009 when we looked at bortezomib monotherapy in newly diagnosed myeloma patients, which is a very challenging population because they're newly diagnosed. They obviously require treatment.

We found excellent compliance with not only nerve conduction testing but also the skin biopsy, to your point. And we required that it be just these tiny little punctures done sequentially across therapy. And we saw this neurite fallout with this microangiopathic 6th signal, didn't we, from that analysis, which was quite intriguing, to echo the feasibility on the one hand and on the other hand, the hypothesis around the small fiber question.

DR. DOUGHERTY: Actually, I wanted to follow up on something with your cohort and your experience because in the other cohorts that are susceptible to CIPN, all of those patients are

Page 140

having surgery. Myeloma stands out as one of the few liquid tumors that results in CIPN, but oftentimes myeloma patients will present with a lot of back pain because of all the erosion.

So I am wondering, have you noticed any relationship between a prior history of pain and then a later development of CIPN?

DR. RICHARDSON: Patrick, that's a great question. I was thinking exactly about that because obviously, skeletal [indiscernible] involvement by myeloma is ubiquitous, ultimately, and also, it's uniquely the one heme cancer in which this occurs. You just don't see it in acute leukemia. You don't see it very rarely in lymphoma, the subsets of diffuse large B cell and so on, but it's very rare.

So you're absolutely right. Our patients come in on analgesics of a variety of sorts. Obviously, we have a lot of confounders because steroids are tremendously effective as analgesics in our disease. I was going to take home just what you said because I think that's a very interesting

Page 141

point.
I think from what we see as underlying risk factors, obviously, we see more African Americans affected by this illness, which is interesting to learn about the risk of CIPN from African Americans. We see obviously an older population. So there are all sorts of preexisting factors.
Also frankly, obesity is a risk factor amongst women for myeloma, which is not I think a widely appreciated fact. So there are lots of things which may drive this increased risk for myeloma neuropathy that we see from our therapeutics.
The one thing that I missed in the presentation from the FDA was the failure to include in the list of neuropathic drugs the IMiDs, the thalidomide classically. And also frankly, Revlimid, lenalidomide, has its own neurotoxicity, about 20 percent. I was just interested in why that wasn't on the immunomodulatory section because I thought that was really interesting.
DR. HOWIE: I think it was there. It was

Page 142

intended to be there if it was not.
DR. RICHARDSON: Not an issue, just to say that it's obviously --
DR. HOWIE: But to get back to the combination --
DR. RICHARDSON: -- thalidomide we see the same as well --
DR. HOWIE: Correct.
DR. RICHARDSON: And frankly, I thought what was really interesting was to see the immunotherapeutic size in the IOs having neurotoxicity as well.
DR. DWORKIN: Before we call on Gordon, I hope this doesn't preempt what you're going to say, it seems to me that there is an emerging consensus that if one of the tables in the article that we are going to be preparing from this meeting is research agenda, that it will be worth considering that a major bullet in the research agenda would be to further develop and qualify skin-punch biopsy as a biomarker for clinical trials of CIPN.
At least in my hearing, your question a few

Page 143

minutes ago stimulated that as an important research agenda question.
Gordon?
DR. G. SMITH: I have a very specific question for you, but I want to echo what Roy said about the challenges of recruitment and even studying this patient population.
I think one of the things I've really learned from working with our oncologists is their tremendous dedication to their patients, which is a model for all of us. My father died of cancer, and I learned a lot about the care model in our cancer centers, which is something I often talk about in our neuroscience center as something we ought to replicate. So I think working together is really important.
I do want to emphasize that what Roy said, that non-glabrous skin biopsy is extremely well tolerated, and we've done probably tens of thousands of these. We're routinely doing them now in cancer patients repetitively without any problems, the non-glabrous skin biopsy. Our

Page 144

technician has had, I think, about 150. He does them on himself whenever he needs normal skin. He's maybe not the most normal person.
(Laughter.)
DR. G. SMITH: So it can be done.
The question have is, have you done biopsies on the side of the digit? Jin Lee and Amanda Peltier have both looked at glabrous skin in diabetes and CMT respectively, and I'm told by them it's relatively well tolerated to do 2-millimeter punches viral digit. They at least tell me their patients will actually come back for a second.
DR. DOUGHERTY: Yes. We've done biopsies both in thenar and hyper-thenar eminence. Notably, the counts don't really come out all that different. We did both index finger and the edge of the pinkie finger, and again --
DR. G. SMITH: Like this?
DR. DOUGHTERTY: Yes, about right there. In our experience, the counts aren't that different, and the pain, it still hurts, but at least it's not the folks' index fingers so they can still type at

Page 145

least. So yes, you can move around.
Again, just from a grants perspective, I was always really worried about just that question. Well, where exactly on the finger would you biopsy et cetera? That's why, again, I was attracted to this noninvasive method of measuring because you can use the fingerprint whirls as a modulus. You can come back to the same spot again and again and get those repeat counts. So that was the built-in strategy that I didn't comment about.
But again, it's not entirely clear to me -- and again, Roy brought up the issue of correlating between function.
What I don't have a good correlation to in function is once you move into hairy skin because there, the numbers jump up quite quickly. And if I use the volar surface forearm data, I would have no correlation. So that now pushes this back to the glabrous skin biopsies.
I would proceed with caution pushing the ENFs necessarily because where you will have to go to get repeat biopsies, as has been pointed out,

Page 146

you're going to have to go up into glabrous skin. I agree, biopsying repeatedly in the forearm or down on the calf is not a big deal. It does not hurt the next day. Just don't look at it because it's bloody and I'll pass out, if it's mine. If you're bleeding, it's fine with me. But if I'm bleeding, I'm going to pass out.
(Laughter.)
DR. DOUGHERTY: So that can be done, but I think we would probably need a little more validation initially that would show that within a given spot in a large compartment such as the volar forearm, as folks go through chemotherapy, that those counts drop in a predictable way. Then we would have something solid to move forward with.
DR. BRELL: Another thought might be for -- and I don't know if you have any experience with this, with the chemotherapies that also involve the toes and the feet. If you can biopsy even further down from the calf, maybe around the ankle, it might be closer to the end [ph] terminals and easier to tolerate.

Page 147

DR. DOUGHERTY: We deliberately used the hands, the upper limb, because I was really worried about wound healing issues as you get down in the lower limb. I have no basis other than I was afraid of the idea, and so I didn't want to go that way.
But yes, the calf has been used a lot. Polydefkis at Hopkins has done that, so it should be perfectly safe. We just didn't do it because I was worried that it would be a problem, and we would be shut down by the IRB or somebody. So that's why I picked the upper limb.
But yes, there is data out there. Like I say, folks have done the lower limb. Again, you get down past the calf and down toward the ankle, and you're just getting into a more potentially problematic spot to put a biopsy at.
DR. DWORKIN: Dr. Cleary?
DR. CLEARY: I was going to talk again about the enrollment issue. I think it is a real issue.
I would distinguish between two settings. One is if after the chemotherapy, if after someone

Page 148

develops neuropathy, I think patients will be extremely motivated. I actually think it will be an easy sell, and I think the biopsies, also patients will do, because on a lot of our clinical trials in oncology, we're doing tumor biopsies.
I agree with what Dr. Richardson said, that the biopsies of the skin would be feasible if the patient already has neuropathy.
I think the more challenging setting is going to be if you start the intervention right when the person starts chemotherapy. So for example, if you're starting an oxaliplatin-containing regimen and you start the anti-neuropathy agent at the same time, I think that's a harder setting. It's doable, but it's harder.
The reason it's harder is there's so much going on about explaining to the patient about the oxaliplatin-containing chemotherapy. However, it has been done. There was a clinical trial of vitamin B12 infusions when people got oxaliplatin chemotherapy. So we could talk to that study team about their experience about enrollment. So it has

Page 149

been done.
DR. DWORKIN: Charles?
DR. LOPRINZI: A comment with regards to the skin biopsies. I think it's very interesting from a scientific standpoint and all that sort of stuff, and I wouldn't discourage it in studies, in situations where patients want -- or laboratory investigators or investigators want to do that.
It's not something I would recommend for big intergroup trials for multiple, those sort of things. I don't know that it adds to. If you see something on that and there's symptoms or a function doesn't change, is that really going to make a difference? It's really their function and their symptoms that really are the bottom line.
I think it is interesting, and I could say the same thing about reflexes and neurological component of that. But I don't know want to get into the, oh, you have to do this in all situations because I don't think it's really necessary.
DR. RICHARDSON: Charles, if I could make one comment from our bortezomib experience. We had

Page 150

a multicenter trial, and we enrolled a good phase 2 number, if my memory serves me right, about 50, 60 patients. We were able to do the biopsies on a subset at specialist centers with a neurology team like with Pat and Tony Amato involved.
So that's how we did it. We had a subset, and we very carefully studied 12 patients. And to Pat's point, built a kind of relationship with them, which allowed that to go forward.
To your point, Pat, we actually did them 10 centimeters up, didn't we, Pat, from the lateral malleolus of the leg. People actually seemed to prefer that over the hand. They were a little bit concerned that this would be more challenging, so just to reassure you. And these patients, they weren't on steroids, though. It was bortezomib monotherapy, so they weren't getting steroid-based therapy, but we didn't have any issues with healing.
DR. DOUGHERTY: It's important in myeloma to target the lower limb because that's where the neuropathies emerge common --

Page 151

DR. RICHARDSON: I couldn't agree with you more. That's where the bortezomib neuropathy first manifests itself. You're quite right.
DR. DWORKIN: Roy and then Simon.
DR. FREEMAN: I want to get away from skin biopsies -- I'm sure we'll come back to it again -- and get back to predictors because I think predictors are of potential importance with proof-of-concept trials if you want to recruit a small number of subjects, you want to maximize the likelihood of patients getting a chemotherapy-induced peripheral neuropathy.
Picking up on the point that James Cleary made about there being reluctance of patients to take preventative therapy, true preventative therapy before the emergence of a chemotherapy peripheral neuropathy.
If you want to do such a trial, where there may be a greater likelihood of success, if you were to be before the toxin is given and exerts its effect, one of the ways that one might be able to do such a trial more efficiently would be to have

Page 152

good strong predictors.
Now, Lynn Howie mentioned that there's certain situations in which you, for example, don't want to include those patients in the trial, out-of-control diabetic patients. But again, we had a discussion over tea about this. A controlled diabetic patient may be one that you could consider including.
But we've heard now different views on what might and might not be good predictors, and I want to try and flesh this out a little bit. And I'll start off with your table 2, which was an interesting table. There was what looked to me like a very strong predictor, and that was the nondominant hand working on the grooved pegboard.
Did I read that one correctly? Not the dominant one but the nondominant one.
DR. DOUGHERTY: Yes, at baseline.
DR. FREEMAN: Can I finish the question? It's quite a long question. There's that, and then there looked like there was a really strong sex difference in predicting the peripheral neuropathy.

Page 153

The extent of that being a powerful predictor, I'd never seen before.

So I want you to talk a little bit about that, and then I want to hear from the rest of the panel the views of Guido, who really said that one trial has smoking as a predictor, another doesn't, that a lot of these psychosocial factors are much softer than the biology.

So if we want to conduct an efficient trial, I think we need to know what are the predictors and what are not the predictors.

DR. DOUGHERTY: Right. To your first comment, the slotted pegboard test, that's simply a crude measure of sensory motor function at baseline. Again, that was only at baseline. As patients went on through the trial, in fact, they get better from practice.

As an initial screen, yes, the bumps test, any one of these crude psychophysical tests, or simple psychophysical tests, or the slotted pegboard seemed to be predictive of which group was more predisposed to develop CIPN. That's true.

Page 154

The male and female thing, Joanna and I actually talked about this onside, she has made the same observation. She was asking me what I thought the biology was. I don't think there's any biology there at all. I think men are just better liars than women are.

(Laughter.)

DR. DOUGHERTY: They just aren't tell you that they have neuropathy because they know that if they tell you, you're likely going to cut their dose back, so they're just going to lie.

DR. BRELL: I understand the need to have a very homogenous population. It makes complete sense when doing clinical trials, and we certainly need these predictors. But just about all of the predictors for CIPN are predictors for cancer. So all the gastrointestinal cancers are associated with being overweight. Some African Americans are at higher risk, tobacco.

So we won't be able to accrue very many patients if we don't figure out a way to control for these risk factors because the patients are

Page 155

going to have them, and that's how they develop their cancer.

DR. DWORKIN: Simon?

DR. HAROUTOUNIAN: I just wanted to make a note on the feasibility of the biomarker testing, especially skin biopsy in subsets of patients because we're now doing a clinical trial in pregabalin in chemotherapy-induced peripheral neuropathy, and we do have an optional skin biopsy in the study.

About 50 percent of the patients -- and these are patients who already have developed CIPN -- they would not participate -- that's what they're telling us. They would not participate in the study if the biopsy was an absolute requirement.

I think we might lose about 50 percent or so, maybe depending on the setting, of patients if we make it as a -- just from a patient recruitment, enrollment perspective.

DR. DASTROS-PITEI: From a predictor's perspective, in those CIPNs, which we know that

Page 156

they are occurring in 80 percent of the patients, would you still need to preselect these patients in some way, when we know that 80 to 90 percent of them will develop CIPN within hours of the chemotherapy start?

DR. HOWIE: I think there's a difference between thinking about a high-risk population for developing peripheral neuropathy and thinking about trying to seek an indication for everyone who's receiving that drug.

So I think it depends on what your development strategy is as to how much you want to control for it or not because I think that you can have a strategy where you're saying, in patients who are high risk as defined by X, Y, and Z, this agent works to reduce the risk of chemotherapy-induced peripheral neuropathy. It's just how that development strategy is being pursued.

DR. DWORKIN: Charles, did you have a question?

DR. LOPRINZI: You do want a uniformed group of patients. If you have a very small group, then

Page 157

you have to have them fairly uniform. If it's a bigger group, it's a randomized design, that takes care of most of the things. And I can give an illustration of that in a moment. It depends on how long I go for this part.

But that will take care of it, and then you can stratify it because there are only so many things the statistician will allow you to stratify because of how many groups you have, then you pick the most important of them.

Let me give this quick example. We had patients with anorexia-cachexia years ago, 450 patients on a clinical trial, all sorts of different cancers, all sorts of different stages of their disease. They had advanced -- they had at least four months survival, and they had anorexia-cachexia. They were losing weight. And we randomized them to megestrol acetate versus placebo on them.

I wanted to see whether or not we could see in a situation like that whether the drug we're looking at might affect survival. So I asked the

Page 158

statistician to take all these patients, regardless of what they were getting, and just break them up into group A and B, and do that 20 times, and give me survival curves for the apples and oranges and all that stuff, all sorts of different cancers.

In fact, they did 20 times, and the survival curves were not statistically different in any of them, and my statistician said I can do that with bootstrapping and do it 10,000 times. I said, okay, thank you, do that. And the number of times these curves were statistically significantly different from each other with these varied groups of patients was 5 percent, p equals 0.05. That was without stratification.

If we threw in the stratification factors that we had figured out for these patients from the study, it dropped it down to 4 percent. So if you got the randomized design, it takes care of it if you have reasonable numbers of patients, and then adding your stratification helps a little bit more.

DR. DOUGHERTY: Charles, the basic assumption there is that you're going to do

Page 159

hundreds of patients.

DR. LOPRINZI: Well, this was one of 50 patients on this particular trial, but with a couple of hundred patients, I think you could see the same sorts of things in there. But the point is the randomization will take care of it. It won't do it for a 5-patient study or 20-patient study or 30 or 40 or 50, but if you're going to do these sort of studies and you're going to do a placebo-controlled trial, you probably need 100, 200, 300, 400, 500 patients. If you need 3,000 patients, then it's not enough of a difference to make a difference there.

DR. DOUGHERTY: No, my point being, you're making a trial now so ridiculously expensive, it can't be done. I mean, that's going to cost -- well, we could add that to the national debt.

DR. LOPRINZI: I think if you're going to do a randomized placebo-controlled trial for these things for prevention and whatnot, you're talking about 100, 200, 300 patients. I think that's

Page 160

ballpark. I'm not a statistician, but the experience has been you need that. You don't need 20 patients. You don't need a thousand patients.

DR. DOUGHERTY: But 100 is completely differently powered than 2 or 3 or 400. As you're quickly scaling, the dollar signs are ka-ching, ka-ching, ka-ching.

I think I would focus on a more homogenous smaller trial than just -- and I do agree with you. If you have enough patients, you can control for everything because it will all homogenize, but for some sort of a potential therapeutic, it's going to have to be a fairly focused, I think, very homogenous group.

DR. LOPRINZI: If you go that route, you say this has got to be patients between the age of 30 and 40 because older age have that, and they've got to be blond, and they got to be this and this and this, then you've got this drug that fits for this and doesn't fit for anything else. You got to use some common sense in there.

What we've utilized in ours is no

Page 161

neuropathy, no past neuropathy. On several of our studies, we have allowed them to have diabetes as long as they have no neuropathy from that, and then there are a bunch of other criteria in there, but it's not that hard to do that.

DR. DWORKIN: Our next question or comment is from the only person who's done a successful trial in CIPN of that size, Ellen.

DR. LAVOIE SMITH: I was just going to comment on, again, thinking about predictors and risk factors, and first of all, to remind us that those risk factors will vary based on whether we're talking about neuropathy or pain.

In our duloxetine study because we were using a drug to target central nervous systems mechanisms in a population with chronic pain, we did stratify by diabetes and did not exclude that population, and found no differences in the end result.

So is that because the pathophysiologic mechanisms of diabetes -- I don't know enough about this. But is there a central effect of diabetes,

Page 162

or is it more peripheral? So if it's more peripheral, then the fact that somebody has diabetes shouldn't influence whether or not we get a central nervous system mechanism related effect.

Depending upon the outcome, depending upon what we think the underlying pathophysiology might be, whether or not we worry about certain predictors may be more or less important.

DR. DWORKIN: Personally, I agree that I wouldn't expect diabetes to moderate the treatment effect of duloxetine in a CIPN clinical trial.

DR. LAVOIE SMITH: That's right.

DR. DWORKIN: What I worry about, though, it sounds like surprisingly Roy is a little less worried about it, is if you're assessing not only pain but the peripheral neuropathy in the trial, is there going to be some confusion in your endpoint between patients who've got symptoms associated with their DPN versus their CIPN?

But that's a completely separate issue than addressed by your stratification. That's a question of whether clinical or subclinical DPN in

Page 163

the sample of patients affects your assessment of what your primary endpoint is, which is CIPN.

DR. LAVOIE SMITH: We stratified because we thought that that was going to be an important concern, that if we didn't think about diabetes, then that might be a limitation, so that's why we did it and found no difference.

I guess what I'm saying is that it's an argument that supports depending upon the design and the outcome and the mechanism, that a predictor, we just have to think about them carefully and not exclude patients because they have diabetes if it's not really relevant.

DR. HERTZ: Bob?

DR. DWORKIN: Sharon, yes.

This is Dr. Sharon Hertz, who joined us late. Dr. Hertz is the director of the Division of Anesthesia, Analgesia, and Addiction Products at FDA. Sharon?

DR. HERTZ: Thank you. Sorry for the late arrival.

Just getting back to the diabetes thing, I

Page 164

guess I have a few more questions, though, because what I can imagine with a drug like duloxetine and a situation with diabetes is it depends on the extent of the diabetes, the duration, any evidence of preexisting symptoms prior to initiating the chemo.

I would think it would be potentially possible to include these patients, but it sounds like it could, at least for a symptomatic trial as opposed to a disease modification based on mechanism trial, it could just add background noise. Because duloxetine is already approved for the symptoms of diabetic neuropathy, so if nothing else, it just might add some background noise and reduce your sensitivity to detecting the signal specific to the CIPN.

It's interesting that you were able to detect the signal regardless, and so that's just an interesting thing. And I'm just wondering, were there constraints around the type or extent or control of the diabetics in your study?

DR. LAVOIE SMITH: We allowed patients to

Page 165

participate if they had asymptomatic, so they didn't have -- they may have had diabetes, but they didn't have symptoms at baseline. It might have been, again, a question of degree, right? If we had included people that had symptomatic diabetic neuropathy, then maybe our outcomes would have been diluted.

DR. HERTZ: Did they have any baseline electrophysiology, F waves, anything like that?

DR. LAVOIE SMITH: No.

DR. HERTZ: No?

DR. LAVOIE SMITH: No.

DR. DWORKIN: Dr. Cleary?

DR. CLEARY: Getting to trial design, the one trial that I'm aware of that's looked at FOLFOX is infusing -- was a phase 3 placebo-controlled trial looking at calcium infusions before and after FOLFOX, trying to see if it lessened the neuropathy.

Similar to a point made before, it was a large study. It was 353 patients. Unfortunately, it was negative, but it just shows that these

Page 166

trials to get statistical power are going to have to be large.

However, getting to your point, I do think small studies are useful, and maybe talking about what Dr. Richardson was talking about before, in those smaller studies, that's where we could do the biomarkers with the biopsies, whereas with these larger studies, we wouldn't do the biopsies. We would just really try to see if there was a signal or not a signal.

DR. BRELL: I think we're talking now about experimental design and trying to find answers, and we need these very involved, very complex trials testing a multitude of things. But at the end of the day, we're going to have to take these activities that we're using to assess the patients and try to correlate them with something that can be more readily done in the clinic and more readily done in a phase 3 trial.

That's going to take a lot, but just for the clinical trial's sake, we need the complexity. But we'll have to dampen that down when it eventually

Page 167

goes to the community.

DR. DWORKIN: To some extent, Dr. Cleary, the way I think about this is I use clinical trials in relapsing and remitting multiple sclerosis as an example, where the phase 2 trials are smaller and use MOI [ph] endpoints, and the phase 3 trials are substantially larger, longer in duration and have clinical endpoints.

Going back to Gordon's initial question, is there a possible role in phase 2 for the biomarkers in developing treatments for CIPN, but then later on, the larger trials would look at the clinical endpoints.

DR. CLEARY: I completely agree. We're doing the same thing in oncology where we're doing tumor biopsies to see if the drug's hitting the cancer target in small phase 1 and phase 2 studies, but in a large phase 3 study, we're not doing biopsies just to help accrual.

DR. DWORKIN: Gordon?

DR. G. SMITH: Yes, I was going to make that same point, so I won't make it again. But I do

Page 168

want to make a somewhat different point that touches really on the intersection between biomarkers and PROs.

We, for instance, are in the midst of a multicenter lifestyle-based trial for diabetic neuropathy, and one of our primary outcome measures is a patient-reported outcome measure. But you can imagine that there are probably multiple different ways that a lifestyle-based intervention may mediate a change in the PRO.

In this setting, we're using a biomarker in the statistical analysis that's way beyond my comprehension to understand the mechanism by which the intervention may mediate change in the PRO. Is it through the change in biomarkers, or is it through other salutary effects of exercise?

DR. DASTROS-PITEI: If the biomarkers are important perhaps at the proof-of-concept stage, in the early stages of identifying drug effect, when we move forward, I think to the point about diabetes, I think the diabetes point is actually beyond that. I think the other factors that may

Page 169

influence may add noise to the study design.
Would you feel that excluding other neuropathies, not only diabetic but of other causes, will be sufficient to reduce that noise, let's say, in the mid stages of development or later on?
DR. FIELDS: I think in general in these trials to avoid the noise or confusion, we do exclude patients with other neuropathies.
DR. DASTROS-PITEI: That's what I'm thinking, that by using neuropathy at baseline, presence of neuropathy at baseline of any other cause before the CIPN has occurred --
DR. FIELDS: That would be excluded --
DR. DASTROS-PITEI: -- they would come out of the trial from the beginning?
DR. FIELDS: Yes.
DR. HERTZ: It depends. It depends what you're looking and where you think the target of the drug is. So if you have something that wouldn't impact other neuropathies and you're going to be looking at symptoms that are responsive or

Page 170

other outcomes that are responsive to that intervention, then you can decide whether or not you need to cut down on that, if it would be relevant to actually create noise or not. If it's something more nonspecific, then that depends on how much you think you have a noise issue and a sick detection issue.
Clearly, it can be done with patients who have diabetes under some constraints, and we don't know how far one can push that in terms of the extent of potential overlapping diseases. I don't think that there's a clear answer yet.
DR. DWORKIN: Guido?
DR. CAVALETTI: Related to this point, maybe it's naive, but how would you suggest to screen patients for having or not having a neuropathy, to which extent we have to investigate those patients? On a clinical basis done by a neurologist, by an oncologist, on a biopsy, on a history, on the fact that they consume alcohol? It's not so easy probably.
DR. LOPRINZI: I think there's a difference,

Page 171

too, in terms of I think you said you would clearly exclude people who have neuropathy from something else, but not people who are at risk for such as age, and not exercising, and drinking a bit of alcohol, and diabetes. But if they have diabetic neuropathy -- and most of us in practice have done it by history and examination. We don't biopsy every patient that comes in to prove that they don't have these sorts of things.
I think that's what's going to be in practice at the end of the day when you have a drug that you're going to use for prevention of, or treatment of, eventually you're not going to go and say we got to biopsy to make sure you don't have anything before I give this to try and prevent it. It's just not feasible.
DR. CAVALETTI: No, Charles. I understand your point. My question was a little bit provocative because of course, I can't screen a patient, I understand, if he has a neuropathy or not.
My question was, which is the level? Is it

Page 172

only because he is at risk? No, this is the answer. It's not just because he's at risk. But how many patients aged 70 or 65 with some impairment in the reflexes, has a neuropathy? Is it just aging?
So again, I'm not really convinced that being too strict in the enrollment of this population would really improve the quality of the data. I think if someone is clear in neuropathy because he has -- let's say in retinal neuropathy that is well known, of course, I wouldn't include it. But I think the priority, we need to stay a little bit closer to real life.
We have a lot of patients 70 years old, no reflexes, it is not a disease. It is not a neuropathy. It's just age. So I think we should have a very clear idea of what we consider a patient with a neuropathy before stating that we don't want to enroll patients with neuropathy in a clinical trial on CIPN.
DR. HOWIE: I'll defer this to further discussion from the COA group, but it may be, too,

Page 173

that having baseline assessment and having that patient be their own control can help better understand the actual effect of the drug.

One of the things about PROs in the cancer space is that cancer patients have a lot of symptom burden regardless of what the treatment is, and so to figure out what the change, if any, in symptom burden is due to the anti-cancer therapy, you have to know what the symptom burden was to begin with.

That's been one of the big issues about PROs in the oncology space is trying to figure out what's the baseline symptomatology, what's the effect of the drug, and then what's the unfortunate effect of the progressive disease.

That is still a work in progress, but I think that if you're thinking about potential heterogeneity among the patients as far as their baseline risk, knowing what the intrapatient change is might be helpful.

DR. DASTROS-PITEI: Even before the injury occurs, so at least you know what these patients have come in into the study before, let's say, the

Page 174

chemotherapy induces the chemotherapy-induced neuropathy, right.

DR. HOWIE: Right. That may be as simple as filling out their symptom assessment sheet, which is the endpoint.

DR. LOPRINZI: Whenever you're using PROs, you always get it at baseline and at follow-up, not just at follow-up. You want change from baseline.

DR. DWORKIN: We have time for two questions. Simon first and then Jen.

DR. HAROUTOUNIAN: I was just wondering what an appropriate screening tool for that would be. Is it a quantitative sensory testing short battery? Is it a questionnaire? Is it a simple neurological exam? What might meet the level that we want to assess at baseline and then look at follow-up?

DR. HOWIE: We don't make any recommendations. What COA typically does is the researchers or the sponsor comes forward with a proposed plan and gives advice based on that.

DR. DWORKIN: This is a hugely challenging question, Simon. Roy and I were smiling at each

Page 175

other.

I'm convinced as a non-physician that Guido's assessment of the 70-year-old patient he just described would end up in a different place than a non-neurologist doing an assessment of that patient than a 23-year-old study coordinator hired out of college to work on clinical trials.

I think we could talk for hours about study execution issues just with respect to your question of how do you evaluate whether there's a peripheral neuropathy in a patient who's being recruited for one of these studies. We don't have the time for that before lunch.

Jen, you get the last word, last question.

DR. GEWANDTER: My comment is related. I was just going to say that I think that's a very hard question, but obviously, excluding people who have the symptoms that are included in your outcome I think we probably can all agree is a good idea. Like if the patient presents with numbness and tingling already, then we would want to exclude them.

Page 176

DR. HOWIE: Even endpoint is going to change based --

DR. GEWANDTER: Yes. And I think that if they have the symptoms already that you're going to look at, then it's going to be confused by -- but if they have a deficient reflex, which I think we would argue that the 23-year-old in the trial is probably not going to be able to find necessarily accurately, that might not necessarily reflect a confusion in the outcome that we're interested in like numbness and tingling, potentially.

DR. CAVALETTI: I'll just make a brief comment. Of course, when we decide to include or not the patient with neuropathy, we have two major concerns. One is quite easy to be solved. I would not include a patient with something that makes me difficult to understand if something has changed, and that's very clear.

The big issue is not this one. The big issue is, is this patient exposed to a higher risk or not? If Pat's results are correct, we have a population that can be screened in theory because

Page 177

they have a different risk of developing the CIPN, the more serious CIPN.

My question was based on that. If we use very, very strict criteria to include patients within these trials, we accept the risk of probably leaving out of the trial those patients with a higher risk of developing CIPN.

Again, my suggestion is to be not too strict in enrollment criteria for these kind of things. If a patient has no story and no symptoms, who cares about the fact -- we would randomize those patients, and of course -- this is another point raised by Charles -- we need to run fairly big sizes, unfortunately. This is not good news because it costs.

But again, if we have 55 years -- that's right, Joanna. If we are 55 years later here talking about which is the best way to screen patients, which is the best way to assess, which is the drug, probably we have not a simple problem to be addressed. That's probably the point.

DR. DWORKIN: Thank you very much. It's an

Page 178

excellent challenge for us to think about over lunch. We have a one-hour lunch break. I don't know where it is.

Valerie could you -- mezzanine where we had dinner last night. We'll see you all promptly at 1:00.

(Whereupon, at 12:04 p.m., a lunch recess was taken.)

Page 179

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

(1:16 p.m.)

DR. FREEMAN: Let's begin the afternoon. It's a pleasure to introduce my co-chair, Jennifer Gewandter, a pleasure not just because you're going to hear a great talk, but also as you all know, she's done all of the backbreaking work putting this meeting together, and we all owe her an enormous amount of thanks just for that.

Jennifer is an assistant professor at the University of Rochester School of Medicine and Dentistry, and why don't you come up, Jennifer?

Presentation – Jennifer Gewandter

DR. GEWANDTER: Thank you. Thanks, Roy, for that introduction.

Today I'm going to cover the methodological challenges of studying CIPN during chemotherapy. So I'm not going to discuss the trials that Dr. Horn mentioned that would occur after the end of chemotherapy.

Today for my talk, I have three main goals. First, I'm going to outline the design challenges

Page 180

and issues to consider when designing a CIPN study during chemotherapy. Next, I'm going to summarize how published RCTs have addressed these design challenges in the past, and finally, propose topics for our design discussion.

These are the main challenges as I see them. First, you have to pick from one of multiple trial objectives. Second, as we've had some discussion already, you have to choose your eligibility criteria. Then you have to decide how to measure CIPN and turn those measurements into trial endpoints. And then also even though are some data available for the epidemiology and natural history of CIPN, these data are limited, and we have to think about how that can affect our studies. And finally, some specific challenges for the analyses of these trials.

There are four general categories of objectives for CIPN studies during chemotherapy. You can do a primary prevention study where you initiate the preventive treatment before chemotherapy starts. You can do a secondary

Page 181

prevention study where you initiate the treatment after the start of chemotherapy but before any CIPN symptoms are detectable. You can do a tertiary prevention study where you initiate the preventive treatment after detection of early neuropathy signs or symptoms in order to prevent them from worsening, or you can do a symptomatic treatment trial where you're treating established CIPN symptoms.

Now, in regards to the prevention studies, I think we've covered this a little bit already today. It might be a little bit logistically easier to do a secondary prevention study than a primary prevention study, and a tertiary prevention study could have higher power with fewer patients. But both secondary prevention and tertiary prevention studies could potentially miss the therapeutic window that a primary prevention study would hit. So these are the things we need to consider when deciding between these objectives.

What have the currently published RCTs done? We did a systematic review of randomized controlled

Page 182

trials of pharmacologic treatments for CIPN that were used concurrently with chemotherapy, and they also had to be focused mainly on CIPN to be included in our review and published before November of 2015.

We identified 38 RCTs. Thirty-six of them had some kind of prevention design. Twenty-three had a primary prevention design so the treatment was initiated before or on the same day as the chemotherapy. In 10 of them, the exact timing was not clear, but there was no indication that CIPN symptoms had appeared prior to treatment.

In one of them, the timing was described as "as close as possible to the beginning of chemotherapy," in another, "ideally before the first cycle but required to be before the second cycle," and finally, "within four days of the first dose of chemotherapy."

In these trials, there could be a mix of populations, or a mix of objectives. So some patients could actually be getting primary prevention and some could be getting secondary.

Page 183

Then there were two symptomatic treatment trials.

The next challenge is eligibility. I think we covered this quite a bit today, but the way I think about this is that we're trying to balance the feasibility of recruitment and the generalizability of the study results with the internal validity of the study, so the ability of the study to give an accurate effect estimate of the treatment for the population that was included in the study.

For all trials of CIPN during chemotherapy, this can be particularly challenging because, as we've spoken about today, there are multiple cancer types. There are multiple chemotherapy types, and within those types, there are multiple agents. And within those agents, there are multiple dosing regimens, and all of these things can create variability in our outcome measures.

You also have the question of early stage versus metastatic, which we've also addressed. On the one hand including only patients with metastatic chemotherapy could be good for earlier

Page 184

studies where we have a safety concern, but on the other hand, if you include patients with metastatic cancer, they're more likely to discontinue the study or their chemotherapy treatment for reasons other than neuropathy, which can hurt the study.

Then something we've talked about a lot, should we include patients who have other conditions that are associated with neuropathy like diabetes, alcoholism, or HIV? Should we include patients who had prior exposure to neurotoxic treatments whether it be cancers or chemotherapies or HIV treatments but don't have any symptoms associated with neuropathy yet?

Finally, should we exclude concomitant treatments for neuropathy, and if we do decide we want to include them, what are they? We don't really know for sure, so how would we define that group of treatments?

What's been done so far in the literature? As far as the type of cancer, a lot of the studies include only one cancer type, so all of these, with the most common being GI cancers, then the

Page 185

remainder of the studies included either two cancer types or multiple cancer types.

Interestingly, 40 percent included both early and advanced stage cancers, and 21 percent included only advanced cancers. The remainder of the articles did not say what stage cancers were included in the studies.

For treatments, 60 percent of the studies used platinums only, and this is not a big surprise given the majority of the cancers that were studied were GI cancers. Then I'm not going to read the remainder there, but you can see that there were some studies that used multiple different types of chemotherapy in the same study.

One thing that I found interesting was that 40 percent of the studies specifically stated that they included only 1 regimen, and what I mean by regimen is 1 dosing paradigm. Those were the results for the chemotherapy and cancer-related exclusion criteria.

For the neuropathy-related exclusion criteria, just like I think we all agreed on in the

Page 186

discussion, over 80 percent of the studies excluded patients with preexisting neuropathy. Then the studies were half and half split whether they allowed patients to have diabetes or not.

Approximately 40 percent excluded neuropathy treatments, and that ranged in the studies anywhere from a list of drugs like anti-epileptics, antidepressants, and vitamins to a statement saying something like patients who are on drugs thought to alter neuropathy were excluded.

The other exclusion criteria that occurred commonly in the studies were previous neurotoxic chemotherapies, previous chemotherapies of any kind, alcoholism, and a minimum life expectancy as well as previous radiation therapy.

That applies to all studies for CIPN, and then for studies in which the goal is symptomatic treatment, you have to define what you mean by CIPN. So we talked a little bit about this earlier as well. Can you define CIPN using an assessment tool, or do you need a clinician diagnosis? If you are using an assessment tool, who can administer

Page 187

it? Do you need a neurologist? Can it be another clinician? Could it be a research assistant?

Also, when are you going to assess CIPN in relation to chemotherapy treatment? Are you interested in the acute-type symptoms that we heard talked about this morning, or are you interested maybe in the cumulative symptoms that increase over time with cumulative dosage of chemotherapy? Those would be measured most likely before a dose of chemotherapy.

Then how in relation to the enrollment in the study, when are you going to measure them? If you detect neuropathy if you're interested in acute symptoms, do you treat people right away, or would you wait till the next cycle?

Also, do you have a minimum severity requirement for CIPN or just the presence of CIPN? If there is a minimum severity requirement, which symptoms are you interested in? This will very likely be determined by what the primary outcome or primary endpoint is of your trial.

There were only two symptomatic treatment

Page 188

trials, so we don't have a lot of examples to go by in the literature in terms of the studies that were conducted during chemotherapy. But in one study, they included patients who were reporting a distressing acute neurotoxicity after administration of their oxaliplatin-based chemotherapy, and in the other study, they were including patients who had greater than or equal to 3 out of 10 on either pain, numbness, or tingling scores.

Measurement is my next challenge. For all trials of CIPN, I think we all know this, that there is a lot of variability in between patient symptom and sign presentation, and this occurs even within one type of chemotherapy.

I've listed a few of the symptoms here, but as you all know, there are more. The challenge really is taking this amalgam of symptoms and turning it into one primary outcome measure that is clinically meaningful and sensitive to change.

I'm not going to talk very much about this because we are having a session tomorrow dedicated

Page 189

to outcome measures, but one thing that I will bring up to think about is just this idea of should we be including composite measures that include symptoms and signs, or both, and should we potentially be trying to think about targeting to only a few symptoms if we think our drug could work for those symptoms.

For example, an easy and obvious one is if we have an analgesic that we know works for pain, in other conditions, we would probably think about maybe making pain our primary endpoint for that trial. But in the future, potentially we'll have things that maybe would target numbness, and if that's an important symptom, it could potentially ease our measurement if we could focus on that.

I'm just listing here, these are the primary outcome measures 22 of the studies identified one that were used in the trials that we reviewed. Really, the take home message here is that it's all over the place. There really isn't a consensus on what we should be using for CIPN in measurement.

We have at the top clinician- or

Page 190

patient-reported symptom or function interference measures, and then clinician-reported symptom and sign measures. There were a few studies that based their primary outcome measure on sign measures only, and then there was one study that looked at the receipt of 6 cycles of chemotherapy without significant peripheral neuropathy as their primary outcome measure.

One other thing I wanted to mention, other than outcome measures, it's important to think about the variability that can be introduced into the severity of CIPN measurements because the severity depends on the type of chemotherapy, the cumulative dosage of chemotherapy, the timing of the dosing regimen, as well as the time since the last dose of chemotherapy.

The times since the last dose of chemotherapy can be affected by dose delays and discontinuations, as well as the scheduling of assessments, so how precise you are when scheduling your assessments.

Obviously, a lot of these things are

Page 191

dependent on the number of different chemotherapy regimens that you include in the study. If you only include one chemotherapy regimen, you might be able to decrease a lot of these issues that would complicate measurement of CIPN.

The one thing that we can control in our studies fairly easily is the scheduling of the assessments. What has been done in the past, 9 of the prevention trials reported the timing of the assessments in relation to chemotherapy; 7 of them made the assessments prior to the chemotherapy doses; and 2 of them made the assessments on very specific days after the chemotherapy doses. That was also done in the one symptomatic treatment trial that reported the timing. The rest of the studies did not specify when their assessment were made.

I'd like to emphasize that this doesn't mean that they weren't specific about it when they did their study. It could just be not super great reporting. But it does highlight that it's really important to be specific and consistent so that

Page 192

you're measuring the same thing all the time and we don't introduce too much variability in the outcomes.

After measurement, we have to decide how are we going to use those measurements and how are we going to turn them into trial endpoints. This is a challenge in prevention studies because there are a lot of options. We can use a neuropathy occurrence measure, we can use a neuropathy severity measure, or we can use how much chemotherapy is received as a measure.

Then, for example, just within the neuropathy severity category, you could measure it at a specified cycle number, at a specified time point after the initiation of chemotherapy, at a specific time point after the completion of chemotherapy, and over a summary of multiple time points during chemotherapy. So there are a lot of different options to choose from.

When trying to decide between these different endpoints, we should consider things that might introduce variability or affect the power of

Page 193

our analyses.
Just to give a couple of examples -- and this may be a little less relevant if we're only going to be including one regimen in our studies, but in studies that don't include only one regimen, there's variability in timing of the chemotherapy dosing. This will likely have more of an effect on outcomes that measure severity of neuropathy than those just look at occurrence of neuropathy by the end of chemotherapy. But then if you want to occurrence of neuropathy by the end of chemotherapy, you have to consider that that's a dichotomous endpoint and could potentially have lower power.
In another example, regardless of the endpoint you'd choose, if a lot of patients discontinue their chemotherapy due to causes other than neuropathy before they get neuropathy, your trial's likely going to have trouble detecting a difference between the groups.
If a lot of people discontinue due to neuropathy, then a neuropathy occurrence endpoint

Page 194

or an endpoint that looks at the amount of chemotherapy received won't be affected by these discontinuations at all, but on the other hand, endpoints that look at severity at a particular time point could be affected because the time between when the patients discontinue chemotherapy and the planned time of assessment of their severity, the severity of their neuropathy could change drastically.
These are just a couple examples that I have given here, but these are the types of things that we need to think about when we're deciding and we're planning trials and when we're making recommendations about which endpoints are the best for these types of studies.
What was done in the past? Again, just like with the outcome measures, the types of endpoints are all over the place in these studies. Occurrence of neuropathy by the end of chemotherapy was the most commonly used endpoint, and then one study used a time-to-occurrence endpoint.
Then most of the remainder of the studies

Page 195

used some type of severity either at completion of chemotherapy, or a specific cycle, or a summary of multiple time points. Then one study each looked at severity after a specific time point after initiation of chemotherapy and after completion of chemotherapy. Then again, there was that one study that looked at the number of patients who received 6 cycles as their primary endpoint.
For symptomatic treatment trials, it's a little bit less complicated. I can think of fewer options for the endpoints. So obviously, you can look at severity at one or multiple specified time points after chemotherapy infusions or before chemotherapy infusions. You could look at the percentage improvement in symptoms, and this could either be from the time you initiate the experimental treatment or potentially relative to a previous chemotherapy dose where no experimental treatment was given.
For both of these options, you could look at these endpoints after either a single dose of chemotherapy or over multiple doses of

Page 196

chemotherapy. If you look at these endpoints after only a single dose of chemotherapy, you eliminate a lot of the issues that come up with chemotherapy discontinuations or the variability in dosing regimens, but on the other hand, it might be more clinically meaningful to look at the treatment over multiple chemotherapy doses. At that time, you really have to think again about some of these other issues that I mentioned when discussing prevention endpoints.
The next challenge that I'm going to talk about is the limited epidemiology and natural history data that we have. In order to conduct prevention trials, it's really important to have a good understanding of the natural history. This is important when you're choosing what endpoint you want to use, and it's also important when you're deciding how big the studies have to be.
Unfortunately, our neuropathy incidence rates by cancer and chemotherapy type are not that reliable. There's a lot of variability. This is probably because the studies often use inconsistent

Page 197

CIPN measurement tools, and the question is whether these estimates will be useful when we're using different assessment tools potentially in our study. So better understanding of the natural history would really help us in planning our studies.

The other thing is I know a lot of oncologists will say that patients will discontinue chemotherapy due to their neuropathy, but I have not been to find any actual data that give those rates. If you want to make the endpoint of your study whether or not someone finishes chemotherapy or dose reduces, it's really important to know how many people are going to actually discontinue chemotherapy. Obviously, this is going to be different depending on which population of patients you're including, which type of cancer and what stage of cancer. A better understanding of these things would really help us.

Finally, for all trials, not just prevention trials, I think we all know that CIPN affects the quality of life of patients, but there actually is

Page 198

little data out there in the published data that helps us understand which symptoms are the most important to patients. If we had some more data on this, it might help us design our primary endpoints to be things that would be the most likely to be clinically meaningful to patients.

The final challenge is in the analyses. For all trials of any type, we have to accommodate missing data from participants who discontinue a trial, and this is always a challenge. But an extra challenge in CIPN studies comes from the fact that the neuropathy-causing agent or the chemotherapy is sometimes altered after randomization, and it can also be affected by the experimental treatment.

We have to figure out how do we deal with participants who discontinue or delay chemotherapy in the analyses. So what if someone discontinues their chemotherapy, but you're still able to assess their neuropathy or follow them? So they haven't discontinued your study, but they didn't get the chemotherapy that you thought they were going to

Page 199

get in the beginning.

How have people handled this so far in the published literature? There were 9 prevention studies that indicated how they handled this. So in 6, patients who didn't reach a minimum cycle number or cumulative dosing of chemotherapy were eliminated from the analyses. In 2, patients were eliminated if they didn't complete the planned chemotherapy all the way up to the time point of the assessments, and then 1 study used a summary statistic that was prorated for the number of chemotherapy cycles received.

In the symptomatic trial that indicated how they handled these participants, the participants who discontinued chemotherapy before they achieved what they called a responder status, which was the endpoint, were called non-responders.

I've covered all of the challenges that I see or that I think of when I think about designing these studies, and now I would like to outline the things that I'm hoping we can talk about in our discussion.

Page 200

Our first goal is to establish recommendations for the eligibility criteria related to the following things on the slide as well as other things that you guys might think of as well. We covered some of these already, but I think it's probably worth revisiting.

I just wanted to note that I think these recommendations might be different depending on the study objectives.

Second, we'd like to create a list of recommended endpoints, including the advantages and disadvantages of some of these endpoints, and potentially create a roadmap of future research that can support our recommendations or help clarify them.

Finally, we'd like to create recommendations regarding how to handle participants who prematurely discontinue chemotherapy. For example, I'd like to discuss the following possibilities and their merits. Obviously, including all participants are randomized regardless of the chemotherapy they received, that's a traditional

Page 201

ITT analysis, and that obviously will prevent us from getting a biased estimate, but if a lot of participants discontinue before getting a reasonable amount of chemotherapy to get a neuropathy, this could make it difficult for us to detect a true treatment effect.

So is it reasonable to remove participants who don't receive a minimum cumulative dosage of chemotherapy? And if that's reasonable, how do we define what that minimum dosage is?

Would it be reasonable to adjust for the amount of chemotherapy that has been received or not? Which of these are reasonable as primary analyses or potentially only as sensitivity analyses? And if they're identified only as sensitivity analyses, what would that mean to the FDA in terms of an indication? Would that be meaningful to them?

With that, I'll end here, and I'd just like to thank the people who helped me put the talk together, especially Roy and Bob really had a lot of input on how to get everything in my brain in a

Page 202

hopefully potentially clear manner. And the rest of the people listed here are co-authors on the systematic review that we've submitted for publication.

(Applause.)

DR. FREEMAN: Wasn't that a wonderful talk?

What we will do is now have two of the three discussants, third discussant Yan Zhou is here as an observer, not as a discussant for reasons beyond my capability of understanding.

You will explain that to me one day, won't you?

The first is going to be Scott Evans, who is a senior research scientist at Harvard University. I'm getting the other way around.

The first is going to be Mike McDermott, who is a professor of biostatistics and neurology at the University of Rochester Medical Center, Rochester, New York. He's spoken at these meetings many times, and he and Scott are probably the only two statisticians in the world who give entertaining talks, so we look forward to this.

Page 203

(Laughter.)

Presentation – Michael McDermott

DR. McDERMOTT: Roy has just set you up for disappointment, that's for sure.

(Laughter.)

DR. McDERMOTT: These are some of the things that Jen mentioned that I'm going to focus on for just a few minutes. Outcome measurement is going to predominate what I talk about because that's really, I think, the hardest thing to think about in these studies. I'll say a little bit about some strategies for analysis and maybe just a little bit about defining the population, but we've talked about some of those issues already.

When thinking about how to define outcome for people, I think that it's important to try to think about what really constitutes success for treatment for an individual patient, and there are many different things to think about. Certainly, absence of neuropathy would be fantastic, having less severe neuropathy, less time with neuropathy, less time with important neuropathy, the ability to

Page 204

complete your chemotherapy regimen without interruption and with minimal discomfort, or even going a bit further than this, having a good response considering both the neuropathy outcome and the cancer-related outcome. Those are some of the things to consider.

When I first spoke with Jen about this, I haven't worked in this area at all before, she was explaining some of the complications that she just discussed. One of the things that occurred to me at first was, well, it seems that you are concerned about not only the neuropathy but how is the patient going to be doing overall clinically. And part of that, of course, is how they not only complete the chemotherapy but respond to it perhaps, too. So is there some way of integrating all of that information into some sort of composite outcome?

Now, I suspect that people don't consider the cancer outcome so much because it's sort of an off-target effect, one could argue, and one might expect if you have a neuropathy treatment to have

Page 205

minimal effect on that dimension of the outcome. But on the other hand, chemotherapy success is arguably more important to the patient so that it could be that a composite that incorporates both of those dimensions is useful.

I'm going to talk mainly about some ideas about incorporating the interruption or discontinuation of chemotherapy with other measures of severity, and Scott Evans, who is going to follow me, will talk also about some ideas for combining information from different aspects of this.

One of the things that I have been thinking about is this notion in a prevention trial of -- and this is very common -- time to an important event occurs. And time to neuropathy has been used in some of these trials and arguably is an important outcome to consider.

How meaningful that is depends, of course, on how severe I think the neuropathy is that you're preventing. So if somebody is going to develop neuropathy but it is relatively mild and transient,

Page 206

preventing it isn't the end all and be all, perhaps. On the other hand, if it's going to be very severe or it's going to persist for a long time, then it would be very important to prevent.

I will talk about in a few minutes how I think that continuing to follow the severity of that neuropathy even after it occurs might be important to consider in some of these trials, even if you're talking about prevention trials.

Also, presence or severity of neuropathy in at a fixed time point or selected time point after chemotherapy, I think may not adequately account for the duration of the neuropathy symptoms or the overall severity of the neuropathy throughout the course of chemotherapy.

Looking at neuropathy at a fixed time point or at very few time points, I am not sure is going to capture everything that one would want to capture, either. So in my mind, I think that we should be thinking about considering both severity and the duration of neuropathy throughout the course of the chemotherapy whether it's a

Page 207

prevention trial or a trial of treatment.

So the outcome of something like area under the severity time curve in that sense appeals to me, that even if the neuropathy is transient, you still, as long as you get neuropathy, would seemingly care about how severe it is and how long it lasts.

So I tried to come up with some integration of the severity over time. It seems like a reasonable way to try to think about approaching the problem of measurement in this condition.

Now, if you have different chemotherapy regimens and different timing of when you have cycles and so forth, that can complicate things a bit, particularly if you have different durations of chemotherapy. But one can always normalize area under the curve, for example, to account for how long you've had the chemotherapy, for example, in order to deal with that.

One issue, I should go back, at the very bottom here, is how frequently can symptoms be measured. If it's something you have to come into

Page 208

the clinic for, that's going to be not so frequently, but if it's going to be a patient-reported outcome that you can have every week or even every day, that would be I think a lot easier to fit into this framework. So that's something to think about in terms of what kind of outcomes to consider here that you want to measure over time.

The complication, of course, one of the main ones is this concept of interrupting or discontinuing chemotherapy, which is going to happen in some people. And if you're thinking about an area under the curve type of measure, then that's going to be perhaps raise the issue of missing data, but it depends on what you are trying to measure.

There are a couple of different kinds of areas under the curve that you might think about quantifying here. One is I'm just going to forget about the fact that they've discontinued or interrupted chemotherapy, and I'm just going to continue measuring the severity over time anyway,

Page 209

and that's going to be their outcome regardless. So that's one strategy.

Another strategy is to think about it as, well, what I really want to know is what would the area under the curve have been if they had stayed on chemotherapy. Now, we're not going to observe that, but maybe that's the thing that we're actually trying to estimate.

If that's the case, those are two different kinds of measurements, right, two different kinds of outcomes. We have to think about how we deal with the missing data problem, depending upon which of those we think is more relevant to try to quantify.

What some people I think have done in some of these trials is used what they call a prorated area under the curve. They measure the area under the curve up until a certain point, and then they discontinue chemotherapy. And after that, they just say, well, half the time they had this area under the curve so let's just double it and make it that the rest of the time.

Page 210

If they discontinue chemotherapy, their area under the curve probably in that second half would have been a lot higher than it was in the first half. So there are obviously problems with just simple prorating. One has to think about the missing data problem in maybe a more sophisticated way to deal with this in an appropriate way.

So continuing with this complication, I think that the way one deals with it may depend on why one discontinues chemotherapy. If you discontinue it for reasons other than neuropathy, then perhaps one could argue, well, let's just go ahead and keep measuring the severity over time and just use the area under the curve that results.

People are going to discontinue chemotherapy in both groups. It hopefully would have nothing to do with the treatment being administered for the neuropathy. If that's the case, then that's going to happen in some people, and that's just going to be the noise that we have to deal with. That's one way to deal with it.

Another way to deal with it is let's suppose

Page 211

that people discontinue for reasons unrelated to neuropathy, but we're going to stop following them at that anyway and just sort of impute what would have happened to them if they had stayed on the chemotherapy and base that imputation on people who actually completed chemotherapy. And you have an idea of how they did up to the point where that person discontinued. So you can use that information to try to impute what would have happened to that person had they continued on chemotherapy anyway.

I think that there are reasonable ways to try to deal with that issue. I think the more complicated issue is how you deal with people who discontinue chemotherapy due to neuropathy because those are the people who are coming off of chemotherapy, and if they had stayed on, perhaps they would have had more severe neuropathy, so how do you deal with that problem?

That's a more difficult imputation problem because you're flying blind in a way. You're trying to impute something that you really have no

Page 212

really good information on how to impute it.

One way to deal with it is something like worst case imputation. Give them the worst severity that they have experienced or that anyone could experience or something like that. But those are sort of ad hoc ways of I think getting at the problem.

Leaving that aside for the moment, in terms of analyses, I think that a couple of points Jen brought up, one is that I don't think that one should be excluding people from analysis regardless of what happens to them. One of the important principles I think in clinical trials is to try to preserve the benefits of randomization, and by that, you try to keep everybody in the study and included in the analyses and the treatment groups to which they're originally assigned.

Now, how you deal with missing data and so forth in the outcomes is a different issue, but the important thing is you deal with them somehow. You don't just keep people out of the analysis because that's what can lead to bias of unknown magnitude

Page 213

and direction depending upon who you exclude from the analysis. So I think that's one principle that, if at all possible, we should try to follow.

The other is that I would advise trying to avoid adjusting for things that happened after randomization such as adjusting for cumulative dosage of chemotherapy that people received or something like that. I think what you want to try to do is incorporate things like interruption or discontinuation of chemotherapy somehow into the measurement of outcome.

I've already said a few words about that. I'll say another couple of words.

I want to borrow an idea from another area of neurology. This happens in trials of ALS, and there are some similarities I think with CIPN in the sense that in traditional ALS trials, one tries to see if treatment has an effect on function by following people over time in terms of, in this case, the ALS Functional Rating Scale.

So one tries to see what the trajectory of decline is over time in the treated group versus

Page 214

the placebo group, and the complication in ALS is that 40 to 50 percent of the people are going to be dead before nine months is over, which is a typical duration of some of these trials.

So you have this problem where you're trying to measure function over time, but you've got a lot of mortality mixed in there. How do you deal with those two kinds of outcomes? When somebody's dead, they're not functioning, but it isn't necessarily the case that you can just assign a zero for their function and be done with it.

The similarity here is that in CIPN, you might be measuring something like some integrated severity over time area under the curve type of measure, but you've got people who are discontinuing chemotherapy, so you have a similar kind of maybe more important endpoint occurring that's interrupting your ability to measure the area under the curve.

The idea behind what's called a joint rank analysis is to try to incorporate both of these things but rank people first according to what one

Page 215

could consider perhaps the more important endpoint.

The way this works is that overall you would just rank everybody from worst to best outcome, and the first thing you would do is consider the people who discontinued chemotherapy and rank them from earliest discontinuation to latest discontinuation. So you rank them from, again, worst to best. And then the people who've completed chemotherapy, you rank those people according to area under the curve from worst to best.

You get an overall ranking of worst to best outcome, but essentially what you're doing is that the people who are discontinuing chemotherapy, again because of neuropathy, was severe enough to discontinue chemotherapy, you would argue they should be assigned the worst outcomes, and then the people that continued chemotherapy but had worst to best outcomes in terms of AUC, you have this complete ranking of people.

Now, the assumption here, of course, is that people who have discontinued chemotherapy have had worse outcomes than people who've completed

Page 216

chemotherapy but maybe have some severe area or some high area under the curve. That's something to think about, but that's one idea of how to approach this dual problem of having different kinds of endpoints going on at the same time.

A couple points about the study population, we've already talked about this I think. Ideally, especially in a prevention study, what you want to avoid is having -- I don't know if you want to avoid this, but from a clinical trial's point of view, having 90 percent of the people not experience neuropathy, from the patients' point of view, that's a good thing. From a trial point of view, not such a good thing.

You want to have people at risk if you can identify them of having neuropathy due to chemotherapy. Now, I take the point that you don't want to have people in the study who experience neuropathy for reasons that are not due to the chemotherapy so that has to be, of course, considered.

This issue about heterogeneity of cancer

Page 217

types, chemotherapy types, dosages and so forth, obviously, it's going to be cleaner to have within study homogeneity. Then of course, you have to balance that with the difficulties of recruiting patients, obviously.

So it may be unavoidable to allow some of these factors to vary in a study, but one would have to strongly consider stratifying by these factors, especially in the analysis if one were to allow them to vary in this study.

Obviously, allowing these things to vary is going to lead to more variability in the outcomes, but if you can stratify by some of these factors, that will in the analysis reduce that variability and still preserve, I think, a good deal of power.

The final couple points I want to make are about study planning, and I think that extensive natural history data, as somebody has already mentioned -- I think Joanna mentioned earlier that having an effort like that go on is going to be enormously helpful in coming up with sensible plans for these studies.

Page 218

I think that even more ideal would be if we had data from many placebo groups of clinical trials. One of the things I've learned over the years in conducting clinical trials is that natural history groups don't necessarily behave the same as placebo groups in clinical trials, particularly if the outcomes are somewhat subjective. I think that that's something to be aware of.

Sometimes what happens in studies that are not in the context of treatments being given, the behavior of people can be somewhat different than in the context of a clinical trial. That's a caution in terms of the use of natural history data.

The other thing one can do in terms of sample size planning, especially at the stage that I perceive that the field is at, at the moment, if one is going to conduct a trial, there are a lot of uncertainties regarding what the sample size inputs are, the variability, or the rates of some event occurring and so forth.

There have been a lot of papers in the past

Page 219

15 years about the wisdom of sample size re-estimation that happens within the context of the study. You accumulate information on part of the clinical trial cohort, and then in some way, you can use that data to re-estimate what the sample size should be; in other words, to reinform the assumptions that you make about the sample size calculation to perhaps adapt that midstream so that you make sure that at the end of the study, you end up with at least approximately adequate power. So that's a strategy that can be helpful perhaps in this context.

Finally, I'm not sure even why I put this slide together because what effect size would be important to detect? Obviously, that's going to depend on the outcome of interest, but in the absence of good data on some of these outcomes, even if you had good data, sometimes it's very difficult to come up with the effect size that's of minimal importance to try to detect in a trial. So I think that some work needs to be done in this area in order to think about how large these trials

Page 220

need to be.

If you're thinking about something, for example, like this joint rank analysis that I was proposing a few slides ago, how does one think about power in that context? Well, if it's a rank analysis like that, then what the power depends on is something that's a little bit nonstandard. It's the probability that X is greater than Y.

What does that mean? It means that if you took a randomly selected person from a treatment group and a randomly selected person from the placebo group, it's the probability that the person on treatment would do better than the person on placebo. If the treatment doesn't work, that probability is a half.

So how far away from a half would that have to be in order to make it important to try to detect is the way to think about it, and that's what drives the sample size in that kind of study.

Those are the things that -- I think that I'm done with that; some things to think about in terms of outcome and analysis, and I'm sure we'll

Page 221

talk about that a lot more later.
(Applause.)
DR. FREEMAN: As you see, we're considering these three talks all as one package, and we'll have a break and then the discussion.
The third talk is by Scott Evans, who is a senior research scientist at Harvard University. He has contributed substantially to the HIV research study group, and people may know him from these conferences previously.
Come up, Scott.
Presentation – Scott Evans
DR. EVANS: Thank you very much.
Statistics, we have a saying that there are lies, damn lies, and alternative facts.
(Laughter.)
DR. EVANS: Maybe applies to Mike and I being good speakers.
I did want to thank Jen and Bob and Roy for the opportunity to be part of this interesting and informative meeting over today and tomorrow. I want to thank Jen for an excellent presentation.

Page 222

Mike and I actually had a chance to chat about Jen's slide, and I agree with what Mike has said. He's done such a thorough job at explaining many of the issues that it frees me up to discuss what Bob referred to this morning, potentially some novel or innovative out-of-the-box thinking.
What I'd like to show you now is something a little bit different, and it may be provocative. Please excuse me if I don't know as much about CIPN as everyone else in the room, but what I'm going to show you are some ideas that are being developed in other areas of medicine, and I'm going to try to motivate why they're being developed and how they may or may not apply in CIPN.
We have this somewhat hard problem here where chemotherapy affects peripheral neuropathy, but then it turns around and peripheral neuropathy management may affect a cancer outcome. The failure of chemotherapy may be due to a downstream consequence of failure to manage peripheral neuropathy. Then if you change chemotherapy, then the chemo may again have effects on peripheral

Page 223

neuropathy outcomes. So you've got a really difficult problem here.
Now, I want to motivate thinking about should we try to disentangle all of the different types of outcomes, different parts of patient outcomes, that can happen during the course of treatment of any disease, so let me try to motivate this.
Here's a bit of a test. Suppose you measure a duration of peripheral neuropathy, or maybe you measure an AUC as Mike described either using -- maybe you figure out how to set this up using the TNS, something representing a total disease burden based on the duration and severity of peripheral neuropathy.
Shorter duration is better, or is it? The faster that a patient withdraws from chemo, the shorter the duration, potentially failing the chemo because of the withdrawal, or the faster the patient dies, the shorter the duration. Not necessarily shorter is always better.
Interpretation of any AUC or duration or any

Page 224

of that measure needs context of what else is happening to the patient. This happens a lot. Obviously, if the patient is not surviving, that plays into how you might interpret certain things.
Here's another question. Suppose the person you care about the most has just been diagnosed with a cancer requiring chemotherapy? You've got three treatment options for preventing or treating chemotherapy-induced peripheral neuropathy, A, B, and C, three treatments.
Let's suppose there are two outcomes you're most worried about. There's the peripheral neuropathy outcome, and there's a chemotherapy outcome. And let's suppose they're both binary, either it goes well or it doesn't go so well.
Now, luckily enough, we had a randomized trial that compared A, B, and C. It's going to help us make our decision. We have 100 patients in each arm. Here's the peripheral neuropathy outcome for all three arms, 50 percent in all three arms.
Here's the chemotherapy failure rate in the three arms, 40 percent in A, 50 percent in B and C.

Page 225

Which treatment do you choose? Well, they all have the same peripheral neuropathy rate. A has the lowest chemo failure, so probably you're leaning towards A. It seems reasonable. We're all reasonable people here. B and C are somewhat indistinguishable.

Now, this is analysis of each of the endpoints, and this is what we typically do in trials. We say here's endpoint number 1. I'm going to aggregate what happens over treatment A. I'm going to aggregate what happens in treatment B. I'll make a contrast between the two, and I'm going to repeat that for the other outcomes.

I'm going to switch that around. Instead of analyzing the endpoints, I'm going to analyze what happened to the patients. Now, there are four possible outcomes if you've got a binary peripheral neuropathy outcome and a binary chemotherapy outcome. Let's look at what happens to the patients.

Now, in A what happened is that the association between peripheral neuropathy and

Page 226

whether you failed chemotherapy or not, there was no association, no correlation. But peripheral neuropathy was positively correlated with good chemo failure outcomes in B and negatively correlated with C such that your rate of chemotherapy success without peripheral neuropathy is 30 percent in A, 0 percent in B, and 50 percent in C.

What's happening? Well, our culture in trials is that we take the patients in the trials, we analyze each of the endpoints, and there are thoughts these days about how to turn this around. Isn't the point of a trial in collecting information on outcomes to evaluate how the patients are doing? Instead of using the patients to analyze the endpoints, use the endpoints to analyze what happens to the patient.

My father told me many years ago, the order of operations is important. What he meant by that is again, instead of aggregating over treatment A, aggregating over treatment B, making a comparison for endpoint number 1, and then repeating that for

Page 227

all the other endpoints, and then at the end, trying to put it together and make sense of it, it's not quite the right order.

What we need to be doing is thinking about how patients are doing, taking our endpoints within patient, then aggregating over treatment A and aggregating over treatment B and making comparisons. That's what representing how well two treatments compare to another in a pragmatic way.

This is what we're going to show you, and I'll show you some examples about how this is progressing in other areas.

Here's another question about benefit-risk. We've got toxicities. We've got benefits and so forth. During the analysis of a trial, you define analysis populations. You do an efficacy analysis, you do ITT. You do a safety analysis, you do a safety population. Those populations are not the same.

Then at the end, you combine the efficacy analyses and the safety analysis to do a benefit-risk analysis. To whom does this

Page 228

benefit-risk analysis apply? I ask you this because I've been teaching clinical trials for 15 years, and I don't know the answer. But that's what we do.

We published a paper recently that described this particular vision in clinical trials, and if you look at what we do today in terms of treatment effects, on the left side you see -- well, we usually estimate few treatment effects, and by "few," I mean usually in a clinical trial, we estimate a global treatment effect for the patient population.

But tomorrow -- and we already see the movement -- is what we're going to do is we're going to be taking a look at individual patient characteristics and be able to estimate personalized effects for individual patients. That's the personalized medicine movement. But the flip side of that is looking at the endpoints where right now we have many. We measure efficacy. We measure toxicity. We measure quality of life.

Now, tomorrow doesn't necessarily mean that

Page 229

we're going to measure any fewer, but somehow we're going to have to compose that information in a more reasonable way to try to make sense of it. It may become a patient outcome rather than analyzing each of the endpoints in its own separate analyses.

These were a few of the papers that came out recently. The top one, again, you'll recognize, Using Outcomes to Analyze Patients Rather Than Patients to Analyze the Outcomes: A Step Towards Pragmatism in Benefit-Risk Evaluation.

A couple of ways to do some analyses, which I'm going to talk about actually quite related. The win ratio was proposed by Stuart Pocock, a statistician in Europe, and is very related to another statistic that I proposed called DOOR, which is Desirability of Outcome Ranking.

You think about what those words mean. Desirability of outcome, and we're talking about at a patient level, the desirability of their outcome. And what I'm going to show you is a potential adoption or adaptation of that to perhaps this area.

Page 230

Now, I know some people from Washington University, a colleague of mine, a friend of mine, David Clifford, I heard him once say to a colleague, he said, "Treat the patient, not the disease."

So we're going to take this as somewhat of a perspective. And what if we evaluate the intervention by how well they treat the patient rather than trying to divide and conquer on every outcome? A systematic evaluation of the benefits and harms and a bit more pragmatism in the research question we're after.

Here's an example, and again, the naivete of it, but you might think of it this way. This is a desirability of outcome ranking for CIPN or a potential simple place to start. Suppose there's an ordinal categorical outcome, five levels? The top and the bottom levels are easy. The bottom level is the patient dies. Everything goes wrong. Nothing could be worse. The top level is everything goes right. Chemotherapy goes well. No peripheral neuropathy outcomes, toxicities are

Page 231

minimal. Everybody is happy.

But then there are layers in between, so a second category might be you have a positive chemo response but you've got some issues with peripheral neuropathy. Maybe below that there are negative chemo responses with either small or large peripheral neuropathy problems.

It doesn't have to be five levels. It doesn't have to be defined this way. This is just somewhat of a generic example, but I'm going to show you an example of something like this that was applied elsewhere.

The way you might think of an analysis of this is here are the five categories, and you have a control group. For the control group, the patients fall wherever they fall in these five categories. What are you looking for with the new treatment?

Well, I'm looking for some sort of northward migration of the patients relative to control, and if I can get some northward migration in a benefit-risk, a global sense, we're doing better.

Page 232

So the idea is can we get some sort of a shift northward with treatment, and that's in a global sense, a benefit-risk totality sense.

There are a couple of different ways you can analyze this. One is what we term the DOOR probability, which is essentially what Mike described. This is the probability that if you randomly take a patient in the new experimental arm, you'll have a more desirable outcome than the patient in the control arm.

This is a probability that is -- although it's perhaps new and you're not used to it, but some of you treat patients. You have to make a choice. Do I treat them with A, or do I treat them with B? Are You asking me about what the hazard ratio is or what the p-value on the T test is?

It would seem to me that one of the most intuitive things for you to ask is what's the probability the patient is going to be better off on treatment A than treatment B. But here it is. This is the calculation. Or you can do a win ratio, which is a relative measure of that, which

Page 233

is what Pocock had proposed, the win ratio.
Beyond that, you could also do something called partial credit, and I'll end with this partial credit idea, but it takes a little while to sink in and a minute to explain.
Let me simplify it to four categories for a minute. Suppose you get your peripheral neuropathy/chemotherapy outcome in four categories. The top category, again, everything goes right. Patient survives. They have good cancer and peripheral neuropathy outcomes. Bottom category is death, but a couple of layers in between, mild problems in category 2, more severe problems in category 3, but they all survive.
What we're going to do is think about scoring these categories. We're going to score it like an academic test. If you're in the top category, you get 100. Everything went right, perfect score. You die, you get a zero. If you're in the middle two categories, you're going to get partial credit.
Now, I'm going to show you how you might

Page 234

think about the partial credit problem. Of course, if you're doing a trial, you want to prespecify and be transparent and all of that, and you can survey expert clinicians in the room. It'd be interesting to see what you say, but I'm going to show you another idea, too.
There's also ways you can get this from the patient. If you're giving quality of life instruments from the patient, you could say well, look, let me take the patients in the top category. They have sort of an average quality of life score through what you've given them. Now let me look at the patients in the second category. They're telling me what their quality of life is.
So maybe the ratio of the second category to the first category tells me about how to score that second category, straight from the patients.
Of course, if we survey, there's going to be lots of different opinions about how you might do this. I'm going to say, well, fine, smart people can disagree, and who am I to say what your partial credit should be?

Page 235

What I'm going to do is show you an analysis that shows you how two treatments compare no matter what you choose, and if you want to make a different choice than you, that's fine. I'll show you what your answer is.
This is called partial credit. On the right side, you see the scores, 100 on the top, 0 on the bottom. What I'm going to do is show you a plot where the partial credit for category 2 is on the vertical axis, the partial credit for category 3 is on the horizontal axis.
If you decide you're an easy grader, all you got to do is survive and you win, this is equivalent to mortality. I give 100 as long as you survive. 100 is the score, then you're in the upper right-hand corner.
What I'm showing in these lines are contours of similar treatment effects when I compare the academic scores of treatment with control. So in D, what I see is a 5-point advantage for category D. If you follow the line down, you'll see the number that -- the red line in the middle

Page 236

represents where two treatments would be equivalent in this particular case. I didn't show you the exact -- this was an actual dataset in which we ran this.
The red line represents a line where if you had those combinations of partial credit, two treatments would be completely equivalent.
If you decide you want to score 100 to 100, all you got to do is survive, you're in the upper right-hand corner, and you get 5-point advantage for the new treatment. If you're in the lower left-hand corner, you say, listen, he's a tough grader. Unless you survive with a good cancer outcome and no peripheral neuropathy, you're getting a zero. In that particular case, there's a 6-point advantage for the control.
Now you could take another extreme and say well, listen, I'll score 100 for category 2 but a zero, in which case it's about 11-point advantage for new treatment, or you can compromise and say, well, if I do 80/60, maybe it's about a 4-point advantage for the new treatment.

Page 237

This particular plot is constructed based on the data that's collected from the trial, but it allows you some personalized decision where you might face the case where you've got a 20-year-old woman who wants to make a different choice than a 75-year-old man. This may allow you for some personalized choices, if you'd like to do that.

I guess maybe I'll end there. Thanks.

(Applause.)

DR. FREEMAN: It is about 2:10, I think. We had asked Dan for a break at 2:00 to 2:30, which seemed a little premature to me, but even so, let's go ahead with that. Maybe come back at 2:35, and we'll dissect these three interesting and provocative talks.

(Whereupon, at 2:20 p.m., a recess was taken.)

Q&A and Panel Discussion

DR. FREEMAN: Okay, folks. Let's begin the final session of the day. If speakers and panel members can come up, we'll try and finish on time. There's a lot of stuff going on which you can join

Page 238

in on. There's the Affordable Care Act hearings.

(Laughter.)

DR. FREEMAN: There's the Gorsuch nomination. There's the Trump company in collusion with the Russians. The choice is all yours. Lots of fun in Washington this week.

I do want to introduce two speakers or two participants on the panel who I have not yet introduced. That's Matt Jarpe, who's the associate vice president of biology of Regenacy Pharmaceuticals in Boston and Ellen Smith, who is an associate professor at the University of Michigan School of Nursing from Ann Arbor, Michigan.

I think the way to do this this afternoon because there is a lot to discuss is to begin by asking with respect to the previous three talks that you heard whether there are any questions which fall under the heading of clarification questions. And then I'm going to go through somewhat systematically because there was an enormous amount of information, all of the issues

Page 239

that came up in Jen's talk and then in the talk by the two statisticians.

Yes?

DR. DOUGHERTY: One of the assumptions that I seem to hear -- and I am happy to be corrected -- was that the organizing principle to the data structure would be time, the length of time on therapy, et cetera, but not cumulative dose. There's been repeated studies, amongst those mine, that have clearly shown that the level of neurotoxicity is clearly dependent on the cumulative dose of the agent and not necessarily the number of cycles. Now, number of cycles does impact the effect on the tumor, but here we're talking about a toxicity and not an anti-tumor effect.

The reason, just to clarify why I think cumulative dose is important, most chemotherapeutic agents are quite polar, so they don't distribute into the adipose tissue. You're going to have a very high initial plasma level, and that's going to hit the ganglion, which again, I'm assuming that

Page 240

the ganglion in the peripheral endings are the substrate of importance, with a much higher dose.

I was just looking for clarification in that assumption.

DR. FREEMAN: I'm going to say let's go in the order of speakers, Jen to Mike to Scott, and then the other two panel members if they wish to contribute.

DR. GEWANDTER: I think that in what's been done in the literature, there was really only that the cumulative dose to chemotherapy hasn't been used so far, but I do think that's a reasonable endpoint to use. I agree with you that the cumulative dose is more important than the time.

Maybe we could think about doing some kind of area under the curve that is in relation to dose instead of time. But I think when Mike was -- I won't speak for Mike.

I'll let you answer what you were talking about with area under the curve.

DR. McDERMOTT: Feel free.

DR. GEWANDTER: Okay.

Page 241

(Laughter.)
DR. GEWANDTER: When Mike was using time --
DR. McDERMOTT: Interpretation of the question.
DR. GEWANDTER: -- I think what he was saying was that instead of just using a time to event or a cumulative dose to event, that especially depending on the grade or the severity of neuropathy that you're looking for to be that event, potentially what's more meaningful is the continual trajectory upward and how long that lasts.
When I'm thinking about it, how long that lasts wouldn't just necessarily be until the end of chemotherapy but potentially long after chemotherapy is over. I think that from that perspective, that's why talking about time in terms of trying to -- instead of just having it be a one event of time to event, try to look at it over time. And I'm not sure if there would be a way to somehow normalize to the cumulative dose instead of time.

Page 242

DR. McDERMOTT: I couldn't imagine saying that better.
DR. GEWANDTER: Thank you.
DR. McDERMOTT: I think the other thing is that I'm not sure that there's -- maybe you can comment on this, but I'm not sure there is a compelling reason why you might expect the cumulative dose to be different in the treated group and in the untreated group other than, of course, for interruptions or discontinuations.
I guess the point I was trying to make is that I think a lot of studies look at severity at fixed time points, but I think that some integration over the course of chemotherapy is what I was trying to advocate. How you bring dose into that, I'm not exactly sure, but that was the principle.
DR. FREEMAN: Scott?
DR. EVANS: Not sure I have much to add. I'm not sure I fully understand the question.
I think your point is that cumulative dose may be the major or a major contributing factor

Page 243

about peripheral neuropathy outcomes. But of course, in the context of a randomized trial, you're going to be comparing your treatment strategies, and the doses are going to be what the doses are.
You can build that into -- you can figure out if I can use lower -- reduce the doses somehow, then I can study strategies that would reduce doses and may have better peripheral neuropathy outcomes and maybe even with circularity have better chemotherapy outcomes.
I'm not sure I fully grasp -- I guess I'm thinking in terms of randomized trials, trying to figure out whether particular interventions work. I'm not going to be adjusting for how things were dosed. You get a randomized trial. You're going to compare randomized strategies.
DR. FREEMAN: Matt, any thoughts?
DR. JARPE: I feel like I do understand the question, and the fact that the statisticians don't makes me think I may not understand it.
(Laughter.)

Page 244

DR. JARPE: I tried to think of visualizing this. If you were to plot cumulative dose versus neuropathy severity on a graph, what's that going to look like? Say it's correlated, so you would expect that to be a line more or less; is that fair to --
DR. DOUGHERTY: Yes. I showed a number of slides earlier that showed the toxicity getting greater and greater.
DR. JARPE: Right.
DR. DOUGHERTY: The very last bar graph in those slides was one year after. All the rest were cumulative dose. So as the patients got more and more agent, they showed more and more toxicity.
When I organized that by just cycle, then things don't follow such a nice clear graded pattern, and that's because some people, neuropathy may emerge, say, at cycle 2, cycle 4, cycle 5. So that time factor is not necessarily predictive. But when you move it back to once you've achieved, say, 200 milligrams cumulative dose or 250 milligrams cumulative dose, now the signs of

Page 245

toxicity start to emerge. And so --
DR. JARPE: Does the severity --
DR. DOUGHERTY: -- a really small skinny person will be -- what that means is going to be on therapy longer.
Again, if you power it adequately so that you have equal numbers of small and heavier people in your study, you'll be fine. But if you haven't got that partitioned out carefully, then you're going to miss things.
To me, the thing that is most predictive of toxicity is the cumulative dose that the nervous system sees.
DR. JARPE: If you had a group that had just chemotherapy and a group that had chemotherapy plus your preventative agent and you plotted that cumulative dose versus neuropathy severity, you would expect them to cluster --
DR. DOUGHERTY: I think that's where you're going to get your best possibility of seeing an effect. It's not going to be the number of cycles that each group took. It's going to be if you look

Page 246

at the cumulative dose for each group, one group is showing toxicity at one rate, and the other group hopefully showing a toxicity at a different rate.
DR. JARPE: I guess the question then, could you statistically set your analysis to find a difference between those two groups? It seems like you should be able to.
DR. DOUGHERTY: I don't know any statistics. I mean, the only statistics I know is like when they're really obvious. Is there a zero in that category?
(Laughter.)
DR. DOUGHERTY: There's something in this one. So that's why I was asking why was the assumption time and not cumulative dose?
DR. McDERMOTT: I wouldn't think of it as an assumption. I think that we're talking about maybe two slightly different things. One is how you define the person's outcome, and so in that context, we're talking about integrating severity over time.
What you're talking about is what predicts

Page 247

outcome, and if dose predicts outcome as you say, then like you said, it would be sensible to make sure that you have that predictor be evenly distributed between treatment groups at the outset ideally. Whether that be on the basis of somebody's body weight or you know what their regimen is going to be, whatever it is, but you stratify by that in the beginning and in the analysis so that you can reduce the variability that's associated with that. But I think that that would be the way that you would deal with it in the trial.
So it isn't that we would want to ignore that, but personally, I was talking mainly about measurement of -- trying to quantify somebody's outcome.
DR. FREEMAN: Gordon?
DR. G. SMITH: Yes. You've really helped me think about this, but now I'm more confused. I've been kind of puzzling in my mind this dosing issue, and it seems to me that -- an oncologist will have to help me -- that even within the confines of a

Page 248

clinical trial, if there's an effective agent at preventing chemotherapy, presumably there will be fewer dose reductions because of adverse events in the treated group.
What I've been puzzling in my mind is if that's the case, the cumulative dose in the treatment group will actually be higher, which then could increase your risk of CIPN.
So I think what I'm hearing from your point, which I think is really good, is maybe one way of integrating these two issues is to look at this dose toxicity curve and compare it between the placebo and treated groups.
DR. DOUGHERTY: If your agent's working, then those patients will stay on therapy and that your --
DR. G. SMITH: Then they may get more -- they'll still get the chemo. They may get neuropathy, but they'll get a higher dose. And I don't know how in a trial you could prevent that from happening.
DR. FREEMAN: James? Sorry.

Page 249

DR. GEWANDTER: You wouldn't prevent that from happening. That could be your outcome. So you could make some kind of composite that would include the percentage of planned chemotherapy the person received and something somehow estimating their toxicity or their neuropathy.

DR. FREEMAN: I'm interested on the regulatory side because this is obviously a challenge. One can create a caricature where there's a wonder drug. Patients fly through the trial. They get their full complement of chemotherapy, but they have a neuropathy because they do do that, whereas patients who are on placebo drop out. They develop neuropathic features during the trial. And then six months later when we've satisfied Lynn Howie's safety concerns, patients are assessed at that time point, and those that got active drug plus chemo have a worse neuropathy than those who were in the trial.

I'm creating a caricature, and I know that. But I'm interested from the regulatory standpoint, is there any way that one can create some kind of

Page 250

an endpoint which factors in both the amount of chemotherapy received and whatever outcome we decide, some kind of normalization by chemotherapy? Is that conceivable? Does that exist in other spheres?

DR. HERTZ: It sounds like you're describing some type of responder definition that takes into account different aspects of the treatment related to the particular scenario, in this case, prevention.

There are many different situations which rely on a variety of responder definitions. We don't have quite as many. Our responder definitions tend to be really more percentage change, yes or no, when that suits someone. But for instance, in a GI division when they're looking at agents to manage or prevent nausea and vomiting, they don't really look at nausea per se, but they look at vomiting episodes plus the use of antiemetics because the more antiemetic, the less vomiting. So you have to take that all into account.

Page 251

I feel like there's probably something there that could be developed analogous to dose of the treatment and the actual outcome with some type of definition based on what might be capable of demonstrating either separation for the treatments groups that's somehow clinically relevant.

It would have to be explored. To the extent that there are databases to start looking at that once trials move forward, I think it would be interesting to explore different things there.

So it sounds like that would be something akin to looking at a responder definition. Otherwise, when you have opposite movement that both mean the same thing in terms of good and/or bad depending on the direction, it can be very challenging.

DR. FREEMAN: James?

DR. CLEARY: I was going to say I'm not as worried about the dose reductions of chemotherapy and the cumulative dose. I agree. I think cumulative dose of chemotherapy does predict how bad the neuropathy will be, but if it's a

Page 252

randomized trial, I think we'll get the same on both arms.

I keep talking about the calcium magnesium trial that Charles ran. When he did that study, he wasn't thinking about whether one group got more dose reductions of FOLFOX or the other because you think with randomization, it's all going to even out.

DR. LOPRINZI: Let me comment on that. When going back to look at that trial and our outcomes, our first statistician actually fit very nicely with what he ended up saying there, and we looked at area under the curve over time.

When you have an inactive agent, which the calcium magnesium was, then the doses were all the same. How many patients got 100 oxaliplatin dose, how many had stopped oxaliplatin and what the average dose was, they all were nicely correlated with each other or had the same pattern.

If, however, you have a defective agent -- because most of the people who stop their oxaliplatin dose, stop because of neuropathy. So

Page 253

if you have an effective agent, you're able to then give more of the oxaliplatin. Whether you actually have to, we'll find out in a while from the IDEA trial that's going to be presented at ASCO this year, I understand, with 3 months versus 6 months. Then you may have that problem.

The other way of looking at it is a slope in the curve over dose or time, and that way, you could see if they are different there by dose. If, in fact, you've given more dose to one arm, you can check the slope per dose, and then see your differences there.

When we actually set up the initial trial, we did think about all those different things, and since it was a negative study, everything just lined up as it should. Now, if we saw that neuropathy is the same but they got a whole big dose, then we would have changed our opinion on things, that it made a difference in that.

DR. FREEMAN: Okay. Any other -- Sharon, yes?

DR. HERTZ: I think given how early we are

Page 254

in thinking about these designs, when studies are being conducted, even if they're commercial or otherwise, it would be nice to take a look at some of these different approaches, either as secondary or post hoc style analyses, and start to get a feel for what's reflecting the outcomes that are considered valuable and start to build that data to support what might be useful for a commercial development plan.

DR. LOPRINZI: That's actually a wonderful idea, and there are a number of trials where there's a protocol and there's a manuscript at the end. Looking at that would be probably darn helpful, if I were the FDA and look and say, hey, what happened to these past trials and what made sense and what didn't, and throw out all the things Loprinzi did, and then you got the answer.

(Laughter.)

DR. LOPRINZI: But that is a great idea.

DR. FREEMAN: Any other clarifying questions? Then what we will do is go through somewhat systematically what has been covered this

Page 255

afternoon.

Good. Okay. So --

DR. McDERMOTT: Can I make one quick comment on the last points that were being made about I guess the -- one of the points is that the active treatment group, if I'm understanding correctly, might get more of the chemotherapy that's prescribed because the anti-neuropathy agent is working. Okay. So I finally got that straight.

I think that the analysis I was proposing, the joint rank, what would happen there is that people in the placebo group would then have more interruptions or discontinuations of chemotherapy, and so that would then perhaps properly reflect what the benefit was of the anti-neuropathy agent.

They might have more neuropathy at the end, but they would still in a sense have a better outcome. Now, the question is whether that's a sensible thing or not, I suppose.

DR. EVANS: Maybe I can comment on that, too, because we've had this issue in other studies. If it turns out that that strategy, if you have not

Page 256

only a peripheral neuropathy advantage but then because they're able to tolerate therapy better, that you may also have a better chemotherapy advantage.

When you start to think about these compositions that I talked about or Mike was discussing, sometimes you can even gain sample size efficiency because the effects are happening in both dimensions. You get to add them up, and you see a totality of evidence. I not only have to win here, but I'm building in a composite information where I have advantages elsewhere.

So the advantages start to add up in totality, so sometimes you can get smaller sample sizes in those kinds of trials.

Now, if it turns out it's going the other way, you get a different problem because you're weighing benefits and harms, and you really got to figure out is the benefit I'm getting worth what I'm giving up, and you have to think that through.

DR. FREEMAN: I've got one clarification question mainly for the statisticians, and that is

Page 257

the challenge of differentiate. To take a step back, we've spoken about symptomatic treatment on the one hand and disease-modifying treatment on the other hand. Clearly, at the extremes, these are two very discrete kinds of trials and perhaps even with discrete endpoints, but there is a gray zone in between.

This is a challenge or has been a challenge in a number of diseases in which disease-modifying therapy has been attempted. Parkinson's disease is one of the best examples of this where at the end of the study, it has often been very difficult to know whether a treatment was disease-modifying or whether it was symptomatic.

This could well be the case over here, and it obviously is a major issue as far as labeling, what is a drug going to be called. And that never really came up in any of the two of your discussions, and it is a concern. Just knowing about the couple of drugs that are circulating at the moment, they may be symptomatic treatments, and how do we address that issue?

Page 258

The obvious thing is to say, well, what happens when you stop the drug, but it's more complicated than that, I think.

DR. McDERMOTT: I have a little bit of experience with this in the Parkinson's world, and if you're familiar with some of those delayed starts sorts of studies, it's just inherently very difficult to try to get at mechanism in a clinical trial. That's just number one.

So you try these manipulations of stopping drug to see what happens to people after you withdraw. Do they maintain a benefit over time, for example, and there are just so many difficulties with doing that.

Probably what I would anticipate regulators would tell you is that you need to have some evidence not only clinically but on a biomarker level that tells you something about mechanism in order to try to get at that issue. I don't know that it's going to be easy to get at clinically, especially in a condition like this with so many different treatments going on at the same time.

Page 259

DR. FREEMAN: Scott, any additional comments?

(Dr. Evans gestures no.)

DR. FREEMAN: Anybody else, any other comments on that? It is an issue and will be an issue.

(No response.)

DR. FREEMAN: Okay. can you put the slides up? These are the terminal 3 slides of Jennifer's talk, which really sum up, I think, the issues that are on the table, essentially going through a clinical trial from start to finish.

The first question is who should enter the clinical trial. And there was some discussion this morning about end stage, metastatic, treatment failures, but I think we need to flesh this out a little bit as we move forward in terms of developing a final work product.

Any comments on the first, maybe two, localized or metastatic cancers, or the one or multiple cancer types?

DR. RICHARDSON: Well, I think you have to

Page 260

be very disease specific. Essentially, just speaking in the myeloma space, newly diagnosed patients have a very different profile than those who are multiply relapsed. And as Jim and I were talking about with Joanna earlier, now in myeloma, our patients are living 10, 15, 20 years where before they lived 2 or 3 if they were lucky. We're moving into a very different era of designing new trials.

This is one of the reasons, for example, we did our initial assessment in bortezomib newly diagnosed, untreated naive patients because you essentially couldn't -- that was the cleanest signal you could get to best understand what was going on.

The other thing is that, obviously, you've got combination therapies and how they impact. And again, speaking to the myeloma space, we have to be very treatment specific because the interaction between, say, an antibody and our IMiDs and our proteasome inhibitors is quite different to that, for example, of just the IMiDs and proteasome

Page 261

inhibitors alone.
So again, there are a lot of variables, but I think in our disease, we will be thinking primarily of newly diagnosed, relapsed, and then relapsed refractory.
I thought the FDA's position that you come into the end stage situation, for us in myeloma any way, is probably not ideal. I think you've got surround sound with so many things going on, and as you look to risk factors for CIPN, renal dysfunction being one of them, as our patients get sicker, their renal dysfunction tends to worsen. Frankly, we'd want to be in the upfront space.
The good news in the FDA is we have a fabulous relationship with our division. There's Anne Farrell and colleagues. I'm not sure if it would come under her or go somewhere else, but the fact is they understand the disease extremely well so we're well placed, the best place where we should be, speaking specifically for us.
DR. FREEMAN: What about the solid tumor people? Yes, Charles?

Page 262

DR. LOPRINZI: If you have safe stuff, calcium magnesium, which we've given and that sort of thing, then -- and we actually didn't use either localized or metastatic. We used NED. A person had to have -- NED is no evidence of disease.
So they had primary colon cancer or rectal cancer, didn't really matter which there -- you can say they're different, but it's basically the same -- or they could have had metastatic disease, which was completely resected.
We wanted a population that was curatively treated, not likely to recur during the six months of chemotherapy, less than 5 percent chance of recurrence during that period of time, and so you have a relatively healthy group of people, and that way, you get your best endpoint for there.
If you use metastatic disease, then they've had chemotherapy before, although some are newly diagnosed metastatic, but you don't know if their cancers will respond. They might fail over two months of therapy, and you're not going to be able to get your endpoint very well.

Page 263

Now, if you have a drug that you don't know if it's safe to give, et cetera, et cetera, how safe it is you think it is, but then I think a pilot evaluation for safety in the metastatic disease setting looking for neuropathy makes some sense to me. But trying to get the end neuropathy -- that's for the safety aspect of it, for the end neuropathy endpoint, I think you really need a more adjuvant setting. It's much, much cleaner a process of things.
The other part of the thing on cancer type, on our other study whether a person had pancreas cancer or colon cancer, if they're both NED and likely to go through it, I don't know that the cancer type -- I probably wouldn't mix that with myeloma because those are too disparate, but otherwise, it's really the effect on the drug that you're looking at.
Just like our nausea and vomiting studies, if they're getting FOLFOX, we don't care what it's for. We just want to see the effect of the drug and if we can counteract that effect of the drug.

Page 264

DR. DOUGHERTY: I totally agree with Charles and Paul. You want a group that is otherwise treatment naive.
Unfortunately, Paul, your myeloma cohort is such a crazy, chaotic clinical course, don't know if I would start with Velcade. That's a tough agent to deal with. But the adjuvant setting, platinum, taxane-type therapy, those folks are going to go through a pretty steady clean chemotherapy regimen, and it would probably be the easiest group to target.
DR. RICHARDSON: If I may, Pat, just comment on that, though. I think we're seeing greater stability now with three-drug, four-drug regimens, and we're seeing extraordinarily long survivals. I think we're a more stable population than perhaps we were.
But you're right, if you're going in with your real toxicity driver, which in our case would be the bortezomib, basically the good news there is you know what you had before, it's been highly well studied, and it's well validated. So your

Page 265

comparisons can be helpful.
I think also frankly, that as we were discussing earlier, some of our alternative treatments unfortunately have different toxicities that made them just as challenging. We probably will remain bortezomib focused in our work in myeloma for neuropathy, but with the understanding, to your point, that we want a relatively stable population.
DR. DOUGHERTY: Is that time to initial transplant now fairly constant, or is that still very --
DR. RICHARDSON: It's a great question. You see, the confounder we have in myeloma is that alkylators following neurotoxic therapies now have their own intrinsic neurotoxicity that we see, which points to this cumulative effect that's so interesting, probably free-radical-mediated. Who knows?
In fact, transplants being pushed back. We're becoming more and more like diffuse large B cell where with the advent of antibodies,

Page 266

particularly daratumumab, we've basically got R-CHOP rituxan. So basically RVd dara, for example, is probably going to be R-CHOP rituxan or equivalent.
We also have a new drug called ixazomib, which is an oral boronate peptide with much less neurotoxicity that's coming forward as well, but it's not as much -- it's not as efficacious as bortezomib, generally speaking. So we're seeing a different paradigm in transplants being pushed back.
DR. FREEMAN: James, any additional comment? Patrick?
DR. CLEARY: I agree with what's been said about trying to get patients who haven't been treated before with chemotherapy, not caring so much about what diagnosis they have, but making sure they get the same regimen. We use FOLFOX in pancreatic cancer, gastric cancer, colon cancer.
The one other thing I'll say is that the one difference might be sometimes in, say, rectal cancer, we'll use 8 cycles of FOLFOX, but in colon

Page 267

cancer, we'll use 12 in a curative setting. So just being aware that even though it's the same chemo, there might be a different number of cycles.
In a trial design, I would say this is a patient who is getting, say, FOLFOX, never been treated before, and is going to get a planned 12 cycles or however many cycles.
DR. FREEMAN: Let me ask a clarification question since you mentioned that. There's been some discussion initiated by Patrick about cycle versus a cumulative dose.
Is there linearity in the toxicity of accumulated dose? Are there cutoffs? Is there a point -- and perhaps Guido can comment on this better than anybody.
Picking up on Pat's point about the cumulative dose being so critical, is this a linear effect?
DR. CLEARY: It's definitely a linear effect in that the more cycles of chemotherapy he has, the higher the amount of toxicity. I think it makes sense that the higher the cumulative dose, the

Page 268

higher the rate of toxicity, but I haven't really seen that studied in that way.
What I can just tell you in general practice is the risk of a patient coming in and telling me they have neuropathy for the first time goes up every time I see them. So the more cycles they get, the higher the risk.
DR. FREEMAN: Cycles.
DR. LOPRINZI: And they're going to be pretty well correlated. Some people might dose-reduce, so it might make a little bit of a difference, but it's a 10 percent.
Let me just make one other clarification. I would not say they couldn't have had previous chemo. I'd rather say they couldn't have previous neurotoxic chemotherapy. For example, with breast cancer, AC chemotherapy, which is non-neurotoxic, that's okay. And then when they receive their paclitaxel, then you start your preventive process there, so no previous neurotoxic type chemotherapy.
DR. FREEMAN: We're going to come to that because I think there is some divergence of views

Page 269

on that issue, which now would be a good time to flesh that out.

Joanna and --

DR. BRELL: I'll just make one comment that hasn't been made yet, is it depends on what our secondary outpoints are as to whether or not we use patients who are having adjuvant therapy with all their tumor resected or with metastatic disease. Because if we need that tumor safety issue, testing a group of adjuvant patients, we won't get to measure any disease outcomes.

If we don't want to wait for disease-free survival or overall survival, at least tumor recurrence, time to progression, we won't get any of that with an adjuvant therapy. But if we use an early metastatic cohort such as the colorectal cancer patients getting their first metastatic or second metastatic regimen, we could get those other tumor outcomes without having a 20-year trial.

DR. CLEARY: Just following that, I agree with that. And maybe using the metastatic patients for those early outcome measures and also for the

Page 270

biomarker data we were talking about this morning. So maybe on the metastatic patients, you could do the biopsy, just very small trials, and then when you want to do a large phase 3, you can move into the adjuvant setting.

DR. RICHARDSON: I think you still have to be very careful, though, because you could lose your signal in that end-stage population for all the biological reasons that we've heard about because your interventions -- to your point, Charles, if you think of it, there's endothelial damage we've talked about. AC are both pretty vascular toxic, aren't they?

So would that in any way change? Would that be a variable that would change your outcome for the non quote/unquote "neurotoxics"?

The reason why I say this is because we've seen this pattern of alkylator-based injury that's neurotoxic that we never saw before. It points to an interaction that I think can occur pre or post. So if you've had prior alkylator, you can be more prone, and if you've had alkylator after you've had

Page 271

proteasome inhibition and IMiD, you can also see it flare. So it's not that one excludes the other, if you see what I mean.

My other comment would be to your point about cumulative dose. In myeloma, we see with thalidomide that there's a cumulative effect. Interestingly with bortezomib, it doesn't appear to be the case. It plateaus around cycle 5 and 6, and if you haven't had neurotoxicity that's of note by then, generally speaking, you don't see it.

We also see some fascinating variances. We see, for example, in light chain disease highly responsive patients who are a little bit more prone to neurotoxicity versus classic isotypes like IgG or IgA. And these are real interesting nuances that are actually quite tricky to tease out, but they appear to be quite real.

DR. FREEMAN: Does that in any way relate to the likelihood of an underlying perhaps subclinical neuropathy?

DR. RICHARDSON: Great question. We don't really have the numbers to comment on that for

Page 272

those patients who've been properly studied, but hypothetically, it would seem to make sense. In other words, there must be an inflammatory profile perhaps with a light chain patient.

There's definitely biological difference. Light chain patients, for example, are more prone to have kidney injury, obviously, which may change that as well. But moreover, they tend to be more bone avid. They tend to therefore have more likelihood of -- to Pat's point, they may have had more opioid exposure. They are endless confounders that could then contribute to that.

DR. FREEMAN: Any other comments on this specific topic? Scott --

DR. EVANS: I can make a comment.

DR. FREEMAN: -- and then whoever that was over there.

DR. EVANS: The answer always depends on what your question is, and I'm not sure there's one right answer to this. This is the constant struggle between whether I've got enough sensitivity in the trial to detect an effect versus

Page 273

can I be pragmatic in answering a real-world question.

Typically in trials, we're a bit more focused on biology and mechanisms of action and can I show an effect in earlier phase trials. We're supposed to get a bit more generalizable and pragmatic as we move to late phase trials, but there's also been a question about even whether our late phase trials are pragmatic enough.

Califf was trying to move us in that direction. I'm not sure we're going to continue to move in that direction with him gone.

The idea behind the pragmatism is you get closer to addressing the question, and if you throw this into clinical practice, what's going to happen? And if you start excluding people, whether it's for diabetes or whatever, and they're a big part of the population, then you're not addressing the question of what happens if you throw it into clinical practice.

That's a little bit different than if you're the drug company. You're just trying to somehow

Page 274

get on the market, but then if it gets on the market and gets thrown out there and you've got no data on anybody who's in these subgroups of patients, that's not a great thing either.

There's one other idea that can be thought about for some of these cases, and I just got an email at the break from a colleague of mine. I'm sitting on a DSMB for a trial that was an adaptive enrichment trial. They start out with two cohorts of patients and play the trial forward.

There's some advance methodologies in place such that you evaluate how that's going, and if it turns out both cohorts are looking promising, you continue with both cohorts, but if it's only looking promising for one cohort, then you drop one off.

Now, there's a selection process there, which increases -- has a multiplicity consequence to it and you have to do some fancy adjustment for it. And there's a lot of adaptive design integrity things to make sure you've got it under control. But there may be opportunities where if you start

Page 275

broad and narrow later, now with great caution, that there are consequences to selection along the way. But those types of things are becoming possible, and they're sort of thought leaders about how to deal with that.

DR. FREEMAN: Go ahead.

DR. HAROUTOUNIAN: I just wanted to raise one point that I think we didn't consider when thinking about adjuvant setting or maybe metastatic setting for, for example, oxaliplatin used in peripheral neuropathy, is that in the adjuvant setting, patients would typically get their 12 cycles of FOLFOX, which is very standardized. But in the adjuvant setting, patients may continue the 12, and then as palliative treatment, some patients get additional rounds of chemo.

I think this is something that may introduce some noise if we're to focus our initial efficacy study in the metastatic patient setting.

DR. BRELL: Like we said, depending on what the other outcomes are, and so somewhere, we have to make sure there's no effect on the cancer. I

Page 276

don't think we're trying to build one phase 3, tell-all trial right now. I think we're speculating what it could be, but we're probably going to have to start thinking about some smaller trials to get to where we can design the phase 3 study.

DR. FREEMAN: That's a good working approach.

DR. GEWANDTER: I guess this question is really for Sharon, or maybe Lynn really needed to be here, too, for this.

If we did the first study in the metastatic setting and there was no demonstration of efficacy on the neurotoxicity, but it showed that there was no effect on the cancer, I don't know if that's considered -- would a phase 2 study be good enough for that endpoint, and then it wouldn't matter what the result was on the neurotoxicity, and then move to efficacy in the adjuvant setting where it's cleaner? Would that be reasonable, like if your goal in the first study is really safety, and then you move for efficacy?

Page 277

DR. HERTZ: That's a very good question. The input we get from oncology about the concern of reducing long-term survival through the use of interventions for CIPN, we don't know yet exactly what would allay those concerns.

I think it's possible the scenario that you just described could be one way to do that. It's hard to say. I guess we would have to look at what the agent was, what the risk was of it interfering, and what the data were based on that, how long patients were followed, and whether that plus other evidence was enough to allay that concern. But that's one of the biggest areas of the consults that we get from the oncologists, is the initial population and the risk for changing long-term survivability, so we would have to look at all that.

Most of my answers today are going to be we don't know because we don't know. We don't have a ton of experience. Pam described to you what we've been seeing and where we're trying to use related experience to help guide programs, and obviously,

Page 278

we're working closely with the oncology divisions, but the answers are not yet in. But it sounds like that could be. It's just hard to say yes.

DR. GEWANDTER: Of course. It wouldn't be a deal breaker if you didn't show efficacy in the metastatic population but then you did show the efficacy on the neuropathy in the adjuvant setting.

I guess that would be the concern, is if you do it metastatic setting and then you don't show efficacy, you don't want to kill the drug based on that from what I'm hearing from everyone.

DR. HERTZ: Right. I think that's true in a very broad and general sense. If you choose to study one subgroup of a population, and you are starting off with the most severe, and it's not there but there's still reason to believe there could be value in other settings, prevention or milder treatment, there's no reason why that study couldn't proceed based on that set setting, that series of data points.

DR. BRELL: I think we would have to treat any new agent for neuropathy like a new agent, and

Page 279

that would be phase-1-type studies where you don't look at efficacy. Efficacy is not the point in phase 1 treatment trials. So this would be modeled after a phase 1 study.

AARC, there's a publication, I don't know how many years back now, but it talked about really the basics of how you would design each of these studies. They have that for therapeutic drugs for cancer, and then they also have where symptom management drugs could fall in as well. It might be wise for us to look at some of that and think about this as a phase 1.

DR. FREEMAN: Let's move on to the one -- and we're moving thoroughly -- one or more multiple chemotherapy types, agents, arrangements.

Now, the take-home message that at least I got is you want to be homogenous over here. You want to use one agent, and even within class, there are sufficient variations in the toxicity, the time course of the chemotherapy-induced peripheral neuropathy that one shouldn't even do a study of drugs within the same class.

Page 280

Is there any nuance to that at all? Is there any way the statement that I made should be reconsidered and have greater granularity than I'm implying? Charles?

DR. LOPRINZI: It depends.

DR. FREEMAN: Good.

DR. LOPRINZI: I think in the adjuvant setting, the curatively treated and that stuff, one regimen and maybe one disease, but one regimen makes sense for that thing and one drug. Taxanes and the oxaliplatin or the paclitaxel taxane are the two biggest ones.

If you're asking the question what about treatment of established neuropathy, then I feel less strongly about it. If, in fact, you have four or five drugs that might work, the four or five that cause the neurotoxicity, and you have an agent that might work for one drug, people say, well, you should pick one, so you do that, well you've got a 1 out of 5 time chance of even picking the right one in that setting. And sometimes it's better to do a more general, and then do a subset analysis in

Page 281

doing that.
We did previous trials looking at baclofen, [indiscernible] ketamine, and didn't say it had to be any particular one drug.
Ellen, you did a taxane or oxaliplatin, so you had the two there. That makes a bunch of sense for me, and you looked at a subset analyses and that sort of stuff, but you used the whole thing from there.
DR. FREEMAN: I'm sorry to interrupt, but I want to be sure. Are you talking about acute treatment in disease modifying, or are you talking about chronic treatment?
DR. LOPRINZI: The first part, we talked about the adjuvant prevention --
DR. FREEMAN: Yes, yes.
DR. LOPRINZI: -- and the second one is treatment of established.
DR. FREEMAN: So are we talking about symptomatic treatment of an established neuropathy?
DR. LOPRINZI: Yes. People are done with chemo --

Page 282

DR. FREEMAN: Ellen Smith's study?
DR. LOPRZINI: Yes.
DR. FREEMAN: Okay.
DR. LOPRINZI: And others along that way. So done with their neuropathy -- done with their neurotoxic chemotherapy, ideally out for three or four months or longer, and then they go ahead, and you're treating that established neuropathy only because the patient's having problems, which could be numbness, tingling, pain.
DR. FREEMAN: We're not so much, in fact, not at all really focusing on that which compared to the issues that we are discussing is pretty straightforward. It's not straightforward at all, but compared to these other issues, it's pretty straightforward.
Any other comments, any other nuance with the treatment?
(No response.)
DR. FREEMAN: Okay. Let's move on then to what I think is perhaps more controversial, and that is either -- and I'm going to group these

Page 283

together because I think they're fairly similar -- patients who either have a subclinical neuropathy because they are predisposed to, prediabetic patients, diabetic patients, patients who have received HIV neurotoxic therapy, chemotherapy, patients who may have drunk excessive amounts of alcohol, patients who have a preexisting neuropathy, whether it's diagnosed using standard clinical neurophysiology or it's Patrick's pegboard test.
There really were two themes over here. The one that I think both Guido and I espoused, that is to say that not just that we don't want them in the trial, but that we actually do want them in the trial because these are the patients that are going to actually show the chemotherapy-induced peripheral neuropathy, and it's going to make our study have a much smaller SOP size, perhaps even have a greater effect size if the drug works, whereas the view of Charles and others was that we exclude those patients.
It would be nice to flesh this out a little

Page 284

bit, have this controversy at least have a little bit more flesh to it.
DR. LOPRINZI: Let me clarify. I don't think I said that you necessarily have to exclude those patients. We didn't exclude them. They could have had diabetes, but they couldn't have neuropathy associated with that. But we didn't exclude those, and we didn't exclude people who were overweight or who didn't exercise.
DR. FREEMAN: Okay. Then I suppose the question is, if we say they have neuropathy and they don't have symptoms associated with the neuropathy that would cloud the assessment, the point made by Jennifer earlier, why exclude those?
DR. LOPRZINI: I don't understand. You said they had the neuropathy but they don't have symptoms?
DR. FREEMAN: They don't have symptoms.
DR. LOPRINZI: Well, I don't know about that because I'm not doing these extra neuropathy tests or anything extra like that. Any patient that I have that I put on a clinical trial as an

Page 285

oncologist, if they have neuropathy it's because they say I've got numbness, tingling, shooting, burning pain. If I miss a reflex on somebody, that doesn't mean they have neuropathy.

DR. FREEMAN: I understand. There are fairly simple tests from Patrick's test to testing reflexes --

DR. LOPRINZI: Yes, but --

DR. FREEMAN: -- tuning fork, something that's not too elaborate. But the average clinician would say, yes, there's vibration loss. There's no pain. There's not even any numbness, but there's -- I'm trying to make this discrete for everybody, and in doing so, I'm creating a caricature. Vibration sense is decreased. Patrick's pegboard test or feeling the bumps is decreased.

So these patients we would say have a clinical neuropathy, not even a subclinical neuropathy but a clinical neuropathy, why not have them in the trial?

DR. DOUGHERTY: Let me clarify. The

Page 286

patients that we've tested and detected what I'm calling subclinical neuropathy, if you handed them a neuropathy questionnaire, you would come up with zero. You would basically conclude based on talking to them -- and in cursory examination, pinprick is not decreased. They usually don't have any change in grip strength or gait.

It's only when you have them do something really fine, really standardized that you can now pick up. But if they just walked into your clinic, you would say this patient does not have neuropathy. And that's for what is disease tumor related, and we've detected this, as I said, both in patients where you would expect it, non-small cell lung, myeloma, but as well in colorectal where you wouldn't expect this to occur; even head and neck cancer patients have subclinical neuropathies.

So you may be wiping out a whole bunch of your cohort if you're going to say we're going to give you a pegboard test. If you show two standard deviations out of the expected norm for your age, you're excluded. That's probably an important

Page 287

group. You may even want to enrich for that group because they're more predisposed. You're likely to get the occurrence of neuropathy with your treatment so you actually have a robust group to test. Otherwise, just stratify for it and let it sort itself out.

The overt neuropathies, diabetic, alcoholic, HIV -- I think we had this discussion earlier -- if they're already symptomatic and they have symptoms that are going to interfere with your expected measurement outcome, you're creating a real complication.

So if they have those as risk factors, diabetes, alcoholism, and HIV, I wouldn't necessarily kick them out, but if they are overtly symptomatic, then you're probably just creating a large problem.

DR. FREEMAN: That's I think the point made very nicely by Jen and Sharon.

DR. HERTZ: As a neurologist, I'm a little distressed by some of what we're saying because what could end up happening is a very different use

Page 288

of terminology here. Using no evidence of neuropathy in one setting may have just not looked for and detected evidence of neuropathy in another.

I think that as we think about this, and particularly as we think about it, whether we decide to include people with concurrent neuropathy or not, it might be helpful to define what is that going to be. Is it going to be there's nothing on somewhat coarse level testing, or is it really nothing in terms of what we define as the baseline?

I would argue that your asymptomatic diabetics probably all had neuropathy if they had long-standing type 2, and I could probably find it with the right set of tools. But that's okay because they met a certain criteria, and up to that criteria, you did not find an effect.

I don't know that there needs to be one specific answer about that. My request is that we think about how to define, in terms that we can all agree on, the presence or absence of neuropathy in people who either have clear risk factors, like diabetics or other exposures, and people who are

Page 289

simply at risk for conditions that could. But I think that understanding whether those conditions have an effect or not could be very difficult to discern if we're not defining the baseline the same.

DR. FREEMAN: Yes, Bob?

DR. DWORKIN: So, Roy, I want to see if I understand what I think you're proposing. It sounds like you're saying if a patient with diabetes has subtle signs of peripheral neuropathy but no symptoms, you would include that patient.

Presumably, you mean in a trial where the endpoint is a symptom measure like a patient-reported outcome of symptoms but not signs as an endpoint because they've already got subtle signs from their diabetes.

As I was struggling to understand this, I guess that sort of makes sense. They've got subtle signs of DPN, no symptoms of DPN, and you're going to do a trial to look at symptoms of CIPN. On the face of it, that sounds reasonable. However, I'm not a neurologist.

Page 290

If we're going to do some kind of prevention trial that could last 3 to 6 months, isn't it possible that the diabetic with subtle signs at baseline develops symptoms of diabetic peripheral neuropathy over the next six months, that then totally confounds your ability to assess symptoms of CIPN?

I would still vote for excluding even the subtle signs DPN patient because ultimately in a 3- to 6-month trial, that patient can develop burning pain or numbness from his or her DPN.

DR. FREEMAN: The way I'm thinking of this is -- I'm making this -- I'm creating extremes over here for purposes of discussion.

So to answer your question, let me be very specific and say that with diabetic peripheral neuropathy, are we talking, as Sharon implied, of a 10-, 15-year disease for somebody who has subtle signs? And when I say subtle signs, is this neurophysiology, is this skin biopsy, is this detailed clinical examination? That's not going to change significantly in six months, and if it does,

Page 291

let's hope randomization takes care of it.

I think there are ways of dealing with it, but the advantage of that is that if our chemotherapy is neurotoxic and if a predisposing neuropathy really makes the neurotoxicity manifest and our drug works, we will see. We will be able to test our drug.

DR. DWORKIN: I came prepared with a backup question because I thought you'd have an answer. It seems if we accept that, then there's another problem, which is it means your endpoint for the CIPN trial has to be limited to symptoms, and we heard this morning that there is great interest at the agency in function.

I just wonder do we want to do large challenging trials where our endpoint is limited to patient-reported outcomes, and we can't look at signs and we don't look at function because the diabetics in the trial already have subtle signs.

DR. FREEMAN: I would say I wouldn't necessarily accept that premise because I would say that if we stratify by the presence of diabetes and

Page 292

we have cutoffs, and we say that we're going to randomize them, then we can look at anything. I don't think you are precluded from looking at signs or symptoms or function because of randomization and stratification.

Guido, you had some views. What do you think?

DR. CAVALETTI: I think the major issue, again, is what we decide to use as a threshold to assess those patients. And again, the position might be different depending if we are looking for something that might confuse our interpretation of the results.

In this case, to me, it's very clear. All those patients who are not symptomatic using the patient-reported outcome measure that will be selected as the primary endpoint can be admitted to the study, otherwise, we will not be able to capture changes, and it's quite simple.

What is tricky to me is that if we presume that the preexisting damage is a predisposing factor, we need to start discussing which of those

Page 293

neuropathies we don't want to have into the study. For diabetic patients, I'm sure that we can randomize because it's a bit difficult for me to talk about diabetic neuropathy because it's very hard right now to find patients with diabetic neuropathy in Italy, for instance, because our diabetologists are so aggressive that they just have 111 glucose blood level, they would be killed by the diabetologist. So it's difficult find to patients with a real diabetic neuropathy right now, but they are frequent, so you can randomize.

HIV patients, probably they are not so frequent in this population, so maybe we could stay on the safe side and exclude those patients. There would be probably one or two per trial. But then we have a lot of other tricky conditions, alcoholic patients, which is the definition.

So we need to set up a clinical or an instrumental or a patient-reported outcome again to say those patients have a neuropathy that necessarily excludes those patients from the trial.

In my mind, it probably should be discussed

Page 294

case by case. I understand that is not the best way to approach a clinical trial protocol, of course, but I would accept the cost to admit all the patients provided that you have a baseline examination that satisfies all your requirements to have a correct evaluation on the endpoint at the end of the study.

Again, the point is the method we use because I've heard about paraneoplastic neuropathy in cancer patients. It was 1994 when I started my first trial on ovarian cancer patients, and we found that patients with stage 3 ovarian cancer had, let's say, 40 percent incidence of peripheral neuropathy without having onconeural antibodies.

There was relationship between the stage and this rate of neuropathy, but we were investigating those patients on a physiological basis. Out of the entire cohort of ovarian cancer patients, two of them had pathologic neurologic examination, but half of the population had neurophysiological abnormalities.

So is it to say that patients with ovarian

Page 295

cancer has peripheral neuropathy, clinical examination, 2 out of, I don't know, 100 patients, or neurophysiology, 50 out of 100 patients. That's a critical issue, what we want to use to say this patient has neuropathy.

DR. FREEMAN: Before we move on, maybe one other detail, which I think is worth resolving, and that is -- and again, let me make the extreme case just for discussion -- patient who has received neurotoxic therapy previously, a taxane, a platin, but even with Guido's most exquisite testing, does not have evidence of a neuropathy, do we exclude those patients from these kinds of trials, and if so, why?

DR. LOPRINZI: That's for me?

DR. FREEMAN: It was definitely. I was aiming it directly at you.

DR. LOPRINZI: I would exclude.

DR. FREEMAN: I know.

DR. LOPRINZI: Why would I exclude? One, it may be that they got some neurotoxic chemotherapy and it's going to be predisposed, and therefore,

Page 296

they only need a little bit more, but that could be the same argument as the diabetic, et cetera, et cetera.

On the other hand, there are some people who are more prone to get neurotoxic chemotherapy-induced peripheral neuropathy and others who are not. Maybe people who have Charcot-Marie-Tooth type genetic abnormalities, and this is a person who if they had a lot of chemo before, they didn't get it, and so you have the other aspect.

Three, there aren't that many of them, and there are enough other patients for it. Those are the reasons I would think about not including them.

DR. FREEMAN: There is another side of the coin, before Guido speaks, is that those patients that received neurotoxic therapy and did not get a peripheral neuropathy, are they somehow protected and maybe not for the reasons you're saying but where you don't want them in the trial for other reasons?

Guido?

DR. CAVALETTI: For exactly this point, I

Page 297

would exclude those patients because probably they are resistant. They are probably lucky enough to be protected by chemotherapy-induced neurotoxicity. We don't know why. But they would exclude for that reason.

DR. DOUGHERTY: That's the answer I thought Charles was going to give.

DR. CAVALETTI: Exactly, but we agree.

DR. LOPRINZI: That's what I tried to say.

(Laughter.)

DR. FREEMAN: While we're talking about this, perhaps this might be the time, although it wasn't discussed earlier, biomarkers, genetic predisposition, is there anything new that you can add to this discussion, and should this be a factor in any chemotherapy-induced peripheral neuropathy discussion?

DR. HAROUTOUNIAN: There have been a few papers on risk factors, sodium channel abnormalities, TNS transfers, et cetera. It probably makes sense to have those as additional risk factors as we would collect some demographic

Page 298

factors. I don't see reason as an explorative type of outcomes, why not collect them if there is some evidence that those could be associated with specific toxicity.

DR. CAVALETTI: I fully agree. The major issue with the candidate gene studies that have been done so far, the beginning of the story was that all the genes were related to the anti-cancer effect of the drugs, so there was probably nothing to do with neurotoxicity. The genewide screening, some of these that have been done so far were negative, so they were unable to confirm anything.

What is the main issue in all these studies is the assessment of the neurotoxicity was done with the NCI CTC. It's like going with a Ferrari to buy milk at the supermarket. It's nonsense. So we need to collect genomic data from properly characterized populations, not using the NCI CTC. That's obviously too rough for such a sophisticated analysis.

DR. FREEMAN: Okay.

DR. RICHARDSON: The only thing I would just

Page 299

add to that, if I may, is just the whole construct that in our myeloma experience, we actually looked at disease characteristics. In other words, we did a sort of biomarker analysis of the tumor in terms of certain gene expression profiles, and certain genes that downstream, influence inflammatory responses were associated with higher risk of neuropathy.

So looking not just at the genotype of the patient but also the genotype of the tumor is recommended because essentially, we've already hinted at that, that there's a relationship between disease biology and neurotoxicity, and that we find quite informative actually with the work we did with the bortezomib study.

DR. FREEMAN: Any additional comments so far?

(No response.)

DR. FREEMAN: We've got roughly another 10, 15 minutes left. We are not going to cover everything, but this is what the final summing up session is. I think a lot of these details, I'm

Page 300

not sure they'll need to be covered in much detail again.

Concomitant treatments for neuropathy, I think on Jennifer's initial slide, she had this in quotes. What were these? I know things like B12 and --

DR. GEWANDTER: Yes. Most commonly, it was antidepressants, SSRIs, anti-epileptics, and vitamin B12 and other vitamins. Honestly, a lot of times, it just said people were excluded who had treatments thought to prevent neuropathy so they didn't really say in the papers a lot of times.

DR. FREEMAN: Charles and others who've done these kinds of trials, any issues that we need to deal with?

DR. LOPRINZI: A couple of things, one, if they're taking vitamin E because they think that that was helpful for it -- and there are some reports of people who either start or stop antioxidants, that they get more neuropathy, and that might be because either they start because of neuropathy or they were getting neuropathy and they

Page 301

stopped it because there are stories both ways.
Where we've kind of been before, if there's no proof that it's beneficial, then we haven't tried to exclude it. If they're taking something for established neuropathy -- but then I don't allow them on with neuropathy like gabapentin. If they're taking an antidepressant because of depression but not for neuropathy, then we've not excluded them before.
So I wouldn't be taking people who have neuropathy, so it wouldn't be neuropathy, but if you're taking drugs that might affect neuropathy, I don't feel quite as strongly about that aspect. It's not like those drugs work that well that we know about.
DR. LAVOIE SMITH: Well, with maybe the exception antidepressants given that we know that one might have an effect. And it depends upon the drug that we're testing, so the other thing to consider is drugs that would have a combined synergistic side effect profile that might be contraindicated.

Page 302

I'd be a little bit concerned about duloxetine, but of course we have no evidence that anything else works. But is that because the trial designs were not sufficient, so do we really know that they don't work?
DR. LOPRINZI: I agree with you, probably not duloxetine because it's been shown clearly to be beneficial, not as beneficial as we want, but the only one that really has been. But if venlafaxine, which are mixed data, much negative as positive, I wouldn't feel as strongly on that. But if it interacted with the drug that you're planning to give, then yes, I agree.
DR. FREEMAN: I can say I personally would be concerned about doing any kind of trial in which pain was part of the endpoint using any alpha 2 delta ligand like pregabalin, or an SNRI, or a tricylic. I would just feel -- to me, that's troublesome. I don't know if I see Bob nodding.
DR. DWORKIN: Yes. What's often done with clinical trials in painful diabetic peripheral neuropathy is to allow SSRIs for depression or

Page 303

anxiety because there's not really any good evidence that they have analgesic effects. There's some, but weak. That way the patients who are depressed or have generalized anxiety disorder are allowed treatment, but you exclude the dual reuptake inhibitors.
DR. LOPRINZI: If they were taking regular Tylenol because they had arthritis, then you could say, well, they're taking something for pain. I don't feel terribly strongly on it one way or the other.
DR. FREEMAN: Others, any other comments on this? And here, I think, Daniela, you were one of the people in the audience who's thought more about this than most of us. Any thoughts on these eligibility criteria, what have you done in your clinical trial?
DR. DASTROS-PITEI: I was wondering about the comments because some of these patients, we know that many of the other drugs have not shown to have effect apart from duloxetine in a relatively small study, which may be more of an argument that

Page 304

they may work. But if it was on a stable dose, would you still allow them with the condition that they stay on a stable dose? They're on a stable dose, and they stay on.
DR. GEWANDTER: I think we think that it might be a good idea when it's a treatment trial because they still have pain or whatever symptoms of a minimum level. But for prevention, I think it's a little bit more worrisome because if one of those drugs would hide pain that comes up and if pain is part of your outcome, then that could be a problem because you don't know if it would work for them.
So I think that, personally, if I were going to do a prevention study and pain was going to be part of my composite or one of my main things, then I would also want to exclude those drugs. But if numbness was my main outcome, then I wouldn't be as concerned. I think it depends on what your outcome is.
DR. DASTRO-PITEI: Which in a way takes us back to the PROs and to the measures and what are

Page 305

we looking for because we all agreed that this indication, the CIPN, is not so dominated by pain. It's more the numbness and the tingling, the dysesthesia, the paresthesia.

I'm still thinking about this discussion about perhaps co-primaries or co -- maybe co-primaries is too far to go, but how do we look at the PROs and the discontinuation rates, or the cumulative dose? Are we going to look at this together --

DR. GEWANDTER: Composite, you mean.

DR. DASTROS-PITEI: Composite, yes.

DR. GEWANDTER: That's maybe tomorrow. That's tomorrow's discussion.

(Laughter.)

DR. FREEMAN: I'm hoping a good night's sleep will clarify that for all of us, but I'm not optimistic.

(Laughter.)

DR. DASTRO-PITEI: Also, can I just say we have gone away from NCI CTCAE, which has been the staple of CIPN measures in the past. Is this

Page 306

something which the room feels that is probably not that relevant anymore?

DR. GEWANDTER: I don't think it's a great outcome. I would not choose that outcome for my CIPN study, but we're going to talk about measures tomorrow.

DR. BRELL: And we're misusing it by saying it's an outcome measure because it's not. It's meant for developing drugs, is really what it was meant for. In addition, it's not validated.

DR. LOPRINZI: I would always use it, but I'm agreeing with you. It would not be my primary outcome, but I would always use it so you have that background to compare to all the other studies that have been done that had used it. And it's easy to use. You just have that clinician fill that thing out. But it's not the primary -- a patient-reported outcome is much better from all indications. But I'd still use it for a baseline of where we were before and to compare and contrast.

DR. BRELL: I would just argue the

Page 307

correlation is not that good with anything else. I understand historically that it would be good to look at that. I see your point, but I just don't think it's gotten us anywhere to date.

DR. FREEMAN: Any other thoughts and comments? Simon.

DR. HAROUTOUNIAN: Something that we haven't discussed, I think, especially in the context of treatment trials is differences in patient sensory phenotypes due to the chemotherapy-induced peripheral neuropathy.

We're phenotyping quite a bit of patients, and sometimes they have profound differences in the way that the neuropathy presents itself in terms of if we're thinking about C fiber damage or A delta fiber damage, cold hypersensitivity versus numbness versus hyposensitivity, et cetera.

The question is, them being in the prevention trials is less relevant, but in the treatment trials, should we at least try to get -- I'm not talking about very extensive QST battery, but at least some sense either stratifying

Page 308

or just getting some baseline data because potentially, they might have different mechanisms in terms of their neuropathy, and then potentially different drugs may work differentially in those patients.

DR. FREEMAN: Yes. That's a big discussion, and maybe we can save that for tomorrow.

Any other questions before we close for the day?

(No response.)

Adjournment

DR. FREEMAN: We have two more slides to deal with, but I think those will be suitable for discussion tomorrow afternoon.

I think this was a very, very helpful session. Great talks, very helpful panel discussion. We'll see you tomorrow. Enjoy your dinner.

(Applause.)

(Whereupon, at 3:59 p.m., the meeting was adjourned.)

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